Topic model with Batch effects

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Introduction

In RNA-seq experiments, we often encounter samples coming from different batches. The batches may be determined by the different amplification procedures, sequencing machines or even sequencing lanes used for sequencing. When such effects are present in the samples, it becomes difficult to separate out the biological effects from the technical effects (the latter is often relatively stronger). The topic model or the grade-of membership model has been used to cluster the samples based on their RNA-seq reads counts data (see paper). In the paper, we have shown that the topic model is sensitive to the presence of batch effects, however we have not been able to present a solution to that problem. Here, we try to address the issue of how one can tackle batch effects in a topic model type framework.

We first present the standard topic model framework

Standard Topic Model

Let c_{ng} be the counts of reads for sample n and gene g. Let c_{n+} be the sum of reads for sample n, also called the *library size*.

$$(c_{n1}, c_{n2}, \cdots, c_{nG}) \sim Mult(c_{n+}, p_{n1}, p_{n2}, \cdots, p_{nG})$$

$$p_{ng} = \sum_{k=1}^{K} \omega_{nk}\theta_{kg} \qquad \sum_{k} \omega_{nk} = 1 \quad \forall n \qquad \sum_{g} \theta_{kg} = 1 \quad \forall k$$

Here $\omega_{n.}$ represents the topic proportions for n th samples. On the other hand $\theta_{k.}$ represents the probability distribution on the genes for the kth topic or cluster.

Topic model with Batch effects

One way batch effects may be incorporated in the above model would be to make the topic distribution for each cluster/ topic a function of the batch the sample is coming from. Then we can write the above model as

$$(c_{n1}, c_{n2}, \cdots, c_{nG}) \sim Mult(c_{n+}, p_{n1}, p_{n2}, \cdots, p_{nG}) \tag{1}$$

$$p_{ng} = \sum_{k=1}^{K} \omega_{nk}\theta_{b(n):k,g} \qquad \sum_{k} \omega_{nk} = 1 \quad \forall n \qquad \sum_{g} \theta_{b(n):k,g} = 1 \quad \forall k, \quad b(n) \in \{1, 2, \cdots, B\} \tag{2}$$

Prior Specification

Note that the above the model is analogous to applying topic model separately for each batch. The problem with that approach is that we will not be able to track which biological cluster in Batch 1 corresponds to which biological cluster in Batch 2. We expect each cluster distribution to have some common features across different batches despite getting effected by batch effects and we want to account for that similarity in patterns. In order to do that, we assume for each cluster k

$$(\theta_{b:k,1}, \theta_{b:k,2}, \cdots, \theta_{b:k,G}) \sim Dir_G\left(\theta_{k1}, \theta_{k2}, \cdots, \theta_{kG}\right) \qquad b \in \{1, 2, \cdots, B\} \tag{3}$$

which is same as saying that for each batch, we are generating a sample from the cluster with mean $(\theta_{k1}, \theta_{k2}, \cdots, \theta_{kG})$, representing the cluster k.

The above specification is analogous to the assumptions in normal linear models with batch effects,

$$y_{nl} = \mu_{t(n):b(n),l} + e_{nl} = \mu + \tau_{t(n)} + \beta_{b(n)} + e_{nl} \qquad e_{nl} \sim N(0, \sigma_e^2)$$

where $t(n)$ in the treatment effect and $b(n)$ is the batch effect. We often assume that

$$\beta_b \sim N(0, \sigma_b^2) \qquad b \in \{1, 2, \cdots, B\}$$

Then

$$\mu_{t(n):b(n),l} \sim N(\mu + \tau_{t(n)}, \sigma_e^2) := N(\mu_{t(n)}, \sigma_e^2) \qquad \forall l$$

Notice that the treatment effects under different batches are a random sample from a distribution whose mean is the overall treatment effect. Note that σ_b term is the tuning parameter for each batch, that takes into account the inherent variability in a batch. We can also put such a scaling parameter in our model Equation 11.

Then for each k,

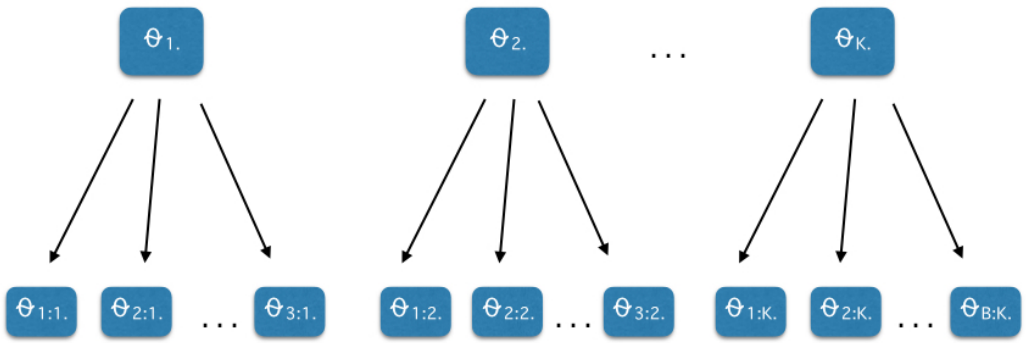
$$(\theta_{b:k,1}, \theta_{b:k,2}, \cdots, \theta_{b:k,G}) \sim Dir_G\left(\alpha_b\theta_{k1}, \alpha_b\theta_{k2}, \cdots, \alpha_b\theta_{kG}\right) \qquad b \in \{1, 2, \cdots, B\}$$

However, as of now, I am assuming that $\alpha_b = 1$ for all batches and working with the simpler model.

We assume a prior for θ_{kg}.

$$(\theta_{k1}, \theta_{k2}, \cdots, \theta_{kG}) \sim Dir_G\left(\frac{1}{KG}, \frac{1}{KG}, \cdots, \frac{1}{KG}\right) \qquad \forall k \tag{4}$$

So, essentially we have a hierarchical structure in the θ's, on combining Equation 11 and Equation 4.



We can assume the same prior for ω as in standard topic model, given by

$$(\omega_{n1}, \omega_{n2}, \cdots, \omega_{nK}) \sim Dir_K\left(\frac{1}{K}, \frac{1}{K}, \cdots, \frac{1}{K}\right) \qquad \forall n$$

Model Specifications

We can assume that

$$c_{n+} \sim Poi(\lambda_n) \tag{5}$$

Combining Equation 1 and Equation 5, we get

$$c_{ng} \sim Poi\left(\lambda_n \sum_k \omega_{nk}\theta_{kg}\right) \tag{6}$$

Let z_{nkg} represents the number of counts from sample n and gene g that comes from k th subgroup or cluster. By definition,

$$\sum_{k=1}^{K} z_{nkg} = c_{ng}$$

Since the summation of two independent Poisson random variables is also a Poisson variable with mean equal to the sum of the means of the original random variables, we can infer that

$$z_{nkg} \sim Poi\left(\lambda_n \omega_{nk} \theta_{b(n):k,g}\right)$$

Let z_{bkg} be the latent variable representing the number of reads coming from the b th batch, k th subgroup/ cluster and gene g.

$$z_{bkg}|\theta_{b:k,g} \sim Poi\left(\theta_{b:k,g} \sum_{b(n):b} \omega_{nk}\lambda_n\right)$$

$$z_{kg}|\theta_{b:k,g} \sim Poi\left(\sum_b \theta_{b:k,g} \sum_{b(n):b} \omega_{nk}\lambda_n\right)$$

We can write

$$\begin{aligned} E(z_{kg}|\theta_{kg}) &= E\left(\sum_b E\left(z_{bkg}|\theta_{b:k,g}\right)|\theta_{kg}\right) \\ &= E\left(\sum_b \theta_{b:k,g} \sum_{b(n):b} \omega_{nk}\lambda_n|\theta_{kg}\right) \\ &= \theta_{kg} \sum_n \omega_{nk}\lambda_n \end{aligned}$$

However despite a simple looking expression for the expectation, the distribution of z_{bkg} or z_{kg} given θ_{kg} is pretty complicated.

$$z_{bkg}|\theta_{kg} \sim \prod_{b=1}^{B} \frac{\Gamma(\sum_g \theta_{kg})}{\Gamma(\sum_g z_{bkg} + \sum_g \theta_{kg})} \prod_{g=1}^{G} \frac{\Gamma(z_{bkg} + \theta_{kg})}{\Gamma(\theta_{kg})} \theta_{kg}^{1/KG} \tag{7}$$

and

$$z_{kg} = \sum_b z_{bkg} \tag{8}$$

This density is difficult to handle and will be time expensive to solve for θ using this density function. Therefore, we resort to a more simplified approach, through EM algorithm type mechanism to obtain parameter updates at each step.

Model Estimation

Suppose at the end of update n, the current estimates we have are $\omega_{nk}^{(m)}$, $\theta_{b:k,g}^{(m)}$ and $\theta_{kg}^{(m)}$. We use these iterates to obtain refined estimates $\omega_{nk}^{(m+1)}$, $\theta_{b:k,g}^{(m+1)}$ and $\theta_{kg}^{(m+1)}$. We first update the $\theta_{b:k,g}^{(m+1)}$ given the known parameter values using EM algorithm.

$$\mathcal{L}(z_{bkg}|\theta_{b:k,g}) := Poi\left(\theta_{b:k,g}\sum_{b(n):b}\omega_{nk}\lambda_n\right) \tag{9}$$

or

$$\mathcal{L}(z_{bk1}, z_{bk2}, \cdots, z_{bkG}|\theta_{b:k,.}) := Mult\left(z_{bk+}, \theta_{b:k,1}, \theta_{b:k,2}, \cdots, \theta_{b:k,G}\right) \tag{10}$$

$$\pi(\theta_{b:k,.}|\theta_{k.}) \propto \prod_{g=1}^{G}\theta_{b:k,g}^{\theta_{kg}} \tag{11}$$

We define the E-step of the EM algorithm as follows (done separately for each k)

$$\mathcal{Q}\left(\theta_{b:k,.}|C_{N\times G}, \theta_{b:k,.}^{(m)}, \theta_{k.}^{(m)}, \omega^{(m)}\right) = \mathbb{E}_{Z|C_{N\times G},\theta_{b:k,.}^{(m)},\theta_{k.}^{(m)},\omega^{(m)}}\left(log\ \mathcal{L}(z_{bk1}, z_{bk2}, \cdots, z_{bkG}|\theta_{b:k,.}) + log\ \pi(\theta_{b:k,.}|\theta_{k.}^{(m)})\right) \tag{12}$$

We next perform the M-step and we obtain the following solutions for $\theta_{b:k,g}$s.

$$\theta_{b:k,g}^{(m+1)} := \frac{\mathbb{E}\left(z_{b:k,g}|C_{N\times G}, \theta_{k.}^{(m)}, \omega^{(m)}\right) + \theta_{kg}^{(m)}}{\sum_g \mathbb{E}\left(z_{b:k,g}|C_{N\times G}, \theta_{k.}^{(m)}, \omega^{(m)}\right) + 1} \tag{13}$$

The expectation over $[z_{b:k,g}|C_{N\times G}, \theta_{b:k,.}^{(m)}, \theta_{k.}^{(m)}, \omega^{(m)}]$ is given by the following

$$\mathbb{E}\left(z_{b:k,g}|C_{N\times G}, \theta_{b:k,.}^{(m)}, \theta_{k.}^{(m)}, \omega^{(m)}\right) := c_{ng}\frac{\omega_{nk}^{(m)}\theta_{b:k,g}^{(m)}}{\sum_{h=1}^{K}\omega_{nh}^{(m)}\theta_{b:h,g}^{(m)}}$$

Once we obtain the estimates $\theta_{b:k,g}^{(m+1)}$, then we would like to update $\theta_{kg}^{(m+1)}$ conditional on $\theta_{b:k,g}^{(m+1)}$ for all $b \in \{1, 2, \cdots, B\}$.

One can assume $\theta_{b:k,.}^{(m+1)}$ for all b to be a random sample of size B (same as number of batches) given $\theta_{k.}$ and given the data, we want to estimate the parameters $\theta_{k.}$. However estimating MLE of the Dirichlet parameters is not easy (specially with so many parameters-G is usually pretty big), and requires Newton-Raphson Method (check paper). One can obtain a MOM (Methods of Moments) type estimator with a tuning parameter ν as follows.

$$\theta_{kg}^{(m+1)} = \frac{1}{B+\nu}\sum_{b=1}^{B}\theta_{b:k,g}^{(m+1)} + \frac{\nu}{B+\nu}\frac{1}{G}$$

instead of the MLE estimator derived from the conditional distribution of z_{kg} given θ_{kg} as given in Equation 7 and Equation 8. However as discussed earlier, the original conditional distribution of $z_{kg}|\theta_{kg}$ seems difficult to handle.

We fix the batch b. Then given $\theta_{b:k,g}^{(m+1)}$, we can estimate $\omega_{nk}^{(m+1)}$ from $\omega_{nk}^{(m)}$ and $\theta_{b:k,g}^{(m+1)}$ using similar convex optimization technique used by Matt Taddy in his paper.

At the end of these steps, we will have $\omega_{nk}^{(m+1)}$, $\theta_{b(n):k,g}^{(m+1)}$ and $\theta_{kg}^{(m+1)}$. We can these use these to update the parameters further and we continue till the log-likelihood converges.