Crystallography News

British Crystallographic Association

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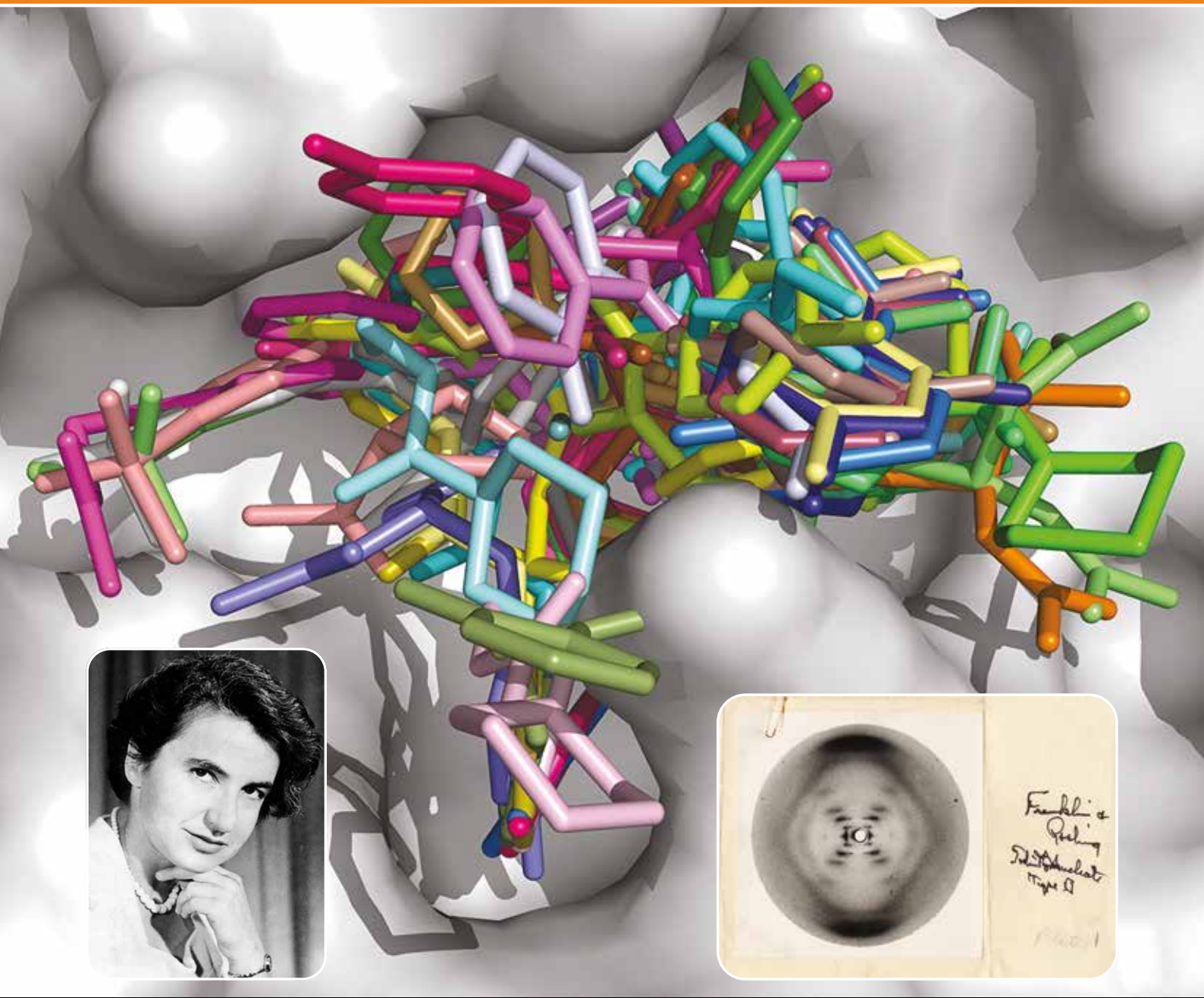

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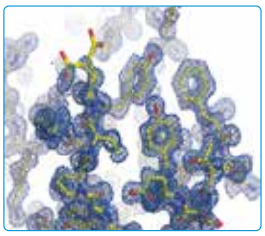

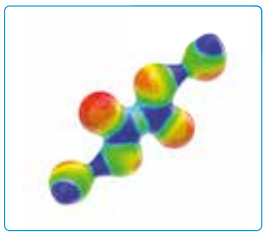

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British Crystallographic Association

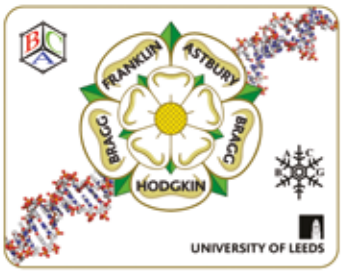
Bursaries for conference attendance in 2020/21

Bursaries and awards are available as normal to BCA members through the Arnold Beevers Bursary Fund and the BCA Industrial Group.

BCA members who are students/post-docs/junior or non-permanent staff are eligible to apply for bursaries to attend BCA Spring meetings and other crystallographic meetings. Applications should be made via the website:
https://crystallography.org.uk/prizes/bursaries

Additional Carers grants are available to BCA members at any career stage:
https://industrial.crystallography.org.uk/bursaries-and-awards/

Applications for ABBF and IG bursaries can be made at the ABBF portal on the BCA website, and for the Carers award on the IG website



Contents

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CRYSTALLOGRAPHY NEWS is published quarterly (March, June, September and December) by the British Crystallographic Association, and printed by North Wolds, York. Text should preferably be sent electronically as MSword documents (any version - .docx, .doc, .rtf or .txt files) or else on a PC disk. Diagrams and figures are most welcome, but please send them separately from text as .jpg, .gif, .tif, or .bmp files. Items may include technical articles, news about people (eg awards, honours, retirements etc), reports on past meetings of interest to crystallographers, notices of future meetings, historical reminiscences, letters to the editor, book, hardware or software reviews.
Please ensure that items for inclusion in the September 2020 issue are sent to the Editor to arrive before 25 July 2020.

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

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This month's cover:

The active site of the SARS-CoV-2 main protease; Rosalind Franklin; her key X-ray photo.

From the President

It is a pleasure to welcome **John Finney** as the new editor of Crystallography News, filling the capacious shoes of our much loved, and widely missed, previous editor **Carl Schwalbe**. John has had a long and very distinguished career using X-ray and neutron crystallography, and scattering techniques, to investigate the structure of water. He was a student of the great **J.D. Bernal**, a polymath sometimes referred to as simply "Sage". Those not working at the biological end of crystallography may not be aware of Bernal's remarkable contributions, and would probably find it interesting to read about him. As well as thanking John for taking over the mantle, I would like to reiterate my thanks to **Simon Coles** for keeping the newsletter running so efficiently in the interim period.

I sat down to write this column on a wet Saturday in mid-April, in a world that had changed suddenly and dramatically. I expected to be reminiscing about a great Spring Meeting in Leeds, and looking out from my window over our village recreation ground, where two teams of enthusiastic children would have been playing a football match. There would normally have been excited shrieks from the players and cheers from the watching parents, but there is only birdsong. The pitch is occupied by a few jackdaws while a red kite circles silently overhead. This is the new reality of the Coronavirus lockdown in rural Oxfordshire, but the change must be even more dramatic for those readers living in a city. It is, of course, devastating for those who have lost loved ones in the pandemic. When you read this, things may well have changed, but it is very hard to predict exactly how. Chances are that your copy of this June issue of Crystallography News will have been delivered to your laboratory address and it may be very old news when you first see it.

The lockdown has been an opportunity for reflection on the importance of a wide range of science, from our beloved crystallography to virology, medicinal chemistry, vaccine design and epidemiological modelling, on our well-being. It also brings into focus the importance of key workers, not least on the hazardous front line of the NHS and care homes. In addition, we should think of the essential support of cleaners, supermarket staff, pharmacists, teachers, police, emergency workers, delivery drivers, bin men and ladies etc., and we might compare their contribution to society, and their pay packets, with, to choose a random example, hedge fund managers currently encouraging investors to cash in on cheap shares depressed by the pandemic crisis. I hope our political masters will take careful note when developing policy in the future.

The solution to our predicament in the Covid-19 pandemic lies clearly with science, and certainly not in remedies peddled on social media, and even by senior politicians in some countries. Finding the exit route depends on a fuller understanding of the SARS-CoV-2 virus structure and function, and development of vaccine and drug treatments. Crystallography, together with cryo-EM, has been at the forefront, with structures of key virus components determined with astonishing speed and international co-operation. At the time of writing, there are 131 structures of viral components in the Protein Data Bank (PDB), the majority being crystal structures, with a further 14 in the EM Data Bank. The main targets are the spike glycoprotein, that sits on the surface of the virus and binds receptors on human cells to mediate entry, the replicase complex, that copies the viral RNA genes, and the protease, that cuts up newly synthesized viral proteins in infected cells into correctly-sized, active units. Crystallizing viral proteins can be challenging, but we already had experience with the very similar SARS and MERS viruses, and the UK has some of the best virus crystallography expertise. The vast majority of the 131 crystal structures in the PDB are of complexes of the protease with ligands that might be potential lead compounds for drug design. This remarkable work was carried out at the Diamond Light Source, and an article describing it appears elsewhere in this issue. Effective combination drug therapies, such as for HIV, aim at inhibiting more than one critical phase of virus reproduction, and the replicase complex is also a key drug target. This is more complex and difficult to crystallize, but structures have been done using the latest cryo-EM methodology, incidentally the subject of the Bragg Lecture that we would have heard from **Richard Henderson** at the Spring Meeting. Some antiviral drugs act by inhibiting replication of the RNA, and a recent structure of the SARS-CoV-2 replicase shows the antiviral drug Remdesivir bound in its active site. There are crystal and cryo-EM structures for the spike glycoprotein and its complexes with the receptor, as well as with an antibody from a human patient who recovered from the infection. Structural data like these provide essential underpinning for design of therapies and vaccines. Not so long ago, it would have taken years to achieve what has been done in the last three months. Our structural science now allows us to react to emergencies in real time, and this will contribute to saving lives.

The BCA Council is operating during the lockdown, and met in a videoconference on 6th April, which would have been the first day of the Spring Meeting. It will continue to meet on a normal schedule, and plan for future activities in the expectation of a relaxation of the lockdown. The Annual General Meeting should also have taken place at the Spring Meeting, but it will now be held on the 18th June using webinar technology. The 2021 Spring Meeting will be held in Leeds on 29th March-1st April, with much of the programme carried over from 2020. An exciting development, previously planned for 2021, is to hold the meeting jointly with the British Association for Crystal Growth.

There will be Council elections this year, on the usual schedule. The posts available for election are:

- BCA President
- One Ordinary Member
- Education and Outreach Co-ordinator

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 the 30th September.

Finally, I would like to offer my best wishes to all of you, and your families, at this difficult time.

Simon Phillips

BCA Council 2020

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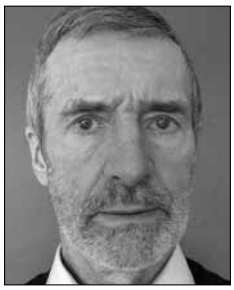
(The dates in parentheses indicate the end of the term of office).

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

From the Editor



WELCOME to the first ever "lockdown" issue of Crystallography News! For obvious reasons, its content is not what you would normally expect for the issue that follows the annual Spring Meeting, but I hope you will find what's on offer both of interest and stimulating.

When I had my arm twisted to take on the Crystallography News editor's job, I thought this first issue would be a doddle. All I'd have to do would be to collect the reports of the Spring Meeting scientific sessions, add a couple of items I'd already got in hand, revise the Meetings of Interest section and Hey Presto! Job done and off to the designer!

The best laid plans etc. etc. etc… With the cancellation of the Leeds Spring Meeting, the Crystallography News cupboard was left pretty bare, and I was left with having to find lots of crystallographic news when most of that news was of cancelled and postponed meetings, and when colleagues were busy trying to sort out their online lectures and remote examinations for the coming term – as well as teach their kids at home.

I needn't have worried. Following emails asking for material, members responded magnificently – not only by providing more material than I could squeeze in (helpfully giving a base for the September issue), but also meeting the copy deadline! Many thanks to everyone who did respond, either by contributing material or suggesting articles of potential interest that I could follow up on. So I hope you find what's in this issue of interest – from a celebration of Rosalind Franklin on the occasion of the 100th anniversary of her birth, through the impressive collaborative response of crystallographers to the Covid-19 pandemic and an article on a continuing controversy on the structure of water, to a trip down memory lane to see how X-ray data were taken in days – or rather decades – gone by. And we still do have some meeting reports – not only from the days when we could get together in person but also of a first experience of a virtual conference. And finally we have some memories of a fondly-remembered colleague.

Simon Coles in the last issue and Simon Phillips in this one have mentioned something of my scientific background, which began in the mid-1960s working as a research assistant to J.D. Bernal in the Birkbeck College Crystallography Department. In addition to working on my Ph.D. on the structure of simple liquids, together with Paul Barnes (now at UCL) and the Liquid Group's Experimental Officer Ian Cherry, I got involved in other things that interested Bernal, including the Polywater affair which I think we helped to bury – though that taught me a lot about some of the less positive aspects of scientific research. After my Ph.D. had been put to bed, I appeared to have been in the right place at the right time and moved directly into a lectureship at Birkbeck, where I was fortunate enough to build up the Liquids Group, which worked on a range of non-crystalline systems including amorphous metal alloys, globular proteins (yes – there are features that proteins have in common with some kinds of liquids!), water and aqueous solutions, and the role of water in biological processes, as well as partially-crystalline systems such as several of the high pressure ices. After five years out of university during the early days of the ISIS Pulsed Neutron Spallation Source, I was enticed to UCL to set up its Condensed Matter and Materials Physics group.

Working in Bernal's department in the late 1960s gave me a broad view of crystallography. In addition to the work that was then going on in Birkbeck on protein structure determination, virus structure and assembly, cement and liquids, the generalised crystallography concepts that Bernal was developing left their mark on me. Those ideas encompassed not only the importance of local five-fold symmetry in the structural disorder inherent in liquids, but also pointed to the possibility of extended space-filling structures involving non-crystallographic symmetry that were realised – following predictions by Alan Mackay at Birkbeck – in quasicrystals. So I hope you will not be too upset if my predilection for disorder in condensed matter systems infiltrates from time-to-time into the pages of Crystallography News.

With taking on this job, I've obviously begun to think about how Crystallography News can best serve the interests of BCA members. I've got some ideas, but it's not my newsletter -it's yours: so I'd like to hear from you what you think. Is the mix of articles that you've been used to seeing what you want? Is there too much emphasis on some things, too little on others? Are there things missing that you'd like to see in the newsletter? Would you like more articles on very recent crystallography-based advances (like the Covid-19 one in this issue)? A letters column? Book reviews? Job postings? More articles on active controversies in structural science such as the one in this issue on models of water structure? Do let me have your thoughts and suggestions – as well as contributions for future issues. Just email me at john.finney@ucl.ac.uk.

As there's no Puzzle Corner this issue (any volunteers?), you might get some (non-crystallographic) amusement from the accompanying Larry cartoon. In the early 1980s, this was used – with Larry's permission – as a 'logo' for the Birkbeck Crystallography Liquids Group. Question: why was it appropriate then, and why wouldn't it make sense today? There's a pint (or equivalent) at the 2021 Spring Meeting for the first five correct answers. [Hint: locked-down over 70s should find this easier!].

Finally, when you next have a glass in hand, you might also like to work out what the other accompanying image tells you about one of the systems whose structures I'm particularly pleased about having worked on. It also perhaps tells you something about how I'm getting through the current lockdown by mixing work with pleasure. Looking at the magic three letters on the label, perhaps I'll save the bottles I have left for the 49th BCA Spring Meeting in the early 2030s...

John Finney

New dates for your diaries

As you are fully aware, the Covid-19 pandemic has forced the rescheduling of several important Crystallographic meetings.

Don't forget to note these new dates! And to join in electronically to the BCA AGM!

BCA AGM (webinar)

18th June 2020

BCA Spring Meeting

29th March-1st April 2021
University of Leeds, UK.
https://crystallography.org.uk/spring-meetings/#next-meeting

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

14th-22nd August 2021
Prague, Czech Republic.
http://www.iucr25.org/

BCA Corporate Membership

The BCA values its close ties with commercial companies involved with crystallography. To enhance these contacts, the BCA offers Corporate Membership. Corporate Membership is available on an annual basis and includes the following benefits:

- Up to 10 free BCA memberships for your employees.
- 10% discount on exhibition stands at the annual BCA Spring meeting.
- Free insert in the annual Spring Meeting delegate pack.
- Two free non-residential registrations to the annual Spring Meeting.
- Ten complimentary copies of the quarterly Crystallography News.
- Corporate Members will be listed in every Crystallography News and on the BCA website with clickable links to your organisation's website.

Corporate Membership is currently **£800** for one year.

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- The professional organisation for crystallographers in the UK
- A broad range of meetings organised by the BCA and its subject groups
- Preferential members' rates for such meetings
- Eligibility of students and postdocs for an Arnold Beevers Bursary award
- A copy of Crystallography News every quarter
- Optional E-mail notifications of news items and meeting information
- Influence on the development of crystallography and the BCA

For current rates, and to join, please see **www.crystallography.org.uk/membership/**

Rosalind Franklin

THIS year marks the 100th anniversary of the birth on 25th July 1920 of Rosalind Franklin, whose pivotal contribution to the discovery of the structure of DNA has been increasingly recognised since her untimely death from ovarian cancer at the age of 37 in 1958. The debate rages on as to whether, if she had lived longer, she would have been among the three awardees of the 1962 Nobel Prize in Physiology or Medicine, which went to Francis Crick, James Watson, and Maurice Wilkins "for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material." Each Nobel Prize can be bestowed on a maximum of three people and is never awarded posthumously.

Rosalind Franklin (1920-1958)
Pictorial Press Ltd / Alamy Stock Photo

A realisation of the vital importance of Rosalind Franklin's work has only gradually gained traction. Very belatedly, her name is becoming much better known and the public are being disabused of the veracity of the scurrilous comments about her in the famous book, 'The Double Helix', an account written by James Watson of the DNA structure discovery. It was not until 1999 that Watson finally said that '…the Franklin photograph was the key event…' i.e., he at last admitted that Photo 51 was absolutely essential information for construction of the model.

So what was Photo 51 and why was it so important? I will try to give a brief and distilled account below. Much has already been written on the subject and the interested reader is referred to more detailed descriptions listed at the end of this piece.

Rosalind Franklin (RF) was born in London to Muriel and Ellis Franklin. In January 1932 she went to St Paul's Girls' School, where she shone at both sport and in her studies. Her mother wrote: 'All her life, Rosalind knew exactly where she was going, and at 16 she took science as her subject.'

In summer 1938, Rosalind visited Paris and started her lifelong love of France and all things French. Newnham College, Cambridge was her next destination where she read Natural Sciences with a focus on Chemistry, at which she excelled. Interestingly, there is a 'note to self' in one of her 1939 exercise books which is a sketch of a helical structure of nucleic acid with a nearby question saying 'Geometrical basis for inheritance?'. Her final year research project went well and was supervised by Fred Dainton. However, she did not actually 'graduate' until 1948 since women were not awarded degrees by Cambridge until 1947.

In 1942 she registered for a Cambridge PhD but worked as an 'Assistant Research Officer' in Kingston for the British Coal Utilisation Research Association (BCURA) on the permeability to gas (helium) and shrinkage in water of coals as a function of temperature. Her 1945 PhD thesis was entitled "The physical chemistry of solid organic colloids with special reference to coal and related materials" and in 1946 she published her first peer reviewed paper (of 37) putting forward the hypothesis of 'molecular sieves', very important for constructing effective WWII gas masks.

For her first postdoctoral position she happily returned to her beloved France and worked from 1947- 51 in Paris, studying the crystallography of coal & graphite under Jacques Mering at the Laboratoire Central des Services Chimiques de l'Etat. She felt that at work 'women engaged as equals'. She expertly carried out powder diffraction on amorphous solids with monochromatic X-rays and identified the carbons that turned into graphite when heated to 3000 °C ('graphitising carbon') and those that did not ('non-graphitising carbon', a rigid finely porous mass). This work resulted in five papers published in 1948 and her first letter to Nature in 1950.

At the beginning of 1951 she took up a 3-year Turner & Newall Fellowship at King's College, London to work under John Randall on proteins in solution and changes in their structure on heating or dehydration, causing them to denature. She was concerned about her lack of knowledge in the new research field: 'I am, of course, most ignorant about all things biological, but I imagine most X-ray people start that way' (as an ex-nuclear physicist, I can sympathise with this view!). However, just before she arrived, Randall suddenly changed her project to the investigation of some DNA fibres that Maurice Wilkins, also working at King's with Randall, had obtained in May 1950 from Rudolf Signer in Berne. Randall wrote '…This means that as far as the experimental X-ray effort is concerned there will be at the

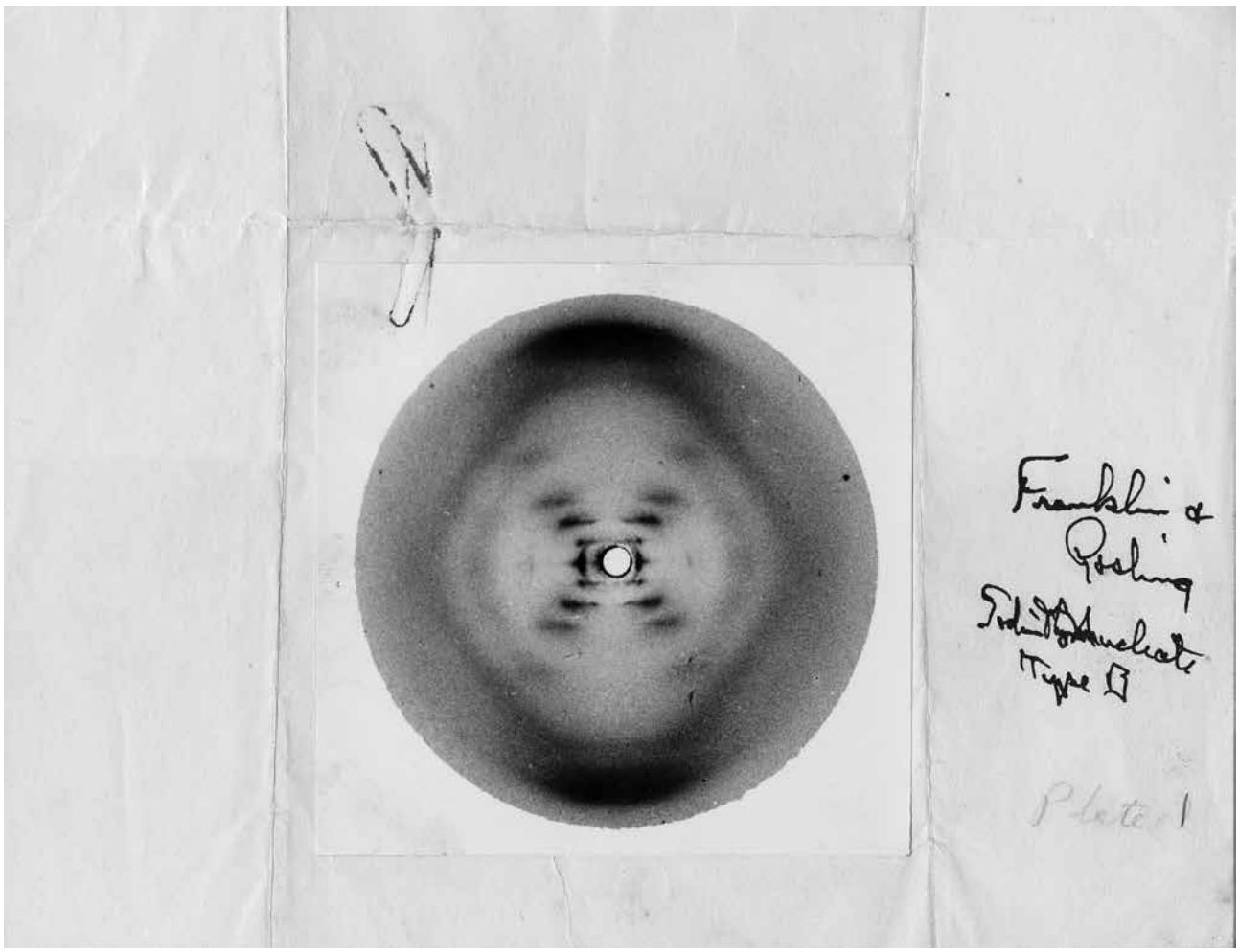


Photo 51 *Courtesy Ava Helen and Linus Pauling Papers, Oregon State University Libraries*

moment only yourself and Gosling…'. Unfortunately Randall neglected to communicate this new arrangement to Wilkins, even though Wilkins and Ray Gosling (a research student) had already obtained good diffraction X-ray patterns from the DNA fibres. This omission set the scene for difficulties between Wilkins and RF which quickly escalated over the first 6 months of 1951 while RF was building new equipment to control the humidity of the DNA fibres.

The situation between RF and Wilkins reached such an impasse that, in October 1951, Randall directed RF and Gosling to work on the A (dehydrated) form of DNA using the Signer fibres and the best X-ray camera, and Wilkins to concentrate on the B (hydrated) form with some other fibres that did not crystallise well. Photo 51 was taken by RF and Gosling in May 1952 with a tilted camera, giving the clearest photo yet obtained, but it was of the B form (92% humidity) on which they were not supposed to be working, so it was set aside. The tilted camera enabled RF to carry out cylindrical section Patterson calculations for the first time. The X-ray generator was a prototype fine-focus device built at Birkbeck by Ehrenberg and Spear and given to Wilkins and Gosling, but then used solely by RF and Gosling.

By January 1953, Gosling wanted to finish his thesis and he showed Photo 51 to Wilkins, who in turn, unknown to RF, showed it to James Watson (JW) when he visited King's from Cambridge. JW was working there with Francis Crick (FC) on building a model of DNA with newly obtained permission from W.L.Bragg, the head of the Cavendish Laboratory. Bragg had previously banned them from pursuing further DNA modelling following a previous embarrassing incorrect model (helical with the bases on the outside) that they had trumpeted in 1952. From X-ray work by William Astbury in Leeds and Alex Stokes' calculations predicting diffraction patterns, DNA was already known to be a 2 or 3 stranded helix. Wilkins also told JW the RF experimental values: a 34.4 Å repeat with the bases stacked 3.4 Å apart. Meanwhile, RF found that someone had tampered with her laboratory notebooks.

On the 9 February, FC and JW were shown RF's December 1952 MRC Review Committee report by Max Perutz. This report was not marked confidential, but the results in it were unpublished. It gave the space group of the B form DNA as face centred monoclinic (C2), and specified the unit cell dimensions and angles. FC realised that C2 gave a vital clue to the structure, since the DNA looked the same either way up, implying two antiparallel helical chains. Erwin Chargaff had already found that in DNA the number of Adenines(A)+Guanines(G) and Thymines(T)+Cytosines(C) were identical. Another critical piece of the puzzle was solved when postdoc Jerry Donohue, who shared the model builders office, suggested that the bases were the keto and not their assumed enol forms.

By 7th March 1953, FC and JW had built a model apparently consistent with the known information. Each purine (A,G) was paired with a pyrimidine (T,C) across the inside of the double helix formed by two antiparallel carbon-phosphate backbones. Wilkins saw it on 12th March and then told everyone at King's about it. RF was about to leave

King's where she felt she could no longer work in the same environment as Wilkins. She and Gosling had already sent off two papers on the structure of A form DNA and had nearly finished one on B, of which she was very near having the structure. How much RF ever knew about which of her results was shown to whom and when they were shown, remains a matter of debate.

In mid-March 1953, funded by the Agricultural Research Council (ARC), RF moved to Birkbeck College where John D. Bernal ('Sage') provided a supportive and happy environment for her new research group working on virus structure. Her office was on the 5th floor of a bomb-damaged house: 'I swapped a palace for a slum'. The X-ray lab. was in the basement and leaked, an umbrella being required during experiments! Here she worked on RNA and Tobacco Mosaic Virus (TMV), the first virus to be discovered (1892). Bernal thought the world of her and supported/protected her, calling her a 'brilliant experimentalist' and writing later: 'As a scientist, Miss Franklin was distinguished by extreme clarity and perfection in everything she undertook. Her photographs are among the most beautiful X-ray photographs of any substance ever taken.' Aaron Klug, a future Nobel Prize winner (Chemistry 1962) met Rosalind at Birkbeck and transferred to study viruses in collaboration with her. By 1955 her group consisted of 3 postgraduate students: James Watt, John Finch, and Ken Holmes, and also Don Caspar (who first coined the phrase 'structural biology') on a Fellowship.

From interpreting fibre diffraction patterns, and using multiple isomorphous replacements methods, she determined the first virus structure, showing that the 50 MDa TMV had a diameter of 150 Å with the RNA coiled round a hollow inside (Nature 1955). The first model was made using 288 bicycle handle bar grips! However, Norman Pirie, an influential ARC figure, fundamentally disagreed with this result, threatening the ARC funding to RF's group.

The structure allowed the TMV infection process to be understood, and a famous model of the virus was displayed at the 1958 World Trade Fair (Expo1958) in Brussels. To aid the highly calculation-intense interpretation of the X-ray diffraction patterns, a `computer' was employed: she was called Mrs Cratchby! Results on pea streak, potato, turnip, tomato and cucumber viruses were reported in 7 papers in 1956, and 6 in 1957. The group then expanded their focus from plant viruses to started work on the Polio virus.

During her time at Birkbeck, RF went on two two-month-long tours of America (1954, 1956) and she thoroughly enjoyed the recognition and respect she was given there. It was on the second of these that she experienced abdominal pains which were the first sign of the illness which would cut her life so short.

Rosalind has received much belated posthumous recognition that sadly she did not live to witness, with at least 39 buildings or projects named after her.

There has been much controversy regarding Franklin's contribution to the unravelling of the structure of DNA. A balanced account was given in Nature by Aaron Klug in 1968: 'Dr Klug discusses Dr Franklin's contribution to the discovery of the structure of DNA in the light of accounts given by Professor Watson in his book The Double Helix and by Dr Hamilton in a recent article in Nature.'

In 2017, under the Planning Act of 1990, Historic England listed her tomb as of "special architectural or historic interest", with the official description (which sums up the her scientific impact very well): "the tomb commemorates the life and achievements of Rosalind Franklin, a scientist of exceptional distinction, whose pioneering work helped lay the foundations of molecular biology; Franklin's X-ray observation of DNA contributed to the discovery of its helical structure."

Notably, last year the University of Portsmouth announced that on 2nd September it was changing the name of its James Watson Halls to Rosalind Franklin Halls. Perhaps this act shows in microcosm the growing appreciation of the impact of Franklin's life and work, somewhat redressing the balance in the previous mis-allocation of credit.

Further Reading:

Rosalind Franklin, The Dark Lady of DNA by Brenda Maddox HarperCollinsPublishers 2002

My sister Rosalind Franklin by Jenifer Glynn Oxford University Press 2012

Many thanks to Jenifer Glynn and Daniel Franklin (nephew) for checking this account.

Elspeth F Garman
(University of Oxford)

BCA Council Elections

Elections for BCA Council will take place this year, on the usual schedule.

The posts available for election are:

- BCA President
- One Ordinary Member of Council
- Education and Outreach Co-ordinator

Any two Members may make nominations, and such nominations should be accompanied by the candidate's written consent to serve if elected.

Nominations must be received by the Secretary (**secretary@crystallography.org.uk**) by the 30th September.

Diamond's fight against SARS-CoV-2

ABOUT a month before the UK had seen its first case of COVID-19, Zihe Rao's group (Shanghai Tech), a leading Chinese group working on SARS-CoV-2 (the causative agent) contacted Dave Stuart. They had solved the liganded structure of the main protease (M^{pro}) but with their own country already stricken with nearly 10,000 cases of COVID-19, and in lockdown, they reached out for help.

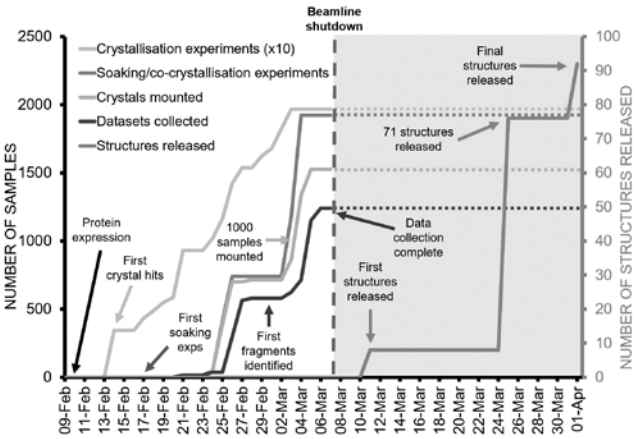
The coronavirus main protease (M^{pro}) is one of two proteases encoded by SARS-CoV-2. They are essential for the virus lifecycle as they convert long polyproteins into their smaller functional units. Furthermore, the architecture of the M^{pro} active site, which performs chemistry, is well conserved with other pathogenic viruses such as picornaviruses and caliciviruses. M^{pro} is a very tempting target for therapeutic intervention to treat the disease cause rather than only being able to treat the symptoms. Inhibitors have been developed over this enzyme previously, based on work started on the SARS-CoV-1 and MERS viruses. However, nothing has passed clinical trials and reached the market. We decided that with using the full weight of the structural biology pipeline at The UK's National synchrotron Diamond Light Source (Diamond), we would be able to rapidly accelerate the development of inhibitors against this target.

M^{pro} is similar in structure and function to the homologues found in other coronaviruses. Importantly, work on these homologues described the importance of producing the protein without any additional amino acids at the beginning or end of the M^{pro} sequence as they interfere with the structure of the active site and inhibit the enzyme's activity. Scientists in the Walsh group at Diamond designed a construct that produced a native N-terminus (the end of the protein produced by the ribosome first) by using the peptide cleavage capacity inherent in the M^{pro} enzyme. These genes were synthesised and arrived on Monday 10th February. By midweek the protein was expressed, and purification was in progress. First crystal plates were set up on Thursday 13th, and small clusters of needles were present the following day. Although the crystals were of very poor quality, the speed with which they appeared allowed us to optimise rapidly. The first full dataset was collected on beamline I04 at Diamond on Friday 21st February, and the structure was solved to a resolution of 2 Å. This was an important milestone as it provided a structure with an empty active site. This meant that new drug-like molecules could be soaked into the crystals to see how they potentially bound with this active site. This process of cloning, expression, purification and crystallisation would normally take weeks or even months, but due to the importance of the work towards the global health emergency and the collaborations, it was achieved in just a few days.

This was not a normal project in which only one diffracting crystal was needed. A system was required that would consistently produce well diffracting crystals. To achieve this, microseeding was used to produce crystals in conditions that would not otherwise nucleate. Once optimised, this gave tight control of the number of crystals produced per drop. Additionally, DMSO was introduced to the optimisation experiments early so that the protein crystals would be more likely to tolerate soaking with DMSO-solubilised fragments.

This construct and others like it, along with purified protein have been shared with other groups in the UK and around the world, allowing multiple inhibitor studies to be carried out by varying methods (NMR, SPR, Mass Spectrometry etc.) to accelerate the research.

Fragment screening of M^{pro}



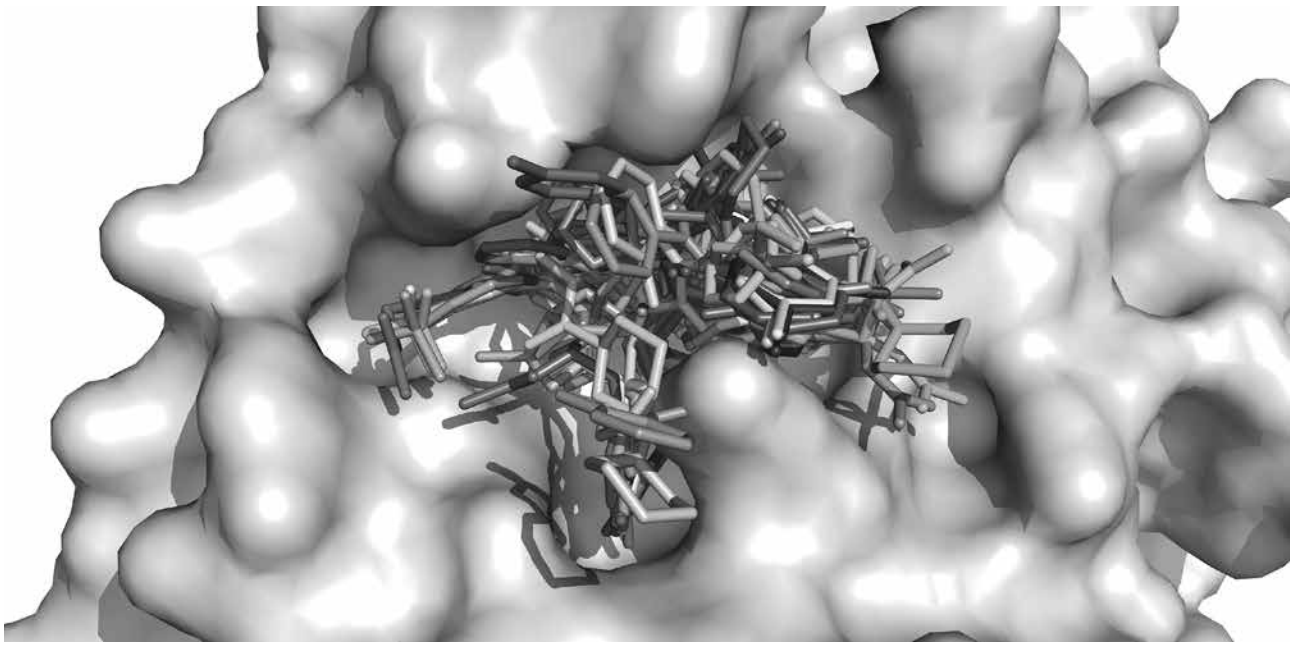
Timeline of crystallographic fragment screen

As M^{pro} is a cysteine protease, it was possible to lead two fragment screening campaigns in parallel.

In the Weizmann Institute of Science (Israel), London and his co-workers looked for covalent fragments in their library of ~1000 mild electrophilic fragments using intact protein mass spectrometry. They reliably identified ~80 potential hits that labelled >30%, and this result was immediately communicated to the Diamond team for those hits to also be included in the structural work.

Meanwhile, scientists from von Delft's group at Diamond used their XChem fragment screening facility to search for non-covalent fragments.

On the 17th February, initial soaking experiments with small molecule fragments were started. In the course of ~2 weeks, nearly 1500 crystals were soaked or co-crystallised with small fragment compounds from four different libraries. All data were collected prior to the synchrotron shutdown on the 6th March. Diamond's fast auto-processing pipelines combined with XChem Explorer data management software and PanDDA (Pan-Dataset Density Analysis) methods resulted in the identification of the initial fragment hits as early as the 29th February. By 1st April, all structures of the hits were released in the Protein Data Bank and all raw data were uploaded to the Zenodo repository in CERN.



M^{pro} active site with the 66 diverse fragments.
https://www.diamond.ac.uk/covid-19/for-scientists/Main-protease-structure-and-XChem.html

This massive campaign identified 91 diverse fragments, 66 of which sampled the M^{pro} active site and its specificity subsites either covalently (44) or non-covalently (22). This effort led to a wealth of structural data and opportunities for growing and merging of compounds for follow-up activities. It triggered international collaborations, crowdsourcing and crowdfunding initiatives in order to progress those hits into compounds that matter in the fight against COVID-19.

This research has been a true collaborative effort involving the following:

- Group of Martin Walsh – Claire Strain-Damerell, David Owen, Petra Lukacik
- XChem and I04-1 (Frank von Delft) – Alice Douangamath, Daren Fearon
- XChem Industrial Liaison Group – Ailsa Powell, Alexandre Dias
- Group of Nir London (Weizmann Institute, Israel) – Efrat Resnick, Paul Gehrtz, Rambabu Reddi
- Protein Crystallography Group of SGC-Oxford (Frank von Delft) – Conor Wild, Tobias Krojer
- Fragalysis Team (Frank von Delft) – Rachael Skyner, Anna Carbery
- I04-1 Beamline Team (Frank von Delft) – Jose Brandao-Neto, Louise Dunnett
- Diamond MX Group – Mark Williams, David Aragao, Halina Mikolajek, Adam Crawshaw, Marco Mazzorana, Katherine McAuley, Ralf Flaig, Dave Hall, Dave Stuart
- Diamond scientific software group – Graeme Winter, Markus Gerstel, Richard Gildea
- CRUK Newcastle Drug Discovery Unit – Mike Waring, Martin Noble

At the time of writing these results were up to date. However, given the importance and rapid experiments taking place new results may already be available. All the latest details can be found on the Diamond webpages https://www.diamond.ac.uk/covid-19.html.

David Owen, Alice Douangamath, Petra Lukacik, Daren Fearon, Tobias Krojer and Anna Warren

ISIS Disordered Materials User Group Meeting

21-22 January 2020

IF you are a pulsed neutron user, you'll know about the ISIS User Groups. These are groups of users organised around areas of science and groups of ISIS instruments. Many of these – an obvious example being the Crystallography User Group – are of clear interest to BCA members, but as systems of scientific and technological interest are becoming larger and of greater structural complexity, more attention is being given to understanding structure, interactions and changes at the intermediate and longer distance ranges.

Much of this work is associated with the Disordered Materials User Group. During my time at ISIS in the 1980s and 1990s, disordered materials work focussed mainly on liquids and glasses, but with the bringing on stream of new instrumentation such as NIMROD, which in a single run can access spatial scales from the microscopic to the mesoscopic, this widening of accessible systems led naturally to this group name.

These ISIS User Groups run periodic User Meetings. In addition to discussing facility developments, for example upgrades to, or new, instrumentation and support services, users are encouraged to present their recent work. As much of this work is often frontier work in progress, the discussions at these meetings give opportunities for community input into how emerging problems might be tackled.

The latest meeting of the user group, which took place on 21 and 22 January 2020 in Abingdon, Oxfordshire, was the largest to date. Normally around 40 to 50 users take part, but this year the number jumped to an impressive 79, reaching the capacity of the venue. But not only was the attendance impressive – so also was the range and variety of the science presented, perhaps reflecting the increasing capabilities of the ISIS instrumentation, data analysis software, and the support facilities which are enabling increasingly complex and variable environmental conditions. What was also notable and very encouraging was the fact that most of the 30 or so speakers were students and postdocs who could give good talks.

Proceedings were kicked off by Disordered Materials Group Leader **Daniel Bowron** giving a short update on planned instrument developments during the long shutdown due to start in early 2021. Upgrades to the SANDALS instrument will essentially double the neutron flux on the sample, while GEM has been upgraded to present users with a cleaner neutron beam. A beam imaging camera is being developed for NIMROD to ease reliable sample placement in the beam, while a new electrochemical cell and sample changer has also been built. Discussions are taking place on a possible new instrument that will be optimised for total scattering measurements of particularly complex systems (for example crystalline and liquid mixed samples) that will be of particular interest to the nanotechnology and chemical engineering community. **Sarah Youngs** followed on by describing the changes that had occurred over the last two years to the ISIS Deuteration Facility. She showed how the use of the facility for producing deuterated samples for users has not only continued to increase (producing sample materials for 88 experiments in 2019) but has also responded to the increase in complexity of the systems being studied by developing and implementing appropriate routes to the deuterated targets.

The rest of the day and a half was taken up by 15-20 minute scientific talks relevant to spatial scales from the astronomical (Martian geology, interstellar ice) to the sub-atomic (quantum dots). Specific systems ranged from relatively simple crystals (spin-ices), through molecular-level glasses and liquids, to nanostructures and large scale structures such as liquid crystalline-type assemblies and solutions of quite complex molecules.

Many of these were concerned not just with elucidating structures – challenging as that may be for the complex multicomponent disordered systems that the instruments and the data analysis software are now able to handle – but with trying to understand processes in complex environments that are relevant in the applied world.

Perhaps a few examples will illustrate the ambitious work that is being tackled.

Of particular interest to pharmaceutical companies is the ability to control the crystal form of a drug formulation. In tackling this, **Katharina Edkins** (Manchester) sought to understand how the structure of the solution – in particular how solute-water solvent interactions might influence whether a drug substance crystallised as a hydrate or not. A clear conclusion was that the molecular interactions in the solution can indeed influence the outcome of the crystallisation process, and work continues to elucidate more detail in specific systems. Another project of direct pharmaceutical interest – still at an early stage – explored the targeting of drug delivery using polymers containing both the therapeutic group and a targeting moiety. Using contrast variation (one of the key advantages of using neutrons), **Alison Paul** (Cardiff) told us how the drug can influence the structure of the delivering polymer and how the polymer conformation can influence the kinetics of drug release. A project in its early days, but of clear medical interest.

Two other sets of experiments probing the 'solidification' process from solution I found of particular interest. First, **Annela Seddon** (Bristol), told us about her work that tries to predict what characteristics of molecules and their environment are required for effective gel formation. Her work looked at the molecular packing in the solution state, how this changes as the solution converts to the gel state, and finally the molecular packing in the gel state. In addition to looking at the controlling influence of cations, concentration, buffer and temperature on the packing, she also underlines how chirality can have a dramatic effect. Secondly, **Chris Howard** (UCL) explained how he has used electron microscopy and electron diffraction in addition to neutron scattering to probe the formation of nanosheets and nanoribbons, materials which have both wide applications and promise novel emergent properties.

An appropriately random loose packed assembly of the participants in the January 2020 meeting of the ISIS Disordered Materials User Group. Credit: ISIS Pulsed Neutron and Muon Facility.

Several talks related to aspects of energy storage and production. Noting that sodium sulphate is used as a 'fining' agent to reduce the bubbles in radwaste glasses, **Shuchi Vaishnav** (Sheffield Hallam) explained that excess sulphur remaining in the glass has potentially serious consequences for long-term secure storage. Aiming to find a way to better incorporate the sulphur in the borosilicate matrix, her measurements have built up a detailed structural model of the glass, with particular emphasis on the near- and next-nearest neighbour environment of the sulphur. Two other energy-materials related projects focussed on battery electrolytes. Noting some of the advantages of non-crystalline over crystalline systems such as isotropic conduction, the absence of grain boundaries and the ability to vary composition to optimise properties, **Isaac Abrahams** (Queen Mary London) described his work on Li ion conduction in phosphate glasses. Also on the battery front, **Anders Jensen** (also Queen Mary) took us through his experiments on the conductivity of sodium in hydrochars (produced by the pyrolysis of biomass). He showed how temperature led to increasing pore size and crystallinity, and how appropriate thermal treatment could optimise the conductivity through small graphitic domains making available many diffusion pathways. And that the greater the crystalline order, the lower the battery capacity.

A significant recent instrumentation advance has been the ability to do NMR on samples within the neutron instrument sample chamber. This setup was used by **Terri-Louise Hughes** (Manchester) to explore on NIMROD how liquid confinement can affect the catalytic process. Taking the example of the hydrogenation of benzene in MCM41, her initial results quantified how the local liquid structure in confinement differed from that in the bulk, with work continuing to follow the changes occurring during the catalytic process.

As **Daniel Bowron** commented at the end of the meeting, the talks showed an 'incredible diversity' of really interesting science, both pure and with potentially major applications. It was a very stimulating two days, and demonstrated to me how ISIS disordered materials science has come on quite dramatically in the last few years.

Postscript

Had there been a prize for the best title, I'd have given it to Alan Soper for his title "Water as a mixture, and other muddled thinking". It was a masterly demonstration of how to use thermodynamics and how it can be connected to molecular structure to demolish a disturbing bandwagon that continues to roll despite its previous death some 50 years ago…

See his article on page 17 to get a flavour of some of the arguments.

John Finney

In a social distancing situation, keeping up the spirits of research and other teams when they cannot get together physically is a challenge. After several weeks of lockdown, you'll no doubt have experience of ways of trying to deal with this problem remotely (send them in for the next issue?). Two – perhaps not surprisingly C2H5OH-related – ones I came across in the first week of lockdown might be called a virtual pub and a virtual wine bar. The former – appropriately named The Quarant Inn – is where the ISIS Disordered Materials User Group get together for a pub quiz and BYOB drinking session. In the latter 'Wine and Words' idea used by my friends at the John Muir Trust, team members log in with a glass of wine and read some of their favourite passages from the books that inspire them. Obviously adaptable to a virtual bar of crystallographers who could talk about the structures that inspire them! Or their favourite space groups perhaps?

John Finney

CCP4 Study Weekend: Model building and beyond

Nottingham, 7-9 January 2020

Some personal thoughts on organising my fave meeting

HOW does an international meeting look behind the scenes? Should you ever try and put one together? Good news is, I might be able to answer almost 50% of that. The last few months have seen my becoming a cog at the organisational level of the structural biology machine. A tiny little cog, considering the growing set of conferences and journals that checkpoint research history. Months after my appointment as co-editor of Acta Crystallographica Section F: Structural Biology Communications – or Acta F in crystallographic friendly terms – I got the huge responsibility to orchestrate a meeting for ~400 structural biologists. The CCP4 Study Weekend was knocking on my door.

Did I enjoy it? Yes. Would I do it again? Maybe. Why? Because in spite of how wonderful it was, I did not succeed in creating the sort of conference I had wanted it to be. In case you are curious about it, here I would like to offer you a look into the kitchen of this prestigious meeting. Hopefully, what I have learned from this experience will be useful to other people who, like us, want to bring the conference model into the 21st century.

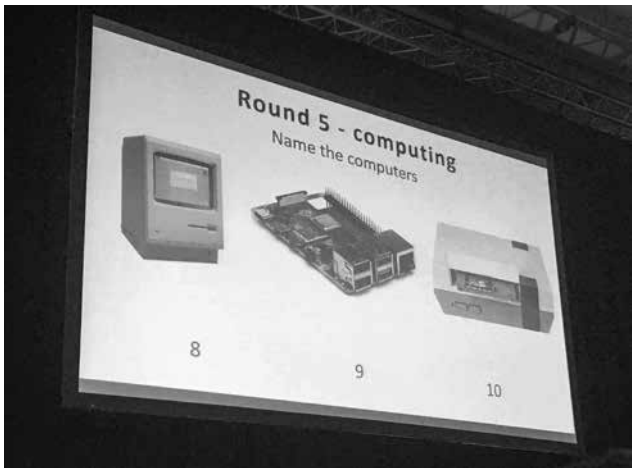
The Collaborative Computational Project 4 (CCP4) exists to produce and support a world-leading, integrated suite of programs that allows researchers to determine macromolecular structures by X-ray crystallography. It's based at the Science and Technology Facilities Council (STFC) at Harwell, and the STFC is the sole sponsor of the event. For this reason, most of the heavy lifting is done by STFC personnel, commanded by Karen McIntyre. Without her support, we would have been clueless, and missed all the deadlines in the process.

We – that's me, together with Robbie Joosten (NKI, The Netherlands) and Alan Roseman (University of Manchester), my co-organisers – tried our best at achieving gender balance and having good international representation. Although the programme did have a bit more than 50% male speakers and chairs, women contributed more than half of the most memorable moments. Some involved science, some rode on personal charisma, but all were wrapped in boldness and made talks more engaging. Ignore gender balance at your own peril!

The meeting suffered two last minute cancellations: Victor Lamzin (EMBL, Hamburg) and Maya Topf (Birkbeck College, London). We had organised an all-female tag team introduction with structural biology legends Helen Saibil and York Structural Biology Lab's own Eleanor Dodson. In retrospect, I believe it was foolishly ambitious of us to ask both speakers to cram decades of research into a single 45 minute slot; so, the additional time on their session due to not having Victor's talk straight afterwards fortuitously saved the day. Even more incredibly, we were able to cover Maya's absence with a former postdoc of hers, Agnel Joseph. He gave a fantastic talk with roughly a few hours notice, and discussed many of the ideas Maya had in mind for her slot – a huge credit to Maya and her group.

Wah Chiu (SLAC National Accelerator Laboratory, USA) addressing a well-filled theatre.

We tried to introduce the provision of childcare for the first time ever, but it would have required logistic changes (closure of certain rooms and toilets) and, crucially, a bigger budget than we had. Having seen children at this year's meeting, I am ever more adamant that there is a strong demand for it, and will keep pushing the idea until it becomes standard practice.



One of the quiz slides.

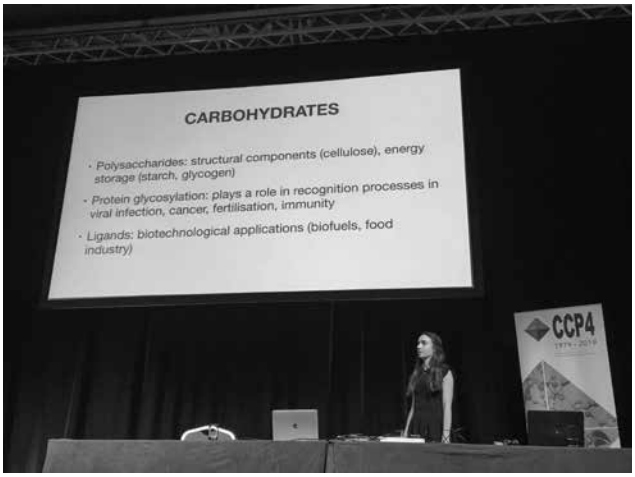
I had the pleasure to welcome everyone and introduce the meeting and our initiatives to get people more involved in it. We had organised a quiz (see image) for the mixer event on the first night, plus stickers with different icons to show your keywords to other people and help in networking; we had analysed all feedback from the past few years forensically, so we knew there was an appetite for a more compelling social session. Also, we had introduced an illustration competition whose winner will help design the cover of the special issue of Acta Crystallographica Section D: Structural Biology, which will carry the proceedings of the meeting early in 2021. A slide show with the competing images was shown on the screens at all times, and attendees could scan a QR code containing a description of the image and how it was created. Try scanning the QR code in the accompanying figure to see how this works!

One of the images competing for the Acta D cover.

I am very thankful that there was a great turnout for the "What's new in CCP4" session early on day one. It has not always been the case, and developers very much appreciate not talking to a half-empty room. During the main sessions, I loved the way the speakers referenced each other's talks, as I think it contributed to enhancing the natural flow in the programme. We kept the time the best we could, but there were moments of nervousness. Telling a speaker to wrap up after overrunning is painful; asking the next speaker to make their talk shorter to compensate is even more painful. I have learned a valuable lesson here.

One final note on the presentations: as the focus in structural biology keeps shifting to biology, formula-heavy talks seem to be less welcome than ever. So if you're thinking of filling your slides with integrals... just don't. At least not for this target audience.

The meeting saw a great presence from the York Structural Biology Lab. and the wider York fellowship: 17 attendees, Mihaela Atanasova (York University – pictured) presented her work on carbohydrate structure determination; K. Cowtan, Stuart McNicholas and Haroldas Bagdonas demonstrated the use of our software tools during lunchtime; K. Cowtan talked about automated protein model building; Eleanor Dodson introduced standard practice in model building; and finally, myself at the helm.



Mihaela Atanasova presenting her work.

As I have stated, I would have liked to boost inclusivity at the meeting a bit more than we managed to. I am happy that we seem to have started a conversation on a few fronts though, most saliently on childcare. Now, I am left wondering that perhaps a better way of disrupting the rigid conference model would be to create something new, accessible, inclusive at all levels and free from tradition. A conference that provides a testing ground for new ideas that other meetings can adopt.

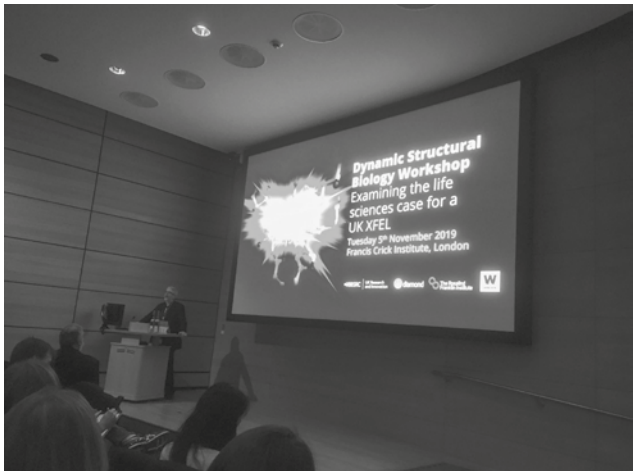
Nobody's gonna travel second class. There'll be equality. And no suppression of minorities.

Well alright*.

** Lyrics shamefully stolen from Supersonic Rocket Ship by The Kinks*

Jon Agirre
(University of York)

The UK XFEL Consultation exercise



For nearly a year now there has been an ongoing exercise by STFC to:

"develop the science case for a potential UK X-ray free-electron laser (XFEL). We are seeking input to the process from across the scientific community. STFC is supporting this activity, on behalf of UKRI, with Jon Marangos (Imperial College) the project lead and John Collier (Director CLF) the STFC project champion. A key element will be an assessment of the level of interest within the UK Scientific Community."

To that end there has been an extensive set of Town Meetings. The overall kick-off meeting was held at The Royal Society in July 2019. This has a helpful website with the presentation files of most speakers also available: **https://www.clf.stfc.ac.uk/Pages/XFEL-royal-society.aspx**
The speakers were:

John Collier – "Welcome and the STFC context"

Jon Marangos – "Introduction to the 2019/20 UK XFEL Science Case Project"

Massimo Altarelli – "X-ray FEL Science: The International Perspective"

Ian Robinson – "Opportunities for advanced materials and nanotechnology"

Justin Wark – "Opportunities for high energy density science"

Phillippe Wernet – "New opportunities for chemical sciences at current and future x-ray free-electron lasers"

Dan Eakins – "Opportunities in engineering materials"

Allen M. Orville – "Enabling Tools for the Era of Dynamic Structural Biology: 'yes, please – all of the above'"

Jasper van Thor – "Opportunities in biomolecular dynamics"

Jim Clarke – "The shape of FELs to come"

It is emphasised by STFC that:

High brightness ultra-fast x-ray pulses from an X-ray FEL allow the simultaneous imaging of atomic scale structure, electronic state and dynamics in a material. There is no other technology that can do that. The unique science opportunities that these machines can open-up include:

- *Access to structural dynamics.*
- *New modes of nanoscopic imaging.*
- *Access to transient states.*
- *The potential to capture rare events.*

STFC organised a number of themed Scientific and Technical Workshops around the country in order to feed into the revised science case. The dates and locations of these through 2019 are listed below.

- Oct 2nd Matter at Extreme Conditions (Edinburgh)
- Nov 5th Dynamic Structural Biology (Crick)
- Nov 13th Frontiers in Physical Sciences (Imperial)
- Nov 27th Quantum Materials & Nanotechnology (Southampton)
- Dec 4th Applied and Industrial Research with XFELS (Warwick)
- Dec 11th Chemical Dynamics & Energy (Newcastle)

The UK has considered such a new, FEL, light source on home soil several times before. I recall the 4th Generation Light Source (4GLS), Sapphire and the New Light Source (see **https://stfc.ukri.org/about-us/where-we-work/daresbury-laboratory/future-light-sources/**). Also the UK joined Euro XFEL in Hamburg, then withdrew, then rejoined. We also had participated in helping with instrument developments at the Linac Coherent Light Source (LCLS) at the SLAC National Accelerator Laboratory, USA.

But, now, I sense a new mood with respect to this latest consultation exercise. Also, dare one think it, the new UK government is maybe looking for a clear demonstration of a homeland initiative, separate and distinct from our participation in European projects, that it can launch with new money. A UK XFEL could be part of taking the UK up towards 3% of GDP spent on scientific research.

At the time of writing Prof. Jon Marangos (Imperial College), the Project Lead is writing the Science Case, gathering up all the steerings that were offered, pro and con, at these various Town Meetings. I am enthusiastic about the possibilities for biomolecular structure determination, both time-resolved and static. My flash presentation that I prepared for the Newcastle event is entitled "What is the structural chemistry of the living organism at its temperature and pressure". I have placed my talk at Zenodo (**https://zenodo.org/record/3565339#.XoNIS2Z7ntQ**) I am very much in accord with STFC's declaration, mentioned above, of *New modes of nanoscopic imaging: These can be used for seeing the nanoscopic arrangements in nanotechnology and life-sciences free from radiation damage and adverse effects of sample preparation (e.g. in situ imaging of the function of biomolecular assemblies at operating temperature).* I also expanded on this theme in an article I wrote for Acta Cryst D recently (**http://journals.iucr.org/d/issues/2020/02/00/nw5093/index.html**).

John R. Helliwell
(Manchester University)

Being unable to participate in person in conferences over the last three months has encouraged many of us to take the plunge and try virtual conferencing. Although most of the conference reports in this issue are for ones that took place before March 2020, this one from Lucy Saunders describes her first go at attending a virtual meeting, and comments on how useful she found it.

NIST Virtual Conference on Molecular Capsules: from Design to Application (22-23 March 2020)

I was tipped off about this NIST Virtual Conference by an eagle-eyed PhD student the weekend before it took place. I was very excited at the prospect of hearing from some actual scientists, having been working at home already for one (just one!) week. I was also looking forward to hearing about the interesting characteristics and functions of the type of materials that we frequently get popping up on the beamline on I19 at Diamond.

The conference was hosted by NIST and co-organised by Kathleen Schwarz (NIST, USA), Angela Stelson (NIST, USA) and Angela Grommet (Weizmann Institute of Science, Israel) and ran for two days over Sunday 22nd and Monday 23rd March 2020. Registration for the meeting was free and participants logged in using the video conferencing app. Zoom. Across the two days there were 200 to 250 participants logging in and coming from all time zones. Each speaker shared their screen with the conference audience and participants had the opportunity to message questions which the speaker then answered at the end of their talk. I tuned in for the second day and thoroughly enjoyed talks from Mike Ward at the University of Warwick, who revealed how the outsides of coordination cage hosts also have a role to play in catalysis, and from Jonathan Nitschke at the University of Cambridge who spoke about the recent development of cages decorated with long appendages that exhibited ionic liquid properties below 100 C.

I really enjoyed being a part of this meeting and, in a situation that prevents attendance in person, it is brilliant that we have an alternative to the traditional scientific conference format. Through meetings like this one, the scientific community can stay connected and continue to share the exciting research they have been working on.

Lucy Saunders (Diamond)

Two-State Model of Water: a Case of Mistaken Identity

WE have probably all heard of court cases where a person, previously convicted of a crime and sent to prison, is found, on further investigation, to be innocent, and that the original case that convicted them was flawed due to inadmissible or insufficient evidence being presented at the original trial. Sometimes the error is not found until many years have passed, and inevitably the person falsely convicted finds it very hard to be accepted back into society.

The idea that water is a mixture of two types of water of different structures, is, in the opinion of this author, a good example of a case of scientific mistaken identity. The model can be made to explain many of the so-called "anomalies" of water, yet suffers from some fundamental defects, which, despite repeated attempts to raise awareness of, seem to go overlooked in the literature by those who wish to propagate the "two state" model. In this article I will support my view by referring to three of the more serious logical flaws in the model. These are: (1) if water is a mixture of two states, what exactly is it a mixture of? (2) the mixture model overlooks a fundamental aspect of both the statistical mechanics and small angle scattering properties of mixtures. Finally, (3) claims that water is a mixture are based on incorrect interpretations of spectroscopic, scattering, and computer simulation data, and ignore the most important aspect of water, namely that, more than any other common liquid, the bulk of the configurational entropy of water – that which gives rise to its high specific heat, low vapour pressure, and high boiling point – is stored in its orientational structure. I will address each of these concerns in detail, particularly (2) and (3), and will propose that until these matters are dealt with appropriate scientific rigour, the mixture model of water will remain nothing more than what it always has been, a convenient abstraction which avoids us having to come to terms with the real complexity of liquid water.

What are the components of the water mixture?

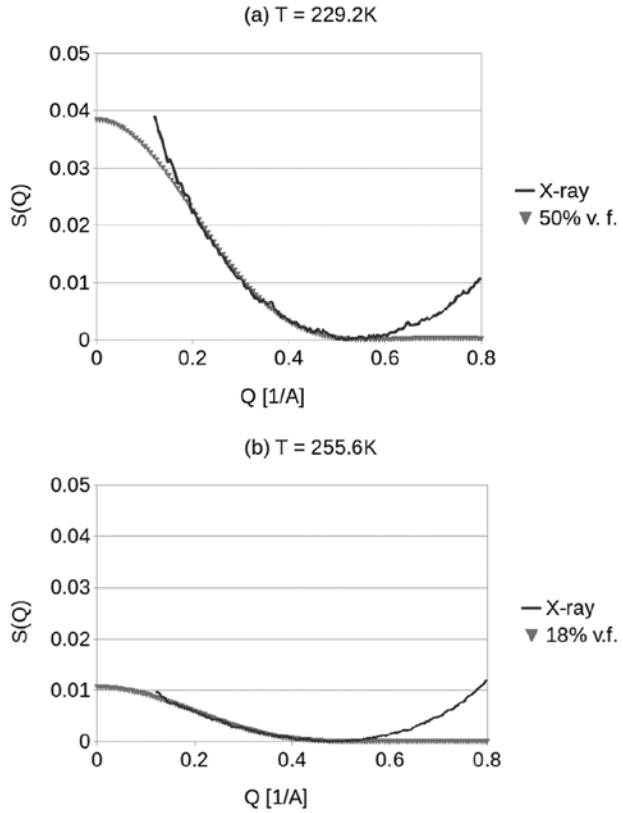
According to Röntgen, "water is a saturated solution of ice in a liquid composed of simpler molecules" (Dorsey, 1940). Ideas analogous to this recur frequently throughout the history of the study of water. George Walrafen was a strong proponent of the idea (Walrafen, 1968) as was Wilse Robinson (Vedamuthu, Singh, & Robinson, 1994), and the idea has taken root again in the past decade or so, based on high resolution X-ray scattering experiments, (Huang et al., 2009; Kim et al., 2017) and spectroscopy experiments (Kringle, Thornley, Kay, & Kimmel, 2019), as well as a growing body of theoretical work (Holten & Anisimov, 2012; Shi, Russo, & Tanaka, 2018). It has even reached the popular science press with articles in New Scientist (Sanderson, 2018) and Chemistry World (Brazil, 2020). The general theme of these ideas is quite well summarised by Robinson who claims that fits to the temperature dependence of the density of water "indicate the presence of capacious intermolecular bonding with a density extremely close to that of ordinary ice-Ih, intermixed with compactly bonded regions having a density near that of the common dense forms of ice, in particular ice-II." Similar kinds of ideas emerge in the other cited works, although I think it is fair to say most authorities nowadays do not regard actual crystalline ice to be present in water. We know this, since on average, based on the water diffusion constant of ~2 x 10-5 cm2/s, a single water molecule will diffuse roughly 150,000 times its own diameter in 1 second. Such rapid diffusion surely cannot support any form of ice structure for very long? However there is no consensus in regard to how large the patches of differently-structured water are or what they might look like. According to Anders Nilsson (quoted in (Brazil, 2020)) the distinguishable patches of water contain between 50 and 100 water molecules, whereas for the two-state model of (Shi et al., 2018) only 4.38 molecules are involved on average. Both these numbers are however at odds with the claimed correlation length of water, around 4 Å, (Kim et al., 2017) which would imply the patches contain roughly 9 molecules on average.

Mixture models misinterpret the scattering function, F(Q), of water

If you admit, as is done in much of the work cited above, that water is a mixture of patches of higher and lower density, even if these patches are rapidly fluctuating as some have claimed (Brazil, 2020), then you have to accept that the statistical mechanics of mixtures is different from that of pure materials. That this is the case has been demonstrated extensively in the work of J.G. Kirkwood (Kirkwood & Buff, 1951) and is addressed in the book by Cusack (Cusack, 1987). In a mixture the structure factor, F(Q), where Q is the wave vector change ($= 4\pi\sin\theta/\lambda$) in the radiation scattering experiment, no longer approaches the compressibility limit at Q = 0, as it does in a single component fluid. Instead an additional contribution to the structure factor related to the concentration fluctuations between the two components or states has to be included. The corollary of the above statements is that if S(Q) tends to the compressibility limit as $Q \rightarrow 0$, then the fluid, by definition, cannot be a mixture of two (or more) components!

An equivalent result occurs in the theory of small angle scattering from mixtures, which demonstrates a rise in scattering at small Q, related to the size of distinct scattering patches of different density and the magnitude of the difference in scattering density inside and outside.(Glatter & Kratky, 1982) The nature of this effect has nothing to do with whether the system is to be regarded as homogeneous or inhomogeneous, or whether the patches are short-lived or long-lived, fluctuating or stationary: it is a simple and direct consequence of there being distinguishable regions of different density in the material. In Figure 1 I show an attempt to reproduce the low angle scattering of water, as reported by (Kim et al., 2017) at two temperatures, using a simple model with spherical patches of different density in an otherwise uniform fluid. It is found that in order to reproduce approximately the rise in scattering at low Q, the density difference between the inside and outside of the patches, which have a radius of about 4 Å, analogous to the correlation length deduced in the same work, is in the region of 1-2 % of the density outside. This is much smaller than the sort of density differences of the two components that are supposed to occur in the mixture models cited above, and of a size

Figure 1. Consequence of mixture model for small angle scattering.



Small angle X-ray data for water as reported by (Kim et al., 2017) (solid lines) at two temperatures, 229.2K (a) and 255.6K (b). The triangles show an estimate of the scattering based on assuming uniform spherical patches of density (A. K. Soper, 1997) of radius 4.0 Å (a) and 4.2 Å (b), with density differences compared to the surrounding bulk density of 1.70% and 1.38% respectively. The assumed volume fractions (v.f.) of these patches was taken from the prediction made by Holten and Anisimov (Holten & Anisimov, 2012) at the respective temperatures. These points are not intended to be exact fits to the data as such, because the assumed spherical shape of the patches is probably too simplistic in practice. They are simply intended to indicate the likely size of the density contrast that might give rise to the observed data. We note that the spherical model shows inverted parabolic behaviour at low Q, as expected for the Guinier region. No such region is present in the X-ray data, making the calculation of the size of the purported density patches as performed in (Kim et al., 2017) unreliable.

expected from the compressibility alone. The bottom line of all this is simple: the observed rise in scattering at low Q in water is far too small to be consistent with the idea that water is a mixture of distinct species of water molecules. In other words, regions of different distinguishable densities simply do not exist in water.

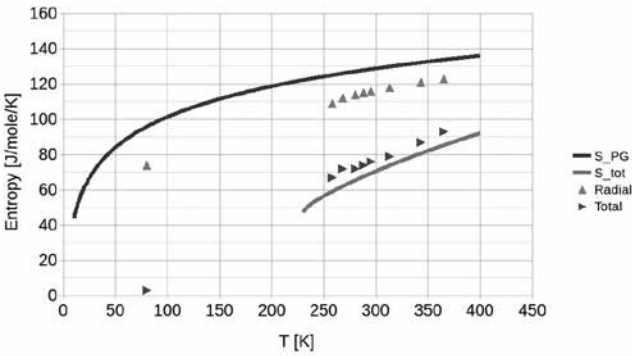
Existing interpretations of the small angle X-ray scattering data of water also overlook an essential feature of small angle scattering, namely, if you want to assess the size of the scattering particles, you must be able to access the Guinier region of the scattering pattern.(Glatter & Kratky, 1982) In this region the scattering adopts the shape of an inverted parabola as a function of Q: the curvature of this parabola is a direct measure of the radius of gyration of the scattering particle. Without that information, any stated particle size is open to being contradicted by improved experiments. None of the small angle scattering data from water shown in (Huang et al., 2009; Kim et al., 2017) show the Guinier region, so that quoted correlation lengths extracted from those data are speculative at best.

Water is an orientational liquid

Our third quarrel with two-state models of water relates to their seemingly complete disregard for the strongly, indeed uniquely, *orientational* nature of the structure of water. Several reports have invented order parameters which attempt to delineate the two types of water, so-called 'ordered', lower density water, and 'disordered', higher density water. These parameters generally ignore the 6-dimensional orientational structure and dynamics of water, even though this structure and dynamics is readily accessible in computer simulations of water. Instead they are based primarily on the separation of neighbouring molecules, with little reference if any to their relative orientations. Yet we know from the study of dense crystalline ices that highly ordered networks of hydrogen bonded water molecules can inter-penetrate, allowing the formation of dense, ordered structures which involve non-bonded molecules in close proximity. Based on the limited data that are available, it seems likely that such inter-penetrating networks of bonded water molecules occur in the liquid state as well at high density. Mixture models of water make no allowance for that structure, which occurs mostly under applied pressure. (Soper & Ricci, 2000) Our definite view is that models that do not build in this propensity for water to remain hydrogen bonded with pronounced orientational correlations under conditions of higher density will have no validity in the longer run.

To emphasize these points, Figure 2 shows a recent calculation of the pair contribution to the configurational entropy of water for a series of temperatures near ambient as well as for the case of low density amorphous ice (LDA) at 80K (Soper, 2019). Here the results using the full orientational pair correlation function are compared with using just the radial function on its own. It is immediately apparent that the orientational contribution provides about three-quarters of the configurational entropy of water. Moreover the full term drops close to zero, as expected, for LDA, but remains finite for the radial term on its own in this case. It is well known that the specific heat of water appears to undergo some sort of hiatus near 230 K, and on the basis of the evidence in this figure, this can only arise from

Figure 2. Configurational entropy of water and amorphous ice.



The total entropy of water as a function of temperature (lower line), as determined from the known temperature dependence of the specific heat of water, is calculated as the perfect gas component (upper line) plus a configurational component (triangles, arrows). The pair contribution to this configurational component is shown here, for the purely radial distribution function (triangles) and for the full orientational pair correlation function (arrows), as derived from empirical potential structure refinement of neutron and x-ray diffraction data from water. It becomes clear that the radial component accounts for only about one quarter of the total configurational entropy. Adapted from (Soper, 2019) where more details can be found.

changes to the orientational term, such as a "freezing in" of orientational motion. Whilst it is certainly true, as shown in (Soper, 2019), that higher density forms of amorphous ice such as HDA have increased entropy compared to LDA, the increase in entropy is marginal (around 10%) compared to the magnitude of the total configurational entropy, so that these higher density forms of amorphous ice still have low entropy. Near ambient conditions, the changes in entropy with increasing density are smaller even than this, so statements that water is a mixture of low density 'ordered' and higher density 'disordered' states are quite meaningless in practice.

Isosbestic points

One of the most commonly cited justifications for assuming that water is a mixture of two components is the observation that when you change some state variable, such as pressure or temperature, the spectral response of the material for some intermediate state between the start and end points can be represented as a linear combination of the spectra at the end points. This was observed in the Raman scattering of water as a function of temperature by Walrafen, and in the X-ray diffraction patterns of water as a function of pressure, by Robinson. The same behaviour has been recently been observed in the IR spectra of thin films of water at ~200K to assert that transiently supercooled water can be regarded as a mixture of two states. (Kringle et al., 2019)

However the view of water as a strongly orientational liquid suggests that the average environment of a water molecule changes both spatially and orientationally as you change the density or temperature. If that is so, changes to the IR spectra, which are in any case a local probe of a water molecule's environment, or the X-ray diffraction patterns are simply reflecting this changing environment, and cannot be used to conclude that water is a mixture. Geissler makes exactly this point in a theoretical study from 2005, which often gets overlooked when discussing mixture models of water.(Geissler, 2005)

Summary and conclusion

The above account draws attention to a number of flaws in the idea that water is a mixture of two structurally-different components. In particular it becomes clear that nobody really knows, if water really is a mixture, what it is a mixture of. The two-state of model of water does not work because, to reproduce the observed small angle X-ray scattering of water, you have to assume density differences of between 1 or 2% between the two states, which is much smaller than what is typically assumed in two-state models. Furthermore, since it is normally assumed the structure factor data, F(Q), go to the compressibility limit at Q = 0, this must, by definition, exclude the possibility that water is a mixture of distinguishable states. Meanwhile, attempts to estimate the size of the differently structured patches are stymied by the lack of Guinier scattering in the diffraction patterns. Finally the mixture interpretation of spectroscopic and computer simulation data of water fails to take account of the uniquely orientational nature of water structure and dynamics.

For all these reasons, we regard the two-state model of water to be nothing more than a convenient fitting exercise, that ignores key aspects of the real fluid.

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Squaring the blue four-circle

FROM the 1960s to the 1980s, X-ray data collection in many laboratories relied on the Hilger & Watts diffractometer, which some may well remember using, fondly or perhaps not. Collecting macromolecular data often took several months, during which power-dips and other electrical instabilities, cooling-system floods, crystal-slippage, radiation-decay and capillary-breakage, as well as helium gas and paper-tape shortages, all took their toll on your sanity. In the days before automatic indexing, usually the hardest part was determining the orientation matrix. This involved pre-aligning the crystal using a precession camera, transferring it to the diffractometer and then locating a number of strong reflections, usually axial, orthogonal and of known index. Arguably, it was good training for coronavirus stress. As these machines have long since gone to the great resting-place for diffractometers, it seemed interesting to catalogue their history and last year I committed some details to a Wikipedia page and a blog (referenced therein: https://hilgerwatts.blogspot.com/), which has many more details and historical documents than would fit here.

Hilger & Watts was based in several locations but diffractometer production centred on the Camden Town factory, which was the largest employer in the area. The company had a long history, dating back to the middle of the 19th century, specialising in production of scientific instruments (mostly optical), many of which were commissioned in large numbers by the MoD during both world wars. They also supplied space-flight instruments to NASA.

The first X-ray diffraction instrument to be produced commercially was known as the linear diffractometer. This had been developed by Uli Arndt and David Phillips at the Royal Institution (RI) in London. In those pre-internet days, the setting angles for each reflection had to be calculated using the EDSAC computer in Cambridge. To overcome this inconvenience, the team set about developing an analogue method of determining these angles involving protractors and a scale drawing of the crystal lattice. Quoting from Uli Arndt's autobiography (Personal X-ray Reflections, Athena, 2006): "David remarked to me one Friday what a pity it was that the rotations of the protractors could not be linked directly to those of the crystal shafts". Dr Arndt then describes how the following weekend he borrowed a Meccano set from the son of a sailing friend to try out possible linkages for an automatic diffractometer. Having established the feasibility from such humble beginnings, the subsequent design and prototyping took another two years, complicated by the fact that Dr Arndt had to spend a year on sabbatical in Wisconsin, communicating with the RI team by trans-Atlantic mail. Following his return to London, a prototype of the machine was exhibited at the Physical Society and was eventually manufactured under license by Hilger & Watts, who went

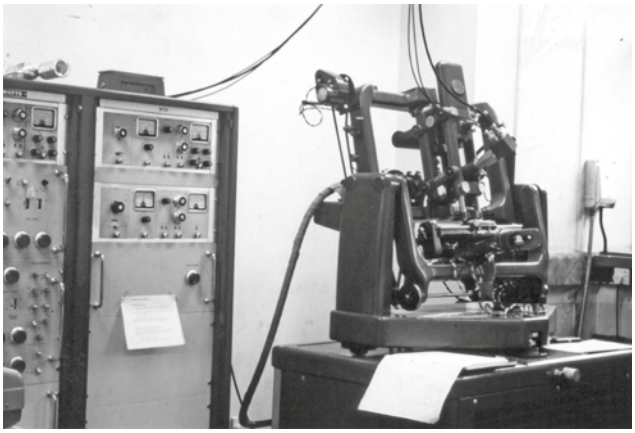


Fig 1. A Hilger & Watts Y190 linear X-ray diffractometer.

on to sell around 100 of these instruments worldwide, as the Y190 model (Fig. 1), in the late 1950s – early 1960s. In 1963 (a year of some biological significance for the author) the RI team adapted the linear diffractometer so that it could effectively measure 3 reflections at a time. This proved to be crucial for the structure determination of lysozyme, which followed two years later.

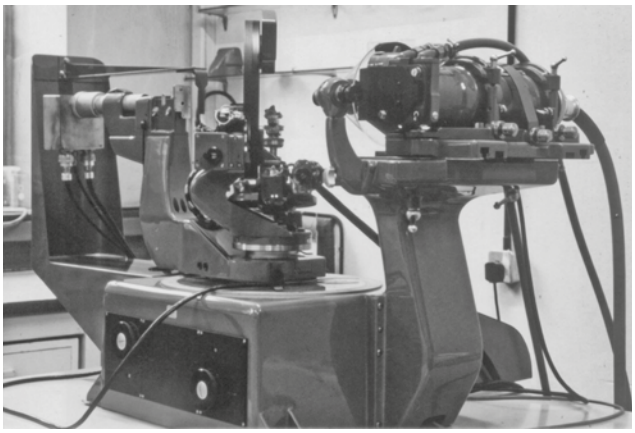


Fig 2. The unmistakably elegant style of the Hilger & Watts Y290 four-circle diffractometer.

By the late 50s it was clear that the instrument of the future would be the four-circle diffractometer. Developments in computer control of machine tools would mean that, before long, each diffractometer would have its own digital computer for controlling data collection and the built-in analogue device was to become a thing of the past. Around this time, Dr Arndt had realised that the relatively well-funded field of neutron diffraction had not invested significantly in the development of automatic diffractometers. This led to a collaboration with Terry Willis at the Atomic Energy Research Establishment, Harwell, where "there was a large staff of engineers... who were somewhat under-employed". Their considerable instrument-design skills led to the rapid development of the

Fig 3. The control electronics for a Y290 diffractometer including the PDP-8 minicomputer.

world's first automated four-circle diffractometer which, again, was manufactured under license by Hilger & Watts, this time as the Y290 model (Figs. 2-4). The very early machines used a Ferranti computer for controlling the instrument and "gave a lead of at least two years over any other similar instrument on the market". However, there were reliability issues with the computer control and this led Hilger & Watts to develop improved electronics in partnership with the University of Manchester where both Prof. David B.G. Edwards (Computer Science) and Owen S. Mills (Chemistry) were involved. On their advice, the cheaper and more compact DEC PDP-8 (right-hand side of Fig. 3) became the computer of choice and the resulting improved models of the diffractometer were given an unforgettable pale blue colour. One of the production engineers claimed that the electronic research department in Camden had PDP-8 No 4 from DEC, so Hilger & Watts was likely to have been one of DEC's very first PDP-8 customers. The book 'Single Crystal Diffractometry' by Arndt and Willis (C.U.P., 1966) has photographs and other excellent diagrams showing the construction of both diffractometers, and is available online. For commercial production of the Y290, Hilger & Watts would go on to win two Queen's Awards to Industry, the first for Services to Export in 1966 and the second for Technological Achievement in 1968.

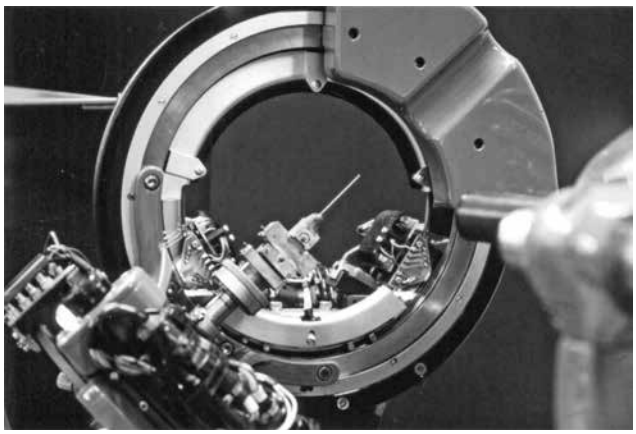


Fig 4. Close-up of the crystal on a Y290 showing the distinctive chi-circle of the Eulerian cradle.

The Y290 diffractometer had an optical motor-positioning system based on moiré fringes which were recorded by photocells – sometimes the user would find that after checking the centring of their crystal under a bright light and forgetting to turn it off, the diffractometer motors would then completely lose their settings and the resulting data would be useless. The X-ray data were written to paper tape by teletype and, by the mid-1980s, users were struggling to find computer facilities which could still read their tapes for downstream analysis. In the 1970s, David Phillips, by now at the University of Oxford, developed an interesting 5-circle version of the machine which could measure up to five X-ray reflections in each scan due to the addition of a tiltable linear array of 5 counters to the detector arm.

Some recollections from a former Hilger & Watts engineer, Derek Coggrave: "I started work there around 1962/63. The reason for employing me was that the production of the linear diffractometer was due to start and I would be assigned to test and install it. The linear diffractometer didn't last long because it was superseded by the four-circle. On my first visit to Japan to install a four circle there was no instruction manual for the instrument. The customer complained and the agent became very agitated. I was there for about seven weeks and so wrote a manual by hand for the user in the evenings and weekends. The agent had the thing typed and the drawings copied and this was given to the customer before I left. Later this was then used to produce the official version. It is amazing that in just over fifty years we have advanced from the PDP-8 with 4K of memory and costing around £8K (my house only cost £5.7K at the time)."

"There was an interesting letter in the FT recently about the RI where David Phillips was mentioned. That struck a note with me because I went there several times to install and service a four-circle for Prof. Phillips. After a couple of years the instrument was moved to Oxford when he moved there. It was around 1965/6 I went to the RI with Len Wood for the installation. One difficulty was the hydraulic lifts and getting heavy items to the upper floors. The transformer, which weighed half a ton, made the lift sink as soon as the first two wheels reached the lift floor. A toss of a coin determined who stayed in the lift and with help, the transformer was run into the lift as fast as we could push it. As my colleague and the transformer sank from view, we climbed the stairs and waited. Thankfully, after a few minutes he, the lift and transformer reappeared."

"Later, another colleague servicing the instruments worked until around 10 pm. Turning the lab lights off he found the rest of building in darkness. He groped his way to the front door – locked and bolted. Daunted by a night alone in the RI he climbed upwards looking for help. Seeing light around the edge of a door, he knocked loudly expecting a porter. However, the flat was occupied by Sir Lawrence Bragg (the Director of the RI) who appeared in his dressing gown, produced a set of keys and allowed my colleague's exit."

"Prior to that, probably around 1962/63 I had quite often visited the department in Oxford run by Dorothy Hodgkin. I installed her linear diffractometer with Len Woods. We were always encouraged to entertain the customer so Len and myself took Dorothy to the Royal Oxford Hotel for lunch a couple of times. We were quite right-wing in our politics and she was very left, although we didn't know it at the time. However, she was always extremely polite and very gracious. In comparison, on one occasion when we were in the RI, the telephone in the lab rang so I answered it. Before I could ask who was calling Dr Arndt rushed in yelling at me for picking the receiver up. Prof. Phillips on the other hand was always very polite but was inclined to ask rather quizzical and penetrating questions, testing whether one was up to the job. But, he was always quite content provided things were done to his satisfaction."

Some comments from Prof Lindsay Sawyer (Edinburgh): "The pale blue Y290 4-circle was their Mark 2 version. Physics in Edinburgh had a Mark 1 (same colour as the

linear diffractometer) which relied on a huge box of Ferranti electronics and too coarse gratings for positioning the circles. Positioning to 1/10 of a fringe was unreliable at the time and most of the folk in the lab became expert at keeping the thing going to finish data-collection. There was also a peg-legged night watchman who did the night shift. The Edinburgh (ex-RI) linear diffractometer had 3 counters so if you had an orthogonal space group (like me) you could collect 3 layers at the same time. Eddie Komorowski collected 6 Å triclinic data on it, 1 layer at a time! The output on the linear diffractometer was 5-hole paper tape, on the 4 circle, 8-hole. I may still have some rolls somewhere. Happy days!"

More from Derek Coggrave: "In July 1968 Hilger & Watts was taken over by Rank Precision Industries – Rank had a large cash flow from their vast Xerox copier production. However, selling scientific instruments tends to be a one off process. Another issue was that Hilger & Watts had growing problems of its own. Many of the managerial positions were occupied by long serving employees who had spent decades engaged in the production of optical instruments and had no knowledge of electronics or the science involved. Secondly, the catalogue of instruments they manufactured was, as far as I remember, around ninety. Many only sold a few each year: no doubt uneconomic. The main housing of these devices was often a casting and it was always difficult to reach the adjustment mechanisms. I can remember using dental mirrors, torches, dental probes to hook springs and right-angled screwdrivers."

Rank chose to move their Camden operation to Thanet in Kent, to an iconic 1960s factory that was large enough to locate all their functions on one site. "The prime purpose at Hilger & Watts was the design and building of scientific instruments for a limited market, which because of technological developments was subject to sudden change and required a process of constant redesign and upgrades. A lot of investment was required in personnel and equipment, which presumably was not forthcoming, so the company fell apart. Rank lost patience. Oxford Instruments, which at the time was a competitor of Hilger & Watts, has thrived until today. So, I believe the opportunity was there but the management skills and the will to succeed was wanting." Thus, over time almost everything was sold-off or wound-down, although the successful company Hilger Crystals still operates at the Thanet site today.

I am very grateful to Prof. Dave Watkin (University of Oxford) for provision of the photographs.

It would be interesting to hear from anyone with further recollections of these instruments – email me at jon.cooper@ucl.ac.uk.

Jon Cooper
(UCL)

The 2020 Winter Crystallography Meeting

November 2nd-3rd 2020
Milton Hill House Hotel
Steventon, Abingdon, Oxfordshire

The Winter Crystallography Meeting brings together ISIS & Diamond users with members of the BCA Physical Crystallography Group in a two day celebration of structural science.

As always we hope to put together a diverse and exciting programme. Ph.D. students and early career researchers are particularly encouraged to apply to give talks and present posters!

More information will be posted on www.pcg-scmp.org in due course. Registration will open in September.

Obituary – Cyrus Chothia

Some personal reminiscences

IN August 1977, I arrived at the MRC Laboratory of Molecular Biology to begin a one-year Sabbatical with Michael Levitt. When I arrived, I found Michael packing cartons – he was leaving for The Salk Institute. An inauspicious start to my visit to Cambridge!

What happened? Max Perutz took me up to the Canteen for tea. I remember being impressed that the head of the lab., no less a person than Max Perutz, would take the trouble with a temporary visitor. Then he suggested: 'If you are interested in analysis of protein structure, why don't you work with Cyrus Chothia?'

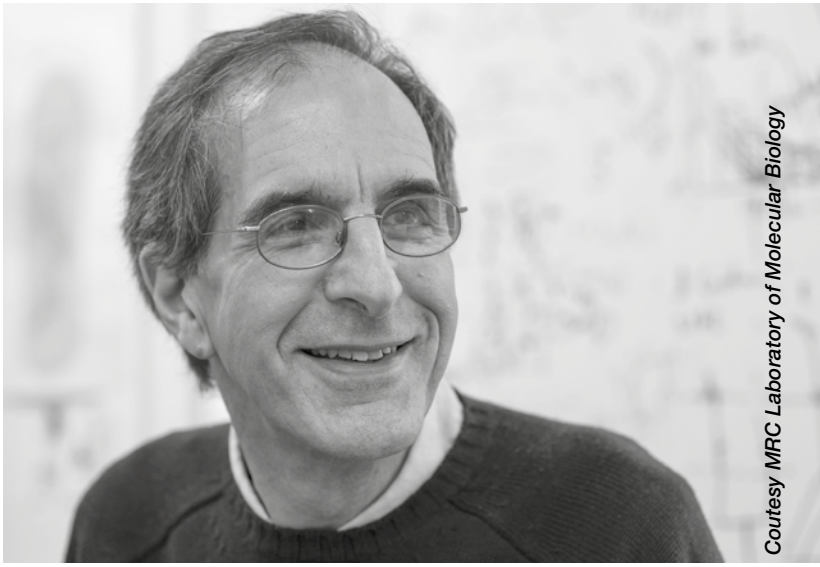
This needs to be placed in context. Cyrus was not on the staff of the LMB. He was attached to the laboratory of Peter Pauling at UCL and did not even have visitor status at the LMB. When I arrived Cyrus was finishing up his work with Joyce Baldwin on the conformational change in haemoglobin.

Readers should ask themselves: Would their institution have welcomed a rank outsider, as Cyrus was then? Would their heads of department suggest that a visitor work with such an outsider? This is one of the things that has made the Laboratory of Molecular Biology, and Max Perutz's leadership of it, unique. It has allowed the immensely-talented permanent staff and visitors – and even non-visitors! – to achieve their legendary successes[1].

Later, the Laboratory did hire Cyrus, and he served with great distinction. He accrued, trained and encouraged a group of students and colleagues, many of whom went on to become leaders in the field in their own right. He was elected a Fellow of The Royal Society in 2000.

Back in August 1977, Cyrus proposed to me a study of globin structures. What made this project possible and timely was the publication of globin structures from a much larger range of species, and a set of more widely-diverged proteins, than had previously been available. Scientists who now deal with both a very large Protein Data Bank, and the relative ease of solving protein structures, will have difficulty appreciating the situation 40 years ago. Then, the PDB would release a few structures in 'bursts' every three months. One would scan the new structures, and ask, 'What questions can we now address?' Nor would many solved structures actually be deposited and released. Cyrus and I spent considerable time and effort 'chatting up' often reluctant crystallographers to send us coordinates, and to collaborate with us in analysis of their structures.

The work proceeded well but slowly. (Cyrus was always extremely patient with me, although I know he had many occasions to recall a famous comment of Winston Churchill. During World War II, Churchill remarked: 'The Americans can always be counted on to do the right thing … after they have tried all other possibilities.') Despite this, we worked extremely well together. Like any good marriage we complemented each other: Cyrus had a background in chemistry and crystallography, and I came more from the maths/physics side. We joined forces to do biology! Both Cyrus's work with Joyce on haemoglobin, and our work together on evolution of the globins, ended up as lengthy papers in the Journal



Coutesy MRC Laboratory of Molecular Biology

of Molecular Biology[2] No one can deny that the Medical Research Council got its money's worth – they didn't pay Cyrus a penny while he worked on these projects.

Cyrus and I were able to give a fairly thorough account of the structural similarities and differences among the globins then available. We felt that we understood the intimate details of the evolution in this family, which suggested some general ideas about how proteins evolve.

Cyrus continued to spend a day a week in London, interacting with Peter Pauling's lab. at UCL. I often accompanied him, especially after (now Sir) Tom Blundell at Birkbeck organised a weekly protein structure seminar series. We enjoyed the big city and often combined professional activities with recreational ones – a highlight being going with Cyrus to a blockbuster Titian retrospective exhibition.

After returning to the U.S. for two years, I returned to Cambridge in 1981. Cyrus and I extended our work to additional protein families, including cytochromes c, and β–sheet proteins: plastocyanin and azurin, and immunoglobulin domains. At one point I said to Cyrus that this was getting to be sort of 'crank turning'. He responded with another idea – looking at mechanisms of conformational changes in insulin.

A mystery that had emerged from the crystal structures of the two-zinc and four-zinc forms of pig insulin was the conformation of the sidechain of phenylalanine B25. In both forms, in one of the molecules of the dimer the sidechain of PheB25 packs into its own monomer; in the other molecule it points across the dimer interface to pack against the other monomer. We traced these conformational changes to an impulse from crystal-packing interactions, transmitted to the dimer interface.[3] This opened the door to a new series of projects: looking at conformational changes in citrate synthase and lactoferrin.

In 1986, we worked at putting together the results on protein evolution adduced in studies of individual families:

(1) It was possible to distinguish a 'core' of a family of proteins, from the 'periphery'. The core was a set of major secondary-structural elements, including the active site, that maintained the same general topology.

(2) Restricted to the core, there was a relationship between deviation of amino-acid sequence and deviation of the backbone of the structures. Different protein families fell on a single curve.

This suggested that we could predict the quality to be expected of a homology model. Thus, if you brought to us an amino-acid sequence of a protein of unknown structure, and we determined the protein of known structure for which the amino-acid sequence was most similar, we could interpolate in our curve and predict the r.m.s. deviation of the core of the model. You could then decide whether the quality of the model was sufficient for you to pursue the modelling or not. We also recognised that in many protein families, the structure of the active site is better conserved than other parts of the structure.

(This is what you would get 'for free' – just using the closest relative of known structure as the model. Contemporary homology modelling gives results that are very much better than suggested by those early results.)

Cyrus and I first presented these results at a meeting at The Royal Society. Cyrus generously allowed me to speak. It was quite successful – Cyrus and I were very pleased when Max Perutz made a point of complimenting us on the work.

At that point we thought we should test these ideas by picking a protein of unknown structure, making the homology model, and seeing whether it fit our prediction. What example to choose?

There was no point in predicting a known structure as success would not claim general credibility. Conversely, there would be no point in predicting a structure that might not be solved for ten years. Like CASP, we wanted a structure that was in progress – a true blind test, but one that offered the possibility of checking the model against the experimental structure fairly promptly.

Now, the dumbest possible choice of a structure for this purpose would be an immunoglobulin. Our theory dealt only with the core of the structure. For immunoglobulin domains the core of the structure corresponds to the framework, which is quite constant in structure. The interest in the structures of antibody variable domains was in the complementarity-determining regions – loops between strands of β–sheet, which are outside the framework/core. Our methods predicted nothing about the quality of modelling of loops.

At that time César Milstein had crystallised the Fab fragment of immunoglobulin D1.3, the first crystal of a monoclonal antibody. The LMB was of course well supplied with expert protein crystallographers, and César tramped up and down the corridor hoping to persuade one of them to solve the structure. He really wanted to keep the project in the building. But for some reason (which I still do not understand) they all turned him down. Roberto Poljak (who also died last year) was at the Institut Pasteur in Paris. He and César had been students together in Argentina, and César approached him. Roberto took on the D1.3 project.

Here was a structure in progress, and Cyrus and I decided to make it our test case for prediction. Wait! you will say, didn't you just give good reasons why an antibody would not be an intelligent choice? True, but we had still another constraint – we had to be able to get along with the crystallographer solving the structure. At the Pasteur, Simon Phillips was working on D1.3. We knew Simon well, as he had worked at the LMB on structures of sperm whale myoglobin. And in fact the collaboration worked as smoothly as we had hoped. It also involved numerous trips to Paris, which Cyrus and I much enjoyed.

But of course we recognised that interest in antibody structures focussed on the complementarity-determining loops. We extended our work on homology modelling of cores of structures to sequence-structure relationships in loops. This soon developed into a separate project, one which occupied us, Cyrus's students, and a colleague Anna Tramontano, for many years. The best-known idea to come out of the work is the idea of 'canonical structures', conformations of five of the six antigen-binding loops determined by loop length and specific signature patterns in the sequences.

Cyrus and I continued to stay in very close touch. A highlight of recent years was speaking at the awards ceremony honouring Cyrus with the ISCB Senior Scientist Prize in 2015.

All colleagues in the field will feel the professional loss. But to me, in addition, he and Jean were as close as family, and I miss him as I would miss a near relative.

Arthur Lesk
(Penn State)

Footnotes:

[1] Once Nature wrote around to people soliciting one-sentence comments that they could use in advertising. I wrote: 'To keep up with important breakthroughs in molecular biology, you need read only the Cambridge Evening News … or Nature.' Unsurprisingly, they didn't use this.

[2] Baldwin, J. & Chothia, C. (1979), J. Mol. Biol. 129, 175-220; Lesk, A.M. & Chothia, C. (1980). J. Mol. Biol. 136, 231-270.

[3] Chothia, C., Lesk, A.M., Dodson, G.G. & Hodgkin, D.C. (1983). Nature 302, 500-505.

Volume 68 (June 2020) of *Biographical Memoirs of Fellows of The Royal Society* contains Biographical Memoirs of two of our crystallographic colleagues: Guy Dodson (by Eleanor) https://doi.org/10.1098/rsbm.2019.0042) and Aaron Klug (by Tony Crowther) https://doi.org/10.1098/rsbm.2019.0034. These are fascinating – not only to read but to see the pictures!

Meetings of interest

In the current pandemic situation, many meetings are being cancelled or postponed. At the time of writing, all the meetings listed here were scheduled to go ahead, but there are likely to have been further changes since going to press. 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.

1st Jun 2020 – 5th Jun 2020
ICDD Clinic – Fundamentals of X-ray Powder Diffraction
Newtown Square, United States.
http://www.icdd.com/xrd/

8th Jun 2020 – 12th Jun 2020
ICDD Clinic – Advanced Methods in Powder Diffraction
Newtown Square, United States.
http://www.icdd.com/xrd/

13th Jun 2020 – 27th Jun 2020
22nd National School on Neutron and X-ray Scattering
Argonne & Oak Ridge National Laboratories, United States.
Virtual Event
https://www.anl.gov/education/national-school-on-neutron-and-xray-scattering

15th Jun 2020 – 22nd Jun 2020
13th Annual CCP4/APS Crystallographic School:
From data collection to structure refinement and beyond
Chicago, United States.
http://www.ccp4.ac.uk/schools/APS-2020/index.php

15th Jun 2020 – 26th Jun 2020
22nd National School on Neutron and X-ray Scattering
Virtual Event
https://www.anl.gov/education/national-school-on-neutron-and-xray-scattering

15th Jun 2020 – 19th Jun 2020
Introducing photons, neutrons and muons for condensed matter physics and materials science. A PSI course for master students
Paul Scherrer Institute, Switzerland.
https://indico.psi.ch/event/7949/

1st Jul 2020 – 3rd Jul 2020
60th Anniversary Meeting of the British Biophysical Society
Nottingham, UK.
https://britishbiophysics.org/posts/2019/2019-05-5-bbs2020/

12th Jul 2020 – 16th Jul 2020
American Conference on Neutron Scattering
Boulder, CO, USA.
https://www.mrs.org/acns-2020

15th Jul 2020 – 17th Jul 2020
RIXS-REXS 2020: Workshop on Resonant Elastic and Inelastic X-ray Scattering 2020
Port Jefferson, United States.
https://www.bnl.gov/rixsrexs2020/

27th Jul 2020 – 31st Jul 2020
Polarized Neutrons for Condensed Matter Investigations
Annapolis, MD, United States.
https://pncmi2020.umd.edu/

30th Jul 2020 – 1st Aug 2020
2nd COMPPÅ Symposium on Membrane Protein Production and Analysis
Columbia University Medical Centre, New York, United States.
https://www.comppaa.org/

2nd Aug 2020 – 7th Aug 2020
ACA2020.
Virtual Event
https://www.acameeting.com/

19th Aug 2020 – 22nd Aug 2020
Electron Crystallography School – 3D Electron Diffraction/ MicroED Bridging Small Molecule and Macromolecular Crystallography
Tabor, Czech Republic.
https://www.xray.cz/iucr/workshops/tabor/default.htm

31st Aug 2020 – 11th Sep 2020
24th JNCS Laboratory Course – Neutron Scattering 2020
Jülich, Germany.
https://www.fz-juelich.de/jcns/EN/Leistungen/ConferencesAndWorkshops/LabCourse/_node.html

31st Aug 2020 – 4th Sep 2020
CMD2020GEFES: Condensed Matter General Conference
Madrid, Spain.
https://eventos.uam.es/28512/detail/2020-joint-conference-of-the-condensed-matter-divisions-of-eps-cmd-and-rsef-gefes.html

2nd Sep 2020 – 5th Sep 2020
VIII-th Crystallographic Symposium (NCS-2020)
Varna, Bulgaria.
http://bgcryst.com/symp20/

2nd Sep 2020 – 6th Sep 2020
Euroscience Open Forum (ESOF2020)
Trieste, Italy.
https://www.esof.eu/en/

20th Sep 2020 – 24th Sep 2020
23rd European Symposium on Quantitative Structure-Activity Relationship
Barcelona, Spain.
https://www.euroqsar2020.org/

23rd Sep 2020 – 25th Sep 2020
ILL and ESS European Users Meeting
Lund, Sweden.
http://neutrons4europe.com/

24th Sep 2020 – 26th Sep 2020
23rd Heart of Europe Bio-Crystallography Meeting (HEC23)
Vierzehnheiligen, Franconia, Germany.
https://www.hec23.uni-bayreuth.de/en/index.html

28th Sep 2020 – 2nd Oct 2020
ICDD Clinic – Rietveld Refinement & Indexing
Newtown Square, United States.
http://www.icdd.com/rietveld/

1st Oct 2020 – 2nd Oct 2020
Italian Crystal Growth – Crystal growth: from Theory to Application
Torino, Italy.
https://www.icg2020.net/

3rd Oct 2020 – 5th Oct 2020
10th International Conference of the Hellenic Crystallographic Association
Athens, Greece.
https://www.iucr.org/calendar/events/topics/general/10th-international-conference-of-the-hellenic-crystallographic-association

4th Oct 2020 – 6th Oct 2020
2nd Joint Meeting of the "Young Crystallographers" (DGK) and the "Young Crystal Growers" (DGKK)
Freiberg, Germany.
https://dgk-home.de/aks/jkyc/freiberg-2020/

19th Oct 2020 – 23rd Oct 2020
Crete 2020 – 1st International CryoEM Symposium/ Workshop
Heraklion, Crete, Greece.
https://cryoemcrete.com/

1st Nov 2020 – 5th Nov 2020
Crystallography for Space Sciences
Addis Ababa, Ethiopia.
Contact: Eyasu Leta: **letaeyasu@yahoo.com**

18th Jan 2021 – 23rd Jan 2021
Third Pan African Conference on Crystallography
Nairobi, Kenya.
https://pccr3africa.org/

29th Mar 2021 – 1st Apr 2021
British Crystallographic Association Spring Meeting
University of Leeds, UK.
https://crystallography.org.uk/spring-meetings/#next-meeting

14th Jun 2021 – 18th Jun 2021
16th International Conference on Surface X-ray and Neutron Scattering (SXNS16)
Lund, Sweden.
https://www/snxs16.org

29th Jun 2021 – 2nd Jul 2021
AFC 2020: Congress of the French Association of Crystallography
Grenoble, France.
https://afc2020.afc.asso.fr

4th Jul 2021 – 10th Jul 2021
6th European Crystallographic School (ECS6)
Budapest, Hungary.
https://www.ecs6.chemcryst.hu/

18th Jul 2021 – 23rd Jul 2021
11th Liquid Matter Conference
Prague, Czech Republic.
http://www.lmc2020.cz/

30th Jul 2021 – 4th Aug 2021
71st ACA Annual Meeting
Baltimore, MD, United States.
https://www.amercrystalassn.org/future-meetings

9th Aug 2021 – 14th Aug 2021
IUCr2020 Computing School
Nove Hrady, Czech Republic.
https://www.xray.cz/iucr/workshops/nh/default.htm

11th Aug 2021 – 13th Aug 2021
School on SAXS/SANS and BioSAXS/BioSANS data analysis
Kutná Hora, Czech Republic.
https://www.xray.cz/iucr/workshops/kh/default.htm

11th Aug 2021 – 14th Aug 2021
Electron Crystallography School
Tabor, Czech Republic.
https://www.xray.cz/iucr/workshops/tabor/default.htm

12th Aug 2021 – 14th Aug 2021
TOPAS Intensive Course
Prague, Czech Republic.
https://www.xray.cz/iucr/workshops/topas/

14th Aug 2021 – 22nd Aug 2021
Twenty-Fifth Congress and General Assembly of the International Union of Crystallography
Prague, Czech Republic.
http://www.iucr25.org/

24th Aug 2022 – 28th Aug 2022
Thirty Third European Crystallographic Meeting (ECM33)
Versailles, France.
https://www.ecm33.fr/

12th Sep 2021 – 17th Sep 2021
15th Biennial Conference on High Resolution X-Ray Diffraction and Imaging (XTOP 2020)
Minsk, Belarus.
https://www.xtop2020.atomicus.by/

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