Single Crystal Diffraction and Protein Crystallography Instruments

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Qualitative and quantitative assessments have been made of the performance of generic single crystal instruments for the source options available at the ESS, via detailed flux/reflection intensity/resolution calculations. The nature of single crystal diffraction measurements, particularly those involving hydrogen atoms, make it difficult to produce a single figure-of-merit relating performance between different sources, particularly as optimisation of instrumentation at existing sources is proceeding rapidly. Nonetheless, the huge increase in flux of pulsed neutrons at the ESS will lead to qualitative new opportunities in instrument performance, with a factor 40 increased brightness in the sharp pulse, and time-averaged flux equal to that of the most intense reactor sources.

We have assessed the requirements for single crystal neutron diffraction in a range of areas covering chemistry, physics, materials science and biology, and related these requirements to the likely available facilities on ESS. This has been carried out within the framework of the following generic instrument types:

- Chemical Crystallography
- High Resolution Macromolecular Crystallography/Protein Crystallography
- High Resolution (short d & low $\Delta Q/Q$) and Diffuse Scattering
- Low Resolution Biological Crystallography
- “Single Reflection” Measurements

Clearly instrumentation for single crystal diffraction normally requires good resolution (in all three dimensions of reciprocal space, normally covered in two spatial and one time-of-flight dimensions in detector space) which means that in every case we favour the short pulse option. Clearly most of our generic instruments will be optimally located on the 50Hz target, with one optimally placed on the 10Hz target. The 16.6Hz long pulse target is only a marginal option for our instrument types.

We have not attempted to design instruments as such, but rather define the framework into which single crystal instruments would fit with respect to the ESS source parameters. Nonetheless we can reinforce several messages regarding instrument design. The resolution of a diffractometer on a short pulse time-of-flight source is dependent on the flight path (instrument length) and on the detector characteristics. Gaining resolution by extending the length of instruments has implications for frame overlap and can favour the adoption of a low repetition rate target (the 10Hz target) to maintain bandwidth, an important feature in time-of-flight single-crystal diffraction. The alternative involves discrete or continuous rephasing of the frame, which may be unfavourable in many situations. This is true, for example, in rapid time-resolved studies where the whole snapshot of reciprocal

space is ideally obtained in a single shot as the diffraction pattern may be evolving rapidly, and also in measurements of the whole diffraction pattern, where quantitative interpretation of the pattern can be helped by having it measured continuously. Our assumptions on single crystal instrumentation are also based on the availability of efficient, large-area, position-sensitive detectors, and we assume that large area coverage ($\geq 2\pi$) can be obtained if necessary. We assume a reasonable degree of detector development to allow individual modules of say 200mm x200mm, 60% efficiency at 1Å, and 1-1.5mm pixel resolution to be available, and that these can be combined to form a quasi-continuous detector array. We also assume the full range of standard neutron sample environment can be made available in the presence of these detector arrays and that polarisation analysis of white beams will be addressed.

We have based our considerations on the target-moderator options available at present. However, it is clear that for several of the instruments, and certainly for the macromolecular crystallography applications, provision of an intermediate temperature, 130K, moderator would lead to further significant gains (3-5 in flux) and we urge re-examination of this possibility. We also note that in the case of at least the biological instruments, additional optimisation of medium-long wavelength flux on a low power target, due to enhanced target-moderator configurations in such a low power scenario, may cause the 10Hz option to become more favourable.

Introduction

Our choice of a generic suite of single crystal instruments is based on original discussions of instrumentation at ESS [1]. Our assessments of the performance of these instruments have been based on detailed flux/reflection intensity/resolution calculations which have been carried out in the past, notably involving one of our group (Jauch). These comprehensive assessments have included:

Assessments based on analyses of predicted reflection intensities in single-crystal instruments.

- the original SNQ report in 1984 [2], from which we note the Jauch and Dachs paper on single crystal diffraction [3] and also a paper from Mogens Lehmann (ILL) on low resolution crystallography [4];
- the 1996 Jauch paper on single crystal diffraction at long pulse spallation sources [5];
- the original ESS large unit cell study - Working Group convened by Mogens Lehmann, and including Jauch & Wilson along with Clive Wilkinson (EMBL) and Lennart Sjölin (Stockholm). The report of this group was issued as ILL Report ILL97/JA19T [6].

We start from the pulse length requirements dictated by the problem dependent parameters d_{min} ($\equiv Q_{max}$) and a (the cell edge).

For single-crystal diffraction, the parameter d_{min}^2/a defines the pulse length requirements and hence constrains the source-moderator choice.

	D_{min}(Å)	a(Å)	d_{min}^2/a (Å)
Chemical cryst.	0.4	30	0.0053
Physical cryst.	0.2	15	0.0026
High resolution bio.	1.2	100	0.0144
	1.5	200	0.0113
	2.4	200	0.0288
Low resolution bio.	6	300	0.12

Leading to the following basic requirements

	L(m)	dt(ms)	Moderator
Chemical cryst.	15	30	thermal poisoned
Physical cryst.	15	10	thermal poisoned
High resolution bio.	40	110	cold coupled
Low resolution bio.		very large	cold coupled

In terms of flux we note the need to optimise the "effective flux" on the sample $\phi(\lambda)\lambda^2$ (proportional to the measured intensity), in the wavelength range of interest.

Chemical Crystallography

ESS can revolutionise neutron chemical crystallography, offering more parametric measurements and the study of very small crystals.

Standard chemical crystallography is a "high resolution" technique, typically requiring the measurement of d-spacings to as low as 0.35-0.4Å. This also requires good Q-space resolution to allow for peaks to be separated and therefore integrated accurately. A short pulse is therefore best, around 30 μs pulse length.

To maximise the flux in the region of interest a thermal poisoned moderator would be chosen (with the option of intermediate 130K poisoned moderator), with high flux at 1 Å or lower but also retaining significant flux in the region up to and beyond 2-3 Å. Sharp pulses are required for good Q-space resolution to high Q, so a decoupled moderator.

This instrument type can have a medium path length (15m) on a 50Hz source, where the band-width will be adequate.

We note also here that such an instrument could also serve for the measurement of magnetisation densities from flipping ratios if an efficient white-beam spin polariser is available.

Such an instrument type on ESS will be world-leading, and will offer the opportunity for qualitatively new science to be opened up, for example, in parametric measurements and in the use of very small crystals.

High Resolution Macromolecular Crystallography (Protein Crystallography)

ESS can make high resolution neutron protein crystallography more routine, increasing the impact of neutrons in this important and expanding area.

The definition of high resolution here implies measurements to a d-spacing of typically 1.5-1.8 Å, on unit cell edges of up to 150-200 Å. However, it is now well established that some hydrogen/deuterium positions in proteins can also be established reliably at lower resolution if necessary, say d_{min} of 2.4 Å, which greatly facilitates the experiment. Once again there is the need to resolve peaks well to allow for adequate integration implying a short pulse source.

A cold, coupled moderator (see below for a discussion of the background implications) is the most obvious choice for this instrument, with a length of 40m chosen to regain some of the resolution lost by coupling. The question can be asked as to why a cold and not a thermal moderator in the high resolution macromolecular field? The optimum wavelength range is 1.8-3 Å and the effective flux conditions are not dissimilar for both temperatures:

λ	$f(\lambda)\lambda^2$ (cold)	$f(\lambda)\lambda^2$ (thermal)
1.8Å	9	27×10^{12}Å /s/cm^2/sr
3Å	42	10

In the desired wavelength range the cold moderator, however, has a much better line shape. At 2 Å, dt is 40 μs for the cold moderator but 85 μs for the thermal moderator Furthermore, dt/t is constant between 2 and 3 Å for the cold moderator. With such short pulses even a 15m flight path may also be acceptable.

However, the choice of moderator is not quite so straight-forward, since in this case a medium cold moderator (130K) is undoubtedly best, with optimal flux (or more particularly the

"effective flux", $\phi(\lambda)\lambda^2$) in the 2-5 Å region, offering a factor 3-5 improvement over the cold or ambient options. If the instrument is relatively long, then coupling (or "partial" coupling) to a pulse width of, say, 100 μs would be acceptable (though see the Aside below).

As noted in the original Lehmann Working Group report [6], a 40m instrument on a 50Hz source gives a restricted bandwidth ($\Delta\lambda$=2 Å), so a reduced repetition-rate target is a possibility for this instrument, particularly if low power moderator options can enhance the flux in the important region.

This instrument on ESS promises to be world-leading, even in comparison with the dramatic developments on e.g. LADI at the ILL (the reduction in background due to the time-of-flight Laue method being very important here). This is particularly true if a 130K moderator is available.

Aside – peak width and background

Coupling (or "partially" coupling) to a pulse length of up to 100 or even 200 μs offers increased flux, but the reduced resolution has consequences not only for peak separation but also for the background from "chemical" samples. The broader pulses lead to significant build up of background under Bragg peaks (incoherent scattering plus long reflection tails which becomes increasingly less ideal as the pulse is broadened/resolution lessened). Hence, it is not just sheer flux but signal/background which is important in determining the instrument performance.

While sheer flux is important, the control of background levels is also important in single-crystal diffraction, particularly from hydrogen-containing materials. The time-of-flight Laue technique has advantages here, in "stretching" the background throughout the data collection frame.

Quantitatively, both peak height P and P/B ratio are important. For large unit cells the signal is generally lower than the background so that

$$\sigma(P)/P = [2/(P\times P/B)]^{1/2} \qquad (1)$$

and the sheer flux is also very important.

In addition to the signal/background ratio, if peaks overlap very severely then there can be problems in separating the peak from the background. Even full-profile methods such as Rietveld refinements of powder data can suffer from this problem, and in cases (i) and (ii) under consideration here we have the added complication that much of our "background" is coming from hydrogen incoherent scattering; the cross-section of this is wavelength-dependent. The consequence is that even if good peak modelling/intensity extraction software is available, the underlying physics of the scattering in the sample can make the situation more complicated.

High Resolution Diffraction

The ability of short pulse spallation sources to offer very high flux of short wavelength neutrons gives the opportunity for very high resolution single-crystal applications in physics.

Here we consider very high Q measurements, to d-spacing of 0.2 Å or less, primarily for "physics" measurements, e.g. anharmonicity. Frequently this must also be accompanied by another high resolution aspect – high $\Delta Q/Q$ resolution to allow the examination, for example, of incommensurate or satellite reflections or of diffuse scattering close to Bragg peaks (e.g. critical scattering). This instrument type clearly requires a short pulse source and a pulse width of around 10-15 μs.

The need for very high epithermal flux places us on an ambient, thermal, moderator, which with the need for very sharp pulses to maintain very high resolution will be decoupled and poisoned.

The instrument would be envisaged to be of medium length (15m) on the 50Hz source; there is no problem with band-width.

This instrument type would be world-leading, and accessing very high Q values is potentially unique on a pulsed source.

Diffuse Scattering

The ability of time-of-flight Laue diffraction to measure fully resolved, continuous 3D volumes of reciprocal space offers unique opportunities in the measurement and interpretation of diffuse scattering.

During the discussions in our working group a diffuse scattering instrument type became separate from the high resolution instrument. This instrument type refers to diffuse scattering which is not necessarily close to Bragg peaks. It must, however, maintain good Q resolution and hence requires a short pulse source, with a pulse width of around 50 μs.

The instrument, since it examines often weak non-Bragg peak scattering, requires good intensity at both high and low Q, and should couple this with extremely low (ideally "zero") background. In addition the instrument set-up must be well understood and reproducible to allow accurate corrections.

Related to this, it is clear that band width is also important, to allow reliable collection of a continuous diffraction pattern over all of reciprocal space/Q values for whole pattern modelling, for example using probability density function and related techniques – like those carried out by the Disordered Materials community.

Such diffuse scattering measurements would be ideally carried out on a medium-length instrument on a low repetition rate source (e.g. 10Hz) as wide simultaneous band-width is needed. It would of course be possible in principle to slew choppers continuously to cover the full necessary Q-range but why do this if a good flux instrument sitting on a 10Hz source can yield a sufficiently wide band in a single shot with the ability to be normalised accurately and consistently? The moderator would have to be decoupled for high resolution, but

the need for good flux over the whole Q-range means that a medium-cold or cold moderator would be most appropriate.

This instrument type would be world-leading on ESS, with the potential for fully 3-D resolved measurements of reciprocal space volumes unique on a pulsed source.

Low Resolution Biological Crystallography

Low resolution biological neutron crystallography offers access to new areas of study such as membrane protein and protein-nucleic acid complexes. ESS will offer a highly competitive alternative instrumentation option to the best reactor facilities in this important area.

For low resolution biological crystallography (typically to a d-spacing of 6-8 Å on a 200-500 Å cell edge) we require a high flux of long wavelength neutrons. A long pulse source is an option here, while if a short pulse option is chosen, we would clearly require a cold, coupled moderator. However, we must always be wary of the problems of pile-up of incoherent background (see (ii) above). Resolution is not a major issue here and so this instrument can probably be of medium length, on a 50Hz source.

Such an instrument would open up new areas of biology, for example in the study of membrane protein and protein-nucleic acid complexes, if fully optimised. Capacity is also important here – in the biological sciences area we must offer more instrumentation to meet the needs and demands of this large and expanding community. Structural biology is now focusing upon understanding interactions of complex systems and we should be looking to pursue this important area on ESS even if the instrument gains over reactor possibilities are rather lower than some others.

Our preliminary conclusion is that this instrument type on the ESS would offer significant gains on the leading existing steady state instrumentation, with an optimised moderator.

"Single Reflection" Measurements

An optimised single-crystal instrumentation suite on ESS will offer the ability to track rapidly individual reflection intensities as they change under the influence of changing external environment.

This type of measurement is an extremely important component of, for example, the programme on D10 at the ILL. We have therefore benchmarked this instrument type.

The aim is to follow a single peak (or very limited selection of reflections) as a function of some external variable (e.g. temperature, pressure, magnetic field),. Q-space resolution is also often important to follow the development of, for example, critical scattering, twinning, or incommensurate propagation vectors.

Thus the requirements are for a very high point by point flux over a limited wavelength range, clearly opening up the long pulse option, but noting that high Q-space resolution may also be required.

However, there is also the need to have also a more standard

"chemical crystallography" capability on the same instrument to characterise important sample characteristics (such as extinction etc. under the same data collection conditions as those in which the single peak changes are followed. This can still be achieved in the long pulse case, but is less obviously favourable.

We note that some of the single peak measurements can of course be done on a 15m instrument with the poisoned thermal moderator, but will often involve complex sample environment.

Such an instrument type can be competitive with the best steady-state options, given the same time-averaged flux.

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