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A Method for the Extension and Refinement of Crystallographic Protein Phases Utilizing the Fast Fourier Transform

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A method is formulated for refining and/or extending a set of crystallographic phases by real-space convolution utilizing the fast Fourier-transform algorithm. The method is applied to extending a set of myoglobin phases and the results show that high-resolution structural information can be obtained from high-resolution intensities and low-resolution phases.

Increasing interest is being shown in the application of the Karle & Hauptman (1956) tangent formula to refining and/or extending a set of crystallographic protein phases. Tangent formula calculations are presently done as reciprocal-space convolutions, and computer-time considerations limit the number of reflections which can be considered. Moreover, the non-negativity property of the electron-density function, which is assumed by this method, is only approximately satisfied when applied to data short of atomic resolution, and cannot be directly imposed on these data. Nor can other desirable adjustments of the electron-density function be made easily. We present a real-space method for phase extension and refinement involving the calculation of sharpened electron densities by a fast Fourier-transform algorithm, which minimizes these difficulties and is much simpler conceptually.

It is closely related to, but not analytically equivalent to, the tangent formula, and is also similar to the 'phase correction' techniques of Hoppe & Gassmann (1968). The method is here applied to predicting a set of myoglobin phases between 3 and 2 Å resolution. The predicted phases were generated from 2 Å intensities and from 3 Å phases obtained by the method of multiple isomorphous replacement. The extended (2 Å) electron density map showed noticeable improvement over the 3 Å map.

The method

Sayre (1952) showed that a relationship between structure factors (F's) can be derived from the fact that, for structures composed of like atoms, the electron density function, $\varrho(x,y,z)$, and its square are very nearly alike. Applying this condition to a sharpened electron density function or E map (ϱ_E), consisting essentially of point atoms, calculated from normalized structure factors (E's), one obtains the self-convolution

$$E_{\mathbf{h}} = C_{\mathbf{h}} \sum_{\mathbf{k}} E_{\mathbf{k}} E_{\mathbf{h}-\mathbf{k}} , \tag{1}$$

where C is real and, in principle, constant for a given resolution, and the E's are complex. Equating real and imaginary parts of equation (1), and dividing, yields the tangent formula:

$$\tan \varphi_{\mathbf{h}} = \frac{\sum_{\mathbf{k}} |E_{\mathbf{k}} E_{\mathbf{h}-\mathbf{k}}| \sin(\varphi_{\mathbf{k}} + \varphi_{\mathbf{h}-\mathbf{k}})}{\sum_{\mathbf{k}} |E_{\mathbf{k}} E_{\mathbf{h}-\mathbf{k}}| \cos(\varphi_{\mathbf{k}} + \varphi_{\mathbf{h}-\mathbf{k}})} . \tag{2}$$

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(This equation was actually obtained by Karle & Hauptman on the basis of statistical arguments.)

The phase, $\varphi_{\mathbf{h}}$, of a given reflection **h** is thus written in terms of the amplitudes and phases of the complete set of reflections. Where **h** is contained in the set of **k**, this cyclic process is one of 'refinement'; when this is not the case, it is 'extension'. (In the extension calculations presented in the next section, the **k**'s are the reflections out to 3 Å resolution and the **h**'s are those from 3 to 2 Å resolution.) Many sequential combinations of extension and refinement are obviously possible. The application of equation (2) to extending a set of protein phases ordered by E value magnitudes, rather than resolution, has been explored by Coulter (1969).

As currently evaluated this equation requires a number of operations proportional to $N_{\mathbf{h}} \times N_{\mathbf{k}}$, where $N_{\mathbf{h}}$ is the number of reflections (**h**) being refined or extended and $N_{\mathbf{k}}$ is the number of reflections (**k**) being used for this process. Calculation times can be considerably reduced from this N^2-type dependence by adopting a mathematically equivalent, but computationally faster, procedure involving Fourier transforms and particularly, the Cooley–Tukey (Cooley & Tukey, 1965) 'fast Fourier' algorithm. [An early formulation of this approach was given by Zwick (1968).] The method would be to simply calculate ϱ_E, the Fourier transform of the E's [represented below as $T(E_{\mathbf{k}})$], square it, and take the inverse transform:

$$E_{\mathbf{h}} = C_{\mathbf{h}} T^{-1}[\{T(E_{\mathbf{k}})\}^2] . \tag{3}$$

The phases of $E_{\mathbf{h}}$ thus calculated are combined with the *observed* amplitudes to generate a new ϱ_E for visual inspection or further cycling.

It is important to note that ϱ_E must be sampled more finely than its transform if the inverse Fourier operation is to yield accurate $E_{\mathbf{h}}$'s [see, *e.g.*, discussion of Lipson & Cochran (1966) who suggest sampling ϱ in any direction at 3 times the highest index observed in that direction]. Evaluation of equation (3) requires two transform operations. (The time for squaring is negligible.) If the problem were one-dimensional, and conventional Fourier methods were used, this real space calculation would exhibit the same N^2-type dependence as is shown by the reciprocal-space convolution, since the Fourier operation itself requires of order N^2 operations. This is not the case in three dimensions: The real space approach of equation (3) even with conventional Fourier programs, may be faster than the reciprocal space (tangent formula) method because the Beevers–Lipson procedure reduces Fourier calculations to significantly less than of order N^2 dependence. In many cases, however, even greater time savings can be achieved by the use of the Cooley–Tukey 'fast-Fourier' algorithm, and this is the technique which we have utilized here. [The power of the algorithm for speeding up convolution calculations was first explored by Stockham (1966).] The algorithm is also quite convenient, since, as it is usually programmed, it can be used equally well for both forward and reverse transforms, while conventional programs generally do not provide for performing the $\varrho_E \rightarrow E$ Fourier operation.

The Cooley–Tukey algorithm

The Cooley–Tukey algorithm (CTA) evaluates a transform sampled at M points in of order $M \log_2 M$ operations. From the point of view of a crystallographer, this algorithm can be considered to be essentially a generalization of the Beevers–Lipson factorialization method, so that even one-dimensional summations can be speeded up. (This is done by converting the scalar product, hx, into a vector dot product, $\mathbf{h} . \mathbf{x}$, where the dimensionality of the vector space is the number of bits required to specify these two numbers and where the binary representation of h and x specifies their vector components in this space.)

While in principle, this algorithm should be much faster than conventional Fourier methods, it has some features which diminish its comparative advantage. As presently programmed, the algorithm generates the same number of function values in both real and reciprocal space. Because of the sampling requirements of equation (3) mentioned earlier, the size of both forward and reverse transform calculations will be set by the number of points for which ϱ_E must be evaluated, and thus many very high resolution reflections will be unnecessarily considered. Secondly, existing, CTA programs do not utilize space group symmetry (although use can be easily made of Friedel's relation).

Even with these limitations Fourier calculations with the CTA are likely to be much faster than with conventional programs, when the complete transform can be held in core storage (as was the case in the present work). The CTA has also been programmed for use with auxiliary storage (tapes or disc) by Singleton (1967) and by Brenner (1968). For such applications, calculation times are slower and highly dependent upon the particular computer system configuration being used.

Both of the above-cited limitations (non-utilization of space group symmetry and consideration of many unnecessary reflections) are probably not intrinsic to the algorithm, and we are currently trying to modify it to take these factors into account. The second limitation is, in some sense, an advantage in that many of the complexities which space group considerations introduce into conventional Fourier or tangent formula calculations are here simply avoided.

The Cooley–Tukey algorithm also suffers somewhat in flexibility in that the transform domain is a parallelepiped, each of whose sides is sampled at 2^i points, where i is some integer. This is not an absolute requirement, but most programs deal with this case. Generally, the number of points sampled in any direction should be a highly composite number, if the algorithm is to yield substantial benefit.

The CTA–Fourier program used by us (which makes use of the Friedel relation) was written by Norman Brenner of the M. I. T. Lincoln Laboratories. A more detailed discussion of some computational aspects of this work is given in a later section of this paper.

The method, continued: modifying the density function

In an application of equation (2) to refining phases of cytochrome-C at 4Å resolution, Weinzierl, Eisenberg & Dickerson (1969) draw attention to the fact that the existence of negative regions of density (generated by series termination and other errors) may be a source of difficulty. The tangent formula gives the phases of the squared E map. If the $E_{\bar{k}}=E_{000}$ term is included in both the numerator and denominator of equation (2), the zero level of the 'implied' E map will be properly adjusted and the map *ideally* will be free of negative regions. However, series termination and other errors nevertheless generate such regions which will, effectively, be squared into false peaks. A reciprocal space calculation with equation (2) cannot deal with this problem. However, in the real space method discussed here, all negative values of ϱ_E are simply set to zero before squaring. Thus the present approach, aside from its computational advantages, should be more powerful, analytically, than the tangent formula.

We wish to clarify and emphasize this point by noting that equating to zero, negative density regions, or more generally, setting minimum significance levels, can be used by itself, *i.e.* without squaring, for phase extension in resolution. This has been shown by Kartha (1969), in calculations on small test molecules. (The use of this method for generating new phases at a given resolution or for refinement of 'old' phases has not, to our knowledge, been tested.)

Nevertheless; squaring ϱ_E after minimum-level truncation should yield additional dividends, since it introduces further information beyond the positivity of the density function, namely its atomicity. This will depend, of course, on resolution. However, it is not unreasonable to expect that the phases of the squared and minimum-truncated ϱ_E may be superior to those of the merely truncated ϱ_E, even when individual atoms are not resolved, since the spatial distribution of electron density values may still approximate the atomic more closely than it resembles some set of random positive numbers. The question deserves further study. For the calculations presented in the next section, we have used both minimum level truncation and squaring, and have not attempted to separate out their relative contributions to the phase extension example.

It is worth stressing that use of squaring for phase extension/refinement does *not* result simply in sharpening, although that effect is inevitably also obtained. More sharpening would result from using the calculated E amplitudes with the calculated phases for the ϱ_E synthesis; the use of observed E values, however, produces qualitative changes in the feature of the map. (The view that intensity information specifies only peak heights and not positions is commonly heard, but is clearly incorrect.)

Other modifications of the density function may be desirable before the inverse transform is taken and its phases are used for a new cycle. For example, a maximum truncation level can be set, in addition to a minimum level, to prevent a multi-cycle phase refinement from diverging because of repeated enhancements of the strongest peaks.

The phas ecorrection methods of Hoppe & Gassmann are similar to the techniques discussed here. In their 1968 paper, these authors are principally concerned with the automatic completion of partial structural solutions, and the modification of ϱ is tailored to this particular application. They utilize reciprocal space calculations, but emphasize that for large structures, real space methods are much faster. In phase correction, ϱ is modified by a combination of square and cubic terms. The square term functions as it does here in the present paper; the cubic term essentially serves the purpose of limiting the maximum density level. This polynomial method is needed for the reciprocal space approach, but can be discarded in real space calculations in favor of more intuitively-justifiable modifications (which may be difficult to represent analytically in a reciprocal space convolution expression). Thus, in more recent work, Hoppe, Gassmann & Zechmeister (1969) also propose, for the real space approach, the previously mentioned and quite simple technique of maximum-level truncation, essentially in place of the cubic. (They use this method in their linear form.) We may also note that, when done in reciprocal space, phase correction shares with the tangent formula the further disadvantage of improperly treating negative density regions.

Our present method differs from real-space phase correction principally in that we use E's, and thus our approach closely resembles the familiar tangent formula of Karle & Hauptman, while Hoppe & Gassmann deal with F's and the unsharpened, ordinary, density map. Because the E map exhibits more severe series termination effects than the F map, minimum-level truncation is likely to be more critical and thus more useful for phase extension, in the former case; likewise squaring might be more valid at lower resolution for ϱ_E than it would be for ϱ. Perhaps equivalently, the statistical arguments which favor the use of E's, rather than F's, in the tangent formula would support their use in real space methods as well. However, these questions should certainly be tested empirically.

We hope this brief discussion helps clarify some of the interrelationships between these several methods, which are all really based upon a few exceedingly simple physical principals.

Application of the method to extending a set of myoglobin phases

A situation commonly found in protein structure analysis occurs when intensity information can be obtained beyond the resolution range for which phases are available. This is not uncommon in the neighborhood of 3Å resolution beyond which it becomes increasingly difficult to obtain accurate phases, although amplitudes may well extend to 2 Å resolution or below.

To what extent is equation (3) useful for calculating phases in practice? We have attempted to answer this by calculating phases from 3 to 2 Å which are then combined with the observed (3 to 2 Å) amplitudes to give an extended Fourier synthesis, hopefully superior to the 3 Å map. If successful this approach would facilitate the interpretation of electron density maps. At low resolution (for example, 3 Å to 2 Å extension), it would help in tracing the course of the polypeptide chain; at high resolution (*e.g.* 2 to 1·5 Å extension) it could yield, without bias from an existing model, more reliable val-

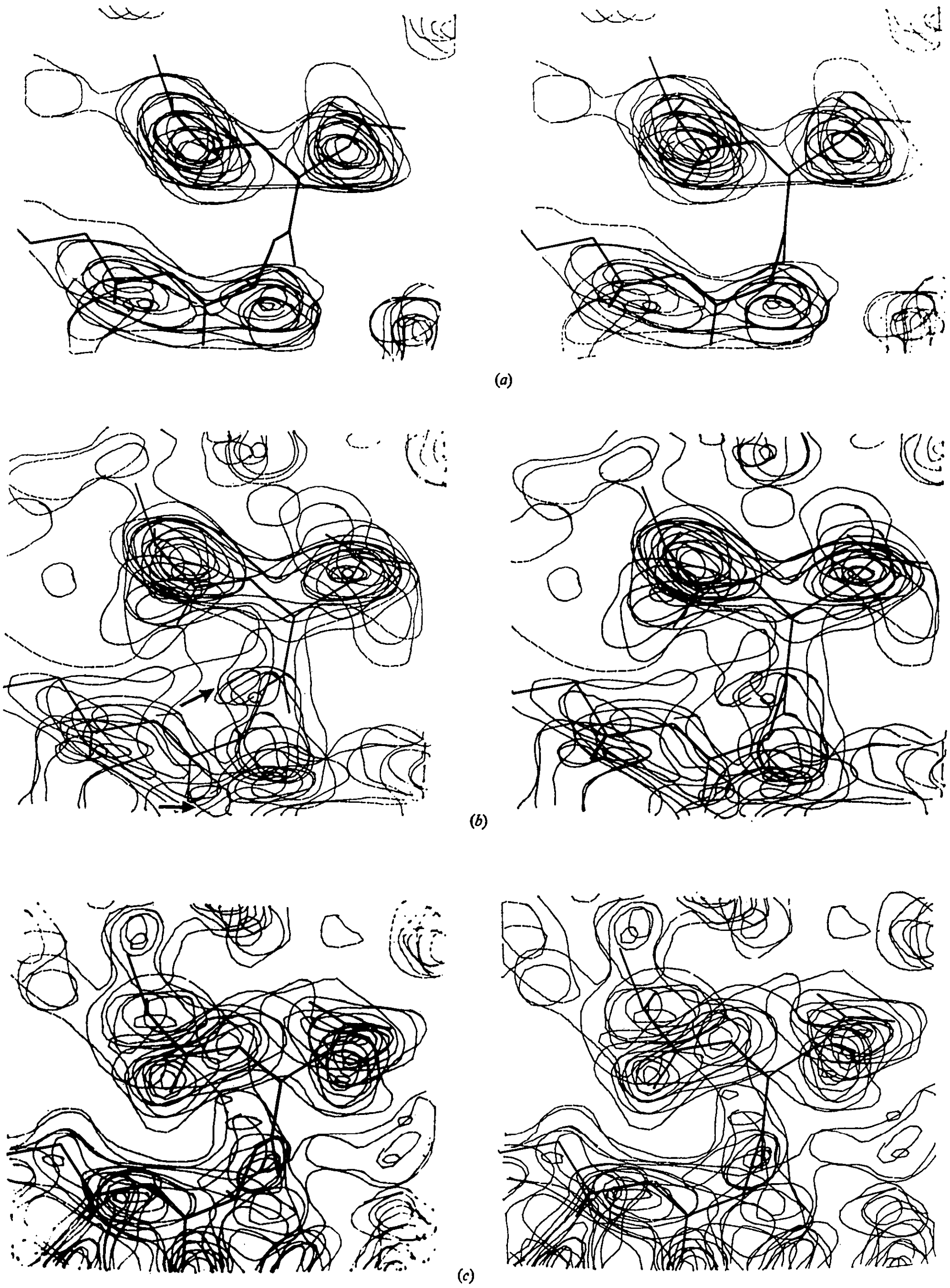

Fig. 1. Stereo pair photographs of the electron density of myoglobin in a region of the *H* helix. A model of the molecule based on the 2 Å coordinates is superimposed. (*a*) Electron density distribution using E_{obs}, φ_{obs} to 3 Å, (*b*) density distribution using extended phases, (*c*) electron density distribution using E_{obs}, φ_{obs} to 2 Å.

ues for atomic coordinates and possibly reveal new atoms not clearly defined in previous maps. This high resolution case, for myoglobin and vitamin B-12, has been considered by Hoppe & Gassmann (1964) with a reciprocal space convolution of F's.

From a set of about 9000 2 Å myoglobin intensities, we first computed the normalized structure factors E_{obs}, using the K-curve method of Karle, Hauptman & Christ (1958). The origin term, $E(0,0,0)$, was calculated on the basis of the 2400 myoglobin atoms in the unit cell, thus effectively ignoring the solvent contribution to the intensities. With values of E_{obs} and isomorphous phases, φ_{obs}, to 3 Å resolution, we computed an electron density map. Fig. 1(*a*) shows a portion of the map in a region containing the first four residues of the H helix. (We avoided the region around the heme because of possible ripple effects introduced by the iron). A model of this part of the helix was constructed on a graphics display from a set of myoglobin coordinates, and was superposed over a display of the electron density sections. To extend the phases, the electron density was first modified by eliminating all negative regions and then squared. The inverse transform of the squared structure gave both unscaled amplitudes, E_{calc} and the required phases φ_{calc}. A comparison between the predicted φ_{calc} and true (isomorphous) phases φ_{obs} between 2 and 3 Å gave an average phase difference, $\langle|\varphi_{\text{obs}}-\varphi_{\text{calc}}|\rangle$, of 82°. (90° is expected for random results.) Since Weinzierl, Eisenberg & Dickerson (1969) showed that the error in phases calculated through the tangent formula decreased with increasing E_{obs}, we accepted those values of φ_{calc} for which the corresponding E_{obs} values was greater than 1. This gave some 2000 values of φ_{calc} for which $\langle|\varphi_{\text{obs}}-\varphi_{\text{calc}}|\rangle$ was now 78°. An electron density map was computed with Fourier components comprising values of $\{E_{\text{obs}}, \varphi_{\text{calc}}\}$ between 3 and 2 Å for which $E_{\text{obs}} > 1$ in addition to all values of $\{E_{\text{obs}}, \varphi_{\text{obs}}\}$ to 3 Å. Fig. 1(*b*) shows the region of this extended map corresponding to that in Fig. 1(*a*). (This extended map was noticeably superior to the map based upon all of the extended reflections, indicating that the improvement in phase statistics is significant).

For comparative purposes, we also generated a map using all $\{E_{\text{obs}}, \varphi_{\text{obs}}\}$ to 2 Å, shown in Fig. 1(*c*). All maps were evaluated over the unit cell at approximately half-Ångstrom intervals, and were contoured starting from identical lowest density values. The intervals chosen for contouring the 2 Å and the 2 Å-extended maps was twice that used for the 3 Å map. (The smaller interval did not give any increased detail.)

The extended map of Fig. 1(*b*) shows several desirable features (see arrows) not present on the 3 Å map [Fig. 1(*a*)], which correlate with the known myoglobin structure, and resemble the 2 Å map. In particular notice the additional density in the region of atoms linking the upper and lower portions of the chain, and in the lower central region just above the labelling of the photographs. Fig. 1(*b*) also generally shows more peaks in areas close to atomic positions. Density corresponding to atoms external to this portion of helix were present on both the extended and 2 Å maps (and absent on the 3 Å map) although the peaks on the former were shifted slightly relative to those of the latter.

An examination of other sections of density in a region distant from the H helix showed similar improvements as a result of extending the phases from 3 to 2 Å resolution. Further improvement of the results should be possible by combining extension with refinement, *i.e.* performing more than a single cycle and experimenting with phase selection criteria involving comparisons of E_{obs} and E_{calc}.

Computational aspects

In the present example, the transform was evaluated entirely within the core memory of an IBM 360/95. The myoglobin unit cell is (64·5, 30·9, 34·7), and at 2 Å, the limiting (h,k,l) values are (30, 15, 17). The transform was evaluated at 128 × 64 × 64 – or about one-half million – points, and took about 50 seconds. This corresponds roughly to half-Ångstrom sampling of the cell, somewhat more than is needed according to Lipson & Cochran. In reciprocal space, this array includes reflections within index limits of (64, 32, 32) – clearly very many more than are needed to generate ϱ_E or are of interest for the phase extension. (A (64 × 32 × 32) array size would fall somewhat short of the Lipson–Cochran sampling proposal, being approximately twice rather than three times the 2 Å (h,k,l) limits. However it would be most interesting to see if phase extension and/or refinement would work with this reduced array, since a much smaller core memory can be used and the calculation would be 24 times faster because of the $M \log_2 M$ dependence.)

A cycle of extension thus required less than two minutes of computer time and yielded calculated intensity and phase values for $N_h \simeq 9000$ (asymmetic unit) reflections to 2 Å from $N_k \simeq 3000$ reflections to 3 Å. While only 2000 of the 9000 phases were used here, in other applications and with proper weighting schemes, for example, weighting by figures of merit, one might well consider utilizing all the calculated quantities. Even with smaller core machines, where auxiliary storage must be used, the present real-space approach to (modified) tangent formula calculations should still give very significant time savings. The advantage of the Cooley–Tukey algorithm over conventional Fourier programming under such conditions is a separate consideration which will depend on the detailed nature of the crystallographic problem and on the computer facilities which are available. To emphasize the point, however, that in-core transforms by the Cooley–Tukey algorithm are exceedingly fast, we note that if the 7094 had a much larger core size, a transform such as is considered here would take only about 10 minutes, even without use of Friedel's symmetry. This is obtained by an $M \log_2 M$ extrapolation from data given in the Cooley–Tukey (1965) paper.

Concluding remarks

Real space modified tangent formula convolutions utilizing the Cooley & Tukey fast Fourier algorithm are fast and convenient. A single cycle of phase extension from 3 to 2 Å produces definite improvements in the 3 Å electron density map. Further work in this and other applications is in progress.

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Entschmierung von fehlerbehafteten Röntgen-Kleinwinkel-Streukurven

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The experimentally determined small-angle X-ray scattering curve is approximated by a Fourier series. For smoothing the scattering curve a limit for the correlation range of the difference of the electron density from the average is presupposed. The smoothing, the correction of the slit width error by deconvolution and the differentiation for the correction of slit height error are carried out with the Fourier coefficients. The smeared scattering curve is reconstructed by Fourier synthesis. The method makes it possible to correct scattering curves with random and no-random errors working with digital computers in on-line or off-line technique.

Einführung

Bei Strukturuntersuchungen mit Hilfe der isotropen Röntgen-Kleinwinkelstreuung (RKWS) werden aus Intensitätsgründen meist Diffraktometer mit Schlitzgeometrie (Kratky, 1967) benutzt. Hierbei tritt eine, als Verschmierung (Kratky, Porod & Skala, 1960) bezeichnete, apparativ bedingte Verzerrung der Streukurven auf. Sie muss im allgemeinen vor der weiteren Auswertung der Streukurven rechnerisch eliminiert werden. Die experimentellen Methoden zur Registrierung der RKWS sind in den letzten Jahren wesentlich verbessert worden. Es ist möglich, RKWS-Diagramme mit automatisch gesteuerten Diffraktometern mit einem Fehler, der kleiner als 1 % ist, zu registrieren. Diese Messgenauigkeit darf durch die notwendige Entschmierung nicht in Frage gestellt werden. Daher sind in den letzten Jahren verschiedene Methoden dafür diskutiert und erprobt worden.

Übersichten über die verschiedenen analytisch-numerischen Methoden, die als Entschmierung bezeichnet werden, geben Hossfeld (1968), Lake (1967), Fjedorov (1968), Fjedorov, Andrejeva, Volkova & Voronin (1968) und Taylor & Schmidt (1967). Es sind strenge mathematische Lösungen für die die Verschmierung beschreibende Integralgleichung von Mazur & Wims