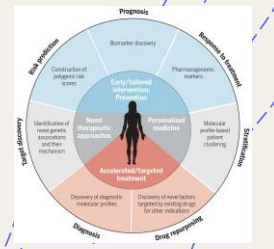
Computational Genomics (in space) Concepts and applications in Translational Research

Christoforos Nikolaou

Computational Genomics Group, BSRC “Alexander Fleming”

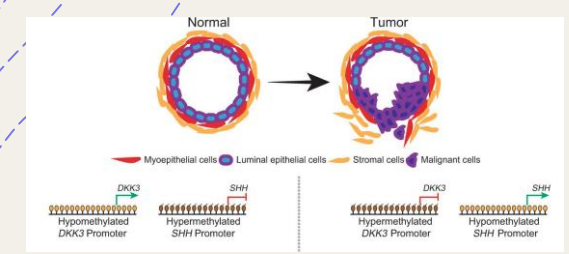
4th Immunology Workshop for clinicians - Heraklion, June 2023

Translational –omics



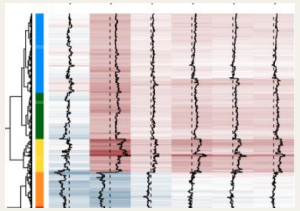
Genomics

Gene Associations, Annotation of Variants of Unknown Significance, Polygenic Risk scores, Pharmacogenomics



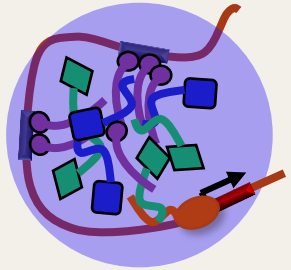
Epigenomics

Cancer Methylation patterns, Epi-drugs that modulate DNA and histone modifications



Transcriptomics

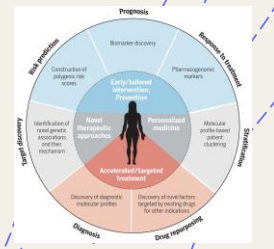
Molecular Signatures, Biomarker discovery, new targets



Genome Structure in 1D and 3D

Novel mechanisms for mis-expression, Discovery of by-stander genes, Regulatory cascades that provide new leads for disease.

Translational –omics



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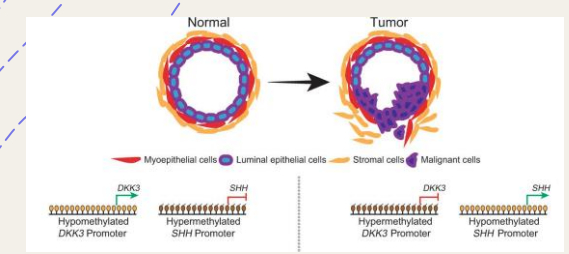

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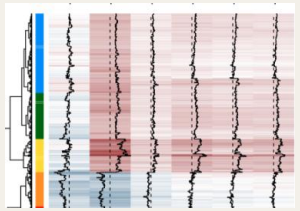

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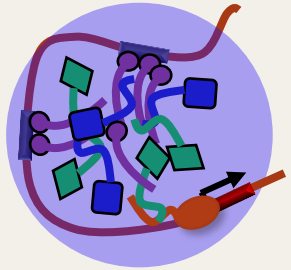

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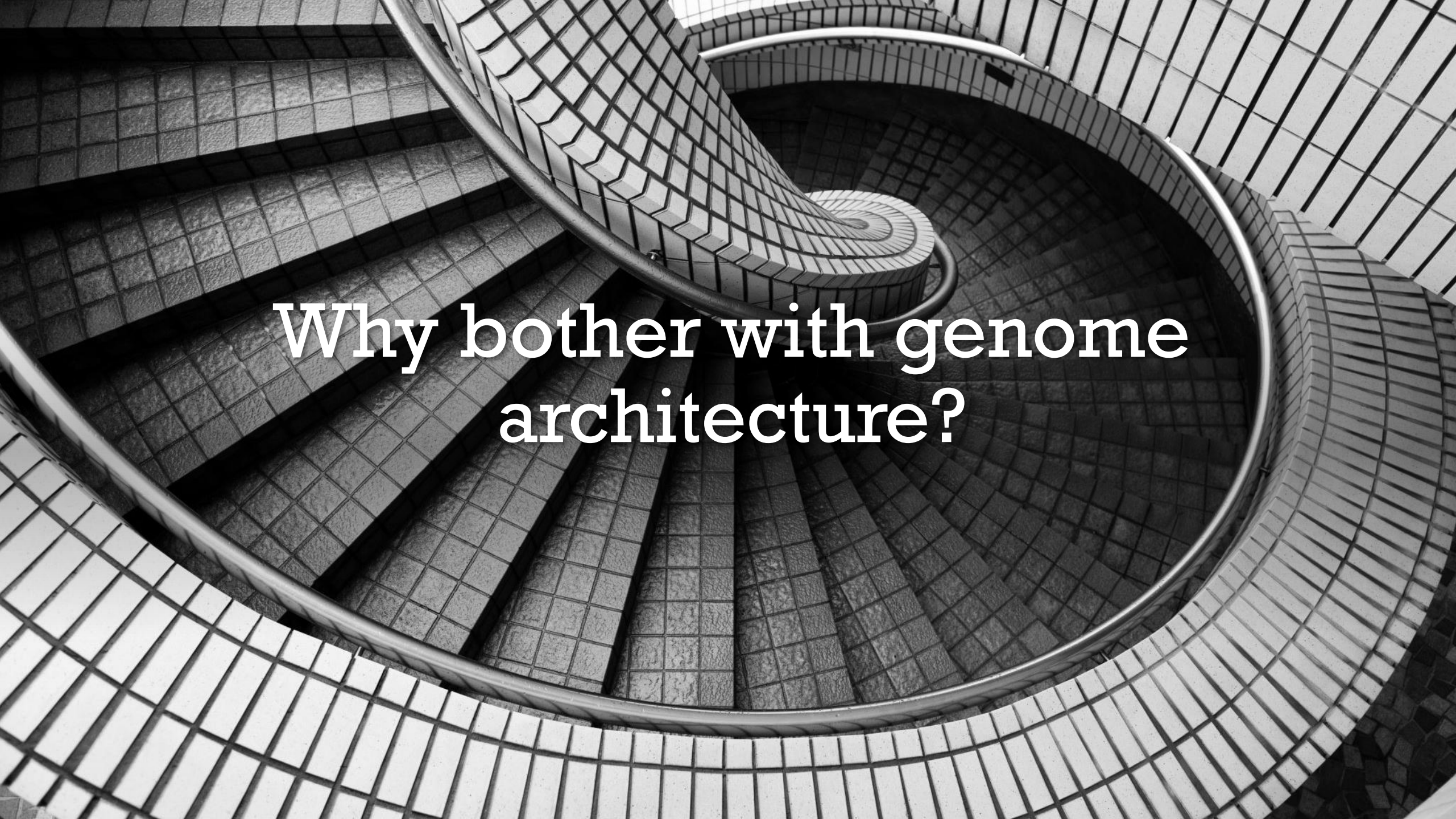
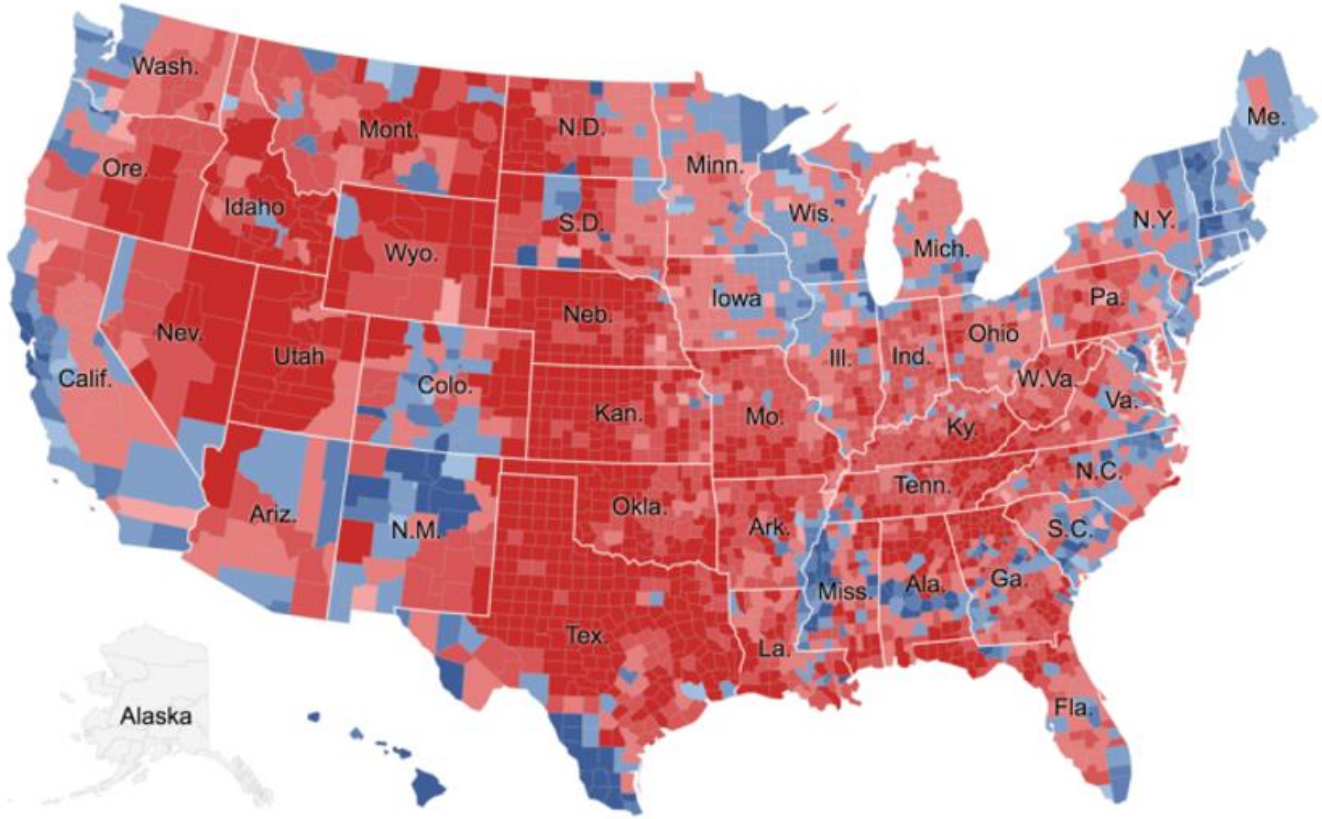
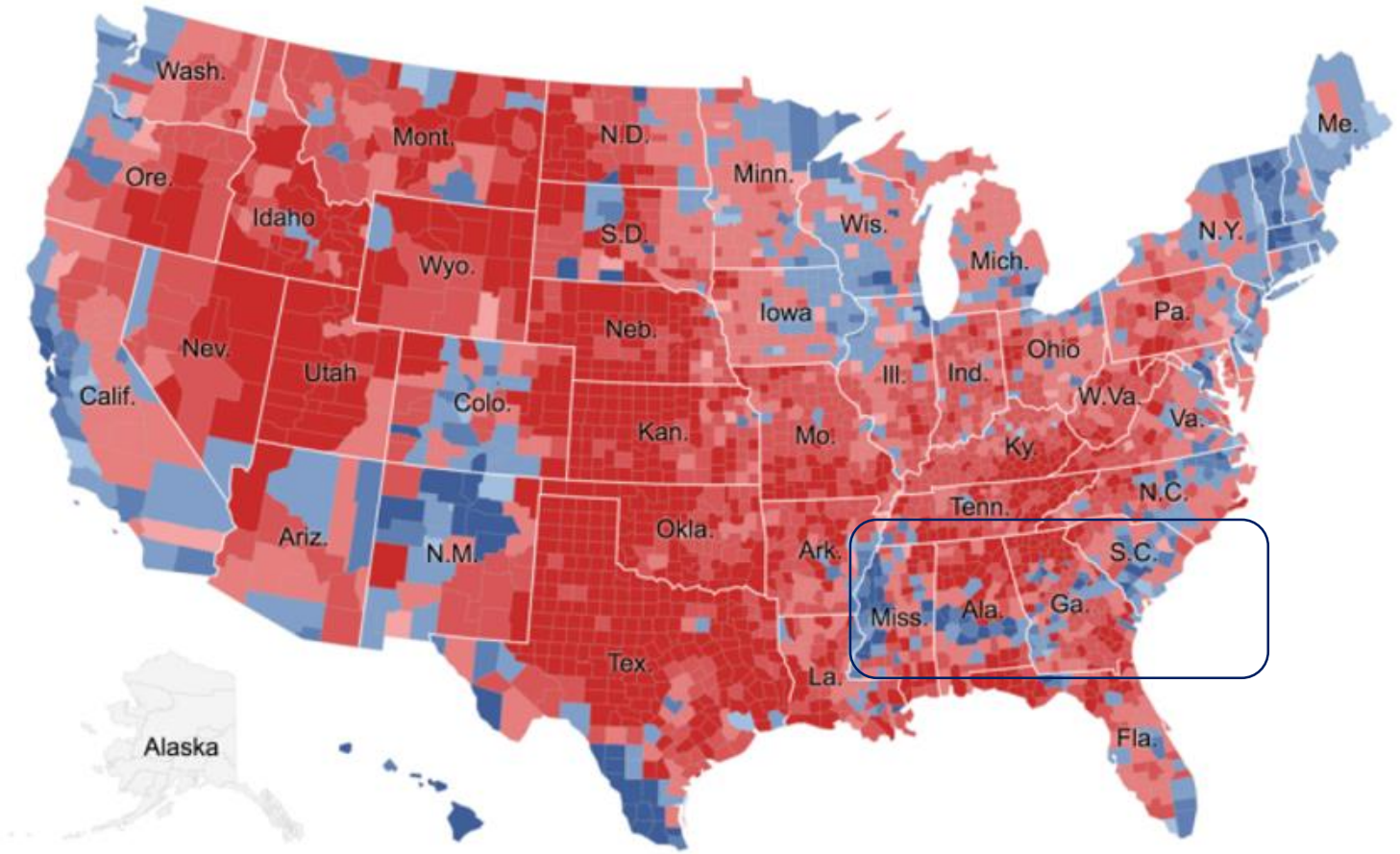

Why bother with genome architecture?

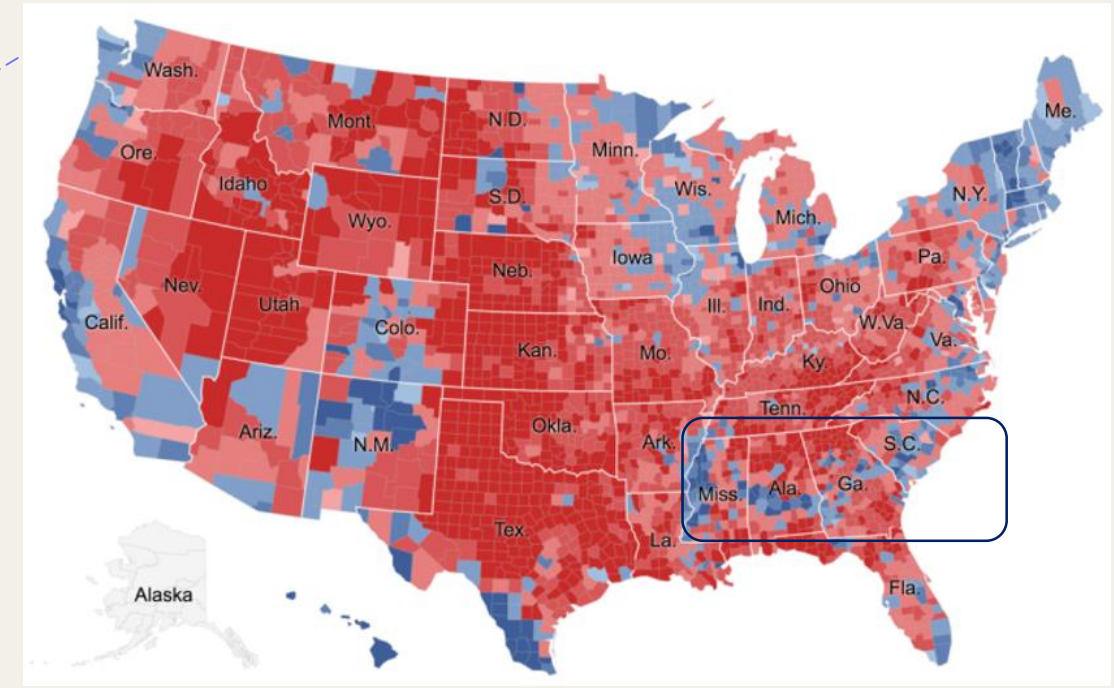
Mapping a property…

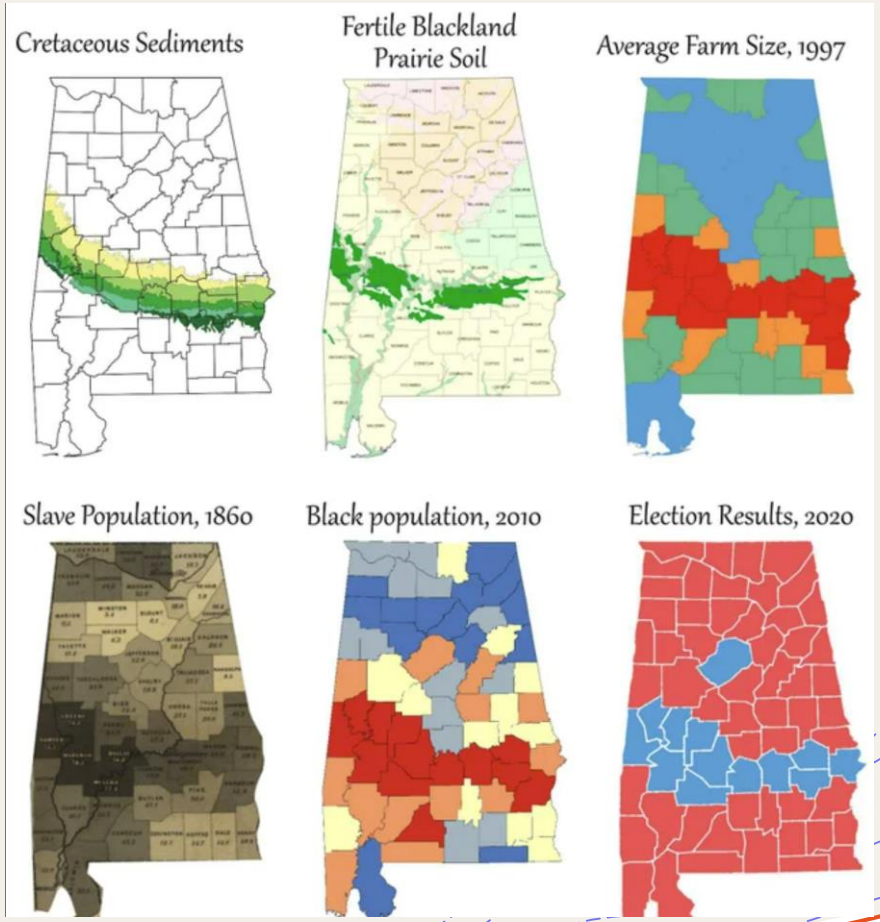


...sometimes reveals strange patterns

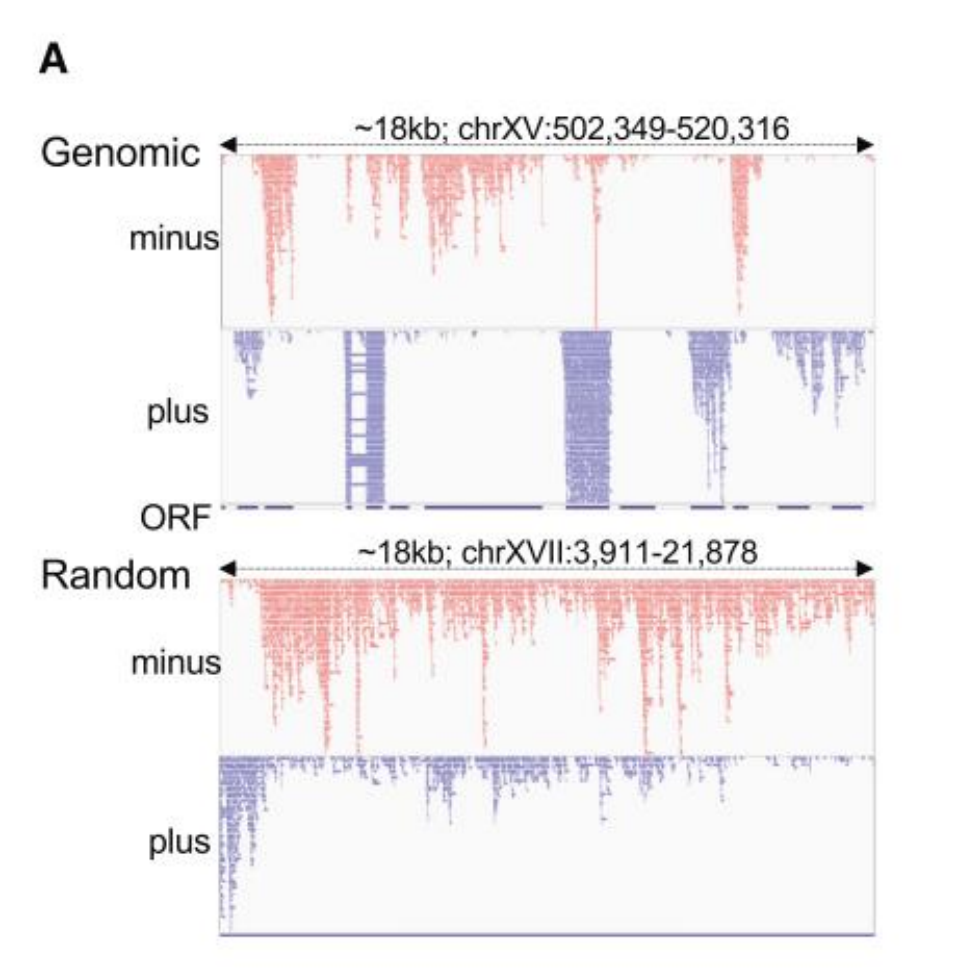


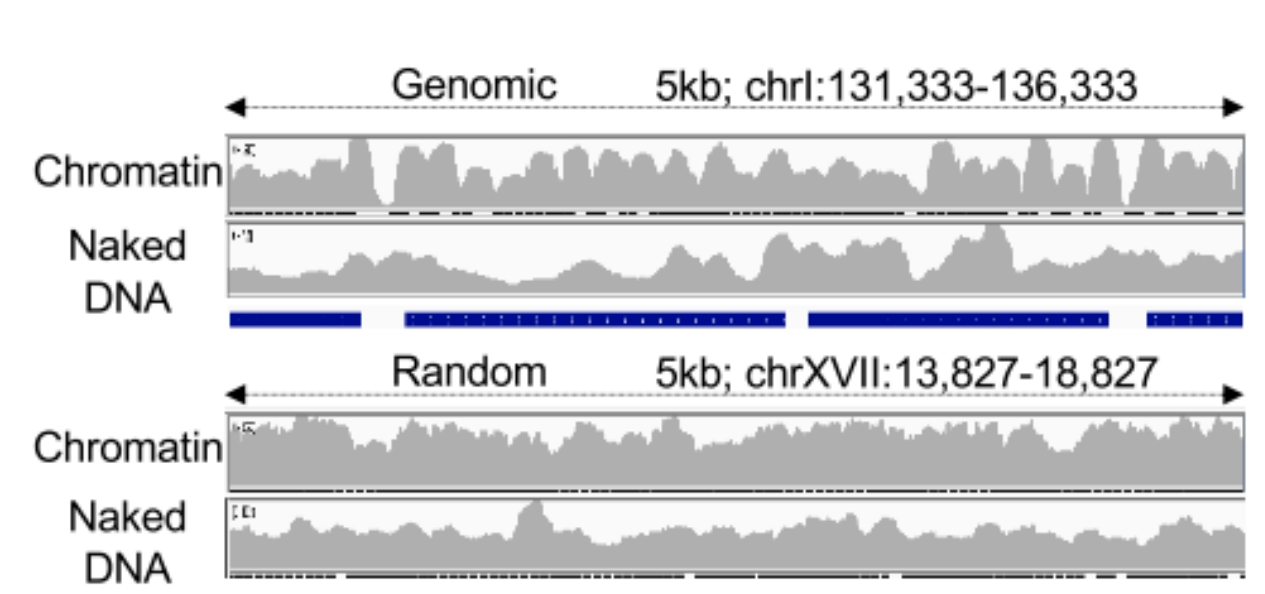
which, in turn, may provide new insights





Why genome structure in 1D matters





Struhl lab, Mol Cell 2023

The Question(s)

Can we **segment the linear genome** in “territories” where pervasive **activity** is crystalized into **function**?

How may these functional/structural territories be associated with other biological functions.

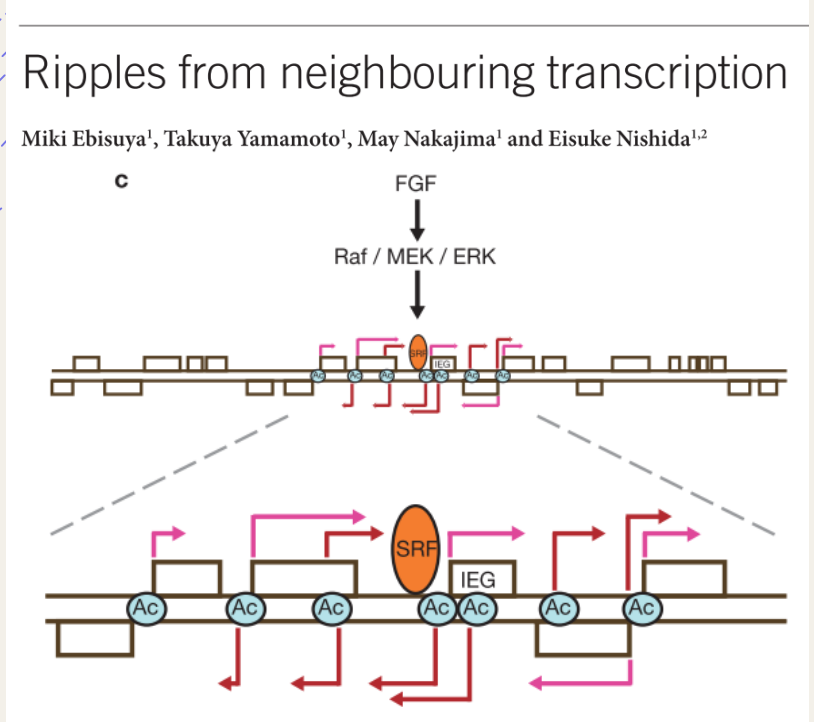
Spatial genomics properties in one dimension

Gene expression, differential expression and co-expression

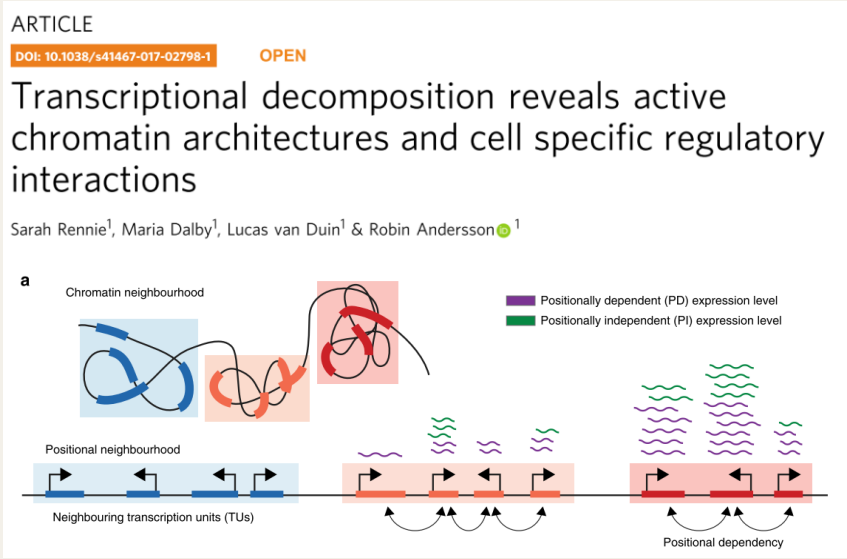
Epigenetic/epigenomic markers

Chromatin Accessibility

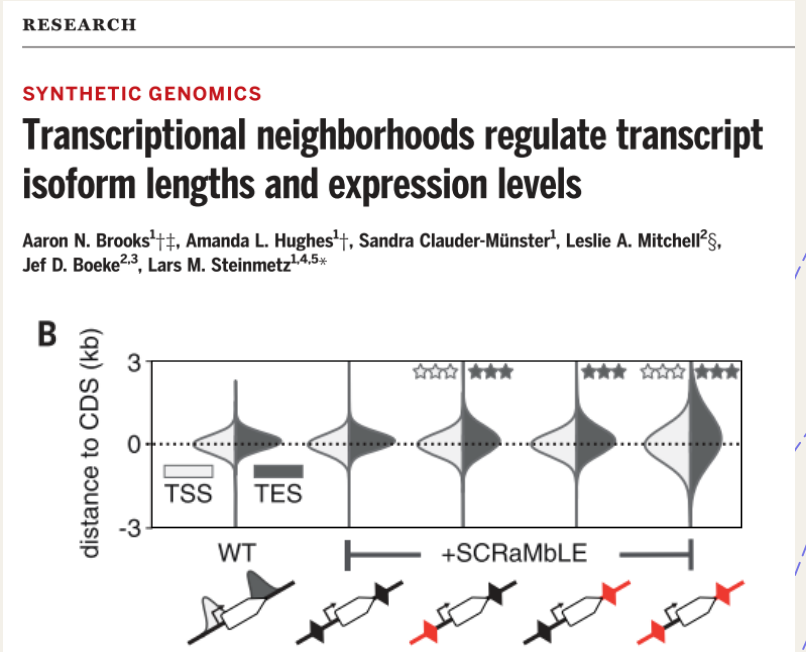
Gene transcription is spatially dependent



Nishida lab, Nat Cell Biol 2008



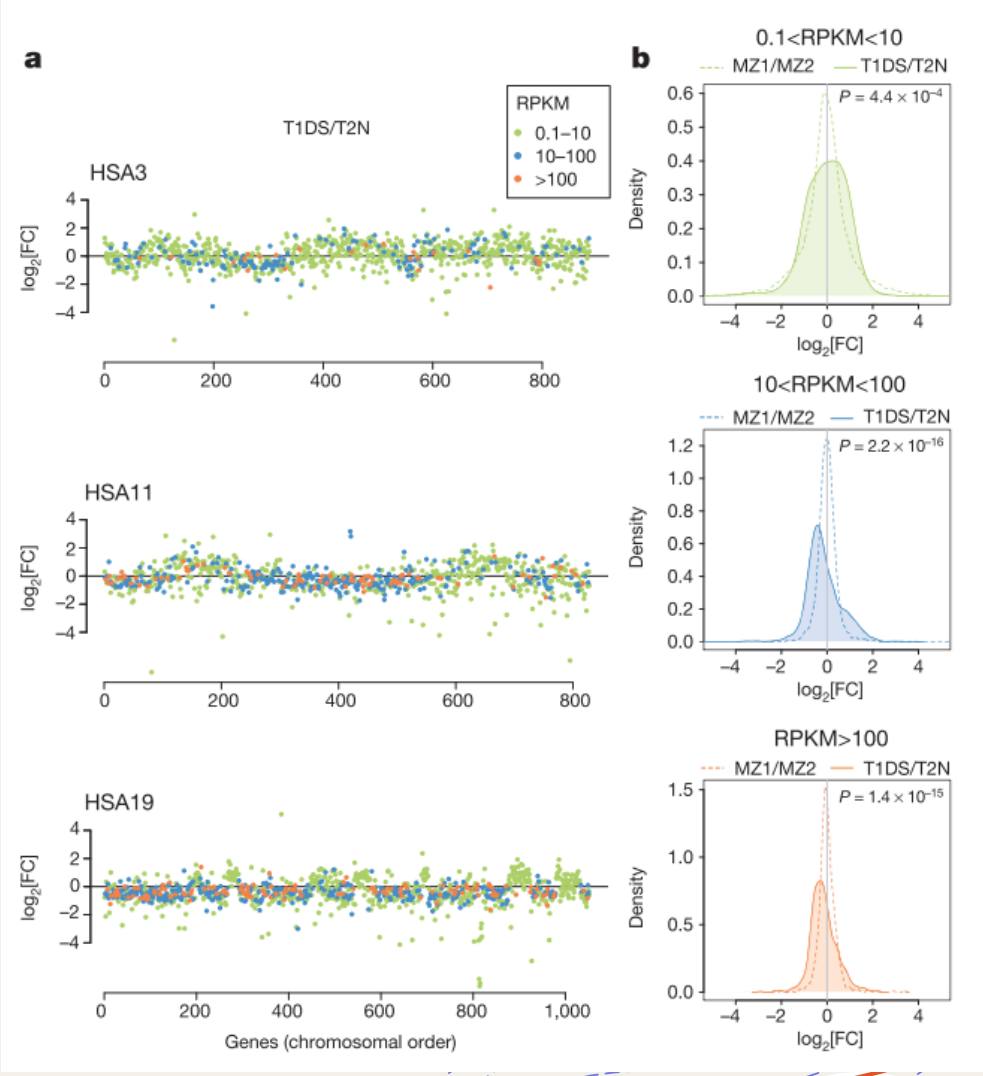
Andersson lab, Nat Comm 2018



Steinmetz lab, Science 2022

Spatial Organization of Gene Expression in disease

Over- and under-expression takes place in localized areas of the linear genome in Down Syndrome.

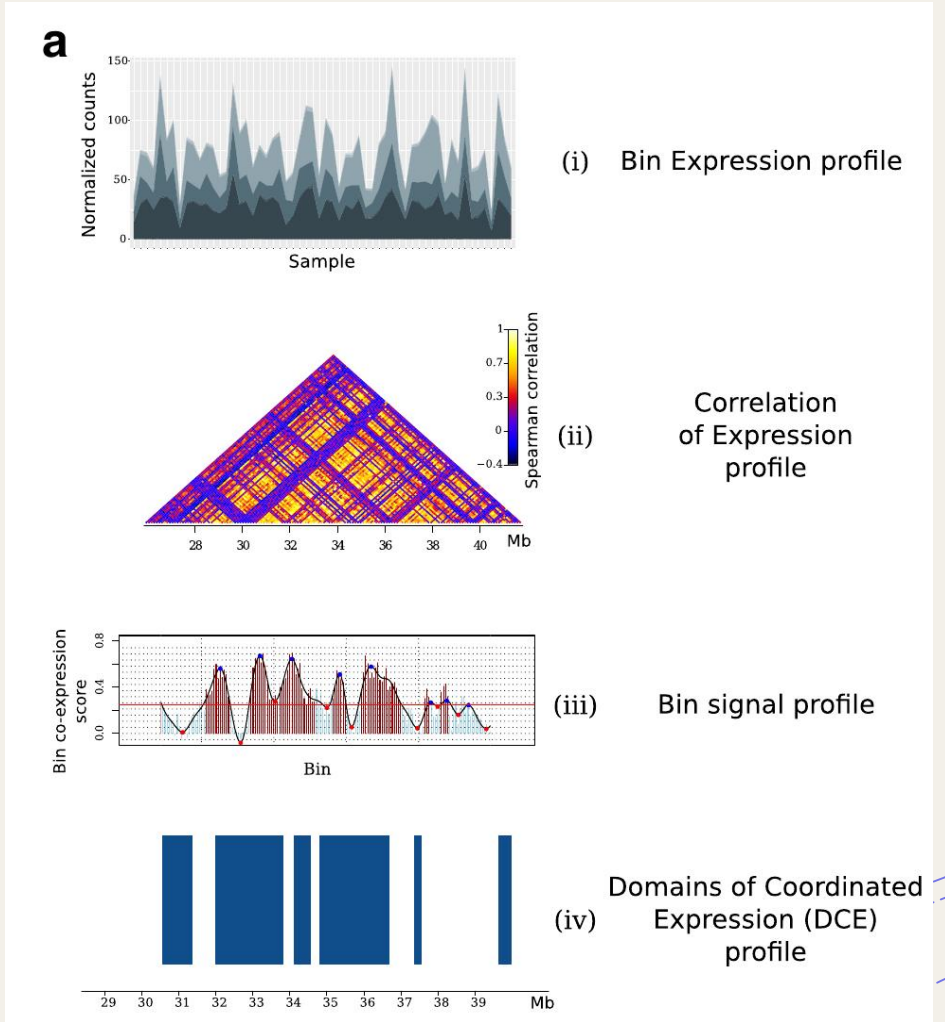


Antonarakis lab, Nature 2014

Spatial Organization of Gene co-Expression in disease

Domains of co-ordinated expression from multi-RNAseq profiles.

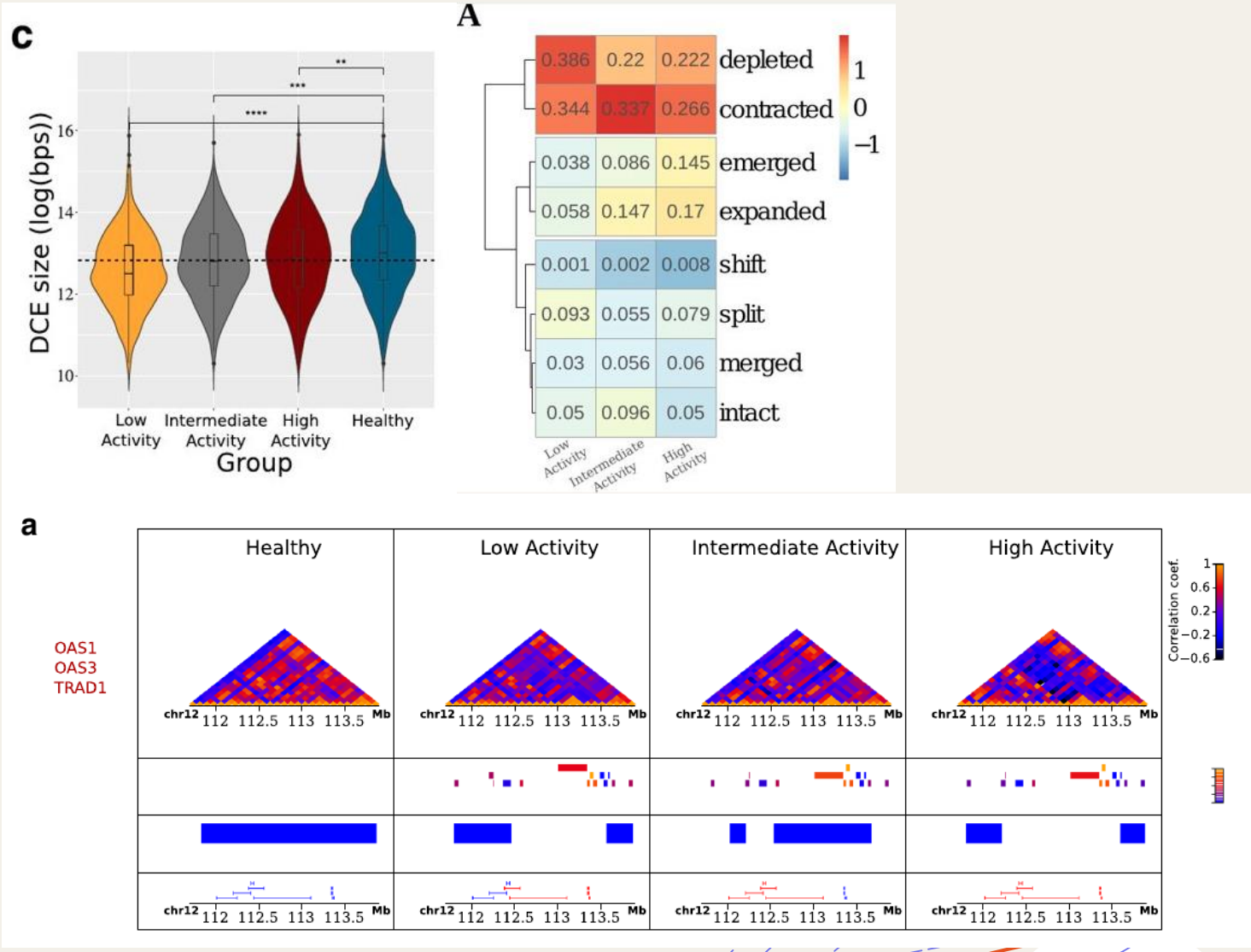
Areas of the genome with increased co-expression



Nikolaou, Bertsias and Boumpas labs, Scientific Reports 2020

Spatial Organization of Gene co-Expression in disease

Domains of co-ordinated expression are **more dispersed, shorter and more fragmented** in a group of ~150 SLE patients, compared to a group of 50 healthy individuals.

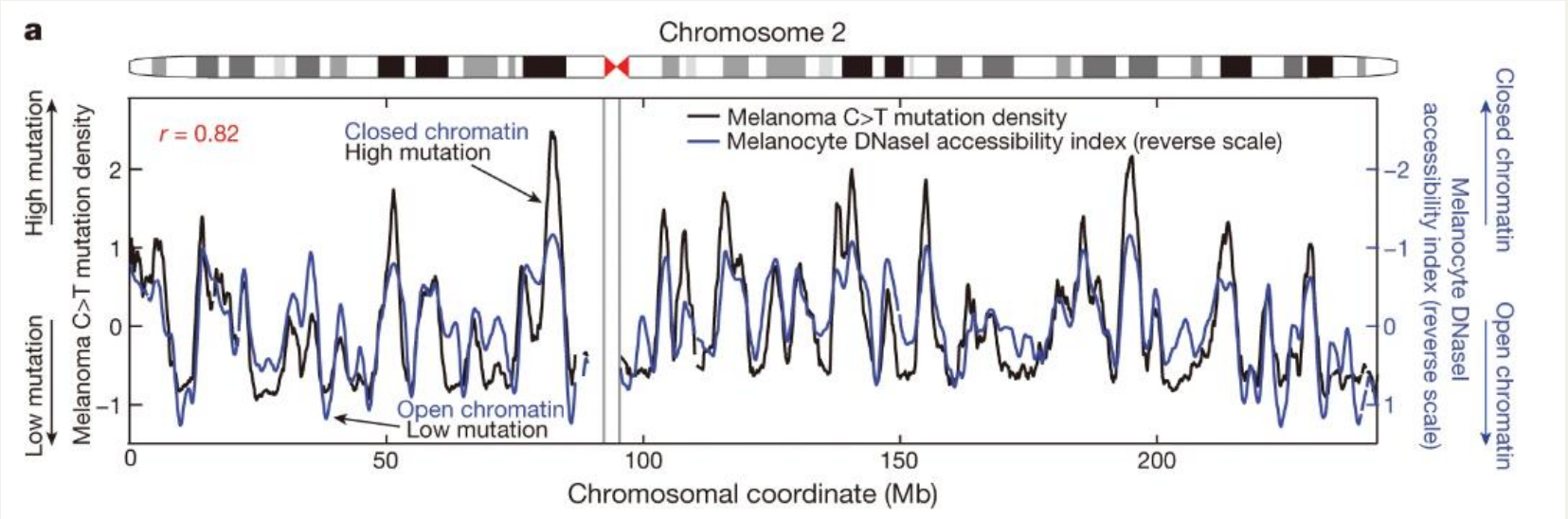


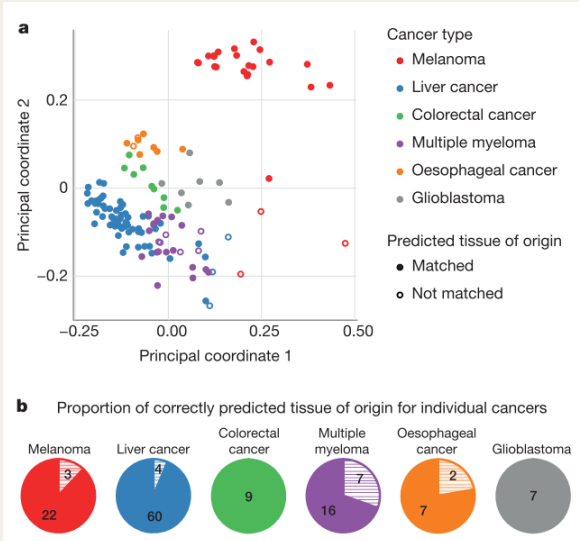
Nikolaou, Bertsias and Boumpas labs, Scientific Reports 2020

Regions of differential chromatin accessibility

Mutation rates in cancer are enriched in particular areas of decreased chromatin accessibility.

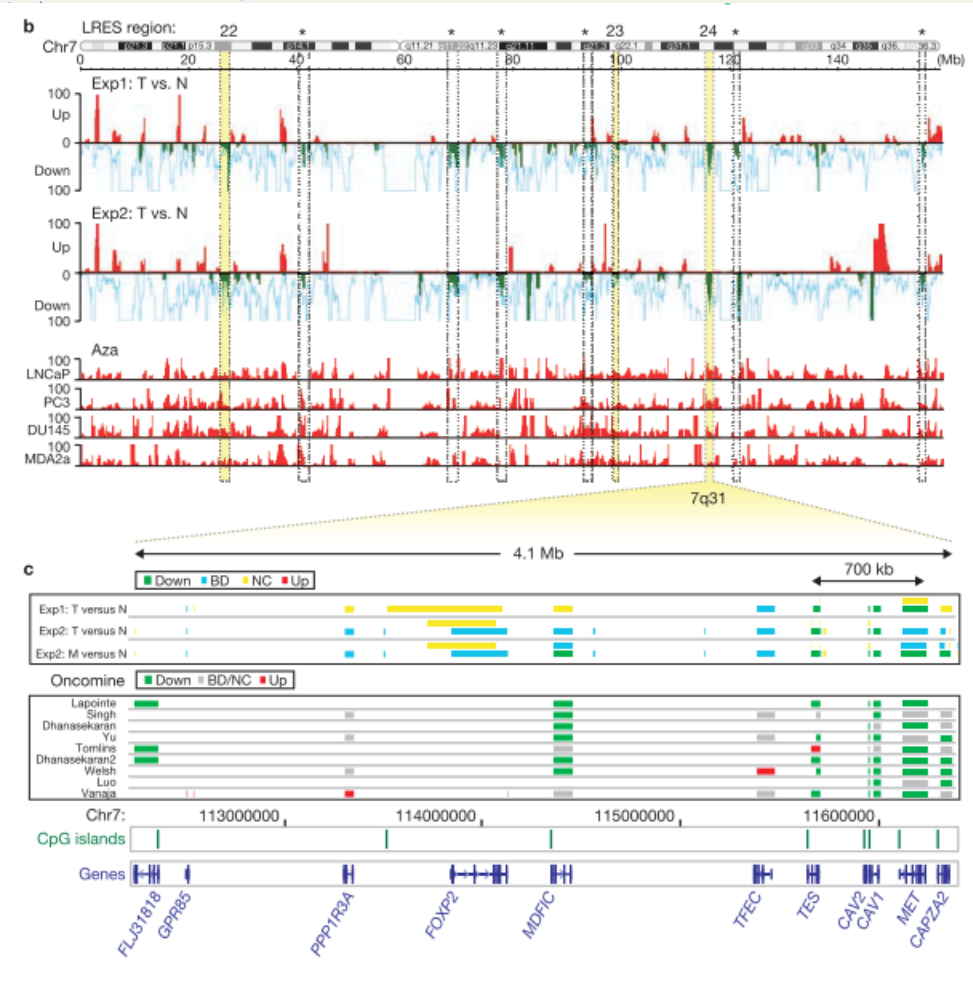
Mutations can be matched with tissue of origin based on accessibility patterns





Stamatoyannopoulos and Sunyaev labs, Nature 2015

Long Range Epigenetic Silencing



Clark lab, Nature Cell Biology 2010

Epigenetic silencing in cancer occurs in extensive regions.

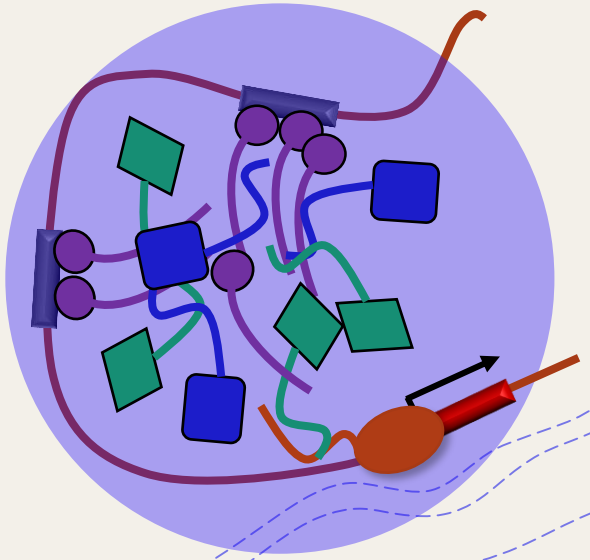
Domains of the genome where under-expression is consistently reversed by methlyl-transferase inhibition (azacitidine).

Spatial genomics properties in three dimensions

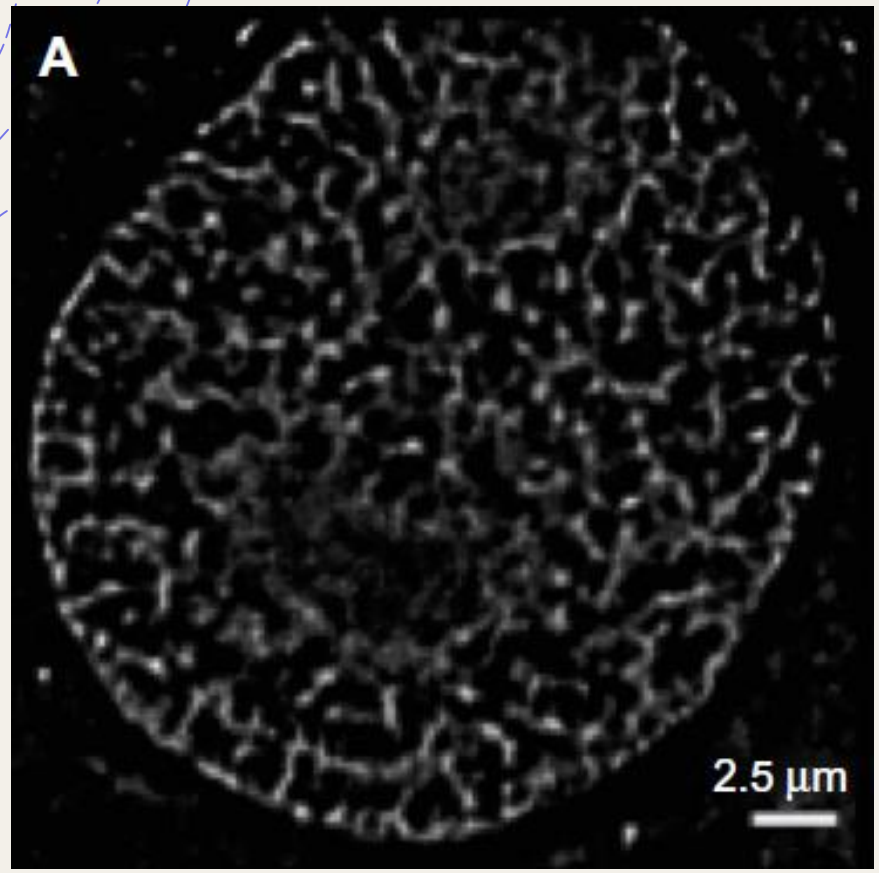
Gene activation in 3D

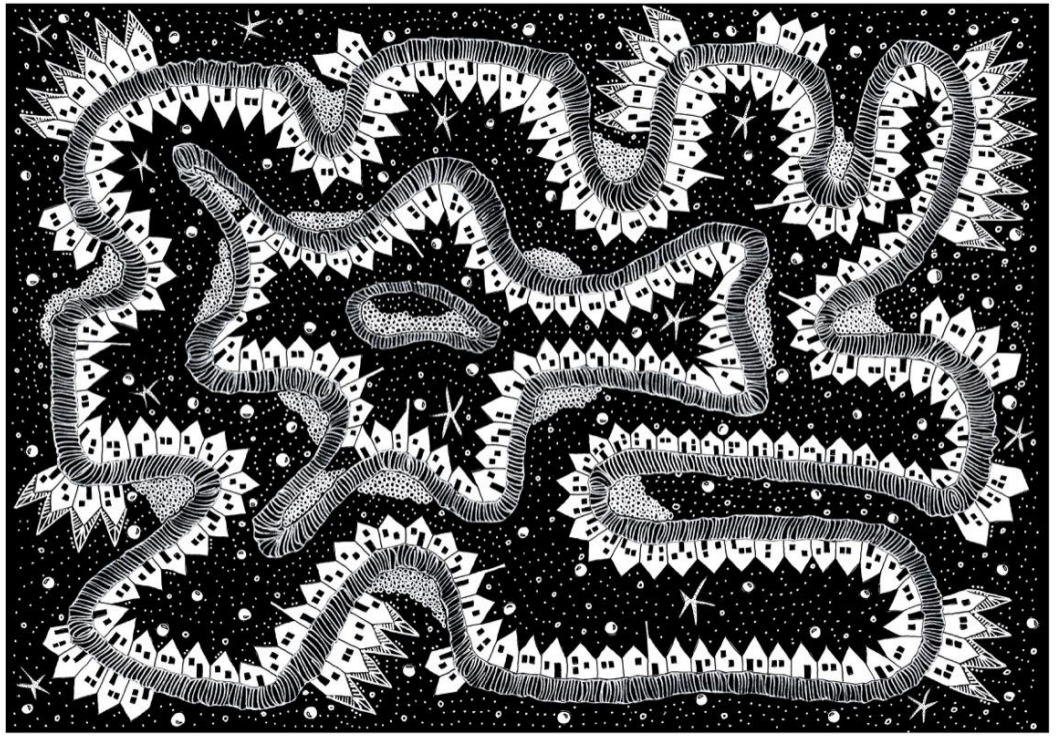
Gene activation in three-dimensional transcriptional condensates

Spatial transcriptomics and 3D cell environments



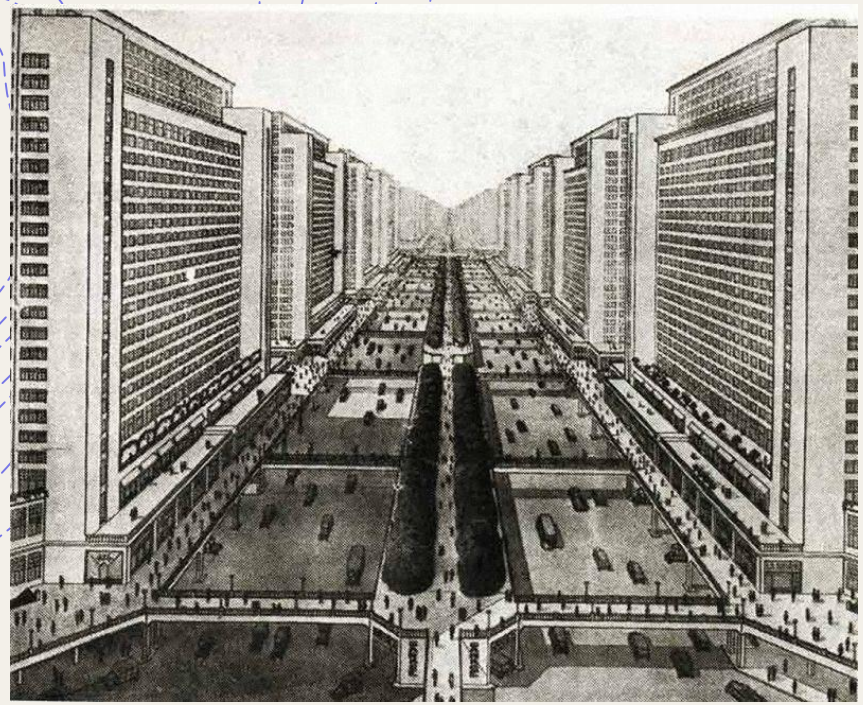
*"In Zoe the lack of Signs does not allow you to the understand the function of each building: **You are lost in an indivisible environment**."*
Italo Calvino, Invisible Cities



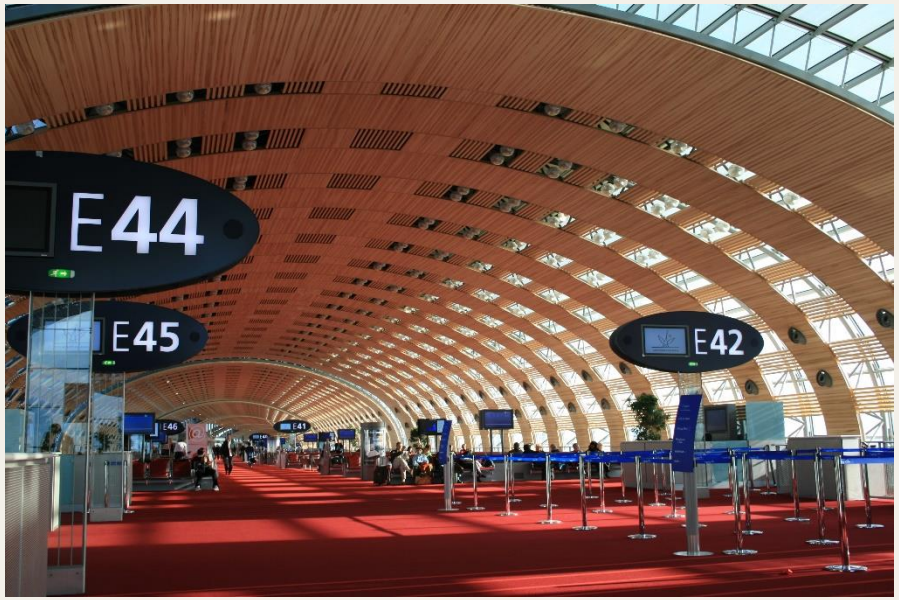


Left: A 2D live cell DNA dSTORM image, adapted from Benke A, Manley S. ChemBioChem. 2012
Right: Artistic representation of Calvino's city of Zoe by Karina Puente Frantzen

Utopian Architecture ("ου τόπος" = no place)



La ville radieuse (Le Corbusier, 1930)



Paris CDG Airport

The lack of landmarks is a characteristic of "ultra-designed" architectural structures, in which the **sense of space is by definition arbitrary**. *("ου τόπος" = no place)*

Most urban landscapes have, in contrast, developed through **gradual aggregation of distinguishable** architectural elements.

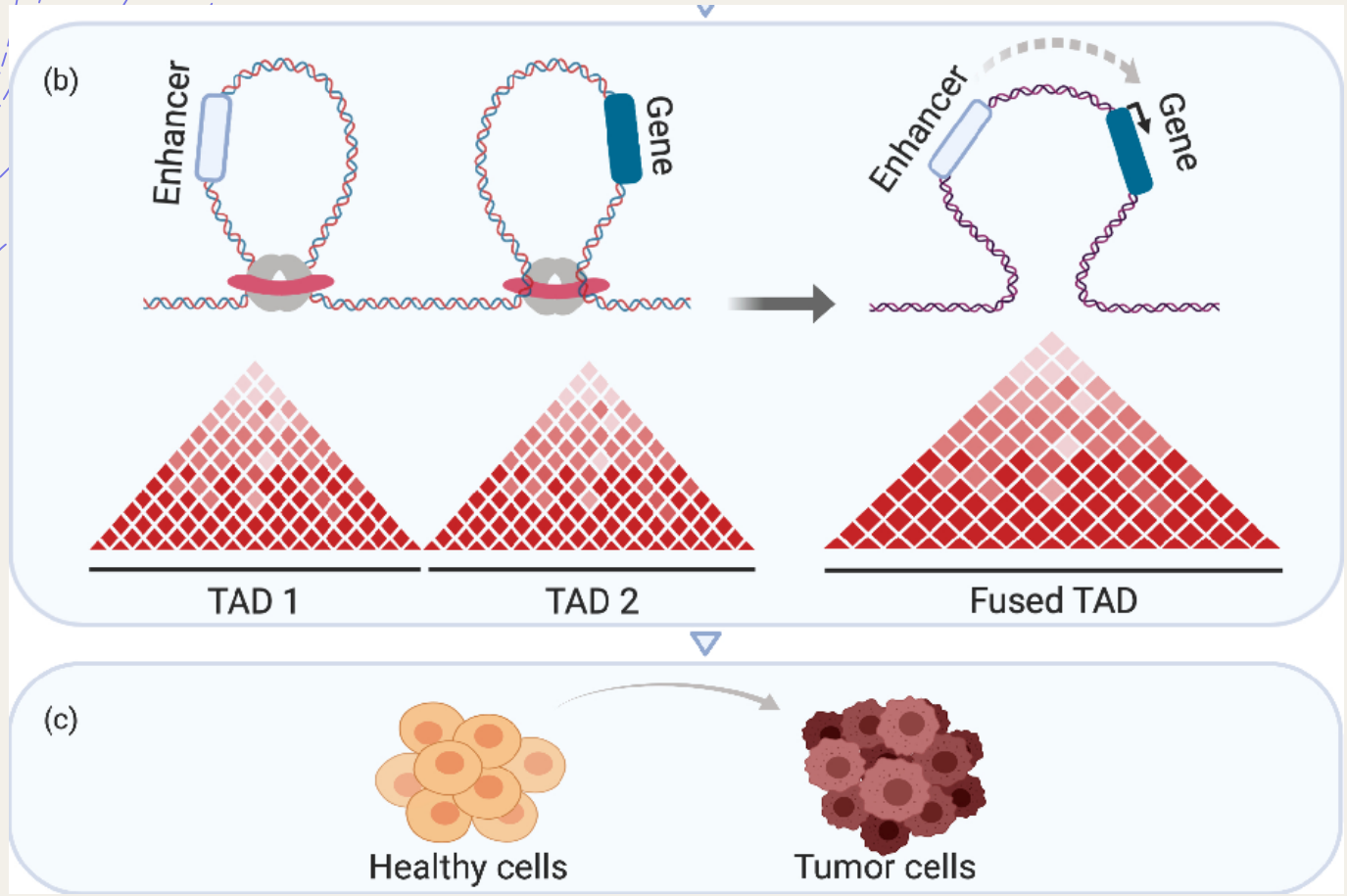
Aerial view of Paris (2017)

The Question(s)

Can we identify architectural **landmarks** in the 3D nucleus of eukaryotes?

And if so, what can we learn from their positions and their dynamics?

Why Genome Structure in 3D matters



Lazaris, Aifantis and Tsirigos, Trends in Cancer 2020

Genomic elements function in proximity to each other.

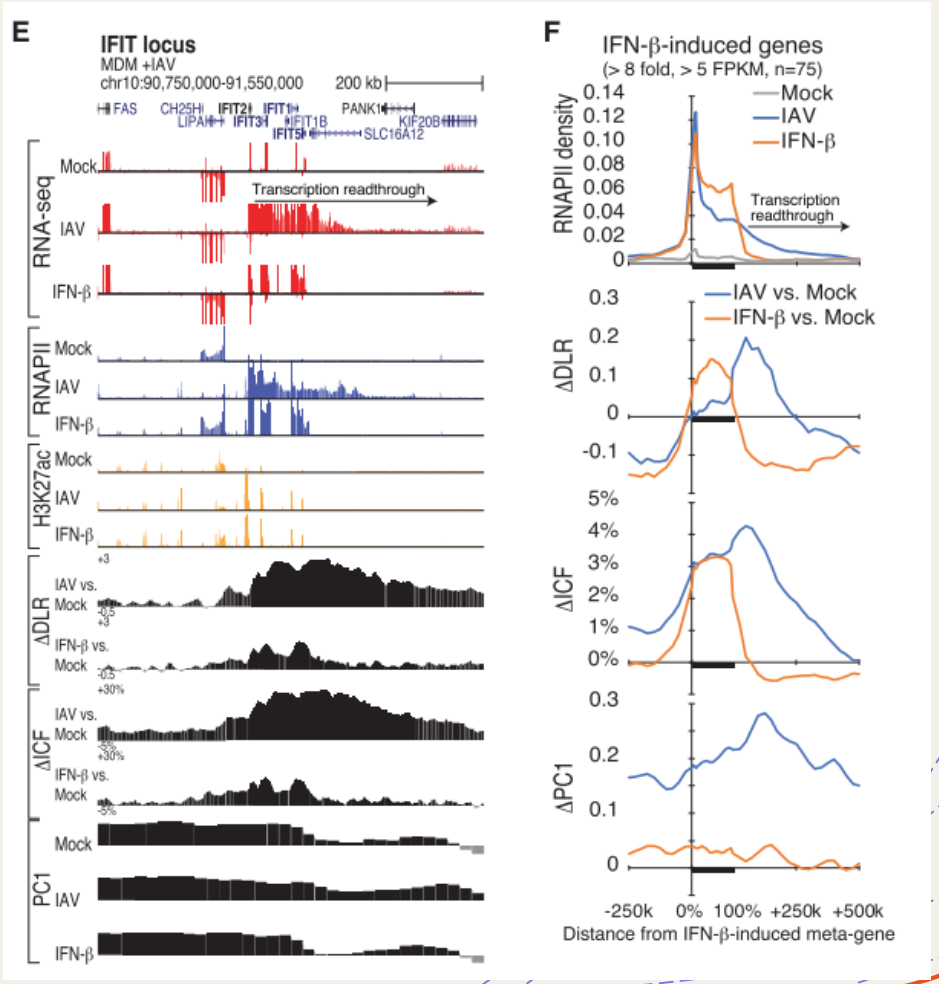
Proximity is linked to the 3D genome structure.

The 3D genome is robust but flexible and can be (dys)regulated.

Transcriptional perturbations in 1D and 3D reorganization in inflammation

Influenza A infection **affects transcriptional termination**.

Readthrough transcription leads to 3D genome reorganization in **changing compartments** and affecting local and distal DNA contacts.

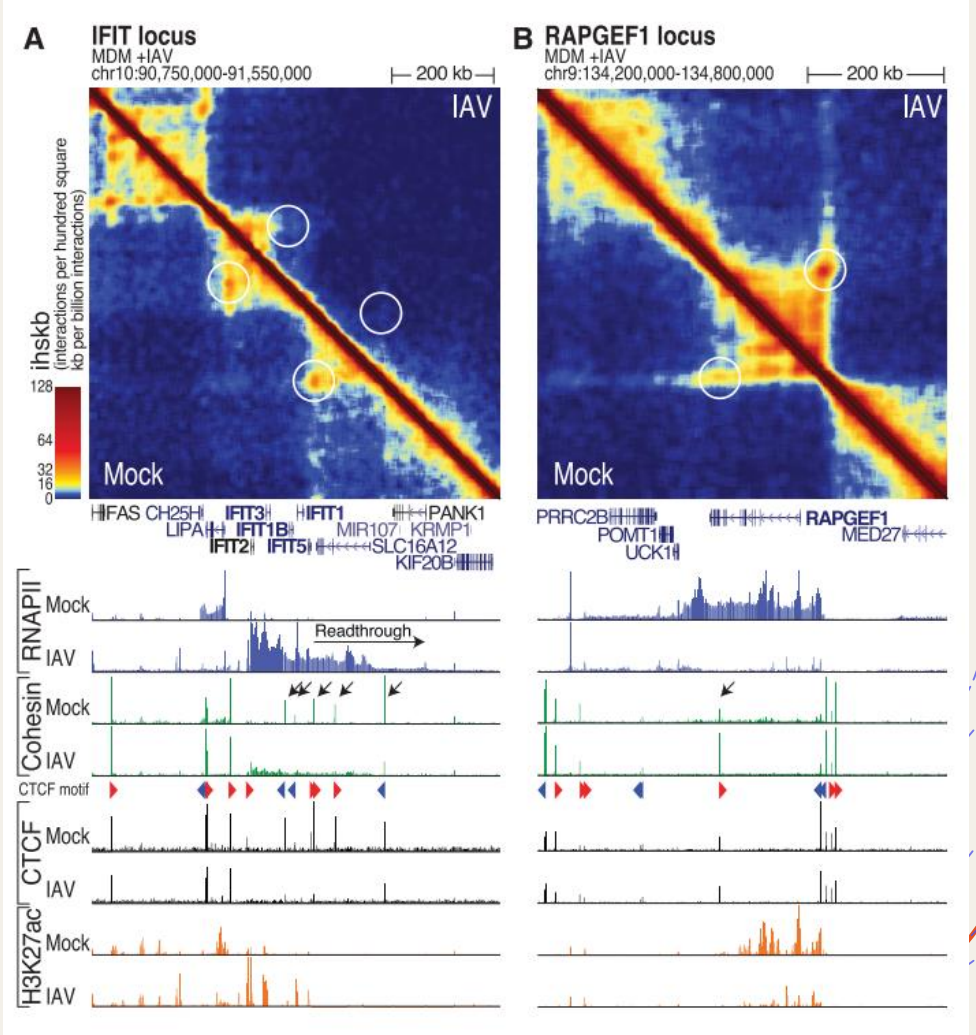


Brenner lab, Cell 2018

Transcriptional perturbations in 1D and 3D reorganization in inflammation

Readthrough transcription **displaces cohesin** and leads to the abolition of loop contacts.

Repressed genes maintain both cohesin and CTCF binding patterns and further strengthen the existing structure.



Brenner lab, Cell 2018

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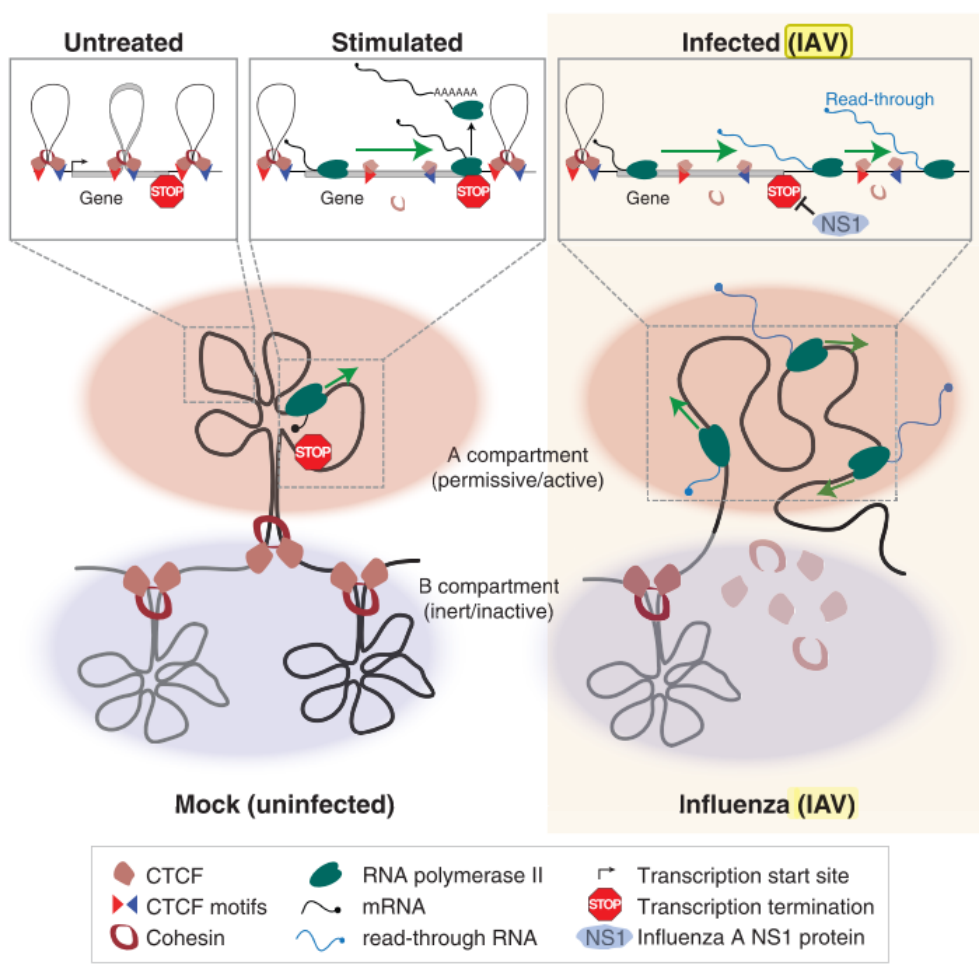
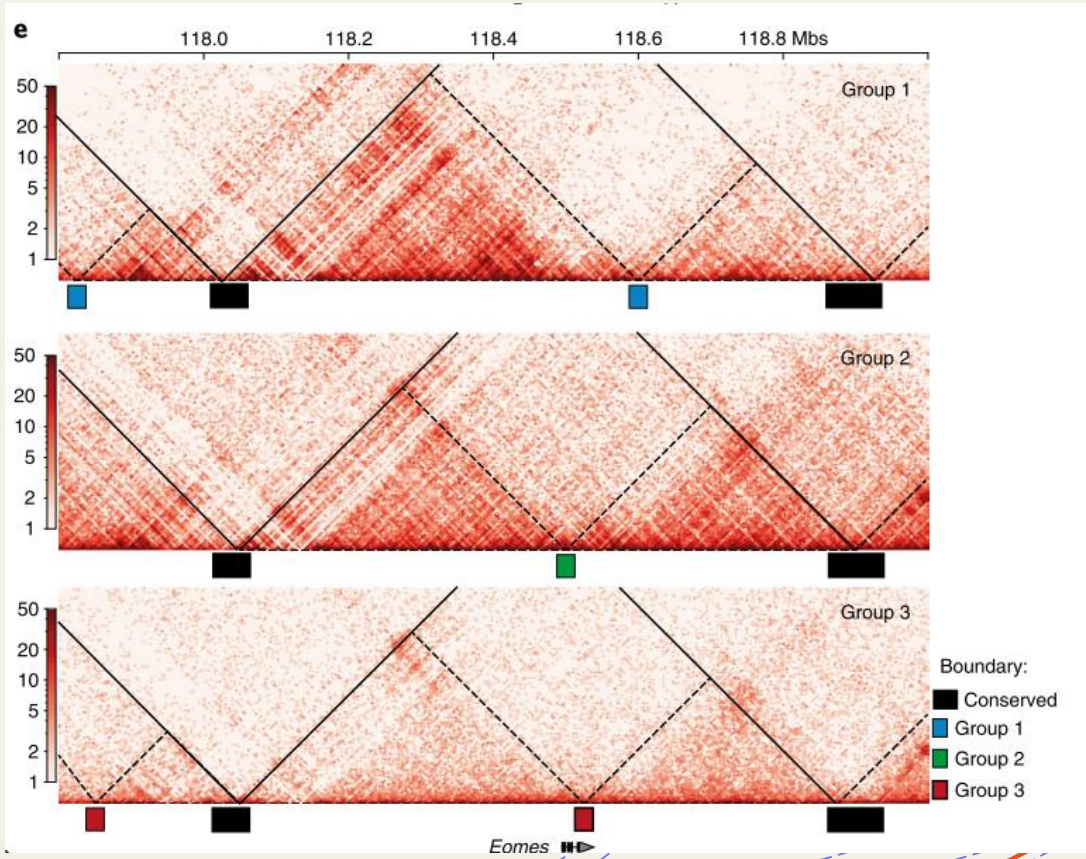


Brenner lab, Cell 2018

3D reorganization in the differentiation of the immune system

Innate lymphocytes (ILCs) can be grouped in three types, each with distinct genome organization.

E.g. only in one of the three groups does the genome structure allow the ***Eomes*** gene to contact conserved, cognate regulatory elements.

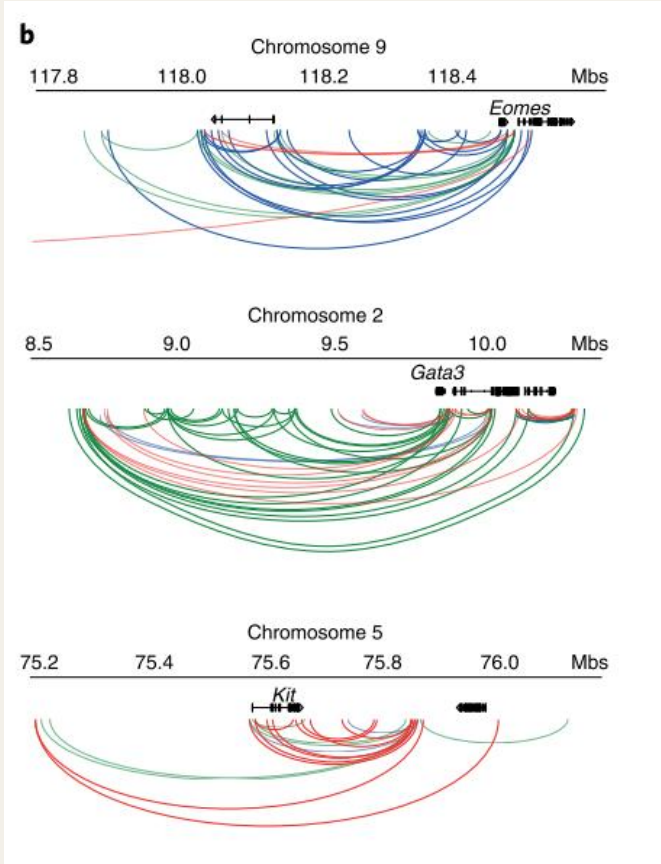


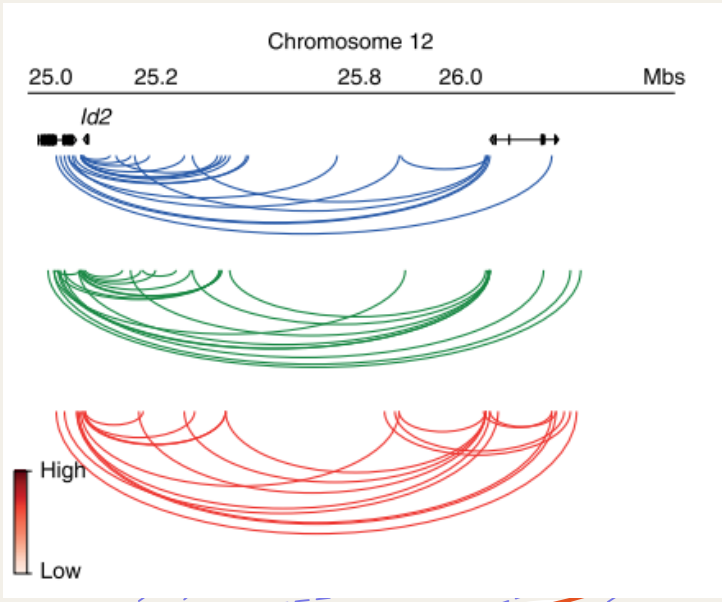
Henao-Mejia lab, Nature Immunology 2023

3D reorganization in the differentiation of the immune system

Alternative promoter-enhancer contacts among gene groups is generalized.

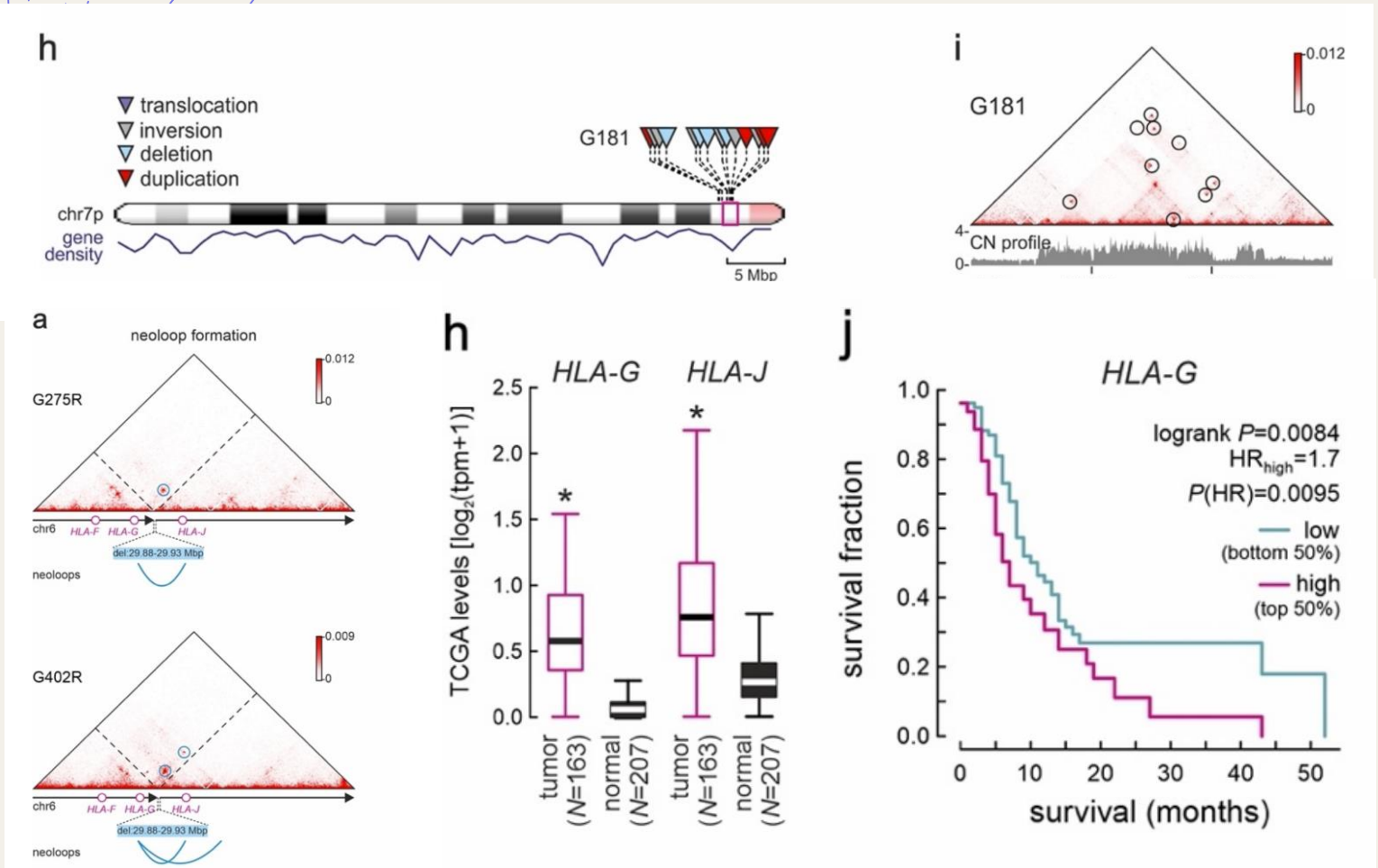
Some key genes as **Id2** are prominent in all three types.





Henao-Mejia lab, Nature Immunology 2023

Structural heterogeneity in the genomes of cancer patients



Papantonis and Pallini labs, BioRxiv 2023

Structural variants in the genomes of gliobastoma patients leads to the **creation of new 3D contacts** (neoloops).

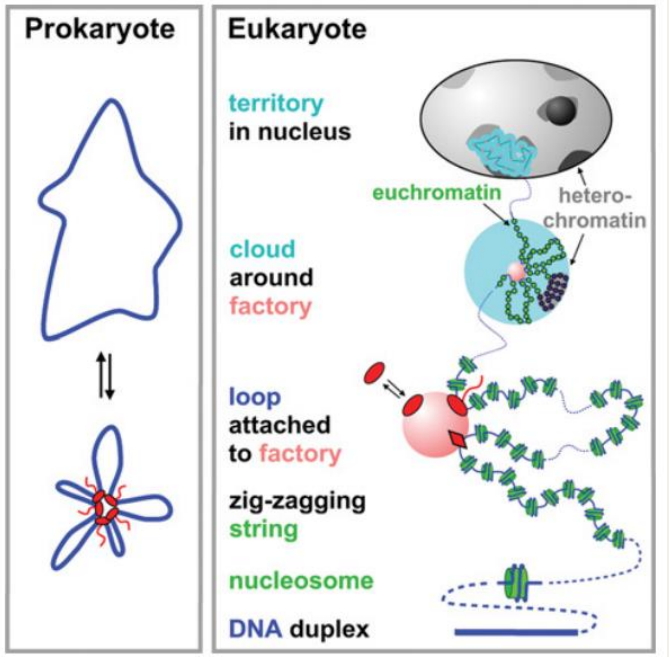
Neoloops are associated with **increased expression of nearby key genes** in tumours.

Genome Structure in Development & Disease

Condensates, Factories, Phase-separations and other curious entities

Transcription factories

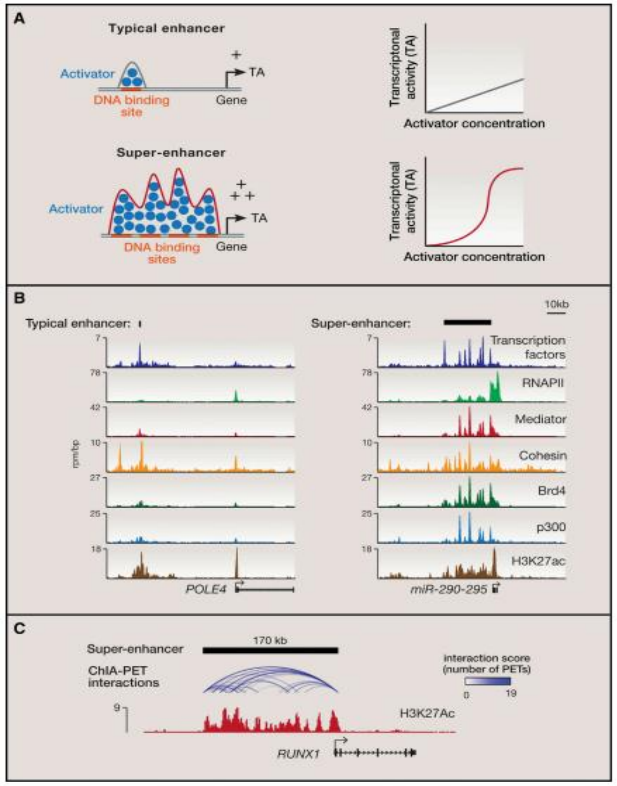
David R.F. Carter*, Christopher Eskiw† and Peter R. Cook‡[1]
*Cranfield Health, Cranfield University, Cranfield, Bedfordshire MK43 0AL, U.K., †Laboratory of Chromatin and Gene Expression, The Babraham Institute, Babraham Research Campus, Cambridge CB22 3AT, U.K. and ‡The Sir William Dunn School of Pathology, University of Oxford, South Parks Road, Oxford OX1 3RE, U.K.



Leading Edge
Perspective
Cell

A Phase Separation Model for Transcriptional Control

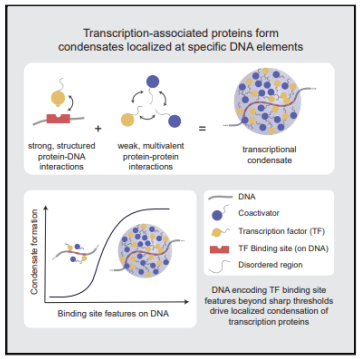
Denes Hnisz,[1,10] Krishna Shrinivas,[2,7,8,10] Richard A. Young,[1,3,*] Arup K. Chakraborty,[2,4,5,6,7,8,*] and Phillip A. Sharp[3,9,*]



Article
Molecular Cell

Enhancer Features that Drive Formation of Transcriptional Condensates

Graphical Abstract



Authors
Krishna Shrinivas, Benjamin R. Sabari, Eliot L. Coffey, ..., Phillip A. Sharp, Richard A. Young, Arup K. Chakraborty

Correspondence
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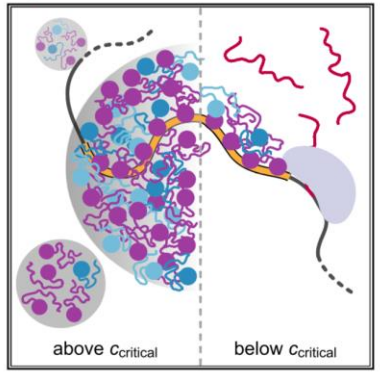
In Brief

Shrinivas et al. demonstrate that specific types of motif compositions encoded in DNA drive localized formation of transcriptional condensates. These findings explain how phase separation can occur at specific genomic locations and shed light on why only some genomic loci become highly active enhancers.

Article
Molecular Cell

Transcription activation is enhanced by multivalent interactions independent of phase separation

Graphical abstract



Authors
Jorge Trojanowski, Lukas Frank, Anne Rademacher, Norbert Mücke, Pranas Grigaitis, Karsten Rippe

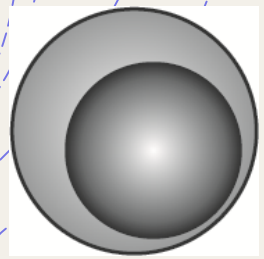
Correspondence
karsten.rippe@dkfz.de

In brief

Phase separation of TFs into condensates has been proposed to enhance transcription activation. Trojanowski et al. show that a high propensity of TFs to engage in multivalent interactions is needed for their full activation capacity independent of TF assembly into phase-separated liquid-like droplets.

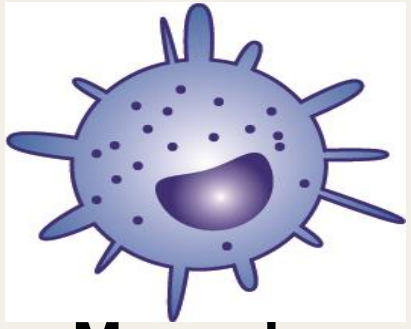
Genome Structure in Development & Disease

Our system of study: B-cell to macrophage transdifferentiation



C/EBPa-ER

BLaER cells
Human B-cell line



Macrophages

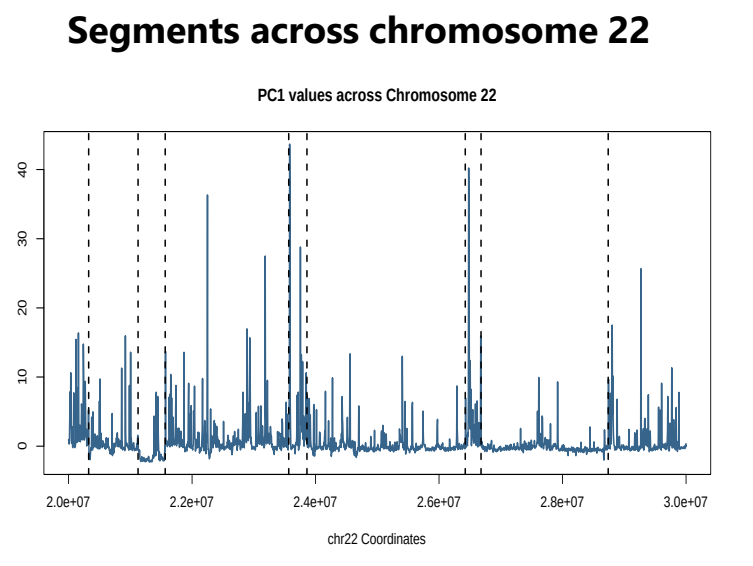
Type of experiment	0d	1d	7d
ATAC-seq	✓	✓	✓
C/EBPa ChIP-seq	✓	✓	✓
H3K27ac ChIP-seq	✓	✓	✓
H3K4me3 ChIP-seq	✓	✓	✓
Hi-C	✓	✓	✓

Nikolaou and Graf labs, Bioinformatics 2023

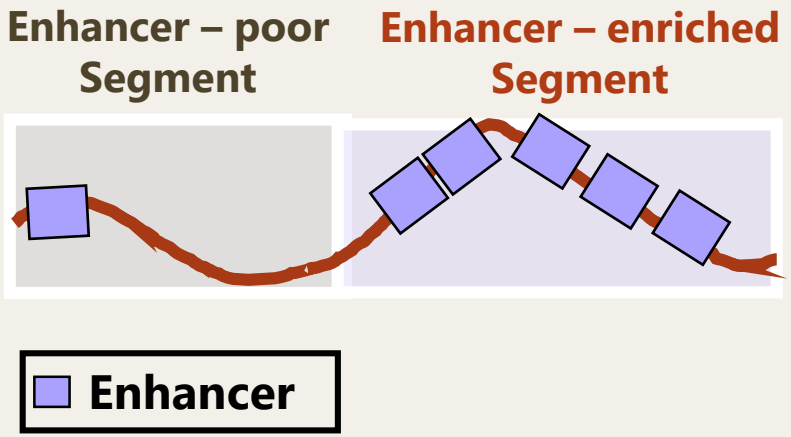
Genome Structure in 3D and Transcriptional Activation

SEGCOND: the first method to predict transcriptional condensates

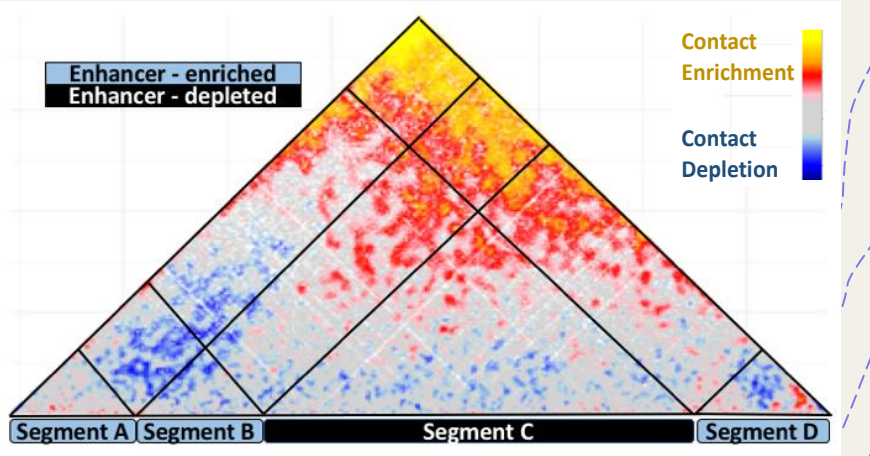
1 Segmentation



2 Annotation



3 Integration of Hi-C data



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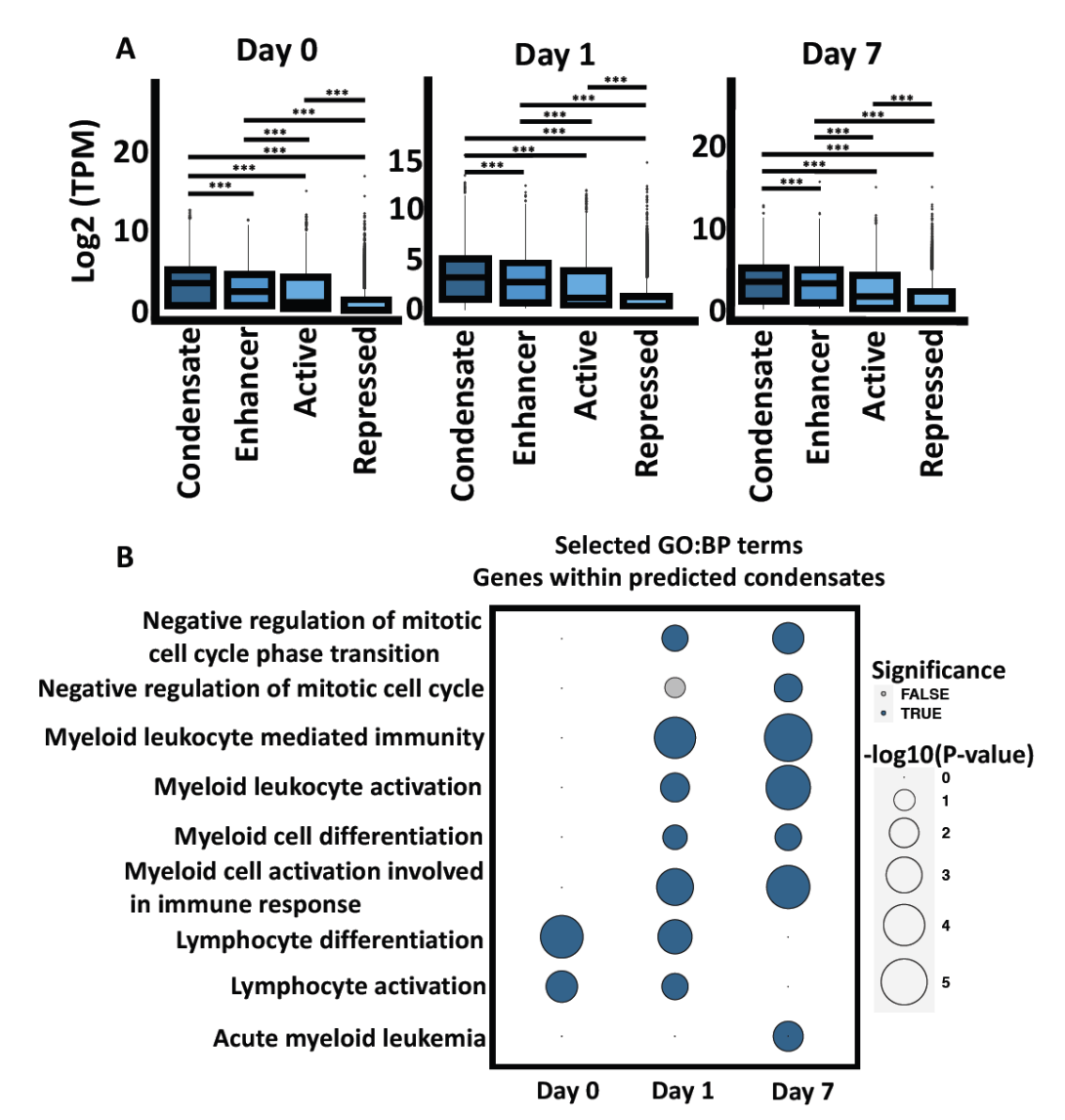
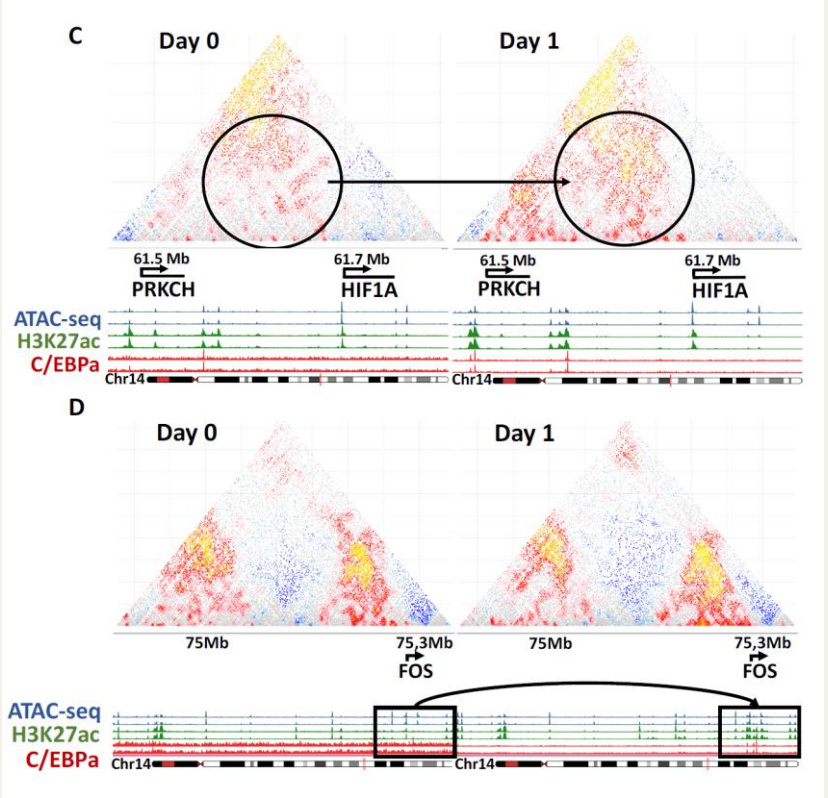
SEGCOND identifies a transcriptionally ultra-active subset of genomic elements





Identification of 3D regions of extreme transcriptional activity during a process, disease or perturbation

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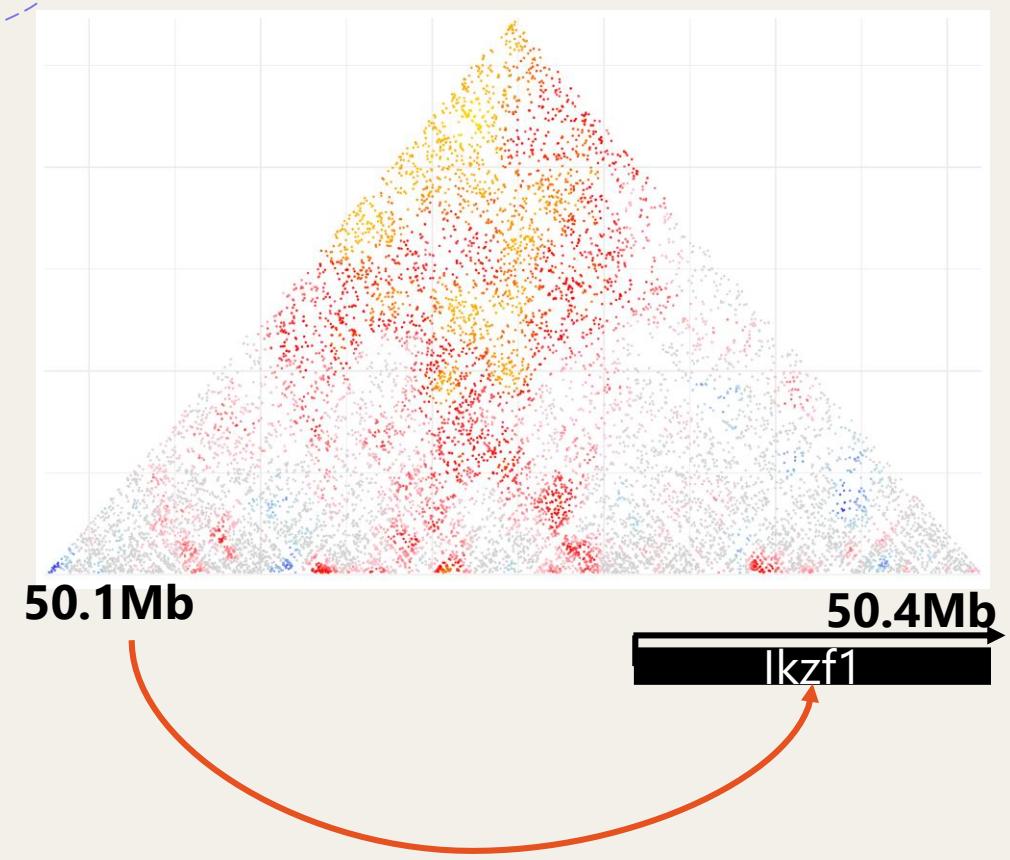
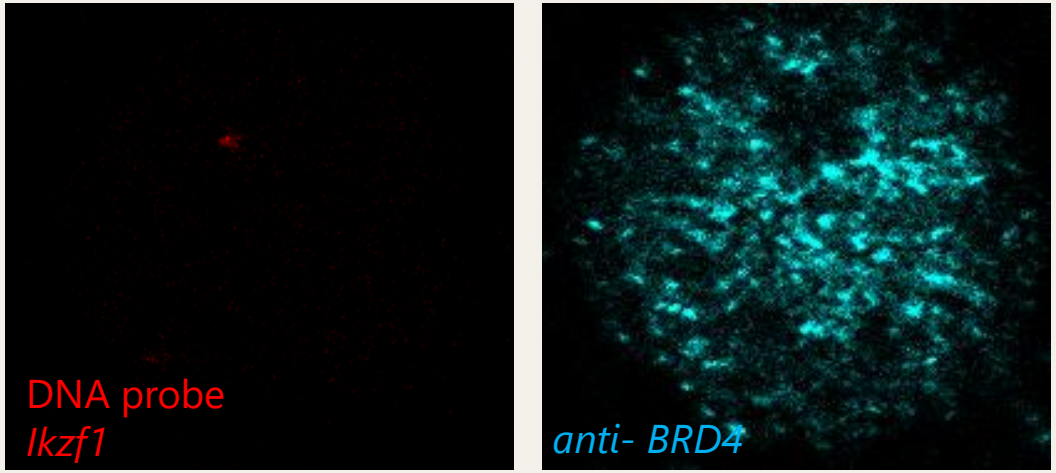
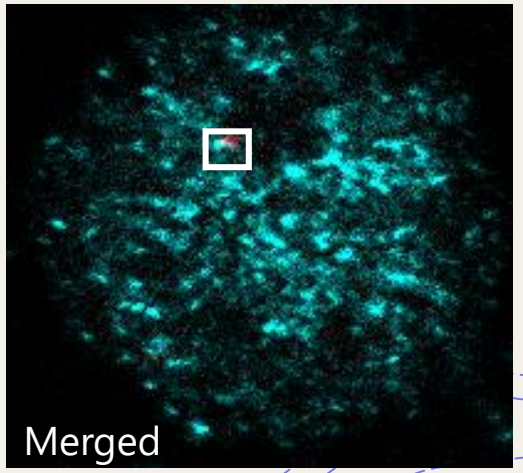
Genome Structure in 3D and Transcriptional Activation

Experimental validation of a transcriptional condensate: Ikzf1

PTC example : *Ikzf1*
locus on Chromosome 7

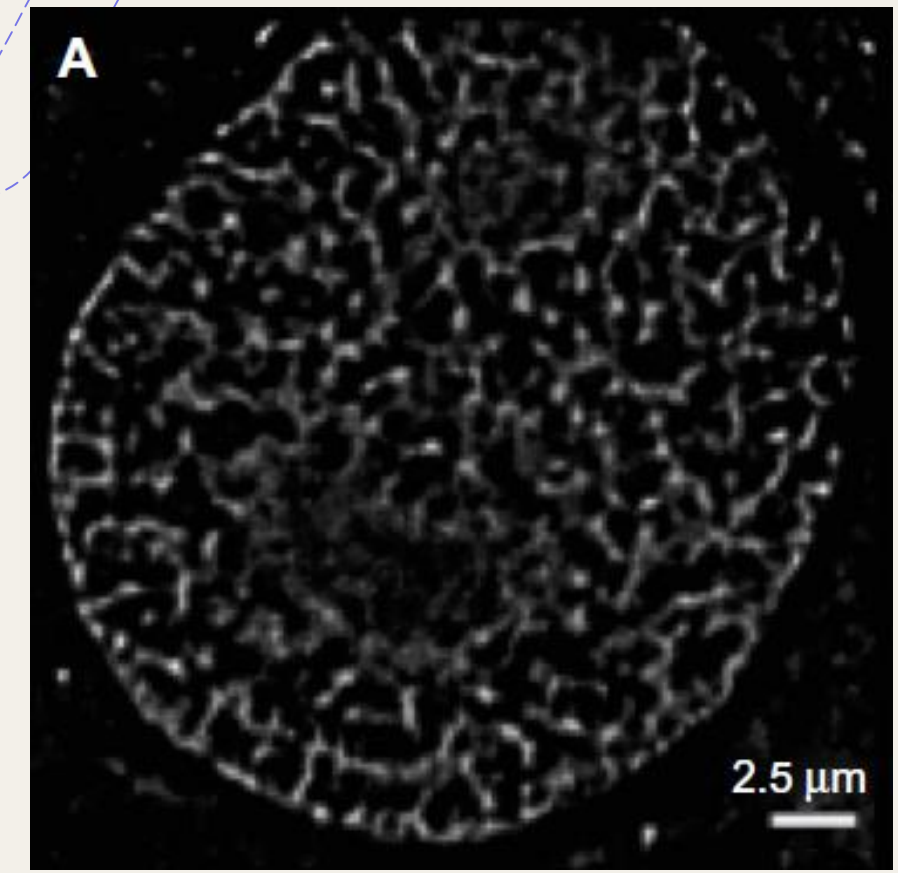


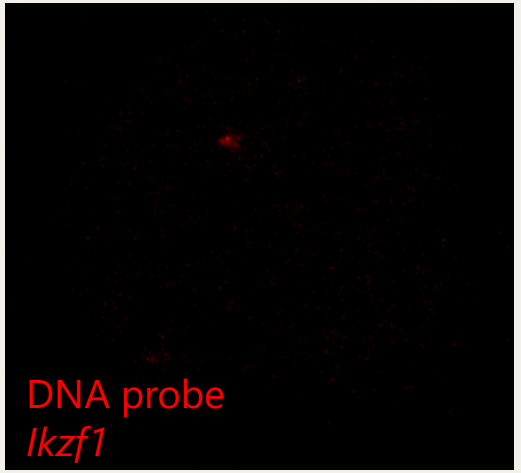


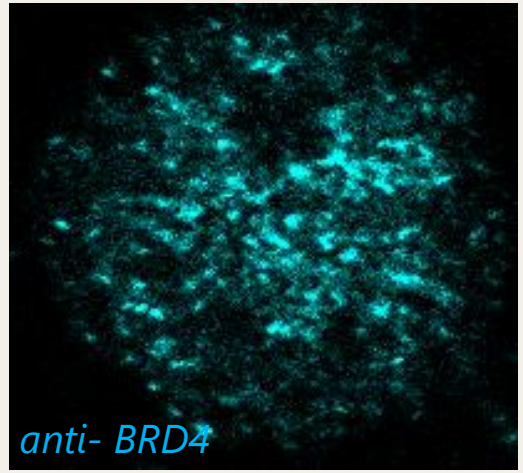


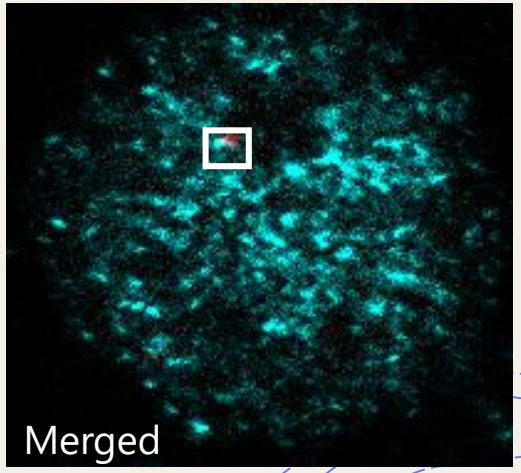
Nikolaou and Graf labs, (unpublished)

Visible Genomic Landscapes in 3D (that matter)









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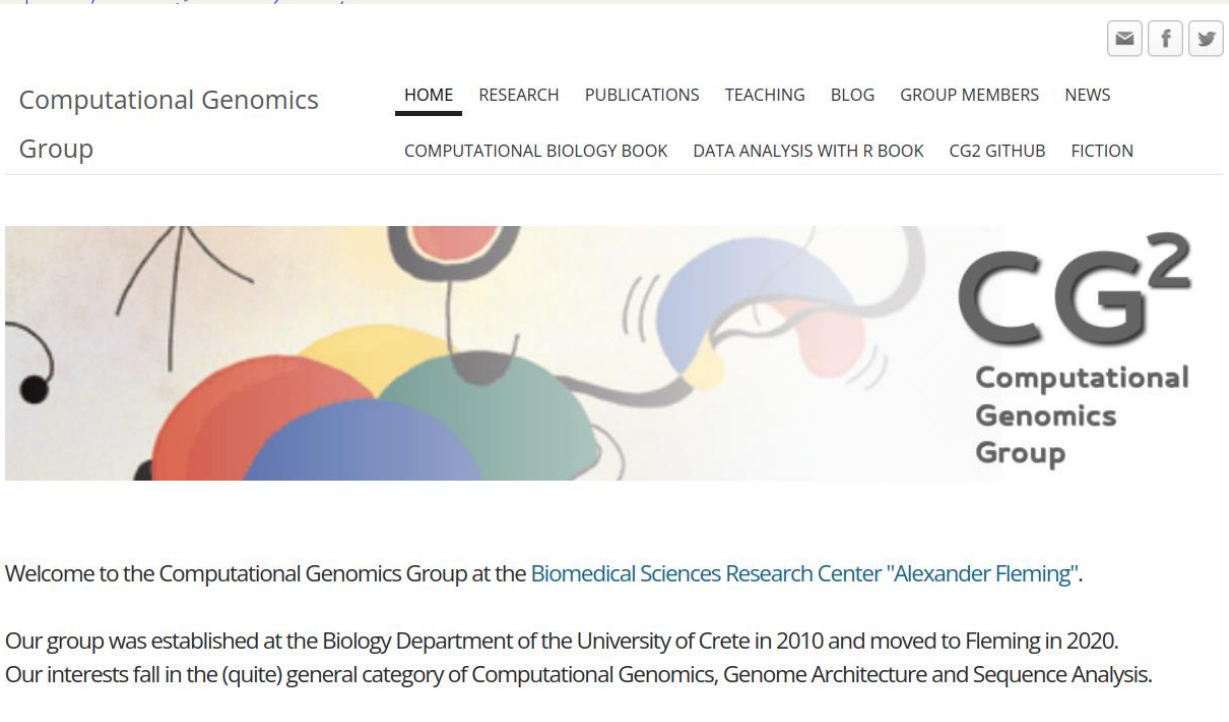
Genome architecture has evolved in order to allow for a combination of **flexibility and robustness**

What happens in both 1D and 3D space can be used to explain mechanistic aspects of every possible genomic/nuclear process

Computational Genomics Group

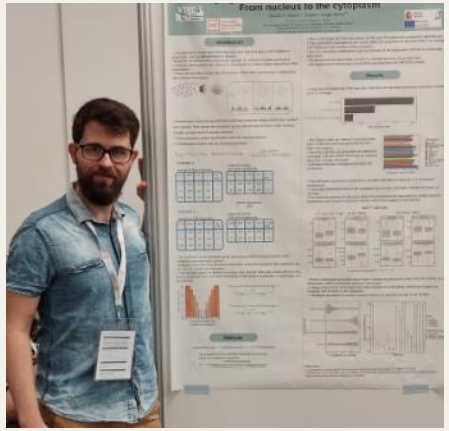


www.computational-genomics.weebly.com

People

Nikos Vakirlis

Athanasia Stavropoulou



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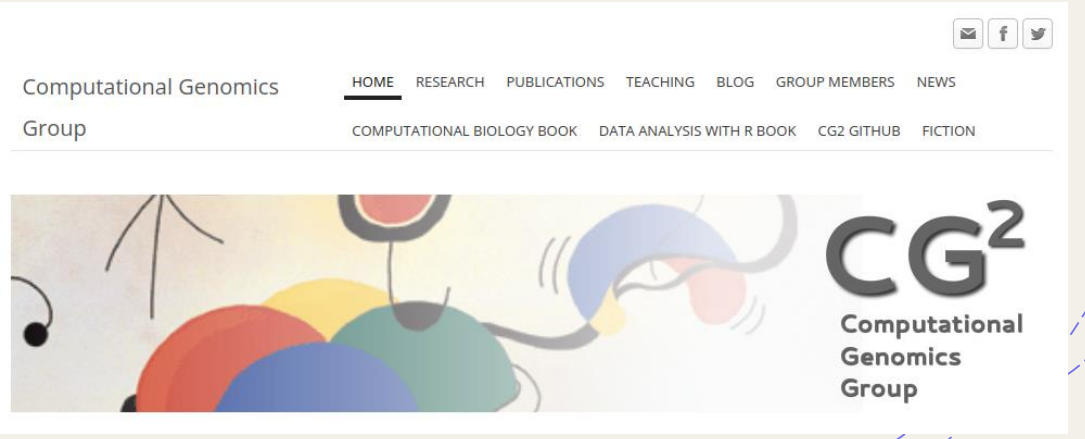
Emilios Tassios

Sofia Papanikolaou

Klio Maria Verrou



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