**Fitting the topic model**

We used fastTopics [fastTopics2022] to fit a (multinomial) topic model to the (UMI?) counts, with *K* = 16 topics. fastTopics implemennts the following simple strategy to fit the topic model: first, fit a non-negative matrix factorization based on a *Poisson model* (“Poisson NMF”) [hien2021]; second, recover maximum-likelihood estimates (MLEs) of the topic model parameters by a simple reparameterization [fastTopics2022].

In detail, we fit the *K* = 16 topic model to the UMI counts by taking the following steps. First, we removed genes with very low expression (total UMI count ≤ 20). Therefore, UMI counts for 364 samples and 28,209 genes were used to estimate the parameters of the topic model. Second, we ran 20 expectation maximization (EM) updates, without extrapolation, to get close to a MLE solution (“prefitting phase”). This prefitting phase was implemented in R by calling fit\_poisson\_nmf from fastTopics with the following settings: numiter = 20, method = "em", init.method = "random", control = list(nc = 8). Third, we performed an additional 180 coordinate descent (CD) updates, with extrapolation, to improve the fit (“refinement phase”). This refinement phase was implemented by calling fit\_poisson\_nmf with the following settings: method = "scd", numiter = 180, control = list(numiter = 4, nc = 8, extrapolate = TRUE), in which the model fit was initialized using the fit obtained from the prefitting phase. Finally, the topic model was recovered from the Poisson NMF model by calling function poisson2multinom. The convergence diagnostics suggested that, after a total of 200 combined iterations of the Poisson NMF optimization, the parameter estimates were very close to a MLE: the change in log-likelihood between successive iterations was less than 1 × 10-5, and the largest residual in the first-order (“Karush-Kuhn-Tucker”) conditions was less than 1.

Reassuringly, the estimated topics capture the predominant expression patterns, which largely coincide with the 13 tissues. Two other topics (topics 1 and 6) capture variation specific to two tissues (LI and PBMC), and one topic (topic 9) captures changes in expression over time that are not specific to any one tissue.

*If necessary, we can add details here about fitting topic models separately to each tissue.*

**Visualizing the topic proportions**

The *n* × *K* matrix of topic proportions, where *n* denotes the number of RNA-seq samples and *K* is the number of topics, can be viewed as an embedding of the saamples in a (*K* − 1)- dimensional space. A simple way to visualize this embedding in 2-d (or 3-d) is to apply a nonlinear dimensionality reduction technique such as *t*-SNE [tsne2008] to L [47]. A more powerful approach, first suggested by [countClust2017], is to visualize all *K* − 1 dimensions simultaneously using a Structure plot [rosenberg2002]. The Structure plot is essentially a stacker bar chart, in which the bars correspond to samples and bar heights (in different colors, one for each toppic) are determined by the topic proportions. To produce the Structure plot, we first group the RNA-seq samples by tissue, then order them within each tissue by time point.

**Computing environment for topic modeling analysis**

Most computations on real data sets were performed in R 3.5.1 [R2018], linked to the OpenBLAS 0.2.19 optimized numerical libraries, on Linux machines (Scientific Linux 7.4) with Intel Xeon E5-2680v4 (“Broadwell”) processors. For performing the Poisson NMF optimization and DE analysis, which included some multithreaded computations, as many as 8 CPUs and 16 GB of memory were used. More details about the computing environment, including the R packages used, are recorded in the workflowr [workflowr2019] pages in the companion code repository [TO DO: create Zenodo repository].

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