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

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Introduction

- 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 statistically significant different from zero dose
- Estimation can be performed by modeling approach or multiple comparison procedures

Outline

Introduction

Multiple comparison procedures:

- Performance of methods depends on the underlying - a-priori unknown - dose-response shape
- Assumptions about the dose response shape often difficult to elicit and hard to justify

Assumptions

Set of increasing dose levels $i = 0, 1, 2, \ldots, k$ with a-priori unknown monotone or unimodal 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.

Control of the type I error

Control of the error rate for underestimating the true MED

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

Under weak monotonicity the FWE is also controlled if the error rate of underestimating the true MED is controlled.

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.

Procedure

1. Perform all k one-sided comparisons with the zero dose and use single step Dunnett's procedure to adjust for multiplicity.
   1. If no dose can be declared significantly superior to the zero dose, then no dose level is declared as MDD and the procedure stops.
   2. If one or more test statistics exceed Dunnett's critical value, let ℓ denote the largest index of such test statistic.
2. Perform the following sequential procedure.
   1. Set $\ell := \ell - 1$.
   2. If $\ell > 0$ and if an unadjusted one-sided two-sample t-test rejects $\mu_0 \geq \mu_\ell$, then go to (2a).
   3. Otherwise, go to (3).
3. Set the minimal identified effective dose M to $\ell + 1$.

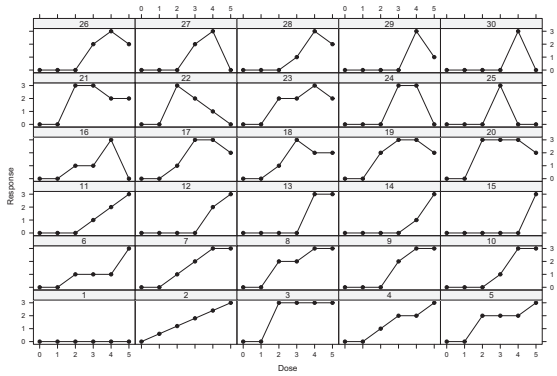
Procedure

It can be shown that the error rate of underestimating the true MED is controlled strongly for monotone or unimodal shapes

Proposition

$P(M < m) \leq \alpha$ *for monotone or unimodal shapes*

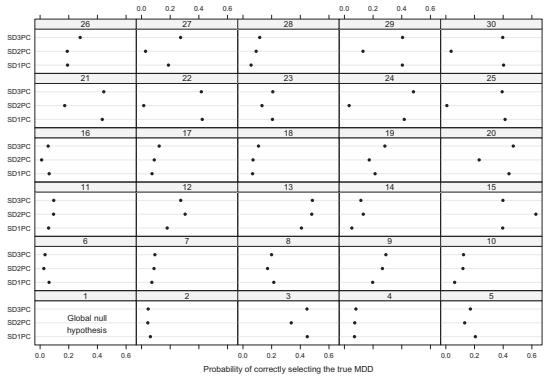
Dose-response shapes investigated



Simulations

- Simulation study for 30 scenarios based on 1E6 runs
- Data generated to follow a normal distribution with $n_i = 10$ for $k = 5$ positive dose levels with $\sigma = \sqrt{n}$
- Introduced approach (SD3PC) compared with
  - Step-down version of Dunnett's procedure (SD1PC)
  - Step-down application of two-sample t-tests (SD2PC)

Probability of correctly selecting the true MDD



Discussion and Conclusion

- Novel method combines the advantages of two other methods
- Not applicable to multi-modal dose-response relationships
- Controls the probability in underestimating the true MED
- Best or almost always close second in terms of power
- Advantage to interpret the results from a clinical point of view