Structure determination of genomes and genomic domains by satisfaction of spatial restraints

Marc A. Marti-Renom Genome Biology Group (CNAG) Structural Genomics Group (CRG)





Structural Genomics Group

http://www.marciuslab.org







Integrative Modeling Platform

http://www.integrativemodeling.org Russel, D. et al. PLOS Biology 10, e1001244 (2012).



From Alber, F. et al. Nature 450, 695–701 (2007).







Resolution Gap

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

Know	edge								
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100		10 ³			1.06			DNA length	t
10		10			10			10	nt
								Volume	
10 ⁻⁹		10 ⁻⁶	1	0 ⁻³		10 ⁰		10 ³	μm³
								Time	
10 ⁻¹⁰	10 ⁻⁸	10 ⁻⁶	10 ⁻⁴	10 ⁻²		10 [°]	10 ²	10 ³	S
								Resolution	
10 ⁻³			10 ⁻²				10 ⁻¹		μ



Hybrid Method

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

Experiments



Computation





Hi-C technology

Lieberman-Aiden, E. et al. Science 326, 289-293 (2009). http://3dg.umassmed.edu





Biomolecular structure determination 2D-NOESY data



Chromosome structure determination 3C-based data



Integrative Modeling

http://www.integrativemodeling.org





Genome Organization

Dekker, J., Marti-Renom, M. A. & Mirny, L. A.Nat Rev Genet (2013)





Human α -globin domain

Baù, D. et al. Nat Struct Mol Biol (2011).





TAD's response to hormone

Le Dily, F. et al. Submitted.





Human α -globin domain

ENm008 genomic structure and environment



The ENCODE data for ENm008 region was obtained from the UCSC Genome Browser tracks for: RefSeq annotated genes, Affymetrix/ CSHL expression data (Gingeras Group at Cold Spring Harbor), Duke/NHGRI DNasel Hypersensitivity data (Crawford Group at Duke University), and Histone Modifications by Broad Institute ChIP-seq (Bernstein Group at Broad Institute of Harvard and MIT).

ENCODE Consortium. Nature (2007) vol. 447 (7146) pp. 799-816



Human $\alpha\text{-globin}$ domain

ENm008 genomic structure and environment





Representation



Scoring





Optimization





Clustering





Not just one solution









The "Chromatin Globule" model





D. Baù et al. Nat Struct Mol Biol (2011) 18:107-14 A. Sanyal et al. Current Opinion in Cell Biology (2011) 23:325-33.



On TADs and hormones





Davide Baù



François le Dily



Progesterone-regulated transcription in breast cancer



Vicent et al 2011, Wright et al 2012, Ballare et al 2012

> 2,000 genes Up-regulated> 2,000 genes Down-regulated

Regulation in 3D?



Experimental design





Are there TADs? how robust?





Are TADs homogeneous?





Do TADs respond differently to Pg treatment?







Do TADs respond differently to Pg treatment?



Pg induced fold change per TAD (6h)





Modeling 3D TADs





61 genomic regions containing 209 TADs covering 267Mb



How TADs respond structurally to Pg?







Model for TAD regulation





Acknowledgments



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