Optimized graphical testing procedures

Dr. rer. nat. Dennis Görlich (dennis.goerlich@uni-muenster.de)

Dr. rer. nat. Robert Kwiecien,

Prof. Dr. rer. nat. et med. habil. Andreas Faldum

Westfälische Wilhelms-Universität Münster

Institut für Biometrie und Klinische Forschung

Schmeddingstrasse 56

48149 Münster

Overview

1. Motivation

2. Graphical multiple testing procedures

3. Evolutionary algorithm for optimization

4. Simulation study

5. Outlook

Motivation

- Clinical trials often are planned to answer several equally important hypotheses simultaneously.

- Graphical multiple testing procedures as propopsed by Bretz et al. provide a viable tool to set up statistical designs for clinical trials.
  (applicable for suitable set of hypotheses)

- The development of a suitable graphical design is a task that requires much experience and thought on the desired properties of the statistical tests.

What is a good graphical multiple testing procedure, given a planning alternative?

Graphical multiple test procedures

After Bretz et al. (2009):

Given a set **H** of m elementary hypotheses H_i, the specification of

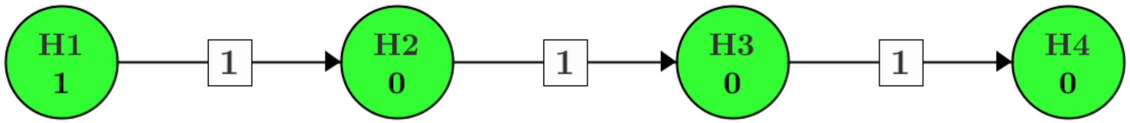
- a local significance levels $\boldsymbol{\alpha} = (\alpha_1, \dots, \alpha_m)$ with $\sum_i \alpha_i = \alpha$
- a $m \times m$ transition matrix $\boldsymbol{G} = (g_{ij})$
  with $0 \leq g_{ij} \leq 1, \quad g_{ii} = 0, \ \sum_k g_{ik} \leq 1, \forall\, i, j = 1, \dots, m$
- an update algorithm

defines a short cut for a consonant closed test procedure with weighted Bonferroni tests for the intersection hypotheses.

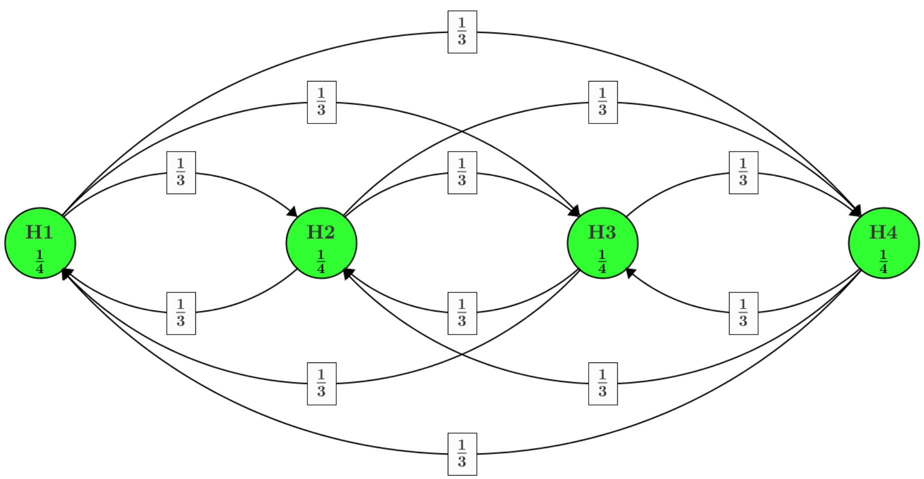
Bretz, Maurer, Brannath, Posch, 2009,
„A graphical approach to sequentially rejective multiple test procedures“, Statistics in Medicine, 28:586-604

Graphical multiple test procedures

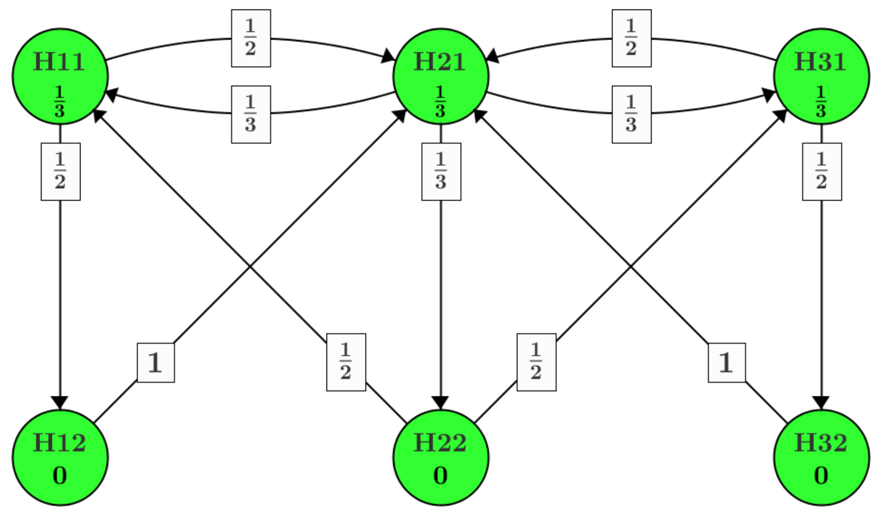
Fixed sequence procedure



Bonferroni-Holm procedure



Procedure from Bretz et al. 2011



Graphical multiple test procedures

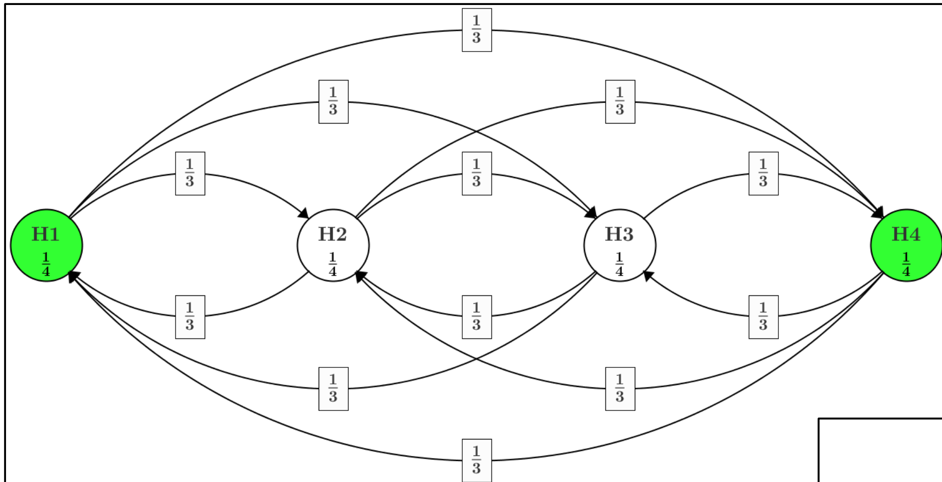
$\alpha = 0.05$

p1=0.0001

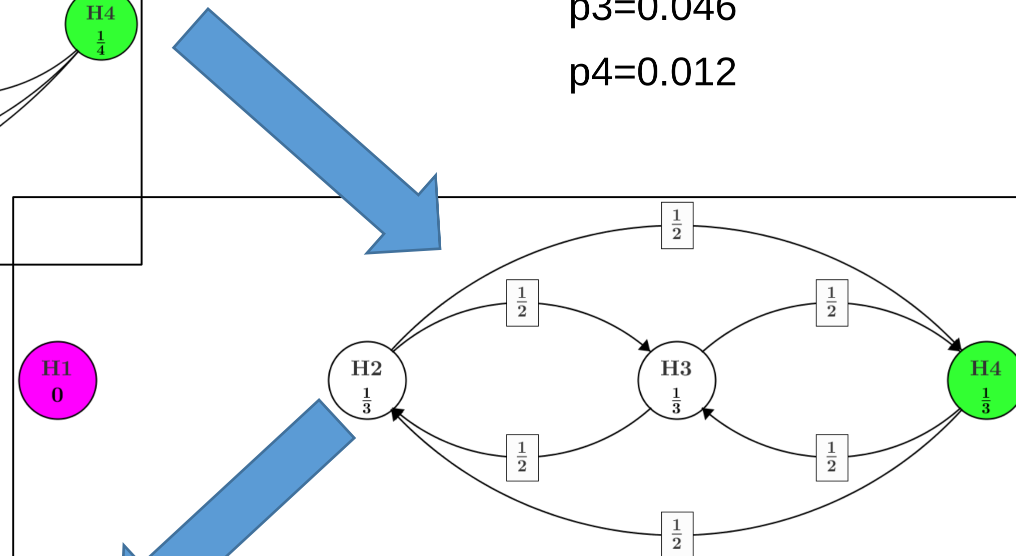
p2=0.823

p3=0.046

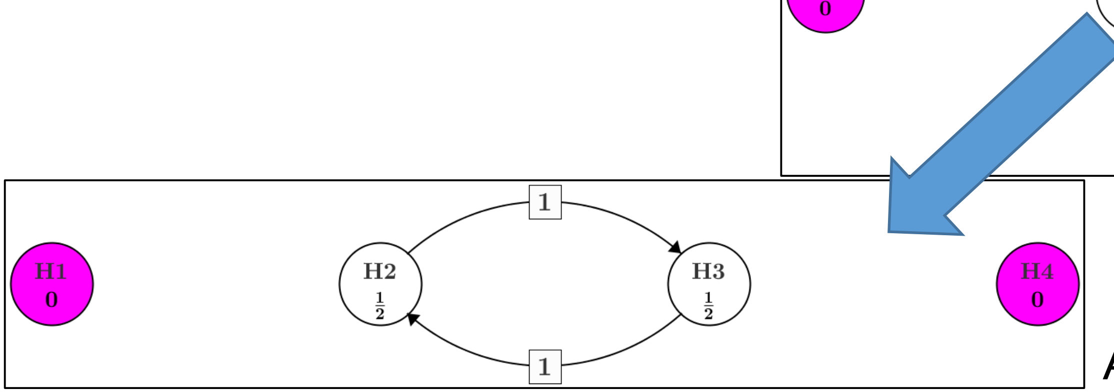
p4=0.012



Initial graph

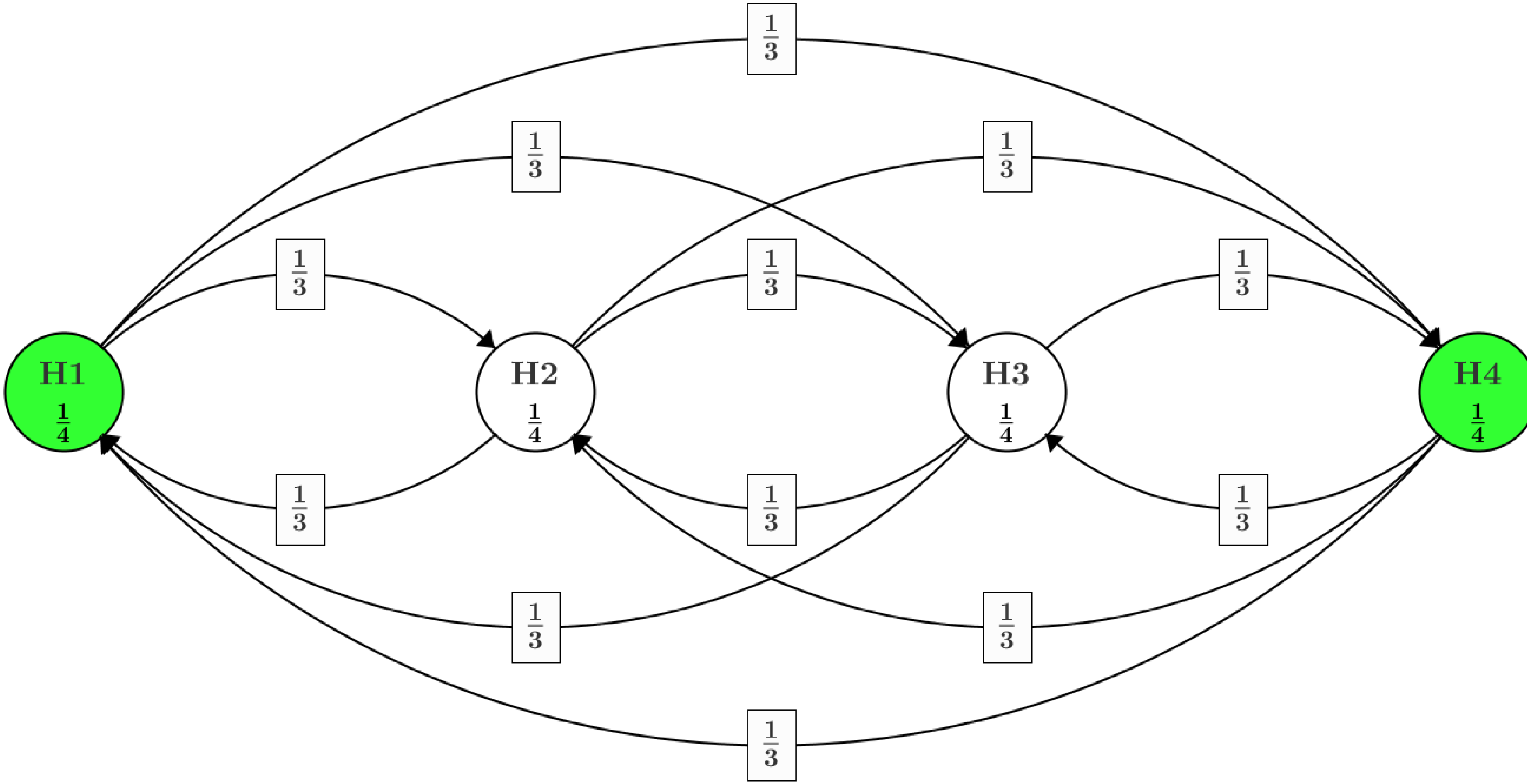


After 1st rejection



After 2nd rejection

Can we optimize these graphical designs?



Optimization problem

A multiple test problem among the elementary hypotheses $(H_i)_{i \in I}$ a sequential rejective testing procedure T is characterized by the transition weight matrix $\boldsymbol{G} = \left(g_{ij}\right)_{i,j \in I}$ and node weight vector $\mathbf{w} = (w_i)_{i \in \mathrm{I}}$.

Given

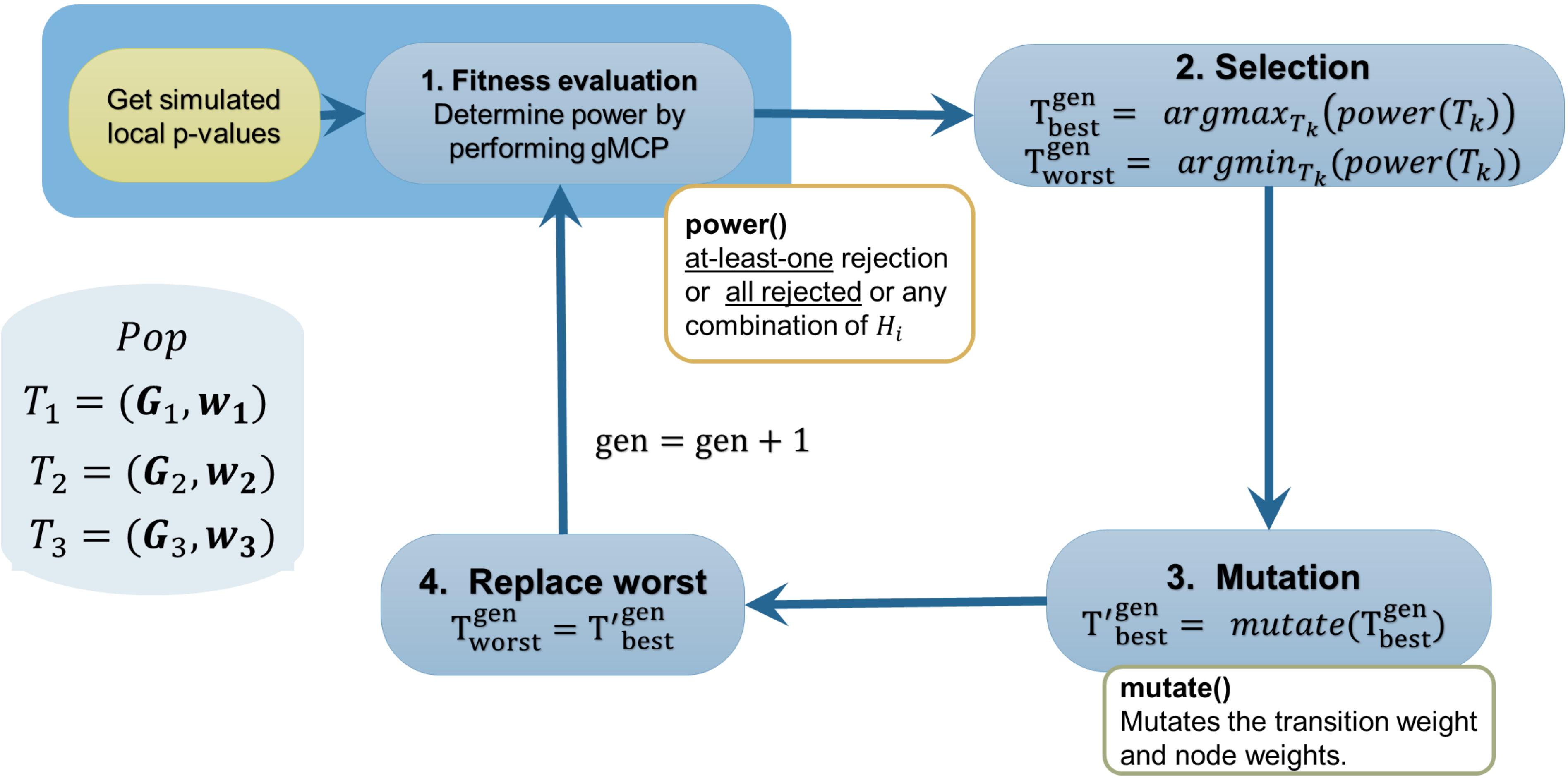
- a planning alternative **K**
- and a fitness function f(**G**,**w, K**)

the optimal multiple testing problem (**G***,**w***) has to be identified by maximizing f(**G**,**w**,**K**).

Here power is used as fitness measure

- at-least-one rejection
- reject all hypotheses
- reject an arbitrary subset of hypotheses

Evolutionary algorithm



Implementation: R, package `gMCP`

A simulation study

Clinical trial with

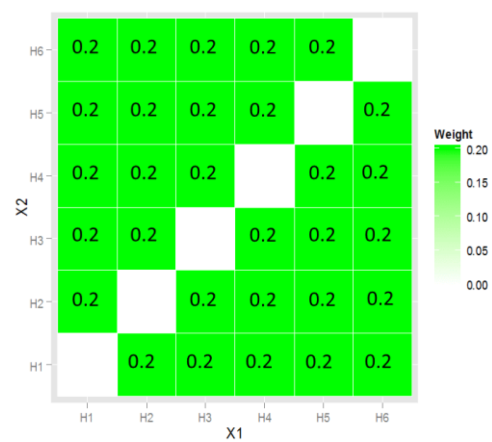
- 1 group of N patients
- 6 continous test statistics $\sim N(d_i, 1), i = 1,..,6$
- One-sample t-Tests with $H_i: d_i = 0, i = 1,..,6$
- Planning alternatives:

$$K_1: d_1 = 0 \qquad K_2: d_2 = 0.1 \qquad K_3: d_3 = 0.1$$

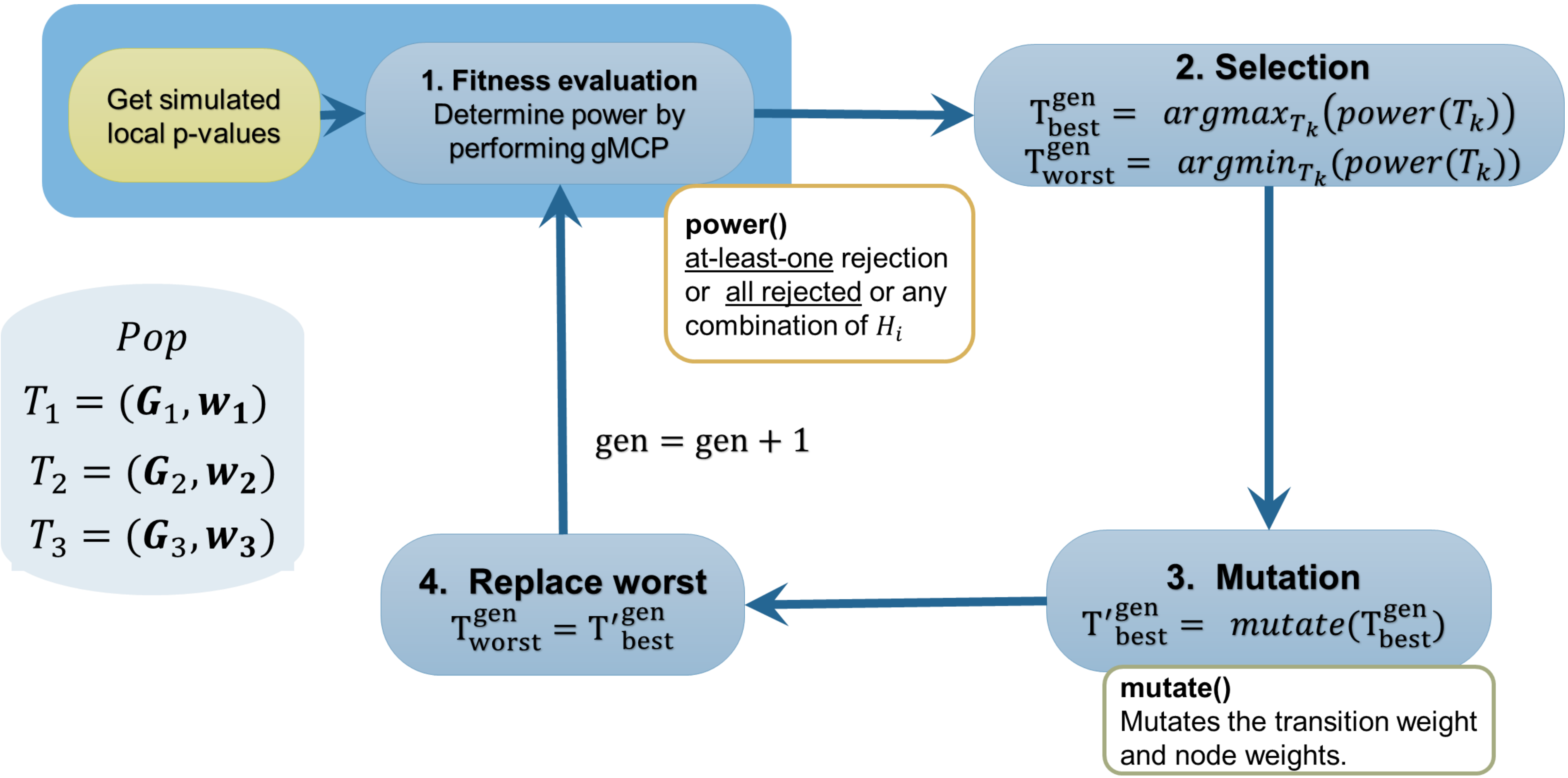
$$K_4: d_4 = 0.2 \qquad K_5: d_5 = 0.3 \qquad K_6: d_6 = 0.4$$

Inititalisation = Bonferroni-Holm

$$w_1 = 0.1667$$
$$w_2 = 0.1667$$
$$w_3 = 0.1667$$
$$w_4 = 0.1667$$
$$w_5 = 0.1667$$
$$w_6 = 0.1667$$

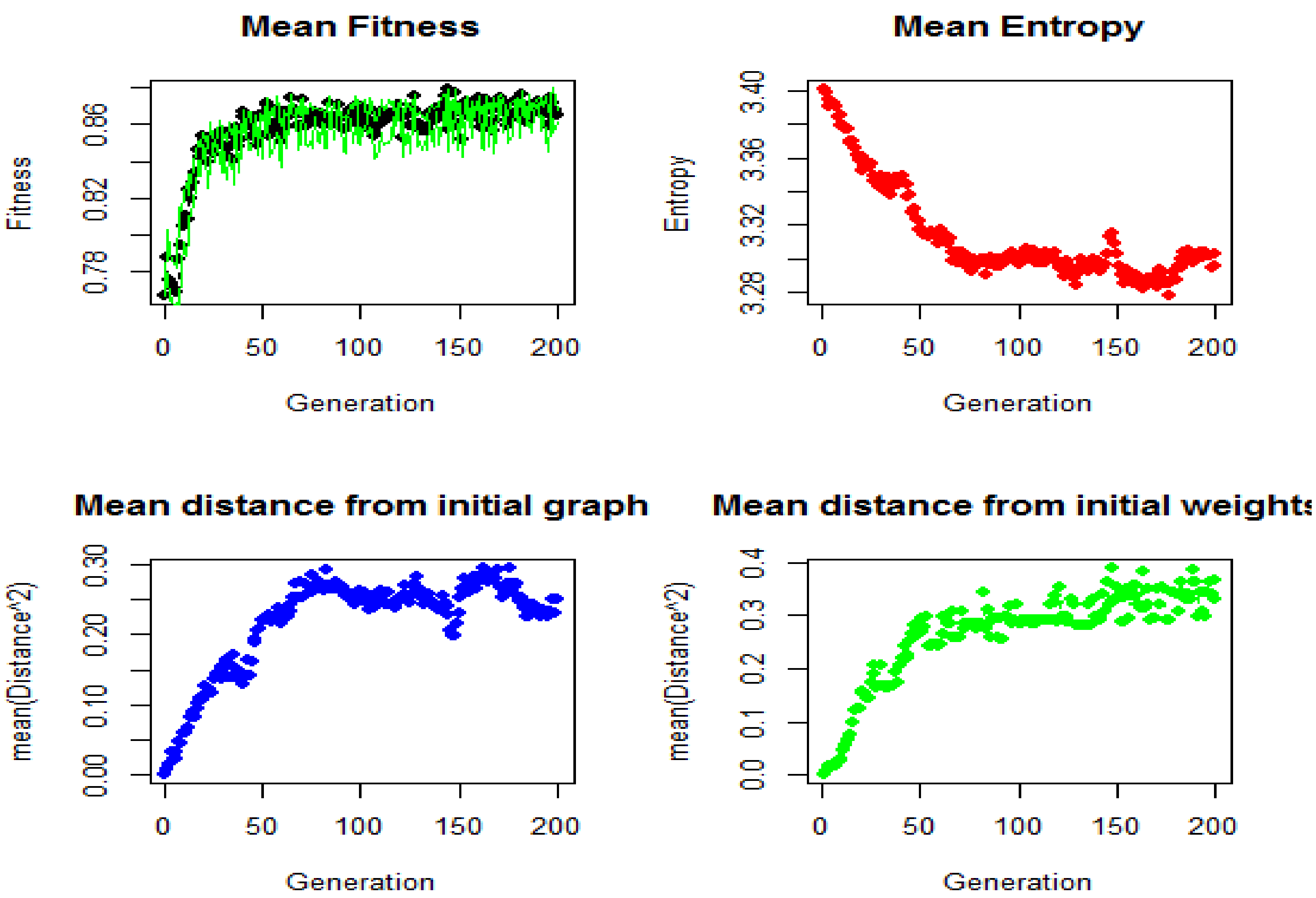


Evolutionary algorithm

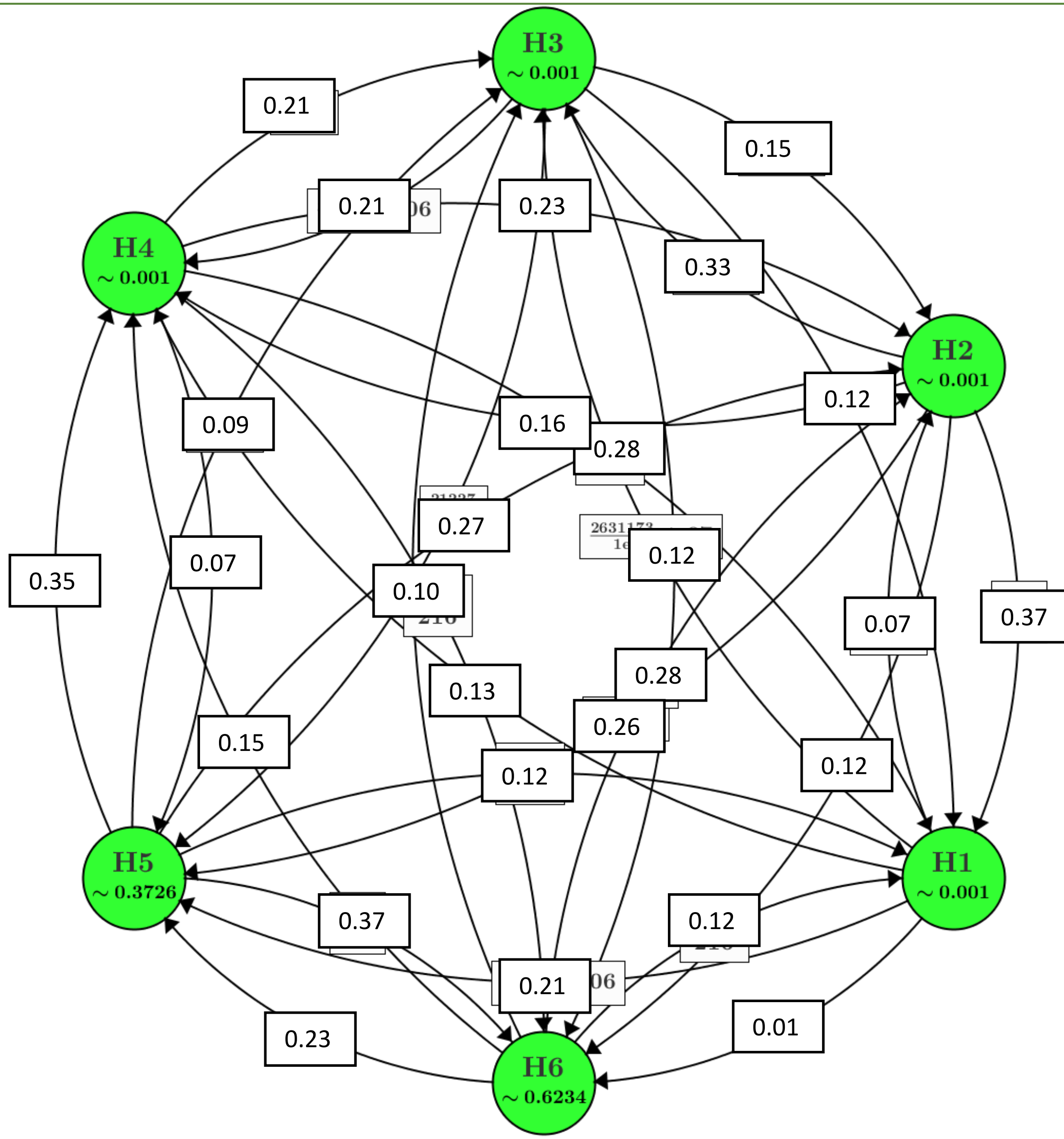


Implementation: R, package `gMCP`

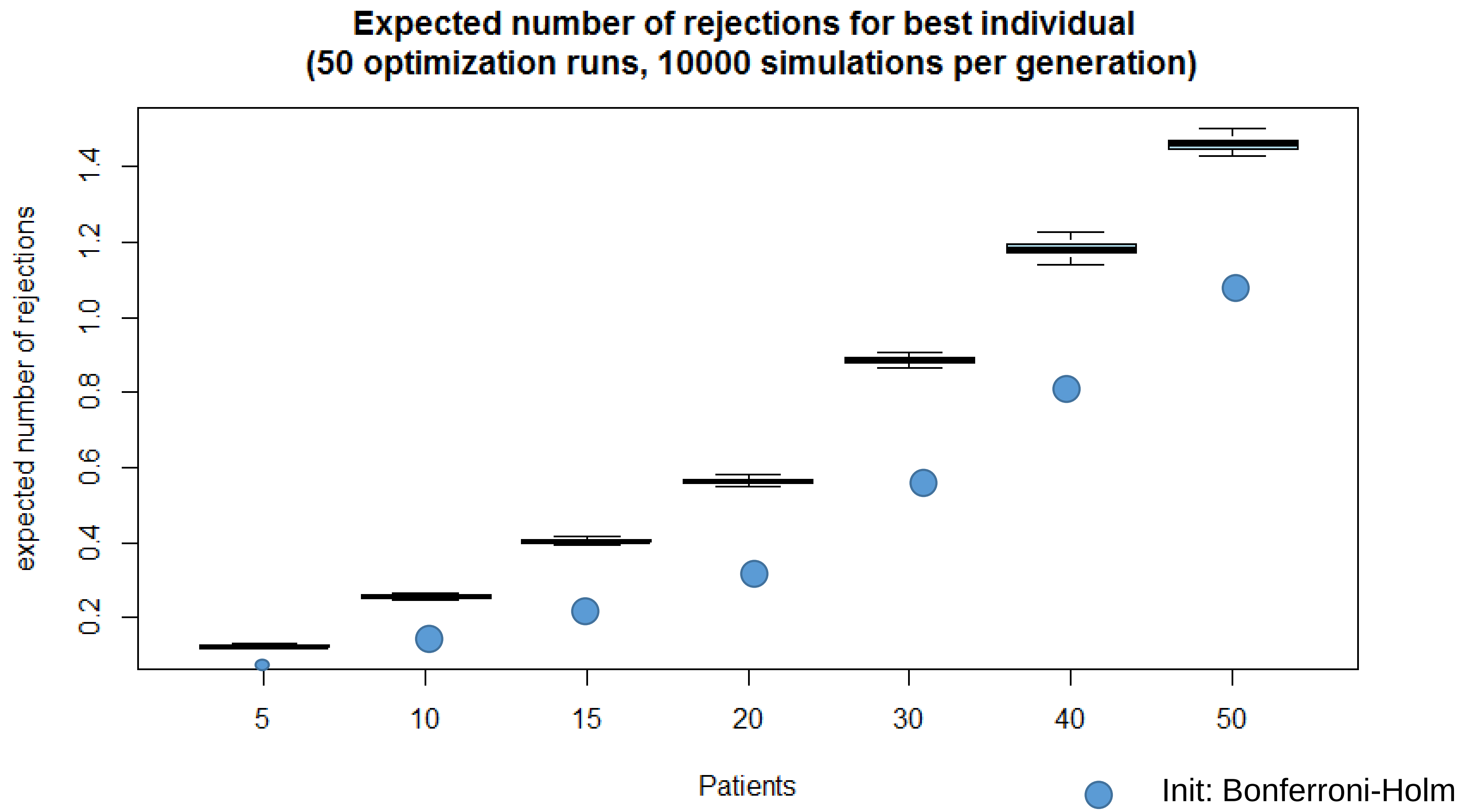
Exemplary optimization run



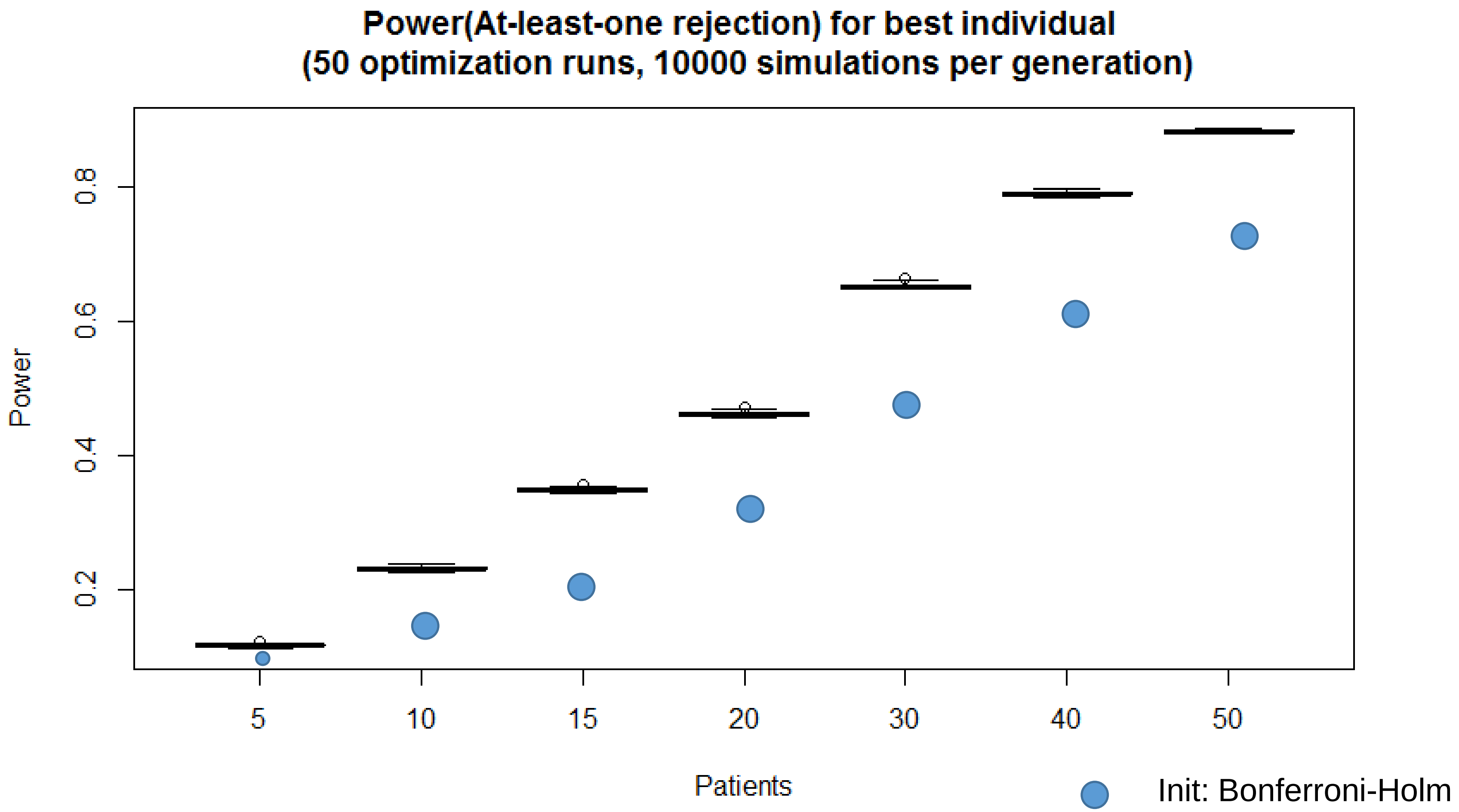
Exemplary optimization run



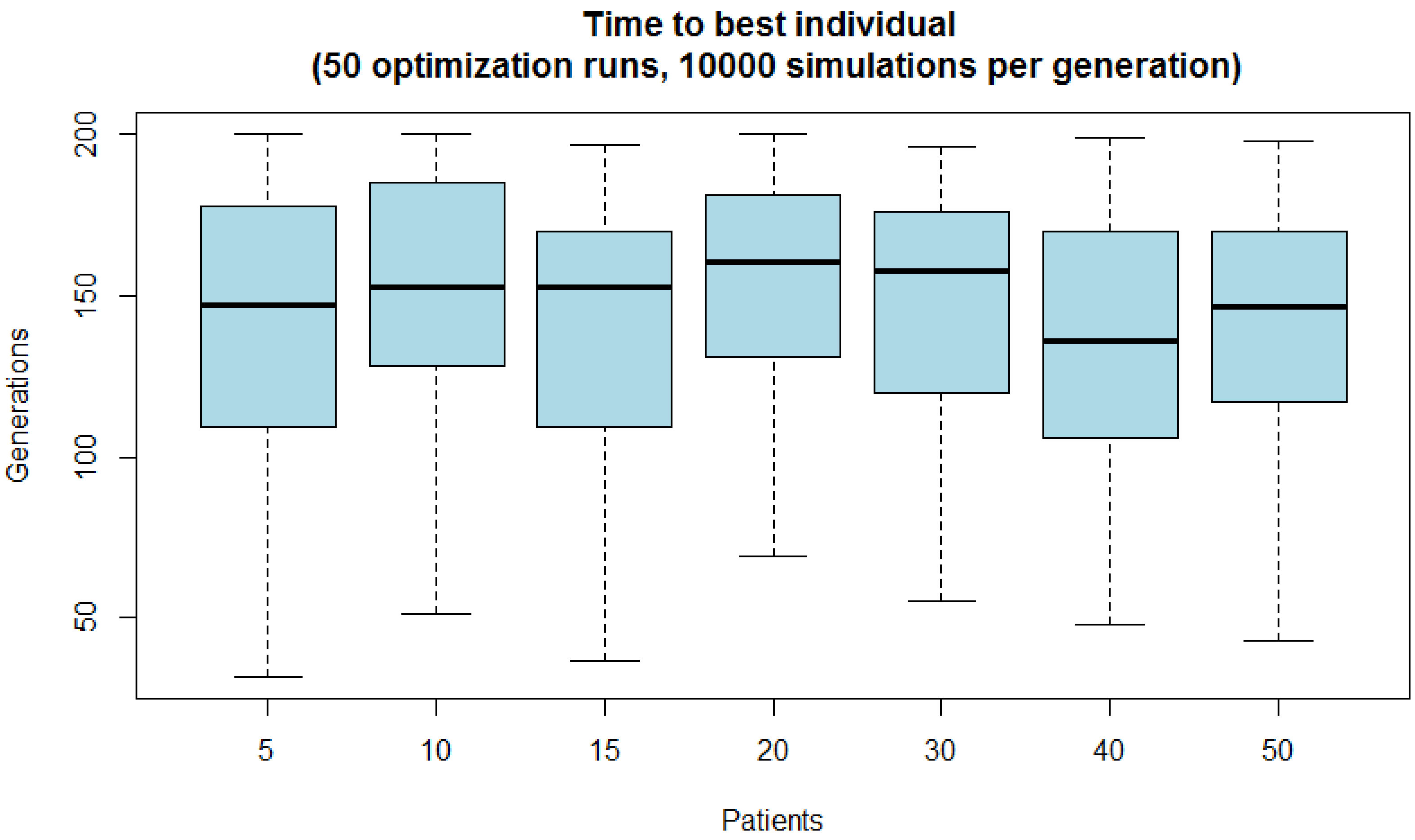
Expected number of rejections



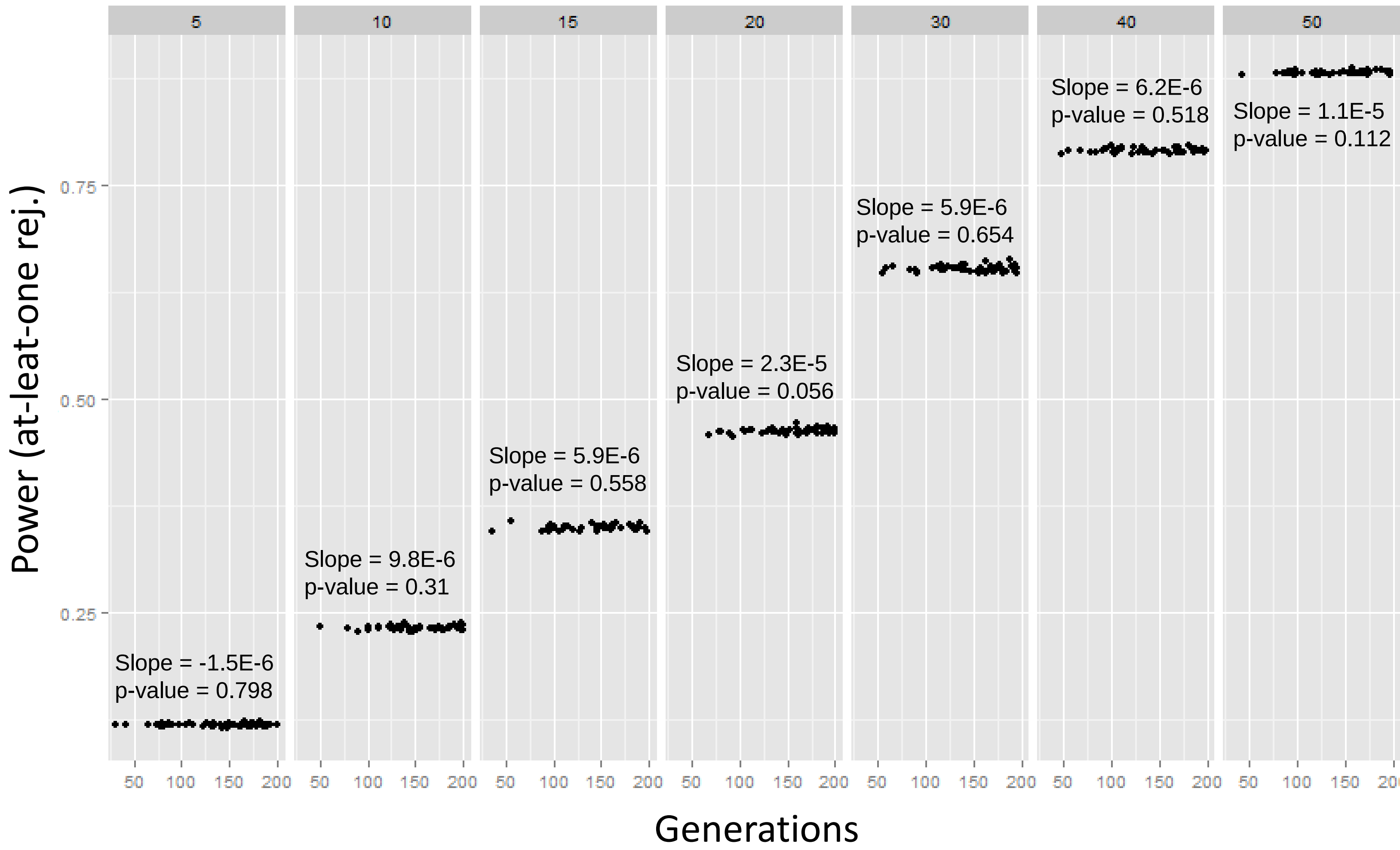
Power (at least one rejection)



Time to best individual

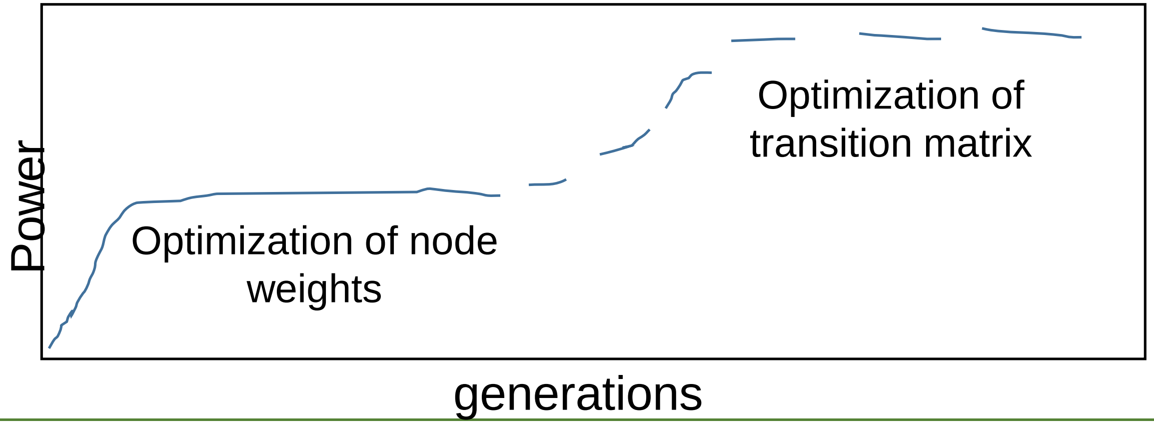


Does time have an effect on fitness?



Summary

- Graphical multiple test procedures can be optimized with respect to power.
- Given a planning alternative the main factor for optimization seems to be the node weights **w**.
- Length of opt. runs: Later found optimal solutions does not seem to be much better with respect to power.



Outlook

- EA parameters / characteristics (population size, adaptive mutation strength).
- Contraints on the design need to be maintained during optimization.
- Optimization for multiple fitness values simultaneously, e.g., maximizing the power to reject two primary hypotheses and the expected rejections.
- Optimization and simultanous sample size determination given a desired power.

Optimized graphical testing procedures

Dr. rer. nat. Dennis Görlich (dennis.goerlich@uni-muenster.de)

Dr. rer. nat. Robert Kwiecien,

Prof. Dr. rer. nat. et med. habil. Andreas Faldum

Westfälische Wilhelms-Universität Münster

Institut für Biometrie und Klinische Forschung

Schmeddingstrasse 56

48149 Münster

Workshop „Adaptive Designs and Multiple Testing procedures“

26.06.-28.06.2015