MEDICAL UNIVERSITY OF VIENNA

Stopping rules for sequential trials in high-dimensional data

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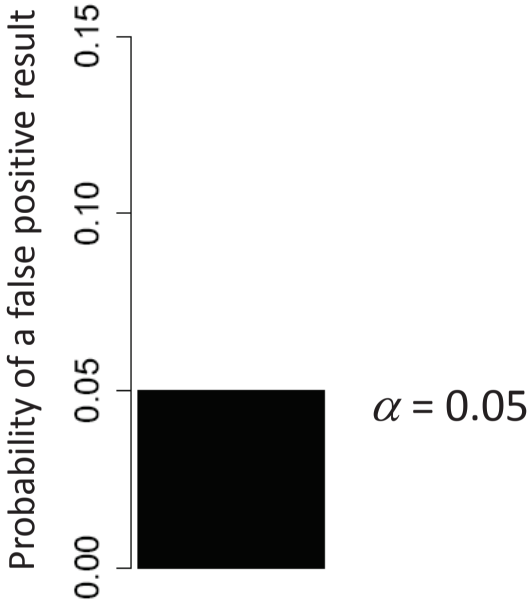
Hunting for significance inflates the probability of a false positive result



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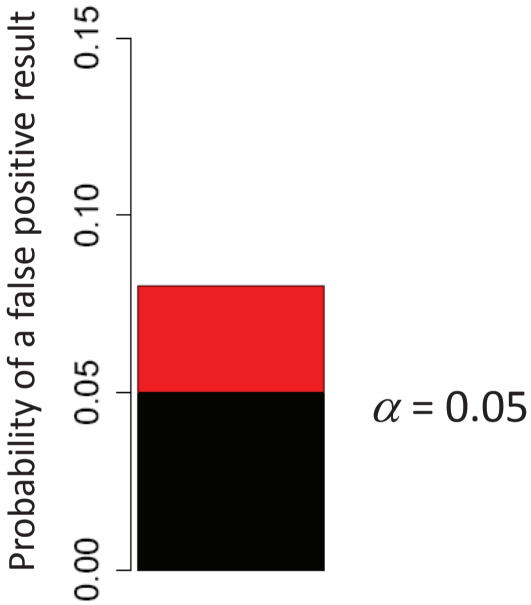

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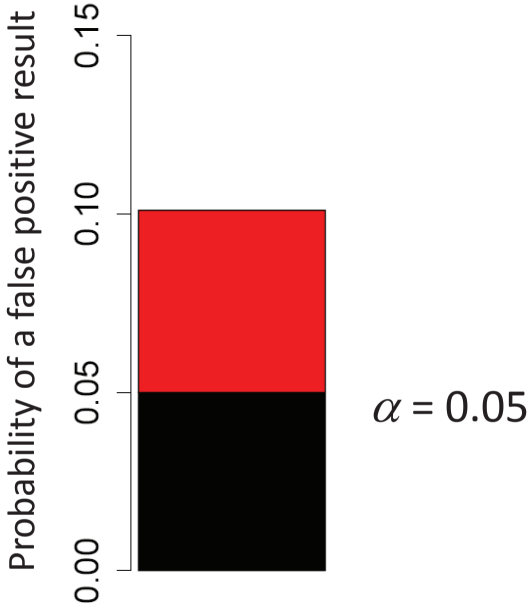

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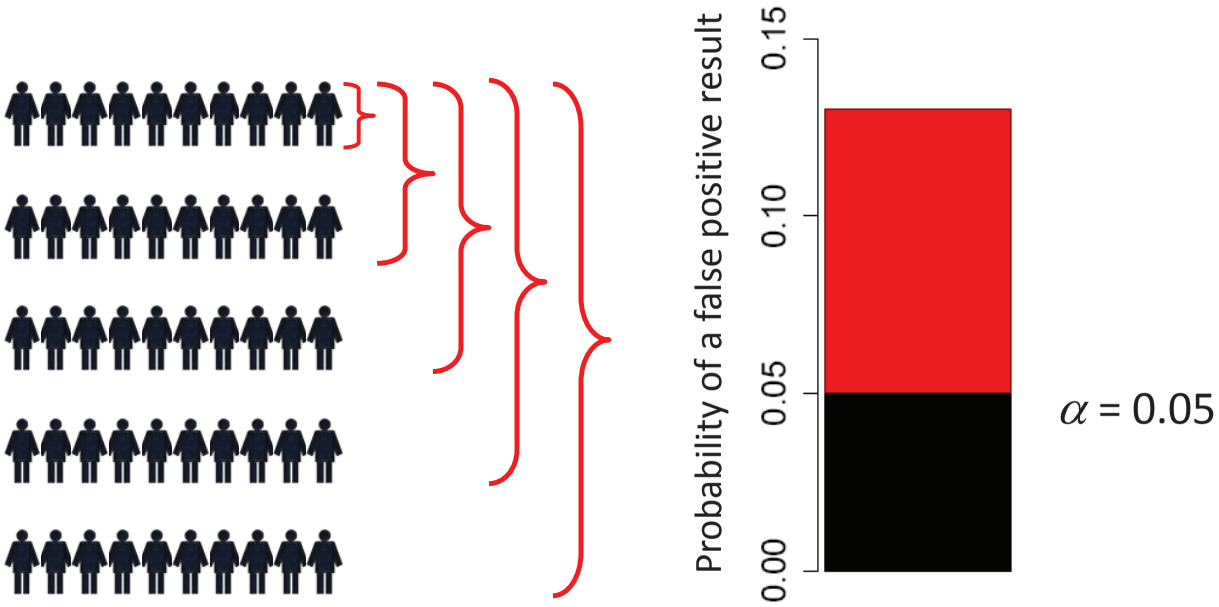


Conclusion I

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

What about very many hypotheses?

Many hypotheses

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

$$H_{0i}: \mu_i = 0 \quad \text{versus} \quad H_{1i}: \mu_i \neq 0, \qquad i=1,\ldots,m$$

The False Discovery Rate (FDR)

Benjamini and Hochberg, 1995

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

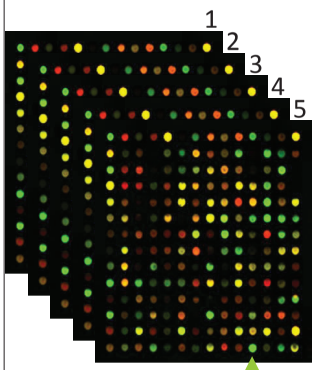
V : number of erroneously rejected null hypotheses

R : number of rejected null hypotheses

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

- Order the individual p-values $p_{(1)} \leq \ldots \leq p_{(m)}$
- $d = \text{argmax}_i \{p_{(i)} \leq i\alpha/m\}$
- 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 Yekutieli, 2001)



Analysis controlling the FDR at level α

1 spot $\hat{=}$ 1 hypothesis

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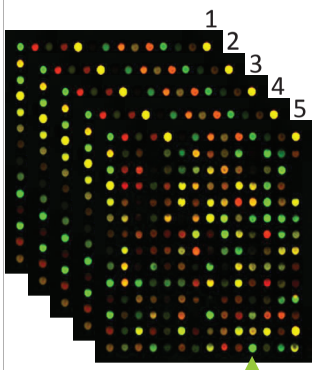
Stop the experiment.

Reject all significant hypotheses.

Retain all others.



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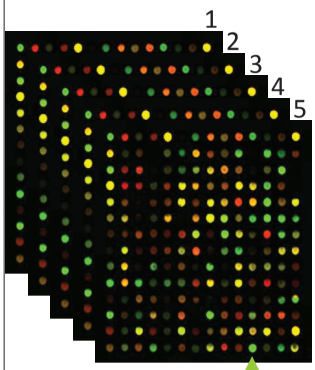

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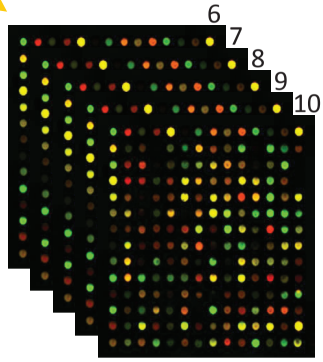

Analysis controlling the FDR at level α for pooled data

1 spot $\hat{=}$ 1 hypothesis

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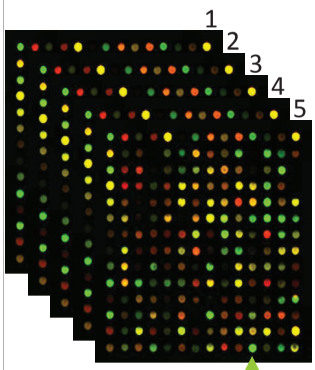

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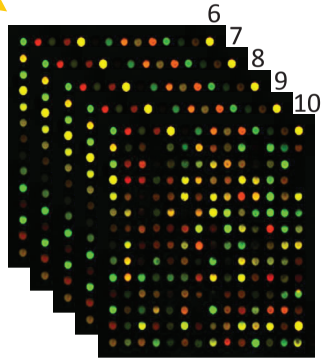
Analysis controlling the FDR at level α

Stop ...

Reject ...

Retain ...



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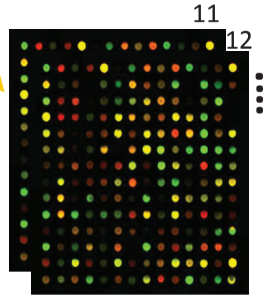

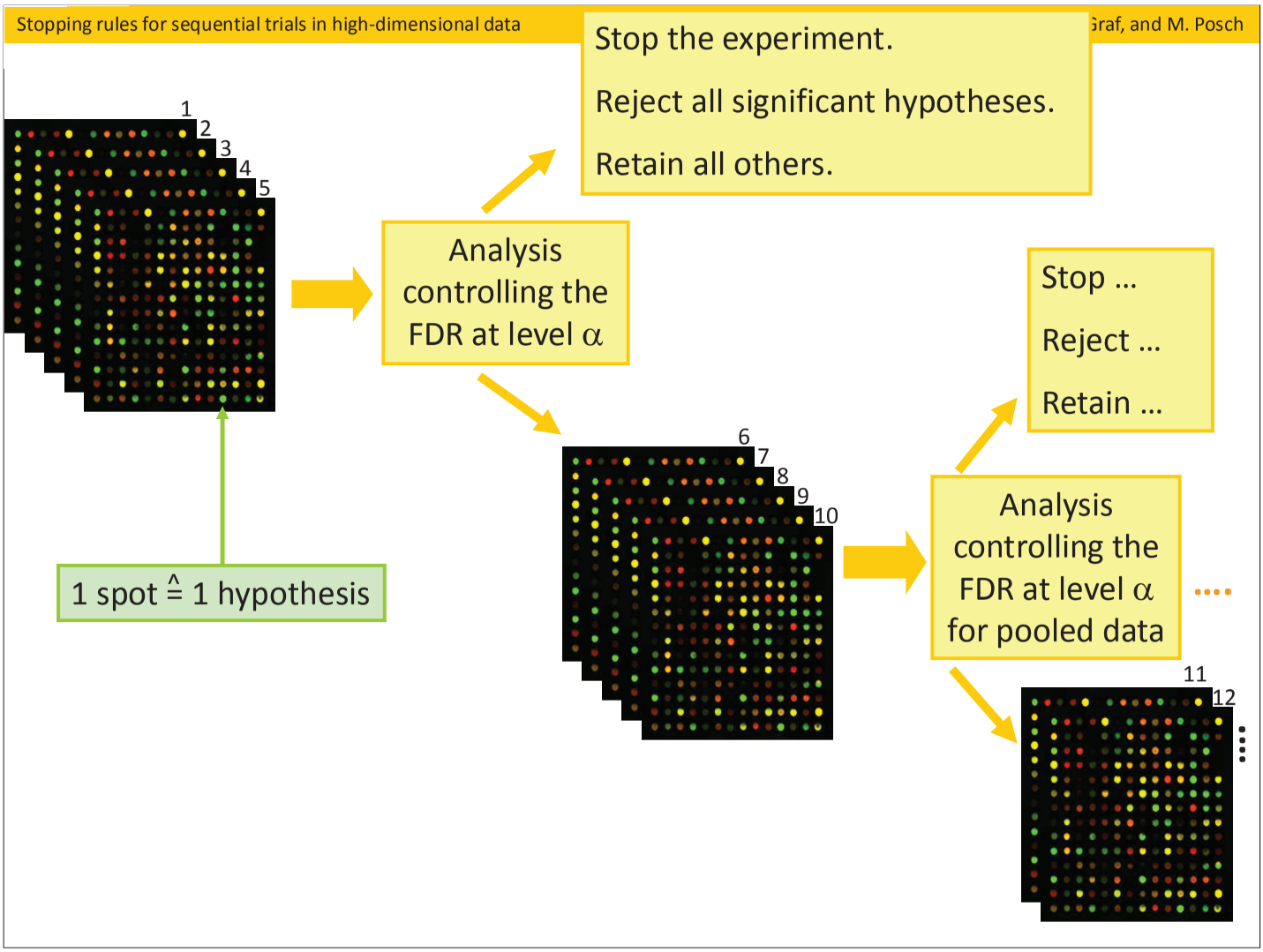

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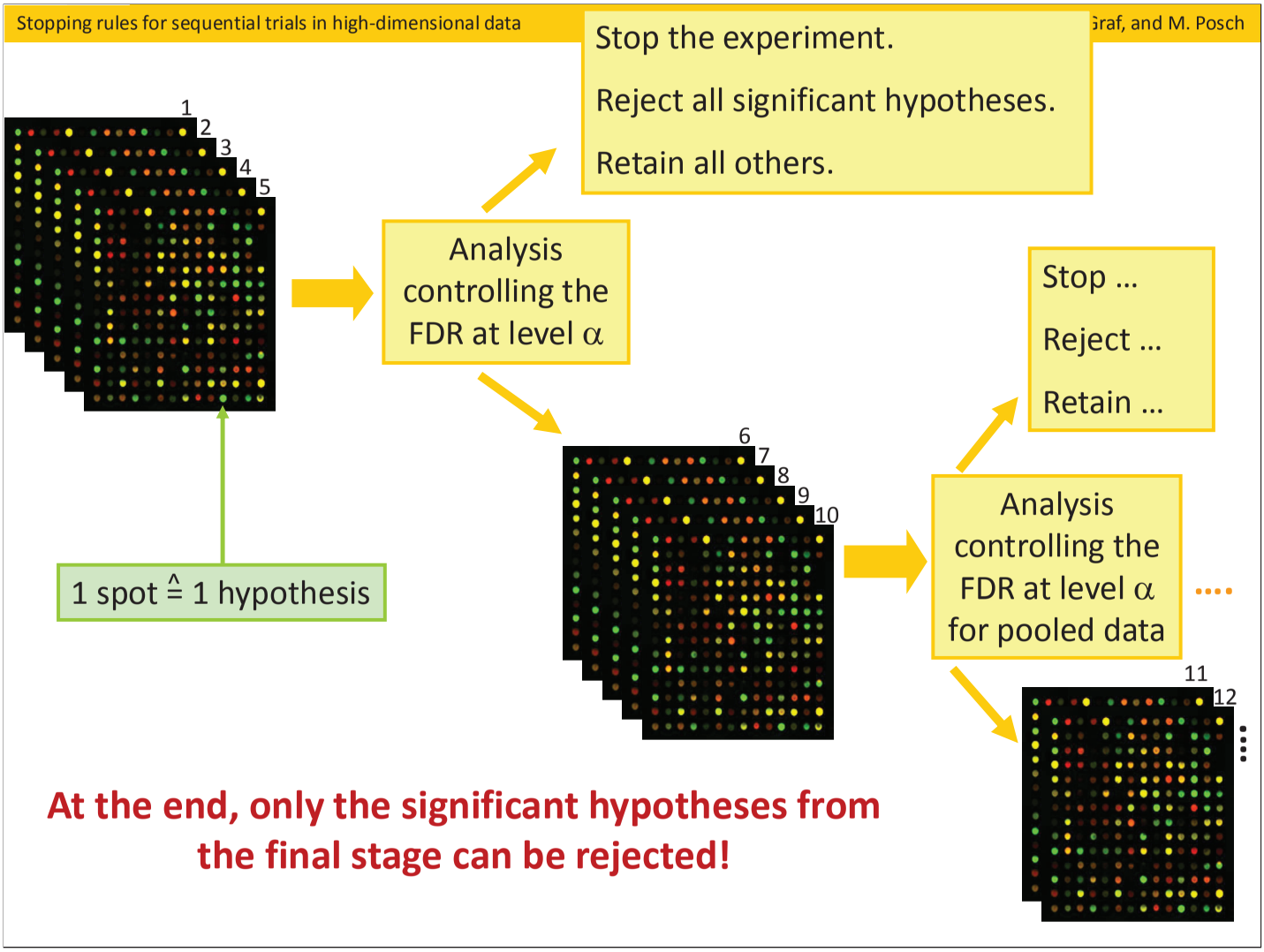

At the end, only the significant hypotheses from the final stage can be rejected!

What is the effect of unadjusted repeated analyses on the FDR?

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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 $m \rightarrow \infty$, 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

Stopping for futility	Early rejection
▪ Futility boundary $\alpha_1 > \alpha$	▪ Proportion of rejected H0 ▪ Δ Proportion of rejected H0 ▪ False Negative Rate ▪ Δ False Negative Rate ▪ False Non Discovery Rate ▪ Concordance (and at least *s(m)* hypotheses can be rejected)

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 *FNR* is estimated from the data

- γ: 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
- $R_k(\gamma) = \#\{p_{ik} < \gamma_k\}$

$$\widehat{FNR}_k = 1 - \frac{R_k(\gamma_k) - \hat{m}_{0k}\gamma_k}{m - \hat{m}_{0k}}$$

Stop as soon as $\Delta FNR < 0.05$

- ΔFNR is based on the increment of the stagewise FNR:

$$\Delta FNR_k = FNR_k - FNR_{k-1}$$

with $FNR_0 = 1$.

- In each stage ΔFNR is estimated as described before:

$$\Delta\widehat{FNR}_k = \widehat{FNR}_k - \widehat{FNR}_{k-1}$$

Stop as soon as the concordance of the rejected hypotheses from stage to stage > 0.9

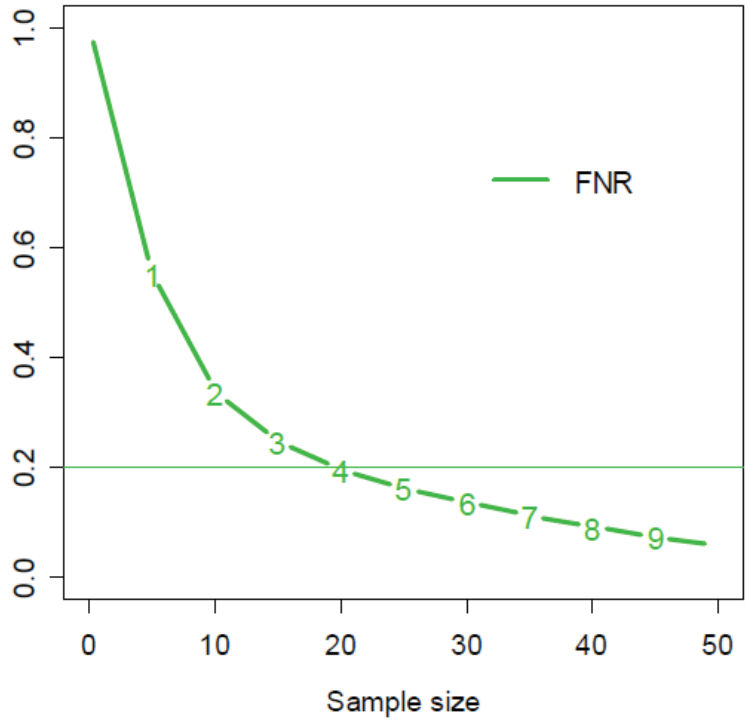
- Concordance (CO) measures the proportion of significant genes in stage *k* which were also significant in stage *k-1*:

$$\mathrm{CO}_k = \sum_i (H_{ir_{k-1}} H_{ir_k}) / \sum_i H_{ir_k}$$

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, μ/σ=0.5

True *FNR* for different sample sizes: Theoretical curve



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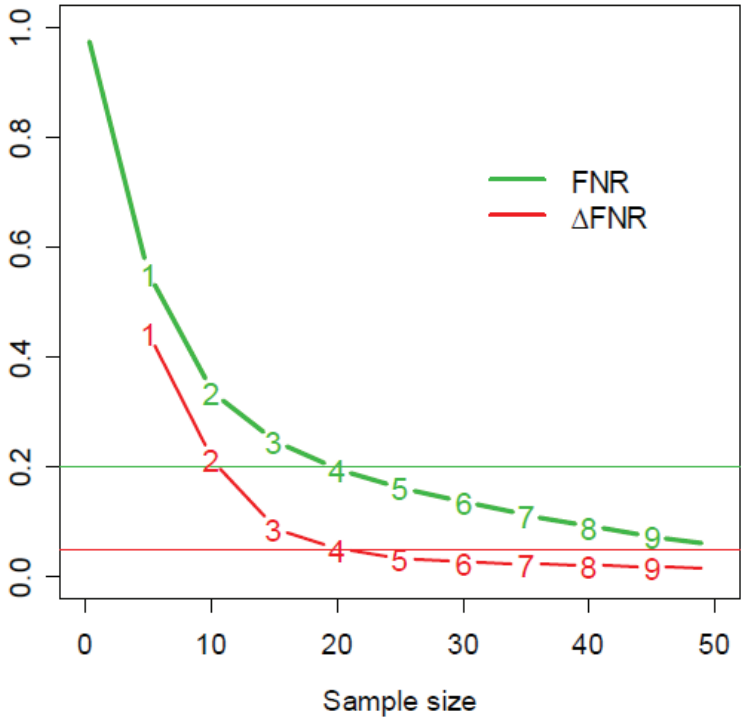
True ΔFNR for different sample sizes: Theoretical curve



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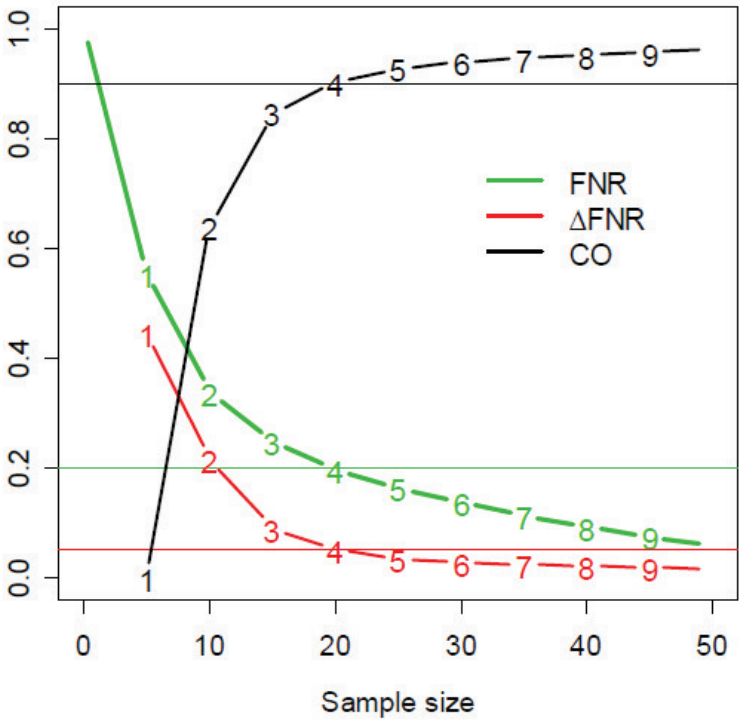
True CO for different sample sizes: Theoretical curve



Simulation study (50000 runs)

The setting:

- m=5000 / 50000
- m_0/m=0.9, μ/σ=0.5
- 10 stages with stage-wise sample sizes of 5
- z-tests, α = 0.05
- Stopping rules: FNR<0.2, ΔFNR<0.05, CO>0.9, *s(m)*>9

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Independent data

The FDR is controlled at level α = 0.05 for the 3 considered stopping criteria.

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Independent data	Equi-correlated data (ρ = 0.5)
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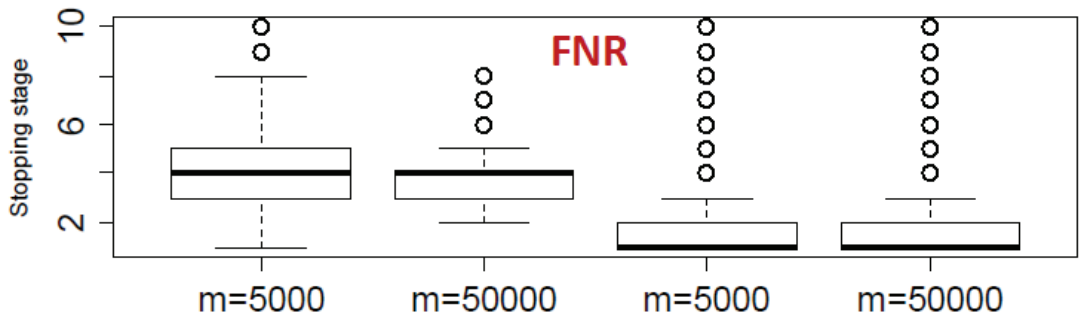
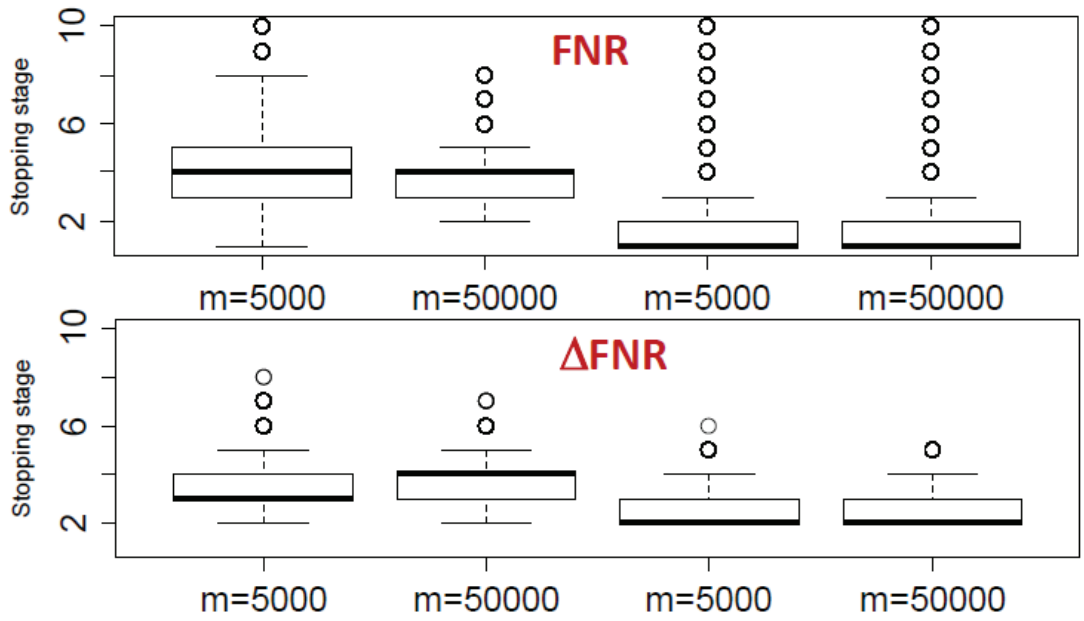


Independent data | Equi-correlated data



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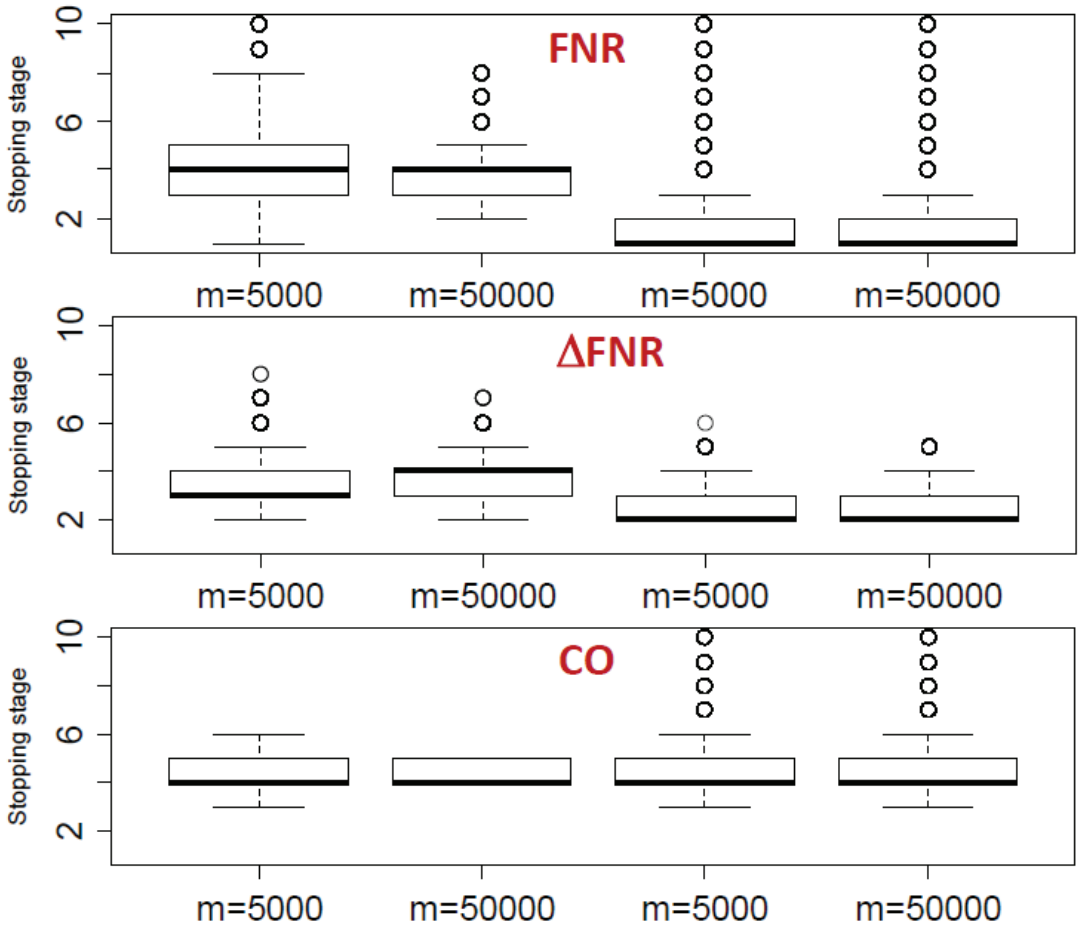

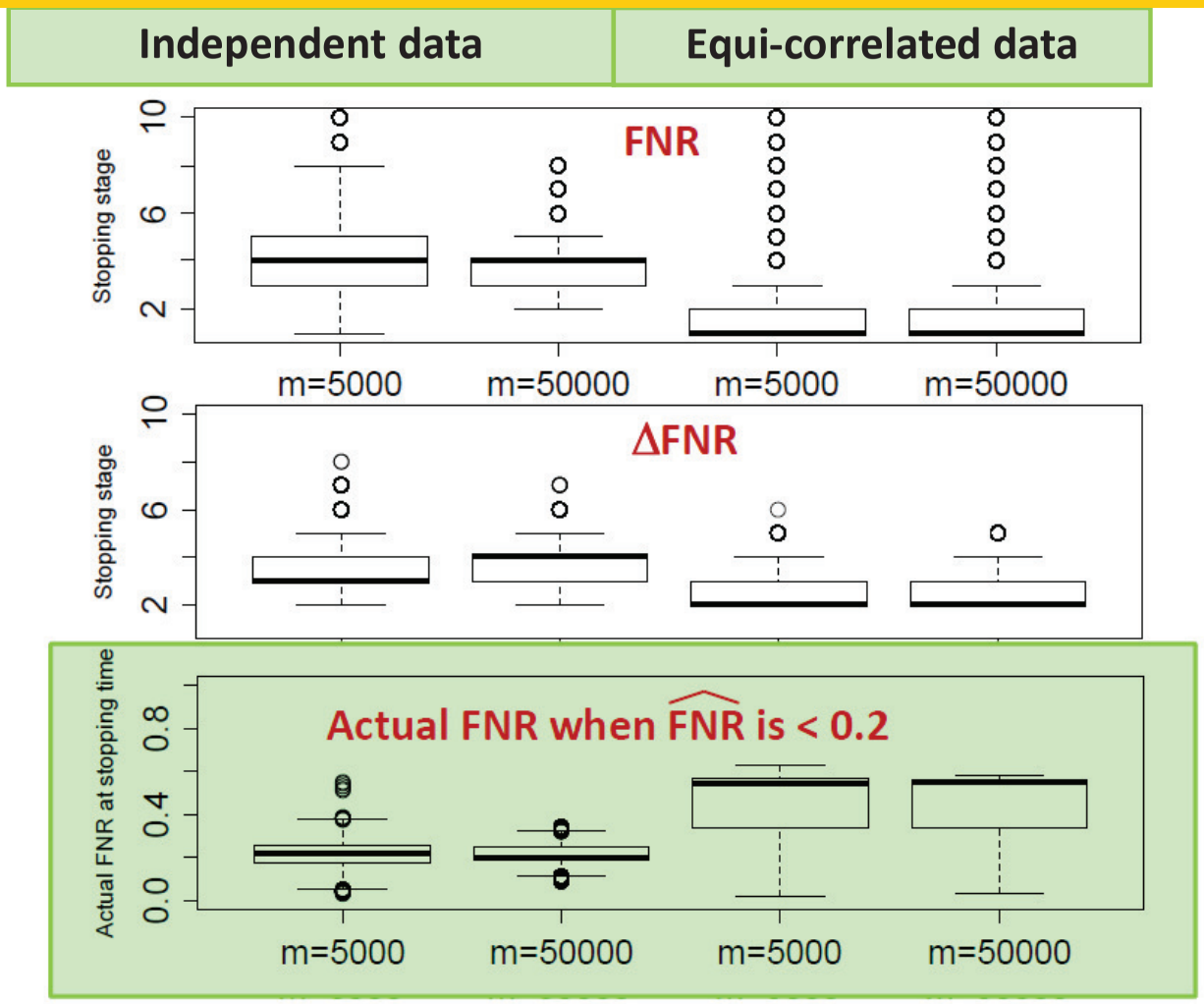

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Discussion

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

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