HERITABILITY ESTIMATION IN HIGH DIMENSIONAL LINEAR MIXED MODELS

A. BONNET, E. GASSIAT, AND C. LÉVY-LEDUC

Abstract. We propose in this paper a novel and efficient methodology for estimating the heritability in high dimensional linear mixed models. Our approach is based on a maximum likelihood strategy and can deal with sparse random effects. We establish that our estimator of the heritability is $\sqrt{n}$-consistent in the general case under mild assumptions and that it satisfies a central limit theorem in the case where the random effect part is not sparse which gives as a byproduct a confidence interval for the heritability. Some Monte-Carlo experiments are also conducted in order to show the finite-sample performance of our estimator. Our approach is implemented in the R package HiLMM which is available from the web page of the first author and which will be soon available from the Comprehensive R Archive Network (CRAN).

1. Introduction

For many complex traits in human populations, one can observe a huge gap between the genetic variance explained by population studies and the variance explained by specific variants found thanks to genome wide association studies (GWAS). This gap has been called by [10] and [11] the “dark matter” of the genome or the “dark matter” of heritability. To estimate this lacking heritability when the considered trait is the height, [19] suggested the use of linear mixed models. Such models are defined as follows:

$$Y = X\beta + Zu + e,$$

where $Y = (Y_1, \ldots, Y_n)'$ is the vector of observations (phenotypes), $X$ is a $n \times p$ matrix of predictors, $\beta$ is a $p \times 1$ vector containing the unknown linear effects of the predictors, $u$ and $e$ correspond to the random effects.

Originally, this model appeared in order to explain how the genetic component of a quantitative trait is correlated between relatives, see [4]. It has also been extensively used in quantitative genetics in order to estimate the heritability of traits and breeding values, see for instance [9]. In the GWAS, where [19] suggested the use of linear mixed models, the goal is...
to measure genotypes at a large number of single nucleotide polymorphisms (SNP) -typically 300,000 to 500,000- in large sample of individuals -typically, 1000- in order to identify genetic variants that explain phenotypes variations. More precisely, in this application, the \( \mathbf{u} \) component \( u_i \) of \( \mathbf{u} \) corresponds to the effect of the \( i \)th SNP on the phenotype and \( \mathbf{e} \) corresponds to the environmental effect.

Moreover, in (1), following the assumptions of [18], \( \mathbf{Z} = (Z_{i,j}) \) is a \( n \times N \) matrix such that the \( Z_{i,j} \) are random variables which are defined from a matrix \( \mathbf{W} = (W_{i,j})_{1 \leq i \leq n, 1 \leq j \leq N} \) as follows:

\[
Z_{i,j} = \frac{W_{i,j} - \overline{W}_j}{s_j}, \quad i = 1, \ldots, n, \quad j = 1, \ldots, N,
\]

where

\[
\overline{W}_j = \frac{1}{n} \sum_{i=1}^{n} W_{i,j}, \quad s_j^2 = \frac{1}{n} \sum_{i=1}^{n} (W_{i,j} - \overline{W}_j)^2, \quad j = 1, \ldots, N.
\]

In (2) and (3) the \( W_{i,j} \)'s are such that for each \( j \) in \( \{1, \ldots, N\} \) the \( (W_{i,j})_{1 \leq i \leq n} \) are independent and identically distributed random variables and such that the columns of \( \mathbf{W} \) are independent. With this definition the columns of \( \mathbf{Z} \) are empirically centered and normalized. In GWAS experiments, for each \( j \), the \( (W_{i,j})_{1 \leq i \leq n} \) are i.i.d binomial random variables with parameters 2 and \( p_j \), see for instance [18] and [6]. More precisely, \( W_{i,j} = 0 \) (resp. 1, resp. 2) if the genotype of the \( i \)th individual at locus \( j \) is \( qq \) (resp. \( Qq \), resp. \( QQ \)) where \( p_j \) is the frequency of \( Q \) allele at locus \( j \). In the GWAS framework \( \mathbf{Z} \) is thus a matrix having a number of rows equal to the number of individuals in the experiment that is \( n \approx 1000 \) and a number of columns equal to the number of SNPs taken into account in the experiment, namely \( N \approx 500,000 \).

Since all the SNPs are not necessarily causal, that is do not explain a given phenotype, we shall assume that

\[
u_i \sim^{i.i.d.} (1 - q)\delta_0 + q\mathcal{N}(0, \sigma_u^2), \quad \text{for all} \ 1 \leq i \leq N \quad \text{and} \quad \mathbf{e} \sim \mathcal{N} \left( 0, \sigma_e^2 \text{Id}_{\mathbb{R}^n} \right),
\]

where \( \text{Id}_{\mathbb{R}^n} \) denotes the \( n \times n \) identity matrix and \( q \) is in \( (0, 1] \). With this modeling, \( q \) actually corresponds to the proportion of non null components in \( \mathbf{u} \) that is to the proportion of causal SNPs. The second part of (4) means that the environmental effects are assumed to be i.i.d among the individuals. Note that this model encompasses the classical linear mixed models, when \( q = 1 \), where the random vectors \( \mathbf{u} \) and \( \mathbf{e} \) are assumed to be Gaussian random vectors with a diagonal covariance matrix.
In Model (1) with (2), (3), (4), one can observe that

\[ \text{Var}(Y|Z) = Nq\sigma_u^* + \sigma_e^2 \text{Id}_{\mathbb{R}^n} \],

where \( R = \frac{ZZ'}{N} \).

Inspired by [14], Model (1) can be rewritten by using the following parameters:

\[ \sigma^* = Nq\sigma_u^2 + \sigma_e^2 \] and \( \eta^* = \frac{Nq\sigma_u^2}{Nq\sigma_u^2 + \sigma_e^2} \).

Thus,

\[ \text{Var}(Y|Z) = \eta^* \sigma^* \text{Id}_{\mathbb{R}^n} \].

The parameter \( \eta^* \) which belongs to \([0, 1]\) is called the heritability in the case \( q = 1 \), see for instance [18], and determines how the variance is shared between \( u \) and \( e \). It actually corresponds to the proportion of phenotypic variance explained by the causal variants.

Several approaches can be used for estimating the heritability in the case where \( q = 1 \). Among them, we can quote the REML (REstricted Maximum Likelihood) approach, originally proposed by [13] and described for instance in [15], which consists in estimating \( \sigma_u^* \) and \( \sigma_e^* \) for estimating \( \eta^* \). However, this type of approach is based on iterative procedures that require expensive matrix operations. Hence, several approximations have been proposed such as the AI algorithm ([5]) which is used for instance in the software GCTA (Genome-wide Complex Trait Analysis) described in [19]. Other approximations have also been proposed in the EMMA algorithm ([8]). For further details on the different approximations that could be used we refer the reader to [14]. The latter paper proposes another methodology for estimating the heritability which consists in rewriting Model (1) with the parameters (5) and in using an eigenvalue decomposition of the matrix \( R \). According to the numerical experiments conducted in [14] their approach has the lowest computational burden among the available algorithms.

The high dimensional linear mixed model where \( u \) is sparse, that is the case where \( q < 1 \), which is the most realistic case for the applications that we have in view, has been studied according two directions: detection and estimation. Concerning the detection field in this framework, we are only aware of the work of [1] in which a testing procedure for detecting a sparse vector in high dimensional linear sparse regression model is also proposed and compared with the one proposed by [7]. As for the procedures dedicated to the heritability estimation, there exist, to the best of our knowledge, only two approaches: the approach of [18] who propose to approximate the genetic correlation between every pair of individuals across the set of causal SNPs by the genetic correlation across the set of all SNPs and the approach
of [6] who propose a methodology based on MCEM (Monte-Carlo expectation-maximization) developed by [17]. However, as far as the estimation issue in the high dimensional linear mixed model is concerned, the authors of these papers did not establish the theoretical properties of their estimators.

In this paper, we propose a novel and computationally efficient estimator of \( \eta^* \), described below, which is based on the parametrization with \( \sigma^* \) and \( \eta^* \) of [14] and which can deal with matrices \( Z \) of size \( 1000 \times 500,000 \). Moreover, we prove that this new estimator is \( \sqrt{n} \)-consistent in the following asymptotic framework: \( n \to \infty \) and \( N \to \infty \) such as \( n/N \to a > 0 \) and satisfies under mild assumptions a central limit theorem in both cases \( q = 1 \) and \( q < 1 \).

Note that in our asymptotic framework where \( \eta^* \) is a constant and \( N \) tends to infinity \( \sigma_u^* \) tends to 0 as \( N \) tends to infinity.

In the sequel, up to considering the projection of \( Y \) onto the orthogonal of the image of \( X \) and for notational simplicity, we shall focus on the following model

\[
Y = Zu + e ,
\]

where the assumptions on \( u \) and \( e \) are given in [1]. In the case where \( q = 1 \), observe that

\[
Y \mid Z \sim \mathcal{N} \left( 0, \eta^* \sigma^* R + (1 - \eta^*) \sigma^* \sigma^2 \text{Id}_{\mathbb{R}^n} \right).
\]

Let \( U \) be an orthogonal matrix (\( U'U = UU' = \text{Id}_{\mathbb{R}^n} \)) such that \( URU' = \text{diag}(\lambda_1, \ldots, \lambda_n) \) is a diagonal matrix having its diagonal entries equal to \( \lambda_1, \ldots, \lambda_n \). Hence, in the case where \( q = 1 \) and conditionally to \( Z \), \( \tilde{Y} = U'Y \) is a zero-mean Gaussian vector with covariance matrix equal to \( \text{diag}(\eta^* \sigma^* \lambda_1 + (1 - \eta^*) \sigma^2, \ldots, \eta^* \sigma^2 \lambda_n + (1 - \eta^*) \sigma^2) \), where the \( \lambda_i \)'s are the eigenvalues of \( R \). The maximum likelihood approach, in the case \( q = 1 \), would lead to estimate \( \eta^* \) by \( \hat{\eta} \) defined as a maximizer of

\[
L_n(\eta) = -\log \left( \frac{1}{n} \sum_{i=1}^{n} \frac{\tilde{Y}_i^2}{\eta(\lambda_i - 1) + 1} \right) - \frac{1}{n} \sum_{i=1}^{n} \log (\eta(\lambda_i - 1) + 1) ,
\]

where the \( \tilde{Y}_i \)'s are the components of the vector \( \tilde{Y} = U'Y \). Note that \( L_n \) indeed corresponds to the conditional log-likelihood optimized with respect to \( \sigma^2 \) up to some irrelevant constants.

We shall establish in Theorem 2 which is proved in Section ??, that this strategy produces \( \sqrt{n} \)-consistent estimators of \( \eta^* \) even in both cases: \( q = 1 \) and \( q < 1 \) and also that this estimator satisfies a central limit theorem which provides as a by-product confidence intervals for \( \eta^* \).

In addition, this approach is implemented in the R package HiLMM which is available from
the web page of the first author and which will be soon available from the Comprehensive R Archive Network (CRAN).

2. Theoretical results

Observe that another way of writing Model (6) with the parameters defined in (5) consists in writing

$$
Y = \frac{1}{\sqrt{N}}Zt + \sigma^* \sqrt{1 - \eta^*} \varepsilon ,
$$

where $\varepsilon$ is a $n \times 1$ Gaussian vector having a covariance matrix equal to identity and $t = (t_1, \ldots, t_N)'$ is a random vector such that

$$
t_i = \frac{\sigma^* \sqrt{\eta^*}}{\sqrt{q}} w_i \pi_i ,
$$

where the $w_i$'s and the $\pi_i$'s are independent, $w = (w_1, \ldots, w_N)'$ is a Gaussian vector with a covariance matrix equal to identity and the $\pi_i$'s are i.i.d Bernoulli random variables such that $P(\pi_1 = 1) = q$.

The estimator $\hat{\eta}$ is defined as a maximizer of $L_n(\eta)$ for $\eta \in [0, 1 - \delta]$ for some small $\delta > 0$, $L_n$ being given in (7). We shall study the asymptotic properties of $\hat{\eta}$ as $n$ and $N$ tend to infinity in a comparable way, that is when $n/N \rightarrow a > 0$. To understand the asymptotic behavior of $\hat{\eta}$, we shall first prove its consistency, then use a Taylor expansion of the derivative of $L_n$ around $\hat{\eta}$ in the usual way. The computations as can be seen in (7) involve empirical means of functions of the eigenvalues $\lambda_i$ of $R = ZZ'$.

The following lemma ensures that the result of [12] which gives the empirical spectral distribution of sample covariance matrices $ZZ'/N$ holds even when the entries $Z_{i,j}$ of the
matrix $Z$ are not i.i.d. random variables but when $Z$ is obtained by empirical standardization of a matrix $W$ satisfying (A1).

**Lemma 1.** Under (A1), as $n, N \to \infty$ such that $n/N \to a > 0$, the empirical spectral distribution of $R_N = ZZ'/N$: $F^{R_N}(x) = n^{-1} \sum_{k=1}^{n} \mathbb{1}_{[\lambda_k \leq x]}$ tends almost surely to the Marchenko-Pastur distribution defined as the distribution function of $\mu_a$ where, for any measurable set $A$,

$$
\mu_a(A) = \begin{cases} 
1 - \frac{1}{a} & \text{if } a > 1 \\
\nu_a(A) & \text{if } a \leq 1 
\end{cases}
$$

with

$$
d\nu_a(\lambda) = \frac{1}{2\pi} \frac{\sqrt{(a_+ - \lambda)(\lambda - a_-)}}{a_+ a_-} \mathbb{1}_{[a_- a_+]}(x) dx, \ a_{\pm} = (1 \pm \sqrt{a})^2. \tag{9}
$$

In $F^{R_N}(x)$, the $\lambda_k$’s denote the eigenvalues of $R_N$.

Our first main result is the $\sqrt{n}$-consistency of the estimator $\hat{\eta}$.

**Theorem 1.** Let $Y = (Y_1, \ldots, Y_n)'$ satisfy Model (8) with $\eta^* > 0$ and the entries $W_{i,j}$ of $W$ satisfy (A1). Then, for all $q$ in $(0,1]$, as $n, N \to \infty$ such that $n/N \to a \in (0,1]$,

$$
\sqrt{n}(\hat{\eta} - \eta^*) = O_P(1).
$$

Such a result is a theoretical cornerstone to legitimate the use of an estimator. However, statistical inference has to be based on confidence sets. The next step is thus to find the asymptotic distribution of $\sqrt{n}(\hat{\eta} - \eta^*)$. Define for any $\eta \in [0,1]$ and $\lambda \geq 0$

$$
g(\eta, \lambda) = \frac{\lambda - 1}{\eta(\lambda - 1) + 1}.
$$

Define also

$$
\hat{\sigma}^2_n = \left\{ \frac{1}{n} \sum_{i=1}^{n} g(\hat{\eta}, \lambda_i)^2 - \left( \frac{1}{n} \sum_{i=1}^{n} g(\hat{\eta}, \lambda_i) \right)^2 \right\}
$$

and

$$
\hat{\sigma}^2(a, \eta^*) = \left\{ \int g(\eta, \lambda)^2 d\mu_a(\lambda) - \left( \int g(\eta, \lambda) d\mu_a(\lambda) \right)^2 \right\}. \tag{10}
$$

We are now ready to state our second main result about the asymptotic distribution of $\sqrt{n}(\hat{\eta} - \eta^*)$. For general $q$, the result only holds when the entries of $Z$, that is the random variables $Z_{i,j}$ are i.i.d. standard Gaussian. Indeed, as may be seen when computing the variances, we need to be able to find the asymptotic behavior of empirical means of functions of the eigenvalues together with the eigenvectors of the matrix $R = ZZ'/N$. 

Theorem 2. Let $Y = (Y_1, \ldots, Y_n)'$ satisfy Model (3) with $\eta^* > 0$ and assume that the random variables $Z_{i,j}$ are i.i.d. $N(0,1)$. Then for any $q \in (0,1]$, as $n,N \to \infty$ such that $n/N \to a > 0$,
\[ \sqrt{n}(\hat{\eta} - \eta^*) \]
converges in distribution to a centered Gaussian random variable with variance
\[ \tilde{\sigma}^2(a, \eta^*, q) = \frac{2}{\tilde{\sigma}^2(a, \eta^*)} + 3a^2 \eta^* q \left( \frac{1}{q} - 1 \right) S(a, \eta^*) \]
where
\[ S(a, \eta^*) = \left[ \int \frac{\lambda}{(\eta^*(\lambda - 1) + 1)^2} d\mu_a(\lambda) - \int \frac{\lambda}{(\eta^*(\lambda - 1) + 1)} d\mu_a(\lambda) \int \frac{\lambda - 1}{(\eta^*(\lambda - 1) + 1)} d\mu_a(\lambda) \right]^2. \]

In the case where $q = 1$, the result holds in the general situation described in (A1), and allows us to propose confidence sets with precise asymptotic confidence level.

Theorem 3. Let $Y = (Y_1, \ldots, Y_n)'$ satisfy Model (3) with $\eta^* > 0$ and the entries $W_{i,j}$ of $W$ satisfy (A1). Then as $n,N \to \infty$ such that $n/N \to a > 0$,
\[ \hat{\sigma}_n \sqrt{\frac{n}{2}} (\hat{\eta} - \eta^*) \]
converges in distribution to $N(0,1)$.

Let us now give some additional comments on the previous results. Firstly, it has to be noticed that none of the limiting variance depends on $\sigma^*$. Secondly, Theorem 2 is proved here only in the case where the $Z_{i,j}$ are i.i.d. Gaussian. This is because we used several times that the matrix of eigenvectors of $ZZ'/N$ is independent of the eigenvalues, and uniformly distributed on the set of orthonormal matrices. We think that the result of Theorem 2 is also valid when the $Z_{i,j}$ are defined from the $W_{i,j}$ satisfying (A1), as suggested by the numerical results obtained in Section 3. To prove it requires new results in an active research topic of the random matrix theory field. We can observe in the expression of $\tilde{\sigma}^2(a, \eta^*)$ given in Theorem 2 that the presence of $q$ is counterbalanced by the presence of $a^2$. This will be confirmed by the results obtained in the numerical results obtained in Section 3. Finally, we can see that asymptotic confidence intervals for $\eta^*$ can be derived from Theorems 2 and 3. However, in the case $q < 1$, the computation of the confidence interval requires the knowledge of $q$ which is of course unknown in a real data framework or at least an estimation of it.
3. Numerical experiments

In this section, we first explain how to implement our method and then we illustrate the theoretical results of Section 2 on finite sample size observations for both cases: $q = 1$ and $q < 1$. We also compare the results obtained with our approach to those obtained by the GCTA software described in [18] and [19] which is a reference in quantitative genetics.

3.1. Implementation. In order to obtain $\hat{\eta}$, we used a Newton-Raphson approach which is based on the following recursion: starting from an initial value $\eta_p^0$, 

$$
\eta^{(k+1)} = \eta^{(k)} - \frac{L'_n(\eta)}{L''_n(\eta)}, \quad k \geq 1,
$$

where $L'_n$ and $L''_n$ denote the first and second derivatives of $L_n$ defined in (7), respectively. The closed form expression of these quantities are given in (13) and (25), respectively. In practice, this approach converges after at most 20 iterations and is not sensitive to the initialization, namely to the value of $\eta_p^0$.

3.2. Results in Model (4) when $q = 1$. We shall first consider the performance of the estimator $\hat{\eta}$ when $q = 1$ for $\eta^*$ in $\{0.3, 0.5, 0.7\}$, $n = 1000$, $\sigma^*_u = 0.1$ and for $a$ in $\{0.01, 0.02, 0.05, 0.1, 0.2, 0.5, 1\}$, where $a = n/N$. We generated 500 data sets according to Model (1) using these parameters and $Z$ as defined in (2) where the $W_{i,j}$ are binomial random variables with parameters 2 and $p_{ij}$. In our experiments the $p_{ij}$'s are uniformly drawn in $[0.1, 0.5]$. The corresponding boxplots of $\hat{\eta}$ are displayed in Figure 1. We can see from this figure that our approach provides unbiased estimators of $\eta^*$ and that the smaller the $a$ the larger the empirical variance.

In order to illustrate the central limit theorem given in Theorem 3 we first display in Figure 2 the histograms of $\hat{\sigma}_n(n/2)^{1/2} (\hat{\eta} - \eta^*)$ along with the p.d.f of a standard Gaussian random variable for $\eta^* = 0.5$ and different values of $a$. We can see that the Gaussian p.d.f fits well the data in all the considered cases. We also display in Figure 7 the values of $n^{-1/2} \sqrt{2\hat{\sigma}_n^{-2}}$ and the empirical standard deviation of $(\hat{\eta} - \eta^*)$ averaged over all the experiments. As shown in Theorem 3 we also observe empirically that both quantities are very close.

In practice, the value of $\hat{\sigma}_n^{-1}(n/2)^{-1/2}$ can be used for deriving confidence intervals for $\eta^*$. As we can see from Figure 7 our approach leads to very accurate confidence intervals for $a$ larger than 0.1 even in finite sample size cases.
Figure 1. Boxplots of $\hat{\eta}$ for different values of $a$, for $\eta^* = 0.3$ (left), $\eta^* = 0.5$ (middle) and $\eta^* = 0.7$ (right). The true value of $\eta^*$ is displayed each boxplot with a bold point.

Figure 2. Histograms of $\hat{\sigma}_n (n/2)^{1/2} (\hat{\eta} - \eta^*)$ for $\eta^* = 0.5$ and $a = 0.05$ (left), $a = 0.1$ (middle), $a = 0.5$ (right) and the p.d.f of a standard Gaussian random variable in plain line.

Let us now compare our results with those obtained with the software GCTA. As we can see from Figure 4 which displays the boxplots of $\hat{\eta}$ for different values of $a$ when $\eta^* = 0.7$, the results found by our approach and GCTA are very close. In both cases, we observe that when $a$ is close to 1 the estimations of $\eta^*$ are very accurate but when $a$ is small the standard error becomes very high.

3.3. Results in model 4 when $q < 1$. This section is dedicated to the study of the performance of $\hat{\eta}$ when $q < 1$. We generated 500 data sets according to Model 4 for $\eta^* = 0.7$,
Figure 3. Values of $n^{-1/2}\sqrt{2\sigma^2_n}$ ("•") and the empirical standard deviation of $\hat{\eta} - \eta^*$ (plain line) for several values of $\eta^*$ (0.3 (left), 0.5 (right)).

Figure 4. Boxplots of $\hat{\eta}$ for different values of $a$, using our method (left) and GCTA (right).

$a \in \{0.05, 0.1, 0.5, 1\}$, different values of $q$ and $Z$ defined in (2) where the $W_{i,j}$ are binomial random variables with parameters 2 and $p_j$. In our experiments the $p_j$’s are uniformly drawn in $[0.1, 0.5]$.

Figure 5 displays the boxplots of $\hat{\eta}$ for these parameters. We can see from this figure that for small values of $a$, the estimation of $\eta^*$ is not altered by the presence of null components. When $a$ is close to 1, we obtain the same result if $q$ is not too high ($q \leq 0.05$).

In order to illustrate the central limit theorem given in Theorem 2, we first display in Figure 6 the histograms of $\sigma^{-1}_n n^{1/2} (\hat{\eta} - \eta^*)$ along with the p.d.f of a standard Gaussian random variable for $\eta^* = 0.7$, two values of $q$: $q = 0.01$ and $q = 0.1$ and $a = 0.5$ (top) and
two values of $a$: $a = 0.2$ and $a = 0.5$ with $q = 0.5$ (bottom). Here, $\tilde{\sigma}_n$ is the empirical version of $\tilde{\sigma}(a, \eta^*, q)$ where $\tilde{\sigma}$ is replaced by $\hat{\sigma}_n$ and $S(a, \eta^*)$ is replaced by its empirical version with the eigenvalues of $R$. When $a$ is large ($a = 0.5$), we can see that the higher $q$ the better the Gaussian p.d.f fits the histograms.

We also display in Figure 7 the values of $n^{-1/2}\tilde{\sigma}_n$ and the empirical standard deviation of $(\hat{\eta} - \eta^*)$ averaged over all the experiments for $\eta^* = 0.7$ and $q = 0.5$. As shown in Theorem 2, we observe empirically that both quantities are very close. We also display in this figure the value of $n^{-1/2}\tilde{\sigma}_n$ with $q = 1$ which boils down to consider the asymptotic standard deviation found in the non sparse model. We can see from this figure that neglecting the term depending on $q$ leads to underestimate the asymptotic variance of $\hat{\eta}$ and that this difference is all the more striking that $a$ is close to 1.

Figure 5. Boxplots of $\hat{\eta}$ for different values of $q$, with $\eta^* = 0.7$ and $a = 1$ (top left), $a = 0.5$ (top right), $a = 0.1$ (bottom left) and $a = 0.05$ (bottom right). The boxplots are based on 500 replications.
Figure 6. Histograms of $\hat{\sigma}_n^{-1} n^{1/2} (\hat{\eta} - \eta^*)$ for $a = 0.5$ and $q = 0.01$ (top left), $q = 0.1$ (top right), and for $q = 0.5$, $a = 0.2$ (bottom left) and $a = 0.5$ (bottom right).

4. Discussion

In the course of this study, we have shown that our method is a very efficient technique which has two main features which make it very attractive. Firstly, it gives access to the estimation of the heritability as well as to the associated confidence intervals in high dimensional linear models where the random effect part is allowed to be sparse. Secondly, our approach has a very low computational burden which makes its use possible on real data coming from GWAS.

However, the confidence intervals depend on $q$ which is in general not available in a real data framework. It would thus be interesting to propose a way to estimate consistently this
Figure 7. Values of $n^{-1/2} \tilde{\sigma}_n$ with the real value of $q$ ($q = 0.5$) ("•"), $q = 1$ (dotted line) and the empirical standard deviation of $(\hat{\eta} - \eta^*)$ (plain line) for $\eta^* = 0.7$.

Parameter. A possible solution would be to investigate the theoretical consistency of the approach proposed by [6], or to take inspiration from the work of [1]. This question will be the subject of a future work.

5. Proofs

Let us write the singular value decomposition (SVD) of the $n \times N$ matrix $Z/\sqrt{N}$ as

$$\frac{1}{\sqrt{N}}Z = U (\sqrt{D} 0) V'$$

where $U$ (already introduced in Section 1) is a $n \times n$ orthonormal matrix, $V$ is a $N \times N$ orthonormal matrix and $\sqrt{D}$ is a $n \times n$ diagonal matrix having its diagonal entries equal to $\sqrt{\lambda_i}$, the $\lambda_i$'s being the eigenvalues of $R = ZZ'/N$ previously defined. Thus, (8) rewrites as

$$\tilde{Y} = U'Y = (\sqrt{D} 0) V't + \sigma^* \sqrt{1 - \eta^*} \tilde{\varepsilon},$$

where $\tilde{\varepsilon} = U'\varepsilon$ is a $n \times 1$ centered Gaussian vector having a covariance matrix equal to identity.

We shall use repeatedly the following lemma which is proved in Section 5.3.

Lemma 2. Let $\tilde{Y}$ be defined by (11) and $H$ be a $n \times n$ diagonal matrix, then

$$\text{Var}(\tilde{Y}'HY|Z) = 2\sigma^* \text{Tr} \left[ H^2 \{(1 - \eta^*)Id_{\mathbb{R}^n} + \eta^*D\}^2 \right] + 3\sigma^* \eta^* \left( \frac{1}{q} - 1 \right) \sum_{1 \leq i \leq N} M_{ii}^2,$$
where
\[
M = V \begin{pmatrix} DH & 0 \\ 0 & 0 \end{pmatrix} V',
\]
and
\[
\text{Var} \left( \hat{Y}' \hat{H} \hat{Y} | Z \right) \leq 2\sigma^4 \text{Tr} \left[ H^2 \{(1 - \eta^*) \text{Id}_{\mathbb{R}^n} + \eta^* D\}^2 \right] + 3\sigma^4 \eta^2 \left( \frac{1}{q} - 1 \right) \text{Tr}[D^2 H^2].
\]

Another useful lemma will be the following.

**Lemma 3.** Under (A1) let \( h : \mathbb{R}^+ \to \mathbb{R}^+ \) be such that there exist \( \alpha > 0 \) and \( C \) such that for all \( n \),
\[
\mathbb{E} \left( \frac{1}{n} \sum_{i=1}^{n} h(\lambda_i)^{1+\alpha} \right) \leq C.
\]
Then
\[
\frac{1}{n} \sum_{i=1}^{n} h(\lambda_i) = \int h(\lambda) d\nu_\alpha(\lambda) + o_p(1).
\]

The proof of this lemma follows from the application of Lemma 1 to the bounded function \( h\mathbb{1}_{h \leq M} \), and the Markov inequality applied to the empirical mean of \( h\mathbb{1}_{h > M} \).

**Lemma 4.** Under (A2) let \( n, N \to \infty \) be such that \( n/N \to a > 0 \). Then there exists \( C \) such that for all \( n \),
\[
\mathbb{E} \left[ \frac{1}{n} \sum_{i=1}^{n} \lambda_i^2 \right] \leq C.
\]
To prove the lemma, notice that \( \sum_{i=1}^{n} \lambda_i^2 = \text{Tr}[Z'Z]/N^2 \). But
\[
\mathbb{E} \left( \text{Tr} \left( (Z'Z)^2 \right) \right) = \sum_{k \neq k'} \sum_{i,j} \mathbb{E}(Z_{i,k}Z_{j,k}) \mathbb{E}(Z_{i,k'}Z_{j,k'}) + \sum_k \sum_i \mathbb{E}(Z_{i,k}^2) = nN(N-1) + N(N-1)n(n-1) \left( \frac{1}{n-1} \right)^2 + n^2 N
\]
where the values of the involved expectations may be found in the proof of Lemma 1 in Section 5.3. We thus have
\[
\mathbb{E} \left[ \frac{1}{n} \sum_{i=1}^{n} \lambda_i^2 \right] \leq 2 + \frac{n}{N}
\]
which ends the proof.
5.1. **Proof of Theorem** \(\dagger\) The first step is to prove the consistency of \(\hat{\eta}\). We shall first prove that \(L_n(\eta)\) converges uniformly for \(\eta \in [0, 1 - \delta]\) in probability to \(L(\eta)\) given by

\[
L(\eta) = -2 \log \sigma^* - \log \int \left[ \frac{\eta^*(\lambda) - 1 + 1}{\eta(\lambda - 1) + 1} \right] d\mu_\eta(\lambda) - \int \log \eta(\lambda - 1) + 1) d\mu_\eta(\lambda).
\]

Using Lemma \(\mathcal{Z}\) with \(H\) with diagonal entries \(1/(\eta(\lambda_i - 1) + 1)\), we get that

\[
\var{\frac{1}{n} \sum_{i=1}^{n} \frac{\hat{Y}_i^2}{\eta(\lambda_i - 1) + 1} | Z} \leq \frac{\sigma^4}{n^2} \sum_{i=1}^{n} 2 \left( \frac{\eta^*(\lambda_i - 1) + 1}{\eta(\lambda_i - 1) + 1} \right)^2 + 3 \left( \frac{1}{q} - 1 \right) \left( \frac{\eta^* \lambda_i}{\eta(\lambda_i - 1) + 1} \right)^2
\]

\[
\leq \sigma^4 \left( 2 + 3 \left( \frac{1}{q} - 1 \right) \right) \frac{1}{n^2} \sum_{i=1}^{n} \left( \frac{\lambda_i + 1}{\delta} \right)^2
\]

since \(\eta \in [0, 1 - \delta]\). Now, using Lemma \(\mathcal{H}\) we get that

\[
\frac{1}{n^2} \sum_{i=1}^{n} \left( \frac{\lambda_i + 1}{\delta} \right)^2 = o_P(1)
\]

which leads to

\[
\frac{1}{n} \sum_{i=1}^{n} \frac{\hat{Y}_i^2}{\eta(\lambda_i - 1) + 1} = \mathbb{E} \left[ \frac{1}{n} \sum_{i=1}^{n} \frac{\hat{Y}_i^2}{\eta(\lambda_i - 1) + 1} | Z \right] + o_P(1)
\]

\[
= \sigma^2 \frac{1}{n} \sum_{i=1}^{n} \frac{\eta^*(\lambda_i - 1) + 1}{\eta(\lambda_i - 1) + 1} + o_P(1).
\]

Now, using Lemma \(\mathcal{X}\) and Lemma \(\mathcal{A}\) we easily get that \(\frac{1}{n} \sum_{i=1}^{n} \frac{\eta^*(\lambda_i - 1) + 1}{\eta(\lambda_i - 1) + 1}\) converges in probability to \(\int \frac{\eta^*(\lambda) - 1 + 1}{\eta(\lambda - 1) + 1} d\mu_\eta(\lambda)\) and \(\frac{1}{n} \sum_{i=1}^{n} \log[(\eta(\lambda_i - 1) + 1)]\) converges in probability to \(\int \log(\eta(\lambda - 1) + 1) d\mu_\eta(\lambda)\) so that \(L_n(\eta) = L(\eta) + o_P(1)\).

To prove that the convergence is uniform over \([0, 1 - \delta]\), we just need to prove that

\[
\sup_{\eta \in [0, 1 - \delta]} |L_n'(\eta)| = O_P(1).
\]

We have

\[
L_n'(\eta) = \left( \frac{1}{n} \sum_{i=1}^{n} \frac{\hat{Y}_i^2}{(\eta(\lambda_i - 1) + 1)} \right) \left( \frac{1}{n} \sum_{i=1}^{n} \frac{\hat{Y}_i^2}{\eta(\lambda_i - 1) + 1} \right)^{-1} - \frac{1}{n} \sum_{i=1}^{n} \frac{\lambda_i - 1}{\eta(\lambda_i - 1) + 1}.
\]

A study of \(\eta \rightarrow \left( \frac{1}{n} \sum_{i=1}^{n} \frac{\hat{Y}_i^2}{(\eta(\lambda_i - 1) + 1)} \right) \left( \frac{1}{n} \sum_{i=1}^{n} \frac{\hat{Y}_i^2}{\eta(\lambda_i - 1) + 1} \right)^{-1}\) shows that it is decreasing and that it takes negative values for \(\eta \in [0, 1 - \delta]\), so that its absolute value is maximum for
\( \eta = 1 - \delta \). Thus

\[
\sup_{\eta \in [0,1-\delta]} |L'(\eta)| \leq \frac{1}{\delta} \left( \frac{1}{n} \sum_{i=1}^{n} \hat{Y}_i^2 |\lambda_i - 1| \right) \left( \frac{1}{n} \sum_{i=1}^{n} \hat{Y}_i^2 \right)^{-1} + \frac{1}{n\delta} \sum_{i=1}^{n} |\lambda_i - 1|
\]

\[
\leq \frac{2}{\delta} + \frac{1}{\delta} \left( \frac{1}{n} \sum_{i=1}^{n} \hat{Y}_i^2 \lambda_i \right) \left( \frac{1}{n} \sum_{i=1}^{n} \hat{Y}_i^2 \right)^{-1} + \frac{1}{n\delta} \sum_{i=1}^{n} \lambda_i.
\]

But

\[
\frac{1}{n\delta} \sum_{i=1}^{n} \hat{Y}_i^2 = \sigma^2 + o_P(1)
\]

and using the same reasoning as previously,

\[
\frac{1}{n} \sum_{i=1}^{n} \hat{Y}_i^2 \lambda_i = \sigma^2 \frac{1}{n} \sum_{i=1}^{n} \lambda_i + o_P(1) = O_P(1)
\]

which give (12). We thus have proved

\[
\sup_{\eta \in [0,1-\delta]} |L_n(\eta) - L(\eta)| = o_P(1) \tag{14}
\]

Now, using Jensen’s inequality, we easily get that for all \( \eta \in [0,1] \), \( L(\eta) \leq L(\eta^*) \), with equality if and only if \( \eta = \eta^* \). This together with (14) gives

\[
\hat{\eta} = \eta^* + o_P(1) \tag{15}
\]

The next step is to prove that \( \sqrt{n}(\hat{\eta} - \eta^*) = O_P(1) \). Let us first note that \( \hat{\eta} \) satisfies the following equation:

\[
\sqrt{n}(\hat{\eta} - \eta^*) = \frac{\sqrt{nL_n'(\eta^*)}}{L_n''(\hat{\eta})}, \quad \hat{\eta} \in (\hat{\eta}, \eta^*) \tag{16}
\]

We first prove the asymptotic convergence of \( L_n''(\hat{\eta}) \).

**Lemma 5.** Let \( Y = (Y_1, \ldots, Y_n)' \) satisfy Model (5) with \( \eta^* > 0 \) and the entries \( W_{i,j} \) of \( W \) satisfy (A1). Then, for all \( q \) in \( (0,1] \), as \( n, N \to \infty \) such that \( n/N \to a \in (0,1] \), for any random variable \( \tilde{\eta} \) such that \( \tilde{\eta} \in (\hat{\eta}, \eta^*) \),

\[
L_n''(\tilde{\eta}) = -\sigma^2 \delta^2(a, \eta^*) + o_P(1)
\]

**Lemma 5** is proved in Section 5.4.

Let us now focus on the properties of \( L_n'(\eta^*) \). Using the following notation

\[
U_i = \frac{\hat{Y}_i}{\sqrt{\eta^*(\lambda_i - 1) + 1}},
\]

\[
L_n'(\eta^*) = \sum_{i=1}^{n} U_i^2 (\lambda_i - 1) + o_P(1)
\]

**Lemma 5** is proved in Section 5.4.

Let us now focus on the properties of \( L_n'(\eta^*) \). Using the following notation

\[
U_i = \frac{\hat{Y}_i}{\sqrt{\eta^*(\lambda_i - 1) + 1}},
\]

\[
L_n'(\eta^*) = \sum_{i=1}^{n} U_i^2 (\lambda_i - 1) + o_P(1)
\]
we see that \( \sqrt{n}L_n'(\eta^*) \) can be rewritten as follows:

\[
\left\{ \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \left( U_i^2 - \frac{1}{n} \sum_{j=1}^{n} U_j^2 \right) g(\eta^*, \lambda_i) \right\} \left( \frac{1}{n} \sum_{i=1}^{n} U_i^2 \right)^{-1}
\]

\[
= \left\{ \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \left( U_i^2 - 1 \right) + \left( 1 - \frac{1}{n} \sum_{j=1}^{n} U_j^2 \right) \right\} g(\eta^*, \lambda_i) \left( \frac{1}{n} \sum_{i=1}^{n} U_i^2 \right)^{-1}
\]

\[
= \left\{ \frac{1}{\sqrt{n}} \sum_{i=1}^{n} (U_i^2 - 1) g(\eta^*, \lambda_i) \right\} \left( \frac{1}{n} \sum_{i=1}^{n} U_i^2 \right)^{-1} - \left\{ \frac{1}{\sqrt{n}} \sum_{j=1}^{n} (U_j^2 - 1) \right\} \left( \frac{1}{n} \sum_{i=1}^{n} g(\eta^*, \lambda_i) \right) \left( \frac{1}{n} \sum_{i=1}^{n} U_i^2 \right)^{-1},
\]

where

\[
g(\eta, \lambda) = \frac{\lambda - 1}{\eta(\lambda - 1) + 1}.
\]

But using Lemma 2 and Lemma 3 we get

\[
\text{Var} \left[ n^{-1/2} \sum_{j=1}^{n} (U_j^2 - 1)|Z \right] = O_P(1)
\]

Moreover, by Lemma 3 \( n^{-1} \sum_{i=1}^{n} g(\eta^*, \lambda_i) \) converges in probability to \( \int g(\eta^*, \lambda)d\mu_\alpha(\lambda) \). Thus,

\[
\sqrt{n}L_n'(\eta^*) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} (U_i^2 - 1) \left( g(\eta^*, \lambda_i) - \int g(\eta^*, \lambda)d\mu_\alpha(\lambda) \right) + o_P(1), \quad n \to \infty. \tag{18}
\]

Using again Lemma 2 and Lemma 3 we obtain

\[
\sqrt{n}L_n'(\eta^*) = O_P(1).
\]

This, together with Lemma 5 and (16) ends the proof of Theorem 1.

5.2. Proof of Theorem 2. Notice first that all previous results may be used, replacing (A1) by the assumption that the \( Z_{i,j} \) are i.i.d. standard Gaussian. Indeed, in this case, Lemma 1 reduces to the original result of [12], Lemma 3 only involves Lemma 1 and truncation arguments, and the computations leading to Lemma 4 still hold. Thus, Theorem 1 and Lemma 5 also still hold.

Let us now prove that \( \sqrt{n}L_n'(\eta^*) \) converges in distribution to a centered Gaussian. Define \( H \) the diagonal \( n \times n \) matrix with diagonal entries

\[
H_i = \frac{1}{\eta^*(\lambda_i - 1) + 1} \left[ g(\eta^*, \lambda_i) - \int g(\eta^*, \lambda)d\mu_\alpha(\lambda) \right].
\]
Define 

\[ L_n = \frac{1}{\sqrt{n}} \tilde{Y}' H \tilde{Y}. \]

Then using (18) and Lemma 3 we have

\[ \sqrt{n}L_n^*(\eta^*) = L_n - \mathbb{E}[L_n|Z] + o_P(1). \]

Now using Lemma 2 we get that setting \( s_n^2 = \text{Var}[L_n|Z] \),

\[ s_n^2 = 2\sigma^4 \frac{1}{n} \text{Tr} \left[ H^2 ((1 - \eta^*) I_{d_{\mathbb{R}^n}} + \eta^* D)^2 \right] + 3\sigma^4 \eta^* \left( \frac{1}{q} - 1 \right) \frac{1}{n} \sum_{i=1}^N M_{i,i}^2 \]

\[ = 2\sigma^4 \frac{1}{n} \sum_{i=1}^n \left( g(\eta^*, \lambda_i) - \int g(\eta^*, \lambda) d\mu_\alpha(\lambda) \right)^2 \]

\[ + 3\sigma^4 \eta^* \left( \frac{1}{q} - 1 \right) \frac{1}{n} \sum_{i=1}^n \sum_{k,l=1}^n \lambda_{kl} \lambda_{lk} H_k H_l V_{i,k} V_{i,l}^2. \]

The first term in this sum converges as \( n, N \rightarrow \infty \) to \( 2\sigma^4 \tilde{\sigma}^2(a, \eta^*) \).

Under the assumption that the \( Z_{i,j} \) are i.i.d. standard Gaussian, the matrix of eigenvectors \( V \) is Haar distributed on the orthonormal matrices, and is independent of \( (\lambda_i)_{1 \leq i \leq n} \), see [2] chapter 10. Conditionally to the eigenvalues \( (\lambda_i)_{1 \leq i \leq n} \), we thus get that

\[ \mathbb{E} \left[ \frac{1}{n} \sum_{i=1}^n \sum_{k,l=1}^n \lambda_{kl} \lambda_{lk} H_k H_l V_{i,k} V_{i,l}^2 | D \right] = \left( \frac{1}{N} \sum_{k=1}^n \lambda_k H_k \right)^2 (1 + o(1)) \]

converges to

\[ a^2 \left[ \frac{\lambda (\lambda - 1)}{(\eta^* (\lambda - 1) + 1)^2} d\mu_\alpha(\lambda) - \frac{\lambda}{(\eta^* (\lambda - 1) + 1)} d\mu_\alpha(\lambda) \right] \left[ \frac{\lambda - 1}{(\eta^* (\lambda - 1) + 1)} d\mu_\alpha(\lambda) \right]^2 \]

and

\[ \text{Var} \left[ \frac{1}{n} \sum_{i=1}^n \sum_{k,l=1}^n \lambda_{kl} \lambda_{lk} H_k H_l V_{i,k} V_{i,l}^2 | D \right] = o_P(1) \]

so that

\[ s_n^2 = 2\sigma^4 \tilde{\sigma}^2(a, \eta^*) + 3\sigma^4 \eta^* \left( \frac{1}{q} - 1 \right) S(a, \eta^*) + o_P(1). \]

Denote \( \Delta \) the diagonal \( N \times N \)-matrix with diagonal entries \( \Delta_i = \frac{\sigma^* \sqrt{\tilde{\sigma}^2}}{\sqrt{q}} \pi_i \). Let us now write

\[ L_n - \mathbb{E}(L_n|Z) = L_n - \mathbb{E}[L_n|\Delta, Z] + \mathbb{E}[L_n|\Delta, Z] - \mathbb{E}[L_n|Z]. \]

We first have

\[ \mathbb{E}[L_n|\Delta, Z] - E[L_n|Z] = \sigma^* \eta^* \frac{1}{\sqrt{n}} \sum_{i=1}^N \left( \frac{\pi_i^2}{q} - 1 \right) M_{i,i} \]
whose variance, conditionally to $Z$ is

$$s^2_{n,1} = \sigma^4 \eta^2 \left( \frac{1}{q} - 1 \right) \frac{1}{n} \sum_{i=1}^{N} M^2_{i,i}.$$ 

In the same way as for $s^2_n$ we get that

$$s^2_{n,1} = \sigma^4 \eta^2 \left( \frac{1}{q} - 1 \right) S(a, \eta^*) + o_P(1).$$

Let

$$\xi_i = \left( \frac{\pi_i^2}{q} - 1 \right) M_{i,i} = \left( \frac{\pi_i^2}{q} - 1 \right) \sum_{k=1}^{n} \lambda_k \eta^* (\lambda_k - 1) + 1)^2 V^2_{i,k}.$$ 

Since $\eta^* > 0$, the function $\lambda \mapsto \frac{\lambda(\lambda-1)}{(\eta^* (\lambda_k - 1) + 1)^2}$ is bounded, and $\sum_{k=1}^{n} V^2_{i,k} \leq \sum_{k=1}^{N} V^2_{i,k} = 1$. Also, the variables $\left( \frac{\pi_i^2}{q} - 1 \right)$ are uniformly bounded by $1/q$. Thus

$$\frac{1}{n} \sum_{i=1}^{n} \mathbb{E} \left[ \xi_i 1_{|\xi_i| \geq cn} |Z\right] = 0$$

for large enough $n$. Then, by Lindeberg’s Theorem, conditionally to $Z$,

$$\frac{1}{s^2_{n,1}} (\mathbb{E} [L_n | \Delta, Z] - \mathbb{E} [L_n | Z])$$

converges in distribution to $\mathcal{N}(0, 1)$.

Let us now set

$$s^2_{n,2} = s^2_n - s^2_{n,1}$$

and notice that $s^2_{n,2}$ converges to

$$2\sigma^4 \sigma^2 (a, \eta^*) + 2\sigma^4 \eta^* \left( \frac{1}{q} - 1 \right) S(a, \eta^*).$$

We shall prove that, conditionally to $Z$ and $\Delta$, $(L_n - \mathbb{E}(L_n | \Delta, Z))/s_{n,2}$ converges in distribution to $\mathcal{N}(0, 1)$, and thus also unconditionally. Write

$$L_n = \frac{1}{\sqrt{n}} \begin{pmatrix} w' & \varepsilon' \end{pmatrix} B \begin{pmatrix} w \\ \varepsilon \end{pmatrix}$$

where $B$ is the $(N + n) \times (N + n)$-matrix

$$B = \begin{pmatrix} \Delta & 0 \\ 0 & \sigma^* \sqrt{(1 - \eta^*)} I_{d_{\mathbb{R}^n}} \end{pmatrix} \begin{pmatrix} V & DH & 0 \\ 0 & 0 & V' \sqrt{V} \sqrt{DH} \end{pmatrix} \begin{pmatrix} \Delta & 0 \\ 0 & \sigma^* \sqrt{(1 - \eta^*)} I_{d_{\mathbb{R}^n}} \end{pmatrix}.$$
Here, $\tilde{V}$ is the $N \times n$-matrix which consists of the first $n$ columns of $V$. Let $\phi$ be the characteristic function of $(L_n - \mathbb{E}(L_n|\Delta, Z))/s_{n,2}$ conditionally to $Z$ and $\Delta$. Notice first that if $b_j, j = 1, \ldots, n + N$ are the eigenvalues of $B$, we may write

$$L_n - \mathbb{E}[L_n|\Delta, Z] = \frac{1}{\sqrt{n}} \sum_{j=1}^{N+n} b_j (e_j^2 - 1).$$

for random variables $e_j$ i.i.d. standard Gaussian. Thus

$$\phi(t) = \prod_{j=1}^{N+n} \left[ \left( 1 - 2i \frac{tb_j}{s_{n,2}\sqrt{n}} \right)^{-1/2} \exp \left( -i \frac{tb_j}{s_{n,2}\sqrt{n}} \right) \right]$$

and Taylor expansion leads to

$$\log \phi(t) = \sum_{j=1}^{N+n} \left[ -\frac{1}{2} \log \left( 1 - 2i \frac{tb_j}{s_{n,2}\sqrt{n}} \right) - i \frac{tb_j}{s_{n,2}\sqrt{n}} \right]$$

$$= -i^2 \frac{1}{ns_{n,2}^2} \sum_{j=1}^{N+n} b_j^2 + O \left( \frac{1}{n\sqrt{ns_{n,2}^3}} \sum_{j=1}^{N+n} b_j^2 \right).$$

We shall now prove that $\frac{1}{ns_{n,2}^2} \sum_{j=1}^{N+n} b_j^2$ converges to 1/2. Tedious computations give

$$\sum_{j=1}^{N+n} b_j^2 = \text{Tr}(B^2)$$

$$= \text{Tr}(\Delta M \Delta^2 M \Delta) + \sigma^4 (1 - \eta^2) \text{Tr}(H^2) + 2\sigma^2 (1 - \eta^*) \text{Tr}[\Delta^2 \tilde{V} D H^2 \tilde{V}^T].$$

Using the distribution of $V$ and its independence on $D$ we get

$$\mathbb{E} \left[ \sum_{j=1}^{N+n} b_j^2 | D \right] = 2\sigma^4 \text{Tr} \left[ H^2 ((1 - \eta)^* I_{d_{\mathbb{R}^n}} + \eta^* D) \right]$$

$$+ 2\sigma^4 \eta^2 \left( \frac{1}{q} - 1 \right) \left( \frac{1}{N} \sum_{k=1}^{n} \lambda_k H_k \right)^2 (1 + o(1))$$

so that

$$\mathbb{E} \left[ \frac{1}{n} \sum_{j=1}^{N+n} b_j^2 | D \right] = 2\sigma^4 \tilde{a}^2 (a, \eta^*) + 2\sigma^4 \eta^* (\frac{1}{q} - 1) S(a, \eta^*) + o_P(1).$$

Moreover, tedious computations again give

$$\text{Var} \left[ \frac{1}{n} \sum_{j=1}^{N+n} b_j^2 | D \right] = o_P(1).$$
and we obtain that
\[ \frac{1}{n} \sum_{j=1}^{N+n} b_j^2 = \frac{1}{2} + o_P(1). \]

We shall now prove that \( \frac{1}{n} \sum_{j=1}^{N+n} b_j^2 = o_P(1). \) To do so, it is enough to prove that \( \max_j |b_j| = o_P(\sqrt{n}). \) Notice that for any normed vector \( A = (A_1, A_2) \in \mathbb{R}^{N+n} \) where \( A_1 \in \mathbb{R}^N \) and \( A_2 \in \mathbb{R}^n \),

\[ \max_j |b_j| \leq A'B_A. \]

Now,

\[ A'B_A = A'_1(\Delta M \Delta) A_1 + 2\sigma^* \sqrt{1 - \eta^*} A'_1(\Delta \tilde{V} \sqrt{\tilde{D} H}) A_2 + \sigma'^2 (1 - \eta^*) A'_2 H A_2. \]

First, since \( \eta^* > 0 \), all entries of \( H \) and \( D \) and \( HD \) are uniformly bounded and so are all entries of \( \Delta \). We thus get \( A'_2 H A_2 = O(1) \) and \( A'_1(\Delta \tilde{V} \sqrt{\tilde{D} H}) A_2 = O(1) \). Then, using the distribution of \( V \) and its independence on \( D \) we get

\[ E[A'_1(\Delta M \Delta) A_1 | D] = o_P \left( \frac{1}{N} \sum_{i=1}^{n} \lambda_i H_i \right) \]

and

\[ \text{Var}[A'_1(\Delta M \Delta) A_1 | D] = o_P(1), \]

so that \( A'B_A = O_P(1) \). We have thus proved that \( \max_j |b_j| = O_P(1) = o_P(\sqrt{n}) \).

Thus \( \phi(t) \) converges in probability for all \( t \) to \( \exp(-t^2) \) and the convergence may be strengthened by contradiction to an a.s. convergence, so that conditionally to \( Z \) and \( \Delta \), \( (L_n - E(L_n|\Delta, Z))/s_{n,2} \) converges in distribution to \( N(0,1) \).

Now, conditionally to \( Z \) and \( \Delta \), \( (L_n - E(L_n|\Delta, Z))/s_{n,2} \) converges in distribution to a Gaussian random variable independent of \( \Delta \). Thus conditionally to \( Z \), \( L_n - E[L_n|\Delta, Z] \) and \( E[L_n|\Delta, Z] - E[L_n|Z] \) converge in distribution to independent Gaussian variables, so that their sum converges in distribution to a centered Gaussian with variance the sum of the variances, namely the limit of \( s_{n,2}^2 \), and Theorem 2 is proved.
5.3. **Proof of Theorem** 3 Using Lemma 5 and (16), there remains to prove that \( \sqrt{nL_n'(\eta^*)} \) converges in distribution to \( \mathcal{N}(0, 2\sigma^* \tilde{\sigma}^2(a, \eta^*)) \) and that \( \hat{\sigma}_n^2 \) converges in probability to \( \tilde{\sigma}^2(a, \eta^*) \).

Notice first that when \( q = 1, \) \((U_1, \ldots, U_n)|Z\) is a centered Gaussian vector with a covariance matrix equal to \( \sigma^2 \times \text{the identity matrix}. \) We shall prove that conditionally to \( Z \), \( \sqrt{nL_n'(\eta^*)} \) converges in distribution to \( \mathcal{N}(0, 2\sigma^* \tilde{\sigma}^2(a, \eta^*)) \) so that the result still holds unconditionally. Using (18), it is only needed to prove it for \( \frac{1}{\sqrt{n}} \sum_{i=1}^{n} (U_i^2 - 1) \left( \int g(\eta^*, \lambda) \, d\mu_a(\lambda) \right) \).

Now, conditionally to \( Z \), the variance of \( \sum_{i=1}^{n} (U_i^2 - 1) \left( \int g(\eta^*, \lambda) \, d\mu_a(\lambda) \right) \) is

\[
 s_n^2 = \frac{2\sigma^* \tilde{\sigma}^2}{n} \sum_{i=1}^{n} \left( \int g(\eta^*, \lambda) \, d\mu_a(\lambda) \right)^2.
\]

Since \( \eta^* > 0, \) \( g(\eta^*, \lambda) \) is a bounded function of \( \lambda, \) and using Lemma 8

\[
 s_n^2 = 2\sigma^* \tilde{\sigma}^2(a, \eta^*) + O_P(1).
\]

Also, setting \( \xi_i = (U_i^2 - 1) \left( \int g(\eta^*, \lambda) \, d\mu_a(\lambda) \right) \) and \( C \) an upper bound of \( |g(\eta^*, \lambda)|, \) we get that for any \( c > 0, \)

\[
 \frac{1}{n} \sum_{i=1}^{n} \mathbb{E} \left[ \xi_i^2 \text{1}_{|\xi_i| \geq c n} | Z \right] \leq 4C^2 \sigma^* \tilde{\sigma}^2 \mathbb{E} \left[ (U_1^2 - 1)^2 \text{1}_{2C|U_1^2 - 1| \geq c n} \right] = o(1).
\]

Then, using Lindeberg’s Theorem, conditionally to \( Z \), \( \sqrt{nL_n'(\eta^*)} \) converges in distribution to \( \mathcal{N}(0, 2\sigma^* \tilde{\sigma}^2(a, \eta^*)) \) and thus also unconditionally.

The fact that \( \hat{\sigma}_n^2 \) converges in probability to \( \tilde{\sigma}^2(a, \eta^*) \) is a straightforward consequence of Taylor expansion, the fact that \( g(\eta^*, \lambda) \) and its derivative with respect to \( \eta \) in the neighborhood of \( \eta^* \) are bounded functions of \( \lambda, \) and Slutsky’s Lemma.

5.4. **Proofs of technical lemmas.**

**of Lemma** 7 For proving this lemma, we shall use Theorem 1.1 of [3]. Observe that for all \( j = 1, \ldots, N, \)

\[
 \sum_{i=1}^{n} Z_{i,j} = 0 \tag{19}
\]

and

\[
 \sum_{i=1}^{n} Z_{i,j}^2 = n. \tag{20}
\]
Moreover, for each \( j \), the random variables \((Z_{i,j})_{1 \leq i \leq n}\) are exchangeable. Thus, we deduce from \((20)\) that for all \( i = 1, \ldots, n \) and \( j = 1, \ldots, N \), \( E(Z_{i,j}^2) = 1 \). Hence, by \((19)\), we get that
\[
0 = \left( \sum_{i=1}^{n} Z_{i,j} \right)^2 = \sum_{i=1}^{n} Z_{i,j}^2 + \sum_{1 \leq i \neq m \leq n} Z_{i,j}Z_{m,j},
\]
which, by \((20)\), implies that for all \( j = 1, \ldots, N \) and \( i \neq m = 1, \ldots, n \),
\[
E(Z_{i,j}Z_{m,j}) = -\frac{n}{n(n-1)} = -\frac{1}{n-1}.
\]
Thus, the matrix \( T = T_n \) defined in Theorem 1.1 of \([3]\) is equal to \( T = n/(n-1)I_{\mathbb{R}^n} - J_n/(n-1) \), where \( J_n \) is a \( n \times n \) matrix having all its entries equal to 1. Hence the eigenvalues of \( T \) are 0 with multiplicity 1 and \( n/(n-1) \) with multiplicity \((n-1)\), which gives Assumption 3 of Theorem 1.1 of \([3]\). It is thus enough to check if Assumption 1 holds. For this, we shall use Corollary 1.1 of \([3]\).

Let us first check Condition (1.4). Observe that, for \( i \neq m \), \( E[(Z_{i,j}Z_{m,j} - t_{m,i})^2] = E(Z_{i,j}^2Z_{m,j}^2) - t_{m,i}^2 \). By \((20)\), for all \( j = 1, \ldots, N \),
\[
n^2 = \left( \sum_{i=1}^{n} Z_{i,j}^2 \right)^2 = \sum_{i=1}^{n} Z_{i,j}^4 + \sum_{1 \leq i \neq m \leq n} Z_{i,j}^2Z_{m,j}^2.
\]
Since the \((Z_{i,j})_{1 \leq i \leq n}\) are exchangeable for each \( j = 1, \ldots, N \), we get that for all \( j = 1, \ldots, N \),
\[
n = E[Z_{1,j}^4] + (n-1)E[Z_{1,j}^2Z_{2,j}^2].
\]
Thus, for all \( j = 1, \ldots, N \), \( E[Z_{1,j}^2Z_{2,j}^2] \leq n/(n-1) \), which with the definition of the \( t_{m,i}'s \) gives the result.

Let us now check Condition (1.5). Since the random variables \((Z_{i,j})_{1 \leq i \leq n}\) are exchangeable, it is enough to prove that, uniformly in \( k \),
\[
\begin{align*}
(1) & \quad E[Z_{1,k}^4] = o(\sqrt{n}), \\
(2) & \quad E[Z_{1,k}^2Z_{2,k}^2] - 1 = o(1), \\
(3) & \quad E[Z_{1,k}^3Z_{2,k}] = o(1), \\
(4) & \quad \sqrt{n}E[Z_{1,k}^2Z_{2,k}Z_{3,k}] = o(1), \\
(5) & \quad nE[Z_{1,k}Z_{2,k}Z_{3,k}Z_{4,k}] = o(1), \quad \text{as } n \to \infty.
\end{align*}
\]
Observe that (1) implies (2). Using \((19)\), by expanding \(0 = \left( \sum_{i=1}^{n} Z_{i,k} \right)^2 \left( \sum_{i=1}^{n} Z_{i,k}^2 \right)\) and taking the expectation, we get that (1) and (3) imply (4). By expanding \(0 = \left( \sum_{i=1}^{n} Z_{i,k} \right)^4\),
which comes from (19), and by taking the expectation, (1) and (3) imply (5). Hence, it is enough to prove (1) and (3) to conclude the proof of Lemma 1.

Let us first prove (1). By the definition of $Z_{1,k}$ given in (2), we get that for all $k$, $Z_{1,k} \leq n$. Hence,

$$Z_{1,k}^2 \leq \frac{(W_{1,k} - \overline{W}_k)^2}{2\sigma_k^2} 1_{\{s_k^2 > 2\sigma_k^2\}} + n 1_{\{s_k^2 > 2\sigma_k^2\}} ,$$

and, by the assumptions on the $W_{i,k}$'s and on the $\sigma_k$'s,

$$E(Z_{1,k}^4) \leq \frac{W_0^2}{2\kappa^2} + 2n^2 \mathbb{P}(s_k^2 > \sigma_k^2) .$$

Theorem A of [16, p. 201] implies that the second term of the previous inequality tends to zero as $n \to \infty$ uniformly in $k$, which concludes the proof of (1).

Let us now prove (3). Using (19), we get $Z_{1,k}^3 (\sum_{i=1}^n Z_{i,k}) = 0$. By expanding this equation and taking the expectation, we obtain that $E(Z_{1,k}^4) + \sum_{i=2}^n E(Z_{1,k}^3 Z_{i,k}) = 0$. Since the $(Z_{i,k})_{1 \leq i \leq n}$ are exchangeable: $E(Z_{1,k}^3 Z_{2,k}) = -E(Z_{1,k}^4)/(n-1) = o(n^{-1/2})$, where the last equality comes from (1).

$\square$

of Lemma 2. Using (11) and the independence assumptions, we get

$$\text{Var}(\tilde{Y}'H\tilde{Y}|Z) = \text{Var} \left[ v'V \begin{pmatrix} DH & 0 \\ 0 & 0 \end{pmatrix} v' + 2\sigma^* \sqrt{1-\eta^*} v'V \begin{pmatrix} \sqrt{D} \\ 0 \end{pmatrix} H\tilde{e} + \sigma^*2(1-\eta^*)\tilde{e}'H\tilde{e}|Z \right]$$

$$= \text{Var} \left[ v'Mv|Z \right] + 4\sigma^*2(1-\eta^*) \text{Var} \left[ v'V \begin{pmatrix} \sqrt{D} \\ 0 \end{pmatrix} H\tilde{e}|Z \right] + 2\sigma^*4(1-\eta^*)^2 \text{Tr}(H^2) ,$$

where $M = V \begin{pmatrix} DH & 0 \\ 0 & 0 \end{pmatrix} V'$. Using the independence assumptions, we get that

$$4\sigma^*2(1-\eta^*) \text{Var} \left[ v'V \begin{pmatrix} \sqrt{D} \\ 0 \end{pmatrix} H\tilde{e}|Z \right] = 4\sigma^*4\eta^*(1-\eta^*) \text{Tr}(BB') = 4\sigma^*4\eta^*(1-\eta^*) \text{Tr}(DH^2) ,$$

(23)
where $B = V \left( \sqrt{D} \right) H$. Moreover, $E(v' M v | Z) = \sigma^* \eta^* \text{Tr}(D^2 H^2)$ and

$$E[(v' M v)^2 | Z] = \frac{\sigma^* \eta^*}{q^2} \left[ 2q^2 \sum_{1 \leq i \neq j \leq N} M_{ij}^2 + q^2 \sum_{1 \leq i \neq i' \leq N} M_{ii} M_{i'i'} + 3q \sum_{1 \leq i \leq N} M_{ii}^2 \right]$$

$$= \sigma^* \eta^* \left[ 2 \text{Tr}(M^2) - 2 \sum_{1 \leq i \leq N} M_{ii}^2 + \text{Tr}(M) \right]$$

$$= \sigma^* \eta^* \left[ 2 \text{Tr}(D^2 H^2) + \text{Tr}(M) \right] + 3 \left( \frac{1}{q} - 1 \right) \sum_{1 \leq i \leq N} M_{ii}^2 \right].$$

Thus,

$$\text{Var}(v' M v | Z) = \sigma^* \eta^* \left[ 2 \text{Tr}(D^2 H^2) + \frac{3}{q} \sum_{1 \leq i \leq N} M_{ii}^2 \right]. \quad (24)$$

The proof of the equality in Lemma 2 follows from (22), (23) and (24). The proof of the inequality in Lemma 2 follows now from

$$\sum_{1 \leq i \leq N} M_{ii}^2 \leq \sum_{1 \leq i, j \leq N} M_{ij}^2 = \text{Tr}(D^2 H^2).$$

\[ \square \]

of Lemma 4 The second derivative of $L_n$ is given by

$$L''_n(\eta) = \left( - \frac{2}{n} \sum_{i=1}^{n} \frac{\hat{y}_i^2 (\lambda_i - 1)^2}{\eta(\lambda_i - 1) + 1} \right) \left( \frac{1}{n} \sum_{i=1}^{n} \frac{\hat{y}_i^2}{\eta(\lambda_i - 1) + 1} \right)^{-1}$$

$$+ \left( \frac{1}{n} \sum_{i=1}^{n} \frac{\hat{y}_i^2 (\lambda_i - 1)^2}{\eta(\lambda_i - 1) + 1} \right)^2 \left( \frac{1}{n} \sum_{i=1}^{n} \frac{\hat{y}_i^2}{\eta(\lambda_i - 1) + 1} \right)^{-2} + \frac{1}{n} \sum_{i=1}^{n} \frac{(\lambda_i - 1)^2}{\eta(\lambda_i - 1) + 1} \right]^{-2}.$$

(25)

In particular for $\eta = \eta^*$, we have

$$\frac{1}{n} \sum_{i=1}^{n} \frac{\hat{y}_i^2}{\eta^*(\lambda_i - 1) + 1} = 1 + o_P(1),$$

and using as previously Lemma 2, Lemma 3 and the fact that all functions of $\lambda$ involved in the empirical means are bounded since $\eta^* > 0$, we get

$$\frac{2}{n} \sum_{i=1}^{n} \frac{\hat{y}_i^2 (\lambda_i - 1)^2}{\eta(\lambda_i - 1) + 1} = \frac{2\sigma^* \eta^*}{n} \sum_{i=1}^{n} \frac{(\lambda_i - 1)^2}{\eta(\lambda_i - 1) + 1} + o_P(1)$$

$$= 2\sigma^* \int \frac{(\lambda - 1)^2}{\eta(\lambda - 1) + 1} d\mu_\alpha(\lambda) + o_P(1)$$
26 A. BONNET, E. GASSIAT, AND C. LÉVY-LEDUC

and

\[
\frac{1}{n} \sum_{i=1}^{n} \frac{\tilde{Y}_i^2(\lambda_i - 1)}{\{\eta(\lambda_i - 1) + 1\}} = \frac{\sigma^2}{n} \sum_{i=1}^{n} \frac{(\lambda_i - 1)}{\{\eta(\lambda_i - 1) + 1\}} + o_P(1)
\]

\[
= \sigma^2 \int \frac{\lambda - 1}{\{\eta(\lambda - 1) + 1\}} \ d\mu_a(\lambda) + o_P(1)
\]

leading to

\[L''_n(\eta) = -\sigma^2 \tilde{\sigma}^2(a, \eta^*) + o_P(1).\]

Using Slutzky’s Lemma and \(\hat{\eta} = \eta^* + o_P(1)\), there just remains to prove that for small enough \(\alpha > 0\),

\[
\sup_{|\eta - \eta^*| \leq \alpha} |L''_n(\eta) - L''_n(\eta^*)| = O_p(\alpha).
\]

But this comes easily from

\[
\sup_{|\eta - \eta^*| \leq \alpha} |L''_n(\eta) - L''_n(\eta^*)| \leq \alpha \sup_{|\eta - \eta^*|} |L^{(3)}_n(\eta)|
\]

where \(L^{(3)}_n(\eta)\) is the third derivative of \(L_n(\eta)\), and a similar handling of empirical means as before. Indeed, all functions of \(\lambda\) involved are bounded as soon as \(\alpha\) is such that \(\eta^* \geq 2\alpha\).

Acknowledgments

The authors would like to thank Edouard Maurel-Segala and Maxime Février for stimulating discussions on random matrix theory and Thomas Bourgeron and Roberto Toro for having led us to study this very interesting subject and for the discussions that we had together on genetic topics.

References

[1] E. Arias-Castro, E. J. Candès, and Y. Plan. Global testing under sparse alternatives: ANOVA, multiple comparisons and the higher criticism. The Annals of Statistics, 39(5):2533–2556, 2011.

[2] Z. Bai and J. W. Silverstein. Spectral analysis of large dimensional random matrices. Springer Series in Statistics. Springer, New York, second edition, 2010.

[3] Z. Bai and W. Zhou. Large sample covariance matrices without independence structures in columns. Statistica Sinica, 18:425–442, 2008.

[4] R. Fisher. The correlation between relatives on the supposition of mendelian inheritance. Trans. Roy. Soc. Edinb., 52:399–433, 1918.
[5] A. Gilmour, R. Thompson, and B. Cullis. Average information reml: An efficient algorithm for variance parameter estimation in linear mixed models. *Biometrics*, 51(4):1440–1450, 1995.

[6] D. Golan and S. Rosset. Accurate estimation of heritability in genome wide studies using random effects models. *Bioinformatics [ISMB/ECCB]*, 27(13):317–323, 2011.

[7] Y. I. Ingster, A. B. Tsybakov, and N. Verzelen. Detection boundary in sparse regression. *Electronic Journal of Statistics*, 4:1476–1526, 2010.

[8] H. M. Kang, N. A. Zaitlen, C. M. Wade, A. Kirby, D. Heckerman, M. J. Daly, and E. Eskin. Efficient control of population structure in model organism association mapping. *Genetics*, 178:1709–1723, 2008.

[9] M. Lynch and B. Walsh. *Genetics and Analysis of Quantitative Traits*. Sunderland, M, 1998.

[10] B. Maher. Personal genomes: The case of the missing heritability. *Nature*, 456(7218):18–21, 2008.

[11] T. A. Manolio, F. S. Collins, N. J. Cox, D. B. Goldstein, L. A. Hindorff, D. J. Hunter, M. I. McCarthy, E. M. Ramos, L. R. Cardon, A. Chakravarti, J. H. Cho, A. E. Guttmacher, A. Kong, L. Kruglyak, E. Mardis, C. N. Rotimi, M. Slatkin, D. Valle, A. S. Whittemore, M. Boehnke, A. G. Clark, E. E. Eichler, G. Gibson, J. L. Haines, T. F. C. Mackay, S. A. McCarroll, and P. M. Visscher. Finding the missing heritability of complex diseases. *Nature*, 461(7265):747–753, 2009.

[12] V. Marchenko and L. Pastur. Distribution of eigenvalues for some sets of random matrices. *Math. USSR, Sb.*, 1:457–483, 1968.

[13] H. Patterson and R. Thompson. Recovery of inter-block information when block sizes are unequal. *Biometrika*, 58:545–554, 1971.

[14] M. Pirinen, P. Donnelly, and C. C. A. Spencer. Efficient computation with a linear mixed model on large-scale data sets with applications to genetic studies. *The Annals of Applied Statistics*, 7(1):369–390, 2013.

[15] S. Searle, G. Casella, and C. McCulloch. *Variance Components*. Wiley Series in Probability and Statistics. Wiley, New Jersey, 1992.

[16] R. Serfling. *Approximation theorems of mathematical statistics*. Wiley series in probability and mathematical statistics. Wiley, New York, NY, 1980.

[17] G. C. G. Wei and M. A. Tanner. A Monte Carlo Implementation of the EM Algorithm and the Poor Man’s Data Augmentation Algorithms. *Journal of the American Statistical Association*, 85(411):699–704, 1990.

[18] J. Yang, B. Benyamin, B. P. McEvoy, S. Gordon, A. K. Henders, D. R. Nyholt, P. A. Madden, A. C. Heath, N. G. Martin, G. W. Montgomery, M. E. Goddard, and P. M. Visscher. Common snps explain a large proportion of the heritability for human height. *Nature Genetics*, 42(7):565–569, 2010.

[19] J. Yang, S. H. Lee, M. E. Goddard, and P. M. Visscher. GCTA: A tool for genome-wide complex trait analysis. *The American Journal of Human Genetics*, 88(1):76 – 82, 2011.
