Error-Function Diffusion: A Dopamine–Fick's Model

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Summary

Estimation and modeling of drug diffusion in tissue is necessary for successful combatting of many brain disorders. An obvious method for determining the size and shape of the region of the brain affected by a drug consists of actually removing tissue and measuring the quantity of drug in certain core samples. We were given measurements of 50 core samples spread in three dimensions around the point of injection, and were asked to estimate the size and shape of the region affected by the drug. We treated the data from the core samples as densities rather than scintillation counts by simply dividing the scintillation count by a unit volume of one core. Continuity of the dispersion allowed us to assume that representing the data by point densities within each core is valid.

Research on diffusion in tissue suggested two types of models for estimating both size and shape: an exponential function, and a distribution based on Fick's law. The latter offers a general description for similar diffusion problems, and the application of appropriate boundary conditions yielded a superior model for the dispersion of dopamine based on the standard error function (erf). Subsequent modifications yielded a still better fit. Our final model was the function

$$C(x, y, z) = 51103 - 51319 \operatorname{erf}\left[0.6(x + 0.3)^2 + (y + 0.1)^2 + (z + 0.4)^2\right],$$

a function of position yielding the dopamine concentration at the point (x, y, z).

We evaluated the quality of our model by measuring the average absolute residual between our estimator and the data points. We also compared the residuals with those from an exponential model, which was fairly accurate, and found that the erf model was better still.

We were tempted to make assumptions about our data based on the shape of computed level curves and surfaces. However, the arguments

for many of these were so weak as to merit no investigation into further modifications of the model.

Assumptions

We made the following assumptions:

1. We will not be asked to describe past or future distributions.
2. Spread of the drug is due solely to diffusion and to a monodirectional current.
3. The tissue is homogeneous, containing no preferred routes of transfer for the dopamine.
4. There are no boundary surfaces.
5. The density distribution is continuous with respect to position.
6. The initial injection of dopamine occurred exactly in the center of the middle rear cylinder and was instantaneous.
7. Scintillation counts are converted to amounts per unit volume and each density is assumed to be at the center of the measured cylinder.
8. The absorption of the drug does not affect its dispersion pattern.
9. All 50 core samples were removed simultaneously.

Justification of Assumptions

1. **One point in time:** Since no information was given on how much time has elapsed since the injection, the rate at which the distribution is changing cannot be determined.
2. **Reasons for dispersion:** Movement of extracellular substances does occur in the cerebrospinal fluid bathing the brain [Marsden 1984, 116]. Literature suggests that both constant and transient currents exist within this fluid. However, the nonconstant flows are small in comparison to the steady currents. From graphs of the data, we see that the distribution is fairly constant with respect to distance from the highest concentrations, indicating that no major distortions exist which could be expected from nonsimple currents.

   The literature also states that "Major transport of oxygen, carbon dioxide, glucose, and metabolites is due not to net movement of fluid but to simple diffusion across the capillary walls and through the interstitial fluid"; so

diffusion can be expected to account for the basic distribution, allowing a current to make secondary contributions [Bradbury 1979, 1, 27].

3. **Tissue homogeneity:** Brain tissue is a collection of nerve cells that are macroscopically similar [Gardner 1975, 136]. The cerebrospinal fluid bathing the tissue is also of a consistent makeup. The radial symmetry observed earlier suggests that there are no preferred routes for the dopamine.

4. **Boundary surfaces:** We have no knowledge of the environment outside of the samples taken. So we have no reason to assume that there are any membranes or other disruptive boundaries within the affected region of the brain which might influence the distribution of the drug.

5. **Continuity of dispersion:** Natural dispersion processes tend to be continuous, and there is no reason to assume that discontinuities exist.

6. **Point of injection:** The injection was made near the center of the cylinder with the highest concentration, and there is no reason to assume that it was not made at the exact center. We regard the injection as a point-source impulse and not as a directed velocity with an interval of injection.

7. **Density measure:** Some measure of density distribution is needed. Since the dispersion within each cylinder is unknown, its center is a logical choice to place the data. Also, the amount of the dopamine within the cylinder, divided by its volume, is the average density within this structure. Since the distribution is already assumed to be continuous, the intermediate value theorem ensures that there is a point within the cylinder which has this density. The true location for a point with this density cannot vary farther from the center than the boundaries of the cylinder itself.

8. **Drug absorption:** No information is given about the absorption rates of the drug into the tissue, so no meaningful influences of nonlinear absorption can be inferred.

9. **Simultaneous core removal:** If this assumption is not made, then data on when each core was removed is essential to any model.

Analysis of the Problem

As is often the case, a good first step with this problem is to draw a picture. While it is difficult to draw three dimensions in space and a fourth dimension for dopamine concentration, we can easily separate the data into two groups, the front and the back, and then draw two sets of level curves.

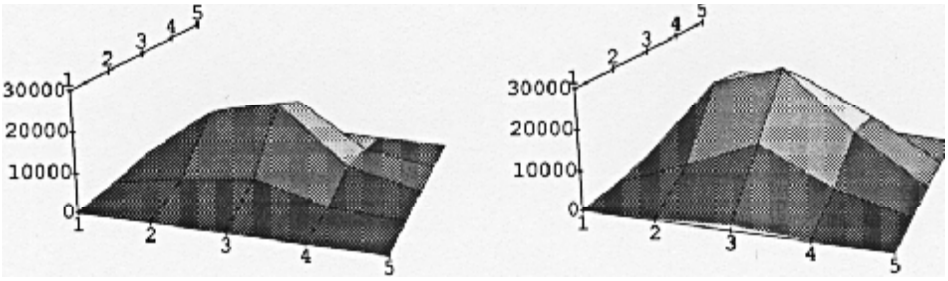

Figure 1. X-Y position versus concentrations, for front (left) and back (right).

Doing so gives a good idea of the "shape" of the data. In **Figure 1**, we provide one view of each row of tissue samples.

We see from the contour maps in **Figure 2** that the data are symmetric about some center. Since we made the assumption that the only way the drug could spread was through diffusion and outside forces, these graphs lead us to believe that the dominant dispersion was due to diffusion.

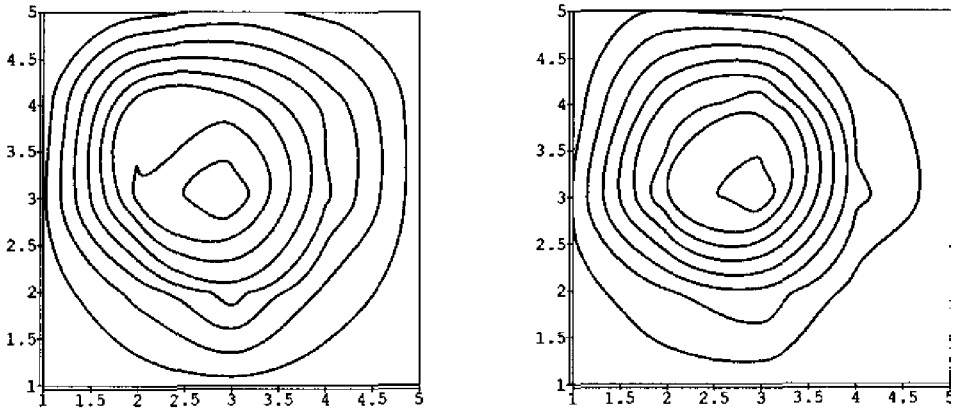

Figure 2. Contour view of sample data, for front (left) and back (right).

The data in the figures are treated as ordered triplets (x, y, c) for the convenience of being able to create a graphical representation, where c is the concentration. In the following estimator models, however, the data are treated as ordered quadruples (x, y, z, c), as there are three spatial dimensions in the data. Our coordinate system is centered at the injection point, placing $(0, 0, 0)$ in the center of the middle back cylinder. Our x-axis extends negatively to the left, the y-axis extends positively from rear to front, and the z-axis extends positively toward the top.

The Exponential Model

Our first model of the shape and size of the region of diffusion is based on an exponential estimator. Exponential models are commonly used to describe diffusion in a homogeneous medium [Twiner 1962, 40]. The exponential estimator we use is a function of the distance from the point of highest concentration. If diffusion is the only force, then this point would be the point of injection, $(0, 0, 0)$. Taking into account other forces, such as currents, would change the situation. We use the exponential function

$$C(x, y, z) = B \exp\left(A \operatorname{dist}(x, y, z)\right),$$

where C is the concentration at the point (x, y, z) and dist (x, y, z) is the Euclidean distance from the highest point of concentration to the point (x, y, z). We transform the data by taking the natural logarithm of the concentrations and find the linear estimator

$$\ln\left(C(x, y, z)\right) = 11.81 - 2.30 \operatorname{dist}(x, y, z).$$

Regression analysis of this fit to the data is surprisingly encouraging. There are only two points indicated by our software as outliers (lying more than two standard residuals away), and the R^2 coefficient is 83.2%, more than high enough to indicate good correlation.

One of the outlier points is the point with the highest concentration. The cause for this is obvious, as an exponential function grows very rapidly at its point of symmetry, far more rapidly than is useful for our model. While this feature may seem a necessary evil of the model, we prefer to look for a model that more closely resembles the data.

Our first modification is to assume that the dopamine experienced the effects of a current that shifted the point of highest concentration to a new center. With the center at $(-0.3, -0.1, -0.4)$, the only change in our model of a concentration function is the distance function. The new distance function measures the Euclidean distance from the point (x, y, z) to the new proposed center. Using linear regression on the transformed variables, we obtain

$$\ln\left(C(x, y, z)\right) = 11.85 - 2.24 \operatorname{dist}(x, y, z).$$

The R^2 coefficient is 88.1%, indicating a better fit than the original model. Another indication of better fit is the average absolute residual. In the previous model it was 3.86×10^3; in the new model it is 1.84×10^3.

Fick's Law and the erf Function

In our efforts to find a better model for the diffusion, we came across Fick's law, a common model for diffusion. The basic form of Fick's Law is

$$(-AD)\frac{\partial C}{\partial R} = J,$$

with

A	the cross-sectional area for flux,
D	the diffusion coefficient for binary mixture,
R	the distance of point from center of diffusion,
$C(R,T)$	the concentration as a function of R at time T, and
J	the flux of diffusing material.

E.L. Cussler [1976, 19] gives the following technique for using this equation to solve for the concentration levels. First, the mass balance equation

$$-\frac{\partial C}{\partial T} = \frac{\partial J}{\partial R} + CV$$

is used, with

T	time and
V	the velocity of fluid in which diffusion occurs.

Fick's law indicates what flux, or movement of the diffusing material, is generated by the imbalance of concentrations. The mass balance equation determines how the concentration at each point is affected by amounts of the substance diffusing through it. For now, we assume that $V = 0$; that is, we ignore any mass movement of the drug because of flows.

Combining the two equations yields the partial differential equation

$$\frac{\partial C}{\partial T} = AD\frac{\partial^2 C}{\partial R^2}.$$

With the substitution

$$Y = \frac{R}{\sqrt{4ADT}},$$

so that

$$Y = FR \quad \text{with} \quad F = \frac{1}{\sqrt{4ADT}},$$

the equation takes the form

$$\frac{d^2C}{dY^2} + 2Y\frac{dC}{dY} = 0.$$

The grouped constant F accounts for the unknown values of D and T, both of which are constant, since the tissue is assumed to be homogeneous and the concentration function describes a particular time. The general solution to this equation is

$$C = K + B\int_0^Y e^{-x^2}dx.$$

Using the boundary conditions

$$C(\infty) = 0 \text{ and } C(0) = C_0,$$

we solve for the related constants K and B:

$$C(0) = K + B\int_0^0 e^{-x^2}dx = C_0, \text{ so } K = C_0;$$

and

$$C(\infty) = K + B\int_0^\infty e^{-x^2}dx = B\left(\frac{\sqrt{\pi}}{2}\right) + K = 0,$$

so

$$B = -\frac{(2K)}{\sqrt{\pi}} = \frac{(-2C_0)}{\sqrt{\pi}}.$$

Therefore, the concentration as a function of distance from the center of the diffusion process is

$$C(Y) = C_0 + \frac{(-2C_0)}{\sqrt{\pi}}\int_0^Y e^{-x^2}dx = C - C_0 \operatorname{erf}(Y),$$

where $Y = FR$ and erf is the standard normal error function

$$\operatorname{erf}(x) = \frac{2}{\sqrt{\pi}}\int_0^\infty e^{-x^2}dx = \Phi(x) - \frac{1}{2},$$

where Φ is the cumulative distribution function of a standard normal random variable (with mean 0, variance 1).

In order to determine the value of F, the center of the distribution is assumed to be at the origin and C_0 is assumed to be the round number 30,000, which is slightly higher than the largest concentration observed. The values of F needed to generate a few of the raw data points are then determined from their distances from the center. For example, using the point with scintillation count 3182, we have $R = 1.61$ and

$$30,000 - 30,000 \operatorname{erf}(FR) = 3,182,$$

so $F = 0.7135$ from tables for the error function [Beyer 1986, 527].

The values found indicate that F lies between 0.3 and 0.8. We next do least-squares fits for the coefficients for different F values within this range, varying the F value until the sum of the absolute values of the residuals is minimized. The best average absolute residual for the 50 data points is 2,130, with corresponding function $36,334 - 37,258 \operatorname{erf}(0.60R)$.

We notice that the coefficients for the constant and erf term are nearly equal, just as predicted by the general solution. This agreement can be taken as evidence that this curve fits the results predicted by theory. The

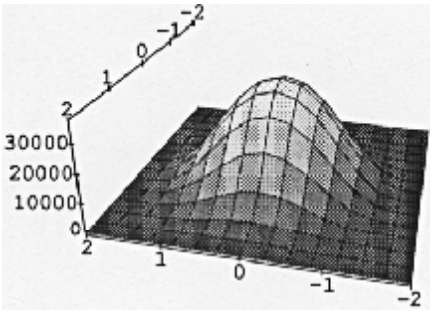

Figure 3. The erf function model for the back row.

concentrations produced by this equation in the plane containing the centers of the rear cylinders look like **Figure 3**.

If any currents exist within the cerebrospinal fluid where the drug was injected, the result would be a translation of the distribution. The concentrations would move evenly if the flow is constant and not experience any distortions as a result of the current.

Plots of the data suggest that the center of the distribution is slightly to the left and down from the middle of the tissue sample. The decrease of the values from front to back indicates also that the center is behind the origin.

By perturbing the position of the center and the value of F, a new fit can be found with residuals smaller than for other positions in the region. With the center at $(-0.3, -0.1, -0.4)$, the residuals are minimized over F at $F = 0.69$, with average absolute residual of 1270 and corresponding function $51,103 - 51,319\,\mathrm{erf}\,(0.69R)$. Once again, we notice that the values of the constant and erf terms are nearly the same, as they should be to ensure the boundary conditions at infinity.

A further method for analyzing the fit to the data is to pick a core and compute the corresponding level curve, to see if the level curve intersects the core. If it does, the model correctly predicts the measured density for some point in the cylinder. For our fit, not only does every level curve intersect the corresponding cylinder, but each comes closer to the center of the cylinder than to any extreme edge.

We show in **Figure 4** the concentration plots for the planes passing through the centers of the front and back cylinders.

Results

Using the last erf estimate, we are able to describe easily the shape of the dispersion. The region with dopamine in it has to be a sphere around the center chosen, because of the symmetry of the function we use. The only question is how large its radius is. We may assume, for example, that the drug is not effective at concentrations below 50 scintillation counts per

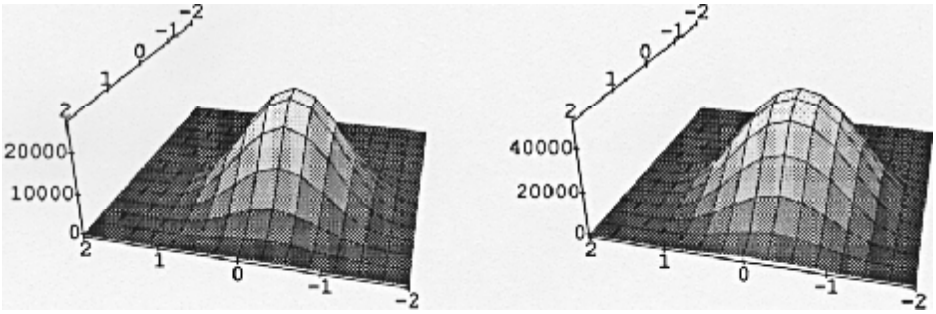

Figure 4. Modified erf model for front (left) and back (right) rows.

unit volume, and proceed to solve the equation at this bound, arriving at a distance of 2.86 mm. Therefore, the effective drug is in the sphere centered at $(-0.3, -0.1, -0.4)$ with radius 2.86 mm. Beyond 2.94 mm, the model predicts no dopamine. It is reassuring to have this touch of realism in our model, since many other models predict traces of dopamine out to infinity.

One might be tempted to try to find a distorted shape to the dispersion; but without strong arguments based on either the specific host tissue or the flow of cerebral fluid, all such arguments rest too heavily on shaky assumptions. A spherical dispersion pattern seems unsatisfyingly simple; but without other information, there is no reason to apply any nonspherical model, especially since the erf model fits so well.

Strengths and Weaknesses

The greatest strength of this model is simply that the estimator function fits the sample data so well. The relatively low average value for the absolute residuals shows that the function prescribes concentrations that are in line with the measured data. Furthermore, the mathematics of the model is deeply entrenched in appropriate physical models of diffusion.

The error function used also allows for extrapolation of the estimator to determine concentrations outside the sample area without losing precision. Other methods that depend solely on connecting the data points, such as splining or brute-force numerical methods, might generate functions that coincidentally fit the data points; but those functions cannot be used effectively for estimating the overall shape of the affected region.

Our solution allows for an extension of the model to a time-dependent solution. If data were available for the dispersion of the drug at other times, then the value of D, the diffusion constant in our equations, might be determined. This would yield a further variation that would be useful in producing estimators for all time values.

Since the method predicts concentrations that constantly decay as a function of distance, level surfaces can be determined for any value of the drug

concentration. This is a simple way of determining drug threshold levels, which may be necessary in dosage sizes and redosage times.

The model suffers some from its dependence on distance from the point of highest concentration. Quite possibly our minimum average residual is not the true minimum, since there is uncertainty about the point of highest concentration. Fortunately, we know that the point we use as center is close to the true center, thus guaranteeing a close approximation to the true minimum average residual. Our iterative method of numerical solution is straightforward but imprecise. An analytic solution may exist, but we feel having one could improve the model only slightly.

The plots of the data (without splining or other interpolating functions) may indicate some asymmetry that is not present in our model. Distortions may in fact exist in the data, but modeling them without understanding why they occur is a waste of resources.

Possible improvements of this model abound. For example, we assumed, based on the continuous nature of the diffusion function, that we could treat the scintillation counts as point densities in the center of corresponding cylinders. Given sufficient time, one could transform the data into probability density functions centered in the cylinder and assess the probabilities that the densities, in fact, were at the center of each cylinder.

Further extensions could account for possible asymmetries in the data, based on irregularities in the neural tissue, initial needle velocity of the injection, nonsimultaneous core removal, or other factors. Also, it may be possible to modify the model to account for nonlinear absorption rates, disruptions due to transport cavity irregularities, or dopamine bonding, if there are strong arguments for the presence of such phenomena.

References

Bradbury, Michael. 1979. *The Concept of a Blood-Brain Barrier.* Chichester, UK: Wiley.

Beyer, W.H. 1986. *Standard Mathematical Tables.* 25th ed. Akron, OH: Chemical Rubber Company Press.

Cussler, E.L. 1976. *Multicomponent Diffusion.* New York: Elsevier.

Gardner, Ernest M.D. 1975. *Fundamentals of Neurology.* Philadelphia, PA: Saunders.

Marsden, C.A. 1984. *Measurement of Neurotransmitter Release In Vivo.* Chichester, UK: Wiley.

Twiner, Sidney B. 1962. *Diffusion and Membrane Technology.* New York: Reinhold.