DANISH SINGLE-CELL NETWORK NEWSLETTER

JANUARY - 2023

THIS MONTH'S HIGHLIGHTS:

scChIX-seq infers dynamic relationships between histone modifications in single cells

Yeung, J., Florescu, M., Zeller, P. et al.

Droplet-based transcriptome profiling of individual synapses

Niu, M., Cao, W., Wang, Y. et al.

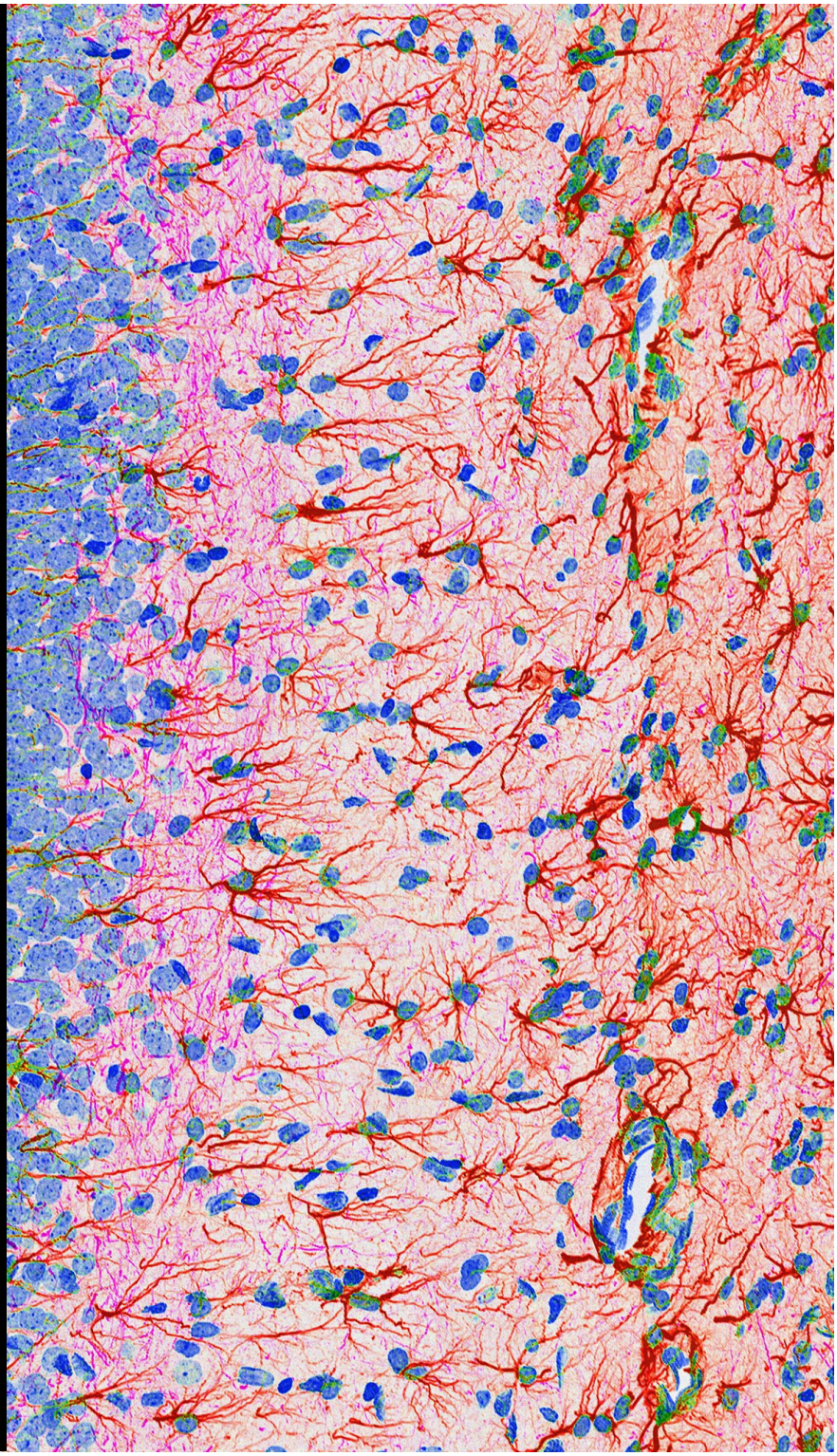
Clustering of single-cell multi-omics data with a multimodal deep learning method

Lin, X., Tian, T., Wei, Z. et al.

Multiomic single-cell lineage tracing to dissect fate-specific gene regulatory programs

Jindal, K., Adil, MT., Yamaguchi, N. et al.

COVER IMAGE
Author: Thomas J. Deerinck, University of California, San Diego
Title: Stained rat brain section (2003)



UNIVERSITY OF COPENHAGEN

UPCOMING EVENT

3rd Danish Single Cell Meeting:
Biotechnology and Application to Biology

https://singlecell.ku.dk/3rd-danish-single-cell-meeting-biotechnology-and-application-to-biology/

Time and place: April 26th-27th 2023; Natural History Museum of Denmark, Øster Voldgade 5-7, 1350 Copenhagen (dinner & postersession at Mærsk Tower, Blegdamsvej 3B, 2200 København)

Deadline for registration: 26stMarch

---

scChIX-seq infers dynamic relationships between histone modifications in single cells

Yeung, J., Florescu, M., Zeller, P. *et al. Nature Biotechnology* (2023), https://doi.org/10.1038/s41587-022-01560-3

The authors of this study designed **scChIX-seq,** a novel **experimental and computational framework to map multiple histone modifications in single cells**. It multiplexes two histone marks in a single cell, then uses computational methods to deconvolve the signal and identify the distinct histone marks. The framework **learns the cell-type-specific correlation structure between histone marks**, so it does not require prior assumptions about their genomic distributions. The method **uses an MNase-based approach (sortChIC)**, but the computational framework **can be applied to Tn5-based strategies as well**. The method is flexible in the histone modifications that can be used and can reveal biological insights by multimodal analysis of histone marks in single cells. To test the accuracy of scChIX-seq, the authors used purified cell types and whole bone marrow and found that the method could accurately map multiple histone marks. However, the maximum number of cuts at a specific base pair location is limited by the copy number in the cell and there may be limitations with the current binning strategy and multinomial model. Nevertheless, scChIX-seq offers an exciting new tool for multimodal analysis of chromatin profiling in single cells, providing a powerful way to analyze the interplay between different histone modifications in a way that would otherwise be impossible.

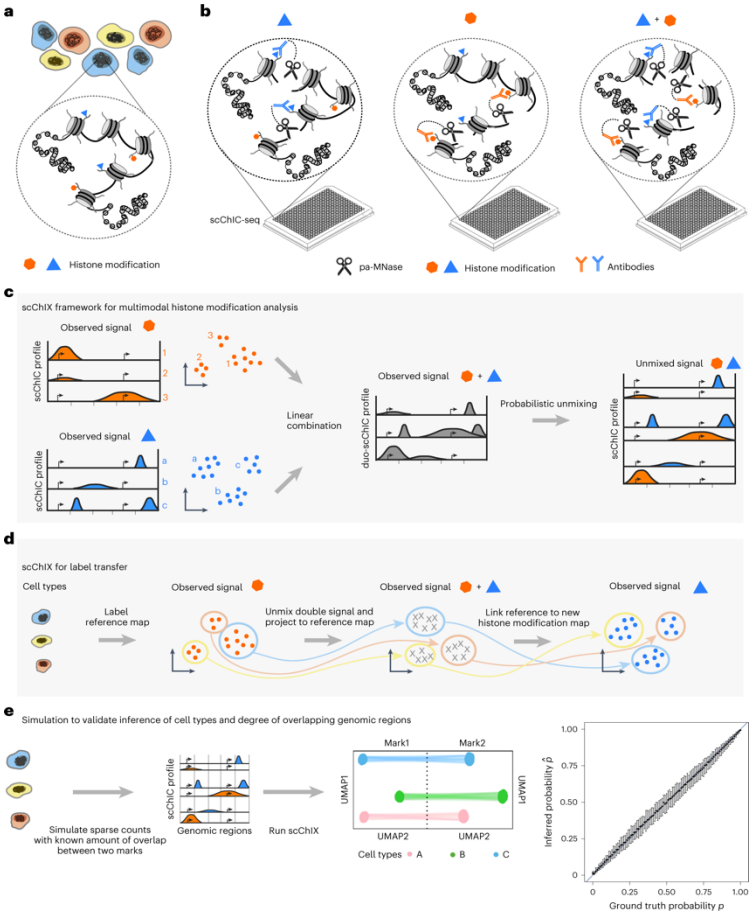


Figure 1. Overview of the scChIX-seq method.

Droplet-based transcriptome profiling of individual synapses

Niu, M., Cao, W., Wang, Y. *et al.* *Nature Biotechnology* (2023), https://doi.org/10.1038/s41587-022-01635-1

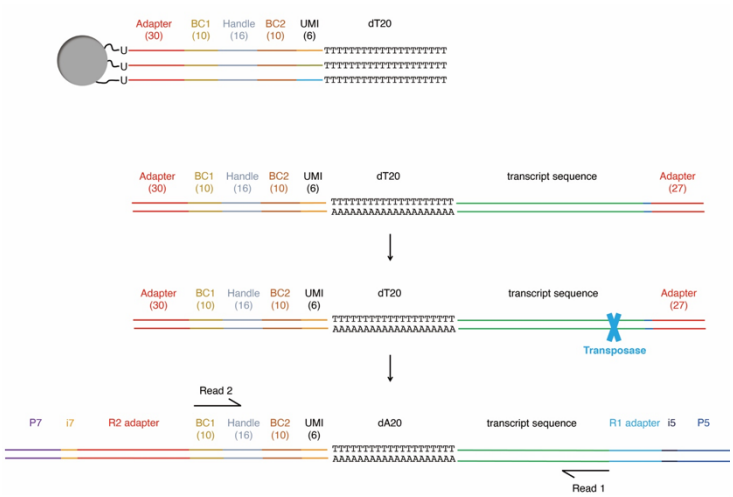


Figure 2. MATQ-Drop library preparation and sequencing strategy.

The first study focuses on the development of a new high-throughput method for profiling the molecular heterogeneity among individual synapses which play a crucial role in mediating signal transmission. Despite their importance, a comprehensive understanding of synapses is limited by the lack of methods to profile the molecular heterogeneity of individual synapses at scale. To address this issue, the authors introduce a new platform called "Multiple-Annealing-and-Tailing-based Quantitative single-cell RNA sequencing in Droplets" **(MATQ-Drop) for transcriptome profiling of individual synaptosomes**. The platform was used to profile both mouse and human brain samples and was successful in detecting subclusters among synaptosomes that are linked to different neuronal subtypes. The authors also show that their platform can be used to profile synaptopathy, or changes in the molecular makeup of synapses, in an Alzheimer's disease mouse model. The results of this study demonstrate that **MATQ-Drop is a high-throughput, single-synaptosome transcriptome profiling tool** that has the potential to greatly advance our understanding of the molecular heterogeneity of individual synapses. The authors believe that this new platform will play a key role in future discoveries in the field of neuroscience.

Clustering of single-cell multi-omics data with a multimodal deep learning method

Lin, X., Tian, T., Wei, Z. *et al.* *Nature Communications* (2022), https://doi.org/10.1038/s41467-022-35031-9

Researchers have developed a novel method called **scMDC** to overcome the challenge of **combining different data sources for clustering of single-cell multi-omics data**. scMDC is a **deep learning method that jointly models mRNA and ADT/ATAC data** by using a multimodal autoencoder, deep K-means clustering, and a KL-loss. The result is an end-to-end model that explicitly characterizes different data sources and jointly learns latent features for clustering analysis. Simulation and real-data experiments have shown that **scMDC outperforms existing single-cell methods on different multi-omics datasets**. Its linear scalability makes it a promising solution for analyzing large multi-omics datasets. The clustering results from scMDC are essential for downstream analyses such as differential expression and gene set enrichment analysis, enabling researchers to profile cell types at a functional level. All in all, scMDC is a powerful and efficient tool for single-cell multi-omics data analysis, offering a new level of insight into cellular diversity and function.

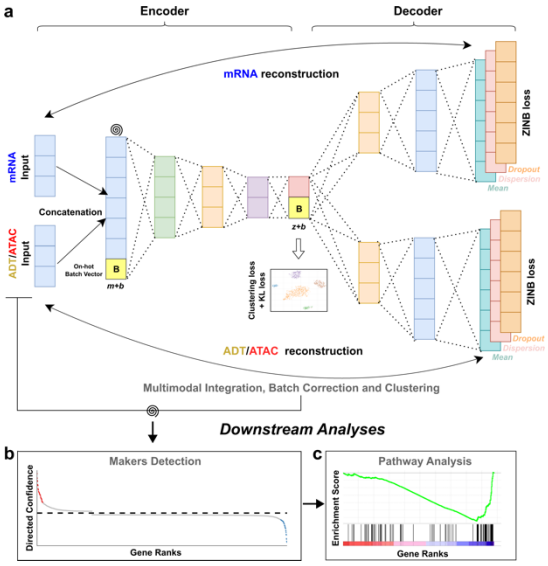


Figure 3. The architecture of scMDC.

Multiomic single-cell lineage tracing to dissect fate-specific gene regulatory programs

Jindal, K., Adil, MT., Yamaguchi, N. *et al. bioRxiv* (2022), https://doi.org/10.1101/2022.10.23.512790

The researchers have developed **CellTag-multi**, a method for **single-cell lineage tracing across transcriptome (RNA) and epigenome (chromatin accessibility) assays**. They applied CellTag-multi to two biological systems: hematopoiesis (formation of blood cells) and induced endodermal progenitor (iEP) reprogramming (conversion of one cell type to another). In hematopoiesis, the researchers showed that considering both RNA and epigenome state improved the predictability of cell fate compared to using either modality alone. In iEP reprogramming, they found that the early stages of fate conversion were dominated by changes in distal regulatory regions of the epigenome and that Foxd2 promotes successful reprogramming while Zfp281 leads to an "off-target" reprogrammed state. The researchers also demonstrated that inhibiting TGF-beta signaling enhances on-target reprogramming while blocking downstream TGF-beta signaling might prohibit entry onto the off-target trajectory. The results suggest that **single-cell lineage tracing provides rich information on gene regulation** and offers unique **insights into the specification and maintenance of cell identity.**

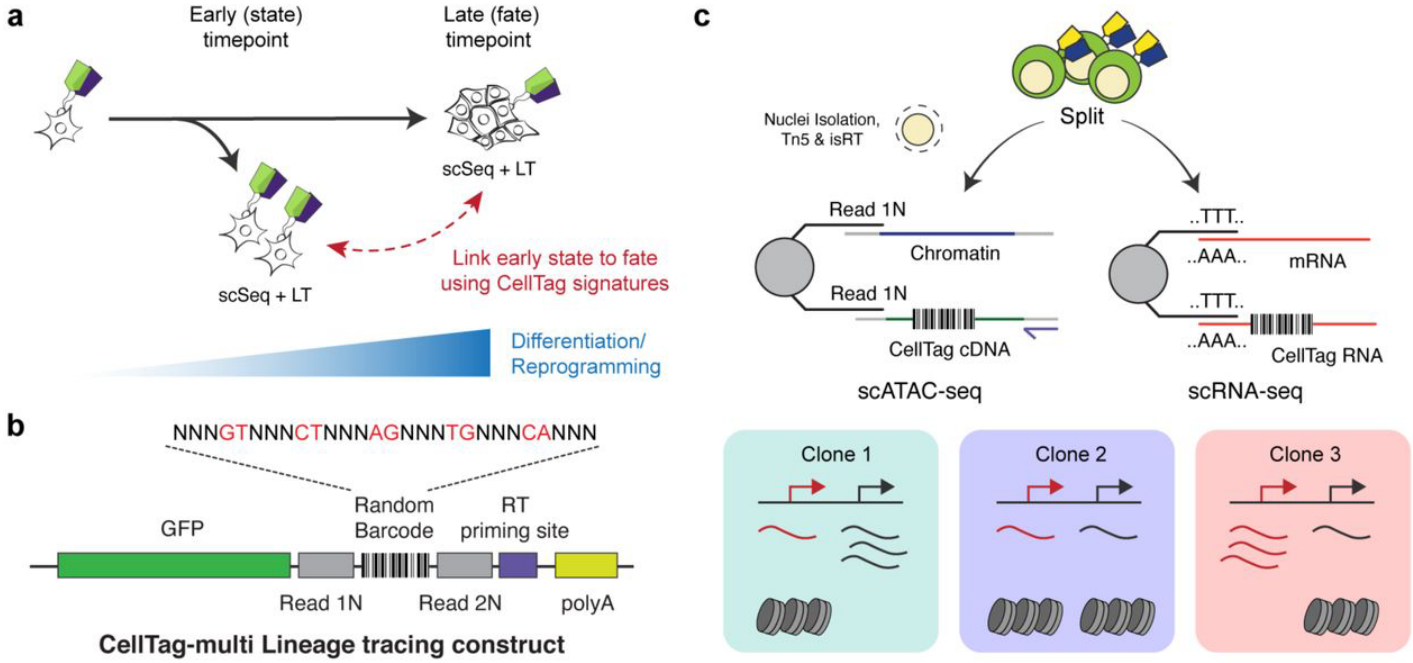


Figure 4. Overview of the CellTag-multi method.

New papers from Danish researchers:

Coassolo, L. *et al.* (2023) "Mapping transcriptional heterogeneity and metabolic networks in fatty livers at single-cell resolution", iScience, 26(1). https://doi.org/10.1016/j.isci.2022.105802.

Kim, J. *et al.* (2023) "Neighbor-specific gene expression revealed from physically interacting cells during mouse embryonic development", Proceedings of the National Academy of Sciences, 120(2). https://doi.org/10.1073/pnas.2205371120.

Next Single Cell Seminar

Time and place: 24th February 2023, Panum Faculty Club, room 16.6.16 and Zoom (Link)

9:00 – 10:00

PhD student Frederik Nørby Friis Sørensen, Khodosevich lab

Network analysis of epileptic TSC2 pediatric patients

10:00 – 11:00

Postdoc Mette Q. Ludwig, Pers lab

Transcriptional states underlying cagrilintide signaling in the dorsal vagal complex

---

If you would like to announce anything single cell related, e.g. job announcement, event, your published paper, technology development etc., please contact us.

Contact: katarina.dragicevic@bric.ku.dk