Using prior information to boost power in correlation structure support recovery

Ziyang Ding and David Dunson
Department of Statistical Science, Duke University
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Abstract

Hypothesis testing of structure in correlation and covariance matrices is of broad interest in many application areas. In high dimensions and/or small to moderate sample sizes, high error rates in testing is a substantial concern. This article focuses on increasing power through a frequentist assisted by Bayes (FAB) procedure. This FAB approach boosts power by including prior information on the correlation parameters. In particular, we suppose there is one of two sources of prior information: (i) a prior dataset that is distinct from the current data but related enough that it may contain valuable information about the correlation structure in the current data; and (ii) knowledge about a tendency for the correlations in different parameters to be similar, so that it is appropriate to consider a hierarchical model. When the prior information is relevant, the proposed FAB approach can have significant gains in power. A divide-and-conquer algorithm is developed to reduce computational complexity in massive testing dimensions. We show improvements in power for detecting correlated gene pairs in genomic studies, while maintaining control of Type I error or false discover rate (FDR).

Keywords: Correlation structure testing; Frequentist assisted by Bayes; High-dimensional data; Multiple hypothesis testing; Prior information.
1 Introduction

In this article, we consider the problem of inferring the locations of zeros in a $q \times q$ correlation matrix $P$ given a sample of $n$ independent $q$-dimensional normal random vectors $x_1, \ldots, x_n$, when prior information about entries of $P$ is available. This problem can be expressed statistically as testing

$$H_{0wv} : \rho_{wv} = 0 \quad \text{versus} \quad H_{1wv} : \rho_{wv} \neq 0,$$

for each of the $q(q-1)/2$ unique entries of $P$, with $\rho_{wv}$ denoting the correlation between the $w^{th}$ and $v^{th}$ variables. This testing problem is commonly known as support recovery of a correlation structure, or correlation structure testing, which is a fundamental problem in multivariate analysis. There are important applications in finance (Chen et al., 2020), biology (Van Rheenen et al., 2019), and many other fields.

This article proposes a methodology for improving power in frequentist support recovery by exploiting prior information. This prior information takes one of two forms: (i) a prior dataset is available that contains information on the correlation parameters of interest in the current dataset, but with the prior dataset distinct enough so that it does not make sense to merge the datasets; and (ii) knowledge that the correlation parameters for different pairs of variables tend to be related, so that it is reasonable to borrow information. In case (i) for simplicity in exposition we assume that the external dataset $X_{\text{ext}}$ has the same format as $X$, though modifications to account for the case in which $X_{\text{ext}}$ measures a distinct but overlapping set of variables are straightforward. In case (ii) we assume that prior information relevant for testing $H_{0wv}$ vs $H_{1wv}$ takes the form of test statistics for other pairs of variables.

Finding zeros in the correlation matrix is mainly achieved via one of two general approaches. The first is estimation-based, using a sparseness favoring correlation matrix estimator; for example, via $\ell_1$-penalized maximum likelihood. Related works include Friedman et al. (2008); Bickel and Levina (2008); Lam and Fan (2009); Rothman et al. (2009); Cai et al. (2011); Fan et al. (2016) and Cai et al. (2016). The second general approach is testing-based, in which we form hypotheses on individual correlation coefficients in the matrix being zero. Examples of this approach include work by Yuan and Lin (2006); Cai et al. (2011, 2013); Cai and Zhang (2016); Kundu et al. (2019) and Lee et al. (2021). Refer to
Cai (2017) and Na et al. (2021) for an overview of related methods. This article focuses on the testing-based approach. We aim to improve the accuracy of correlation matrix support recovery through the use of prior information, either through external data or borrowing information from a current dataset. Relevant external data may be from a previous related study that provides (potentially imperfect) information on the locations of zeros in $P$.

Apart from research on correlation and covariance structure testing, there is also a previous related literature that seeks to improve power for hypothesis testing in general, either by exploiting prior information of various types or introducing auxiliary information. One popular approach that helps gain power for adaptive FDR-controlling procedures by estimating the overall proportion of true nulls is derived by Storey (2002). Another general category of approaches include prior weights in the testing procedure, with these prior weights providing information on hypotheses that should be more or less likely 
a priori.

Genovese et al. (2006) developed a weighted variation of the Benjamini-Hochberg (BH) procedure (Benjamini and Hochberg, 1995a). Related approaches can be found in Dobriban et al. (2015) and Dobriban (2016). Other work has included prior information through other mechanisms; for example, by assuming the side information is independent of the $p$-values (Roquain and Van De Wiel, 2009), or by allowing for data-dependent weighting (Hu et al., 2010; Zhao and Zhang, 2014; Ignatiadis et al., 2016; Durand, 2019; Lei and Fithian, 2018; Ignatiadis and Huber, 2021). Another idea is to exploit a prior ordering to concentrate power on more “promising” hypotheses near the top of the ordering (Barber and Candès, 2015; G’Sell et al., 2016; Li and Barber, 2017; Lei and Fithian, 2016). The above methods provide a rich toolbox through improving power with the introduction of certain types of external information. However, the focus has been largely on including direct prior information about the different hypotheses under consideration, with a set of $p$-values provided as input and not informed by this prior information - what is informed is the decision rule based on these $p$-values.

In our work, focusing on the correlation support recovery problem, we take the different approach of including prior information relevant to the correlations under consideration, instead of the hypotheses directly, with this prior information used in obtaining the $p$-values. The proposed method is based on the frequentist assisted by Bayes (FAB) procedure of Hoff (2021). To simplify the methodology, we rely on Fisher-transformations of the correlation
coefficients and associated asymptotic approximations. Prior information is incorporated via a probabilistic model linking different hypothesis tests. The resulting p-values can be used to maintain Type I error rates and FDR control. When the prior information is appropriate, power can be improved relative to tests that ignore this information. To reduce computational complexity and facilitate implementations in high dimensions, we introduce asymptotic approximations and a divide-and-conquer strategy, while providing asymptotic theory supporting these approaches. We provide examples incorporating external information of different types for FAB testing. For instance, if the entries of $P$ are the population-level correlations among a set of $q$ genes, then knowledge about the positive regulation between a pair of genes in a well-studied biological pathway can constitute external information about $P$. Alternatively, external information can take the form of a posited low-rank structure for $P$, which determines groups of entries whose signs and magnitudes are similar.

2 Preliminaries

In this section, we briefly review some past techniques needed to construct our FAB correlation structure test. Section 2.1 reviews the well known Fisher variance stabilizing function under the context of correlation testing. Section 2.2 reviews the “frequentist assisted by Bayes” (FAB) approach developed by Hoff (2021), the methodology that we extend into the correlation structure testing setting.

2.1 Fisher-transformed correlation coefficient

Our focus is on testing the hypotheses in (1). Denote the sample Pearson correlation coefficient as

$$
\hat{\rho}_{wv} = \frac{\sum_{i=1}^{n} (x_{iw} - \bar{x}_w)(x_{iv} - \bar{x}_v)}{\sqrt{\sum_{i=1}^{n} (x_{iw} - \bar{x}_w)^2 \sum_{i=1}^{n} (x_{iv} - \bar{x}_v)^2}}
$$

(2)

for each of the $q(q-1)/2$ unique entries of $P$. Under the null hypothesis $H_{0wv}$, the statistic

$$
t_{\rho_{wv}}(X) = \hat{\rho}_{wv} \sqrt{(n-2)/(1 - \hat{\rho}_{wv}^2)}
$$

(3)

has an asymptotic t-distribution with $n - 2$ degrees of freedom, so a level-$\alpha$ test can be constructed by rejecting $H_{0wv}$ when $|t_{\rho_{wv}}(X)|$ exceeds the $1 - \alpha/2$ quantile of the $t_{n-2}$
distribution. Typically, however, an approximately level-$\alpha$ test is constructed using Fisher’s transformed test statistic (Fisher, 1915)

$$T_{\rho_{wv}}(X) = F(\hat{\rho}_{wv}) = \frac{1}{2} \log \frac{1 + \hat{\rho}_{wv}}{1 - \hat{\rho}_{wv}}$$

which is approximately distributed as

$$T_{\rho_{wv}}(X) \sim N\left(F(\rho_{wv}), \frac{1}{n-3}\right)$$

Because its variance is approximately constant as a function of $\rho_{wv}$, the statistic $T_{\rho_{wv}}(X)$ can be used to construct more flexible and stable hypothesis tests than those based on $t_{\rho_{wv}}(X)$ or using the exact sampling distribution of $\hat{\rho}_{wv}$. The approximate normality of $T_{\rho_{wv}}(X)$ is useful to our strategy for incorporating external information into testing the dependence structure of $P$.

2.2 FAB Testing

Given an iid sample $x_i \sim N(\theta, \sigma^2)$, $i = 1, \ldots, n$, suppose interest focuses on testing

$$H_0 : \theta = 0 \quad \text{versus} \quad H_1 : \theta \neq 0$$

Supposing $\sigma$ is known, the $p$-value for the classical uniformly most powerful unbiased (UMPU) test has closed form

$$p^{\text{UMPU}} = 1 - |\Phi(\bar{x}/\sigma) - \Phi(-\bar{x}/\sigma)|.$$ 

Under the null hypothesis $H_0$, $p^{\text{UMPU}}$ is uniformly distributed in the interval $(0, 1)$, so the Type I error rate of the UMPU test may be controlled at level $\alpha$ by rejecting the null when $p^{\text{UMPU}} < \alpha$. The FAB test introduced by Hoff (2021) leverages the fact that for any offset random variable $b$ that is independent of $\bar{x}/\sigma$, the “FAB $p$-value”

$$p^{\text{FAB}} := 1 - |\Phi(\bar{x}/\sigma + b) - \Phi(-\bar{x}/\sigma)|$$

is also uniformly distributed under the null hypothesis $H_0$.

**Theorem 2.1.** (Hoff, 2021) Let $Z$ and $b$ be independent random variables with $Z \sim N(0,1)$. Then $\Pr(1 - |\Phi(Z + b) - \Phi(-Z)| < u) = u$
Rejecting the null when \( p^{\text{FAB}} < \alpha \) is therefore also an \( \alpha \)-level frequentist test. However, the power of the FAB test may be greater than that of the UMPU test if \( b \) is chosen carefully. We use external information to inform our choice of \( b \) for correlation structure hypothesis testing. We reserve the explanation of our specific approach to incorporating external information for Section 3, and highlight the most important aspects of the general FAB testing approach here:

1. For the case of testing several hypotheses, a probability model—called a “linking model”—is proposed. Combined with the sampling model for the test statistics, the linking model can be used to perform FAB tests for each parameter of interest; in our case, these are the \( \rho_{jk} \).

2. The offset term \( b_{jk} \) for each hypothesis test must be inferred from information independent from the test statistics. It could be inferred either completely from an external dataset or from independent information within the same dataset. Details regarding the two situations will be discussed in Section 3.1.1 and Section 3.1.2.

3. The design of the linking model impacts the power of FAB tests, but it does not affect the Type I error when \( b_{jk} \) is independent of the test statistic.

3 Methodology

In this section, we describe our methodology for FAB correlation structure testing. The commonly used notation in the paper is listed in Table 1. In Section 3.1 we adapt the methods in Section 2.2 to the setting of correlation coefficient testing. This section focuses on forming the FAB test on a single correlation coefficient given external information. In Section 3.2 we address the computational challenge of performing \( O(q^2) \) FAB tests for correlation structure by adopting a divide-and-conquer approach.
| Notation | Definition |
|----------|------------|
| **Function** | | 
| $F(\cdot)$ | Fisher’s z-transformation. Defined in Equation 4 |
| **Variables** | | 
| $P, \rho, \rho$ | Matrix, vector, and scalar valued true correlation |
| $Z, z, z$ | Matrix, vector, and scalar valued Fisher-transformed true correlation |
| $\Omega_z, \omega_z, \omega_z$ | Matrix, vector, and scalar valued true correlation of Fisher-transformed correlation estimators: $\text{Cor}(\tilde{z}_1, \tilde{z}_2)$ |
| $m_j, v_j$ | FAB offset mean and variance of the $j^{th}$ test |
| $G_j$ | Decorrelation matrix of the $j^{th}$ test |
| **Estimator** | | 
| $\hat{\cdot}$ | Estimator constructed from direct test statistics. |
| $\tilde{\cdot}$ | Estimator constructed from indirect information conditionally independent from test statistics. |
| **Indexing** | | 
| $i \in \{1 : n\}$ | $i$ is the index of subjects $\{X_i\}_{i \in \{1 : n\}} := \{X_1, X_2, \ldots X_n\}$ |
| $j \in \{1 : p\}$ | $j$ is the index of test statistics $\{\tilde{z}_j\}_{j \in \{1 : p\}} := \{\tilde{z}_1, \tilde{z}_2, \ldots \tilde{z}_p\}$ |
| $k \in \{1 : m\}$ | $k$ is the index of hypothesis group $\{\tilde{z}^{(k)}\}_{k \in \{1 : m\}} := \{\tilde{z}^{(1)}, \tilde{z}^{(2)}, \ldots \tilde{z}^{(m)}\}$ |
| $n$ | Total number of samples |
| $q$ | Total number of dimensions of subject $X$ |
| $p$ | Total number of tests. $p = q$ if hypothesis tests are on sample mean. But $p = q(q - 1)/2$ if tests are on pairwise correlation. |
| $m$ | The total number hypothesis groups. Formal description introduced in Section 3.2. |
| $-j$ | A negative sign before an index indicates every other index instead of this index. For example, $\tilde{z}_{-j} := \{\tilde{z}_1, \ldots \tilde{z}_{j-1}, \tilde{z}_{j+1}, \ldots, \tilde{z}_p\}$. |

Table 1: Notation of frequently used parameters
3.1 FAB Correlation Testing

As introduced in Section 2.1, the distribution of the Fisher-transformed sample correlation coefficient $\hat{z}_{wv}$ approximately follows the normal distribution

$$\mathbb{E}(\hat{z}_{wv}) = F(\hat{\rho}_{wv}) \sim \mathcal{N}(F(\rho_{wv}), \frac{1}{n-3})$$  \hspace{1cm} (7)

The approximate normality of the statistic $z_j$ allows us to adapt the FAB methodology for testing described in Section 2.2. For notational simplicity in what follows, we simplify the indexing by using a single index $j = 1, \ldots, p = q(q-1)/2$ for the different $w,v$ pairs.

Suppose we are testing the $j^{th}$ correlation $\rho_j$ based on its observed Fisher transformed correlation coefficient $\hat{z}_j$. The FAB correlation test improves power of the test on $\hat{z}_j$ by borrowing information from some other statistics $\hat{z}'_j$, which can be statistics from a purely external dataset $\hat{z}^\text{ext}_j$ (take $\hat{z}'_j = \hat{z}^\text{ext}_j$ as in Section 3.1.1) or can be statistics from other tests $\hat{z}_j$ within the same dataset as $\hat{z}_j$ (take $\hat{z}'_j = \hat{z}_j$ as in Section 3.1.2). The test statistics $z_j$ and the indirect information source $z'_j$ are modeled jointly using the following model:

$$z = \begin{bmatrix} \hat{z}_j \\ \hat{z}'_j \end{bmatrix} \sim \mathcal{N} \left( z := \begin{bmatrix} z_j \\ z'_j \end{bmatrix}, \frac{1}{n-3} \Omega_z := \frac{1}{n-3} \text{Cor}(z) \right)$$  \hspace{1cm} (8)

$$z \sim \mathcal{N}(\mu := W\eta, \Psi)$$  \hspace{1cm} (9)

Equation 8, which specifies the distribution of the observed Fisher-transformed correlation coefficient $\hat{z}_j := F(\hat{\rho}_j)$ and that of other observed statistics $\hat{z}'_j$, is called the sampling model. Equation 9, which is a custom designed prior distribution on the true Fisher-transformed correlation $z_j$ that “links” the true parameter $z_j$ with $z'_j$, is called the linking model. This linking model allows sharing of information between $z_j$ and $z'_j$ with $\mu$ having a lower dimensional representation $\eta$ with $\text{dim}(\eta) < \text{dim}(\mu)$. The lower dimensional structure is characterized by a factor model as $\mu = W\eta$, in which the factor loading matrix $W$ is pre-defined, whereas $\eta$ is unknown and will be estimated using empirical Bayes. When testing is based on $\hat{z}_j$, FAB borrows indirect information from $\hat{z}'_j$ in the sampling model and shares it with $\hat{z}_j$ via the linking model, therefore improving power.

As described in Hoff (2021), we can form a FAB test that is approximately Bayes-
optimal with respect to power using the following form for the offset terms $b_j$:

$$
p_j^{\text{FAB}} := 1 - |\Phi(\frac{z_j \sqrt{n - 3} + \tilde{b}_j}{\sqrt{\frac{3}{n-3}}} - \Phi(-\frac{z_j \sqrt{n - 3}}{\sqrt{\frac{3}{n-3}}}))|
$$

(10)

$$
\tilde{b}_j := \frac{2\tilde{m}_j}{\tilde{v}_j \sqrt{n - 3}} \quad \tilde{m}_j := \mathbb{E}\left[z_j | \tilde{\mu}(\tilde{z}_j^\perp), \tilde{\Psi}(\tilde{z}_j^\perp), \tilde{z}_j^\perp\right] \quad \tilde{v}_j := \mathbb{V}\left[z_j | \tilde{\mu}(\tilde{z}_j^\perp), \tilde{\Psi}(\tilde{z}_j^\perp), \tilde{z}_j^\perp\right]
$$

where $\tilde{z}_j^\perp$ is the indirect information, drawn from $\bar{z}$, that is independent from the test statistics $z_j$. $\tilde{\mu}, \tilde{\Psi}$ are estimators of $\mu, \Psi$ is estimated only from indirect information $\tilde{z}_j^\perp$ to ensure independence with test statistics $\bar{z}_j$ as required by Theorem 2.1, and $\tilde{m}_j, \tilde{v}_j$ are the posterior mean and variance of $z_j$ based on the empirical Bayes prior $z \sim \mathcal{N}(\tilde{\mu}, \tilde{\Psi})$ and indirect data likelihood $\mathcal{L}(\tilde{z}_j^\perp; z)$. Therefore, $\tilde{\mu}, \tilde{\Psi}, \tilde{m}_j, \tilde{v}_j$ are functions of only $\tilde{z}_j^\perp$, and $g : \bar{z} \mapsto \tilde{z}_j^\perp$ is a “make-independence” function $g$ of $\bar{z}$ to ensure all the later calculated statistics, $\tilde{\mu}, \tilde{\Psi}, \tilde{m}_j, \tilde{v}_j$, are independent with $\bar{z}_j$.

The construction of such $g$ functions depends on the application scenario. If $\bar{z}_j$ comes from an external data source (scenario when $\bar{z}_j = \bar{z}_j^{\text{ext}}$), the correlation matrix $\Omega_z$ of $\bar{z}$ is block-diagonal. Hence, the independent indirect information $\tilde{z}_j^\perp$ can be easily sourced from $\bar{z}$ with a trivially constructed function $g$. However, if $\bar{z}_j$ is sourced from other test statistics within the same dataset as $\bar{z}_j$ (scenario when $\bar{z}_j = \bar{z}_{-j}$), the correlation matrix $\Omega_z$ of $\bar{z}$ may be unknown. Under such circumstances, construction of $g$ requires more effort.

We split the discussion according to the two different scenarios - external or internal information. Section 3.1.1 introduces cases when $\bar{z}_j = \bar{z}_j^{\text{ext}}$, so that $\bar{z}_j \perp \bar{z}_j'$ innately. Section 3.1.2 discusses when $\bar{z}_j' = \bar{z}_{-j}$ is sourced from the same dataset so that independence is not automatic.

### 3.1.1 $\bar{z}_j = \bar{z}_j^{\text{ext}}$: Sampling Model Using External Data

This section focuses on the scenario when $\bar{z}_j'$ is calculated using an external dataset, so that $\bar{z}_j \perp \bar{z}_j'$ conditional on the true parameter. The method assumes the historical or external dataset shares a similar correlation structure as the current dataset. For example, in studying dependence across genes in their expression levels using single cell RNAseq data, it is common to collect data under similar conditions. For instance, in the current setting, we may be interested in identifying correlated pairs of genes for squamous epithelium cells, while borrowing information from data previously collected for cuboidal epithelium cells. There is substantial similarity in mRNA expression profiles for related cell types.
(Van Lommel, 2003). Hence, we treat the latter (cuboidal) dataset as the external dataset, from which \( \tilde{z}_j = \tilde{z}_j^{\text{ext}} \) are calculated. As \( \tilde{z}_j' \) is from a different dataset that is independent from \( \tilde{z}_j \), the required independence of \( \tilde{m}_j, \tilde{v}_j \) is satisfied. The following sampling model summarizes the distribution of \((\tilde{z}_j, \tilde{z}_j')^T\)

\[
\tilde{z} = \begin{bmatrix} \tilde{z}_j \\ \tilde{z}_j' := \tilde{z}_j^{\text{ext}} \end{bmatrix} \sim N\left( \begin{bmatrix} z_j \\ z_j' := z_j^{\text{ext}} \end{bmatrix}, \frac{1}{n-3} \Omega_z = \frac{1}{n-3} \begin{bmatrix} 1 & 0 \\ 0 & \Omega_{z_j'} \end{bmatrix} \right) \tag{11}
\]

The function \( g \) can be simply constructed as a decorrelation matrix \( G_j \), a \( p \times (p-1) \) dimensional matrix obtained by deleting the column corresponding to \( \tilde{z}_j \) from \( I_p \). In the arrangement of Equation 11, as \( \tilde{z}_j \) is in the first dimension of \( \tilde{z} \), the first column of \( I_p \) is deleted to construct \( G_j \)

\[
G_j = \begin{bmatrix} 0_{1 \times (p-1)} \\ I_{(p-1) \times (p-1)} \end{bmatrix}
\]

As a result, the indirect information \( G_j^T \tilde{z} = \tilde{z}^j \) is independent from \( \tilde{z}_j \). Thus, we can obtain an empirical Bayes estimator for \( \tilde{\eta}, \tilde{\Psi} \) solely from the marginal distribution of the indirect information \( \tilde{z}^j = G_j^T \tilde{z} \) as in Equation 12. The estimator can be obtained via maximum likelihood or \( l_2 \) penalization, as long as it is independent from \( \tilde{z}_j \).

\[
G_j^T \tilde{z} \sim \mathcal{N}_{p-1} \left( G_j^T W \tilde{\eta}, G_j^T \left( \frac{1}{n-3} \Omega_z + \Psi \right) G_j \right) \tag{12}
\]

The posterior of \( z \) given the indirect information \( \tilde{z}^j \) and the empirical Bayes estimated prior parameters \( \tilde{\eta}, \tilde{\Psi} \) can be easily obtained using linear algebra:

\[
z|G_j^T \tilde{z}, \tilde{\eta}, \tilde{\Psi} \sim \mathcal{N}_{p}(m, V)
\]

\[
V = \left[ \tilde{\Psi}^{-1} + (n-3)G_j \left( G_j^T \Omega_z G_j \right)^{-1} G_j^T \right]^{-1}
\]

\[
m = V \left[ \tilde{\Psi}^{-1} W \tilde{\eta} + (n-3)G_j \left( G_j^T \Omega_z G_j \right)^{-1} G_j^T \tilde{z} \right]
\tag{13}
\]

With \( m, V \) calculated, the FAB \( p \)-value can then be simply calculated as in Equation 10, where \( \tilde{m}_j, \tilde{v}_j \) are defined as the posterior mean and variance of \( z_j \). In our arrangement of Equation 11, \( \tilde{m}_j, \tilde{v}_j \) are the first row of \( m \) and the first row first column element of \( V \) respectively, as \( z_j \) is in the first dimension of \( z \).
3.1.2 \( \tilde{z}_j' = \tilde{z}_{-j} \): Sampling Model Using Internal Data

In the absence of an external dataset containing a similar correlation structure, we can borrow information across the different Fisher-transformed correlation coefficients in the same dataset. It is well known that borrowing across seemingly unrelated parameters can yield statistical dividends. In the motivating gene expression application, it is plausible to suppose that the correlations between other pairs of genes are informative about the correlation between a particular pair of interest. This motivates letting \( \tilde{z}_j' = \tilde{z}_{-j} \) to draw indirect information from other hypotheses’ test statistics \( \tilde{z}_{-j} \) to assist the testing on \( z_j \). However, independence between \( \tilde{z}_j' \) and \( \tilde{z}_j \) does not hold any longer. Furthermore, the correlation matrix \( \Omega_z \) is completely unknown. Additional estimations and statistical procedures on \( \Omega_z \) are needed to ensure the validity of the FAB correlation test. The formal sampling model in this scenario is specified as

\[
\tilde{z} = \begin{bmatrix} \tilde{z}_j \\ \tilde{z}_j' := \tilde{z}_{-j} \end{bmatrix} \sim \mathcal{N}\left( z = \begin{bmatrix} z_j \\ z_j' := z_{-j} \end{bmatrix}, \frac{1}{n-3} \Omega_z \right) \tag{14}
\]

First, assuming that \( \Omega_z \) is known and \( \tilde{z}_j \perp \perp \tilde{z}_j \), we can extract independent information by constructing \( G_j \) as a decorrelation matrix, whose columns form a basis of the null space of \( \tilde{z}_j \)’s corresponding column of \( \Omega_z \) (which is the first column of \( \Omega_z \) in the arrangement of Equation 14). As \( \tilde{z} \) is normally distributed, the indirect information \( G_j^\top \tilde{z} = \tilde{z}_j^\top \) is independent from \( \tilde{z}_j \). However, in reality \( \Omega_z \) is unknown and requires estimation. In fact, we can construct a consistent estimator \( \tilde{\Omega}_z \) for \( \Omega_z \), from which we can also construct a consistent estimator \( \tilde{G}_j \) for the decorrelation matrix \( G_j \) due to the continuous mapping theorem. This consistent estimator of \( \tilde{G}_j \) suffices to provide asymptotic independence between \( \tilde{z}_j \) and \( \tilde{G}_j^\top \tilde{z} \).

**Theorem 3.1.** Let \( \tilde{\Omega}_z \xrightarrow{pr.} \Omega_z \) and \( \sqrt{n + 3} (\tilde{z} - z) \xrightarrow{dist.} r \), where \( r \sim \mathcal{N}_p(0, \Omega_z) \). Then as \( n \to \infty \)

1. \( \text{Cor} \left[ \tilde{G}_j^\top \tilde{z}, \tilde{z}_j \right] \to 0 \)

2. \( \text{Pr} \left( \left\{ \sqrt{n} \tilde{G}_j^\top (\tilde{z} - z) \in A \right\} \cap \left\{ \sqrt{n} (\tilde{z}_j - z_j) \in B \right\} \right) \to \text{Pr} \left( \tilde{G}_j^\top r \in A \right) \times \text{Pr} \left( r_j \in B \right) \)

where the columns of \( G_j \) form a basis spanning the null space of the \( \tilde{z}_j \)-corresponding column.
of $\Omega_z$; the columns of $\tilde{G}_j$ form a basis spanning the null space of the $\tilde{z}_j$-corresponding column of $\tilde{\Omega}_z$; and $A \subset \mathbb{R}^{n-1}$ and $B \subset \mathbb{R}$ are measurable sets.

**Proof.** As $\tilde{G}_j$ is constructed by Gram-Schmidtting the consistent estimator $\hat{\Omega}_z$, there exist continuous function that maps $\hat{\Omega}_z$ to $\tilde{G}_j$. Therefore we have that $\hat{G}_j \xrightarrow{pr.} G_j$. Also, define $\tilde{H}_j$ and $H_j$ be $p \times p$ matrices obtained by binding the standard basis vector $(1, 0, \ldots, 0)^\top$ to $\tilde{G}_j$ and $G_j$, respectively. We also have that $\tilde{H}_j \xrightarrow{pr.} H_j$. Hence, both results follows by Slutsky’s theorem, as $\tilde{H}_j \sqrt{n + \tilde{3}(\tilde{z} - z)} \xrightarrow{dist.} H_j^r = (G_j^r r, r_j)$ and we know that $G_j^r r \perp r_j$. 

Hence, the challenge is in obtaining a consistent estimator of $\Omega_z$, the correlation matrix of a set of Fisher-transformed correlation coefficients $\tilde{z}$. As we have only one measurement of $\tilde{z}$, to consistently estimate $\Omega_z$, we apply the bootstrap.

**Theorem 3.2.** Let $\tilde{Z}_B^* := \{\tilde{z}_1^*, \tilde{z}_2^*, \ldots, \tilde{z}_B^*\}$ be $B$ bootstrap samples. Define $\tilde{\Omega}_z^*$ as the bootstrap estimator of $\Omega_z$ based on the $B$ bootstrap samples $\tilde{Z}_B^*$. Then, $\tilde{\Omega}_z^* \xrightarrow{pr.} \Omega_z$.

We may reduce this Theorem into a simple case when $\tilde{z}$ is two-dimensional.

**Theorem 3.3.** Let $\tilde{z} := (\tilde{z}_a, \tilde{z}_b)^\top$ be the joint vector of a pair of Fisher-transformed Pearson correlation estimators. Denote the set of $B$ bootstrap samples for the Fisher-transformed-correlation pair $\tilde{Z}_B^* := \{\tilde{z}_1^*, \tilde{z}_2^*, \ldots, \tilde{z}_B^*\}$, with each sample $\tilde{z}_B^*$ as an estimator of $z$ inferred from the $b^{th}$ re-sampled dataset. Then, define the true correlation coefficient between $\tilde{z}_a$ and $\tilde{z}_b$ as $\omega_z$. Then, the bootstrap estimator

$$\tilde{\omega}_z^* := \frac{\sum_{i=1}^B (\tilde{z}_{a_i}^* - \tilde{z}_a)(\tilde{z}_{b_i}^* - \tilde{z}_b)}{\sqrt{\sum_{i=1}^B (\tilde{z}_{a_i}^* - \tilde{z}_a)^2 \sum_{i=1}^B (\tilde{z}_{b_i}^* - \tilde{z}_b)^2}} \xrightarrow{pr.} \omega_z$$

The proof of Theorem 3.3 is in Appendix A. Theorem 3.3 shows the pairwise consistency of $\tilde{\omega}_z^*$. The bootstrap estimator $\tilde{\Omega}_z^*$ constructed by concatenating each $\tilde{\omega}_z^*$ is a consistent estimator for $\Omega_z$. Theorem 3.3 implies Theorem 3.2. Under such consistency, the distribution of each FAB $p$-value converges to a uniform(0,1) distribution asymptotically. Hence, it is reasonable to use $\tilde{\Omega}_z^*$ as $\Omega_z$ to construct the decorrelation matrix $\tilde{G}_j$. The FAB $p$-value inference algorithm is summarized in Algorithm 1.
Algorithm 1: General Bootstrap FAB correlation test

Result: FAB $p$-values for $p = q(q - 1)/2$ correlation tests

Input: Fisher-transformed coefficient estimator $\hat{z}$ calculated from the $q$

dimensional data $X$

Sample: $B$ bootstrap samples $\hat{Z}_B^* := \{\hat{z}_1^*, \hat{z}_2^*, ..., \hat{z}_B^*\}$ by re-sampling $n$ samples from $X$ with replacement for $B$ times.

Calculate: correlation matrix estimator $\hat{\Omega}_z$ for $\hat{z}$ from bootstrap samples $\hat{Z}_B^*$

for $j = 1, 2, ..., p$ do

Construct: $\hat{G}_j$ as the matrix whose columns form a basis for the null space of
the $\hat{z}_j$ corresponding column of $\hat{\Omega}_z$

Calculate: Empirical Bayes estimator for $\hat{\eta}, \hat{\Psi}$ from indirect information
$\hat{z}_j^\Psi = \hat{G}_j^T \hat{z}$

Calculate: Conditional mean and variance of $z_j|\hat{\eta}, \hat{\Psi}, \hat{z}^\Psi$ as in Equation 13,
denoted as $\hat{m}_j, \hat{v}_j$

Obtain: FAB $p$-value $p_j^{FAB}$ as defined in Equation 10.

end

Return: $\{p_j^{FAB}\}_{j=1}^p$

3.2 FAB Correlation Structure Testing

Section 3.1 builds the foundation of using FAB for correlation coefficient testing. To extend
the methodology to testing every element in a large correlation matrix, computational cost
needs to be reduced. This section proposes a simple divide-and-conquer method that
reduces computation complexity while building a bridge that connects FAB and UMPU
correlation tests.

We focus on the linking model in Equation 9. The linking model is constructed with $z$
the $q(q - 1)/2$ dimensional vectorized Fisher-transformed correlation matrix $Z = F(P)$. We
sub-divide $z$ into several groups of sub-vectors, with tests sharing information within but
not across groups. This is expressed mathematically as

\[
\begin{bmatrix}
\tilde{z}^{(1)} \\
\vdots \\
\tilde{z}^{(m)}
\end{bmatrix}
\sim \mathcal{N}
\begin{pmatrix}
\begin{bmatrix}
\vdots \\
\tilde{z}^{(m)}
\end{bmatrix} \\
\begin{bmatrix}
\vdots \\
\Omega_{\tilde{z}}^{(m)}
\end{bmatrix}
\end{pmatrix}
\]

(15)

\[
\begin{bmatrix}
z^{(1)} \\
\vdots \\
z^{(m)}
\end{bmatrix}
\sim \mathcal{N}
\begin{pmatrix}
\begin{bmatrix}
W^{(1)} & \cdots & 0
\end{bmatrix} \\
\begin{bmatrix}
\vdots & \ddots & 0
\end{bmatrix} \\
0 & 0 & W^{(m)}
\end{pmatrix}
\begin{bmatrix}
\begin{bmatrix}
\eta^{(1)}
\end{bmatrix} \\
\begin{bmatrix}
\vdots & \ddots & 0
\end{bmatrix} \\
0 & 0 & \Psi^{(m)}
\end{bmatrix}
\]

(16)

The question marks in Equation 15 represent the cross-covariance matrix between \(\tilde{z}^{(k_1)}\) and \(\tilde{z}^{(k_2)}\) when \(k_1 \neq k_2\). The block-diagonal design of the linking model in Equation 16 prohibits sharing of information across groups while still being a valid linking model. The FAB \(p\)-value calculation, which involves large matrix manipulation, can be reduced to the following equivalent calculation involving smaller-scale matrix calculations:

\[
\tilde{z}^{(k)} \sim \mathcal{N}(\tilde{z}^{(k)}, \Omega_{\tilde{z}}^{(k)})
\]

(17)

\[
z^{(k)} \sim \mathcal{N}(W^{(k)}\eta^{(k)}, \Psi^{(k)})
\]

(18)

for all \(k \in \{1 : m\}\). This simplification reduces dimensions of matrix manipulation for each test and therefore achieves better scalability. Compared with the full FAB correlation test without grouping and the block-diagonal structure of \(W\), the approach limits sharing of information to within the same test groups. This restriction does not necessarily harm power, as the grouping-enabled more granular linking model can potentially provide better flexibility and fit, which are key factors determining the power. When \(m\), the total number of test groups, equals 1, this reduces to the original FAB correlation test, whereas when \(m = p\), there is equivalence to the UMPU correlation test. Thus, this divide-and-conquer approach establishes a granularity spectrum from the vanilla UMPU to the full FAB correlation test without changing the number of individual hypotheses.

Each one of the \(p\) tests is assigned into one group vector \(\tilde{z}^{(k)}\) equipped with a model parameterized by \(W^{(k)}\) and \(\eta^{(k)}\). The design of \(W^{(k)}\) and the grouping of tests are arbitrary. For the design of \(W^{(k)}\), it can be as simple as a \(p(k) \times 1\) dimensional matrix of ones, if an external dataset is not available, or a matrix with columns of any power of the external data \(\tilde{z}_{\text{ext}}^{(k)}\), if external data are available. The prior represents a single mean model

\[
\forall j \in \{1, \ldots, p(k)\}, \quad z_j^{(k)} \sim \mathcal{N}(\eta^{(k)}, \psi^{(k)})
\]
and the latter simulates a multivariate linear regression between the true parameter $z^{(k)}$ and the parameter’s external observations $\mathcal{Z}^{(k)}_{\text{ext}}$

$$z^{(k)} \sim \mathcal{N}\left(\sum_{d=0}^{D}(\mathcal{Z}^{(k)}_{\text{ext}})^d \cdot \eta_d, \Psi^{(k)}\right)$$

Hierarchical structure can also be added to form Bayesian shrinkage on $\eta$. The design is highly flexible. For grouping, a convenient yet useful approach would be to assign Fisher-transformed correlation coefficients $\mathcal{Z}_j$ that are likely to share similar values into the same group, based exclusively on estimation from external knowledge. For example, consider 9 test statistics generated from the testing dataset $\{\mathcal{Z}_1, \mathcal{Z}_2, \mathcal{Z}_3, \mathcal{Z}_4, \mathcal{Z}_5, \mathcal{Z}_6, \mathcal{Z}_7, \mathcal{Z}_8, \mathcal{Z}_9\}$ and their corresponding statistics generated from the external auxiliary dataset $\{\mathcal{Z}_{\text{ext}}^j\}_{j=1:9}$. We can rank $\{\mathcal{Z}_{\text{ext}}^j\}_{j=1:9}$ by their magnitude. Suppose the resulting order is $\mathcal{Z}_{\text{ext}}^5 > \mathcal{Z}_{\text{ext}}^4 > \mathcal{Z}_{\text{ext}}^8 > \mathcal{Z}_{\text{ext}}^1 > \mathcal{Z}_{\text{ext}}^3 > \mathcal{Z}_{\text{ext}}^9 > \mathcal{Z}_{\text{ext}}^6 > \mathcal{Z}_{\text{ext}}^7 > \mathcal{Z}_{\text{ext}}^2$. Then, suppose $m = 3$, the final group assignment is $\{\mathcal{Z}_5, \mathcal{Z}_4, \mathcal{Z}_8\}_{(1)}$, $\{\mathcal{Z}_1, \mathcal{Z}_3, \mathcal{Z}_9\}_{(2)}$, and $\{\mathcal{Z}_6, \mathcal{Z}_7, \mathcal{Z}_2\}_{(3)}$. We illustrate such an assignment mechanism in Figure 1. This is similar to the idea of developing local regression models between $z$ and $\mathcal{Z}^\text{ext}$, which is helpful to address the global non-linearity between $z$ and $\mathcal{Z}^\text{ext}$ by offering local regression between $\mathcal{Z}^{(k)}$ and $\mathcal{Z}^{(k)}_{\text{ext}}$ for all $k \in \{1 : m\}$. 

15
The most convenient way of constructing the linking model is to design \( W^{(k)} \) as a \( p^{(k)} \times 1 \) dimensional matrix of ones. This design indicates that each scalar correlation coefficient from \( z^{(k)} \) originates from the same component and shares the same scalar mean \( \eta^{(k)} \). Mathematically, this can be expressed as:

\[
\mathbf{z} \sim \mathcal{N}(I, \psi^2 I_p) \tag{19}
\]

\[
\mathbf{I} = \begin{bmatrix} \mathbf{1}_p^{(1)\times 1} & \cdots & 0 \\ \vdots & \ddots & 0 \\ 0 & 0 & \mathbf{1}_p^{(m)\times 1} \end{bmatrix}, \quad \mathbf{\eta} = \begin{bmatrix} \eta^{(1)} \\ \vdots \\ \eta^{(m)} \end{bmatrix}, \quad \psi^2 \mathbf{I}_p = \begin{bmatrix} \psi^{2}_{(1)} \mathbf{I}_{p^{(1)}} & \cdots & 0 \\ \vdots & \ddots & 0 \\ 0 & 0 & \psi^{2}_{(m)} \mathbf{I}_{p^{(m)}} \end{bmatrix}
\]

The design in Equation 19 will be used in Section 4 for simulation. The way to perform the FAB correlation test in one group is identical as in Algorithm 1. To perform the FAB test for all correlation groups, simply apply algorithm 4 \( m \) times iteratively for each group.
4 Simulation

In this section, we apply simulation studies to demonstrate the effectiveness of the FAB correlation structure test. Section 4.1 evaluates the methods of Section 3.1.1, where we assume a similar external dataset is available to provide indirect information for testing. Section 4.2 evaluates the methods of Section 3.1.2, where we only assume the availability of prior information on grouping.

The simulated data generating process is identical for both subsections. We generated positive semi-definite covariance matrix $\Sigma$ by letting $\Sigma = U^T U + I_q$, where $U$ is a randomly generated $l \times q$ dimensional matrix with $l < q$, $l = 50$ and $q = 100$. Each row of $U$ is randomly masked with a proportion of zeros. The proportion is modulated until $\Sigma$ has a similar number of zero and non-zero entries. This randomly generated covariance matrix $\Sigma$, accompanied with a random mean vector, is used to generate the observable data $X$.

4.1 $\bar{z}_j' = \bar{z}_{-j}^{ext}$: Sampling Model Using External Data

We first explore a specific case where $n = 100$, $q = 100$, and a similar external dataset also has $n^{ext} = 100$. This external dataset $X^{ext}$ is generated from the same $\Sigma$ as the testing dataset but with an additional random noise. To speed up computation, we applied the divide-and-conquer approach of Section 3.2. We manually set each group to contain 50 hypotheses, thus resulting into $m = 99$ hypothesis groups. The group assignment is based on their external data magnitude order as described at the end of Section 3.2. Applying the linking model from Equation 19, the full model for the $j^{th}$ test within the $k^{th}$ test group is

$$
\begin{bmatrix}
\bar{z}_j \\
(\bar{z}_{-j})^{(k)}
\end{bmatrix} \sim \mathcal{N}
\left(\begin{bmatrix}
z_j \\
(z_{-j})^{(k)}
\end{bmatrix}, \frac{1}{n-3} \begin{bmatrix}
1 & 0 \\
0 & \Omega_{(z_{-j})^{(k)}}
\end{bmatrix}\right)
$$

$$
z \sim \mathcal{N}(1_{p(k)} \times 1 \eta^{(k)}(k), \psi^2_{(k)} I_{p(k)})
$$

The simulation generated 2231 true null hypotheses and 2719 alternative hypotheses. The same hypothesis appears twice in the upper and lower triangle part of the covariance matrix $\Sigma$. In this case, we count them as one hypothesis. It appears that the borrowing of information in our FAB approach leads to some UMPU $p$-values being pushed down below the pre-specified threshold for significance. This phenomenon is illustrated in Figure 2b.
Figure 2: UMPU vs FAB p-values when $\tilde{z}_j = \tilde{z}_{ext}^j$ is external. The left sub-figure 2a is the ranked UMPU and FAB p-values. FAB produced more small p-values and resulted in more rejections. The right sub-figure 2b is a UMPU versus FAB p-value scatter plot. Some of the originally small UMPU p-values are pushed to larger values.

Figure 3a shows the distribution of FAB p-values under the true null hypothesis, compared to that of UMPU, with both being uniformly distributed. Hence, the Type I error is controlled. Meanwhile, Figure 3b demonstrates the distribution of the FAB p-values under the alternative hypothesis is generally tilted towards the left, compared to that of UMPU, indicating a larger power and agreeing with Figure 2a.

Figure 3: Distribution of UMPU and FAB p-values, when $\tilde{z}_j = \tilde{z}_{ext}^j$ is external, under null (Figure 3a) and alternative (Figure 3b) hypotheses. Under true null hypotheses, the distribution of UMPU and FAB p-values are uniform. Under the alternative hypothesis, FAB leads to more small p-values.
We generated datasets with all nine combinations of \((n, q)\) within \(n \in \{50, 100, 200\}\) and \(q \in \{50, 100, 200\}\). Within each configuration, we run both FAB and UMPU correlation structure tests on 10 different randomly generated datasets. The results are in Table 2. FAB maintains Type I error control at \(p = 0.05\). Under all \((n, q)\) configurations, we notice a boost in power ranging from 12.52% – 23.80% comparing to UMPU. The power increment is inversely related to sample size; as sample size increases, more tests will be rejected, leaving less room for improvement for FAB. Furthermore, the FAB offset component \(b_j\) in its \(p\)-value expression as in Equation 10 also shrinks in value when \(n\) increases.

|                | \(n = 50\) |       | \(n = 100\) |       | \(n = 200\) |       |
|----------------|------------|-------|------------|-------|------------|-------|
| \(q = 50\)    |            |       |            |       |            |       |
| Not Reject     | 0.9502     | 0.9510| 0.9541     | 0.9483| 0.9509     | 0.9525|
| Reject         | 0.0498     | 0.0490| 0.0459     | 0.1854| 0.2822     | 0.4008|
|                | (+23.77%)  | (+17.39%) | (+14.06%)  |        |            |       |
| \(q = 100\)   |            |       |            |       |            |       |
| Not Reject     | 0.9483     | 0.9509| 0.9525     | 0.9483| 0.7130     | 0.5948|
| Reject         | 0.0517     | 0.0490| 0.0475     | 0.1910| 0.2870     | 0.4052|
|                | (+21.58%)  | (+20.28%) | (+12.52%)  |        |            |       |
| \(q = 200\)   |            |       |            |       |            |       |
| Not Reject     | 0.9488     | 0.9499| 0.9486     | 0.9488| 0.6968     | 0.5787|
| Reject         | 0.0512     | 0.0501| 0.0514     | 0.1940| 0.3032     | 0.4213|
|                | (+23.80%)  | (+18.90%) | (+13.19%)  |        |            |       |

Table 2: \(\alpha, \beta\), Type I, II Confusion Matrix of FAB Correlation Structure Tests when \(\tilde{z}_j' = \tilde{z}_{-j}^{\text{ext}}\) is external

4.2 \(\tilde{z}_j' = \tilde{z}_{-j}\): Sampling Model Using Internal Data

All FAB \(p\)-values are calculated via Algorithm 1. We set the group size to 5 in our analyses in this section, with a total number of groups of \(m = 990\). There are 2220 true null hypotheses and 2730 alternative hypotheses. In Figure 4a we observe that FAB rejects more hypothesis.
Figure 4: UMPU vs FAB p-values when $\bar{z}_j' = \bar{z}_{-j}$. The left sub-figure 2a is the ranked UMPU and FAB p-values. FAB produces more small p-values, which resulted in more rejections. The right sub-figure 2b is a UMPU versus FAB p-value scatter plot.

Figure 5a demonstrates the distribution of FAB p-values under the true null hypothesis, compared to that of UMPU, with both approximately uniformly distributed. Figure 5b shows that under the alternative hypothesis, FAB p-values using bootstrap are also generally smaller. The ranking of p-values for FAB and UMPU is demonstrated in Figure 4a.

Figure 5: Distribution of UMPU and FAB p-values, with $\bar{z}_j' = \bar{z}_{-j}$, under null (Figure 5a) and alternative (Figure 5b) hypotheses. Under true null hypothesis, the distribution of UMPU and FAB p-values are both uniform. Under the alternative hypothesis, FAB p-values are shrunk to smaller values, which indicates higher power.

The bootstrap method for the FAB test yields 10.01% – 18.64% more power comparing
Table 3: $\alpha, \beta$, Type I, II Confusion Matrix of FAB Correlation Structure Tests comparing to UMPU using Bootstrap

to UMPU. Detailed results are shown in Table 3. In Figure 6 we verify the relationship between $n$ and $B$ and the $p$-value distribution. Under all circumstances, increasing $B$ and $n$ improves the Type I error control.

5 Application

This section applies our FAB correlation structure tests to datasets obtained from the Cancer Dependency Map portal (DepMap, 2019). The Cancer Dependency Map contains an extensive collection of genomics data, including measurements of gene expression, RNAi and CRISPR dependency, and drug sensitivity gathered from over 1,000 cancer cell types. The biological pathways active in these cancer cells can, in part, be described by gene-to-gene interactions, which can be inferred from the correlation structure in each genomics dataset. For instance, the correlation between genes in an expression dataset could indicate the presence of positive or negative regulation between genes. Correlation between genes in a CRISPR dependency dataset could indicate that two genes share an identical function because their deletion has similar adverse effects across cancer cell types. Because gene-to-gene interactions may be similar across cancer tissue types or specific technologies, rich genomics datasets such as those found in the Cancer Dependency Map present opportunities for sharing information using FAB structure tests.

Our first application of the FAB structure test uses a correlation matrix derived from RNAi dependency data (McFarland et al., 2018) to test correlation coefficients derived
Figure 6: FAB $p$-value under null for different $(n, B)$ configuration
from CRISPR dependency data (Meyers et al., 2017). Both datasets in our application contain 280 genes with dependency scores measured on 525 cancer cell types. Although RNAi and CRISPR are different technologies, they are both designed to measure genetic loss-of-function, so one might expect that the correlation structures uncovered by these technologies are similar, though not identical. Our second application uses a correlation matrix derived from 67 Breast cancer cell types to test the correlation structure derived from 206 Lung cancer cell types. These datasets each have 277 measured genes. Again, while these cancers and their regulatory networks are biologically distinct, one would expect some similarities between their correlation structures.

As the ground truth for the correlation structure is unknown for real data, we use as an imperfect surrogate published results for similar datasets (Subramanian et al., 2005; Rouillard et al., 2016). We take gene pairs that are declared as significantly correlated in these findings as ground truth. Gene pairs that are not declared as correlated are not necessarily uncorrelated but can be due to a lack of power in rejecting the null hypothesis. We use a list of 41,327 previously reported gene pairs as ground truth for those correlations that are non-zero. These pairs were curated from microarray experiments and downloaded from the Molecular Signatures Database.

Only genes appearing in the ground truth dataset will be considered in our analysis. Focusing on these genes, and removing observations containing missing data and no variance genes, the RNAi and CRISPR datasets are reduced to an identical set of 69 measured genes, with the sample sizes equal to 107 and 519, respectively. Out of the $60 \times 70/2 = 2415$ pairs of genes, 165 pairs were declared as correlated in previous published results based on different datasets. We report the empirical power as the number of rejected pairs out of the 165 divided by 165. Figure 7a plots the testing dataset’s Fisher-transformed correlation coefficients $\hat{Z}$ against that of the auxiliary dataset ($\hat{Z}_{ext}$). We performed a simple linear regression between entries of $\hat{Z}$ and $\hat{Z}_{ext}$; a line through the origin provided an excellent fit, and hence was used as the linking model as in Equation 16. Hence, $W^{(m)} = [\hat{z}_{ext1}, \ldots, \hat{z}_{extp_m}]^\top$.

We limit each test group size to 120 tests. The bootstrap FAB correlation test algorithm 1 is utilized to generate $p$-values. Figure 7b plots the sorted $p$-values for FAB test (red) and traditional two-sided UMPU test (blue) below $\alpha = 0.05$. Clearly, FAB results in more overall rejections than UMPU. The power also increased from UMPU’s 31 correct rejections.
to 38 correct rejections among the 165 alternative hypotheses.

Figure 7: $p$-value and power comparison between FAB and UMPU under case 1, RNAi assisted by CRISPR. A: There is a statistically significant relationship between correlation coefficients of RNAi expression dataset and CRISPR dataset. C: Ranked FAB and UMPU $p$-values. FAB results in more $p$-values smaller than 0.05. B: Rejected gene pairs of FAB, D: rejected gene pairs of UMPU. FAB results more rejections than UMPU.

We applied an identical data pre-selection strategy for the lung cancer and breast cancer datasets in case 2. After pre-selection, the lung cancer testing dataset and breast cancer auxiliary dataset contain 206 and 61 measurements for 67 measured genes, with 162 gene pairs declared as correlated. Figure 8 (a) demonstrates a strong positive linear relationship between $\hat{Z}$ and $\hat{Z}_{ext}$, with $R^2 = 0.3463$. In the linking model, we let

$$W^{(m)} = \begin{bmatrix} 1 & \hat{z}_{ext}^{(1)} \\ \vdots & \vdots \\ 1 & \hat{z}_{ext}^{(p_m)} \end{bmatrix}$$  \hspace{1cm} (20)$$

We also applied ridge shrinkage at the level of $\lambda = 0.01$ on the estimator of $\eta^{(m)}$. Similar to the group assignment in the first case, each test group is also comprised of 120 individual
tests. As indicated in Figure 8b, FAB rejects more hypotheses than UMPU does in general, with 96 correctly rejected hypotheses as opposed in 88 for UMPU among the 162 “true” alternatives.

Figure 8: $p$-value and power comparison between FAB and UMPU under case 2, lung cancer assisted by breast cancer. A: There is a statistically significant relationship between correlation coefficients of lung breast expression dataset and breast cancer dataset. C: Ranked FAB and UMPU $p$-values. FAB results in more $p$-values smaller than 0.05. B: Rejected gene pairs of FAB, D: rejected gene pairs of UMPU. FAB results more rejections than UMPU.

In addition to comparing with UMPU, we also compare FAB with the AdaPT method designed to incorporate outside information in FDR control (Lei and Fithian, 2018). In contrast to our approach, AdaPT takes a set of pre-computed independent $p$-values as input and uses available side information to help define a sequence of adaptive thresholds. The $p$-values are then compared sequentially against this sequence of thresholds to determine rejections. FAB, on the other hand, uses available side information to generate $p$-values, which are then subject to traditional $p$-value thresholds that ignore the side information. As AdaPT uses side information to directly determine rejection thresholds, we anticipate...
that discoveries made by AdaPT may be less robust to the quality and informativeness of the external information.

To compare the three approaches, we apply the vanilla Benjamini-Hochberg (BH) (Benjamini and Hochberg, 1995b) procedure on UMPU p-values, vanilla BH procedure on FAB p-values, and take UMPU p-values as input for the AdaPT method. In Figure 9a and Figure 10a, the numbers of discoveries under a series of target FDR thresholds are recorded for UMPU, FAB, and AdaPT under both cases 1 and 2. FAB results in uniformly more discoveries than UMPU, but its advantage over AdaPT depends on the quality of the external dataset. In the first case, as demonstrated in Figure 7, \( \hat{\mathbf{Z}}_{\text{ext}} \) explains less variation \( (R^2 = 0.0637) \) in \( \hat{\mathbf{Z}} \) than in the second case. Thus, the outside information is less informative in the first case, and AdaPT resulted in fewer discoveries in the first case compared to the second case. In contrast, FAB had a similar advantage over the UMPU in both cases. Our conjecture is that FAB can better take advantage of noisy side information.

![Graph A](image1)

![Graph B](image2)

Figure 9: Discoveries comparison between UMPU, FAB, and AdaPT under control of theoretical FDR: Case 1, RNAi assisted by CRISPR. A: total number of discoveries of UMPU, FAB, and AdaPT under a series of theoretical FDR values. FAB results in more discoveries. B: Empirical data’s observed FDR versus the theoretical FDR for FAB under the same model configuration as the application. FAB maintains FDR control.
6 Discussion

This article develops a frequentist assisted by Bayes (FAB) testing methodology for support recovery of correlation structure. Our work has demonstrated the flexibility of the FAB framework in learning from indirect information to assist hypothesis testing on correlation coefficients both when indirect information is sourced directly from external datasets or

Figure 10: Discoveries comparison between UMPU, FAB, and AdaPT under control of theoretical FDR: Case 2, Lung assisted by Breast. A: total number of discoveries of UMPU, FAB, and AdaPT under a series of theoretical FDR values. AdaPT results in more discoveries uniformly. B: Empirical data’s observed FDR versus the theoretical FDR for FAB under the same model configuration as the application. FAB maintains FDR control.

Due to sharing of information via the linking model within test groups, FAB p-values tend to be positively correlated. Hence, the BH procedure may be conservative. To investigate FDR control, we generated simulated data having identical configuration, including the sample size $m$ and data dimension $q$, with the real datasets in both cases. We repeated the same FAB analyses as used for the real data across 10 simulation replicates for each case. In Figure 9b and Figure 10b, we recorded the observed FDR against the theoretical FDR on the simulated data for each case. FAB controls FDR at the specified levels in each case.
different tests within the same dataset. The simulation results have demonstrated improvement of power while maintaining asymptotic control of Type I error in both the independent and bootstrap cases. The real data application has also illustrated the methodology’s capability to improve power while still offering FDR control empirically. Our results suggests that the FAB correlation structure testing framework is a “Type I error safe” yet flexible framework that allows customization of the predictive linking model to improve power.

Our methodology was not explicitly developed with a focus on controlling FDR and multiple testing error. Instead we have focused on developing an approach to include outside information in obtaining \( p \)-values that will lead to increased power in correlation structure testing if the outside information was indeed informative. One can then use these \( p \)-values as inputs into any appropriate FDR or other multiple testing method. For simplicity we focused on Benjamini-Hochberg in our illustration. However, given the correlation in the \( p \)-values it may be more appropriate to use alternative procedures that accommodate dependence among the \( p \)-values (Efron, 2007; Romano et al., 2008; Sun and Tony Cai, 2009; Fan et al., 2012; Ramdas et al., 2019)

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SUPPLEMENTARY MATERIAL

Software Reproducible R code is available at Github repository.

File Reproducible rmd files and their knitted html, including all produced data and image results are also included in the Github repository above.

Proof of Theorem Attached in Appendix A.

Appendix A Proof of Theorem

We first introduce some important concepts that are necessary for the proof.
Definition A.1. Let $X_1, X_2, \ldots, X_n \sim F$ and $T(X_1, X_2, \ldots, X_n, F)$ a given $p$-dimensional multivariate functional. The bootstrap distribution of $T$ is defined as

$$H_{\text{Boot}}(X) = P_* \left( \bigcap_{j=1}^p \{ T_j(X_1^*, \ldots, X_n^*, F) \leq x_j \} \right)$$

where $(X_1^*, \ldots, X_n^*)$ is an iid sample of size $n$ re-sampled from the empirical CDF $F_n$. We use the notation $P_*$ to denote probabilities under the bootstrap distribution.

Definition A.2. Let $F, G$ be two CDFs on a sample space $\mathcal{X}$. Let $\rho(F, G)$ be a metric on the space of CDFs on $\mathcal{X}$. For $X_1, X_2, \ldots, X_n \sim F$, and a given functional $T(X_1, X_2, \ldots, X_n, F)$, let

$$H_n(X) = P_F \left( \bigcap_{j=1}^p \{ T_j(X_1, X_2, \ldots, X_n, F) \leq x_j \} \right)$$

$$H_{\text{Boot}}(X) = P_* \left( \bigcap_{j=1}^p \{ T_j(X_1^*, X_2^*, \ldots, X_n^*, F) \leq x_j \} \right)$$

We say that the bootstrap is weakly consistent under $\rho$ for $T$ if $\rho(H_n, H_{\text{Boot}}) \xrightarrow{pr} 0$ as $n \to \infty$. We say that the bootstrap is strongly consistent under $\rho$ for $T$ if $\rho(H_n, H_{\text{Boot}}) \xrightarrow{a.s.} 0$.

Definition A.3. We define the Kolmogorov metric as

$$K(F, G) = \sup_{-\infty < x < \infty} |F(x) - G(x)|$$

where $F, G$ are 2 CDFs.

Theorem A.1. Let $X_1, \ldots, X_n$ be multivariate iid samples with CDF $F$. Let $\text{Cov}_F(X) = \Sigma_X$ be finite and the mean $\mu$ be finite. Define functional $T(X_1, X_2, \ldots, X_n, F) = \sqrt{n}(\bar{X} - \mu)$. Then $K(H_{\text{Boot}}, H_n) \xrightarrow{a.s.} 0$ as $n \to \infty$.

Proof. The consistency of the bootstrap for the sample mean under finite second moments holds under the multivariate case. We record the conclusion of such consistency under the Kolmogorov metric. See Shao and Tu (2012) for proof.

Theorem A.2. Define bivariate random variable $X := (y, z)^\top$ and $X \in \mathcal{L}_4(\mathbb{R}^2)$. Define functional $T_{\hat{\rho}}(X_1, \ldots, X_n, F)$ as

$$T_{\hat{\rho}_n}(X_1, \ldots, X_n, F) = \sum_{i=1}^n (y_i - \bar{y})(z_i - \bar{z}) / \left[ \sum_{i=1}^n (y_i - \bar{y})^2 \sum_{i=1}^n (z_i - \bar{z})^2 \right]^{1/2}$$

Then, $K(H_{\text{Boot}}, H_n) \xrightarrow{a.s.} 0$ as $n \to \infty$ for $T_{\hat{\rho}}$. 29
Proof. Define the extended 5-dimensional random variable as $X_{\text{extend}} = (y, z, y^2, z^2, yz)^\top$. As $X \in \mathcal{L}_4$, we know that $X_{\text{extend}} \in \mathcal{L}_2$. Thus $\Sigma_{X_{\text{extend}}}$ is finite. By Theorem A.1, we deduce that

$$K \left( H_{\text{Boot}} \left[ T(X_{\text{extend}}^*, F_n) \right], H_n \left[ T(X_{\text{extend}}^*, F) \right] \right) \xrightarrow{\text{a.s.}} 0$$

$n \to \infty$. This implies that

$$\sup_{-\infty < z < \infty} |H_{\text{Boot}} \left[ T(X_{\text{extend}}^*, F_n) \right] - H_n \left[ T(X_{\text{extend}}^*, F) \right]| \xrightarrow{\text{a.s.}} 0$$

$$\Rightarrow H_{\text{Boot}} \left[ T(X_{\text{extend}}^*, F_n) \right] - H_n \left[ T(X_{\text{extend}}^*, F) \right] \xrightarrow{\text{a.s.}} 0$$

$$\Rightarrow T(X_{\text{extend}}^*, F_n) - T(X_{\text{extend}}^*, F) \xrightarrow{\text{dist.}} 0$$

Since $\bar{y}, \bar{z}, \bar{y}^2, \bar{z}^2, \bar{yz}$ are sufficient statistics of $\hat{\rho}_n$, the correlation coefficient between $Y$ and $Z$, there exist continuous function $\xi : T \mapsto T_{\hat{\rho}}$. Thus, by continuous mapping theorem:

$$T(X_{\text{extend}}^*, F_n) - T(X_{\text{extend}}^*, F) \xrightarrow{\text{dist.}} 0 \Rightarrow T_{\hat{\rho}}(X_{\text{extend}}^*, F_n) - T_{\hat{\rho}}(X_{\text{extend}}^*, F) \xrightarrow{\text{dist.}} 0$$

which implies that $\hat{\rho}^* - \hat{\rho} \xrightarrow{\text{dist.}} 0$. 

Now we are prepared to begin the proof of Theorem 3.3.

**Theorem A.3.** Let $\hat{Z} := (z_a, z_b)^\top$ be the joint vector of a pair of Fisher-transformed Pearson correlation estimators that can be correlated. Denote the set of $B$ bootstrap samples for the Fisher-transformed-correlation pair $\hat{Z}_B := \{z_{1a}^*, z_{1b}^*, \ldots, z_{B}^* \}$, with each sample $z_{B}^*$ as an estimator to $z$ inferred from the $b^{th}$ re-sampled dataset. Then, define the true correlation coefficient between $z_a$ and $z_b$ as $\omega_z$. Then, the bootstrap estimator

$$\hat{\omega}_z^* := \frac{\sum_{i=1}^{B} (z_{ai}^* - \bar{z}_a^*) (z_{bi}^* - \bar{z}_b^*)}{\sqrt{\sum_{i=1}^{B} (z_{ai}^* - \bar{z}_a^*)^2} \sum_{i=1}^{B} (z_{bi}^* - \bar{z}_b^*)^2} \xrightarrow{\text{pr.}} \omega_z$$

Proof. Replace the random variable $X$ described in Theorem A.2 with $X := \hat{Z}$. Clearly $\hat{Z} \in \mathcal{L}_4(\mathbb{R}^2)$. Therefore, by Theorem A.2, we directly have $\hat{\omega}_z^* - \omega_z \xrightarrow{\text{dist.}} 0$, where $\omega_z := T_{\hat{\rho}}(z, F)$. Furthermore, we already know that the Pearson correlation coefficient $\omega_z$ is a consistent estimator of $\omega_z$. Therefore, $\omega_z \xrightarrow{\text{pr.}} \omega_z$. As $\hat{\omega}_z^*$ also converges in distribution to $\omega_z$, given
any $\epsilon > 0$, when $n \to \infty$, we have
\[
\mathbb{P}(|\hat{\omega}_z - \omega_z| < \epsilon) \to 0 \Rightarrow \int_{-\infty}^{\infty} \mathbb{I}[|x - \omega_z| < \epsilon] f_{\hat{\omega}_z}(x) dx \to 0
\]
\[
\Rightarrow \int_{\omega_z - \epsilon}^{\omega_z + \epsilon} f_{\hat{\omega}_z}(x) dx \to 0
\]
\[
\Rightarrow F_{\hat{\omega}_z}(\omega_z + \epsilon) - F_{\hat{\omega}_z}(\omega_z - \epsilon) \to 0
\]
\[
\Rightarrow [F_{\hat{\omega}_z^*}(\omega_z + \epsilon) - F_{\hat{\omega}_z}(\omega_z + \epsilon)] - [F_{\hat{\omega}_z^*}(\omega_z - \epsilon) - F_{\hat{\omega}_z}(\omega_z - \epsilon)] + [F_{\hat{\omega}_z}(\omega_z + \epsilon) - F_{\hat{\omega}_z}(\omega_z - \epsilon)] \to 0
\]
\[
\Rightarrow F_{\hat{\omega}_z^*}(\omega_z + \epsilon) - F_{\hat{\omega}_z^*}(\omega_z - \epsilon) \to 0
\]
\[
\Rightarrow \int_{-\infty}^{\infty} \mathbb{I}[|x - \omega_z| < \epsilon] f_{\hat{\omega}_z^*}(x) dx \to 0
\]
\[
\Rightarrow \mathbb{P}(|\hat{\omega}_z^* - \omega_z| < \epsilon) \to 0
\]

Therefore, $\hat{\omega}_z^* \overset{lnr.}{\to} \omega_z$, and $\hat{\omega}_z^*$ is also a consistent estimator of $\omega_z$.
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