surfaces and free energies of activation. Dauber & Hagler (1980) used crystal structures to parametrize the 'non-bonded' interactions or packing, nuclear repulsion and hydrogen bonding. Potentials or closely related probability distributions have been determined from databases also for packing calculations as a function of residue pairs (Singh & Thornton, 1990; Narayana & Argos, 1984; Gregoret & Cohen, 1990; Ponder & Richards, 1987) and for hydrogen bonding (Baker & Hubbard, 1984; Taylor & Kennard, 1984; Ippolito, Alexander & Christianson, 1990). Many other applications have also been published which testify to the growing recognition of the wealth and variety of information available from structural databases.

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The Phase Problem and its Relation to the Spin-Glass Problem

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Abstract

The maximum-entropy method of image reconstruction is discussed in the context of the crystallographic phase problem. Entropy is the function to be maximized in a space of phases which has dimension equal to the number of structure-factor constraints. The function $\int[1-\exp(-\rho/\rho_0)]\,dV$ is proposed as a suitable one. An analogy between the phase problem and the spin-glass problem of condensed-matter

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physics is discussed. This analogy has instigated a study of the geometry of the entropy surface in the space of unknown phases for a simple model and preliminary results are presented.

1. Introduction

The maximum-entropy method (Gull & Daniell, 1978) which has been studied for some time in other fields has recently attracted some interest in the context of the crystallographic phase problem (Narayan & Nityananda, 1981, 1982; Narayan, Nityananda & Vani 1983; Collins, 1982).

The technique involves the maximization of the 'entropy'

$$S=\int f[\rho(\mathbf{r})]\,\mathrm{d}V \qquad (1)$$

with respect to the unknown phases for fixed values of the structure amplitudes

$$|F_{\mathbf{H}}|=|(1/V)\int \rho(x,y,z)\exp[-i(hx+ky+lz)]\,\mathrm{d}x\,\mathrm{d}y\,\mathrm{d}z|.$$

f is some suitable real function of $\rho(\mathbf{r})$.

It has been shown (Narayan, Nityananda & Vani, 1983) that by maximizing the 'entropy' with respect to the unknown phases we obtain

$$\partial S/\partial\varphi_{\mathbf{H}}=(2/V)|F_{\mathbf{H}}||G_{\mathbf{H}}|\sin(\varphi_{\mathbf{H}}-\theta_{\mathbf{H}})=0,$$

where

$$G_{\mathbf{H}}=|G_{\mathbf{H}}|\exp(i\theta_{\mathbf{H}})=\int f'[\rho(\mathbf{r})]\exp(2\pi i\mathbf{H}.\mathbf{r})\,\mathrm{d}V.$$

We can write the vanishing of the gradient as

$$\varphi_{\mathbf{H}}=\theta_{\mathbf{H}} \quad \text{or} \quad \varphi_{\mathbf{H}}=\theta_{\mathbf{H}}+\pi. \qquad (2)$$

Using this property of the maximum-entropy solution we introduce in § 2 a maximum-entropy interpretation to direct methods. It has been noted (Narayan *et al.*, 1983) that when none of the phases are available the final map depends on the initial map and on the algorithm used. In § 3 we discuss the similarity between the problem in hand and the spin-glass problem. What these problems have in common is frustration which leads to a rich structure of extrema. In § 4 we perform a numerical analysis of the solution space in order to understand this behaviour. Finally, in § 5 we give the results of the analysis and summarize our conclusions.

2. What happens when 'entropy' is maximized

Two widely discussed proposals for the form of f in (1) are

(i) $f(\rho)=\ln(\rho)$

(ii) $f(\rho)=-\rho\ln(\rho)$,

where the arguments in favour of one or other form are based on combinatorial and/or probabilistic considerations.

In this paper we adopt the viewpoint that the maximum-entropy method is a variational technique of obtaining an electron-density map that agrees simultaneously with the observed amplitudes and with the physical constraints based on *a priori* knowledge of the characteristics of the density function. These physical constraints include positivity and atomicity, *i.e.* the density map has a flat baseline with peaks and takes positive values everywhere.

With this view, the conventional direct-methods approach to the phase problem can also be interpreted in the maximum-entropy framework as briefly explained below. [See also Bricogne (1984) for a somewhat different viewpoint.]

Cochran (1952) proposed that maximization of $\int\rho^3$ discriminates against negative electron density and encourages the formation of positive peaks.

Here $f(\rho)=\rho^3$ and $f'(\rho)=3\rho^2$.

Sayre (1952) observed that when the physical constraints on the density function are satisfied and the atoms are approximately equal and well resolved then the electron density is roughly proportional to its square, *i.e.* $\rho=k\rho^2$, which implies that the phase of ρ is like the phase of ρ^2. Thus the true map satisfies the maximization condition (2) for the function $\int\rho^3$ in the equal-atom case. Now,

$$\int\rho^3\,\mathrm{d}V=V\sum_{\mathbf{H}_1}\sum_{\mathbf{H}_2}|F_{\mathbf{H}_1-\mathbf{H}_2}F_{-\mathbf{H}_1}F_{\mathbf{H}_2}|\times\cos(\varphi_{\mathbf{H}_1-\mathbf{H}_2}+\varphi_{-\mathbf{H}_1}+\varphi_{\mathbf{H}_2}).$$

Maximization of $\int\rho^3$ involves satisfying the triplet relationships $\varphi_{\mathbf{H}_1-\mathbf{H}_2}+\varphi_{-\mathbf{H}_1}+\varphi_{\mathbf{H}_2}=0$.

We call the system frustrated if $\varphi_{\mathbf{H}_1-\mathbf{H}_2}+\varphi_{-\mathbf{H}_1}+\varphi_{\mathbf{H}_2}\neq 0$ for some $\mathbf{H}_1$, $\mathbf{H}_2$. The global maximum arises whenever $\varphi_{\mathbf{H}_1-\mathbf{H}_2}+\varphi_{-\mathbf{H}_1}+\varphi_{\mathbf{H}_2}=0$ for all $\mathbf{H}_1$, $\mathbf{H}_2$. The unfrustrated solution corresponds to the global maximum which will be $\varphi_{\mathbf{H}}=0$ for all $\mathbf{H}$, *i.e.* the modulus map. However, this is not our desired solution. Hence in order to arrive at the desired solution we make compromises by letting certain triplets remain unsatisfied. In general, it is not straightforward to establish which could be the best compromise, although several generations of rather successful direct-methods programs have emerged.

In the direct-methods approach [see Ladd & Palmer (1980) for a complete review] to the problem, the constraint $\int\rho^3=$ maximum is used to derive the tangent formula

$$\tan\varphi_{\mathbf{H}_1}=\frac{\sum_{\mathbf{H}_2}|F_{\mathbf{H}_2}F_{\mathbf{H}_1-\mathbf{H}_2}|\sin(\varphi_{\mathbf{H}_2}+\varphi_{\mathbf{H}_1-\mathbf{H}_2})}{\sum_{\mathbf{H}_2}|F_{\mathbf{H}_2}F_{\mathbf{H}_1-\mathbf{H}_2}|\cos(\varphi_{\mathbf{H}_2}+\varphi_{\mathbf{H}_1-\mathbf{H}_2})}.$$

To begin with, phase relationships are set up which become terms in the tangent formula. The strong reflections are selected and phases assigned to either a small number of them or to all reflections. New phases are determined and the complete set of phases refined using the tangent formula. Certain figures of merit are used to detect a correct solution and stop phase determination at that point.

However, the advantage of tackling the problem variationally is that one can think in real space. Also, one could think of suitable functions other than ρ^3 whose maximization incorporates higher-order invariants like quartets which are believed to be more powerful than just triplets.

The reason we have not in this work considered the customary functions $\int \log(\rho)$ and $\int -\rho \log(\rho)$ is that, for a general set of phases, ρ takes negative values and, as in Narayan *et al.* (1983), a constant should be added to ρ to make it positive. Hence, the function being maximized keeps varying. This is not suitable for our present purposes.

In this context we propose to examine another function, $S=\int [1-\exp(-\rho/\rho_0)]\,dV$, where ρ_0 is a value close to the baseline.

The motivation behind this function is as follows. Like ρ^3, the function 'punishes' negative values of ρ. Unlike ρ^3, the function does not 'reward' peaks once they grow much larger than the baseline. The parameter ρ_0 controls the 'reward and punishment' as explained later.

Here

$$f(\rho)=1-\exp(-\rho/\rho_0)$$
$$f'(\rho)=(1/\rho_0)\exp(-\rho/\rho_0).$$

On the true map, where ρ has flat baseline and peaks, $f'(\rho)$ has troughs corresponding to the peaks and flattened peaks corresponding to the baseline (Fig. 1). The condition (2) is satisfied (strictly only for equal and well resolved atoms) and hence the true map is a solution to the maximum-entropy equations.

For any wrong map which will have peaks in the wrong position and negative excursions of ρ, the corresponding $f'(\rho)$ will have peaks corresponding to negative ρ and the rippled baseline of ρ manifests as ripples in $f'(\rho)$ as shown in Fig. 2.

Now, maximization of $\int [1-\exp(-\rho/\rho_0)]\,dV$ will involve shifting the phases so as to iron out the negative ripples in ρ. In the process the peaks in ρ are also expected to shift to the right positions.

The Taylor-series expansion of the function 1-exp $(-\rho/\rho_0)$ is

$$1-\exp(-\rho/\rho_0)=\rho/\rho_0-\rho^2/2!\rho_0^2+\rho^3/3!\rho_0^3$$
$$-\rho^4/4!\rho_0^4+\rho^5/5!\rho_0^5-\dots.$$

When ρ_0 takes high values compared to the ρ's of

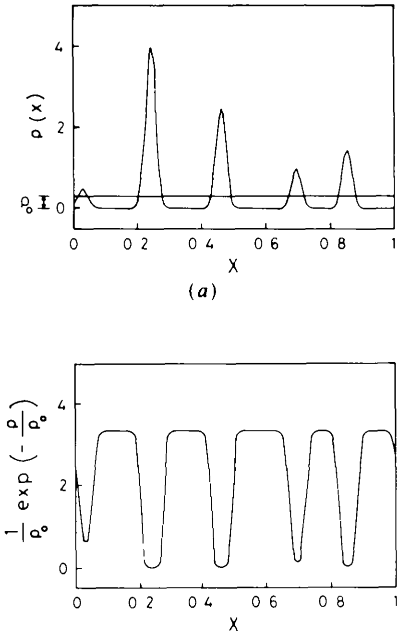

Fig. 1. (*a*) The true one-dimensional image consisting of five unequal peaks. The horizontal line indicates the value ρ_0. (*b*) Plot of $(1/\rho_0)\exp(-\rho/\rho_0)$ *versus* *x*, showing that it is also a structure with five atoms, the atoms here are negative, have a different shape and are all nearly equal.

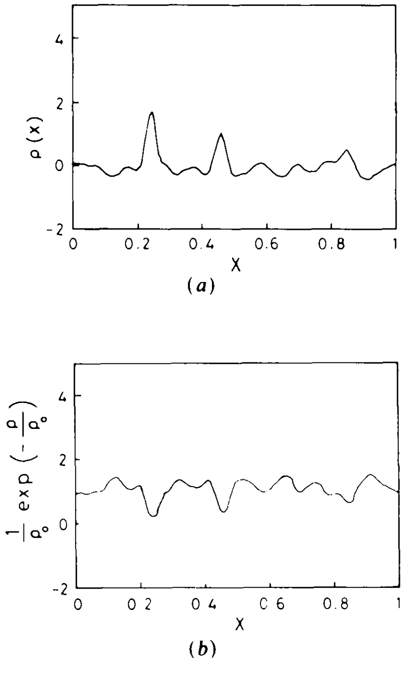

Fig. 2. (*a*) Image obtained by introducing a phase error to the map in Fig. 1(*a*). There are peaks in wrong positions and negative excursions of ρ. (*b*) The corresponding plot of $(1/\rho_0)\times\exp(-\rho/\rho_0)$ showing ripples corresponding to negative ρ in (*a*).

interest, we could approximate the function by

$$1-\exp(-\rho/\rho_0)=\rho/\rho_0-\rho^2/2!\rho_0^2 +\rho^3/3!\rho_0^3-\rho^4/4!\rho_0^4.$$

Now, $\int \rho$ and $\int \rho^2$ are phase independent being given by F_{000} and $(1/V)\sum|F_{hkl}|^2$. Maximization of $\int 1-\exp(-\rho/\rho_0)$ would be equivalent to maximization of ρ^3 in the lowest approximation (for large ρ_0). For smaller values of ρ_0 other invariants enter as well. Hence, the value of ρ_0 determines the extent to which the phases interact. In this way it plays a similar role to the additive constant C in Narayan *et al.* (1983).

Also since in the Taylor expansion of the function the cubic and quartic terms have different signs we could expect a conflict between invariant relationships of different orders.

3. A spin-glass connection?

This problem in the form just described bears some resemblance to the well known spin-glass problem of condensed-matter physics which involves the minimization of the Hamiltonian $\mathscr{H}=\sum_{i>j}J_{ij}s_is_j$ with respect to s_i. (See the review by Mezard, Parisi & Virasoro, 1988.)

Here s_i is a spin on each of the N sites, all coupled through a random symmetric matrix with elements J_{ij} that are statistically independent and Gaussian distributed.

$$\bar{J}_{ij}=0 \quad \text{and} \quad \bar{J}^2_{ij}=1/N.$$

Owing to the randomness of the J_{ij}, it is not possible to satisfy all the interactions at once, which results in frustration in the system. Analytical work and numerical experiments have shown the existence of many metastable states which can be arranged in a hierarchical manner based on the 'distances' between them (Rammal, Toulouse & Virasoro, 1986).

In the crystallographic phase problem, the interactions refer to the invariant relationships entered into by phases. It is not possible to satisfy all the interactions at once except for the trivial case when the phase $\varphi_{\mathbf{H}}=0$ for all $\mathbf{H}$. Failure to satisfy any of these relationships results in frustration. As a consequence, one can think of more than one solution to this problem.

Hence, both problems aim at finding the extrema in the presence of conflicting requirements.

4. Numerical analysis

The similarity with spin glasses just mentioned has instigated a numerical analysis of the 'entropy' landscape in a simple model. The analysis was done by means of the tabu search (Amaldi & Nicolis, 1989), described below.

We consider a one-dimensional centrosymmetric structure $\rho(x)$ that extends over the range $-\frac{1}{2}\le x\le\frac{1}{2}$. We assume that the data consist of the Fourier amplitudes F_H, $H=0,1,\ldots,32$. Fig. 3 shows the function when phases are given the true values.

The function being centrosymmetric and the origin fixed at a centre of symmetry, the phases take discrete values 0 or π.

Tabu search

The method identifies a maximum and moves on to neighbouring maxima by flips of the phase variables. By flipping the phase $\varphi_{\mathbf{H}}$, one means changing its value to $\varphi_{\mathbf{H}}+\pi$.

For the example under consideration, there are 2^{32} possible solutions. Let the initial phase configuration be $\varphi=(\varphi_1,\varphi_2,\ldots,\varphi_n,\ldots,\varphi_{32})$. We now flip one phase at a time and calculate the corresponding S ('entropy') values; *i.e.* to phase flip $\varphi_h\to\varphi_h+\pi$ corresponds a new S value, S^h. S^h = entropy corresponding to the configuration $(\varphi_1,\varphi_2,\ldots,\varphi_h+\pi,\ldots,\varphi_{32})$.

We then accept that flip $\varphi_k\to\varphi_k+\pi$ which takes us to the largest new value of S, which could be lower than the current value.

$$S_{\text{new}}=S^k=\max(S^1,S^2,\ldots,S^k,\ldots,S^n).$$

This procedure is followed at every stage.

Since there exist only a finite number of different configurations in solution space, the system will inevitably get locked into a cyclic mode. In order to avoid visiting the same configuration too soon, *i.e.* to increase the length of the period, the flip that has been accepted is entered into a tabu list and is not considered for the next L steps. The tabu list is updated at every stage.

However, this scheme also allows a tabooed phase flip to be considered if it would lead us to better regions of search. To this end, an aspiration function A is defined on the set of S values as follows.

At every step $A(S)$ will be the largest value of S encountered so far. Recall that S_{new} is the largest value of S corresponding to one of the allowed phase flips.

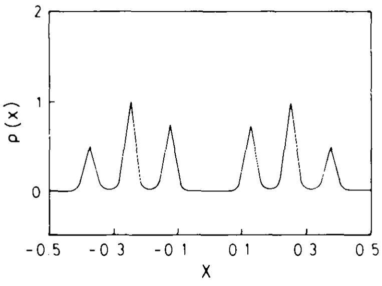

Fig. 3. The one-dimensional image on which the tabu search analysis was done.

If $S_{\text{new}} < S_{\text{previous}}$ and if there exists a phase flip $\varphi_k \to \varphi_k + \pi$ which is tabooed and for which $S^k > A(S)$, then the taboo status of φ_k is overridden and the flip $\varphi_k \to \varphi_k + \pi$ is accepted.

This scheme is ideally suited for our purpose as it gives us a good picture of the way our entropy function varies over the solution space. One should, however, note that the tabu search is basically a heuristic approach and there is as yet no proof that it visits all maxima of interest or finds the optimal route between them.

5. Results and discussion

The tabu search was carried out for the two different 'entropy' functions

(i) $S = \int \rho^3 \, \mathrm{d}V$

(ii) $S = \int [1 - \exp(-\rho/\rho_0)] \, \mathrm{d}V$

and the entropy landscape, *i.e.* entropy variations as one moves along the tabu path, is shown in Figs. 4 and 5.

The true structure is seen to be at a local maximum with a wide basin of attraction, *i.e.* a wide range of initial guesses from which to reach the solution. This suggests the general suitability of the cost functions examined.

However, the landscape for both functions presents multiple maxima where the local maxima could represent solutions at which some of the phase relationships are satisfied. In real space they appear to represent maps in which fragments of the structure can be identified. Narayan *et al.* (1983) noted that multiple copies of a fragment can be recognized at a local maximum.

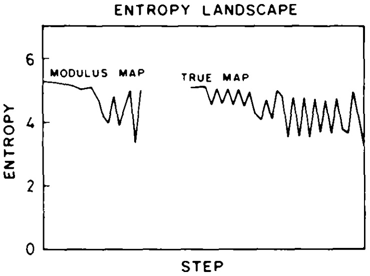

Fig. 4. Plot of $\int \rho^3$ in the space of unknown phases showing the rugged landscape.

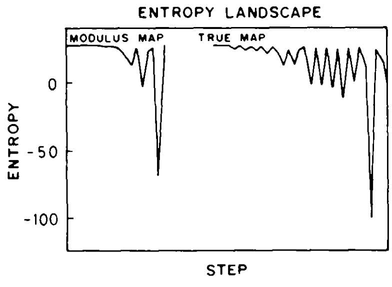

Fig. 5. Plot of $\int [1 - \exp(-\rho/\rho_0)] \, \mathrm{d}V$ in the space of unknown phases showing the presence of multiple maxima.

In order to look at the geometry of the space of solutions we define a permissible route between two solutions as one connected by single phase-flip passages. The natural notion of distance between two solutions a and b is defined as

$$d(a, b) = \max_{(\text{path } a \to b)} \{\min(S)\}.$$

It is not yet possible to comment on whether such a distance would order the solutions on a hierarchical generating tree for any 'entropy' function.

Considering the complexity of the landscape for such a simple one-dimensional structure, one could expect a truly complicated situation in more realistic structures. Hence the problem posed, *i.e.* maximize the entropy with respect to unknown phases, is a challenging one. Conventional numerical techniques are likely to get stuck at a false maximum. However, some of the false maxima are useful as they give fragments of the structure and combining other crystallographic methods it may be possible to pull out the complete structure from this partial information.

Work is in progress to devise numerical algorithms which will take us to useful maxima. The parallel with the spin-glass problem proposed in this paper may prove a useful guide in importing ideas and techniques from an entire class of very well studied problems.

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