AN EVALUATION OF AN INCOMPLETE BLOCK DESIGN
FOR THE ANALYSIS OF TREATMENT EFFICACY
FOR CLINICAL MASTITIS

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The purpose of this paper is to suggest a method of analyzing
data from clinical mastitis trials when the response of interest is
binary (success/failure) in nature, and the type of experimental
design adheres to an incomplete block form. This approach is
referred to as an "Empirical Bayes" strategy in statistical
literature and incorporates over-dispersion commonly associated
with binomial trials by developing a likelihood expression based on
the beta-binomial distribution. As a result, this procedure
recovers interblock information that logistic regression,
conditional logistic regression, and chi-square methods are unable
to utilize, thereby obtaining a more efficient estimate of the
parameter of interest, the log-odds ratio between two competitive
mastitis therapies. This particular application of the methodology
focuses on evaluating the usefulness of different analytical
techniques for comparing treatment efficacy for clinical mastitis
in a typical Holstein dairy herd.

OBJECTIVE

The objective of this study is to demonstrate that an
incomplete block analysis of typical mastitis trials utilizes more
information from the sample data, and exhibits a smaller asymptotic
variance than existing methodologies. Within the context of an
incomplete block design, a Holstein dairy cow can be considered to
be the block unit, an individual quarter can be considered to be
the experimental unit, and the response to the mastitis treatment
(success/failure to recover) can be considered to be the binary
outcome of interest.

Existing procedures (chi-square methods, logistic regression,
and conditional logistic regression) only include information from
each cow (block unit) which has been given both possible treatment
allocations within itself. If the design is unbalanced, which is
often the case in contagious disease studies, or there is missing
data (commonly experienced in experimental field trials), then
these procedures ignore the information from these particular cows.
Intuitively, it appears that there should be extra information from
those animals about the log-odds ratio between the two competing
therapies, which should be included in the analysis of the trial
(Dohoo, 1987).

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METHOD

Simulation studies were based on an actual Veterinarian Epidemiological field study carried out at the University of Guelph investigating the efficacy of a particular mastitis therapy (Montgomery, 1989). Data sets of 40 cows each were randomly generated representing the average herd size in Southern Ontario Dairy Farms. Three block designs were investigated; balanced, moderately unbalanced, and severely unbalanced. Either treatment A, or treatment B was applied to an individual quarter (experimental unit) within a particular cow (block unit) which happened to be infected with a diagnosed case of mastitis. The response (recovery from infection) was recorded after four days. The log-odds ratio between the two competing therapies was the parameter of interest, and it was estimated using logistic regression, conditional logistic regression, and the proposed Empirical Bayes Incomplete Block analysis.

The design allocations were as follows,

1. Balanced Design: Each of the 40 cows receives treatment A on two quarters, and treatment B on two quarters.

2. Moderately Unbalanced Design: Ten cows receive treatment A on two quarters, treatment B on two quarters. Ten cows receive treatment A on three quarters, and B on one quarter. Ten cows receive treatment A on one quarter, and B on three quarters. Ten cows receive treatment A on all four quarters.

3. Severely Unbalanced Design: Ten cows receive treatment A on three quarters, treatment B on one quarter. Ten cows receive treatment A on one quarter, and B on three quarters. Ten cows receive treatment A on all four quarters. Ten cows receive only treatment B on all four quarters.

Each of the log-odds ratio values in Table 1, are the average of the log-odds ratio estimates for one hundred generated data sets, consisting of 40 cows each.

Originally the logistic model (Cox, 1970) was considered to analyze the relative treatment efficacies, however because of the small stratum size, this particular analysis lends itself to the use of a conditional logistic regression model (Breslow and Day, 1980). The balanced allocation of the two treatments within a cow (2-A's, 2-B's), gives rise to "matching" which increases the bias and variance of the log-odds ratio parameter (Pike, Hill, and Smith, 1980). By using a conditional approach, which conditions on the observed block (cow) totals, better estimation is possible. Note: The cows which have all treatment A, or all treatment B applied to their quarters, are completely ignored by existing analytical procedures.
The Empirical Bayes procedure assumes that each individual cow's immunological resistance is likely to differ, and hence follow a beta probability distribution. Quarters within a particular cow would be expected to have a similar resistance to infectious agents, and be binomially distributed. Using these distributional assumptions, it is possible to derive a likelihood expression (Montgomery, Allen, and Ryan, 1988), such that the log-odds ratio between two competing mastitis therapies can be estimated. Both the fixed effects of interest (log-odds ratio) and the random effect (immunological differences among cows) can thus be incorporated into the analysis. Optimization of the resultant likelihood equation can be accomplished using a modified simplex procedure (Press et al., 1986). Variance estimates for the log-odds ratio can be obtained using the Observed Fisher's Information Matrix (Efron and Hinkley, 1978). Note: The likelihood expression includes information from both complete and incomplete blocks, thus utilizing all the possible information in the study data.

RESULTS

Table 1 illustrates the bias and variance properties of the respective procedures. The actual log-odds ratio is 2.0.

CONCLUSIONS

The results from the design simulations imply that the proposed model obtained log-odds ratio estimates with a bias less then or equivalent to other existing procedures. The empirical standard error of the log-odds ratio estimates for the proposed model are at least half the size of the comparative techniques. This suggests that the proposed model recovered extra information that the alternative methods were unable to utilize. In summary, the Empirical Bayes strategy for the analysis of incomplete block designs is recommended as a viable procedure for evaluating the treatment efficacy in clinical mastitis trials, as it models extra-binomial variation (over-dispersion), recovers interblock information (from unbalanced data), and obtains a short interval estimate for the parameter of interest.

Table 1: Comparison of Bias and Variance

<table>
<thead>
<tr>
<th>Design Type</th>
<th>Proposed Model</th>
<th>Logistic Reg'n</th>
<th>Conditional Reg'n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balanced</td>
<td>1.878 0.2293</td>
<td>2.133 0.8341</td>
<td>2.120 0.4245</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.845 0.2501</td>
<td>3.920 0.8240</td>
<td>2.216 0.5217</td>
</tr>
<tr>
<td>Severe</td>
<td>1.774 0.2703</td>
<td>4.155 0.9929</td>
<td>2.221 0.6056</td>
</tr>
</tbody>
</table>

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