Influencing Absolute Structure Determination

Amber L. Thompson

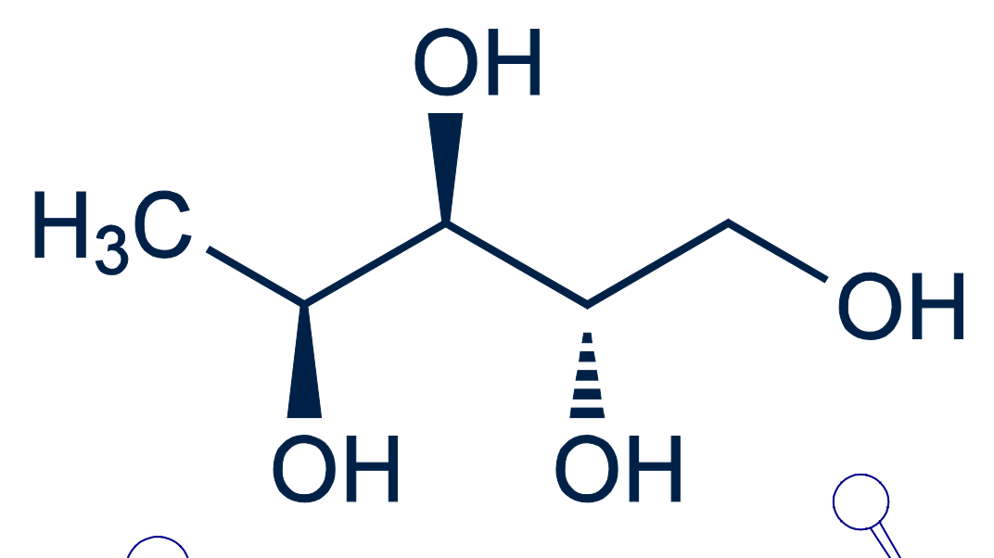
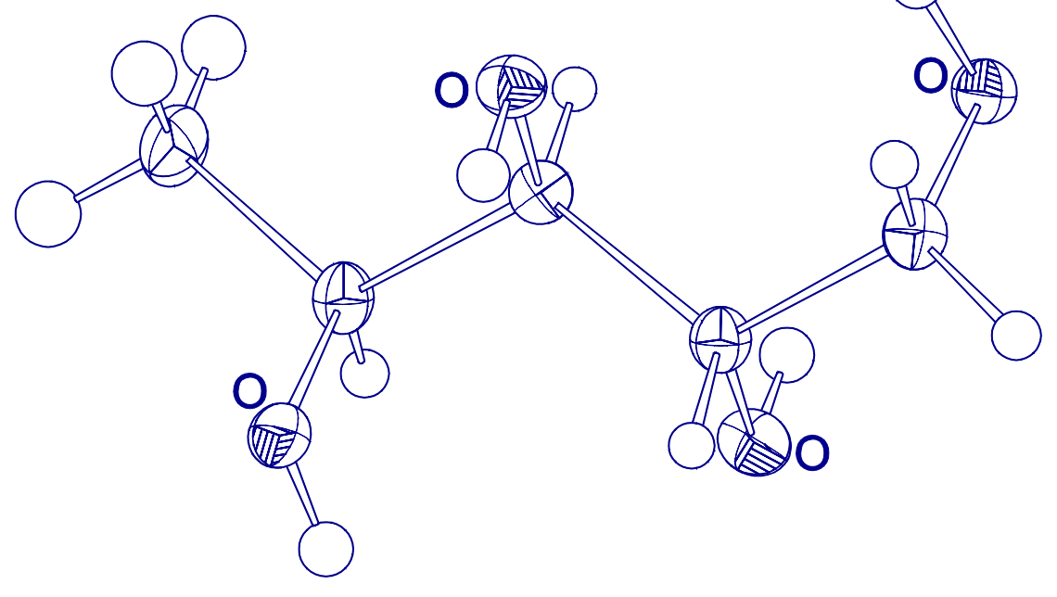
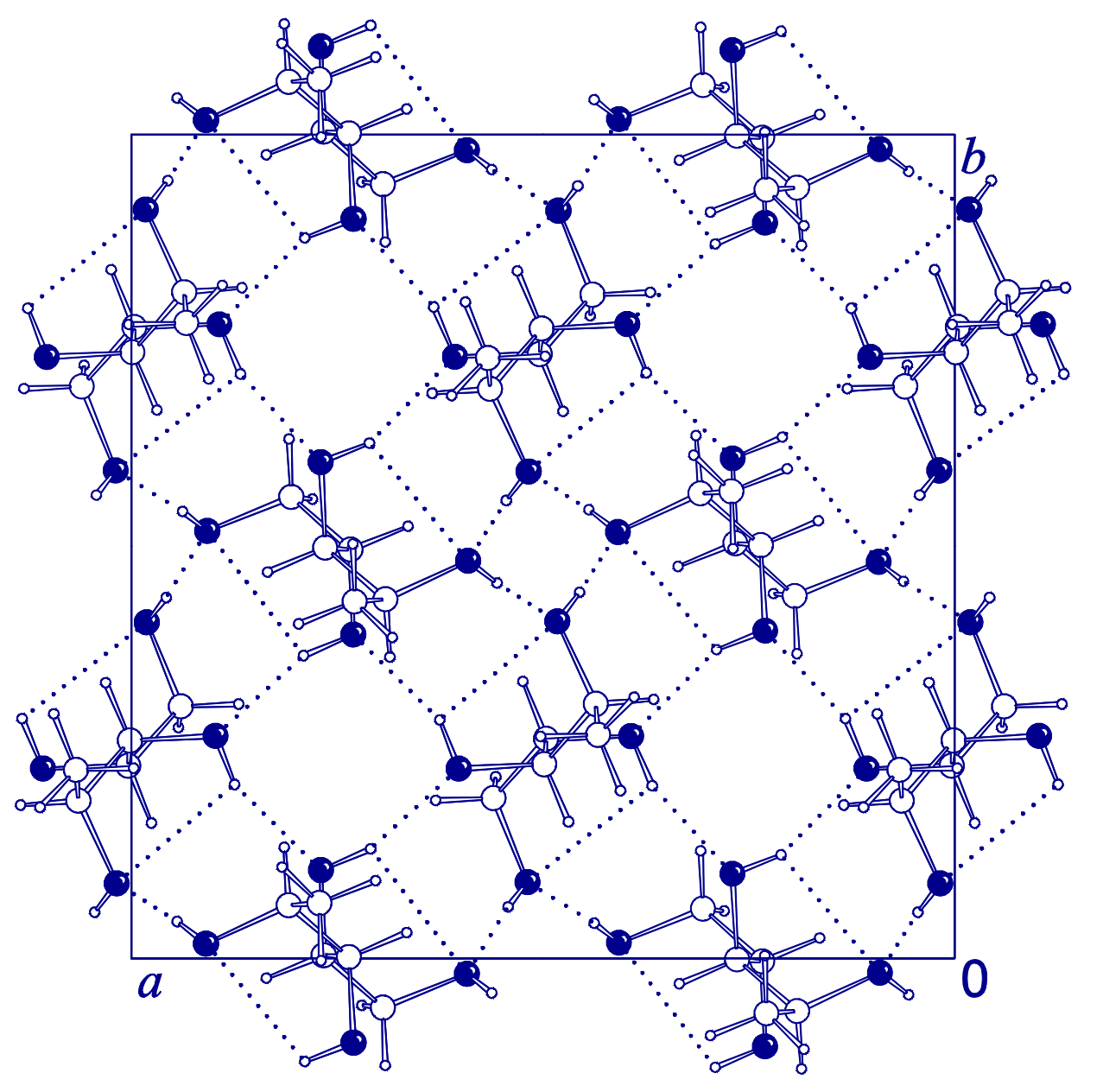
Chemical Crystallography, Department of Chemistry, Oxford, UK

Contact – amber.thompson@chem.ox.ac.uk

CRYSTALS
is available free
of charge from
www.xtl.ox.ac.uk

1-deoxy-arabinitol – a.k.a. "Rabbity"

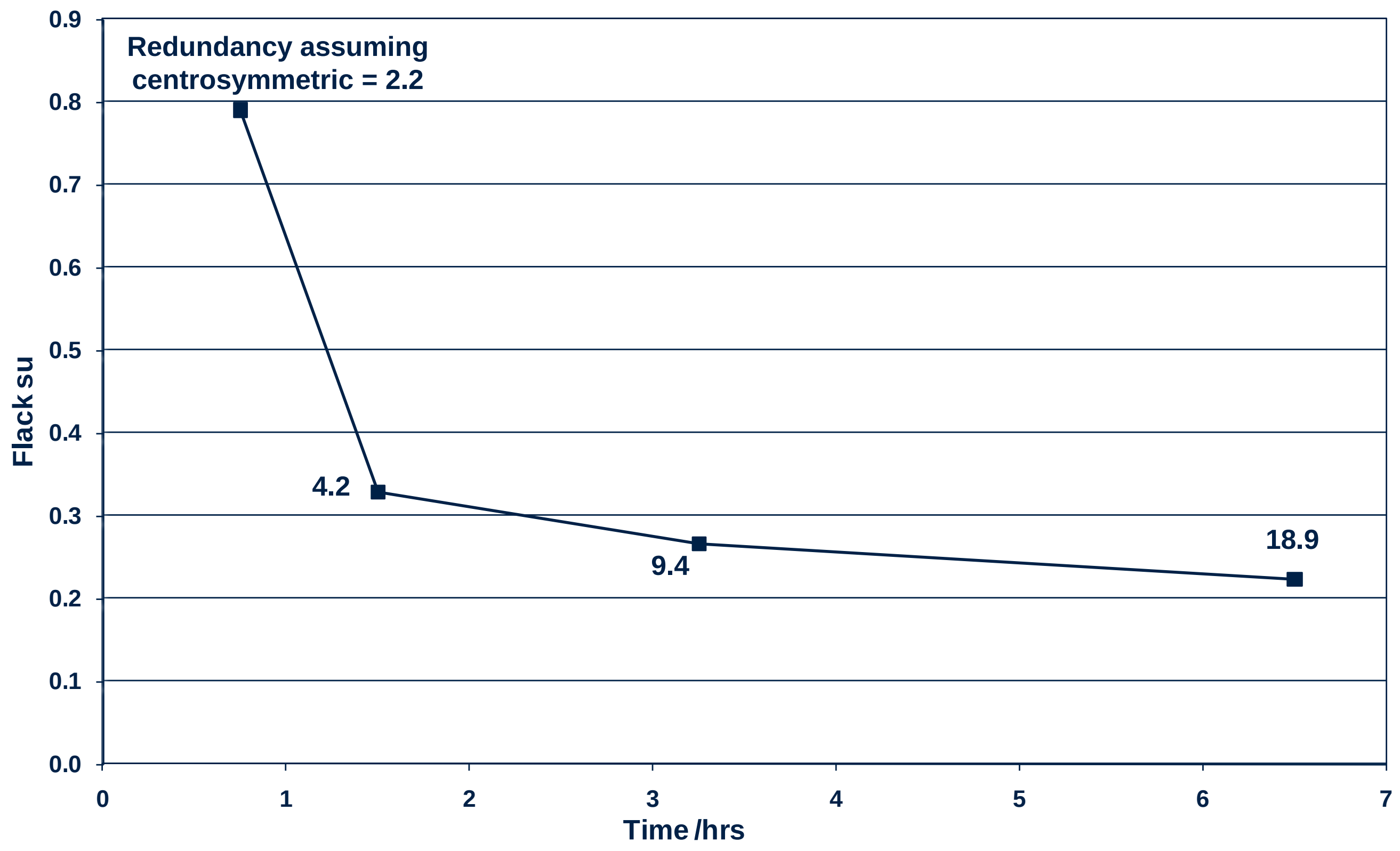
- Absolute structure determination has concerned scientists for more than six decades[1] and it is even more relevant today with the increase in targeted asymmetric synthesis.
- It is often commented that the Flack *x* parameter[2] and, as importantly, its standard uncertainty are influenced by Friedel completeness, redundancy, counting statistics, and data acquisition temperature.
- 1-deoxy-D-arabinitol was synthesised in order to evaluate its therapeutic potential, but it has shown that the stereochemistry at four diastereomeric tetraols are very difficult to distinguish between by NMR spectroscopy.
- The relative stereochemistry was originally reported and the absolute configuration was determined by the use of D-erythronolactone as the starting material.[3]

- "Rabbity" has a number of key characteristics that make it an ideal test crystal for studying influences on the Flack *x* parameter, or more specifically the standard uncertainty:
    - It forms nice crystals without disorder that diffract reasonably well for their size.
    - High symmetry ($I4_1$) means it is relatively quick to get a high redundancy data collection.
    - Pseudo-symmetry (*a* glide) means there are strong and weak reflections.
    - The presence of approximate inversion symmetry makes absolute structure determination non-trivial.

Completeness & Redundancy

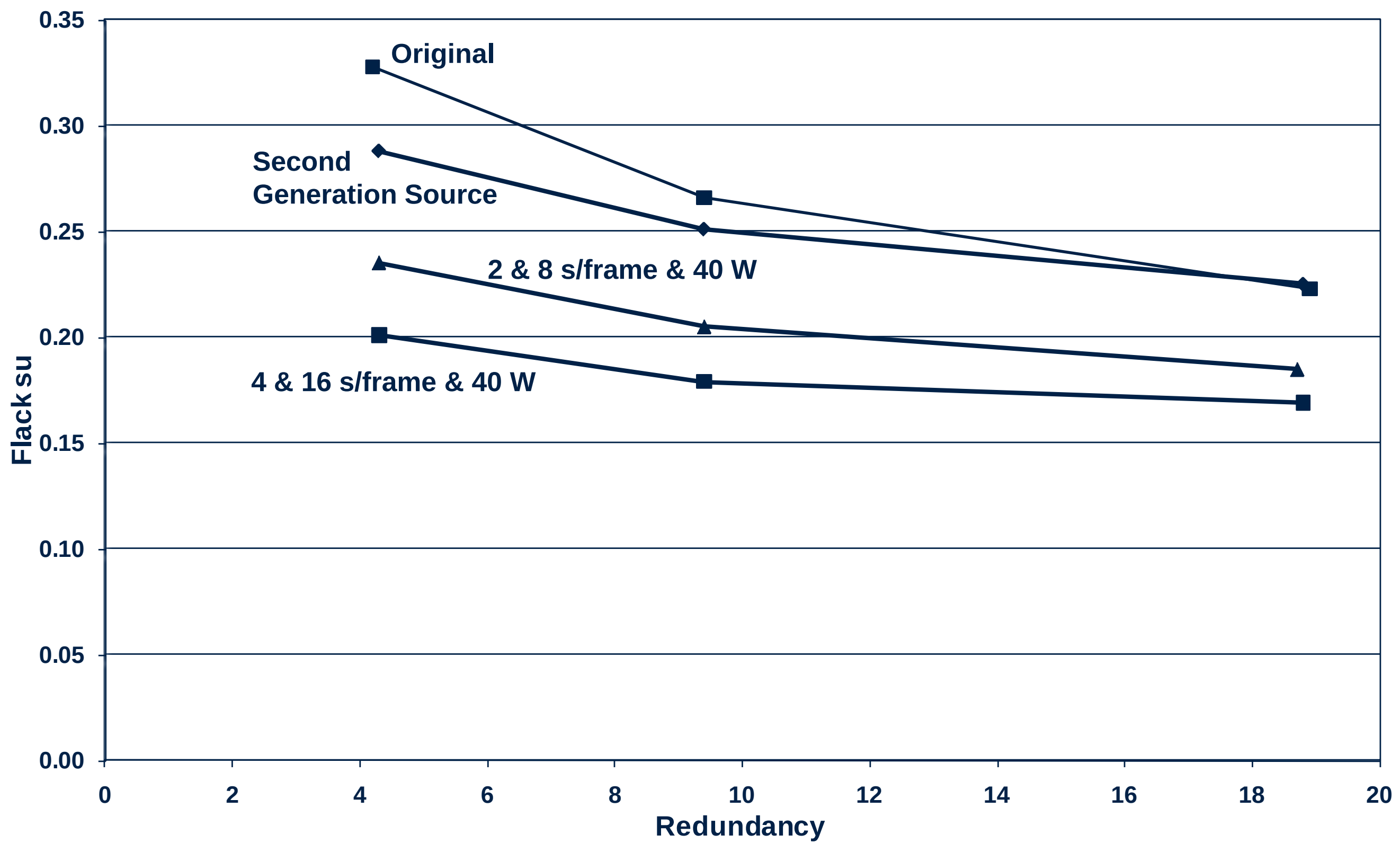
- Data were collected using an Oxford Diffraction (Agilent) SuperNova diffractometer with an Atlas detector.
- The strategy calculator was used to collect:
    - A minimal, collection assuming the data were centrosymmetric.
    - A complete dataset assuming Friedel pairs were inequivalent.
    - Approximately 10-fold and 20-fold redundant data collections taking four and eight times as long as the first.
- All data were collected with the same count time (2 & 8 s/frame for the low and high angle respectively), scan width (1°) and detector distance (51 mm) and all data were processed from the same orientation matrix.



- It is clear that in critical cases it is very important to ensure good Friedel coverage.
- In contrast, although the redundancy clearly reduces the standard uncertainty, there are diminishing returns.

Intensity & Acquisition Time

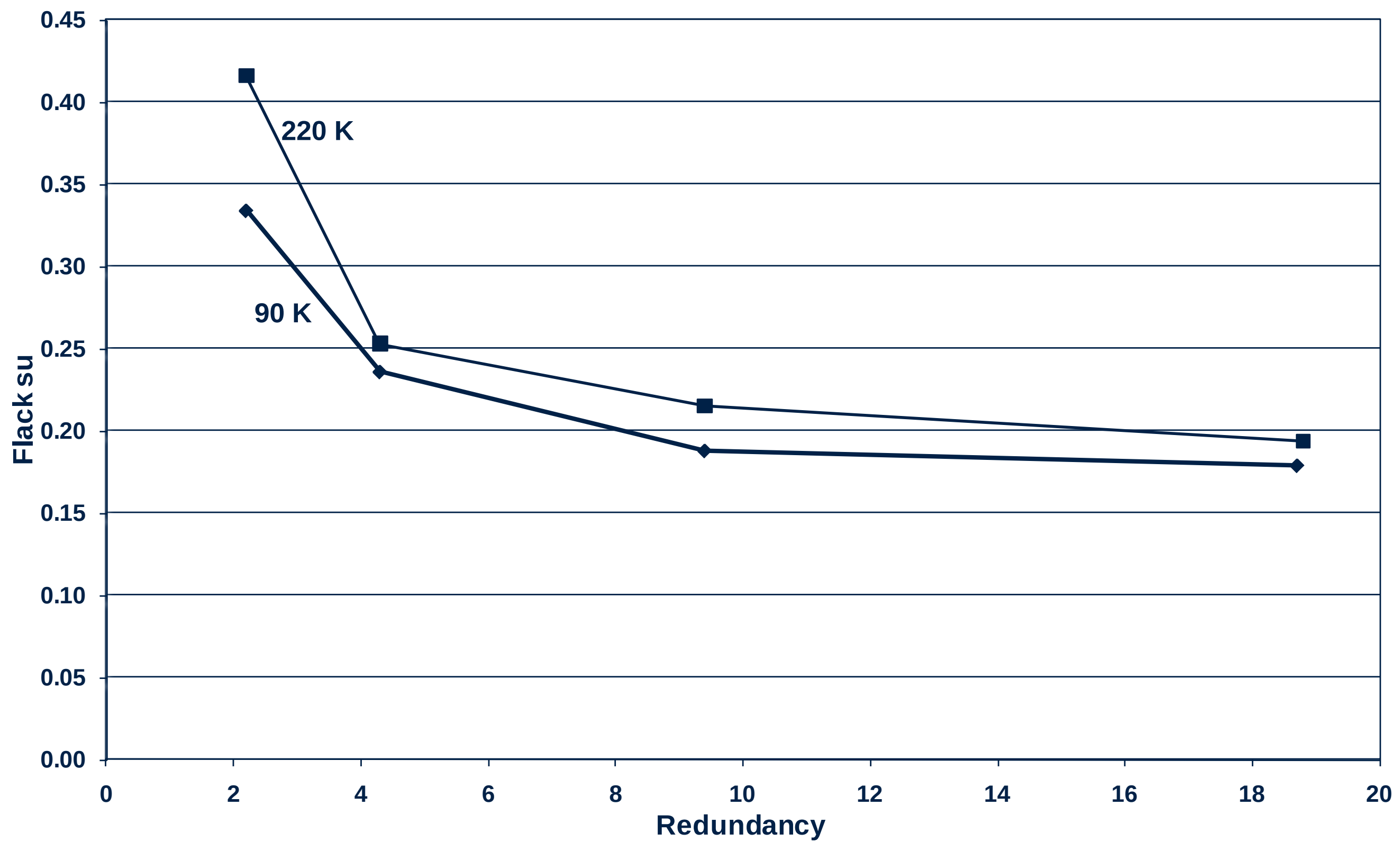
- The experiment was repeated following an upgrade to the New Second Generation Source.
- Data were collected with the generator set to 20 W (as before), and with the generator set to 40 W both with 2 & 8 s/frame and 4 & 16 s/frame, doubling and quadrupling the effective count time.
- As before all refinements were carried out using CRYSTALS.[4]



- Increasing both the intensity and the acquisition time clearly improve the standard uncertainty, however the cost is not insignificant.
- The Second Generation Source and doubling the power may have financial implications, but more serious in an efficient laboratory, is the time cost.
- The 4-fold redundant dataset with 2 & 8 s/frame took 1.5 hr, the largest redundancy at 4 & 16 s/frame took 26 hr.

Data Acquisition Temperature

- Four datasets were collected at each of 220 K and 90 K:
    - A minimal collection (assuming the data were centrosymmetric); a complete dataset assuming Friedel pairs were inequivalent, and approximately 10-fold and 20-fold redundant data collections.
- The crystal was cooled at 120 K/hr between temperatures and the data were processed from the same orientation matrix:



- It is clear from the results presented here that the advice given is generally good:
    - Friedel completeness has an enormous impact on the standard uncertainty and reducing the temperature helps, so in general these seem to be a good strategy.
    - Increasing the redundancy and/or acquisition times although improving the standard uncertainty, can be very costly in terms of time; even in this high symmetry system, an improvement from 0.11(23) to -0.10(17) cost *nearly a day of instrument time*.

1. Interest began with Bijvoet *et al.* (1951, *Nature London*, 168, 271–273) and their careful measurement of just 15 pairs of reflections using a Weissenberg camera and a specially constructred zirconium X-ray tube (λ = 0.786 Å, i.e. close to the the Rb Kα-absorption edge at 0.865 Å to enhance the anomalous scattering). The Rodgers *η* (1981, *Acta Cryst.*, A37, 734–741) and Flack *x* (1983) parameters and their inclusion in refinement software ensured that absolute structure determination was widely available. More recently, there have been further recent developments by Parsons & Flack (2004, *Acta Cryst.*, A60, s61) and Hooft *et al.* (2009, *Acta Cryst.*, A65, 19–321).
2. Flack, H. D. (1983). *Acta Cryst.*, A39, 876–881; Flack, H. D. & Bernardinelli, G. (2000). *J. Appl. Cryst.*, 33, 1143–1148.
3. Jenkinson, S. F., Cruz, F. P., Booth, K. V., Fleet, G. W. J., Izumori, K., Yuc C-Y. & Watkin, D. J. (2008). *Acta Cryst.* E64, o1010–o1011.
4. Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* 36, 1487; Cooper, R. I., Thompson, A. L. & Watkin, D. J. (2010). *J. Appl. Cryst.* 43, 1100–107; Thompson, A. L. & Watkin, D. J. (2011). *J. Appl. Cryst., submitted*.