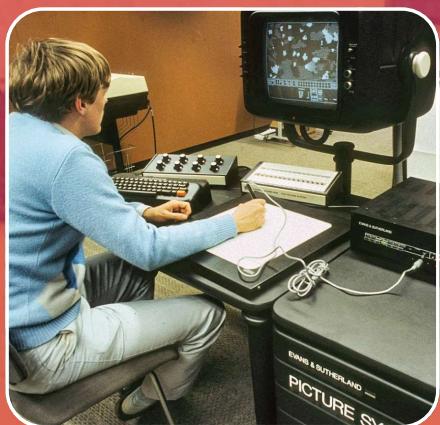
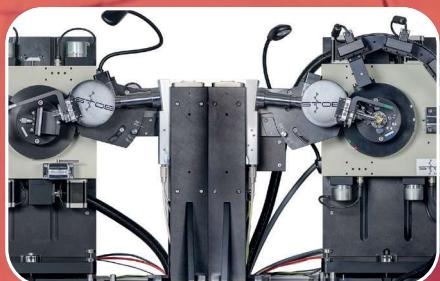


Crystallography News

British Crystallographic Association

Issue No. 171 December 2024

ISSI 1467-2790



ECM34, Denver DXC, SWSBC and the Life Sciences XFEL Townhall

Spring Meeting 2025

News from the CCDC

Focus on Stoe

ECM34 Padova 2024

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p8	South West Structural Biology Consortium	p17
p9	XFEL life sciences town hall meeting	p21
p11	Schrödinger's aperiodic crystal	p28

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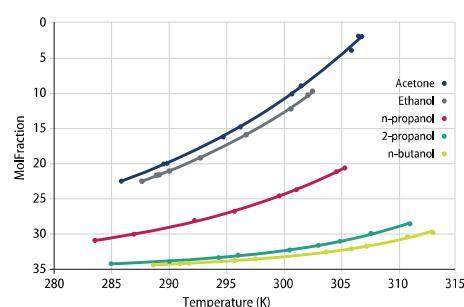
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British Crystallographic
Association

ABBF Conference Bursaries 2025

Bursaries are available for BCA members to attend national/international crystallographic meetings in 2025 and 2026.

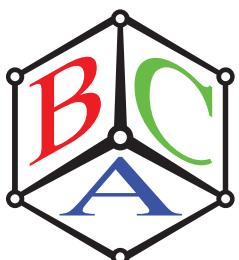
Local meetings and virtual meetings (with no travel) are supported.
Eligible members may apply every year.

Apply early for in person attendance at international meetings.
Successful local/virtual meeting bursary winners are still eligible.

Further information on the eligibility criteria and
the application portal is available here:
<https://crystallography.org.uk/prizes/bursaries>

Additional carers grants are also available to BCA members
at any career stage:

<https://industrial.crystallography.org.uk/bursaries-and-awards/>





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CRYSTALLOGRAPHY NEWS is published quarterly (March, June, September and December) by the British Crystallographic Association, and printed by North Wolds, York. Text should preferably be sent electronically as MSword documents (any version - .docx, .doc, .rtf or .txt files) or else on a PC disk. Diagrams and figures are most welcome, but please send them separately from text as .jpg, .gif, .tif, or .bmp files. Items may include technical articles, news about people (eg awards, honours, retirements etc), reports on past meetings of interest to crystallographers, notices of future meetings, historical reminiscences, letters to the editor, book, hardware or software reviews. Please ensure that items for inclusion in the March 2025 issue are sent to the Editor to arrive before 25 January 2025.

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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.

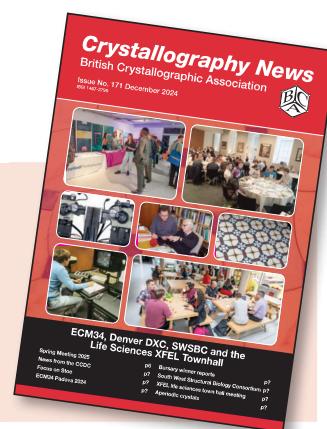
Printed by BHW Print Group
Unit 8, Malton Enterprise Park, 17 Cherry Farm Close,
Malton, North Yorkshire YO17 6AS
Tel: 01653 697261
Web: www.BHWprintgroup.com

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This month's cover:

A collage of crystallographic conferences, equipment and conundrums.



From the President



I was lucky enough to be at the Winter Crystallography Meeting in late October, a combined CCG/PCG/ISIS/Diamond event. It was a fantastic display of crystallographic science, suitably packed out with participants (congratulations to all concerned on the formidable organisation!). The Winter Meeting has traditionally been a

joint venture between the ISIS Crystallography Group and the PCG and is always a comforting fixture of the colder months. The changes over recent years have brought new contributions from related groups which have enriched the already diverse range of science on show. It is also a meeting at which many old friends and colleagues can be found, and the session dedicated to the 40th anniversary of ISIS expanded on this through a wonderful walk by **Stephen Hull** (ISIS) through the history of both instrumentation and, equally importantly, the people making the facility much more than the sum of its parts. The fact that much of the rest of the meeting was displaying ISIS's recent scientific contributions felt particularly appropriate, with Diamond and its work featuring equally strongly as a younger, but no less heavyweight, counterpart. It was also fantastic to see the significant contributions from other techniques and local scale facilities bringing crystallographic secrets to light. The Winter Meeting is also the traditional venue for the presentation of the Malvern Panalytical Thesis Prize and the lecture from the winner, whose identity remains a closely guarded secret until that moment. Congratulations again to **Madeleine Geers** (Nottingham/ILL) on her award. I will leave it there as hopefully a future edition of *Crystallography News* will fill you in on the other activity across the busy programme.

I would like to pass on one piece of news from this year's Spring Meeting which has previously gone unannounced in *Crystallography News*: the award of the BSG Blue John poster prize. This year the prize was awarded to **Augustinas Silale** (Newcastle) for the poster entitled "Structural basis of iron piracy by a prominent human gut symbiont." Courtesy of Jon Cooper here is the story behind the award. This curiously named trophy was inaugurated by the BSG well over 30 years ago in 1991 and comprises a piece of Blue John crystal mounted on an oak plinth. Within ten years of its discovery in Derbyshire in about 1750, it became fashionable to have Blue John on one's fireplace, so by 1770 there were sixteen mines working on the hill where it was discovered. The French described the mineral as 'Blue jaune' after its colour which is basically yellow with bands of blue. The French name was subsequently corrupted by the English to 'Blue John', the name by which it is now known. Our congratulations to Augustinas for this award.



The BSG Blue John Crystal poster prize.
Photography by the previous winner, Jake Hill (Bradford).

I would also like to bring to your attention the sad news of the passing of **Professor Peter Main** (York), a very strong supporter of the crystallographic community and an honorary member of the BCA since 2006.

As the long winter nights are drawing in it is occasionally pleasant to think that Spring will soon be here again, and with it our central calendar event of the year, the Spring Meeting. I hope you have also received the flurry of emails announcing that the time has come for getting into gear for next year's iteration which will take place at the University of Leeds, 14th-17th April. I realise that those contributing to the organisation have been very much in gear for some time now and I take this opportunity to thank them for what promises to be a fantastic programme! Registration is open and I encourage you all to put your thoughts towards abstracts and logistics for April.

With that, I should bring my column to an end and wish you all an enjoyable and restful Christmas and New Year!

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



WE begin this issue with the programme for the 2025 Spring Meeting which is looking very exciting and we follow this with the latest news from the CCDC. We then have a very interesting report by **John Helliwell** (Manchester) on the ECM34 held in Padova this year, followed by the ABBF recipient reports on the ECM and the Denver

X-ray Conference. A great account of the SWSBC held in Bath in early July is given by **Mark Roe** (Sussex) and we then have a report on the UK XFEL Townhall meeting which was held at the Royal Society at the end of July 2024 on "Life Sciences and Biomedicine." This was one of a series of meetings held around the UK in the last 12 months or so to discuss the applications of the proposed new UK XFEL source. Other townhall meetings were held on the following themes, many of interest to crystallographers: "Ion beams", "Catalysis", "Energy, environmental and climate technologies", "Electronics, photonics and quantum technologies", "Advanced materials and manufacturing", "Frontiers of measurement technology", "Materials, chemistry and biology at extreme conditions", "Fundamental physics, quantum computing and AI" and "Engineering biology, genomics and healthcare." Members who attended any of these meetings are most welcome to contribute reports to future issues of *Crystallography News*.

In May this year, Nature published the latest AI model from DeepMind for prediction of protein interactions, AlphaFold3 [1]. I was reminded of this by attending the above mentioned life sciences XFEL townhall meeting a couple of months later in July. My only real-life contact with AI specialists was as an undergraduate when one of my short-lived duties was manning a stand at the annual Fresher's Fair, where the stalls for the student societies were arranged in alphabetical order. As a staunch amateur astronomer, at the time anyway, our stand (AstroSoc) was always next to the stall for the Artificial Intelligence Society. In some way that has become an axiom of my life - AI is something best left to the computer scientists and mathematicians next door! Of course, things have come a very long way over the last 40 years, so do members have any experiences of using AlphaFold3 that they might be willing to report briefly here? The *Crystallography News* editor is just an e-mail away!

Indeed, I asked the very same question on the CCP4 bulletin board and received several replies. I have tried to summarise the findings in a short article (Seeing eye to AI with expert systems) towards the end of this issue. Someone also pointed out the recent award of the Nobel prize in this field. Quoting directly from nobelprize.org: "The Nobel Prize in Chemistry 2024 is about proteins, life's ingenious chemical tools. David Baker has succeeded with the almost impossible feat of building entirely new kinds of proteins. Demis Hassabis and John Jumper have developed an AI model to solve a 50-year-old problem: predicting proteins' complex structures. These discoveries hold enormous

potential." We offer our many congratulations to the prize winners and all of those involved in this work.

We then have an article by **István Hargittai** (Budapest) on Aperiodic Crystals followed by what I hope are some relevant comments on the work of Sir Aaron Klug FRS in the structural virology sphere. As promised, Puzzle Corner has returned with a vengeance, as has Down Memory Lane, with some reminiscences of computer graphics technology in the 1970's and 80's.

Sadly, two ex-Birkbeck crystallographers have passed away in the last few months; Professor Brendan Howlin (Surrey) and Dr Tapan Chattopadhyay. Brendan, whose inaugural lecture we reported on only last year, was an expert in molecular simulations, computational chemistry and drug design, Tapan in the small molecule crystallography field. Both will be sorely missed and we offer our deepest condolences to their colleagues, friends and families.

Back in March this year we had a short Down Memory Lane article on the electron diffractionist George Finch who spent a significant part of his early career participating in efforts to climb Mount Everest, until he fell out with the rest of the team. Sadly, the next climb without him proved fatal for two of the team, George Mallory and Andrew Irvine. We reported that Mallory's remains were not found until 1999 and that Irvine's remains had never been located. However, members may be aware that on 11th October this year, the media widely reported that one of Irvine's boots with a sock having his name clearly embroidered on the label, had been found by climbers just a few months over 100 years since that fateful ascent.

Barring any intervening disasters, the arrival of 2025 will mark the beginning of my third year as editor – a role which, I believe anyway, has a three year term, so do consider if this is something you would like to do! I could possibly hang on for another year or two beyond my current term (March 2026), if really needed, but in the interests of scientific diversity, etc, by then it might well be time for the non-biological communities to have greater representation in these pages. Just a thought!

Finally, I must close by wishing members the very best for the coming season of good cheer and for the new year!

Jon Cooper
UCL

References

- [1] Abramson, J., Adler, J., Dunger, J. et al. Accurate structure prediction of biomolecular interactions with AlphaFold 3. *Nature* 630, 493–500 (2024). <https://doi.org/10.1038/s41586-024-07487-w>

BCA Spring Meeting 2025

SESSION DETAILS

ESCG Early Career Satellite Meeting

Monday 14 April 2025

University of Leeds

Early Stage Crystallographers Group (ESCG)

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:

Rupert Beckett Lecture Theatre, Michael Sadler Building

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

Rupert Beckett Lecture Theatre, Michael Sadler Building

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

Room: Rupert Beckett Lecture Theatre, Michael Sadler Building

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 2024 Main Meeting Programme

Room: Rupert Beckett Lecture Theatre, Michael Sadler Building

11:30 – 12:15

Lonsdale Lecture

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

Speaker: TBC

Title TBC

13:00 – 13:45

BSG Plenary

Session Chair: TBC

Speaker: **Elton Zeqiraj** (University of Leeds)

Title TBC

14:00 – 15:30 Parallel Sessions

PCG: Open session I

Session Chair: **Lewis Owen** (University of Sheffield)

BSG: Engineering Biology

Session Chair: TBC

Keynote: **Ross Anderson** (University of Bristol)

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

Session Chair: **Toby Blundell** (Durham) and **Sam Lewis** (Cardiff)

Keynote: **Simon Coles** (University of Southampton)

16:15 – 17:45 Parallel Sessions

PCG: Computational Modelling in Crystallography

Session Chair: Johnathan Skelton (University of Manchester)

Keynote: TBC

BSG: Open session

Session Chair: **Natalie Tatum** (Newcastle University) and **TBC**

Keynote: TBC

CCG: Polymorphism, hydrates and co-crystals

Session Chair: **Iain Oswald** (Strathclyde)

Keynote: TBC

18:00 – 18:45

PCG Plenary

Room: Rupert Beckett Lecture Theatre, Michael Sadler Building

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

CCG Plenary

Room: Rupert Beckett Lecture Theatre, Michael Sadler Building

Session Chair: **Hamish Yeung** (University of Birmingham)

Speaker: **Lucia Maini** (Bologna)

Be a crystallographer to investigate the past, the present and the future!

10:15 – 11:45 Parallel Sessions

IG: Amorphous modelling

Session Chair: **Tony Bell** (Sheffield Hallam University) and **Natalie Johnson** (CCDC)

Keynote: TBC

Title TBC

BSG/CCG: In-situ crystallography

Session Chair: **Phoebe Allan** (University of Birmingham)

Keynote: **Amy Thompson** (Diamond Light Source)

VMXi: a high-throughput, in-situ crystallography beamline to harness the advantages of multi-crystal strategies

PCG: Complementary techniques

Session Chair: **Evie Ladbrook** (Warwick) and TBC

Keynote: TBC

Title 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.

15:15 – 16:45 Parallel Sessions Workshops

Workshop: Determining a protein crystal structure in 2025 (BSG/CCP4?)

Session Chair: **Adam Crawshaw** (Diamond Light Source) and TBC

Keynote: TBC

Workshop Outreach (CCG/ESCG/CCDC)

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

Keynote: **Ilaria Gimondi** (CCDC)

Workshop Rietveld refinement (PCG/IG)

Session Chair: **Tony Bell** (Sheffield Hallam University) and **Lewis Owen** (University of Sheffield)

Keynote: Jeremy Cockroft (UCL)

17:15 – 18:00

Dorothy Hodgkin Prize Lecture: Name

Room: Rupert Beckett Lecture Theatre, Michael Sadler Building

Session Chair: TBC

Speaker: TBC

Title TBC

18:00 – 19:00

BCA Annual General Meeting

Room: Rupert Beckett Lecture Theatre, Michael Sadler Building

19:30 – 01:00

Conference Dinner & Cèilidh

Thursday 17 April 2025

09:00 – 09:45

IG Plenary

Room: Rupert Beckett Lecture Theatre, Michael Sadler Building

Session Chair: **Tony Bell** (Sheffield Hallam University)

Keynote: **John Helliwell** (Manchester)

Adding Open Science to the Modern Discovery and Applications Toolbox in Crystallography

10:15 – 11:45 Parallel Sessions

CCG: Open session

Session Chair: TBC

Keynote: TBC

PCG: Open session II

Session Chair: **Helen Playford** (ISIS Neutron and Muon Source)

Keynote: TBC

BSG: Integrative Structural Biology

Session Chair: TBC

Keynote: **Jaime Blaza** (Leeds)

Using Cryo-EM and symmetry expansion to understand how Rubisco is bound together to accelerate carbon fixation

12:15 – 13:45 Parallel Sessions

CCG/PCG: Coordination polymers and porous materials

Session Chair: **Lauren McHugh** University of Liverpool

Keynote: **Valentina Colombo** (University of Milan)

In situ insights into adsorption and catalysis in metal-organic frameworks

PCG: Phase Transitions

Session Chair: **Struan Simpson** (University of Warwick)

Keynote: TBC

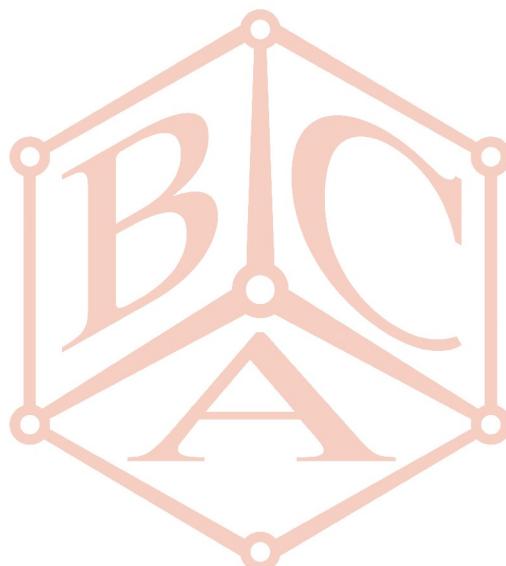
BSG: “Mechanisms and disease

Session Chair: TBC

Keynote: **Wyatt Yue** (Newcastle University)

Structural biology at the crossroad of metabolic enzyme disorders and drug discovery

CLOSE OF CONFERENCE



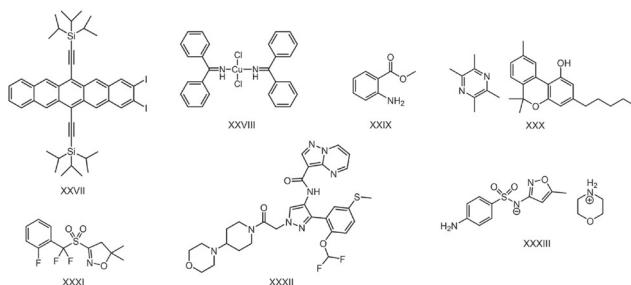
News from the Cambridge Crystallographic Data Centre

Results of the 7th CSP Blind Test Published – Overcoming Pharmaceutical and Other Materials Issues Before They Exist

Two scientific papers have been published detailing the findings from the 7th Crystal Structure Prediction (CSP) Blind Test. To coincide with these publications, the Cambridge Crystallographic Data Centre (CCDC) has released a CSP Blind Test database containing 171,679 entries from 207 different landscapes.

CSP predicts the most likely crystal structures to form from a given molecule, based on its 2D chemical structure. Most methods use informatics and computational science techniques. Predicting more stable structures leads to many benefits including improved manufacturing processes, patent protection and breaking as well as the potential discovery of new and improved materials.

[Read more at the CCDC website.](#)



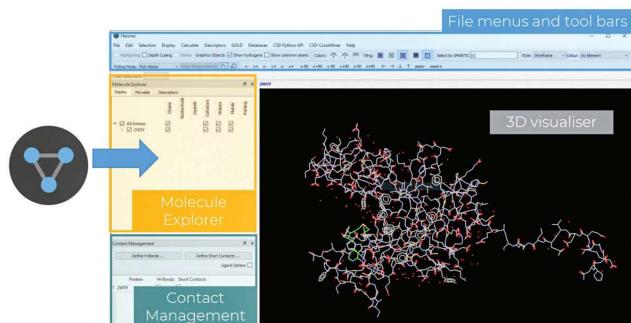
BioChemGraph – CSD Data Linked to PDBe, ChEMBL and Other Sources via UniChem

In the era of data-driven biology, integrating information from different resources is essential yet often challenging. The BioChemGraph project addresses this challenge by creating infrastructure that consolidates structural, functional and biochemical annotations for small molecules and their targets from key resources: the Protein Data Bank (PDB), the ChEMBL database, and the Cambridge Structural Database (CSD). [Read more at the CCDC website.](#)

Recent Blogs

Getting Started with Protein-Ligand Docking Using GOLD

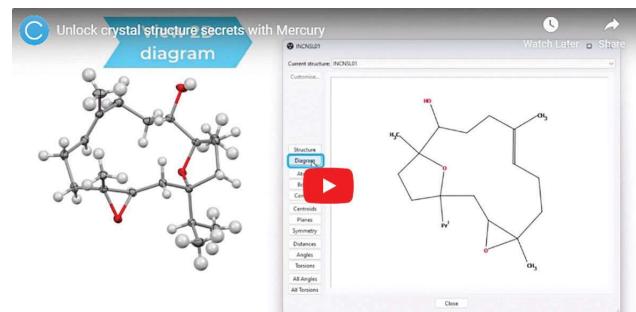
Like all the components of the CSD-Discovery suite, GOLD is a knowledge-based tool for drug design. It uses the structural information stored in the Cambridge Structural Database (CSD) to make reliable predictions and empower molecular discovery in different steps of the drug design pipeline. GOLD has proven success in virtual screening, lead optimisation and identifying the correct binding mode of active molecules. [Read more at the CCDC website.](#)



[Check out all our blogs at the CCDC website.](#)

New video: Unlock crystal structure secrets with Mercury

This 5-minute video shows you how to discover more about crystal structures using the More Info feature in CCDC's Mercury. This tool allows you to retrieve all text-numeric information about selected CSD structures (including many optional information fields), together with detailed descriptions of contacts and crystallographic symmetry along with summaries of user-defined objects and measurements, such as centroids, planes, distances and more. [Watch now at the CCDC website.](#)



If you would like to suggest topics for our workshops, webinars and CSDU online training modules in 2025, please email us at hello@ccdc.cam.ac.uk.

Ana Machado,
CCDC

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Focus on STOE

BEFORE the seminal discoveries of Röntgen, von Laue and the Braggs, crystals were primarily described and categorized by their external habit. To accurately measure the facets, optical goniometers were used (see Fig.1). Peter Stoë, a precision mechanic at the University of Heidelberg developed and produced these goniometers in collaboration with Prof. Goldschmidt, leading to the founding of STOE in 1887. Shortly after its founding, STOE instruments gained recognition within the crystallographic community and were exported worldwide [1]. Stoë and Goldschmidt also began incorporating X-ray sources into their machines. In fact, Prof. Goldschmidt corresponded with Lawrence Bragg, inviting him to visit the University of Heidelberg in the 1930s.



Fig. 1. An early STOE two-circle reflecting optical goniometer (c.1920). This photograph by Mark McElyea was reproduced from the mineralogy.eu website with permission.

In the 1960s, following the rise of X-ray diffraction techniques, Prof. Wölfel of the Technical University of Darmstadt acquired the company and relocated it to its current site. Here STOE began manufacturing computer-controlled X-ray diffractometers like the 4-circle diffractometer system "STADI4". In the late 1970s STOE developed its own powder diffraction geometry – a combination of the Guinier and the Debye-Scherrer cameras. This innovation allowed for the use of a truly monochromatic beam and facilitated sample preparation. Since then, STOE has introduced numerous innovations, including the first image plate diffractometer, accessories like the STOE HEATSTREAM or the coin cell battery holder and most recently the fully automatic alignment of the STOE STADI P powder diffractometers.

Today, we continue focusing exclusively on high precision X-ray diffraction instruments, all of which are manufactured at our site in Darmstadt, Germany. Each component of our goniometers is crafted from blocks of metal, carefully cut, turned, or milled, and further processed to achieve their

final form. These components, whether large or small, are assembled by our precision mechanics and brought to life by our electronics team. Our instruments are completed when they undergo thorough testing in our laboratory by application scientists before being shipped to customers worldwide. Additionally, our software is developed in-house, enabling seamless communication between programmers and scientists for quick testing and implementation of new features. This close collaboration between our scientists, programmers, and manufacturing teams fosters efficient problem-solving and innovation, especially when colleagues suggest improvements or customers request customized solutions.

Recently we had the privilege to work with two outstanding projects. At the Karlsruhe Institute of Technology (KIT) we had already connected not one, but two diffractometers – one single crystal, one powder – to a MetalJet source, resulting in two independently operating, extraordinarily fast and brilliant diffractometers. To increase the measurement capabilities even further, we recently set up an additional MetalJet at KIT now resulting in two single crystal diffractometers connected to one source and two powder diffractometers to another!

In another project, we recently customized a STOE STADIVARI instrument to fit a large and heavy sample environment chamber [2], which allows studying the impact of an applied electric current on a flat sample under variable temperature with X-ray diffraction in a reflection type geometry. This request required rethinking the goniometer to carry the heavy chamber while maintaining extreme precision. We also had to ensure ample space for peripheral connections and access to all necessary goniometer positions to produce meaningful data. Overcoming challenges, such as supporting heavy loads while ensuring precise movements, is one of STOE's key strengths. With this instrument, our customers can test their samples in the chamber and thus arrive at the synchrotron with optimized, well-planned measurements.

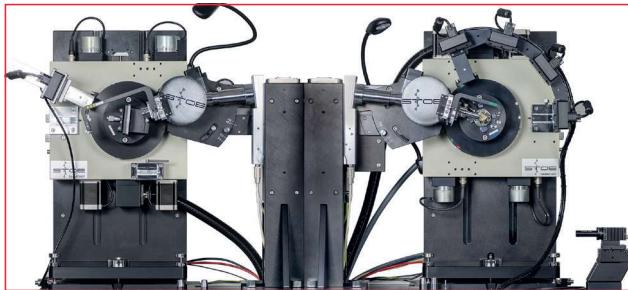
Beyond our day-to-day operations, the inventive spirit never sleeps at STOE! This inventiveness recently led to the development of the "Beam Optimization 2.0", a hard- and software upgrade for the STOE STADI P machines allowing for fully automatic alignment with a precision equivalent to the precision of our application scientists.

John Kollath, STOE sales scientist, says about working at STOE: "Since its founding, STOE has been dedicated to producing extremely accurate crystallographic instruments, fostering generations of precision mechanics and scientists who develop, upgrade and manufacture diffractometers. This dedication to utmost precision continues to drive us today as we create diffraction instruments for leading researchers in the UK and worldwide. We are proud that we can support you with equipment featured in numerous high-ranking publications. However, amidst all this, we never forget to create a fun working environment that allows creativity to thrive."



If this piques your curiosity, please explore our instruments and opportunities at www.stoe.com or contact us directly at info@stoe.com. We are always looking forward to engaging scientific discussions and tackling new challenges.

Laura C. Folkers,
STOE Customer Relations – Science and Technology



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Meeting Reports

34th European Crystallographic Meeting (ECM34), Padova

ARRIVING in towards Padova bus station from Venice airport on Sunday August 25th a group of crystallographers including myself disembarked at our respective bus stops. It was early afternoon, very sunny and hot. Day zero, on the Monday, was for the workshops leading up to the opening ceremony, including the ECA Perutz Prize lecture by **Mariusz Jaskólski** (Poznań) spanning chemical and protein crystallography, then the first of two plenary lectures, this one by **Kristina Djinović-Carugo** (EMBL Grenoble) on muscle proteins using the integrative structural biology approach. I attended the first half of the Neutron Protein Crystallography at ESS workshop in the morning, not least having chaired the ESS advisory committee for neutron macromolecular crystallography for the past ten years. For the afternoon I was an organiser of the Crystallography in Schools Workshop splendidly overviewed by **Erhard Irmer** (Göttingen) who had obtained his PhD with George Sheldrick and then entered school teaching. This opening day concluded with the welcome reception, as usual meeting many colleagues within the frame of the extensive exhibition. There were 850 participants and we mingled happily. We were yet to learn how to best navigate the building, to be described at the closing ceremony by the ECA President **Marijana Đaković** (Zagreb) as an “Escher like experience.”

I was involved in two poster judging panels. The first one was as Chairman of the SIG6 (Instrumentation and Experimental Techniques) Jacek Grochowski Memorial Poster Prize. Jacek was my co-chairman of the SIG6 in its first period and who had died tragically from a heart attack en route from the synchrotron in Hamburg back to Krakow. I had secured funds to have a memorial prize these past ten ECMs but now the funding was newly from the Cinelli instruments company from Italy. The other poster prize judging I did was for the IUCr biology category. With a mobile phone app but no printed booklet or pdf I resorted to my usual method of browsing all of them. The breadth and depth were of a very high quality. Over breakfast in my hotel with Bernard Spingler I recalled that in my opinion his was the best ever method at ECM Basle of colour labels on posters according to which prize they wished to be considered for.

Through the combined efforts at the programme planning meetings of the three SIGs (early career, retired/senior and education respectively) there were several really useful microsymposia describing good practice as well as some regular pitfalls that can occur in the life of a crystallographer of all types. I spoke in one of these on the Cruickshank diffraction precision index methodology for atom coordinate position error estimation, which with colleagues in Bangalore, we had extended to include an online webserver. By harnessing multiple processing softwares from a single set of diffraction images error estimates on B factors were obtainable, as well as a cross check on Cruickshank coordinate error estimates. In one of these sessions a

speaker had a joke halfway through to “reinvigorate their audience.” The next day I could initially only recall their joke. So, handle that speaking approach with care e.g. maybe don’t tell too good a joke.

The other sessions I selected to attend involved some usual tough choices. But a very useful feature of the conference app was its organisation so that each microsymposium’s speakers, as well as the associated posters in the same theme, were neatly grouped together including all their abstracts. This helped me not only pick the one to attend but also for the parallel one I had missed, I could readily catch up later.

Of the Keynotes that especially caught my attention I would mention the survey by **Tony Linden** (Zürich) of crystallographic computing over the decades, and before computers, who coupled that history with a survey of crystallography schools including of course the long running annual Zürich School. Equally gripping was the Keynote by **Giovanna Scapin** (Nanolmaging Services) whose lifelong experience again shone through her description of structural biology in drug design punctuated by the Erice Schools every six years on that topic, of which she had attended every one. **Carol Brock** (Kentucky) was a gem sparkling speaker within a microsymposium describing her excursions into viewing a vast number of small molecular crystal packings across a variety of themes. The first Ludovico di Sanseverino Outreach Prize was awarded to **Claire Murray** (DLS) who described in her marvellous lecture her work at Diamond with schools on a calcium carbonate powder diffraction round robin study, then her science careers board game and finally her work to redress the poor gender balance of scientists portrayed in science textbooks in Ireland. Authors were telling her that their new books now had a better balance as they strived to meet her very reasonable complaints.

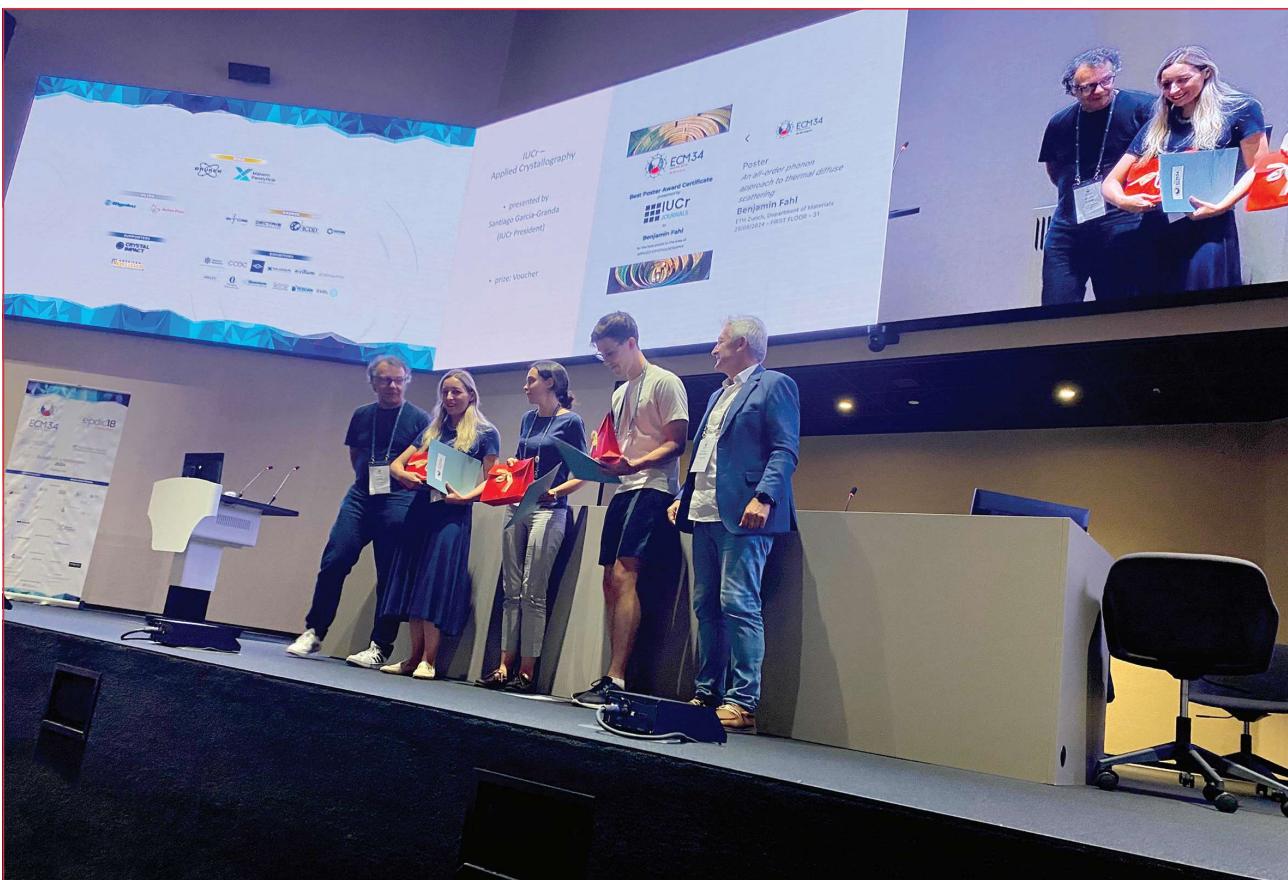
The closing plenary was a clever selection by the organisers of **Jon Wright** (ESRF), the ID11 principal beamline scientist, who combined single crystal and powder diffraction, as well as imaging. This then contented the ECM34 crystallographers and the just arriving EPDIC attendees. There were about 80 people who were attending both. ECM34 had about 850 participants and EPDIC about 250 participants. **Gilberto Artioli** (Padova) and **Giuseppe Zanotti** (Padova) the lead organisers of ECM34 were both on stage presenting these attendance statistics also documenting the approximately 2/3 to 1/3 gender split and the around 50 countries of origin. Top attendance naturally was Italy, the UK was second. Unexpectedly Gilberto Artioli called to the stage **Bill Clegg** (Newcastle) to do a repeat performance of his winning Science Slam Crystallographer’s story to Mozart’s music with interludes between verses for audience clapping. Rapturous applause concluded this fine performance, truly worthy of Flanders and Swan.

The big memory of Padova itself for me was the Palazzo Bo, the University of Padova’s museum which I was able to

visit on the afternoon of my arrival day. Their tour had a very good number of stopping points with QR codes to load an audio explanation of each room and display onto my phone. The anatomy dissection lecture theatre comprising a near vertical arrangement of student benches looking down on a professor's dissections was an architectural marvel.

The next ECM is a joint effort of Poland and Ukraine with both their delegates on stage to take the baton on from Padova to Poznań.

John R Helliwell,
Manchester.



On the stage of the main auditorium at the Closing Ceremony are the IUCr poster prizewinners, the Poster Prizes Coordinator **Michele Cianci** (Ancona), far left, and the IUCr President **Santiago García Granda** (Oviedo), far right. Next to Prof Cianci is **Lucrezia Catapano** (MRC LMB, Cambridge) whose poster reported on the expansion of the protein crystal structure refinement program REFMAC to include neutron studies (photo by John Helliwell).

The SIG6 Instruments and Experimental Techniques Poster Prize was awarded to Eleanor Keil (Southampton) for her work on understanding CO₂ uptake in ZIFs using an X-ray and electron diffraction combined study. Full details will appear in due course along with all the official photos. The winner is accompanied on the left and right by **Michele Cianci** (Ancona) and **John Helliwell** (Manchester), respectively.



Arnold Beevers bursary awardee reports

I arrived in the beautiful Italian city of Padova, a short bus ride west of Venice, for the 34th European Crystallographic Meeting (26th – 31st Aug 2024). I was very excited for this conference and knew it was going to be one to remember, not only for the incredible weather and delicious cuisine, but the programme and list of speakers looked fantastic.

The conference commenced with a very nice plenary given by **Kristina Djinović Carugo** (EMBL, Grenoble) who presented their recent findings using an integrative structural biology strategy to investigate the structural architecture of the muscle Z-disk. This talk was followed by the Perutz Prize, this year awarded to the very deserving **Mariusz Jaskólski** (Poznan). The evening came to a close with welcome cocktails and catching up with good friends before heading into the city centre for delicious Italian cuisine.

The next three days covered a vast range of topics from electron diffraction, crystal engineering and the use of extreme conditions X-ray diffraction. Highlights for me included the session discussing approaches and tools for learning crystallography efficiently and avoiding misconceptions, particularly the talk by **Juan Manuel García-Ruiz** (Granada) on using a group of chimpanzees to help understand the origin of the crystals' allure, including the properties of crystals that fascinate hominids. Another talk I really enjoyed was given by **Helena Shepherd** (Kent) presenting her PhD student Lee Birchall's work on the use of co-crystals as a modular approach to smart material discovery. On the third day I got to present my PhD work in the session Nucleation and Crystal Growth. This was a fantastic opportunity that presented lots of possibilities for discussion and collaboration.

During the lunch breaks I enjoyed visiting the vendor exhibition, as this was a great way to talk to companies about their emerging technologies, as well as to pick up a few of the freebies on offer!

There were also plenty of social events planned including a string quartet concert, student mixer and science slam, won by **Bill Clegg** (Newcastle) for his incredible crystallography composition in the style of Mozart. The conference dinner was held at the stunning Piazza della Frutta which was the perfect evening before the last day of the ECM34.

The conference came to a close with the poster prizes, followed by Bill Clegg's wonderful composition yet again, due to popular demand. Overall, the breadth of topics covered meant it was a very stimulating conference and a great event to attend in the final year of my PhD.

Jessica Metherall, Newcastle

Denver X-ray Conference

The Denver X-ray Conference returned to Colorado in 2024 (5th – 9th August, Westminster, Colorado), kicking off with two days of workshops focussing on essential skills for the use of X-rays in diffraction, fluorescence and tomography, engaging seasoned academics and early career researchers

alike. The Machine Learning for X-ray Analysis sessions presented new ways to approach analysing large datasets, including writing scripts in Python and the Quantitative XRF session introduced the fundamentals of XRF data analysis for newcomers to the field, both providing me with essential skills to take forward in my research.

The International Centre for Diffraction Data (ICDD) Early Career Network (which is open to all ECRs working in crystallography) held a workshop led by **Charlene Greenwood** (Keele), exploring routes through academia and challenges along the way. This session featured talks from **Emily Arnold** (DLS) on moving countries, **Jessica Lyza** (Alfred) on moving from industry to full time academia and myself on applying for grants as an ECR. The session was well attended and facilitated networking opportunities between ECRs working across a range of disciplines.

The workshop sessions were followed by lively poster sessions on XRD and XRF, where poster prizes were awarded to myself, **Hibiki Shirata** (Meiji, Japan), **Niklas Pyrlik** (DESY, Hamburg) and **Adarsh Kabekkodu** (Downington, PA) in the XRD session and **Anik Chowdhury** (DuPont), **Benard Patawah** (Illinois), **Sebastian Hauser** (Ulm, Germany) and **Andrew M. Crawford** (Northwestern) with **Michael Wojcik** (Argonne National Laboratory) as runner up in the XRF session.

The plenary session on Biomedical Imaging featured fascinating talks from: **Olga Antipova** (Argonne National Laboratory) on the use of synchrotron X-ray fluorescence in biological and medical applications, including cancer, neurodegenerative disease and biomaterialization; **Stuart Stock** (Northwestern) on X-ray diffraction applications in understanding shark vertebrae structure and function; and **Andrew Nelson** (Western Ontario) on the use of X-ray and



Presenters in the Early Career Network session at the Denver X-ray Conference (DXC): Sarah Gosling (Keele), Emily Arnold (DLS), Jessica Lyza (Alfred), Charlene Greenwood (Keele, session chair and ECR network coordinator)

computed tomography to study Egyptian and Peruvian mummies, revealing cultural and biological insights into their deaths and burials.

Oral sessions ranged from Mining, Recycling and Sustainable Materials and Energy Materials Characterisation to Cultural Heritage and Trace Analysis. The Micro XRF and Synchrotron Applications session featured talks on ancient gold, plutonium emission lines and daguerreotypes (an early photographic process), while the Biomedical session featured talks on the development of new technologies for analysing biological tissue, the analysis of soft tissue and calcifications for discovering cancer biomarkers and detailed analysis of hydroxyapatite using pairwise distribution functions, or PDFs.

The focus of this conference on biomedical applications of X-ray analysis methods was of particular interest for me as this is a cross-disciplinary field that is not always featured in the crystallography or biological spaces, therefore having a platform to present and discuss this work was a highlight for me. High attendance by ECRs was also fantastic and presented multiple opportunities for networking and discussing ways to improve and expand my work.

Sarah Gosling, Keele



Plenary speakers at the DXC: Scott Misture (Alfred, session chair), Andrew Nelson (Western Ontario), Olga Antipova (Argonne National Laboratory) and Stuart Stock (Northwestern).



XRF Poster Session Award Winners: Michael Wojcik (Argonne National Laboratory), Sebastian Hauser (Ulm, Germany), Dan Paas (MOXTEK, poster judge), Helen Muccitelli (MOXTEK, poster judge), Mark Samways (AMETEK, poster judge), Benard Patawah (Illinois), Andrew Crawford (Michigan), Diane Eichert (ELETTRA, poster judge), Martina Schmeling (Loyola, Chicago, poster judge) and Anik Chowdhury (DuPont).



XRD Poster Session Award Winners: Tom Watkins (ORNL, poster judge), Niklas Pyrlik (DESY, Hamburg), Hibiki Shirata (Meiji, Japan), Sarah Gosling (Keele) and Adarsh Kabekkodu (Downington, PA).

Diffraction Methods in Structural Biology, Berlin 22nd-27th July 2024

Due to the generosity of the BCA's Arnold Beevers Bursary Fund and also the meeting organisers, as a retiree I was able to accept an invitation to speak at the Diffraction Methods Conference held at the Max Plank's wonderful meeting venue in Harnack House, Berlin, Germany in late July 2024. The location, accommodation and catering were all superb! The history of this meeting is that the biennial Gordon Research Conference on Diffraction Methods in Structural Biology was not approved for 2024. It had been held in alternate years in New England since 1976 apart from 2020 when it was postponed due to the pandemic. The 2024 meeting broadly followed the tried and tested GRC day plan and included a 15 minute introductory slot for each broad topic by the session chair. The scientific program was organised by **Graeme Winter** (DLS) and **Kunio Hirata** (RIKEN), who had been elected as Chair and Co-chair by the attendees at the 2022 GRC meeting. Local organisation was amazingly efficient and professional due to the sterling efforts of **Ashwin Chari** (MPI-Göttingen) and **Arwen Pearson** (Hamburg). The meeting was preceded by a replacement for the Gordon Research Seminar (GRS) for early career researchers, organised along similar lines by **Helena Taberman** (DESY) and **Ali Ebrahim** (CUNY), who again had been elected to this task in 2022. As a superannuated researcher, I did not qualify as 'early career' and thus arrived in Berlin (by train) for the opening of the meeting on the evening of Monday 22nd July. The first session was entitled "The measurement strikes back or the return of the experiment" with an introduction by **Graeme Winter** (DLS) and talks from **Nick Pearce** (Finland) on "Drowning in data: Multidataset-driven computational approaches to macromolecular structure determination" and an impromptu talk (due to the scheduled speaker's arrival being delayed) by **Ashwin Chari** (MPI-Göttingen) on factors to consider when collecting very high-resolution X-ray data (as good as 0.59 Å in some cases) to obtain exquisite biological detail on ligand binding modes. This talk was after my own heart as

Ashwin emphasised the importance of considering the dose absorbed by the sample and optimising the X-ray beam conditions, such as using a top-hat beam profile (e.g. as now routinely available at P14, EMBL, PETRA-III) to achieve homogeneous irradiation of the crystal.

On Tuesday morning we had sessions on the ‘Development of radiation sources over the last two decades’ introduced by **Janet Smith** (Michigan) with talks by **Katherine McAuley** (PSI, Switzerland) and Clemens Schulze-Briese (Dectris) who both provided interesting historical context to recent X-ray source and detector developments. This was followed by a session on ‘Making great use of the sources we have today – in many respects we are in a golden age’ which was introduced by **Manfred Weiss** (HZB, Berlin) who notably put a price tag of €100,000/publication. In this session **Adrian Mancuso** (DLS) covered XFELs, **Dean Myles** (Oak Ridge) neutron sources and **Robert Bucker** (Rigaku) electron diffraction. In the afternoon there was the first of two very well attended and lively Community Challenge discussions on ‘Handling the data deluge’ and then a poster session before dinner.

The posters were all on electronic boards from which all the posters could be accessed. These were nobly driven to Berlin from Hamburg and back by **Bodo Krause-Kyora** (PHYSnet Director, Hamburg) for the occasion. I have to admit that I struggled with the poster boards a bit (old dogs, new tricks, etc) but I felt they represented the technology to come! The evening session addressed ‘Possibilities and challenges afforded by new sources’ and was introduced by **Thomas Schneider** (EMBL, Hamburg) with talks from **Daniele de Sanctis** (ESRF) on a ‘Serial microsecond crystallography at ESRF-EBS’ (EBS stands for Extremely Brilliant Source, and it certainly is, allowing microsecond exposure times for MX images!) and **Yelyzaveta Pulnova** (ELI ERIC, Czechia) on ‘Compact sub-picosecond X-ray plasma source for ultrafast time-resolved diffraction and spectroscopy at ELI Beamlines’ who reported that 300 fs pulses were now available from their laser driven plasma X-ray source.

The next day (Wednesday) we started thinking about data processing with a session on ‘Data processing: how did we get to here?’ introduced by an expert synchrotron practitioner: **James Holton** (UCSF, LBNL and SLAC, Berkeley, USA) and expounded by **Ana Gonzalez** (MAX-IV, Lund); ‘Look ma, no hands!!! Autoprocessing at MX synchrotron beamlines, a brief history and current trends’ and the world XDS expert, **Kay Diederichs** (Konstanz) on ‘Data processing: how did we get to here, and where do we go?’ Among other interesting observations, he advocated revision of the contents of the traditional ‘Table 1’ in MX papers, with the statistics of unmerged rather than merged data being quoted. We moved on to hear about ‘Current interesting topics in data processing’ introduced by **Jeney Wierman** (Cornell) and with three talks from **Kevin Dalton** (SLAC) on ‘Scaling or stochastic variational inference for X-ray diffraction data’, **Clemens Vonrhein** (Global Phasing) on ‘Optimising experimental outcomes: improving model construction, refinement, analysis and deposition via better (meta)data handling’ and **Kunio Hirata** (RIKEN) on a ‘Case study of small wedge synchrotron crystallography: Enhancing structural information in micro- and nano-crystals through extensive data collection’ which engendered lively discussion.

The second Community Challenge discussion was on ‘Training the next generation’ – a very important topic with many ideas aired and chewed over. More poster discussion followed and the evening session was on ‘Future trends and opportunities in the analysis of scattered radiation’ introduced by CrystFEL software guru **Thomas White** (DESY) with a talk from **Iris Young** (LBL) on ‘Experimenting with new technologies in serial femtosecond crystallography’ who pointed out that if all the XFEL pulses produced a diffraction image for analysis, 1.6 PB of data would result from one shift i.e. far too much data which would necessitate triage, speed and focus being implemented in the downstream software. A second talk by **Gerhard Hofer** (Stockholm) on ‘Serial electron diffraction for fast high resolution structure determination’ described a radiation damage free structure of HEWL at 0.85 Å resolution. This talk was very relevant to me as we are looking for applications of our recently released RADDSE-ED software.

On Thursday morning **Gérard Bricogne** (Global Phasing) introduced and talked about the ‘Interpretation and use of intensities: a potted history’ after which I spoke on ‘Diffraction intensity as a radiation damage progression metric and intensity decay models’ covering some of the new work in our new *Protein Science* paper (Dickerson et al (2024) **33**: e5005).

Arnaud Basle (Newcastle) then led a session on ‘Current methods 1: recovering phases and proposing a model’ with talks from **Saori Maki-Yonkura** (RIKEN) on ‘Measurement of charges and chemical bonding in Cryo-EM SPA’, **Lucrezia Catapano** (MRC-LMB) on ‘Enhancing structural refinement of macromolecules obtained from neutron crystallography’ and **Andrea Thorn** (Hamburg) on ‘What could be seen in a map without model bias?’

In the afternoon there was an excursion to BESSY, but I opted for a wonderful walking tour led by Ashwin Chari of the buildings and gardens surrounding Harnack House. He explained some of the fascinating history of the scientists who had worked at the Kaiser Wilhelm Institut fuer Physik and how the Max Planck Society had come into existence. After dinner we continued hearing about ‘Current methods 2: optimising agreement between model and measurements’ with an introduction by **Dorothee Liebschner** (LBL) and talks from **Alisia Fadini** (Cambridge) on ‘Modern hardware boosts the throughput of raw macromolecular X-ray crystallography data’ and **Florence Tama** (Nagoya) on ‘Phase retrieval software for reconstructing high-resolution, large-volume 3D density maps of biological assemblies.’

On the penultimate day, Friday, **Ilme Schlichting** (MPI, Heidelberg) introduced ‘Hypothesis testing as the essence of experiment’ and **Thomas Barends** (MPI, Heidelberg) told us about ‘Fantastic hypotheses and how to test them’ taking us on a nail biting detective story of tracking down the mechanism of action of myoglobin, followed by **Allen Orville** (DLS) on his time resolved MX XFEL measurements and how to lower the significant barriers that exist for researchers to undertake such experiments. We then genuinely went ‘Into the fourth (and higher) dimension’ led expertly by **Briony Yorke** (Leeds) before hearing from **Paulina Dominiak** (Warsaw) on ‘Your data are already four-dimensional! Enhancing three-dimensional spatial representations through the inclusion of electron density and its associated

properties', **Martin Fuchs** (NSLS-II) on 'Multiple temperature and time-resolved serial crystallography at NSLS-II' and **Elke De Zitter** (IBS) on 'Identifying and modelling low-occupancy states in macromolecular crystallography' whom I had heard in Brno at an iNext Discovery meeting in June and I enjoyed the repeat to understand more of her work.

The mandatory Business meeting and electronic survey (thanks Arwen!) was followed for me by very interesting and useful discussions over a delicious dinner outside and accompanying drinks. On the last day, Saturday, we started a bit later for a wrap-up session entitled 'Where are we going?' i.e. what are we as a community looking at over the coming couple of years? This session also involved the handover by **Graeme Winter** (DLS) to the next Chair, **Kunio Hirata** (RIKEN) and Co-Chair, **Ashwin Chari**

(MPI-Göttingen). Kunio led, urging us 'to make diffraction great again' before a fascinating talk from **Takahiro Kosugi** (Tohoku) on 'Diffraction Methods for current and future protein design' – highly relevant right now with the award of the 2024 Nobel Prize for Chemistry to **David Baker** (Washington). The final talk of the meeting was given by **Arwen Pearson** (Hamburg) and was entitled 'Quo vadis Diffraction', a thought-provoking end to the meeting and about which I could write an entire article. After helping to dismantle the electronic poster boards, I took a train to Hamburg. Altogether I thoroughly enjoyed the meeting and am very grateful that support from the BCA enabled me to attend.

Elsbeth Garman,
Oxford.



Attendees of the Diffraction Methods in Structural Biology conference, Berlin, July 2024.



PPXRD-18

Pharmaceutical Powder
X-ray Diffraction Symposium

6 - 9 May 2025

The Cambridge Crystallography Data Centre (CCDC)
Cambridge, United Kingdom

PPXRD-18, XRD Training for the Pharmaceutical Scientist, CCDC, Cambridge, 6th-9th May 2025

The Pharmaceutical Powder X-ray Diffraction Symposium is designed to create a forum for the exchange of knowledge and cutting-edge ideas among those interested in the combined fields of XRD and pharmaceutical sciences. It typically includes a full-day workshop, followed by several important sessions focussed on practical applications of X-ray analysis in the study of pharmaceutical materials. Topics include patent and regulatory issues, formulation, product development, drug delivery, polymorphs, amorphous and nanomaterials, complimentary techniques and much more.

Since 1999, ICDD has hosted 17 PPXRDs in various parts of the world. The host locations typically rotate and symposiums have been held in USA, Europe, and Asia.

Please visit our website - <https://www.icdd.com/ppxrd/> – for more information on travel, registration, abstract submission, exhibits and more.

If you have any questions, please email – ppxrd@icdd.com.

South West Structural Biology Consortium 2024

THE South West Structural Biology Consortium (SWSBC) meeting was held this year in Bath on the 1st-2nd July 2024, being organised by **Susan Crennell** (Bath) and sponsored by CCP4, Abcam, Applied Photophysics, Bio-Rad, Brand, CliniSciences, Constant Systems, Douglas Instruments, iLab Solutions, Merck, New England Biolabs, Molecular Dimensions, PCR Biosystems, SLS, SWISSCI and ThermoFisher. The meeting was opened by **Philip Ingham** (Bath), Head of Life Sciences, who gave us some background information on the Department and its work in the biochemical, pharmacological and biodiversity spheres, covering the full spectrum of biological processes “from conception to decomposition.”

The first talk was given by **Kyle Gregory** (Bath) entitled “Structural insights into domain selective inhibition of angiotensin-1 converting enzyme (ACE) by a series of dipropyl compounds.” ACE is found throughout the body and is a type I transmembrane glycoprotein. It contains two catalytic domains, both having Zn-dependent carboxypeptidase activity, but with different selectivities. ACE converts angiotensin I to angiotensin II by cutting two amino acids from C-terminal end which has an effect on blood pressure. Current inhibitors hit both domains, but a domain selective inhibitor may be better. The S2 site shows some differences and modelling was used to predict whether designed compounds that were the same in S1, S1' and S2' subsites were N- or C-domain binders. These were checked with inhibition assays on individual domains and followed up with crystallography, demonstrating that one compound was very selective for the N-terminal domain, apparently due to a hydrogen bond with Arg 381 in the S2 pocket. No apparent consistency with modelling was seen though, showing that exploiting S2 site may not be the best approach – it appears that distal residues influence the inhibition, mainly due to driving closure of the enzyme. Future work will involve exploring these distal effects and also the interdomain cooperativity.

The next talk was from **Liliana Oliveira** (Portsmouth) on “Substrate morphology preference and synergy in PET hydrolases can be controlled by extensive surface charge engineering.” Current plastic production has a heavy fossil-fuel footprint, requiring large amounts of oil and gas to be utilised. Most of this new plastic eventually goes to landfill or is down cycled leading to environmental pollution. The group are investigating the use of cutinase enzymes to break the plastics back down to the monomers of the same quality as the virgin monomers, thus breaking the need for continual oil/gas consumption. This requires enzymes that promote >90% depolymerisation. Most work up to this point has been to improve the enzymes, i.e. heat tolerance. The enzyme of interest, SfCut, has very different reaction rates with amorphous powder to amorphous film. It also has a large pH dependence, so they tested to see if the high negative surface charge affected the substrate specificity. The charge mutant (Sflnv) now degrades amorphous film and amorphous powder in a similar manner and the rate is not pH

dependent. Liliana also found that by mixing both enzymes (wild type and mutant) a synergistic effect is seen. This is thought to be due to the charge on the Sflnv is masking the charge on the SfCut, thus allowing more total enzyme to get to the negatively charged PET surface. This should reduce processing costs as less pre-processing of the plastic needs to take place.

The third talk was from **Elodie Wells** (Southampton) on “Navigating the first year of my PhD: Investigating structure function relationships of LILRB3 and its immunomodulating antibodies.” LILRB3 is a leukocyte immunoglobulin fold like receptor. It is a type-1 transmembrane glycoprotein with 4 C2-type Ig-like domains. Ligand binding initiates ITIM signalling, recruiting phosphatases which result in repressing the immune response. The project involved studying the structure function relationships of LILRB3 with 4 different immunomodulatory antibodies. The structures were investigated with crystallography and SAXS. High purity protein was easy to get, but crystals were initially hard to produce, with only native protein crystals as yet, i.e. no crystals of a complex were obtained so far. SAXS shows that the antibodies bind at different points on the LILRB3, but this work is only at low resolution and so it does not show the interface in any detail. It was important to get the best models to use in analysis, thus they used model recycling in CoLabFold to get best LILRB3 model, ABodyBuilder to get antibody fragment models and HADDOCK2.4 to dock the two structures together. They then used the SAXS data, alanine scanning mutagenesis and SPR to epitope map the binding sites for validation of the models.

Nicholas Harmer (Exeter) then delivered a “Murder mystery gamification session to consolidate analytical biochemical techniques learning.” He introduced the concept of using games to aid knowledge acquisition. He defined a serious game as a discrete, stand alone game that has an educative purpose and gamification as that which adds value to the education rather than providing the education. Thus the game helps consolidate learning and team work and is generally fun. He introduced a murder mystery based on “Among Us” that covers four techniques (HPLC, SDS-PAGE, MS, Western Blot). It has a modular design, so other techniques can be incorporated and the results are anonymised, so no-one else knew whether they got the correct result or not. New data sets are created every time the game is played, so can it be re-run many times. Some data are deliberately wrong (students know this) and so they cannot trust everything and this has to be accounted for (unlike normal undergraduate laboratory sessions which almost always work). He finished by running a fun demonstration of the game for everyone in the room.

The last talk of the day was from **Éilís Braggington** (Diamond) on “Structural biology at the electron Biologimaging Centre (eBIC).” eBIC is now 10 years old. It offers peer reviewed free access for cryo-EM, tomography and micro-ED. EM data collection delivers 1000 movies/hr, with aberration free images and fringe free imaging whereas tomography, specifically off axis tomography, delivers in excess of 10

tomograms/hr. Access is through BAG access or rapid access with a standard allocation consisting of 2 days. The speaker showed how the cryo-EM data processing pipeline is mostly automated, up to getting initial 3D views and feeding back on how many images are required for specific resolutions. Tomography has a cryo-FIB milling process with fluorescence targeting of points of interest. Normally grids are prepared in advance of user time, but in difficult cases one can get on-site help from cloning through to structure solution through the Membrane Protein Laboratory (MPL). The facility also has a Chameleon protein dispenser to put protein on self-wicking grids for cases exhibiting aggregation or dissociation. Micro-ED can be performed on <500 nm crystals with a Dectris Singla detector (radiation hard, 4K) on a Glacios. This allows for serial data collection on 100+ positions from a single script.

The second day started with **Otsile Mojanaga** (Bath) on "Structural analysis of the *Mycobacterium tuberculosis* α -Methylacyl-CoA racemase (MCR) active site activity and selectivity." MCRs are involved in the metabolism of branched chain lipids and they are known to racemise either the R- or S-2-methyl CoA epimer to a near 1:1 mixture of epimers. *M. tuberculosis* MCR has 43 % sequence identity to the human enzyme and is a potential drug target against TB. The structure of this dimeric protein has been solved showing that it belongs to the family III CoA transferases. The 39 kDa protein is easily produced in *E. coli* in high yield. Mutants of the active site bases (H126, D156 and E241) have been made to study the hydrogen bonding network in the active site which is formed at the subunit interface and these were also assessed kinetically by a colorimetric assay. All three active site mutants exhibited reduced activity, with H126 being the slowest. Further MCR ligand structures such as ibuprofen were studied by X-ray crystallography and ligands such as this one are coupled to CoA by the enzyme. All of the CoA moieties bound in a very similar manner, the only differences being due to the variation in ligands themselves. The density shows that the structure can accommodate both R and S isomers easily.

Martin Malý (Southampton, CCP4) then introduced "New tools (not only) for serial crystallography in CCP4 9.0." CCP4 v.9.0.000 was released in June 2024 with the first 9.0.001 update coming soon after. It has many updates for processing serial crystallography data where there are 1000's of crystals with 1 image each, which is becoming increasingly common on XFELs and 4th generation synchrotrons. There are also new updates for emerging techniques (time-resolved studies, zero dose and pump-probe experiments). The new DIALS3.19 has tools for SSX data processing and has an added wrapper to import CrystFEL data. MrPARSE (the new generation of MrBUMP with templates created from AlphaFold and the PDB) only requires the input of the data and sequence. COOT1.1 has been released but is hidden at the moment as it is still being improved. The data stored has moved to PDBx/mmCIF format for files since PDB will only accept mmCIF files. Coming soon: the Iris structure validation tool and Servalcat refinement (REFMAC update), which refines against intensities, not structure factors. The latter is beneficial as data are not processed through the French-Wilson procedure which can introduce errors. The main advantage of Servalcat is likely to be for refining structures with anisotropic diffraction data.

Next **Megan Lambert** (Diamond) spoke on "Routine room temperature protein structure determination in situ

at Diamond beamline VMXi: Current status and recent developments." Technical improvements have led from 3 datasets/day at Daresbury in 1999 to 6000 datasets/day at Diamond in 2024. There are now many automated beamlines at synchrotrons around the world, e.g. MASSIF-1 at the ESRF and VMXi at DLS, where Formulatrix imagers are connected directly to the beamline. It has a 10x10um beamsize, 16keV tuneable, pink beam at 5×10^{13} photons/sec and can collect wedges up to 60 degrees. In multi-crystal data collection mode, 200 datasets/hr at resolutions up to 1.6 Å are achievable. Your protein can be sent to the Research Complex at Harwell for setting up (or one can set up plates oneself), the plates are transferred to beamline imagers and when crystals appear data can be collected semi-automatically. Why collect at VMXi? Rapid structure determination, no fishing, no cryocooling, no dehydration, good for crystals that are difficult to cryo-protect or harvest, i.e. complexes, membrane crystals, large crystals. All the user has to do is login to ISPyB, set the imaging schedule and, when crystals are seen, mark the crystals to be shot and select the type of data collection. The beamline has a CHIMP algorithm to automatically mark up to 100 objects per drop – also useful to skip drops that have no crystals in them. One can also do a grid scan on drops of very small crystals and use serial data processing to get a full dataset. Coming soon is RT XChem – no need to mount individual crystals, just shoot in plate – this will often get different hits at RT, possibly due to protein being more flexible at RT. There are still some software issues to sort out for data tracking. Finally they are looking at clustering data sets to determine differences in crystals – i.e. to get more than one structure from a multiplex dataset – thus showing structural dynamics.

The next talk was from **Patrick Shaw Stewart** (Douglas Instruments) on "Sample preparation for routine and advanced structural biology, including serial data collection and microED." Patrick first introduced random microseed matrix screening (rMMS) and stated that it should be part of your normal workflow. It should be used early on in crystallisation process, i.e. screen, get crystals, make seeds, re-screen. This will often give many more hits than in the original screens. Then one can use normal seeding at a lower dilution to improve crystals and control the crystallisation process. On the Douglas robot, the use of the 3-bore tip allows addition of all components at once (0.3 µl protein, 0.2 µl reservoir, 0.1 µl seed). He explained phase diagrams in relation to seeding experiments, showing why you get more hits (hitting both nucleation and metastable zones) and why it was better to use crystals that only appear when seeds are used because the process is controllable rather than down to random nucleation. Often one needs to fit crystal size to the method of diffraction being attempted – neutron diffraction needs big crystals and thus 1 seed per drop would be suitable but for microED one needs lots of seeds to get many small crystals. He suggested to use the microbatch under oil method as this gives the most control with seeds as there is no evaporation. It helps if you find the phase diagram for your target protein because this allows one to optimise size, morphology, resolution and the space group of crystals. It is much easier to do this with microbatch under oil than vapour diffusion as there are fewer variables. A new script for the Douglas robot can give the phase diagram quite easily – one just needs the protein stock, crystallisation cocktail, water and seed stock. The speaker mentioned the development of dynamic light scattering under oil and how cryo-EM screens need denaturants included to increase monodispersity.

Next **Jack Stubbs** (Southampton) talked on “Droplet microfluidics for time resolved serial crystallography.” He stated that there are >220,000 atomic models in the PDB (>84% by SCX) and most of these are at cryo temperatures, but can we collect more data at RT? One can use a set of tools to get as much data as possible to create molecular movies of proteins. This can be done with serial crystallography – continuous supply of crystals, no rotation, RT, 1 crystal = 1 image. The methods covered were fixed targets, injection methods, tape drives or microfluidics. He stated the requirements for time-resolved experiments – the need for small uniform crystals for rapid ligand diffusion, rapid ligand mixing and diffusion as well as tuneable delays to get different steps in the reaction. One could use microfluidics to create individual droplets of different sizes (pL to fL) with varying constituents. As drops get smaller, crystals are harder to form, but throughput is much greater. He showed an example of time resolved studies of Pdx1, which has 20 catalytic steps with timescales from milliseconds to hours. Cryo-trapping experiments have only managed to elucidate 4 of the steps up to now, all with longer timescales. Using microfluidic drops, mixing times of <2ms can be achieved with a 1:1 ratio of crystal and ligand. One can also do droplet merging – one drop with crystal growing and another with the ligand. These are squeezed together to get the two droplets to mix. Work needs to be done on better surfactants for faster mixing and also droplet synchronisation with the beam, either with droplet ejection or an X-ray transmissible fluidic device.

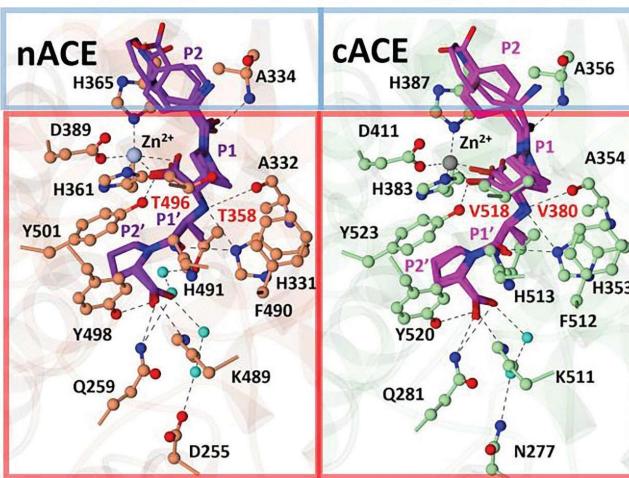
The last talk was from **Courtney Tremlett** (Exeter) on “Exploiting the micro-crystal toolbox to generate a mechanistic understanding of GmhA heptose biosynthesis in *Burkholderia pseudomallei*.” GmhA is the enzyme present in

step 1 of the heptose biosynthesis pathway. It is a tetramer and the four active sites can exhibit positive or negative cooperativity. This enzyme is a focus of drug development. The group were trying to use microcrystals to understand the enzymatic process – the short diffusion distance for ligand occupancy means one can start and stop the process quickly and there is an array of methods available e.g. VMXm, microED (rotation methods), foil, chip and tape-drive SSX for data collection. They used seeding to go from large single crystals to microcrystals. To achieve a larger number of smaller crystals they needed to raise protein concentration from 24 mg/ml to 68 mg/ml. They then used a tape-drive system to get ~500 ms time points and a foil based system for ~2 mins minimum time. They are starting to understand the full enzymatic process, but still more time points required. Initial data shows that some of the active sites are preferentially filled first.

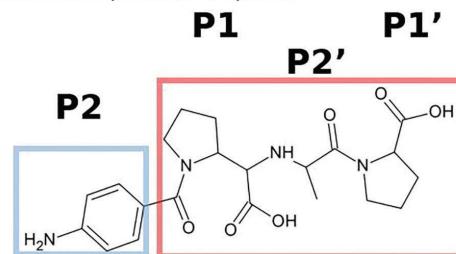
During the meeting, industrial talks were given by **Arjun Thapaliya** (Clinisciences) on “Tools for protein expression and purification: ways to obtain higher yield expression from your cultures,” **Warwick May** (Bio-Rad) on “Bio-Rad stain-free western blot workflow” and **James Bull** (iLab Solutions). Prizes for posters were presented by **Jean van den Elsen** (Bath) to **Joseph Hoff** (Bristol) and **Erin Maughan** (Exeter). In closing remarks, **Susan Crennell** (Bath) reminded attendees that SWSBC 2025 will be held in Sussex. The organisers and sponsors of this year’s meeting are congratulated on their considerable efforts and generosity in delivering such an excellent symposium.

Mark Roe,
Sussex

Targeting the S2 subsite of angiotensin-1 converting enzyme for domain-selective inhibition



- Differences at the S2 subsite of nACE and cACE were targeted to generate a selective inhibitor
- The inhibitors contained a conserved P1, P1' and P2' diprollyl backbone, designed to bind the same in nACE and cACE, with variable P2 moieties to bind selectively (nACE or cACE selective).
- Crystallographic data indicated the ligands bound as predicted, however, the selectivity was not as expected
- Therefore, residues distal to the active site must influence selectivity of these compounds



A slide by Kyle Gregory (Bath) showing structure-based drug design efforts to target angiotensin converting enzyme.



Views of the commercial exhibition at SWSBC 2024 in Bath.



Scenes from the conference lunch area at SWSBC 2024 (photos by Jean van den Alsen).

UK XFEL Townhall Meeting – Life Sciences and Bio Medicine

THIS meeting was held at the Royal Society, London on 29–30th July 2024 and received sponsorship from the UKRI (via BBSRC, STFC and ISPF), DLS and the Oxford Institute for Antimicrobial Research. The meeting began with an introduction by the overall organiser and chair of the first session, **Allen Orville** (DLS), who explained how the UK XFEL project is at the stage of analysing what is needed to deliver the world leading science for a Conceptual Design and Options Analysis report alongside the Science and Technology Case.

To these ends, several townhall events on different research themes have taken place across the UK over the last year or so. Currently the UK has an XFEL Hub at DLS which coordinates resources and training for life science researchers planning to use existing facilities abroad. There is also an equivalent XFEL Hub for physical sciences coordinated by the Central Laser Facility (CLF). The first presentation entitled “Project overview” was given by the project manager **Paul Aden** (UK XFEL) from the design team at STFC Daresbury who described how a series of reports had been prepared, beginning with the strategic review in 2016, followed by the Science Case in 2020. Current options are to either build an XFEL in the UK, on our own (i) or collaboratively (ii), to invest in one or more existing facilities abroad (iii), or to do nothing (iv). The whole project in the UK would likely cost on the £ billion scale depending significantly on scope and scale, and sustainability is an important consideration in the design. If the project goes ahead, another 4 years will be spent on technical design and construction would begin around 2030. The next lecture was given by **John Marangos** (Imperial) who covered the “Science Case Overview of Physics and X-ray Photonics, Condensed Matter and Mechanical Engineering.” The speaker described the prospects of tremendously exciting nanoscale material studies exploiting the relativistic electron pulses delivered by the XFEL undulators and self-amplified spontaneous emission (SASE). These developments have the potential to probe matter at the quantum scale and investigate valence electron dynamics as well as exploiting sub-femto second synchronisation in pump-probe experiments; a case for attosecond (10^{-18} s) time resolution in a new UK XFEL facility. The need for improved X-ray photonics and new physics to study electron dynamics in real time is exemplified by the demand for better clocks from the physical sciences community. There will be many applications in chiral dynamics and materials processing as well as extreme- and shock-physics, not to mention quantum plasmas and high-energy lasers. Next up, **Tom Penfold** (Newcastle) spoke on the subject of the “Science Case for Chemistry and Industrial Applications.” The speaker described the power of XFELs to study solvation dynamics and transient electron coherence as well as exciton dynamics. Energy- and charge transfer-materials, as well as spin dynamics, are research fields for which the XFEL offers tremendous potential, as it does for both reaction dynamics and molecular movies of catalysis. These are fields for which terahertz excitation will shed much light on fast chemical processes and radiolysis. Condensed phase research, quantum materials and nanotechnology stand

to benefit substantially from the proposed instrumentation, as will time-resolved and thermal diffuse scattering studies. There is significant potential for new and improved XFEL science in ultrafast magnetism, along with imaging dynamics and electrodynamics of disorder in quantum materials. The next lecture was given by **Jasper van Thor** (Imperial) who covered the “Science Case for Life Science” invoking biological serial crystallography of the melatonin receptor and enzymes such as photosystem II, methane monooxygenase and DNA photolyase. The prospect of mapping drug-binding activity to receptors in real-time is very strong with the XFEL, and significant contributions to radiation biology and medicine are also anticipated. Such studies require megapixel detectors that deliver around 2 terabytes of data per second and could benefit from a high repetition rate in the 100 kHz – MHz range that may also need precise synchronisation of optical instrumentation. The speaker concluded by highlighting the potential applications of optical parametric chirped-pulse amplification (OPCPA) – a paradigm-shifting technology allowing studies of high-power laser-matter interactions. **David Dunning** (UK XFEL, ASTeC) then spoke on the “Conceptual Design” phase involving applied and industrial manufacturing, additive manufacturing and plasmonic photocatalysis. Nucleation, liquids and compact process replication were covered alongside contributions to AI, engineering biology, telecommunications, semiconductors and quantum technology. **John Marangos** (Imperial) took to the stage again to emphasise the need for the UK XFEL to satisfy future national research demands in advanced technologies, healthcare, knowledge frontiers and net-zero growth, thus contributing to national and global economic strengths. The speaker emphasised how the proposed power range of the source is 4 -15 GeV and how it will use an undulator for lasing the electrons, causing them to bunch up and achieve high brightness levels. In contrast to synchrotron sources where electron bunches are re-used, the lasing process with XFELs spoils the bunches. The speaker outlined the conceptual design process and how it aims to capture requirements from the community and define which choices need to be made for this next generation, top-level facility. The speaker mapped-out the five main XFEL facilities currently operating across the globe and briefly described current proposals for the next generation UK instrument. These are likely to involve a 1 MHz source with additional beam splitting being achieved by five “kickers”, giving a total of six end-stations and dedicated data handling centres.

After a much-needed coffee break, **Chris Schofield** (Oxford) chaired the second session which began with a keynote lecture by **Ilme Schlichting** (Max Planck, Heidelberg) entitled “In biology, the sample is the science.” Ilme described how the first experiments were done at the Linac Coherent Light Source (LCLS) in Stanford in 2009 with an important forum for discussion of XFEL work being the annual Ringberg workshops. The speaker explained that whilst synchrotron sources can deliver 10^{12} photons in one second, XFELs can deliver the same number of photons in one femtosecond (10^{-15} s) to within an order of magnitude, or so. This presents tremendous opportunities for biological

time resolved studies using pump-probe technology. The speaker outlined the almost classical time-resolved study of carbon monoxide dissociating from myoglobin in a reaction which is triggered by flash photolysis. The CO molecule dissociates in less than 0.2 ps in a process that involves large structural changes in the protein, correlated displacements and anisotropic energy flow in the protein. Ilme described how quantum chemistry is driving future work on this system using low fluence photoexcitation and wavepacket analysis. The speaker then described studies on another system, fatty acid photodecarboxylase, an enzyme from *Chlorella* microalgae which generates alkanes from fatty acid substrates. The enzyme also releases CO₂ and has an FAD cofactor, with catalysis involving the formation of an alkyl radical and concomitant bending of the isoalloxazine ring of FAD. XFEL studies have revealed the timescales of CO₂ appearance and subsequent release from the enzyme as being of the order of 300 ps and 100 ps, respectively. The results suggest the involvement of a transient carboxycysteine intermediate in the CO₂ release pathway. The next lecture was given by **Patrick Rabe** (Oxford) and was entitled "Monitoring penicillin ring formation through a crystallographic and spectroscopic lens." The speaker outlined the steps in β-lactam biosynthesis, focussing on isopenicillin N synthase, emphasising that many of the intermediates have been solved crystallographically. The enzyme catalyses a 2-step 4-electron oxidation involving an Fe³⁺ superoxide state, an Fe²⁺ peroxide state and a Fe⁴⁺ ferryl intermediate. Use of acoustic droplet ejection onto a moving tape for delivering samples to the beam after precise soaking intervals and use of D-labelled substrate to exploit the deuterium isotope effect, allowed intermediates to be trapped and analysed structurally. The speaker described studies of the thioaldehyde intermediate and a monocyclic intermediate, emphasising the importance of the water chain in catalysis. Next up, **Briony Yorke** (Leeds) introduced her talk on "Time-resolved studies of the role of UV in cataract formation" by describing how the eye-lens α, β and γ crystallins form in the foetus and have to last the lifetime of the organism since the mature eye-lens is devoid of nuclei for optical clarity. The speaker described studies of the 21 kDa γD crystallin which has a greek-key β-sheet fold and is very stable for a human protein, having a T_m of 83 °C. Interestingly, it has a Trp cluster with 2 Trp residues being provided by each of the two domains. Pump-probe experiments suggest that the Trp residues absorb UV energy and use it to reduce disulphides resulting from oxidative damage. The experiments required the use of an R36S mutant which forms microcrystals suitable for serial crystallographic work. On slow oxidation of the protein, one of the surface cysteines becomes disulphide-linked to a glutathione molecule and UV exposure was shown to remove this adduct within 300 fs via a thiyl radical. Similar Trp-Cys functional coupling has been found in other proteins.

Following lunch in which, true to Royal Society form, guests were treated like nobility, the first afternoon session was chaired by **Kyprianos Hadjidemetriou** (DLS/eBIC). The chair dedicated the session to the late John C H Spence (Arizona) who pioneered the application of XFELs in biology. The first lecture was on the theme of "HeXI & eBIC – using electrons for structural biology" and was given by **Alistair Siebert** (DLS) who described the importance of the eBIC facility at DLS in democratising cryo-EM since 2014 by providing peer-reviewed access to state-of-the-art facilities.

The facility relies on automated single particle analysis (SPA) since one instrument can generate more than 1000 images per hour. The speaker emphasised how tomography is a big growth area in the field, as is ion-beam milling which allows support material surrounding the samples of interest in plates to be removed. 3D structure analysis of fibrous and other samples can then be undertaken by collecting a tilt-series without interference from background scatter. Alistair then introduced the electron diffraction facility HeXI which is currently under construction at DLS. The speaker emphasised how electrons interact with matter about 10⁵ times more strongly than X-rays due to the Coulomb potential being the dominant force and this necessitates the use of smaller crystals, typically 0.3 to 3 μm in size. It is anticipated that electron diffraction data to 1 Å resolution should be achievable with unit cells smaller than 200 Å. The instrument will have a tuneable wavelength, a CMOS detector and significant lead shielding. The next lecture was given by **Radoslav Enchev** (Crick) and was entitled "Enabling time-resolved cryo-EM." The speaker began with the conjecture that the technology behind the well-known resolution revolution in cryo-EM has rather left the sample preparation field somewhat behind – manual blotting and freezing still being the norm in most laboratories. This is something which crystallographers who remember the era when samples were sealed inside glass capillaries with humble beeswax and mounted by hand on state-of-the art instruments with plasticine, will readily relate to. The long-term aim of undertaking time-resolved EM studies is, as in other fields, going to rely on kinetic enrichment of intermediates and reaction synchronisation. The speaker described how one can now achieve mixing of solutions in chips on the millisecond timescale but the technology is still not very satisfactory. Radoslav then described fascinating studies, firstly of the RecA-ssDNA strand invasion repair system which is very important in cancer and then the groEL-ES chaperone which is pivotal in protein transportation and folding pathways. Last in this session, but by no means least, **Keith Moffat** (Chicago) took to the stage energetically to present a lecture on "Dynamics and kinetics in XFEL-based structural biology." The speaker's recommendation was that the UK proposals for an XFEL should focus on mechanism including chemical kinetics, ultrafast reactions and short-lived states. The speaker continued with persuasive arguments to seek improved light activation technologies and reduced noise – particularly to get noise out of the time domain. Suggestions were made to attenuate the X-ray beam and use very large scattering datasets coupled with complementary parallel spectroscopic data and computational methods to observe the weak signal(s) from rare events and/or their evolution from one state to another state. The speaker commented that the amino acid sequences we see in well-studied proteins of today represent molecules that are fit for folding and function. In following this up, Keith speculated that AI-based predictions of protein fold -vs- disorder, as well as time-resolved XFEL studies will likely provide insights into dynamics and how these contribute to function in biology with applications to medicine. It was emphasised that the XFEL community is one that has grown considerably to around 1000 users over the 15 years since its inception in 2009. An overall socioeconomic analysis of the impact of XFELs across all disciplines is part and parcel of the ongoing consultation process. In contrasting many different themes, the speaker concluded his lecture on a retrospective note to emphasise technological developments by showing

a precession camera in an otherwise empty beamline as virtually the sole protein crystallography instrument at CHESS in 1981. Discussion of this and other subjects, such as the potential to exploit coherence of the beam, continued into the coffee break.

The final session of the day was chaired **Alisia Fadini** (Cambridge) and began with a lecture by **Randy Read** (Cambridge) entitled "Prospects for the post-AlphaFold era of structural biology." The speaker described how the Critical Assessment of Structure Prediction (CASP) project began in 1994 when modelling groups were invited to predict a number of soon-to-be-published experimental structures to avoid any bias. These blind-test meetings continued over the years culminating, arguably in 2020, when the new machine-learning AlphaFold algorithm achieved accuracies comparable with those of experimental structure determination, and further improvements were delivered with AlphaFold2. Many challenges remain such as predicting RNA structures, protein ligand complexes, protein ensembles and estimating the accuracy of protein complexes, although further improvements were reported for AlphaFold3 (Abramson et al, 2024). The speaker described AI fragment screening studies of iduronate-2-synthase, mutations of which are associated with the lysosomal storage disorder, Hunter syndrome, using the AlphaFold3 model. The speaker emphasised that experimental phasing techniques such as MIR, MAD and SAD have been rendered largely redundant by these exciting developments in the machine learning field, though molecular replacement remains crucial in crystallographic phasing using AI-generated models. Work is ongoing to persuade AlphaFold to use experimental data. The next lecture was given by **Danny Sahtoe** (Hubrecht Institute, Utrecht) and was entitled "Addressing protein disorder through computational design." The speaker covered a range of subjects connected with protein design and directed evolution, as well as touching on transmembrane pore structures, phage display and nanobodies. Danny covered the computational problem of designing proteins to bind specific ligands, starting from the backbone and then optimising the sequence. The speaker then moved on to the challenging concept of taking a disordered peptide and designing a protein which could bind it as an integral part of its secondary structure e.g. as a strand or hairpin loop within a region of β -sheet. This project has many implications for catching amyloid-forming peptides and the crystal structure of a designed peptide-trap with *in vivo* activity was determined with A β 1-42 bound to it. We note that the 2024 Nobel Prize in Physics awarded to Hopfield and Hinton for their foundational discoveries and inventions in machine learning and artificial neural networks, and in Chemistry to Baker, Hassabis, and Jumper for "[solving] a 50-year-old problem: predicting proteins' complex structures" demonstrate a vital and central role of structural biology. Several discussions acknowledged the enormous potential for these new developments and often pointed to a need for dynamics and functional experimental studies that will eventually enable scientists to create new proteins with new functions that will impact human health and environmental issues. The closing lecture in this session was given by **Eriko Nango** (Tohoku) and was entitled "Time-resolved SFX – pump-probe approaches at SACLA." The speaker mentioned the new 4th generation synchrotron facility NanoTerasu being constructed at Tohoku in Japan. Eriko then described a range of time-resolved experiments on bacteriorhodopsin performed at SACLA on

the Spring-8 campus, using photo activation of samples delivered in droplets and liquid jets. These studies revealed a proton transfer mechanism involving a transient water molecule which was corroborated by quantum mechanical calculations. The speaker then described an interesting time-resolved experiment in which the chemical mechanism of carbon monoxide release from manganese was studied by crystallising a Mn-complex of lysozyme. Sample delivery at SACLA involves a tape system which can operate at 1.5 to 30 cm/s and droplets are dispensed onto it at a frequency of 30 Hz. The binding of NAG to lysozyme was studied using 3 – 5 μ m crystals, showing that after 2 seconds of soaking no ligand could be seen, but at 5 seconds soak time the ligand was definitely present in the maps. To achieve greater time resolution, smaller crystals of approximately 1 μ m size were used and these allowed NAG binding to be detected in the observed electron density after about a 1 second soak time. These studies would seem to set important ground rules for the applicability of soaking experiments in time-resolved work. The speaker concluded by describing studies of diterpene cyclase using serial femtosecond X-ray crystallography (SFX) in which improvements in controlling the temperature and pH allowed the structure of the substrate bound to the enzyme to be determined at high resolution.

The day ended with an excellent conference dinner followed by a fascinating keynote talk from **Richard Neutze** (Gothenburg) entitled "Time resolved studies using XFEL radiation: approaches and opportunities." The speaker began on a historical note by honouring the contributions to the field made by the theoretical physicist Julian Schwinger at Harvard who derived the equations of synchrotron radiation theory from Maxwell's formula in the 1940's. Richard then paid homage to Ken Holmes who was pivotal in establishing the EMBL outstation at the DESY synchrotron in Hamburg in the 1970's. The speaker emphasised the growth of the synchrotron field as exemplified by the new sources in Europe, DLS, MAX-IV, ESRF and Petra-III being just a few. The impact of synchrotron radiation in biology is reflected in the numerous outputs in high impact scientific journals, indeed (biased author alert) biology is probably the field where synchrotron radiation has had the greatest impact. The speaker then moved on to describe the pioneering work done in Oxford by Louise Johnson, Dave Stuart and Janos Hajdu to study catalysis in the crystal in the 1980's – a time when significant headway was made in analysing light-triggered and cyclic reactions using time-resolved Laue techniques. The world's first FEL was built in Stanford by John Madey for his PhD project in the 1960's and pioneering work by Claudio Pellegrini at SLAC led to the first XFEL facility opening in 2009. The speaker showed a video from the 1990's modelling the explosion of a lysozyme molecule upon exposure to an XFEL beam, some 10⁹ fold brighter than sources available at the time. Back then researchers were divided as to whether the diffraction-before-destruction tenet would bear fruit, but indeed it did, although the ambitious proposals for single-particle imaging remain a little behind schedule. The speaker described the development of microjet injection of microcrystals into the beam, culminating in studies such as Petra Fromme's work on determining the structure and mechanisms of photosystems I and II and the analysis by others of ultrafast reactions in photoactive yellow protein. Probably the best studied membrane protein remains bacteriorhodopsin – a system which was famously analysed by EM in the 1970's

in the pioneering work of Richard Henderson, and studies of the photoisomerisation of its retinal cofactor continue to this day. The speaker described work on cytochrome c oxidase, a blue haem copper protein, using photocaged oxygen, which shed light on chloride binding and the involvement of water in the mechanism. Richard emphasised that one of the challenges will be to convince young people of the importance of synchrotron and XFEL radiation sources in structural biology and other disciplines, particularly with the growth of cryo-EM, as a uniquely important structural tool. The speaker concluded by saying that developments in ptychography and X-ray microscopy are now allowing these techniques to approach the capabilities of EM.

The following day began with a session chaired by **Adrian Mancuso** (DLS) who introduced the first speaker, **Philip Johnson** (PSI/SwissFEL) whose lecture was entitled "Time-resolved biology at SwissFEL." Describing the SwissFEL source as consisting of two 12-13 keV LCLS-SACLA-style linacs (Athos and Aramis) which share the same tunnel, the speaker then outlined the features of the Alvra experimental station where structural and spectroscopic studies are undertaken. The station has a Jungfrau detector as well as LCP handling facilities for time-resolved femtosecond crystallography and has been used for studies of rhodopsin, haem proteins and photolyases. Philip then outlined the other biological beamline, Cristallina-MX, where current pump-probe work is mainly plate- and sheet-based, although an injector will be available in future, and spectroscopy is currently a big theme. Next up, **Richard Bean** (European XFEL) spoke on the subject of "Biology at the European XFEL." This 3.4 km long X-ray laser operates in the energy range of 8.5 to 16 GeV and user-experiments can be undertaken at 7 instruments which provide attosecond X-ray pulses. The speaker outlined studies of nanocrystals which are produced *in vivo* by *Bacillus thuringiensis* as a defence mechanism against insect predators. These insect toxins are used in genetically modified crops. Another very interesting project which the speaker described concerns drug discovery for the SARS-CoV-2 Mpro enzyme. Richard ended his talk by touching on some cutting edge developments in X-ray microscopy using such applications as a Bragg magnifier and time-resolved tomography or tomoscopy.

The session after morning coffee was chaired by **Sam Horrell** (Imperial) and began with a lecture by **Katarina Dörner** (European XFEL) entitled "Sample preparation and delivery at the European XFEL." The speaker described the state-of-the-art XBI laboratories at the European XFEL which enable work spanning the full range of structural biology demands from cloning and cell culture to purification, crystallisation and injection of crystals into the beam. Katarina outlined a number of ongoing experiments to develop and optimise focussing jets, aerosols and triple-layer sample-delivery systems for injecting crystals into the beam at MHz frequency. Next up, **Daniela Rupp** (ETH Zurich) spoke on "Imaging free nanoparticles and their ultrafast dynamics with time-resolved coherent diffraction imaging." The speaker began by explaining that the Fourier transform of a plane gives one a projection, or squashed image, of the structure which is consistent with an infinite number of solutions. Historically this has been a method by which small molecule crystallographers have managed to solve planar aromatic compounds where much is known about the chemical structure *a priori* and the ring is parallel with one of

the major zones. The speaker covered experiments on XFEL imaging of silver nanocubes in the gas phase and presented the memetic phase retrieval (MPR) method which is capable of identifying the solution in challenging conditions and the data analysis program is now publicly available. Next, **Allen Orville** (DLS) spoke on the "XFEL Hub at Diamond" which provides applicants with access to several worldwide XFEL facilities, the relative capabilities of which the speaker reviewed in some depth. Allen mentioned the requirements for high frequency acoustic sample ejection with tape delivery systems and described the new Polypico acoustic sample loader at DLS. The last part of this session was a discussion and feedback slot entitled "How can facilities address your short-, medium-, and long-term R&D goals?" This was chaired by **John Helliwell** (Manchester) who put everything in perspective by giving a short historical resume of the UK's efforts in establishing large-scale facilities for structural biology, starting with the Daresbury SRS synchrotron which opened in 1981 and the UK contribution to the ESRF. The chairman mentioned how time-resolved studies have the potential to reveal the mechanism of drug binding (not just the end result) and invited the audience to consider the importance of understanding drug action at this level of detail. John described how the difficulty with time-resolved structural biology has always been the challenge of making the sample amenable to the experiment and emphasised the importance of sample design. **Andrew Leslie** (Cambridge) was invited to express an opinion on behalf of the MRC LMB and conveyed the view that cryo-EM is currently of greater interest to his institute as a tool for analysing structure and function. An interesting point was then made that whilst life science might not currently be the main driver for a UK XFEL, biologists could well become major users.

After lunch, the first of the afternoon sessions was chaired by **Malcolm Skingle** (GSK) and began with a lecture by **Elizabeth Shotton** (DLS) entitled "Industrial science at large-scale infrastructures – the Diamond example." Elizabeth spoke on the role of the Industrial Liaison Team at DLS in helping proprietary researchers from a variety of industries gain access to the DLS facilities. The team members are specialists from a range of scientific backgrounds and provide commercial users with a multi-disciplinary approach to solving research and development problems. The next speaker was **Vadim Cherezov** (South California) who spoke on the subject of "GPCRs, revealing their secrets." Vadim emphasised how approximately one third of all drugs target this protein family as either agonists or antagonists, with the CNS and cardiovascular being major targets. The speaker described the extraordinarily successful application of the lipidic cubic phase (LCP) for crystallisation of these membrane proteins which ultimately allowed his team to determine the structures of 15 different GPCRs using XFEL data. Numerous drug-binding studies have been undertaken such as on complexes of the melatonin MT1 and MT2 receptors which are involved in circadian rhythms, and the angiotensin receptors AT1R and AT2R which are involved in hypertension and nociception (pain), respectively. Screening studies of the AT2 receptor are in progress for discovery and optimisation of non-opioid pain killers. The next lecture, given by **Michael Henning** (LeadXpro) and entitled "Structure-based drug discovery using XFELs" covered the full range of gene-to-structure work and the design decisions made at each stage. The speaker emphasised how X-ray crystallography has already

given us several hundred ligand complexes of GPCR's and cryo-EM is poised to deliver a competitive performance in the near future. Michael described how ion channels have multiple binding sites for different drugs, stressing the importance of this work. The speaker described serial work on the A_{2A} adenosine receptor which was crystallised in syringes using LCP and yielded higher resolution information (1.7 Å) than synchrotron single crystal work had achieved. The speaker mentioned that this seems to be a consistent feature of LCP work. Michael then described some very interesting studies stemming from the fact that drug binding to this protein is photoswitchable. The next speaker was **Tian Geng** (Nxera Pharma, formerly Heptares) who spoke under the general title of an "Industrial perspective on XFELs" and described time-resolved work which her group has done in collaboration with a number of these facilities. The project has led to the A_{2A} receptor being expressed as a fusion protein with bRIL (an engineered thermostable apocytochrome) which improves the permeability of LCP to drugs by keeping the layers further apart and thereby aids soaking experiments.

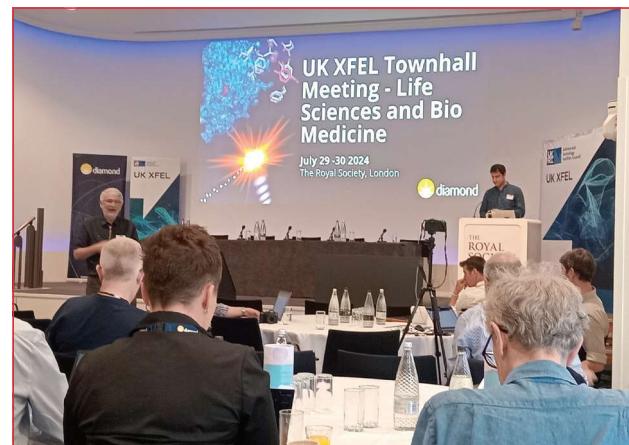
After coffee, the final session of the meeting, which was chaired by **Julia Parker** (DLS), began with a lecture by **Thomas Lane** (DESY) entitled "Time-resolved crystallography captures light-driven DNA repair." The speaker explained how pyrimidine dimers form in DNA as a result of light-driven damage which can be reversed by DNA photolyase. The speaker described the structure of the complex this enzyme makes with an artificial thymine dimer in a double-stranded DNA oligomer and explained that one electron is needed to restore the dimer back to its normal state. The enzyme itself is activated by light due to its FAD cofactor which absorbs a photoelectron and can then either decay back to the ground state or use the electron to reduce the thymine dimer. The speaker described some fascinating experiments to study this process on the nanosecond timescale. These were undertaken at the SwissFEL and generated an excellent time series of intermediates. In its ground state, the flavin cofactor adopts a V-shape in the active site of the enzyme but it was found to buckle markedly in the opposite direction on absorption of light. The enzyme stabilises this buckled form of the cofactor (FAD*) and allows the electron to be transferred to the DNA bases which are released in an ordered manner to reform the DNA duplex. The next lecture was given by **David Leys** (Manchester) on the subject of "Time-resolved MX of light-dependent systems." The speaker described the CarH protein which is a bacterial vitamin B₁₂-dependent photoreceptor that acts as a transcriptional regulator in the biosynthesis of carotenoids. The protein binds to DNA in the dark but upon exposure to light, the subunits of this tetrameric protein dissociate and the DNA is released for transcription. Serial synchrotron studies at I24 at DLS indicate that the adenosyl group of the cofactor which normally ligates the cobalt ion on one side of the corrin ring is displaced by His 132 from the 4-helix bundle domain of the protein. The cobalt is ligated on the other side of the corrin by His 177 from the Rossmann fold domain. This switch within the structure triggers dissociation of the tetramer and the release of DNA from the DNA-binding domains of each monomer. The speaker described quantum mechanical studies of the mechanism and the role of oxygen in forming the light-adapted state of the protein. David then summarised other ongoing studies of a flavin-dependent enzyme at SACLX where it was shown that a covalent

bond forms between the flavin and the substrate on the 10 nanosecond timescale. The final talk in this session was a keynote lecture given by **Dave Stuart** (DLS) which was entitled "Synergies between X-rays and electrons in life science research." The speaker described the challenges of making XFELs more useful to the community at a time when finances are hard and when fragment-screening and SAXS studies are the main growth areas at DLS. The speaker emphasised the historical importance of the Protein Data Bank (PDB) as the key metric in the structural biology field and how XFELs shook the synchrotron paradigm. The reliance of AlphaFold predictions on the existence of well-curated data within the PDB leads one to speculate whether AI might have had similar impacts in the drug design and cell-imaging fields, had similar databases existed for them. The speaker emphasised how structural biology has had many revolutions with one of the most recent being ion-beam milling which allows, for instance, analysis of chromatin by cryo-ET. The speaker moved on to describe the enormous power that EM and AI have in assigning the proteins and their roles in structures of newly discovered viruses. The meeting concluded with closing remarks from **Jim Naismith** (Oxford) who briefly summarised the sentiments of attendees in a masterful way. Jim congratulated the chairs and speakers, and thanked the meeting sponsors who generously supported the event.

Jon Cooper, UCL

Shabir Najmudin, Kings / City – St Georges

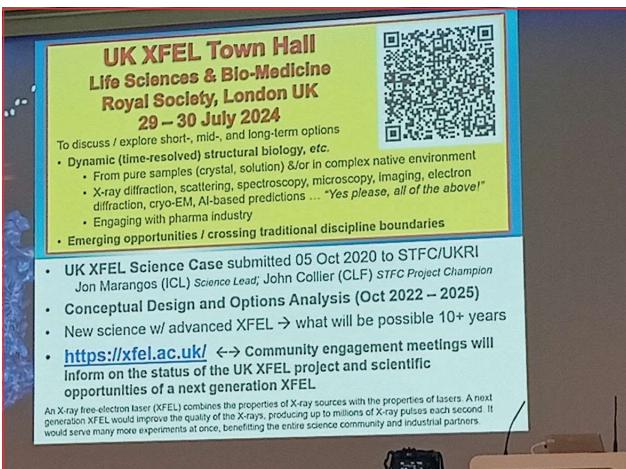
Allen Orville, DLS



The meeting organiser Allen Orville (DLS) on the left, opening one of the sessions at the UK XFEL Townhall Meeting, held at the Royal Society in London (below).



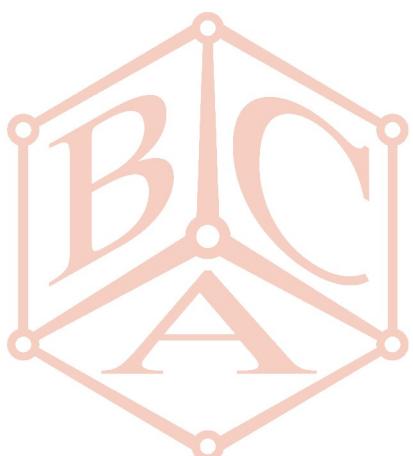
Attendees engaged in intense discussion of the preceding session.



A snapshot of the meeting's mission statement, as a part of the Conceptual Design and Options Analysis phase (left) with a scene from the conference dinner (right).

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Seeing eye to AI with expert systems

As someone who has worked in and out of a laboratory co-inhabited by electron microscopists for a few years, I remember many times working at a graphics terminal and being sat next to someone who was particle picking. Being reminded recently, for some reason, of the incessant click, click, click of the particle picker's mouse, I began to wonder how work in the AI field might be developing to help automate this incredibly repetitive task, which required many tens of thousands of particles in the micrographs to be picked and classified by eye. Of course, nowadays, EM's have direct detector device (DDD) cameras with high detective quantum efficiency (DQE) and these allow micrographs to actually be recorded as movies, rather than single shots.

There is an interesting review of the history of AI in particle picking available as a preprint on ResearchGate [1] and although much of the terminology goes over my head, it seems to be a comparison of six methods, all of which were trained with the same datasets and assessed by the resolution of the reconstructed particle. For one protein, the resolutions achieved by the different programs varied from 2.7 Å to 4.4 Å and for another the best and worst resolutions were 2.8 Å and 8.5 Å. It would seem to be wise to pick your expert system carefully (!) although in most cases they were more consistent and the consistency improves with the number of micrographs used.

Leaving particle picking aside for the time being, the main AI paper of interest to biological crystallographers this year is probably the publication in *Nature* of the AlphaFold3 (AF3) algorithm [2]. The paper claims to have achieved more accurate predictions than current classical docking algorithms and reports that covalent modifications to both proteins and nucleic acids are predicted accurately. I was interested to hear from the practising structural biology community about how successful AF3 is, so I put a question to this effect on the CCP4 bulletin board and got a number of replies.

Two comments were very positive.

"I used it for PPI prediction of a mAb and our target protein and it was surprisingly accurate compared to our crystal structure. Binding of the mAb was less than 0.5 Å rmsd. I was stunned." **Jürgen Bosch** (Case Western Reserve).

"I did the same for a dimer of a structure we just solved but only now writing the paper. AF3 predicted the monomer to an RMS of about 0.3 Å and dimer to about 0.5 Å. Structure not yet in the PDB, but soon." **Joel Sussman** (Weizmann).

In contrast, **Guillermo Montoya** (Novo Nordisk), who kindly pointed me to some interesting "tweetorials" was less enthusiastic about the results on a multi-protein DNA complex, although the individual protein folds were predicted correctly. Likewise, **Patrice Guoet** (Lyon) observed that "AI-predicted hetero-oligomeric structures have to be taken with caution." Patrice's group have also developed a web-server, FoldScript (<https://foldscript.lbcn.fr/>), which allows

automated analysis of quaternary structures modelled by AF2 or 3, in order to guide the user in choosing the most relevant and accurate model. This analysis can be refined by introducing experimentally known interaction data.

Vahéh Oganesyan (AstraZeneca) commented: "I use AF3 quite often to look at domain boundaries by sequence but not necessarily by their spatial arrangement. This is because protein-protein interactions, at least in all cases that I have tried, were not predicted correctly. So my message in short would be: trust to some degree but do not be surprised if it is wrong for cases without analogues in the PDB."

The following is from **Mark Glover** (Alberta). "We had an interesting case for a protein-RNA structure. We had determined the first structure of a FinO family RNA chaperone bound to its RNA target. The structure was deposited in the PDB just after AF3 gathered its training database so we thought this would be a nice test of AF3 for protein-RNA prediction. Our structure is stabilized by two main contacts: recognition of the terminal 3' nucleotide by a hairpin-helix motif in the protein, and recognition of the RNA hairpin by a novel protein N-cap structure. While the structure has no homologs in the database, there are protein-RNA structures in the PDB that do contain those interactions. We ran many different predictions, and we found that AF3 would generally place the RNA over the correct surface on the protein, however the detailed interactions were often wrong. AF3 did get the N-cap interaction in some of the predictions, but never correctly predicted the recognition of the 3' nucleotide."

Members are very welcome to let the editor know of their AF3 experiences.

Jon Cooper,
UCL

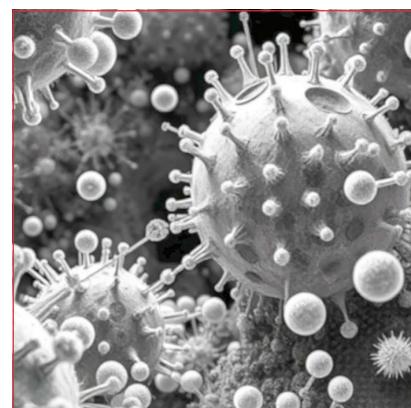


Image generated using the surreal graphics generator at deepai.org

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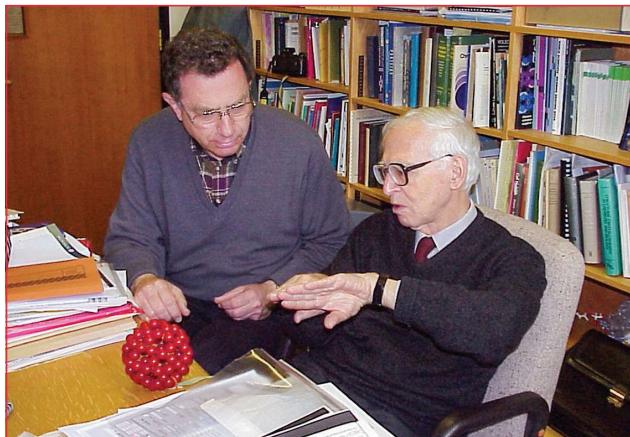
Schrödinger's aperiodic crystal

'AN aperiodic crystal is a structure with sharp diffraction peaks, but without lattice periodicity' [1].¹ This is a modern definition thanks to crystallography having become a science of structures, i.e. more than what classical crystallography is. As far as I know, the theoretical physicist Erwin Schrödinger (1887–1961) was the first to use the term 'aperiodic crystal' in his most influential book "What is Life?" published in 1944, i.e. 80 years ago [2]. The book appeared at a time when the nature of the gene was not yet known but there was intensifying interest and research effort to identify it. Schrödinger's book pointed to the possibility that the gene may be molecular. In a remarkable coincidence, also in 1944, Oswald T. Avery (1877–1955) and his two associates provided experimental evidence that DNA was the substance of heredity [3].

Schrödinger's book hinted at the intriguing possibility that, for understanding life, heretofore unknown physical laws might have to be uncovered. This possibility added to the recent lure of biological research, and both established scientists and budding researchers joined in (see e.g. [4]). Schrödinger's ideas have earned much appreciation, but also criticism. Forty-three years after the publication of the book, Max Perutz noted ungenerously that 'what was true in his book was not original, and most of what was original was known not to be true even when it was written' ([5], p. 558).

To Schrödinger, a small molecule would be an initial seed for the gene. Its extension by mere repetition – the way a crystal is formed – could not lead to the gene because periodicity would exclude carrying information. The other way to extend the initial seed molecule would be to build up a complex organic molecule – proteins could be such systems, or DNA as we know it today. DNA, as it was known in Schrödinger's time, could not be considered the substance of genes as it had been hypothesized to be uniformly repetitive (see e.g. [6]).

Curiously but understandably, Schrödinger's aperiodic crystal has not been related to the aperiodic structures



Aaron Klug's tutorial to István Hargittai in Klug's office at the MRC Laboratory of Molecular Biology, Cambridge, UK, on 18 February 2000 (taken by unknown photographer)

in modern crystallography, i.e. quasicrystals and various classes of incommensurate structures. The reason is that the relationship is not functional, merely semantic. However, an interesting analogy may be drawn between Schrödinger's aperiodic crystal and Aaron Klug's (1926–2018) idea of the fundamental difference between ordinary polymer molecules and biopolymers. The ordinary polymer consists of periodic repetition of the basic motif whereas the biopolymer has variability. From this, Klug recognized that identifying nucleation, i.e. the initial seed, was necessary for understanding the structure of a biopolymer. There was a further lesson in Klug's discovery. When he put together his Nobel lecture for publication, the editor wanted him to delete the picture depicting Klug's original idea of nucleation [7]. Klug admitted that it was wrong in detail, but its inclusion demonstrated a process in science of establishing the truth. Klug referred to the philosopher Alfred N. Whitehead (1861–1947), coauthor with Bertrand Russell of the famous Principia Mathematica, who said 'It is more important that an idea be fruitful than that it be correct' ([7], p. 313). This may also apply to Schrödinger's aperiodic crystal.

István Hargittai,
Budapest

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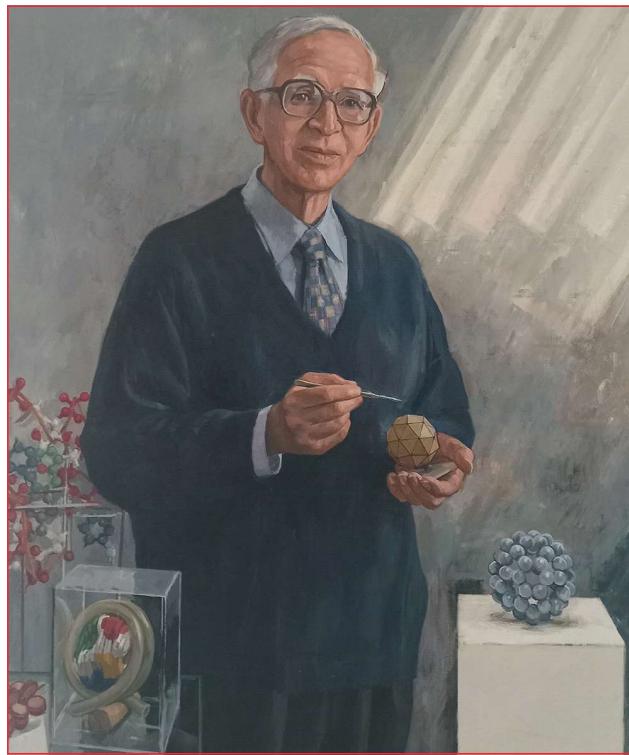
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¹ For a more recent statement, see the IUCr Online Dictionary of Crystallography: 'In aperiodic crystals (incommensurate and quasicrystals) the arrangement is not periodic in three dimensions but is nevertheless still fully ordered, where the ordering follows particular mathematical rules.'

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Going viral

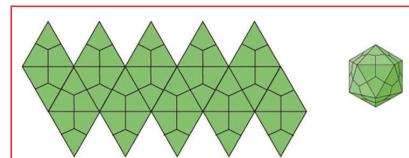
FINDING the previous article in the IUCr Journal as well as spotting a portrait by Jeff Stultiens (shown below) of the Nobel prize winning mathematical physicist, Sir Aaron Klug FRS, at the Royal Society a few months ago said one thing and it was written in the stars! It is now time for members to revise the Caspar and Klug triangulation theory for spherical viruses [1, 2] which incidentally only very slightly predates the editor and, of course, there can be no escape.



A portrait of Sir Aaron Klug FRS by Jeff Stultiens at the Royal Society in London. Photograph by the author.

The following text and most of the figures are adapted from the ViralZone website, written by the Swiss-Prot group of the Swiss Institute of Bioinformatics. Note that the icosahedron has the largest volume-to-surface ratio of all the regular polyhedra and this is likely to be important for the stability and genetic compactness of viruses. We can start by considering 60 identical subunits organized into 20 equilateral triangles creating the faces of an icosahedron. These icosahedral structures exhibit rotational symmetry: 5-fold symmetry at the vertices, 2-fold through the edges and 3-fold through the centre of each triangular face [3]. Each triangular facet can be divided into three symmetrically equivalent parts, called an icosahedral asymmetric unit (IAU), by the central 3-fold symmetry axis. In this case the IAU is one of the 60 identical subunits. Note the underlying honeycomb pattern of hexagons, each of which has a corner cut out so that the pattern can be folded to make the surface of a regular icosahedron in 3D (shown on the right).

Unless stated otherwise the figures in this article are from the ViralZone website (<https://viralzone.expasy.org/8577>) maintained by the Swiss-Prot group of the Swiss Institute of Bioinformatics and are available under a CC BY 4.0 license.



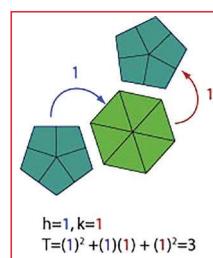
Looking at the paper cutout on the left, we can see that the top and bottom pieces of the icosahedron

are each made of 5 triangular tiles, whereas the central ring is made of 10 such tiles. Studying the icosahedron more, we can see that it has 12 vertices, each being formed by the pentameric assembly of the IAU's. The 2-, 3- and 5-fold axes mentioned above all project out from the centre of the icosahedron and are therefore not parallel to each other.



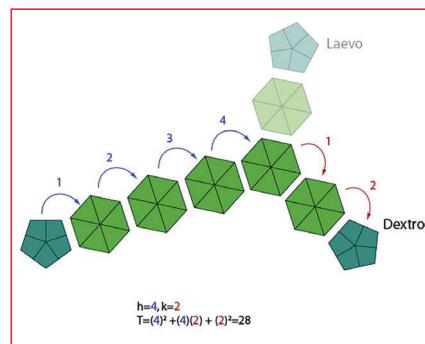
Anyone who has looked at an old football will know that we can space the pentagons out with hexagons, as shown (image: deepai.org).

In the image, the black pentagons are separated by a white hexagon in each direction, but we can use more hexagons and this is where the Caspar-Klug triangulation-number or T -number comes into it. The more hexagons, the higher the T -number. In the first example where there were no separating hexagons and all the pentagons are in contact with each other, the T -number is 1, but for the football example, it is 3, as shown below.



At this point, readers with a biological background will remember that bacteriophages (viruses which attack bacteria) have been divided into types T1 – T7, based on their growth characteristics and appearance of the plaques, where the T simply stands for "type" [4]. These T numbers have nothing to do with Caspar-Klug system

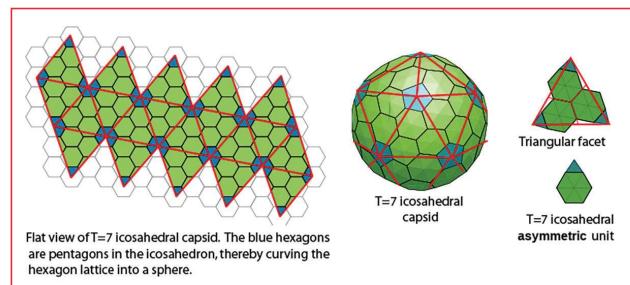
and predate it by about 20 years, in fact the head of the well-known T4 phage has two Caspar-Klug T -numbers: 13 for the caps and 20 for the elongated cylindrical part in between [5]. Confused? You soon will be.



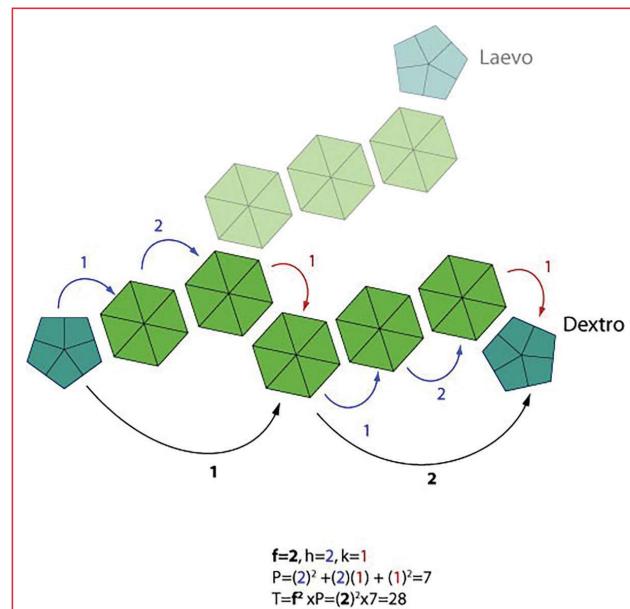
So what exactly is the triangulation T number then? Well, the answer depends a bit how you choose to calculate it but the ViralZone system is the easiest to understand and is shown here.

Starting from the pentamer on the far left, the upward steps to the right, shown with blue arrows, are counted by the h index and the subsequent steps to the lower right in red arrows are increments of k . The T number is given by $T=h^2+hk+k^2$ where h and k are non-negative integers.

Using the above scheme, it is left as an exercise for the reader to show that the T -number for the following virus is 7. As a clue, starting from the blue pentagon on the lower left of the folded capsid (centre), we can count the steps as above and see that $h=2$, $k=1$.

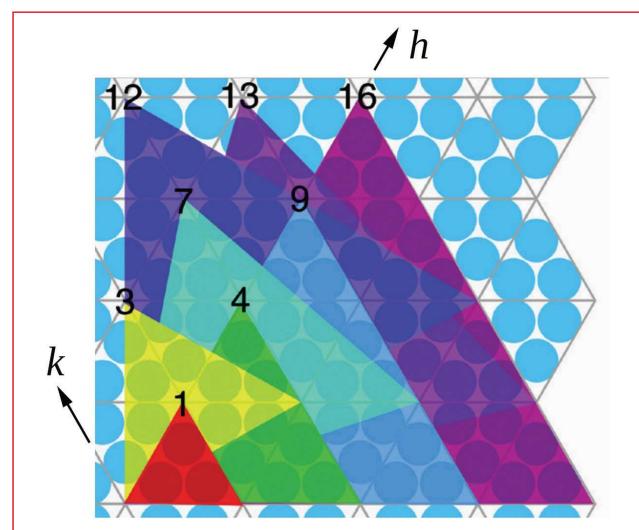


The scheme for determining T originally proposed by Caspar and Klug uses a more symmetric path between the pentamers with a number f representing the number of repeats in the path. This is shown below. In these schemes, note that on stepping from one hexagon to the next, having to turn left or right can alter the chirality of the icosahedron, the dextro and laevo forms being mirror images of one another. Hence, some T numbers are given with a *d* or *l* suffix.



So we have looked at the geometric way in which the Caspar-Klug T -number can be calculated, but so far we have missed an important point which is that it determines the number of quasi-equivalent subunits in the IAU. This is shown below where we see triangles corresponding to the lowest values of T allowed by the Caspar-Klug formula (the T numbers are shown in black). The familiar $T=1$ triangle is shown in red with a 3-fold in the centre and hexagons at each corner, although these become pentamers on the folded surface. If we look at the yellow $T=3$ triangle we can see the hexagon in the middle of three pentagons. We can also see that the IAU of the $T=3$ triangle contains a total of three of the underlying blue circles (2 full circles and 2 halves). With a bit of triangle gazing, we can see that T is indeed the number of background blue circles in each of the IAU's. Note also how the circles are cut up by the edges of the triangles in a symmetric way so that however much of a circle we lose at one end of the triangle's edge, we get it back again at the other end.

Note how the triangles with $T = 1, 4, 9$ and 16 have their top corners at (h, k) values of $(1, 0)$, $(2, 0)$, $(3, 0)$ and $(4, 0)$, respectively. The triangles for $T = 3, 7, 12$ and 13 have their



This figure is from PDB-101 (PDB101.rcsb.org) and is available under a CC BY 4.0 license.

top corners at (h, k) values of $(1, 1)$, $(2, 1)$, $(2, 2)$ and $(3, 1)$, respectively. As an exercise, the reader is encouraged to confirm that the respective T -numbers are correct.

Since the icosahedron has 20 triangular faces, each with a central 3-fold relating the IAU's, it will have $60T$ subunits and 12 of these will form pentamers containing a total of 12×5 or 60 subunits. The number of hexameric subunits is therefore $60T-60$ or $60(T-1)$ subunits which corresponds to $10(T-1)$ hexamers. Often these assemblies are called hexons and pentons. Packing the same protein around either a 5-fold or a 6-fold axis can usually be accomplished without major changes in its structure and this allows viral capsids to be comparatively large with relatively little genetic information being needed for the structural proteins. In fact the satellite tobacco necrosis virus has 60 subunits forming a $T=1$ capsid of 180 \AA diameter containing the RNA genome which codes only for the coat protein. This demonstrates a remarkable sparsity of genetic information, although this virus does need a helper virus to replicate [3].

Finally, despite the elegance of the Caspar-Klug theory, given what we know about protein flexibility, it is perhaps unsurprising that viruses do not strictly obey it – in fact there are many exceptions [6]. Perhaps this is another example of A. N. Whitehead's point that it is more important for an idea to be fruitful than completely correct.

Jon Cooper,
UCL

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Down memory lane

The Evans and Sutherland Picture System 2

MY first encounter with computer graphics being used in a protein crystallography laboratory was in 1984 when a class I was in was shown an Evans and Sutherland (E&S) Picture System 2, or PS2 for short. The display was black-and-white but still it was quite impressive and was one of the things that led me to go into the field as a PhD student. Thus, a year later I had the opportunity to use a colour E&S system, which was appreciably better, for my own research project with Prof Tom Blundell at Birkbeck. The Department of Crystallography PS2 was controlled by a PDP-11/60 which had 128k of RAM while the PS2 itself had 64k of RAM [1]. A few years after that, as a post-doc, I had the privilege of being given an RK07 disk cartridge which cost the department the best part of £1000 and allowed me to store almost 30 MB of my own data, rather than begging, borrowing or stealing space on other peoples' disks. These cartridges had to be placed very carefully in one of the PDP-11 disk drives, each of which was about the size of a domestic washing machine, if not larger. The computer alone cost several times the average UK house price, as did the PS2. Although the technology was brand new in its day, these costs do seem rather excessive for box or two of electronics. I wonder cynically if part of the profit model was to make these machines significantly, but not massively, cheaper than employing the legions of accountants and draftsmen which they would come to replace in the commercial sector. The running costs in terms of electricity and cooling alone were, of course, huge.

Most crystallographic work was done using the program FRODO which was originally written by Alwyn Jones for a different graphics system [2] and had subsequently been modified to work on the E&S by the program's author and by others over the years. Basically the program reads in the structure of the protein as a PDB file and a contoured version of the electron density map. With the PS2, the molecule on display could be rotated in real time and modified by the user by means of a special E&S mouse (or light pen) on a huge framed mouse pad, known as the tablet.

When looking at a protein structure at the level of individual atoms and bonds, only a small part of the molecule can be displayed at any one time or the image rapidly becomes unintelligible. This difficulty is compounded when an electron density map is being displayed, due to the sheer number of contour lines. The PS2 was a vector-drawing system, i.e. the cathode ray tube traced out the individual bonds and map contour lines one-by-one in quick succession and when there were too many to handle, the display used to flash bewilderingly. Whilst these problems were substantially solved in the later E&S models, raster graphics would eventually supersede vector graphics systems due to their speed and substantially reduced cost. However, molecular

graphics for experimental protein crystallography still mostly involves looking at small volumes of electron density, typically around 10 Å in each direction.

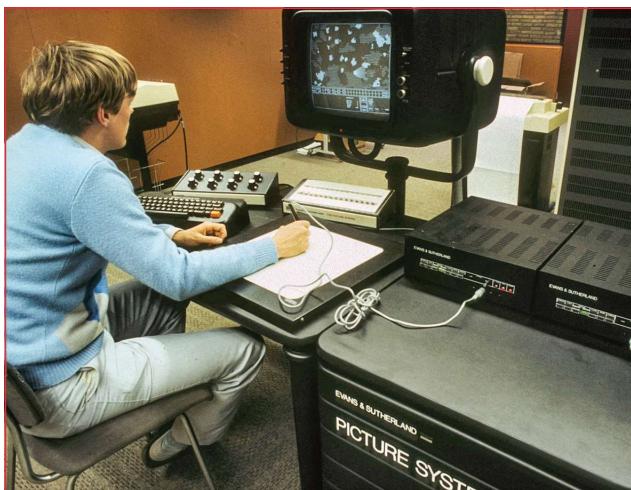
FRODO used to run from a constants file which contained the names of the coordinate file and the map file (both held in binary format) as well as the names of several other files including a stereochemical dictionary containing the standard bond lengths and angles for the 20 amino acids as determined by small molecule crystallography. The program allowed the user to make mutations, insertions and deletions as well as rebuilding the amino acids so that they fitted the electron density as well as possible. One could break individual bonds (BOBR option) to separate a fragment e.g. part of a side chain, and you could then translate or rotate it about a chosen atom (FBRT option). However, when a user moves the atoms or groups of atoms, certain bond lengths and angles will immediately begin to deviate from stereochemically acceptable values and this requires that the structure be regularised to confer it with reasonable geometry, as well as retaining a good fit to the electron density. The regularisation in FRODO (via the REFI command) was done with the Hermans and McQueen (1974) algorithm [3] which uses a classical molecular mechanics approach. Rotation of parts of the molecule around torsion angles was also possible with the TOR menu option. The bonds could be rotated smoothly by the use of virtual sliders which were driven by the mouse or light pen in much the same way that the entire molecule would be rotated for routine inspection of the structure.

Whilst most of these old machines have long gone to the great resting place for computers in the sky, no doubt one or two remain in museums or private collections here and there. Do members know of any or do they have memories, fond or otherwise, of using or programming a PS2? Just let the editor know.

**Jon Cooper,
UCL**

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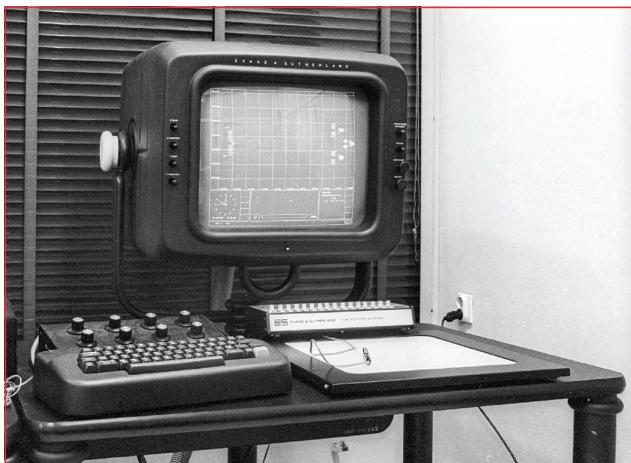
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An Evans and Sutherland Picture System 2 (PS2) equipped with a light-pen and dial box. The back of the PDP-11/60 computer cabinet can be seen on the far right. Colour graphic terminals were also available. This photograph is reproduced with the permission of the Museum Waalsdorp, The Hague, Netherlands.



This photo and most of the following explanation were very kindly provided by Thomas Ferrin (UCSF) showing their system in about 1980. The black cylindrical objects with domed ends are stereo viewers originally made by Bausch and Lomb. They were rotating cylinders that you looked through. They occlude one eye at a time from seeing the screen and their rotation is synchronized with computed left and right eye images. Before the invention of dynamic polarizing lenses they were one of the few ways to see stereo images on a calligraphic display. E&S also marketed a stereo viewer they called the lorgnette. It was based on a rotating disk instead of a rotating cylinder, but otherwise worked in a similar fashion. This photo is the only one showing the E&S mouse (top of the right-hand screen) with which most of the molecular graphics rebuilding work was done.



Another E&S photograph courtesy of the Museum Waalsdorp, dated 1977.



A photo by the author of a slightly dusty but surviving (at least as of about 2020) RK07 disk cartridge for the PDP-11/60. These disks only had a capacity of 30 MB so, at most, only a handful of map files could be stored on one of these. Ideally each user would have had one of these to store their work but due to their expense they often provided storage for several group members at once.



Puzzle Corner

IT has been a couple of issues since our last puzzle but now it returns with a vengeance. The challenge back in June was to identify the plane groups of each of the following floor tile patterns which were photographed in Nairobi bars by John Lisgarten (London). Readers had the additional challenge of compensating for perspective in the photographs which John very kindly sent.



(a)

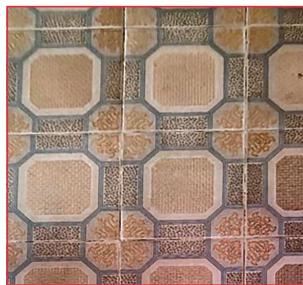


(b)

I had an e-mail from **Philip Bradfield** (Edinburgh) who offered (a) p4 and (b) p4mm (aka p4II) and I believe these are absolutely correct, but let us have a look. Philip was also kind enough to give a reference to the excellent book "Introduction to Crystallography" by F. C. Phillips, 4th edition (Oliver and Boyd, Edinburgh, 1971). In the following two pictures, I have distorted the original photographs slightly (using the free online image editor lunapic.com) to attempt to remove perspective as far as possible so that the symmetry might be a bit clearer and I think the effect works reasonably well.



(a)



(b)

Philip's assignment of (a) to the square plane group *p4* is without doubt correct, as a look at the recommended textbook and the International Tables for Crystallography, Volume 1 (or A) (IUCr, Chester) confirms. Things get slightly more complicated with (b) but again I cannot fault Philip's answer. The International Tables gives this one the short symbol *p4m* or the long symbol *p4mm* reflecting the fact that we have mirror planes along the *x* and *y* axes and that the 4-fold rotational symmetry generates further mirror planes along the diagonals. In contrast, in the book by F. C. Phillips, this plane group is given as *p4II* where the author uses the letter *I* to indicate a mirror *line* rather than a mirror plane, since we are considering symmetry in only a two-dimensional world, where nothing exists outside the plane of the page.

At this point, members are referred to the Wikipedia page for an interesting novel entitled "Flatland: A Romance of Many Dimensions" by Edwin Abbott Abbott (1884, Seeley and Co, London) which was intended to be a satire of Victorian social hierarchy. Interestingly, Abbott was a Cambridge scholar who was awarded the highest honours in classics, mathematics and theology in 1861, so his exceptional geometric abilities cannot be drawn into question! According to Wikipedia, in the story "the Square dreams of a visit to a one-dimensional world, "Lineland", inhabited by men, consisting of lines, while the women consist of "lustrous points". A number of animated versions of the story may be seen by members on YouTube, including one made by Harvard University in 1965 and narrated by Dudley Moore.

Finally, we have our own quiz bonanza from the realms of Flatland with no less than six new floor patterns, all from **John Lisgarten** (London), for members to identify, wherever possible, the plane group symmetry. I gather these were found in churches, hotels and bars in Venice, Rome and London.



(a)



(b)



(c)



(d)



(e)



(f)

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.

Applications are now open for the **20th BCA/CCG Intensive Teaching School on X-ray Structure Analysis**, which will provide participants with a fantastic opportunity to gain a breadth and depth of crystallographic knowledge within a warm and collegial atmosphere.

More information about next year's school and the registration can be found on the following website:
<https://bcacccgschool.crystallography.org.uk/>

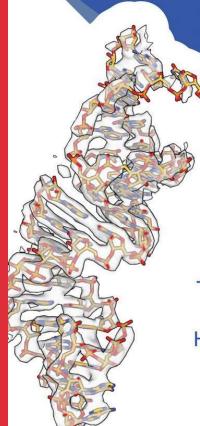
Natalie Pridmore, Durham

By the time you receive this newsletter, there *might just* be time to register for the BSG 2024 Winter meeting on "New Advances and Future Directions in Structural Biology" to be held at the MRCLMB in Cambridge on Friday 6th December. The organisers are **Andrew Carter** (Cambridge) and **Simon Newstead** (Oxford).

More details are on the BSG website (bsg.crystallography.org.uk) and registration is available here: <https://bit.ly/4fDEqfZ>

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- Kelly Nguyen (MRC LMB)
- Tracey Gloster (St Andrews)
- Harry Low (Imperial)
- Helen Cooper (Birmingham)

Town Hall Discussion:

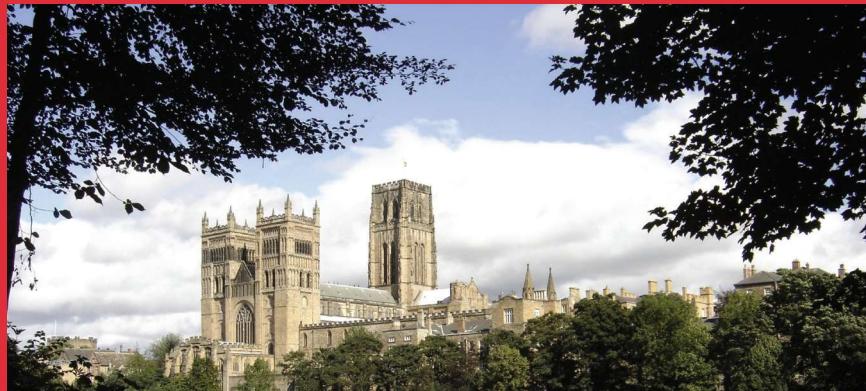
Future directions for structural biology



Registration & programme:
<https://bit.ly/4fDEqfZ>

Organisers: Simon Newstead
Andrew Carter

MRC Laboratory of Molecular Biology
Francis Crick Avenue
Cambridge CB2 0QH



20th Intensive School on X-Ray Structure Analysis

Durham, UK, 29th March – 6th April 2025

<https://bcacccgschool.crystallography.org.uk/>



BCA Spring Meeting, Leeds, 14th-17th April 2025

Preliminary information is available in this issue and you can keep up to date via the BCA website:
www.crystallography.org.uk.

PXRD-18, XRD Training for the Pharmaceutical Scientist CCDC Cambridge 6th-9th May 2025

For details, please see page 16.

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 to 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.



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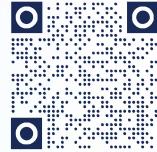
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