Approximate Bayesian inference in high-dimensional applications

Barbara E Engelhardt

Department of Computer Science
Center for Statistics and Machine Learning
Princeton University

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Motivation and question

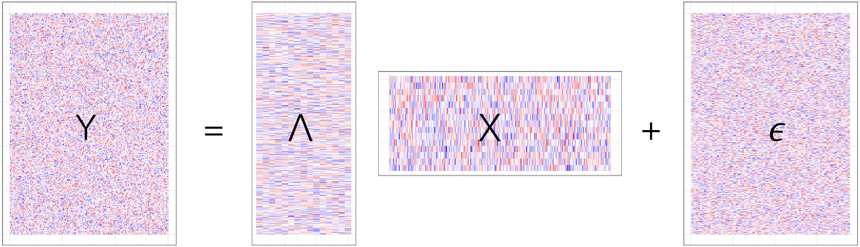
Variational inference is not robust for complex hierarchical models fitted to high-dimensional data

- how can we combine results among different VI estimates?
- what can we say about the estimates from these aggregations?

What problem are we trying to solve?

- Main goal here is parameter inference, not prediction
- Two local optima with the same evidence lower bound (elbo) are not equivalent, because they highlight different signals in the data

Factor analysis: linear map of high dimensional data



Matrix Y is observations of p features over n samples (this is the transpose of classical FA, for data reasons)

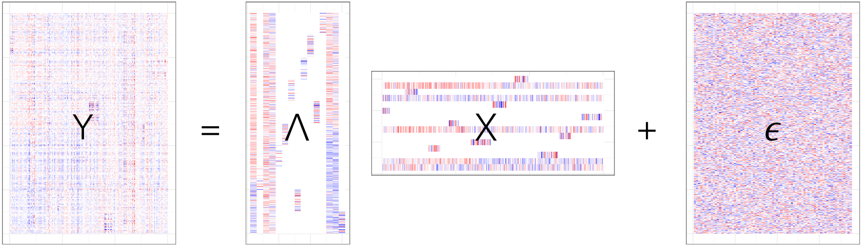
- *Factor analysis*: project matrix Y onto a linear subspace Λ (*loadings*) using weights X (*factors*), assuming Gaussian noise ϵ:

$$Y_{j,i} \sim \mathcal{N}\left(\sum_{k=1}^{K} \Lambda_{j,k} X_{k,i}, \psi_j^{-1}\right)$$

Bayesian biclustering for genomic data

Contributions to variation in gene expression levels are

- sparse & dense in genes: small sets of genes may be affected by covariates
- sparse & dense in samples: genotype, cell type, sex, smoking status



We build a model for *biclustering*, creating non-disjoint clusters in both genes and samples

Bayesian biclustering model

We put a *three parameter beta* prior on the factors and loadings:

$$
\begin{aligned}
\varrho &\sim \mathcal{TPB}(e, f, \nu), \\
\zeta_k &\sim \mathcal{TPB}\left(c, d, \frac{1}{\varrho} - 1\right) \\
\varphi_{i,k} &\sim \mathcal{TPB}\left(a, b, \frac{1}{\zeta_k} - 1\right), \\
\Lambda_{i,k} &\sim \mathcal{N}\left(0, \frac{1}{\varphi_{i,k}} - 1\right),
\end{aligned}
$$

and similarly for factors $\mathbf{X}$ to induce sparsity.

Bayesian biclustering model: Regularization

Regularization on **X** (structurally identical to regularization for Λ), can be written as *[Armagan, Dunson, Clyde 2011]*:

$$
\begin{aligned}
\varphi &\sim \mathcal{G}a(f_X, \xi), \\
\chi &\sim \mathcal{G}a(e_X, \varphi), \\
\kappa_k &\sim \mathcal{G}a(d_X, \chi), \\
\omega_k &\sim \mathcal{G}a(c_X, \kappa_k) \\
\rho_{k,i} &\sim \mathcal{G}a(b_X, \omega_k), \\
\sigma_{k,i} &\sim \pi \mathcal{G}a(a_X, \rho_{k,i}) + (1 - \pi)\delta(\omega_k) \\
x_{k,i} &\sim \mathcal{N}(0, \sigma_{k,i}),
\end{aligned}
$$

Bayesian biclustering model

To allow both sparse and dense factors and loadings, we use a two-component mixture:

$$\varphi_{i,k} \sim \pi \mathcal{TPB}\left(a, b, \frac{1}{\zeta_k} - 1\right) + (1-\pi)\delta(\zeta_k),$$

where the indicator variable z_k has a beta Bernoulli distribution:

$$\begin{aligned} \pi|\alpha, \beta &\sim Be(\alpha, \beta) \\ z_k|\pi &\sim \text{Bern}(\pi), k = \{1, \ldots, K\}. \end{aligned}$$

Recovering gene networks from factor models

Marginalizing over **X**, FA becomes regularized covariance estimation:

$$\begin{aligned}\mathbf{Y}_i &\sim \mathcal{N}_p(0, \Omega) \text{ for } i = 1, \ldots, n \\ \Omega &= \Lambda \Sigma \Lambda^T + \Psi,\end{aligned}$$

where Σ is the $K \times K$ covariance matrix for **X**.

- If we invert Ω, we recover the precision matrix for the genes
- (Normalized) precision matrix represents partial correlation of every gene pair: $cor(x_j, x_{j'} | x_{\neg j, j'})$
- Thresholding the precision matrix (FDR), we recover a Gaussian Markov random field across genes

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Context-specific gene co-expression networks

We can subset the components in the biclustering model to recover interesting types of co-expression networks:

$$\begin{aligned} A &\subseteq \{1, \ldots, K\} \\ \Omega_A &= \Lambda_A \Sigma_{A,A} \Lambda_A^T + \Psi. \end{aligned}$$

If we invert Ω_A, we recover the precision matrix for the genes that load onto the components in A.

We choose to subset A as follows:

- *Ubiquitous networks*: factor is dense across samples
- *Differential networks*: factor modes across two sample subtypes differ
- *Context-specific networks*: factor is non-zero only for sample subtype

Variational expectation maximization

The variational approximation of $p(\mathbf{\Lambda}, \mathbf{X}, \mathbf{z}, \mathbf{o}, \mathbf{\Theta}|\mathbf{Y})$ is written as:

$$q(\mathbf{\Lambda}, \mathbf{X}, \mathbf{z}, \mathbf{o}, \mathbf{\Theta}) = p(\mathbf{\Lambda}|\mathbf{z}, \mathbf{\Theta}_{\mathbf{\Lambda}})p(\mathbf{X}|\mathbf{o}, \mathbf{\Theta}_{\mathbf{X}})p(\mathbf{z}|\mathbf{\Theta}_{\mathbf{\Lambda}})p(\mathbf{o}|\mathbf{\Theta}_{\mathbf{X}})p(\mathbf{\Theta}_{\Lambda})p(\mathbf{\Theta}_{X})$$

where $\mathbf{\Theta}_{\Lambda}$ and $\mathbf{\Theta}_{X}$ denote the parameters of $\mathbf{\Lambda}$ and $\mathbf{X}$, respectively. Then,

$$\begin{aligned}
p(\mathbf{\Lambda}, \mathbf{z}, \mathbf{\Theta}_{\mathbf{\Lambda}}) &= p(\mathbf{\Lambda}|\mathbf{z}, \mathbf{\Theta}_{\mathbf{\Lambda}})p(\mathbf{z}|\mathbf{\Theta}_{\mathbf{\Lambda}})p(\mathbf{\Theta}_{\Lambda}) \\
&= \left[\prod_{j=1}^{p}\prod_{k=1}^{K}\mathcal{N}(\Lambda_{j,k}|\theta_{j,k})\mathcal{G}a(\theta_{j,k}|a, \delta_{j,k})\mathcal{G}a(\delta_{j,k}|b, \phi_k)\right]^{\mathbb{1}_{z_k=1}} \\
&\quad \times \left[\prod_{j=1}^{p}\prod_{k=1}^{K}\mathcal{N}(\Lambda_{j,k}|\phi_k)\right]^{\mathbb{1}_{z_k=0}} \left[\prod_{k=1}^{K}\mathcal{B}ern(z_k|\pi)\right]\mathcal{B}eta(\pi|\alpha, \beta) \\
&\quad \times \left[\prod_{k=1}^{K}\mathcal{G}a(\phi_k|c, \tau_k)\mathcal{G}a(\tau_k|d, \eta)\right]\mathcal{G}a(\eta|e, \gamma)\mathcal{G}a(\gamma|f, \nu).
\end{aligned}$$

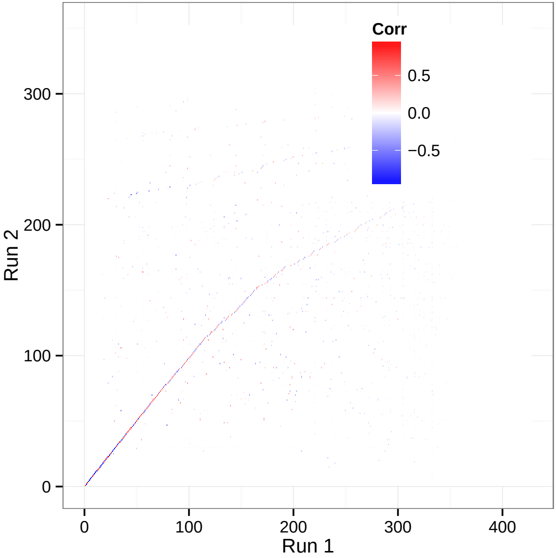
Variational expectation maximization

- random initialization
  - generate parameters from variational approximation
  - specifically, generate $\mathbf{\Lambda} \sim \mathcal{N}(0, I)$
- iterate until convergence
  - E-step
    - compute the expected value of $z_{1:K}$
    - compute the expected value of $\mathbf{X}$
    - compute the expected value of $\mathbf{X}\psi_{j,j}^{-1}\mathbf{X}^T$
  - variational M-step: coordinate ascent variational inference
    - $\hat{\mathbf{\Theta}}_\Lambda = arg \min_{q(\Theta_\Lambda)} KL(q(\mathbf{\Theta}_\Lambda)||p(\mathbf{\Theta}_\Lambda|\mathbf{Y}))$
    - convergence defined by evidence lower bound:

$$elbo(q) = E[\log p(Y, \Theta)] + E[\log q(\Theta)]$$

    - specifically, update Λ in a greedy way

VEM results not robust to random initializations



Variational EM: first try to robustify results

- We run variational EM 1,000 times with random restarts.
- We build a network from the results from each run
- We let each network "vote" on the network edges: edge is in the network if number of models that it appears in is $\geq r$

Related ideas in combining across approximate marginals

- Bagging (bootstrap aggregation) *[Breiman 1996]*
- Firefly Monte Carlo *[Maclaurin & Adams 2014]*
- Median posterior *[Minsker, Srivastava, Lin, Dunson 2014]*
- Structured stochastic variational inference *[Hoffman & Blei 2015]*
- Intersection of sparse factors across tensor decomposition runs *[Hore et al. 2016]*

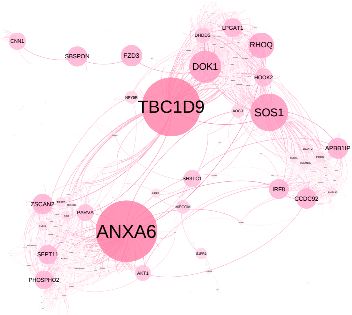
Tissue-specific networks

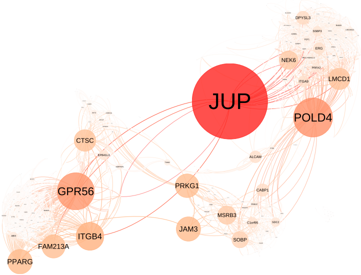
Adipose-specific network

- *RHOQ* involved in glucose uptake
- *ANXA6* reduces cholesterol
- *DOK1* mediates diet-induced obesity

Artery-specific network

- *JUP-81* atherosclerotic plaques
- *PPAR gamma* lipid metabolism and atherogenesis
- *ETS* arterial specification





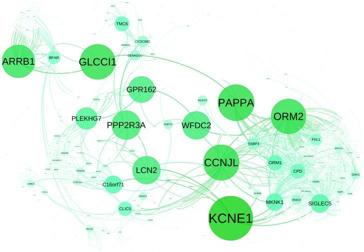
Tissue-specific networks

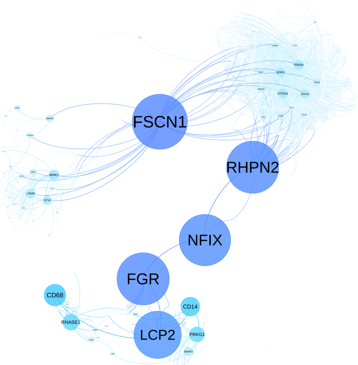
Lung-specific network

- *KCNE1* lung lobectomy responsive
- *PAPPA* lung cancer growth
- *ARRB1* nicotine-induced growth of lung tumors

Skin-specific network

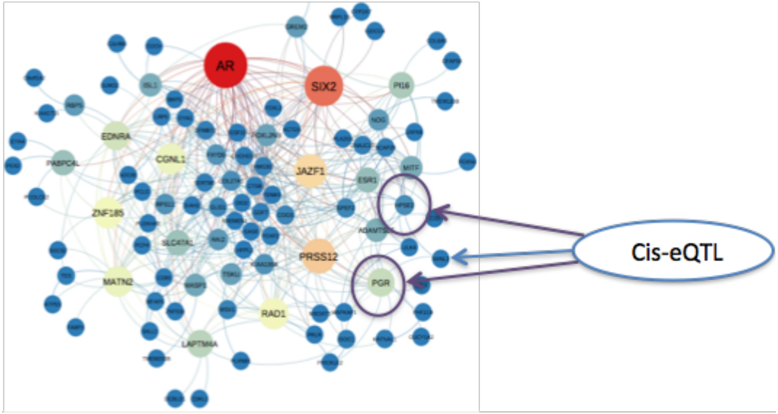
- *RHPN2* cancer initiatiator
- *CD68* skin tumors growth





Validation of network edges

Given a gene of interest A, its associated genetic variant Q, and a gene B that is a neighbor of A in the tissue-specific network, we tested for association between Q and B in out of sample data.



Validated edges

Adipose network validation

- 85 trans-eQTLs ($FDR \leq 0.10$)
- trans-eQTL for *TK2*, deficiency causes abnormal adipose tissues

Artery network validation

- two trans-eQTLs ($FDR \leq 0.10$)
- trans-eQTLs for *PLVAP* and *CYYR1*, unique to artery samples

Lung network validation

- nine trans-eQTLs ($FDR \leq 0.15$)
- trans-eQTL for *DENND1C*, which is unique to lung samples

Skin network validation

- eight trans-eQTLs ($FDR \leq 0.25$)
- trans-eQTLs for *CDH3*, related to juvenile macular dystrophy

Summary

We developed Bayesian biclustering models and fitted these models to gene expression data using variational EM

- to identify sources of gene co-variation;
- to recover gene co-expression networks.

Ongoing work

- developing and formalizing methods to robustify results;
- use stochastic variational inference for additional stochasticity across runs;
- methods to combine across posterior estimates with different (non-Bernoulli) marginals

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- Genotype-Tissue Expression (GTEx)

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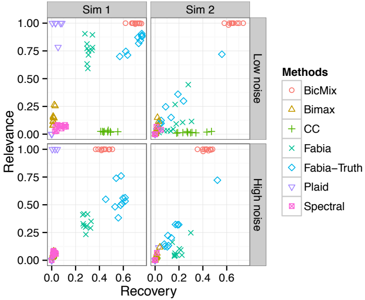
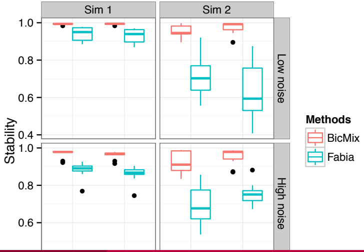
Bayesian biclustering results on simulated data

- *Sim1*: Only sparse components
- *Sim2*: Sparse and dense components

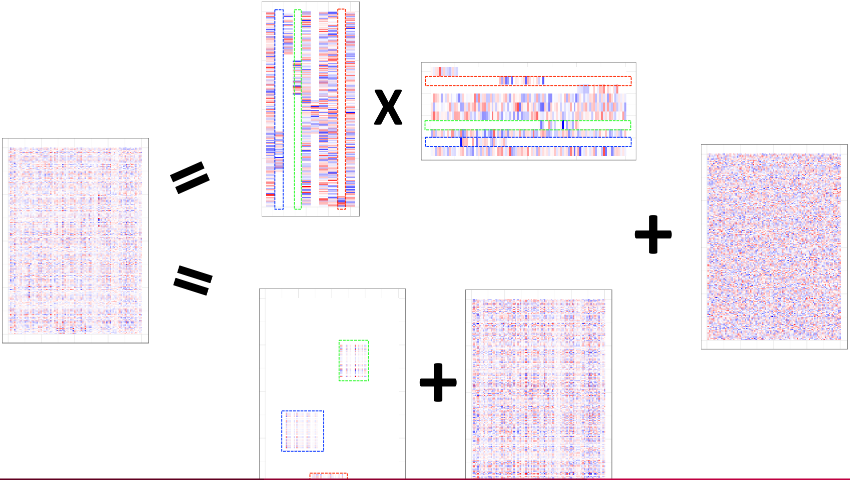
- *BicMix*: Our biclustering method
- *Bimax*: hierarchical clustering
- *CC*: hierarchical clustering
- *Fabia*: latent factor model
- *Plaid*: sparse matrix factorization
- *Spectral*: orthogonal matrix factorization





Biclustering model

Model for biclustering encodes subsets of samples, genes for which covariation is observed

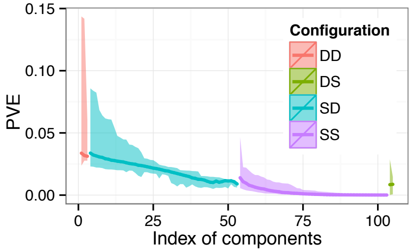


Bayesian biclustering results on GTEx data

- Genotype-Tissue Expression (GTEx) study
- Hundreds of individuals, RNA-seq on > 30 tissues per individual
- Whole-genome sequences for all individuals
- Here: data subset with four tissues, ~ 200 individuals

- BicMix identified 9,854 unique sparse components across 200 runs

- DD = Dense loading, dense factor (population structure)
- SD = Sparse loading, dense factor (age, BMI, batch)
- DS = Dense loading, sparse factor (bad sample)
- SS = Sparse loading, sparse factor (eQTLs, cell type, sex)



Median component-wise PVE for three DD, 50 SD, 50 SS, and two DS components