Expanding Brick Tunnel Randomization to Allow for Larger Imbalance in Treatment Totals with Unequal Allocation

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Abstract
In open-label studies, partial predictability of permuted block randomization provides potential for selection bias. To lessen the selection bias in two-arm studies with equal allocation, a number of allocation procedures that limit the imbalance in treatment totals at a pre-specified level, but do not require the exact balance at the ends of the blocks were developed. In studies with unequal allocation, however, the task of designing a randomization procedure that sets a pre-specified limit on imbalance in group totals has not been completely resolved. Existing allocation procedures either do not preserve the allocation ratio at every allocation or do not include all allocation sequences that comply with the pre-specified imbalance threshold. Kuznetsova and Tymofeyev described the Brick Tunnel (BT) randomization for studies with unequal allocation that preserves the allocation ratio at every allocation and, in the two-arm case, includes all sequences that satisfy the smallest possible imbalance threshold. In this work, we expand two-arm BT randomization to allow for larger imbalance in treatment totals - which lowers selection bias in open-label studies with unequal allocation.

Key Words: unequal allocation, open-label studies, brick tunnel randomization, imbalance in treatment totals, wide brick tunnel

1. Introduction

In clinical trials patients are commonly assigned to one of the studied treatment regimens using randomization [1]. Randomization is employed to reduce bias and make the treatment groups more similar with respect to baseline covariates. Permuted Block (PB) randomization [2] became a standard allocation procedure due to its simplicity and wide-spread availability, flexibility to support equal and unequal allocation to two or more treatment arms, good control of the imbalance in the treatment group sizes throughout the enrollment (at least when the block size is small), and easy adaptation for multi-center trials and stratified randomization.

However, in open-label studies with permuted block randomization, the investigator who knows the sequence of all previous allocations (as is the case in single-center studies or studies with randomization stratified by center) can sometimes deduce the next treatment assignment. This predictability is caused by the property of PB randomization to reach the targeted allocation ratio at the end of each block. Predictability of upcoming assignments, in turn, might lead to a selection bias and thus, biased study results.

To lessen the selection bias in open-label studies, randomization procedures other than permuted block can be employed. Complete randomization [1], where each patient is assigned independently to one of the treatment arms in a pre-specified allocation ratio, is absolutely unpredictable and thus, largely eliminates the selection bias. However, it can result in treatment groups being allocated in ratios very different from the targeted one throughout the enrollment. It makes this procedure susceptible to an accidental bias associated with the time trend; also, in small studies, the total numbers of patients enrolled in each group could quite differ from the target sizes which can negatively impact power or other study design needs.

Biased Coin (BC) randomization designed for two-group studies with 1:1 allocation [3] provides a good balance in treatment assignments throughout the enrollment at the price of some selection bias. However, it does not fully control the imbalance in treatment assignments, as there is a small probability of a relatively large imbalance in moderate size samples [4].

A number of allocation procedures developed for 1:1 allocation to 2 treatment arms can limit the imbalance in treatment assignments at a pre-specified level. Among these procedures are the replacement randomization [5], modified replacement randomization [6], maximal procedure [7], Soares and Wu's big stick design [8], Chen's biased coin design with imbalance tolerance [9], Ehrenfest urn design [10], and Baldi Antognini and Giovagnolli's [11] adjustable biased coin design (with limited allowed imbalance). All these procedures restrict the set of allowed allocation sequences to those for which the absolute difference in numbers of treatment assignments N_{Ai} and N_{Bi} to Treatment A and B after i allocations never exceeds pre-specified threshold b: $|N_{Bi} - N_{Ai}| \leq b$. However, these procedures differ in how they assign the probabilities to the allowed sequences.

The replacement randomization [5] and the maximal procedure [7] assign equal probabilities to all allowed sequences which determines the conditional probability of Treatment A allocation to the (i+1)th subject given the existing group totals N_{Ai} and N_{Bi} after i allocations. The big stick design [8] keeps conditional probability of Treatment A allocation at 0.5 whenever the allocation to both treatments is permissible. Chen's biased coin design with imbalance tolerance [9] follows the biased coin rule in assigning the underrepresented treatment with probability p>1/2 when allowed; however, if the imbalance threshold is reached, the underrepresented treatment is assigned with certainty. With Ehrenfest urn design [10] the allowed imbalance is limited to a pre-specified threshold, and the probability to assign an underrepresented treatment grows when the imbalance grows. Further flexibility is added to the procedure in Baldi Antognini and Giovagnolli's [11] adjustable biased coin design where the probability of Treatment A allocation is a general function of the imbalance in the treatment totals. This function can be defined in a way that limits the imbalance in treatment totals; it can also make the allocation sequences to stay closer to the perfect balance in treatment assignments or be more spread within the allowed space.

In studies with unequal allocation, however, the task of designing a randomization procedure that allows all allocation sequences that comply with the pre-specified imbalance in group totals is not completely resolved. Typically, in a two group study with C_1:C_2 allocation (C_1<C_2) to Treatments A and B, the absolute imbalance in treatment assignments after i allocations is defined as $|N_{Bi} - N_{Ai} \times C_2/C_1|$ (or proportional to this difference) [12, 13]. With permuted block allocation that uses the minimal block size S=C_1+C_2, the imbalance is 0 at the end of each block, that is for $i=mS$, $m=1, 2, 3$…

Salama, Ivanova and Quaqish [12] generalized the maximal procedure for unequal allocation to two treatment groups in the following way. They allowed all allocation sequences for which the absolute imbalance never exceeds a pre-specified threshold b:

$$|N_{Bi} - N_{Ai} \times C_2/C_1| \leq b. \tag{1}$$

They assigned equal probabilities to all permissible sequences.

Kuznetsova and Tymofyeyev [14, 15] pointed out the following problem with this approach: having equiprobable sequences leads to the variations in the allocation ratio from allocation to allocation. For example, in a study with 2:3 allocation to Treatments A and B and b=2, the patients allocated first, second, fourth, and fifth, will be allocated in the 3:5 allocation ratio, while the patient allocated third will be allocated in the 1:1 ratio [14, 15]. Such variations in the allocation ratio from allocation to allocation are undesirable, as they provide a potential for selection and evaluation bias even in double-blind studies; they also provide a potential for accidental bias associated with a time trend, in particular, in multicenter studies [14, 15, 16, 17]. Variations in the allocation ratio also lead to problems with the randomization test [18, 16].

To eliminate variations in the allocation ratio, Kuznetsova and Tymofyeyev offered the Brick Tunnel (BT) Randomization for studies with unequal allocation to $k \geq 2$ treatment arms in C_1:C_2 : … : C_k ratio [14, 15]. The BT randomization allows all allocation sequences that, when depicted as paths on the k-dimensional integer grid, are constrained within the chain of k-dimensional unitary cubes pierced by the allocation ray AR = (C_1u, C_2u, ..., C_ku), $u \geq 0$. The key property of the BT randomization is that the transition probabilities are derived in a way that preserves the allocation ratio at every allocation [14, 15]. An example of the allocation space for 2:3 BT randomization to Treatments A and B is provided in Figure 1 (solid lines).

In the two-group case, the BT randomization has the same the set of allowed allocation sequences as the Salama, Ivanova, and Quaqish [12] randomization with $b = b_{BT}$, where b_{BT} is the height of the BT, but has no variations in the allocation ratio. It can be shown that for $C_1 < C_2$, $b_{BT} = (C_2 -1)/C_1 +1$.

Two-group BT randomization has two nodes (N_{Ai}, N_{Bi}) in each generation i except at the end of the blocks ($i=mS$, $m=1, 2, 3$...), where it has a single node with coordinates (mC_1, mC_2). For one of the nodes, the treatment assignment is deterministic, while allocations to both arms are possible from the other node [14, 15]. The allocation schedule for BT randomization can be easily generated in SAS or another programming language.

The BT randomization sequences ensure that the observed allocation remains very close to the targeted one throughout the enrollment. This is very useful in studies where the allocation ratio leads to a large block size and thus, permuted block randomization can lead to considerable deviations from the targeted allocation ratio within a block.

However, to reduce predictability of the next treatment assignment in a two-group open-label study with unequal allocation, one might want to expand the allocation space to cover strip (1) around the allocation ray wider than the one with $b = (C_2 -1)/C_1 +1$. The ways to do that while preserving the allocation ratio at every allocation have not been previously described. Zhao and Weng [19] described the Block Urn allocation procedure whose allowed space consists of a sequence of overlapping permuted blocks of at least twice the minimal size with the lowest corner at (mC_1, mC_2). When the block size is large, the allocation space is too wide for most applications. Block Urn allocation preserves the allocation ratio at every step, but other than in $1{:}C_2$ randomization, it does not cover the whole strip around the allocation ray.

In this paper we describe the technique that allows adding new nodes to the two-treatment BT randomization while preserving the allocation ratio at every step. In particular, new nodes could be added to the BT allocation space to cover the strip (1). We will call this procedure Wide Brick Tunnel (WBT) randomization. The sequences of the WBT randomization could be made to stay closer to the allocation ray or to be spread more within the strip. The WBT allocation schedule can be easily generated in most programming languages, in particular, in SAS.

In Section 2, we will demonstrate the switch technique that allows expanding the BT randomization to a wider set of allocation sequences while preserving the allocation ratio at every allocation. In Section 3 we will describe the iterative use of the switch technique that adds layers of bricks to the tunnel until the allowed space is filled. We will lay out the details of the implementation of the method In Section 4. We will consider applications of the technique, including those in multi-arm trials with equal or unequal allocation, in Section 5. Discussion completes the paper.

2. Section 2. Adding Nodes to the Brick Tunnel Randomization Space Through the Switch Technique

In this paper, we will visualize an allocation sequence in a two-group study as a path along the integer grid in the 2-dimensional space as described by [7]. The horizontal axis represents allocation to Treatment A, while the vertical axis represents allocation to Treatment B. The allocation path starts at the origin and with each allocation moves either one unit to the right (Treatment A assignment) or one unit up (Treatment B assignment). After i allocations, the allocation path ends up at the node with coordinates (N_{Ai}, N_{Bi}). The observed allocation ratio at this point is close to the targeted ratio $C_1{:}C_2$ if the node (N_{Ai}, N_{Bi}) is close to the allocation ray AR = $(C_1u,\ C_2u), u \geq 0$.

For some allocation procedures (complete randomization, biased coin design [1]), the allocation sequences can venture anywhere on the 2-dimensional grid, while for other allocation procedures (permuted block randomization, block urn design, randomization procedures that restrict the imbalance in the group totals) the sequences are restricted to the allowed allocation space. For $C_1{:}C_2$ allocation that requires $|N_{Bi} - N_{Ai} \times C_2/C_1| \leq b$ the allowed allocation space consists of the strip $\pm\, b$ in height around the allocation ray.

An easy way to add a new node to the allowed space of an allocation procedure is by switching two consecutive treatment assignments with certain probability. Kuznetsova [20] described an example of such a switch to reduce predictability of the permuted block randomization at the end of the block. When the last treatment assignment in a permuted block is switched with the first treatment assignments of the next permuted block, new allocation sequences that do not result in targeted allocation ratio at the end of each block are added to the allocation space. Thus, the treatment assignments at the mS allocations (where S is the block size) will no longer be completely predictable.

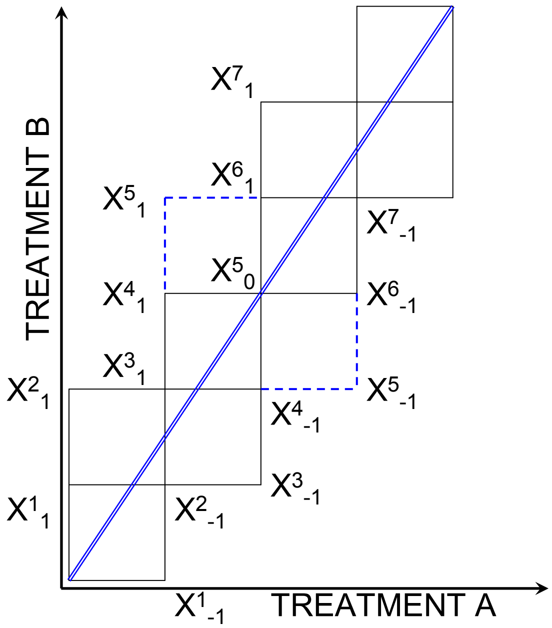

Figure 1: Adding Two Nodes to the 2:3 BT Randomization in the 5th Generation. Solid lines – 2:3 BT allocation space; dashed lines – newly added allocation segments.

If the original randomization procedure preserved the allocation ratio at every step, the expanded procedure where allocations i and $(i+1)$ are allowed to be switched with probability $0<\delta<1$, will also preserve the allocation ratio. By varying the probability of a switch $0<\delta<1$, we can change the probability for an allocation sequence to go through the newly added nodes.

Let us illustrate the switch technique on the example of 2:3 BT randomization to Treatments A and B (S=5). The allowed space for the 10-allocation BT randomization is depicted by solid lines (Figure 1). For BT sequences, we will use the following notations: we will denote the two nodes above and below the allocation ray in generation $i \neq mS$ by X^i_1 and X^i_{-1}, respectively. We will denote the single node in generation $i=mS$ by X^i_0.

Let us add two more nodes to the 5th generation – node X^5_{-1} with coordinates (3, 2) and node X^5_1 with coordinates (1, 4). This could be done by generating a BT randomization sequence and then allowing the 5th and 6th treatment assignments to switch places with probability $0<\delta<1$.

Indeed, the two-step allocation path segment that started in node X^4_1 and had the 5th and 6th allocations to A and B, respectively, as allowed by the BT randomization, will become, after a switch of the 5th and 6th allocations, a BA segment. Thus, the new path (the dashed line going through the node X^5_1 in Figure 1) will pass through the node X^5_1 in the 5th generation. Similarly, the segment BA that started at the node X^4_{-1}, will become, after a switch, AB segment, and thus, will pass through the node X^5_{-1} in the 5th generation (the dashed line going through the node X^5_{-1} in Figure 1).

The switch does not alter the resident probabilities in the 6th generation. Indeed, the new and altered two-step sequences arrive at the same node in the 6th generation, while they split the probability of the original two-step allocation sequence.

Table 1: Original and Reversed 2-Step Allocation Segments From the Nodes in the 4th Generation to the Nodes in the 6th Generation

4th Generation Node	Resident Probability	Original or Reversed 2-step Allocation Segment	2-step Allocation Segment	Conditional Probability of the 2-step Allocation Segment	5th Generation Node	6th Generation Node
X^4_{-1}	3/5	original	BA	2/5×(1-δ)	X^5_0	X^6_{-1}
X^4_{-1}	3/5	reversed	AB	2/5×δ	X^5_{-1}	X^6_{-1}
X^4_{-1}	3/5	original	BB	3/5×(1-δ)	X^5_0	X^6_1
X^4_{-1}	3/5	reversed	BB	3/5×δ	X^5_0	X^6_1
X^4_1	2/5	original	AA	2/5×(1-δ)	X^5_0	X^6_{-1}
X^4_1	2/5	reversed	AA	2/5×δ	X^5_0	X^6_{-1}
X^4_1	2/5	original	AB	3/5×(1-δ)	X^5_0	X^6_1
X^4_1	2/5	reversed	BA	3/5×δ	X^5_1	X^6_1

The new transition probabilities in the 5th and 6th generation as well as the new resident probabilities across the 5th generations nodes X^5_{-1} , X^5_0 , and X^5_1 could be easily derived by listing all 2-step allocation segments (original and reversed) from the 4th generation nodes and their conditional probabilities (Table 1). The original 2:3 BT resident probabilities are taken from [15]. Of note, for the allocation sequences with the same 5th and 6th treatment assignments, the original and reversed segments are the same.

As can be seen from Table 1, from the node X^4_{-1} in generation 4 the allocation path will go to the node X^5_{-1} (allocation to A) with probability 2/5×δ and to the node X^5_0 (allocation to B) with probability 1-2/5×δ. Similarly, the transition probabilities from the node X^4_1 are 3/5×δ and 1-3/5×δ, to the nodes X^5_1 (allocation to B) and X^5_0 (allocation to A), respectively. Thus, the resident probabilities in the 5th generation are:

$R^5_{-1}=R^5_1=6/25\times\delta$,
$R^5_0=1-12/25\times\delta$

By varying the probability of the switch δ, the resident probability in the new node R^5_{-1} (or R^5_1) can be made as high as 6/25 (when δ =1) or as low as 0 (when δ =0).

The transition probabilities from the 5th to the 6th generation are the following. From node X^5_{-1}, the allocation path follows to X^6_{-1} (allocation to B) with probability 1; from X^5_1, the allocation path follow to X^6_1 (allocation to A) with probability 1. From X^5_0, the probability of A allocation is (10-6δ)/(25-12δ), and the probability of B allocation is (15-6δ)/(25-12δ).

3. Iterative Expansion of the Brick Tunnel in Layers of Bricks

The BT randomization can be expanded to cover all the nodes within the strip $\pm\ b$ in height surrounding the allocation ray. We will call the allowed space the Wide Brick Tunnel (WBT) and the allocation procedure the WBT Randomization.

Consider the allowed space for the 2:3 BT randomization depicted on Figure 2 (pale blue solid cells). The space includes the squares on unitary grid (the bricks of the name) pierced by the allocation ray AR=($2u$, $3u$), $u\geq 0$ (slanted double line). Within each block of 5 allocations, the BT consists of two columns, each of two bricks in height. Let us expand the brick tunnel by placing one brick on top of each column and also attaching one brick at the bottom of each column (starting with the second column, as the allocation space is restricted to the positive quadrant of the grid). We will call newly added bricks (shaded with red horizontal stripes) the Layer 1 of bricks; we will call the original BT the Layer 0. Each of the Layer 1 bricks shares two sides with the bricks of the original BT.

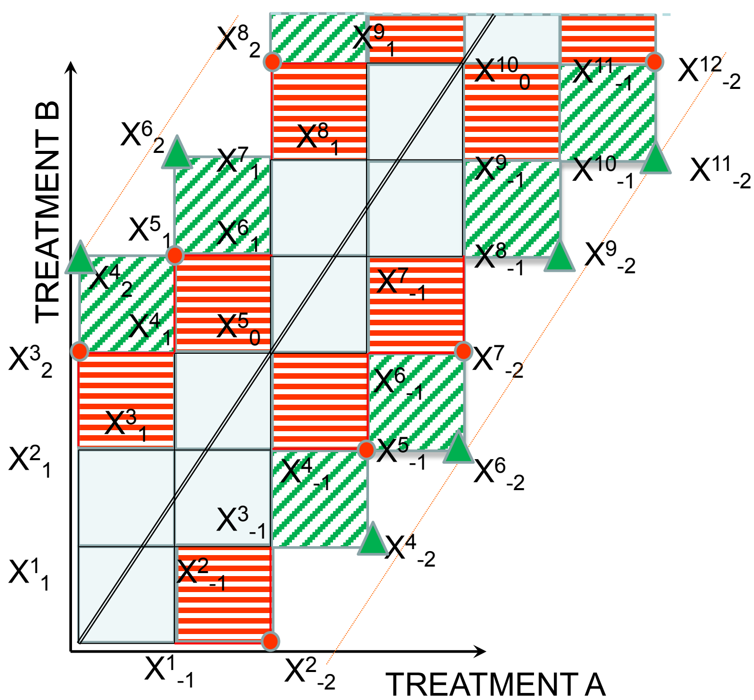

Figure 2: Allowed space for 2:3 BT randomization (shaded solid) and two layers added to it. First layer bricks are shaded with horizontal stripes; second layer bricks are shaded with diagonal stripes.

Together the original BT and the First Layer of bricks cover the nodes of the original BT, the BT shifted one step up, and the BT shifted one step down (within the 1st quadrant). Since the original BT covers all nodes within the strip of height $\pm\ b_{BT}$ around the allocation ray, where $b_{BT} = 2$, the expanded set covers all nodes within the strip of height $\pm\ (b_{BT} + 1) = \pm\ 3$ around the allocation ray. We will call this space a 2:3 Wide Brick Tunnel (WBT) of height $\pm\,3$ and denote it $\text{WBT}_{2:3}(3)$.

Similarly, the second layer of bricks can be added to the allocation space by placing one brick on top of each Layer 1 brick, and attaching one brick below each Layer 1 brick (within the first quadrant of the grid). The Layer 2 bricks are shaded by green diagonal stripes in Figure 2. Together the original BT and the two layers of bricks cover all nodes within the strip $\pm(b_{BT}+2) = \pm 4$ around the allocation ray, or $WBT_{2:3}(4)$ in our notation.

Adding the full 3rd layer of bricks will cover all nodes within the strip ± 5 around the allocation ray, that is $WBT_{2:3}(5)$. However, it is possible to cover a strip wider than $WBT_{2:3}(4)$, but narrower than $WBT_{2:3}(5)$ by adding an incomplete 3rd layer. For example, to cover a strip of height b=4.5, a third layer brick is placed on top of the second column, but not the first column, to form $WBT_{2:3}(4.5)$.

We will denote the nodes within a WBT as following. Within the generation i, the nodes above the allocation ray will be numbered $X^i_1, X^i_2, X^i_3, \ldots$, in the direction away from the allocation ray, while the nodes below the allocation ray will be numbered $X^i_{-1}, X^i_{-2}, X^i_{-3}$, …, in the direction away from the allocation ray.

Now let us explain how WBT randomization sequences can be generated through iterative switching of the allocations on the original BT randomization sequence. We will illustrate the process on the example of expanding the 10-allocation BT randomization to Treatments A and B in 2:3 ratio to cover $WBT_{2:3}(4.5)$ depicted in Figure 3 (Example 2). Of note, $WBT_{2:3}(4.5)$ allocation space is wide enough to include the allocation space for the permuted block randomization with block size 5, but is narrower than the allocation space for the permuted block randomization with block size 10.

The first layer of bricks brings in the new nodes X^2_{-2}, X^3_2, X^5_{-1}, X^5_1, X^7_{-2}, and X^8_2 (marked by red dots on Figure 3) into the allowed space. The node X^2_{-2} is added to the allowed space by switching the 2nd and 3rd treatment assignments of a BT allocation sequence that starts with ABA. Of note, if any other BT sequence has its 2nd and 3rd treatment assignments switched, the new sequence will remain within the original BT allocation space. Similarly, the first layer node X^3_2 is added to the allowed space by switching the 3rd and 4th treatment assignments of a BT allocation sequence that starts with BBA, and so on.

The second layer of bricks contributes nodes X^4_{-2}, X^4_2, X^6_{-2}, and X^6_2 (marked by green triangles on Figure 3). The 3rd, incomplete, layer of brick contributes the two nodes: X^3_{-2}, and X^7_2 (marked by brown pentagons). The i-th generation node of Layer j is added to the allocation space by switching the i-th and the (i+1)-th treatment assignments in the respective allocation sequence that belongs to the allocation space formed by the original BT and all earlier added layers (up to Layer (j-1)).

A 10-allocation $WBT_{2:3}(4.5)$ allocation sequence is generated in the following way. First, a 10-allocation BT allocation sequence is generated as described in [15]. Then, the switches of consecutive pairs of treatments that correspond to addition of a new Layer 1 node are executed with probability δ, in allocation order. After that, the switches are executed for Layer 2, and after that, for Layer 3. The order of the switches is presented in Table 2.

Table 2: Treatment Assignments that Are Switched in the Three Layers of the 10-allocation $WBT_{2:3}(4.5)$ Example (Example 2).

Order of Execution	Layer Being Added	Treatment Assignment That Is Switched With the Next One With Probability δ
1	1	2
2	1	3
3	1	5
4	1	7
5	1	8
6	2	4
7	2	6
8	3	3
9	3	7

It should be noted that when the switches are applied to the 10-allocation BT sequence (Example 2), not all the nodes within the 10 generations inside the strip ± 4.5 in height surrounding the allocation ray are added to the allowed space. While all the nodes in generations 1 through 7 within the strip are included in the allowed space, there are nodes in generations 8, 9, and 10 that are left out. Indeed, by switching the existing allocations, we only obtain the 10-allocation sequences that end up at the node (4, 6) and thus provide exactly the 2:3 allocation ratio at the end of the sequence.

Reaching the exact allocation ratio at the end of the allocation sequence might be needed in some cases - for example, when a small sample at a study center needs to be split in exact ratio. However, in other cases lowering predictability takes higher priority and it might be better to allow an allocation sequence to end up anywhere within the strip after 10 patients are randomized. To fill all the nodes within the strip across the 10 generations, one should start with the BT sequence that has more than 10 allocations – for example, 15 allocations – and proceed with the switches. The resulting 15-allocation sequences will fill all the nodes inside the strip ± 4.5 in height surrounding the allocation ray across the first 10 generations. In the remainder of this paper we will explore the approach where the allocation sequences can end at any node within the WBT and not necessarily result in the exactly targeted allocation ratio.

Example 3 also illustrates the problem that can arise when there are two consecutive allocations in the same Layer j that are to be switched – the first one at the upper border of the allocation space and the second one at the lower border of the allocation space. For some allocation sequences with segments that go along the upper border of Layer j, if both switches are executed, the new sequence falls outside Layers 0 through (j+1).

Indeed, consider the 10-allocation sequence that follows the upper border of the 2nd layer of bricks – the sequence BBBBA BABBA. Suppose, the two consecutive switches in the 3rd layer – the switch of the 7th and 8th treatment assignments and the switch of the 8th and 9th treatment assignments are applied to this sequence. The switch of the 7th and 8th treatment assignments will turn this sequence into the sequence BBBBA BBABA that follows the upper border of the 3rd layer of bricks. When the 8th and 9th treatment assignments of the new sequence are switched next, the resulting sequence BBBBA

BBBAA exits the 4^{th} layer and crosses the border of the allowed space above the allocation ray.

Thus, whenever two consecutive switches can take the sequence outside the designated layer, we will allow only one of the switches to be executed. If the prespecified probability of a single switch $\delta \geq 0.5$, we will execute one the two switches chosen at random. Thus, the probability of the either switch will be 0.5. If $\delta < 0.5$, we will choose one of the two switches at random and then execute it with probability 2δ. Thus, the probability of either switch will be δ.

Not every pair of consecutive switches will take the allocation path two layers above its original layer. In particular, a switch of the two allocations at the bottom border followed by the switch of the two allocations on the top border will carry no such danger. An example is provided by the two consecutive switches in the first layer in Example 3, of the 2^{nd} and 3^{rd} assignments (at the bottom border) and of the 3^{rd} and 4^{th} assignments (at the top border). Thus, these two switches could be executed independently, each with probability δ.

We will discuss how to determine when two consecutive switches in a row present a danger of taking a sequence out of its designated layer in the section on implementation details (Section 4).

4. Implementation Details

This chapter lays out the steps required to generate a WBT randomization sequence that allocates patients to treatments A and B in C_1:C_2 ratio with the imbalance threshold b - $\mathrm{WBT}_{C1:C2}(b)$. The set of all such sequences fills in the strip (1).

Below we will provide the derivations used to generate an allocation sequence.

The number of complete layers in $\mathrm{WBT}_{C1:C2}(b)$ is

$$L=floor(b-b_{BT})=floor(b-(C_2-1)/C_1-1). \qquad (2)$$

$\mathrm{WBT}_{C1:C2}(b)$ might also include some nodes from the (L+1)-th layer.

Consider the allocation space for the C_1:C_2 BT randomization pictured on a two-dimensional unitary grid (Figure 3). It can be visualized as the set of vertical columns of width 1, with C_1 columns per block. The m-th column is located above the horizontal segment [m-1, m], with its top at

$$Y_{top}(m)=ceil(m\times C_2/C_1) \qquad (3)$$

and its bottom at

$$Y_{bot}(m)=floor((m-1)\times C_2/C_1). \qquad (4)$$

The first layer nodes above the BT will be added by placing a brick on top of each column. The node (m, $Y_{top}(m)$) above the m-th column is at the inner corner of the BT.

When allocation A on the top border of BT before the node is switched places with the allocation B after the node, the Layer 1 node (m -1, $Y_{top}(m)$+1) is added to the allocation space. This node is added by switching the allocations

$m+Y_{top}(m)$ and $m+Y_{top}(m)+1$

of the BT sequence, where $Y_{top}(m)$ is defined by (3). The new node and the two new allocation segments form an outer corner of the allocation space (blue dashed lines on Figure 5) of the WBT that includes Layers 0 and 1.

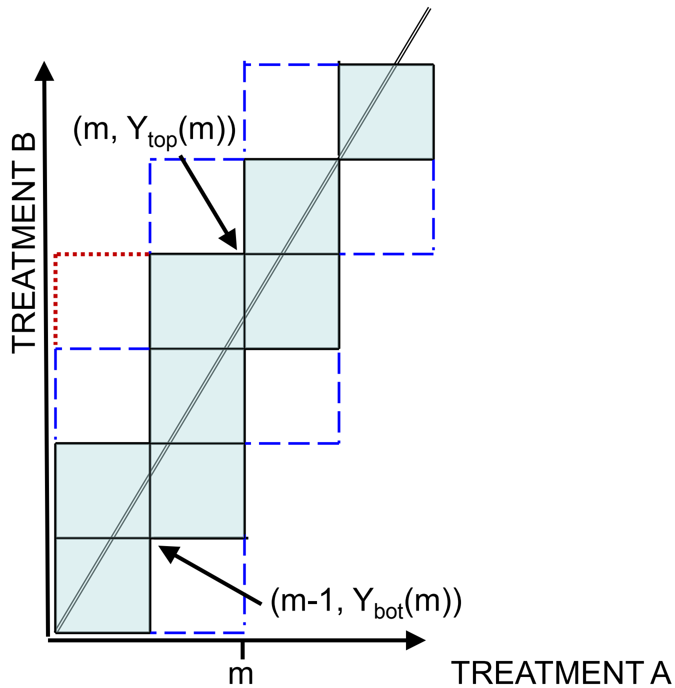

Figure 3: Details of Building WBT Layers. Solid squares: the allocation space for the C_1:C_2 BT. Dashed lines: 1st layer bricks added. Dotted line: two consecutive switches would have generated a node outside of the Layer 1 .

As we can see from Figure 3, now the height of the m-th column with Layer 1 brick added is the same as the height of the (m+1)-th column of the BT. Thus, if the switch $m+Y_{top}(m) \leftrightarrow m+Y_{top}(m)+1$ is followed by the switch of the subsequent allocations, $m+Y_{top}(m)+1$ and $m+Y_{top}(m)+2$, no new segments outside Layer 1 will be added. In general, following the switch $m+Y_{top} \leftrightarrow m+Y_{top}(m)+1$ with the switch $m+Y_{top}(m)+1 \leftrightarrow m+Y_{top}(m)+2$ will add an allocation segment outside Layer 1, if and only if the difference in height between the m-th and (m+1)-th columns is at least two:

$$ceil((m+1)\times C_2/C_1)\text{- } ceil(m\times C_2/C_1)\geq 2. \quad (5)$$

For example, after the 1st layer node is added at the top of the first column on Figure 3 by switching the 3rd and 4th allocations (blue dashed lines), the switch of the new 4th and the existing 5th allocations of the border sequence (red dotted lines) would take the allocation sequence above the 1st Layer.

The 1st Layer nodes will also be added below the BT by attaching a brick to the bottom of each column starting with the second one (the first column has no space in the 1st quadrant below it). The inner corner node of the BT at the bottom of the m-th column is the node (m-1, $Y_{bot}(m)$), where $Y_{bot}(m)$) is defined by (4). When the two allocations on both sides of this node on the bottom border of the BT (B and A) are switched places (blue dashed lines), the Layer 1 node (m, $Y_{bot}(m)$-1) is added to the allocation space. This node is added by switching the allocations

$m\text{-}1+Y_{bot}(m)$ and $m+Y_{bot}(m)$

of the BT sequence following the border segment. The new node and the two new allocation segments form an outer corner of the WBT that includes Layers 0 and 1.

As can be seen from Figure 3, if now the subsequent allocations $m+Y_{bot}(m)$ and $m+Y_{bot}(m)+1$ are switched places, the allocation sequence cannot exit the 1st layer space, as both allocations are to treatment B. Thus, the undesirable border exit can only occur in a pair of consecutive switches where the switch at the top border of the allocation space is followed by the switch at the bottom border of the allocation space, but not the other way.

Layer after layer will be added to WBT above the BT. Similar to Layer 1, the Layer j node (m -1, $Y_{top}(m)+j$) will be added on top of the m-th column, $m \geq 1$, by switching the allocations

$$m+Y_{top}(m)+j \text{ and } m+Y_{top}(m)+j+1, \qquad (6)$$

and the Layer j node (m, $Y_{bot}(m)\text{-}j$) will be added at the bottom of the m-th column, $m \geq j+1$, by switching the allocations

$$m\text{-}j+Y_{bot}(m) \text{ and } m\text{-}j+Y_{bot}(m)+1. \qquad (7)$$

When L complete layers are added to the tunnel, we will determine if any of the nodes of the (L+1)-th layer fit within the strip (1). The (L+1)-th layer node above the m-th column (m -1, $Y_{top}(m)+L+1$) fits within the strip (1) iff

$$Y_{top}(m)+L+1\text{-}(m\text{-}1)\times C_2/C_1 \leq b \quad . \qquad (8)$$

From (3), (8) can be written as

$$ceil(m\times C_2/C_1)\text{-}(m\text{-}1)\times C_2/C_1 \leq b\text{-}L\text{-}1 \qquad (9)$$

Similarly, the (L+1)-th layer node below the m-th column (m, $Y_{bot}(m)\text{-}L\text{-}1$) where $Y_{bot}(m) \geq L+1$ fits within the strip (1) iff

$$m\times C_2/C_1\text{-}(Y_{bot}(m)\text{-}L\text{-}1) \leq b.$$

or, from (4),

$$m\times C_2/C_1\text{-}floor((m\text{-}1)\times C_2/C_1) \leq b\text{-}L\text{-}1 \qquad (10).$$

With all the essentials of the method derived above, the $\mathrm{WBT}_{C1:C2}(b)$ sequence is generated using the following steps:

1. BT allocation sequence is generated per Kuznetsova & Tymofyeyev [15]
2. The number of complete layers L is derived per (2).
3. The nodes in the last, incomplete, (L+1)-th layer, if any, are identified through (9)- (10)
4. Repeat for layers 1 through L+1
    a. the nodes to be switched at the top border of the allocation space within the layer are identified through (6)
    b. separately, the nodes to be switched at the bottom border of the allocation space within the layer are identified through (7)
    c. the allocations at which either top or bottom switches (or both) are possible are ordered sequentially
    d. all consecutive pairs of switches where the switch at the top border is followed by the switch at the low border and condition (5) is met are identified ("bad pairs" of switches); only one switch in such pair can be executed).
    e. each switch that is not a part of a "bad pair" is executed with probability δ
    f. for a "bad pair" of switches, do the following
        i. if $\delta \geq 0.5$, execute one the two switches chosen at random.
        ii. if $\delta < 0.5$, choose one of the two switches at random and then execute it with probability 2δ.

To add further flexibility to the method, probability of a switch δ can vary from layer to layer. When the probability of a switch increases in the outer layers, the resident probability in these nodes also increases.

5. Discussion

In this paper we offered a solution (Wide Brick Tunnel) for previously unresolved problem of designing the unequal allocation procedure for a two-arm study that sets a pre-specified limit for allowed imbalance in treatment totals while preserving the allocation ratio at every step. Existing allocation procedure by Salama et al. [12] includes all sequences that comply with the imbalance threshold, but does not preserve the allocation ratio at every step, while the Block Urn randomization procedure by Zhao and Weng [19] preserves the allocation ratio at every step, but does not include all randomization sequences that satisfy the maximum imbalance condition.

The Brick Tunnel randomization proposed by Kuznetsova and Tymofeyev earlier [14, 15] generates the allocation procedure that preserves the allocation ratio at every step and complies with the smallest possible imbalance threshold. Wide Brick Tunnel randomization increases the threshold and thus, is useful in open-label studies where it reduces the selection bias. We have not performed simulations to quantify the selection bias or average predictability of the treatment assignments in this paper – our goal was to introduce a new technique and describe its properties and applications.

The allocation sequences of the WBT can be made to stay closer to the allocation ray or to be spread more around it by changing the probability of a switch – possibly, from a layer to layer. While using high probability of switch δ increases the resident probabilities in the nodes removed from the allocation ray, they remain low even for δ close to 1. This typically matches the goals of WBT randomization: keep the allocation sequence close to the allocation ray, but allow some restricted deviations to lessen the selection bias in open-label studies. Simulations of long sequences of WBT show that the resident probabilities (and, therefore, the transitional probabilities) converge very soon to some stable values.

The switch technique can be used in multi-arm studies with equal allocation to reduce the predictability of the last assignment in a block. Additionally, the WBT procedure can be used as a part of randomization algorithm in the multi-arm studies with unequal allocation.

WBT allocation sequences are easy to generate. A computer program that implements WBT allocation is available from the authors.

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