

THE “TERM-COUNT LOG-RATIO” STATISTIC FOR TOPIC MODELING ANALYSIS OF DIFFERENTIAL GENE EXPRESSION

PETER CARBONETTO*

1. Differential gene expression. The “log-fold change” statistic is commonly used in microarray and RNA sequencing experiments to quantify expression changes 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.

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

$$(2) \quad \text{lfc}(j, k) = \log_2 \left\{ \frac{n_{jk}}{n_j - n_{jk}} \times \frac{n - n_k}{n_k} \right\},$$

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 .

The aim in 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).

The topic model describes a process for generating an $n \times m$ matrix of counts, X . We begin with the “bag of words” description, which is what is used to describe LDA [1]. In this view, each row i is a document (or gene expression profile), and let m_i be the size of this document; that is, $m_i = \sum_{j=1}^m x_{ij}$. The vector w_i is a vector of terms (or genes) of length m_i (the order of the words or genes appearing in this vector doesn’t matter, hence the “bag of words”). For each $t = 1, \dots, m_i$, the word/gene w_{it} is equal to j with probability $p(w_{it} \mid z_{it} = k) = f_{jk}$, where z_{it} is a variable indicating which topic, $k \in \{1, \dots, K\}$ the word/gene belongs to. The topic indicator variable is in turn generated according to $p(z_{it} = k) = l_{ik}$, where l_{i1}, \dots, l_{iK} is a document-specific probability table.

This process defines a *multinomial* model for the counts x_{i1}, \dots, x_{im} in document/sample i , hence the “multinomial topic model”:

$$(3) \quad x_{i1}, \dots, x_{im} \sim \text{Multinom}(x_{i1}, \dots, x_{im}; m_i, \pi_i),$$

where π_i is a vector of probabilities π_{ij} given by a weighted sum of the word/gene probabilities, or “factors”, f_{jk} ,

$$(4) \quad \pi_{ij} = \sum_{k=1}^K l_{ik} f_{jk}.$$

*Dept. of Human Genetics and the Research Computing Center, University of Chicago, Chicago, IL

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

$$(5) \quad \log p(x) = \sum_{i=1}^n \sum_{j=1}^m x_{ij} \log(\sum_{k=1}^K l_{ik} f_{jk}).$$

As we have investigated in other documents, the multinomial topic model is closely related to a Poisson non-negative matrix factorization of the count data,

$$(6) \quad x_{ij} \sim \text{Poisson}(\lambda_{ij}),$$

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; by “equivalent”, we mean the likelihoods of the two models are the same.

3. The “term-count log-ratio” (*tclr*). Returning to the question of assessing differential gene expression, there are two twists relative to the standard analysis: one, the group (topic) assignments are probabilistic; two, the group assignments are made at the level of genes, not cells. With these two points in mind, I propose the “term-count log-ratio”, 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 :

$$(7) \quad \text{tclr}(j, k) \equiv \log_2 \frac{E[x_j | z_j = k]}{E[x_j | z_j \neq k]}.$$

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

$$(8) \quad \begin{aligned} \text{tclr}(j, k) &= \log_2 \left\{ \frac{E[x_j, z_j = k]}{E[x_j, z_j \neq k]} \times \frac{p(z_j \neq k)}{p(z_j = k)} \right\} \\ &= \log_2 \left\{ \frac{\sum_{i=1}^n E[x_{ij}, z_{ij} = k]}{\sum_{i=1}^n E[x_{ij}, z_{ij} \neq k]} \times \frac{\sum_{i=1}^n p(z_{ij} \neq k)}{\sum_{i=1}^n p(z_{ij} = k)} \right\} \\ &= \log_2 \left\{ \frac{\sum_{i=1}^n x_{ij} p(z_{ij} = k)}{\sum_{i=1}^n x_{ij} p(z_{ij} \neq k)} \times \frac{\sum_{i=1}^n \sum_{j'=1}^m x_{ij} p(z_{ij'} \neq k)}{\sum_{i=1}^n \sum_{j'=1}^m x_{ij} p(z_{ij'} = k)} \right\}, \end{aligned}$$

The probabilities $p(z_{ij} = k)$ in the above expressions are *posterior probabilities*, which, in the multinomial topic model, work out to simply

$$(9) \quad p(z_{ij} = k) = \frac{l_{ik} f_{jk}}{\sum_{k'=1}^K l_{ik'} f_{jk'}}.$$

Here I’ve made use of the property that the topic assignments z_{it} are the same for all $w_{it} = j$, so in a small abuse of notation I’ve written the topic assignments as z_{ij} .

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

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

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

Finally, it is convenient that the *tclr* (8) 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

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