

# THE “TERM-COUNT LOG-RATIO” STATISTIC FOR 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 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,

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

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. Poisson non-negative matrix factorization and the multinomial topic model.** Here we briefly describe the multinomial topic model and Poisson non-negative matrix factorization—these are covered in much more detail in other documents.

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.

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”,

$$(3) \quad \text{tclr}(j, k) = \log_2 \left\{ \frac{x}{y} \right\}.$$

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## REFERENCES

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