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Indium(III) complexes within the protein crystal after HipHop Refinement

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The structure of tetragonal hen egg-white lysozyme soaked in $InCl_3$ solution has been determined to a resolution of 1.43 Å and refined isotropically to the final value of R =14.21. Structures of complex anions *cis*-dichloro-*cis*-dihydroxo-$[InCl_2(OH)_2(H_2O)_2]^-$, *cis*-dichloro-*cis*-dihydroxo-$[InCl_2(OH)_2(H_2O)(OD2\ Asp\text{-}18)]^{2-}$ and *trans*-dichloro-*trans*-dihydroxo-$[InCl_2(OH)_2(O\ Leu\text{-}129)_2]^{3-}$ have been described. These anions differ from products of hydrolysis of $InCl_3$ in water described in other X-ray diffraction studies [1]. The structure has been refined by a novel multisolution HipHop refinement method [2] exploring the conformational landscape by modification of the phases by introduction of water molecules into the model, followed by automated SHELXH refinement [3] and removal of water molecules that do not comply with a minimal electron density, ball shape and a distance from protein. Programs used are available free on http://www.img.cas.cz/hiphop.

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The Patterson deconvolution method for the ab-initio structure solution of large proteins

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Standard tools for the *ab-initio* structure solution of macromolecules diffracting at atomic or quasi-atomic resolution consist of direct methods combined with direct-space refinement procedures. This strategy, which includes both reciprocal- and direct-space techniques, has an effective counterpart represented by Patterson techniques, such as Patterson superposition or vector-search methods. They operate uniquely in direct space and, though developed before direct methods, have been basically underutilized. We have recently revisited the Patterson deconvolution method based on the use of the superposition minimum function [1], which has been successfully applied to the automated *ab-initio* crystal structure solution of proteins [2]. An improved version of this procedure, particularly devoted to the *ab-initio* solution of large proteins at atomic and quasi-atomic resolution, is presented. It makes use of specific filtering algorithms which:

1) operate on the Patterson map in order to eliminate false peaks and the intensity modulation introduced by the ripples surrounding the origin peak;
2) operate on the electron density map in order to reduce the residual Patterson symmetry (centro-symmetry and semin-variant symmetry).

The tools used for filtering consists on both the superposition of one or more Patterson maps to the actual electron density map and the active use of the synthesis

$$FF(\mathbf{u})=V^{-1}\sum_{h} F_h F_h \exp(-2\pi i \mathbf{hu})$$

which provide information about the presence of an inversion centre. The Patterson method is coupled to an improved direct-space refinement, consisting of electron density modification cycles where weight estimates are derived by the method of joint probability distribution functions. The new approach has been implemented in the SIR2006 program and tested on a large set of known protein structures. It proved to be extremely efficient and very rapid in solving proteins containing heavy-atoms and diffracting at atomic resolution, even if they have up to 5000 non-hydrogen atoms in the asymmetric unit. Structures with heavier atom up to Calcium and/or diffracting at resolution up to 1.6Å turn out to be more resistant, even if the results overcome those obtained by the previous direct methods approach. The Patterson approach proved to be nearly independent on the structural complexity and it is able to push further the size limit of the macromolecular structures solvable *ab-initio*.

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