## Joint high-dimensional Bayesian variable and covariance selection with an application to eQTL analysis

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## Overview

- Variable and (inverse) covariance selections have been well-studied separately in high-dimensional problems.
- However, "joint" selection (or estimation) have not been studied until recently.
- We formulate a Bayesian technique and apply it to the analysis of expression quantitative trait loci (eQTL) analysis.
- Joint work with Bani K. Mallick, Texas A\&M University.


## Problem Formulation

- $\mathrm{n}=$ Sample size.
- $X=$ An $n \times p$ matrix of predictors.
- $Y=$ An $n \times q$ matrix of responses.
- We would like to regress $Y$ on $X$.
- Example A: For the same $n$ individuals, we might try to see how their SNP genotype $(\mathrm{X})$ affect their gene expressions $(\mathrm{Y})$.
- Example B: For the same $n$ individuals with cancer, we might try to see how their microRNA (X) affect their mRNA (Y) expressions.
- I have worked on A; I plan to begin work on B.


## Problem Formulation

- Consider the linear Gaussian regression model:

$$
\begin{aligned}
\mathbf{Y}_{n \times q} & =\mathbf{X}_{n \times p} \mathbf{B}_{p \times q}+\boldsymbol{\epsilon}_{n \times q}, \\
\boldsymbol{\epsilon}_{n \times q} & \sim \mathrm{MN}_{n \times q}\left(\mathbf{0}, \mathbf{I}_{n}, \boldsymbol{\Sigma}_{q \times q}\right), \\
\text { i.e. } \operatorname{Vec}\left(\boldsymbol{\epsilon}_{n \times q}\right) & \sim \mathrm{N}_{n q}\left(\mathbf{0}, \mathbf{I}_{n} \otimes \boldsymbol{\Sigma}_{q \times q}\right) .
\end{aligned}
$$

- The unknowns are $\mathrm{B}_{p \times q}$ and $\Sigma_{q \times q}$.
- The dimensions are $p q$ and $q(q+1) / 2$. Often much larger than $n$.
- Typical values: $n=100, p=500$ to $3000, q=100$.


## Basics of variable and covariance selection

- When $p$ and $q$ are larger than $n$, it becomes necessary to determine a sparse set of predictors and inverse covariance matrix elements.
- Variable selection: Find out the important predictors.
- Typical assumption: Errors are i.i.d (i.e., $\boldsymbol{\Sigma}_{q \times q}=\sigma^{2} \mathbf{I}_{q}$ ).
- Covariance selection: Find out the important inverse covariance matrix elements.
- For Gaussian models: $\boldsymbol{\Sigma}_{i, j}^{-1}=0 \Longleftrightarrow Y_{i} \perp Y_{j} \mid$ rest.
- Typical assumption: No covariates (i.e., $\mathbf{B}_{p \times q}=0$ ).
- We do a joint selection. This is being done only recently.


## Previous Work in variable selection

- Variable selection with i.i.d errors.
- Frequentist: Lasso (Tibshirani, 1996, JRSSB) and its various extensions using $\ell_{1}$ penalty.
- Bayesian: Stochastic Search Variable Selection (George and McCulloch, 1997, JASA) and its extensions using sparsity prior.


## Previous Work in covariance selection and estimation

- (Inverse) Covariance selection in Gaussian graphical model with zero mean.
- Frequentist: Meinshausen and Bühlmann (2006, Ann. Stat.), Graphical Lasso (Friedman et al, 2008, Biostatistics), Bickel and Levina (2008, Ann. Stat.) etc.
- Bayesian: Carvalho and West (2007, Biometrika) etc. primarily using hyper-inverse Wishart type of priors.


## Joint modeling of mean and covariance for Seemingly Unrelated Regression

- In a Seemingly Unrelated Regression setting, one might be interested in modeling "both" the mean and the covariance structure.
- Rothman et al. (2010, JCGS) make a frequentist attempt at joint modeling with the MRCE approach. (essentially an iterative approach with alternating lasso() and glasso() steps).
- Yin and Li (2011, Ann. Appl. Stat.) apply a similar approach to gene expression and SNP data.
- Bhadra and Mallick (Biometrics, under revision) take a Bayesian approach.


## Model conditional on indicators

- Consider the model conditional upon indicators $\gamma$ and $\mathbf{G}$.

$$
\mathbf{Y}=\mathbf{X}_{\gamma} \mathbf{B}_{\gamma, \mathbf{G}}+\boldsymbol{\epsilon}, \quad \boldsymbol{\epsilon} \sim \operatorname{MN}\left(\mathbf{0}, \mathbf{I}_{n}, \boldsymbol{\Sigma}_{\mathbf{G}}\right)
$$

- Dimension of $\mathbf{X}_{\gamma}=n \times p_{\gamma}$; dimension of $\mathbf{B}_{\gamma, \mathbf{G}}=p_{\gamma} \times q$; dimension of $\boldsymbol{\Sigma}_{\mathbf{G}}=q \times q$.
- $\gamma_{i}=1 \Rightarrow \mathbf{B}_{i,} \neq 0 ; p_{\gamma}=\sum_{i=1}^{p} \gamma_{i}$.
- $\mathbf{G}$ is a decomposable graph where $\mathbf{G}_{i, j}=1 \Rightarrow \boldsymbol{\Sigma}_{i, j}^{-1} \neq 0$ with $i \neq j ; i, j=1, \ldots, q$.


## Model conditional on indicators: Toy example

- Consider the model conditional upon indicators $\gamma$ and $\mathbf{G}$.

$$
\mathbf{Y}=\mathbf{X}_{\gamma} \mathbf{B}_{\gamma, \mathbf{G}}+\boldsymbol{\epsilon} ; \quad \boldsymbol{\epsilon} \sim \operatorname{MN}\left(\mathbf{0}, \mathbf{I}_{n}, \boldsymbol{\Sigma}_{\mathbf{G}}\right)
$$

- For example, say $p=q=4$. Then $\gamma=(1,0,1,0)$ means only the first and the third predictors are important.
- Let's say G is:

$$
\left[\begin{array}{llll}
1 & 1 & 0 & 0 \\
1 & 1 & 0 & 0 \\
0 & 0 & 1 & 0 \\
0 & 0 & 0 & 1
\end{array}\right]
$$

This means $\boldsymbol{\Sigma}_{1,2}^{-1} \neq 0$, the other off-diagonal terms are 0 .

## Decomposable (or triangulated) graphs



- No chordless cycle of length $\geq 3$.
- Cliques (i.e., the connected components) and separators (i.e., the parts in common between two cliques) can be found in polynomial time (NP-complete for general graphs).
- The overall density splits as:
$f(y)=\prod_{j=1}^{k} f\left(y c_{j}\right) / \prod_{j=2}^{k} f\left(y_{s_{j}}\right)$.


## Bayesian hierarchical model

$$
\begin{aligned}
\left(\mathbf{Y}-\mathbf{X}_{\gamma} \mathbf{B}_{\gamma, \mathbf{G}}\right) \mid \mathbf{B}_{\gamma, \mathbf{G}}, \boldsymbol{\Sigma}_{\mathbf{G}} & \sim \operatorname{MN}_{n_{\times q}}\left(\mathbf{0}, \mathbf{I}_{n}, \boldsymbol{\Sigma}_{\mathbf{G}}\right), \\
\mathbf{B}_{\gamma, \mathbf{G}} \mid \boldsymbol{\gamma}, \boldsymbol{\Sigma}_{\mathbf{G}} & \sim \operatorname{MN}_{p_{\gamma} \times \boldsymbol{q}}\left(\mathbf{0}, \mathbf{c}_{p_{\gamma}}, \boldsymbol{\Sigma}_{\mathbf{G}}\right), \\
\boldsymbol{\Sigma}_{\mathbf{G}} \mid \mathbf{G} & \sim \operatorname{HiW}_{\mathbf{G}}\left(b, d \mathbf{I}_{q}\right), \\
\gamma_{i} & \stackrel{\text { i.i.d }}{\sim} \operatorname{Ber}\left(w_{\gamma}\right) \text { for } i=1, \ldots, p, \\
\mathrm{G}_{k} & \stackrel{\text { i.i.d }}{\sim} \operatorname{Ber}\left(w_{G}\right) \text { for } k=1, \ldots, q(q-1) / 2, \\
w_{\gamma}, w_{G} & \sim \operatorname{Uniform}(0,1) .
\end{aligned}
$$

## Mariginalization of $B_{\gamma, \mathbf{G}}$ and $\boldsymbol{\Sigma}_{\mathbf{G}}$

- Remember from the last slide

$$
\begin{aligned}
\epsilon & \sim \operatorname{MN}_{n \times q}\left(\mathbf{0}, \mathbf{I}_{n}, \boldsymbol{\Sigma}_{\mathbf{G}}\right), \\
\mathbf{B}_{\gamma, \mathbf{G}} \mid \gamma, \Sigma_{\mathbf{G}} & \sim \operatorname{MN}_{p_{\gamma} \times q}\left(\mathbf{0}, c \mathbf{I}_{p_{\gamma}}, \boldsymbol{\Sigma}_{\mathbf{G}}\right) . \\
\Rightarrow \mathbf{X}_{\gamma} \mathbf{B}_{\gamma, \mathbf{G}} \mid \gamma, \boldsymbol{\Sigma}_{\mathbf{G}} & \sim \operatorname{MN}_{n \times q}\left(0, c\left(\mathbf{X}_{\gamma} \mathbf{X}_{\gamma}^{\prime}\right), \boldsymbol{\Sigma}_{\mathbf{G}}\right) . \\
\Rightarrow \mathbf{Y} \mid \gamma, \boldsymbol{\Sigma}_{\mathbf{G}} & \sim \mathrm{MN}_{n \times q}\left(0, \mathbf{I}_{n}+c\left(\mathbf{X}_{\gamma} \mathbf{X}_{\gamma}^{\prime}\right), \boldsymbol{\Sigma}_{\mathbf{G}}\right) .
\end{aligned}
$$

- Define $\mathbf{T}=\mathbf{A Y}$ where $\mathbf{A A}^{\prime}=\left(\mathbf{I}_{n}+c\left(\mathbf{X}_{\gamma} \mathbf{X}_{\gamma}^{\prime}\right)\right)^{-1}$.

$$
\begin{aligned}
\Rightarrow \mathbf{T} \mid \boldsymbol{\gamma}, \boldsymbol{\Sigma}_{\mathbf{G}} & \sim \operatorname{MN}_{n \times q}\left(\mathbf{0}, \mathbf{I}_{n}, \boldsymbol{\Sigma}_{\mathbf{G}}\right) \\
\boldsymbol{\Sigma}_{\mathbf{G}} \mid \mathbf{G} & \sim \operatorname{HIW}_{\mathbf{G}}\left(b, d \mathbf{I}_{q}\right) \\
\Rightarrow \mathbf{T} \mid \gamma, \mathbf{G} & \sim \operatorname{HMT}_{\mathbf{G}}\left(b, \mathbf{I}_{n}, d \mathbf{I}_{q}\right)
\end{aligned}
$$

## The marginalized model

- After the marginalization of $\mathbf{B}_{\gamma, \mathbf{G}}$ and $\boldsymbol{\Sigma}_{\mathbf{G}}$, the resultant distribution is a "hyper matrix t ".
- This is a special type of "t-distribution" whose density splits over cliques and separators, given the graph.
- The marginalization has now resulted in a collapsed Gibbs sampler: need to sample only two quantities ( $\gamma$ and $\mathbf{G}$ ) instead of four $\left(\mathbf{B}_{\gamma, \mathbf{G}}, \boldsymbol{\Sigma}_{\mathbf{G}}, \gamma\right.$ and $\left.\mathbf{G}\right)$.
- Terms that were integrated out can always be sampled at the posterior, since we are working in a conjugate framework.


## MCMC for $\gamma$ given $\mathbf{G}$ and $\mathbf{T}$

(1) Given the current $\gamma$, propose $\gamma^{*}$ by either (a) changing a non-zero entry in $\gamma$ to zero with probability $\left(1-\alpha_{\gamma}\right)$ or (b) changing a zero entry in $\gamma$ to one, with probability $\alpha_{\gamma}$.
(2) Calculate $f\left(\mathbf{t} \mid \gamma^{*}, \mathbf{G}\right)$ and $f(\mathbf{t} \mid \gamma, \mathbf{G})$ where $f$ denotes the HMT density.
(3) Jump from $\gamma$ to $\gamma^{*}$ with probability

$$
r\left(\gamma, \gamma^{*}\right)=\min \left\{1, \frac{f\left(\mathbf{t} \mid \gamma^{*}, \mathbf{G}\right) p\left(\gamma^{*}\right) q\left(\gamma \mid \gamma^{*}\right)}{f(\mathbf{t} \mid \gamma, \mathbf{G}) p(\gamma) q\left(\gamma^{*} \mid \gamma\right)}\right\}
$$

## MCMC for $\mathbf{G}$ given $\gamma$ and $\mathbf{T}$

(1) Given the current G, propose $\mathbf{G}^{*}$ by either (a) changing a non-zero edge in $\mathbf{G}$ to zero with probability $\left(1-\alpha_{G}\right)$ or (b) changing a zero entry in $\mathbf{G}$ to one, with probability $\alpha_{G}$.
(2) Calculate $f\left(\mathbf{t} \mid \gamma, \mathbf{G}^{*}\right)$ and $f(\mathbf{t} \mid \gamma, \mathbf{G})$ where $f$ denotes the HMT density.
(3) Jump from $\mathbf{G}$ to $\mathbf{G}^{*}$ with probability

$$
r\left(\mathbf{G}, \mathbf{G}^{*}\right)=\min \left\{1, \frac{f\left(\mathbf{t} \mid \mathbf{G}^{*}, \gamma\right) p\left(\mathbf{G}^{*}\right) q\left(\mathbf{G} \mid \mathbf{G}^{*}\right)}{f(\mathbf{t} \mid \mathbf{G}, \gamma) p(\mathbf{G}) q\left(\mathbf{G}^{*} \mid \mathbf{G}\right)}\right\}
$$

## Regeneration of $\mathbf{B}_{\gamma, \mathbf{G}}$ in the posterior

- $\mathbf{B}_{\gamma, \mathbf{G}}$ is the $p_{\gamma} \times q$ matrix of regression coefficients.
- By marginalizing it out we lose the association between the SNPs and expression levels necessary for an eQTL analysis.
- However, due to the conjugate structure, can be regenerated in the posterior conditional on $\hat{\gamma}$ and $\hat{\mathbf{G}}$.
- Generate $\boldsymbol{\Sigma}_{G} \mid \mathbf{Y}, \mathbf{B}_{\gamma, \mathbf{G}}, \gamma, G$ from $\operatorname{HIW}_{G}\left\{b+n, d \mathbf{l}_{q}+\left(\mathbf{Y}-\mathbf{X}_{\gamma} \mathbf{B}_{\gamma, \mathbf{G}}\right)^{\prime}\left(\mathbf{Y}-\mathbf{X}_{\gamma} \mathbf{B}_{\gamma, \mathbf{G}}\right)\right\}$.
- Generate $\mathbf{B}_{\gamma, \mathbf{G}} \mid \mathbf{Y}, \boldsymbol{\Sigma}_{G}, \gamma, G$ from $\operatorname{MN}_{p_{\gamma} \times q}\left\{\left(\mathbf{X}_{\gamma}^{\prime} \mathbf{X}_{\gamma}+c^{-1} \mathbf{I}_{p_{\gamma}}\right)^{-1} \mathbf{X}_{\gamma}^{\prime} \mathbf{Y},\left(\mathbf{X}_{\gamma}^{\prime} \mathbf{X}_{\gamma}+c^{-1} \mathbf{I}_{p_{\gamma}}\right)^{-1}, \boldsymbol{\Sigma}_{G}\right\}$.


## Simulation study 1

- We choose $p=498, q=300$ and $n=120$.
- The eleven true predictors are $\{30,40,57,62,161,239,269$, 322, 335, 399, 457\}.
- True adjacency matrix for $\mathbf{G}$ is shown below.



## Results: Posterior probabilites




- Left: Posterior probabilities for $\gamma$, true variables circled in red.
- Right: Posterior probabilities for G, compare with true graph.


## Results: Does joint selection help over individual selection of variables and covariances?



- Left: ROC curve for $\gamma$, solid line: joint estimation, broken line: diagonal graph.
- Right: ROC curve for G, solid line: joint estimation, broken line: zero mean model.


## Simulation study 2

- We choose $p=498, q=100$ and $n=120$.
- Consider 3 true predictors \{30, 161, 239\}. Associations between predictors and responses are generated according to following table:

| SNP $(\tilde{p})$ | Transcript $\left(\tilde{q}_{p}\right)$ |
| :---: | :---: |
| 30 | $1-20,71-80$ |
| 161 | $17-20$ |
| 239 | $1-20,71-80$ |

- Corresponding elements of $\mathbf{B}$ have sd 0.3.
- Rest of the responses are simulated from noise with sd 0.1.


## Simulation study 2: The true graph



## Results: Posterior probabilites




- Left: Posterior probabilities for $\gamma$, true variables circled in red.
- Right: Posterior probabilities for G, with a cutoff on the posterior probabilities of edge inclusion set to 0.4


## Results: Association analysis between SNPs and transcripts




- Left: Association of SNP 161 with all the 100 transcripts, showing enhanced association for transcripts 17-20.
- Right: association of SNP 239 with all the 100 transcripts, showing enhanced association for transcripts 1-20 and 71-80.


## eQTL Analysis

- Essentially, this is a regression problem where $\mathbf{X}=$ An $n \times p$ matrix of SNPs (Single Neucleotide Polymorphisms) and $\mathbf{Y}=$ An $n \times q$ matrix of gene expression data, for the same set of $n$ individuals.
- An eQTL analysis tries to infer the $p \times q$ matrix $\mathbf{B}$, trying to associate genetic variability to the gene expressions.
- It's long been known that the genes are a part of a regulatory/interaction nework.
- Statistically speaking, it is unreasonable to assume independence among the $q$ traits.


## Application to human eQTL analysis

- $\mathrm{n}=60$ unrelated individuals of Northern and Western European ancestry from Utah (CEU).
- SNP data publicly available from International Hapmap project (http://hapmart.hapmap.org).
- A total of $p=3125$ SNPs found on 5' UTR of mRNA with minor allele frequency $\geq 0.1$
- Gene expression data are also publicly available from the Sanger Institute website (ftp://ftp.sanger.ac.uk/pub/genevar).
- We work with $\mathrm{q}=100$ most variable transcripts out of a total of 47293.


## Results

- Controlling for FDR at $5 \%$ level yields 8 globally significant SNPs and 38 non-zero inverse covariance matrix elements.
- Yields a total of 43 significant associations.
- Chen et al. (2008, Bioinformatics) detected a slightly higher number of associations by considering both 3' and 5' UTRs simultaneously.
- Yields a total of 55 significant edges.


## Open questions and current investigations

- Could the technique be extended to more flexible models, e.g. models that can handle a nonlinear mean function?
- Is it possible to show simultaneous variable and graph selection consistency?
- What about non-Bayesian approaches?


## References

(1) Bhadra, A. and Mallick, B. K. (2012). Joint high-dimensional Bayesian variable and covariance selection with an application to eQTL analysis. (under revision, Biometrics)
(2) Dawid, A. P. and Lauritzen, S. L. (1993). Hyper Markov laws in the statistical analysis of decomposable graphical models. (Ann. Statist. 21, 1272-1317)
(3) Lauritzen, S. L. (1996). Graphical Models. (Oxford University Press)

