Order-restricted Scores Test for the Evaluation of Population-based Case-control Studies when the Genetic Model is Unknown

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Abstract

Objective: The Cochran-Armitage linear trend test for proportions is commonly used for genotype-based analysis of candidate gene association. Depending on the underlying genetic mode of inheritance, the use of model-specific scores maximises the power. Commonly, the underlying genetic model, i.e., additive, dominant or recessive mode of inheritance, is a priori unknown. Permutation tests for the analysis of association studies appropriate for both inference and identification of the underlying mode of inheritance are suggested.

Methods: Maximum tests using standardised Cochran-Armitage tests having power under all three models have been proposed for case-control studies. We reformulate the problem and propose a conditional maximum test of scores-specific linear-by-linear association tests. For both maximum-type and quadratic test statistics the asymptotic expectation and covariance can be derived in a closed form and the limiting distribution is known.

Results: We extend the area of application to stratified designs, studies involving more than two groups and the simultaneous analysis of multiple loci by means of multiplicity-adjusted p-values for the underlying multiple Cochran-Armitage trend tests. The new test is applied to reanalyse a study investigating genetic components of different subtypes of psoriasis.

Conclusion: A new and flexible inference tool for association studies is available both theoretically as well as practically since already available software packages can be easily used to implement the suggested test procedures.

1 Objectives

In population-based case-control studies the association between a candidate allele and a disease can be evaluated by the Cochran-Armitage (CA) trend test [1], regardless of whether or not Hardy-Weinberg equilibrium holds [8]. The CA test is based on a set of scores assigned to the alleles. For genotypes aa, Aa, or AA, with A denoting a high risk candidate allele and a any of the other alleles, three-dimensional scores vectors optimising the power of the CA test against dominant, additive, and recessive alternatives can be defined. Thus, if the underlying mode of inheritance is known, the choice of an appropriate score vector and thus trend test test is obvious. However, in situations where the underlying genetic model is unknown choosing the 'wrong' score vector leads to a substantial loss of power as shown by Freidlin et al. [2]. Consequently, inference procedures with good power under *all* three genetic models are of special interest. An intuitive idea is to construct a test based on all three possible trend tests, for example utilising the maximum of the standardised test statistics of the CA tests which are optimal under the dominant, additive, and recessive model. Actually, such a test was proposed and investigated by Freidlin et al. [2]. The distribution of this maximum test, called MAX test hereafter, under the null hypothesis of equal genotype distribution in cases and controls is approximated by simulation procedures by Freidlin et al. [2] since the unconditional asymptotic distribution is hard to derive.

Table 1: Genotype distributions for cases and controls.

	Cases	Controls	Total
aa	r_{aa}	s_{aa}	n_{aa}
aA	r_{aA}	s_{aA}	n_{aA}
AA	r_{AA}	s_{AA}	n_{AA}
Total	R	S	N

In this paper, we embed the MAX test as suggested by Freidlin et al. [2] into a flexible framework for conditional independence tests introduced by Strasser and Weber [11]. The merits of doing so are i) the distribution for the MAX test can be easily approximated by a three-dimensional normal distribution, ii) tests for stratified designs, designs with more than two groups and to multiple loci can be defined in a rather straightforward way, ii) the most likely underlying mode of inheritance can be 'estimated' by multiplicity-adjusted p-values for the three CA statistics under test, and iv) the analysis of genetic association studies using the MAX test and its newly introduced extension can be performed by already available software implementations of the Strasser and Weber [11] framework.

2 Methods

2.1 Maximum Test

For case-control studies on candidate gene association the data are typically given by the empirical genotype distribution in both groups. For a simple bi-allelic marker the data can be presented in a 3×2 contingency table, where A is the high risk candidate allele and a is any of the other alleles (see Table 1).

We are interested in a comparison of the genotype distributions of cases and controls, i.e., the probabilities $p_j = P(\text{case has genotype } j)$ and $q_j = P(\text{control has genotype } j)$ for $j \in \{aa, aA, AA\}$, especially in procedures with power against ordered alternatives:

$$H_0 : p_j = q_j \text{ vs. } H_1 : p_j < q_j \quad \text{for } j \in \{aa, aA, AA\}.$$

The CA test statistic with scores $\xi = (\xi_{aa}, \xi_{aA}, \xi_{AA})$ basically (modulo standardisation) reads

$$\text{CA}(\xi) = \sum_{j \in \{aa, aA, AA\}} \xi_j r_j. \tag{1}$$

If the mode of inheritance is best described by the dominant model, the scores $\xi_{\text{dom}} = (0, 1, 1)$ (genotype aa vs. aA and AA) will lead to a trend test with maximal power. Under the recessive model the score vector $\xi_{\text{rec}} = (0, 0, 1)$ (aa and aA vs. AA) is power optimal whereas a linear trend represented by scores $\xi_{\text{add}} = (0, 1, 2)$ should be chosen when the

Table 2: Genotype distribution reformulated.

i	$\mathbf{Y}_i$	$\mathbf{X}_i$	w_i	$h(\mathbf{Y}_i)$	$g_{\text{add}}(\mathbf{X}_i)$	$g_{\text{dom}}(\mathbf{X}_i)$	$g_{\text{rec}}(\mathbf{X}_i)$
1	Case	aa	r_{aa}	1	0	0	0
2	Case	Aa	r_{aA}	1	1	1	0
3	Case	AA	r_{AA}	1	2	1	1
4	Control	aa	s_{aa}	0	0	0	0
5	Control	Aa	s_{aA}	0	1	1	0
6	Control	AA	s_{AA}	0	2	1	1

mode if inheritance is additive [8, 10]. However, the underlying genetic model is rarely known *a priori*. Motivated by the problem of choosing the 'right' score vector, Freidlin et al. [2] proposed the MAX test as the maximum of three standardised CA tests with scores $\xi_{\text{dom}}, \xi_{\text{add}}$, and ξ_{rec} as a global test for association. An alternative approach [14] is to introduce a parameter η for the score vector $\xi_\eta = (0, \eta, 1)$ and to choose η in a data-driven way.

In the sequel, we present the problem in a slightly different however equivalent way and embed the MAX test into a general framework for conditional inference procedures, derive its limiting distribution and propose extensions to stratified designs, more than two groups and multiple loci.

2.1.1 Reformulation of the Problem

Let $\mathbf{Y}_i$ denote the both groups (cases and controls) and $\mathbf{X}_i$ the genotype for all cells $i = 1, \ldots, n = 6$. The weights w_i represent the number of observations in each cell with total number of observations $N = \sum_i w_i$. The so-called *influence function* h provides us with a zero-one dummy coding of the groups (being one for cases and zero for controls). Moreover, three transformations g of the genotype are under test: g_{dom} assigns scores ξ_{dom} to genotypes (aa, Aa, AA), g_{add} assigns scores ξ_{add} and g_{rec} implements scores ξ_{rec}, cf. Table 2.

2.1.2 Inference Problem and Linear Statistic

We are interested in testing the null hypothesis of independence of grouping $\mathbf{Y}$ and genotype $\mathbf{X}$

$$H_0 : D(\mathbf{Y}|\mathbf{X}) = D(\mathbf{Y})$$

against ordered alternatives. First, we define a three-dimensional statistic $\mathbf{T}$, each dimension being associated with one of the scores g_{add}, g_{dom}, and g_{rec}. Each statistic is defined by the sum of the scores multiplied by the weights associated with cases, i.e., is equivalent

to the Cochran-Armitage statistic (1):

$$\mathbf{T} = (\mathbf{T}_{\text{add}}, \mathbf{T}_{\text{dom}}, \mathbf{T}_{\text{rec}}) = \sum_{i=1}^{n} w_i g(\mathbf{X}_i) h(\mathbf{Y}_i) \in \mathbb{R}^3 \tag{2}$$

with $g(\mathbf{X}_i) = (g_{\text{add}}(\mathbf{X}_i), g_{\text{dom}}(\mathbf{X}_i), g_{\text{rec}}(\mathbf{X}_i))$. Thus, the three-dimensional linear statistic $\mathbf{T}$ is the vector of the unstandardised Cochran-Armitage statistics $(\text{CA}(\xi_{\text{dom}}), \text{CA}(\xi_{\text{add}}), \text{CA}(\xi_{\text{rec}}))$ for the dominant, additive, and recessive model.

2.1.3 Conditional Expectation and Covariance

The distribution of $\mathbf{T}$ depends on the joint distribution of $\mathbf{Y}$ and $\mathbf{X}$, which is unknown under almost all practical circumstances. At least under the null hypothesis one can dispose of this dependency by fixing the genotypes and conditioning on all possible permutations of the groups. This principle leads to test procedures known as *permutation tests*. Strasser and Weber [11] derived closed-form expressions for the conditional expectation $\mu \in \mathbb{R}^{pq}$ and covariance $\Sigma \in \mathbb{R}^{3\times 3}$ of $\mathbf{T}$ under H_0 given all permutations of the groupings.

The conditional expectation of the influence function h is

$$\mathbb{E}(h) = N^{-1} \sum_i w_i h(\mathbf{Y}_i) \in \mathbb{R}$$

with corresponding variance

$$\mathbb{V}(h) = N^{-1} \sum_i w_i \left(h(\mathbf{Y}_i) - \mathbb{E}(h)\right)^2$$

The conditional expectation of the linear statistic $\mathbf{T}$ is

$$\begin{aligned}
\mu &= \mathbb{E}(\mathbf{T}) = \mathbb{E}(h) \sum_{i=1}^{n} w_i g(\mathbf{X}_i), \\
\Sigma &= \mathbb{V}(\mathbf{T}) \\
&= \frac{N}{N-1} \mathbb{V}(h) \times \left(\sum_i w_i \left(g(\mathbf{X}_i) g(\mathbf{X}_i)^\top \right) \right) \\
&- \frac{1}{N-1} \mathbb{V}(h) \times \left(\sum_i w_i g(\mathbf{X}_i) \right) \left(\sum_i w_i g(\mathbf{X}_i) \right)^\top .
\end{aligned} \tag{3}$$

The three-dimensional expectation μ and the three diagonal elements of the covariance matrix Σ contain the mean and the variances for the additive, dominant and recessive (unstandardised) Cochran-Armitage statistics under H_0, as given in (1) and (2), respectively.

Note that the complete covariance structure, and thus the correlation between the elements of the three-dimensional statistic $\mathbf{T}$ is known and can be computed for the data at hand. The corresponding correlation matrix coincides with the correlations obtained for the three CA test statistics by Freidlin et al. [2].

2.1.4 Test Statistics

Based on the three-dimensional statistic $\mathbf{T}$ and its expectation μ and covariance matrix Σ, we can easily construct test statistics and derive their distribution under the conditions described in the null hypothesis. As the number of observations N tends to infinity, Strasser and Weber [11] proved that the limiting distribution of the three-dimensional statistic $\mathbf{T}$ is a three-dimensional normal distribution with expectation μ and covariance Σ. Thus, the asymptotic distribution of a maximum-type statistic

$$c_{\max}(\mathbf{T}, \mu, \Sigma) = \max \left| \frac{\mathbf{T} - \mu}{\mathrm{diag}(\Sigma)^{1/2}} \right|$$

can be evaluated by computing three-dimensional normal probabilities. Alternatively, a quadratic form

$$c_{\mathrm{quad}}(\mathbf{T}, \mu, \Sigma) = (\mathbf{T} - \mu)^\top \Sigma^+ (\mathbf{T} - \mu)$$

follows a χ^2 distribution with two degrees of freedom. The quadratic form, which is a competitor for the MAX test statistic, reveals high power for an average alternative while the maximum-type form for a particular genetic alternative. Therefore, we focus on the maximum-type statistics, particularly because information on the elementary genetic alternative is available by multiplicity-adjusted p-values. Note that, under any circumstances, the exact conditional distribution can be approximated by conditional Monte-Carlo methods, which is especially attractive for small sample sizes N when we can't expect asymptotics to work well.

2.2 Illustration

In order to compare the above test and its implementation with the results reported by Freidlin et al. [2], we reanalyse a study on association between a variant of the epidermal growth factor (EGF) gene and malignant melanoma according to Table 3, Shahbazi et al. [9].

Table 3: Melanoma data

	In situ	Control	Total
AA	6	32	38
AG	8	47	55
GG	10	20	30
Total	24	99	123

The linear statistic $\mathbf{T}$, its conditional expectation μ and the standard deviations $\sigma = \sqrt{\mathrm{diag}(\Sigma)}$ and the corresponding standardised CA statistics are given in Table 4. In

addition, we immediately are provided with the covariance matrix

$$\Sigma = \begin{pmatrix} 4.1579 & 5.6255 & 1.4675 \\ 5.6255 & 10.6845 & 5.0590 \\ 1.4675 & 5.0590 & 3.5915 \end{pmatrix}$$

and corresponding correlation matrix

$$\text{cor}(\Sigma) = \begin{pmatrix} 1.0000 & 0.8440 & 0.3798 \\ 0.8440 & 1.0000 & 0.8167 \\ 0.3798 & 0.8167 & 1.0000 \end{pmatrix}$$

those values are rather similar to the correlations between the three different CA test statistics as reported by Freidlin et al. [2].

Table 4: MAX test for Melanoma data

	$\mathbf{T}$	μ	σ	$(\mathbf{T}-\mu)/\sigma$	p_{asympt}	$p_{\text{step-down}}$
dominant	18	16.5854	2.0391	0.6938	0.3906	0.3302
additive	28	22.4390	3.2687	1.7013	0.0868	0.0654
recessive	10	5.8537	1.8951	2.1879	0.0303	0.0359

The MAX test has a test statistic equal to 2.1879 and its asymptotic p-value is 0.0303 (the minimum of p_{asympt} in Table 4) which is roughly the same p-value as shown in Table 8 of Freidlin et al. [2]. However, this global p-value does not give any information about the underlying genetic model. Multiplicity-adjusted p-values (p_{asympt} in Table 4) for each of the dominant, additive, and recessive tests, indicate which mode of inheritance describes the data best (see Section 3.2 in addition): It seems that the recessive model is appropriate for the Melanoma data.

We might want to check whether the asymptotics work well enough in this situation. The exact conditional p-value is approximated by a conditional Monte-Carlo procedure with 49999 random permutations of the data and the corresponding step-down multiplicity-adjusted p-values [12] are given as $p_{\text{step-down}}$ in Table 4. The small differences between the asymptotic and approximated p-values indicates that using asymptotic distribution is adequate.

2.3 Generalisations

A straightforward generalisation is the consideration of $3 \times k$ tables instead of 3×2 tables, where sub-types of cases are compared with a control. For example, the genotype distribution of healthy control can be compared the genotype of cases with early and late onset of a certain disease. A score can be attached to each group, for example 1 to the control group and $-1/2$ for both the early and late onset cases leading to a linear-by-linear association

test. Alternatively, a trend in the onset of the disease can be described by scores $0, 1, 2$ for the three groups.

In stratified designs, only permutations within each stratum, gender or family history, say, are admissible; so the expectation μ and covariance Σ has to be computed separately for each stratum and is then aggregated over all possible strata.

Finally, it is interesting to consider multiple loci, i.e., multiple genotype distributions, simultaneously. For two loci, we can look at all six CA tests by defining a linear statistic $\mathbf{T}$ containing the three CA tests for the first as well as the three CA tests for the second locus. As a consequence, we can compute the complete covariance matrix and take the underlying correlations between the two loci as well as between the three genetical models into account.

2.4 Computational Details

The **coin** add-on package [3, 4] to the R system for statistical computing [6] provides an implementation of the conditional inference framework sketched in this section. The analysis of an association study by the MAX test only requires to set-up the score function g. Then, the function `independence_test` can be used to perform the MAX test and to compute multiplicity-adjusted p-values. For the Melanoma data, the most important parts of such an analysis are given in the Appendix. All analyses presented in this paper are reproducible by means of the `MAXtest` package vignette accessible from within R via

```
R> vignette("MAXtest", package = "coin")
```

3 Results

3.1 Illustration and Application

Reich et al. [7] investigate the association between psoriasis and polymorphisms of genes encoding tumor necrosis Factor-α and Interleukin-1β where for the IL1B_511 locus the related 3×2 table data are given in Table 5. A control group and two groups of affected people with early and late onset of the disease are under test. One is interested in detecting any deviation from independence of genotype distribution for both loci and the three groups in either females and / or males. Attaching scores $1, -1/2, -1/2$ to the control, early and late onset group results in a linear statistic $\mathbf{T}$ with six elements: three models for each of the two loci.

The multiplicity-adjusted p-values in Table 6 indicate that there is a strong deviation from independence for the TNFA_238 locus. The recessive model has the largest p-value and thus it is not likely that this model is true. The p-values for the dominant and the additive are extremely small, so either of these models could have generated the data. We can simultaneously reject the null hypothesis of independence between the genotype distribution of the IL1B_511 locus and the three groups. Here, the dominant model seems to explain the data best.

Table 5: Psoriasis data

IL1B_511 locus

Male		Control	Early Onset	Late Onset	Total
	CC	75	54	29	158
	CT	93	44	13	150
	TT	14	7	4	25
	Total	182	105	46	333
Female		Control	Early Onset	Late Onset	Total
	CC	76	26	17	119
	CT	69	20	10	99
	TT	18	5	2	25
	Total	163	51	29	243

TNFA_238 locus

Male		Control	Early Onset	Late Onset	Total
	GG	170	71	40	281
	GA	12	33	6	51
	AA	0	1	0	1
	Total	182	105	46	333
Female		Control	Early Onset	Late Onset	Total
	GG	146	43	24	213
	GA	17	8	5	30
	AA	0	0	0	0
	Total	163	51	29	243

Table 6: MAX test for psoriasis data: Asymptotic adjusted p-values

	TNFA_238	IL1B_511
dominant	< 0.0001	0.0407
additive	< 0.0001	0.1051
recessive	0.7241	0.9819

Our analysis improves upon the original analysis of these data by Reich et al. [7] with respect to three points: All three groups and the stratification by gender are taken into account and and the new test makes use of the correlation between the two loci instead of applying a Bonferroni correction in order to maintain an overall significance level.

3.2 Simulation Experiments

It might be questioned if the minimal p-value can be observed for the correct mode of inheritance and thus how good the 'estimator' is under practical circumstances. The frequency of correct model identifications and the power of the MAX test is investigated in some simple situations in the following.

Many different patterns of penetrances f_i, disease prevalence p, sample size of cases and controls R, S can be investigated in a simulation study. We will focus on a high prevalent disease (i.e. $p = 0.5$), penetrances according to a additive, recessive and dominant genetic model (as well as no association characterising the null hypothesis) for a total sample size of $N = 400$ divided into the balanced $R = S = 200$ and several unbalanced sampling schemes. Unbalanced data are of interest because real data examples exist with seriously more controls, see e.g. the data in Table 3, or with seriously more cases, see e.g. the IL13 polymorphism in atopic dermatitis [5], Table 4. For the proposed MAX test both the global power π_{global}(the decision rate in favour of any alternative) and the correct model identification rates ψ_{add},ψ_{rec},ψ_{dom} are compared with the power of the individual genetic model tests π_{add}, π_{rec}, π_{dom} in Table 7.

Per definition all tests control the type I error rates. Clearly, the power is maximal for the individual, unadjusted tests when the genetic model is known (bold marked). But the a priori knowledge of the genetic model is commonly unrealistic. For balanced samples sizes the power of the MAX test is independent of the underlying genetic model and non-inferior smaller compared with the maximum power for the known model. Additionally to the global decision that a significant association exists, the MAX test provide an adjusted p-value for the most likely genetic model. In this case, the identification of the additive model is most difficult because of the both equal competitors, where the identification of the dominant or recessive model is easier (and equal) because the additive model is the only competitor. For unbalanced designs the power decreases although the total sample size remains constant.

Table 7: Type I error rate and empirical power estimates: prevalence $p = 0.5$, 10000 runs

Model	R	S	π_{global}	ψ_{add}	ψ_{rec}	ψ_{dom}	π_{add}	π_{rec}	π_{dom}
Null	200	200	0.048	0.012	0.017	0.019	0.051	0.047	0.049
Dom	200	200	0.85	0.13	0.01	*0.71*	0.75	0.23	**0.91**
Add	200	200	0.84	*0.53*	0.10	0.21	**0.88**	0.71	0.78
Rec	200	200	0.86	0.16	*0.69*	0.01	0.80	**0.91**	0.28
Dom	100	300	0.72	0.16	0.01	*0.55*	0.63	0.21	**0.80**
Add	100	300	0.73	*0.43*	0.14	0.16	**0.78**	0.60	0.65
Rec	100	300	0.77	0.16	*0.60*	0.01	0.67	**0.82**	0.22
Dom	300	100	0.76	0.11	0.01	*0.64*	0.66	0.19	**0.82**
Add	300	100	0.75	*0.42*	0.09	0.24	**0.79**	0.59	0.69
Rec	300	100	0.75	0.17	*0.55*	0.01	0.69	**0.82**	0.24

4 Conclusions

We propose a flexible approach to permutation tests for association of a bi-allelic marker with a disease in population-based case-control studies. The joint conditional asymptotic distribution of the three underlying linear association tests, i.e., Cochran-Armitage tests with optimal scores for additive, dominant, and recessive modes of inheritance, is known and can be used to approximate the distribution of the corresponding maximum statistic. Not only a global p-value can be derived this way but also multiplicity-adjusted p-values for each of the individual models. When the mode of inheritance is unknown, remarkably high correct model selection rates can be achieved. Based on a general framework for conditional inference we extend the MAX test to stratified designs, $3 \times k$ tables as well as multiple endpoints, i.e., multiple loci. Correlations between loci and corresponding association tests are taken into account leading to more powerful multiple test procedure. For small sample sizes, a better approximation of the p-values can be obtained from Monte Carlo resampling techniques. The proposed procedures are easily applicable using the computational tools provided by the R add-on package **coin** as illustrated in the Appendix and a dedicated package vignette. A future modification will be the use of model-specific genomic-control corrected tests analogously to Zang et al. [13] in the possible case of population stratification.

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Appendix

The Melanoma data are be represented by a `table` object in R as follows:

```
R> me <- as.table(matrix(c( 6,  8, 10,
                   32, 47, 20), byrow = TRUE, nrow = 2,
       dimnames = list(Group = c("In situ", "Control"),
                       Genotype = c("AA", "AG", "GG"))))
R> me <- t(me)
R> me

        Group
Genotype In situ Control
      AA       6      32
      AG       8      47
      GG      10      20
```

The function g is implemented by the following function:

```
R> add <- c(0, 1, 2)
R> dom <- c(0, 1, 1)
R> rec <- c(0, 0, 1)
R> g <- function(x) {
       x <- unlist(x)
       cbind(dominant = dom[x], additive = add[x], recessive = rec[x])
   }
```

which then sets up the MAX test for the Melanoma data:

```
R> library("coin")
R> it <- independence_test(me, xtrafo = g, alternative = "greater")
R> it

        Asymptotic General Independence Test

data:  Group by Genotype (AA, AG, GG)
maxT = 2.1879, p-value = 0.03047
```

The multiplicity-adjusted p-values for both inference and estimating the underlying mode of inheritance are computed via:

```
R> pvalue(it, method = "single-step")

  dominant   additive  recessive
0.39065589 0.08686888 0.03034629
```