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A novel iterative solution to the phase problem

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A new Fourier cycling phasing method is proposed based on the mathematical principle of the global minimization. In reciprocal space, the Fourier coefficient is of a mixed form of the normalized structure factors $(2E_{\rm o}^2 - E_{\rm c}^2)\mathbf{E}_{\rm c}$, while in direct space the Fourier map is modified with a peak-picking procedure. This method does not use any preliminary information and does not rely on any critical parameter; it can start with either randomly assigned phases or fixed phases (all zeros). This method performs significantly better than the commonly used forms of Fourier cycling.

1. Introduction

The $F_{\rm o}$ synthesis (Bragg, 1929) is a simple but fundamental Fourier cycling technique; it iteratively calculates the structure factors from a postulated model, and then uses the calculated phases together with the measured amplitudes ($F_{\rm o}$'s) to calculate the density map. It has an amazing property: the newly calculated map usually represents an improved model. Although $F_{\rm o}$ synthesis is explicitly used for refinement (Lipson & Cochran, 1966), it has been found recently that it is also capable of solving structures *ab initio* provided that a suitable direct-space modification is applied and the iteration is kept for hundreds or thousands of times. By simply eliminating the low densities of the map (LDE) in each cycle, some structures can be solved from randomly assigned phases (Shiono & Woolfson, 1992); by flipping the density lower than a critical threshold (charge flipping), many structures can be solved (Oszlányi & Sütő, 2004, 2008; Wu *et al.*, 2006). Here we report a new Fourier cycling method which uses a mixed form of the structure factors as the Fourier coefficient and a new peak-picking procedure for direct-space modification. This method is based on the mathematical principle of the global minimization.

2. An iterative phase solution

Denoting $\{\mathbf{r}_i\}$ (i = 1, 2,..., N) the atomic positions, the structure factor $\mathbf{F}_\mathbf{h}$ for reflection $\mathbf{h}$ can be expressed as

$$\mathbf{F}_\mathbf{h} \equiv F_\mathbf{h}\exp(i\alpha_\mathbf{h}) = \sum_{i=1}^{N} f_i \exp(2\pi i\mathbf{h}\cdot\mathbf{r}_i). \tag{1}$$

Here f_i is the ith atomic scattering factor, which is a special function of $\mathbf{h}$, $F_\mathbf{h}$ is the structure amplitude and $\alpha_\mathbf{h}$ the phase. Mathematically a solution to the phase problem can be obtained by finding a set of vectors $\mathbf{r}_1, \mathbf{r}_2, \ldots, \mathbf{r}_N$ that minimizes the merit function

$$\chi^2(\mathbf{r}_1, \mathbf{r}_2, \ldots, \mathbf{r}_N) = \sum_\mathbf{h} \frac{1}{w^2}(F_{\rm o}^2 - F_{\rm c}^2)^2, \tag{2}$$

where $F_{\rm o}$ and $F_{\rm c}$ are the observed and calculated structure amplitudes (subscript $\mathbf{h}$ is omitted here and hereafter for clarity), respectively. The weight w can be chosen as $\sum_{i=1}^{N} f_i^2$, and then we have

$$\chi^2(\mathbf{r}_1, \mathbf{r}_2, \ldots, \mathbf{r}_N) = \sum_\mathbf{h} (E_{\rm o}^2 - E_{\rm c}^2)^2, \tag{3}$$

where E is the amplitude of the normalized structure factor without the space-group-related factor ε:

$$\mathbf{E} \equiv E\exp(i\alpha) = \sum_{i=1}^{N} e_i \exp(2\pi i\mathbf{h}\cdot\mathbf{r}_i), \tag{4}$$

$$E^2 = \mathbf{E}\;\mathbf{E}^* = \mathbf{E}\sum_{i=1}^{N} e_i \exp(-2\pi i\mathbf{h}\cdot\mathbf{r}_i) \tag{5}$$

and $e_i = f_i/w^{1/2}$ is approximately a constant (Karle, 1991), and for molecules with equal or nearly equal atoms such as C, N and O it is close to $1/N^{1/2}$. Equation (3) defines a $3N$-dimensional non-linear system and its solution is of an iterative nature. The conventional approach to this problem is to take the derivative of equation (3) with respect to all parameters $\mathbf{r}_i = (x_i, y_i, z_i)$ and the minimization (by setting all derivatives to zero) leads to $3N$ simultaneous equations whose solution results in an improvement $(\Delta x_i, \Delta y_i, \Delta z_i)$. However, this approach requires that the initial parameters are reasonably accurate, *i.e.* the initial phase solution is already obtained; otherwise it will easily 'converge' to one of the numerous local minima. Therefore, it has only been used as a refinement procedure in crystallography. In the following we present a new approach that attempts to reduce χ^2 directly.

From equation (3),

$$\begin{aligned}\chi^2(\mathbf{r}_1, \mathbf{r}_2, ..., \mathbf{r}_N) &= \sum_\mathbf{h} E_{\rm o}^4 - \sum_\mathbf{h} (2E_{\rm o}^2 - E_{\rm c}^2)E_{\rm c}^2 \\ &= \sum_\mathbf{h} E_{\rm o}^4 - \sum_\mathbf{h} (2E_{\rm o}^2 - E_{\rm c}^2)\mathbf{E}_{\rm c}\sum_{i=1}^{N} e_i \exp(-2\pi i\,\mathbf{h}\cdot\mathbf{r}_i) \end{aligned} \tag{6}$$

$$= \sum_\mathbf{h} E_{\rm o}^4 - \sum_{i=1}^{N} e_i \sum_\mathbf{h} (2E_{\rm o}^2 - E_{\rm c}^2)\mathbf{E}_{\rm c}\exp(-2\pi i\,\mathbf{h}\cdot\mathbf{r}_i) \tag{7}$$

$$= \sum_\mathbf{h} E_{\rm o}^4 - V\sum_{i=1}^{N} e_i J(\mathbf{r}_i), \tag{8}$$

where e_i is assumed a constant in equation (7), V is the unit-cell volume, and density map $J(\mathbf{r})$ is the inverse Fourier transform ($\mathcal{F}^{-1}$) of a mixed form of the structure factors:

$$J(\mathbf{r}) \equiv \frac{1}{V}\mathcal{F}^{-1}\{(2E_{\rm o}^2 - E_{\rm c}^2)\mathbf{E}_{\rm c}\} \tag{9}$$

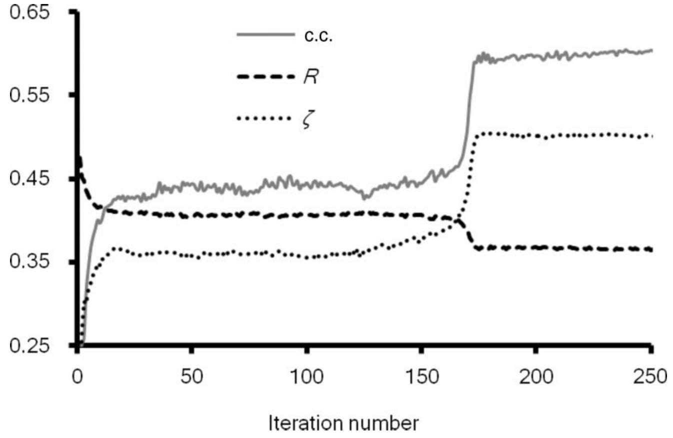


Figure 1
Characteristics of the Fourier iteration process (from structure 1a7y). c.c., correlation coefficient; R, residual R factor; ζ, the average peak height.

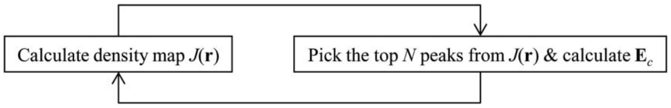
$$= J_c(\mathbf{r}) + 2\Delta J(\mathbf{r}). \tag{10}$$

Here $J_c(\mathbf{r})$ represents the model structure and $\Delta J(\mathbf{r})$ is a difference map:

$$J_c(\mathbf{r}) \equiv \frac{1}{V}\mathcal{F}^{-1}\{E_c^2\mathbf{E}_c\} \tag{11}$$

$$\Delta J(\mathbf{r}) \equiv \frac{1}{V}\mathcal{F}^{-1}\{(E_o^2 - E_c^2)\mathbf{E}_c\}. \tag{12}$$

Since $\sum_{\mathbf{h}} E_o^4$ is a constant, equation (8) indicates that the residue χ^2 for a given model is directly determined by the density values $J(\mathbf{r})$ at the model positions $\{\mathbf{r}_i\}$; accordingly, the top N peaks $\mathbf{r}'_1, \mathbf{r}'_2, \ldots, \mathbf{r}'_N$ of $J(\mathbf{r})$ can be taken as the improved model since the corresponding χ^2 is the minimum; if these top peaks are coincident with the model positions $\mathbf{r}_1, \mathbf{r}_2, \ldots, \mathbf{r}_N$, then the model is not improvable, *i.e.* the difference map $\Delta J(\mathbf{r})$ has no significant features, which indicates that a global minimum of χ^2 is reached. Thus, the density map $J(\mathbf{r})$ has a *self-improving* nature and an iterative solution can be naturally constructed:



It has the same scheme as the F_o synthesis except that the Fourier coefficients are different. To conveniently calculate $\mathbf{E}_c$ with Fourier transform, $J(\mathbf{r})$ can be modified by keeping the top N peaks and setting the rest to zero (peak picking, see details in the next section); this modified $J(\mathbf{r})$ is taken as the model density $J_c(\mathbf{r})$ and its Fourier transform is $E_c^2\mathbf{E}_c$ according to equation (11).

The iteration may start from either randomly assigned phases or fixed phases. A general fixed start is to set all phases to zero; in this case, the corresponding Fourier map has an anomalously strong peak at the origin, which may be replaced with a normal peak or simply excluded from the model.

The iterative process can be monitored by χ^2-related global parameters such as the conventional residual R factor or the correlation coefficient (c.c.). An intuitive global parameter is the average height (ζ) of the top N peaks, which is evident from equation (8) and the ideal average peak height ζ_0 at convergence ($\chi^2 \to 0$) can be calculated for equal-atom structures:

$$\zeta_0 = \frac{1}{V(N)^{1/2}}\sum_{\mathbf{h}} E_o^4. \tag{13}$$

The actual ζ at convergence is usually ~20% less than ζ_0 for crystals containing only light atoms such as C, N and O. Fig. 1 shows the typical curves for the structure with the PDB (Protein Data Bank) code 1a7y (see Tables 1 and 2) with ζ_0 = 0.56. The ζ value normally experiences two jumps (significant and sharp increase in ~10 cycles) and an evolving stage in between. The first jump is at the start and it reaches ~60% of ζ_0 and the second leads to ~80% of ζ_0, which indicates the completion of the evolution from ordinary peaks to atomic peaks. It is found, by examining the evolution process of some solutions, that in the beginning of the evolving stage $J(\mathbf{r})$ usually contains several partial solutions; which one is to emerge depends subtly on the settings, *e.g.* the actual number of peaks used for the model $J_c(\mathbf{r})$. For simple structures, *e.g.* small-molecule crystals with centrosymmetry or heavy atoms, the evolving stage is so short that the second jump immediately follows the first one, which results in a single complete jump. The c.c. curve is similar to the ζ curve and the R curve is complementary to the ζ curve.

Table 1
Comparison of the performance (iteration number at convergence) of five forms of the Fourier iteration method for four test structures (see Table 2).

Parameters: k = 0.03; grid size 0.35 Å pixel^{-1} for hg5135 and rk2244, 0.4 Å pixel^{-1} for 1a7y and 1b0y. '—' indicates a solution is not obtained within 50 000 cycles. All tests start with fixed phases (all zeros).

Method	hg5135	rk2244	1a7y	1b0y
$(2E_o^2 - E_c^2)\mathbf{E}_c$	18	46	171	1554
$(2E_o - E_c)\exp(i\alpha)$	146	688	21794	8103
$E_o\exp(i\alpha)$	210	2514	—	—
$(2F_o - F_c)\exp(i\alpha)$	474	5118	—	—
$F_o\exp(i\alpha)$	855	24903	—	—

Table 2
Test structures.

Nasu is the number of non-H and non-solvent atoms in an asymmetric unit and T is the data-collection temperature. Data sources: hg5135 (Pansuriya *et al.*, 2011) and rk2244 (Narayanan *et al.*, 2010) are from *Acta Crystallographica Section E*; 1a7y (Schafer *et al.*, 1998) and 1b0y (Parisini *et al.*, 1999) are from http://www.pdb.org.

	hg5135	rk2244	1a7y	1b0y
Space group	$P\bar{1}$	$Pna2_1$	$P1$	$P2_12_12_1$
Nasu	120	49	314	631
Volume (Å^3)	4448.3	3326.8	5887.1	65818.3
Resolution (Å)	0.75	0.79	0.94	0.93
T (K)	173	295	133	100
Atoms with $Z > 8$	—	—	—	4Fe, 9S

3. Some implementation details

Peak picking *for direct-space modification* involves two steps: find the peak locations (peak finding) and then modify the density map. However, the commonly used peak-picking procedures (*e.g.* Sheldrick, 2008) do not actually modify the map; they directly use the coordinates of the picked peaks and assign each peak a weight to calculate the structure factors. This is equivalent to a modification that uses only the central pixel of each peak and sets all other pixels of the map to zero. Because of the resolution limit of the diffraction data, an atomic peak in the density map is represented by a volume (defined by the resolution) rather than a single pixel. Therefore, the peak picking used in this Fourier iterative method uses the whole peak. If the resolution is ~1.0 Å or better and the grid size ~0.4 Å pixel^{-1}, the whole peak can be well represented by pixels that reside in a 5 × 5 × 5 grid box centered at the peak pixel and have a distance less than 1.0 Å from the center. To accommodate the overlapped and/or irregularly shaped peaks in the initial stage, the constraint of a minimum interatomic distance 1.2 Å is applied and a pixel is evaluated using the following peak-finding procedure: for the 3 × 3 × 3 box centered at pixel (i, j, k), first sum up the pixel values in each of the three 9-pixel planes along the i axis S_{i-1}, S_i and S_{i+1}; if $S_i > S_{i-1}$ and $S_i > S_{i+1}$, then do the same along the j axis; if $S_j > S_{j-1}$ and $S_j > S_{j+1}$, then examine the k planes; if $S_k > S_{k-1}$ and $S_k > S_{k+1}$, then pixel (i, j, k) is the center of a peak. To speed up this process, one only needs to evaluate pixels that have values larger than a threshold (*e.g.* $0.2\zeta_0$); it is even better to change the threshold dynamically.

The number of peaks N_p to be kept for the above direct-space modification is not necessarily the same as the actual number of atoms N. This method normally works with N_p in the range of $0.4N$ to $1.0N$ and in this range no choice is always better. Since the actual N may not be known but the cell volume V is always known, a parameter k can be introduced: $N_p = kV$. The normal range of k is 0.02–0.05 for small-molecule structures and 0.015–0.04 for macromolecular structures; therefore a general k value 0.03 is usually used. In fact, many structures, especially those containing heavy atoms, can be solved with much lower k and even faster. For example, the structure 1b0y (see Tables 1 and 2) can be solved in 1554 cycles with $k = 0.03$, and only 120 cycles with $k = 0.001$ ($N_p = 65$).

This method works in the space group $P1$ and the symmetry information is not used. The normalized structure factors are calculated by dividing $F_o^2(\mathbf{h})$ by the mean value in the corresponding shell, and a Wilson plot or an overall thermal parameter is not needed.

4. Examples

Table 1 lists five forms of the Fourier iteration method and their performance for four test structures (see Table 2). It can be seen that the first form $(2E_o^2 - E_c^2)\mathbf{E}_c$ from equation (9) performs significantly better than the commonly used forms $F_o\exp(i\alpha)$, $E_o\exp(i\alpha)$, $(2F_o - F_c)\exp(i\alpha)$ and $(2E_o - E_c)\exp(i\alpha)$. Actinomycin D (1a7y), a difficult structure for charge flipping that utilizes two critical parameters (Oszlányi & Sütő, 2005), can be solved very easily with the proposed method. Using a 2.4 GHz processor and the Fourier transform library FFTW (Frigo & Johnson, 2005) the CPU time is 2 s for structure hg5135, 2 s for rk2244, 12 s for 1a7y and 993 s for 1b0y.

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