Epigénétique et variabilités génomiques

Journée de formation

Évolution des génomes, évolution de l'Homme.

14 Mai 2013

thomas.heams@agroparistech.fr

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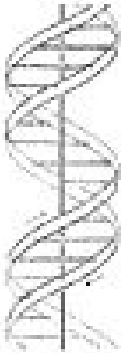
F. Crick & J. Watson

April 25, 1953 NATURE

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid



R. Franklin

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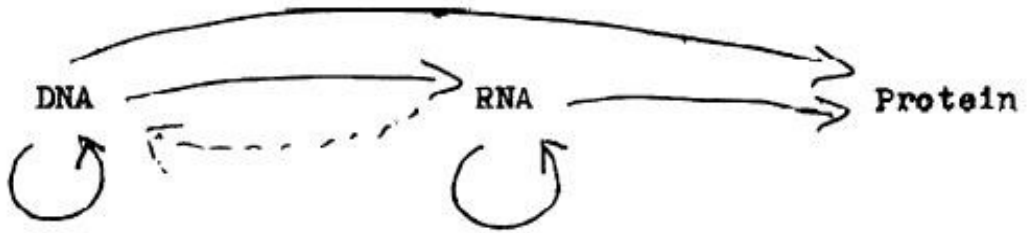
Ideas on Protein Synthesis (Oct. 1956)

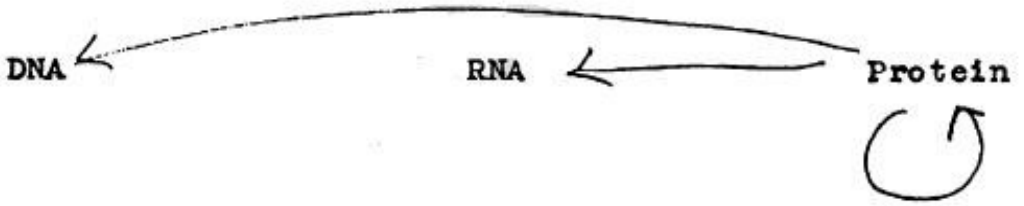
The Doctrine of the Triad.

The Central Dogma: "Once information has got into a protein it can't get out again". Information here means the sequence of the amino acid residues, or other sequences related to it.

That is, we may be able to have



but never



where the arrows show the transfer of information.

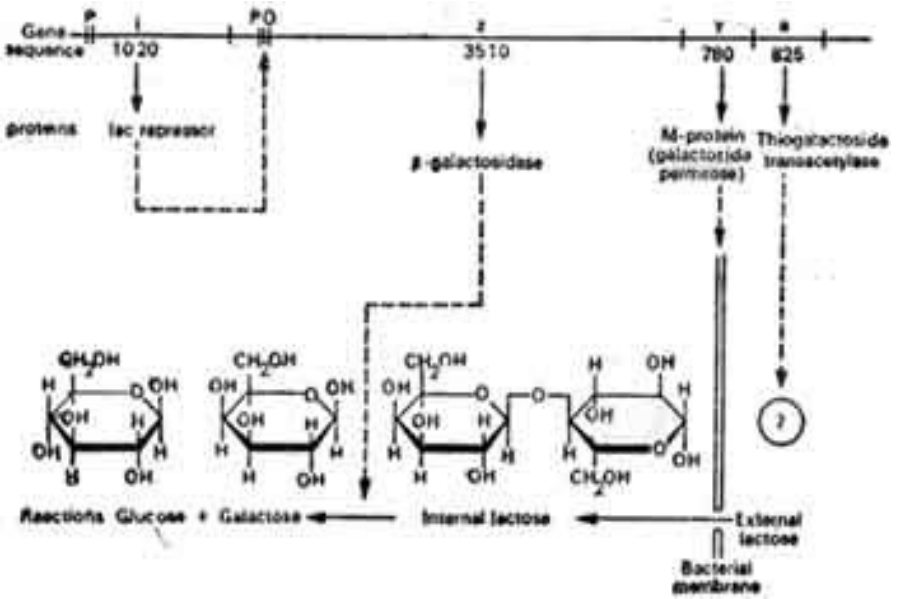
REVIEW ARTICLE

Genetic Regulatory Mechanisms in the Synthesis of Proteins †

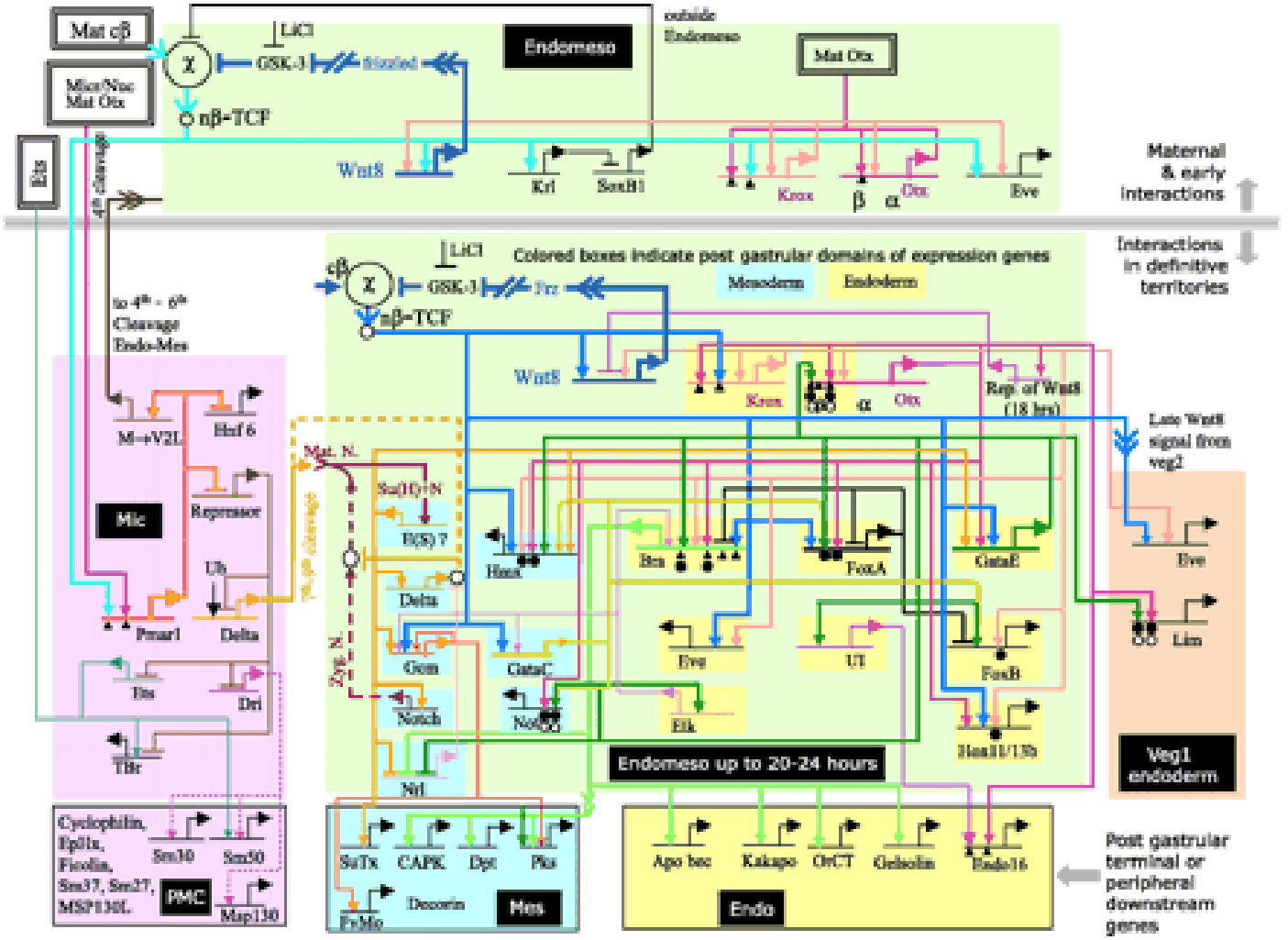
FRANÇOIS JACOB AND JACQUES MONOD

Services de Génétique Microbienne et de Biochimie Cellulaire, Institut Pasteur, Paris

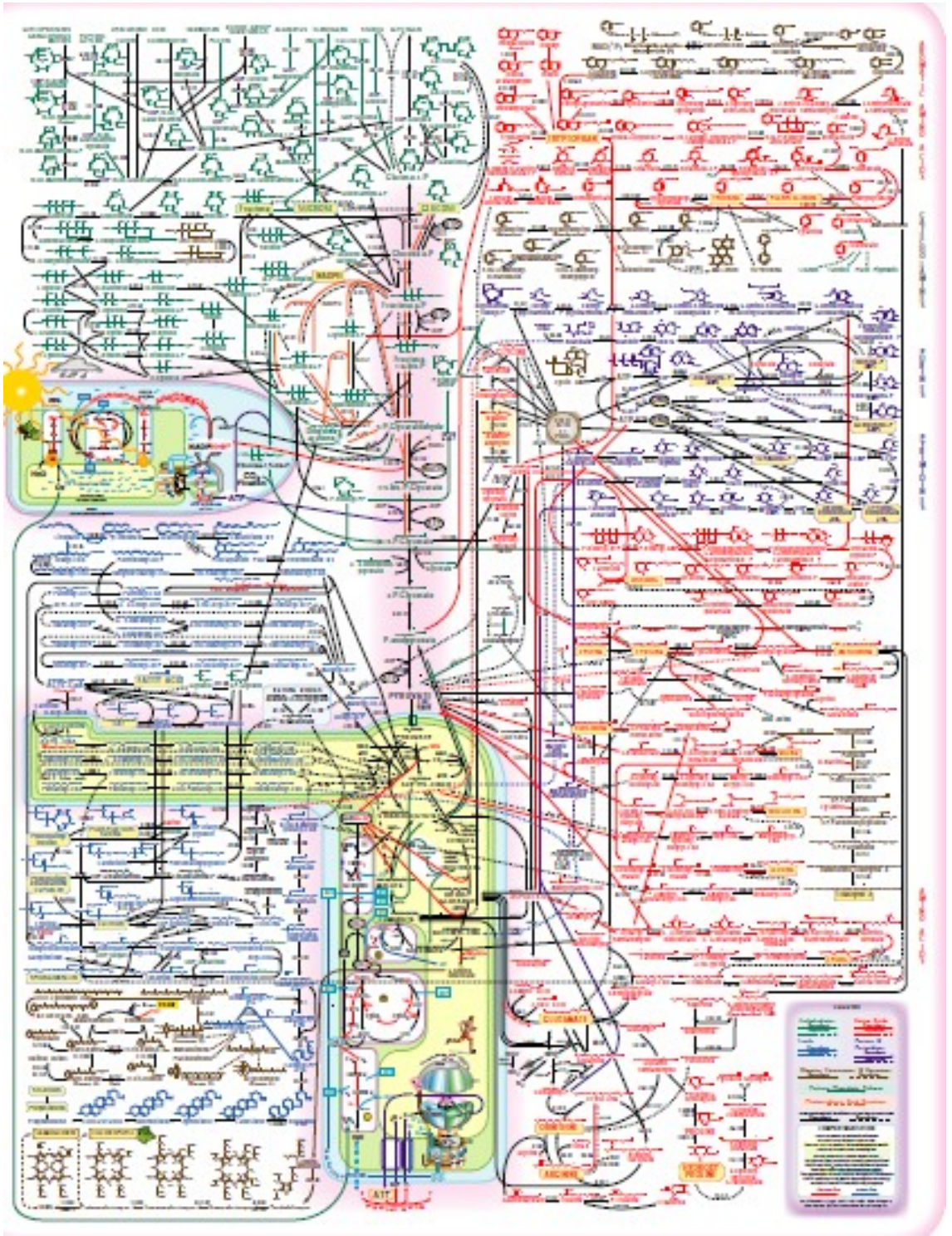
(*Received 28 December 1960*)



« *A Genomic Regulatory Network for Development* »



Davidson *et al*, 2002



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LETTER

doi:10.1038/nature11149

Programmable single-cell mammalian biocomputers

Simon Ausländer[1], David Ausländer[1], Marius Müller[1], Markus Wieland[1] & Martin Fussenegger[1,2]

Nature 2010

REVIEW ARTICLE

Bacteria as computers making computers

Antoine Danchin

Génétique des Génomes Bactériens, Institut Pasteur, Paris, France

FEMS Microbiol Rev 2009

Comparing genomes to computer operating systems in terms of the topology and evolution of their regulatory control networks

Koon-Kiu Yan[a], Gang Fang[a], Nitin Bhardwaj[a], Roger P. Alexander[a], and Mark Gerstein[b,a,c,1]

PNAS 2010

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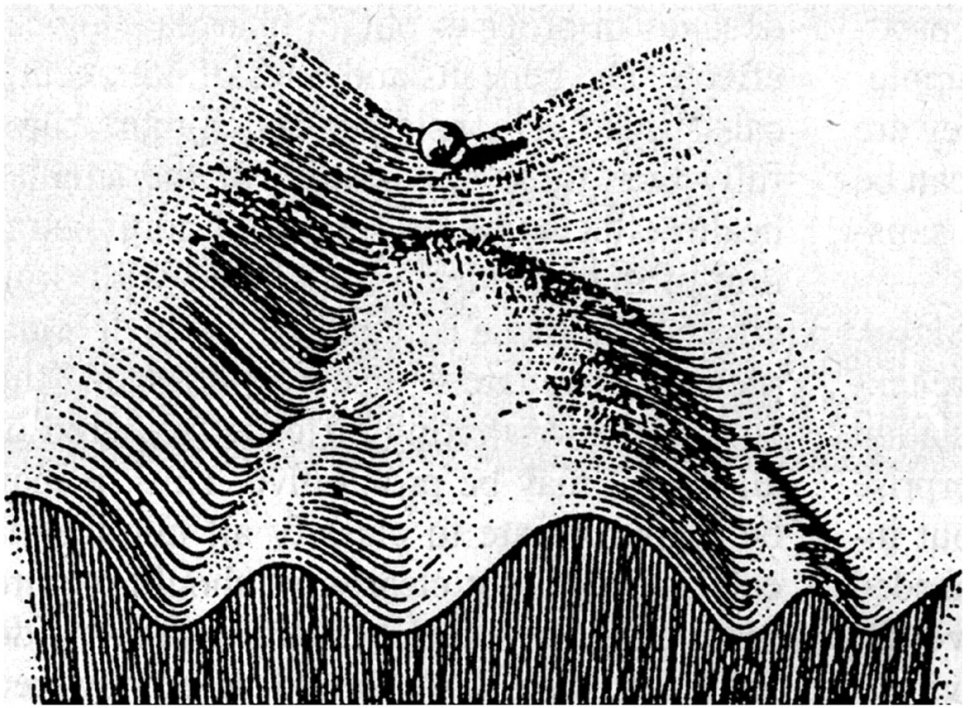
Tout invite à assimiler la logique de l'hérédité à celle d'une calculatrice.
Rarement modèle imposé par une époque aura trouvé une application plus fidèle.

François Jacob,
la Logique du Vivant, 1970

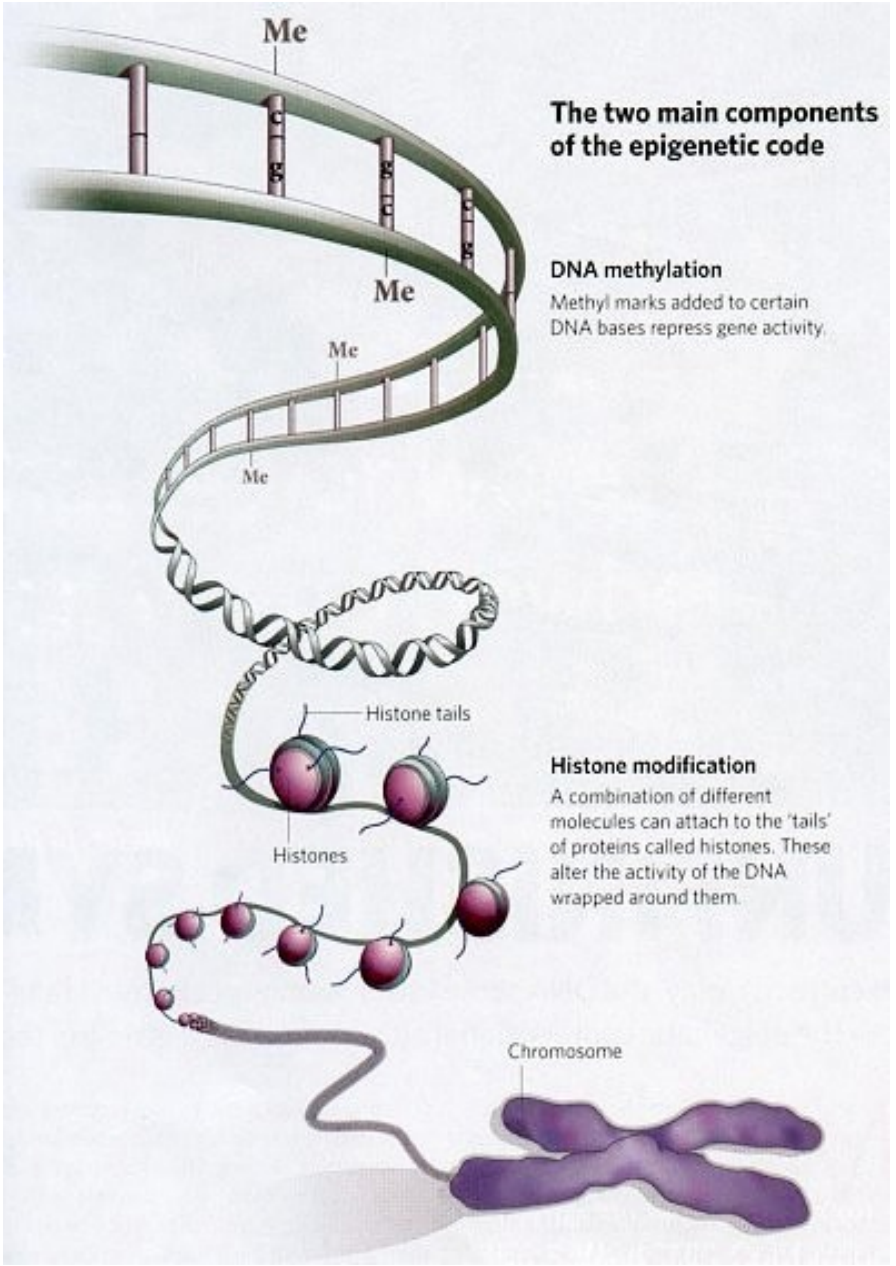
Epigénétique



Conrad Waddington

« *Epigenetics* » 1942

Paysage épigénétique (tiré de *Strategy of the genes*, 1957)



Nature 441: 143-145. 11 May 2006

L'épigénétique
Une nouvelle frontière (?)

Modifications
-fonctionnelles à séquence constante
-(partiellement) héritables

Modifications chimiques Sur l'ADN

Modification dans l'organisation 3D de la chromatine
=Territoires chromosomiques

Interférence ARN

Expression aléatoire

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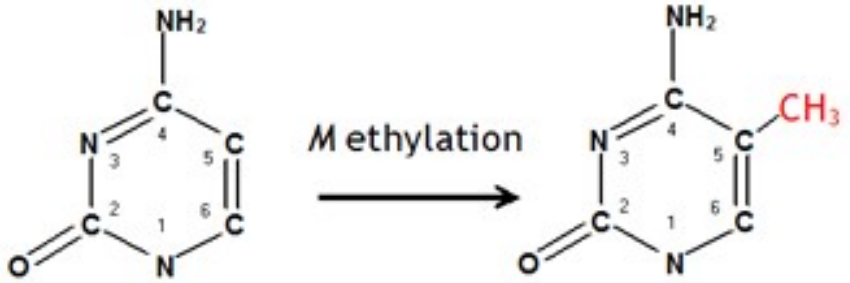
Méthylation de l'ADN



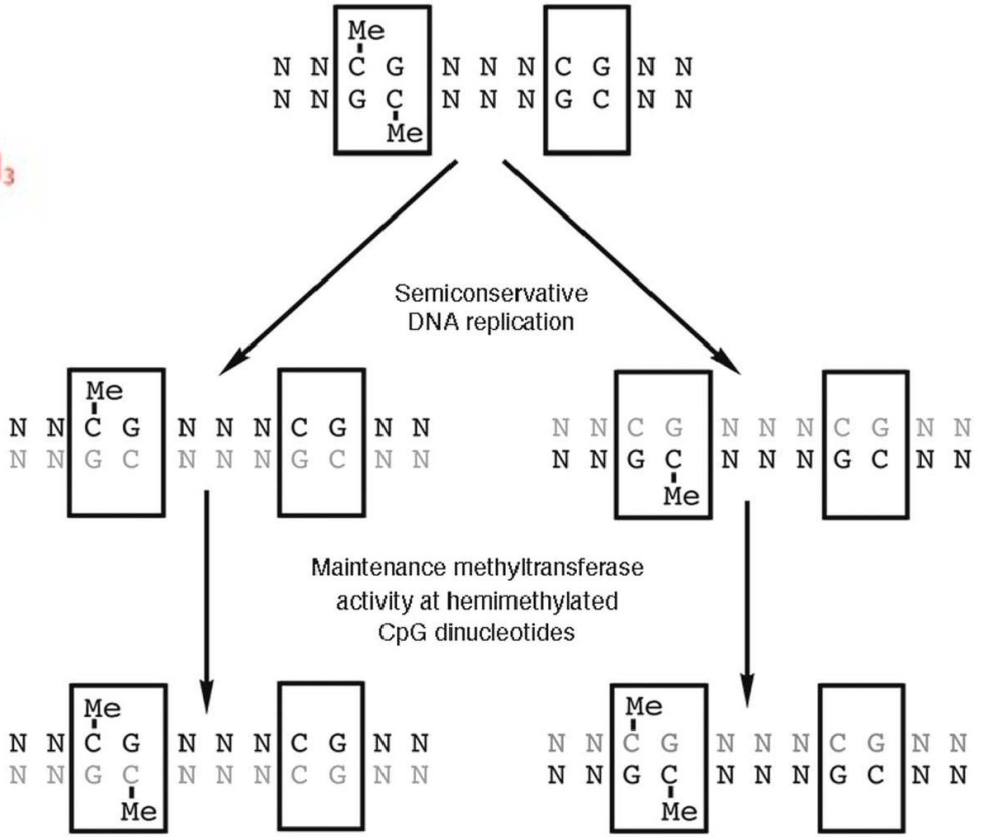


Figure 1. Maintenance methylation at CpG sites in mammalian DNA. The current view of DNA methylation in mammals involves de novo methylation in germ cells of the previous generation and in the early embryo, followed by maintenance methylation during development. Hemimethylated sites are thought to be the target for DNA methyltransferases of the DNA methyltransferase-1 (Dnmt1) family. As discussed in the text, this model is probably oversimplified to some degree.

DNA Replication and Human Disease © 2006 Cold Spring Harbor Laboratory Press, Chapter 7, Figure 1.

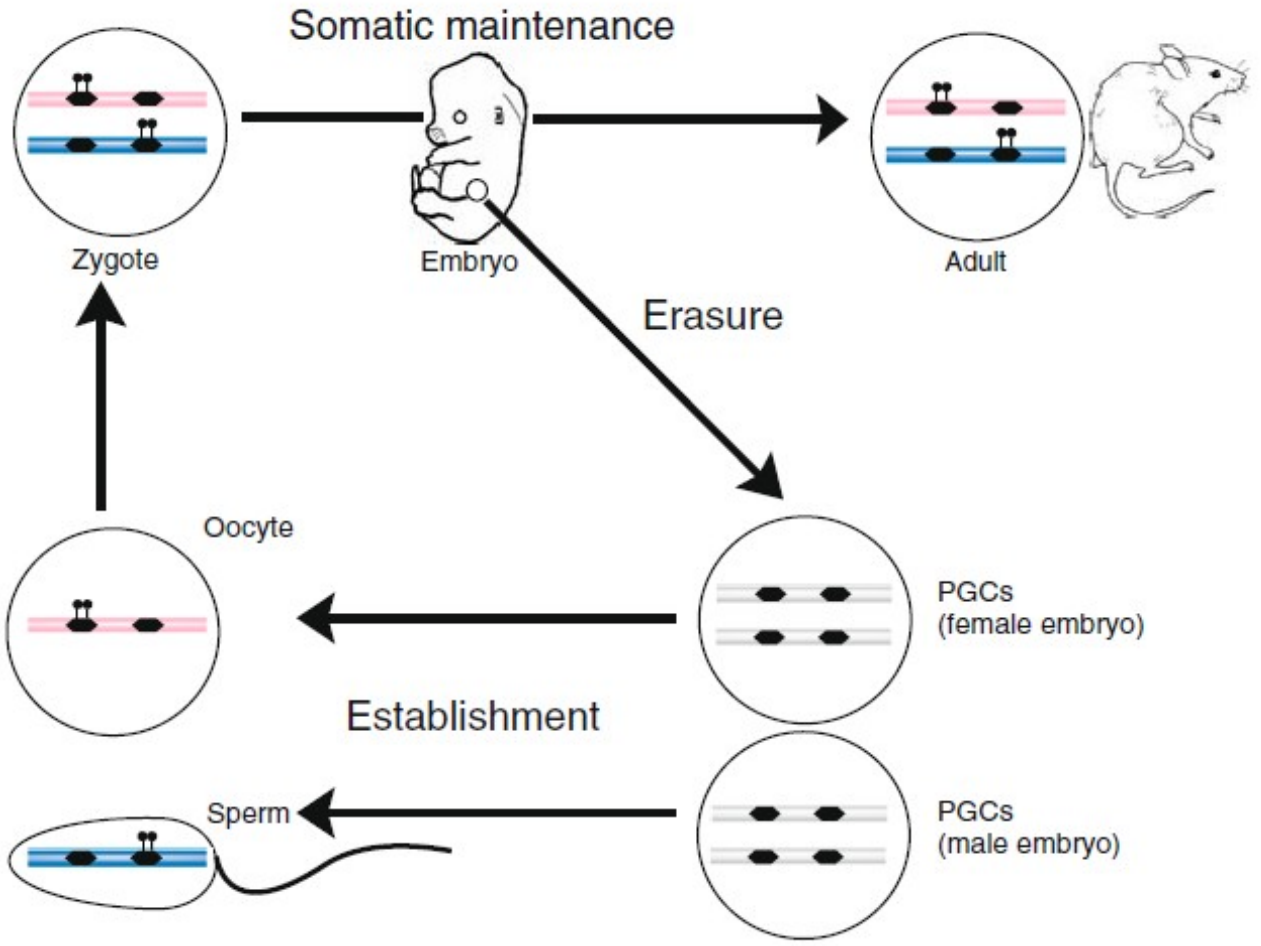
http://www.bio.miami.edu

La méthylation peut être transmise de parent à enfant dans la lignée germinale, et est centrale dans certaines formes d'hérédité épigénétique

La méthylation est **essentielle au développement normal de l'embryon** : elle permet d'éteindre certains gènes qui n'ont plus à être exprimés une fois qu'ils ont joué leur rôle, ou d'atténuer l'expression génétique pour maintenir l'identité cellulaire.

La méthylation de l'ADN **pourrait avoir evolué comme un mécanisme de défense** contre l'ADN viral, qui est inactivé par des enzyme de méthylation de l'ADN. L'existence de fragments d'ADN méthylés, silencieux, tout au long de notre génome pourrait être la trace d'anciens virus parasites dégradés et séquestrés

Empreinte génomique : méthylation allélique différentielle



Kacem & Feil, 2009

Exemple : Igf2 chez la souris (Insulin-like growth factor gene)

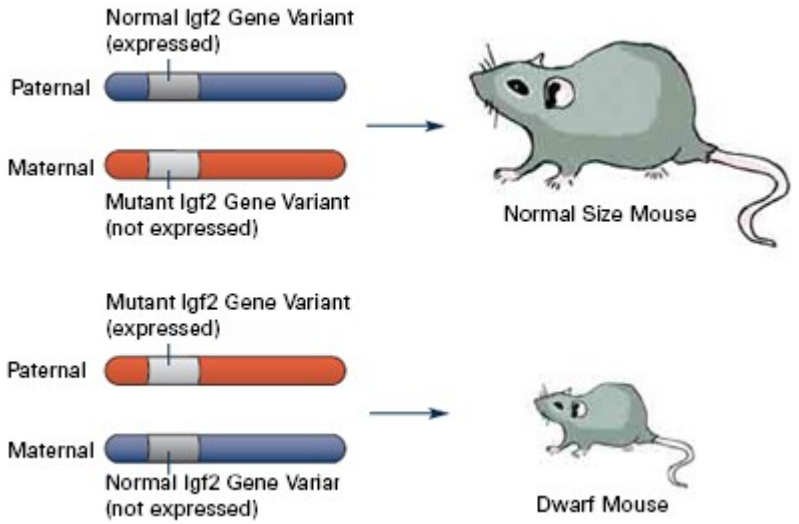
Un des premiers gènes soumis à empreinte découvert est Igf2 chez la souris. Le produit de ce gène est nécessaire pour la croissance normale de l'embryon, mais seul l'allèle paternel est exprimé. La copie maternelle est très méthylée, et silencieuse

Le gène peut muter et devenir inactif dans chaque gamète:

Ovocyte : une mutation résulte en un allèle maternel non fonctionnel
Spermatozoide: une mutation résulte en un allèle paternel non fonctionnel

Comme l'allèle maternel est silencieux, hériter d'un allèle maternel muté n'aura pas d'effet : le souriceau grossira normalement

Mais à l'inverse, hériter d'un allèle paternel muté conduira à l'expression de ce seul allèle et donc à du nanisme



http://www.bio.miami.edu

High-Resolution Analysis of Parent-of-Origin Allelic Expression in the Mouse Brain

2010

Christopher Gregg,[1,2]*† Jiangwen Zhang,[3]* Brandon Weissbourd,[1,2] Shujun Luo,[5] Gary P. Schroth,[5] David Haig,[4] Catherine Dulac[1,2]†

Genomic imprinting results in preferential expression of the paternal or maternal allele of certain genes. We have performed a genome-wide characterization of imprinting in the mouse embryonic and adult brain. This approach uncovered parent-of-origin allelic effects of more than 1300 loci. We identified parental bias in the expression of individual genes and of specific transcript isoforms, with differences between brain regions. Many imprinted genes are expressed in neural systems associated with feeding and motivated behaviors, and parental biases preferentially target genetic pathways governing metabolism and cell adhesion. We observed a preferential maternal contribution to gene expression in the developing brain and a major paternal contribution in the adult brain. Thus, parental expression bias emerges as a major mode of epigenetic regulation in the brain.

Mais...

NEWS IN FOCUS

GENETICS

RNA studies under fire

High-profile results challenged over statistical analysis of sequence data.

Nature News, 2012

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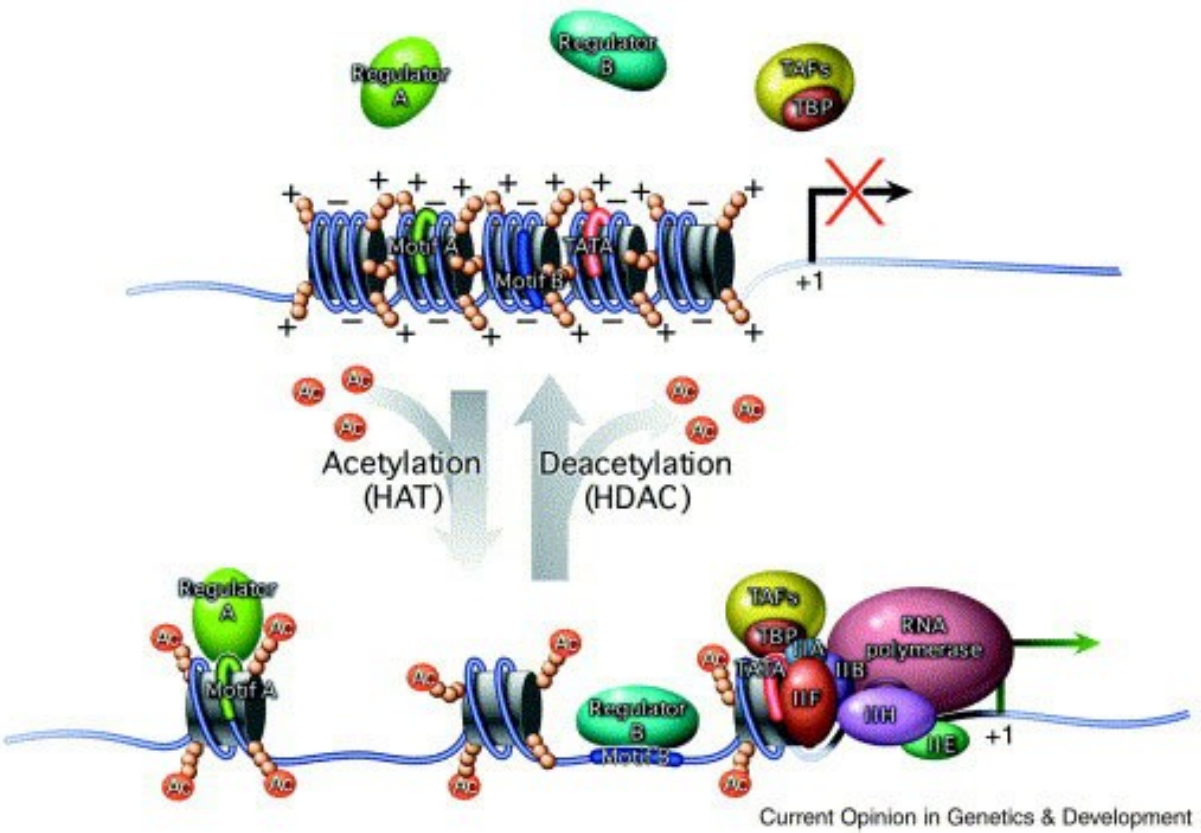
Une autre marque épigénétique : l'acétylation des histones



D'après Hsieh & Gage, 2004

REVIEW

Translating the Histone Code

Thomas Jenuwein[1] and C. David Allis[2]

2001

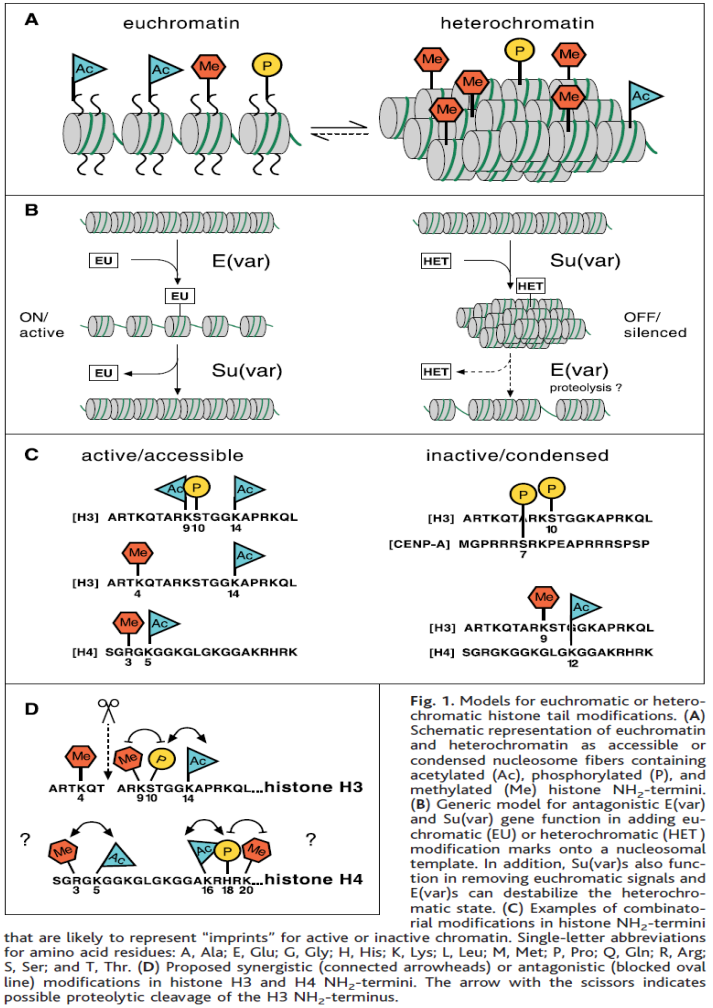
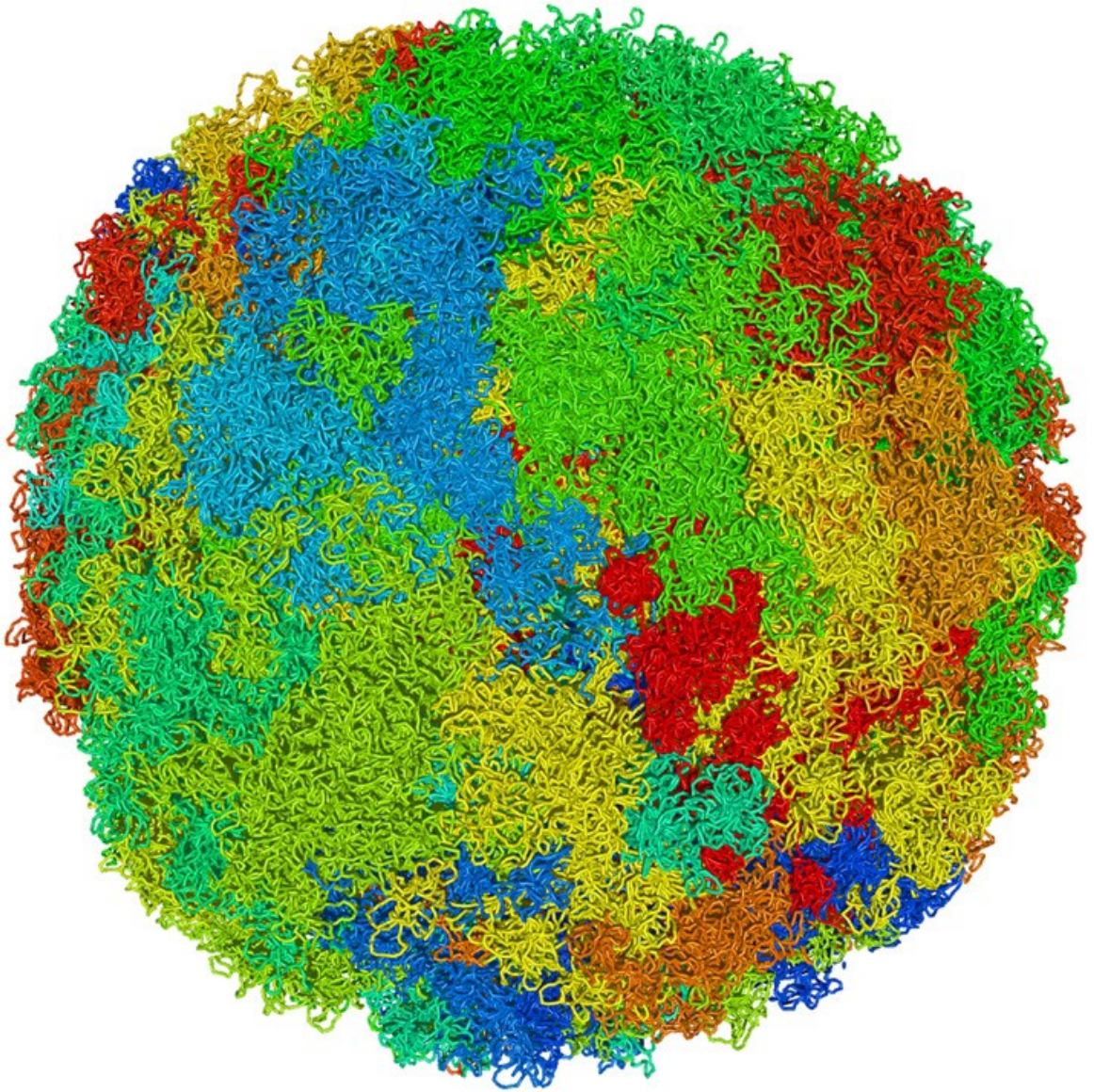


Fig. 1. Models for euchromatic or heterochromatic histone tail modifications. (**A**) Schematic representation of euchromatin and heterochromatin as accessible or condensed nucleosome fibers containing acetylated (Ac), phosphorylated (P), and methylated (Me) histone NH_2-termini. (**B**) Generic model for antagonistic E(var) and Su(var) gene function in adding euchromatic (EU) or heterochromatic (HET) modification marks onto a nucleosomal template. In addition, Su(var)s also function in removing euchromatic signals and E(var)s can destabilize the heterochromatic state. (**C**) Examples of combinatorial modifications in histone NH_2-termini that are likely to represent "imprints" for active or inactive chromatin. Single-letter abbreviations for amino acid residues: A, Ala; E, Glu; G, Gly; H, His; K, Lys; L, Leu; M, Met; P, Pro; Q, Gln; R, Arg; S, Ser; and T, Thr. (**D**) Proposed synergistic (connected arrowheads) or antagonistic (blocked oval line) modifications in histone H3 and H4 NH_2-termini. The arrow with the scissors indicates possible proteolytic cleavage of the H3 NH_2-terminus.

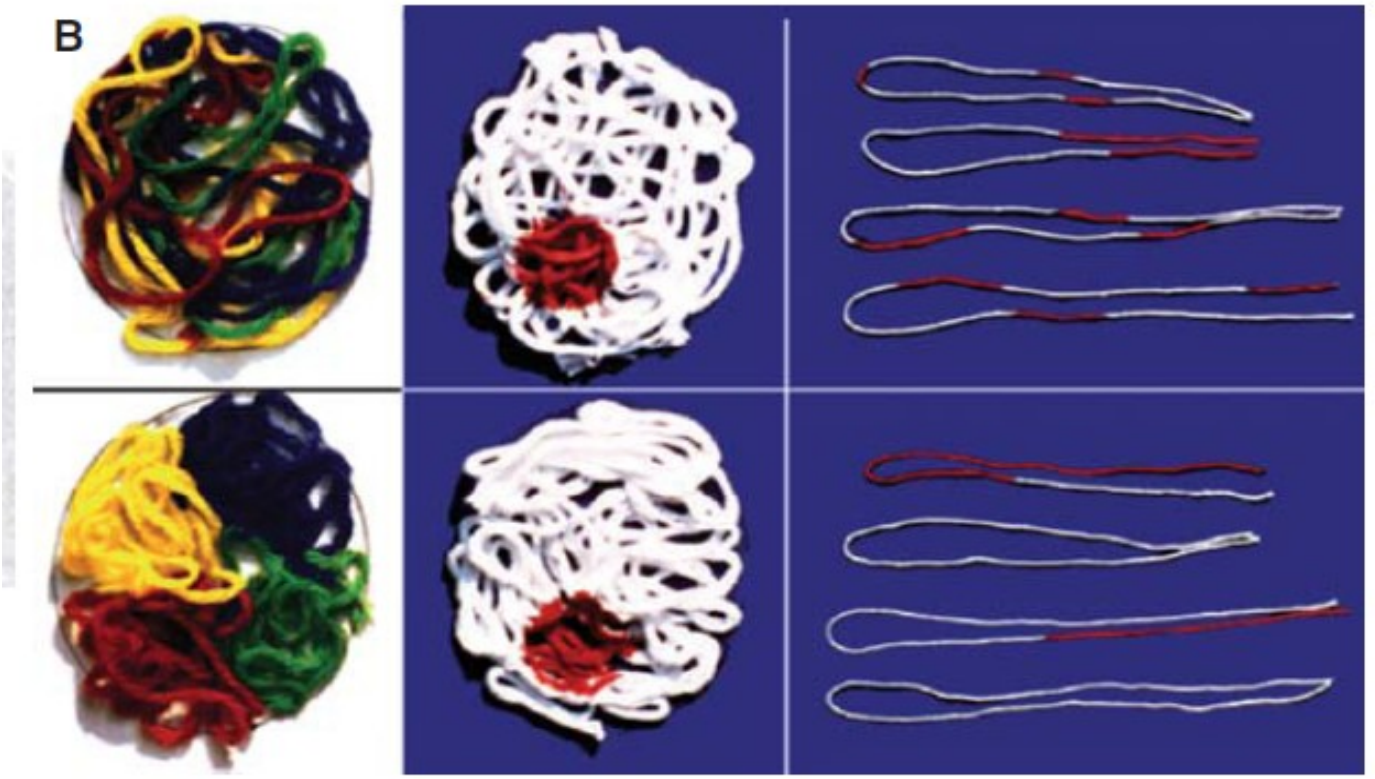
Territoires chromosomiques



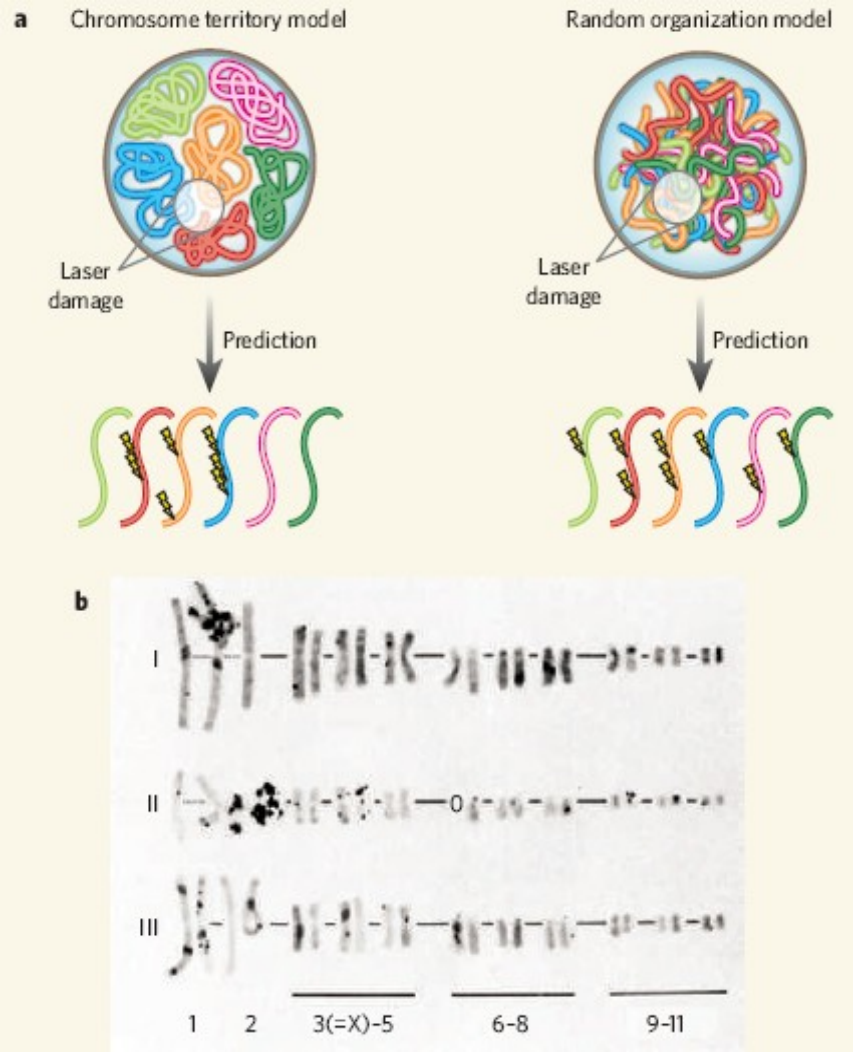
Knoch, 2002

?

A la fin du 19ème siècle, C. Rabl et Th. Boveri émettent l'hypothèse que pendant l'interphase, les chromosomes gardent leur intégrité

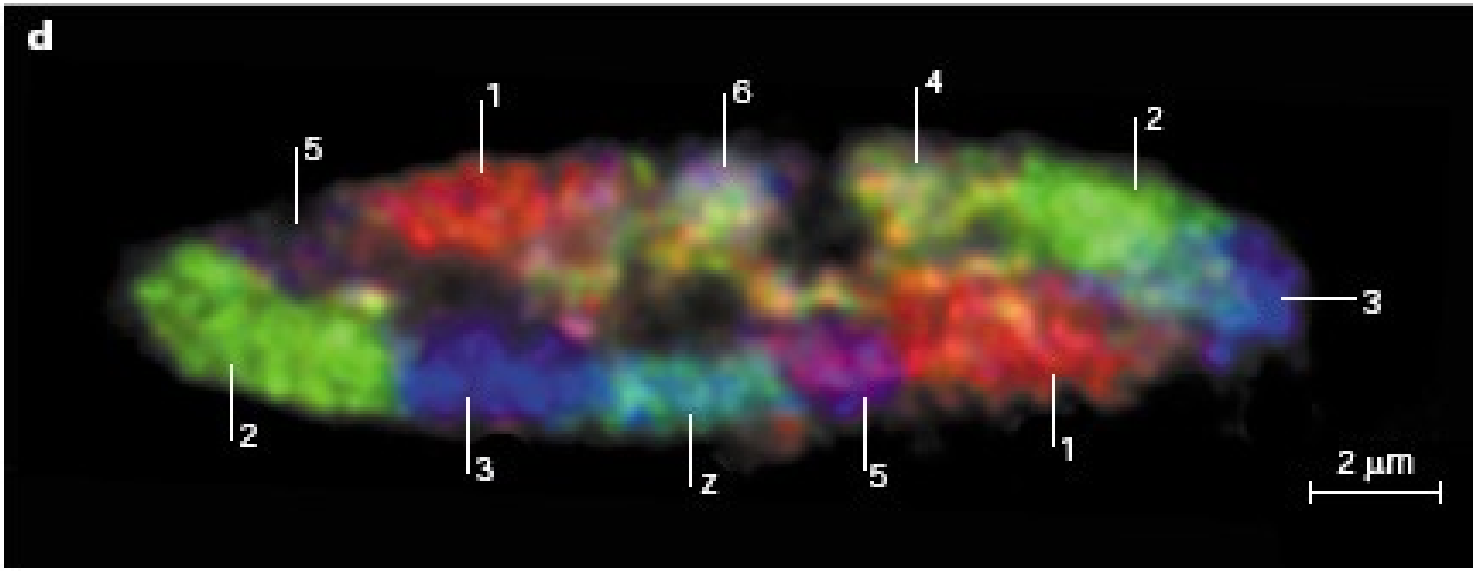


Cremer *et al*, 1982 (in Cremer & Cremer 2010)



Cremer & Cremer 2010

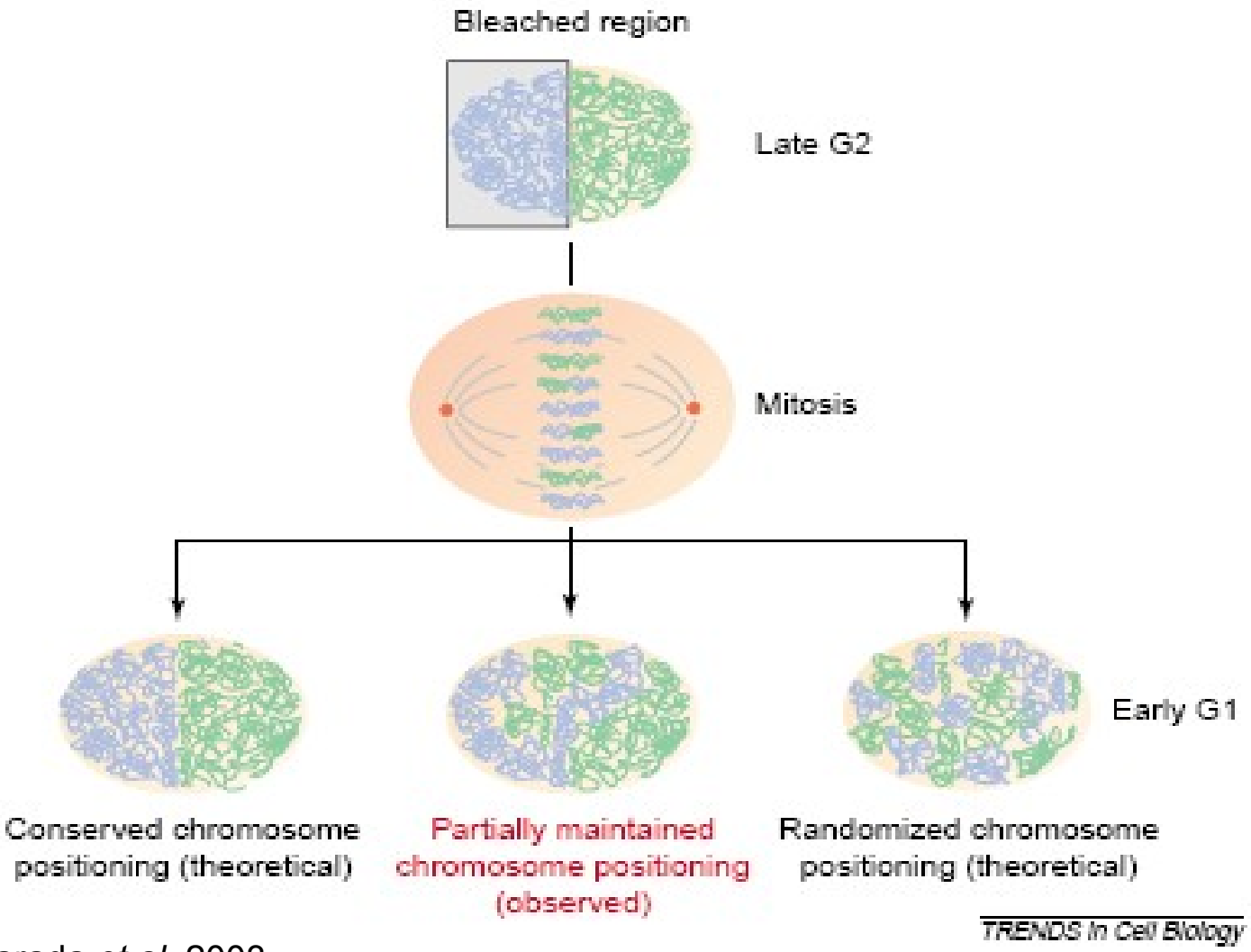
Confirmation dans les années 1980 par Thomas et Christoph Cremer



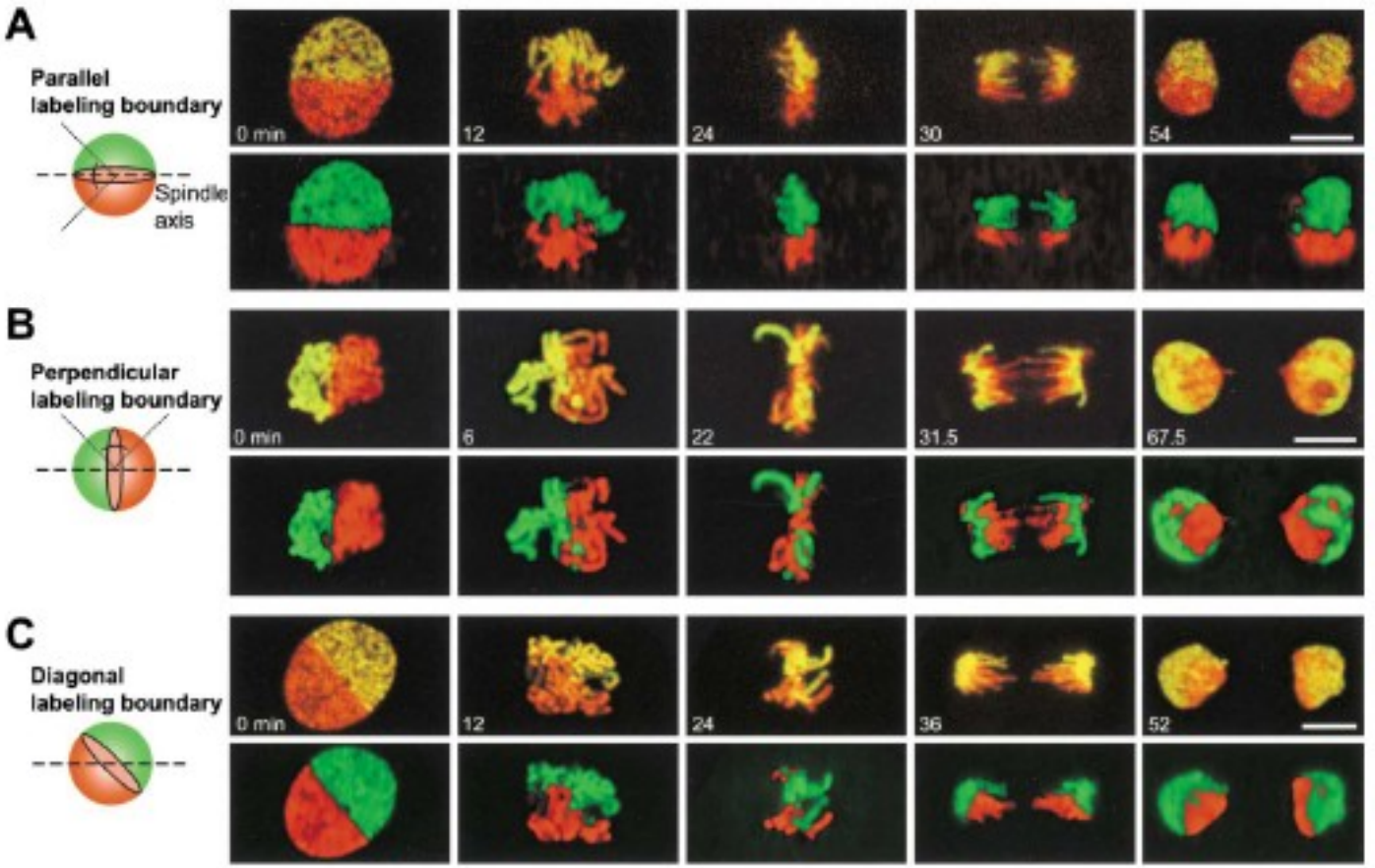
Cremer & Cremer, 2001

Noyau de cellule (Poulet) à l'interphase (G. gallus)

Mise en évidence d'une persistence partielle de la distribution interphasique après la division celllulaire

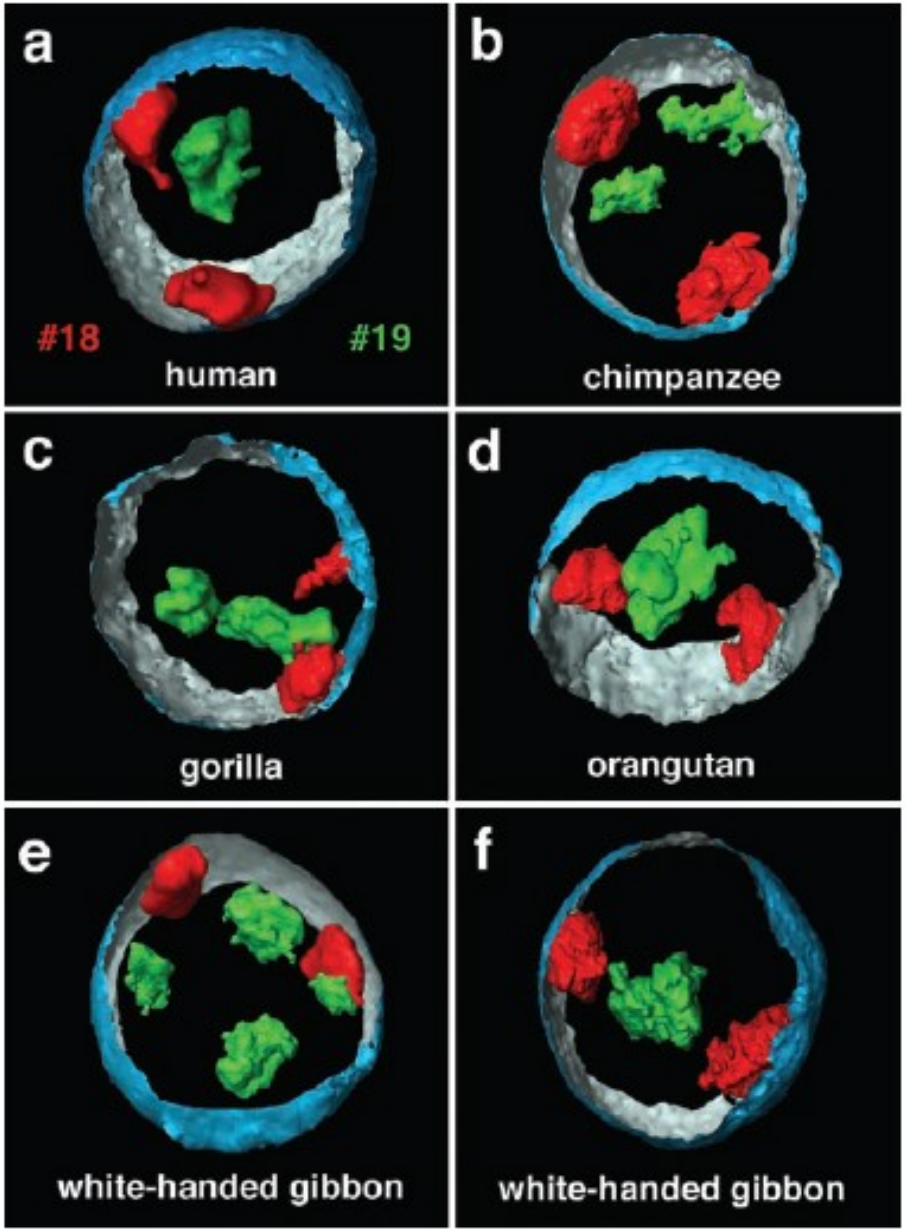


Parada *et al*, 2003

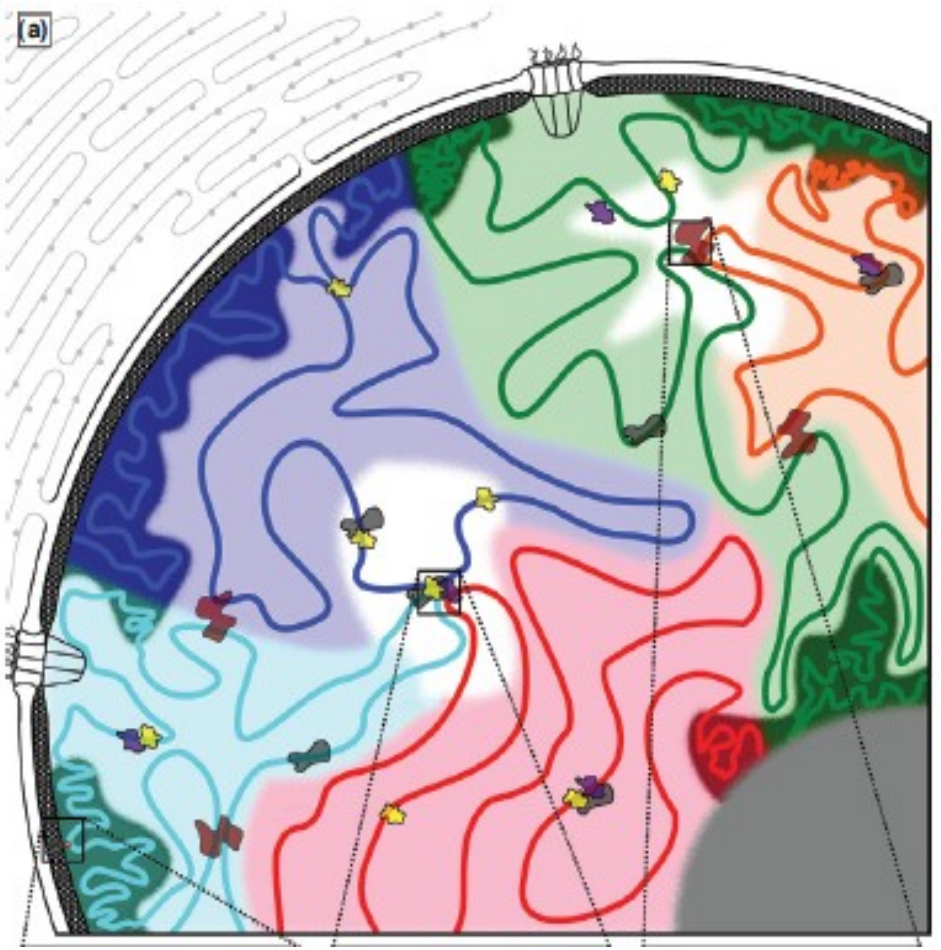


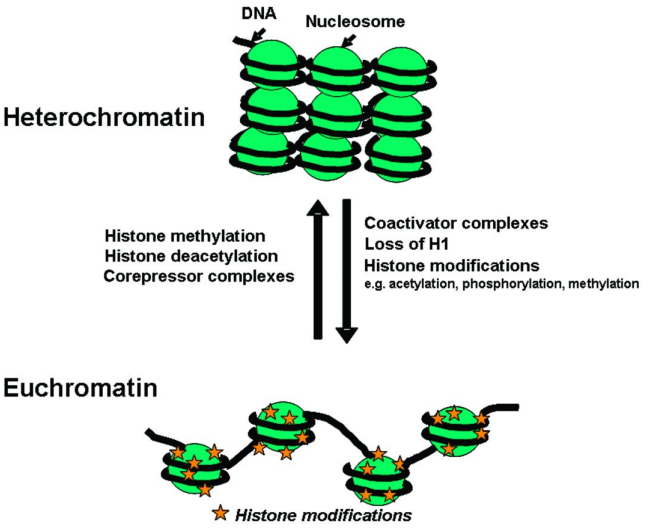
Gerlich *et al,* 2003

Conservation évolutive des territoires chromosomiques



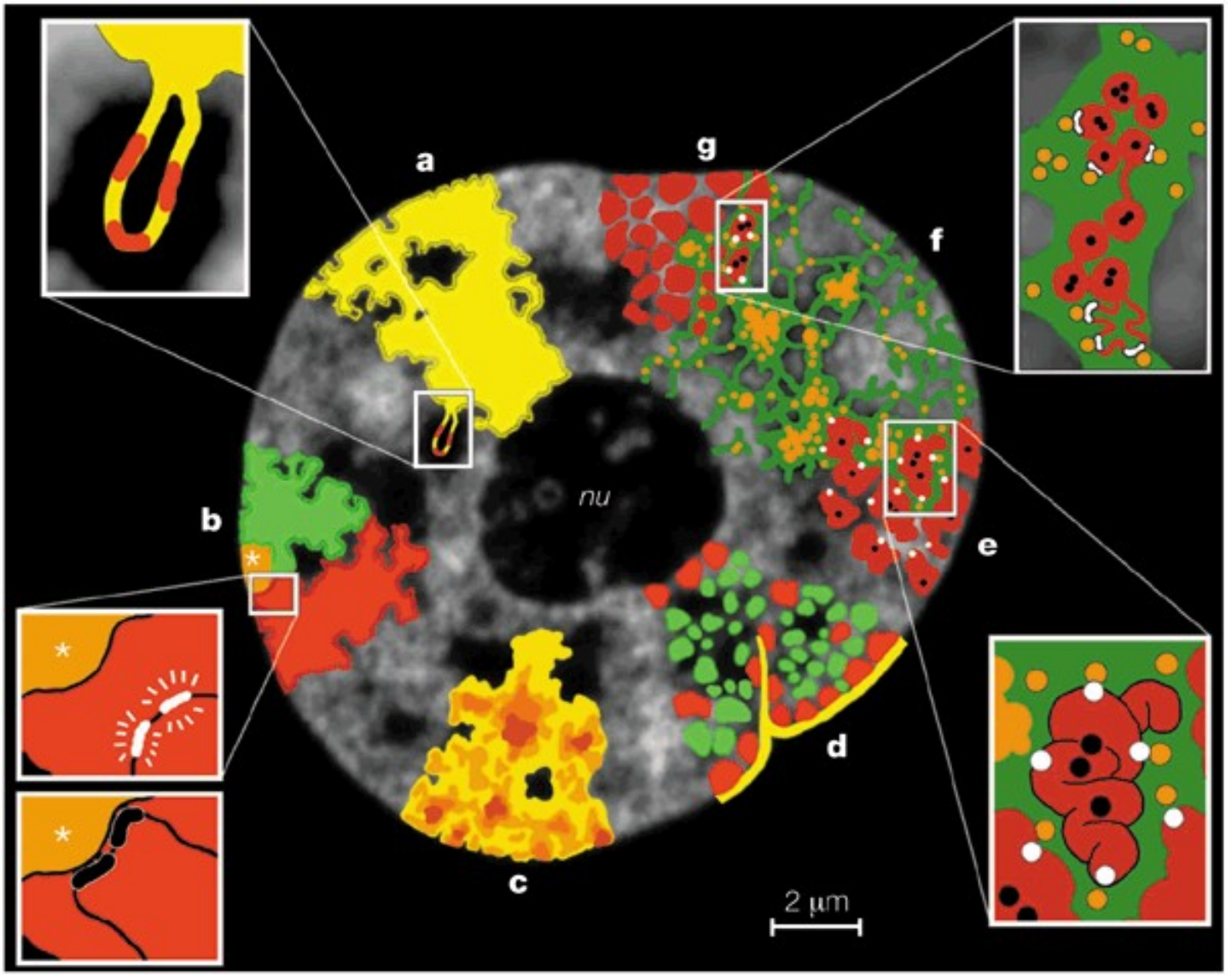
Tanabe *et al*, 2007



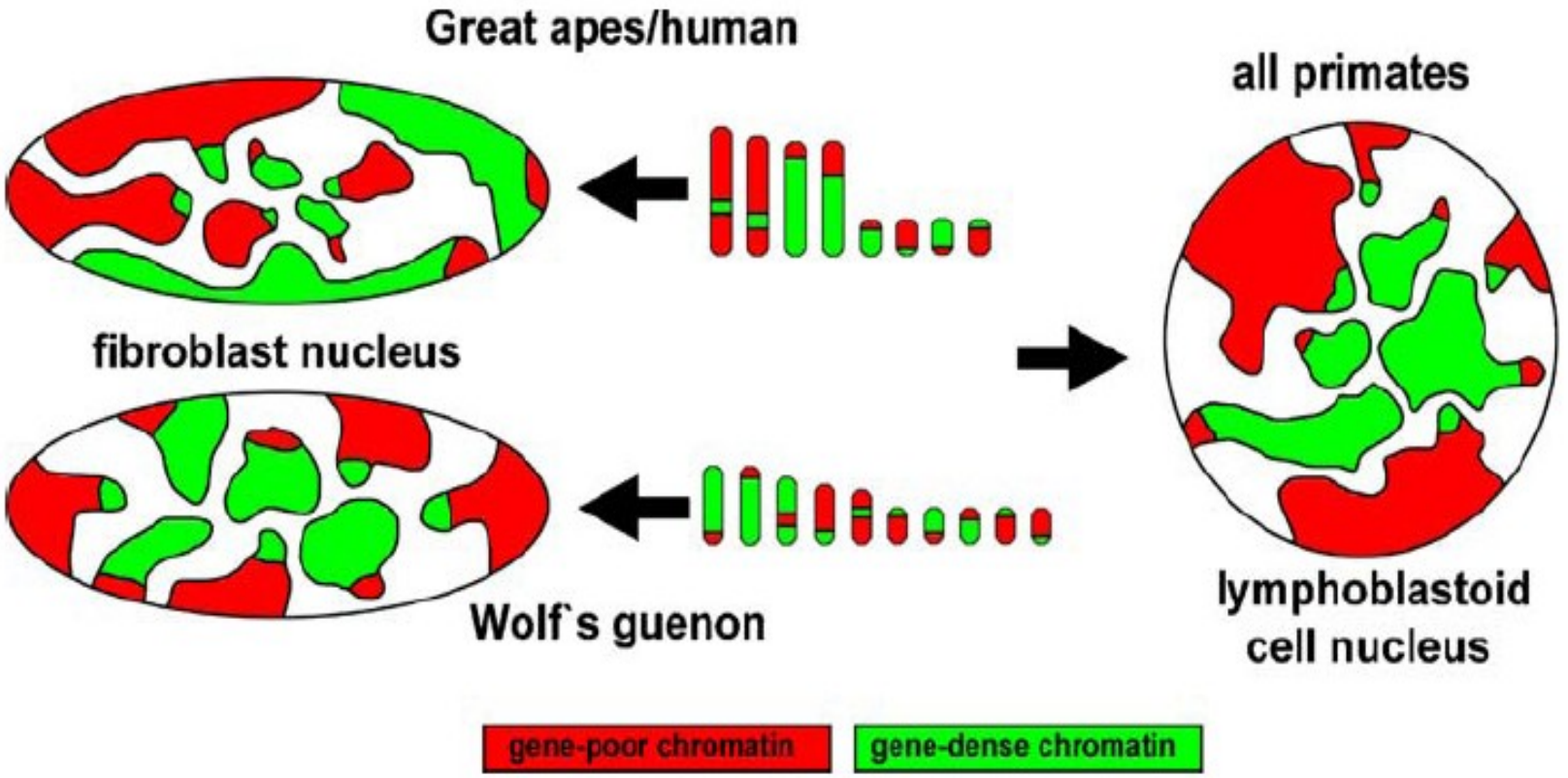


Geyer *et al*, 2011

Plusieurs niveaux de complexité



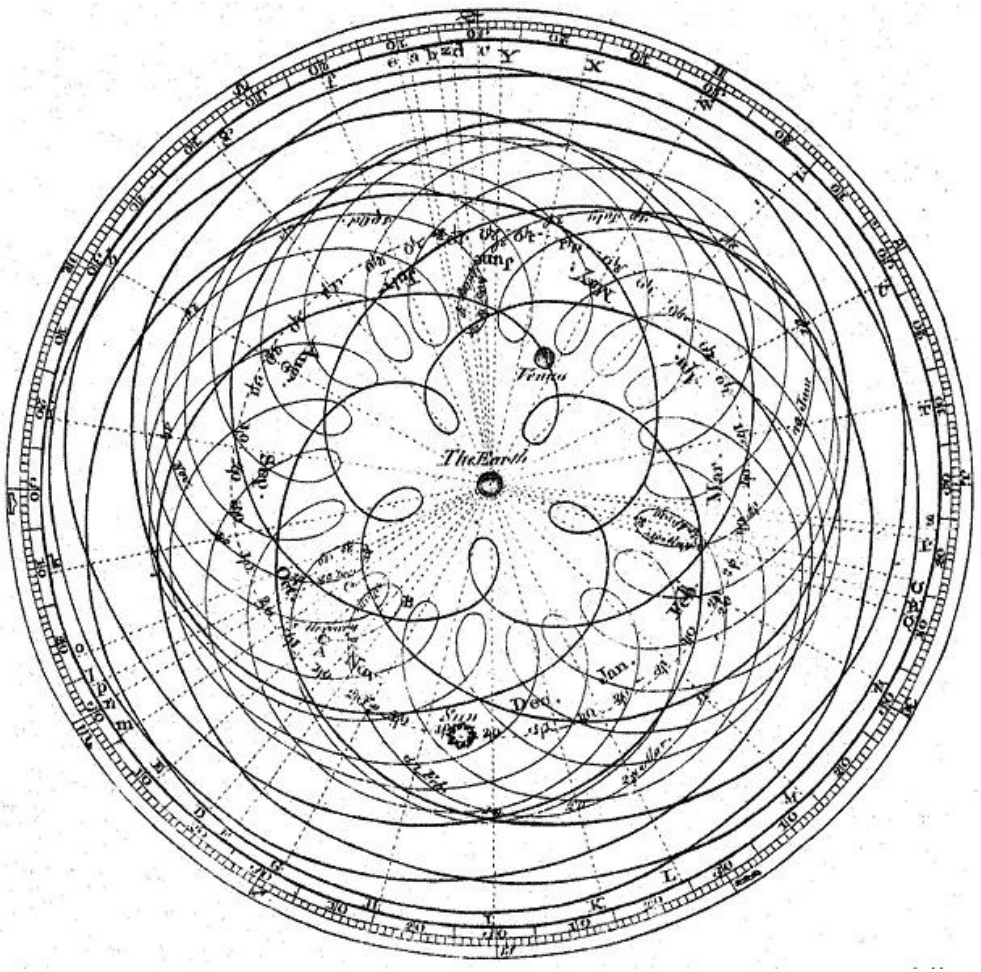
Cremer & Cremer, 2001



Neusser *et al*, 2007

‘Lamarckian’ mechanisms in darwinian evolution

Eva Jablonka
Marion J. Lamb
Eytan Avital



« ***Epi...*** »

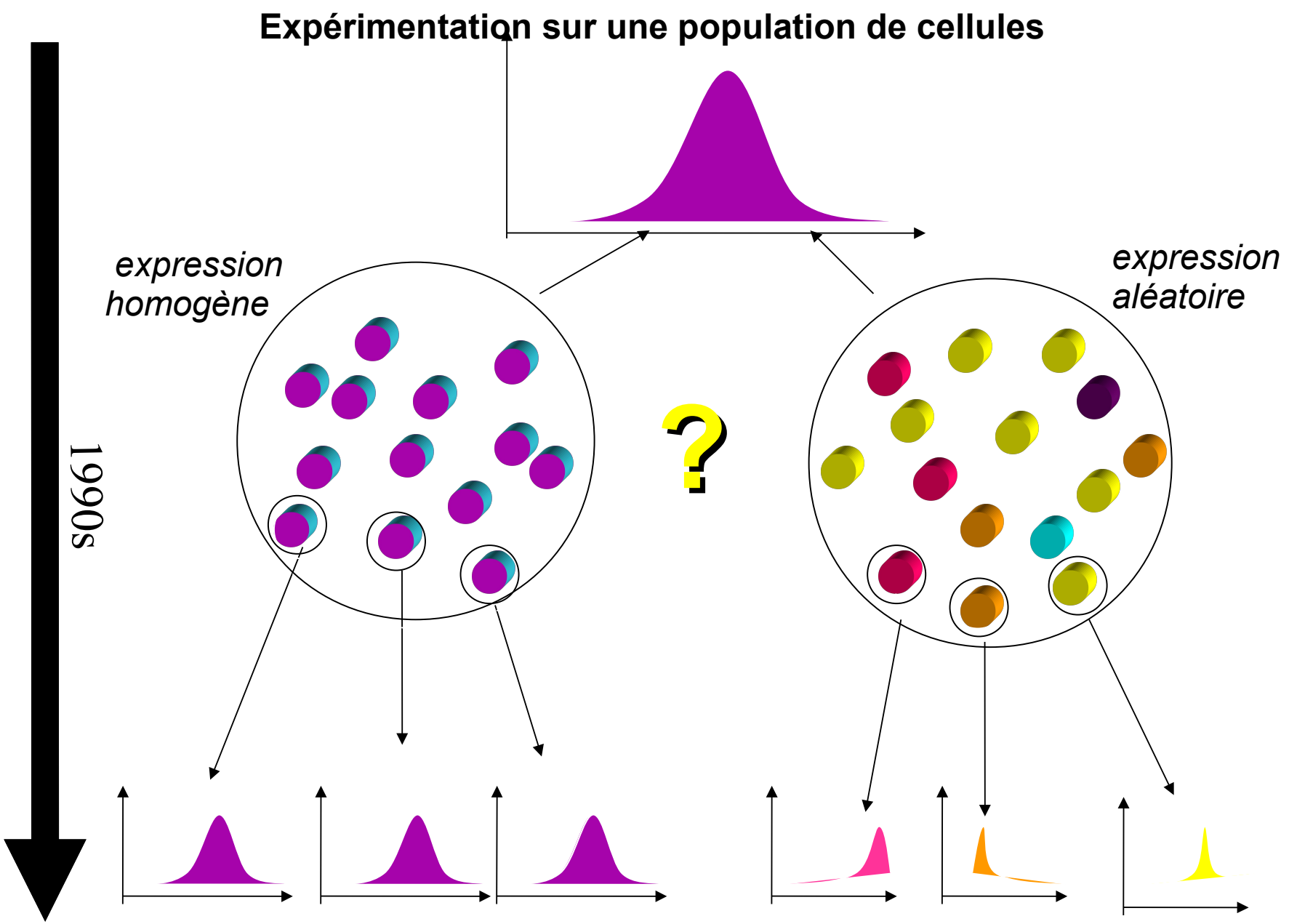
Épicycles : décrits dès le 3ème siècle avant JC, éléments du système géocentrique de Ptolémée (2ème siècle après JC)

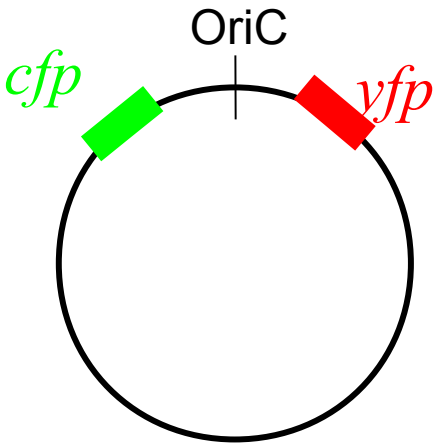
Abandonnés à la fin de la révolution copernicienne...

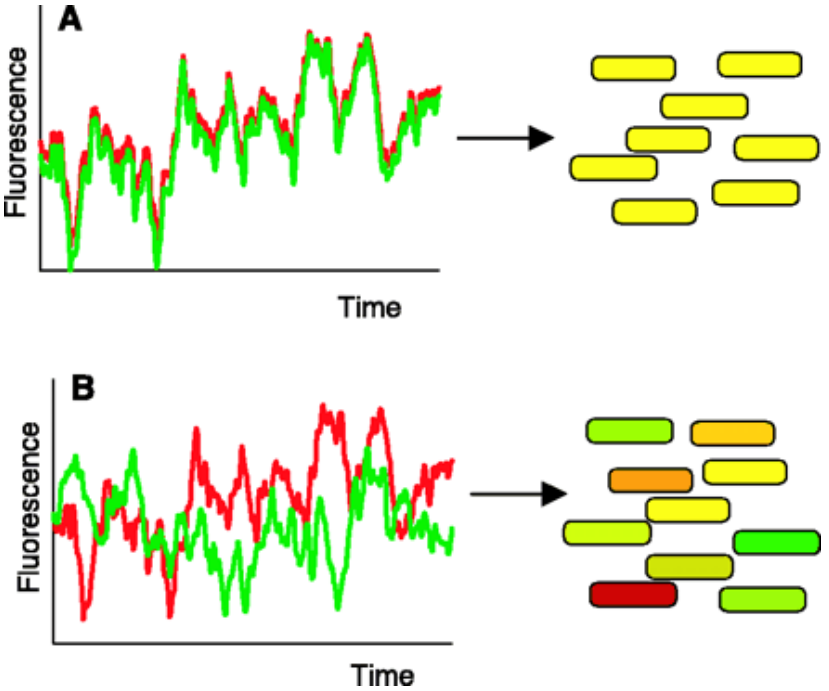
Une expression *stochastique* des gènes ?

"The mechanism causing cats to beget cats and fish to beget fish is hardwired in the genomic DNA (...) "
(Davidson et al*, 2002)*

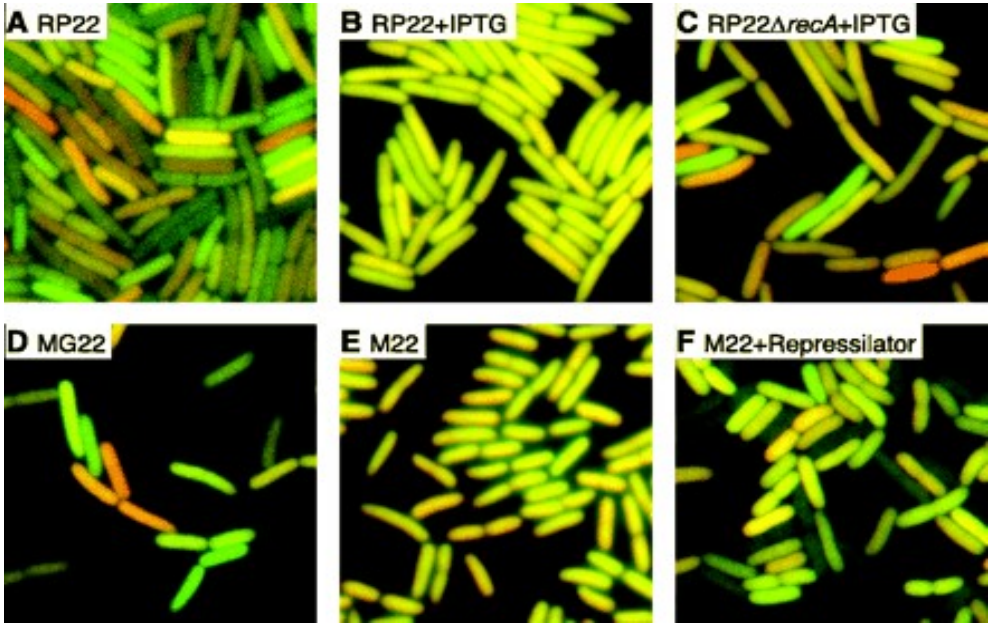
"The large number of cell states that are present in the lifetime of an organism and the reproducibility with which they are generated indicates the existence not just of programmes but also of mechanisms that ensure their reliable execution"
(Arias & Hayward, 2006)

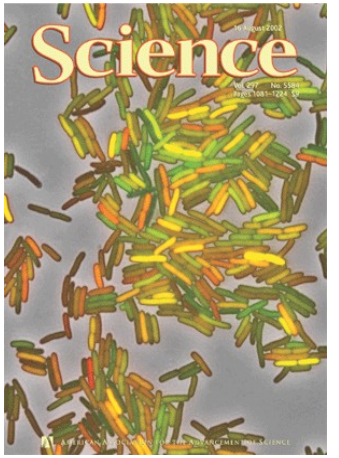

Expérimentation sur une population de cellules
expression homogène
expression aléatoire
1990s
?
Expérimentation sur des cellules individuelles





Elowitz et al*, 2002*





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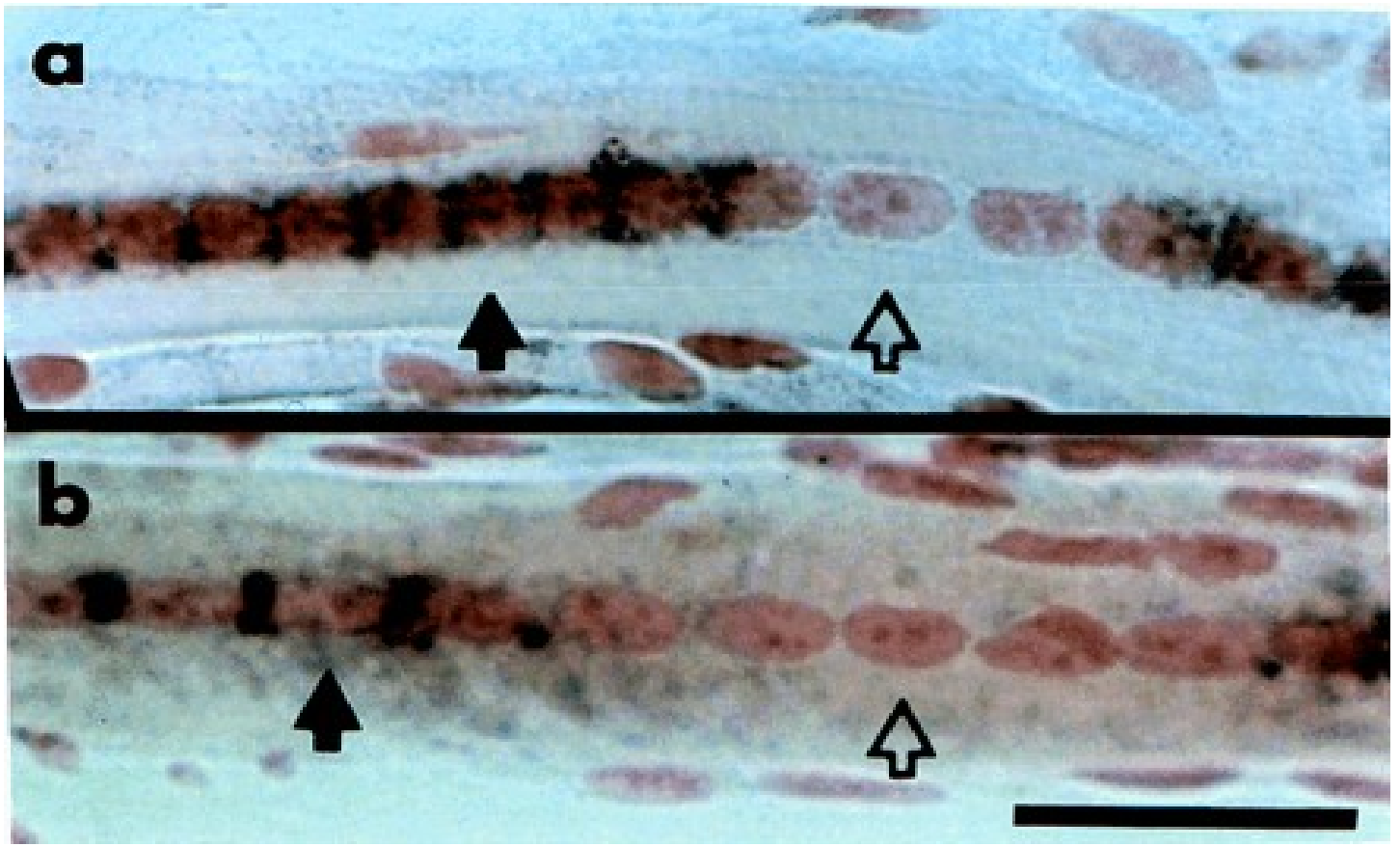
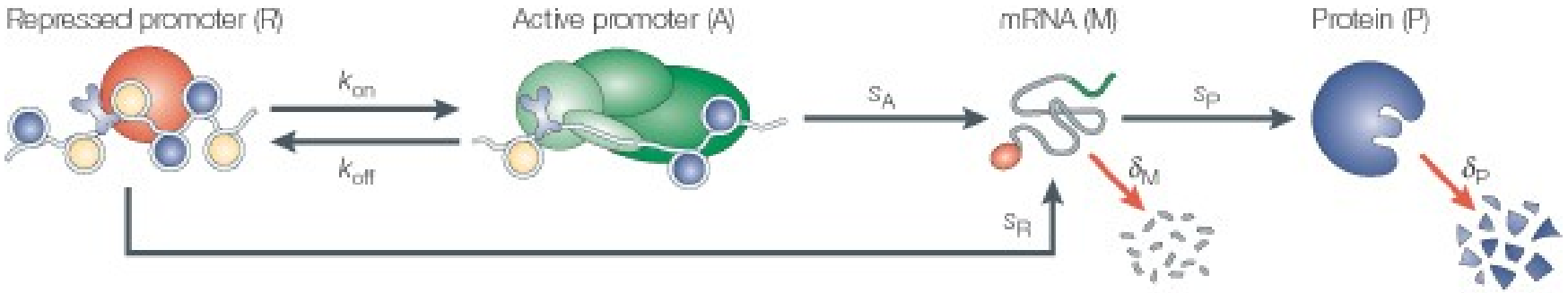


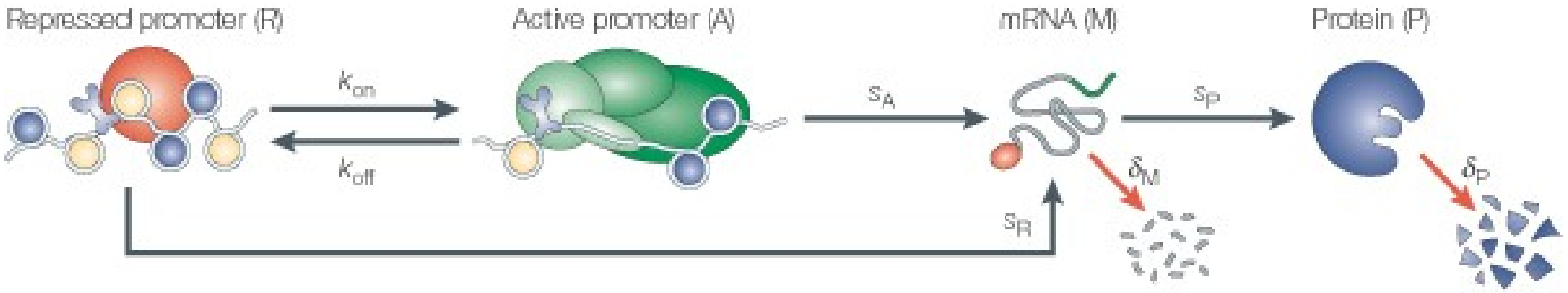
Newland *et al*, 1998

Expression différentielle du gène α -SA au sein d'une fibre musculaire multinucléée (souris)



L ’expression génétique est un processus multiétapes

Kaern et al, *2005*



Kaern et al, *2005*

L ’expression génétique est un processus multiétapes

Les structures nucléaires sont très dynamiques

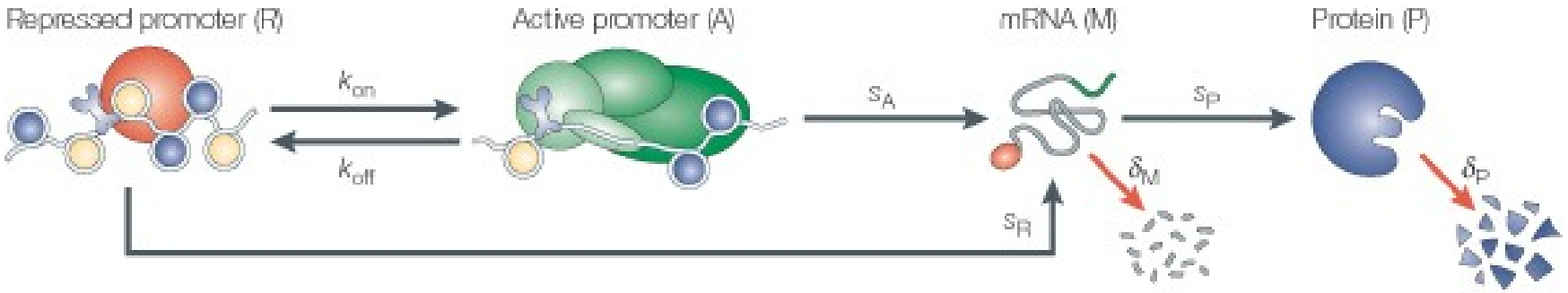
Exemples : Chromatine ⟷ H1 : 1 minute

Activateurs de la transcription (parfois <1/cellule !)

Complexe d ’initiation de la transcription

“Usines” à transcription : ↗ Probabilité transcription

Localisation : 2500 sites *seulement*



Kaern et al, *2005*

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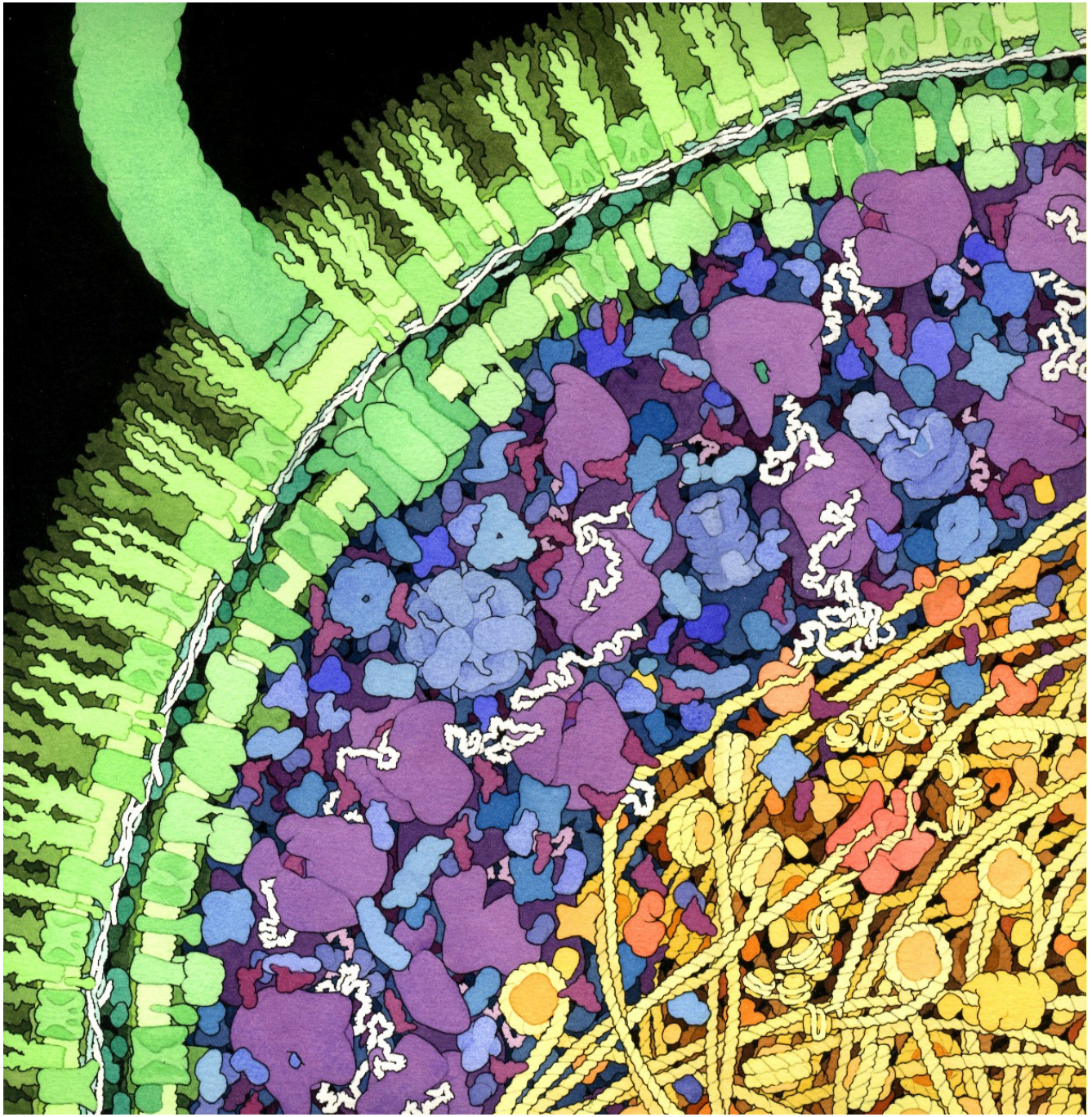
Localisation : 2500 sites *seulement*

La disponibilité des molécules régulatrices est fluctuante

80% des protéines : -100 copies/cellule

Exemples : PBP2 (division cellulaire) 20 copies/cellule
Primase dnaG (initiation réplication) 50 à 100
Deoxyribopyrimidine photolyase(réparation ADN):10 à 20

⟶ **+ Effet d'échantillonnage**



Encombrement macromoléculaire

Goodsell, 1993

OPEN ACCESS Freely available online

PLoS one

Influence of Stochastic Gene Expression on the Cell Survival Rheostat after Traumatic Brain Injury

Daniel R. Rojo[1], Donald S. Prough[1], Michael T. Falduto[2], Deborah R. Boone[1], Maria-Adelaide Micci[1], Kristen M. Kahrig[1], Jeanna M. Crookshanks[1], Arnaldo Jimenez[3], Tatsuo Uchida[1], Jeremy C. Cowart[1], Bridget E. Hawkins[1], Marcela Avila[1], Douglas S. DeWitt[1], Helen L. Hellmich[1]*

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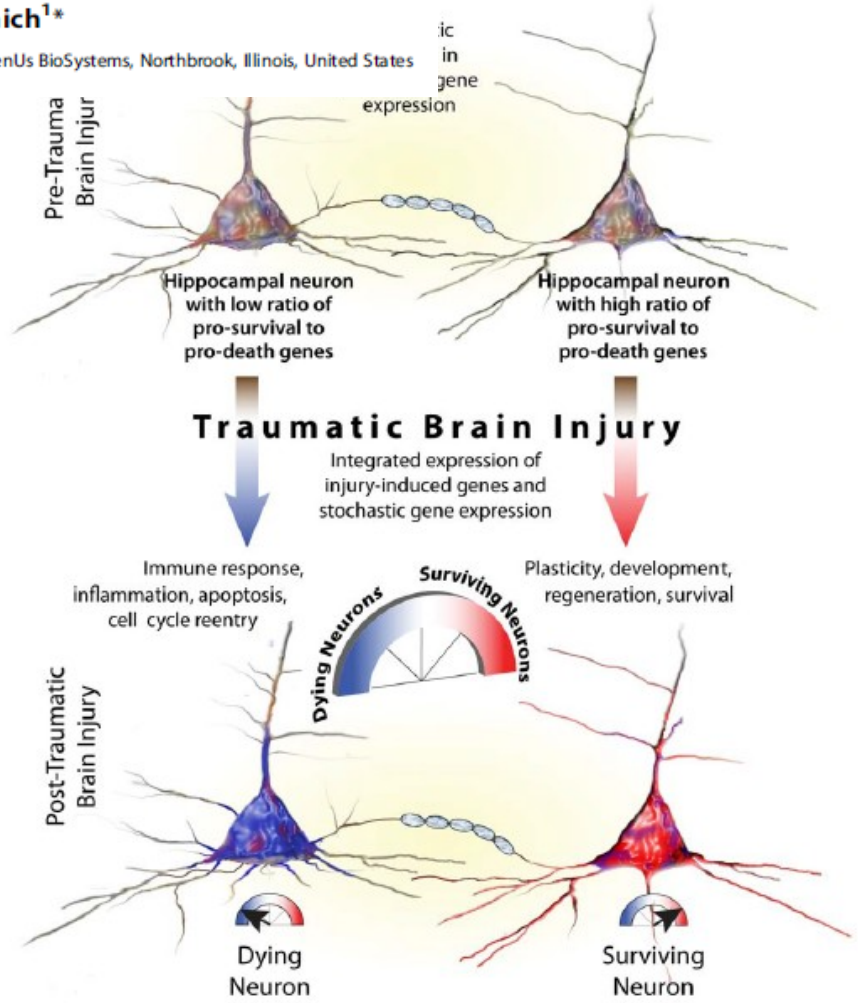

Figure 7. Rheostat model of neuronal survival after traumatic brain injury.
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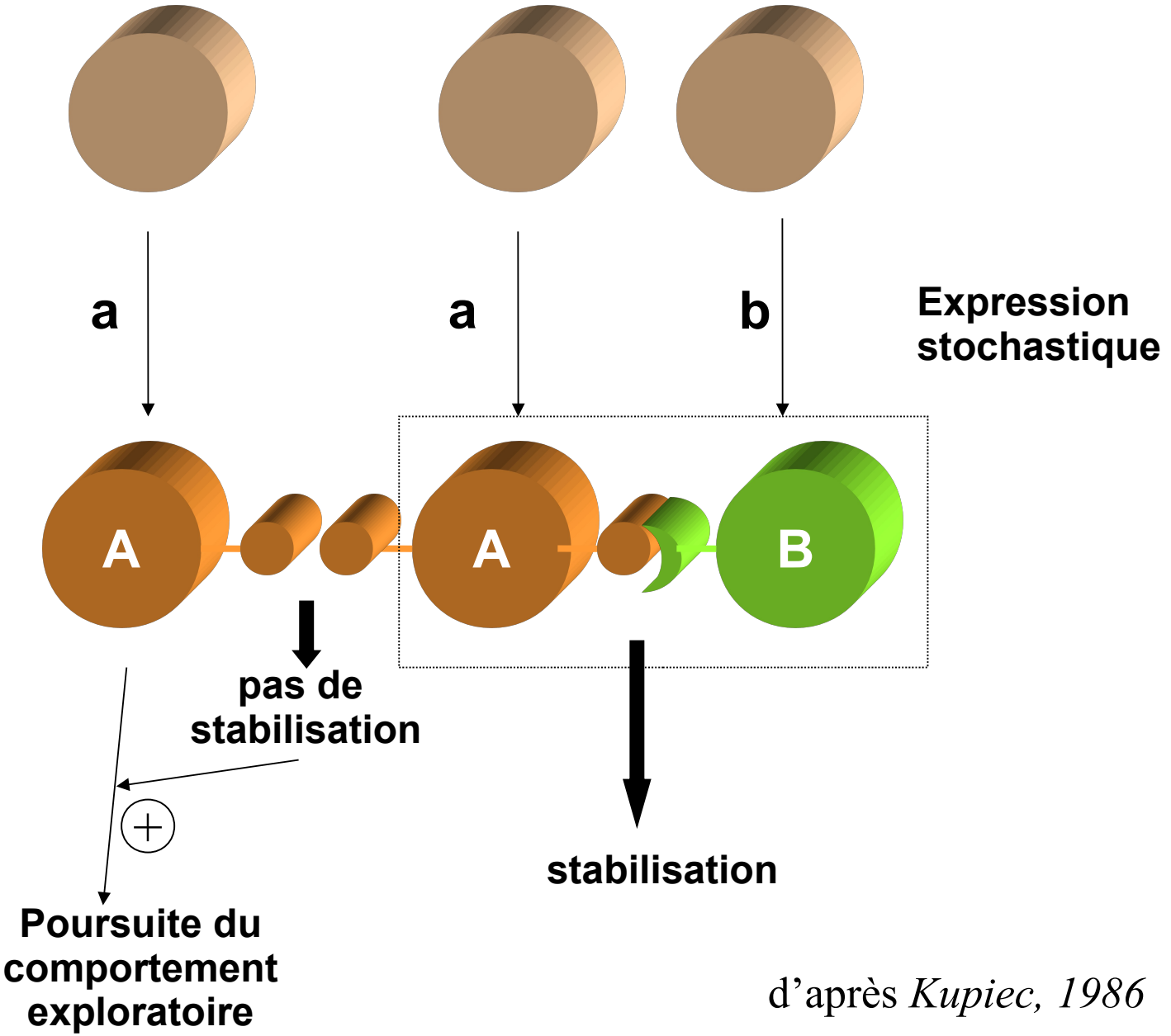
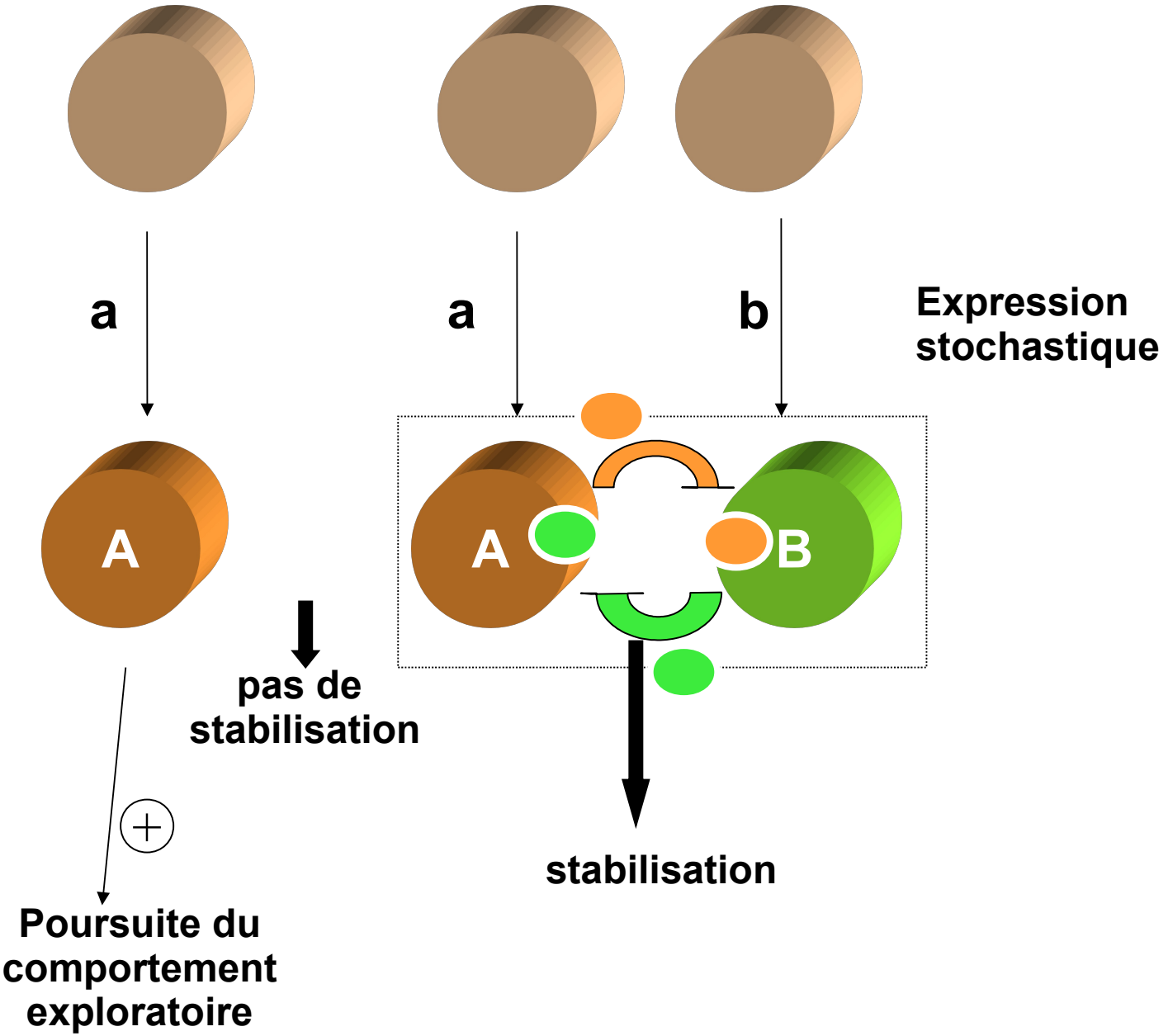
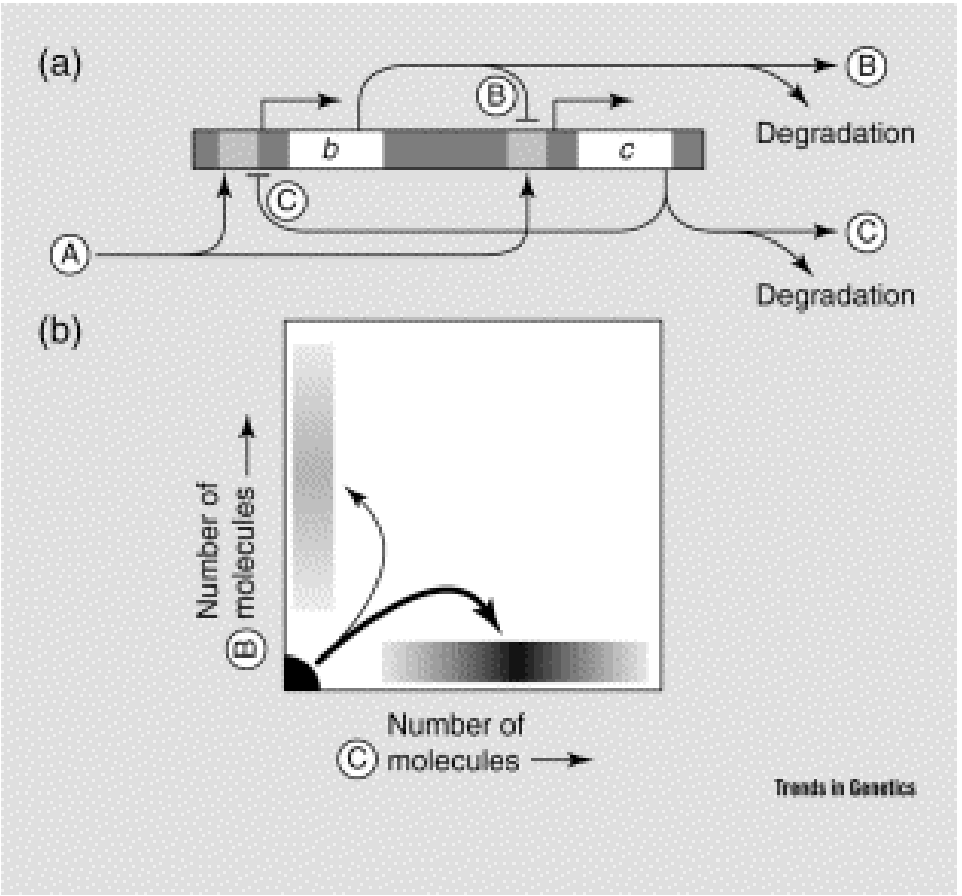


d'après *Kupiec, 1986*

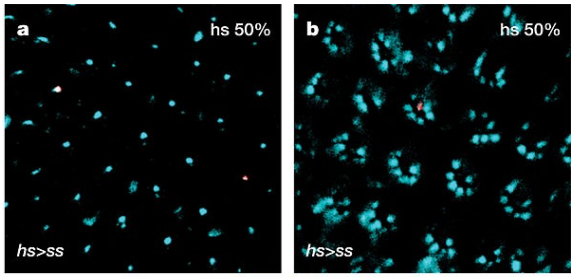

a
a
b
Expression stochastique
A
A
B
pas de stabilisation
stabilisation
Poursuite du comportement exploratoire

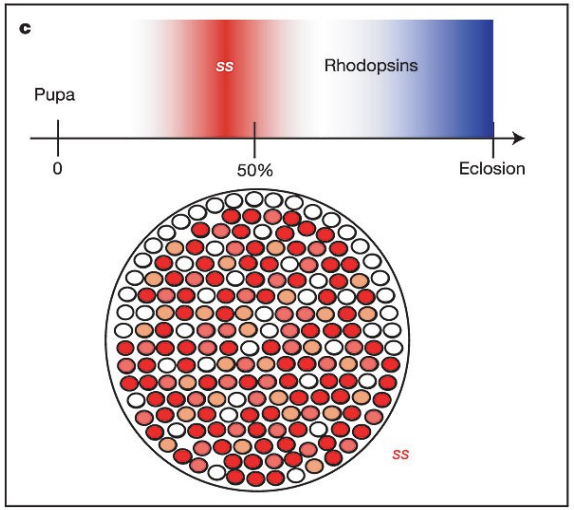
Fonctionnement déterministe et résultat aléatoire

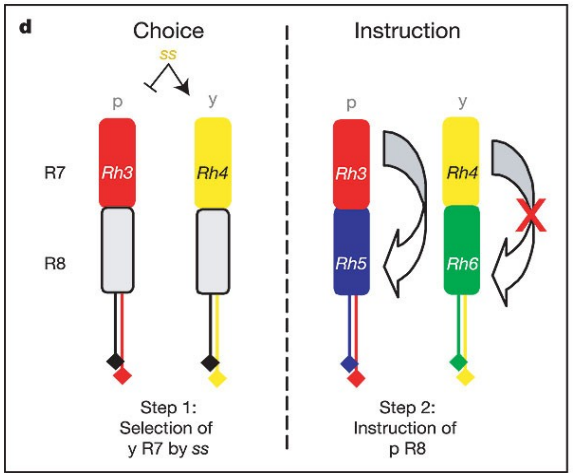


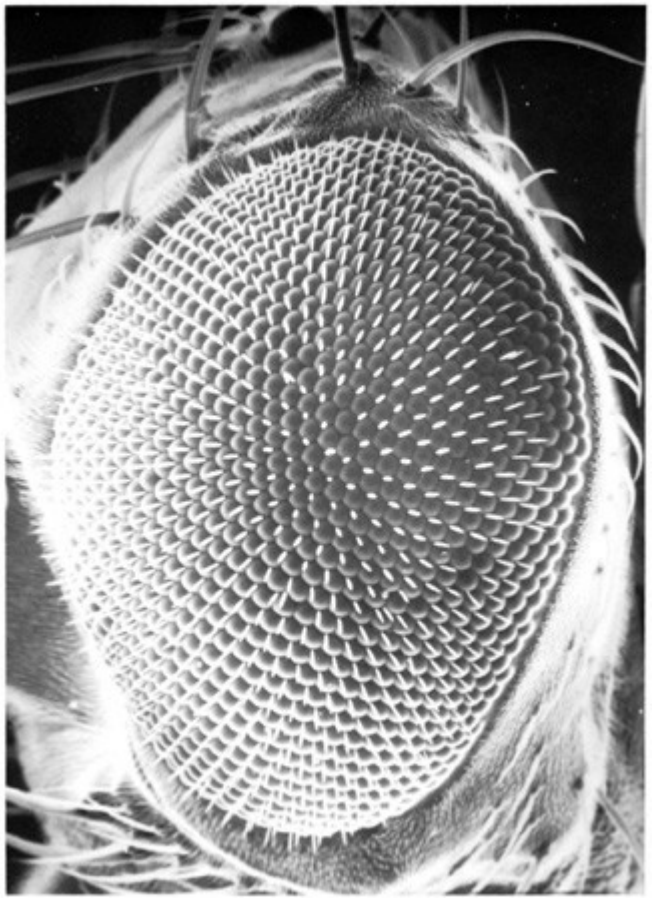
Arkin & McAdams, 1999

Expression stochastique de *spineless* et différenciation





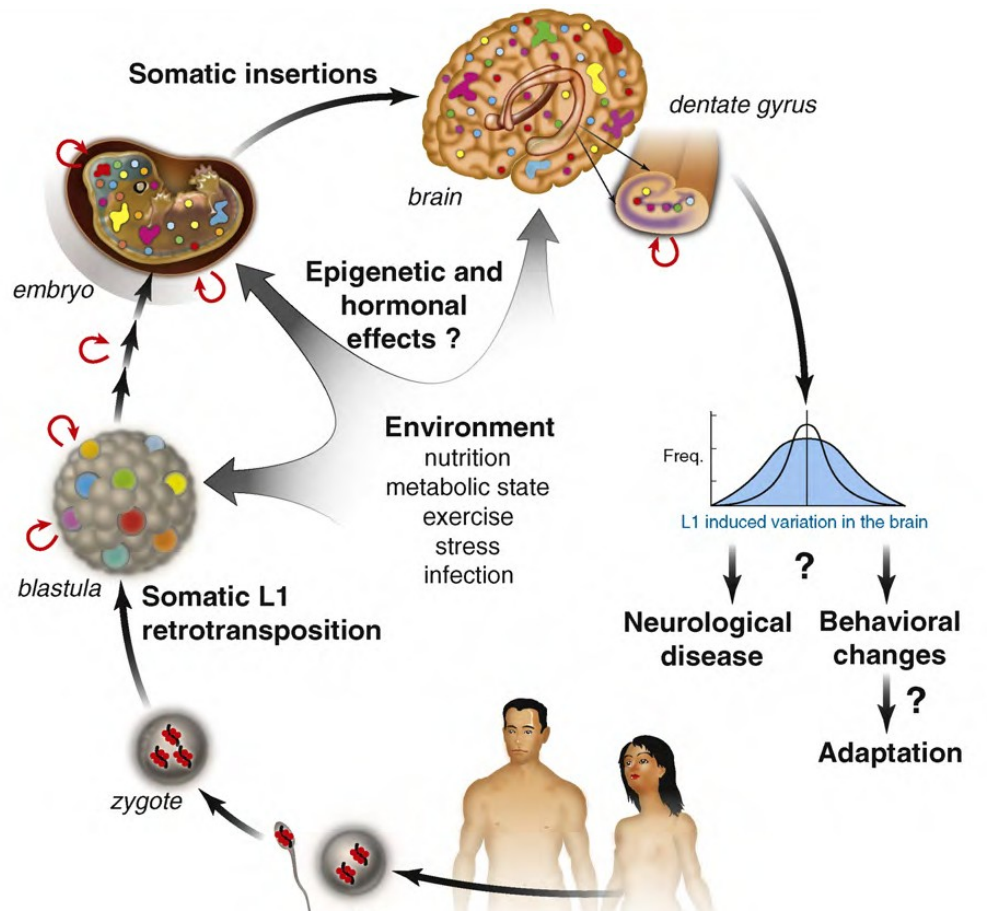




Wernet et al*, 2006*

Un génome mosaïque

LINE-1 (L1) elements are retrotransposons that insert extra copies of themselves throughout the genome using a 'copy and paste' mechanism. L1s comprise nearly ~20% of the human genome and are able to influence chromosome integrity and gene expression upon reinsertion. Recent studies show that L1 elements are active and 'jumping' during neuronal differentiation. New somatic L1 insertions could generate 'genomic plasticity' in neurons by causing variation in genomic DNA sequences and by altering the transcriptome of individual cells. Thus, L1-induced variation could affect neuronal plasticity and behavior. We discuss potential consequences of L1-induced neuronal diversity and propose that a mechanism for generating diversity in the brain could broaden the spectrum of behavioral phenotypes that can originate from any single genome.



Singer *et al*, 2010

Copy Number Variation across European Populations

Wanting Chen[1], Caroline Hayward[2], Alan F. Wright[2], Andrew A. Hicks[3], Veronique Vitart[2], Sara Knott[4], Sarah H. Wild[5], Peter P. Pramstaller[3,6,7], James F. Wilson[5], Igor Rudan[5,8], David J. Porteous[1]*

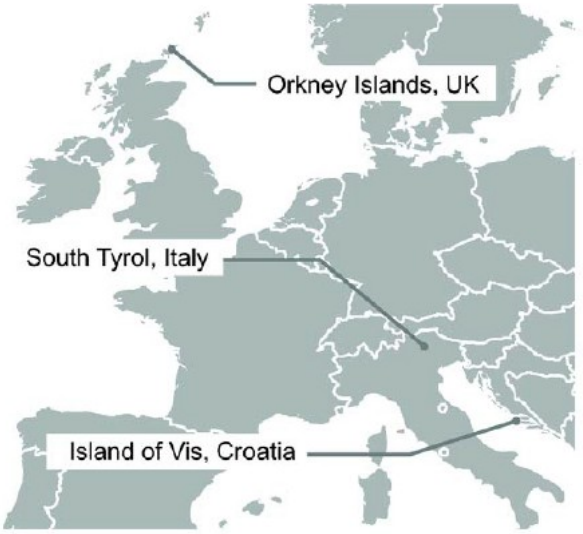


Figure 1. Geographic distribution of study samples.

Table 1. Characteristics of Copy Number Variants (CNVs) in Dalmatian, Orcadian and South Tyrolean populations.

Population	Sample size	CNV carriers (percentage of carriers in population)	Number of CNVs	CNVs per person	Amplifications	Deletions	CNV mean length (kb)
Vis	965	702 (72.7%)	1384	1.43	803	581	216
Orkney	691	367 (53.1%)	630	0.91	324	306	192.6
South Tyrol	1133	895 (79.0%)	2002	1.77	1033	969	201.6
Combined	2789	1964(70.4%)	4016	1.44	2160	1856	205.1

doi:10.1371/journal.pone.0023087.t001

Widespread RNA and DNA Sequence Differences in the Human Transcriptome

Mingyao Li,[1]* Isabel X. Wang,[2]* Yun Li,[3,4] Alan Bruzel,[2] Allison L. Richards,[5] Jonathan M. Toung,[6] Vivian G. Cheung[2,7,8]†

The transmission of information from DNA to RNA is a critical process. We compared RNA sequences from human B cells of 27 individuals to the corresponding DNA sequences from the same individuals and uncovered more than 10,000 exonic sites where the RNA sequences do not match that of the DNA. All 12 possible categories of discordances were observed. These differences were nonrandom as many sites were found in multiple individuals and in different cell types, including primary skin cells and brain tissues. Using mass spectrometry, we detected peptides that are translated from the discordant RNA sequences and thus do not correspond exactly to the DNA sequences. These widespread RNA-DNA differences in the human transcriptome provide a yet unexplored aspect of genome variation.

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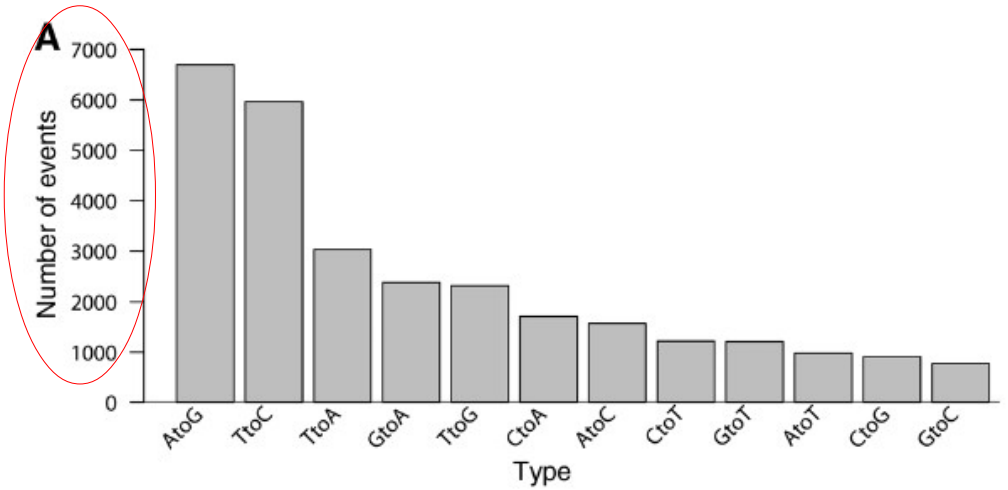

Mais... → « Evidence of alterned DNA stirs debate » *Nature News, 2011* → ?

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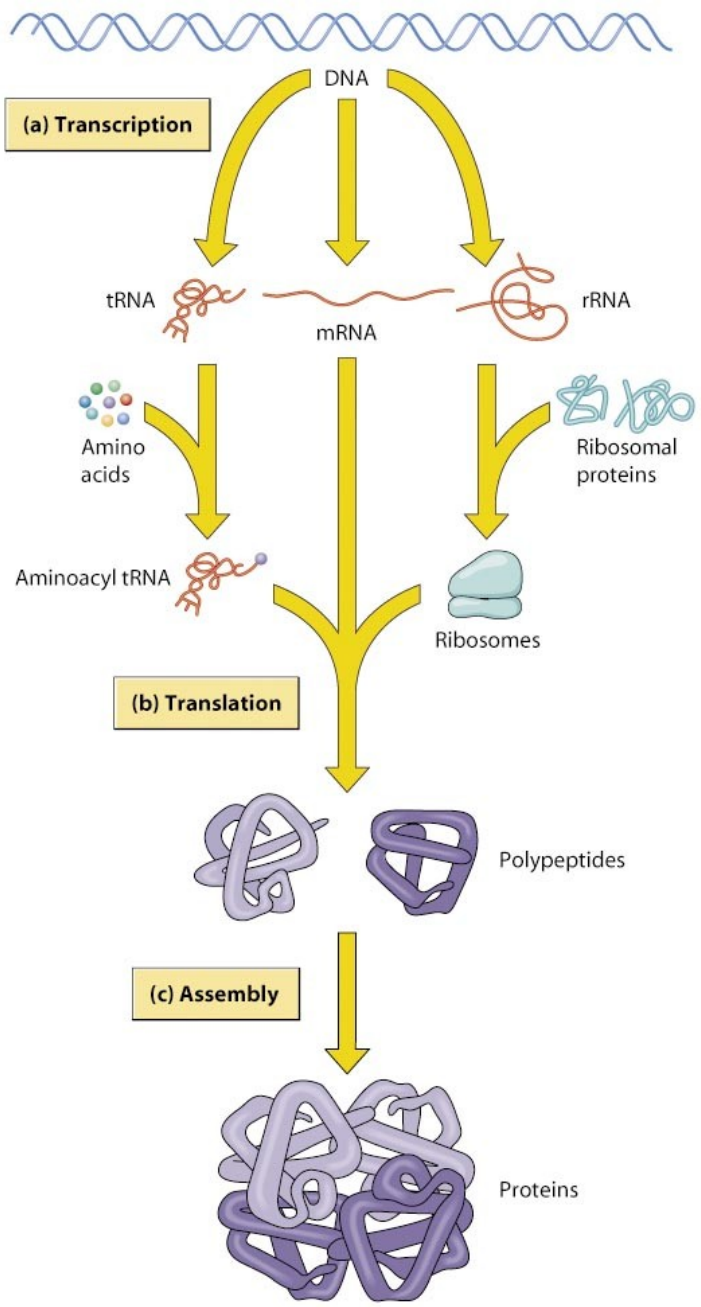

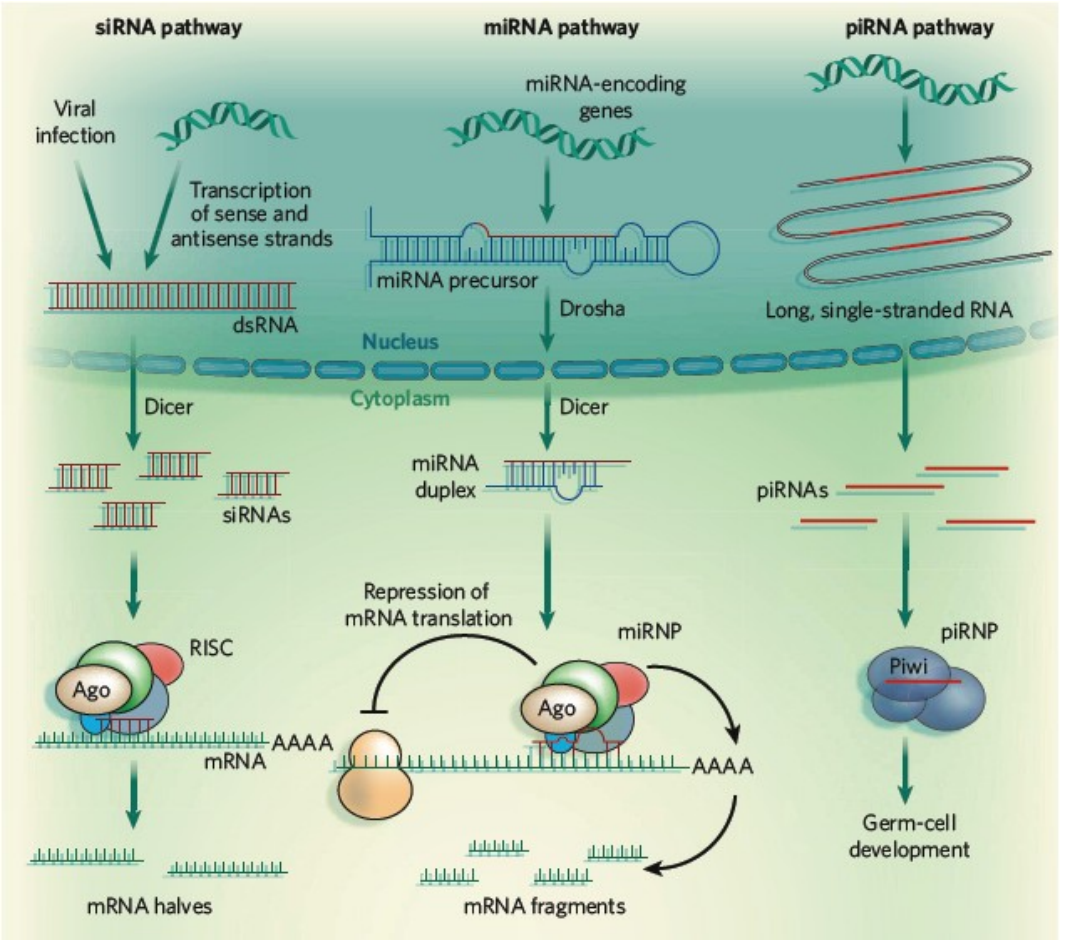

RNA Maps Reveal New RNA Classes and a Possible Function for Pervasive Transcription

Philipp Kapranov,[1] Jill Cheng,[1] Sujit Dike,[1] David A. Nix,[1] Radharani Duttagupta,[1] Aarron T. Willingham,[1] Peter F. Stadler,[2] Jana Hertel,[2] Jörg Hackermüller,[3] Ivo L. Hofacker,[4] Ian Bell,[1] Evelyn Cheung,[1] Jorg Drenkow,[1] Erica Dumais,[1] Sandeep Patel,[1] Gregg Helt,[1] Madhavan Ganesh,[1] Srinka Ghosh,[1] Antonio Piccolboni,[1] Victor Sementchenko,[1] Hari Tammana,[1] Thomas R. Gingeras[1*]

2007

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Harm van Bakel[1], Corey Nislow[1,2], Benjamin J. Blencowe[1,2], Timothy R. Hughes[1,2*]

2010

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Michael B. Clark[1], Paulo P. Amaral[1☯], Felix J. Schlesinger[2☯], Marcel E. Dinger[1], Ryan J. Taft[1], John L. Rinn[3], Chris P. Ponting[4], Peter F. Stadler[5], Kevin V. Morris[6], Antonin Morillon[7], Joel S. Rozowsky[8], Mark B. Gerstein[8], Claes Wahlestedt[9], Yoshihide Hayashizaki[10], Piero Carninci[10], Thomas R. Gingeras[2*], John S. Mattick[1*]

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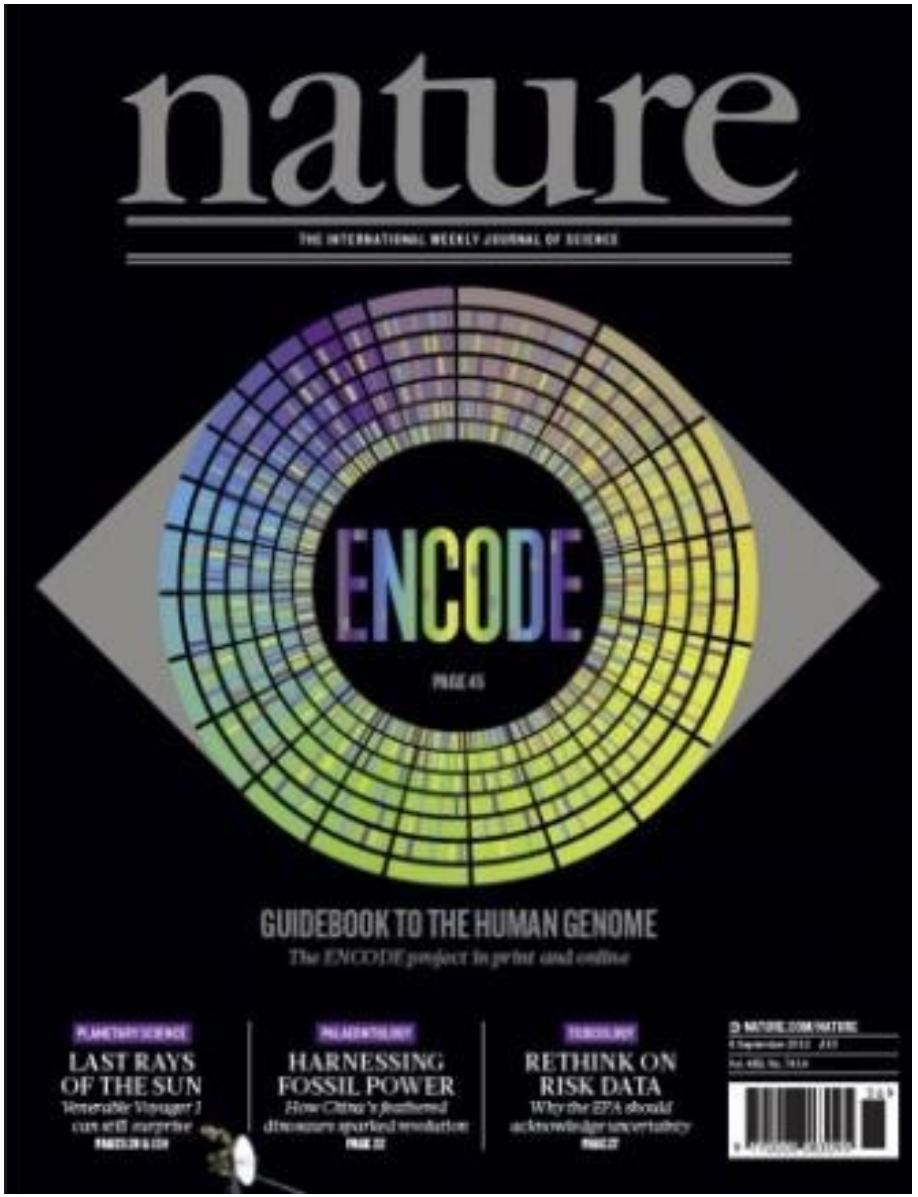

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Merci de votre attention !