STATISTICAL MODELS FOR THE
ANALYSIS OF CERTAIN TOXICOLOGICAL EXPERIMENTS

by

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ABSTRACT

This paper provides a review of the current state-of-the-art with regard to the analysis of data generated via laboratory experiments designed to investigate the teratogenic or toxicological effect of certain compounds. In such experiments, the response of interest is typically binary in nature, namely, the occurrence or not of death (or of some particular abnormality) in each fetus in a litter of animals.

This paper discusses the advantages and disadvantages of the various models and methods of analysis which have been proposed for dealing with this type of data, and recommendations are made regarding which techniques seem to be most appropriate.
1. INTRODUCTION

In laboratory experiments designed to investigate the teratogenic or toxicological effect of certain compounds, the response of interest is frequently binary in nature, namely, the occurrence or not of "affected" fetuses or implantations in a litter. The "effect" under consideration is generally fetal death or the occurrence of some particular malformation.

The statistical treatment of such data generally requires that the variations in response be described by some underlying probabilistic model, and hence the quality of any subsequent statistical inferences will necessarily depend on how well such a model describes the phenomenon under study.

It is the purpose of this paper to discuss various models and methods of analysis which have been proposed for dealing with this type of data, and to make some recommendations regarding which techniques seem to be most appropriate.

To establish notation, let us suppose that there are \( l_1 \) litters in the \( i \)-th group (\( i = 0 \) for control group and \( i = 1 \) for treatment group), the \( j \)-th litter in the \( i \)-th group being of size \( n_{ij} \), \( j = 1, 2, \ldots, l_i \). Let

\[
x_{ij} = \sum_{k=1}^{n_{ij}} x_{ijk},
\]
where $x_{ijk}$ is a dichotomous variable taking the value 1 if the k-th fetus in the j-th litter of the i-th group possesses the attribute of interest and taking the value 0 if the attribute is not present. Thus, $X_{ij}$ is the observed total number of affected fetuses out of the $n_{ij}$ under consideration. Further, let

$$\hat{p}_{ij} = \frac{x_{ij}}{n_{ij}},$$

$$\hat{p}_i = \frac{\sum_j x_{ij} / \sum_j n_{ij}}{\sum_j n_{ij} \hat{p}_{ij} / \sum_j n_{ij}},$$

$$\bar{p}_i = \frac{\sum_j \hat{p}_{ij} / \ell_i}{\ell_i}.$$ 

Note that $\bar{p}_i$ involves no weighting of the $\{\hat{p}_{ij}\}$ by litter size, which can be a problem with small samples.

### 2. TYPES OF MODELS

Consider the following two probabilistic models.

**MODEL A:** For the j-th litter in the i-th group, the set $\{n_{ij}, x_{ij}, p_{ij}\}$ is a realization of the trivariate set of random variables $\{N_i, X_i, P_i\}$, where

(i) the marginal distribution of $N_i$ is defined on the non-negative integers, with, say,

$$\Pr(N_i = n) = \pi_{in}, \ n = 0, 1, 2, \ldots ;$$

(ii) the marginal density of $P_i$ on the interval $[0, 1]$ is, say, $f_i(p)$;

(iii) the conditional distribution of $X_i$ given $N_i = n_{ij}$ and $P_i = p_{ij}$ is (typically taken to be) binomial, namely

$$\Pr(X_i = x_{ij} / n_{ij}, p_{ij}) = \binom{n_{ij}}{x_{ij}} p_{ij}^{x_{ij}} (1-p_{ij})^{n_{ij}-x_{ij}}, \ x_{ij} = 0, 1, \ldots, n_{ij}. \quad (1)$$
Here, \( n_{ij} \) and \( x_{ij} \) are observable, but \( p_{ij} \) is not observable.

**Comments.** Condition (iii) implicitly assumes that, conditional on \( N_i = n_{ij} \) and \( P_i = p_{ij} \), the within-litter Bernoulli responses are mutually independent, which is often not a realistic assumption. Also, note that \( 0 \leq x_i \leq N_i \), that \( N_i \) and \( P_i \) may or may not be assumed to be independent, and that \( \Pr(N_i = 0) = \pi_{10} \) may or may not be assumed to be equal to zero.

**MODEL B:** For the \( j \)-th litter in the \( i \)-th group, the set \( \{x_{ij}, \lambda_{ij}\} \) is a realization of the bivariate set of random variables \( \{X_i, \Lambda_i\} \), where

(i) the marginal density of \( \Lambda_i \) on the interval \( [0, \infty) \) is, say, \( g_i(\lambda) \);
(ii) the conditional distribution of \( X_i \) given \( \Lambda_i = \lambda_{ij} \) is (typically taken to be) Poisson, namely

\[
\Pr(X_i = x_{ij} / \lambda_{ij}) = \frac{\lambda_{ij}^{x_{ij}} e^{-\lambda_{ij}}}{x_{ij}!}, \quad x_{ij} = 0, 1, \ldots, \infty.
\]

Here, \( x_{ij} \) is observable, but \( \lambda_{ij} \) is not observable.

**Comments.** Model B (in contrast to Model A) completely ignores litter size and considers only the number (and not the proportion) of dead or malformed fetuses.

In the next two sections, we will consider some particular methodologies associated with Models A and B.

2.1. **Methods Associated With Model A.**

For

\[
\mu_i = \int_0^1 p f_i(p) dp
\]

and for \( \pi_{10} = 0 \), VanRyzin [9] has shown that \( \bar{p}_i \) is the minimum-variance linear (in the \( \hat{p}_{ij} \)) unbiased, strongly consistent \( (\bar{p}_i \rightarrow \mu_i \) with probability 1 as \( \ell_i \rightarrow \infty \) estimator of \( \mu_i \), and that \( \sqrt{\ell_i} (\bar{p}_i - \mu_i) / s_i \) converges
in distribution to \( \mathcal{N}(0,1) \) as \( \ell \to \infty \), where

\[
s_i^2 = \frac{1}{(\ell - 1)} \sum_j (\hat{p}_{ij} - \overline{p}_i)^2.
\]

When \( 0 \leq \pi_{10} < 1 \), we do not have an identifiable estimation problem if the joint distribution of \( N_i \) and \( P_i \) is unrestricted; however, the above properties will hold for an estimator based only on litters with \( n_{ij} > 0 \) as long as \( N_i \) and \( P_i \) are independent. When \( P_i \) is related to \( N_i \), which is likely to be the case in many biological and reproductive systems, VanRyzin develops a moment estimator for \( \mu_i \).

A statistical test of \( H_0: \mu_1 = \mu_0 \) can be constructed based on the asymptotic properties of \( \overline{p}_1 \) and \( \overline{p}_0 \). Hoel [4] has discussed an application of these results to the problem of estimating the probability of death and the probability of a malformation given that the fetus is alive.

Results Conditional on Fixed \( \{n_{ij}\} \)

Southward and VanRyzin [8] compared the variances of \( \hat{p}_i \) and \( \overline{p}_i \), which are functions of the unknown quantities \( \sigma^2_i = \int_0^1 (p - \mu_i)^2 f_i(p)dp \) and \( \tau_i = \int_0^1 (1-p)f_i(p)dp \); they concluded that neither \( \hat{p}_i \) nor \( \overline{p}_i \) is for all choices of \( f_i(p) \) relatively more efficient than the other. They derived the minimum-variance linear unbiased estimator of \( \mu_i \) and developed an asymptotically optimal confidence interval for \( \mu_i \) which involved estimates of \( \sigma^2_i \) and \( \tau_i \).

Williams [10] assumed that model (1) held, took \( f_i(p) \) to be a beta distribution with parameters \( \alpha_i \) and \( \beta_i \), and worked with the beta-binomial model

\[
\Pr(X_i = x_{ij} | n_{ij}) = \binom{n_{ij}}{x_{ij}} \frac{B(x_i, 1 + x_{ij}, n_{ij} + \beta_i - x_{ij})}{B(\alpha_i, \beta_i)},
\]
where \( B(\alpha_i, \beta_i) = \frac{\Gamma(\alpha_i) \Gamma(\beta_i)}{\Gamma(\alpha_i + \beta_i)} \). Under this model, the within-litter responses are conditionally independent, but are unconditionally dependent. The parameters \( \mu_i = \alpha_i (\alpha_i + \beta_i)^{-1} \) and \( \sigma_i^2 = \mu_i (1 - \mu_i)(\alpha_i + \beta_i + 1)^{-1} \) are estimated by maximum likelihood, and treatment and control groups are compared with respect to these parameter values by using asymptotic likelihood ratio tests. Haseman and Soares [3] have shown by simulation that Williams' procedure tends to yield inflated Type I error rates.

Gladen [2] has proposed the use of a jackknifed estimator of \( \mu_i \) of the form

\[
\tilde{p}_i = \hat{p}_i + (\ell_i - 1) \bar{y}_i,
\]

where

\[
\bar{y}_i = \frac{1}{\ell_i} \sum_j y_{ij} = \frac{1}{\ell_i} \sum_j \frac{(x_{ij} - n_{ij}) \hat{p}_i}{(\ell_i - n_{ij})}.
\]

It is easy to show that \( \tilde{p}_i = \sum_j w_{ij} \hat{p}_{ij} \) and that \( \tilde{p}_i = \bar{p}_i \) when \( n_{ij} = n_i \).

One can regard (e.g., see Miller [7]) either \( (\tilde{p}_i - \mu_i)/\tilde{s}_i \) or \( (\hat{p}_i - \mu_i)/\tilde{s}_i \) as having approximately a t-distribution with \( (\ell_i - 1) \) degrees of freedom, where

\[
\tilde{s}_i^2 = \ell_i^{-1} (\ell_i - 1) \sum_j (y_{ij} - \bar{y}_i)^2.
\]

To compare treatment and control groups, one can work with the statistic

\[
(\tilde{p}_i - \tilde{p}_0)/(\tilde{s}_i^2 + \tilde{s}_0^2)^{1/2},
\]

which has an approximate t-distribution with \( (\ell_i + \ell_0 - 2) \) df under \( H_0 \).

Gladen claims that the real advantage of the jackknife approach shows up when dealing with small samples and variable litter sizes; she argues that its use leads to more realistic standard error estimates than those based directly on the binomial distribution, e.g., like \( \hat{s}_i^{1/2} \). However, note that \( \tilde{p}_i \) can take a value outside the interval \([0,1]\).
Starting with model (1), Gladen shows that $(\tilde{p}_i - \mu_i)/\tilde{s}_i$ and $(\hat{p}_i - \mu_i)/\hat{s}_i$ are both asymptotically $N(0,1)$ under the assumption that the litter sizes come from some bounded distribution. Asymptotic efficiency results based on the beta-binomial model using observed litter size distributions and estimated parameter values for three particular data sets (presented in Section 3) indicated that $\tilde{p}_i$ (or, equivalently, $\hat{p}_i$) was almost fully efficient, while $\bar{p}_i$ was somewhat less efficient but still respectable. Some of her simulation results will be mentioned in Section 3.

Results Conditional on Fixed $\{n_{ij}\}$ and $P_i = p_i$

Kupper and Haseman [5] considered a two-parameter generalization of model (1) of the form

$$
Pr(X_i = x_{ij}/n_{ij}, p_i) = \binom{n_{ij}}{x_{ij}} p_i^{x_{ij}} (1-p_i)^{n_{ij}-x_{ij}} \left\{ 1 + \frac{\theta_i}{2p_i^2(1-p_i)^2} \left[ (x_{ij}-n_{ij}p_i)^2 + x_{ij}(2p_i-1) - n_{ij}p_i^2 \right] \right\},
$$

where $\theta_i$ is the covariance between any two responses within the same litter. This correlated-binomial model allows for the possibility of negative intra-litter correlation, while Williams' beta-binomial model permits only supra-binomial variation. As with Williams' model, likelihood ratio tests are employed to assess the significance of treatment-control differences, and the use of either model necessitates consideration of boundary conditions with regard to maximization of the corresponding likelihood functions. A comparison between the correlated-binomial and beta-binomial models will be presented in Section 3.
Altham [1] considered another two-parameter generalization of model (1) of the form
\[
\Pr(X_i = x_{ij}/n_{ij}, p_1) = \left(\frac{n_{ij}}{x_{ij}}\right)^{x_{ij}} \left(1 - \frac{p_1}{x_{ij}}\right)^{(n_{ij} - x_{ij})} \delta_i^{x_{ij}} / f(p_1, \delta_i, n_{ij}),
\]
where
\[
f(p_1, \delta_i, n_{ij}) = \sum_j \left(\frac{n_{ij}}{x_{ij}}\right)^{x_{ij}} \left(1 - \frac{p_1}{x_{ij}}\right)^{(n_{ij} - x_{ij})} \delta_i^{x_{ij}}.
\]
This model reduces to (1) when \( \delta_i = 1 \); if \( \delta_i > 1 \), the distribution is (strongly) unimodal and more sharply peaked than the binomial, which implies negative intra-litter association; for \( 0 < \delta_i < 1 \), the distribution is more diffuse than the binomial and the intra-litter responses are positively correlated. Altham compares this model to the correlated-binomial model, and generally seems to prefer the latter.

Other Procedures

A commonly used approach is to employ ordinary \( \chi^2 \) tests (CHI) for comparing \( \hat{p}_1 \) and \( \hat{p}_0 \). Haseman and Soares [3] have shown that such tests tend to operate at much above nominal significance levels (see Section 3), the main reason being that they involve the use of binomial standard errors.

Most other approaches involve the use of t-tests or Mann-Whitney U-tests (MWU) or the \( \{\hat{p}_{ij}\} \) or on transformations thereof. Popular transformations are the Freeman-Tukey binomial (FTB) variance-stabilizing arc-sine transformation
\[
\frac{1}{2} \left[ \sin^{-1} \sqrt{\frac{x_{ij}}{n_{ij} + 1}} + \sin^{-1} \sqrt{\frac{x_{ij} + 1}{n_{ij} + 1}} \right],
\]
or the arc-sine transformation (ARC)
\[
\begin{align*}
\sin^{-1}\left(\frac{x_{ij}}{n_{ij}}\right) & \quad \text{if } x_{ij} \neq 0, \\
\sin^{-1}\frac{1}{4n_{ij}} & \quad \text{if } x_{ij} = 0 \\
\sin^{-1}(1) - \sin^{-1}\frac{1}{4n_{ij}} & \quad \text{if } x_{ij} = n_{ij}.
\end{align*}
\]

2.2. Methods Associated With Model B

McCaughran and Arnold [6] take \( g_i(\lambda) \) to be a gamma distribution, so that the unconditional distribution of \( X_i \) is negative binomial. They employ the method of moments to estimate parameters of interest, then perform a variance-stabilizing transformation which depends on the parameter estimates, and then do t-tests on the transformed data to assess treatment-control differences.

The Freeman-Tukey Poisson (FTP) transformation

\[
\sqrt{x_{ij}} + \sqrt{x_{ij} + 1}
\]

has also been utilized, with t-tests performed on the transformed data.

3. SOME SIMULATION RESULTS

Haseman and Soares [3] utilized the empirical distributions of fetal death presented in Table 1 to illustrate that such data rarely can be adequately modeled using a binomial or a Poisson distribution (see Table 2). They then constructed three infinite populations having the same relative frequencies of fetal death as the control groups shown in Table 1. From each population two random samples of 20 pregnant females were drawn, and comparisons of fetal death were made by chi-square (CHI) and by a Student's t-test based on the Freeman-Tukey transformation for Poisson counts (FTP), the Freeman-Tukey transformation for binomial
proportions (FTB), and the arc-sine transformation (ARC). The Mann-Whitney U-test based on the proportion of dead implants (MWU) was also considered. The process was repeated 5000 times for each population, and the frequency with which each test rejected the null hypothesis of no effect was recorded. It was found (see Table 3) that all procedures except chi-square appeared to be operating at approximately the correct level of significance. As far as power considerations are concerned, a number of computer simulations with various distributions of fetal death led to the following conclusions: (1) For treatments producing no pre-implantation loss, differences in power among the four procedures for detecting increases in fetal death were generally slight, with no one procedure being consistently superior to any other; (2) As pre-implantation losses increased in the treated group, FTP became progressively worse relative to the other three procedures for detecting increases in fetal death.

Gladen [2] also conducted some simulation studies using these three control populations as well as three others. Her results supported the findings of Haseman and Soares, and she also found that her jackknife procedure performed about as well as the FTP, FTB, ARC and MWU approaches.

Finally, Table 4 presents a comparison of the beta-binomial and correlated-binomial model fits to the three data sets considered by Haseman and Soares. As can be seen, there is little difference between the fits of the two models, and the improvement in fit relative to the binomial distribution is quite impressive.
RECOMMENDATIONS

Based on all these results, what should we do? Motivated by the KISS philosophy ("keep it simple, stupid"), I would be inclined to use a Mann-Whitney U-test on the \( \hat{p}_{ij} \) to compare treatment and control groups, since it seems to operate at about the right significance level, appears to have power comparable to other more complex procedures, and is simple to understand, explain and use. When the study design is of the multi-factor type (involving, for example, additional factors like time period or strain of mice), then an analysis of variance using the FTB or ARC transformation would be appropriate.

REFERENCES


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a These five females had 12/12, 8/13, 7/14, 7/17 and 13/20 dead implants.

b These six females had 7/7, 8/8, 5/9, 6/9, 10/10 and 7/13 dead implants.

C These nine females had 7/10, 8/10, 6/11, 8/11, 6/12, 6/12, 7/13, 7/14 and 9/14 dead implants.
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\[ X^2_3 = 63.6^c \quad 75.1^c \quad 16.0^b \quad 30.5^c \quad 67.8^c \quad 74.0^c \]

(test of fit)

\(^a\)See Haseman and Soares [3] for the complete distributions of fetal death.

\(^b\) \( p < 0.01 \).

\(^c\) \( p < 0.001 \).
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*aBased on 5000 iterations. Test procedures are defined in the text.*
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