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# Author's Commentary: The Outstanding Brain-Drug Papers

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The problem reviewed here—the estimation of the spatial distribution of a drug injected in brain tissue—has a story that demonstrates that outstanding undergraduates can contribute to applied mathematical research.

In the autumn of 1982, Paula Altschul, a former precalculus student, introduced me to Mark F. Dubach, a friend of hers who was completing a dissertation in physical anthropology on the effect of intracerebral dopamine injections. He needed a mathematical estimate to convince both himself and his dissertation committee of the scientific validity of his assessment of the region of the brain affected by the drug.

At the time, even at the University of Washington's prestigious health sciences research complex, the computational equipment available limited the testing of a mathematical model: The IMS Associates 8080 microcomputer offered only 56KB of internal memory and supported only a rudimentary version of BASIC, which ran overnight to perform a nonlinear regression.

To accommodate such equipment, we first assumed a distribution that uniformly filled an ellipsoid (to be estimated through regression) and vanished outside. We grouped each row of five cylindrical punches into a parallelepiped, intersecting the ellipsoid in a region shaped like a candy bar near the center and like a piece of a cheese-wheel near the boundary. This crude mathematical model had an analytical expression involving only inverse tangents and algebra, which the equipment could handle. A few months later, the results became a part of Dr. Dubach's dissertation [1983, 356], while the details of the integral calculus appeared in Nievergelt [1984].

Several years later, but only a couple of blocks away from Dr. Dubach's laboratory, we finally obtained the time, money, and permission to use the University's CDC Cyber 180/855 mainframe computer and the FORTRAN software routines of the International Mathematical and Statistical Library (IMSL). That system took about a minute to fit a homogeneous anisotropic diffusion and absorption model [Nievergelt 1990], which resembles the two Outstanding MCM papers.

The paper from California Polytechnic State University contains interesting simplifying assumptions. For instance, the replacement of three-dimensional integration by a three-dimensional mean-value theorem constitutes an insightful application of advanced calculus in a situation limited

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by time. As another example, the assumptions of a constant cross-sectional flux area and of a single space-time variable lead to a distribution modeled by the "error function," which closely fits the data but lacks a derivative at the origin. The lack of a derivative suggests that the drug spread only during the injection; otherwise, the elliptic diffusion equation would have yielded an analytic solution [Hörmander, 1963, 101]. Though Hörmander's work still remains beyond the reach of most undergraduates (at least in the U.S.), its applicability may convince students that abstract theory can provide important insight into practical phenomena.

The team from Cal Poly also mentions the drawbacks of using splines to interpolate the data. Grace Wahba of the Statistics Dept. of the University of Wisconsin–Madison notes that an alternative approach would be to use smoothing splines, which do not fit the data exactly, but smooth it [Wahba 1990].

The paper from Humboldt State University, in contrast, derives from the diffusion equation an analytic, anisotropic, Gaussian distribution. Their original FORTAN programs to fit the distribution to the data is less fancy than the use of Mathematica and may appear to be reinventing the wheel; but the design of programs for integration, for optimization, and for solving equations also demonstrates strong resourcefulness to solve a problem from scratch. This paper, too, made an interesting simplifying assumption, that the principal directions of the diffusion lie in the directions of the coordinate axes. The assumption leads to a diagonal diffusion tensor, instead of a more general quadratic form represented by a positive definite (symmetric) matrix (the last topic may have disappeared from many linear algebra curricula).

The two Outstanding papers suggest several conclusions:

- There are outstanding undergraduates capable of applying abstract mathematics and sophisticated computational systems to a concrete problem, at a level at which they could assist researchers.
- They are able and willing to learn additional theory, which would considerably narrow the gaps between the current undergraduate mathematics curriculum and, on the one hand, real applications of mathematics, and, on the other, the allegedly better preparation of foreign students.
- The Mathematical Contest in Modeling is effective in providing an incentive for students to learn mathematics and in providing the community with an objective measure of what undergraduates can *do*.

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# About the Author

Yves Nievergelt graduated in mathematics from the École Polytechnique Fédérale de Lausanne (Switzerland) in 1976, with concentrations in functional and numerical analysis of PDEs. He obtained a Ph.D. from the University of Washington in 1984, with a dissertation in several complex variables under the guidance of James R. King. He now teaches complex and numerical analysis at Eastern Washington University.

Prof. Nievergelt is an associate editor of *The UMAP Journal*. He is the author of several UMAP Modules, a bibliography of case studies of applications of lower-division mathematics (*The UMAP Journal* 6 (2) (1985): 37–56) (in which the Brain-Drug Problem was discussed explicitly), and *Mathematics in Business Administration* (Irwin, 1989).

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