

DYNAMIC GENE COEXPRESSION ANALYSIS WITH CORRELATION MODELING

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To better understand the difference in biological processes among populations, we aim to study the effect of genetic ancestry on gene coexpression. We propose a method that can model the covariance between two variables to vary against a continuous covariate. We apply variable transformation to utilize past works on heteroskedasticity, and we offer a score test statistic that is robust to model misspecification, computationally simple, and inferentially unaffected by low sample size. Subsequently, we expand the method to test relationships between one hub-gene and many other genes to obtain a more global view of the coexpression network. Simulations show that the proposed method, compared to alternatives, has higher statistical power under more diverse scenarios with much less computational cost. We apply this method to GTEx data to analyze the dynamic behavior of the African Americans' gene coexpression against their genetic ancestry, and we identify transcription factors whose coexpressions with their target genes change with the genetic ancestry. We believe this method can be applied to a wide array of problems that require covariance modeling.

1. Introduction.

Gene coexpression is widely studied to understand how genes are functionally connected and to often provide insights into analyzing the transcriptional regulatory system. This biological system is extremely complicated to fully and accurately comprehend when available data is limited, but we can still get vital pieces of information by focusing on a few key genes and study how they are connected to their other genes. For example, we can isolate one transcription factor gene and study how it is connected to its target genes. We define this quality of a transcription factor as its "local connectivity." This biological problem leads us to the next problem: how does local connectivity vary across various phenotypic conditions? Past works have studied how subjects in different disease statuses show distinct coexpression patterns, contributing to a better understanding of the disease

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at a molecular level [6]. Another phenotype of interest is the genetic ancestry of admixed population. Genetic ancestry is already known to play a critical role in other molecular phenotypes including DNA methylation and gene expressions [20, 8], and so we believe it has an important role in the inter-gene relationships as well. Therefore, in this paper, we study how the local connectivity of transcription factor genes changes with ancestry. Specifically, we study the gene coexpression of African American subjects to identify candidate transcription factors whose effects on their targets vary with the proportion of African ancestry in their genome. This analysis will help us better comprehend how genes are differentially regulated in distinct populations.

The above problem can be translated into a statistical problem of modeling the covariance matrix of the expression levels of multiple genes. We can start from its simplest form by studying the expression levels of two genes. We build a statistical model that can explain how their correlation varies against genetic ancestry. This problem can easily be generalized into any covariance modeling problem for bivariate data outside the field of genetics. Variance modeling has been widely studied in the context of heteroskedasticity [1, 9, 24], and correlation modeling under discrete conditions has been studied in the context of differential network [14], but dynamic correlation modeling has been less explored.

Li (2002) addresses the most similar scientific problem to ours [15, 16]. The paper uses the term “liquid association” (LA) to conceptualize the internal evolution of the coexpression pattern for a pair of genes. He analyzes the coexpression that changes across the different cellular states that cannot be directly observed by using the expression level of another gene to represent the cellular state. Other studies built on the liquid association to better identify cell states that affect coexpression [7, 26, 25], most focusing on expanding the test to genome-scale. However, methods based on liquid association have some limitations. First, it restricts the covariate to be a 1-dimensional vector, and cannot be generalized to test local ancestry. Second, it treats the covariate as a random variable that follows a normal distribution, which genetic ancestry does not. Third, it only tests the linear relationship between the covariate and the coexpression. Lastly, the proposed test statistic does not have a closed-form null distribution and requires a permutation test, leading to computational inefficiency.

We propose a different methodology to solve the continuously-varying

covariance problem. We first assume that the two genes' expression levels follow a bivariate normal distribution. Then, we apply a simple variable transformation to induce independence, effectively changing the multivariate covariance modeling problem to a univariate variance modeling problem. Next, we apply a traditional score test for heteroskedasticity [1] where the null hypothesis is that the coexpression does not vary with the covariate. This method is generalizable to non-normal, multivariate covariates, and it is also applicable to a non-linear relationship between the variance and the covariate. Moreover, the score test statistic asymptotically follows a chi-squared distribution, and hence it is easily expandable to a large number of tests without excessive computational burden. Subsequently, we tackle the local connectivity problem by expanding the scope of the problem from the relationship of two genes to the relationships between one gene and multiple genes. When the number of genes is smaller than the sample size, the desired statistical properties apply to the new combined test statistic as well.

The rest of the paper is organized as follows. First, we lay out the framework for the score test that tests whether the covariance between bivariate normal variables varies against a continuous covariate X . Then we propose a way to combine the pair-wise test statistics for one gene and test the global null that the local connectivity of one variable does not change with genetic ancestry. Next in the simulation section, we show that the proposed method has distinct advantages compared to alternatives such as the likelihood ratio test or liquid association. Finally, we share our real data analysis results using GTEx data for African Americans' transcriptome and genome. We end with a discussion about limitations of the method, possible future directions, and potential applications to fields outside genetics.

2. Methods.

2.1. *Test for connectivity between two genes* . We assume the data $\mathbf{y}_i = \mathbb{R}^2$, $i = 1, 2, \dots, N$ independently follows bivariate normal distribution. The covariate matrix $X \in \mathbb{R}^{N \times P} = \{\mathbf{x}_{ip}\}_{i=1, p=1}^{N, P}$ is assumed full-rank with $P < N$.

$$(2.1) \quad \begin{aligned} \begin{bmatrix} y_{i1} \\ y_{i2} \end{bmatrix} &= \begin{bmatrix} b_1 \\ b_2 \end{bmatrix} + \begin{bmatrix} \mathbf{x}_i^T \boldsymbol{\beta}_1 \\ \mathbf{x}_i^T \boldsymbol{\beta}_2 \end{bmatrix} + \begin{bmatrix} u_{i1} \\ u_{i2} \end{bmatrix} \\ \begin{bmatrix} u_{i2} \\ u_{i2} \end{bmatrix} &\sim \mathcal{N} \left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \rho_{11} & \rho_{12}(\mathbf{x}_i, \boldsymbol{\alpha}) \\ \rho_{12}(\mathbf{x}_i, \boldsymbol{\alpha}) & \rho_{22} \end{bmatrix} \right) \end{aligned}$$

β_1 and β_2 are coefficients with length P for the mean term. ρ_{11} and ρ_{22} are fixed scalars but ρ_{12} is a function of \mathbf{x} and unknown parameter of interest α with length P .

Above model is close to a multivariate regression model of \mathbf{y}_i against covariate \mathbf{x}_i with intercept \mathbf{b}_0 , slope $[\beta_1 \ \beta_2]$, and error term \mathbf{u}_i but is different in that its error variance depends on the covariate \mathbf{x}_i through some parameter α . The function ρ_{12} represents a specific but unknown form of heteroskedasticity between the two variables 1 and 2. We additionally assume that the diagonal entries of Σ are fixed and do not depend on \mathbf{x}_i . In the context of gene coexpression of African Americans, \mathbf{y}_i is gene expression level of an African American individual i at two selected genes. \mathbf{x}_i is a P -dimensional covariate matrix for individual i that holds information about genetic ancestry. It can be a scalar that represents the proportion of African ancestry in the genome, a vector of the first few principal components of the genotypes, or a vector of local ancestry at multiple loci. In the application section (4), we focus on scalar \mathbf{x}_i for straightforward interpretability.

The parameter of interest is α , and others $(\mathbf{b}, \beta, \rho_{11}, \rho_{22})$ are nuisance parameters. Here, we develop a method to test the following null hypothesis.

$$(2.2) \quad \alpha = \mathbf{0}$$

Although we can work directly with bivariate normal likelihood from (2.1), we propose a variable transformation to make the likelihood much simpler without losing any information.

$$(2.3) \quad \begin{aligned} \begin{bmatrix} w_i \\ v_i \end{bmatrix} &= \begin{bmatrix} \frac{y_{i1}}{\sqrt{\rho_{11}}} + \frac{y_{i2}}{\sqrt{\rho_{22}}} \\ \frac{y_{i1}}{\sqrt{\rho_{11}}} - \frac{y_{i2}}{\sqrt{\rho_{22}}} \end{bmatrix} = \\ &\begin{bmatrix} \frac{b_1}{\sqrt{\rho_{11}}} + \frac{b_2}{\sqrt{\rho_{22}}} \\ \frac{b_1}{\sqrt{\rho_{11}}} - \frac{b_2}{\sqrt{\rho_{22}}} \end{bmatrix} + \mathbf{x}_i^T \begin{bmatrix} \frac{\beta_1}{\sqrt{\rho_{11}}} + \frac{\beta_2}{\sqrt{\rho_{22}}} \\ \frac{\beta_1}{\sqrt{\rho_{11}}} - \frac{\beta_2}{\sqrt{\rho_{22}}} \end{bmatrix} + \begin{bmatrix} u_{wi} \\ u_{vi} \end{bmatrix} \\ \begin{bmatrix} u_{wi} \\ u_{vi} \end{bmatrix} &\sim \mathcal{N} \left(\mathbf{0}, \begin{bmatrix} 2 + \frac{2\rho_{12}(\mathbf{x}_i^T, \alpha)}{\sqrt{\rho_{11}\rho_{22}}} & 0 \\ 0 & 2 - \frac{2\rho_{12}(\mathbf{x}_i, \alpha)}{\sqrt{\rho_{11}\rho_{22}}} \end{bmatrix} \right) \end{aligned}$$

For notational convenience, we define the following two variance parameters.

$$(2.4) \quad \sigma_{wi}^2 = 2 + \frac{2\rho_{12}(\mathbf{x}_i, \alpha)}{\sqrt{\rho_{11}\rho_{22}}}, \quad \sigma_{vi}^2 = 2 - \frac{2\rho_{12}(\mathbf{x}_i, \alpha)}{\sqrt{\rho_{11}\rho_{22}}}$$

Now, the two variables w_i and v_i are independent, and the bivariate likelihood is equal to the sum of two univariate likelihoods.

$$\begin{aligned}
 \ell(\boldsymbol{\alpha}, \mathbf{b}, \boldsymbol{\beta}, \rho_{11}, \rho_{22}) = & \\
 (2.5) \quad & -\frac{N}{2} \log(2\pi) - \frac{1}{2} \sum_{i=1}^N \log(\sigma_{wi}^2) - \sum_{i=1}^N \frac{(w_i - \mu_{wi})^2}{\sigma_{wi}^2} \\
 & -\frac{N}{2} \log(2\pi) - \frac{1}{2} \sum_{i=1}^N \log(\sigma_{vi}^2) - \sum_{i=1}^N \frac{(v_i - \mu_{vi})^2}{\sigma_{vi}^2}
 \end{aligned}$$

where

$$\begin{aligned}
 \mu_{wi} &= \frac{b_1}{\sqrt{\rho_{11}}} + \frac{b_2}{\sqrt{\rho_{22}}} + \mathbf{x}_i^T \left(\frac{\boldsymbol{\beta}_1}{\sqrt{\rho_{11}}} + \frac{\boldsymbol{\beta}_2}{\sqrt{\rho_{22}}} \right) \\
 \mu_{vi} &= \frac{b_1}{\sqrt{\rho_{11}}} - \frac{b_2}{\sqrt{\rho_{22}}} + \mathbf{x}_i^T \left(\frac{\boldsymbol{\beta}_1}{\sqrt{\rho_{11}}} - \frac{\boldsymbol{\beta}_2}{\sqrt{\rho_{22}}} \right)
 \end{aligned}$$

This transformation effectively changes the covariance modeling problem to variance modeling problem, and we can apply the results from literature on univariate heteroskedasticity. Given the likelihood (2.5), we have two well-known tools to test the null hypothesis (2.2): likelihood ratio test and Rao's score test [1].

One one hand, likelihood ratio test requires the full specification of the function ρ to estimate the maximum likelihood estimate (MLE) of $\boldsymbol{\alpha}$ both under the null hypothesis and under the alternative hypothesis. One straightforward function for ρ is any kind of sigmoid function bounded to $(-1, 1)$ such as logistic function, hyperbolic tangent function, or any cumulative distribution supported on the whole real line. For the input of ρ , we can use simple linear form of $\mathbf{x}_i^T \boldsymbol{\alpha}$, or we can also allow non-linearity by using higher order polynomial or even generalized additive models. There are two problems with the likelihood ratio test. One, as mentioned in the previous section, we would like to impose as little assumption on the specific form of heteroskedasticity as possible. If ρ is highly mis-specified, we sacrifice a lot of statistical power. Two, most of the reasonable assumptions of ρ , such as the sigmoid functions mentioned above, do not lead to a closed form MLE of $\boldsymbol{\alpha}$ under the alternative hypothesis. It would require us to numerically optimize the likelihood, leading to computational inefficiency, especially when the test space is large as in our application of gene coexpression.

On the other hand, Rao's score test, unlike the likelihood ratio test, only requires the MLE of α under the null hypothesis [23]. Moreover, under a mild assumption of linearity and additivity ($\rho(\mathbf{x}_i, \alpha) = \rho(\mathbf{x}_i^T \alpha)$), the test statistic does not depend on the form of ρ while maintaining its asymptotic property as long as ρ is twice differentiable. Therefore, we define $\alpha \in \mathbb{R}^p$ as the linear coefficients and finalize our model below

$$(2.6) \quad \rho_{12}(\mathbf{x}_i, \alpha) = \rho_{12}(\mathbf{x}_i^T \alpha + \alpha_0).$$

Under the null hypothesis, $\rho_{12}(\mathbf{x}_i, \alpha) = \rho_{12}(\alpha_0)$ is a constant. However, we believe the linearity and additivity assumptions are standard for the incipient stage of the analysis. Also, since ρ can take any non-linear form, (2.6) still is a flexible framework especially compared to the likelihood ratio test. In order to test (2.2), we expand the result from Breusch and Pagan (1979) to derive the test statistic [1].

The score test allows us to replace all the nuisance parameters with the MLEs under the null hypothesis. We can therefore replace $\alpha_0, \beta, \mathbf{b}, \rho_{11}$, and ρ_{22} with their respective MLEs that result from ordinary least squares linear regression. The first derivative of the likelihood evaluated at $\alpha = \mathbf{0}, \alpha_0 = \hat{\alpha}_0, \beta = \hat{\beta}, \mathbf{b} = \hat{\mathbf{b}}, \rho_{11} = \hat{\rho}_{11}, \rho_{22} = \hat{\rho}_{22}$ is

$$(2.7) \quad \begin{aligned} \tilde{\mathbf{d}}_\alpha &= \frac{\partial \ell(\alpha, \mathbf{b}_0, \beta)}{\partial \alpha} \Big|_{\alpha=\mathbf{0}, \alpha_0=\hat{\alpha}_0, \beta=\hat{\beta}, \mathbf{b}=\hat{\mathbf{b}}, \rho_{11}=\hat{\rho}_{11}, \rho_{22}=\hat{\rho}_{22}} = \\ &= -\frac{\rho'_{12}(\alpha_0)}{2\sqrt{\rho_{11}\rho_{22}}} \sum_{i=1}^N \left(\frac{\mathbf{x}_i}{\hat{\sigma}_w^2} \left(1 - \frac{\hat{u}_{wi}^2}{\hat{\sigma}_w^2} \right) - \frac{\mathbf{x}_i}{\hat{\sigma}_v^2} \left(1 - \frac{\hat{u}_{vi}^2}{\hat{\sigma}_v^2} \right) \right) \end{aligned}$$

where $\hat{\sigma}_w^2 = \sum_{i=1}^N \hat{u}_{wi}^2 / N$ and $\hat{\sigma}_v^2 = \sum_{i=1}^N \hat{u}_{vi}^2 / N$ as the error variance from linear regression. Similarly, \hat{u}_{wi}^2 and \hat{u}_{vi}^2 are the residuals from the linear regression of (2.3). The Fisher information for α is

$$(2.8) \quad \begin{aligned} \tilde{\mathcal{I}}_{\alpha\alpha^T} &= \mathcal{I}_{\alpha\alpha^T} \Big|_{\alpha=\mathbf{0}, \alpha_0=\hat{\alpha}_0, \mathbf{b}=\hat{\mathbf{b}}, \beta=\hat{\beta}, \rho_{11}=\hat{\rho}_{11}, \rho_{22}=\hat{\rho}_{22}} \\ &= \frac{\rho_{12}^2(\hat{\alpha}_0)}{4\hat{\rho}_{11}\hat{\rho}_{22}} \cdot 2 \cdot \left(\frac{1}{\hat{\sigma}_w^2} + \frac{1}{\hat{\sigma}_v^2} \right) \sum_{i=1}^N \mathbf{x}_i \mathbf{x}_i^T \end{aligned}$$

All other second-order derivatives are $\mathbf{0}$ when the covariates are centered.

The test statistic q for the variables 1 and 2 is

$$(2.9) \quad q = \tilde{d}_{\alpha}^T \tilde{I}_{\alpha\alpha}^{-1} \tilde{d}_{\alpha} = \frac{1}{2} \left(\frac{1}{\hat{\sigma}_w^4} + \frac{1}{\hat{\sigma}_v^4} \right)^{-1} \left(\sum_{i=1}^N \mathbf{x}_i \left(\frac{\hat{\sigma}_w^2 - \hat{u}_{wi}^2}{\hat{\sigma}_w^4} - \frac{\hat{\sigma}_v^2 - \hat{u}_{vi}^2}{\hat{\sigma}_v^4} \right) \right)^T \left(\sum_{i=1}^N \mathbf{x}_i^T \mathbf{x}_i \right)^{-1} \left(\sum_{i=1}^N \mathbf{x}_i \left(\frac{\hat{\sigma}_w^2 - \hat{u}_{wi}^2}{\hat{\sigma}_w^4} - \frac{\hat{\sigma}_v^2 - \hat{u}_{vi}^2}{\hat{\sigma}_v^4} \right) \right)$$

where the unknown function ρ has been canceled out. Every component of the test statistic is easily acquired from the data, and the computational burden is low. Most importantly, it is flexible as it allows any form of heteroskedasticity ρ . Under this setting, Breusch and Pagan (1979) proves that q asymptotically follows χ_P^2 [1].

$$(2.10) \quad q \rightarrow \chi_P^2$$

PROPOSITION 1. *Consider the model in (2.1). If all the covariates are centered, $\sum_{i=1}^N x_{ip} = 0$ for $p = 1, \dots, P$, and the non-diagonal term follows the function ρ_{12} as defined in (2.6), the statistic in (2.9) follows χ_P^2 under the null hypothesis (2.2).*

However, even though the introduced test statistic has convenient asymptotic properties, the sample size is not large enough in many applications. The error is in the order of N^{-1} [12], and many Monte Carlo experiments show that the test rejects the null hypothesis less frequently than indicated by its nominal size [10, 11, 13]. In response, corrections have been suggested [5, 12, 13], and we apply Honda's method to ensure the asymptotic properties even under the small sample size. The details of the small-sample correction as well as the derivation of the test statistic, are shared in the Appendix.

2.2. Test for Local Connectivity . In section (2.1), we proposed the test statistic q that tests a pair of variables 1 and 2 to measure the evidence that their correlation changes with respect to the covariate X . As a natural extension to the pair-wise test statistic, we can repeat the procedure for more than 2 variables. In particular, we can study one transcription factor with multiple target genes to test whether the local connectivity of the transcription factor varies with genetic ancestry. In this section, we propose a way to combine the test statistics to test a new global null hypothesis.

The global null hypothesis for variable 1 extends (2.2) as follows,

$$(2.11) \quad \mathbf{H}_0^{(1)} : \alpha_{12} = \alpha_{13} = \cdots = \alpha_{1K} = \mathbf{0},$$

where the superscript in $\mathbf{H}_0^{(1)}$ indicates that the null hypothesis applies to variable 1. Under $\mathbf{H}_0^{(1)}$, no other variables' correlation with variable 1 changes across the different values of X . We believe testing the global null (2.11) improves the statistical power when the “hot spot” variables or “hub” variables are connected to a lot of other nodes forming cliques or modules. In the context of gene coexpression network, we know that transcription factors regulate the gene expression of multiple genes, and if one transcription factor varies with respect to the covariate, the transcriptions of those genes regulated by that transcription factor are likely to be correlated with the covariate as well.

Combining multiple test statistics can have either positive or negative impact; the procedure can accrue relevant evidence to improve the statistical power, or it can accumulate noise to do the exact opposite. Therefore, we must carefully decide how to combine the test statistics based on the alternative hypothesis we would like to leverage against, and the alternative hypothesis must be constructed to reflect our prior knowledge about the covariance structure.

Chen (2012) discusses two ways to construct the alternative hypothesis [3] for testing the global null. One way, called a sparse alternative, is to test whether only a small number among all tests have non-zero effects while all other tests are null. Another way is to test if at least one test has a non-zero effect size. Based on our prior knowledge in biology and coexpression network, we assume that there are many small signals instead of few big ones, so we propose a simpler linear combination of the test statistics

$$(2.12) \quad d_1 = q_{12} + q_{13} + \cdots + q_{1K} = \sum_{k=2}^K q_{1k}.$$

We believe combining the test statistics like (2.12) improves the statistical power because even if the effect sizes for each gene pair may be too small to be detected, when combined they can form a stronger signal.

We now derive the null distribution of d_1 to test (2.11). Although q_{1k} separately follow χ_P^2 , they are correlated to one another, so their null distribution is not trivial. We start by re-writing the pair-wise score statistic

q (ommitting gene pair index for now) as a sum of χ_1^2 variables as below. Our null hypothesis tests for all covariates at the same time, so we can orthogonalize X to make $\frac{1}{N} \sum_{i=1}^N \mathbf{x}_i \mathbf{x}_i^T$ an identity matrix without affecting the testing procedure. Let \tilde{X} be the orthogonalized covariate matrix, and \tilde{x}_{ip} be the corresponding entries with $\sum_{i=1}^N \tilde{x}_{ip} = 0$ and $\sum_{i=1}^N \tilde{x}_{ip}^2 = n$. Then (2.9) can be alternatively written as follows, where we define r_p .

(2.13)

$$q = \sum_{p=1}^P \left(\frac{1}{\sqrt{N}} \sqrt{\frac{\hat{\sigma}_w^4 \hat{\sigma}_v^4}{\hat{\sigma}_w^4 + \hat{\sigma}_v^4}} \sum_{i=1}^N x_{ip} \left(\frac{\hat{\sigma}_w^2 - \hat{u}_{wi}^2}{\hat{\sigma}_w^4} - \frac{\hat{\sigma}_v^2 - \hat{u}_{vi}^2}{\hat{\sigma}_v^4} \right) \right)^2 = \sum_{p=1}^P r_p^2$$

For each p , r_p follows the standard normal distribution by the central limit theorem.

$$\begin{aligned} E \left(x_{ip} \left(\frac{\hat{\sigma}_w^2 - \hat{u}_{wi}^2}{\hat{\sigma}_w^4} - \frac{\hat{\sigma}_v^2 - \hat{u}_{vi}^2}{\hat{\sigma}_v^4} \right) \right) &= x_{ip} E \left(\frac{\hat{\sigma}_w^2 - \hat{u}_{wi}^2}{\hat{\sigma}_w^4} \right) E \left(\frac{\hat{\sigma}_v^2 - \hat{u}_{vi}^2}{\hat{\sigma}_v^4} \right) = 0 \\ \text{Var} \left(x_{ip} \left(\frac{\hat{\sigma}_w^2 - \hat{u}_{wi}^2}{\hat{\sigma}_w^4} - \frac{\hat{\sigma}_v^2 - \hat{u}_{vi}^2}{\hat{\sigma}_v^4} \right) \right) &= x_{ip}^2 \left(\text{Var} \left(\frac{\hat{\sigma}_w^2 - \hat{u}_{wi}^2}{\hat{\sigma}_w^4} \right) + \text{Var} \left(\frac{\hat{\sigma}_v^2 - \hat{u}_{vi}^2}{\hat{\sigma}_v^4} \right) \right) \\ &= \frac{\hat{\sigma}_w^4 + \hat{\sigma}_v^4}{\hat{\sigma}_w^4 \hat{\sigma}_v^4} \end{aligned}$$

This confirms the previous result

$$\sum_{p=1}^P r_p^2 \rightarrow \chi_P^2$$

Now, we acquire a closed-form covariance structure of r . First, we begin with a multivariate central limit theorem to write the following in terms of r .

$$(2.14) \quad \mathbf{r}_{1,p} = \begin{bmatrix} r_{12,p} \\ r_{13,p} \\ \dots \\ r_{1K,p} \end{bmatrix} \rightarrow N_{K-1}(\mathbf{0}, H_1) \quad \forall p = 1, \dots, P$$

H_1 is a $(K-1) \times (K-1)$ matrix where $(k-1, \ell-1)$ th element is $\eta_{1k,1\ell}$ for $k, \ell = 2, \dots, K$. From (2.13), it is easy to see that H_1 has 1 at the diagonals. Also, $\eta_{1k,1\ell}$ converges in probability to

$$(2.15) \quad \begin{aligned} & \frac{(\tau_{23} + 2\tau_{12}\tau_{23})(\tau_{12}^2 + 1)(\tau_{13}^2 + 1) + \tau_{12}\tau_{13}(6 + 2(\tau_{12}^2 + \tau_{13}^2 + \tau_{23}^2))}{(1 - \tau_{12}^2)(1 - \tau_{13}^2)\sqrt{(1 + \tau_{12}^2)(1 + \tau_{13}^2)}} \\ & - \frac{\tau_{12}(\tau_{13}^2 + 1)(4\tau_{13} + 2\tau_{12}\tau_{23}) + \tau_{13}(\tau_{12}^2 + 1)(4\tau_{12} + 2\tau_{13}\tau_{23})}{(1 - \tau_{12}^2)(1 - \tau_{13}^2)\sqrt{(1 + \tau_{12}^2)(1 + \tau_{13}^2)}} \end{aligned}$$

where

$$\tau_{k\ell} = \frac{\rho_{k\ell}}{\sqrt{\rho_{kk}\rho_{\ell\ell}}}.$$

The derivation is in the Appendix.

Then, d_1 can be written as the sum of L2 norm of $\mathbf{r}_{1,p}$ with a known distribution,

$$(2.16) \quad d_1 = \sum_{p=1}^P \|\mathbf{r}_{1,p}\|_2^2 = \sum_{p=1}^P \sum_{k=2}^K r_{1k,p}^2.$$

Let $H_1 = U_1 \Lambda_1 U_1^T$ be the eigen-decomposition of the covariance matrix H_1 in (??), where the diagonal matrix Λ has eigenvalues $\lambda_{12}, \dots, \lambda_{1K}$ in a decreasing order. Then, we can next consider the transformation $\mathbf{r}_{1,p}^* = U \mathbf{r}_{1,p}$ that follows normal distribution with diagonal covariance matrix $N_{K-1}(\mathbf{0}, \Lambda_1)$. Note that $\|\mathbf{r}_{1,p}\|_2^2 = \|U \mathbf{r}_{1,p}\|_2^2$ due to the orthogonal invariance of L2 norm. Then,

$$(2.17) \quad \begin{aligned} \sum_{p=1}^P r_{1k,p}^{*2} &\sim \Gamma\left(\frac{P}{2}, \frac{\lambda_{1k}}{2}\right), \quad k = 2, \dots, K \\ d_1 &= \sum_{p=1}^P r_{12,p}^{*2} + \dots + \sum_{p=1}^P r_{1K,p}^{*2} \sim \sum_{k=2}^K \Gamma\left(\frac{P}{2}, \frac{\lambda_{1k}}{2}\right) \end{aligned}$$

Assuming that we know the true, symmetric, positive definite H_1 , we can acquire positive λ_{1k} for $k = 2, \dots, K$, and we have expressed the null distribution of d_1 as the sum of distributions of independent gamma variables. We can computationally simulate this null distribution easily. Alternatively, Moschopoulos (1985) provides another interpretation by expressing the cumulative distribution in a form of infinite sum, but the method is inconvenient in practice [18].

In (2.15), we define the element-wise mapping $\phi : \Sigma \rightarrow H$, but in practice, we do not know true Σ . As other nuisance parameters, we can use its maximum likelihood estimate instead. It is clear from the construction of H that if we can estimate a well-conditioned, symmetric, positive definite correlation matrix $\hat{\Sigma}$, $\phi(\hat{\Sigma})$ is also symmetric and positive definite. When N is sufficiently larger than K , empirical covariance matrix $\hat{\Sigma}$ of $[y_{1i} \ y_{2i} \ y_{3i}]$ is a pretty good consistent estimator for Σ , and replacing Σ with $\hat{\Sigma}$ in computing H can guarantee that the test statistic (2.12) converges in distribution to (2.17).

PROPOSITION 2. *Under the setting of Proposition 1, and two additional assumptions that (1) the covariates have been orthogonalized so that $\frac{1}{N} \sum_{i=1}^N \mathbf{x}_i \mathbf{x}_i^T$ is a P by P identity matrix and that (2) H_1 is strictly positive definite, d_1 asymptotically follows the sum of Gamma distributions as defined in (2.17) under the global null hypothesis (2.11).*

However, when K is much larger than n , an accurate estimation of Σ is a difficult problem. We therefore turn to a permutation test and shuffle the covariate vector to test against the true response data that preserves the correlation structure of the network. The permutation procedure is valid under the assumption in (2.1).

We use the sequential precision-improvement permutation test, similar to one suggested by Chen (2012) [3]. Permutation test often results in a poor resolution of p -values which can lead to imprecise inference especially when we need to correct for the testing of multiple hypotheses. Meanwhile, performing a large number of permutations for many genes can be computationally wasteful. In order to find balance, as we proceed with incrementally larger number of permutations, we count the number of cases that led to more extreme degree statistics than the observed d_k . After the minimum number of permutations predefined by the user (1000 in our analysis), if two extreme cases, compared to the true statistic, were found, the permutation procedure is terminated early. If there are less than 2 such cases observed, we perform 100 more permutations and re-check the number of extreme cases and early termination. We repeat until it reaches the predefined maximum number of permutation (10^6 in our case), which is designed to give a good enough resolution of p -value given the number of tests that we are performing.

3. Simulation Studies. In this section, we evaluate the proposed method through simulations. We focus on the pairwise analysis and compare the performance of the proposed score test with two other alternatives - liquid association and likelihood ratio test.

First we check the calibration of test statistics under the null hypothesis. We sample X from the univariate standard normal distribution to match the required setting of liquid association. We simulate the data matrix Y from

$$\mathbf{y}_i \sim \mathcal{N}_2 \left(\mathbf{b}_0 + \mathbf{x}_i^T \boldsymbol{\beta}, \begin{bmatrix} 1 & \bar{\rho} \\ \bar{\rho} & 1 \end{bmatrix} \right)$$

where $\bar{\rho}$ was randomly selected from uniform distribution ranging from -1

and 1 and each element of \mathbf{b}_0 and β from standard normal distribution. We test different sample sizes of $N = 500, 100, 30$ to check the behavior of each method under the null hypothesis. For each N , we sample X once, and generate Y 1,000 times. The likelihood ratio test was designed to assume hyperbolic tangent model for ρ ,

$$(3.1) \quad \rho(\mathbf{x}_i^T \boldsymbol{\alpha}) = \frac{e^{\mathbf{x}_i^T \boldsymbol{\alpha}} - 1}{e^{\mathbf{x}_i^T \boldsymbol{\alpha}} + 1},$$

which is the inverse of Fisher transformation, $\frac{1}{2}\mathbf{x}_i^T \boldsymbol{\alpha} = \frac{1}{2} \log \left(\frac{1+\rho}{1-\rho} \right)$. Fisher-transformed ρ asymptotically follows normal distribution, so it works well when X is drawn from normal distribution. We use *optim* function in R to find $\hat{\boldsymbol{\alpha}}_{\text{MLE}}$ under the alternative hypothesis.

The results show that all three methods control the type I error at the nominal size well, where score and likelihood ratio test statistics both follow χ_1^2 closely. So we focus on the small sample case $N = 30$ as that is close to the size of the real data of African Americans' gene expression level.

Next we generate the data under the alternative hypothesis to compare the statistical power. For fixed $N = 30$, we again draw X from standard normal distribution. Then for $i = 1, \dots, N$, we generate $\rho(\mathbf{x}_i^T \boldsymbol{\alpha})$ from hyperbolic tangent function in (3.1). Given ρ , we draw Y from (??) with varying levels of α , 1000 times each. The hyperbolic tangent model places the likelihood ratio test at an advantage because the model is correctly specified, so as a contrasting case, we use a quadratic model to generate ρ as follows. Subtracting 0.99 is to ensure numerical stability.

$$(3.2) \quad \rho(\mathbf{x}_i^T \boldsymbol{\alpha}) = (\mathbf{x}_i^T \boldsymbol{\alpha} - 0.1)^2 - 0.99$$

Since the likelihood ratio test assumes a wrong model, it is expected to lose power. Also, since quadratic function is highly non-linear, liquid association is expected to have poor performance as well. Figure (1) (a) and (b) show the shape of ρ with respect to X with varying levels of α .

Table (1) summarizes the result. It counts the proportion of simulations which showed p -values less than 0.05 out of 1,000 total simulations. When ρ is generated from hyperbolic tangent function, likelihood ratio test generally outperforms the other two methods, as expected since the model is correctly specified in LR test. Score test, although does not assume any model on ρ ,

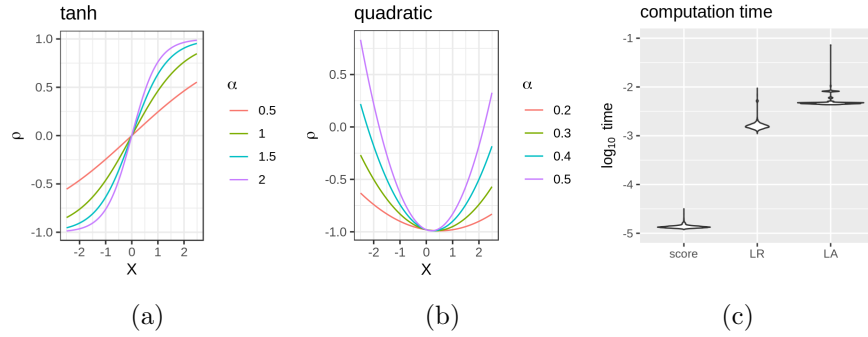


Fig 1: (a)-(b) The two heteroskedastic functions ρ used to generate data. Simulation results in Table (1) show that score test outperforms LA in both cases, and that LA particularly suffers in capturing the non-linear relationship in quadratic model. Likelihood ratio test performs better than score test when the model is correctly specified, but when the model is mis-specified, score test performs better. (c) The computational burden is much lower in the proposed method compared to the other two. LR test requires numerical optimization for finding MLEs, and LA requires permutation test.

does not lose as much power as liquid association does. Meanwhile, when ρ is generated from quadratic function, score function clearly outperforms the other two methods. The proposed score test is robust to the shape of heteroskedasticity. Figure (1) (c) shows the distribution of computation times of each method in the scale of \log_{10} for 1000 simulations under quadratic model with $\alpha = 0.5$. The score test is the most efficient, because the likelihood ratio test requires numerical estimation of MLEs both under the null and under the alternative hypothesis while liquid association requires permutation test for inference.

4. Applications to GTEx Data. We next apply this method to African American samples from GTEx. We aim to find a group of genes that change its coexpression structure as the genome’s proportion of African ancestry changes. The proportion of African ancestry for each individual is defined as global ancestry, and it is referred from software LAMP [19]. The data sets are explained in more detail in the Appendix.

We first conduct the data analysis on the supra-pubic skin tissue (not sun exposed), where 31 African American samples are available. Due to low sample size, we restrict our search space to only transcription factors, which

ρ	tanh					quadratic					
α	0		0.5	1	1.5	2		0.2	0.3	0.4	0.5
score	0.052		0.206	0.542	0.795	0.910		0.627	0.587	0.539	0.531
LA	0.054		0.180	0.511	0.722	0.828		0.042	0.047	0.058	0.079
LR	0.046		0.247	0.693	0.965	0.992		0.533	0.438	0.371	0.338

TABLE 1

Proportion of simulations for each method that showed p -value < 0.05 at given data generating model and α level. We use two functions for ρ , hyperbolic tangent and quadratic function. The likelihood ratio test was conducted under the assumption that ρ is hyperbolic tangent (tanh) function. Proposed score test performs better than liquid association in all cases.

are known to have high correlation with many other genes. Therefore, if their impact sizes on other genes are different based on genetic ancestry, such relationship could have important biological implications.

4.1. Data. We use the genotype data and normalized gene expression level data from GTEx V6p release [17] to apply the method to the African American samples and their gene coexpression network. The data has been pre-processed by GTEx as explained in the GTEx portal (<https://gtexportal.org>). In order to select African Americans from the available samples, we first inferred the local ancestry of the samples who identified themselves as European Americans or African Americans and verified that their genetic ancestry is consistent. For local ancestry inference, we use the software LAMP that reaches as high as 98% accuracy level for distinguishing YRI and CEU ancestry [19]. We also need the reference minor allele frequency from the pure population, so we used data from 1000 Genome Project. For the initial setting of hyperparameters in LAMP, we use 7 for the number of generations of admixture, 0.2 and 0.8 for the initial proportion of CEU and YRI population, and 10^{-8} for recombination rate, but the results are robust to these settings. LAMP returns local ancestry at each SNP as the count of African chromosomes (0, 1, or 2) at each locus, and we use the SNP closest to the center of the gene to represent the local ancestry of the entire gene. Around 92% of the genes show no recombination event in all of the subjects, and less than 3% of the genes have more than one individual with ancestry switch within the gene, so we believe this is a valid approximation.

We define global ancestry as a value between 0 and 1 that quantifies the proportion of African chromosome in each subject. We first estimate it

by averaging the inferred local ancestry, and this estimate is cross-checked with principal component analysis which can effectively cluster the subjects into subpopulations [21]. We also include pure YRI and CEU population for PCA, and most African Americans lie strictly between the YRI and CEU population showing a two-way admixture between pure Europeans and pure Africans. We observed some outliers that were not placed between pure populations, and so we removed them. We also observed some self-identified Europeans whose genetic ancestry is more than 10% African, and we include them in our analysis as African Americans.

The expression levels provided by GTEx were measured using RNA-seq for 38,498 genes in the autosomal chromosomes. For each tissue, only genes with RPKM higher than 0.1 were included. Then the expression levels are normalized, log-transformed, and corrected for technical artifacts by GTEx Consortium.

We limit our analysis of real data to transcription factors. We acquired a list of transcription factors from TFcheckpoint database [2]. We also acquire a list of target genes for each transcription factors from TF2DNA database [22]. We only took into consideration target genes with the highest binding scores.

4.2. Analysis. For each transcription factor encoding gene k , we compute the pair-wise test-statistic q_{kj} for all its target genes $j = 1, \dots, J_k$. Then, we compute $d_k = \sum_{j=1}^{J_k} q_{kj}$ to test the hypothesis that correlation between the transcription factor k and its targets remain the same across different genetic industry.

We first compare two discrete networks between European Americans and African Americans using binary indicator vector as the covariate X , i.e. $x_i = 1$ if subject i is African American, and $x_i = 0$ if subject i is European American. We first compute scores q_{kj} for all the transcription factor encoding gene k and its target genes $j = 1, \dots, J_k$. Then we sum over all the targets for each transcription factor to compute d_k . Then we divide the sum with the number of targets to make a heuristic comparison against χ_1^2 distribution. This procedure essentially observes the average score of all the target genes for a given transcription factor encoding gene, and under the null, the expectation is 1, although the variance is not trivial due to

high dependence. Then we choose the top 10 genes with the highest score to further analyze them using the permutation test.

We repeat the same procedure for the African American samples, where X is the vector of global ancestry ranging from 0.3 to 0.95.

4.3. Results. Table (2) summarizes the top 20 transcription factors with the highest d_k values with their p -values computed from sequential permutation tests for two cases: (1) comparing two discrete networks, one of African Americans and the other of European Americans, (2) comparing continuously varying coexpression network among African Americans with respect to their global ancestry.

AA vs EA			AA only		
genes	p -value	tissue	genes	p -value	tissue
ZNF474	$< 10^{-6}$	adrenal gland	ZBTB20	$1.62 \cdot 10^{-5}$	adipose
HOXA4	$< 10^{-6}$	artery	KLF7	$3.46 \cdot 10^{-5}$	adipose
SP5	$< 10^{-6}$	artery	ISL2	$4.00 \cdot 10^{-5}$	blood
ZNF638	$< 10^{-6}$	breast	ZNF285	$6.58 \cdot 10^{-5}$	heart
MEF2C	$< 10^{-6}$	fibroblasts	E2F5	$8.00 \cdot 10^{-5}$	adrenal gland
HMBOX1	$< 10^{-6}$	fibroblasts	SREBF1	$8.55 \cdot 10^{-5}$	nerve
TFCP2L1	$< 10^{-6}$	esophagus	ZKSCAN3	$8.62 \cdot 10^{-5}$	heart
SMARCC2	$< 10^{-6}$	esophagus	NR4A2	$9.00 \cdot 10^{-5}$	blood
TFDP2	$< 10^{-6}$	esophagus	ZNF682	$1.29 \cdot 10^{-4}$	adipose
DZIP1L	$< 10^{-6}$	lung	TFAP2E	$1.44 \cdot 10^{-4}$	adrenal gland
TAX1BP1	$< 10^{-6}$	stomach	SMAD7	$1.48 \cdot 10^{-4}$	artery
ZFHX4	$< 10^{-6}$	testis	ZSCAN4	$1.65 \cdot 10^{-4}$	muscle skeletal
ZBTB20	$2.28 \cdot 10^{-5}$	adipose	ZNF528	$1.90 \cdot 10^{-4}$	skin
HOXB7	$2.53 \cdot 10^{-5}$	artery	HOXB6	$2.30 \cdot 10^{-4}$	esophagus
ZSCAN4	$3.58 \cdot 10^{-5}$	muscle skeletal	FOXK1	$2.70 \cdot 10^{-4}$	lymphocytes
ZSCAN9	$6.19 \cdot 10^{-5}$	muscle skeletal	ZNF440	$2.86 \cdot 10^{-4}$	skin
ZNF799	$6.43 \cdot 10^{-5}$	testis	HOXB6	$3.03 \cdot 10^{-4}$	artery
ZKSCAN3	$8.37 \cdot 10^{-5}$	heart	PLAGL2	$3.17 \cdot 10^{-4}$	artery
SMAD7	$1.19 \cdot 10^{-4}$	artery	MYB	$3.57 \cdot 10^{-4}$	nerve
POU6F2	$1.14 \cdot 10^{-4}$	testis	POU6F2	$3.92 \cdot 10^{-4}$	testis

TABLE 2

5. Discussion. In this paper, we proposed a method to test whether covariance between bivariate normal variables changes with continuous covariates. We further expand our scope of analysis by looking at “local connectivity” - how one variable’s connectivity with multiple other variables change with continuous covariates. We provide a real data example using gene coexpression by identifying major transcription factor genes that are

differentially connected with its targets by individuals' genetic ancestry.

Although the coexpression network is often considered sparse and the sparsity assumption can possibly help with the estimation of H in (2.14), we did not make any structural assumption on the covariance matrix. When we dynamically model the covariance to vary across the continuous genetic ancestry, the sparsity assumption becomes highly restrictive. Such an assumption would require the coexpression between two genes is 0 across all possible genetic ancestry for most genes. In contrast, we believe it is plausible that genes are independent in some ancestry while highly correlated in some other ancestry. More generally, we lack prior information on how the coexpression matrix would change across ancestry, and we are open to finding any possible patterns. Therefore, we did not assume any specific structure on the covariance matrix of \mathbf{y}_i .

Although our method is more flexible than other alternatives for covariance testing, it still requires a few important modeling assumptions. First, all the results only hold when the data follows Gaussian distribution. Second, when there are more variables than the available sample size, as often is the case for many modern data sets, we ultimately turn to a permutation test, not being able to take the computational advantage of the theoretical results. Third, the underlying heteroskedasticity could be more complex than what is formulated in (2.6), such as cases where there are interactions among the covariates. These limitations of the methods propose possible future research topics: (1) non-parametric version of correlation analysis that can be generalized to any distributions, (2) better way to estimate H in (2.14) when $K > N$ to preserve asymptotic results, and (3) a new testing method for ρ that can take into account the interaction effects among the covariates.

We believe the proposed method can be applied to data problems in diverse domains, especially where certain "hub" variables are connected to many other variables as in the gene regulatory network. Many network problems, such as protein interactions, metabolic networks, co-authorship network, and semantic network, are known to have - or have something close to - scale-free topology, indicating that the important variables in those networks can be tested against others. For example, we can study the relationships between the word "ache" and a set of vocabularies of body parts ("stomach", "muscle", "tooth", "head", etc.) and test whether the relationships become stronger as the language users grow older. The proposed correlation analysis will provide insights into the building blocks of diverse network problems by

looking at the relationship between every pair of variables.

6. Appendix.

6.1. *Derivation of q .* We start from the model in (2.1). The hat notation is used to note the maximum likelihood estimates. The nuisance parameters can be replaced with their respective maximum likelihood estimators under the null hypothesis. When $\boldsymbol{\alpha} = \mathbf{0}$, $\alpha_0 = \hat{\alpha}_0$, $\hat{\boldsymbol{\beta}}$ and $\hat{\mathbf{b}}$ can be acquired from ordinary linear squares estimates. The variance terms $\hat{\rho}_{11}$ and $\hat{\rho}_{22}$ are

$$\hat{\rho}_{11} = \frac{\sum_{i=1}^N (y_{i1} - b_1 - \mathbf{x}_i^T \hat{\boldsymbol{\beta}}_1)^2}{N}$$

$$\hat{\rho}_{22} = \frac{\sum_{i=1}^N (y_{i2} - b_2 - \mathbf{x}_i^T \hat{\boldsymbol{\beta}}_2)^2}{N}$$

Then we look at the likelihood after the variable transformation in (2.3).

$$(6.1) \quad \begin{aligned} \ell(\boldsymbol{\alpha}, \alpha_0, \mathbf{b}, \boldsymbol{\beta}, \rho_{11}, \rho_{22}) = & \\ & -\frac{N}{2} \log(2\pi) - \frac{1}{2} \sum_{i=1}^N \log(\sigma_{wi}^2) - \sum_{i=1}^N \frac{(w_i - \mu_{wi})^2}{\sigma_{wi}^2} \\ & -\frac{N}{2} \log(2\pi) - \frac{1}{2} \sum_{i=1}^N \log(\sigma_{vi}^2) - \sum_{i=1}^N \frac{(v_i - \mu_{vi})^2}{\sigma_{vi}^2} \\ \mu_{wi} = & \frac{b_1}{\sqrt{\rho_{11}}} + \frac{b_2}{\sqrt{\rho_{22}}} + \mathbf{x}_i^T \left(\frac{\boldsymbol{\beta}_1}{\sqrt{\rho_{11}}} + \frac{\boldsymbol{\beta}_2}{\sqrt{\rho_{22}}} \right), \quad \mu_{vi} = \frac{b_1}{\sqrt{\rho_{11}}} - \frac{b_2}{\sqrt{\rho_{22}}} + \mathbf{x}_i^T \left(\frac{\boldsymbol{\beta}_1}{\sqrt{\rho_{11}}} - \frac{\boldsymbol{\beta}_2}{\sqrt{\rho_{22}}} \right) \\ \sigma_{wi}^2 = & 2 + \frac{2\rho_{12}(\mathbf{x}_i^T \boldsymbol{\alpha} + \alpha_0)}{\sqrt{\rho_{11}\rho_{22}}}, \quad \sigma_{vi}^2 = 2 - \frac{2\rho_{12}(\mathbf{x}_i^T \boldsymbol{\alpha} + \alpha_0)}{\sqrt{\rho_{11}\rho_{22}}} \end{aligned}$$

Then we compute the first and second derivative of the log likelihood with respect to $\boldsymbol{\alpha}$ when all other nuisance parameters are replaced with their respective maximum likelihood estimates. The following results help the computation of the derivative.

$$\begin{aligned} \frac{\partial \sigma_{wi}^2}{\partial \boldsymbol{\alpha}} &= \frac{2\mathbf{x}_i \rho'_{12}(\mathbf{x}_i^T \boldsymbol{\alpha} + \alpha_0)}{\sqrt{\rho_{11}\rho_{22}}}, & \frac{\partial \sigma_{vi}^2}{\partial \boldsymbol{\alpha}} &= -\frac{2\mathbf{x}_i \rho'_{12}(\mathbf{x}_i^T \boldsymbol{\alpha} + \alpha_0)}{\sqrt{\rho_{11}\rho_{22}}} \\ \frac{\partial \sigma_{wi}^2}{\partial \rho_{11}} &= -\frac{\rho_{12}(\mathbf{x}_i^T \boldsymbol{\alpha} + \alpha_0)}{\sqrt{\rho_{11}^3 \rho_{22}}}, & \frac{\partial \sigma_{vi}^2}{\partial \rho_{11}} &= -\frac{\rho_{12}(\mathbf{x}_i^T \boldsymbol{\alpha} + \alpha_0)}{\sqrt{\rho_{11} \rho_{22}^3}} \end{aligned}$$

We additionally define \hat{u}_{wi}^2 and \hat{v}_{wi}^2 as the residuals from the linear regression: $(w_i - \hat{\mu}_{wi})^2$ and $(v_i - \hat{\mu}_{vi})^2$ respectively, where $\hat{\mu}_{wi}$ and $\hat{\mu}_{vi}$ are μ_{wi} and μ_{vi} with \mathbf{b} and $\boldsymbol{\beta}$ replaced with $\hat{\mathbf{b}}$ and $\hat{\boldsymbol{\beta}}$.

The maximum likelihood estimates for σ_{wi}^2 and σ_{vi}^2 are as follows.

$$\begin{aligned}
 \hat{\sigma}_{wi}^2 &= \frac{1}{N} \sum_{i=1}^N \hat{u}_{wi}^2, & \hat{\sigma}_{vi}^2 &= \frac{1}{N} \sum_{i=1}^N \hat{u}_{vi}^2 \\
 (6.2) \quad \mathbf{d}_{\alpha} &= \frac{\partial \ell}{\partial \alpha} = - \sum_{i=1}^N \frac{1}{2\sigma_{wi}^2} \cdot \frac{\partial \sigma_{wi}^2}{\partial \alpha} - \sum_{i=1}^N \frac{-(w_i - \mu_{wi})^2}{2\sigma_{wi}^4} \frac{\partial \sigma_{wi}^2}{\partial \alpha} \\
 &\quad - \sum_{i=1}^N \frac{1}{2\sigma_{vi}^2} \cdot \frac{\partial \sigma_{vi}^2}{\partial \alpha} - \sum_{i=1}^N \frac{-(v_i - \mu_{vi})^2}{2\sigma_{vi}^4} \frac{\partial \sigma_{vi}^2}{\partial \alpha} \\
 &= -\frac{1}{2\sqrt{\rho_{11}\rho_{22}}} \sum_{i=1}^N \mathbf{x}_i \rho'_{12}(\mathbf{x}_i^T \alpha + \alpha_0) \cdot \left(\frac{1}{\sigma_{wi}^2} - \frac{u_{wi}^2}{\sigma_{wi}^4} - \frac{1}{\sigma_{vi}^2} + \frac{u_{vi}^2}{\sigma_{vi}^4} \right) \\
 &= -\frac{1}{2\sqrt{\rho_{11}\rho_{22}}} \sum_{i=1}^N \mathbf{x}_i \rho'_{12}(\mathbf{x}_i^T \alpha + \alpha_0) \cdot \left(\frac{1}{\sigma_{wi}^2} \left(1 - \frac{u_{wi}^2}{\sigma_{wi}^2} \right) - \frac{1}{\sigma_{vi}^2} \left(1 - \frac{u_{vi}^2}{\sigma_{vi}^2} \right) \right)
 \end{aligned}$$

Plugging in $\mathbf{0}$ for α and maximum likelihood estimators for all nuisance parameters, we get the score function as below.

$$\begin{aligned}
 \tilde{\mathbf{d}}_{\alpha} &= \mathbf{d}_{\alpha} \big|_{\alpha=\mathbf{0}, \alpha_0=\hat{\alpha}_0, \mathbf{b}=\hat{\mathbf{b}}, \beta=\hat{\beta}, \rho_{11}=\hat{\rho}_{11}, \rho_{22}=\hat{\rho}_{22}} \\
 (6.3) \quad &= -\frac{\rho'_{12}(\alpha_0)}{2\sqrt{\rho_{11}\rho_{22}}} \sum_{i=1}^N \frac{\mathbf{x}_i}{\hat{\sigma}_w^2} - \frac{\mathbf{x}_i}{\hat{\sigma}_v^2} - \frac{\mathbf{x}_i \hat{u}_{wi}^2}{\hat{\sigma}_{wi}^4} + \frac{\mathbf{x}_i \hat{u}_{vi}^2}{\hat{\sigma}_{vi}^4} \\
 &= -\frac{\rho'_{12}(\alpha_0)}{2\sqrt{\rho_{11}\rho_{22}}} \sum_{i=1}^N \left(\frac{\mathbf{x}_i}{\hat{\sigma}_w^2} \left(1 - \frac{\hat{u}_{wi}^2}{\hat{\sigma}_w^2} \right) - \frac{\mathbf{x}_i}{\hat{\sigma}_v^2} \left(1 - \frac{\hat{u}_{vi}^2}{\hat{\sigma}_v^2} \right) \right)
 \end{aligned}$$

For the second derivative,

$$\begin{aligned}
 (6.4) \quad \frac{\partial^2 \ell}{\partial \alpha \partial \alpha^T} &= \sum_{i=1}^N \frac{\mathbf{x}_i \mathbf{x}_i^T \rho''_{12}(\mathbf{x}_i^T \alpha + \alpha_0)}{2\sqrt{\rho_{11}\rho_{22}}} \cdot \left(\frac{1}{\sigma_{wi}^2} \left(1 - \frac{u_{wi}^2}{\sigma_{wi}^2} \right) - \frac{1}{\sigma_{vi}^2} \left(1 - \frac{u_{vi}^2}{\sigma_{vi}^2} \right) \right) \\
 &\quad + \frac{\mathbf{x}_i \mathbf{x}_i^T \rho_{12}'^2(\mathbf{x}_i^T \alpha + \alpha_0)}{4\rho_{11}\rho_{22}} \left(-\frac{1}{\sigma_{wi}^4} + \frac{u_{wi}^2}{2\sigma_{wi}^6} + \frac{1}{\sigma_{vi}^4} + \frac{u_{vi}^2}{2\sigma_{vi}^6} \right) \\
 &= \sum_{i=1}^N \frac{\mathbf{x}_i \mathbf{x}_i^T \rho''_{12}(\mathbf{x}_i^T \alpha + \alpha_0)}{2\sqrt{\rho_{11}\rho_{22}}} \cdot \left(\frac{1}{\sigma_{wi}^2} \left(1 - \frac{u_{wi}^2}{\sigma_{wi}^2} \right) - \frac{1}{\sigma_{vi}^2} \left(1 - \frac{u_{vi}^2}{\sigma_{vi}^2} \right) \right) \\
 &\quad + \frac{\mathbf{x}_i \mathbf{x}_i^T \rho_{12}'^2(\mathbf{x}_i^T \alpha + \alpha_0)}{4\rho_{11}\rho_{22}} \left(\frac{2}{\sigma_{wi}^4} \left(1 - \frac{u_{wi}^2}{2\sigma_{wi}^2} \right) + \frac{2}{\sigma_{vi}^4} \left(1 - \frac{u_{vi}^2}{2\sigma_{vi}^2} \right) \right)
 \end{aligned}$$

$$(6.5) \quad \mathcal{I}_{\alpha\alpha^T} = E \left(\frac{\partial^2 \ell}{\partial \alpha \partial \alpha^T} \right) = \sum_{i=1}^N \frac{\mathbf{x}_i \mathbf{x}_i^T \rho'_{12}(\mathbf{x}_i^T \alpha + \alpha_0)}{4\rho_{11}\rho_{22}} \left(\frac{1}{\sigma_{wi}^4} + \frac{1}{\sigma_{vi}^4} \right)$$

Plug in the maximum likelihood estimates:

$$(6.6) \quad \begin{aligned} \tilde{\mathcal{I}}_{\alpha\alpha^T} &= \mathcal{I}_{\alpha\alpha^T} \big|_{\alpha=\mathbf{0}, \alpha_0=\hat{\alpha}_0, \mathbf{b}=\hat{\mathbf{b}}, \beta=\hat{\beta}, \rho_{11}=\hat{\rho}_{11}, \rho_{22}=\hat{\rho}_{22}} \\ &= \frac{\rho'_{12}(\hat{\alpha}_0)}{4\hat{\rho}_{11}\hat{\rho}_{22}} \cdot 2 \cdot \left(\frac{1}{\hat{\sigma}_w^2} + \frac{1}{\hat{\sigma}_v^2} \right) \sum_{i=1}^N \mathbf{x}_i \mathbf{x}_i^T \end{aligned}$$

Additionally, we can see that $\tilde{\mathcal{I}}_{\alpha\beta_1^T} = \tilde{\mathcal{I}}_{\alpha\beta_2^T} = \mathbf{0}$

$$(6.7) \quad \frac{\partial \ell}{\partial \alpha \partial \beta_1} = \frac{1}{\sqrt{\rho_{11}\rho_{22}}} \sum_i \mathbf{x}_i \mathbf{x}_i^T \rho_{12}(\mathbf{x}_i^T \alpha + \alpha_0) \left(\frac{u_{wi}}{\sqrt{\rho_{11}}\sigma_{wi}^4} + \frac{u_{vi}}{\sqrt{\rho_{11}}\sigma_{vi}^4} \right)$$

$$\tilde{\mathcal{I}}_{\alpha\beta_1^T} = \frac{\rho_{12}(\hat{\alpha}_0)}{\sqrt{\rho_{11}^3\rho_{22}}} \left(\frac{1}{\hat{\sigma}_{wi}^4} E \left(\sum_{i=1}^n \mathbf{x}_i \mathbf{x}_i^T \hat{u}_{wi} \right) + \frac{1}{\hat{\sigma}_{vi}^4} E \left(\sum_{i=1}^n \mathbf{x}_i \mathbf{x}_i^T \hat{u}_{vi} \right) \right) = \mathbf{0}$$

$\tilde{\mathcal{I}}_{\alpha\rho_{11}}$ is

$$(6.8) \quad \begin{aligned} \frac{\partial \ell}{\partial \alpha \partial \rho_{11}} &= \\ &= \sum_{i=1}^N -\frac{\mathbf{x}_i \rho'_{12}(\mathbf{x}_i^T \alpha + \alpha_0)}{2\sqrt{\rho_{11}^3\rho_{22}}} \left(\frac{1}{\sigma_{wi}^2} \left(1 - \frac{u_{wi}^2}{\sigma_{wi}^2} \right) - \frac{1}{\sigma_{vi}^2} \left(1 - \frac{u_{vi}^2}{\sigma_{vi}^2} \right) \right) \\ &+ \frac{\mathbf{x}_i \rho_{12}(\mathbf{x}_i^T \alpha + \alpha_0) \rho'_{12}(\mathbf{x}_i^T \alpha + \alpha_0)}{2\rho_{11}^2\rho_{22}} \left(\frac{1}{\sigma_{wi}^4} \left(1 - \frac{u_{wi}^2}{2\sigma_{wi}^2} \right) - \frac{1}{\sigma_{vi}^4} \left(1 - \frac{u_{vi}^2}{2\sigma_{vi}^2} \right) \right). \\ \tilde{\mathcal{I}}_{\alpha\rho_{11}} &= \frac{\rho_{12}(\hat{\alpha}_0) \rho'_{12}(\hat{\alpha}_0)}{2\rho_{11}^2\rho_{22}^2} \sum_{i=1}^N \mathbf{x}_i \left(\frac{1}{2\hat{\sigma}_w^4} + \frac{1}{2\hat{\sigma}_v^4} \right) \end{aligned}$$

and $\tilde{\mathcal{I}}_{\alpha\rho_{22}}$ is similar. We can see that above equals to zero under a small condition that the covariates are centered. The centering of covariates plays no role in inference.

Finally, we get our score statistic
(6.9)

$$q = \tilde{d}_{\alpha}^T \tilde{I}_{\alpha\alpha}^{-1} \tilde{d}_{\alpha} = \frac{1}{2} \left(\frac{1}{\hat{\sigma}_w^4} + \frac{1}{\hat{\sigma}_v^4} \right)^{-1} \left(\sum_{i=1}^N \mathbf{x}_i \left(\frac{\hat{\sigma}_w^2 - \hat{u}_{wi}^2}{\hat{\sigma}_w^4} - \frac{\hat{\sigma}_v^2 - \hat{u}_{vi}^2}{\hat{\sigma}_v^4} \right) \right)^T \\ \left(\sum_{i=1}^N \mathbf{x}_i^T \mathbf{x}_i \right)^{-1} \left(\sum_{i=1}^N \mathbf{x}_i \left(\frac{\hat{\sigma}_w^2 - \hat{u}_{wi}^2}{\hat{\sigma}_w^4} - \frac{\hat{\sigma}_v^2 - \hat{u}_{vi}^2}{\hat{\sigma}_v^4} \right) \right)$$

6.2. *Derivation of $\eta_{12,13}$.* We start from the test statistic q computed when the covariates have been orthogonalized.

$$q = \sum_{p=1}^P \left(\frac{1}{\sqrt{N}} \sqrt{\frac{\hat{\sigma}_w^4 \hat{\sigma}_v^4}{\hat{\sigma}_w^4 + \hat{\sigma}_v^4}} \sum_{i=1}^N x_{ip} \left(\frac{\hat{\sigma}_w^2 - \hat{u}_{wi}^2}{\hat{\sigma}_w^4} - \frac{\hat{\sigma}_v^2 - \hat{u}_{vi}^2}{\hat{\sigma}_v^4} \right) \right)^2 = \sum_{p=1}^P r_p^2$$

r_p for each p follows standard normal distribution by the central limit theorem.

$$\begin{aligned} E \left(x_{ip} \left(\frac{\hat{\sigma}_w^2 - \hat{u}_{wi}^2}{\hat{\sigma}_w^4} - \frac{\hat{\sigma}_v^2 - \hat{u}_{vi}^2}{\hat{\sigma}_v^4} \right) \right) &= x_{ip} E \left(\frac{\hat{\sigma}_w^2 - \hat{u}_{wi}^2}{\hat{\sigma}_w^4} \right) E \left(\frac{\hat{\sigma}_v^2 - \hat{u}_{vi}^2}{\hat{\sigma}_v^4} \right) = 0 \\ \text{Var} \left(x_{ip} \left(\frac{\hat{\sigma}_w^2 - \hat{u}_{wi}^2}{\hat{\sigma}_w^4} - \frac{\hat{\sigma}_v^2 - \hat{u}_{vi}^2}{\hat{\sigma}_v^4} \right) \right) &= x_{ip}^2 \left(\text{Var} \left(\frac{\hat{\sigma}_w^2 - \hat{u}_{wi}^2}{\hat{\sigma}_w^4} \right) + \text{Var} \left(\frac{\hat{\sigma}_v^2 - \hat{u}_{vi}^2}{\hat{\sigma}_v^4} \right) \right) \\ &= \frac{\hat{\sigma}_w^4 + \hat{\sigma}_v^4}{\hat{\sigma}_w^4 \hat{\sigma}_v^4} \end{aligned}$$

We can re-write $r_{12,p}$ as following as a pre-processing to compute $\text{cov}(r_{12,p}, r_{12,p})$,

$$\begin{aligned} \hat{\sigma}_w^2 &= 2 + \frac{2\hat{\rho}_{12}}{\sqrt{\hat{\rho}_{11}\hat{\rho}_{22}}} = 2 + 2\hat{\tau}_{12} \\ \hat{\sigma}_v^2 &= 2 - \frac{2\hat{\rho}_{12}}{\sqrt{\hat{\rho}_{11}\hat{\rho}_{22}}} = 2 - 2\hat{\tau}_{12} \end{aligned}$$

where ρ_{12} is the constant correlation between variables 1 and 2 under the null hypothesis. Note that asymptotically $\hat{\sigma}_w^2$ converges to σ_w^2 in probability, and so does $\hat{\rho}_{12}$ to ρ_{12} . We also define $\hat{\tau}_{13} = \frac{\hat{\rho}_{13}}{\sqrt{\hat{\rho}_{11}\hat{\rho}_{33}}}$, $\hat{\tau}_{23} = \frac{\hat{\rho}_{23}}{\sqrt{\hat{\rho}_{22}\hat{\rho}_{33}}}$

(6.10)

$$\begin{aligned} r_{p,12} &= \frac{1}{\sqrt{2N}} \frac{1}{\sqrt{8(1 + \hat{\tau}_{12}^2)}} \sum_{i=1}^N x_{ip} \left((2 - 2\hat{\tau}_{12}) - \frac{2 - 2\hat{\tau}_{12}}{2 + 2\hat{\tau}_{12}} (\hat{u}_{1i} + \hat{u}_{2i})^2 \right) \\ &\quad - \left((2 + 2\hat{\tau}_{12}) - \frac{2 + 2\hat{\tau}_{12}}{2 - 2\hat{\tau}_{12}} (\hat{u}_{1i} - \hat{u}_{2i})^2 \right) \\ &= \frac{1}{\sqrt{16N(1 + \hat{\tau}_{12}^2)}} \sum_{i=1}^N x_{ip} \left(\frac{4((\hat{\tau}_{12}^3 - \hat{\tau}_{12}) - \hat{u}_{1i}\hat{u}_{2i}(\hat{\tau}_{12}^2 + 1) + \hat{\tau}_{12}(\hat{u}_{1i}^2 + \hat{u}_{2i}^2))}{(1 - \hat{\tau}_{12})(1 + \hat{\tau}_{12})} \right) \\ &= \frac{1}{\sqrt{N(1 + \hat{\tau}_{12}^2)}} \sum_{i=1}^N x_{ip} \left(\frac{(\hat{\tau}_{12}^3 - \hat{\tau}_{12}) - \hat{u}_{1i}\hat{u}_{2i}(\hat{\tau}_{12}^2 + 1) + \hat{\tau}_{12}(\hat{u}_{1i}^2 + \hat{u}_{2i}^2)}{(1 - \hat{\tau}_{12})(1 + \hat{\tau}_{12})} \right) \end{aligned}$$

Similarly,

$$r_{p,13} = \frac{1}{\sqrt{N(1 + \hat{\tau}_{13}^2)}} \sum_{i=1}^N x_{ip} \left(\frac{(\hat{\tau}_{13}^3 - \hat{\tau}_{13}) - \hat{u}_{1i}\hat{u}_{3i}(\hat{\tau}_{13}^2 + 1) + \hat{\tau}_{13}(\hat{u}_{1i}^2 + \hat{u}_{3i}^2)}{(1 - \hat{\tau}_{13})(1 + \hat{\tau}_{13})} \right)$$

$$\text{cov}(r_{12,p}, r_{13,p}) = E(r_{12,p}r_{13,p}) - E(r_{12,p})E(r_{13,p}) = E(r_{12,p}r_{13,p})$$

Then, after some algebra,

(6.11)

$$\begin{aligned} \eta_{12,13} = E \sum_{i=1}^N x_{ip}^2 & \frac{\hat{u}_{i1}^2 \hat{u}_{2i} \hat{u}_{3i} (\hat{\tau}_{12}^2 + 1)(\hat{\tau}_{13}^2 + 1) + \hat{\tau}_{12} \hat{\tau}_{13} (\hat{u}_{1i}^2 + \hat{u}_{2i}^2)(\hat{u}_{1i}^2 + \hat{u}_{3i}^2)}{N(1 - \hat{\tau}_{12}^2)(1 - \hat{\tau}_{13}^2) \sqrt{(1 + \hat{\tau}_{12}^2)(1 + \hat{\tau}_{13}^2)}} \\ & - \frac{\hat{\tau}_{12}(\hat{\tau}_{13}^2 + 1)(\hat{u}_{1i} \hat{u}_{3i})(\hat{u}_{1i}^2 + \hat{u}_{2i}^2) + \hat{\tau}_{13}(\hat{\tau}_{12}^2 + 1)(\hat{u}_{1i} \hat{u}_{2i})(\hat{u}_{1i}^2 + \hat{u}_{3i}^2)}{N(1 - \hat{\tau}_{12}^2)(1 - \hat{\tau}_{13}^2) \sqrt{(1 + \hat{\tau}_{12}^2)(1 + \hat{\tau}_{13}^2)}} \end{aligned}$$

(6.12)

$$\begin{aligned} & = \frac{(\tau_{23} + 2\tau_{12}\tau_{13})(\tau_{12}^2 + 1)(\tau_{13}^2 + 1) + \tau_{12}\tau_{13}(6 + 2(\tau_{12}^2 + \tau_{13}^2 + \tau_{23}^2))}{(1 - \tau_{12}^2)(1 - \tau_{13}^2) \sqrt{(1 + \tau_{12}^2)(1 + \tau_{13}^2)}} \\ & - \frac{\tau_{12}(\tau_{13}^2 + 1)(4\tau_{13} + 2\tau_{12}\tau_{23}) + \tau_{13}(\tau_{12}^2 + 1)(4\tau_{12} + 2\tau_{13}\tau_{23})}{(1 - \tau_{12}^2)(1 - \tau_{13}^2) \sqrt{(1 + \tau_{12}^2)(1 + \tau_{13}^2)}} \end{aligned}$$

from

$$\begin{aligned} E(\hat{u}_{i1}^4) &= 3, & E(\hat{u}_{i1}^3 \hat{u}_{i2}) &= 3\tau_{12}, & E(\hat{u}_{i1}^2 \hat{u}_{i2}^2) &= 1 + 2\tau_{12}^2, \\ E(\hat{u}_{i1}^2 \hat{u}_{i2} \hat{u}_{i3}) &= \tau_{23} + 2\tau_{12}\tau_{13}. \end{aligned}$$

6.3. *Small Sample Correction.* Although the introduced test statistic q asymptotically follows χ_1^2 , the sample size is not large enough in many applications. The statistic has its error in the order of N^{-1} [12], and many Monte Carlo experiments show that the test rejects the null hypothesis less frequently than indicated by its nominal size [10, 11, 13]. In response, Harris (1985) used Edgeworth expansion to obtain the distribution and moment generating function to order n^{-1} of the test statistic [12]. Building on this expansion, Honda (1986) and Cribari-Neto and Ferrari (2001) proposed corrections to the critical value or to the test statistic that allows better inference even when the sample size is small while preserving the asymptotic properties. [4, 5, 13]

Honda (1988) provided a closed-form formula to adjust the critical value in the order of $O(n^{-1})$ to correct the type I error of the test. This adjustment, only depending on the covariate, sample size, and the degrees of freedom, but not on the data, is a cubic function with respect to C_γ , the critical value at the level of type I error γ , i.e. $P(\chi_P^2 \geq C_\gamma) = \gamma$, and we refer to this cubic function as g defined as follows.

$$(6.13) \quad \begin{aligned} g(C_\gamma) = C_\gamma + C_\gamma \left(\frac{A_3 - A_2 + A_1}{12NP} \right) + C_\gamma^2 \left(\frac{A_2 - 2A_3}{(12NP(P+2))} \right) + \\ C_\gamma^3 \left(\frac{A_3}{12NP(P+2)(P+4)} \right) = C_\gamma + \tilde{g}(C_\gamma) \end{aligned}$$

where the scalars A_1 , A_2 , and A_3 follow the notation of Honda (1988) directly.

One of the desirable properties of g would be monotonicity, because regardless of sample size, we would like to maintain the same ordering of the strength of evidence against the null. This turns out to be almost always true in practice. The derivative of $g(C)$ is

$$g'(C_\gamma) = \frac{A_3}{12NP} \left(\frac{A_3 - A_2 + A_1 + 12NP}{A_3} + \frac{2(A_2 - 2A_3)}{(P+2)A_3} C_\gamma + \frac{3}{(P+2)(P+4)} C_\gamma^2 \right)$$

A_3 is strictly positive by definition, and we can solve the above quadratic equation to see in which case the derivative is positive [4]. In other words, we can study when the following discriminant is complex.

$$\sqrt{\left(\frac{2(A_2 - 2A_3)}{(P+2)A_3} \right)^2 - 4 \cdot \frac{3A_3(A_3 - A_2 + A_1)}{(P+2)(P+4)A_3} - 4 \cdot \frac{3 \cdot 12NP}{(P+2)(P+4)}}$$

The first two terms inside the square root are $O(1)$ and the last term is $O(n)$, so we can see that the discriminant becomes complex quickly as n increases. Also when the covariates are simulated from normal distribution, $g'(C)$ was always positive unless $n < 3$.

Similar argument is offered in Cribari (1995) [4]. Based on the correction of the critical value in (6.13), Cribari (1995) proposes to subtract the correction $\tilde{g}(C_\gamma)$ so that

$$P(q \geq g(C_\gamma)) = P(q \geq C_\gamma + \tilde{g}(C_\gamma)) = P(q - \tilde{g}(C_\gamma) \geq C_\gamma).$$

This treats the correction as de-biasing instead of changing the overall shape of the distribution. Although this adjustment of the test statistic corrects the size of the test at a given threshold, it prevents further analysis when we combine the test statistics in section (2.12).

Instead, we aim to adjust the test statistic so that the overall shape of null distribution is closer to χ_P^2 . We assume a large enough sample size for monotonicity of g and define the inverse function of g to propose the new adjusted test statistic $\tilde{q}_{12} = g^{-1}(q)$

$$\gamma = P(\chi_P^2 \geq C_\gamma) = P(q \geq g(C_\gamma)) = P(g^{-1}(q) \geq C_\gamma)$$

Our final test statistic \tilde{q}_{12} is the real solution to the following equation

$$q - g(C_\gamma) = 0$$

which is guaranteed to be unique by the monotonicity of g . The cubic equation can be solved both analytically and numerically efficiently given the covariate X .

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