SOME CONSIDERATIONS IN THE ANALYSIS
OF RATES OF CHANGE
IN LONGITUDINAL STUDIES

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SUMMARY

Several estimators of mean rate of change are discussed and compared in unbalanced longitudinal data. Commonly used variance estimates corresponding to these estimators are also evaluated and recommendations made as to the choice of method. An example is presented which illustrates some difficulties often encountered in the analysis of longitudinal clinical data sets.
INTRODUCTION

Medical research often involves repeated measurements on each study participant. This is especially true in studies designed for patient follow-up. Proper statistical analysis then needs to consider the correlation between measurements on the same subject. Similar problems arise in survey research (cluster sampling) and in agriculture (e.g., split plot designs), but many medical applications share features not as common in other areas. Sample sizes in medical studies tend to be smaller than those in surveys. Missing data, uncontrollable variables and other practical aspects of patient follow-up, make many studies of this type suffer from considerable imbalances in design. Finally, interest is often focused on modelling rate of change with either time or another controlled or uncontrolled factor.

To our knowledge, none of the major statistical program packages have features at the present time for analysis of this type of data. Laird and Ware\textsuperscript{1} have introduced a remarkably flexible approach to analysis of longitudinal data. The method, however, requires a special program and relatively large data sets. Furthermore, it is more appropriate for final rather than exploratory analyses. Standard statistical packages, such as BMDD\textsuperscript{2}, SPSS\textsuperscript{3} and SAS\textsuperscript{4} provide programs only for balanced data, except BMDP3V which is expensive to run and does not have the capacity to model rates of change.

As a simplification, statisticians instead often reduce the data to regression coefficients (typically slopes) by fitting individual curves to study subjects. The purpose of this paper is to discuss different approaches to the analysis of such coefficients. The methods include unweighted analysis, fixed effect weights and the iteratively obtained weights of Hui and Berger\textsuperscript{5}. We compare the properties of the resulting estimators and their
variance estimates. An example is presented which illustrates some inherent
problems and assumptions.

**METHODS AND NOTATION**

We assume that data will be collected longitudinally on n subjects. A
variable X is measured \( m_i \) times on subject \( i \), simultaneously with a continuous
response variable Y. Interest is focused on the rate of change in Y relative
to X as quantified by regression slope \( \beta_i \) for subject \( i \). Unless otherwise
specified, the \( \beta_i \) are assumed normally distributed across subjects with
mean \( \mu_\beta \) and variance \( D \).

In all the approaches discussed, analysis begins by estimation of the
individual \( \beta_i \). The usual least squares estimator of \( \beta_i \) is denoted by \( b_i \).
Following an unweighted approach, the parameter \( \mu_\beta \) is estimated by

\[
\hat{\mu}_\beta = \frac{\sum b_i}{n} = \bar{b}_u
\]

with variance estimate

\[
\hat{\text{Var}}_u = \left( \frac{\sum (b_i - \bar{b}_u)^2}{n(n-1)} \right)
\]

As noted above, however, the \( b_i \) may be determined with different precision and
should, for statistical optimality, be weighted by the inverse of their
variance. We denote the variance of \( b_i \) conditional on \( \beta_i \), by \( d_i \). If \( \beta_i \) and
\( d_i \) are assumed statistically independent, the total variance of \( b_i \) is
\( D + d_i \). In the usual regression situation, \( d_i \) is estimated by

\[
\hat{d}_i = s_i^2 / \sum_{i=1}^{m_i} (x_{ij} - \bar{x}_i)^2 = s_i^2 / SS x_i
\]
where \( s_i^2 \) is an estimate of the residual variance \( \sigma_i^2 \) of the original data points around the regression line and \( SSX_i = \sum_{j=1}^{m_i} (x_{ij} - \bar{x}_i)^2 \). We note that the true \( d_i \) may vary across \( i \) because of differences in either \( \sigma_i^2 \) or \( SSX_i \).

For a balanced design, by definition, \( SSX_i = SSX_i' \) for all \( i, i' \). In general, however, lack of control over \( X \) and/or missing data cause \( SSX_i \) to vary with \( i \). Although \( \{SSX_i\} \) can be thought of as arising from a random process, analysis is usually performed conditional on \( \{SSX_i\} \). In this paper \( \{SSX_i\} \) is, therefore, considered fixed unless otherwise noted.

Following Hui and Berger, \( \sigma_i^2 \) may be estimated by the individual residual variances ("unpooled" estimates), by pooling \( s_i^2 \) across \( i \) or by a "compromise" approach

\[
(s_i^2)_{\text{comp}} = \frac{(m_i-2) s_i^2 + \hat{\tau}}{2\nu + (m_i - 2)}
\]

(Equation 4)

Here, \( \nu \) and \( \tau/2 \) are parameters of a gamma distribution assumed to underlie \( 1/\sigma_i^2 \). The estimation of these parameters is beyond the scope of this discussion. We include the approach to obtain a comparison for the other methods in the Monte Carlo studies. For these purposes, \( \nu \) and \( \tau \) are assumed known rather than estimated.

Once estimates of \( \sigma_i^2 \) have been obtained, \( \hat{\mu}_\beta \) and \( D \) are estimated by iteration between the equations

\[
\hat{\mu}_\beta = \bar{b}_o = \left\{ \sum_{i=1}^{n} \frac{1}{b_i} \right\} \div \left\{ \sum_{i=1}^{n} \frac{1}{D + d_i} \right\}
\]

(Equation 5)

and

\[
\operatorname{tr}^{35} \quad 5.7 \quad 5
\]
\[ D = \frac{n}{\sum_{i=1}^{m} \frac{1}{D + d_i}} \left[ \frac{\left( m_i (m_i - 1)^{-1} (b_i - \bar{b}_o)^2 - d_i \right) / (D + d_i)^2}{\sum_{i=1}^{m} (D + d_i)^{-2}} \right] \] (6)

Equation (6) is slightly modified from Hui and Berger\(^5\) for small sample sizes. Convergence is usually rapid. We estimate the variance of \( \hat{b}_o \) by

\[ \hat{\text{Var}}_o = \left( \sum_{i=1}^{n} \frac{1}{D + d_i} \right)^{-1} \] (7)

The above approach (Hui and Berger\(^5\)) can be generalized to incorporate a design or a covariate (across subjects) on the \( \beta_i \). We explore this only in the example below.

Finally, at least in situations with relatively minor imbalance, one is tempted to proceed as if the data were balanced. Whereas BMDP2V and BMDP4V will not allow this, SAS procedure GLM runs and leaves interpretation of the results to the user. Since GLM was not designed for random effects the resulting estimate of \( \hat{\mu}_\beta \) is that of a fixed effect analysis (i.e., \( D = 0 \)).

\[ \hat{\mu}_\beta = \bar{b}_f = \frac{\sum_{i=1}^{n} (SSX_i) (b_{i1}) / (SSX_i)} {\sum_{i=1}^{n} SSX_i} \] (8)

Mimicking an analysis such as performed for balanced designs by BMDP2V, one would choose the mean square corresponding to the interaction of subjects by \( X \) as the error term. Using sequential sums of squares, the variance of \( \bar{b}_f \) is then inherently taken as

\[ \hat{\text{Var}}_f = \frac{\sum_{i=1}^{n} SSX_i (b_{i1} - \bar{b}_f)^2}{((n - 1) \sum_{i=1}^{n} SSX_i)} \] (9)

We note that this is a proper estimate of the standard error if \( D = 0 \)

tr35  5.7  6
and $\sigma_i^2$ are all assumed equal. The unweighted and fixed effect approaches may, therefore, be considered as limiting cases to the optimally weighted approach when $d_i$ or $D$ are 0, respectively.

**SOME PROPERTIES OF THE ESTIMATORS OF MEAN TREND**

Under the assumptions of linearity and independence of $\beta_i$ from $d_i$, all the weighted as well as the unweighted estimators are unbiased. It is important to note, however, that violation of these assumptions may enter in practice and have profound effects. To clarify the implications, we regard the $\{SSX_i\}$ as random for a moment.

Clearly, nonlinearity is more serious in unbalanced than in balanced data. In the latter case, the linear slope describes a trend over the given range of $x$, whereas in the former interpretation becomes unclear. With nonlinearity, imbalance also introduces dependence between $\beta_i$ and $d_i$ since both depend on the range of $x$ for subject $i$. Other subtle dependencies may be introduced between $b_i$ and $s_i^2$.

Correlation between $d_i$ and $\beta_i$ can also be caused by nonrandomly missing data. If, for example, $\beta_i$ represents a response to treatment, subjects who respond well may be more or less likely to appear for followup visits. In this situation, the unweighted mean slope $\bar{E}_u$ is an unbiased estimator of $\mu_\beta$, whereas the weighted means are biased.

More specifically

$$E\left(\sum \frac{w_i b_i}{\sum w_i} \right) = \sum E\left(\frac{w_i}{\sum w_j} b_i \right) = \sum \text{cov}\left(\frac{w_i}{\sum w_i}, b_i \right) + \mu_\beta$$
Here \((w_i)\) are any weights and \(\sum \text{cov} \left( \frac{w_i}{\sum w_j}, b_i \right)\) represents the bias.

Turning back to the case of uncorrelated \(\beta_i\) and \(d_i\) and again considering \(\{SSX_i\}\) fixed, we compare the estimators by computing their variances. For the unweighted estimator \(\overline{E}_u\)

\[
\text{Var} \left( \frac{\sum b_i}{n} \right) = \frac{D}{n} + \frac{1}{n^2} \left( \sum \frac{1}{SSX_i} \right) \sigma^2
\]

where \(\sigma^2\) is the expected value of \(\sigma_i^2\). For the optimally weighted estimator, we have

\[
\text{Var} \left( \frac{\sum (D+d_i)^{-1} b_i}{\sum (D+d_i)^{-1}} \right) = E \left( \frac{1}{\sum (D+d_i)^{-1}} \right)
\]

The optimality of the weights \((D+d_i)^{-1}\) follows from Cauchy’s inequality. In practice, the weights are estimated, with potential loss of optimality.

The "fixed effect" estimator \(\overline{E}_f\) has variance

\[
\text{Var} \left( \frac{\sum SSX_i b_i}{\sum SSX_i} \right) = E \left( \frac{\sum SSX_i^2 \text{Var}(b_i)}{(\sum SSX_i)^2} \right) =
\]

\[
= E \left\{ \frac{\sum [SSX_i D + (SSX_i) \sigma_i^2]}{(\sum SSX_i)^2} \right\}
\]

\[
= D \left( \frac{\sum SSX_i^2}{(\sum SSX_i)^2} \right) + \sigma^2 \left( \frac{1}{\sum SSX_i} \right)
\]

We find that the variance of \(\overline{E}_f\) is less than that of \(\overline{E}_u\) if

tr35 5.7 8
\[
\frac{\sum SSX_i^2}{(\sum SSX_i)^2} + \sigma^2 \frac{1}{\sum SSX_i} < \frac{D}{n} + \frac{1}{n^2} \sum \frac{1}{SSX_i} \sigma^2
\]

or
\[
\frac{d}{D} > \frac{\sum (SSX_i - \overline{SSX})^2 \sum (1/SSX_i)}{\sum SSX_i \left( \frac{\sum SSX_i \sum (1/SSX_i)}{n} - n \right)}
\]

where \(d\) is the expected value of \(d_i\). In other words, the "fixed effect" weights give smaller variance of the estimator if within subject variability is sufficiently large. The right hand side of expression (10) depends on the degree and type of imbalance. When imbalance is substantial, the right hand side is formally approximated by \(CV^2(\text{SSX}_i)\).

**PROPERTIES OF THE VARIANCE ESTIMATORS**

Formula (2) gives the obvious and unbiased estimator of the variance of \(\overline{b_i}\). The variance estimator (7) is often used for the optimally weighted \(\overline{b_o}\). It is expected to underestimate the true variance, when estimated rather than true optimal weights are used. The degree of underestimation is investigated in the Monte Carlo studies below.

The estimator (9) is chosen since it is the direct generalization of the correct variance estimate in the balanced case. It can easily be seen, however, that (9) will underestimate the variance in unbalanced data since

\[
E \left( \frac{\sum SSX_i (b_i - \overline{b}_i)^2}{(n-1) \sum SSX_i} \right) / \text{Var}(\overline{b}_i)
\]

\[
= \frac{1}{n-1} \frac{D \left( \sum SSX_i \right)^2 + \sigma^2 \left( \sum SSX_i \right)}{D \left( \sum (SSX_i)^2 + \sigma^2 \left( \sum SSX_i \right) \right) - 1}
\]
which is \(<\ 1\) by Cauchy's inequality. The quantity \(\sigma^2\) is again the expected
value of \(\sigma_i^2\).

We also note that (11) is a decreasing function of \(D/\sigma^2\) with limit

\[
\frac{1}{n-1} \left\{ \frac{\left( \sum SSX_i \right)^2}{\sum (SSX_i)^2} - 1 \right\}
\]

(12)
as \(\frac{D}{\sigma^2} \to \infty\).

**MONTE CARLO STUDIES**

**Method**

Random regression slopes and variances were generated in a variety of
situations. The estimators (1), (5) and (8) of \(\mu_B\) and their corresponding
variance estimates (2), (7) and (9) were computed for each generation. Mean
square errors of the estimators of \(\mu_B\) (equal the variance here) and the mean
of the variance estimates across 1,000 generations were computed. Each
generation followed the steps:

1. A specified set of \(\{SSX_i\}\) with corresponding degrees of freedom was
   used for each set of generations. The \(\{SSX_i\}\) and degrees of freedom
   chosen were:

   (a) Three sets of generations with sample size \(n = 20\), the first
   being balanced \(SSX_i = 2.5\), df = 7; the second having seven
   subjects with \(SSX_i = 2.86\), df = 7, five with 1.87, df = 5; and
   the third with ten \(SSX_i = 6.339\), df = 7, five with
   \(SSX_i = 2.958\), df = 5 and five with \(SSX_i = 1.057\), df = 3. This
   sequence illustrates increasing imbalance such as might arise
   from incomplete followup. The quantity \(\sum (SSX_i)^{-1}\) was kept
constant for comparability.

(b) Sets of generations arising from increasing numbers of replicates of

\[
\{SSX_i\} = \{156.35, 134.08; 9.12, 3.89, .52\}
\]
\[
\{df_i\} = \{36, 12, 4, 2, 6\}
\]

This extremely unbalanced setup originated from a random sample of the exponential distribution.

2. The \(\sigma^2_i\) were generated from the density

\[
\pi (\sigma^2) \propto \sigma^{-(\nu + 1)} \exp (- \frac{\tau}{2\sigma^2})
\]

Tables 1-4 represent three sizes of mean \(\sigma^2\) with three different degrees of variability among \(\sigma^2_i\) within each size. In both sets of tables, the three \(\sigma^2\)'s correspond to d/D of approximately 0.1, 1.0 and 10 respectively.

3. The \(\{s^2_i\}\) were generated based on a Chi-square distribution of \(s^2_i/\sigma^2_i\) (given \(\sigma^2_i\)) with \(df_i\) degrees of freedom.

4. The variance D of the \(\beta_i\) was taken as 1 in all situations.

5. The \(b_i\) \(i = 1, \ldots, n\) were generated from normal distributions with mean 0 (\(\mu_\beta\) can be assumed to be 0 without loss of generality) and variances

\[
D + d_i = D + \frac{\sigma^2_i}{SSX_i}
\]

The results presented in Tables 1 and 3 are the relative efficiencies of each estimator vis-a-vis a weighted estimator using the optimal weights. The
results in Tables 2 and 4 are percent mean estimated/true variance. The relative efficiency numerators were obtained as

$$\frac{1000}{\sum_{i}^{n} \left( \sum_{1} (D + d_{i})^{-1} b_{i} \right) / \left( \sum_{1} (D + d_{i})^{-1} \right)^{2}}$$

This expression has the advantage of reflecting the variability in the particular samples generated, while having expected value $1/\sum (D + d_{i})^{-1}$.

Results

We first compare the unweighted and fixed effect weight estimators with those based on estimated optimal weights. As expected, the relative efficiency of the unweighted estimator is good in situations with small within subject variability. Conversely, with large $E(\sigma_{i}^{2})$, the fixed effect estimator performs well. In the middle range, however, both estimators perform increasingly poorly with increasing degree of imbalance. The use of these two estimators cannot be recommended when the degree of imbalance is similar to or exceeding the "intermediate" imbalance situation in Table 1 (unless within or between subject variability is known to be small).

An additional problem concerns the increasing degree of underestimation of the variance of the fixed effect estimator with increasing imbalance. We note, however, that an adjustment may be made by formula (12). This provides an expected lower bound for the degree of underestimation for given $\{SSX_{i}\}$. For the unbalanced cases in Tables 1 and 2, formula 12 gives .97 and .76 respectively; whereas, in Table 4, the fractions are .29, .40 and .42 respectively. In the situations investigated, therefore, formula (12) gives a reasonable estimate of the degree of underestimation. The few situations where Table 2 or Table 4 values are lower than expected are due to random
variation as evidenced by comparison with the unweighted variance estimator.

Turning to comparison of the three methods for estimation of optimal weights, we note that results are very similar across a range of situations. The "compromise" method has the advantage of performing very well in all situations. Simple methods for estimating the required parameters, \( n \) and \( \tau \), are presently under study and seem to be feasible. Given a choice between pooling or not pooling \( s^2_1 \), pooling seems to be generally advantageous except in situations where variability in \( s^2_1 \) is extreme.

The variance estimator (7) is quite acceptable in sample sizes exceeding \( n = 20 \) (or lower when \( E(s^2_1) \) is small).

**EXAMPLE**

The clinical aspects of the research project in this example are discussed in detail by Farrell et al.\(^6\). Briefly, response of plasma linoleic acid level (expressed in percent of total fatty acids) to linoleate feeding was assessed in a group of premature neonates. The purpose of the statistical analyses was modelling this response, investigating differences between subgroups, and, finally, projecting the intake needed for normalization of plasma linoleic acid (for use in further clinical trials).

The data presented pertains to sixty-four neonates who started linoleate feedings at various points during the first three weeks of life. No interventions were instated to change standard care, leading to large imbalances and differences between intake levels. Preliminary analyses showed mean intake per kilogram of body weight averaged over two days to be the best predictor of plasma level. (Plasma measurements were always at least three days apart.) Inclusion of zero feeding lead to difficulties. Therefore, the analyses presented here include only measurements subsequent to initiation of
fatty acid feeding. Exclusion of neonates with fewer than two remaining data points led to a final sample size of \( n = 53 \).

Figure 1 shows dose response relationships for a subsample of ten neonates. A more rapid response is observed at low intakes. Nonetheless, straight lines were fit as a first approximation. The three estimators of mean response (1), (5) and (8) were respectively .0163, .0114 and .0103 where a pooled \( s^2_1 \) of 12.38 was used in (8). Between infant variance \( D \) was estimated at .000038, and the estimated standard errors of the mean slopes were .00247, .00119 and .00076. Other quantities of interest were \( \sum SSX_i = 7.46 \times 10^7 \), \( \sum (SSX_i)^2 = 2.35 \times 10^{14} \), and \( \sum (SSX_i)^{-1} = .001 \), leading to \( d/D = 6.1 \). The right hand side of Formula (10) is 1.27 (\( CV^2(\hat{SSX_i}) = 1.24 \)) predicting that the fixed effect estimator is likely to have smaller true variance than the mean unweighted estimator. Formula (12) indicates that the estimated variance (9) may be as low as 44% of the true variance here. In addition, the relevance of mean slope may be questioned in light of potential nonlinearity. In this data set, the two weighted slopes essentially describe long term trends since neonates fed higher amounts also tend to have larger \( SSX_i \).

The more elaborate model of Hui and Berger\(^5\) was fit allowing \( \mu_B \) to depend on adjusted average intake (denoted by \( \tilde{x} \)). Adjusted average intake (see Hui and Berger\(^5\)) is the intake at which a straight line slope would approximate the derivative of a curvilinear relationship. Following Figure 2, response was assumed related to average intake by a hyperbolic curve. The equation fit using MINITAB\(^7\) MACRO:S performing regression with iteratively fitted weights was found to be

\[
\mu_B(\tilde{x}) = .0037 + 7.9 (1/\tilde{x}) \tag{13}
\]

\( \text{tr35} \quad 5.7 \quad 14 \)
The estimate of D was .0000145 and the hyperbolic coefficient was significant at $p < .001$. Residual plots (Figures 3 and 4) indicate that the model fits well and that residuals are near normally distributed. Differences between relevant subgroups were also investigated using similar methodology and found to be nonsignificant. Equation (13) indicates that the true dose response relationship for each neonate has a linear as well as a logarithmic component. Such curves were fit for the purpose of projecting intake levels required for normalization. Projections differed little from the linear fit at high intake levels, but the logarithmic component was important at low intakes.

CONCLUSION

In longitudinal studies, analysis of linear relationships between variables can often be reduced to analysis of regression coefficients. Missing data and imbalances present a challenge, however. When the data is nearly balanced, unweighted analysis or fixed effect weights can be used as in balanced data. Unless either within or between individual variabilities can be ignored, relative efficiency of these approaches quickly becomes less than satisfactory as the degree of imbalance increases. In addition, the variance estimator corresponding to fixed effect weights seriously underestimates true variance with moderate to severe imbalance. As an alternative, the approach of Hui and Berger⁵ provides nearly optimal weighting schemes.

It is important to be aware of difficulties in interpretation when relationships are not truly linear. These difficulties are magnified by imbalance. Modelling slopes by the approach of Hui and Berger⁵ provides a means for exploring underlying models.
ACKNOWLEDGEMENTS

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REFERENCES


Table 1: Relative Efficiency of Weighting Schemes versus Optimal Weights
with Increasing Degree of Imbalance, 1,000 Generations/Cell

\[ n = 20 \quad \sum (SSX_i)^{-1} = 8 \]

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<th>E(\sigma^2)</th>
<th>CV(\sigma^2)</th>
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<td>.99</td>
<td>.79</td>
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</table>
Table 2: Estimated Variance as Fraction of True Variance with Increasing Degree of Imbalance, 1,000 Generations/Cell

\[ n = 20 \quad \sum (SSX_i)^{-1} = 8 \]

<table>
<thead>
<tr>
<th>Balanced Design</th>
<th>Slight Imbalance</th>
<th>Intermediate Imbalance</th>
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<tr>
<td>( df_i = 7 )</td>
<td>( df_1 = 7 )</td>
<td>( df_1 = 7 )</td>
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<tr>
<td>( i = 1 \ldots 20 )</td>
<td>( i = 1 \ldots 15 )</td>
<td>( i = 1 \ldots 10 )</td>
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<tr>
<td>( \sum (SSX_i) = 50 )</td>
<td>( \sum (SSX_i) = 52.3 )</td>
<td>( \sum (SSX_i) = 63.5 )</td>
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<tr>
<td>( \sum (SSX_i)^2 = 125 )</td>
<td>( \sum (SSX_i)^2 = 140.2 )</td>
<td>( \sum (SSX_i)^2 = 451.2 )</td>
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</table>

<table>
<thead>
<tr>
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<th>Unw Fixed</th>
<th>Unw Fixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>( E(\sigma_i^2) )</td>
<td>( CV(\sigma_i^2) )</td>
<td>( \hat{opt}_p )</td>
<td>( \hat{opt}_c )</td>
</tr>
<tr>
<td>( .25 )</td>
<td>( 1 )</td>
<td>( 1.09 )</td>
<td>( 1.11 )</td>
</tr>
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<td>( .25 )</td>
<td>( .22 )</td>
<td>( .96 )</td>
<td>( .96 )</td>
</tr>
<tr>
<td>( .25 )</td>
<td>( .16 )</td>
<td>( .88 )</td>
<td>( .88 )</td>
</tr>
<tr>
<td>( 2.5 )</td>
<td>( 1 )</td>
<td>( .95 )</td>
<td>( .95 )</td>
</tr>
<tr>
<td>( 2.5 )</td>
<td>( .22 )</td>
<td>( .96 )</td>
<td>( .96 )</td>
</tr>
<tr>
<td>( 2.5 )</td>
<td>( .16 )</td>
<td>( 1.01 )</td>
<td>( 1.03 )</td>
</tr>
<tr>
<td>( 25 )</td>
<td>( 1 )</td>
<td>( 1.00 )</td>
<td>( 1.05 )</td>
</tr>
<tr>
<td>( 25 )</td>
<td>( .22 )</td>
<td>( .95 )</td>
<td>( 1.04 )</td>
</tr>
<tr>
<td>( 25 )</td>
<td>( .16 )</td>
<td>( 1.00 )</td>
<td>( 1.08 )</td>
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</table>
Table 3: Relative Efficiency of Weighting Schemes versus Optimal Weights for Three Sample Sizes.

1,000 Generations/Cell.

Large degree of imbalance with \( \{SSX_j\} \) and \( \{df_j\} \) the appropriate number of replicates of \( \{156.4; 134.1; 9.1; 3.9; 0.52\} \) and \( \{36, 12, 4, 2, 6\} \) respectively.

<table>
<thead>
<tr>
<th>TYPE OF WEIGHTS:</th>
<th>( \sigma_1^2 )</th>
<th>( \alpha \sigma_1^2 )</th>
<th>( \hat{\sigma}_1^2 )</th>
<th>( \hat{\alpha} \sigma_1^2 )</th>
<th>( \hat{\sigma}_1^2 )</th>
<th>( \hat{\alpha} \sigma_1^2 )</th>
<th>( \hat{\sigma}_1^2 )</th>
<th>( \hat{\alpha} \sigma_1^2 )</th>
<th>( \hat{\sigma}_1^2 )</th>
<th>( \hat{\alpha} \sigma_1^2 )</th>
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<tr>
<td>( \sum (SSX_1)^{-1} = 2.30 )</td>
<td>( \sum SSX_1 = 303.97 )</td>
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<tr>
<td>( \sum (SSX_1)^{-1} = 9.2 )</td>
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<td>( \sum (SSX_1)^{-1} = 22.96 )</td>
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Columns: unw, fixed, \( \alpha \sigma_1^2 \), \( \hat{\sigma}_1^2 \), \( \hat{\alpha} \sigma_1^2 \), \( \hat{\sigma}_1^2 \), \( \hat{\alpha} \sigma_1^2 \), \( \hat{\sigma}_1^2 \), \( \hat{\alpha} \sigma_1^2 \), \( \hat{\sigma}_1^2 \), \( \hat{\alpha} \sigma_1^2 \).
Table 4: Estimated Variance as Fraction of True Variance for Three Sample Sizes.
Large degree of imbalance (See Table 3). 1,000 Generations/Cell.

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<td>\1.09</td>
<td>.50</td>
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</table>
FIGURE 1. Dose response curves for a subsample of ten neonates

FIGURE 2. Fitted slope as a function of adjusted average intake

FIGURE 3. Predicted slope versus standardized residual

FIGURE 4. Standardized residual versus normal scores