`mash` No Baseline

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1 Purpose

The purpose of this document is to propose a method for extending `mash` to estimate 'true' effects across conditions in a setting in which no obvious baseline exists. We assume that we observe noisy, uncentered averages $\hat{\boldsymbol{C}}_{jr}$ in each of R conditions, and seek to estimate the underlying true 'deviations' from average measurement across conditions and can be seen as the effects in `mash`.

Here, the use of bold-face notation indicates a vector, while matrix quantities are typeset in capital but unboldface letters.

2 Defining the Old Model

For a given gene-snp pair, $\boldsymbol{b}$ represents the R vector of unknown standardized effect. We model the prior distribution from which $\boldsymbol{b}$ is drawn as a mixture of multivariate *Normals*.

$$\boldsymbol{b}|\boldsymbol{\pi}, \mathbf{U} \sim \sum_{\mathbf{k},\mathbf{l}} \pi_{\mathbf{k},\mathbf{l}}\ N_{\mathbf{R}}(\mathbf{0}, \omega_{\mathbf{l}}\mathbf{U}_{\mathbf{k}}) \tag{1}$$

Furthermore, for a given gene-snp pair, the Likelihood on $\boldsymbol{b}$:

$$\hat{\boldsymbol{b}}|\boldsymbol{b} \sim N_R(\boldsymbol{b}, \hat{V}) \tag{2}$$

Now, we observe for each gene j a vector of uncentered noisy average feature expression $\hat{\boldsymbol{C}}$ across R conditions:

$$\hat{\boldsymbol{C}}|\boldsymbol{C} \sim N_R(\boldsymbol{C}, \hat{V}) \tag{3}$$

where the 'true' uncentered averages $\boldsymbol{C}$ can be written as follows:

$$\boldsymbol{C}|\mu, \boldsymbol{v} = \mu\mathbf{1} + \boldsymbol{v} \tag{4}$$

Where μ is a scalar that is the mean of the 'true' uncentered averages $\boldsymbol{C}$.

$\boldsymbol{v}$ is a zero-centered mixture of multivariate normals:

$$\boldsymbol{v}|\boldsymbol{\pi}, \mathbf{U} \sim \sum_{\mathbf{k},\mathbf{l}} \pi_{\mathbf{k},\mathbf{l}}\ N_{\mathbf{R}}(\mathbf{0}, \omega_{\mathbf{l}}\mathbf{U}_{\mathbf{k}}) \tag{5}$$

Critically, our quantity of interest now, $\boldsymbol{v}$ represents the true 'deviations' from average gene expression across each condition and can be seen as the effects in `mash`.

3 Applications

We will again apply a two-step process to our selection of covariance matrices, where we select a set of denoised 'pattern' matrices U_k by using the EM algorithm on the max effects across conditions, and then expanding this list by a fixed grid of scalar weights ω_l such that we conclude with a list of $P = KxL$ covariance matrices Σ. We can then:

- estimate the p prior weights $\boldsymbol{\pi}$ on this fixed P-list of covariance matrices from a training matrix of randomly selected feature expression measurements across conditions
- compute the posterior distribution $\boldsymbol{v}|L\hat{\boldsymbol{C}}, \boldsymbol{s_j}$

  Let

$$L\boldsymbol{C} = L\mu\mathbf{1} + L\boldsymbol{v} \tag{6}$$

  L is the RxR centering matrix $L_r = I_r - \frac{1}{r}\mathbf{1}\mathbf{1}^\top$ which removes the mean of each R column vector.

  Then :

$$\begin{aligned} L\boldsymbol{C} &= L\mu\mathbf{1} + L\boldsymbol{v} \\ L\boldsymbol{C} &= 0 + L\boldsymbol{v} \\ L\hat{\boldsymbol{C}} &= L\boldsymbol{v} + E \end{aligned} \tag{7}$$

  Where $E \sim \mathcal{N}(0, L\hat{V}L')$

3.1 Selecting The Covariance Matrices

We initiate our set of covariance matrices for the denoising step as before in `mash`, where now we compute the empirical covariance matrices and a variety of dimensional reductions on the feature-centered JxR *matrix* of maximum average, $L\hat{C}'$ instead of $\hat{C}$ alone. In practice, we actually use the matrix of maximum uncentered Z statistics.

Now for each gene J at each component k, integrating over $\boldsymbol{v}$,

$$
\begin{aligned}
L\boldsymbol{C} &\sim \mathcal{N}(0, LU_kL') \\
L\hat{\boldsymbol{C}} &\sim \mathcal{N}(0, LU_kL' + L\hat{V}L')
\end{aligned}
\tag{8}
$$

And thus we can use the Bovy et al algorithm invoked in both the Extreme Deconvolution package and in 'Sarah's MixEm' where:

$$
T_{jp} = LU_kL' + L\hat{V}_jL' \tag{9}
$$

And as mentioned, L is the RxR centering matrix for each gene, and $w_j = L\hat{\boldsymbol{C}}_j$.

Recall that our previous approach was simplified by the fact that $\boldsymbol{w}_j$ was simply $\hat{\boldsymbol{b}}_j$ and the projection matrix was simply the I_r identity matrix. Our inference on $\boldsymbol{b}$ was analogous to their inference on $_j$.

As before, we are interested in returning the prior covariance U_k matrices of the 'true' deviations $\boldsymbol{v}$, which we will then rescale by choosing a set of ω that are appropriate to $L\hat{\boldsymbol{C}}$ to comprise a set of $P = KxL$ prior covariance matrices Σ.

and choose the set of π that maximizes compute the following likelihood at each of the P components:

$$
L\hat{\boldsymbol{C}}_j \sim \mathcal{N}(0, L\Sigma_pL' + L\hat{V}_jL') \tag{10}
$$

4 Posteriors

Now, as before we can compute a posterior distribution such that:

$$
\boldsymbol{v}|L\hat{\boldsymbol{C}}, \pi, \Sigma, \boldsymbol{s} \sim N(\mu^1, U^1) \tag{11}
$$

Where at each of the P components for each gene J

$$
\begin{aligned}
\mu^1_{jp} &= \Sigma_pL'T^{-1}_{jp}L\hat{\boldsymbol{C}}_j \\
U^1_{jp} &= \Sigma_p - \Sigma_pL'T^1_{jp}L\Sigma_p
\end{aligned}
\tag{12}
$$

And

$$
\boldsymbol{v} \sim \sum_p \tilde{\pi}_p\mathcal{N}(\mu^1_p, U^1_p) \tag{13}
$$

Where

$$\tilde{\pi}_{jp} = \frac{\mathcal{N}(L\hat{\boldsymbol{C}}; 0, T_{jp})}{\sum_p \mathcal{N}(L\hat{\boldsymbol{C}}; 0, T_{jp})} \tag{14}$$

5 Differences required over `mash` implementation

- We will now work with a matrix of observed column-centered gene averages, $L\hat{C}'$ in order to:
  1. initialize our choice of U_k;
  2. choose the maxes by which to denoise,
  3. choose our set of scales, ω_l
  4. compute our hierarchical weights, $\boldsymbol{\pi}_p$ as well as our posteriors.
- The new distribution we seek to estimate for each j is then $v|L\hat{\boldsymbol{C}}, \boldsymbol{s}_j$

Some questions:

- How is using $\boldsymbol{w}_j$ as $L\hat{\boldsymbol{C}}_j$ as the data from which we estimate our model different than initializing with the vectors of $\hat{\boldsymbol{b}}$ that have been computed on *feature centered data*?
- I think it is because we are now broadly incorporating the centering information into our prior on $L\boldsymbol{C}$ as well, such that at each component for each gene, $L\boldsymbol{C}_j \sim \mathcal{N}(0, L\Sigma_{jp}L')$.
- If this is the case, we will probably need to denoise all of the initiation matrices (not just the multirank Uk) since previously our projection matrix was the Identity
- Since our input will still be that matrix of uncentered noisy averages and their standard errors, our scaling parameter ω ought to be chosen consistent with $L\hat{C}$, and not $\hat{C}$, since this will tend to scale with the true deviations $\boldsymbol{v}_j$.