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Statistical Geometry. II. Numerical Solution *via* the Single Pixel Equation

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Abstract

A simple single pixel equation (SPE) is presented which, when solved self-consistently for each pixel, can yield *exact* solutions to the statistical inversion problem for diffraction data outlined in paper I of this series [Wilkins, Varghese & Lehmann (1983). *Acta Cryst.* A**39**, 47–60]. The SPE approach was used to obtain the results presented in I and is shown here to have both practical and heuristic advantages in that it: (i) provides a very transparent approach to the task of solving the fundamental equations of the statistical geometric problem, (ii) can greatly improve the rate of convergence and (iii) readily allows the convexity of the constraint contributions to be monitored and, if desired, controlled. For the important case of 'phase refinement' *via* constraint (1) of I and the assumption of: (i) a complete data set of E_k up to the resolution limit of the data and (ii) uniform errors (*i.e.* $\sigma_{k,1} = \sigma$), it is shown that the *maximum-entropy structure* (*MES*) *can be fully refined via the SPE in only one Fourier transform cycle*, and so should be extremely efficient for biological macromolecules.

1. Introduction

In the first paper in this series (Wilkins, Varghese & Lehmann, 1983, hereafter termed I), we laid the foundations for an information-theory-based approach, termed statistical geometry (SG), to the crystallographic inversion problem and presented (see also Gull & Daniell, 1978) a set of N coupled non-linear equations (eqs. I.14*a*) for the discrete distribution, $\mathbf{p}$, of scattering density in the unit cell. If the SG method of structure determination and refinement is to be made a practical tool applicable to biological macromolecules, then highly efficient methods of solving these equations must be developed (*cf.*, *e.g.*, Gull & Daniell, 1978; Collins, 1982). This paper and the following one in the series (Wilkins, 1983) are both directed to that end.

In the present paper we develop and discuss a new approach to the exact numerical solution of these non-linear equations which proceeds *via* a single pixel approximation (SPA) and in many ways resembles the mean-field-type of approximations often encountered in quantum mechanics and statistical mechanics. Because of its simplicity, such an approach offers both heuristic and practical advantages (*e.g.*, improved convergence properties) although it need not necessarily lead to a solution. For a very important special case, namely that of 'phase refinement' using constraint (1) of I alone and some other typically reasonable assumptions (see § 4) it is shown that the structure can be *fully refined* (within the SG framework) *via the SPE in only one Fourier transform cycle*, and so offers an extremely efficient approach to structure refinement even for biological macromolecules.

2. The single pixel approximation (SPA)

Following the notation and definitions introduced in I and starting from equations (I.14) we may Taylor expand the exponent there to first order in p_j about an *arbitrary* trial structure, $\mathbf{p}^t = \mathbf{p}^{(0)}$, and write

$$p_j = \exp\left\{-\lambda_0 - \boldsymbol{\lambda}.\left[\mathbf{f}_j^{1,(0)} + \sum_{j'}(p_{j'} - p_{j'}^{(0)})\mathbf{f}_{j'j}^{2,(0)}\right]\right\} \quad \text{for } j = 1, \ldots, N, \tag{1}$$

where λ_0 is the Lagrange multiplier associated with the normalization constraint (termed the structural freedom in I) and $\boldsymbol{\lambda}$ the Lagrange multiplier vector

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associated with the constraint-function vector, $\mathbf{f}(\mathbf{p})$. Notation for derivatives of $\mathbf{f}$ w.r.t. p_j is as given in (I.17) so that, for example, $\mathbf{f}^2_{j';j}\{0\}$ denotes the second derivative of $\mathbf{f}$ w.r.t. p_j and $p_{j'}$ evaluated at $\mathbf{p}^{(0)}$. Explicit expressions for constraint derivatives are given in Table 1 of I for the particular constraints discussed there. It may be noted that equations (1) are in fact *exact* for constraints (1) and (3) in Table 1 of I, since all higher constraint-function derivatives (*i.e.* for $\nu > 2$) are zero.

At this point, however, we introduce an approximation in order to proceed; namely we include only the case $j' = j$ in the summation on the r.h.s. of (1) and write

$$\ln p_j + [\boldsymbol{\lambda}.\mathbf{f}^2_{jj}(\mathbf{p}^t)]\, p_j + [\boldsymbol{\lambda}.\mathbf{f}^1_j(\mathbf{p}^t) - p^t_j \boldsymbol{\lambda}.\mathbf{f}^2_{jj}(\mathbf{p}^t) + \lambda_0] = 0, \quad \text{for } j = 1, \ldots, N. \tag{2}$$

Equations (2) are a self-consistent set of equations for each p_j alone in terms of the state $\mathbf{p}^t$ and λ_0. The coupling between different p_j only occurs *via* the self-consistently determined field λ_0. Thus equations (2) resemble self-consistent mean-field approximations in statistical mechanics, such as the Curie–Weiss approximation for ferromagnetism or, in quantum mechanics, such as the Hartree–Fock approximation for a many-fermion system. In the magnetic context, λ_0 resembles an externally applied magnetic field and $\mathbf{p}^t$ the 'frozen-in' configuration of spins. The appropriate value of λ_0 in (2) is the one which normalizes $\mathbf{p}$. For each $\mathbf{p}^t$ and $\boldsymbol{\lambda}$, one may seek to solve the single pixel approximation (SPA) given by (2) for $\mathbf{p}$, which we shall call $\mathbf{p}^{\mathrm{SPA}}(\boldsymbol{\lambda};\mathbf{p}^t)$. Self-consistent solution of the SPA approximation occurs when $\mathbf{p}^{\mathrm{SPA}} = \mathbf{p}^t$, in which case both the Taylor expansion approximation involved in going from (I.14) to (1) and the approximation involved in going from (1) to (2) become *exact* and $\mathbf{p}^{\mathrm{SPA}}(\boldsymbol{\lambda}) = p(\boldsymbol{\lambda})$, so that a *full self-consistent solution to the statistical geometrical problem has been reached.*

It may be noted that the simple iterative procedure (see, *e.g.*, Gull & Daniell, 1978) is equivalent to solving (2) iteratively *without* the terms involving $\mathbf{f}^2_{jj}(\mathbf{p}^t)$. For positive $\boldsymbol{\lambda}.\mathbf{f}^2_{jj}(\mathbf{p}^t)$, these additional terms tend to restore the iterate toward the trial structure, $\mathbf{p}^t$. Also, it may be noted that the SPA keeps the full non-linearity of the entropy (Skilling, private communication).

2.1. *Properties of the single pixel equation*

Mathematically, equation (2) is of the general form

$$\ln p_j + U_j\, p_j + V_j = 0, \tag{3}$$

where U_j and V_j depend on $\mathbf{p}^t$, $\boldsymbol{\lambda}$ and λ_0 but not on $\mathbf{p}$, and are readily obtained by equating coefficients between (2) and (3). This is a transcendental equation having 1, 2 or 0 real solutions for p_j, depending on the values of U_j and V_j (see Appendix 1 and Fig. 1). A *sufficient condition* for (3) to have one and only one solution is that

$$U_j = \boldsymbol{\lambda}.\mathbf{f}^2_{jj}(\mathbf{p}^t) \geq 0, \tag{4a}$$

which corresponds to the assumption that the sum of constraint contributions to the single site j is convex. By comparison, in § 2.3 of I it was pointed out that a sufficient condition to guarantee a unique solution for $\mathbf{p}(\boldsymbol{\lambda})$ was that $\boldsymbol{\lambda}.\mathbf{f}(\mathbf{p})$ be convex. Since (4*a*) is a necessary but not sufficient condition for the convexity of $Q(\mathbf{q})$, it follows that the SPA will lead to unique solutions for $\mathbf{p}(\boldsymbol{\lambda})$ whenever unique solutions exist, although it will also lead to unique solutions even when multiple solutions exist. Because of the simple form of the SPA, it is easy to monitor the occurrence of non-uniqueness in solutions and to overcome the problem if necessary (see § 3). For

$$-\exp\{V_j - 1\} \leq U_j = \boldsymbol{\lambda}.\mathbf{f}^2_{jj}(\mathbf{p}^t) < 0, \tag{4b}$$

(3) has two solutions with the lower branch (see Fig. 1) for p_j clearly being the more physical one. While for U_j outside the ranges of (4*a*) and (4*b*), no solution to (3) exists.

It should be noted that practical determination of $\mathbf{p}(\boldsymbol{\lambda};\mathbf{p}^t)$ *via* the SPA involves only one evaluation of $\mathbf{f}^1_j(\mathbf{p}^t)$, which is typically the most time-consuming step in the calculations as it involves a Fourier transform operation. The task of solving (2) and determining the appropriate λ_0 (see Appendix 2) *both* occur inside the $\mathbf{f}^1_j(\mathbf{p}^t)$-evaluation loop (see Fig. 2). An efficient iterative solution scheme for solving (2) is given in Appendix 1 and in some respects resembles iterating (2) from left to right, whereas all other iterative approaches to the solution of (I.14) appear to proceed from right to left (see *e.g.*, Gull & Daniell, 1978; Willingale, 1981; Collins, 1982). This observation probably explains the very slow convergence found when seeking to solve (I.14) by right to left iteration and suggests that extension of the SPA to small clusters of pixels may also prove worthwhile and provide a *local* hierarchy of equations for solving the structure-determination problem in $\mathbf{p}$ space.

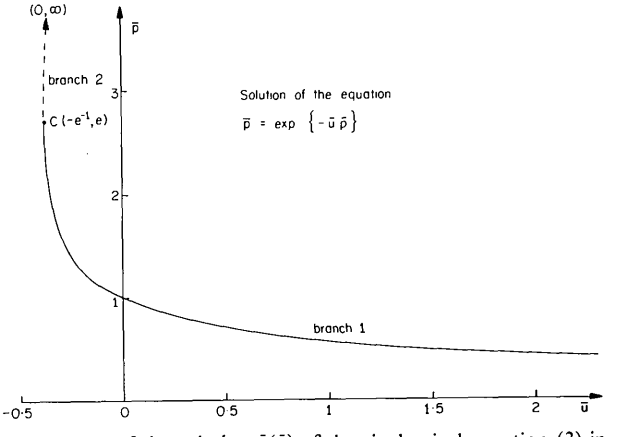

Fig. 1. Plot of the solution $\bar{p}(\bar{u})$ of the single pixel equation (3) in reduced form (see Appendix 1) as a function of $\bar{u}$, showing two branches for $-e^{-1} \leq \bar{p} \leq 0$.

It should also be noted that one cannot guarantee that the SPA will lead to a full self-consistent solution, $\mathbf{p}(\boldsymbol{\lambda})$. Clearly, the closer $\mathbf{p}^t$ is to $\mathbf{p}(\boldsymbol{\lambda})$ the better the method should work. In practice we have found no convergence difficulties when only the first constraint is present, even when $\mathbf{p}^t$ starts from the flat map. On the other hand, when constraint (2) is included, convergence of $\mathbf{p}^{(n)}(\boldsymbol{\lambda};\mathbf{p}^t)$ to $\mathbf{p}(\boldsymbol{\lambda})$ can be quite slow.

3. Enforced convexity

If only convex constraints are considered, then $\mathbf{p}(\boldsymbol{\lambda})$ is unique (see Wernecke, 1977, and also I). However, if non-convex constraints are considered [*e.g.*, constraint (2) in Table 1 of I], then the solution for $\mathbf{p}(\boldsymbol{\lambda})$ need not be unique and, in practical terms, one would like to have a $\mathbf{p}^t$ sufficiently close to the correct solution so as to help avoid jumping into a false maximum in $Q(\mathbf{p})$. This matter was partly discussed in I where one approach to the problem which was suggested was to solve first for $\mathbf{p}(\boldsymbol{\lambda})$ for all convex constraints and then slowly introduce non-convex constraints. A further aid to avoiding false maxima and the possibility of obtaining trial solutions oscillating between different false maxima, is somehow to enforce the constraint functions to be always convex.

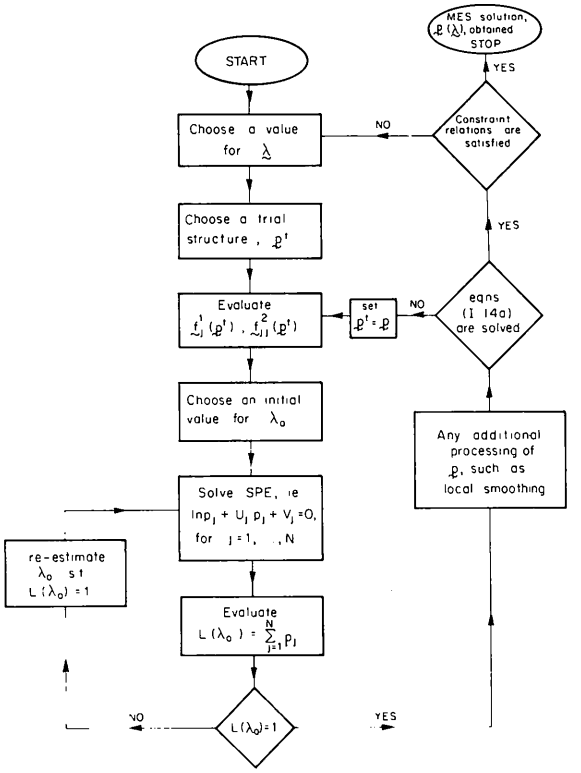

Fig. 2. Flow chart for the iterative self-consistent solution of (I.14) subject to the constraints (I.11) *via* the single pixel approximation (2).

In the case of the results presented in Fig. 1 of I, this was done using the SPA and taking $A_k/|P_k| = 1$ in the expression for $f^2_{2,jj}$, and corresponds to estimating $f^2_{2,jj}$ under the assumption that measured and model amplitudes are equal. This assumption is obviously very good when one is near the correct solution. If no assumption like this is made, then model Fourier coefficients, P_k, which have a small magnitude (especially common in the early stages of a refinement) can lead to very large contributions to $f^2_{2,jj}$, both positive and negative, which are clearly inimical to the attempted determination of $\mathbf{p}(\boldsymbol{\lambda})$.

4. The special case of the first constraint with uniform errors and a complete set of structure-factor data

In this section we consider the special case where only constraint (1) of I is operating, and so corresponds essentially to the task of phase refinement for a partially known structure. To make matters even simpler, we in addition assume that: (i) all structure factors E_k are approximately known and (ii) their errors are uniform (*i.e.* $\sigma_{k,1} = \sigma$ for all k). Then we may immediately write (using Table 1 of I and Appendix 1 of I)

$$f^1_{1,j}(\mathbf{p}) = \frac{1}{\sigma^2 N_1}\sum_k (P_k - E_k)\exp\{-2\pi ijk/N\}$$
$$= \frac{N}{N_1}\frac{1}{\sigma^2}(p_j - e_j), \qquad (5)$$

where e_j is the Fourier inverse of E_k, so that $f^1_{1,j}(\mathbf{p})$ is nothing but a scaled difference density for the jth pixel, between the trial structure, $\mathbf{p}$, and an experimental structure, $\mathbf{e}$ (which need not be everywhere positive, although we assume it is normalized, *i.e.* $E_0 = 1$). Clearly, $f^1_{1,j}(\mathbf{p})$ here is a purely local property of the jth pixel.

Consider now the task of self-consistently solving the fundamental equations (I,14*a*) given (5), which corresponds to solving

$$p_j = \exp\{-\tilde{\lambda}_1 p_j + (\tilde{\lambda}_1 e_j - \lambda_0)\}, \qquad (6a)$$

where $\lambda_1 = \tilde{\lambda}_1 N/N_1\sigma^2$ and (6*a*) is clearly of exactly the same form as the SPE, (3), but with

$$U_j = \tilde{\lambda}_1; \quad V_j = \tilde{\lambda}_0 - \tilde{\lambda}_1 e_j. \qquad (6b)$$

(6*a*) may thus be solved for $\mathbf{p}(\lambda_1)$ by the techniques outlined in Appendices 1 and 2. Notably, the only time a Fourier operation is involved is in the initial calculation of e_j from E_k, and this is required *only once* even if λ_1 is varied. Also, the evaluation of $f_1[\mathbf{p}(\lambda_1)]$ may in fact be carried out in $\mathbf{p}$ space using Parseval's theorem, and so the correct value of λ_1 determined such that $f_1[\mathbf{p}(\lambda_1)] = C_1$, without involving calculation of a Fourier transform, *viz.*

$$f_1(\mathbf{p}) = \frac{1}{2N_1}\frac{1}{\sigma^2}\sum_k |P_k - E_k|^2$$

$$= \frac{N}{2N_1}\frac{1}{\sigma^2}\sum_j (p_j - e_j)^2. \qquad (7)$$

By means of the assumptions above, we have been able to reduce the structure-refinement problem in the SG framework to a relatively simple numerical task, comparable in magnitude to that of the Fourier transformation operation itself. In practice, there are clearly going to be some difficulties in applying the simple approach described above. For example, the initial data set may be incomplete, in which case the problem may be overcome by assuming

$$E_k = P_k, \qquad (8)$$

for missing k values, where in practice one could take $P_k = P'_k$, with P'_k an initial structure factor based on an initial structure $\mathbf{p}'$. Obviously, the smaller the number of 'holes' in the data set the better the method should work. On other aspects of the structure refinement problem, we note that:

(i) the method gives support to the local nature of the refinement problem in $\mathbf{p}$ space and to the SPA approach in general (see § 2), especially when constraint (1) of I is the main operative constraint. It can easily be seen that the SPA approach outlined in § 2 reduces to exactly the same values for U_j and V_j as (6*b*) above, and the present assumptions. Thus, the SPA approach should be particularly efficient under these conditions, when the data set for E_k is nearly complete and when the errors are nearly uniform.

(ii) at any time one may choose the number of evaluation points in $\mathbf{p}$ space, N, to be larger than the Shannon limit for the data and thereby seek to obtain [using (8) above] superresolution in the refinement of $\mathbf{p}$. By the inverse process, one may correspondingly seek to carry out some degree of phase extension when Fourier transforming to $\mathbf{k}$ space.

(iii) at the end of a refinement cycle yielding the MES $\mathbf{p}(\lambda_1)$ s.t. $f_1(\mathbf{p}) = C_1$, one may seek to improve E_k by taking phases (and perhaps some amplitudes) from $\mathbf{p}(\lambda_1)$ and then repeat the refinement of the structure using the new set of e_j (see Collins, 1982).

(iv) one may group a whole set of pixels together (say background density due to solvent in a protein crystal) and treat the whole set as one average pixel, by averaging over the e_j's in the set and regarding the p_j determined *via* (6*a*) as an average p_j for the pixels in the set.

(v) other forms of structure averaging, such as non-crystallographic averaging, may similarly be carried out without any need for Fourier transformation between p_j and P_k.

(vi) the present special case is obviously an ideal case for using as the first stage in a more detailed treatment of the structure-refinement problem. For example, after having established the maximum-entropy structure, $\mathbf{p}(\lambda)$, appropriate for unit weights, one may then introduce a more subtle weighting scheme and continue refinement *via* the SPA (§ 2).

(vii) another aspect which emerges very clearly from the present discussions is the conjugate nature of λ_1 and σ^2. It is only the ratio of these two variables which enters the calculation (*i.e.* λ_1) and not their absolute values. Thus, letting $\lambda_1 \to \infty$ is mathematically equivalent to letting $\sigma^2 \to 0$ (see also Varghese & Wilkins, 1983) and one is, in principle, able to treat the case of *exact data* (*cf.* Collins, 1982).

(viii) for a given set of e_j, the refinement of $f_1(\mathbf{p})$ *via* λ_1 will certainly have a lowest possible value ≥ 0 [since $f_1(\mathbf{p})$ is a convex function, see § 4 of I] and may have a limiting value $\geq C_1 \geq 1$, thus providing a natural limit to the degree of refinement possible with the given set of e_j.

(ix) the present approach readily extends to the case where prior probabilities, m_j, are included in the entropy expression, *viz.* $S = -\sum_j p_j \ln(p_j/m_j)$ (Jaynes, 1968).

4.1 *Application to macromolecular structure refinement*

We are currently using the above special case of the SPE to help refine 2·9 Å data from neuraminidase (unit cell 124 × 124 × 181 Å) and are able to obtain three-dimensional maximum-entropy structures, $\mathbf{p}(\lambda_1)$, with $1{\cdot}3 \times 10^6$ pixels in the asymmetric unit cell, in approximately 200 s of CPU time on a CYBER76 (Varghese & Wilkins, 1983). The solutions to the SG problem thus obtained are exact to arbitrary numerical accuracy (*cf.* Collins, 1982) and involve only one Fourier transformation operation for a given set of E_k. In practice, the above calculations gave normalization of $\mathbf{p}$ to better than 0·5% and involved two passes in λ_0 (*i.e.* 100 s/pass).

5. Conclusion

The SPA can provide a simple and relatively transparent approach to the exact numerical solution of the statistical inversion problem for diffraction data, and has been found to be both instructive and practically useful. For certain special cases, the statistical geometric problem can be solved exactly within the SPE framework using only one Fourier transformation operation. Some results on a simple one-dimensional model structure have been obtained using the SPA (Wilkins, Varghese & Lehmann, 1983; Varghese & Wilkins, 1983).

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APPENDIX 1
Discussion of the transcendental equation

Consider

$$\ln(p) + up + v = 0 \qquad (A1.1)$$

which can be written in reduced form as

$$\bar{p} = \exp\{-\bar{u}\bar{p}\}, \qquad (A1.2)$$

where

$$\bar{p} = p\exp\{v\}; \quad \text{and} \quad \bar{u} = u\exp\{-v\}. \quad (A1.3)$$

Using simple algebra it can readily be shown (see Fig. 1) that (A1.3) has:

(i) one solution if $u \geq 0$.

(ii) two solutions if $-\exp\{-1\} < u\exp\{-v\} < 0$.

(iii) no solutions if $u < -\exp\{v-1\}$.

The coordinates of the critical point $(\bar{u}_c,\bar{p}_c)$ are $(-e^{-1},e)$.

In practice, (A1.1) can be solved for p by numerical iteration for p using Newton's method, *viz.*

$$p^{(1)} = [1 + up^{(0)}]\exp\{-up^{(0)} - v\} \times [1 + u\exp\{-up^{(0)} - v\}]^{-1}. \quad (A1.4)$$

APPENDIX 2
Determination of λ_0

In practice, we have found it adequate to determine λ_0 in the SPE by successive iteration using Newton's method. If $\rho^{(0,0)}$ is the solution (not necessarily a probability distribution) to (A1.1) obtained when $\lambda_0 = \lambda_0^{(0)}$, then the improved estimate for λ_0 is given by

$$\lambda_0^{(1)} = \lambda_0^{(0)} + \left[-1 + \sum_j \exp\{-U_j^{(0)}\rho_j^{(0,0)} - V_j^{(0)}\}\right] \times \left[\sum_j \exp\{-U_j^{(0)}\rho_j^{(0,0)} - V_j^{(0)}\}/[1 + U_j^{(0)}\rho_j^{(0,0)}]\right]^{-1}, \qquad (A2.1)$$

where $U_j^{(0)}$ and $V_j^{(0)}$ are evaluated in the trial probability distribution $p^{(0)}$. Notably, λ_0 may be refined without re-evaluation of $U_j^{(0)}$ and $V_j^{(0)}$, and hence does not involve heavy computation.

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Statistical Geometry. III. Accelerated Convergence using Contrast Amplification

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Abstract

A method for greatly improving the efficiency of numerical procedures for solving the fundamental equations of the statistical geometric method [Wilkins, Varghese & Lehmann (1983). *Acta Cryst.* A**39**, 47–60] is presented. The method involves optimizing the step length in a one-dimensional search based on two trial solutions. For constraint functions, f_r, which have derivatives $f_{r,j}^1 = \partial f_r/\partial p_j$, which are linear in **p**, it is shown that the one-dimensional search does *not* involve any additional Fourier transforms (*i.e.* lengthy computations).

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1. Introduction

In order to make the statistical geometric (SG) method outlined in I (Wilkins, Varghese & Lehmann, 1983) a practical tool for the structure determination and refinement of biological macromolecules, it is essential that highly efficient methods for solving the fundamental equations (I.14) (see also Gull & Daniell, 1978) be developed. Simple iteration of these equations (see Gull & Daniell, 1978) is found to converge only weakly (in Borel sum) and slowly. In the second paper of this series (Wilkins, 1983, hereafter termed II), we outlined some improved methods of solution of the SG problem