scMerge: Integration of multiple single-cell transcriptomics datasets leveraging stable expression and pseudo-replication

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scMerge Framework

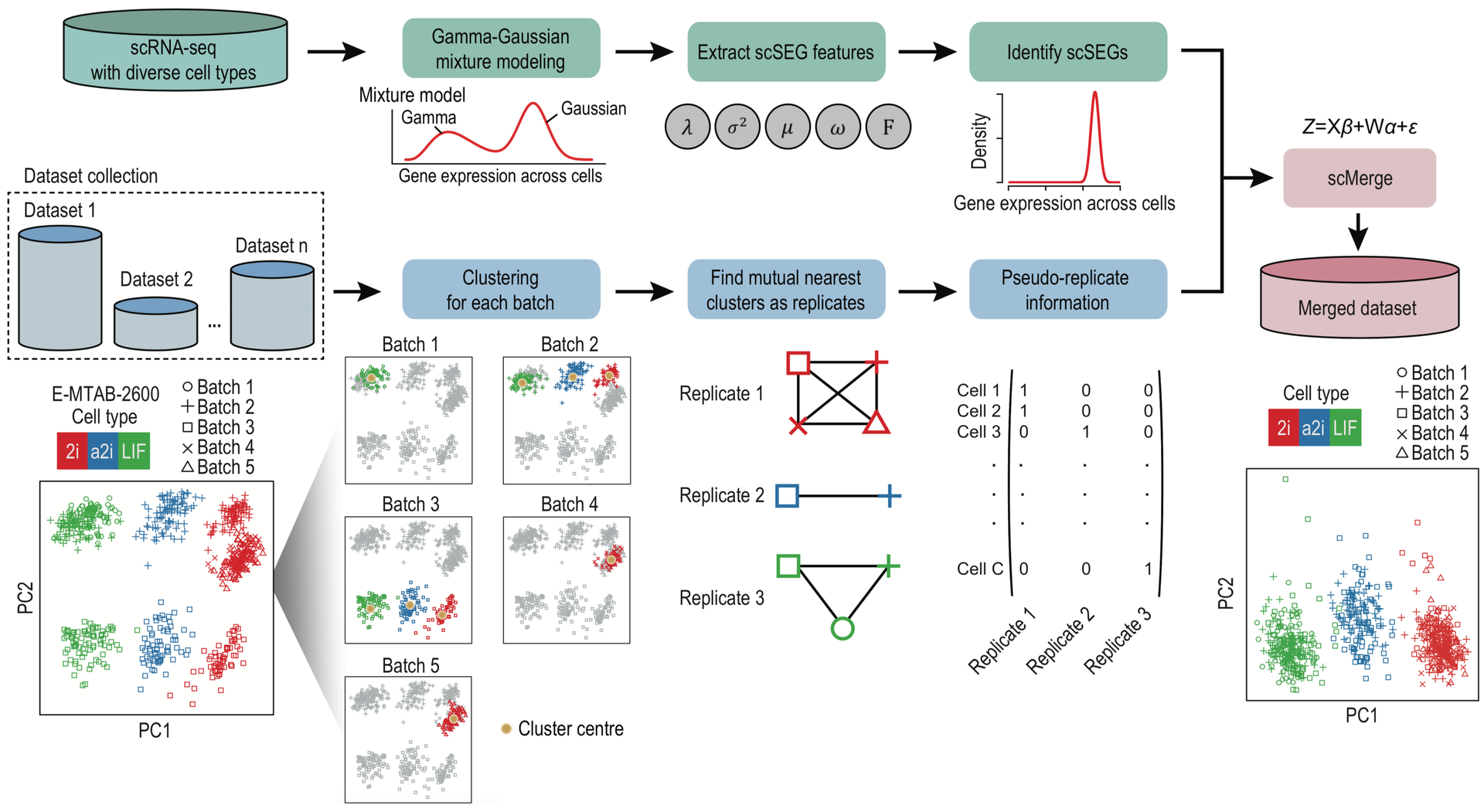
Concerted examination of multiple collections of single cell RNA-seq data promises further biological insights that cannot be uncovered with individual datasets.

The **scMerge** algorithm consists of three key components:

(i) the identification of ***stably expressed genes (scSEGs)*** via a Gamma-Gaussian mixture model (Ghazanfar et al. 2016) for use as 'negative controls' for estimating unwanted factors;

(ii) the construction of ***pseudo-replicates*** to estimate the effects of unwanted factors;

(iii) the adjustment of the datasets with unwanted variation using a ***fastRUVIII*** model with the negative control genes and pseudo-replicates, resulting in a single merged dataset.

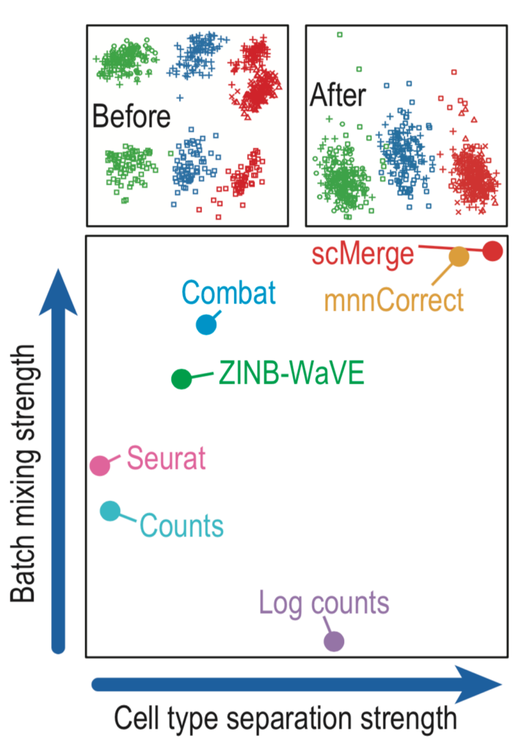


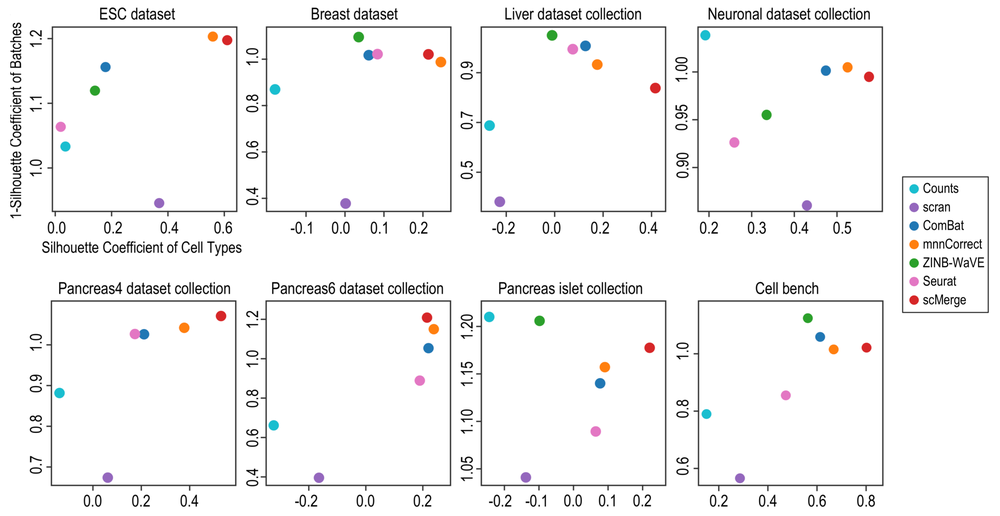
Dataset collections

Name	Accession	Organism	Tissue/organ source	# of cell types	# of cells	Protocol
mESC	E-MTAB-2600	Mouse	mESC	3	704	SMART-seq/C1
Breast	GSE113197	Human	Breast cancer	3	24520	10x Chromium
Liver	GSE87795 GSE90047 GSE87038 GSE96981	Mouse	Liver	8	1249	SMART-seq/C1 SMART-seq2 SMART-seq2 SMART-seq/C1
Neuronal	SRP065920 GSE75413	Mouse	Neuronal	2	145	SMART-seq2 STRT-seq
Pancreas6 / Pancreas4	GSE81608 GSE83139 GSE86469 E-MTAB-5061	Human	Pancreas	6	4566	SMART-seq/C1 SMART-seq/C1 SMART-seq/C1 SMART-seq2
Pancreas6	GSE85241	Human	Pancreas	6	1773	Cel-seq2
Pancreas6	GSE84133	Human/mouse	Pancreas Islets	13	8569	inDrop
CellBench	NA	Human	Adenocarcinoma cell lines	3	1401	Cel-seq2, Drop-seq, & 10x Chromium
Embryogenesis	GSE45719 GSE57249 E-MTAB-3321	Mouse	Embryogenesis	10+	2144	SMART-seq SMARTer SMART-seq2
Embryogenesis	GSE44183 E-MTAB-3929	Human/mouse	Embryogenesis	10+	2144	Tang et al., 2010 SMART-seq2
Embryogenesis	GSE36552 GEO66507	Human	Embryogenesis	10+	2144	Tang et al., 2010 SMARTer

Dataset collections that are used in this study.

Evaluation





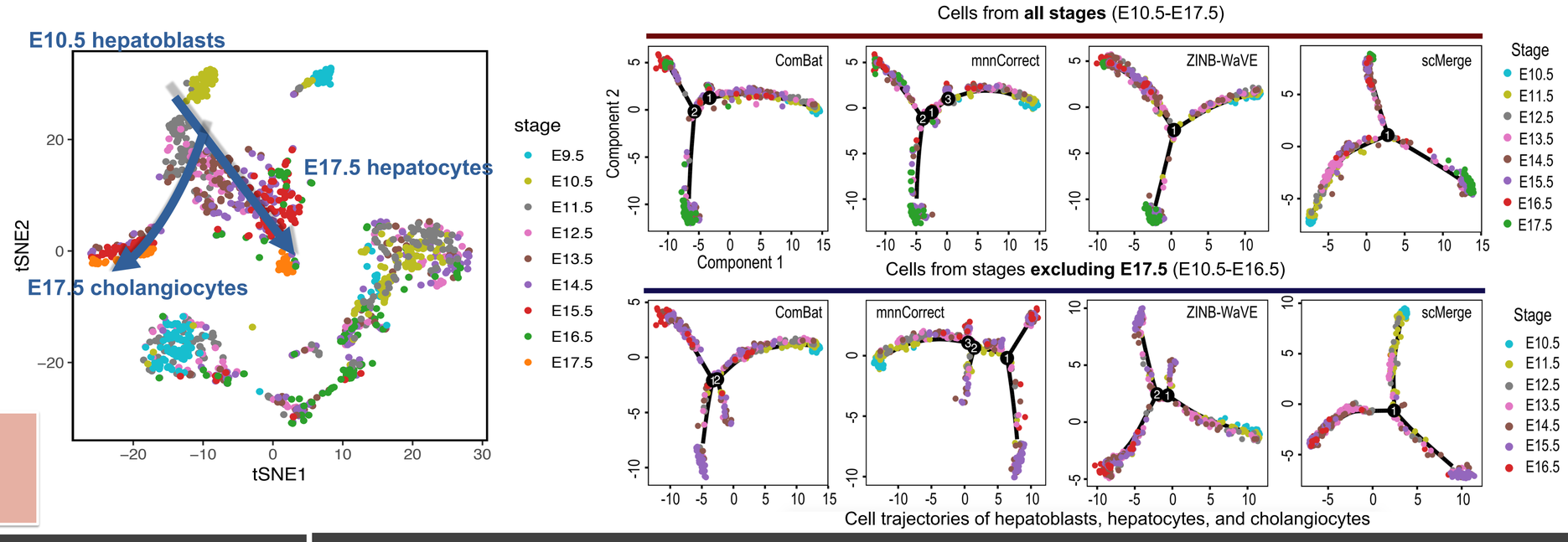
Results: scMerge performed favorably in terms of maintaining strong biological signal and reducing unwanted variation such as batch and/or data-specific noise in seven data collections that cover different tissues, species and protocols.

Case study: Integration of four mouse fetal liver single-cell RNA-seq datasets

Summary: To illustrate the capability of scMerge to enable further downstream analyses, we examined the stability when faced with incomplete data.

Approach: We reconstructed the cell trajectories, using Monocle 2, of hepatoblasts, hepatocytes, and cholangiocytes for both the full Liver data collection and for a subset of the original Liver data collection; with E17.5 time point of GSE90047 removed.

Results: scMerge was most consistent with the full Liver data collection and agrees with current literature.



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Further information

The scMerge R package and more case studies are available at https://sydneybiox.github.io/scMerge

Reference:

Ghazanfar et al. BMC Systems Biology 2016, 10(Suppl 5):127 doi: 10.1186/s12918-016-0370-4
Lin et al. BioRxiv 2018, doi: https://doi.org/10.1101/393280

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