A framework for estimation of area under the concentration versus time curves (AUCs) in complete and incomplete sampling designs

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September 24, 2008

Outline

Pharmacokinetic studies

- Pharmacokinetic studies what the body does to a drug
- Frequently measures the concentration of the drug in the blood
- AUC is a measure of drug exposure
- Nonclinical in vivo animal studies have to be completed before starting clinical studies in humans

Sampling design

- Serial sampling design
- Batch design
- Complete data design

The model

Under the additive heteroscedastic model the observed concentration for treatment k for subject i at time t is

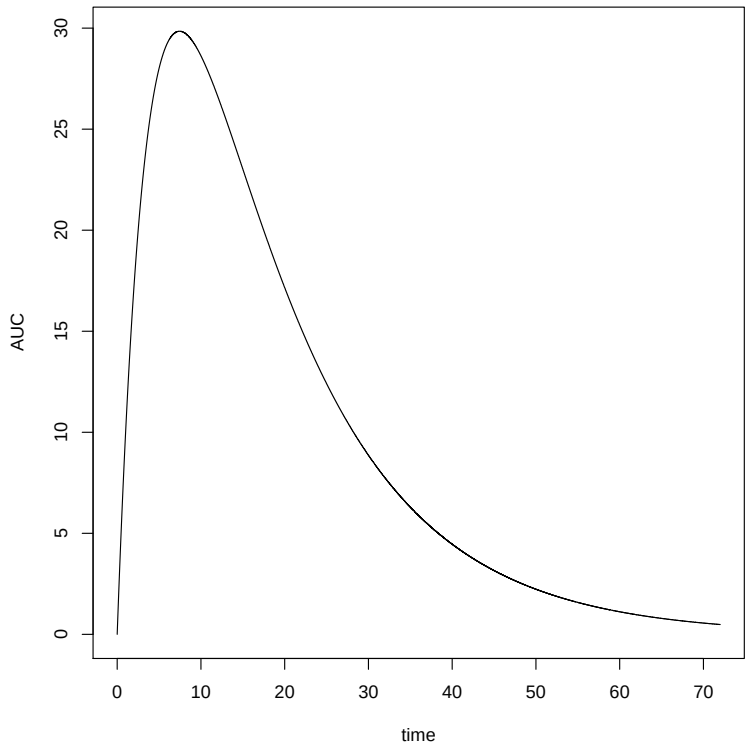
$$Y_{itk} = \mu_{tk} + \epsilon_{itk},$$

where $\epsilon_{itk} \sim G_{tk}$.

Theoretical AUC

The theoretical AUC from 0 to the last observed time point for treatment k is

$$AUC_k = \int_0^{t_{last}} \mu_{tk} dt.$$

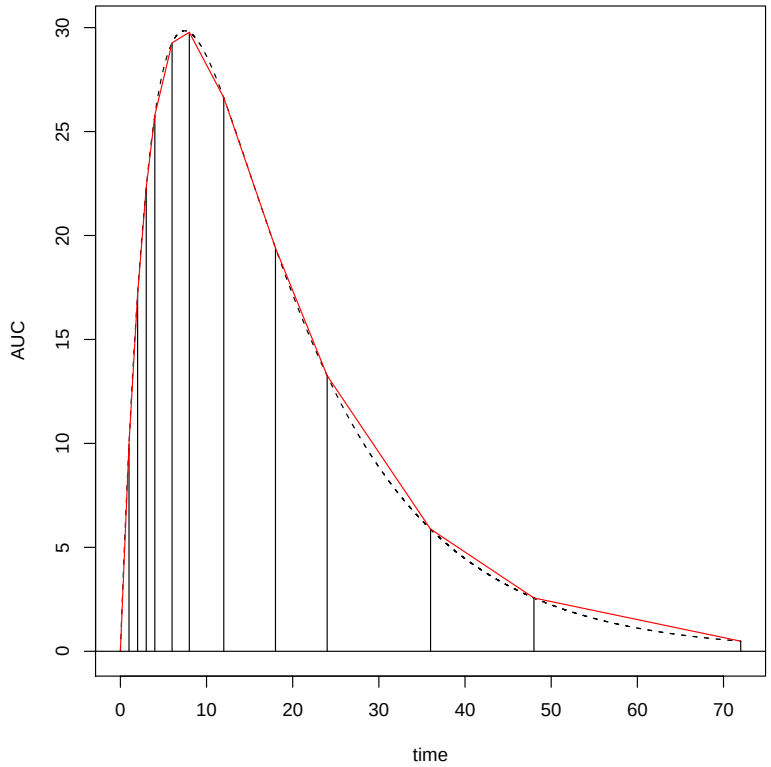


Using the linear trapezoidal rule

$$AUC_k = \sum_{j=1}^{J} w_j \mu_{t_j k}$$

The weights, w_j, equal

$$\begin{aligned} w_1 &= \frac{1}{2}(t_2 - t_1) \\ w_j &= \frac{1}{2}(t_{j+1} - t_{j-1}) \\ w_J &= \frac{1}{2}(t_J - t_{J-1}) \end{aligned}$$



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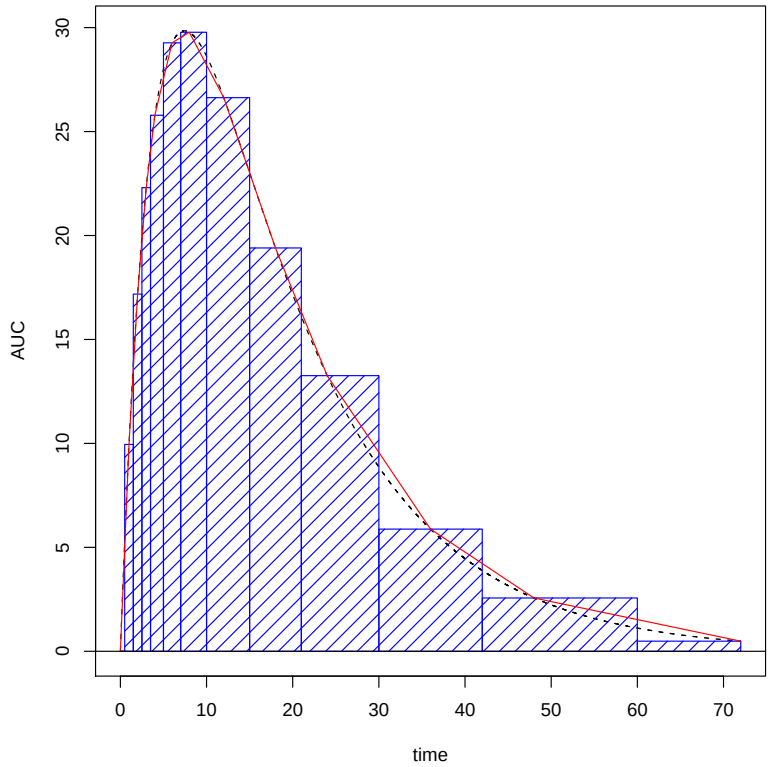
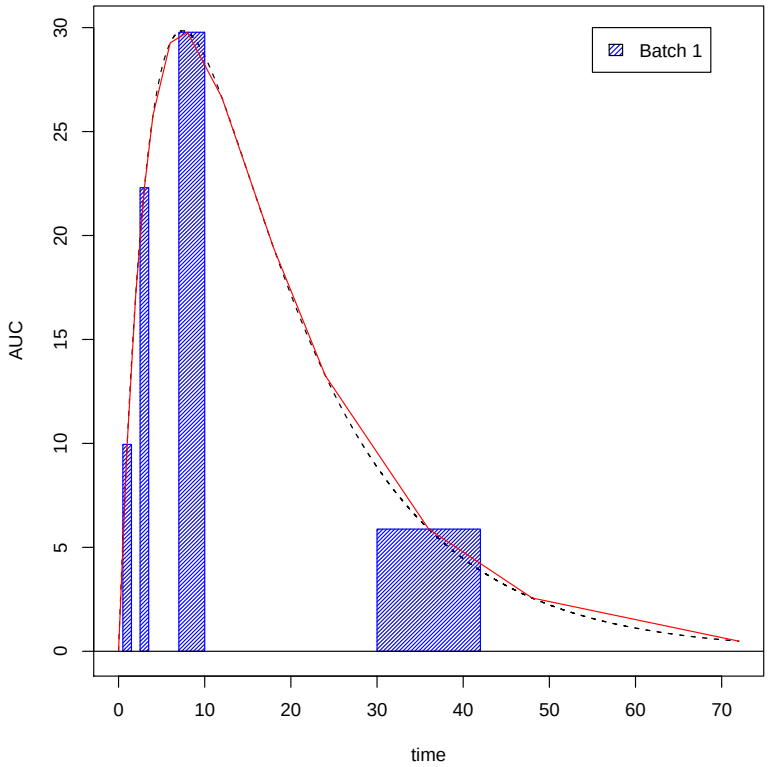


Estimating the AUC

- B batches with n_{bk} subjects
- $J_b \subseteq \{1, \ldots, J\}$ are indices of time points investigated in batch b

$$\widehat{AUC_k} = \sum_{b=1}^{B} \frac{1}{n_{bk}} \sum_{i=1}^{n_{bk}} \sum_{j \in J_b} w_j Y_{it_jk}$$



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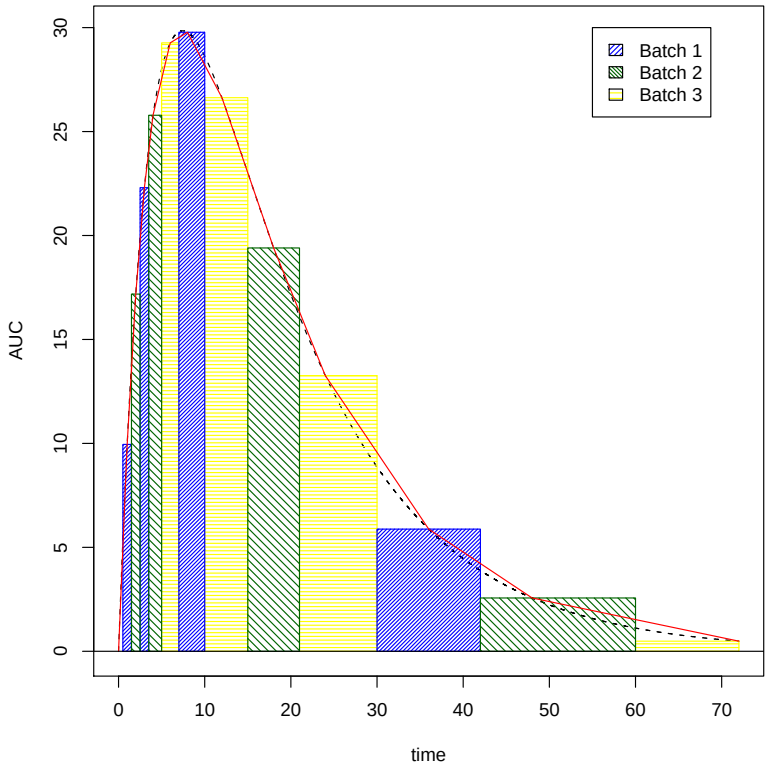


Asymptotic distribution

Assuming that $n_{bk} = n_k$,

$$\frac{\widehat{AUC_k} - AUC_k}{\theta_k} \xrightarrow{d} N(0,1)$$

where

$$\theta_k^2 = \frac{1}{n_k} \sum_{b=1}^{B} \sum_{j \in J_b} \sum_{l \in J_b} w_j w_l \sigma_{t_j, t_l, k}.$$

Asymptotics for linear combinations

For constants $c_1, \ldots, c_K$ satisfying $\sum_{j=1}^{K} c_j < \infty$ we also can show that

$$\frac{\sum_{k=1}^{K} c_k \widehat{AUC}_k - \sum_{k=1}^{K} c_k AUC_k}{\tau} \xrightarrow{d} N(0,1)$$

where

$$\tau^2 = \sum_{k=1}^{K} c_k^2 \theta_k^2.$$

t-interval

$$\left[\widehat{AUC_k} + t_{\nu_k,\frac{\alpha}{2}}\hat{\theta}_k \; ; \widehat{AUC_k} + t_{\nu_k,1-\frac{\alpha}{2}}\hat{\theta}_k\right]$$

where

$$\nu_k = \frac{\left(n_k\hat{\theta}_k^2\right)^2}{\sum_{b=1}^{B}\frac{\left(s_{bk}^2\right)^2}{n_k-1}}, \qquad \hat{\theta}_k^2 = \sum_{b=1}^{B}\frac{s_{bk}^2}{n_k}$$

and

$$s_{bk}^2 = \frac{1}{n_k-1}\sum_{i=1}^{n_k}\left(\sum_{j\in J_b} w_j Y_{it_jk} - \frac{1}{n_k}\sum_{l=1}^{n_k}\sum_{j\in J_b} w_j Y_{lt_jk}\right)^2.$$

Generalized jackknife interval

$$\left[\widehat{AUC_k} + z_{\frac{\alpha}{2}}\tilde{\theta}_k \; ; \widehat{AUC_k} + z_{1-\frac{\alpha}{2}}\tilde{\theta}_k\right]$$

where $\tilde{\theta}_k^2$ is the generalized leave-d-out jackknife estimator (Singer and Berger, 2003).

Data generation

- 10,000 simulations
- one-compartmental model with first order absorption and elimination

$$Y_{it} = 71.429\left(e^{-0.0693t} - e^{-0.231t}\right) + \epsilon_{it}$$

- 3 batches with time points {1,4,12,36}, {2,6,18} and {3,8,24} hours

Normal distributed concentrations

n	ρ	Confidence Interval			
		asymptotic	t-interval	bootstrap-t	gen. jackknife
3	0	0.849 (0.1398)	0.923 (0.1822)	0.928 (0.2112)	0.894 (0.1614)
	0.3	0.849 (0.1644)	0.925 (0.2149)	0.925 (0.2484)	0.895 (0.1898)
	0.6	0.849 (0.1855)	0.923 (0.2420)	0.923 (0.2792)	0.894 (0.2142)
	0.9	0.847 (0.2053)	0.921 (0.2681)	0.923 (0.3097)	0.891 (0.2371)
5	0	0.874 (0.1109)	0.906 (0.1232)	0.910 (0.1269)	0.899 (0.1208)
	0.3	0.874 (0.1304)	0.906 (0.1450)	0.907 (0.1492)	0.900 (0.1421)
	0.6	0.876 (0.1468)	0.907 (0.1633)	0.908 (0.1683)	0.902 (0.1599)
	0.9	0.874 (0.1621)	0.908 (0.1803)	0.907 (0.1855)	0.901 (0.1765)
10	0	0.891 (0.0791)	0.903 (0.0824)	0.903 (0.0827)	0.902 (0.0821)
	0.3	0.891 (0.0931)	0.905 (0.0969)	0.902 (0.0973)	0.904 (0.0966)
	0.6	0.884 (0.1052)	0.896 (0.1096)	0.895 (0.1101)	0.896 (0.1092)
	0.9	0.889 (0.1163)	0.901 (0.1211)	0.903 (0.1217)	0.900 (0.1207)
100	0	0.898 (0.0253)	0.899 (0.0254)	0.898 (0.0254)	0.899 (0.0254)
	0.3	0.895 (0.0297)	0.897 (0.0298)	0.895 (0.0298)	0.897 (0.0298)
	0.6	0.897 (0.0335)	0.899 (0.0336)	0.897 (0.0336)	0.899 (0.0336)
	0.9	0.896 (0.0370)	0.897 (0.0371)	0.895 (0.0371)	0.897 (0.0371)

Table 1: Empirical coverage for normally distributed concentrations with 3 and 4 time points per batch using a nominal coverage of 90%.

Log-normal distributed concentrations

n	ρ	Confidence Interval			
		asymptotic	t-interval	bootstrap-t	gen. jackknife
3	0	0.847 (0.1375)	0.920 (0.1802)	0.925 (0.2101)	0.890 (0.1588)
	0.3	0.852 (0.1617)	0.922 (0.2124)	0.924 (0.2475)	0.895 (0.1867)
	0.6	0.843 (0.1823)	0.918 (0.2391)	0.920 (0.2780)	0.888 (0.2106)
	0.9	0.840 (0.2017)	0.919 (0.2651)	0.920 (0.3107)	0.888 (0.2329)
5	0	0.867 (0.1090)	0.902 (0.1214)	0.906 (0.1258)	0.896 (0.1187)
	0.3	0.868 (0.1285)	0.902 (0.1431)	0.899 (0.1485)	0.896 (0.1400)
	0.6	0.868 (0.1446)	0.903 (0.1612)	0.902 (0.1677)	0.897 (0.1575)
	0.9	0.875 (0.1600)	0.906 (0.1785)	0.905 (0.1859)	0.899 (0.1743)
10	0	0.881 (0.0783)	0.894 (0.0816)	0.895 (0.0824)	0.893 (0.0813)
	0.3	0.889 (0.0918)	0.902 (0.0956)	0.900 (0.0965)	0.900 (0.0952)
	0.6	0.884 (0.1038)	0.897 (0.1081)	0.895 (0.1092)	0.896 (0.1077)
	0.9	0.889 (0.1148)	0.902 (0.1197)	0.901 (0.1211)	0.901 (0.1192)
100	0	0.900 (0.0250)	0.901 (0.0251)	0.899 (0.0251)	0.901 (0.0251)
	0.3	0.893 (0.0293)	0.894 (0.0294)	0.893 (0.0294)	0.894 (0.0294)
	0.6	0.894 (0.0331)	0.895 (0.0332)	0.894 (0.0333)	0.895 (0.0332)
	0.9	0.896 (0.0366)	0.898 (0.0367)	0.897 (0.0367)	0.898 (0.0367)

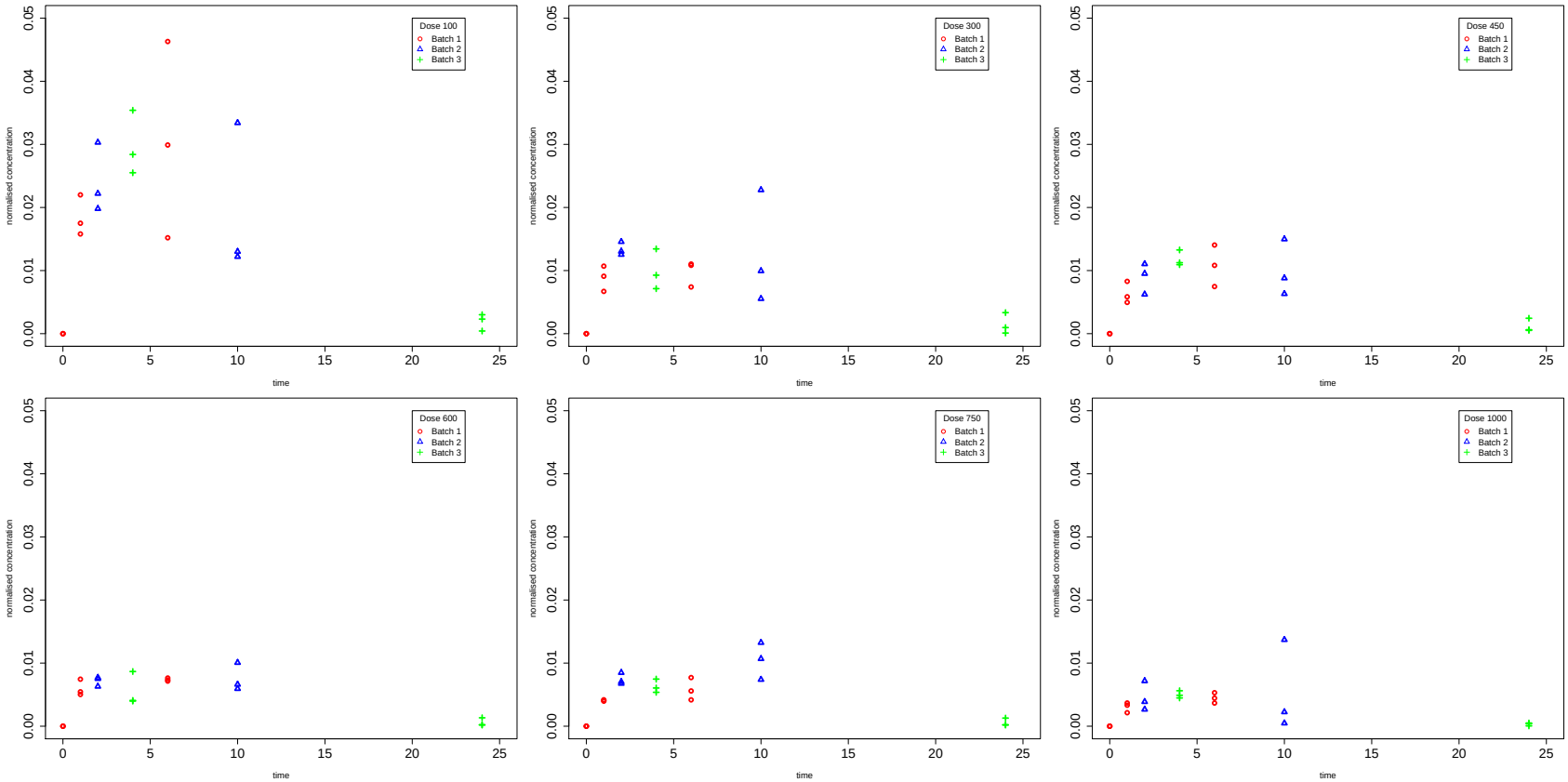
Table 2: Empirical coverage for log-normal-distributed concentrations with 3 and 4 time points per batch using a nominal coverage of 90%.

The setting

- Toxicokinetic study at dose levels (100, 300, 450, 600, 750 and 1000 mg/kg)
- 3 batches with 3 female rats
- Identification of minimum dose for which dose proportionality is rejected

The data

Figure 1: Dose normalised concentration per dose level.



The test

The alternative of a saturable absorption can be tested by

$$H_{0i} : \mu_1 = \ldots = \mu_i \quad vs. \quad H_{1i} : \mu_1 = \ldots = \mu_{i-1} < \mu_i \quad (2 \leq i \leq k),$$

whereas the alternative of a saturable metabolism leads to

$$H_{0i} : \mu_1 = \ldots = \mu_i \quad vs. \quad H_{1i} : \mu_1 = \ldots = \mu_{i-1} > \mu_i \quad (2 \leq i \leq k),$$

where $\mu_1, \ldots, \mu_k$ are the dose-normalized AUCs.

Reverse Helmert contrasts

Table 3: Coefficients for reverse Helmert contrasts.

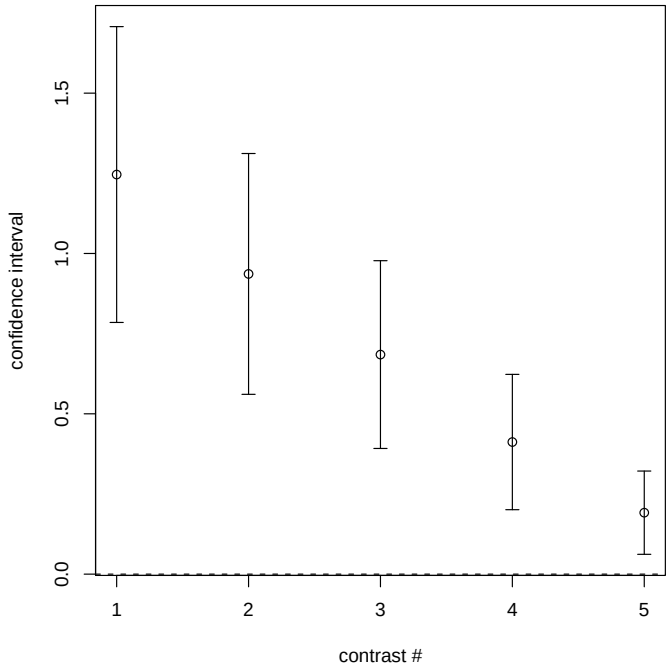
Contrast	Dose in mg/kg					
	100	300	450	600	750	1000
	c_1	c_2	c_3	c_4	c_5	c_6
1	5	-1	-1	-1	-1	-1
2	4	-1	-1	-1	-1	0
3	3	-1	-1	-1	0	0
4	2	-1	-1	0	0	0
5	1	-1	0	0	0	0

Results

Table 4: Summary of tests with two-sided p-values.

Hypothesis	Estimate	p-value
H_{06}	1.2462	0.0000
H_{05}	0.9362	0.0002
H_{04}	0.6847	0.0004
H_{03}	0.4120	0.0023
H_{02}	0.1917	0.0127

Figure 2: Two-sided 95% confidence intervals.



Summary

- generalized jackknife method has nominal coverage for all sample sizes
- t-interval is a fast alternative for moderate and large sample sizes
- linear combinations of AUCs can be used to test for dose proportionality

Future Research

- Sample size comparison between different designs
- Concentrations below the detection limit
- Establishing equivalence using ratios of AUCs

References

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