Genetic factors influencing the response to the therapy

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Integrated DEsign and AnaLysis of small population group trials

Politechnika Wrocławska

Team

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- Stanford University (USA): Chiara Sabatti, Emmanuel Candès, Hua Tang, Ewout van den Berg (IBM Research Center), Weijie Su (University of Pennsylvania), Christine Peterson (University of Texas)
- Medical University of Vienna (Austria): Florian Frommlet, Franz König
- Tulane University (USA): Alexej Gossmann
- Ecole Polytechnique (France): Julie Josse

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Schedule

- Why to consider genetic background ?

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- Association Studies

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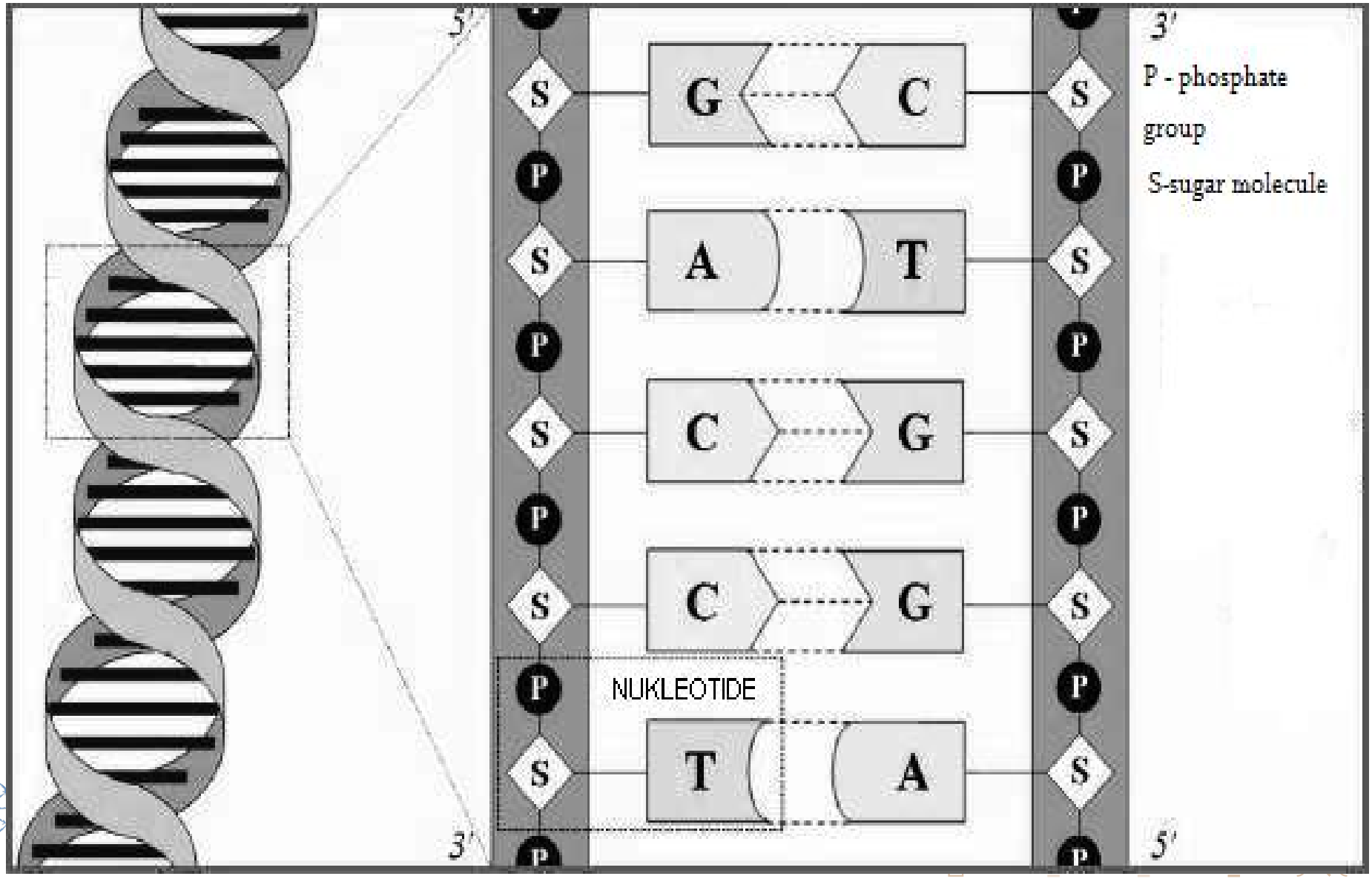
- Gene expression data - SLOPE and subspace clustering
- Simulation study in the context of clinical trials

DNA Structure



Genetic variability

- About 99,9% of genetic information is the same for all people.
- A ***polymorphism*** is a difference in DNA structure, which is present in at least 1% of population
- A ***Single Nucleotide Polymorphism(SNP)*** is a polymorphism with the difference in the single base:
  - A typical SNP: a position in DNA in which
    - 85% of population has Cytosine(C)
    - 15% has a Thymine(T).
- There are usually two forms of a SNP at a given locus
- three genotypes : AA, Aa, aa.

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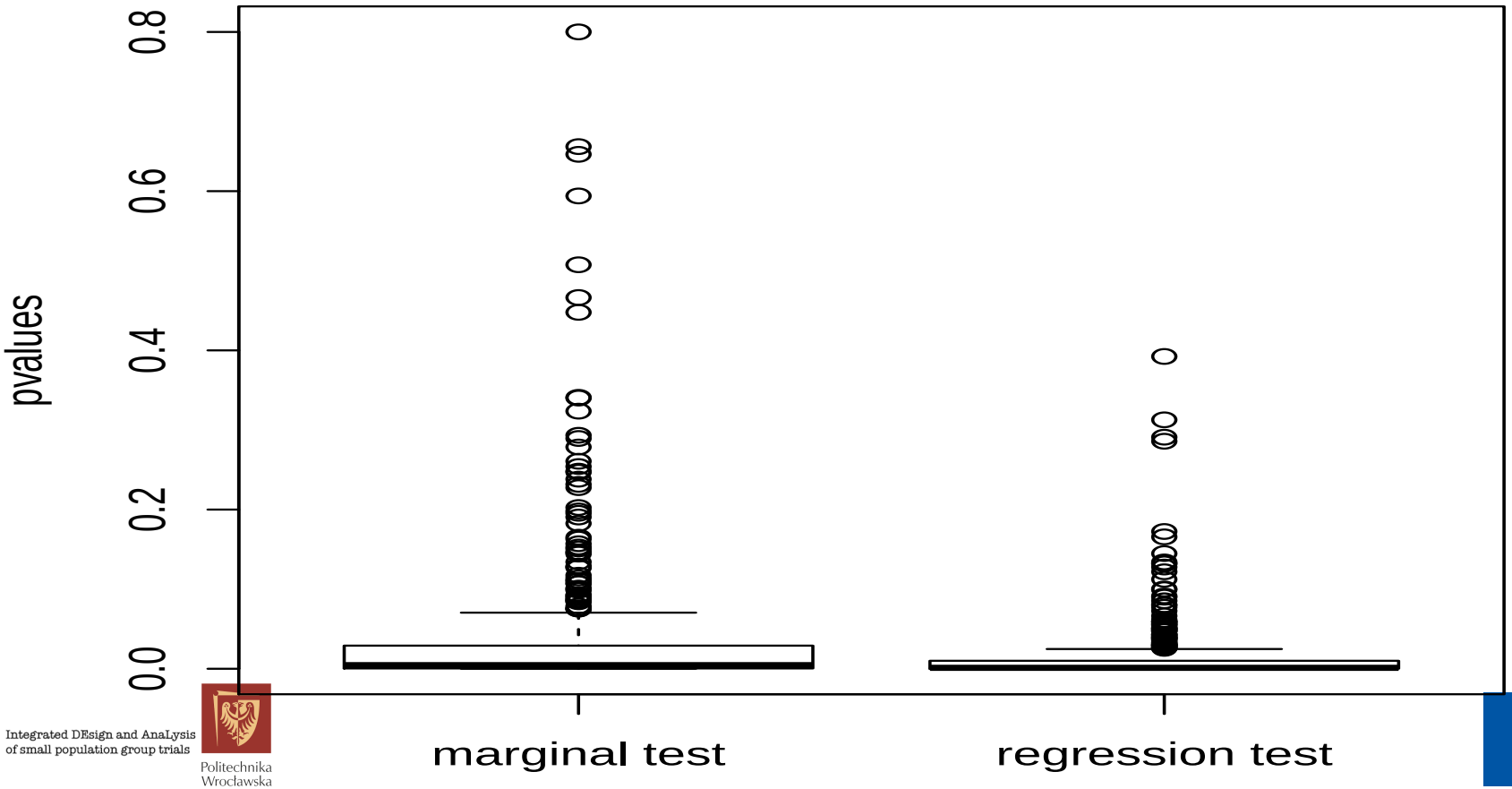
Examples: change in blood pressure, cholesterol level, etc.

Simulation example - Increasing the power of detection of treatment effects

20 influential genes, no gene-treatment interaction
gain in power 93% vs 83%



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Data structure

$Y = (Y_1, \ldots, Y_n)^T$ - trait values for n patients

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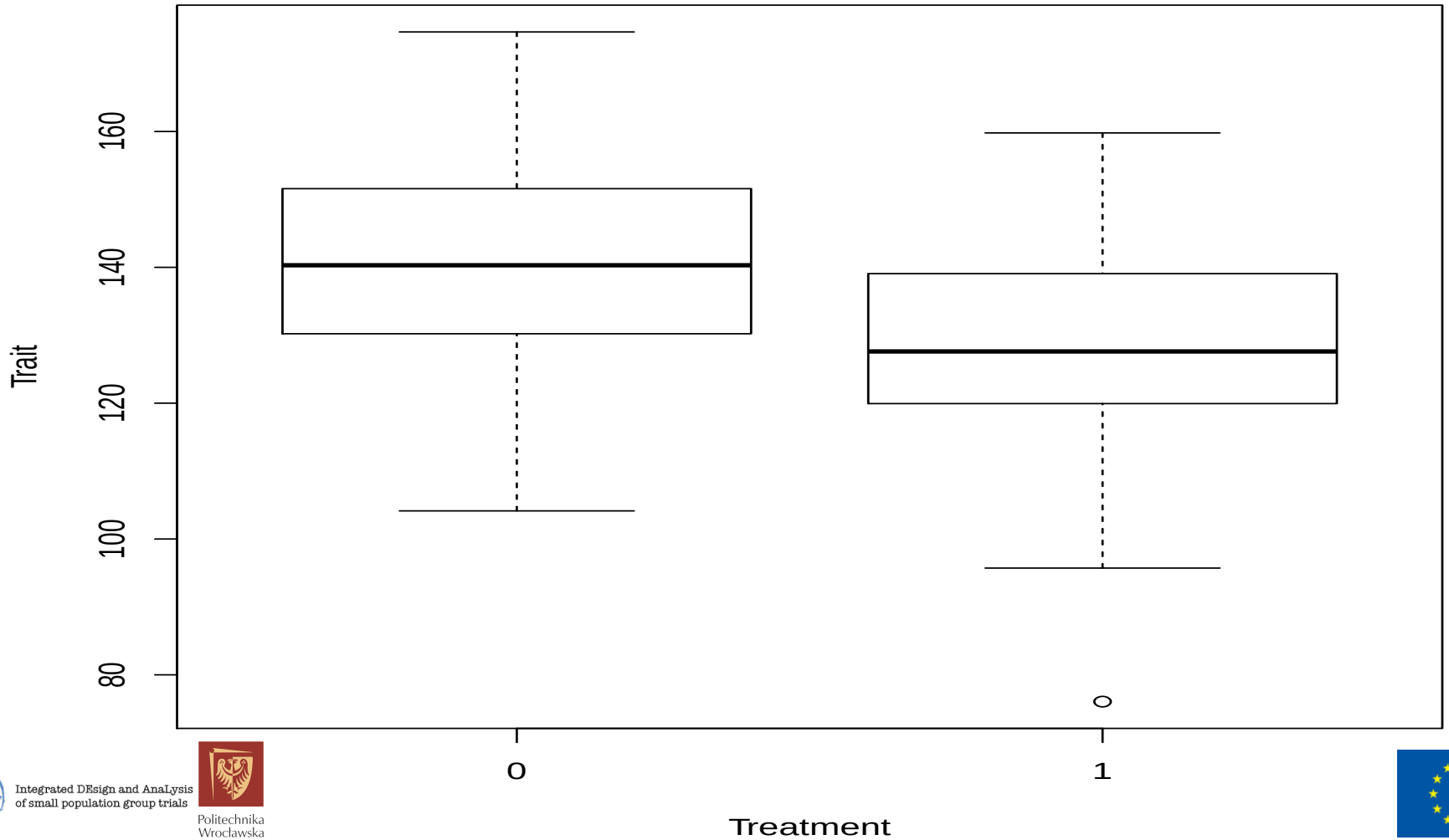
Usual coding

$$Z_{ij} = \begin{cases} 0 & \text{gdy} \quad G_{ij} = AA \\ 1 & \text{gdy} \quad G_{ij} = Aa \\ 2 & \text{gdy} \quad G_{ij} = aa \end{cases}$$

Simulation example - lowering blood pressure



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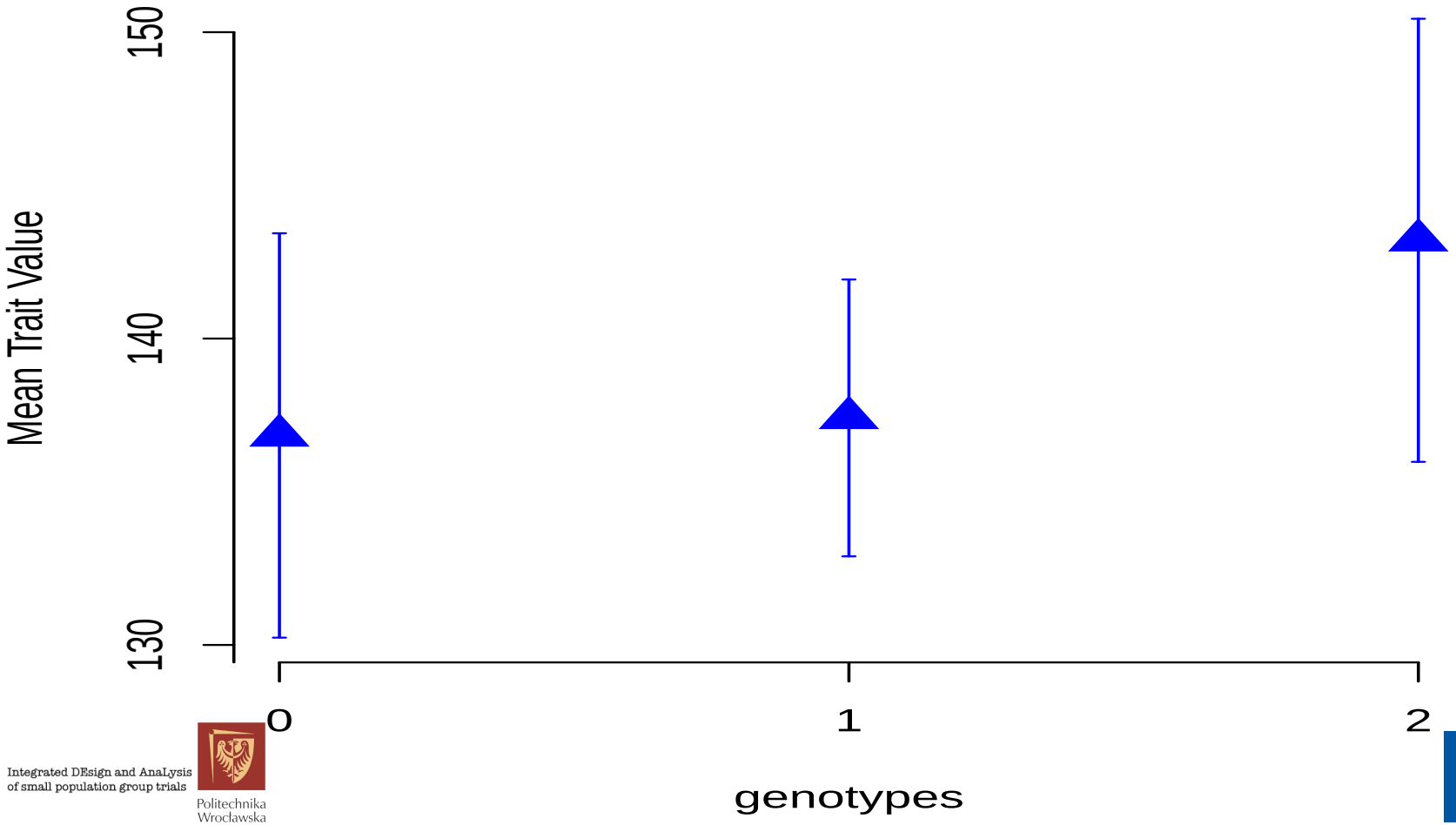
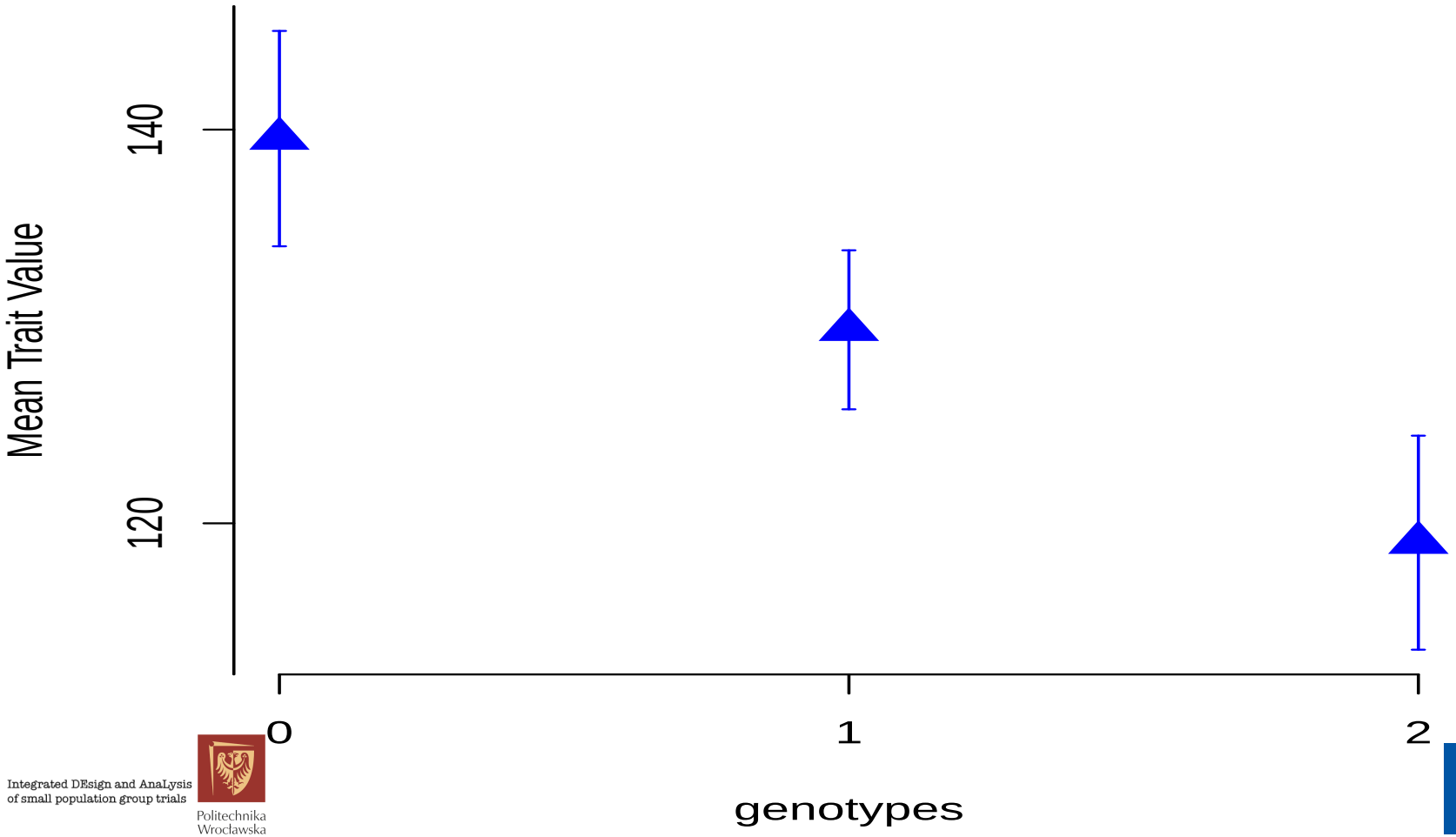
Control group



Treatment group



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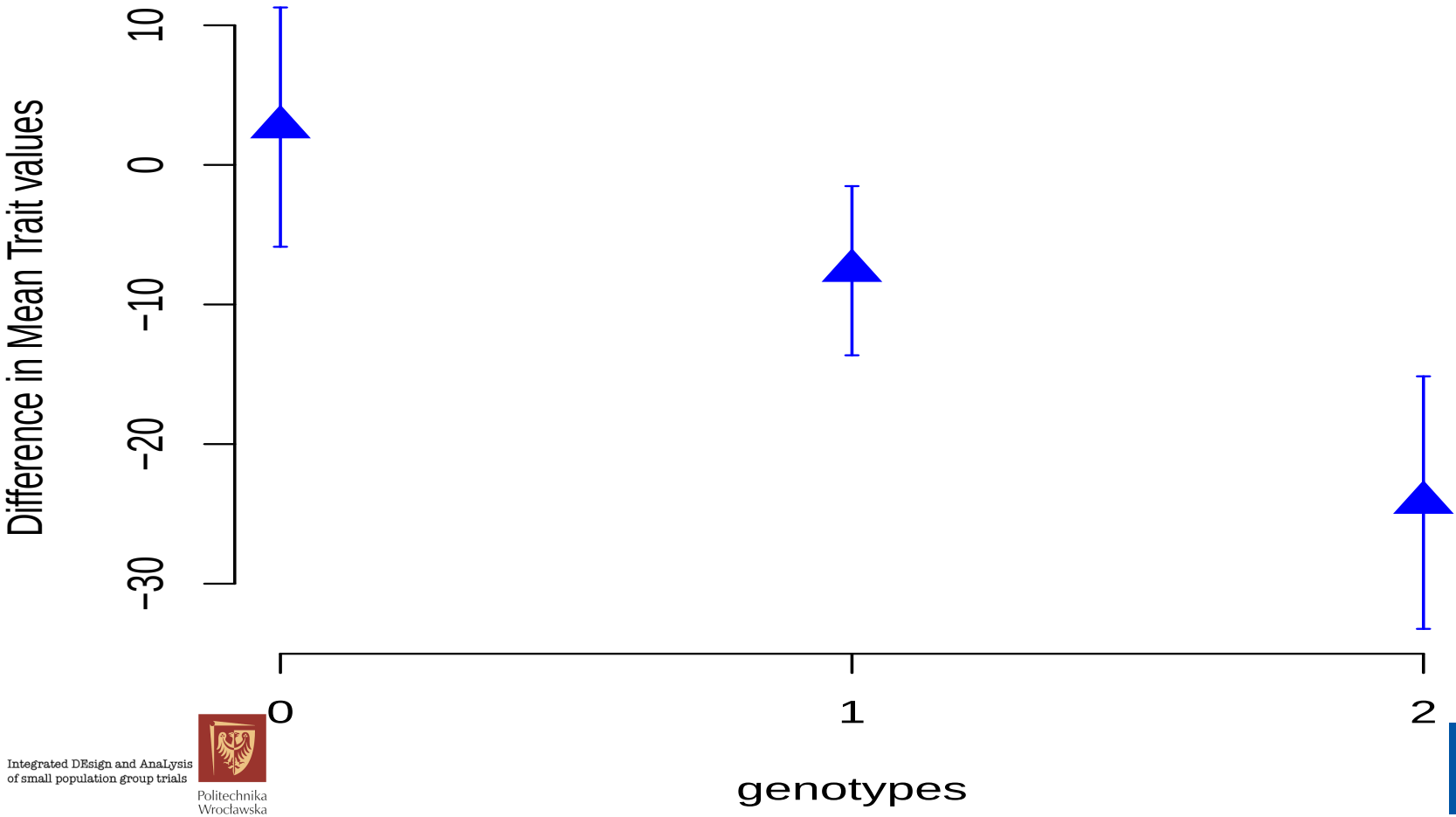
Treatment effect



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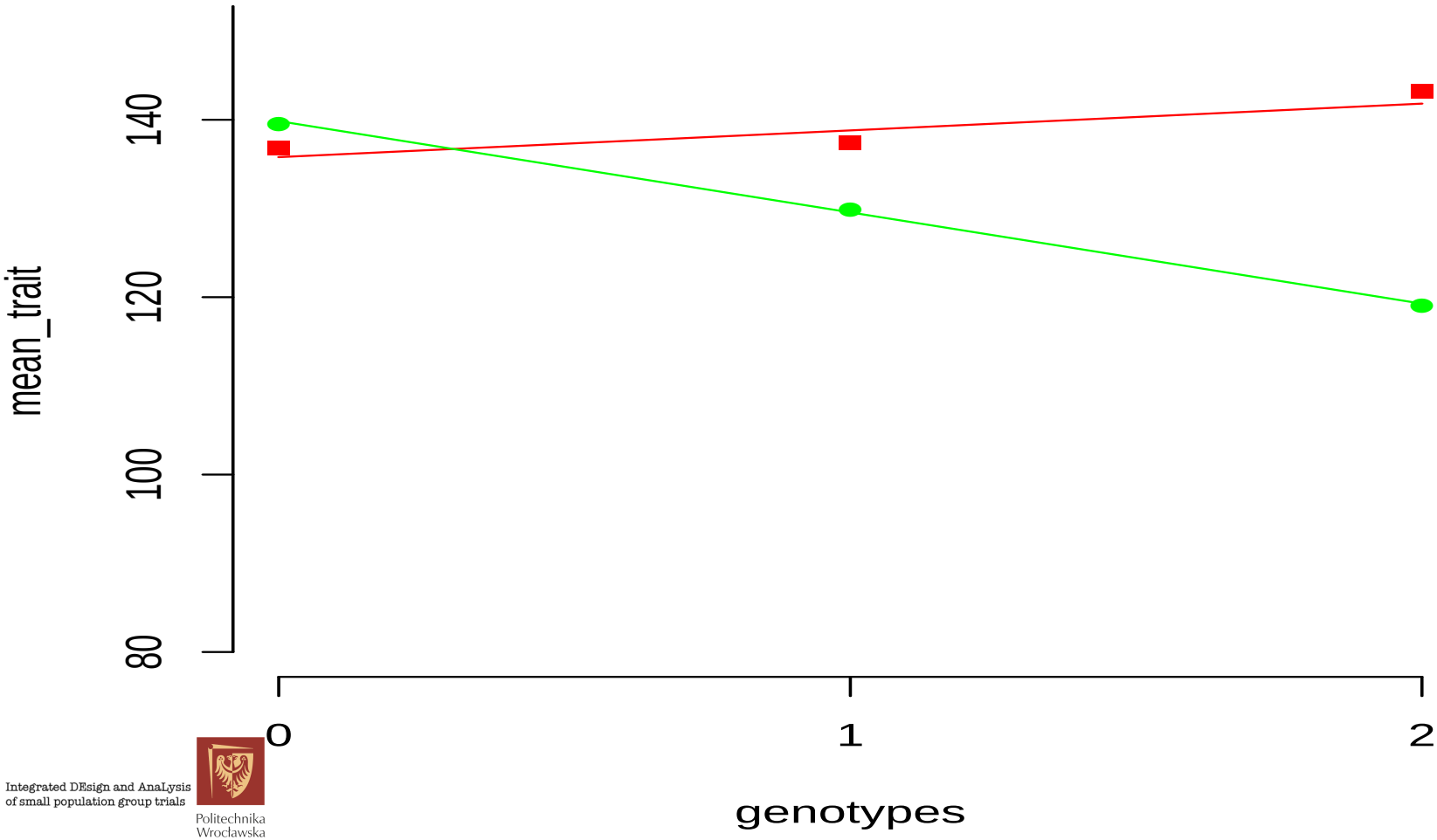
Gene-Treatment Interaction



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Statistical model

Identification of genetic background

$Y_i = \beta_0 + \sum_{j=1}^{m} \nu_j Z_{ij} \quad \epsilon_i \sim N(0, \sigma_\epsilon^2) \quad .$

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$$R(Z) = E(Y|T = 1, Z) - E(Y|T = 0, Z) = \beta_1 + \sum_{j=1}^{m} \gamma_j Z_{ij}$$

Simple linear regression

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$\hat{\beta}_j$: least squares estimate β_j

$$\hat{\beta}_j \sim N(\beta_j, \sigma_j^2)$$

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$$H_{0j} : \beta_j = 0 \quad \text{vs} \quad \beta_j \neq 0$$

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$$\alpha = 0.05, p_0 = 2000 \rightarrow E(V) = 100$$

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Multiple testing procedures

Bonferroni correction (FWER control): Apply significance level $\frac{\alpha}{p}$.

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Benjamini-Hochberg procedure (FDR control)

(1) Sort p-values: $|p|_{(1)} \leq |p|_{(2)} \leq \ldots \leq |p|_{(p)}$

(2) Identify the largest j such that

$$|p|_{(j)} \leq \alpha \frac{j}{p}, \tag{1}$$

Call this index j_{SU}.

(3) Reject $H_{(j)}$ if and only if $j \leq j_{\mathsf{SU}}$

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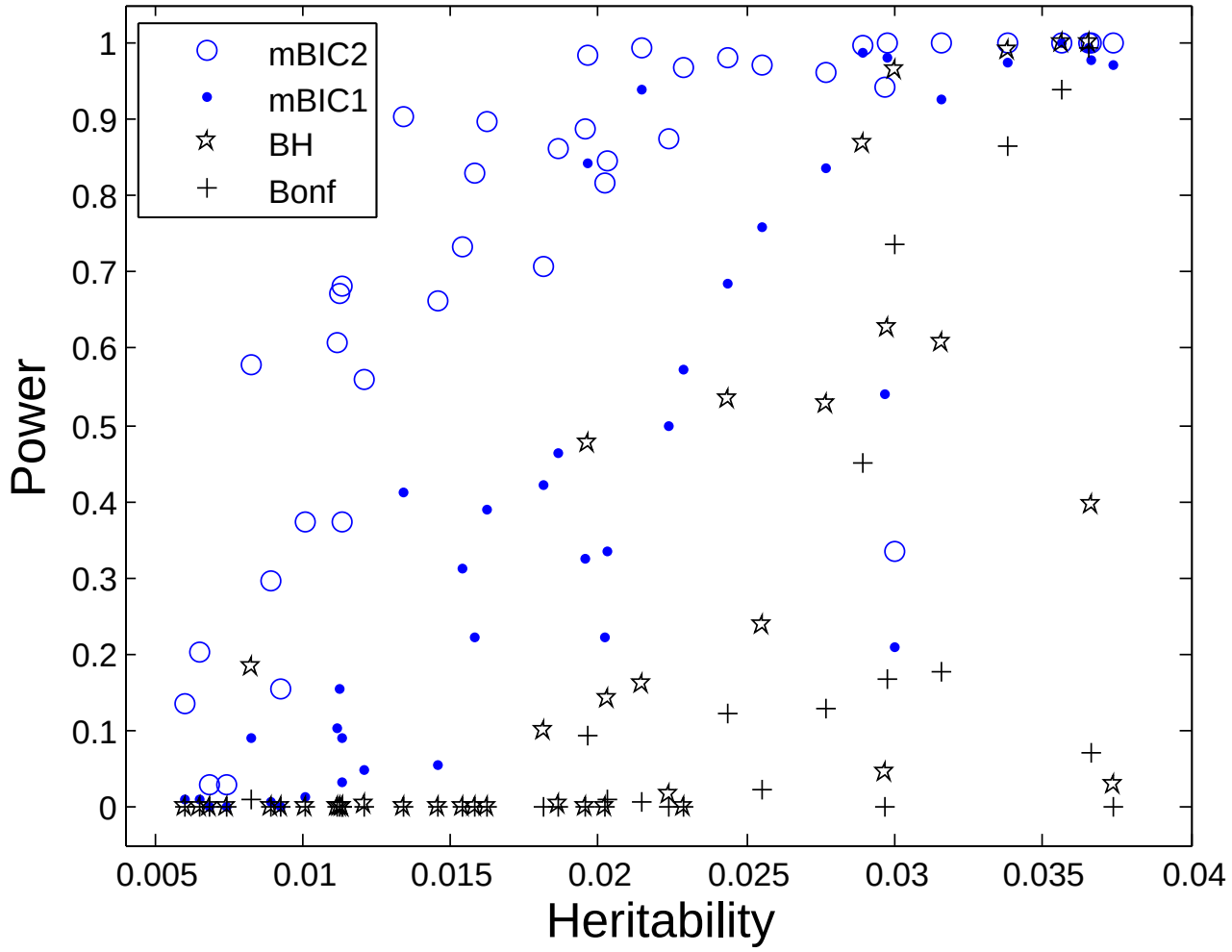
- β_j uniformly distributed over the interval [0.27, 0.66]

Power



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Model selection criteria (1)

Goal: Estimation of β in model

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Model selection criteria: minimize $||Y - X\beta||^2 + pen(k)$

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AIC $pen(k) = 2k$, BIC $pen(k) = k \log n$ incur many false discoveries when p is large

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Bogdan et al. (Genetics, 2004), Żak-Szatkowska and Bogdan (CSDA,2011), Frommlet et al. (CSDA, 2012)

combining BIC and RIC and BHRIC penalty

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Problem in GWAS - loss of power due to multiple testing, large sample sizes needed

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$$\begin{aligned} \text{mBIC2}(X_M, Z_A) &= n \log \text{RSS} + (k_1 + k_2) \log n + 2k_1 \log(p/4) \\ &\quad + 2k_2 \log(p^{eff}/4) - 2\log(k_1!) - 2\log(k_2!) \end{aligned}$$

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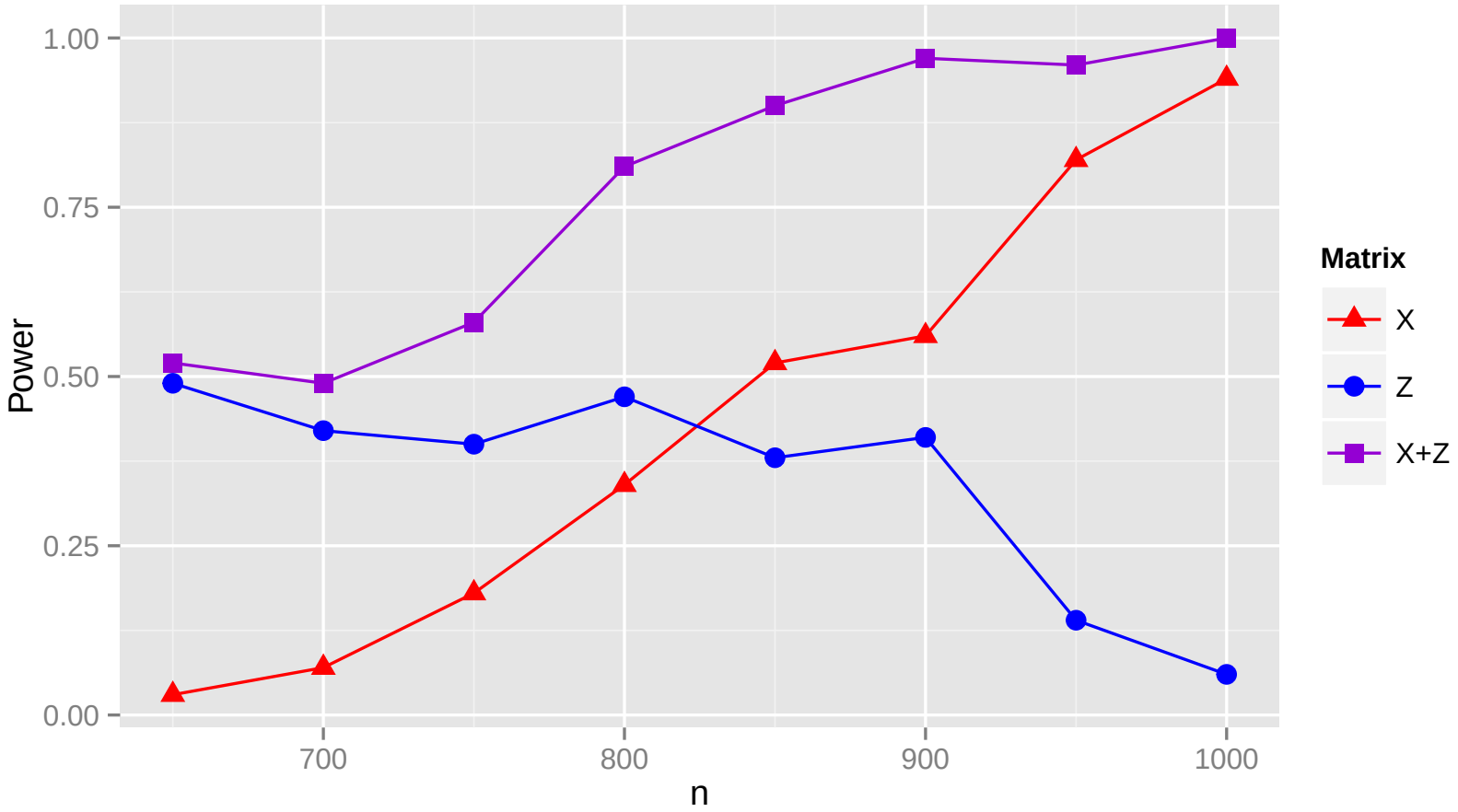
Admixtures (3)



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M. Bogdan, E. van den Berg, C. Sabatti, W. Su, E. J. Candès, "SLOPE – Adaptive Variable Selection via Convex Optimization", *Annals of Applied Statistics*, **9** (3), 1103–1140, 2015.

SLOPE estimate is given by

$$\min_{b\in\mathbb{R}^p} \quad \frac{1}{2}\|y - Xb\|_{\ell_2}^2 + \lambda_1|b|_{(1)} + \lambda_2|b|_{(2)} + \cdots + \lambda_p|b|_{(p)},$$

where $\lambda_1 \geq \lambda_2 \geq \cdots \geq \lambda_p \geq 0$ and $|b|_{(1)} \geq |b|_{(2)} \geq \cdots \geq |b|_{(p)}$

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SLOPE is the extension of LASSO in the direction of BH procedure, controls FDR for sparse signals and weakly correlated predictors

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M. Bogdan, E. van den Berg, C. Sabatti, W. Su, E. J. Candès, "SLOPE – Adaptive Variable Selection via Convex Optimization", *Annals of Applied Statistics*, **9** (3), 1103–1140, 2015.

SLOPE estimate is given by

$$\min_{b\in\mathbb{R}^p} \quad \frac{1}{2}\|y - Xb\|_{\ell_2}^2 + \lambda_1|b|_{(1)} + \lambda_2|b|_{(2)} + \cdots + \lambda_p|b|_{(p)},$$

where $\lambda_1 \geq \lambda_2 \geq \cdots \geq \lambda_p \geq 0$ and $|b|_{(1)} \geq |b|_{(2)} \geq \cdots \geq |b|_{(p)}$

$\lambda_1 = \ldots = \lambda_p = \sqrt{2\log p}$ - LASSO Bonferroni corrected

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R package *SLOPE* available on CRAN, by E. Patterson

Application for real GWAS

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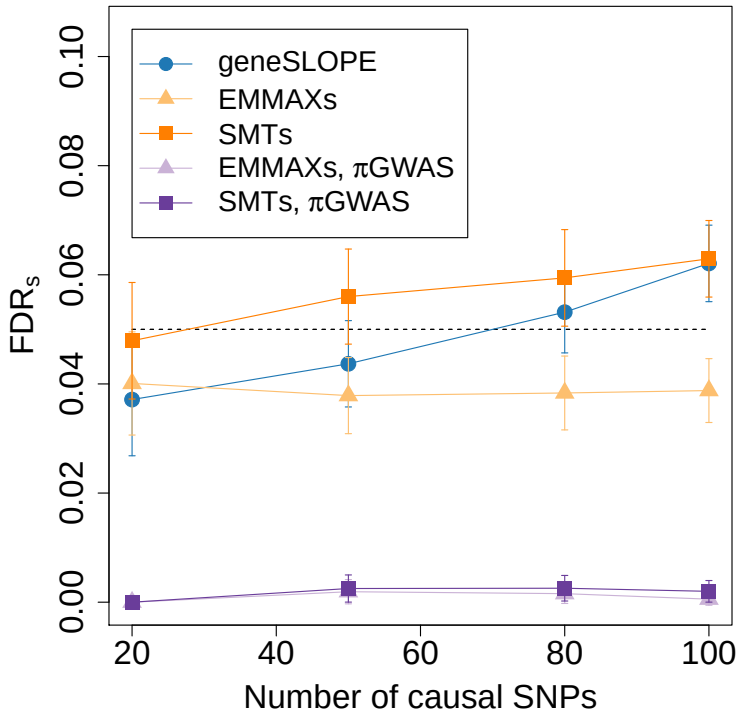
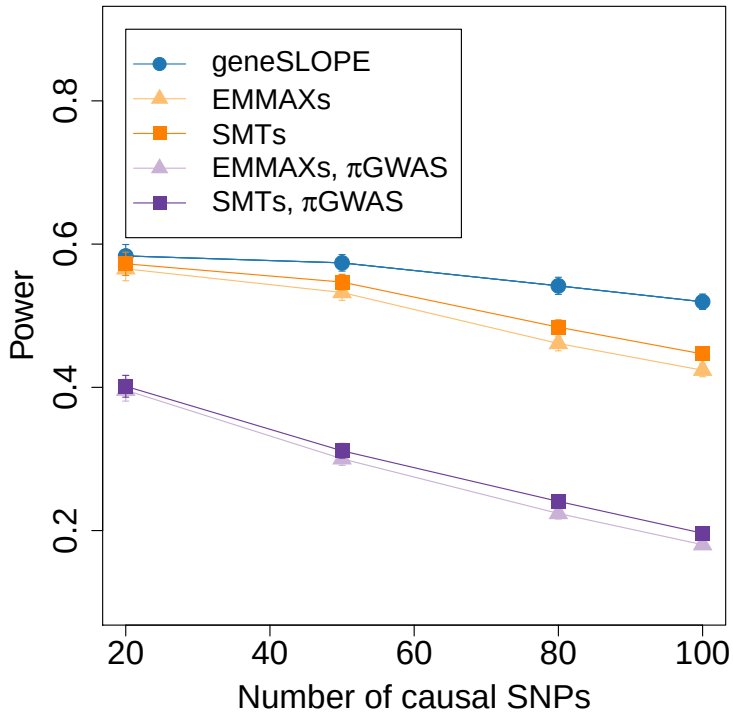

geneSLOPE
EMMAXs
SMTs
EMMAXs, πGWAS
SMTs, πGWAS
FDR$_s$
0.00
0.02
0.04
0.06
0.08
0.10
20
40
60
80
100
Number of causal SNPs


geneSLOPE
EMMAXs
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Power
0.2
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GroupSLOPE (1)

D. Brzyski, A. Gossmann, W.Su, M. Bogdan, "Group SLOPE - adaptive selection of groups of predictors", arXiv: 1610.04960, 2016

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R package *grpSLOPE* available on CRAN by A. Gossmann

A. Gossmann, S. Cao, D. Brzyski, L. Zhao, H. Deng, and Y. Wang, "A sparse regression method for group-wise feature selection with false discovery rate control", invited for *IEEE/ACM Transactions on Computational Biology and Bioinformatics*

Simulations

$n = 5402$, $p = 26233$ - roughly independent SNPs

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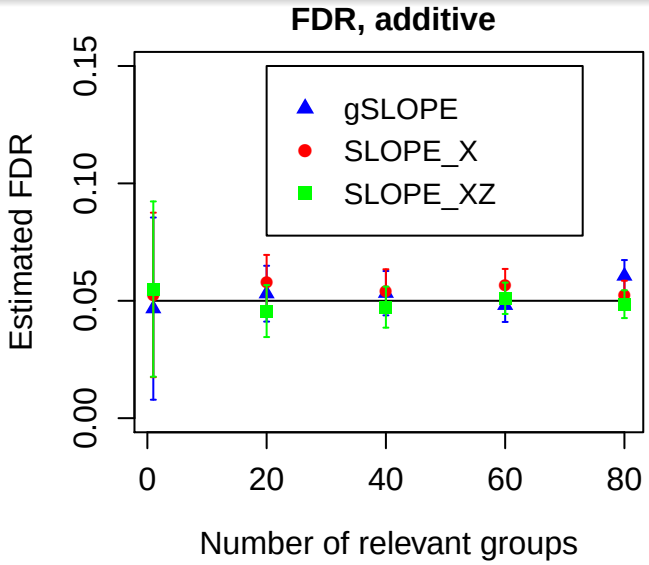
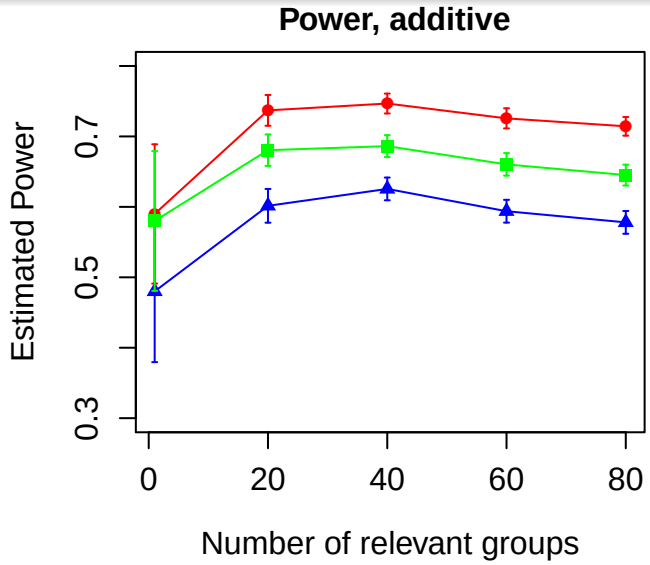
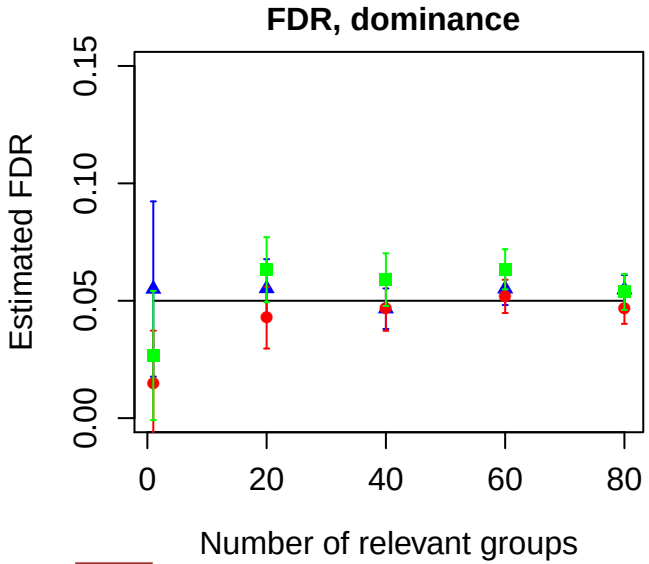
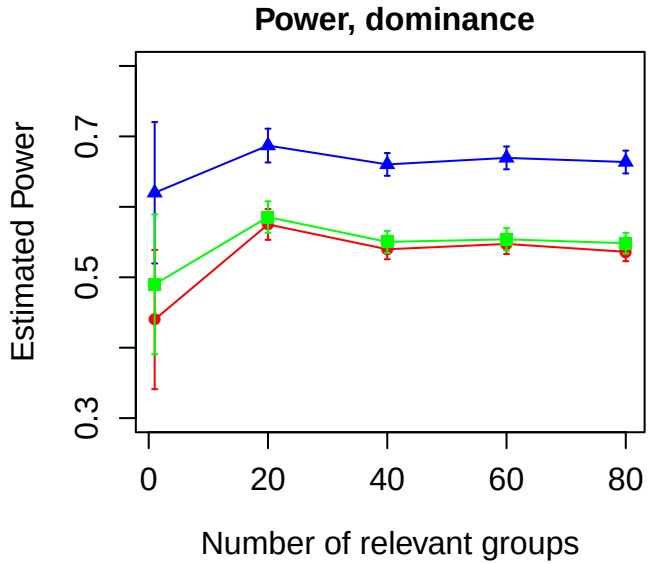
One group contains two columns: additive and dominance dummy variable for a given SNP

Simulation results









Integrated DEsign and AnaLysis of small population group trials

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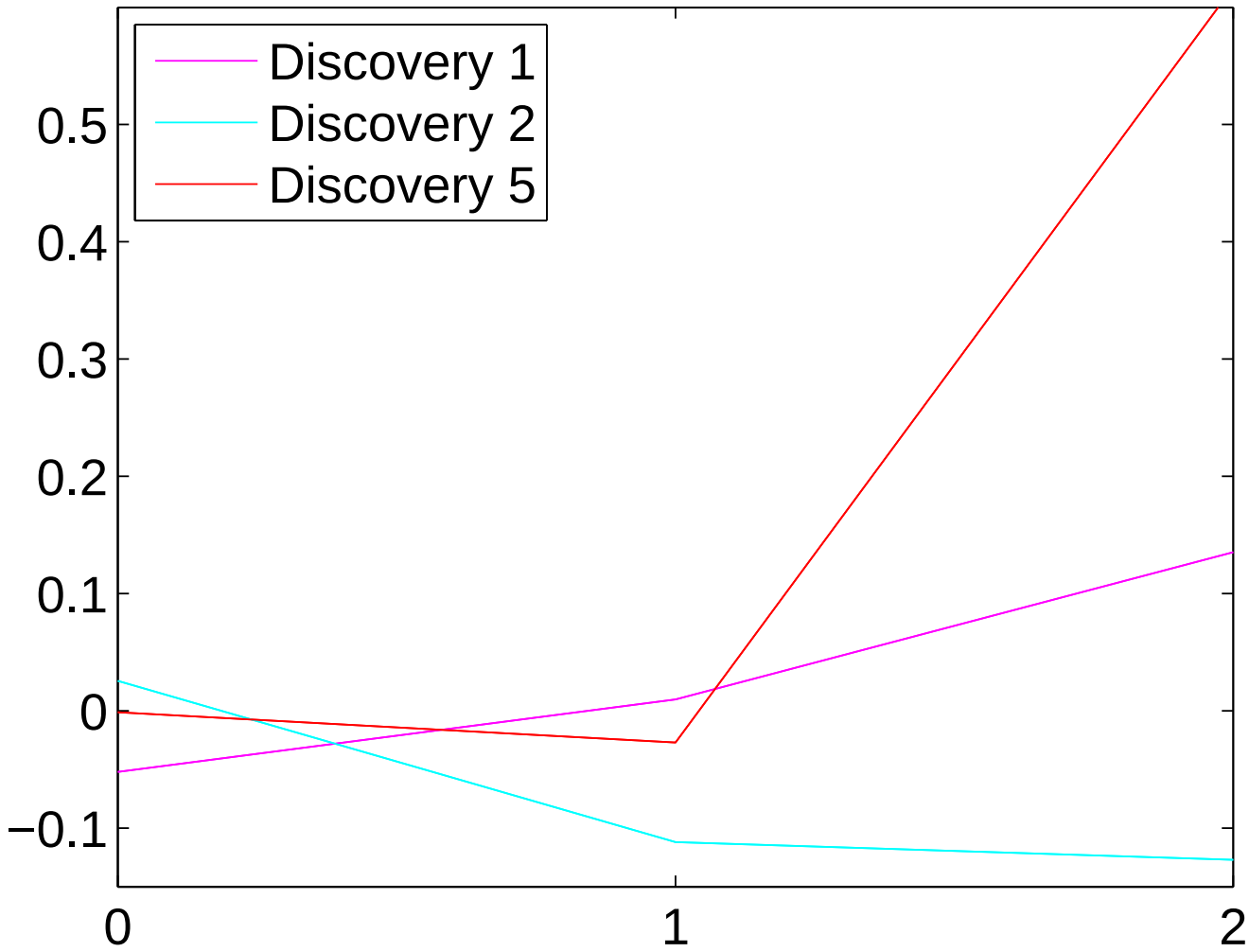
Genes Influencing Level of Triglicerides

5 new discoveries with group SLOPE - recessive rare genetic variants. Discovery 5 - 37 rare homozygotes



Personalized therapies (1)

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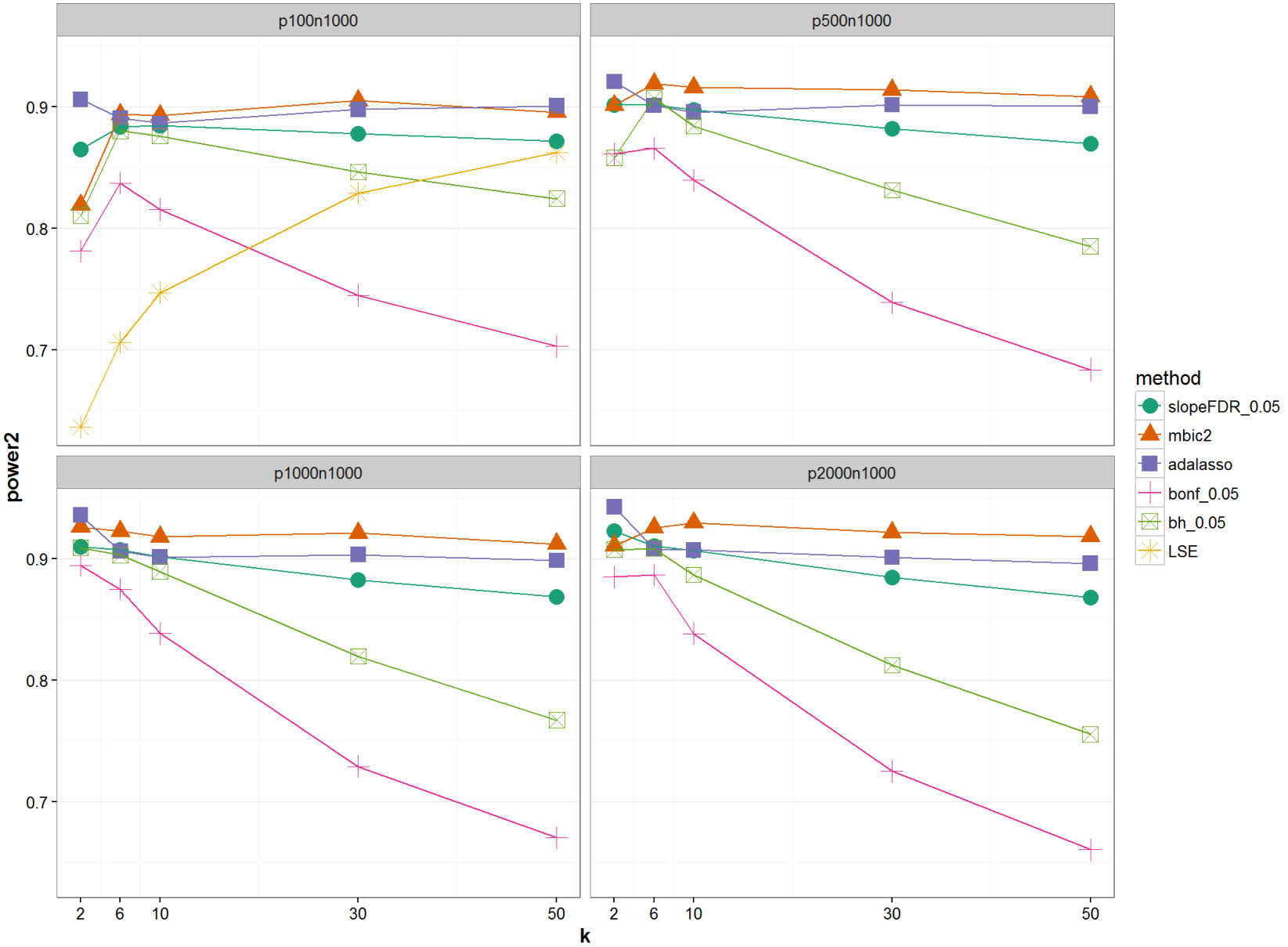
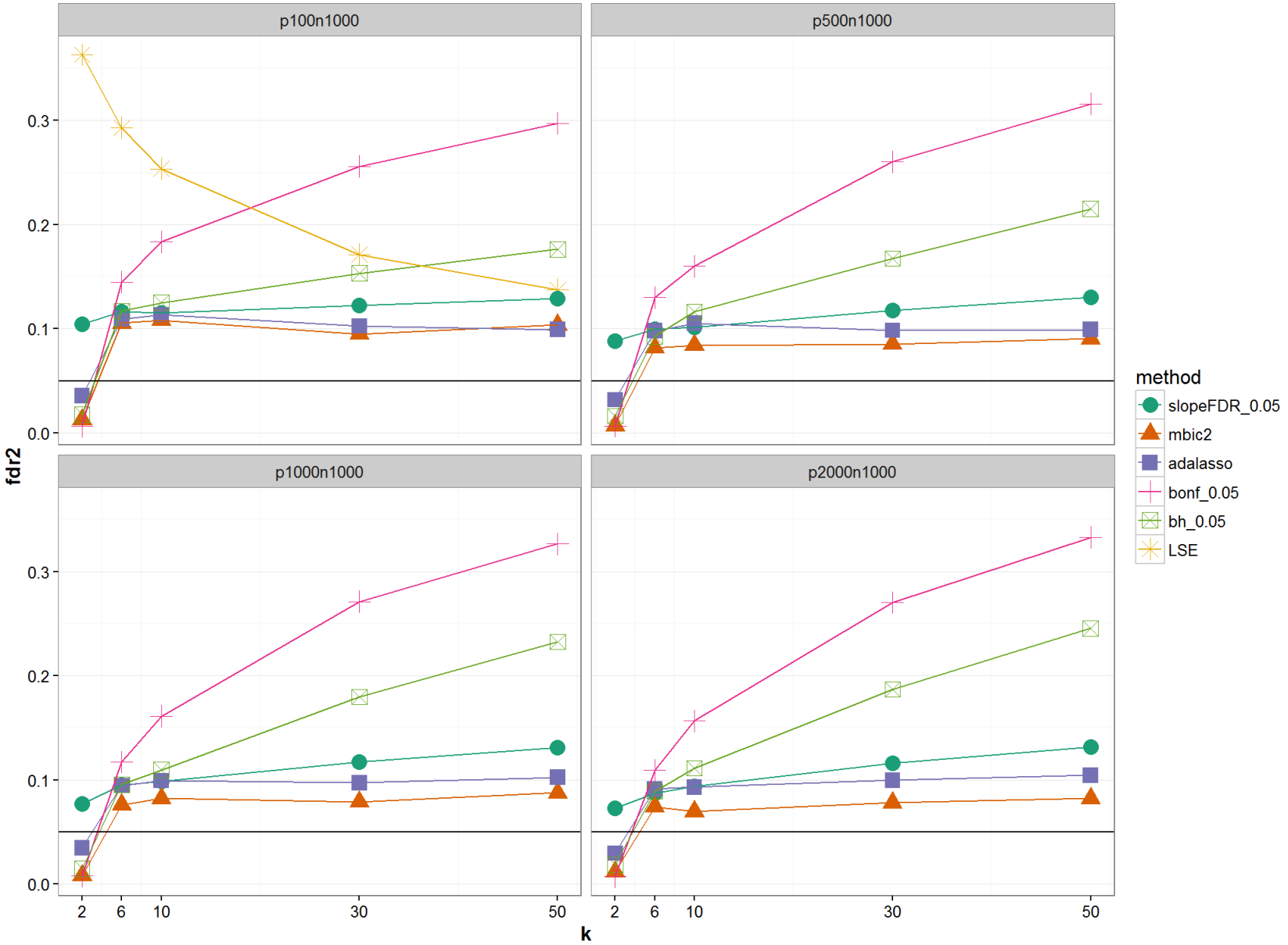
Two new tests:

- Test for the treatment effect within the selected model.
- Use part of the sample to identify the model and test for the treatment effect in selected patients from the second group.

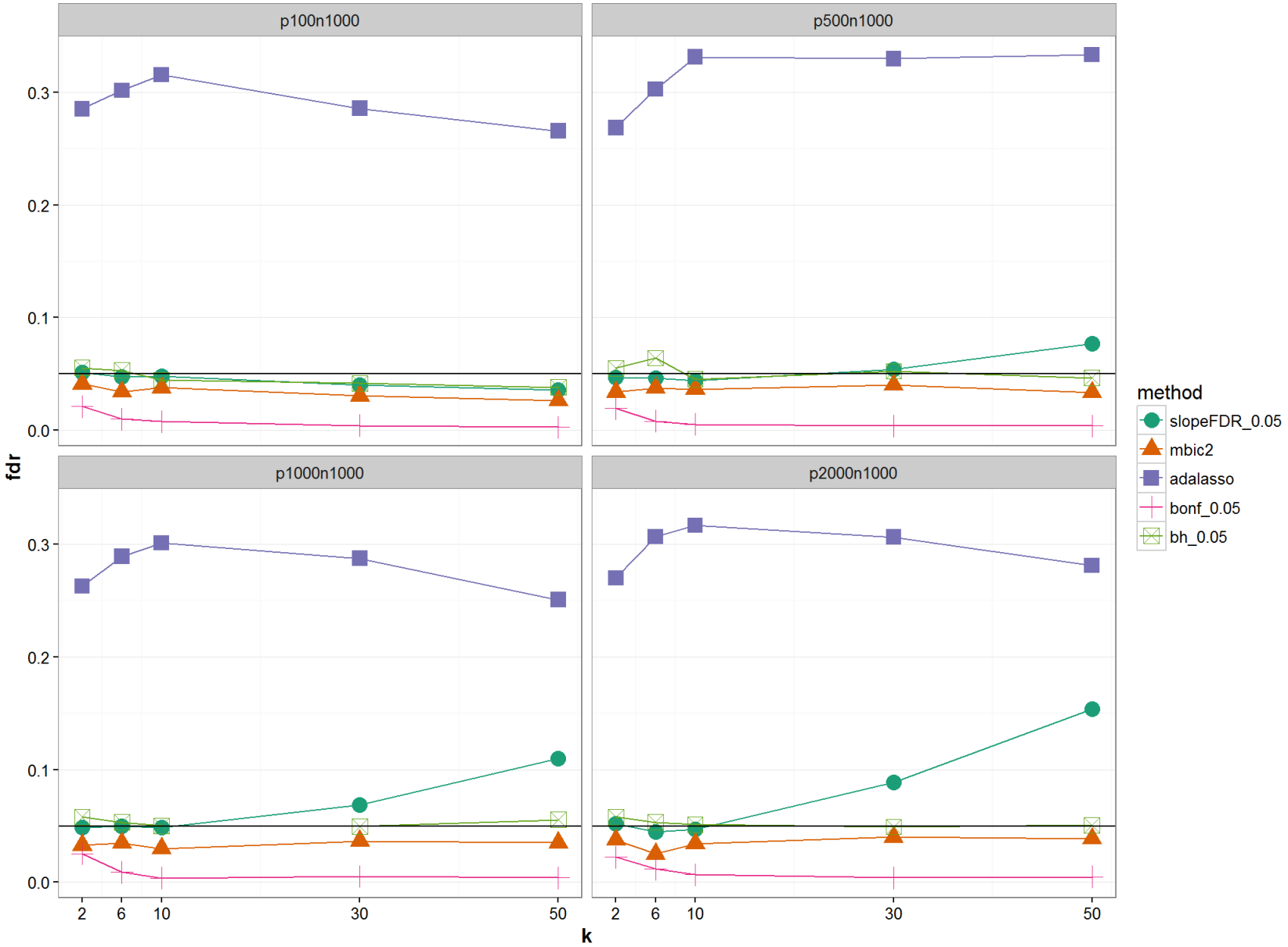
Power at the patient's level



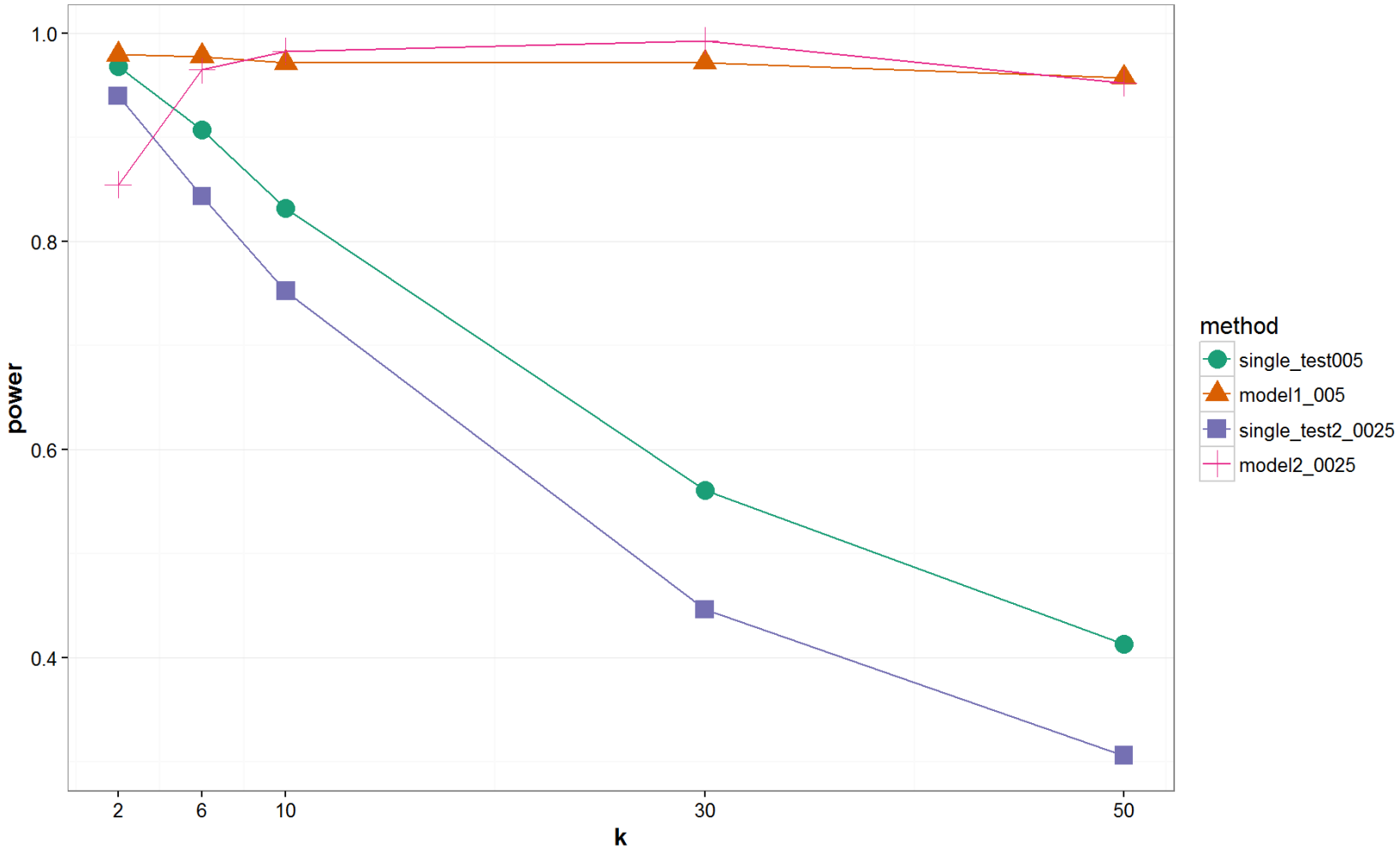
FDR at the patient's level



FDR at the gene level



Power for testing the treatment effect



Integrated DEsign and AnaLysis of small population group trials

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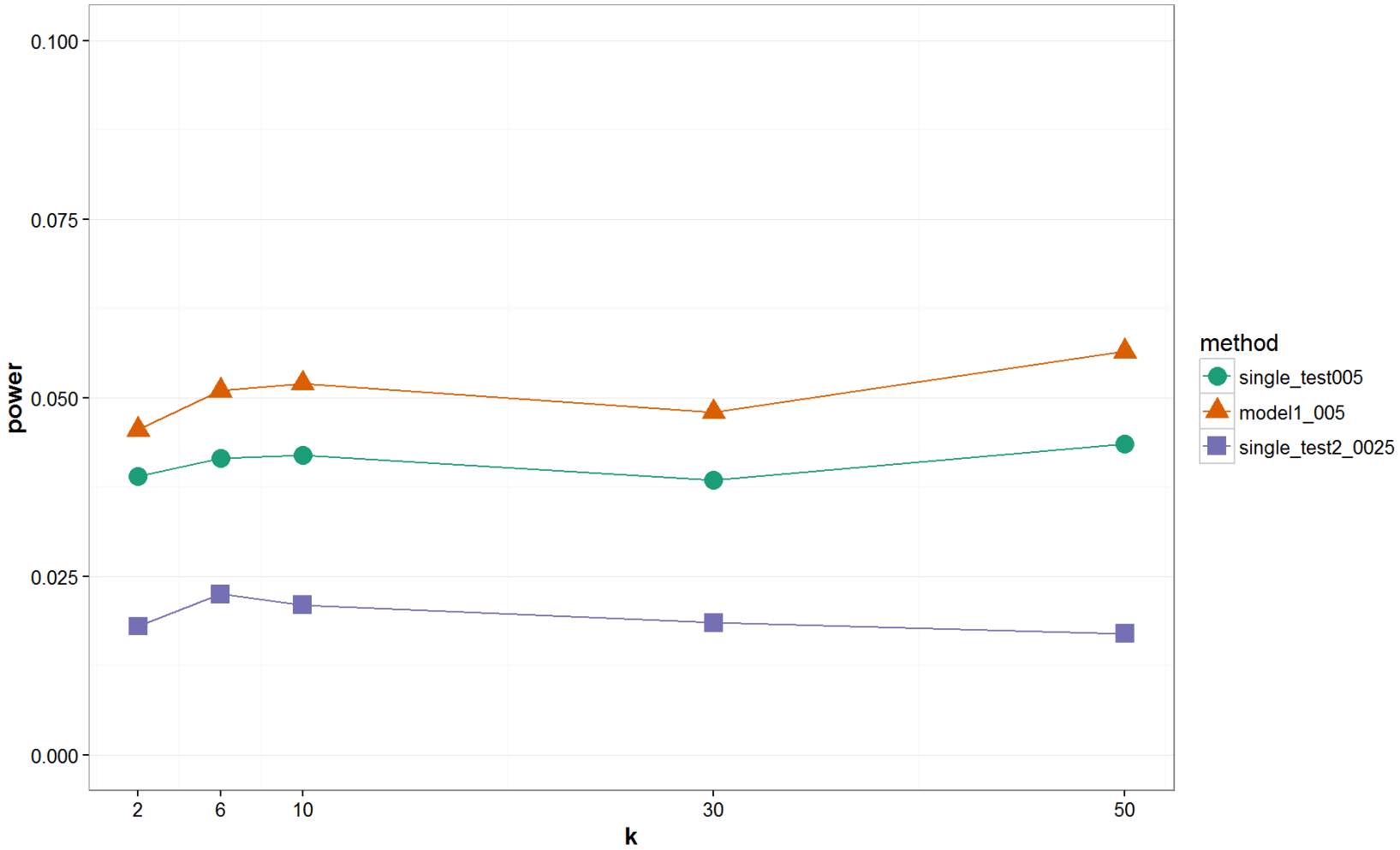
Type I error



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Transition curve for LASSO

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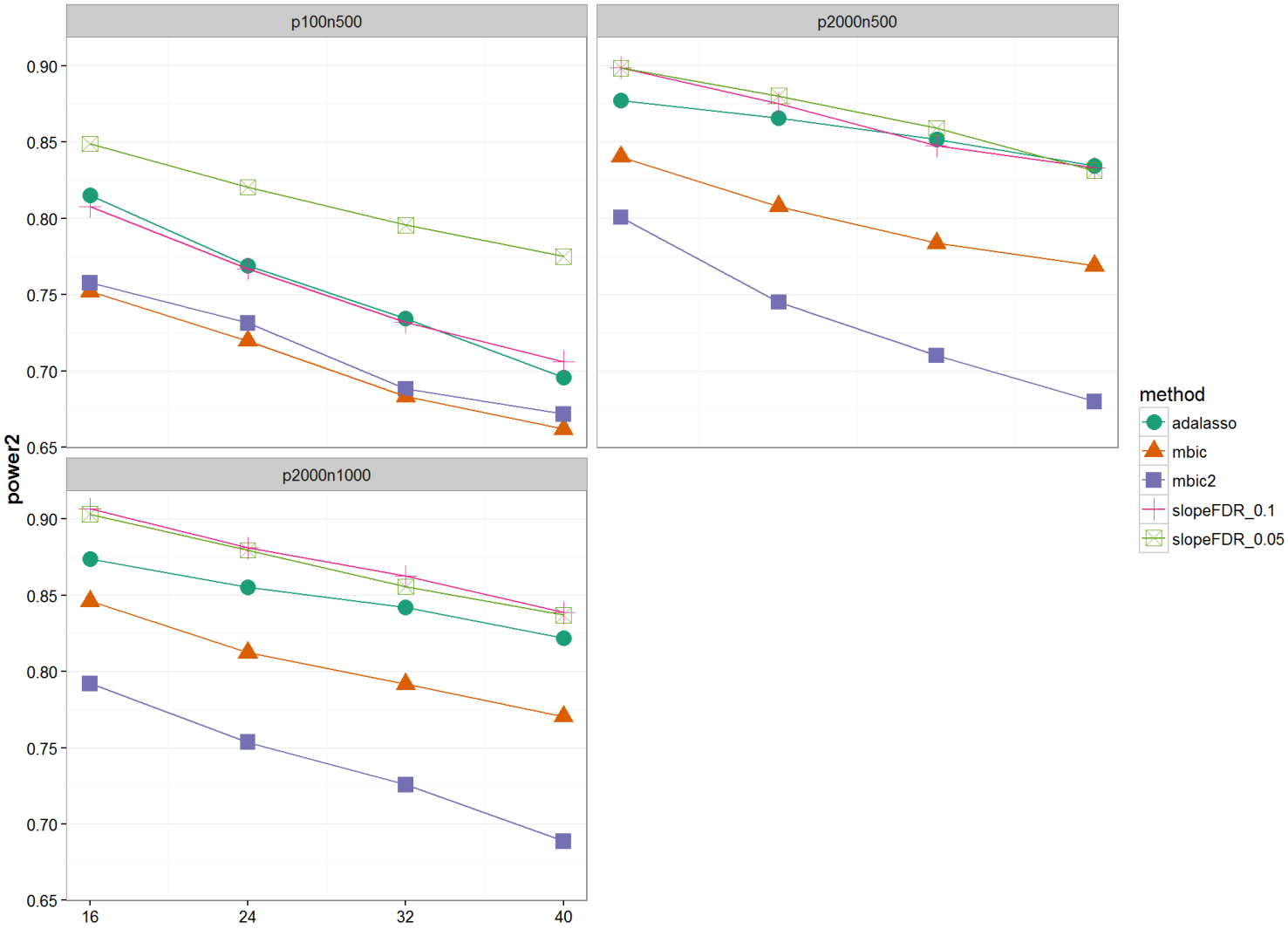
Other direction of current research - concentrate on prediction properties also in correlated designs e.g. gene expression data

Power at the patient's level - hidden factors (proxy for gene expressions)

$$X_{n\times p} = F_{n\times r}C_{r\times p} + \epsilon, \quad Y = F\beta + \epsilon$$



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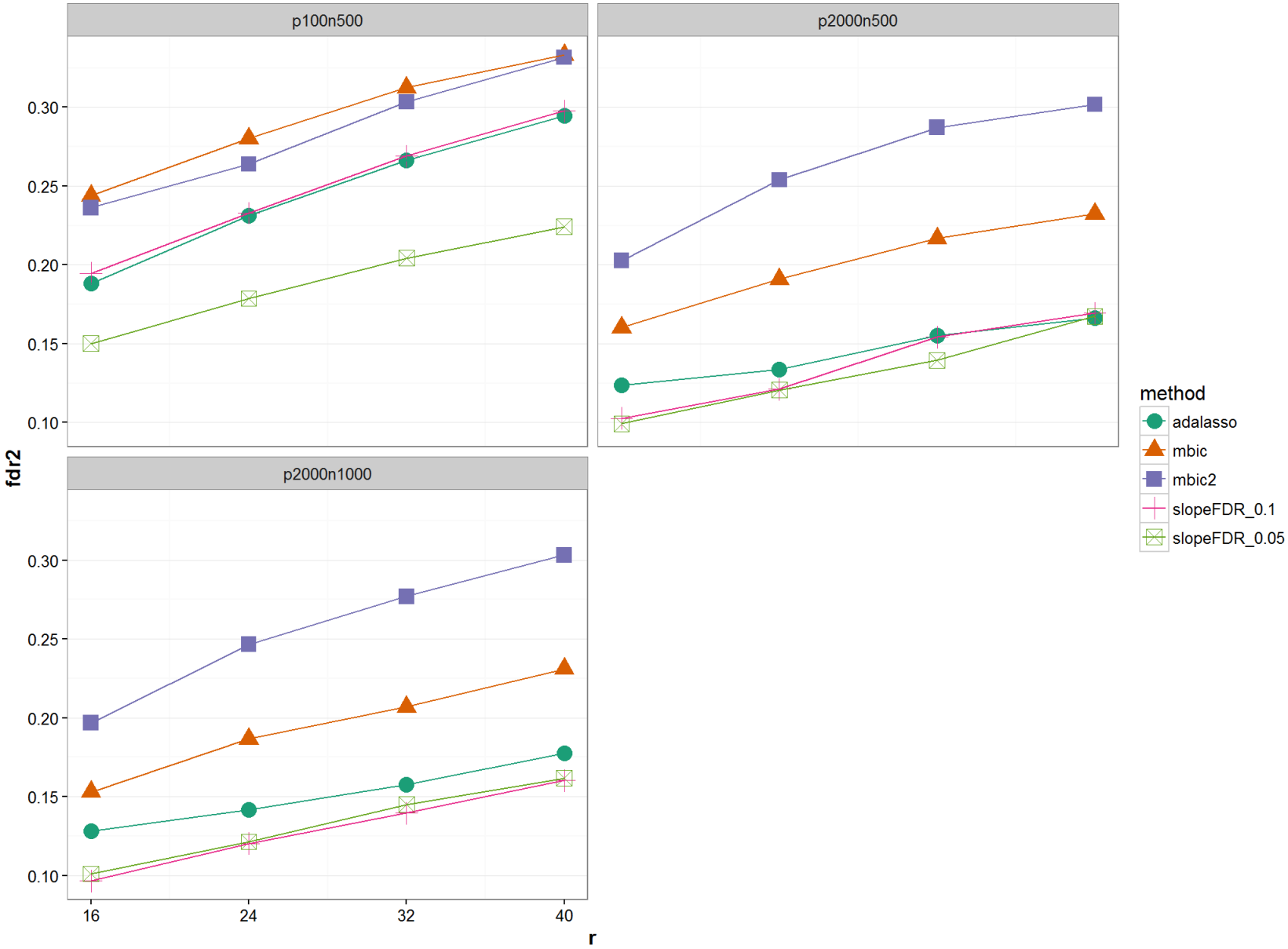

Analyzing Gene Expression Data (2)

R package *ClustofVar* available on *github* by P. Sobczyk - identification of genetic pathways by subspace clustering and modified BIC

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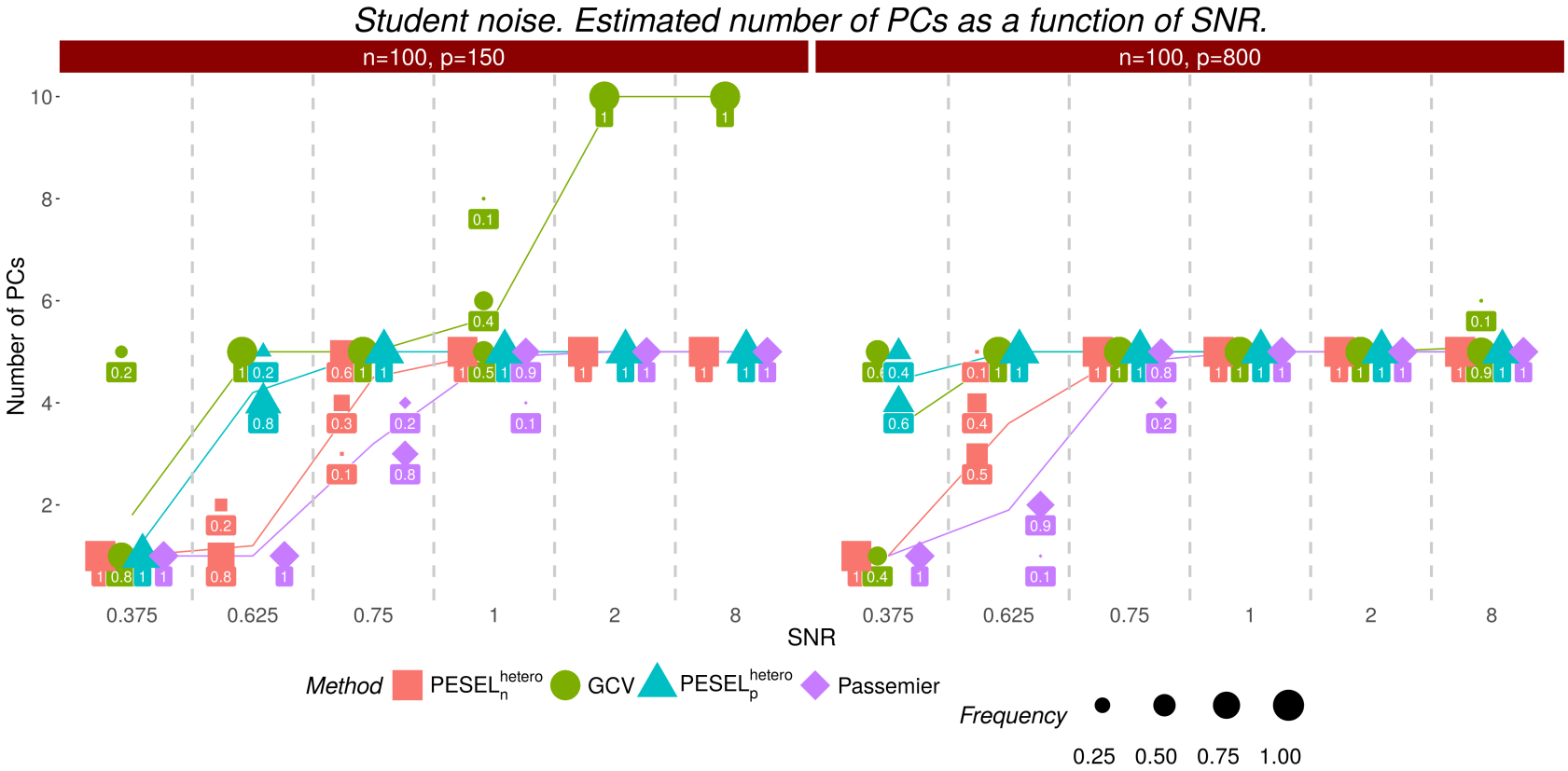
Student noise. Estimated number of PCs as a function of SNR.
n=100, p=150
n=100, p=800
Number of PCs
10
8
6
4
2
0.375
0.625
0.75
1
2
8
SNR
Method
PESEL$_n^{hetero}$
GCV
PESEL$_p^{hetero}$
Passemier
Frequency
0.25
0.50
0.75
1.00

Publications (1)

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- D. Brzyski, A. Gossmann, W.Su, M. Bogdan, "Group SLOPE - adaptive selection of groups of predictors", arXiv, 2016.
- S. Lee, D. Brzyski, M. Bogdan, "Fast Saddle-Point Algorithm for Generalized Dantzig Selector and FDR Control with the Ordered l_1-Norm", *Proceedings of AISTATS2016, JMLR:W and CP* **vol.51**, 780–789, 2016.

Publications (2)

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- P. Szulc, M. Bogdan, F. Frommlet, H. Tang, "Joint Genotype- and Ancestry-based Genome-wide Association Studies in Admixed Populations", biorxiv, doi: http://dx.doi.org/10.1101/062554, 2016.
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R packages

- *SLOPE* by E. Patterson
- *geneSLOPE* by P. Sobczyk
- *grpSLOPE* by A. Gossmann
- *bigstep* (mBIC, mBIC2) by P. Szulc
- *ClustofVar* by P. Sobczyk