A SAS/IML® PROGRAM FOR RANDOMIZATION ANALYSIS OF DOSE RESPONSE CURVES

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1. INTRODUCTION

Randomization analyses of response curves were introduced by Zerbe (1979a, 1979b) for the completely randomized and randomized blocks design. The analyses provide the ability to test treatment effects over any specified interval. Computation of the exact distribution of the test statistic which would require evaluating every permutation of the data is avoided. This is accomplished with an approximation using the standard F distribution with synthesized degrees of freedom.

This procedure is quite useful when the data do not meet the assumptions of parametric analyses or when each subject's data cannot be modeled with functions belonging to the same family in the sense discussed by Laird and Ware (1982). Medical models applying these procedures have appeared in the literature (e.g., Goldberg, et al. (1980); Albert, et al. (1982); Chapelle, et al. (1982); Hsi, et al. (1983)).

Two SAS/IML programs are described in the paper that perform the analyses for each of the designs. In addition, a general interpolation procedure is described to increase the use of the interpolation program before analysis is performed using the completely randomized design program.

2. THE RANDOMIZATION MODEL

In randomized designs, subjects are randomly assigned to treatment groups. This randomization of subjects to treatments creates a probability structure which makes it possible to construct the distribution of a test statistic under permutation theory, given the responses have been observed.

Consider a completely randomized study with n subjects and g groups, the ith group being assigned ni subjects. Let \( Y_{ij}(t) \) be the observed response of the subject assigned position \( j, (j = 1 \ldots n_i) \), in group \( i, (i = 1 \ldots g) \), at time \( t \) in the interval \( (a, b) \). In order to formulate a mathematical model which will allow incorporation of a probability structure, define \( \psi_{ik}(t) \) as the response curve that would be observed if subject \( k \) were assigned the \( j \)th position in group \( i \). Since subject \( k \) could be assigned to any of the \( n_i \) groups, there are \( n_i g \) possible response curves over the interval \( (a, b) \). Assume the model,

\[
\psi_{ik}(t) = \mu(t) + \tau_i(t) + \epsilon_{ik}(t),
\]

where \( \mu(t) \) is the overall mean response curve, \( \tau_i(t) \) is the response effect of group \( i \), and \( \epsilon_{ik}(t) \) is the error curve associated with subject \( k \). With this model it is assumed that no subject by group interaction exists and that the sum of the group effects is zero throughout the interval \( (a, b) \). Now consider a randomized blocks design with \( m \) treatments and \( n \) blocks each with \( m \) experimental units. Let \( Y_{ik}(t) \) be the response curve observed for the plot in the \( k \)th block which was assigned treatment \( i; k = 1, \ldots, n; i = 1, \ldots, m \) over the interval \( (a, b) \). We may then define the mathematical model,

\[
\phi_{ik}(t) = \mu(t) + \beta_i(t) + \epsilon_{ik}(t)
\]

where \( \phi_{ik}(t) \) is the response curve that would be realized if plot \( j \) were assigned treatment \( i \) within block \( k \). Then, \( \mu(t) \) is the overall mean response, \( \beta_i(t) \) is the block effect, \( \epsilon_{ik}(t) \) is the treatment effect, and \( \epsilon_{ik}(t) \) is the error curve associated with experimental unit \( j \) within block \( k \). As in the completely randomized design it is assumed that there is no treatment by block or treatment by plot interaction and that the sum of the treatment effects is zero for all \( t \in (a, b) \). The probability structure induced by the physical act of randomization can now be imposed upon these mathematical models to yield stochastic models appropriate for hypothesis testing. The stochastic model for the completely randomized design is,

\[
Y_{ij}(t) = \mu(t) + \tau_i(t) + \epsilon_{ij}(t).
\]

For the randomized blocks design the stochastic model is

\[
Y_{ik}(t) = \mu(t) + \beta_i(t) + \tau_i(t) + \epsilon_{ik}(t).
\]

In order to test for treatment effects over an interval of time, Zerbe (1979a) has suggested that sums of squared distances for between (B), within (W), and total variation (T) are reasonable statistics for the completely randomized design. These sums of squares are given in (5).

\[
B = \sum_i n_i \int_a^b \left( \bar{Y}_{i}(t) - \bar{Y}(t) \right)^2 dt
\]

\[
W = \sum_{i,j} \sum_k \int_a^b (Y_{ijk}(t) - \bar{Y}_{ij}(t))^2 dt
\]

\[
T = \sum_{i,j} \sum_k \int_a^b (Y_{ijk}(t) - \bar{Y}(t))^2 dt
\]

For testing treatment effects with a randomized blocks design, Zerbe (1979b) suggested sums of squared distances for treatment (G), block (H), residual (R), and total variation (Q). These are given in (6).

\[
G = n \sum_i \int_a^b (\bar{Y}_{i}(t) - \bar{Y}(t))^2 dt
\]

\[
S = m \sum_k \int_a^b (\bar{Y}_{k}(t) - \bar{Y}(t))^2 dt
\]
\[ R = \sum_{k} \sum_{m} \int_{a}^{b} \left(Y_{k}(t) - Y_{j}(t) - Y_{j}(t) + Y_{j}(t)\right)^{2} dt \]
\[ Q = \sum_{k} \sum_{m} \int_{a}^{b} \left(Y_{k}(t) - Y_{j}(t)\right)^{2} dt \]

Examination of the expected mean squares for \( F/(q-1) \)
and \( W/(n-q) \) under the probability structure induced by
randomization makes the ratio \( F = [B/(q-1)]/[W/(n-q)] \),
an attractive statistic to test for treatment effect in the
completely randomized design. This is analogous to ordinary
one-way analysis of variance. Similarly, for the randomized
blocks design, use \( F = [G/(m-1)]/[R/(m-1)(n-1)] \)
to test for treatment effects as in ordinary two-way
analysis of variance. Computation of the exact distribution of
more freedom for the standard

\[ Q = \sum_{k} \sum_{m} \int_{a}^{b} \left(Y_{k}(t) - Y_{j}(t)\right)^{2} dt \]

Clearly, the computations for any interval \((a, b)\) are identical
except for the matrix \( C \) which depends on \((a, b)\). Computation
of the matrix \( C \) for an interval \((a, b)\) is simplified when
the response curves are linearly interpolated between
responses observed at the same set of \( q \) times for every subject.
If we let \( Y_{k}(t) \) be the linearly interpolated response curve
between \( q \) measurements taken at times \( t_{1} < t_{2} < \ldots < t_{q} \),
then
\[ c_{m}(t) = \frac{t_{m+1} - t}{t_{m+1} - t_{m}} \]
\[ c_{m+1}(t) = \frac{t - t_{m}}{t_{m+1} - t_{m}} \]  
where \( t_{m} \leq t \leq t_{m+1}, m = 1, 2, \ldots, q - 1 \).

The program evaluates the matrix \( C \) for each interval by
calculating the elements of the vector \( c(t) \) in (7) using the
equations in (9) and then summing the integrals of \( c(t)c'(t) \)
over the intervals between adjacent times. Computation of
the sums of squares in (5) may then be performed for the
interval \((a, b)\).

4. THE INTERPOLATION PROCEDURE

The program executes analysis assuming that each subject's
response is represented by a linearly interpolated curve.

The program also assumes that these curves are obtained
from the same set of discrete measurements for each subject
with respect to time. In order to expand the use of the
program to include data sets with different subjects mea­sured
at different times, another SAS/IML program is used
to interpolate data points.

The program requires the data for every subject and
also a set of time points at which interpolated values are to
be computed. The output gives a value for each subject at
each of the time points specified, provided each subject has
responses at times allowing the interpolation, No extrapolation
outside a subject's response range is done.

The algorithm is quite simple. Let subject 8 have re­

sponses \( t_{1} \ldots t_{q} \) at times \( t_{1} \ldots t_{q} \), respectively. Suppose that
interpolated values \( R_{1} \ldots R_{m} \) are desired for times \( T_{1} \ldots T_{m} \),
respectively. Then for each \( T_{j} = i \ldots m \), a search is done to
determine the interval \((t_{i}, t_{j+1})\), in which \( T_{j} \) resides.
When this is completed, exactly one of the following conditions
will hold:

1) \% if \( j \) such that \( T_{j} = t_{j} \), \( j = 1 \ldots k \)
2) \% if \( j \) such that \( t_{j} < T_{j} < t_{j+1}, j = 1 \ldots k \)
3) \% if \( j \), \((T_{j} < t_{j} \) or \( \vee j, (T_{j} > t_{j}, j = 1 \ldots k \)

When 1) is true, the times are equal and subsequently
the responses are equal and \( R_{k} = t_{j} \). When 2) is true, the
specified time falls within two times at which a response
was observed. In this case a linearly interpolated response is
calculated as,

\[ R_{k} = t_{j} + \frac{(t_{j+1} - r)(t_{j+1} - t_{j})}{(t_{j+1} - t_{j})} \]  

When 3) is true, the specified time falls outside the range
of a subject's observed responses. An error message is pro­
duced which indicates that at least one time specified for
interpolation is out of the range of the data for at least one
subject. A matrix of indicator variables is supplied with the error message to aid in determining the time and subject that caused the error.

5. EXAMPLE

As an example of the use of the program, the data in Table 1 was analyzed. Each row represents data for a single rat over time; the time in days heading each of the columns. Each data point represents the sum of four scores, one for each paw. Each paw is scored on a 0-4 point scale for severity of inflammation, 0 for none up to 4 for severe. The study consists of 3 groups; control, compound A, and compound B. Figure 1 displays the data means and standard errors for each treatment at each time point. The investigator is interested in three hypotheses. Is there an effect due to any of the treatments compared to control over the entire 60 days.

Even though each of the treatment groups were studied over 60 days, the times of observation differed from group to group. For this reason an interpolation was done to fulfill the requirement of the program that each subject be represented by the same linear combination of measurements (see Table 2). By taking the union of the time points across treatments to be the set of measurement times, each linearly interpolated response curve remained unchanged. This was true because the imputed points fell on the original curves and linear interpolation of the new curves merely retrenched the original curves.

Results of the analysis on the interpolated curves for the hypothesis that all of the observed response curves are equal are shown in Table 3. Notice that the significant effect found due to treatment did not identify which treatment was effective. In order to determine which treatment was effective, separate analyses needed to be performed for each treatment with the control. These analyses were easily accomplished by subsetting the data. As expected from viewing Figure 1, the significant effect found was due primarily to Compound B.

6. DISCUSSION

The program just described provides a general analysis for many types of data, allowing the functional form of the observed response curves to be approximated by a smoothing procedure or made explicit. The curve used in the program is approximated by smoothing with a linear interpolation between the observed points. This method simplifies computation of the integrals in (5) and (6) to the quadratic forms in (8). Another program written by Rickard (1988) performs the same analysis for (negative) exponential growth curves assuming the functional form \( Y = a - b \exp(-gt) \) for each curve. Because the limits of the integral may be specified, both programs test interval specific hypotheses.

In addition to the generality of the functional form and the ability to test specific intervals of interest, the costly computation of the exact permutation distribution of the test statistic is avoided with an approximation by an F-distribution with synthesized degrees of freedom. Multiple comparisons for this procedure have been discussed by Zerbe and Murphy (1986), Fouts et al. (1985), and Nelson (1987). A version of the program with multiple comparisons and contrasts is available from the author (see Nelson, 1988).

### Table 1. Sum of Swelling Scores for Each Rat

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<tr>
<th>Treatment</th>
<th>Days</th>
<th>Control</th>
<th>12</th>
<th>24</th>
<th>36</th>
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### Table 2. Sum of Swelling Scores for Each Rat

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### Table 3. Results of Analysis Over the Entire Interval, 0 to 60 Days

RESULTS FROM ANALYSIS IN INTERVAL:

<table>
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<tr>
<th>SUMS OF SQUARES</th>
<th>BETWEEN 1351.187</th>
<th>WITHIN 5695.494</th>
<th>TOTAL 5046.681</th>
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</thead>
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<tr>
<td>SYNTHESIZED DEGREES OF FREEDOM</td>
<td>F(5,39)</td>
<td>4.52</td>
<td>0.006</td>
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<tr>
<td>p-VALUE</td>
<td>4.205</td>
<td>0.006</td>
<td></td>
</tr>
</tbody>
</table>

1261
Figure 1. Mean Scores and Standard Errors for Each Group Over Time

REFERENCES


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