s3.m2.p3 **Maximal Likelihood refinement. It works, but why?** V.Y.Lunin, A.G.Urzhumtsev, *Institute of Mathematical Problems of Biology, RAS, Pushchino 142290 Russia; LCM³B, Facultés des Sciences, Université Henri Poincaré, Nancy I, France.*
Keywords: likelihood, structure refinement, macromolecules.

Last years the so called maximal likelihood refinement (ML-refinement) had been proven as a useful tool, which significantly extends the possibilities of refinement. Nevertheless, the reasons for this success are not well explained yet and are worthy of discussion.

The goal of the conventional structure refinement may be formulated as to find ***the structure*** possessing of structure factor (s.f.) magnitudes which are ***as close as possible*** to the observed magnitudes. Opposite, the goal of ML-refinement is not to find the final structure, but to find a ***raw model*** which provides with the maximal chance to improve it by small modifications to the ***full agreement*** with the observed magnitudes.

This goal of the conventional refinement seems to be quite reasonable when the model is complete and the X-ray experiment is precise so that the s.f. magnitudes calculated with the use of the full set of exact atomic coordinates are equal to the corresponding observed values. The goal is not so evident in some other cases, for example, when the current model is incomplete. In such situations the s.f. magnitudes calculated with the exact coordinates of partial model atoms are not equal, in general, to the observed magnitudes, but differ from them in unknown quantities corresponding to the absent atoms. So, the conventional refinement fits the calculated s.f. magnitudes to inappropriate values. While the atoms in the correct atomic positions for a part of structure do not allow to reproduce the observed structure factor magnitudes correctly, their exist a chance to get these values if the absent atoms are added to the model with randomly chosen coordinates. One can expect that it would be less chance to reproduce the observed magnitudes correctly when the randomly chosen atomic positions are added to a wrong partial model than to the exact one. Therefore, it seems reasonable to look for the partial model coordinates which provide maximal probability to improve the model when generating the coordinates for absent atoms randomly. Such idea is nothing but the maximal likelihood principle.

It is possible to show that the ML-refinement may be considered as an attempt to fit the calculated (from an incomplete model) structure factors magnitudes to some modified experimental magnitudes. The modification consists in reduction of values of structure factor magnitudes: week magnitudes becomes zeros while others decrease their values. The cut-off level and the degree of reduction depend on the partial model quality. If the current model is good then the modified magnitude values are close to the observed ones and ML-refinement is reduced to the conventional refinement.

s3.m2.p4 **Use of collective variables to model anisotropic displacements; implementation in the macromolecular refinement program REFMAC.** M.D. Winn[1], M. Isupov[2] and G.N. Murshudov[1,3]. [1]*Daresbury Laboratory, Daresbury, Warrington, WA4 4AD.* [2]*Dept of Chemistry and Biological sciences,University of Exeter,Exeter.* [3]*Chemistry Department, University of York, Heslington, York, YO1 5DD. Correspondence e-mail: m.d.winn@dl.ac.uk*
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An essential step in macromolecular refinement is the selection of model parameters which give as good a description of the experimental data as possible, while retaining a realistic data to parameter ratio. This is particularly true of the choice of atomic displacement parameters where the move from individual isotropic to individual anisotropic refinement involves a six-fold increase in the number of required parameters. Thus, at medium resolution, while the effects of anisotropic displacements may be significant, it is not possible to model them with individual anisotropic displacement parameters.

The number of refinement parameters can be greatly reduced by using collective variables rather than independent atomic variables, and one of the simplest examples of this is the TLS parameterisation for describing the translation, libration and screw-rotation displacements of a pseudo-rigid body[1]. Refinement of TLS parameters has been implemented in the maximum likelihood refinement program `REFMAC`. Use of a previously implemented FFT procedure[2] means that TLS refinement is fast and convenient.

We describe the implementation of TLS refinement in `REFMAC` and give examples of its use. In particular, we have studied cases where a small number of TLS groups have been used to model the anisotropy of whole molecules or domains. With 20 refinement parameters per group, this means that the number of extra parameters required is of the order of 100, but nevertheless reductions in the free-R factor of several percent are found. Additionally, differences in displacement parameters between NCS-related molecules are accounted for well by the TLS parameterisation.

The methodology of refining collective parameters rather than atomic parameters can be used more generally, provided the eigenvectors relating the collective variables to the atomic variables are known. One possible set of eigenvectors can be found by diagonalising the Hessian of a simplified force field for the molecule in question or for subsets of that molecule (the normal modes corresponding to the chosen force field). Preliminary results from such refinements will be presented.

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