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SUMMARY

Wald statistics are proposed as alternatives to test for the Hardy-Weinberg equilibrium in some genetic systems. Such statistics are asymptotically equivalent to Pearson's χ^2 statistics and in many cases are computationally simpler, since they do not require the calculation of the restricted maximum likelihood estimates of the gene frequencies. The proposed technique is illustrated through examples involving the MN and ABO blood classification systems. Although the required calculations may be easily performed on a pocket calculator, indication for the use of a categorical data computer subroutine (GENCAT) is provided.

Key words and phrases: Wald statistics, Hardy-Weinberg law, ABO blood group.

1. INTRODUCTION

Consider a genetic system with r condominant alleles, $A_1,\ldots,A_r$ in a single locus; let q_i, $i=1,\ldots,r$, $\sum_{i=1}^{r} q_i=1$ denote the corresponding probabilities of ocurrence in a given population. The system is said to be in Hardy-Weinberg equilibrium if the $\binom{r+1}{2}$ genotypes A_iA_j, $i,j=1,\ldots,r$, $j\geq i$ occur with probabilities

$$p_{ij} = \begin{cases} q_i^2 & \text{if } i=j \\ 2q_iq_j & \text{if } j>i \end{cases} \qquad (1)$$

A problem of general concern to geneticists is to test whether a given population satisfies the Hardy-Weinberg equilibrium conditions based on the evidence provided by a sample of n observational units for which the observed genotype frequencies are n_{ij}, $i,j=1,\ldots,r$, $j\geq i$. Among the available test statistics, the most frequently used are Pearson's χ^2 criterion for large samples (see Li(1976) for example) and a few variations of Fisher's exact test for small samples (see, Chapco(1976) or Elston and Forthofer (1977), for example). More recently, a Bayesian test was suggested by Pereira and Rogatko (1984) for some special cases.

In situations where dominance relations are present the Hardy-Weinberg equilibrium hypothesis no longer corresponds to (1) and depends on the specific dominance patterns. For example, in the ABO blood group classification system, where the O allele is recessive and the A and B alleles are codominant the relations are:

$$\begin{aligned} p_O &= q_O^2 \\ p_A &= q_A^2 + 2q_Oq_A \\ p_B &= q_B^2 + 2q_Oq_B \\ p_{AB} &= 2q_Aq_B \end{aligned} \qquad (2)$$

where q_A, q_B and q_O are the probabilities of occurence of the A,B and O alleles, respectively and p_O, p_A, p_B and p_{AB} correspond to the probabilities of the OO,(AA,AO), (BB,BO) and AB phenotypes respectively. Tests of the hypothesis (2) may be conducted via the same statistics mentioned above, although the corresponding computational aspects are fairly more complicated. In particular, it involves iterative procedures to obtain the maximum likelihood estimates of q_O, q_A and q_B required for Pearson's χ^2 statistic (see Rao (1973, p.370), for example).

In this paper we propose an alternative test statistic for Hardy-Weinberg equilibrium hypothesis which is asymptotically equivalent to Pearson's χ^2 statistic and avoids the computation of the restricted maximum likelihood estimates of the gene frequencies. In Section 2 we outline the rationale for the proposed test and comment on its asymptotic properties. In Section 3 we illustrate the application of the technique with numerical examples from the literature, indicating how to use a computer package for the analysis of categorical data to perform the calculations.

2. THE PROPOSED TEST PROCEDURE AND ITS ASYMPTOTIC PROPERTIES

Consider initially a genetic system with r condominant alle les in a single locus. Let $\underset{\sim}{p}=(p_{11},p_{12},\ldots,p_{1r},p_{22},\ldots,p_{2r},\ldots,p_{rr})'$ denote the r(r+1)/2 vector of genotype probabilities and $\underset{\sim}{n}=(n_{11},n_{12},\ldots,n_{1r},n_{22},\ldots,n_{2r},\ldots,n_{rr})'$ the r(r+1)/2 vector of observed genotype frequencies which follows the multinomial distribution:

$$P\{\underset{\sim}{n}\} = n! \prod_{j\geq i} \frac{p_{ij}^{n_{ij}}}{n_{ij}!}$$

It can be easily shown that the r(r+1)/2 relations in (1) are equivalent to the following r(r-1)/2 ones:

$$p_{ij}^2 = 4p_{ii}p_{jj} \;,\; i,j=1,\ldots,r,j>i \qquad (3)$$

Then, letting $\underset{\sim}{F}(\underset{\sim}{p})$ be a r(r-1)/2 vector valued function for which the $(ij)^{th}$ element, j>i is $p_{ij}^2-4p_{ii}p_{jj}$ it follows that the Hardy-Weinberg equilibrium hypothesis (1) may be written as:

$$\underset{\sim}{F}(\underset{\sim}{p}) = \underset{\sim}{0} \qquad (4)$$

If the p_{ij}'s are sufficiently large it follows by Central Limit Theory that $\hat{\underset{\sim}{p}}=\underset{\sim}{n}/n$ has an asymptotic multinormal distribution with mean vector $\underset{\sim}{p}$ and covariance matrix $\underset{\sim}{V}(\underset{\sim}{p})=n^{-1}(\underset{\sim}{D}_{\underset{\sim}{p}}-\underset{\sim}{p}\underset{\sim}{p}')$ where $\underset{\sim}{D}_{\underset{\sim}{p}}$ is a diagonal matrix with the elements of $\underset{\sim}{p}$ along the main diagonal. As indicated in Bhapkar (1966), a Wald statistic to test (4) is given by:

$$Q = \underset{\sim}{F}(\hat{\underset{\sim}{p}})'\left[\underset{\sim}{V}_{\underset{\sim}{F}}(\hat{\underset{\sim}{p}})\right]^{-1}\underset{\sim}{F}(\hat{\underset{\sim}{p}}) \qquad (5)$$

where $\underset{\sim}{V}_{\underset{\sim}{F}}(\hat{\underset{\sim}{p}})$ is a consistent estimate of the asymptotic covariance ma trix of $\underset{\sim}{F}(\hat{p})$, say $V_F(\underset{\sim}{p})$. Using Taylor series methods, it can be shown that $V_F(\underset{\sim}{p}) = \underset{\sim}{H}(\underset{\sim}{p})\underset{\sim}{V}(\underset{\sim}{p})\underset{\sim}{H}'(\underset{\sim}{p})$, where $\underset{\sim}{H}(\underset{\sim}{p}) = \left[\frac{\partial F(\underset{\sim}{z})}{\partial \underset{\sim}{z}}\Big|_{\underset{\sim}{z}=\underset{\sim}{p}}\right]$. Under the hypothesis (4) the statistic Q follows an asymptotic χ^2 distribution with r(r-1)/2 degrees of freedom. Bhapkar (1966) demonstrated that Q is algebraically identical to Neyman's minimum χ^2 statistic and thus shares the same asymptotic optimality properties of Pearson's χ^2 statistic or Wilks' likelihood ratio criterion.

Consider, for example, the MN blood group classification system. The Hardy-Weinberg equilibrium hypothesis in this case, corresponds to $p_{MN}^2 = 4p_M p_N$, where p_M, p_{MN} and p_N denote the probabilities of the M, MN and N genotypes, respectively. Taking $F(\underset{\sim}{p}) = p_{MN}^2 - 4p_M p_N$ where $\underset{\sim}{p} = (p_M, p_{MN}, p_N)'$ we obtain

$\underset{\sim}{H}(\underset{\sim}{p}) = 2\,(-2p_N,\ p_{MN}, -2p_M)$ and the Wald statistic (5) reduces to:

$$Q = \frac{n(\hat{p}_{MN}^2 - 4\hat{p}_M\hat{p}_N)^2}{16\hat{p}_M\hat{p}_N\left[(\hat{p}_M+\hat{p}_N) - 4\hat{p}_M\hat{p}_N + 2\hat{p}_{MN}^2\right] + 4\hat{p}_{MN}^3(1-\hat{p}_{MN})} \qquad (6)$$

where $\hat{p}_M$, $\hat{p}_{MN}$ and $\hat{p}_N$ correspond to the observed proportions of genotypes M, MN and N respectively. Under the null hypothesis, Q follows an asymptotic χ^2 distribution with 1 degree of freedom.

From (5) it is clear that the proposed procedure does not require the computation of restricted maximum likelihood estimates ; therefore it is of special interest in cases where such computations involve elaborate procedures. This is generally the situation when dominance relations are present, as in the ABO blood group classification system, which we consider next. First note that (2) is equivalent to:

$$(p_A+p_O)(p_B+p_O) = (p_{AB}/2+\sqrt{p_O})^2 \tag{7}$$

(an outline of the proof is indicated in the appendix). Now, following Bhapkar (1966), a test of (7) can be undertaken via a Wald statistic of the form (5) where $\hat{p}=(\hat{p}_A,\hat{p}_B,\hat{p}_O,\hat{p}_{AB})'$ is the vector of observed phenotype proportions and $F(p)=(p_A+p_O)(p_B+p_O)-(p_{AB}/2+\sqrt{p_O})^2$. Since here $H(\hat{p})=(A,B,C,D)$ with $A=\hat{p}_B+\hat{p}_O$, $B=\hat{p}_A+\hat{p}_O$, $C=\hat{p}_O-\hat{p}_{AB}-\hat{p}_{AB}/2\sqrt{\hat{p}_O}$ and $D=-(\hat{p}_{AB}/2+\sqrt{\hat{p}_O})$ it follows that (5) reduces to:

$$Q = \frac{n\{AB - D^2\}^2}{A^2\hat{p}_A+B^2\hat{p}_B+C^2\hat{p}_O+D^2\hat{p}_{AB}-E^2} \tag{8}$$

where $E=A\hat{p}_A+B\hat{p}_B+C\hat{p}_O+D\hat{p}_{AB}$. Under the null hypothesis Q follows an asymptotic χ^2 distribution with 1 degree of freedom.

3. NUMERICAL ILLUSTRATION

Here we compare the observed values of the Wald statistics (6) and (8) with the corresponding Pearson χ^2 statistics for sets of MN and ABO blood group classification data obtained from the literature. Results are indicated in Table 1; in all cases there was close agreement between the two statistics.

Table 1

Observed values of Wald and Pearson χ^2 statistics for Hardy-Weinberg equilibrium tests in MN and ABO blood group classification datasets.

Source	Observed phenotype frequencies	Wald statistic	Pearson χ^2 statistic
Crow(1950,p.154)	n_M=137; n_{MN}=196; n_N=87	1.19(P=0.275)	1.22(P=0.269)
Crow and Kimura (1970,p.36)	n_M=362; n_{MN}=634; n_N=282	0.027(P=0.869)	0.029(P=0.865)
Rao(1973,p.402)	n_A=120; n_B=79; n_O=121; n_{AB}=33	0.412(P=0.521)	0.44(P=0.507)
Rao(1973,p.402)	n_A=95; n_B=121; n_O=118; n_{AB}=30	0.367(P=0.544)	0.35(P=0.554)
Elandt-Johnson (1971,p.401)	n_A=725; n_B=258; n_O=1073; n_{AB}=72	0.0001293(P=1.000)	0.0001293(P=1.000)

Although the observed values of the above Wald statistics may be easily obtained by hand, it is possible to carry out the calculations via appropriate computer software. This is particularly attractive in cases where either $\underset{\sim}{V}_F(\underset{\sim}{p})$ is a matrix or the corresponding expression involves cumbersome algebraic manipulation. In this direction, a convenient computer program is GENCAT (Landis et al.(1976)). Among other capabilities related to the analysis of categorical data, it provides estimates of asymptotic covariance matrices of functions of the parameters of multinomial distributions. Essentially, the partial derivatives $\underset{\sim}{H}(\underset{\sim}{p})$ are computed as a product of standard terms via the "chain rule" for functions which may be expressed as compositions of linear, logarithmic and exponential operations.

In the case of the MN system, we have $F(p)=A_2\exp\{A_1\log p+c\}$ where $\log(.)$ and $\exp(.)$ are the elementwise vector logarithmic and exponential operators, respectively (i.e. the i^{th} element of $\log p$ is $\log p_i$ and of $\exp p$ is $\exp p_i$), $A_1=\begin{bmatrix}0&2&0\\1&0&1\end{bmatrix}$, $c=\log 4$ and $A_2=[1\ -1]$. Thus $H(p)=A_2 D_{a_1} A_1 D_p^{-1}$ where D_x denotes a diagonal matrix with the elements of x along the main diagonal and $a_1=\exp A_1\log p$. In the case of the ABO system, we have $F(p)=A_4\exp A_3\log A_2\exp A_1\log p$ where

$$A_1=\begin{bmatrix}1&0&0&0\\0&1&0&0\\0&0&1&0\\0&0&\frac{1}{2}&1\end{bmatrix},\ A_2=\begin{bmatrix}1&0&1&0&0\\0&1&1&0&0\\0&0&0&\frac{1}{2}&1\end{bmatrix},\ A_3=\begin{bmatrix}1&1&0\\0&0&2\end{bmatrix}\ \text{and}\ A_4=[1\ -1],$$

Here, $H(p)=A_4D_{a_3}D_{a_2}^{-1}A_2D_{a_1}A_1D_p^{-1}$ where $a_1=\exp A_1\log p$, $a_2=A_2\exp A_1\log p$ and $a_3=A_3\log A_2\exp A_1\log p$.

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APPENDIX

We present here a short proof of the following fact:

If p_A, p_B, p_O and p_{AB} are nonnegative real numbers satisfying (7) and

$$p_A+p_B+p_O+p_{AB} = 1 \qquad (9)$$

then the real numbers $q_O=\sqrt{p_O}$, $q_A=\sqrt{p_A+p_O} - \sqrt{p_O}$ and $q_B=\sqrt{p_B+p_O} - \sqrt{p_O}$ are nonnegative and satisfy both (2) and

$$q_A+q_B+q_O = 1 \qquad (10)$$

Proof: A simple calculation shows that the first three relations in (2) are verified. Expressing $x=q_O+q_A+q_B$ in terms of p_A, p_B, p_O and p_{AB} we obtain $\sqrt{p_A+p_O} + \sqrt{p_B+p_O} = x+\sqrt{p_O}$. Squaring both members we get:

$$2\sqrt{(p_A+p_O)(p_B+p_O)} = x^2+2x\sqrt{p_O} - p_O-p_A-p_B \qquad (11)$$

Also, from (7) and (9) we get:

$$2\sqrt{(p_A+p_O)(p_B+p_O)} = 1-p_A-p_B-p_O+2\sqrt{p_O} \qquad (12)$$

From (11) and (12) it follows that x must be a solution of the quadratic equation:

$$x^2+2x\sqrt{p_O} - (1+2\sqrt{p_O}) = 0 \qquad (13)$$

Since such equation has 1 as its unique positive solution (10) follows The last relation in (2) is a consequence of (7), (9) and (10).

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