DIRECT METHODS
History and Community Development

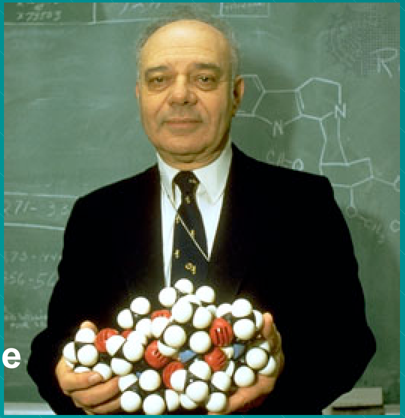
a personal account

Davide Viterbo

Università del Piemonte Orientale
“A. Avogadro”, Alessandria, Italy

The birth of direct methods

I was not there, but I had accounts from many of the “fathers”



J. Karle

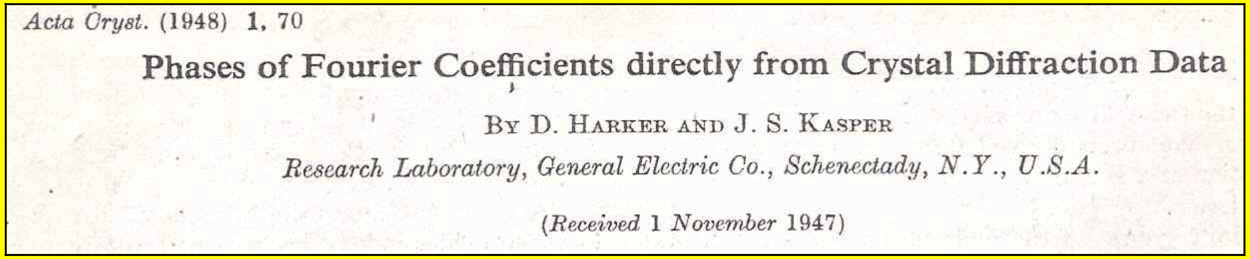
D.Sayre

M.M.Woolfson

H.Hauptman

F. Bertaut

From measured intensities to phases



Acta Cryst. (1948) 1, 70

Phases of Fourier Coefficients directly from Crystal Diffraction Data

By D. Harker and J. S. Kasper

Research Laboratory, General Electric Co., Schenectady, N.Y., U.S.A.

(Received 1 November 1947)

1948
THE FIRST STEP
HARKER & KASPER INEQUALITIES

Cauchy inequality: $\left|\sum_{j=1}^{N} a_j b_j\right|^2 \leq \sum_{j=1}^{N} |a_j|^2 \sum_{j=1}^{N} |b_j|^2$

Unitary structure-factor equation in $P\overline{1}$

$$U_H = \sum_{j=1} n_j \cos 2\pi H \cdot r = \sum_{j=1} a_j b_j$$

with $a_j = n_j^{1/2}$ **and** $b_j = n_j^{1/2} \cos 2\pi H \cdot r$

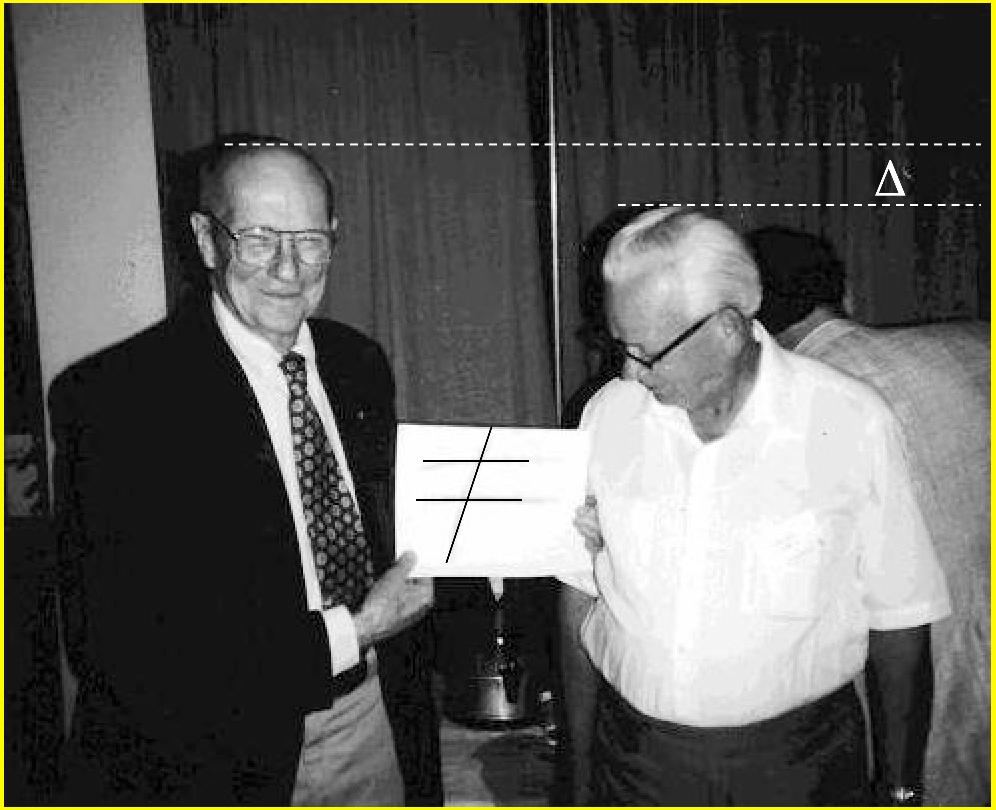
gives: $U_H^2 \leq \left(\sum_{j=1}^{N} n_j\right)\left(\sum_{j=1}^{N} n_j \cos^2 2\pi H \cdot r\right).$

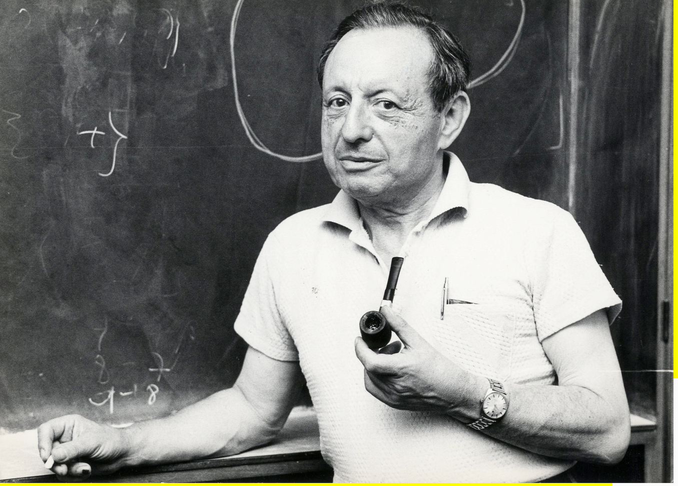
first summation = 1 and

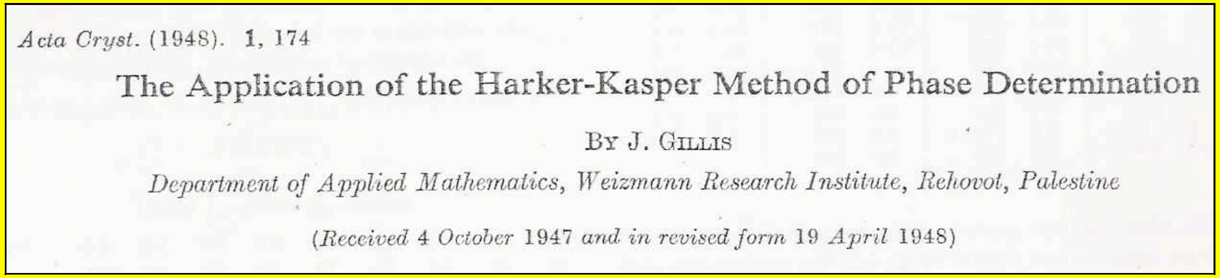
$$\cos^2 2\pi H \cdot r = \frac{1}{2}(1 + \cos 2\pi\, 2H \cdot r)$$

therefore $U_H^2 \leq \frac{1}{2}(1 + U_{2H}).$

If $U_H^2 > \frac{1}{2}$ **then** $U_{2H} \geq 0$







Acta Cryst. (1948). **1**, 174

The Application of the Harker-Kasper Method of Phase Determination

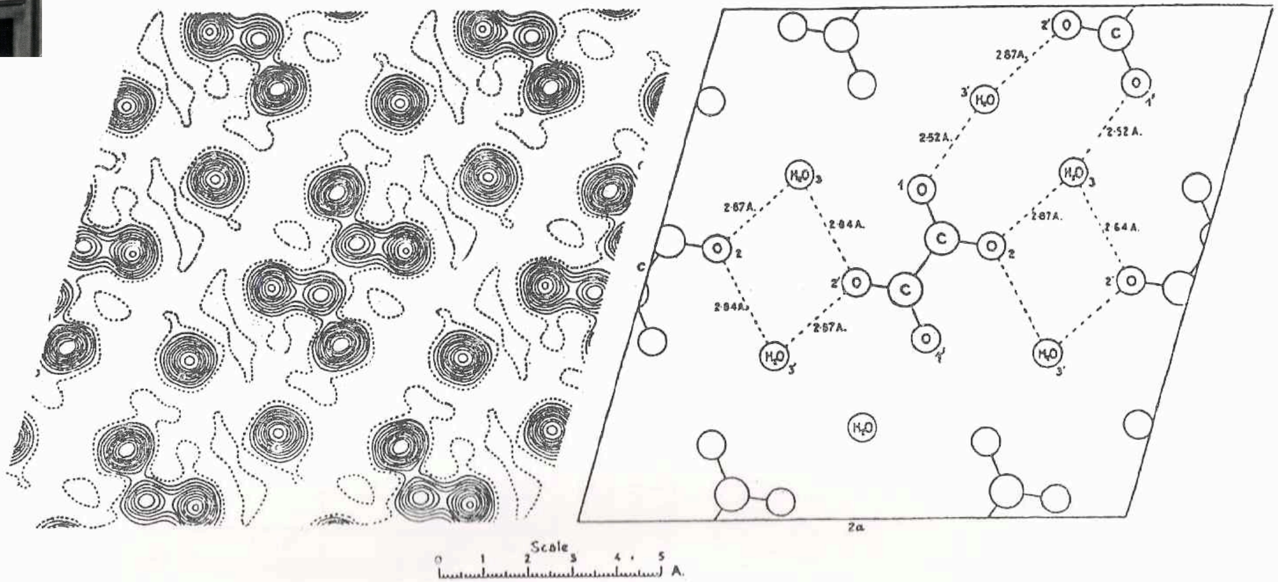
By J. Gillis

Department of Applied Mathematics, Weizmann Research Institute, Rehovot, Palestine

(Received 4 October 1947 and in revised form 19 April 1948)

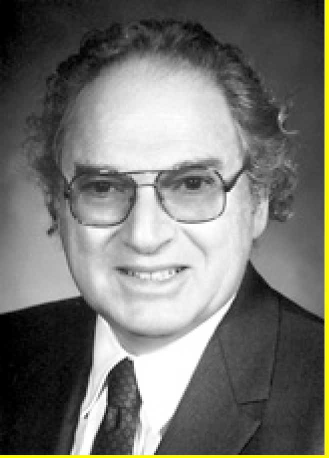
Joseph Gillis 1948

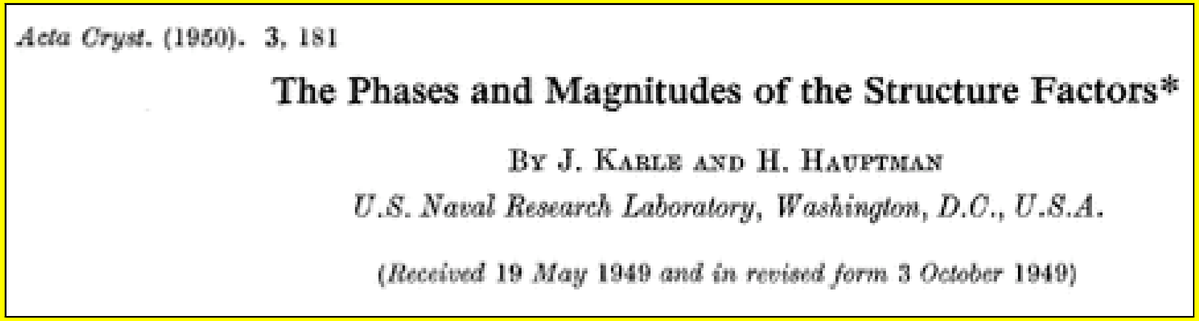
- Oxalic acid dihydrate redetermined
  using for the first time inequalities
- Symbols to represent signs
- Fixing origin



- Hint of probability arguments:

There were many instances ……, in which both signs satisfied an inequality, one by a comfortable margin and the other by a relatively narrow margin. In almost all such cases it was the former sign which was the correct one. This suggest that the method may have “reserves of power” in the sense that stronger inequalities than those used are in fact satisfied.





Acta Cryst. (1950). **3**, 181

The Phases and Magnitudes of the Structure Factors*

BY J. KARLE AND H. HAUPTMAN

U.S. Naval Research Laboratory, Washington, D.C., U.S.A.

(Received 19 May 1949 and in revised form 3 October 1949)

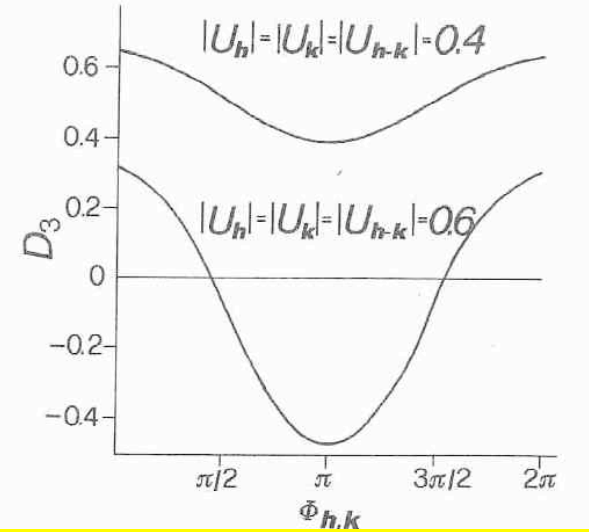
General inequality in determinant form, from positivity of the electron density function

$$D_m = \begin{vmatrix} U_0 & U_{-\mathbf{h}_1} & U_{-\mathbf{h}_2} & \cdots & U_{-\mathbf{h}_n} \\ U_{\mathbf{h}_1} & U_0 & U_{\mathbf{h}_1-\mathbf{h}_2} & \cdots & U_{\mathbf{h}_1-\mathbf{h}_n} \\ U_{\mathbf{h}_2} & U_{\mathbf{h}_2-\mathbf{h}_1} & U_0 & \cdots & U_{\mathbf{h}_2-\mathbf{h}_n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ U_{\mathbf{h}_n} & U_{\mathbf{h}_n-\mathbf{h}_1} & U_{\mathbf{h}_n-\mathbf{h}_2} & \cdots & U_0 \end{vmatrix} \geq 0.$$

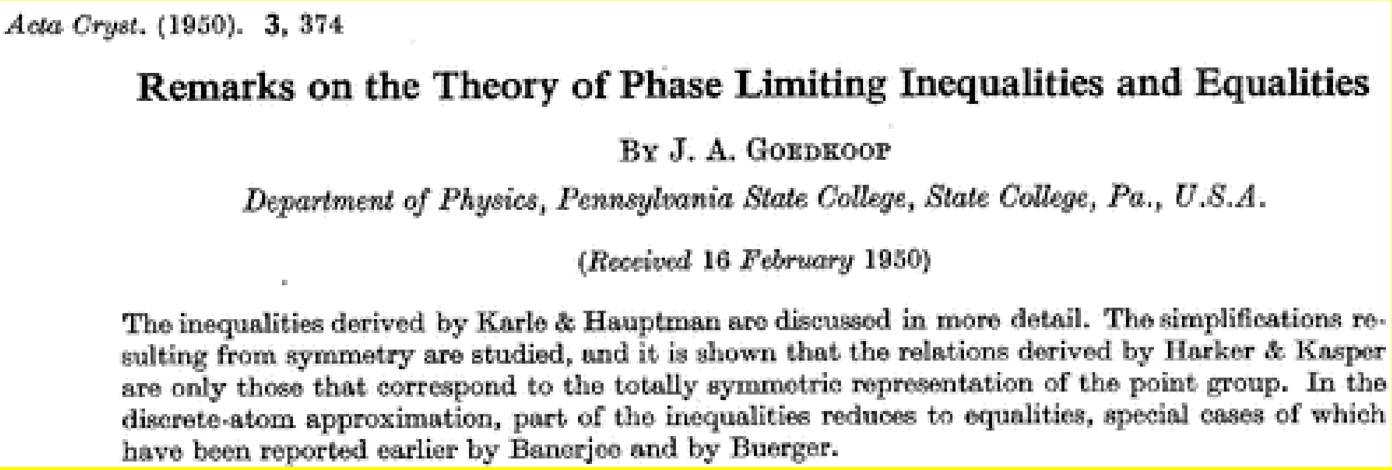
$$D_3 = \begin{vmatrix} 1 & U_h & U_k \\ U_{-h} & 1 & U_{-h+k} \\ U_{-k} & U_{h-k} & 1 \end{vmatrix}$$

$$1 - |U_h|^2 - |U_k|^2 - |U_{h-k}|^2 + 2\,|U_h U_k U_{h-k}| \cos \Phi_{h,k} \geq 0$$

$$\Phi_{h,k} = \boxed{\phi_h - \phi_k - \phi_{h-k}}$$



Goedkoop introduced symmetry



Acta Cryst. (1950). **3**, 374

Remarks on the Theory of Phase Limiting Inequalities and Equalities

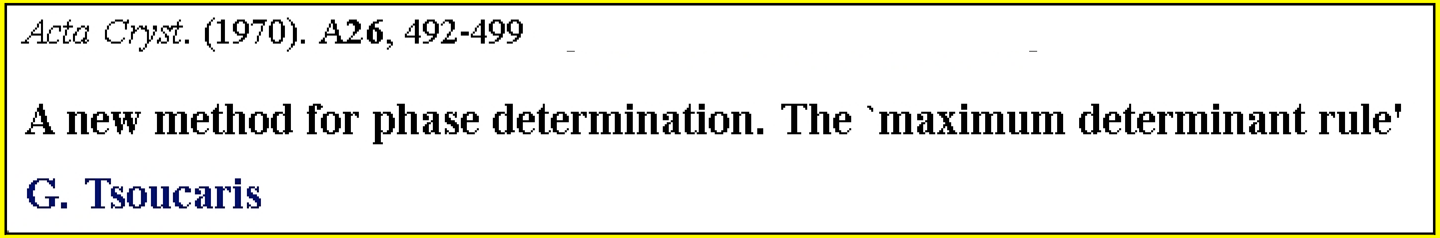
By J. A. Goedkoop

Department of Physics, Pennsylvania State College, State College, Pa., U.S.A.

(*Received 16 February* 1950)

The inequalities derived by Karle & Hauptman are discussed in more detail. The simplifications resulting from symmetry are studied, and it is shown that the relations derived by Harker & Kasper are only those that correspond to the totally symmetric representation of the point group. In the discrete-atom approximation, part of the inequalities reduces to equalities, special cases of which have been reported earlier by Banerjee and by Buerger.

Later George Tsoucaris and his group analyzed the Karle-Huptman determinants from the probability point of view and explored their use



Acta Cryst. (1970). A**26**, 492-499

A new method for phase determination. The `maximum determinant rule'

G. Tsoucaris

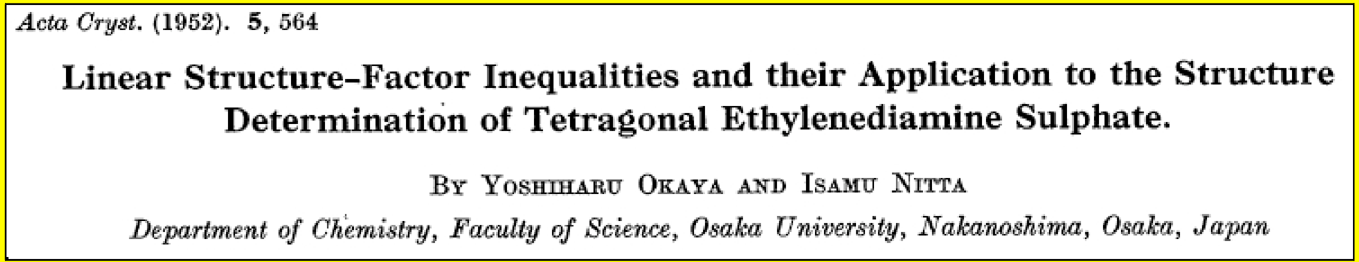
Acta Cryst. (1974). A**30**, 342-353

Phase determination from the Karle-Hauptman determinant. II. Connexion between inequalities and probabilities

C. de Rango, G. Tsoucaris and C. Zelwer

Okaya & Nitta and Zachariasen

Use of symbols – symbolic addition

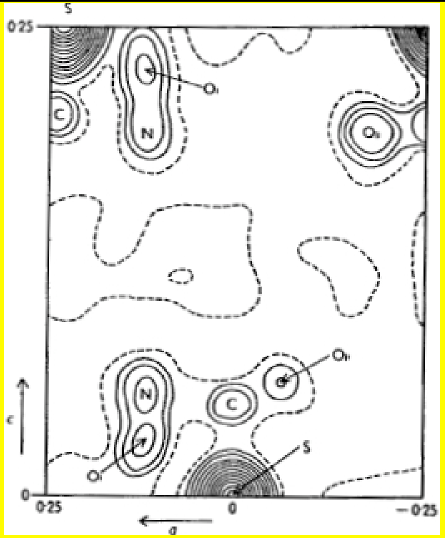


Acta Cryst. (1952). **5**, 564

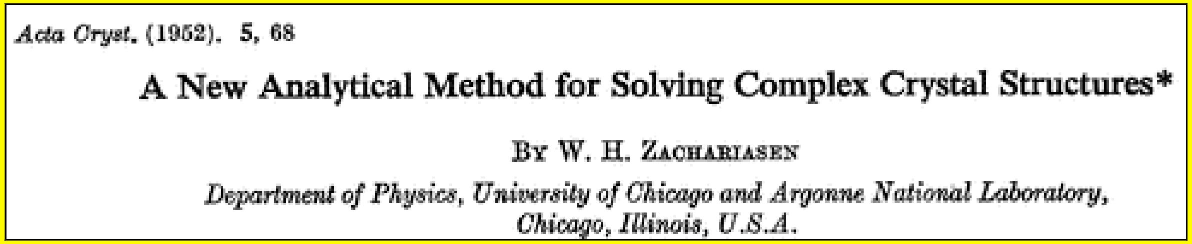
Linear Structure-Factor Inequalities and their Application to the Structure Determination of Tetragonal Ethylenediamine Sulphate.

By Yoshiharu Okaya and Isamu Nitta

Department of Chemistry, Faculty of Science, Osaka University, Nakanoshima, Osaka, Japan



Electron density (x,z) projection of Ethylenediamine Sulphate computed using the signs determined by the linear inequality method

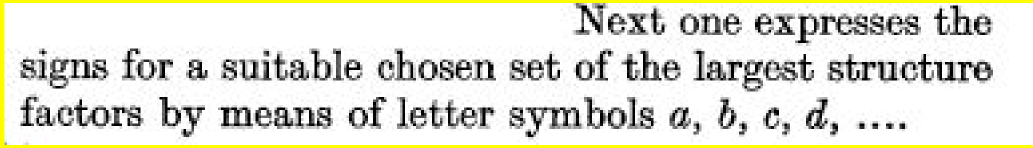


Acta Cryst. (1952). **5**, 68

A New Analytical Method for Solving Complex Crystal Structures*

By W. H. Zachariasen

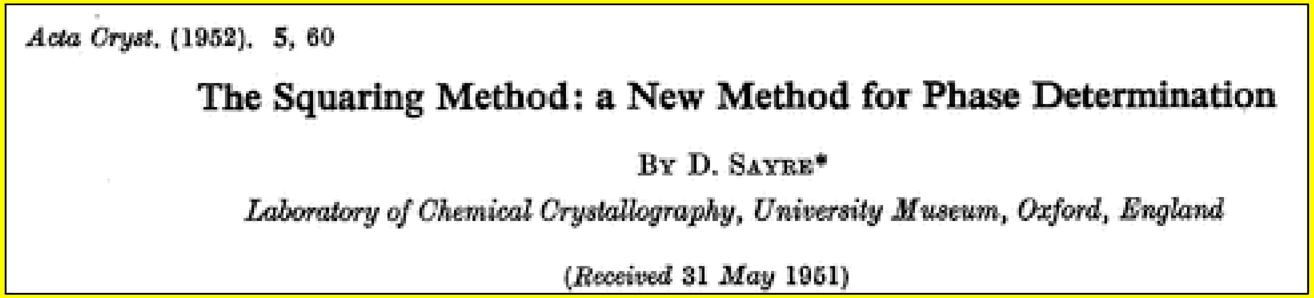
Department of Physics, University of Chicago and Argonne National Laboratory, Chicago, Illinois, U.S.A.



Next one expresses the signs for a suitable chosen set of the largest structure factors by means of letter symbols *a*, *b*, *c*, *d*, ...

Method applied to solve the structure of metaboric acid

1952 Sayre equation (positivity and atomicity)



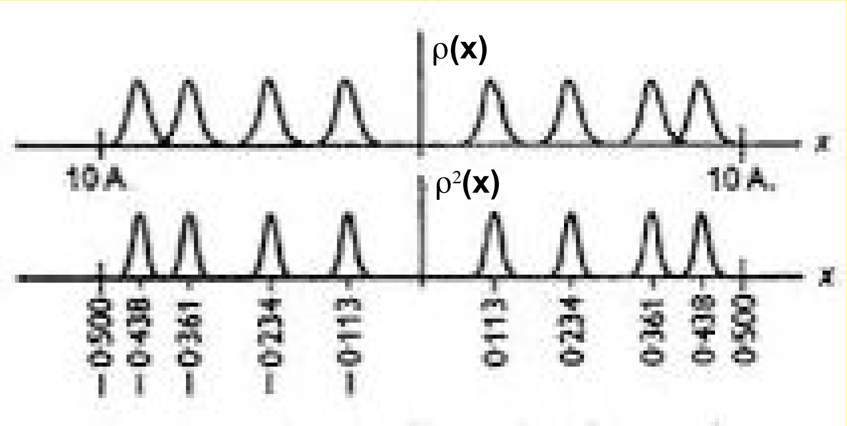
Acta Cryst. (1952). 5, 60

The Squaring Method: a New Method for Phase Determination

By D. Sayre*

Laboratory of Chemical Crystallography, University Museum, Oxford, England

(*Received* 31 *May* 1951)



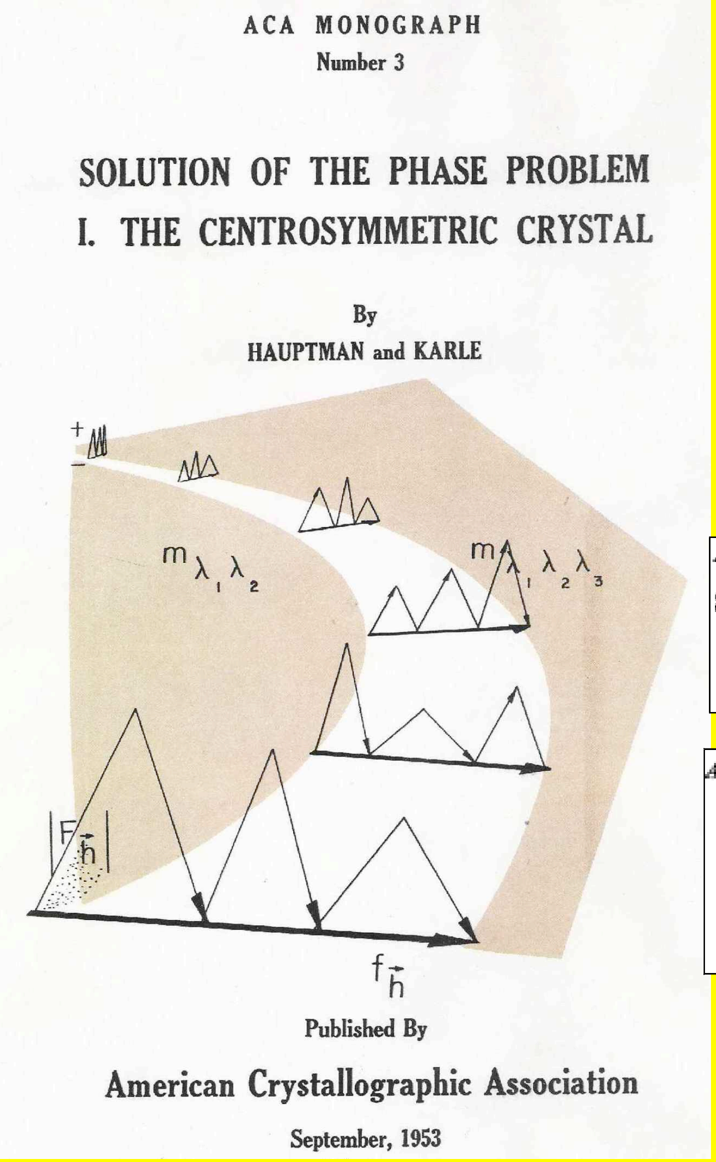
For positive, almost equal and separate atomic peaks ρ²(x) is similar to ρ(x) with maxima at same positions

$$F_{\mathbf{h}} = \frac{\theta_{\mathbf{h}}}{V}\sum_{\mathbf{k}} F_{\mathbf{k}} F_{\mathbf{h-k}} \qquad \theta_{\mathbf{h}} = \frac{f_{\mathbf{h}}}{g_{\mathbf{h}}}$$

$$|F_{\mathbf{h}}|^2 = \frac{\theta_{\mathbf{h}}}{V}\sum_{\mathbf{k}} |F_{-\mathbf{h}} F_{\mathbf{k}} F_{\mathbf{h-k}}| \exp[i\boxed{(\phi_{-\mathbf{h}} + \phi_{\mathbf{k}} + \phi_{\mathbf{h-k}})}]$$

David Sayre told me that one day in 1951, while attending his DPhil course in Oxford, he went to the library without any specific purpose. He picked up a book on *Fourier transforms*, started reading and the *squaring* idea came to his mind. He immediately devised a one dimensional example to verify the idea and the next day he knew that the doctor title was in his hands and wrote the short communication for Acta Crystallographica.

1953 Karle & Hauptman monograph



ACA MONOGRAPH
Number 3

SOLUTION OF THE PHASE PROBLEM
I. THE CENTROSYMMETRIC CRYSTAL

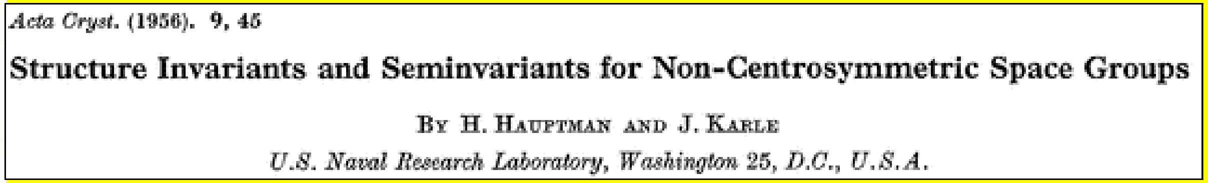
By
HAUPTMAN and KARLE

Published By
American Crystallographic Association
September, 1953

First ambitious attempt at giving a systematic description of Direct Methods, followed by several developments:

- Definition of structure invariants and seminvariants
- Formulae Σ_1, Σ_2 (triplets), Σ_3
- Extension to non-centrosymmetric structures
- Introduction of probabilistic approaches
- Derivation of probability formulae
- Tangent formula.

Several other people contributed to these initial theoretical developments.

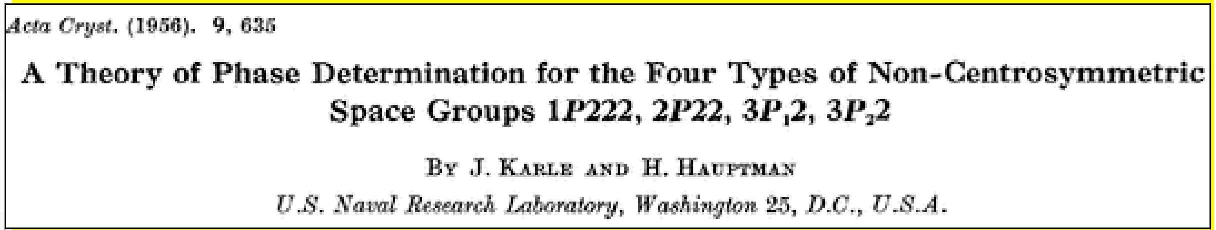


Acta Cryst. (1956). 9, 45

Structure Invariants and Seminvariants for Non-Centrosymmetric Space Groups

By H. Hauptman and J. Karle

U.S. Naval Research Laboratory, Washington 25, D.C., U.S.A.



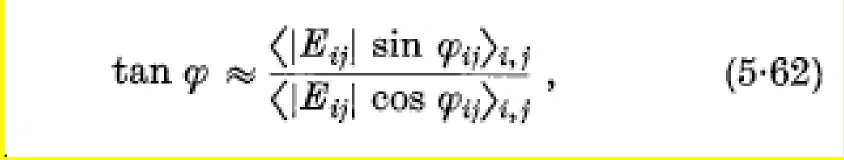
Acta Cryst. (1956). 9, 635

A Theory of Phase Determination for the Four Types of Non-Centrosymmetric Space Groups 1P222, 2P22, 3$P_1$2, 3$P_2$2

By J. Karle and H. Hauptman

U.S. Naval Research Laboratory, Washington 25, D.C., U.S.A.

First appearence of tangent formula



$$\tan\varphi \approx \frac{\langle|E_{ij}|\ \sin\varphi_{ij}\rangle_{i,j}}{\langle|E_{ij}|\ \cos\varphi_{ij}\rangle_{i,j}}, \qquad (5\cdot62)$$

1953-1966

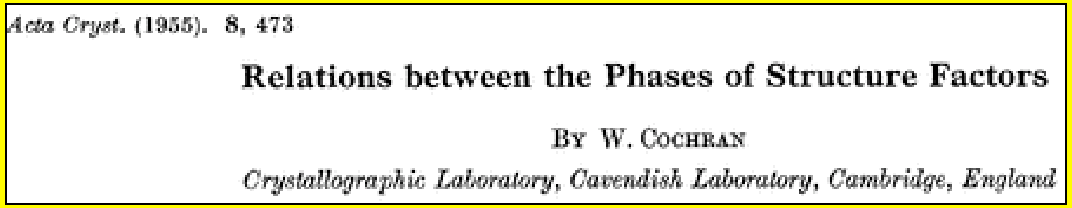
Several theoretical developments with different probabilistic approaches were published by Cochran, Woolfson, Bertaut, Klug and others.

Acta Cryst. (1955). 8, 1

The Theory of Sign Relations Between Structure Factors

By W. Cochran and M. M. Woolfson

Crystallographic Laboratory, Cavendish Laboratory, Cambridge, England

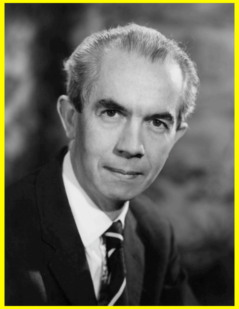


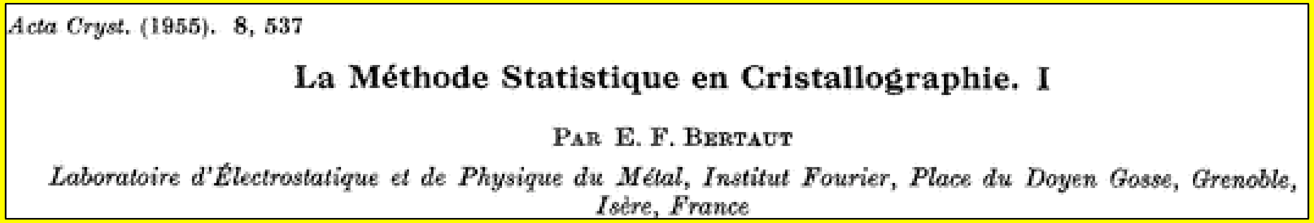
Acta Cryst. (1955). 8, 473

Relations between the Phases of Structure Factors

By W. Cochran

Crystallographic Laboratory, Cavendish Laboratory, Cambridge, England





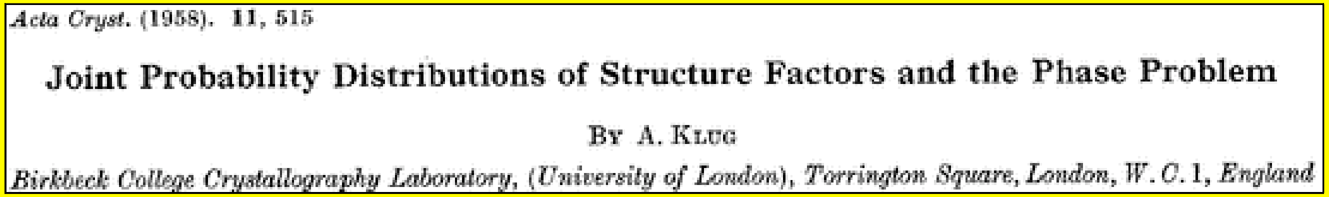
Acta Cryst. (1955). 8, 537

La Méthode Statistique en Cristallographie. I

Par E. F. Bertaut

Laboratoire d'Électrostatique et de Physique du Métal, Institut Fourier, Place du Doyen Gosse, Grenoble, Isère, France

Their probabilistic approaches inspired the original work by Carmelo Giacovazzo

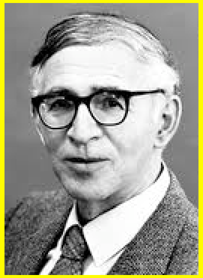


Acta Cryst. (1958). 11, 515

Joint Probability Distributions of Structure Factors and the Phase Problem

By A. Klug

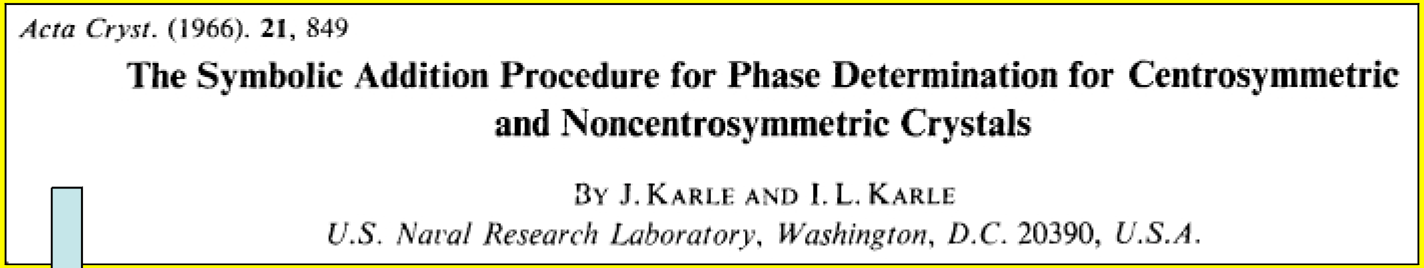
Birkbeck College Crystallography Laboratory, (University of London), Torrington Square, London, W.C. 1, England



1953-1966

The mathematical formalism discouraged most chemical crystallographers and the practical applications of direct methods where very limited.

***Only very few crystal structures were solved. What happened in 1966*?**



Acta Cryst. (1966). **21**, 849

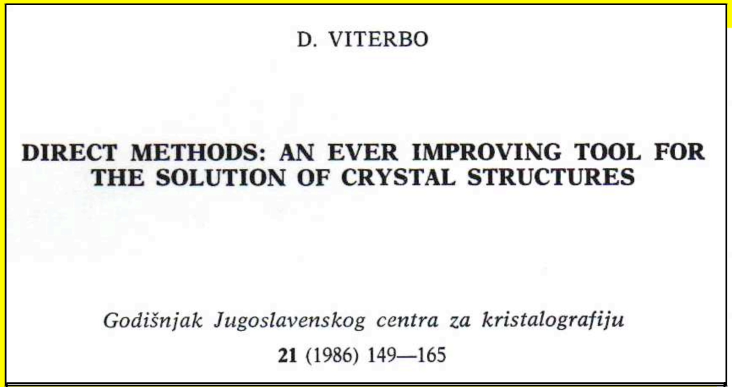
The Symbolic Addition Procedure for Phase Determination for Centrosymmetric and Noncentrosymmetric Crystals

By J. Karle and I. L. Karle

U.S. Naval Research Laboratory, Washington, D.C. 20390, U.S.A.

This paper, giving a number of practical rules for the solution of crystal structures by direct methods, was the seed for the rapid increase in their use.

***Isabella Karle* was the key person.**



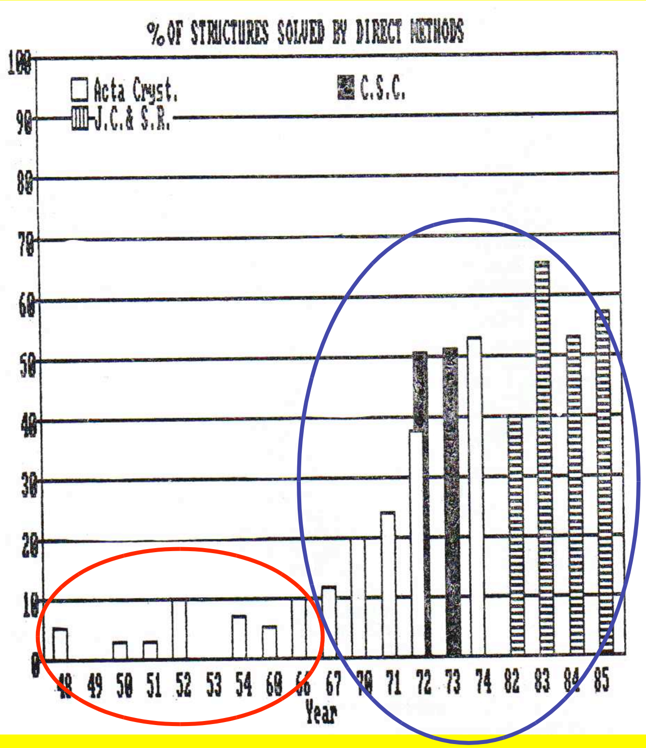
D. VITERBO

DIRECT METHODS: AN EVER IMPROVING TOOL FOR THE SOLUTION OF CRYSTAL STRUCTURES

Godišnjak Jugoslavenskog centra za kristalografiju

21 (1986) 149—165

Lecture given in Padova in 1986 after the Nobel Prize conferred on Karle & Hauptman in 1985

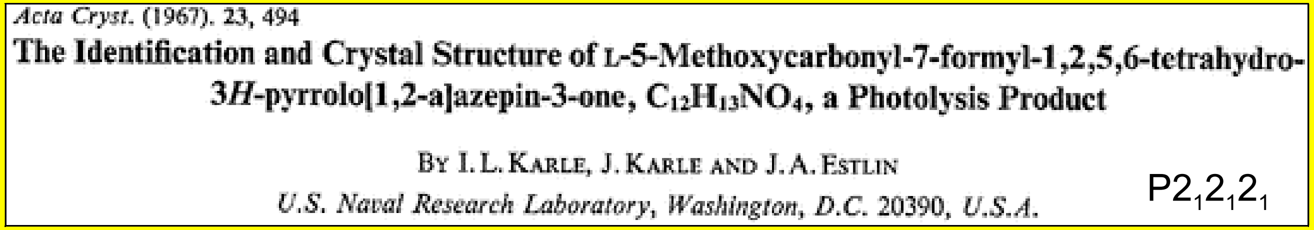


Analysis of structure solution methods I carried out in 1986

1953-1966

The mathematical formalism discouraged most chemical crystallographers and the practical applications of direct methods where very limited.

Only very few crystal structures were solved. N.c. structure in 1967.



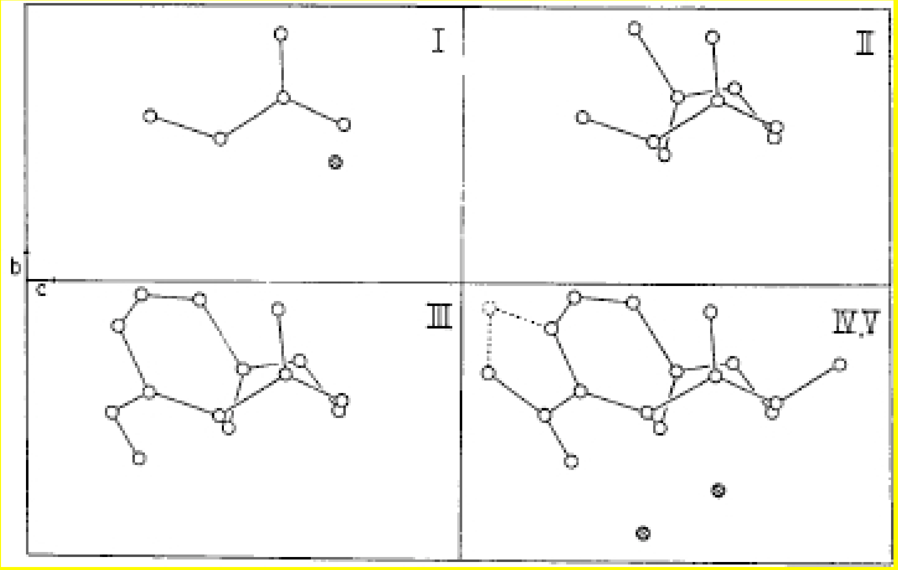
Acta Cryst. (1967). 23, 494

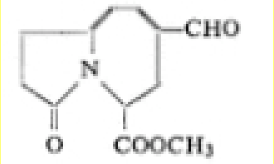
The Identification and Crystal Structure of L-5-Methoxycarbonyl-7-formyl-1,2,5,6-tetrahydro-3*H*-pyrrolo[1,2-a]azepin-3-one, $C_{12}H_{13}NO_4$, a Photolysis Product

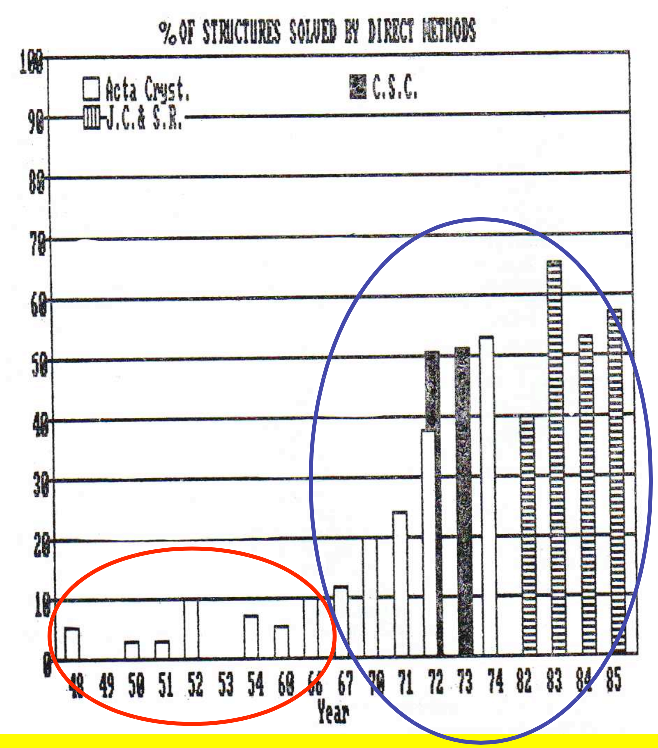
By I. L. Karle, J. Karle and J. A. Estlin

U.S. Naval Research Laboratory, Washington, D.C. 20390, U.S.A.

$P2_12_12_1$







I – map with phases from manual symbolic addition
II,III,IV,V – maps after cycles of tangent formula expansion and refinement

Photholisis product: used as test structure for many years

I started my self-thought crystallographer career in 1962: two years to solve the three atom structure of glyoxime!

Acta Cryst. (1966). **20**, 73

The Crystal and Molecular Structure of Glyoxime

First published paper

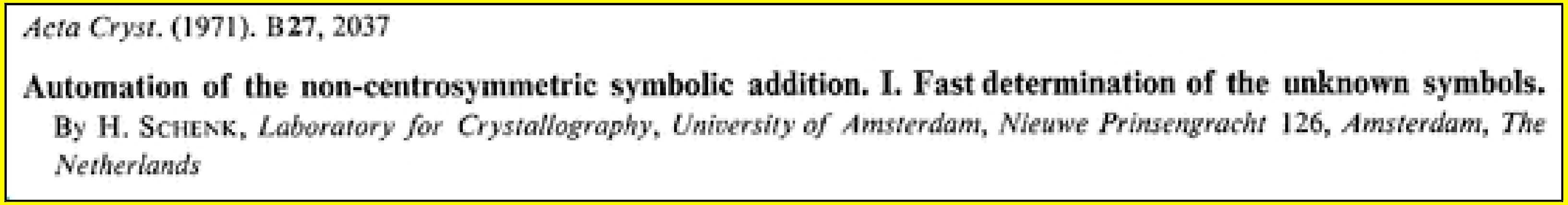
BY M. CALLERI AND G. FERRARIS
Istituto di Mineralogia dell'Università di Torino, Italy

AND D. VITERBO
Istituto di Chimica-Fisica dell'Università di Torino, Italy

PROGRAMMING DIRECT METHODS IN THOSE EARLY DAYS

The normal rule was that each lab and often each crystallographer was writing computer programs for local or individual use. FORTRAN was the most common language, but some “gurus” used the machine language of the local computer.

A number of programs carrying out symbolic addition for centrosymmetric structures was set up. At the same time were written several programs to extend by tangent formula the phases of non centrosymmetric structures obtained by manual symbolic addition. An early automation of non-centro symbolic addition was proposed by H. Schenk



Acta Cryst. (1971). B27, 2037

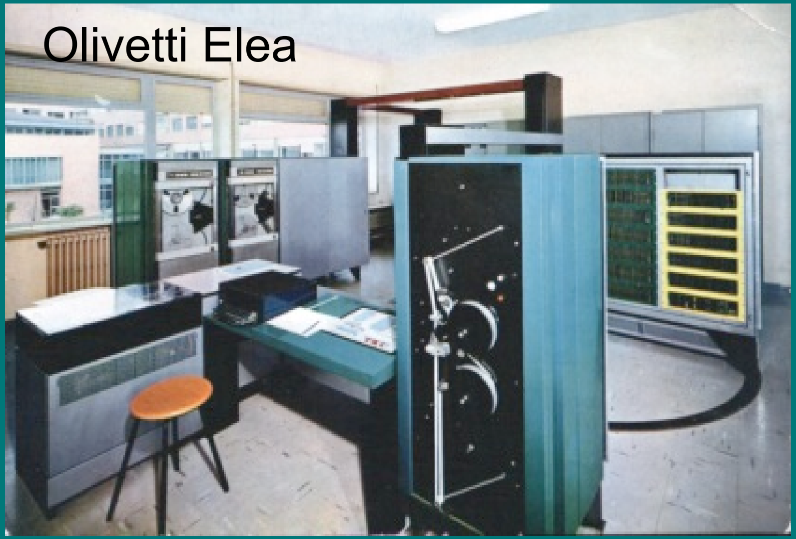
Automation of the non-centrosymmetric symbolic addition. I. Fast determination of the unknown symbols.

By H. Schenk, *Laboratory for Crystallography, University of Amsterdam, Nieuwe Prinsengracht* 126, *Amsterdam, The Netherlands*

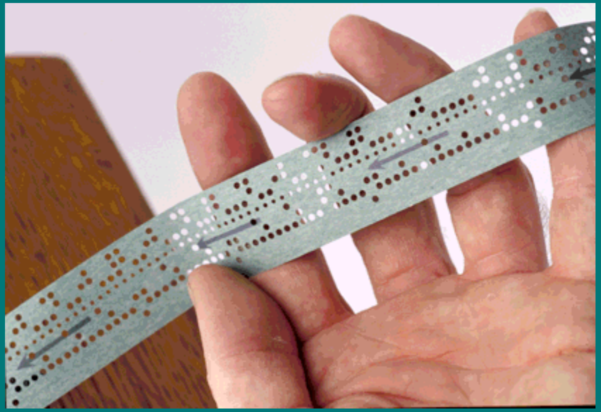
In 1968 in Oxford I started my interest for direct methods. Together with John Hodder I stared writing in Fortran a symbolic addition program for centro structures, while John was using the machine language of the KDF9 installed in Oxford. I never used my program to solve a new structure, but glyoxime could be solved in few minutes. I suppose my Fortran version (requested by J. Rollet) was used on the new computer in Oxford. In those times, together with Lodovico Riva (the Erice boss), I used successfully the tangent formula program TANFOR, written by Sam Matherwell in Cambidge.

Mainframes had usually 32K rom, input was by punched cards or tape, output on slow and noisy line-printers or even teletypes, external memory on magnetic tapes.

Life was difficult but exciting!


Olivetti Elea


```
407M(1,J)=M(2,2*J-1):410NEXTJ:420FORJ=1TO100:425T(2,J)=0:426S(2,J)=0:427M(2,J)=0
```




IBM 7090

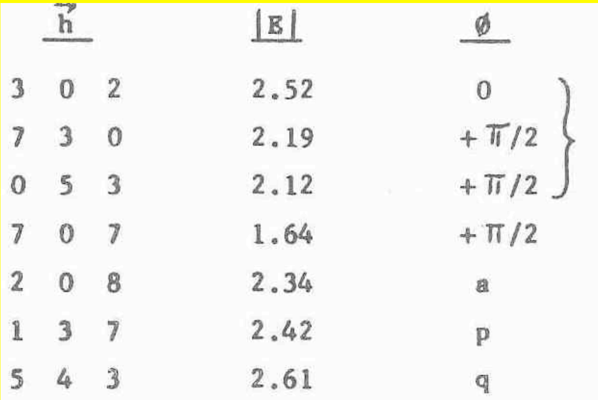
Michael Woolfson, with the help of Mario Nardelli and his group organized the first NATO Advanced Study Institute in Parma in September 1970

DIRECT and PATTERSON METHODS of SOLVING CRYSTAL STRUCTURES

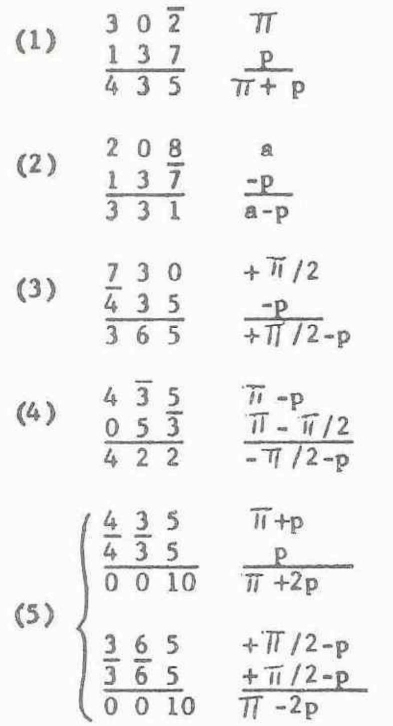
- It was my first encounter with so many important crystallographers. Paul Ewald was there and gave a memorable lecture on diffraction theory.
- The students reacted to “NATO” and interrupted a lecture by Martin Buerger on Patterson vector methods.
- The next year the school was repeated in York, while I was spending a year there with Michael Woolfson.
- These two schools were the ground on which the *Erice Crystallography Schools* originated.

I told Michael of the “Ettore Majorana Center”, founded by Antonino Zichichi in Erice; a wonderful set up to organize schools and workshops. I also told him that my friend Lodovico Riva di Sanseverino was in a privileged position to explore the possibility of having a school there: not only he was born in Sicily from a noble family, but he was leaving in Bologna, and was lecturer by the same university in which Zichichi (also Sicilian) was full professor of physics. The way was open to the 1974 Erice School.

DIRECT and PATTERSON METHODS of SOLVING CRYSTAL STRUCTURES
NATO Advanced Study Institute, Parma, September 1970

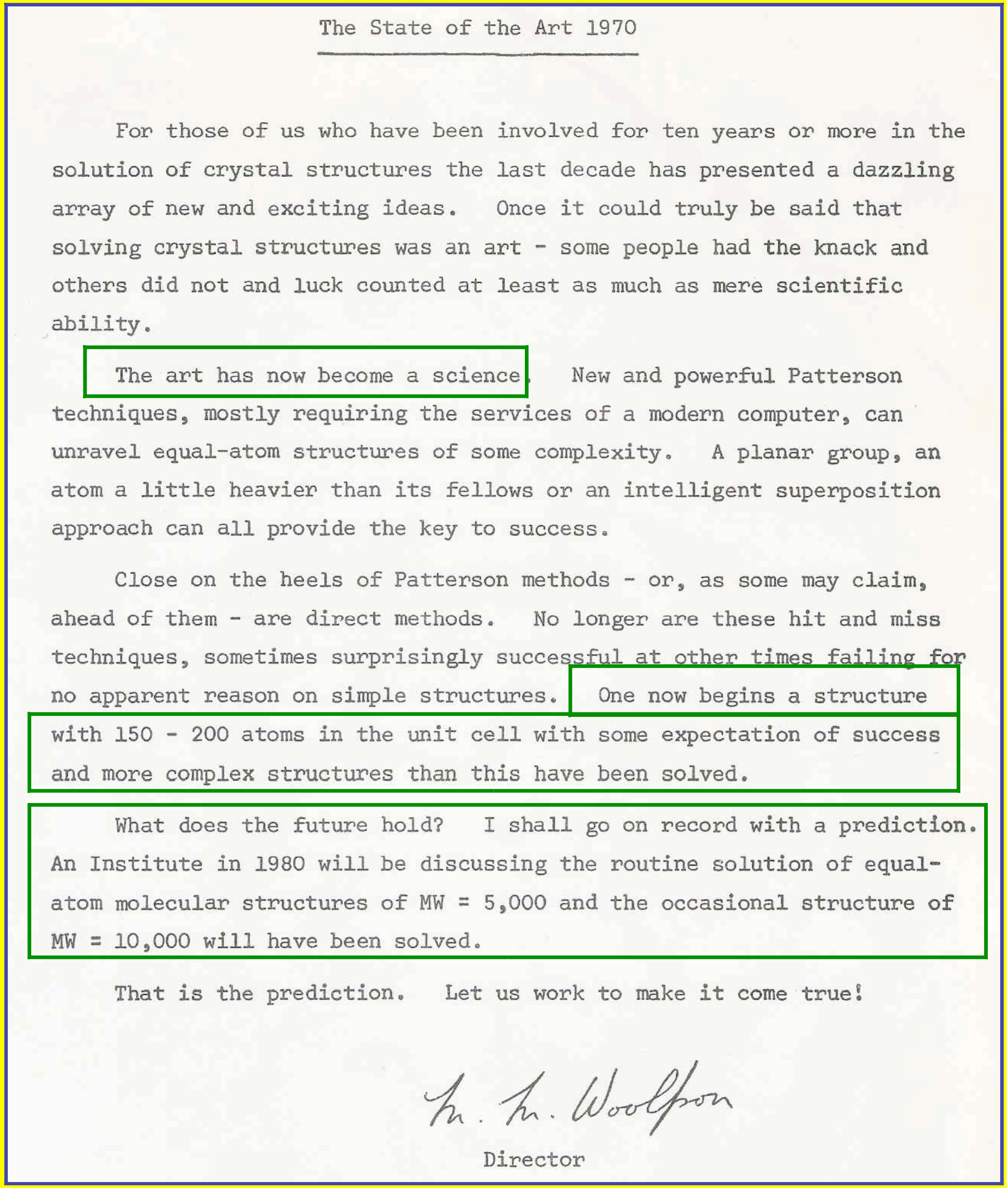


$\vec{h}$			|E|	Ø
3	0	2	2.52	0
7	3	0	2.19	+ π/2
0	5	3	2.12	+ π/2
7	0	7	1.64	+ π/2
2	0	8	2.34	a
1	3	7	2.42	p
5	4	3	2.61	q



(1)	3 0 $\bar{2}$	π
	1 3 7	p
	4 3 5	π + p
(2)	2 0 8	a
	1 3 $\bar{7}$	-p
	3 3 1	a - p
(3)	7 3 0	+ π/2
	$\bar{4}$ 3 5	-p
	3 6 5	+ π/2 - p
(4)	4 $\bar{3}$ 5	π - p
	0 5 $\bar{3}$	π - π/2
	4 2 2	- π/2 - p
(5)	4 3 5	π + p
	$\bar{4}$ $\bar{3}$ 5	p
	0 0 10	π + 2p
	3 6 5	+ π/2 - p
	$\bar{3}$ $\bar{6}$ 5	+ π/2 - p
	0 0 10	π - 2p

Symbolic addition tutorial by Isabella Karle



The State of the Art 1970

For those of us who have been involved for ten years or more in the solution of crystal structures the last decade has presented a dazzling array of new and exciting ideas. Once it could truly be said that solving crystal structures was an art - some people had the knack and others did not and luck counted at least as much as mere scientific ability.

The art has now become a science. New and powerful Patterson techniques, mostly requiring the services of a modern computer, can unravel equal-atom structures of some complexity. A planar group, an atom a little heavier than its fellows or an intelligent superposition approach can all provide the key to success.

Close on the heels of Patterson methods - or, as some may claim, ahead of them - are direct methods. No longer are these hit and miss techniques, sometimes surprisingly successful at other times failing for no apparent reason on simple structures. One now begins a structure with 150 - 200 atoms in the unit cell with some expectation of success and more complex structures than this have been solved.

What does the future hold? I shall go on record with a prediction. An Institute in 1980 will be discussing the routine solution of equal-atom molecular structures of MW = 5,000 and the occasional structure of MW = 10,000 will have been solved.

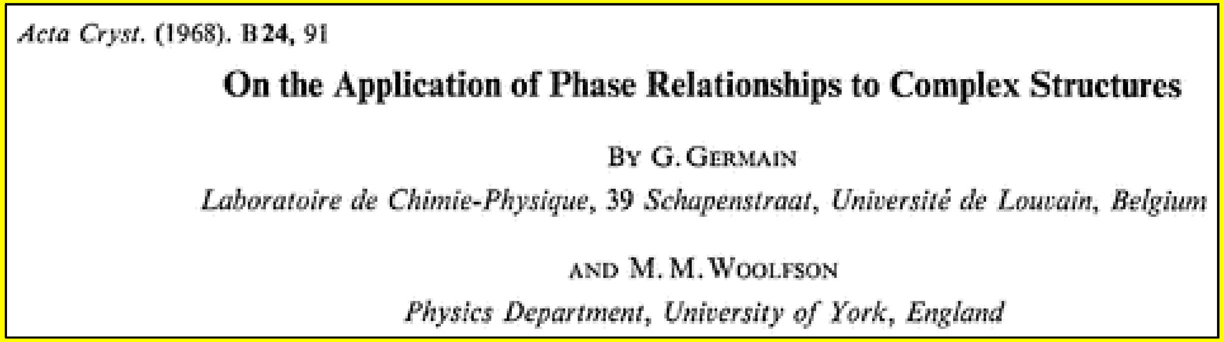
That is the prediction. Let us work to make it come true!

M. M. Woolfson

Director

The MULTISOLUTION method and birth of the MULTAN program

Permuted numerical values ($\pi/4$, $3\pi/4$, $-\pi/4$, $-3\pi/4$), instead of symbols, are given to the "starting" phases and each set of permuted values is expanded and refined by tangent formula.



Acta Cryst. (1968). B**24**, 91

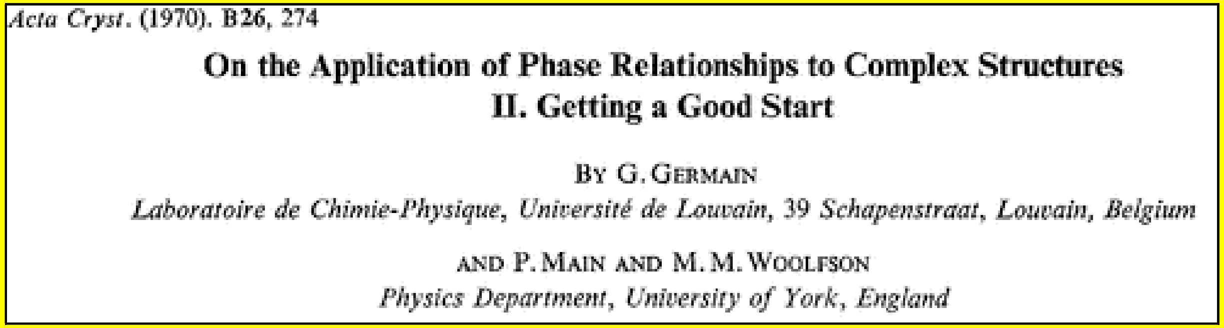
On the Application of Phase Relationships to Complex Structures

By G. Germain

Laboratoire de Chimie-Physique, 39 Schapenstraat, Université de Louvain, Belgium

and M. M. Woolfson

Physics Department, University of York, England



Acta Cryst. (1970). B**26**, 274

On the Application of Phase Relationships to Complex Structures
II. Getting a Good Start

By G. Germain

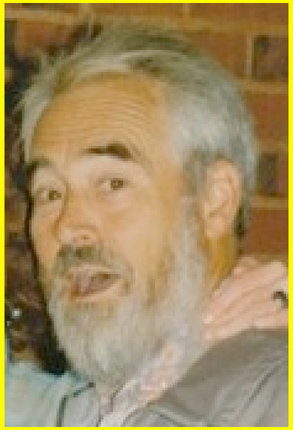
Laboratoire de Chimie-Physique, Université de Louvain, 39 Schapenstraat, Louvain, Belgium

and P. Main and M. M. Woolfson

Physics Department, University of York, England

MULTAN became soon a widely used program and was constantly improved to solve increasingly difficult and complex structures.

The problems due to the presence of heavy atoms and the use of difference structure factors were analyzed by Paul Beurskens and his group in Nijmegen



Acta Cryst. (1975). A**31**, 813-817

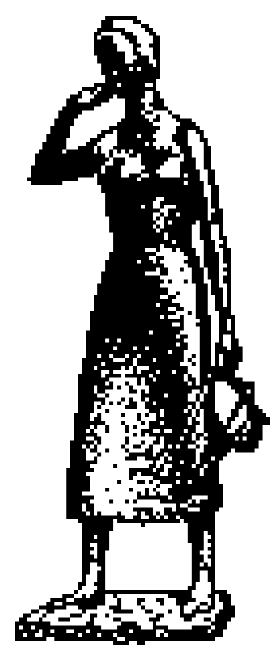
The application of direct methods to centrosymmetric structures containing heavy atoms. II

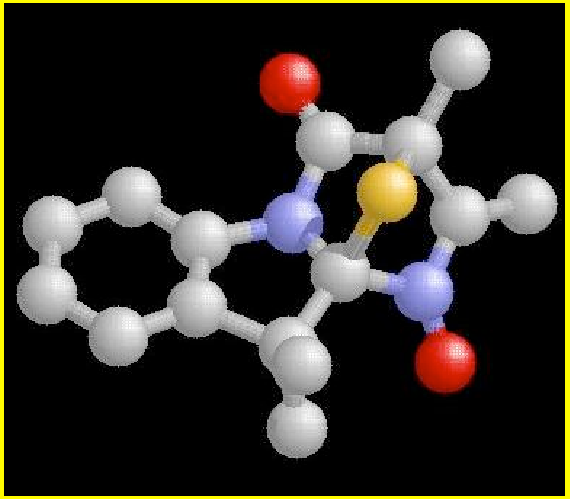
R. O. Gould, T. E. M. van den Hark and P. T. Beurskens

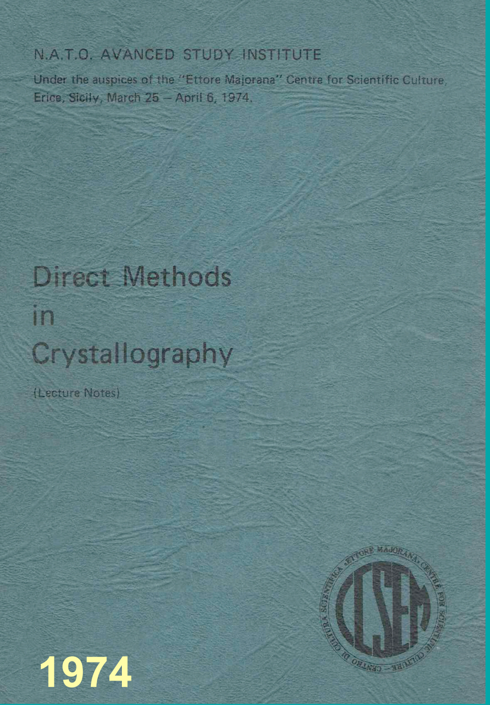
Acta Cryst. (1976). A**32**, 816-821

The application of direct methods to non-centrosymmetric structures containing heavy atoms

Th. E. M. van den Hark, P. Prick and P. T. Beurskens







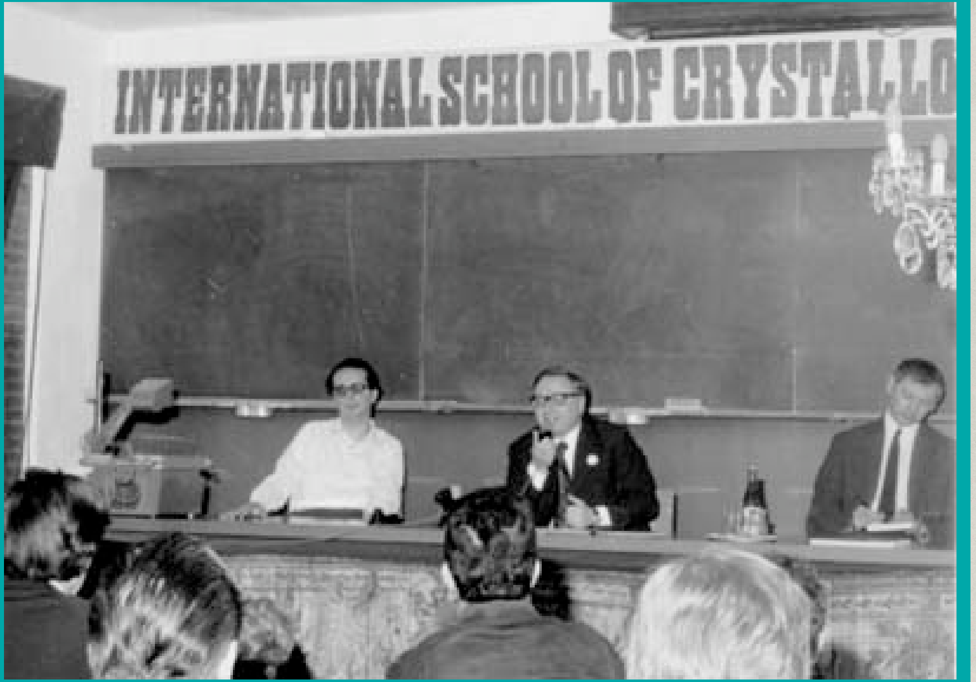
N.A.T.O. AVANCED STUDY INSTITUTE

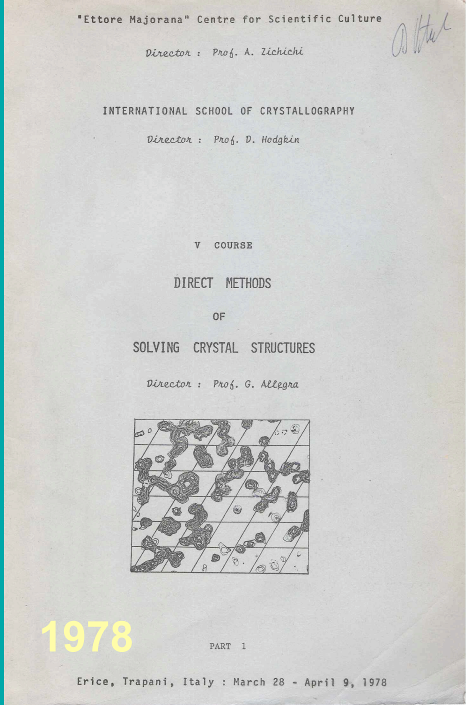
Under the auspices of the "Ettore Majorana" Centre for Scientific Culture,
Erice, Sicily, March 25 – April 6, 1974.

Direct Methods
in
Crystallography

(Lecture Notes)

1974





"Ettore Majorana" Centre for Scientific Culture

Director : Prof. A. Zichichi

INTERNATIONAL SCHOOL OF CRYSTALLOGRAPHY

Director : Prof. D. Hodgkin

V COURSE

DIRECT METHODS

OF

SOLVING CRYSTAL STRUCTURES

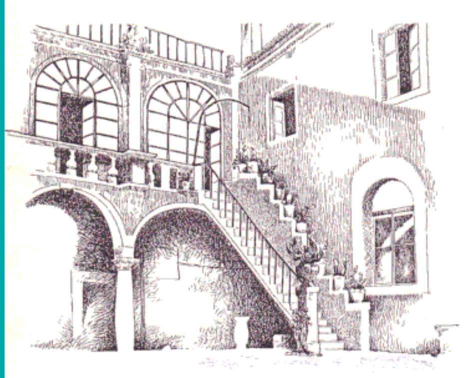
Director : Prof. G. Allegra

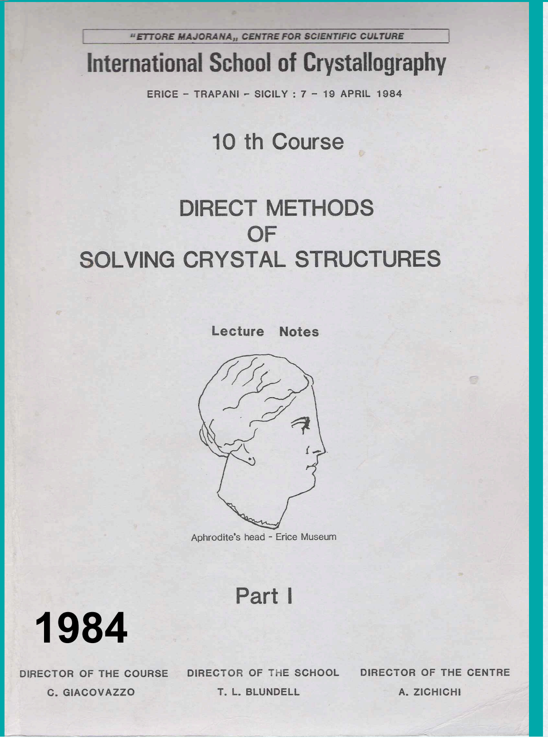
1978

PART 1

Erice, Trapani, Italy : March 28 - April 9, 1978

ERICE





"ETTORE MAJORANA" CENTRE FOR SCIENTIFIC CULTURE

International School of Crystallography

ERICE – TRAPANI – SICILY : 7 – 19 APRIL 1984

10 th Course

DIRECT METHODS
OF
SOLVING CRYSTAL STRUCTURES

Lecture Notes

Aphrodite's head - Erice Museum

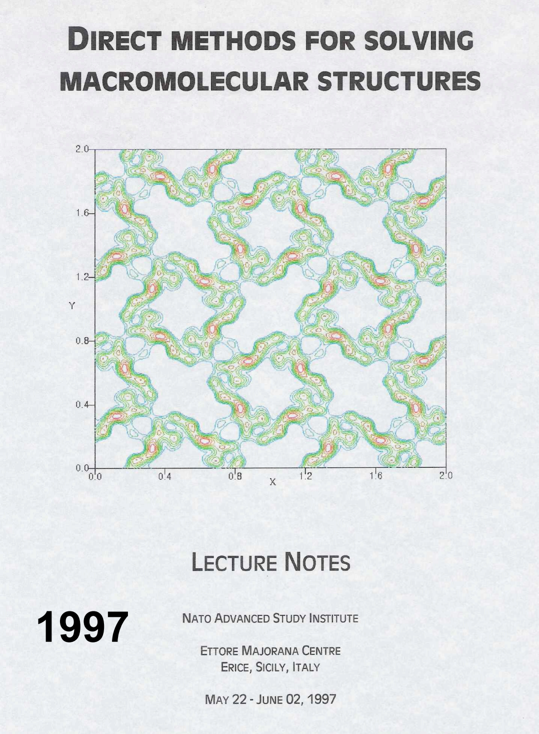
Part I

1984

DIRECTOR OF THE COURSE
C. GIACOVAZZO

DIRECTOR OF THE SCHOOL
T. L. BLUNDELL

DIRECTOR OF THE CENTRE
A. ZICHICHI



DIRECT METHODS FOR SOLVING
MACROMOLECULAR STRUCTURES

LECTURE NOTES

1997

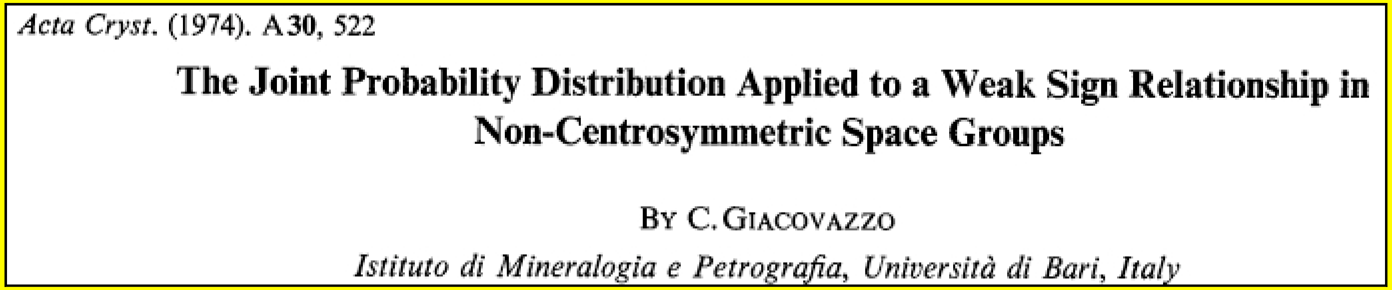
NATO ADVANCED STUDY INSTITUTE

ETTORE MAJORANA CENTRE
ERICE, SICILY, ITALY

MAY 22 - JUNE 02, 1997

Erice 1978 group photograph

An important outcome of the first Erice school was that **Carmelo Giacovazzo**, who attended the course as student, made his choice of devoting himself to the development of Direct Methods (he had already started). In 1984 he was the director of the course (with big contrasts with Lodovico).



Acta Cryst. (1974). A**30**, 522

The Joint Probability Distribution Applied to a Weak Sign Relationship in Non-Centrosymmetric Space Groups

BY C. GIACOVAZZO

Istituto di Mineralogia e Petrografia, Università di Bari, Italy

Acta Cryst. (1976). A**32**, 91

A Probabilistic Theory of the Cosine Invariant $\cos(\varphi_h+\varphi_k+\varphi_l-\varphi_{h+k+l})$

Acta Cryst. (1977). A**33**, 933–944

A General Approach to Phase Relationships: The Method of Representations

BY CARMELO GIACOVAZZO

Erice 1984

Durban 2003

Acta Cryst. (1979). A**35**, 401–412

A Probabilistic Theory of Two-Phase Seminvariants of First Rank *via* the Method of Representations. IV. Practical Aspects and Applications

BY CARMELO GIACOVAZZO

Istituto di Mineralogia, Palazzo Ateneo, Università, 70121 Bari, Italy

RICCARDO SPAGNA

Laboratorio di Strutturistica Chimica 'G. Giacomello', CNR (Area della Ricerca di Roma), Via Salaria Km 29 300, 000 16 Monterotondo Stazione (Roma), Roma, Italy

IVAN VICKOVIĆ

Zavod za opću i anorgansku kemiju, Prirodoslovno-matematički fakultet Sveučilišta, Ul. Socijalističke Revolucije 8, 41000 Zagreb, Yugoslavia

AND DAVIDE VITERBO

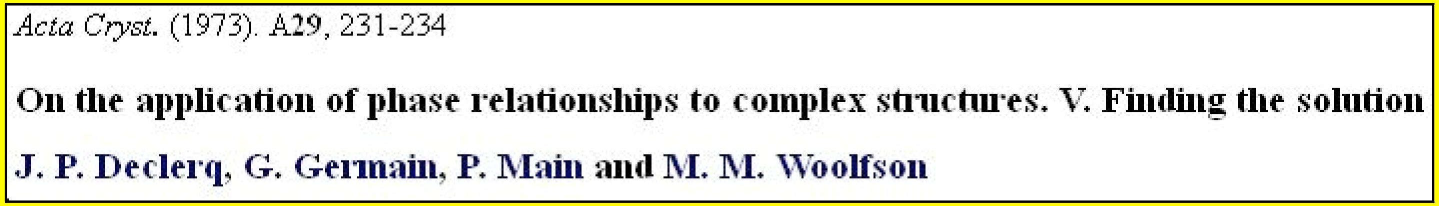
Istituto di Chimica-Fisica, Università, Corso M. D'Azeglio 48, 10125 Torino, Italy

York 1975 group photograph

Main developments in the 70's and 80's

- **Improvements and evolutions of the *Multisolution* approach: strengthening the starting set of phases, weighted tangent formula, new figures of merit, etc.**
- **Use of quartets and identification by Schenk of negative quartets.**
- **Application of the "*neighboring principle*" (Hauptman) and of the "*representation theory*" (Giacovazzo) to the estimate of structure invariants and seminvariants.**
- **Estimates of triplets and negative quartets.**
- **Introduction of *Magic Integers* and their use.**
- **From magic integers to random phases.**
- **Successful use of random starting sets of phases.**

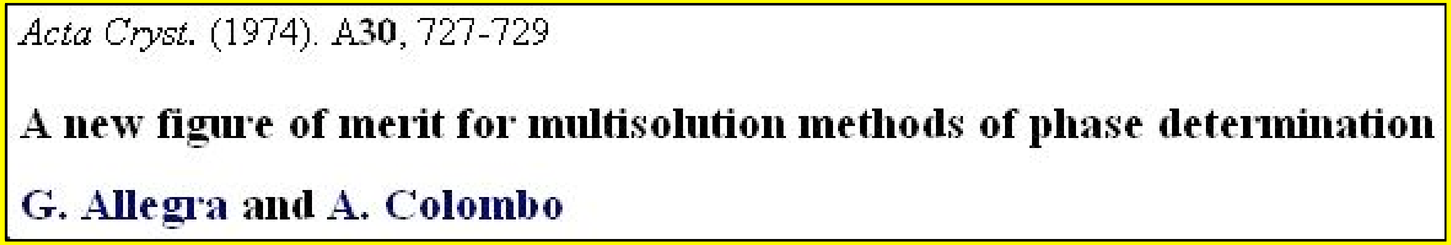
Improvements and evolutions of the *Multisolution* approach



Acta Cryst. (1973). A**29**, 231-234

On the application of phase relationships to complex structures. V. Finding the solution

J. P. Declerq, G. Germain, P. Main and M. M. Woolfson



Acta Cryst. (1974). A**30**, 727-729

A new figure of merit for multisolution methods of phase determination

G. Allegra and A. Colombo

Acta Cryst. (1979). A**35**, 757-764

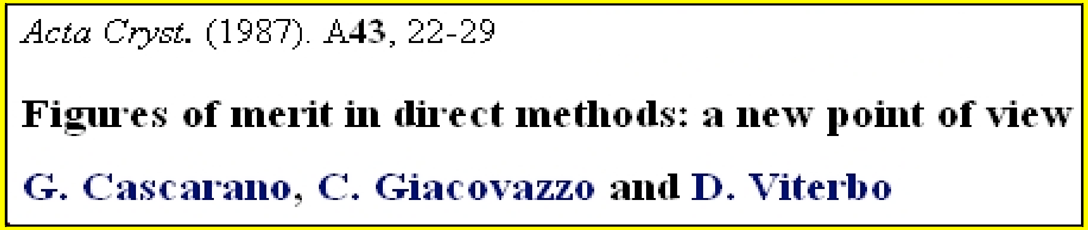
A theoretical weighting scheme for tangent-formula development and refinement and Fourier synthesis

C. Giacovazzo

$$\tan \phi_h = \frac{\sum_j w_{k_j} w_{h-k_j} \left|E_{k_j} E_{h-k_j}\right| \sin\left(\phi_{k_j} + \phi_{h-k_j}\right)}{\sum_j w_{k_j} w_{h-k_j} \left|E_{k_j} E_{h-k_j}\right| \cos\left(\phi_{k_j} + \phi_{h-k_j}\right)} = \frac{T_h}{B_h}$$

$$w_h = \min(0.2\,\alpha, 1)$$

$$\alpha_h = 2N^{-1/2}|E_h|(T_h^2 + B_h^2)^{1/2}$$



Acta Cryst. (1987). A**43**, 22-29

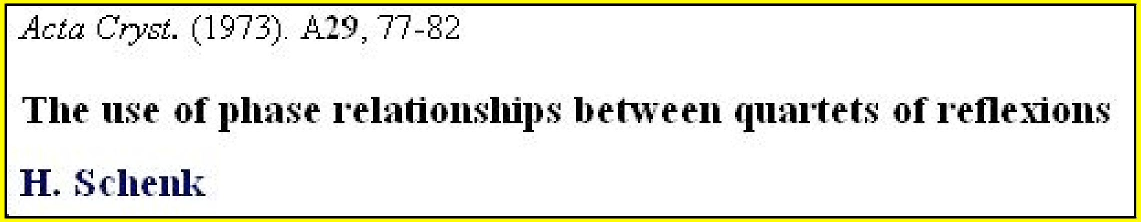
Figures of merit in direct methods: a new point of view

G. Cascarano, C. Giacovazzo and D. Viterbo

$$\mathrm{NQUEST} = \frac{\sum_r G_r \cos Q_r}{\sum_r |G_r|\, D_1(|G_r|)} = \frac{T_4}{B_4}$$

Quartets and their use

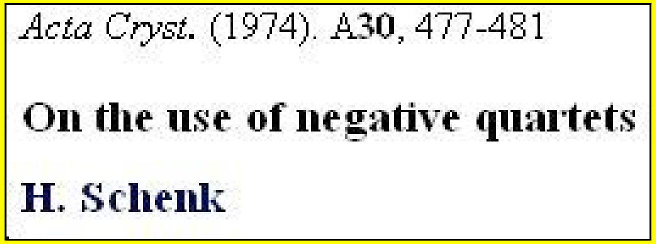
$$Q = \varphi_{\mathbf{h}} + \varphi_{\mathbf{k}} + \varphi_{\mathbf{l}} + \varphi_{-\mathbf{h}-\mathbf{k}-\mathbf{l}}.$$



Acta Cryst. (1973). A29, 77-82

The use of phase relationships between quartets of reflexions

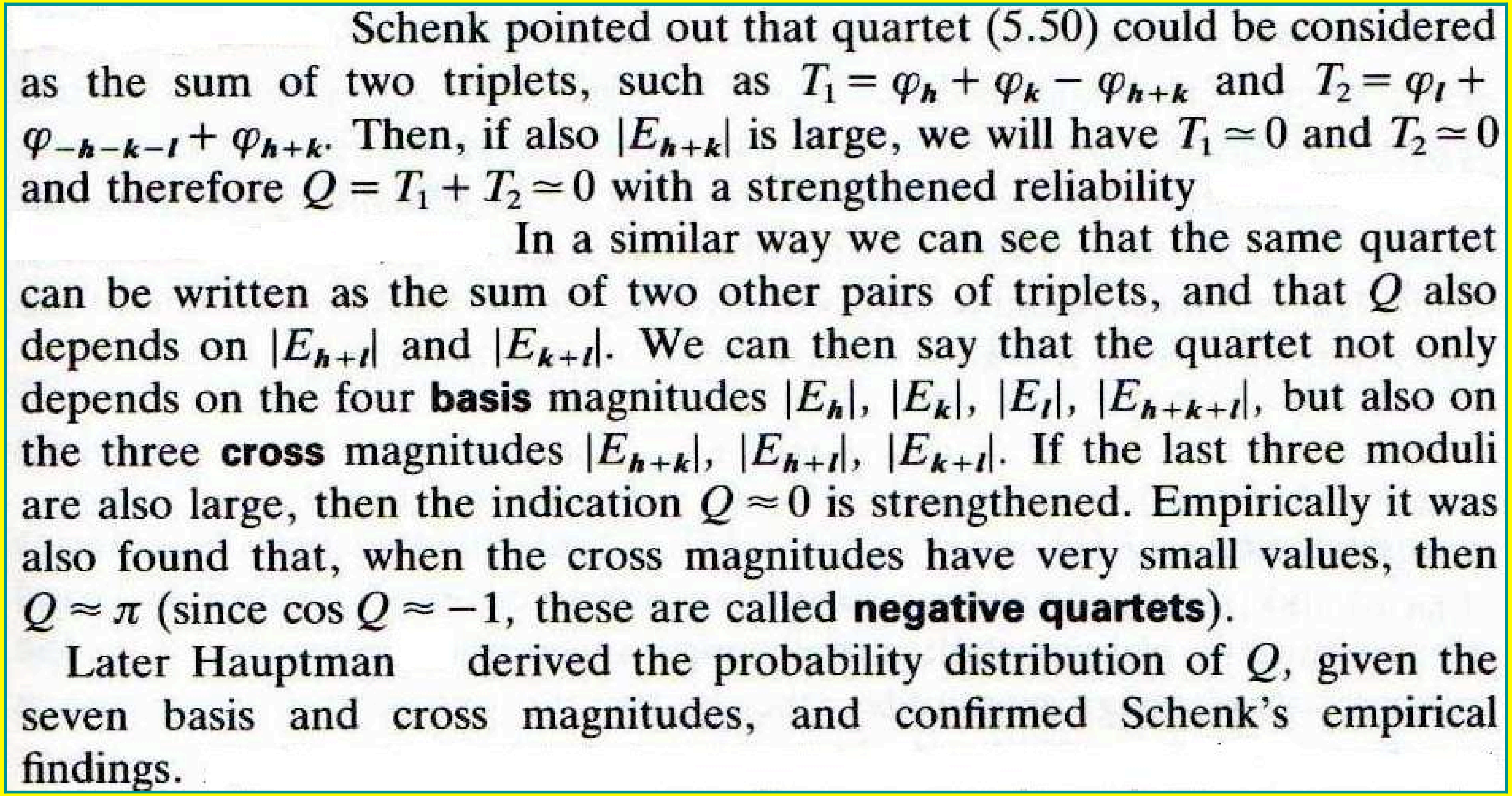
H. Schenk



Acta Cryst. (1974). A30, 477-481

On the use of negative quartets

H. Schenk



Schenk pointed out that quartet (5.50) could be considered as the sum of two triplets, such as $T_1 = \varphi_{\mathbf{h}} + \varphi_{\mathbf{k}} - \varphi_{\mathbf{h}+\mathbf{k}}$ and $T_2 = \varphi_{\mathbf{l}} + \varphi_{-\mathbf{h}-\mathbf{k}-\mathbf{l}} + \varphi_{\mathbf{h}+\mathbf{k}}$. Then, if also $|E_{\mathbf{h}+\mathbf{k}}|$ is large, we will have $T_1 \simeq 0$ and $T_2 \simeq 0$ and therefore $Q = T_1 + T_2 \simeq 0$ with a strengthened reliability

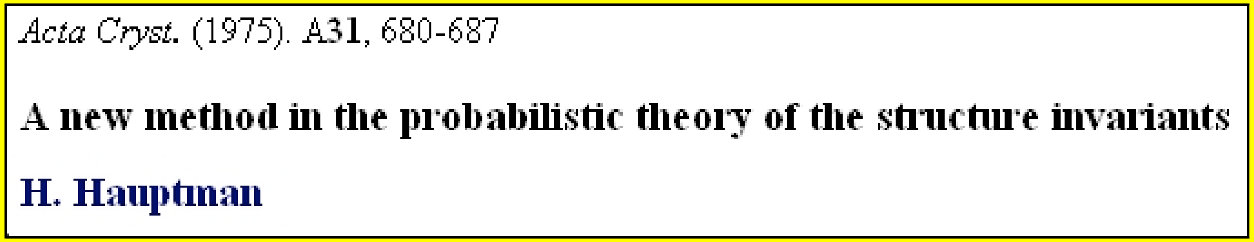
In a similar way we can see that the same quartet can be written as the sum of two other pairs of triplets, and that Q also depends on $|E_{\mathbf{h}+\mathbf{l}}|$ and $|E_{\mathbf{k}+\mathbf{l}}|$. We can then say that the quartet not only depends on the four **basis** magnitudes $|E_{\mathbf{h}}|$, $|E_{\mathbf{k}}|$, $|E_{\mathbf{l}}|$, $|E_{\mathbf{h}+\mathbf{k}+\mathbf{l}}|$, but also on the three **cross** magnitudes $|E_{\mathbf{h}+\mathbf{k}}|$, $|E_{\mathbf{h}+\mathbf{l}}|$, $|E_{\mathbf{k}+\mathbf{l}}|$. If the last three moduli are also large, then the indication $Q \approx 0$ is strengthened. Empirically it was also found that, when the cross magnitudes have very small values, then $Q \approx \pi$ (since $\cos Q \approx -1$, these are called **negative quartets**).

Later Hauptman derived the probability distribution of Q, given the seven basis and cross magnitudes, and confirmed Schenk's empirical findings.

Neighborhood principle (Hauptman) and Representation theory (Giacovazzo)

Estimate of structure invariants and seminvariants

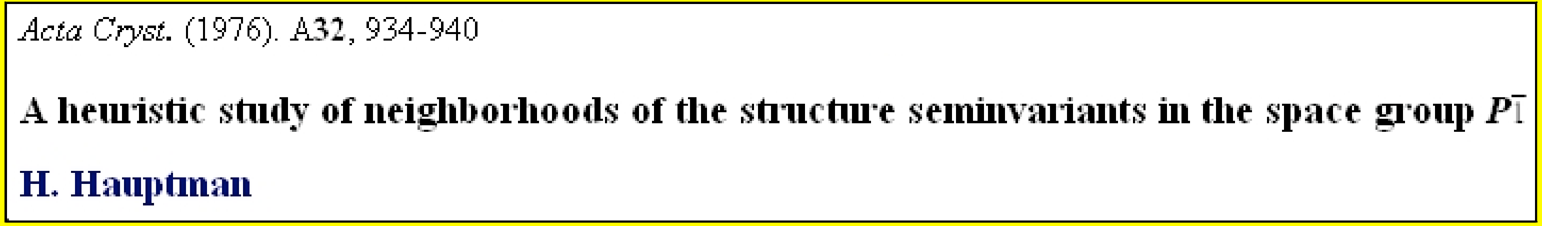
***H.H. reciting his prayers*: "Structure invariants are those linear combination of phases, whose value does not depend on the choice of origin. Structure seminvariants are those linear combination of phases, whose value does not depend on the choice of origin, provided this is one of the "permissible" origins of the given space group."** *(To be recited with the intonation of an American rabbi)*



Acta Cryst. (1975). A**31**, 680-687

A new method in the probabilistic theory of the structure invariants

H. Hauptman



Acta Cryst. (1976). A**32**, 934-940

A heuristic study of neighborhoods of the structure seminvariants in the space group $P\bar{1}$

H. Hauptman

Acta Cryst. (1978). A**34**, 562-574 |

The estimation of the one-phase structure seminvariants of first rank by means of their first and second representations

C. Giacovazzo

Acta Cryst. (1980). A**36**, 362-372 |

The method of representations of structure seminvariants. II. New theoretical and practical aspects

C. Giacovazzo

Estimates of quartets

$$Q = \varphi_h + \varphi_k + \varphi_l + \varphi_{-h-k-l}$$

Acta Cryst. (1975). **A31**, 671-679

A joint probability distribution of seven structure factors

H. Hauptman

Acta Cryst. (1977). A33, 50-54

On different probabilistic approaches to quartet theory

C. Giacovazzo

$\cos Q = \frac{I_1(G)}{I_0(G)}$ and when R_{h+k}, R_{h+l} and R_{k+l} are small the sum of their squares is less than 2 and G and cosQ are negative

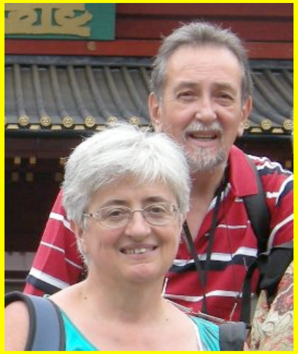
$$G = \frac{2N^{-1} R_h R_k R_l R_{h+k+l} (R^2_{h+k} + R^2_{h+l} + R^2_{k+l} - 2)}{1 + \tanh[(R^2_{h+k} + R^2_{h+l} + R^2_{k+l})/3]}$$

and of triplets

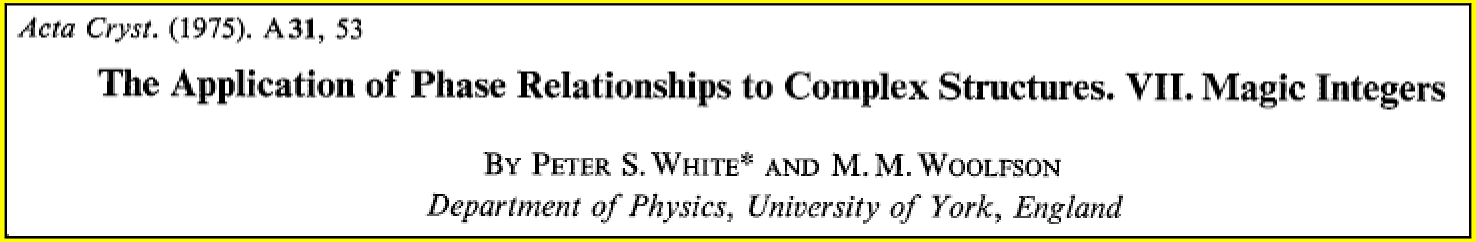
Acta Cryst. (1984). **A40**, 278-283

The method of representations of structure seminvariants. The strengthening of triplet relationships

G. Cascarano, C. Giacovazzo, M. Camalli, R. Spagna, M. C. Burla, A. Nunzi and G. Polidori



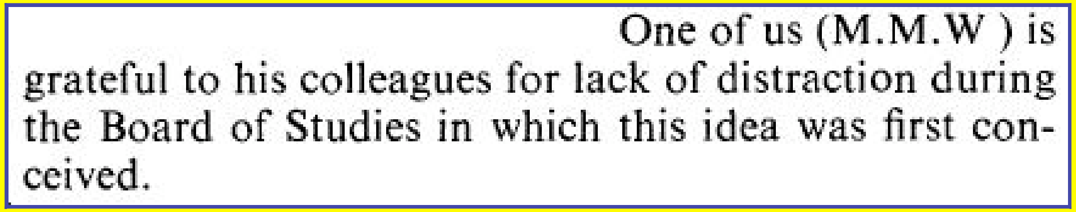
Magic Integers



Acta Cryst. (1975). A**31**, 53

The Application of Phase Relationships to Complex Structures. VII. Magic Integers

BY PETER S. WHITE* AND M. M. WOOLFSON
Department of Physics, University of York, England



One of us (M.M.W) is grateful to his colleagues for lack of distraction during the Board of Studies in which this idea was first conceived.

Acta Cryst. (1977). A33, 750-757

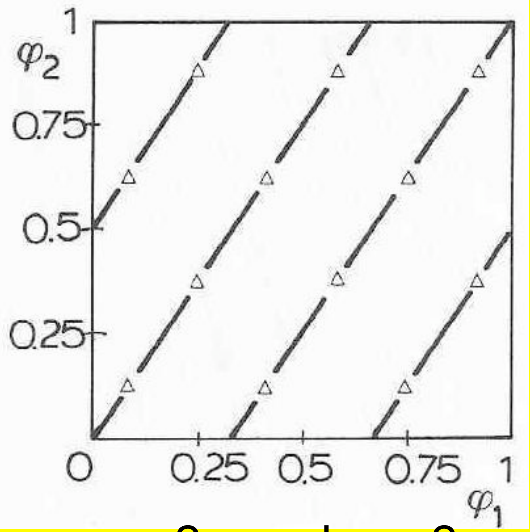
On the application of phase relationships to complex structures. XI. A theory of magic integers

P. Main

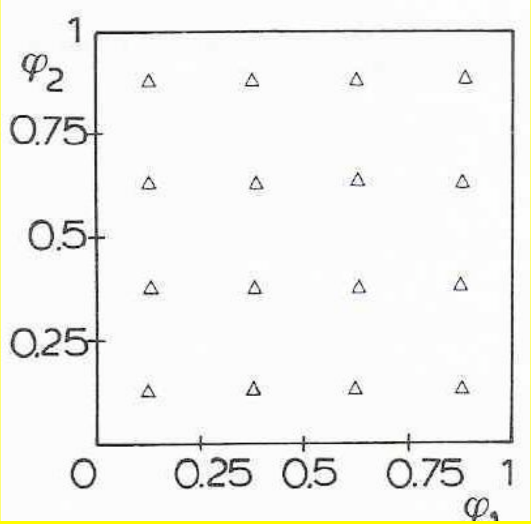
Phases are expressed as

$$\varphi_i = m_i x \bmod(1)$$

Only one symbol for several phases. The phase space is explored by scanning 0<x<1. An optimal way for exploring the phase space, with a small increase in phase error.



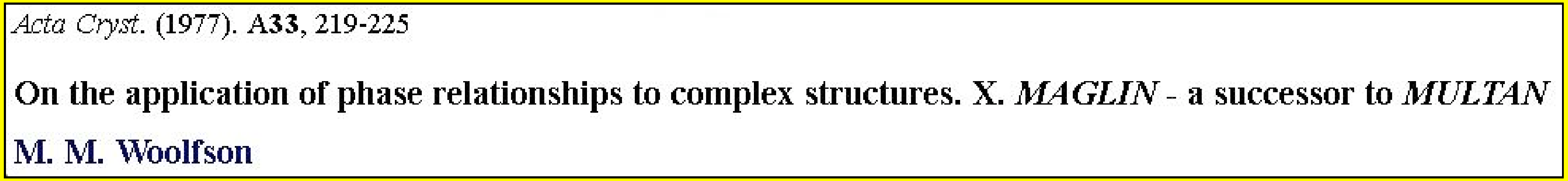
φ_1 =2x and φ_2 =2x



quadrant permutation

From magic integers to random phases

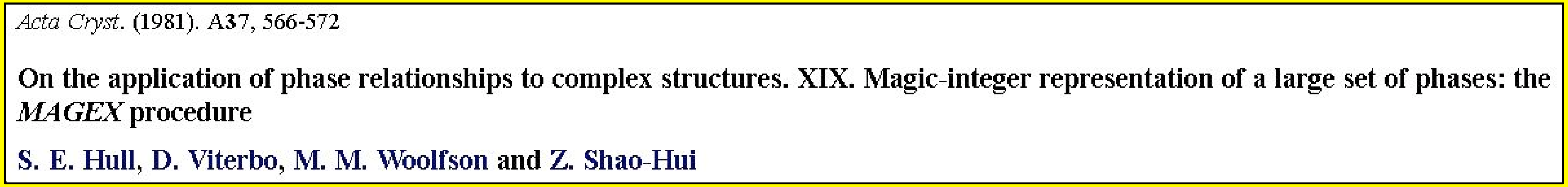
As the number of phases represented in terms of magic integers increases, also the phase error increases



Acta Cryst. (1977). A**33**, 219-225

On the application of phase relationships to complex structures. X. *MAGLIN* - a successor to *MULTAN*

M. M. Woolfson

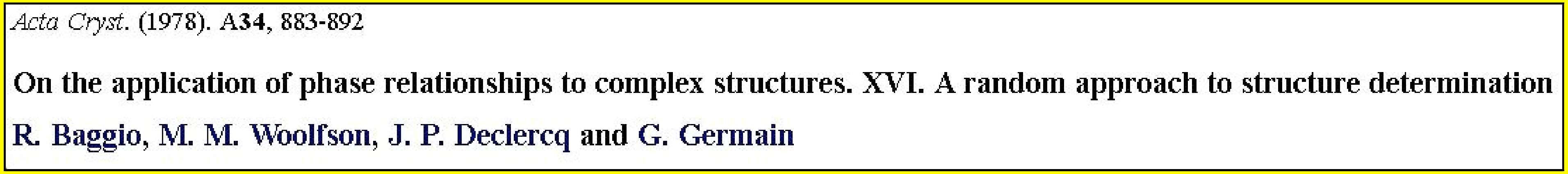


Acta Cryst. (1981). A**37**, 566-572

On the application of phase relationships to complex structures. XIX. Magic-integer representation of a large set of phases: the *MAGEX* procedure

S. E. Hull, D. Viterbo, M. M. Woolfson and Z. Shao-Hui

If MAGLIN and MAGEX can solve structures, we might as well give random values to the starting phases!



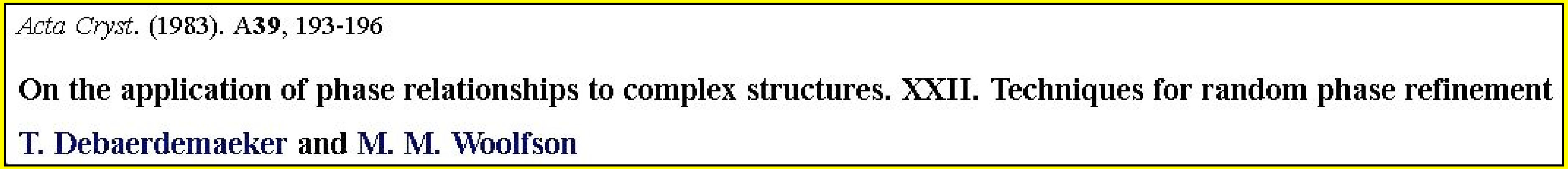
Acta Cryst. (1978). A**34**, 883-892

On the application of phase relationships to complex structures. XVI. A random approach to structure determination

R. Baggio, M. M. Woolfson, J. P. Declercq and G. Germain

Successful use of random starting sets of phases

The use of a large starting set of random phases turned out to be successful. It also made life easier: no more need to choose proper reflections to fix the origin and enantiomorph. Alternatives to the tangent formula were tried to expand and refine random phases

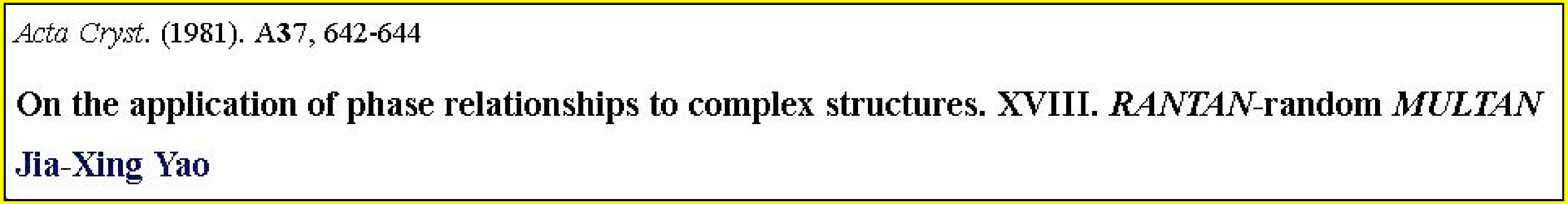


Acta Cryst. (1983). A**39**, 193-196

On the application of phase relationships to complex structures. XXII. Techniques for random phase refinement

T. Debaerdemaeker and M. M. Woolfson

But tangent formula proved to work very well



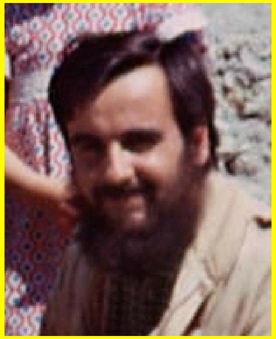
Acta Cryst. (1981). A**37**, 642-644

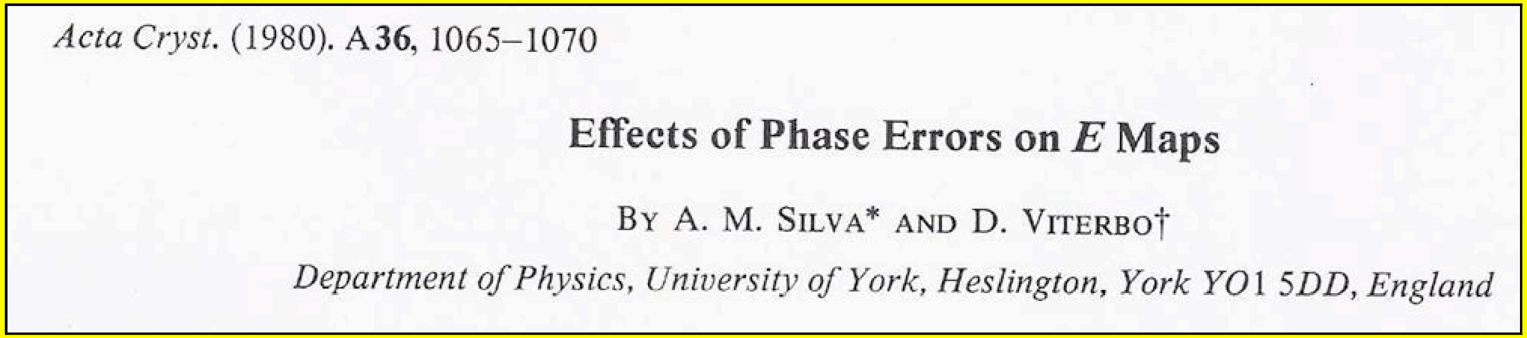
On the application of phase relationships to complex structures. XVIII. *RANTAN*-random *MULTAN*

Jia-Xing Yao

Random phases have then became the standard approach in almost all subsequent procedures

Why can we start from random phases?
The phase-error function





Acta Cryst. (1980). A**36**, 1065–1070

Effects of Phase Errors on *E* Maps

BY A. M. SILVA* AND D. VITERBO†

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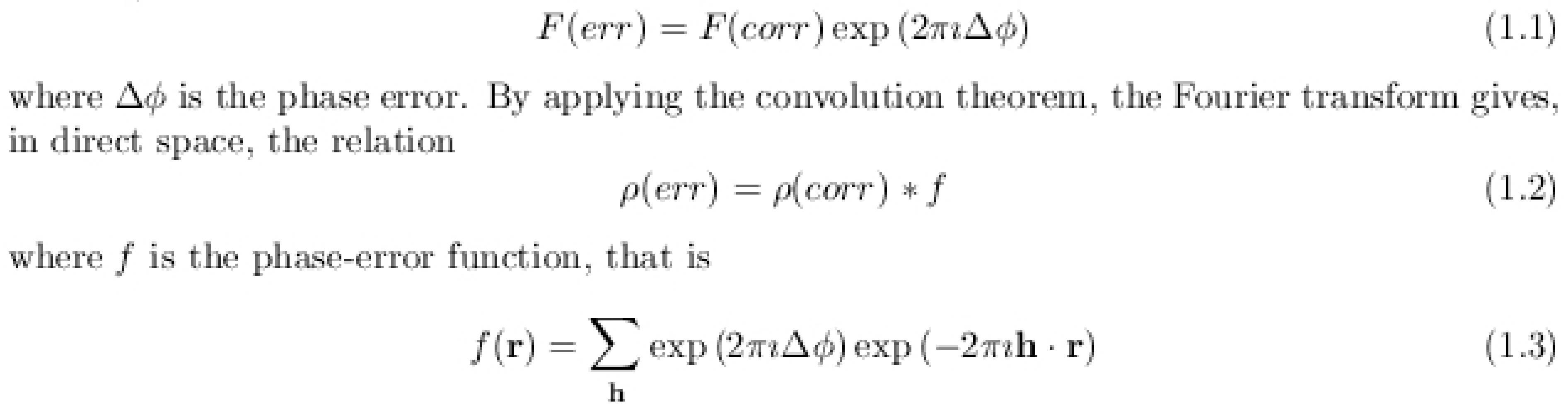


$$F(err) = F(corr)\exp(2\pi i\Delta\phi) \tag{1.1}$$

where $\Delta\phi$ is the phase error. By applying the convolution theorem, the Fourier transform gives, in direct space, the relation

$$\rho(err) = \rho(corr) * f \tag{1.2}$$

where f is the phase-error function, that is

$$f(\mathbf{r}) = \sum_{\mathbf{h}} \exp(2\pi i\Delta\phi)\exp(-2\pi i\mathbf{h}\cdot\mathbf{r}) \tag{1.3}$$

For random Δφ's *f*(r) has only a peak at the origin, that becomes wider as Δφ increase. Convolution with ρ*(corr)* only broadens the peaks but does not make a mess of the map.

Software developments

- As mentioned a large number of computer programs was developed.
- Some of them became more popular.
- Hardware fast improvements allowed increasing software potentialities and efficiency.
- Graphic tools became available.

1963-1972
A long list from my lecture in 1986

Table 1

List of D. M. programs developed in the years 1963—1972.

1 — SIGN CORRELATION — Beurskens P. T. (1963) *Tech. Report*, Univ. of Pittsburgh.

2 — PHASER, SIGNIE — Ammon H. L. (1964); Ammon H. L. & Jensen L. H. (1967) *Acta Cryst.*, **23**, 805.

3 — SYMB. ADD. — Long R. E. (1965) *Doctoral Thesis*, Univ. of California, Los Angeles.

4 — FAME, MAGIC, LINK, SYMPL, TANG — Dewar R. B. K. & Stone A. (1965), Univ. of Chicago, Illinois.

5 — SORTE — Bednowitz A. L. & Post. B. (1966) *Acta Cryst*, **21**, 566.

6 — MAGENC — Tsai C. (1966) *Ph. D. Thesis*, Indiana Univ.

7 — PHASE — Stewart R. F., Hall S. R. *et al.* (1967) *XRAY67*, Univ. of Maryland.

8 — SYMB. ADD. — Hall S. R. & Ahmed F. R. (1968) *NRC System of Crystallographic Programs*, Ottawa.

9 — LSAM — Germain G. & Woolfson M. M. (1968) *Acta Cryst.*, **B24**, 91.

10 — TANFOR — Larson A. C. & Motherwell W. D. S. (1968) Univ. of Cambridge.

11 — AUDICE — Spek A. L. (1968) Univ. of Utrecht.

12 — AUTOMATIC SYMB. ADD. — Schenk H. (1969) North Holland, Amsterdam.

13 — MULTISOL. — Zechmeister R. K. (1969) *Dissertation*, T. H., München.

14 — MULTAN (SIGMA2, CONVERGE, FASTAN) — Germain G., Main P. & Woolfson M. M. (1969) Univ. of York & Louvain.

15 — SYMB. ADD. — Hodder O. J. R., Prout C. K., Rollet J. S. & Viterbo D. (1969) Univ. of Oxford.

16 — MULTISOL. — Drew M. G. B., Templeton D. H. & Zalkin A. (1969) *Acta Cryst.*, **B25**, 261.

17 — GAASA — Lindgren O., Lindquist O. & Nyborg J. (1970) *Acta Chem. Scand.*

18 — DEVIN — Riche C. (1970) *C. R. Acad. Sc. Paris*, Ser C, **271**, 396.

19 — S. I. LEAST SQUARES — Hauptman H., Fisher J. & Weeks C. M. (1971) *Acta Cryst.*, **B27**, 1550.

20 — SYMB. ADD. — Norrestam R. *et al.* (1971) *Acta Cryst.*, **B27**, 2066.

21 — DIRECTO, DIRECT1, DIRECT2 — Goldberg I. & Shmueli U. (1971) *Acta Cryst.*, **B27**, 2173.

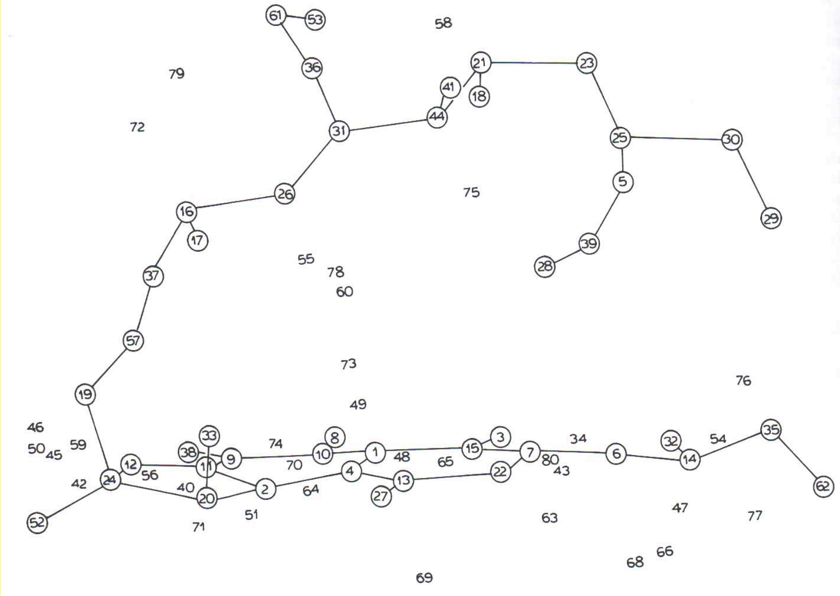
22 — GSAM — James V. J. & Grainger C. T. (1972) *Cryst Struct. Commun.*, **1**, 111.

D. VITERBO

DIRECT METHODS: AN EVER IMPROVING TOOL FOR THE SOLUTION OF CRYSTAL STRUCTURES

Godišnjak Jugoslavenskog centra za kristalografiju

21 (1986) 149—165



Lineprinter graphical output of an E-map after manual interpretation

After 1972

I will only mention the most popular programs

- As mentioned **MULTAN** had several children, but, after the setting up of the first organic version in 1970 during a CECAM workshop in Paris, kept developing and remained the most popular software from the York group.
- **DIRDIF** developed by Paul Beurskens and his group in Nijmegen is very efficient in handling partial structures using difference structure factors. It also allows Patterson vector search.
- **SIMPEL** developed by Henk Schenk and his group in Amsterdam (Overbeek & Schenk, 1976, *Computing in Crystallography*, Delft Univ. Press, p. 108) allowed a complete automation of symbolic addition.

After 1972

SHELX-76

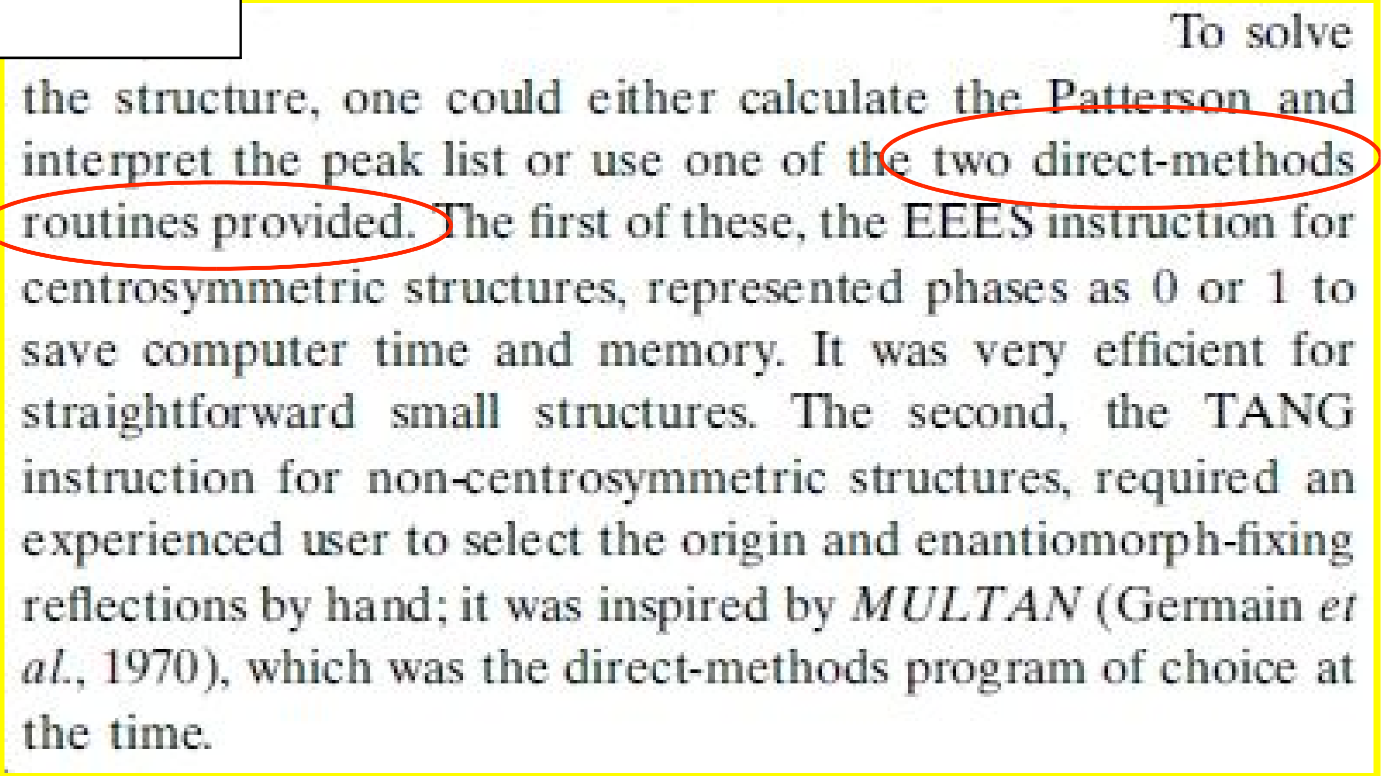
George Sheldrick wrote the first version of his “best seller” program, allowing to go from raw intensity data to the refined structure. Direct methods procedures were available as mentioned in his recent historic paper

Acta Cryst. (2008). **A64**, 112-122

A short history of *SHELX*

G. M. Sheldrick

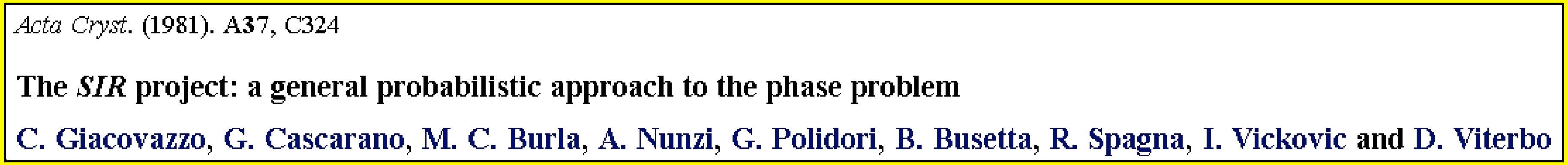
I have been an affectionate user of all SHELX versions



To solve the structure, one could either calculate the Patterson and interpret the peak list or use one of the two direct-methods routines provided. The first of these, the EEES instruction for centrosymmetric structures, represented phases as 0 or 1 to save computer time and memory. It was very efficient for straightforward small structures. The second, the TANG instruction for non-centrosymmetric structures, required an experienced user to select the origin and enantiomorph-fixing reflections by hand; it was inspired by *MULTAN* (Germain *et al.*, 1970), which was the direct-methods program of choice at the time.

After 1972

- The successive versions of **SHELX**, from -86 on, introduced several improvements also in the direct method procedures
- Around 1980 the first version of the **SIR program** was set up by a group of people lead by Carmelo Giacovazzo. Gianluca was there from the very beginning and is still there: he can tell you all about the developments of the SIR project.



Acta Cryst. (1981). A37, C324

The *SIR* project: a general probabilistic approach to the phase problem

C. Giacovazzo, G. Cascarano, M. C. Burla, A. Nunzi, G. Polidori, B. Busetta, R. Spagna, I. Vickovic and D. Viterbo

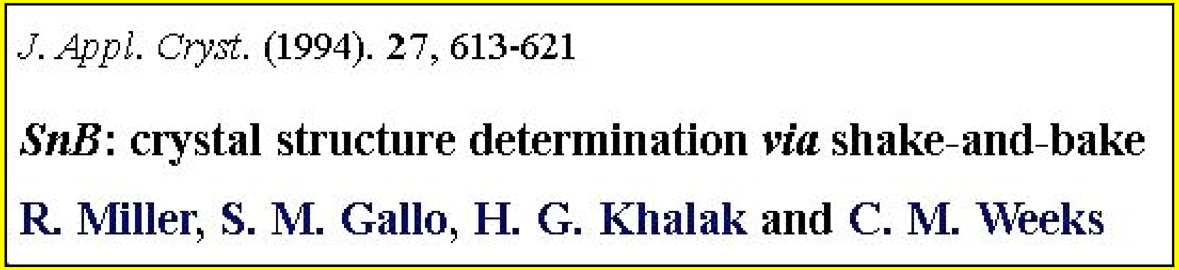
Let me just tell you another gossip. When George Sheldrick first heard of our SIR project his comment was: “*A computer program written by a group of people is like a camel designed by a committee!*”. This was the expected reaction of a “lonely programmer”, but fortunately he was later proved to be wrong.

1985 Nobel prize to Hauptman and Karle

For their outstanding achievements in the development of direct methods for the determination of crystal structures

After 1972

In the early 90’s the group lead by Herbert Hauptman in Buffalo developed a new procedure called “***Shake & Bake***” (**SnB** at http://www.hwi.buffalo.edu/snb/). The idea of combining phase refinement in reciprocal space (carried out using the Minimal Principle) with an appropriate modification of the electron density in real space was introduced for the first time. This was the launch of the present very successful “***Dual Space***” procedures .



J. Appl. Cryst. (1994). **27**, 613-621

SnB**: crystal structure determination *via* shake-and-bake**

R. Miller, S. M. Gallo, H. G. Khalak and C. M. Weeks

Science **259**, 1430-1433.

On the Application of the Minimal Principle to Solve Unknown Structures

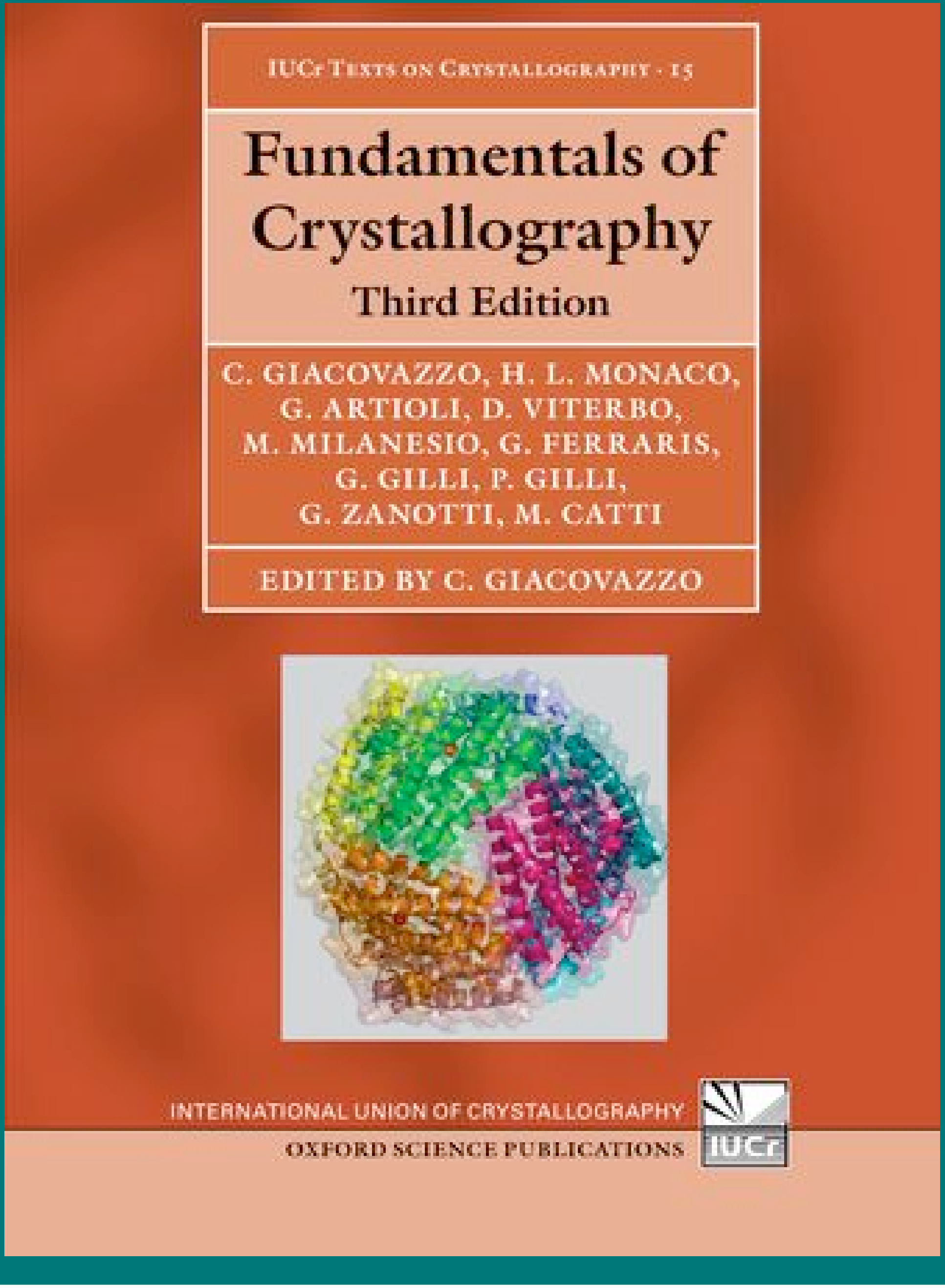
Russ Miller,* George T. DeTitta, Rob Jones David A. Langs,
Charles M. Weeks, and Herbert A. Hauptman

And then…..

- History becomes “present”.
- My direct involvement in Direct Methods ended.
- I kept my interest and, most important, my friendship with many of the people involved.
- I have recollections of exciting moments (I tried to illustrate in the previous slides), but also of contrasts (I can only tell, but not report in written form).
- It will be the task of young people to change into “history” the years from the early 90’s to the present century.
- TODAY: large biological molecules and complex systems can be tackled; solution from neutron and powder data is possible.
- I am not going to make predictions for the FUTURE, as they always prove wrong, but I am very optimist.

The present is described in this book!

A bit of advertising!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I thank all those with whom I shared this adventure and apologize for any omission or incorrect recollection

THANK YOU FOR YOUR ATTENTION