

Although an essential step, cell functional annotation often proves particularly challenging from single-cell transcriptional data. Several methods have been developed to accomplish this task. However, in most cases, these rely on techniques initially developed for bulk RNA sequencing or simply make use of marker genes identified from cell clustering followed by supervised annotation. To overcome these limitations and automatize the process, we have developed two novel methods, the single-cell gene set enrichment analysis (scGSEA) and the single-cell mapper (scMAP). scGSEA combines latent data representations and gene set enrichment scores to detect coordinated gene activity at single-cell resolution. scMAP uses transfer learning techniques to re-purpose and contextualize new cells into a reference cell atlas. Using both simulated and real datasets, we show that scGSEA effectively recapitulates recurrent patterns of pathways' activity shared by cells from different experimental conditions. At the same time, we show that scMAP can reliably map and contextualize new single-cell profiles on a breast cancer atlas we recently released. Both tools are provided in an effective and straightforward workflow providing a framework to determine cell function and significantly improve annotation and interpretation of scRNA-seq data.