

Global Transcriptional Optimization

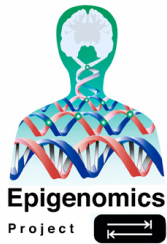
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Epigenomics Project

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ECSB II, 31 March 2009



Control of gene expression

How are genes turned on and off with such delicate and adaptive precision?

How can many of them switch in such a concerted manner and in so little time?

Maaløe et al., 1957



Diffusion, co-localization & genome architecture

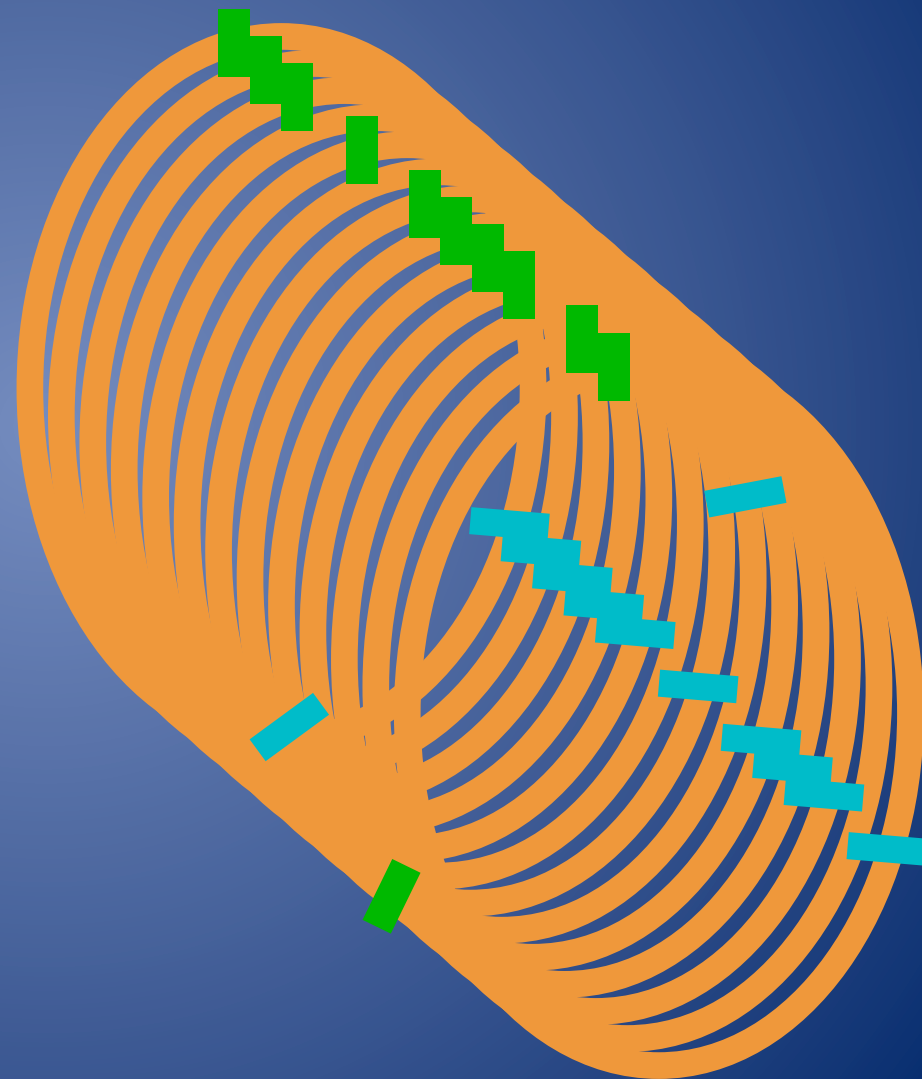
- 1) Diffusion limits the efficacy of biochemical networks, and that generates spatial localization;
- 2) Genomic organisation optimizes spatial localization of biochemical networks, and that structures chromosomes;
- 3) One part of the genomic information is dedicated to chromosome structure.



The transcription-based solenoidal model of chromosomes

1. Co-regulated genes tend to position periodically along the chromosome.
2. *This distribution is consistent with a solenoidal organization of chromosomes, that results in spatial proximity of the interacting partners.*
3. This spatial proximity enhances the rate kinetics, thus contributing to overall transcription efficiency.

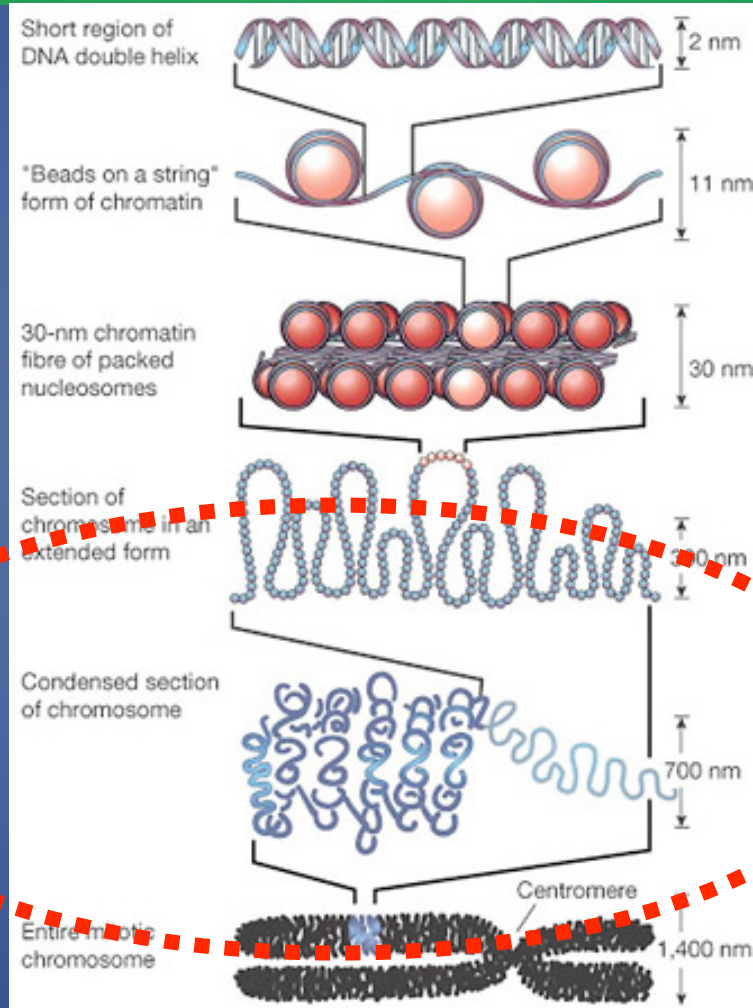
Kepes et al., 2003



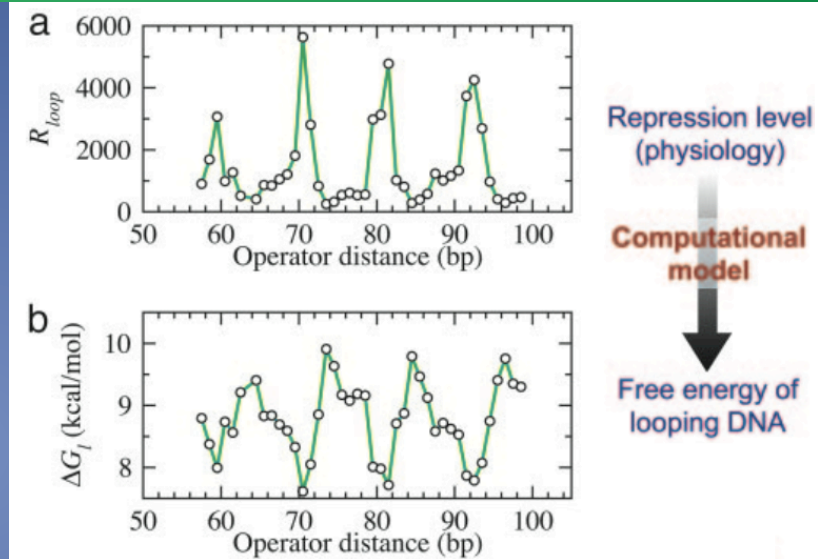
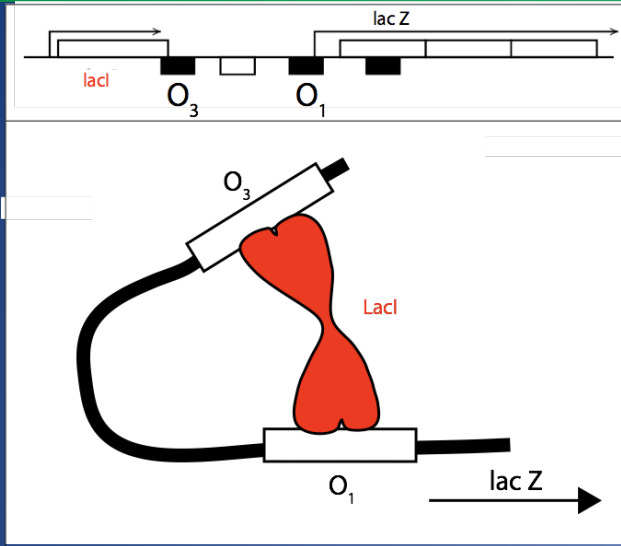


Epigenomics
Project

Scale



Spatial proximity enhances rate kinetics



The case of the lactose repressor:

70-fold optimization of transcriptional regulation

A DNA loop induced by

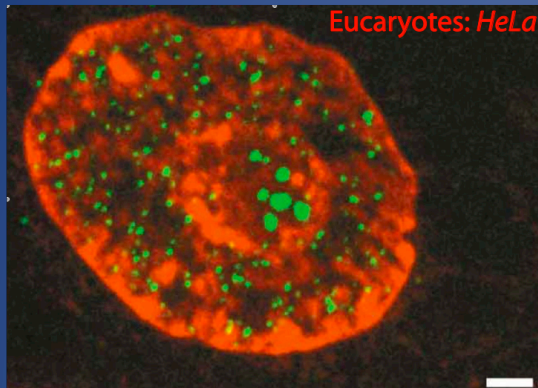
- bivalency of the repressor and
- the presence of 2 binding sites 'O'.

Müller-Hill, 1999

Vilar & Leibler, 2003



Transcriptional regulation & chromosome structure



Cook, Nature Genetics, 2002

2 μ m

Similar active genes cluster in specialized transcription factories

Meng Xu and Peter R. Cook

J. Cell Biology, 2008



Cabrera & Jin, Mol. Microbiol., 2003

1 μ m

Two types of localization of the DNA-binding proteins within the *Escherichia coli* nucleoid

Talukder Ali Azam^{1,2}, Sota Hiraga³ and Akira Ishihama^{1,*} Genes to Cells, 2000

Spatial organization of DNA chains induced by gene co-localization

- Simulations Monte-Carlo off-lattice d'un modèle de polymère discrétisé (modèle de Kratky-Porod)
- L'énergie de courbure spécifie la longueur de persistance l_p
- Auto-évitement du polymère

$l_p = 50 \text{ nm}$, $R = 1 \text{ nm}$ (équivalent ADN nu)

Distance entre site de liaisons = l_p

Energie de liaison = $-4 k_B T$ avec un rayon d'action = 4 nm

Longueur total du chromosome $L = 16 l_p$

ADN nu : $l_p \approx 50 \text{ nm} \Rightarrow L \approx 800 \text{ nm}$ soit $\sim 2.5 \text{ kbps}$

Fibre de chromatine 30 nm : $l_p \approx 50\text{--}200 \text{ nm} \Rightarrow L \approx 0.8\text{--}3.2 \mu\text{m}$ soit $\sim 7.5\text{--}30 \text{ kbps}$ (150 bps/nm)

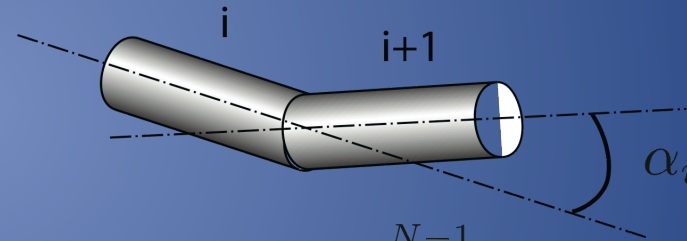
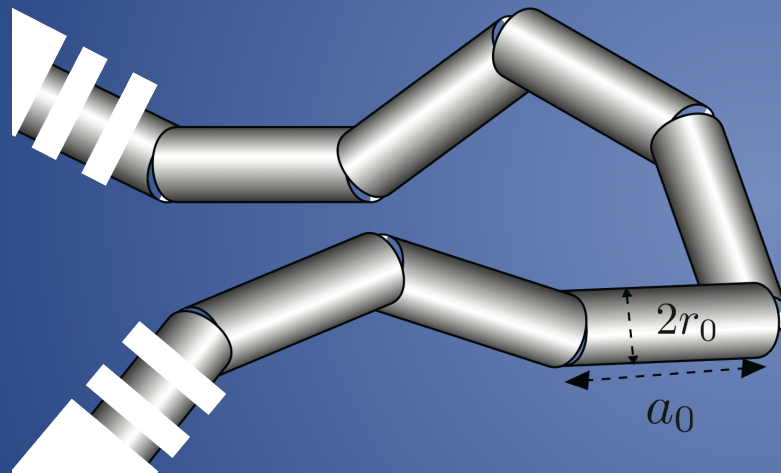
Temps de formation du solénoïde : \sim secondes



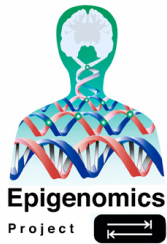
Spatial organization of DNA induced by gene co-localization

Polymer model off-lattice

Discrete implementation of a self-avoiding semi-flexible polymer
Monte Carlo / Metropolis



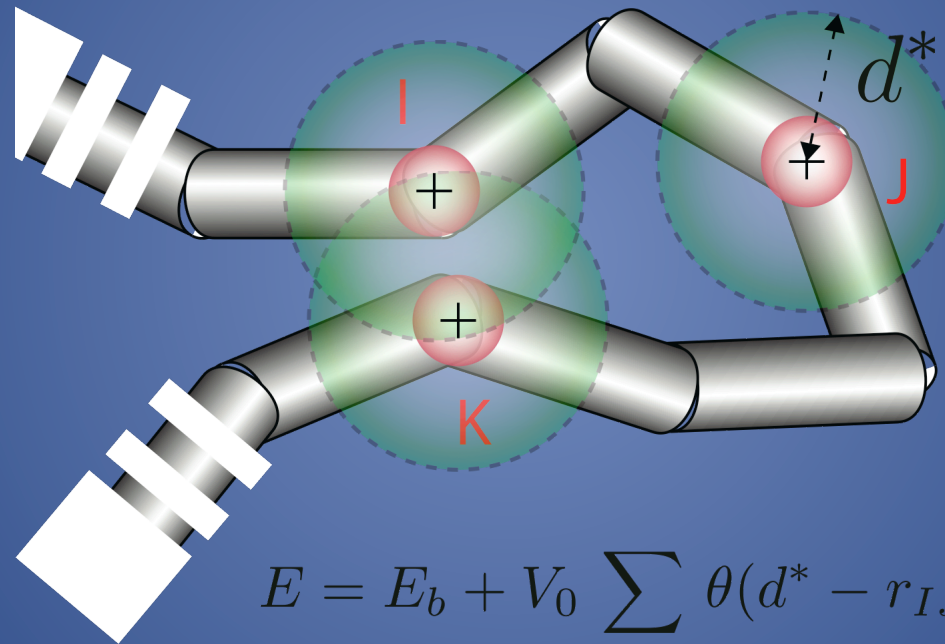
$$E_b = \frac{K}{2} \sum_{i=0}^{N-1} \alpha_i^2$$



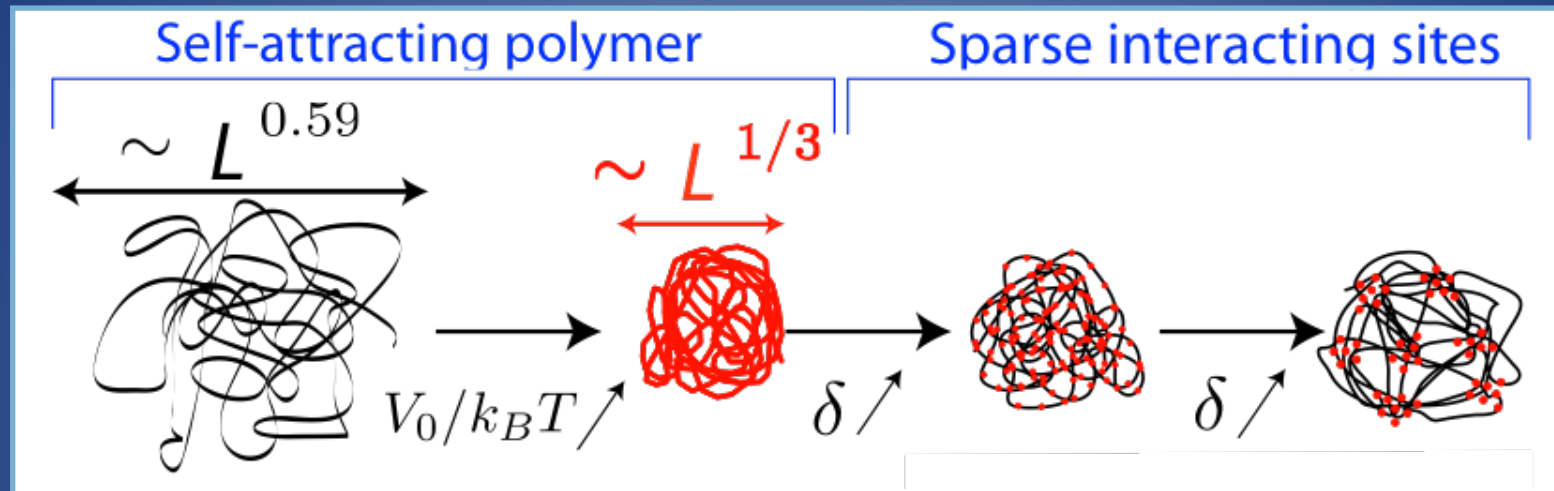
Spatial organization of DNA induced by gene co-localization

With localized interaction sites

Mimicks bridging of two DNA sites by one bivalent transcription factor



Transcription factories: micro-phase transition



$$\delta = \frac{\text{Distance between co-regulated genes}}{\text{Polymer persistence length}}$$

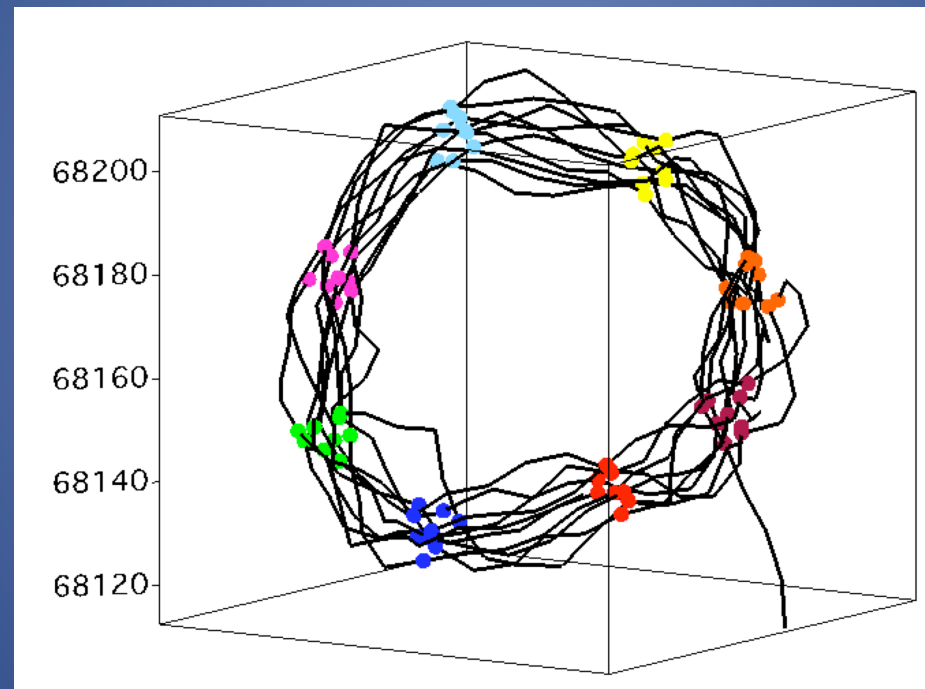
$$V_0/k_B T \sim \frac{\text{TF binding energies}}{\text{Thermal energy}}$$



Multiplicity of Transcription Factors favors solenoidal-type gene co-localization

Include several types of interacting sites, denoted by different colors

i.e. several transcription factors, each with its own set of target genes

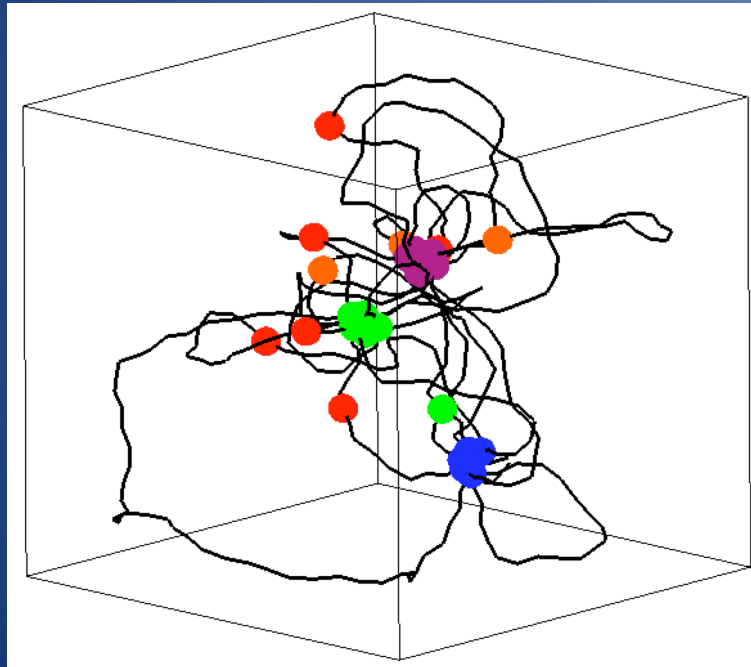




Gene position regularities are crucial for their co-localization

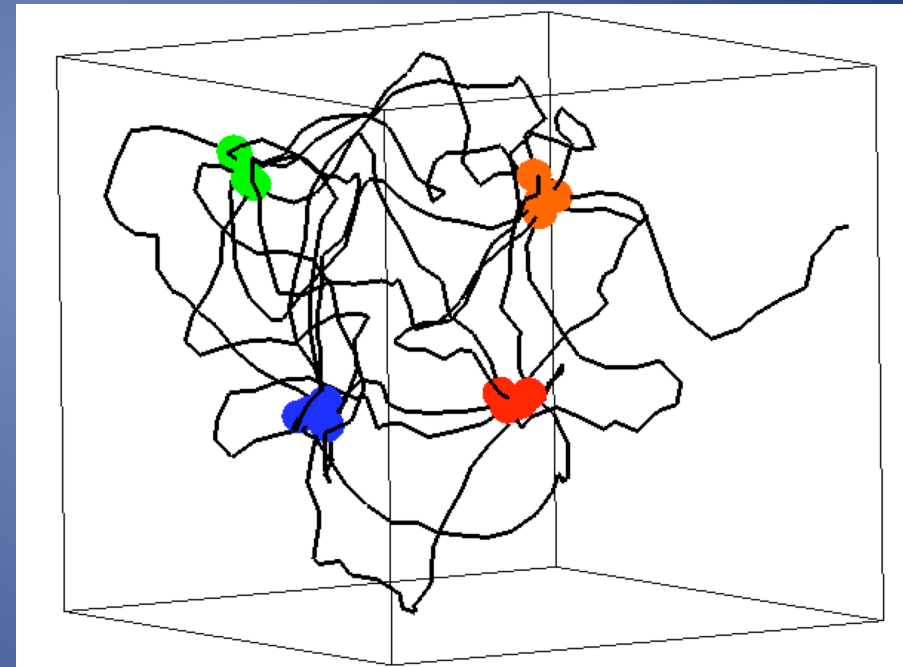
Random site positioning

Site co-localization is partial
No collective optimization



Periodic site positioning

Site co-localization is efficient
Good collective optimization

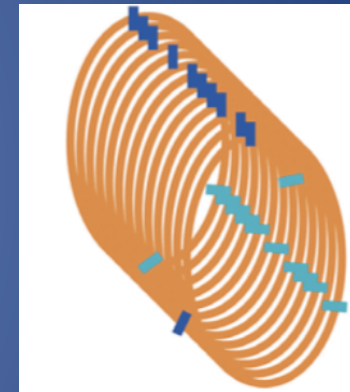




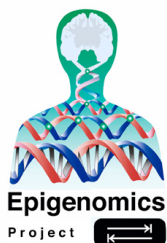
Detection of site position periodicities

* Several observations

- * Transcription regulation in bacteria (Képès, 2003; Carpentier et al., 2005; Allen et al., 2006)
- * Transcription regulation in yeast (Képès, 2003)
- * Phylogenetically conserved genes (Wright et al., 2007)



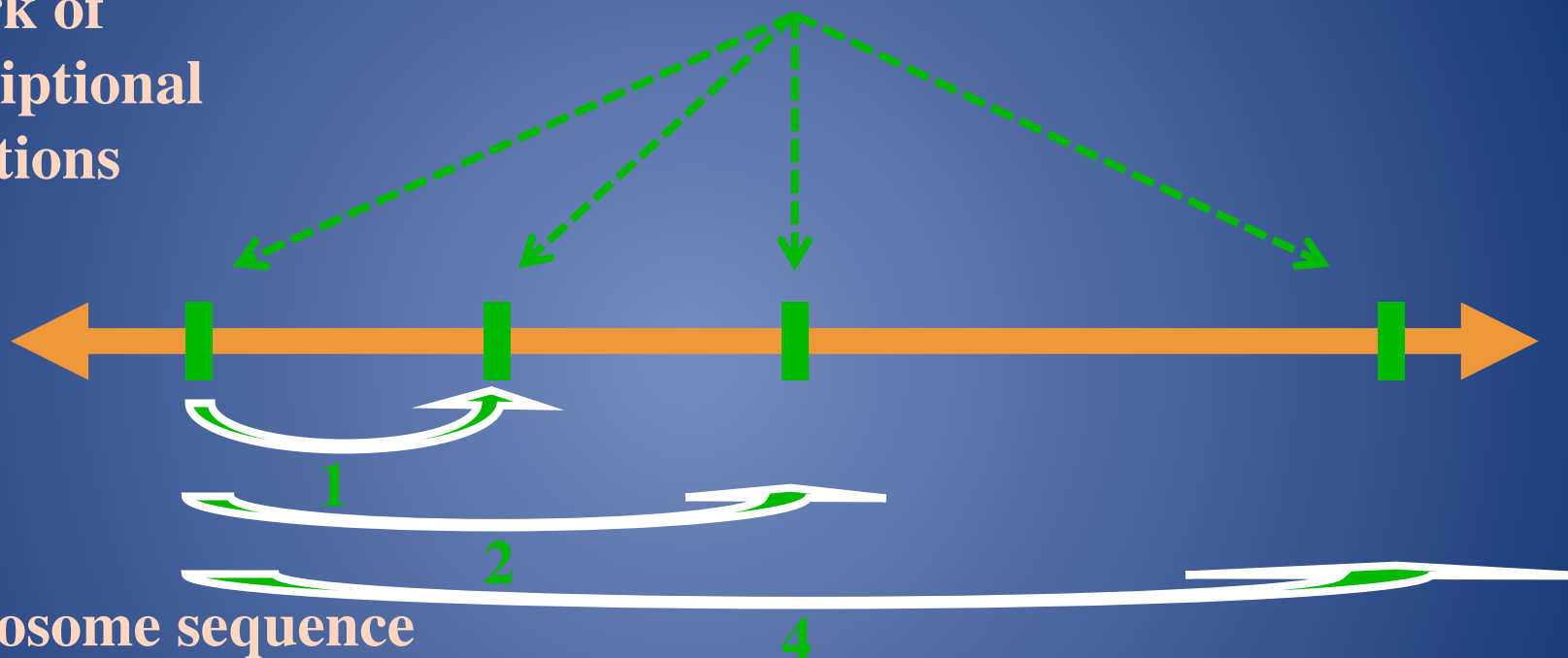
Képès, ComPlexUs, 2003



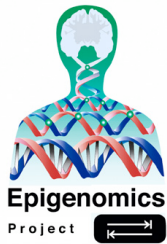
Genomic and transcriptomic data

A given Transcription Factor

Network of transcriptional interactions



Chromosome sequence
-> Gene positions



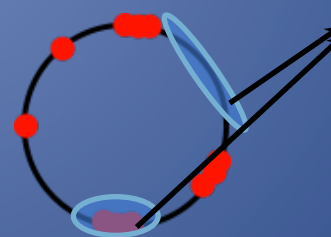
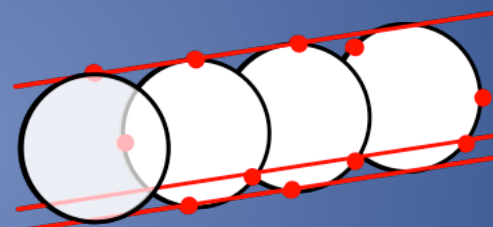
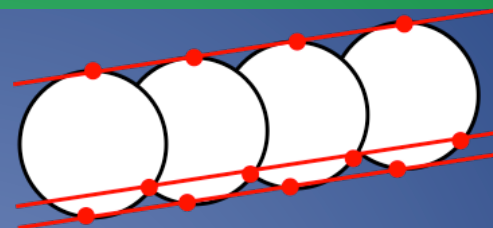
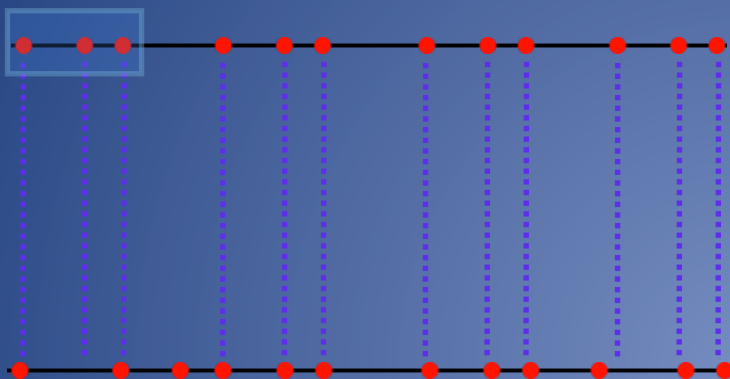
Detection of periodicities: the problem

- * Sparse and noisy data in essence
- * Complex environment
- Wrong data ...



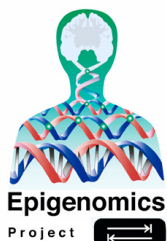
Detection of periodicities: a solution

* Solenoidal coordinates

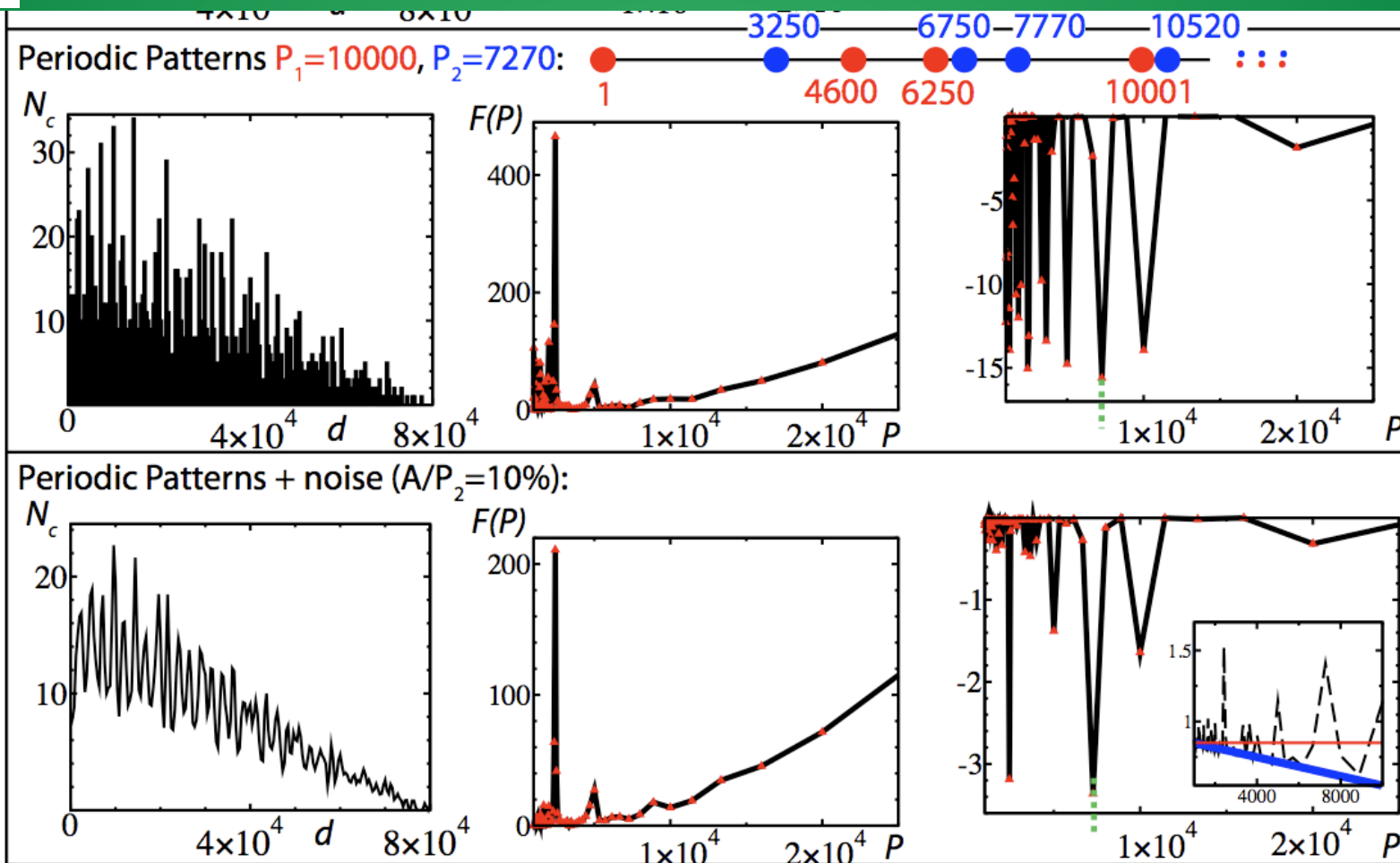


Score

$$- \sum_{x_{ij}} \log(\text{p-value}(x_{ij}))$$



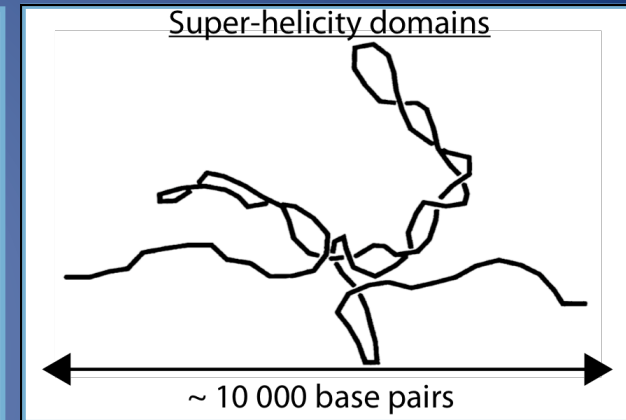
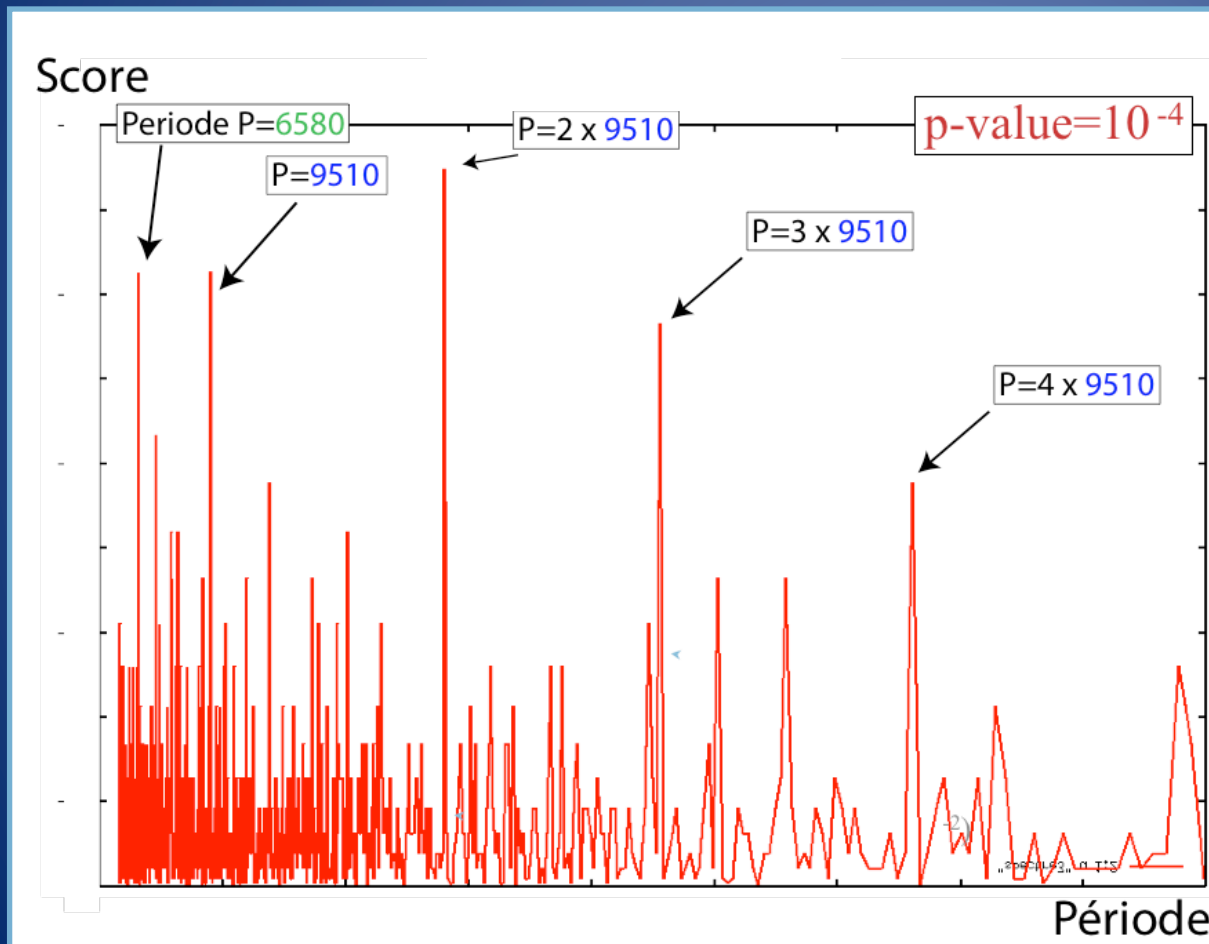
Comparison to Fourier analysis





Genome organization: transcriptional regulation

* Periodicity of CRP binding sites in *E. coli*





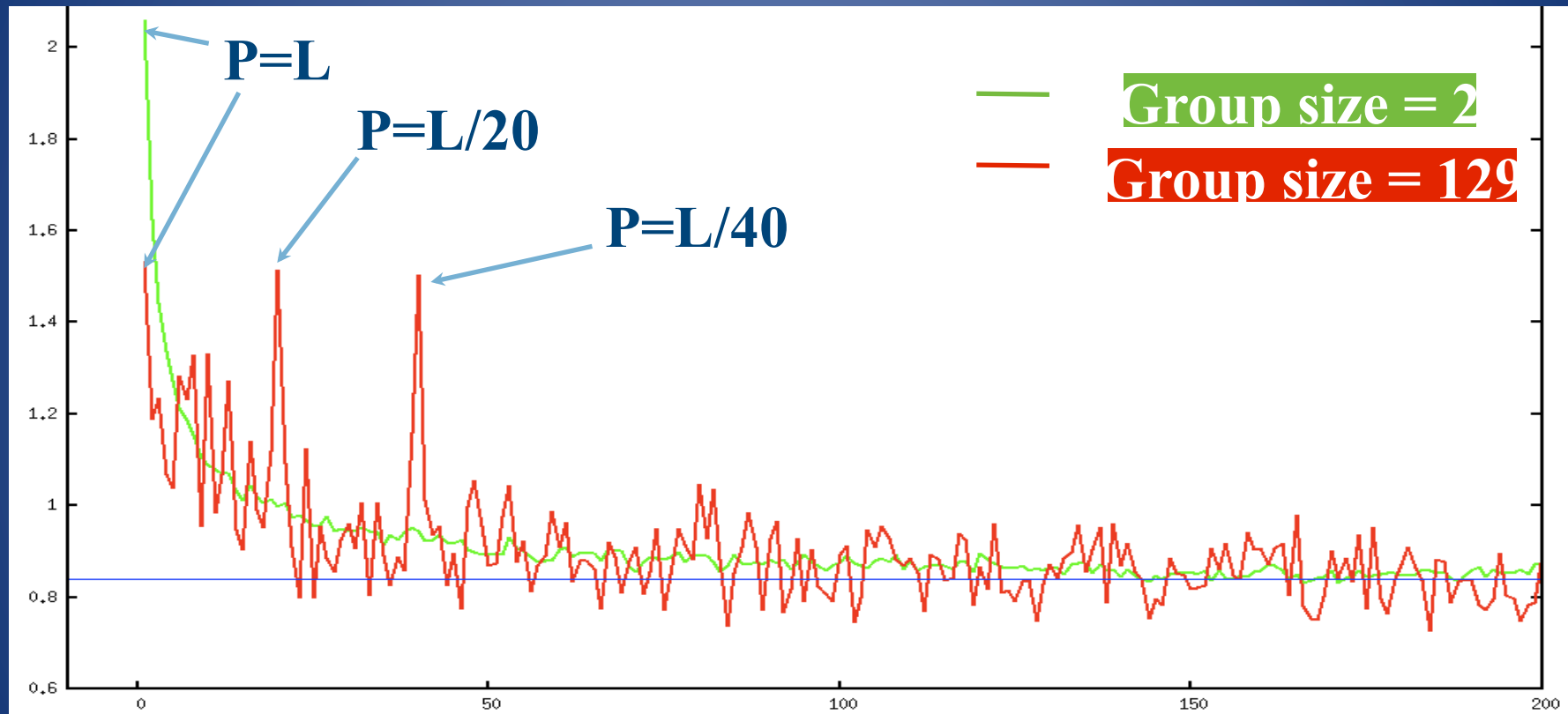
Conclusions

- * Great deal of order in genomes
 - * Small-scale data analysis
- * Genome order is related to chromosome structuring
 - * Polymer physics



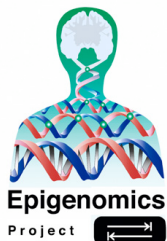
Solenoidal approach

Score



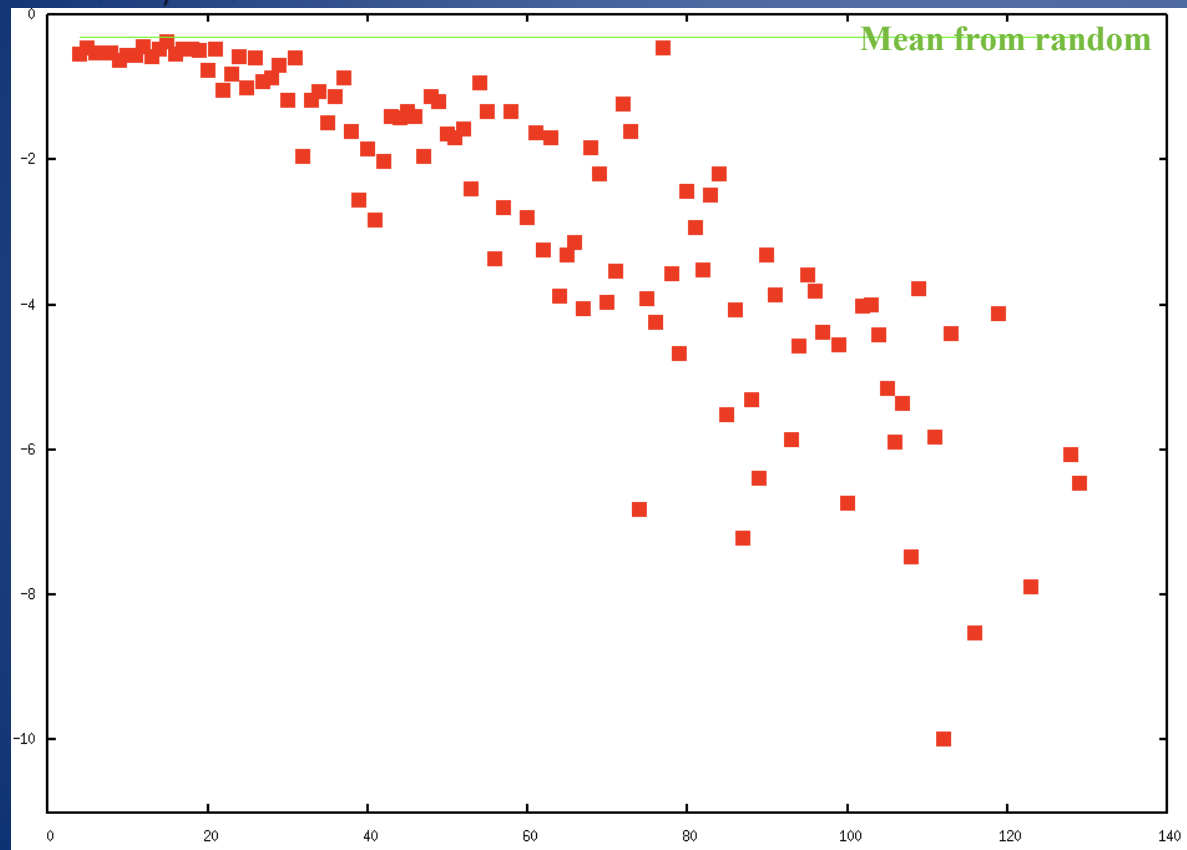
L=Genome length

L/Period



1D - 3D co-localization transition

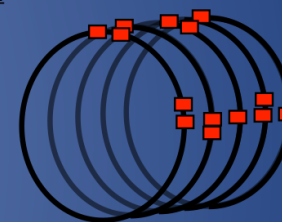
$\log(p_L/40)$



1D Co-localization



3D Co-localization



Képès, ComPlexUs, 2003

Group size



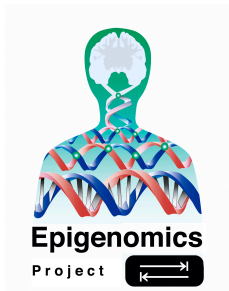
Conclusions / Questions

- **Co-regulated genes tend to position periodically**
- **Periodical positioning, together with variety of binding proteins, strongly favor**
 - **Gene clustering**
 - **Solenoidal 3-D organization of chromosomes**
- **Gene clustering optimizes transcriptional regulation** (Müller-Hill, Leibler ...)
- **Transcription occurs in focal points** (Misteli, Cook, Cremer ...)
- **What are the biotechnological implications for such studies?**
- **Are we on the verge of epigenetic engineering, following genetic engineering?**



Relevant Team Publications

1. Guelzim, N., Bottani, S., Bourgine, P. & Képès, F. Topological and causal structure of the yeast transcriptional regulatory network. *Nature Genet.* 31, 60-63 (2002).
2. Képès, F. Periodic epi-organization of the yeast genome revealed by the distribution of promoter sites. *J. Mol. Biol.* 329, 859-865 (2003).
3. Képès, F. & Vaillant, C. Transcription-based solenoidal model of chromosomes. *ComPlexUs 1*, 171-180 (2003).
4. Képès, F. Periodic transcriptional organization of the *E. coli* genome. *J. Mol. Biol.* 340, 957-964 (2004).
5. Mercier, G., Berthault, N., Touleimat, N., Képès, F., Fourel, G., Gilson, E. and Dutreix, M. A haploid-specific transcriptional response to irradiation in *Saccharomyces cerevisiae*. *Nucleic Acids Res.* 33, 6635-6643 (2005).
6. Matte-Tailliez, O., Hérisson, J., Ferey, N., Magneau, O., Gros, P. E., Képès, F. and Gherbi, R. Yeast Naked DNA Spatial Organization Predisposes to Transcriptional Regulation. *Lecture Notes in Computer Science 3980*, pp. 222 - 231. In "Computational Science and Its Applications - ICCSA 2006: International Conference, Glasgow, UK, May 8-11, 2006. Proceedings, Part I (Editors: Marina Gavrilova, Osvaldo Gervasi, Vipin Kumar, C. J. Kenneth Tan, David Taniar, Antonio Laganà, Youngsong Mun, Hyunseung Choo) (2006).
7. Banzhaf, W., Beslon, G., Christensen, S., Foster, J.A., Képès, F., Lefort, V., Miller, J.F., Radman, M. and Ramsden, J.J. From Artificial Evolution to Computational Evolution: a research agenda. *Nature Reviews Genetics* 7, 729-735 (2006).
8. Leclercq S, Képès F. Épigénomique et Morphodynamique. *Proceedings of "Déterminismes et complexités: de la physique à l'éthique (autour d'Henri Atlan)"* (eds. Bourgine, Chavalarias, Cohen-Boulakia), La Découverte, Paris; ISBN 978-2-7071-5090-5 (2008).



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