1. GENERAL RELATIONSHIPS AND TECHNIQUES

$$-\sum_{\mathbf{h}\in\mathscr{H}} W_{\mathbf{h}} \frac{\partial|F_{\mathbf{h}}^{\mathrm{calc}}|}{\partial\mathbf{x}_j}(|F_{\mathbf{h}}^{\mathrm{calc}}| - |F_{\mathbf{h}}|^{\mathrm{obs}})$$

$$= -\mathscr{R}e\left[\sum_{\mathbf{h}\in\mathscr{H}} g_j(\mathbf{h})(-2\pi i\mathbf{h})W_{\mathbf{h}}(|F_{\mathbf{h}}^{\mathrm{calc}}| - |F_{\mathbf{h}}|^{\mathrm{obs}})\right.$$
$$\left.\times \exp(i\varphi_{\mathbf{h}}^{\mathrm{calc}})\exp(-2\pi i\mathbf{h}\cdot\mathbf{x}_j)\right].$$

The setting up and solution of the normal equations lends itself well to computer programming and has the advantage of providing a thorough analysis of the accuracy of its results (Cruickshank, 1965*b*, 1970; Rollett, 1970). It is, however, an expensive task, of complexity $\propto n \times |\mathscr{H}|^2$, which is unaffordable for macromolecules.

1.3.4.4.7.2. Booth's differential Fourier syntheses

It was the use of Fourier syntheses in the completion of trial structures which provided the incentive to find methods for computing 2D and 3D syntheses efficiently, and led to the Beevers–Lipson strips. The limited accuracy of the latter caused the estimated positions of atoms (identified as peaks in the maps) to be somewhat in error. Methods were therefore sought to improve the accuracy with which the coordinates of the electron-density maxima could be determined. The naive method of peak-shape analysis from densities recalculated on a $3\times 3\times 3$ grid using high-accuracy trigonometric tables entailed 27 summations per atom.

Booth (1946*a*) suggested examining the rapidly varying derivatives of the electron density rather than its slowly varying values. If

$$\rho(\mathbf{x}) = \sum_{\mathbf{h}} F_{\mathbf{h}}\exp(-2\pi i\mathbf{h}\cdot\mathbf{x})$$

then the gradient vector $\nabla_{\mathbf{x}}\rho$ of ρ at $\mathbf{x}^0$

$$(\nabla_{\mathbf{x}}\rho)(\mathbf{x}^0) = \sum_{\mathbf{h}} F_{\mathbf{h}}(-2\pi i\mathbf{h})\exp(-2\pi i\mathbf{h}\cdot\mathbf{x}^0)$$

can be calculated by means of three Fourier summations from the 3×1 vector of Fourier coefficients

$$(-2\pi i\mathbf{h})F_{\mathbf{h}}.$$

Similarly, the Hessian matrix of ρ at $\mathbf{x}^0$

$$[(\nabla_{\mathbf{x}}\nabla_{\mathbf{x}}^T)\rho](\mathbf{x}^0) = \sum_{\mathbf{h}} F_{\mathbf{h}}(-4\pi^2\mathbf{h}\mathbf{h}^T)\exp(-2\pi i\mathbf{h}\cdot\mathbf{x}^0)$$

can be calculated by six Fourier summations from the unique elements of the symmetric matrix of Fourier coefficients:

$$-4\pi^2\begin{pmatrix} h^2 & hk & hl \\ hk & k^2 & kl \\ hl & kl & l^2 \end{pmatrix}F_{\mathbf{h}}.$$

The scalar maps giving the components of the gradient and Hessian matrix of ρ will be called differential syntheses of 1st order and 2nd order respectively. If $\mathbf{x}^0$ is approximately but not exactly a maximum of ρ, then the Newton–Raphson estimate of the true maximum $\mathbf{x}^*$ is given by:

$$\mathbf{x}^* = \mathbf{x}^0 - [[(\nabla_{\mathbf{x}}\nabla_{\mathbf{x}}^T)\rho](\mathbf{x}^0)]^{-1}[\nabla_{\mathbf{x}}\rho(\mathbf{x}^0)].$$

This calculation requires only nine accurate Fourier summations (instead of 27), and this number is further reduced to four if the peak is assumed to be spherically symmetrical.

The resulting positions are affected by series-termination errors in the differential syntheses. Booth (1945*c*, 1946*c*) proposed a 'back-shift correction' to eliminate them, and extended this treatment to the acentric case (Booth, 1946*b*). He cautioned against the use of an artificial temperature factor to fight series-termination errors (Brill *et al.*, 1939), as this could be shown to introduce coordinate errors by causing overlap between atoms (Booth, 1946*c*, 1947*a,b*).

Cruickshank was able to derive estimates for the standard uncertainties of the atomic coordinates obtained in this way (Cox & Cruickshank, 1948; Cruickshank, 1949*a,b*) and to show that they agreed with those provided by the least-squares method.

The calculation of differential Fourier syntheses was incorporated into the crystallographic programs of Ahmed & Cruickshank (1953*b*) and of Sparks *et al.* (1956).

1.3.4.4.7.3. Booth's method of steepest descents

Having defined the now universally adopted R factors (Booth, 1945*b*) as criteria of agreement between observed and calculated amplitudes or intensities, Booth proposed that R should be minimized with respect to the set of atomic coordinates $\{\mathbf{x}_j\}_{j\in J}$ by descending along the gradient of R in parameter space (Booth, 1947*c,d*). This 'steepest descents' procedure was compared with Patterson methods by Cochran (1948*d*).

When calculating the necessary derivatives, Booth (1948*a*, 1949) used the formulae given above in connection with least squares. This method was implemented by Qurashi (1949) and by Vand (1948, 1951) with parameter-rescaling modifications which made it very close to the least-squares method (Cruickshank, 1950; Qurashi & Vand, 1953; Qurashi, 1953).

1.3.4.4.7.4. Cochran's Fourier method

Cochran (1948*b,c*, 1951*a*) undertook to exploit an algebraic similarity between the right-hand side of the normal equations in the least-squares method on the one hand, and the expression for the coefficients used in Booth's differential syntheses on the other hand (see also Booth, 1948*a*). In doing so he initiated a remarkable sequence of formal and computational developments which are still actively pursued today.

Let $\rho_{\mathrm{C}}(\mathbf{x})$ be the electron-density map corresponding to the current atomic model, with structure factors $|F_{\mathbf{h}}^{\mathrm{calc}}|\exp(i\varphi_{\mathbf{h}}^{\mathrm{calc}})$; and let $\rho_{\mathrm{O}}(\mathbf{x})$ be the map calculated from observed moduli and calculated phases, *i.e.* with coefficients $\{|F_{\mathbf{h}}|^{\mathrm{obs}}\exp(i\varphi_{\mathbf{h}}^{\mathrm{calc}})\}_{\mathbf{h}\in\mathscr{H}}$. If there are enough data for ρ_{C} to have a resolved peak at each model atomic position $\mathbf{x}_j$, then

$$(\nabla_{\mathbf{x}}\rho_{\mathrm{C}})(\mathbf{x}_j) = \mathbf{0} \quad \text{for each } j \in J;$$

while if the calculated phases $\varphi_{\mathbf{h}}^{\mathrm{calc}}$ are good enough, ρ_{O} will also have peaks at each $\mathbf{x}_j$:

$$(\nabla_{\mathbf{x}}\rho_{\mathrm{O}})(\mathbf{x}_j) = \mathbf{0} \quad \text{for each } j \in J.$$

It follows that