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# AN EVALUATION OF NUMERICAL INTEGRATION ALGORITHMS FOR THE ESTIMATION OF THE AREA UNDER THE CURVE (AUC) IN PHARMACOKINETIC STUDIES

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## ABSTRACT

Six numerical integration algorithms based on linear and log trapezoidal methods as well as four cubic-spline methods were proposed for estimation of area under the curve (AUC). These six different algorithms were implemented using IMSL/IDL™ command language and evaluated using data simulated under five different dosing conditions and two different sampling conditions. Comparisons between AUC estimations using these six different algorithms and the theoretical results were made in terms of both overall AUC values and the superimposability of the concentration–time profiles. In well designed studies with ample data points, the algorithm based on IMSL/IDL™ function CSSHAPE with concavity preservation gave the best performance. In contrast, when the frequency of blood collection was limited, the algorithm based on the log trapezoidal rule proved to be stable with reasonable accuracy, and is recommended as the practical method for numerical interpolation and integration in pharmacokinetic studies. Algorithms based on the combination of the log trapezoidal rule and cubic-spline methods using IMSL/IDL™ function CSSHAPE can be developed to enhance overall performance.

KEY WORDS Area under the curve Numerical integration Cubic spline Trapezoidal method Log trapezoidal method

## INTRODUCTION

The area under the concentration–time curve (AUC) is one of the most important parameters in pharmacokinetic analysis. A function of dose and clearance, it is often used as a direct indicator of the extent of bioavailability of a drug. The value of AUC may be determined by fitting an analytic function $C(t)$ based on a compartmental model to experimental concentration ($C$) versus time ($t$) data, and integrating $C(t)$ analytically. Alternatively, it may be estimated by direct numerical integration of the data.[1] Although a variety of direct numerical integration algorithms for AUC estimation have been reported,[2–4]

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the linear trapezoidal method remains the most commonly used despite its tendency to produce systematic biases reflecting the concavity and spacing of the data.[5] The popularity of the linear trapezoidal method is due largely to its simplicity, compared with other algorithms based on relatively complicated interpolating methods, the computer software for which has been developed mainly for local use and is not generally accessible.[2,3]

Recent advancements in computer technology have resulted in a number of sophisticated spline interpolation methods that are suitable for pharmacokinetic applications. These programs are commercially available,[6–8] and can be readily used to estimate the AUC values for any given set of concentration–time observations. In the present study, algorithms based on these spline methods as well as the classical trapezoidal methods were proposed and applied to data simulated under various dosing and sampling conditions. Comparisons between estimations using these different algorithms and the theoretical results were made in terms of both overall AUC values and the superimposability of the concentration–time profiles.

## SYSTEM AND METHODS

These algorithms were implemented using the IMSL/IDL™ command language on a VAXstation 4000-60 under the VMS operating system. IMSL/IDL™ is a complete computing environment for the interactive analysis and visualization of scientific and engineering data. The C/Math/Library, designed by IMSL, has been integrated into the structure of the Interactive Data Language (IDL™) by RSI.[7]

In order to evaluate these numerical integration algorithms, simulated data without noise were generated under various dosing and sampling conditions. The superimposability of the concentration–time profiles is judged by the sum of absolute differences between the theoretical and the calculated AUC value at each time interval. Comparisons between these numerical integration methods were made in terms of both the percentage differences between the theoretical and the calculated total AUC values and the superimposability of the concentration–time profiles.

### *Dosing condition 1: intravenous bolus injection*

In a linear time-invariant system, the plasma concentration of drug, $C_\delta(t)$, at time $t$ following a unit single intravenous bolus dose can be approximated by a polyexponential equation:[9]

$$C_\delta(t) = \sum_{k=1}^{m} (c_k \, e^{-\lambda_k t}) \tag{1}$$

and for a single dose of $D_{IV}$

$$C_{IV}(t) = D_{IV} \sum_{k=1}^{m} (c_k e^{-\lambda_k t}) \tag{2}$$

If plasma drug concentration values $C_i$ are measured at times $t_i$ ($i = 1, \ldots, n$), the area under the curve AUC at each time interval is:

$$AUC_{t_i}^{t_{i+1}} = \int_{t_i}^{t_{i+1}} C_{IV}(t)\,dt = D_{IV} \sum_{k=1}^{m} \left[ \frac{c_k}{\lambda_k} (e^{-\lambda_k t_i} - e^{-\lambda_k t_{i+1}}) \right] \tag{3}$$

The total AUC from 0 to $t_n$ is

$$AUC_0^{t_n} = D_{IV} \sum_{k=1}^{m} \left[ \frac{c_k}{\lambda_k} (1 - e^{-\lambda_k t_n}) \right] \tag{4}$$

The following set of parameters was used: $m = 2$, $D_{IV} = 50$ mg, $c_1 = 0{\cdot}1\ L^{-1}$, $c_2 = 0{\cdot}025\ L^{-1}$, $\lambda_1 = 2{\cdot}0\ h^{-1}$, $\lambda_2 = 0{\cdot}2\ h^{-1}$.

*Dosing condition 2: constant-rate intravenous infusion*

If a drug is administered intravenously at a constant rate $k_0$ for a time period $t_0$, the plasma concentration, $C_0(t)$, of unchanged drug at time $t$ can be approximated by the following equation:

$$C_0(t) = k_0 \sum_{k=1}^{m} \left[ \frac{c_k(1 - e^{-\lambda_k t})}{\lambda_k} - \frac{c_k(1 - e^{-\lambda_k (t - t_0)})}{\lambda_k} u(t - t_0) \right] \tag{5}$$

where $u(t)$ is the unit step function:

$$u(t) = 0 \quad \text{for } t < 0 \tag{6}$$

$$u(t) = 1 \quad \text{for } t \geqslant 0 \tag{7}$$

The following equations for AUC were derived:

$$\begin{aligned} AUC_{t_i}^{t_{i+1}} = {} & k_0 \sum_{k=1}^{m} \left[ \frac{c_k}{\lambda_k} (t_{i+1} - t_i) - \frac{c_k}{\lambda_k^2} (e^{-\lambda_k t_i} - e^{-\lambda_k t_{i+1}}) \right] \\ & - k_0 \sum_{k=1}^{m} \left[ \frac{c_k}{\lambda_k} ((t_{i+1} - t_0) u(t_{i+1} - t_0) - (t_i - t_0) u(t_i - t_0)) \right] \\ & + k_0 \sum_{k=1}^{m} \left[ \frac{c_k}{\lambda_k^2} | u(t_{i+1} - t_0) - u(t_i - t_0) | \right] \\ & - k_0 \sum_{k=1}^{m} \left[ \frac{c_k}{\lambda_k^2} (u(t_{i+1} - t_0) e^{-\lambda_k (t_{i+1} - t_0)} - u(t_i - t_0) e^{-\lambda_k (t_i - t_0)}) \right] \end{aligned} \tag{8}$$

$$\mathrm{AUC}_0^{t_n} = k_0 \sum_{k=1}^{m} \left[ \frac{c_k}{\lambda_k} t_n - \frac{c_k}{\lambda_k^2}(1 - e^{-\lambda_k t_n}) \right] - k_0 \sum_{k=1}^{m} \left[ \frac{c_k}{\lambda_k}(t_n - t_0) u(t_n - t_0) \right]$$

$$+ k_0 \sum_{k=1}^{m} \left[ \frac{c_k}{\lambda_k^2} u(t_n - t_0) \right] - k_0 \sum_{k=1}^{m} \left[ \frac{c_k}{\lambda_k^2} u(t_n - t_0) e^{-\lambda_k (t_n - t_0)} \right] \quad (9)$$

The following set of parameters was used: $m = 2$, $k_0 = 50\ \mathrm{mg\ h^{-1}}$, $t_0 = 4{\cdot}0\ \mathrm{h}$, $c_1 = 0{\cdot}1\ \mathrm{L^{-1}}$, $c_2 = 0{\cdot}025\ \mathrm{L^{-1}}$, $\lambda_1 = 2{\cdot}0\ \mathrm{h^{-1}}$, $\lambda_2 = 0{\cdot}2\ \mathrm{h^{-1}}$.

*Dosing condition 3: first-order absorption*

Assuming a first-order drug-absorption rate $k_a$ from a drug dosage formulation of dose $D_A$, the plasma concentration, $C_A(t)$, of drug at time $t$ can be approximated by the following equation:

$$C_A(t) = \sum_{k=1}^{m} \left[ \frac{D_A k_a c_k}{k_a - \lambda_k} (e^{-\lambda_k t} - e^{-k_a t}) \right] \qquad \lambda_k \neq k_a \quad (10)$$

The following equations for AUC were derived:

$$\mathrm{AUC}_{t_i}^{t_{i+1}} = \sum_{k=1}^{m} \left[ \frac{D_A k_a c_k}{k_a - \lambda_k} \left( \frac{e^{-\lambda_k t_i} - e^{-\lambda_k t_{i+1}}}{\lambda_k} - \frac{e^{-k_a t_i} - e^{-k_a t_{i+1}}}{k_a} \right) \right] \quad (11)$$

$$\mathrm{AUC}_0^{t_n} = \sum_{k=1}^{m} \left[ \frac{D_A k_a c_k}{k_a - \lambda_k} \left( \frac{1 - e^{-\lambda_k t_n}}{\lambda_k} - \frac{1 - e^{-k_a t_n}}{k_a} \right) \right] \quad (12)$$

The following set of parameters was used: $m = 2$, $D_A = 100\ \mathrm{mg}$, $k_a = 3{\cdot}0\ \mathrm{h^{-1}}$, $c_1 = 0{\cdot}1\ \mathrm{L^{-1}}$, $c_2 = 0{\cdot}025\ \mathrm{L^{-1}}$, $\lambda_1 = 2{\cdot}0\ \mathrm{h^{-1}}$, $\lambda_2 = 0{\cdot}2\ \mathrm{h^{-1}}$.

*Dosing condition 4: consecutive first-order drug release and first-order absorption*

Assuming a first-order drug-release rate $k_r$ from an oral dosage form of $D_{RA}$, and assuming a first-order drug-absorption rate $k_a$, the plasma concentration, $C_{RA}(t)$, of drug at time $t$ can be approximated by the following equation:

$$C_{RA}(t) = \sum_{k=1}^{m} \frac{-D_{RA} k_r k_a c_k (k_a - \lambda_k) e^{-k_r t} + (\lambda_k - k_r) e^{-k_a t} + (k_r - k_a) e^{-\lambda_k t})}{(k_r - k_a)(k_a - \lambda_k)(\lambda_k - k_r)} \quad (13)$$

where $k_r \neq k_a \neq \lambda_k$.

The following equations for AUC were derived:

$$\mathrm{AUC}_{t_i}^{t_{i+1}} = \sum_{k=1}^{m} \frac{-D_{\mathrm{RA}} k_{\mathrm{a}} c_k (\mathrm{e}^{-k_{\mathrm{r}} t_i} - \mathrm{e}^{-k_{\mathrm{r}} t_{i+1}})}{(k_{\mathrm{r}} - k_{\mathrm{a}})(\lambda_k - k_{\mathrm{r}})} + \sum_{k=1}^{m} \frac{-D_{\mathrm{RA}} k_{\mathrm{r}} c_k (\mathrm{e}^{-k_{\mathrm{a}} t_i} - \mathrm{e}^{-k_{\mathrm{a}} t_{i+1}})}{(k_{\mathrm{r}} - k_{\mathrm{a}})(k_{\mathrm{a}} - \lambda_k)}$$

$$+ \sum_{k=1}^{m} \frac{-D_{\mathrm{RA}} k_{\mathrm{r}} k_{\mathrm{a}} c_k (\mathrm{e}^{-\lambda_k t_i} - \mathrm{e}^{-\lambda_k t_{i+1}})}{\lambda_k (k_{\mathrm{a}} - \lambda_k)(\lambda_k - k_{\mathrm{r}})} \tag{14}$$

$$\mathrm{AUC}_{0}^{t_n} = \sum_{k=1}^{m} \frac{-D_{\mathrm{RA}} k_{\mathrm{a}} c_k (1 - \mathrm{e}^{-k_{\mathrm{r}} t_n})}{(k_{\mathrm{r}} - k_{\mathrm{a}})(\lambda_k - k_{\mathrm{r}})} + \sum_{k=1}^{m} \frac{-D_{\mathrm{RA}} k_{\mathrm{r}} c_k (1 - \mathrm{e}^{-k_{\mathrm{a}} t_n})}{(k_{\mathrm{r}} - k_{\mathrm{a}})(k_{\mathrm{a}} - \lambda_k)}$$

$$+ \sum_{k=1}^{m} \frac{-D_{\mathrm{RA}} k_{\mathrm{r}} k_{\mathrm{a}} c_k (1 - \mathrm{e}^{-\lambda_k t_n})}{\lambda_k (k_{\mathrm{a}} - \lambda_k)(\lambda_k - k_{\mathrm{r}})} \tag{15}$$

The following set of parameters was used: $m = 2$, $D_{\mathrm{RA}} = 200$ mg, $k_{\mathrm{r}} = 1{\cdot}0\ \mathrm{h}^{-1}$, $k_{\mathrm{a}} = 3{\cdot}0\ \mathrm{h}^{-1}$, $c_1 = 0{\cdot}1\ \mathrm{L}^{-1}$, $c_2 = 0{\cdot}025\ \mathrm{L}^{-1}$, $\lambda_1 = 2{\cdot}0\ \mathrm{h}^{-1}$, $\lambda_2 = 0{\cdot}2\ \mathrm{h}^{-1}$.

*Dosing condition 5: consecutive zero-order drug release and first-order absorption*

Assuming a zero-order drug-release rate $k_z$ from the controlled-release oral dosage form of dose $D_{\mathrm{ZA}}$, and assuming a first-order drug-absorption rate $k_{\mathrm{a}}$, the plasma concentration, $C_{\mathrm{ZA}}(t)$, of drug at time $t$ can be approximated by the following equation:

$$C_{\mathrm{ZA}}(t) = k_{\mathrm{z}} \sum_{k=1}^{m} \frac{c_k(\lambda_k(1 - \mathrm{e}^{-k_{\mathrm{a}} t}) - k_{\mathrm{a}}(1 - \mathrm{e}^{-\lambda_k t}))}{\lambda_k(\lambda_k - k_{\mathrm{a}})}$$

$$- k_{\mathrm{z}} \sum_{k=1}^{m} \left[ \frac{c_k(\lambda_k(1 - \mathrm{e}^{-k_{\mathrm{a}}(t - t_0)}) - k_{\mathrm{a}}(1 - \mathrm{e}^{-\lambda_k(t - t_0)}))}{\lambda_k(\lambda_k - k_{\mathrm{a}})} u(t - t_0) \right] \tag{16}$$

where $t_0 = D_{\mathrm{ZA}}/k_{\mathrm{z}}$, and $\lambda_k \neq k_{\mathrm{a}}$.

The following equations for AUC were derived:

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