Mixed model for binary observations

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Summary

The problem of testing the equality of two treatments on basis of replicated binary observations is considered. Models for replicated binary observations are proposed and used in construction of a mixed model for the given experimental design. Tests derived from versions of the mixed model are exemplified.

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1. Introduction

In a clinical trial the effects of two drugs are to be compared. Each drug is administered m times to each of n patients. After every administration the presence or absence of the drug effect is observed. Denote by X_{ijk} the response of the i-th patient (i = 1,...,n) to the j-th presentation (j = 1,...,m) of a drug k(k = 1,2); X_{ijk} equals one if the drug effect is observed and zero in the opposite

right square one of the analyse free is observed and zero in the opposite case. In Table 1 results of a trial with n = 7 and m = 4 are summarized (replacing a subcript by a plus-sign means summation with respect to that subscript).

patient i	drug 1 ×i+1	drug 2 × ₁₊₂	× _{i++}
1	4	3	7
2	4	2	6
3	• 4	1	5
4	3	0	3
5	2	2	4
6	2	1	3
7	1	3	4

Table 1. Results of drug comparison trial with n = 7, m = 4.

Let $x_{(i)} = (x_{i11}, x_{i12}, \dots, x_{im2})$ denote the observations from the i-th patient. The vectors $x_{(1)}, \dots, x_{(n)}$ are to be considered as independently and identically distributed; order effects of drug administration are assumed to be absent.

Let $p_k = P(X_{ijk} = 1)$. In this paper we derive tests of the nullhypothesis of no_difference between the two drugs, H_0 : $p_1 = p_2$, against the alternative H_1 : $p_1 > p_2$.

In Section 3 we propose models for the above described experimental design and solve the testing problem within these models. The proposed models allow, in analogy with mixed models of analysis of variance, the components of $X_{(i)}$ to be possibly dependent. The dependence structure is introduced by using models for dependent binary replications as proposed in Section 2.

2. Models for dependent binary replications

For the purpose of this section let $X = (X_1, \ldots, X_m)$ be a random vector with zero-one components. The vector X is to be considered as a vector of replications so that the probability distribution of X should be invariant under permutations of the components of X. From this it follows that $P(X = x) = P(X_1 = x_1, \ldots, X_m = x_m)$ has to be constant for all vectors x with the same value of Σx_1 .

Crowder (1978) used the beta-binomial distribution for modelling the variability among replications in a factorial design. When employed in the present context this distribution leads to

$$P(X = x, \Sigma x_{i} = r) = \frac{\prod_{i=1}^{r} (\gamma.\pi + i-1) \cdot \prod_{i=1}^{m-r} (\gamma(1-\pi) + i-1)}{\prod_{i=1}^{m} (\gamma + i-1)}$$
(1)

where $\gamma > 0$ and $0 < \pi < 1$ are the model parameters.

We propose the following general model for the probability distribution of X

$$P(X = x, \Sigma x_{i} = r) = C.exp \left\{ \sum_{s=0}^{m} \alpha_{s}.\delta(s,r) \right\}$$
(2)

where $\alpha_0 = 0$; $\delta(i,j)$ equals one if i = j and zero otherwise; $\alpha_1, \ldots, \alpha_m$ are parameters of the model and C is a normalizing constant,

$$C = 1/\{\sum_{s=0}^{m} {m \choose s} \exp (\alpha_s)\}.$$

The model is general, because the number of model parameters equals to the number of possible outcomes of ΣX_3 .

A more parsimonious version of (2) is given by

$$P(X = x, \Sigma x_{i} = r) = C.exp \{\alpha_{1}.r + h(r)\}$$
 (3)

where α_1 and α_2 are parameters of the model, C is a normalizing constant and h(.) is a suitably chosen non-linear function, for example

$$h(\Sigma x_{i}) = (\Sigma x_{i})(\Sigma x_{i}^{-1})/2 = \sum_{i < j} X_{i} X_{j}.$$
(4)

With n(.) defined by (4) the model (3) is equivalent to

$$P(X_{m} = x_{m} | X_{1}, \dots, X_{m-1}) = \frac{\exp \{x_{m}(\alpha_{1} + \alpha_{2} \sum_{i=1}^{m-1} X_{i})\}}{1 + \exp\{\alpha_{1} + \alpha_{2} \sum_{i=1}^{m-1} X_{i}\}},$$

a linear model for conditional probabilities on the logistic scale; note that this model is formally the multivariate normal density function with a binary argument vector.

In both two-parameter models (1) and (3) the independence of vector components is controlled by one parameter. The components of X are independent if $\gamma \rightarrow \infty$ under (1) and if $\alpha_2 = 0$ under (3); in that case is ΣX_i binomially distributed. The marginal distributions obtained from any of the above models depend on m and are analytically complicated for models (2) and (3). The models (2) and (3) belong to the exponential family of distributions and allow simple sufficient statistics, unlike the model (1). For reasons of mathematical comfort we propose to use the models (2) and (3) of modelling the probability distribution of replicated binary observations.

3. Mixed models for binary observations

In analogy with standard mixed models a model for a probability distribution of the vector $x_{(i)}$ of Section 1 should include drug and patient effects. Random patient effects can be modelled by imposing one of the replication structures of Section 2 on all 2.m components of the vector $X_{(i)}$. The probability of observing a certain drug effect should be a monotone function of the "true" difference between the two drugs. These demands are met in following two models:

$$P(X_{(i)} = x_{(i)}) = C.exp \left\{ \sum_{k=1}^{2} \sum_{s=0}^{m} \alpha_{s} \cdot \delta(s, x_{i+k}) + \sum_{s=0}^{2m} \beta_{s} \cdot \delta(s, x_{i+k}) + \right\}$$

+
$$a(g(x_{i+1}) - g(x_{i+2})))$$
, (5)

$$P(X_{(i)} = x_{(i)}) = C.exp \left\{ \sum_{k=1}^{2} (\alpha_1 x_{i+k} + \alpha_2 x_{i+k}^2) + \beta_1 x_{i+i} + \beta_2 x_{i+i}^2 + a(g(x_{i+1}) - g(x_{i+2})) \right\},$$
(6)

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where C is a normalizing constant, a is a drug difference parameter, g(.) is a suitably chosen function defining the scale on which the drug difference enters the model, for example g(x) = x or g(x) = log(x+1) and { α_s }, { β_s } are parameters controlling dependence among replications. The parameters { β_s } control dependence among all 2m observations from one patient and may be interpreted as due to random patient effects. The parameters { α_s } control dependence among m replications on each drug and thus represent patient-drug interactions. The model (5) employs the replication structure (2), the model that given by (3) and (4).

The testing problem of Section 1 now becomes that of testing $H_0:a = 0$ against $H_1:a > 0$. Writing down the probability function of the entire sample $X_{(1)}, \ldots, X_{(n)}$ standard theory (Lehmann (1959)) leads to the uniformly most powerful test among all unbiased tests. Let $V = \Sigma(g(X_{i+1}) - g(X_{i+2})),$ $A_s = \Sigma \Sigma \delta(s, X_{i+k}), s = 0,1,\ldots, m,$ k i

$$B_{s} = \Sigma \delta(s, X_{i++}), s = 0, 1, ..., 2m,$$

$$Z_1 = X_{+++} = \Sigma s A_s = \Sigma s B_s,$$

$$Z_2 = \sum_{i k} \sum_{k=1}^{\infty} X_{i+k} = \sum_{k=1}^{\infty} A_k$$

$$Z_3 = \sum_{i} X_{i++}^2 = \sum_{i} S^2 B_s$$

Let v denote the value of V realized in the experiment. The critical level of significance obtained with the optimal test is determined as

$$P(V \ge v | \{A_{s}\}, \{B_{s}\}, a = 0)$$
 and
 $P(V \ge v | Z_{1}, Z_{2}, Z_{3}, a = 0)$

under the model (5) respectively the model (6). To perform the test one has to find the number n_s of vectors $x = \{x_{ijk}\}$ with fixed observed values of statistics S used in conditioning and to determine the number $n_{v,s}$ of the vectors x with fixed S and with V $\geq v$. Then

$$P(V \ge v | S, a = 0) = n_{V,S}/n_{S}$$

Consider the models (5) and (6) with the parameters $\{\alpha_s\}$ respectively the parameter α_2 set to zero. These are models without patient-drug interactions. Under both these models the test of H_0 is obtained in a similar way as above. The test under the reduced model (5) is readily performed. With the choice g(x) = x the conditional distribution of v is under H_0 that of a sum of n independent hypergeometric random variables and can be approximated by the normal distribution. Cox (1966) derived this test from fixed-effects logistic model.

The model (5) contains under H₀ 3m-1 independent parameters, the reduced model (5) with { α_s } absent 2m independent parameters. As there are 2m binary observations from one patient the test of H₀ is impossible with one patient only under the model (5). Under the reduced model (5) such test -the Fisher's exact test for a two by two table- is possible and its power can be made arbitrarily high by increasing the number of replications m.

4. Numerical example

In this section we apply tests derived in the preceding section to data of Table 1. The tests considered are those derived from the following models with g(x) = x:

1. Reduced model (5), that is model (5) with $\{\alpha_{c}\}$ omitted.

2. Reduced model (6), that is model (6) with α_p omitted.

- 3. Model (5).
- 4. Model (6).

From Table 1 we find v = $x_{i+1} - x_{i+2} = 8$, $z_1 = x_{i+1} = 32$, $z_2 = \Sigma\Sigma x_{i+k}^2 = 96$, $z_3 = \Sigma x_{i+1}^2 = 160$, $(A_0, \dots, A_4) = (1,3,4,3,3)$, $(B_0, \dots, B_8) = (0,0,0,2,2,1,1,1,0)$. Computations lead to critical levels of significance as summarized in Table 2.

model	critical level of significance
reduced (5)	0.0142 (normal approx. 0.0154)
reduced (6)	0.0142
(5)	0.1007
(6)	0.0978

Table 2. lest results under different models

Under the reduced model (5) only $\{B_s\}$ are used in conditioning. Thus values of $\{x_{i++}\}$ are fixed to permutations of those in Table 1. The computations involve independent hypergeometric variables. Under the reduced model (6) values of $\{x_{i++}\}$ are restricted by fixed value of $z_3 = \Sigma x_{i++}^2$. There are 112 distinct vectors $\{B_s\}$ with the given value z_3 . For each of these possibilities the calculations as under the reduced model (5) were performed and combined to the value given (the critical levels lie between 0.01407 and 0.01431). We remark that under the reduced model (5) the $B_0 + B_8$ patients with either absence of any response or with complete response are not employed while they are employed under the reduced model (6). The enumerating algorithm is more involved under models (5) and (6).

5. Discussion and conclusions

For the testing problem of Section 1 specific tests are derived in Section 3 and exemplified in Section 4. The tests are based on different specifications of proposed models for mixed-model experimental design with binary observations (other specifications and thus other tests being clearly possible). The exemplified tests correspond to mixed models (5) and (6) and to reduced models (5) and (6). Under the genuine mixed models (5) and (6) the test of H_0 is impossible unless the data provide information on between patient variation. This type of models is clearly warranted if generalization to patient population is aimed at. The numerical example shows that if an unproper model is used the significance level can be substantially biased. This fact is of course known in the classical mixed model analysis of variance.

Valid ad hoc tests for our problem are readily obtained. Examples are the permutational paired Student's t-test or the signed rank test, both applied to pairs (x_{i+1}, x_{i+2}) , i = 1, ..., n. These tests employ in general smaller (conditional) sample space than the tests derived under models (5) and (6) and are also bounded to be less powerful under these models. The computational burden of the tests derived in Section 3 is however larger than that of the mentioned ad hoc tests.

The type of models proposed in Section 2 and 3 is flexible enough to be useful in some other experimental designs as well. Number of problems in constructing tractable models for binary observations however remains to be solved. For example one would like to have simple models allowing different numbers of dependent binary replications within each patient.

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References

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