

# TOPIC MODELING ANALYSIS OF DIFFERENTIAL GENE EXPRESSION

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**1. Differential gene expression.** The “log-fold change” statistic is commonly used in microarray and RNA sequencing experiments to quantify expression differences between two conditions (e.g., [2, 3]). To motivate the ideas below, I write the log-fold change for gene  $j$  and condition  $k$  as a ratio of two conditional expectations,

$$(1) \quad \text{lfc}(j, k) \equiv \log_2 \frac{E[x_j \mid \text{condition} = k]}{E[x_j \mid \text{condition} \neq k]},$$

where  $x_j$  is the measured expression level (e.g., UMI count) of gene  $j$ . In experiments where the conditions are inferred—for example, by running a machine learning algorithm to cluster the expression profiles—this quantity could represent the difference in gene expression between cells inside and outside a cluster.<sup>1</sup>

The aim of the next sections is to define an analogue to the log-fold change statistic for topic modeling.

**2. The multinomial topic model and Poisson non-negative matrix factorization.** Here we briefly describe the multinomial topic model, and its connection to Poisson non-negative matrix factorization (Poisson NMF).

We begin with the “bag of words” description, which was used to describe the LDA model [1]. In this view, each document (or gene expression profile)  $i$  is represented as a vector of terms/genes,  $w_i = (w_{i1}, \dots, w_{is_i})$ , where  $s_i$  is the size of document  $i$ . (The order of the words or genes appearing in this vector doesn’t matter, hence the “bag of words.”) Each  $w_{it} \in \{1, \dots, m\}$  is term/gene  $j$  with probability  $p(w_{it} = j \mid z_{it} = k) = f_{jk}$ , in which we have introduced  $z_{it}$ , a variable indicating which topic  $k \in \{1, \dots, K\}$  the word/gene is drawn from. The topic indicator variables for document  $i$  are in turn generated according to  $p(z_{it} = k) = l_{ik}$ .

This process also defines a *multinomial* model for an  $n \times m$  matrix of counts  $x_{ij}$ :

$$(2) \quad x_{i1}, \dots, x_{im} \sim \text{Multinom}(x_{i1}, \dots, x_{im}; s_i, \pi_i),$$

where  $x_{ij} = \sum_{t=1}^{s_i} \delta_j(w_{it})$  is the number of times term/gene  $j$  appears in document/cell  $i$ , and the probabilities  $\pi_{ij}$  are weighted sums of the “factors”  $f_{jk}$ ,

$$(3) \quad \pi_{ij} = \sum_{k=1}^K l_{ik} f_{jk}.$$

The log-likelihood for the multinomial topic model, ignoring terms that do not depend on the model parameters, has a simple expression:

$$(4) \quad \log p(x) = \sum_{i=1}^n \sum_{j=1}^m x_{ij} \log(\sum_{k=1}^K l_{ik} f_{jk}).$$

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<sup>1</sup>Supposing  $n_k$  out of a total of  $n$  gene expression profiles (cells) are from condition  $k$ , then  $\text{lfc}(j, k)$  can be computed as  $\text{lfc}(j, k) = \log_2 \{n_{jk} / (n_j - n_{jk}) \times (n - n_k) / n_k\}$ , where  $n_j$  is the total expression of gene  $j$  among all expression profiles, and  $n_{jk}$  is the total expression of  $j$  among all cells in condition (or cluster)  $k$ .

As we have shown elsewhere, the multinomial topic model is closely related to a Poisson non-negative matrix factorization of the count data,

$$(5) \quad x_{ij} \sim \text{Poisson}(\lambda_{ij}),$$

where  $\lambda_{ij} = \sum_{k=1}^K \hat{l}_{ik} \hat{f}_{jk}$ . Given a Poisson NMF fit, an equivalent multinomial topic model can be easily recovered, as we have shown elsewhere.

**3. The “term-count log-ratio” (*tclr*).** Returning to the question of assessing differential gene expression, there are two new twists when done in the context of topic modeling:

1. The cluster (topic) assignments are probabilistic.
2. The cluster assignments are made at the level of genes, not cells.

I propose a statistic, the “term-count log-ratio,” to address these two points. It is the (logarithm of the) expected expression level of gene  $j$  conditioned on assignment to topic  $k$  over the expected expression level of gene  $j$  conditioned on not being assigned to topic  $k$ :

$$(6) \quad \text{tclr}(j, k) \equiv \log_2 \frac{E[x_j \mid \text{topic} = k]}{E[x_j \mid \text{topic} \neq k]}.$$

For a given gene  $j$  and topic  $k$ ,  $\text{tclr}(j, k)$  can be calculated as

$$(7) \quad \begin{aligned} \text{tclr}(j, k) &= \log_2 \left\{ \frac{E[x_j, \text{topic} = k]}{E[x_j, \text{topic} \neq k]} \times \frac{p(\text{topic} \neq k)}{p(\text{topic} = k)} \right\} \\ &= \log_2 \left\{ \frac{\sum_{i=1}^n \sum_{t=1}^{s_i} \delta_j(w_{it}) \phi_{ijkt}}{\sum_{i=1}^n \sum_{t=1}^{s_i} \delta_j(w_{it}) (1 - \phi_{ijkt})} \times \frac{\sum_{i=1}^n \sum_{t=1}^{s_i} \phi_{ijkt}}{\sum_{i=1}^n \sum_{t=1}^{s_i} 1 - \phi_{ijkt}} \right\}, \end{aligned}$$

where  $\phi_{ijkt}$  denotes the posterior probability of  $z_{it} = k$  given  $w_{it} = j$ ,

$$(8) \quad \begin{aligned} \phi_{ijkt} &\equiv p(z_{it} = k \mid w_{it} = j) \\ &= \frac{p(w_{it} = j \mid z_{it} = k) p(z_{it} = k)}{\sum_{k'=1}^K p(w_{it} = j \mid z_{it} = k') p(z_{it} = k')} \\ &= \frac{l_{ik} f_{jk}}{\sum_{k'=1}^K l_{ik'} f_{jk'}}. \end{aligned}$$

Since the topic assignments  $z_{it}$  do not depend on  $t$ —that is, we can drop the “ $t$ ” subscript from  $\phi_{ijkt}$ —the expression for the *tclr* simplifies somewhat:

$$(9) \quad \text{tclr}(j, k) = \log_2 \left\{ \frac{\sum_{i=1}^n x_{ij} \phi_{ijk}}{\sum_{i=1}^n x_{ij} (1 - \phi_{ijk})} \times \frac{\sum_{i=1}^n \sum_{j'=1}^m x_{ij'} \phi_{ij'k}}{\sum_{i=1}^n \sum_{j'=1}^m x_{ij'} (1 - \phi_{ij'k})} \right\}$$

At the maximum-likelihood solution (MLE) of the  $l_{ik}$ ’s and  $f_{kl}$ ’s, the *tclr* statistic simplifies further:

$$(10) \quad \text{tclr}(j, k) = \log_2 \left\{ \frac{\sum_{i=1}^n x_{ij} \phi_{ijk}}{\sum_{i=1}^n x_{ij} (1 - \phi_{ijk})} \times \frac{\sum_{i=1}^n s_i l_{ik}}{\sum_{i=1}^n s_i (1 - l_{ik})} \right\}.$$

This is because, at the MLE, the loadings  $s_{ik}$ ,  $k = 1, \dots, K$ , for a given document/cell  $i$  should be proportional to the sums  $\sum_{j=1}^m x_{ij} \phi_{ijk}$ .

Finally, it is convenient that the *tclr* (7) will be the same if we replace the multinomial topic model parameters  $l_{ik}$  and  $f_{jk}$  with the corresponding parameters of the Poisson NMF,  $\hat{l}_{ik}$  and  $\hat{f}_{jk}$  (proof not given).

## REFERENCES

- [1] D. M. BLEI, A. Y. NG, AND M. I. JORDAN, *Latent Dirichlet allocation*, Journal of Machine Learning Research, 3 (2003), pp. 993–1022.
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- [3] J. QUACKENBUSH, *Microarray data normalization and transformation*, Nature Genetics, 32 (2002), pp. 496–501.