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# PLAY-THE-WINNER DESIGNS, GENERALIZED PÓLYA URNS, AND MARKOV BRANCHING PROCESSES

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**Abstract**

The randomized play-the-winner rule, an adaptive design for clinical trials aimed at placing more patients on the better of two treatments, may be modeled as a generalized Pólya urn. The urn model may, in turn, be embedded in a Markov branching process, and results from the theory of these processes may then be used to prove results for the urn model, and hence for the randomized play-the-winner scheme. Under a mild condition for the success probabilities $p_A$ and $p_B$ for the two treatment arms, results from the theory of Markov branching processes show that the (random) probability of assignment to a given treatment is asymptotically normal; we extend this result to show that, under this same condition, the probability of assignment to a given treatment and the number of patients assigned to that treatment have a limiting bivariate normal distribution. Some generalizations of this result are discussed.

**1. Introduction.** Consider a clinical trial in which patients are accrued sequentially and immediately are assigned to treatment A or

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treatment B. Adaptive designs for such clinical trials attempt to assign more patients to the better of the two treatments, while seeking to maintain some randomness as a basis for inference. Thus the results of the treatments on previous patients will influence treatment assignments of current patients. We assume that the results of treatment are known immediately; some relaxation of this condition is possible.

There is a rather extensive literature on adaptive assignment methods; see, for example, Bather (1985), Armitage (1985) and the accompanying discussion, or Rosenberger and Lachin (1993) for an introduction to some of the issues surrounding these methods. Our contribution will focus on one particular method of adaptive assignment, the randomized play-the-winner (RPW) rule [see Wei and Durham (1978)]. Here we assume the outcomes are dichotomous; we denote the two kinds of outcome by S or F. A population model is assumed for the patients, with $p_A \equiv P\{\text{Outcome } S \text{ on treatment } A\}$, $p_B \equiv P\{\text{Outcome } S \text{ on treatment } B\}$, $q_A \equiv 1 - p_A$, and $q_B \equiv 1 - p_B$. Let $p_n$ be the probability that the $n$th patient is assigned to treatment A. In the simplest version of the RPW rule,

(1.1)
$$p_n = \frac{1 + S_A(n-1) + F_B(n-1)}{n+1},$$

where $S_A(k)$ denotes the number of patients with outcome $S$ on treatment $A$ among the first $k$ patients, and $F_B(k)$ denotes the corresponding number of patients with outcome $F$ on treatment $B$. Thus if treatment $A$ is doing well relative to $B$ early in the trial, more patients will tend to be placed on treatment $A$, and vice-versa. Of course, $p_A$ and $p_B$ will not be known; exact and asymptotic inference procedures for these parameters under the RPW rule are discussed in Wei, Smythe, Lin, and Park (1990).

**2. Urn models.** Suppose an urn has balls of two types (or colors), $A$ and $B$. Initially there are $\alpha$ balls of each type in the urn. Whenever a new patient is accrued, a ball is drawn at random and replaced. If the ball is of type $A$, the patient is assigned to treatment $A$. If the ball is of type $B$, the patient is assigned to treatment $B$. When the response of a previous patient on a treatment becomes known, a ball of type $A$ is added to the urn if the response is $S$ on treatment $A$ or $F$ on treatment $B$, and a ball of type $B$ is added if the response is $F$ on treatment $A$ or

$S$ on treatment $B$. If $p_n$ again represents the probability that the $n$th patient is assigned to treatment $A$, it is easy to check that

$$p_n = \frac{\alpha + S_A\,(n-1) + F_B\,(n-1)}{(n-1) + 2\alpha},$$

which reduces to (1.1) in the case $\alpha = 1$. This urn model is a particularly simple example of a generalized Pólya urn (GPU) model [see Athreya and Ney (1972)], which was first noted by Wei (1979).

**3. Markov branching processes.** As outlined in Athreya and Ney (1972), there is a close correspondence between certain GPU models and Markov branching (MB) processes, which we briefly describe in our case of interest.

Our MB process will have particles of two types ($A$ and $B$); we start with $\alpha$ particles of each type. The particles have independent exponential "timers" with parameter 1 in each case. When the timer "goes off," a particle of type $A$ produces a new particle of type $A$ with probability $p_A$, or a new particle of type $B$ with probability $q_A$, and its timer is "reset" with an independent exponential (1) time. The new particles all have exponential (1) timers, independent of each other and of the "parent" particles; all the particles now "reproduce" according to the rules above when their timers go off. The *split times*, the times at which particles reproduce, are almost surely distinct. We refer to a split as a *Type A split* if a particle of type $A$ is reproducing at that split time, and as a *Type B split* if a particle of type $B$ is reproducing. Under our rules for the MB process, the probability of a Type A split at any time is simply the number of Type A particles in existence at that time, divided by the total number of particles in existence (similarly for Type B particles). Thus, in terms of the urn model in Section 2, a Type A split corresponds to drawing a Type A ball from the urn and a Type B split corresponds to drawing a Type B ball from the urn.

Define $N_n$ to be the number of Type A splits among the first $n$ splits and $A_n$ to be the number of particles of type $A$ after $n$ splits (of either type). It is not difficult to check that $A_n$ has exactly the same distribution as the number of balls of type $A$ in the urn, described in Section 2, after $n$ draws from the urn. We may view the GPU model as being embedded in the MB process, an idea which appears to be due to Athreya and Karlin (1968). Results from MB processes, therefore,

imply corresponding results for these urn models, and thus for RPW assignment schemes which, as shown in Section 2, correspond to urn models of this type.

For our RPW model, $N_n$ represents the number of patients among the first $n$ that are assigned to treatment $A$. Results for MB processes give [see Athreya and Karlin (1967)]

$$\frac{N_n}{n} \overset{a.s.}{\to} Q \text{ as } n \to \infty,$$

where $Q = q_B/(q_A + q_B)$. Results of Athreya and Karlin (1968) show that

$$p_n \overset{a.s.}{\to} Q \text{ as } n \to \infty,$$

and that, under some conditions (see Section 4),

$$\sqrt{n}\,(p_n - Q) \to N(0, c)$$

in law, where $N(0, c)$ denotes a normal random variable with mean 0 and variance $c$. The results of Athreya and Karlin do not identify the variance $c$, but it can be deduced with some effort from their arguments. Athreya and Karlin (1967) raised the question of asymptotic normality of the number of Type A splits $N_n$, which in our model is the number of patients assigned to treatment $A$.

**4. Joint asymptotic normality of the number of type A splits and the number of particles of type A.** In the following discussion, we take $\alpha = 1$ for simplicity. Note that $N_n$ and $A_n$ are hopelessly intertwined, in that

$$E\{N_{n+1} - N_n \mid F_n\} = \frac{A_n}{n+2},$$

where $\Im_n \equiv \sigma(A_1, \ldots, A_n, N_1, \ldots, N_n)$, the sigma-algebra generated by all splits and reproductions in the first $n$ split times. This suggests that we should consider the vector $(A_n, N_n)$. Let $X_n \equiv A_n - (n+2)Q$ and $Y_n \equiv N_n - (n+2)Q$. Also, let $\delta = p_A - q_B$.

THEOREM 4.1. *If* $\delta < 1/2$, *as* $n \to \infty$,

$$\left(\frac{X_n}{\sqrt{n}}, \frac{Y_n}{\sqrt{n}}\right)$$

*approaches a bivariate normal distribution with variance-covariance matrix*

$$\Sigma_0 = \begin{bmatrix} 1 & 1+2\delta \\ 1+2\delta & 3+2\delta \end{bmatrix} \frac{Q(1-Q)}{1-2\delta}.$$

SKETCH OF PROOF. [The complete proof can be found in Rosenberger (1992).] The argument is similar to one in Mahmoud and Smythe (1992). Define $\triangle X_{i+1} \equiv X_{i+1} - X_i$ and $\triangle Y_{i+1} \equiv Y_{i+1} - Y_i$. Then

$$E\{\triangle X_{i+1} \mid \Im_i\} = \frac{A_i}{i+2} - Q,$$

$$E\{\triangle Y_{i+1} \mid \Im_i\} = \delta\left(\frac{A_i}{i+2} - Q\right).$$

Thus

$$Z_{nk} \equiv \sum_{i=1}^{k} \left\{ b_{in}\left(\triangle X_{i+1} - \delta\left(\frac{A_i}{i+2} - Q\right)\right) + c_{in}\left(\triangle Y_{i+1} - \left(\frac{A_i}{i+2} - Q\right)\right)\right\},$$

$k = 1, \ldots, n$, is a martingale in $k$ for each fixed $n$, for any choice of constants $\{b_{in}\}$ and $\{c_{in}\}, i = 1, \ldots, n$. Given $\alpha_1$ and $\alpha_2$, choose $\{b_{in}\}$ and $\{c_{in}\}$ such that

$$Z_{nn} = \alpha_1 X_n + \alpha_2 Y_n + o\left(n^{1/2}\right).$$

This involves solving a system of linear equations for $\{b_{in}\}$ and $\{c_{in}\}$, which can be done recursively. A martingale central limit theorem of Hall and Heyde (1980) and the Cramér-Wold device (Billingsley, 1968) may be applied to give the result, with the variance-covariance matrix calculated from the urn probabilities and the coefficients $\{b_{in}\}$ and $\{c_{in}\}$. □

REMARK 1. In terms of the RPW design, this result says that

$$\left\{\sqrt{n}\,(p_n - Q)\,, \sqrt{n}\left(\frac{N_n}{n} - Q\right)\right\}$$

is asymptotically bivariate normal.

REMARK 2. The form of $\sum_0$ in Theorem 4.1 makes clear why $\delta$ is restricted to values less than 1/2; i.e., to $p_A + p_B < 3/2$. There is a "phase change" at $\delta$=1/2. It turns out that if $\delta$=1/2, normalization by $(n \log n)^{1/2}$ will produce a normal limit for $Y_n$; for $\delta > 1/2$, normalization by $n^{1-\delta}$ produces an a.s. limit to an unknown (presumably non-normal) random variable. The latter two results follow from combining the analysis above with the results of Wei, Smythe, Lin, and Park (1990), and are analogous to known results for the limiting behavior of $X_n$ [see Athreya and Karlin (1968)].

**5. Generalizations.**

*5.1. More than one particle created per split.* Consider first the case, when in either type of split, exactly $\beta$ new particles are created; that is, a Type A split produces $A$ new particles of type $A$ and $\beta - A$ particles of type $B$; a Type B split produces $B$ new particles of type $B$ and $\beta - B$ new particles of type $A$, where $A$ and $B$ are random variables on $\{1, \ldots, \beta\}$. The splitting particles continue to live on with a new exponential "lifetime." Let $\mathbf{E}$ be the expectation matrix,

(5.1)
$$\mathbf{E} \equiv \begin{bmatrix} E_{AA} & E_{AB} \\ E_{BA} & E_{BB} \end{bmatrix},$$

where $E_{ij}$ is the expected number of particles of type $j$ produced by a type $i$ split, $i, j$=$A, B$. The matrix $\mathbf{E}$ has two real eigenvalues, $\lambda < \lambda_1$.

Let $\boldsymbol{\xi}$, with components $\xi_1$ and $\xi_2$, be a right eigenvector for $\lambda$. Athreya and Karlin (1968) show that if $2\lambda < \lambda_1$, then

$$n^{-1/2}\left(\xi_1 A_n + \xi_2 B_n\right) \rightarrow N\left(0, k\right)$$

in law, for constant $k$, where $B_n \equiv (2\alpha + n) - A_n$, the number of balls of type $B$ in the urn at time $n$.

For the RPW design described earlier,

$$\mathbf{E} = \begin{bmatrix} p_A & q_A \\ q_B & p_B \end{bmatrix},$$

and the eigenvalues are $p_A + p_B - 1$ and 1; the condition $2\lambda < \lambda_1$ then becomes $p_A + p_B < 3/2$, or $\delta < 1/2$, the condition of Theorem 4.1.

In the more general case where $\beta$ new particles are created at each split, joint asymptotic normality continues to hold, provided that $E_{AA} - E_{BB} < \beta/2$. The variance-covariance matrix is more complicated, but can be obtained explicitly with modest effort.

*5.2. More than two outcomes.* As a corollary to the extension given above, we give here just one example of how the RPW methodology could be extended to accommodate clinical trials with more than two possible outcomes. Suppose that three outcomes are identified: call them H, M, L, which could be thought of as ordinal, with outcome H being better than outcome M and outcome M being better than outcome L. One could establish the following rule: if treatment A results in outcome H (with probability $p_{1A}$), 2 balls of type A are added to the urn; if treatment A results in outcome M (with probability $p_{2A}$), 1 ball of each type is added to the urn; if treatment A results in outcome L (with probability $p_{3A}$), 2 balls of type B are added to the urn, where $p_{1A} + p_{2A} + p_{3A} = 1$. Similarly, if treatment B results in outcome H (with probability $p_{1B}$), 2 balls of type B are added to the urn; if treatment B results in outcome M (with probability $p_{2B}$), 1 ball of each type is added to the urn; if treatment B results in outcome L (with probability $p_{3B}$), 2 balls of type A are added to the urn, where $p_{1A} + p_{2A} + p_{3A} = 1$. The condition for asymptotic normality in Theorem 4.1 then becomes

$p_{1A} - p_{3B} < (1/2)\{1 - (p_{2A} - p_{2B})\}$. Estimation of parameters for this model could be carried out by an extension of the procedures in Wei, Smythe, Lin, and Park (1990).

*5.3. Random number of particles created in a split.* If the number of particles produced at each split is allowed to be random, the problem is more difficult. In this case,

$$P\{\text{Type } A \text{ split}\} = \frac{A_n}{A_n + B_n},$$

and denominator is random. The difficulty is caused by the fact that the proof of Theorem 4.1 relies on the linearity in $A_i$ of $E\{\triangle X_{i+1} \mid \Im_i\}$ and $E\{\triangle Y_{i+1} \mid \Im_i\}$, which is no longer the case here.

With a random number of particles produced, we let $p^A_{jk}$ be the probability that $j$ particles of type $A$ and $k$ particles of type $B$ are produced in a Type A split, and $p^A_{jk}$ be the probability that $j$ particles of type $A$ and $k$ particles of type $B$ are produced in a Type B split. We assume

$$\sum_j \sum_k j^2 p^A_{jk} < \infty, \quad \sum_j \sum_k k^2 p^A_{jk} < \infty,$$

$$\sum_j \sum_k j^2 p^B_{jk} < \infty, \quad \sum_j \sum_k k^2 p^B_{jk} < \infty.$$

If $2\lambda < \lambda_1$, where $\lambda$ and $\lambda_1$ correspond to eigenvalues of $\mathbf{E}$ given in (5.1), the central limit result of Athreya and Karlin still holds. We conjecture that the analog of Theorem 4.1 holds in this case as well.

*5.4. More than two types of particles.* The concepts of MB processes and GPUs extend easily to more than two types of particles, and the embedding of the urn models in the MB processes is completely analogous to the two-type case. The analysis of the split times is extended to this case in Smythe (1995).

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