Model Selection in Basket Clinical Trials

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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. This has introduced the concept of basket trials.

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.

In comparison to traditional trials, this type of trial allows for new drugs to be tested and approved more quickly.

• When analysing early phase basket trials a dilemma arises in terms of discarding or incorporating data from other subgroups. This is due to the rarity of the disease creating small basket sizes, requiring us to use information borrowing.
• Information borrowing may be valid under the exchangeability assumption that all baskets share a common genetic aberration, they all have a similar response to treatment. 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. Power is the probability of claiming efficacy.

Models

<table>
<thead>
<tr>
<th>Models</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>( p_i )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mu_1 )</td>
<td>1</td>
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<tr>
<td>( \mu_2 )</td>
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<td>1</td>
<td>0</td>
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<tr>
<td>( \mu_3 )</td>
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<td>( \mu_4 )</td>
<td>0</td>
<td>1</td>
<td>1</td>
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</tr>
<tr>
<td>( \mu_5 )</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 1: Models for 3 baskets

Bayes Factor

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

Bayes factor is the ratio of two statistical models represented by their marginal likelihood. If \( BF_{i,j} \geq 1 \) then evidence supports \( \mu_j \) over \( \mu_i \) in terms of model fit. If equal to 1 then they are the same, else \( \mu_i \) is preferred.

A model is selected if \( BF_{i,j} > 1 \) for all \( j \). Below I have experimented with the model selection with different sample sizes, \( n_k \), the responses for 4 baskets where the first three are fixed and the fourth varies.

Trial Process

Hypothesis:

\[ H_0 : p_k \leq q_0 \quad \text{vs.} \quad H_1 : p_k \geq q_0 \]

The aim is to estimate the unknown response rate \( p_k \) and decide whether a treatment is effective in basket \( k \). We fix the sample size and response rate and simulate the data. Next, we compute the posterior probabilities \( \Pr(p_k > q_0|D) \) for each basket, where \( q_0 \) is the null response rate and \( D \) is the observed data. If \( \Pr(p_k > q_0|D) > Q \) then deem the treatment effective in basket \( k \). \( Q \) is calibrated to control error rates under a null scenario.

Bar chart of 6 possible scenarios for 5 baskets. 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.

References
