Stopping rules for sequential trials in high-dimensional data

Sonja Zehetmayer, Alexandra Graf, and Martin Posch

Center for Medical Statistics, Informatics and Intelligent Systems
Medical University of Vienna

Supported by FWF - Funds Nr. T401 and P23167
Hunting for significance inflates the probability of a false positive result

\[ \alpha = 0.05 \]
Hunting for significance inflates the probability of a false positive result

\[ \alpha = 0.05 \]
Hunting for significance inflates the probability of a false positive result
Hunting for significance inflates the probability of a false positive result

\[ \alpha = 0.05 \]
Conclusion I

- Testing a single hypothesis repeatedly at several interim analyses at level $\alpha$ ("Hunting for significance"), increases the probability of a false positive result.
- Solution: Group sequential tests: adjust $\alpha$

What about very many hypotheses?
Many hypotheses

- \( m \) hypotheses (genes), e.g., microarray study

\[ H_{0i}: \mu_i = 0 \quad \text{versus} \quad H_{1i}: \mu_i \neq 0, \quad i=1,...,m \]
The False Discovery Rate (FDR)
Benjamini and Hochberg, 1995

\[
FDR = E\left( \frac{V}{\max\{R, 1\}} \right)
\]

\(V\) : number of erroneously rejected null hypotheses

\(R\) : number of rejected null hypotheses

FDR of the experiment is controlled according to Benjamini and Hochberg (1995)

- Order the individual p-values \(p_{(1)} \leq \ldots \leq p_{(m)}\)
- \(d = \arg\max_i \{p_{(i)} \leq i\alpha/m\}\)
- Reject all hypotheses with p-values \(p_{(1)} \ldots p_{(d)}\)

This is a conservative procedure for controlling the FDR if the test statistics are independent or positively dependent (Benjamini and Yekutiel, 2001)
Analysis controlling the FDR at level $\alpha$

1 spot $\overset{\wedge}{=} 1$ hypothesis
Stopping rules for sequential trials in high-dimensional data

Analysis controlling the FDR at level $\alpha$

Stop the experiment.
Reject all significant hypotheses.
Retain all others.

$1$ spot $\hat{}$ $1$ hypothesis
Stopping rules for sequential trials in high-dimensional data

S. Zehetmayer, A. Graf, and M. Posch

Analysis controlling the FDR at level $\alpha$

Stop the experiment.
Reject all significant hypotheses.
Retain all others.

1 spot $\hat{=} 1$ hypothesis

Analysis controlling the FDR at level $\alpha$
for pooled data
Stopping rules for sequential trials in high-dimensional data

S. Zehetmayer, A. Graf, and M. Posch

Stop the experiment.
Reject all significant hypotheses.
Retain all others.

Analysis controlling the FDR at level $\alpha$

Stop ...
Reject ...
Retain ...

Analysis controlling the FDR at level $\alpha$ for pooled data

1 spot $\overset{\wedge}{=} 1$ hypothesis
Stopping rules for sequential trials in high-dimensional data

S. Zehetmayer, A. Graf, and M. Posch

Analysis controlling the FDR at level $\alpha$

Stop the experiment.
Reject all significant hypotheses.
Retain all others.

1 spot $\rightarrow$ 1 hypothesis

Analysis controlling the FDR at level $\alpha$ for pooled data

Stop ...
Reject ...
Retain ...

1 2 3 4 5

6 7 8 9 10

11 12
At the end, only the significant hypotheses from the final stage can be rejected!
What is the effect of unadjusted repeated analyses on the FDR?
What is the effect of unadjusted repeated analyses on the FDR?

Depends on the number of true null hypotheses $m_0$:

- In case of $m_0/m < 1$:
  For $m \to \infty$, the FDR is controlled asymptotically regardless of the stopping stage (under suitable assumptions).

- In case of $m_0/m = 1$ (global $H_0$):
  A constraint on the stopping rule has to be imposed:
  Stop early only if at least a certain number $s(m)$ of hypotheses can be rejected.
  Then early stopping hardly occurs.

Then the FDR is controlled asymptotically
(Posch, Zehetmayer, Bauer, 2009)
Stopping the experiment

<table>
<thead>
<tr>
<th>Stopping for futility</th>
<th>Early rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Futility boundary $\alpha_1 &gt; \alpha$</td>
<td>- Proportion of rejected H0</td>
</tr>
<tr>
<td></td>
<td>- $\Delta$ Proportion of rejected H0</td>
</tr>
<tr>
<td></td>
<td>- False Negative Rate</td>
</tr>
<tr>
<td></td>
<td>- $\Delta$ False Negative Rate</td>
</tr>
<tr>
<td></td>
<td>- False Non Discovery Rate</td>
</tr>
<tr>
<td></td>
<td>- Concordance</td>
</tr>
<tr>
<td>(and at least $s(m)$ hypotheses can be rejected)</td>
<td></td>
</tr>
</tbody>
</table>

Stopping rules for sequential trials in high-dimensional data

S. Zehetmayer, A. Graf, and M. Posch
Stop as soon as the FNR is < 20%
e.g., Zehetmayer & Posch (2010)

- Multiple Type II Error
- Expected proportion of not-rejected true alternative hypotheses among all true alternative hypotheses

\[
FNR = E \left( 1 - \frac{R - V}{m - m_0} \right)
\]

- \( R \): # of rejections
- \( V \): # of false rejections
- \( m \): # of hypotheses
- \( m_0 \): # of true null hypotheses
In each stage $k$ the \textit{FNR} is estimated from the data

- $\gamma$: critical value from the FDR-controlling procedure
- The p-values corresponding to the true null hypotheses are uniformly distributed.

\[
FNR_k = E\left(1 - \frac{R_k - V_k}{m - m_0}\right) = 1 - \frac{E(R_k) - m_0 \gamma_k}{m - m_0}
\]

- $\hat{m}_{0k}$: estimator for $m_0$
- $R_k(\gamma) = \#\{p_{ik} < \gamma_k\}$

\[
\hat{FNR}_k = 1 - \frac{R_k(\gamma_k) - \hat{m}_{0k} \gamma_k}{m - \hat{m}_{0k}}
\]
Stop as soon as $\Delta FNR < 0.05$

- $\Delta FNR$ is based on the increment of the stagewise FNR:
  $$\Delta FNR_k = FNR_k - FNR_{k-1}$$
  with $FNR_0 = 1$.

- In each stage $\Delta FNR$ is estimated as described before:
  $$\Delta FNR_k = \widehat{FNR}_k - \widehat{FNR}_{k-1}$$
Stop as soon as the concordance of the rejected hypotheses from stage to stage > 0.9

- Concordance (CO) measures the proportion of significant genes in stage $k$ which were also significant in stage $k-1$:

$$CO_k = \sum_i (H_{ir_{k-1}} H_{ir_k}) / \sum_i H_{ir_k}$$

where $H_{ir_k} = 1$ if hypothesis $i$ was significant in stage $k$ and 0 else with $CO_1=0$. 
Example: $m_0/m=0.9, \mu/\sigma=0.5$

True FNR for different sample sizes: Theoretical curve
Example: $m_0/m = 0.9, \mu/\sigma = 0.5$

True $\Delta FNR$ for different sample sizes: Theoretical curve
Example: $m_0/m = 0.9$, $\mu/\sigma = 0.5$

True CO for different sample sizes: Theoretical curve

Stopping rules for sequential trials in high-dimensional data

S. Zehetmayer, A. Graf, and M. Posch
Simulation study (50000 runs)

The setting:
- $m=5000 / 50000$
- $m_0/m=0.9, \mu/\sigma=0.5$
- 10 stages with stage-wise sample sizes of 5
- z-tests, $\alpha=0.05$
- Stopping rules: FNR<0.2, $\Delta$FNR<0.05, CO>0.9, $s(m)>9$
Simulation study (50000 runs)

The setting:
- \( m = 5000 / 50000 \)
- \( m_0/m = 0.9, \mu/\sigma = 0.5 \)
- 10 stages with stage-wise sample sizes of 5
- \( z \)-tests, \( \alpha = 0.05 \)
- Stopping rules: FNR<0.2, \( \Delta \)FNR<0.05, CO>0.9, \( s(m) > 9 \)

<table>
<thead>
<tr>
<th>Independent data</th>
</tr>
</thead>
<tbody>
<tr>
<td>The FDR is controlled at level ( \alpha = 0.05 ) for the 3 considered stopping criteria.</td>
</tr>
</tbody>
</table>
Simulation study (50000 runs)

The setting:

- \( m=5000 / 50000 \)
- \( m_0/m=0.9, \mu/\sigma=0.5 \)
- 10 stages with stage-wise sample sizes of 5
- z-tests, \( \alpha = 0.05 \)
- Stopping rules: FNR<0.2, \( \Delta \)FNR<0.05, CO>0.9, \( s(m)>9 \)

<table>
<thead>
<tr>
<th>Independent data</th>
<th>Equi-correlated data (( \rho = 0.5 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>The FDR is controlled at level ( \alpha = 0.05 ) for the 3 considered stopping criteria.</td>
<td>The FDR is controlled at level ( \alpha = 0.05 ) for the 3 considered stopping criteria.</td>
</tr>
</tbody>
</table>
Independent data

Equi-correlated data

Stopping rules for sequential trials in high-dimensional data

S. Zehetmayer, A. Graf, and M. Posch
Stopping rules for sequential trials in high-dimensional data

S. Zehetmayer, A. Graf, and M. Posch

Independent data

Equi-correlated data

Stopping stage

m=5000  m=50000  m=5000  m=50000

FNR

ΔFNR
Stopping rules for sequential trials in high-dimensional data

S. Zehetmayer, A. Graf, and M. Posch

**Independent data**

**Equi-correlated data**

![Box plots for FNR, ΔFNR, and CO for different stopping stages and data types](image)

- **FNR**
  - m=5000
  - m=50000

- **ΔFNR**
  - m=5000
  - m=50000

- **CO**
  - m=5000
  - m=50000
Stopping rules for sequential trials in high-dimensional data

**Independent data**

**Equi-correlated data**

- FNR
- ΔFNR

**Actual FNR when FNR is < 0.2**

- m=5000
- m=50000
- m=5000
- m=50000

S. Zehetmayer, A. Graf, and M. Posch
The Family Wise Error Rate

- Replace the BH procedure by the Bonferroni test
- If no multiplicity adjustment for the repeated looks is applied, the FWER may be inflated (Armitage, 1969)
- If stopping rules are applied, that are asymptotically deterministic, the sequential procedure controls the FWER
  - Reason: The sequential procedure degenerates to a fixed sample size procedure

- For the considered stopping rules and scenarios the FWER is controlled at level $\alpha = 0.05$. 
Outlook

- Muralidharan (2010) considered an empirical bayes mixture method for effect size estimation (mean values and standard deviations)
- We try to apply the estimated values for a power estimation.

\[
\text{Power}\left(\text{reject} \mid \text{effect sizes} > \Delta\right)
\]
Is it necessary to adjust for the number of looks?

- If the number of hypotheses is very large, multiple analyses hardly inflate the error rate.

Is this the solution to the sequential problem?

There are limitations

- Result applies only for large $m$
- Convergence rate depends on $m_0/m$ and the alternative
- Appropriate stopping rules
- Increment - Rules seem to work better – however the performance depends on the stage-wise sample size
Selected References

- Pawitan et al. (2005) Bioinformatics.