Groupwise cross-correlation mining in bi-view data

Finding stable groups of cross-correlated features with application to eQTL analysis

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Outline

1. Bimodules: groups of significant cross-correlated features in bi-view data
    - Bi-view data and Bimodules
    - Stable bimodules and the Bimodule Search Procedure (BSP)
2. Application to genomics
    - Introduction to eQTL analysis
    - Using BSP for groupwise eQTL analysis
3. Theoretical analysis of BSP
    - Asymptotics of BSP
    - Null correlation networks

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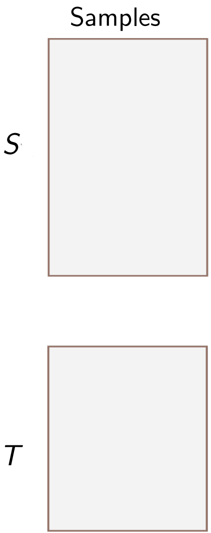
Bi-view data



Measurements of two types of features

$S = \{s_1, \dots, s_p\}$ & $T = \{t_1, \dots, t_q\}$

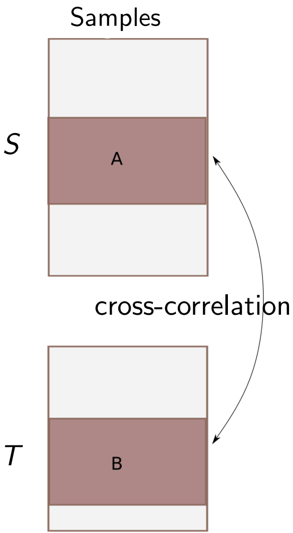
on n common samples. Typically $p, q \geq n$.

Examples

- Samples represent time and measure:
  S $=\{p$ temperature stations$\}$ and
  T $=\{q$ precipitation stations$\}$ worldwide.
- Samples represent habitats and measure
  S $=\{p$ environmental features$\}$ and
  T $=\{q$ microbial species$\}$ abundance.

How are features from S and T associated?

Exploratory problem of interest



We distinguish between two types of correlations

cross-correlation (CC) b/w features $s \in S$ and $t \in T$

intra-correlation b/w features $s, s' \in S$ or $t, t' \in T$.

Bimodule (rough definition)

(A, B) is a bimodule if

- $A \subseteq S$ and $B \subseteq T$
- A and B have significant aggregate CC.

Motivation to aggregate CCs

- Capture complex associations between feature groups A and B
- Improve power by amplifying weak signal

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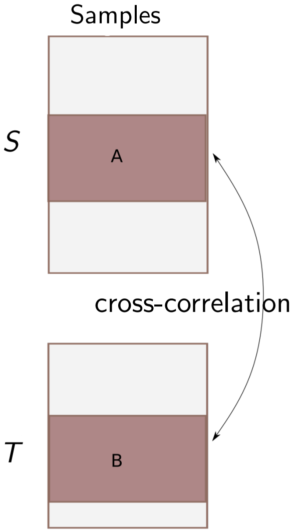

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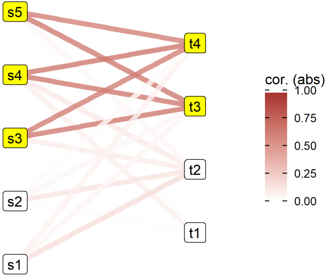
Network perspective

cross-correlation networks



$S = \{s_1, \ldots, s_5\},\ T = \{t_1, \ldots, t_4\}$

Weights: sample correlation (abs.)

Bimodules: communities in this network.

Example: $A = \{s_3, s_4, s_5\}$ and $B = \{t_3, t_4\}$.

Community (rough definition)

Nodes in a community are more correlated, on average, to nodes inside the community than to nodes outside.

Network perspective

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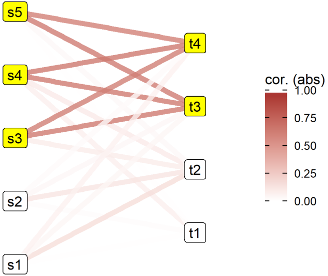

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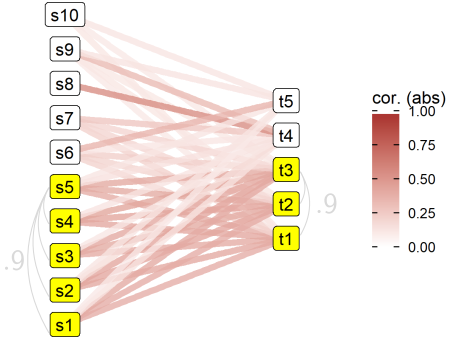
Almost cross-correlation communities: role of intra-correlations



(A, B) is a community in the CC network.

Likely to see this community by chance in random data? Yes

- Depending only on CC can mislead.
- Must account for *intra-correlations* while assessing bimodule significance.

$$A = \{s_1, \ldots, s_5\}, \; B = \{t_1, t_2, t_3\}$$

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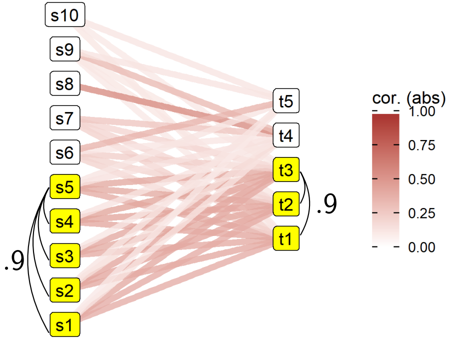

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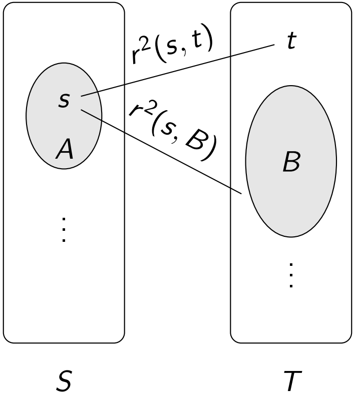
Stable Bimodules



$r(s,t)$: sample correlation of s, t

$r^2(A', B') \doteq \sum_{s \in A'} \sum_{t \in B'} r^2(s,t)$

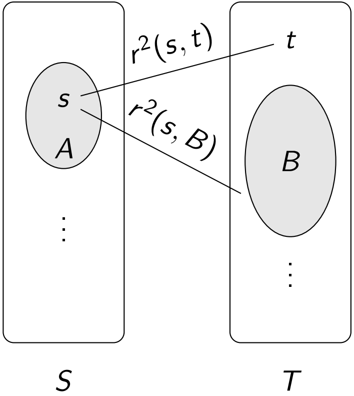
Stable bimodule (definition)

(A, B) is a *stable bimodule* if

$$A = \{s \in S \mid r^2(s,B) \text{ is significant}\}, \text{ and}$$
$$B = \{t \in T \mid r^2(A,t) \text{ is significant}\}.$$

- Recursive definition like a community based on aggregate correlations $r^2(s,B)$ & $r^2(A,t)$.
- Interest in connected stable bimodules.
- “Significance” quantified using hypothesis testing that accounts for inflation in variance of $r^2(s,B)$ due to intra-correlations.

Bimodule Search Procedure (BSP)



$r(s,t)$: sample correlation of s & t
$r^2(A,B) \doteq \sum_{s\in A} \sum_{t \in B} r^2(s,t)$

Stability is equivalent to $(A,B) = (\Gamma_S(B), \Gamma_T(A))$ where

$$\Gamma_S(B) \doteq \{s \in S \mid r^2(s,B) \text{ is significant}\}$$
$$\Gamma_T(A) \doteq \{t \in T \mid r^2(A,t) \text{ is significant}\}.$$

Hence, we can find stable bimodules by iterating

$$B_k = \Gamma_T(A_{k-1}); A_k = \Gamma_S(B_k) \quad k = 1, 2, \ldots$$

till sets don't change, starting from suitable $A_0 \subseteq S$.

Bimodule Search Procedure (BSP)

Starting from singletons $A_0 = \{s\} \subseteq S$, iterate the definition till fixed point is reached (or sets cycle).

Covergence on real data
Example of an iterative search

Quantifying significance using hypothesis testing

How to quantify Γ_T defined as:

$$\Gamma_T(A) \doteq \{t \in T \mid r^2(A,t) \text{ is significant}\}.$$

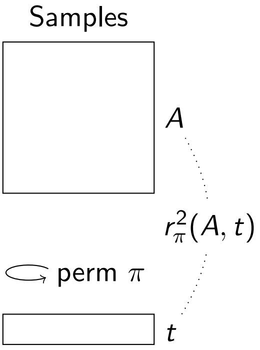
Steps

1. $\forall t \in T$ obtain p-value $p(A,t)$ from $r^2(A,t)$ (see right)
2. reject p-values using multiple-testing correction γ_α

$$\Gamma_T(A) = \{t \in T \mid p(A,t) \le \gamma_\alpha\}$$

at some level $\alpha \in (0,1)$.

Multiple testing correction The adaptive threshold γ_α chosen from [Benjamini and Yekutieli, 2001] controls FDR at α.

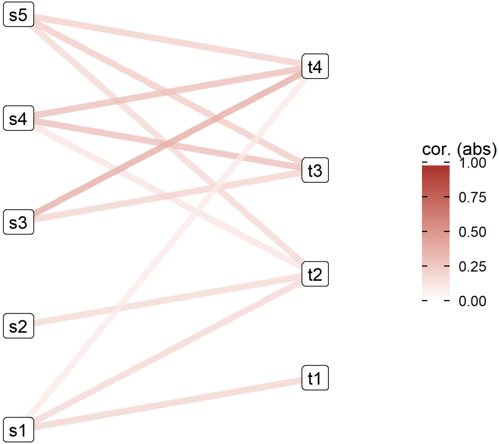


Permutation p-value

$$\mathbb{P}_\pi\left(r^2_\pi(A,t) \ge r^2_{obs}(A,t)\right)$$

Fast analytical approximation

Bimodule Search Procedure: example run



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$(A_1, B_1) = (A_2, B_2)$

Stable bimodule found.

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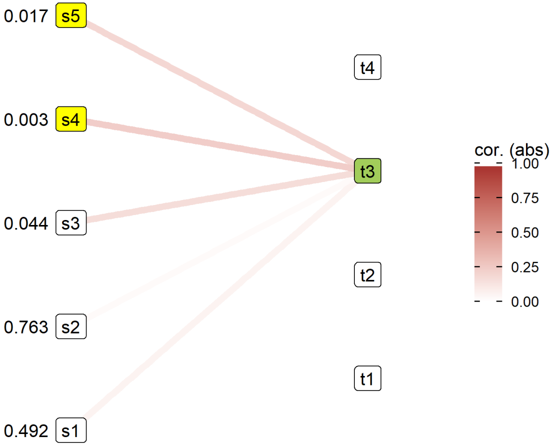

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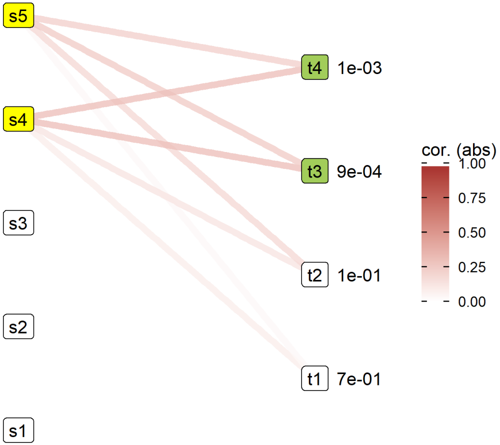

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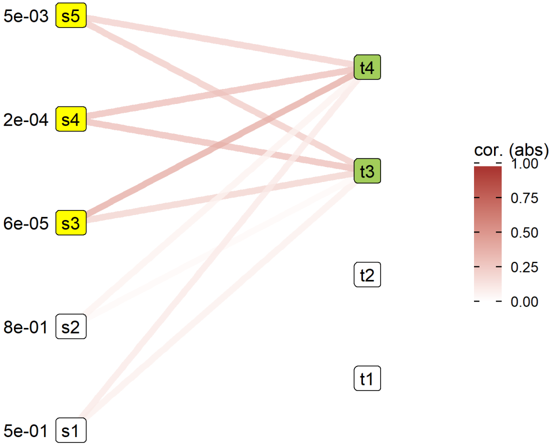

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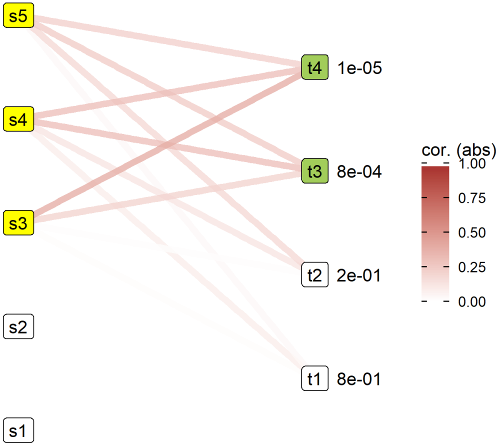

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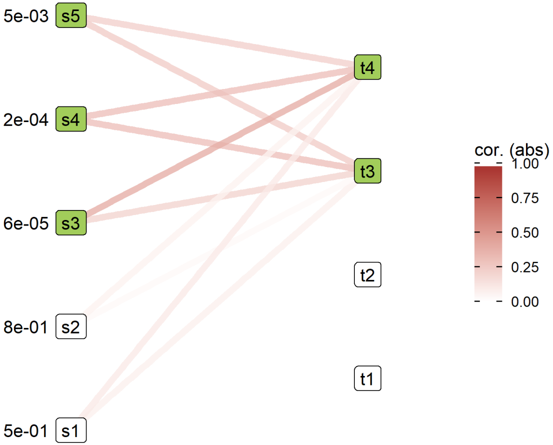

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Stable bimodule found.

Bimodule Search Procedure (pseudo code)

```
Initialize $A_0 = \{s\} \subseteq S$.

For $k = 0, \ldots, k_{max}$:

    • Calculate $p(A_k, t)$ for each $t \in T$
    • Let $B_k = \{t \in T \mid p(A_k, t) \leq \gamma_\alpha\}$ be indices rejected by BY($\alpha$).
    • Calculate $p(s, B_k)$ for each $s \in S$
    • Let $A_{k+1} = \{s \in S \mid p(s, B_k) \leq \gamma_\alpha\}$ be indices rejected by BY($\alpha$).

Output : $(A_{k_{max}}, B_{k_{max}})$ if it is non-empty ($A_{k_{max}} \neq \emptyset$) and a fixed point ($A_{k_{max}} = A_{k_{max}+1}$).
```

Bimodule Search Procedure (Software)

R package https://github.com/miheerdew/cbce.

Features

- Fast and parallel implementation (Analytical approximation to the permutation distribution + RCpp + Microsoft ROpen)
- Permutation based procedure to select primary parameter $\alpha \in (0, 1)$.
- Allows overlapping bimodules (and filtering for duplicates).
- Code tested and documented

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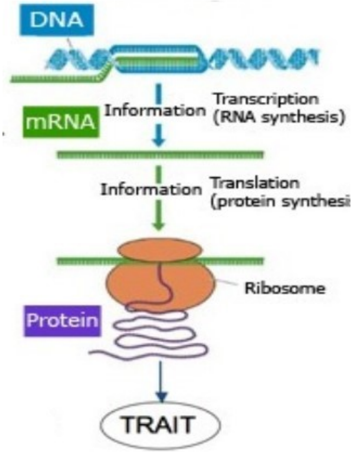
Concepts from genomics (simplified version)

genome.gov/genetics-glossary



Gene expression Process used by cells to assemble protein molecules based on a gene.

Gene A region of the genome that encodes for a protein; ∼20K genes identified in humans.

Single nucleotide polymorphism (SNP) A location on the genome that has a nucleotide variation within the population.

Genetic basis of gene expression Millions of SNPs are identified in humans. Which ones influence traits?

Expression quantitative trait loci (eQTL)

A genomic region (e.g. SNP) that influences the expression level of one or more genes.

Data from GTEx project (v8)

from gtexportal.org

NIH funded GTEx project

A large collection of multi-tissue eQTL data from donors.

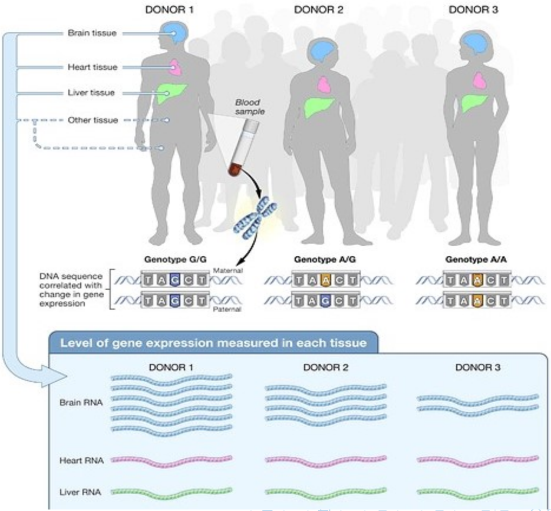
Individuals densely genotyped

Measurements for 4.9 million SNPs encoded as $\{0, 1, 2\}$ (MAF).

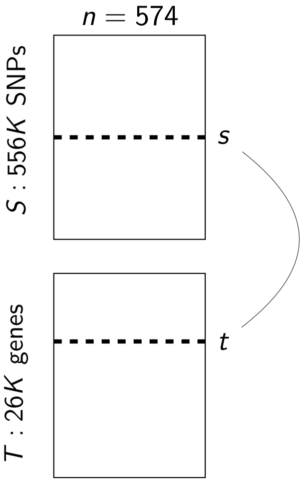
Expression measured in multiple tissues

RNA sequencing used to measure expression of genes.

Normalization, quality control, and covariate correction performed.



eQTL analysis for Thyroid data



Thyroid expression data from $n = 574$ donors for

$T = \{26K \text{ genes}\}$

$S = \{556K \text{ representative SNPs}\}$ selected using LD-pruning

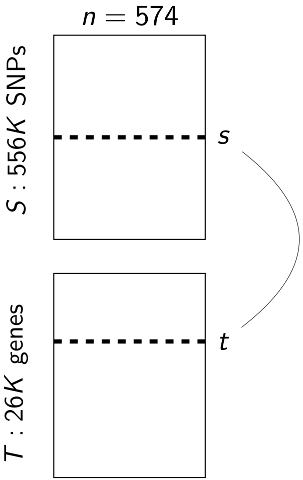
standard eQTL analysis

Find pairs $s \in S$ and $t \in T$ for which $r^2(s,t)$ is significant after *accounting for multiple-testing (MT)*.

Analysis-type	Pairs considered	MT correction
cis-analysis	local only	substantial
trans-analysis	all pairs ($\sim 10^{10}$)	huge

Distal eQTLs are harder to detect because of smaller effect size and huge MT burden.

eQTL analysis for Thyroid data



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Groupwise eQTL: find SNP-gene bimodules

Instead of pairs, search for SNP-gene bimodules, i.e.
bimodule (A, B), where $A \subseteq$ SNPs and $B \subseteq$ Genes are correlated.

Motivation:

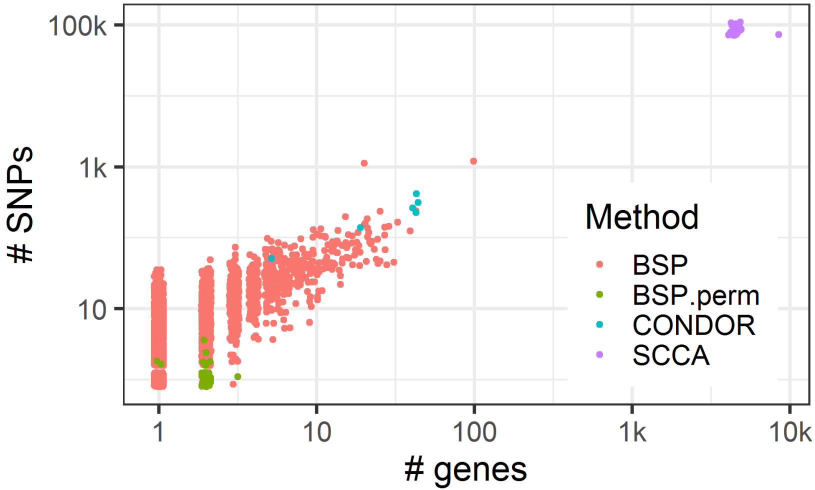
- Platig et al. (2016) find SNP-gene bimodules by community detection on a bipartite graph obtained from standard eQTL analysis.
- They show that bimodules may represent a group of SNPs that disrupt the functioning of gene regulatory networks and contribute to diseases
- Find bimodules using BSP by *aggregating effects* and *accounting for intra-correlations*.

Running BSP on Thyroid data

Highlights

- $\alpha = 0.03$ chosen using permutation.
- Most iterations lead to a (often empty) fixed point. search details
- Effective number of bimodules: 3305.
- Runtime 4.7 hrs (20-core/2.4 GHz).
- Bimod size range: 1-1000 SNPs & 1-100 genes. plot
- Median sizes: 7 SNPs and 1 gene.

Sizes of bimodules discovered by various methods



Obtaining networks from bimodules

A SNP-gene bimodule (A, B) has significant aggregate correlation between A and B.

But which edges $(s, t) \in A \times B$ are significant?

Threshold at $\tau \in (0, 1)$**:** $E_\tau(A, B) = \{(s, t) \mid r^2(s, t) \geq \tau^2,\ s \in A, t \in B\}$

How to choose τ?

Conservative estimate of strongest edges

Since a bimodule must be connected, choose the largest $\tau^* \in (0, 1)$ so that $(A \sqcup B, E_{\tau^*}(A, B))$ is a connected graph.

$E_{\tau^*}(A, B)$ are called *essential-edges* of the bimodule.

Thyroid network statistics

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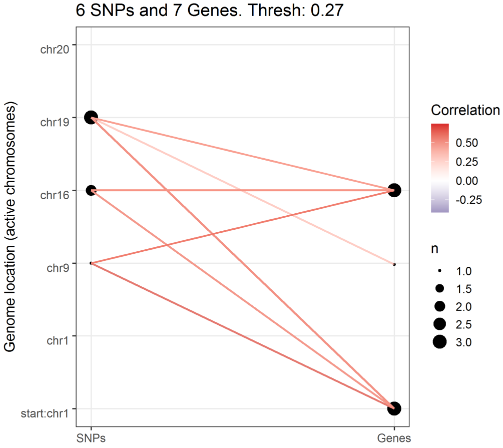
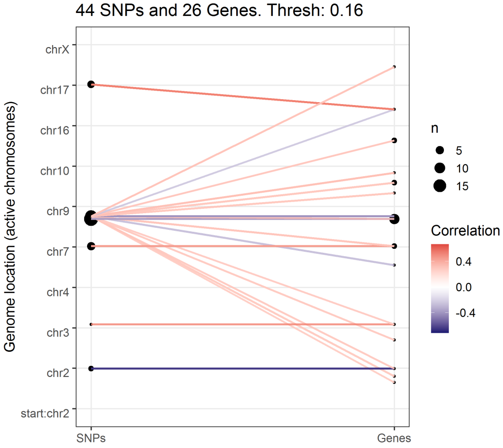
Thyroid network statistics

Essential-edge networks in GTEx thyroid data

examples from two bimodules





Comparing bimodules to standard eQTL analysis

Standard eQTL analysis performed using MatrixEQTL ($\alpha = 0.05$).

Bimodules find most standard eQTLs

84% of eQTLs from trans-analysis, and 51% of eQTLs from cis-analysis. But note

- bimodules find SNP-gene networks not just pairs, and
- cis-analysis improves power by restricting to local pairs.

New potential eQTLs from bimodules

Essential-edges from bimodules reveal 300 local and 8.8k distal SNP-gene pairs that

- are not detected by standard analysis,
- but show significance at the network level.

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Analysis of genomic locations of bimodules

Recall BSP does not use genomic locations of SNPs and Genes. Nevertheless

Proximity of SNPs and genes within the bimodule.

- Almost all (99.3%) bimodules have at least one local SNP-gene pair.
- In addition, almost half of the larger bimodules found gene and SNPs that had distal effects.

Chromosomal locations of SNPs and genes from bimodules.

- Bimodule SNPs and Genes distributed across all 23 chromosomes.
- Most small bimodules (95%) were restricted to single chromosome.
- Nearly half of the larger bimodules spanned 2-11 chromosomes each.

Enrichment of known gene sets in bimodules

The GO database (http://geneontology.org/) contains collection of gene sets known to be associated with biological functions.

- Consider our 145 bimodules that have 7 or more genes.
- We used Fisher's test to assess overlap of gene sets from these bimodules with GO sets.
- Gene sets from 18 bimodules had significant overlap with gene sets associated to known biological processes.
- But the associated function did not seem thyroid relevant.

Repeating above process with randomly chosen gene sets of the similar sizes did not detect significant association.

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Recipe for BSP asymptotics & population stable bimodules

- Suppose columns of the data matrix $D_n = \begin{bmatrix} \mathbb{X} \\ \mathbb{Y} \end{bmatrix}$ consist of i.i.d. realizations of a random vector $(X, Y)^t$ distributed as $\mathcal{N}_{p+q}(0, \Sigma)$.
- This defines a (random) BSP update function

$$\Gamma_n : 2^{S \cup T} \to 2^{S \cup T}$$

  whose fixed points are stable bimodules.
- How to establish of BSP asymptotics as $n \to \infty$?

Recipe:

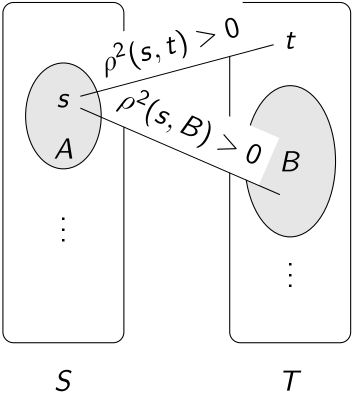
1. Identify $\Gamma : 2^{S \cup T} \to 2^{S \cup T}$ so that $\Gamma_n \xrightarrow{P} \Gamma$ pointwise.
2. Identify fixed points of Γ, and show they are reached by iterating Γ for k steps.

Lemma (BSP Asymptotics)

Assuming 1 & 2 above, with high probability as $n \to \infty$, the BSP on D_n will

- *find a stable bimodule within k iterations,*
- *and all the stable bimodules will be fixed points of Γ (population stable bimodules).*

Population picture in the large sample regime $n \gg \min(p, q)^2$



Population cross-correlation network with edge (s, t) if $\rho(s, t) \neq 0$.

In this regime:

- $\Gamma : 2^{S \cup T} \to 2^{S \cup T}$ is the neighborhood relation in the population cross-correlation network (PCCN).
- The (minimal & non-empty) fixed points of Γ are exactly the connected components of the PCCN.

Theorem (Dewaskar and Nobel, 2022)

When $n \gg \max(p, q)^2$, with high probability as $n \to \infty$, the BSP iterations starting from singleton set $\{s\} \subseteq S$ will reach a stable bimodule, which is a (non-trivial) connected component of the PCCN.

Null correlation network

Consider i.i.d. observations $X_1, \ldots, X_n \in \mathbb{R}^p$ of $\mathcal{N}_p(\mu, \Sigma_p)$.

Denote for $i, j \in \{1, \ldots, p\}$

$$S_n(i,j) : \text{sample covariance, and}$$
$$R_n(i,j) : \text{sample correlation.}$$

High-dimensional covariances

$S_n \to \Sigma_p$ as $n \to \infty$ for fixed p.

But global consistency may fail

$$\lambda(S_n) \not\to \lambda(\Sigma_p)$$

when $p \geq n$ (Jonstone, 2001).

Consider $\Sigma_p = I_p$ and sample correlation network

$$\mathcal{G}_{n,p} \doteq (V_p = \{1, \ldots, p\}, W_{n,p} = R_n).$$

Problem: Study asymptotic properties of $\mathcal{G}_{n,p}$.

Applications to *Correlation Network Mining*. E.g. methods that detect (in networks derived from Σ_p)

- Edges [Cai, 2017]
- Hubs [Hero and Rajaratnam, 2011]
- Cliques [Devroye, György, Lugosi, Udina 2011]
- Communities [Arias-Castro, Bubeck, Lugosi].

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Some properties of the random correlation network $\mathcal{G}_{n,p}$

Correlations and uniform points on the sphere. With $U_1, \ldots, U_p$ i.i.d. Unif$(\mathbb{S}^{n-2})$,

$$(R_n(i,j) : i,j \in [p]) \overset{d}{=} (\langle U_i, U_j \rangle : i,j \in [p]) \,.$$

Related work

1. $(n^{-1} \log p \to \beta)$ Max & min angle between points $\{U_i\}_{i=1}^{p}$ [Cai, Fan, Jiang, 2013]
2. $(n^{-1} \log p \to 0)$ Dense geometric graph formed by the points $\{U_i\}_{i=1}^{p}$ behaves like an ER random graph (e.g. [Basak, Bhamidi, Chakraborty, and Nobel, 2016]).

My interest

- Understand *stable modules* in $\mathcal{G}_{n,p}$. If $A \subseteq [p]$ is a stable module then $\{U_i\}_{i \in A}$ cluster around the mean $\bar{U}_A$.
- Study sizes of maximal clusters of $\{U_i\}_{i=1}^{p}$ to provide false discovery guarantees for the Module Search Procedure.

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Conclusion

We looked at

- **Bimodules:** statistically significant communities in bipartite correlation networks derived from multi-view data.
- **BSP**: iterative testing procedure to find *stable* bimodules.
- **Application to eQTL analysis**: using BSP to detect SNP-gene sub-networks and potentially new eQTLs.
- **Related theoretical problems**: Asymptotics as $n, (p \vee q) \to \infty$:
  1. BSP asymptotics via its update function.
  2. Asymptotics of the null correlation network via properties of uniformly distributed points on the sphere.

Thank you

Manuscript `https://arxiv.org/pdf/2009.05079.pdf`

Software `https://github.com/miheerdew/cbce`.

Collaborators

- John Palowitch (Google)
- Mark He (Columbia University)
- Andrew Nobel (UNC Statistics and Operations Research)
- Michael Love (UNC Biostatistics)

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- NIH R01 HG009125-01
- NSF DMS-1613072

We don't perform permutation: moment based analytical approximation

Permutation p-values Permuting the sample labels of t using π, define the p-value

$$p(A,t) \doteq \mathbb{P}_{\pi}\left(r_{\pi}^{2}(A,t) \geq r^{2}(A,t)\right),$$

which conditions on correlations in A.

Monte-Carlo estimation too slow. For faster analytical approximation to the null distribution of $T = r_{\pi}^{2}(A,t)$:

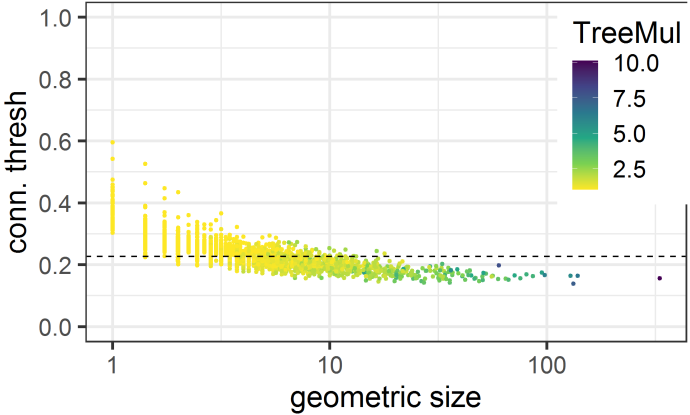
- Approximate the first three moments of T based on the eigenvalues of matrix X_A [Zhou, Gallins and Wright, 2019].
- Fit a shifted gamma distribution determined by the first three moments of T

BSP Thyroid search details

Search details

- 304K attempted searches.
- Majority (277K) give empty set in the first iteration.
- Few (20) did not terminate within 20 iterations.
- Remaining reached a fixed point in 20 iterations.
- 92.3% of these fixed points contained the seed singleton.

Network statistics from Thyroid



Smaller bimods are connected mainly by strong local associations (large τ^*). E_{τ^*} is tree-like. **Larger bimods** are connected by strong local + weak distal associations (small τ^*). E_{τ^*} has upto 10x more edges than a tree.