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

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Integrative Modeling Platform

http://www.integrativemodeling.org



From: Russel, D. et al. PLOS Biology 10, e1001244 (2012).







Complex genome organization

Takizawa, T., Meaburn, K. J. & Misteli, T. The meaning of gene positioning. Cell 135, 9–13 (2008).





Complex genome organization

Cavalli, G. & Misteli, T. Functional implications of genome topology. Nat Struct Mol Biol 20, 290–299 (2013).



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Resolution Gap

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





Hybrid Method

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

Experiments



Computation



Structure determination by satisfaction of spatial restraints



Biomolecular structure determination 2D-NOESY data



Chromosome structure determination 3C-based data









TADbit previous applications...

Baù, D. et al. Nat Struct Mol Biol (2011). Umbarger, M. A. et al. Mol Cell (2011).



Distinct structural transitions of chromatin topological domains correlate with coordinated hormone-induced gene regulation

François Le Dily et al. Genes and Development (2014)









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)



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Modeling 3D TADs



61 genomic regions containing 209 TADs covering 267Mb





How TADs respond structurally to Pg?







How TADs respond structurally to Pg?









Model for TAD regulation





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