stream Feature selection -Dimensionality reduction → ELPiGraph: structure learning and fitting Finalized structure S5 S4 Input 1656 cells Standard deviation 4768 genes Single-cell expression data Mean **GMP PAGA TSCAN** single-cell graph PAGA graph PAGA path gene₁ Resolution 1 gene₂ high-dimensional space node Initialize embedding distance gene₁ Resolution 2 metric, measure choose gene₂ kNN, partition path, node graph connectivity randompatitioning walk distance distance PC 1 Elpigraph pcreode Seeding initial graph structure Generating and fitting candidate topologies Final graph structure Hierarchical i) Raw singlecell data placement Down-sampling v) Shortest path topology ii) Down-Consensus OData point alignment ◆ Graph node Contractive spring Repulsive spring sampled data Exploring structure space with topological graph grammars Graph construction vi) Realigned topology i) Graph metric slingshot (closeness) Charecterized nodes End-state representative identification topology iv) Identified end-states high Racid/StemID High **DDRTree** dimension Graph based (principal tree noisy differential learning + dimension tSNE scRNA-seq analysis reduction) dataset SimplePPT Partition clusters of cells Normalization strongly dimension) **UMAP** Pseudotime connecting assignment **PCA** components L1-graph principal graph learning in the same dimesion StemID score ⊐multipotent cells Monocle3 Clustering (Louvain

123456789

clustering)