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A generalized drop-the-loser rule for multi-treatment clinical trials

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Abstract

Urn models are popular for response adaptive designs in clinical studies. Among different urn models, Ivanova's drop-the-loser rule is capable of producing superior adaptive treatment allocation schemes. Ivanova [2003. A play-the-winner-type urn model with reduced variability. Metrika 58, 1–13] obtained the asymptotic normality only for two treatments. Recently, Zhang et al. [2007. Generalized drop-the-loser urn for clinical trials with delayed responses. Statist. Sinica, in press] extended the drop-the-loser rule to tackle more general circumstances. However, their discussion is also limited to only two treatments. In this paper, the drop-the-loser rule is generalized to multi-treatment clinical trials, and delayed responses are allowed. Moreover, the rule can be used to target any desired pre-specified allocation proportion. Asymptotic properties, including strong consistency and asymptotic normality, are also established for general multi-treatment cases.

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1. Introduction

In clinical studies, it is common that subjects arrive sequentially and then each person is assigned randomly to one of K available treatments. Response adaptive designs are useful randomization tools that formulate treatment allocation as a function of previous responses. One major purpose of response adaptive designs is to develop treatment allocation schemes, so that more subjects receive the treatments that have performed better thus far in the study. At the same time, it is important to maintain an adequate level of randomness in the allocation process to provide a solid foundation for statistical inferences.

A large class of response adaptive designs is generated from urn models. An urn contains K different types of balls, representing K different treatments. When a subject arrives, a ball is drawn at random with replacement. If the ball is of type k, the subject receives treatment k. The responses of subjects after treatment play an essential role in updating the urn. The basic strategy is to "reward" more balls to successful treatments.

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An early important urn model for adaptive design was proposed by Wei and Durham (1978). Given two treatments ($K = 2$), the randomized play-the-winner (RPW) rule was used for treatment allocation. With the RPW rule, the urn is updated at each stage by adding one additional ball of the same treatment type if the response of a subject to this treatment is a success, and adding one additional ball of the opposite treatment type if the response is a failure. Wei (1979) generalized the RPW rule to multi-treatment cases ($K > 2$) and developed the generalized Pólya urn (GPU) model. For GPU, the urn is updated at each stage by adding one additional ball of the same treatment type if the response of a subject to this treatment is a success, and adding an additional $1/(K - 1)$ ball of the other $K - 1$ treatment types if the response is a failure.

A useful randomized version of the GPU, which is called the randomized Pólya urn (RPU), was proposed by Durham et al. (1998). Unlike the GPU, the RPU design only rewards balls to successful treatments. The success of a treatment generates a new ball of the same treatment type, whereas the urn remains unchanged if the response is a failure. For the RPU, the urn process can be embedded in the family of continuous-time pure birth processes with linear birth rate (Yule processes). The embedding technique of RPU enables the derivation of important limiting properties of the urn process (Ivanova and Flournoy, 2001).

With the framework of embedding the urn process in a continuous-time birth and death process (Ivanova et al., 2000; Ivanova and Flournoy, 2001), Ivanova (2003) formulated the drop-the-loser (DL) urn and established the asymptotic normality for the special case of two treatments. Among various urn models, the DL rule is reported to produce superior treatment allocation results in terms of reducing the number of failures and the variability of the randomization procedure (Rosenberger and Hu, 2004). A discussion of the DL rule is given in Section 2.

To cover a wider spectrum of clinical applications such as delayed responses and pre-specified treatment allocation targets, Zhang et al. (2007) extended the DL rule. However, their discussion of the generalized drop-the-loser (GDL) rule is limited to two treatments ($K = 2$). The main objective of this paper is to generalize the GDL rule to multi-treatment cases where $K > 2$ and establish its asymptotic properties. The allocation scheme of the GDL rule will be provided in Section 3. Then, in Section 4, the asymptotic properties, including strong consistency and asymptotic normality, will be given. In particular, the asymptotic normality of Ivanova's DL rule will be obtained for general multi-treatment cases. Simulation studies on treatment allocation proportions will be presented in Section 5. Section 6 conclude the paper.

2. Drop-the-loser rule

We first outline the mechanism of the DL rule. The allocation scheme is as follows: consider an urn that contains $K + 1$ different types of balls. Balls of types $1, 2, \ldots, K$ are called treatment balls that represent K different treatments. Balls of type 0 are called immigration balls. Initially, there are $Z_{0,k}$ balls of type k ($k = 0, 1, 2, \ldots, K$) in the urn. Let $\mathbf{Z}_0 = (Z_{0,0}, Z_{0,1}, Z_{0,2}, \ldots, Z_{0,K})$ be the initial urn composition. After m draws, the urn composition changes to $\mathbf{Z}_m = (Z_{m,0}, Z_{m,1}, Z_{m,2}, \ldots, Z_{m,K})$. When a subject arrives, one ball is drawn randomly from the urn without replacement. If a treatment ball of type k is drawn, then the subject will receive treatment k. The response is then observed after the patient is treated. If the treatment is a success, then the corresponding ball (i.e. type k) is replaced. Consequently, the urn composition remains unchanged, $\mathbf{Z}_{m+1} = \mathbf{Z}_m$. However, if the treatment is a failure, the corresponding ball is not replaced, so $Z_{m+1,k} = Z_{m,k} - 1$ and $Z_{m+1,j} = Z_{m,j}$ for $j \neq k$.

If an immigration ball is selected, then no subject is treated and the ball is returned to the urn together with K additional treatment balls, one for each treatment type. Thus, $Z_{m+1,0} = Z_{m,0}$ and $Z_{m+1,k} = Z_{m,k} + 1$, $k = 1, 2, \ldots, K$. The function of the immigration ball is to avoid the extinction of a particular type of treatment ball.

With respect to the treatment allocation mechanism, there is one major difference between the DL rule and the RPU. For the DL rule, the successful treatments receive no reward, but the failed treatments are penalized by losing a corresponding ball in the urn. In contrast, the RPU procedure rewards successful treatments without penalizing the losers. The allocation proportions of the RPU may converge to extreme limits. For instance, if one of the treatments has a considerably higher efficacy, the allocation proportion of it always converges to 1, whereas the other inferior treatments will have their allocation proportions converge to 0.

The variability of allocation proportions should be an important concern in choosing different types of response adaptive designs. In clinical studies, one concern is to increase power in the discrimination of the efficacy of different treatments. Hu and Rosenberger (2003) showed that the power is a function of limiting allocation proportions. For given allocation proportions, the asymptotic power is a decreasing function of the variability of the allocation proportions.