The Performance of Statistical Methods for Combining Relative Bioactivity estimates

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Outline

Background

1. Biological assays are designed to estimate the bioactivity of a test preparation against a standard preparation.
2. A series of bioassay runs may be performed to improve the precision of the bioactivity.
3. Several methods are available for estimating a relative bioactivity for parallel line bioassays.
4. Little attention has been paid on these methods in the last few decades and more attention shifted towards meta-analysis.
5. Focus on parallel line bioassays.

Research hypothesis

Assessing the performance of the statistical methods used to estimate a common relative bioactivity.

Performance measures

Coverage probabilities of the 95% confidence intervals

Length of the 95% confidence intervals.

Suppose H bioassay runs with I=2 preparations are considered. The statistical model is as follows:

$$y_{hijk} = \alpha_{hi} + \beta_h x_{hij} + \varepsilon_{hijk} \tag{1}$$

The relative bioactivity is estimated as:

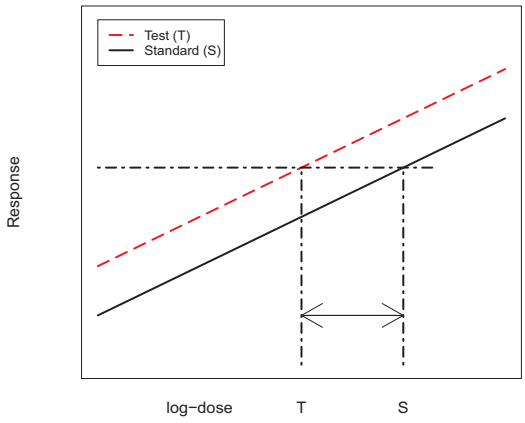
$$\hat{\mu}_h = \frac{\hat{\alpha}_{h2} - \hat{\alpha}_{h1}}{\hat{\beta}_h} \quad \text{or simply} \quad \hat{\mu}_h = \frac{\hat{\alpha}_T - \hat{\alpha}_S}{\hat{\beta}} \tag{2}$$

The combined relative bioactivity is estimated as:

$$\hat{\mu} = \frac{\sum \hat{\omega}_h \hat{\mu}_h}{\sum \hat{\omega}_h} \tag{3}$$

and its confidence interval is given as : $\hat{\mu}_l, \hat{\mu}_u = \hat{\mu} \pm t_{df_c} \cdot \hat{\sigma}_{\hat{\mu}}$

Figure: Graphical representation of the relative bioactivity



Methods for combining bioactivities

1. Ordinary unweighted average: $\hat{\omega}_h = 1$
2. Weighted average methods:
   - (i) Bliss (1952) method
     - Homogeneous $\hat{\mu}_h$: $\hat{\omega}_h = (\hat{\sigma}_h^2)^{-1}$
     - Heterogeneous $\hat{\mu}_h$: $\hat{\omega}_h = (\hat{\sigma}_B^2 + \hat{\sigma}_h^2)^{-1}$
   - (ii) Cochran (1954) method,
     - Homogeneous $\hat{\sigma}_h^2$ & $\hat{\mu}_h$: $\hat{\omega}_h = 1$
     - Homogeneous $\hat{\sigma}_h^2$ & heterogeneous $\hat{\mu}_h$: $\hat{\omega}_h = 1$ with $\hat{\sigma}_{\hat{\mu}} = \sqrt{\hat{\sigma}_{B*}^2 / H}$
     - Heterogeneous $\hat{\sigma}_h^2$ & homogeneous $\hat{\mu}_h$: $\hat{\omega}_h = (\hat{\sigma}_h^2)^{-1}$
     - Heterogeneous $\hat{\sigma}_h^2$ & $\hat{\mu}_h$: $\hat{\omega}_h = (\hat{\sigma}_{B*}^2 + \hat{\sigma}_h^2)^{-1}$
   - (iii) Morse and Bickle (1967) method.

Methods *cont.*

1. Maximum likelihood methods: Assume homogeneous $\hat{\sigma}_h^2$
   - (i) Armitage, Bennett, and Finney (1976) method,
     - Based on approximate confidence regions.
   - (ii) Williams (1978) method,
     - Based on exact confidence regions.
   - (iii) Meisner, Kushner, and Laska (1986) method.
     - Also based on exact confidence regions but different from Williams (1978) exact confidence regions.
2. Random effects model.
   - Individual/raw data is used instead of aggregated data.

Design of the simulation study

1. The simulated individual data is based on model 1 and mean parameters are assumed to be $\mu_{\alpha_1} = \mu_{\alpha_2} = 10$, and $\mu_\beta = 1$.
2. Variances for the intercepts for both preparations are assumed equal ($\sigma^2_{\alpha_1} = \sigma^2_{\alpha_2} = \sigma^2_\alpha$). Three levels are used (where $\sigma^2 = 0.01$):
   (i) No variation : $\sigma^2_\alpha = 0$
   (ii) Some little variation : $\sigma^2_\alpha = 0.4\sigma^2$
   (iii) Moderate variation : $\sigma^2_\alpha = 0.8\sigma^2$
   (iv) Large but not extreme variation : $\sigma^2_\alpha = 2\sigma^2$
3. Residuals are simulated from a $N \sim (0, \sigma^2)$
4. The number of bioassay runs is varied: 2, 3, 4, 5, 6 and $n_{sim} = 5000$.

Simulation results: Coverage probabilities

1. Random effects coverage probabilities only when N is at least four.
2. Maximum likelihood methods: Good coverage probabilities only when there was no between variability.

Figure: Coverage probabilities for 2 bioassays

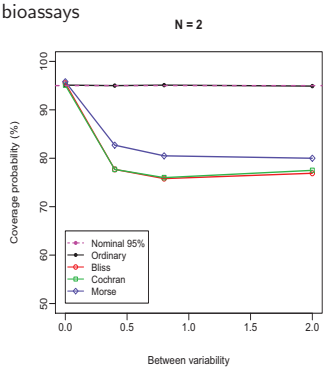


Table: Coverage probabilities for 3 and 4 bioassays

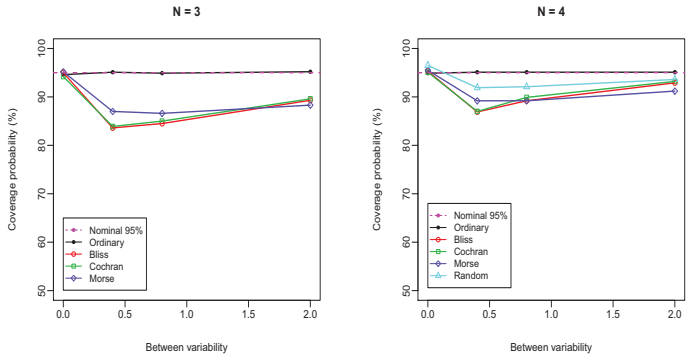
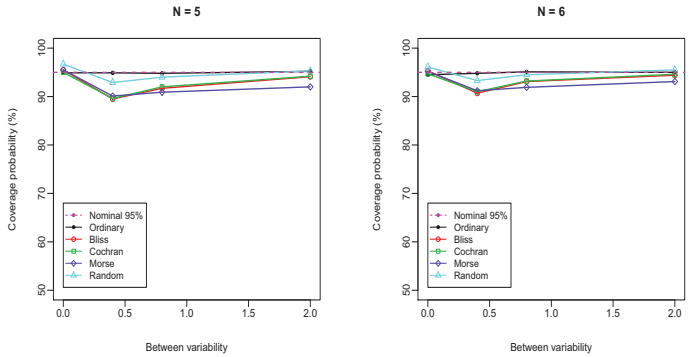


Table: Coverage probabilities for 5 and 6 bioassays



Simulation results: Width of the confidence intervals

Table: Width of the 95% confidence intervals for methods with good coverage probabilities

No. of bioassays	Ordinary	Bliss	Cochran	Morse	RE*
H=2	1.543	1.252	1.272	0.763	-
H=3	0.478	0.434	0.436	0.359	-
H=4	0.317	0.299	0.300	0.266	0.430
H=5	0.253	0.244	0.245	0.224	0.310
H=6	0.216	0.211	0.211	0.196	0.243

* Random effects model

Summary

1. Ordinary unweighted method consistently gave good coverage probabilities but with wide confidence intervals.
2. Weighted average methods: Better coverage probabilities, especially when the number of assays is at least 3.
3. Maximum likelihood methods: All three methods gave good coverage probability only when there was no between variability.
4. Random effects model: Good coverage, but with wide confidence intervals.

In progress ...

1. Currently the weighted average methods outperform other statistical methods.
2. Random effects model using a weighted variance (Hardy & Thompson, 1996 and Sachez-Meca & Marin-Martinez, 2008).
3. Preliminary tests are based on $\alpha = 0.05$, a less restrictive level might improve results (Bancroft, 1964).

Thank you for your attention!