Decision Tools for Adaptive Designs

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Conditional Power

Conditional Power

Definition of Conditional Power (CP):

Conditional probability to reject the null given the stage 1 data and a parameter value θ belonging to the alternative.

CP with Conditional error function approach:

$$q \leq A(\text{stage 1 data}) \quad \Longleftrightarrow \quad \Phi^{-1}(q) \leq \Phi^{-1}\big(A(\text{stage 1 data})\big)$$

Typically

$$\Phi^{-1}(q) \sim N\big(-\theta\sqrt{I_2}, 1\big)$$

增加的

where I_2 is the (incremental) information of stage 2. Hence,

$$CP_\theta = P_\theta[\text{reject}|\text{stage 1 data}] = \Phi\left(\Phi^{-1}\big(A(\text{stage 1 data})\big) + \theta\sqrt{I_2}\right)$$

$$= 1 - \Phi\left(\Phi^{-1}\big(1 - A(\text{stage 1 data})\big) + \theta\sqrt{I_2}\right)$$

Explicit formula

With a two-arm z-test: $I_2 = n_2/(4\sigma^2)$; n_2 second stage sample size.

Fisher's product test:

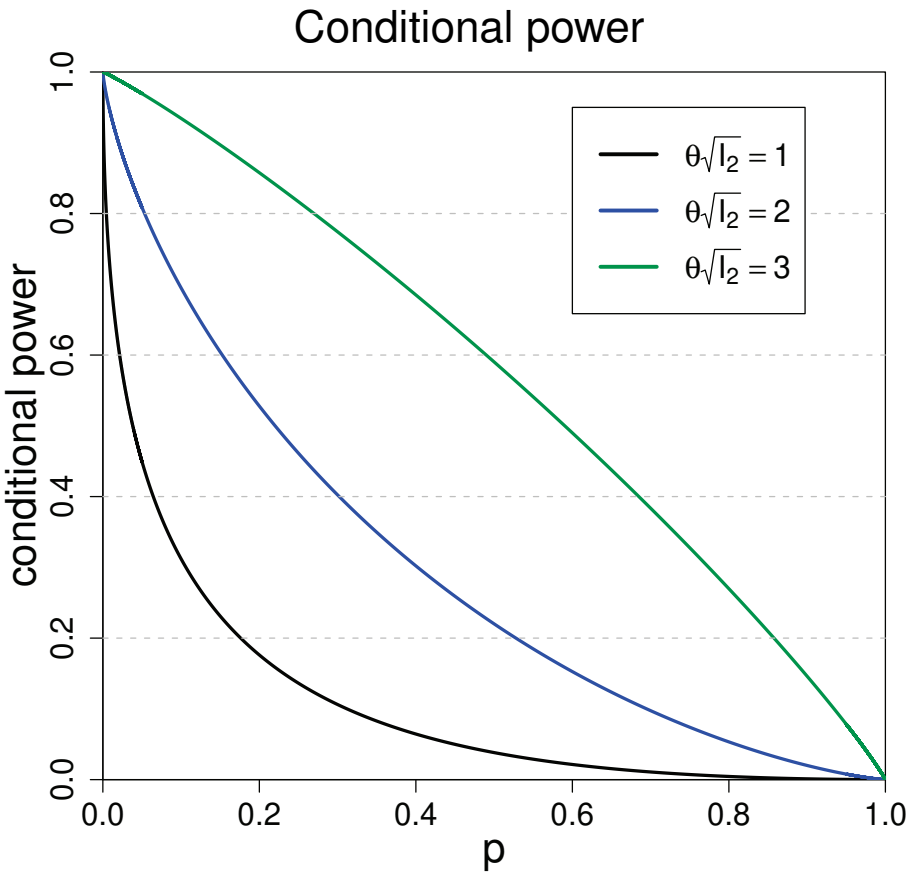
$$CP_\theta = \Phi\left(\Phi^{-1}\left(\frac{c}{p}\right) + \theta\sqrt{I_2}\right)$$

Inverse normal method:

$$CP_\theta = \Phi\left(\Phi^{-1}\left(\frac{w_1 Z_1 - u_2}{w_2}\right) + \theta\sqrt{I_2}\right)$$

Same conditional power for GSD, then with $w_1 = \sqrt{n_1/(n_1+n_2)}$ (planned sample sizes).

Conditional Power – Properties



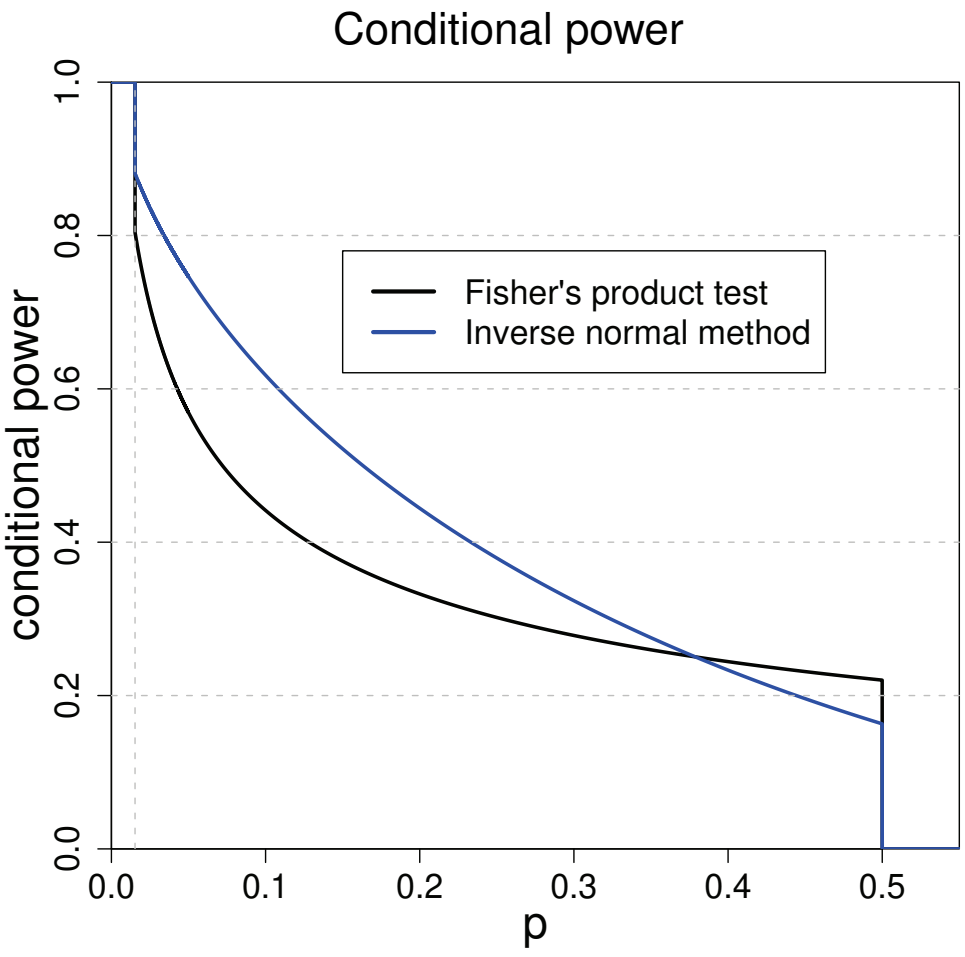
The conditional power

- increases with increasing θ;
- increases with increasing I_2 (second stage sample size);
- decreases with increasing p

Example:

- Inverse normal method
- $\alpha = 0.025$
- $\alpha_0 = 1, \alpha_1 = 0$

Conditional Power – Examples



- θ_t, θ_c . . . mean responses under t and c, resp.
- $H_0 : \theta_t \leq \theta_c$ vs. $H_1 : \theta_t > \theta_c$
- $\alpha = 0.025$
- $n_1 = 100$
- $\alpha_0 = 0.5$
- $\alpha_1 = 0.015$
- $\theta_0 = 0.25$

Early stopping with CP

futility无用

- It has been suggest (already for GSD) to stop the trial for futility if $CP_\theta(\text{stage 1 data})$ is small, i.e. below some cp_0, for the planning alternative θ.

存在一对一的对应关系

- There is one-to-one correspondence between α_0 and cp_0:

$$cp_0 = \Phi\left(\Phi^{-1}\left(A(\alpha_0) + \theta\sqrt{I_2}\right)\right)$$

$$\alpha_0 = A^{-1}\left(\Phi\left(\Phi^{-1}(cp_0)\right) - \theta\sqrt{I_2}\right)$$

- E.g. $\alpha = 0.05$, $\alpha_0 = 0.5$, $\alpha_1 = 0.0233$ and power is 90%;

  Inverse normal combination test ($w_1 = \sqrt{0.5}$): $cp_0 = 0.33$;

  Fisher's product test: $cp_0 = 0.48$ (see Figure 7.1 in WaBr16).

Sample size adaptations

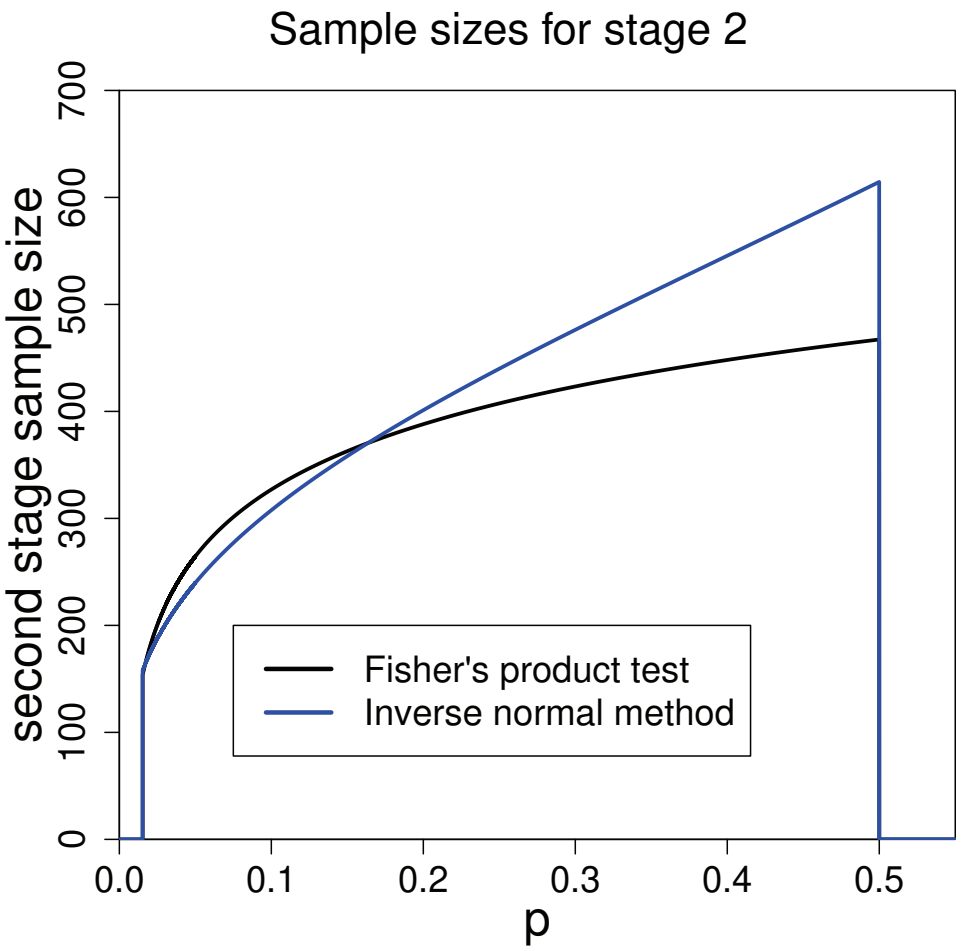
Sample size adaptations based on conditional power

- Given interim data either stop the trial or choose the stage 2 sample size such that the conditional power is at least π, e.g., $\pi = 0.8$.给定中间数据要么停止试验，要么选择阶段2样本大小，使得条件幂至少为 π
- *Rational:* If we continue with the trial then we want to have a "good chance" ($\geq \pi$) to finally reject the null hypothesis.
- If we continue with stage 2 then we choose the second stage sample size

$$n_2 = \left\{ \Phi^{-1}(\pi) - \Phi^{-1}\left(A[\text{stage 1 data}]\right) \right\}^2 / (I_1 \cdot \theta^2)$$

where I_1 is the information per observation (e.g. $I_1 = 0.5/\sigma^2$ in a two-armed clinical trial).

Sample size adaptations based on conditional power



- θ_t, θ_c . . . mean responses under t and c, resp.
- $H_0 : \theta_t \leq \theta_c$ vs. $H_1 : \theta_t > \theta_c$
- $\alpha = 0.025$
- $n_1 = 100$
- $\alpha_0 = 0.5$, $\alpha_1 = 0.015$
- stage 2 sample size s.th.

$$CP_{\theta_0=0.25} = 0.9$$

- Overall power 90%,

  independent from c.e.f.

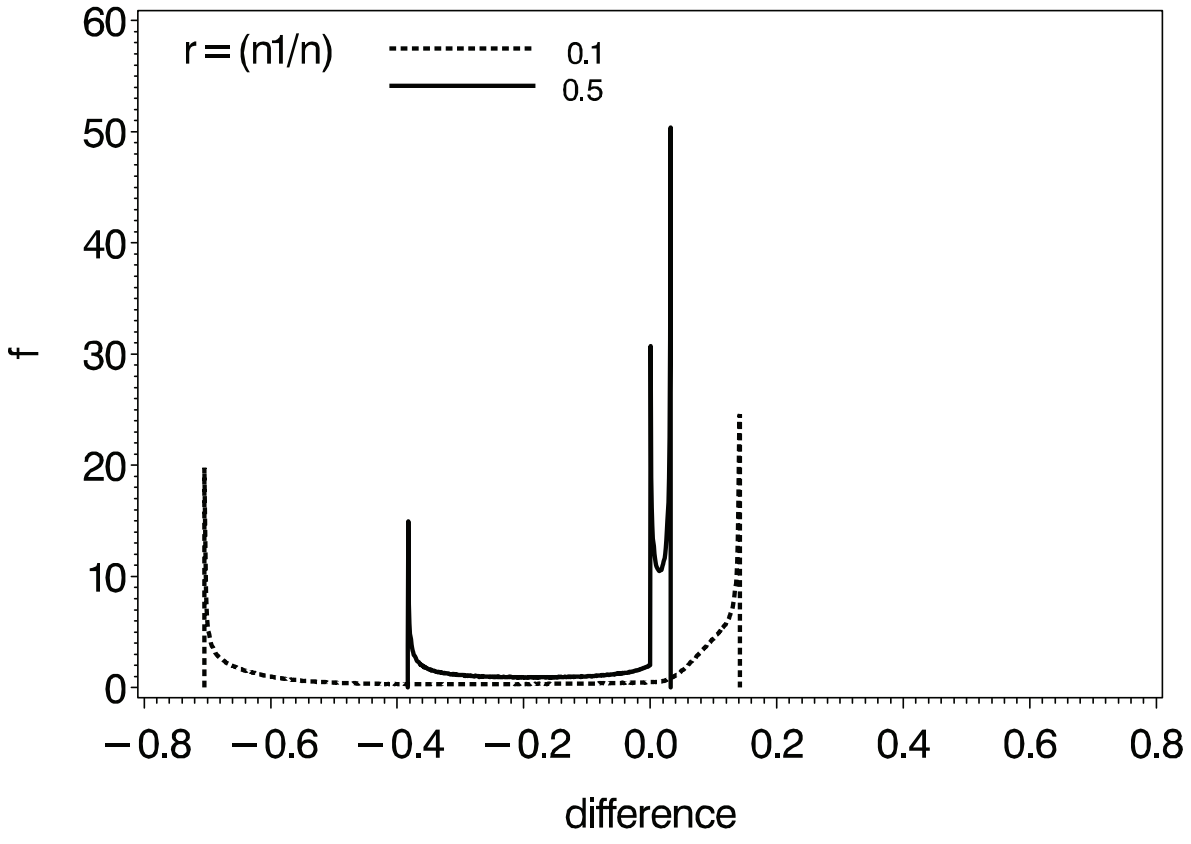
Which effect in the conditional power calculation?

Several possibilities have been considered

- Using the effect size θ_0 initially原来 used for planning the trial (θ_0 minimal relevant effect size).
- Using the interim estimate $\hat{\theta}_1$ of θ (if belonging to the alternative) in the hope to estimate the conditional power under true unknown effect.
- Using a weighted sum of the initial and estimated effect size or a posterior mean for some given prior distribution.

使用最初用于计划试验的效果大小θ0（θ0最小相关效果大小）。
使用 θ 的中间估计 θ 1（如果属于替代），希望估计真实未知效应下的条件幂。
对某些给定的先前分布使用初始和估计的效应大小或后验均值的加权和。

How good can we estimate the true conditional power? (Bauer and König 2006)



Density of difference between true and estimated CP:

- median is 0;
- density spreads to left much more than to the right
- relatively high chance for a substantial underestimation of true CP

How good can we estimate the true conditional power? – Conclusions

(BAUER AND KÖNIG 2006)

- Using the interim estimate for estimating the conditional power can be quite misleading and can lead to a severe underestimation of the true conditional power.
- One should not over-interpret the interim data.不应过度解释临时数据
- It seems better to use the minimal relevant alternative θ_0, and, if necessary, to adjusted it only **carefully** by what we have learned at stage 1.似乎最好使用最小相关替代θ0，并且如果有必要，只能根据我们在第1阶段学到的内容进行仔细调整