A MODIFICATION OF A PERCENTILE ESTIMATION PROCEDURE BASED ON GENERALIZED POLYA URNS.

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Abstract

Adaptive designs find an important application in the estimation of unknown percentiles for an underlying dose-response curve. A non-parametric adaptive design was suggested by Mugno et al. (2004) to simultaneously estimate multiple percentiles of an unknown dose-response curve via generalized Polya urns. In this paper, we examine the properties of the design proposed by Mugno et al. (2004) when delays in observing responses are encountered. Using simulations, we evaluate a modification of the design under varying group sizes. Our results demonstrate unbiased estimation with minimal loss in efficiency when compared to the original compound urn design.

1 Introduction

Dose-response studies are conducted primarily in Phase II efficacy trials to estimate prespecified dose percentiles or the underlying dose-response function of an investigational drug. A standard dose selecting trial randomizes subjects to several fixed dose groups and analyzes the data after all the responses have been obtained. There are two major disadvantages with this approach. The first being the risk of unnecessarily exposing patients to suboptimal dose levels and the second being inefficient utilization of resources. For a review of ethical issues with conventional randomized design, see Rosenberger and Lachin (1993) and Bather (1985).

Response-adaptive designs have been used as an alternative to the traditional randomization scheme to overcome these issues. Generally speaking, in response adaptive designs, treatment assignment is a function of the response information accrued up to that point in time in the study. Interim analyses are conducted after each patient response is obtained and subsequent patient doses are determined from responses sequentially gathered during the study. Adaptive designs reduce the number of patients exposed to less effective doses and

also open up the possibility of early termination of the trial, offering significant ethical and cost advantages while increasing the probability of success. Adaptive designs and its advantages over the conventional approach have been discussed extensively in the literature; see Bauer (2004), Hu and Rosenberger (2006), Rosenberger (1996), Flournoy and Rosenberger (1995) and Hu and Ivanova (2004), to name a few for details.

Various adaptive designs using stochastic approximation methods and urn models have been developed. See Chow and Chang (2007). Here, we focus our attention on the generalized Polya urn (GPU) model and its extensions. Extensions of this design involving simultaneous estimation of several percentiles, referred to as the compound urn design may be found in Mugno et al. (2004). In their paper, they implemented a sequential response-adaptive design to simultaneously target three quartiles. The design properties were studied and the dose estimates were concluded to be unbiased, efficient and robust against poor and biased prior information. An advantage of the compound urn design lies in being able to estimate dose percentiles by employing both parametric and non-parametric techniques.

Usually in clinical trials, patient responses are not instantly obtained. Delayed responses are often associated with oncology and psychiatry trials and is a relevant issue. In an adaptive design, this delays the randomization of the subsequent subject to the next dose level and can notably lengthen the duration of the trial.

To tackle this issue, subjects are randomized in cohorts to dose levels as responses from previous cohorts become available. Properties of adaptive designs for clinical trials with delayed responses have been discussed by Hu and Zhang (2004) and Bai et al. (2002). To investigate the effect of delayed response in an adaptive urn design, we examine the compound urn model reviewed by Mugno et al. (2004) for a group sequential scheme. We estimate percentiles of interest and evaluate its properties.

2 Review of Methods

In this paper we focus our efforts on urn models, which is only one of the various approaches to accomplish response-adaptive randomization. The generalized Polya urn (GPU) model was first introduced by Athreya and Karlin (1968) as the "generalized Friedman's urn" and then discussed by Wei (1979) for randomizing patients into different treatment groups. This design can similarly be applied to randomize patients into different dose levels of the same treatment. More details are provided in Athreya and Ney (1972).

The GPU design can be described as follows: Consider patients being randomized to **K** dose levels for a treatment that is under investigation. The urn consists of **K** balls, each representing a particular dose level. When a patient is accrued into the clinical trial, a ball is randomly drawn with replacement from the urn and the patient is assigned that particular dose j. If the patient response indicates success, n_1 balls representing dose j are added to the urn. If the patient response indicates failure, n_2 balls each, of dose levels not equal to j are added to the urn. This design mitigates the probability of patients being randomized to a sub-optimal dose levels.

The GPU has been modified for adaptive randomization in dose-response studies to estimate percentiles of interest. Rosenberger and Grill (1997) efficiently estimated quartiles of a dose-response curve using the GPU. Assuming randomization to **K** dose levels, the initial urn composition (IUC) is first chosen. The different strategies have been outlined by Rosenberger and Grill (1997). Once the IUC has been chosen, a ball is randomly chosen from the urn with replacement and the patient is randomized to the representing dose level. A positive response from the patient elicits the addition of k (>1) balls for each of the lower dose levels, while a negative response prompts the addition of k balls for each of the higher dose levels in the urn. Thus the urn is updated after each patient response is obtained. To estimate percentiles other than the ED50, say the ED100π, where $\pi \in [0,1]$, the skewing

factor is defined as,

$$g = \begin{cases} \frac{\pi}{1-\pi} & , \pi \leqslant 0.5 \\ \frac{1-\pi}{\pi} & , \pi > 0.5 \end{cases}$$

When estimating a percentile greater than the ED50, as before, subject non-response implies that k balls are to be added to the urn for each of the k higher dose levels. Subject response implies that k balls are to be added to the urn corresponding to the k lower levels with probability g and k balls are to be added all corresponding to the dose just administered with probability *1 - g*. Targeting percentiles less than the ED50 may be done using similar rules.

Mugno et al. (2004) extended the adaptive GPU proposed by Rosenberger and Grill to a compound urn design to simultaneously target several percentiles of a dose-response curve. A compound urn design is obtained by combining several GPU designs, each targeting a single percentile. These compound urn designs were found to be robust against poor and biased prior information due to their adaptive nature. These designs were also found to be very efficient when the IUC were centered around the true quartiles. The advantage of the compound urn model lies in being able to simultaneously estimate multiple percentiles. The design also allows for both non-parametric and parametric estimation techniques.

The algorithm of the compound urn design requires that patient response be obtained before the subsequent patient is randomized. Due to the nature of the study, our response of interest may not be instantly obtained. Delayed responses are encountered in many practical situations. Bai et al. (2002) describes an adaptive placebo-controlled clinical trial of fluoxetine in depression as an example where the outcome was not immediately ascertainable. A clinical trial investigating the overall survival of patients is another example of a situation where delayed responses are encountered. Being unable able to obtain immediate responses delays the randomization of the next subject and subsequently slows down the clinical trial.

Subject recruitment is a challenge in medical trials and an adaptive design that can minimize delays is called for.

When dealing with delayed responses, instead of following the traditional algorithm of updating the urns after each patient response is obtained, the urns are updated after all patient responses from the previous cohort are obtained. The algorithm is as follows:

1. A cohort of size r will be enrolled into the trial.
2. All subjects in the cohort will be assigned a specific dose of the drug.
3. The urn will be updated once responses have been obtained from all subjects in the cohort.
4. Using the updated urn, the next cohort of subjects will be assigned a dose.

A trade off in efficiency is expected when considering delays in the algorithm as compared to the original compound urn design.

3 Simulation Study

We conduct a simulation study to evaluate the properties of the compound urn design under accrual groups of various sizes.

Here we only explore the logistic family of dose-response functions of the location-scale form,

$$log\left(\frac{\pi(x)}{1-\pi(x)}\right) = \beta(x-\alpha) \tag{1}$$

Thus, the MLE for a prespecified target percentile can be derived as:

$$\hat{\mu} = \hat{\alpha} + \frac{log\left(\frac{\pi}{1-\pi}\right)}{\hat{\beta}} \tag{2}$$

It has been shown in Mugno (2001) that, provided that the urns are generated independently and each targets an arbitrary percentile, the MLE of a percentile is a consistent, asymptotically normally distributed and efficient estimate for the corresponding percentile under the dependent sampling scheme of the compound GPU design.

Throughout the simulation, we generate data as specified in Mugno et al. (2004). We replicate the results of the compound urn design for patient cohorts of size 3, 4, 6, 25 and 50. The parameters are similar to the original study (Mugno et al. (2004)) with the goal being estimation of the three quartiles (true ED25=32, ED50=37 and ED75=42) of the dose-response curve, assuming $\alpha = 37$ and $\beta = 0.22$. The urn is assumed to have K = 71 levels and simulations are performed for k = 5, N =100 trials per iteration for 8000 iterations.

As in Mugno et al. (2004), a dual GPU design is considered where two urns are used, one targeting ED25 and the other targeting ED75. To be consistent with the design in Mugno et al. (2004) and for the sake of comparability of results, the two urns are initially populated using IUC4, where the initial urn content for the estimation of ED25 and ED75 is concentrated around the best guess of the truth, i.e. around levels 32 and 42 respectively.

The trial begins with the enrollment of the first cohort of patients of size n into the study. Adopting the terminology used in urn problems, a ball is randomly selected from the urn and all patients in the first cohort are subjected to that level. Once the patient responses from the cohort are obtained, the urn is updated using all the n responses and another ball is randomly selected. A trial is performed at this level for the next cohort of patients of size n.

The estimates and standard deviations for the MLE estimates are given in Table 1. Simulation results demonstrate unbiased parametric estimates without any drastic loss in efficiency relative to the original sequential compound urn design.

The behavior of non-parametric estimates such as the empirical mean of the allocation distribution and the mode of dose levels were also investigated. The empirical mean is given

Table 1: MLE estimates and standard deviations obtained for IUC4

Cohort Size	p = 0.25	p = 0.50	p = 0.75
3	31.92(1.56)	37.03(1.30)	42.13(2.23)
4	31.97(1.54)	37.03(1.15)	42.10(1.83)
6	31.94(1.53)	37.00(1.15)	42.06(1.78)
25	31.92(1.60)	36.99(1.11)	42.06(1.62)
50	31.91(1.61)	36.99(1.09)	42.06(1.62)

by $\sum_{i=1}^{K} x_i N_i(n)/n$, where $N_i(n)/n$ is the proportion of trials at dose level x_i. As specified in Mugno et al. (2004), an unbiased non-parametric estimate of the target percentile can also be obtained using the empirical mode of each individual urn.

The estimates of the empirical mean and mode are given in Table 2. These non-parametric estimates are observed to be approximately unbiased with standard deviations decreasing with increasing cohort size.

Table 2: Empirical mean, mode and standard deviations obtained for IUC4

Cohort Size	Statistic	p = 0.25	p = 0.75
3	Empirical Mean	31.90(1.32)	41.80(2.31)
	Empirical Mode	31.48(2.22)	42.32(2.92)
4	Empirical Mean	31.91(1.24)	41.87(2.04)
	Empirical Mode	31.48(2.14)	42.32(2.75)
6	Empirical Mean	31.93(1.07)	41.90(1.63)
	Empirical Mode	31.50(2.05)	42.21(2.45)
25	Empirical Mean	31.99(0.49)	41.98(0.55)
	Empirical Mode	31.57(1.91)	41.98(2.01)
50	Empirical Mean	31.99(0.28)	42.00(0.28)
	Empirical Mode	31.70(2.00)	41.71(1.99)

Parameters of the true dose-response curve are seldom known. To investigate how efficiency and bias were affected when the initial urn contents were not concentrated about the target percentiles, additional simulations were conducted. The urn contents were concentrated three dose levels lesser than the truth. The empirical mean, the parametric estimates,

the mode for dose-levels and the standard deviations for the MLE estimates obtained are given in Table 3 and 4. The results obtained suggested parametric estimates that were unbiased, with slight change in efficiency. With increase in cohort size, the change in efficiency appears to be modest and negligible. Non-parametric estimates under this design were found to be biased with standard deviations similar to that obtained in Table 2 using IUC4. Non-parametric estimates and their standard deviations are given in Table 4.

Table 3: MLE estimates and standard deviation obtained for IUC concentrated 3 doses lesser from the truth

Cohort Size	p = 0.25	p = 0.50	p = 0.75
3	32.04(1.39)	37.22(1.70)	42.40(2.91)
4	32.00(1.39)	37.20(1.58)	42.40(2.74)
6	32.00(1.37)	37.17(1.51)	42.33(2.61)
25	32.00(1.36)	37.09(1.23)	42.18(2.11)
50	32.00(1.41)	37.08(1.20)	42.17(2.00)

Table 4: Empirical mean, mode and standard deviations obtained for IUC concentrated 3 doses lesser from the truth

Cohort Size	Statistic	p = 0.25	p = 0.75
3	Empirical Mean	29.60(1.35)	37.66(2.46)
	Empirical Mode	28.95(2.25)	38.83(3.26)
4	Empirical Mean	29.57(1.23)	37.78(2.21)
	Empirical Mode	28.96(2.17)	38.82(3.01)
6	Empirical Mean	29.50(1.08)	37.93(1.76)
	Empirical Mode	28.91(2.06)	38.81(2.62)
25	Empirical Mean	29.19(0.49)	38.72(0.58)
	Empirical Mode	28.79(1.94)	38.87(2.01)
50	Empirical Mean	29.00(0.28)	39.00(0.28)
	Empirical Mode	28.70(1.97)	38.70(1.99)

4 Discussion & Conclusion

The primary goal of of this paper has been to expand on the response-adaptive compound urn design introduced by Mugno et al. (2004) to a group-sequential enrollment scheme and study its properties. We have investigated the properties of the urn design when there is a delay in obtaining responses using simulations. The results suggest unbiased parametric estimates and minimal loss in efficiency as compared to the original compound urn design regardless of how the initial urn contents are chosen. We conclude that the response-adaptive compound urn design can be used in clinical practice to simultaneously estimate multiple percentiles without experiencing a huge loss in efficiency when subjects are enrolled in cohorts.

The weakness of this method lies in regarding the cohort size (r) to be fixed throughout each trial. Enrollment of patients do not occur at fixed time points in a clinical trial. In practice, patients are enrolled as they volunteer and deemed eligible. Thus, the ideal situation would be to update the urn with the availability of patient responses than waiting for all the responses from the previous cohort. We have examined the operating characteristics of the design in the occasion that the primary outcome of the trial is binary in nature. E.g non-existence of a symptom, occurrence of an event, death, cure etc. This design introduced by Mugno et al. (2004) could be modified for situations where patient responses might be categorical or continuous in nature.

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