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Variance in randomized play-the-winner clinical trials

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Abstract

We derive the exact variance of the allocation proportions in a clinical trial employing a randomized play-the-winner design. Such a result has application in planning studies. © 1997 Elsevier Science B.V.

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1. Motivation

The randomized play-the-winner rule (Wei and Durham, 1978) is an adaptive randomization design occasionally used in clinical trials (see, for example, Bartlett et al., 1985; Tamura et al., 1994). The rule can be best depicted as an urn model. Initially an urn contains α_A type A particles and α_B type B particles. Patients are assumed to arrive sequentially and will be randomly assigned to either treatment A or treatment B. When a patient is ready for assignment to treatment, a particle is drawn from the urn. If a type A particle is drawn, the patient is assigned to treatment A. If a type B particle is drawn, the patient is assigned to treatment B. The particle is replaced and the patient's response, assumed to be dichotomous (e.g., success/failure) is observed. Response is assumed to be observable before the next patient is ready for randomization. If the patient's response was a success on treatment A or a failure on treatment B, β type A particles are added to the urn. If the patient's response was a success on treatment B or a failure on treatment A, β type B particles are added to the urn. In this way, the allocation proportions are skewed away from 0.5 according to whether treatment A or treatment B is doing better thus far in the trial. Such a design has obvious ethical consequences (see Rosenberger and Lachin, 1993 for a discussion). In most cases, $\alpha_A = \alpha_B$, unless there is prior information that one wants to incorporate into the initial urn composition. For notational purposes, let $\alpha = \alpha_A + \alpha_B$.

Let p_A and p_B be the underlying probabilities of success given treatments A and B were assigned, respectively, and let $q_A = 1 - p_A$, $q_B = 1 - p_B$. Let $\boldsymbol{N}_n \equiv (N_{An}, N_{Bn})$, where N_{An} and N_{Bn} are the numbers of patients

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assigned to treatments A and B, respectively, in a trial of n patients. Previous work (Rosenberger and Sriram, 1997) has shown that

$$E\{N_{An}\} = \sum_{i=1}^{n} \frac{\alpha_A + \beta(i-1)q_B}{\alpha + \beta(i-1)} \prod_{k=i+1}^{n} \left(1 + \frac{\beta\lambda}{\alpha + \beta(k-1)}\right),$$

where $\lambda = p_A - q_B$. So given any underlying success probabilities (which can be chosen a priori by the physician), we can give the exact expected allocation proportions of the trial. Some measure of variability is also desirable. In this paper, we derive the exact variance.

Letting $v_A = q_B/(q_A + q_B)$ and $v_B = 1 - v_A$, it is well-known (see Wei, 1979 for example) that

$$N_{An}/n \xrightarrow{\text{a.s.}} v_A.$$

Rosenberger (1992) shows that, when $\lambda < 0.5$,

$$\sqrt{n}\left(\frac{N_{An}}{n} - v_A\right) \xrightarrow{\mathscr{L}} \mathrm{N}\left(0, v_A v_B \frac{3 + 2\lambda}{1 - 2\lambda}\right). \tag{1.1}$$

However, there is a phase transition at $\lambda = 0.5$. When $\lambda = 0.5$, the limit law is

$$\sqrt{\frac{n}{\ln n}}\left(\frac{N_{An}}{n} - v_A\right) \xrightarrow{\mathscr{L}} \mathrm{N}(0, \sigma^2), \tag{1.2}$$

where σ^2 is unknown. When $\lambda > 0.5$, the limiting distribution is unknown and is presumed to be non-normal. In the subsequent development, we derive the exact variance of N_{An} and discuss its asymptotic form when $\lambda \geqslant 0.5$.

2. Jordan representation

Let $\boldsymbol{Y_0} = (\alpha_A, \alpha_B)$ represent the initial urn composition and let $\boldsymbol{Y_n} \equiv (Y_{An}, Y_{Bn})$ represent the urn composition after n trials. Note that $|\boldsymbol{N_n}| = n$ and $|\boldsymbol{Y_n}| = \alpha + \beta n$, where $|\cdot|$ is the $\mathscr{L}_1$-norm. Letting $\boldsymbol{M} = ((m_{ij}))$ be the urn's generating matrix, i.e., m_{ij} is the expected number of balls added to the urn of type j, $j = A, B$, given type i was drawn, $i = A, B$. Then $\boldsymbol{M} = \beta \boldsymbol{P}$, where

$$\boldsymbol{P} = \begin{bmatrix} p_A & q_A \\ q_B & p_B \end{bmatrix}.$$

Putting $\boldsymbol{P}$ in its Jordan form, we obtain

$$\boldsymbol{P} = [\boldsymbol{\Psi}_1 \quad \boldsymbol{\Psi}_2] \begin{bmatrix} 1 & 0 \\ 0 & \lambda \end{bmatrix} \begin{bmatrix} \boldsymbol{\phi}_1 \\ \boldsymbol{\phi}_2 \end{bmatrix},$$

where $\boldsymbol{\Psi}_1 = (1,1)'$, $\boldsymbol{\Psi}_2 = (-v_B, v_A)'$, $\boldsymbol{\phi}_1 = (v_A, v_B)$, and $\boldsymbol{\phi}_2 = (-1, 1)$. We can write $\boldsymbol{N_n} = (\boldsymbol{N_n}\boldsymbol{\Psi}_1)\boldsymbol{\phi}_1 + (\boldsymbol{N_n}\boldsymbol{\Psi}_2)\boldsymbol{\phi}_2$, leading to

$$E\{\boldsymbol{N}_n'\boldsymbol{N}_n\} = E\{[\boldsymbol{\phi}_1'(\boldsymbol{N_n}\boldsymbol{\Psi}_1) + \boldsymbol{\phi}_2'(\boldsymbol{N_n}\boldsymbol{\Psi}_2)]\,[(\boldsymbol{N_n}\boldsymbol{\Psi}_1)\boldsymbol{\phi}_1 + (\boldsymbol{N_n}\boldsymbol{\Psi}_2)\boldsymbol{\phi}_2]\}.$$

Since $\boldsymbol{N_n}\boldsymbol{\Psi}_1$ is a constant, subtracting off $E(\boldsymbol{N}_n')E(\boldsymbol{N}_n)$ leaves only the term

$$\boldsymbol{\phi}_2'\boldsymbol{\phi}_2(E\{\boldsymbol{\Psi}_2'\boldsymbol{N}_n'\boldsymbol{N}_n\boldsymbol{\Psi}_2\} - [E\{\boldsymbol{N}_n\boldsymbol{\Psi}_2\}]^2) \tag{2.1}$$

in the variance–covariance matrix of $\boldsymbol{N_n}$. We now derive and solve recurrences for the moments in (2.1) and others that are needed for their calculation.

3. Derivation

Let $c=\alpha/\beta$, let $k_n=\alpha+(n-1)\beta$, and let $\Gamma(\cdot)$ be the gamma function. First we note that

$$E\{\boldsymbol{Y}_n\boldsymbol{\Psi}_2\}=E\{E\{\boldsymbol{Y}_n|\boldsymbol{Y}_{n-1}\}\}\boldsymbol{\Psi}_2=E\left\{\boldsymbol{Y}_{n-1}+\frac{\beta}{k_n}\boldsymbol{Y}_{n-1}\boldsymbol{P}\right\}\boldsymbol{\Psi}_2=E\left\{\boldsymbol{Y}_{n-1}\boldsymbol{\Psi}_2\left(1+\frac{\lambda}{c+n-1}\right)\right\},$$

which implies that

$$E\{\boldsymbol{Y}_n\boldsymbol{\Psi}_2\}=\boldsymbol{Y}_0\boldsymbol{\Psi}_2\,\frac{\Gamma(c+\lambda+n)}{\Gamma(c+n)}\,\frac{\Gamma(c)}{\Gamma(c+\lambda)}. \tag{3.1}$$

Next note that $E\{\boldsymbol{N}_0\boldsymbol{\Psi}_2\}=0$ and

$$E\{\boldsymbol{N}_n\boldsymbol{\Psi}_2\}=E\{E\{\boldsymbol{N}_n|\boldsymbol{Y}_{n-1},\boldsymbol{N}_{n-1}\}\}\boldsymbol{\Psi}_2=E\left\{\boldsymbol{N}_{n-1}+\frac{1}{k_n}\boldsymbol{Y}_{n-1}\right\}\boldsymbol{\Psi}_2.$$

So

$$E\{\boldsymbol{N}_n\boldsymbol{\Psi}_2\}=\sum_{j=0}^{n-1}E\left\{\frac{\boldsymbol{Y}_j\boldsymbol{\Psi}_2}{k_{j+1}}\right\}=\frac{\boldsymbol{Y}_0\boldsymbol{\Psi}_2}{\beta}\,\frac{\Gamma(c)}{\Gamma(c+\lambda)}\sum_{j=0}^{n-1}\frac{\Gamma(c+\lambda+j)}{\Gamma(c+1+j)}, \tag{3.2}$$

by (3.1).

For second moments, let $\Delta\boldsymbol{N}_n=\boldsymbol{N}_n-\boldsymbol{N}_{n-1}$ and $\Delta\boldsymbol{Y}_n=\boldsymbol{Y}_n-\boldsymbol{Y}_{n-1}$. We note from the argument leading to (3.1) that

$$E\{\boldsymbol{Y}_n|\boldsymbol{Y}_{n-1}\}=\frac{\beta}{k_n}\boldsymbol{Y}_{n-1}\boldsymbol{P}. \tag{3.3}$$

Let $g_n=E\{\boldsymbol{\Psi}_2'\boldsymbol{Y}_n'\boldsymbol{Y}_n\boldsymbol{\Psi}_2\}$, with $g_0=(\boldsymbol{Y}_0\boldsymbol{\Psi}_2)^2$. Then

$$g_n=g_{n-1}+2E\{\boldsymbol{\Psi}_2'\,\Delta\boldsymbol{Y}_n'\,\boldsymbol{Y}_{n-1}\boldsymbol{\Psi}_2\}+E\{\boldsymbol{\Psi}_2'\,\Delta\boldsymbol{Y}_n'\,\Delta\boldsymbol{Y}_n\,\boldsymbol{\Psi}_2\}. \tag{3.4}$$

The middle term on the RHS of (3.4) is $2\beta\lambda g_{n-1}/k_n$. By conditioning on $\boldsymbol{Y}_{n-1}$ we immediately find

$$E\{\Delta\boldsymbol{Y}_n'\,\Delta\boldsymbol{Y}_n\}=\frac{\beta^2}{k_n}\begin{bmatrix}Y_{A(n-1)}p_A+Y_{B(n-1)}q_B & 0\\ 0 & Y_{A(n-1)}q_A+Y_{B(n-1)}p_B\end{bmatrix}.$$

Recognizing that $E\{\Delta\boldsymbol{Y}_n\}\boldsymbol{\Psi}_1=\beta$ and, using (3.1), $E\{\Delta\boldsymbol{Y}_n\}\boldsymbol{\Psi}_2=\lambda E\{\boldsymbol{Y}_{n-1}\}\boldsymbol{\Psi}_2/(c+n-1)$ gives

$$\beta E\{\Delta\boldsymbol{Y}_n\}=\beta^2\boldsymbol{\phi}_1+\frac{\lambda}{\beta}\boldsymbol{Y}_0\boldsymbol{\Psi}_2\,\frac{\Gamma(c)}{\Gamma(c+\lambda)}\,\frac{\Gamma(c+\lambda+n-1)}{\Gamma(c+n)}\boldsymbol{\phi}_2.$$

Hence

$$\begin{aligned}A_n&\equiv E\{\boldsymbol{\Psi}_2'\,\Delta\boldsymbol{Y}_n'\,\Delta\boldsymbol{Y}_n\,\boldsymbol{\Psi}_2\}\\ &=\beta^2 v_A v_B+\beta\lambda(v_A-v_B)(\alpha_B v_A-\alpha_A v_B)\,\frac{\Gamma(c)}{\Gamma(c+\lambda)}\,\frac{\Gamma(c+\lambda+n-1)}{\Gamma(c+n)}.\end{aligned} \tag{3.5}$$

Substituting into (3.4) gives the recursion

$$g_n=\left(1+\frac{2\lambda}{c+n-1}\right)g_{n-1}+A_n,$$

which has as its solution

$$g_n = \frac{\Gamma(c+2\lambda+n)}{\Gamma(c+n)} \sum_{j=0}^{n} A_j \frac{\Gamma(c+j)}{\Gamma(c+2\lambda+j)}, \tag{3.6}$$

where the $\{A_j\}$ are defined in (3.5).

We do a similar analysis for $h_n = E\{\boldsymbol{\Psi}_2' \boldsymbol{Y}_n' \boldsymbol{N}_n \boldsymbol{\Psi}_2\}$, where $h_0 = 0$. We again work with the recursive form

$$h_n = h_{n-1} + E\{\boldsymbol{\Psi}_2' \boldsymbol{Y}_{n-1}' \Delta \boldsymbol{N}_n \boldsymbol{\Psi}_2\} + E\{\boldsymbol{\Psi}_2' \Delta \boldsymbol{Y}_n' \boldsymbol{N}_{n-1} \boldsymbol{\Psi}_2\} + E\{\boldsymbol{\Psi}_2' \Delta \boldsymbol{Y}_n' \Delta \boldsymbol{N}_n \boldsymbol{\Psi}_2\}. \tag{3.7}$$

The second and third terms on the RHS of (3.7) are obtained by conditioning as $\boldsymbol{\Psi}_2' E\{\boldsymbol{Y}_{n-1}' \boldsymbol{Y}_{n-1}\} \boldsymbol{\Psi}_2 / k_n$ and $\beta \boldsymbol{\Psi}_2' E\{\boldsymbol{P}' \boldsymbol{Y}_{n-1}' \boldsymbol{N}_{n-1}\} \boldsymbol{\Psi}_2 / k_n$, respectively. For the fourth term, note that

$$E\{E\{\Delta \boldsymbol{Y}_n' \Delta \boldsymbol{N}_n | \boldsymbol{Y}_{n-1}\}\} = \frac{\beta}{k_n} \boldsymbol{P}' \operatorname{diag}\{E\{\boldsymbol{Y}_{n-1}\}\},$$

so

$$E\{\boldsymbol{\Psi}_2' \Delta \boldsymbol{Y}_n' \Delta \boldsymbol{N}_n \boldsymbol{\Psi}_2\} = \frac{\lambda}{c+n-1} \boldsymbol{\Psi}_2' \operatorname{diag}\{E\{\boldsymbol{Y}_{n-1} \boldsymbol{\Psi}_2\}\}.$$

We write $E\{\boldsymbol{Y}_{n-1}\} = \boldsymbol{\phi}_1 (E\{\boldsymbol{Y}_{n-1}\} \boldsymbol{\Psi}_1) + \boldsymbol{\phi}_2 (E\{\boldsymbol{Y}_{n-1}\} \boldsymbol{\Psi}_2)$, thereby giving

$$\frac{\lambda}{c+n-1} E\{\boldsymbol{Y}_{n-1}\} = \lambda \beta \boldsymbol{\phi}_1 + \frac{\lambda}{\beta} \boldsymbol{Y}_0 \boldsymbol{\Psi}_2 \frac{\Gamma(c)}{\Gamma(c+\lambda)} \frac{\Gamma(c+\lambda+n-1)}{\Gamma(c+n)} \boldsymbol{\phi}_2.$$

Hence

$$\begin{aligned} B_n &\equiv E\{\boldsymbol{\Psi}_2' \Delta \boldsymbol{Y}_n' \Delta \boldsymbol{N}_n \boldsymbol{\Psi}_2\} \\ &= \beta \lambda v_A v_B + \lambda (v_A - v_B)(\alpha_B v_A - \alpha_A v_B) \frac{\Gamma(c)}{\Gamma(c+\lambda)} \frac{\Gamma(c+\lambda+n-1)}{\Gamma(c+n)}. \\ &= \frac{A_n}{\beta} + (\lambda - 1) \beta v_A v_B. \end{aligned} \tag{3.8}$$

Substituting into (3.7) gives the recursion

$$h_n = \left(1 + \frac{\lambda}{c+n-1}\right) h_{n-1} + B_n + \frac{g_{n-1}}{\beta(c+n-1)},$$

which has as its solution

$$h_n = \frac{\Gamma(c+\lambda+n)}{\Gamma(c+n)} \sum_{j=1}^{n} \left(B_j + \frac{g_{j-1}}{\beta(c+j-1)} \right) \frac{\Gamma(c+j)}{\Gamma(c+\lambda+j)}, \tag{3.9}$$

where the $\{B_j\}$ are defined by (3.8) and (3.5) and the $\{g_j\}$ are defined by (3.6) and (3.5).

Finally, we set $i_n = E\{\boldsymbol{\Psi}_2' \boldsymbol{N}_n' \boldsymbol{N}_n \boldsymbol{\Psi}_2\}$, yielding the recurrence

$$i_n = i_{n-1} + 2E\{\boldsymbol{\Psi}_2' \Delta \boldsymbol{N}_n' \boldsymbol{N}_{n-1} \boldsymbol{\Psi}_2\} + E\{\boldsymbol{\Psi}_2' \Delta \boldsymbol{N}_n' \Delta \boldsymbol{N}_n \boldsymbol{\Psi}_2\}. \tag{3.10}$$

The second term on the RHS of (3.10), by conditioning on $\boldsymbol{Y}_{n-1}$, is $2h_{n-1}/k_n$. For the third, $E\{\Delta \boldsymbol{N}_n' \Delta \boldsymbol{N}_n\} = \operatorname{diag}\{E\{\boldsymbol{Y}_{n-1}\}\}/k_n$, so $\beta \lambda E\{\boldsymbol{\Psi}_2' \Delta \boldsymbol{N}_n' \Delta \boldsymbol{N}_n \boldsymbol{\Psi}_2\} = B_n$. Hence

$$i_n = \sum_{j=1}^{n-1} \frac{2h_j}{\beta(c+j)} + \sum_{j=1}^{n} \frac{B_j}{\beta \lambda}, \tag{3.11}$$

with obvious interpretation if $\lambda = 0$. Here the $\{h_j\}$ are defined by (3.9), (3.8), (3.6), and (3.5), and the $\{B_j\}$ are defined by (3.8) and (3.5).

Substituting (3.11) and (3.2) into (2.1) yields the main result:

$$\operatorname{Var}(N_{An})$$

$$= 2v_A v_B \sum_{l=0}^{n-2} \frac{\Gamma(c+l)}{\Gamma(c+2\lambda+l)} \sum_{k=l+1}^{n-1} \frac{\Gamma(c+2\lambda+k-1)}{\Gamma(c+k+\lambda)} \sum_{j=k}^{n-1} \frac{\Gamma(c+j+\lambda)}{\Gamma(c+j+1)} \tag{3.12}$$

$$+ \frac{2\lambda}{\beta}(v_A - v_B)(\alpha_B v_A - \alpha_A v_B)\frac{\Gamma(c)}{\Gamma(c+\lambda)}$$

$$\times \sum_{l=0}^{n-2} \frac{\Gamma(c+\lambda+l-1)}{\Gamma(c+2\lambda+l)} \sum_{k=l+1}^{n-1} \frac{\Gamma(c+2\lambda+k-1)}{\Gamma(c+k+\lambda)} \sum_{j=k}^{n-1} \frac{\Gamma(c+j+\lambda)}{\Gamma(c+j+1)} \tag{3.13}$$

$$- \left\{ \frac{(\alpha_B v_A - \alpha_A v_B)}{\beta} \frac{\Gamma(c)}{\Gamma(c+\lambda)} \sum_{j=0}^{n-1} \frac{\Gamma(c+j+\lambda)}{\Gamma(c+j+1)} \right\}^2 \tag{3.14}$$

$$+ n v_A v_B + 2\lambda v_A v_B \sum_{k=1}^{n-1} \frac{\Gamma(c+k)}{\Gamma(c+k+\lambda)} \sum_{j=k}^{n-1} \frac{\Gamma(c+j+\lambda)}{\Gamma(c+j+1)} \tag{3.15}$$

$$+ \frac{1}{\beta}(v_A - v_B)(\alpha_B v_A - \alpha_A v_B)\frac{\Gamma(c)}{\Gamma(c+\lambda)} \sum_{k=1}^{n-1} \frac{\Gamma(c+\lambda+k-1)}{\Gamma(c+k)} \tag{3.16}$$

$$+ \frac{2\lambda}{\beta}(v_A - v_B)(\alpha_B v_A - \alpha_A v_B)\frac{\Gamma(c)}{\Gamma(c+\lambda)}$$

$$\times \sum_{k=1}^{n} \frac{\Gamma(c+\lambda+k-1)}{\Gamma(c+k+\lambda)} \sum_{j=k}^{n-1} \frac{\Gamma(c+\lambda+j)}{\Gamma(c+j+1)}. \tag{3.17}$$

4. Asymptotics and approximations

Terms (3.12)–(3.17) give the exact variance for any parameters in an easily programmable form. Now we give asymptotics and approximations, using Stirling's formula and integral approximations. We develop these informally, though everything could be made rigorous, if one desires.

Analysis of (3.12)–(3.17) yields terms that are of order $n^{2\lambda}$ (of order $n \ln n$ when $\lambda = 1/2$), of order n, and of order $n^{\lambda} \ln n$. We are only interested in terms that are of exact order n and higher, so we ignore terms (3.16) and (3.17), which are $O(n^{\lambda} \ln n)$. Term (3.15) can be written as

$$n v_A v_B \left(\frac{1+\lambda}{1-\lambda}\right)\{1 + o(1)\}. \tag{4.1}$$

Terms (3.13) and (3.14) are of order $n^{2\lambda}$. Term (3.12) is the most important. It can be approximated by

$$\frac{v_A v_B}{\lambda^2}\left\{\left\{\sum_{l=0}^{n-2}(c+l)^{-2\lambda} n^{2\lambda}\right\} - \frac{2n}{1-\lambda} + n\right\}. \tag{4.2}$$

For example, consider the derivation of (4.2) from (3.12) for $\lambda > 0$. By Stirling's formula the innermost sum is

$$\sum_{j=k}^{n-1} (c+j)^{\lambda-1}\{1+\mathrm{O}(j^{-1})\}.$$

Since $(c+j)^{\lambda-1} = \int_j^{j+1} (c+x)^{\lambda-1}\,\mathrm{d}x + \mathrm{O}(j^{\lambda-2})$, this sum is $\lambda^{-1}\{(c+n)^{\lambda} - (c+k)^{\lambda}\} + \mathrm{O}(k^{\lambda-1})$. Evaluating the middle sum similarly gives

$$\frac{2}{\lambda^2}\{(c+n)^{2\lambda} - 2(c+n)^{\lambda}(c+l+1)^{\lambda} + (c+l+1)^{2\lambda}\} + \mathrm{O}(n^{\lambda}).$$

Evaluating the outer sum in the same manner gives (4.2) with an error of $\mathrm{o}(n)$. Note that the first term of (4.2) is a valid asymptotic expansion only as $c \to \infty$. A correction for this is given in (4.4).

If $\lambda = 1/2$, we get $4v_A v_B n \ln n$, indicating that the σ^2 in (1.2) should be $4v_A v_B$. It is interesting to note this binomial-like behavior at the phase change. When $\lambda < 1/2$, combining (4.1) with (4.2) yields the asymptotic variance of $\{(3+2\lambda)/(1-2\lambda)\}v_A v_B$, given in (1.1).

Now consider the case $\lambda > 1/2$. The sum in (4.2) is dominated by its terms near $l = 0$; it can be approximated by $\sum_{l=0}^{\infty}(c+l)^{-2\lambda}$. If c is fairly large, yet small compared to n, we can approximate the sum using the integral

$$\int_c^{\infty} x^{-2\lambda}\,\mathrm{d}x = \frac{c^{1-2\lambda}}{2\lambda - 1}.$$

For example, if $c = 5$ and $\lambda = 0.6$, the relative error is 2%. Terms (3.13) and (3.14) contribute to the asymptotics for $\lambda > 1/2$. Interestingly, if the initial urn is started at the limiting distribution; i.e., if $\alpha_A/\alpha_B = v_A/v_B$, the terms vanish. Up to a factor $1 + \mathrm{o}(1)$, terms (3.13) and (3.14) can be written as

$$\frac{(v_A - v_B)(\alpha_B v_A - \alpha_A v_B)}{\lambda^2 \beta}\frac{\Gamma(c)}{\Gamma(c+\lambda)}c^{-\lambda}n^{2\lambda} - \frac{(\alpha_B v_A - \alpha_A v_B)^2}{\lambda^2\beta^2}\left\{\frac{\Gamma(c)}{\Gamma(c+\lambda)}\right\}^2 n^{2\lambda}.$$

If c is reasonably large, this becomes approximately

$$\frac{(\alpha_B v_A - \alpha_A v_B)}{\lambda^2\beta^2}\left\{\frac{v_A - v_B}{\beta} - (\alpha_B v_A - \alpha_A v_B)\right\}\left(\frac{n}{c}\right)^{2\lambda}.$$

To summarize, we give the following approximation to terms (3.12)–(3.17):

$$\mathrm{Var}(N_{An}) \doteq \frac{1}{\lambda^2}\left(\frac{n}{c}\right)^{2\lambda} D_n - n v_A v_B (1+\lambda)^2,$$

where

$$D_n = \frac{v_A v_B}{1-2\lambda}c^{2\lambda}[(c+n)^{1-2\lambda} - c^{1-2\lambda}] - (\alpha_B v_A - \alpha_A v_B)^2 + \frac{(v_A - v_B)(\alpha_B v_A - \alpha_A v_B)}{\beta}. \tag{4.3}$$

Using Eqs. (4.3) captures the logarithmic behavior at $\lambda = 0.5$ and avoids an undue increase in the variance approximation for λ near 0.5 due to the factor $1 - 2\lambda$ in the denominator of D_n. Further, for $\lambda < 0.5$, it gives the correct asymptotic variance. For $\lambda > 0.5$, it has the correct $n^{2\lambda}$ term, though the coefficient is off by a small multiple. To correct for this,

$$\frac{1}{\lambda^2}\left(\frac{n}{c}\right)^{2\lambda}\frac{v_A v_B}{1-2\lambda}c^{2\lambda}[(c+n)^{1-2\lambda} - c^{1-2\lambda}]$$

can be replaced by

$$\frac{v_A v_B}{\lambda^2} \sum_{l=0}^{n-2} \frac{\Gamma(c+l)}{\Gamma(c+l+2\lambda)} n^{2\lambda}. \tag{4.4}$$

5. Discussion

For large randomized play-the-winner clinical trials, where λ is presumed not to exceed 0.5, the limiting distribution does not depend on the initial urn composition. The fact that it does when $\lambda > 0.5$ leads one to question whether the randomized play-the-winner rule should be used in that scenario. Such clinical trials with high success rates on both treatments are rare, but possible. It is well-known for a small randomized play-the-winner trial ($n = 12$) that the selection of the initial urn composition was pivotal (see Bartlett et al., 1985), and its improper selection led to somewhat disastrous results.

The randomized play-the-winner rule is a special case of the *generalized Friedman's urn* (GFU; Athreya and Karlin, 1968). Such an urn model has been suggested for use in clinical trials of $K > 2$ treatments (Wei, 1979), bioassay (Rosenberger et al., 1997), and psychophysics experimentation (Rosenberger and Grill, 1997). A general exact and asymptotic theory for the GFU has been actively sought. Elements of this emerging theory can be found in recent work of Aldous et al. (1988), Bagchi and Pal (1985), Gouet (1989, 1993), Mahmoud and Smythe (1991, 1992, 1995), Mahmoud et al. (1993), and Smythe (1996). Using the Jordan form of the generating matrix, as we did in this paper, should enable variance computations of much more complicated designs with larger generating matrices, but we leave that for the industrious reader.

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Note added in proof

The authors thank Padmanabhan Seshaiyer for finding the computational error:

Equation (3.16): The upper limit of the summand should be n instead of $n-1$.

Equation (3.17): The upper limit of the outer summand should be $n-1$ instead of n.

Equations (3.12) and (3.13): The outer summand should start at $l=1$ instead of $l=0$. All subsequent terms with $l=0$ should be replaced with $l=1$, including equations (4.2), (4.4), and several quantities in the middle of page 238.

The previous correction is compensated by adding an additional term, which we will call (3.18), to be added after (3.17):

$$+\frac{2}{\beta^2}(\alpha_B v_A - \alpha_A v_B)^2 \frac{\Gamma(c)}{\Gamma(c+2\lambda)} \sum_{j=1}^{n-1} \frac{\Gamma(c+\lambda+j)}{\Gamma(c+j+1)} \sum_{k=1}^{j} \frac{\Gamma(c+2\lambda+k-1)}{\Gamma(c+\lambda+k)}.$$

This term arises from the A_0 term in equation (3.6). The omission of this term affects several terms in the asymptotic approximation in Section 4, in particular, equation (4.3) and two of the three equations immediately above it (not numbered).

Equation (4.3): remove $-(\alpha_B v_A - \alpha_A v_B)^2$. This term should also be removed from the equation found 4 lines above (4.3).

In the equation 6 lines above (4.3), the factor

$$\left\{\frac{\Gamma(c)}{\Gamma(c+\lambda)}\right\}^2 \text{ should be replaced with } \left\{-\frac{\Gamma(c)}{\Gamma(c+2\lambda)} + \left(\frac{\Gamma(c)}{\Gamma(c+\lambda)}\right)^2\right\}.$$