Novartis Institutes for BioMedical Research
Oncology Data Science

Denoising of Single Cell Sequencing Data with Probabilistic Deep Learning

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Overview

- Single-cell CRISPR screens in drug target identification (**WHY?**)
- A technical issue in single-cell CRISPR screens (**WHAT?**)
- How do we solve it with machine learning? (**HOW?**)
- Generalization ability?

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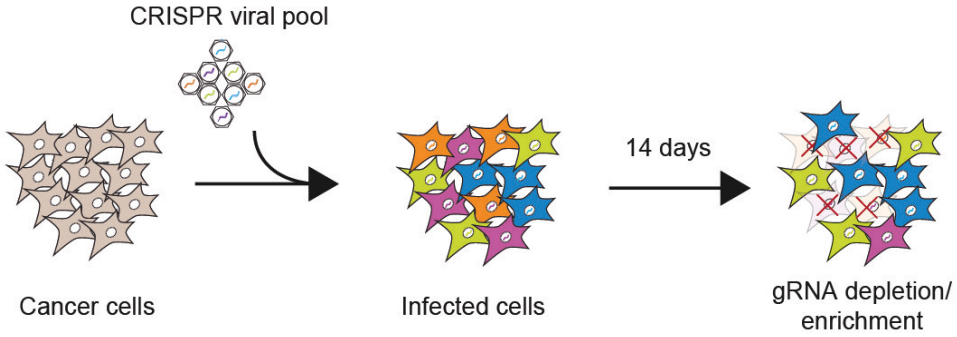
Genetic screens in drug target identification



- Functional genomics identify targets regulating cancer cell proliferation

Novartis' Project DRIVE
Broad's Project Achilles
Sanger's Project Score

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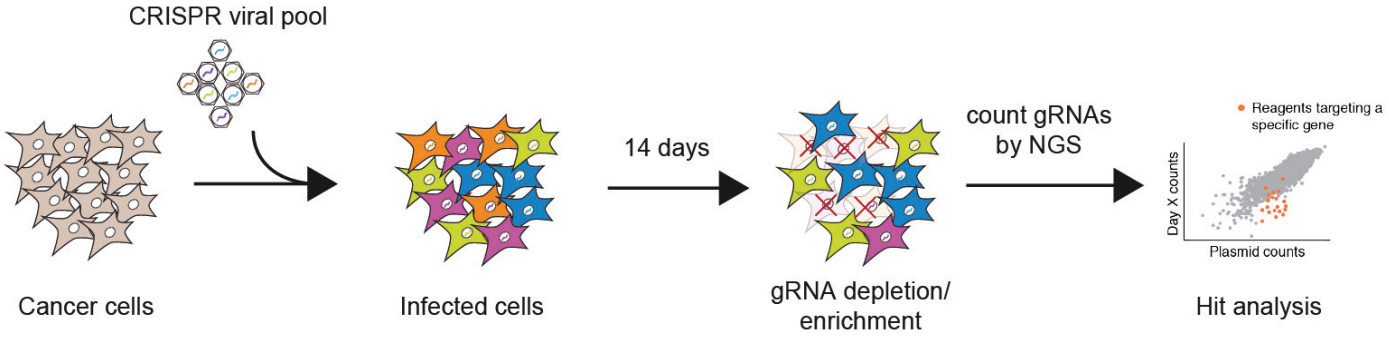
Genetic screens in drug target identification



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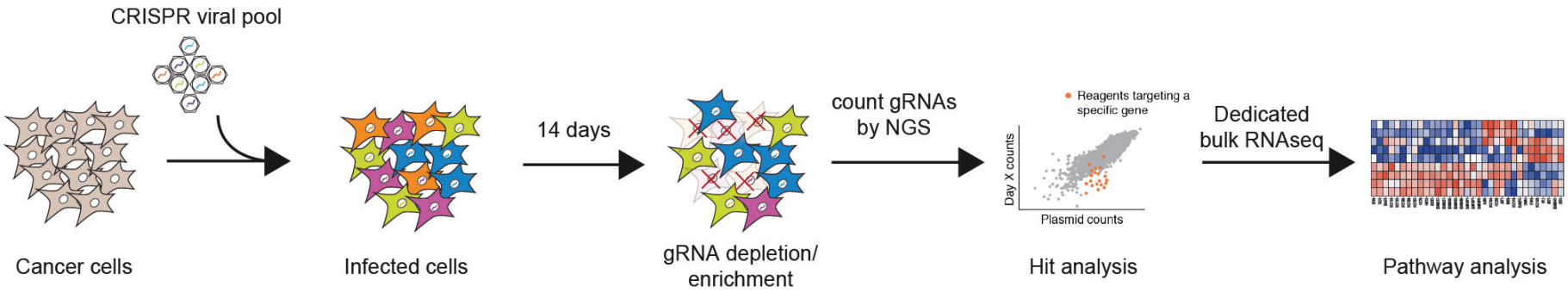

- Functional genomics identify targets regulating cancer cell proliferation
- Dedicated bulk RNA-seq validation identifies target-specific signatures
- Low efficiency

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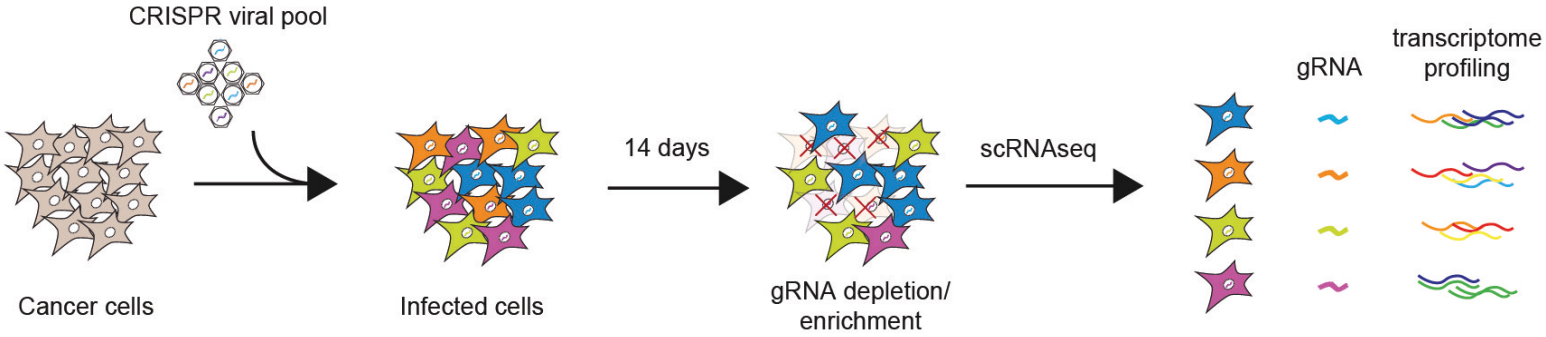
Single-cell omics facilitate drug target identification



- Single-cell CRISPR screens = functional screens + single cell RNA-seq
- Assignment of the gRNA is crucial

Dixit, A. et al. 2016, Cell
Adamson, B. et al. 2016, Cell

Xie, S. et al. 2017, Molecular Cell
Jaitin, D.A. et al. 2016, Cell

Datlinger, P. et al.
2017, Nature Methods

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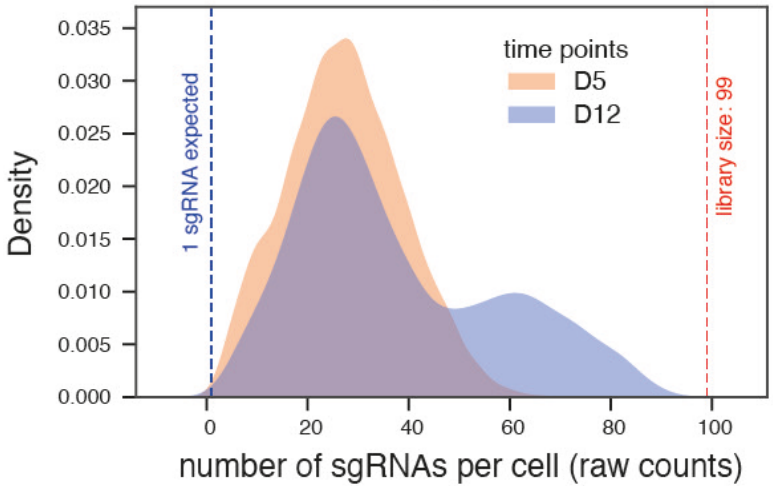
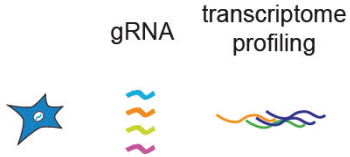
single-cell data is highly noisy





How can we identify the true signal?

Multiple gRNAs are detected in every cell

Sheng, C. et al. 2022, bioRxiv

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Overview

- Single-cell CRISPR screens in drug target identification (**WHY?**)
- A technique issue in single-cell CRISPR screens (**WHAT?**)
- How do we solve it with machine learning? (**HOW?**)
  1) Investigated the details of the technology
  2) Built a deep generative model based on the finding
  3) Optimized the model with synthetic data
  4) Validated the model in real cases
- Generalization ability?

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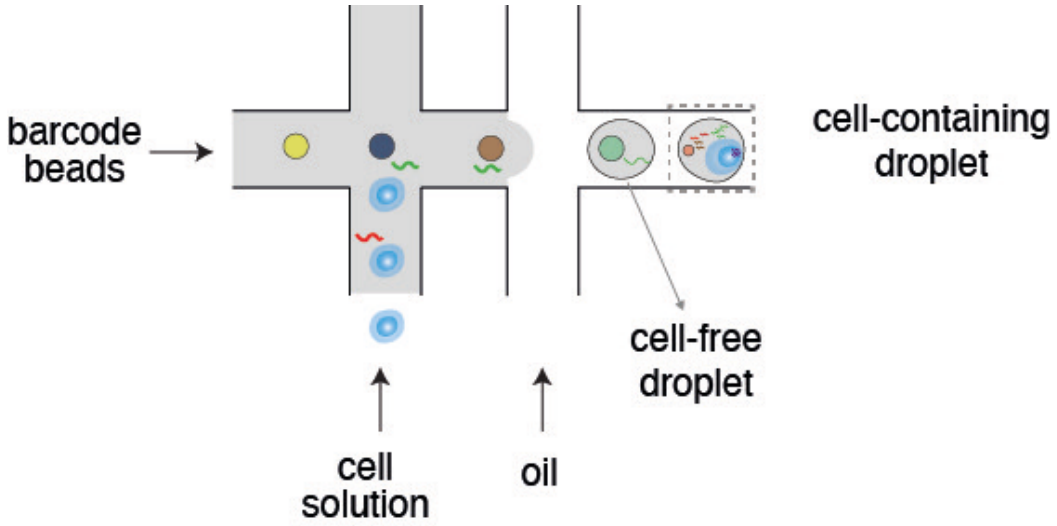
How is the noise generated?



- RNAs are released from broken cells and they float around in single cell suspension
- Droplets capture not only cells but also ambient RNAs (i.e. floating RNAs)

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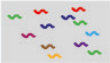
ambient pool

genes	ambient frequency
	0.45
	0.15
	0.05
	0.2
	0.05
	0.1
total	1



- Frequency of each RNA varies

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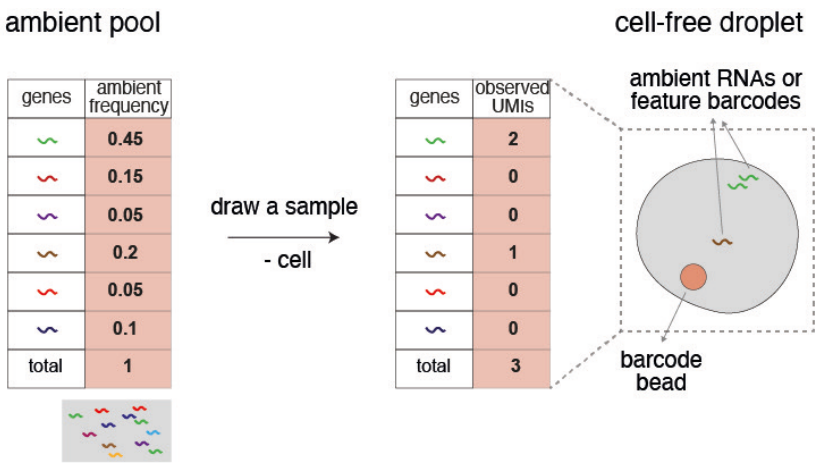

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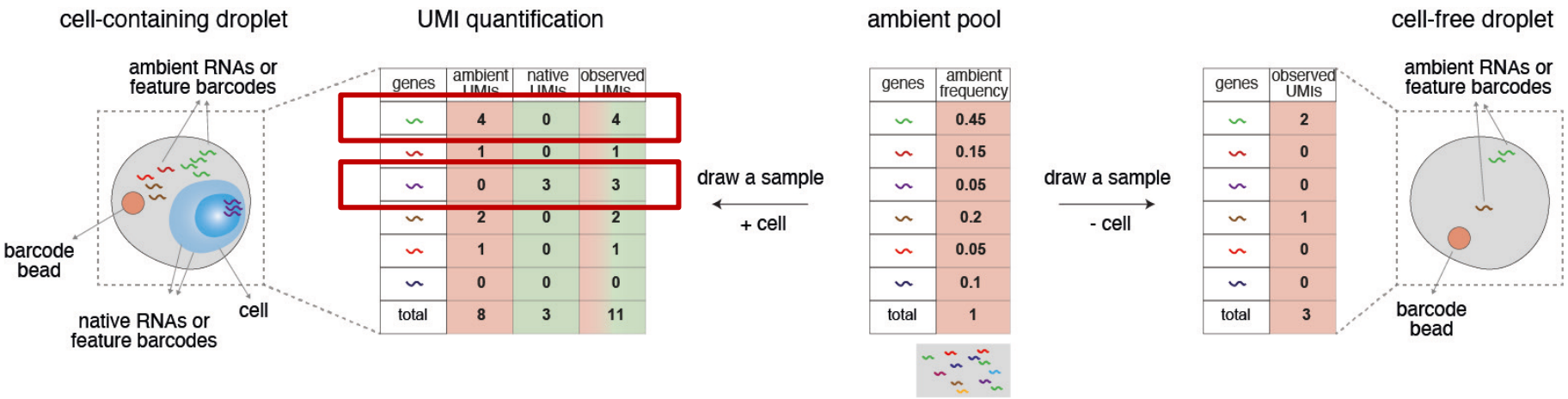

- Frequency of each RNA varies
- Hard to distinguish between noise and true signal by their raw counts

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A deep generative model simulates the generation of noise

$$(1-\varepsilon) \times \beta + \varepsilon \times \alpha = \theta$$

biological signal — technical noise

$$x \mid d \sim Multinomial(d, prob=\theta)$$

Sheng, C. et al. 2022, bioRxiv
https://github.com/Novartis/scAR

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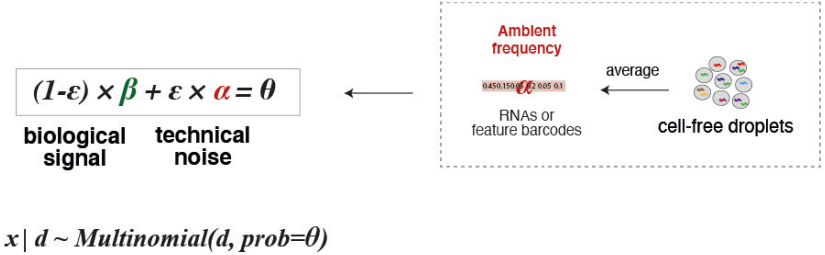
A deep generative model simulates the generation of noise



$$x \mid d \sim Multinomial(d, prob=\theta)$$

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Autoencoder

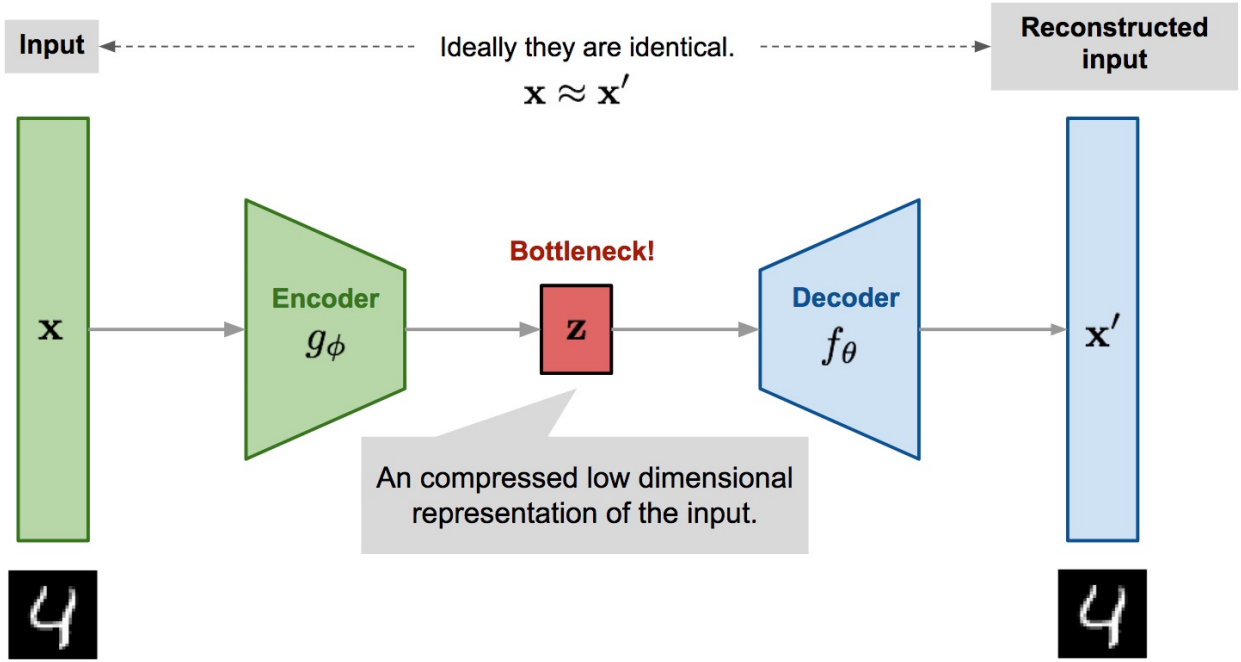

Image from https://lilianweng.github.io/posts/2018-08-12-vae/

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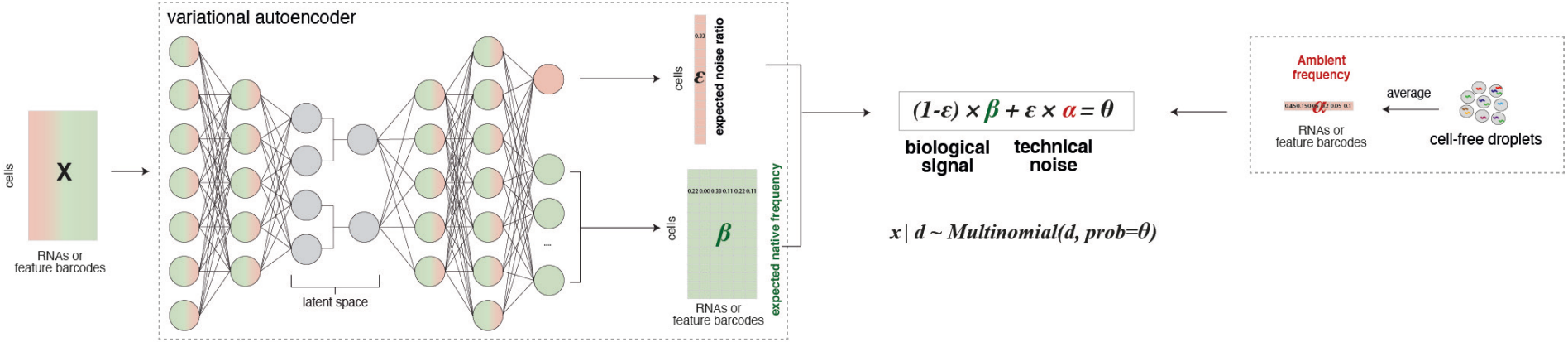

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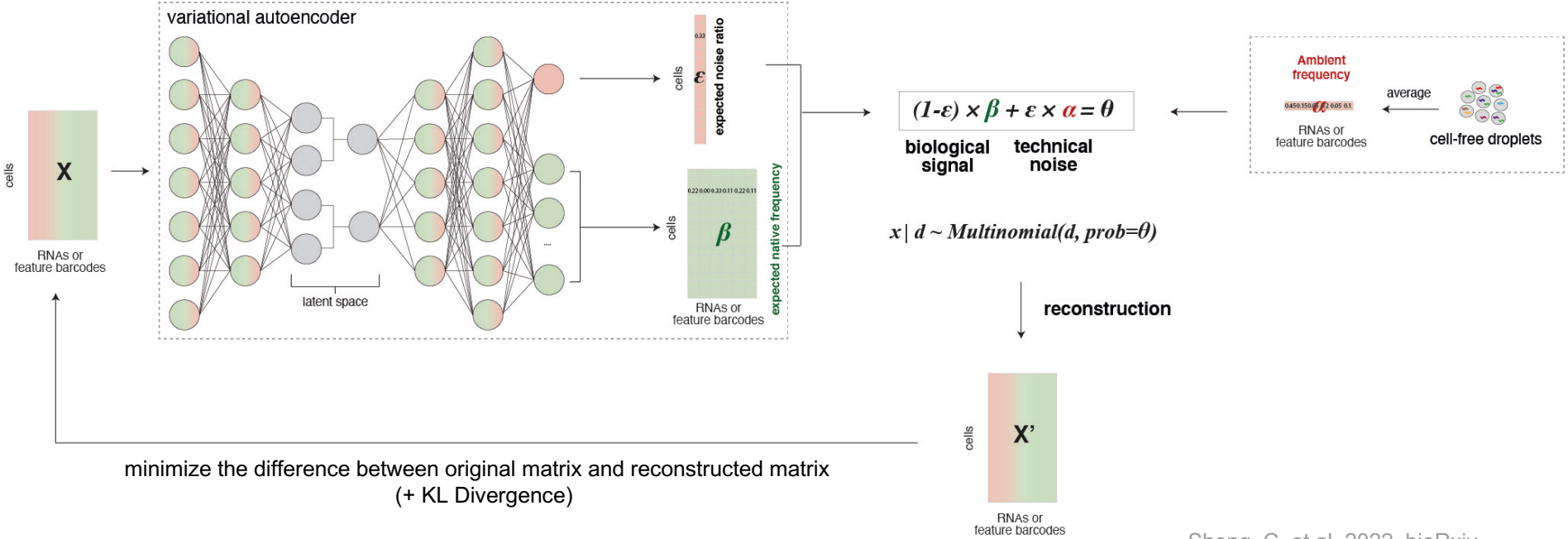

minimize the difference between original matrix and reconstructed matrix
(+ KL Divergence)

Sheng, C. et al. 2022, bioRxiv
https://github.com/Novartis/scAR

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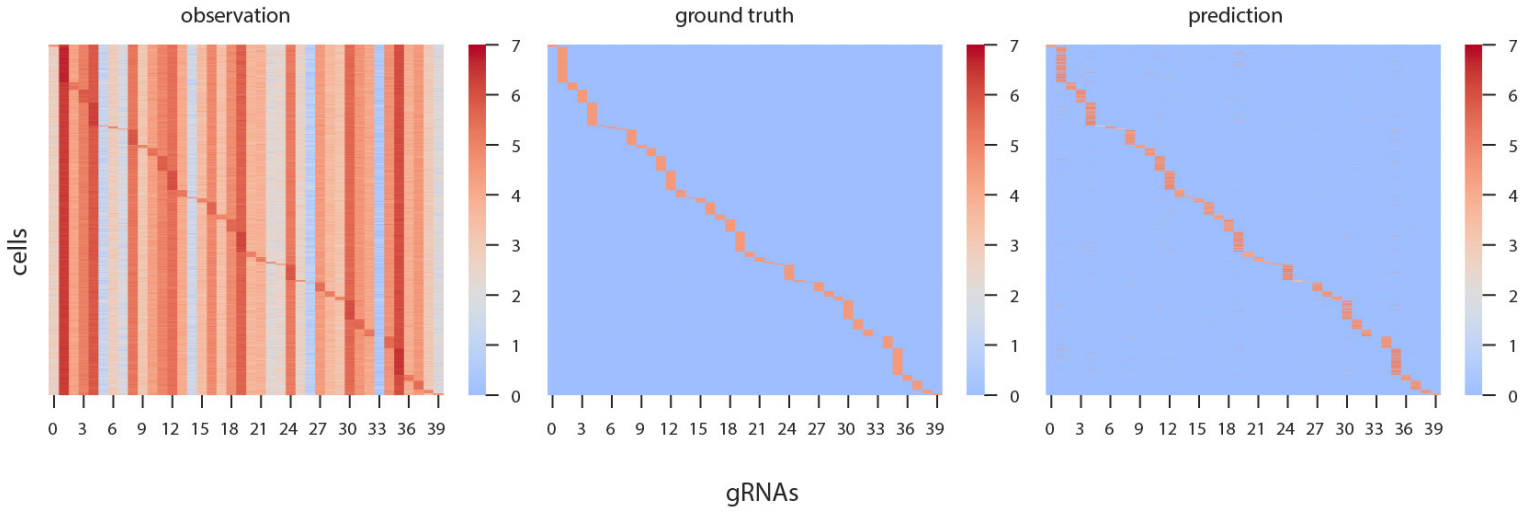
Model validation with synthetic data



Noise level: 97.5%
scAR: 89%

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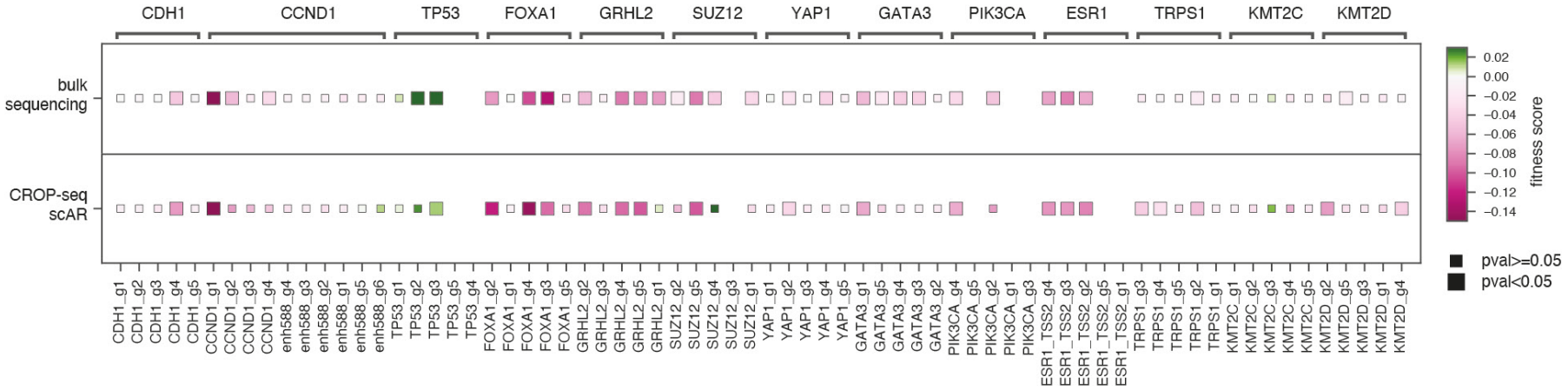
scAR enables hit analysis in single-cell CRISPR screens



- scAR identifies most of lethal gRNAs

Sheng, C. et al. 2022, bioRxiv

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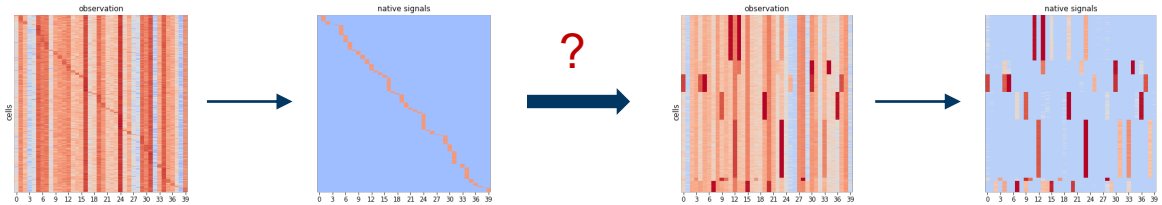

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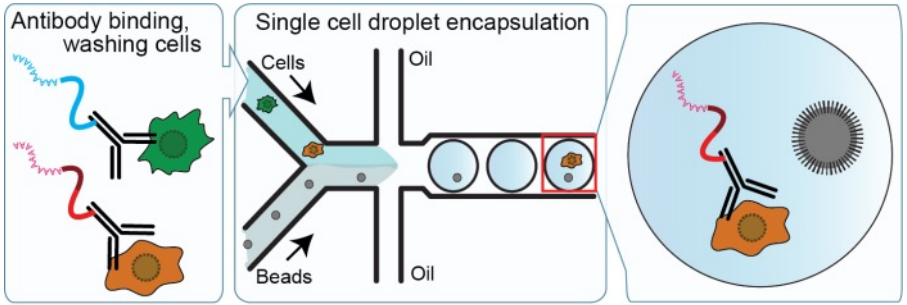
CITE-seq



Stoeckius, M., et al. 2017, *Nature Methods*

- It allows simultaneous measurement of single cell transcriptome and proteins
- It becomes more and more popular in Immuno-oncology

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scAR removes background noise in CITE-seq

- CD20 is a protein that exclusively expressed in B cells

Sheng, C. et al. 2022, bioRxiv

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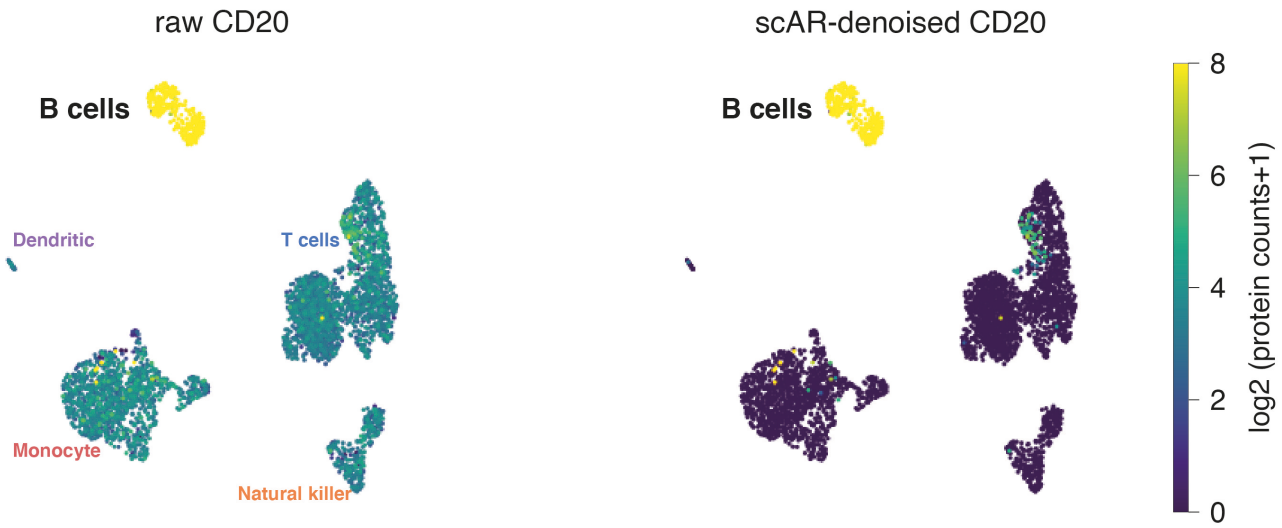
scAR removes background noise in CITE-seq



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Sheng, C. et al. 2022, bioRxiv

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Summary

- Single-cell technologies have huge potential in drug target identification, however, they suffer from substantial noise.
- We developed a ML approach (called scAR) to remove the background noise.
- We applied scAR to several single-cell technologies, and it shows high performance.

GitHub: https://github.com/Novartis/scAR/

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Sven Schuierer

Walter Carbone

Postdoc program

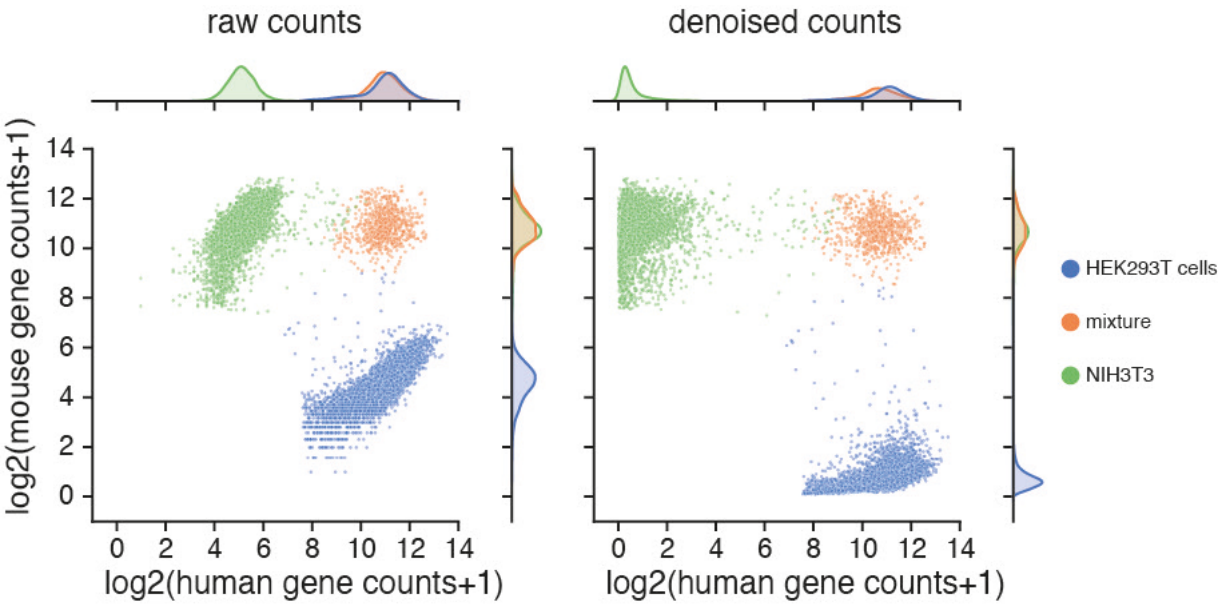
Anne Granger

OpentoWork

Caibin Sheng

Data scientist, single cell analysis, machine learning, AI drug devel...

scRNAseq



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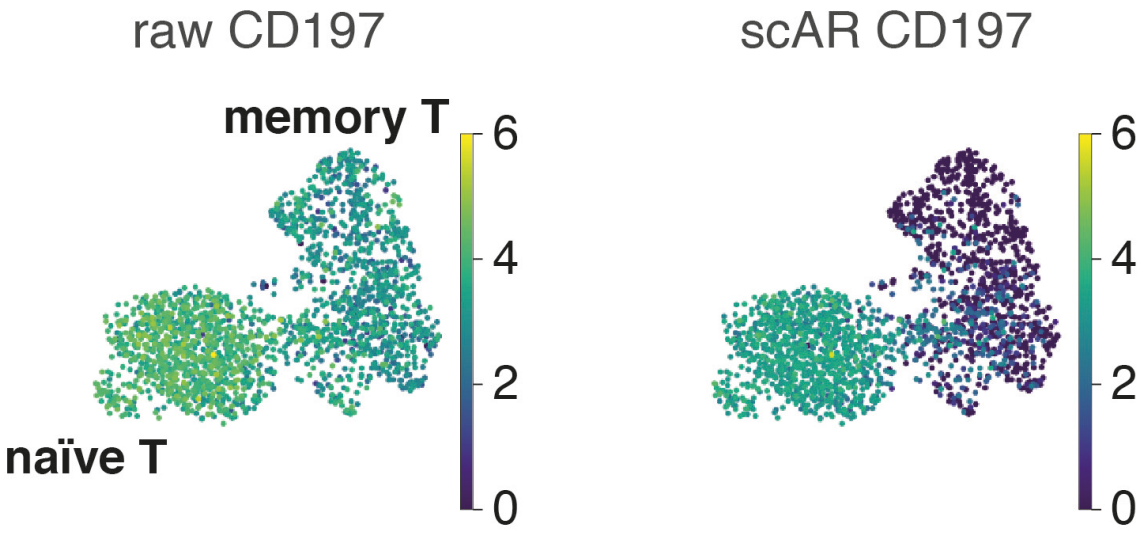
scAR improves immunophenotyping



- CD197 is a protein marker to distinguish between memory T and naïve T cells

Sheng, C. et al. 2022, bioRxiv

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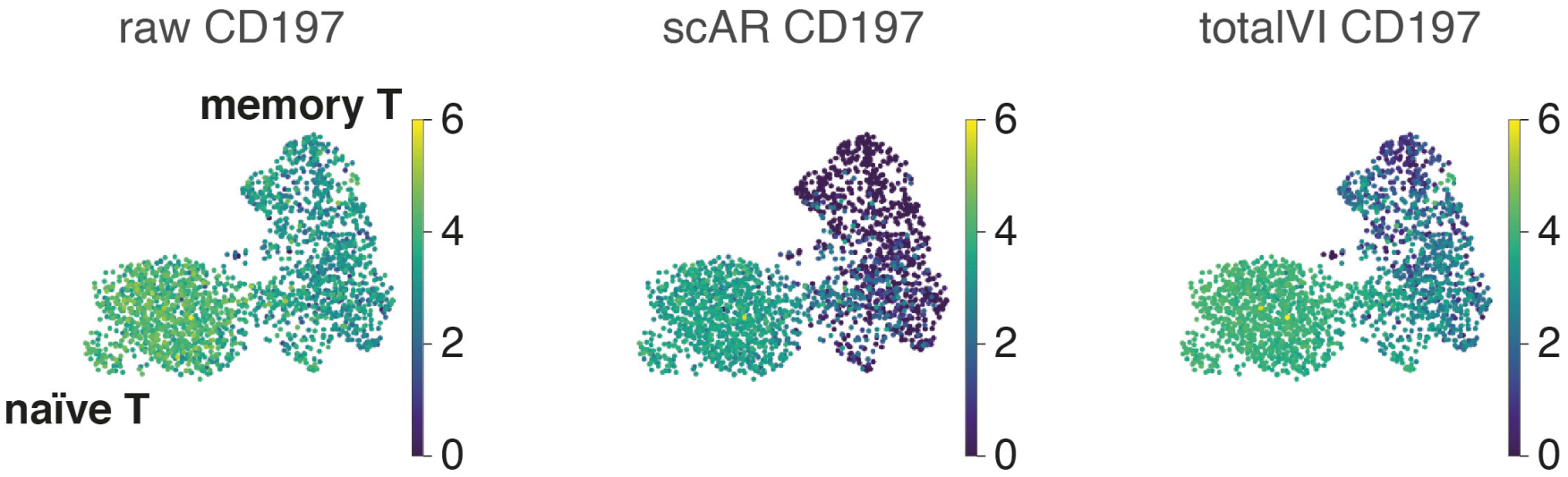
scAR outperforms the state-of-the-art approach



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Gayoso, A. et al. 2021, Nature Method
Sheng, C. et al. 2022, bioRxiv

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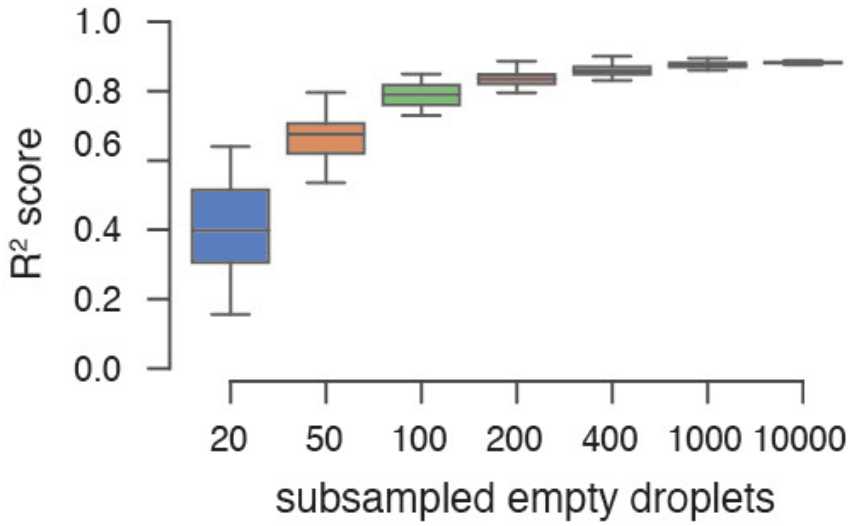

- Frequencies of sgRNAs are consistent in randomly sampled empty droplets
- Background signal is not random noise but deterministic

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