ELSEVIER

An Interactive Computer Program for Determining Areas Bounded by Drug Concentration Curves Using Lagrange Interpolation

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The LAGRAN method of Rocci and Jusko for determining the area of plasma concentration curves has been implemented in a user-friendly form. Drug concentration versus time data may be entered using the keyboard or imported in the form of simple text files from spreadsheets or other software. The MSDOS program allows prompt graphic observation of the data. The effect of selecting different fitting modes for each segment of the curve may be viewed interactively using this graphic display. Pharmacokinetic parameters that are provided by the program include mean residence time, variance of the residence time, plasma clearance, and steady-state volume of distribution.

Key Words: AUC; Computer program; Lagrange; Parameter estimation; Pharmacokinetics

Introduction

Useful pharmacokinetic parameters can be obtained by determining the area (AUC) under drug plasma concentration versus time curves. Rocci and Jusko (1983) described a technique using lagrange polynomials to interpolate concentration levels during the intervals between measurements. The advantage of such polynomials is that the fitted curves pass exactly through the measured data points. Storey and Davies (1986) implemented a program using a combination of spline fitting and Simpson's rule to calculate AUC. The advantage of their method is that it results in a simple program, but there is no graphic display to readily confirm the quality of the fit. Borsi et al. (1988) introduced the PharmCalc program to automate the calculation of AUC for methotrexate infusions using the trapezoidal method. PharmCalc produces a graphic printout of the data. Wijnand (1992) has described the SIMF&KA and ESTF&KA programs employing the regression method of truncated areas for linear pharmacokinetics. Results are provided in printed form. Another approach has been to use programs such as NONLIN (Weiner, 1986) to determine the value of parameters that give the best fit of the data to some proposed model. These parameters can then in some instances be used to determine AUC. For extravascular drug input or constant infusions, NONLIN (V4.2) uses the linear trapezoidal method for determining AUC.

The current program provides an interactive implementation of Rocci and Jusko's lagrangian method, which with linear and logarithmic trapezoidal options allows broad flexibility. The lagrangian fitting mode is most suitable for rapidly changing areas of considerable curvature. The linear or logarithmic trapezoidal modes describe the gradually diminishing regions effectively and avoid the possibility of oscillatory lagrangian solutions (Yeh and Kwan, 1978). Ready access to a graphic display of the data allows prompt user feedback during the fitting procedure.

The program has been written (in Turbo C, Borland International) so that it is compatible with the broadest range of MSDOS computers as possible. The program will run on 8088 (or better) machines and requires no co-processor. The program generates monochrome graphics and is compatible with display adapters ranging from CGA to SVGA.

Methods

Each interval between data points is fitted separately. A cubic lagrangian is generated from a total of four data points, the two boundary points of the interval in question and their immediate neighbors. The first and

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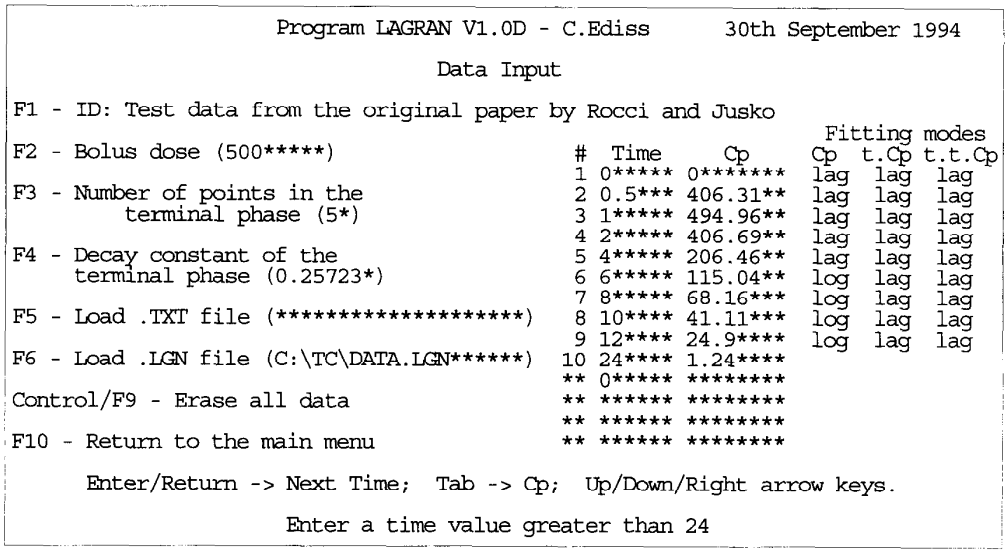

Figure 1. The Data Input screen.

last intervals are characterized by a quadratic lagrangian obtained from three data points, the two boundary points and the only available neighbor.

Data are seldom collected over periods long enough to ensure that the drug has been completely eliminated from the system. Thus, in order to obtain the complete area under the curve, it is necessary to have some means of estimating the area for the remaining time from the last data collection point to infinity. It is assumed that the drug concentration decays exponentially during this period. The existence of such a monoexponential phase is one of the properties most often used in non-compartmental methods (Gillespie, 1991). The decay constant can be entered manually or determined by the method of weighted least squares applied to a selected number of final data points. Detailed algorithms are described by Rocci and Jusko (1983).

The area bounded by three functions are obtained by the program: the area of drug concentration versus time (AUC), the product of time and concentration versus time (AUTC), and the product of (time)^2 and concentration versus time (AUT2C).

The pharmacokinetic parameters (assuming a bolus intravenous dose) that can be determined from these areas include:

Mean residence time, MRT = AUTC/AUC

Variance of the residence time, VRT = (AUT2C/AUC) − (AUTC/AUC)^2

Plasma clearance, Cl_p = Dose/AUC

Steady state volume of distribution, V_D^{ss} = (Dose × AUTC)/(AUC^2)

The user interacts with the program by making function key selections from a hierarchal system of menus. From the main menu, the Data Input area (F3) is used to provide the program with experimental values. Then the Display Graphics area (F5) may be viewed to see how well the data has been fitted. The user may alternate between the Data Input screen and the Display Graphics screen to tailor the fitting modes and other input parameters to improve the fit. This interactive capability expedites prompt convergence toward optimal conditions. A report of the results may be displayed (F6) or printed (F7). Input data and parameters may be saved (F4) for subsequent re-examination.

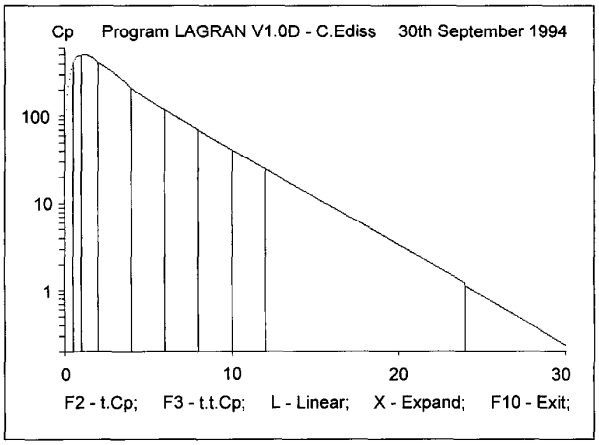

Figure 2. The Graphics Display screen.

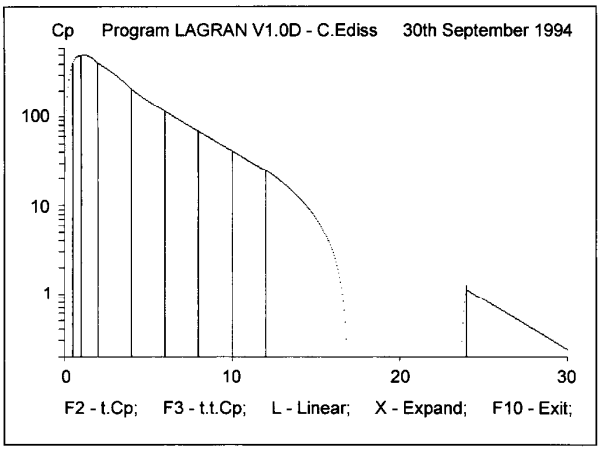

Figure 3. An example of ill-fitting data displayed on the Graphics Display screen.

The main focus of the Data Input screen (Figure 1) is a scrolling template into which time (t) and concentration (C_p) values may be entered. By default each interval is flagged to be fitted by the lagrangian method (*lag*). Occasionally the graphic display demonstrates that the lagrangian solution for a particular interval can result in widely oscillatory interpolations. The visual impact of the graphic display provides a useful tool for identifying these troublesome areas and in these instances trapezoidal (*lin*) or exponential (*log*) fitting modes may be selected. Separate modes (*lag*, *lin*, or *log*) may be assigned for each segment of each function C_p, $t \cdot C_p$, or $t^2 \cdot C_p$.

Results and Discussion

The data set employed in Rocci and Jusko's original description of the method is shown in Figure 1. Note that the last four intervals have been flagged for exponential fitting. The corresponding Graphics Display screen is shown in Figure 2. The effect of fitting the last four intervals by the lagrangian method is shown in Figure 3. The graphic display readily exposes troublesome areas and results in swifter correction than would be obtained from results viewed in tabular form. A typical printout of the results produced by the program is shown in Figure 4.

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Lagran Report for the file 'C:\DATA.LGN'          30th September 1994

ID : Test data from the original paper by Rocci and Jusko

Number of data points = 10    Bolus Dose = 500

Number of data points in the terminal phase = 5
Decay constant of the terminal phase = 0.25723    Half life = 2.69465
Cp value at the beginning of the terminal phase = 1.12015

 Time       Cp        Area(Cp)        Area(t.Cp)       Area(t.t.Cp)
    0        0
                    114.81 (lag)      47.09 (lag)      13.24 (lag)
  0.5   406.31
                    234.97 (lag)     173.60 (lag)     139.74 (lag)
    1   494.96
                    472.09 (lag)     680.17 (lag)    1038.13 (lag)
    2   406.69
                    609.05 (lag)    1732.34 (lag)    5064.29 (lag)
    4   206.46
                    308.72 (lag)    1529.20 (lag)    7566.12 (lag)
    6   115.04
                    179.13 (log)    1235.40 (lag)    8594.46 (lag)
    8    68.16
                    107.00 (log)     953.66 (lag)    8535.42 (lag)
   10    41.11
                     64.66 (log)     706.33 (lag)    7733.31 (lag)
   12    24.90
                     94.65 (log)    1277.49 (lag)   25317.26 (lag
   24     1.24


Partial AUC   =   2185.09,  Total AUC   = 2189.44
Partial AUTC  =   8335.29,  Total AUTC  = 8456.73
Partial AUT2C =  64001.96,  Total AUT2C = 67454.47

Plasma Clearance = 0.228368
Steady State Volume of Distribution = 0.882073
Mean Residence Time = 3.862500
Variance of the Residence Time = 15.890034
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Figure 4. A typical printed report produced by the program.

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By using the method of weighted least squares to characterize the terminal phase, the resulting exponential does not in general pass through the last data point. Thus, although this method does give a good estimate of the exponential decay constant, it introduces a discontinuity in the curve (Figure 2). The program may force the trailing exponential to pass through this last data point in the following way: First, a reasonable number of the final data points are selected to characterize the exponential tail (5 in the example shown), and the program determines the corresponding decay constant. Then the Data Entry area may be revisited, and the number of data points in the terminal phase changed to zero. The previous decay constant is retained, but the exponential decay is now anchored to the last data point. Thus the usual displacement at the beginning of the trailing exponential may be avoided.

The program has been used for its original purpose in the evaluation of the pharmacokinetics of Hydralazine (Semple et al., 1990) and Methyldopa (Skerjanec et al., 1995). It has also proved useful in the field of radiation dosimetry. The integration of activity versus time data is used to produce cumulated activity and, ultimately, radiation dose (McQuarrie et al., 1994).

The modular nature of the program readily permits the inclusion of improvements. For instance a fourth fitting mode in addition to *lag*, *lin*, or *log* could readily be accommodated without requiring an extensive redesign of the data input area. Also the statistical selection of the number of data points in the terminal phase implemented by Kowalski (1994) could be included as an option. Other suggested improvements include the calculation of AUC within user-selected arbitrary time boundaries and the accommodation of infusions and multiple dosing.

Availability

The program may be obtained directly by mail from the authors upon receipt of a formatted disk of the desired format. Alternatively the authors will attempt to respond to e-mail requests (directed to cediss@pharmacy.ualberta.ca), provided the desired electronic delivery mode is clearly specified.

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