

# A Global Transcriptional Scheme in Microorganisms

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Epigenomics Project

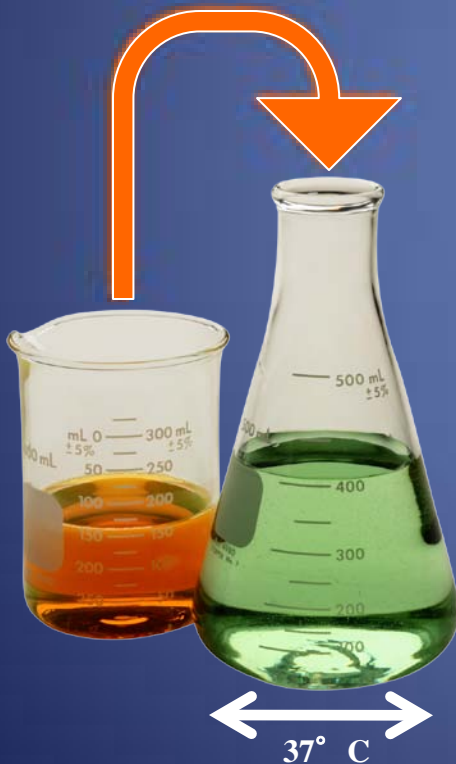
Genopole®, CNRS UPS3201, Université d'Évry, PRES UniverSud Paris

**Nottingham, March 19, 2010**

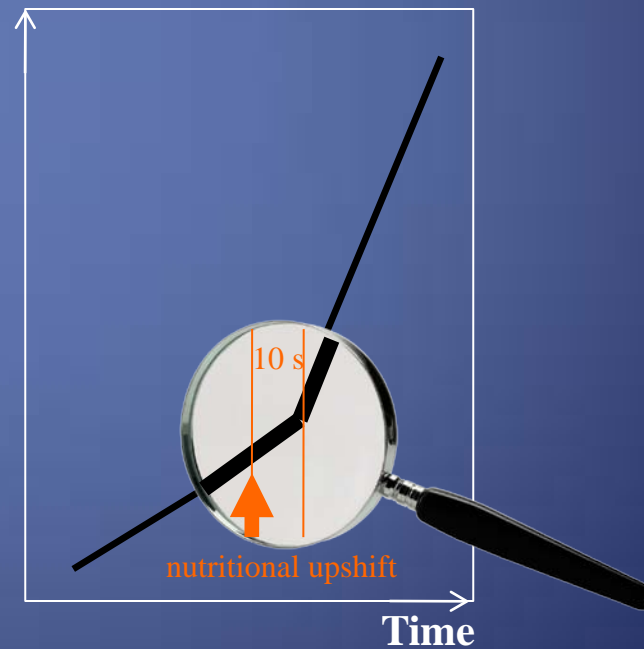
# Control of gene expression

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?



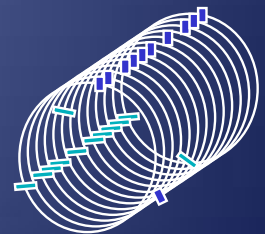
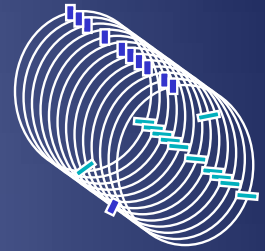
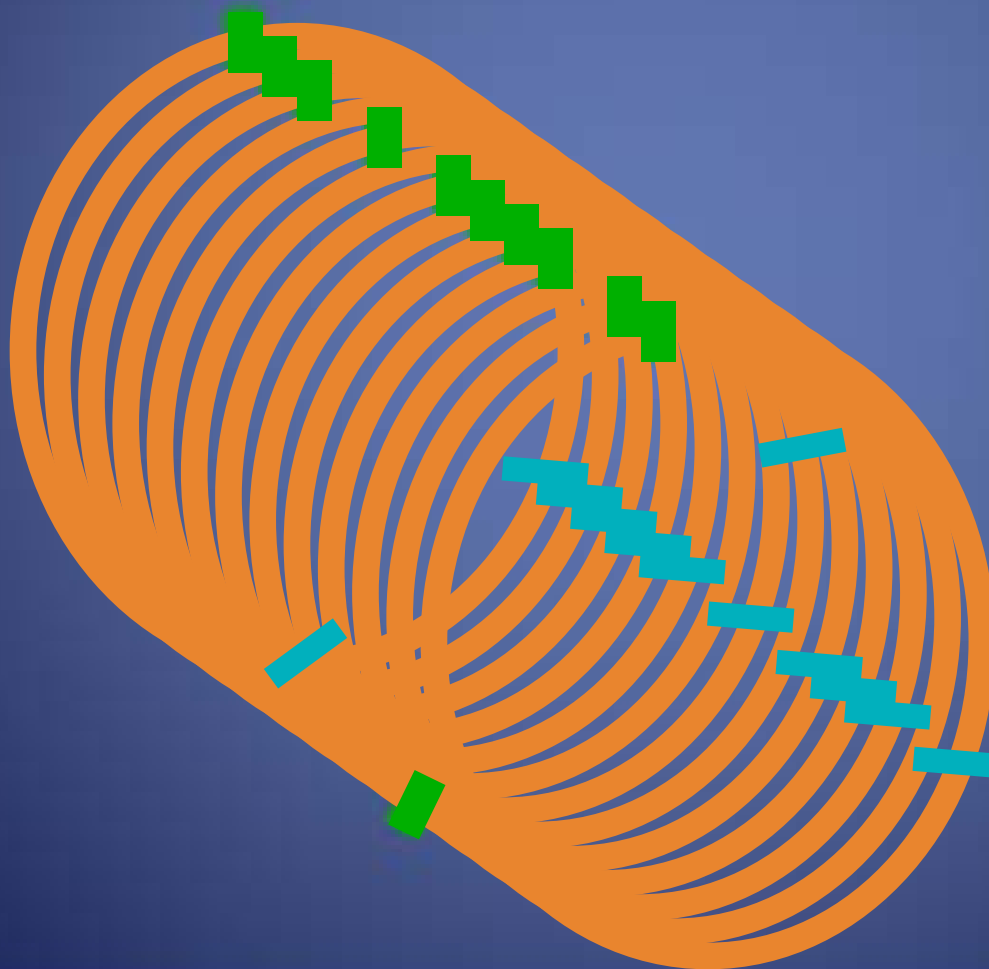
log Ribosome accumulation



*(Kjeldgaard, Mauløe, 1958)*

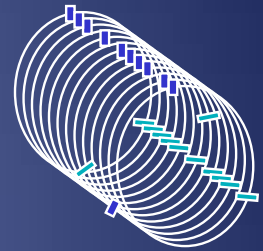
# The transcription-based solenoidal model of chromosomes

Is there a global transcriptional scheme in cells?



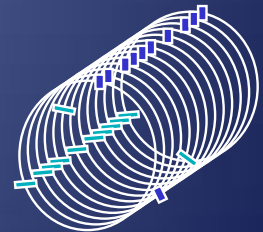
# The transcription-based solenoidal model of chromosomes

1. Transcription occurs in focal points
2. Transcription is sensitive to gene 1D position & 3D clustering
3. Co-regulated genes tend to position periodically
4. 1D periodicity strongly favors 3D clustering and solenoid
5. TF variety strongly favors 3D clustering and solenoid
6. Gene 3D clustering evolutionarily favors 1D periodicity

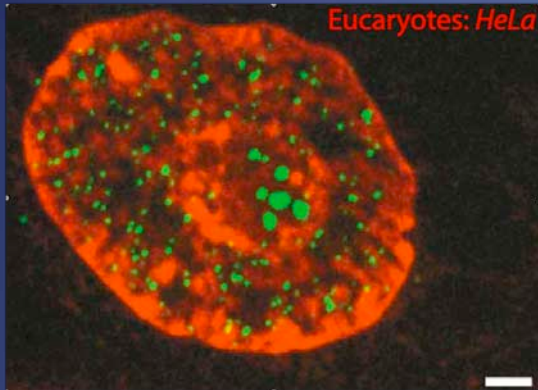


## *One Project*

1. *Rational genome-wide regulatory engineering*



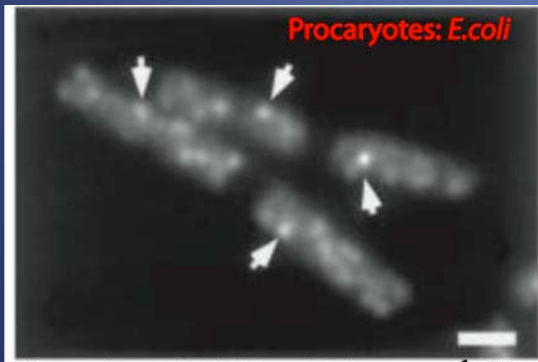
# 1 - Transcription occurs in focal points



Cook, Nature Genetics, 2002 2  $\mu$ m

Similar active genes cluster in specialized transcription factories

Meng Xu and Peter R. Cook J. Cell Biology, 2008



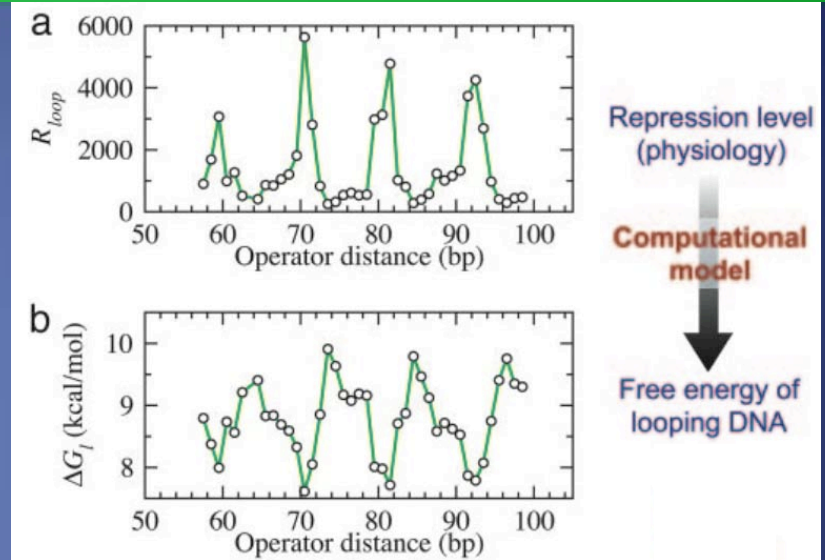
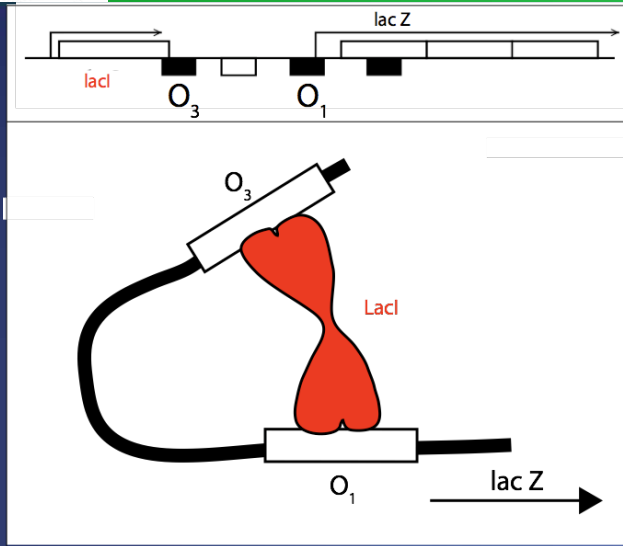
Cabrera & Jin, Mol. Microbiol., 2003 1  $\mu$ m

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

Talukder Ali Azam<sup>1,2</sup>, Sota Hiraga<sup>3</sup> and Akira Ishihama<sup>1,\*</sup> Genes to Cells, 2000

(Cook, Cremer, Errington, Gasser, Hiraga, Misteli ...)

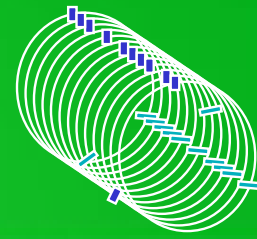
# 2 - Transcription is sensitive to gene 1D position & 3D clustering



- TF = lactose repressor:  
**70-fold optimization of transcriptional regulation**  
 A DNA loop induced by
- bivalency of TF and
  - bivalency of TFBS 'O'.

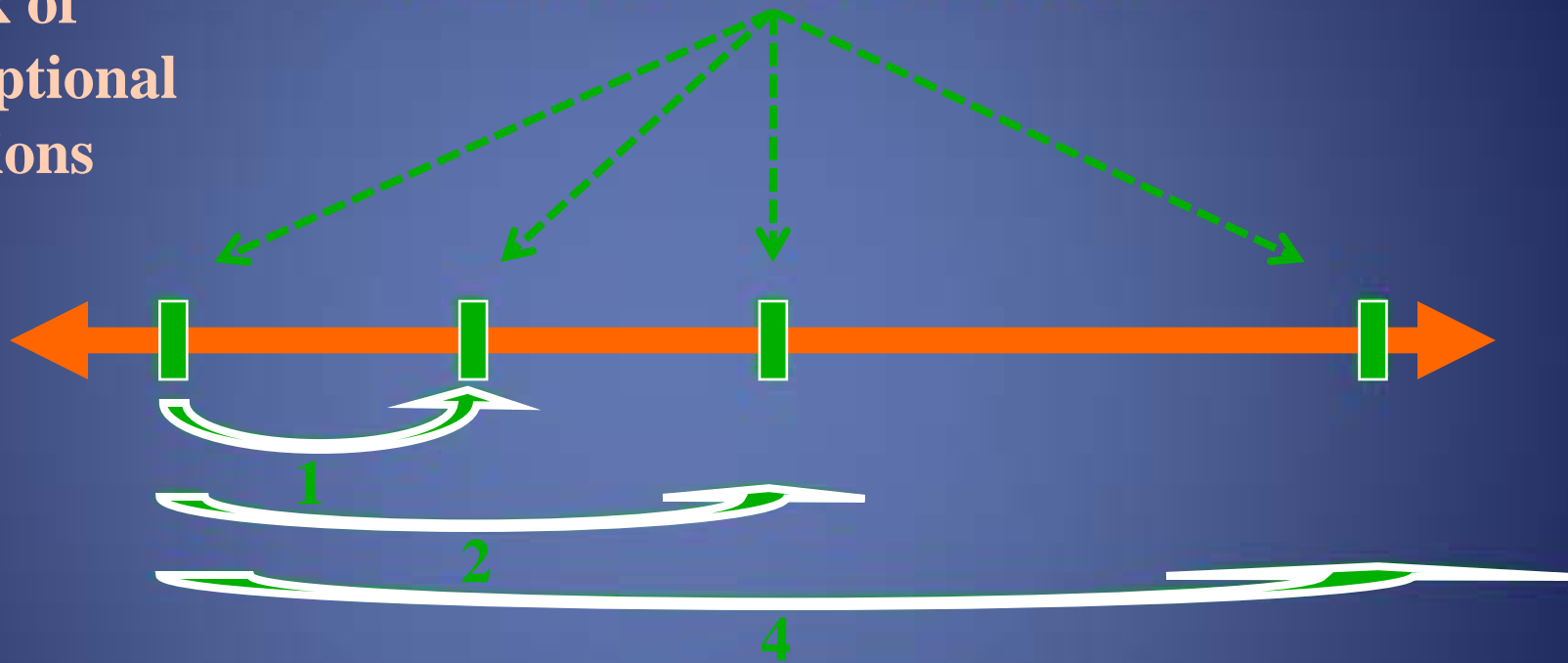
(Müller-Hill, 1999 ;  
Vilar & Leibler, 2003)

# 3 - Co-regulated genes tend to position periodically



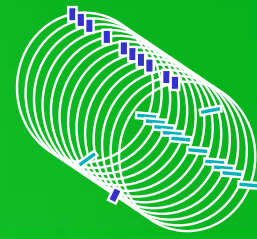
Network of transcriptional interactions

A given Transcription Factor

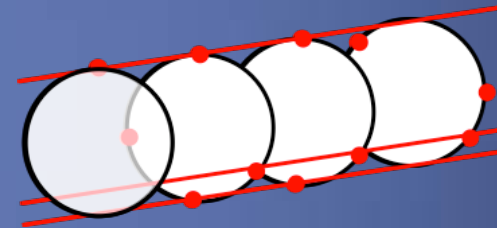
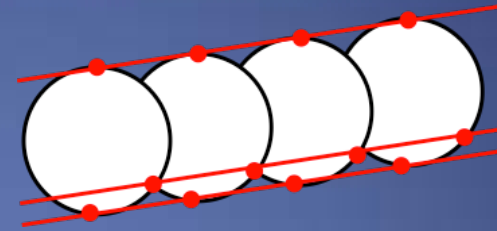
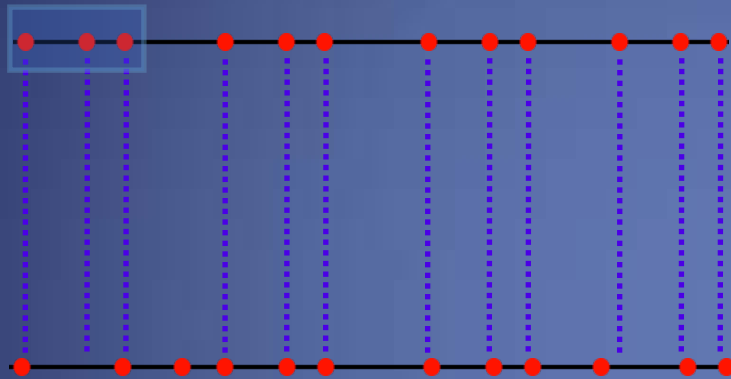


Chromosome sequence

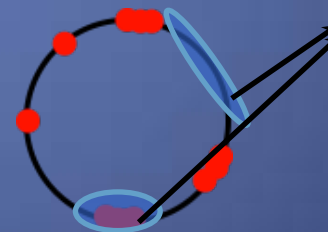
# Co-regulated genes tend to position periodically



## Solenoidal coordinates



Data are:  
sparse  
noisy  
wrong

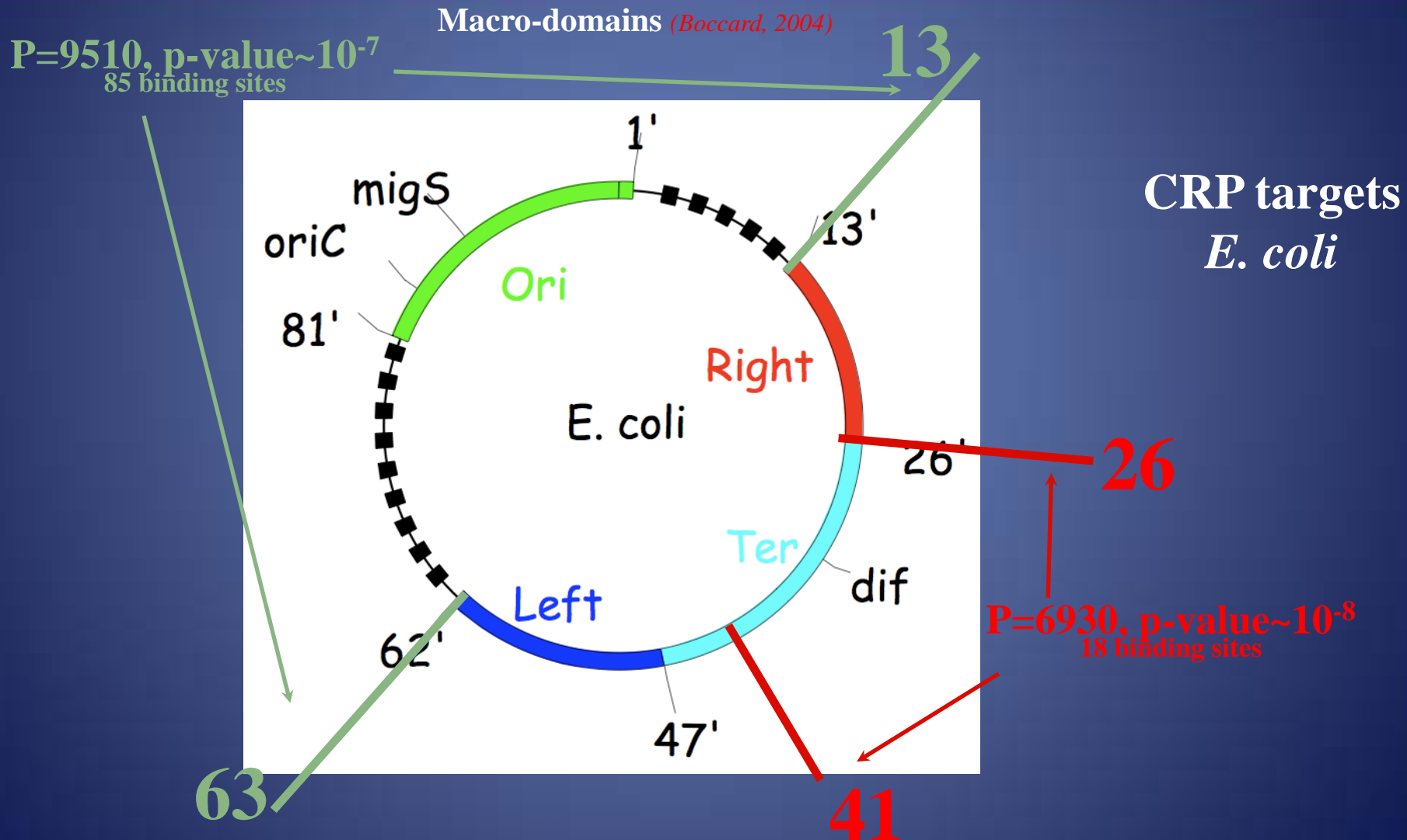
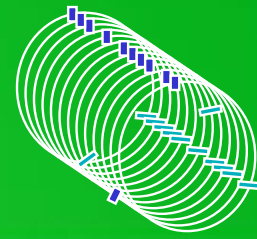


Score

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



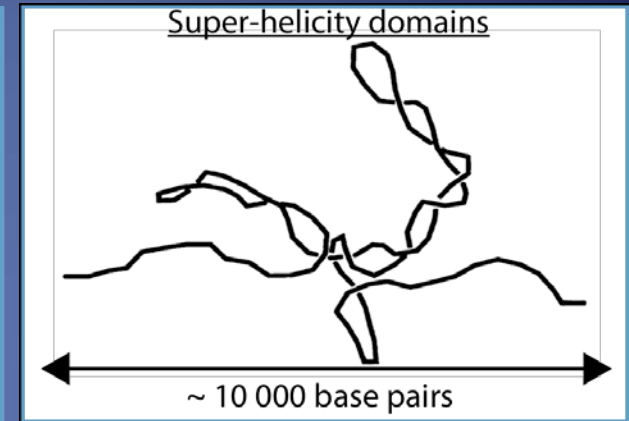
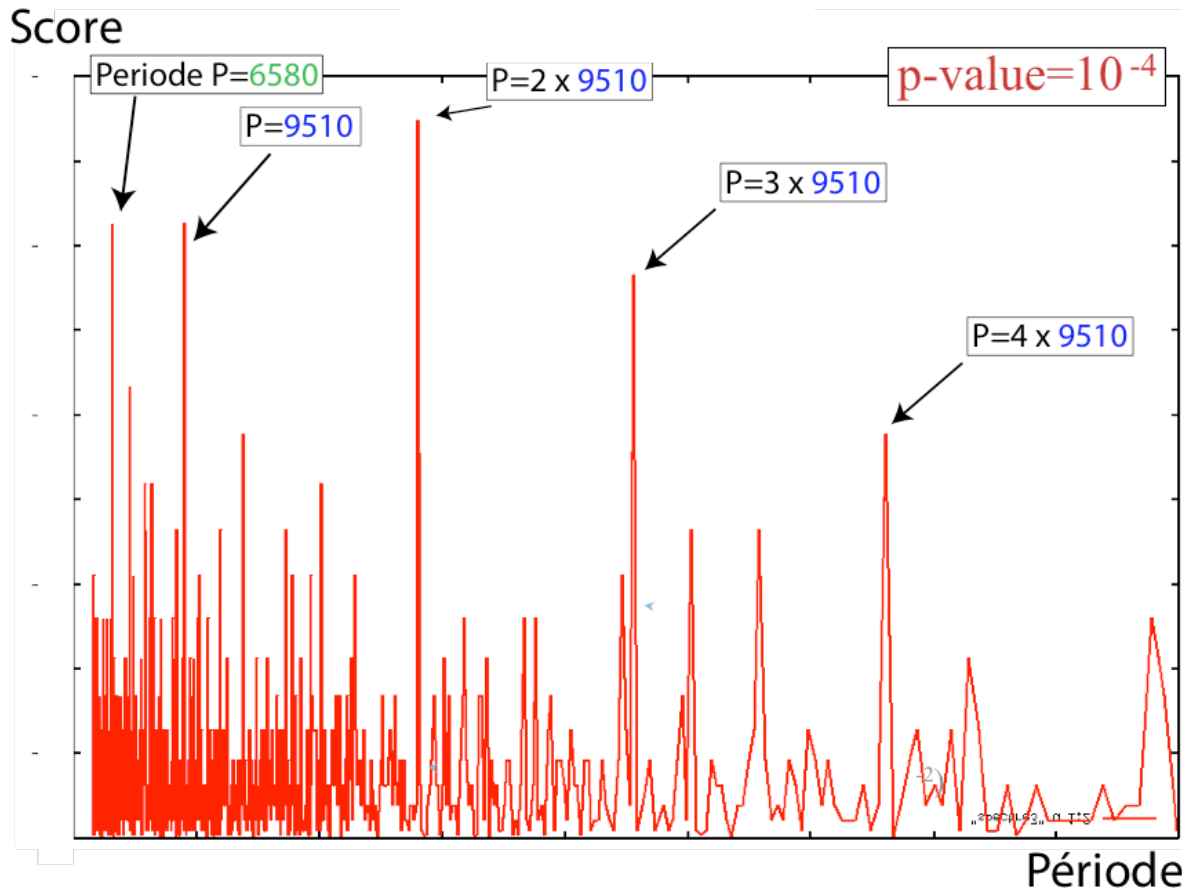
# Co-regulated genes tend to position periodically





# Genome organization: transcriptional regulation

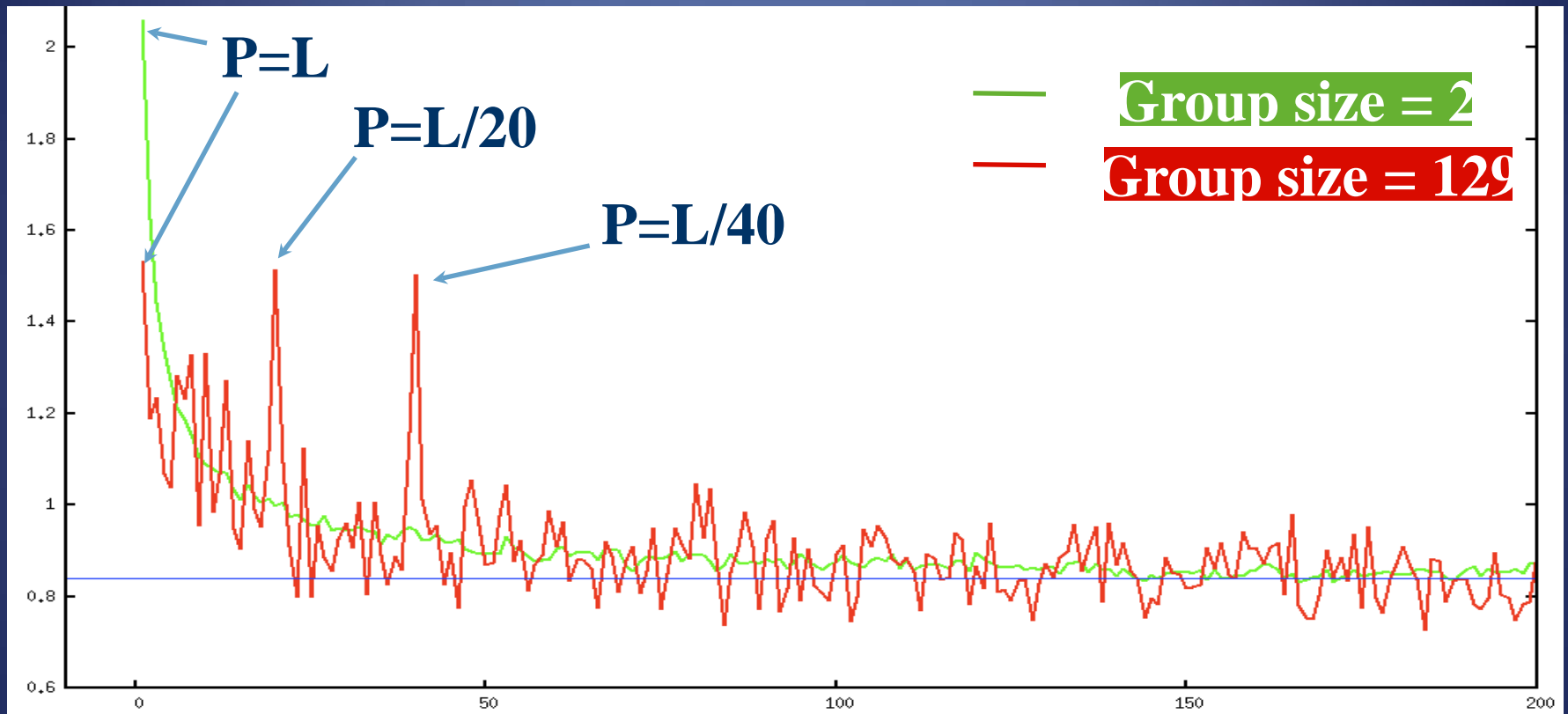
## \* Periodicity of CRP binding sites in *E. coli*





# Solenoidal approach

Score



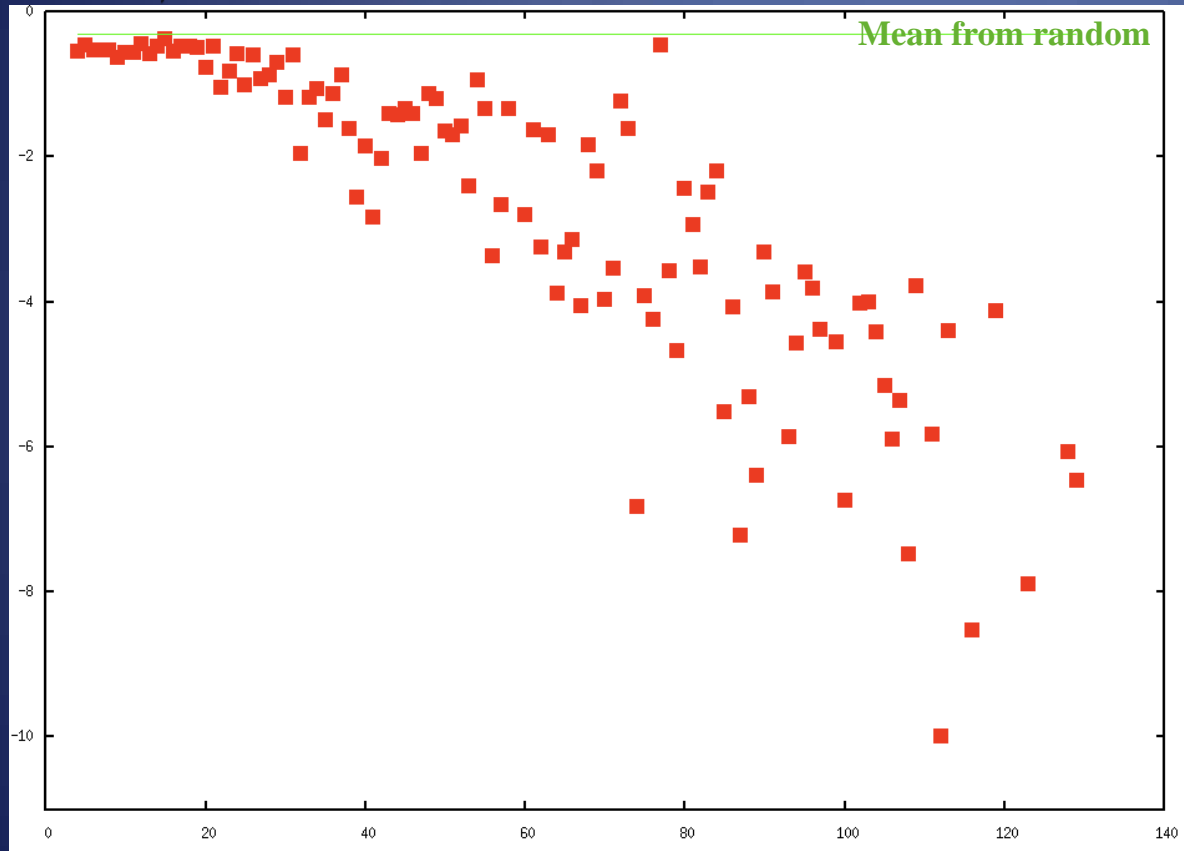
L=Genome length

L/Period



# 1D / 3D co-localization transition

$\log(p_L/40)$

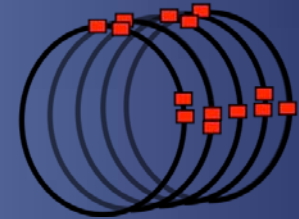


Group size

1D Co-localization

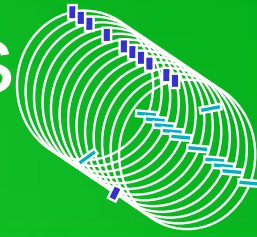


3D Co-localization



*(Képès, ComPlexUs, 2003)*

# 4 - 1D periodicity strongly favors 3D clustering and solenoid



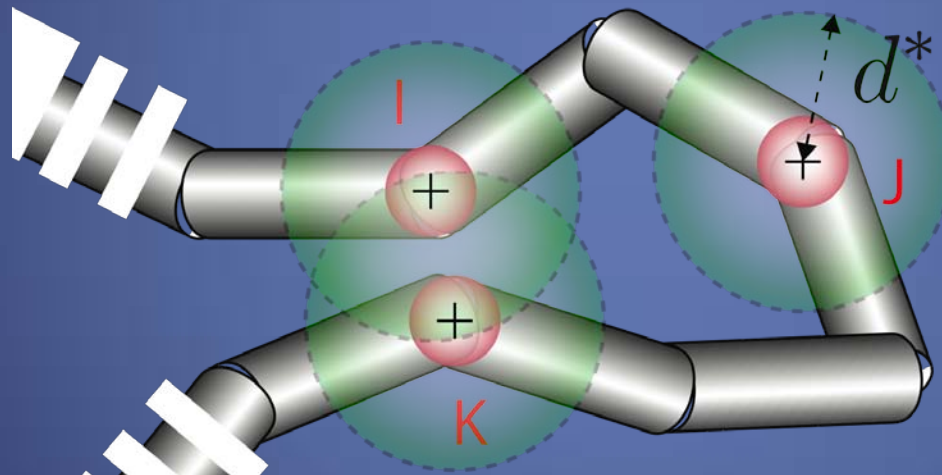
## Polymer model off-lattice

Discrete implementation of a self-avoiding semi-flexible polymer

Monte Carlo / Metropolis

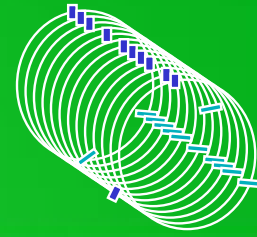
## With localized interaction sites

Mimicks bridging of two DNA sites by one bivalent transcription factor

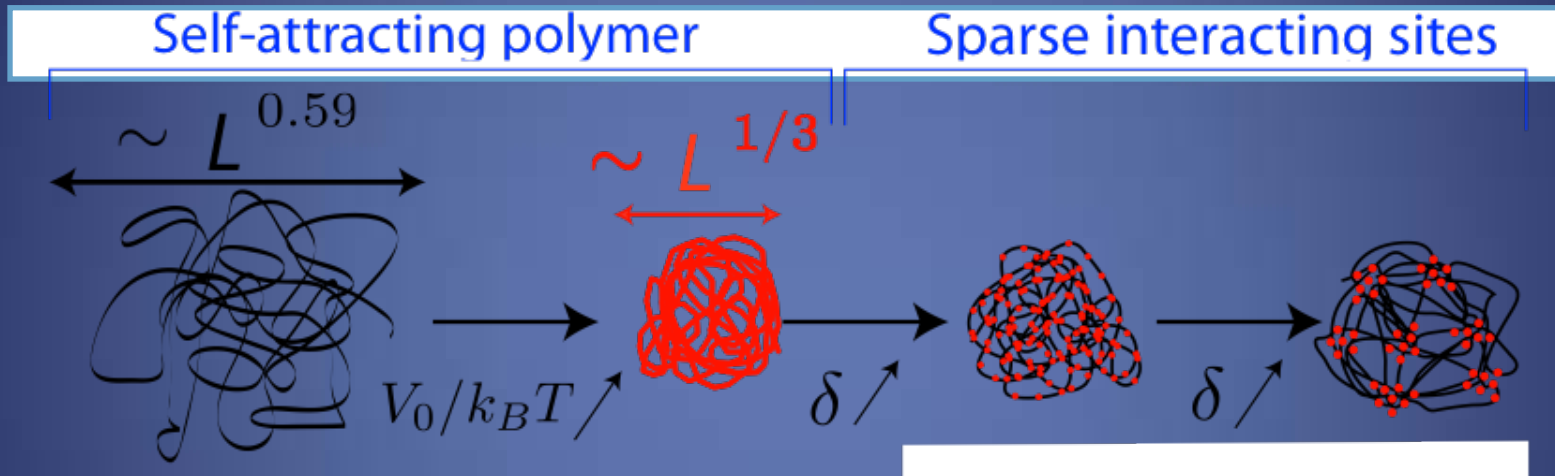


$$E = E_b + V_0 \sum_{\langle I, J \rangle} \theta(d^* - r_{IJ})$$

# 1D periodicity strongly favors 3D clustering and solenoid



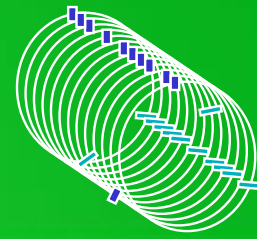
## A micro-phase transition



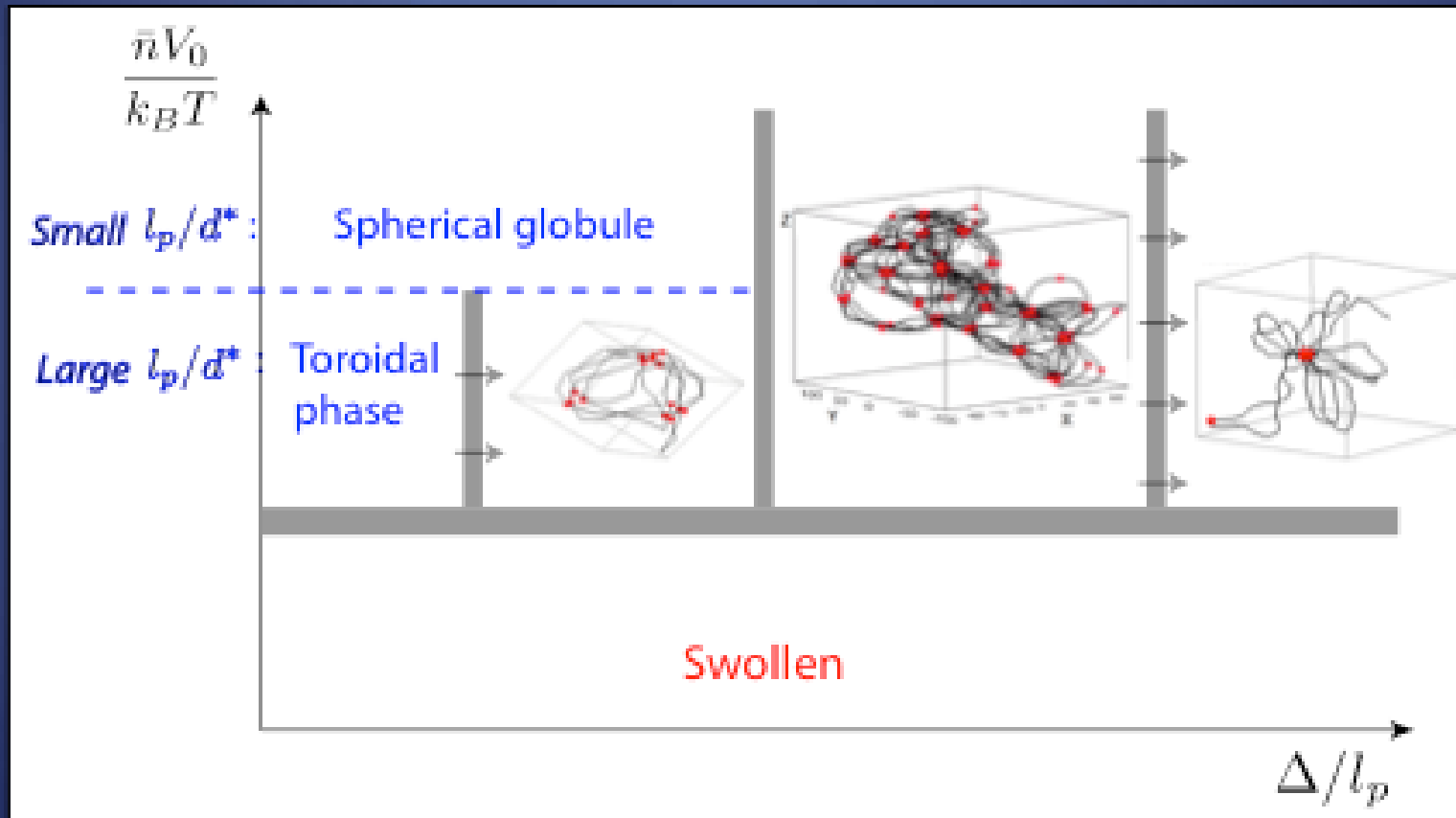
$$\delta = \frac{\text{Distance between co-regulated genes}}{\text{Polymer persistence length}}$$

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

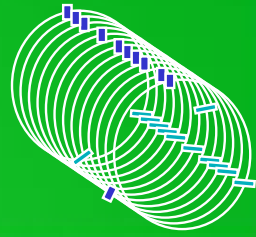
# 1D periodicity strongly favors 3D clustering and solenoid



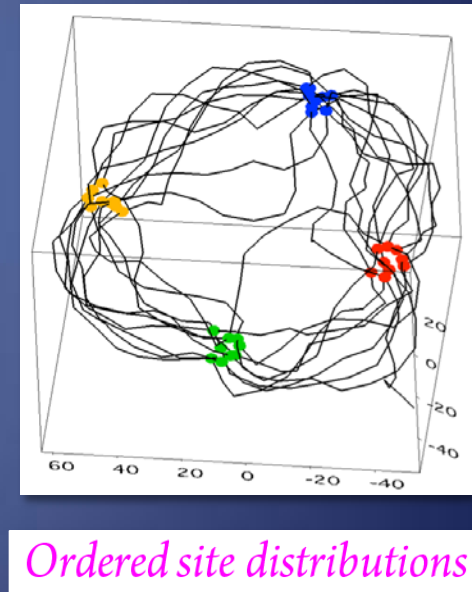
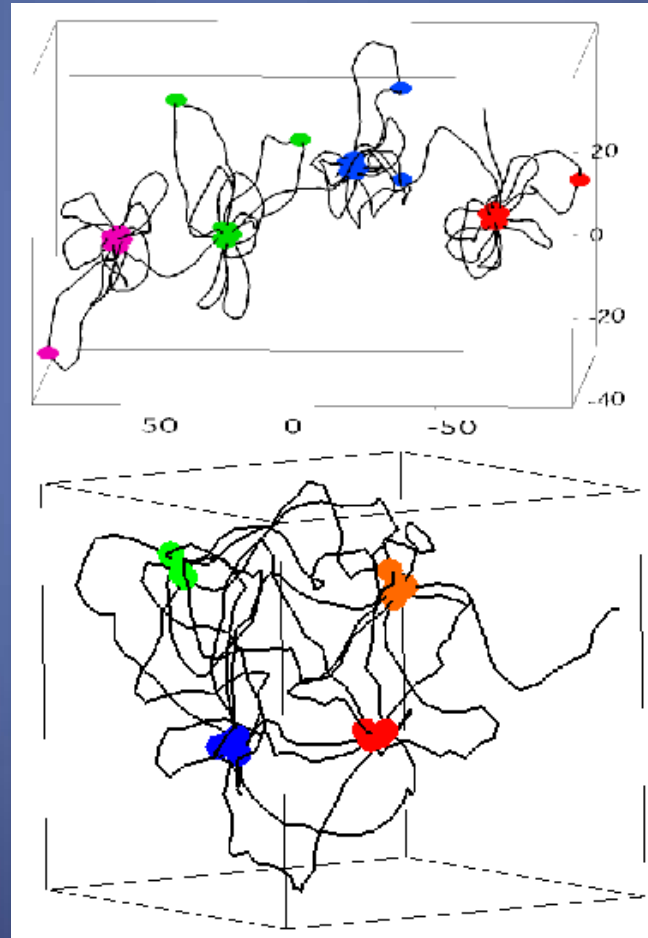
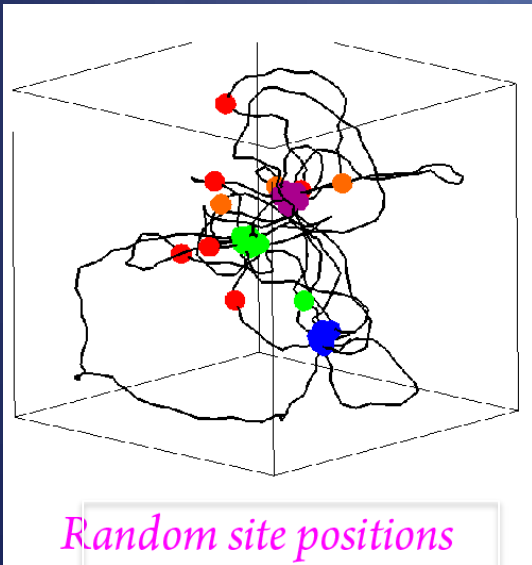
## Topological ordering of DNA around the foci



# 1D periodicity strongly favors 3D clustering and solenoid

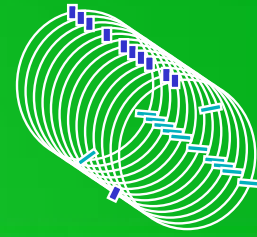


- Gene organization is crucial for a **robust** and **efficient** transcriptional regulation  
→ i.e. for efficient and robust transcriptional regulation



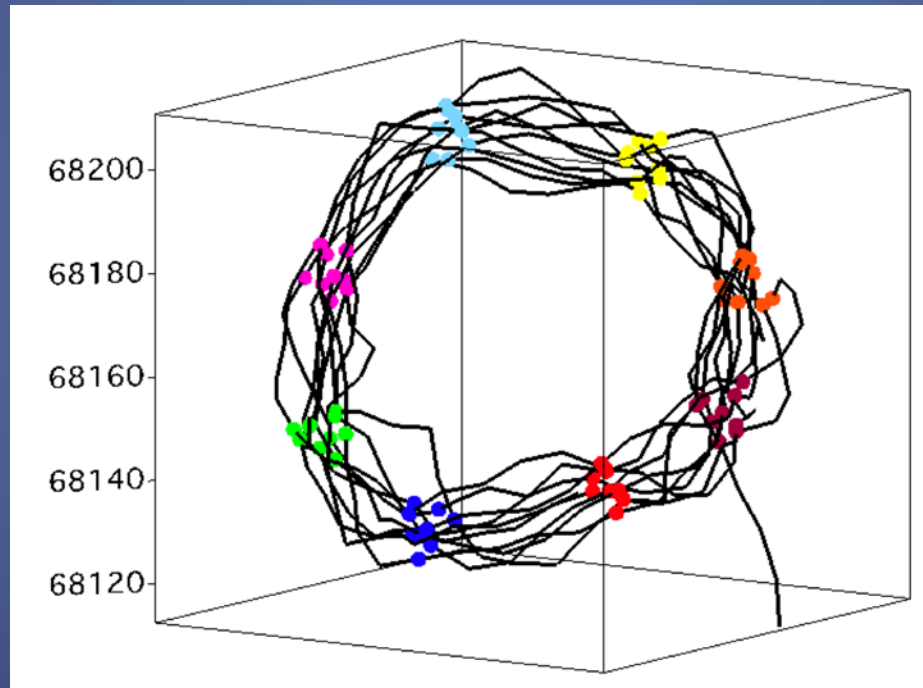


# 5 - TF variety strongly favors 3D clustering and solenoid

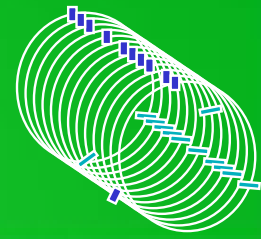


Include several types of interacting sites, denoted by different colors

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

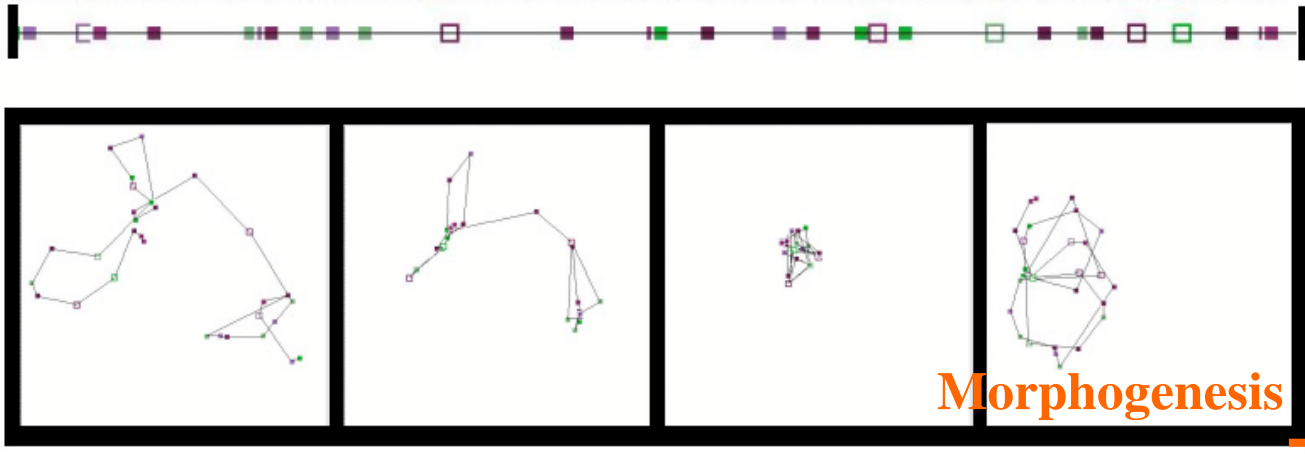


# 6 - Gene 3D clustering evolutionarily favors periodical



1D

Before evolution : random gene positions



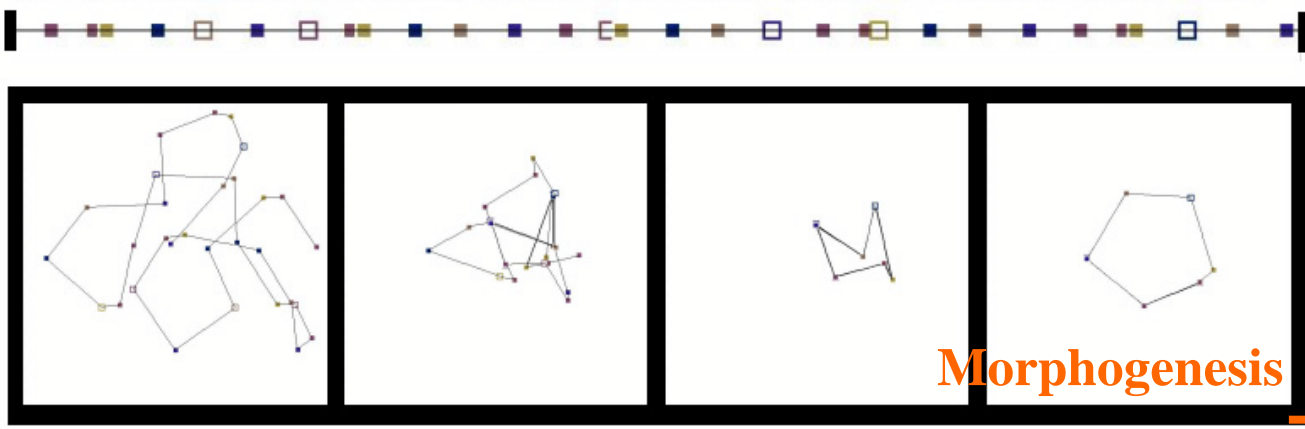
3D

Morphogenesis

↓ Evolution

1D

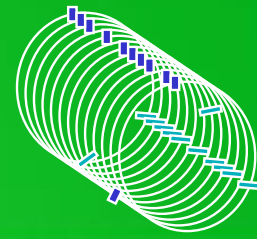
After evolution : regular gene positions



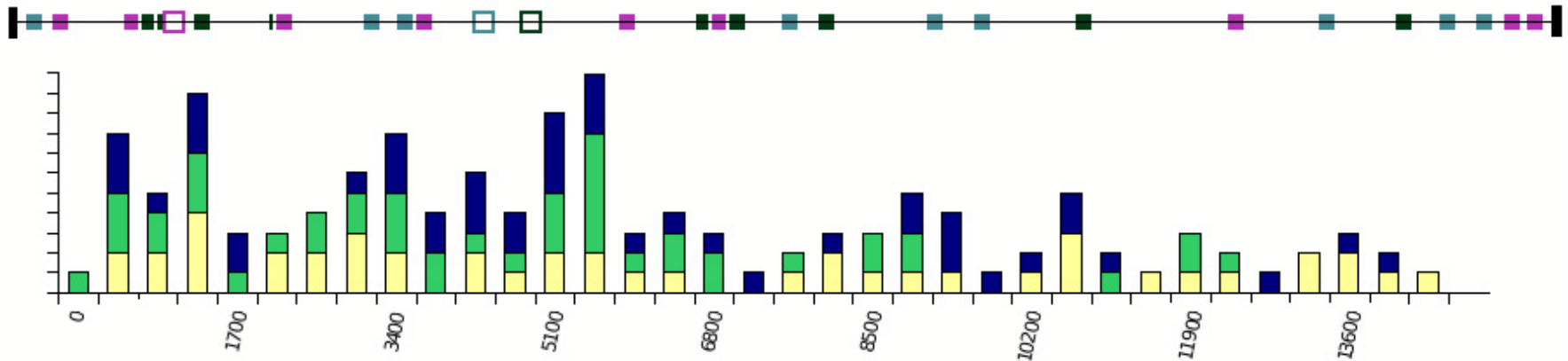
3D

Morphogenesis

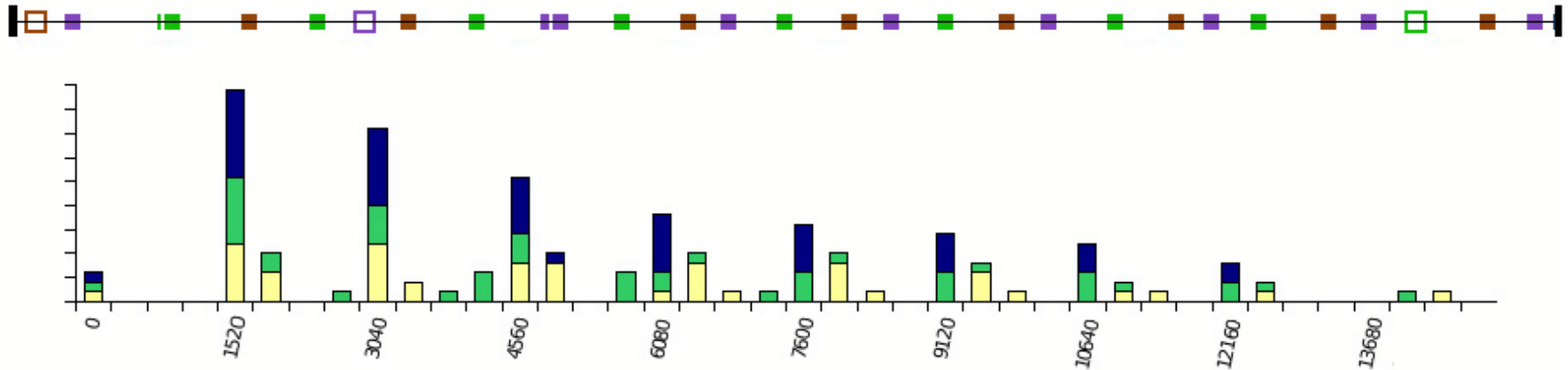
# 6 - Gene 3D clustering evolutionarily favors periodical



Initial random state



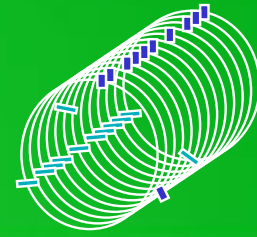
Final evolved state



3 sets of 10 genes each *(W. Banzhaf, S. Leclercq & F. Képès)*



# 1 - Rational genome-wide regulatory engineering



Given a set of 15 genes involved in one synthetic metabolic pathway.  
How do we co-regulate them?

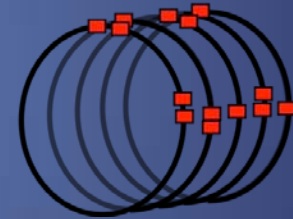
Hyper-operons (3D co-localization) is a principle that Nature is using.

Biotechnology could apply this principle. *(Képès, ComPlexUs, 2003)*

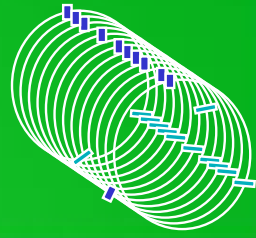
1D Co-localization



3D Co-localization

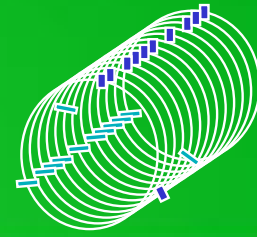


# Conclusions



- **Co-regulated genes tend to position periodically** (*Képès, 2003a; 2003b; 2004; Mercier et al., 2005*)
- **Gene 3D clustering evolutionarily favors periodical positioning** (*Leclercq et al., 2008*)
- **Periodical positioning, together with variety of binding proteins, strongly favor**
  - **Gene 3D clustering**
  - **Solenoidal 3D organization of chromosomes** (*Junier et al., 2010*)
- **Gene 3D clustering optimizes transcriptional regulation** (*Müller-Hill, Leibler ...*)
- **Transcription occurs in focal points** (*Misteli, Cook, Cremer ...*)

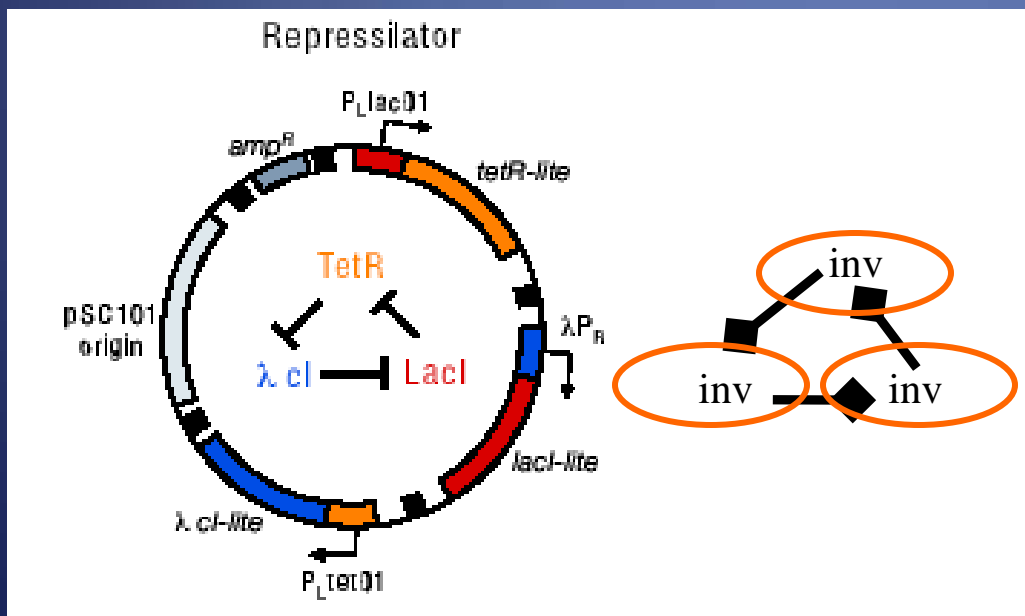
# Questions



- *What are the biotechnological implications for such studies?*
- *Are we on the verge of epigenetic engineering, following genetic engineering?*

**Tom Knight:** « Another way to deal with complexity is to get rid of it »

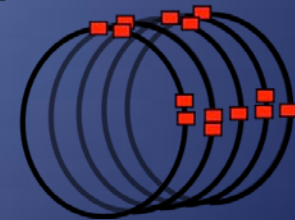
**François Kepes:** « Another way to deal with complexity is to put it to use »



1D Co-localization



3D Co-localization



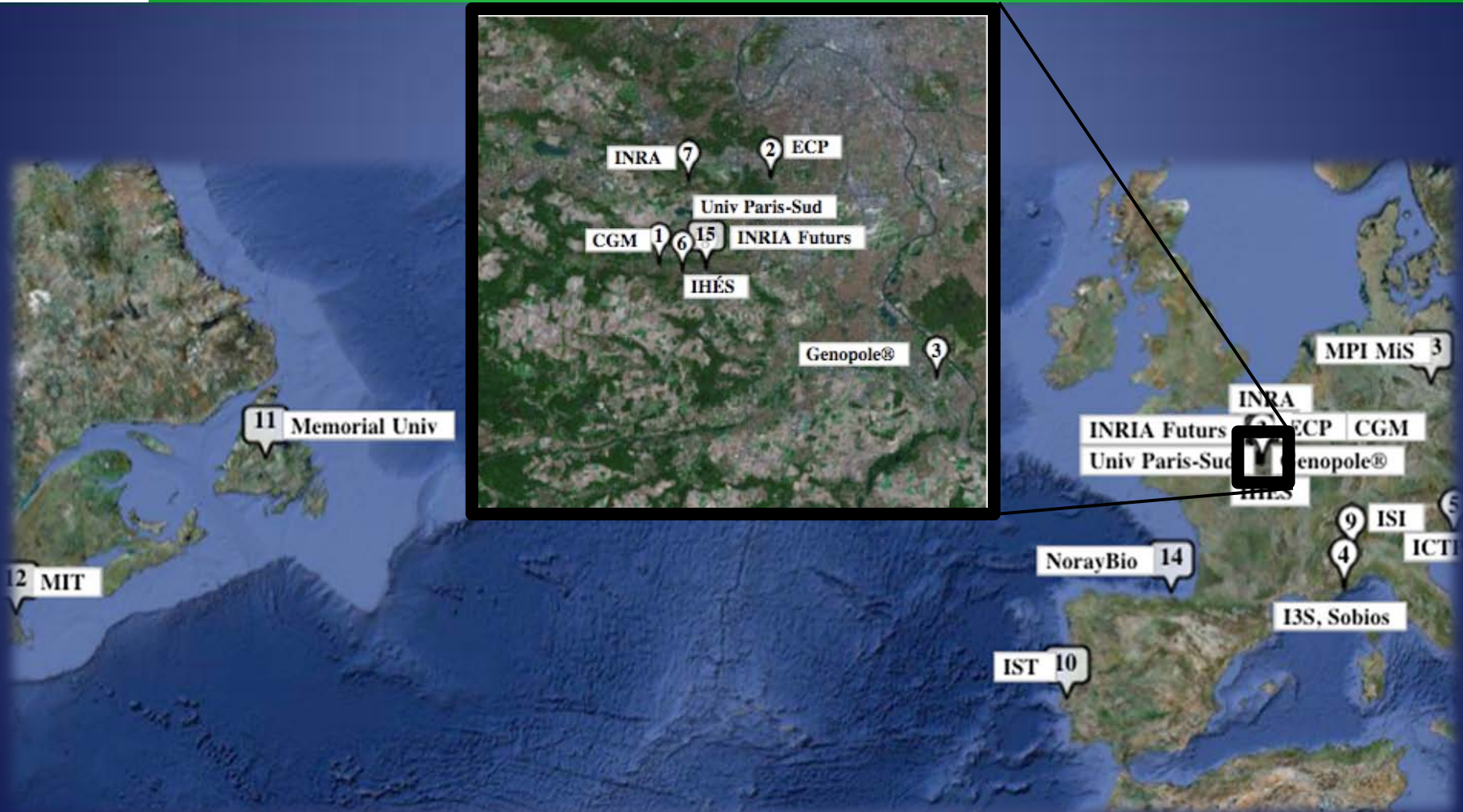
*(Kepes, ComPlexUs, 2003)*



# Relevant Team Publications

1. Guelzim, N., Bottani, S., Bourguine, 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": Glasgow, UK, May 8-11, 2006. *Proceedings, Part I*; Eds: Gavrilova, M. et al. (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. Bourguine, Chavalarias, Cohen-Boulakia), *La Découverte, Paris*; ISBN 978-2-7071-5090-5 (2008).
9. Manceny, M., Aiguier, M., Le Gall, P., Hérisson, J., Junier, I., and Képès, F. "Spatial Information to Restrict the Dynamics of Genetic Regulatory Networks" - In *BICoB 2009 - International Conference on BioInformatics and Computational Biology*, LNBI 5462, 270-281 (2009).
10. Junier, I., Martin, O., Képès, F. Spatial and topological organization of DNA chains induced by gene co-localization. *PLoS Computational Biology* 6(2): e1000678 (2010).

# External Collaborations





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Laurent Jannière

Hamid Nouri

François Képès

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INSTITUT DES HAUTES ÉTUDES SCIENTIFIQUES  
Fondation reconnue d'utilité publique

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Olivier Martin

Martin Weigt

Riccardo Zecchina

/ Matteo Marsili

Rui Dilao

Wolfgang Banzhaf

Marc Schoenauer

Marc Aiguier

Julio Font



***Collaborations***