Distribution of Dopamine in the Brain

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Summary of Results

We construct a three-dimensional unsteady-state mass transport model to predict the behavior of dopamine levels in the brain. The model is based on the principles of molecular diffusion, first-order decay, and instantaneous point-source input. We exhibit an analytical solution to the governing partial differential equation.

We apply the given data on distribution of dopamine, in the brain of a laboratory subject subsequent to an intracerebral injection, to calibrate the parameters of the model. We use two-dimensional curve-fitting and a five-dimensional gridsearch optimization routine. We then use a numerical integration scheme to sum the model concentrations over space so that they could be compared directly to the data values.

The model shows good order-of-magnitude agreement between the predicted and observed data, but it does not demonstrate good arithmetic agreement. The addition of a stochastic component into the analysis does not improve the predictive capability of the model.

We do a rudimentary analysis of the sensitivity of the model to changes in the parameter values. The model responds equally to perturbations of all relevant parameters, and it shows a fair degree of stability under parameter changes.

Hypotheses and Assumptions

Dopamine is one of the catecholamines found in the brain and nervous system, where it functions as a neurotransmitter. It is present in varying quantities throughout the brain, where it may be either synthesized or metabolized. For example, in certain regions of the rat brain, natural dopamine concentrations range from 0.6 to 7.4 ppm, or, equivalently, from 10 to 119 unit counts/mm^3 of cerebral tissue. Based on this fact, we assume the background levels of dopamine in the sample are negligible.

Table 1.
Symbols used.

a, b, c, d, e, f the coefficients of the 2-D regression equations

C the computed dopamine concentration (counts/mm^3)

D the diameter of a sample cylinder (mm)

E_x, E_y, E_z the diffusion coefficients in space (mm^2/unit time)

i a subscript indicating the i^{th} cylinder

j a subscript indicating the j^{th} element of the i^{th} cylinder

k the coefficient of dopamine decay (1/unit time)

L the length of a sample cylinder (mm)

M the mass of the instantaneous point source (counts)

m_i the observed mass of dopamine for the i^{th} cylinder (counts)

$\hat{m}_i$ the predicted mass of dopamine for the i^{th} cylinder (counts)

$\tilde{m}_i$ the predicted mass of dopamine for the i^{th} cylinder (counts)

R_i the difference between the logarithms of the observed and predicted values for the mass of dopamine in the i^{th} cylinder (unitless)

R_i' a normally distributed random variable

t time

x, y, z the three-dimensional spatial coordinates (mm)

x_s, y_s, z_s the spatial coordinates of the point source (mm)

$\Delta x, \Delta y, \Delta z$ spatial steps for numerical integration (mm)

According to the literature, dopamine tracing experiments are commonly performed on laboratory mammals. Methods that draw very small brain tissue samples (as with the given data set) commonly draw tissue from deep within the brain. The volumes of the brains of the subjects typically range from about 0.2 cm^3 to 25 cm^3. For an approximately spherical brain, 20 mm represents a good average brain diameter for a laboratory animal. Based on these two considerations, it is safe to assume from the data that the size of the sample region is negligible compared to the rest of the brain, and that the sample was taken nowhere near the boundaries of the brain.

The development of the mathematical model requires several additional assumptions regarding the physiological and biochemical characteristics of the brain, as well as about the data set. We justify many of these assumptions during the course of developing the model. We assume, for instance, that the cerebrum can be considered as roughly homogeneous in nature, and that diffusion and decay govern the transport of dopamine throughout the brain, while we neglect advection processes (analogous to seepage). In addition, we assume that a single dopamine injection was administered; that the location of the injection is known in the y-direction to be in the center of the rear vertical section of sample cylinders; and that while the exact time of the sampling is not known, sufficient time elapsed between the injection and the taking of samples that the length of time necessary to accomplish each can be considered negligible.

While the mechanisms governing the behavior of dopamine in the cerebrum may be enormously complex, reasonable predictive capability can be obtained by assuming that *molecular diffusion* and *constituent decay* comprise the principal means of dopamine transport in the brain. The process is therefore assumed to be governed by a second-order parabolic partial differential equation. Equations of this form apply to a wide variety of problems, including mass transport, fluid dynamics, and heat transfer.

Model Formulation

The development of a mathematical model for predicting dopamine levels in the brain requires consideration of mass transport in three spatial dimensions and time. A common representation of the unsteady-state diffusive mass transport equation that neglects constituent production but considers a first-order rate of decay is

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial x}\left(E_x \frac{\partial C}{\partial x}\right) + \frac{\partial}{\partial y}\left(E_y \frac{\partial C}{\partial y}\right) + \frac{\partial}{\partial z}\left(E_z \frac{\partial C}{\partial z}\right) - kC, \quad (1)$$

where

C is dopamine concentration (counts/mm^3),

x, y, z are the three-dimensional spatial coordinates (mm),

t is time,

E_x, E_y, E_z are the diffusion coefficients in each spatial dimension (mm^2/time unit), and

k is the coefficient of constituent decay (1/time unit).

Realistically, E_x, E_y, E_z, and k are all be functions of both space and time. Unfortunately, the values of these terms are generally not be known in advance. In addition, the solution to this more general form of the equation requires numerical methods, which can often be extremely costly. By assuming constant values of E_x, E_y, E_z, and k over space and time (homogeneity), (1) can be rewritten as

$$\frac{\partial C}{\partial t} = E_x \frac{\partial^2 C}{\partial x^2} + E_y \frac{\partial^2 C}{\partial y^2} + E_z \frac{\partial^2 C}{\partial z^2} - kC.$$

For the case of an instantaneous point source at time $t = 0$, this equation possesses an analytical solution of the form

$$C(x,y,z,t) = \frac{M}{(4\pi t)^{3/2}(E_x E_y E_z)^{1/2}} \times$$

$$\exp\left\{-\frac{(x-x_s)^2}{4tE_x} - \frac{(y-y_s)^2}{4tE_y} - \frac{(z-z_s)^2}{4tE_z} - kt\right\}, \qquad (2)$$

where

M is the mass of the instantaneous point source (counts), and

x_s, y_s, z_s are the coordinates of the point source (mm).

This solution does not consider the interaction of dopamine at a boundary interface. However, due to the assumption that the samples were drawn from well within the interior of the brain, no consideration need be given to boundary conditions.

We assume that both the injection time and the time to take the samples can be considered negligible, so that the data are considered as taken at a single point in time. We scale the time variable so that 1 time unit corresponds to the time elapsed before samples were taken.

Numerical Integration Scheme

Since the data are expressed in counts and because the model predicts values of dopamine concentration, it is necessary to integrate the values of the dependent variable (C) over each cylinder so that direct comparisons may be made with the data. Unfortunately, the integral of (2) over space does not possess an analytical representation and must therefore be integrated numerically.

We employ a three-dimensional rectangular integration scheme for this model. The molar mass (m_i) of dopamine for the i^{th} cylinder is computed as

$$m_i = \int\int\int C(x,y,z)\,dV_i \approx \sum_j C_{ij}\,\Delta x \Delta y \Delta z,$$

where C_{ij} refers to the computed dopamine concentration in the j^{th} "differential" element of the i^{th} cylinder. Letting the diameter of a sample cylinder be D, we employ uniform spatial steps of $\Delta x = \Delta y = \Delta z = D/6$, a value chosen to achieve balance between accuracy of results and computational economy.

Parameter Estimation

At first glance, the model may seem to have as many as eight parameters: $M, x_s, y_s, z_s, E_x, E_y, E_z$, and k. We remove the y-coordinate of the instantaneous source from consideration by simply assuming $y_s = L/2$. That is, we assume that the injection took place on the plane that bisects the rear vertical section of samples. In this way, the values of C will always be symmetrical about that plane.

Unlike the remaining parameters, the values of x_s and z_s are not obtained by comparing the model to the data. Instead, we use the statistical package Minitab to estimate a two-dimensional quadratic regression equation based upon the data points on the interior of the sample grid. The regression equation is

$$C(x,z) = ax^2 + bz^2 + cxz + dx + ez + f,$$

where C denotes the regressed value for the dopamine concentration in x and z, and a, b, c, d, e, and f are all constant coefficients. We obtain the values of x_s and z_s by simply finding the maximum on the curve (i.e., setting the partial derivatives equal to zero and solving the equations). Of course, one of these curves exists for each of the two vertical sections of data provided (front and rear). Even so, as can be seen in **Table 2**, the values of x_s and z_s obtained for each case show excellent agreement; and so we choose the averages of these values for the model.

We determine the remaining parameters of the model by using a grid-search optimization routine. The criterion used for convergence is a simple

Table 2.
Estimated values for x_s and z_s.

	x_s	z_s
Rear vertical section	3.271	2.686
Front vertical section	3.265	2.766
Average value	3.268	2.726

sum of the squared residuals between the data and the model predictions. The objective function to be minimized is thus

$$\sum_i (m_i - \hat{m}_i)^2,$$

where m_i is to the observed molar mass of dopamine in the i^{th} cylinder, and $\hat{m}_i$ is the value predicted by the model.

Realistically, of course, the actual mass of the injection should be a known quantity, as opposed to an unknown parameter. The treatment of M as a model parameter is further complicated by a strong positive correlation with the decay coefficient k. We therefore use the optimization routine to find a range into which the actual magnitude of M should fall, and then treat the value as a constant thereafter. The gridsearch consistently indicates that the instantaneous source should be in the range of 1×10^6 to 1.5×10^6 counts of dopamine. We therefore assume a value of 10 μg (about 1.4×10^6 counts) of dopamine for the injection.

Finally, the gridsearch indicates that the values of E_x and E_z are very highly correlated, which fact appears to justify our assuming that they are equivalent. This assumption, along with those described above, reduces the model calibration to a three-parameter optimization problem. The optimal parameters of the model appear in Table 3.

Table 3.
Optimal model parameter values.

Parameter	Optimal Value
E_x, E_z	0.375
E_y	0.275
k	0.140
Z	1.157×10^6

Results

Table 4 shows the data for the observed dopamine mass levels within the cylinders and **Table 5** shows the predicted values made by the fully calibrated model. The absolute values of the residuals for each vertical section are depicted in **Figure 1**.

Table 4.
Observed dopamine levels (counts).

Rear vertical section

164	442	1320	414	188
480	7022	14411	5158	352
2091	23027	28353	13138	681
789	21260	20921	11731	727
213	1303	3765	1715	453

Front vertical section

163	324	432	243	166
712	4055	6098	1048	232
2137	15531	19742	4785	330
444	11431	14960	3182	301
294	2061	1036	258	188

Table 5.
Predicted dopamine levels (counts).

Rear vertical section

153	753	1087	406	42
1518	7454	10808	4042	419
4424	21796	31534	11764	1213
3312	16320	23593	8800	907
688	3394	4886	1821	187

Front vertical section

95	466	672	251	26
939	4609	6682	2499	259
2735	13476	19497	7273	750
2048	10090	14587	5441	561
426	2098	3021	1126	116

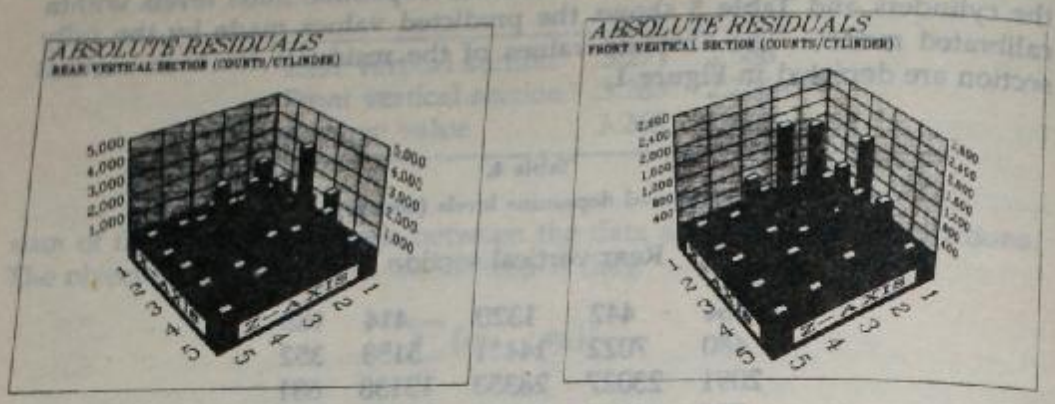

Figure 1. Absolute residuals for rear and front vertical sections.

While the given data set represents conditions at only a single point in time (arbitrarily chosen to be t=1), the model can predict dopamine concentrations over time as well as space. The concentrations at the rear vertical section are given at two different points in time (t=1 and t=4) in **Figure 2.**

As we noted previously, background quantities of dopamine in the brain can typically be found at levels of about 10 counts/mm^3, although the model assumes these values to be zero. We define the *sphere of influence* of the point source to include all points with concentrations at or above this background level. **Figure 3** shows three-dimensional contours of constant concentration representing this sphere of influence. Together with **Figure 2**, this figure demonstrates that as the concentration contour expands, the concentration peak flattens out near the source.

It is interesting to note that although the background concentration contour expands outward at first, it reaches a maximum size before shrinking back again toward the location of the injection. Furthermore, this maximum surface never reaches the boundary of the brain. This result is consistent with the assumption that boundary conditions need not be considered as having an impact on dopamine transport in the brain.

Statistical Analysis

We conduct a statistical analysis of the residuals between observed data and predicted values, to evaluate the performance of the mathematical model. We examine the residual distribution, investigate the correlations and statistical dependence associated with the residuals, and perform a stochastic analysis of the model.

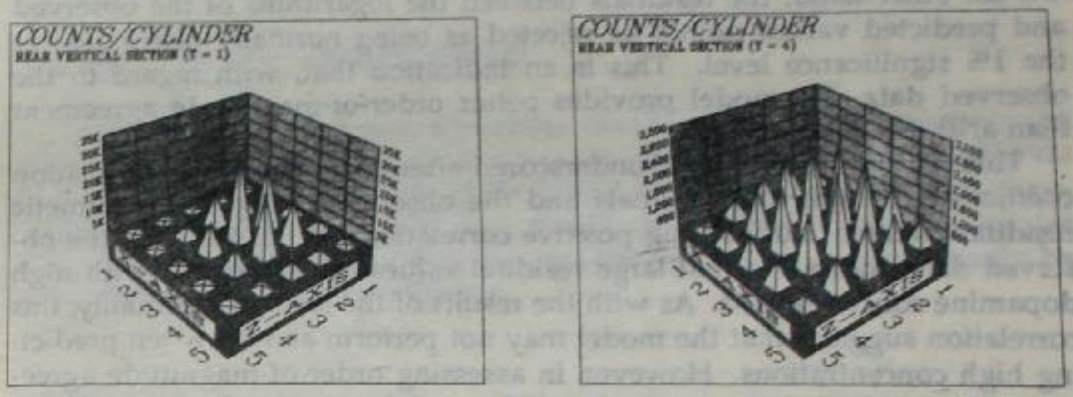

Figure 2. Dopamine concentrations at the rear vertical section at $t = 1$ and at $t = 4$.

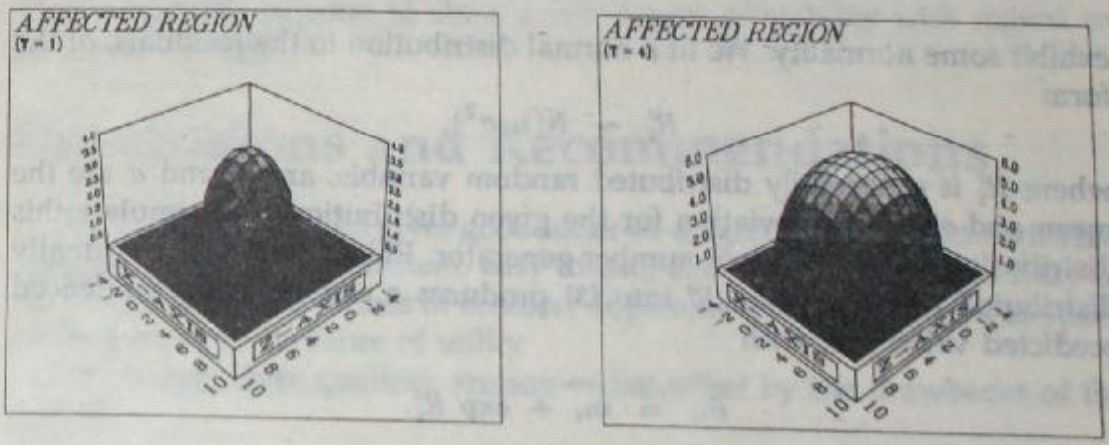

Figure 3. The affected region (sphere of influence) at $t = 1$ and at $t = 4$.

For the ideal case of a model that accurately predicts the values in a given data set, the residuals should be normally distributed about zero. We examine two forms of the residual to see if they fit a normal distribution: simple arithmetic residual values, and the residuals of the logarithms of the observed and predicted results. Unfortunately, the arithmetic residuals fail to demonstrate normal behavior even below the 1% significance level. On the other hand, the residuals between the logarithms of the observed and predicted values cannot be rejected as being normally distributed at the 1% significance level. This is an indication that, with regard to the observed data, the model provides better order-of-magnitude agreement than arithmetic agreement.

This conclusion is further underscored after considering the correlation coefficients relating the residuals and the observed data. The arithmetic residuals show a fairly strong positive correlation ($\rho = 0.586$) with the observed data, indicating that large residual values are associated with high dopamine concentrations. As with the results of the tests for normality, this correlation suggests that the model may not perform as well when predicting high concentrations. However, in assessing order-of-magnitude agreement, the residuals between the logarithms of the observed and predicted results show a much lower positive correlation ($\rho = 0.212$) with dopamine concentrations, thereby supporting the conclusion that the model maintains good order-of-magnitude agreement at all dopamine concentrations.

Because it is possible that the biochemical synthesis and metabolism of dopamine in the brain may exhibit stochastic behavior, we perform a stochastic analysis of the model. We introduce a random component into the deterministic model, thereby mimicking natural variability. As already stated, the residuals (R_i) between the logarithms of the observed and predicted concentrations, defined as

$$R_i = \ln(\hat{m}_i) - \ln(m_i),$$

exhibit some normality. We fit a normal distribution to the residuals, of the form

$$R_i' \sim N(\mu, \sigma^2),$$

where R_i' is a normally distributed random variable, and μ and σ are the mean and standard deviation for the given distribution. We simulate this distribution using a random number generator. Reintroducing the normally distributed residual value R' into (3) produces a stochastically influenced predicted value ($\tilde{m}$), with

$$\tilde{m}_i = m_i + \exp R_i'.$$

In this way, we compute a stochastically influenced version of the dependent variable, based on the randomly generated residual terms applied to the deterministic model.

After we incorporate this random component, the model shows very close agreement for a large percentage of observations but also exhibits extreme outliers; the stochastic input appears to introduce a great deal of instability. In addition, the overall statistical characteristics (mean, standard deviation, etc.) demonstrate a decrease in model performance. As a result, introducing a stochastic component into the model does not improve its predictive capability.

Sensitivity Analysis

We conduct a rudimentary sensitivity analysis, evaluating changes in the residual sum of squares for perturbations in the parameter terms, to provide a rough idea of the sensitivity of the model to variations in individual parameter values while also providing an indication of the relative sensitivies to the various parameters. Each parameter was varied independently by 10%. The results appear in Table 6.

Table 6.
Model sensitivity to perturbations of 10% in the parameters.

Parameter	Change in sum of squared residuals (%)
E_x or E_z	5.27
E_y	5.77
k	5.67

The model demonstrates a similar sensitivity to all of the parameter values. Furthermore, in each case the percentage change in the residual sum of squares is about half the percentage change in the parameter. The model therefore appears to show a fair degree of stability with regard to parameter changes.

Conclusions and Recommendations

The calibrated model gives good order-of-magnitude agreement with the data values. It is fast, efficient, easy to use, and very stable. The ability of the model to predict values of cerebral dopamine over time as well as space gives it an extra measure of utility.

Of course, these qualities are somewhat offset by the drawbacks of the model:

- The statistical analysis demonstrates that the model fails to give especially good arithmetic agreement with the data.

- The analytical solution proceeds from the assumptions that the brain is treated as a homogeneous (though not isotropic) medium, the rate of dopamine metabolism is constant over space and time, and there exist no unusual transport conditions on the boundaries of the brain. To assume otherwise would necessitate the use of numerical techniques.

- The assumption of parameter homogeneity also disregards any possible dependence of dopamine behavior on physiological and biochemical factors such as temperature, pH, or the presence of potentially synergistic species.

- The model assumes that no advective transport takes place, though an advective component could easily be added to the model. However, the use of an analytic solution requires that this term also be constant over time and space. Given this fact, and the fact that the data set describes dopamine concentrations at only a single point in time, an advection term would not add any utility to the existing model.

- Finally, the assumption of negligible background dopamine levels may not be appropriate.

Model performance might be improved as a result of increased data collection (perhaps considering temporal as well as spatial variation), better information on the specific conditions of the experiment, possible evaluation of the model for a variety of laboratory animals, and greater consideration of the neurochemical and physiological aspects of dopamine behavior in the brain.

References

Bennett, C.O., and J.E. Myers. 1982. *Momentum, Heat and Mass Transfer.* New York: McGraw-Hill.

Bird, R.B., W.E. Stewart, and E.N. Lightfoot. 1960. *Transport Phenomena.* New York: Wiley.

Blinkov, S.M., and I.I. Glezer. 1968. *The Human in Figures and Tables.* New York: Basic Books.

Bradley, P.B., ed. 1975. *Methods in Brain Research.* New York: Wiley.

Carslaw, H.S., and J.C. Jaeger. 1959. *Conduction of Heat in Solids..* London: Oxford University Press.

Harleman, D.R.F. 1973. *Transport Processes in Water Quality Control.* Cambridge, MA: MIT Press.

Hines, W.W., and D.C. Montgomery. 1980. *Probability and Statistics in Engineering and Management Science.* New York: Wiley.

Lehninger, A.L. 1982. *Principles of Biochemistry*. New York: Worth.

Metzler, D.E. 1977. *Biochemistry*. New York: Academic Press.

Nolte, J. 1981. *The Human Brain*. St. Louis, MO: C.V. Mosby.

Walker, R.J. 1986. Biosynthesis, storage and release of dopamine. In *The Neurobiology of Dopamine Systems*. Manchester, UK: Manchester University Press.