This Week's Citation Classic®

Hauptman H & Karle J. *Solution of the phase problem. I. The centrosymmetric crystal.* New York: American Crystallographic Association, 1953. 87 p.
[Naval Research Laboratory, Washington, DC]

A crystal's structure determines its diffraction pattern: both the intensities and phases of the diffraction maxima, and conversely. Only the intensities are obtainable from the diffraction experiment; the phases cannot be measured directly. However, due to the atomicity of real structures and the abundance of available intensities, the lost phase information can be found in the measurable intensities. [The *SCI*® indicates that this book has been cited in over 475 publications since 1955.]

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M. von Laue, W. Friedrich, and P. Knipping's discovery of the diffraction of X rays by crystals in 1912 was a watershed event in modern science. While researchers understood immediately that this experiment held the key to determining crystal and molecular structures, a fundamental obstacle soon became apparent. Although the intensities of the diffraction maxima could be measured, their phases, also required to proceed from the diffraction experiment to the desired crystal structure, could not be measured directly. Since arbitrary values for the phases could presumably be prescribed, it was generally believed that the observed intensities were not sufficient to determine unique values for the phases. Therefore, the so-called "phase problem" (to determine the phases from the measured intensities) was unsolvable, even in principle. This erroneous view was so deeply ingrained that, for almost 40 years, no one made a concerted attempt to solve the phase problem.

Thus, when I joined my colleague, Jerome Karle, at the Naval Research Laboratory in 1947, the phase problem was still the central problem of X-ray crystallography—it had remained unsolved and was regarded as unsolvable. We soon discovered that the key to its solution was the known property of real crystals, atomicity.

Molecules consist of atoms, and for our purposes the actual crystal structure could be replaced by an idealized one consisting of discrete, nonvibrating, point atoms. In this way the phase problem was transformed from one having no solution in principle to one that was greatly overdetermined because the number of observed intensities usually exceeds by far the number of parameters (atomic position coordinates) needed to fix the structure.

Recognition of the overdetermination of the problem suggested the use of probabilistic techniques for its solution. The unknown atomic position vectors were assumed to be random variables, uniformly and independently distributed. The unknown phases, as functions of the primitive random variables, were themselves random variables. The conditional probability distribution of selected linear combinations of the phases (the so-called structure invariants) could then be found. In favorable cases the distributions lead to reliable estimates for the structure invariants and the latter, as certain well-defined linear combinations of the phases, lead to unique values for the phases.

The essential contribution of our monograph was the introduction of probabilistic techniques to solve the phase problem and the recognition of the central role of the structure invariants that serve to link the desired phases with the measured intensities.

I believe our monograph has been frequently cited[1,2] because it provides the theoretical foundation for the solution of the phase problem, the central problem of X-ray crystallography and the one having the most important consequences for structural chemistry and the biomedical and material sciences. Another reason may be that the problem had generally been thought to be unsolvable, even in principle.

[Editor's note: Dr. Hauptman shared the 1985 Nobel Prize for chemistry with Jerome Karle for their achievements in developing direct methods for determining crystal structures. A recent *Current Contents*® essay[3] describes the work that led to this award.]

1. **Bricogne G.** Maximum entropy and the foundations of direct methods. *Acta Crystallogr. A—Found. Crys.* 40:410-45, 1984.
2. **Karle J & Hauptman H.** A theory of phase determination for the four types of non-centrosymmetric space groups $1P222$, $2P22$, $3P_12$, $3P_22$. *Acta Crystallogr.* 9:635-51, 1956. (Cited 455 times.)
3. **Garfield E.** The 1985 Nobel chemistry prize to Jerome Karle and Herbert A. Hauptman and the physics prize to Klaus von Klitzing contrast delayed versus "instant" recognition. *Current Contents* (44):3-12, 3 November 1986.

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