

NCOMP—A Windows-Based Computer Program for Noncompartmental Analysis of Pharmacokinetic Data

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Abstract □ The computer program NCOMP performs noncompartmental analysis of pharmacokinetic data obtained from iv bolus, continuous infusion, and oral modes of administration. Integration of area-under-the-curve and area-under-the-first-moment-curve is done by either Lagrange polynomials or the hybrid method of Purves, which uses parabola-through-the-origin and log trapezoidal algorithms. Written for Microsoft Windows, NCOMP is designed to be used in conjunction with a spreadsheet program for graphical display and handling of data. NCOMP interactively aids the user in determining how best to extrapolate the areas to time infinity and in estimating the time zero concentration for iv bolus data.

Noncompartmental analysis (NCA) provides a means of obtaining the primary pharmacokinetic parameters of a drug without the nonlinear regression inherent to compartmental analyses.¹ Since its introduction in the late 1970s, NCA appears to have supplanted compartmental analyses, at least in initial characterization of drug pharmacokinetics. Several of the most popular computer programs² performing NCA provide only linear and log trapezoidal methods of computing areas despite the demonstrated superiority of other methods.^{3,4} Described in this report is NCOMP, a computer program implementing two such methods in the Microsoft Windows environment. Numerical integration can be done by either Lagrange polynomials or the hybrid parabola-through-the-origin and log trapezoidal method introduced by Purves (methods 9 and 9A).⁴ Integration by Lagrange polynomials is based on the program LAGRAN by Rocci and Jusko.⁵ Developed in 1983 for time-sharing mainframe computers, LAGRAN is considerably extended through the cut-and-paste exchange of data with other programs and data visualization using a Windows spreadsheet program.

Computational Methods

Area under the curve (AUC) and area under the moment curve (AUMC) are integrated by NCOMP from time zero to infinity with total clearance (CL), mean residence time (MRT), and volume of distribution at steady state (Vd_{ss}) computed as follows:

$$CL = \frac{\text{dose}}{\text{AUC}} \quad (1)$$

$$\text{MRT} = \frac{\text{AUMC}}{\text{AUC}} \quad (2)$$

$$Vd_{ss} = \frac{\text{dose} \cdot \text{AUMC}}{(\text{AUC})^2} \quad (3)$$

For administration by zero-order infusion, MRT and Vd_{ss} are

computed with correction for the duration of the infusion (T)⁶:

$$\text{MRT} = \frac{\text{AUMC}}{\text{AUC}} - \frac{T}{2} \quad (4)$$

$$Vd_{ss} = \frac{\text{dose} \cdot \text{AUMC}}{(\text{AUC})^2} - \frac{\text{dose} \cdot T}{2\text{AUC}} \quad (5)$$

Determination of AUC and AUMC requires accurate estimation of the partial areas bounded by data points and careful extrapolation of area from the time of the last data point to infinity. For the first requirement, the area between adjacent time points $t(i)$ and $t(i+1)$ is computed by choosing either Lagrange polynomials or the hybrid method of Purves. In the former, cubic Lagrange polynomial segments are constructed for data points at times $t(i-1)$, $t(i)$, $t(i+1)$, and $t(i+2)$, with evaluation of the integral of the polynomial between $t(i)$ and $t(i+1)$. The higher degree of the cubic Lagrange polynomial makes it generally better than linear or log trapezoidal interpolation in matching the concavity of the curve formed by the data points.³ However, unrealistic oscillations in cubic polynomials occasionally result from erratic or irregularly spaced data points. Consequently, graphical examination and, where necessary, correction of the interpolation are required and are central features of NCOMP. Coefficients of the Lagrange polynomial are computed by subroutine POLCOE in *Numerical Recipes in FORTRAN*,⁷ a more compact and efficient alternative to the standard method of solving systems of linear equations used by LAGRAN.

During concentration buildup at early times in absorption or infusion data, the method of Purves⁴ fits and integrates the polynomial $ct^2 + dt$, the "parabola-through-the-origin" (PTTO), for each successive pair of data points. The PTTO polynomial is able to replicate the negative curvature of this region of the concentration-time plot, unlike either the linear or log trapezoidal methods. Where concentrations are declining from the maximum value, log trapezoidal integration—now appropriate to the positive curvature—replaces use of the PTTO method. Because it does not require graphical inspection of the data points and the functions used to interpolate between them, the method of Purves is simpler and faster in the analysis of data than the use of Lagrange polynomials. However, when the data points are noisy or ill-placed, integration by the Lagrange method with inspection and correction may be preferable.

Extrapolated portions of the AUC and AUMC are formally computed using the time (t^*) and concentration (C^*) of the last measured data point as follows:¹

$$\text{terminal AUC} = \int_{t^*}^{\infty} C dt = \frac{C^*}{\lambda_n} \quad (6)$$

$$\text{terminal AUMC} = \int_{t^*}^{\infty} tC dt = \frac{t^*C^*}{\lambda_n} + \frac{C^*}{\lambda_n^2} \quad (7)$$

The terminal disposition rate constant (λ_n) is estimated by NCOMP from the least squares slope of the logarithm of

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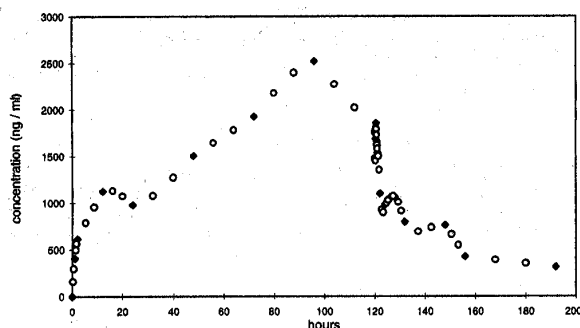


Figure 1—Concentration–time profile of an experimental thymidylate synthase inhibitor administered to humans in a five day infusion. Open circles are points generated by the interpolating polynomial, and solid diamonds are observed concentrations.

concentration plotted against time. Using the plotting capability of Excel, NCOMP also aids determination of the number of terminal data points defining the slope. Because error in the measurement of a single point—that at time t^* —will substantially affect the areas computed in eqs 6 and 7, C^* is instead computed from the linear regression.

Program Demonstration

NCOMP interactively prompts the user for information such as dose, mode of administration, and integration method through a scrollable text window interface. Concentration–time data may be typed in, pasted in from a spreadsheet or other application, or read in from a text file. For intravenous (iv) bolus administration, NCOMP furnishes linear and exponential functions, fit to a user-selected number of initial points, for extrapolating concentration back to time zero. Integration by the Purves method proceeds without user intervention. Integration by the Lagrange method, in contrast, produces for each pair of successive data points a partial area as well as two uniformly spaced interpolating points. Both the data and interpolating points are printed to the text window of NCOMP. With the mouse, the user highlights this numerical output, copies it to the Windows clipboard with a single keystroke, and runs an Excel macro plotting the points to the screen.

Aberrant interpolating points identify partial areas where the Lagrange polynomial is inappropriate. For such areas, the user may choose to reintegrate by either the linear or log trapezoidal methods. The user is prompted for the partial areas to be corrected and the method. Subsequently, partial areas and interpolating points are recalculated. Data and interpolating points are again printed to the text window for visualization with Excel. This process is iterated as necessary and then is repeated for the AUMC curve. A plot generated by this process is illustrated in Figure 1 for observed serum concentrations of an experimental thymidylate synthase inhibitor administered by 5-day continuous infusion.⁸

As an example, 12 data points equally spaced between $t = 0.3$ and 3.6 were simulated with the formula $C(t) = 1000 \exp(-t)(1 + 0.20N(0,1))$, where $N(0,1)$ denotes a normal distribution, with mean zero and variance one, used to add noise to the data. NCOMP estimated $C(0)$ as 1124, computed AUC and AUMC between $t = 0.0$ and 3.6 by Lagrange interpolation, and extrapolated each of the areas to time infinity. No corrections to the Lagrange integration were necessary. The results are shown in Table 1. The AUC and AUMC produced by Lagrange integration are 1076 and 1037, respectively. Repeating this example with the Purves method of integration

Table 1—Part of the NCOMP Report File^a

Interval	Time ^b	AUC		AUMC	
		Area	% Total	Area	% Total
1	.30	293.34	27.26	41.67	4.02
2	.60	206.51	19.19	90.06	8.68
3	.90	147.59	13.71	110.95	10.70
4	1.20	102.14	9.49	104.41	10.07
5	1.50	83.14	7.73	114.72	11.06
6	1.80	70.42	6.54	113.51	10.94
7	2.10	49.31	4.58	97.29	9.38
8	2.40	39.50	3.67	87.63	8.45
9	2.70	25.82	2.40	66.16	6.38
10	3.00	16.98	1.58	47.70	4.60
11	3.30	9.49	.88	30.06	2.90
12	3.60	9.72	.90	33.61	3.24
13	infinity	22.25	2.07	99.52	9.59
totals		1076.22		1037.29	

Parameter	Value
CL	18.58
MRT	.96
Vd_{ss}	17.91
Terminal K	1.15
Terminal $t_{1/2}$.60
CP estimated at longest time	25.51

^a For a dose of 20 000 units, ideal values of AUC, AUMC, CL, MRT, and Vd_{ss} are 1000, 1000, 20, 1, and 20, respectively. ^b Zero time concentration of 1124.25 was obtained by three-point log linearized extrapolation.

Table 2—Diagnostic Output for Number of Data Points (N) Defining Terminal Elimination

N	R^{*2} ^a	Final Conc	Zero Moment		First Moment	
			Area	% Total	Area	% Total
2	1.0000	34.10	-140.16	-15.34	71.54	7.09
3	.1110	33.07	530.39	33.48	10414.94	91.74
4	.6284	28.11	32.10	2.96	152.21	13.96
5	.8035	27.16	27.42	2.54	126.38	11.88
6	.8858	25.51	22.25	2.07	99.52	9.59
7	.9118	26.36	24.38	2.26	110.34	10.53

^a The square of Pearson's correlation coefficient.

produces similar AUC and AUMC values of 1072 and 1033, respectively.

NCOMP assists in determining the number of data points defining the terminal disposition phase by creation of a semilog plot in Excel as well as by diagnostic information like that in Table 2. Noise in the data resulted in a larger concentration for the final data point ($t = 3.6$) than for the penultimate data point ($t = 3.3$). Hence, use of only these two points produces a negative extrapolated area in Table 2. Though selection of seven points yields a line with the highest R^2 correlation value in the semilog plot, upon examination of the semilog plot, the last six points were instead chosen. Thus, while the information in Table 2 is useful, it should not replace plotting the data.

In summary, by providing integration by Lagrange polynomials and by the Purves method as well as graphical display with Excel, NCOMP makes noncompartmental analysis both accurate and convenient. The program is written in portable FORTRAN 77 with the Windows 3.1 interface⁹ provided by linking the QuickWin library supplied with Microsoft FORTRAN 77 version 5.1. Excel, version 5.0 or later, is required to utilize the plotting macros. Other Windows spreadsheets or plotting programs might be used with analogous macros created by the user. The program is available at no cost by contacting the authors (preferably by email at p_laub@fcc.edu).

References and Notes

1. Gibaldi, M.; Perrier, D. *Pharmacokinetics*, 2nd ed.; Marcel Dekker: New York, 1982.
2. For example, the programs Pharm-NCA (Simed) and WinNON-LIN (Scientific Consulting, Inc.).
3. Yeh, K. C.; Kwan, K. C. *J. Pharmacokinet. Biopharm.* **1978**, *6*, 79-98.
4. Purves, R. D. *J. Pharmacokinet. Biopharm.* **1992**, *20*, 211-226.
5. Rocci, M. L., Jr.; Jusko, W. J. *Comp. Progr. Biomed.* **1983**, *16*, 203-216.
6. Perrier, D.; Mayersohn, M. *J. Pharm. Sci.* **1982**, *71*, 372-373.
7. Press, W. H.; Teukolsky, S. A.; Vetterling, W. T.; Flannery, B. P. *Numerical Recipes in FORTRAN*, 2nd ed.; Cambridge University: New York, 1992.
8. O'Dwyer, P. J.; Laub, P. B.; DeMaria, D.; Qian, M.; Reilly, D.; Giantonio, B.; Johnston, A. L.; Wu, E. Y.; Bauman, L.; Clendeninn, N. J.; Gallo, J. M., unpublished results.
9. Adaptation of NCOMP to the Windows 95 operating system is in progress.

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