**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)… and (5) recover F, L from W, H. The prefitting phase was implemented by. The refinement phase was implemented with a second call to fit poisson nmf, with numiter = 1000, method = "scd", control = list(numiter = 4,extrapolate = TRUE), in which the model fit was initialized using the fit obtained from the prefitting phase. The topic model fit was recovered by calling the function poisson2multinom.

**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].

[fasttopics2022] Carbonetto, P., Luo, K., Dey, K., Hsiao, J., Sarkar, A., Hung, A., Stephens, M.: fastTopics: Fast Algorithms for Fitting Topic Models and Non-negative Matrix Factorizations to Count Data. (2022). R package version 0.6-97.

[hien2021] Hien, L.T.K., Gillis, N.: Algorithms for nonnegative matrix factorization with the Kullback–Leibler divergence. Journal of Scientific Computing 87(3), 93 (2021)

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