Sparse sampling designs: a new method for estimating the complete AUC and its standard error

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Introduction

The area under the curve (AUC) is a pharmacokinetic parameter widely used in toxicokinetics and bioequivalence studies as a measure of drug exposure. In order to perform statistical comparisons, the parameter values and their variances in the different groups/treatments are necessaries. Estimation of AUC variance in sparse sampling designs (where each subject is sampled once or more than once but not at all time points) is not straightforward. The aim of the present work was to develop a new mathematical method for estimating the complete area under the curve (AUC) and its standard error that could be applied in different experimental designs and amenable to be implemented in standard calculation worksheets.

Materials and Methods

The AUC value estimation is based on the trapezoidal rule, as was described by Yuan[1].

Eq 1. $$AUC_0^t = \sum_{i=i}^{n}\sum_{j=1}^{m} w_{ij}\cdot C_{ij}$$

Eq 2. $$w_{ij} = \frac{t_{j+1} - t_{j-1}}{2\cdot n_j} = J\ Vector \quad \text{For j=1 to m-1}$$

Eq 3. $$w_{im} = \frac{t_m - t_{m-1}}{2\cdot n_m} = J\ Vector \quad \text{For the last time}$$

The method to calculate the standard error of the concentrations assumes a mixed effect model, where the experimental concentration is estimated by adding the subject effect and the residual effect to the mean concentration.

Eq 4. $$C_{ij} = \overline{C}_j + S + R$$

In this model, the subject effect and the residual effect have been considered proportional deviations to the mean concentrations.

Eq 5. $$S = eta_i\cdot\overline{C}_j \quad \text{where: eta}\sim N(0, S^2_{eta})$$

Eq 6. $$R = eps_{ij}\cdot\overline{C}_j \quad \text{where: eps}\sim N(0, S^2_{eps})$$

Then, these values are used to construct the variance-covariance of concentrations matrix (called V matrix) in the next way:

- diagonal elements (variance values) = $\overline{C}_j\cdot\overline{C}_j\cdot\left(s^2_{eta} + s^2_{eps}\right)$
- non-diagonal elements (covariance values):
  - in the same subject = $\overline{C}_{j1}\cdot\overline{C}_{j2}\cdot s^2_{eta}$
  - otherwise = 0

This way, the estimated variance-covariance of the concentrations is later transmitted to the variance of the mean AUC (Eq. 7).

Eq 7. $$s^2_{AUC} = J'\cdot V\cdot J$$

The aim of this work was to expand this new mathematical method for estimating the complete area under the curve (AUC), from time zero to infinite, and its standard error. Furthermore this procedure includes the extrapolation for calculating the terminal slope, the extrapolation to the initial concentration in case of intravenous administrations and the transmission of this variability to standard error of AUC. The extrapolation to infinite is done by adding the ratio between the average concentration of the last time and the terminal slope to Eq. 1:

Eq 8. $$AUC_0^{\infty} = \sum_{i=1}^{n}\sum_{j=1}^{m} w_{ij}\cdot C_{ij} + \frac{\sum C_m}{n_m}\Big/ k_{el}$$

Eq 9. $$k_{el} = \frac{\sum_{i=1}^{n}\sum_{j=m-m_s}^{m} t_{ij}\sum_{i=1}^{n}\sum_{j=m-m_s}^{m} Ln(C_{ij}) - n_s\sum_{i=1}^{n}\sum_{j=m-m_s}^{m} t_{ij}Ln(C_{ij})}{n_s\sum_{i=1}^{n}\sum_{j=m-m_s}^{m} t_{ij}^2 - \left(\sum_{i=1}^{n}\sum_{j=m-m_s}^{m} t_{ij}\right)^2}$$

And then the transmission error is added to the corresponding element in J vector:

Eq 10. $$\delta\left(\frac{\sum_{i=1}^{n} C_{im}}{n_m\cdot k_{el}}\right)\Big/\delta C_{ij}$$

- for the data points used to calculate the slope:

Eq 11. $$w_{ij} = w_{ij} + \frac{1}{k_{el}^2}\cdot\left(\frac{\sum_{i=1}^{n} C_{im}}{n_m}\cdot\frac{n_s\cdot t_{ij} - \sum_{i=1}^{n}\sum_{j=m-m_s}^{m} t_{ij}}{C_{ij}\cdot\left(n_s\sum_{i=1}^{n}\sum_{j=m-m_s}^{m} t_{ij}^2 - \left(\sum_{i=1}^{n}\sum_{j=m-m_s}^{m} t_{ij}\right)^2\right)}\right)$$

- for the data points of the last time:

Eq 12. $$w_{ij} = w_{ij} + \frac{1}{k_{el}^2}\cdot\left(\frac{k_{el}}{n_m} + \frac{\sum_{i=1}^{n} C_{im}}{n_m}\cdot\frac{n_s\cdot t_{ij} - \sum_{i=1}^{n}\sum_{j=m-m_s}^{m} t_{ij}}{C_{ij}\cdot\left(n_s\sum_{i=1}^{n}\sum_{j=m-m_s}^{m} t_{ij}^2 - \left(\sum_{i=1}^{n}\sum_{j=m-m_s}^{m} t_{ij}\right)^2\right)}\right)$$

In all above equations C_{im} is the concentration for the last time in each *i* subject, n_m the number of subjects of the last time, n_s is the number of data points to calculate k_{el}, C_{ij} and t_{ij} are concentration and time for time point *j* for individual *i*, *m* is the number of time points and finally m_s is the number of time points to calculate k_{el}.

In the case of intravenous administrations, the extrapolation to zero time was done using a similar procedure, estimating the first derivative from the extrapolation of logarithmic concentration from the two first data time. Data and results for intravenous administration are not shown.

The oral data were simulated using NONMEM V (pharmacokinetic model and parameters used are shown in Table 1 and Figure 1) for 100 groups of 20 subjects each one. According to this model and parameters the true value of AUC is 5.092 mg·h/L. Different sampling scenarios from the simulated data were proposed corresponding to the next experimental designs (Figure 2):

1. Design 1: Complete design with 20 subjects and 12 samples per subject (240 samples)
2. Design 2: Complete design with 5 subjects and 12 samples per subject (60 samples)
3. Design 3: Batch design with 20 subjects where each subject is sampled at 3 time point. There are 4 batches covering a total of 12 time points (60 samples).
4. Design 4: Random design with 20 subjects where each subject is sampled at 3 time point and where two subject can coincide in only one time (60 samples).

Parameter	Value	Variability
K_p (h^{-1})	1.22	-
K_a (h^{-1})	1.73	0.198
K_{el} (h^{-1})	0.488	0.053
Vc (L)	0.944	-
K_{12} (h^{-1})	1.18	-
K_{21} (h^{-1})	1.56	0.022
σ^2	-	0.0213
Dose (mg)	4	-
AUC (mg·h/L)	5.092	-

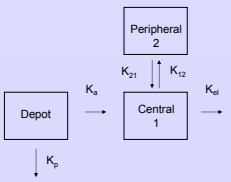

Table and Figure 1. Parameters and model used for data simulation

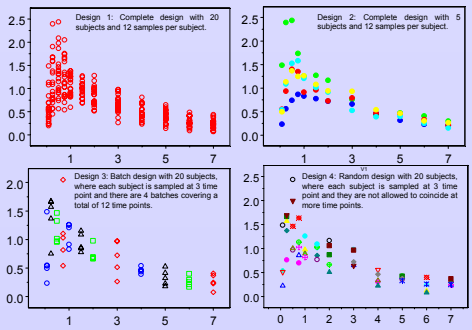

Figure 2. Simulated plasma concentrations obtained using NONMEM V to construct the experimental designs.

Results:

The values of AUC and standard error were obtained for each design (Table 2). The results did not show statistical differences for the AUC values between the designs (Fig 3), but there were differences between the values of the standard error ($p<0.05$) Fig (4). The Post Hoc test of Scheffe between the SE showed the existence of two groups (Table 3), as the SE in the desing 2 is higher than in the other designs.

Design	AUC (mg·h/L)	SE (mg·h/L)
1. Complete (20 id)	5.123	0.103
2. Complete (5 id)	5.089	0.336
3. Batch	5.098	0.144
4. Random	5.093	0.143

Table 2. Arithmetic mean of AUC and Standard Error (SE) in each design

Design	Groups	
	1	2
1. Complete (20 id)	0.103	
2. Complete (5 id)		0.336
3. Batch	0.144	
4. Random	0.143	

Table 3. Scheffe test between the SE of the designs.

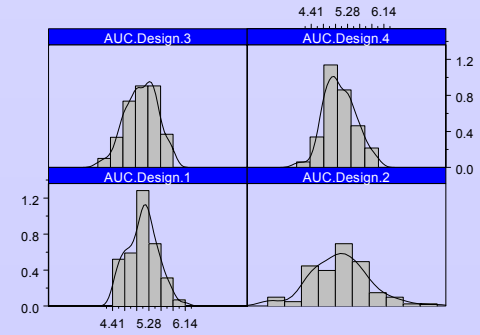

Figure 3. Distribution of 100 AUC values obtained in each design.

Finally, the variance estimations were used to construct the confidence intervals (CI) using the Bailer-Satterthwaite[2] method in order to evaluate the performance of the new approach (Table 4).

Design	95%CI coverage (%)
1. Complete (20 id)	93
2. Complete (5 id)	91
3. Batch	98
4. Random	98

Table 4. Confidence Interval (CI) coverage calculated as the percent of times that the true AUC value is included in the CI limits.

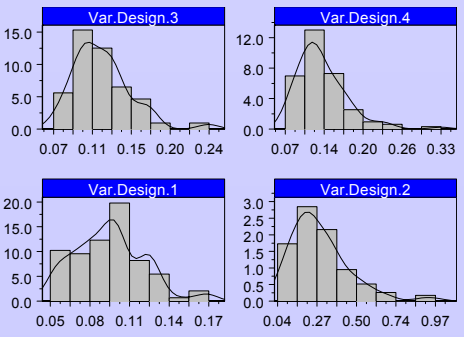

Fig 4. Distribution of 100 standard variances values obtained in each design.

Conclusion:

This procedure can be applied for non-compartmental AUC and standard error estimation independently of the design used, and gives furthermore a security in the AUC calculated value. The estimation of AUC is more accurate in designs with more subjects with the same full number of samples. Despite the AUC values and SE in the complete and sparse designs are similar, the IC does no reach the nominal value of 95% for the complete design. This can be due the higher number of degree freedom calculated by Satterthwaite, the lower range of 95% CI.

References:

[1]Yuan, J., 1993. Estimation of variance for AUC in animal studies. J Pharm Sci. 82, 761-763.
[2]Nedelman, J. R. 1998. An extension of Satterthwaite's approximation applied to pharmacokinetics. J Biopharm Stat 8(2): 317-28

Acknowledges:

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