Giacovazzo. Replacing in the distributions the Cochran concentration parameter of a triplet by the corresponding $P10$ parameter of the same triplet remarkably improves the behaviour of the distributions although further improvements are needed. Their maximization requires better probabilistic theories; in particular, higher efficiency for the estimation of negative quartet invariants.

The tangent formula (including triplets and quartet contributions) based on the mathematical approach of Giacovazzo proved to be the only one suitable for phase expansion and refinement. The formula was included in a random approach to structure determination. The additional use of quartets was not helpful owing to the limited accuracy of quartet estimates. Replacing in the triplet contribution the Cochran concentration parameter by the corresponding $P10$ parameter remarkably improved the efficiency of the phasing process. But again the combination of $P10$ estimated triplets with quartets proved less efficient. The reason for such a failure is ascribed to the limited accuracy of the probabilistic formulae estimating quartets. A substantial improvement of such formulae is considered a necessary condition for the success of the active use of the quartets in the phasing process.

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Conjugate-Direction Minimization: an Improved Method for the Refinement of Macromolecules

BY D. E. TRONRUD

Howard Hughes Medical Institute and Institute of Molecular Biology, University of Oregon, Eugene, OR 97403, *USA*

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Abstract

A novel method of function minimization that combines the power of the diagonal approximation to the normal matrix with conjugate directions is described. This method approaches closer to the local minimum than the methods that are commonly used in macromolecular refinement. The weaknesses of the current methods are analyzed to explain the advantage of the conjugate-direction method.

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1. Introduction

A persistent problem with macromolecular refinement is that the R factors of the final models are higher than those obtained in small-molecule structures. Over the last ten years, even though the same basic type of model is used to represent the molecule, average R factors have decreased from about 20 to 16%. The difference is due to the sophistication of the refinement methods used. It seems likely that further improvement could be achieved if more powerful techniques were available.

In pursuit of this goal, a modification of the conjugate-gradient method of function minimization (Fletcher & Reeves, 1964) has been developed that uses more information about the function being minimized than any method currently used. In particular, it uses explicit knowledge of the diagonal elements of the normal matrix together with implicit knowledge of the off-diagonal terms learned from the history of the refinement to determine better search directions in the parameter space. This method can determine a set of parameters that agree better with the observations in less computer time than the methods described previously.

2. Overview of function minimization

The theoretical basis of all refinement methods used in the latter stages of high-resolution refinement are the same. The analysis begins by making a Taylor-series expansion of the function being minimized about the current estimate for the values of the parameters of the model ($\mathbf{x}_0$). The Taylor-series expansion is

$$f(\mathbf{x}) = f(\mathbf{x}_0) + \mathbf{g}^T(\mathbf{x}_0)\mathbf{d} + \tfrac{1}{2}\mathbf{d}^T\mathbf{N}(\mathbf{x}_0)\mathbf{d} + \ldots, \quad (1)$$

where $\mathbf{g}(\mathbf{x})$ is the gradient of the function, $\mathbf{N}(\mathbf{x})$ is the second derivative or normal matrix, $\mathbf{d}$ is the shift vector that takes $\mathbf{x}_0$ to $\mathbf{x}$ and the superscript T denotes the transpose. The higher-order terms are always assumed to be negligible.

To find the value of $\mathbf{x}$ where $f(\mathbf{x})$ is minimal we take the derivative of (1) with respect to $\mathbf{x}$ and solve for $\mathbf{d}$ when $\mathbf{g}(\mathbf{x})$ is $\mathbf{0}$. The result is

$$\mathbf{d} = -\mathbf{N}^{-1}(\mathbf{x}_0)\mathbf{g}(\mathbf{x}_0) \quad (2)$$

and

$$\mathbf{x} = \mathbf{x}_0 + \mathbf{d}. \quad (3)$$

$\mathbf{x}$ defines the minimum in all cases where the higher-order terms are in fact zero and where $\mathbf{N}$ is positive definite, which is always the case in this application.

3. The macromolecular problem

Equations (2) and (3) require that the normal matrix be calculated and inverted. This matrix is of size $n \times n$, where n is the number of parameters in the model. For many macromolecular structures this number is of the order of 10 000. The calculation and inversion of such a matrix is impractical. To refine large models a method must be chosen that avoids these steps.

The authors of the several commonly used refinement packages have chosen different ways to avoid this problem. The program *X-PLOR* (Brünger, Kuryan & Karplus, 1987) uses the method of simulated annealing in the early stages of refinement. *TNT* (Tronrud, Ten Eyck & Matthews, 1987) and *X-PLOR* (in later stages) both use the conjugate-gradient method. *SFRF* (Agarwal, 1978) and *EREF* (Jack & Levitt, 1978) both use a diagonal approximation to the normal matrix, while *CORELS* (Sussman, Holbrook, Church & Kim, 1977) and *PROLSQ* (Hendrickson & Konnert, 1980) use a sparse-matrix approximation.

4. Review of the conjugate-gradient method

Without complete knowledge of the normal matrix, minimization of a quadratic function requires repeated cycles. In each cycle a shift vector is chosen ($\mathbf{d}_k$ for cycle k) and the minimum along that direction is found with a line search. The minimization of a function along a direction reduces the problem to one parameter, called α. The new values for the full set of parameters (for cycle $k+1$) are

$$\mathbf{x}_{k+1} = \mathbf{x}_k + \alpha_{k+1}\mathbf{d}_{k+1}. \quad (4)$$

The value of α_{k+1} is set to the value that minimizes $f(\mathbf{x}_j + \alpha_{k+1}\mathbf{d}_{k+1})$. It defines the minimum along the shift vector $\mathbf{d}_{k+1}$.

The particular set of directions searched determines the rate of convergence. For example, if one chooses to search along the axes of parameter space, first varying the x parameter of the first atom, then the y parameter and so on, the minimum can only be found after a number of cycles many times greater than n.

Many cycles are required when one parameter at a time is varied because the parameters (and therefore the shift directions) are interdependent; thus, in subsequent cycles, previously searched directions must be searched again. The number of cycles could be reduced if a series of directions could be identified that were independent. This independence is described mathematically as the direction vectors being conjugate to the normal matrix (Luenberger, 1973), which is defined explicitly as $\mathbf{d}_l^T\mathbf{N}\mathbf{d}_m = 0$ when $l \neq m$.

A conjugate-direction method is one in which a series of directions are devised that are conjugate with respect to the normal matrix but do not require the normal matrix for their determination. In the particular conjugate-direction method called the conjugate-gradient method, the direction vector for cycle

$k+1$ is determined from

$$\mathbf{d}_{k+1} = -\mathbf{g}_k + \beta_{k+1}\mathbf{d}_k \quad (5)$$

$$\beta_{k+1} = \mathbf{g}_k^T\mathbf{g}_k / \mathbf{g}_{k-1}^T\mathbf{g}_{k-1}, \quad (6)$$

where β_{k+1} is chosen to ensure that $\mathbf{d}_{k+1}$ is conjugate to all previous directions. $\mathbf{d}_0$ and β_1 are defined to be $\mathbf{0}$ and 0, respectively, which results in the first cycle being a steepest-descent cycle ($\mathbf{d}_1 = -\mathbf{g}_0$).

5. Limitations of the conjugate-gradient method

The fundamental limitation of the conjugate-gradient method is that it requires, in general, n cycles to reach the minimum. We need a procedure that will perform most of the function minimization in the first few cycles.

The eigenvalues of the normal matrix (Leunberger, 1973) provide information about how a method will refine parameters in the early cycles. The normal matrix describes the shape of the minimum of the function and its eigenvalues determine how oblong the neighborhood of the minimum is. Because the normal matrices for the functions usually minimized in macromolecular refinement are nearly diagonal, there is a close correspondence between the eigenvectors and the parameters of the model. For a perfectly diagonal normal matrix, the eigenvectors are the axes of parameter space and the diagonal elements, or curvatures, are the eigenvalues.

The method of steepest descent works best when all the eigenvalues or diagonal elements are equal. If they are not equal, the parameters with the greatest curvatures dominate. The conjugate-gradient method must infer the differences in curvature from the history of the search but this takes more cycles than we give the method in practice.

This problem is especially serious when positional parameters are compared to thermal parameters. The curvatures for positional parameters are much larger than those for thermal parameters; therefore, refinement of thermal parameters is blocked by the influence of the positional parameters. This effect is usually avoided by refining thermal parameters with the positional parameters held constant and *vice versa.*

A more intractable problem arises because the curvatures associated with numerically large thermal parameters are much smaller than those of smaller thermal parameters. In all models produced by refinement using the conjugate-gradient method and methods that simplistically incorporate curvatures, the large thermal factors are poorly refined and probably should have even larger values than those obtained during the refinement process. In addition, atom types with many electrons, such as sulfur and iron, have large curvatures. The thermal-factor shifts of these atoms will be overestimated, resulting in an oscillation about the correct value.

6. Improvements in the conjugate-gradient method

The conjugate-gradient method uses the steepest-descent method to produce its first shift direction or 'seed' direction. The rate of convergence of early cycles can be improved if a seed that incorporates as much information as is practical about the function is used. We would like a direction that includes compensation for the differences in the eigenvalues of the normal matrix. Since in X-ray crystallography the diagonal terms of the normal matrix dominate, a diagonal approximation to the normal matrix provides a powerful and quick alternative to the steepest-descent method of generating shift directions. In this procedure the search direction is calculated by

$$\mathbf{d}_{k+1} = -\mathbf{N}_{d,k}^{-1}\mathbf{g}_k \quad (7)$$

where $\mathbf{N}_{d,k}$ is the diagonal approximation to the normal matrix for the parameters of cycle k. For the fastest rate of convergence, this shift vector should be used as a seed for conjugate-direction searches. It is not clear, however, how one should calculate β in (6).

The refinement problems that we address are the wide range of magnitude of the eigenvalues of the normal matrix and the existence of off-diagonal terms. If we could choose a different set of parameters for which the normal matrix was simpler, the rate of convergence would improve. Ideally, one would choose a system of parameters such that all the eigenvalues were equal and all the off-diagonal elements were zero; then one cycle of steepest-descent minimization would suffice.

Let us assume that we have determined a matrix ($\mathbf{M}$) that will transform the usual crystallographic parameters into such a set of parameters ($\mathbf{x}'$). The transformations between the familiar parameters and the new ones will be

$$\begin{aligned} \mathbf{x}' &= \mathbf{M}\mathbf{x}, & \mathbf{x} &= \mathbf{M}^{-1}\mathbf{x}', \\ \mathbf{g}' &= \mathbf{M}^{-1T}\mathbf{g}, & \mathbf{g} &= \mathbf{M}^T\mathbf{g}', \\ \mathbf{N}' &= \mathbf{M}^{-1T}\mathbf{N}\mathbf{M}^{-1}, & \mathbf{N} &= \mathbf{M}^T\mathbf{N}'\mathbf{M}. \end{aligned} \quad (8)$$

We can perform Fletcher-Reeves conjugate-gradient minimization on the function using this new parameter space. The equations will be the same (4)-(6) but with primes added,

$$\mathbf{x}'_{k+1} = \mathbf{x}'_k + \alpha_{k+1}\mathbf{d}'_{k+1}, \quad (9)$$

$$\mathbf{d}'_{k+1} = -\mathbf{g}'_k + \beta'_{k+1}\mathbf{d}'_k \quad (10)$$

and

$$\beta'_{k+1} = \mathbf{g}_k^T\mathbf{g}'_k / \mathbf{g}_{k-1}'^T\mathbf{g}'_{k-1}. \quad (11)$$

Instead of working with the $\mathbf{x}'$ parameters we can substitute back to the original $\mathbf{x}$ parameters. The resulting equations are

$$\mathbf{x}_{k+1} = \mathbf{x}_k + \alpha_{k+1}\mathbf{M}^{-1}\mathbf{d}'_{k+1} \quad (12)$$

$$\mathbf{M}^{-1}\mathbf{d}'_{k+1} = -\mathbf{M}^{-1}\mathbf{M}^{-1T}\mathbf{g}'_k + \beta'_{k+1}\mathbf{M}^{-1}\mathbf{d}'_k \quad (13)$$

and

$$\beta'_{k+1} = \frac{\mathbf{g}_k^T\mathbf{M}^{-1}\mathbf{M}^{-1T}\mathbf{g}_k}{\mathbf{g}_{k-1}^T\mathbf{M}^{-1}\mathbf{M}^{-1T}\mathbf{g}_{k-1}}. \quad (14)$$

In these equations the shift vectors $\mathbf{d}'$ are all premultiplied by $\mathbf{M}^{-1}$. It would be simpler to eliminate this complication by simply defining $\mathbf{d} = \mathbf{M}^{-1}\mathbf{d}'$. The final equations for conjugate-direction refinement, derived from recombined parameters, but operating on the 'native' parameters are

$$\mathbf{x}_{k+1} = \mathbf{x}_k + \alpha_{k+1}\mathbf{d}_{k+1}, \quad (15)$$

$$\mathbf{d}_{k+1} = -\mathbf{M}^{-1}\mathbf{M}^{-1T}\mathbf{g}'_k + \beta'_{k+1}\mathbf{d}_k \quad (16)$$

and

$$\beta'_{k+1} = \mathbf{g}_k^T\mathbf{M}^{-1}\mathbf{M}^{-1T}\mathbf{g}_k / \mathbf{g}_{k-1}^T\mathbf{M}^{-1}\mathbf{M}^{-1T}\mathbf{g}_{k-1}. \quad (17)$$

At this point, the matrix $\mathbf{M}$ is undefined. The optimal choice for $\mathbf{M}$ would require that $\mathbf{M}^{-1T}\mathbf{N}\mathbf{M}^{-1}$, the normal matrix for the new parameters, is equal to the identity matrix. To calculate the optimal $\mathbf{M}$ we need both the normal matrix and its inverse; thus, we made no gains in computational efficiency over the full matrix method. However, if we recognize that in crystallography $\mathbf{N}$ is almost diagonal we can set $\mathbf{M} = \mathbf{N}_d^{1/2}$. Then $\mathbf{M}^{-1}\mathbf{M}^{-1T}$ in (15), (16) and (17) may be replaced by $\mathbf{N}_d^{-1}$. Making this substitution, we obtain

$$\mathbf{d}_{k+1} = -\mathbf{N}_d^{-1}\mathbf{g}_k + \beta'_{k+1}\mathbf{d}_k \quad (18)$$

and

$$\beta'_{k+1} = \mathbf{g}_k^T\mathbf{N}_d^{-1}\mathbf{g}_k / \mathbf{g}_{k-1}^T\mathbf{N}_d^{-1}\mathbf{g}_{k-1}. \quad (19)$$

The seed direction ($\mathbf{d}_1$ when $\beta'_{k+1} = 0$ and $\mathbf{d}_0 = \mathbf{0}$) is now the shift calculated from the diagonal approximation to the normal matrix, as we desired. In addition, however, we have an equation for β. In summary, we have a minimization method where the diagonal terms of the normal matrix are explicitly included and the off-diagonal elements are dealt with *via* a set of conjugate directions.

Agarwal (1978) suggested a similar method; however, his equation for β was incorrect. In the present nomenclature, his proposal for β was

$$\beta = \mathbf{d}_k^T\mathbf{d}_k / \mathbf{g}_k'^T\mathbf{g}'_k. \quad (20)$$

In conjugate-gradient refinement β is equal to the ratio of the length of the gradient at point k divided by that length at point $k-1$. Because k should be closer to the minimum than point $k-1$, β should be less than unity. An estimate of Agarwal's β can be achieved by examining his β for cycle 2, which is

$$\beta_2 = \mathbf{g}_0'^T\mathbf{g}'_0 / \mathbf{g}_1'^T\mathbf{g}'_1. \quad (21)$$

As before, the parameters after cycle 1 should be closer to the minimum than the starting parameters, resulting in $\beta_2 > 1$. This value results in the undesirable outcome that the previous cycle's direction is considered more important than the direction calculated from the current parameters. This now explains why Agarwal found it necessary to place an empirical upper limit of 0.4 on β. The value of β calculated with (19) typically falls between 0.5 and 0.9. The empirical value of 0.4 falls closer to the typical value than either setting β to zero [and using (7)] or using the equation of Agarwal (1978).

7. Some comparisons

Parallel-refinement runs were performed to compare the convergence properties of the four types of function minimization described in the text. These methods are steepest descent (SD), conjugate gradient (CG), diagonal approximation to the normal matrix (also called 'gradient over curvature' or GC) and the new conjugate-direction (CD) method. The test structure was the thermolysin–phosphoramidon inhibitor complex (Weaver, Kester & Matthews, 1977) using data collected between 20 and 2.3 Å resolution (a total of 13 730 reflections). The starting model was the 'native' coordinates of thermolysin (Holmes & Matthews, 1982) with a crude phosphoramidon model appended and displaced solvent atoms removed. The starting model, which contained a total of 2637 atoms, was known to contain a number of errors. The initial R factor was 21.7%.

Refinement was carried out using the *TNT* refinement package (Tronrund, Ten Eyck & Matthews, 1987), modified to include the new conjugate-direction method as an option. [The crystallographic portions of the diagonal elements of the normal matrix were calculated by the method of Agarwal (1978)]. All four methods were run with the thermal parameters held constant because the refinement methods that do not use curvatures cannot simultaneously vary both positional and thermal parameters. Separate tests were made to compare GC and CD refinement in which both positional and thermal parameters were allowed to change simultaneously. The only differences between these test runs were the set of parameters varied and the method used. All other aspects, such as weights, were identical. The results of these tests are displayed in Fig. 1.

The methods that use curvatures (GC and CD) are superior to the methods that do not (SD and CG). After 15 cycles of refinement, the conjugate-gradient run is similar to the 'gradient-over-curvature' method because the diagonal elements of the normal matrix for the positional parameters are all approximately equal and the conjugate-gradient method can accommodate their differences relatively quickly. However, this is not the case for all types of parameter; shifts in B factors that are numerically small

and numerically large have different effects on the value of the function.

The comparison between the run of gradient-over-curvature refinement and the run of conjugate-direction refinement in which both *XYZ* and *B* values were varied shows the clear superiority of the new method. The *R* factor of the model produced by 20 cycles of conjugate-direction refinement was 13.2% and still falling, with good geometry (bond-length r.m.s. error 0.027 Å and bond-angle r.m.s. error 3.5°).

The reason the new method produces a lower value for $f(\mathbf{x})$ is not because the other methods are stuck in higher local minima. For the conjugate-gradient or the conjugate-direction methods to work they must be close enough to a minimum that the higher-order terms of the Taylor-series expansion are insignificant. Each method will proceed to the minimum of the expansion, which is the local minimum. That minimum is the same for the two methods because the function itself is unchanged, only the set of directions to be searched has been altered by the new method. Eventually, the conjugate-gradient or steepest-descent method will descend as low as the conjugate-direction method; it will simply take many more cycles to get there. Fig. 1 shows that after 20 cycles even the new method has not reached a minimum. Methods with even greater power of convergence should be able to produce parameter sets where $f(\mathbf{x})$ is even lower, using affordable amounts of computer time.

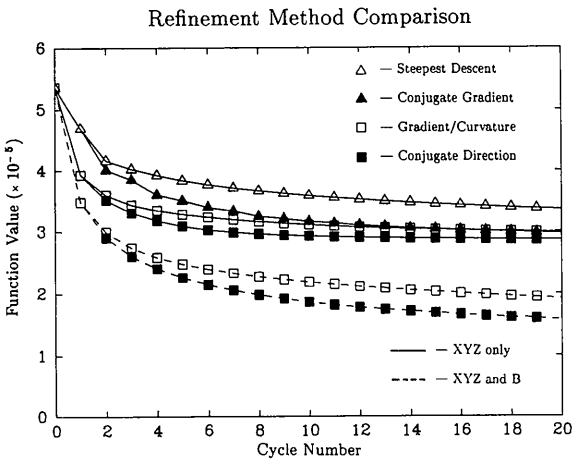

Fig. 1. The drop in the value of the function that is minimized in refinement over 20 cycles of refinement. Four different methods of minimization are compared. In some test runs (solid lines) only the positional parameters were varied while in the rest (broken lines) both the positional and thermal parameters were varied. The function is $\sum [F_o(hkl) - F_c(hkl)]^2$ after the F_o's and F_c's have been scaled to each other, plus the sum of the geometry deviation terms. The methods represented with triangles required 18.5 min of CPU time per cycle on a VAX 3600 computer. The methods represented with squares required the additional calculation of curvatures and took 22 min per cycle. This plot demonstrates that the conjugate-direction method produces a lower function value for a given number of cycles of refinement.

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