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A trigonometric minimum model for refinement

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Refinement of model parameters against observed diffraction data is a widely used technique across many specializations of crystallography. In most cases gradient-driven minimization is employed, usually in combination with exact or approximate second derivatives. Ultimately, such methods are variations of Newton's method for iterative root finding and assume a quadratic model around the minimum. The parameter adjustments d in each iteration are determined as the ratios of 1st and 2nd derivatives: $d = -f'/f''$, where f is the function to be minimized. While the success of this approach is evident through the innumerable results it has produced, it is obviously handicapped by singularities if f'' approaches zero. In such cases naïve use of Newton's method leads to overestimated, unfeasible parameter adjustments. Consequently, all practical minimization algorithms include shift damping, line search, or trust region methods to achieve numerical stability.

A systematic inspection of crystallographic target functions commonly used in the refinement of atomic coordinates reveals that near-zero or negative 2nd derivatives occur systematically, well within the convergence radius. We observe that in this context a trigonometric (sine or cosine) function is always a better fit to the shape of the minimum, compared to the quadratic model underlying Newton's method. The trigonometric minimum model leads to the formula $d = -w/\pi \arctan(\pi/w\, f'/f'')$ for the estimate of the parameter adjustment. This function is free of singularities; computer implementations use atan2(). By design the maximum shift length is w, which is the half-width of the minimum.

The trigonometric minimum model allows us to achieve numerical stability by injecting easily obtainable prior knowledge into the minimization procedure, through the parameter w. We will report results of systematically comparing conventional minimizations with minimizations using the trigonometric minimum model.

Keywords: refinement, Newton's method, knowledge-based approach

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Fragment-based interpretation of crystallographic low-resolution electron density maps: a case study

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In this study we use the program MOLREP [1] to rapidly screen plausible molecular fragments into the electron density and attempt to improve the sensitivity of the scores from MOLREP by evaluating the real space map correlation coefficient (map-cc). We conduct systematic study on the effect of data resolution, experimental phases, model quality and fragment shape on the success of automatic map fitting from 4 to 10 Å resolutions. We show that although a low-resolution electron density map has much ambiguity, a fragment-based approach can provide a plausible structural model that can infer biological function. Here we use the complexes of Rabex-5-ubiquitin [2], and demonstrate that the unique mode of ubiquitin binding can still be correctly placed, consistent with the conclusion drawn from the original structure determined at a higher resolution. Finally we quantify the effectiveness of the scores in classifying the solution as in the real-life scenario where the solution is unknown. We conclude that the extension of MOLREP with map-cc could empower structural biologists to interpret experimental electron density at as low as 10 Å with plausible models.

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Advances in the ab initio VLD phasing algorithm

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The ab initio VLD phasing algorithm is based on the properties of a new difference Fourier synthesis and allows the recovery of the correct structure starting from a random model working in the correct space group. New coefficients for the difference electron density $\rho_q = \rho - \rho_p$ have been obtained by using the joint probability distribution function $P(E, E_p, E_q)$, where E and E_p are the normalized structure factors of the target and of a model structure [1]: they are the sum of the classical difference term $(mF\text{-}DF_p)$ with a flipping term, depending on the model and on its quality. The new phasing algorithm does not require the use of structure invariants and semi-invariants. The first application of this algorithm to a large set of small-molecule structures allowed to verify the suitability of this new approach [2]. Then the structural complexity range of the applications was extended to medium-size molecules and to proteins, provided the data have atomic resolution: the VLD algorithm is able to provide at the end of the procedure molecular models that are automatically interpreted in a chemical sense [3].

To improve the efficiency of the algorithm we modified the approach described in the previous papers by integrating it with *RELAX* procedure [4],[5] to translate molecular fragments correctly oriented but incorrectly located. The new procedure has been implemented in SIR2011, the future release of the package SIR, and it has been checked on a large set of small-medium size structures and on proteins.

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Macromolecular High-Resolution Data Evaluated by Invariom Refinement

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