RIA: a novel Regression-based Imputation Approach for single-cell RNA sequencing

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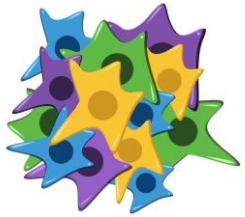
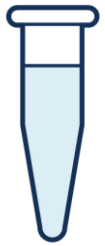
Background

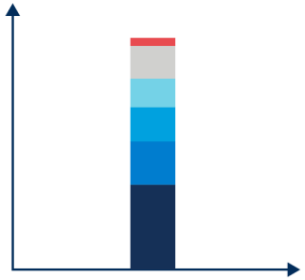
Single – Cell RNA Sequencing



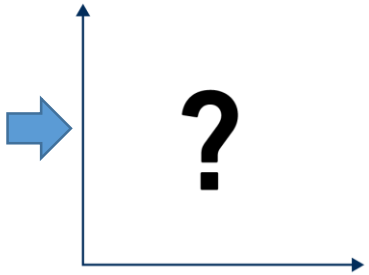
Tissue



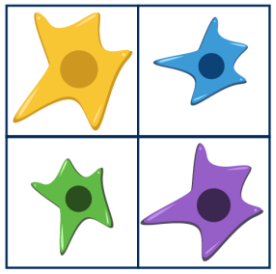
Bulk-Cell analysis



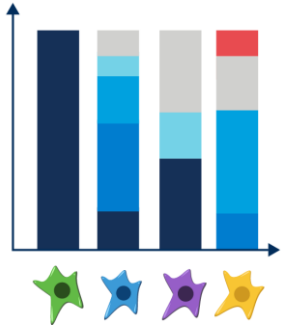
Average expression from all cells



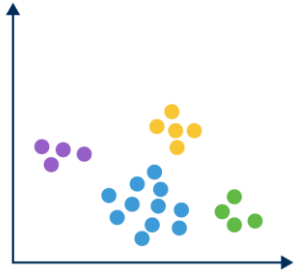
No cellular heterogeneity revealed



Single-Cell Analysis

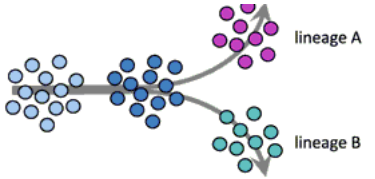


Each cell-type has a unique expression profile

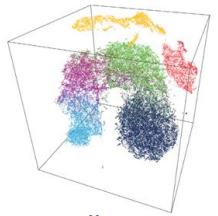


Reveal heterogeneity and subpopulation expression variability

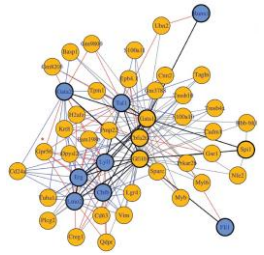
Application



Cell lineage analysis



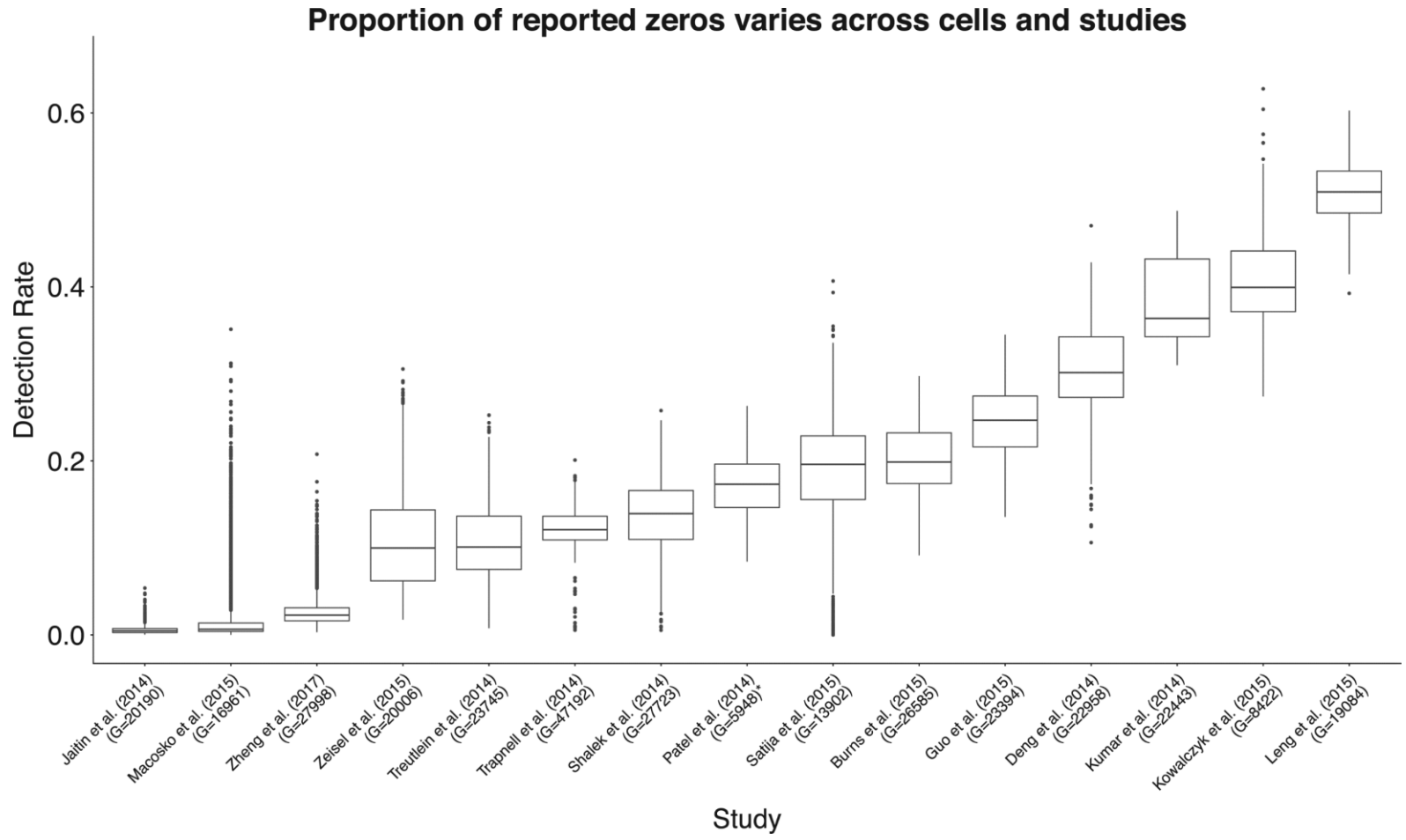
Cell type analysis



scRNAseq network inference

Source: 10xgenomics.com

Dropout Events

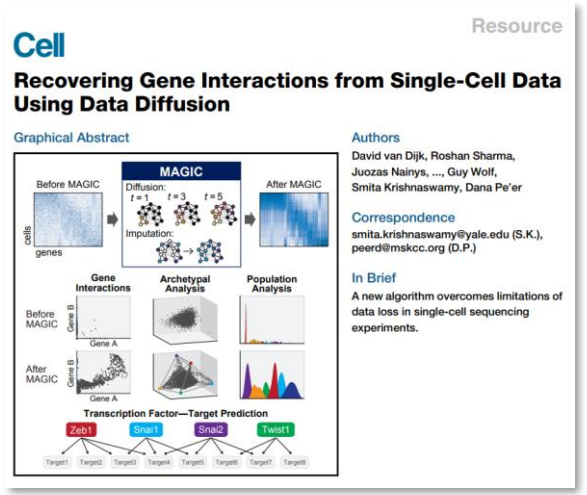


Dropout introduces zero expression value of genes in datasets.

Single – Cell RNAseq Imputation State of The Art

MAGIC [van Dijk et al., 2017]:

- **Citation:** 123
- **Lab:** Krishnaswamy Lab - Yale
- Using Markov Affinity-based Graph Imputation


Resource

Cell

Recovering Gene Interactions from Single-Cell Data Using Data Diffusion

Graphical Abstract

Authors
David van Dijk, Roshan Sharma, Juozas Nainys, ..., Guy Wolf, Smita Krishnaswamy, Dana Pe'er

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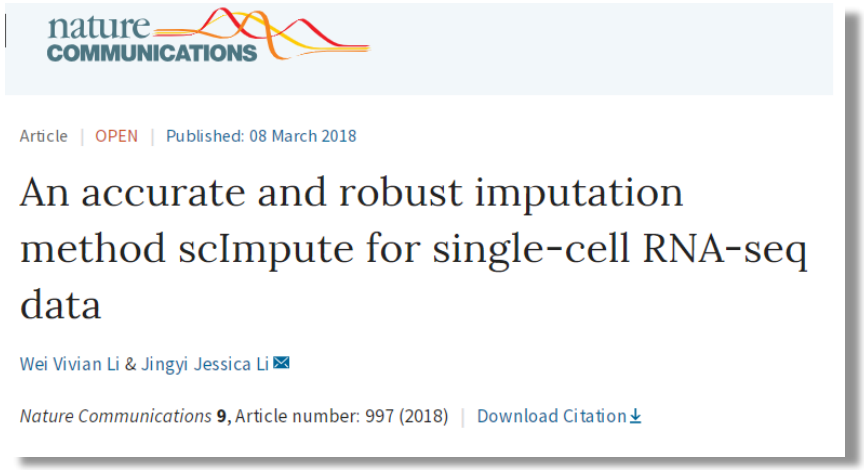
In Brief
A new algorithm overcomes limitations of data loss in single-cell sequencing experiments.

scImpute [Kwak et al., 2017]:

- **Citation:** 104
- **Lab: UCLA**
- Using statistical approach.


nature COMMUNICATIONS

Article | OPEN | Published: 08 March 2018

An accurate and robust imputation method scImpute for single-cell RNA-seq data

Wei Vivian Li & Jingyi Jessica Li

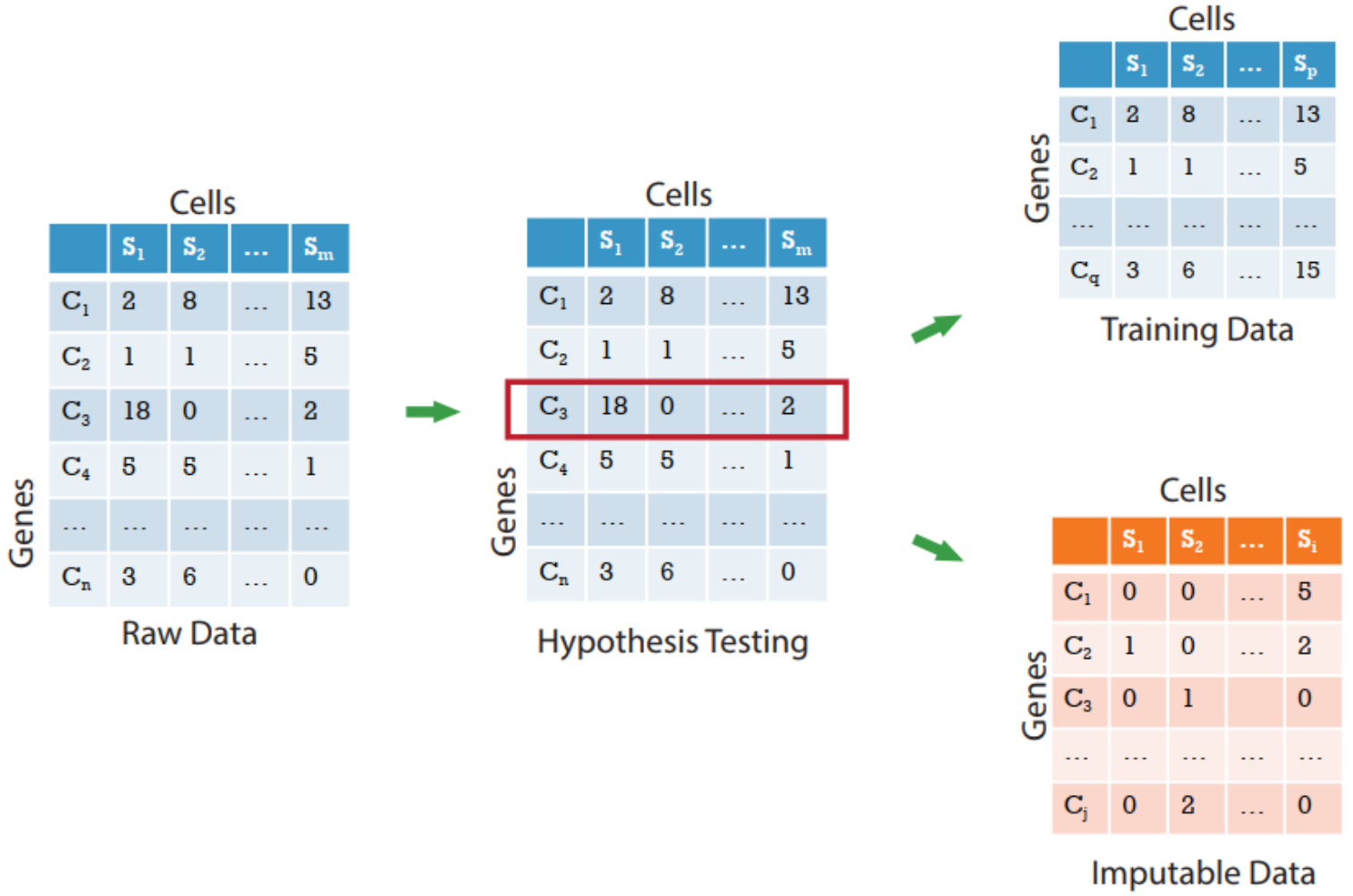
Nature Communications **9**, Article number: 997 (2018) | Download Citation

Method: RIA a novel Regression-based Imputation Approach for single-cell RNA sequencing

RIA

- Identifying genes that are impacted by dropouts
- Impute using genes with high confidence

Hypothesis Testing and Dropout Identification

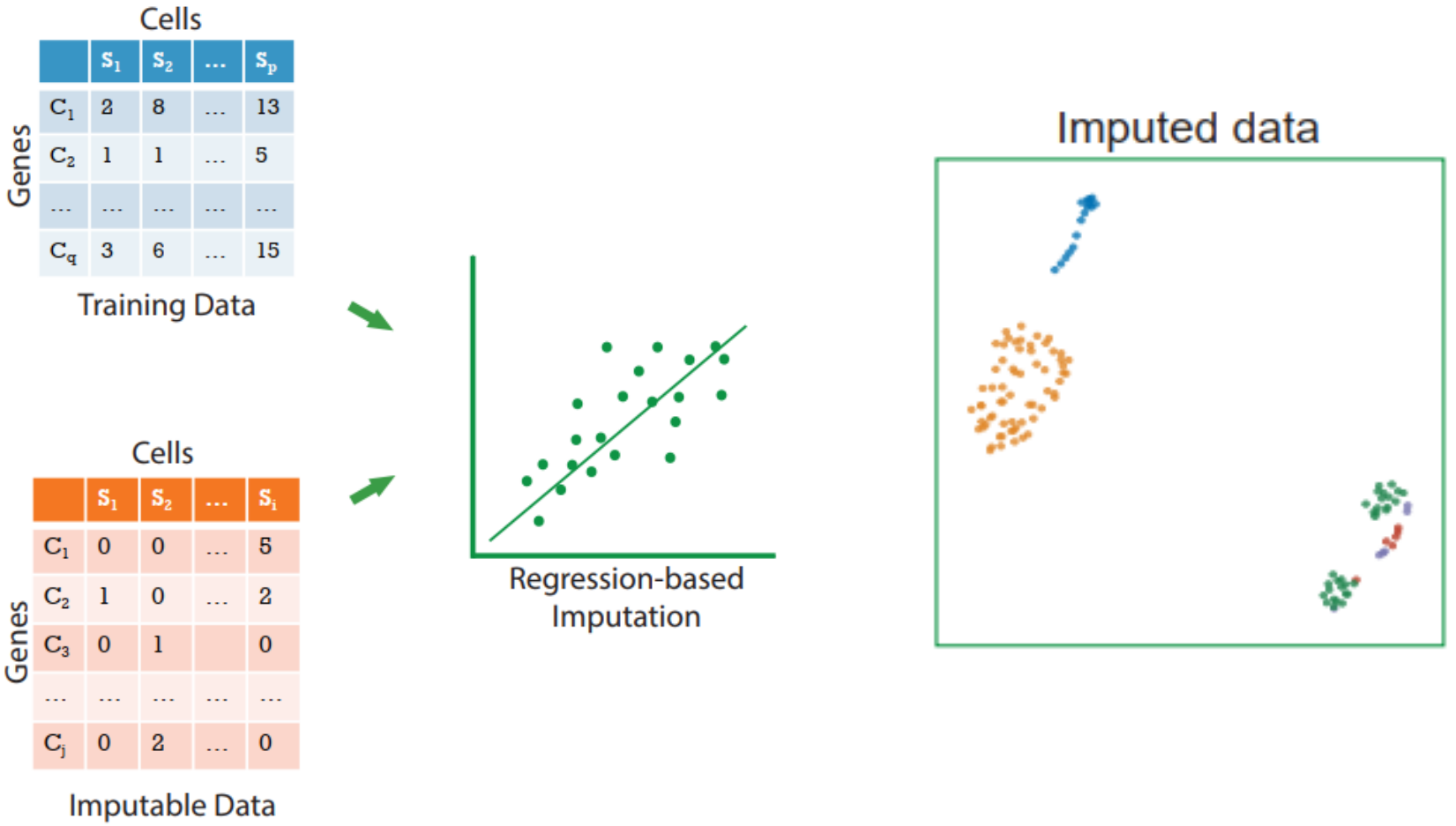


	S_1	S_2	...	S_m
C_1	2	8	...	13
C_2	1	1	...	5
C_3	18	0	...	2
C_4	5	5	...	1
...	...	...	...	...
C_n	3	6	...	0

	S_1	S_2	...	S_p
C_1	2	8	...	13
C_2	1	1	...	5
...	...	...	...	...
C_q	3	6	...	15

	S_1	S_2	...	S_i
C_1	0	0	...	5
C_2	1	0	...	2
C_3	0	1		0
...	...	...	...	...
C_j	0	2	...	0

Generalized Linear Regression Model



RIA Overview

Hypothesis testing approach

Generalized linear model

Results

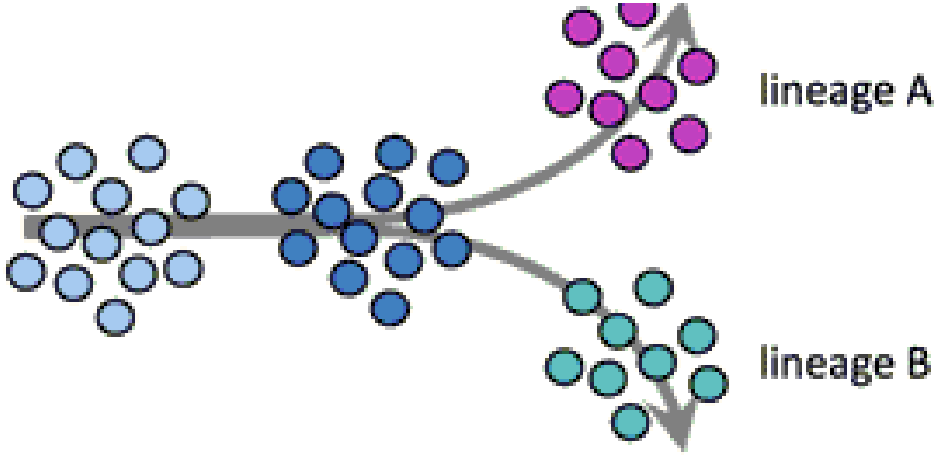
Data an Evaluation Metrics

- MAGIC
- scImpute

TABLE I
SINGLE-CELL DATA OBTAINED FROM NIH GEO

Dataset	Accession ID	Size	K	Organism	Protocol
Biase[27]	GSE57249	49	4	Mouse Embryo	SMARTer
Yan[28]	GSE36552	90	6	Human Embryo	Tang
Goolam[29]	E-MTAB-3321	124	5	Mouse Embryo	Smart-Seq2
Deng[30]	GSE45719	268	6	Mouse Embryo	Smart-Seq2
Zeisel[31]	GSE60361	3,005	9	Mouse Brain	STRT-Seq

Cell type clustering



Time-trajectory inference

RIA Improves the Cells Clustering Results

TABLE II
COMPARISONS USING ADJUSTED RAND INDEX (ARI).

Dataset	Adjusted Rand Index			
	Raw	RIA	scImpute	MAGIC
Biase	0.558	**0.711**	-0.009	0.154
Yan	0.558	**0.573**	0.507	0.029
Goolam	0.501	**0.914**	0.321	0.197
Deng	0.549	**0.815**	0.229	0.483
Zeisel	0.738	**0.768**	0.689	0.289

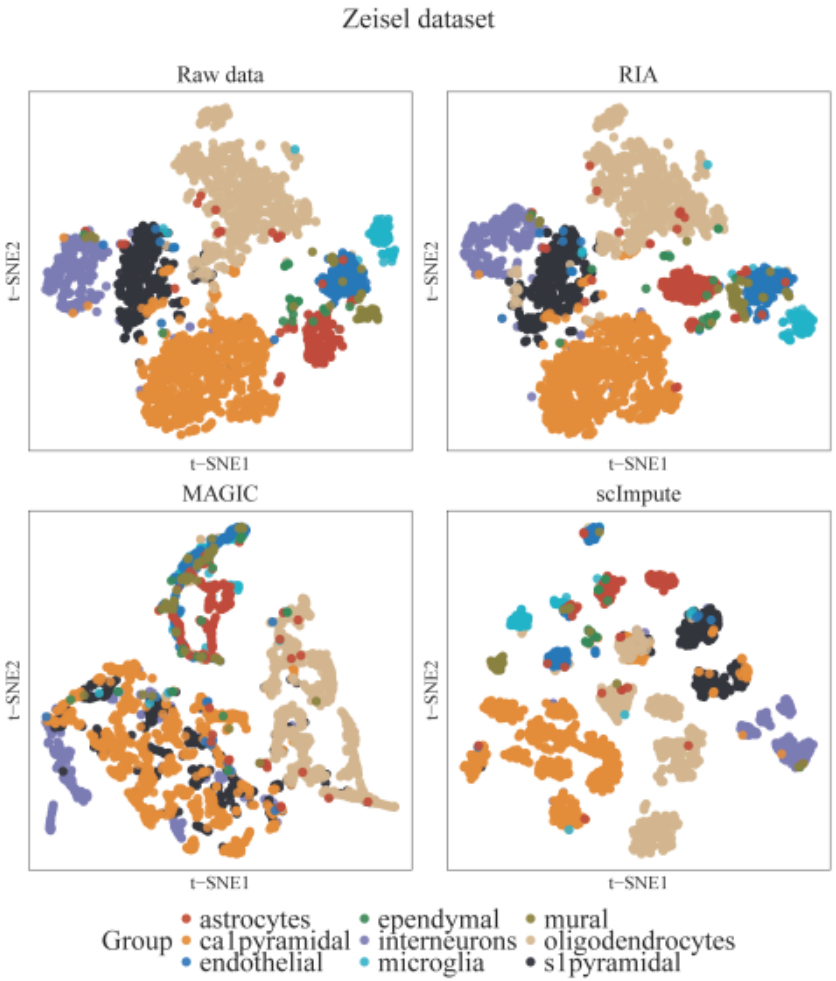
TABLE III
COMPARISON USING JACCARD INDEX

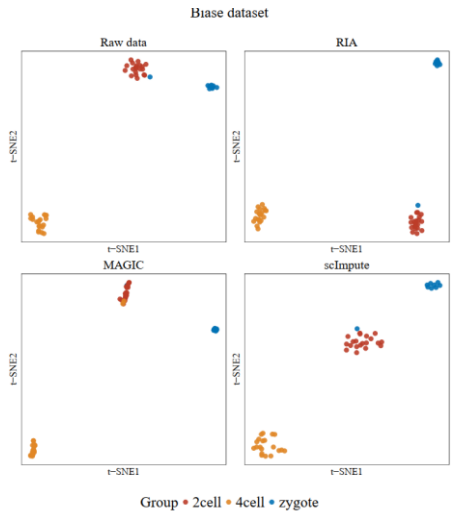
Dataset	Jaccard Index			
	Raw	RIA	scImpute	MAGIC
Biase	0.589	**0.708**	0.339	0.289
Yan	0.498	**0.498**	0.473	0.146
Goolam	0.496	**0.892**	0.375	0.312
Deng	0.524	**0.781**	0.395	0.518
Zeisel	0.651	**0.683**	0.605	0.285

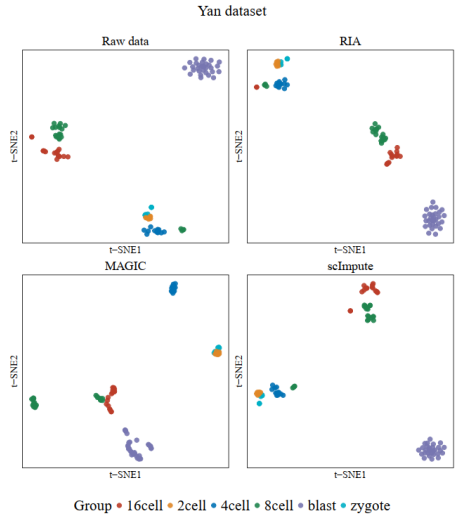
TABLE IV
COMPARISON USING PURITY INDEX

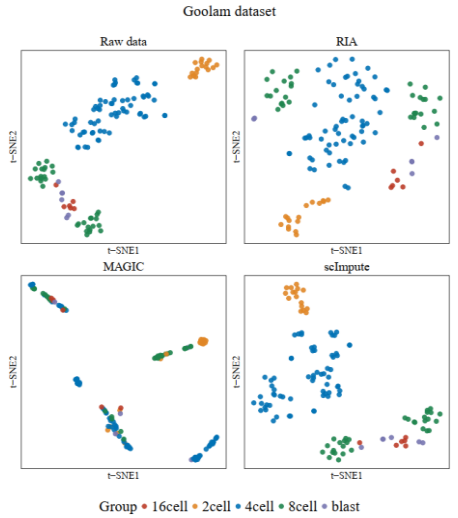
Dataset	Purity Index			
	Raw	RIA	scImpute	MAGIC
Biase	0.795	**0.836**	0.449	0.612
Yan	0.711	**0.778**	0.733	0.467
Goolam	0.822	**0.952**	0.693	0.621
Deng	0.805	**0.839**	0.627	0.750
Zeisel	0.876	**0.893**	0.840	0.668

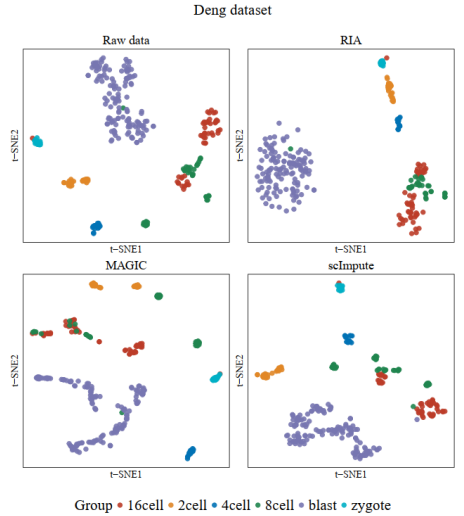
RIA Preserves Original Transcriptome Landscape



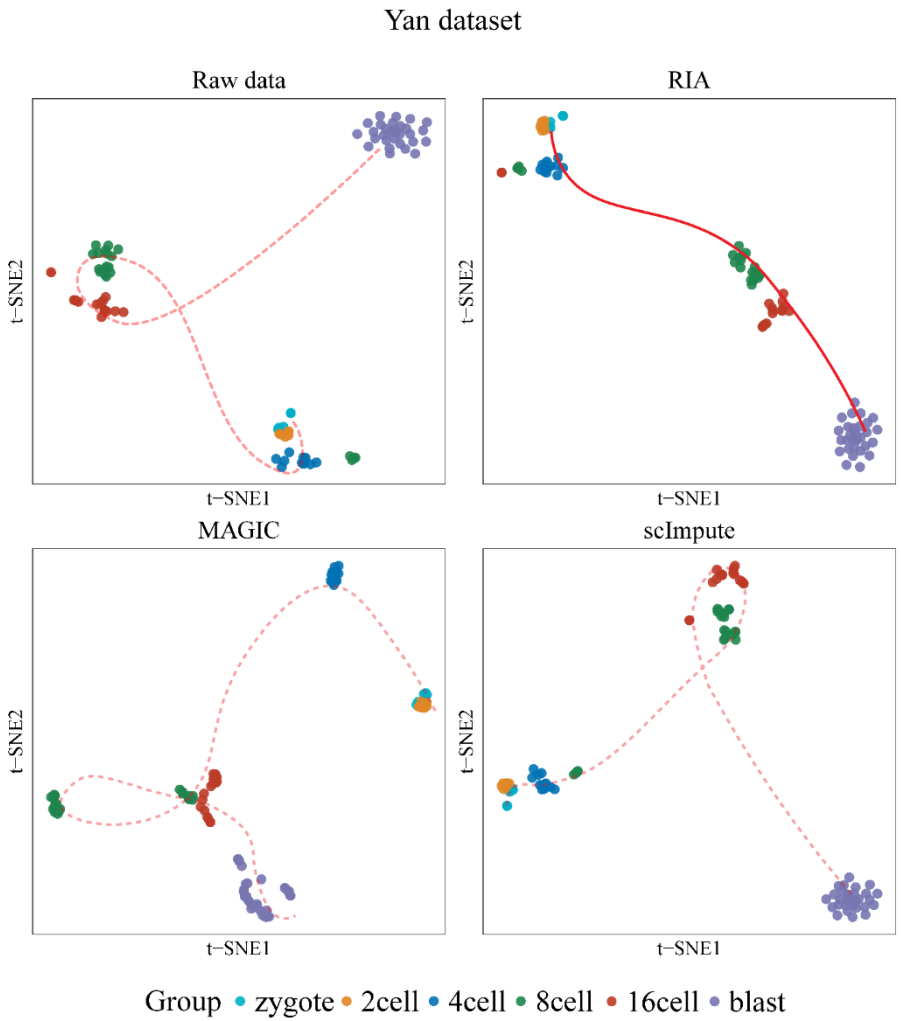


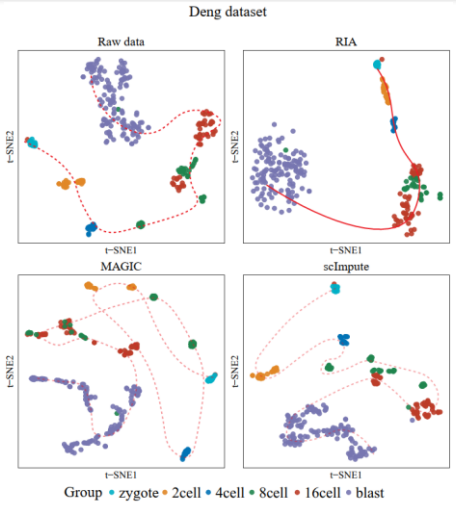


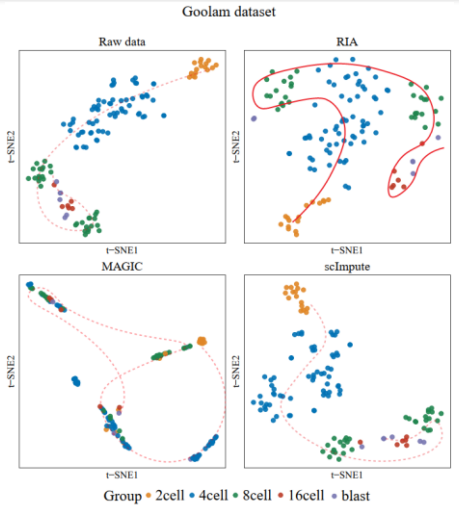


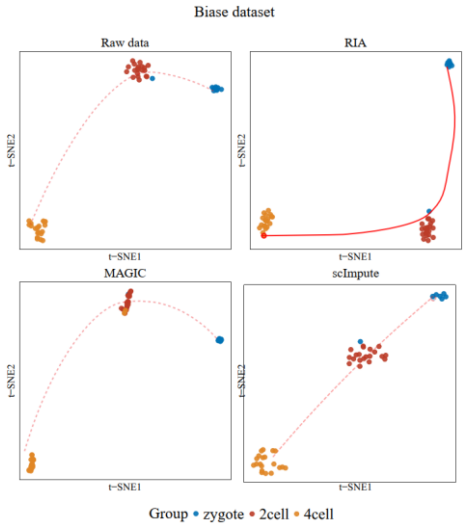


RIA Improves Time Trajectory Inference for TSCAN









Conclusion

- RIA presents a new method to recover missing values caused by dropout events in scRNA-seq data.
- RIA uses a statistical hypothesis testing to identify the set of genes that are likely to be affected by dropouts.
- RIA imputes missing values by using highly correlated genes that share similar biological characteristics.
- RIA dramatically outperforms existing state-of-the-art approaches in improving the identification of cell populations.
- RIA is able to recover temporal trajectories in embryonic development stages.
- RIA is a fast method that can impute thousands of cells with tens of thousands of genes in minutes.

Acknowledgements

People in Bioinformatics Lab at University of Nevada Reno

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References

[1]. Kharchenko, P. V., Silberstein, L., & Scadden, D. T. (2014). Bayesian approach to single-cell differential expression analysis. *Nature methods*, *11*(7), 740.

Q & A

Thank you!