P-BEST: IN-BETWEEN RANDOMIZATION AND MINIMIZATION

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Clinical studies

- The quality of a clinical study depends on:
  - Design
  - Blinding
  - Randomization
  - Measurements

- We will focus on
  - **Randomization: Allocation of subjects to treatment through a process governed by chance**

Randomization

- To avoid **confounding bias** by producing study groups comparable in unknown as well as known factors
- To provide a sound statistical basis
  - Permits construction of valid tests of statistical inference
- To avoid **bias in selection and allocation** of subjects arising from predictability of treatment assignments

Randomization

- Pure: like tossing a coin
  - Does not produce exactly the prespecified proportions of subjects in each study group
    - Reduction in the power of the study, for example:
      in case of n_1=20 and n_2=20, power=90%
      in case of n_1=18 and n_2=22, power=88.2%
      in case of n_1=15 and n_2=25, power=86.5%
      probability to have a difference of more than 8 infants = 15%
  - May produce occasional long sequences of the same treatment assignment
    - Unwanted homogeneity among subjects entered at approximately the same time

Randomization

- Block: blocks in which treatments are equally represented
  - Keep the numbers of subjects in the different groups closely balanced at all times
  - Last treatment allocation in a block is predictable
- Stratified: consideration of stratification factors
  - Achieve approximate balance of important characteristics (ex: gender, age, smoking, …)
  - For each stratum, block randomization; only feasible with a small number of strata

Randomization

- Minimization
  - Take into account the allocation of all previous randomized subjects
  - Assign the next subject in a way which minimizes the imbalance
  - Deterministic procedure

  - With P-Best
  - To avoid too much predictability, introduction of a probability for the allocation to the “best” treatment

Example of minimization

- 3 treatment groups (A, B, C)
- 1 factor (age) with 3 levels
- 84 subjects have already been randomized

age	A	B	C
20-40	16	15	13
40-50	3	4	5
50-60	10	10	8
Total	29	29	26

Example of minimization

Nestl
Good Food, Good L

To group A

age	A	B	C	|A-B|	|B-C|	|C-A|	Imbalance
20-40	16+1	15	13	4	4	16	
40-50	3	4	5	1	1	4	
50-60	10	10	8	0	4	4	
Total	29+1	29	26	5	9	24	38

To group B

age	A	B	C	|A-B|	|B-C|	|C-A|	Imbalance
20-40	16	15+1	13	0	9	9	
40-50	3	4	5	1	1	4	
50-60	10	10	8	0	4	4	
Total	29	29+1	26	1	14	17	32

To group C

age	A	B	C	|A-B|	|B-C|	|C-A|	Imbalance
20-40	16	15	13+1	1	1	4	
40-50	3	4	5	1	1	4	
50-60	10	10	8	0	4	4	
Total	29	29	26+1	2	6	12	20

Minimization

- Imbalance for one factor *i*
  - L_i *levels*
  - n_{jA} and n_{jB}*:* status before new subject randomized

If allocated to treatment A:

$$\sum_{j=1}^{L_i}\left(n_{jA}+1-n_{jB}\right)^2$$

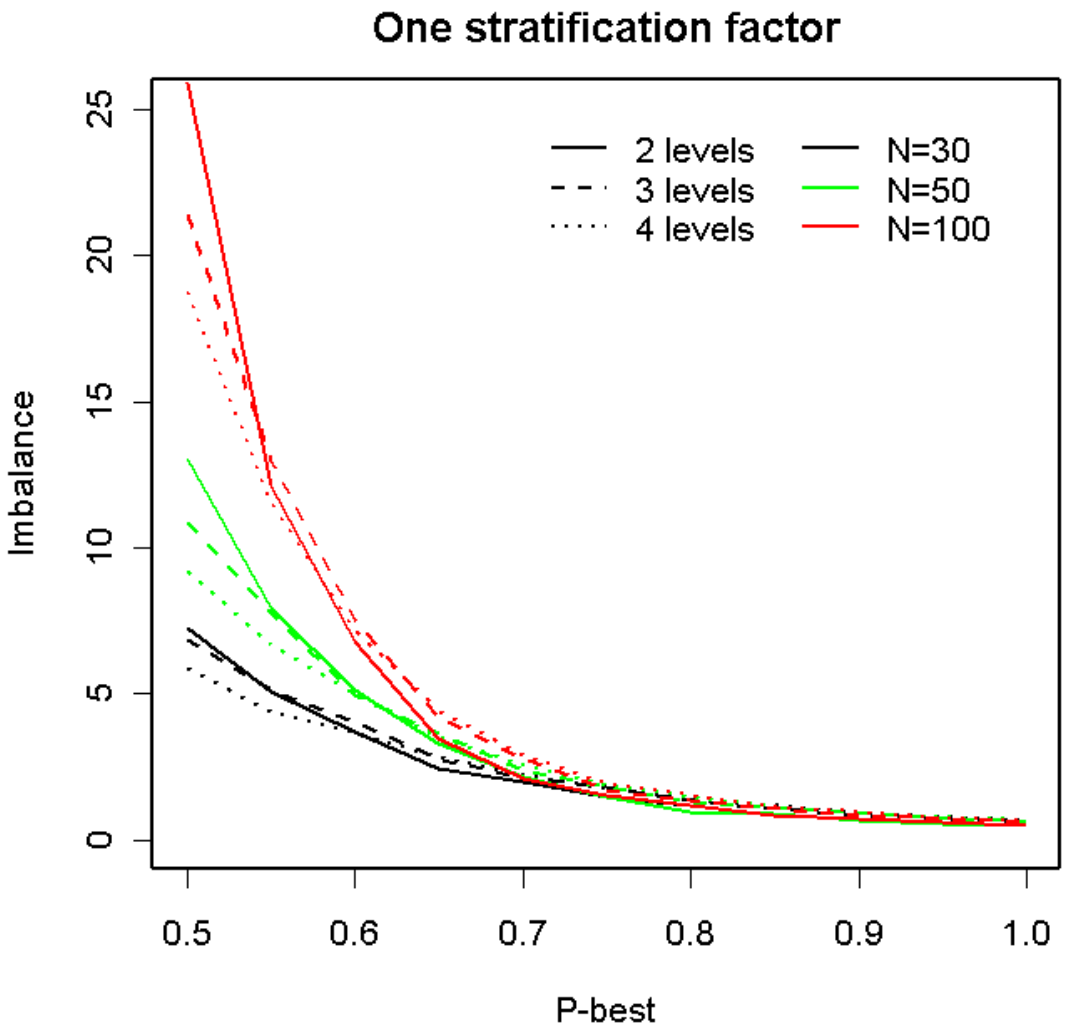
If allocated to treatment B:

$$\sum_{j=1}^{L_i}\left(n_{jA}-n_{jB}-1\right)^2$$

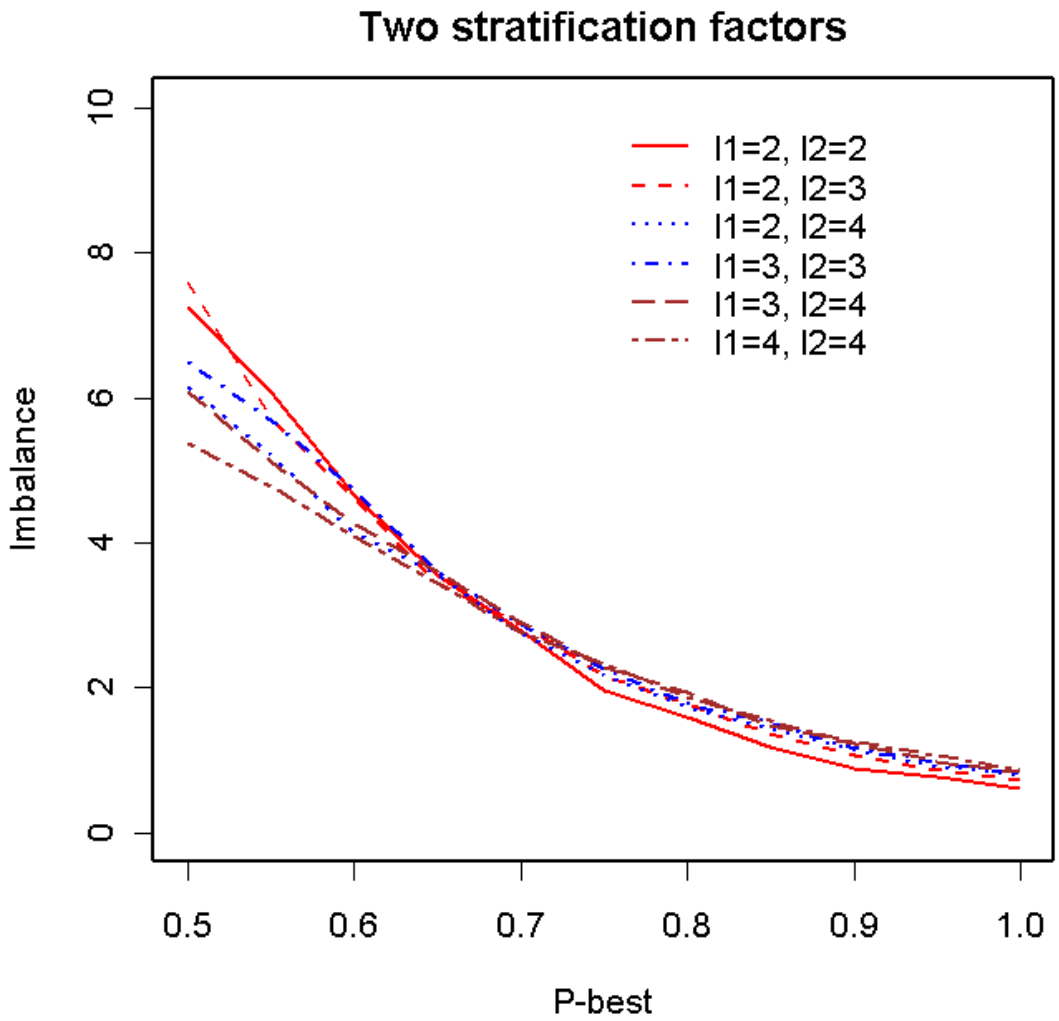
Minimization

- Simulations
  - Determine influence of P-Best on imbalance
  - 1000 simulations
  - 2 treatment groups (at the end same number of subjects)
  - N = 30, 50, 100 in total
  - # levels of a stratification factor = 2, 3, 4

Minimization



Minimization



Minimization

- Choice of a P-Best of 80%
  - Good compromise
  - Does not depend on N and on number of levels

Randomization program

- Goals
  - To computerize the minimization with P-best
  - User-friendly interface for the caregivers
  - To be able to deal with several stratification factors

- It is called “Trial Balance”

Randomization program