FAST COMMUNICATIONS

On the *ab initio* phase determination by maximum entropy

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Abstract. In spite of some results reported recently, numerical and theoretical work still indicates that entropy alone is not, in general, a reliable figure of merit to select phases in the *ab initio* problem.

Discussion. In their article, Sjölin, Prince, Svensson & Gilliland (1991) (SPSG hereafter) suggest that 'the total entropy of a map is an extremely powerful figure of merit for the choice of phases in macromolecular structures'. On the other hand, previous experience with small-crystal and macromolecular data indicates that such a statement is not in general true (Bryan & Banner, 1987; Navaza, 1985, 1986). The discrepancy may have its origin in the definition of the domain of starting phases: in SPSG only 32 sign combinations were explored, among the 2^{16} possible ones for the starting 16 centric reflections. It may then be argued that the authors have been performing phase refinement and extension instead of *ab initio* phasing, a less difficult problem where it was found that entropy methods could be fruitfully applied (Podjarny, Moras, Navaza & Alzari, 1988; Navaza, 1986). A more fundamental reason, however, can be ascribed to the mathematical procedure described in SPSG, which precludes a correct exploration of the domain of possible phases of the structure factors.

The trouble comes with the phases φ appearing in equation (5) in SPSG, which expresses the maximum entropy map $m(\mathbf{r})$ as a function of the *real* Lagrange multipliers ν. Using a slightly different notation, we write their formula as

$$m(\mathbf{r}) = \exp\left[\sum_{\mathbf{h}\in H} \nu_{\mathbf{h}}\exp(i\varphi_{\mathbf{h}})\exp(-2\pi i\mathbf{h}\mathbf{r})\right]. \quad (1)$$

H denotes the set of reciprocal vectors corresponding to the fitted reflections and $\varphi_{\mathbf{h}}$ the phase of the Fourier coefficient $F(\mathbf{h})$ of $m(\mathbf{r})$.

Equation (1) is valid in the *ab initio* case; the phases φ are functions of the ν's: they are the *result* of an *unconstrained optimization* problem with respect to the Lagrange multipliers. Consequently, the Hessian matrix must take into account the variations of the φ's with respect to the ν's. This Hessian turns out to be indefinite and the *ab initio* problem has, as expected, several solutions.

On the other hand, if the phases of the structure factors are available (trial phases or inferred from any prior information), then the Lagrange multipliers are complex variables λ and, instead of (1), we have

$$m(\mathbf{r}) = \exp\left[\sum_{\mathbf{h}\in H} \lambda_{\mathbf{h}}\exp(-2\pi i\mathbf{h}\mathbf{r})\right]. \quad (2)$$

If the data are consistent, the optimization problem has now a unique solution. In other words, for given phases and moduli of the structure factors, there is a unique set of λ's whose associated map, given by (2), has Fourier coefficients agreeing with the data. Again, the λ's are the *result* of an *unconstrained optimization* problem and cannot be forced to take prescribed values (except of course the restrictions imposed by the space-group symmetry).

By contrast, the procedure described in SPSG consists in working with (1) instead of (2), assuming that the φ's are given, and in driving the real numbers ν to *fit the moduli* of the observed structure factors. Comparing (1) with (2), we see that the φ's should be the phases of the λ's – which are not known in advance. As a result, this hybrid formulation presents several inconsistencies. In particular, it is easy to show that uniqueness of the solution, as claimed in SPSG, precludes the existence of different maps, hence different entropies of the maps, for the different possible values of the centric phases ($\varphi = 0$ or π). Indeed, let $\{\nu(\varphi)\}$ be the optimal Lagrange multipliers

associated with a given set of phases $\{\varphi\}$; then, if we change $\varphi_\mathbf{h}$ to $\tilde{\varphi}_\mathbf{h} = \varphi_\mathbf{h} + \pi$ for an arbitrary number of reflections, the corresponding optimal $\nu_\mathbf{h}(\tilde{\varphi})$ will simply be $-\nu_\mathbf{h}(\varphi)$; this is clear from (1), which also tells us that the map $m(\mathbf{r})$ is unchanged, in contradiction with the results presented in SPSG. Thus, either the optimization problem described in SPSG is correct and there is a unique solution, independent of any sign combination, or there are several solutions and the algorithm of SPSG is not correct. In this latter case, the true Hessian matrix *cannot* be positive definite and *cannot* be given by equations (7) to (10) in SPSG (we recall that a function whose matrix of second derivatives, *i.e.* the Hessian, is everywhere positive semidefinite has at most one minimum). In any case, the procedure is not appropriate to explore the domain of possible phases of the structure factors.

The *ab initio* problem in crystallography is a very difficult one indeed. The Lagrangian approach by maximum entropy, already developed by Navaza (1985, 1986), has been given a firm mathematical basis: both for the statistical aspect (Gamboa, 1989; Dacunha-Castelle & Gamboa, 1990) and for its formulation as an optimization problem (Borwein & Lewis, 1991; Decarreau, Hilhorst, Lemaréchal

& Navaza, 1991). To find a point where the gradient of the entropy with respect to the phases vanishes is a relatively easy task (given the available software); but the real numerical issue is to have a local maximum, *i.e.* a negative definite Hessian – quite another problem! All our experiments have unambiguously indicated that the entropy of a map is not a reliable figure of merit.

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LETTERS TO THE EDITOR

Contributions of a scientific nature intended for this section should be submitted to the Editor or any of the Co-Editors of Acta Crystallographica *or* Journal of Applied Crystallography.

X-ray anomalous-dispersion data and biomacromolecular crystal structure reports

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X-ray anomalous scattering has been playing an ever increasing role in structural crystallography during the last four decades (Bijvoet, Burgers & Hägg, 1969; Srinivasan, 1972; Ramaseshan & Abrahams, 1975). The need for careful preservation of intensity (or amplitude) data on *Bijvoet pairs* that may be collected through diffractometry or any other mode of collection and for the data to be available in suitable form in order to be able to extract $F(H)$ and $F(\bar{H})$ values individually was emphasized earlier (Srinivasan, 1970). With the advent of synchrotron radiation this aspect assumes, all the more, high importance since λ tunability enables larger values of the dispersion components f' and f'' to be realized (*e.g.* see Templeton & Templeton, 1990). The type of 'core structure' determination demonstrated for tartaric acid (Srinivasan & Chacko, 1967; Srinivasan, 1976) has been found useful for the location of S atoms in the case of a protein structure (Sheriff

& Hendrickson, 1987), by first locating a heavier anomalous scatter (Fe). This also points to the possibility of a reductionistic approach to phase solution in protein crystallography since, from Bijvoet differences, the smaller set of anomalous scatters can be located, which can possibly act as the nucleus for enlarging the structure to the full protein. The anisotropic behaviour of dispersion effects (Templeton & Templeton, 1990) is also representable by this approach.

Apart from the above essentially unique solution to the phase problem by the single-wavelength anomalous-dispersion (SWAD) technique (Srinivasan & Chacko, 1970; Karle, 1985), extension to two wavelengths (Srinivasan & Chacko, 1970) and multiple-wavelength anomalous-dispersion (MAD) techniques (*e.g.* see Fourme & Hendrickson, 1990) hold promise in macromolecular crystallography. Study of finer variation in λ-dependent