18.2.8. Conclusions

Simulated annealing has dramatically improved the efficiency of crystallographic refinement. A case in point is the combination of torsion-angle molecular dynamics with cross-validated maximum-likelihood targets. These two independent developments interact synergistically to produce less model bias than any other method to date. The combined method dramatically increases the radius of convergence, allowing the productive refinement of poor initial models, *e.g.* those obtained by weak molecular-replacement solutions (Rice & Brünger, 1994; Adams *et al.*, 1997, 1999).

Simulated annealing can also be used to provide new physical insights into molecular function which may depend on conformational variability. The sampling characteristics of simulated annealing allow the generation of multi-conformer models that can represent molecular motion and discrete disorder, especially when combined with the acquisition of high-quality data (Burling *et al.*, 1996). Thus, simulated annealing is also a stepping stone towards development of improved models of macromolecules in solution and in the crystalline state.

The computational developments discussed in this review are implemented in the software suite *Crystallography & NMR System* (Brunger *et al.*, 1998). A pre-release of the software suite is available upon request.

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references