Flexible Designs: How Efficient? How necessary?

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Plan of talk

1. Motivation for adaptive sample size designs.

2. “Variance spending” and related methods.

3. *Example 1:* A hypothesis test with a single, final analysis.

4. Formulating the real testing problem.

5. A catalogue of group sequential tests.

6. *Example 2:* A group sequential test with adaptive re-design.

A variety of adaptive and flexible procedures

- Adapting the sample size to estimates of nuisance parameters.
- Adaptive randomisation rules designed to allocate fewer subjects to the inferior treatment.
- Flexibility to change treatment, outcome or response during a study.
- Re-assessing the power requirement in response to interim data.

§1 Motivation: Prototype example

Balanced parallel design

$$X_{Ai} \sim N(\mu_A, \sigma^2), \quad X_{Bi} \sim N(\mu_B, \sigma^2)$$

$$Y_i = X_{Ai} - X_{Bi} \sim N(\theta, 2\sigma^2)$$

$$\theta = \mu_A - \mu_B$$

The MLE of θ is $\widehat{\theta} = \overline{X}_A - \overline{X}_B$.

Without loss of generality, suppose $2\sigma^2 = 1$.

Aim: to Test $H_0 : \theta = 0$ versus $H_1 : \theta > 0$

with Type I error rate α, e.g. $\alpha = 0.025$.

Fixed sample design

Initially aim for power $1 - \beta$ at target effect size $\theta = \delta$.

Hence set sample size

$$n \;=\; (z_\alpha + z_\beta)^2 \, \frac{2\sigma^2}{\delta^2} \;=\; \left(\frac{z_\alpha + z_\beta}{\delta} \right)^2$$

per treatment arm, where $z_\alpha = \Phi^{-1}(1 - \alpha)$, etc.

(Recall $2\sigma^2 = 1$.)

MLE, Z and score statistics

For this test:

$$\begin{aligned}
\widehat{\theta} &= \overline{X}_A - \overline{X}_B = \overline{Y} && \sim N(\theta,\ n^{-1}) \\
Z &= \widehat{\theta}\sqrt{n} && \sim N(\theta\sqrt{n},\ 1) \\
S &= \widehat{\theta} n = \sum Y_i && \sim N(\theta n,\ n)
\end{aligned}$$

Working with information rather than sample size, we can generalise to

- other designs (e.g. crossover, general linear model)
- other endpoints (e.g. binary data, survival data).

Data at an intermediate stage

After a fraction r of the sample size (information) is collected,

$$\begin{aligned}\widehat{\theta}_1 &\sim N(\theta,\, \tfrac{1}{rn}),\\ S_1 &\sim N(\theta rn,\, rn).\end{aligned}$$

Intermediate results may be examined, even though a formal interim analysis was not planned.

Disappointing results

- Suppose $\widehat{\theta}_1$ is positive but smaller than the hoped for effect size δ.
- It is unlikely that H_0 will be rejected (low conditional power).
- However, the magnitude of $\widehat{\theta}_1$ is clinically meaningful.
- It appears the original target effect size δ was over-optimistic.

Can this trial be “rescued” ?

Revising the sample size

- Let $\xi = \delta / \widehat{\theta}_1$ and suppose $\xi > 1$.

- With hindsight, we wish we had designed the test with power $1 - \beta$ at $\theta = \delta / \xi$ rather than at $\theta = \delta$.

- This would have required the larger sample size $\xi^2 n$ instead of n.

- One might collect extra observations in the remainder of the study to make a total sample size of $\xi^2 n$.

Naive test leads to inflated Type I error

Suppose we behave as if the sample size $\xi^2 n$ was pre-planned and compute

$$Z = \left(\overline{X}_A - \overline{X}_B\right) \sqrt{\xi^2 n}.$$

Since ξ is a function of the first stage data, Z is *not* $N(0, 1)$.

The test that rejects when $Z > z_\alpha$ does not have Type I error α.

Type I error rate is inflated

- typically by 30% to 40% (Cui, Hung & Wang, *Bmcs,* 1999)
- can more than double (Proschan, Follmann & Waclawiw, *Bmcs,* 1992).

Should we worry about inflation of Type I error?

Pocock:

> “Control of Type I error is a vital aid to prevent a flood of false positives into the medical literature.”

Why not just start over?

Perhaps we should just throw away the data and start again with a new, larger trial.

This is inefficient and wasteful of data.

This procedure would also inflate the Type I error rate. If repeated, it leads to a Type I error rate of almost one! (“sampling to a foregone conclusion”, Cornfield, *JASA,* 1966.)

“Flexible/adaptive” procedures

Bauer and Köhne (1994). *Biometrics.*

Proschan and Hunsberger (1995). *Biometrics.*

Wassmer (1998). *Biometrics.*

Lehmacher and Wassmer (1999). *Biometrics.*

Fisher, Lloyd (1998). Self-designing clinical trials. *Statist. in Med.*

Cui, Hung and Wang (1999). *Biometrics.*

Chi and Liu (1999). *J. Biopharm. Statist.*

Müller and Schäfer (2001). *Biometrics.*

Denne (2001). *Statist. in Med.*

Jennison and Turnbull (2002). *Submitted.*

§2 Variance spending

A fixed sample of n observations can be divided into

$$\begin{aligned} \text{stage 1:} \qquad S_1 &= \textstyle\sum_{i=1}^{rn}(X_{Ai} - X_{Bi}), \\ \text{stage 2:} \qquad S_2 &= \textstyle\sum_{i=rn+1}^{n}(X_{Ai} - X_{Bi}). \end{aligned}$$

Then

$$\begin{aligned} S_1 &\sim N(rn\theta,\, rn), \\ S_2 &\sim N(\{1-r\}n\theta,\, \{1-r\}n), \\ S_1 + S_2 &\sim N(n\theta,\, n) \end{aligned}$$

and

$$Z = \frac{S_1 + S_2}{\sqrt{n}} \sim N(0,1) \quad \text{under } H_0\text{: } \theta = 0.$$

Variance spending — continued

If the stage 2 sample size is modified to $\gamma(1-r)n$ after seeing S_1,

$$S_1 \sim N(rn\theta,\, rn)$$

and, conditionally on S_1,

$$S_2' \sim N(\gamma\{1-r\}n\theta,\, \gamma\{1-r\}n).$$

Under H_0: $\theta = 0$,

$$\gamma^{-1/2}\, S_2' \sim N(0,\, \{1-r\}n)$$

unconditionally. Hence

$$Z = \frac{S_1 + \gamma^{-1/2}\, S_2'}{\sqrt{n}} \sim N(0,1) \quad \text{under } H_0.$$

Lloyd Fisher, *Statistics in Medicine*, 1998

Fisher explains “variance spending” as the construction of a Z statistic from components with pre-specified variances.

Under H_0,

$$W_1 \;=\; \frac{S_1}{\sqrt{n}} \;\sim\; N(0,\, r),$$

$$W_2 \;=\; \frac{S_2'}{\sqrt{\gamma n}} \;\sim\; N(0,\, 1-r)$$

and

$$Z \;=\; W_1 + W_2 \;\sim\; N(0,1).$$

Cui, Hung & Wang, *Biometrics*, 1999

Cui et al consider the joint distribution of weighted sample sums.

They show that, under H_0,

$$(S_1,\ S_1 + \gamma^{-1/2}\, S_2')$$

has the same joint distribution as the original

$$(S_1,\ S_1 + S_2).$$

This result generalises to a group sequential setting with K analyses and one or more re-design points.

Conditional Type I error probability

In the original test, the conditional Type I error probability after stage 1 is

$$P_{\theta=0}\{S_1 + S_2 > z_\alpha\sqrt{n} \mid S_1 = s_1\}. \qquad (1)$$

If stage 2 sample size is modified and a rule defined that preserves the conditional error probability (1), overall Type I error rate α is maintained.

- The methods of Fisher and Cui et al do this.
- Jennison & Turnbull (2002) show that any unplanned design modification *must* have this property.
- Müller & Schäfer (2001) and Denne (2001) use this construction in adaptive group sequential designs.

Variance spending — notes

- For $\gamma > 1$, second stage observations are down-weighted. The final statistic Z is not sufficient for θ — so the efficiency of this approach is suspect.

- The distribution of Z under $\theta \neq 0$ is not simple. The inter-relation of stages 1 and 2 needs to be properly treated in power calculations.

We shall assess power and average sample size of this method in an example with a specific rule for the stage 2 sample size.

$\S$3 Example 1

Original fixed sample design:

To test H_0: $\theta = 0$ with Type I error rate α and power $1 - \beta$ at $\theta = \delta$. The study needs $n = (z_\alpha + z_\beta)^2/\delta^2$ observations.

After stage 1:

From rn observations, we find $\widehat{\theta}_1 = \delta/\xi$ and decide to aim for power $1 - \beta$ at $\theta = \delta/\xi$.

We modify the second stage sample to $\gamma(1 - r)n$ and follow the variance spending approach, creating

$$Z = (S_1 + \gamma^{-1/2} S_2')/\sqrt{n}.$$

Choice of γ

Treating γ as fixed (!) we obtain

$$E(Z) \;=\; \{r + \sqrt{\gamma}(1-r)\}\sqrt{n}\,\theta.$$

A test designed for power $1-\beta$ at δ/ξ has sample size $\xi^2 n$ and statistic

$$Z' \;\sim\; N(\xi\sqrt{n}\,\theta,\, 1).$$

Equating $E(Z)$ and $E(Z')$ gives

$$\xi = r + \sqrt{\gamma}(1-r) \quad \text{or} \quad \gamma = \left(\frac{\xi - r}{1-r}\right)^2 \tag{2}$$

to determine our modified sample size.

Sample size rule, with truncation

Aim for power $1-\beta$ at $\theta=\delta/\tilde{\xi}$ where

$$\tilde{\xi}=\tilde{\xi}(\widehat{\theta}_1)=\begin{cases}4 & \text{for} \quad \widehat{\theta}_1\le\delta/4,\\ \delta/\widehat{\theta}_1 & \quad\quad \delta/4<\widehat{\theta}_1<2\delta,\\ 0.5 & \quad\quad \widehat{\theta}_1\ge 2\delta.\end{cases} \tag{3}$$

Note that reduction in sample size is possible for high values of $\widehat{\theta}_1$.

If the interim look is at the halfway point, i.e., $r=0.5$, the second stage inflation factor, from (2), is

$$\gamma(\widehat{\theta}_1)\;=\;4\{\tilde{\xi}(\widehat{\theta}_1)-0.5\}^2\;\in\;(0,49).$$

Properties of the test

Power

$$P_\theta\{\text{Reject } H_0\} = P_\theta\{Z > z_\alpha\} = \int P_\theta\{Z > z_\alpha | \widehat{\theta}_1\} f_\theta(\widehat{\theta}_1)\, d\widehat{\theta}_1$$

where $f_\theta(\widehat{\theta}_1)$ is the $N(\theta,\, 1/(rn))$ density of $\widehat{\theta}_1$ and

$$Z \;=\; \{S_1 + \gamma(\widehat{\theta}_1)^{-1/2}\, S_2'\}/\sqrt{n}.$$

Average Sample Number

$$ASN(\theta) = rn + (1-r)n \int \gamma(\widehat{\theta}_1) f_\theta(\widehat{\theta}_1)\, d\widehat{\theta}_1.$$

Example

Initial test:

Type I error rate: $\alpha = 0.025$.

Power: $1 - \beta = 0.9$ at $\theta = \delta$.

Planned sample size: $n = 10.5/\delta^2$ per treatment arm.

Modification:

Intermediate look after $n/2$ observations per treatment arm.

Inflation factor $\gamma(\widehat{\theta}_1) \, = \, 4\{\tilde{\xi}(\widehat{\theta}_1) - 0.5\}^2 \, \in \, (0, 49)$.

Total sample size is in the range $(0.5n, \, 25n)$.

Also, stop for “futility” at stage 1 and accept H_0 if $\widehat{\theta}_1/\delta < -0.173$, in which case conditional power under $\theta = \delta/4$ is less than 0.8.

Figure 1. Power functions of Variance Spending test and Fixed Sample test with power 0.9 at $\theta = \delta$.

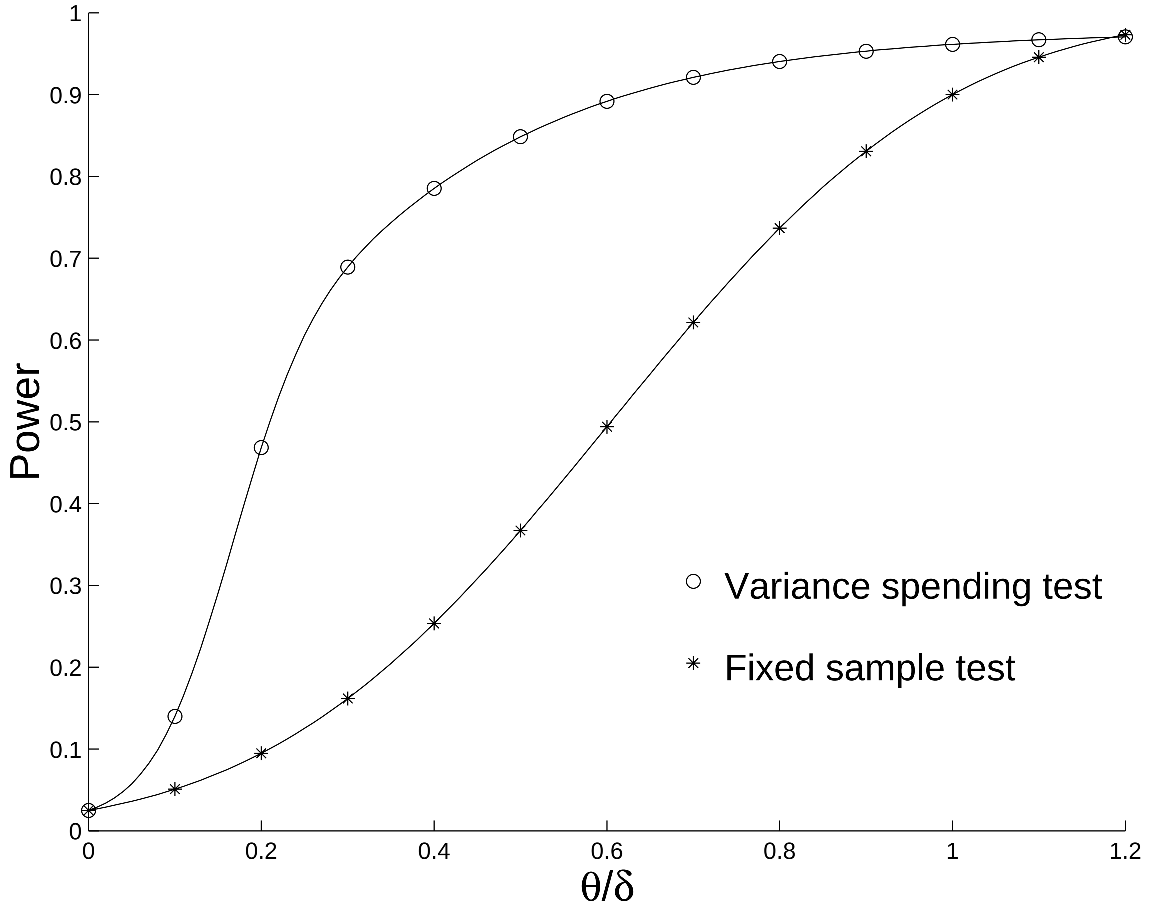


Figure 2. Power functions of Variance Spending test and Fixed Sample test with power 0.9 at $\theta = 0.6\,\delta$.

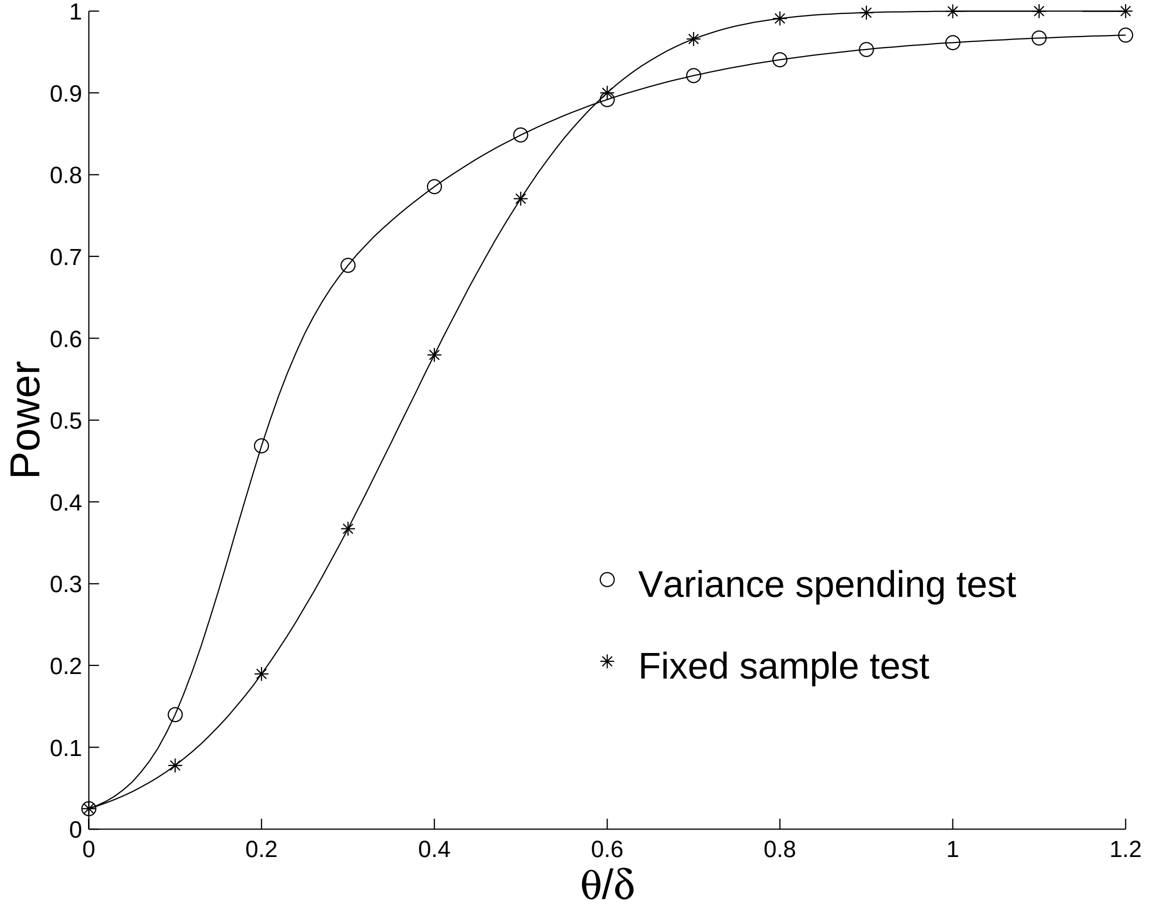
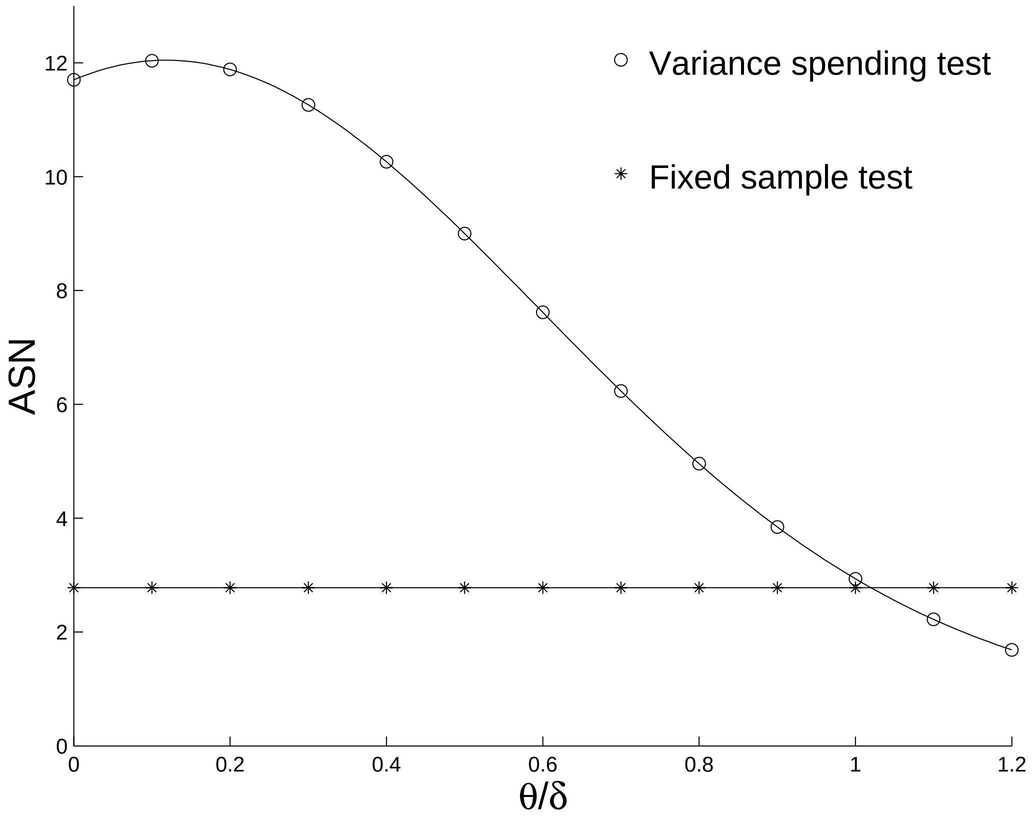


Figure 3. ASN curves of Variance Spending test and Fixed Sample test with power 0.9 at $\theta = 0.6\,\delta$.



ASN scale is in multiples of the original fixed sample size, n.

Inefficiency: Use of a non-sufficient statistic

Total sample size is $N = rn + \gamma(1-r)n$.

Ignoring randomness in γ, the final statistic has distribution

$$\{S_1 + \gamma^{-1/2}\, S_2'\}/\sqrt{n} \;\sim\; N([r + \gamma^{1/2}\{1-r\}]\sqrt{n}\theta, 1)$$

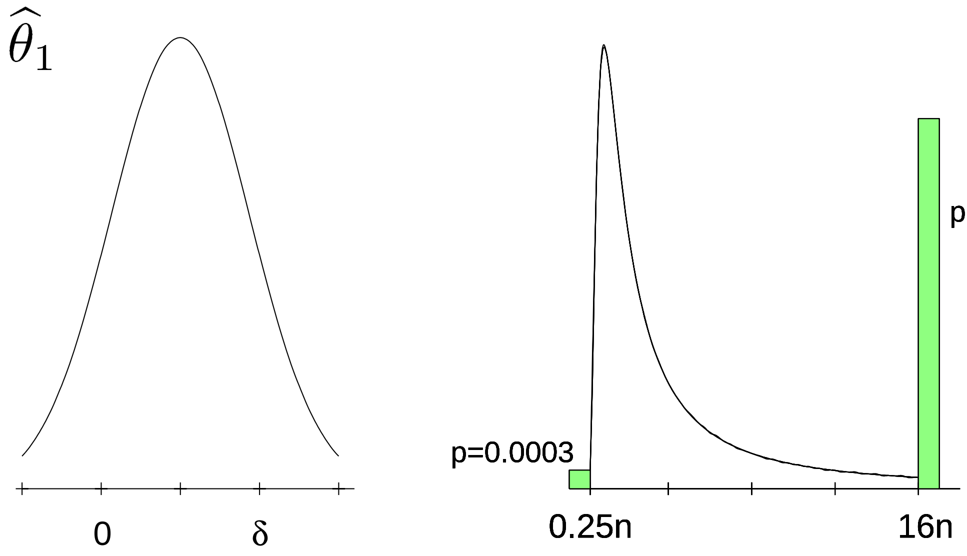
so the effective sample size is $N_{\textit{eff}} = (r + \gamma^{1/2}\{1-r\})^2 n$.

For $r = 1/2$, the “inefficiency” $N/N_{\textit{eff}}$ is:

γ	0	0.5	1	2	4	10	49	∞
Inefficiency	2	1.03	1	1.03	1.11	1.27	1.56	2

Inefficiency: Variable sample size, based on noisy $\widehat{\theta}_1$

For $\theta = 0.5\delta$



$N_{\textit{eff}}$

$E(N_{\textit{eff}})$
$= 6.17n$

A fixed sample test with $6.17n$ observations would have power 0.98.

The variance spending design gives power 0.85 at $\theta = 0.5\delta$.

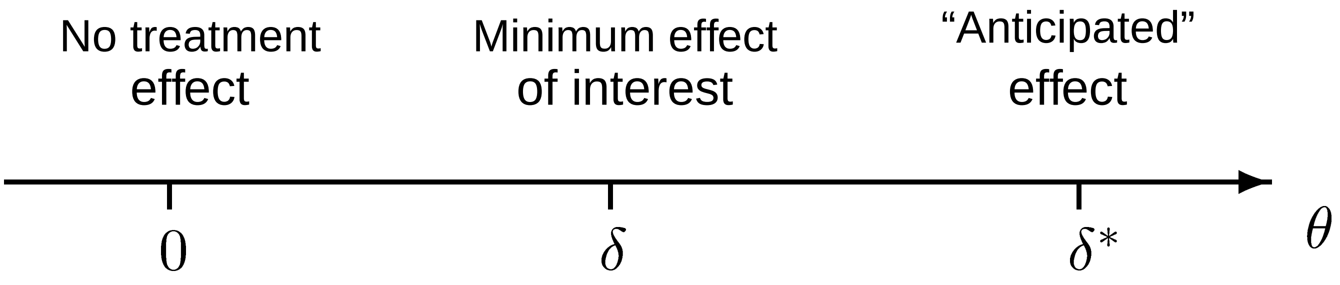
§4 Formulating the testing problem

Test H_0: $\theta = 0$ with:

Type I error rate α,

power $1 - \beta$ at $\theta = \delta$,

low ASN at $\theta = \delta^* \gg \delta$.



It should not be necessary to see $\widehat{\theta}_1 = \delta$ before realising a treatment effect of this size is (just) worth pursuing.

Group sequential setting

Analyse data after $n_1, n_2, \ldots, n_K$ observations, with early stopping to reject H_0: $\theta = 0$ or to accept H_0.

Standard group sequential test:

Fix targets for $n_1, \ldots, n_K$ — maybe not equally spaced.

Sequentially planned sequential test:

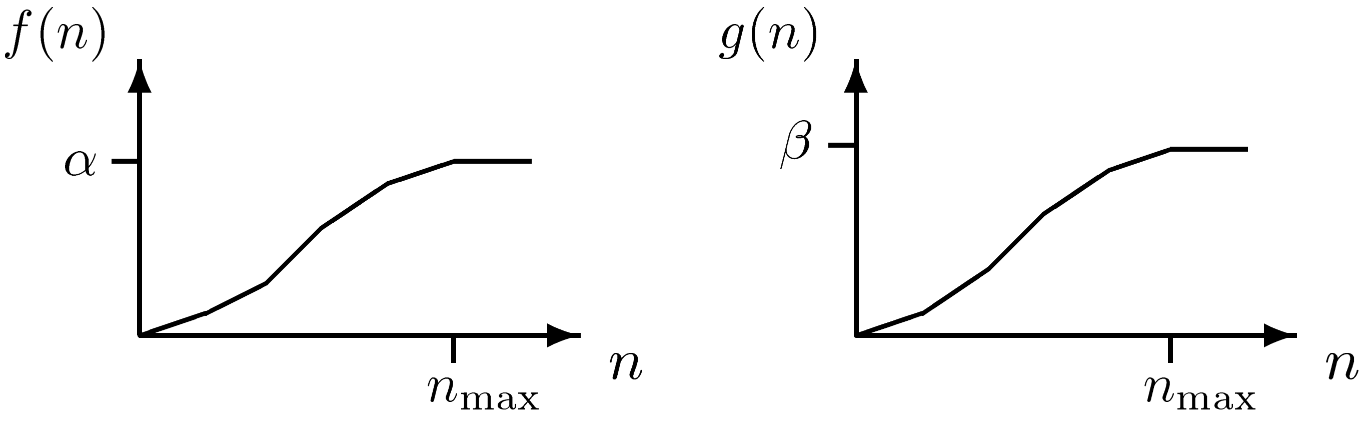
Allow n_k to depend on data at analysis $k - 1$ (Schmitz, Springer-Verlag, 1993) — as in adaptive tests.

Efficient tests

Optimal tests or families of efficient tests can be found within these frameworks (Barber & Jennison, *Bmka*, 2002).

§5 Group sequential tests

One-sided error spending tests: Functions $f(n)$ and $g(n)$ specify Type I and Type II error to spend when n observations have been observed.



At analysis k with cumulative sample size n_k, set boundaries so that

$$P_{\theta=0}\{\text{Reject } H_0 \text{ by analysis } k\} = f(n_k),$$

$$P_{\theta=\delta}\{\text{Accept } H_0 \text{ by analysis } k\} = g(n_k).$$

Power family of error spending tests

Take

$$f(n) = \begin{cases} \alpha \left(\frac{n}{n_{\max}} \right)^{\rho} & n < n_{\max} \\ \alpha & n \geq n_{\max} \end{cases}$$

$$g(n) = \begin{cases} \beta \left(\frac{n}{n_{\max}} \right)^{\rho} & n < n_{\max} \\ \beta & n \geq n_{\max} \end{cases}$$

Choose $n_{\max}$ so that boundaries meet up at $n = n_{\max}$ for, say, K equally sized groups.

Setting $\rho = 1$ gives a boundary similar to a Pocock test,

$\rho = 3$ approximates an O'Brien & Fleming test.

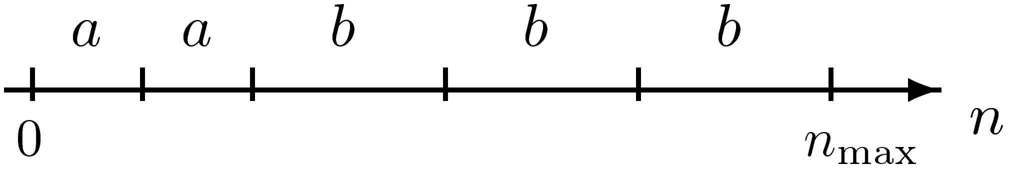
Attaining low ASN under high values of θ

Values $\rho = 1$ or $\rho = 0.75$ spend error at a high rate early on.

Also, a few *very* early analyses are desirable.

1. *Small groups / large groups*

M groups of a observations, followed by $K - M$ groups of size b.



2. *Geometric pattern*

$$n_k = \gamma^{K-k}\, n_{\max} \quad (\gamma < 1)$$

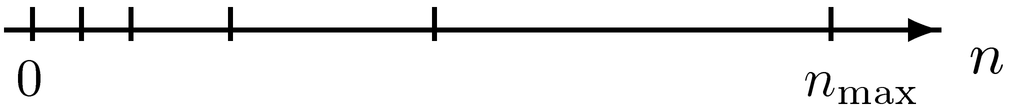


Figure 4. Five group, one-sided error spending test with $\rho = 1$. Type I error rate is 0.025 and power 0.9 is attained at $\theta = 0.33\,\delta$.

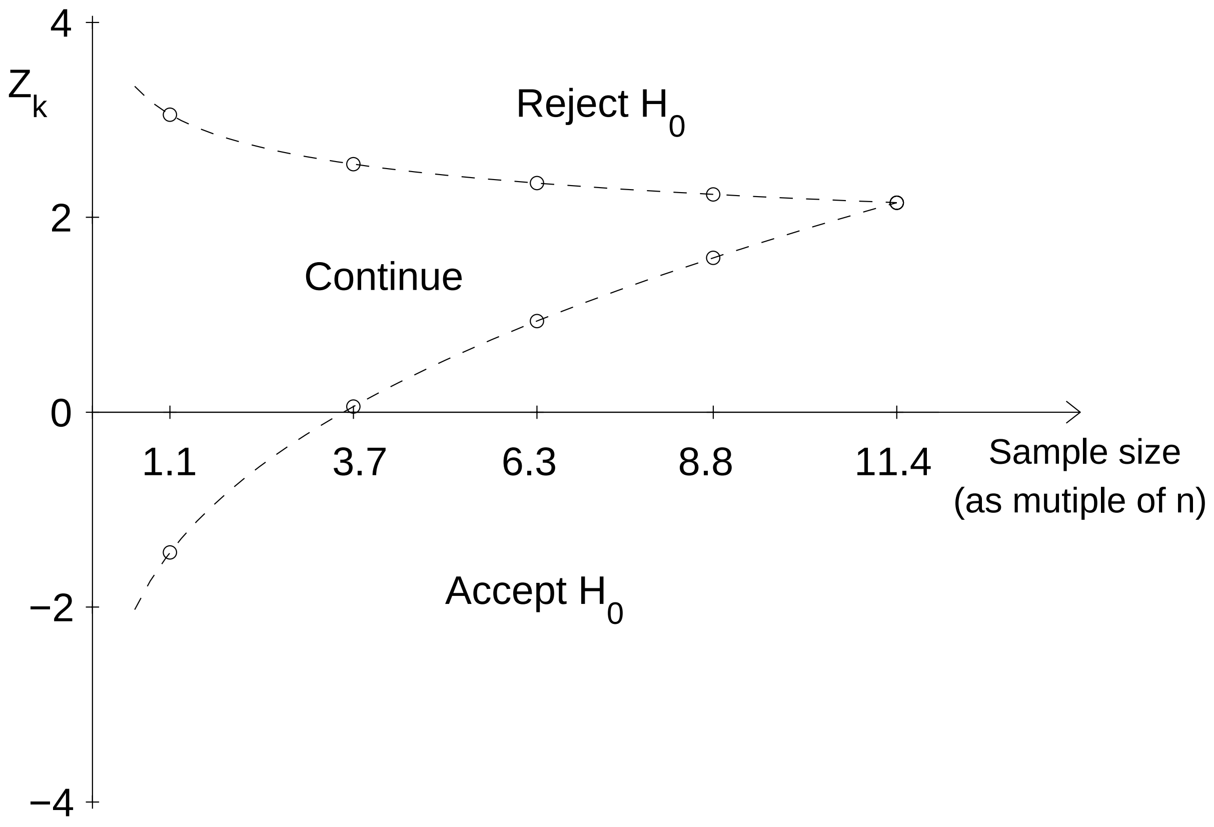


Figure 5. Power functions of Variance Spending test and 5 Group test with power 0.9 at $\theta = 0.33\,\delta$.

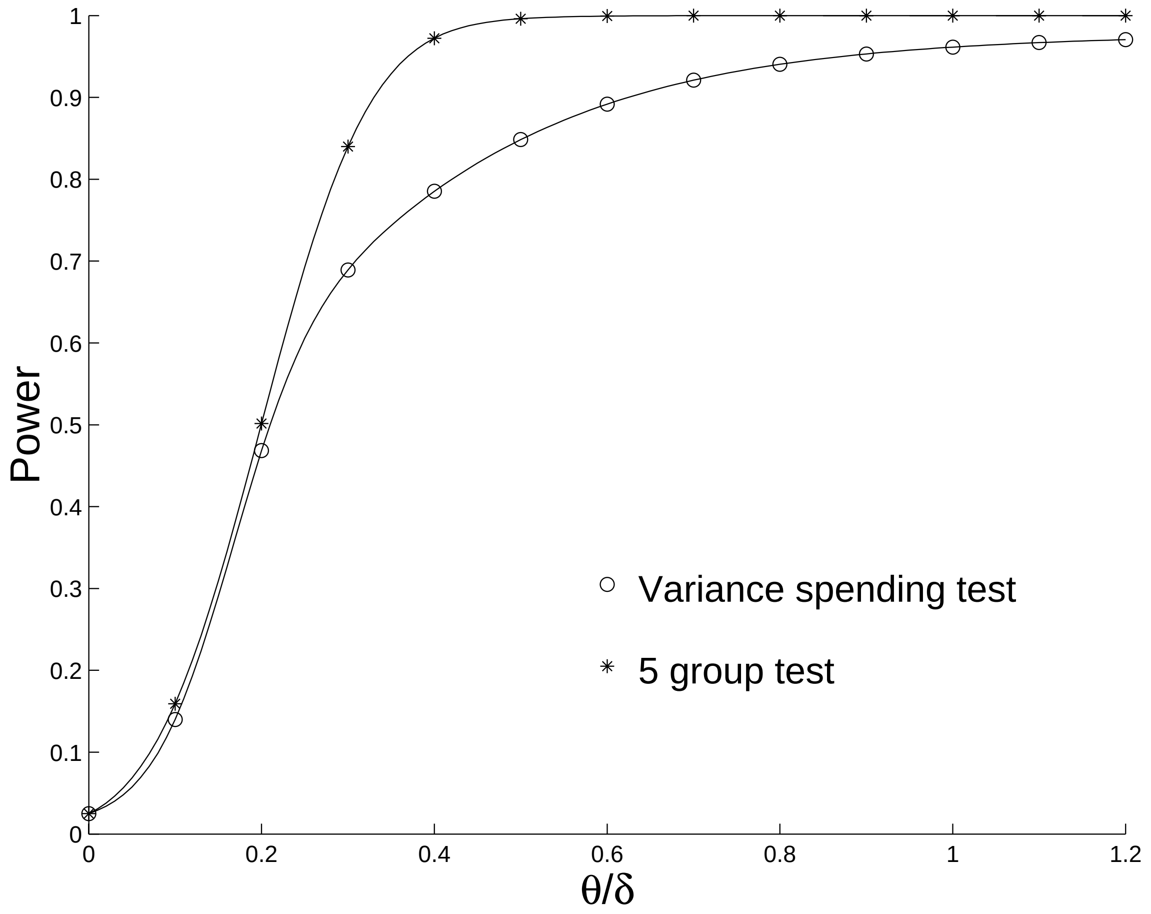
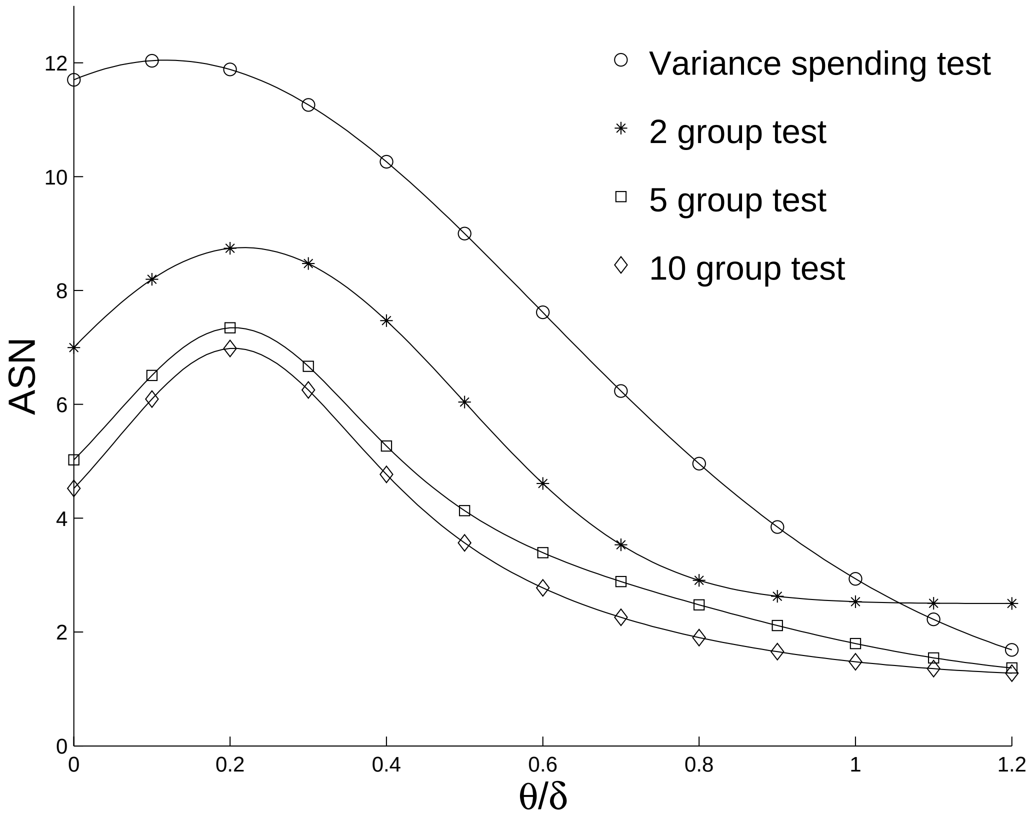


Figure 6. ASN curves of Variance Spending test and 2, 5 and 10 Group tests with power 0.9 at $\theta = 0.33\,\delta$.



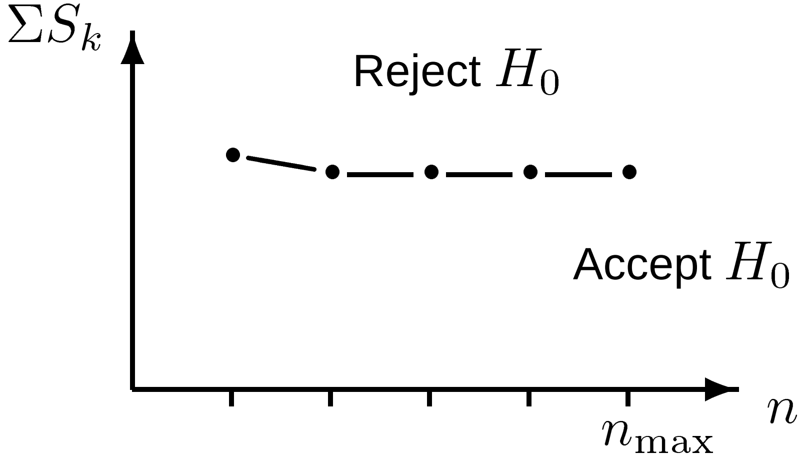
ASN scale is in multiples of the original fixed sample size, n.

§6 Example 2: A Cui, Hung & Wang (1999) design

Original group sequential design:

To test H_0: $\theta = 0$ with Type I error rate 0.025 and power 0.9 at $\theta = \delta$.

Observations taken in 5 groups; early stopping allowed to *reject* H_0.



$n_{\max} = 10.8/\delta^2$, cf fixed sample size, $n = 10.5/\delta^2$.

Design modification

Cui et al suggest adjusting the design at just one interim analysis.

Changing design at stage 3:

Group 4

Original plan: $S_4 =$ sum of $n/5$ terms $(X_{Ai} - X_{Bi})$

Revised plan: $S'_4 =$ sum of $\gamma\, n/5$ terms $(X_{Ai} - X_{Bi})$

Use $\gamma^{-1/2}\, S'_4$ in place of S_4, preserving the null distribution.

Group 5 — similarly.

Example

As in Example 1, aim for the effective sample size needed in the original test to attain power 0.9 at $\theta = \widehat{\theta}_1$.

At the 3rd analysis of 5, fraction of the total sample size is $r = 0.6$.
Set $\tilde{\xi} = \delta/\widehat{\theta}_1$ truncated to the range $(0.6, 3)$.

Then

$$\gamma(\widehat{\theta}_1) \; = \; \frac{\{\tilde{\xi}(\widehat{\theta}_1) - 0.6\}^2}{(1-0.6)^2}.$$

Hence $\gamma \; \in \; (0, 36)$ and total sample size $\in \; (0.6n, \; 15n)$.

Figure 7. Power functions of Cui et al 5 Group Adaptive test and Fixed Sample test with power 0.9 at $\theta = \delta$.

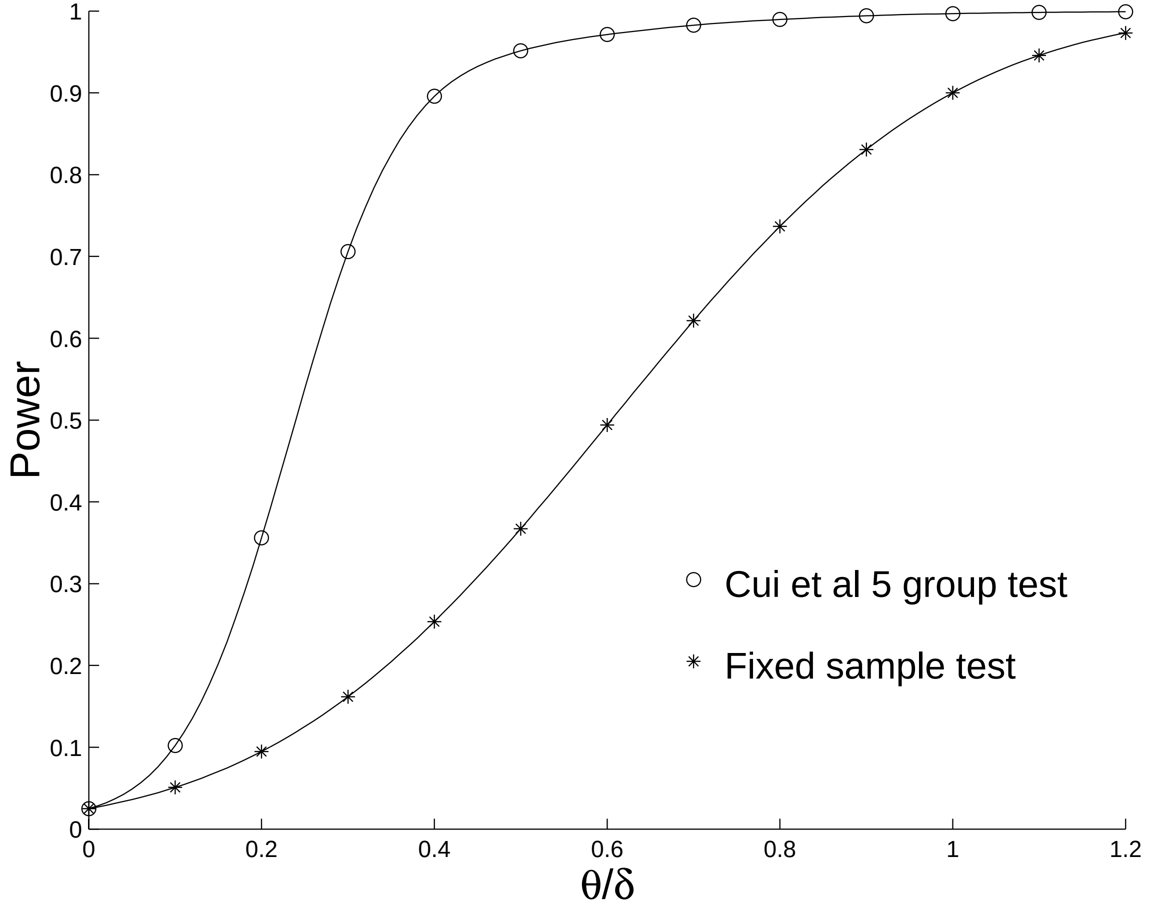
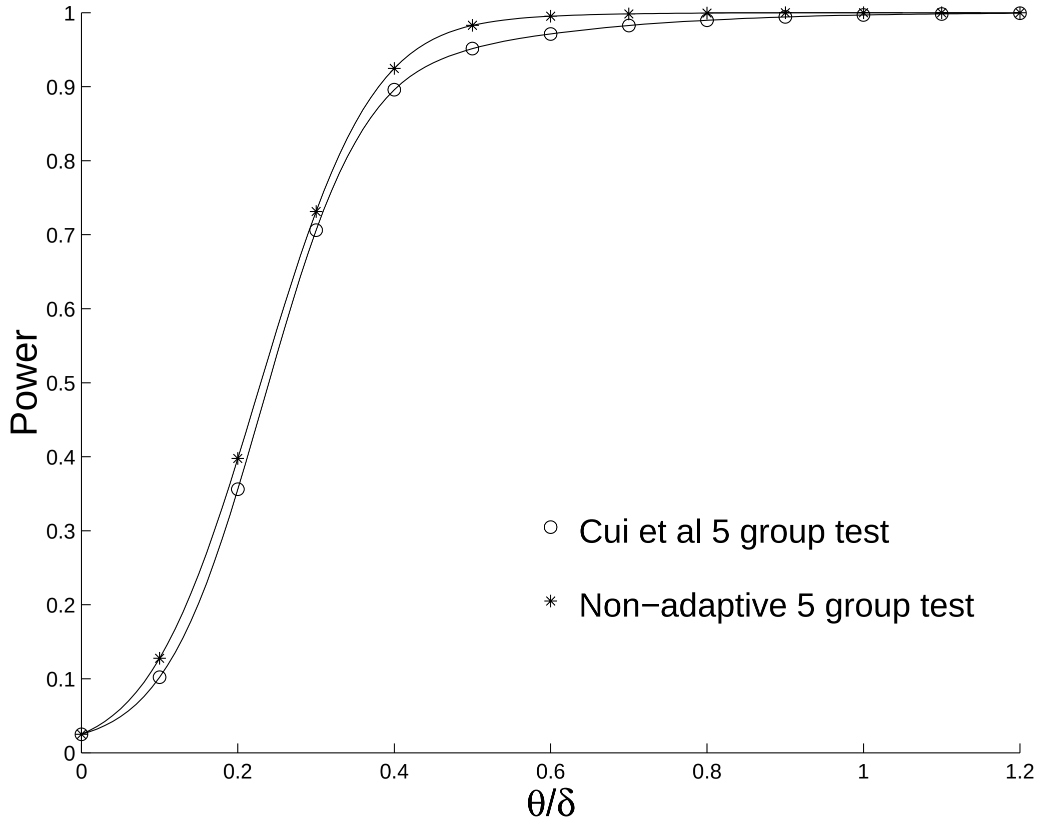
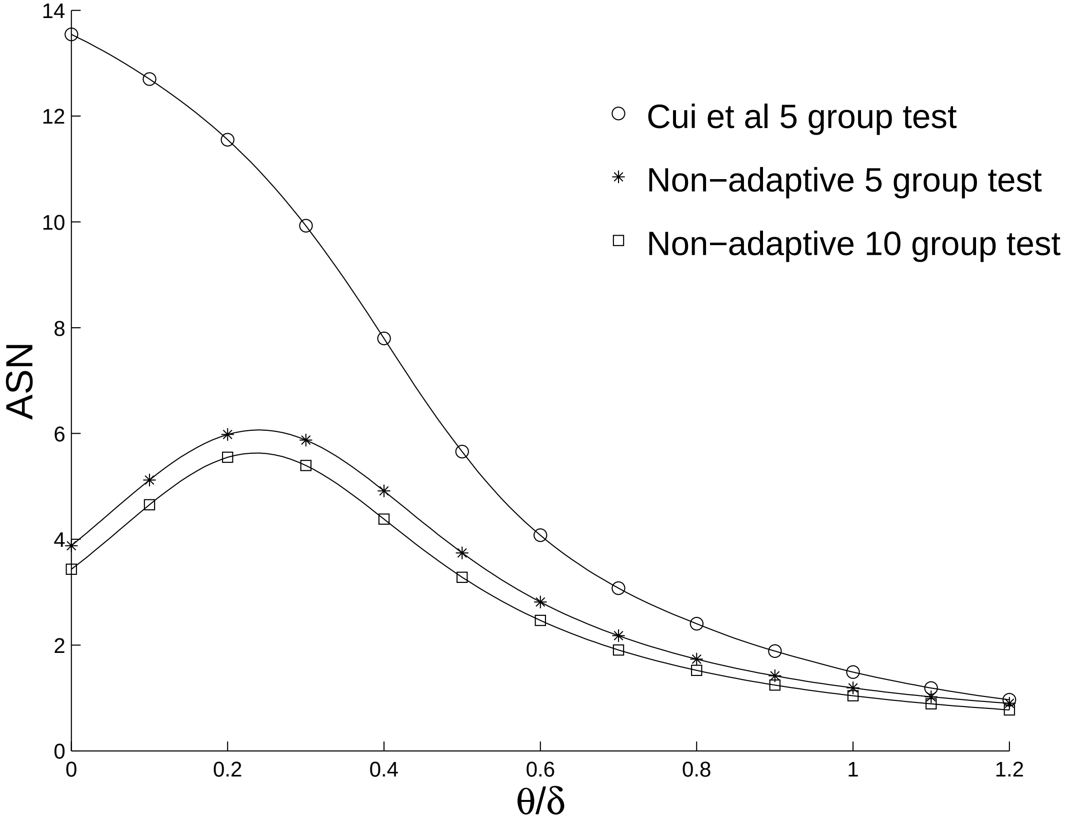


Figure 8. Power functions of Cui et al 5 Group Adaptive test and Non-Adaptive 5 Group test with power 0.9 at $\theta = 0.38\,\delta$.



The non-adaptive test is a ρ-family error spending test with $\rho = 0.75$.

Figure 9. ASN curves of Cui et al 5 Group Adaptive test and Non-Adaptive 5 and 10 Group tests with power 0.9 at $\theta = 0.38\,\delta$.



ASN scale is in multiples of the original fixed sample size, n.

Example 3: Shen & Fisher (*Biometrics,* 1999) designs

Testing H_0: $\theta = 0$ with Type I error rate α.

Initially calculate the total sample size N_1 giving power $1 - \beta$ at $\theta = \delta$.

Collect observations in blocks of pre-specified size,

e.g., $B_1 = N_1/2$, $B_2 = B_3 = \ldots = N_1/6$.

Data in block j provide $Z_j \sim N(0, 1)$ under H_0.

Allocate block j a weight w_j, dependent on data in blocks $1, \ldots, j-1$.

When $\sum_1^m w_j^2 = 1$, the sum $\sum_1^m w_j Z_j \sim N(0,1)$ under H_0,

so reject H_0 if $\sum_1^m w_j Z_j \geq z_\alpha$.

Shen & Fisher designs

Weights and Stopping Rule

Before sampling block j, compute target additional sample size N_j

if $B_j \geq N_j$, make this the last block, setting

$$w_j^2 = 1 - \sum_{i=1}^{j-1} w_i^2,$$

otherwise, set (say)

$$w_j^2 = \frac{B_j}{N_j}\left(1 - \sum_{i=1}^{j-1} w_i^2\right).$$

Shen & Fisher designs

Stopping to accept H_0

Stop for “futility” after block j if $\widehat{\theta}_j$ is low.

Version (1): compare $\widehat{\theta}_j$ with δ.

Version (2): compare $\widehat{\theta}_j$ with $\tilde{\delta}$ ($\tilde{\delta} < \delta$).

Figure 10. Power functions of Shen & Fisher Adaptive test (1) and Fixed Sample test with power 0.9 at $\theta = \delta$.

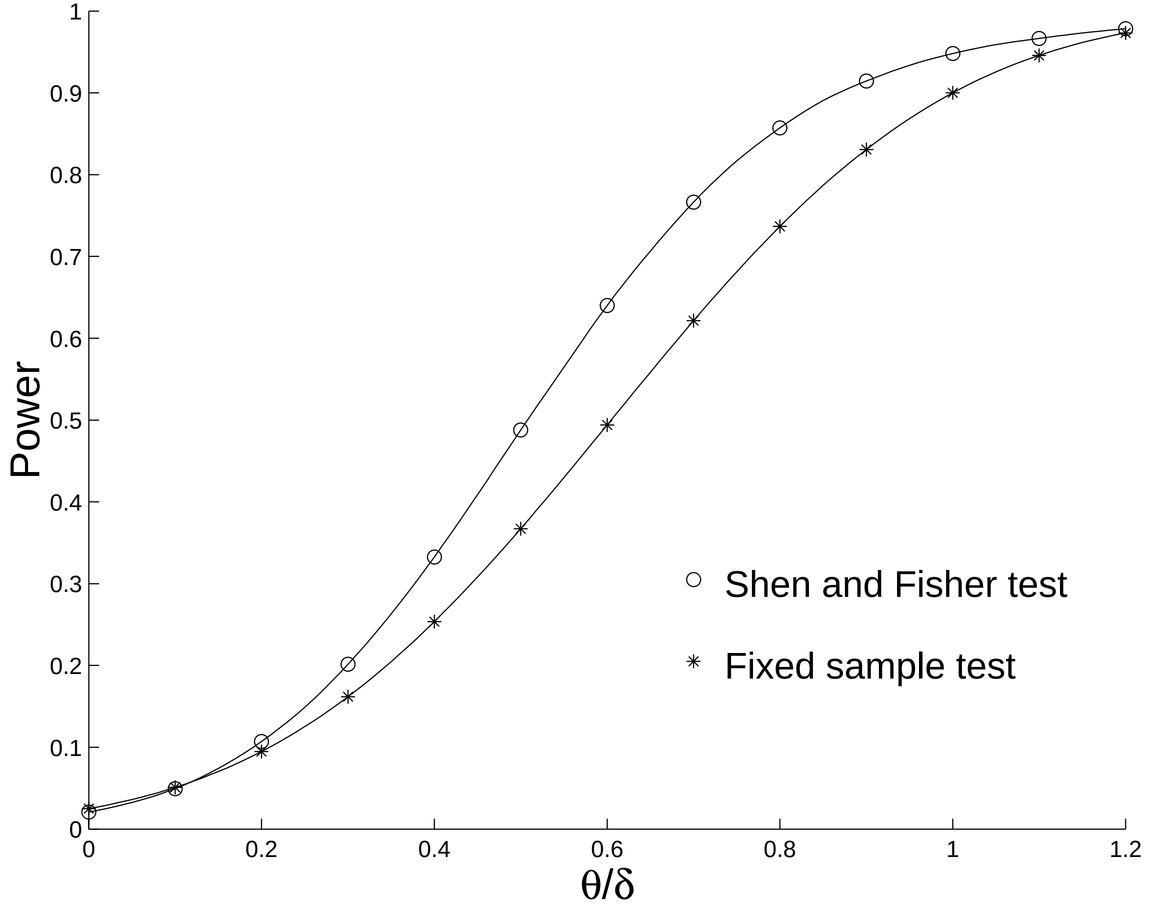
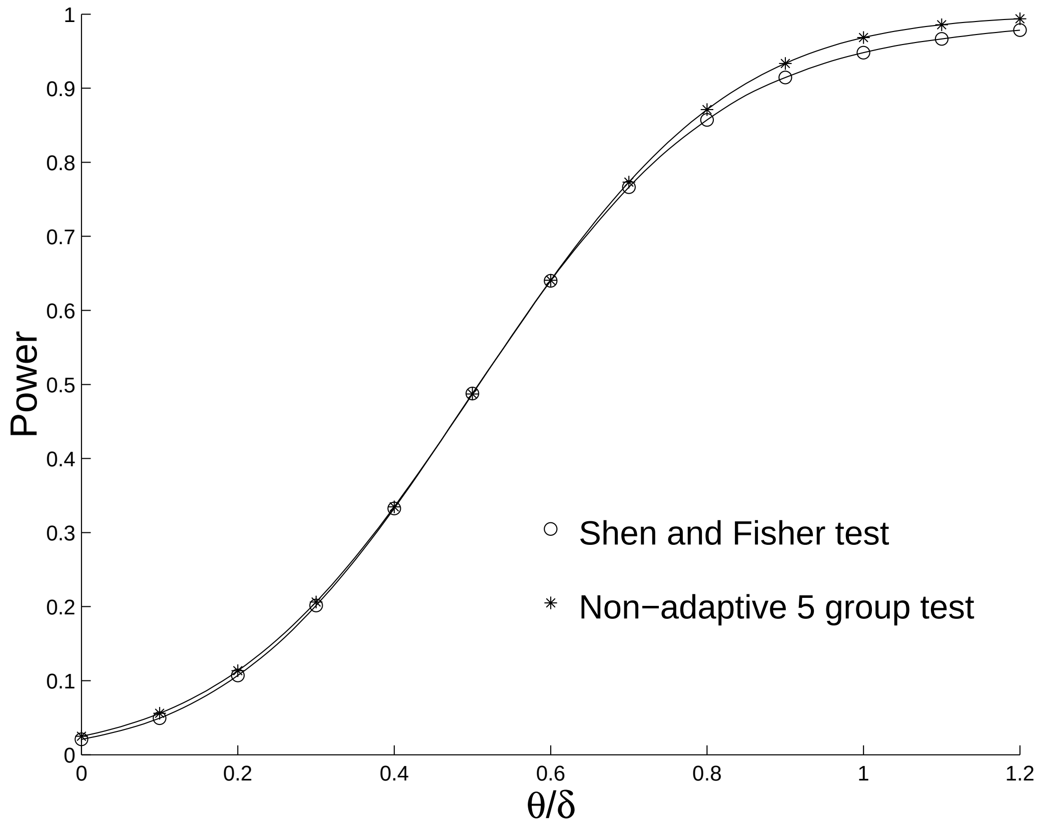
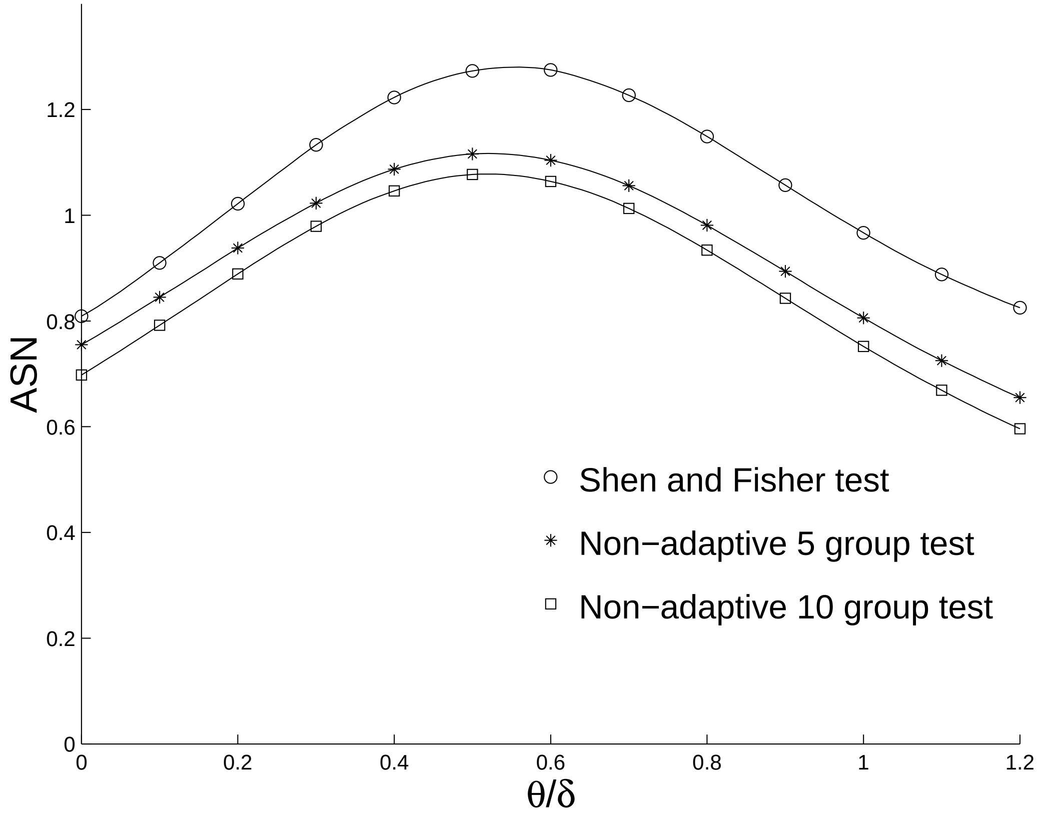


Figure 11. Power functions of Shen & Fisher Adaptive test (1) and Non-Adaptive 5 Group test with power 0.9 at $\theta = 0.84\,\delta$.



The non-adaptive test is a ρ-family error spending test with $\rho = 1$.

Figure 12. ASN curves of Shen & Fisher Adaptive test (1) and Non-Adaptive 5 and 10 Group tests with power 0.9 at $\theta = 0.84\,\delta$.



ASN scale is in multiples of the original fixed sample size, n.

Figure 13. Power functions of Shen & Fisher Adaptive test (2) and Fixed Sample test with power 0.9 at $\theta = \delta$.

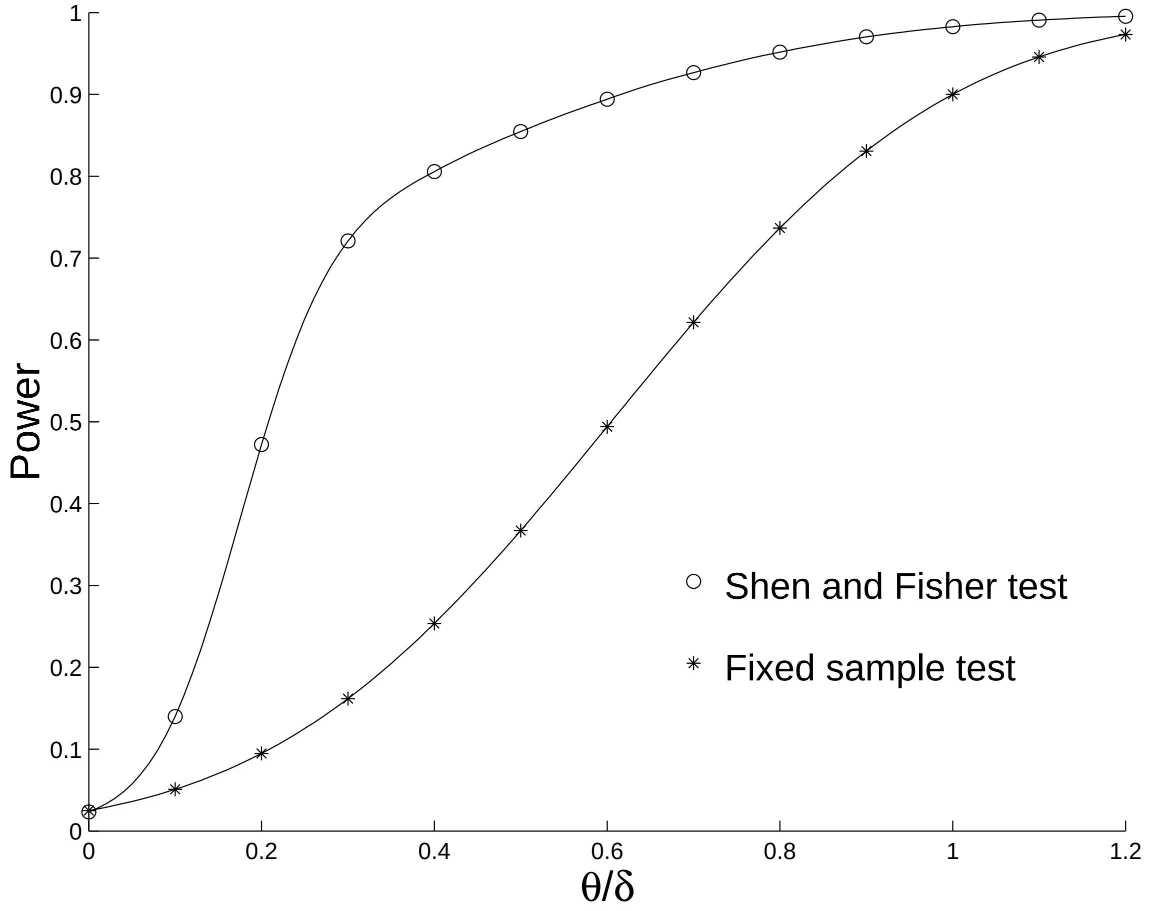
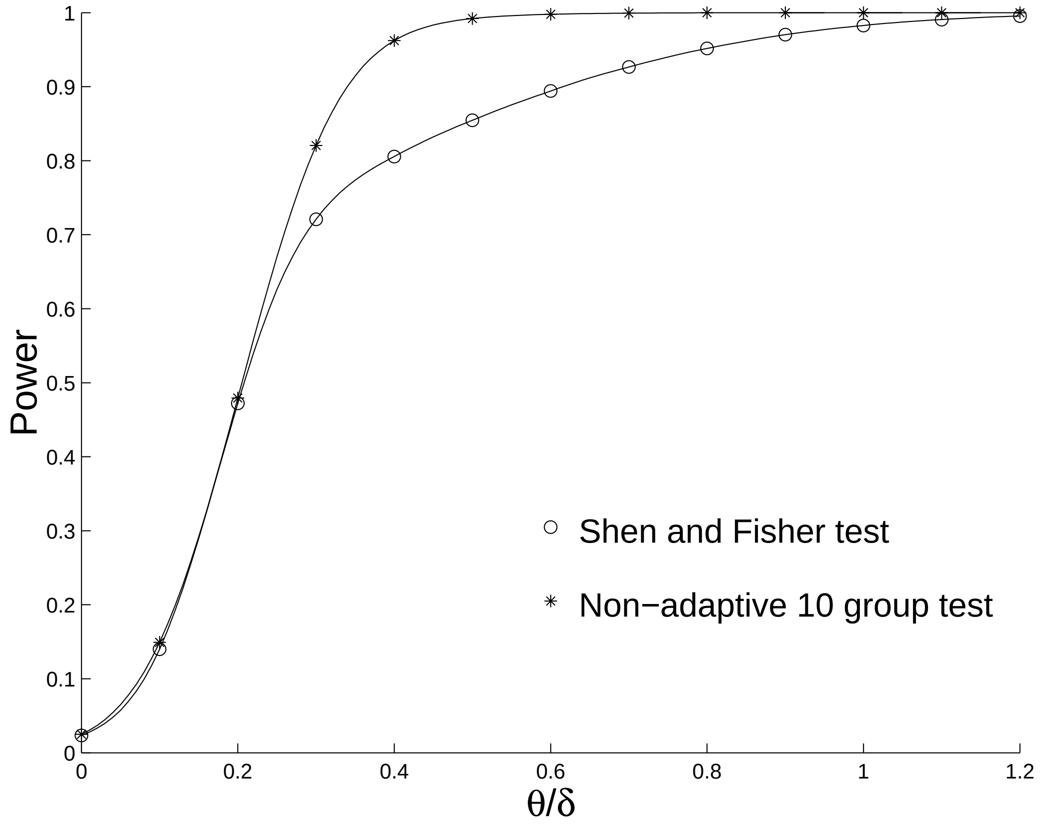
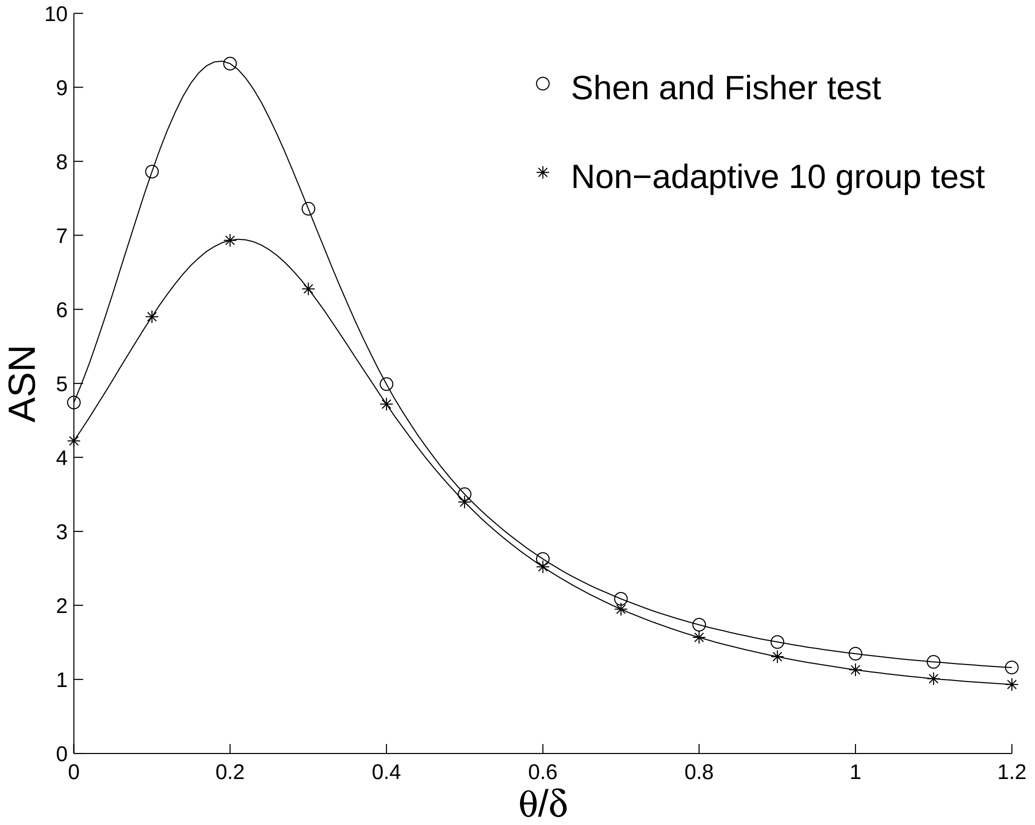


Figure 14. Power functions of Shen & Fisher Adaptive test (2) and Non-Adaptive 10 Group test with power 0.9 at $\theta = 0.34\,\delta$.



The non-adaptive test is a ρ-family error spending test with $\rho = 0.75$.

Figure 15. ASN curves of Shen & Fisher Adaptive test (2) and Non-Adaptive 10 Group test with power 0.9 at $\theta = 0.34\,\delta$.

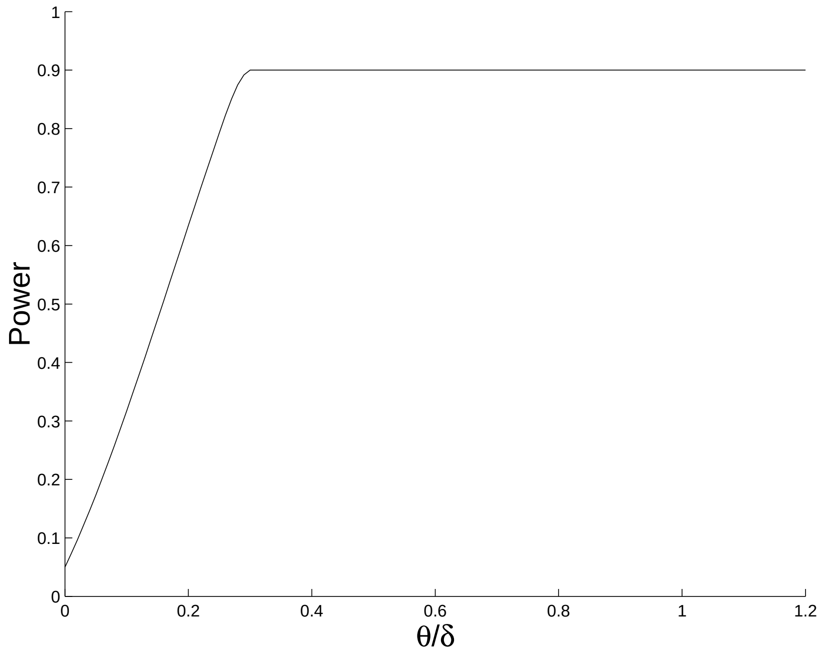


ASN scale is in multiples of the original fixed sample size, n.

Setting power: Philosophy?

Shen and Fisher (1999) refer to setting power $1 - \beta$ at effect size δ where δ is an *estimate* of θ.

This implies a target power function of the following form (!)



Conclusions

- It is possible to rescue a study found, at an interim stage, to be lacking in power — but the flexibility to do this has a price.
- Better practice is to

  think through power requirements fully

  specify θ values at which low sample size is most important

  before embarking on a study.
- Standard types of non-adaptive group sequential tests meet these needs effectively and provide easily interpretable results.
- A little planning can save a lot in sample size and credibility!