Brick Tunnel Randomization, Overcoming Inconvenient Allocation Ratio

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Outline

- Motivating examples
  - Existing randomization procedures and their limitation
- Allocation ratio preserving procedure
- Brick tunnel randomization (BTR)
  - Implementation
  - WBTR
- Applicability

Problem

- Studies with unequal allocation to two or more treatments groups might require randomization with inconvenient target allocation ratio
  - (i.e. large block size for the permuted block procedure)
  - Special needs of adaptive design studies
  - Multi-center studies (several treatments and stratified by center)
  - Small studies

Example 1. Adaptive dose ranging study

- "Frequent adaptation" type of design that utilizes changes in allocation ratio during the study
  - Cohort size: 10-15 patients
- The allocation ratio for the next cohort of patients is 14:21:25
- Permuted block size = 60
  - Too large for a cohort of 10-15
- Could lead to a subject allocation very different from the targeted one
  - Example: Under CR probability that N2 <N1 or N3<N2 is more than 50%

Example 2.
AD with Sample Size Re-estimation

- Clinical program consist of 3 efficacy study of a similar design
  - 1:1:1 allocation to 3 arms (PLB & 2 doses)
  - Planned sample size is 150 subjects per arm
  - Three study are planned to be run in parallel although heterogeneity in enrollment speed is very likely
  - Sample size re-estimation at interim analysis is based on pooling of information from all studies

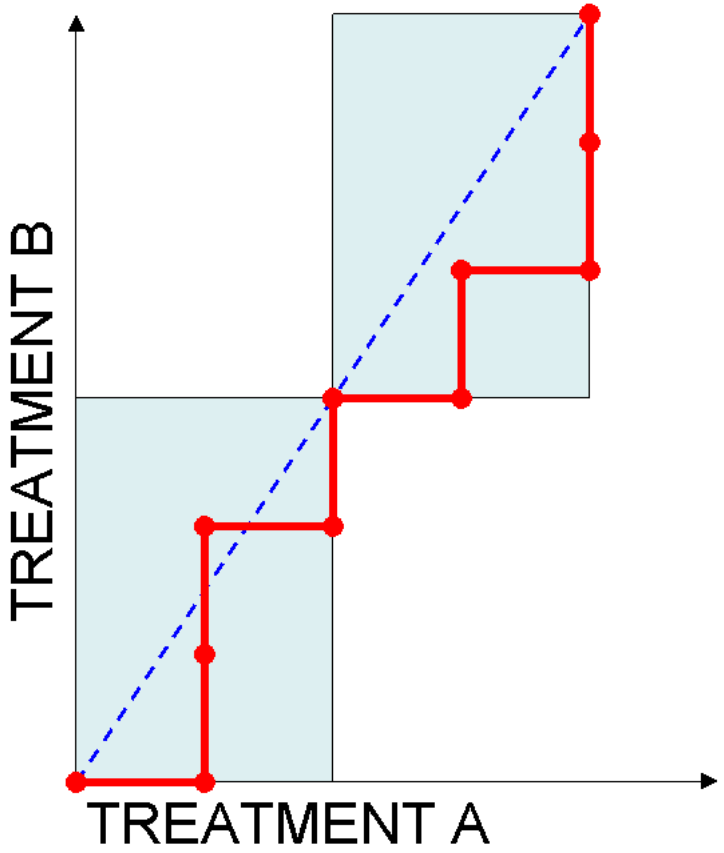
Example 2 (cont.)

- Depending on interim results, sample size could be increased by 50 or 100 additional subjects for one or two doses & PLB
  - I.e. different (disproportionate) increase by dose
- For a particular study, an actual sample size at IA is unknown at the planning stage as timing of IA fixed by total SS in 3 studies
- Allocation resulting in final Ns per arm exactly as designed lead to inconvenient randomization ratio (with lots of possible scenarios)
- E.g.

	PLB	Dose 1	Dose 2
N at IA	133	130	132
Planned N at final	150+50	150+50	150
Left to randomize	**67**	**70**	**18**

- A possible solution can be an approximation with "convenient" allocation ration and "over-" and "under-" run of the size at final

Visualizing Randomization Sequence

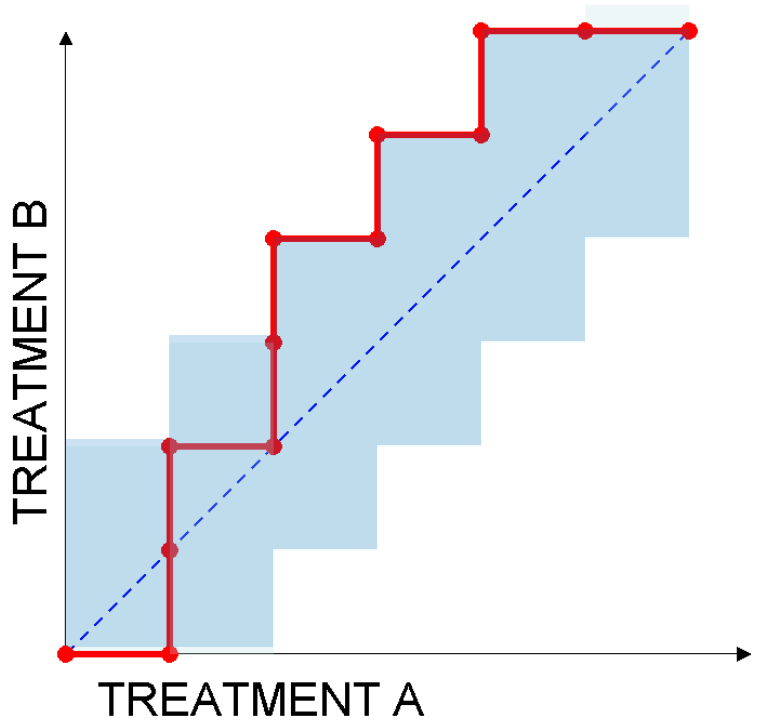


- Example: 2-Arm study with 2:3 allocation to treatments *A* and *B* (blue line – allocation ray)
- Permuted block randomization with block size=5
- Allocation path (in red) can be plotted on a 2-dimentional grid (*ABBABABABB*)

  Step to the right - allocation to *A*

  Step up - allocation to *B*
- Blue space: allowed space for PB allocation paths

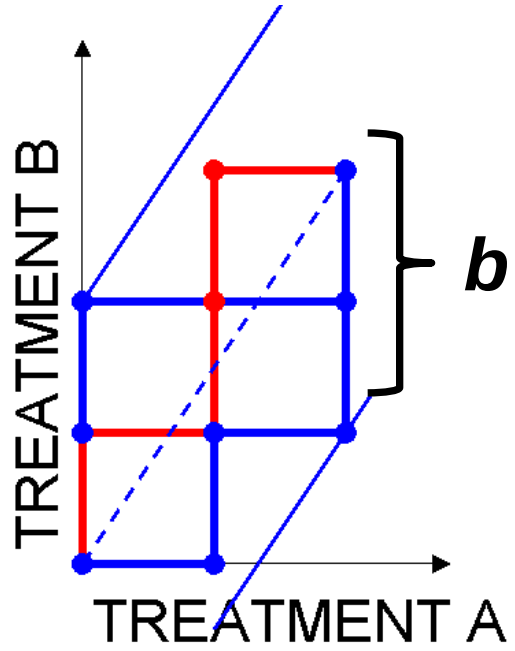
Maximal Procedure (MP) [Berger et al 2003]



- Defined for 2-arm study with **1:1 allocation**
- Allows all allocation sequences for which imbalance N_A-N_B never exceeds specified limit (maximum imbalance)
- Mainly used for open-label studies to reduce predictability vs. PB

- Blue dashed line: allocation ray
- Blue space: allowed space for MP allocation paths
- Red line: example of the allocation path

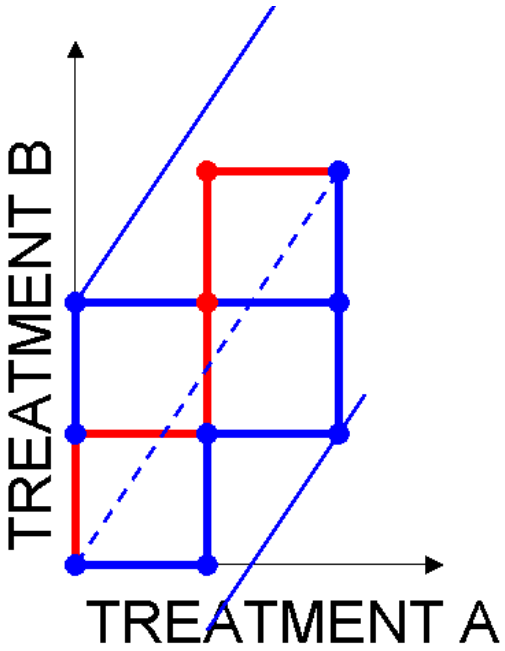
Generalization of Maximal Procedure for Unequal Allocation [Salama et al. 2008]



- Blue dashed line: Ray for 2:3 randomization
- Blue borders: borders of the allowed space with *b*=2
- Red line: example of the allocation path

- Allowed paths that stay within a strip $\pm b$ in height surrounding the allocation ray.
- Every permissible sequence has an equal probability to be chosen as an allocation sequence.
- Assigning equal probabilities to all paths creates a problem

Why Assigning Equal Probabilities to All Permissible Sequences Creates a Problem?



- **Changes in the unconditional allocation ratio from allocation to allocation**
- 2:3 allocation for SP with b=2
- 8 allowed sequences of 5 allocations:

  ABABB ABBAB ABBBA BAABB
  BABAB BABBA BBAAB BBABA
- 1st, 2nd, 4th, and 5th patients are allocated in **3:5** ratio, not 2:3
- 3rd patient is allocated in 1:1 ratio

Procedure that changes unconditional allocation ratio could question study validity

- Failure to ensure that that the unconditional allocation ratio is the same for every position in allocation sequence is highly undesirable
  - Knowledge that the chances to be allocated to an active treatment are higher at certain allocation steps might lead to a **selection bias**
  - If there is a time trend it could also result in an **accidental bias** [K&T 2011]
  - Problem with re-randomization tests [K&T 2012]
- **This problem does not exist for equal allocation (as the set of allocation sequence is symmetric)**

Allocation Ratio Preserving (ARP) Procedure Definition

- Let Ω be a set of all allocation sequences $w = (w_1, \ldots w_N)$ generated by a procedure:

  if treatment k assigned at the i-th allocation wi=k

  Procedure is ARP if
  - For all *i=1,…,N* and for all *k=1,…,K*

    $$\sum_{\omega \in \Omega} Prob(\omega)\, I\{\omega_i = k\} = \varrho_k$$

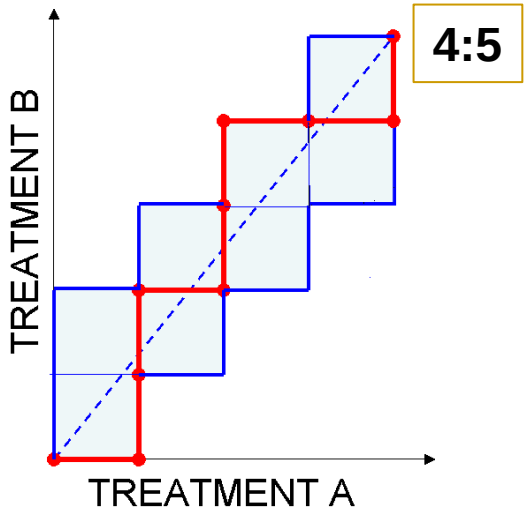
    ϱ_k - is the target allocation ratio for treatment k

Examples

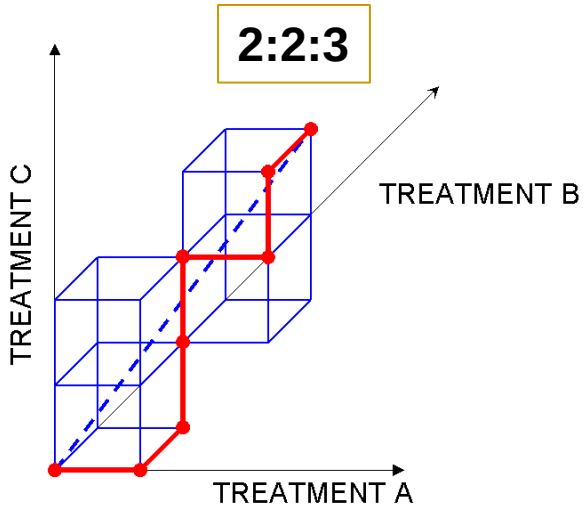
ARP Procedure	Non-ARP Procedure
Complete Randomization; Permuted Block	The unequal allocation extension of bias coin randomization and minimization [Han et. al. 2008]
Drop-the-loser [Ivanova 2003]	The double adaptive bias coin design DABCD [Hu & Zhang 2004]
BTR, WBR [Kuznetsova & Tymofyeyev (2009,2011)]	Maximal Procedure [Salama et. al. 2008]
…	….

Brick Tunnel (BT) Randomization

- Allocation path stay close to the allocation ray defined by the target allocation
  - **Good imbalance control at each subject allocation step**
- APR property
- If predictability of the next assignment is an issue (like in open-label study), being able to extend space for possible assignment sequences (Wide BTR)

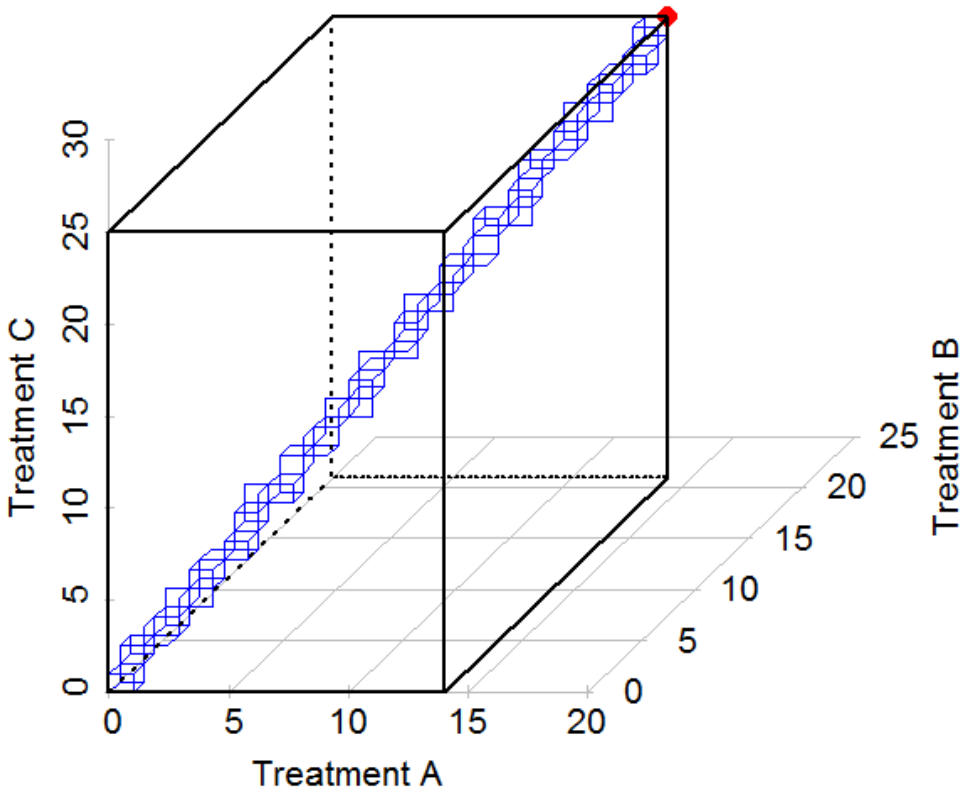


a)



b)

BT Randomization for 14:21:25 Allocation to Treatments A, B, and C



- Instead of occupying the whole 14×21×25 permuted block, BTR sequences are constrained to a chain of cubes along the allocation ray AR=(14u, 21u, 25u)
- Good approximation of the targeted allocation ratio even for short cohorts of 10-15 subjects
- Could allocate any number of patients not fixed in advance

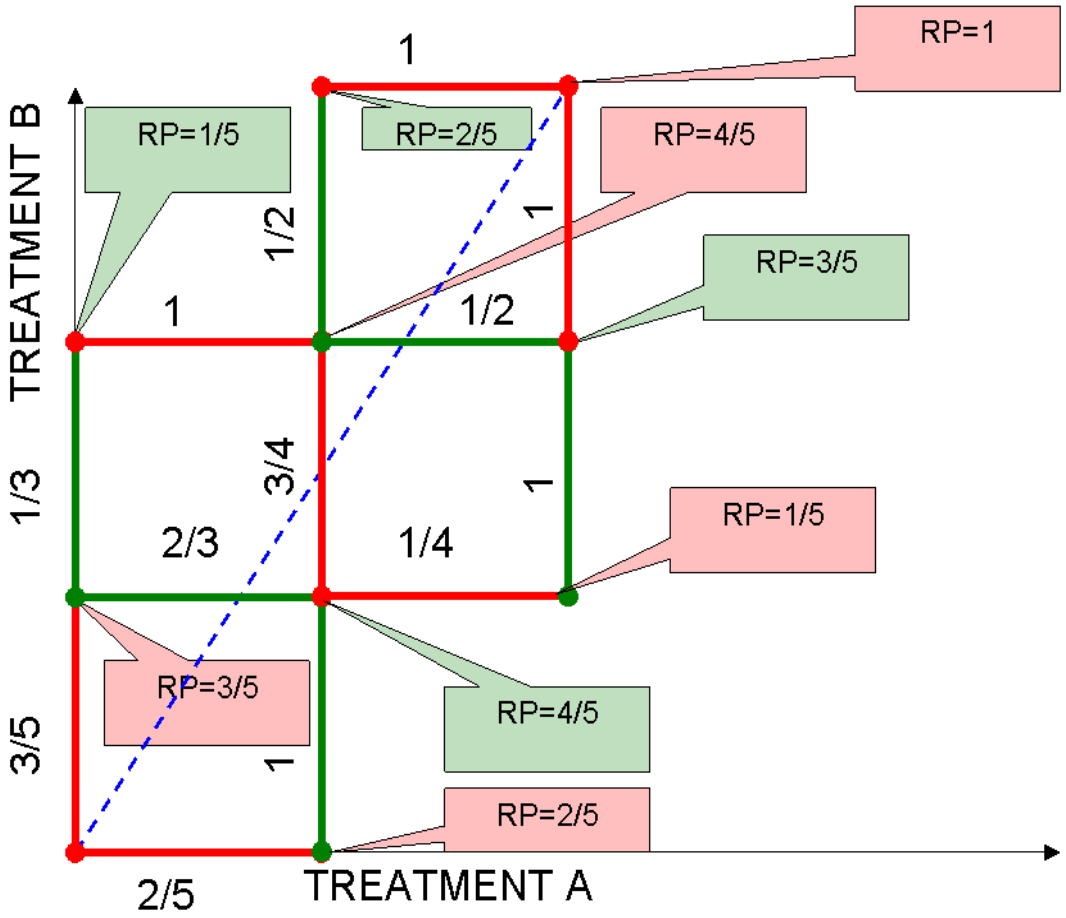
Key elements of BTR specification

- To specify BTR procedure need
  - **Allocation space**: Set of possible nodes that can be realized after i allocation steps (generations)
    - defined by the usual coordinates in K-dim space,
    - e.g. (K=2) Node Xj at the i-th generation : (N^i_A, N^i_B)
  - **Node Residence Probability (RP)**. = prob. that allocation sequence resides at a particular node after i generations
  - **Transition probabilities (TP):** = probability of the next assignment being to treatment 1,2,…,K
    - i.e. Need to define K transition probability for each node

How to compute BTR sets of nodes, RTs and TPs?

- K=2 (i.e. two-treatment case)
  - Explicit simple calculation,
  - Each generation has exactly 2 nodes in BT randomization
  - Unique way to specify nodes, RP and TP
- K=3
  - BTR is not uniquely defined in general
  - Explicit solution by Kuztensova [in press]
- K>3 ...
  - Need to rely on an iterative algorithm

Example. Defining Transitional Probabilities for 2:3 Allocation



Iterative algorithm

- At each step (generation) derive TP for the current set of nodes
- Given TP, calculate RPs for set of nodes in the next generation

Sequence Probability for 2:3 Allocation resulted from BT

Sequence	Prob.	Sequence	Prob.
ABABB	0.10	BABAB	0.15
ABBAB	0.15	BABBA	0.15
ABBBA	0.15	BBAAB	0.10
BAABB	0.10	BBABA	0.10

These sequence probabilities would ensure that That all subjects (regardless their allocation number) have 40% chance to be randomized to A and 60% change to B

Linear System to Solve while defining BTR for general K

- Given the set of nodes in the current generation,
- Find TP, p_{jl} (from node j in the treatment direction *l*) such that:
  - p_{jl} belongs to [0,1]
  - Probability to leave a node is 1 **(C^1)**
  - ARP condition:

$$\sum_{nodes\ \ in\ \ generation} RP_{node} \times TP_{\ \ in\ direction\ \ of\ TRT\ \ k} = \rho_k \qquad \textbf{(}C^{ARP}\textbf{)}$$

  - Some p_{jl} <- 0 due to BT geometry constrains **(C^{geom})**

Turning the System into the Optimization Problem

Find the vector of transition probabilities

$$p^{*} = [p_{11}, \ldots, p_{1K}, p_{21}, \ldots, p_{2K}, \cdots, p_{m1}, \ldots, p_{mK}]$$ such that

$$\min_{p} \quad ED(p) + \gamma \times U(p)$$

$$C \times p = \begin{bmatrix} C^{1} \\ C^{ARP} \\ C^{geom} \end{bmatrix} \times p = b$$

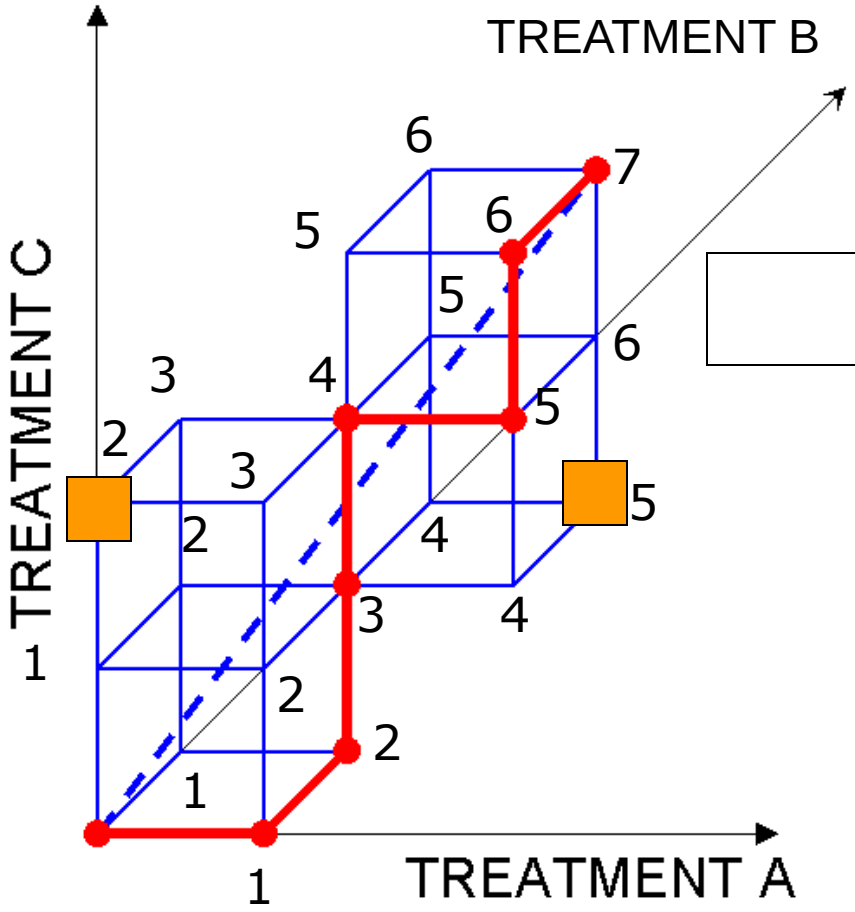
$$0 \leq p \leq 1$$

- C is matrix
- Notation for superscript of $C^{(\ldots)}$, corresponds to the conditions' notation from the previous slide

Where *ED* is the sum of expected distances from the nodes in the to the point of perfect balance in next generation

γ>=0 and *U(p)* some function to seek "special" properties of the transition probabilities.

Defining the Transition Probabilities for 2:2:3 Example



- Orange squares: nodes that got eliminated from the allowed space

Software

- btRandomization R package

```
library(btRandomization)
tunnel = constructBT(w=c(1,1,4))
allocSeq = generateAllocSeq(tunnel)
```

Generate 100K reps to observe that there are 18 unique equally likely sequences of length 6

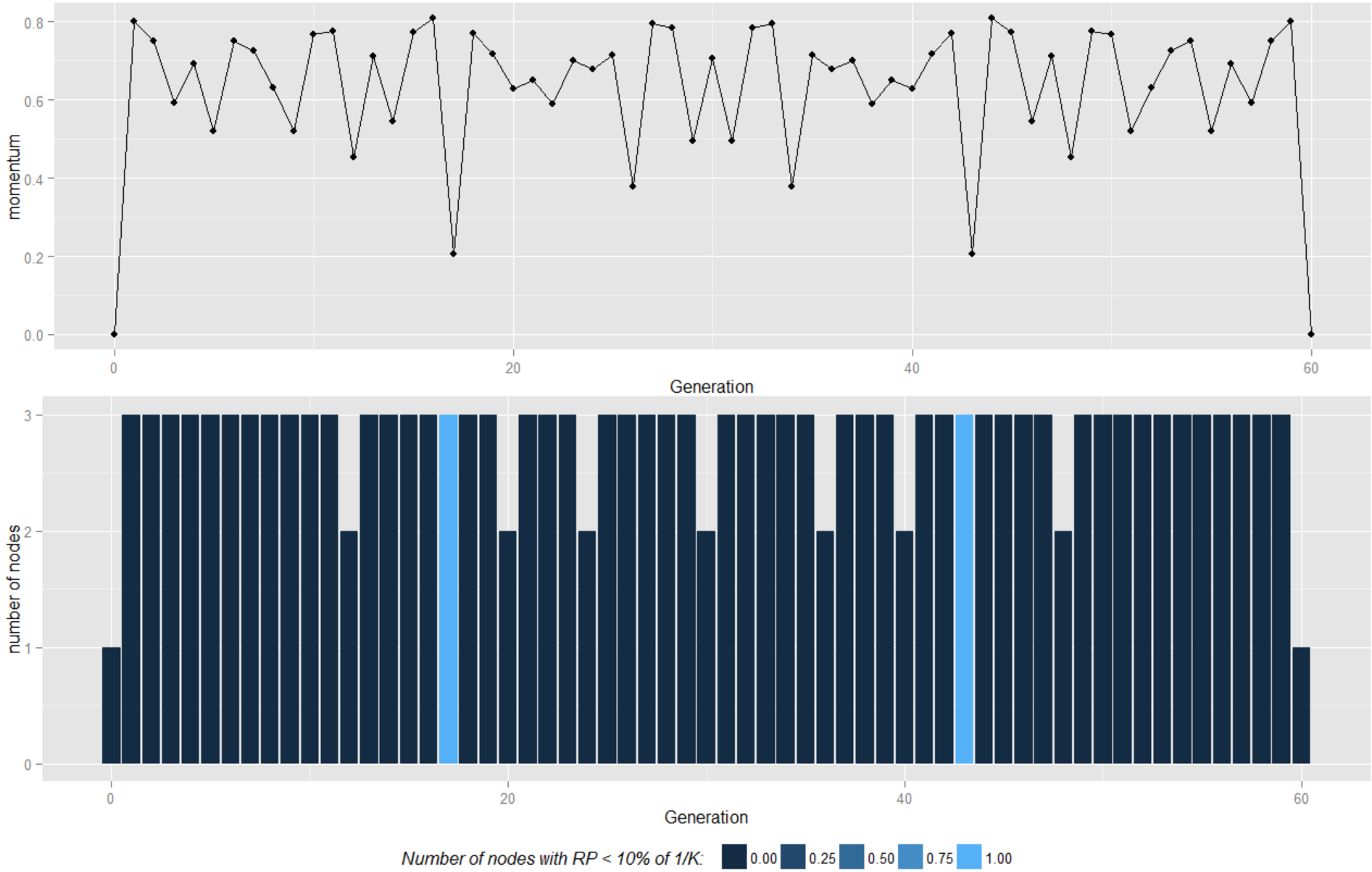
133 **2**33 **1**33 3**2**3 **1**33 33**2**	3**1**3 **2**33 3**1**3 3**2**3 3**1**3 33**2**	33**1** **2**33 33**1** 3**2**3 33**1** 33**2**
233 133 **2**33 313 **2**33 331	3**2**3 133 3**2**3 313 3**2**3 331	33**2** 133 33**2** 313 33**2** 331

BTR, allocation ratio is 14:21:25, algorithm converged

Parameters: optimType=minED, boundaryOn=TRUE (no trim), secProp=none, G=0.000010;

$$\text{Momentum} = \sum RP * D$$

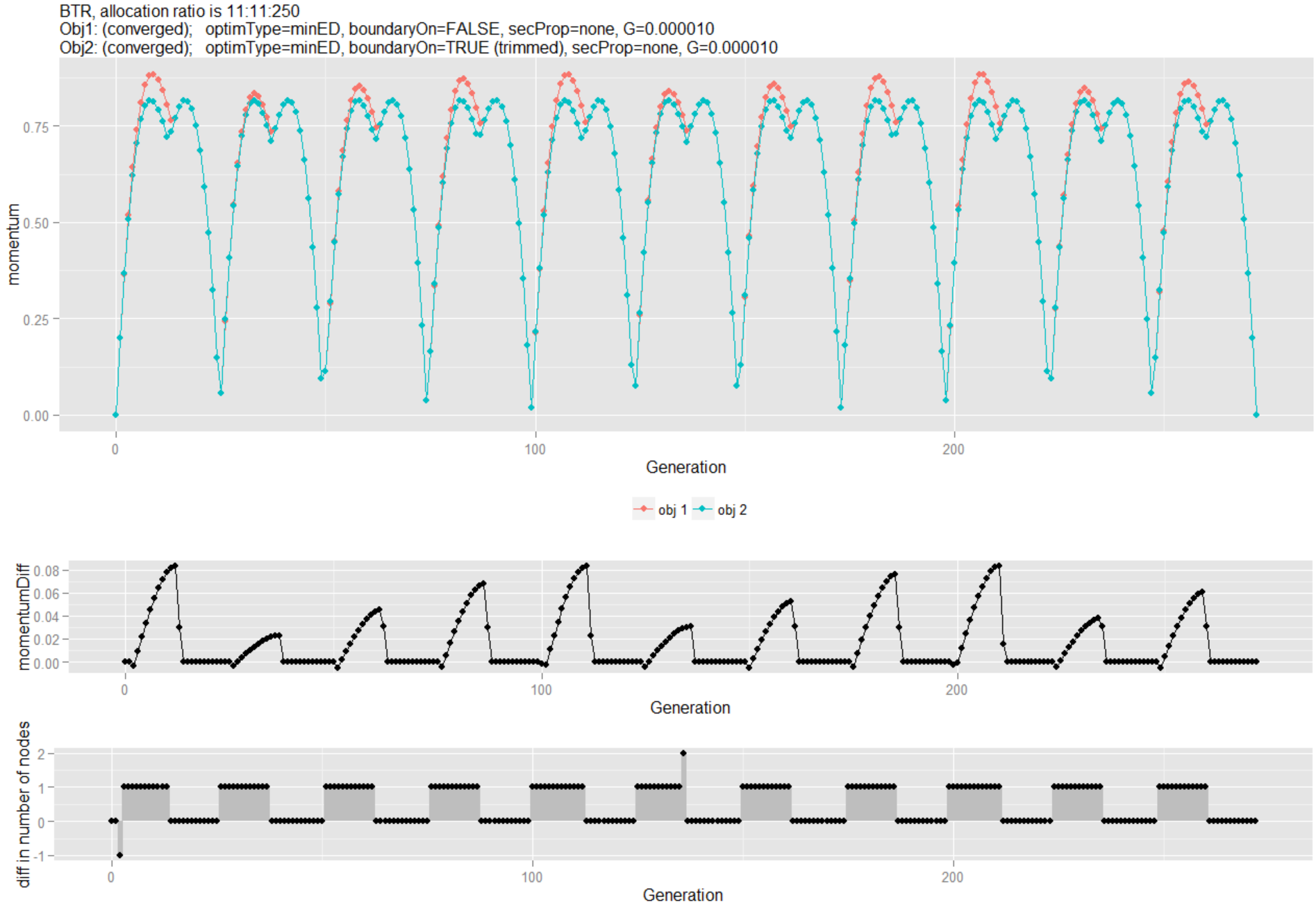
where D – distance from node the point of perfect balance

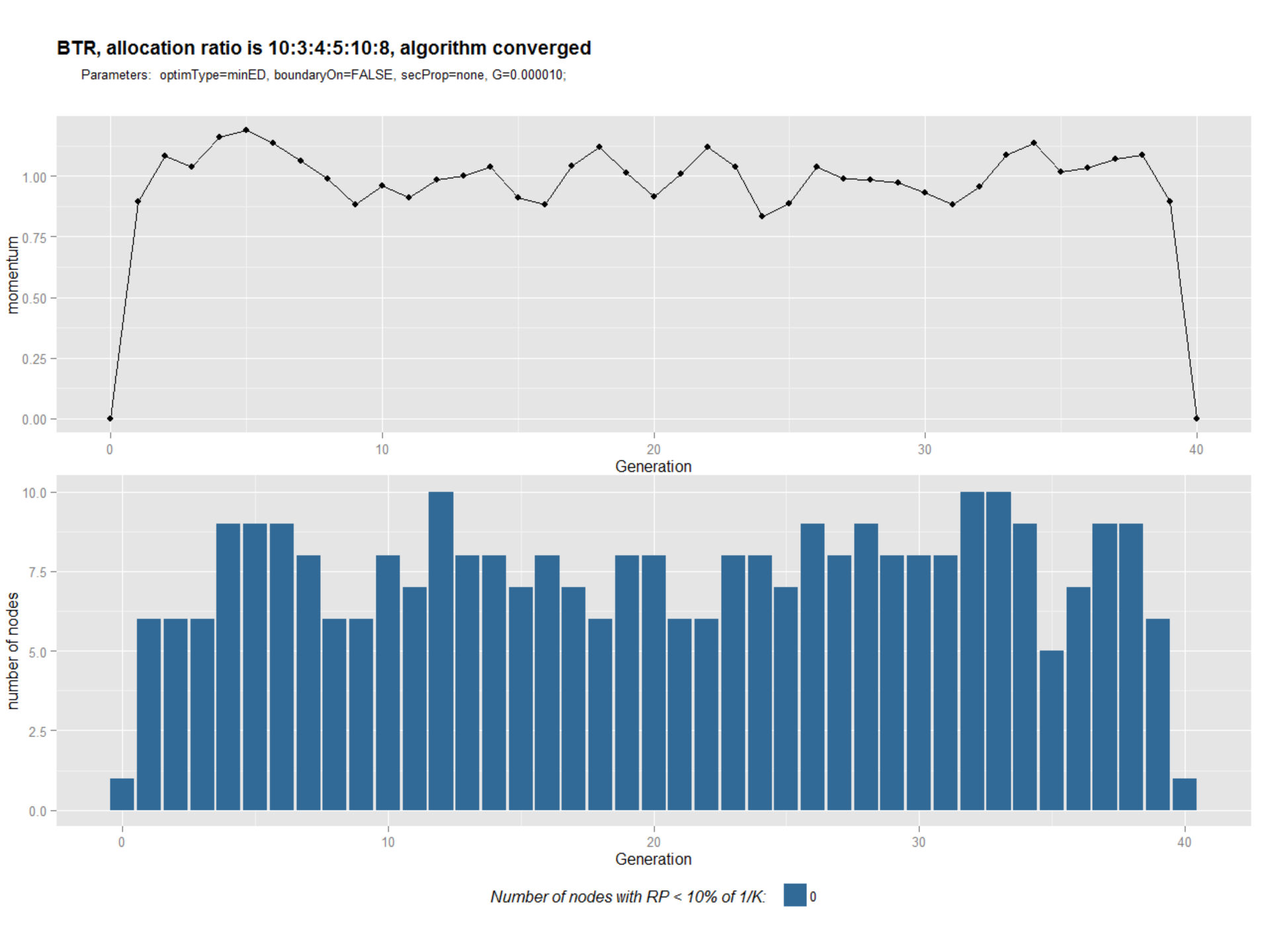


Discussion points and challenges with the iterative construction algorithm

- Since we minimize distance to the point of perfect balance in each generation, can drop the constrains due to BT geometry, i.e. $C^{(geom)}$ rows in LP problem?

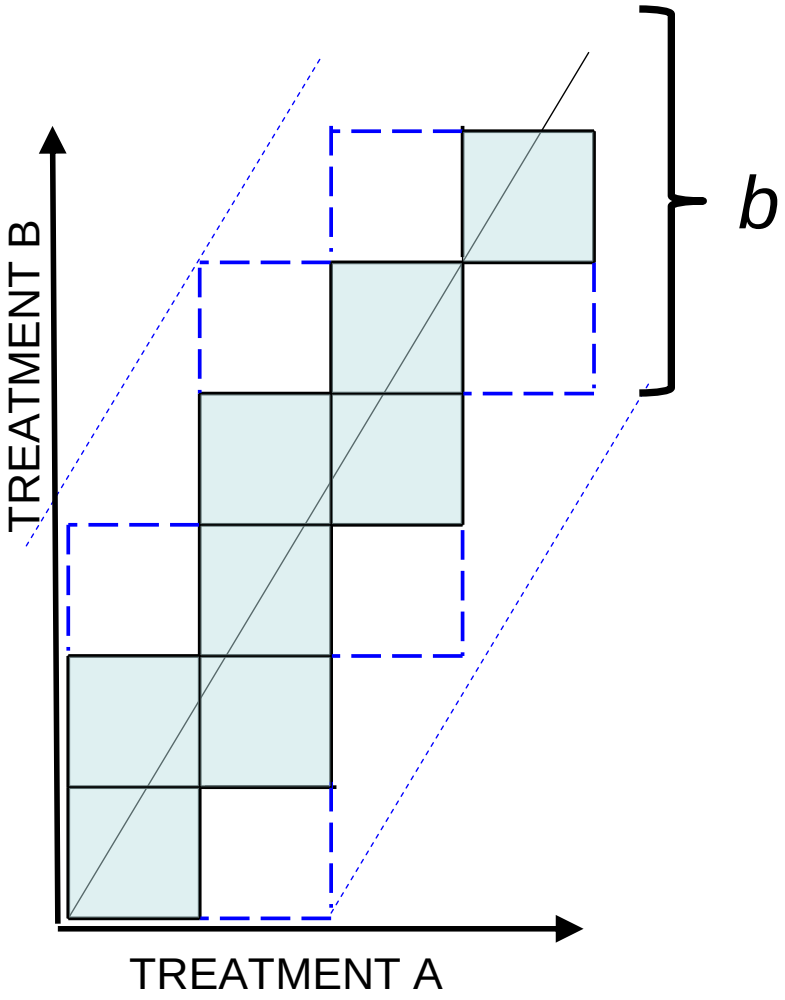
- Lack of stability due to the accumulation of errors in the iterative algorithm
  - Even the minuscular value of the transition probability (instead of a 0) can open a new node in the next generation, which effect the tunnel geometry.


BTR, allocation ratio is 11:11:250
Obj1: (converged); optimType=minED, boundaryOn=FALSE, secProp=none, G=0.000010
Obj2: (converged); optimType=minED, boundaryOn=TRUE (trimmed), secProp=none, G=0.000010
momentum
0.00
0.25
0.50
0.75
0
100
200
Generation
obj 1
obj 2
momentumDiff
0.00
0.02
0.04
0.06
0.08
0
100
200
Generation
diff in number of nodes
-1
0
1
2
0
100
200
Generation


BTR, allocation ratio is 10:3:4:5:10:8, algorithm converged
Parameters: optimType=minED, boundaryOn=FALSE, secProp=none, G=0.000010;
momentum
1.00
0.75
0.50
0.25
0.00
0
10
20
30
40
Generation
number of nodes
10.0
7.5
5.0
2.5
0.0
0
10
20
30
40
Generation
Number of nodes with RP < 10% of 1/K:
0

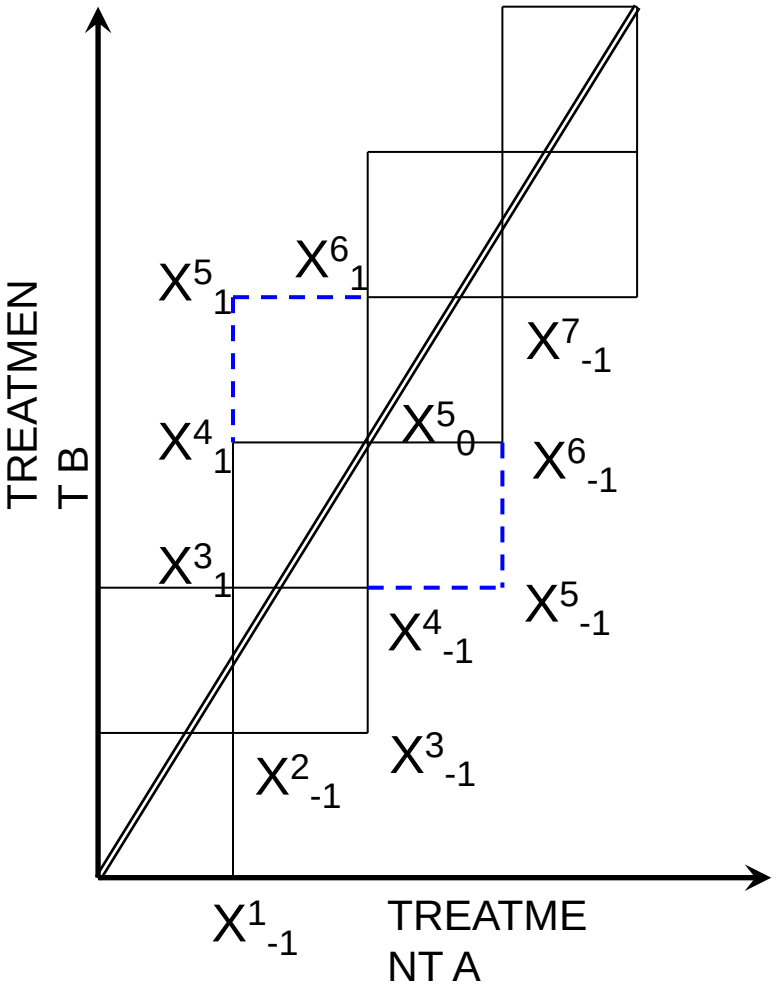
Wide Brick Tunnel Randomization

- Two-arm case
- BT can be expanded to cover a wider strip around the allocation ray
  - Useful mainly for open-label studies
- Nodes within ±*b* of Allocation Ray are added



Wide BTR

- Add nodes to the allocation path by switching two consecutive treatment assignments
  - **A B B A B A** …
  - Probability of the switch controls RP in the added nodes
- Expand the allocation space by a repeated use of the switches to cover the whole strip of AR *+/- b*
- ARP procedure [K&T 2014]



Summary of Applications for BTR

- In adaptive design studies to implement inconvenient allocation ratios
  - Dose finding studies with frequent adaptation
  - Stage-wise adaptive designs and sample size re-estimation
- In non-adaptive designs, large block size is a problem in multi-center studies with small centers and center-based allocation
  - Reduce potential for accidental bias associated with time trend vs permuted block schedule
- If a richer set of allocation sequences is needed, another layer of bricks could be added around a tunnel
  - Mainly applicable to 2-arm studies
  - In open-label studies, might add extra bricks at the end of blocks for better blinding

Questions…

Piccard, Henriot, Ehrenfest, Herzen, de Donder, Schrödinger, Verschaffelt, Pauli, Heisenberg, Fowler, Brillouin,
Debye, Knudsen, Bragg, Kramers, Dirac, Compton, Broglie, Born, Bohr,
Langmuir, Planck, Curie, Lorentz, Einstein, Langevin, Guye, Wilson, Richardson
(1927 Fifth Solvay International Conference on Electrons and Photons)

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Source Work by the Authors

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