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STUDENT VERSION
LSD AND PROBLEM SOLVING

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Abstract: We describe the use of a two compartment model of a linear system of first order linear differential equations to model lysergic acid diethylamide (LSD) in the body. We provide the data from the literature. We offer students the opportunity to build a two compartment model to fully analyze the administration and absorption of LSD in 8 student volunteers. We also compare the model predictions with problem-solving performance on simple arithmetic activities given to subjects over the time of distribution and absorption of the LSD.

STATEMENT

In the 1960's there was quite a bit of interest in the drug lysergic acid diethylamide (LSD), *much* interest, from Timothy Leary [3], to government intelligence organizations [5], to scientists [6], to individuals, to reporters writing about the 60's scene. They say that if you can remember the 60's then you did not live the 60's, for if you could remember then you were not stoned enough on drugs and were pretty square. Well, I was square and did not even inhale [2], but I did not have an interest in academic papers in applied mathematics or LSD research back in the 60's for I was doing my graduate work in Noetherian rings and that kept me "clean." So I missed the papers described below and did not first come upon them until browsing in the late 70's.

One of the issues surrounding the use of LSD was what it did to mind performance—enhance, detract, alter? Thus, there were a number of studies conducted to measure the effects of LSD on mental processes. One study [6] attempted to see if there was a correlation between a subject's ability to perform simple arithmetic tasks and the concentration of LSD in the tissues of the body. In an earlier study [1] five normal male volunteer subjects, ages 21 to 25, were administered 2 mcg (ng) of LSD per kilogram of body mass doses of d-lysergic acid diethylamide (LSD-25) intravenously over a 1.5 minute period. Blood samples were then drawn at 5, 15, 30, 60, 120, 240, and 480 minutes

	Time (hr)	0.0833	0.25	0.5	1.0	2.0	4.0	8.0
Subject 1	Plasma Conc (ng/ml)	11.1	7.4	6.3	6.9	5.	3.1	0.8
	Perform Score (%)	73	60	35	50	48	73	97
Subject 2	Plasma Conc (ng/ml)	10.6	7.6	7.	4.8	2.8	2.5	2.
	Perform Score (%)	72	55	74	81	79	89	106
Subject 3	Plasma Conc (ng/ml)	8.7	6.7	5.9	4.3	4.4	—-	0.3
	Perform Score (%)	60	23	6	0	27	69	81
Subject 4	Plasma Conc (ng/ml)	10.9	8.2	7.9	6.6	5.3	3.8	1.2
	Perform Score (%)	60	20	3	5	3	20	62
Subject 5	Plasma Conc (ng/ml)	6.4	6.3	5.1	4.3	3.4	1.9	0.7
	Perform Score (%)	78	65	27	30	35	43	51

Table 1. Summary of data collected [1, 4] on 5 male volunteers who were administered LSD and then tested on performance (Perform Score (%)) on simple addition questions. Both performance Score and Plasma Concentrations of LSD were recorded at 5, 15, 30, 60, 120, 240, and 480 minutes after the initial infusion of LSD.

and these were tested for concentration levels of LSD. "To obtain a crude index of performance, subjects were given one of a series of equivalent tests, consisting of simple addition problems, after each blood sample was drawn."[1, p. 612] This information is given in Table 1.

Model Building Using Compartment Models

The papers [6, 4] use a simple compartment model in which there are two compartments, Plasma (inner) compartment and Tissue (outer) compartment. See Figure 1. Neither paper gives the form of the model using differential equations. Rather, [6] gives the closed form analytic solution for concentrations of LSD in the two compartment that one can obtain from the linear system of first order differential equations for $C_P(t)$ (ng/ml), the concentration of LSD in the plasma compartment, and $C_T(t)$ (ng/ml), the concentration of LSD in the tissue compartment. The paper [4] refers to these results.

In Figure 1 we offer a model for LSD flow between plasma and tissue compartments in the human body. Defend this model, paying careful attention to assumptions and units.

This figuring out of units and initial concentration is sometimes a difficult bookkeeping activity, but it is essential if we are to proceed and be good applied mathematicians. The conversion expression (1) will help. We also point out that the "density of human plasma (and human tissue) is about 1 kilogram per liter." Thus we use, where appropriate, either mass in kilograms or volume in liters, equivalently, as our measure.

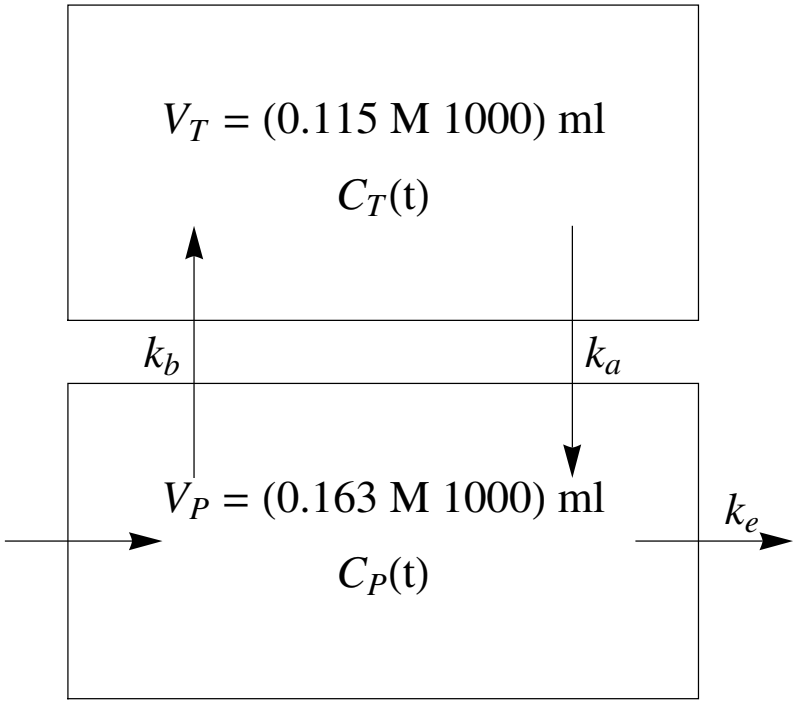

Figure 1. Two compartment model for LSD flow between plasma and tissue compartments in the human body where the volume (in milliliters) of the plasma (V_P) is 16.3% of the volume or mass (M) of the body and the volume of the tissue (V_T) portion of the body is 11.5% of the volume or mass of the body.

$$V_P = \underbrace{(0.163M)}_{\text{kg of plasma}} \cdot \underbrace{(1)}_{\text{liter/kg}} \cdot \underbrace{(1000)}_{\text{ml/liter}} \cdot = \underbrace{(163M)}_{\text{ml of plasma}} \tag{1}$$

Using the notion of "simple change in something," in this case amount of LSD in each compartment we can produce the system of differential equations in (2). We discourage them from building rate of change models of just concentration as they can be difficult with units. The last term in the equation for $C_T'(t)$ in (2) reflects the exponential decay of the LSD in the tissue compartment due to excretion.

$$\begin{aligned} V_P C_P'(t) &= k_a V_T C_T(t) - k_b V_P C_P(t) - k_e V_P C_P(t) \\ V_T C_T'(t) &= k_b V_P C_P(t) - k_a V_T C_T(t)\,. \end{aligned} \tag{2}$$

We note that $C_P(0) = 12.2699$, for originally LSD was injected at a concentration of 2,000 ng per kg of body mass for each subject and so we have an initial concentration in the plasma of $12.2699 = \frac{2000M}{.163M1000}$ ng of LSD/kg of body mass. Since no LSD is in the tissues at the start (we

presume!), $C_T(0) = 0$. Also we have $V_P = (0.163M \cdot 1000)$ ml and $V_T = (0.115M \cdot 1000)$ ml in milliliters, where M is the subjects' body mass in kilograms. For the mass devoted to the plasma in a normal body is about 16.3% while the mass devoted to the tissues is about 11.5%.

We need to estimate the rate term parameters k_a, k_b, and k_e, each with units $1/hr$ if we are to fully understand this process. In the literature [6] the average set of concentrations for all 5 subjects at each time, respectively, is used to fit the solutions using the least square criterion in which we square the difference between the analytic solution for $C_P(t_i)$ and the actual average concentration of LSD (ng/kg) in the plasma for $t = 0.833, .25, .5, 1.0, 2.0, 4.0, 8.0$ hrs. Of course we could take individual subjects and estimate their respective parameters k_a, k_b, and k_e, and we have done that.

You can now use *Mathematica* or another CAS to get closed form solutions for $C_P(t)$ and $C_T(t)$ from (2). You will obtain sums of exponentials with messy terms involving k_a, k_b, and k_e. If we place the average values (for all 5 subjects) of the concentration of LSD in the plasma at each time $t = 0.8333, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0$ into an array, calling it a, with time as the first coordinate and this concentration of LSD in the plasma at the corresponding time as the second coordinate we have 7 (from observations) time-concentration data pairs and from these we form the sum of square errors (3) between the model $C_P(t)$ values and the observed values for concentration of LSD in the plasma. Call the latter $O_1, i = 1, 2, \ldots, 7$.

$$SSE(k_a, k_b, k_e) = \sum_{i=1}^{7} (C_P(t_i) - O_i)^2 \tag{3}$$

You are now prepared to build your final model with all the parameters and compare the model prediction with the data.

ACTIVITY

Build a mathematical model which will predict successfully the levels of LSD in the bloodstream and correlate these levels with the performance data on the arithmetic problems given to the subjects. Be sure to give crisp assumptions and define all variables, units, and relationships clearly and render a connected analysis. Then summarize your results.

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