

DARESBUURY LABORATORY
INFORMATION QUARTERLY
for
PROTEIN CRYSTALLOGRAPHY

An Informal Newsletter associated with Collaborative Computational Project No. 4
on Protein Crystallography

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EDITORIAL

PELLA MACHIN

Photographic film scanning continues to be a subject of importance to most protein crystallography groups. On this theme, Keith Wilson, (in association with the CCP) is organising a workshop on 'the processing of X-ray oscillation photographs' to be held in Oxford, in March, 1981. Attendance at the meeting will be restricted to 15-20 people, all of whom must be active in the field of film processing. Any queries about this should be directed to Keith Wilson, Laboratory of Molecular Biophysics, Department of Zoology, South Parks Road, Oxford, OX1 3PS (Oxford 56789).

This issue of the newsletter contains remarks on some other meetings - both the recent Daresbury Study Weekend on 'Refinement' and the IUCr meeting in Ottawa next year.

This newsletter provides a good way of circulating information to protein crystallography groups. Ian Tickle has described the Birkbeck graphics system in this issue - does anyone else have any information on graphics which may be of interest to other groups? Have there been any further activities on the CRAY? Has anyone completed any interesting computational based research work recently - why not put an abstract of the paper in the next issue of this newsletter, so that other people can read about it? All contributions are welcome!

GRAPHICS AT BIRKBECK COLLEGE

IAN TICKLE (BIRKBECK)

The Scene [for those of you who are familiar with the people at Birkbeck]

All is silence, except for the rub-a-dub noise of a rubber making short shrift of pencil marks on paper.

It is 9.00 a.m. in "114" and "more power to the elbow" is at work. Pity the poor, lost souls who tried to sneak a crafty booking on the PDP11 before the authorised time! Now they will be lucky to get away with a stealthy 10 minutes on the "Decwriter" and 12K maximum, the day after tomorrow.

After the paper carve-up, the room resounds to a cacophony of whirring fans, tapping lineprinters and extracting gases ("very hostile environment"; courtesy Alwyn Jones). However, to see the blurring hands of "more power" on the E and S tablet, moving the stylus over the surface, it might as well be the interior of a country church on a weekday morning. What concentration!

Minutes pass. Ah! Who's this that's just entered with purposeful gait, flickering eyes taking in all with a few well-directed glances? Why, it's the "Lord of the Rings". Today he is to modify "frodo" so that it will sequence any named protein automatically, in 3 minutes flat! "Should be finished by twelve" he asserts modestly, in reply to your gaze of absolute awe and wonderment.

"Nothing to it!" a voice of supreme confidence interjects. This is "nothing's impossible". Ever since his initial halcyon days on the '11', he knows full well that all succeeding work on the E and S is merely a slightly extended copy of his original work. He may well be right - he certainly did do a good job!

Now two others have taken over the tablet operation. "Gotta get the sequence right" and "lend a helping hand" are at work. Is it due to the sheer complexity of the problem that work on this small piece of protein structure on the

screen is taking a bit longer than usual? Or is it due to some other more attractive distraction? Who knows?

Later, one may catch a glimpse of "water sprite" at work. "A program a day keeps the doctors at bay" is his motto. You must watch carefully if you are to observe one of his programs in the making; from conception to completion they take mere minutes - and all of them masterpieces!

A movement and 'Decwriter' noise now draws one's attention to the figure sitting alone in the corner. "'Ave alook any second now" is at work. He knows that everyone is waiting with bated breath for his completed work. Could it be that he actually enjoys keeping us all in suspense? No, the reality is that he has long since completed his work, but works secretly into the night with his program, completing the work of each group in the department. Soon he will publish many papers, culminating in the Nobel Prize for chemistry. Who would have thought it? (Perhaps the author?)

Thus ends a typical day in "114", the hub of the crystallographic universe (at least to those who frequent it!). Most remember to steer clear when "Got to hand it to 'em" is around!

The System

The Computer Graphics Unit of the Crystallography Department is a workstation on the Science Research Council network, with access via leased telephone lines to the IBM 370/165 and CRAY-1 computers at the Daresbury Laboratory, near Warrington, and to computer graphics facilities at the Rutherford Laboratory, near Didcot.

The local hardware configuration consists of an Evans and Sutherland Picture System 2 with a dedicated host mini-computer, a DEC PDP-11/60. The Picture System has a number of special features designed to produce a real-time display of a line-and-character representation of moving or changing 3-dimensional complex objects. The 3-dimensionality of the image on a high-performance cathode-ray tube is heightened by chipping, perspective and intensity depth-cueing, all implemented in hardware. The main interface with the human operator is a magnetically-sensitive 'pen' and a tablet-digitizer which can be programmed so that the operator has full interactive control over what is

displayed, giving the impression that he/she is actually manipulating the picture.

The PDP-11/60 minicomputer controls the storage and flow of the data to be displayed on the Picture System. The storage devices comprise a 800/1600 bpi magnetic tape drive and two DEC RKO7 disc drives with 28 Mbyte cartridges. The PDP-11/60 also controls another graphical device, a Varian Statos electrostatic printer-plotter used principally to obtain hard copies of the Picture System display.

Communications with the SRC network is done via CAMAC interfacing modules controlled by a PDP-11/04, to which a card reader, paper-type punch, line-printer and several visual display units are also attached.

Program packages which have been implemented include BILDER (written by Dr. R. Diamond of MRC Cambridge) and FRODO (written by Dr. T.A. Jones while at TH Munich and developed at Birkbeck). These are both designed as molecular modelling programs and ease the normally lengthy tasks of (i) building a large molecular model of, for example, an enzyme into a representation of the atomic density distribution derived from X-ray or neutron scattering experiments; (ii) obtaining the atomic coordinates from the model; and (iii) extracting information on the crystal and molecular structure from the atomic coordinates.

An existing molecular energy minimisation program, already in use on the main-frame batch-processing computers, has been enhanced by addition of the graphics display software. This is a tentative step towards studying the folding of large molecules, in particular proteins, although owing to the complexity of the system it is only possible to 'play back' the minimisation path in real-time. Actual real-time molecular dynamics has, however, been realised by graphical simulation of a system of 2-dimensional hard disks, a model for studying many-body interactions.

Other programs developed by members of the department include: ALOOK (originally written for a less versatile display system by Dr. D. Richardson while at University College, London), which allows the user to specify atom selection criteria so that the picture of a large molecule can be edited to show only a particular sub-structure of interest; POLY, which was originally designed to display complex polyhedra, but which can also be used to display large molecules in their entirety; NEWGEN (originally written by Dr. A. Wonacott of Imperial

College, London) which displays calculated X-ray oscillation diffraction patterns in order to facilitate indexing the observed patterns; and FITS which allows interactive display and manipulation of several independent molecules simultaneously ("docking").

The importance of interactive computer graphics as a scientific tool lies in the fact that data is assimilated by the researcher most readily when presented pictorially, and that this effect is heightened if the picture behaves in exactly the same way as a real object held in the hands would.

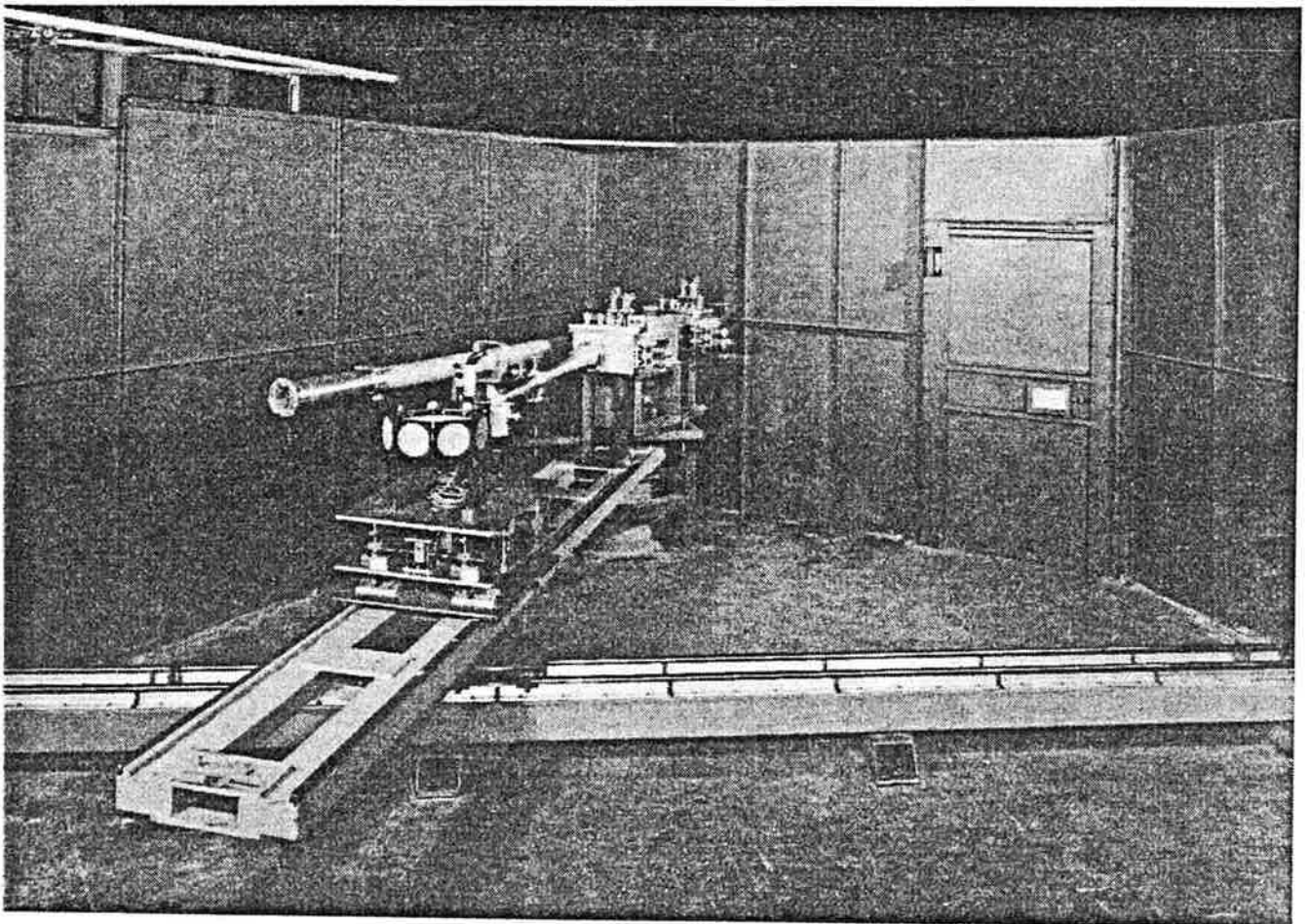
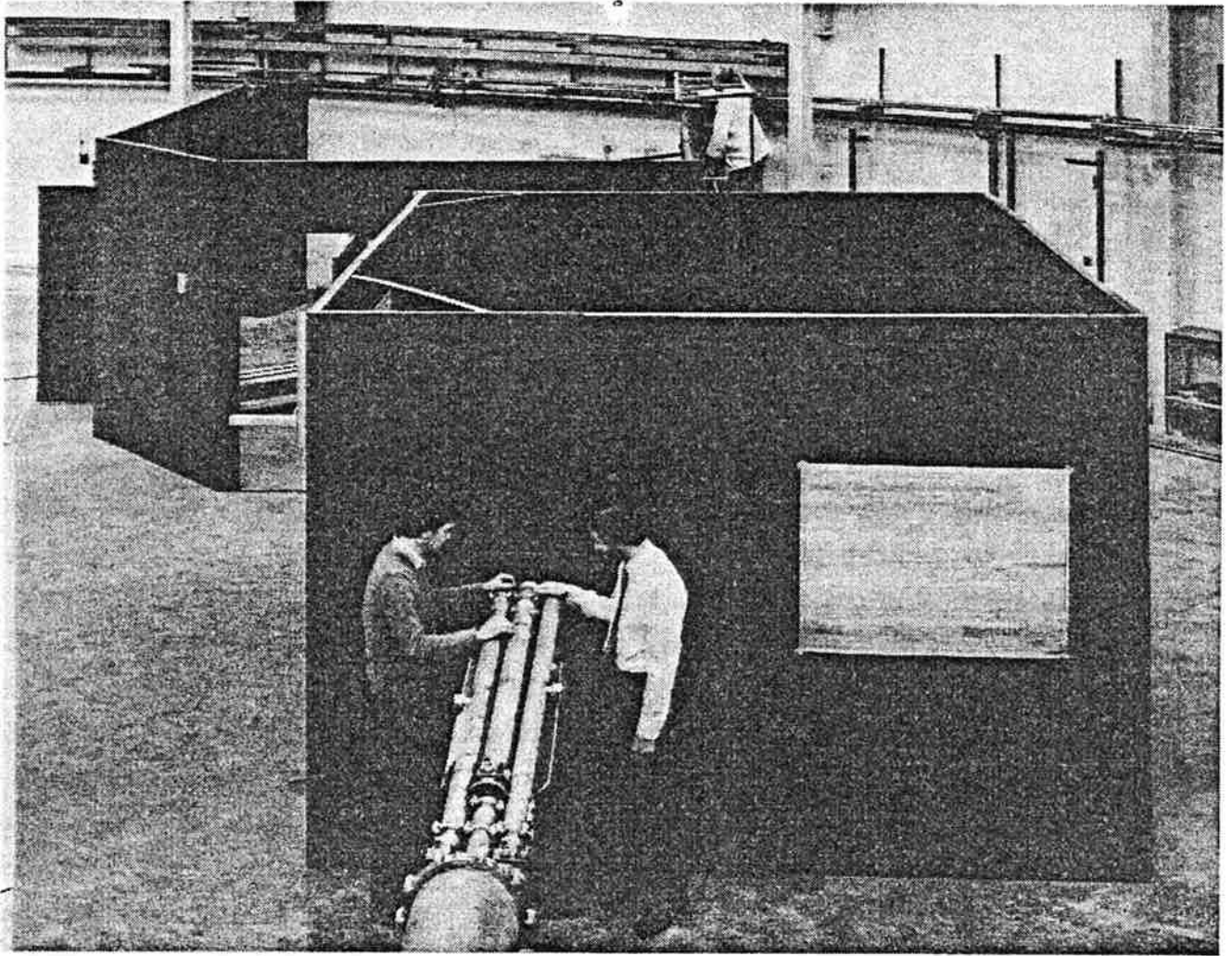
PROTEIN CRYSTALLOGRAPHIC DATA COLLECTION ON THE SRS

JOHN HELLIWELL (KEELE/DARESBUY LABORATORY)

We are rapidly approaching first scheduled beam time on the SRS (due late February) and so it is an appropriate time to give news of progress on the protein crystallography workstation on the first X-ray beam line 7. The attached photograph indicates the apparatus as it was seen on the SRS Inauguration day on November 7th, which includes all the basic hardware necessary to start experiments if there was beam down the line. The beam line and an overall layout are shown separately. Of course, the real test is the commissioning of the apparatus under beam conditions but various performance tests have been made on monochromator crystals, vacuum equipment, alignment systems and rotation camera on an individual basis. The station is presently being 'hard wired' for the necessary computer control of stepper motors (including limit switches). Software for the control of the 19 steppers has been written and tested on individual motors by Dr. Trevor Greenhough of Keele. Radiation protection will be provided by a walk-in type safety enclosure (see background of photograph), hence the need for motor control. It is hoped to simplify arrangements when operation, with beam, commences provided satisfactory agreement can be reached with the Radiation Safety Section here at Daresbury.

In the first 6 months of operation a total of 136 shifts of beam time have been requested by users out of a total feasible of 210 in such a period. For the second 6 months of operation a focussing mirror system will be installed which will provide even larger fluxes intercepted by the sample. Sometime during this second period the workstation will be converted for some fibre diffraction work, probably one 6 week cycle per annum.

Future plans for crystallography include of course the TV diffractometer development of Enraf-Nonius; approval for purchase has now been given and it is hoped to place an order soon for delivery to the SRS in early 1982. This should fit in well with the development program of the wiggler beam line.



PROF. TOM BLUNDELL (BIRKBECK)

The next meeting of the International Union of Crystallography will be held in Ottawa, Canada, next year from 16th to 25th August. For the first time for many years there will be a very full programme concerned with biological macromolecules. The Congress discourse will be given by Prof. Dorothy Hodgkin; there will be general lectures by Prof. Sir David Phillips, Prof. Michael Rossmann, Prof. Heinrich Sturmann, and Dr. Bill Wright of IBM; there will be microsymposia on protein structure and function, on DNA structures, on protein nucleic acid interactions, on anomalous dispersion methods using synchrotron radiation, and on protein refinement as well as ad hoc sessions on the application of neutrons and synchrotron X-rays to protein crystallography. The Programme Committee of the IUCr has strongly supported this change of direction, but those who have encouraged them to do this will look very foolish if protein crystallographers do not now attend in their hundreds - and, of course, protein crystallographers will have missed a very exciting programme!"

DARESBUURY STUDY WEEKEND ON REFINEMENT

P.A. MACHIN (DARESBUURY LABORATORY)

A Study Weekend on 'Refinement of Protein Structures' was held at Daresbury on 15-16 November in association with the Collaborative Computational Project in protein crystallography. The meeting was attended by 80 participants with representatives from about 8 foreign countries as well as from most of the UK protein crystallography groups. The high number of participants (the original limit was for 50 people!) reflects the current interest in this topic, particularly with the availability of fast computers such as the CRAY-1.

The invited speakers at the meeting were:

Wayne Hendrickson
Mike James
Joel Sussman
Ramesh Agarwal
Wolfgang Steigemann
Jan Hermans
Eleanor Dodson
David Moss
Bob Diamond
Bill Pulford
Ian Tickle
Bhat

We were most fortunate that these people were available not only to talk at the meeting but to contribute throughout via the discussions.

The meeting was over two days and the topics covered in the main sessions were as follows:

Restrained and constrained least squares

Fast Fourier techniques

Comparison and experinece with refinement techniques

- Discussion Session:
- i) What do you minimise?
constrained, restrained or ...?
 - ii) How do you calculate gradients?
 - iii) Which weighting functions?
 - iv) What are the biases inherent in the methods?
 - v) How do you find out whether you are right?

Modelling disordered structure: side chains and solvent

Should you improve your MIR phases before starting refinement

Results and computational aspects of refinement on the CRAY-1

The importance of refined structures to the understanding of enzyme action

The program for the weekend was structured in such a way as to leave an adequate amount of time for discussion after each group of related papers, and in addition there was a two hour discussion session led by David Moss. These discussion sessions went extremely well (expertly chaired by Tom Blundell, David Phillips, Dorothy Hodgkin, David Blow) with lively contributions from a large number of participants. The discussions generated a wide range of points which no doubt will be the subject of much future work as well as producing a stimulating exchange of ideas. Of the many topics discussed two stand out as particular problems for further consideration: the choice of weighting schemes (in restrained refinement) that are meaningful and avoid bias towards a "desired" structure; and the method of modelling the often disordered aqueous component of the protein crystals. Both of these topics were considered in some detail and although many interesting ideas were expressed, there is clearly scope for further analysis.

The value of a well refined structure was quite evident and any effort put into

refinement is clearly worthwhile. This was well illustrated by Mike James (Edmonton) in his description of the refined structures of 4 versions of a serine protease (SGPA native, plus 3 peptide ligands) where the clear view of the atomic detail at the active site of the enzyme makes possible a detailed interpretation of the enzyme action.

Proceedings of the meeting will be produced and sent to participants. Anyone else who requires a copy should write to me requesting the same.

Finally I would like to thank all the participants for contributing to what seems to have been a very successful meeting.

The First Group Meeting of the Northern England
Protein Crystallographers

At various times protein crystallographers from York, Daresbury, Leeds, Keele and Sheffield had expressed interest in discussing related research problems with their Northern English counterparts. To meet this need the first ad hoc meeting of these groups was held at The University of Sheffield on the 28th October 1980. Approximately 25 people were treated to a brief and wide ranging programme of seminars followed by ample discussion.

The work of the CCP-4 was featured at this meeting. John Campbell (Daresbury) gave a brief summary of the features which should be considered when writing software for protein crystallography. It was agreed that the ways in which different laboratories use the facilities provided by the CCP-4 should be considered and this is to be included in the next meeting.

Ron Cooper (Leeds) provided details of the hardware and software being developed in Leeds for scanning and processing rotation camera data. The discussion which followed, particularly between the Daresbury and Leeds groups who have similar scanners, highlighted the need to quantify some of the features of hardware and software. The proposed Oxford meeting in the Easter vacation of '81 would be suitable for this purpose.

Eleanor Dodson (York) went on to describe her experience with the rotation function, primarily using the method of Crowther to provide a set of starting phases for an $I 2_1 3$ crystal form of insulin using the structural data for the R_3 solved insulin.

Rob Stansfield (Sheffield) discussed the problem of unambiguously determining the course of the polypeptide chain in horse spleen apoferritin at 2.8\AA resolution and of determining interactions among 24 subunits which arrange themselves in 432 symmetry as an approximate truncated rhombic dodecahedron.

Finally John Helliwell (Keele/Daresbury) brought us up to date with progress with the SRS at Daresbury and what it will be able to offer protein crystallographers at various stages of its development.

It was agreed that future meetings should be held, possibly on a biannual basis alternately in Leeds and Sheffield.

Prof. Tony North agreed to organise the next meeting in Leeds where further related research problems could be discussed.