where $V_{\mathbf{h}}$ is the volume of cell (**h**) and $\mathbf{S}_n$ is the position, in the nth crystallographic asymmetric unit, of cell (**p**) corresponding to **S** in known cell (**h**). Let

$$A_{p,\,n}\exp(i\gamma_n) = \sum_{\mathbf{h}} \mathbf{F}_{\mathbf{h}} G_{\mathbf{hp}_n} \exp(-2\pi i \mathbf{h}\cdot\mathbf{S}),$$

which are the coefficients of the molecular transform for the known molecule placed into the nth asymmetric unit of the **p** cell. Thus

$$\mathbf{F}_{\mathbf{p}}(\mathbf{S}) = \frac{U}{V_{\mathbf{h}}} \sum_{n=1}^{N} A_{\mathbf{p},\,n} \exp[i(\gamma + 2\pi \mathbf{p}\cdot\mathbf{S}_n)]$$

or

$$\mathbf{F}_{\mathbf{p}}(\mathbf{S}) = \frac{U}{V_{\mathbf{h}}} \sum_{n=1}^{N} A_{\mathbf{p},\,n} \exp[i(\gamma_n + 2\pi \mathbf{p}_n\cdot\mathbf{S})],$$

where $\mathbf{p}_n = [\boldsymbol{C}_n^T]\mathbf{p}$ and $\mathbf{S} = \mathbf{S}_1$. Hence

$$|\mathbf{F}_{\mathbf{p}}(\mathbf{S})|^2 = \left(\frac{U}{V_{\mathbf{h}}}\right)^2 \sum_n \sum_m \big(A_{\mathbf{p},\,n} A_{\mathbf{p},\,m} \times \exp\{i[2\pi(\mathbf{p}_n - \mathbf{p}_m)\cdot\mathbf{S} + (\gamma_n - \gamma_m)]\}\big),$$

and then from (2.3.7.3)

$$T(\mathbf{S}) = \left(\frac{U}{V_{\mathbf{h}}}\right)^2 \sum_{\mathbf{p}} \sum_n \sum_m \Big(|\mathbf{F}_{\mathbf{p},\,\mathrm{obs}}|^2 A_{\mathbf{p},\,n} A_{\mathbf{p},\,m} \times \exp\{i[2\pi(\mathbf{p}_n - \mathbf{p}_m)\cdot\mathbf{S} + (\gamma_n - \gamma_m)]\}\Big), \qquad (2.3.7.4)$$

which is a Fourier summation with known coefficients $\{|\mathbf{F}_{\mathbf{p},\,\mathrm{obs}}|^2 A_{\mathbf{p},\,n} A_{\mathbf{p},\,m} \times \exp[i(\gamma_n - \gamma_m)]\}$ such that $T(\mathbf{S})$ will be a maximum at the correct molecular position.

Terms with $n = m$ in expression (2.3.7.4) can be omitted as they are independent of **S** and only contribute a constant to the value of $T(\mathbf{S})$. For terms with $n \neq m$, the indices take on special values. For instance, if the **p** cell is monoclinic with its unique axis parallel to **b** such that $\mathbf{p}_1 = (p, q, r)$ and $\mathbf{p}_2 = (\bar{p}, q, \bar{r})$, then $\mathbf{p}_1 - \mathbf{p}_2$ would be $(2p,\ 0,\ 2r)$. Hence, $T(\mathbf{S})$ would be a two-dimensional function consistent with the physical requirement that the translation component, parallel to the twofold monoclinic axis, is arbitrary.

Crowther & Blow (1967) show that if $\mathbf{F}_M$ are the structure factors of a known molecule correctly oriented within the cell of the unknown structure at an arbitrary molecular origin, then (altering the notation very slightly from above)

$$T(\mathbf{S}) = \sum_{\mathbf{p}} |\mathbf{F}_{\mathrm{obs}}(\mathbf{p})|^2 \mathbf{F}_M(\mathbf{p}) \mathbf{F}_M^*(\mathbf{p}[\boldsymbol{C}]) \exp(-2\pi i \mathbf{p}\cdot\mathbf{S}),$$

where $[\boldsymbol{C}]$ is a crystallographic symmetry operator relative to which the molecular origin is to be determined. This is of the same form as (2.3.7.4) but concerns the special case where the **h** cell, into which the known molecule was placed, has the same dimensions as the **p** cell.

R-factor calculations are sometimes used to determine the position of a known molecular fragment in an unknown cell, particularly if only one parameter is being searched. Such calculations are computationally less convenient than the Fourier methods described above, but can be more sensitive. All these methods can be improved by simultaneous consideration of packing requirements of the molecular fragments (Harada *et al.*, 1981; Hendrickson & Ward, 1976; Rabinovich & Shakked, 1984). Indeed, packing considerations can frequently limit the search volume very considerably.

2.3.7.4. *Position of a noncrystallographic symmetry element in a poorly defined electron-density map*

If an initial set of poor phases, for example from an SIR derivative, are available and the rotation function has given the orientation of a noncrystallographic rotation axis, it is possible to search the electron-density map systematically to determine the translation axis position. The translation function must, therefore, measure the quality of superposition of the poor electron-density map on itself. Hence $\mathbf{S}_x = \mathbf{S}_{x'} = \mathbf{S}$ and the function (2.3.7.1) now becomes

$$T(\mathbf{S}) = \frac{2}{V_{\mathbf{h}}^2} \sum_{\mathbf{h}} \sum_{\mathbf{p}} |\mathbf{F}_{\mathbf{h}}||\mathbf{F}_{\mathbf{p}}| G_{\mathbf{hp}} \cos[\alpha_{\mathbf{h}} + \alpha_{\mathbf{p}} - 2\pi(\mathbf{h} + \mathbf{p})\cdot\mathbf{S}].$$

This real-space translation function has been used successfully to determine the intermolecular dyad axis for α-chymotrypsin (Blow *et al.*, 1964) and to verify the position of immunoglobulin domains (Colman & Fehlhammer, 1976).

2.3.8. Molecular replacement

2.3.8.1. *Using a known molecular fragment*

The most straightforward application of the molecular-replacement method occurs when the orientation and position of a known molecular fragment in an unknown cell have been previously determined. The simple procedure is to apply the rotation and translation operations to the known fragment. This will place it into one 'standard' asymmetric unit of the unknown cell. Then the crystal operators (assuming no further noncrystallographic operators are present in the unknown cell) are applied to generate the complete unit cell of the unknown structure. Structure factors can then be calculated from the rotated and translated known molecule into the unknown cell. The resultant model can be refined in numerous ways.

More generally, consider a molecule placed in any crystal cell (**h**), within which coordinate positions shall be designated by **x**. Let the corresponding structure factors be $\mathbf{F}_{\mathbf{h}}$. It is then possible to compute the structure factors $\mathbf{F}_{\mathbf{p}}$ for another cell (**p**) into which the same molecule has been placed N times related by the crystallographic symmetry operators $[\boldsymbol{C}_1], \mathbf{d}_1;\ [\boldsymbol{C}_2], \mathbf{d}_2;\ \ldots;\ [\boldsymbol{C}_N], \mathbf{d}_N$. Let the electron density at a point $\mathbf{y}_1$ in the first crystallographic asymmetric unit be spatially related to the point $\mathbf{y}_n$ in the nth asymmetric unit of the **p** crystal such that

$$\rho(\mathbf{y}_n) = \rho(\mathbf{y}_1), \qquad (2.3.8.1)$$

where

$$\mathbf{y}_n = [\boldsymbol{C}_n]\mathbf{y}_1 + \mathbf{d}_n. \qquad (2.3.8.2)$$

From the definition of a structure factor,

$$\mathbf{F}_{\mathbf{p}} = \sum_{n=1}^{N} \int_U \rho(\mathbf{y}_n) \exp(2\pi i \mathbf{p}\cdot\mathbf{y}_n)\, \mathrm{d}\mathbf{y}_n, \qquad (2.3.8.3)$$

where the integral is taken over the volume U of one molecule. But since each molecule is identical as expressed in equation (2.3.8.1) and since (2.3.8.2) can be substituted in equation (2.3.8.3), we have

$$\mathbf{F}_{\mathbf{p}} = \sum_{n=1}^{N} \int_U \rho(\mathbf{y}_1) \exp[2\pi i \mathbf{p}\cdot([\boldsymbol{C}_n]\mathbf{y}_1 + \mathbf{d}_n)]\, \mathrm{d}\mathbf{y}_1. \qquad (2.3.8.4)$$

Now let the molecule in the **h** crystal be related to the molecule in the first asymmetric unit of the **p** crystal by the noncrystallographic symmetry operation

$$\mathbf{x} = [\boldsymbol{C}]\mathbf{y} + \mathbf{d}, \qquad (2.3.8.5)$$

references