Model Selection in Basket Clinical Trials

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August, 2022

Introduction

- Through the use of enhanced technology in biomarker development and genomic medicine, targeted therapy on a **specific genomic aberration** has become a main focus for oncology research.

Basket Trial

A **basket trial** enrolls patients with multiple histological cancer types that share the same genomic aberration. It assesses the efficacy of a particular targeted therapy simultaneously on all of the enrolled indications.

Basket Trials

This type of trial allows for new drugs to be tested and approved more quickly.

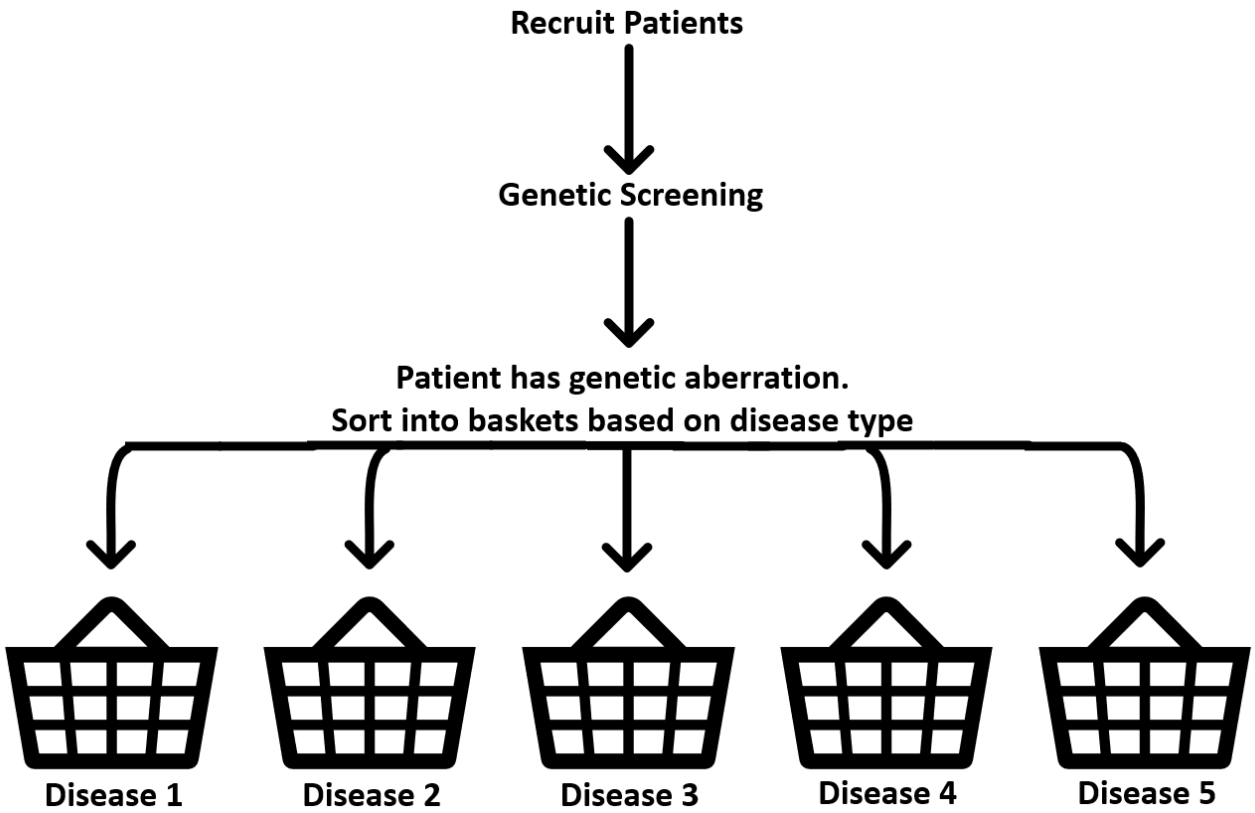


Figure 1: Diagram of basket trials

Information Borrowing

- Due to the rarity of the disease this produces small basket sizes.
- Information borrowing may be valid under the **exchangeability assumption**, that as all baskets share a common genetic abberation.
- With this assumption in mind we can **borrow information** from one basket when making inference on another.
- Borrowing information can increase **power**, reduce **type I error**, and improve the efficiency when trials are homogeneous.

Models

Baskets can be split into two groups.

1. **Exchangeability groups** within which information borrowing takes place through pooling of responses
2. **Non-Exchangeability groups** which are treated as independent.

If we have three baskets, then there are 5 possible models.

Models	**1 2 3**	p_i
μ_1	1 1 1	1
μ_2	1 1 0	2
μ_3	1 0 1	2
μ_4	0 1 1	2
μ_5	0 0 0	3

Table 1: Models for 3 baskets

Marginal Likelihood

For each model we calculate the marginal likelihood and Bayes factor using a prior Beta(1,1) for p_k values, where y_k is the response vector.

Marginal Likelihood

$$p(D|\mu_j) = \Pi_{k=1}^{K} \binom{n_k}{y_k} \times \Pi_{p=1}^{p_j} \frac{B(a_{(jp)}, b_{(jp)})}{B(a_0, b_0)}$$

where

$$a_{(jp)} = a_0 + \Sigma_{k \in \Omega_{jp}} y_k, \quad b_{(jp)} = b_0 + \Sigma_{k \in \Omega_{jp}} (n_k - y_k)$$

Bayes Factor

Bayes factor is the ratio of two statistical models represented by their marginal likelihood.

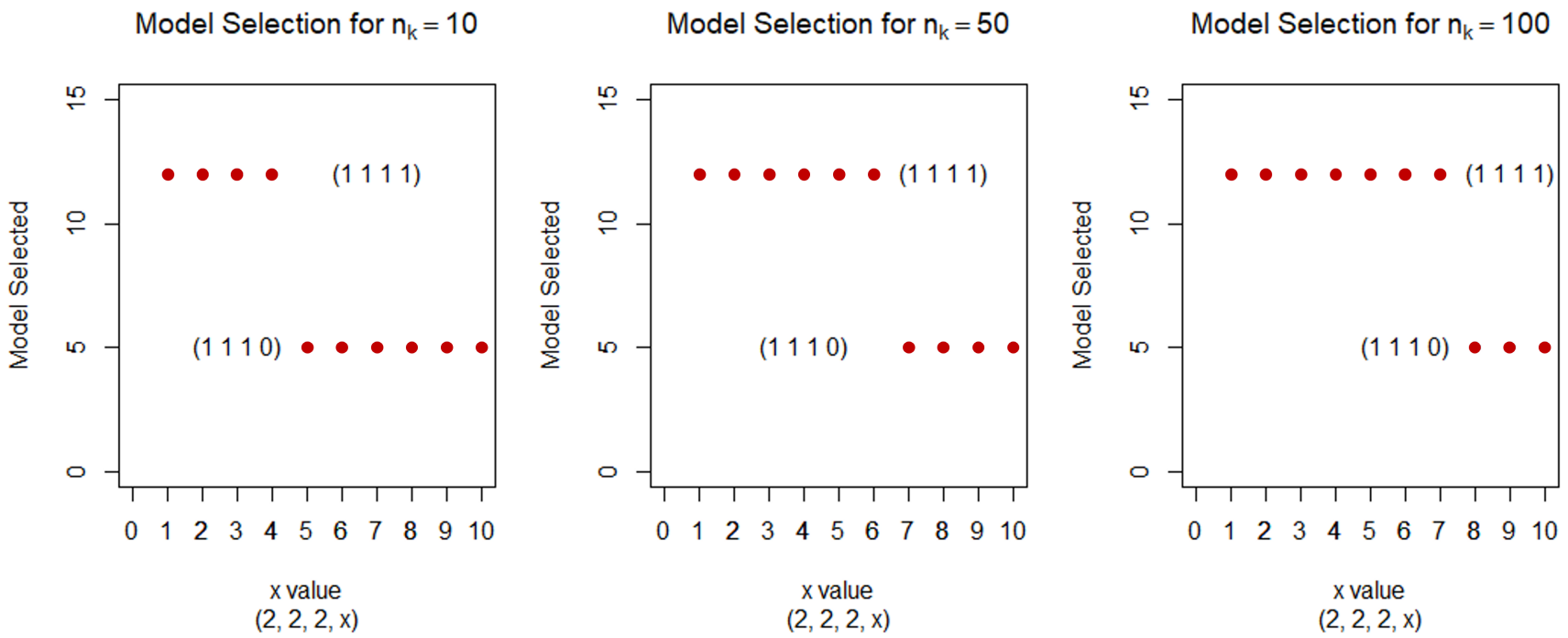
Bayes Factor

$$BF_{i,j} = \frac{p(D|\mu_i)}{p(D|\mu_j)}$$

If $BF_{i,j} \geq 1$ then evidence supports μ_i over μ_j in terms of model fit. If equal to 1 then they are the same, else μ_j is preferred.
A model i is selected if $BF_{i,j} > 1$ for all j.

Model Selection Experiment

I have experimented with the model selection with different sample sizes, n_k, and the responses for 4 baskets where the first three are fixed and the fourth varies.



Hypothesis:

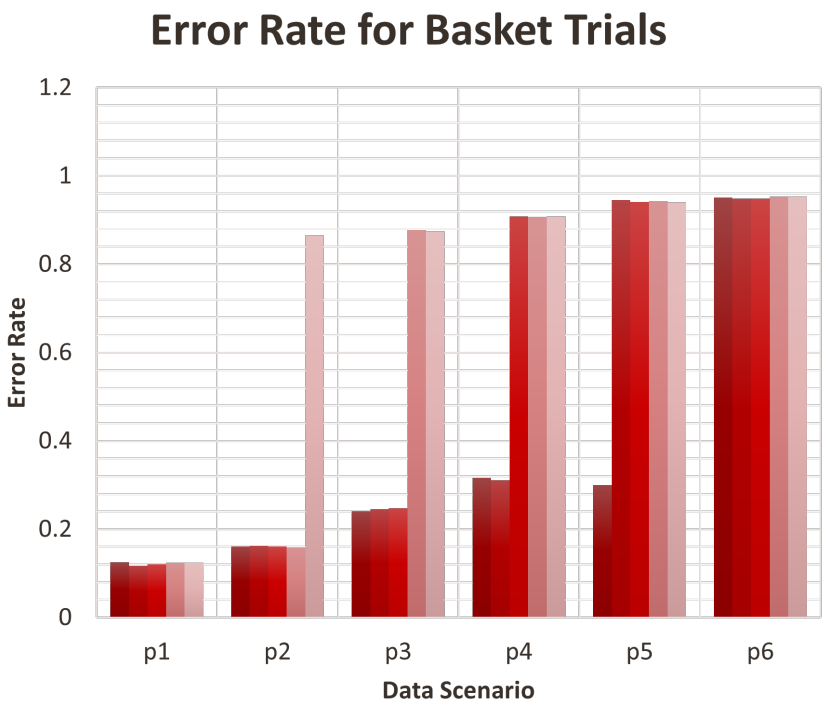
$$H_0 : p_k \leq q_0 \quad vs. \quad H_1 : p_k \geq q_0$$

The aim is to estimate the **unknown response rate** p_k and decide whether a treatment is effective in basket k.

- Fix the sample size and response rate and simulate the data.
- Compute the **posterior probabilities** $\mathbb{P}(p_k > q_0|D)$ for each basket, where q_0 is the null response rate and D is the observed data.
- If $\mathbb{P}(p_k > q_0|D) > Q$ then deem the treatment effective in basket k.
- Q is calibrated to control error rates under a null scenario.

Error Rate

The graph displays the simulation scenario with 5 baskets, sample space of 13 and null response rate for each scenario stated below.



The results show if we increase the response rate the error rate inflates.

p_1	(0.15,0.15,0.15,0.15,0.15)
p_2	(0.15,0.15,0.15,0.15,0.45)
p_3	(0.15,0.15,0.15,0.45,0.45)
p_4	(0.15,0.15,0.45,0.45,0.45)
p_5	(0.15,0.45,0.45,0.45,0.45)
p_6	(0.45,0.45,0.45,0.45,0.45)

Conclusion

$$\text{Type I Error Rate} = \text{P}(\text{Reject } H_0 | H_0 \text{ true})$$
$$\text{Power} = \text{P}(\text{Reject } H_0 | H_1 \text{ true})$$

To conclude the use of a **Bayesian hierarchical model** to borrow across patient groups inflates error rates above the nominal level when baskets are heterogeneous but improves power.
The next stage of research would be to consider other model selection methods.

[1] M. A. Psioda, J. Xu, Q. Jiang, C. Ke, Z. Yang, and J. G. Ibrahim, "Bayesian adaptive basket trial design using model averaging," *Biostatistics (Oxford, England)*, vol. 22, no. 1, pp. 19–34, 2021.

[2] V. Bogin, "Master protocols: New directions in drug discovery," *Contemporary Clinical Trials Communications*, vol. 18, p. 100568, 2020.