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SAYRE EQUATION, TANGENT FORMULA AND SAYTAN

FAN HAI-FU
Institute of Physics, Chinese Academy of Sciences
Beijing 100080, P. R. China

## 1. Notation


$V$   the volume of a unit cell
**r**   real-space positional vector defined within a unit cell
$\rho$ (**r**)     electron density function with **r** as argument
**h**   reciprocal-lattice vector, which corresponds to the diffraction index *hkl*
$\mathbf{F_h}$   the structure factor with **h** as argument; the Fourier transform of $\rho$ (**r**)
$\mathbf{F^{sq}_h}$ the Fourier transform of $\rho^2(\mathbf{r})$
$f_j$   the scattering factor of the $j^{th}$ atom in the unit cell
$f^{sq}_j$   the scattering factor of the $j^{th}$ 'squared atom' in the unit cell
$F_\mathbf{h}$   the magnitude of $\mathbf{F_h}$

$\varphi_\mathbf{h}$   the phase of $\mathbf{F_h}$

$\Phi_3$   $= \varphi_{-\mathbf{h}} + \varphi_{\mathbf{h'}} + \varphi_{\mathbf{h-h'}}$ , the three-phase structure invariant
$\mathbf{E_h}$   the normalised structure factor corresponding to $\mathbf{F_h}$
$E_\mathbf{h}$   the magnitude of $\mathbf{E_h}$
$\sigma_n$   $= \Sigma_j (Z_j)^n$, $Z_j$ is the atomic number of the $j^{th}$ atom in the unit cell, $n$ is an integer


## 2. Sayre's equation

The Sayre equation [1] is an exact equation linking structure factors. It holds under the following conditions:

    i)   positivity;
    ii)   atomicity;
    iii)   equal-atom structure.

Given a crystal structure represented by $\rho$ (**r**), we can construct a 'squared structure' expressed as

$$\rho^2(\mathbf{r}) = \rho(\mathbf{r}) \times \rho(\mathbf{r}) \quad . \tag{1}$$

According to the convolution theorem, the Fourier transform of (1) yields

$$\mathbf{F}_{\mathbf{h}}^{sq} = \frac{1}{V} \sum_{\mathbf{h'}} \mathbf{F}_{\mathbf{h'}} \mathbf{F}_{\mathbf{h-h'}} \quad , \tag{2}$$

where

$$\mathbf{F}_{\mathbf{h}} = \sum_{j=1}^{N} f_j \exp(i2\pi \mathbf{h} \cdot \mathbf{r}_j) \quad . \tag{3}$$

Since $\mathbf{F}^{sq}{}_{\mathbf{h}}$ is the Fourier transform of $\rho^2(\mathbf{r})$, according to (2) the 'squared structure' can be determined through the convolution of structure factors $\mathbf{F}_{\mathbf{h}}$. Now if we can find the relationship between $\rho^2(\mathbf{r})$ and $\rho(\mathbf{r})$, then the $\mathbf{F}^{sq}{}_{\mathbf{h}}$ in (2) can be converted to $\mathbf{F}_{\mathbf{h}}$ leading to an equation linking structure factors. If the first two conditions mentioned above are satisfied, i.e. we have i) $\rho(\mathbf{r}) \geq 0$, ii) the electron densities of different atoms do not overlap, then $\rho^2(\mathbf{r})$ and $\rho(\mathbf{r})$ will have the same number of maxima (atoms) situated at the same positions. We can write

$$\mathbf{F}_{\mathbf{h}}^{sq} = \sum_{j=1}^{N} f_j^{sq} \exp(i2\pi \mathbf{h} \cdot \mathbf{r}_j) \quad . \tag{4}$$

If the third condition is also satisfied, we have $\mathbf{F}_{\mathbf{h}} / \mathbf{F}^{sq}{}_{\mathbf{h}} = f / f^{sq}$ and hence

$$\mathbf{F}_{\mathbf{h}} = \frac{f}{f^{sq}V} \sum_{\mathbf{h'}} \mathbf{F}_{\mathbf{h'}} \mathbf{F}_{\mathbf{h-h'}} \quad . \tag{5}$$

Equation (5) is Sayre's equation.

An important outcome of Sayre's paper, and two other papers published alongside that of Sayre by Cochran [2] and Zachariasen [3], was the relationship between the signs of structure factors in centrosymmetric case:

$$S_{\mathbf{h}} \sim S_{\mathbf{h'}} S_{\mathbf{h-h'}} \quad , \tag{6}$$

where $\sim$ means 'probably equals'. This can be seen from (5); if $\mathbf{F}_{\mathbf{h}}$ is a large structure factor then it is more likely than not that a large product on the right hand side will have the same sign (phase). The probability for (6) to be true was given by Woolfson [4] and more generally by Cochran and Woolfson [5]

$$P(s_{\mathbf{h,h'}}) = \frac{1}{2} + \frac{1}{2} \tanh\left( \frac{\sigma_3}{\sigma_2^{3/2}} \left| E_{\mathbf{h}} E_{\mathbf{h'}} E_{\mathbf{h-h'}} \right| \right) \quad . \tag{7}$$

During the early days of direct methods, the sign relationships were used in various ways to solve centrosymmetric structures or centrosymmetric projections of non-centrosymmetric structures [3, 6, 7]. A very successful technique of applying Sayre's equation in *ab initio* phasing is the *SAYTAN* method, which will be described later in this paper. On the other hand, Sayre's equation and its variations have also been successfully used in phase extension and refinement for a wide variety of structures, from proteins to aperiodic crystals [8].

It should be noticed that, while the three conditions mentioned above are necessary for deriving the Sayre equation, they are not satisfied exactly in practice. It is useful to know what would happen when one or more conditions does not hold. In theory, any violation of the three conditions would lead to the collapse of equation (5). However even in this case equation (2) is still valid. Consequently results of applying Sayre's equation would tend to $\rho^2(\mathbf{r})$ rather than $\rho(\mathbf{r})$. The problem is: to what extent will $\rho^2(\mathbf{r})$ and $\rho(\mathbf{r})$ resemble each other? For example, in neutron diffraction the scattering factor of some elements is negative leading to 'negative atoms' in the density function $\rho(\mathbf{r})$. When Sayre's equation is used with neutron diffraction data, the result, approximately $\rho^2(\mathbf{r})$, will differ from $\rho(\mathbf{r})$ mainly in that the negative atoms are changed to positive ones. In another case, if the crystal contains heavy atoms together with light atoms, the map resulting from Sayre's equation will have heavy atoms heavier and light atoms lighter than those in $\rho(\mathbf{r})$. Hence in many cases Sayre's equation may still be applicable even when the three conditions are not completely fulfilled.

### 3. Cochran's distribution

The three-phase relationship

$$\varphi_{-\mathbf{h}} + \varphi_{\mathbf{h'}} + \varphi_{\mathbf{h-h'}} \sim 0 \quad (\text{modulo } 2\pi) \quad . \tag{8}$$

and the probability distribution of

$$\Phi_3 = \varphi_{-\mathbf{h}} + \varphi_{\mathbf{h'}} + \varphi_{\mathbf{h-h'}} \quad , \tag{9}$$

were given by Cochran [9]

$$P(\Phi_3) = \left[ 2\pi I_0(\kappa_{\mathbf{h,h'}}) \right]^{-1} \exp\left( \kappa_{\mathbf{h,h'}} \cos \Phi_3 \right) \quad , \tag{10}$$

where

$$\kappa_{\mathbf{h},\mathbf{h}'} = 2\sigma_3\sigma_2^{-3/2} E_{\mathbf{h}} E_{\mathbf{h}'} E_{\mathbf{h}-\mathbf{h}'} \tag{11}$$

for non-equal-atom structures and

$$\kappa_{\mathbf{h},\mathbf{h}'} = 2N^{-1/2} E_{\mathbf{h}} E_{\mathbf{h}'} E_{\mathbf{h}-\mathbf{h}'} \tag{12}$$

for equal-atom structures.

The derivation of (10) is based on the *central limit theorem*: Given a set of n independent random variables, $x_i$, with means $<x_i>$ and variances $\sigma_i^2$, the function

$$y = \sum_{i=1}^{n} a_i x_i \tag{13}$$

has a probability distribution that tends, as n becomes large, to a normal (Gaussian) distribution

$$P(y) = \frac{1}{\sigma_y (2\pi)^{1/2}} \exp\left[ -\frac{(y - <y>)^2}{2\sigma_y^2} \right] \tag{14}$$

with mean $<y> = \sum_{i=1}^{n} a_i <x_i>$ and variance $\sigma_y^2 = \sum_{i=1}^{n} a_i \sigma_i^2$.

It has been shown by Kitaigorodskii [10] that, taking $\cos(2\pi\mathbf{h}.\mathbf{r}_j)$ as $x_i$ and taking $\mathbf{F_h}$ as $y$ , for a crystal in space group $P\bar{1}$ containing more than 10 atoms in the unit cell, the probability distribution of $\mathbf{F_h}$ tends, to a good approximation, to a Gaussian distribution. Now let the trigonometric factors

$$\genfrac{}{}{0pt}{}{\sin}{\cos}[2\pi(-\mathbf{h})\cdot\mathbf{r}_j] \genfrac{}{}{0pt}{}{\sin}{\cos}(2\pi\mathbf{h}'\cdot\mathbf{r}_j) \genfrac{}{}{0pt}{}{\sin}{\cos}[2\pi(\mathbf{h}-\mathbf{h}')\cdot\mathbf{r}_j] \quad ,$$

where $\genfrac{}{}{0pt}{}{\sin}{\cos}$ means 'sin' or 'cos', be the independent random variables $x_i$ and the product $E_{\mathbf{-h}} E_{\mathbf{h}'} E_{\mathbf{h}-\mathbf{h}'}$ be the function $y$. Assuming the probability distribution of both the real and the imaginary component of $y$ tend to a Gaussian distribution, and assuming the amplitudes $E_{\mathbf{-h}}$, $E_{\mathbf{h}'}$ and $E_{\mathbf{h}-\mathbf{h}'}$ are known, we would finally obtain Cochran's distribution (10).

## 4. The tangent formula

From equations (9) and (10), if there are more than one pair of known phases, $\varphi \in_{h'}$ and $\varphi_{h-h'}$, associated with the same $\varphi \in_h$, then the total probability distribution for $\varphi \in_h$ will be

$$P(\varphi_h) = \prod_{h'} P_{h'}(\Phi_3) = N \exp\left(\sum_{h'} \kappa_{h,h'} \cos \Phi_3\right) \quad , \tag{15}$$

where $N$ is a normalising factor.

Let

$$\alpha \sin\beta = \sum_{h'} \kappa_{h,h'} \sin(\varphi_{h'} + \varphi_{h-h'}) \tag{16}$$

and

$$\alpha \cos\beta = \sum_{h'} \kappa_{h,h'} \cos(\varphi_{h'} + \varphi_{h-h'}) \tag{17}$$

(15) becomes

$$P(\varphi_h) = \left[2\pi I_0(\alpha)\right]^{-1} \exp[\alpha \cos(\varphi_h - \beta)] \quad . \tag{18}$$

By maximising $P(\varphi_h)$ in (18) we have $\varphi_h = \beta$. Then from (16) and (17) we obtain

$$\tan\varphi_h = \frac{\sum_{h'} \kappa_{h,h'} \sin(\varphi_{h'} + \varphi_{h-h'})}{\sum_{h'} \kappa_{h,h'} \cos(\varphi_{h'} + \varphi_{h-h'})} \quad . \tag{19}$$

with

$$\alpha = \left[\left(\sum_{h'} \kappa_{h,h'} \sin(\varphi_{h'} + \varphi_{h-h'})\right)^2 + \left(\sum_{h'} \kappa_{h,h'} \cos(\varphi_{h'} + \varphi_{h-h'})\right)^2\right]^{1/2} \tag{20}$$

indicating the reliability of the estimation of $\varphi_h$. This is the tangent formula introduced by Karle and Hauptman [11], which is the most widely used formula in direct methods. The form of the tangent formula given here differs a little from, but is equivalent to, that of the original one.

It is easily obtained from Sayre's equation a formula similar to (19) but with quite different meaning. By splitting equation (5) into the real and the imaginary parts and by dividing the imaginary part with the real part, it follows

$$\tan\varphi_{\mathbf{h}} = \frac{\sum\limits_{\mathbf{h'}} F_{\mathbf{h'}} F_{\mathbf{h-h'}} \sin(\varphi_{\mathbf{h'}} + \varphi_{\mathbf{h-h'}})}{\sum\limits_{\mathbf{h'}} F_{\mathbf{h'}} F_{\mathbf{h-h'}} \cos(\varphi_{\mathbf{h'}} + \varphi_{\mathbf{h-h'}})} \quad . \tag{21}$$

Equation (21) may be regarded as the angular portion of Sayre's equation. It differs from (19) in that the summation in (21) should include all available $\mathbf{h'}$ terms, while that in (19) may just include a few or even only one term of $\mathbf{h'}$. Besides, (21) is an exact equation, while (19) gives the most probable value of $\varphi_{\mathbf{h}}$. The tangent formula is much easier to use for *ab initio* phasing. A historical breakthrough on the application of direct methods was made by Karle and Karle [12] when they solved the non-centrosymmetric crystal structure of L-arginine dihydrate by the symbolic-addition procedure using the tangent formula. A few years later a systematic procedure to use the tangent formula and a computer program *MULTAN* (MULtisolution TANgent-formula method) [13] were introduced by Woolfson and his colleagues. The development and application of the *MULTAN* and related procedures led to the domination of direct methods in solving small molecular structures.

### 4. *SAYTAN*

The basic idea behind *SAYTAN* is to use not only the relationship among phases but also that among amplitudes implied in Sayre's equation. The philosophy is that a good set of phases should satisfy a system of Sayre equations.

$$\mathbf{E_h} = \frac{K}{g_{\mathbf{h}}} \sum_{\mathbf{h'}} \mathbf{E_{h'}} \mathbf{E_{h-h'}} \quad , \tag{20}$$

where $g_{\mathbf{h}}$ is the scattering factor for 'squared' atoms and $K$ is an overall scaling constant, which allows for the fact that only structure factors with large magnitude are included on the right-hand side. The derivation started with the following residual for a system of Sayre equations:

$$R = \sum_{\mathbf{h}} \left| g_{\mathbf{h}} \mathbf{E_h} - K \sum_{\mathbf{h'}} \mathbf{E_{h'}} \mathbf{E_{h-h'}} \right|^2 \quad . \tag{21}$$

As a condition that $R$ should be a minimum it is necessary that

$$\frac{\partial R}{\partial \varphi_{\mathbf{h}}} = 0 \quad \text{for all } \mathbf{h}$$

and this leads to the Sayre-equation tangent formula [14]

$$\varphi_{\mathbf{h}} = \text{ phase of } \left[ \sum_{\mathbf{h''}} \left( g_{\mathbf{h}} + g_{\mathbf{h''}} + g_{\mathbf{h-h''}} \right) \mathbf{E_{h''} E_{h-h''}} - 2K \sum_{\mathbf{h''}} \mathbf{E_{h-h''}} \sum_{\mathbf{h'}} \mathbf{E_{h'} E_{h''-h'}} \right].$$
(22)

As is seen the Sayre-equation tangent formula includes both triplet and quartet terms. A distinctive feature of the Sayre-equation tangent formula is that it can use the information from Sayre equations for which the values of $E_{\mathbf{h}}$ are small, ideally zero. As is well known in powder-method crystal-structure analysis, a good structure model should satisfy the weakest reflections as well as the strongest. The Sayre-equation tangent formula tends to develop phase sets, which satisfy the smallest magnitudes as well as the largest. Since it uses extra information *SAYTAN* is more effective than *MULTAN* , either giving a solution in fewer trials or giving a solution where *MULTAN* would not.

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