

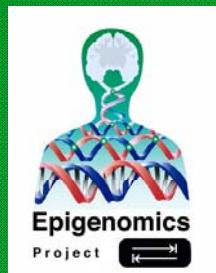
Synthetic and Integrative Biology

François Kepes

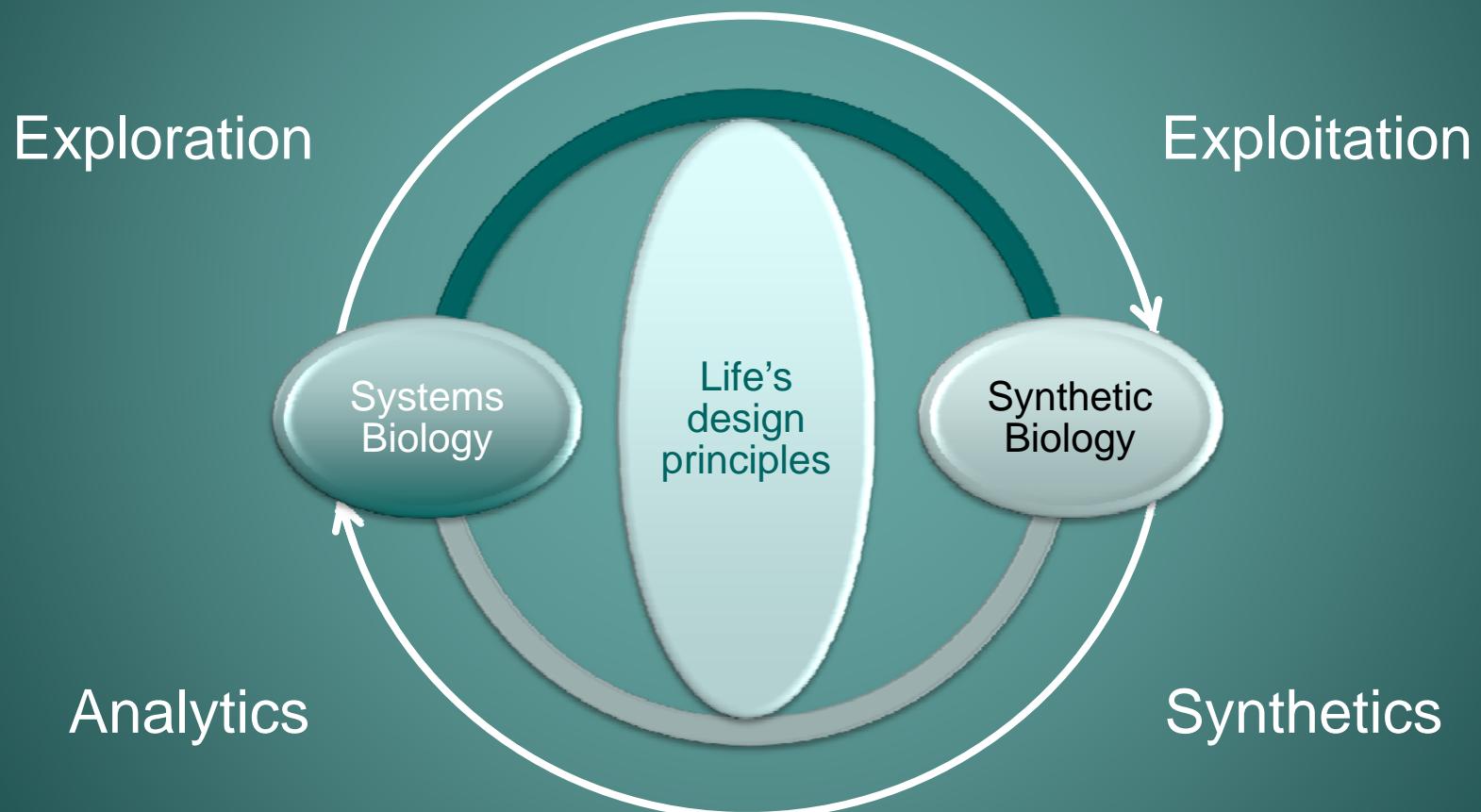
Epigenomics Project

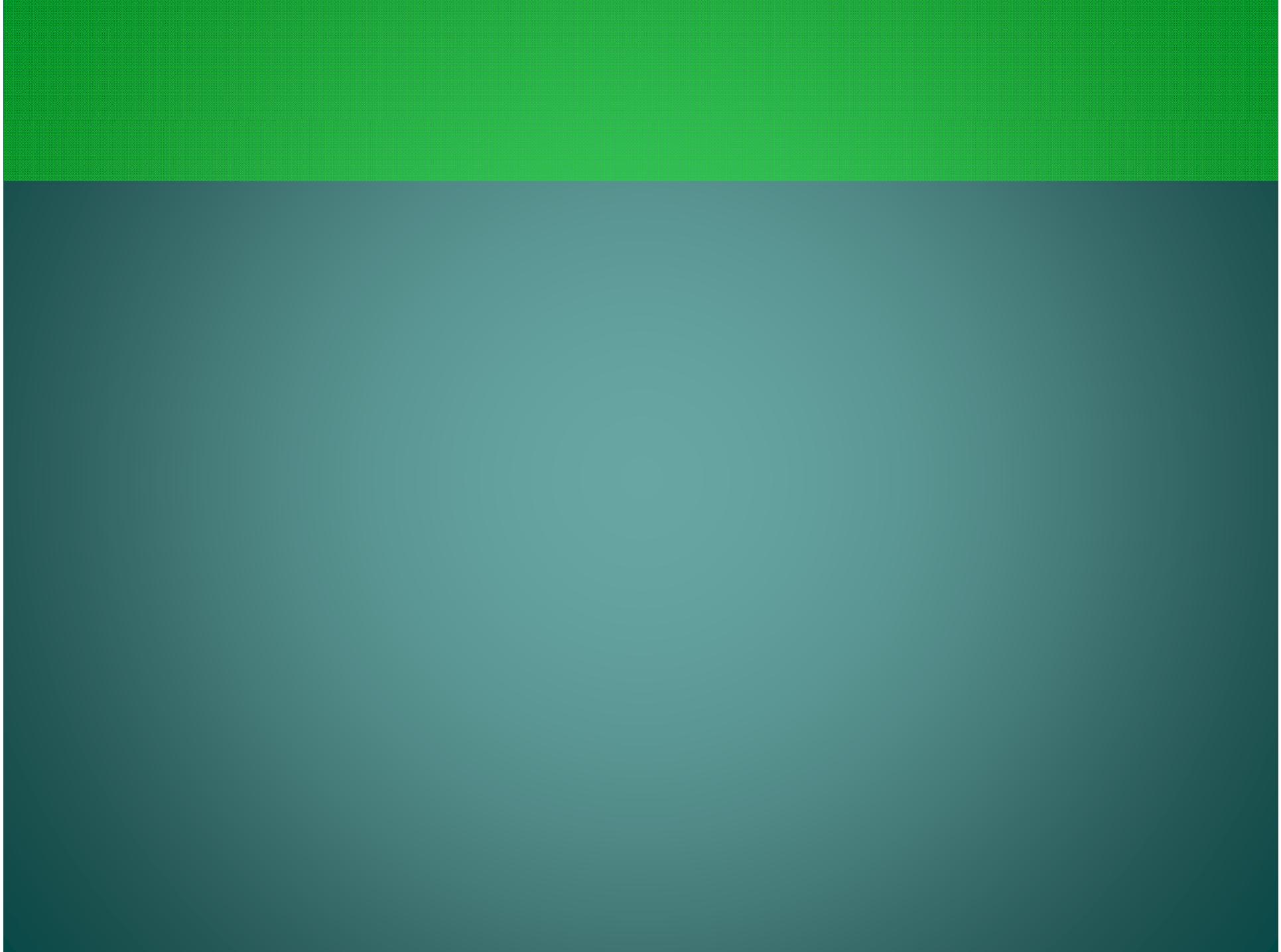
Genopole®, CNRS UPS3201, Université d'Évry Val d'Essonne, PRES UniverSud Paris

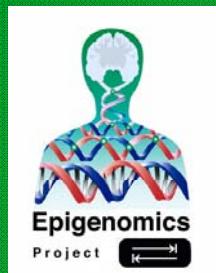
From Synthetic Chemistry to Synthetic Biology
Collège de France, May 2009



Coupling analytics and synthetics



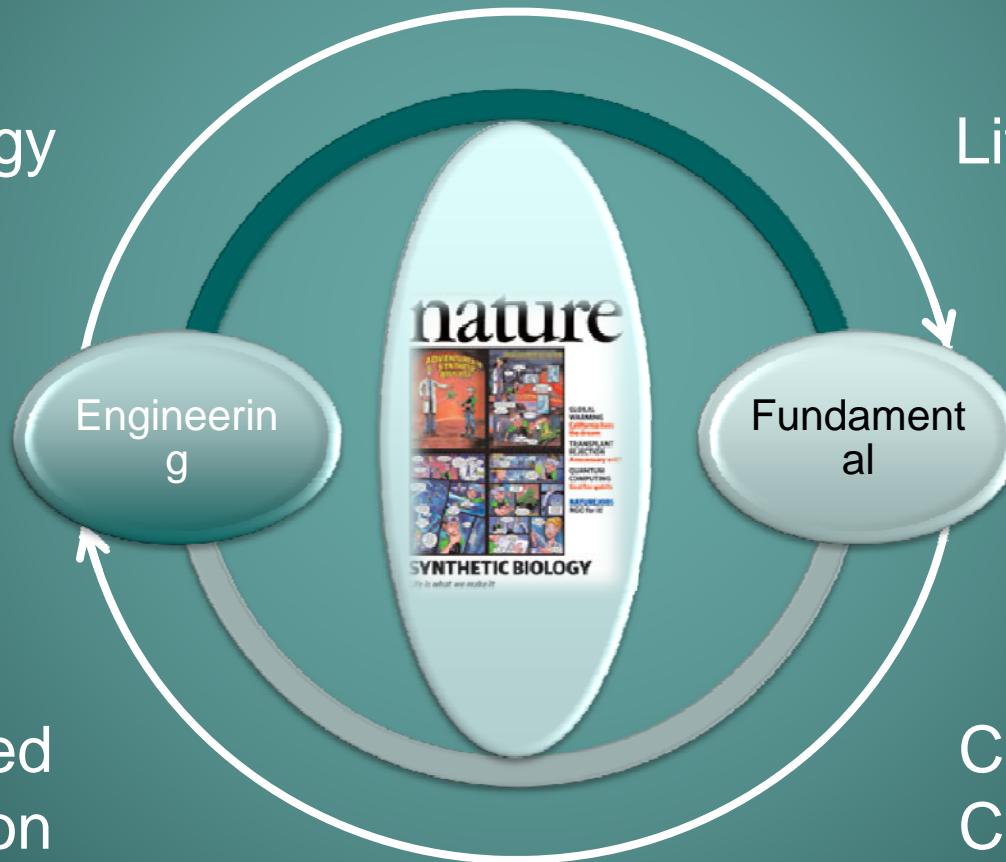




Scope

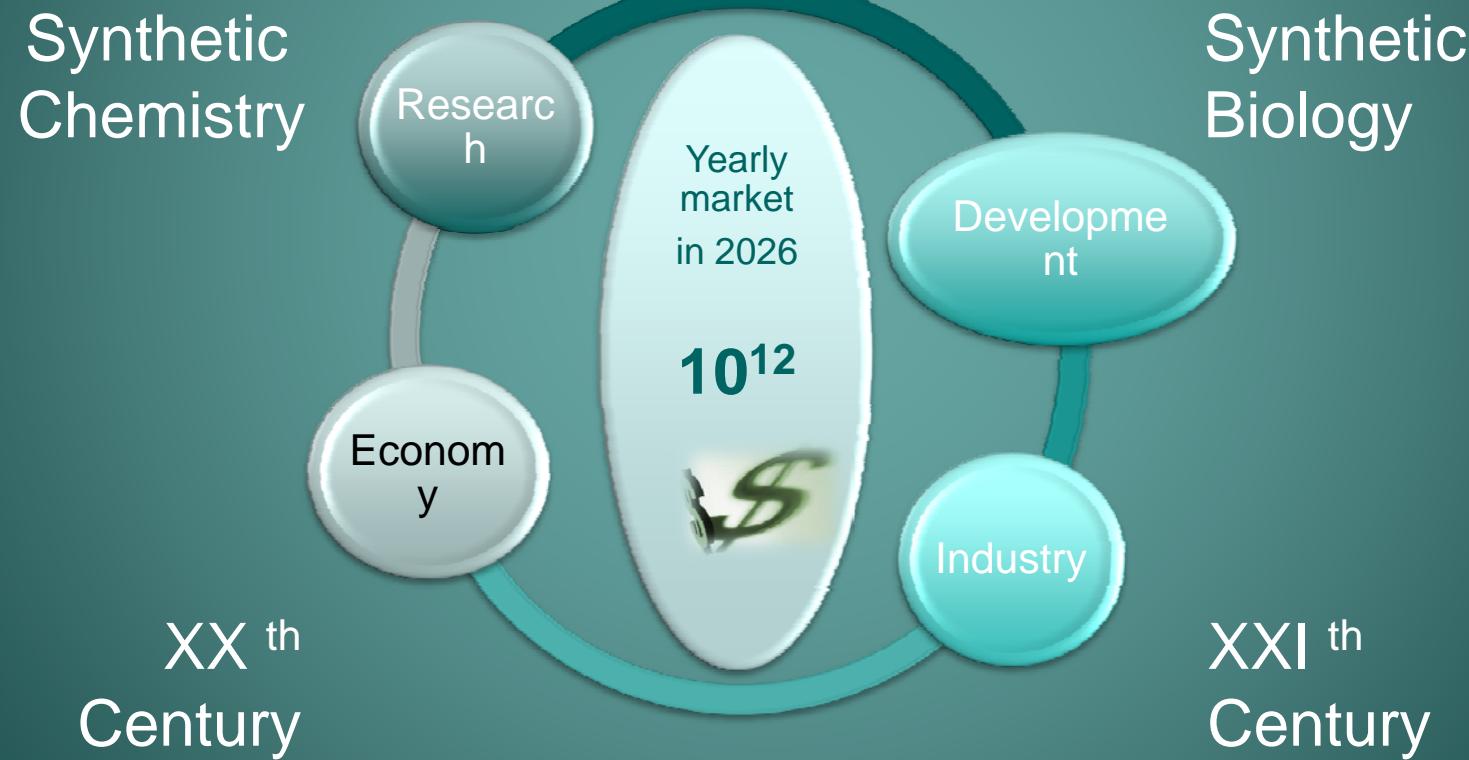
Biotechnology

Life Sciences



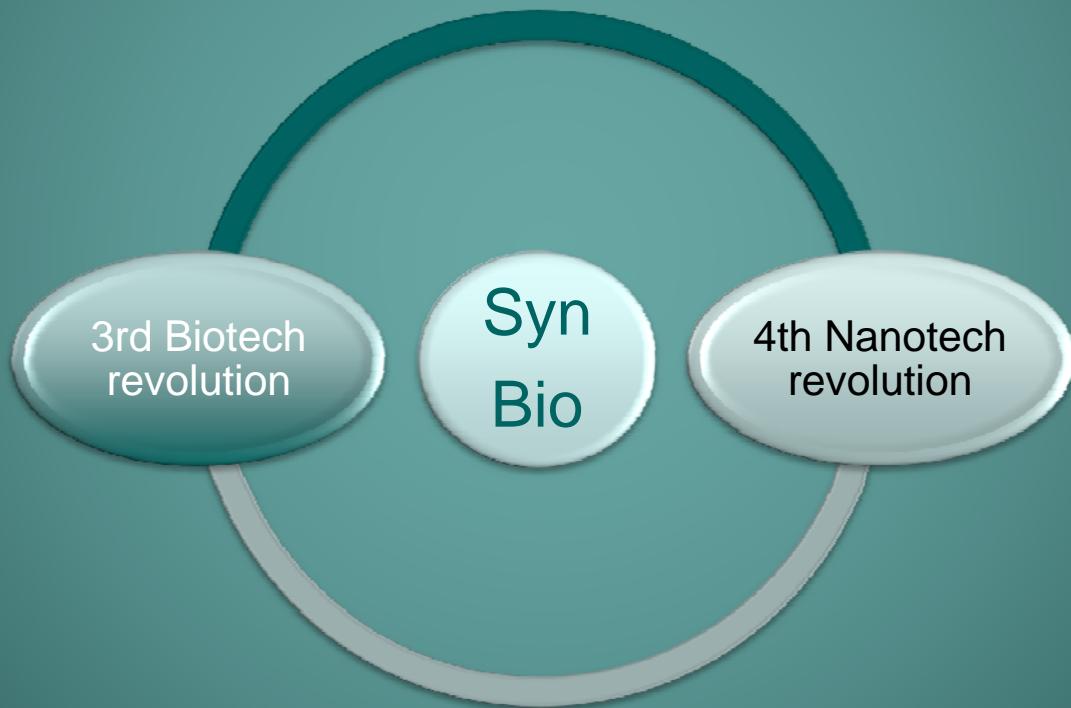


Perspective





A revolution ?





Stages in human mastering over desirable properties of live matter

Hunting & harvesting

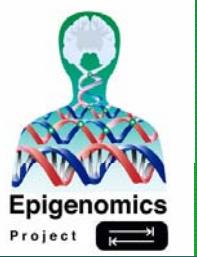
Breeding & crops

Controlled breeding

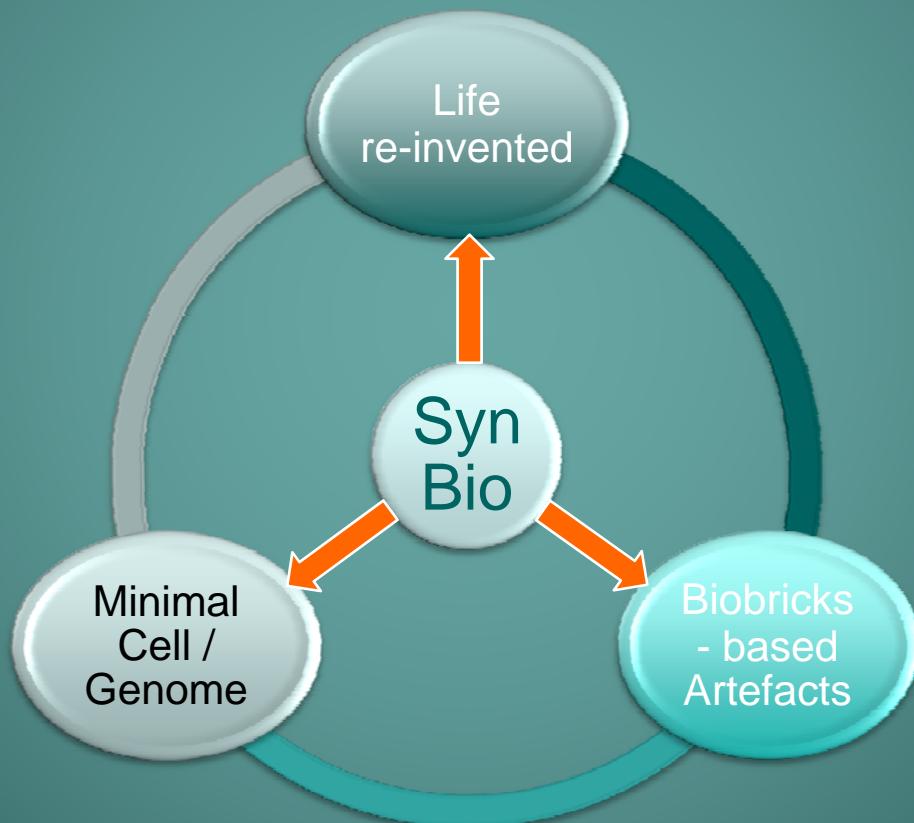
Systematic controlled breeding

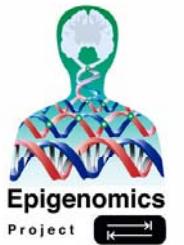
Directed genetic modification

Rational conception of modification



Contents





Design levels

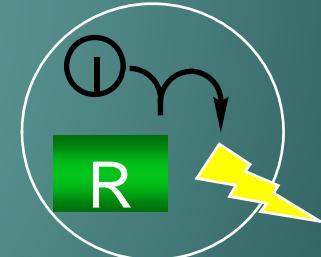
SYSTEMS

- Organism; Chassis; Nanomachine



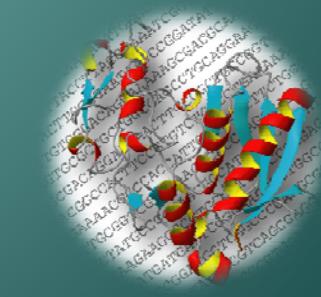
DEVICES

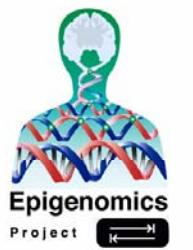
- Regulatory circuit; Metabolic pathway



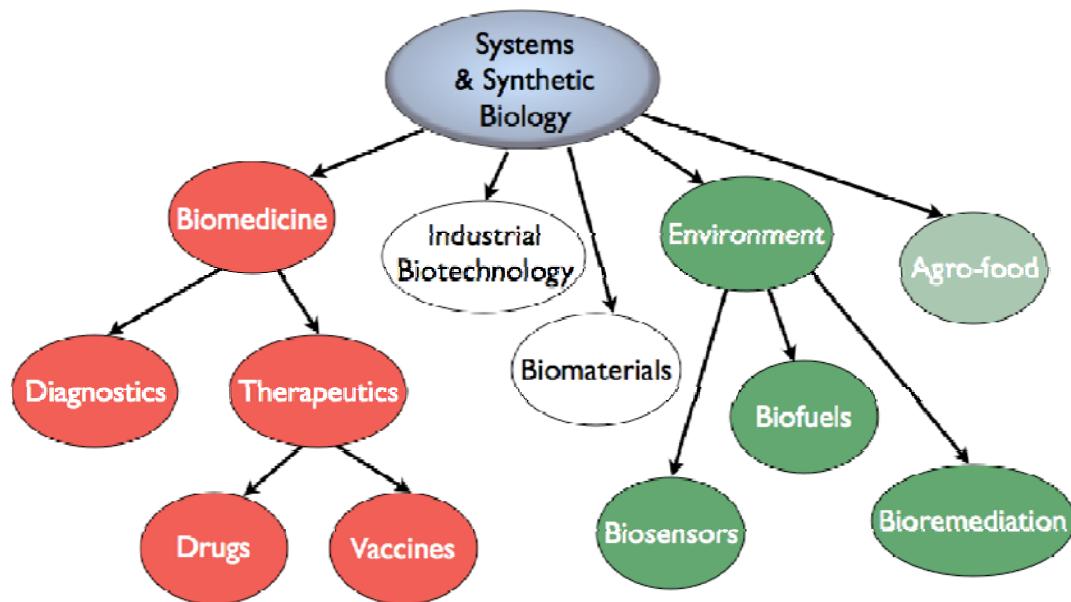
BIO-BRICKS

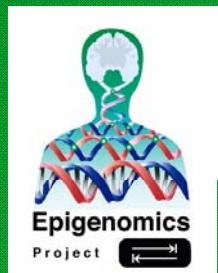
- Protein; RNA





Applications



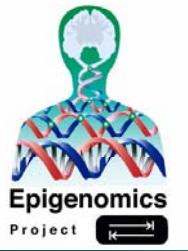


Control of gene expression

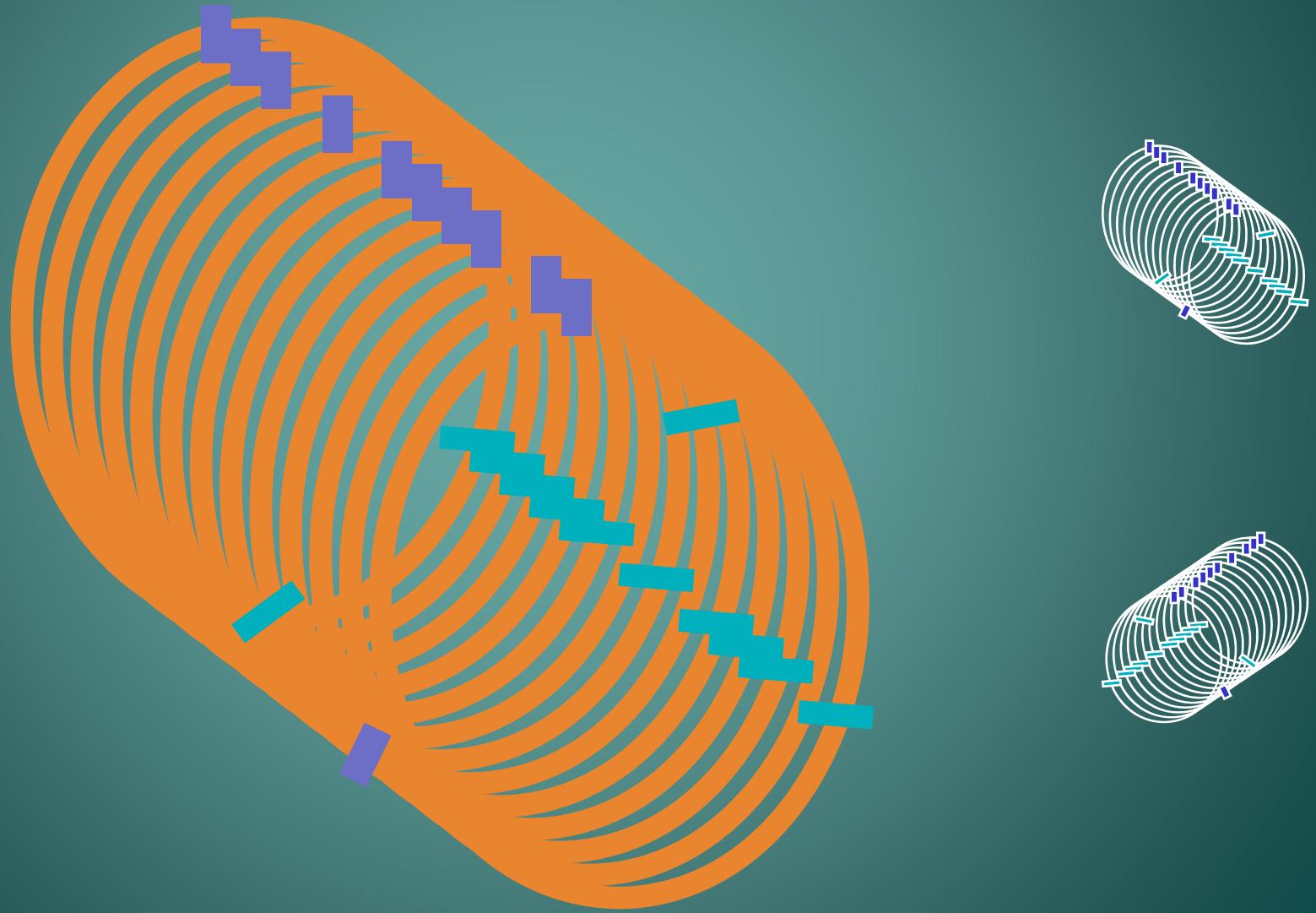
How are genes turned on and off with such delicate and adaptive precision?

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

Maaløe et al., 1957



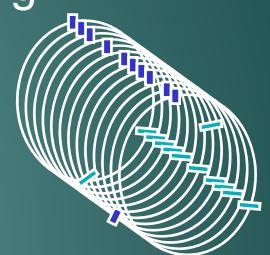
The transcription-based solenoidal model of chromosomes





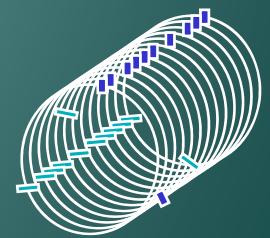
The transcription-based solenoidal model of chromosomes

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



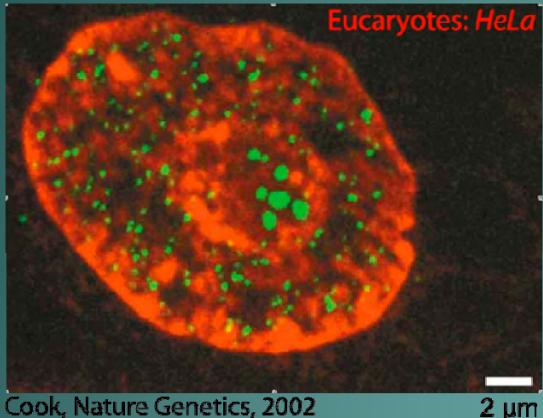
Project

- *Extensions*
- *Positional effects on gene expression*
- *Rational genome-wide regulatory engineering*





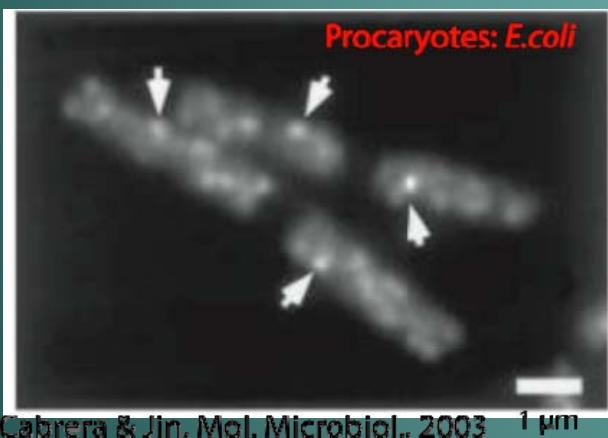
Transcription occurs in focal points



Similar active genes cluster in specialized transcription factories

Meng Xu and Peter R. Cook

J. Cell Biology, 2008



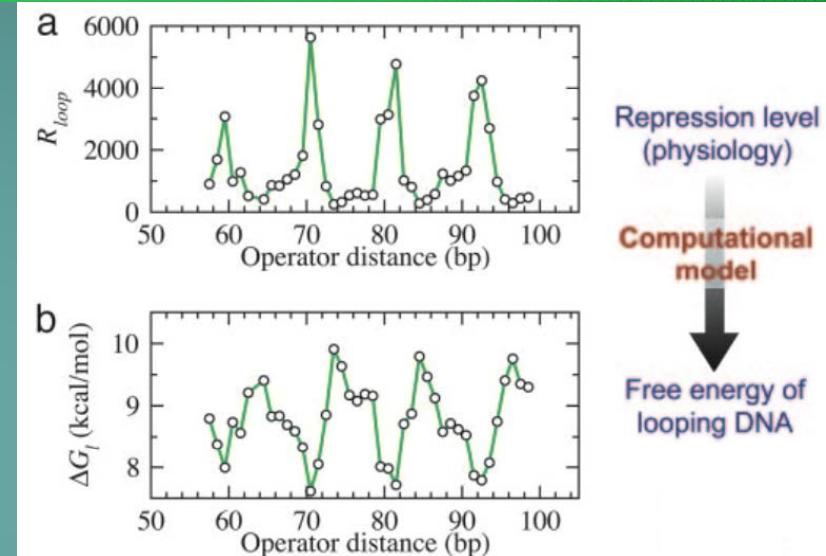
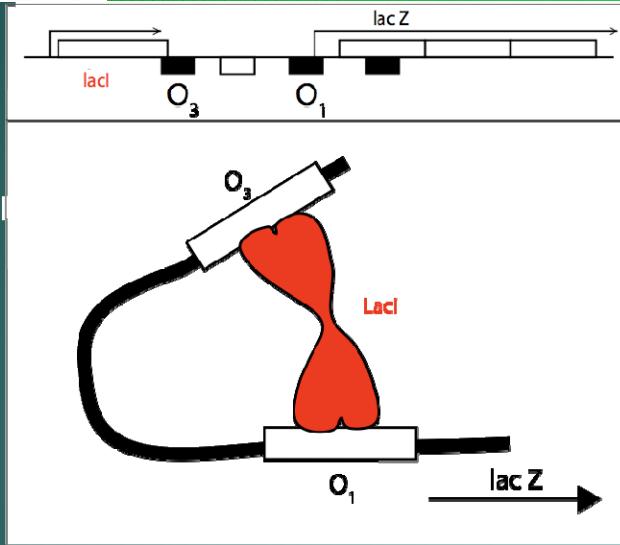
Two types of localization of the DNA-binding proteins within the *Escherichia coli* nucleoid

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

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



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



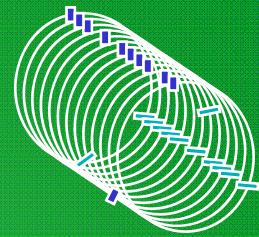
TF – lactose repressor:
70-fold optimization of transcriptional regulation
A DNA loop induced by

- bivalency of TF and
- bivalency of TFBS ‘O’.

Müller-Hill, 1999
Vilar & Leibler, 2003



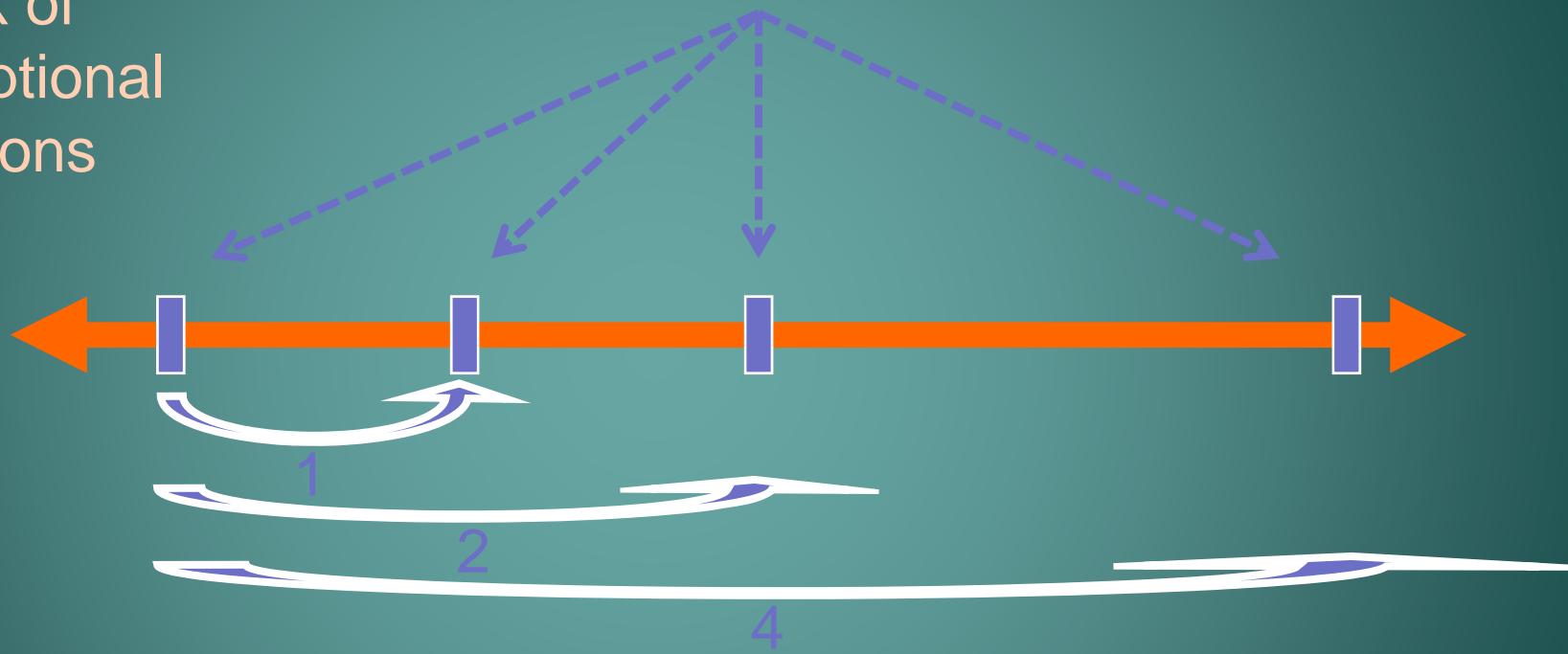
Co-regulated genes tend to position periodically

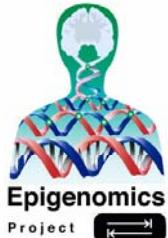


Network of
transcriptional
interactions

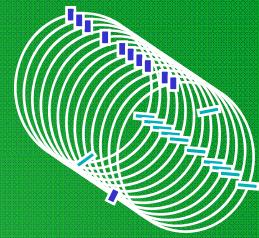
A given Transcription Factor

Chromosome
sequence

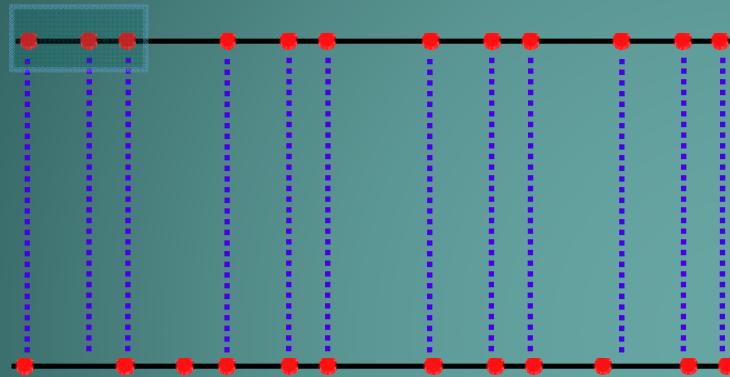




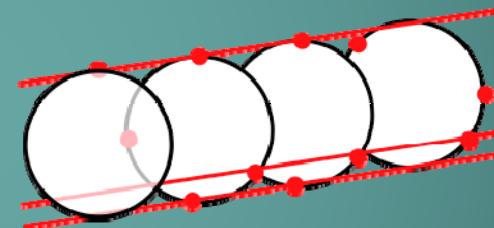
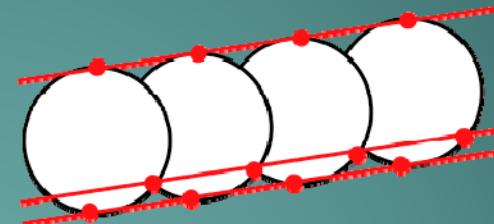
Co-regulated genes tend to position periodically



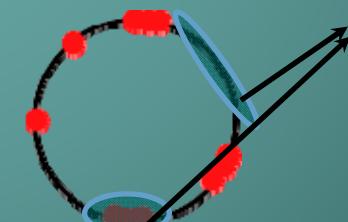
Solenoidal coordinates



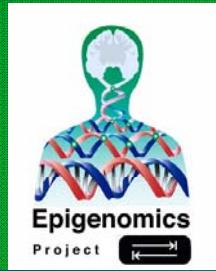
Data are:
sparse
noisy
wrong



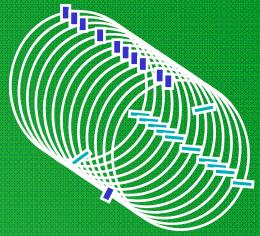
Score



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

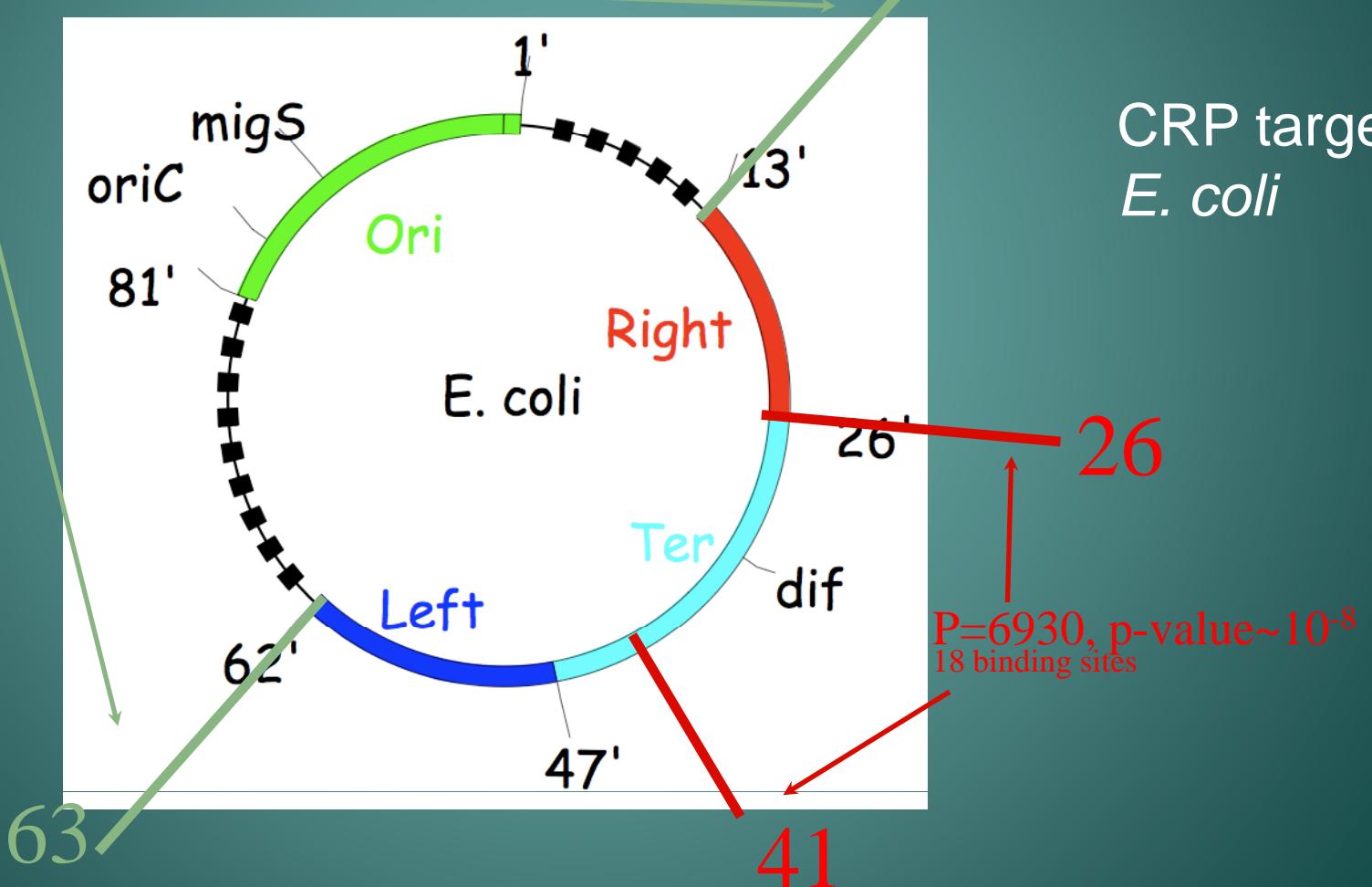


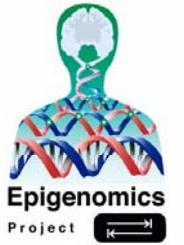
Co-regulated genes tend to position periodically



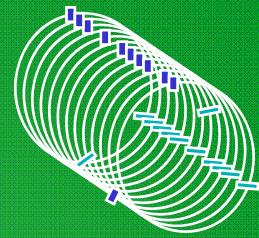
P=9510, p-value~ 10^{-7}
85 binding sites

Macro-domains (Boccard, 2004)





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



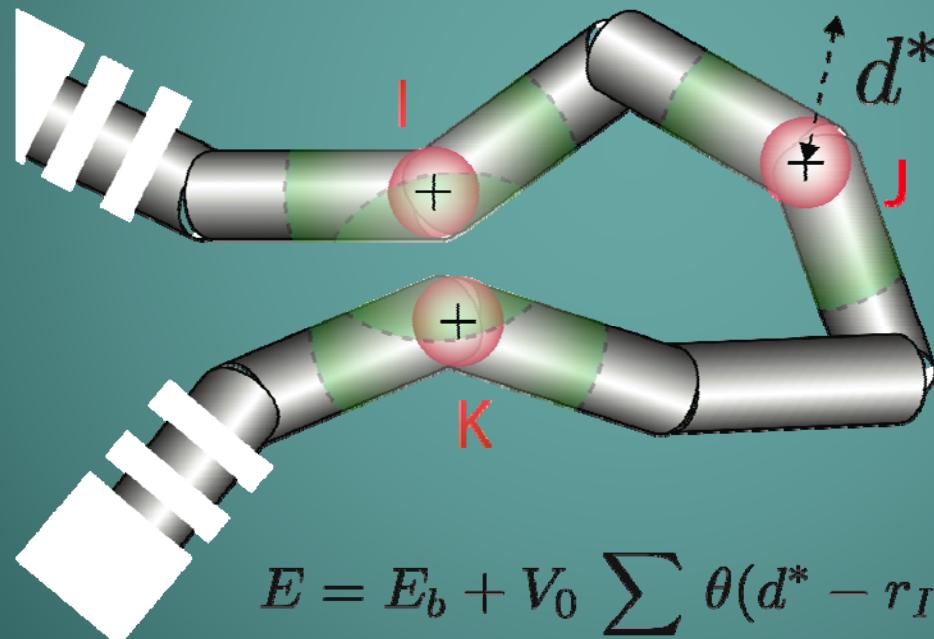
Polymer model off-lattice

Discrete implementation of a self-avoiding semi-flexible polymer

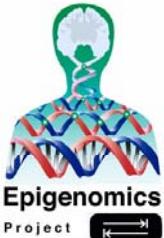
Monte Carlo / Metropolis

With localized interaction sites

Mimicks bridging of two DNA sites by one bivalent transcription factor



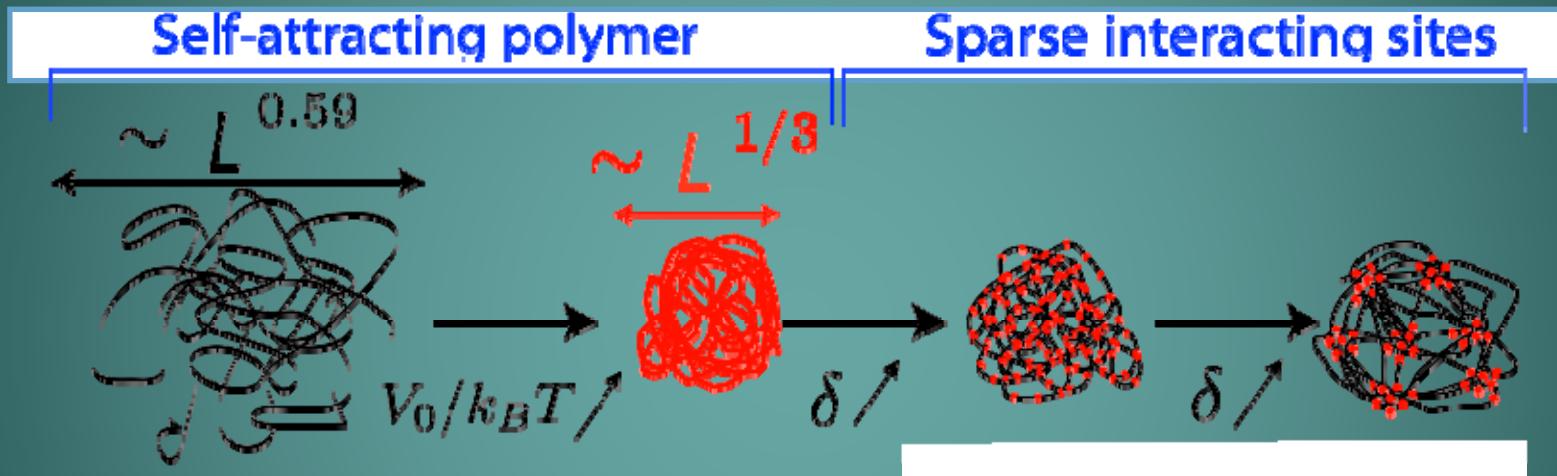
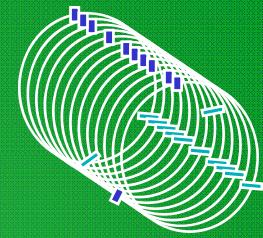
$$E = E_b + V_0 \sum_{\langle I, J \rangle} \theta(d^* - r_{IJ})$$



1-D periodicity strongly favors

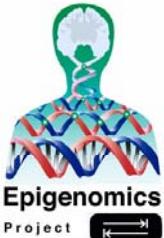
3-D clustering and solenoid

A micro-phase transition

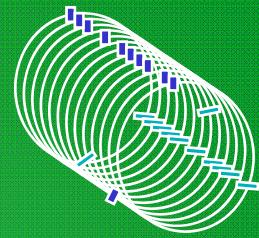


$$\delta = \frac{\text{Distance between co-regulated genes}}{\text{Polymer persistence length}}$$

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

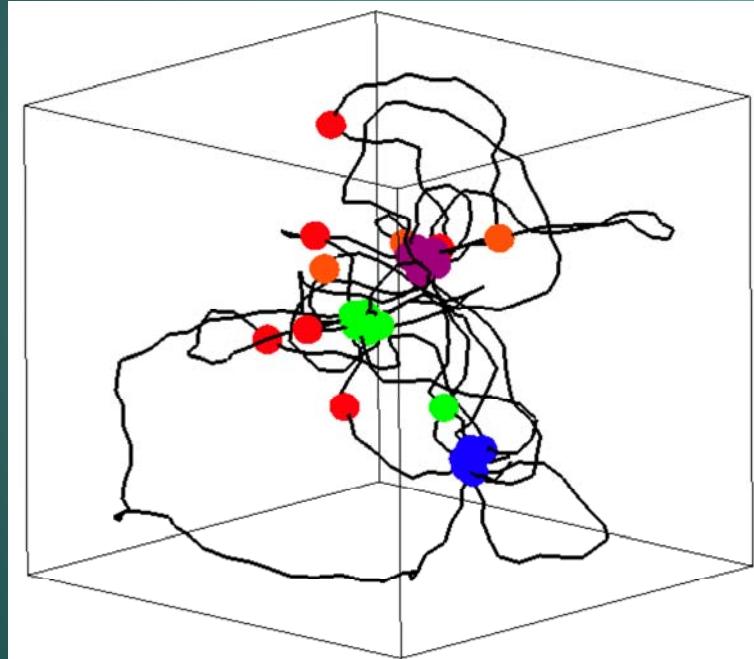


1-D periodicity strongly favors 3-D clustering and solenoid



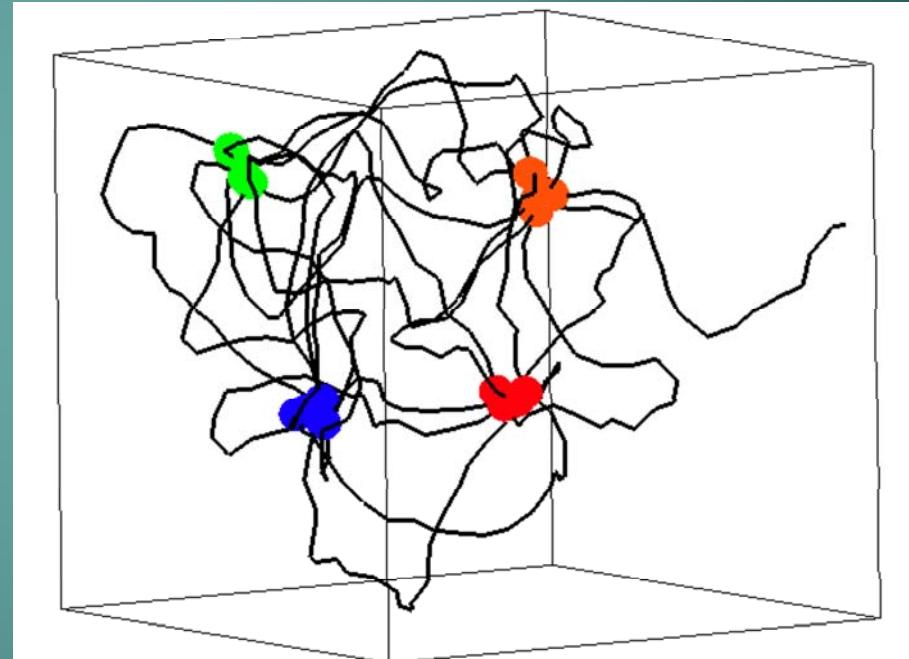
Random site positioning

Site co-localization is partial
No collective optimization



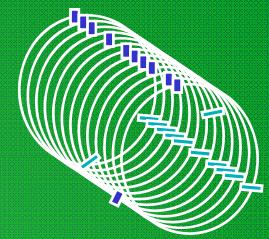
Periodic site positioning

Site co-localization is efficient
Good collective optimization



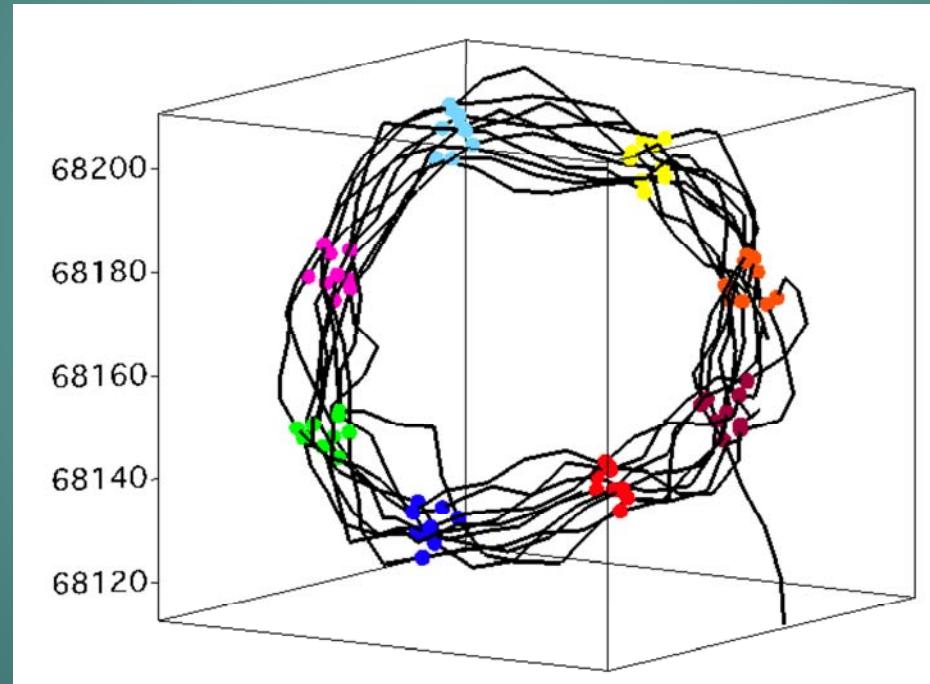


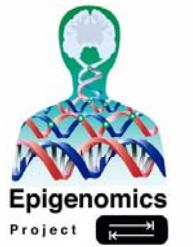
TF variety strongly favors 3-D clustering and solenoid



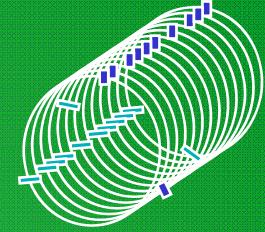
Include several types of interacting sites, denoted by different colors

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





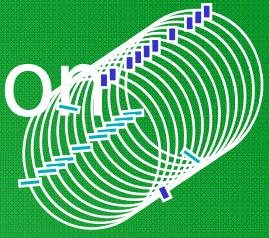
Extensions



- Other scales
- Other organisms
- Other DNA metabolisms
- An evolutionary model

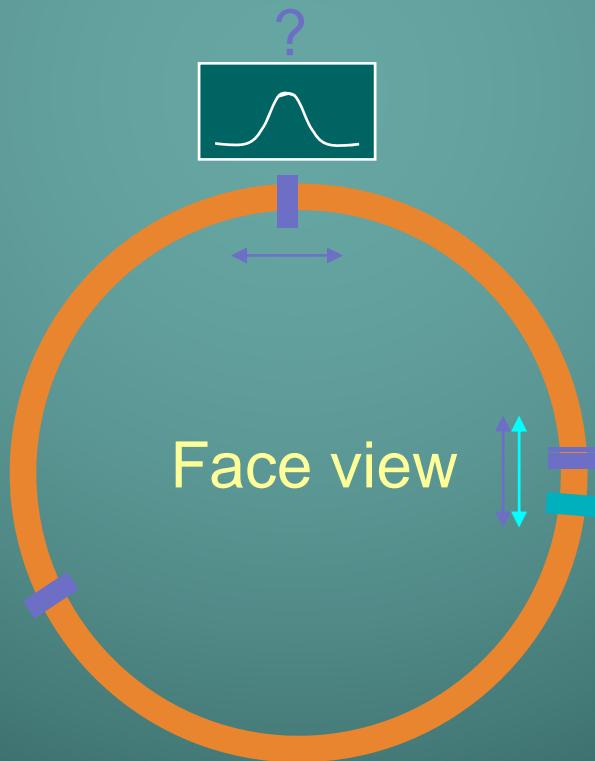


positional effects on gene expression



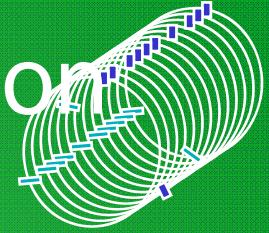
Three approaches to the function that governs transcription optimization in relation to angular position:

1. Theoretical, *ab initio* -> physical model
2. Data-driven, empirical -> stylized facts
3. Bench, empirical -> stylized facts

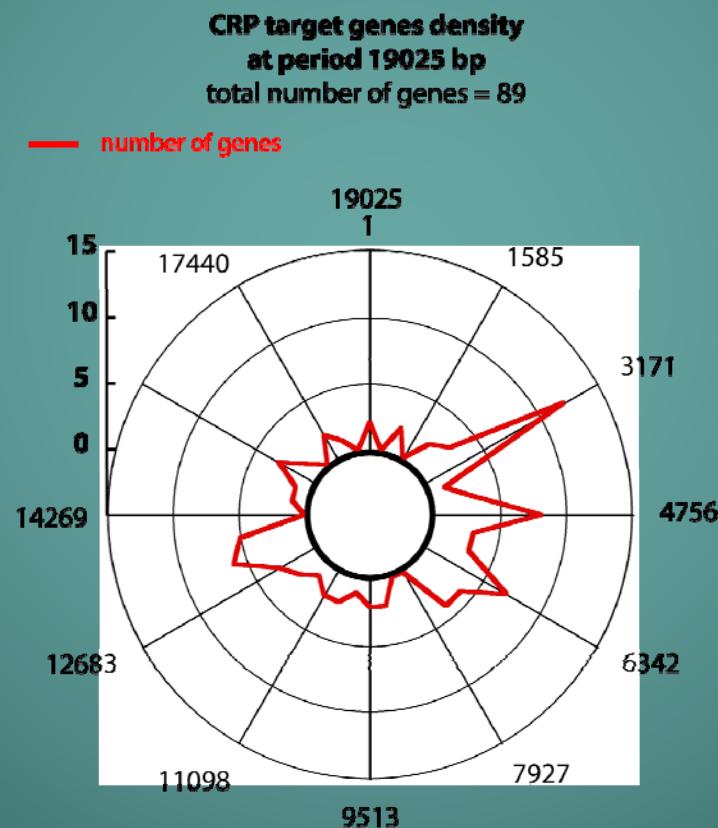


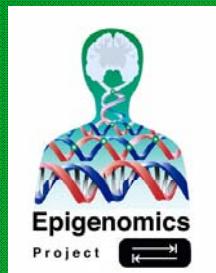


positional effects on gene expression

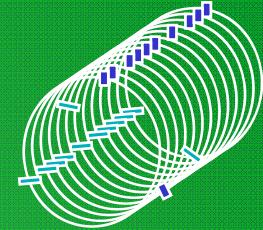


2. Data-driven empirical approach -> stylized facts

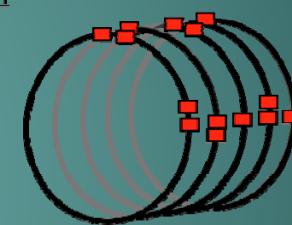




More ...



1D Co-localization



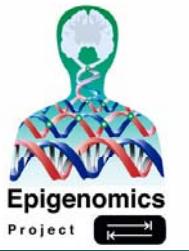
3D Co-localization

Super-operons?

Biotechnological implications?

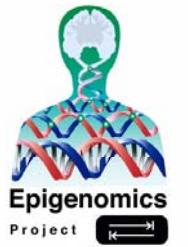
Epigenetic engineering?

Képès, ComPlexUs, 2003

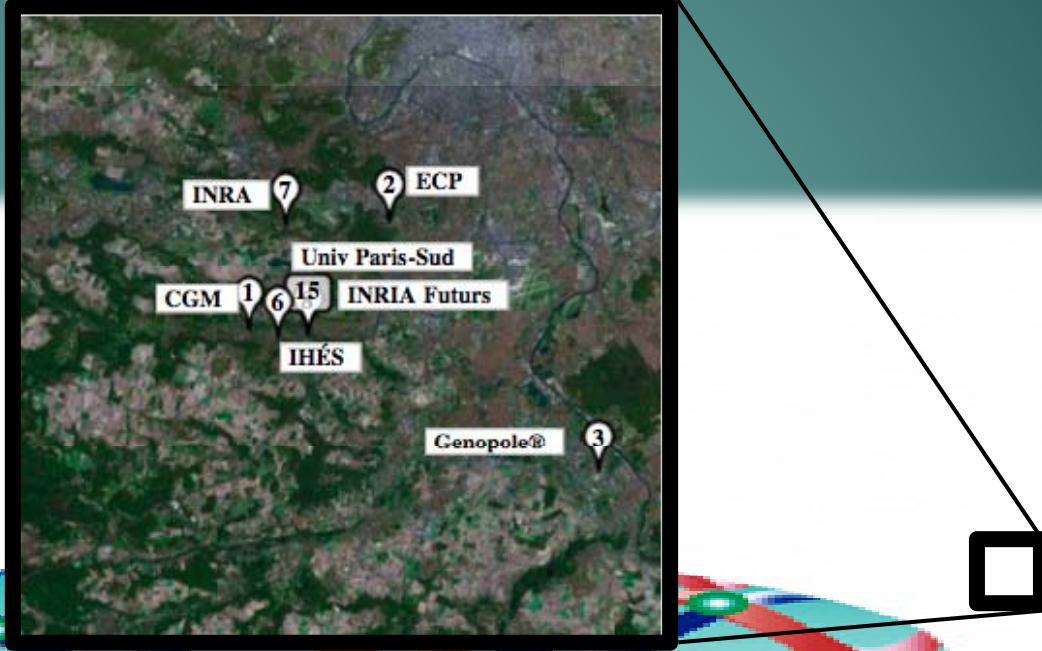


Relevant Team Publications

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).



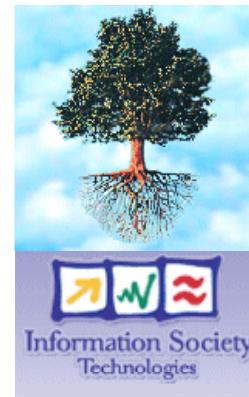
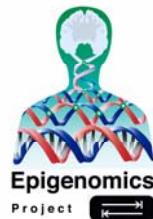
External Collaborations





*Christophe Pakleza
Joan Hérisson
Ivan Junier
Mohamed Elati
Thimo Rohlf
François Képès*

MEGA Team



Annick Lesne
Arndt Benecke



Olivier Martin
Martin Weigt
Riccardo Zecchina
/ Matteo Marsili
Rui Dilao
Wolfgang Banzhaf
Marc Schoenauer
Marc Aiguier
Julio Font

Collaborations