Unblinded Sample-Size Modification for Fisher's Exact Test

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October 4, 2010

Research supported by FWF grant P21763

Topic of this talk

Fully flexible sample-size modification in Fisher's exact test

- during an unblinded interim analysis,
- without a prespecified sample-size modification rule.

Construction of a test based on the conditional error principle

- in the presence of a nuisance parameter,
- discrete test statistics.

Literature overview

Proschan and Hunsberger (1995)

Introduce conditional error principle

Müller and Schäfer (2001, 2004)

Introduce natural conditional error function

Timmesfeld et al. (2007)

Construct a test after sample-size increase in t-test based on the natural conditional error function

Review of the conditional error principle

Sample-size modification for the z-test

Extend conditional error principle to nuisance parameters

Sample-size modification for Fisher's exact test (randomized)

Optimally apply conditional error principle with discrete data

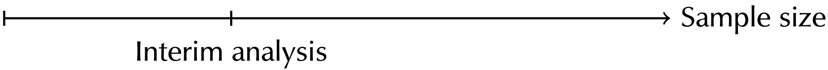
Sample-size modification for Fisher's exact test (non-randomized)

Sample-size modification with z-test

Normally distributed observations with mean μ and variance 1

Point hypothesis $\mu = 0$ against alternative $\mu > 0$

Data-dependent selection of sample size
during an interim analysis by an unknown adaptation rule



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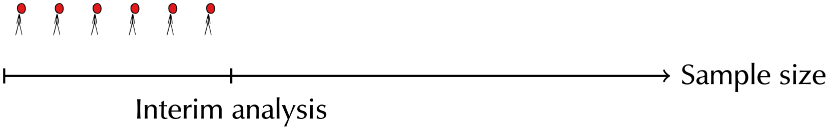

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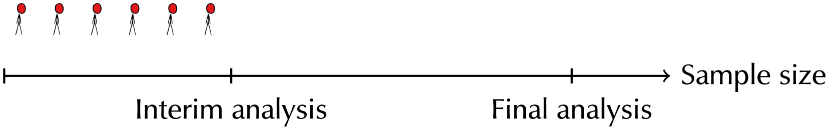

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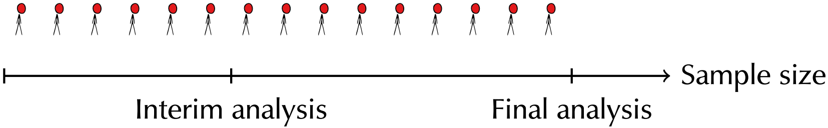

Sample-size modification for Fisher's exact test

In treatment: Observations with success probability θ_t
In control: Observations with success probability θ_c

Point hypothesis $\theta_t = \theta_c$ against alternative $\theta_t > \theta_c$

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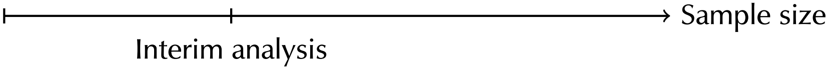

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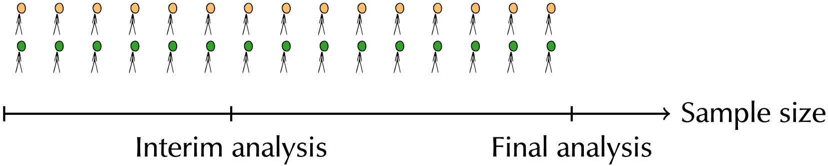

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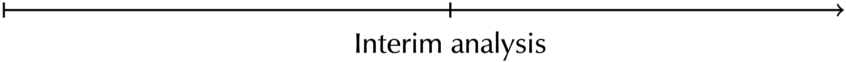
Setup for sample-size modification with the z-test

Observations normally distributed with mean μ

Test $\mu = 0$ against $\mu > 0$



Setup for sample-size modification with the z-test

Observations normally distributed with mean μ

Test $\mu = 0$ against $\mu > 0$

First stage

Fixed sample size m

First-stage z-statistic X

Interim analysis

Setup for sample-size modification with the z-test

Observations normally distributed with mean μ

Test $\mu = 0$ against $\mu > 0$

First stage

Fixed sample size m

First-stage z-statistic X

Second stage

Data-dependent size $n = N(X)$

Second-stage z-statistic Y_n

Interim analysis

Naive approach

Standard z-test of level α for predefined sample size $m+n$

Reject if $Z > \Phi^{-1}(1-\alpha)$ with overall z-statistic

$$Z = \sqrt{\frac{m}{m+n}}X + \sqrt{\frac{n}{m+n}}Y_n.$$

With data-dependent sample size $n = N(X)$,
serious error inflation possible:

- If X is small, choose n large.
- If X is large, choose n small.

Worst case (Proschan and Hunsberger, 1995):
Nominal level $\alpha = 5\,\%$, but actual error $11.5\,\%$

Approach that ensures error control

- We want a test $\varphi(X, N, Y_N)$ so that $E_0[\varphi] = \alpha$.
- We do not know the adaptation rule $N(X)$.

Conditional error principle (Proschan and Hunsberger, 1995)

1. Predefine a $[0, 1]$-valued statistic A of X so that $E_0[A(X)] = \alpha$
2. For each n, set $\varphi(X, n, Y_n) = \mathbb{1}\{Y_n > \Phi^{-1}(1 - A(X))\}$ so that

$$E_0[\varphi \,|\, X = x] = A(x) \quad \text{for a.e. } x$$

Conditional error principle

For all n: $E_0[\varphi(X, n, Y_n) \mid X = x] = A(x)$ for a.e. x

$\Downarrow$

$E_0[\varphi(X, N(X), Y_{N(X)}) \mid X = x] = A(x)$ for a.e. x

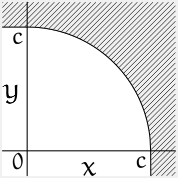
$\Downarrow$

$E_0[\varphi] = E_0[A]$ and $E_0[A] = \alpha$

Two examples of conditional error functions

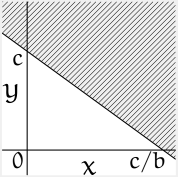
Circular conditional error function

$$A(x) = \begin{cases} 1 - \Phi(c) & \text{for } x \leqslant 0 \\ 1 - \Phi\left(\sqrt{c^2 - x^2}\right) & \text{for } 0 < x \leqslant c \\ 1 & \text{for } c < x \end{cases}$$



Linear conditional error function (Parameter $b > 0$)

$$A(x) = 1 - \Phi(c - bx) \quad \text{for } x \in \mathbb{R}$$



Choose the constant c so that $\int A \, d\Phi = \alpha$.

Conditional error principle with preplanned test

- Preplanned second-stage sample size n_*
- Standard z-test φ_* for preplanned sample size $m + n_*$
- Use error rates of φ_* as conditional error function
- If no modification necessary ($N = n_*$), we can use φ_*, since $E_0[\varphi_* \mid X = x] = A(x)$ for a.e. x
- Attractive: Small change $\Rightarrow$ Test similar to preplanned test!

Natural conditional error function (Müller and Schäfer, 2001)

$$A(x) = 1 - \Phi\left(\sqrt{1 + (m/n_*)}\,\Phi^{-1}(1-\alpha) - \sqrt{(m/n_*)}\,x\right)$$

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Sample-size modification with Fisher's exact test

Success probabilities θ_t in treatment and θ_c in control

Test for $\theta_t = \theta_c$ against $\theta_t > \theta_c$

Problem of comparing two binomial distributions!

First stage

Fixed sample size m
X_t = successes in treatment
X_+ = successes in both groups

Second stage

Data-dependent size $n = N(X)$
$Y_{t,n}$ = successes in treatment
$Y_{+,n}$ = successes in both groups

Interim analysis

Notation

- Main parameter $\psi = (\theta_t/(1-\theta_t))/(\theta_c/(1-\theta_c))$
- Nuisance parameter $\lambda = (\theta_t + \theta_c)/2$
- Point hypothesis $\psi = 1$ against one-sided alternative $\psi > 1$
- Versions P_λ^x of the conditional distribution given $X = x$ for parameter value λ under hypothesis $\psi = 1$
- Versions E_λ^x of the conditional expectation generated by P_λ^x

Conditional error principle

Bad idea

Choose a conditional error function A of X.
Try to construct a test φ with

$$E_\lambda^x[\varphi] \leqslant A(x) \quad \text{for all } \lambda \text{ and all } x$$

Problem: Usually, the only test that remains is the test $\varphi \equiv 0$.

Good idea (Müller and Schäfer, 2004)

Prespecify a family A_λ, indexed by λ, of conditional error functions and select the test φ so that

$$E_\lambda^x[\varphi] \leqslant A_\lambda(x) \quad \text{for all } \lambda \text{ and all } x$$

Which family of conditional error functions?

Natural conditional error functions

Preplan a Fisher's exact test of level α test φ_* with fixed design
Define

$$A_\lambda(x) = E_\lambda^x[\varphi_*]$$

- Use Fisher's exact test as preplanned test φ_*
- If no sample-size modification necessary, we can use φ_*
- Attractive: Test similar to preplanned test!

Which test decision function?

Simultaneous exhaustion of conditional error:

$$E_\lambda^x[\varphi] = A_\lambda(x) \quad \text{for all } \lambda \text{ and all } x. \tag{1}$$

Possible for sample-size increase in t-test (Timmesfeld et al., 2007)

In general impossible $\Rightarrow$ conservative test:

$$E_\lambda^x[\varphi] \leqslant A_\lambda(x) \quad \text{for all } \lambda \text{ and all } x. \tag{2}$$

For (2), many tests possible. Most of them unattractive (like $\varphi \equiv 0$)

Efficient conditional error exhaustion

Select a weight function π over nuisance parameter space.

Optimal test

- The test φ satisfies $E_\lambda^x[\varphi] \leqslant A_\lambda(x)$ for all λ and all x
- For every test ϕ that satisfies $E_\lambda^x[\phi] \leqslant A_\lambda(x)$ for all λ and x

$$\int E_\lambda^x[\phi] d\pi(\lambda) \leqslant \int E_\lambda^x[\varphi] d\pi(\lambda) \quad \text{for all } x$$

Note 1: Posterior distribution after first stage sensible choice of π.
Note 2: If simultaneous exhaustion possible, this will be solution.

Optimization problem in terms of conditional levels

Fix observed first-stage data x and chosen sample size n.

$$E_\lambda^x[\varphi] = E_\lambda^x\Big[\underbrace{E^x[\varphi \mid Y_{+,n} = k]}_{\xi(k)}\Big]$$

Pointwise (for each x and n), find ξ as solution of:

$$\begin{aligned} \text{maximize} \quad & \int E_\lambda^x[\xi]\, d\pi(\lambda) \\ \text{subject to} \quad & E_\lambda^x[\xi] \leqslant A_\lambda(x) \quad \text{for all } \lambda \\ \text{with respect to} \quad & \xi \text{ a } [0,1]\text{-valued statistic of } Y_{+,n} \end{aligned}$$

Simplify notation

Define

- $p_{k\lambda} = P^x_\lambda[Y_{+,n} = k]$ for all λ and $k = 0, \ldots, 2n$.
- $q_k = \int P^x_\lambda[Y_{+,n} = k] d\pi(\lambda)$ for $k = 0, \ldots, 2n$.
- $r_\lambda = A_\lambda(x)$ for all λ

Linear semi-infinite program

$$\begin{aligned}
\text{maximize} \quad & \sum_{k=0}^{2n} q_k \xi_k \\
\text{subject to} \quad & \sum_{k=0}^{2n} p_{k\lambda} \xi_k \leqslant r_\lambda \quad \text{for all } \lambda \\
\text{with respect to} \quad & \xi_k \in [0, 1] \quad \text{for } k = 0, \ldots, 2n
\end{aligned}$$

Solving optimization problem

ξ solution of linear semi-infinite program:

- Finite number of unknowns
- Linear objective function
- Infinite number of linear constraints

Accelerated central-cutting plane algorithm Betrò (2004):

- Iteratively constructs a sequence of solutions
- At each step, current solution is conservative
- Solutions come arbitrary close to optimal solution

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From conditional levels to corresponding test

In the last section: After obtaining ξ, choose randomized test

$$\varphi = \mathbb{1}\{Y_{t,n} > C(Y_{+,n})\} + R(Y_{+,n})$$

with critical values C and randomization values R.

If we want a nonrandomized conditional test of the form

$$\varphi = \mathbb{1}\{Y_{t,n} > C(Y_{+,n})\}$$

we must assign levels that can be exhausted without randomization.

This leads to the additional constraints

$$\xi_k \in \Xi_k = \{P^x[Y_{t,n} > c \mid Y_{+,n} = k] : c \in \mathbb{N}\}$$

Nonrandomized test for discrete second-stage data

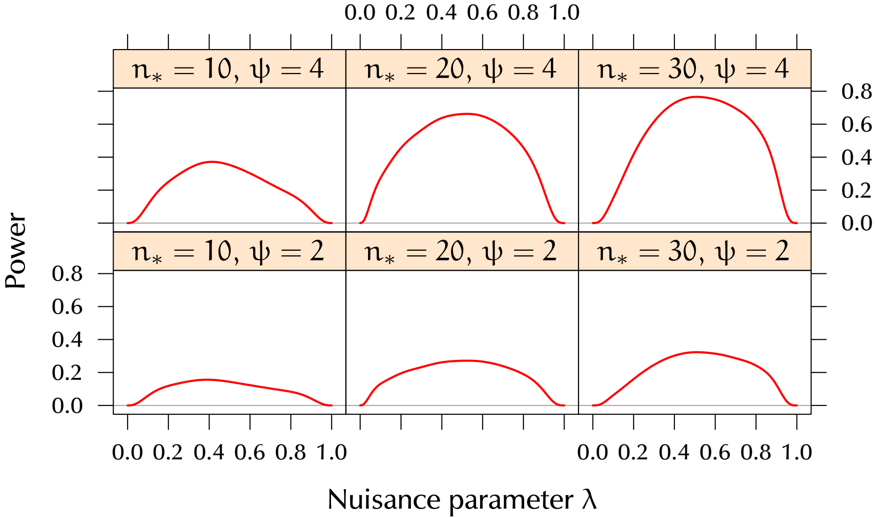
Nonrandomized test $\Rightarrow$ Constraints $\xi_k \in \Xi_k$

Combinatorial optimization problem

$$\begin{aligned} &\text{maximize} && \sum_{k=0}^{2n} q_k \xi_k \\ &\text{subject to} && \sum_{k=0}^{2n} p_{k\lambda} \xi_k \leqslant r_\lambda \quad \text{for all } \lambda \\ &\text{with respect to} && \xi_k \in \Xi_k \quad \text{for } k = 0, \dots, 2n \end{aligned}$$

Solve by branch-and-bound with relaxations to randomized tests

Power of resulting test



Summary

Conditional error principle with Fisher's exact test

- Consider only tests that ensure error control
- Exhaust conditional error as efficiently as possible
- Numerically solve the resulting optimization problem