Table 16.1.8.1
Overall success rates for full structure solution for hirustasin using different two-atom search vectors chosen from the Patterson peak list

Resolution (Å)	Two-atom search fragments	Solutions per 1000 attempts
1.2	Top 100 general Patterson peaks	86
1.2	Top 300 general Patterson peaks	38
1.2	One vector, error = 0.08 Å	14
1.2	One vector, error = 0.38 Å	41
1.2	One vector, error = 0.40 Å	219
1.2	One vector, error = 1.69 Å	51
1.4	Top 100 general Patterson peaks	10
1.5	Top 100 general Patterson peaks	4
1.5	One vector, error = 0.29 Å	61

may be used to generate further atoms using a full Patterson superposition minimum function or a weighted difference synthesis.

In the case of the small protein BPTI (Schneider, 1998), 15 300 attempts based on 100 different search vectors led to four final solutions with mean phase error less than 18°, although none of the globally highest PMF values for any of the search vectors corresponded to correct solutions. Table 16.1.8.1 shows the effect of using different two-atom search fragments for hirustasin, a previously unsolved 55-amino-acid protein containing five disulfide bridges first solved using *SHELXD* (Usón *et al.*, 1999). It is not clear why some search fragments perform so much better than others; surprisingly, one of the more effective search vectors deviates considerably (1.69 Å) from the nearest true S–S vector.

16.1.9. *Shake-and-Bake*: an analysis of a dual-space method in action

The *Shake-and-Bake* algorithm generated the *SnB* program written in Buffalo at the Hauptman–Woodward Institute, principally by Charles Weeks and Russ Miller (Miller *et al.*, 1994; Weeks & Miller, 1999*a*). *SHELXD* (Usón & Sheldrick, 1999; Schneider & Sheldrick, 2002) and later *HySS* (Grosse-Kunstleve & Adams, 2003) were both inspired by *SnB* and employ the *Shake-and-Bake* philosophy with various modifications, in particular involving the use of the Patterson function to obtain starting phases. It is instructive to see how such software works in detail.

16.1.9.1. Flowchart and program comparison

A flowchart for the generic *Shake-and-Bake* algorithm, which provides the foundation for these programs, is presented in Fig. 16.1.9.1. It contains two refinement loops embedded in the trial-structure loop. The first of these loops (steps 5–9) is a dual-space phase-improvement loop entered by all trial structures, and the second (steps 11–14) is a real-space Fourier-refinement loop entered only by those trial structures that are currently judged to be the best on the basis of some figure of merit. These loops have been called the internal and external loops, respectively, in previous descriptions of the *SHELXD* program (*e.g.* Sheldrick & Gould, 1995; Sheldrick, 1997, 1998). Currently, the major algorithmic differences between the programs are the following:

(*a*) During the reciprocal-space segment of the dual-space loop (Fig. 16.1.9.1, step 5), *SnB* can perform tangent refinement or use parameter shift to reduce the minimal function [equation (16.1.4.2)] or an exponential variant of the minimal function (Hauptman *et al.*, 1999). *SHELXD* performs Karle-type tangent expansion (Karle, 1968). During tangent or parameter-shift refinement with *SnB*, all phases computed in the preceding structure-factor calculation (steps 4 or 9) are refined. During tangent expansion in *SHELXD*, the phases of (typically) the 40% highest calculated E magnitudes are held fixed, and the phases of the remaining 60% are determined by using the tangent formula. If there is a tendency for *SHELXD* to produce uranium-atom solutions, more phases should be held fixed in the tangent phase expansion.

(*b*) In real space, *SnB* uses simple peak picking, varying the number of peaks selected on the basis of structure size and composition. *SHELXD* contains provisions for all the forms of peak picking described above.

(*c*) *SnB* relies primarily on the minimal function [equation (16.1.4.2)] as a figure of merit whereas *SHELXD* uses the correlation coefficient [equation (16.1.6.1)], calculated using all data, after the final dual-space (internal) cycle and in the real-space (external) loop. In addition, *SHELXD* calculates a further correlation coefficient, CC_{weak}, calculated in the same

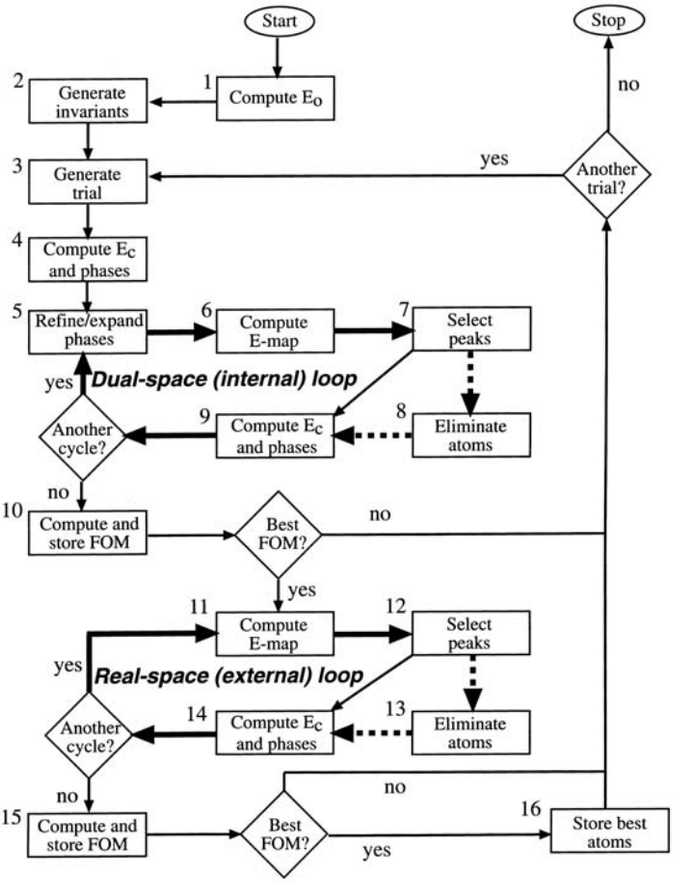

Figure 16.1.9.1
A flowchart for the *Shake-and-Bake* procedure, which is implemented in both *SnB* and *SHELXD*. The essence of the method is the dual-space approach of refining trial structures as they shuttle between real and reciprocal space. In the general case, steps 7 and 12 are any density-modification procedure, and steps 9 and 14 are inverse Fourier transforms rather than structure-factor calculations. The optional steps 8 and 13 take the form of *iterative peaklist optimization* or *random omit maps* in *SHELXD*. Any suitable starting model can be used in step 3, and *SHELXD* attempts to improve on random models (when possible) by utilizing Patterson-based information. Step 4 is bypassed if phase sets (random or otherwise) provide the starting point for the dual-space loop. *SHELXD* enters the real-space loop if the FOM (correlation coefficient) is within a specified threshold (1–5%) of the best value so far.