Letters

Will Holography Revolutionize Crystallography?

A Research News article (28 Jan., p. 384) by Thomas H. Maugh and several other news items (*1*) concerning a holographic technique (*2*) and its postulated impact on x-ray crystallography have appeared recently. According to the article in *Science*, the technique "shows great promise for converting x-ray data almost directly to a three-dimensional image of the structure that shows the spatial positions of the individual atoms precisely." This quotation and other statements suggest a misunderstanding of the problems and procedures of both contemporary crystallography and holography.

The classical and persistent problem in crystallography is the phase problem. The experimental and mathematical procedures for determining phase angles from the observed x-ray intensities are reliable but fairly complicated. Crystallographers would certainly welcome a straightforward universal solution; unfortunately, the reported holographic technique does not address the phase problem. It is applicable only to the three-dimensional Fourier summation used to transform the set of previously phased complex structure factors into a three-dimensional electron density function.

The *Science* article also states that the holographic "optical technique has the additional advantage that it cuts down on the noise or error associated with locating the centers of atoms. This results, in part, from the fact that digital integrations in the Fourier transformation must necessarily be truncated to make the calculation manageable. When the transformation is performed optically, the integration is complete and there is less noise." What is the truncation referred to here? The truncation of the infinite Fourier series of structure factor coefficients to a finite series arises because the experimental observations are confined to a sphere about the origin of the reciprocal lattice. This truncation of observational data is independent of computational method. There are no approximations involved in using a finite Fourier summation here instead of an integration since the periodic nature of the crystal inherently provides only a three-dimensional sampling of the frequency domain (the reciprocal lattice). An analog calculation involving photographic steps and representational approximations cannot be more precise than the rigorous numerical formulation of the same calculation using the same input data.

One feature the optical technique does provide is a continuum of density in two-dimensional sections of the three-dimensional density function, whereas the numerical methods provide only sampling on a three-dimensional grid. In practice, however, the extent of input data does not justify using a sampling interval less than about 0.1 angstrom. Incidentally, the optically calculated sections will still have to be sampled and digitized before quantitative interpretation is possible, which means that ultimately a three-dimensional interpolation is required in either case.

A comparison of the economics for the convenient and quite inexpensive three-dimensional fast Fourier numerical calculation with that for a combination of numerical, graphic, coherent optical, and photographic steps is most likely to favor the former. The reported graphic step of plotting the hologram (*3*) that encodes a two-dimensional set of complex Fourier coefficients for one section through the density function requires an elaborate film plotter not generally available in computer centers.

A possibility for useful crystallographic application of the reported holographic technique is that of display. One might imagine a holographic image of the complete density function for a protein molecule scaled to 1 or 2 centimeters per angstrom and used to replace the computer-drawn contoured density sections currently used in a Richards optical comparator (*4*). Closer examination indicates that a "holographic Richards Box" might provide more disadvantages than advantages. In addition to the many technical problems of producing and projecting selected portions of a faithful three-dimensional holographic image, which necessarily must be approximated by noninteracting two-dimensional sections through the function (*5, 6*), we have the problem that it is very difficult to visualize important characteristics, such as centroids, second moments, and critical points, from a sectionally sampled three-dimensional cloud of continuously varying luminescence. A contour representation depicting selected surfaces of constant density is much easier to interpret. It appears that "windowing" of density levels, which could produce contours, is not a well-developed optical processing technique (*7*).

An important factor in contemporary crystallography is that considerable progress currently is being made in the simultaneous manipulation of contoured density maps and molecular models with interactive computer graphics, and this development may replace the Richard's Box altogether. Many of us learned diffraction theory with the aid of optical techniques such as the optical transform (*8*). The pedagogical value of optical techniques in crystallography undoubtedly will benefit from the addition of holographic optical processing and Fourier summation methods of the type described in (*2, 3, 5–7*).

The use of holography to display computer-drawn molecular models (*6*) has received some attention, and that approach might have some impact on crystallographic methodology. A completely different holographic approach that could revolutionize crystallography involves the postulated 1-angstrom x-ray laser (*9*). If a coherent x-ray source becomes available and hologram recording and reconstruction schemes are realized, it is conceivable that such a system could provide another experimental solution to the phase problem.

The supposedly new "Fourier-domain projection theorem" (*1, 2*) used in the calculation of sections is simply a commonly used factorization of the three-dimensional Fourier series summation and a restatement of the well-known principle that, for spaces which are Fourier mates, a projection in one space corresponds to a central section in the other (*10*). In summary, the reported holographic "breakthrough" in crystallography does not address the key problems of crystallography. For the problems it does address, superior solutions already exist.

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References and Notes

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Probability of the Pittsburgh Deaths

In attempting to decide whether the three deaths following swine flu vaccination in Pittsburgh were coincidental, Mitchell Gail (Letters, 11 Mar., p. 934) infers on the basis of a simple probabilistic calculation that "the chance that some clinic would experience three or more deaths on some day during the first week of the inoculation program is appreciable and could easily be as high as 10 percent, even if the vaccine is perfectly safe."

Gail's calculation is perfectly correct as far as it goes, but what needs to be stressed is that the result is extremely sensitive to the assumptions one makes and to the numbers one substitutes in the formulas. Furthermore, he has ignored three significant features of the Pittsburgh incident, all clearly indicated in the very first paragraph of Philip M. Boffey's article (News and Comment, 5 Nov. 1976, p. 590): the deaths were sudden, the three individuals were all inoculated within an hour of each other, and all died within 6 hours of being inoculated.

To make the discussion clearer, let us consider a 10-hour working day of a clinic divided into time intervals of duration τ (for example, 1 hour) and denote by $n(\tau)$ the number of patients of the appropriate age group who visit the clinic during one of the designated τ intervals. Let α be the mortality rate (per person per day) of the age group in question, so that $\alpha n(\tau)$ is the expected number of deaths during the day of those (in the appropriate age group) who came to be inoculated during the specified time interval of duration τ. The probability that the number of deaths will be less than three is

$$\{1 + \alpha n(\tau) + \tfrac{1}{2}[\alpha n(\tau)]^2\}e^{-\alpha n(\tau)}$$

which is approximately [for small $\alpha n(\tau)$]

$$1 - [\alpha n(\tau)]^3/6$$

and the probability that three or more deaths will be recorded in one of 1000 clinics on one day in a week is

$$1 - \{1 - [\alpha n(\tau)]^3/6\}^{700\times 10/\tau}$$

Assuming with Gail that 1000 people visit a clinic every day we can set

$$n(\tau) = 100\tau$$

and the desired probability comes out (approximately) to be

$$\tfrac{7}{6}\,\alpha^3 10^9 \tau^2$$

Gail sets $\alpha = 10^{-4}$ and $\tau = 10$, that is, a day is taken to be the basic unit, which yields 11.6 percent. This is larger than the 10.3 percent that Gail gets because the approximation used above is a little too crude in the numerical range he considers.

Since the Pittsburgh inoculations preceding the three deaths were given within an hour, a good case can be made for taking $\tau = 1$, thus decreasing the probability by a factor of 100. Also, Gail's α is an overall death rate which includes lingering causes of death such as cancer. If one focuses on the fact that the deaths in question were sudden, a decrease of α by a factor of 2 seems not unreasonable. Moreover, since the deaths occurred within 6 hours of the visits to the clinic, it seems justifiable to take α to be the death rate per 6 hours, thereby decreasing it by an additional factor of 4, which would reduce the probability by another factor of 512. Hence, we conclude that the chance that the three Pittsburgh deaths occurred by coincidence is about 1 in 500,000, rather than 1 in 10 as Gail concludes.

We are, of course, well aware that by taking $\tau = 1$ we can be accused of using selectively a posteriori information (that is, that the three who died have all been inoculated within an hour). However, by the same token, taking $\tau = 10$ constitutes selective disregard of a given piece of information.

It all boils down to a definition of coincidence, and our calculation shows that the result depends very sensitively on the definition. Our calculation can be looked upon as a simple statistical test of the hypothesis that the batch of vaccine used during the crucial hour was faulty. This justifies the use of hourly intervals as units. All in all we think that, since a reasonable definition could yield a very low estimate of the probability of an accidental coincidence, it would have been only prudent to investigate very carefully the Pittsburgh deaths.

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Labeling Theory

Jane M. Murphy's article, "Psychiatric labeling in cross-cultural perspective," (12 Mar. 1976, p. 1019) severely criticizes the "sociological" or "relativistic" approach to mental disorders. Although the article contains some valid points, the author has ignored crucial evidence which supports the "sociological" approach. Contrary to Murphy's claims, a certain percentage of American patients who have "problems in living" are labeled psychotic. These individuals would not be reliably diagnosed as psychotic in transcultural comparisons. The treatments (for example, hospitalization) which follow from their being labeled psychotic may at times be damaging. The following evidence tends to support these contentions.

1) It should be emphasized that the author's central thesis is correct: the major psychoses (schizophrenia and manic-depressive psychosis) appear to be found universally (*1*). Murphy, however, claims that "sanity appears to be distinguishable from insanity by cues that are very similar to those used in the Western world." This statement implies a universality of signs and symptoms and a reliability of diagnoses which do not exist. Recent cross-national studies of psychiatric diagnosis have demonstrated that the recognition and diagnosis of symp-