Feature Discovery in Small-Sized Experiments in Early Drug Development

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Context

- Pre-clinical pharmacological research
- Biomarker discovery
- (Multi-) Omics

Problem

- Increasing popularity machine learning
- High hopes for better, more, easier discoveries

However

- High dimensionality: up to 10.000 and more features
- Extremely small sample sizes (10 to 50)

And

- Little is known about the performance of methods in these extreme situations

Therefore

- Need for a neutral comparison study

Research questions

- How do ‘traditional’ hypothesis tests compare to ‘modern’ statistical methods in these situations?
- Which methods are better suited for different scenarios?
- What are limitations and weaknesses of the different methods?

→ Proposal of guidelines: “How (not) to”

Included methods

- Welch’s t-test with FDR control
- Welch’s t-test with empirical Bayes based selection bias correction using Tweedie’s formula
- Logistic regression with L1 regularization
- Random forests based RFE
- Support vector machine based RFE

Simulation study

- Variety of scenarios
  - Data generating mechanism
  - Sample size
  - Number of features
  - Number of predictive features
  - Degree of discriminativeness
- Estimands
  - Number of true/false detections
  - Chance of true/false detection
  - Discriminative ability:
    - AUC
      - (Bias)
      - (Variance)

Challenges

- Selection of methods
- Computational demands
- Integration of results and visualization

Example analysis