



CCP4 NEWSLETTER ON PROTEIN CRYSTALLOGRAPHY

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Contents

1. [News from CCP4](#)
Peter Briggs, Martyn Winn, Sue Bailey, Alun Ashton, David Brown, Charles Ballard
2. [SC: measuring shape complementarity at protein-protein interfaces](#)
Mike Lawrence
3. [ANISOANL - analysing anisotropic displacement parameters](#)
Martyn Winn
4. [LAPACK in CCP4 4.1](#)
Peter Briggs
5. [A System for storing Annotated Diffraction Data](#)
John Badger
6. [CCP4 Molecular Graphics](#)
Liz Potterton
7. [ARP/wARP goes CCP4i](#)
Anastassis Perrakis, Liz Potterton and Victor Lamzin
8. [Vector-Search Methods in Molecular Replacement](#)
Carmen Álvarez-Rúa, Javier Borge and Santiago García-Granda
9. [MAPSLICER: an interactive viewer for contoured map sections](#)
Peter Briggs
10. [Protein Crystallography Specialist Users Group Meeting](#)
Pierre Rizkallah
11. [Maximum-Likelihood Refinement of Atomic Models using Least-Squares Criterion](#)
P. Afonine, V.Y. Lunin and A. Urzhumtsev
12. [CCP4i Chart Interface](#)
Paul Emsley
13. [Efficient calculation of the exact matrix of the second derivatives](#)
Alexandre G. Urzhumtsev and Vladimir Y. Lunin
14. [Reports from the Daresbury Protein Crystallography Data Collection Workshop](#)
Liz Duke and Jasveen Chugh
15. [Improvement of noisy maps by bulk solvent correction](#)
A. Fokine and A. Urzhumtsev
16. [Multiple rotation function](#)
L. Urzhumtseva & A. Urzhumtsev
17. [An Open Source Multi-purpose Programming Environment for Macromolecular Crystallography](#)
Thomas Hamelryck and Morten Kjeldgaard
18. [Recent improvements to Mosflm - version 6.11](#)
Harry Powell

19. [Recent CCP4BB Discussions](#)
Maria Turkenburg
20. [CCP4/Max-INF Workshop on Refinement and Validation of Macromolecular Structure](#)
Eleanor Dodson

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[CCP4 Main Page](#) 

[Newsletter contents...](#) 

Efficient calculation of the exact matrix of the second derivatives

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1. Introduction

Recently, several groups (Murshudov *et al.*, 1997; Templton, 1999; Tronrud, 1999) reported some advances in calculation of an approximate matrix of the second derivatives (Hessian or normal matrix) for crystallographic criteria which, in particular, is used in optimisation methods. In fact, the gradient methods need only the product of this matrix by a given vector which can be calculated rapidly and directly, without explicit matrix calculation (Lunin & Urzhumtsev, 1985). The second-order minimisation methods need an inverted Hessian matrix with an inversion being very sensible to approximations; as a consequence, algorithms for the calculation of the *exact* Hessian matrix [H] must be developed in this case. Moreover, it is important to know to calculate such matrix for combined minimisation criteria, with a mixture of different structure-factor depending criteria (crystallographic criterion in what follows), geometric criteria and others. This knowledge can influence the choice of the optimisation methods which vary in computation time per iteration, in the number of iterations necessary to arrive to a similar result, and in radius of convergence.

The direct calculation of the normal matrix of a crystallographic criterion needs of order of MNI operations (derivative of the contribution of every reflection with respect to every couple of parameters). Here N is the number of atomic parameters, M is the number of structure factors. In order to gain CPU time, some authors use a sparse matrix (Sussman *et al.*, 1977; Hendrickson & Konnert, 1980; Dodson, 1981; Guillot *et al.*, 2001). To estimate the full matrix of the second derivatives for the weighted least-squares fit of the magnitudes Templton (1999) suggested a statistical approach. Murshudov *et al.* (1997) and Tronrud (1999) developed the FFT technique suggested for this goal by Agarwal (1978). In particular, in the case of atomic parameters \mathbf{q} as independent variables, Tronrud (1999) proposed a practical algorithm which needs

$$T_{HT} = C_1NI + C_2M \ln M \quad (1)$$

operations to calculate the principal part of the matrix [H]

$$\sum_{\mathbf{h}} w(\mathbf{h}) \frac{\partial |F(\mathbf{q}, \mathbf{h})|}{\partial q_j} \frac{\partial |F(\mathbf{q}, \mathbf{h})|}{\partial q_k} \quad (2)$$

traditionally neglecting the second term

$$\sum_{\mathbf{h}} w(\mathbf{h}) [|F(\mathbf{q}, \mathbf{h})| - F_0(\mathbf{h})] \frac{\partial^2 |F(\mathbf{q}, \mathbf{h})|}{\partial q_j \partial q_k} \quad (3)$$

Similar formulae were derived by Murshudov *et al.* (1997) for the case of the maximum likelihood criterion. At the same time, the use of Fast Differentiation Algorithm (Baur & Strassen, 1983; Kim *et al.*, 1984; for crystallographic applications see Lunin & Urzhumtsev, 1985) allows to calculate rapidly the *exact* matrix of the second derivatives with respect to atomic parameters for both these criteria and to generalise this result for other cases.

2. Fast Differentiation Algorithm and crystallographic refinement

Traditionally, it is considered that the gradient methods are much more time consuming than the methods without derivatives, and that generally every computation of a gradient needs about N times CPU more than a single value of the function, N being the number of variables. However, several groups (*e.g.*, Baur & Strassen, 1983; Kim *et al.*, 1984) have shown the following result and its conclusions:

Fast Differentiation Algorithm (FDA)

For any function of N variables, calculation of a single value of which takes the time T , an algorithm exists to calculate its *exact* gradient faster than in $4T$ *independently on the number N of variables.*

FDA : Conclusion 1

For any function of N variables, calculation of a single value of which takes the time T , an algorithm exists to calculate its *exact* derivative along a given direction faster than in $4T$ *independently on the number N of variables and without a gradient calculation.*

FDA : Conclusion 2

For any function of N variables, calculation of a single value of which takes the time T , an algorithm exists to calculate the *exact* product of the matrix of the second derivatives by a given direction faster than in $20T$ *independently on the number N of variables.*

In practice, when some common expressions can be saved in memory, the time to calculate all 4 objects, namely the function f itself, its gradient ∇f , the function derivative along a given direction \mathbf{s} and the product $[\mathbf{H}]\mathbf{s}$ of the Hessian matrix $[\mathbf{H}]$ by the same direction, can be estimated rather by $4T$ where T stands for the time of a single calculation of the function value (Urzhumtsev *et al.*, 1989).

FDA shows that the crucial point in the fast optimisation of crystallographic functional is a fast calculation of structure factors. A fast way of their calculations (Sayre, 1951; Ten Eyck, 1977)

needs about

$$T_f = C_1 N + C_2 M \ln M \quad (4)$$

operations (C_1 and C_2 are some constants), instead of CNM operations for a direct calculation.

FDA gives the same amount of operations for the gradient calculation being applied to a least-squares criterion depending on atomic parameters (Lunin, 1978, unpublished; Lifchitz, in Agarwal, 1981) or to other crystallographic criteria (Lunin & Urzhumtsev, 1985; Urzhumtsev *et al.*, 1989).

Moreover, because the n -th column of the matrix $[H]$ of the second derivatives represents the product of this matrix by the direction $(0, 0, \dots, 0, 1, 0, \dots, 0)$ where 1 is in the n -th position, the whole *exact* matrix of the second derivatives composed from N columns can be calculated by

$$T_{HE} = C_1 N I + C_2 N M \ln M \quad (5)$$

operations. However, a faster and more general way to calculate the exact Hessian matrix can be suggested.

Let a function $R(y_1(x_1, \dots, x_N), \dots, y_M(x_1, \dots, x_N))$ depend on M variables y_1, \dots, y_M with every y_m depending in turn on N variables x_1, \dots, x_N . The chain rule formula:

$$\frac{\partial^2 R}{\partial x_j \partial x_k} = \sum_m \sum_n \frac{\partial^2 R}{\partial y_m \partial y_n} \frac{\partial y_n}{\partial x_k} \frac{\partial y_m}{\partial x_j} + \sum_m \frac{\partial R}{\partial y_m} \frac{\partial^2 y_m}{\partial x_j \partial x_k} \quad (6)$$

can be rewritten as

$$\Delta_x R = [dy/dx] [\Delta_x R] [dy/dx]^T + [\Delta_x y] \nabla_y R \quad (7)$$

Here $[\Delta_x y]$ is a tensor composed of M matrices $[\Delta_x y_1], [\Delta_x y_2], \dots, [\Delta_x y_M]$. If the gradient $[\nabla_y R]$ is supposed to be known (the calculations are carried out accordingly to the FDA) then the operations needed to get $[\Delta_x R]$ are the operations to calculate the matrix products in (7) plus those to calculate $[\Delta_x y]$

Formula (7) can be simplified for a number of special cases.

Special case 1: If the criterion R is additive, *i.e.* can be presented by a sum of individual contributions, not necessarily quadratic, from the components of the vectors y

$$R(y) = \sum_m f(y_m) \quad (8)$$

then the matrix $[\Delta_y R]$ becomes diagonal. An example is the least-squares fit of the calculated data to the experimental ones.

Special case 2: When the variables y depend linearly on the variables x , $y = [A] x$, the second

term in the formula is absent and (7) becomes

$$\Delta_{\mathbf{x}}\mathbf{R} = [\mathbf{A}][\Delta_{\mathbf{x}}\mathbf{R}][\mathbf{A}]^T \quad (9)$$

An example of such linear dependence is the relation between the electron density and its structure factors.

Special case 3: Quite often variables \mathbf{x} contribute to variables \mathbf{y} locally, i.e. each of x_1, x_2, \dots, x_N contribute only to a small number C_y of variables y_k , $C_y \ll M$. Complementary, every y_k may depend only on a small number of C_x parameters x_j , $C_x \ll N$. The matrix $[\mathbf{dy} / \mathbf{dx}]$ becomes sparse giving an essential reduction in the number of calculations. An example of such dependence is the calculation of any field (e.g., an electron density) from an atomic model where atoms have a limited radius of contribution and are separated each from others.

It is easy to see that the calculation of normal matrix for crystallographic criteria can profit the features of all particular cases discussed above and it can be shown that the total amount of operations necessary to calculate the exact matrix of the second derivatives of the crystallographic least-squares criterion with respect to the atomic parameters is

$$T_{\text{HC}} = C_1M + C_2M \ln M + C_3NI \sim C_{12} M \ln M + C_3NI \quad (10)$$

where C_1, C_2, C_3 and C_{12} are some constants which do not depend neither on the number of structure factors M nor on the number of atoms N . This estimate is the same as (1) for an *approximate* matrix where the second-order terms $\partial^2 f^2 \mathbf{R} / \partial \mathbf{F}^2$ are neglected from the beginning and is better than (5) which is obtained for the *exact* matrix by simple N -times calculation of the product of a matrix by a direction following a coordinate axis.

The same amount of operations is enough to calculate the matrix for the intensity least-squares criterion (Sheldrick & Schneider, 1997), for the phase criterion (Lunin & Urzhumtsev, 1985; Pannu *et al.*, 1998), for the maximum likelihood criterion (Bricogne & Irwin, 1996; Pannu & Read, 1996; Read, 1997; Murshudov *et al.*, 1997; Pannu *et al.*, 1998).

In the general situation when the criterion cannot be represented by a sum of contributions from many small subsets of structure factors, the total number of computer operations becomes :

$$T_{\text{HG}} = C_6MI \ln M + C_3NI \quad (11)$$

If the independent parameters are not atomic ones (e.g., parameters for a rigid groups refinement), the matrix with respect to independent parameters can be calculated in the same way.

3. Direct calculation of the inverted Hessian matrix

The formula (7) gives also an idea that for some special cases the inverted matrix of the second derivatives can be obtained directly without calculation the Hessian matrix itself. Indeed, if the transformation $\mathbf{y}(\mathbf{x})$ is linear, $\mathbf{y} = [\mathbf{A}] \mathbf{x}$, then

$$[\Delta_{\mathbf{x}}\mathbf{R}]^{-1} = [\mathbf{A}^{-1}]^T [\Delta_{\mathbf{y}}\mathbf{R}]^{-1} [\mathbf{A}^{-1}] \quad (12)$$

If $[A]$ corresponds to the Fourier transformation, the inverse operation is the inverse Fourier transform for which the matrix $[A^{-1}]$ can be written immediately. The matrix $[\Delta_{\mathbf{r}}R]^{-1}$ can be easily calculated for many crystallographic criteria, in particular for such important criteria as the least-squares or maximum likelihood functionals. Therefore, when the independent parameters are density values at the grid points the inverse Hessian matrix can be easily and directly calculated for these criteria as

$$[\Delta_{\mathbf{r}}R] = \begin{pmatrix} u(\mathbf{r}_1 + \mathbf{r}_1) & u(\mathbf{r}_2 + \mathbf{r}_1) & \dots & u(\mathbf{r}_K + \mathbf{r}_1) \\ u(\mathbf{r}_1 + \mathbf{r}_2) & u(\mathbf{r}_2 + \mathbf{r}_2) & \dots & u(\mathbf{r}_K + \mathbf{r}_2) \\ \dots & \dots & \dots & \dots \\ u(\mathbf{r}_1 + \mathbf{r}_K) & u(\mathbf{r}_2 + \mathbf{r}_K) & \dots & u(\mathbf{r}_K + \mathbf{r}_K) \end{pmatrix} \quad (13)$$

where all elements of the matrix (13) are presented by the same function calculated as a Fourier series at different points \mathbf{r} . In order to calculate this function at a grid compatible with the number of Fourier coefficients M , estimating $K \sim M$, the number of operations needed is about $C_2 M \ln M$ (Cooley & Tukey, 1965; Ten Eyck, 1973). This results shows that the minimisation methods of simple iteration, usually applied for density modification procedures, can be replaced not only by the gradient methods (Sayre, 1972, and Sayre & Toupin, 1975, for the particular Sayre criterion; Lunin, 1985, for the general case) but even by the methods of the second order. In this case the computational expenses are practically the same as those for the simple iteration methods.

4. Conclusion

In the case of the crystallographic least-squares or maximum likelihood refinement of atomic model, the *exact* matrix of second derivatives can be calculated by

$$T_{\text{HC}} = C_{12} M \ln M + C_3 N I \quad (14)$$

Operations where M is the number of structure factors, N is the number of atomic parameters and C_{12} and C_3 are some constants which do not depend neither on M nor on N . This algorithm suggests step-by-step recalculation of the matrix with respect to variables of different levels of the molecular models (structure factors, density, atomic parameters etc.). The same iterative calculations are basic steps for the fast gradient calculation (Lunin & Urzhumtsev, 1985). It should be noted that such way of calculation allows easily to add the contribution from any other criteria of the same type or of any other type of models, *e.g.*, phase criterion, stereochemical criteria, criteria depending on the electron density etc. Therefore, the formulae which give the expression of the gradient (or of the Hessian matrix) of a crystallographic criterion directly in terms of atomic parameters can be useful for understanding but may be rather misleading algorithmically.

The full material with details of corresponding derivations will be reported elsewhere (paper in preparation for *Acta Crystallographica*).

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[Newsletter contents...](#)

