DANISH SINGLE-CELL NETWORK NEWSLETTER

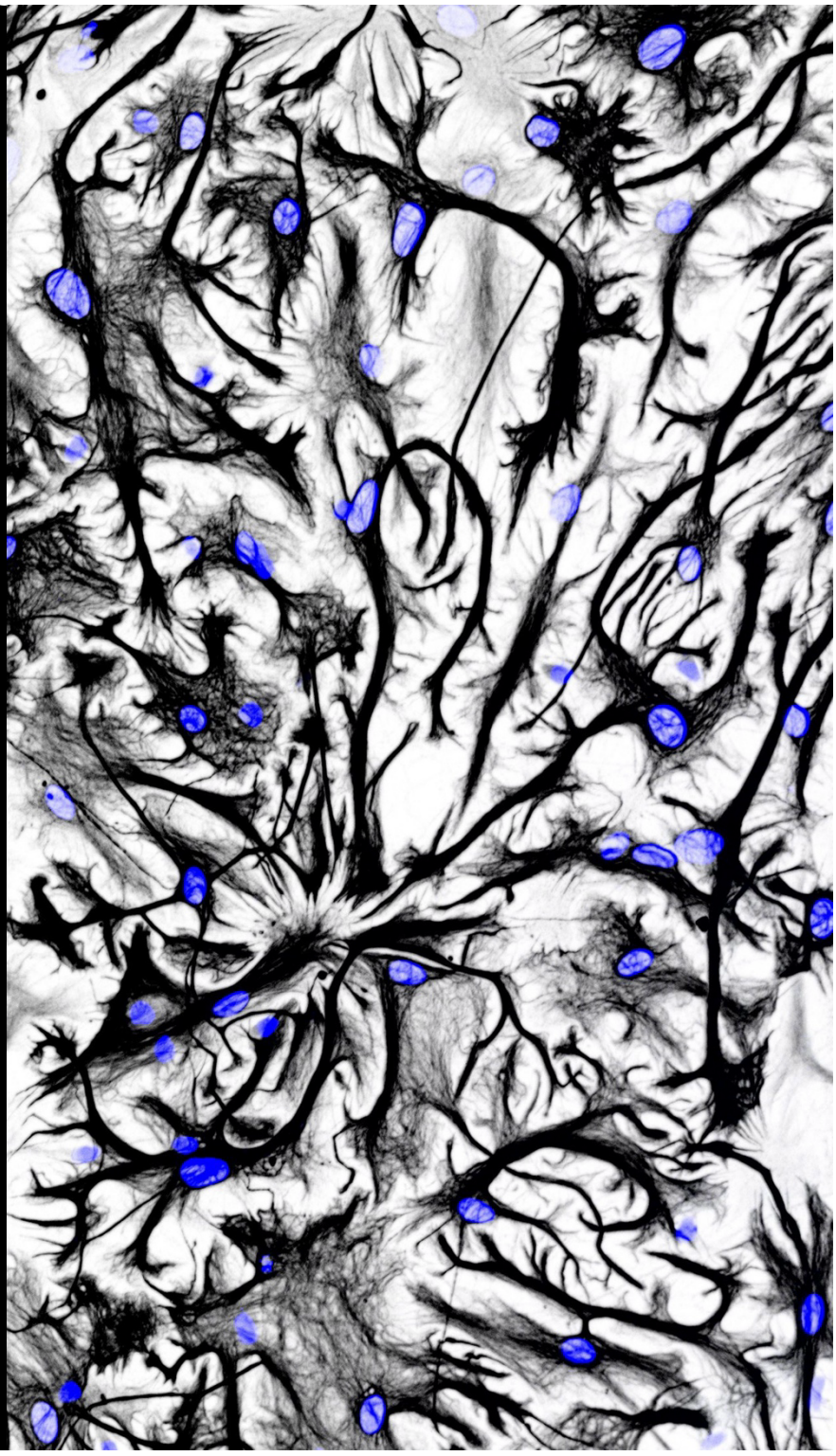
NOVEMBER - 2023

THIS MONTH'S HIGHLIGHTS:

Robust mapping of spatiotemporal trajectories and cell–cell interactions in healthy and diseased tissues
Pham, D., Tan, X., Balderson, B. et al.

Transcriptomic diversity of cell types across the adult human brain
Siletti, K., Hodge, R., Mossi Albiach, A.

INVADEseq to identify cell-adherent or invasive bacteria and the associated host transcriptome at single-cell-level resolution
Galeano Niño, J.L., Wu, H., LaCourse, K.D.



COVER IMAGE
Author: Bas van Bommel
Freie Universität Berlin, Department of Biochemistry
Berlin, Germany
Title: Rat astrocytes, confocal (2023)

UNIVERSITY OF COPENHAGEN

Robust mapping of spatiotemporal trajectories and cell–cell interactions in healthy and diseased tissues

Pham, D., Tan, X., Balderson, B. *et al. Nature Communications* (2023), https://doi.org/10.1038/s41467-023-43120-6

In their research, the team developed three specialized algorithms within stLearn to enhance the processing of spatial transcriptomics (ST) data. These algorithms address crucial challenges, including the identification of dynamic biological trajectories within tissue sections, robust detection of cell–cell communication, and the management of data sparsity. The stLearn toolkit, known for its versatility, is applicable across various biological settings and remains effective even with only spatial location and gene expression information. Notably, their PSTS algorithm advances trajectory inference, surpassing existing pseudotime methods and providing a comprehensive overview of dynamic processes across anatomically defined regions.

Their SCTP analysis, designed to reduce false-positive detection rates in the study of cell–cell interactions, utilizes spatial constraints and incorporates distribution, gene expression, and knowledge of ligand–receptor interactions. Additionally, stLearn includes stSME, an algorithm that improves the quality of noisy or incomplete spatial sequencing data by integrating morphological similarities, physical distance, and gene expression similarities. Despite its utility, the toolkit operates in 2D space, presenting limitations that require future advancements for a more complete understanding of spatial transcriptomics.

In summary, the algorithms developed by the team have undergone rigorous testing and validation, positioning stLearn as a valuable platform for spatial and imaging data analysis. The team is committed to maintaining and developing the software to ensure its continued utility in the ever-expanding landscape of ST datasets.

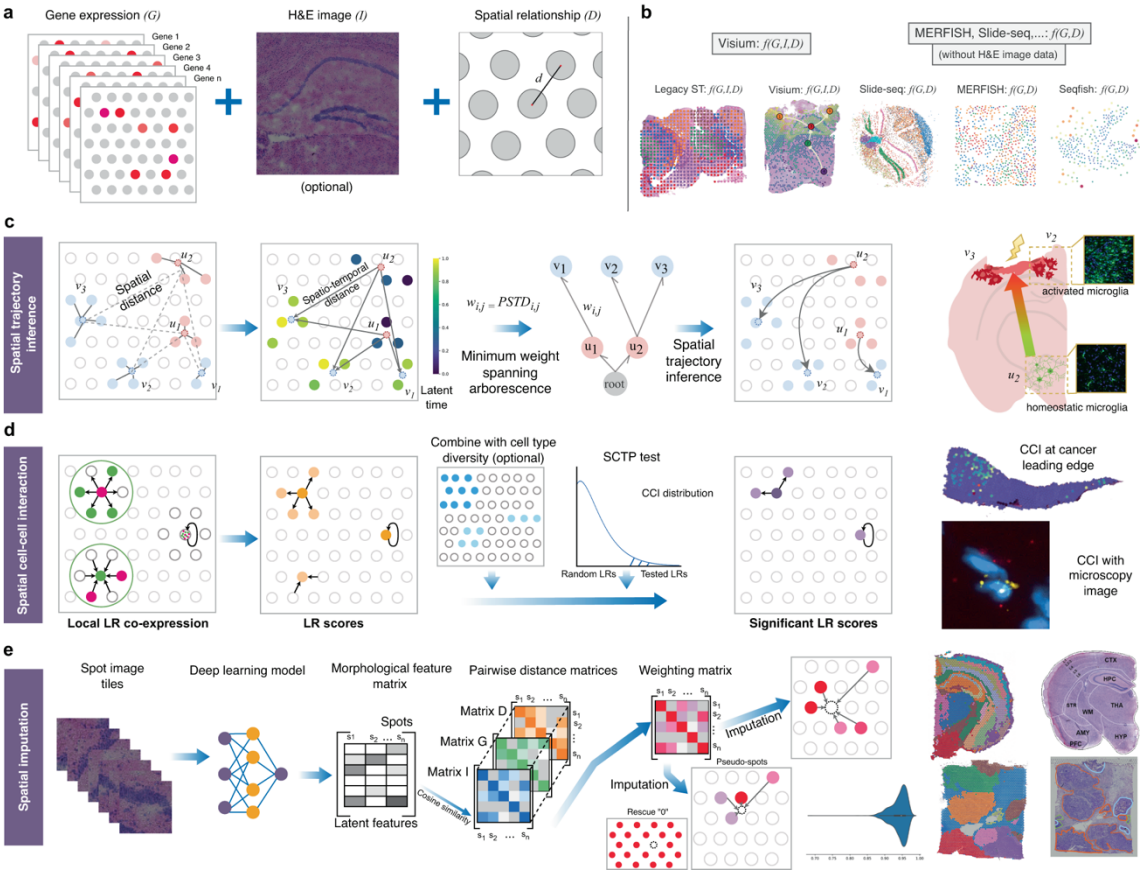


Figure 1. Overview of stLearn

Transcriptomic diversity of cell types across the adult human brain

Siletti, K., Hodge, R., Mossi Albiach, A. *et al.* *Science Advances* (2023), https://doi.org/10.1126/science.add7046

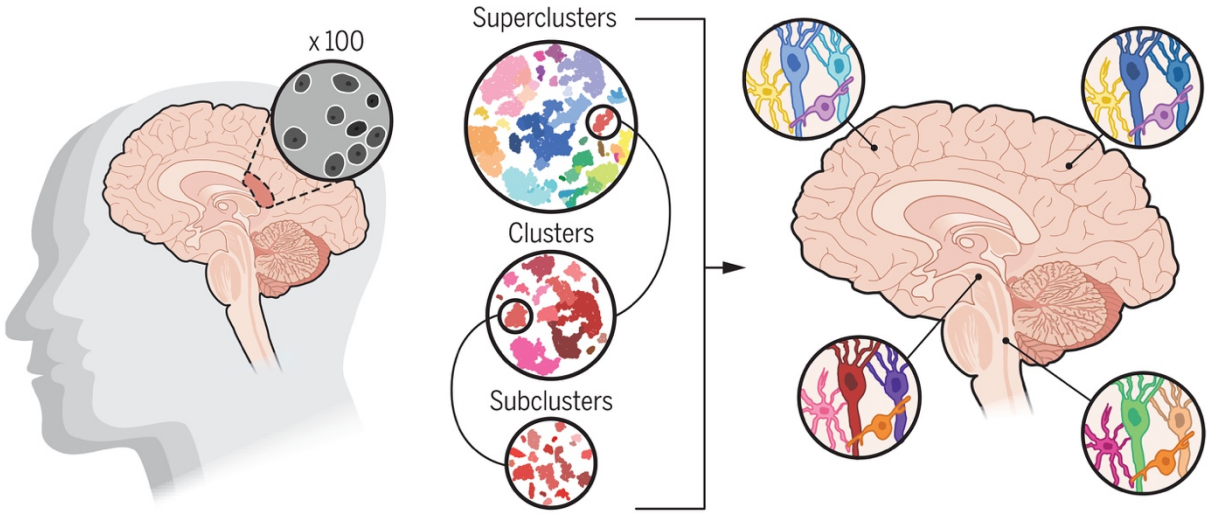


Figure 2. Cellular diversity in the human brain

In this study, the authors aim to provide an overview of transcriptomic diversity across the human brain through single-nucleus RNA sequencing. The research acknowledges the challenges associated with profiling human tissue, emphasizing difficulties in distinguishing and replicating dissections across donors. While the dataset surpasses three million cells, the authors caution against definitive mapping of cell types to precise anatomical locations due to dissection complexities.

The study sheds light on regional and developmental variations across the brain, revealing a significant gap in understanding neuronal diversity outside the telencephalon. Notably, splatter neurons exhibit unexpected molecular complexity, expressing neuropeptides, neurotransmitters, and other genes in intricate patterns. The findings underscore the necessity of profiling individual brain nuclei for a complete understanding of cellular diversity.

The study highlights how regional and developmental origins strongly shape adult transcriptomic types. For example, astrocytes display region-specific types with specialized functions, while certain superclusters represent migratory cell types appearing in multiple dissections. The authors stress the importance of a thorough understanding of region-specific cellular diversity for disease treatment. For instance, the unique composition of the telencephalon's oligodendrocytes and the midbrain's dopaminergic lineages may have relevance for diseases like multiple sclerosis and Parkinson's.

In conclusion, this work establishes a critical foundation for exploring the brain's diverse neural circuitry and its implications for human health. Despite the dataset's limitations, the study provides valuable insights into regional variations, developmental influences, and the molecular complexity of specific neuronal populations, urging future research to delve into the epigenomic and functional properties of distinct transcriptomic states.

INVADEseq to identify cell-adherent or invasive bacteria and the associated host transcriptome at single-cell-level resolution

Galeano Niño, J.L., Wu, H., LaCourse, K.D. *et al. Nature Protocols* (2023), https://doi.org/10.1038/s41596-023-00888-7

Researchers introduced INVADEseq, a novel approach that allows for the identification and analysis of cell-associated bacteria and the host transcriptome at the single-cell level. Traditional scRNAseq techniques primarily focus on the gene expression of eukaryotic cells, as they rely on poly(A) selection of RNA. However, this approach limits the ability to capture the microbial component of the tumor microenvironment, as bacterial RNA lacks a poly(A) tail.

To overcome this limitation, the INVADEseq method modifies the 10x Genomics 5' scRNAseq protocol by introducing a primer that targets a conserved region of the bacterial 16S ribosomal RNA gene. This "add-on" approach enables the generation of eukaryotic and bacterial DNA libraries at the single-cell level, allowing for the identification of single cells with intracellular bacteria. The method has been successfully applied to human cancer cell lines and patient tumor specimens, detecting the proportion of human cells that harbor bacteria, identifying the identities of human cells and intracellular bacteria, and uncovering host transcriptional programs that are modulated based on associated bacteria. The method has been validated to detect cell-associated bacteria and has shown increased sensitivity with higher infection rates. However, the exact level of sensitivity is challenging to assess due to variability in cell adhesion and invasion dynamics.

The INVADEseq approach has broad applications and can be used to identify and profile host-bacterial interactions in various mammalian fluids or tissue specimens. It can enhance our understanding of host-bacterial interactions in different clinical contexts, such as cancer types known to harbor intratumoral bacteria or human diseases like inflammatory bowel disease or cystic fibrosis. The method can also be adapted to detect other microorganisms, such as fungi, by introducing primers targeting conserved regions of their RNA. It provides a valuable tool for studying cell-associated bacteria and their impact on the host transcriptome at the single-cell level. It overcomes the limitations of standard scRNAseq approaches in capturing the microbial component of the tumor microenvironment and has broad applications in various research areas.

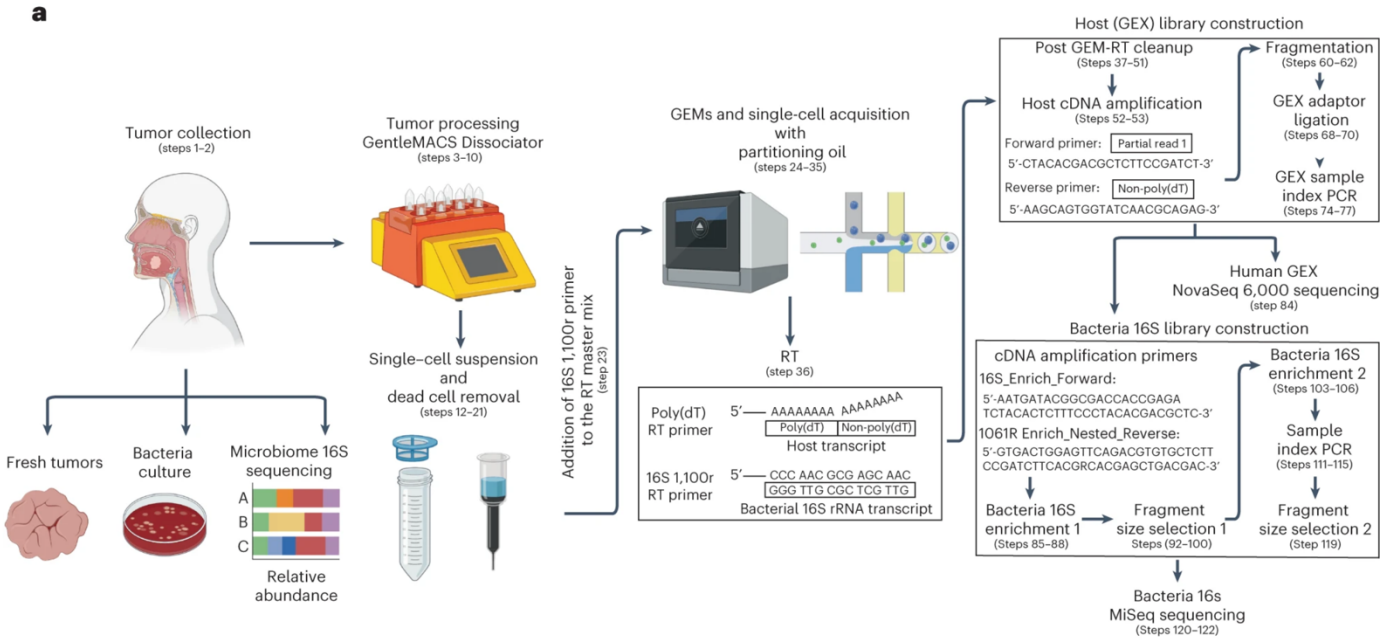


Figure 3. INVADEseq protocol.

Next Single Cell Seminar

Time and place:15th December 2023, Maersk Tower top floor, 7.15.92

9:00 – 9:45

Carmelo Bellardita, Department of Neuroscience, UCPH

Microphagens reside in the muscle spindle to control sensorimotor function at millisecond timescale

9:45 – 10:30

Xian Xin, Khodosevich lab, BRIC, UCPH

Unraveling Epileptogenesis Mechanisms via scRNA-seq from Scn2ap.A263V Mouse Model

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

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