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Some Statistical Properties of Efficiency Robust Tests with Applications to Genetic Association Studies

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ABSTRACT. Although efficiency robust tests are preferred for genetic association studies when the genetic model is unknown, their statistical properties have been studied for different study designs separately under special situations. We study some statistical properties of the maximin efficiency robust test and a maximum-type robust test (MAX3) under a general setting and obtain unified results. The results can also be applied to testing hypothesis with a constrained two-dimensional parameter space. The results are applied to genetic association studies using case–parents trio data.

Key words: boundary, constrained parameter space, genetic studies, maximin efficiency, MAX, nuisance parameter, score test

1. Introduction

In testing the association between a genetic marker with genotypes $\{G_0, G_1, G_2\}$ and a binary trait, the null hypothesis is $H_0 : \lambda_1 = \lambda_2 = 1$, where $\lambda_i = \text{pr}(\text{case} \mid G_i)/\text{pr}(\text{case} \mid G_0)$ is a genotype relative risk (GRR) ($i = 1, 2$) by taking G_0 as the reference. There are two types of parameter space for the GRRs. $\Lambda = \{(\lambda_1, \lambda_2) : \lambda_1 \geq 0, \lambda_2 \geq 0\}$ is an unconstrained one. The null point $(1, 1)$ is an inner point of Λ. In genetic association studies, however, three common genetic models are of interest under the alternative hypothesis H_1, which are recessive, additive, and dominant if $\lambda_1 = 1$ and $\lambda_2 > 1$, $\lambda_1 = (1 + \lambda_2)/2$ and $\lambda_2 > 1$, and $\lambda_1 = \lambda_2$ and $\lambda_2 > 1$, respectively. Specifying a genetic model under H_1 reduces the number of parameters from two (λ_1, λ_2) to one (λ_2). Under H_1, without loss of generality, let j in G_j stand for the number of the risk allele in the genotype ($j = 0, 1, 2$). Here, we point out that the risk allele might not be known beforehand; the usual way is to take the allele with allele frequency less than 0.5 as a 'risk' allele and use a two-sided test. Actually, if the risk allele is given in G_2, the score test $z(\theta)$ given in (2) is positive. If the other allele is the risk allele, then $z(\theta)$ is negative. Because we make inference based on $z^2(\theta) \sim \chi^2_2$, it does not need to be known which allele has the higher risk. In this paper, we consider the genetic model in which the effect of a heterozygote lies between those of two homozygotes. Then, a constrained parameter space is more appropriate for the GRRs, denoted as $\Lambda_C = \{(\lambda_1, \lambda_2) : \lambda_2 \geq \lambda_1 \geq 1\} \subset \Lambda$, which contains the three common genetic models as special cases and also the models among them. The null point is on the boundary of Λ_C.

Let $(\lambda_1, \lambda_2) \in \Lambda$ and $(\lambda_1, \lambda_2) \neq (1, 1)$. Consider a transformation, $\lambda_2 = \lambda$ and $\lambda_1 = 1 - \theta + \theta\lambda_2 = 1 - \theta + \theta\lambda$, where $1/\theta$ is the slope between (λ_1, λ_2) and the null point, under which Λ becomes $\Lambda(\theta) = \{(\lambda, \theta) : \lambda \geq 0, \theta \in (-\infty, \infty)\}$. If we apply the transformation to Λ_C, it becomes $\Lambda_C(\theta) = \{(\lambda, \theta) : \lambda \geq 1, \theta \in [0, 1]\}$. The three common genetic models

correspond to $\theta = 0$, 1/2, and 1, respectively. For both $\Lambda(\theta)$ and $\Lambda_C(\theta)$, the null hypothesis becomes $H_0 : \lambda = 1$, under which θ is not defined. Under H_1, Λ_C has no genetic models specified, but $\Lambda_C(\theta)$ contains all scientifically plausible models for genetic association studies, indexed by $\theta \in [0, 1]$.

Denote the likelihood of the genetic data with sample size n as $L_n(\lambda_1, \lambda_2, \alpha)$ for $(\lambda_1, \lambda_2) \in \Lambda$ (or Λ_C), which also includes possible nuisance parameter α. See online supporting information (Appendices S1–S3) for various forms of $L_n(\lambda_1, \lambda_2, \alpha)$ in applications. By introducing θ, the likelihood can be written as $L_n(1-\theta+\theta\lambda, \lambda, \alpha)$ for $(\lambda, \theta) \in \Lambda(\theta)$ (or $\Lambda_C(\theta)$). Testing $H_0 : \lambda_1 = \lambda_2 = 1$ with $\text{Ł}_n(\lambda_1, \lambda_2, \alpha)$ is quite different from testing $H_0 : \lambda = 1$ with $L_n(1 - \theta + \theta\lambda, \lambda, \alpha)$. The latter needs to specify θ. If θ can be correctly specified, the score test based on $\Lambda(\theta)$ (or $\Lambda_C(\theta)$) is asymptotically most powerful and more powerful than the score test based on Λ (or Λ_C) (Sasieni, 1997; Zheng *et al.*, 2003, 2006, 2009a, 2012).

In practice, the true genetic model is rarely known and often misspecified. Pearson's chi-squared test can be obtained as the score test for $H_0 : \lambda_1 = \lambda_2 = 1$ with $L_n(\lambda_1, \lambda_2, \alpha)$ for $(\lambda_1, \lambda_2) \in \Lambda$, which follows asymptotically χ^2_2 under H_0, where χ^2_k is a chi-squared distribution with k degrees of freedom. On the other hand, the trend test assuming the additive model can be obtained as the score test for $H_0 : \lambda = 1$ with $L_n((1 + \lambda)/2, \lambda, \alpha)$. It follows asymptotically that χ^2_1 under H_0. When θ is correctly specified, the trend test is more powerful than Pearson's test. However, when the true model cannot be specified correctly and each model of $\Lambda_C(\theta)$ is scientifically plausible, Pearson's test is more efficiency robust than the trend test in the sense that the lowest power of Pearson's test across all models in $\Lambda_C(\theta)$ is higher than that of the trend test. A definition of efficiency robustness is given in Section 2.

The performance of the preceding trend test and Pearson's test depends on which genetic model in $\Lambda_C(\theta)$ is true. When θ is known, denote the score test for $H_0 : \lambda = 1$ with $L_n(1 - \theta + \theta\lambda, \lambda, \alpha)$ for $(\lambda, \theta) \in \Lambda_C(\theta)$ as $z(\theta)$ (Section 3.2). When θ is unknown, we consider a family of score tests $T_0 = \{z(\theta) : \theta \in [0, 1]\}$. Although Pearson's test is more efficiency robust than $z(\theta)$ when θ is misspecified, two other types of robust tests, the maximin efficiency robust test (MERT) (Gastwirth, 1966, 1985) and MAX3 or MAX (Freidlin *et al.*, 2002; Zheng *et al.*, 2009a), are also studied. The former is a linear combination of several score tests, whereas $\text{MAX3} = \max_{\theta=0,1/2,1} |z(\theta)|$ and $\text{MAX} = \max_{\theta\in[0,1]} z^2(\theta)$. Zheng *et al.* (2009a) showed that MAX outperforms Pearson's test when $(\lambda_1, \lambda_2) \in \Lambda_C$ because MAX can be regarded as a constrained score test for $H_0 : \lambda_1 = \lambda_2 = 1$ with $(\lambda_1, \lambda_2) \in \Lambda_C$, whereas Pearson's test is an unconstrained score test with $(\lambda_1, \lambda_2) \in \Lambda$. For $\theta \in [0, 1]$, it has been shown that MAX3 and MAX have very comparable power (Zheng *et al.*, 2012, p. 171) and that MAX3 is often more powerful than Pearson's test (Zheng *et al.*, 2006).

Although the previous discussions regarding efficiency robust tests and power comparison are based on a case–control genetic association study, they are also applicable to other genetic study designs, for example, association studies for quantitative traits (So & Sham, 2011), family-based association studies using case–parents trios (Schaid & Sommer, 1993), and linkage studies using affected sibs (Whittemore & Tu, 1998; Gastwirth & Freidlin, 2000). A summary of the likelihoods of different genetic study designs with notations $L_n(\lambda_1, \lambda_2, \alpha)$ is given in online Appendices S1–S3.

In this paper, we focus on the MERT and MAX3. Some of their statistical properties have been studied for each study design separately. For example, Gastwirth & Freidlin (2000) derived the MERT using case–parents trios, and Freidlin *et al.* (2002) derived the MERT using case–control data. The methods to derive the MERTs for the two study designs are different. Zang *et al.* (2010) proved that $z(1/2)$ is a linear combination of $z(0)$ and $z(1)$ using case–control data, so that the computation of the p-value of MAX3 can be simplified using this linear relationship. But no covariates are allowed in Zang *et al.* (2010). The same linear relationship of

$(z(0), z(1/2), z(1))$ was shown to hold using case–parents trios in Zheng *et al.* (2012, p. 387). Our goal is to unify and extend the aforementioned results of the MERT and MAX3 using a general likelihood function. Hence, for example, the linear property of the score tests of Zang *et al.* (2010) can be applied to all the earlier study designs with covariates. Moreover, we show that such a linear relationship holds for $(z(\theta_0), z(\theta), z(\theta_1))$ for $\theta \in (\theta_0, \theta_1) \subset [0, 1]$, where $[\theta_0, \theta_1]$ is an arbitrary subset of $[0, 1]$. Under the general setting, the results can be used to approximate the p-value and power of MAX3. The results are illustrated by a real application to genetic association studies using case–parents trios. Other potential applications of the results are mentioned in the discussion section.

2. Efficiency robustness

Denote $\Theta = [0, 1]$. If $\theta^* \in \Theta$ is the true value under H_1, Pitman's asymptotic relative efficiency (ARE) of $z(\theta)$ relative to $z(\theta^*)$ is given by $e(z(\theta), z(\theta^*)) = \rho^2_{\theta,\theta^*}$, where ρ_{θ,θ^*} is the asymptotic null correlation of $z(\theta)$ and $z(\theta^*)$ (Gastwirth, 1966, 1985). Let T_1 be a set of all convex linear combinations of T_0, where $T_0 = \{z(\theta) : \theta \in [0, 1]\}$ and $z(\theta)$ is given by formula (2) in Section 3.2. The MERT, z_{MERT}, is defined as a test satisfying $\inf_{\theta\in\Theta} e(z_{\text{MERT}}, z(\theta)) = \sup_{z\in T_1} \inf_{\theta\in\Theta} e(z, z(\theta))$ (Gastwirth, 1966, 1985; Birnbaum and Laska, 1967). A test in T_1 satisfying the aforementioned property is called a test with the most efficiency robustness in T_1. We only focus on the MERT in T_1. It is not trivial to find the MERT in general (Birnbaum & Laska, 1967). Following Gastwirth (1985), we call $(z(\theta_L), z(\theta_U))$ the extreme pair of T_0 if $\rho_{\theta_L,\theta_U} > 0$ is the minimum of any pair-wise correlation of two tests in T_0. Then, from Gastwirth (1985), the MERT in T_1 exists, is unique, and has a simple expression given by

$$z_{\text{MERT}} = \{z(\theta_L) + z(\theta_U)\} / \left\{2\left(1 + \rho_{\theta_L,\theta_U}\right)\right\}^{1/2},$$

if $(z(\theta_L), z(\theta_U))$ is the extreme pair of T_0 and the following holds:

$$\rho_{\theta_L,\theta} + \rho_{\theta,\theta_U} \geq 1 + \rho_{\theta_L,\theta_U} \quad \text{for any } \theta \in \Theta. \tag{1}$$

The preceding discussion of the efficiency robustness and the MERT does not restrict to $\Theta = [0, 1]$. It holds if $\Theta = [\theta_0, \theta_1]$. For all applications in the literature (e.g. Freidlin *et al.*, 1999; Gastwirth and Freidlin, 2000; Freidlin *et al.*, 2002; Zheng *et al.*, 2002, 2012), the extreme pair is always the endpoints of Θ, *which* is not clear if this is still true under the general setting that we describe in Section 3.1.

3. Properties of efficiency robust tests under a general setting

3.1. General setting

We consider $\Lambda_C = \{(\lambda_1, \lambda_2) : \lambda_2 \geq 1, 1 + \theta_0(\lambda_2 - 1) \leq \lambda_1 \leq 1 + \theta_1(\lambda_2 - 1)\}$, which is a cone formed by two rays from the null point $(1, 1)$ with slopes $1/\theta_0$ and $1/\theta_1$, respectively, where θ_0 and θ_1 are known or given and $-\infty < \theta_0 < \theta_1 < \infty$. When $\theta_0 = 0$ and $\theta_1 = 1$, Λ_C is given before. Under the transformation, $\lambda_2 = \lambda$ and $\lambda_1 = 1 - \theta + \theta\lambda$, Λ_C becomes $\Lambda_C(\theta) = \{(\lambda, \theta) : \lambda \geq 1, \theta \in \Theta = [\theta_0, \theta_1]\}$, where θ cannot be estimated under $H_0 : \lambda = 1$.

In addition to introducing $[\theta_0, \theta_1]$ for [0,1], as a general setting, we also allow for nuisance parameters $\alpha \in R^m$ $(m \geq 0)$ in the analysis, which are estimable under H_0. We will show that statistical properties of the MERT, such as (1) and how to find the extreme pair, still hold under the aforementioned setting for all study designs with a general likelihood function described in the following.

3.2. Score statistics and asymptotic null correlations

Under the preceding setting, let the likelihood function be $L_n(\lambda_1, \lambda_2, \alpha) = \prod_{i=1}^{n} f(Y_i \mid \lambda_1, \lambda_2, \alpha, X_i)$, where Y_i is the outcome of the ith individual, (λ_1, λ_2) are the parameters of interest, α is a vector of parameters for the covariate $X_i = (x_{i1}, \ldots, x_{im})^{\mathrm{T}}$ $(i = 1, \ldots, n; m \geq 0)$, and n is the sample size. Denote the log-likelihood function as $l_n(\lambda_1, \lambda_2, \alpha)$. Let H_0 be $(\lambda_1, \lambda_2) = (1, 1)$ and α^* be the true value of α. Under the transformation, $l_n(\lambda_1, \lambda_2, \alpha) = l_n(1 - \theta + \theta\lambda, \lambda, \alpha)$ with three variables $x_1 = 1 - \theta + \theta\lambda$, $x_2 = \lambda$, and $x_3 = \alpha$. Denote $l_{n,u} = \partial l_n / \partial x_u$ $(u = 1, 2, 3)$, $l_{n,uv} = \partial^2 l_n / \partial x_u \partial x_v$ $(u = 1, 2; v = 1, 2, 3)$, $l_{n,33} = \partial^2 l_n / \partial x_3 \partial x_3^{\mathrm{T}}$, and $L_{uv}(\alpha^*) = E_{H_0}(l_{1,uv}(1, 1, \alpha^*))$ $(u, v = 1, 2, 3)$. Under the transformation, the null hypothesis becomes $H_0 : \lambda = 1$.

The following regularity conditions are assumed.

(i) For $(\lambda, \theta) \in \Lambda(\theta)$ and any α, the orders of partial derivatives are exchangeable, so $l_{n,uv} = l_{n,vu}$ $(u, v = 1, 2)$ and $l_{n,uv} = l_{n,vu}^{\mathrm{T}}$ $(u = 1, 2;\ v = 3)$. The orders of partial derivatives and integration are also exchangeable.
(ii) The regularity conditions for the existence and uniqueness of the maximum likelihood estimator for α under H_0, denoted as $\hat{\alpha}_n$, hold for $\theta \in (-\infty, \infty)$.
(iii) Given $(\lambda, \theta) \in \Lambda(\theta)$ and α, all the third-order partial derivatives of the log-likelihood function exist and are bounded.
(iv) $L_{33}(\alpha)$ exists and $-L_{33}(\alpha)$ is positive definite for any α.
(v) $(z(\theta_i), z(\theta_j))$ follows asymptotically a bivariate normal distribution for $\theta_i, \theta_j \in (-\infty, \infty)$.
(vi) There exists N such that when $n > N$, θ_0 and θ_1 satisfy $\hat{\rho}_{\theta_0,\theta_1} \geq \epsilon > 0$ for some real number ϵ independent of n, where $\hat{\rho}_{\theta_0,\theta_1}$ is a consistent estimator of ρ_{θ_0,θ_1}.

Condition (v) is used when studying properties of the MERT and MAX3, and condition (vi) is used when studying the MERT. All the regularity conditions are for unconstrained $\Lambda(\theta)$ except for condition (vi), which states that the constrained space $\Lambda_C(\theta)$ cannot be too large so that θ_0 and θ_1 can be the extreme pair for the MERT defined in Section 2 (with $\Theta = [\theta_0, \theta_1]$).

Let $\Theta = [\theta_0, \theta_1]$. Under regularity conditions (i)–(iv), the score test for H_0 can be written as (online Appendix S4)

$$z(\theta) = \frac{n^{-1/2} \{l_{n,2}(1, 1, \hat{\alpha}_n) + \theta l_{n,1}(1, 1, \hat{\alpha}_n)\}}{\left\{A(\hat{\alpha}_n)\theta^2 + 2B(\hat{\alpha}_n)\theta + C(\hat{\alpha}_n)\right\}^{1/2}}, \tag{2}$$

where $A(\alpha) = L_{13}(\alpha)L_{33}^{-1}(\alpha)L_{31} - L_{11}(\alpha)$, $B(\alpha) = L_{23}(\alpha)L_{33}^{-1}(\alpha)L_{32}(\alpha) - L_{21}(\alpha)$, and $C(\alpha) = L_{23}(\alpha)L_{33}^{-1}(\alpha)L_{32}(\theta) - L_{22}(\alpha)$. Under H_0, $z^2(\theta) \sim \chi_1^2$ for a given $\theta \in \Theta$. Denote $\rho_{\theta_i,\theta_j} = \lim_{n\to\infty} \mathrm{cor}_{H_0}(z(\theta_i), z(\theta_j))$ for $[\theta_i, \theta_j] \subseteq \Theta$ and

$$\sigma(\alpha, \theta_i, \theta_j) = A(\alpha)\theta_i\theta_j + B(\alpha)(\theta_i + \theta_j) + C(\alpha). \tag{3}$$

Then (online Appendix S4),

$$\rho_{\theta_i,\theta_j} = \frac{\sigma(\alpha^*, \theta_i, \theta_j)}{\{\sigma(\alpha^*, \theta_i, \theta_i)\sigma(\alpha^*, \theta_j, \theta_j)\}^{1/2}}. \tag{4}$$

A consistent estimator of ρ_{θ_i,θ_j}, $\hat{\rho}_{\theta_i,\theta_j}$, is to replace α^* with $\hat{\alpha}_n$. It follows from condition (vi) that $\rho_{\theta_0,\theta_1} > 0$, which is required for the MERT of the pair $(z(\theta_0), z(\theta_1))$ to be $\{z(\theta_0) + z(\theta_1)\}/\left\{2\left(1 + \rho_{\theta_0,\theta_1}\right)\right\}^{1/2}$ (Gastwirth, 1966). Although $\rho_{\theta_0,\theta_1} > 0$ always holds when $[\theta_0, \theta_1]$ is determined by the applications, in theory, $\rho_{\theta_0,\theta_1} < 0$ can happen. In the proof of Theorem 1,

we show $A(\alpha) \geq 0$. If $\theta_0 + \theta_1 = 0$, $A(\alpha^*) > 0$, and $|\theta_1|$ is sufficiently large, then $\rho_{\theta_0,\theta_1} = -A(\alpha^*)\theta_1^2 + C(\alpha^*)$ can be negative.

3.3. Linear dependence and robust properties

Regularity conditions (i)–(iv) are required for Theorems 1 and 2, and all the regularity conditions are required for Theorem 3. All the proofs are given in online Appendix S5.

Theorem 1. *Let* $\theta \in [\theta_i, \theta_j] \subseteq \Theta$.

(a) $z(\theta) = w_i(\theta)z(\theta_i) + w_j(\theta)z(\theta_j)$, *where*

$$w_i(\theta) = \sigma^{1/2}(\hat{\alpha}_n, \theta_i, \theta_i)(\theta_j - \theta)/\left\{\sigma^{1/2}(\hat{\alpha}_n, \theta, \theta)(\theta_j - \theta_i)\right\},$$

$$w_j(\theta) = \sigma^{1/2}(\hat{\alpha}_n, \theta_j, \theta_j)(\theta - \theta_i)/\left\{\sigma^{1/2}(\hat{\alpha}_n, \theta, \theta)(\theta_j - \theta_i)\right\}.$$

Let $W_l(\theta) = \lim_{n\to\infty} w_l(\theta)$ $(l = i, j)$. *Then,* $z(\theta) = W_i(\theta)z(\theta_i) + W_j(\theta)z(\theta_j) + o_P(1)$.

(b) *Under* H_0, $W_l(\theta)$ *has the same form as* $w_l(\theta)$ *in (a) except that* $\hat{\alpha}_n$ *is replaced with* α^*. *Moreover,* $W_l(\theta) = (\rho_{\theta,\theta_l} - \rho_{\theta,\theta_{i+j-l}}\rho_{\theta_i,\theta_j})/(1-\rho^2_{\theta_i,\theta_j})$ $(l = i, j)$, $W_i(\theta) + W_j(\theta) > 1$, *and* $W_i^2(\theta) + W_j^2(\theta) + 2W_i(\theta)W_j(\theta)\rho_{\theta_i,\theta_j} = 1$.

Theorem 2. *Let* $\theta \in [\theta_i, \theta_j] \subseteq \Theta$.

(a) $\rho_{\theta_i,\theta} + \rho_{\theta,\theta_j} \geq 1 + \rho_{\theta_i,\theta_j} \geq \rho^2_{\theta_i,\theta} + \rho^2_{\theta,\theta_j}$. *Hence, (1) holds.*

(b) *For any* $s, t \in [\theta_i, \theta_j]$, $\rho_{s,t} \geq \rho_{\theta_i,\theta_j}$. *Thus,* ρ_{θ_i,θ_j} *is the minimum for any two tests in* $\{z(\theta) : \theta \in [\theta_i, \theta_j]\}$, *and* $\rho_{\theta_i,s}$ (ρ_{s,θ_j}) *is a decreasing (an increasing) function in* $s \in [\theta_i, \theta_j]$.

Theorem 3. *We have the following properties for the MERT.*

(a) *The MERT in the family of all convex linear combinations of* $\{z(\theta) : \theta \in [\theta_i, \theta_j] \subseteq \Theta\}$ *is asymptotically*

$$z_{\mathrm{MERT}} = \frac{z(\theta_i) + z(\theta_j)}{\sqrt{2\left(1 + \rho_{\theta_i,\theta_j}\right)}} \sim \frac{z(\theta_i) + z(\theta_j)}{\sqrt{2\left(1 + \hat{\rho}_{\theta_i,\theta_j}\right)}} \sim N(0,1) \text{ under } H_0, \tag{5}$$

where $\sim$ *means having the same asymptotic distribution. The ARE of* z_{MERT} *relative to the optimal score test has a lower bound* $(1 + \rho_{\theta_i,\theta_j})/2$.

(b) *Any test* $z(\theta) \in \{z(\theta) : \theta \in [\theta_i, \theta_j] \subset \Theta\}$ *has smaller minimum ARE over* $\theta \in \Theta$ than $(1 + \rho_{\theta_i,\theta_j})/2$.

From Theorems 1 and 2, $z(\theta) \in T_0 = \{z(\theta) : \theta \in \Theta\}$ is asymptotically a linear combination of the score tests using the endpoints, which are always the extreme pair. Zang *et al.* (2010) proved the same linear relationship in Theorem 1 only for the case–control data with $\theta_0 = 0$, $\theta = 1/2$, and $\theta_1 = 1$ and without adjusting out covariates (i.e. the dimension of α is $m = 1$). Theorems 2 and 3 generalize the corresponding results of Gastwirth (1966, 1985), with which the MERT in T_1 can be obtained for any sub-interval of Θ without verifying (1) each time.

3.4. Asymptotic properties for MAX3

Applying the linear relationship of the score tests under a special study design, Zang *et al.* (2010) studied the asymptotic null distribution of MAX3 and expressed it in terms of single

integrations. By applying Theorem 1, their result can be applied under the general setting. Recently, applying the result of Zang *et al.* (2010), Wang *et al.* (2012) studied a Bayes factor based on MAX3, in which the asymptotic distribution of MAX3 is derived using the linearity of the trend tests under H_1 for case–control data and $\theta_0 = 0$, $\theta = 1/2$, and $\theta_1 = 1$. The analogy of their result can be obtained under the general setting as well.

Under H_0, under regularity condition (v), $(z(\theta_0), z(\theta_1))^{\mathrm{T}} \sim N(0, \Omega)$ asymptotically, where $\Omega = (\omega_{ij})_{2\times 2}$ with $\omega_{ii} = 1$ $(i = 1, 2)$ and $\omega_{12} = \rho_{\theta_0,\theta_1}$. A consistent estimator of Ω is denoted as Ω_n with ρ_{θ_0,θ_1} replaced by $\hat{\rho}_{\theta_0,\theta_1}$. Denote the density of the data y as $f(y \mid 1-\theta+\theta\lambda, \lambda, \alpha)$. Under H_1, for fixed $(\lambda, \theta) \in \Lambda_C(\theta)$ and α^*, denote $\alpha_\theta = \alpha(\lambda, \theta) = \arg\sup_\alpha \int f(x \mid 1-\theta+\theta\lambda, \lambda, \alpha^*) \log f(x \mid 1, 1, \alpha)\, \mathrm{d}x$, which is consistently estimated by $\hat{\alpha}_n$. Let $\tilde{W}_l(\theta)$ be the same as $W_l(\theta)$, $l = i, j$, given in Theorem 1 except that α^* is replaced with α_θ. Because $\hat{\alpha}_n \to \alpha_\theta$ (almost surely) under H_1 (Huber, 1967; Pfanzagl, 1969), from Theorem 1(a), we have $z(\theta) = \tilde{W}_0(\theta) z(\theta_0) + \tilde{W}_1(\theta) z(\theta_1) + o_P(1)$ for $\theta \in (\theta_0, \theta_1)$. Let

$$s(\theta, \alpha) = l_{1,2}(1, 1, \alpha) + \theta l_{1,1}(1, 1, \alpha) - \{L_{23}(\alpha) + \theta L_{13}(\alpha)\} L_{33}^{-1}(\alpha) l_{1,3}(1, 1, \alpha), \tag{6}$$

$\mu(\lambda, \theta) = E_{H_1,\alpha^*}(s(\theta, \alpha_\theta))$, $u(\lambda, \theta) = s(\theta, \alpha_\theta) - \mu(\lambda, \theta)$, $\tau^2(\lambda, \theta) = E_{H_1,\alpha^*}(u(\lambda, \theta)^2)$, $\tilde{\sigma}(\lambda, \theta, \theta) = \tau^2(\lambda, \theta)/\sigma(\alpha_\theta, \theta, \theta)$, and $\tilde{\Omega} = \left(\tilde{\omega}_{ij}\right)_{2\times 2}$ with

$$\tilde{\omega}_{12} = E_{H_1,\alpha^*}\{u(\lambda, \theta_0) u(\lambda, \theta_1)\} / \{\sigma(\alpha_\theta, \theta_0, \theta_0)\sigma(\alpha_\theta, \theta_1, \theta_1)\}^{1/2},$$

$\tilde{\omega}_{11} = \tilde{\sigma}(\lambda, \theta_0, \theta_0)$, and $\tilde{\omega}_{22} = \tilde{\sigma}(\lambda, \theta_1, \theta_1)$. A consistent estimator of $\tilde{\Omega}$ is $\tilde{\Omega}_n$ with α_θ replaced with $\hat{\alpha}_n$. Denote ϕ and Φ as the probability density and cumulative distribution functions of $N(0, 1)$. A proof of the following result is given in online Appendix S5.

Theorem 4. *Assume that regularity conditions (i)–(v) hold.* $\mathrm{pr}(\mathrm{MAX3} \le t)$ *under* H_0 *can be obtained as a special case of* $\mathrm{pr}(\mathrm{MAX3} \le t)$ *under* H_1. *Hence, we first give an expression under* H_1:

(a) *Under* H_1,

$$\left(z(\theta_0) - \frac{n^{1/2}\mu(\lambda, \theta_0)}{\sigma^{1/2}(\alpha_\theta, \theta_0, \theta_0)}, z(\theta_1) - \frac{n^{1/2}\mu(\lambda, \theta_1)}{\sigma^{1/2}(\alpha_\theta, \theta_1, \theta_1)}\right)^{\mathrm{T}} \to N\left(\mathbf{0}, \tilde{\Omega}\right),$$

in distribution. Denote $\eta_i = \mu(\lambda, \theta_i)/\sigma^{1/2}(\alpha_\theta, \theta_i, \theta_i)$ $(i = 0, 1)$, $\tilde{t}_{0\pm}^{(n)} = (t \pm \sqrt{n}\eta_0)/\sqrt{\tilde{\omega}_{11}}$, $\tilde{t}_{1\pm}^{(n)} = (t \pm \sqrt{n}\eta_1)/\sqrt{\tilde{\omega}_{22}}$, $\tilde{v}_{0\pm}^{(n)} = (v \pm \sqrt{n}\eta_0)/\sqrt{\tilde{\omega}_{11}}$ *where* $v = t(1 - W_1(\theta))/W_0(\theta)$, $\tilde{\rho}_{\theta_0,\theta} = \tilde{W}_0(\theta)\sqrt{\tilde{\omega}_{11}}/\sqrt{\tilde{\omega}_{22}} + \tilde{\rho}_{\theta_0,\theta_1}\tilde{W}_1(\theta)$ *where* $\tilde{\rho}_{\theta_0,\theta_1} = \tilde{\omega}_{12}/(\tilde{\omega}_{11}\tilde{\omega}_{22})^{1/2}$, *and*

$$\tilde{\tilde{t}}_{1\pm}^{(n)} = \left[t \pm \sqrt{n}\left\{\tilde{W}_0(\theta)\eta_0 + \tilde{W}_1(\theta)\eta_1\right\}\right] / \sqrt{\tilde{\omega}_{22}}.$$

Then, for fixed $(\lambda, \theta) \in \Lambda_C(\theta)$ *and* $t > 0$, *when n is sufficiently large,*

$$\mathrm{pr}(\mathrm{MAX3} \le t) \approx \tilde{G}_n(t) = \tilde{I}_{1n}(t) - \tilde{I}_{2n}(t) - \tilde{I}_{3n}(t),$$

where

$$\tilde{I}_{1n}(t) = \int_{-\tilde{t}_{0+}^{(n)}}^{\tilde{t}_{0-}^{(n)}} \left\{ \Phi\left(\frac{\tilde{t}_{1-}^{(n)} - \tilde{\rho}_{\theta_0,\theta_1} x}{\sqrt{1-\tilde{\rho}_{\theta_0,\theta_1}^2}} \right) - \Phi\left(\frac{-\tilde{t}_{1+}^{(n)} - \tilde{\rho}_{\theta_0,\theta_1} x}{\sqrt{1-\tilde{\rho}_{\theta_0,\theta_1}^2}} \right) \right\} \mathrm{d}\Phi(x),$$

$$\tilde{I}_{2n}(t) = \int_{-\tilde{t}_{0+}^{(n)}}^{-\tilde{v}_{0+}^{(n)}} \left\{ \Phi\left(\frac{-\tilde{\tilde{t}}_{1+}^{(n)} - \tilde{\tilde{\rho}}_{\theta_0,\theta} x}{\tilde{W}_1(\theta)\sqrt{1-\tilde{\rho}_{\theta_0,\theta_1}^2}} \right) - \Phi\left(\frac{-\tilde{t}_{1+}^{(n)} - \tilde{\rho}_{\theta_0,\theta_1} x}{\sqrt{1-\tilde{\rho}_{\theta_0,\theta_1}^2}} \right) \right\} \mathrm{d}\Phi(x),$$

$$\tilde{I}_{3n}(t) = \int_{\tilde{v}_{0-}^{(n)}}^{\tilde{t}_{0-}^{(n)}} \left\{ \Phi\left(\frac{\tilde{t}_{1-}^{(n)} - \tilde{\rho}_{\theta_0,\theta_1} x}{\sqrt{1-\tilde{\rho}_{\theta_0,\theta_1}^2}} \right) - \Phi\left(\frac{\tilde{\tilde{t}}_{1-}^{(n)} - \tilde{\tilde{\rho}}_{\theta_0,\theta} x}{\tilde{W}_1(\theta)\sqrt{1-\tilde{\rho}_{\theta_0,\theta_1}^2}} \right) \right\} \mathrm{d}\Phi(x).$$

(b) *Under* H_0, $\eta_0 = \eta_1 = 0$, $\tilde{\omega}_{11} = \tilde{\omega}_{22} = 1$, $\tilde{\omega}_{12} = \rho_{\theta_0,\theta_1} = \tilde{\rho}_{\theta_0,\theta_1}$, *and* $\tilde{W}_i(\theta) = W_i(\theta)$ $(i = 0, 1)$. *Hence,* $\tilde{t}_{0\pm}^{(n)} = \tilde{t}_{1\pm}^{(n)} = \tilde{\tilde{t}}_{1\pm}^{(n)} = t$, $\tilde{v}_{0\pm}^{(n)} = v$, and $\tilde{\tilde{\rho}}_{\theta_0,\theta} = \rho_{\theta_0,\theta}$ *for any* $\theta \in (\theta_0, \theta_1)$. $\tilde{I}_{jn}$, $j = 1, 2, 3$, *no longer depend on* n, *and by symmetry,* $\tilde{I}_{2n} = \tilde{I}_{3n}$ *under* H_0. *Specifically, for fixed* $\theta \in \Theta$ *and* $t > 0$, *as* $n \to \infty$,

$$\mathrm{pr}(\mathrm{MAX3} \le t) \to G(t) = 2\{I_1(t) - I_2(t)\},$$

where

$$I_1(t) = \int_0^t \left\{ \Phi\left(\frac{t - \rho_{\theta_0,\theta_1} x}{\sqrt{1-\rho_{\theta_0,\theta_1}^2}} \right) - \Phi\left(\frac{-t - \rho_{\theta_0,\theta_1} x}{\sqrt{1-\rho_{\theta_0,\theta_1}^2}} \right) \right\} \mathrm{d}\Phi(x),$$

$$I_2(t) = \int_{\frac{t(1-W_1(\theta))}{W_0(\theta)}}^t \left\{ \Phi\left(\frac{t - \rho_{\theta_0,\theta_1} x}{\sqrt{1-\rho_{\theta_0,\theta_1}^2}} \right) - \Phi\left(\frac{t - \rho_{\theta_0,\theta} x}{W_1(\theta)\sqrt{1-\rho_{\theta_0,\theta_1}^2}} \right) \right\} \mathrm{d}\Phi(x).$$

The asymptotic null distribution of MAX3 depends on ρ_{θ_0,θ_1}, $\rho_{\theta_0,\theta}$, *and* $(W_0(\theta), W_1(\theta))$. *In practice, they can be estimated by replacing* α^* *with* $\hat{\alpha}_n$.

4. An application to genetic association using trio data

4.1. Detailed formulas

Testing genetic association using parents and their diseased offspring, Schaid & Sommer (1993) considered the conditional likelihood for an offspring with genotype $\{G_0, G_1, G_2\}$ given the parental mating type (MT) and given that the offspring has the disease. Refer to online Appendix S3 for a detailed discussion of this study design and the derivation of the likelihood function given later. The conditional likelihood uses only three MTs: $G_0 \times G_1$, $G_1 \times G_1$, and $G_1 \times G_2$ with sample sizes n_1, n_2, and n_3, respectively. Let $n = n_1 + n_2 + n_3$ be the total sample size. The genotype counts for all offspring within each of the three MTs can be obtained, denoted as (n_{10}, n_{11}), (n_{20}, n_{21}, n_{22}), and (n_{31}, n_{32}), respectively, where the second subscript is the number of the risk allele in the offspring genotype. The log-likelihood function is (Schaid and Sommer, 1993) $l(\lambda_1, \lambda_2) = (n_{11} + n_{21} + n_{31})\log(\lambda_1) + (n_{22} + n_{32})\log(\lambda_2) - n_1\log(\lambda_1 + 1) - n_2\log(\lambda_2 + 2\lambda_1 + 1) - n_3\log(\lambda_1 + \lambda_2)$. In this application, there is no nuisance parameter α ($m = 0$). Under H_0, $(\lambda_1, \lambda_2) = (1, 1)$, and under H_1, $(\lambda_1, \lambda_2) \in \Lambda_C \backslash \{(1, 1)\}$. Apply the transformation in Section 1 with $\theta \in [0, 1]$. Then, the score test is $z(\theta) = n^{-1/2}(l_{n,1}\theta + l_{n,2})/(A\theta^2 + 2B\theta + C)^{1/2}$, where $l_{n,1} = n_{11} + n_{21} + n_{31} - n_1/2 - n_2/2 - n_3/2$, $l_{n,2} = n_{22} + n_{32} - n_2/4 - n_3/2$, $A = (n_1 + n_2 + n_3)/(4n) = 1/4$,

$B = -(n_2/8 + n_3/4)/n := -p_2/8 - p_3/4$, and $C = (3n_2/16 + n_3/4)/n := 3p_2/16 + p_3/4$, where $p_i = n_i/n$, $i = 1, 2, 3$, are fixed by the design. For any $\theta_1, \theta_2 \in [0, 1]$, $\rho_{\theta_1,\theta_2} = \{A\theta_1\theta_2 + B(\theta_1 + \theta_2) + C\}/\{(A\theta_1^2 + 2B\theta_1 + C)(A\theta_2^2 + 2B\theta_2 + C)\}^{1/2}$. Hence, $\rho_{0,1} = p_2/\{(3p_2 + 4p_3)(3p_2 + 4p_1)\}^{1/2}$, $\rho_{0,1/2} = \{2(p_2 + p_3)\}/\{(3p_2 + 4p_3)(p_2 + 1)\}^{1/2}$, and $\rho_{1/2,1} = \{2(p_1 + p_2)\}/\{(3p_2 + 4p_1)(p_2 + 1)\}^{1/2}$. Because there is no α, $w_i(\theta) = W_i(\theta) = \tilde{W}_i(\theta)$ $(i = 0, 1)$. In particular, when $\theta = 1/2$, $W_0(1/2) = \{(3p_2 + 4p_3)(p_2 + 1)\}^{1/2}/2$, and $W_1(1/2) = \{(3p_2 + 4p_1)/(p_2 + 1)\}^{1/2}/2$.

When $\theta = 1/2$, $z^2(1/2)$ is identical to the transmission disequilibrium test (TDT) of Spielman *et al.* (1993). For any $[\theta_0, \theta_1] \subseteq [0, 1]$ covering $\theta = 1/2$, from Theorem 3, the MERT given in (5) is always more efficiency robust than the TDT. Because $\rho_{0,1} \leq 1/3$, the MERT for $[0, 1]$ has low ARE relative to the optimal test. In general, a more efficiency robust test is MAX3 when the null correlation of the extreme pair is <1/2 (Freidlin *et al.*, 1999). From Theorem 2, for any $[\theta_0, \theta_1] \subset [0, 1]$, $\rho_{\theta_0,\theta_1} > \rho_{01} > 0$. When a prior study can be used to reduce the space $[0, 1]$ to $[\theta_0, \theta_1] \subset (0, 1)$, the efficiency of the MERT for $[\theta_0, \theta_1]$ increases and is close to that of a maximum-type test based on $[\theta_0, \theta_1]$ when $\rho_{\theta_0,\theta_1} > 1/2$.

Theorem 4(b) can be used to find critical values or p-values of MAX3 with $(\theta_0, \theta, \theta_1) = (0, 1/2, 1)$. Let t_{MAX3} be the observed value of MAX3. Then, the p-value of MAX3 can be approximated by

$$p = 1 - 2\{I_1(t_{\mathrm{MAX3}}) - I_2(t_{\mathrm{MAX3}})\},$$

where $\rho_{\theta_0,\theta_1} = \rho_{0,1}$ and $\rho_{\theta_0,\theta} = \rho_{0,1/2}$ and $W_0(\theta) = W_0(1/2)$ and $W_1(\theta) = W_1(1/2)$ given earlier. To find a critical value t^*_{MAX3} for MAX3 with a 0.05 significance level, we need to find it from

$$I_1\left(t^*_{\mathrm{MAX3}}\right) - I_2\left(t^*_{\mathrm{MAX3}}\right) = 0.95/2.$$

Under H_1, Theorem 4(a) can be used to approximate its power. Let the true model be $\theta^* \in [0, 1]$ under H_1, although we are interested in $\theta^* = 0, 1/2, 1$. Denote $\sigma(\theta^*, \theta^*) = A\theta^{*2} + 2B\theta^* + C$. From (6), $s(\theta^*) = l_{1,2} + \theta^* l_{1,1}$. But $l_{n,2} + \theta^* l_{n,1}$ is a sum of independent and identically distributed variables. Thus, $\mu(\lambda, \theta^*) = E_{H_1}(s(\theta^*)) = E_{H_1}(l_{n,2} + \theta^* l_{n,1})/n = E\{(n_{22} + n_{32} - n_2/4 - n_3/2) + \theta^*(n_{11} + n_{21} + n_{31} - n_1/2 - n_2/2 - n_3/2)\}/n$. Thus,

$$\mu(\lambda, \theta^*) = \left(p_{22} - \frac{1}{4}\right) p_2 + \left(p_{32} - \frac{1}{2}\right) p_3 + \theta^* \left\{\left(p_{11} - \frac{1}{2}\right) p_1 + \left(p_{21} - \frac{1}{2}\right) p_2 + \left(p_{31} - \frac{1}{2}\right) p_3\right\},$$

where all p_{ij}, in terms of (λ, θ^*), are given in Table S1 (the last column) in online Appendix S3, where λ is specified under H_1 and $p_i = n_i/n$, $i = 2, 3$. Then, $u(\lambda, \theta^*) = s(\theta^*) - \mu(\lambda, \theta^*)$ and $\tau^2(\lambda, \theta^*) = E_{H_1}(u^2(\lambda, \theta^*)) = \mathrm{var}_{H_1}(s(\theta^*)) = \mathrm{var}_{H_1}(l_{n,2} + \theta^* l_{n,1})/n$. Let $\hat{p}_{ij}$ be the maximum likelihood estimator of p_{ij}. Then, by the independence of the data among different MTs, we have

$$\begin{aligned}
\tau^2(\lambda, \theta^*) &= \frac{1}{n}\mathrm{var}_{H_1}\left\{n_2\hat{p}_{22} + n_3\hat{p}_{32} + \theta^*(n_1\hat{p}_{11} + n_2\hat{p}_{21} + n_3\hat{p}_{31})\right\} \\
&= \frac{1}{n}\left\{n_1^2\mathrm{var}_{H_1}\left(\theta^*\hat{p}_{11}\right) + n_2^2\mathrm{var}_{H_1}\left(\hat{p}_{22} + \theta^*\hat{p}_{21}\right) + n_3^2\mathrm{var}_{H_1}\left(\hat{p}_{32} + \theta^*\hat{p}_{31}\right)\right\} \\
&= \theta^{*2}\{p_1p_{11}(1 - p_{11}) + p_2p_{21}(1 - p_{21}) + p_3p_{31}(1 - p_{31})\} \\
&\quad - 2\theta^*(p_2p_{21}p_{22} + p_3p_{31}p_{32}) + p_2p_{22}(1 - p_{22}) + p_3p_{32}(1 - p_{32}),
\end{aligned}$$

where p_{ij} are replaced with p_{ij} in Table S1 and p_i with n_i/n. We also need to find $E_{H_1}(u(\lambda,0)u(\lambda,1)) = \mathrm{cov}_{H_1}(s(0),s(1))$ given by

$$\begin{aligned}&\frac{1}{n}\mathrm{cov}_{H_1}\left(n_2\hat{p}_{22}+n_3\hat{p}_{32}, n_2\hat{p}_{22}+n_3\hat{p}_{32}+n_1\hat{p}_{11}+n_2\hat{p}_{21}+n_3\hat{p}_{31}\right)\\ &\quad=\frac{1}{n}\mathrm{cov}_{H_1}\left(n_2\hat{p}_{22}, n_2\hat{p}_{22}+n_2\hat{p}_{21}\right)+\frac{1}{n}\mathrm{cov}_{H_1}\left(n_3\hat{p}_{32}, n_3\hat{p}_{32}+n_3\hat{p}_{31}\right)\\ &\quad=p_2p_{22}p_{20}.\end{aligned}$$

Hence, $\tilde{\sigma}(\lambda,\theta^*,\theta^*) = \tau^2(\lambda,\theta^*)/(A\theta^{*2}+2B\theta^*+C)$, which leads to $\tilde{\omega}_{11} = \tau^2(\lambda,0)/C$, $\tilde{\omega}_{22} = \tau^2(\lambda,1)/(A+2B+C)$, and $\tilde{\omega}_{12} = p_2p_{22}p_{20}/\{C(A+2B+C)\}^{1/2}$. Then,

$$\tilde{\rho}_{0,1} = \frac{p_2p_{22}p_{20}}{[\{p_2p_{22}(1-p_{22})+p_3p_{32}(1-p_{32})\}\{p_1p_{11}(1-p_{11})+p_2p_{20}(1-p_{20})\}]^{1/2}}.$$

Finally, $\eta_0 = \mu(\lambda,0)/C^{1/2}$ and $\eta_1 = \mu(\lambda,1)/(A+2B+C)^{1/2}$. Hence, given t, λ, $\theta=\theta^*$, and n, all the variables used in approximating $\mathrm{pr}_{H_1}(\mathrm{MAX3}\le t)$ are explicitly given earlier.

4.2. Numerical results for MAX3

First, we find theoretical (t^*_{MAX3}) and empirical ($\hat{t}^*_{\mathrm{MAX3}}$) critical values for MAX3 with a nominal level of 0.05. In online Appendix S6 (Table S2), the conditional probabilities given in Table S1 are written under H_0 and under H_1 for a given genetic model $\theta^* = 0, 1/2, 1$.

Let p be the minor allele frequency (MAF) of the marker of interest in the population. If we screen case–parents trio data in the population for the three informative MTs, $I: AA\times AB$, $II: AB\times AB$, and $III: AB\times BB$ (Table S1), under the Hardy–Weinberg equilibrium in the population, the probabilities of these three information MTs are given by $\mathrm{pr}(I) = 4p(1-p)^3$, $\mathrm{pr}(II) = 4p^2(1-p)^2$, and $\mathrm{pr}(III) = 4p^3(1-p)$. Define $p_1 = \mathrm{pr}(I)/\{\mathrm{pr}(I)+\mathrm{pr}(II)+\mathrm{pr}(III)\}$, $p_2 = \mathrm{pr}(II)/\{\mathrm{pr}(I)+\mathrm{pr}(II)+\mathrm{pr}(III)\}$, and $p_3 = \mathrm{pr}(III)/\{\mathrm{pr}(I)+\mathrm{pr}(II)+\mathrm{pr}(III)\}$, so that $p_1+p_2+p_3=1$. Let n be the total number of trios and $n_i = p_in$ ($i=1,2,3$). We set $n=1000$. In Table 1, given MAF, we report p_i, n_i; $\rho_{0,1/2}$, $\rho_{0,1}$, and $\rho_{1/2,1}$; $W_1(\theta)$ and $W_0(\theta)$ with $\theta=1/2$; and the critical values. t^*_{MAX3} is calculated using Theorem 4(b), and $\hat{t}^*_{\mathrm{MAX3}}$ is obtained from 10,000 replicates with trio data generated using the conditional probabilities under H_0 given in Table S2 and fixed n_i from Table 1. Although the theoretical

Table 1. *Screening probabilities for three mating types p_i ($i=1,2,3$), counts n_i ($i=1,2,3$), ρ_{θ_i,θ_j} ($\theta,\theta_j=0,1/2,1$), and $W_i(\theta)$ ($i=0,1$) with $\theta=1/2$ given $n=1000$ and minor allele frequency (MAF) p. Theoretical critical values t^*_{MAX3} based on Theorem 4(b) and simulated values $\hat{t}^*_{MAX3}$ are also reported for the nominal level 0.05*

MAF	Prob	Count	ρ_{θ_i,θ_j}	$W_i(\theta)$	t^*_{MAX3}	$\hat{t}^*_{\mathrm{MAX3}}$
0.15	$p_1=0.8281$	$n_1=828$	$\rho_{0,1/2}=0.4365$	$W_0(\theta)=0.3439$	2.286	2.304
	$p_2=0.1461$	$n_2=146$	$\rho_{0,1}=0.1024$	$W_1(\theta)=0.9045$		
	$p_3=0.0258$	$n_3=26$	$\rho_{1/2,1}=0.9397$			
0.30	$p_1=0.6203$	$n_1=620$	$\rho_{0,1/2}=0.6032$	$W_0(\theta)=0.4976$	2.297	2.305
	$p_2=0.2658$	$n_2=266$	$\rho_{0,1}=0.1312$	$W_1(\theta)=0.8046$		
	$p_3=0.1139$	$n_3=114$	$\rho_{1/2,1}=0.8699$			
0.45	$p_1=0.4020$	$n_1=402$	$\rho_{0,1/2}=0.7223$	$W_0(\theta)=0.6230$	2.301	2.297
	$p_2=0.3289$	$n_2=329$	$\rho_{0,1}=0.1422$	$W_1(\theta)=0.6987$		
	$p_3=0.2691$	$n_3=269$	$\rho_{1/2,1}=0.7873$			

Table 2. *Theoretical power (π) and empirical power ($\hat{\pi}$) of MAX3 given $n = 1000$, minor allele frequency (MAF), a genetic model θ^*, and λ, using the critical values in Table 1*

		$\lambda = 1.1$		$\lambda = 1.3$		$\lambda = 1.5$	
MAF	θ^*	π	$\hat{\pi}$	π	$\hat{\pi}$	π	$\hat{\pi}$
0.15	0	0.077	0.083	0.287	0.301	0.612	0.630
	1/2	0.112	0.118	0.568	0.581	0.931	0.937
	1	0.243	0.255	0.962	0.960	1.000	1.000
0.30	0	0.111	0.112	0.572	0.578	0.929	0.937
	1/2	0.120	0.125	0.599	0.598	0.942	0.937
	1	0.214	0.208	0.932	0.925	1.000	1.000
0.45	0	0.153	0.157	0.790	0.803	0.993	0.992
	1/2	0.123	0.119	0.604	0.605	0.939	0.939
	1	0.173	0.165	0.853	0.843	0.998	0.999

critical values slightly depend on the MAFs, they are all around 2.30 and close to the simulated ones.

Next, we calculate the theoretical power of MAX3, $\pi = \mathrm{pr}_{H_1}(\mathrm{MAX3} \geq t)$, using Theorem 4(a) and simulate the empirical power of MAX3 with 10,000 replicates, $\hat{\pi} = \hat{\mathrm{pr}}_{H_1}(\mathrm{MAX3} \geq t)$, using the conditional probabilities in Table S1 (or Table S2) with fixed n_i in Table 1 given MAF. The critical values in Table 1 are also used as t. The results are reported in Table 2, which also shows that the empirical and theoretical results match well, especially for moderate MAFs.

4.3. Simulation to compare tests

Simulation studies comparing $z^2(\theta)$ with different θ and MAX3 have been reported before (Zheng *et al.*, 2002). The purpose of our simulation study here is to examine the usefulness of the MERT, when the genetic model space $\theta \in [0, 1]$ can be reduced on the basis of a prior study. For example, if previous evidence strongly suggests that the recessive model ($\theta = 0$) can be removed from the consideration, we may consider $\theta \in [\theta_0, \theta_1] = [1/2, 1]$. From Theorem 3 and (5), the MERT for $\theta \in [1/2, 1]$ is given by $z^2_{\mathrm{MERT}} = \{z(1/2) + z(1)\}^2/\{2(1 + \rho_{1/2,1})\}$. Accordingly, we consider $\mathrm{MAX3} = \max\{|z(1/2)|, |z(3/4)|, |z(1)|\}$. For comparison, we also consider $\mathrm{MAX} = \max_{\theta \in [1/2,1]} z^2(\theta)$. Simulation results with 10,000 replicates are reported in Table 3. In the simulation, $n = n_1 + n_2 + n_3$ trios are screened from a total of 3000 trios with a given MAF, and λ is chosen so that the optimal score test under a given genetic model

Table 3. *Empirical power of $z^2(1)$, $z^2(1/2)$ (the transmission disequilibrium test (TDT)), z^2_{MERT}, MAX3, and MAX with a given minor allele frequency (MAF) and genetic model θ^*. The nominal level is 0.05*

MAF	θ^*	TDT	$z^2(1)$	z^2_{MERT}	MAX3	MAX
0.15	1/2	0.819	0.774	0.807	0.803	0.803
0.15	1	0.786	0.833	0.818	0.820	0.820
0.30	1/2	0.816	0.726	0.801	0.801	0.802
0.30	1	0.709	0.830	0.802	0.801	0.802
0.45	1/2	0.809	0.627	0.770	0.778	0.779
0.45	1	0.648	0.845	0.800	0.815	0.816

$\theta^* = 0, 1/2, 1$ has about 80% power. The result of Davies (1987) is used here to estimate the power of MAX. The power of MAX3 is estimated from the simulations. When the recessive model ($\theta^* = 0$) is removed, by applying Theorems 2 and 3, the two robust tests can be obtained without proving (1) for the reduced model space and identifying the new extreme pair. Among $z^2(1/2)$ (the TDT), $z^2(1)$, and z^2_{MERT}, z^2_{MERT} always has the highest minimum power between the two genetic models. Moreover, MAX3 and MAX have very similar power, and z^2_{MERT} also has similar power compared with MAX3 and MAX. This shows, when the model space can be reduced using prior independent data, z_{MERT} for the reduced model may not only have power advantage but also have advantage of the asymptotic normality.

When $\theta \in [1/2, 1]$, the minimum correlation is $\rho_{1/2,1} = 2(n_1+n_2)/\{(3n_2+4n_1)(2n_2+n_1+n_3)\}^{1/2} \geq \{(n_1+n_2)/(n_1+2n_2+n_3)\}^{1/2}$. If we substitute the counts, n_1, n_2, and n_3, with their sampling probabilities $4p(1-p)^3$, $4p^2(1-p)^2$, and $4p^3(1-p)$, we have $\rho_{1/2,1} \geq (1-p)^{1/2}$. Then, $\rho_{1/2,1}$ has a lower bound of 0.707 with the three MAFs compared with $\rho_{0,1} \leq 1/3$. The smaller the MAF, the higher is the efficiency of z^2_{MERT} when $\theta \in [1/2, 1]$, which is consistent with the findings in Table 1, where z^2_{MERT} has a higher minimum power with MAF = 0.15.

4.4. An application

To illustrate the use of the proposed methods, we consider a marker on chromosome 6 near the human leucocyte antigen region (ID: rs239558), which is shown to be associated with rheumatoid arthritis (Amos *et al.*, 2006). The genotype counts are $(n_{10}, n_{11}) = (20, 29)$, $(n_{20}, n_{21}, n_{22}) = (4, 15, 8)$, and $(n_{31}, n_{32}) = (10, 34)$. For the model space $\theta \in [0, 1]$, the p-values are 0.00095 for $z^2(0)$, 0.00072 for $z^2(1/2)$ (the TDT), 0.081 for $z^2(1)$, 0.00067 for z^2_{MERT}, 0.0019 for MAX3 $= \max_{\theta=0,1/2,1} |z(\theta)|$, and 0.0011 for MAX $= \max_{\theta\in[0,1]} z^2(\theta)$. z^2_{MERT} has the smallest p-value, followed by the TDT. MAX3 and MAX have similar p-values, which are greater than that of z^2_{MERT}.

If prior results indicate that the true genetic model is more likely recessive or additive or in between the two, we can consider $\theta \in [0, 1/2]$. From the methods studied here, z^2_{MERT} is based on $z(0)$ and $z(1/2)$, which are also the extreme pair. Then, we consider MAX3 $= \max(|z(0)|, |z(1/4)|, |z(1/2)|)$ and MAX $= \max_{\theta\in[0,1/2]} z^2(\theta)$. The new p-values become 0.00032 for z^2_{MERT}, 0.00070 for MAX3, and 0.00069 for MAX.

5. Discussion

We have studied some properties of efficiency robust tests under a general setting, which unify and extend previous results derived for specific applications. More specifically, our results can be applied when the alternative hypothesis is constrained with the null point on the boundary of the parameter space. Through a transformation, we change the hypothesis testing problem with a constrained parameter space to a problem with an unknown model parameter θ and derive the score test $z(\theta)$ as a function of θ. Another simple but important feature of our method is that, after the transformation, we denoted the log-likelihood function as $l_n(1-\theta+\theta\lambda, \lambda, \alpha)$, not $l_n(\lambda, \theta, \alpha)$. The former allows us to obtain the score test and the asymptotic correlation in simple closed forms. We considered two robust tests, the MERT and MAX3, based on a family of score tests $\{z(\theta) : \theta \in \Theta\}$. The literature for the robustness of tests is more broad. For example, as mentioned by a reviewer, we do not consider validity robustness. Moreover, we did not consider how to choose a robust score and use $z(\theta)$ based on that robust score, as studied by Huang *et al.* (2009) for robust tests of two-sample problems.

There is a trade-off between efficiency and robustness. If we can accurately guess or estimate θ using prior data, using the score test $z(\theta)$ with θ is more powerful than using Pearson's test or MAX3. On the other hand, if no prior knowledge for θ is available and the minimum

correlation of the score tests over Θ is low, MAX3 is more robust than the one-degree-of-freedom score test.

In genetic association studies, particularly in genome-wide association studies (GWASs), a large number of genetic markers (from 500,000 to millions) are tested. The markers that are associated with a disease are often not disease loci. The associations are detected because of the linkage disequilibrium (correlation) between the markers and the disease loci, which actually distorts the genetic models at the markers even when the true genetic models at the disease loci are known or can be correctly specified (Zheng *et al.*, 2009b; Vukcevic *et al.*, 2011). Although the trend (score) test $z(\theta)$ with $\theta = 1/2$ is commonly used, it may not be robust to detect markers with non-additive genetic models. In fact, Sladek *et al.* (2007) applied MAX3 in a GWAS for type 2 diabetes, which identified several markers that would not have been identified if $z(1/2)$ were used alone. Ranking and selecting markers in GWAS using MAX3 have also been shown to be *a more useful approach* than using $z(1/2)$ alone (Li *et al.*, 2008).

Our application focused on genetic association studies. But it can be useful in other settings. An example described by Barndorff-Nielsen and Cox (1994, p. 109) is $Y_1 \sim N(\psi \cos\eta, 1)$ and $Y_2 \sim N(\psi \sin\eta, 1)$. The null hypothesis is $H_0 : \psi = 0$, under which η is not defined. Rewrite $N(\psi \sin\eta, 1) = N(\psi \cos\eta \tan\eta, 1) = N(\lambda\theta, 1)$ with $\lambda = \psi \cos\eta$ and $\theta = \tan\eta$. H_0 is equivalent to $\lambda = 0$. Hence, $Y_1 \sim N(\lambda, 1)$ and $Y_2 \sim N(\lambda\theta, 1)$. The efficiency robust tests can be derived for $\theta \in [\theta_0, \theta_1]$. From our results, θ_0 and θ_1 form the extreme pair. The performance of the MERT depends on the length of $\theta_1 - \theta_0$. Our results can also be applied to a testing hypothesis with a constrained parameter space, such as Λ_C described in this paper, through a transformation to introduce model index parameters.

We restricted our attention to a two-dimensional parameter space, which is most relevant to single-marker genetic association studies. Our results can be extended to high-dimensional setting, which needs further research. Robust properties and potential linear dependence of score statistics for a high-dimensional parameter space would be useful or provide insight when developing robust procedures for testing gene–environment and gene–gene interactions.

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