An urn model and the odds ratio-based design for clinical trials

Gopal K. Basak*,†, Atanu Biswas‡,† and Stanislav Volkov§

March 5, 2008

Abstract

We study the limiting behaviour of a generalized Pólya urn, motivated by adaptive data-dependent allocation designs, which are used in Phase III clinical trials in order to allocate a larger number of patients to the better treatment. We establish rigorous limiting results for the model, including the Central Limit Theorem, thus providing the theoretical background for using the odds ratio-based adaptive designs.

Key words and phrases: adaptive designs, Central Limit Theorem, limiting allocation probability, odds ratio estimates, play-the-winner rule.

AMS subject classification: 60F05, 62K99.

*E-mail: gkb@isical.ac.in
†Indian Statistical Institute, 203 B.T. Road, Calcutta 700 108, India
‡E-mail: atanu@isical.ac.in
§(Corresponding author) Department of Mathematics, University of Bristol, BS8 1TW, U.K. E-mail: S.Volkov@bristol.ac.uk
1 Introduction

A generalized Pólya urn (GPU) model, also called generalized Friedman’s urn by Athreya and Karlin (1968), can be described as follows. Start with an urn initially containing $Y_0$ balls of type $i$, $i \in \{A, B\}$. If a ball of type $i$ is drawn, $i \in \{A, B\}$, $R_{ij}$ additional balls of type $j$ ($j \in \{A, B\}$) are added to the urn, where in general $R_{ij}$ is allowed to be random, or even depending on the results of the previous draws. An extensive review of various urn models can be found in Janson (2004) and Pemantle (2007). At the same time, urn models are closely related to the allocation designs in statistics, which are often used in Phase III clinical trials, in order to allocate a larger number of patients to the better treatment, see e.g. Zelen (1969), Wei and Durham (1978), Wei (1979), Bartlett et al. (1985), Tamura et al. (1994), Ivanova (2003), Ivanova et al. (2000) and Biswas and Dewanji (2004).

In this paper, we study the odds ratio based design (ORBD) that allocates a patient to a treatment with probability proportional to the current estimate of the odds ratio in favour of that treatment.

Let $p_A = 1 - q_A$ and $p_B = 1 - q_B$ be the (unknown) success probabilities of two treatments $A$ and $B$, respectively. Let $S_{A,n}$ and $F_{A,n}$ be the number of successes and failures of treatment $A$ at the end of the $n$-th trial; similarly, we define $S_{B,n}$ and $F_{B,n}$ for treatment $B$. Then the odds ratio is defined by $\theta := p_A q_B / (q_A p_B)$, and its current estimate is $\hat{\theta} = \hat{p}_A \hat{q}_B / (\hat{q}_A \hat{p}_B)$, with $\hat{p}_i = S_{i,n} / (S_{i,n} + F_{i,n})$ being the observed proportion of successes resulted from treatment $i = A, B$. Now we would like to assign (randomly) the $(n + 1)$-st patient to treatment $A$ or $B$, depending on our estimate of $\theta$ by time $n$. Since $\theta \in (0, \infty)$, a natural transformation of $\theta$ to be used for assigning the allocation probability would be $\theta \mapsto f(\theta) = \theta / (1 + \theta)$. It is easy to verify that this mapping $f : (0, \infty) \mapsto (0, 1)$ assumes the a priori
symmetry\(^1\) of treatments \(A\) and \(B\), and also \(f(\theta) = 1/2\) corresponds to the equivalence of the two treatments, when \(p_A = p_B\). Thus our model postulates that the probability of choosing a treatment is proportional to the odds ratio associated with that particular treatment by the time when the decision is made:

\[
P(\text{choose treatment } A \text{ at the } (n+1)\text{st trial} \mid \text{past data}) = \frac{S_{A,n}/F_{A,n}}{S_{A,n}/F_{A,n} + S_{B,n}/F_{B,n}} = \frac{S_{A,n}F_{B,n}}{S_{A,n}F_{B,n} + S_{B,n}F_{A,n}}.
\]

(1)

This is a simple example of an adaptive data-dependent allocation designs are used in Phase III clinical trials. The idea here is that while trying to establish which of the two treatments is in fact better, we would like to allocate more patients to a statistically better treatment during the trial itself, thus addressing the trade-off between the efficient estimation and more ethical treatment of the participants. Indeed, since \(S_{A,n}/F_{A,n}\) is our estimate by time \(n\) of the odds ratio of the success rate of treatment \(A\), the larger this quantity is, the more justified it is to allocate next patient to treatment \(A\) (and similar for treatment \(B\)). Also, the odds ratio is a popular concept amongst biomedical practitioners.

An odds ratio-based rule was originally proposed by Kadane (1996), and subsequently generalized by Rosenberger, Vidyashankar and Agarwal (2001). Rosenberger et al. (2001) used a logistic distributional assumption to incorporate covariates into the design and proposed a covariate-adjusted log odds ratio rule. Yet a detailed study was not carried out there, neither theoretical nor numerical. In comparison, in our present work we do not consider any covariates but study analytical properties of the design, thus providing the theoretical basis for its usage in practice.

Finally, note that the rule (1) can be seen indeed as an urn model as follows. We calculate \(S_{A,n}, S_{B,n}, F_{A,n}\) and \(F_{B,n}\) for each \(n\). For the allocation

\(^1\)that is, \(f(1/\theta) = 1 - f(\theta)\)
of the \((n+1)\)-st patient, we use an urn which contains \(S_{A,n}F_{B,n}\) balls of type \(A\) and \(S_{B,n}F_{A,n}\) balls of type \(B\). After obtaining the response of the \(n\)-th patient, we add \(F_{B,n}\) balls of type \(A\) or \(S_{B,n}\) balls of type \(B\) for a success or failure if the \((n+1)\)-st patient is treated by treatment \(A\). If the \(n\)-th patient is treated by treatment \(B\), we add an additional \(F_{A,n}\) balls of type \(B\) or \(S_{A,n}\) balls of type \(A\) for a success or failure of the treatment. In short, for the response of the \((n+1)\)st patient we add \(S_{A,n+1}F_{B,n+1} - S_{A,n}F_{B,n}\) balls of type \(A\) and \(S_{B,n+1}F_{A,n+1} - S_{B,n}F_{A,n}\) balls of type \(B\) to the urn. We use this urn to allocate the \((n+2)\)-nd patient. We use a fair coin for allocations until the sample odds ratio is properly defined, i.e., both \(S_{A,n}F_{B,n}\) and \(S_{B,n}F_{A,n}\) are non-zero. Thereafter we use the urn above.

The rest of the paper is organized as follows. In Section 2 we provide some limiting results, including our main result, the Central Limit Theorem for the odds ratio based design. Section 3 contains most of the proofs. Additionally, in the Appendix we illustrate the proposed odds ratio based design using some real data. Section 4 concludes.

## 2 Limit theorems

Throughout the rest of the paper we assume \(0 < p_A < 1\) and \(0 < p_B < 1\). We also assume that for some \(n_0 > 0\)

\[
\min\{S_{A,n_0}, F_{A,n_0}, S_{B,n_0}, F_{B,n_0}\} > 0,
\]

to make our model non-trivial.

Let us define the events \(E_A = \{\text{treatment } A \text{ is chosen } i.o.\}\) and \(E_B = \{\text{treatment } B \text{ is chosen } i.o.\}\). Obviously, on the event \(E_A\) we have

\[
\lim_{n \to \infty} \frac{S_{A,n}}{F_{A,n}} = \frac{p_A}{q_A} \quad \text{a.s.}
\]
since $S_{A,n} \ (F_{A,n})$ counts the number of successes (failures resp.) in the sequence of independent i.i.d. Bernoulli trials. By the same token on $E_B$

$$\lim_{n \to \infty} \frac{S_{B,n}}{F_{B,n}} = \frac{p_B}{q_B} \text{ a.s.}$$

**Lemma 1** The probability of choosing the treatment $A$ converges a.s. to

$$\tilde{\gamma} := \frac{p_A q_B}{p_A q_B + p_B q_A} \quad (2)$$

**Proof.** Let $\rho_A := \lim_{n \to \infty} \frac{S_{A,n}}{F_{A,n}}$. While $\rho_A = \frac{p_A}{q_A}$ a.s. on the event $E_A$, on the event $E_A^c$ the limit $\rho_A$ exists as well, and is positive a.s. since the sequence $S_{A,n}/F_{A,n}$ simply does not change starting from some large $n$. Similarly, there exists a.s. $\rho_B := \lim_{n \to \infty} \frac{S_{B,n}}{F_{B,n}}$. While $\rho_A$ and $\rho_B$ may be a priori random, $\mathbb{P}(\rho_A > 0) = \mathbb{P}(\rho_B > 0) = 1$. Therefore, the probability of choosing treatment $A$, after the $n$-th trial,

$$\gamma^{(n)} = \frac{S_{A,n}}{F_{A,n}} \frac{F_{A,n}}{S_{A,n} + S_{B,n}}$$

a.s. converges as $n \to \infty$ to $\rho_A/(\rho_A + \rho_B)$. Fix some small $\delta > 0$ and let $\Omega_\delta = \{\rho_A/(\rho_A + \rho_B) > \delta\}$. On the event $\Omega_\delta$ there is an $N_1 = N_1(\omega) > 0$ such that for $n \geq N_1$ the probability of choosing treatment $A$ is at least $\delta/2$, therefore by the (conditional) Borel-Cantelli lemma, with probability one, treatment $A$ will be chosen infinitely often, hence

$$\mathbb{P}(\Omega_\delta \cap E_A^c) = 0.$$

At the same time $\mathbb{P}(\Omega_\delta) \uparrow 1$ as $\delta \downarrow 0$, since $\rho_A/(\rho_A + \rho_B) > 0$ a.s. This, in turn, implies $\mathbb{P}(E_A^c) = 1$; similarly $P(E_B^c) = 0$, and consequently $\mathbb{P}(E_A \cap E_B) = 1$.

Finally, on the intersection of the events $E_A$ and $E_B$ we have

$$\lim_{n \to \infty} \frac{S_{A,n} F_{B,n}}{S_{A,n} F_{B,n} + S_{B,n} F_{A,n}} = \frac{\lim_{n \to \infty} S_{A,n} F_{B,n}}{\lim_{n \to \infty} S_{A,n} F_{B,n} + \lim_{n \to \infty} S_{B,n} F_{B,n}} = \frac{p_A / q_A}{p_A / q_A + p_B / q_B}$$
yielding the statement of the lemma. 

Next we are going to apply Corollary 4.2 of Ethier and Kurtz (1986) to our urn model. This is somewhat related to the Theorem 2.1 in Basak et al. (1997), who studied the convergence of recursion to the stochastic differential equation under more explicit setup. Let

\begin{align*}
W^{(n)}_1 &= \frac{q_A S_{A,n} - p_A F_{A,n}}{\sqrt{S_{A,n} + F_{A,n}}} \\
W^{(n)}_2 &= \frac{q_B S_{B,n} - p_B F_{B,n}}{\sqrt{S_{B,n} + F_{B,n}}} \\
W^{(n)}_3 &= \frac{S_{A,n} + F_{A,n} - \bar{\gamma}_n}{\sqrt{n}},
\end{align*}

where \(\bar{\gamma}\) is given by (2). Without loss of generality we may assume that \(n \equiv S_{A,n} + F_{A,n} + S_{B,n} + F_{B,n}\) (which corresponds to the responses being immediate).

The proof of the following statement is presented in Section 3.

**Theorem 1** Let \(W^{(n)} = (W^{(n)}_1, W^{(n)}_2, W^{(n)}_3)^T\). Then, as \(n \to \infty\),

\[W^{(n)} \Rightarrow \mathcal{N} \left( \begin{bmatrix} 0 \\ p_A q_A \\ 0 \\ \bar{\gamma}^{1/2}(1 - \bar{\gamma}) \end{bmatrix}, \begin{bmatrix} 0 & \bar{\gamma}^{1/2}(1 - \bar{\gamma}) & 0 & \bar{\gamma}^{1/2}(1 - \bar{\gamma})^{1/2} \\ 0 & 0 & p_B q_B & -\bar{\gamma}(1 - \bar{\gamma})^{1/2} \\ \bar{\gamma}^{1/2}(1 - \bar{\gamma}) & 0 & 0 & \beta \\ 0 & -\bar{\gamma}(1 - \bar{\gamma})^{1/2} & \beta & 0 \end{bmatrix} \right)\]

in distribution, where

\[
\beta = \frac{2\bar{\gamma}(1 - \bar{\gamma})^2}{p_A q_A} + \frac{2\bar{\gamma}^2(1 - \bar{\gamma})}{p_B q_B} + \bar{\gamma}(1 - \bar{\gamma}).
\]

**Theorem 2** Let \(V^{(n)} = \sqrt{n}(S_{A,n}/F_{A,n} - p_A/q_A, S_{B,n}/F_{B,n} - p_B/q_B)^T\). Then, as \(n \to \infty\),

\[V^{(n)} \Rightarrow \mathcal{N} \left( \begin{bmatrix} 0 \\ 0 \\ 0 \\ p_A q_B + p_B q_A \end{bmatrix}, \begin{bmatrix} p_A q_B + p_B q_A \\ q_A q_B \\ 0 \\ q_B q_A \end{bmatrix} \right) \]

in distribution.
Note that using the delta method, one can compute the asymptotic distribution of any smooth of function of $S_{A,n}/F_{A,n}$ and $S_{B,n}/F_{B,n}$. In particular, if we denote $\gamma(n) = \frac{S_{A,n}F_{B,n}}{S_{A,n}F_{B,n} + S_{B,n}F_{A,n}}$ and $\theta(n) = \frac{S_{A,n}F_{A,n}}{S_{B,n}F_{B,n}}$ then, as $n \to \infty$,

$$\sqrt{n} (\gamma(n) - \bar{\gamma}) \Rightarrow N(0, \sigma_{\gamma}^2),$$

$$\sqrt{n} (\theta(n) - (p_Aq_B)/(q_Ap_B)) \Rightarrow N(0, \sigma_{\theta}^2)$$

in distribution, with

$$\sigma_{\gamma}^2 = \frac{q_Aq_B(p_A^2 + p_B^2)}{(p_Aq_B + pbqa)^2},$$

$$\sigma_{\theta}^2 = \left( \frac{p_Aq_B}{q_Ap_B} \right)^2 \left( \frac{1}{\bar{\gamma}p_Aq_A} + \frac{1}{(1-\bar{\gamma})p_Bq_B} \right).$$

### 3 Proof of the main theorems

**Proof of Theorem 1.** Sometimes, where it does not create any confusion, we will omit the super- and subscript $(n)$ and $n$. Then

$$S_A = p_A(S_A + F_A) + W_1\sqrt{S_A + F_A}, \quad F_A = q_A(S_A + F_A) - W_1\sqrt{S_A + F_A},$$

$$S_B = p_B(S_B + F_B) + W_2\sqrt{S_B + F_B}, \quad F_B = q_B(S_B + F_B) - W_2\sqrt{S_B + F_B}$$

and

$$S_A + F_A = \bar{\gamma}n + W_3\sqrt{n}, \quad S_B + F_B = (1-\bar{\gamma})n - W_3\sqrt{n}.$$ 

Then the probability to choose treatment $A$ at time $n$ is

$$\gamma(n) = \bar{\gamma} \equiv \frac{S_AF_B}{S_AF_B + S_BF_A} = \bar{\gamma} + \frac{1}{\sqrt{n}} \frac{\sqrt{1-\bar{\gamma}}p_Bq_BW_1 - \sqrt{\bar{\gamma}}p_Aq_AW_2}{\sqrt{\bar{\gamma}(1-\bar{\gamma})(p_Aq_B + pbqa)^2}} + O(n^{-3/2})$$

$$= \bar{\gamma} + \frac{1}{\sqrt{n}} \frac{\sqrt{1-\bar{\gamma}}p_Bq_BW_1 - \sqrt{\bar{\gamma}}p_Aq_AW_2}{\sqrt{p_Aq_Bp_Bq_A}(p_Aq_B + pbqa)} + O(n^{-3/2}) \quad (3)$$
Then the conditional increment of $W^{(n+1)} - W^{(n)} \mid \mathcal{F}_n$ has the following distribution:

<table>
<thead>
<tr>
<th>Probability</th>
<th>$W_1^{(n+1)} - W_1^{(n)}$</th>
<th>$W_2^{(n+1)} - W_2^{(n)}$</th>
<th>$W_3^{(n+1)} - W_3^{(n)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\gamma p_A$</td>
<td>$-\frac{W_1}{2(S_A + F_A)} + \frac{q_A}{\sqrt{S_A + F_A}}$</td>
<td>0</td>
<td>$-\frac{W_3}{2n} + \frac{1 - \tilde{\gamma}}{\sqrt{n}}$</td>
</tr>
<tr>
<td>$\gamma q_A$</td>
<td>$-\frac{W_1}{2(S_A + F_A)} - \frac{p_A}{\sqrt{S_A + F_A}}$</td>
<td>0</td>
<td>$-\frac{W_3}{2n} + \frac{1 - \tilde{\gamma}}{\sqrt{n}}$</td>
</tr>
<tr>
<td>$(1 - \gamma)p_B$</td>
<td>0</td>
<td>$-\frac{W_2}{2(S_B + F_B)} + \frac{q_B}{\sqrt{S_B + F_B}}$</td>
<td>$-\frac{W_3}{2n} - \frac{\tilde{\gamma}}{\sqrt{n}}$</td>
</tr>
<tr>
<td>$(1 - \gamma)q_B$</td>
<td>0</td>
<td>$-\frac{W_2}{2(S_B + F_B)} - \frac{p_B}{\sqrt{S_B + F_B}}$</td>
<td>$-\frac{W_3}{2n} - \frac{\tilde{\gamma}}{\sqrt{n}}$</td>
</tr>
</tbody>
</table>

where all entries are up to the term $O(n^{-3/2})$, except those with the zeros, which are exact. Consequently,

$$
E((W^{(n+1)} - W^{(n)}) \mid \mathcal{F}_n) = \begin{pmatrix}
-\frac{\gamma W_1}{2(S_A + F_A)} \\
-\frac{(1 - \gamma)W_2}{2(S_B + F_B)} \\
-W_3/2n + \frac{\gamma - \tilde{\gamma}}{\sqrt{n}}
\end{pmatrix} + O(n^{-3/2})
$$

$$
= \frac{1}{n} \begin{pmatrix}
-W_1/2 \\
-W_2/2 \\
-W_3/2 + \frac{\sqrt{1 - \tilde{\gamma}}p_B q_B W_1 - \sqrt{\gamma} p_A q_A W_2}{\sqrt{p_A q_A p_B q_B (p_A q_B + p_B q_A)}}
\end{pmatrix} + O(n^{-3/2})
$$

$$
= \frac{1}{n} \Gamma W + O(n^{-3/2}),
$$

where

$$
\Gamma = -\frac{1}{2} I + \Pi
$$

8
with $I$ being $3 \times 3$ unity matrix and

$$
\Pi = \begin{pmatrix}
0 & 0 & 0 \\
0 & 0 & 0 \\
\tilde{\gamma}^{1/2}(1 - \tilde{\gamma}) & \tilde{\gamma}(1 - \tilde{\gamma})^{1/2} & 0
\end{pmatrix}.
$$

Also,

$$
\mathbb{E} \left( \left( W^{(n+1)} - W^{(n)} \right)^T \left( W^{(n+1)} - W^{(n)} \right) | \mathcal{F}_n \right) = \begin{pmatrix}
\frac{PAQA}{n} & 0 & 0 \\
0 & \frac{PBQB}{n} & 0 \\
0 & 0 & \frac{\tilde{\gamma}(1 - \tilde{\gamma})}{n}
\end{pmatrix} + O(n^{-3/2}) = \frac{1}{n} \Delta^2 + O(n^{-3/2}), \tag{5}
$$

where

$$
\Delta = \begin{pmatrix}
\sqrt{PAQA} & 0 & 0 \\
0 & \sqrt{PBQB} & 0 \\
0 & 0 & \sqrt{\tilde{\gamma}(1 - \tilde{\gamma})}
\end{pmatrix}.
$$

Now to check the conditions of Corollary 4.2 of Ethier and Kurtz (1986), let $b(x) = \Gamma x$, with all they eigenvalues of $\Gamma$ having negative real parts. By the Sylvester’s theorem, there exist a positive definite matrix $D$ such that $D\Gamma + \Gamma^T D$ is negative definite. Hence for all $x \in \mathbb{R}^d$

$$
2b(x)^T(Dx) + Tr(a(x)D) \leq -C_0 |x|^2 + C_1
$$

for some constants $C_0, C_1 > 0$ where $a(x) = \Delta \Delta^T$ is positive definite. It is well established that these characteristics define a Markov process (an Ornstein-Uhlenbeck type process) governed by the stochastic differential equation

$$
dX_t = \Gamma X_t dt + \Delta dB_t \tag{6}
$$
in 3 dimensions, with the unique invariant measure whose density is Gaussian, with zero mean and covariance matrix \( \int_0^\infty e^{\Gamma t} \Delta^\top e^{\Gamma^\top t} dt \). Thus, \textit{a fortiori}, martingale problem defined by \((L, \mu)\) is well-posed for each \( \mu \in \mathcal{P}(\mathbb{R}^3) \), where

\[
L = \frac{1}{2} \sum_{i,j} a_{ij}(x) \frac{\partial^2}{\partial x_i \partial x_j} + \sum_{i=1}^3 (\Gamma(x)) \frac{\partial}{\partial x_i},
\]

with

\[
a_{ij}(x) = \sum_{k=1}^3 \sigma_{ik}(x)\sigma_{jk}(x).
\]

According to Corollary 4.2 of Ethier and Kurtz (1986, p. 355), to get the weak convergence of \( \{W_n\} \) to \( \{X_t\} \), defined by the above stochastic differential equation, it is sufficient to check the local convergence of characteristics \( b_n \rightarrow b \) and \( a_n \rightarrow a \), and the negligibility criteria outside a compact ball (the third condition of Corollary 4.2), where

\[
b_n(x) = n \mathbb{E} (W_n^{(n+1)} - W_n^{(n)}|W_n^{(n)} = x), \quad \text{and} \quad a_n(x) = \mathbb{E} ((W_n^{(n+1)} - W_n^{(n)})(W_n^{(n+1)} - W_n^{(n)})^T|W_n^{(n)} = x). \]

By (4) and (5), as \( n \rightarrow \infty \) \( \sup_{|x| \leq r} |b_n(x) - b(x)| \rightarrow 0 \) and \( \sup_{|x| \leq r} |a_n(x) - a(x)| \rightarrow 0 \) respectively, for any \( r > 0 \). Also, using similar arguments as in equation (4) and using the inequality \((a + b)^4 \leq 8(a^4 + b^4)\), we obtain

\[
E((W_1^{(n+1)} - W_1^{(n)})^4 \mid W^{(n)} = x) \leq 8\gamma p_A \left[ \left( \frac{x_1}{2(S_A + F_A)} \right)^4 + \left( \frac{q_A}{\sqrt{S_A + F_A}} \right)^4 \right] + 8\gamma q_A \left[ \left( \frac{x_1}{2(S_A + F_A)} \right)^4 + \left( \frac{p_A}{\sqrt{S_A + F_A}} \right)^4 \right] = 8\gamma p_A \left[ (x_1/2)^4 + q_A^4 \right] O((n\bar{\gamma})^{-4}) + 8\gamma q_A \left[ (x_1/2)^4 + p_A^4 \right] O((n\bar{\gamma})^{-4}) = O(n^{-2}),
\]
since $W^{(n)} = O(n^2)$. Similarly, for $W_2,$

$$E((W_2^{(n+1)} - W_2^{(n)})^4 \mid W^{(n)} = x)$$

$$\leq 8(1 - \gamma)p_B \left[ \left( \frac{x_2}{2(S_B + F_B)} \right)^4 + \left( \frac{q_B}{\sqrt{S_B + F_B}} \right)^4 \right]$$

$$+ 8(1 - \gamma)q_B \left[ \left( \frac{x_2}{2(S_B + F_B)} \right)^4 + \left( \frac{p_B}{\sqrt{S_B + F_B}} \right)^4 \right]$$

$$= 8(1 - \gamma) \left\{ p_B \left[ O \left( \frac{x_2^4}{(2n(1 - \gamma))^4} \right) + O \left( \frac{q_B^4}{(n(1 - \gamma))^2} \right) \right] \right\}$$

$$+ q_B \left[ O \left( \frac{x_2^4}{(2n(1 - \gamma))^4} \right) + O \left( \frac{p_B^4}{(n(1 - \gamma))^2} \right) \right]$$

$$= O(n^{-2}).$$

Finally, for $W_3,$

$$E \left( (W_3^{(n+1)} - W_3^{(n)})^4 \mid W^{(n)} = x \right)$$

$$\leq 8\gamma \left[ \left( \frac{x_3}{2n} \right)^4 + \left( \frac{1 - \gamma}{\sqrt{n}} \right)^4 \right] + 8(1 - \gamma) \left[ \left( \frac{x_3}{2n} \right)^4 + \left( \frac{\gamma}{\sqrt{n}} \right)^4 \right]$$

$$= O\left( \frac{x_3^4}{n^4} \right) + 8\gamma O\left( \frac{(1 - \gamma)^4}{n^2} \right) + 8(1 - \gamma) O\left( \frac{\gamma^4}{n^2} \right)$$

$$= O(n^{-2}).$$

Hence, since for any three-dimensional vector $y$ by Cauchy-Schwarz inequality $|y|^4 \leq 3(y_1^4 + y_2^4 + y_3^4),$ we have $n \sup_{|x| \leq r} E (|W_{n+1} - W_n|^4 \mid W_n = x) \to 0$ as $n \to \infty,$ implying by Chebyshev’s inequality that

$$n \sup_{|x| \leq r} p_n \{ x, \{ y : |y - x| \geq \delta \} \} \to 0.$$
Thus, by Corollary 4.2 of Ethier and Kurtz (1986) the distribution of \( W^{(n)} \) converges to the stationary (invariant) distribution of the diffusion process which is governed by (6), where \( X \) is a 3-dimensional vector and \( dB_t \) is a 3-dimensional Brownian motion. Since this is a linear equation, its solution is given by

\[
X_t = e^{\Gamma t} X_0 + \int_0^t e^{\Gamma(s-t)} \Delta dB_s.
\]

Therefore, the stationary distribution \( X_\infty \) is Normal with mean \((0, 0, 0)^T\) and variance

\[
\text{Var} (X_\infty) = \int_0^\infty e^{\Gamma s} \Delta \Delta^T e^{\Gamma^T s} ds = \begin{pmatrix}
p A q A & 0 & \tilde{\gamma}^{1/2} (1 - \tilde{\gamma}) \\
0 & p B q B & -\tilde{\gamma} (1 - \tilde{\gamma})^{1/2} \\
\tilde{\gamma}^{1/2} (1 - \tilde{\gamma}) & -\tilde{\gamma} (1 - \tilde{\gamma})^{1/2} & \beta
\end{pmatrix}.
\]

A crucial observation to compute this variance is that

\[
e^{\Gamma s} = \exp \left\{ -\frac{s}{2} I + s \Pi \right\} = \sum_{k=0}^{\infty} \frac{(-1)^k s^k}{k!} \left[ \frac{1}{2^k} I - \begin{pmatrix} k \end{pmatrix} \frac{1}{2^{k-1}} \Pi \right] = e^{-s/2} (I + s \Pi)
\]

since \( \Pi \) is nilpotent, hence

\[
e^{\Gamma s} \Delta \Delta^T e^{\Gamma^T s} = e^{-s} (I + s \Pi) \Delta^2 (I + s \Pi^T) = e^{-s} \left[ \Delta^2 + s \left( \Pi \Delta^2 + \Delta^2 \Pi^T \right) + s^2 \left( \Pi \Delta^2 \Pi^T \right) \right]
\]

\[
= e^{-s} \begin{pmatrix}
p A q A & 0 & 0 \\
0 & p B q B & 0 \\
0 & 0 & \tilde{\gamma} (1 - \tilde{\gamma})
\end{pmatrix} 
+ s \begin{pmatrix}
0 & 0 & \sqrt{\tilde{\gamma}} (1 - \tilde{\gamma}) \\
0 & 0 & -\tilde{\gamma} \sqrt{1 - \tilde{\gamma}} \\
\sqrt{\tilde{\gamma}} (1 - \tilde{\gamma}) & -\tilde{\gamma} \sqrt{1 - \tilde{\gamma}} & 0
\end{pmatrix}
+ s^2 \begin{pmatrix}
0 & 0 & 0 \\
0 & 0 & 0 \\
0 & 0 & \tilde{\gamma} (1 - \tilde{\gamma})^2 + \frac{\tilde{\gamma}^2}{p A q A} + \frac{\tilde{\gamma}^2}{p B q B}
\end{pmatrix}.
\]
Proof of Theorem 2. Using the same notations and representations as in the proof of Theorem 1, observe that if we denote $A = S_A + F_A$, $B = S_B + F_B$, then

$$A = \overline{\gamma}n + W_3\sqrt{n}, \ B = (1 - \overline{\gamma})n - W_3\sqrt{n}$$

and hence

$$S_A = p_A A + W_1\sqrt{A}, \quad F_A = q_A A - W_1\sqrt{A}$$
$$S_B = p_B B + W_2\sqrt{B}, \quad F_B = q_B B - W_2\sqrt{B}$$

Consequently,

$$\frac{S_A}{F_A} - \frac{p_A}{q_A} = \frac{W_1\sqrt{A}}{q_A(q_A A - W_1\sqrt{A})},$$
$$\frac{S_B}{F_B} - \frac{p_B}{q_B} = \frac{W_2\sqrt{B}}{q_B(q_B B - W_2\sqrt{B})},$$

implying

$$\sqrt{n} \left[ \frac{S_A}{F_A} - \frac{p_A}{q_A} \right] = \frac{W_1\sqrt{A/n}}{q_A(q_A A/n - W_1\sqrt{A/n^2})},$$
$$\sqrt{n} \left[ \frac{S_B}{F_B} - \frac{p_B}{q_B} \right] = \frac{W_2\sqrt{B/n}}{q_B(q_B B/n - W_2\sqrt{B/n^2})}.$$

Since from Theorem 1 it follows that $A/n \to \overline{\gamma}$ and $B/n \to (1 - \overline{\gamma})$ at least in probability, we have

$$\sqrt{n} \left[ \frac{S_A}{F_A} - \frac{p_A}{q_A} \right] = \frac{W_1\sqrt{\gamma}}{q_A^2\overline{\gamma}} + o(1),$$
$$\sqrt{n} \left[ \frac{S_B}{F_B} - \frac{p_B}{q_B} \right] = \frac{W_2\sqrt{1 - \gamma}}{q_B^2(1 - \overline{\gamma})} + o(1)$$

immediately yielding the result of Theorem 2. \(\blacksquare\)
Appendix: an example: fluoxetine hydrochloride

As an example of the application of the design we use part of the data from Tamura et al. (1994) on the treatment of patients with depressive disorder. In order to relate to our formalization of the models (1), we consider an indicator of treatment: $A$ for fluoxetine and $B$ for placebo. The response is measured as a change in the biomarker HAMD$_{17}$. If HAMD$_{17}$ is reduced by more than 50%, it is viewed as a success, otherwise it is a failure, as considered in the paper by Tamura et al. (1994). There are 88 observations out of 89, since one observation in the original data set did not have any response.

From the data, we observe that the ORBD will assign a probability 0.697 of allocation of the next patient to fluoxetine. From the data set, we obtain $\hat{p}_A = 0.610$ and $\hat{p}_B = 0.405$. Treating these values as the true values, we carry out a simulation study with 88 patients using the odds ratio based design. The expected proportion of allocation (with SD) are reported in Table 1 and shows proximity of the results.

<table>
<thead>
<tr>
<th>$p_a$</th>
<th>$p_b$</th>
<th>$\gamma$</th>
<th>$p_a/q_a$ (S.E.)</th>
<th>$p_b/q_b$ (S.E.)</th>
<th>$\hat{\gamma}$ (S.E.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6098 (88)</td>
<td>0.4048 (88)</td>
<td>0.6968</td>
<td>1.5764 (0.4299)</td>
<td>0.6978 (0.2631)</td>
<td>0.6917 (0.0974)</td>
</tr>
<tr>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>1.0187 (0.3214)</td>
<td>0.9872 (0.3084)</td>
<td>0.5073 (0.1092)</td>
</tr>
</tbody>
</table>

Table 1. Simulation results with probabilities of success observed in the experiment, compared with simulation results for the case of equal probabilities of success. Sample size: $n = 88$. 

14
4 Conclusion and open problems

This paper provides a theoretical justification of using odds ratio based adaptive allocation design, proposed by Rosenberger and et al. (2001).

The proposed procedure can be extended to more general settings. For example, in the presence of covariates, a logit model can be assumed, as in Rosenberger et al. (2001). As it was mentioned, unfortunately, they did not study theoretical properties of the design, which could be an interesting research problem.

Also, the presented method can be extended to situations with more than just 2 treatments. For example, in the case of 3 treatments with the probabilities of success \( p_A (= 1 - q_A) \), \( p_B (= 1 - q_B) \) and \( p_C (= 1 - q_C) \) respectively, the probability of allocating an entering patient to the first treatment can be set as the current estimate of

\[
\frac{p_A}{q_A} + \frac{p_B}{q_B} + \frac{p_C}{q_C}
\]

One can try obtain the limiting results in a similar fashion in such a multi-treatment setup.

Acknowledgment

The authors would like to thank Peter Green for many helpful comments.

References


