Direct Linear Plotting Method for Estimation of Pharmacokinetic Parameters

Keyphrases □ Pharmacokinetics—direct linear plotting method of parameter estimation □ Direct linear plotting method—estimation of pharmacokinetic parameters

To the Editor:

Recently, a method was described (1) for estimating the parameters of a single-compartment linear pharmacokinetic model following intravenous bolus dose administration. This method is based on the following relationship:

$$\ln C = \ln C_0 - Kt \qquad \text{(Eq. 1)}$$

where C_t is the concentration at some time, t, after bolus administration of a drug that results in an initial concentration of C_0 and K is the first-order elimination rate constant. This equation may be rearranged to yield:

$$\ln C_0 = \ln C + Kt \qquad \text{(Eq. 2)}$$

For each C, t data point, a straight line could be generated. The equation is of the general form:

$$Y = b + XM \qquad \text{(Eq. 3)}$$

where Y is $\ln C_0$, b is $\ln C$, X is K, and M is t. By using a pair of data values (C_1, t_1 and C_2, t_2), two such lines can be generated. The X-axis coordinate of the point of intersection of these lines provides an estimate for the K parameter (K_i), and the Y-axis coordinate of this point of intersection provides an estimate of $\ln C_0$ ($\ln C_{0i}$). Thus, K_i can be calculated according to:

$$K_i = \frac{\ln C_2 - \ln C_1}{t_1 - t_2} \qquad \text{(Eq. 4)}$$

and C_{0i} is calculated by substituting K_i into Eq. 2 and using values for either data point (C_1, t_1 or C_2, t_2), *e.g.*:

$$\ln C_{0i} = t_1 K_i + \ln C_1 \qquad \text{(Eq. 5)}$$

When more than two sets of data are available, the K_i and $\ln C_{0i}$ values must be calculated for all possible combinations of data pairs. The median of all calculated K_i values provides the best estimate of K, and the median of all calculated $\ln C_{0i}$ values provides the best estimate of $\ln C_0$. The selection of median values minimizes the effect of outliers on the parameter estimate; *i.e.*, an estimate that differed greatly from the true parameter would markedly affect the mean of all estimates but would have no greater effect on the median than would an estimate that was only slightly different than the true parameter value. This series of calculations and comparisons is readily performed by the microcomputer.

It is not the purpose of this communication to justify the use of the direct linear plotting (DLP) method of parameter estimation. Previous findings (1) indicate that this method is superior to standard nonlinear regression (with and without weighting correction) when the assumption of equal variance for all experimental data points is violated; *i.e.*, when outliers are present. However, in the absence of outliers, simple unweighted nonlinear regression performs best. Non-normal distribution of error might be expected when analytical results are periodically affected by a large magnitude. For example, a micropipet that periodically dispenses only 30–50% of the labeled volume would result in a non-normal distribution of errors. In this situation, parameter estimation using the DLP method would be favored.

Table I—Pharmacokinetic Parameter Estimates

Parameter	Actual Value	Regression Estimate	Regression Percent Error	DLP Estimate	DLP Percent Error
A	50	81.4	62.8	56.9	13.8
α	0.8	1.05	31.2	0.85	6.2
B	10	10.12	1.2	8.9	−11.0
β	0.08	0.078	−2.5	0.073	−8.7

This communication describes a program written for the microcomputer[1], using BASIC language, which facilitates the application of the DLP method of parameter estimation. In addition, the program allows for sequential parameter estimates (stripping). This program allows extension of the DLP method to polyexponential equations. As output, the program provides standard exponential (unweighted) regression values for C_0 and the rate constant K, the correlation coefficient, and estimated values for all observed concentration data. The program then provides K_i and C_{0i} values for all intersections already described and provides the numbers of intersection values that are

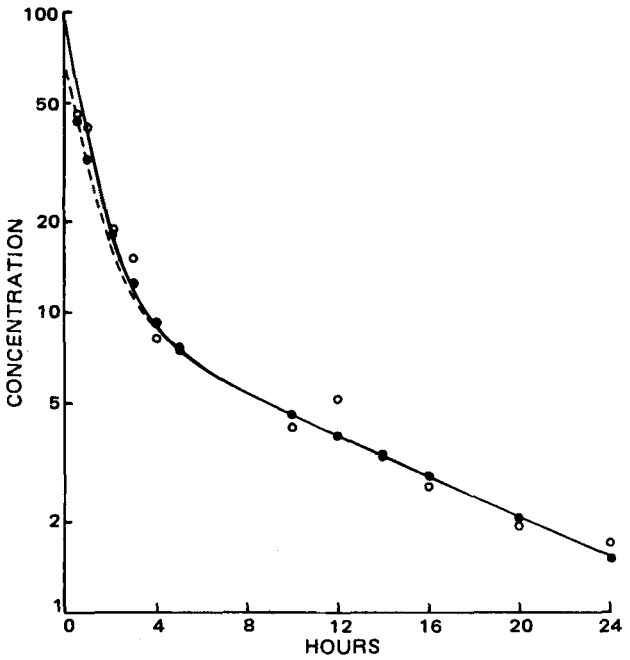

Figure 1—*Simulated concentration* versus *time data without error (●) and including error (○). The solid line is the best fit line obtained by stepwise unweighted nonlinear regression analysis. The broken line is the best fit line obtained by stepwise application of the DLP method.*

[1] APPLE II plus, DOS 3.2.1.

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less than and greater than the given value. Thus, the median parameters are selected by the user. Once selected, these intersection values are used to calculate predicted concentration values for each observed value.

The performance of the DLP program is shown in the following example. Concentrations expected at time 0.5, 1, 1.5, 2.0, 3, 4, 5, 10, 12, 14, 16, 20, and 24 hr were simulated for the biexponential equation:

$$C_t = 50e^{-0.8t} + 10e^{-0.08t} \quad \text{(Eq. 6)}$$

Error with a coefficient of variation of either 5 or 20% was randomly assigned to the simulated concentrations such that four of the 12 observations were affected by the larger error. The results are shown in Fig. 1. The program was used to strip the curve. Concentrations observed between 10 and 24 hr were used for the β-phase, and those between 0.5 and 5 hr were used for the α-phase. The results of parameter estimation using sequential regression (stripping) and the DLP method are shown in Table I. In this example, DLP produced better estimates of A and α (13.8 and 6.2% error) than did sequential regression analysis (62.8 and 31.2% error). Estimates of B and β were somewhat better using regression (1.2 and −2.5% error) than with the DLP method (13.8 and 6.2% error). The large errors made by regression analysis in estimating A and α indicate that DLP estimates for the entire curve were superior.

The determination of the importance of the DLP method of parameter estimation in pharmacokinetics will require further experimentation. It is hoped that the described program will facilitate this process.

(1) L. Endrenyi and H.-Y. Tang, *Comp. Biomed. Res.*, **13**, 430 (1980).

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BOOKS

REVIEWS

Introduction to Pharmaceutical Dosage Forms. By HOWARD C. ANSEL. Lea & Febiger, Washington Square, Philadelphia, PA 19106. 1981. 408 pp. 18.5 × 26 cm.

The format and presentation of this third edition are the same as in the previous one, but the material has been revised to the current official compendia. The book is intended "to introduce the beginning pharmacy students to medicinal and pharmaceutic substances, the methods of their incorporation into pharmaceutical dosage forms, and the utilization of these forms in patient care."

The discussions on heritage, terminology, code of ethics, regulations, and drug substances should satisfactorily orient beginning students in their first professional course in pharmacy. The appendix defines drug categories and discusses measurements, and tables of official preparations are given. Pharmaceutical products are logically treated from the viewpoint of administration route, and the classes of pharmaceutical preparations also are discussed. Numerous photographs illustrate equipment, processing, and packaging.

However, the presentation of dosage form design in terms of biopharmacy, formulation, and practice is inadequate. Whether the curriculum of a college is arranged to present a preparations–physical pharmacy sequence or a technology series of courses, the scope of this text restricts its use to an orientation course because of its superficial presentation of theory and pharmacy principles and limited discussion of techniques and manufacturing principles.

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Pharmaceutical Calculations, 2nd Ed. By JOEL L. ZATZ. John Wiley & Sons, 605 Third Ave., New York, NY 10016. 1981. 388 pp. 13.3 × 25 cm. Price $17.50.

Pharmaceutical calculations continues to be one of the most frustrating subjects to teach in any pharmacy curriculum. The complete accuracy required in answering many problems, the mixing of different metrology systems, the frequent use of conversions, and the simultaneous introduction of pharmaceutical terminology confound many students. This ongoing dilemma has resulted in pharmaceutical calculations being taught and evaluated in a variety of ways at different schools of pharmacy. No single textbook can solve the distress frequently associated with calculations, but Joel Zatz's second edition goes a long way to making it all more bearable.

The book is longer than the first edition by 77 pages because it now has an appendix containing instruction and problems on temperature conversion, alcohol proof strength, and sodium chloride equivalents in addition to the inclusion of alligation and a greatly expanded section on milliequivalents.

The cover of the book describes the structure of the text succinctly: "The progression of topics within each chapter and in the overall structure of the book constitutes a programmed format that permits self-paced learning and builds upon previously learned concepts to reinforce understanding. Students participate actively and are able to concentrate on calculations that are most difficult for them. Emphasis is on practical approaches to meeting accuracy requirements in filling prescriptions and manufacturing."

This book is designed to fit into the usual first general pharmacy course, to serve as a text in a calculations course or as a self-instruction text apart from the formal classroom, or to be an aid for review, and it does all of these well.

It is difficult to find much about the text to criticize. About all one can say is that it does not contain a section on commercial arithmetic which some instructors prefer to include in their course, and there are a few prescription problems for oral preparations containing amaranth (Red No. 2) which was banned in time to have been deleted from the new edition.

In conclusion, while working examples from the text, the reviewer finds it refreshing to solve for "j" (for Joel?) rather than to always hunt for the usual unknown "x."

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