Matrix Ash

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Abstract

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Author Summary

Variation in gene expression is an important mechanism underlying susceptibility to complex disease. The simultaneous genome-wide assay of gene expression and genetic variation allows the mapping of the genetic factors that underpin individual differences in quantitative levels of expression (expression QTLs; eQTLs). By analyzing these effects across multiple tissues, we exploit the information that the effect of the gene-snp pair in one tissue can provide about its effect in alternative tissues. Furthermore, quantifying the effect size as opposed to simply calling QTLs present or absent reveal many patterns of sharing of effects among tissues which differ in both sign an magnitude. We provide a novel framework for estimating effect sizes across multiple subgroups, considering the evidence contained in all subgroups jointly, which provides a powerful and detailed insight into quantitative heterogeneity present in the genome.

Introduction

Variation in gene expression is an important mechanism underlying susceptibility to complex disease.

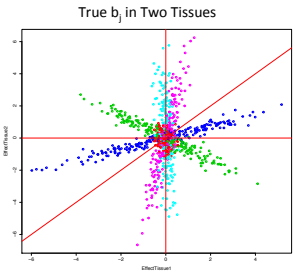
The simultaneous genome-wide assay of gene expression and genetic variation allows the mapping of the genetic factors that underpin individual differences in quantitative levels of expression (expression QTLs; eQTLs). The availability of this information provides immediate insight into a biological basis for disease associations identified

through genome-wide association (GWA) studies, and can help to identify networks of genes involved in disease pathogenesis.

Initial approaches to quantify the effect of a particular SNP on gene expression considered only one tissue at a time, and ignored the effect of the SNP on gene expression in other tissues. This fails to exploit the power of shared genetic variation in effects on expression - i.e. the information that the effect of the gene snp pair in one tissue can provide about the effect in another- and limits our understanding of multiple-tissue phenotypes. Available methods are limited not only in their ability to *jointly analyze data on all tissues* to maximize power, but also in simultaneously *allowing for both qualitative and quantitative differences among eQTLs* present in each tissue. Indeed, past attempts at quantifying heterogeneity of eQTLs were limited in the number of tissues considered and also the level of heterogeneity considered. Qualitative heterogeneity refers to calling a snp 'active' or 'inactive' in a given tissue. Indeed, previous work has referred to the setting in which the gene-snp pair is active in all tissues as 'shared' and active in only one as 'tissue-specific'. However, a QTL may be'active' in all or many tissues and with varying magnitude or sign; we refer to this as quantitative heterogeneity. Quantifying the effect sizes of the gene-snp pair across tissues considering the evidence contained in all tissues jointly thus reveals new patterns of activity across tissues, which differ in their relationship in sign and magnitude within and between tissues. - thus effects can be 'shared' but not 'consistent' across tissues. We aim to learning about patterns of sharing across tissues within a SNP and among SNPs, which join to help us better understand the global and snp-specific patterns of effects of genetics on gene expression Use the whole genome to imagine that all gene-snp pairs belong to a finite number of groups, where each group is characterized by pattern of sharing of effects across tissues

Not only do we have many tissues, we also have an entire genome from which to 'learn' about these patterns of sharing. For each of J gene-snp pairs, we observe an R dimensional vector of standardized effect sizes $\hat{b}$ and their standard error and assume that these effects descend from some true effect size $\boldsymbol{b}$. Thus as an additional level of combining information, we assume that each eQTL may follow a particular pattern of activity characterized by its effects across tissues. Within these groups, the tissues exhibit characteristic patterns of sharing, which can be captured by considering the covariance structure of the genetic effects among tissues. This lends itself to a natural mixture model, in which we assume all the gene-snp pairs arise from a mixture of a finite number of Gaussian distributions with unknown parameters. Because of the the multivariate nature of this activity, within a particular 'pattern of sharing' some tissues may be more active than others, but not completely on or off. Thus each component of the mixture is defined by the prior covariance matrix from which the vector of standardized effect sizes $\boldsymbol{b}$ is thought to be drawn. The covariance matrix of the true effects thus reflects a particular pattern of sharing, such that the diagonal elements of the component-specific covariance matrix then represents the variance of the effect size within and and the off–diagonal between tissues . A large prior variance in one tissue and small in another means that effects in the first tissue tend to be large while effects in tissue two tend to be small. Because we can't know the 'true covariance matrix' for each gene-snp pair, we aim to assemble a list which sufficiently captures the various patterns, and then 'learn' the relative proportions of each pattern of sharing from the data. One can now model each vector of effect sizes $\boldsymbol{b}$ each as arising from a mixture that captures all the covariance patterns.

As a critical innovation on our previous method (1001[?, ?]) these matrices contain distinct diagonal and off-diagonal elements which reflect data-specific patterns of variation within and covariance between subgroups (tissues). This captures the variation in effect sizes within and between subgroups better than restricting effects to



simply 'shared' or 'unshared' between subgroups.

Previous work from our lab considered only the idea that the covariance between two tissues was the same across tissues thought to contain a QTL in a given pattern, or 'configuration', and thus failed to incorporate the much richer covariance structure between tissues.

The primary novelty of this approach l is *to estimate this multivariate posterior distribution on the effect size in a data-sensitive way* - i.e., using the mixture model to capture information about the covariance structure among subgroups (here, tissues). Thus we might identify a situation in which it is common to have large effects in some tissues and not others, and thus if a gene-snp pair demonstrates a small effect in one of the 'off issues', we might be inclined to conclude that it is indeed a member of this particular class and shrink the small effect in this tissue accordingly. However, if we see the same small effect in a setting in which 'similar tissues' have large effects, we might 'shrink' this effect size less, due to our high prior belief in the SNP's effectiveness garnered from adjacent tissues.This is in contrast to a univariate shrinkage approach, in which all effects of the same size would be 'shrunk' equivalently, due to lack of information garnered from adjacent tissues

An additional novelty is that in learning something about the effect size in each tissue for a given gene-snp pair, we can make statements about the degree of heterogeneity - that is the proportion of the time we expect a SNP to have effects of different sign. We will be confident in our ability to identify the direction of the effect for A SNP with a large effect and relatvilely high precision, and thus we can use an estimate of the posterior mean in each component and the proportion to quantify the distribution of gene SNP pairs who have effects of opposite direction (or lack convincing evidence of effects in a consistent direction across tissues).

0.1 So what are the Prior Covariance Matrices $U_k s$ specifiying?

Suppose we have just two tissues

- Direction defined by relative ratio in effect size between tissues, specified in prior covariance of $\boldsymbol{b}$

Generative U_k for blueSNPs $\begin{pmatrix} Var(b_1) = blue2.0 & Cov(b_1, b_2) = 0.56 \\ Cov(b_2, b_1) = 0.56 & Var(b_2) = blue0.20 \end{pmatrix}$

Additional novelty: Ratio between tissues is flexible (not simply shared or tissue-specific) and data sensitive (stay-tuned)

To illustrate the utility of using a variety of covariance matrices, consider that we have snps of 4 'types' here defined, by their effects in tow tissues. eQTL of the blue class tend to have large effects in tissue 1 and small in tissue 2, while snps in the purple class have very large effects in tissue 2 and small effects in tissue 2. These directions are thus specified in the prior covariance matrix which defines the direction - here simply ratio - in prior effect size between tissues,

The 45 degree angle and the lines would be simply using tissue specific or shared effects, while we can have a much richer understanding of the relationship between effect sizes using a set ofcovariance matrices that aims to recapitulate patterns found in the data

0.2 Why care about the effect size?

- Comparisons among tissues in which the QTL is called active, and among gene-snp pairs with a similar degree of activity in a given tissue.
- The addition of the quantitative comparison captures the continuous nature of biological phenomenon.
- How confident are we in the sign of the effect?
- Acknowledge the many patterns of sharing present in the data, wide array of prior covariance matrices allows our gene-snp pair to find it's true pattern of sharing

Given that an eQTL is called active in two tissues, we want to make more statements about our confidence in the sign and magnitude of the effect among tissues.

Similarly, if many SNPs are called active in a particular tissue, we can resolve differences among these gene=snp pairs and using this wide array of prior covariance matrices allows our gene snp pair to find it's true pattern of sharing.

Adaptive Shrinkage: So why does the likelihood increase at the 'right component'? Consider the univariate case. Here, think about x as $\hat{b_1}$, and σ as $U_{k[1,1]] + \hat{V}_{j[1,1]}$.

To compute the likelihood at each component:

$$f(x \mid \sigma) = \frac{1}{\sigma\sqrt{2\pi}}\, e^{-\frac{(x)^2}{2\sigma^2}} \tag{1}$$

We can see that this will be largest when σ^2 approaches the MLE, which where is simply $\hat{b}^2$. This is the intuition behind the bayes factor being the largest at the 'true component'.

Materials and Methods

We assume the following mixture prior for the R dimensional vector of true effects, $\boldsymbol{b_j}$ represents the genetic effect of SNP-gene pair j across $R = 44$ tissues:

$$\boldsymbol{b_j}|\boldsymbol{\pi}, \mathbf{U} \sim \sum_{\mathbf{k,l}} \pi_{\mathbf{k,l}}\, N_{\mathbf{R}}(\mathbf{0}, \omega_{\mathbf{l}}\mathbf{U_k}) \tag{2}$$

Each component of the mixture distribution is characterized by these prior covariance matrices, U_k which capture the pattern of effects across tissues. Critically, this prior distribution is the same for all J - hence the hierarchical incorporation of shared information.

0.3 Covariance Matrices

For a given ω_l, we specify 4 'types' of RxR prior covariance matrices $U_{k,l}$.

1. $U_{k=1,l} = \omega_l\, \mathbf{I}_R$
2. $U_{k=2,l} = \omega_l \mathrm{X}_z$ The (naively) estimated tissue covariance matrix as estimated from the column-centered J $\times R$ matrix of Z statistics, Z_{center}: $\frac{1}{J}\ {Z_{center}}^t\ Z_{center}$

3. $U_{k=3,l} = \omega_l \ \frac{1}{J} \ V_{1...p} \ d^2_{1...p} \ V^t_{1..p}$ is the rank p eigenvector approximation of the tissue covariance matrices, i.e., the sum of the first p eigenvector approximations, where $_{1...p}$ represent the eigenvectors of the covariance matrix of tissues and $_{1...p}$ are the first p eigenvalues.

4. $U_{k=4:4+Q-1,l} = \frac{1}{J}((\Lambda\mathbf{F})^t\Lambda\mathbf{F})_q$ corresponding to the q_{th} sparse factor representation of the tissue covariance matrix

5. $U_{k=4+Q,l} = \frac{1}{J} \ (\Lambda\mathbf{F})^t\Lambda\mathbf{F}$ is the sparse factor representation of the tissue covariance matrix, estimated using all q factors.

6. $U_{k=5+Q:R+4+Q,l} = \frac{1}{J} \ ([100..]'[100...])$

7. $U_{k=R+5+Q,l} = \frac{1}{J} \ ([111...]'[111...])$

8. [1000...] or [111...] represent configurations such that given membership,$\boldsymbol{b_j}$ arise from the same prior variance.

0.4 Deconvolution

To retrieve a 'denoised' or 'deconvoluted' estimate of the non-single rank dimensional reduction matrices, we then perform deconvolution after initializing the EM algorithm with the matrices specified in (2), (3) and (5). The final results of this iterative procedure preserves the rank of the initialization matrix, and allows us to use the 'true' effect component as missing data in deconvoluting the prior covariance matrices. In brief, this algorithm works by treating not only the component identity but also the true effect $\boldsymbol{b_j}$ as unobserved data, and maximizing the likelihood over the expectation of the complete data likelihood, considering the values $\boldsymbol{b_j}$ as extra missing data (in addition to the indicator variables q_{ij}) (Bovy et al, 2014). This allows us to write down the 'full data' log likelihood as follows:

$$\begin{aligned} \phi &= \sum_J \sum_K q_{jk} ln\alpha_k N(\hat{\boldsymbol{b_j}}|0, U_k + V_j) \\ \phi &= \sum_J \sum_K q_{jk} ln\alpha_k N(\boldsymbol{b_j}|0, U_k) \end{aligned} \tag{3}$$

Where α_k represents π_k and q_{jk} is the latent identifier variable.

0.5 Posterior Quantities

We know that for a single multivariate *Normal* the posterior on $\boldsymbol{b}|U_0$ is simply:

$$\boldsymbol{b}|\hat{\boldsymbol{b}} \sim N_R(\boldsymbol{\mu}_1, U_1)$$

where:

- $\boldsymbol{\mu}_1 = U_1(\hat{V}^{-1}\hat{\boldsymbol{b}})$;
- $U_1 = (U_0^{-1} + \hat{V}^{-1})^{-1}$.

Furthermore, a mixture-multivariate normal prior and a normal likelihood yields a mixture multivariate posterior, where the final posterior distribution is simply a weighted combination of multivariate normal distributions, each now characterized by it's posterior mean $\boldsymbol{\mu}_{1k}$ and covariance $U_1 = (U_0^{-1} + \hat{V}^{-1})^{-1}$.

$$p(\boldsymbol{b}|\hat{\boldsymbol{b}}, \hat{V}, \hat{\boldsymbol{\pi}}) = \sum_{k=1,l=1}^{K,L} \sim N_R(\boldsymbol{\mu}_{1kl}, U_{1kl})\tilde{\pi}_{k,l} \tag{5}$$

where the posterior mixture weight $\tilde{\pi}_{k,l}$ is simply

$$\tilde{\pi}_{k,l} = \frac{p(\hat{\boldsymbol{b}}_j|\hat{V}_j, z_j = k, l)\hat{\pi}_{kl}}{\sum_{k=1,l=1}^{K,L} p(\hat{\boldsymbol{b}}_j|\hat{V}_j, z_j = k, l)\hat{\pi}_{kl}} \tag{6}$$

1 Testing and Training

In order to determine the optimal number and rank of the covariance matrices, we divide our data set into a training and test data set, each containing 8000 genes.

In the training set, we proceed as above: choosing the top SNP for each of the 8000 genes, creating a list of covariance matrices through deconvolution and grid selection of these top 'training gene-snp' pairs.

Then, within the training data, we similarly choose a random set of gene-snp pairs (restricting our analysis to genes contained in the training set. Again, we choose 20,000 random-gene snp pairs and use the EM algorithm to learn the mixture proportions π from this data set.

We then use the KxL vector of π from the training set to estimate the log likelihood of each data point in the test data set. If our model is 'overfit' to the training data set, than a larger number of covariance matrices may actually decrease the test log-likelihood.

I found that the K=1188 set of covariance matrices containing the Identity, the denoised empirical covariance matrix, rank 5 SFA approximation and rank 3 SVD approximation as well as 5 single-rank SFA factors and the 45 *eqtl.bma.lite* configurations maximized this likelihood.

2 Training and Testing Procedure: Estimating Hierarchical Weights

We wish to choose the model which best maximizes the probability of observing the data set.

Incomplete Data likelihood:

$$L(\boldsymbol{\pi}; \hat{\boldsymbol{b}}) = \prod_{j=1}^{J} \sum_{k}^{K} \pi_k P(\hat{\boldsymbol{b_j}}|z_j = k) \tag{7}$$

- To estimate the hierarchical prior weights π_k: compute the likelihood at each each gene snp pair j by evaluating the probability of observing $\hat{\boldsymbol{b_j}}$ given that we know the true $\boldsymbol{b_j}$ arises from component k
- Use the EM algorithm to estimate the optimal combination of weights: How often does this particular covariance matrix occur in the data?

We then use these weights to estimate the test set log likelihood.

Results

Discussion

Supporting Information

Acknowledgments

References

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