Leveraging 3D Genome and Methylation Signatures to Develop a Comprehensive Cell Atlas

The BRAIN Initiative Cell Census Network (BICCN)

The Brain Research Through Advancing Innovative Neurotechnologies Initiative, commonly known as the BRAIN Initiative, represents a monumental research endeavor overseen by the National Institute of Health. This collaborative project aims to decode the mysteries of the brain, ranging from individual cells and synapses to comprehensive brain circuits and functions.

In this case study, we discuss how the BRAIN initiative leveraged Arima technology to develop a comprehensive 3D multi-omic atlas of the mouse brain. This study leverages the mouse as a model due to its significant translational utility and complex, yet analogous, brain structure to humans.

Challenge: Building a Multi-Dimensional Atlas of the Brain

The primary challenge addressed by the BRAIN Initiative is the intricate complexity of the brain's cellular architecture. Understanding the brain requires not just mapping its physical structure but also decoding the molecular and genetic interactions within individual cells and across cell networks. Traditional research methods fall short in capturing the dynamic and multi-dimensional nature of these interactions.

Technology

Arima Single Cell Methyl-3C technology enables simultaneous capture of methylation and conformation signatures which can help illuminate the mechanisms that drive gene expression for a given cell-type.

Approach: Integration of Single Cell RNA and ATAC data with novel Single Cell Methylation and Conformation Data

At the heart of the BRAIN Initiative's success is the integration of advanced technologies to map the brain's cellular architecture. These technologies include:

Single Cell Methylation and Conformation: This approach focuses on uncovering the epigenetic landscape and the three-dimensional organization of the genome within individual cells. By employing technologies such as single cell methyl-3C sequencing (sc-m3C-seq), researchers can examine how DNA methylation patterns and the physical arrangement of chromatin contribute to gene regulation and cellular identity at a highly granular level.

Single Cell RNA and ATAC: Single Cell RNA sequencing (scRNA-seq) provides a detailed view of gene expression patterns in individual cells, highlighting the active genes that contribute to cellular functions. ATAC sequencing (ATAC-seq), on the other hand, offers insights into chromatin accessibility, identifying regions of the genome that are open and potentially active in regulating gene expression.

Integration of Technologies: By combining the detailed insights obtained from Single Cell Methylation, Conformation, RNA, and ATAC technologies, researchers can construct comprehensive spatial maps that illustrate not only gene expression profiles and chromatin accessibility but also the epigenetic states and 3D genome architecture of cells within the brain. This integrated approach allows for a multifaceted understanding of how various molecular and genetic factors interact within complex cellular networks, providing a holistic view of brain function and organization.

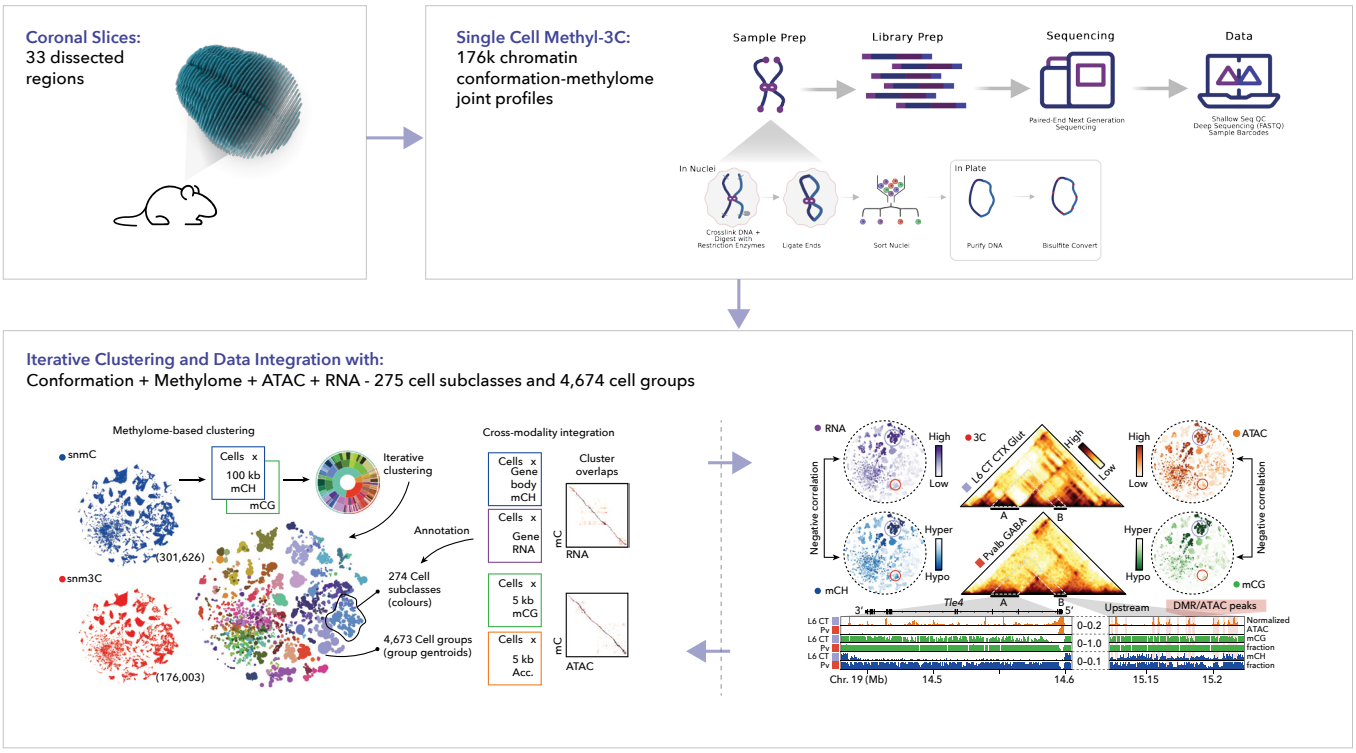

Figure 1. Building a 3D Multi-Omic Map of the Adult Mouse Brain

Building a 3D Multi-Omic Map of the Adult Mouse Brain

Single Cell Methyl-3C sequencing technology delivers intricate insights into the gene-regulatory elements and chromatin conformations that dictate cellular identity and function. By mapping these elements and conformations, sc-m3C-seq aids in constructing a detailed atlas of the brain's cellular hierarchy and epigenetic landscape. Insights gained by Liu, et al. include the following:

Epigenetic Heterogeneity and Regulatory Candidates: Intragenic epigenetic variability suggests top candidates for exploring causal regulatory relationships.

Chromatin Compartment Switches: Active and silent chromatin compartment switches link to gene modulation and DNA methylation changes.

High-Resolution Chromatin Profiles: Chromatin conformation diversity reveals complex gene interactions and candidate loci for gene regulation studies.

These insights significantly benefit researchers by offering a deep understanding of cellular mechanisms, revealing potential novel gene regulatory networks, and providing a guide for studying the intricate relationship between genetics and epigenetics in brain development and function.

Impact: A Comprehensive Atlas of the Adult Mouse for Brain

Through the utilization of sc-m3C-seq, the BRAIN Initiative has achieved a significant milestone in creating a comprehensive cell-specific atlas of the mouse brain. This atlas encompasses over 301,626 methylomes and 176,003 chromatin conformation-methylome profiles, illustrating the vast molecular and genetic diversity across different brain regions and cell types. Iterative clustering of these datasets resulted in 4,673 cell groups and 274 subclass labels. With these datasets, researchers were able to:

Construct Comprehensive Gene Regulatory Networks: Novel relationships between transcription factors, target genes, and differentially methylated regions highlight regulatory dynamics.

Map Transcription Factor Influence: Identified key transcription factors and cell-type specific regulatory patterns that impact gene expression.

Unveil Neural Function: Leveraging molecular, transcriptomic, and epigenomic diversity for new neural function insights.

Researchers in this study provide an unprecedented depth of understanding into the mouse brain's cellular composition, enabling the discovery of new gene regulatory mechanisms, the identification of critical transcription factors, and insights into neural functions, thereby setting a new foundation for neuroscience research.

Translational Utility and Next Steps

These insights are instrumental in understanding the molecular underpinnings of neurological disorders. By identifying cell-type-specific regulatory elements and methylation patterns, researchers can pinpoint the aberrant neural circuits and cell types implicated in diseases, thereby opening new avenues for targeted therapeutic interventions. For example, these methods have been employed to begin classification of human Alzheimer brain and fibroblast samples to characterize differences between healthy and disease samples.

Conclusion

The BRAIN Initiative has revolutionized our understanding of the brain's complex cellular architecture through the integration of cutting-edge technologies. Single cell methyl-3C sequencing, in particular, has provided invaluable insights into the epigenetic and 3D genomic underpinnings of cellular identity and function. As researchers continue to leverage these technologies, the path towards deciphering the mysteries of brain function and dysfunction becomes increasingly clear, paving the way for innovative treatments and therapies.

References

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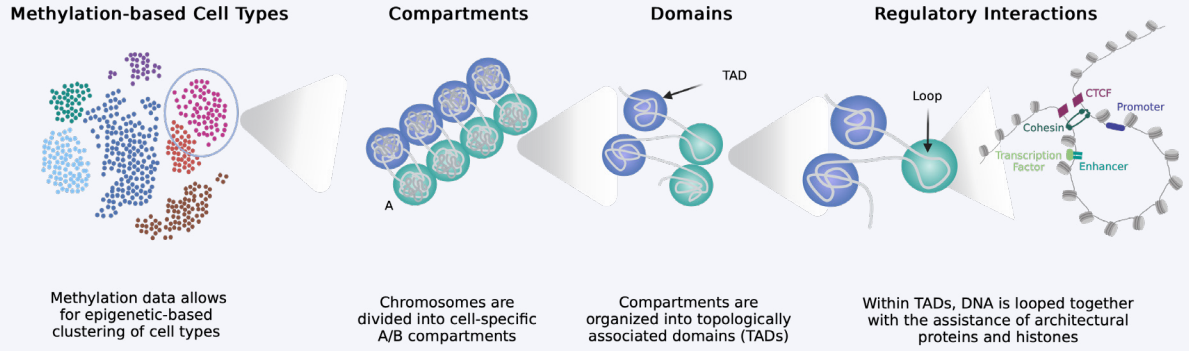
Arima Single Cell Methyl-3C Services

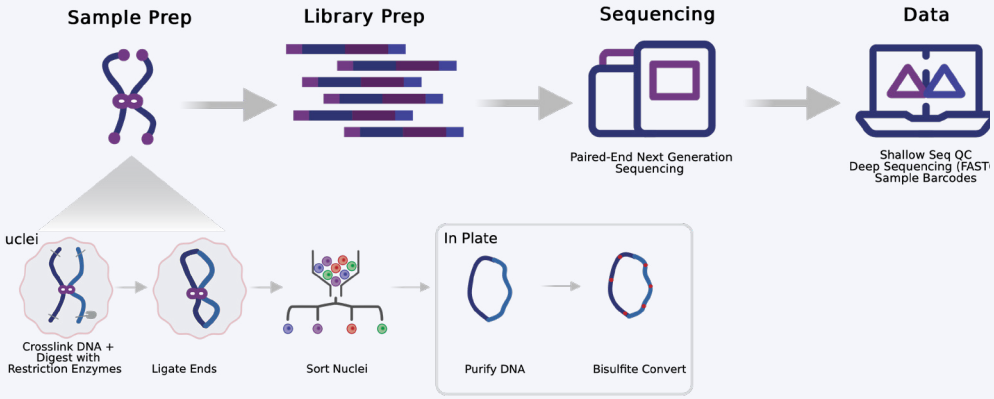
Generate Multi-Omic Methylation + 3D Conformation Data

Single cell methyl-3C sequencing (sc-m3C-seq) represents a pioneering advancement in profiling 3D genome structures and DNA methylation patterns at the resolution of individual cell types. This technology merges the principles of 3C/Hi-C techniques with bisulfite sequencing, offering unprecedented insights into the chromatin interactions and methylation status within complex tissues like the brain.



Arima Single Cell Methyl-3C Workflow

Arima Genomics offers Single Cell Methyl-3C services, providing end-to-end solutions for researchers aiming to explore the genetic and cellular diversity of the brain through methylation and 3D genome folding signatures. From sample preparation to data analysis, Arima's technology facilitates a deeper understanding of the brain's epigenetic landscape and cellular classifications.



Specifications

Sample Input	Frozen Tissue: 20 – 40 mg Cells: 2 – 4 million cells ~200 cells / cell type classified
Sequencing	2 x 150 PE reads ≥2M reads / cell
Data Output	≥80k Long-Cis 3D contacts / cell %mCG ~ 70-80%

Deliverables	Shallow Sequencing QC Deep Sequencing QC Deep Sequencing FASTQ data Table of Cell Barcode Sequences

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