Finding Stable Groups of Cross-Correlated Features 
in Two Data Sets With Common Samples

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Abstract

Data sets in which measurements of different types are obtained from a common set of samples appear in many scientific applications. In the analysis of such data, an important problem is to identify groups of features from different data types that are strongly associated. Given two data types, a bimodule is a pair \((A, B)\) of feature sets from the two types such that the aggregate cross-correlation between the features in \(A\) and those in \(B\) is large. A bimodule \((A, B)\) is stable if \(A\) coincides with the set of features that have significant aggregate correlation with the features in \(B\), and vice-versa. We develop an, iterative, testing-based procedure called BSP to identify stable bimodules. BSP relies on approximate p-values derived from the permutation moments of sums of squared sample correlations between a single feature of one type and a group of features of the second type. We carry out a thorough simulation study to assess the performance of BSP, and present an extended application to the problem of expression quantitative trait loci (eQTL) analysis using recent data from the GTEx project. In addition, we apply BSP to climatology data to identify regions in North America where annual temperature variation affects precipitation.

Key terms – Iterative testing, permutation distribution, bipartite correlation network, eQTL analysis, temperature and precipitation covariation.

1 Introduction

Driven by the ongoing development and application of moderate and high-throughput measurement technologies in fields such as genomics, neuroscience, ecology, and atmospheric science, researchers are often faced with the task of analyzing and comparing two or more data sets derived from a common set of samples. In most cases, different technologies measure different features, and capture different information about the samples at hand. While one may analyze the data arising from different technologies separately, additional and potentially important insights can be gained

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Figure 1: Illustration of multi-view data and a bimodule \((A, B)\) (shaded). The two data matrices, measuring features of Type 1 and Type 2, are matched by samples. The bimodule has the property that the aggregate cross-correlation between features from \(A\) and \(B\) is statistically significant. The columns \(A\) and \(B\) need not be contiguous.

from the joint (or integrated) analysis of the data sets. Joint analysis, also called multi-view or multi-modal analysis, has received considerable attention in the literature, see Lahat et al. (2015); Meng et al. (2016); Tini et al. (2019); Pucher et al. (2019); McCabe et al. (2019) and the references therein for more details.

In what follows we will refer to the measurements arising from a particular technology as a data type, and will restrict our attention to problems in which two data types, referred to as Type 1 and Type 2, with numerical features are under study. We are interested in identifying associations between groups of measured features in the two data types in an unsupervised setting that does not make use of auxiliary information about the samples. In particular, we wish to identify pairs \((A, B)\), where \(A\) is a set of features of Type 1 and \(B\) is a set of features of Type 2, such that the aggregate correlation between features in \(A\) and \(B\) is large. (Here and in what follows, we consider the standard Pearson correlation.) The problem of identifying sets of highly correlated features within a single data type has been widely studied, typically through clustering and related methods. Borrowing from the use in genomics of the term “module” to refer to a set of correlated genes, we refer to the feature set pairs \((A, B)\) of interest to us as bimodules. The term bimodule has also appeared, with somewhat different meaning, in Wu et al. (2009), Patel et al. (2010), and Pan et al. (2019).

We will refer to correlations between features of different data types as cross-correlations, and note that this usage differs from that in time-series analysis. Correlations among features of the same data type will be referred to as intra-correlations. Cross-correlations provide information about connections and interactions between different data types. These relationships are of interest in many applications, for example, in studying the relationships between genotype and phenotype in genomics (discussed in Section 5 below), temperature and precipitation in climate science (discussed in Section 6 below), habitation of species and their environment in ecology (see, e.g., Dray et al., 2003), and in identifying brain regions associated with experimental tasks (McIntosh et al., 1996) in neuroscience.

In seeking to uncover relationships between two data types, many existing methods identify sets of latent features that best explain the joint covariation between the two data types, often by optimizing an objective over the space spanned by the data features (see the survey Sankaran and Holmes, 2019). In contrast, BSP and related methods identify a pair of feature subsets, one from each data type, having large aggregate cross-correlation (see Figure 1). Bimodules provide
evidence for the coordinated activity of features from different data types. Coordination may arise, for example, from shared function, causal interactions, or more indirect functional relationships. Bimodules can assist in directing downstream analyses, generating new hypotheses, and guiding the targeted acquisition and analysis of new data. By definition, bimodules capture aggregate behavior, which may be significant when no individual pair of features has high cross-correlation, or when the cross-correlation structure between the feature groups is complex. As such, the search for bimodules can leverage low-level or complex signals among individual features to find higher order structure.

1.1 Bimodule Search Procedure and Stable Bimodules

In this paper we propose and analyze the Bimodule Search Procedure (BSP), which is a method for identifying stable bimodules in moderate to high dimensional data sets. BSP is based on multiple testing principles and approximate permutation p-values. BSP does not require formulating or fitting a detailed statistical model, or making detailed distributional assumptions about the data.

A key feature of BSP is that it seeks stable bimodules. A bimodule \((A, B)\) is stable if \(A\) coincides with the features of Type 1 that are significantly associated in aggregate with the features in \(B\), and \(B\) coincides with the features of Type 2 that are significantly associated in aggregate with the features in \(A\). Formal definitions of stable bimodules in the population and sample setting are given in Section 2 and Section 3 respectively. In the population setting, stability has close connections with the connectivity of the bipartite graph representing the cross-correlations of the Type 1 and Type 2 features. This connection is pursued throughout the paper, and in particular, provides a principled way to extract an association network from a bimodule. BSP employs fast, moment-based approximations to permutation p-values for sums of squared correlations. These p-values explicitly account for the intra-correlations of the features in \(A\) and \(B\), attenuating the significance of aggregate cross-correlation when these intra-correlations are high.

The informal definition of a bimodule raises two issues that need to be addressed in practice. The first issue is overlap: a small change in the elements of a bimodule will often yield another bimodule, and as such, distinct bimodules can exhibit substantial overlap. In many applications, e.g., the study of gene regulatory networks, overlap of interacting feature sets is the norm, and the ability to capture this overlap is critical for successful exploratory analysis. Nevertheless, extreme overlap can impede interpretation and downstream analyses. We deal with overlap in two ways. First, our focus on stable bimodules eliminates most small perturbations from consideration. Second, in cases where we find two or more empirical bimodules with large overlap, we employ a simple post-processing step to identify a representative bimodule from the overlapping group (see Section 3.3).

The second issue is containment: one bimodule may be contained in another. In practice, we wish to identify minimal bimodules, namely those that are not properly contained in another bimodule. In the population setting, minimal bimodules correspond to connected components of the cross correlation network (see Section 2.2) and are easily identified. In the sample setting minimality is more complicated, and we rely instead on a network-based notion of robust connectivity that ensures that a bimodule cannot be partitioned into two groups of features without some significant cross-correlation edge connecting the two groups (see Section 3.3).
1.2 Expression Quantitative Trait Loci Analysis

Much of the existing work on bimodule discovery is focused on the integrated analysis of genomic data. To motivate and provide context for this work, and the methods introduced here, we briefly discuss the problem of expression quantitative trait loci (eQTL) analysis in genomics. An application of BSP to eQTL analysis is given in Section 5.

Genetic variation within a population is commonly studied by considering single nucleotide polymorphisms, called SNPs. A SNP is a single site in the genome where there is variation in the paired nucleotides among members of the population. The value of a SNP for an individual is the number of reference nucleotides appearing at that site, which takes the values 0, 1, or 2. After normalization and covariate correction, the value of a SNP may no longer be discrete.

eQTL analysis seeks to identify SNPs that affect the expression of one or more genes; a SNP-gene pair for which the expression of the gene is correlated with the value of the SNP is referred to as an eQTL. Identification of eQTLs is an important first step in the study of genomic pathways and networks that underlie disease and development in human and other populations (see Nica and Dermitzakis, 2013; Albert and Kruglyak, 2015).

In modern eQTL studies it is common to have measurements of 10-20 thousand genes and 2-5 million SNPs on hundreds (or in some cases thousands) of samples. Identification of putative eQTLs or genomic “hot spots” is carried out by evaluating the correlation of numerous SNP-gene pairs, and identifying those meeting an appropriate multiple testing based threshold. In studies with larger sample sizes it may be feasible to carry out trans-eQTL analyses, which consider all SNP-gene pairs regardless of genomic location. However, it is more common to carry out cis-eQTL analyses, in which one restricts attention to SNP-gene pairs for which the SNP is within some fixed genomic distance (often 1 million base pairs) of the gene’s transcription start site, and in particular, on the same chromosome (c.f. Westra and Franke, 2014; GTEx Consortium, 2017). We use the prefixes cis- and trans- to refer to the type of eQTL analysis, while using adjectives local and distal to denote the proximity of the discovered SNP-gene pairs. In particular, cis-eQTL analyses seek to discover local eQTLs, while trans-eQTL analyses seek to discover both local and distal eQTLs.

As a result of multiple testing correction needed to address the large number of SNP-gene pairs under study, both trans- and cis-eQTL analyses can suffer from low power. Several methods have been proposed to improve the power of standard eQTL analysis, including penalized regression schemes that try to account for intra-gene or intra-SNP interactions (Tian et al., 2014, and references therein) and methods that consider gene modules as high-level phenotypes to reduce the burden of multiple-testing (Kolberg et al., 2020). As an alternative, one may shift attention from individual SNP-gene pairs to SNP-gene bimodules, that is, to sets of SNPs and genes with large cross-correlation. As genes often act in concert with one another, bimodule discovery methods can gain statistical power from group-wise interactions, by borrowing strength across individual SNP-gene pairs. Further, it is known that activity in a cell may be the result of a regulatory network of genes rather than individual genes (Chakravarti and Turner, 2010). Hence bimodules may represent a group of SNPs that disrupt the functioning of gene regulatory networks and contribute to diseases (Platig et al., 2016).
1.3 Existing Approaches to Discover Bimodules

1.3.1 Community detection in bipartite networks

Since bimodules are defined in terms of cross-correlations, it is natural to investigate them in the context of the bipartite cross-correlation network, which is formed by connecting pairs of features from different data types with a weighted edge, where the weight is equal to the square of the (sample or population) cross-correlation between the features. CONDOR (Platig et al., 2016) identifies bimodules by applying a community detection method to an unweighted bipartite graph obtained by thresholding the sample cross-correlations. One could, in principle, extend this approach by leveraging other community detected methods (Beckett, 2016; Barber, 2007; Liu and Murata, 2010; Costa and Hansen, 2014; Pesantez-Cabrera and Kalyanaraman, 2016) for weighted and unweighted bipartite networks. In another network based approach taken in Huang, Wuchty, Ferdig, and Przytycka (2009), an algorithm to enumerate bipartite cliques is used to enhance eQTL discovery.

The approach taken here is network based, but differs from community-detection based approaches such as CONDOR. While stable population bimodules can be defined in terms of the population cross-correlation network, the sample cross-correlation network is not a sufficient statistic for stable sample bimodules, which also account for the intra-correlations between features of the same type.

1.3.2 Other approaches to discover bimodules

One might search for bimodules by applying a standard clustering method such as k-means to a joint data matrix containing standardized features from the two data types, and treating any cluster with features from both data types as a bimodule. While appropriate as a “first look”, this approach requires specifying the number of clusters, imposes the constraint that every feature be part of one, and only one, bimodule, and, most importantly, does not distinguish between cross- and intra-correlations.

Sparse canonical correlation analysis (sCCA) (Waaijenborg et al., 2008; Witten et al., 2009; Parkhomenko et al., 2009) is a well known technique to study the relationship between two data types. These methods find pairs of sparse linear combinations of features from the two data types that are maximally correlated. For the purpose of finding bimodules, we may regard each such canonical covariate pair as a bimodule consisting of the features appearing in the linear combination.

Finally, in the context of eQTL analysis, methods based on Gaussian graphical models (Cheng et al., 2012, 2015, 2016) and penalized multi-task regression (Chen et al., 2012) have also been used to find bimodules. In the former work, the authors fit a sparse graphical model with a hidden variables that model interactions between sets of genes and sets of SNPs. In Chen et al. (2012), the gene and SNP networks derived from the respective intra-correlations matrices are used in a penalized regression setup to find a network-to-network mapping in the same spirit as bimodules.

1.4 Overview of the Paper

The next section introduces basic notation and presents the definition and properties of stable bimodules at the population level. In particular, we establish connections between stable population bimodules, Nash equilibria in a simple two-player game, and the connected components of the bipartite network of population cross-correlations. Section 3 is devoted to the testing-based definition
of stable bimodules in the sample setting, and a description of the Bimodule Search Procedure. In addition, we outline the computation of p-values for BSP and discuss a way to obtain robustly connected networks from sample bimodules. Section 4 is devoted to a simulation study that makes use of a complex model to capture some of the features observed in real multi-view data. Here we compare the performance of BSP with CONDOR and sCCA. Section 5 describes and evaluates the results of BSP and CONDOR applied to an eQTL dataset from the GTEx consortium. In particular, we examine the bimodules produced by BSP using a variety of descriptive and biological metrics, including comparisons with, and potential extensions of, standard eQTL analysis. In Section 6, we present the results of BSP applied to inter-annual temperature and precipitation measurements in North America.

2 Stable Population Bimodules

In this section we set out the basic notation and stochastic assumptions underlying our study of bimodules, and characterize stable bimodules at the population level.

2.1 Notation and Stochastic Setting

We assume that we have access to data sets of two different types obtained from a common set of $n$ samples. Let $X$ be an $n \times p$ matrix containing the data of Type 1, and let $Y$ be an $n \times q$ matrix containing the data of Type 2. The $i$th row of $X$ and $Y$ contain the measurements of Type 1 and Type 2, respectively, on the $i$th sample. The columns of $X$ and $Y$ correspond to the measured features of each type. Index features of Type 1 by $S = \{s_1, s_2, \ldots, s_p\}$, and those of Type 2 by $T = \{t_1, t_2, \ldots, t_q\}$. We assume that the rows of the joint matrix $[X, Y]$ are independent copies of a random (row) vector

\[(X, Y) = (X_{s_1}, \ldots, X_{s_p}, Y_{t_1}, \ldots, Y_{t_q}).\]

For each $s \in S$ let $X_s$ be the column of $X$ corresponding to feature $s$, and for each $t \in T$ let $Y_t$ be the column of $Y$ corresponding to feature $t$. For $s \in S$ and $t \in T$ let $\rho(s,t)$ be the population correlation between the random variables $X_s$ and $Y_t$, and let $r(s,t)$ denote the sample correlation between $X_s$ and $Y_t$ based on $[X, Y]$. For $A \subseteq S$ and $B \subseteq T$ define the aggregate squared correlation between $A$ and $B$ by

\[\rho^2(A, B) = \sum_{s \in A, t \in B} \rho^2(s,t), \quad (1)\]

\[r^2(A, B) = \sum_{s \in A, t \in B} r^2(s,t). \quad (2)\]

For singleton sets we will omit brackets, writing $\rho^2(s,B)$ and $\rho^2(A,t)$ instead of $\rho^2(\{s\},B)$ and $\rho^2(A,\{t\})$.

2.2 Stable Population Bimodules

We begin our analysis of bimodules at the population level, where the aggregate cross-correlation between $A$ and $B$ can be measured by the quantity $\rho^2(A, B)$ defined in (1). One might select pairs
(A, B) using a penalized score based on \( \rho^2(A, B) \), but the definition of a meaningful score, development of an efficient search procedure, and extension to the sample setting are each challenging tasks. As an alternative, we shift our attention from performance measures to stability criteria that are based on the structure of the population cross-correlations. The basic idea is contained in the following definition.

**Definition 2.1.** A pair \((A, B)\) of non-empty sets \(A \subseteq S\) and \(B \subseteq T\) is a stable (population) bimodule if

1. \(A = \{s \in S \mid \rho^2(s, B) > 0\}\) and
2. \(B = \{t \in T \mid \rho^2(A, t) > 0\}\).

A stable bimodule \((A, B)\) is minimal if it does not properly contain another stable bimodule.

Thus \((A, B)\) is a stable population bimodule if \(A\) is exactly the set of features in \(S\) that are correlated with at least one features in \(B\), and \(B\) is exactly the set of features in \(T\) that are correlated with at least one features in \(A\). It is useful to consider stable bimodules in the context of the network of cross-correlations.

**Definition 2.2.** The population cross-correlation network \(G_p\) is the weighted bipartite network with vertex set \(S \cup T\), edge set \(E_p = \{(s, t) \in S \times T \mid \rho(s, t) \neq 0\}\), and weight function \(w_p : E \rightarrow [-1, 1]\) given by \(w_p(s, t) = \rho(s, t)\).

**Definition 2.3.** The set of vertices \(C = A \cup B\) where \(A \subseteq S\) and \(B \subseteq T\) is a connected component of \(G_p\) if \(C\) is a maximal connected set in \(G_p\) with \(|C| > 1\). In other words, both \(A\) and \(B\) are non-empty, the bipartite graph on vertices \(A\) and \(B\) with edge set \(E_p \cap (A \times B)\) is connected, and there are no edges in \(E_p\) that connect vertices in \((S \cup T) \setminus C\) and those in \(C\).

The following elementary lemma shows that stable bimodules are closely related to the connected components of \(G_p\). One may also establish an elementary connection between population bimodules and Nash equilibria in a simple two-player game; see Supplementary Materials [SI] for proofs and more details.

**Lemma 1.** A pair \((A, B)\) of non empty sets with \(A \subseteq S\) and \(B \subseteq T\) is a population bimodule if and only if \(A \cup B\) is a union of connected components of \(G_p\). Moreover, \((A, B)\) is a minimal population bimodule if and only if it is a connected component of \(G_p\).

Thus, stable population bimodules depend only on the edges of the network \(G_p\). The bipartite structure of the network suggests a simple iterative procedure to identify minimal stable bimodules. Beginning with \(B_0 = \{t\}\) for some \(t \in T\), iteratively update feature sets \(A_k\) and \(B_k\) via the rules

\[
A_{k+1} = \{s \in S \mid \rho^2(s, B_k) > 0\} \quad \text{and} \quad B_{k+1} = \{t \in T \mid \rho^2(A_{k+1}, t) > 0\}.
\]

until \(A_{k+1} = A_k\) and \(B_{k+1} = B_k\). This update procedure corresponds to the breadth first search algorithm for finding the connected component of \(t\) in \(G_p\) (see, e.g., [Cormen et al., 2009]). Repeating this procedure with different \(t \in T\) finds the connected components of \(G_p\), which by Lemma 1 are the minimal stable population bimodules. As we will see below, the situation for sample bimodules is substantially more complicated.
3 Stable Sample Bimodules and the Bimodule Search Procedure

In practice, the population cross-correlations $\rho(s, t)$ are unknown, and the search for bimodules is based on the observed data matrices $[X, Y]$. One may simply replace the population correlations with their sample counterparts $r(s, t)$ in Definition 2.1, but when working with continuous data $r(s, t) \neq 0$ (even if $\rho(s, t) = 0$), and in this case the only stable bimodule is the full index set $(S, T)$. To address this, we replace the condition $\rho^2(s, B) > 0$ by $r^2(s, B) > \hat{\gamma}$, where the threshold $\hat{\gamma}$ is derived from the application of an FDR-controlling multiple testing procedure to approximate $p$-values for the statistics $\{r^2(s, B) : s \in S\}$. An analogous approach is taken for the conditions $\rho^2(A, t) > 0$.

3.1 Permutation Null Distribution and P-values

Here we detail our approach to assessing the significance of the statistics $r^2(s, B)$ and $r^2(A, t)$, based on a permutation null distribution. We assume throughout that the data $[X, Y]$ is fixed.

Definition 3.1. Let $P_1, P_2 \in \{0, 1\}^{n \times n}$ be chosen independently and uniformly from the set of all $n \times n$ permutation matrices. The permutation null distribution of $[X, Y]$ is the distribution of the data matrix

$$[\tilde{X}, \tilde{Y}] \doteq [P_1 X, P_2 Y].$$

Let $P_\pi$ and $E_\pi$ denote probability and expectation, respectively, under the permutation null. For $s \in S$ and $t \in T$ let $R(s, t)$ be the (random) sample-correlation of $\tilde{X}_s$ and $\tilde{Y}_t$ under the permutation null.

The permutation null distribution is obtained by randomly reordering the rows of $X$ and, independently, doing the same for the rows of $Y$. Note that permutation preserves the sample correlation between features in $S$, and between features in $T$, but it nullifies the cross-correlations between features in $S$ and $T$. Indeed, as shown in [Zhou et al. 2013], $E_\pi[R(s, t)] = 0$ for each $s \in S$ and $t \in T$.

Definition 3.2. For $A \subseteq S$ and $B \subseteq T$ define the permutation p-value

$$p(A, B) \doteq P_\pi\left(R^2(A, B) \geq r^2(A, B) \right)$$

where $R^2(A, B) \doteq \sum_{s \in A, t \in B} R^2(s, t)$ and the observed sum of squares $r^2(A, B)$ is fixed.

The permutation p-value $p(A, B)$ is the probability, under the permutation null, that the aggregate cross-correlation between the features in $A$ and $B$ exceeds its observed value in the data. Small values of $p(A, B)$ provide evidence in favor of the hypothesis that $\rho^2(A, B) > 0$. As the permutation distribution preserves the correlations among features in $A$ and among features in $B$, the p-value $p(A, B)$ accounts for the effects of these correlations when assessing the significance of $r^2(A, B)$.

For the p-value $p(A, B)$ used in following sections, either $A$ or $B$ will always be a singleton set. In this case, we omit brackets and write $p(s, B)$ instead of $p(\{s\}, B)$ and $p(A, t)$ instead of $p(A, \{t\})$. 

8
3.2 Stable Sample Bimodules

In order to define stable bimodules in the sample setting, we replace the condition \( \rho^2(s, B) > 0 \) by the requirement that the observed value of \( r^2(s, B) \) be significant under the permutation distribution, and similarly, we replace the condition \( \rho^2(A, t) > 0 \) by the requirement that the observed value of \( r^2(A, t) \) be significant under the permutation distribution. In order to properly account for the multiplicity of the index sets \( S \) and \( T \), we make use of a multiple testing procedure that controls the false-discovery rate (FDR) of the significant indices.

Let \( p = p_1, \ldots, p_m \in [0, 1] \) be the p-values associated with a family of \( m \) hypothesis tests, with order statistics \( p(1) \leq p(2) \cdots \leq p(m) \). Given a target false discovery rate \( \alpha \in (0, 1) \), the multiple testing procedure of Benjamini and Yekutieli (2001) rejects the hypotheses associated with the smallest p-values \( p(1), \ldots, p(k) \) where

\[
p(k) = \max \left\{ p(j) : \frac{m p(j)}{j} \leq \frac{\alpha}{\sum_{i=1}^{m} i^{-1}} \right\} \equiv \tau_{\alpha}(p) \tag{5}
\]

As shown in Benjamini and Yekutieli (2001), regardless of the joint distribution of the p-values in \( p \), the expected number of false discoveries among the rejected hypotheses is at most \( \alpha \). Note that \( \tau_{\alpha}(p) \) acts as an adaptive significance threshold for the p-values in \( p \): given \( p \), we reject the hypothesis associated with \( p_j \) if and only if \( p_j \leq \tau_{\alpha}(p) \).

**Definition 3.3.** (Stable Sample Bimodule) Let \([X, Y]\) and \( \alpha \in (0, 1) \) be given. A pair \((A, B)\) of non-empty sets \( A \subseteq S \) and \( B \subseteq T \) is a stable sample bimodule at level \( \alpha \) if

1. \( A = \{ s \in S \mid p(s, B) \leq \tau_{\alpha}(p_B) \} \) and
2. \( B = \{ t \in T \mid p(A, t) \leq \tau_{\alpha}(p_A) \} \)

where \( p_B = \{ p(s, B) \}_{s \in S} \) and \( p_A = \{ p(A, t) \}_{t \in T} \).

In words, \((A, B)\) is a stable sample bimodule if \( A \) is exactly the set of features in \( S \) that are significantly correlated with the features in \( B \), and at the same time \( B \) is exactly the set of features in \( T \) that are significantly correlated with the features in \( A \). When no ambiguity will arise, we will refer to stable sample bimodules simply as stable bimodules.

Although the definition of stable bimodules in the sample setting parallels that in the population setting, the sample setting, which is based on testing of unknown quantities, is substantially more complicated.

As noted in Lemma 1, stable population bimodules are unions of connected components of the population cross-correlation network. However, stable sample bimodules cannot be recovered in a straightforward way from the sample cross-correlation network, nor do they correspond to unions of connected components of this network after removing edges with small weights. Another difference concerns the potential aggregation of small effects. The condition \( p(s, B) \leq \tau_{\alpha}(p_B) \) can be written equivalently as \( r^2(s, B) \geq \tilde{\gamma}(s, B) \) where \( \tilde{\gamma}(s, B) \) depends on \( s, B \), and \( p_B \). The latter condition may be satisfied even if the feature \( s \) is not significantly correlated with any individual feature in \( B \). Similar remarks apply to \( p(A, t) \).

Another, more important, difference between the population and sample settings is the role of intra-correlations. A likely side-effect of any directed search for bimodules \((A, B)\), stable or otherwise, is that the sample intra-correlations of the features in \( A \) and \( B \) will be large, often significantly larger than the intra-correlations of a randomly selected set of features with the same
cardinality. Failure to account for inflated intra-correlations will lead to underestimates of the standard error of most test statistics, including the sum of squared correlations used here, which will in turn lead to anti-conservative (optimistic) assessments of significance and oversized feature sets. As noted above, the permutation distribution leaves intra-correlations unchanged, while ensuring that cross-correlations are equal to zero. In this way the permutation p-values \( p(s, B) \) and \( p(A, t) \) directly account for the effects of intra-correlations among features in \( B \) and \( A \) respectively.

### 3.3 The Bimodule Search Procedure (BSP)

We adapt the simple iterative search procedure for population bimodules described at the end of Section 2 using the significance based characterization of sample bimodules in Definition 3.3. The result is an iterative, testing-based search procedure for stable bimodules. Iterative testing procedures have been applied in single data-type settings for community detection in unweighted Wilson et al. (2014) and weighted Palowitch et al. (2016) networks, differential correlation mining Bodwin et al. (2018), and association mining for binary data Mosso et al. (2021). In these papers a stable set of significant nodes or features is identified through the iterative application of multiple testing. However, the hypotheses of interest and their associated test statistics vary substantially depending on the application. Further, the approximate p-values in these papers were derived from asymptotic normal and binomial approximations, rather than the more complicated permutation moment fitting used here.

**Input:** Data matrices \( X \) and \( Y \) and parameter \( \alpha \in (0, 1) \).

**Result:** A stable bimodule \((A, B)\) at level \( \alpha \), if found.

1. Initialize \( A' = \{s\} \subseteq S \) and \( A = B = B' = \emptyset \);
2. while \((A', B') \neq (A, B)\) do
   3. \((A, B) \leftarrow (A', B')\);
   4. Compute \( p(A, t) \) for each \( t \in T \) and let \( p_T \leftarrow (p(A, t))_{t \in T} \);
   5. \( B' \leftarrow \{t \in T \mid p(A, t) \leq \tau_\alpha(p_T)\} \); // Indices rejected by the B-Y procedure
   6. Compute \( p(s, B') \) for each \( s \in S \) and let \( p_S \leftarrow (p(s, B'))_{s \in S} \);
   7. \( A' \leftarrow \{s \in S \mid p(s, B') \leq \tau_\alpha(p_S)\} \); // Indices rejected by the B-Y procedure
3. end
4. if \(|A||B| > 0 \) (\( A, B = (A', B') \) then
5. return \((A, B)\);
6. end

**Algorithm 1:** Bimodule Search Procedure (BSP)

An overview of BSP is given in Algorithm 1. If BSP terminates at a non-empty fixed point, then its output is a stable bimodule at level \( \alpha \). Unlike its population counterpart, BSP is not guaranteed to terminate in a finite number of steps. As the procedure operates in a deterministic manner, and the number of feature set pairs is finite, BSP will terminate at a (possibly empty) fixed point or enter a limiting cycle. To limit computation time, the bimodule search is terminated if the loop at Line 2 exceeds 20 iterations. In our simulations and real-data analyses (described below) the 20 iteration limit was rarely reached. Further details on how BSP deals with cycles and limits large sets can be found in Supplementary Materials S2.1.

In practice, BSP is initialized with each singleton pair \((\{s\}, \emptyset)\) for \( s \in S \), and each singleton pair \((\emptyset, \{t\})\) for \( t \in T \). When either of the sets \( S \) or \( T \) is large, we use additional strategies to
speed up computation, e.g., randomly selecting a smaller subset of features for initialization. See Supplementary Materials S2.2 for more details.

The constant $\alpha \in (0, 1)$ is the only free parameter of BSP; we will refer to it as the false discovery parameter. While $\alpha$ controls the false discovery rate at each step of the search procedure, this does not guarantee control on the false associations (i.e. $(s,t)$ such that $\rho(s,t) = 0$) within the stable bimodules. In general, BSP will find fewer and smaller bimodules when $\alpha$ is small, and find more numerous and larger bimodules when $\alpha$ is large. In practice, we employ a permutation based procedure to select $\alpha$ from a fixed grid of values based on the notion of edge-error introduced in Section 4.2.1. See Supplementary Materials S2.3 for details.

Simulations and theoretical calculations suggest that singleton bimodules ($(s), (t)$) at a given level $\alpha \in (0, 1)$ can occur even in completely random data if $|S|$ and $|T|$ are large enough.

To minimize the detection of spurious singleton bimodules, we discard bimodules $(A,B)$ with $p(A,B) > \frac{\alpha}{|S||T|}$, where the threshold is the Bonferroni correction at level $\alpha$ for singleton bimodules. Alternatively, one can simply discard singleton bimodules with p-values exceeding the Bonferroni threshold.

In some cases, BSP may find bimodules having substantial overlap. For this, we assess the effective number of distinct bimodules and select an equal subset of representative bimodules for subsequent analysis. Details of this step can be found in Supplementary Materials S2.4.

### 3.3.1 Robust connectivity and essential edges

Unlike the population setting, stable sample bimodules found by BSP starting from singleton sets of features are not guaranteed to be minimal. Moreover, checking minimality of bimodules is computationally challenging. As an alternative, we assess the strength of connectivity of a bimodule. To this end, consider the sample cross-correlation network $G_s$, which is the weighted bipartite network with vertex set $S \cup T$, edge set $E = S \times T$, and weight function $w(s,t) = r(s,t)$. 

**Definition 3.4.** For each $\tau > 0$, let $G^\tau_s$ be the unweighted bipartite network with vertex set $S \cup T$ and edge set $E(\tau) \doteq \{(s,t) \in S \times T | |w(s,t)| \geq \tau\}$. For each feature set pair $(A,B)$ define the connectivity threshold given by

$$\tau^*(A,B) \doteq \max\{\tau \in [0, 1] : A \cup B \text{ is connected in } G^\tau_s\}. \quad (6)$$

Intuitively, $\tau^*(A,B)$ is the strength of the weakest link necessary to connect $(A,B)$ in $G_s$. This alternatively means that the feature set $A \cup B$ cannot be partitioned into two non-empty groups of features without a cross-correlation edge of magnitude at least $\tau^*(A,B)$ connecting the two groups. In practice, we observe that the bimodules found by BSP have relatively high connectivity thresholds (e.g. see Section 5.3.3), indicating that these bimodules are robustly connected.

Next we define the essential-edges of $(A,B)$ to be those that are present at the connectivity threshold

$$\text{essential-edges}(A,B) \doteq (A \times B) \cap E(\tau^*(A,B)). \quad (7)$$

One may regard $E(\tau) \cap (A \times B)$ as an estimate of the edges $(s,t) \in A \times B$ with $\rho(s,t) \neq 0$; the choice of $\tau > 0$ affects the fraction of false discoveries in this estimate. The value $\tau = \tau^*(A,B)$ is the most conservative threshold subject to the constraint that $A \cup B$ is connected in $G^\tau_s$, and the essential edges are those of the resulting graph. Assuming that the bimodule $(A,B)$ is connected in the population network, we expect the essential-edges to be a conservative estimate of the true edges in the population network.
3.3.2 Approximation of p-values

Recall that BSP is not based on an underlying generative or distributional model. The method relies on the permutation based p-values \( p(s, B) \) and \( p(A, t) \), derived under the assumption that the samples are independent and identically distributed. A total of \(|S| + |T|\) p-values are calculated in each iteration of the loop at Line 2 in Algorithm 1. Accounting for multiple initializations, several billion p-value calculations are required for typical genomic data sets, and the resolution of these p-values must be high enough to allow for multiple-testing correction.

When \(|S|\) or \(|T|\) is large, calculating the p-values \( p(s, B) \) and \( p(A, t) \) using a standard Monte Carlo permutation scheme is not feasible. As an alternative, we make use of ideas from Zhou et al. (2013) and Zhou et al. (2019) to approximate the permutation p-values \( p(A, t) \) and \( p(s, B) \) using the tails of a location-shifted Gamma distribution that has the same first three moments as the sampling distribution of \( R^2(A, t) \) under the permutation null.

Although the first three moments of \( R^2(A, t) \) can be computed exactly (Zhou et al., 2013), to further speed computation we use instead the eigenvalue conditional moments of \( R^2(A, t) \) (see Zhou et al., 2019), which depend only on the eigenvalues of the intra-correlation matrix of the features in \( A \), and not on \( t \). The analytical formula for the eigenvalue conditional moments is based on a normality assumption for the data generating distribution, but one may show that the weaker assumption of spherical symmetry is sufficient. In practice, the additional assumptions used in the moment approximation do not appear to limit the applicability of BSP. Accuracy of the p-value approximations is briefly discussed in Supplementary Materials S2.6.

4 Simulation Study

To assess the effectiveness of BSP, we carried out a simulation study in which a variety of true bimodules of different strengths and sizes were present in the underlying distribution of the samples. In this section, we provide an overview of the study, and an assessment of the results from BSP and competing methods CONDOR and sCCA (which were described in sections 1.3.1 and 1.3.2).

Simulation studies incorporating fewer than ten embedded bimodules have been conducted for methods based on sCCA (Waaijenborg et al., 2008; Parkhomenko et al., 2009; Witten et al., 2009) and graphical models (Cheng et al., 2016, 2015). Existing studies are relatively simple, and do not emphasize the network structure of many applications. In order to emulate the complexity of eQTL analysis and similar applications, we designed a simulation study in which \( K = 500 \) bimodules of various strengths, sizes, network structures, and intra-correlations were planted in a single large dataset. The planted bimodules were then connected by confounding edges to make their recovery more challenging. Recall that BSP is not based on an underlying generative model: the model used in the simulation study is for assessment purposes only.

4.1 Details of the Simulated Data

We generated a single large dataset having \( n = 200 \) samples and two measurement types, with \( p = 100,000 \) and \( q = 20,000 \) features, respectively. The number of features is of the same order of magnitude as in the eQTL dataset considered in Section 5. Following the notation at the beginning of Section 2, we denote the two types of features by index sets \( S = \{s_1, s_2 \ldots s_p\} \) and \( T = \{t_1, t_2 \ldots t_q\} \). For each individual, the joint \( p + q \) dimensional measurement vector is independently drawn from a multivariate normal distribution with mean 0 ∈ \( \mathbb{R}^{p+q} \) and \((p + q) \times (p + q)\) covariance matrix.
matrix $\Sigma$. The covariance matrix $\Sigma$ is designed so that it has $K = 500$ true bimodules of various sizes, network structures, signal strengths and intra-correlations.

As it is difficult to generate structured covariance matrices while maintaining non-negative definiteness, we instead specify a generative model for the $p + q$ dimensional random row vector $(X, Y) \sim \mathcal{N}_{p+q}(0, \Sigma)$. To begin, we partitioned the first-half of the $S$-indices $\{s_1, \ldots, s_{\lceil p/2 \rceil}\}$ into $K$ disjoint subsets $A_1, A_2, \ldots, A_K$ with sizes chosen according to a Dirichlet distribution with parameter $(1, 1, \ldots, 1) \in \mathbb{R}^K$. In the same way, we generated a Dirichlet partition $B_1, B_2, \ldots, B_K$ of the first-half of $T$ indices $\{t_1, \ldots, t_{\lfloor q/2 \rfloor}\}$ independent of the previous partition. The feature-set pairs $(A_i, B_i)$ constitute the true bimodules, while the features in second-half of the $S$- and $T$-indices are not part of true bimodules. Next, the random sub-vectors $(X_{A_i}, Y_{B_i})$ corresponding to the true bimodules were generated independently for each $i \in [K]$ using a graph based regression model described below.

Let $(A, B)$ be a feature set pair, and suppose that $\rho \in [0, 1)$ and $\sigma^2 > 0$ are given. Let $D \in \{0, 1\}^{[A] \times [B]}$ be a binary matrix, which we regard as the adjacency matrix of a connected bipartite network with vertex set $A \cup B$. Then the random row-vector $(X_A, Y_B)$ is generated as follows:

$$X_A \sim \mathcal{N}_{|A|}(0, (1 - \rho)I + \rho U) \quad \text{and} \quad Y_B = X_A D + \epsilon,$$

where $\epsilon \sim \mathcal{N}_{|B|}(0, \sigma^2 I)$ and $U$ is a matrix of all ones. To understand the bimodule signal produced by this model, note that $\rho$ governs the intra-correlation between features in $A$ and that for any $t \in B$, the variable $Y_t$ is influenced by features $X_s$ such that $(s, t)$ is an edge in the adjacency matrix $D$.

For each of the true bimodules $(A_i, B_i)$ in the simulation, we independently chose parameters $\rho_i$, $\sigma^2_i$, and $D_i$ to produce a variety of behaviors while maintaining the inherent constraints between them (see Supplementary Materials S3.1).

Features $X_s$ with $j > \lceil p/2 \rceil$ are independent $\mathcal{N}(0, 1)$ noise variables. Features $Y_t$ with $r > \lfloor q/2 \rfloor$ are either noise (standard normal) or they are bridge variables that connect two true bimodules. In more detail, for every pair of distinct bimodules $(A_k, B_k)$ and $(A_t, B_l)$ with $1 \leq k < l \leq K$, with probability $q = \frac{15}{K}$, we connect the two bimodules by selecting at random (and without replacement) an index $r > \lfloor q/2 \rfloor$ and making it a bridge variable by defining

$$Y_{t_r} = X_s + X_{s'} + \epsilon \quad \text{with} \quad \epsilon \sim N(0, \sigma^2_t),$$

for a randomly chosen $s \in A_k$ and $s' \in A_t$. The noise variance $\sigma^2_t$ in (9) is chosen so that the correlation between $Y_{t_r}$ and $X_s$ (and $X_{s'}$) is equal to the average of the maximum correlation of the bimodules that are being connected. If $Y_{t_r}$ is not a bridge variable, it is taken to be noise (standard normal).

Prior to the addition of bridge variables, the connected components of the population cross-correlation network are just the bimodules $(A_k, B_k)$. Once bridge variables have been added, the population cross-correlation network will have a so-called giant connected component comprising a substantial portion of the underlying index space $S \times T$. While theoretical support for the presence of giant component in our simulation model comes from the study of Erdős-Rényi random graphs [Bollobás, 2001], such components have also been observed in empirical eQTL networks [Fagny et al., 2017; Platig et al., 2016]. Although the giant component is itself a stable population bimodule, since we only add a small number (348) of bridge variables, the majority of the cross-correlation signal is in the more densely connected sets $(A_k, B_k)$, which we continue to refer to as the true bimodules.
4.2 Running BSP and Related Methods

We applied BSP to the simulated data using the false discovery parameter $\alpha = 0.01$, which was selected to keep the edge-error estimates under 0.05 (Supplementary Materials S2.3). This tuning procedure is purely based on the observed data, and does not require knowledge of the ground truth. The search was initialized from singletons consisting of all the features in $T$ and 1% of the features in $S$, chosen at random. In what follows, feature-set pairs identified by BSP (or some other method, when clear from context) will be referred to as detected bimodules. BSP detected 319 unique bimodules while the effective number (Supplementary Materials S2.4) of detected bimodules was 301.5.

To obtain bimodules via CONDOR (Platig et al., 2016), we applied Matrix-eQTL (Shabalin, 2012) to the simulated dataset with $S$ considered as the set of SNPs and $T$ considered as the set of genes, to extract feature pairs $(s, t) \in S \times T$ with q-value less than $\alpha = 0.05$. Next, we formed a bipartite graph on the vertex set $S \cup T$ with edges given by the significant feature pairs found in the previous step. The largest connected component of this graph, made up of 28,876 features from $S$ and 6,455 features from $T$, was passed through a bipartite community detection software (Platig, 2016) which partitioned the nodes of the sub-graph into 112 bimodules.

We applied the sCCA method of Witten et al. (2009) to the simulated data to find 100 bimodules. More precisely, for various penalty parameters $\lambda \in [0, 1]$, we ran sCCA (Witten and Tibshirani, 2020) to find 100 canonical covariate pairs with the $\ell_1$ norm constraint of $\lambda \sqrt{p}$ and $\lambda \sqrt{q}$ on the coefficients of the linear combinations corresponding to $S$ and $T$ respectively. Initially, we considered $\lambda = 0.233$, chosen by the permutation based procedure provided with the software. However the resulting bimodules were large and had high edge-error (Supplementary Materials S3.2). Based on a rough grid search, we then ran the procedure with each value $\lambda \in \{0.01, 0.02, 0.03, 0.04, 0.06\}$ to obtain smaller bimodules.

4.2.1 Comparing performance of the methods

In the simulation study described above, we measure the recovery of a true bimodule $(A_t, B_t)$ by a detected bimodule $(A_d, B_d)$ using the two metrics:

$$\text{recall} = \frac{|A_t \cap A_d| |B_t \cap B_d|}{|A_t||B_t|} \quad \text{and} \quad \text{Jaccard} = \frac{|A_t \cap A_d| |B_t \cap B_d|}{|(A_t \times B_t) \cup (A_d \times B_d)|}.$$

Recall captures how well the true bimodule is contained inside the detected bimodule, while Jaccard measures how well the two bimodules match. When assessing the recovery of a true bimodule under a collection of detected bimodules (like the output of BSP), we choose the detected bimodule with the best recall or Jaccard, depending on the metric under consideration.

As shown in Figure 2, the BSP Jaccard for true bimodules was influenced primarily by the cross-correlation strength $\sqrt{r_{A,B}^2/(|A||B|)}$ of the true bimodule, though the intra-correlation parameter $\rho$ used in the simulation was also seen to have an effect (Figure 2, left). Most bimodules with cross-correlation strength above 0.4 were completely recovered, while those with strength below 0.2 were not recovered. For strengths between 0.2 to 0.4, there was a variation in Jaccard, with smaller Jaccard for bimodules having larger values of $\rho$ (Figure 2 left). The effect of $\rho$ on Jaccard was expected since BSP accounts for the intra-correlation among features of the same type.

The intra-correlation parameter $\rho$ did not have significant effect on CONDOR Jaccard, since the method does not account for intra-correlations. Hence, here we only consider the effects of the
cross-correlation strength of true bimodules on CONDOR Jaccard (Figure 2, green curve on the right). Regardless of the cross-correlation strength, CONDOR Jaccard remained low. This was because CONDOR bimodules often overlapped multiple true bimodules; indeed, 102 of the 112 CONDOR bimodules overlapped with two or more (up to 19) true bimodules, compared with only 21 of the 319 BSP bimodules. However, the results for CONDOR recall (Figure 2, purple curve on the right) show that most true bimodules with significant cross-correlation strengths were contained inside some CONDOR bimodule.

To assess the false discoveries in detected bimodules, we measured the edge-error of detected bimodules. The edge-error is the fraction of the essential-edges of a detected bimodule that are not part of the simulation model, that is, edges not contained in any true bimodule and not in the set of bridge edges. The average edge-error for BSP bimodules was 0.03, and 90% of the detected bimodules had edge-error under 0.05. In contrast, the average edge-error for CONDOR bimodules was 0.08, and 90% of the detected bimodules had edge-error under 0.14. The larger edge-error among CONDOR bimodules may have arisen because the method does not account for intra-correlations.

Concerning sCCA, the sizes of the detected bimodules were at least an order of magnitude larger than sizes of the true bimodules when $\lambda$ exceeded 0.04 (Figure S2, Supplementary Materials S3.2). Thus we only considered $\lambda \leq 0.04$. For $\lambda = 0.03$ and 0.04, the detected bimodules had large edge-error (average error 0.47 and 0.65, respectively), while for $\lambda = 0.01$ and 0.02 the true bimodules had poor recall (95% of the true bimodules had recall below 0.02 and 0.23, respectively). Further details of the results are given in Supplementary Materials S3.2. A potential shortcoming of our application of sCCA was that we chose the same penalty parameter $\lambda$ for each of the 100 bimodules. We expect that the results of sCCA would improve if one chose a different penalty parameter for each bimodule. However, Witten et al. (2009) do not provide explicit guidelines to chose different penalty parameters for each component (bimodule), and directly doing a permutation-based grid search each time would be exceedingly slow.
We also studied the performance of BSP and CONDOR on a simulation study with larger sample size $n = 600$. As expected, both methods were able to recall bimodules with lower cross-correlation strengths than earlier. However, both BSP and CONDOR had lower Jaccard than in the $n = 200$ simulation (Supplementary Materials S3.3). We discuss this behavior in Section 7.

5 Application of BSP to eQTL Analysis

Here we describe the application of bimodules to the problem of expression quantitative trait loci (eQTL) analysis discussed in Section 1. The NIH funded GTEx Project has collected and created a large eQTL database containing genotype and expression data from postmortem tissues of human donors. A unique feature of this database is that it contains expression data from many tissues. We applied BSP, CONDOR and standard eQTL-analysis to $p = 556,304$ SNPs and $q = 26,054$ thyroid expression measurements from $n = 574$ individuals. A detailed account of data acquisition, preprocessing, and covariate correction can be found in Supplementary Materials S4.1.

The 556K SNPs considered were a representative subset chosen from 4.9 million (directly observed and imputed) autosomal SNPs with minor allele frequency greater than 0.1. Using a representative set decreased computation time and reduced the multiple testing burden in each iteration of BSP. We used an LD pruning software SNPRelate (Zheng, 2015) to select the representative subset of SNPs (see Supplementary Materials S4.1 for details). As SNPs exhibit local correlation due to linkage disequilibrium (LD), the selection process should not reduce the statistical power of BSP.

5.1 Results of BSP

We applied BSP to the thyroid eQTL data with false discovery parameter $\alpha = 0.03$ selected to keep the edge-error under 0.05 (details in Supplementary Materials S4.2). The search was initialized from singleton sets of all genes and half of the available SNPs, chosen at random. Thus the search procedure in Section 3.3 was run $p/2 + q \sim 304K$ times. BSP took 4.7 hours to run on a computer with a 20-core 2.4 GHz processor (further processor details are provided in Supplementary Materials S4.3). The search identified 3744 unique bimodules with p-values below the significance threshold of $\frac{p_	ext{q}}{p_	ext{q}} = 3.45 \times 10^{-12}$ (see Section 3.3). The majority (277K) of the searches terminated in the empty set after the first step; of the remaining 27K searches, the great majority identified a non-empty fixed point within 20 steps. Only 20 searches cycled and did not terminate in a fixed point. Among the searches taking more than one iteration, 94% terminated by the fifth step. Among searches that found a non-empty fixed point, 92.3% of the fixed points contained the seed singleton set of the search.

The effective number (see Supplementary Materials S2.4) of bimodules was 3304, slightly smaller than the number of unique bimodules. We applied the filtering procedure described in Supplementary Materials S2.4 to select from the unique bimodules a subfamily of 3304 bimodules that were substantially disjoint. The selected bimodules had SNP sets ranging in size from 1 to 1000, and gene sets ranging in size from 1 to 100 (Figure 3); the median size of the gene and SNP sets was 1 and 7, respectively.

If required, BSP can be run in a faster (less exhaustive) or slower (more exhaustive) fashion by selecting a smaller or larger fraction of SNPs from which to initialize the search procedure. The effective number of discovered bimodules was only slightly smaller (3258) when initializing with 10% of the SNPs.
5.2 Running Other Methods

Standard eQTL analysis was performed by applying Matrix-eQTL (Shabalin, 2012) twice to the data, first to perform a *cis*-eQTL analysis within a distance of 1MB and next to perform a *trans*-eQTL analysis. In each case, SNP-gene pairs with BH (Benjamini and Hochberg, 1995) q-value less than 0.05 were identified as significant. Matrix-eQTL identified 186K *cis*-eQTLs and 73K *trans*-eQTLs.

To obtain CONDOR bimodules (Platig et al., 2016), we applied Matrix-eQTL to identify both *cis-* and *trans*-eQTLs with BH q-value under the threshold .2, chosen as in Fagny et al. (2017). The resulting gene-SNP bipartite graph formed by these eQTLs was passed through CONDOR’s bipartite community detection pipeline (Platig et al., 2016), which partitioned the nodes of largest connected component of this graph into 6 bimodules.

We also applied the sCCA method of Witten et al. (2009) using the permutation based parameter selection procedure (Witten and Tibshirani, 2020) on the covariate-corrected genotype and expression matrices to identify 50 bimodules. The identified bimodules were large, containing roughly 100K SNPs and 4K-8K genes (Figure 3), making them difficult to analyze and interpret. The identified bimodules also exhibited moderate overlap: the effective number was 25. As such, we excluded the sCCA bimodules from subsequent comparisons. Analysis of sCCA on the simulated data (Section 4.2.1) suggests that the method may be able to recover smaller bimodules with a more tailored choice of its parameters.

5.3 Quantitative Validation

In this subsection, we apply several objective measures to validate and understand the bimodules found by BSP and CONDOR.

5.3.1 Permuted data

In order to assess the propensity of each method to detect spurious bimodules, we applied BSP and CONDOR to five data sets obtained by jointly permuting the sample labels for the expression measurements and most covariates (all except the five genotype PCs), while keeping the labels for genotype measurements and genotype covariates unchanged. Each data set obtained in this way is a realization of the permutation null defined in Definition 3.1. BSP found very few (5-12) bimodules in the permuted datasets compared to the real data (3344). CONDOR found no bimodules in any of the permuted datasets.

5.3.2 Bimodule sizes

Most (89%) bimodules found by BSP have fewer than 4 genes and 50 SNPs, but BSP also identified moderately sized bimodules having 10-100 genes and 30-1000 SNPs (see Figure 3). The bimodules found by CONDOR were moderately sized, with 10-100 genes and several hundred SNPs, except for a smaller bimodule with 5 genes and 43 SNPs. On the permuted data, most bimodules found by BSP have fewer than 2 genes and 2 SNPs.

As a one dimensional measure, we define the *geometric size* of a bimodule \((A,B)\) to be the geometric mean \(\sqrt{|A||B|}\) of its gene and counts, or equivalently, the square root of the number of gene-SNP pairs in the bimodule.
5.3.3 Connectivity threshold and network sparsity

Stable bimodules capture aggregate association between groups of SNPs and genes, however it is unclear how to recover individual SNP-gene associations within these bimodules. Motivated by the network perspective, in Section 3.3.1 we proposed evaluating for each bimodule \((A, B)\), the connectivity threshold \(\theta\) and the corresponding network of essential edges \(\mathcal{E}(A,B)\) between \(A\) and \(B\). To understand the structure of the network of essential edges, we further calculated the tree-multiplicity

\[
\text{TreeMul}(A, B) = \frac{|\text{essential-edges}(A, B)|}{|A| + |B| - 1},
\]

which measures the number of essential edges relative to the number of edges in a tree on the same node set. \(\text{TreeMul}(A, B)\) is never less than 1, and takes the value 1 exactly when the essential edges form a tree.

For bimodules found by BSP, the connectivity thresholds ranged from 0.14 to 0.59 and tree-multiplicities ranged from 1 to 10; the smaller values of the former and larger values of latter were associated with bimodules of larger geometric size (Figure S4, Supplementary Materials S4.4). Smaller bimodules had large connectivity thresholds and a tree-like essential edge network; in other words, such bimodules were connected under a small number of strong and local (see Section 5.4.2) SNP-gene associations. On the other hand larger bimodules had lower connectivity thresholds, meaning that we had to include weaker and often distal (see Section 5.4.2) SNP-gene associations to connect such bimodules. After including the weaker SNP-gene edges, although the association network for large bimodules had tree-multiplicity around 10 (Figure S4, Supplementary Materials S4.4), these networks were still sparsely connected compared to the complete bipartite graph on the same nodes.
### Analysis type

| Analysis type   | % eQTLs found among bimodules | % bimodules connected by eQTLs |
|-----------------|-------------------------------|-------------------------------|
| cis-eQTL analysis | 84%                          | 70%                          |
| trans-eQTL analysis | 51%                          | 88%                          |

Table 1: Comparison of BSP and standard eQTL analysis. A gene-SNP pair is said to be found among a collection of bimodules if the gene and SNP are both part of some common bimodule. On the other hand, we say that a bimodule is connected by a collection of eQTLs if under the gene-SNP pairs from the collection, the bimodule forms a connected graph.

### 5.4 Biological Validation

In order to assess potential biological utility of bimodules found by BSP, we compared the SNP-gene pairs in bimodules to those found by standard cis- and trans-eQTL analysis, studied the locations of the SNPs, and examined the gene sets for enrichment of known functional categories.

#### 5.4.1 Comparison with standard eQTL analysis

As described earlier, the bimodules produced by CONDOR are derived directly from SNP-gene pairs identified by cis- and trans-eQTL analysis. Table 1 compares these eQTL pairs with those found in bimodules identified by BSP. Recall that cis-eQTL analysis considers only local SNP-gene pairs (improving detection power by reducing multiple testing), while trans-eQTL analysis and BSP do not use any information about locations of the SNPs and genes. We find that half of the pairs identified by cis-eQTL analysis and most of the pairs identified by trans-eQTL analysis appear in at least one bimodule.

Bimodules capture sub-networks of SNP-gene associations rather than individual eQTLs, and as such individual SNP-gene pairs in a bimodule need not be eQTLs. In fact, the results of Section 5.3.3 suggest that the association networks underlying large bimodules may be sparse. Define a bimodule \((A, B)\) to be connected by a set of eQTLs if the bipartite graph with vertex set \(A \cup B\) and edges corresponding to the eQTLs is connected. As shown in Table 1, a significant fraction of BSP bimodules are not connected by SNP-gene pairs obtained by cis-eQTL and trans-eQTL analysis, respectively. The discovery of such bimodules suggests that the sub-networks identified by BSP cannot be found by standard eQTL analysis, and that these sub-networks can provide new insights and hypotheses for further study.

To identify potentially new eQTLs using BSP, we examine bimodule connectivity under the combined set of cis- and trans-eQTLs. All of the bimodules with one SNP or one gene are connected by the combined set of eQTLs (Supplementary Materials S4.5), and therefore all edges in these bimodules are discovered by standard analyses. On the other hand, 224 out of the 358 bimodules with geometric size larger than 10 were not connected by the combined set of eQTLs. In Figure 4, we plot the correlations corresponding to SNP-gene pairs that appear as essential-edges (Section 3.3.1) in one or more bimodules with geometric size above 10, along with the correlation thresholds for cis-eQTL (blue line) and trans-eQTL (red line) analysis. Around 300 local edges (i.e. the SNP is located within 1MB of the gene transcription start site) and 8.8K distal edges do not meet the correlation thresholds for cis- and trans-eQTL analysis, respectively, but show evidence of importance at the network level, and may be worthy of further study.
Figure 5: The gene-SNP association network for two BSP bimodules mapped onto the genome. The network of essential edges was formed by thresholding the cross-correlation matrix for the bimodule at the connectivity threshold (Section 3.3.1).

5.4.2 Genomic locations

We studied the chromosomal location and proximity of SNPs and genes from bimodules found by BSP and CONDOR. While CONDOR uses genomic locations as part of the cis-eQTL analysis in its first stage, BSP does not make use of location information. Genetic control of expression is often enriched in a region local to the gene (GTEx Consortium, 2017). All CONDOR bimodules, and almost all (99.3%) BSP bimodules, have at least one local SNP-gene pair (the SNP is located within 1MB of the gene transcription start site). In 93.5% of the smaller BSP bimodules (geometric size 10 or smaller) and 54.8% of the medium to large BSP bimodules (geometric size above 10) each gene and each SNP had a local counterpart SNP or gene within the bimodule.

For each bimodule, we examined the chromosomal locations of its SNPs and genes. All SNPs and many of the genes from the six CONDOR bimodules were located on Chromosome 6; two CONDOR bimodules also had genes located on Chromosome 8 and Chromosome 9. The SNPs and genes from the BSP bimodules were distributed across all 23 chromosomes: 170 of the 2947 small bimodules spanned 2 to 5 chromosomes and 152 of the 358 medium to large bimodules spanned 2 to 11 chromosomes; however the remaining bimodules were localized to a chromosome each.

Figure 5 illustrates the genomic locations of two bimodules found by BSP, with SNP location on the left and gene location on the right (only active chromosomes are shown). In addition, the figure illustrates the essential edges (Section 3.3.1) of each bimodule. The resulting bipartite graph provides insight into the underlying associations between SNPs and genes that constitute the bimodule. See Supplementary Materials S4.6 for more such illustrations.
5.4.3 Gene Ontology enrichment for bimodules

The Gene Ontology (GO) database contains a curated collection of gene sets that are known to be associated with different biological functions (c.f. [Gene Ontology Consortium, 2014] [Booij et al., 2000] [Rhee et al., 2008]. The topGO [Alexa and Rahnenfuhrer, 2018] package assesses whether sets in the GO database are enriched for a given gene set using Fisher's test. For each of the 145 BSP bimodules having a gene set \( B \) with 8 or more elements, we used topGO to assess the enrichment of \( B \) in 6463 GO gene sets of size more than 10, representing biological processes; however these significant sets were not apparently related to thyroid-specific function. We retained results with significant BH \( q \)-values (\( \alpha = .05 \)). Of the 145 gene sets considered, 18 had significant overlap with one or more biological process. Repeating with randomly chosen gene sets of the same size yielded no results. The significant GO terms for BSP and CONDOR can be found in Supplementary Materials S4.7.

6 Application of BSP to North American Temperature and Precipitation Data

6.1 Introduction

The relationship between temperature and precipitation over North America has been well documented ([Madden and Williams, 1978] [Berg et al., 2015] [Adler et al., 2008] [Livneh and Hoerling, 2016] [Hao et al., 2018]) and is of agricultural importance. For example, Berg et al. (2015) noted widespread correlation between summertime mean temperature and precipitation at the same location over various land regions. We explore these relationships using the Bimodule Search Procedure. In particular, the method allows us to search for clusters of distal temperature-precipitation relationships, known as teleconnections, whereas previous work has mostly focused on analyzing spatially proximal correlations.

We applied BSP to find pairs of geographic regions such that summer temperature in the first region is significantly correlated in aggregate with summer precipitation in the second region one year later. We will refer to such region pairs as T-P (temperature-precipitation) bimodules. T-P bimodules reflect mesoscale analysis of region-specific climatic patterns, which can be useful for predicting impact of climatic changes on practical outcomes like agricultural output.

6.2 Data Description and Processing

The Climatic Research Unit (CRU TS version 4.01) data ([Harris et al., 2014]) contains daily global measurements of temperature (\( T \)) and precipitation (\( P \)) levels on land over a \( .5^\circ \times .5^\circ \) (360 pixels by 720 pixels) resolution grid from 1901 to 2016. We reduced the resolution of the data to \( 2.5^\circ \times 2.5^\circ \) (72 by 144 pixels) by averaging over neighboring pixels and restricted to 427 pixels corresponding to the latitude-longitude pairs within North America. For each available year and each pixel/location we averaged temperature (\( T \)) and precipitation (\( P \)) over the summer months of June, July, and August. Each feature of the resulting time series was centered and scaled to have zero mean and unit variance. The data matrix \( X \), reflecting temperature, had 115 rows containing the annual summer-aggregated temperatures from 1901 to 2015 for each of the 427 locations. The data matrix \( Y \), reflecting precipitation, had 115 rows containing the annual summer-aggregated precipitation from 1902 to 2016 (lagged by one year from temperature) for each of the 427 locations.
Analysis of summer precipitation versus summer temperatures lagged by 2 years, and temperatures from different seasons (winter T; summer P of the same year) in the same year did not yield any bimodules.

### 6.3 Bimodules Search Procedure and Diagnostics

We ran BSP on the processed data with the false discovery parameter $\alpha = 0.045$, selected from the grid \{0.01, 0.015, 0.02, ..., 0.05\} to keep edge-error under 0.1 (see Figure S7, Supplementary Materials S5). BSP searches for groups of temperature and precipitation pixels that have significant aggregate cross-correlation. Temperature and precipitation are known to be spatial and temporally auto-correlated. Although BSP does not use spatial locations of the pixels, it directly accounts for spatial-correlations. The permutation null (Definition 3.1) used in BSP imposes an exchangeability assumption on samples which may fail under temporal auto-correlation. The temporal auto-correlation in our data was moderate, ranging from 0.10 to 0.30 for various features.

BSP found five distinct bimodules, while the effective number (Supplementary Materials S2.4) of bimodules was three. After the filtering step (Supplementary Materials S2.4), the two bimodules illustrated in Figure 6 and another bimodule with 80 temperature pixels and 5 precipitation pixels remained. We omitted a further analysis of the last bimodule since its precipitation pixels were same as those of bimodule $B$ in Figure 6 and its temperature pixels were geographically scattered.

**CRU: T(JJA)-P(JJA, offset), 1901-2016, $\alpha = .045$**

![Figure 6: Bimodules of summer temperature and precipitation in North America from CRU observations from 1901-2016. The left bimodule (A) contains 149 temperature locations (pixels) and 6 precipitation locations. The right bimodule (B) contains 53 temperature and 5 precipitation locations.](image)

Temperature pixels in the two bimodules are situated distally from the precipitation pixels, but the temperature and precipitation pixels within a bimodule form blocks of contiguous geographical regions. Since BSP did not use any location information while searching for these bimodules, these effects might have a common spatial origin.

The locations from the bimodules occupy large geographical areas on the map. The precipitation pixels from the bimodule on the left in Figure 6 form a vertical stretch around the eastern edge of the Great Plains and are correlated with temperature pixels in large areas of land in the Pacific Northwest, Alaska, and Mexico. In the second bimodule Figure 6 (right) precipitation pixels in...
the southern Great Plains around Oklahoma are strongly correlated with temperature pixels in the
Northwestern Great Plains. An anomalously hot summer Oregon in one year in the Northwest
suggests an anomalously rainy growing season in the following year in the Southern Great Plains.
Pixel-wise positive correlations are confirmed in Supplementary Materials S5.

The coastal proximity in all the temperature clusters suggest influences of oscillations in sea sur-
f ace temperatures. Aforementioned patterns from both bimodules map to locations of agricultural
productivity, such as in Oklahoma and Missouri (Figure 6).

The bimodules found by BSP only consider the magnitudes of correlations between the tempera-
ture and precipitation pixels. Upon further analysis of these bimodules we see that the significantly
correlated temperature and precipitation pixels are positively correlated in the Great Plains region.
These results agree with findings on concurrent T-P correlations in the Great Plains (Zhao and
Khalil 1993 [Berg et al. 2015 [Wang et al.] 2019], which noted widespread correlations between
summertime mean temperatures and precipitation at the same location over land in various parts
of North America, notably the Great plains. Our findings show strong correlations between north-
w estern (coastal) temperatures and Great Plains precipitation and generally agree with findings
in the literature. For example, Livneh and Hoerling (2016) considered the relationship between
hot temperatures and droughts in the Great Plains, noting that hot temperatures in the summer
are related to droughts in the following year on the overall global scale. The results of Livneh
and Hoerling (2016) preface the results contained within the above bimodules, but the latter are
additionally able to find regions where this effect is significant.

Our findings demonstrate the utility of BSP in finding insights into remote correlations between
precipitation and temperature in North America. Further research may build on these exploratory
findings and create a model that can forecast precipitation in agriculturally productive regions
around the world.

7 Discussion

The Bimodule Search Procedure (BSP) is an exploratory tool that searches for groups of features
with significant aggregate cross-correlation, which we refer to as bimodules. Rather than relying
on an underlying generative model, BSP makes use of iterative hypothesis-testing to identify stable
bimodules, which satisfy a natural stability condition. The false discovery threshold \( \alpha \in (0, 1) \) is
the only free parameter of the procedure. Efficient approximation of the p-values used for iterative
testing allow BSP to run on large datasets.

At the population level, stable bimodules can be characterized in terms of the connected compo-
nents of the population cross-correlation network. At the sample level, stable bimodules depend on
both cross-correlations and intra-correlations, which are not part of the cross-correlation network.
Nevertheless, the network perspective provides insights in both the simulation study and the real
data analysis.

Using a complex, network-based simulation study, we found that BSP was able to recover most
true bimodules with significant cross-correlation strength, while simultaneously controlling the false
discovery of edges having network-level importance. Among true bimodules with similar cross-
correlation strengths, those with lower intra-correlations were more likely to be recovered than those
with higher intra-correlations, reflecting the incorporation of intra-correlations in the calculation of
p-values; the effects of intra-correlations were most pronounced when the cross-correlation strength
was moderate.
When applied to eQTL data, BSP bimodules identified both local and distal effects, capturing half of the eQTLs found by standard cis-analysis and most of the eQTLs found by standard trans-analysis. Further, a substantial proportion of bimodules contained SNP-gene pairs that were important at the network level but not deemed significant under pairwise trans-analysis.

At root, the discovery of bimodules by BSP and CONDOR is driven by the presence or absence of correlations between features of different types. A key issue for these, and related, methods is how they behave with increasing sample size. In general, increasing sample size will yield greater power to detect cross-correlations, and therefore one expects the sizes of bimodule to increase. While this is often a desirable outcome, in applications where non-zero cross-correlations (possibly of small size) are the norm, this increased power may yield very large bimodules with little interpretive value. Evidence of this phenomena is found in the simulation study where, due to the presence of bridge-edges between true bimodules, increasing the sample size from \( n = 200 \) to \( n = 600 \) yields larger BSP bimodules, which often contain multiple true bimodules (Supplementary Materials S3.3). This may well reflect the underlying biology of genetic regulation: the omni-genic hypothesis of Boyle et al. (2017) suggests that a substantial portion of the gene-SNP cross-correlation network might be connected at the population level.

An obvious way to address “super connectivity” of the cross-correlation network is to change the definition of bimodule to account for the magnitude of cross-correlations, rather than their mere presence or absence. Incorporating a more stringent definition of connectivity in BSP would require modifying the permutation null distribution and addressing the theory and computation behind such a modification, both of which are areas of future research.

**SUPPLEMENTARY MATERIAL**

**Supplementary Materials:** The attached PDF file contains some proofs about population stable bimodules (Section S1), some implementation details of BSP (Section S2), and further details about the simulation study (Section S3), eQTL analysis (Section S4), and climate analysis (Section S5).

**BSP software package:** [https://github.com/miheerdew/cbce](https://github.com/miheerdew/cbce)

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28
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Supplement to Finding Stable Groups of Cross-Correlated Features in Two Data Sets With Common Samples

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Contents

S1 Consequences of stability at the population level  2

S2 BSP implementation details  3
  S2.1 Dealing with cycles and large sets  3
  S2.2 Initialization heuristics for large datasets  3
  S2.3 Choice of $\alpha$ using half-permutation based edge-error estimates  4
    S2.3.1 Half-permutation  4
  S2.4 Filtering overlapping bimodules  5
  S2.5 Covariate correction  6
  S2.6 Checking our p-value approximation  6

S3 Simulation details  7
  S3.1 Simulation model for each true bimodule  7
  S3.2 Results from sCCA  9
  S3.3 Performance of BSP and CONDOR on increasing sample size  9

S4 GTEx results  11
  S4.1 Data acquisition and preprocessing  11
  S4.2 Choice of false discovery parameter to BSP  11
  S4.3 Hardware and software stack  11
  S4.4 Bimodule connectivity thresholds and network sparsity  11
  S4.5 Connectivity of bimodules under edges from combined eQTL analysis  13
  S4.6 Bimodule association networks  13
  S4.7 Gene Ontology  13

S5 Climate analysis details  18
S1 Consequences of stability at the population level

Here we prove that population stable bimodules are: (a) unions of connected components of the population cross-correlation network, and (b) are the Nash Equilibria of a certain two player game. First let us start with the proof of Lemma 1.

Proof of Lemma 1. For any subsets $F \subseteq S$ and $G \subseteq T$ note that $\rho^2(F, G) > 0$ if and only if $(F \times G) \cap E_p \neq \emptyset$. Let $\text{Nb}(s) \doteq \{ t' \mid (s, t') \in E_p \}$ and $\text{Nb}(t) \doteq \{ s' \mid (s', t) \in E_p \}$ and denote the neighborhoods of $s$ and $t$ in the graph $G_p$. The two conditions in Definition 2.1 are equivalent to saying

$$A = \bigcup_{t \in B} \text{Nb}(t)$$

and

$$B = \bigcup_{s \in A} \text{Nb}(s),$$

respectively. Equivalently, since $G_p$ is a bipartite graph, the set of nodes $H = A \cup B$ satisfies the property

$$H = \text{Nb}(H) \quad (1)$$

where $\text{Nb}(C) \doteq \bigcup_{v \in C} \text{Nb}(v)$ for any subset of vertices $C \subseteq S \cup T$.

First, let us show that any $H$ satisfying (1) is a union of connected components. For any $r \in S \cup T$, note that the connected component containing $r$ (if $r$ is not an isolated vertex) is defined by $C(r) \doteq \bigcup_{i=0}^{\infty} C_i$ where $C_0 = \{ r \}$ and $C_i = \text{Nb}(C_{i-1})$ for each $i \geq 1$. For $r \in H$, repeatedly applying (1) shows that $r \in C(r) \subseteq H$ and hence

$$H = \bigcup_{r \in H} C(r). \quad (2)$$

Since (1) holds and $G_p$ is a simple graph, each $r \in H$ has at least one other neighbor. Hence $C(r)$ is indeed a connected component for each $r \in H$.

Next, suppose that $H$ is a union of connected components (hence no $r \in H$ is isolated and (2) holds), we will show that (1) holds. Since $\text{Nb}(C(r)) \subseteq C(r)$ for any $r$, if $H$ satisfies (2) then $\text{Nb}(H) \subseteq H$. Further since each vertex in $H$ is a neighbor of some vertex in its connected component, we must have $\text{Nb}(H) \supseteq H$. Hence (1) is satisfied and $H$ is a stable population bimodule. □

The notion of stability in Definition 2.1 has close connections with Nash equilibrium (Nash, 1950) in game theory. To make this precise, fix an $\epsilon > 0$, and consider the reward function $\Phi_\epsilon$ that for any $A \subseteq S$ and $B \subseteq T$ takes the value

$$\Phi_\epsilon(A, B) \doteq \sum_{s \in A} \sum_{t \in B} \rho^2(s, t) - \epsilon |A| |B|. \quad (3)$$

Consider a two player game in which player 1 chooses a subset $A \subseteq S$, player 2 chooses a subset $B \subseteq T$, and the payoff to both the players is $\Phi_\epsilon(A, B)$. In this setting, a pair of subsets $(A^*, B^*)$ is called a Nash equilibrium if

$$\max_{A \subseteq S} \Phi_\epsilon(A, B^*) = \Phi_\epsilon(A^*, B^*) = \max_{B \subseteq T} \Phi_\epsilon(A^*, B).$$

The following elementary lemma shows that bimodules are the just Nash equilibria in this game.
Lemma A. Let $\delta = \min \{ \rho^2(s, t) \mid s \in S, t \in T, \rho(s, t) \neq 0 \}$ and $\epsilon_0 = \delta(\max(|S|, |T|))^{-1}$. If $\epsilon \in (0, \epsilon_0)$ then the non-empty Nash equilibria of the game with reward function $\Phi_{\epsilon}$ coincides with the family of stable population bimodules.

Proof. Suppose $0 < \epsilon < \epsilon_0$. Fix $A \subseteq S$ and observe that for any $B \subseteq T$

$$\Phi_{\epsilon}(A, B) = \sum_{t \in B} \sum_{s \in A} (\rho^2(s, t) - \epsilon)$$

$$= \sum_{t \in B} (\rho^2(A, t) - \epsilon |A|). \quad (4)$$

Since $\epsilon |A| < \epsilon_0 |A| \leq \delta$, for any $t \in T$, if $\rho^2(A, t) > 0$ then $\rho^2(A, t) - \epsilon |A| > 0$. Hence the maximum over subsets $B \subseteq T$ will be uniquely attained at

$$\arg \max_{B \subseteq T} \Phi_{\epsilon}(A, B) = \{ t \in T \mid \rho^2(A, t) - \epsilon |A| > 0 \} = \{ t \in T \mid \rho^2(A, t) > 0 \} \quad (5)$$

Similarly, if we fix $A \subseteq T$, we can show

$$\arg \max_{A \subseteq S} \Phi_{\epsilon}(A, B) = \{ s \in S \mid \rho^2(s, B) > 0 \} \quad (6)$$

Hence the pair of non-empty sets $(A^*, B^*)$ is a Nash equilibrium if and only if

$$A^* = \{ s \in S \mid \rho^2(s, B^*) > 0 \} \text{ and } B^* = \{ t \in T \mid \rho^2(A^*, t) > 0 \}.$$

These conditions are the same as those required for $(A^*, B^*)$ to be a population bimodule (Definition 2.1). \qed

S2 BSP implementation details

S2.1 Dealing with cycles and large sets

In practice, we do not want the sizes of the sets $(A_k, B_k)$ in the iteration to grow too large as this slows computation, and large bimodules are difficult to interpret. Therefore the search procedure is terminated when the geometric size of $(A_k, B_k)$ exceeds 5000. In some cases, the sequence of iterates $(A_k, B_k)$ for $k \in \{1, \ldots, k_{\text{max}} \}$ will form a cycle of length greater than 1, and will therefore fail to reach a fixed point. To search for a nearby fixed point instead, when we encounter the cycle $(A_k, B_k) = (A_l, B_l)$ for some $l < k - 1$, we set $(A_{l+1}, B_{l+1})$ to $(A_k \cap A_{k-1}, B_k \cap B_{k-1})$ and continue the iteration.

S2.2 Initialization heuristics for large datasets

When $|S| \gg |T|$, we initialize BSP from all the features in $T$, but only from a subset of randomly chosen features in $S$. BSP sometimes discovers identical or almost-identical bimodules when starting from different initializations, often from features within the said bimodule. This problem is particularly prominent for large bimodules which may be rediscovered by thousands of initializations. Hence, to avoid some of this redundant computation, we may skip initializing BSP from features in the bimodules that have already been discovered.
S2.3 Choice of $\alpha$ using half-permutation based edge-error estimates

To select the false discovery parameter $\alpha$ for BSP, we estimate the edge-error for each value of $\alpha$ from a pre-specified grid. The edge-error is an edge-based false discovery notion for bimodules, defined as the average fraction of erroneous essential-edges (defined in Section 3.3.1) among bimodules. Since we do not know the ground truth, we estimate the edge-error for BSP by running it on instances of the half-permuted dataset in which the sample labels for half of the features from each data type have been permuted. Further details are given below.

S2.3.1 Half-permutation

Comparing results between the original and permuted data (Definition 3.1) allow us to assess the false discoveries from BSP when there are no true associations between features from $S$ and $T$. However, we often expect associations between at least some variables from $S$ and $T$ (in fact, these are the ones that we want to find). To create a null distribution where some of pairs of features from $S$ and $T$ are correlated and some are not, we use the following half-permutation scheme. Let $(X, Y)$ denote the original data, where $X$ and $Y$ are measurements matrices for the two data types. We generate a half-permuted dataset $(\tilde{X}, \tilde{Y})$ as follows:

1. Randomly select half the features, $\hat{S} \subseteq S$ and $\hat{T} \subseteq T$, from each data type.

2. Randomly permute the rows of the submatrix of $X$ that corresponding to the columns $\hat{S}$, and call the resulting matrix $\tilde{X}$. In other words, the submatrix corresponding to the features $S \setminus \hat{S}$ is the same in $X$ and $\tilde{X}$, while the sample labels of the submatrix of $\tilde{X}$ corresponding to features in $\hat{S}$ have been permuted $X_{\hat{S}} = P_1 X_{\hat{S}}$ by a random permutation matrix $P_1$.

3. Similarly, permute the rows of matrix $Y$ corresponding to the features $\hat{T}$ using another independent permutation matrix $P_2$. Call the resulting matrix $\tilde{Y}$.

Note that, together, the “half-permutation” steps 2 and 3 temper the cross-correlation between pairs of features in $\hat{S} \times T \cup S \times \hat{T}$. Let $B = \{(A_1, B_1), (A_2, B_2) \ldots (A_K, B_K)\}$ be the collection of bimodules in the half-permuted data $(\tilde{X}, \tilde{Y})$. We will assume that the collection $B$ is already filtered for overlaps (Section S2.4 below). We define the edge-error estimate for the collection $B$ as

$$\text{edge-error}(B) = \frac{1}{|B|} \sum_{(A, B) \in B} \frac{|\text{essential-edges}(A, B) \cap (\hat{S} \times T \cup S \times \hat{T})|}{|\text{essential-edges}(A, B)|}. \quad (7)$$

In practice, we generate half-permuted datasets and use the edge-error estimate (7) to choose $\alpha$ as follows. First, we generate a pre-specified number $N$ of
instances of the half-permuted dataset. If the covariates are present, we correct for them after the half-permutation step. Next, for each $\alpha$ among a range of values, e.g., $\{0.01, 0.02, \ldots, 0.05\}$, we run BSP with false discovery parameter $\alpha$ over the each of the half-permuted datasets and calculate the average edge-error (7) of the resulting collection of bimodules for that value of $\alpha$, averaged over all the $N$ half-permuted instances. We can then choose an $\alpha$ from the grid that has average edge-error smaller a pre-specified value like 0.05. Generally smaller values of $\alpha$ tend to have smaller edge error, so we choose the largest value of $\alpha$ from the grid that has acceptable edge error. However, we may chose a smaller value of $\alpha$ if the bimodules are too large.

A caveat with the above procedure to select $\alpha$ is that the edge-error estimates may be quite variable even when averaged over a large number $N$ of half-permuted datasets. One explanation for this variability is that different $\hat{S}$ and $\hat{T}$ are chosen for each instance of the half-permutation. Nevertheless, if we observe variability we choose a more conservative value of $\alpha$. As seen in Section 4.2.1, even without access to the ground truth, we were able to keep the true edge-error under 0.05 by using the above strategy to select $\alpha$.

### S2.4 Filtering overlapping bimodules

Running BSP starting from different initializations may lead to a collection $\mathcal{B} = \{(A_1^*, B_1^*), (A_2^*, B_2^*), \ldots, (A_J^*, B_J^*)\}$ of $J$, potentially repeating and overlapping, bimodules. A typical bimodule might occur multiple times in $\mathcal{B}$, and distinct bimodules in $\mathcal{B}$ might have substantial overlap. To reduce duplication, we count the effective number of disjoint bimodules in the collection $\mathcal{B}$ and propose a way to select a subset of those many bimodules from $\mathcal{B}$ that are most disjoint. Details follow.

We use the following definition $N_e(\mathcal{B})$ of effective number of disjoint bimodules among the collection $\mathcal{B}$, adapted from Shabalin et al. (2009):

$$N_e(\mathcal{B}) = \sum_{(A,B) \in \mathcal{B}} \frac{1}{|A||B|} \sum_{s \in A, t \in B} \frac{1}{C_B(s,t)},$$

where

$$C_B(s,t) = \sum_{(A,B) \in \mathcal{B}} \mathbb{1}_{s \in A, t \in B}$$

is the number of bimodules that contain the pair $(s,t)$. As noted in Shabalin et al. (2009), the measure $N_e$ has the property that if there were $r$ distinct bimodules in $\mathcal{B}$, all disjoint when considered as collection of feature pairs, then $N_e(\mathcal{B}) = r$.

When there is substantial overlap between the bimodules in $\mathcal{B}$, $N_e(\mathcal{B})$ is typically smaller than $|\mathcal{B}|$. We can then choose $N = \lceil N_e(\mathcal{B}) \rceil$ most distinct representative bimodules among $\mathcal{B}$, as follows.

**Cluster the collection of bimodules $\mathcal{B}$ into $N$ groups** We use hierarchical agglomerative clustering using the average linkage method (see Hastie...
et al., 2009) based on the distance metric given by

$$d_J((A_1, B_1), (A_2, B_2)) = 1 - \frac{|A_1 \times B_1 \cap A_2 \times B_2|}{|A_1 \times B_1 \cup A_2 \times B_2|}$$  (10)

When we consider the bimodules as a collection of feature pairs, the metric $d_J$ is simply the Jaccard distance between the bimodules.

**Select one representative bimodule from each cluster** Let $\mathcal{C} \subseteq \mathcal{B}$ be one of the $N$ bimodule clusters obtained in the previous step. We select a bimodule representative $(A, B) \in \mathcal{C}$ from this cluster that maximizes the following importance score:

$$\text{is}_\mathcal{C}(A, B) = \sum_{s \in A, t \in B} \sum_{(A', B') \in \mathcal{C}} I\{s \in A', t \in B\}.$$  (11)

The score $\text{is}_\mathcal{C}(A, B)$ aggregates the importance of each feature pair within $(A, B)$, measured using the number of (potentially repeating) bimodules from $\mathcal{C}$ the feature-pair was a part of. Bimodules that are larger and have more overlapping pairs will be preferred as representatives under this scheme.

**S2.5 Covariate correction**

In some cases the data matrices $[X, Y] \in \mathbb{R}^{n \times (p+q)}$ are accompanied by one or more covariates like sex, platform details and PEER factors that must be accounted for by removing their effects before discovering bimodules. Suppose we are given $m$ such linearly independent covariates $v_1, \ldots, v_m \in \mathbb{R}^n$. Here we describe how to modify BSP to remove their effects. First, we residualize each column of the original data $[X, Y]$ by setting up a linear model with explanatory variables $v_1, \ldots, v_m$. Denote the resulting matrix by $[X', Y'] \in \mathbb{R}^{n \times (p+q)}$ that has columns which are projections of those of $[X, Y]$ onto the subspace orthogonal to $v_1, \ldots, v_m$. We would like to now run BSP on $[X', Y']$, however since the columns of $[X', Y']$ lie on an $n' = n - m'$ dimensional subspace, the independence assumption of p-value calculations in Section 3.3.2 would fail. However, as argued in Zhou et al. (2013), it is enough to replace the sample size $n$ with the effective sample size of $n'$ in the p-value calculations.

**S2.6 Checking our p-value approximation**

To check the uniformity of our approximate p-value under the permutation null, we chose a bimodule $(A, B)$ found in Section 5 and a $t \in B$. Then we randomly permuted the labels of gene $t$ ($10^5$ times), computing our p-value approximation $\hat{p}(A, t)$ in each case. Hence we are assessing the uniformity of $\hat{p}(A, t)$ under the permutation null distribution. The result in Figure S1 shows that the computed p-values are almost uniform but extremely small p-values show anti-conservative behavior. A potential reason for this anti-conservative behavior is that the tails
Figure S1: Assessing the accuracy of our p-value estimate \( \hat{p}(A,t) \): We used the eQTL data from Section 5 and chose a bimodule with 24 SNPs (used as \( A \)) and selected \( t \) to be a gene from the same bimodule. We then performed \( 10^5 \) random permutation of the sample labels for the gene \( t \) and repeatedly estimated \( \hat{p}(A,t) \) for each permutation after removing the effects of covariates (Appendix S2.5).

of test statistic under the permutation distribution may be heavier compared to the tails of the location-shifted Gamma distribution that we use to approximate it, since the permutation distribution is discrete distribution which explicitly depends on the exact entries of the data matrices.

S3 Simulation details

S3.1 Simulation model for each true bimodule

As described in Section 4, given \( \rho, \sigma \in [0,1] \) and a binary adjacency matrix \( D \in \{0,1\}^{|A|\times|B|} \) representing a connected bipartite graph on vertices \( A \) and \( B \) (called the regressor-graph), the variables \((X_A,Y_A)\) for a bimodule \((A,B)\) can be simulated as

\[
X_A \sim N_{|A|}(0,(1-\rho)I+\rho U) \quad \text{and} \quad Y_B^t = D^t X_A^t + \epsilon,  \tag{12}
\]

where \( U \) is the matrix of all ones and \( \epsilon \sim N(0,\sigma^2) \). The parameters \( \rho, \sigma \in [0,1] \) and \( D \) appearing in (12) are chosen independently for each true bimodule \((A,B)\) as follows:

1. Choose a constant \( \beta \in [0,1] \) uniformly at random. With \( d = \lceil \beta \rceil \), let \( D \) be the adjacency matrix of the \( d \)-regular bipartite connected graph
on vertex sets $A$ and $B$ formed by independently connecting each vertex $t \in B$ to $d$ randomly chosen vertices from $A$. If the resulting graph is not connected, set $\beta$ to $\beta + \Delta \beta$ where $\Delta \beta = 0.1$ and repeat the previous step till the resulting bipartite graph is connected.

2. Randomly choose $\rho \in [0, 1]$ and $\eta \in [0, .8]$ subject to the constraint $\delta = 1 + \rho(d - 1) \geq \eta^2 d$. We satisfy this constraint by first uniformly generating $\rho$ and then generating $\eta$ uniformly from $[0, \min(\sqrt{\delta d^{-1}}, .8)]$.

3. Finally let $\sigma = \sqrt{\delta(\delta - \eta^2 d)} / \eta$.

The constants $(\rho, \beta, \eta)$ in the above procedure have the following intuitive role: $\rho$ is the intra-correlation between any two features from the set $A$, $\beta \in [0,1]$ controls the edge density of the of the regressor-graph $D$, and $\eta$ is the cross-correlation between features from $B$ and adjacent features from $A$ in the regressor-graph. The following Lemma shows that our choice of parameters indeed results in population cross-correlation of $\eta$ between features connected by the regressor-graph:

**Lemma B.** Fix $\rho, \eta \in [0, 1]$, $a, b \in \mathbb{N}$ and $d \in \{1, 2 \ldots a\}$ so that $\delta = 1 + \rho(d - 1) \geq \eta^2 d$. Suppose $X$ is a $a$-dimensional random vector with covariance matrix $\text{Cov}(X) = \rho U_a + (1 - \rho) I_a$, where $U_a \in \mathbb{R}^{a \times a}$ is the matrix of all ones and $I_a \in \mathbb{R}^{a \times a}$ is the identity matrix. Next suppose $D$ is a $\{0, 1\}$ valued $a \times b$ dimensional matrix that has exactly $d$ ones in each column. Finally let $\sigma = \sqrt{\delta(\delta - \eta^2 d)} / \eta$ and suppose the $b$-dimensional random vector $Y$ is given by

$$Y = D^t X + \epsilon$$

where $\epsilon$ is another $b$-dimensional random vector independent of $X$ with $\text{Cov}(\epsilon) = \sigma^2 I_b$. Then

$$\text{Cor}(X, Y) \odot D = \eta D$$

(13)

where $\text{Cor}(X, Y) \in \mathbb{R}^{a \times b}$ is the cross-correlation matrix between random vectors $X$ and $Y$, and $\odot$ represents the element-wise product of matrices (i.e., the Hadamard product).

**Proof.** Since we are concerned with covariances, we can assume by mean centering that $EX = 0 \in \mathbb{R}^a$ and $EY = E\epsilon = 0 \in \mathbb{R}^b$. Note that $D^t e_a = d e_b$ and $U_a = e_a e_a^t$, where $e_r = (1, \ldots, 1)^t \in \mathbb{R}^r$ for $r \in \{a, b\}$. Hence using independence of $X$ and $\epsilon$:

$$\text{Cov}(Y) = E(YY^t) = D^t E(XX^t) D + E(\epsilon \epsilon^t)$$

$$= D^t \text{Cov}(X) D + \text{Cov}(\epsilon) = D^t (\rho e_a e_a^t + (1 - \rho) I_a) D + \sigma_2 I_b$$

$$= \rho (D^t e_a)^t (D^t e_a) + (1 - \rho) D^t D + \sigma_2 I_b$$

$$= \rho d^2 e_b e_b^t + (1 - \rho) D^t D + \sigma^2 I_b$$

Since all the diagonal entries of $D^t D$ have the value $d$,

$$\text{diag}[\text{Cov}(Y)] = (\rho d^2 + (1 - \rho)d + \sigma^2) I_b = (d \delta + \sigma^2) I_b = \left(\frac{\delta}{\eta}\right)^2 I_b$$

(14)
where for any square matrix $A$, diag[$A$] denotes the diagonal matrix obtained from $A$ by setting all the off-diagonal entries of $A$ to 0.

We can similarly calculate the cross-covariance between $X$ and $Y$
\[
\text{Cov}(X, Y) = E(XY^t) = E(XX^t)D = (\rho e_a e_a^t + (1 - \rho)I_a)D
\]
\[
= \rho de_a e_a^t + (1 - \rho)D,
\]
and also finally the cross-correlation between $X$ and $Y$ using (15), (14) and diag[Cov($X$)] = $I_a$:
\[
\text{Cor}(X, Y) = \text{diag}[\text{Cov}(X)]^{-\frac{1}{2}} \text{Cov}(X, Y) \text{diag}[\text{Cov}(Y)]^{-\frac{1}{2}}
\]
\[
= \frac{\eta}{\delta} (\rho de_a e_b^t + (1 - \rho)D) = \frac{\eta}{\delta} (\rho \bar{D} + (1 - \rho + \rho \delta)D)
\]
\[
= \eta \bar{D} + \eta \rho \delta^{-1} \bar{D}.
\]

where $\bar{D} = 1 - D$. In particular this shows (13).

\section*{S3.2 Results from sCCA}

We ran sCCA on the simulated dataset to search for 100 canonical covariates for a range of values of the penalty parameter $\lambda$. The sizes of the bimodules for various values of $\lambda$ can be seen in Figure S2. For $\lambda \in \{0.01, 0.02, 0.03, 0.04, 0.23\}$, the first two columns of the following table show the number of true bimodules (TB) that overlapped with each detected bimodule (DB) and the edge-error of each DB averaged over all DBs. The last column shows the top 5 (or bottom 95) percentile recall among the true bimodules.

| $\lambda$ | # TBs that overlap with each DB | edge-error | recall of TB (95%-tile) |
|-----------|-------------------------------|------------|------------------------|
| .01       | .97                           | .09        | .02                    |
| .02       | .96                           | .19        | .23                    |
| .03       | 1.97                          | .48        | .62                    |
| .04       | 6.47                          | .65        | .95                    |
| .23       | 281                           | .89        | 1                      |

The parameter value $\lambda = 0.01$ has small edge-error, but poor recall. The recall improves on increasing $\lambda$, but the edge-error degrades.

\section*{S3.3 Performance of BSP and CONDOR on increasing sample size}

We increased that sample size of the simulation study in Section 4 to $n = 600$, and re-ran BSP and CONDOR with the same parameters as earlier. The average edge-error for BSP and CONDOR was 0.05 and 0.10 respectively. As seen in Figure S3, BSP and CONDOR both recall most bimodules with cross-correlation strength above 0.3, however Jaccard for BSP and CONDOR has degraded. This can be explained by noting that 25% or BSP bimodules now overlapped with two or more true bimodules compared to 6% when $n = 200$. 

9
Figure S2: The sizes of sCCA bimodules for various values of the penalty parameter $\lambda$ along with sizes of the true bimodules.

Figure S3: Average recall and Jaccard for true bimodules in the simulation with 600 samples.
S4 GTEx results

S4.1 Data acquisition and preprocessing
We obtained genotype and thyroid expression data for 574 individuals from the dbGap website (accession number: phs000424.v8.p1). We directly used the filtered and normalized gene expression data and covariates provided for eQTL analysis but filtered the SNPs in the genotype data using the LD pruning software SNPRelate Zheng (2015). The software retained 556K autosomal SNPs with minor allele frequency above 0.1 such that all pairs of SNPs within each 500KB window of the genome had squared correlation under $(0.7)^2$. The latter threshold was chosen to balance the number of retained SNPs and information loss.

There were 68 covariates provided for the Thyroid tissue consisting of the top 5 genotype principle components; 60 PEER covariates, and 3 additional covariates for sequencing platform, sequencing protocol, and sex. We accounted for these covariates by the modification to BSP mentioned in Appendix S2.5.

S4.2 Choice of false discovery parameter to BSP
We chose the false discover parameter $\alpha$ for BSP from the grid \{0.01, 0.02, 0.03, 0.04, 0.05\} by finding the largest $\alpha$ that kept the average edge-error estimates based on $N = 5$ half-permutations under 0.05 (see Appendix S2.3). However our error estimates were variable as we obtained $\alpha = 0.05$ in one instance and $\alpha = 0.03$ in another. We conservatively chose $\alpha = 0.03$.

S4.3 Hardware and software stack
The various methods used in this analysis were run on a dedicated computer that had Intel (R) Xeon (R) E5-2640 CPU with 20 parallel cores at 2.50 Hz base frequency, and a 512 GB random access memory along with L1, L2 and L3 caches of sizes 1.3, 5 and 50 MB respectively. The computer ran Windows server 2012 R2 operating system and we used the Microsoft R Open 3.5.3 software to perform most of our analysis, since it has multi-core implementations of linear algebra routines.

S4.4 Bimodule connectivity thresholds and network sparsity
Figure S4 shows two network statistics for bimodules found by BSP – connectivity threshold and tree-multiplicity. All bimodules have tree multiplicity under 10. This shows that the association network for large bimodules, particularly having low connectivity-thresholds, is sparse.
Figure S4: Connectivity-threshold and tree-multiplicity for BSP bimodules compared to their geometric size. The horizontal dotted line represents the threshold obtained from standard trans-analysis.
S4.5 Connectivity of bimodules under edges from combined eQTL analysis

Here we examine which bimodules are connected under the combined edges from cis-eQTL and trans-eQTL analysis, based on geometric size of the bimodule. Figure S5 (left) shows that all the bimodules that have either one gene or one SNP are connected. Hence, these bimodules could have been recovered using standard eQTL analysis. On the other hand if we restrict to bimodules with two or more genes and SNPs, we see that (Figure S5; right) the fraction of connected bimodules tends to decrease as the geometric size of the bimodules increases.

S4.6 Bimodule association networks

See the plots in Figure S6.

S4.7 Gene Ontology

18 out of the 145 BSP gene sets, and 1 out of the 5 CONDOR gene sets that we considered had significant overlap with GO categories. Among the 40 GO terms detected by the CONDOR, 27 terms were also found among the 135 terms detected by BSP. The GO terms that were discovered for the two methods did not seem specific to thyroid, the tissue under investigation. Complete list of the GO terms for the two methods is as follows. Significant GO terms for BSP:

| GO.ID     | Term                                                    | bimod. |
|-----------|---------------------------------------------------------|--------|
| GO:0060333| interferon-gamma-mediated signaling pathway             | 1      |
| GO:0002478| antigen processing and presentation of e...              | 1      |
| GO:0019884| antigen processing and presentation of e...              | 1      |
| GO:0048002| antigen processing and presentation of p...              | 1      |
| GO:ID              | Term                                | Count |
|-------------------|-------------------------------------|-------|
| GO:0019882        | antigen processing and presentation  | 1     |
| GO:0019886        | antigen processing and presentation of e... | 1     |
| GO:0002495        | antigen processing and presentation of p... | 1     |
| GO:0002504        | antigen processing and presentation of p... | 1     |
| GO:0034341        | response to interferon-gamma         | 1     |
| GO:0071346        | cellular response to interferon-gamma | 1     |
| GO:0031295        | T cell costimulation                 | 1     |
| GO:0031294        | lymphocyte costimulation             | 1     |
| GO:002768         | immune response-regulating cell surface ... | 1     |
| GO:002764         | immune response-regulating signaling pat... | 1     |
| GO:0050851        | antigen receptor-mediated signaling path... | 1     |
| GO:0002682        | regulation of immune system process   | 1     |
| GO:0022409        | positive regulation of cell-cell adhesio... | 1     |
| GO:0002253        | activation of immune response         | 1     |
| GO:0002429        | immune response-activating cell surface ... | 1     |
| GO:0002757        | immune response-activating signal transd... | 1     |
| GO:0002759        | immune response-activating signal transd... | 1     |
| GO:0050870        | positive regulation of T cell activation | 1     |
| GO:1903039        | positive regulation of leukocyte cell-ce... | 1     |
| GO:0042590        | antigen processing and presentation of e... | 1     |
| GO:0045806        | negative regulation of endocytosis     | 2     |
| GO:0050911        | detection of chemical stimulus involved ... | 3     |
| GO:0007608        | sensory perception of smell           | 3     |
| GO:0009593        | detection of chemical stimulus        | 3     |
| GO:0007606        | sensory perception of chemical stimulus | 3     |
| GO:0035459        | cargo loading into vesicle            | 3     |
| GO:0050906        | detection of stimulus involved in sensor... | 3     |
| GO:000838         | very long-chain fatty acid metabolic pro... | 4     |
| GO:0006732        | coenzyme metabolic process            | 4     |
| GO:0006417        | regulation of translation             | 5     |
| GO:0034248        | regulation of cellular amide metabolic p... | 5     |
| GO:0010608        | posttranscriptional regulation of gene e... | 5     |
| GO:0046597        | negative regulation of viral entry into ... | 6     |
| GO:0035455        | response to interferon-alpha          | 6     |
| GO:0035456        | response to interferon-beta           | 6     |
| GO:0046596        | regulation of viral entry into host cell | 6     |
| GO:0045071        | negative regulation of viral genome repl... | 6     |
| GO:1903901        | negative regulation of viral life cycle | 6     |
51 GO:0060337 type I interferon signaling pathway 6
52 GO:0071357 cellular response to type I interferon 6
53 GO:0034340 response to type I interferon 6
54 GO:0045069 regulation of viral genome replication 6
55 GO:0048525 negative regulation of viral process 6
56 GO:0019079 viral genome replication 6
57 GO:0046718 viral entry into host cell 6
58 GO:1903900 regulation of viral life cycle 6
59 GO:0030260 entry into host cell 6
60 GO:0044409 entry into host 6
61 GO:0051806 entry into cell of other organism involv... 6
62 GO:0051828 entry into other organism involved in sy... 6
63 GO:0043901 negative regulation of multi-organism pr... 6
64 GO:0034341 response to interferon-gamma 6
65 GO:0050792 regulation of viral process 6
66 GO:0051607 defense response to virus 6
67 GO:0051701 interaction with host 6
68 GO:0043903 regulation of symbiosis, encompassing mu... 6
69 GO:0009615 response to virus 6
70 GO:0051225 spindle assembly 7
71 GO:0007030 Golgi organization 7
72 GO:0007051 spindle organization 7
73 GO:0010256 endomembrane system organization 7
74 GO:0000226 microtubule cytoskeleton organization 7
75 GO:0007017 microtubule-based process 7
76 GO:0070925 organelle assembly 7
77 GO:0007010 cytoskeleton organization 7
78 GO:0007156 homophilic cell adhesion via plasma memb... 8
79 GO:0098742 cell-cell adhesion via plasma-membrane a... 8
80 GO:0098609 cell-cell adhesion 8
81 GO:0007155 cell adhesion 8
82 GO:0022610 biological adhesion 8
83 GO:0007416 synapse assembly 8
84 GO:0007267 cell-cell signaling 8
85 GO:0006355 regulation of transcription, DNA-templat... 9
86 GO:1903506 regulation of nucleic acid-templated tran... 9
87 GO:2001141 regulation of RNA biosynthetic process 9
88 GO:0006351 transcription, DNA-templated 9
89 GO:0097659 nucleic acid-templated transcription 9
90 GO:0032774 RNA biosynthetic process 9
91 GO:0051252 regulation of RNA metabolic process 9
92 GO:2000112 regulation of cellular macromolecule bio... 9
93 GO:0010556 regulation of macromolecule biosynthetic... 9
94 GO:0019219 regulation of nucleobase-containing comp... 9
95 GO:0031326 regulation of cellular biosynthetic proc... 9
96 GO:0034654 nucleobase-containing compound biosynthe... 9
15
143 GO:0048015 phosphatidylinositol-mediated signaling 13
144 GO:0048017 inositol lipid-mediated signaling 13
145 GO:0006882 cellular zinc ion homeostasis 14
146 GO:0055069 zinc ion homeostasis 14
147 GO:0010273 detoxification of copper ion 14
148 GO:1900169 stress response to copper ion 14
149 GO:0061687 detoxification of inorganic compound 14
150 GO:0097501 stress response to metal ion 14
151 GO:0071294 cellular response to zinc ion 14
152 GO:0071280 cellular response to copper ion 14
153 GO:0046916 cellular transition metal ion homeostasi... 14
154 GO:0071276 cellular response to cadmium ion 14
155 GO:0046688 response to copper ion 14
156 GO:0055076 transition metal ion homeostasis 14
157 GO:0072488 ammonium transmembrane transport 15
158 GO:0006089 lactate metabolic process 16
159 GO:0006882 cellular zinc ion homeostasis 17
160 GO:0055069 zinc ion homeostasis 17
161 GO:0006882 cellular zinc ion homeostasis 18
162 GO:0055069 zinc ion homeostasis 18

Significant GO terms for CONDOR

| GO.ID     | Term                                                                 | bimod |
|-----------|----------------------------------------------------------------------|-------|
| GO:0050852| T cell receptor signaling pathway                                      | 1     |
| GO:0050851| antigen receptor-mediated signaling path...                           | 1     |
| GO:0063555| regulation of transcription, DNA-templat...                           | 1     |
| GO:1903506| regulation of nucleic acid-templated tran...                         | 1     |
| GO:2001141| regulation of RNA biosynthetic process                               | 1     |
| GO:0060333| interferon-gamma-mediated signaling path...                           | 2     |
| GO:0002478| antigen processing and presentation of e...                           | 3     |
| GO:0019884| antigen processing and presentation of e...                           | 3     |
| GO:0048002| antigen processing and presentation of p...                           | 3     |
| GO:0019886| antigen processing and presentation of e...                           | 3     |
| GO:002495 | antigen processing and presentation of p...                           | 3     |
| GO:0002504| antigen processing and presentation of p...                           | 3     |
| GO:0019882| antigen processing and presentation                                     | 3     |
| GO:0031295| T cell costimulation                                                  | 3     |
| GO:0031294| lymphocyte costimulation                                              | 3     |
| GO:0060333| interferon-gamma-mediated signaling path...                           | 3     |
| GO:0050852| T cell receptor signaling pathway                                      | 3     |
| GO:0050870| positive regulation of T cell activation                              | 3     |
| GO:1903039| positive regulation of leukocyte cell-ce...                           | 3     |
| GO:0050778| positive regulation of immune response                               | 3     |
| GO:0002253| activation of immune response                                         | 3     |
| GO:0050851 | antigen receptor-mediated signaling pathway | 3 |
| GO:0022409 | positive regulation of cell-cell adhesion | 3 |
| GO:0071346 | cellular response to interferon-gamma | 3 |
| GO:0051251 | positive regulation of lymphocyte activation | 3 |
| GO:1903037 | regulation of leukocyte cell-cell adhesion | 3 |
| GO:0034341 | response to interferon-gamma | 3 |
| GO:0002696 | positive regulation of leukocyte activation | 3 |
| GO:0050863 | regulation of T cell activation | 3 |
| GO:0050867 | positive regulation of cell activation | 3 |
| GO:0007159 | leukocyte cell-cell adhesion | 3 |
| GO:0050776 | regulation of immune response | 3 |
| GO:0002429 | immune response-activating cell surface | 3 |
| GO:0002684 | positive regulation of immune system process | 3 |
| GO:0006955 | immune response | 3 |
| GO:0022407 | regulation of cell-cell adhesion | 3 |
| GO:0045087 | innate immune response | 3 |
| GO:0002768 | immune response-regulating cell surface | 3 |
| GO:0045785 | positive regulation of cell adhesion | 3 |
| GO:0002455 | humoral immune response mediated by cytokine | 3 |
| GO:0051249 | regulation of lymphocyte activation | 3 |
| GO:0019221 | cytokine-mediated signaling pathway | 3 |
| GO:0042110 | T cell activation | 3 |

### S5 Climate analysis details

Figure S7 shows the edge-error estimates we used to choose $\alpha$. Table S3 shows a summary of cross-correlations for each precipitation pixel from the two BSP bimodules.

### References

John F. Nash. Equilibrium points in n-person games. *Proceedings of the National Academy of Sciences*, 36(1):48–49, 1950. ISSN 0027-8424. doi: 10.1073/pnas.36.1.48. URL https://www.pnas.org/content/36/1/48.

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Yi-Hui Zhou, William T Barry, and Fred A Wright. Empirical pathway analysis, without permutation. *Biostatistics*, 14(3):573–585, 2013.
Figure S6: Out of 31 BSP bimodules that had genes on 3 or more chromosomes and SNPs on 2 or more chromosomes, we selected 9 bimodules that looked interesting. The bipartite graph for each bimodule is formed out of the essential edges (Section 5.3.3).
Figure S7: Average edge-error estimates for BSP results for the climate data based on 100 half-permutations (Section S2.3.1) for $\alpha$ ranging from 0.01 to 0.05. The edge-error estimates exceed 0.05 for the first time at $\alpha = 0.045$.

Table S3: Summary of the cross-correlations for each precipitation ($P$) pixel in the two BSP bimodules $A$ and $B$ from the climate data. Each entry shows the mean and standard deviation of the cross-correlations of each $P$ in the bimodule with other $T$ pixels in the same bimodule. Results show that all of the cross-correlations tend to be strong and positive.
