Bayesian Adaptive Randomisation Revisited

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Aptiv Solutions.
Adaptive Ideas Are Not New

ON THE LIKELIHOOD THAT ONE UNKNOWN PROBABILITY EXCEEDS ANOTHER IN VIEW OF THE EVIDENCE OF TWO SAMPLES.

By WILLIAM R. THOMPSON. From the Department of Pathology, Yale University.

Biometrika, 1933

- Ethical Design – concentrating on delivering the best treatment to the most patients
ON THE THEORY OF APPORTIONMENT.

By William R. Thompson.

Annals of Mathematics,. 1935

as in the case $k = 2$, we may apportion individuals among the $k$ rival treatments by assigning to each $T_i$ the portion, $f_i$, or making the chance of this assignment equal $f_i$, respectively.
Simple Idea

- At some point in a trial we have the following data:

<table>
<thead>
<tr>
<th>Trt A</th>
<th>Trt B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>.</td>
<td>.</td>
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<tr>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

\[ r_A / n_A \quad \text{r_B / n_B} \]

- If \( \pi_A \) and \( \pi_B \) are the response rates of each treatment then

\[ P(\pi_A < \pi_B \mid \text{Data}) \]

- measures the “superiority” of B over A.

- Thompson proposed patients be randomised to A and B in the ratio

\[ 1 - P(\pi_A < \pi_B \mid \text{Data}) \]

\[ P(\pi_A < \pi_B \mid \text{Data}) \]
2 x 2 Contingency Table
Data Structure

<table>
<thead>
<tr>
<th></th>
<th>Response</th>
<th>No Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment A</td>
<td>( r_1 (\pi_A) )</td>
<td>( n_1-r_1 (1-\pi_B) )</td>
</tr>
<tr>
<td>Treatment B</td>
<td>( r_2 (\pi_B) )</td>
<td>( n_2-r_2 (1-\pi_B) )</td>
</tr>
</tbody>
</table>

**Likelihood**
\[
\propto \pi_A^{r_1} (1 - \pi_A)^{n_1-r_1} \pi_B^{r_2} (1 - \pi_B)^{n_2-r_2}
\]

**Prior**
\[
\propto \pi_A^{\alpha_1-1} (1 - \pi_A)^{\beta_1-1} \pi_B^{\alpha_2-1} (1 - \pi_B)^{\beta_2-1}
\]

**Posterior**
\[
\propto \pi_A^{r_1+\alpha_1-1} (1 - \pi_A)^{n_1-r_1+\beta_1-1} \pi_B^{r_2+\alpha_2-1} (1 - \pi_B)^{n_2-r_2+\beta_2-1}
\]
2x2 Contingency Table - Posterior Inference

"Uninformative Priors" : $\alpha_A = \beta_A = \alpha_B = \beta_B = 1$

- For a uniform prior ($\alpha_1 = \alpha_2 = \beta_1 = \beta_2 = 1$ - Thompson) the probability of interest is

$$\text{Prob}(\pi_A < \pi_B \mid \text{Data}) = \sum_{k=0}^{n_1 - r_1} \frac{(n_1 + n_2 - r_1 - r_2 - k) \left( r_1 + r_2 + 1 + k \right)}{(n_2 - r_2) \left( r_2 \right)} \frac{\left( n_1 + n_2 + 1 \right)}{\left( n_1 + 1 \right)}$$

based on the cumulative hypergeometric function - as is Fisher's exact test (Raiffa & Schlaifer, Applied Statistical Decision Theory, 1960; Altham JRSSB, 1969); Cook and Nadarajah (Biometrical J, 2006).

- von Liebermeister C. Über Wahrscheinlichkeitsrechnung in Anwendung auf therapeutische Statistik. (Sammlung klinischer Vorträge, 1877).
Thompson’s Practical Interpretation

- Thompson (1935) proved the identity:

\[
\sum_{k=0}^{n_1-r_1} \frac{(n_1 + n_2 - r_1 - r_2 - k)(r_1 + r_2 + 1 + k)}{n_2 - r_2} \left(\frac{n_1 + n_2 + 1}{n_1 + 1}\right) = \sum_{k=0}^{\min(b-1, W-w)} \frac{W}{w + \alpha} \left(\frac{B}{b - 1 - \alpha}\right) \left(\frac{W}{W + B}\right) \left(\frac{w + b - 1}{w + b - 1}\right)
\]

where: \(W = n_1 + 1\), \(B = n_2 + 1\), \(w = n_1 - r_1\) and \(b = n_2 - r_2\)

- This second term is the probability under sampling without replacement from a mixture of \(W\) white balls and \(B\) black balls that we will get \(w\) white balls before \(b\) black balls

- For \(W = n_1 + 1\), \(B = n_2 + 1\) : choose A if \(w = n_1 - r_1 + 1\) white balls occur before \(b = n_2 - r_2 + 1\) black balls
Thompson (1935)  
Mechanical Randomisation & Simulation
Thompson (1935)
Mechanical Randomisation & Simulation

$r_1=2$, $n_1-r_1=2$, $r_2=4$, $n_2-r_2=3$

$W=5$, $B=8$, $w=3$, $b=5$
### Thompson (1935)
**Bayesian Adaptive Simulation**

<table>
<thead>
<tr>
<th>$\pi_A$</th>
<th>$\pi_B$</th>
<th>$n_1+n_2$</th>
<th>$n_1$</th>
<th>$r_1$</th>
<th>$r_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>0.00</td>
<td>20</td>
<td>2, 1, 1, 1</td>
<td>2, 1, 1, 1</td>
<td>18, 19, 19, 19</td>
</tr>
<tr>
<td>1.00</td>
<td>0.50</td>
<td>40</td>
<td>5, 9, 7, 5</td>
<td>5, 9, 7, 5</td>
<td>35, 31, 33, 35</td>
</tr>
<tr>
<td>0.50</td>
<td>0.00</td>
<td>40</td>
<td>6, 2, 3, 5</td>
<td>2, 2, 2, 2</td>
<td>34, 38, 37, 35</td>
</tr>
<tr>
<td>0.75</td>
<td>0.25</td>
<td>100</td>
<td>3, 4</td>
<td>3, 3</td>
<td>97, 96</td>
</tr>
<tr>
<td>1.00</td>
<td>0.75</td>
<td>100</td>
<td>14,10</td>
<td>14,10</td>
<td>86, 90</td>
</tr>
<tr>
<td>0.75</td>
<td>0.50</td>
<td>100</td>
<td>23, 14</td>
<td>17, 11</td>
<td>77, 86</td>
</tr>
<tr>
<td>0.50</td>
<td>0.25</td>
<td>100</td>
<td>10, 13</td>
<td>5, 6</td>
<td>90, 87</td>
</tr>
<tr>
<td>0.25</td>
<td>0.00</td>
<td>100</td>
<td>4, 6</td>
<td>1, 1</td>
<td>96, 94</td>
</tr>
</tbody>
</table>

- Known as Thompson Sampling used in:
  - Machine learning, music emotion modelling, action comparisons in prefrontal cortex, A/B testing in web-design, online marketing
Bayesian AD – Thall & Wathen (EJC, 2007)

Type-I Error Based on T&W Criterion

- Thall & Wathen illustration is based on:
  - $N = 200$

- Stopping Rules
  - If $P(p_A < p_B | \text{Data}) > 0.99$ stop and “choose” B
  - If $P(p_A < p_B | \text{Data}) < 0.01$ stop and “choose” A (futility)

- What does the type I error look like?
- A complication is that the control rate, $p_A$, is a nuisance parameter
Thall & Wathen (EJC, 2007) N=200
Randomisation Probability \( \pi_A = 0.25 \), \( \pi_B = 0.30(0.10)0.90 \)

(10^5 simulations)
Variability of Randomisation Probabilities

$\pi_A = 0.25 \; , \; \pi_B = 0.455$
Bayesian Adaptive Randomisation
Thall and Wathen (Eur J Cancer, 2007)

- Early instability
- Thall and Wathen (2007)

\[
\frac{P(\pi_A < \pi_B \mid \text{Data} )^C}{P(\pi_A < \pi_B \mid \text{Data} )^C + (1 - P(\pi_A < \pi_B \mid \text{Data} ))^C}
\]
Bayesian Adaptive Randomisation
Impact of Choice of $C$

P($\pi_A < \pi_B | Data$)$^C$

C=1.0 - Thompson
C=0.4
C=0.2
C=0 - Equal Randomisation
Bayesian Adaptive Randomisation
Impact of Choice of C

- Thall and Whalen recommend $C = \frac{n}{2N}$
  - $n =$ current sample size
  - $N =$ study’s maximum sample size
- Begins with $C=0$, ends with $C=1/2$
- $C=1/2$ “works well in many applications”
Variability of Randomisation Probabilities

$\pi_A = 0.25 \quad , \quad \pi_B = 0.455$
Adjustment to Stopping Criteria to Achieve type I error control

![Graph A](image1)

![Graph B](image2)

![Graph C](image3)

![Graph D](image4)
Criticism of This Approach

- Korn and Freidlin (J Clin Oncol, 2011)
- Their simulations “show”:
  - Thall & Wathen AD inferior to 1:1 randomisation in terms of information, benefits to patients in trial
- True
- I agree with Don Berry (J Clin Oncol 2011) that the greatest benefits are likely to accrue for trials with more than 2 arms
- Rather as in the case of $T=1$ in the group sequential case greater complexity gives more scope for Bayesian designs
Thall & Wathen (EJC, 2007) N = 200
Randomisation Probability

\[ \pi_A = 0.25 \quad , \quad \pi_B = 0.30(0.10)0.90 \]

(10^5 simulations)

- Troxacitabine (T) in acute myeloid leukemia (AML) combined with cytarabine (A) or idarubicin (I)
- Adaptive randomization to:
  - IA vs TA vs TI
- Max n = 75
- End point: Time to Complete Remission (< 50 days)
Adaptive Randomization

- Assign 1/3 to IA (standard, 0) throughout (unless only 2 arms)
- Adaptive to TA (1) and TI (2) based on current results
  - Time to success : Exponential
  - Prior(Median : $m_i$) = Gamma(2.001, 4.624) (i=0,1,2)
  - Initial randomization : $p_0=p_1=p_2=1/3$
  - Define : $q_1=P(m_1<m_0|\text{data})$, $q_2=P(m_2<m_0|\text{data})$, $r=P(m_1<m_2|\text{data})$
  - Then
    \[
    \pi_1 = \frac{2q_1^2}{3(q_1^2 + q_2^2)} , \quad \pi_2 = \frac{2q_2^2}{3(q_1^2 + q_2^2)}
    \]
Adaptive Randomization

- If at any time \( q_1 > 0.85 \) or \( q_2 > 0.85 \) – either TA or TI were outperforming IA – IA would be dropped
- If both TA and TI were still in the study randomisation probabilities would be

\[
\pi_1 = \frac{r^2}{(r^2 + (1-r^2))}, \quad \pi_2 = \frac{1-r^2}{(r^2 + (1-r^2))}
\]

- If at any time \( q_1 < 0.15 \) or \( r < 0.15 \) – TA being outperformed by either TI or IA - TA would be dropped
- If at any time \( q_2 < 0.15 \) or \( r > 0.85 \) – TI being outperformed by either TA or IA - TI would be dropped
- If only IA and one investigational arm \( k \) remains, randomisation probabilities is

\[
\pi_k = \frac{q_k^2}{(q_k^2 + 1 - q_k^2)} \quad \text{or} \quad \pi_0 = 1 - \pi_k
\]

- An arm that dropped out could be reopened if information (i.e., CR by day 49) became available from patients previously randomly assigned to that arm or if the other arms performed sufficiently poorly, subsequent to closure of the arm in question.

- The operating characteristic of the design was identified by simulation
## Study Operating Characteristics

<table>
<thead>
<tr>
<th>True Probabilities</th>
<th>Prob (choose arm 0 superior)</th>
<th>Prob (choose arm 1 superior)</th>
<th>Prob (choose arm 2 superior)</th>
<th>Mean Sample Sizes</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_0$</td>
<td>$P_1$</td>
<td>$P_2$</td>
<td>$n_0$</td>
<td>$n_1$</td>
</tr>
<tr>
<td>0.3</td>
<td>0.3</td>
<td>0.6</td>
<td>0.025 (0.005)</td>
<td>0.178 (0.145)</td>
</tr>
<tr>
<td>0.3</td>
<td>0.3</td>
<td>0.5</td>
<td>0.020 (0.007)</td>
<td>0.118 (0.097)</td>
</tr>
<tr>
<td>0.3</td>
<td>0.2</td>
<td>0.3</td>
<td>0.101 (0.029)</td>
<td>0.449 (0.321)</td>
</tr>
<tr>
<td>0.4</td>
<td>0.2</td>
<td>0.2</td>
<td>0.540 (0.299)</td>
<td>0.238 (0.102)</td>
</tr>
<tr>
<td>0.5</td>
<td>0.3</td>
<td>0.5</td>
<td>0.209 (0.157)</td>
<td>0.154 (0.114)</td>
</tr>
<tr>
<td>0.3</td>
<td>0.6</td>
<td>0.6</td>
<td>0.005 (0.004)</td>
<td>0.507 (0.501)</td>
</tr>
</tbody>
</table>
Study Results

CR < 50 days:

IA : \(\frac{10}{18} = 56\%\)

TA : \(\frac{3}{11} = 27\%\)

TI : \(\frac{0}{5} = 0\%\)
Current View of the Originators
Peter F. Thall, Patricia S. Fox and J. Kyle Wathen

  - a nontrivial probability of greatly unbalancing sample size in the wrong direction
  - increased bias in the final inferences due to continuous treatment comparison, which is increased if there is parameter drift, and
  - logistical difficulties during trial conduct in recording, either accurately or at all, patient covariates at accrual.
Optimal Allocation

- Neyman allocation
  
  - Prob allocation to B = \frac{\sqrt{\pi_B (1-\pi_B)}}{\sqrt{\pi_B (1-\pi_B)} + \sqrt{\pi_A (1-\pi_A)}}

- RSIHR allocation (Rosenberger et al. (Biometrics, 2001))
  
  - Prob allocation to B = \frac{\sqrt{\pi_B}}{\sqrt{\pi_B} + \sqrt{\pi_A}}

- *Sequential maximum likelihood procedure* uses empirical estimates in place of population values
Randomisation Probabilities to B
Rosenberger et al (2001) – $\pi_B = \{0.10 \ (0.10) \ 0.9 \ 0\}$
# Simulation Results


Table 1

*Simulated values of $E\{N_{A,n}/n\}$ (SD) for the optimal adaptive rule (A), Neyman allocation (N), the RPW rule (R), and equal allocation (E) (5000 replications)*

<table>
<thead>
<tr>
<th>$p_A$</th>
<th>$p_B$</th>
<th>$n$</th>
<th>A</th>
<th>N</th>
<th>R</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.1</td>
<td>200</td>
<td>0.50 (0.06)</td>
<td>0.50 (0.06)</td>
<td>0.50 (0.03)</td>
<td>0.50 (0.03)</td>
</tr>
<tr>
<td>0.3</td>
<td>0.3</td>
<td>200</td>
<td>0.50 (0.05)</td>
<td>0.50 (0.04)</td>
<td>0.50 (0.04)</td>
<td>0.50 (0.03)</td>
</tr>
<tr>
<td>0.5</td>
<td>0.5</td>
<td>200</td>
<td>0.50 (0.04)</td>
<td>0.50 (0.04)</td>
<td>0.50 (0.06)</td>
<td>0.50 (0.03)</td>
</tr>
<tr>
<td>0.7</td>
<td>0.7</td>
<td>200</td>
<td>0.50 (0.04)</td>
<td>0.50 (0.04)</td>
<td>0.50 (0.10)</td>
<td>0.50 (0.03)</td>
</tr>
<tr>
<td>0.9</td>
<td>0.9</td>
<td>200</td>
<td>0.50 (0.04)</td>
<td>0.50 (0.06)</td>
<td>0.50 (0.19)</td>
<td>0.50 (0.03)</td>
</tr>
<tr>
<td>0.1</td>
<td>0.2</td>
<td>526</td>
<td>0.42 (0.04)</td>
<td>0.43 (0.04)</td>
<td>0.47 (0.02)</td>
<td>0.50 (0.02)</td>
</tr>
<tr>
<td>0.1</td>
<td>0.3</td>
<td>162</td>
<td>0.39 (0.06)</td>
<td>0.42 (0.05)</td>
<td>0.44 (0.04)</td>
<td>0.50 (0.04)</td>
</tr>
<tr>
<td>0.1</td>
<td>0.4</td>
<td>82</td>
<td>0.38 (0.07)</td>
<td>0.42 (0.06)</td>
<td>0.40 (0.05)</td>
<td>0.50 (0.05)</td>
</tr>
<tr>
<td>0.4</td>
<td>0.6</td>
<td>254</td>
<td>0.45 (0.04)</td>
<td>0.50 (0.03)</td>
<td>0.40 (0.05)</td>
<td>0.50 (0.03)</td>
</tr>
<tr>
<td>0.6</td>
<td>0.9</td>
<td>82</td>
<td>0.45 (0.06)</td>
<td>0.58 (0.06)</td>
<td>0.29 (0.13)</td>
<td>0.50 (0.05)</td>
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<td>0.9</td>
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<td>0.32 (0.13)</td>
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</tr>
<tr>
<td>0.8</td>
<td>0.9</td>
<td>526</td>
<td>0.48 (0.02)</td>
<td>0.57 (0.04)</td>
<td>0.38 (0.12)</td>
<td>0.50 (0.02)</td>
</tr>
</tbody>
</table>
Bayesian Optimal Allocation

• As far as I am aware there have been no attempts to devise a Bayesian approach considering both variance and treatment failure

\[ L(\theta, \hat{\theta}) = \prod_{i=1}^{I} p_{i}^{r_{i}} q_{i}^{s_{i}} (\theta - \hat{\theta})^{2} \]

• There have been of course:
  - bandit designs minimising treatment failure,
  - myopic attempts to minimise a loss function

\[ L(\theta, \hat{\theta}) = \pi_{A}^{r_{1}} (1 - \pi_{1A})^{n_{1} - r_{1}} \pi_{B}^{r_{2}} (1 - \pi_{B})^{n_{2} - r_{2}} (\theta - \hat{\theta})^{2} \]

  where \( \theta = \pi_{A} \pi_{B} \)

• A simple approach: Use posterior expected values in place of ML estimates
Conclusion

- Problems are caused by adapting after every result
- Reduce to a “group sequential” type design with limited adaptations
- Move away from Thompson Sampling
- Consider adaptive RSHIR sampling use posterior mean
- Further investigation of loss function approaches