Personalized cell-type-specific *-omics* Profile Deconvolution and Inference

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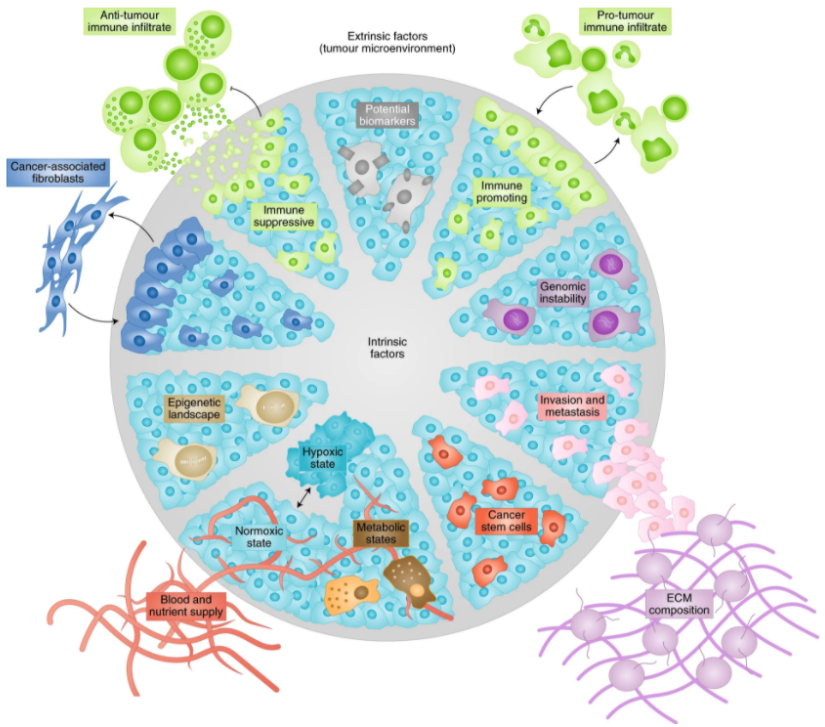
The building block of life

Robert Hooke's drawing of cork cells. Image obtained from Micrographia.

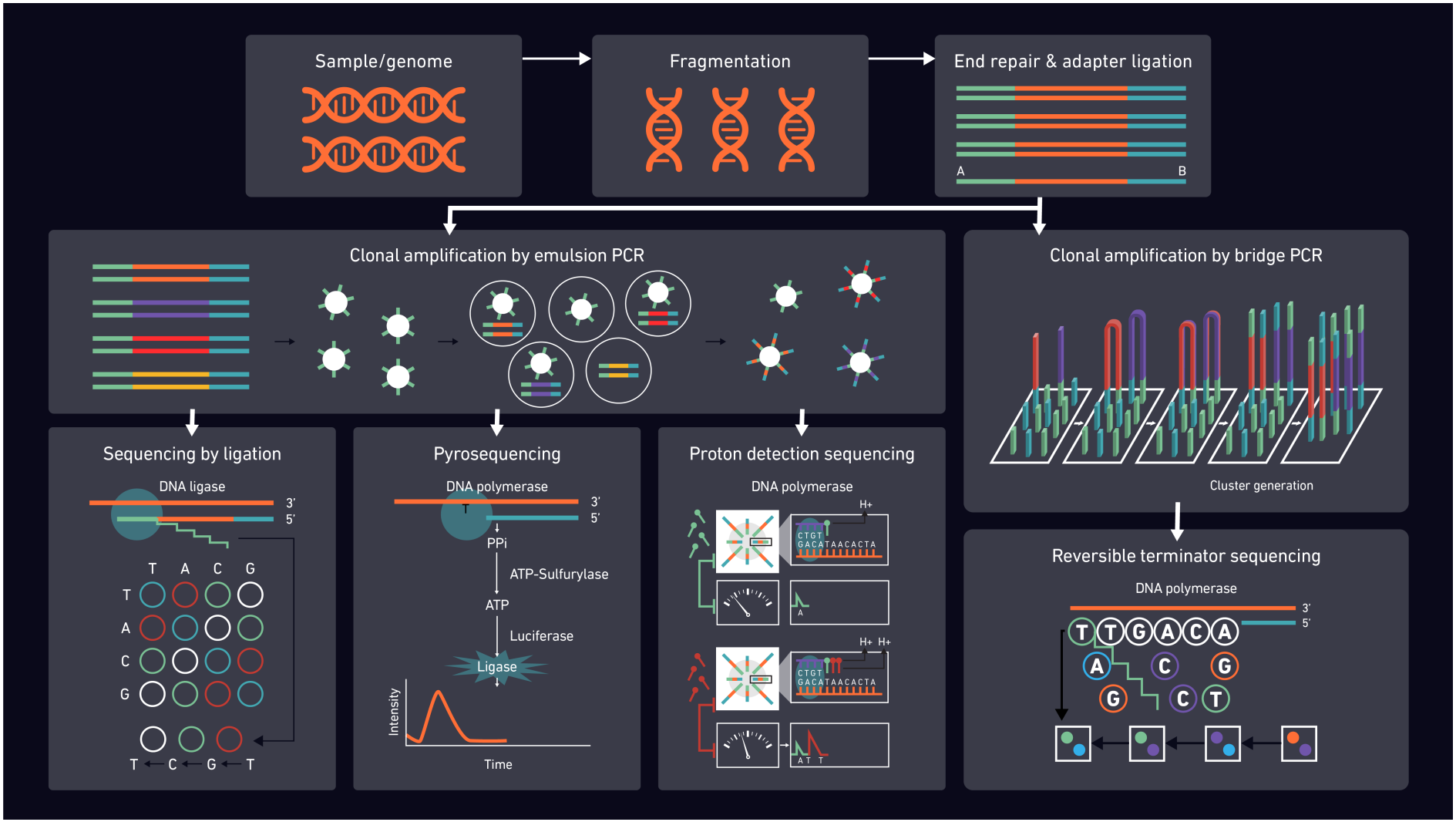
Heterogeneous mixture

- Human tissues have diverse cell types/states.
- Traditional RNA-seq ("bulk" RNA-seq) can measure **averaged signal** across millions of cells.



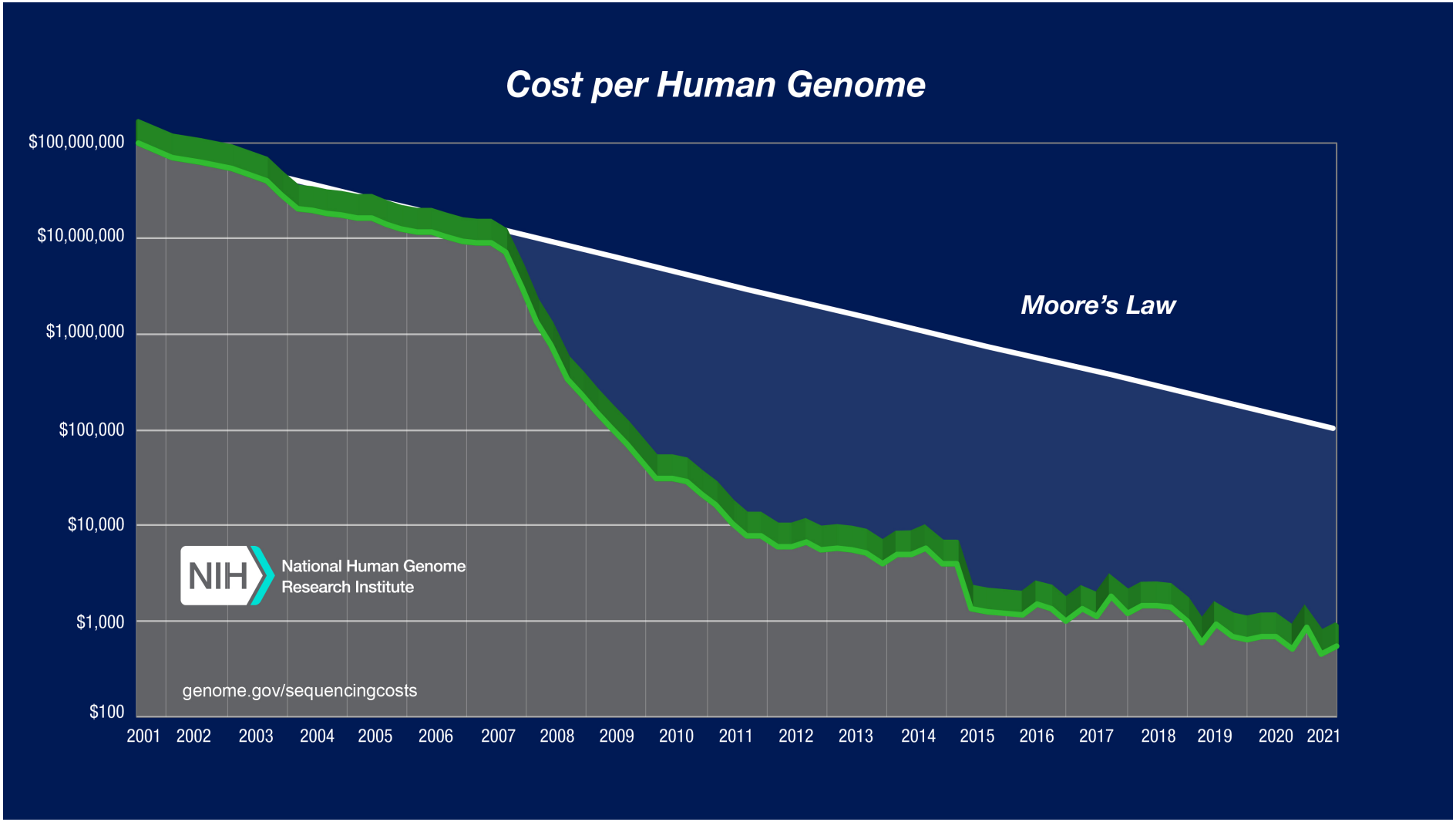
Lawson et al. Nature. https://www.nature.com/articles/s41556-018-0236-7

Second Generation Sequencing



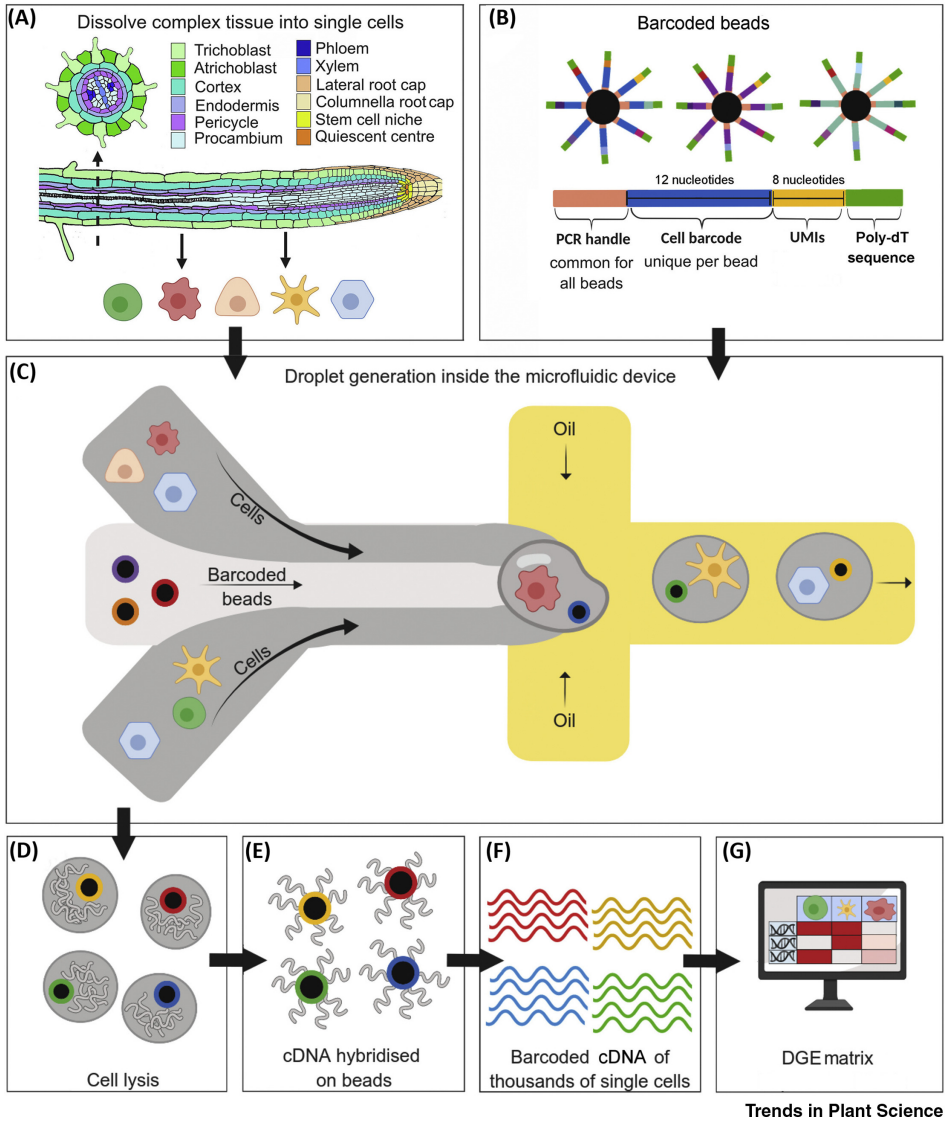
Athina Gkazi, Principle 2G sequencing platforms and chemistries. Technology Networks Genomics Research.

Sequencing costs

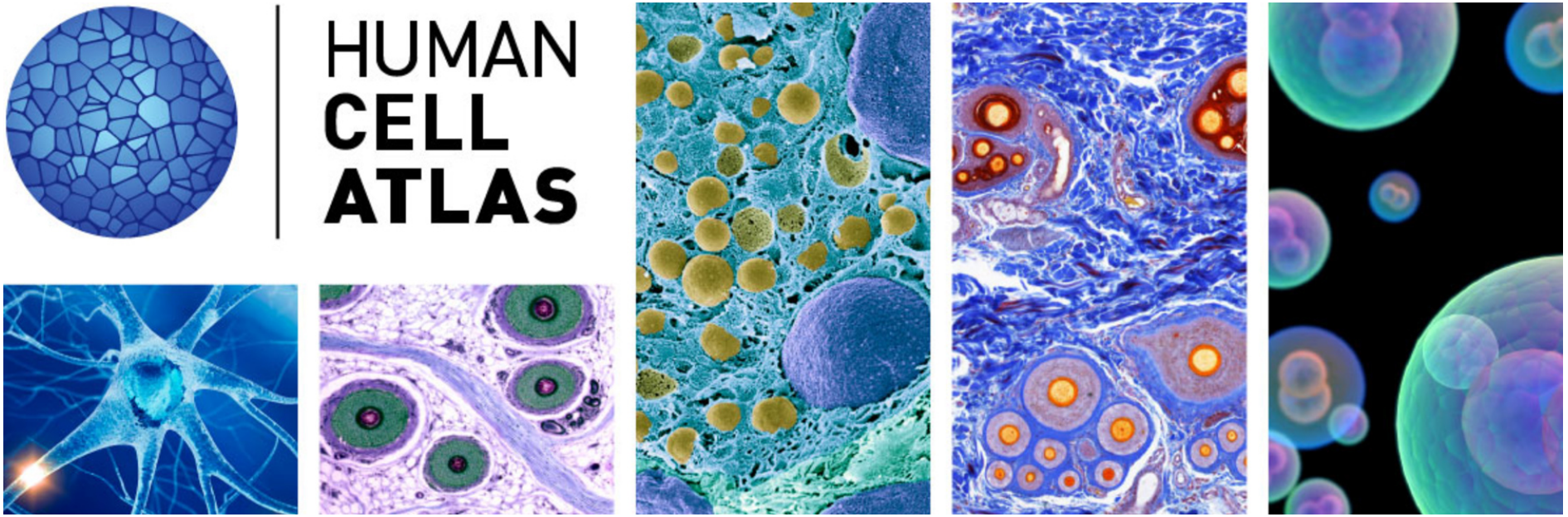


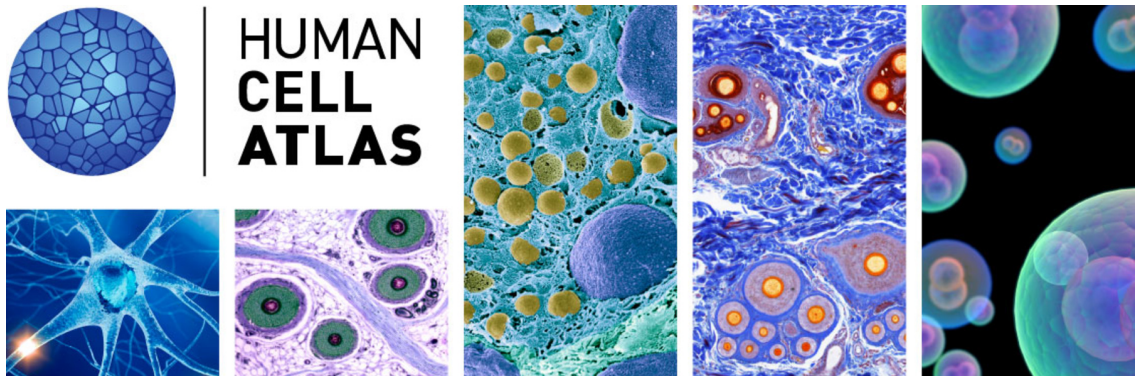
NIH/NHGRI - DNA Sequencing Costs: Data

Single-cell sequencing: a high-resolution avenue



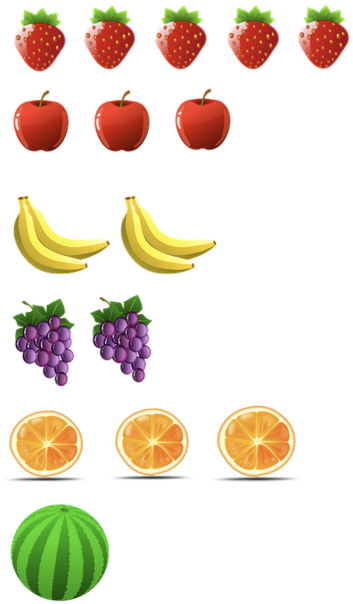
https://doi.org/10.1016/j.tplants.2019.10.008


HUMAN
CELL
ATLAS



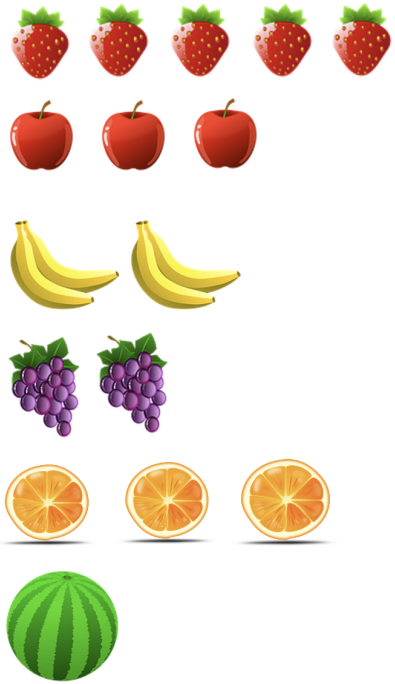
Bulk RNA-seq

Single-cell RNA-seq

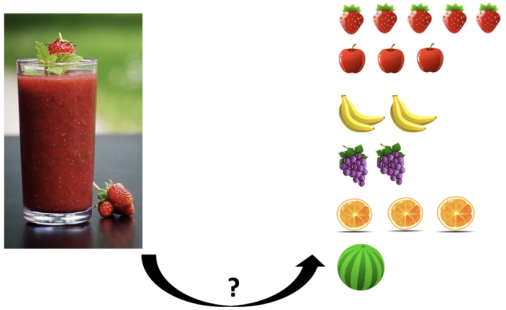


Deconvolution

?



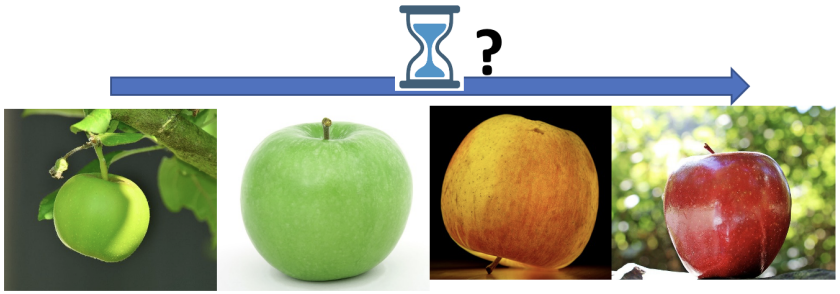
Deconvolution and beyond



Smoothie A use:

?

Smoothie B use:



1. Personalized and cell-type-specific transcriptome reference panel recovery.
2. Improved deconvolution using personalized reference panel.
3. A hybrid neural network model for scRNA-seq cell type prediction.

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2. Improved deconvolution using personalized reference panel.
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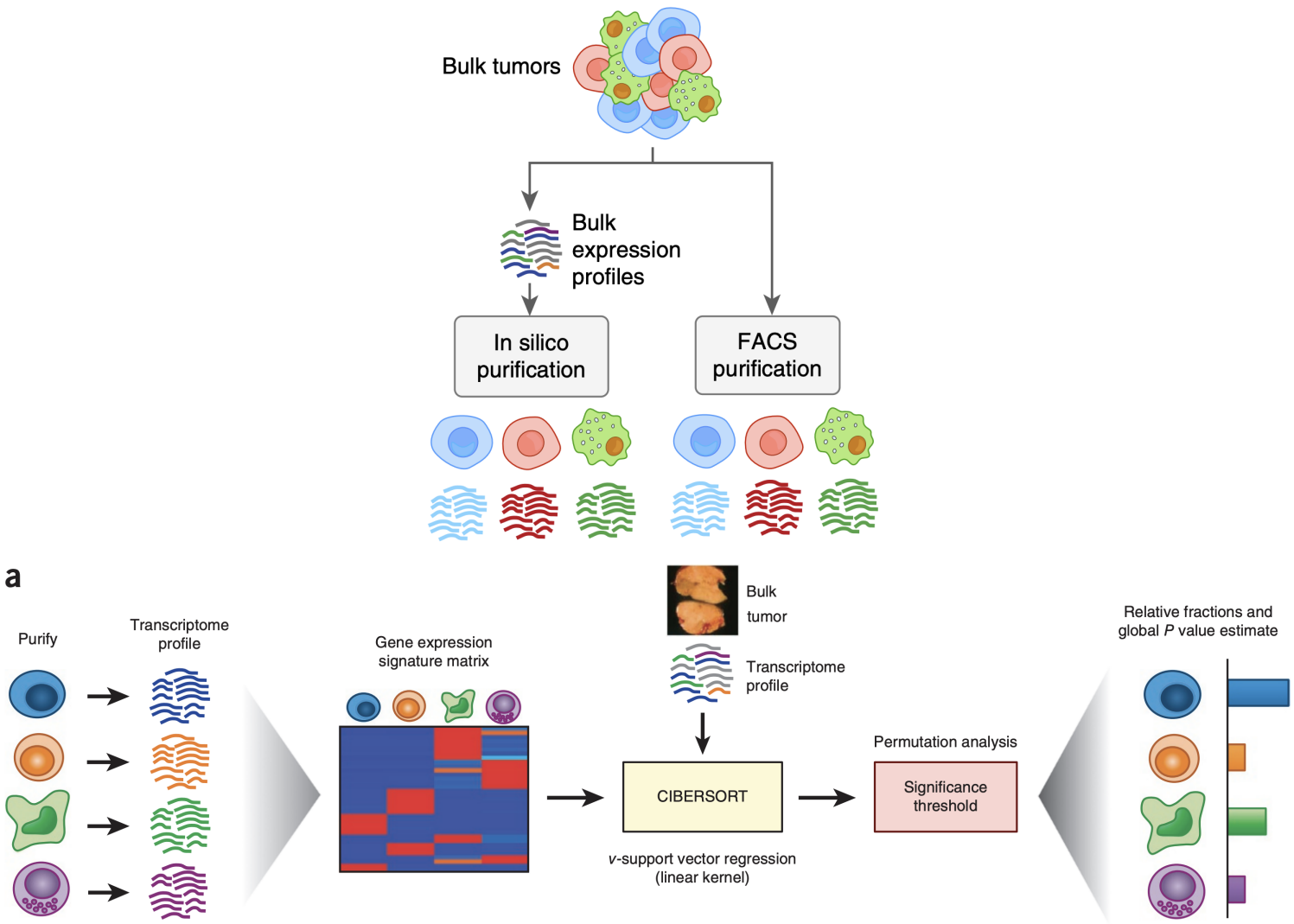
Bulk RNA-seq data

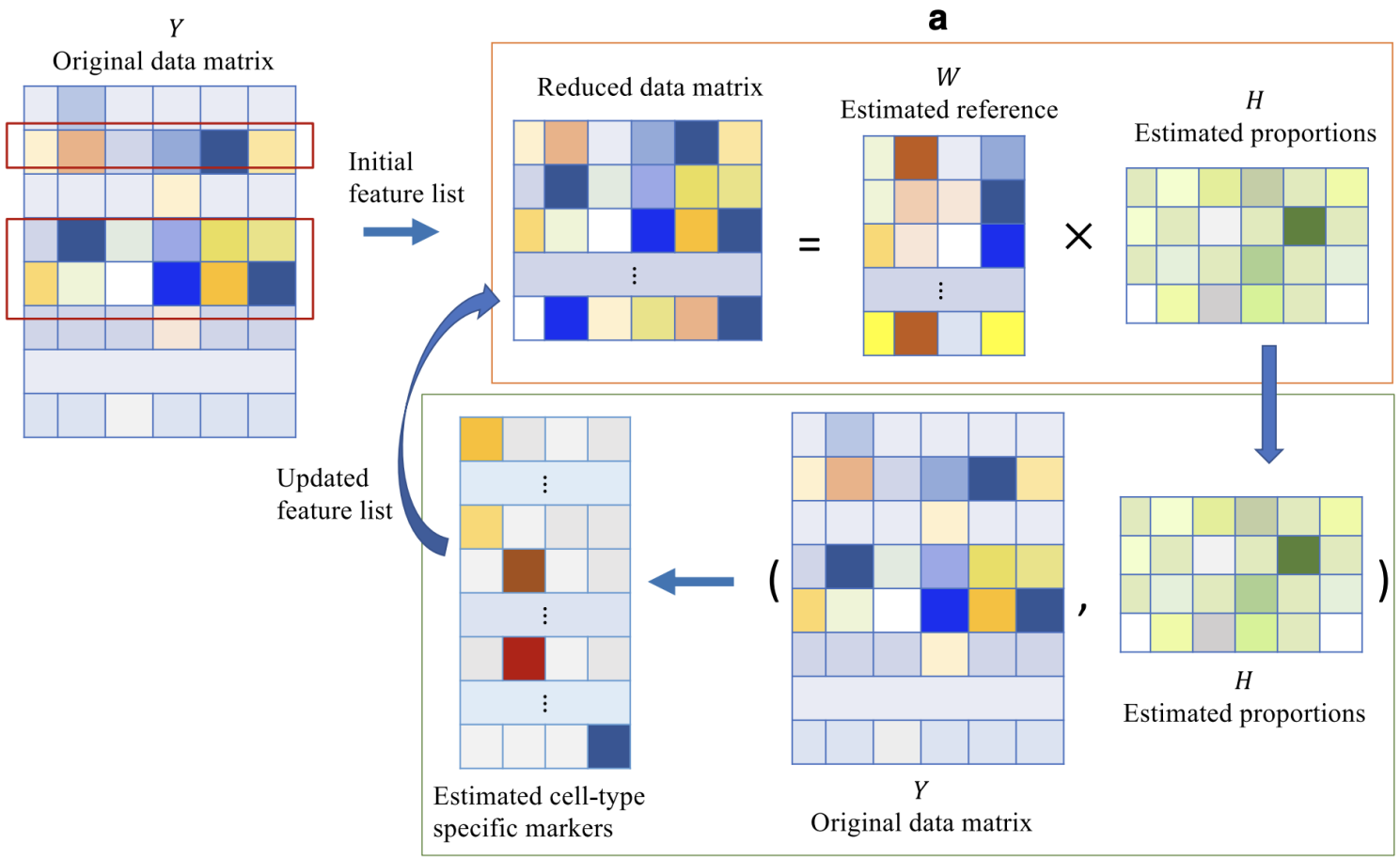
```
> GeneExpData
       Case_5_Spl_2 Case_7_Spl_3 Case_3_Spl_2 Case_6_Spl_1 Case_8_Spl_3 Case_3_Spl_3 Case_6_Spl_3 Case_9_Spl_3 Case_4_Spl_1
gene1           467          649           38           42           36          104          103          117          188
gene2            26           26           55           57           57          157          159          177          151
gene3           233          151          289          266          259           67           67           71           68
gene4            94          111           40           42           35           72           72           81           44
gene5            30           39           41           37           41           36           51           36           89
gene6            47           41           88           83           79           38           41           43           29
gene7           138           90           86           78           81           61           55           54          143
gene8           100           78          112          101          101           88           85           86           65
gene9            36           42           36           35           36           77           73           74          165
gene10           29           32          121          136          115           40           40           42           48
> 
```

Cell composition of complex tissues



Newman et al. Nat Biotechnol. 2019; Newman et al. Nat Methods. 2015

Cell composition of complex tissues

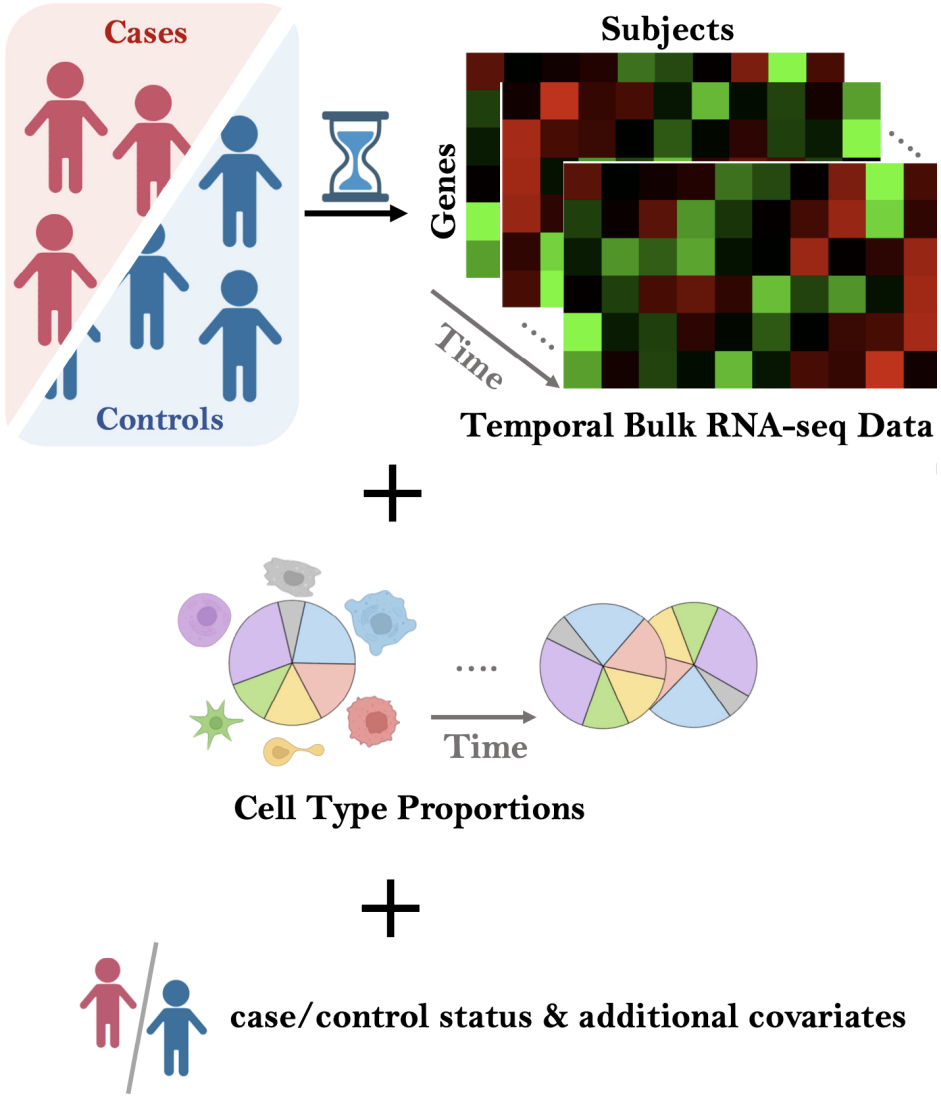


Li et al. Genome Biology 2019

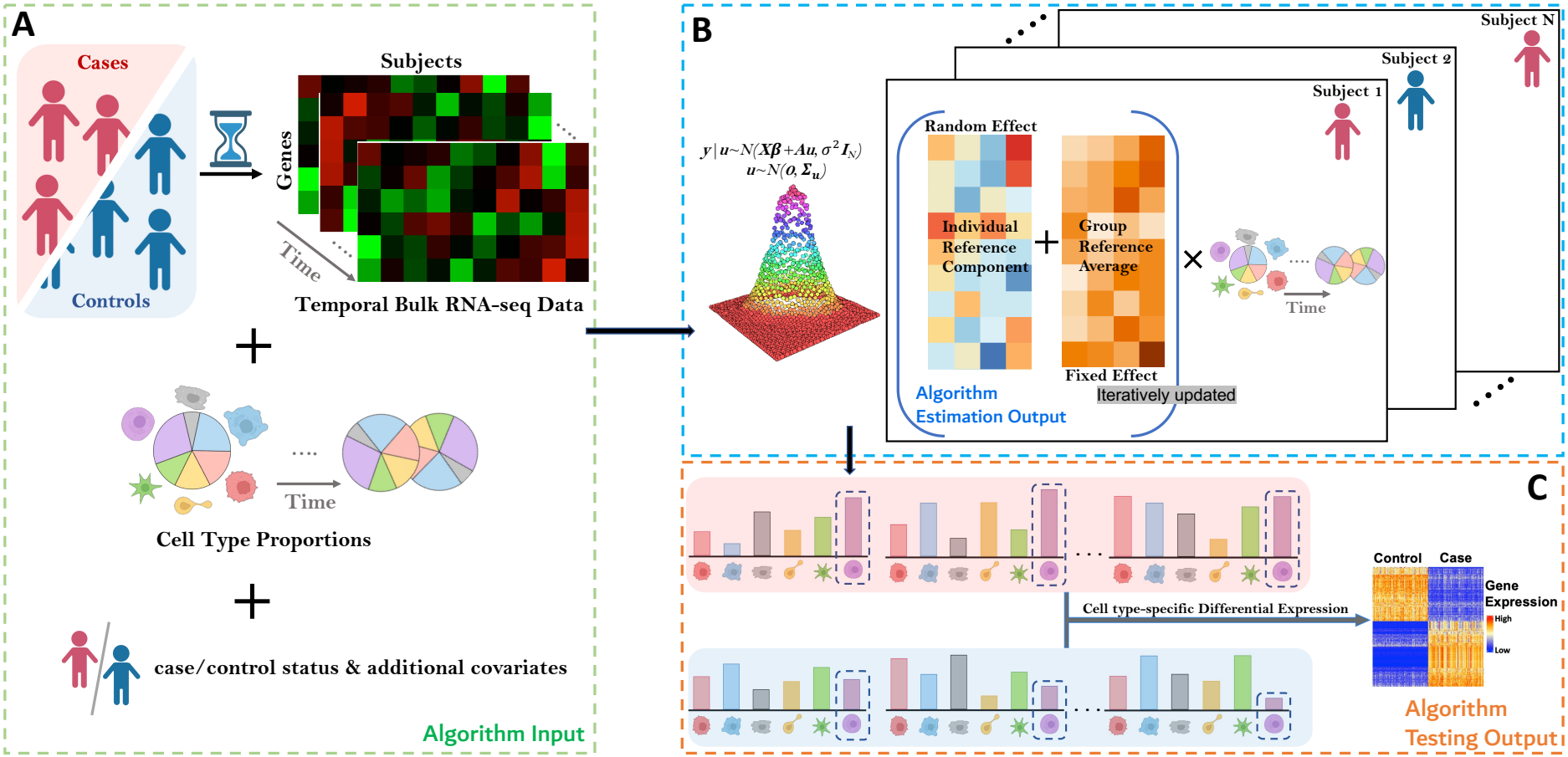
Existing problems

- Lack of individual-level reference profile.
- Repeatedly measured samples over the same individual are not optimally used.
- Bias in subsequent differential expression testing.

Data structure



Proposed method



Data: Gene expression data from bulk RNA-seq

For one specific gene:

- Subject is index by j, where $j \in 1, 2, ...J$.
- For each subject j, there are T_j longitudinal observations.
- y_{jt}: the observed gene expression for subject j at time t.

$$\boldsymbol{y} = (y_{11}, y_{12}, \cdots, y_{1T_1}, \cdots, y_{J1}, y_{J2}, \cdots, y_{JT_J})^T_{N\times 1}$$

Here, $N = \sum_{j=1}^{J} T_j$.
Other known inputs:

- Number of cell types: K.
- Cell type proportions: θ_{jT_jk}, naturally $\sum_{k=1}^{K} \theta_{jT_jk} = 1$.
- Binary scalar z_j to indicate the subject's disease status: (e.x. cancer vs. normal).

The mixed-effect model

$$\boldsymbol{y} = \boldsymbol{X}\boldsymbol{\beta} + \boldsymbol{A}\boldsymbol{u} + \boldsymbol{\varepsilon}$$

$$\boldsymbol{\varepsilon} \sim N(\boldsymbol{0}, \sigma_0^2 \boldsymbol{I})$$

$$\boldsymbol{u} = \begin{pmatrix} u_{11} \\ u_{21} \\ \vdots \\ u_{J1} \\ \vdots \\ u_{1K} \\ u_{2K} \\ \vdots \\ u_{JK} \end{pmatrix}_{Q \times 1}$$

$$\boldsymbol{\beta} = \begin{pmatrix} m_1 \\ m_2 \\ \vdots \\ m_K \\ \beta_1 \\ \beta_2 \\ \vdots \\ \beta_K \end{pmatrix}_{2K \times 1}$$

Towards EM algorithm setup

$$\boldsymbol{w} = (\boldsymbol{y}, \boldsymbol{u}) := (\boldsymbol{w}_{obs}, \boldsymbol{w}_{mis}) \quad \boldsymbol{w}_{obs} := \boldsymbol{y} \quad \boldsymbol{w}_{mis} := \boldsymbol{u}$$

$$\boldsymbol{w}_{obs} | \boldsymbol{w}_{mis} = \boldsymbol{y} | \boldsymbol{u} \sim N(\boldsymbol{X}\boldsymbol{\beta} + \boldsymbol{A}\boldsymbol{u}, \sigma_0^2 \boldsymbol{I})$$

$$\boldsymbol{w}_{mis} = \boldsymbol{u} \sim N(\boldsymbol{0}, \Sigma_U)$$

So we have:

$$\begin{pmatrix} \boldsymbol{w}_{obs} \\ \boldsymbol{w}_{mis} \end{pmatrix} = N\left[\begin{pmatrix} \boldsymbol{X}\boldsymbol{\beta} \\ \boldsymbol{0} \end{pmatrix}, \begin{pmatrix} \boldsymbol{V} & \boldsymbol{A}\Sigma_U \\ \Sigma_U^T \boldsymbol{A}^T & \Sigma_U \end{pmatrix} \right]$$

Towards EM algorithm setup

$$\boldsymbol{w} = (\boldsymbol{y}, \boldsymbol{u}) := (\boldsymbol{w}_{obs}, \boldsymbol{w}_{mis}) \quad \boldsymbol{w}_{obs} := \boldsymbol{y} \quad \boldsymbol{w}_{mis} := \boldsymbol{u}$$

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So we have:

$$\begin{pmatrix} \boldsymbol{w}_{obs} \\ \boldsymbol{w}_{mis} \end{pmatrix} = N\left[\begin{pmatrix} \boldsymbol{X}\boldsymbol{\beta} \\ \boldsymbol{0} \end{pmatrix}, \begin{pmatrix} \boldsymbol{V} & \boldsymbol{A}\Sigma_U \\ \Sigma_U^T \boldsymbol{A}^T & \Sigma_U \end{pmatrix} \right]$$

Theorem

If $X = (X_1, X_2)$, *and* $X \sim N[\begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \begin{pmatrix} \Sigma_{11} & \Sigma_{12} \\ \Sigma_{21} & \Sigma_{22} \end{pmatrix}]$, *then* $[X_1|X_2] \sim N(\mu_{1|2}, \Sigma_{1|2})$, *where* $\mu_{1|2} = \mu_1 + \Sigma_{12}\Sigma_{22}^{-1}(X_2 - \mu_2)$ *and* $\Sigma_{1|2} = \Sigma_{11} - \Sigma_{12}\Sigma_{22}^{-1}\Sigma_{21}$.

E-step & M-step

Define: $\boldsymbol{s} = \boldsymbol{A}\boldsymbol{u} + \boldsymbol{X}\boldsymbol{\beta} - \boldsymbol{y}$

E-step:

$$E[\boldsymbol{u}|\boldsymbol{w}_{obs} = \boldsymbol{y}] = \Sigma_U^T \boldsymbol{A}^T \boldsymbol{V}^{-1}(\boldsymbol{y} - \boldsymbol{X}\boldsymbol{\beta})$$

$$E\left[\boldsymbol{s}^T\boldsymbol{s}|\boldsymbol{w}_{obs} = \boldsymbol{y}\right] = tr(\boldsymbol{A}\Sigma_p\boldsymbol{A}^T) + (\boldsymbol{A}\boldsymbol{\mu}_p + \boldsymbol{X}\boldsymbol{\beta} - \boldsymbol{y})^T(\boldsymbol{A}\boldsymbol{\mu}_p + \boldsymbol{X}\boldsymbol{\beta} - \boldsymbol{y})$$

$$E\left[\boldsymbol{u}_k^T\boldsymbol{u}_k|\boldsymbol{w}_{obs} = \boldsymbol{y}\right] = tr(\Sigma_{p_k}) + \boldsymbol{\mu}_{p_k}^T\boldsymbol{\mu}_{p_k}$$

M-step:

$$\hat{\boldsymbol{\beta}}^{(t+1)} = (\boldsymbol{X}^T\boldsymbol{X})^{-1}\boldsymbol{X}^T(\boldsymbol{Y} - \boldsymbol{A}E_{\eta(t)}(\boldsymbol{u}^{(t)}))$$

$$\hat{\sigma}_0^{2(t+1)} = \frac{E_{\eta(t)}\left[(\boldsymbol{Y} - \boldsymbol{X}\boldsymbol{\beta} - \boldsymbol{A}\boldsymbol{u})^T(\boldsymbol{Y} - \boldsymbol{X}\boldsymbol{\beta} - \boldsymbol{A}\boldsymbol{u})\right]}{N}$$

$$\hat{\sigma}_k^{2(t+1)} = \frac{E_{\eta(t)}(\boldsymbol{\mu}_k^T\boldsymbol{\mu}_k)}{J}$$

Simulation setup

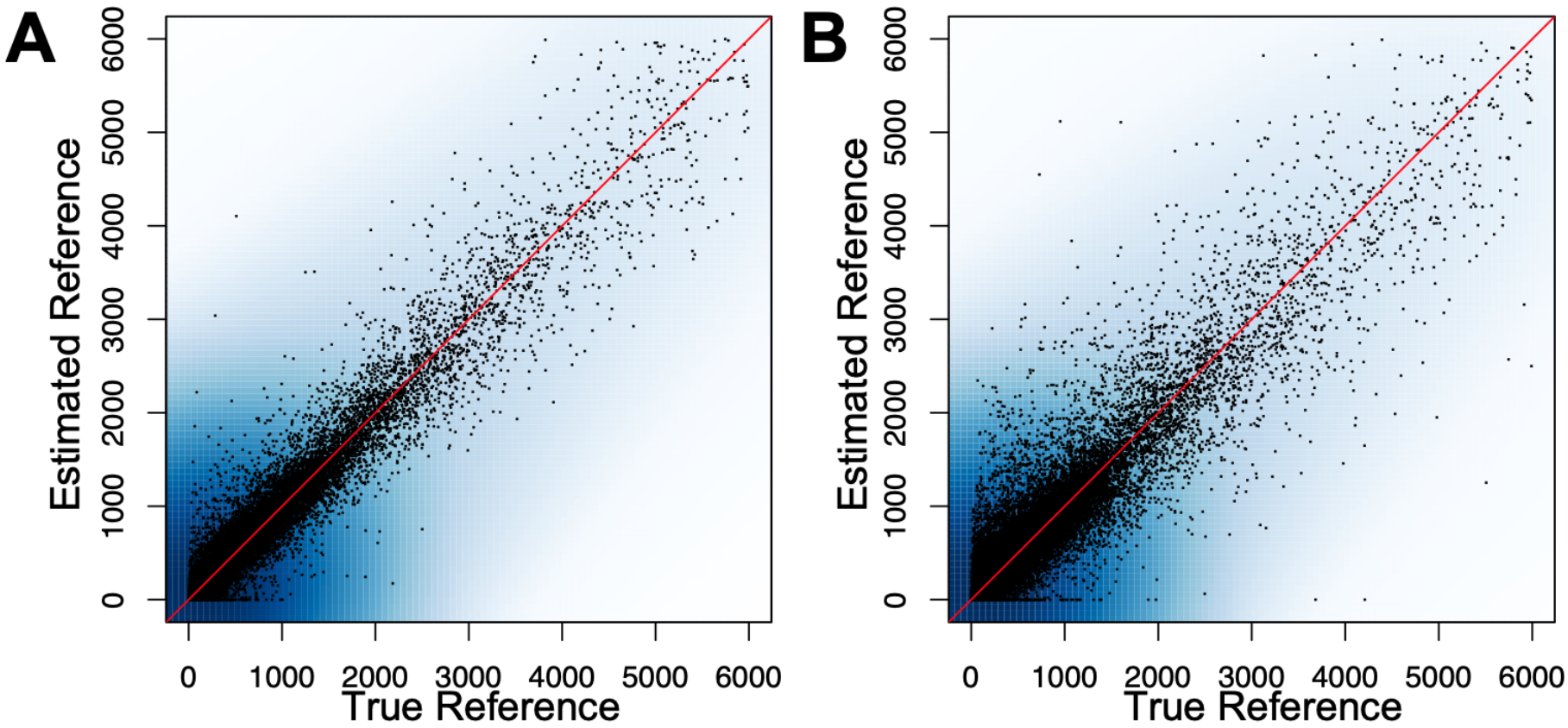
- N = 50, 100, 150, 200
- LFC = 0(null), 0.5, 0.75, 1.0, 1.25, 1.5.
- 10% or 0%(null) csDEG.
- 6 cell types
- Reference panel generated from real bulk cell line.
- Proportions from Dirichlet with parameters from scRNA-seq data.
- Gamma-Poisson for observed counts.

Simulation procedure

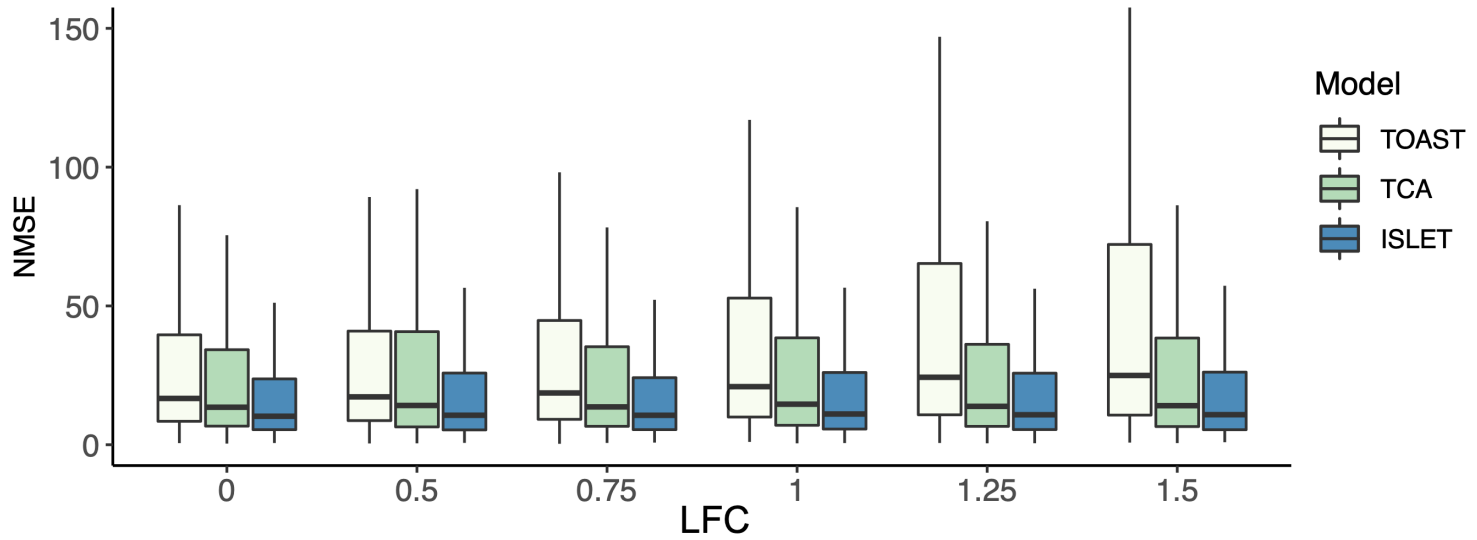
1. $$\boldsymbol{\mu}_{g,K\times 1} \sim MVN(\hat{\boldsymbol{m}}, \hat{\boldsymbol{\Sigma}}_m)$$
$$\boldsymbol{\phi}_{g,K\times 1} \sim MVN(\hat{\boldsymbol{d}}, \hat{\boldsymbol{\Sigma}}_d)$$
2. $$\boldsymbol{M}_{G\times K} = [\boldsymbol{\mu}_1, \boldsymbol{\mu}_1, ..., \boldsymbol{\mu}_G]^T; \boldsymbol{\Phi}_{G\times K} = [\boldsymbol{\phi}_1, \boldsymbol{\phi}_2, ..., \boldsymbol{\phi}_G]^T$$
3. $$\boldsymbol{X}^i_{G\times K} \sim Gamma\{shape = \frac{1}{\exp(\boldsymbol{\Phi})}, scale = \exp(\boldsymbol{M}) \cdot \exp(\boldsymbol{\Phi})\}$$
4. $$\boldsymbol{\theta}_{it} \sim Dir(\boldsymbol{\alpha})$$
5. $$\boldsymbol{r}_{it} = \boldsymbol{X}^i \boldsymbol{\theta}_{it}$$
$$\boldsymbol{y_{it}} | \boldsymbol{r}_{it} \sim Poisson(\boldsymbol{r}_{it})$$

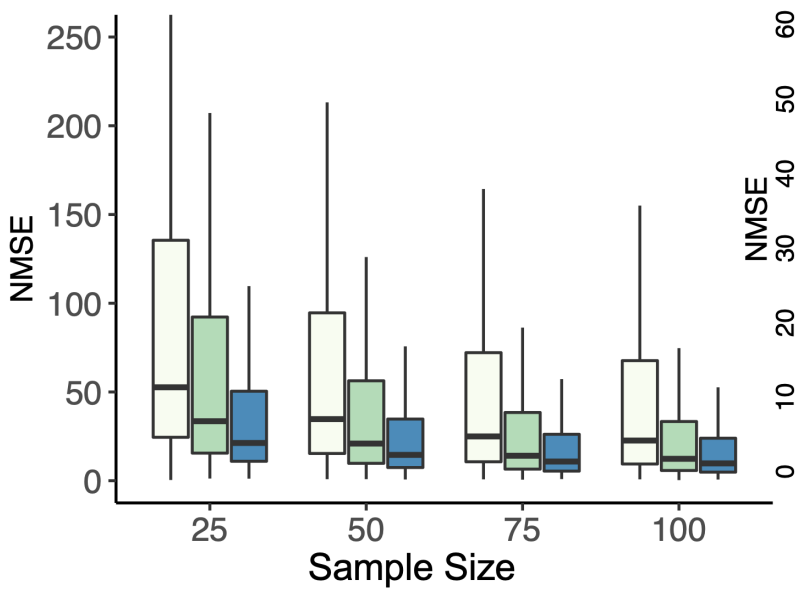
Simulation results

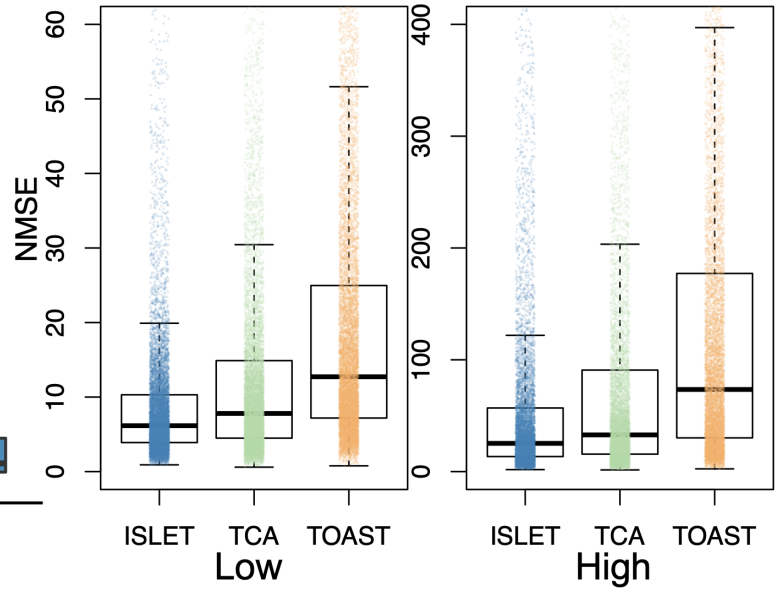
Individual reference panel recovery



Individual reference panel recovery







Hypothesis testing

To test cell-type-specific DE genes, we can test each hypothesis:
$H_0 : \beta_k = 0$
Using the (observed) marginal likelihood function:

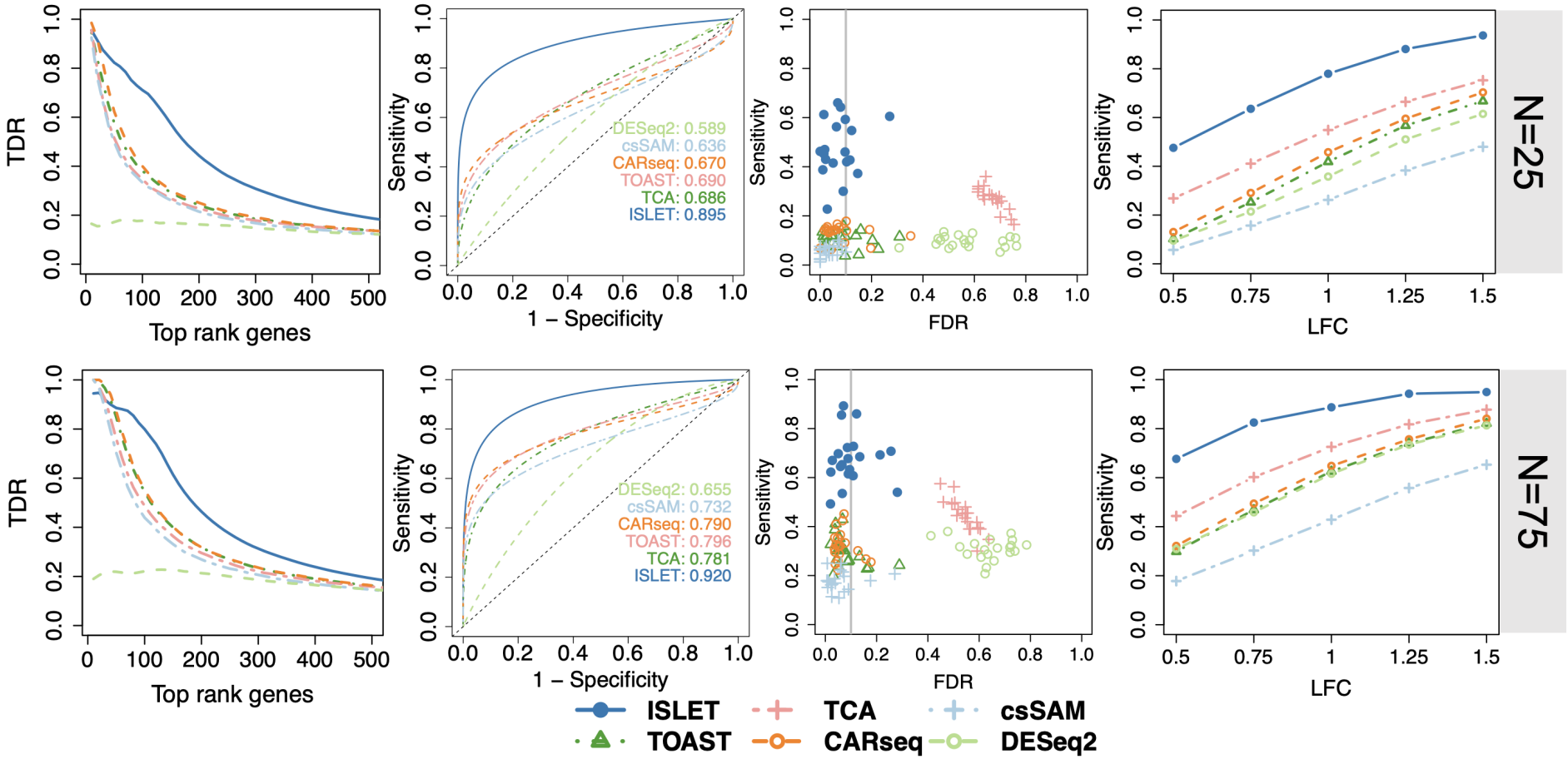
$$l(\boldsymbol{\beta}, \boldsymbol{\sigma}) = \ln f(\boldsymbol{y}; \boldsymbol{X}, \boldsymbol{A}, \boldsymbol{\beta}, \boldsymbol{\sigma})$$

The Likelihood Ratio Test (**LRT**) test statistics can be constructed:

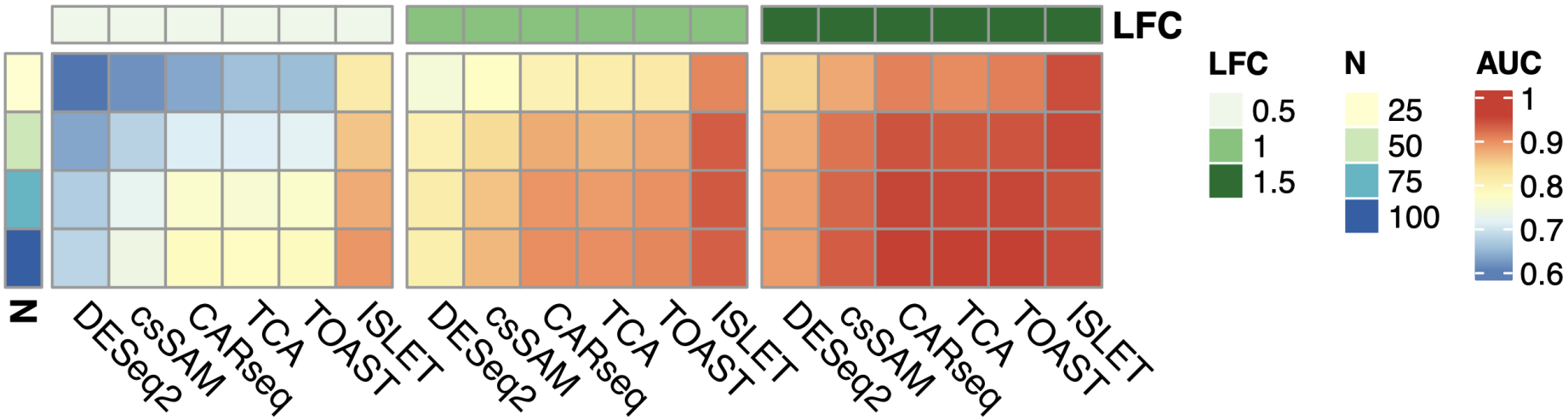
$$\Lambda = 2(l(\hat{\boldsymbol{\beta}}, \hat{\sigma}) - l(\tilde{\boldsymbol{\beta}}, \tilde{\sigma}))$$

$\hat{\boldsymbol{\beta}}, \hat{\sigma}$: the EM estimate for the full model.
$\tilde{\boldsymbol{\beta}}, \tilde{\sigma}$: the estimate for the reduced model under H_0.
Ref dist'n: $\lambda \sim \chi^2_d$

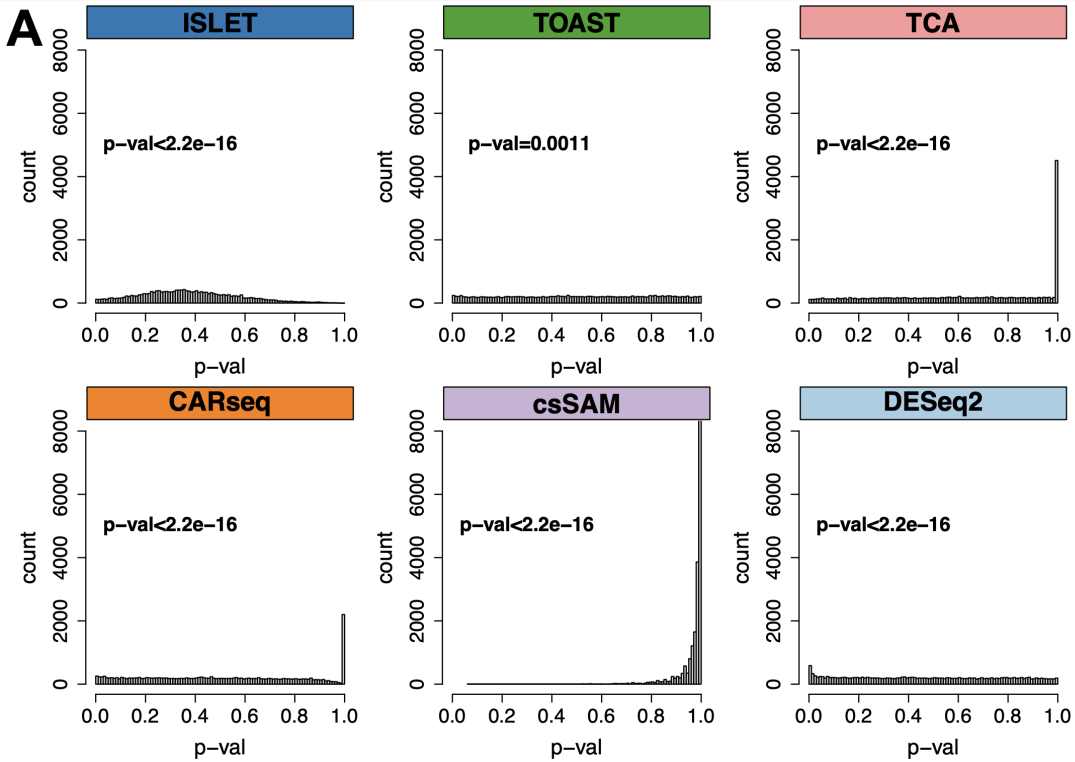
Identifying cell-type-specific DE genes

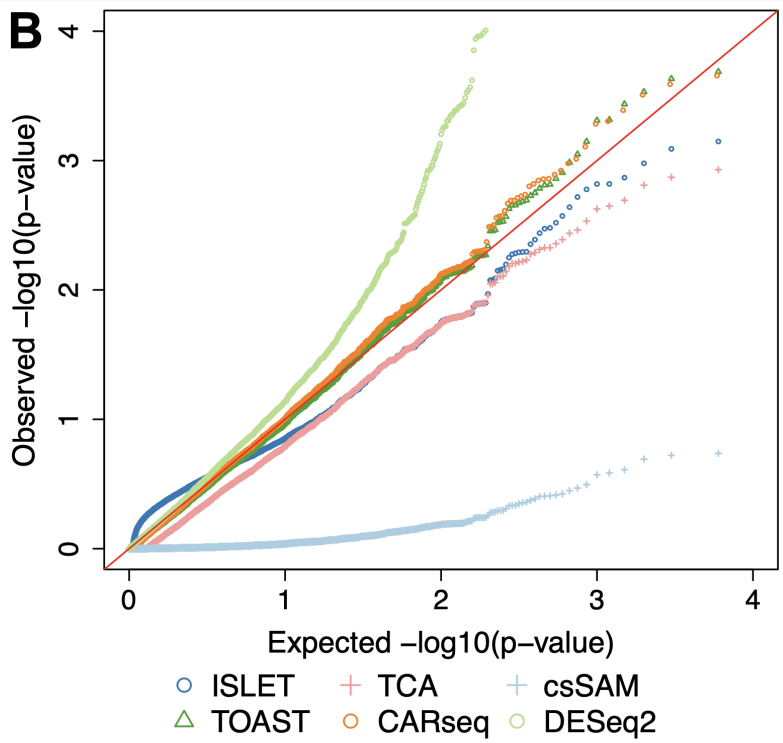


Identifying cell-type-specific DE genes



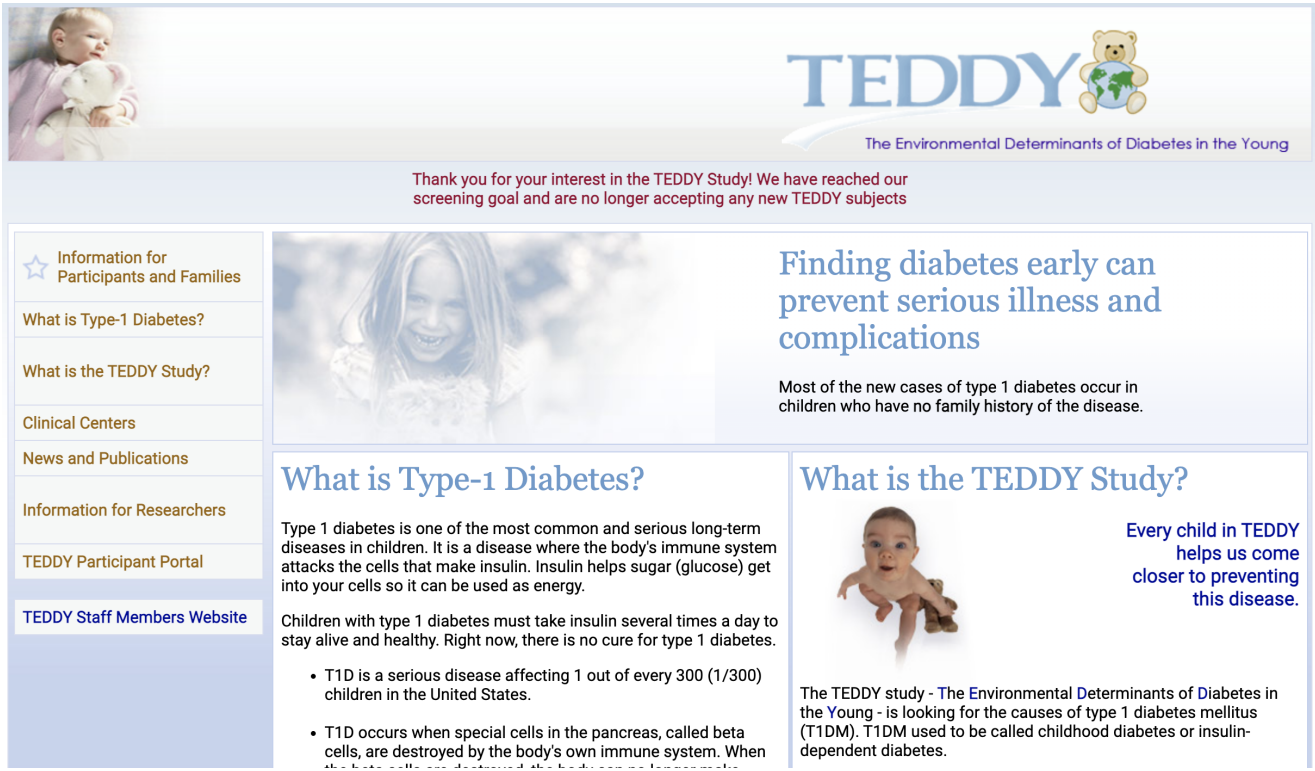
Type I error under the null



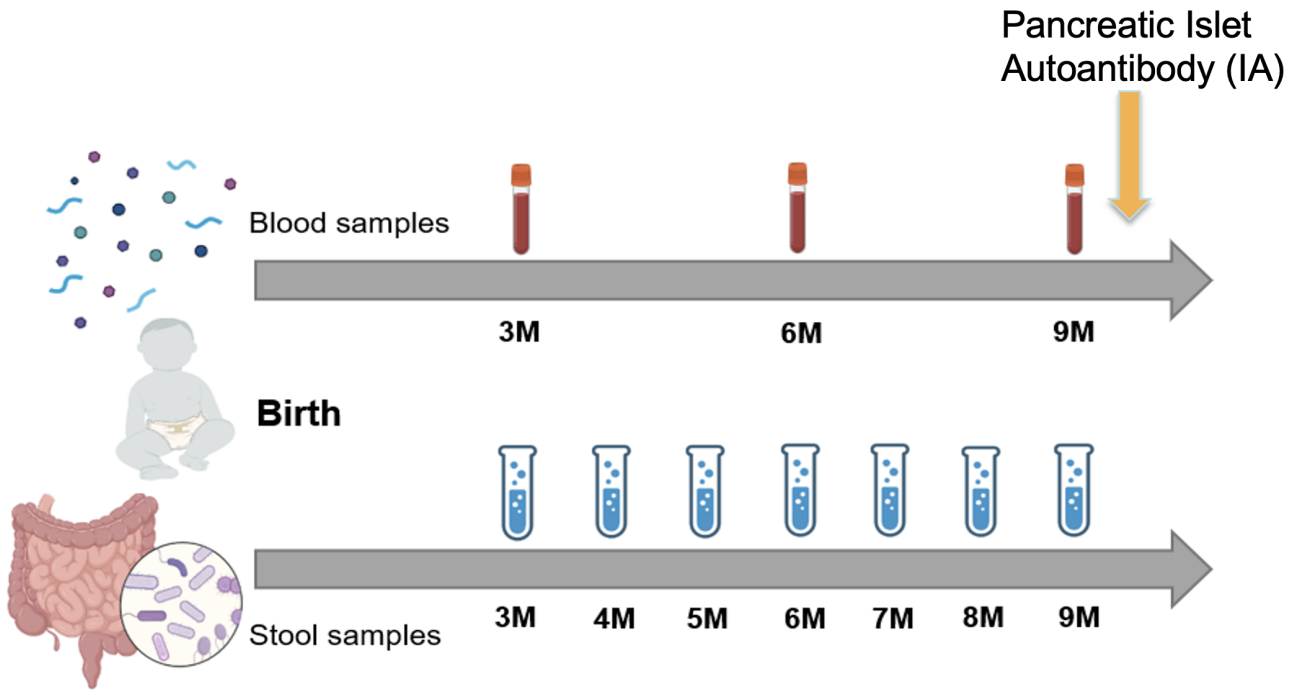


Real data: TEDDY

The Environmental Determinants of Diabetes in the Young

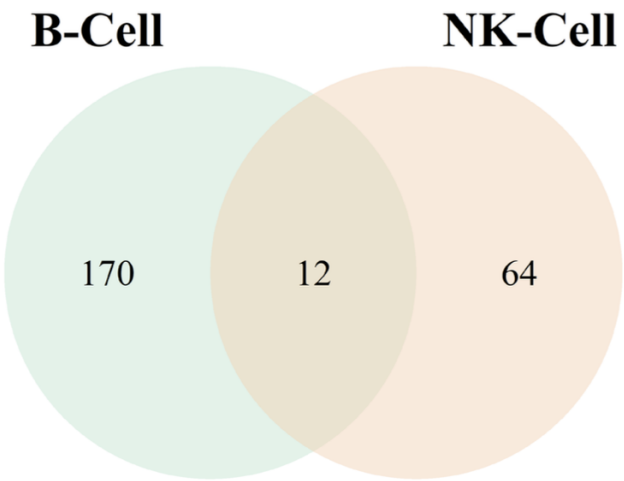


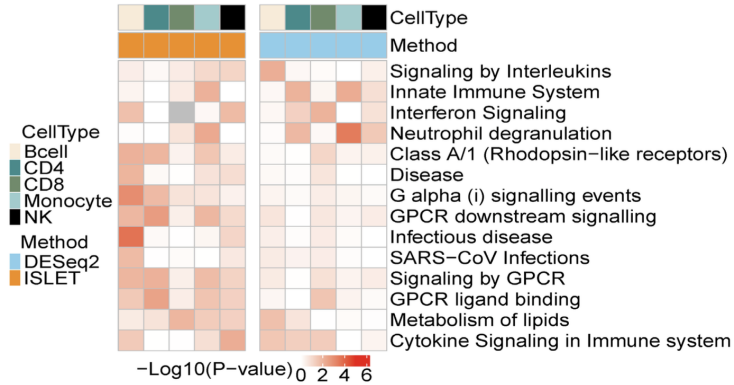
TEDDY Data



Six clinical centers in four countries: U.S., Finland, Germany, and Sweden.
Prospective cohort: 8,676 high-risk infants were enrolled from birth and followed every 3 months, for blood sample collection and islet autoantibody (IAbs) measurement.
Developing IA (cases) started at 9 months with a plateau between 1-2 years of age.

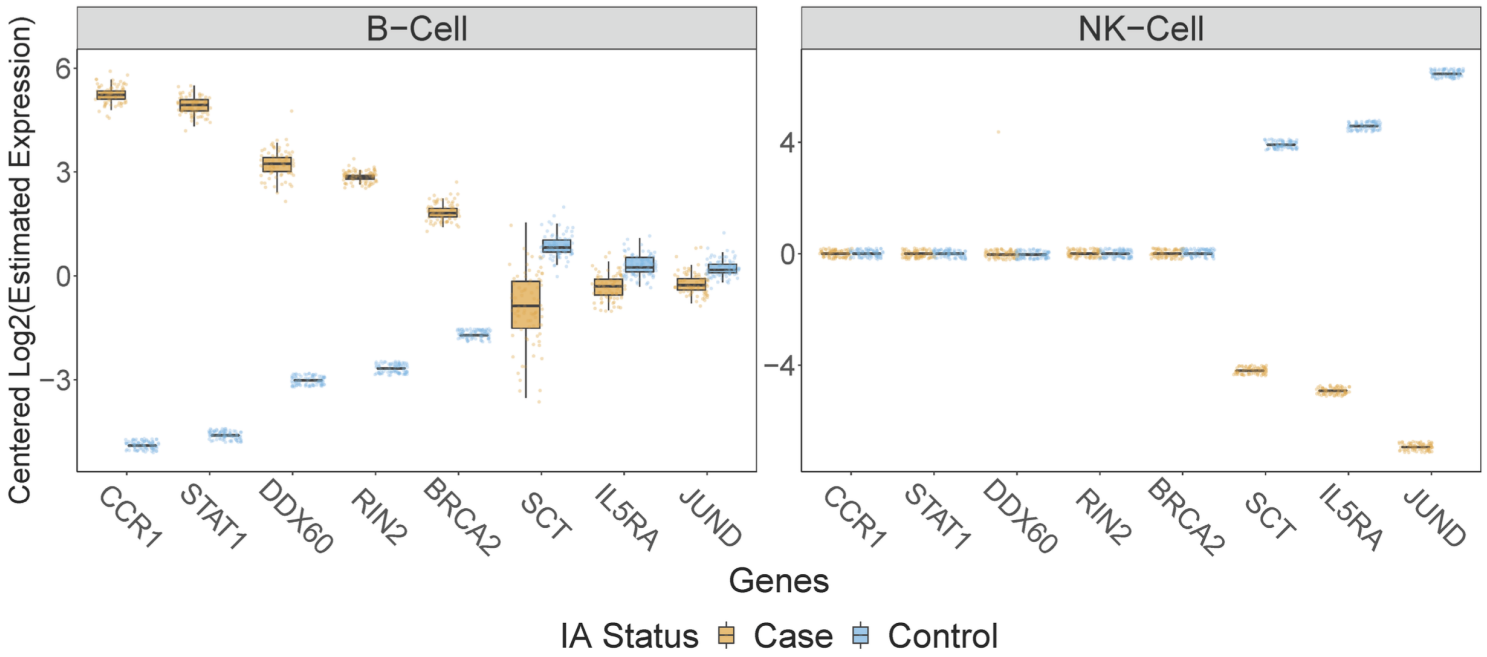
Real data: age-independent effect





IA-signatures strongly enriched in B cells and NK cells transcripts, kinases, and TFs.

Real data: age-independent effect

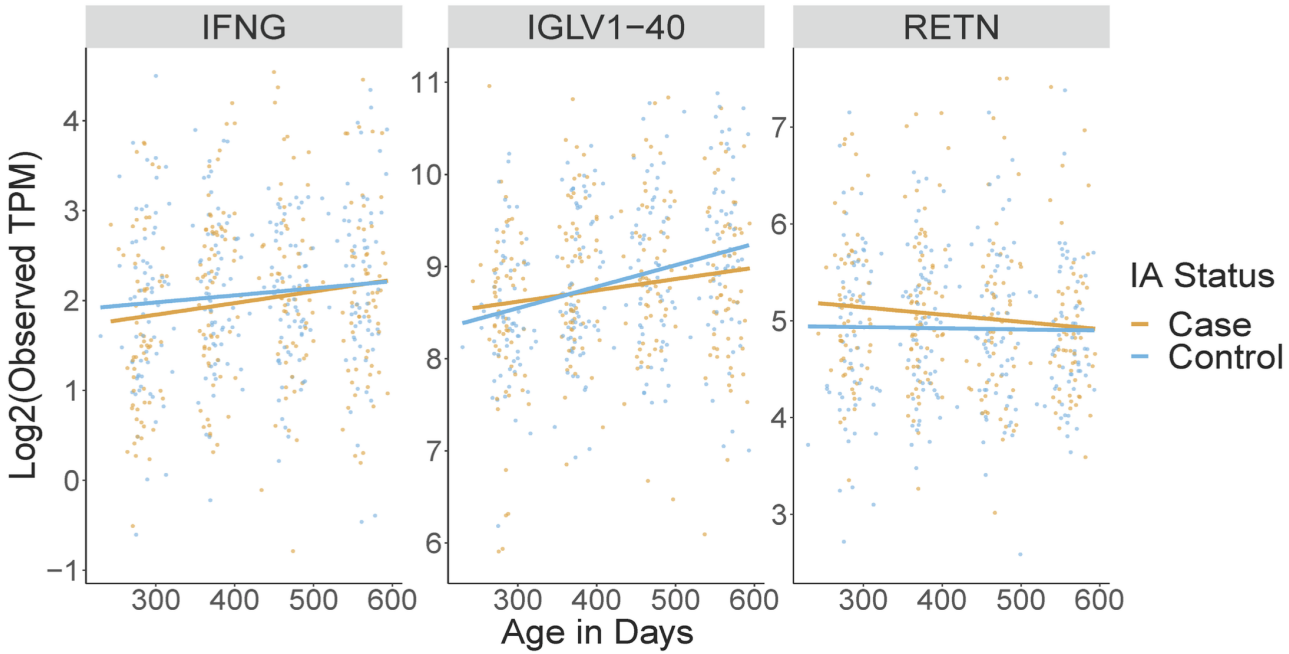


IFN-β-inducible genes in vitro and IFN-indicible transcriptional signatures in human PBMCs were also found prior to the development of autoantibodies (BABY DIET).

CCR1 (chemokine receptor): increased risk of IA in TEDDY among participants who experienced virus infection.

SCT, IL5RA, JUND: regulation of immune response.

Real data: change rate



RETN: Diabetes study found SNPs associated with plasma resistin and glucose levels.
IGLV1-40: neutralizing activity related to protective antibody responses in infants.
More significant and less ambiguous than TEDDY microarray.

ISLET available on Bioconductor

ISLET: **I**ndividual-**S**pecific Ce**LI** Typ**E** Referencing **T**ool

https://bioconductor.org/packages/ISLET/

Individual-specific and cell-type-specific deconvolution using ISLET

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9 September 2022

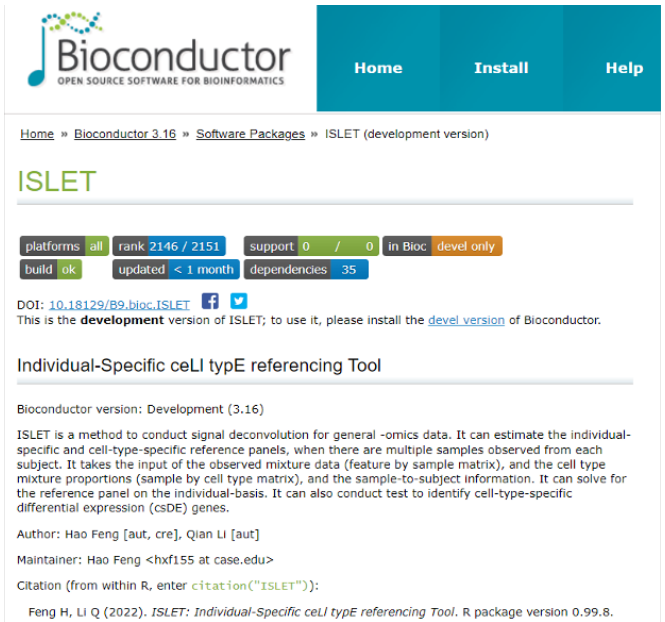
Abstract

This vignette introduces the usage of the Bioconductor package ISLET (Individual-Specific ceLI typE referencing Tool). Complementary to classic deconvolution algorithms, ISLET can take cell type proportions as input, and infer the individual-specific and cell-type-specific reference panels. ISLET also offers functions to detect cell-type specific differential expression (csDE) genes. Additionally, it can test for csDE genes change rate difference between two groups, given an additional covariate of time points or age. ISLET is based on rigorous statistical framework of Expectation–Maximization(EM) algorithm, and has parallel computing embedded to provide superior computational performance.

Package

ISLET 0.99.8

Contents



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Home » Bioconductor 3.16 » Software Packages » ISLET (development version)

ISLET

platforms all | rank 2146 / 2151 | support 0 / 0 | in Bioc devel only
build ok | updated < 1 month | dependencies 35

DOI: 10.18129/B9.bioc.ISLET
This is the **development** version of ISLET; to use it, please install the devel version of Bioconductor.

Individual-Specific ceLI typE referencing Tool

Bioconductor version: Development (3.16)

ISLET is a method to conduct signal deconvolution for general -omics data. It can estimate the individual-specific and cell-type-specific reference panels, when there are multiple samples observed from each subject. It takes the input of the observed mixture data (feature by sample matrix), and the cell type mixture proportions (sample by cell type matrix), and the sample-to-subject information. It can solve for the reference panel on the individual-basis. It can also conduct test to identify cell-type-specific differential expression (csDE) genes.

Author: Hao Feng [aut, cre], Qian Li [aut]

Maintainer: Hao Feng <hxf155 at case.edu>

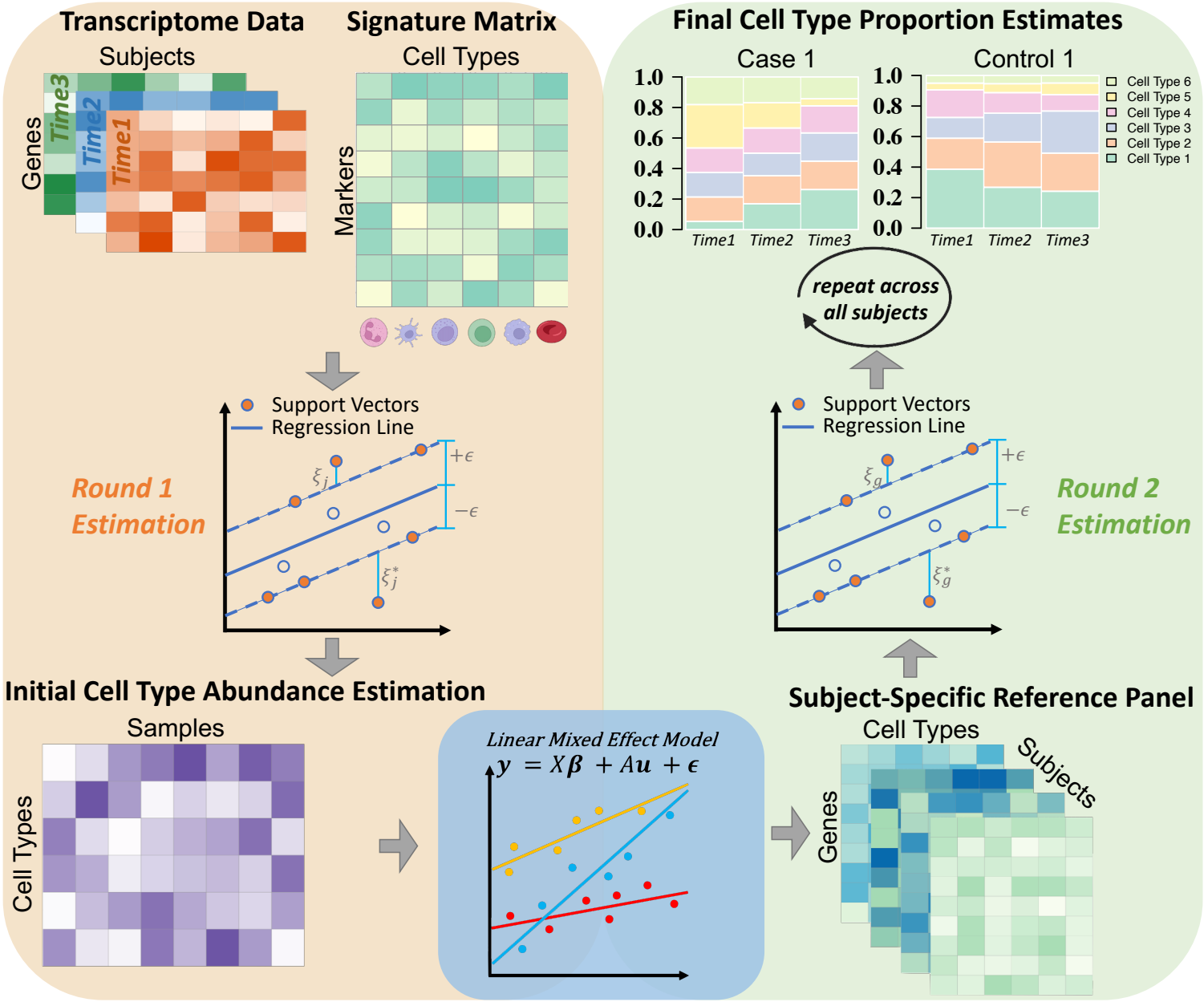
Citation (from within R, enter `citation("ISLET")`):

Feng H, Li Q (2022). *ISLET: Individual-Specific ceLI typE referencing Tool*. R package version 0.99.8.

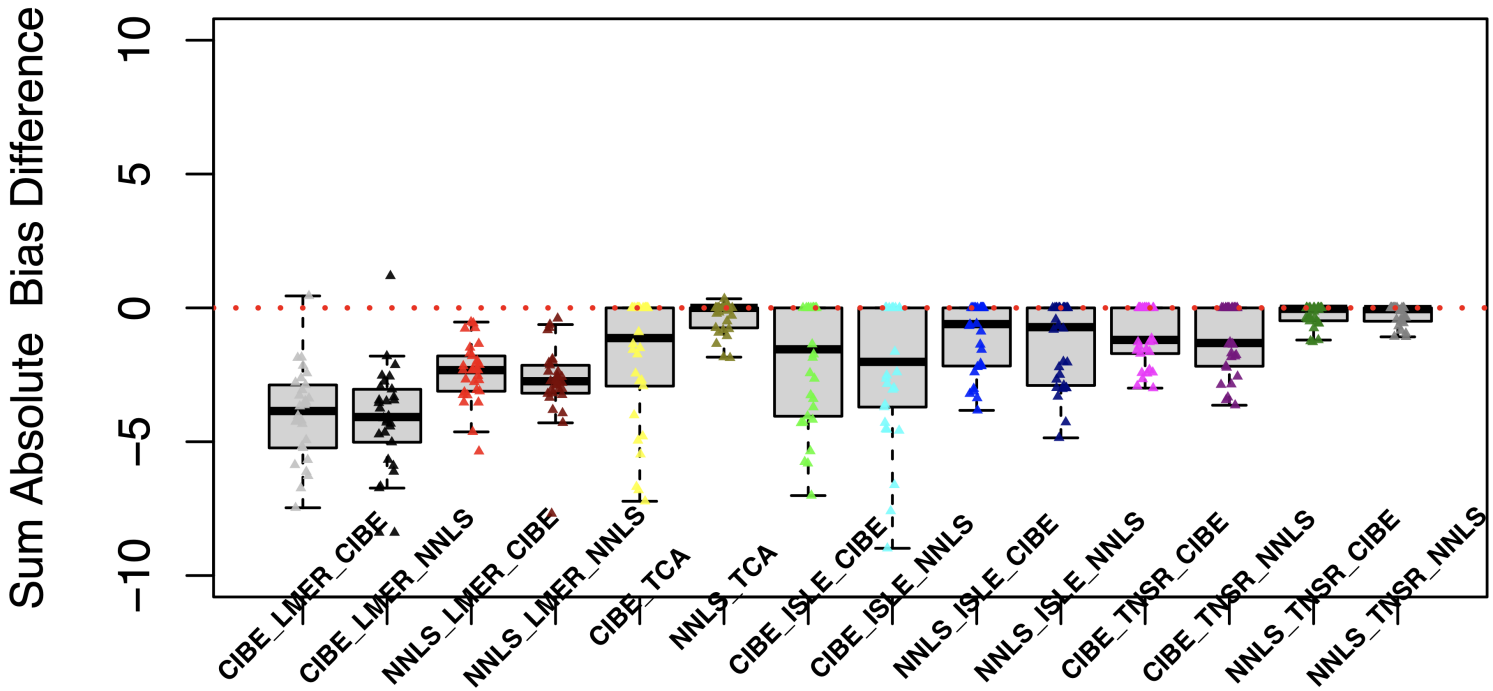
Personalized (better) reference panel $\Rightarrow$ More accurate deconvolution?

1. Personalized and cell-type-specific transcriptome reference panel recovery.
2. Improved deconvolution using personalized reference panel.
3. A hybrid neural network model for scRNA-seq cell type prediction.

Model for improved deconvolution



Simulation: improved estimation

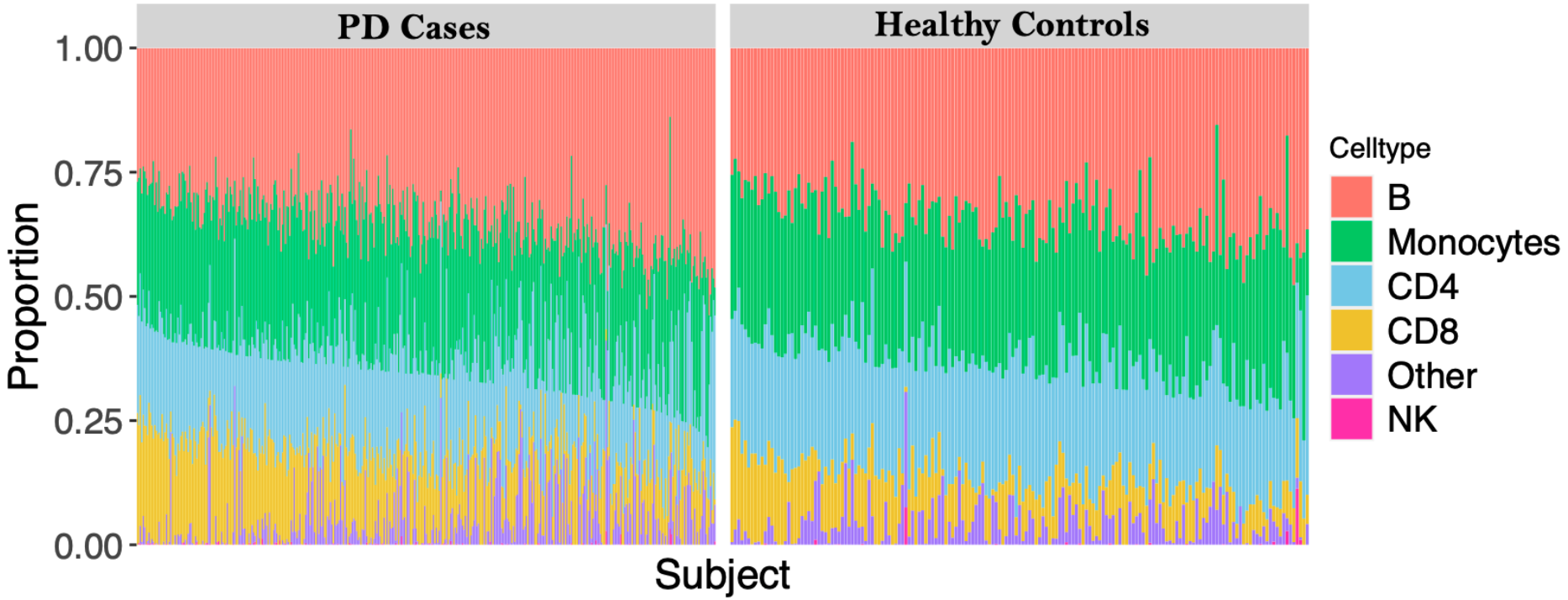


Initial marker genes:300	CIBE_LMER_CIBE	CIBE_LMER_NNLS	NNLS_LMER_CIBE	NNLS_LMER_NNLS	CIBE_TCA	NNLS_TCA	CIBE_ISLE_CIBE
err:0-5% N:25 LFC:0.5	-3.51(1.56)	***-3.95(1.92)***	-1.68(1.3)	-1.8(1.42)	-2.21(1.96)	-0.33(0.85)	1.21(20.15)
err:0-5% N:25 LFC:0.75	***-5.2(7)***	-4.18(1.95)	-2.41(1.1)	-2.72(1.32)	-1.93(2.39)	-0.34(0.58)	13.82(40.99)
err:10%-20% N:25 LFC:0.5	***-2.83(1.34)***	-3.27(1.64)	-1.69(1.07)	-1.66(1.16)	-0.1(4.84)	0.65(3.79)	13.74(41.37)
err:10%-20% N:25 LFC:0.75	***-3.13(1.76)***	-3.3(2.26)	-2.21(0.88)	-2.4(1.23)	0.19(3.09)	1.5(2.9)	9.59(35.68)
err:0-5% N:50 LFC:0.5	-7.97(3.44)	***-8.97(3.86)***	-2.81(4.52)	-3.7(2.94)	-6.6(4.92)	-0.8(2.2)	5.76(52.49)
err:0-5% N:50 LFC:0.75	***-10.77(12.7)***	-9.28(4.97)	-4.66(1.82)	-5.3(2.26)	-4.68(5.35)	-0.9(1.66)	9.6(60)
err:10%-20% N:50 LFC:0.5	-6.14(2.27)	***-6.48(2.86)***	-3.28(1.79)	-3.11(1.95)	1.63(15.12)	2.07(10.22)	2.26(38.29)
err:10%-20% N:50 LFC:0.75	-6.59(3.1)	***-7.05(4.28)***	-4.51(1.69)	-4.8(2.08)	0.87(5.21)	2.24(7.06)	21.41(77.72)

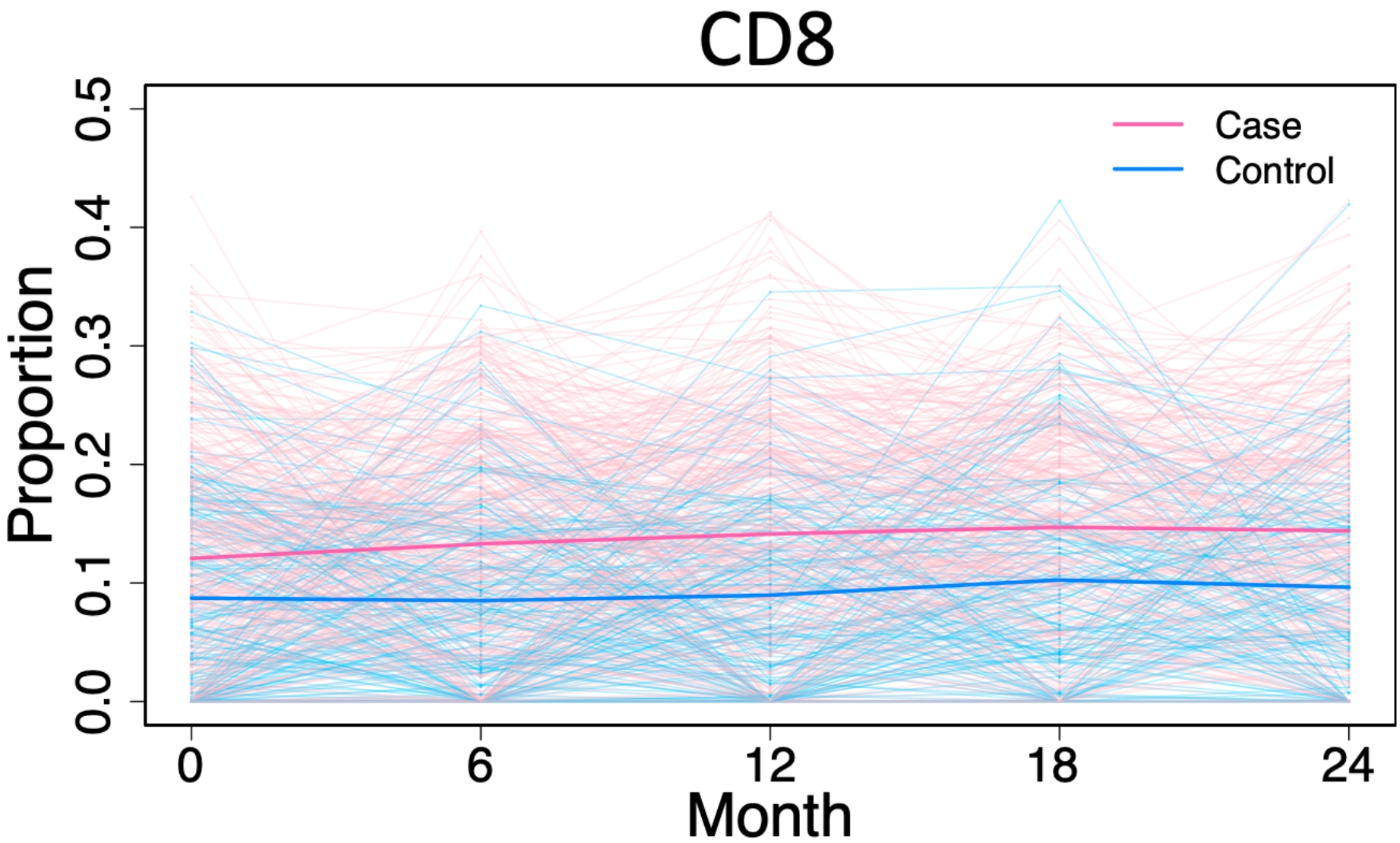
Real data analysis: PDBP

- 399 PD subjects and 173 controls
- 2,599 longitudinal samples over 2 years
- Whole blood transcriptome

Real data analysis: PDBP



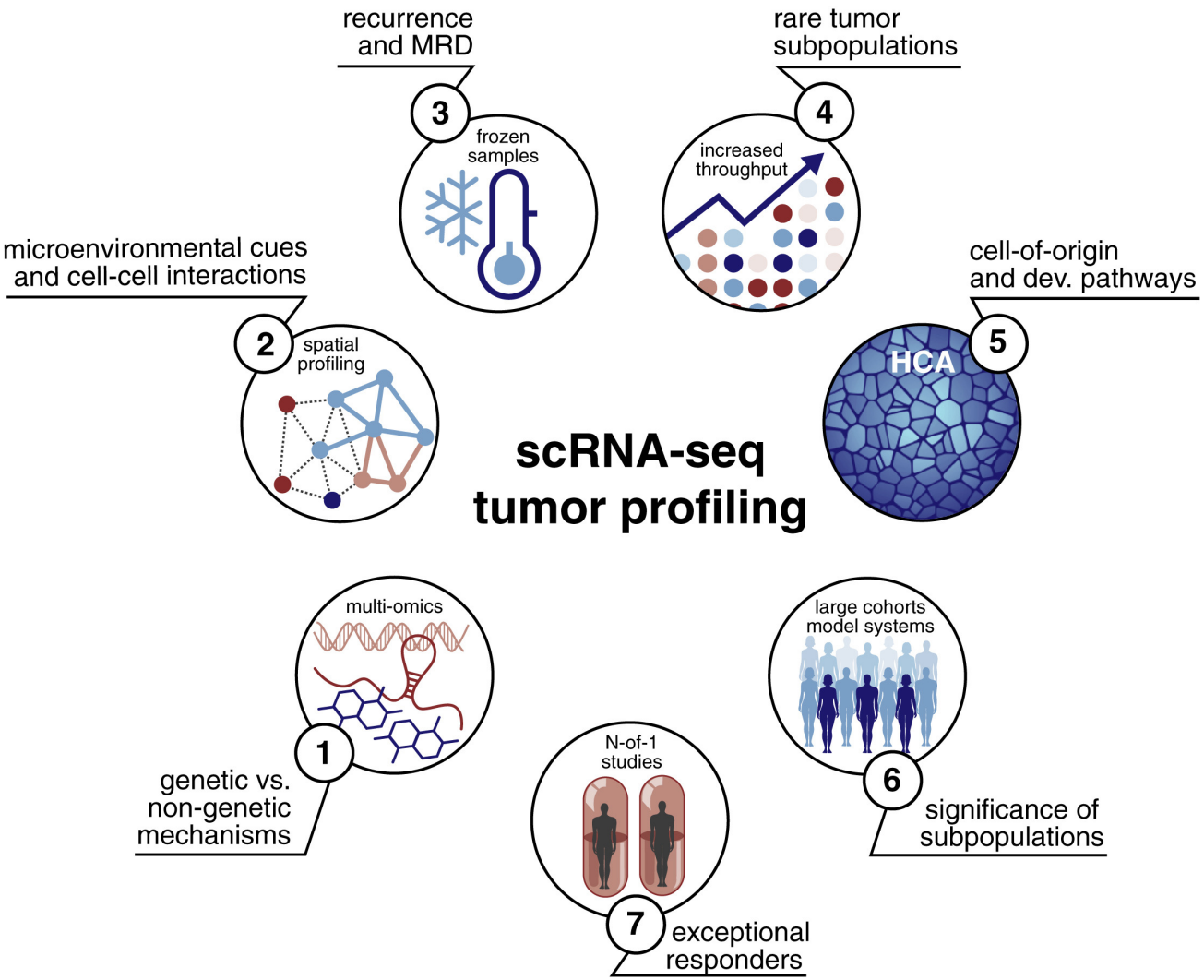
Real data analysis: PDBP



interim summary for personalized deconvolution

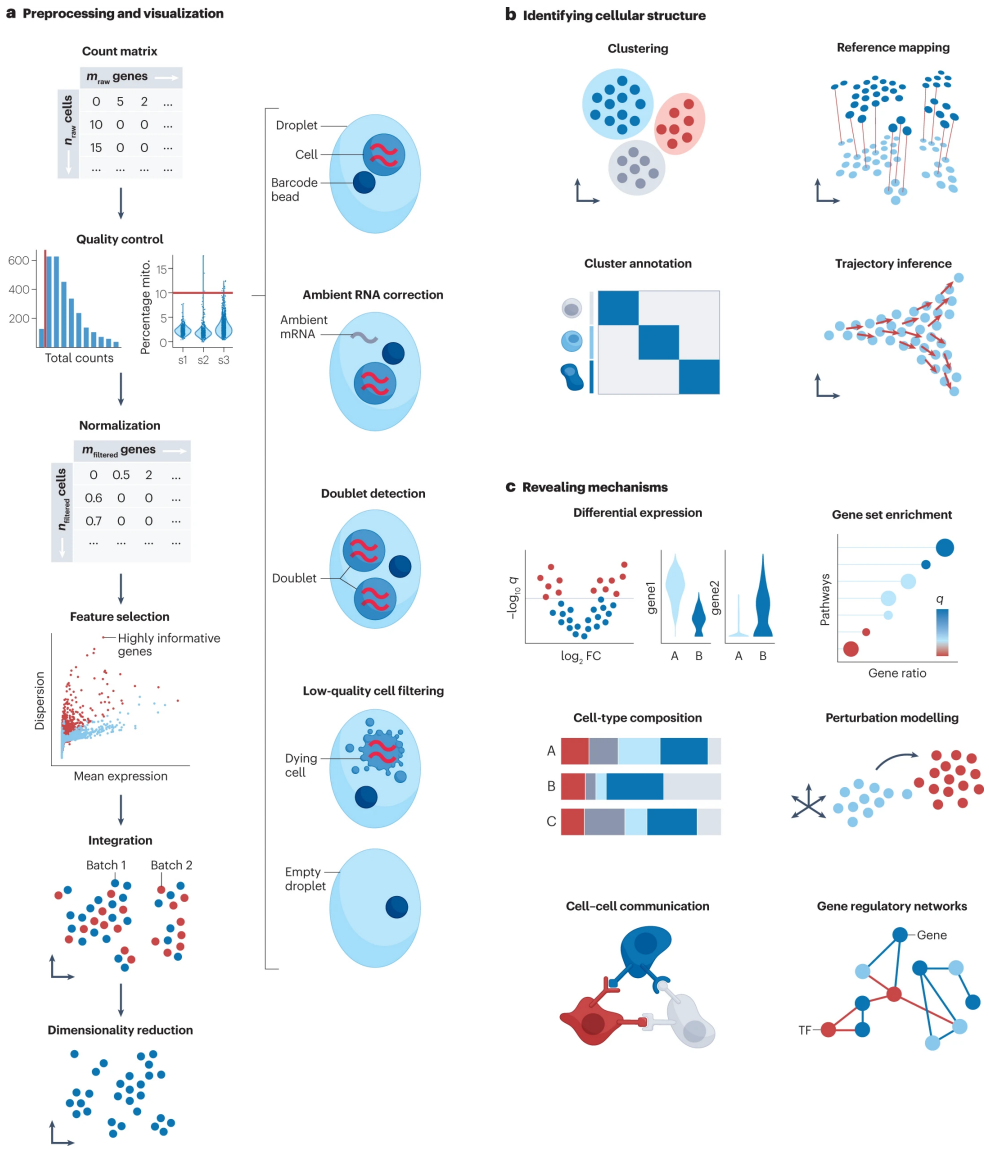
- Statistical frameworks to recover individual-specific and cell-type-specific reference panel.
- Optimize the usage of longitudinally measured samples within the same subject.
- Accurate, robust and powerful performance.
- A R/Bioconductor package ISLET.
- Our model successfully identified gene signatures in B, NK and CD4+ T cells, prior to the onset of pancreatic β-cell autoantibody.
- Our model deconvoluted cell type proportions aligned with low-throughput experiments in PD.

scRNA-seq questions in cancer biology



Suvà, M. L., Tirosh, I. (2019). Single-cell RNA sequencing in cancer: lessons learned and emerging challenges. Molecular cell, 75(1), 7-12.

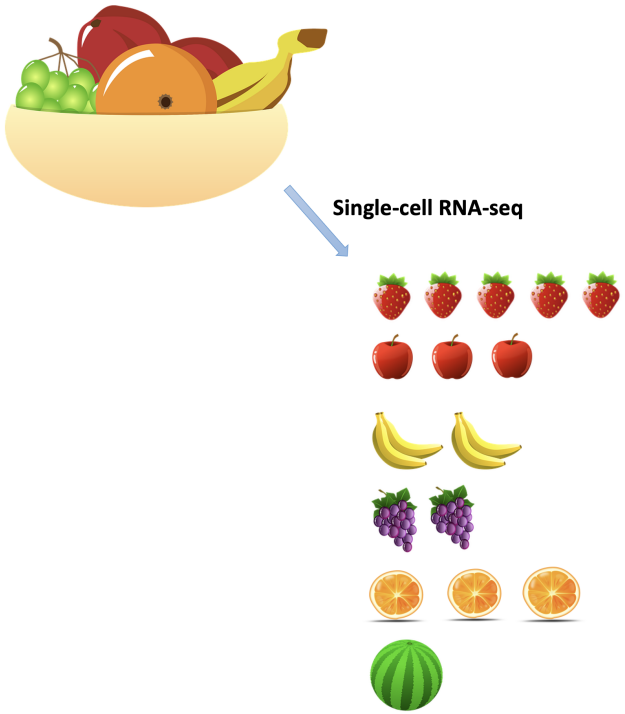
scRNA-seq data analysis



- **Data preprocessing**
  - Normalization
  - Batch effect correction
  - Imputation
- **Data analyses**
  - Cell clustering
  - **Cell type identification**
  - Differential expression
  - Pseudo-time construction
  - Rare cell type discovery;
  - alternative splicing; allele specific expression
  - RNA velocity
- **Visualization**
  - *t*-SNE, UMAP

Heumos, L., Schaar, A.C., Lance, C. et al. Best practices for single-cell analysis across modalities. Nat Rev Genet (2023).

1. Personalized and cell-type-specific transcriptome reference panel recovery.
2. Improved deconvolution using personalized reference panel.
3. A hybrid neural network model for scRNA-seq cell type prediction.



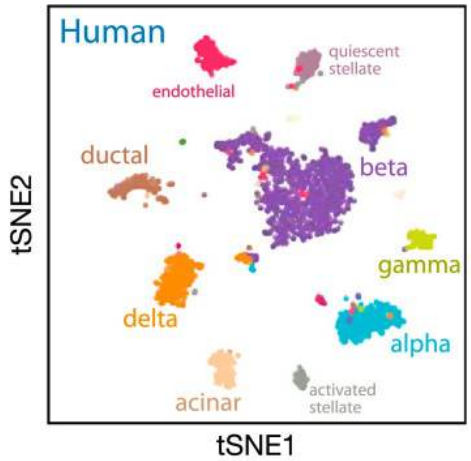
scRNA-seq data

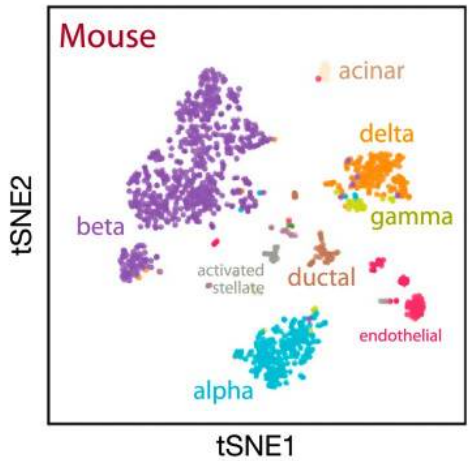
```
> Baron_counts[1:20,1:9]
```

	human2_lib1.final_cell_0001	human2_lib1.final_cell_0002	human2_lib1.final_cell_0003	human2_lib1.final_cell_0004	human2_lib1.final_cell_0005	human2_lib1.final_cell_0006
SST	3476	3340	0	2962	3367	3008
INS	24	5	6	6	6	7
GCG	8	11	1995	8	4	10
REG1A	1	0	0	0	0	0
PPY	1	0	0	0	1	2
TTR	10	1	273	13	4	1
IAPP	3	0	2	3	1	0
REG3A	0	2	0	0	0	0
PRSS2	0	0	0	0	0	0
CTRB2	0	0	0	0	0	0
REG1B	0	0	0	0	0	0
SPINK1	0	0	3	0	0	0
SERPINA1	89	26	362	20	5	13
SERPINA3	0	0	0	0	0	0
EEF1A1	44	21	66	52	43	30
OLFM4	0	0	0	1	0	0
GNAS	71	15	103	90	67	49
FTL	14	5	24	5	12	3
CTRB1	0	0	0	0	0	0
TMSB4X	7	5	5	6	4	5

Cell type identification

- Sequencing output of scRNA-seq is anonymous in terms of cell identities.
- Annotating the cells is a key task in scRNA-seq data analysis.





Baron et al. Cell Systems. doi: 10.1016/j.cels.2016.08.011

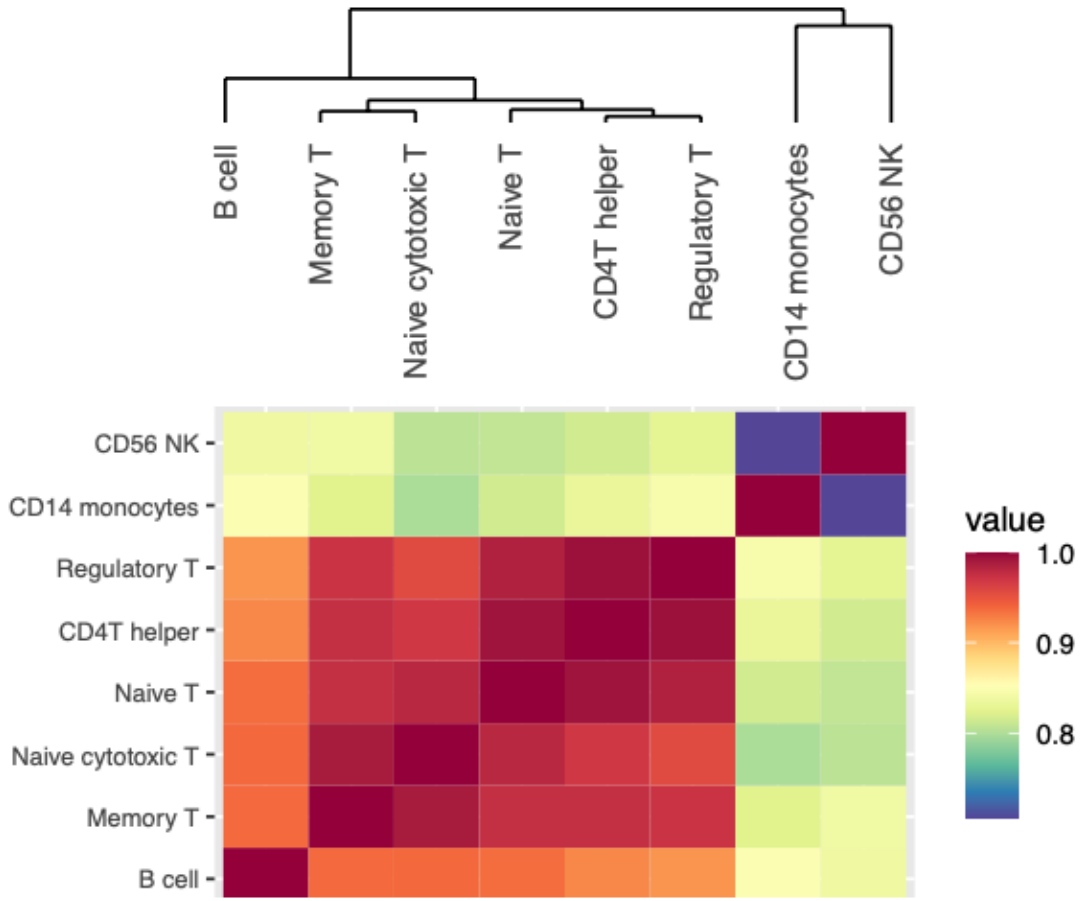
Cell type identification methods

- Two-step approach: Clustering (unsupervised) + labeling.
  - Seurat, SC3, TSCAN, etc...
  - Laborious, time consuming, not best projection, rely on marker gene heavily.
- One-step approach: supervised labeling.
  - scmap, CHETAH, CellAssign, etc...
  - (1) marker-based, (2) correlation-based, and (3) tree structure based.
  - Not suitable for novel cell type discovery.

Our aims

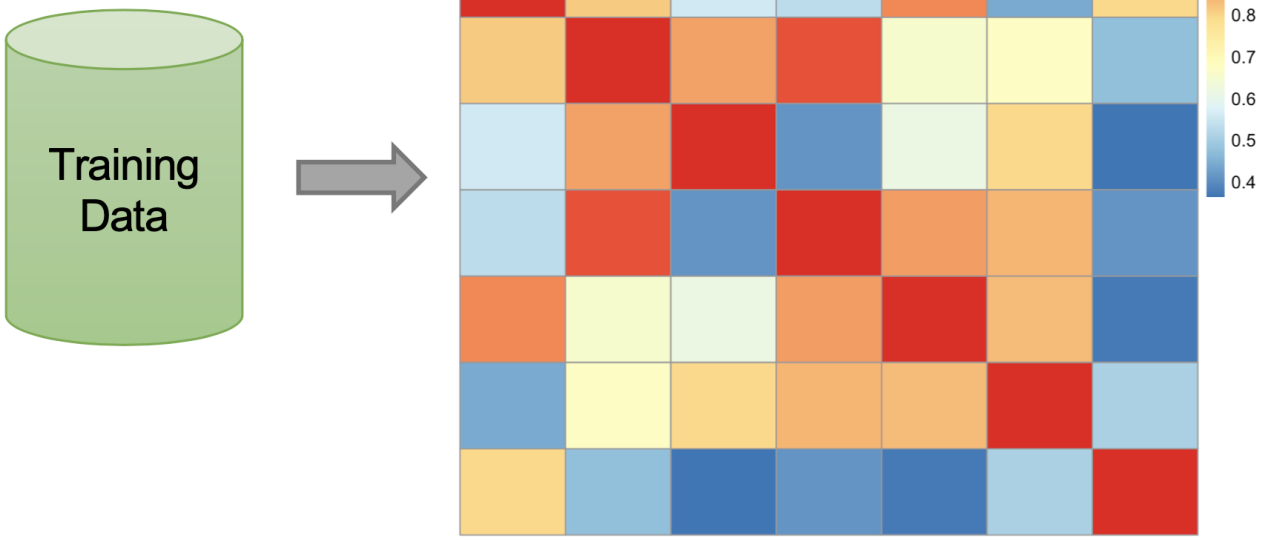
- **Exhaustive**: Annotate all cells.
- **Reliable**: Leverage on massive amount of well-studied existing scRNA data.
- **Flexible**: Adopt different prediction strageties, depending on correlation.

Correlations of cell types



High-correlation cell types pose major challenges.

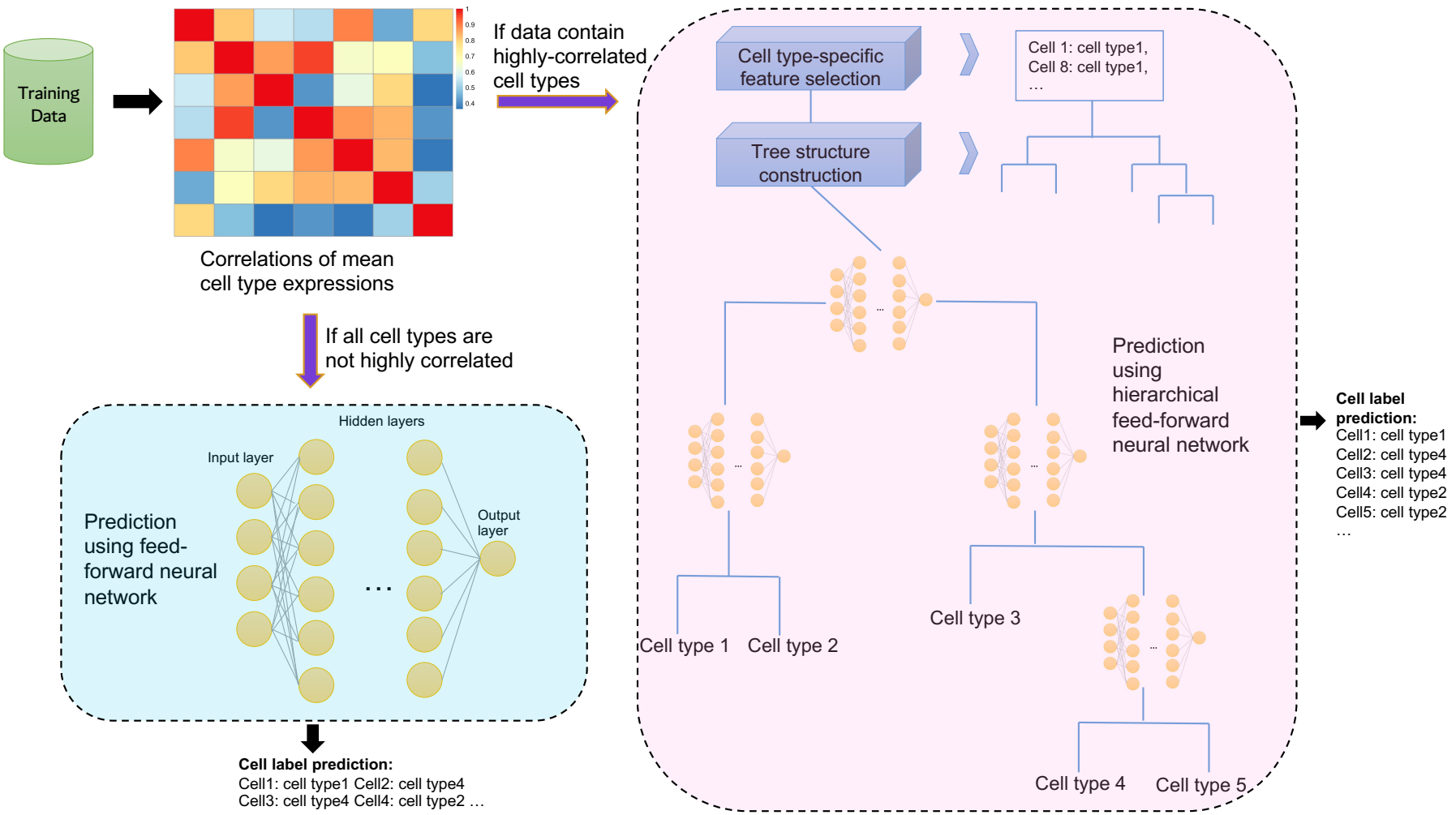
Tackle the issue of high-correlation



Correlations of mean cell type expressions

How about adopting a flexible approach?

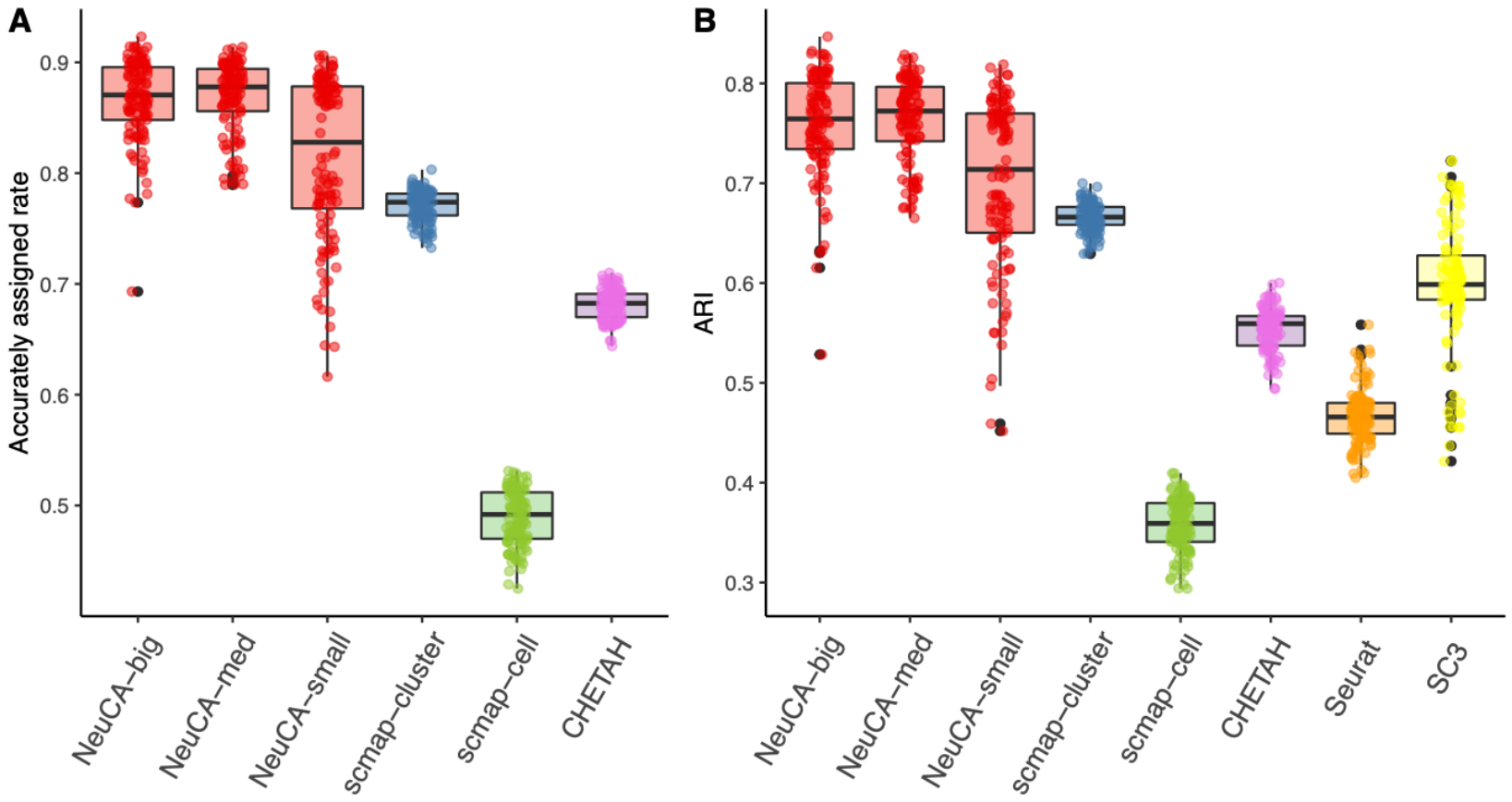
Our method: a neural network-based cell annotation



Wires inside the cogs

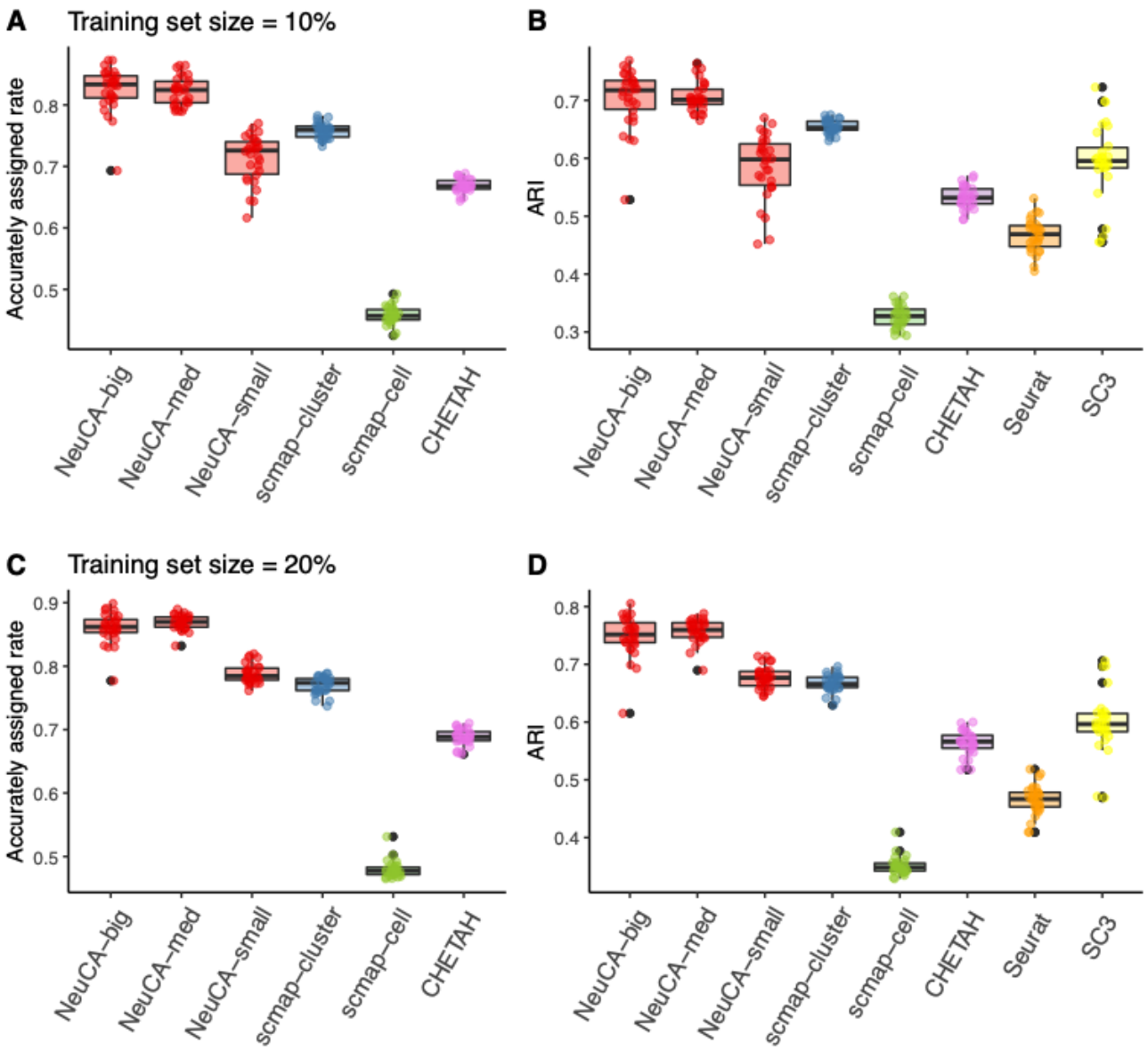
- Route 1: feed-forward neural-network
  - feature selection.
  - 3 model sizes: big, medium, small. (256 to 64 units/nodes)
  - activation function: Rectified Linear Unit (ReLU).
  - output: Softmax.
  - categorical cross-entropy loss.
- Route 2: marker-guided hierarchical neural-network
  - feature selection (gene-specific sensitivities).
  - cell type hierarchical tree.
  - hierarchical neural-network tree.
  - similar model sizes as Route 1.

Simulation results: real-data based

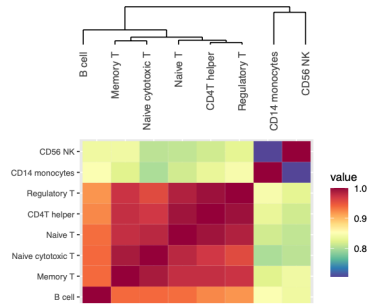


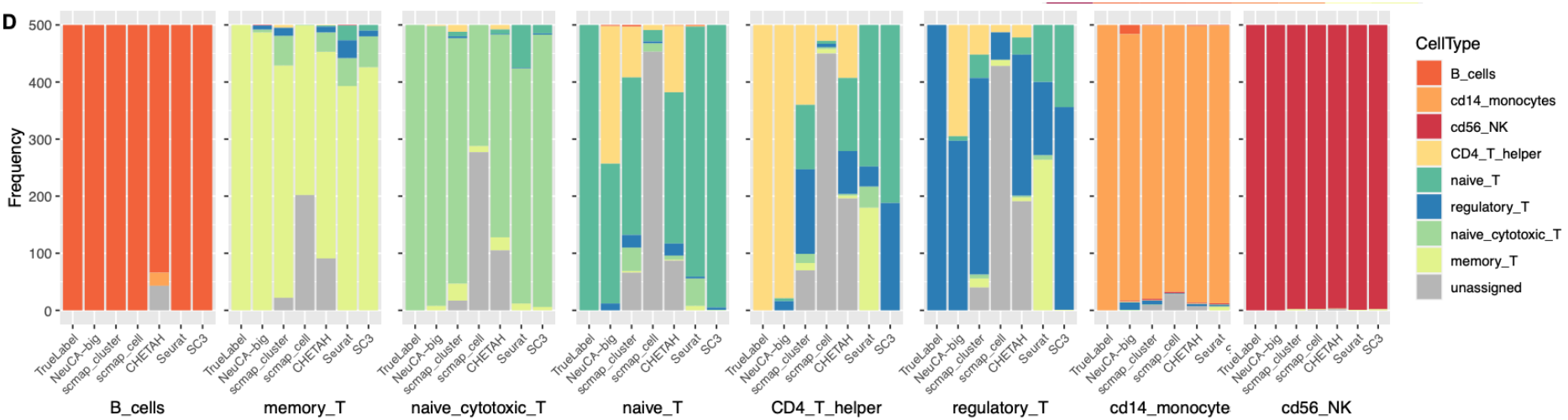
- 10X PBMC scRNA-seq data.
- 80 Monte Carlo simulations are conducted and aggregated.
- Training set proportion ranging from 10% to 80%.

Simulation results

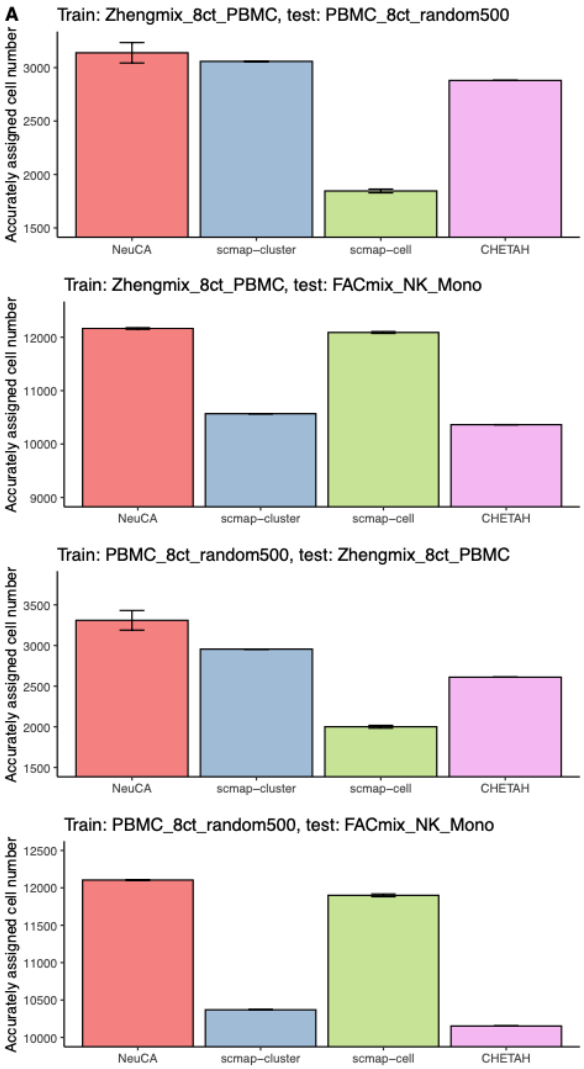


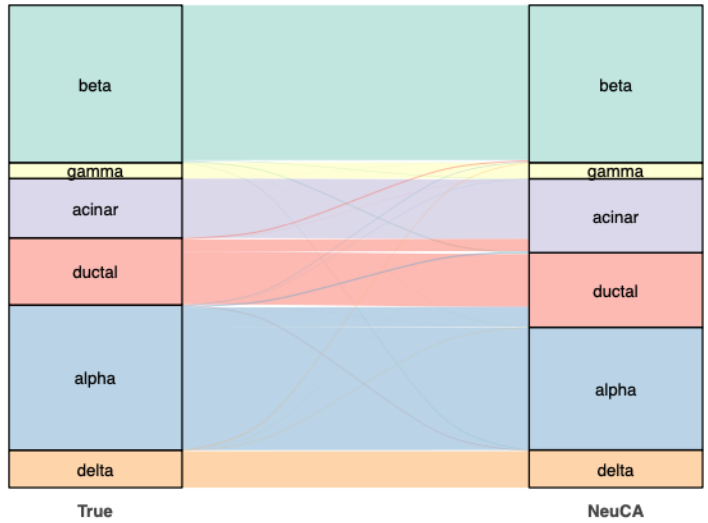
Real data results

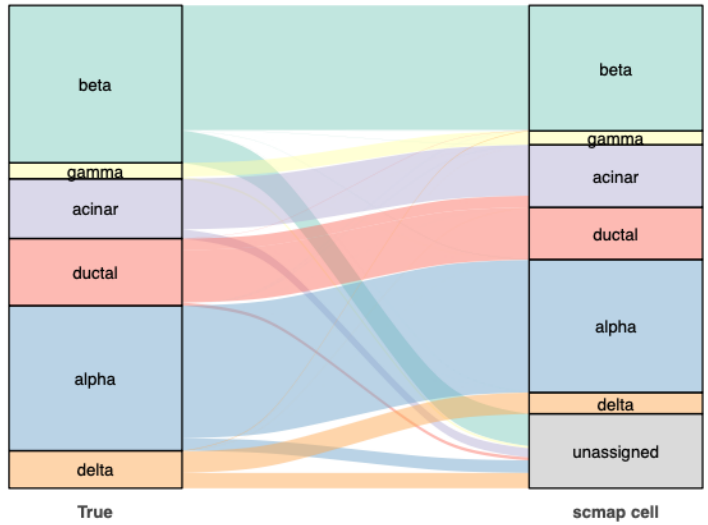




Real data results

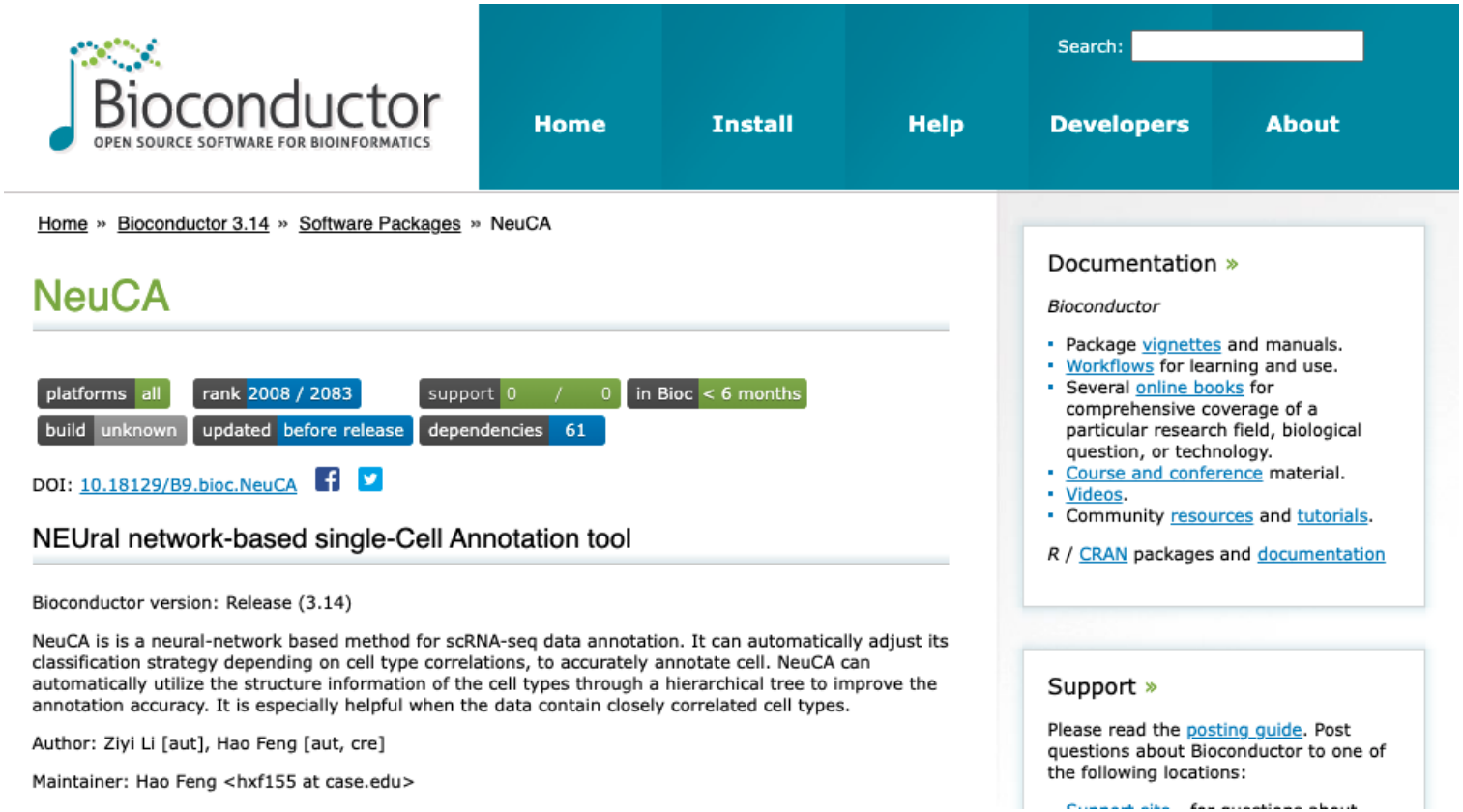






Software: NeuCA

On Bioconductor: https://bioconductor.org/packages/NeuCA

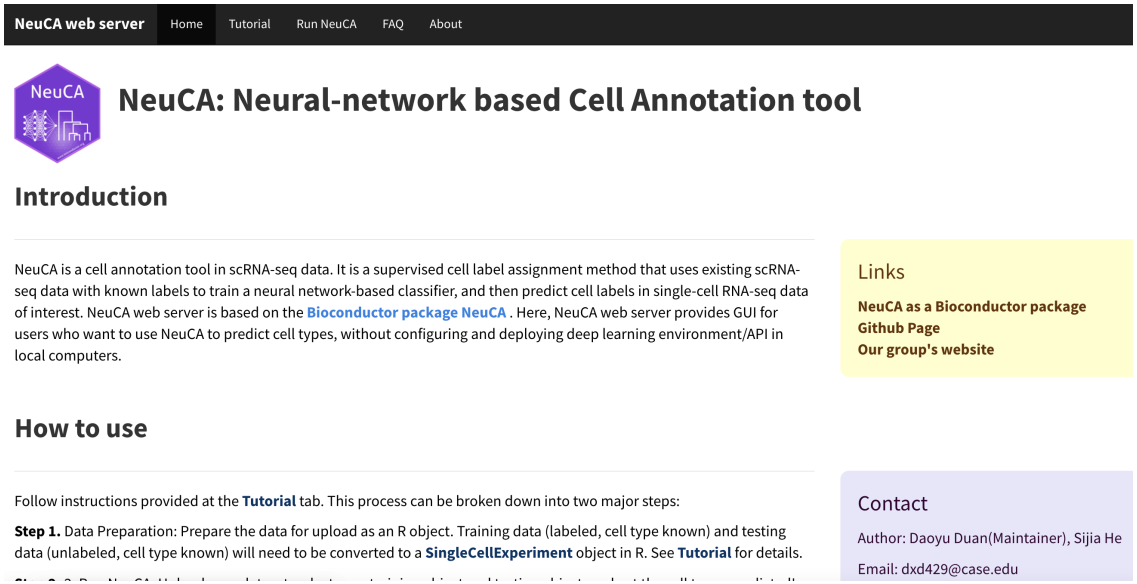


Usage

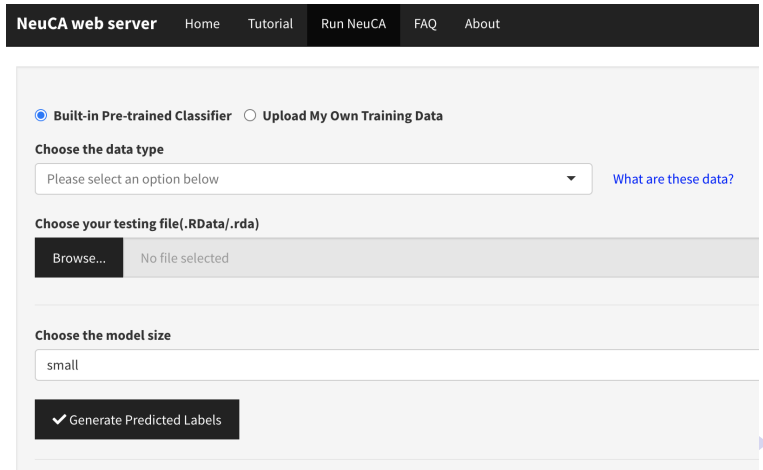
```
NeuCA(train, test, model.size = "big", verbose = FALSE)
```

NeuCA web server

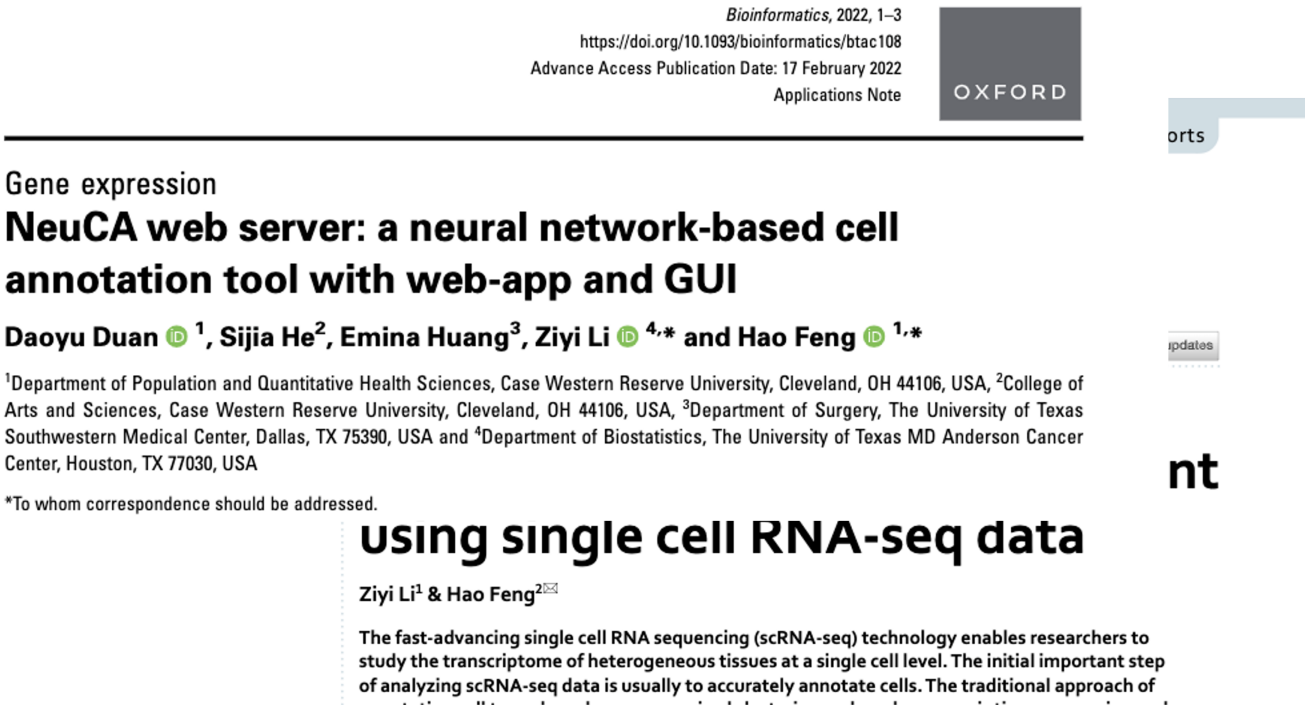
R Shiny App: https://statbioinfo.shinyapps.io/NeuCA



- (Human) Molar
- (Human) Choroid Plexus
- (Human) Healthy Lung
- (Human) Aging Skin
- (Human) Fetal Maternal Decidual
- (Human) Muscle
- (Human) Bronchoalveolar from COVID-19 Patients
- (Human) Adult Retina
- (Human) Fetal Gut
- (Mouse) Enteric
- (Mouse) Hippocampus
- (Mouse) Spinal Cord



Publication



Bioinformatics, 2022, 1–3
https://doi.org/10.1093/bioinformatics/btac108
Advance Access Publication Date: 17 February 2022
Applications Note

OXFORD

Gene expression

NeuCA web server: a neural network-based cell annotation tool with web-app and GUI

Daoyu Duan [1], Sijia He[2], Emina Huang[3], Ziyi Li [4,*] and Hao Feng [1,*]

[1]Department of Population and Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH 44106, USA, [2]College of Arts and Sciences, Case Western Reserve University, Cleveland, OH 44106, USA, [3]Department of Surgery, The University of Texas Southwestern Medical Center, Dallas, TX 75390, USA and [4]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

*To whom correspondence should be addressed.

using single cell RNA-seq data

Ziyi Li[1] & Hao Feng[2]✉

The fast-advancing single cell RNA sequencing (scRNA-seq) technology enables researchers to study the transcriptome of heterogeneous tissues at a single cell level. The initial important step of analyzing scRNA-seq data is usually to accurately annotate cells. The traditional approach of

NeuCA web server: doi.org/10.1093/bioinformatics/btac108
NeuCA methodology: doi.org/10.1038/s41598-021-04473-4

... but so what?

scRNA-tools tsunami

https://www.scrna-tools.org/

Zappia and Theis *Genome Biology* (2021) 22:301
https://doi.org/10.1186/s13059-021-02519-4

Genome Biology

REVIEW Open Access

Over 1000 tools reveal trends in the single-cell RNA-seq analysis landscape

Luke Zappia[1,2] and Fabian J. Theis[1,2,3*]

scRNA-tools tsunami

https://www.scrna-tools.org/

Zappia and Theis *Genome Biology* (2021) 22:301
https://doi.org/10.1186/s13059-021-02519-4

Genome Biology

REVIEW Open Access

Over 1000 tools reveal trends in the single-cell RNA-seq analysis landscape

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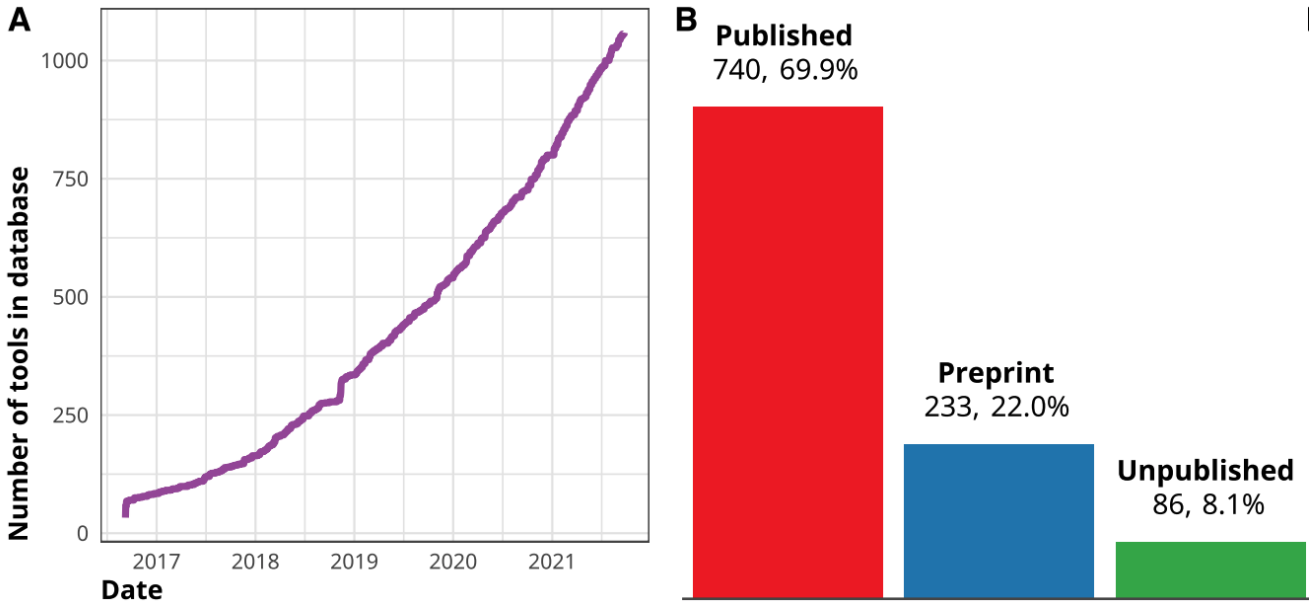

The grand trajectory

"*the evolution of the field and a change of focus from ordering cells on continuous trajectories to integrating multiple samples and making use of reference datasets*"

"*open science practices reward developers with increased recognition and help accelerate the field*"

Acknowledgement

- Leslie Meng
- Daoyu Duan
- Wen Tang

- Qian Li

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- Ziyi Li

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