

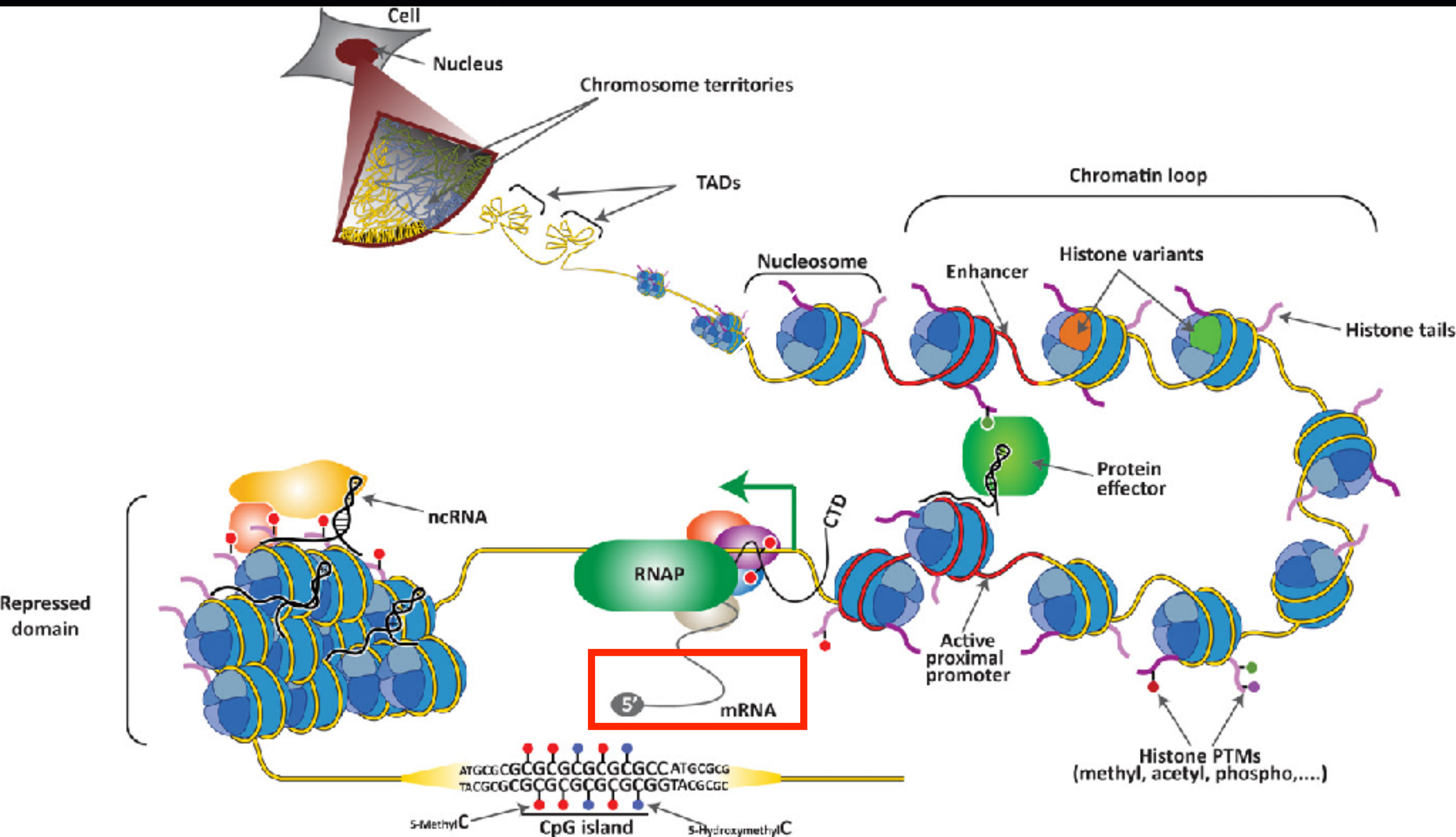
Single-cell RNAseq Analysis Based on Network

Wenliang Wang

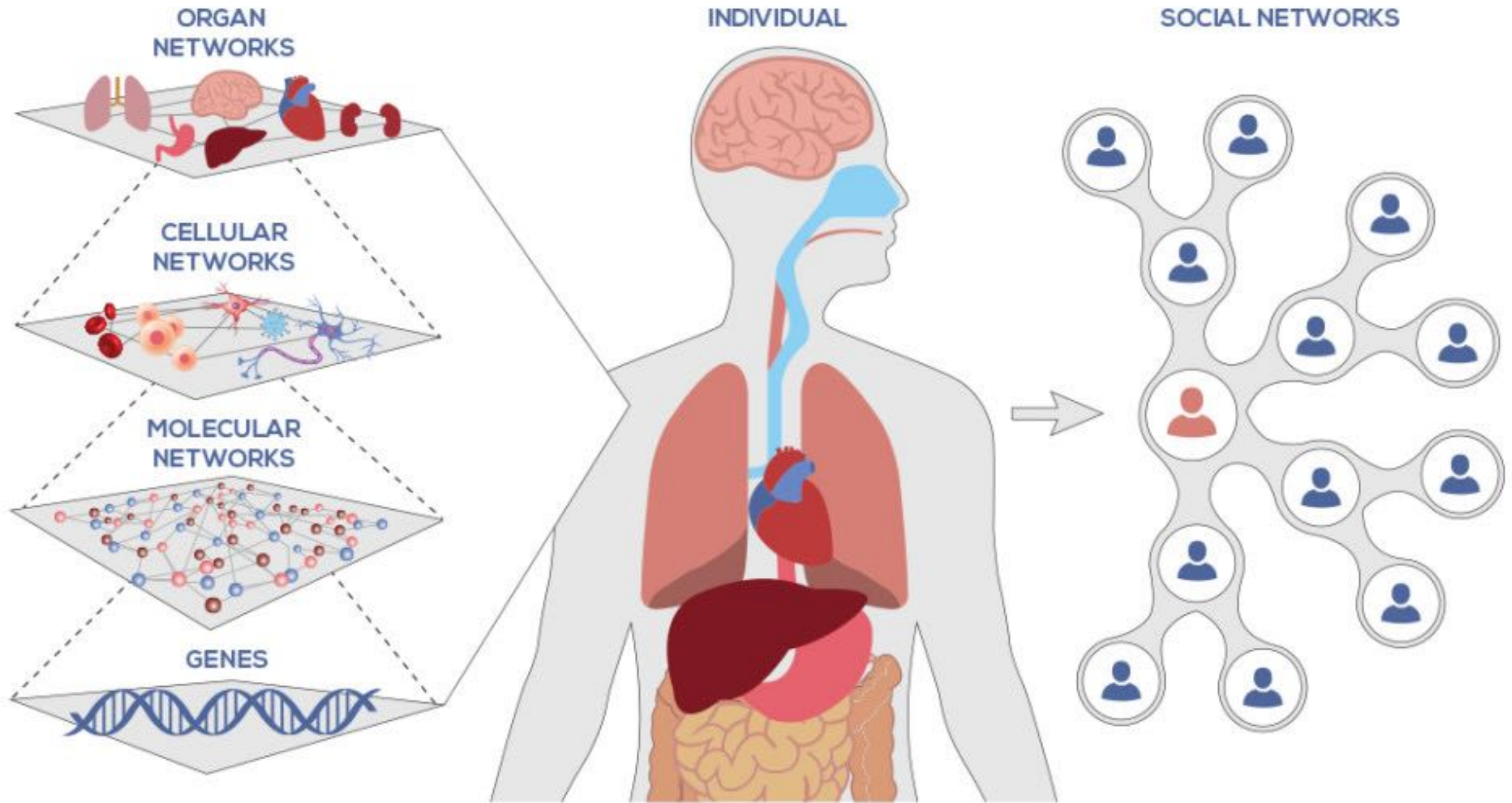
26/07/2018

<https://github.com/wangwl/SingleCellNotes>

Transcription in the cell



Network

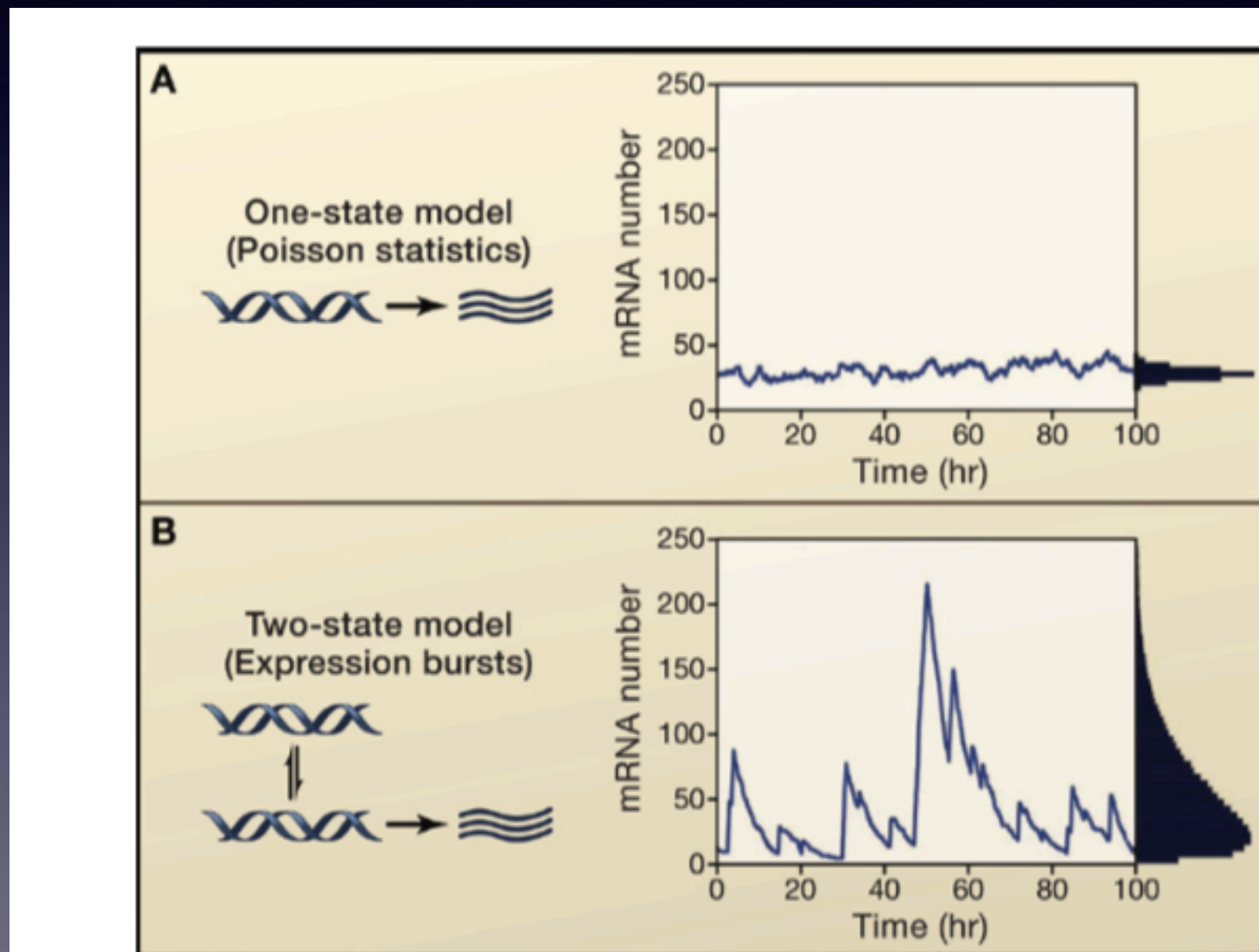


Why?

- Network is biological nature
 - Dependency among genes
- Dropouts
 - Systematic technical noise
 - Transcriptional bursting

Transcriptional bursting

- Also known as transcriptional pulsing, is a fundamental property of genes in which transcription from DNA to RNA can occur in "bursts" or "pulses". —Wikipedia



Inferred network from RNAseq data

- Infer regulatory network activity
 - SCENIC
- Transfer gene expression profile to gene pair independency
 - sample-specific network

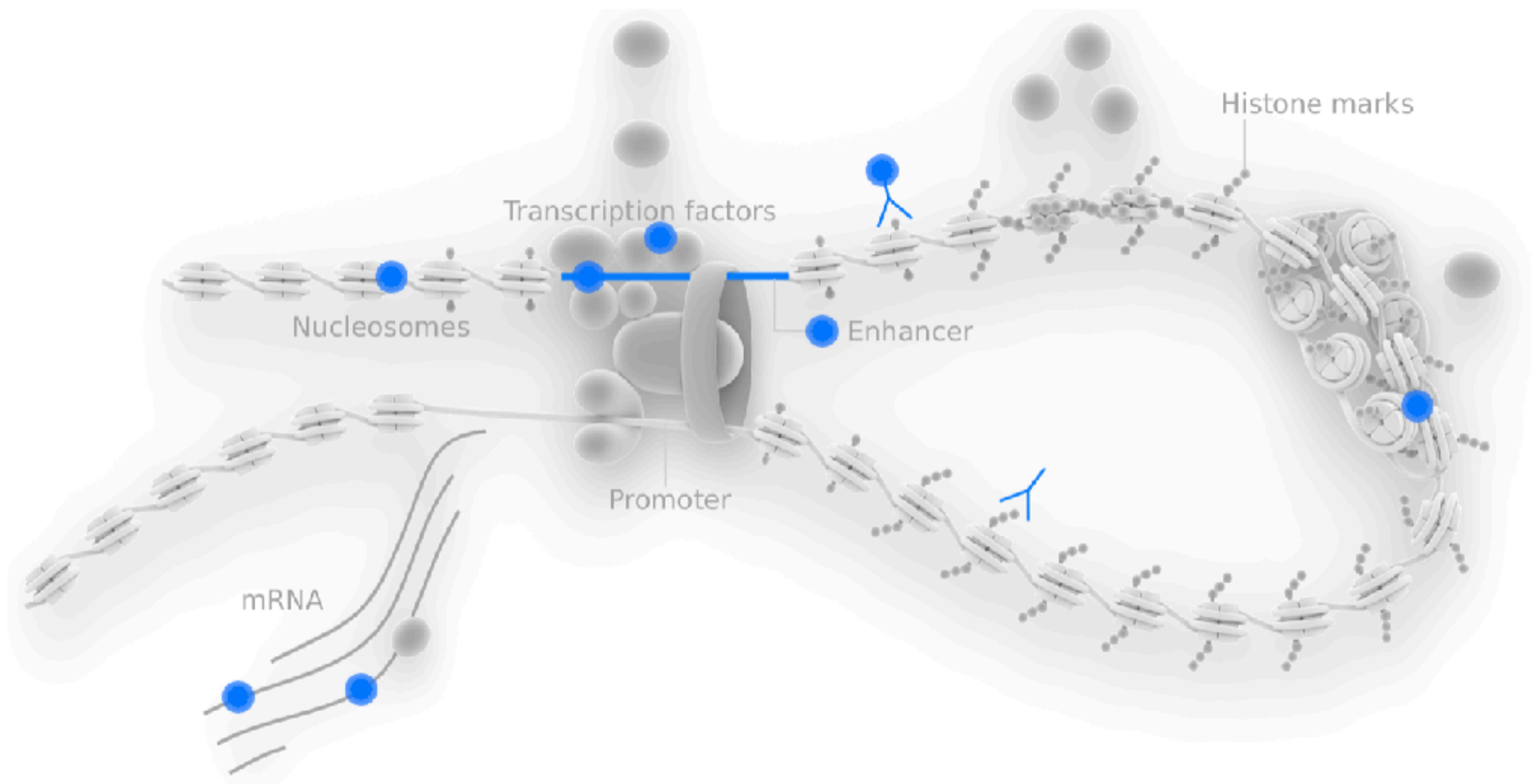
SCENIC

Stein Aerts

Laboratory of Computational Biology.VIB-KU Leuven
Center for Brain & Disease Research. Leuven,
Belgium

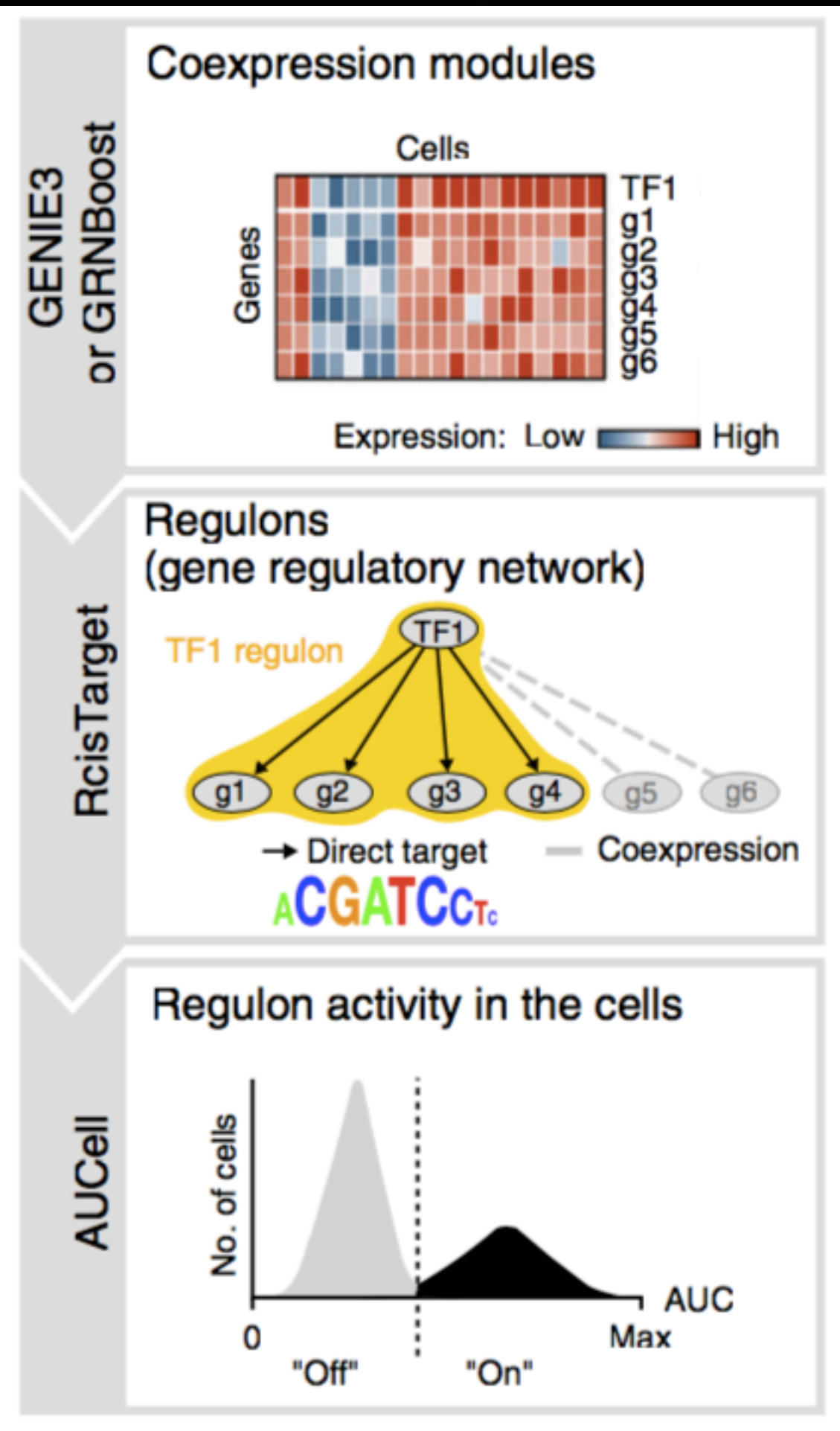


Aibar S, González-Blas C B, Moerman T, et al. SCENIC: single-cell regulatory network inference and clustering[J]. Nature methods, 2017, 14(11): 1083.

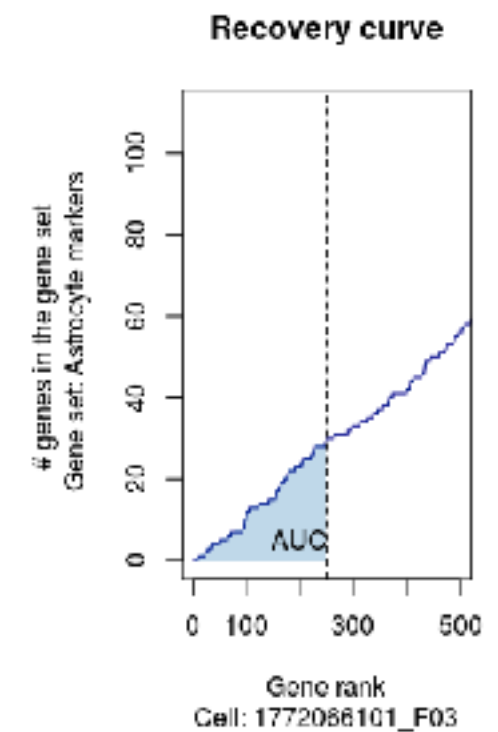
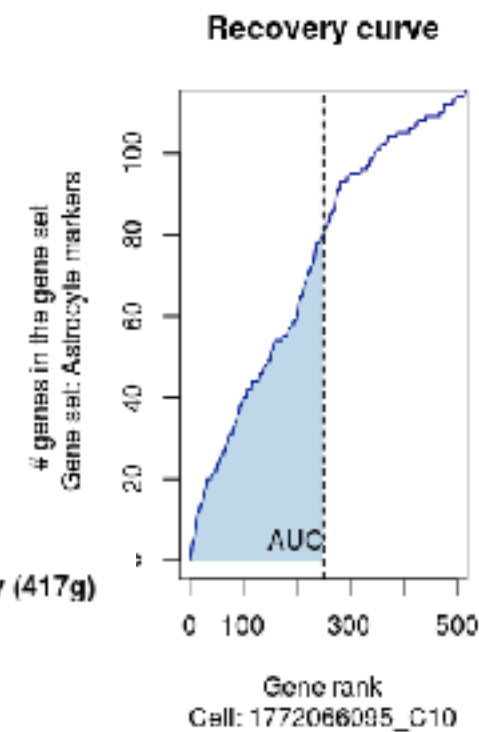
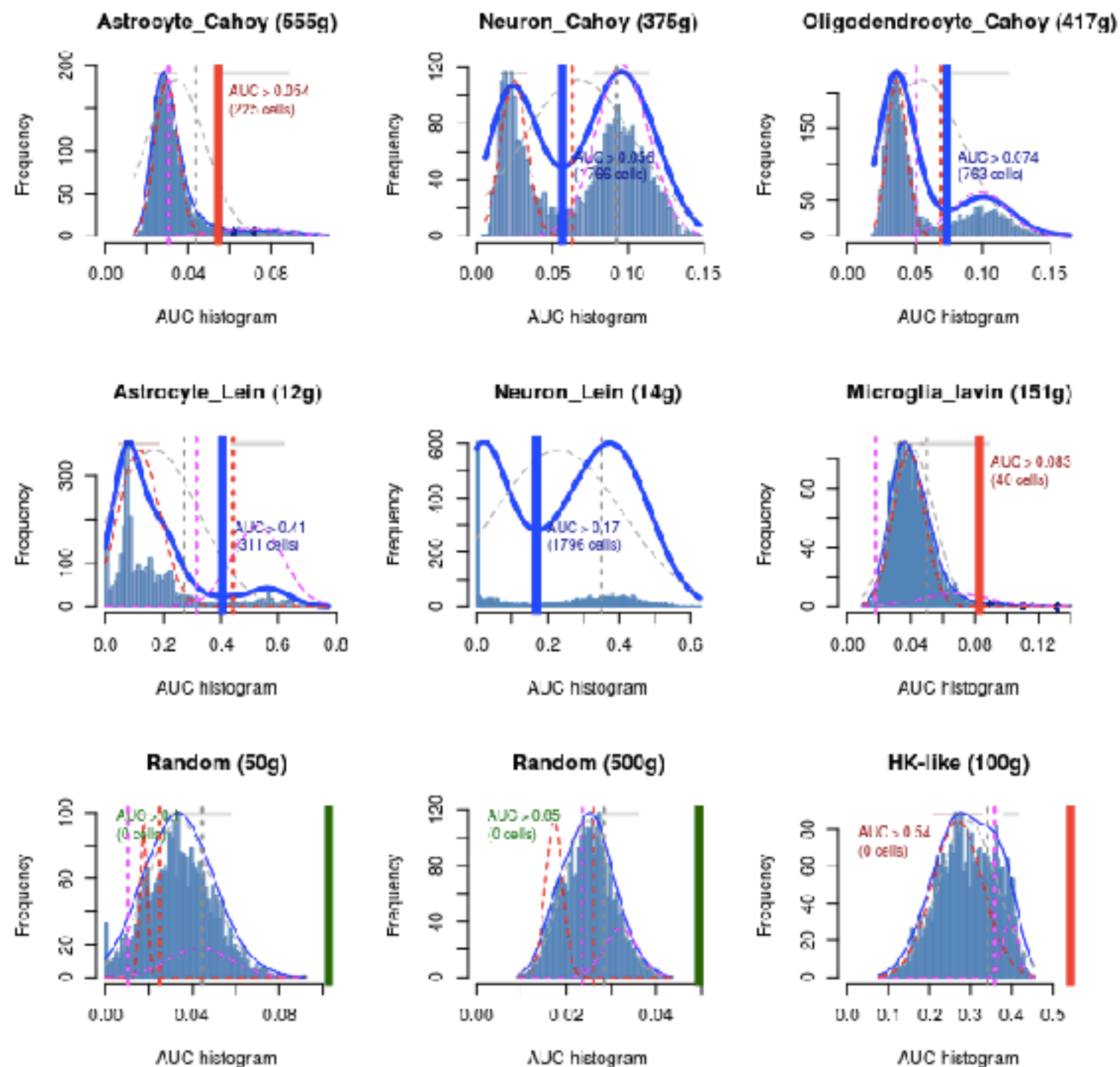


Workflow

- GENIE3, identify potential GRN based on co-expression
- RcisTarget, to perform the TF-motif enrichment analysis and identify the direct targets.
- AUCell, to score the activity of regulons (or other gene sets) in single cells.



AUCCell

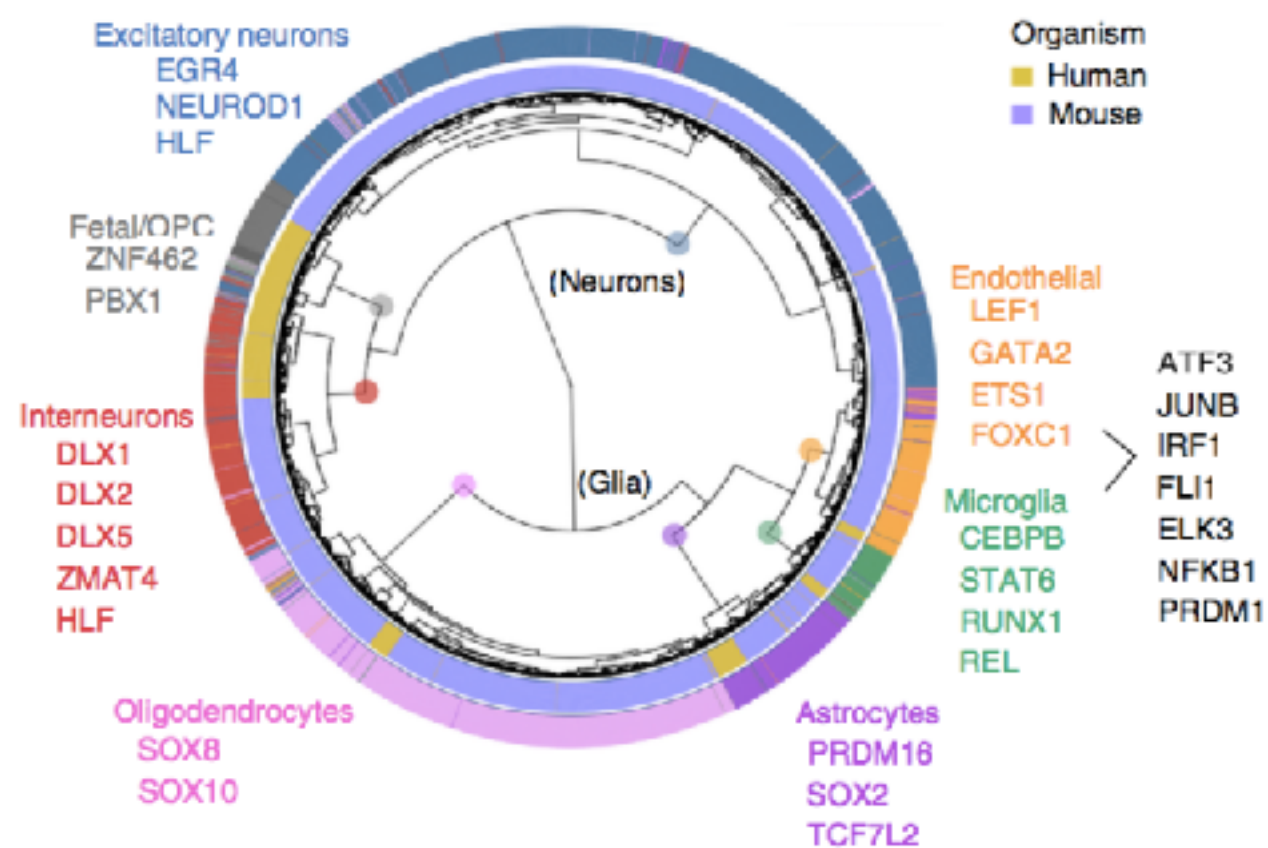


Performance

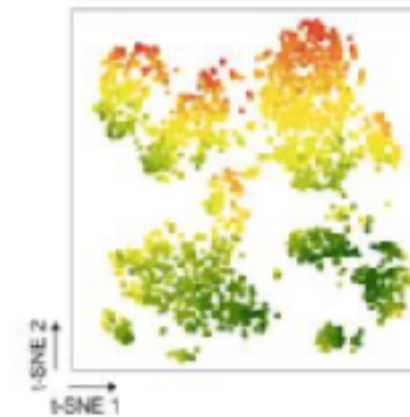
SCENIC identified cell types that are represented by only a few cells

Identify cell complex states from diverse origins

Robust to dropouts and batch effect



c t-SNE on expression

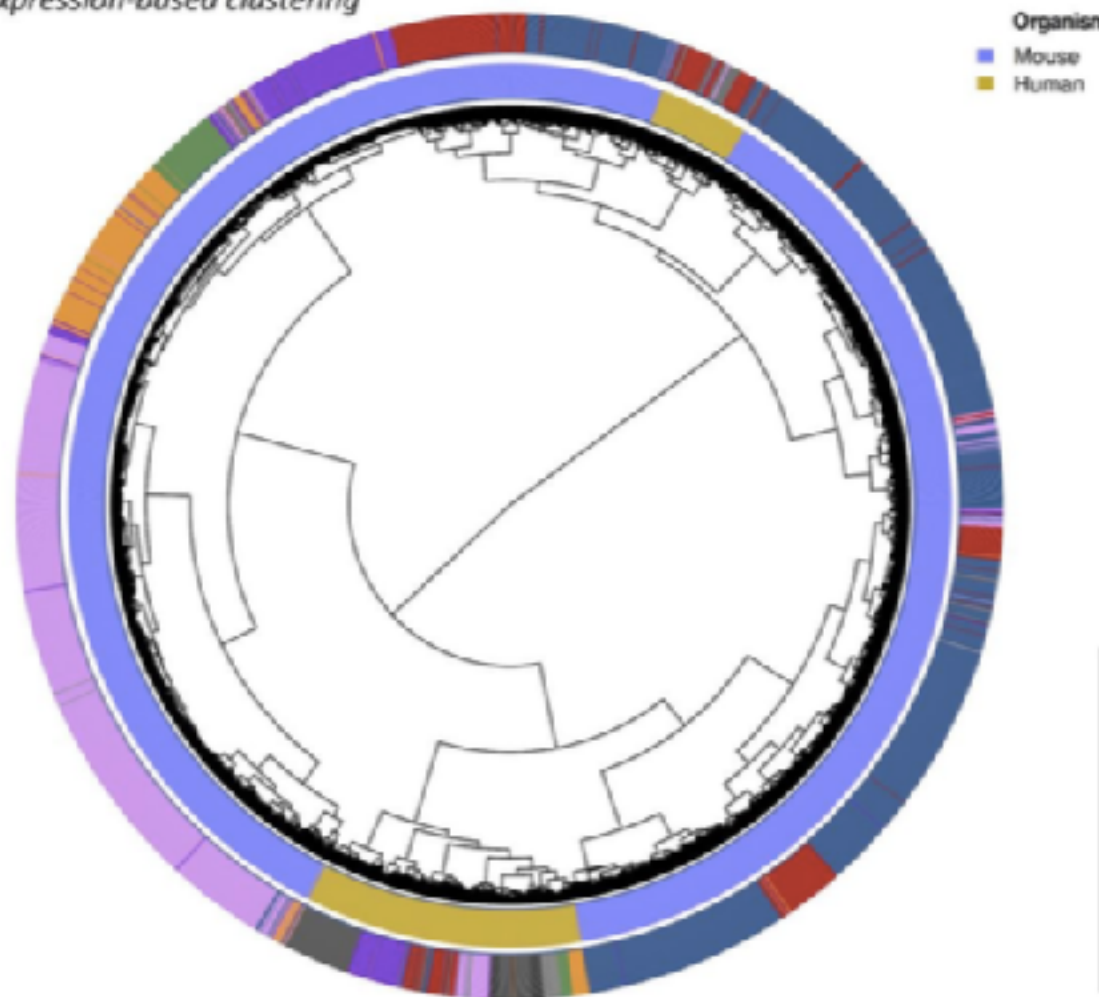


d t-SNE on GRN



detected genes:
1000 2000 8000

Expression-based clustering



Aibar S, González-Blas C B, Moerman T, et al. SCENIC: single-cell regulatory network inference and clustering[J]. Nature methods, 2017, 14(11): 1083.

Sample-specific network

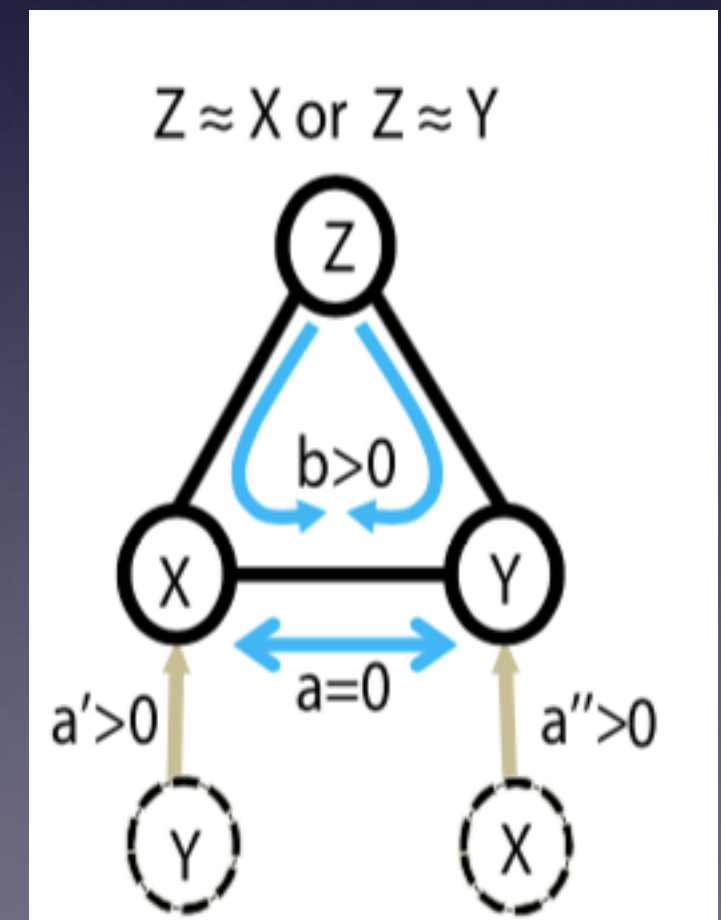
Luonan Chen
SIBS



Zhao J, Zhou Y, Zhang X, et al. Part mutual information for quantifying direct associations in networks[J]. Proceedings of the National Academy of Sciences, 2016, 113(18): 5130-5135.

Liu X, Wang Y, Ji H, et al. Personalized characterization of diseases using sample-specific networks[J]. Nucleic acids research, 2016, 44(22): e164-e164.

- PMI to construct network
- Sample-specific network based on a reference network
- Use gene pair mutual independency for downstream analysis



Network from prior knowledge

- Signaling entropy
 - SCENT, MCE
- Network embedding
 - SCRL
- Smoothing gene expression
 - netSmooth
- Composite measurement
 - projection of expression

Signaling entropy

Andrew Teschendorff
CAS-MPG Computational Biology Institute, Shanghai
University College London



Banerji C R S, Miranda-Saavedra D, Severini S, et al. Cellular network entropy as the energy potential in Waddington's differentiation landscape[J]. Scientific reports, 2013, 3: 3039.

Teschendorff A E, Enver T. Single-cell entropy for accurate estimation of differentiation potency from a cell's transcriptome[J]. Nature communications, 2017, 8: 15599.

Shi J, Teschendorff A, Chen W, et al. Quantifying Waddington's epigenetic landscape: a comparison of single-cell potency measures[J]. bioRxiv, 2018: 257220.

SCENT workflow

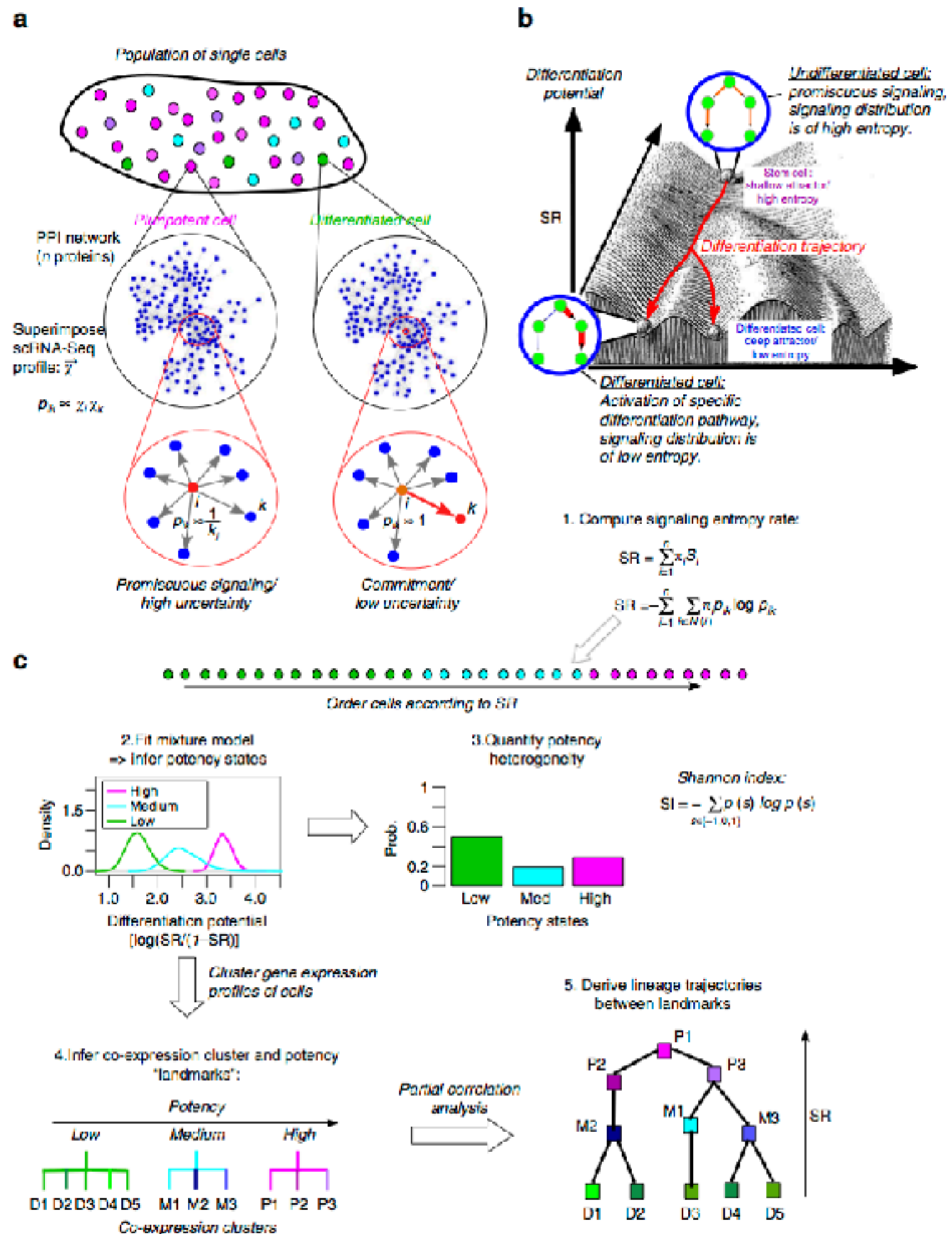
1. Compute SR

2. Inference of SR distribution of single cell population

3. Quantifying intercellular heterogeneity

4. Inference of single cell landmark

5. lineage trajectory



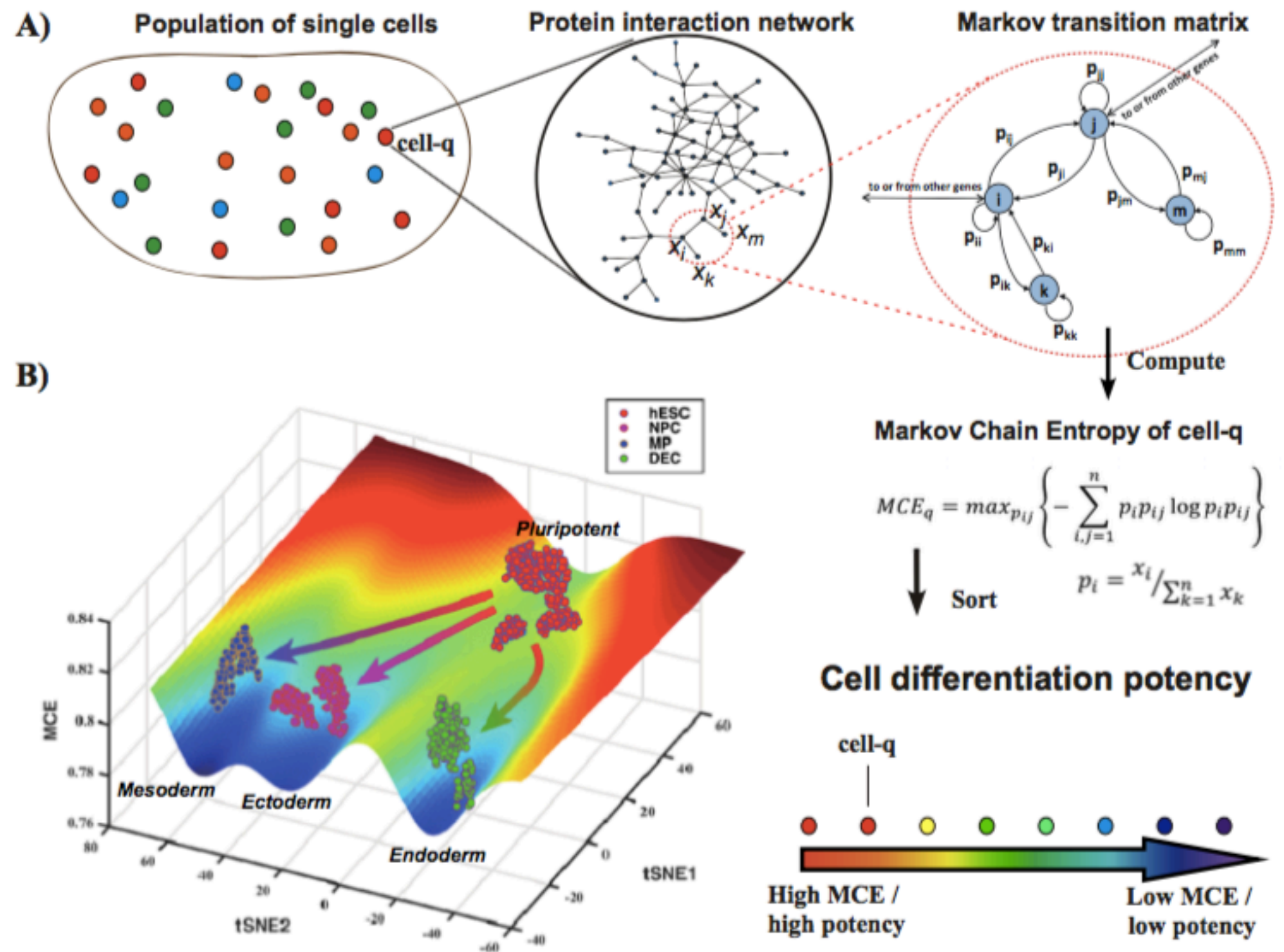
Compute SR

- Construct PPI network from database
- Cal edge weight based on the expression level
- Signaling entropy rate for each node
- Network signaling entropy rate for each sample

Maybe we can use the edge weight or node SR for downstream analysis.
It's kind of similar to Sample-specific network.

MCE

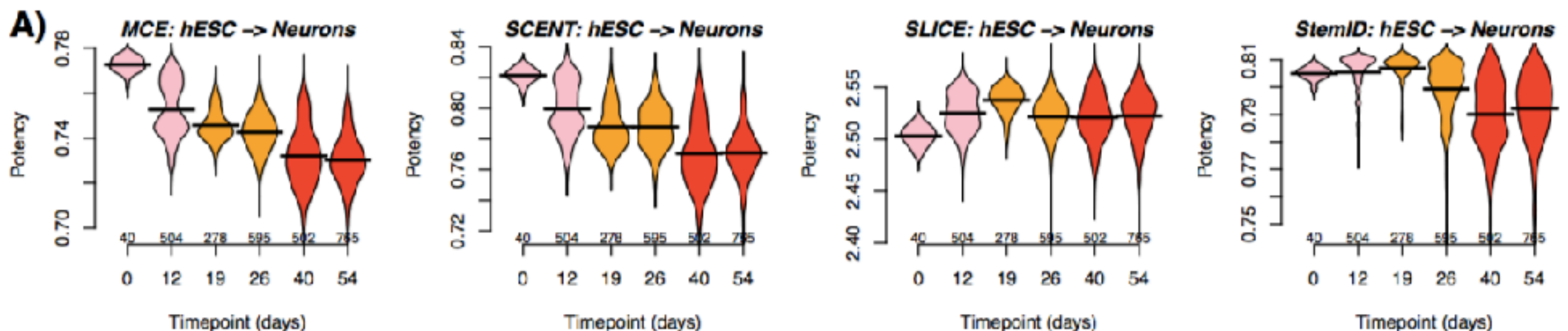
Another method to calculate entropy



Shi J, Teschendorff A, Chen W, et al. Quantifying Waddington's epigenetic landscape: a comparison of single-cell potency measures[J]. bioRxiv, 2018: 257220.

Performance

- Signaling entropy approximate differentiation potency
- Correlation is independent of cell cycle
- Outperforms SLICE and StemID
- Robust to dropouts, normalization





Director of Center for Systems Biology, UT Dallas

Director of Center for Synthetic and Systems Biology, THU

Guest Professor, school of Information Science and Technology and Medical School, THU

Li X, Chen W, Chen Y, et al. Network embedding-based representation learning for single cell RNA-seq data[J]. Nucleic acids research, 2017, 45(19): e166-e166.

- Cell-ContextGene network from RNAseq data
- Gene-ContextGene network from prior knowledge
- Train a low dimensional matrix with the edges

Workflow

A

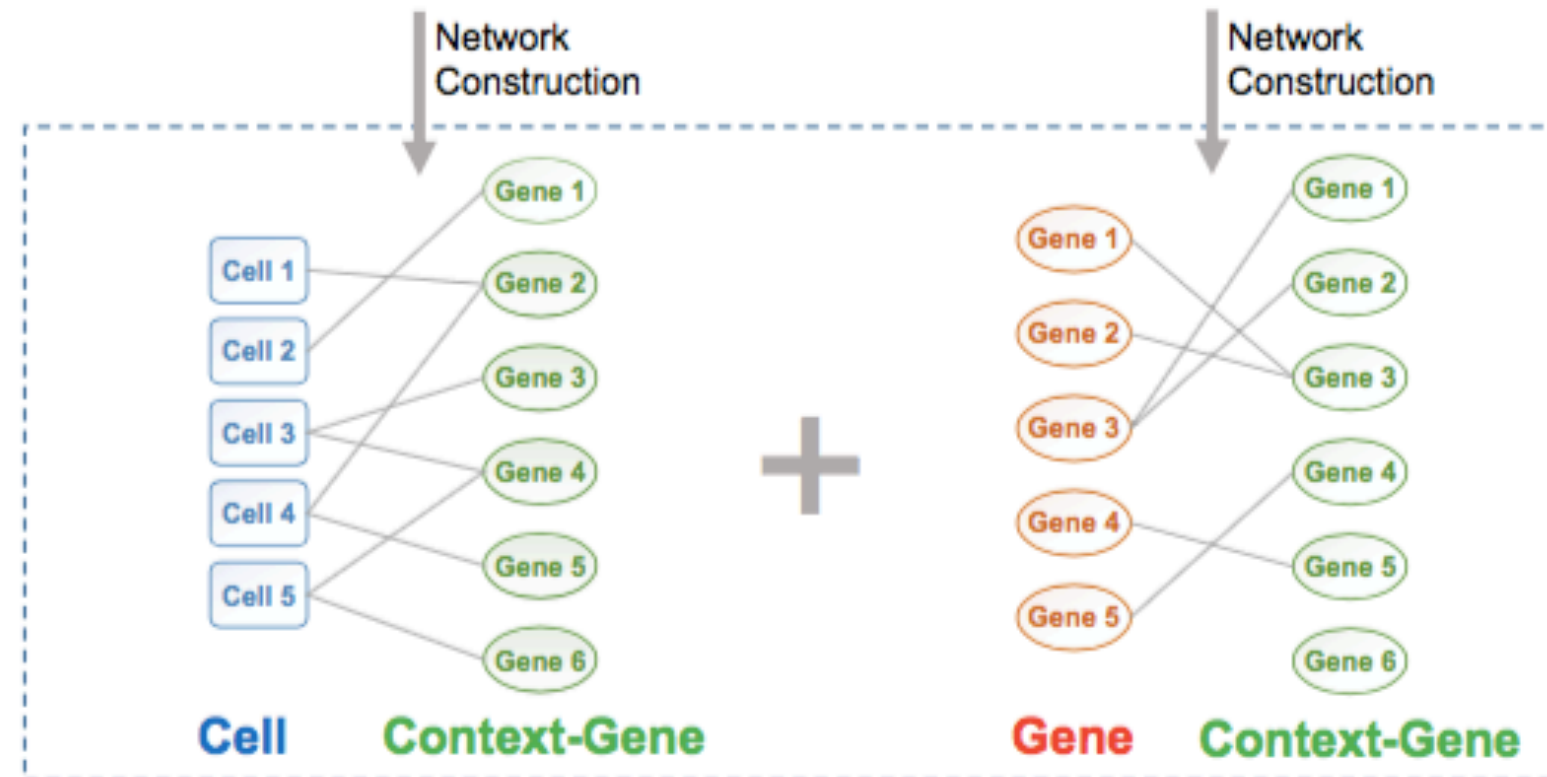
scRNA-seq data

	Gene1	Gene2	Gene3	Gene4	Gene5	Gene6
Cell1	0	5	0	0	0	0
Cell2	3	0	0	0	0	0
Cell3	0	0	100	50	0	0
Cell4	0	56	0	0	10	0
Cell5	0	0	0	99	0	10

Pathway data

	Gene1	Gene2	Gene3	Gene4	Gene5
Gene1	0	0	1	0	0
Gene2	0	0	1	0	0
Gene3	1	1	0	0	0
Gene4	0	0	0	0	1
Gene5	0	0	0	1	0

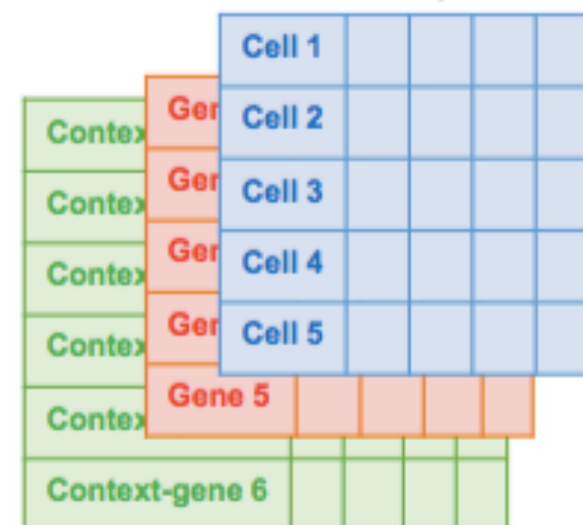
B



C

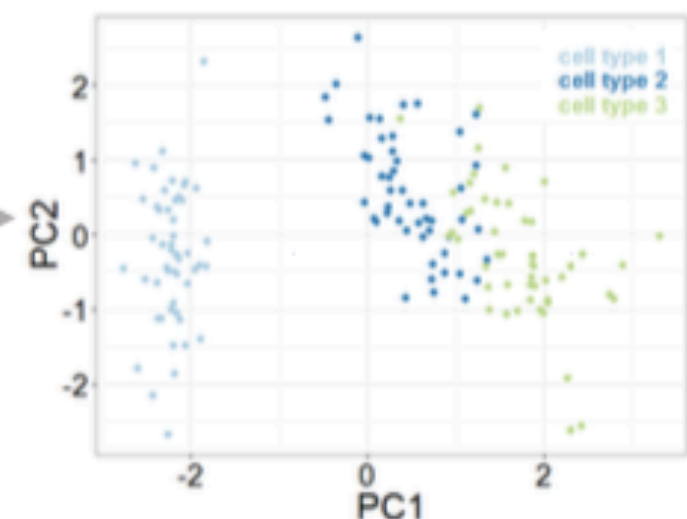
Joint bipartite network embedding

Low dimensional representation



D

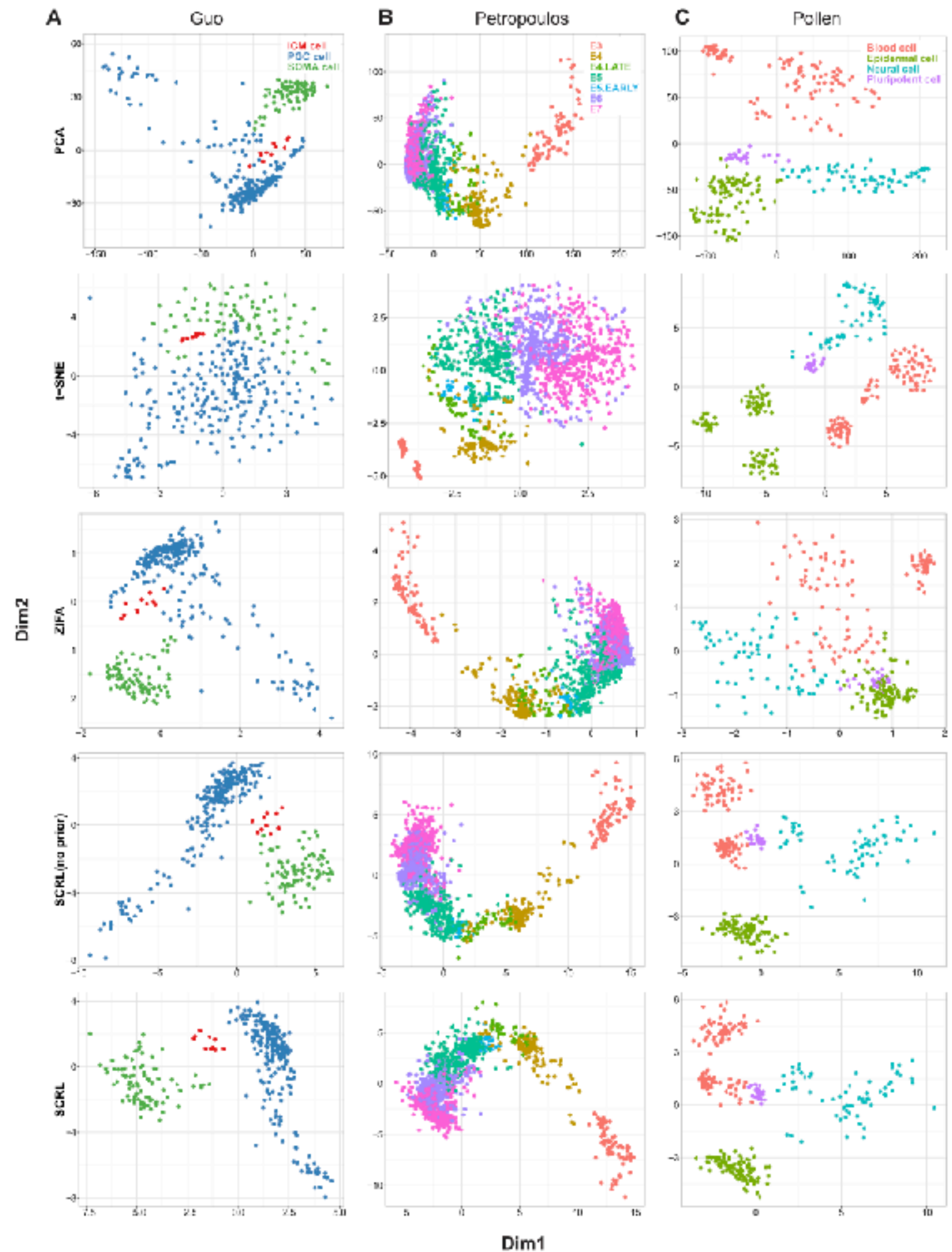
2D visualization



- Minimize distribution probability divergence of genes in the same cell

Performance

- SCRL outperforms other dimension reduction methods
- Efficient, applicable to large data set
- Integration of multiple network is extendable

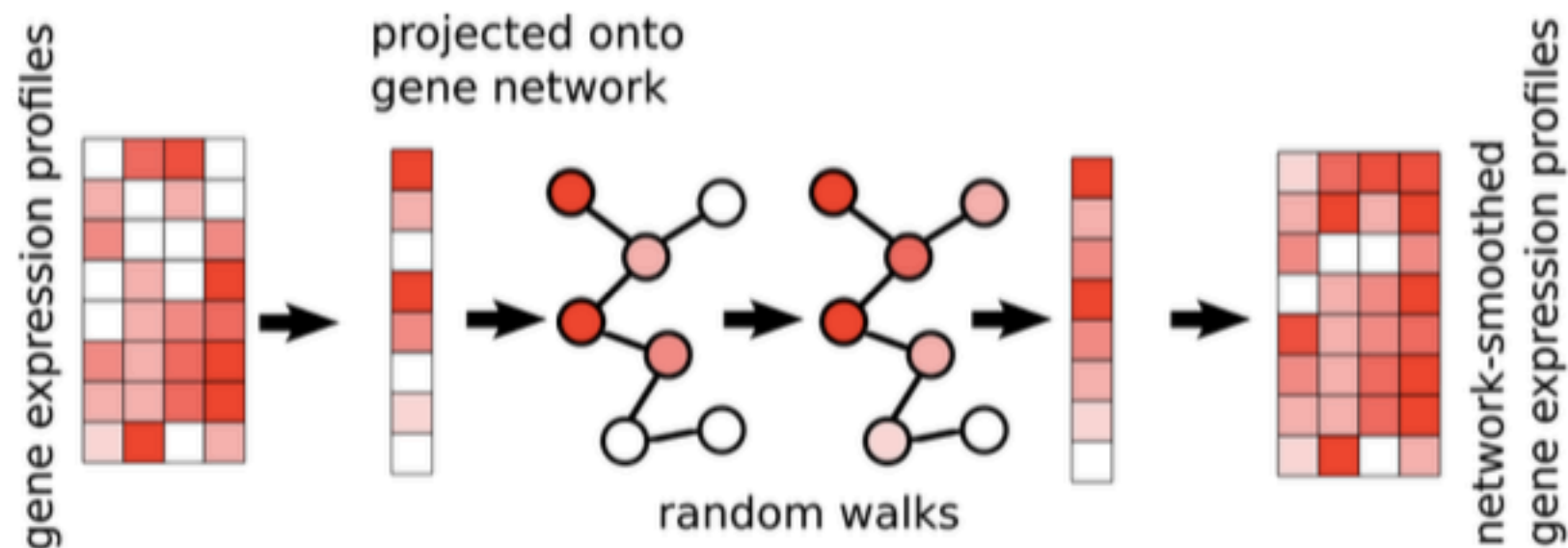


netSmooth

Altuna Akalin, PhD, Group Leader
Bioinformatics platform, MDC-Berlin



Ronen J, Akalin A. netSmooth: Network-smoothing based imputation for single cell RNA-seq[J]. F1000Research, 2018, 7.



Work going on.....

<https://github.com/wangwl/SingleCellNotes>

- Details of the algorithms (How the tools work)
- Other single-cell computational methods
- Benchmark work on these methods.