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British Crystallographic Association

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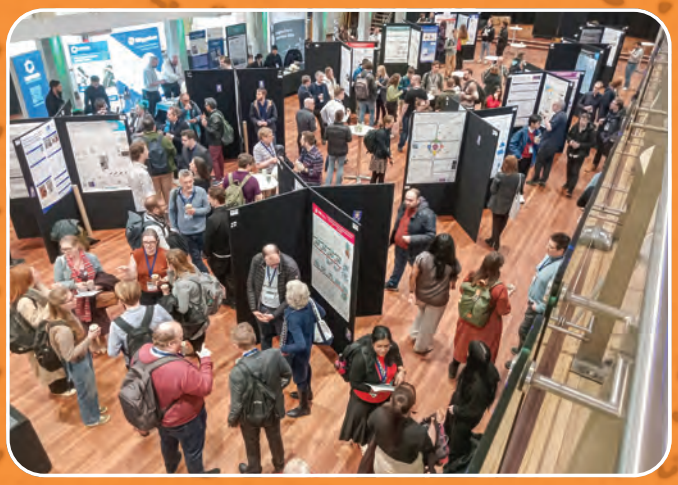
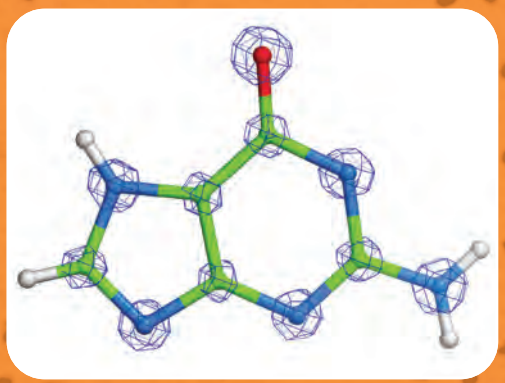
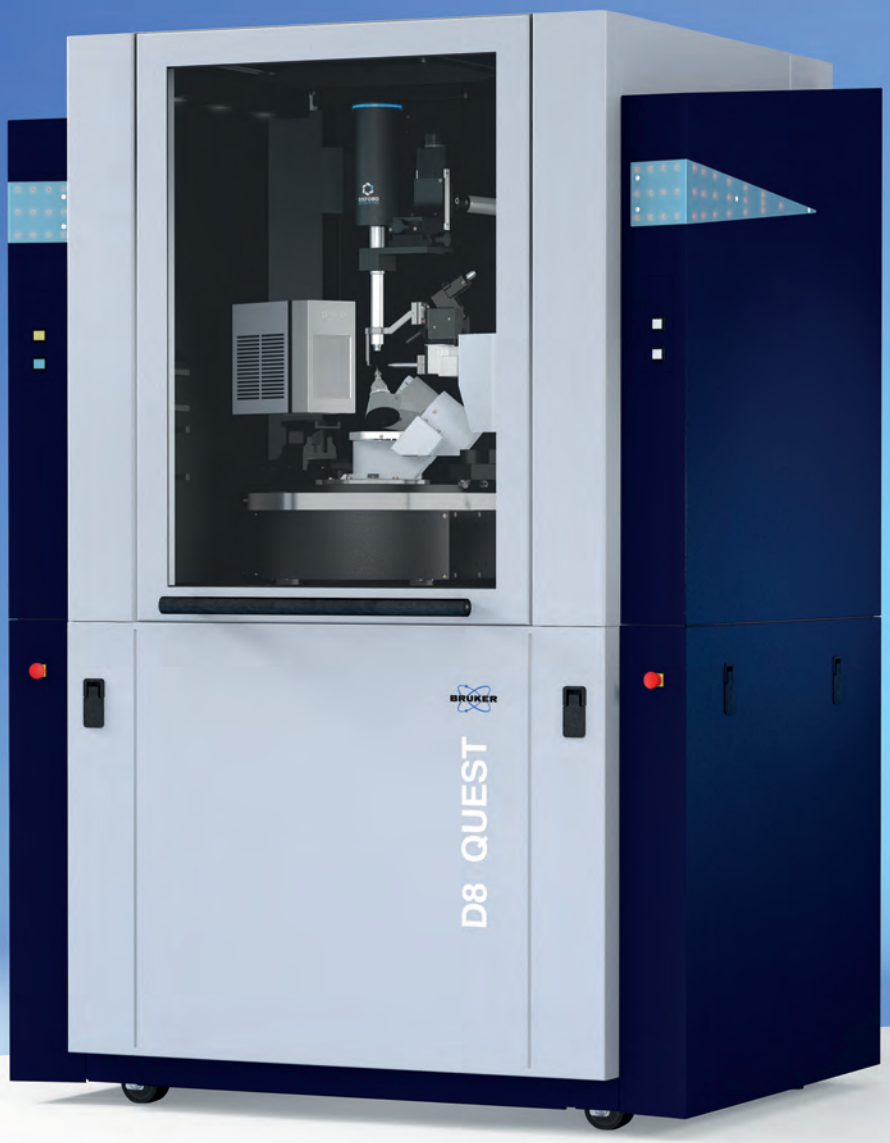




Spring Meeting 2026



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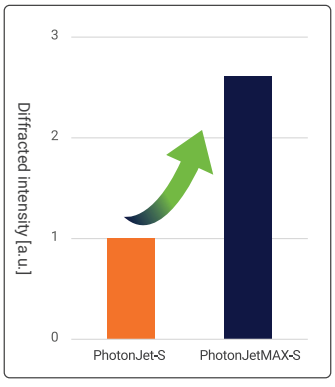

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This month's cover:

Our front page is dominated by scenes from the 2026 Spring Meeting in Leeds.

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From the President

THE Spring Meeting is a great event for many reasons, for me perhaps the most important is the combination of the reporting of new science and the renewal in strength of the community. For much of the year the Groups are busy with their own meetings and members focus on their particular specialities.

But just before Easter every year a good fraction of the membership come together as a cross-disciplinary network to exchange ideas and knowledge (and those who couldn't attend peruse the reports in the subsequent CN issues!). Across the programme, from the Early Stage Crystallographers' Group satellite meeting through to the closing prize sessions, we saw a great demonstration of crystallography as a technically exacting and groundbreaking science, but at the same time a very human enterprise. On that note, the networking over tea and coffee, the conference dinner and the cèilidh were hugely enjoyable as always, thanks to all attendees for your enthusiastic participation, particularly in the latter! There were many scientific highlights, and I hope you enjoy finding out more in the reports in this issue. I will just take my chance to plug one of them by happily cramming invertebrates into this column – I recommend a web search for jumping bristletails only after reading the BCA Prize Lecture report later on in this issue for some context!

Many thanks are due to all involved in organising such an excellent meeting and making it such a success. In particular, I'd like to recognise **Lewis Owen** (Sheffield) as Programme Chair, **Suzanna Ward** (CCDC) as Vice-President, and HG3 for their work in creating the programme and making the meeting run so smoothly, especially given this year's change in format. I'd also to thank all of the exhibitors for giving us a chance to engage with the latest developments, and the sponsors for helping to make the meeting possible and supporting attendance via bursaries.

I have a few changes in Council to announce: Suzanna Ward is ending her second Vice-Presidential term a year early due to the pressure of other commitments and Claire Naylor's two terms of office have also come to an end. Heartfelt thanks to Suzanna and Claire for their friendly, super-efficient and dedicated service and leadership. Jere Tidey has kindly agreed to take over as acting Vice-President until elections take place later this year, with Suzanna swapping into his Ordinary Member role. I'd like to welcome **Mark Montgomery** (Syngenta) who joins Council as Treasurer, **Anuradha Pallipurath** (Leeds) who is co-opted to Council to prepare a bid for IUCr2038 and **Laksha Parameswaran** (Bruker) for taking on the role of EDI co-opted member to formalise strategy and best practice on this front. We also have new Group Representatives in **Rachael Wilkinson** (Leicester) for the BCG and **Daniel Rainer** (NCS) for the ESCG, and an extra welcome to Daniel also as ESCG Chair.

Looking forward to next year, I can pass on the good news that **Jon Agirre** (York) will be next year's Programme Chair, so please give him your support by contributing ideas and speakers as invitations to do so come through your Group committees. Also, in a spatially unrelated development, I can announce that we will be moving to York for our next Spring Meeting, 22nd-24th March 2027. Please put the dates in your diary!

Alex Gibbs,
St Andrews

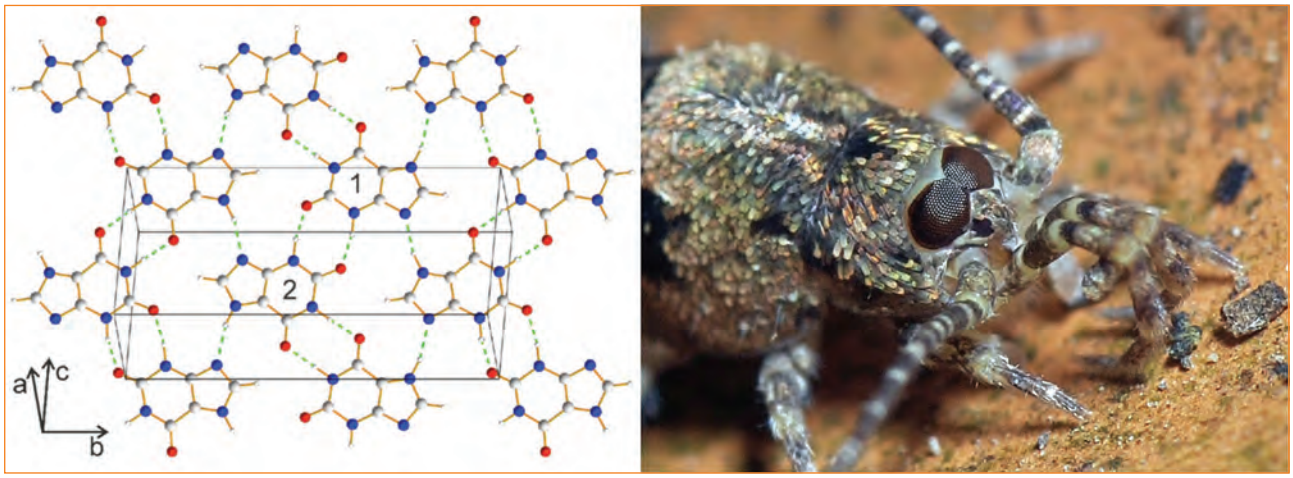

*Figure 1 (left) Structure of synthetic xanthine (Hughes et al., (2025). **Crystal Growth & Design 25**, 895-902), (right) a biogenic form in jumping bristletail eyes (Christophe Quintin, via Wikipedia, CC BY-SA 4.0).*

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

From the Editor

WE begin this issue with the ABBF bursary winner reports from the truly excellent Spring Meeting in Leeds. A very big thank you to the 2026 programme chair Lewis Owen (Leeds) for masterminding such an outstanding event. We follow this up with a report by Judith Howard (Durham) on the very sad yet fascinating George Sheldrick memorial session which was organised in honour of George's life and very considerable work. We then have a series of short reports on the BCA Prize Lecture, the Lonsdale Lecture, the Parkin Lecture and the two Early Career Prize lectures, and we follow these up with a detailed report on the BSG sessions. I regret that I ran out of time in preparing the reports on the other sessions (CCG, ESCG, IG, PCG) but I promise these will appear in the next issue which comes out over the Summer break. I must take this opportunity to thank the many chairs and others who very kindly provided session reports and lecture notes this year. We also have our regular sections on News from the CCDC, Meetings of Interest and Puzzle Corner as well as Letters to the Editor.

I decided to concentrate on making a picture for this editorial and it is shown below. For some reason, I was recently reminded (probably by the Spring Meeting) of an occasion around 40 years ago when I asked my long-suffering PhD supervisor (a protein crystallographer) if I could solve a small molecule structure because I wanted to see how it was done! Anyway, my request was politely declined but the interest remained and it is something that I have been following up on only recently. Hence, I decided to make a few pictures of molecules which can be solved from data available freely in Crystallography Open Database (COD) [1], one of which is shown below and others can be found later on in this issue.

The central picture in the collage shows the structure of the compound CPHPC which was developed for treatment of amyloid disease [2]. Its structure was originally determined by the NCS in Southampton at 0.77 Å resolution back in the early twenty-teens and is publicly available with COD-ID 2310142. After extracting the reflection data, I was able to solve the structure with Richard Cooper's excellent GUI for CRYSTALS [3] using the Superflip direct methods program [4], so maybe I can now call myself a self-taught chemical crystallographer! Incidentally, the website for Superflip mentions that it uses several algorithms which the protein community have developed, so perhaps we are coming full circle here. Although the CRYSTALS GUI is written for Windows, I had no trouble installing and running it on Linux with Wine and a few auxiliary programs that the shoot-me-down gamers have developed. Incidentally, another windows- or MAC-only program which I often use for making electron density pictures and other figures, CueMol [5], runs perfectly well on Linux via Wine, too.

More importantly, I must raise my hat to the expertise of the NCS team since I was not able to beat their refinement *R*-factor. On looking at the refinement statistics, I was very interested to see that CRYSTALS uses *reversals* (the percentage of parameter shifts which change sign) to help decide when the refinement has converged. That is something which I had not thought of, or remember coming across, before. I think the idea is that as the refinement converges, the atoms stop moving in a consistent direction from one cycle to the next and begin to hop backwards and forwards about their preferred positions in steps of ever decreasing size. Hence the percentage of parameter shifts which reverse direction in successive cycles increases to around 50 % as the process converges. I have to confess that this explanation comes largely from Google's AI overview but do remember that I am only a beginner! I should also mention that my own speculative thoughts on geometric refinement are touched on in an article which appears towards the end of this issue on maintaining planarity in modelled structures.

The remaining crystal pictures in the collage were taken by the editor at the Sedgwick Museum of Earth Sciences in Cambridge and are, starting from the green crystal forest at the top, Pyromorphite from Cornwall and then, in clockwise order, Amethyst (SiO2) from Brazil (purple), Wolfenite (PbMoO4) from Arizona (orange) and clear yellow sulphur crystals on calcite from Sicily. I regret that I did not make a note of what the white crystals on the left border are, but feel free to let me know. I think its fair to say that this collage is a truly cosmopolitan one.

Jon Cooper,
UCL

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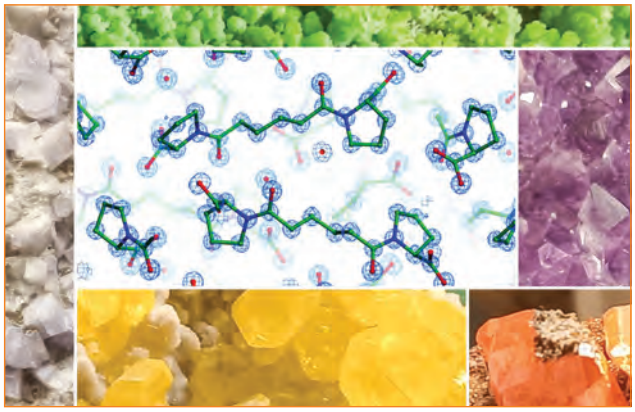


A crystallographer's collage.

2026 Spring Meeting reports

Arnold Beevers Bursary Fund awardee reports

Rebecca Clulow, Uppsala

The British Crystallographic Association spring meeting took place at the University of Leeds from the 30th March to the 1st April this year. The first day of the meeting was predominantly devoted to a satellite meeting for early career scientists with the main meeting kicking off in the evening with the Lonsdale lecture which was given this year by **Samantha Chong** (Liverpool). There were plenaries from all four of the major groups of the BCA (BSG, CCG, PCG and IG) of particular interest for me was the PCG plenary which was given by **Abbie McLaughlin** (Aberdeen) who presented her work on ion conductors. There were also a range of parallel sessions covering a broad range of topics with PCG sessions on functional, energy and quantum materials as well as an open session and a workshop/seminar on pairwise distribution function (PDF) analysis given by **Dave Keen** (ISIS). The early career prizes for the CCG and PCG were both presented at the meeting to **Sam Lewis** (Cardiff/DLS) and **Adam Sapnik** (Copenhagen) respectively. Their prize lectures gave a great insight and introduction to their work and contributions to the field. The conference also provided plenty of time and opportunity to network with other researchers working within crystallography. Poster sessions, lunches and coffee breaks allowed for a more relaxed social setting for discussions, culminating in a conference dinner and party. All in all, it was an informative and highly enjoyable few days and I hope to be back soon!

Ben Tragheim, Sheffield

The BCA Spring Meeting has always been a highlight conference of mine throughout the time I attended as a PhD student, and that pleasingly remains the same attending as a postdoctoral research associate this year. I am always so intrigued to hear about the latest crystallographic research arising from each of the special interest groups, but a particular highlight of mine from this year comes from the PCG Energy Materials session.

This session, chaired by **Ashok Menon** (Warwick), started off with a fascinating keynote talk delivered by **Julia Payne** (St Andrews) under the title "Exploring structure-property relationships in organic inorganic metal halides for optoelectronic applications." Julia introduced her talk covering the necessity to discover new materials for energy applications and the importance in understanding their structure/property changes under operational conditions. A large number of case studies of organic inorganic metal halides were explored, closely related to the canonical $CH_3NH_3PbI_3$ perovskites but instead adopting layered-derivative structures of the archetypal perovskite octahedral moiety. Compositionally, notable systems of interest included $MXDBi(I_{5-x}Br_x)_5$, $[H_3N(CH_2)_5NH_3]PbBr_4$ and Cs_4MBiX_{10} (M = Ga, Fe, In; X = I, Br). In these studies, the structure-properties relationships were resolved using a range of complementary techniques including diffraction, photoelectron emission and UV-vis spectroscopies and computational modelling by collaborators. Chemical effects such as intercalation of Br_2 and the role of the organic cation were explored, where ultimately device fabrication of solar cells was performed with preliminary, but nicely promising results, obtained.

Next in the session was **Stephen Hull** (ISIS) who gave an intriguing talk on "Developments for neutron powder diffraction studies of energy materials." Stephen's talk opened up with the importance of using neutrons to measure the presence of lighter elements (e.g. Li^+) in Li-battery-based materials, while also discussing limitations and practicalities of this. However, the main focus of the talk involved contexts of solid oxide fuel cells, especially those based on CeO_2. A highlighted study involved the use of neutron total scattering and PDF techniques, under high temperatures and partial oxygen pressures, to resolve the structural responses in Gd- and Nd-doped CeO_2 compositions. Through reverse Monte Carlo analysis methods, corroborated by computational energy calculations, the different correlations of oxygen vacancy pairs and cation-cation pairs were ascertained and used to rationalise bulk conducting properties. This echoed that recent advancements in ancillary equipment for neutron diffraction studies allow energy materials to be studied in conditions as close to their operational state as possible.

The following talk was a particular highlight of mine as **Erin Carroll** (Sheffield), a PhD student in the same group as myself, gave a great talk on "The importance of neutron diffraction for understanding structure-property relationships in A-site deficient $NaNbO_3$." Erin compellingly explained the need for Pb-free ceramics for capacitors and dielectrics in pulsed power and power electronic, whereby $NaNbO_3$-based ceramics may be the desired candidate. The system of interest studied was the solid solution $Na_{1-3x}Nd_xNbO_3$ where dielectric permittivity data indicated a dramatic change in electrical state with fine doping increments, but laboratory X-ray diffraction techniques were not sensitive enough to resolve accurate structural transformations causing this. Erin then presented how only by using neutron total scattering and powder diffraction techniques it became possible to identify correct structural polymorphs and the presence of diffuse scattering, which was then speculated to be the cause of changes in the observed ionic conduction behaviour.

Finally, **James Steele** (Cambridge), who recently completed their PhD, gave a stimulating and coherent talk on "Sodium vacancy, nickel charge and orbital order: structural evolution in electrochemically desodiated Na_xNiO_2." The central question to be answered was elucidating the relationship between structure and electrochemical properties in Na_xNiO_2, whereupon James explored this through impressive operando synchrotron X-ray and neutron powder diffraction techniques. The observed structural changes induced were Na^+/vacancy ordering, Ni charge ordering, and the degree of Jahn-Teller distortions occurring within Na_xNiO_2, and these were used to rationalise electrochemical properties.

It was an absolute delight to be able to attend this year's meeting and I look forward to attending again in the future!

George Sheldrick memorial session

THIS special session was held on Tuesday 31st March 2026 (13:30-15:00) to commemorate George, titled *"George Sheldrick: his life and impact"* and was chaired by Judith Howard, FRS (Durham). Before and after the session, video tributes by members of the crystallography community, collected by the ECA, were played. These can be viewed at https://ecanews.org/blog/2025/09/24/remembering-george-sheldrick/.

The keynote lecture entitled "Sheldrick the legend, George the man" was given by **Bill Clegg** (Newcastle). Bill was deliberately wearing a red jumper as a nod to George and he noted that while he and George worked together at various points over the years, Bill was never actually supervised by George, though many people think he was.

Bill started with a brief mention of some of George's scientific achievements but mainly focussed on George's life in general and how Bill's had intersected with George's on various occasions. This also highlighted some of the parallels between the paths the two had taken and shared many personal memories and photos. Thanks was given to George's family for providing and allowing him to use family photos in his talk.

The clear message was that while George was a brilliant scientist, it was his personality that most impressed people and drew them to him. Many examples were given of George being humble and inclusive, including that George didn't insist on being an author on group papers, as long as his contribution was appropriately acknowledged, and that some of George's comments that Bill remembers well are "I take good ideas from others and make them work well" and "Bill didn't work for me, he worked with me."

Trying to give a clear sense of the man Bill had known, George's sense of humour was mentioned at multiple points. With some examples including jokes in the codes used for SHELX, such as EEES, ISOR, WIGL and PLOP and the sharing of an anecdote about George being expected to teach crystallography in German immediately upon moving to Germany and him telling the students, in German, "my mother tongue is not German, my mother tongue is Fortran."

All of these and the many other memories that Bill shared, gave the audience, which contained many people who had worked with or interacted with George but also many younger crystallographers who had never the opportunity to meet George, a unique and empathetic insight into the man behind the legend. This resulted in a long applause, following the talk, both in honour of George and in appreciation of Bill's candour.

The second speaker was **Dietmar Stalke** (George-August-Universität Göttingen) giving a talk titled "GMS as a lecturer and supervisor – the somewhat less familiar side." He spoke about George teaching in German and how he still found ways for his sense of humour to come through, such as making up his own symmetry key, for space group tables, including balding heads and smiley faces. Dietmar, like many others, started to work with George while doing his teacher training. While some did go on to be teachers, Dietmar realised he was more interested in research through working with George. They collaborated all the way to the end of Dietmar's Habilitation. Later they became colleagues at Göttingen. George paid for Dietmar's postdoc (which was not usual in the German system) and Dietmar always felt like George treated him as a colleague rather than a supervisee, allowing Dietmar to drive the direction of his own research. While he mentioned that George could spot and solve issues with structures very quickly, and George's intelligence was alluded to throughout, the focus of the talk highlighted George's humour, inclusivity and kindness, echoing George's own priorities.

Eleanor Dodson (York) was the third speaker with a talk titled "George's Protein Epiphany." She acknowledged that she didn't know George as personally as the previous two speakers, but she knew him predominately as a colleague/researcher and in this way, he still left a large impression. Eleanor reminisced about how George enjoyed thinking about the hitches and his nostrils would flare when a new challenge had been presented, due to his excitement. She spoke about how he realised that the ShelX refinement could work for proteins, with a few adjustments and different restraints needing to be considered for proteins.

Eleanor recalled that at an IUCr conference, after someone had spoken about how ShelX would never work for proteins and couldn't deal with more than 1000 atom structures, when it was George's turn to speak, he announced they had indeed solved a structure with 1001 atoms. It is the only time she remembers him being smug.

Eleanor finished her talk by postulating that the reason crystallographers generally seem to be nice people could be because we understand that we are all dependent on each other's areas of expertise and hence the importance of collaboration.

The final talk "From SHELX to Olex2 and beyond – evolving George's legacy for the next generation of crystallography" was given by **Horst Puschmann** (OlexSys and Durham). Horst showed the history of the technique from the discovery of X-rays, through their interaction with crystals, the Bragg equation, the development of ShelX, to quantum crystallography and Hirshfeld atom refinement (HAR). He highlighted how the development of computers has kept pace with crystallography experiment development and keeps allowing us to explore further than we could previously.

Taking a leaf out of George's book, of taking a good idea and improving on it, Olex2 started by making a GUI (graphical user interface) for George's program to help visualise the programming language. (George did not have any issues with this, he understood the value of collaboration). Horst showed an example of what incorrectly

assigned atoms looked like in the text and in the visual software.

Horst remembers George giving little ‘puzzles’, asking “can you do…” to help identify what was lacking, to allow improvement. He also shared a memory of once working on a problem when George walked past, looked, said “that’s wrong” and carried on walking.

As we start to move beyond Sheldrick in the crystallography timeline, and likely away from relying on the independent atom model, to the more common use of non-spherical models (in the same way we once moved from isotropic to anisotropic atom refinement), we remember the work that has led us to this point. George’s contributions and keenness to collaborate have given us good foundations and precedence for continued collaborative development and innovation.

From all the talks, it was very clear how much of an impact George has made on the global community, not just because of his science but because of who he was as a person. The chair closed by thanking all speakers for sharing their memories about George in such a personal, amusing and interesting manner.

There will be further sessions in George’s memory at the IUCr this summer in Calgary.

Judith Howard FRS,
Durham

Left to right: ***Horst Puschmann,*** *(OlexSys and Durham),* ***Judith Howard*** *(Durham, chair),* ***Eleanor Dodson*** *(York),* ***Bill Clegg*** *(Newcastle) and* ***Dietmar Stalke*** *(Göttingen).*

BCA Prize Lecture

THE 2026 BCA Prize lecture was chaired by Alex Gibbs (St Andrews) and was given by Kenneth Harris (Cardiff) who spoke on the subject of "Advancing structural understanding of crystalline materials through multi-technique synergy." The speaker introduced the range of techniques encompassing his work including powder diffraction and solid state NMR (ssNMR) and made the interesting observation that it was only in the early 90s that the technology allowed the first organic compound to have its structure solved by powder diffraction. Peak overlap is the main problem due to the relatively large unit cell size of organics and is compounded by low symmetry.

The breakthrough in this case was the advent of direct space recycling in which random trial structures are generated and the powder patterns calculated for comparison with the observed data. This allows the model to be modified and pattern recalculated so that the whole process can then be repeated as many times as needed for convergence. The process relied on breaking the problem down to the minimum number of independent variables (in this case 12) by making assumptions about the rigidity of certain groups in the structure. The speaker then moved on to solid state grinding experiments which can generate mixed compound crystals and these can be analysed by a range of techniques such as 3D-ED, density functional theory (DFT) calculations, ssNMR, vibrational spectroscopy and thermal analysis. The use of ssNMR in a number of cases confirmed the crystal structure analysis. The speaker moved on to cover X-ray photoelectron spectroscopy, ^{13}C-NMR and Rietveld refinement of powder structures. The speaker gave an example of ibuprofen co-crystallised with proline which was initially analysed by DFT geometry optimisation followed by ssNMR. Another example presented was that of alloxazine and its interconversion to isoalloxazine tautomers which was explored using computational approaches based on powder, DFT and ssNMR analyses. Analyses of the biological molecules L-tyrosine, vitamin B_{12} and xanthine, which crystallises in kidney and bladder stones, were given along with neutron diffraction studies of ammonium cyanate which showed temperature dependent movement of deuterons in the crystal. The speak concluded by describing some contemporary studies using X-ray birefringence imaging with collaborators at DLS which allows anisotropy within the crystal to be visualised.

*BCA prize lecturer **Kenneth Harris** (Cardiff) with **Alex Gibbs** (St Andrews).*

Lonsdale Lecture

THE 2026 Lonsdale Lecture was chaired by Tom Hitchings (Royal Society of Chemistry) and was given by Samantha Chong (Liverpool) whose talk was entitled "Adventures in diffraction and data. How I learned to stop worrying and love our future AI overlords."

Samantha began by paying tribute to the life and work of Kathleen Lonsdale who was both a pioneering crystallographer and social reformer as well as someone who was imprisoned for their pacifist beliefs during WW2. The speaker's own research programme covers a wide range of topics from powder diffraction to crystal engineering, MOFs and computational crystallography. Samantha outlined the importance of breakthroughs in the application of AI to structural studies such as AlphaFold for the macromolecular community and the chemical large language model (ChemLLM) which excels at predicting synthetic pathways as well as molecular structures. The speaker outlined the role and importance of models in crystallography as well as their limitations before moving on to the development of AI models for digitally-planned syntheses and laboratory automation. With great skill, Samantha painted a big picture of the growing importance of AI in our work as well as keeping her own very important contributions to the study functional organic crystals and the development of methods for accelerated materials discovery in sight.

Parkin Lecture

THE first of the prize lectures awarded at this year's ESCG Satellite Meeting was that of the Parkin Lecture, given by Georgia Orton (Birmingham). The Parkin Lecture was established by the ESCG in honour of the late Dr Andrew Parkin, his contributions to the ESCG and his achievements as both a scientist and a teacher. This Prize Lecture is awarded to an early-stage crystallographer to recognise their outstanding contributions beyond their research, including scientific communication, outreach, education and science policy.

The lecture which was chaired by **Ben Tragheim** (Sheffield) was held just before the start of the main meeting and so was attended by many of those arriving in time for the Lonsdale Lecture. Georgia's talk was entitled "'Is this a crystal?' And other conversation starters" and started off with timely quotes from various academics that described Andrew Parkin well. Along the lines of her title talk, she shared some favourite quotes from conversations across her academic career to date including "crystals have corners", "you don't know what will diffract until you shoot X-rays at it" and concluded with the message that perhaps we should always "treat your crystals with TLC." Georgia then followed up by taking the audience on a journey through her crystallographic career to date which included completing her undergraduate degree at Sheffield, PhD at King College London and finally post doctoral positions at Nottingham and Birmingham leading into her current role at Birmingham. Georgia gave many examples of the different kinds of work she has been involved in, most of which involved the study of metal organic framework (MOF)-based systems, highlighting the importance of fostering collaborations as an early career researcher. Georgia then illustrated the large part she played in organising various workshops and bringing master's students to regular access beam time experiments at DLS.

The speaker described her career as a synthetic chemist working on biomimetics before transitioning to crystallography as well as emphasising her interest in the supramolecular effects of confinement. The speaker covered indium and palladium MOF structures and the associated supramolecular chemistry as well as reactions in the single crystal. Techniques for accessing supramolecular architectures such as self-assembling helical lanthanide compounds were described with a practical emphasis on persuading colleagues in the laboratory context to get on and do crystallography themselves! Pore-first framework materials and the incorporation of flexible ligands thus yielding different MOF structures and allowing the porosity of a material to be tuneable form an important part of the speaker's work. The speaker concluded by reflecting on the achievements of the late Patrick Doheny, also from the Birmingham group, who very sadly passed away last year. This was an incredibly enjoyable Parkin Lecture given by Georgia, and we at the ESCG will look forward to next year's lecture too!

Early Career Prize Lectures

THE CCG Early Career Prize Lecture was given by Sam Lewis (European XFEL) and was entitled "Exploring small molecule serial photocrystallography." The prize which was sponsored by CCDC was presented to the speaker by Suzanna Ward (CCDC) in a session which was chaired by Hamish Yeung (Birmingham). The speaker summarised his background in ultrafast time-resolved crystallographic studies and compared the use of synchrotrons and free electron lasers in such work as well as emphasising the *collection before destruction* philosophy of serial crystallography.

Sam described the range of experimental work which can be undertaken with the XFE instrument at the EuroXFEL. The speaker described the development of the small rotative fixed target approach to overcome difficulties in indexing serial diffraction data and reflection partiality in chemical crystallographic work. Photolytic reaction triggering has been successful but it requires the use of smaller crystals in order to get uniform transmission of the light through the crystals and this has required some methods development in the crystallisation department. The speaker described studies of the α and β polymorphs of trans-cinnamic acid by reverse antisolvent crystallisation. This project required work to improve the indexing efficiency during data processing but ultimately allowed the photolytic transition to the cyclobutane ring to be monitored by the β-angle of indexed datasets.

During his PhD studies at Cardiff University and Diamond Light Source synchrotron, the speaker was principally involved in the development of serial photocrystallographic methods and has demonstrated considerable independence and innovation in subsequent work in this field. Sam gave an interesting and engaging lecture that introduced the technique of serial synchrotron crystallography, its advantages and challenges, and the recent developments for small molecule photocrystallography on fixed targets that he has led at Diamond beamline I19. Improvements include small phi rotations to improve completeness and new data collection, processing and analysis capabilities, which he demonstrated through some very exciting results! The Prize was generously supported by the CCDC again this year, and it was a pleasure to welcome Suzanna Ward from the CCDC to present it to Sam at the Early Career Prize Lecture session.

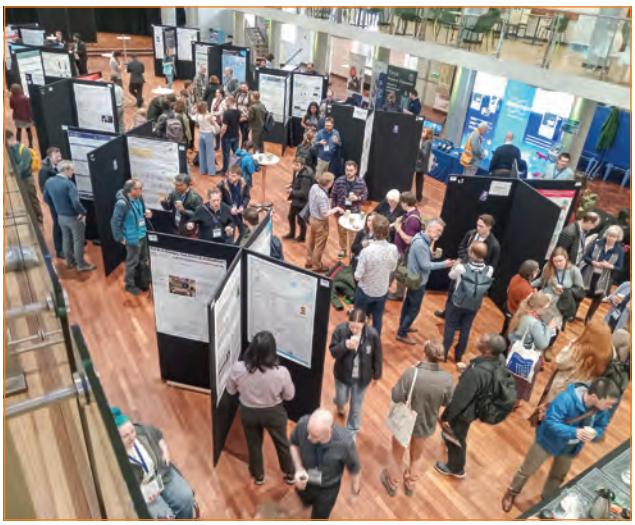
***Hamish Yeung** (Birmingham), CCG Early Career Prize Lecturer **Sam Lewis** (XFEL) and **Suzanna Ward** (CCDC).*

The PCG Early Career Prize Lecture was then delivered by **Adam Sapnik** (Copenhagen) in a session which was chaired by **Lewis Owen** (Sheffield). Adam's lecture was entitled "Disorder, dynamics and DNA" and covered his own background in structural studies which currently focus on total scattering and PDFs in the analysis of nanoclusters formed by 5 to 10 atoms. Amongst the many things described, the speaker explained how PDF peak positions yield inter-atomic distances and the areas under the peaks reveal the coordination number. A wide range of topics was covered, from nanoclusters to MOFs, both crystalline and amorphous, as well as approaches for linking nanoclusters, kinetic bias and defect engineering. Studies included an example of an iron cluster material for which PDF analysis and structure refinement revealed metastable nodes and movements of the iron out of its coordination plane which correlated with enhanced absorption properties. The speaker then described scattering studies of the DNA sequence AGCT which, in the presence of silver nitrate has fluorescence properties that were ultimately rationalised by the final model of the structure. The speaker then moved on to describe XFEL studies and the requirement to tilt the detector in order to get high resolution powder rings, as well as analyses of silver behenate, metallic glass and water.

Jon Cooper, UCL
Evie Ladbrook, Warwick
Mark Montgomery, Syngenta
Ben Tragheim, Sheffield
Hamish Yeung, Birmingham

Scenes from the 2026 BCA Spring Meeting in Leeds.


CCDC



Prize winners

Congratulations to the following spring meeting attendees who were awarded poster or presentation prizes.

Prize	Awardee
RSC (CrystEngComm) CCG prize	**Alex Johnson** (Newcastle)
RSC (CrystEngComm) CCG prize	**Lewis Jackson** (Kent)
ACS publications prize	**Stephen Carr** (Oxford)
PCG poster prize 1	**Nicola Kelly** (Cambridge)
PCG poster prize 2	**James Steele** (Cambridge)
IUCr prize	**Tingting Wang** (Imperial College London)
ACA structural dynamics prize	**Elina Elvelo** (Stockholm)
IG poster prize	**Ben Tragheim** (Sheffield)
David Blow poster prize (BSG)	**Charlotte Hunter** (Durham)
ESCG – poster prize	**Giovanna Barrionuevo Martins** (Newcastle)
ESCG – lecture prize	**Eleanor Keil** (Southampton)
Durward Cruickshank prize	**David Coventry** (Edinburgh)

***Alex Johnson** (Newcastle) and **Lewis Jackson** (Kent) receiving their CCG prizes from **Thomas Hitchings** (RSC).*

***Stephen Carr** (Oxford) receiving the ACS prize from **Alex Gibbs** (St Andrews) with **Nicola Kelly** (Cambridge) and **James Steele** (Cambridge) receiving their PCG poster prizes from **Gwilherm Nénert** (Malvern Panalytical).*

The IUCr prize was awarded to **Tingting Wang** (Imperial College London) and the ACA Structural Dynamics prize to **Elina Elvelo** (Stockholm) by **Alex Gibbs** (St Andrews).

Photographs: **Natalie Pridmore** (Durham).

BSG sessions at the BCA Spring Meeting

THE BSG Plenary lecture was delivered on Tuesday morning by Basil Greber (ICR, London), who described his work on the CDK-activating kinase (CAK) complex. The session was chaired by Natalie Tatum (Newcastle) and the speaker's title was "Mechanistic insight into the function of the human CDK-activating kinase."

The speaker began by introducing cryo-EM and the importance of technical developments in this field as well as the implications for structure-based drug design in therapeutic applications. The speaker moved on to substrate recognition and regulation in transcriptional activation and nucleotide excision repair (NER) of DNA, as effected by cyclin-dependent kinases (CDK) – enzymes which are activated by phosphorylation of the "T loop" allowing a cell-cycle protein, or cyclin, to bind. The subject of the lecture, CAK, is itself a CDK complex formed by CDK7 bound to cyclin H and an activator protein MAT1, which is known to trigger early events in the cell cycle by binding to a transcription factor. Thus, one of the roles of CDK7 is the initiation of transcription by RNA polymerase and the fact that there are a large number of CDK7 homologues has given problems in clinical trials of inhibitors. The CAK complex is key to the phosphorylation of other CDKs, such as CDK2, on their conserved regulatory activation segment or T loop. Engineering CDKs with swapped T loops causes their activation properties to be exchanged.

By determining cryo-EM structures of CAK bound to CDK2, CDK2-cyclin A, CDK1-cyclin B and CDK11 at around 2.5 Å resolution, the speaker described the insights gained into a potentially generalised mechanism of substrate recognition which had not been clearly seen until this work. In particular, it was known that CAK-mediated activation of CDK2 was more efficient than the activation of the cyclin A-bound CDK2 and the structures determined by the speaker give us some indication as to why. When CDK2 is complexed with cyclin A for CAK engagement, the activation segment (T loop) is 13 Å – too far – from the γ-phosphate of ATP for it to be transferred to the target amino acid. Having been able to obtain high resolution structures of the CAK complex – a target of great interest for drug development – the group were then able to analyse many inhibitor-bound structures to further elucidate the selectivity (or lack thereof) of some CDK inhibitors. This was achieved partly by engineering the protein to remove flexible regions and thereby improve grid quality as well as with heroic amounts of microscope time, wherein a total of 24 grids were screened on a Titan Glacios (ThermoFisher), each for 1h (400 – 600 movies), to determine preliminary 2D classes and assess any orientation bias. A second pre-screen consisting of 4 hour collections (1600 – 1800 movies) was used to obtain sufficient data to determine low-resolution structures and confirm the integrity of the complexes. However, the speaker noted that this step could have been omitted as all "positive" grids at the first triaging step yielded high resolution structures on fuller 10 hour data collections (5000 movies) with a Titan Krios G4. Ultimately 12 high resolution (1.9 – 2 Å) cryo-EM structures of bound drugs were obtained, demonstrating the importance of water networks in specificity and selectivity. Differences in the conformations of drugs bound to CDK2 and CDK7 led to further studies aimed at discovering compounds with selectivity for CDK7 due to its importance in cancer. Together, these examples demonstrated the molecular insights into function and drug design possible with high resolution cryo-EM on a target recalcitrant to crystallisation.

*The BSG Plenary Lecturer **Basil Greber** (ICR, London) with session chair **Natalie Tatum** (Newcastle).*

The first BSG session was also on the subject of "Structure-based drug discovery" and was chaired by **Daren Fearon** (DLS) and **Blake Balcomb** (DLS). The keynote speaker was **Chris Cooper** (Surrey) whose title was "From structure determination to structure enablement: re-engineering protein science, platforms and AI to power the next generation of SBDD." The speaker opened the session by describing how structural biology and SBDD have evolved from niche areas into core components of modern drug discovery. He highlighted key technological drivers of this shift, including XFEL, cryo-EM, improved crystallography, and AI/ML tools such as AlphaFold and ligand co-folding methods. Despite this progress, he stressed that producing stable, tractable protein reagents – especially for membrane proteins and dynamic complexes – remains the major bottleneck limiting structural and fragment-based

approaches. Chris noted that emerging solutions such as improved expression systems, AI-designed binders, cell-free synthesis, protein engineering, and biophysical optimisation are beginning to ease these constraints. However, AI still cannot reliably predict protein behaviour, stability or conformational dynamics. He concluded that the future of SBDD lies in integrated, closed-loop pipelines combining structural methods with advanced protein science, engineering, analytics and AI-guided design.

This was followed by three invited speakers. Firstly, a presentation entitled "Crystallographic fragment screening and fragment progression for rational design of novel herbicides against fatty acid thioesterase A" was given by **Ekaterina Kot** (Oxford). This enzyme which is involved in fatty acid synthesis is a promising but underexplored target for tackling herbicide resistance and has the advantage of not being present in animals. To identify potential novel herbicidal compounds, the speaker conducted an XChem crystallographic fragment screen on *Arabidopsis thaliana* FatA, identifying 141 hits across three key sites, with several fragments inducing major conformational changes that narrowed the substrate access channel. The DSI Poised and Enamine Essential screens were used and 64 fragments which were found to bind were tested in an assay. Notably, the top ten hits showed measurable enzymatic potency, which is impressive given that fragments are typically inherently weak binders. Elaboration of one fragment by chemically growing, linking and merging yielded 60 good analogues, one of which improved its affinity 220-fold from ~20 μM to ~90 nM in a single step. Further fragment-merging strategies and SAR studies (structure-activity relationships), along with numerous crystal structures, produced additional sub-micromolar inhibitors, advancing the development of novel herbicides to combat resistance.

We then had a presentation entitled "Towards resolving the binding of anti-cancer drugs to tubulin using 4th-generation synchrotron and XFEL sources" from **Shourav Saha** (Paul Scherrer Institute). The speaker presented his work on using time-resolved crystallography to capture transient binding poses of complex ligands at the colchicine site of tubulin. Shourav discussed the lock-and-key and induced fit models of substrate- and ligand-binding as well as structural dynamics and the application of photoswitchable compounds in experimental time-resolved work. The speaker described work at ID29 (ESRF) on the binding of azo-combrestatin A4 and other colchicine analogues to tubulin. The azo compound can be mixed with a slurry of tubulin α/β dimer crystals and binding is observed to occur only upon illumination, thus demonstrating that this is a photoswitchable binding system. Advances in 4th generation synchrotrons and XFELs, using mix and inject as well as pump probe methods, now allow visualisation of intermediate states across multiple timescales. Shourav highlighted recent progress including cryotrapping with the Spitrobot as well as mix and inject studies at DLS, helping link transient structures to binding kinetics and deepen understanding of drug-tubulin interactions. By using acoustic droplet ejection of colchicine onto grids of tubulin crystals, cryotrapping demonstrated progressive binding of the ligand over a 60 second timescale at I04 (DLS). The speaker proposed a two-step model for binding of colchicine to the dimer and discussed the unique binding characteristics for colchicine derivatives. Incidentally, colchicine happens to be an anti-inflammatory compound of significant medical value in the treatment of gout!

Jasmin Aschenbrenner (DLS) closed the session with an overview of the OpenBind consortium entitled "OpenBind: changing the game in structural biology and properly enabling AI/ML in drug design." The speaker outlined the lengthy drug discovery process covering target identification, screening and compound discovery as well as preclinical studies which are followed by the various phases of clinical trials that are required to achieve new drug approval. Given the success of AI in predicting protein 3D structures, it would seem to have significant potential in replacing, or at least accelerating, many of the drug discovery steps. The speaker

*Speakers and chairs in the BSG session on "Structure-based drug design." **Daren Fearon** (DLS, chair), **Jasmin Aschenbrenner** (DLS), **Chris Cooper** (Surrey), **Ekaterina Kot** (Oxford), **Shourav Saha** (Paul Scherrer Institute) and **Blake Balcomb** (DLS, chair).*

touched on the Boltz2 cofolding model for estimating small molecule – protein binding affinities with great computational efficiency. Jasmin described some of the many successes of the XChem platform at DLS, including the Covid Moonshot Consortium which led to a preclinical candidate drug. The speaker explained that despite major advances in structural biology, AI-driven drug design is still limited by the lack of publicly available paired structure and affinity data. The OpenBind project aims to fill this gap by creating a large, openly accessible dataset of protein-ligand structure/affinity pairs derived from the XChem screening programme for machine learning. This resource is intended to unlock next-generation predictive models and drive a major leap forward in structure-based drug discovery.

The next BSG session on "Complex Structures" was chaired by **Olivia Gittins** (Durham) and featured a range of talks centred around how cryo-electron microscopy (cryo-EM) as a means of visualising large structures can reveal unprecedented detail, thus offering unique insights into biological machinery. The keynote for this session was delivered by **Mohinder Pal** (Kent) who outlined "The role of molecular chaperones in ciliary function" – specifically the molecular chaperone HSP90, its co-chaperone RUVBL1-RUVBL2 and adaptor proteins such as CCDC103 and WDR92. These proteins are involved in the assembly of dynein motors which have a molecular weight of around 2 megadaltons and are responsible for motility of cilia. Motile cilia are present in almost every cell and ciliopathies affect the lungs, heart and fertility. The microtubules within cilia are associated with dynein and it has been shown that clinical mutations in CCDC103 impair dynein assembly and contribute to disease pathology in primary ciliary dyskinesia (PCD). Mohinder's group recently obtained a 3.2 Å cryo-EM structure of the human RUVBL1-RUVBL2-CCDC103 (R2C) complex, providing further understanding of the intricate protein network involved in Hsp90-mediated assembly of dynein motors and how adaptor mutations in CCDC103 cause PCD. R2TP is an inactive decamer but CCDC103 breaks it into a functional hexamer in the complex. The speaker moved on to describe the interaction of R2TP with WDR92, the latter protein being predicted to have a WD40 motif. Alphafold suggested that RPAP3 (a part of R2TP) would bind as an α-helix around the outside of the β-propeller of WDR92. Mohinder then moved on to describe studies of Leishmania, a serious protozoan parasite which is estimated to affect 6 million people worldwide with a million new cases being reported each year. It was shown that the W30R mutation in RPAP3 in *L. mexicana* affects the assembly of the flagella and mutation of a nearby residue (W26A) causes 98 % of the parasite cells to have no flagella. An EM study showed that rudimentary flagella are assembled but they do not have dynein associated with them and are unable to form the full length assembly required for motility. Using the VMXm beamline at DLS a 3 Å resolution structure for the complex was determined as a basis for fragment screening studies.

Next, invited speaker **Frank Bürmann** (Oxford) gave a talk on "Cryo-EM analysis of the DNA-loop extrusion motor MukBEF." The bacterial structural maintenance of chromosome (SMC) complex MukBEF is involved in genome organization and operates through mechanisms of DNA entrapment and loop extrusion. Frank described his work exploring the DNA loading process of MukBEF, obtaining several cryo-EM structures which illuminate the different conformational states that occur following ATP binding and opening of MukBEF's neck gates to expose the DNA capture site. He also described how this process can be disrupted by viruses. The ring-shaped SMC complex associates with DNA and threads a loop of DNA through its centre. Multiple SMC complexes are thus able to pack the DNA up into a compact bunch of loops. MukBEF has an interesting structure consisting of arms and a connecting elbow as well as a hinge region and a globular region formed of ATPase heads. The two arm regions separate at the elbow allowing DNA to be looped in between them in an ATP-dependent manner. The speaker presented a 3D model of the process in which ATP binding moves the heads apart and opens the gate, thus exposing the DNA binding site. Phage T7 produces a protein called gp5.9 and this is a DNA mimic which inhibits MukBEF as a part of subverting the host cell's machinery for its own purposes. The speaker presented numerous interesting results from cryo-EM studies of complexes with DNA accompanied by models of its role in maintenance of the bacterial chromosome.

A talk from **Giedrė Ratkevičiūtė** (Oxford) entitled 'Filling in the GAP(M)s' followed, in which the speaker detailed how malaria-causing plasmodium parasites utilise an actin-myosin motor known as a glideosome for host-cell invasion. An estimated 4.3 billion are at risk of *P. falciparum* infection and there are 282 million cases, with the parasite now being resistant to most drugs. Gliding of the parasite is due to its subpellicular microtubules which lie beneath the plasma membrane, separated from it by a layer of actomyosin. The membrane surrounding the lumen of these microtubules contains glideosome associated proteins or GAPs. GAPMs are a conserved family of integral membrane proteins which link the glideosome motor to the inner membrane complex (IMC) of the parasite to facilitate gliding motility. GAP knockdowns are unable to glide. Giedrė was able to co-express GAPM1, GAPM2 and GAPM3 to form a 1:1:1 heterotrimer which was then imaged by cryo-EM using a Krios, initially at 6.8 Å resolution. The resolution of the analysis was improved considerably by *ab initio* reconstruction and the use of mass-spectrometry data to identify interacting proteins and the use of AlphaFold. This work revealed that each subunit contributes six transmembrane helices, generating a trimeric core with asymmetric features that create a multi-surfaced platform which may accommodate diverse binding partners during different stages of the parasite's development cycle.

The final talk of the session was entitled "Integrating cryo-electron microscopy and AlphaFold reveals new structural insights into one carbon metabolism" and was given by **Thomas McCorvie** (Newcastle). The speaker described his work on human methionine synthase (MTR), a flexible 140 kDa enzyme which is involved in one carbon metabolism at the crossroads of the folate and methionine cycles. MTR regenerates the amino acid methionine from homocysteine, linking the folate cycle and the S-adenosylmethionine (SAMe) cycle. MTR uses cobalamin (vitamin B_{12}) as a cofactor in the reaction, however the structural basis of this interaction and its conformational flexibility was previously unknown. Thomas outlined how he used cryo-EM to determine that MTR exhibits two flexibly tethered halves in the apo state which undergo large conformational rearrangements upon cobalamin binding. The N-terminal half of the protein has a catalytic function while the C-terminal half is involved in binding the cofactor cobalamin. The latter is inactivated

***Frank Burman** (Oxford), **Giedrė Ratkevičiūtė** (Oxford), **Mohinder Pal** (Kent) and **Thomas McCorvie** (Newcastle) spoke in the BSG session on "Complex structures" which was chaired by **Olivia Gittins** (Durham).*

by one reaction cycle but it is reactivated by a sequence of events in which NADPH is used to reduce FAD and this reduces cobalamin again. AlphaFold predictions along with interaction studies, were used to investigate how MTR uses its binding partner methionine synthase reductase (MTRR) to regenerate itself. This revealed that MTRR interacts at two distinct sites within the cobalamin binding C-terminal half of MTR, potentially aiding in its reactivation.

Since the native protein was found to be problematic to study by EM, a screen of substrates was undertaken and methyltetrahydrofolate was found to give very good EM data which yielded a structure at 3 Å resolution. The structures of the complex with cobalamin, hydroxycobalamin and methylcobalamin bound were determined at the same resolution. AlphaFold3 suggested that it is the C-terminal half of MTR which interacts with MTRR in a novel manner and both pull-down studies and analytical gel filtration support this. Current work is aimed at determining the structure of the complex between MTR and its reductase MTRR.

The joint BSG/IG session on "Complementary Techniques" was chaired by **Natalie Johnson** (CCDC). In this session researchers presented a range of engaging talks about using experimental and computational techniques to help answer important structural questions. The keynote was given by **Gabi Heller** (UCL) who spoke on the subject of "Drugging intrinsically disordered proteins." Intrinsically disordered proteins (IDPs) are highly flexible molecules that do not have a stable 3D structure under physiological conditions or when purified, making them a difficult case for designing drugs to bind with them. They are important targets for research as they have a role in many diseases. Gabi presented both computational (molecular dynamics simulations) and experimental (solution and ssNMR) methods that have been used to study interactions between intrinsically disordered proteins and small molecules. Gabi gave the example of work on discovery of amyloid-β aggregation inhibitors, the binding of which can be monitored using thioflavin T fluorescence. Amyloid-β is a 40 amino acid peptide which is associated with Alzheimer's disease. Studies of this system included biolayer interferometry, NMR and MD simulations with NMR restraints. The speaker then described the viral non-coat protein NSP 5A which is an unfolded non-structural protein of approximately 80 amino acids. This has been studied by NMR using ^{19}F labelled tryptophan residues (5-fluoroindole) and the rotational correlation time of a ligand indicates that its binding is highly dynamic. Studies of ligand binding to the nuclear cancer-related protein NUPR1, again using 5-fluoroindole labelling, showed that the potential drug stabilised multimers. Gabi then discussed the question of whether small molecules can target IDPs and introduced Bind Research, the first focussed research organisation in the UK, which aims to develop open access tools to study small molecule binding in disordered proteins and make them druggable.

Next, **Steven Brown** (Warwick) spoke on "Solid-state NMR of pharmaceuticals and plant cell walls", describing ssNMR as a complementary technique to X-ray crystallography, in order to study compounds where obtaining a single crystal proves elusive. The speaker explained how NMR is a technique which gives structural information up to 6 Å from each nucleus. Through the use of high resolution methods such as ^{13}C and magic angle spinning NMR, several examples were shown of applications of the technique in pharmaceuticals. Technical developments such as the development of smaller rotors allow greater resolution in the spectrum and improved visibility of hydrogen peaks. Steven covered studies of several pharmaceuticals including efavirenz, lorlatinib and roxythromycin. A particular highlight was work correlating the NMR relaxation time to thermal ellipsoids in X-ray diffraction structures of these compounds. Steven also spoke about recent work identifying the flaws of previous interpretations of surface to core ratios in ^{13}C NMR spectra when looking at cellulosic materials, including plant cell walls. Wide-angle X-ray scattering (WAXS) and NMR are strongly complementary techniques for characterising the shapes of cellulose microfibrils.

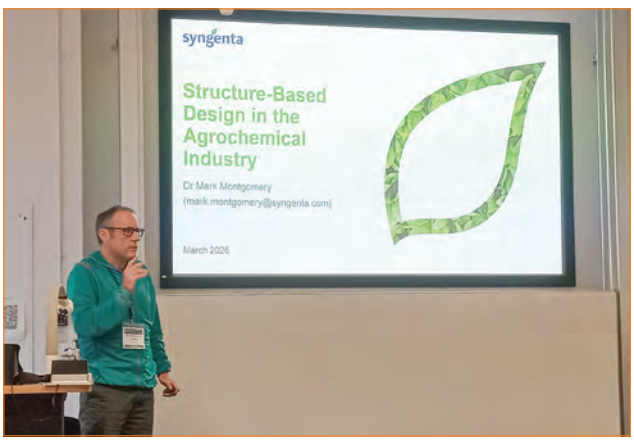
*The BSG/IG joint session on "Complementary Techniques" was chaired by **Natalie Johnson** (CCDC) and included talks from **Emma Hawking** (CCDC), **Steven Brown** (Warwick), **Andrew Leach** (Manchester) and **Gabi Heller** (UCL).*

The next presenter, **Emma Hawking** (CCDC) spoke about "Correlating particle informatics with surface wetting measurements." Wettability is a surface property, describing how well a liquid can spread across a solid surface – which is important in considerations of drug dissolution and manufacturability. Emma presented tools within the CSD Particle Suite that can be used to rationalise surface chemistry, surface roughness and look at probabilistic interactions on the surface. Studies included simulating a slab of molecules to get a full interaction map, looking at the density of H-bonding groups and hydrophobic moieties. The speaker outlined case studies of polymorphs of paracetamol and celecoxib (both non-steroidal anti inflammatory drugs or NSAIDs) in which it was found that hydrogen bonding density is the best indicator of wettability of a crystal facet. The analysis of surface chemistry on facets of single crystals, which were compared to experimental contact angle measurements, were shown to help explain the physical properties of certain crystal facets associated with poor wettability.

The final talk of the session was entitled "Please stop putting up with obviously wrong ligand structures" and was given by **Andrew Leach** (Manchester). The speaker presented 3 case studies of structures in the PDB where the ligand molecules were found to be in unreasonable conformations or configurations. Although in some cases these structures had the best agreement between the model and experimental data, the ligand orientations did not make chemical sense. Andrew then presented a quantum mechanical approach, 'Theoceptors', reducing the system to key residues in order to obtain the correct ligand orientation in the structure by taking into account the energy of the ligand derived from both X-ray and cryo-EM structures.

The examples included lactate dehydrogenase where one of the ligand complexes solved by X-ray crystallography has a very unlikely boat conformation. This was found to be at a very significant energetic disadvantage compared to the chair conformation. Another example was CaV1.2 which is a voltage-gated L-type calcium channel and is a major target for antihypertensive drugs, including dihydropyridines. An EM structure of the drug racemic drug benidipine bound to this protein was found to have been modelled with the least active enantiomer bound to the protein. The complex was remodelled by quantum mechanics with the opposite, more active enantiomer present instead and the fit to the map was as good. The third example given was of the sodium channel Nav1.5 which is a voltage-gated sodium channel protein that is crucial for initiating the rapid upstroke of the cardiac action potential. An EM structure of the complex with the antihypertensive drug felodipine had the ligand modelled in the *cis* rather than the more favourable *trans* form. Use of QM on key residues forming the binding site again yielded a model of the complex with the more energetically plausible isomer fitting the electron density equally well.

The BSG Open Session was chaired by **Rachael Wilkinson** (Leicester) and began with a lecture by **Mark Montgomery** (Syngenta) entitled "Structure-based design in the agrochemical industry." Mark outlined the position of Syngenta in the agrochemical sector with annual sales of $33.4 bn and research work being conducted across the range of synthetic chemistry, bioscience, product safety and toxicology. Mark emphasised the range of challenges which farmers face from weeds, disease, pests and the weather. Cost is a big factor due to the sheer number of weed species as well as pests and fungi. The general philosophy of agrochemical work is encapsulated in the following steps: discover, profile, evaluate, develop and launch. Unlike pharmaceutical development, where testing on people is the final stage of the process, in agrichemicals, compounds can be tested on the target species straight away. When compounds of interest are discovered, be they from natural products, intermediates in syntheses, compounds from *in silico* design, collaborations with academic groups, etc, these are fed into multi-parameter optimisation regarding toxicology, activity, stability, cost of production, IP protection and selectivity. In essence, the steps of design, synthesis, testing and analysis form a design cycle. Mark moved on to discuss structure-based design of nicotinic acetylcholine receptor analogues, namely the neonicotinoids. The receptor has



Mark Montgomery (Syngenta) in the BSG Open Session.

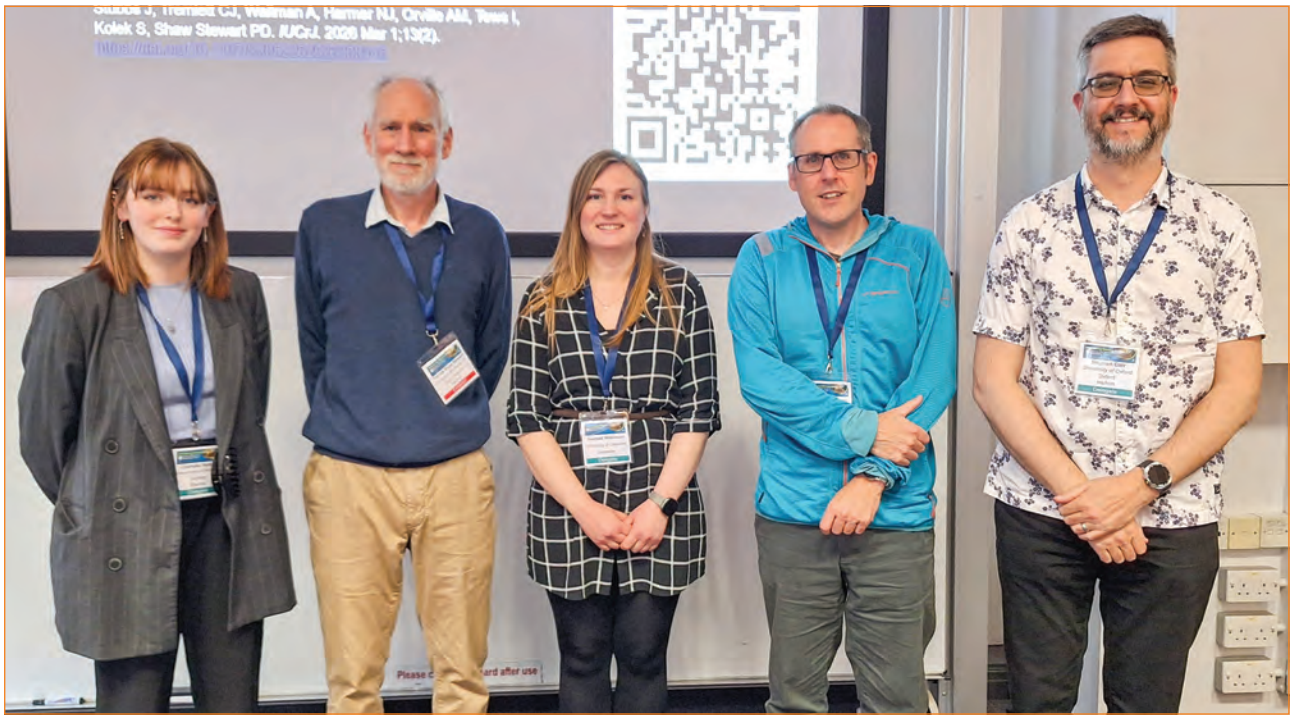
a ligand-binding domain attached to a transmembrane domain and an intracellular domain. Interestingly snails have a water soluble receptor without the transmembrane domain and this was mutated to make it more like the target insect protein of interest. Mark described solving the receptor-bound structures of five competitor compounds as a basis for design and synthesis of novel chemotypes and subsequent testing. The speaker then outlined studies of the ryanodine receptor which is the 0.5 megadalton target for diamide insecticides that has been studied by cryo-EM at eBIC (DLS) to find new inhibitors. Mark emphasised the role of the company in encouraging farmers to alternate the classes of compound that they use to minimise the chance of resistance emerging.

Next up, **Stephen Carr** (Oxford) gave a lecture entitled "Electrochemical control of protein crystals produces molecular movies of redox catalysis" in which time-resolved studies of [NiFe]-hydrogenase were described. The enzyme has hydrophobic gas channels as well as a metal-sulphur cluster in which the iron has two CN ligands and one CO ligand. The enzyme catalyses fast electron transfer and this process has been studied by soaking in redox reagents and maintaining electrochemical potential. The crystals are sealed in infra-red cells for spectroscopic characterisation of their redox state prior to X-ray data collection and this has allowed the proton transfer pathway to be determined. The speaker described how poising the crystals at different potentials isolates different intermediates and comparing their structures allows molecular movies of redox catalysis to be made. A hydroxide ion was observed to bind between the metal ions where the enzyme reduces it to water and releases it in order to reactivate itself for the next catalytic cycle. Time resolved diffraction studies using a 355 nm pump-probe laser allowed the time-course of the reaction to be followed over 5 to 50 ns. Similar studies of photolysis of CO bound to nitrogenase which has a FeMo-cofactor were reported. The speaker also outlined the facilities available at the Centre for Advanced Electron Spin Resonance (CAESR) in Oxford.

Charlotte Hunter (Durham) then spoke on "Studying biomolecular interactions with the Dianthus screening platform" which involves use of a NanoTemper instrument to record the spectral shift in the red or blue directions upon binding of a ligand to a fluorescence-labelled target. The instrument uses 384 well plates for high-throughput screening with excitation being at 590 nm and dual wavelength detection at 650 nm and 670 nm. Usually lysine or cysteine residues in the protein are labelled and the process allows the detection of binders as well as the measurement of their affinities. The system has been used to study cysteine synthase from *Trypanosoma cruzei*, the causative agent of Chagas disease which affects 6 to 8 million people in South America. It is also suitable for studying low molecular weight inhibitors of protein-protein interaction.

Last but not least, the closing speaker in this session was **Patrick Shaw Stewart** (Douglas Instruments Ltd) who spoke on the subject of "Using phase diagrams with microseeding to prepare crystal samples for routine and advanced data collection techniques." Patrick described the process of micro-seeding in crystallisation of both macromolecules and organic compounds as well as emphasising the importance of establishing a phase diagram. This allows one to optimise the number and size of the crystals for the intended experimental method. Patrick described work on a number of organic model systems including paracetamol and aspirin where water actually acts as the precipitant, rather than fulfilling its more familiar role as a diluent.

The final session in the BSG programme was framed as a "Protein design workshop" particularly introducing the application of machine learning methods for *de novo* design. The keynote was given by **Ed Pyzer-Knapp** (co-founder and



***Rachael Wilkinson** (Leicester), centre, chaired the BSG open session which included speakers **Charlotte Hunter** (Durham), **Patrick Shaw Stewart** (Douglas Instruments), **Mark Montgomery** (Syngenta) and **Stephen Carr** (Oxford).*

CSO of Xyme.AI), a start-up focussed on *de novo* enzyme design. His talk was entitled "Closing chemistry's trillion dollar possibility gap with *de novo* enzyme design." Ed began by explaining how around a third of the world's GDP is underpinned by catalysts made from transition or rare earth metals and how evolution has given us enzymes which have the potential to work on the industrial scale with much reduced carbon footprint. Ed emphasised that since today's AI is driven by scale, there is a great need for physical data to inform machine learning when designing for function. Ed described how AI driven *de novo* design can out-perform directed evolution in a process which looks at the energy landscape with a flow-matching model. Ed also described the use of quantum chemistry in generative AI models, physical conditioning and guidance vector fields in a reaction-centric process which out-performs public models and allowed them to design and make an enzyme in 10 days which would have taken a billion years to evolve. Generating robust physical data for training hinges on lab automation, allowing scientists to spend more time ideating and interpreting data as well as designing the science.

***Caitlin Hatton** (Hamburg) with the chair of the BSG "Protein design workshop" **Natalie Tatum** (Newcastle), **Ed Pyzer-Knapp** (Xyme.AI) and **Jennifer Miles** (Leeds).*

Our invited speaker for the workshop session, **Jennifer Miles** (Leeds) demonstrated how protein design can practically be used to modulate function. Her talk entitled "Using motif scaffolding to generate selective designed binders" detailed the design of over 1900 potential binders for the mitotic protein kinase Aurora A based on a small fragment of the inhibitory binding partner protein N-myc. This enzyme is highly expressed in a large number of cancers and is a tightly regulated Ser/Thr kinase with an N-myc binding site that partially overlaps the binding site for peptide substrates. From the 1900 compounds designed using the motif scaffold method of RFdiffusion, 56 were considered to be virtual "hits" by metric workflows, giving a hit rate of 3% and these were ordered as His-tagged constructs from Genscript. Jennifer described in detail the experimental validation of 17 binders through activity assay to determine their IC_{50}'s and ITC which showed that some of them had nM K_d. Interestingly the original N-myc sequence only has a K_d of 12 μM. The structures of nine Aurora A-binder protein complexes were determined at around 1.8 Å resolution and these had RMSD's close to 0.7 Å with the AI-predicted structures. From these structures, the designed binder protein DBS1 was selected for further study and cellular assays indicate that it has specificity over the closely related protein Aurora B, as confirmed by both western blotting and mass spectrometry (MS). GFP-labelled protein was used for overexpression in cells and MS was also used to identify interacting proteins in pull-down experiments and these included TPX2 which is thought to bind due to DBS1 moving a loop of Aurora A. These Aurora A binders are now under development for cell permeability studies.

Finally, **Caitlin Hatton** (Hamburg) demonstrated that single amino acid changes can have drastic impacts on enzyme activity in her talk, "Dimer interface mutations regulate fluoroacetate dehydrogenase activity." The enzyme in question, FAcD, is a homodimeric protein exhibiting half-of-sites reactivity meaning that only one of the two active sites is functional at once but both of the protein subunits are required for activity. The active site is formed by an Asp-His-Asp catalytic triad and the enzyme is capable of acting on a range of halo compounds that are fairly closely related to the substrate. The speaker described a number of interesting mutations including Asp110Asn which becomes stuck at the Michaelis-Menten complex and His280Asn which becomes stuck at the covalent intermediate. These effects have been studied by time-resolved crystallography. The subunit inter-connectivity via allostery can be affected even by subtle mutations, wherein a key serine residue Ser 157, which mediates reaction progression and water co-ordination, can be mutated to increase (Ser157Ala) or negate completely (Ser157Thr) the protein's enzymatic activity. In essence mutating residues at the dimer interface has no effect on the active site structure but can enhance the reaction rate by abolishing the half-of-sites reactivity. Supported by very high resolution protein structures (0.85 Å) obtained using low-dose data from P14 at EMBL, Hamburg, this talk demonstrated the roles of amino acid-level regulation of enzyme catalysis, bringing together the need for physical data and the importance of structural data, as had been discussed throughout the BSG sessions.

Blake Balcomb, DLS
Jon Cooper, UCL
Daren Fearon, DLS
Olivia Gittins, Durham
Natalie Johnson, CCDC
Mark Montgomery, Syngenta
Natalie Tatum, Newcastle
Rachael Wilkinson, Leicester

News from the CCDC

CSD Workshop at IUCr2026

The CCDC will be attending the IUCr 2026 Congress, taking place from 11th-18th August in Calgary, Canada. We are pleased to confirm that we will be running a workshop entitled **Mastering the CSD: Search, Visualise, and Analyse with Confidence on 11th August**.

Through hands-on examples and expert guidance, this workshop will help you build practical skills in CSD searching, crystal structure analysis, and data-driven solid-state investigation.

The CCDC is also attending the main conference, and we look forward to meeting you at the stand and at the sessions. Find out in which sessions the CCDC team is presenting here IUCr2026 – 27th Congress and General Assembly | CCDC

New CCDC Publications

The CCDC team regularly publish the results of their research, often in collaboration with other academic and industrial scientists. Here we share the latest papers published this year.

Understanding crystal surface anisotropy of organic materials via molecular modelling and facet-specific experimental characterisation

This study investigates how crystal structure and morphology influence facet-specific surface properties that are critical to material performance. Using quercetin-dimethylformamide (QDMF) as a model system, computational particle informatics tools were combined with advanced experimental techniques to correlate crystal packing with surface roughness, mechanical strength, and chemical features. The strong agreement between simulations and high-resolution experimental data demonstrates a robust, standardised approach for designing crystalline materials with tailored surface properties.

The crystal chemistry and particle sciences of drug product processing: the Cambridge Structural Database meets the manufacturing classification system

Understanding the materials science of an active pharmaceutical ingredient is essential for successful drug development and manufacturing. Particle attributes and crystallisation processes strongly influence stability, performance, and product quality. This paper reimagines the molecule-to-medicine journey by highlighting how Particle Informatics, linked with crystallographic data from the Cambridge Structural Database, can connect chemical, analytical, and formulation disciplines to support faster and more efficient pharmaceutical development.

Quantifying molecular flexibility using crystallographically accessible conformational space

This work introduces new informatics-based molecular descriptors that quantitatively describe the conformational space accessible to small organic molecules in crystal structures. Based on data from the Cambridge Structural Database (CSD), these continuous measures provide a more nuanced assessment of bond rotatability than traditional binary classifications. Ensemble rotatability scores account for molecular topology and define upper and lower bounds of accessible configuration space, offering deeper insight into molecular flexibility in crystalline environments.

You can explore the full list of CCDC publications on our website.

New self-guided workshop – exploring conformation and non-covalent interactions with Mogul and Aromatics Analyser

A new self-guided workshop is available on our website. It shows how to use Mogul to analyse molecular conformation and validate geometry using data from the Cambridge Structural Database (CSD), helping identify typical and unusual structural features. It also introduces the Aromatics Analyser in Mercury, a neural network-based tool that quantitatively assesses aromatic ring interactions and classifies them as weak, moderate, or strong. Together, these tools help chemists quickly visualise structures and understand stabilising interactions in crystal structures.

By the end of this workshop, you will be able to:

- Select atoms in Mercury using a SMARTS substructure.
- Use Mogul Geometry Check in Mercury to find unusual torsions.
- Use Aromatics Analyser to calculate aromatic interactions of molecules in different environments.

This workshop will take approximately 25 minutes to complete.

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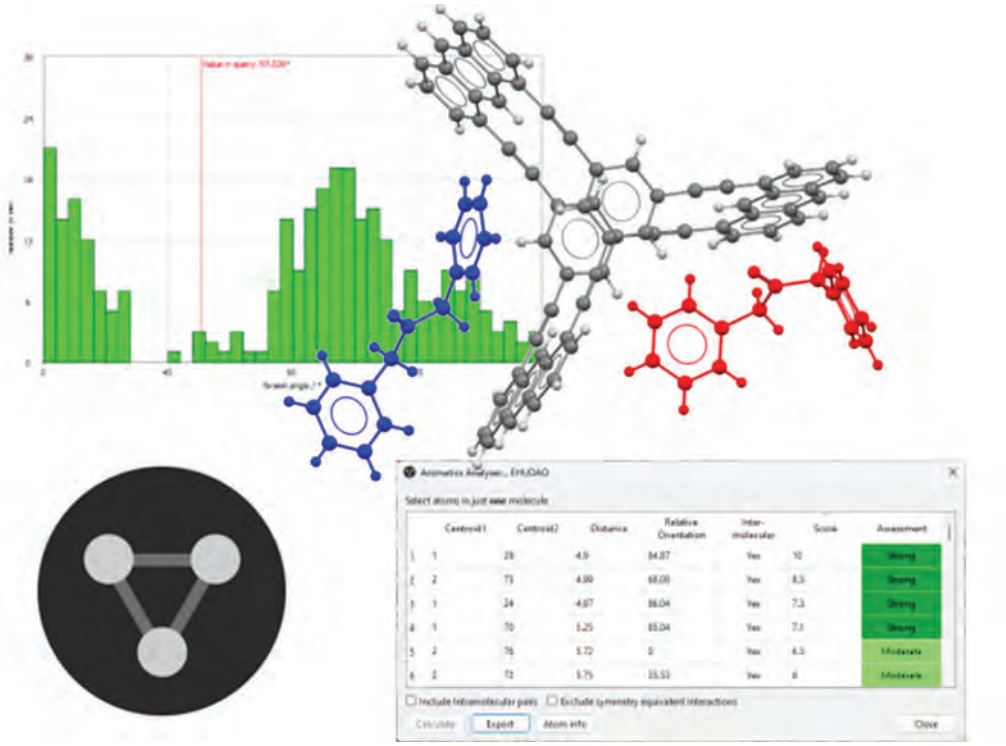
Ana Machado,
CCDC



Fellow Membership of the BCA

Applications are invited for fellow membership of the BCA via the members area of https://www.crystallography.org.uk/

Fellows of the BCA shall have an established career in crystallographic teaching or research and must hold one other class of membership. Fellows will normally have been members for at least five years, but the BCA shall consider exceptions such as those with an established career abroad or members who have taken recent career breaks.

In addition to recognising an established career, fellow membership provides a simple way to support the association. The current rates for fellow membership are set at double those of the member's normal renewal price.

Fellow members of the BCA

Dr David Aragao, Diamond Light Source
Dr Edward Bilbe, Johnson Matthey
Dr Richard Birkinshaw, Walter and Eliza Hall Institute
Dr Jeremy Karl Cockcroft, University College London
Professor Simon Coles, University of Southampton
Dr Susan Crennell, University of Bath
Dr Alex Gibbs, University of St Andrews
Dr Lauren Hatcher, Cardiff University
Dr David Hughes, University of Cambridge
Dr Benson Kariuki, Universiry of Cardiff
Dr Tony Keene, University College Dublin
Dr Mark Montgomery, Syngenta
Dr Lewis Owen, University of Sheffield
Professor Simon Parsons, The University of Edinburgh
Dr Helen Playford, Rutherford Appleton Laboratory
Dr Timothy Prior, University of Liverpool
Dr Georgina Rosair, Heriot-Watt University
Professor Mark R. Sanderson, Imperial College, London
Dr Jeremiah Tidey, University of Warwick
Dr David Walker, University of Warwick
Professor John Wallis, Nottingham Trent University

Letters to the editor

Paul Barnes (1942-2025)

Could I add a little to Jeremy Cockcroft's much-appreciated obituary to my ex-colleague Paul Barnes? Jeremy quoted Bernal's "More results!" exhortation, but the context in which this was delivered throws light on one of Paul's really important early achievements at Birkbeck.

The background is that, following hearing a lecture by the famous interface and colloid scientist Boris Derjaguin (of DLVO theory fame) on his then recently reported discovery of a more stable form of water – later dubbed "polywater." Paul wrote to Bernal asking to join our liquids team that had been tasked with examining the Russian scientist's extraordinary claims. Paul duly arrived to take the lead in this work.

Problems soon arose in that, despite many attempts to reproduce Derjaguin's results (in narrow capillary tubes), we failed! Andrew Brown, in his biography of Bernal [1], sets out the context of the "more results" exhortation as follows:

"On arrival at Bernal's house, they were ushered into a waiting room and Harry Carlisle, who was working on the structure of ribonuclease, was the first to be admitted to the inner sanctum. After some minutes, Barnes was astonished to hear a strangulated cry of 'More results.' It was then his turn to go in with John Finney and Ian Cherry (who was the group's Experimental Officer) to discuss the polywater project, where of course there were no positive results. Bernal's frustration was immediately evident. He turned to Barnes, the new boy, and asked what he was going to do about this sorry state of affairs. Barnes, his brain working feverishly, suggested that he would try to seed the elusive polywater between narrowly spaced plates rather than in capillary tubes as Derjaguin had done. This random proposal found favour with Sage, who then proceeded to hold up Barnes as an example to the others on how the problem should be tackled."

"In the weeks that followed, we still failed to make the stuff – until, that is, we started relaxing the strict conditions under which we were trying to produce it. As we progressively did so – bingo! There the stuff was! But polywater? No way. Mass spectrometry and electron microprobe analysis showed up a number of contaminants. Hence the title of the subsequent Nature paper "Polywater and Polypollutants" [2], with which Paul finally finally put this international 'pathological science' saga to bed."

John Finney,
UCL.

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ChatGPT and crystallography

I read your September 2024 editorial and thought this might amuse you. I asked ChatGPT some months ago to tell me about protein crystallography in the style of J. R. Tolkien, and I got this back:

"Upon the dark and tangled skein of life, there exist threads woven with a cunning beyond the reckoning of Men. These are the great proteins, the complex molecules that hold the very form and function of all living things, from the ancient, whispering Ents to the lowliest of hobbits. Yet their true shape is hidden, a secret buried deep within their twisting folds, guarded from mortal eyes.

To the learned, though, a path has been found to reveal this unseen truth, though it is a long and arduous journey, not for the faint of heart. It begins with the careful gathering of these vital molecules, an endeavor more akin to the purification of a Silmaril than a simple brewing of ale. In vast vats, or sometimes within the bodies of humble creatures, the chosen protein is grown and sorted, until only a single, homogenous substance remains.

Then comes the most precarious stage: the forging of the crystal. The pure protein, like a creature of lore, must be enticed to give up its fluid nature and form an ordered, repetitive array. One mixes it with an array of chemical concoctions, a wizardry of salts and subtle reagents, and sets the mixture aside to rest. For days, or even months, one waits, and watches, in the hope that order will emerge from chaos. If the attempt is successful, tiny, shimmering crystalline structures appear, clear as the most ancient Elvish glass. But if the conditions are not precisely right, only a murky, formless goo remains. It is said that luck plays a part, and perhaps some ancient wisdom long forgotten.

With a finished crystal, the great test can begin. The brittle, precious gem is taken to a place of immense power and precision, where it is struck not with sword or hammer, but with a beam of X-rays – a fierce and penetrating light. As this light passes through the ordered lattice, it is scattered and bent by every atom, casting a pattern of a thousand dots upon a sensitive screen.

This pattern is not a simple image, for the scattered light is beyond mortal comprehension, lacking the vital knowledge of its own nature. To the uninitiated, it is but a riddle of spots, a map without a key. But through the use of potent mathematical lore, and sometimes with the addition of "heavy atoms" – elements that shine brightly in the X-ray's gaze – a path is revealed. With this newfound insight, the scattered light can be reversed, and the invisible shape of the molecule is made manifest.

From the resulting map, a shimmering, three-dimensional model is constructed, and the protein's innermost secrets are laid bare. With its form unveiled, its function may at last be understood, like finding the lost language of a long-dead kingdom. It is a powerful magic, to make the unseen known, and a testament to the endless complexity of creation."

Elspeth Garman,
Oxford

How rigid are proteins?

If you try and run Alphafold3 (https://alphafoldserver.com/) on a complex of a drug with protein and DNA (for example a moxifloxacin complex) the current version does not give you

the ability to put in the drug. Moreover, it has limited knowledge of post-translational modifications you can order on the DNA. Alphafold3 will predict one conformation for the complex – whereas the conformation adopted depends on which drug is bound [1].

The popular modern view of evolution is that eukaryotic cells emerged from archaea and bacteria at about the same time as the great oxidation event [2]. The first three kingdoms of life, viruses, archaea and bacteria, are believed to have emerged earlier [3], and indeed it is hard to imagine how life, before DNA [4], existed without viruses [3].

Rates of evolution are related to genome size [5]; viruses with small genomes have fast mutation rates. Proteins seem to consist of relatively rigid domains connected by flexible linker regions, which may adopt different conformations [6] or become ordered depending on the biological context (e.g. DNA-binding [7]).

Many modern proteins from the fourth (eukaryotic) domain of life are believed to have arisen in the viral world (e.g. [8]). So when Anfinsen [9] identified the tendency of modern oxidised (disulphide containing proteins) to fold up correctly was the answer he found influenced by the evolutionary origins of the proteins? Do extracellular proteins from the 4th (eukaryotic) kingdom tend to be more rigid?

Ben Bax,
Cardiff

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Enzyme therapy in a structural light

THE enzyme L-asparaginase (EC 3.5.1.1) catalyses the hydrolysis of the amino acid asparagine to aspartic acid and ammonia. Many asparaginases also have activity on glutamine, producing glutamic acid instead, along with ammonia. In the current classification of these enzymes they are grouped into three classes, the first of which is formed mainly by the bacterial asparaginases that are divided into two types.

Type I asparaginases are cytosolic, have relatively low affinity for substrate and low glutaminase activity. In contrast, type II enzymes are usually periplasmic, have μM substrate affinities and have comparable asparaginase and glutaminase activities (Boyd & Phillips, 1971; Chohan & Rashid, 2013; Davidson *et al.,* 1977). Type I and type II asparaginases have low sequence similarity e.g. those from *E. coli* have a sequence identity of only 24%. Generally, the enzymes form dimers or tetramers with a subunit molecular mass of 35 kDa.

Biologically, the asparaginases have a wide range of roles. For instance, plants transport nitrogen in the form of L-asparagine from their roots to growing tissues and thus have a high requirement for this enzyme (Atkins *et al*., 1975; Sieciechowicz *et al*., 1988). In bacteria, when amino acids become the primary carbon source in anaerobic conditions, the expression level of asparaginase can increase by 100-fold (Cedar and Schwartz, 1967; Cedar and Schwartz, 1968). This is important since the metabolites of asparagine (and glutamine) can feed into the citric acid cycle. In contrast, the preferred carbon source glucose is a catabolite repressor of asparaginase expression. Thus asparaginases and glutaminases are necessary for cell growth in ammonia-deficient media and their expression is activated by the presence of these amino acids in the medium.

Intriguingly the type II asparaginases have been widely used as very effective chemotherapy treatments for acute lymphoblastic leukaemia (ALL), lymphoblastic lymphoma (LBL) and other hematopoietic malignancies. ALL is the most common childhood acute leukaemia, constituting approximately 80% of childhood leukaemias and 20% of adult leukaemias (Fullmer *et al*., 2010). The history of asparaginase use for ALL treatment can be traced back to the 1950s, when it was found that the progression of murine lymphoma was reduced by guinea pig serum and the active component was a protein (Kidd, 1953). Later in the 1950's it was shown that a transplantable rat carcinoma cell line had an absolute requirement for asparagine (Neuman and McCoy, 1956). In the early 1960s, it was found that it was the asparaginase in guinea pig serum which accounted for its observed anti-lymphoma activity (Broome, 1963a; b).

By 1964 it had been demonstrated that asparaginase from the bacterium *Escherichia coli* had the same antitumor effect

as guinea pig serum (Mashburn and Wriston, 1964). The larger quantities of asparaginase that could be produced from bacteria such as *E. coli* and *Erwinia chrysanthemi* allowed a series of preclinical and clinical studies of the enzyme as an infused drug. The success of this work culminated in widespread therapeutic use of the enzyme from the 1970s onwards as well as the development of a polyethylene glycol modified version (PEG-Asparaginase) which has improved stability and reduced immunogenicity. The effectiveness of asparaginase in the treatment of ALL was demonstrated beyond doubt (Hill *et al*., 1967; Oettgen *et al*., 1967). In recent studies, treatment with asparaginase has been shown to improve event-free survival for ALL from typically less than 10% to over 80% (Möricke *et al*., 2008; Pui *et al*., 2009; Silverman *et al*., 2001).

The high demand for exogenous asparagine by leukemic lymphoblasts (Haskell & Canellos, 1969; Prager & Bachynsky 1968) is due to their low levels of the enzyme asparagine synthetase which is responsible for endogenous asparagine synthesis (Kiriyama *et al*., 1989). Consequently the tumor cells can only obtain this amino acid from the blood stream while healthy cells are not affected by asparaginase treatment because they possess sufficient asparagine synthetase to make enough of it themselves.

This clinical use of an enzyme represents a truly remarkable approach for treatment of neoplastic, or indeed any, disease. The enzyme is also used commercially in the food industry since treatment of foods with L-asparaginase prior to cooking significantly reduces formation of the neurotoxin acrylamide (Friedman, 2003).

A recent paper by Gilski *et al*., (2026) in IUCrJ focusses on the stereoelectronic analysis of the catalytic mechanism of asparaginases based upon the hundreds of crystal structures of this enzyme from all three classes which are now available, although these were filtered down to a defined set of substrate or product complexes. The mechanism involves a β-acyl-enzyme which is formed by a nucleophilic threonine residue attacking the amide carbon of the substrate asparagine. This is followed by the nucleophilic attack of the intermediate by a water molecule which releases the product, L-aspartate (Verma *et al*., 2007). Even in the best studied class I enzymes there is some ambiguity as to the nature of this nucleophilic group since there are two conserved and suggestively positioned threonine sidechains in the active site. Similar ambiguity exists for the other classes where metal ions are also likely to be involved. The paper concludes that Thr 12, rather than Thr 89, in *E. coli* type II asparaginase is likely to be the nucleophilic group and extends this analysis to the other classes and types.

These mechanistic studies relied on creation of a specialised database of corroborated asparaginase structures (Wlodawer *et al*., 2024) and as such will assist greatly in fundamental studies of the enzyme. Indeed, who knows what the future may hold for further engineered forms of asparaginase with improved catalytic efficiency, stability and humanisation.

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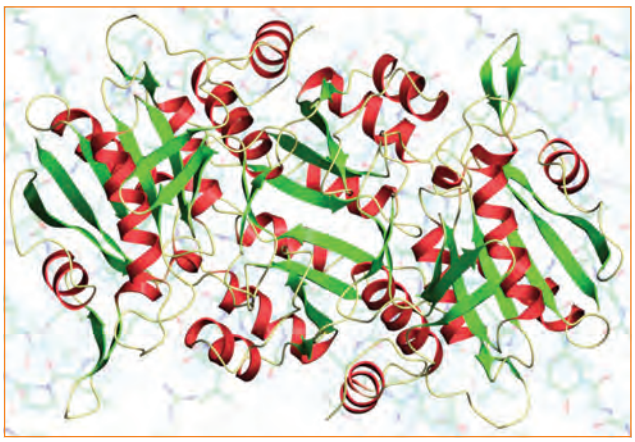
This article originally appeared in *IUCrJ* **13**, 126-127 (https://doi.org/10.1107/S2052252526001557) and is reproduced here with permission.



A dimer of the thermostable L-asparaginase from Thermococcus kodakarensis (RCSB extended ID: pdb_00005ot0; Guo et al ., 2017). Figure prepared using CueMol2 (cuemol.org/en/).

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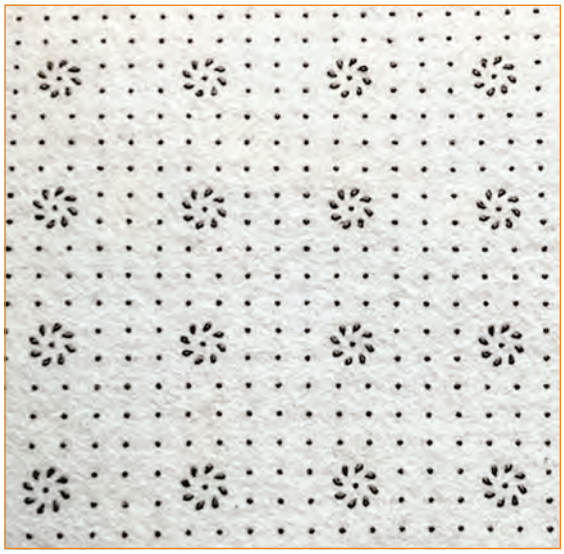
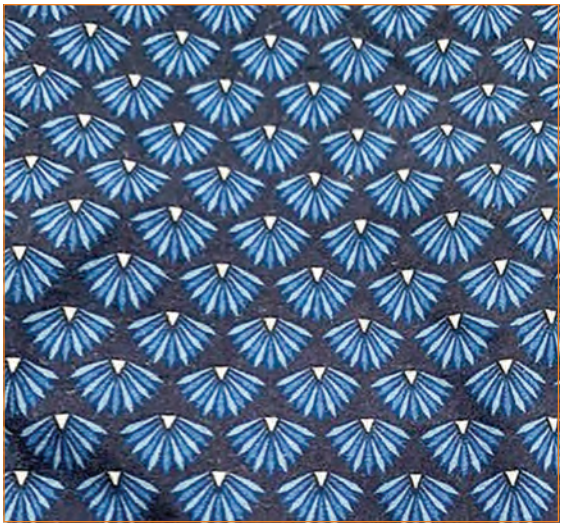
Puzzle Corner

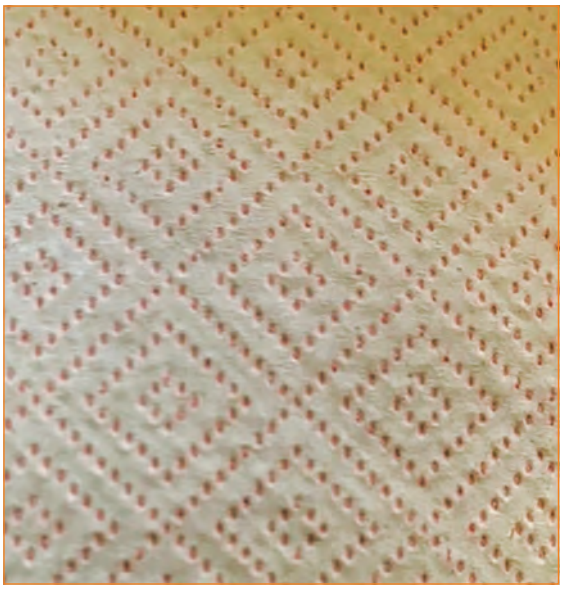
In the last issue we had a seasonally-relevant problem which was originally posted on the CCP4 bulletin board in early January by **Phoebe Rice** (Chicago).

This pattern belongs to the plane group *p* 2. The diad axes are drawn in black and the unit cell is shown in yellow. This is based on the plane groups in the International Tables for X-ray Crystallography (3rd edition, IUCr, 1969).

For the current issue we have four more patterns very kindly provided by **John Lisgarten** (London) for members to identify the corresponding plane group symmetries.







Plane amazing

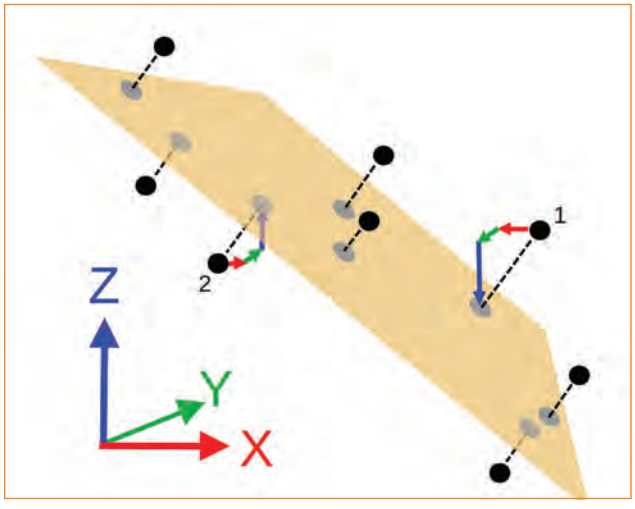
The general equation for a plane is as follows:

$$ax + by + cz + d = 0 \quad [1]$$

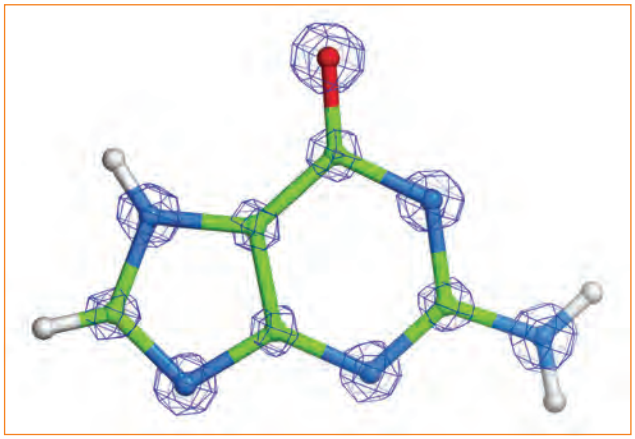
where a, b, c and d are constants. The more mathematically minded may remember that a, b and c govern the direction cosines of a vector normal to the plane with respect to the rectangular Cartesian axes x, y and z. The constant d dictates the distance of this plane from the origin, as measured normal to the plane.

Given the (x, y, z) coordinates of a number of points which lie in or close to a plane, it is possible to use least squares to determine best-fit values of the constants a, b, c and d for that plane.

If the coordinates in question are actually the trial positions of atoms in what should be a planar chemical group, then ultimately we need to determine the shifts to the x, y and z values of each atom which will bring all of the atoms into the plane by the shortest possible route in 3D. In other words each atom should move along a vector normal to the plane surface. In the figure below a collection of atoms (drawn as black spheres) above and below the plane of best fit (beige) are shown. The x, y and z axes are coloured red, green and blue, respectively (the acronym RGB is a good aide-mémoire) and the shifts along these axes for just two of the atoms (numbered 1 and 2) are drawn with the same colour scheme. The resultant normal vectors are shown in black dashed lines for all atoms and their desired positions when projected into the plane are shown as grey shadow-like ellipses.

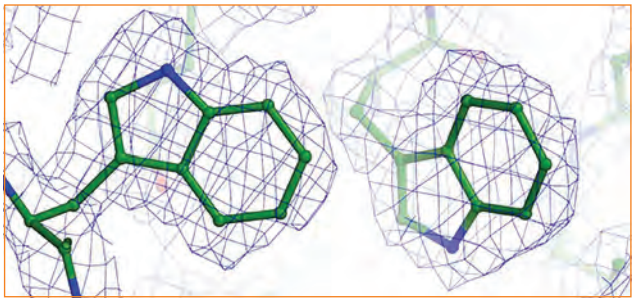


Mathematically, determining the plane of best fit is a jolly complicated process which involves eigenvalues and eigenvectors, not to mention singular value decomposition and principal component analysis, even before we worry about preserving the bond lengths and angles of our structure, so the details are best left to the real experts. Having said that, in practice it is, of course, something which we do very easily and routinely at the click of a button during refinement of a crystal structure when planarity restraints are used.



*The structure of anhydrous guanine at 0.9 Å resolution determined by **Guille, K.** and **Clegg, W.** (2006). Acta Crystallogr. C **62**, 515-517. The data for structure 2015488 were obtained from the Crystallography Open Database (COD).*

With an atomic resolution structure such as the one shown above, planarity restraints are not normally necessary, so most chemical crystallographers will probably be wondering what the actual problem is here. However, anyone who has looked at a protein electron density map will appreciate that aromatic side chains appear as flattened blob-shaped features into which the strictly planar ring group has to be fitted. As with fitting any side chain to its electron density by hand, the process involves a fair amount of subjective fiddling with a molecular graphics program.



The electron density for two tryptophan residues in a protein (PDB extended ID: pdb_00004ape) solved at 2.1 Å resolution, demonstrating that positioning the atoms correctly is somewhat ambiguous without atomic resolution data. The process is greatly aided by constraints (i.e. fitting the indole as a rigid group) or planarity and other geometric restraints during regularisation of the atomic model.

During the fitting of a planar group to its electron density, any movement of the individual atoms relative to the others will disrupt the ideal molecular geometry and this requires correction in a regularising routine. Being able to click on an icon in your graphics program which restores wonderful planarity to an aromatic ring as well as conferring it with correct bond lengths and angles is a routine part of electron density fitting in the macromolecular crystallography world.

Heuristic

I was interested in this process but given my life-long enthusiasm for minimising the complexity of all my problems, I came across a trick on the internet in which you restore planarity by determining shifts to each atom on one axis only. In other words we assume for example that the x and y values for each atom are correct and only the z coordinate has an error that requires correction to bring the atom into the best-fit plane. Given that we are moving the atoms along one axis only, any semblance of correct bond lengths and angles which our initial structure might have had to start with will probably be worsened, but I think we can make up for that later on by applying strictly in-plane corrections to the atom positions.

Its not rocket science, but assuming all the errors reside in z we can recast our original equation as:

$$z = Ax + By + C \quad [2]$$

where $A = -(a/c)$, $B = -(b/c)$ and $C = -(d/c)$. We now have to determine the least squares values of just three constants (A, B and C) from the initial values of x, y and z for each atom. Once A, B and C are known, we can use the values of x and y for each atom (which we assume are without error) to calculate the value of z which puts that atom in the plane of best fit.

The points in 3D (or atoms) give us a series of equations of the form:

$$\begin{aligned} z_1 &= Ax_1 + By_1 + C \\ z_2 &= Ax_2 + By_2 + C \\ z_3 &= Ax_3 + By_3 + C \\ &\vdots \end{aligned}$$

These simultaneous equations can be represented in matrix form as

$$q = Xa$$

where

$$q = \begin{bmatrix} z_1 \\ z_2 \\ z_3 \\ \vdots \end{bmatrix}$$

The X symbol represents the matrix of x and y values which are assumed to be error-free, as follows:

$$X = \begin{bmatrix} x_1 & y_1 & 1 \\ x_2 & y_2 & 1 \\ x_3 & y_3 & 1 \\ \vdots & \vdots & \vdots \end{bmatrix}$$

and a is the matrix of unknown constants

$$a = \begin{bmatrix} A \\ B \\ C \end{bmatrix}$$

Three points would be enough to define the A, B and C values of the plane uniquely. However when more than three points are available, we can use least squares and the general solution for the matrix of unknowns is given by:

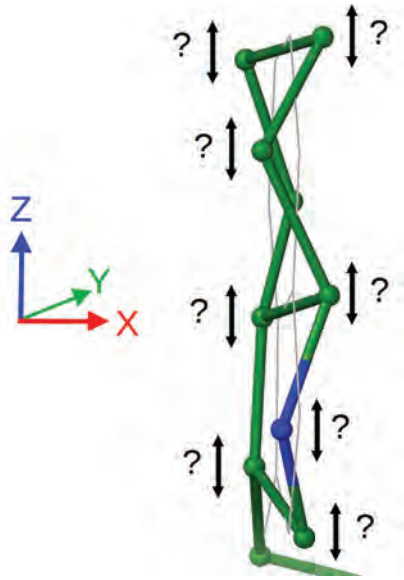
$$a = (X^T X)^{-1} X^T q$$

From the resulting estimates of A, B and C we can calculate the in-plane z-coordinates for the atoms from their respective x and y values using equation [2].

The least squares equations do look plain horrible but the actual calculations can be done relatively easily by your favourite maths package or scripting language and they really do make the atoms beautifully co-planar as they should be. However, there is at least one complication.

This approach should work best when the plane is exactly perpendicular to the z-axis since the structure should be flattened correctly with minimal distortion. This is shown below for an indole ring, the correct geometry of which is shown in pale grey lines. The ring itself is oriented roughly at right angles to the z-axis and the corrections needed on z for each atom in the distorted structure (green) are shown as small black arrows.

There is a problem however when the plane is parallel with the z-axis because no amount of movement in the + or − z direction can bring an out-of-plane atom back into the plane and the solution becomes indeterminate. Even if the plane was slightly tilted towards the z-axis such that the atoms could be moved into the plane by shifting them on z alone, some of them would probably have to move vast distances and the resulting structure would be hugely distorted and probably beyond all hope.



One practical solution is to determine which of the three Cartesian axes is most perpendicular to the plane and this can be done in a program by analysing the effective width of the planar group in the x, y and z directions. If the x-width of this group happens to be lower than the y- and z-widths (as is true in the above figure), all of the out-of-plane errors can be assumed to reside in x instead of y or z and the approach is exactly the same but with the axes swapped around. As with every trick, there must still be situations where it will fail – just drop me a line if you know something I don't!

Stochastic

Tidying up the geometry of the atoms in the plane can be done in a very simple stochastic way which is based on a table of approximate interatomic distances found in high resolution crystal structures of amino acids and polypeptides. For my purposes, these are all rounded to the nearest 0.1 Å – something which purists may baulk at, but it is approximately half the experimental coordinate error in a reasonably high resolution protein structure. The method calculates all of the deviations from these ideal distances within a rebuilt residue and the atom-pair with the worst distance violation is targeted for correction.

Consider two atoms that should be covalently bonded. Since we can calculate the direction of the bond in 3D and determine how much the bond length needs to be increased or decreased to correct it, we could simply move one of the atoms by the required distance along the bond vector. However, there is a good chance that we will make any other bonds which that atom is involved in considerably worse. Maybe we should choose which of the two atoms to move based on the number of covalent bonds made with other atoms, particularly non-hydrogen atoms. The least heavily bonded atom would then be the best candidate so as to minimise disruption to the rest of the structure. However that would require the program to do some additional calculations and rational decision making, which is probably overkill in my situation! Instead, the algorithm takes a slightly different approach which is to take one of the two atoms at random and move it by exactly half of the calculated bond length correction in the right direction and leave the other atom unmoved. At this point the deviations from ideal geometry for the whole residue are recalculated and the worst distance violation found and corrected in exactly the same way as before. The whole process is repeated many times until the worst distance violation is less than 0.1 Å.

As a footnote to the previous paragraph, an alternative strategy for correcting any bond length error would be to move both atoms inwards or outwards along the bond vector by exactly half the distance violation. This would give us a perfect bond length although it would worsen the geometry of other bonds involving both atoms. Bizarrely, this approach gave problems with atoms being caught in a tug of war with two other atoms as the algorithm attempted to correct the same two conflicting distance violations, over and over again. Instead, choosing only one of the atoms to move at random in each cycle helps to stop the whole process becoming stuck trying to correct correlated distance violations cycle after cycle *ad infinitum*.

The only time the program makes a rational decision about which of the two atoms in a pair should be moved is when either of them is a main chain N or C atom. Since the algorithm is aimed at correcting side chain geometry, the main chain N and C atoms are generally kept in fixed positions to preserve reasonable backbone geometry.

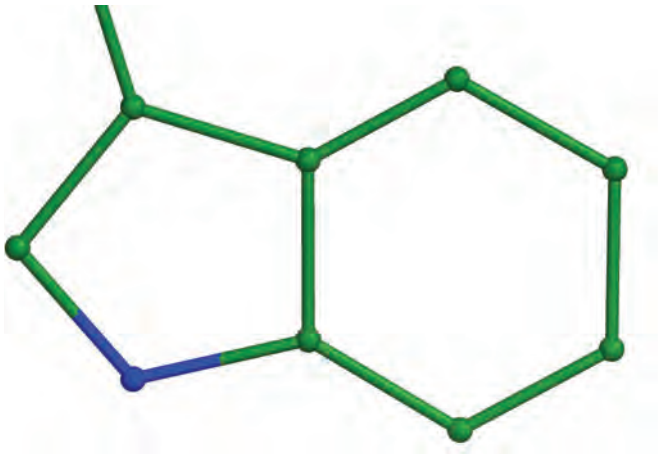
Since all of the atom movements are along interatomic vectors, it is inevitable that most of the applied shifts retain the planarity of an aromatic ring while improving its bonding geometry. The planarity correction can be repeated and followed by further cycles of distance geometry correction as many times as required to give a satisfactory overall RMSD from ideality.

Feel free to suggest other ways the algorithm could be written.

Fantastic

Some more details of the method are described in a short article I wrote for Proteopedia here. Using the approach described above for the least squares fitting of atoms to a plane has been the most effective of my home-brewed methods of restoring perfect planarity to manually rebuilt aromatic rings, such as those of Phe, Tyr and Trp side chains. The latter with their more extensive bicyclic rings proved particularly challenging to my previous efforts!

The two figures below demonstrate the effects of regularising the distorted indole group shown in previous figures. The tryptophan side chain is viewed from the ring edge and face-on.



Simple distance targets can also be used to maintain the planarity of smaller groups with a central trigonal atom (e.g. carboxylates and amides) by calculating the distance between the centroid of the three outer atoms and the central atom. This distance should be very close to zero Å and bad discrepancies can be corrected exactly as for the interatomic distance violations, although in this case it is only the central atom (not the centroid!) which can be moved. For tetrahedral groups, in both the main chain and the side chain, the central atom has to be almost exactly 0.5 Å from the centroid of the three outer non-hydrogen atoms bonded to it. The vector between the central atom and the centroid is the direction along which any shifts to the central atom can be applied in 3D.

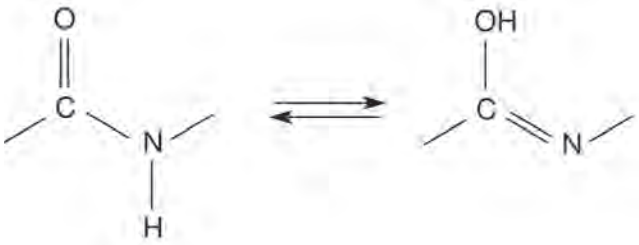
In addition, we can correct main chain and side chain chirality errors by calculating the signed volume of these groups using the determinant function of a maths package. When the chiral volume is negative, the group needs to be inverted. The program uses a fairly crude way of doing this which is to move the central atom to the centroid of the three outer non-hydrogen atoms and one of the outer atoms is shifted the same distance but in exactly the opposite direction in 3D. Subsequent iterations to correct the interatomic distances seem to sort out any remaining anomalies introduced by flipping the hand of the group in this simple way.

Bizarrely, the same stochastic methods can be used to make amino acid residue substitutions or mutations in a protein structure. When converting one side chain type to another, as many atom positions as possible are borrowed from the starting residue. Thus, mutating a given amino acid into one with a smaller side is relatively straightforward. However, replacing a side chain with a larger one means that some of the new atom positions are unknown. In this situation we can make a very crude set of trial positions by budding the new atoms out in a line from the last atom that was present in the original side chain. Simply minimising the geometric deviations using the approach described above, albeit for a somewhat larger number of cycles, is sufficient to give the new side chain eminently reasonable stereochemistry and it can then be fitted to the electron density.

Dear reader, do remember that none of this has been rigorously peer-reviewed but if anyone is at all interested, the editor's *massively minimal minimiser* or *mmm* routine is available as part of the script which runs the Mini Map Aide web site at the following https://minimapai.de

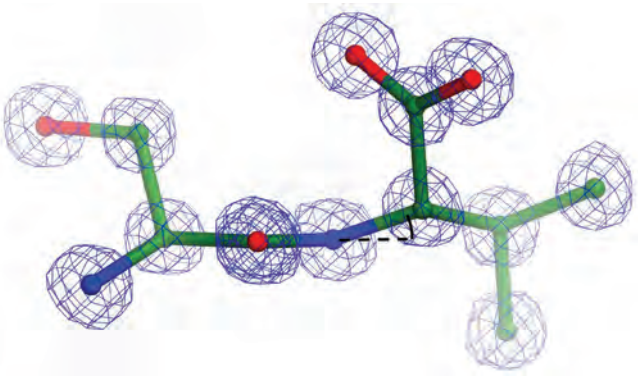
Whilst all of this is a far cry from molecular mechanics (something best left to computational chemists!) it does seem to give reasonable geometry to the side chains and usually takes at most 1 or 2 seconds per residue when running it as a client-side script via an internet browser, even on a humble Android phone.

It is also worth remembering that some groups that are traditionally held to be planar are not strictly flat. A good example, for protein crystallographers at least, is the peptide bond. The predominant and more flexible amide form of the peptide bond tautomerises with a relatively minor (40%) but strictly planar enol form.



Keto-enol tautomerism of the peptide bond. Whilst this phrase is commonly used, it is probably more correct to refer to it as tautomerism of an amide group (left) with its iminol form (right).

As a result the torsion angle of the peptide C-N bond (ω) is known to deviate by up to about 20° from the value of 180° corresponding to perfect planarity. It was speculated that these distortions might be associated with specific features of the protein such as the active site of an enzyme or the binding site of a protein inhibitor but more recent surveys of atomic resolution structures suggest this is not the case. Rather the distortions are merely a consequence of the protein's tertiary structure. These effects are discussed and relevant literature summarised in a commentary by Brian Matthews (2016, *Protein Science* **25,** 776-777). The best estimates give an rms deviation of about 6° on ω with an upper estimate of about 25°, meaning that the distorted peptide bond shown in the 0.8 Å resolution dipeptide structure below, which has a Δω value of 23°, is towards the upper limit of this range.



The structure of a Ser-Val dipeptide reported by Moen, A., Frøseth, M., Görbitz, C. H. and Dalhus, B. (2004) *Acta Crystallogr. C* 60, 564-565. The deviation from planarity of 23° on ω is shown by the small arc. The structure and data are available in the Crystallography Open Database with the identifier 2014266. Note that in this view the carbon atom forming the peptide bond is out of sight exactly behind the carbonyl oxygen atom.

The following open access article on the peptide bond appeared in IUCrJ last year and is a recommended read for members, as is the commentary.

- Panjikar, S. & Weiss, M. S. (2025). Peptide bonds revisited. *IUCrJ,* **12,** 307-321. https://doi.org/10.1107/S2052252525002106
- Chari, A. (2025). Peptide bonds strike back. *IUCrJ,* **12,** 257-258. https://doi.org/10.1107/S2052252525003604

This paper effectively brings the story up to date by analysis of 1024 non-redundant structures in the PDB with resolutions better than 1.2 Å, thus covering almost a quarter of a million peptide bonds. It is interesting that a small number of these (almost 1600) have electron density exactly consistent with protonation of the carbonyl oxygen – an effect which is only possible in the enol form.

Maybe it is time to have another look at some of the atomic resolution structures we worked on a while ago!

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UCL

Acknowledgements

Electron density figures were prepared using CueMol. I am grateful to Shabir Najmudin (City St Georges) and Peter Erskine (London) for commenting on this article.

Meetings of Interest

WHERE ppossible, 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.

2026 Denver X-ray Conference, Lombard, IL, United States, 3rd-7th August 2026

From its humble beginning of 35 participants on the University of Denver campus, to a nationally and internationally recognized annual event, this year, DXC will celebrate 75 years as the leading annual forum on general X-ray analysis, including both X-ray fluorescence and X-ray diffraction. Attendees to the World's largest X-ray conference have access to sessions on the latest advancements in XRD and XRF. Workshops are run by experts who provide training and education on many practical applications of X-ray fluorescence and X-ray diffraction techniques for the study of materials. DXC provides a unique mixture of sessions on training, education, and applications, including state-of-the-art techniques and future developments in X-ray analysis.

More details and registration are available at: **https://www.dxcicdd.com/**.

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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.

More details and registration are available at **https://www.iucr2026.org/**.

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14th International Conference on Inelastic X-ray Scattering, Argonne National Laboratory, United States, 13th-18th September 2026

The 14th International Conference on Inelastic X-ray Scattering (IXS2026) will connect scientists from around the world who are pushing the boundaries of resonant and non-resonant inelastic X-ray scattering to tackle today's most compelling scientific challenges.

More details and registration are available at: **https://web.cvent.com/event/27c946d3-481c-45c4-b460-cd5402449f48/summary**.

16th XTOP Biennial Conference on High-Resolution X-Ray Diffraction and Imaging, Karlsruhe, Germany, 21st-25th September 2026

XTOP brings together scientists working on X-ray diffraction, reflection, grazing-incidence scattering, standing-waves, coherent diffraction, and ptychography techniques, as well as X-ray microtomography, microscopy and other imaging techniques based on phase, diffraction, scattering, or spectroscopic contrasts. XTOP is a leading scientific conference on instrumentation, methods, and applications of laboratory and synchrotron-based X-ray diffraction and imaging techniques.

More details and registration are available at: **https://www.xtop2026.kit.edu/.**

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NYC-ISB26 Integrative Structural Biology symposium, New York Structural Biology Center (NYSBC), United States, 8th-9th October 2026

Integrative structural biology is a powerful approach towards understanding biological macromolecular systems. By combining computational methods with structural science disciplines, spatial and temporal models of macromolecular targets in their in-situ context can be determined. The focus of this workshop is to understand the challenges and opportunities of applying integrative structural biology techniques to one's research. The fields of light microscopy, mass spectrometry, X-ray crystallography, NMR, cryo-EM, and computational methods will be highlighted. The topics will cover the best practices and current research toward building structural models across different resolution scales. This symposium will also offer hands-on demos to explore available instrumentation and panel discussions for integrating conformational changes, flexibility, and dynamics in macromolecular and cellular structures.

More details and registration are available at: **https://nysbc.org/nyc-isb26/**.

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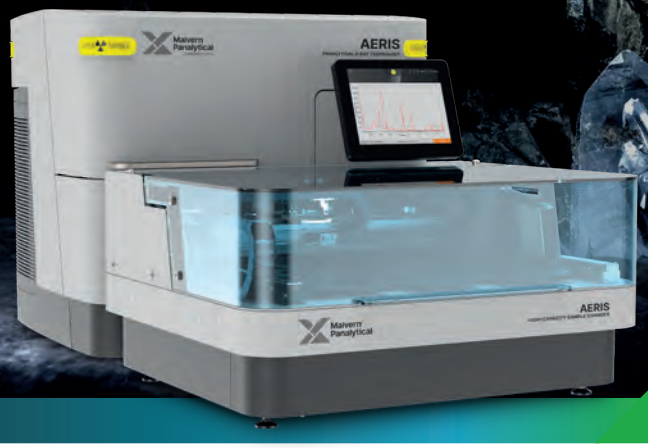

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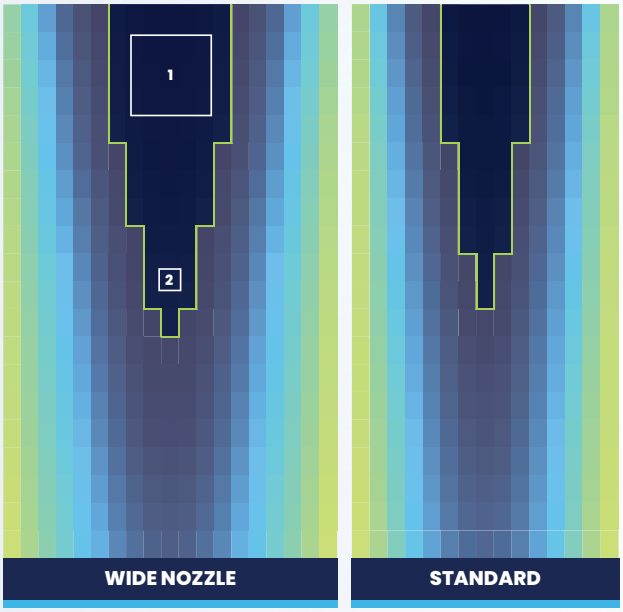

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