A novel method to estimate the minimum effective dose for monotone and non-monotone dose-response relationships

Martin J. Wolfsegger[1], Georg Gutjahr[2], Werner Engl[1] and Thomas Jaki[3]

[1] Baxter Innovations GmbH, Vienna, Austria
[2] Competence Center for Clinical Trials, University of Bremen
[3] Department of Mathematics and Statistics, Lancaster University

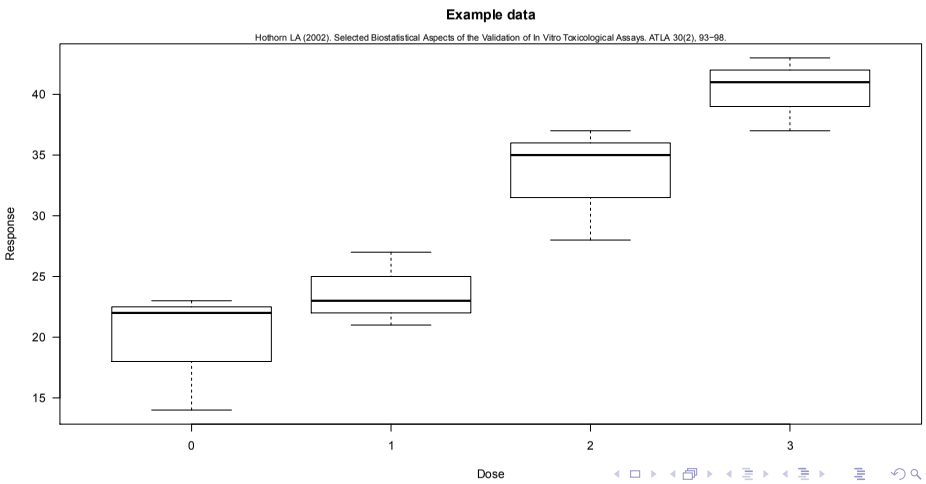
ROeS Conference 2013

Outline

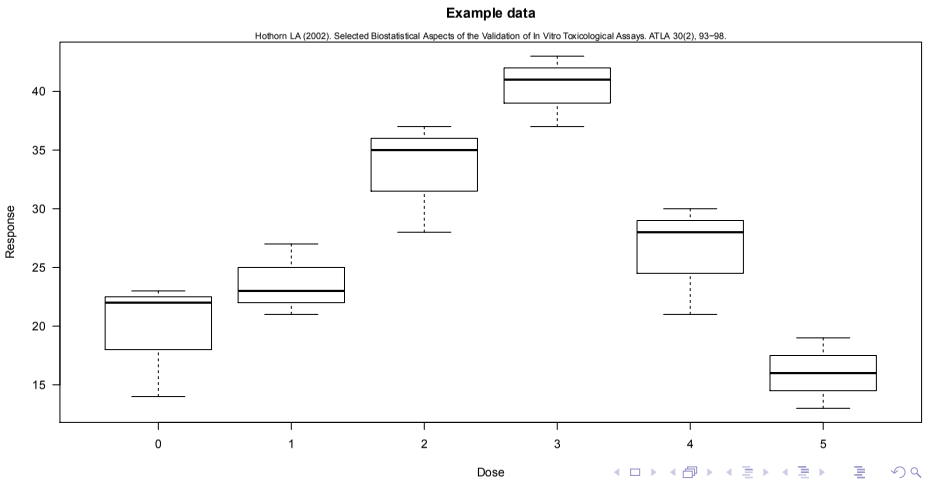
Definition

- Estimation of the minimum effective dose is the objective of many clinical and non-clinical dose-finding trials
- Minimum effective dose (MED): smallest dose producing a clinically important response that can be declared statistically significant different from zero dose
- Minimum detectable dose (MDD): smallest dose that is statistically significant different from zero dose

Motivating example



Motivating example



Assumptions

Set of increasing dose levels $i = 0, 1, 2, \ldots, k$ with a-priori unknown monotone or non-monotone dose-response relationship, where the j-th observation in the i-th group is distributed according to

$$X_{ij} = \mu_i + \varepsilon_{ij} \qquad i = 0, 1, \ldots, k \text{ and } j = 1, 2, \ldots, n,$$

where ε_{ij} are i.i.d. normally distributed with zero mean and a common σ^2

Minimum effective dose

Let m denote the minimal effective dose so that

$$m = \min \{i : \mu_i > \Delta + \mu_0\},$$

for some threshold $\Delta > 0$, and let M denote the smallest dose that is rejected by a hypothesis testing approach via tests of the null hypotheses $(1 \leq i \leq k)$

$$H_{0i} : \mu_i \leq \Delta + \mu_0$$

Control of the type I error

Control of the error rate to underestimate the true MED

$$P(M < m) \leq \alpha$$

Under weak monotonicity, the FWER is also controlled if the error rate of underestimating the true MED is controlled

Procedure

- Combination of Dunnett's procedure and the step-down application of two-sample t-tests
- Hybrid procedure that controls the error rate of underestimating the true MED and is robust in terms of power
  - Data dependent switch from the critical value of Dunnett's procedure to the critical value of the two-sample t-test

Procedure

1. Compare all k doses to the zero dose using one-sided Dunnett's single-step procedure
   (a) If no dose can be declared significantly superior to the zero dose, then no dose is declared as MED and the procedure is stopped
   (b) If one or more test statistics exceed Dunnett's critical value, let ℓ denote the largest index of these test statistics
2. Perform the following sequential procedure
   (a) Set $\ell := \ell - 1$
   (b) If $\ell > 0$ and if the unadjusted one-sided two-sample t-test rejects $\mu_0 \geq \mu_\ell$, then go to (2a), otherwise go to (3)
3. Set the minimum effective dose M to $\ell + 1$

Procedure

Error rate of underestimating the true MED is controlled

Proposition

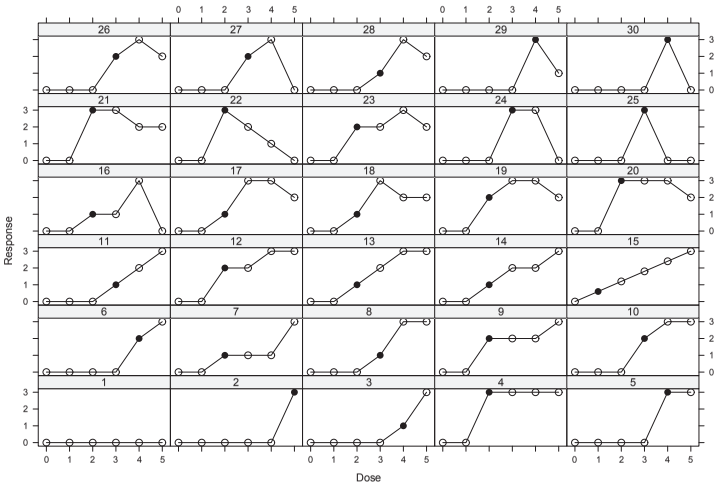
$P(M < m) \leq \alpha$ *for for every parameter configuration*

Proof for known variance and a common sample size

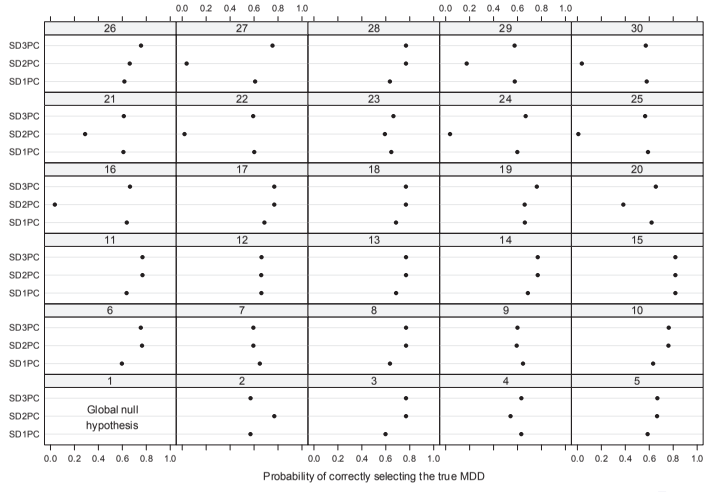
Simulations

- Simulation study for 30 scenarios based on 1E6 runs to identify the MDD
- Data generated to follow a normal distribution with $n_i = 10$ for $k = 5$ positive dose levels with σ chosen to detect the true MDD with a power of 80%, based on the one-sided two-sample t-test unadjusted for multiplicity
- Introduced approach (SD3PC) compared with
  - Step-down version of Dunnett's procedure (SD1PC)
  - Step-down application of two-sample t-tests (SD2PC)

Dose-response shapes investigated



Probability of correctly selecting the true MDD



Discussion and Conclusion

- SD3PC combines the advantages of two other methods
- Proof that the probability in underestimating the true MED is controlled (for known σ^2 and a common sample size)
  - Simulations indicate that the probability in underestimating the true MED is also controlled for equal but unknown variances as well as for unequal sample sizes

Introduction
Model
Procedure
Simulations
Discussion and Conclusion

Discussion and Conclusion

- Best or almost always close second in terms of power
  - Best power in 70% of scenarios
  - SD1PC: Power up to 29% larger and at most 8% smaller
  - SD2PC: Better or identical power in all but 2 scenarios
- Advantage in interpretation from a clinical point of view
- Confidence sets & generalization of the procedure possible