MELTRON: Detecting large scale chromatin decondensation events from 3D contact maps

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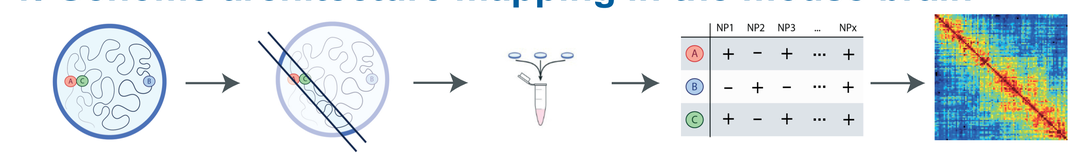
Abstract

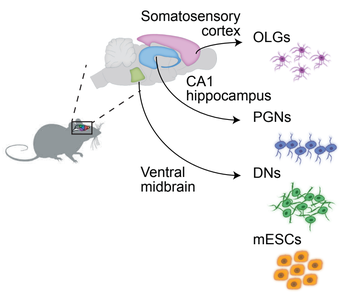
Determining how **chromosomes** are positioned and **folded** within the nucleus has greatly enhanced our understanding of gene regulation. Diverse imaging- and sequencing-based technologies have revealed the existence of chromosome territories and compartments, topologically associating domains (TADs) and promoter-enhancer contacts. These **hierarchical** levels of **genome organization** are **cell-type specific** and important for **gene regulation** mechanisms and specialized cell functions. To map 3D chromatin topology in specific murine brain cell types without tissue disruption, we applied Genome Architecture Mapping (**GAM**), a ligation-free technology that maps **genome topology** by **sequencing** the **DNA content** of ultrathin (~220 nm) nuclear **cryosections**.

We developed **MELTRON**, a statistical framework for detection of **chromatin 'melting'** events characterized by a **decrease** in **chromatin contact densities** over genomic regions of interest. We applied MELTRON to **compare** interaction matrices of embryonic stem cells with dopaminergic neurons, pyramidal glutamatergic neurons or oligodendrocytes, and we discover **cell-type specific** sets of **genes** which display extensive chromatin decondensationor '**melting**'. **Microscopy** and **polymer modeling** confirm the spatial expansion, or **decondensation**, of 'melted' genes. Through integration with scRNA-seq and scATAC-seq data, we uncover that **melting genes** tend to be **highly transcribed** and/or have **high chromatin accessibility**. Additionally, we find that many of the genes with particularly high melting scores possess intricate **RNA processing dynamics** and are associated with **neurological disorders**. Thus, understanding how gene melting relates with regulation will become important to understand mechanisms of neurological diseases.

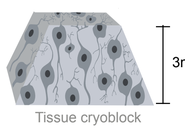
1. Genome architecture mapping in the mouse brain



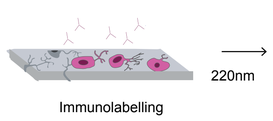
i. Isolation of tissue of interest and cryopreservation



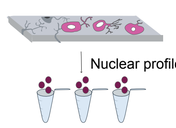
ii. Ultrathin cryosectioning



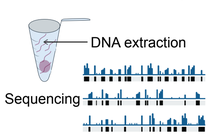
iii. Identification of cell types



iv. Laser microdissection

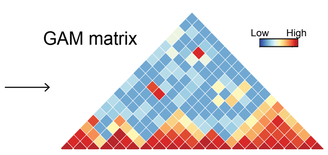


iv. DNA extraction and sequencing



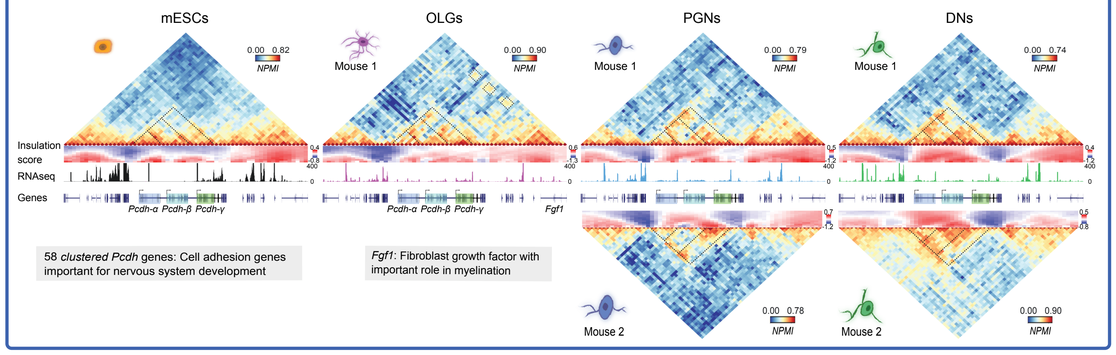
sample	# cells
OLG	870
PGN R1	625
PGN R2	825
DN R1	1755
DN R2	873
mESC	747

v. Data analysis



Integration with:
scRNAseq
Analysis of:
TADs
insulation score
compartments

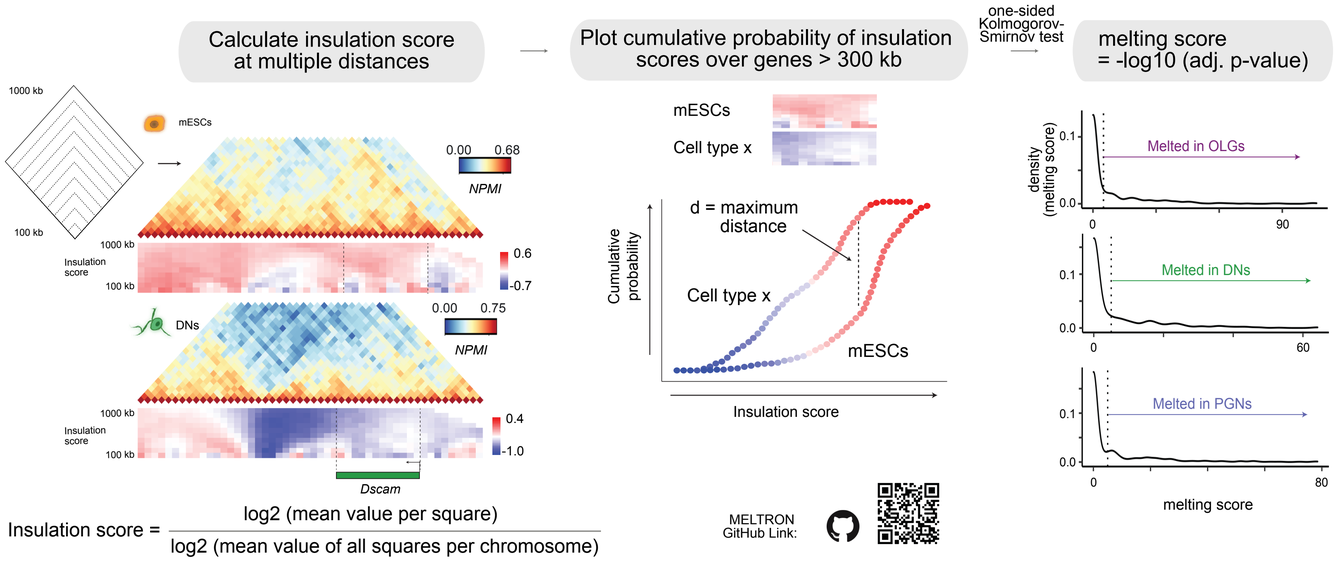
2. GAM captures cell type specific topologies



58 *clustered Pcdh* genes: Cell adhesion genes important for nervous system development

Fgf1: Fibroblast growth factor with important role in myelination

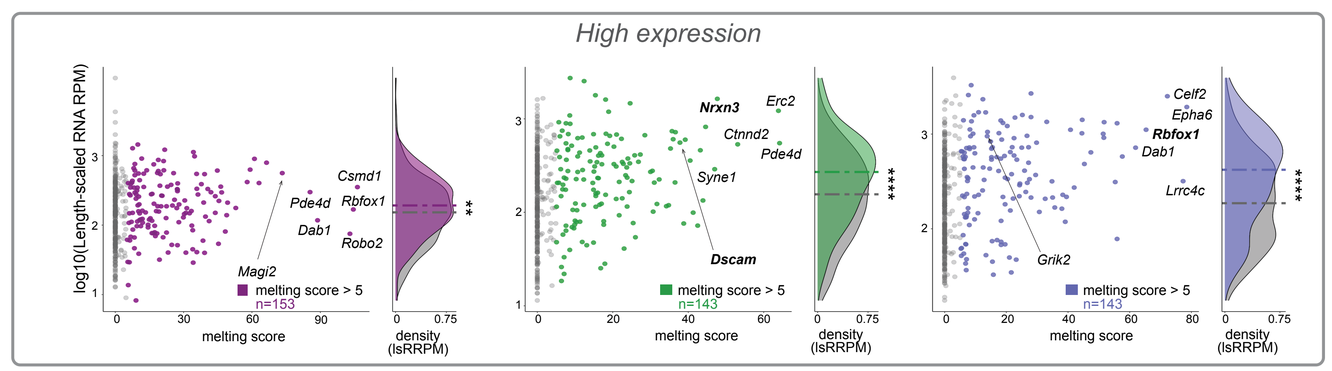
3. MELTRON detects cell-type specific chromatin decondensation



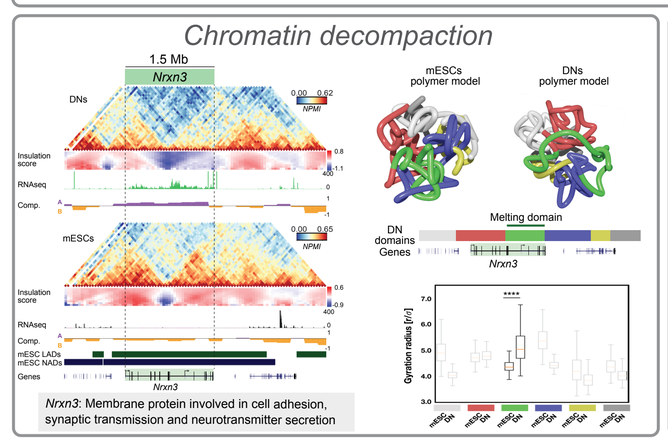
$$\text{Insulation score} = \frac{\log2\ (\text{mean value per square})}{\log2\ (\text{mean value of all squares per chromosome})}$$

MELTRON GitHub Link:

4. Melting is associated with high expression and large-scale 3D chromatin reorganisation in neurons

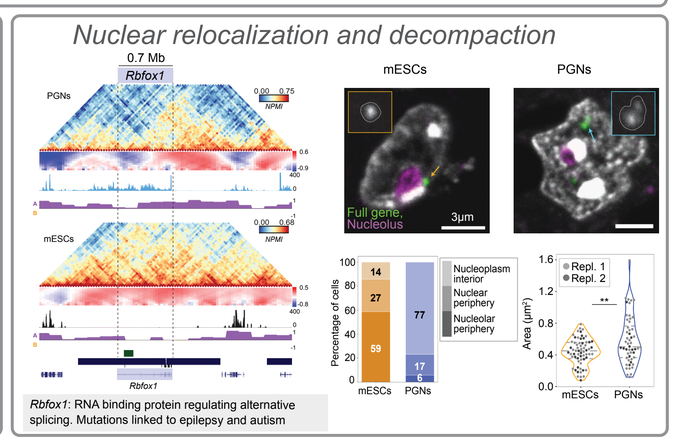


Chromatin decompaction



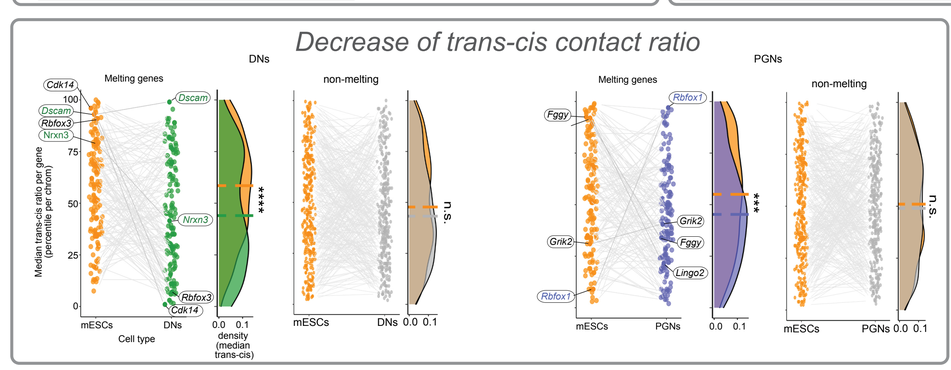
Nrxn3: Membrane protein involved in cell adhesion, synaptic transmission and neurotransmitter secretion

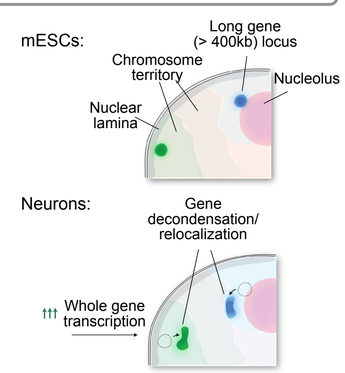
Nuclear relocalization and decompaction



Rbfox1: RNA binding protein regulating alternative splicing. Mutations linked to epilepsy and autism

Decrease of trans-cis contact ratio





Conclusions

Meltron is a statistical framework for detection of differences in contact density at genomic regions of interest
Efficient data structures and multi-core processing allow calculation of melting scores in short time
~150 cell-type specific genes are melted in each of the brain cell-types
Melting genes in brain cells tend to be highly transcribed and spatially decompacted
Melting also occurs in *in-vitro* differentiated dopaminergic neurons where it is also associated with elevated transcription
What effects does melting have on transcription dynamics and genome stability?

References

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SEVENTH FRAMEWORK PROGRAMME
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