Acta Cryst. (1983). A**39**, 252–256

Electron Density: An Exponential Model

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(*Received* 27 *July* 1982; *accepted* 1 *November* 1982)

Abstract

Electron density ideally is positive definite. The imperfect experimental data of an X-ray diffraction experiment do not lead to such a function when the density is obtained from structure factors by the linear relationship of Fourier transformation. At the price of certain but quite small bias, electron density may be represented by an otherwise completely general exponential model. The model is based on iterative correction of a logarithm which yields a density approximation of resolution substantially higher than that afforded by Fourier transformation of structure factors.

1. Introduction

Positive definiteness is a characteristic property of electron density in any chemical system. In crystallographic studies based on X-ray diffraction experiments, positivity has special significance. This is especially evident in cases for which a highly accurate electron density function is itself the object of study and also in the whole area of direct methods, which, in fact, historically were based upon density nonnegativity (Karle & Hauptman, 1950).

Direct methods in reciprocal space often are not revealing of their relationship to corresponding density functions, but in specific cases methods have been developed which involve a clear conceptual dependence on manipulation of density. These methods generally follow the approach given by Sayre (1952). The related methods of phase refinement or correction by density modification as begun by Hoppe & Gassmann (1968) involve explicit manipulation of electron density. None of the density modification methods are absolutely dependent on electron density as a positive-definite function but they are conditioned throughout by the assumption that an ideal density is quite smooth and near zero in a substantial portion of a unit cell. More stringent are the uses of a function of ρ^{-1} for phase refinement (Davies & Rollett, 1976) or resolution enhancement (McLachlan, 1971) which certainly require that continuous electron density be positive.

Filtering formalisms for phasing (Gassmann, 1977) and resolution enhancement (Collins, 1978; Britten & Collins, 1982) also may require electron density to be positive. In fact, the Wiener methods discussed by Collins & Mahar (1982) are used to determine positive-definite density functions which are of maximal sharpness in some sense. That work highlights the need of a general model for positive-definite electron density which can be accurately calculated using all available structure factors. In a recent paper on resolution enhancement (Collins, 1982) it was assumed that a positive-definite exponential model of electron density is general and can yield a good representation of the density. In the present paper we show these assumptions to be correct.

2. The exponential model

A set of structure factors $\hat{F}$ is assumed to exist and be reasonably complete in a range of $\sin\theta/\lambda$ which corresponds to atomic resolution in the density function. Provided the error in a structure factor is small, say the mean error modulus is $<10\%$ of the mean structure-factor modulus, an excellent approximation of the electron density is a routine result of Fourier transformation. Although experimental error and series-termination effects preclude absolute correctness of the computed density, even use of $\hat{E}$, the normalized structure factor (Karle & Karle, 1966), in spite of severe series-termination effects would result in a qualitatively useful density function. In the following discussion normalized structure factors are used unless otherwise specified, and their transform is assumed to show the rippling and negative regions normally associated with severe series-termination error.

The usual density function, constrained only to be real, provides a noncontroversial starting point for constructing an exponential model of density. The model-required positivity can be imposed in a number of ways. If by some conservative operation positive τ is obtained from ξ the transform of $\hat{E}$, then the exponential model gives as an approximation for ξ at the position specified by $\mathbf{x}$

$$\xi_{\mathbf{x}} = \exp\{\ln \tau_{\mathbf{x}}\}. \qquad (2.1)$$

0567-7394/83/020252-05$01.50

In this context a conservative operation is one which changes positive density not more than slightly and at least approximately preserves the general shape of the starting density function.

In order to improve the estimate of ξ but ensure its positivity, a correction is sought for $\ln \tau$ as

$$\delta \ln \tau_{\mathbf{x}} = \delta\tau_{\mathbf{x}}/\tau_{\mathbf{x}}, \tag{2.2}$$

so that an improved estimate of ξ is given by

$$\xi_{\mathbf{x}} = \exp\{\ln \tau_{\mathbf{x}} + \delta\tau_{\mathbf{x}}/\tau_{\mathbf{x}}\}. \tag{2.3}$$

Any ξ obtained by (2.3) may be transformed to give E, then $(\hat{E} - E)$ may be used as the Fourier coefficient of $\delta\tau$. Repeated use of (2.3) in this fashion with the appropriate updating of $\ln \tau$ constitutes a formal solution by approximation for the problem of obtaining an exponential model for electron density.

Equation (2.3) suffers an ill-conditioning due to the τ^{-1} dependence of the correction term. Because the calculation of ξ is a successive approximation procedure, it is permissible to replace τ^{-1} by $w(\tau)$ for which it is required that

$$w(\tau) \geq w(\tau + \varepsilon), \quad 0 \leq \tau \leq \tau + \varepsilon \leq 1{\cdot}0 \tag{2.4a}$$

$$\tau^{-1} \geq w(\tau) \geq \tau_{\max}^{-1}. \tag{2.4b}$$

Such a weight function cannot change the sense of any correction and its effect on final ξ may be made as small as desired by increasing the number of iterations. One type of weight function is given by the family

$$w(\tau) = \tau_{\max}^{-1}[a(-1 + \tau/\tau_{\max})^2 + 1]; \quad 0 \leq a \leq 4. \tag{2.5}$$

The reasonableness of this weight function provides no ensurance that while overcoming the ill-conditioning of (2.3) the modified form has retained suitable convergence properties. This problem awaits empirical tests such as the illustration of this paper and the successful demonstration involving a protein crystal structure (Collins, 1982).

In its form of application (2.3) is

$$\xi_{\mathbf{x}} = \exp\left[\ln \tau_{\mathbf{x}} + w(\tau_{\mathbf{x}})\, V^{-1} \sum_{\mathbf{k} \in K} m_{\mathbf{k}}(\hat{E}_{\mathbf{k}} - E_{\mathbf{k}}) \times \exp\{-2\pi i \mathbf{k}.\mathbf{x}\}\right], \tag{2.6}$$

where $w(\tau)$ is given in (2.5), V is the volume of a unit cell, K denotes the set of reciprocal-lattice points for which there are observations, and $m = (2 - \delta_{\bar{1}})$ is a reflection weighting in which $\delta_{\bar{1}}$ is 1 or 0 depending on whether the reflection is centric or acentric. It is not necessary to restrict ξ to be a real-valued function, but for the present crystallographic application the restriction is assumed and the set of structure factors must conform to Friedel's law. An equation very similar to (2.6) has been given elsewhere (Collins, 1982) as the basis for an iterative procedure to minimize the disagreement between $|\hat{E}|$ and $|E|$ by steps of maximum configurational entropy for the density function.

3. An example

β-Lyxose has been studied in a single-crystal X-ray diffraction experiment and its quantitative structure determination reported by Hordvik (1966). The structure has symmetry $P2_12_12_1$; unit-cell dimensions $a = 9{\cdot}58$, $b = 10{\cdot}35$, $c = 6{\cdot}52$ Å; and four formula units of $C_5H_{10}O_5$ per unit cell. The reported atomic coordinates were used to compute ideal error-free normalized structure factors $\hat{E}$. The scattering factors used were $g_C = 0{\cdot}27$, $g_O = 0{\cdot}36$, and hydrogen atoms were excluded from the calculation. These calculated (normalized) structure factors were used without further modification throughout the example.

The example was designed to be a test and demonstration of the exponential density model as providing an acceptable representation of density for which there is a data set severely truncated in reciprocal space. It is assumed that the transform of the truncated data has been calculated so that it may serve as a starting point for iterative application of (2.6). If the demonstration is to be successful, the procedure must lead to an improvement over the original representation of density.

The iterative procedure beginning with computation of τ from $\hat{E}$ truncated at $\sin\theta/\lambda = 0{\cdot}60$ Å^{-1} is:

(i) to ensure positivity of density, replace τ by the larger of $\tau, \tau_{\max}/100$, then compute and file the logarithm of τ and as initial E, the transform of τ;

(ii) compute (2.6) with $w(\tau)$ given by (2.5) in which $a = 1{\cdot}0$, K restricted such that $|\mathbf{k}|/2 \leq 0{\cdot}6$, and with the phase of E assigned to $\hat{E}$. For a subsequent iteration the logarithm of ξ is the new $\ln \tau$ and the transform of ξ is the new E;

(iii) temporarily scale E to $\hat{E}$ to compute the disagreement factor R as the primary comparison between the observed and modeled data;

(iv) repeat steps (ii) and (iii) until the improvement in R is suitably small.

The weight function of step (ii) was chosen to be far from that of the ill-conditioned equation (2.3) in view of the severe truncation conditions of the example. There are 702 unique structure factors in the range 0–0·60 Å^{-1} in $\sin\theta/\lambda$. All Fourier transformations were carried out on grids of 64 × 64 × 32 to be sure of adequate grid fineness in direct space and suitable transform separation in reciprocal space.

4. Analysis of results

The course of the calculations through six iterations is summarized in Table 1. The value for $R = \sum ||\hat{E}| - |E|| / \sum |\hat{E}|$ is useful for following the progress of the calculations but is of uncertain absolute significance. The general featurelessness of the other sequences of Table 1 suggest that only R as its rate of change is

Table 1. *The course of the calculations*

	Iteration					
R	1	2	3	4	5	6
R	0·29	0·25	0·23	0·22	0·21	0·20
Scale factor*	1·09	1·23	1·25	1·25	1·25	1·24
Density extremes (Å^{-3})	1·30, 0·013	2·2, 0·008	2·1, 0·006	2·3, 0·005	2·4, 0·004	2·5, 0·003
Mean change in phase†	2·0 (3·5)	0·6 (1·1)	0·2 (0·5)	0·1 (0·5)	0·1 (0·4)	0·1 (0·5)
After six iterations $\langle \lvert\alpha_{true} - \alpha_{MEM}\rvert \rangle$†‡ = 2·1 (3·4)						

* Scale factor is κ^{-1}, $\kappa = \sum |\hat{E}||E| / \sum |E||E|$.
† Modulus-weighted averages are given; the corresponding unweighted averages follow in parentheses. All values are in degrees.
‡ α_{true} are the computed ideal phases and α_{MEM} are the phases from Fourier inversion of the exponential density model.

useful in discerning effective convergence to a good exponential model of density. It is possible that a different measure of the difference ($|\hat{E}| - |E|$) would be decisively more useful, but it appears that the other types of tabulated data are useful only to determine that the calculations are progressing in an orderly manner.

Should $R = 0{\cdot}0$ no change could occur upon iteration. This will not occur for experimental data because of the bias, however small, associated with the nonlinear relationship between $\hat{E}$ and the exponential density model. [We follow Wilson (1979) who used 'bias' to denote 'systematic error, arising from inadequacy of mathematical techniques, whereby random errors, of mean value zero in the raw data, become a systematic bias in derived quantities – in the present case in the distribution of electron or other density'.] We assume therefore that a stationary though nonzero value for R is evidence of convergence in an average sense, and that a significantly diminished rate of change in R signals a useful asymptotic approximation to the limiting density model.

Density maps are given in Fig. 1 as projections of the three-dimensional density functions along [001]. The contour levels used are the same for both maps and are integral multiples of an arbitrarily chosen interval; negative contours appear as broken lines. Fig. 1(*a*), the standard map, is a projection of the density obtained by Fourier transformation of (ideal) $\hat{E}$ drawn from the range 0–0·60 Å^{-1} in $\sin\theta/\lambda$. Fig. 1(*b*), the exponential map, is a projection of the density iteratively developed from the same data after the six iterations summarized in Table 1. Identical contouring schemes were used for the two maps, but Fig. 1(*b*) has no negative or zero contour because the density function is positive definite.

The exponential map is about 75% higher than the standard map. Although a small positive bias in the exponential function may have artificially increased the level of the exponential map ~0·5% ξ_{max}, its peak widths at half height are somewhat smaller than those of the standard map. This gives qualitative confirmation of the greater height of the exponential map as significant and corresponds to its obviously greater resolution.

The shortest interatomic separation resolved in the projection of the exponential density is the foreshortened 0·6 Å for C(3)–O(4) and we take the corresponding effective resolution limit to be 0·6 Å or better. In the standard map the longest unresolved separation is 0·8 Å for C(2)–C(5) but because C(2) and C(5) are very nearly resolved we take the effective

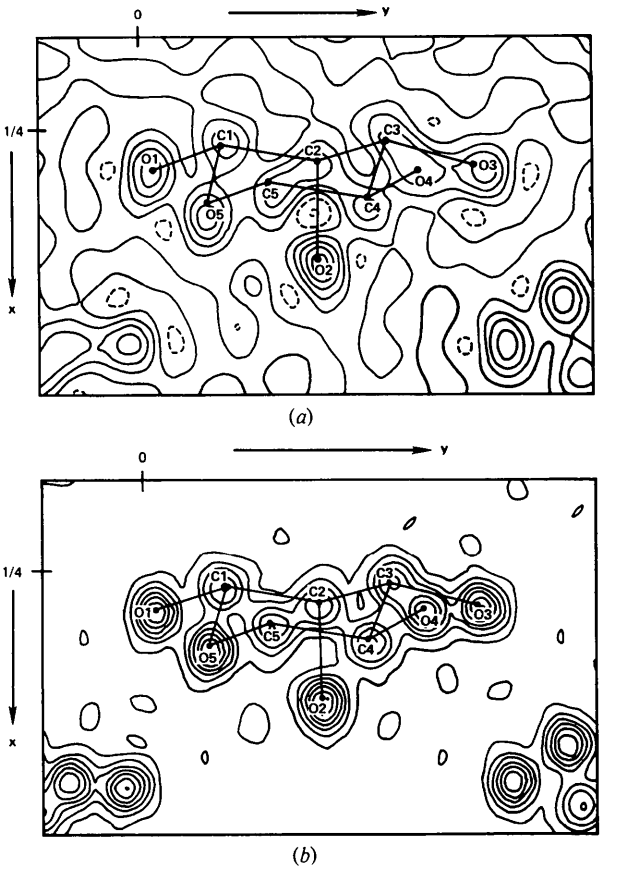

Fig. 1. Projections of density (Å^{-3}) along [001] with contours at integral multiples of the same arbitrary interval; (*a*) is the projection of the standard transform of $\hat{E}$, (*b*) is the projection of the exponential model of density. Negative contours are broken lines.

resolution to be 0·8 Å. If the maxim of equivalence between effective resolution and minimum interplanar spacing of the diffraction record is assumed, then the maps would correspond to diffraction records limited by $\sin\theta/\lambda \sim 0{\cdot}8$ Å^{-1} for the exponential map and $\sim 0{\cdot}6$ Å^{-1} for the standard map. Correction of these values for different resolution properties in two and three dimensions (Wilson, 1979) suggests the smaller values of 0·7 and 0·5 Å^{-1} for the three-dimensional exponential and standard maps respectively. Although these values are of only qualitative significance, their ratios of $>1{\cdot}3$ are determined by the resolutions observed in the two maps. The ratio $>1{\cdot}3$ means that standard three-dimensional Fourier synthesis of structure factors would require substantially more than twice as many data to achieve the same resolution obtainable by computation of an exponential model of electron density as outlined.

In reciprocal space it is desirable to know what agreement there is between $\hat{E}$ and E for $\mathbf{k}$ outside K which gives the range of observations. Of course it is not possible to know $\hat{E}$ beyond the range of observation except in a simulation such as the present example. Here the comparison between $\hat{E}$ and E is carried through the range 0–1·20 Å^{-1} in $\sin\theta/\lambda$, a range twice that of the data upon which the two density functions were based.

All $\hat{E}$ and E were sorted into 12 equal ranges of $\sin\theta/\lambda$, for each of which the scale of E relative to $\hat{E}$ was determined. R calculated for the scaled structure factors within each shell and each scale are given in Table 2. The averaged $R = 0{\cdot}056$ for 0–0·60 Å^{-1} in $\sin\theta/\lambda$ reflects the agreement between features of the transform of E and the perfect transform of $\hat{E}$ after convolution of a simple shape with its spikes. The individual values of R show there is substantial agreement between $\hat{E}$ and E for 0–0·90 Å^{-1} in $\sin\theta/\lambda$. This represents an increase of resolution in the exponential model of density by 50% over that of the standard Fourier transform of structure factors, both models based on the same data.

Table 2. *Some averages dependent on* $\sin\theta/\lambda$

$\sin\theta/\lambda$* (Å^{-1})	Q†	R	Number of contributors
0·05	1·89	0·051	4
0·15	1·67	0·089	28
0·25	1·34	0·060	67
0·35	1·13	0·058	127
0·45	1·01	0·045	196
0·55	0·92	0·058	280
0·65	0·38	0·153	388
0·75	0·28	0·161	516
0·85	0·19	0·230	632
0·95	0·11	0·390	805
1·05	0·04	0·693	965
1·15	0·02	0·739	1151

* The extremes of each range are 0·05 Å^{-1} from the tabulated midpoint.
† $Q = \sum |\hat{E}|\,|E| \,/\, \sum |\hat{E}|\,|\hat{E}|$.

The window in reciprocal space through which data have been observed in the present simulation is the unit-step function. The function is unity for $\sin\theta/\lambda \leq 0{\cdot}6$ Å^{-1} and zero elsewhere. Wilson (1979) points out that the best bias-free estimate of density is the truncated Fourier series, based on the best bias-free structure factors, which may in turn be interpreted as the convolution of the best true density with the transform of the unit-step window. As stated earlier, the exponential density model certainly introduces bias in the density along with the partial deconvolution of structure and window transform implied by the increased resolution.

It is evident that resolution has been increased in the exponential model, but the peak widths of Fig. 1(*b*) make it equally clear that termination-of-series effects are only partially overcome. To the extent that they are overcome, the result can be represented as a change in the window in reciprocal space. The individual scales of Table 2 provide the window shape shown in Fig. 2; in the figure the scale values for structure factors outside the range of observation have been multiplied by 2·05 to make the curve as smooth as possible. For comparison Fig. 2 includes the minimum-bias window of Papoulis (1973) which was fitted by variation of its overall scale and first-zero position to the window for the exponential density model. Papoulis's minimum-bias window is for one dimension so its comparison with a multidimensional result, notwithstanding the ease of first-zero location, must be undertaken with reserve. The Papoulis window is

$$M_k = t[\pi^{-1}\sin\pi s' + (1-s')\cos\pi s'], \quad s' < 1{\cdot}0, \tag{4.1a}$$

where t is the scale of M, $s' = s/s_{\max}$, $s = \sin\theta/\lambda$, and

$$M_k = 0, \quad s \geq s_{\max}. \tag{4.1b}$$

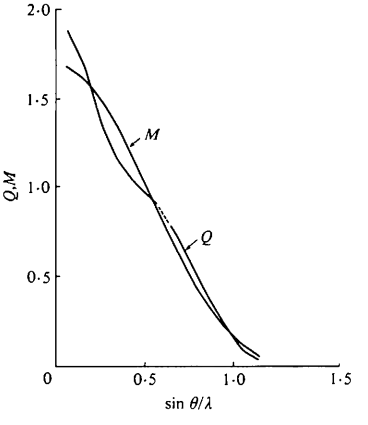

Fig. 2. Data windows: M is the Papoulis minimum-bias window, Q is the implied window for the exponential density of the simulation.

The window was required to have a positive transform and (for fixed t) to minimize the bias defined as proportional to

$$\int_{-\infty}^{\infty} x^2 m_x \, dx, \qquad (4.2)$$

m being the nonnegative transform of M. The window parameters used in Fig. 2 are $t = 1{\cdot}693$ and $s_{max} = 1{\cdot}466$ Å^{-1}. The curve similarities invite a comparison which suggests the effective upper limit of resolution in the exponential density may be substantially greater than the $0{\cdot}90$ Å^{-1} in $\sin\theta/\lambda$ indicated by inspection of the R values given in Table 2.

It appears that the exponential density of this simulation is at a resolution higher than that of the original data by a factor in the range $\sim 1{\cdot}5$–$2{\cdot}0$.

5. Conclusion

In presentation of an information-theoretic density reconstruction procedure, an exponential model was elsewhere (Collins, 1982) presumed to provide a competent representation of electron density. In this paper the same basic procedure of iterative entropy maximization has been developed from the point of view that a good exponential model of density can be obtained by iterative correction of its logarithm.

Wilson's (1979) observation that 'the best objectively determinable estimate of the true density is the truncated Fourier series...' remains unchallenged, and primarily because of the unavoidable bias associated with the nonlinear relationship between density and structure factor in an exponential model. Nevertheless, we have shown that an exponential model of density can be of substantially higher resolution than the truncated Fourier series based on the same structure factors. Moreover, the procedure for deriving the positive-definite density model, which is an entropy maximization procedure (Collins, 1982), yields a density representation which qualitatively displays the property of minimum bias at the substantially higher resolution.

There is no discernible cause for placing an upper bound on the resolution enhancement demonstrated here for the simulation based on β-lyxose. As a practical matter resolution enhancement will be limited by the computational effort invested and this in turn is most likely to be affected by the rapidly diminishing returns of the iterative process. Although the procedure has been demonstrated with experimental data for a protein crystal structure (Collins, 1982), the manner in which error in the structure factors may impede the determination of an exponential density model is unknown and will be the subject of a future study. One definite limit on resolution enhancement is imposed by the fineness of the grid on which the density is represented. The window shape of Fig. 2 suggests that significant resolution enhancement cannot be expected unless the grid fineness is at least twice that which is minimally necessary for representation of the ordinary Fourier transformation of structure factors.

While the power of the procedures given here and elsewhere (Collins, 1982) depends in good measure on the generality of the exponential model, its very generality almost guarantees that more useful specific models can be developed during the solution of most crystallographic problems. For example, if at any stage of a structure determination atoms can be identified and accurately modeled in reciprocal space by available scattering factors, then the implied resolution which attends normal structure-factor least squares greatly exceeds that which is characteristic of routinely analyzed density functions. For the same reasons of generality in the exponential model, nonphysical features in a model density will persist if they are not in disagreement with the experimental moduli. From the perspective of information theory this is required by the procedure of entropy maximization because the entropy maximized is that which measures the change between density iterates. Thus the procedure ensures nothing concerning the final density function except that it is positive definite, it agrees with the data, and it was constructed in steps which are shortest in an information space.

Resolution enhancement, which has been demonstrated in the simulation, makes it clear that an exponential model of density can be good and in some respects better than the objective estimate available as a Fourier series. The model is also quite general although some impairment of generality may arise from the bias introduced by requiring the density to be positive definite.

This work has been supported in part by the Robert A. Welch Foundation through grant A-742 and by the Research Corporation through a Cottrell research grant.

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