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For many years, the SHELX system has included a probability based direct methods program SHELXS. This was written for much slower computers than those currently employed and so is very efficient for the solution of routine small-molecule structures. Although it is still widely used, it is ineffective for larger structures. Its successor SHELXD is based on dualspace recycling [1]; it is slower but able to solve much larger structures, in favourable cases up to about 1000 unique atoms given data to atomic resolution (1.2Å or better). SHELXD can also solve merohedral twins and works well in space groups that created problems for the previous generation of direct methods programs. Subsequently it emerged that SHELXD was also very effective at solving heavy atom substructures from MAD, SAD or SIR data [2,3]. Significant improvements for this purpose were the integration of direct and Patterson methods and the refinement of the occupancies of the sites during the final cycles. Since SHELXD is often able to locate the heavy atom sites from SAD or MAD data in a few minutes, there was a need for a program that is able to produce native phases starting from these sites in a fast, simple and robust manner so that, for example, it could be seen whether the structure had been 'solved' before taking the crystal off the beamline. The program SHELXE [4] that performs density modification by the sphere of influence method was written for this purpose. The atom positions and occupancies from SHELXD turned out to be so accurate that no further refinement of them was required, and several further drastic simplifications were introduced in SHELXE to speed up the phase determination even further. Under special circumstances, i.e. (a) when high quality MAD data are used, (b) when the solvent content is high (>0.6) and especially (c) when the native data extend to extremely high resolution (better than 1.5Å), the maps obtained by SHELXE showed unexpectedly high map correlation coefficients (>0.95) compared with the final refined structures. This approach was successfully applied to the solution of several structures using the very weak anomalous signal from sulfur present naturally in most proteins [5]. These programs are developing by the usual route of Darwinian selection, involving in particular attempts to include chemical and non-crystallographic symmetry information in a general and efficient manner.

<sup>[1]</sup> Sheldrick, G. M., Hauptman, H. A., Weeks, C. M., Miller, M. & Usón, I. (2001). *Internatoinal Tables for Crystallography*, Vol. F, eds. E. Arnold & M. Rossmann, pp. 333-351. Dordrecht: Kluwer.

<sup>[2]</sup> Usón, I. & Sheldrick, G. M. (1999). Curr. Opin. Struct. Biol. 9, 643-648.

<sup>[3]</sup> Schneider, T. R. & Sheldrick, G. M. (2002). *Acta Cryst.* **D58**, 1772-1779.

<sup>[4]</sup> Sheldrick, G. M. (2002). Z. Kristallogr. 217, 644-650.

<sup>[5]</sup> Debreczeni, J. É. et al. (2003). Acta Cryst. **D59**, 393-395; 688-696; 2125-2132.