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DOSE-RESPONSE MODELING OF TRINOMIAL RESPONSES FROM DEVELOPMENTAL EXPERIMENTS

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Abstract: Two frequently used toxicity endpoints for evaluation of developmental effects are the proportion of deaths/resorptions and the proportion of malformations. Either a double beta-binomial model or a Dirichlet-trinomial model can be used to model the two developmental endpoints in the presence of intralitter correlation. Both models assume that the proportion of death/resorption and the proportion of malformation are two independent developmental effects. A quasi-likelihood model is proposed under both double beta-binomial and Dirichlet-trinomial variations. This approach allows for modeling a dependency between the two proportions. Two examples are given for illustration.

Key words and phrases: Beta-binomial, Dirichlet-trinomial, intralitter correlation, quasi-likelihood.

1. Introduction

Two frequently used toxicity endpoints to assess the developmental effect are the proportion of the number of dead/resorbed implants to the total number of implants representing the incidence of prenatal death, and the proportion of the number of malformed fetuses to the total number of live fetuses representing the incidence of malformations. It has been observed that, as dose increases, both the proportions of deaths/resorptions and malformations increase over a subrange of the doses. These two proportions may be correlated as a result of dose effect, and the two endpoints may represent different degrees of responses to a toxic insult, and occur in a dose-related manner (Kimmel and Gaylor (1988)). Chen and Gaylor (1992) observed a positive correlation between the proportion of fetuses with cleft palate and the proportion of prenatal deaths from the analysis of a large scale developmental study of 2, 4, 5-trichlorophenoxyacetic acid.

Litter effect, the tendency for litter mates to respond similarly, is well known in the analysis of developmental responses (Haseman and Kupper (1979)). The statistical model for the analysis of developmental effects has usually been formulated in terms of binary outcomes and using beta-binomial type models or the quasi-likelihood method to account for overdispersion due to the litter effect

(e.g., Williams (1975, 1982), and Prentice (1986)). The main purpose of this paper is to propose a quasi-likelihood approach to model the dependency between the proportion of deaths/resorptions and the proportion of malformations.

2. Parametric Model

Consider an experiment with g treatment groups, a control and $g-1$ dose groups. For each group, there are m_i pregnant females exposed to dose d_i, $i = 1, \ldots, g$. Let n_{ij} denote the number of implants of the jth litter in the ith group, $1 \leq i \leq g$ and $1 \leq j \leq m_i$. If x_{ij} and y_{ij}, respectively, represent the number of dead/resorbed fetuses (dead implants), and the number of malformed live fetuses among the n_{ij}, then $z_{ij} = n_{ij} - x_{ij} - y_{ij}$ represents the number of normal fetuses.

The joint distribution of x_{ij} and y_{ij} can be expressed as a product of two beta-binomial distributions,

$$P(x_{ij}, y_{ij}) = \frac{n_{ij}!\,\Gamma(a_i+w_i)\Gamma(x_{ij}+a_i)\Gamma(n_{ij}-x_{ij}+w_i)}{x_{ij}!\,(n_{ij}-x_{ij})!\,\Gamma(n_{ij}+a_i+w_i)\Gamma(a_i)\Gamma(w_i)} \cdot \frac{(n_{ij}-x_{ij})!\,\Gamma(b_i+c_i)\Gamma(y_{ij}+b_i)\Gamma(n_{ij}-x_{ij}-y_{ij}+c_i)}{y_{ij}!\,(n_{ij}-x_{ij}-y_{ij})!\,\Gamma(n_{ij}-x_{ij}+b_i+c_i)\Gamma(b_i)\Gamma(c_i)},$$

where $a_i > 0$, $b_i > 0$, $c_i > 0$, and $w_i > 0$. This model will be referred as to the double beta-binomial model (Chen et al. (1991)). Under the double beta-binomial model, the means of x_{ij} and $y_{ij}|x_{ij}$ are $E(x_{ij}) = n_{ij}\mu_i$, and $E(y_{ij}|x_{ij}) = (n_{ij} - x_{ij})\xi_i$, where $\mu_i = a_i/(a_i + w_i)$ and $\xi_i = b_i/(b_i + c_i)$. The parameters μ_i and ξ_i represent the mean response probability for deaths/resorptions and malformations, respectively; the intralitter correlations are $\phi_i = (a_i + w_i + 1)^{-1}$ and $\phi_i' = (b_i + c_i + 1)^{-1}$ for death/resorption and malformation, respectively.

Alternatively, Chen et al. (1991) proposed a Dirichlet-trinomial model for x_{ij} and y_{ij},

$$P(x_{ij}, y_{ij}) = \frac{n_{ij}!\,\Gamma(a_i+b_i+c_i)\Gamma(x_{ij}+a_i)\Gamma(y_{ij}+b_i)\Gamma(z_{ij}+c_i)}{x_{ij}!\,y_{ij}!\,z_{ij}!\,\Gamma(n_{ij}+a_i+b_i+c_i)\Gamma(a_i)\Gamma(b_i)\Gamma(c_i)}.$$

Under the Dirichlet-trinomial model, the means of x_{ij} and $y_{ij}|x_{ij}$ are $E(x_{ij}) = n_{ij}\mu_i$, and $E(y_{ij}|x_{ij}) = (n_{ij} - x_{ij})\xi_i$, where $\mu_i = a_i/(a_i + b_i + c_i)$ and $\xi_i = b_i/(b_i + c_i)$. The intralitter correlation is $\phi_i = (a_i + b_i + c_i + 1)^{-1}$; thus, the litter effect is explained by only one parameter. It can be seen that the Dirichlet-trinomial model is a special case of the double beta-binomial model with $w_i = b_i + c_i$.

Several authors have proposed various dose-response functions for modeling developmental effects. In this paper, we assume a logistic-linear dose-response function for both μ and ξ, i.e.,

$$\text{logit}\mu_i = \log[\mu_i/(1-\mu_i)] = \alpha + \beta d_i,$$

and

$$\text{logit}\xi_i = \log[\xi_i/(1-\xi_i)] = \alpha' + \beta' d_i.$$

The maximum likelihood estimates (MLE) of α, β, α' and β' were calculated under the assumption that different intralitter correlation coefficients among ϕ_i and ϕ_i' based on the result of Kupper et al. (1986) that the MLE's of the dose-response coefficients may be biased if the intralitter correlations are wrongly assumed to be equal.

The likelihood ratio test can be applied for the goodness-of-fit of a chosen model. The saturated model is the double beta-binomial model with the parameters μ_i, ξ_i, ϕ_i and $\phi_i', i = 1, 2, \ldots, g$. The likelihood ratio test or Wald test can be used to test the hypothesis that $\beta = 0$ and $\beta' = 0$ to determine if the chemical causes developmental effects. Under the null hypothesis, the test statistic has a χ^2 distribution with 2 degrees of freedom.

3. Quasi-Likelihood Model

Assume that the mean and variance for the proportion of deaths/resorptions are $E(x_{ij}/n_{ij}) = \mu_i$ and $V(x_{ij}/n_{ij}) = \nu_{ij}\mu_i(1-\mu_i)/n_{ij}$, where $\nu_{ij} = 1+\phi_i(n_{ij}-1)$; further assume that $n_{ij} > x_{ij}$, and the mean and variance for the proportion of malformations are $E[y_{ij}/(n_{ij}-x_{ij})] = \xi_i$ and $V[y_{ij}/(n_{ij}-x_{ij})] = \nu_{ij}'\xi_i(1-\xi_i)/n_{ij}'$, where $n_{ij}' = n_{ij}/(1+\mu_i) \geq 1$ and $\nu_{ij}' = 1+\phi_i'(n_{ij}'-1)$. Moreover, let the correlation coefficient between the two proportions $\text{Corr}[x_{ij}/n_{ij}, y_{ij}/(n_{ij}-x_{ij})] = \rho_i$. The parameters ϕ_i and ϕ_i' characterize the intralitter correlations for death/resorption and malformation, respectively; and the parameter ρ_i characterizes the correlation (dependency) between the proportion of deaths/resorptions and the proportion of malformations.

In the parametric model the distribution for the proportion of malformations is conditional on the number of deaths/resorptions with the conditional variance

$$V[y_{ij}/(n_{ij}-x_{ij})|x_{ij}] = [1+\phi_i'(n_{ij}-x_{ij}-1)]\xi_i(1-\xi_i)/(n_{ij}-x_{ij}).$$

The unconditional variance of $y_{ij}/(n_{ij}-x_{ij})$ is

$$V[y_{ij}/(n_{ij}-x_{ij})] = [1+\phi_i'(h_{ij}-1)]\xi_i(1-\xi_i)/h_{ij},$$

where $(1/h_{ij}) = E[1/(n_{ij}-x_{ij})]$.

The mean and the variance functions given in the quasi-likelihood model are based on the same relationship between the mean and variance under the parametric model. The value of n_{ij}' defined above is simply the first order approximation of h_{ij}, i.e.,

$$E[1/(n_{ij}-x_{ij})] = (1/n_{ij})E[1+(x_{ij}/n_{ij})+\cdots] \simeq (1+\mu_i)/n_{ij}.$$

Note that $n_{ij}/(1+\mu_i) < 1$ when $n_{ij} = 1$ and $\mu_i > 0$. In these cases, n'_{ij} will be set to 1. That is, when the litter size is one, the Bernoulli variance for y_{ij} is assumed. An alternative quasi-likelihood model derived from the conditional distribution of $y_{ij}|x_{ij}$ is implemented by letting $n'_{ij} = (n_{ij} - x_{ij})$ and $\rho_i = 0$ (Chen (1991)). Ryan (1992) proposed a simpler model using the Dirichlet-trinomial model with an additional assumption that the overdispersion parameters ν_{ij} and ν'_{ij} are independent of n_{ij} and x_{ij} ($\nu_{ij} = \nu'_{ij} = \nu$). However, the proposed quasi-likelihood model allows for nonzero correlation coefficients between the proportion of deaths/resorptions and the proportion of malformations.

The parameters for the coefficients of the dose-response function can be estimated by iterated reweighted least squares, the parameters for the intralitter correlation coefficients can be calculated by equating the estimates with Pearson chi-square statistics, and the parameters for the correlation coefficients can be estimated from the cross product of the standardized residuals. Specifically, assuming a homogeneous intralitter correlation and a homogeneous correlation coefficient across groups, the estimates for the common ϕ and ϕ' are given by

$$\phi = \frac{1}{(M-2)} \sum_{i=1}^{g} \sum_{j=1}^{m_i} \frac{(x_{ij}/n_{ij} - \mu_i)^2}{[\phi^{-1} + (n_{ij}-1)][\mu_i(1-\mu_i)/n_{ij}]}$$

and

$$\phi' = \frac{1}{(M'-2)} \sum_{i=1}^{g} \sum_{j=1}^{m_i} \frac{[y_{ij}/(n_{ij}-x_{ij}) - \xi_i]^2}{[\phi'^{-1} + (n'_{ij}-1)][\xi_i(1-\xi_i)/n'_{ij}]},$$

where M is the total number of litters and M' is the total number of litters with at least one alive fetuses ($n_{ij} > x_{ij}$), and the estimate for the common ρ is

$$\rho = \frac{1}{M'} \sum_{i=1}^{g} \sum_{j=1}^{m_i} \frac{(x_{ij}/n_{ij} - \mu_i)[y_{ij}/(n_{ij}-x_{ij}) - \xi_i]}{\left[\nu_{ij}\mu_i(1-\mu_i)/n_{ij}\right]^{\frac{1}{2}} \left[\nu'_{ij}\xi_i(1-\xi_i)/n'_{ij}\right]^{\frac{1}{2}}}.$$

Note that in estimating ϕ' and ρ, the terms for which $x_{ij} = n_{ij}$ will not be computed in the summation. The Newton-Raphson method was used in this paper; in each iteration the procedure computed the mean parameters, α, β, α' and β', and the intralitter correlation parameters, ϕ, ϕ' and ρ alternatively until convergence.

The overdispersion parameters under the Dirichlet-trinomial variation are $\nu_{ij} = 1 + \phi_i(n_{ij}-1)$, and $\nu'_{ij} = 1 + [\phi_i/(1-\mu_i+\mu_i\phi_i)](n'_{ij}-1)$. The estimate for ϕ is given by

$$\phi = \frac{1}{M+M'-4} \left\{ \sum_{i=1}^{g} \sum_{j=1}^{m_i} \frac{(x_{ij}/n_{ij} - \mu_i)^2}{[\phi^{-1} + (n_{ij}-1)]\mu_i(1-\mu_i)/n_{ij}} \right.$$

$$+\sum_{i=1}^{g}\sum_{j=1}^{m_i}\frac{[y_{ij}/(n_{ij}-x_{ij})-\xi_i]^2}{[\phi^{-1}+(1-\mu_i+\mu_i\phi)^{-1}](n'_{ij}-1)\xi_i(1-\xi_i)/n'_{ij}}\Bigg\}.$$

The correlation ρ is set to be 0 if independence between the proportion of deaths/resorptions and the proportion of malformations is assumed. If the intralitter correlations are unequal, then ϕ_i and ϕ'_i are equated with chi-square statistics in each group (McCullagh and Nelder (1989, Ch.10)), and ρ_i is computed similarly.

In the quasi-likelihood model, the Wald test is used to test for a dose-response effect, i.e., $\beta = \beta' = 0$.

4. Example

The first example is from the result of a study on developmental effects from exposure of hydroxyurea given to mice. The data considered in this example contained four treatment groups, $0, 150, 200$, and 250 ppm. For each of the four treatment groups, the proportions of deaths/resorptions, in the order of dose level from 0 to 250 ppm, were $0.034, 0.107, 0.451$, and 0.671, the proportions of malformations were $0, 0.064, 0.125$, and 0.303, and the product-moment correlation coefficients between the two proportions were $0, 0.013, 0.041$, and -0.105. The data showed that there was no evidence of association between the two proportions. Therefore, the correlation coefficient between the two proportions were assumed to be zero in the quasi-likelihood analysis.

The parametric analysis included fitting the saturated model and fitting a logistic-linear dose-response function where the intralitter correlations were assumed to be different across groups. The quasi-likelihood analysis included fitting a logistic-linear dose-response function under the two assumptions: a common intralitter correlation or different intralitter correlations across groups. Each model was fitted under these two types of variation: double beta-binomial and the Dirichlet-trinomial. Table 1 presents the results of the fits.

The maximum value of the log-likelihood for the saturated model was -354.79 under the double beta-binomial model, and was -356.32 under the Dirichlet-trinomial model. The likelihood ratio test of the Dirichlet-trinomial model against the double beta-binomial model, i.e. the test for the constraint that $w_i = b_i + c_i$, was not significant at $\alpha = 0.05$. In fitting a logistic dose-response model, the maximum value of the log-likelihood was -357.97 under the double beta-binomial model, and was -359.25 under the Dirichlet-trinomial model. The likelihood ratio test of whether the logistic dose-response function differs from the saturated model was not significant under either the double beta-binomial or the Dirichlet-trinomial model.

Table 1. Results of model fitting with hydroxyurea data

Model		Double beta-binomial				Dirichlet-trinomial			
parameters	Observed	S[a]	A	A'	B'	S	A	A'	B'
μ_0	.034	.034	.024	.004	.012	.034	.023	.023	.012
μ_1	.107	.115	.244	.145	.199	.126	.237	.236	.199
μ_2	.451	.440	.432	.368	.406	.428	.424	.421	.406
μ_3	.671	.669	.641	.668	.652	.664	.635	.631	.652
α			−3.70	−5.49	−4.42		−3.77	−3.74	−4.42
β			.017	.025	.020		.017	.017	.019
ϕ					.218				.176
ϕ_1		.002	.004	1.128		.002	.006	.000	
ϕ_2		.103	.291	.164		.155	.251	.243	
ϕ_3		.332	.332	.591		.293	.289	.452	
ϕ_4		.158	.165	.205		.118	.127	.248	
ξ_0	.0	.0	.002	.002	.003	.0	.002	.002	.003
ξ_1	.064	.062	.046	.043	.054	.054	.051	.044	.053
ξ_2	.125	.131	.128	.119	.128	.152	.139	.121	.129
ξ_3	.303	.300	.309	.292	.275	.312	.327	.289	.280
α'			−6.39	−6.44	−5.70		−6.25	−6.33	−5.78
β'			.022	.022	.019		.022	.022	.019
ϕ'					.232				
ϕ'_1		.0	.0[b]	.0					
ϕ'_2		.271	.237	.397					
ϕ'_3		.294	.290	.492					
ϕ'_4		.120	.121	.562					

a. S : saturated model.
A : parametric model assuming different intralitter correlations.
A' : quasi-likelihood model assuming different intralitter correlations.
B' : quasi-likelihood model assuming a common intralitter correlation, $\phi_i = \phi$ and $\phi'_i = \phi'$ for $i = 1, 2, 3, 4$.

b. ϕ'_1 was set to be 0.

In testing for the dose effect, the Wald test statistic gave a χ^2_2 value of 77.94 under the double beta-binomial model, and 76.84 under the Dirichlet-trinomial model. Alternatively, using the likelihood ratio test for the parametric model, the χ^2_2 was 80.75 under the double beta-binomial model, and was 79.36 under the Dirichlet-trinomial model.

In the quasi-likelihood analysis, assuming different intralitter correlations across groups the χ^2_2 were 44.65 and 76.20 for the double beta-binomial and the Dirichlet-trinomial, respectively. When a common intralitter correlation was

assumed, the χ_2^2 were 50.04 and 44.67 under the double beta-binomial and the Dirichlet-trinomial variation, respectively.

The second example is a study of exposure to the herbicide, 2, 4, 5-trichlorophenoxyacetic acid. The data contained six treatment groups, 0, 30, 45, 60, 75, and 90 mg/kg. For each of the six treatment groups, the proportions of deaths/resorptions were 0.067, 0.096, 0.148, 0.202, 0.323, and 0.386, and the proportions of fetuses with cleft palate (malformation) were 0.002, 0.029, 0.137, 0.358, 0.641, and 0.821, and the product-moment correlation coefficients between the two proportions were −0.041, 0.408, 0.359, 0.626, 0.433, and 0.473. The estimate of the combined correlation coefficient for the six groups was 0.363 (Chen and Gaylor (1992)). The estimated correlation coefficients for 30, 45, 60, and 75 mg/kg dose groups were statistically different from 0. In this example, because of evidence of significant correlation coefficients between the two proportions, the parametric analysis will not be presented. A quasi-likelihood analysis with the assumption of nonzero correlation coefficients between the two proportions were performed. Table 2 presents the results of the four fits.

Table 2. Results of fitting with 2, 4, 5-trichlorophenoxyacetic acid data

Model		Double beta-binomial		Dirichlet-trinomial	
parameters	Observed	A'	B'	A'	B'
μ_0	.067	.062	.057	.064	.055
μ_1	.096	.116	.114	.117	.114
μ_2	.148	.155	.160	.157	.159
μ_3	.202	.205	.219	.207	.219
μ_4	.323	.266	.293	.267	.293
μ_5	.386	.337	.380	.338	.379
α		−2.71	−2.84	−2.69	−2.84
β		.023	.026	.022	.026
ξ_0	.002	.003	.004	.003	.004
ξ_1	.029	.041	.043	.041	.043
ξ_2	.137	.129	.135	.130	.134
ξ_3	.358	.342	.348	.345	.348
ξ_4	.641	.645	.647	.649	.650
ξ_5	.821	.865	.863	.867	.866
α'		−5.67	−5.56	−5.67	−5.60
β'		.084	.082	.084	.083

A': quasi-likelihood model assuming different intralitter correlations.

B': quasi-likelihood model assuming a common intralitter correlation.

Model A' assumes different intralitter correlations with different correlation coefficients across groups. The estimates of the correlation coefficients between the two proportions for each of the groups were $-0.049, 0.456, 0.420, 0.579, 0.367$, and 0.373 under the double beta-binomial quasi-likelihood, and were -0.050, $0.442, 0.394, 0.565, 0.365$, and 0.375 under the Dirichlet-trinomial quasi-likelihood. (Note that the product-moment correlation coefficients, as given above, were $-0.041, 0.408, 0.359, 0.626, 0.433$, and 0.473). Model B' assumes a common intralitter correlation and a common correlation coefficient. The estimate of common correlation coefficient between the two proportions was 0.442 under the double beta-binomial and 0.434 under the Dirichlet-trinomial. (The estimate of the combined correlation coefficient was 0.363). In all, it seems that the quasi-likelihood model provides a reasonable description for the relationship between the two proportions. It is worth noting the difference of the estimates under the two types of variations is small.

In testing for the dose effect, when different intralitter correlations across groups were assumed, the χ^2_2 was 222.85 under the double beta-binomial, and 241.84 under the Dirichlet-trinomial. When a common intralitter correlation was assumed, the Wald test statistic had a χ^2_2 value of 186.51 under the double beta-binomial, and 204.23 under the Dirichlet-trinomial.

5. Discussion

The statistical analysis of developmental toxicity data must account for litter effects. Both parametric or quasi-likelihood methods can be applied for modeling death/resorption and malformation in the presence of litter effect. The double beta-binomial model and Dirichlet-trinomial model were considered in this paper. Both models assume that the proportion of deaths/resorptions and the proportion of malformations are independent. The double beta-binomial model uses two intralitter correlation parameters to describe the litter effect, one parameter for each endpoint; while the Dirichlet-trinomial model uses a single parameter to describe both endpoints. An advantage of using the double beta-binomial model is that the parameters can be estimated by fitting two separate beta-binomial distributions. However, the parameter estimates under the beta-binomial model may not converge when the observed number of deaths/resorptions or malformations is zero. In the first example, the Newton-Ralphon procedure used in this paper fails to converge in fitting the logistic dose-response function to the malformation data; the intralitter correlation in the control groups was set to be 0. The likelihood ratio test under the Dirichlet-trinomial is generally more powerful than the likelihood ratio test under the double beta-binomial model (Chen and Li (1991)).

The quasi-likelihood method does not require full assumption on the distribution, and the estimates of the dose-response coefficients are generally consistent and asymptotically normal even if the structure of intralitter correlations is misspecified (Liang and Zeger (1986)). Moreover, quasi-likelihood estimation is generally more stable than maximum likelihood estimation in the maximization of the log-likelihood.

Kupper et al. (1986) suggested that the heterogeneous intralitter correlation structure should be used to avoid bias in the estimation of dose-response parameters. However, Williams (1988) argued that by allowing the intralitter correlation to vary haphazardly from group to group the estimates of dose-response risks may not be reliable. In the two examples given in this paper, the quasi-likelihood seems to give compatible estimates even with the use of a common intralitter correlation across all groups. In addition, the computation under the homogeneous assumption is much faster and more stable than under the heterogeneous assumption. Alternately, the intralitter correlation parameters may be assumed to be smoothly related to dose (Prentice (1986), McCullagh and Nelder (1989, Ch.10)).

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