#### Genome structure dynamics using sparse interaction datasets

Marc A. Marti-Renom Structural Genomics Group (ICREA, CNAG-CRG)



http://marciuslab.org
http://3DGenomes.org
http://cnag.crg.eu

#### 



## Resolution Gap

Marti-Renom, M. A. & Mirny, L. A. PLoS Comput Biol 7, e1002125 (2011)

Know	edge								
to the second					IDM			$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	
								DNA length	
10 <sup>0</sup>		10 <sup>3</sup>			10 <sup>6</sup>			10 <sup>9</sup>	nt
								Volume	
10 <sup>-9</sup>		10 <sup>-6</sup>	10 <sup>-1</sup>	3		10 <sup>°</sup>		10 <sup>3</sup>	μm³
								Time	
10 <sup>-10</sup>	10 <sup>-8</sup>	10 <sup>-6</sup>	10 <sup>-4</sup>	10 <sup>-2</sup>		10 <sup>0</sup>	10 <sup>2</sup>	10 <sup>3</sup>	S
								Resolution	
10 <sup>-3</sup>			10 <sup>-2</sup>				10 <sup>-1</sup>		μ

Hybrid Method Baù, D. & Marti-Renom, M. A. Methods 58, 300–306 (2012).

**Experiments** 



Computation

# Chromosome Conformation Capture

Dekker, J., Rippe, K., Dekker, M., & Kleckner, N. (2002). Science, 295(5558), 1306–1311. Lieberman-Aiden, E., et al. (2009). Science, 326(5950), 289–293.



## Restraint-based Modeling

Baù, D. & Marti-Renom, M. A. Methods 58, 300–306 (2012).



#### Chromosome structure determination 3C-based data



# Biomolecular structure determination 2D-NOESY data



#### http://3DGenomes.org

Serra, F., Baù, D. et al. PLOS CB (2017)





Baù, D. et al. Nat Struct Mol Biol (2011) Umbarger, M. A. et al. Mol Cell (2011) Le Dily, F. et al. Genes & Dev (2014) Trussart M. et al. Nature Communication (2017) Cattoni et al. Nature Communication (2017)





## TADdyn. Dynamics of chromatin



Marco Di Stefano



**Chain-connectivity interaction** Bending **Lennard-Jones Potential** 

Exploring the time dependent structural rearrangements of SOX2 locus during transdifferentiation

![](_page_9_Picture_1.jpeg)

Stadhouders, R., Vidal, E. et al. (2018) Nature Genetics

![](_page_9_Picture_3.jpeg)

Marco di Stefano

## Transcription factors dictate cell fate

Graf & Enver (2009) Nature

![](_page_10_Figure_2.jpeg)

Transcription factors (TFs) determine cell identity through gene regulation Normal 'forward' differentiation

Cell fates can be converted by enforced TF expression

Transdifferentiation or reprogramming

## Interplay: topology, gene expression & chromatin

Stadhouders, R., Vidal, E. et al. (2018) Nature Genetics

![](_page_11_Figure_2.jpeg)

## Reprogramming from B to PSC

Stadhouders, R., Vidal, E. et al. (2018) Nature Genetics

![](_page_12_Figure_2.jpeg)

![](_page_12_Figure_3.jpeg)

![](_page_12_Figure_4.jpeg)

![](_page_12_Figure_5.jpeg)

## Birth of a TAD border upstream of Sox2

Stadhouders, R., Vidal, E. et al. (2018) Nature Genetics

![](_page_13_Figure_2.jpeg)

# Sox2 overall topological changes Stadhouders, R., Vidal, E. et al. (2018) Nature Genetics

![](_page_14_Figure_2.jpeg)

## TADbit modeling of SOX2 from B cells Hi-C

![](_page_15_Figure_1.jpeg)

Optimal IMP parameters lowfreq=0 , upfreq=1 , maxdist=200nm, dcutoff=125nm, particle size=50nm (5kb)

#### Hi-C maps of reprogramming from B to PSC The SOX2 locus

![](_page_16_Figure_1.jpeg)

![](_page_17_Picture_0.jpeg)

How does these structural rearrangements interplay with the transcription activity?

What are the main drivers of structural transitions?

#### Models of reprogramming from B to PSC The SOX2 locus

![](_page_18_Picture_1.jpeg)

![](_page_19_Figure_1.jpeg)

![](_page_19_Figure_2.jpeg)

![](_page_20_Figure_1.jpeg)

![](_page_20_Figure_2.jpeg)

![](_page_21_Figure_1.jpeg)

![](_page_21_Figure_2.jpeg)

![](_page_22_Figure_1.jpeg)

#### TADdyn: from time-series Hi-C maps to dynamic restraints The SOX2 locus

![](_page_23_Figure_1.jpeg)

# TADdyn: from time-series Hi-C maps to dynamic restraints The SOX2 locus

![](_page_24_Figure_1.jpeg)

#### TADdyn: from time-series Hi-C maps to dynamic restraints The SOX2 locus B cell PSC Βα D2 D4 D6 D8 Harmonic HarmonicLowerBound з Vanishing Raising **Transition** Stable Energy penalty 7,290 **Β -> Β**α 6,984 18,612 2 **Β**α -> **D2** 18,512 6,687 7,390 6,830 D2 -> D4 18,369 6,893 6,291 D4 -> D6 18,971 7,289 D6 -> D8 20,167 6,250 6,093 0 D8 -> ES 6,173 20,679 5,738

#### SOX2 locus structural changes from B to PSC Contacts

![](_page_26_Picture_1.jpeg)

#### SOX2 locus structural changes from B to PSC Contacts

![](_page_27_Picture_1.jpeg)

# SOX2 locus structural changes from B to PSC TAD borders

![](_page_28_Picture_1.jpeg)

![](_page_28_Figure_2.jpeg)

# SOX2 locus structural changes from B to PSC TAD borders

![](_page_29_Picture_1.jpeg)

![](_page_29_Figure_2.jpeg)

#### SOX2 locus structural changes from B to PSC TAD borders

![](_page_30_Figure_1.jpeg)

#### SOX2 locus structural changes from B to PSC Distance to regulatory elements

![](_page_31_Picture_1.jpeg)

![](_page_31_Figure_2.jpeg)

#### SOX2 locus structural changes from B to PSC Distance to regulatory elements

![](_page_32_Picture_1.jpeg)

![](_page_32_Figure_2.jpeg)

#### SOX2 locus structural changes from B to PSC Structural exposure

![](_page_33_Picture_1.jpeg)

![](_page_33_Figure_2.jpeg)

#### SOX2 locus structural changes from B to PSC Structural exposure

![](_page_34_Picture_1.jpeg)

![](_page_34_Figure_2.jpeg)

#### SOX2 locus dynamics changes from B to PSC SOX2 displacement

![](_page_35_Picture_1.jpeg)

![](_page_35_Figure_2.jpeg)

#### SOX2 locus dynamics changes from B to PSC SOX2 displacement

![](_page_36_Picture_1.jpeg)

![](_page_36_Figure_2.jpeg)

#### SOX2 locus dynamics changes from B to PSC SOX2 displacement

![](_page_37_Figure_1.jpeg)

Two dimensional trajectories and area explored over 50s of the CCND1 locus recored before -E2 and after +E2 activation.

Germier ,T., et al, Blophys J. 113, 1383–1394 (2017).

![](_page_37_Figure_4.jpeg)

#### Other regions...

![](_page_38_Figure_1.jpeg)

![](_page_38_Picture_2.jpeg)

![](_page_38_Picture_3.jpeg)

![](_page_38_Picture_4.jpeg)

![](_page_38_Picture_5.jpeg)

![](_page_38_Picture_6.jpeg)

![](_page_38_Picture_7.jpeg)

Sox2 chr3:34649995-34652460

![](_page_38_Figure_9.jpeg)

Nanog chr6:122707565-122714633

![](_page_38_Figure_11.jpeg)

![](_page_38_Figure_12.jpeg)

![](_page_38_Figure_13.jpeg)

#### CEBPa chr7:35119293-35121931

![](_page_38_Figure_15.jpeg)

#### Distance to enhancers

![](_page_39_Figure_1.jpeg)

Active - Inactive - Random

Accessibility

![](_page_40_Figure_1.jpeg)

Active - Inactive - Random

#### Displacement

![](_page_41_Figure_1.jpeg)

Active - Inactive - Random

#### A "cage" model for transcriptional activation

![](_page_42_Picture_1.jpeg)

## stpRNAs, a new type of structural RNAs?

![](_page_43_Picture_1.jpeg)

Irene Farabella

![](_page_43_Picture_3.jpeg)

Marco di Stefano

![](_page_43_Picture_5.jpeg)

#### RNA, nuclear organisation dynamics and architecture

Rinn and Guttman, Science; 345(6202):1240–1241 (2014)

![](_page_44_Figure_2.jpeg)

## RNA, nuclear organisation dynamics and architecture

![](_page_45_Picture_1.jpeg)

#### Chromatin-interlinking IncRNAs

Adapted from: Caudron-Herger et al., Nucleus ;2(5):410-24 (2011)

#### Mitotic chromosome-associated RNAs

Adapted from: Meng et al., Nucleic Acids Res. ;44(10):4934-46 (2016)

#### RNA-DNA triplex in vivo and in vitro

Adapted from: Mondal et al. Nat Commun. 6:7743 (2015)

Are there IncRNAs that act as global architectural factor for chromatin organisation?

Hypothesis: such IncRNA may interact with DNA through triplex formation.

#### IncRNA selection

![](_page_47_Figure_1.jpeg)

#### TFO/PARSE IncRNA profiles

#### **127 triplex forming IncRNA**

with Secondary Structure information based on PARSE

![](_page_48_Figure_3.jpeg)

## TTS profile on Chromosome

![](_page_49_Figure_1.jpeg)

![](_page_49_Figure_2.jpeg)

#### 3D Co-localisation of loci

![](_page_50_Figure_1.jpeg)

#### Enriched Co-localised TTS site

#### ENST00000434346.1

![](_page_51_Picture_2.jpeg)

#### ENST0000541775.1

![](_page_51_Picture_4.jpeg)

## TADdyn modeling

![](_page_52_Figure_1.jpeg)

#### Benchmark measures

Eigen vector correlation & Diagonal cross correlation

![](_page_53_Figure_2.jpeg)

![](_page_53_Figure_3.jpeg)

![](_page_53_Figure_4.jpeg)

![](_page_53_Figure_5.jpeg)

Model

# ENST0000434346.1 TTS in Chr19

total of 3,039 restraints over 620,899 possible (0.5%)

![](_page_54_Figure_2.jpeg)

#### Other stpRNA TTS in Chr19

#### HiC experiment

![](_page_55_Figure_2.jpeg)

#### ENST0000434346.1

![](_page_55_Figure_4.jpeg)

#### ENST0000541775.1

![](_page_55_Figure_6.jpeg)

![](_page_55_Figure_7.jpeg)

![](_page_55_Figure_8.jpeg)

![](_page_55_Figure_9.jpeg)

![](_page_55_Figure_10.jpeg)

1.0

#### RNA & nuclear architecture

![](_page_56_Picture_1.jpeg)

CTCF

![](_page_56_Figure_3.jpeg)

#### TTS and repetitive elements

![](_page_57_Figure_1.jpeg)

## Staple RNA to hold DNA?

![](_page_58_Picture_1.jpeg)

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![](_page_59_Picture_1.jpeg)

![](_page_59_Picture_2.jpeg)

<u>Marco Di Stefano</u> <u>Irene Farabella</u>

David Castillo Yasmina Cuartero Silvia Galan Mike Goodstadt Francesca Mugianesi Julen Mendieta Juan Rodriguez François Serra Paula Soler Aleksandra Sparavier

In collaboration with Ralph Stadhouders (Erasmus MC) and Thomas Graf (CRG)

![](_page_59_Picture_6.jpeg)

![](_page_59_Picture_7.jpeg)

![](_page_59_Picture_8.jpeg)