Crystallography News

British Crystallographic Association

Issue No. 162 September 2022
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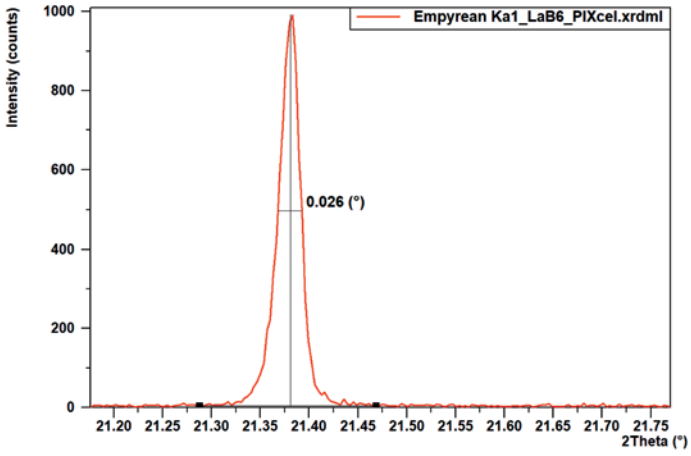

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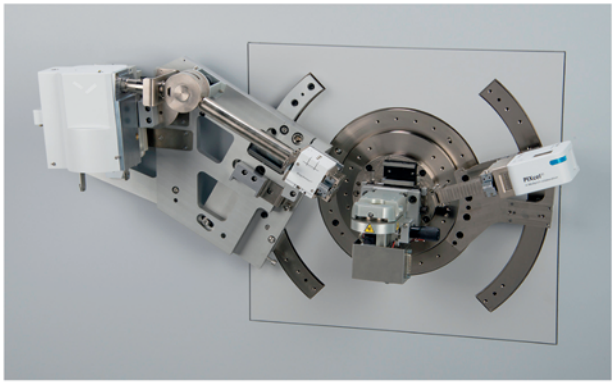

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Please ensure that items for inclusion in the December 2022 issue are sent to the Editor to arrive before 25 October 2022.

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Contents

This month's cover:

Elspeth Garman's granddaughter Madeleine Joy, enthralled by Crystallography News. Crystallography in the genes? (Courtesy – you've guessed it – Elspeth Garman.)

From the President

WELCOME to the September 2022 issue of *Crystallography News.*

I am delighted to note that **Bill Clegg** (Honorary Member and long-time supporter of the BCA, and Emeritus Professor at Newcastle University) has been awarded the twelfth Max Perutz Prize of the European Crystallographic Association (ECA), and I send my wholehearted congratulations. Through his text books and commitment to the biennial BCA/CCG Intensive Teaching School in X-ray Structure Analysis, Bill is well-known to generations of crystallographers in the UK and around the world. Full details of the award are available later in this issue. Bill delivered his Prize Lecture during the opening ceremony of the 33rd European Crystallography Meeting (ECM) in Versailles last month. Reports from this meeting will be included in the December issue.

The BCA Council will be meeting soon, in our modern online format, and we will finalise suggestions for issues brought up at the last AGM – to be taken for approval to the next AGM. I think I prefer this method of slow and stable governance to the alternative. We are also working to improve the methods of collecting and reporting gender and diversity information of our Spring Meeting attendees. Following suggestions from the membership, and to coincide with reaching our 40th Anniversary, we have decided to produce a short history of the BCA comprising historical articles and photographs and some new perspectives on the Association. If you would like to be involved in contributing or editing such a work, please get in touch (don't wait for an invitation).

Council elections are almost upon us once again. This year, the roles of Treasurer and one Ordinary Member of Council are open for nominations. Many thanks to **Hazel Sparkes** for her contributions to Council. She is not eligible for re-election as an Ordinary Member after serving two terms. Thanks also to **Claire Naylor** for conscientiously working as BCA Treasurer for the past three years. Claire has indicated that she is willing to continue in this role for another term, but also that if someone feels a strong calling to take on the job, they should get in touch for further details.

The BCA appoints a Nominating Committee to assist in recruiting candidates to stand for these roles – the primary purpose is to avoid the Council being responsible for nominating candidates to replace itself, which can unintentionally lock-in a lack of representation from within the membership. Thanks to this year's committee, chaired by **Claire Wilson** (CCG) with **Chris Frampton** (IG), **Elspeth Garman** (BSG), **Simon Phillips** (Past President) and **Paz Vaqueiro** (PCG). Although the committee is an important route to encourage balance in the nominations for Council, no power has been removed from members: nominations can still come directly from any two members (with the consent of the candidate) and we strongly encourage members to make use of this method of nomination. Such nominations should be communicated to the current Secretary, **Lauren Hatcher** (secretary@crystallograpy.org.uk) by the end of this month, September 30th.

Planning for next year's BCA Spring Meeting 2023, 3rd – 6th April 2023 at the University of Sheffield is already at an advanced stage, thanks to the work of this year's Programme Committee under the careful guidance of chair **Helen Playford**. Announcements of confirmed parts of the programme can be found in this issue, with more details to follow in December. As usual, I must remind you that the abstract deadline early in the New Year always seems to arrive sooner than expected – so please start thinking now about contributing oral or poster abstracts to one of the scientific sessions. The Monday afternoon and Tuesday morning of the Spring Meeting will be organised and run by the Young Crystallographers Group. The speakers and poster presenters at these sessions are mainly students and early career researchers, but everyone is welcome to attend and support.

Just over 100 miles North, and in the week before the Spring Meeting, the BCA/CCG Intensive Teaching School in X-ray Structure Analysis will take place between 25th March and 2nd April 2023 in Durham. For those members whose interests are located on the small molecule region of the crystallography hypersurface, this course provides a great foundation in structure analysis fundamentals and is always oversubscribed. Sign up your staff, students or yourself at https://bcaccgschool.crystallography.org.uk/ as soon as registration opens.

Congratulations to BCA member **Alex Stanley** who has recently been appointed as IUCr Chief Executive Officer (CEO). Alex served on BCA Council in many roles, most recently as BCA Secretary from 2019-2022.

The IUCr congress is due to be held in Melbourne, Australia from 22nd-29th August 2023 and abstract submission and early bird registration is now open at https://iucr2023.org/. The BCA will be offering travel bursaries through the usual online application process (see opposite the contents page of this issue). The bursary fund has been underused over the last couple of years and the costs of travelling to Melbourne are quite significant; therefore we plan to offer higher than usual assistance to eligible applicants. Applicants should have been BCA members for three months before applying, so please ensure new staff or students have joined the BCA in plenty of time.

We are extremely grateful to the late Professor **Carl Schwalbe** (Honorary Member and *Crystallography News* Editor) who left a bequest in his will for the BCA Arnold Beevers' Bursary Fund. On behalf of the BCA, I would like to thank Carl's family for this generous donation which will enable current and future generations of researchers to attend scientific meetings in the UK and beyond.

John Finney has another two issues of *Crystallography News* to produce before he reaches the end of his term as Editor. I'm pleased to report that **Jon Cooper** (Emeritus Professor of Structural Biology at UCL) has agreed to take over the role, initially for a 3-year stint. Many thanks to him for taking on this important responsibility. I can report from first-hand experience that Jon is currently shadowing John through the process of chasing people to submit their columns on time, and I wish them both well in the handover process.

News and updates can be found on the @britcryst twitter feed. The feed can also be seen on the front page of the BCA website, https://www.crystallography.org.uk/, just below the list of our corporate sponsors in the left-hand column. The twitter account can be used to keep an eye on meeting announcements, reminders of abstract deadlines and news from BCA members.

Richard Cooper

BCA Council 2022

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Elections to BCA Council

There will be elections this year for:

- BCA Treasurer
- Ordinary Member.

Any two Members may make nominations, and such nominations should be accompanied by the written consent of the candidate to serve if elected. These must be received by the Secretary by 30th September 2022.

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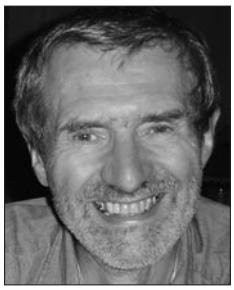
(The dates in parentheses indicate the end of the term of office).

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

From the Editor



MANY of us – especially the protein crystallographers – will remember the stunning announcement in late 2020 by Deep Mind that their AI system AlphaFold had "been recognised as a solution to" the protein folding problem. Such a dramatic claim called for an assessment by recognised experts in the field, so accordingly David Jones (UCL) and Janet Thornton (EMBL-EBI) kindly wrote an initial assessment of the claim for the March 2021 *Crystallography News*. Since then, AlphaFold has predicted – and made publicly available – the structures of many thousands of proteins, further raising questions about the implications for protein crystallography. So it seemed highly appropriate for David and Janet to give an update on the potential of this AI engine, and I'm delighted that this issue features their assessment of both that and its possible implications for those working on experimental structure determination. Spoiler alert! They don't think that the worry that some may be out of a job makes sense! And also on the positive side, they conclude that AlphaFold marks not the end of anything, but the beginning of many new things. I hope you find their forward-looking article interesting and stimulating.

This issue also marks a change in the nature of reports on scientific meetings – at last they are back to being in person! No more are we limited to screenshots of us sitting at our computers, unable to talk to colleagues in the bar or limited to typing questions to speakers in the chat box. Instead we can now meet with real people, talk science in the bar and in front of posters, seed collaborations – and take in the great views surrounding the venues.

A meeting of the ISIS Disordered Materials User Group in June was in fact my first in-person meeting since the pandemic began. It underlined to me in no uncertain terms the absolutely critical need for informal, relaxed in-person meetings if we are to maintain the health of scientific research. However, as a 'hybrid' meeting (with one third of the 90 registered participants being online), it also highlighted the advantages of being able to participate remotely[1]. Unlike some of the hybrid meetings I've 'attended', the technology worked well (despite a few glitches which may well have been problems at the remote participants' ends), enabling the participation of colleagues who, for a range of reasons (e.g. having to do the school run as the partner was away at another meeting) just couldn't make it in person. However, notable by their absence were questions from remote participants, which meant that those there in person didn't get much benefit from the expertise of the remote participants. I have a theory that effective Q&A is just not possible remotely – asking questions by typing into a 'chat' or 'Q&A' window is clunky. Not only does it take your attention away from the talk being given, but also it's not easy to get over in a quick typing any intricacy in a question. And not being able to respond interactively in discussion of a speaker's answer suppresses useful discussion between the questioner and the speaker – much of which did take place between those present in the room itself at this meeting. There's also, of course, the ability to 'network' in the 'corridors' of the meeting (though in this case, the 'corridors' were out on the grass or around the tables outside in the sun!). The weather was kind to us, and the venue highly conducive to informal one-to-one or small group discussions. An enduring – and optimistic – memory is looking over the 'lawn' to see how effective the distributed round table and external seating was in nucleating the person to person interactions that are particularly important to young scientists in the early stages of their careers.

In addition to the article on hybrid conferences referenced below[1], there were a couple of other pieces that particularly caught my eye this last few weeks that are perhaps of particular interest to our younger colleagues.

First, remembering how I was 'scooped' in the early 1970s with respect to early attempts to computer simulate the solvent in a protein crystal, I wish I could have read the advice from one of the five researchers who shared their experiences of how they rallied from being scooped, or faced other apparent failures while working on their Ph.D. projects. Like the student in Bangalore in that article[2] whose protein structure was solved by others, I blamed myself for working too slowly, until I realised that the competition had far better kit than I had. And in my case time showed in the end that the first to publish often produces inferior work that doesn't stand the test of time.

The other paper that caught my eye (actually on the Sociobiology blog) concerned the inevitable negative effects of having to retract a paper after discovering a problem[3]. Although this very brave and honest Ph.D. student naturally felt like a failure, there was a significant silver lining. The student learned how kind people could be about an honest mistake – none of the awful consequences that were imagined actually came to pass. And to have some faith that your fellow scientists will understand. "And then get back to the lab."

Finally, for a bit of fun, watch a multicellular organism naturally crystallise at https://youtu.be/bki2kI8aQvg. Seems pretty obvious physics to me, but still fun!

John Finney

References:

1. For an interesting article in Nature on hybrid conferences, see Benjamin Plackett. The Right Mix: Making a hybrid conference work for all. *Nature* **607**, S1-S3 (2022). doi: https://doi.org/10.1038/d41586-022-01797-7 .
2. How to bounce back from a PhD-project failure. *Nature* **607**, 407-409 (2022). https://www.nature.com/articles/d41586-022-01900-y .
3. Retraction with honor. *Sociobiology*. Posted 16 July 2022 by Joan E. Strassman. https://sociobiology.wordpress.com/2022/07/16/retraction-with-honor/ .

Puzzle Corner

THIS month's puzzle is a little different from usual. It came from an idea from a book where a bad mistake was made, and they 'proved' exactly the opposite of what they set out to do!

The geometric mean of two positive numbers $\sqrt{(ab)}$ is always less than the arithmetic mean $[0.5(a+b)]$. Can you prove this?

Answer to June's puzzle:

1. Seven, Five, Sheep, and Blind: All types of non-crystallographic 'folds.
2. Unit, Jail, Monastic, and Biological: All types of 'cell'.
3. Transform, Synthesis, Analysis, and Series: All words that can be preceded by 'Fourier'.
4. Mono, Tri, Out-patient, and Dental: All 'clinics'.

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- Influence on the development of crystallography and the BCA

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AlphaFold – the end of the protein folding problem or the start of something bigger?

Introduction

IN December 2020, a London-based AI company called DeepMind, now part of Google, made the following announcement about the long-standing protein folding problem: "In a major scientific advance, the latest version of our AI system AlphaFold has been recognised as a solution to this grand challenge by the organisers of the biennial Critical Assessment of Protein Structure Prediction (CASP)". This bold claim, if really true, would of course have many implications for both experimental and computational structural biology, so here we try to put these new results in context and try to provide a perspective on the way forward.

DeepMind addressed this venerable challenge using almost all of our existing knowledge of protein structures, accumulated over 50 years, to train their powerful machine learning algorithms, some of which had already been used in the form of a program called AlphaGo to beat the best human Go players. The paper describing their model was published in Nature in July 2021, along with full working source code, which was a very welcome surprise to the scientific community. Figure 1 shows the 'worst and the best' of AlphaFold *de novo* models. Here we hope to give a balanced overview of what at least we know so far, and try to put the results in the context of experimental structural biology going forward.

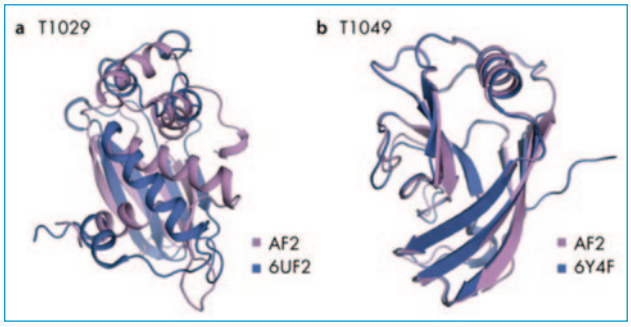

Figure 1: The 'worst' and 'best' of AlphaFold de novo models. The figures show the superposition of the predicted model and the experimental structure determined later. Target T1029 shows that there can still be issues to resolve in terms of multimeric structures or large conformational changes, but target T1049 shows a more typical case, and how good AlphaFold can be at modelling domains with no available template information.

Background

Proteins are the workhorses of molecular biology – doing most of the biochemistry, immunology, structure building and decoding of DNA in all living organisms. These polymers, built as chains of amino acids, have incredible properties, of which perhaps the most important and amazing is that they spontaneously fold into unique 3D structures, which determine their biological functions. Humans have just over 20,000 different proteins, not counting the wider proteome from alternative splicing, each performing a specific role. Currently complete experimental structures (>90% of protein) have been determined for only ~2% of all human proteins, whilst partial structures are available for almost 22% of these proteins. Modelling, based on the structure of a relative from another species, has provided relatively reliable partial models for about 75% of human proteins. For most other organisms the structural coverage is smaller. Having the protein structures contributes to our understanding of how the protein performs its biological function and is essential, for example for drug and vaccine design. Thus, despite efforts from many crystallography laboratories around the world, there are still many, many proteins (UniProt now holds almost 210 million sequences) for which 3-D structures are not available, in some cases because crystallisation proves difficult.

Ever since the first structure of a protein (myoglobin) was solved by Kendrew in 1958 and the realisation from Anfinsen that simple proteins folded up spontaneously in the right environment, there have been many attempts to predict the three-dimensional structure of a protein from its amino acid sequence. In 1969, the first homology model (a model built by comparing the sequences of two closely related proteins, where one already has a known 3-D structure and the other doesn't) was built manually in David Phillips' lab, using the recently determined lysozyme structure to model the structure of the related alpha-lactalbumin. Most commonly, however, attempts to predict protein structure from sequence have relied on computational methods ranging from simple statistical methods to advanced hardware-based molecular dynamics simulators.

The emergence of machine learning has had a large impact in many different scientific fields. In fact, machine learning has been used in structure prediction for almost 30 years, but now extremely powerful machine learning methods, called deep learning, are available as a result of both new algorithm development and also efficient and relatively cheap accelerator hardware. In many ways, the protein folding problem is a perfect arena in which to test machine learning technology – it is complex; the data are well organised, freely available and massive; there are well-tested scoring criteria for success (allowing results-oriented learning); the CASP experiment provides an independent assessment process and there is a large community of people working on it. However, machine learning on such large datasets consumes large amounts of computational resources, especially in the training stages.

The challenge of how to predict protein structure from sequence has engaged many scientists over the years, to the extent that every two years there has been an independent assessment of our current ability to get the right answer – the CASP (Critical Assessment of Techniques for Protein Structure Prediction) meeting. This experiment has been coordinated by John Moult and colleagues (and funded mainly in the US) since its inception in 1993, and has had a profound influence on the field. Every two years, sequences are made available to the predictors, proposed by crystallography labs worldwide, before the structure is determined or at least before the structure has been submitted for publication. The predictors deposit their model coordinates and once the experimental

structure is determined, the predictions are assessed by independent assessors – usually different experts each year. The results are then presented and discussed at the CASP meeting, and then publications from the most successful groups follow about nine months later. At the most recent experiment (CASP14), over 200 groups deposited results and 67,976 predictions were assessed for 84 targets. To date, targets in CASP have always been predominantly based on single domains, rather than whole chains, but the definition of domains is done *post hoc*, with predictors not being given any information on the domain boundaries beforehand. Assessment, on the other hand, is solely based on the individual domains. The target domains are divided into categories according to the difficulty of the challenge, initially judged by sequence similarity to any available template structures in the Protein Data Bank (PDB) and later on during final assessment according to structural similarity.

Over the years, CASP has accumulated a wide variety of unique metrics to assess the quality of the predictions, which has without a doubt made the results harder to understand by people outside the immediate CASP community. At first, CASP made use of well-known metrics such as RMSD, where the root mean square deviation of the model from the experimental structure is calculated, either on just Cα atoms or all heavy atoms. One of the issues with RMSD is that it is oversensitive to arguably less important differences in structure, e.g. in flexible regions such as in long loops or at the termini. RMSD remains the best measure for relatively close predictions, but for '*de novo*' methods, useful cases where methods had managed to capture at least the correct fold were missed when judged by RMSD alone. Consequently, the CASP organisers developed more forgiving metrics that worked across the range of model quality, i.e. from 'correct fold level' to 'close to native structure'. The main metric in CASP has become the GDT score, or more precisely the GDT-TS score (Global Distance Test – Total Score). Briefly, the GDT score is based on the fraction of Cα positions that can be superposed to the experimental structure within a particular distance threshold. Rather than choosing a single threshold, however, GDT-TS makes use of four thresholds (1, 2, 4, 8Å) and an average is taken. So, if you have a poor model where all the Cα atoms can only be superposed to between 4 and 8Å, which would be more or less random, you would get a GDT-TS score of just 25%, but if all Cα atoms can be superposed to less than 1Å then you would get a perfect 100% score. A score of somewhere between 40 and 50 generally indicates that a correct fold has been produced. This means that a model with a GDT-TS score of 100 would at least have all its Cα atoms within 1Å of the equivalent atoms in the experimental structure, but it doesn't necessarily mean perfect agreement. This is certainly a fairly generous metric compared to things like all-atom coordinate error in crystallography, but nonetheless it provides a good way of comparing both hard *de novo* models and easier homology-based models on the same scale.

Results

To see both how structure prediction at CASP has evolved over time and what AlphaFold's contribution has been, Figure 2 shows some of the trends. This plot is a simplified version of a plot shown by John Moult at the CASP14 meeting. The lines show the mean GDT-TS score performance of the groups in various CASP experiments for targets ranging from easy homology modelling targets to hard *de novo* modelling targets. The lowest line shows the state of play at the very first CASP in 1993. One thing that is apparent is even then it was possible to produce excellent models for the easy targets by homology modelling. This is not really surprising, as sequence alignment alone will get you pretty much the right answer for those targets. This doesn't mean that the side chains are correctly placed, of course, and although not discussed here, this certainly has improved across the years that CASP has been running.

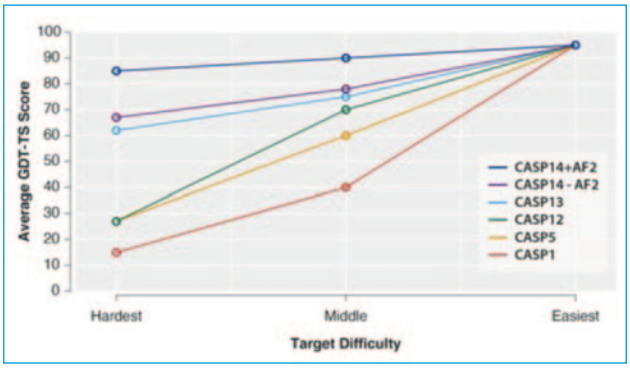

Figure 2: A comparison of pooled results from CASP experiments since CASP1 held in 1993 to the recent CASP14 held in 2020. Targets are divided into the hardest (de novo targets), middle and easiest (simple homology modelling targets). For CASP14 the results are shown with and without the results from AlphaFold (AF2). Data from https://predictioncenter.org/casp14.

The first significant progress that took place in CASP was in the middle of the difficulty range. Methods like Hidden Markov approaches to improve sequence alignment, fold recognition to identify distant relatives and fragment assembly methods, to identify fragments of a known fold and stitch them together, had a major impact. This progress more or less stalled between CASP5 and CASP12, however. Also during this time, at least some of the hardest targets remained intractable for all groups until CASP13 in 2018. Two things contributed to this big jump in accuracy. Firstly, with the rapid growth in sequence data banks, amino acid covariation methods had begun to be used in CASP to pick up correlated mutations in multiple sequence alignments. These evolutionary constraints identify amino acids which are close together in the 3-D structure and allowed even some hard targets to be modelled accurately. The second development that appeared somewhere between CASP12 and CASP13 is that groups started to make use of deep learning methods to get more accurate information from this evolutionary information. AlphaFold is essentially the pinnacle of both of those advances along with some new ones of its own.

Figure 2 shows the impact that AlphaFold had in CASP14. The top line shows the average performance of all groups in CASP14, and the next line shows the same, but with AlphaFold's models excluded. It's quite clear that AlphaFold alone has produced another step change in our ability to model protein domain folds. It was also very consistent, producing a model with a GDT score of 90 or more for two thirds of the targets, with a median score of 92.4 for all targets and a median of 87 even for the hardest targets; it also produced the best model for over 90% of the targets. That's remarkable. Of course, it might be tempting to be critical of the fact that AlphaFold never produces a GDT score of exactly 100, and so clearly doesn't reach the accuracy expected of good crystal structures. However, that would be a naïve view. As a good topical example, Figure 3 shows DeepMind's model for ORF8 of SARS-CoV-2 compared to Chain A of PDB entry 7jtl, which was the official target structure in CASP14. It's clear that AlphaFold has done a very good job here, with a GDT-score of 87, and a Cα RMSD of 1.84Å. At first sight, it would appear that the model, whilst very good, could have

been better. But to put this in context, there is now a second higher resolution crystal structure available for ORF8 with PDB code 7jx6. The resolutions for 7jtl and 7jx6 are 2.04 and 1.61Å respectively. AlphaFold's model still only has a GDT score of 87 to this new structure, which may not be surprising, but what is surprising is that the maximum GDT score *between the two crystal structures* is also only 87. So, despite the low coordinate error we would expect for structures at this resolution, which conformation is the correct one? Can we call AlphaFold's model incorrect when two independently solved structures of the same small protein do not agree? Now inspection of all these structures clearly shows that the differences in this case come down to the large loop between residues 44 and 68 (visible at the top left of Fig. 3), which is probably flexible and perhaps only adopts a stable conformation when bound to its correct ligand. It's also possible that the loop in the two crystal structures is distorted by different crystal contacts. AlphaFold's model may in fact be a better unbiased estimate of the conformation that the loop adopts in free solution. We don't know.

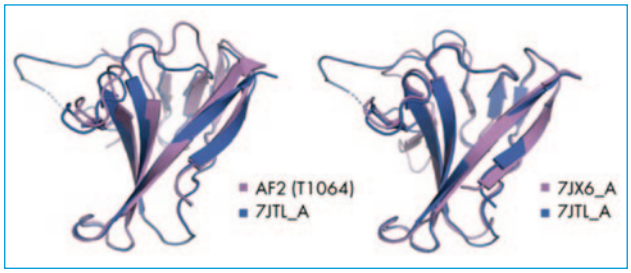

Figure 3: AlphaFold's prediction for SARS-CoV-2 ORF8. This is clearly a good model, but there are differences between the model (AF2) and two independently solved crystal structures (PDB structures 7JTL and 7JX6 A chains).

One very interesting result in CASP14 was that for three or four structures, which the crystallographers were struggling to solve, the AlphaFold models were sufficiently accurate to produce a molecular replacement solution. One such protein was target T1100 (Archaeal Transmembrane Receptor Af1503), provided by one of the CASP14 assessors, Andrei Lupas (Max Planck Institute for Developmental Biology). This protein had been sitting 'in a drawer' since 2010 with native diffraction data available at 3.5Å, but despite there being a reasonable template available in the PDB, no phasing model had ever succeeded in producing a solution. The submitted AlphaFold models, however, produced a clear hit and allowed the structure to be determined. This case is interesting because whilst the domain folds of target T1100 were not in doubt, and many groups produced quite reasonable models, the details of the model clearly were important. As one of the assessors, Nick Grishin, joked, what AlphaFold got right in this case that nobody else did, were the details. This is evident by the fact that the all-atom RMSD for DeepMind's best model for the complete chain was 2.0Å, compared to 4.7Å for the next best group, which is even more impressive when you realize that T1100 is a homodimer (a protein structure made up of two identical copies of the same protein chain) and AlphaFold only submitted a single chain model.

How did DeepMind win CASP?

In more general terms, what DeepMind did that separated them from the chasing pack was that they took the whole CASP prediction process and numerically optimized the whole thing. This approach is commonly known as differentiable programming, and in this specific application is called *end-to-end protein structure prediction*. Basically, the whole process of competing in CASP was captured in a single neural network system, from extracting contact and distance information from the sequence alignments, through the steps of producing an approximate fold (which is where most of us in CASP stop) and finally through to the very difficult process of refining that approximate fold into an accurate all-atom model. All the way to calculating a final RMSD for all of the models generated, in fact. Each of these steps are usually treated as separate parts of the CASP experiment, but here it was implemented in the form of a set of linked neural networks, which made the *whole process fully differentiable*. In other words, they simply did gradient descent on the whole CASP experiment and were able to come up with an unbeatable system by simply training the system to win CASP. They built a modelling system that had the theoretical capability of predicting protein structure at high levels of accuracy, if the optimum parameter settings could be found, and then they basically let the system evolve until it reached the highest level of accuracy. Simple it might sound, and others have proposed more limited approaches along similar lines, but getting all of that to work is still a hugely impressive engineering feat. However, even beyond the engineering challenge, the sheer amount of parameter searching needed is probably way beyond the computational resources available to typical academic researchers, though as computational power becomes cheaper, this may change.

The final publication of the AlphaFold2 paper[1] offered up answers to a lot of unanswered questions that were hanging in the air after the CASP14 meeting was over. The talks by DeepMind at the meeting gave some insight into the workings of the model, but left a lot of gaps, so that researchers enjoyed speculating about what was missing. The basics were obvious from the start. AlphaFold2 was constructed as a set of transformer models using the concept of attention[2].

Transformer models have been extremely successful in tackling natural language processing problems, for example machine translation. The basic function of a transformer is to compute a string of new vectors from a string of input vectors. In the case of human language, these vectors initially represent different words e.g. 'red' or 'apple', but in AlphaFold, these vectors initially represent the 20 different amino acids that make up proteins. A description of how a transformer works is beyond the scope of this article, but basically it means that vectors representing input tokens (for example amino acids) are transformed into new representation vectors based on a weighted average of the original vectors. The weighting comes from the degree of attention (really just similarity) calculated between all pairs, either pairs of vectors from different inputs, or from the same input (called self-attention). Each transformer layer therefore can produce more meaningful representations based on the contexts of the input set of vectors. In the case of a natural language model, with enough transformer layers, English word vectors might end up being transformed into Italian word vectors, simply by training the model on texts taken from the two languages. In the case of AlphaFold, vectors representing amino acids are simply transformed into vectors that represent positions of atoms in 3-D space.

For AlphaFold, the overall system architecture had two main tracks, with the inputs to one track representing the rows and columns of a multiple sequence alignment (MSA), and those of the other track essentially representing the distances between each amino acid in the model. The MSA path allows the network to keep track of amino acid conservation and covariation features, whilst the distance matrix provides the 3-D spatial information for the amino acids. Information is

exchanged between these two tracks, which means that the MSA is reinterpreted as the distance information is improved. Similarly, the distance maps can be improved as the MSA is reinterpreted. At the end, information from the two tracks is fed into the so-called structure module, which embeds the representations in 3-D space i.e. generates a set of atomic coordinates. The job of the structure module is not just to produce a single set of coordinates, but also to make improvements to the initial set of coordinates, again using an attention mechanism, though using a special geometric representation that is invariant to rotations and translations. Here again it was speculated that DeepMind had made use of some new developments in geometric machine learning called SE(3) equivariant attention, but in reality the rotational and translational invariance was achieved using an old trick from structural bioinformatics, where individual local coordinate frames are defined for each residue based on the invariant backbone geometry of amino acids.

In some respects, seeing the final complete description of the method was seen as a little disappointing by some, after the anticipation that built up following the CASP meeting. Not because the method wasn't clever, but simply because there appeared to be no radical new insights that were key to addressing the problem. In many respects, AlphaFold is 'just' a very well-engineered system that takes many of the recently explored ideas in both the bioinformatics and machine learning fields, such as methods to interpret amino acid covariation, and splices them together seamlessly using attention processing.

The AlphaFold Protein Structure Database (https://alphafold.ebi.ac.uk/)

In July 2021, DeepMind, in collaboration with EMBL-EBI, released the AlphaFold predicted structures of the human proteome and the most popular model organisms in the AlphaFold Database [3]. The structures are available open access to all (CC BY-4.0 license) and the data are available for bulk download via FTP (https://ftp.ebi.ac.uk/pub/databases/alphafold). The database is well structured, easy to use by a non-expert and includes a good 3-D viewer. Since then, two more releases have been made – one covering all the annotated protein sequences in UniProt (SwissProt) and most recently (in January 2022) the sequences of organisms on the World Health Organisation's list of 'Neglected Tropical Diseases' and organisms responsible for AMR (AntiMicrobial Resistance). In total there are now about one million structures in the database, covering sequences from 49 organisms. It is anticipated that models for all the sequence entries in UniProt will be made available during 2022, totalling more than 100 million structures[1]. By April 2022, the database was accessed by over 46,000 unique users located worldwide generating 1.5 million page views, illustrating the interest of biologists in the wider biological scientific community in protein models. It will clearly have an impact in the coming years on our understanding of how life works at the molecular level.

Did AlphaFold actually solve the protein folding problem?

In truth, the protein folding problem has never been a thing than can really ever be solved in one go. There are many layers to it, including how a protein fold changes when the ambient conditions are varied, or when the sequence is mutated, or when other molecules interact with it. It is very different from mathematical problems, which are expected to have definitive solutions that are immediately recognized by everyone. Without a doubt, however, AlphaFold's results in CASP14 were remarkably good and certainly represented a major leap forward in the field of protein modelling. Nevertheless, the approach still has some obvious limitations. CASP is a very limited experiment, where tests are only possible on structures solved experimentally in a relatively small window of time (about six months). It therefore has to be borne in mind that CASP only looks at a relatively small sample of test proteins. These proteins are selected not because they cover a wide range of problem cases, but simply because they happen to be being solved during the CASP experiment timeline. Given the time constraints, results do not sample important classes of proteins sufficiently to say whether or not AlphaFold is likely to work on that class of protein.

The models that have been made available via the EBI AlphaFold Database do give us a wider view as to the capabilities of the method, but with those models we generally don't know the correct answers to compare against. Nevertheless, if we look at the models generated for the 20,000 or so genetically encoded human proteins, then a few observations can be made. Firstly, there are many regions in those proteins where AlphaFold is producing essentially random output (see Figure 4). Perhaps rather unwisely, the database was populated by taking each full-length unprocessed protein sequence and feeding it to the neural network. Those of us who have spent a lot of time analysing the human proteome already know that a large fraction of those sequences are disordered and/or low-complexity sequence regions, and it is clear that AlphaFold has really no better idea of what to do with those regions than any previous method. It simply outputs long stretches of 'random coil' with extremely low confidence scores. Given how little experimental data is available for those regions, that's perhaps all we could expect it to do. Not all of the strange looking artefacts produced by AlphaFold can be attributed simply to intrinsically disordered regions. Quite a number of the badly modelled regions will be down to multimeric interactions with either other chains or homomeric interactions with copies of the same chain. The AlphaFold source code (https://github.com/deepmind/alphafold/) and Colab notebook (https://colab.research.google.com/github/deepmind/alphafold/blob/main/notebooks/AlphaFold.ipynb) have been made available and have recently been updated to support predicting multimeric structures.

Continued overleaf.

1. This release was made while this article was in proof: see https://www.nature.com/articles/d41586-022-02083-2, doi: https://doi.org/10.1038/d41586-022-02083-2.

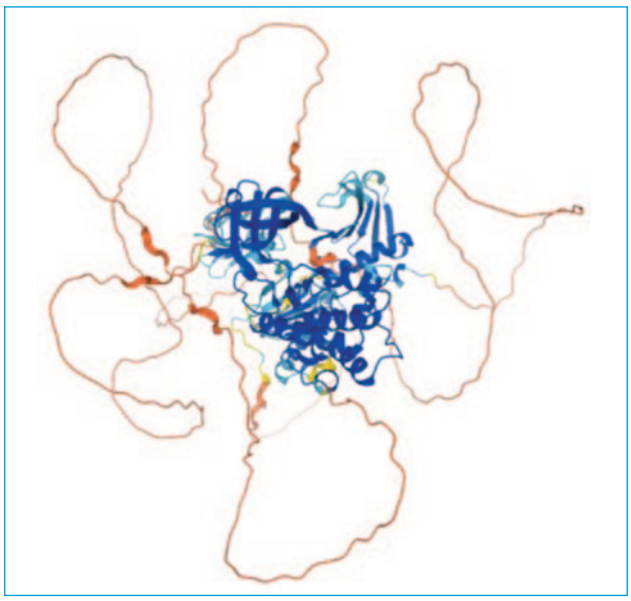

Figure 4: A typical AlphaFold prediction for a human protein sequence (serine/threonine-protein kinase PLK4), taken from the EBI AlphaFold Model Database. The colouring is according to model confidence, with red colours indicating low confidence predictions.

The program also has no way to take account of ligand binding, either small molecules or biological polymers (such as with DNA/RNA/sugars or lipids). In some cases, somewhat surprisingly, a ligand-binding site is correctly modelled, but this can be attributed simply to the fact that the majority of structures in the PDB will have that ligand present in their crystals and so the neural networks will have been trained mostly on the 'holo' form of the structure and are simply reproducing the (useful) biases in the original training data. For example, zinc binding sites (which are very common in protein structures) are often almost identical in the models to an occupied zinc binding site from the PDB, although no zinc is present in the model. From a physical perspective this does not make sense, since the positive charge on the zinc ion clearly stabilises the observed conformation. Without it the conformation would not be energetically stable. As noted on the website: *'AlphaFold is trained to predict the structure of the protein as it might appear in PDB'*.

Certainly, where ligands and their binding to the same protein family is highly variable, immunoglobulin-antibody binding being the most prominent example, AlphaFold does not produce useful results.

There are now many examples of researchers creating 'add-ons' and building tools based on AlphaFold. For example, researchers at the Netherlands Cancer Institute have created AlphaFill (**https://alphafill.eu/**), which adds missing ligands and co-factors to AlphaFold protein structure predictions by using data from related proteins in the PDB[4]. Similarly Agirre and colleagues have added carbohydrate chains to AlphaFold predicted structures[5].

Another fundamental limitation that perhaps has not been emphasized enough is that AlphaFold is dependent on having a reasonably good multiple sequence alignment as input. There is no evidence that (unlike real proteins) it can fold up a single amino acid sequence, but rather that, like previous methods, it is exploiting evolutionary information for its predictions. From a purely practical perspective, especially given the rate at which genome sequencing is taking place, this may not be so important, but there will always be niche proteins for which only one or maybe several related sequences can be found. Then there is the problem of modelling the effects of mutations on protein structures, where AlphaFold generally produces the same answer as it does for the wild type protein. The consequence is that it cannot distinguish benign and pathogenic variants.

Although there was a lot of surprise at how much computational time DeepMind had used to make their CASP models, in practice it seems that the model doesn't require such extreme resources to produce at least acceptable models. Indeed, the pipeline has been streamlined to the point where models can be generated by any user, using Google's free Colab web service, usually in less than half an hour for small to medium-sized proteins. The very best results still require additional processing time to either sample different multiple sequence alignments, or to allow further stochastic searching of the output models, but still for typical models, AlphaFold requires about the same amount of computational time as other popular protein modelling methods.

So, to address the main question, we have to conclude that AlphaFold has not solved the protein folding problem, but certainly has gotten closer than any other method to date. It may be the case that there can never be a definitive single solution to every question that arises from the folding and stability of protein molecules in cells, but for now at least the challenge remains open.

Implications for Experimental Structural Biologists

So, what are the implications of this breakthrough for labs currently involved in experimental structure determination? Reactions on social media from crystallographers ranged from the almost ridiculously enthusiastic to something close to panic. Some clearly think that no prediction can ever replace an experimental structure. Some simply do not believe the results, or at least don't believe that they are representative of the problems they are currently working on. At the extreme end is the worry that some may be out of a job. We don't feel that any of these positions make sense. Firstly, AlphaFold certainly represents a step change in our ability to predict the structures of proteins from amino acid sequences. Any biologist who currently uses any kind of protein modelling or structure prediction tool today is only likely to benefit from these new technological developments.

The first challenge for crystallographers will be to test the accuracy of these predictions through a wide range of appropriate test cases. We need to quantify better the accuracy of the predictions and the limitations of the method. Secondly, many crystallographers have unresolved datasets in a drawer like the aforementioned target T1100 – which might find a solution with a more accurate model for molecular replacement. Approaching DeepMind for predictions may well help to resolve many of these structures – using a combination of experimental data and predicted models.

The other big challenge is of course studying protein interactions with all sorts of ligands. Without such knowledge, the interpretation of how the structure performs its function becomes very difficult. The hope is that progress towards improving our ability to predict such interactions using machine learning will also be made using similar techniques to AlphaFold. Currently, accurate placement of ligands remains challenging, although it is possible in some situations.

At a broader level, in principle we need to work together towards complete structural coverage of the proteome at least for the model organisms, and of course those bacteria and

parasites that cause diseases. The combination of predicted and experimental data will surely move us more rapidly towards this goal. One approach (mirroring the Structural Genomics Initiatives of the 90s), would be to have available structures for all identified domains, which are common throughout life. Such an encyclopaedia would accelerate our ability to interpret genomes, proteomes and their biological functions, and longer term empower cellular tomography to improve our understanding of the proteome content and its distribution throughout all types of cells.

From our perspective, the most exciting thing about this achievement is that this isn't the end of anything, but is really the beginning of many new things. We are convinced that this will enable the field of structural biology to grow and contribute even more to our understanding of life at the molecular level.

David T. Jones, University College London
Janet M. Thornton, European Molecular Biology Laboratory – European Bioinformatics Institute (EMBL-EBI)

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3. K. Tunyasuvunakool *et al.*, *Nature*, **596**, 590 (2021).
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5. H. Bagdonas *et al.*, *Nature Struct. Mol. Biol.* **28**, 869 (2021). https://doi.org/10.1038/s41594-021-00680-9 .

This article is an update of the one originally published in the March 2021 edition of Crystallography News. It will also appear in 'AI for Science', edited by Alok Choudhary, Geoffrey Fox and Tony Hey, World Scientific, Singapore (2022) and is published here with the permission of that book's editors.

BSG Winter Meeting: a note for your diary

THE Winter Meeting of the Biological Structures Group will take place at the Crick Institute in London on 12th December. Its theme will be Dynamic Structural Biology.

For more details contact Mark Roe – M.Roe@sussex.ac.uk.

BCA Spring Meeting 2023

PLANNING is underway for the 2023 BCA Spring Meeting to be held in Sheffield, so please put the dates in your diaries. Details and titles for sessions are given below to inspire you to start thinking about contributing oral or poster abstracts. Remember that the abstract deadline early in the New Year always seems to arrive sooner than expected…

YCG EARLY CAREER SATELLITE MEETING

Monday 3 April 2023

13:00 – 13:30

YCG Opening Plenary

Session Chair: **Thomas Hitchings** *(University of Kent)*
Speaker: **Mark Senn** *(University of Warwick)*
Symmetry assisted insights into ferroic materials

13:30 – 17:15

YCG Research Sessions

Contributed talks from the YCG community.

Session 1: 13:30 – 14:30
Session Chair: **Rebecca Clulow** *(Uppsala University)*

Session 2: 15:00 – 16:00
Session Chair: **Josh Morris** *(Cardiff University)*

Session 3: 16:30 – 17:15
Session Chair: **Alex Campbell** *(University of Edinburgh)*

17:15 – 17:45

YCG Annual General Meeting

18:30 – 21:00

Flash Poster Presentations

Session Chairs: **Phillippa Partridge** *(University of Edinburgh)* & **Julia Gasol Cardona** *(University of Strathclyde)*

19:00

Poster Session with Dinner and Wine

21:00

Evening Concludes

Tuesday 4 April 2023

09:00 – 09:30

Parkin Lecture

Session Chair: **Aly Abdeldaim** *(ISIS Neutron and Muon Source/University of Birmingham)*
Speaker: TBC

09:30 – 10:30

YCG Research Sessions (continued)

Session 4:
Session Chair: **Anna Herlihy** *(ISIS Neutron and Muon Source/Diamond Light Source)*

10:30 – 11:00

YCG Closing Plenary

Session Chair: **Lee Birchall** *(University of Kent)*
Speaker: **Lauren Hatcher** *(Cardiff University)*
Dynamic X-ray diffraction in photoswitchable materials design

BCA 2023 MAIN MEETING

11:30 – 12:15

Lonsdale Lecture

Session Chair: **Anthony Blue Carter** *(University College Dublin)*
Speaker: TBC

13:00 – 13:45

PCG Plenary

Session Chair: **Lewis Owen** *(University of Sheffield)*
Speaker: **Bo Brummerstedt Iversen** *(Aarhus University)*
XFEL Crystallography in Materials Science

14:00 – 15:30

Parallel Sessions

PCG/CCG: Software for Data Processing & Analysis
Session Chair: TBC

CCG/YCG: Crystal Growth
Session Chair: **Jonathan Foster** *(University of Sheffield)*

BSG: Complementary Methods for Structural Biology
Session Chair: **Andrew Burnett** *(University of Leeds)*

16:15 – 17:45

Parallel Sessions

PCG: Phase Transitions
Session Chair: **Arianna Minelli** *(University of Oxford)*

CCG: Databases and associated tools
Session Chair: **Andy Maloney** *(CCDC)*

BSG: Dynamic Structures
Session Chair: **Stephen Muench** *(University of Leeds)*

18:00 – 18:45

CCG Plenary

Speaker: **Kim Jelfs** *(Imperial College London)*

Exploring Supramolecular Materials with Computation

19:00 – 21:00

Poster Session with Dinner and Wine

Wednesday 5 April 2023

09:00 – 09:45

IG Plenary

Session Chair: TBC
Speaker: TBC

10:15 – 11:45

Parallel Sessions

CCG/PCG: Teaching Crystallography
Session Chair: TBC

IG: Industrial XRF
Session Chair: **Tony Bell** *(Sheffield Hallam University)*

BSG: Science for Better Research
Session Chair: **Sam Horrell** *(Diamond Light Source)*

11:45 – 12:15

CCG Annual General Meeting
PCG Annual General Meeting
BSG Annual General Meeting

12:45 – 14:00

Early Career Prize Lectures

Biological Structures Group Early Career Prize

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

Chemical Crystallography Group Prize for Younger Scientists

The CCG will award a prize to a younger scientist who has performed original research in the field of chemical crystallography or the application of crystallographic information to structural chemistry.

14:00 – 15:15

Exhibitor Forum

15:15 – 16:45

Parallel Sessions

YCG/PCG/CCG: Central Facilities Panel Discussion
Session Chairs: **Ben Tragheim** *(University of Warwick)* & **Natalie Pridmore** *(University of Bristol)*

IG: Industrial Crystallography for Pharmaceuticals
Session Chair: **Helen Blade** *(AstraZeneca)*

BSG: Science for Better Health and Wellbeing
Session Chair: TBC

17:15 – 18:00

BCA Prize Lecture

Session Chair: TBC
Speaker: TBC

18:00 – 19:00

BCA Annual General Meeting

19:30 – 01:00

Conference Dinner

Thursday 6 April 2023

09:00 – 09:45

BSG Plenary

Session Chair: TBC
Speaker: **Simon Newstead** *(University of Oxford)*

Decoding the role of Solute Carrier membrane proteins in health and disease

10:15 – 11:45

Parallel Sessions

PCG: Sustainability
Session Chair: **Gabriel Perez Garcia** *(ISIS Neutron and Muon Source/Faraday Institution)*

CCG: Powder Diffraction for Chemical Crystallography
Session Chair: **Iain Oswald** *(University of Strathclyde)*

BSG: Computational Crystallography
Session Chair: TBC

12:15 – 13:45

Parallel Sessions

PCG: Open Session
Session Chair: **Alex Browne** *(University of St Andrews)*

CCG: Crystal Structure Prediction
Session Chair: **Louise Price** *(UCL)*

BSG: 'Difficult Density' Workshop
Session Chair: TBC

CLOSE OF CONFERENCE

The UK National Crystallography

THE UK National Crystallography Service (NCS) has been in continuous operation since 1981 and has been based in Southampton since 1998. It has been a flagship activity throughout this time, supporting a large proportion of the academic research community and aiding them in understanding and publishing their research. It has also been instrumental in defining the state-of-the-art in chemical crystallography. This has ranged from early adoption of automated diffractometers, high-powered sources and area detectors to make a step change in service crystallography, to more recent activities in developing crystallisation technologies and *in situ* experiments. The expertise and equipment make the current facility amongst the widest ranging and highest throughput crystallographic laboratories in the world. Most samples the service deals with cannot be handled by crystallographers operating conventional equipment in their home laboratories.

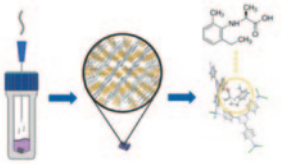
The NCS has just received another 5-year tranche of funding. This comes as a result of a 'Community Statement of Need' exercise which feeds into the requirements for a service and demonstrates the demand. We would like to thank all those who assisted in managing this process, attended workshops and provided feedback. What became clear is that much broader and deeper support, going beyond the traditional realms of service crystallography, is required – this was defined as a set of advanced techniques which are detailed in this article.

To cover this range of techniques it is necessary to combine expertise beyond a single site. Accordingly, we are delighted to announce the formation of a partnership between Southampton and Newcastle universities to deliver the widest possible chemical crystallography capability for the UK.

The primary function of these services is to provide supported routes by which non experts can access these powerful techniques developed by crystallographers. We offer our advanced facilities so that specialist groups can also perform exploratory and screening work, for example in preparation for synchrotron proposals or beamtime.

The NCS runs a call for applications to the service twice per year, but we can also offer a small number of samples on rapid access. For more information or to ask for an allocation, email us at info@ncs.ac.uk. Further information about the service for academic and commercial users, and the techniques described below can be found at www.ncs.ac.uk.

Crystal Sponge



https://www.rigaku.com/webinars/crystalline-sponge/method

Many of us have crystallography service users who desperately seek structural information from barely crystalline samples and oils! This often results in a polite 'quick look', then breaking the inevitable news that it's a hopeless case. Whole areas of the chemistry synthesis community have long since given up on their compounds being suitable for crystallography, with many not even considering it!

Now we can support whole new areas where crystallography is not applicable as obtaining a crystal is illusive, or just not possible. The Crystal Sponge technique enables 'uncrystallisable' compounds, oils and gases to be structurally investigated by single crystal X-ray diffraction. The principle is that the analyte in question is soaked into a porous material and the structure of host+guest is elucidated.

The concept is not new, but is notoriously difficult to undertake. Now the reliable generation of a suitable generic sponge is possible, and the soaking methodology is better understood. The NCS has developed the skills around this technique and the specialist lab required to support it. The technique lends itself very well to pharmaceuticals, but we have also had a lot of success with other small organics and compounds ranging from organometallics to main group materials.

ENaCt

https://www.cell.com/chem/fulltext/S2451-9294(20)30177-7#relatedArticles

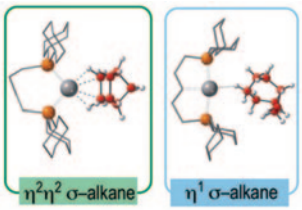
Encapsulated Nanodroplet Crystallisation (ENaCt) is a new approach to crystallisation and we are pleased to announce we have partnered with Indicatrix and Newcastle University to provide an ENaCt crystallisation service as part of the NCS portfolio.

ENaCt uses high throughput robotics to rapidly produce hundreds of screening experiments. Nanolitre droplets of the dissolved material are added to oil droplets, contained in well plates, to slow evaporation. This technique is especially useful if only small amounts of material are available – just 10 mg of material can be used to screen hundreds of crystallisation conditions.

This high-throughput crystallisation service is suitable for rapid polymorph screening as well as finding crystals suitable for full structure analysis. The service will enable the crystallisation of a vast array of sample types generally from the organic soluble small molecule world, although the protocols have been successfully employed previously on systems such as metal organic complexes through to materials previously thought to be 'uncrystallisable'.

Service (NCS)

Gas Environment

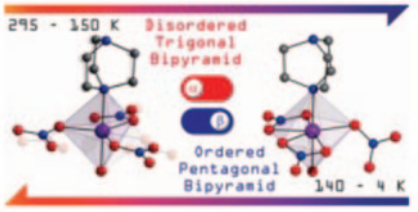


https://pubs.acs.org/doi/10.1021/jacs.8b09364

The interaction or reaction of solids with gases is a fascinating phenomenon with applications from hydrogen storage to catalysis. Acquiring detailed atomic resolution information on the nature of the process and products can be crucial in understanding, developing and engineering these materials. Single crystal X-ray diffraction provides insights into the process, framework interactions and the exact nature of products when exploiting porosity of materials like MOFs for gas capture, filtering, transport. Similarly, one can observe reactions between gases and crystals, e.g. synthesis and solid-state molecular organometallic catalysis.

The NCS has adapted gas cell technology as used on I19 at Diamond to enable this kind of experiment. The challenges for these experiments are in perfecting technical aspects to enable good enough data to fully resolve the structure and in finding the right material/conditions in the first place! The NCS supports projects to screen candidate materials and explore the parameters affecting reaction conditions. We can then collect publication quality data in-house or make a case to use Diamond I19 facilities through several possible access routes (NCS BAG, NCS mediated proposal, independent proposal).

Ultra-low temperature

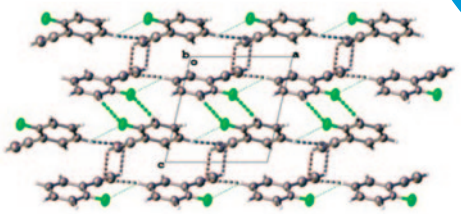


https://pubs.acs.org/doi/full/10.1021/acs.inorgchem.9b00515

Research into ever more exotic materials with technologically driven investigations into properties leads to a requirement to fully understand these systems across a large range of the solid-state phase diagram. The most commonly investigated condition is the variation of temperature. Analysis of structural properties over a wide temperature range can give key insights into the driving forces for the functionality of a compound.

The NCS has previously offered a range of temperatures for measurements predominantly restricted to the liquid N_2 accessible temperature range. The new service operation will expand significantly on the range of temperatures available for studies. This will extend into the ultra-low end of the scale with temperatures accessible for study above 2 K via closed cycle refrigeration and above 30 K through open flow He systems. Structural investigations will vary from simple unit cell mapping to advanced structural studies that either stand alone or can be used to provide preliminary data for future funding applications.

High Pressure

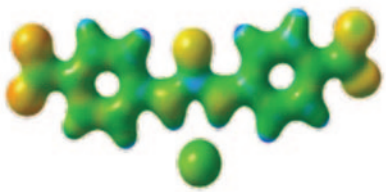


https://pubs.acs.org/doi/10.1021/cg500331u

The search for structure-property relationships in modern materials extends well beyond temperature. Over recent years, investigations into structural evolution with variable pressure have become increasingly attractive and tractable. We now offer these types of studies in a similar way to the variable temperature studies.

The NCS has access to diffractometers optimised for the study of materials under high pressure, principally through the use of shorter wavelength X-radiation. We can explore the effect of pressure on materials using Diamond Anvil Cells, with a variety of pressure transmitting mediums available. The studies available will enable everything from pilot and scoping exercises to note if any transformations occur, through to full structural studies with subsequent analysis of variation in structure and bonding motifs. These studies can again then be used as drivers for longer applications to the NCS, to central facilities or to funding agencies. Due to the nature of the studies, more detailed interactions with the NCS staff will facilitate the best results.

Quantum Crystallography (QCr)



https://doi.org/10.1039/C3CP54858A

Recent software developments and the convergence of crystallography and theoretical chemistry is now enabling a new way of looking at the solid state. By modelling electron distribution more appropriately it is possible to perform more accurate (aspherical) structure refinements; map charge distribution throughout a system; provide quantitative insights into bonding and reactivity; and compute atomic and molecular physico-chemical properties from experimental crystal structures.

These insights can be derived from a high-resolution charge density study or, increasingly, by QCr computation on normal resolution crystal structures. The NCS has a long history of conducting charge density experiments, multipole refinements and electron density analysis and continues to do so. However, QuantumBox, a new EPSRC project in collaboration with the Olex2 team, is setting out to combine the various QCr software packages into a single system that will enable anyone to readily conduct this wide range of analyses. While we are building this, we encourage you to get in touch to collaborate on QCr studies.

Erice School: Crystallography under extreme conditions

STEPPING off the plane into the 32°C heat and bright sunshine of Trapani, Sicily, instantly wiped the stress of UK airports over the Jubilee weekend from mind. The Training School promised crystallography under extreme conditions; relative to Glasgow, these were extreme conditions indeed!

Group photo of School attendees.
Credit: International School of Crystallography.

The School's venue in Erice (a beautiful small historic town crowning a hill 751m above sea level, around 12km from the coast) has a long and proud history of academic, and crystallographic, use. While the first School in 1974 was entitled 'Direct Methods in Crystallography', this was the fourth School to focus on high pressure, backed by enthusiastic responses from courses' previous participants. The title: 'Crystallography under extreme conditions: the future is bright and very compressed'.

A packed seven-day schedule awaited: 34 lectures and four afternoons of workshops were delivered by field experts from across the world, intermingled with the necessary sustenance of beautifully brewed espresso coffee and more fresh local oranges than one knew what to do with.

This School ran concurrently with the 57th course, the first for 'Diffuse Scattering', a rare perk of the two-year lack of in-person meetings which enabled participants of both courses to share introductory lectures on the initial morning, before splitting into their respective courses. Two poster evenings were also shared with the Diffuse Scattering School, giving the participants of both courses fascinating insights into the complementary worlds of research around X-ray techniques used to characterise and probe ordered crystals and amorphous materials, and everything in between.

The lectures spanned the world (and beyond). We heard from researchers based in countries from Brazil to Japan, France to Australia, covering topics as far ranging as the Earth's core to Jupiter's centre, from bacterial survival kilometres below the Earth's crust to pharmaceutical tablet formation. The range of expertise and interests meant there was plenty for everyone to ground themselves in through familiar topics, but also to stretch and apply themselves to new areas of interest.

Dr Helen Maynard-Casey (Australian Centre for Neutron Scattering), one of the directors of the School, opened the scientific programme with an inspiring address covering questions of: why crystallography?; why high-pressure crystallography?; and some of the current challenges and aims of high-pressure research (although the social programme had been well-opened the evening before, in the form of Sicilian Marsala wine and almond biscuits). This set the scene well for an enthralling week.

Dr Kamil Dzuibek (European Laboratory for Non-Linear Spectroscopy) and **Prof. Shanti Deemyad** (University of Utah), the additional directors of the School, gave lectures on phase transitions and stability, and superconductivity, respectively. As an aside, I would like to thank and commend the directors for their work in organising and coordinating the delivery of the School in the face of changing conditions outside their control, especially on the back of such a demanding few years without face-to-face meetings of any kind. Their work, in partnership with the local organisers, resulted in a great time for all involved.

It is a small world inside a high-pressure chamber: previous high-pressure School directors **Prof. Andrzej Katrusiak** (2003, UAM Poznań) gave a lecture on compressibility and anomalous transitions, including discussion of fascinating examples of the rate of pressure change affecting phase transitions, while **Prof. Elena Boldyreva** (2009, Novosibirsk State University) spoke brilliantly on the response of pharmaceutical molecules to external stimuli.

Figure 2: Traditional Sicilian band.

Figure 3: From Erice, looking North over the coastline with a cloud inversion.

The School also offered a selection of tailored workshops. These were incredibly useful hands-on demonstrations and follow-alongs of computational and practical aspects of high-pressure research, such as software for processing both single crystal and powder diffraction data sets, basic DFT simulations, equations of state, loading a diamond anvil cell and the CCDC software suite.

One of my personal highlights may be slightly biased by my penchant for metal-organic chemistry. **Dr Stephen Moggach** (University of Western Australia) gave beautiful illustrations covering phenomena such as coordination bond compressibility and guest-dependent framework response at pressure. Other highlights include a wonderful 16-piece traditional Sicilian band, complete with jaw harp, who played following the welcome dinner, as well as a rooftop bar with particularly stunning views over the coast – unnamed so subsequent years' participants have the joy of coming across it themselves.

As they started, so the lectures finished: **Dr Maynard-Casey** closed with a discussion on means of communicating crystallography, highlighting Lawrence Bragg's belief that "it is our duty, in return for the support we are given, to render an account of our stewardship which is readily understandable by our fellow men [and women]". The IUCr's 'Bragg your pattern' online initiative, coinciding with the 2023 Congress in Melbourne, is a fitting celebration of this.

A discussion of outlooks and perspectives in high-pressure research lead us to reflect that research around extreme conditions has come a long way in a relatively short time. A significant number of synchrotrons now possess dedicated beamlines, and new X-ray sources have enabled reasonably routine in-house measurements. The introduction of fourth generation synchrotrons with further increased brightness, as well as rapidly developing techniques such as X-ray free electron lasers, will enable probing of response to increasingly extreme conditions with unprecedented detail. The high-pressure field certainly has exciting times ahead.

The School closed with a farewell banquet of the finest Sicilian cuisine, followed by a party. A week is not a long time. However, intense training seems to have a way of fostering collegial relationships within an enhanced time scale. Farewells were sincere and well-meant, as new collaborations will no doubt spring from the School's participants in the future, potentially resulting in technique development, new science and good friendship, not necessarily in that order. For crystallography under extreme conditions, the future is indeed bright (and very compressed)!

David Ashworth
University of Strathclyde

Second Intensive Summer School in Physical Crystallography

THE second PCG Intensive Summer School ran in July 2022 in the beautiful setting of The Cosener's House, Abingdon (see image), situated on the bank of the Thames. Made more beautiful by the sunny July weather, respite from the hot summer sun was found – perhaps by design – in the air-conditioned conference room that was to be the base for all lectures and workshops of the school.

These started immediately on the first day with lectures from **Dr Emma McCabe** (Durham University) on group theory which laid a good foundation for the coming days. The cohort of the school was comprised of a blend of physicists and chemists, so the school struck a good balance of both, drawing on existing knowledge of each portion of the group. This blend encouraged peer support and engagement with people in other fields, which was great for fostering a sense of community.

The first full day started with a journey through the reciprocal space with **Prof. Andrew Goodwin** (University of Oxford), before delving into the realm of phonons. In the afternoon, **Dr Fabio Orlandi** (ISIS Neutron and Muon source) introduced us to magnetic space groups and their construction, followed by irreducible representations building nicely on Emma's and Andrew's content. The next morning involved a practical session using ISODISTORT to visualise lattice distortions and practise what had been learnt the day before. This type of session was a common characteristic of the school, with breaks for discussion, working through problems and practice scheduled to cement concepts in people's minds. A flurry of technical talks followed on the topics of inelastic neutron scattering for looking at phonon modes, solid state NMR as a complementary technique, crystallisation of framework materials and an introduction to total scattering for looking at local structure.

The social aspect of the school was particularly welcome after an extended period of online meetings. The first evening icebreaker-style activity was a quiz hosted by **Dr Lewis Owen** (University of Sheffield) with the student teams formed randomly of those from differing institutions. After some left-field lullabies and contentious calculus, the staff team had annihilated the student teams by some margin, but the 'identity operators' (my team!) took the student prize!

The poster session on the second night was a buzz of people excited to share their work with their newly met colleagues. The quality of the posters and scientific content contained within was remarkable, with many discussions continuing in the garden until after dark.

The practical aspect of the school was continued in the content delivered by **Dr Roger Johnson** (UCL) with an introduction to Landau theory involving short breaks to program some of the functions to solidify the concepts. The content on tensors delivered by **Dr Alex Gibbs** (University of St Andrews) was one of my highlights, with the practical for this involving Play-Doh to model and manipulate our tensors to describe the examples provided.

On the final day, after the lectures had finished and all the food of the last few days caught up with us, the collective feeling of everyone was 'cream crackered'. The school thoroughly lived up to its promise of intensity. Still, the support of the lecturers and organisers and the social engagement with peers made this unnoticeable until it was all over, and I was on the train home. I'd thoroughly recommend the experience to any physical crystallographer – there is always more to learn!

Thomas Hitchings
University of Kent

The 2021 Winter Crystallography Meeting

FIRST scheduled for November 2021, then for February 2022, the inaccurately named 'Winter Crystallography Meeting' (as I have come to call the amalgamation of the ISIS and Diamond Crystallography User Group Meetings and the PCG Winter Meeting) finally went ahead on the 16th-17th May 2022 at Milton Hill House near Didcot in Oxfordshire.

There was an air of considerable excitement as people gathered, most for their first in-person meeting since 2019. The programme opened with a fascinating presentation from the 2022 Physical Crystallography Prize winner **Matt Cliffe** (University of Nottingham) who took us through different types of magnetism in coordination frameworks. Following Matt were **Mario Falsaperna** (University of Kent) and **Alexandra Morscher** (University of Liverpool) who both spoke about the crystallography of lithium-containing materials, although from the different perspectives of two-dimensional magnetism and ion conduction respectively. **Sacha Fop** (ISIS Neutron and Muon Source) rounded off the first session with a journey through ion conduction in palmierite-type oxides (I was intrigued to learn that the mineral Palmierite was discovered on Mount Vesuvius and named in honour of physicist Luigi Palmieri, famous for his studies of the volcano).

Session two began with **Simone Anzellini** (Diamond Light Source) who talked about his work to push the conditions on the I15 high-pressure beamline to new highs (of temperature). Next, **Gabriel Perez Garcia** (ISIS/Faraday Institution) gave a whistle-stop tour of the range of *in situ* battery characterisation methods available at ISIS. **Nikolaj Roth** (University of Oxford) described how interesting properties can emerge from local structure in disordered crystals. The final speaker of the session, **Karen Johnston** (Durham University) described an as-yet unsuccessful quest to reproduce the synthesis of a possibly too-good-to-be-true lithium-ion conductor, and the discovery and characterisation (by solid-state NMR) of a family of related materials.

In what is a first for this meeting, we then had a lively session of 'Flash Presentations' where poster presenters had 60 seconds each to advertise their posters. There were some seriously impressive speed-talkers as well as several unlucky ones who were interrupted by the ringing of the bell! The prize for the best Flash went to **Ben Tragheim** (University of Warwick).

The final session of the day started with **Anna Herlihy** (ISIS/Diamond) who presented insights into the structure of barium titanate at high pressure. Then **Alexander Korsunsky** (University of Oxford) talked about blistering in copper-tungsten multi-layers and **Mark Crossman** (University of Warwick) introduced the first results from his newly developed solvothermal reaction cell for *in situ* neutron diffraction. The day concluded with the slightly belated award of the 2021 Malvern Panalytical Thesis Prize to **Chloe Coates** (University of Cambridge) who talked about her Ph.D. work on cadmium cyanide. (As an entertaining side-note, Chloe mentioned that the risk assessment for these materials amounts to 'not as hazardous as they sound like they should be'!

I was unfortunately unable to attend the celebration dinner, but I'm told that the traditional sticky toffee pudding dessert went down well!

Day two opened with the winner of the 2021 BTM Willis Prize, **Joe Paddison** (Oak Ridge National Laboratory, U.S.A.), presenting his work on using diffuse neutron scattering to understand complex magnetism. This was followed by **Alberto Leonardi** (ISIS) talking about disordered nanocrystals and **Alexandra Longcake** (University of Warwick) talking about what happens when you subject rhodium pincer complexes to high pressures. The session concluded with **Sarah Day** (Diamond Light Source) presenting the rather mind-boggling concept of *in situ* studies of space ice!

The final session of the meeting started with **Nick Funnell** (ISIS) presenting work on high pressure total scattering, followed by **Patrick Doheny** (University of Kent) talking about magnetocaloric behaviour in some lanthanide MOFs. Next was **Wesley Surta** (University of Liverpool) who presented his comprehensive model for the binding of sodium ions in amorphous carbon, and announced that the paper on the work had been accepted for publication just hours earlier! **Shi Huang** (University of Hull) spoke about following the crystallisation of an aluminium alloy from the melt, and the session ended with **Jem Pitcairn** (University of Nottingham) who is coincidentally a researcher in the group of Matt Cliffe who opened the meeting! Jem spoke about low-dimensional magnetism in MOFs.

Overall the meeting was, as usual, thoroughly enjoyable and I am grateful to **Craig Bull**, **Steve Hull** and **Sacha Fop** (ISIS) who put together an excellent and varied programme. Planning for the 2022 Winter Meeting (which we hope will actually be held in winter) is underway so watch this space for more information!

Helen Playford, Meeting Organiser
ISIS Neutron and Muon Source

South West Structural Biology Consortium Meeting 2022

THE 2022 edition of the South West Structural Biology Consortium was on the 7th and 8th of July at the University of Bristol, and was the first in-person Consortium since the COVID pandemic. It seems that structural biologists across the south of the UK have been eagerly anticipating a return to in-person events, as more than 130 delegates and exhibitors joined us over the two days at the School of Chemistry to discuss advances in structural biology techniques, the future (and past) of the field, and exciting research being done by the universities of the south.

As always, a large contingent of the attendees were Ph.D. students, who presented their work alongside postdoctoral researchers and group leaders to present an exciting array of research. Topics included the application of serial femtosecond X-ray crystallography for time-resolved analysis of substrate binding, cryoEM investigation of DNA and RNA troubleshooting complexes, and NMR-on-a-chip applications for streamlined characterization of protein-ligand interactions. Notably, **Ivo Tews** (University of Southampton) gave a talk reminding us of the importance of understanding protein dynamics, and that SAXS, NMR and molecular dynamics are important methods to be used in tandem with X-ray crystallography to properly understand protein function and stability. Consequently, **Matt Crump** (University of Bristol) gave a talk discussing advances and applications of NMR in modern times, featuring case studies of its use in structural biology, and revealing a novel and unique ^{13}C, ^{15}N, ^{19}F NMR system for labelling studies that boasts increased sensitivity.

The first plenary lecture was given by the co-founder of the SWSBC and long-time crystallography enthusiast **Leo Brady** (University of Bristol), who marked his retirement from academia the day after the conference. In a fitting end to his long career, Leo spoke to the SWSBC attendees about the wonderful privilege that we have as crystallographers to be able to see the atoms that make up our very nature, and stressed the importance for early-stage researchers to love the work that they do. From his humble beginnings working on insulin and antibodies, 'Splendid times in reciprocal space' detailed Leo's most notable career moments, including notable work within the field of HIV research. Though Leo will be sorely missed, his cycling adventures and retirement plans in his idyllic seaside home are a deserved conclusion for someone so intricately embedded in the history of crystallography in the UK, and the SWSBC.

The second plenary lecture was given by **Tiago Costa** (Imperial College London), a cryoEM specialist in membrane-embedded macromolecular complexes. Tiago revealed the incredible symmetry of Type IV bacterial secretion systems to the audience, as well as the associated F sex pilus from one such

Tiago Costa presenting his cryoEM talk.

*Oral and poster presentation prize winners **Emma Swift** and **Anthony Cheuk**.*

An intent audience for the second plenary lecture.

system which is responsible for DNA conjugation between cells. Through a combination of single-particle cryoEM analysis and a significant amount of biophysical characterization, Tiago revealed the F sex pilus to be a sturdy DNA shuttle used by extremophiles to conjugate DNA in even the harshest of conditions. The talk gave us a useful reminder of the strides that cryoEM continues to make, particularly in relation to large protein complexes, and even included some beautiful architectural symmetry that I'm sure would excite even the most placid crystallographer (*sans* diffraction pattern).

As always, prizes were awarded for the best oral presentation and the best poster presentation. **Anthony Cheuk** (Imperial College London) won the poster presentation with his cryoEM work on the F-type ATP synthase, while **Emma Swift** took the prize for the best oral presentation with her talk on the identification of augmentable sites on the adenovirus knob domain, deduced by homology modelling. Both winners snagged a £50 amazon voucher, as well as an enthusiastic handshake from Paul Race, the PI in charge of organizing SWSBC22. The CCP teams also attended to give us exciting updates about the Cloud and EM software launching in the near future (courtesy of **Maria Fando** (University of Southampton) and **Tom Burnley** (STFC)), while **Kyle Stevenson** (STFC) ran through the CCP4i2 GUI in a live demonstration (a particularly useful talk for early-stage researchers and those beginning to develop their crystallography expertise). Maria in particular caused quite a flurry of interest after revealing that the Cloud service allows simultaneous and parallel processing of data from multiple users, meaning that one lab member may be able to grant access of the data to other members of the lab, and freely share data/results in real time while all members work simultaneously in separate job sessions. Aside from being useful in a structural biology lab, it was noted by many that this could be an excellent tool for teaching the fundamentals of diffraction data processing and structure model building to large classes.

Special thanks should be given to the event sponsors who were able to generously supply funds and be in attendance during the event, including **Patrick Stewart** of Douglas Instruments Ltd, who gave an insightful talk about the new technology that can be applied to protein crystal screening, as well as a reminder of best practices when dealing with protein crystallization. All in all, SWSBC22 appeared to be a successful meeting over a wonderfully sunny (read: swelteringly hot) two days, and we very much look forward to next year's SWSBC, hosted by the University of Southampton.

Rob Barringer
University of Bristol

Single-particle Cryo-EM of Biological Macromolecules

Robert M. Glaeser, Eva Nogales, Wah Chiu

IoP Publishing, May 2021
Hardback ISBN: 9780750330374
Ebook ISBN: 9780750330398
DOI: 10.1088/978-0-7503-3039-8
£120 hardback
£99 ebook

THIS is the book many people have been asking for – a comprehensive account of the theory and practice of single particle cryo-electron microscopy (cryo-EM), the imaging method used to determine the three-dimensional (3D) structures of biological macromolecules and their assemblies. Cryo-EM has been through an explosive period of development to become a prominent approach in structural biology. Its dramatic advances have attracted crystallographers, biochemists and molecular biologists who were previously sceptical or unaware of the power of the method, to apply it to their problems. There is a great demand for a comprehensive documentation of the theory and practice in a single reference text, rather than a profusion of methods articles and brief reviews.

The need is clear – but is it possible to provide a single up to date compilation? This book is a snapshot of the field up to 2020, but things have not stood still since then. For example the emergence of AlphaFold2 with its stunning advance in predicting the fold of individual protein subunits from their sequences has already outdated some aspects of atomic model fitting. The book format has the advantage of being a comprehensive manual, a veritable bible of single particle analysis. But a book cannot be kept up to date in a fast-moving field. The choice of dividing each chapter into 5 or 6 sections, each with a different author, confers the advantage that every section is written by an expert who has thought deeply about the topic and is aware of all the latest developments. On the other hand, the constant change of authors makes the book inhomogeneous, with occasionally jolting shifts in style and approach, repetition of material in different contexts and extensive cross referencing that sometimes impairs readability. Some of the sections would benefit from better copy editing. The ebook format works well with the downloaded Bookshelf app but restricts any printout to only 2 pages. On balance, the advantages outweigh the disadvantages, and this collection provides a unique and valuable resource for practitioners and serious students of the field. It is expensive for students, but well worth providing in any cryo-EM lab.

The book begins with an excellent overview of the field by Nogales, who illustrates the key issues in single particle analysis with a good range of examples. As I started reading through, I was disconcerted by the jumps between authors and topics, with some particularly abrupt transitions from accounts of physical and mathematical basic theory to lists of practical information and protocols. After the overview, we are straight into wave functions and convolutions – a basic physics and maths background is necessary to follow the theory introduced by Glaeser. The box on the different uses and contexts of 'phase' is very welcome, since this is something that students often struggle with. These are essential topics, but biologists will need to look elsewhere for more explanatory figures on the projection theorem.

The second chapter provides comprehensive and useful information on negative stain and cryo-EM sample preparation, indispensable for anyone wishing to start cryo-EM experiments. It begins with a detailed account of negative staining for sample screening, the typical experimental starting point for new single particle cryo-EM projects. It also includes a consideration of preliminary image processing that seems out of place and adds to the inhomogeneity of the book. There is some repetition in the following sections, which cover cryo grid preparation and optimisation, along with discussion of the requirement for thin specimens. The section on grid optimisation by Thompson is particularly clear and well-illustrated.

Data collection is the subject of the third chapter, beginning with a lucid account by Rubinstein of electron-specimen interaction, signal to noise considerations and radiation damage, the ultimate limit to high resolution biological cryo-EM. Then we jump into a practical account of data collection protocols, covering essential methods of low dose and high throughput procedures. This is followed by an authoritative account of defocus, optical corrections and phase plates by Danev, who advises the reader against using the current generation of phase plates for single particle analysis, despite his key role in their development. The final section on data collection covers

movie mode and electron counting, and data acquisition methods at the centre of the resolution revolution brought about by the development of sensitive and high-speed direct electron detectors.

In chapter four, the book becomes more coherent with a series of excellent sections focussed on data processing. Tegunov contributes an instructive section on particle recognition and extraction from micrographs, briefly explaining the use of convolutional neural networks in automated picking, and discussing the various methods available, followed by the use of initial classification steps to identify and exclude unwanted particles ('cleaning up' the data set). This is followed by a detailed account of the theory and practice of image restoration, correction of the image data for the distortions caused by the contrast transfer function. Practical advice is provided on the box size needed to retain all the structural information under different optical conditions. The following section contains a comprehensive overview of the single particle analysis workflow from starting model to 3D structure, for the basic case of a structurally homogeneous data set. The various methods are explained, including considerations of the numbers of particles needed to obtain a high-quality structure. We then turn to the two issues that typically complicate most single particle analyses – heterogeneity and preferred orientation. The section on heterogeneity goes through global 3D classification and then focussed methods used in RELION to apply masking, subtraction or correction of pseudosymmetry. The problem of preferred orientation is treated in a detailed analysis by Lyumkis, who considers the physical chemistry of the interface and analysis of anisotropy and reviews the various approaches to reducing it. The chapter then moves on to post processing, with a section on B factors and map sharpening, and concludes with a section by Zivanov, Nakane & Scheres on an advanced treatment of aberrations and Ewald sphere curvature, effects that must be corrected for to reach atomic resolution. This section requires a mathematical background.

Chapter five covers map validation, an important area that is still evolving. Especially for intermediate and lower resolution maps, there is no foolproof method for establishing the correctness of the structure. The most widely accepted measure, the Fourier shell correlation, can be affected by systematic errors. Its use and pitfalls are discussed by Ludtke. This is followed by a section on bias and over fitting, with practical advice on how to judge the progress of single particle refinement. Finally, Heymann considers the effect of the signal to noise ratio on alignment accuracy. The topic is logically developed in a clear and thoughtful account.

The final chapter covers the interpretation of cryo-EM by atomic model building, starting with a tour by Malhotra, Joseph and Topf of the methods for fitting known components into maps in different resolution ranges, along with consideration of how to evaluate the resulting model fits. The second section goes into more detail on template based and *de novo* atomic model building into cryo-EM maps, model refinement and validation. Then Pintilie, Lawson and Chiu provide a detailed discussion on quality evaluation of the models themselves. This is followed by a discussion of how the Phenix software developed for crystallography has been adapted for model building into cryo-EM maps, refinement and validation. The chapter concludes with an account of structure databases and how to go about deposition of cryo-EM data, maps and the atomic models derived from them.

In summary, this book is a valuable resource for anyone wanting to understand the principles and practice of cryo-EM single particle analysis.

Helen Saibil
Birkbeck College

Congratulations to Bill Clegg, winner of the ECA Max Perutz Prize!

Bill Clegg (Newcastle University), an Honorary member of the BCA, has been awarded the twelfth Max Perutz Prize of the European Crystallographic Association.

As many of us know, Bill has made a tremendous impact on crystallographic science and education during a career spanning nearly five decades – from the days that structures were still solved from photographic films until today when data can be collected within a few minutes thanks to hybrid pixel detectors and multilayer optics.

Bill was a pioneer in the development and exploitation of small-molecule and inorganic single-crystal diffraction at the Daresbury synchrotron, providing a model for many single-crystal synchrotron beamlines around the world. He also realized the importance of wide-ranging access to the Daresbury and later the Diamond Light Source facilities by initiating the UK national service for synchrotron chemical crystallography, and directing it between 2001 to 2010.

The diversity, as well as the number of the topics Bill has worked on is impressive: blending gelators, dye-sensitized solar cells, metal-organic and cationic inorganic framework structures, pendulum pentacoordinate silicon complexes, polyhedral oligomeric silsesquioxane structures, etc., etc., etc… He has also shown a life-long strong commitment to crystallographic teaching: for example, he was part of the organisation and teaching team at 16 BCA intensive X-ray structure analysis courses and has taught at numerous crystallography schools outside the UK.

Thousands of copies have been sold of his 'X-Ray Crystallography' book in the OUP Oxford Chemistry Primer series, a book which has served as the basis for many undergraduate courses in diffraction. He has also presented his ideas on crystallographic education at both the ECA and ACA, very successfully encouraging attendance with imaginative titles such as '*Teaching new dogs old tricks*', '*What I learnt from my first structures*' and '*Opening the black box*'.

Bill's Perutz Prize Lecture was delivered in the largest hall at the *Palais des Congrès* in Versailles during the opening ceremony of the 33rd European Crystallographic Meeting!

UKRI Infrastructure Fund

15th June 2022: A Good Day for UK Structural Science!

On June 15th, UK Research and Innovation (UKRI) announced a £481 million investment in major research and innovation infrastructure over the next three years. With respect to structural science, this included funding of £73 million for both the ISIS Endeavour Programme and ISIS-II project (see *Crystallography News*, December 2021 page 23), and £81.5 million for the first phase of Diamond-II (see *Crystallography News*, September 2020, page 17). Both projects have now had their outline business cases approved by HM Treasury, enabling both laboratories to move on with the development of Full Business Cases. Also successful was the European Bioinformatics Institute (EMBL-EBI) Data Resources for the Life Sciences Phase 2, and the X-Ray Free Electron Laser (XFEL): conceptual design and options analysis scoping project (see *Crystallography News* September 2020 page 11).

Image courtesy of © Diamond Light Source Ltd.

With respect to Diamond, **Andrew Harrison**, Diamond CEO and Senior Responsible Officer for Diamond-II has said:

"Diamond's success owes a great debt of gratitude to the trust and commitment of its funding agencies, the UK Government - through BEIS, UKRI and UKRI's STFC (Science Technology and Facilities Council), and the Wellcome Trust who have provided ongoing support. It is great to see they are fully behind Diamond-II and all have enabled this funding confirmation. This investment will set a course to strengthen the UK's global scientific leadership. We are very pleased indeed to have received this support, but we also have to be prepared for the challenges of delivering the Programme in full with the substantial rise in inflation as well as supply chain issues, in a difficult world situation and also in competition with other international facilities."

The overall programme includes:

- Equipment to replace the synchrotron machine
- Five new beamlines and critical beamline upgrades
- New computing hardware and software
- A new building to house staff and equipment.

Image courtesy of STFC.

For ISIS, **Roger Eccleston**, ISIS Director, has said:

"I am delighted with today's announcement of funding for both the Endeavour Programme and the ISIS-II feasibility studies. The Endeavour Programme will deliver a significant increase in the capabilities and capacity of ISIS, and provide new opportunities for our national and international users, creating new knowledge and addressing global challenges such as the drive to carbon net zero. ISIS-II will be the UK's next generation neutron and muon source providing a step-change increase in capability. Together these exciting projects will ensure UK researchers have access to the unique insights neutrons and muons provide as part of our world-class research infrastructure."

Starting in FY23/24, Endeavour (**https://www.isis.stfc.ac.uk/Pages/Endeavour.aspx**) will provide new instruments and significant upgrades of several others at ISIS. The Endeavour instruments will further ISIS' international scope, and will enable research in areas such as advanced materials and manufacturing, clean energy technologies, and biosciences and healthcare. The scoping funding for the ISIS-II project – the proposal for a next-generation neutron source – will enable initial feasibility and design studies on the high-level parameters, proton driver and target system architectures, and sustainability considerations required to develop a next generation facility as a successor to ISIS.

Image courtesy of EMBL-EBI.

For the European Bioinformatics Institute, **Ewan Birney**, Director of EMBL-EBI has said:

"We're seeing unprecedented volumes of data generated and submitted to us in recent years, so the UKRI funding will enable the essential transformation of our technical infrastructure to respond."

The funding will enable the development of new data platforms and portals to address global priorities, such as antimicrobial resistance, sustainable agriculture and biodiversity loss. And with the EMBL-EBI websites getting 107 million requests on an average day – triple the number over three years ago – this additional support will help make substantial updates for the benefit of users.

With respect to the X-Ray Free Electron Laser (XFEL), £3.2 million pounds has been awarded for a conceptual design and options analysis. This will explore different options to provide access to a second generation XFEL capability for UK scientists. The coherent X-rays can be used to study matter simultaneously on spatial and temporal scales, a capability that allows for a wide range of cutting edge multidisciplinary applications across science and technology. For instance, in bioscience and healthcare, mapping atomic details of viruses and supporting drug discovery.

The details of the full Infrastructure Fund portfolio can be found at **https://www.ukri.org/what-we-offer/creating-world-class-research-and-innovation-infrastructure/funded-infrastructure-projects/**.

ISIS Neutron Training Course 28 February - 9 March 2023

THE ISIS Practical Neutron Training Course is a hands-on course aimed at Ph.D. and post-doctoral researchers who have little or no experience of neutron scattering, but whose future research programme aims to make use of neutron scattering techniques at ISIS.

Course outline:

- **Basic Principles Lectures:** Neutron Time-of-flight, Detectors, Neutron materials and interactions, Instrument Components, Neutron Scattering Theory.
- **Chemistry and Materials Stream:** Powder and single crystal diffraction, Rietveld refinement (GSAS), Molecular Spectroscopy, Diffuse scattering, Non-crystalline materials scattering, Quasi-elastic neutron scattering.
- **Physics Stream:** Neutron diffraction, magnetic Rietveld refinement (Fullprof), inelastic scattering - polycrystals and single crystals.
- **Soft Matter Stream:** Sample preparation and deuteration, Small-angle neutron scattering, Neutron reflectometry.
- **Optional Modules:** Computational methods (DFT), Molecular Dynamics Simulations, Quasi-elastic Scattering for soft or hard matter, Biological SANS data reduction, Polarized reflectometry for soft matter, Engineering strain in Materials, MAPS for catalysis, Dissolve for disordered materials, Phonon analysis.

The course is free to participating students, and includes free accommodation at Cosener's House in Abingdon, and travel expenses within the UK.

For further details please contact the organisers:
helen.c.walker@stfc.ac.uk
alex.hannon@stfc.ac.uk
najet.mahmoudi@stfc.ac.uk.

Further information at
https://www.isis.stfc.ac.uk/Pages/ISIS-Neutron-Training-Course.aspx.

The Industrial Group now has twitter! And wants to hear from you!

News from the Cambridge Crystallographic Data Centre (CCDC)

2022.2 CSD Release (July 2022)

In the 2022.2 CSD release the new CSD-Particle suite https://www.ccdc.cam.ac.uk/solutions/software/csd-particle/ was launched. It is available to all academics with a full CSD licence. With it, you can analyse the mechanical and chemical properties of crystalline particles, to guide formulation decisions and anticipate manufacturing bottlenecks caused by issues in tabletability, wettability, flow, or sticking.

With the CSD-Particle you can predict particle facets, visualize surface chemistry, charge, topology, and interactions, identify potential slip planes, determine H-bond dimensionality, quantify surface chemistry and topology, and more.

Updates were also made to SMARTS, allowing the use of recursive and dot-disconnect SMARTS in the CSD Python API, and Mercury. There is now full implementation of atom conditionals, and variable bond conditions are supported. These changes allow for the automation of large numbers of queries, as well as making it possible to do more complex searches not possible before in ConQuest.

The update is accessible at https://www.ccdc.cam.ac.uk/solutions/whats-new/.

2022 CSD data updates – thank you for your contributions!

There have been 2 major CSD data updates so far this year:

- March 2022: 18,119 new structures (19,435 new entries).
  - This update included 3 new subsets further classifying the MOF subset into groups based on the dimensionality of the framework.
- June 2022: 15,450 new structures (15,998 new entries).

The CSD is almost at 1.2 million entries. As always we are grateful to the crystallography community, who continue to share their data in the CSD, making it accessible to the wider scientific community to enable future research.

Did you know that experimental crystallography data can be submitted without a publication as a *CSD Communication*? You are still recognized as the author and provided with a DOI, the data is securely stored, and made accessible to the wider community to learn from your work. You can even submit paper copy results in this way. Learn more at https://www.ccdc.cam.ac.uk/Community/csd-communications/CSDCommunicationsInformation/ or email deposit@ccdc.cam.ac.uk

CCDC Virtual Workshops and on-demand learning

Join us in October for the next series of CCDC Virtual Workshop! Our Virtual Workshops are free live online sessions designed to introduce you to the CSD and functionality from the CSD Software. You can try the functionality hands-on and ask your questions to our expert tutors. Check our events page https://www.ccdc.cam.ac.uk/News/Events/ to find out dates and topics and to register.

We also continue to curate our collection of on-demand CSDU modules https://www.ccdc.cam.ac.uk/Community/educationalresources/CSDU/ that you can complete at your own pace and earn a completion certificate. The collection available on our website now includes a module on the basics of the CSD Python API https://www.ccdc.cam.ac.uk/Community/educationalresources/CSDU/csd-python-api-101/. Explore all the modules!

New videos: Mercury tutorials, and elements in science fiction

We regularly publish short videos to help scientists at all levels get more from the CSD, Mercury, and other CCDC software.

- This tutorial https://www.youtube.com/watch?v=FvKgc42Xik0 shows you how to label atoms and stereocentres in Mercury.
- This one https://www.youtube.com/watch?v=-JPYCbMqhfE covers how to create, manage and share styles in Mercury.

As part of our ongoing commitment to education and outreach, we also look for ways to inspire the next generation in crystallography. We recently collaborated with the BCA to produce this video https://www.youtube.com/watch?v=uULPCx-GtVg exploring elements and materials referenced in popular science fiction and video games. It's 10-minutes long and suitable to play in classrooms from age 12+.

Explore our YouTube channel here https://www.youtube.com/channel/UCT3mRwMjLxgoAfe8lHIFCoA and subscribe for updates.

Download, use, and contribute scripts to work with crystallography data in the CSD GitHub repo

The CCDC recently launched the CSD GitHub repository, to share scripts to make crystallography and cheminformatics tasks simpler. You can download and use scripts for free, edit and modify them, or submit new scripts to share with the community.

The scripts help to automate a range of tasks, like concatenating MOL2 files, creating CASTEP .cell and .params files for a structure viewed in Mercury, or comparing the packing of a set of structures. Learn more about how it works and how to access the repository here: https://www.ccdc.cam.ac.uk/Community/blog/download-csd-python-api-scripts-github/.

Meetings of interest

WITH a little less concern about the virus (which may or may not be justified!), the conference scene seems to have been significantly revitalised, with quite a lot of new meetings being organised – so you might well find something new and interesting in this list. Most meetings are in-person ones, though some remain online or hybrid. Further information may be obtained from the websites given. Assistance from the IUCr website is gratefully acknowledged.

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

5th Sep 2022 - 9th Sep 2022
Mathematics and Computer Science for Materials Innovation: Crystal Lattice Classifications (ECM33 Satellite meeting)
Liverpool, U.K.
http://kurlin.org/ECM33MACSMIN2022crystal-lattice-classifications.html

7th Sep 2022 - 11th Sep 2022
28th Croatian-Slovenian Crystallographic Meeting
Poreč, Croatia.
http://kristalografi2020.s13.novenaweb.info/

7th Sep 2022 - 8th Sep 2022
STOE User Meeting – online
https://register.gotowebinar.com/register/2536942083395759115

8th Sep 2022 - 9th Sep 2022
STOE User Meeting – in person
Darmstadt, Germany.
https://www.stoe.com/meeting/

11th Sep 2022 - 14th Sep 2022
9th Electron Tomography Conference
Egmond aan Zee, Netherlands.
https://tomo2020.org/

11th Sep 2022 - 16th Sep 2022
XVIII International Small Angle Scattering Conference
Campinas-SP, Brazil. Hybrid.
https://pages.cnpem.br/sas2022/

12th Sep 2022 - 16th Sep 2022
Frederick National Laboratory Cryo-EM Training Workshop
Frederick, MD, U.S.A.
https://frederick.cancer.gov/resources/national-cryo-electron-microscopy-facility/ncef-cryo-em-training-program

16th Sep 2022 - 20th Sep 2022
7th School of Small Angle X-Ray Scattering
Campinas-SP, Brazil.
https://pages.cnpem.br/schoolofsaxs/

21st Sep 2022 - 23rd Sep 2022
Nanoalloys: Recent Developments and Future Perspectives
Faraday Discussion.
London, U.K.
https://rsc.li/nanoalloys-fd2022

22nd Sep 2022 - 24th Sep 2022
24th Heart of Europe Bio-Crystallography Meeting
Dolní Vltavice, Czech Republic.
https://www.xray.cz/hec24/

26th Sep 2022 - 30th Sep 2022
Integrative Data-Intensive Approaches to Drug Design
Heidelberg, Germany.
https://www.euroqsar2022.org/

27th Sep 2022 - 28th Sep 2022
PLM16 – Physics of Living Matter
Marseilles, France.
https://centuri-livingsystems.org/plm16/

3rd Oct 2022 - 7th Oct 2022
Magnetic Structure Determination from Neutron Diffraction Data
Oak Ridge, TN, U.S.A.
https://conference.sns.gov/event/339/

16th Oct 2022 - 21st Oct 2022
School and Conference on Analysis of Diffraction Data in Real Space
Grenoble, France.
https://workshops.ill.fr/event/306/

30th Oct 2022 - 2nd Nov 2022
17th Conference of the Asian Crystallographic Association
Jeju Island, Republic of Korea.
http://www.asca2022.org/

28th Nov 2022 - 30th Nov 2022
V Meeting of the Latin American Crystallographic Association
San José, Costa Rica.
aaraya@cenat.ac.cr

6th Dec 2022 - 10th Dec 2022
IUCr High Pressure workshop 'Advanced High Pressure Crystallography'
Chicago, IL, U.S.A.
https://gsecars.uchicago.edu/education-and-outreach/2022-iucr-high-pressure-workshop-advanced-high-pressure-crystallography/

19th Mar 2023 - 23rd Mar 2023
Neutron and X-ray Scattering in Materials Science (TMS Annual Meeting)
San Diego, CA, U.S.A.
https://www.tms.org/AnnualMeeting/TMS2023

27th Mar 2023 - 30th Mar 2023
Physics of Life 2023
Harrogate, U.K.
https://www.physicsoflife.org.uk/physics-of-life-2023.html

3rd Jul 2023 - 6th Jul 2023
16th International Conference on Materials Chemistry
Dublin, Ireland.
https://www.rsc.org/events/detail/72840/

7th Jul 2023 - 11th Jul 2023
73rd ACA Annual Meeting
Baltimore, MD, U.S.A.
https://www.amercrystalassn.org/future-meetings

20th Aug 2024 - 24th Aug 2024
34th European Crystallographic Meeting (ECM34)
Padova, Italy.
https://ecanews.org/meetings/

22nd Aug 2023 - 29th Aug 2023
26th Congress and General Assembly of the IUCr
Melbourne, Australia.
https://iucr2023.org/

4th Sep 2023 - 8th Sep 2023
CMD30 (Condensed Matter Division of the European Physical Society)
Milano, Italy.
https://eventi.cnism.it/cmd30-fismat

OXFORD CRYOSYSTEMS

CRYOSTREAM 1000

Precise Cryogenic Sample Cooling Made Simple

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KEY FEATURES

X-ray Transparent Nozzle: An optional attachment for the coldhead nozzle, the X-ray transparent extension is made from a durable and low-temperature compatible material that minimises shadowing on the X-ray detector, increasing the amount of useful diffraction data collected without compromising cooling performance. This can either reduce the duration of experiments or improve the signal-to-noise ratio and overall data quality.

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Gas Supply Module: Combines the Nitrogen pump, dry-air supply and touch screen controller into a single, compact and portable enclosure that reduces cabling, simplifies installation and improves the user experience.

Remote Annealing: Controlled and programmable interruption of the gas flow over the sample for annealing without physical manipulation (also available via an open network protocol).

Intelligent Diagnostics: An integrated real-time clock now tracks the use of the system, notifying the user of upcoming service requirements, helping to eliminate unscheduled downtime.

2 Year Standard Warranty: All Cryostream 1000 systems ship with a two year warranty as standard.

For more information, visit our website or contact info@oxcryo.com.

www.oxcryo.com

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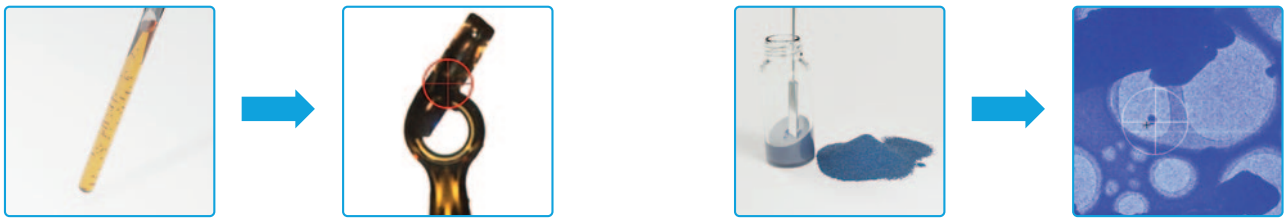

Rigaku oxford diffraction

CrysAlis^{Pro}

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