Zhang *et al.*, 2001 (*IT* F Chapter 15.1)], and structural fragment matching procedures (Terwilliger, 2003*a*) have been added to the arsenal of density-modification methods. Automated mask and molecular-envelope definition has helped to remove the tedium and increase the efficiency and quality of density-modification and symmetry-averaging procedures. Noncrystallographic symmetry averaging among different crystal forms (Perutz, 1954) has become increasingly common, and exploitation of the unit-cell variation among flash-cooled and noncooled forms of the same crystal is a broadly applicable method for phase determination (Das *et al.*, 1996; Ding *et al.*, 1995); soaking crystals in a series of different solvents and buffers can produce an analogous effect (Ren *et al.*, 1995; Tong *et al.*, 1997). Phases from noncrystallographic symmetry averaging and other 'experimental' sources have been incorporated into crystallographic refinement procedures using a number of formalisms (Arnold & Rossmann, 1988; Rees & Lewis, 1983) including maximum likelihood (Pannu *et al.*, 1998).

2.3.8.4. Equivalence of real- and reciprocal-space molecular replacement

Let us proceed in reciprocal space doing exactly the same as is done in real-space averaging. Thus

$$\rho_{\rm AV}(\mathbf{x}) = \frac{1}{N}\sum_{n=1}^{N}\rho(\mathbf{x}_n),$$

where

$$\mathbf{x}_n = [\boldsymbol{C}_n]\mathbf{x} + \mathbf{d}_n.$$

Therefore,

$$\rho_{\rm AV}(\mathbf{x}) = \frac{1}{N}\sum_{N}\frac{1}{V}\left[\sum_{\mathbf{h}}\mathbf{F}_{\mathbf{h}}\exp(2\pi i\mathbf{h}\cdot\mathbf{x}_n)\right].$$

The next step is to perform the back-transform of the averaged electron density. Hence,

$$\mathbf{F}_{\mathbf{p}} = \int_U \rho_{\rm AV}(\mathbf{x})\exp(-2\pi i\mathbf{p}\cdot\mathbf{x})\,{\rm d}\mathbf{x},$$

where U is the volume within the averaged part of the cell. Hence, substituting for $\rho_{\rm AV}$,

$$\mathbf{F}_{\mathbf{p}} = \int_U\left[\frac{1}{NV}\sum_{N}\sum_{\mathbf{h}}\mathbf{F}_{\mathbf{h}}\exp(2\pi i\mathbf{h}\cdot\mathbf{x}_n)\right]\exp(-2\pi i\mathbf{p}\cdot\mathbf{x})\,{\rm d}\mathbf{x},$$

which is readily simplified to

$$\mathbf{F}_{\mathbf{p}} = \frac{U}{NV}\sum_{\mathbf{h}}\mathbf{F}_{\mathbf{h}}\sum_{N}G_{\mathbf{hp}n}\exp(2\pi i\mathbf{h}\cdot\mathbf{d}_n).$$

Setting

$$\mathbf{B}_{\mathbf{hp}} = \frac{U}{NV}\sum_{N}G_{\mathbf{hp}n}\exp(2\pi i\mathbf{h}\cdot\mathbf{d}_n),$$

the molecular replacement equations can be written as

$$\mathbf{F}_{\mathbf{p}} = \sum_{\mathbf{h}}\mathbf{B}_{\mathbf{hp}}\mathbf{F}_{\mathbf{h}} \qquad (2.3.8.12)$$

(Main & Rossmann, 1966), or in matrix form

$$\mathbf{F} = [\boldsymbol{B}]\mathbf{F},$$

which is the form of the equations used by Main (1967) and by Crowther (1967). Colman (1974) arrived at the same conclusions by an application of Shannon's sampling theorem. It should be noted that the elements of $[\boldsymbol{B}]$ are dependent only on knowledge of the noncrystallographic symmetry and the volume within which it is valid. Substitution of approximate phases into the right-hand side of (2.3.8.12) produces a set of calculated structure factors exactly analogous to those produced by back-transforming the averaged electron density in real space. The new phases can then be used in a renewed cycle of molecular replacement. The reciprocal-space molecular replacement procedure has been implemented and tested in a computer program (Tong & Rossmann, 1995).

Computationally, it has been found more convenient and faster to work in real space. This may, however, change with the advent of vector processing in 'supercomputers'. Obtaining improved phases by substitution of current phases on the right-hand side of the molecular replacement equations (2.3.8.1) seems less cumbersome than the repeated forward and backward Fourier transformation, intermediate sorting, and averaging required in the real-space procedure.

2.3.9. Conclusions

Complete interpretation of Patterson maps is no longer used frequently in structure analysis, although most determinations of heavy-atom positions of isomorphous pairs are based on Patterson analyses. Incorporation of the Patterson concept is crucial in many sophisticated techniques essential for the solution of complex problems, particularly in the application to biological macromolecular structures. Patterson techniques provide important physical insights in a link between real- and reciprocal-space formulation of crystal structures and diffraction data.

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