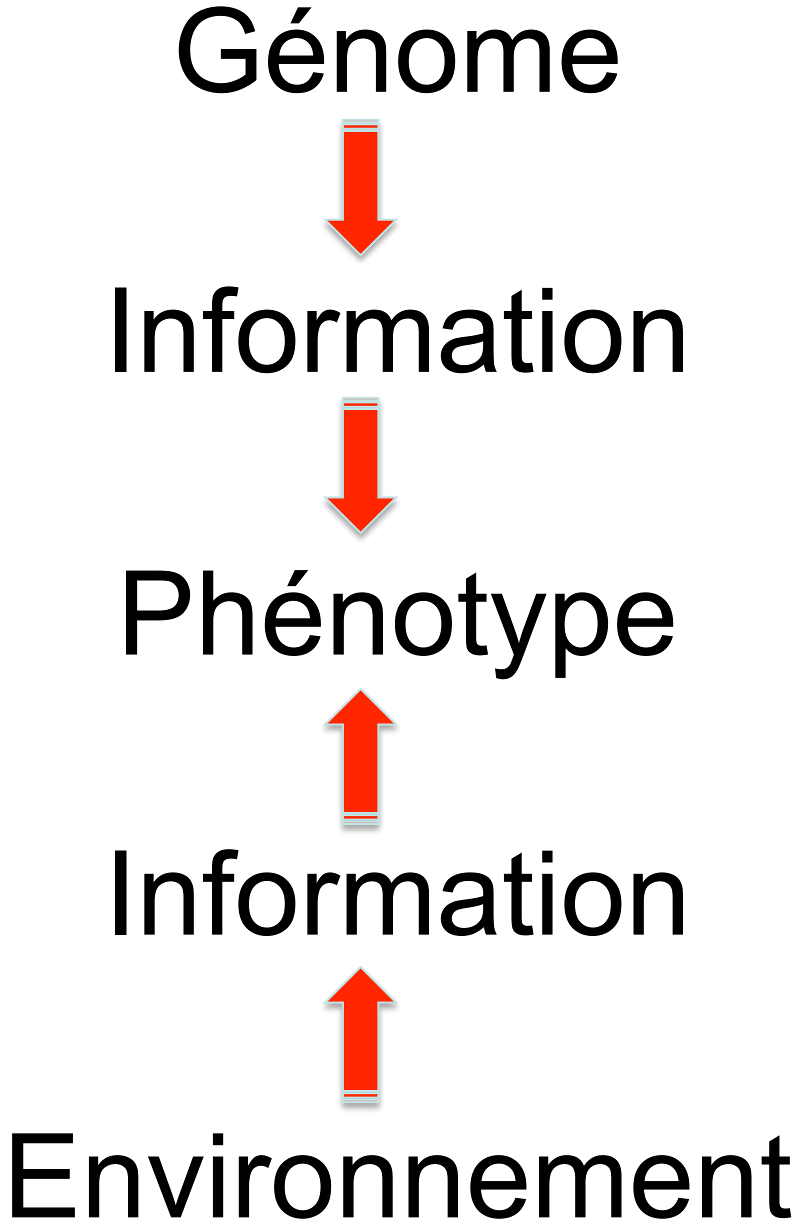
Hasard en biologie : la stochasticité de l’expression génique.

Olivier Gandrillon

Janvier 2014

Le « dogme » central:


Génome
Information
Phénotype
Information
Environnement

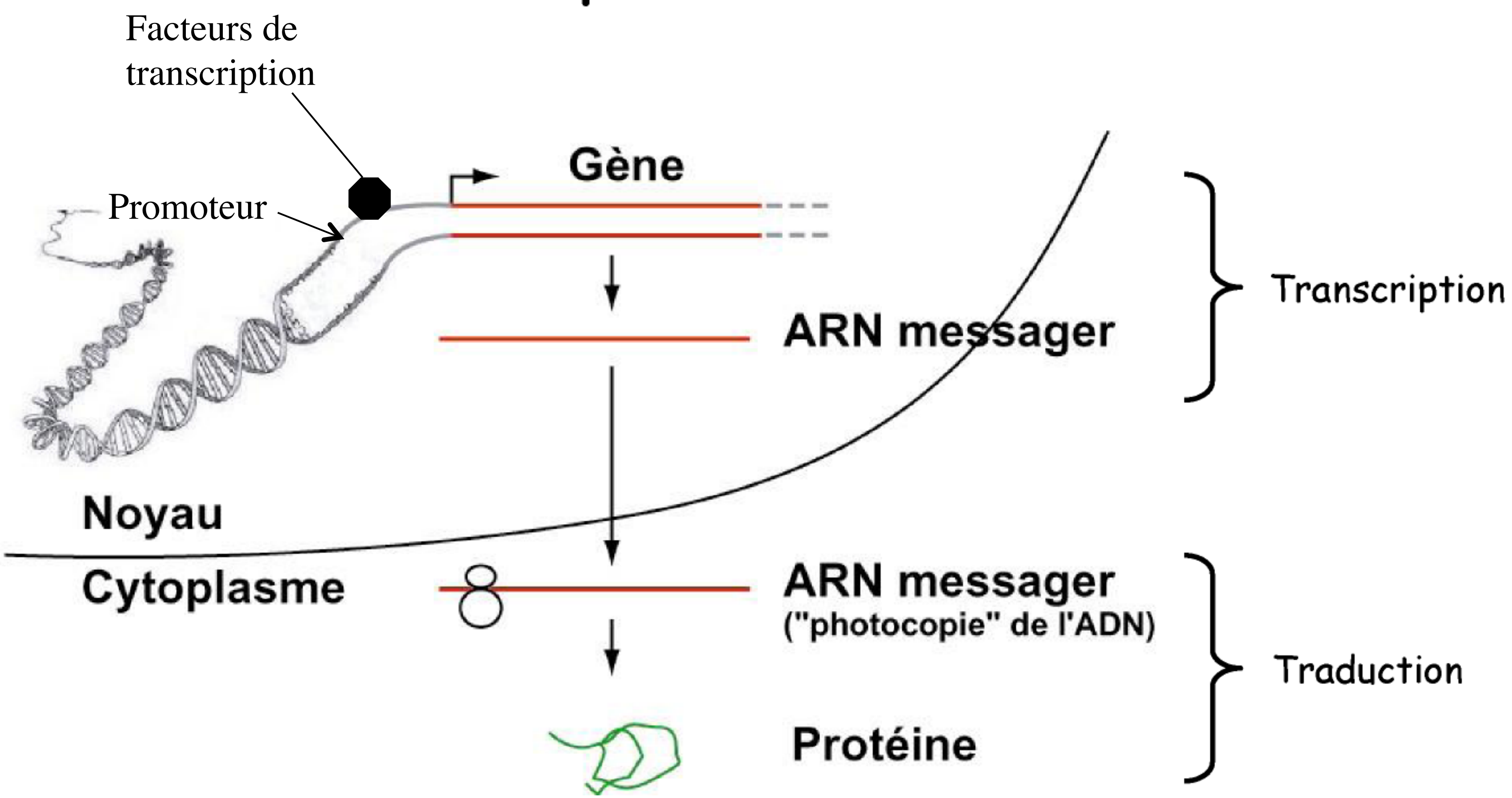
Génome

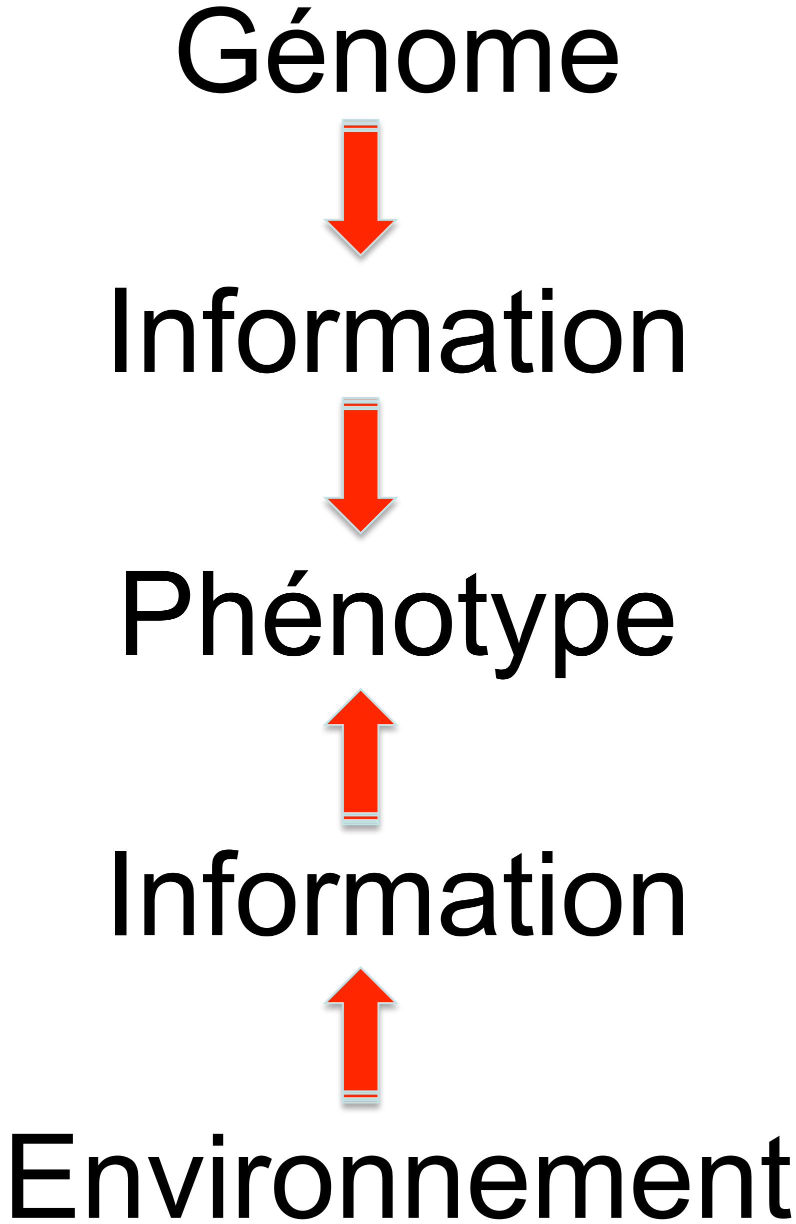
Information

En pratique:
processus dit
d'«expression
des gènes »

Expression des gènes:

Transcription et traduction




Génome
Information
Phénotype
Information
Environnement

Si Génome = fixé

Et

Environnement = fixé

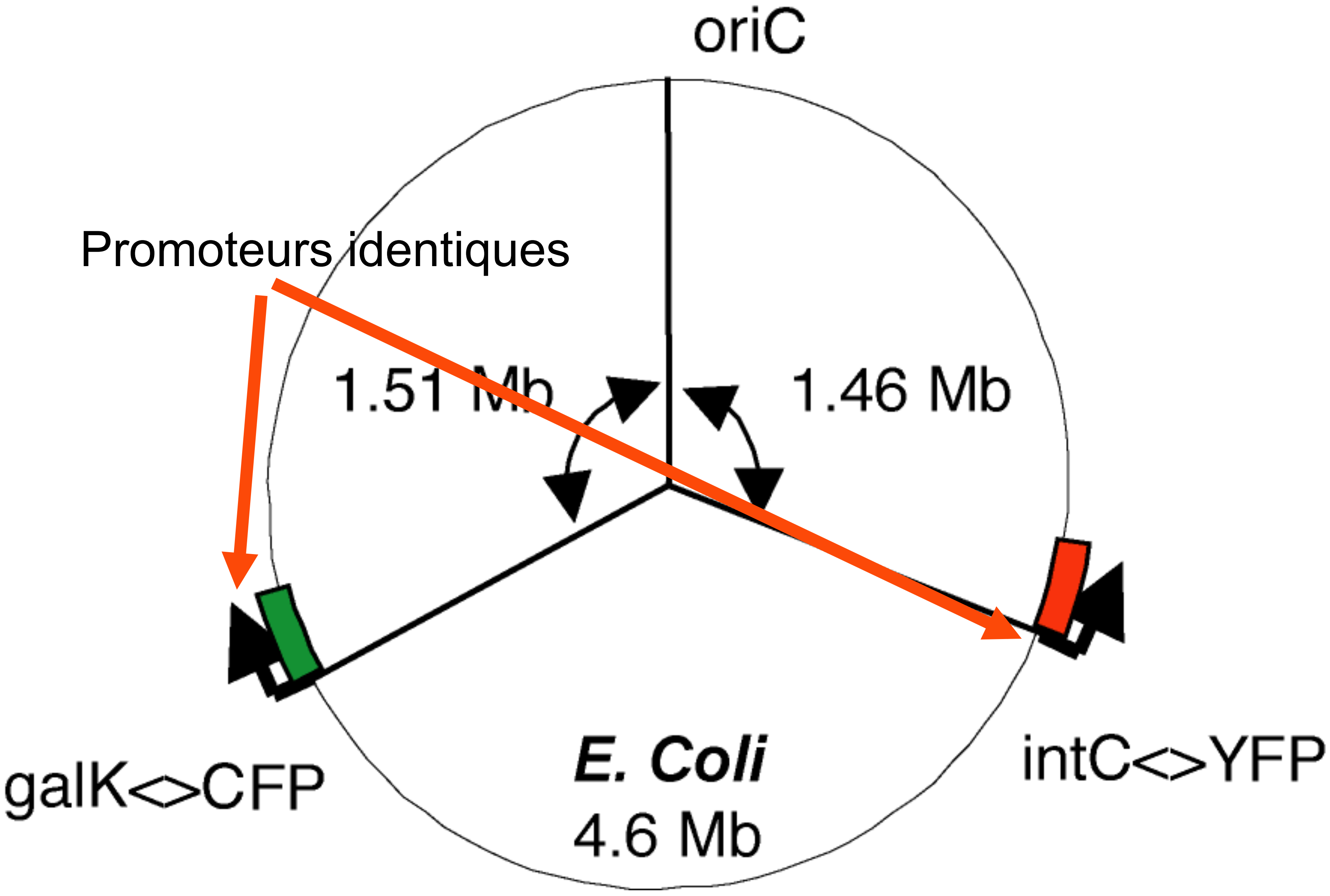
Alors

Phénotype= fixé

Stochastic Gene Expression in a Single Cell

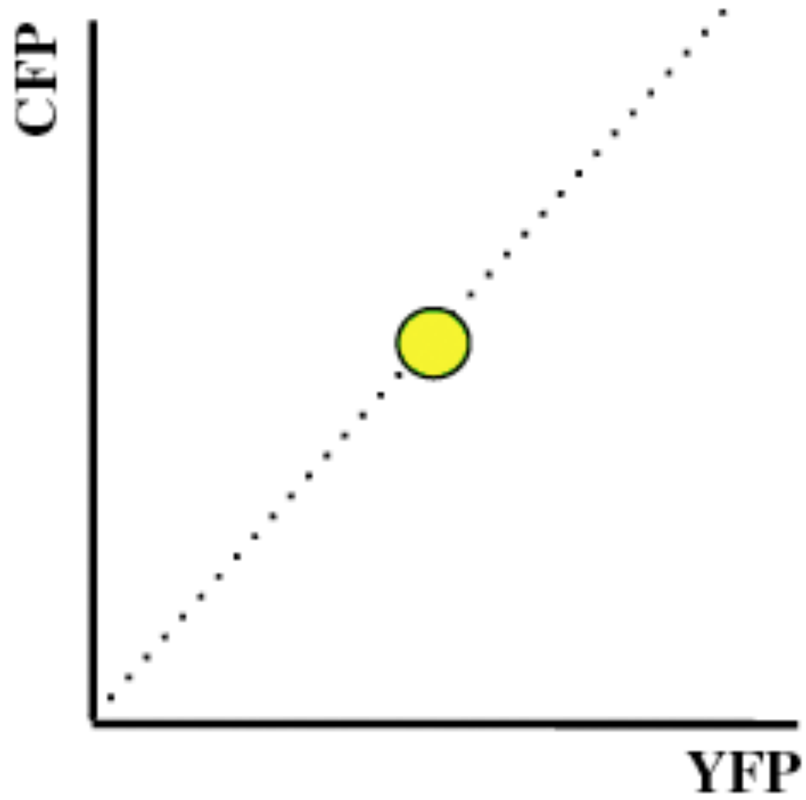
Michael B.Elowitz,Arnold J. Levine,
Eric D. Siggia and Peter S. Swain

SCIENCE (2002) VOL 297, pp 1183-1186

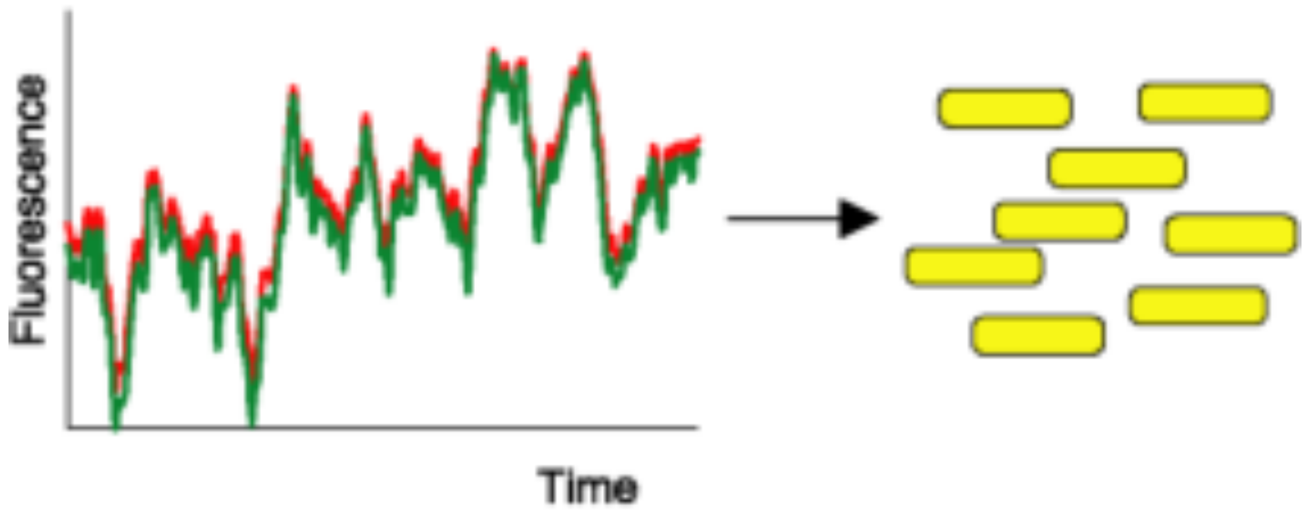


Le dispositif expérimental

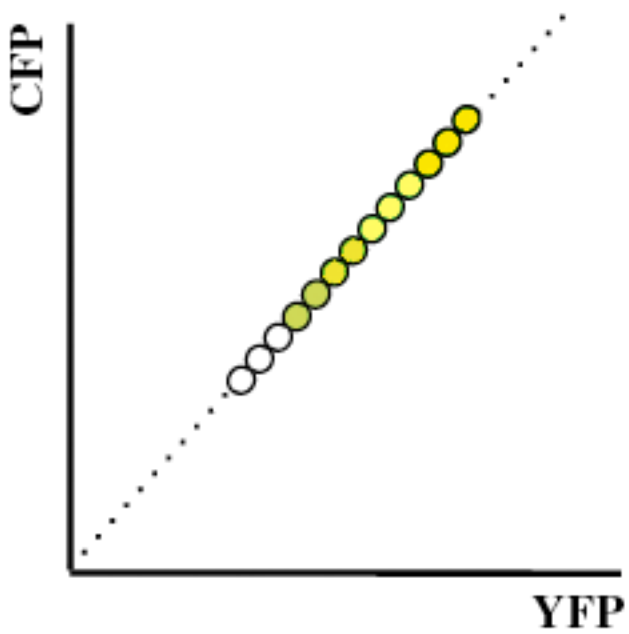
Deux copies d'un gène dans le MEME environnement chromosomique

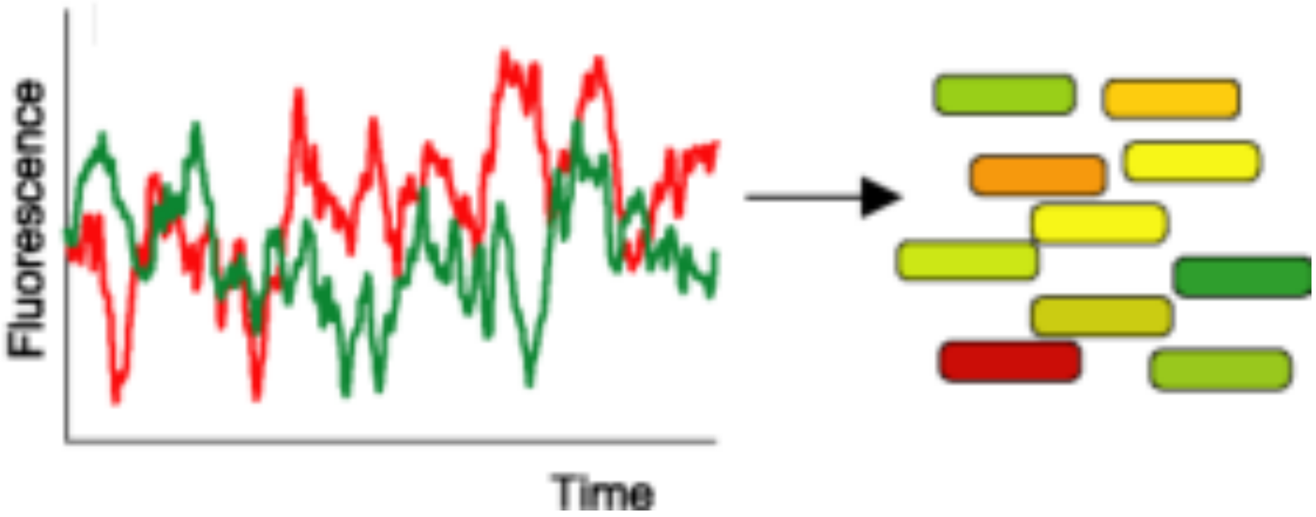


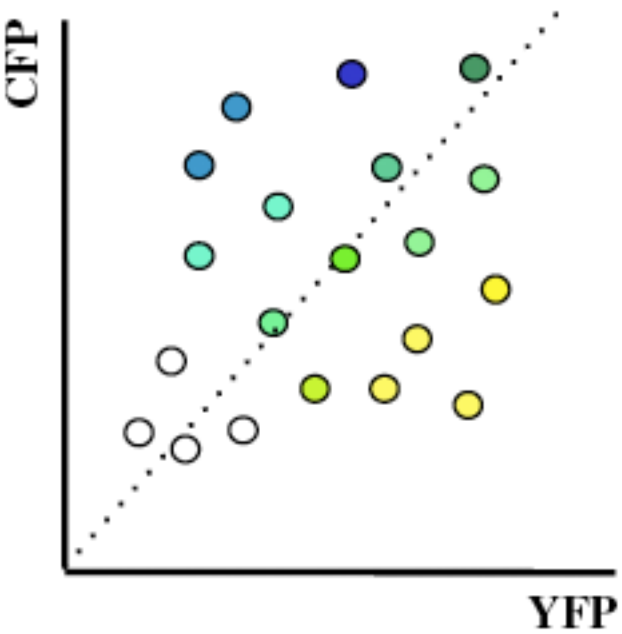
Cas 1: Dans un monde parfaitement déterministe



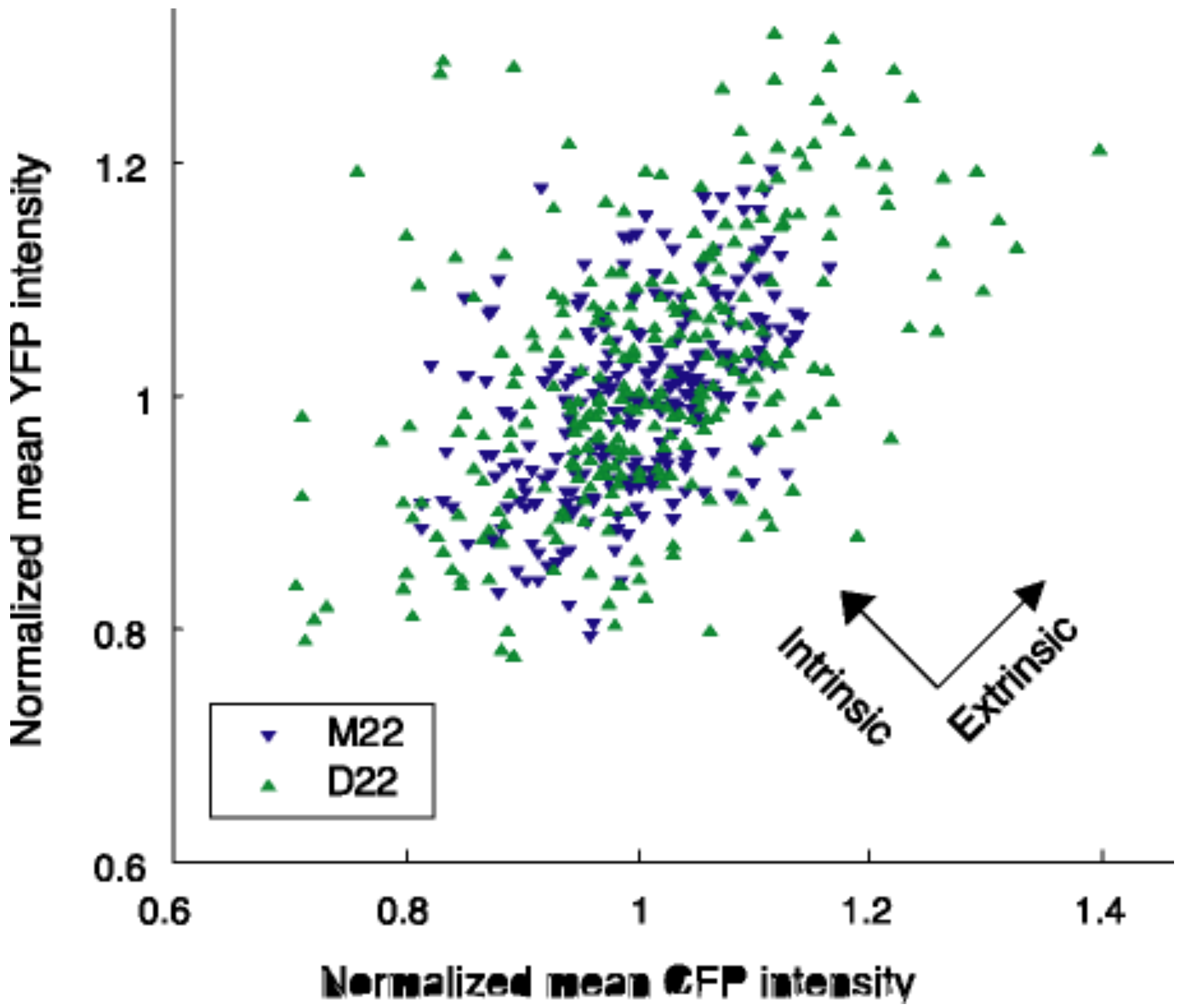
Cas 2: du bruit extrinsèque (corrélé)



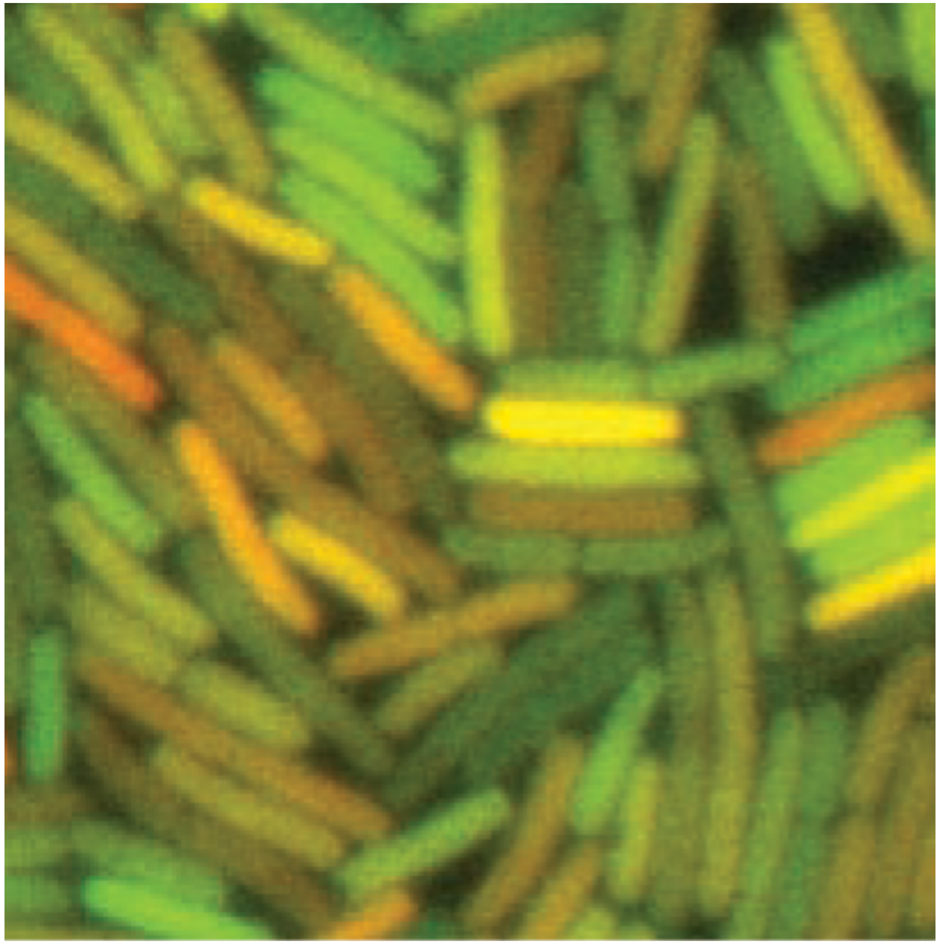




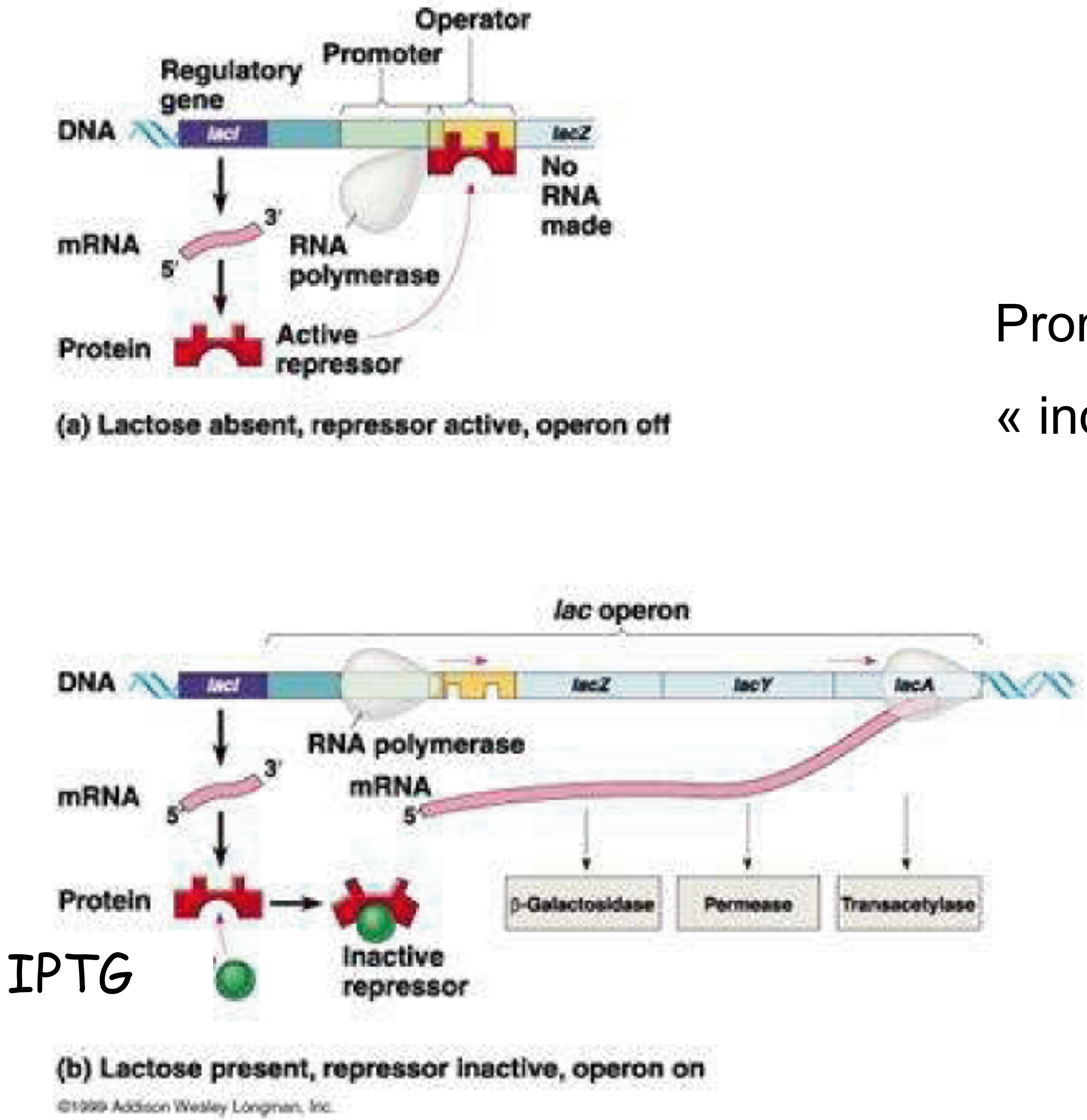
Cas 3= mélange extrinsèque et intrinsèque (décorrélé)



Il y a bien quelque chose qui « échappe » à la double information…



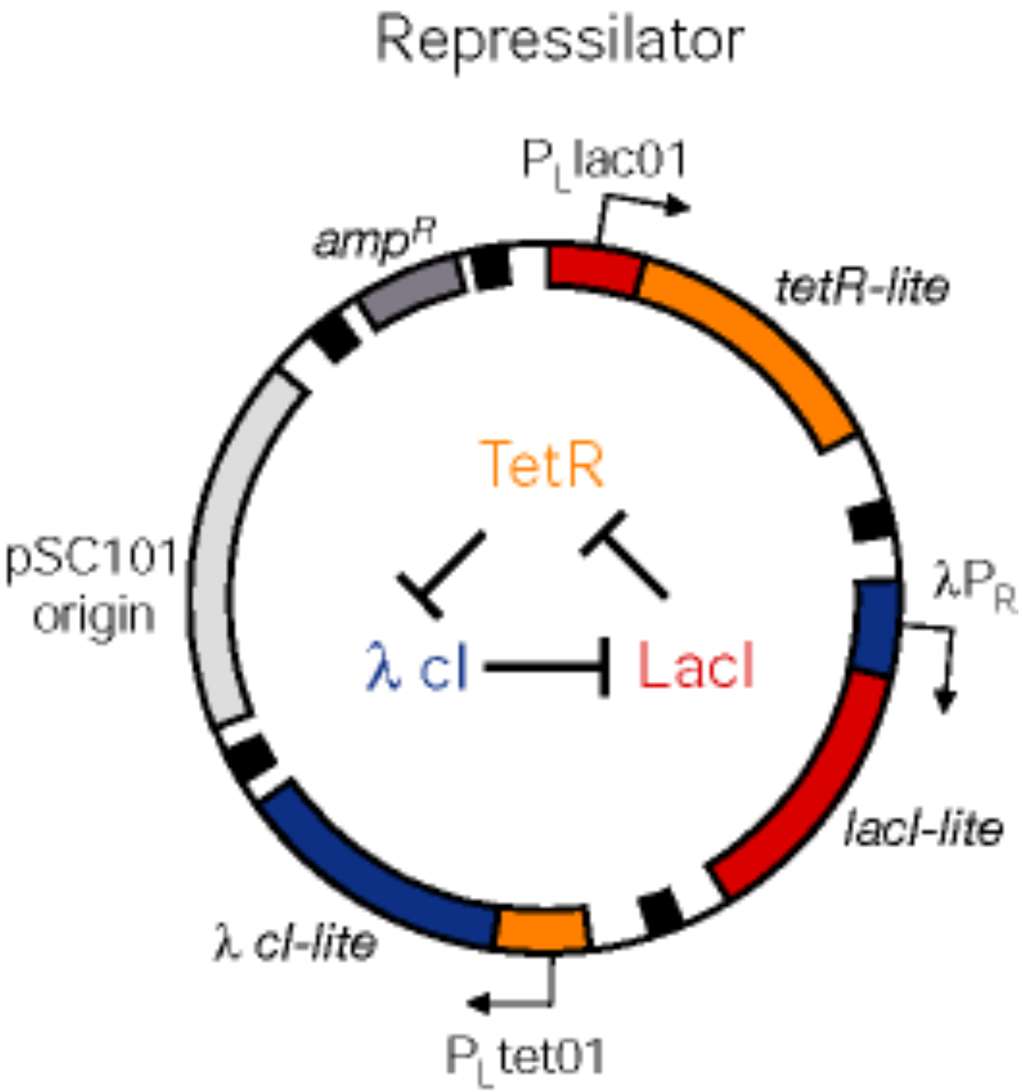
L’expression des gènes est un phénomène probabiliste



Promoteur

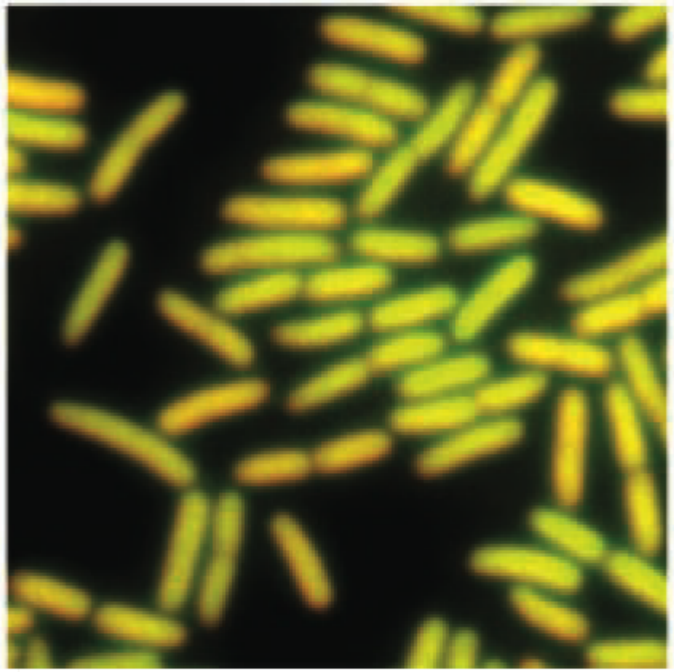
« inductible »

Addition d'un système conduisant à une synthèse périodique de LacI



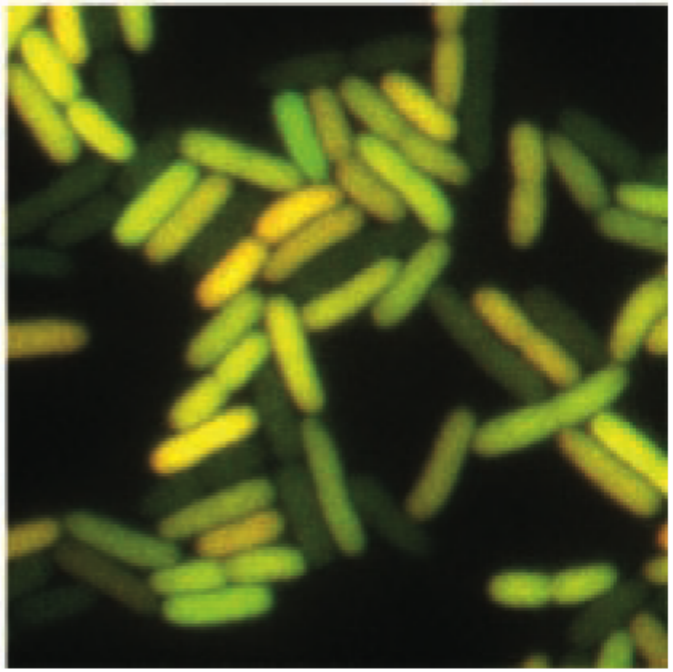
η_{int} 0.05

η_{tot} 0.07



η_{int} 0.12

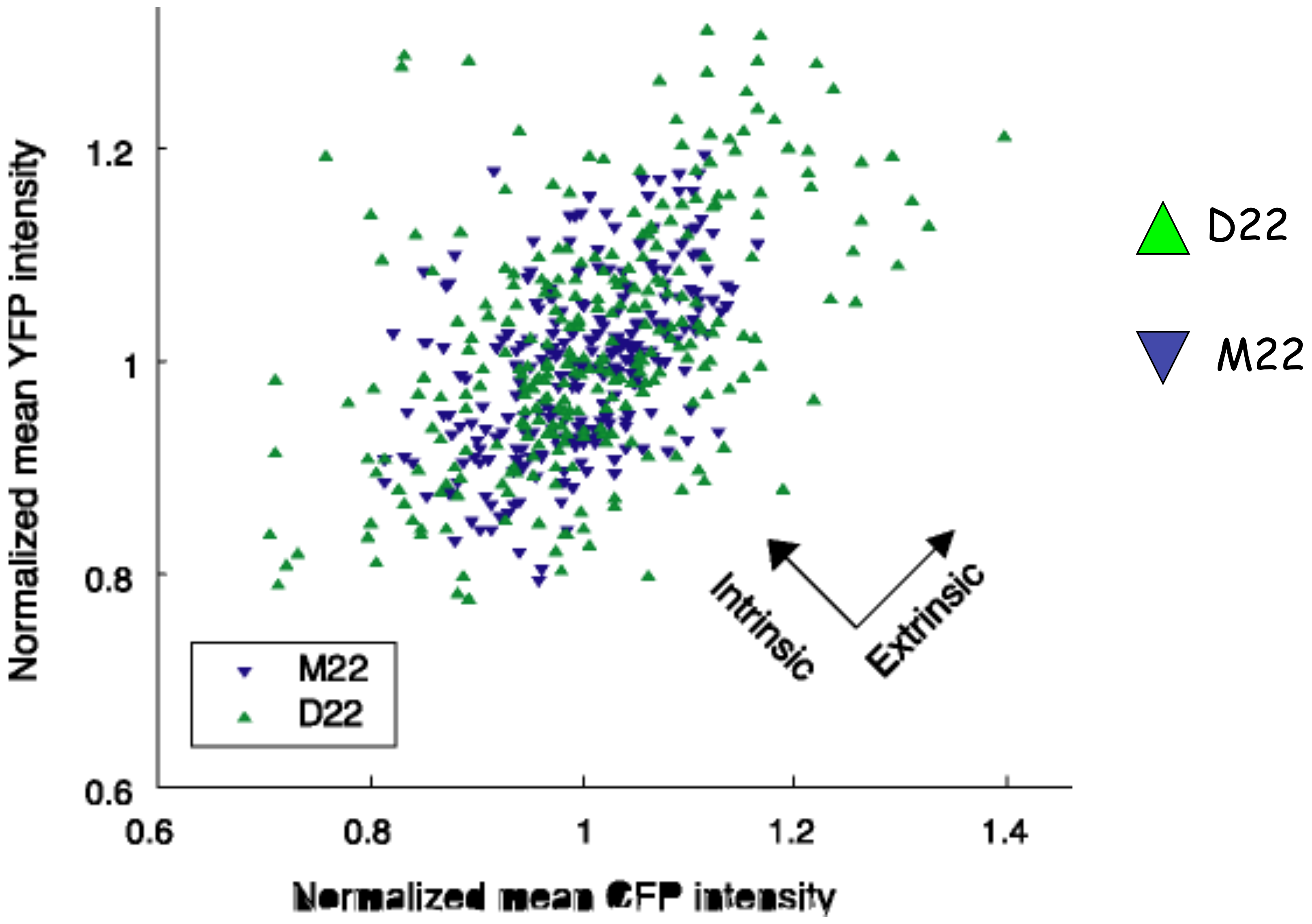
η_{tot} 0.43



L'addition du répréssilateur (?) induit une forte augmentation du bruit (surtout externe mais pas seulement)

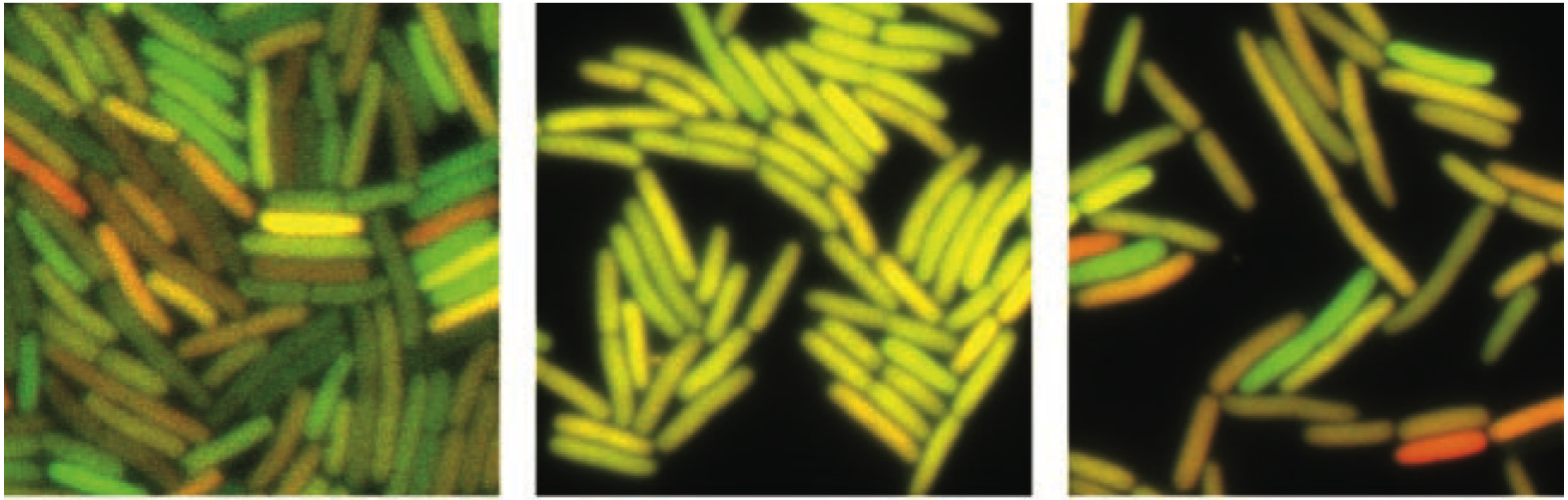
Consistant avec le fait que la théorie prédit que le bruit sera plus fort à l’approche d’un état stable que à l’état stable lui-même

Existe-t-il un «contrôle génétique» du bruit?



Normalized mean YFP intensity
1.2
1
0.8
0.6
0.6
0.8
1
1.2
1.4
Normalized mean CFP intensity
M22
D22
Intrinsic
Extrinsic
D22
M22

D22: beaucoup plus bruitée que M22. Diffère par une délétion du gène RecA. On prend une souche dans une condition non bruitée et on délète RecA:



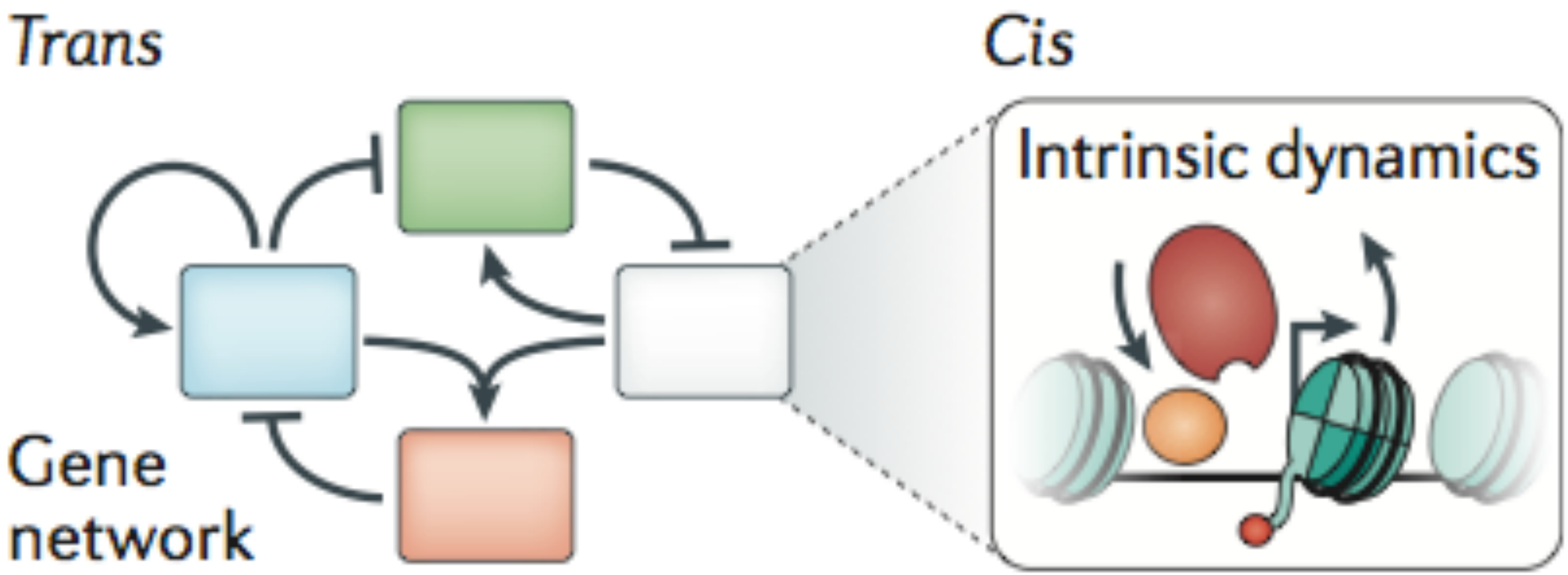
- IPTG | +IPTG | +IPTGΔRecA

$\eta_{int} = 0.25$ | $\eta_{int} = 0.06$ | $\eta_{int} = 0.17$

Difficile d’aller beaucoup plus loin facilement: RecA a été montré avoir une palanquée de fonctions biologiques. Le lien avec le bruit transcriptionnel n’est pas évident.

Devant ce constat, deux axes de recherche complémentaires:

1. Quelles sont les bases moléculaires de ce phénomène?
2. Quelle est la fonction biologique de ce phénomène?



Both Cis and Trans effects shape the overall dynamics

A number of molecular causes have been proposed for the generation and regulation of SGE, including:

1. small molecule numbers {Paulsson, 2005};
2. spatial aspects due to the random diffusion of molecules {van Zon, 2006};
3. the essentially dynamic nature of protein-protein interactions {Coulon, 2010};
4. specific regulatory network architectures {Cagatay, 2009};
5. the non-specificity in protein-protein interactions {Kupiec, 2010};
6. properties of the RecA protein in *Escherichia coli* {Elowitz, 2002} and of the transcriptional elongation machinery in *Saccharomyces cerevisiae* {Ansel, 2008};
7. unequal repartition of the molecular content of the mother cell into the two daughter cells {Huh, 2011};
8. the dynamics of chromatin in eukaryotic cells {Becskei, 2005}.

2. spatial aspects due to the random diffusion of molecules {van Zon, 2006};

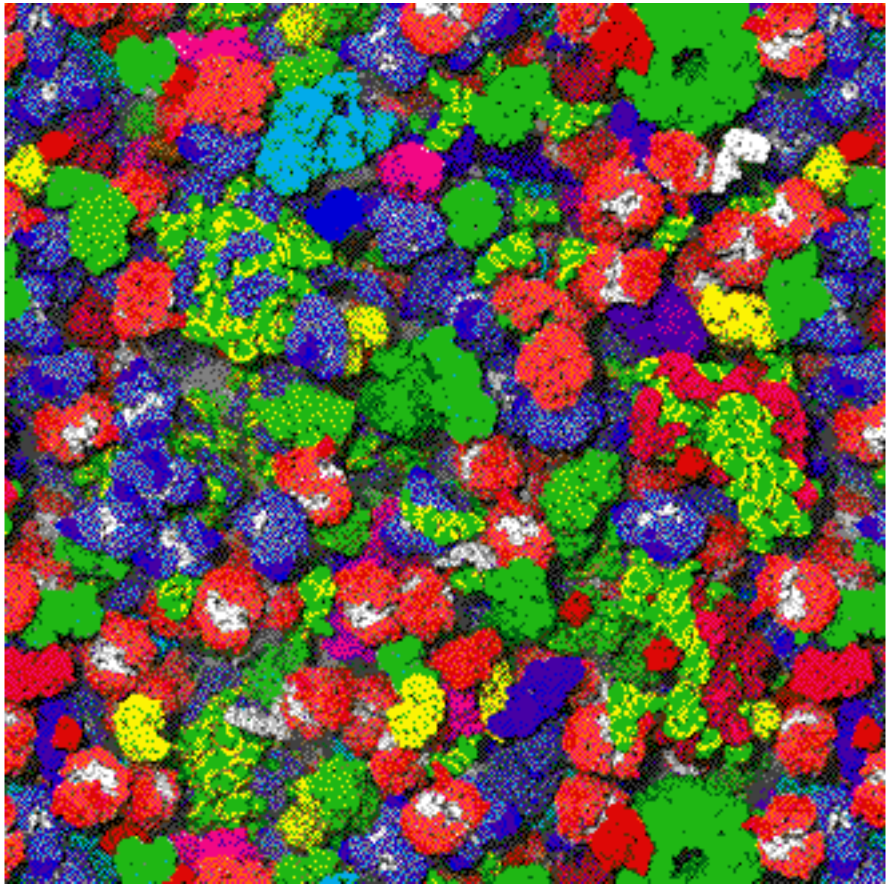
OPEN ACCESS Freely available online
PLoS COMPUTATIONAL BIOLOGY

Diffusion, Crowding & Protein Stability in a Dynamic Molecular Model of the Bacterial Cytoplasm

Sean R. McGuffee[¤], Adrian H. Elcock*

Department of Biochemistry, University of Iowa, Iowa City, Iowa, United States of America

Abstract



Film_prot_dans _Coli.mov

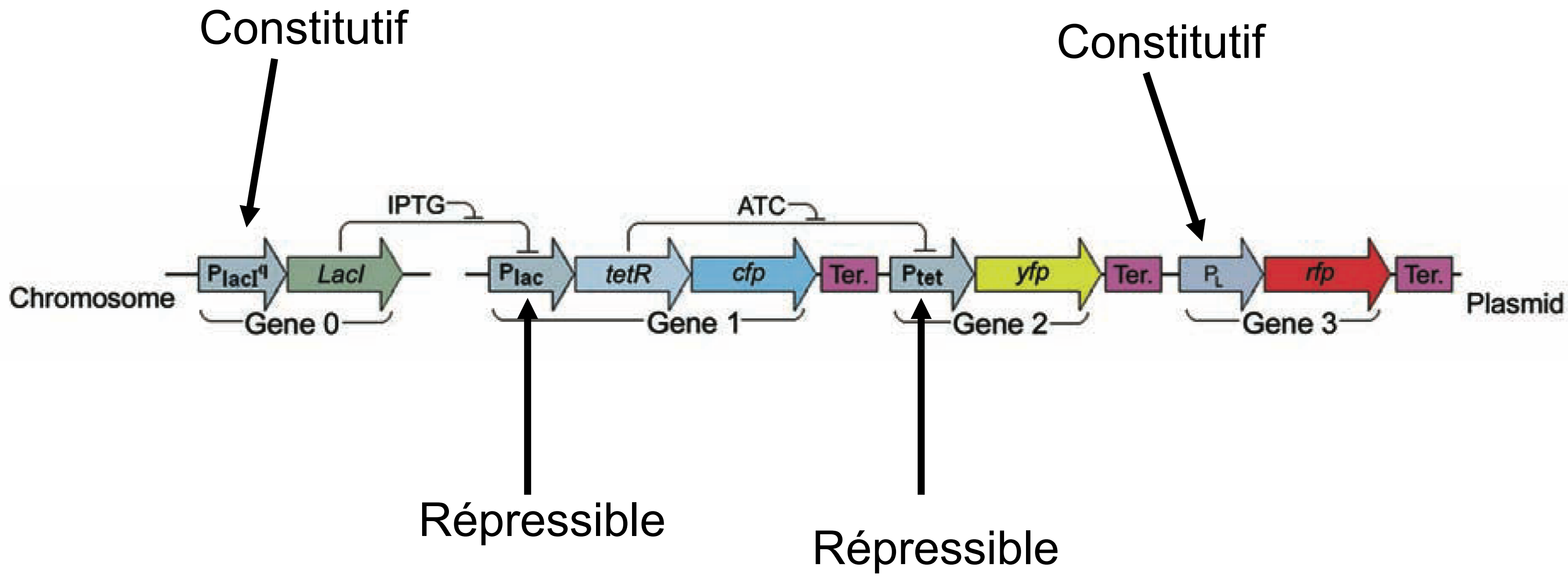
4. specific regulatory network architectures {Cagatay, 2009};

« Any cellular component that suffers intrinsic fluctuations in its own concentration will act as a source of extrinsic noise for other components with which it interacts. »

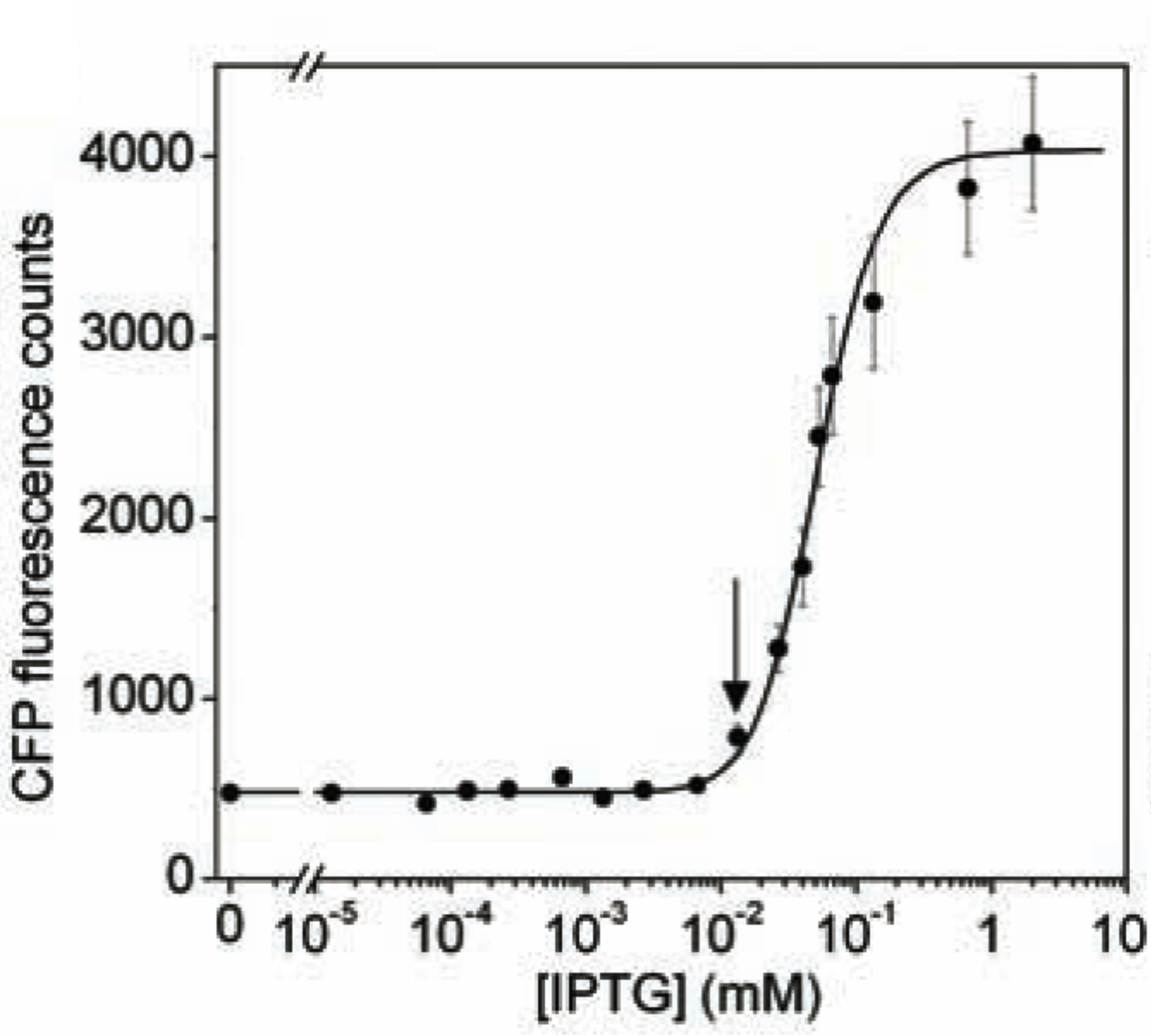
Noise Propagation in Gene Networks

J. M. Pedraza and A. van Oudenaarden

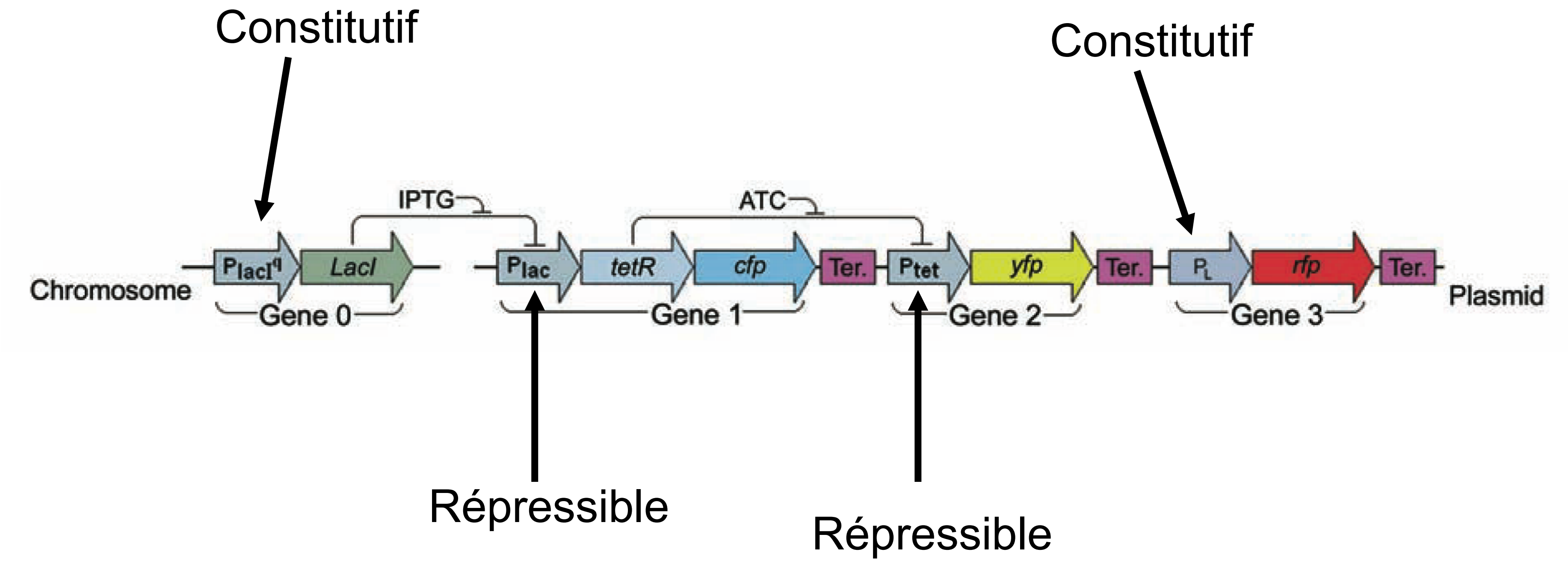
SCIENCE (2005) VOL 307, pp 1965-1969



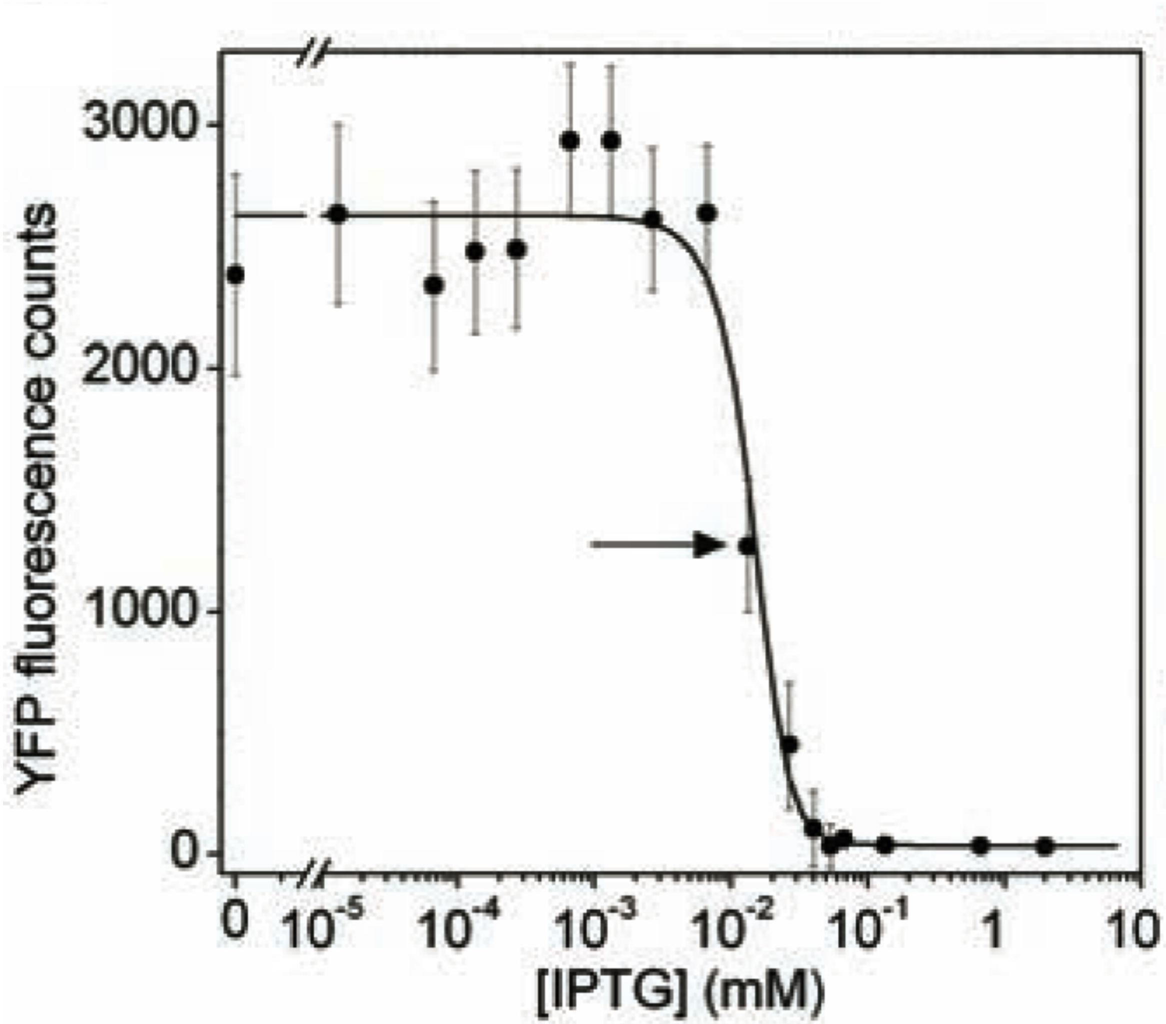
Le dispositif expérimental



Effet direct: IPTG réprime le répresseur

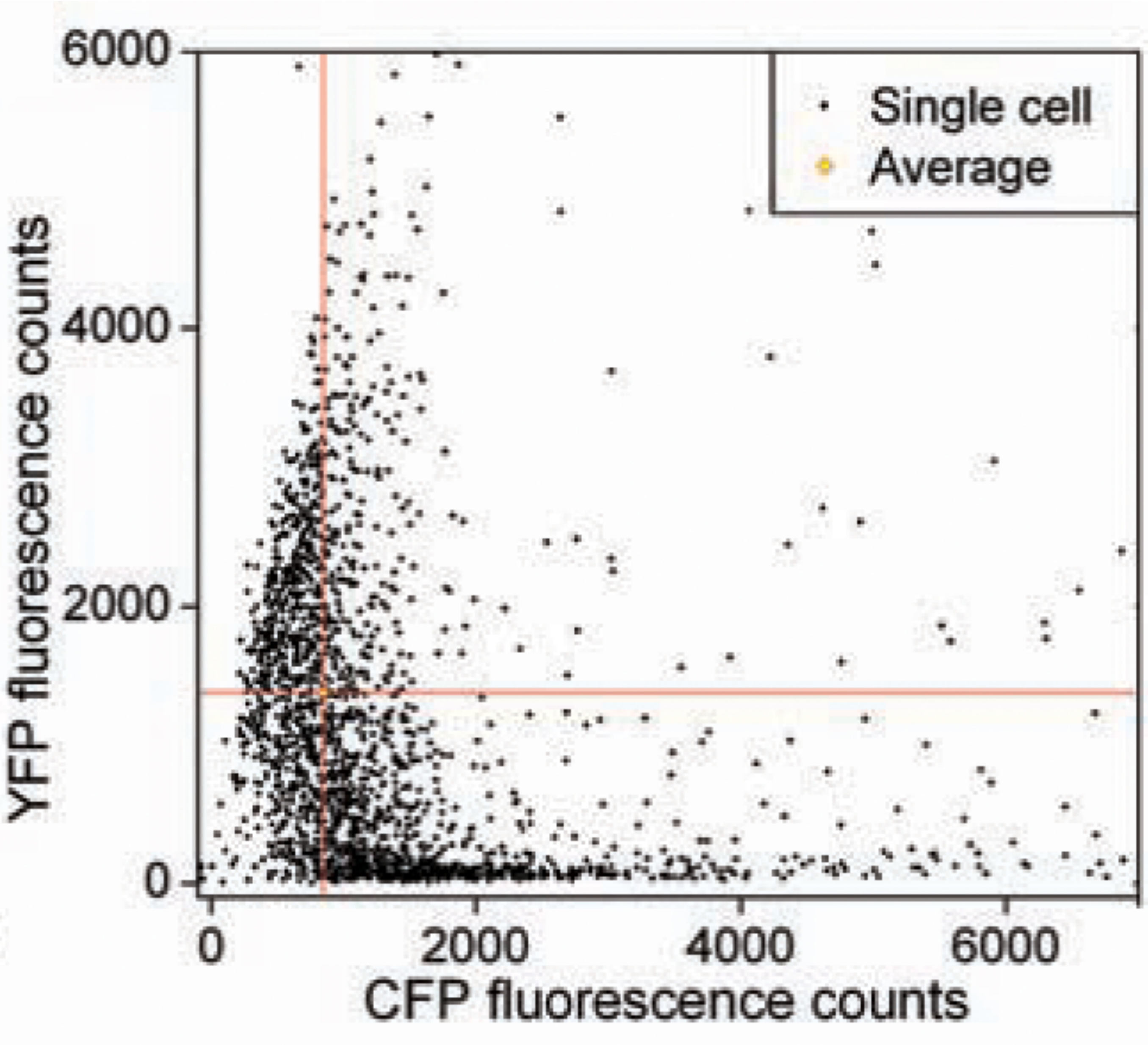


Constitutif
Constitutif
IPTG
ATC
Chromosome
PlacI^q
LacI
Gene 0
Plac
tetR
cfp
Ter.
Gene 1
Ptet
yfp
Ter.
Gene 2
PL
rfp
Ter.
Gene 3
Plasmid
Répressible
Répressible

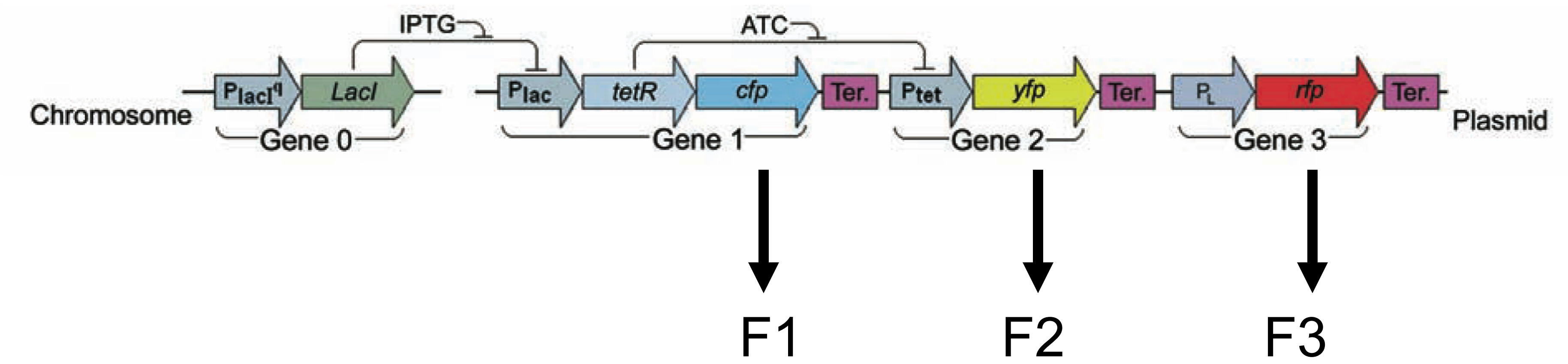


Effet indirect: on augmente la quantité de TetR donc on augmente la répression de yfp

Ce sont des effets moyennés. Que se passe-t-il à l’échelle unicellulaire?


Single cell
Average
6000
4000
2000
0
YFP fluorescence counts
0
2000
4000
6000
CFP fluorescence counts

Pour chaque cellule on mesure trois valeurs de fluorescence



On peut alors calculer un bruit ou une corrélation

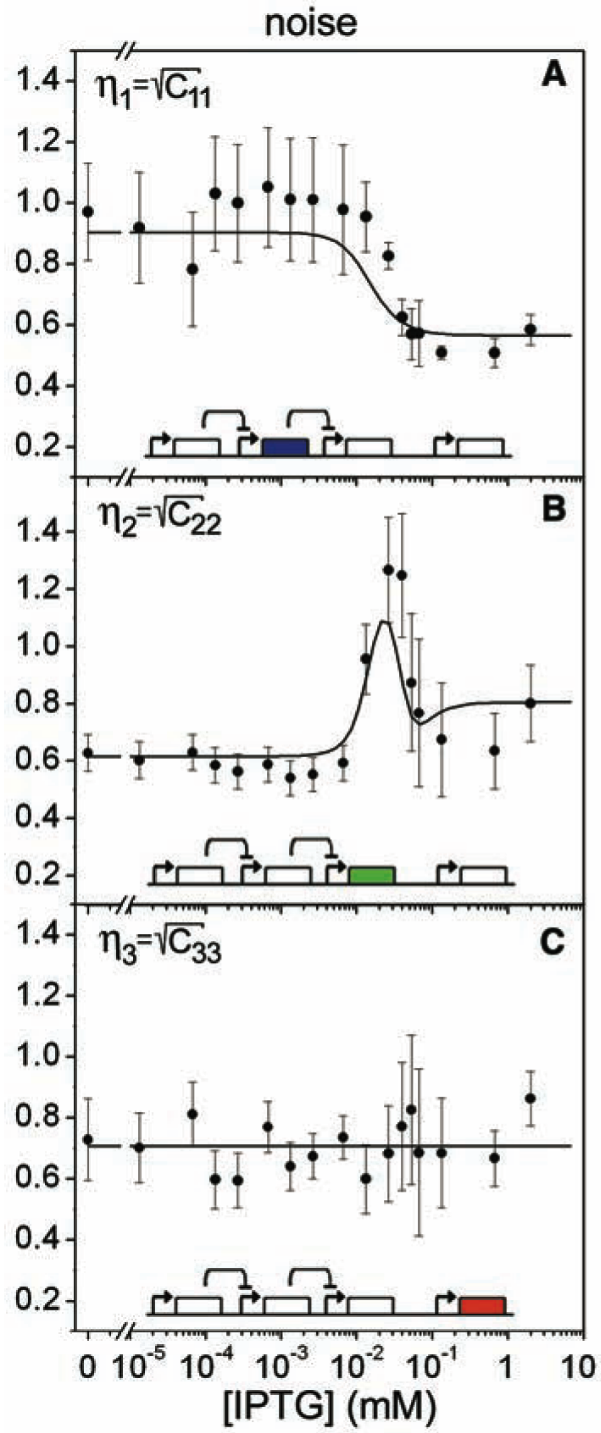
$$C_{ij} = \frac{\langle F_i F_j \rangle - \langle F_i \rangle \langle F_j \rangle}{\langle F_i \rangle \langle F_j \rangle}$$

Avec i = 1, 2 ou 3 et j = 1, 2 ou 3 et <>=moyenne sur l'ensemble des cellules

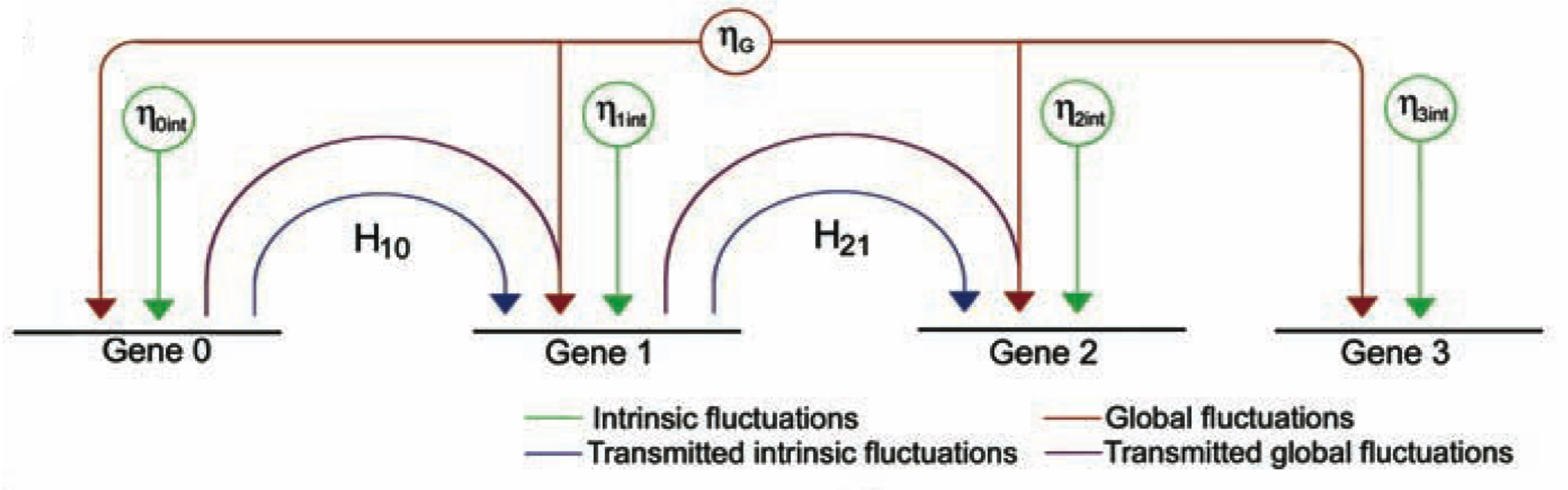
On peut calculer trois auto-corrélations (= bruit^2): C_{11} C_{22} C_{33}
 et trois corrélations croisées C_{12} C_{13} C_{23}.

Clairement PAS trivial..

Bien que la connection 1 -> 2 soit directe (un seul répresseur), le bruit ne se comporte pas du tout pareil



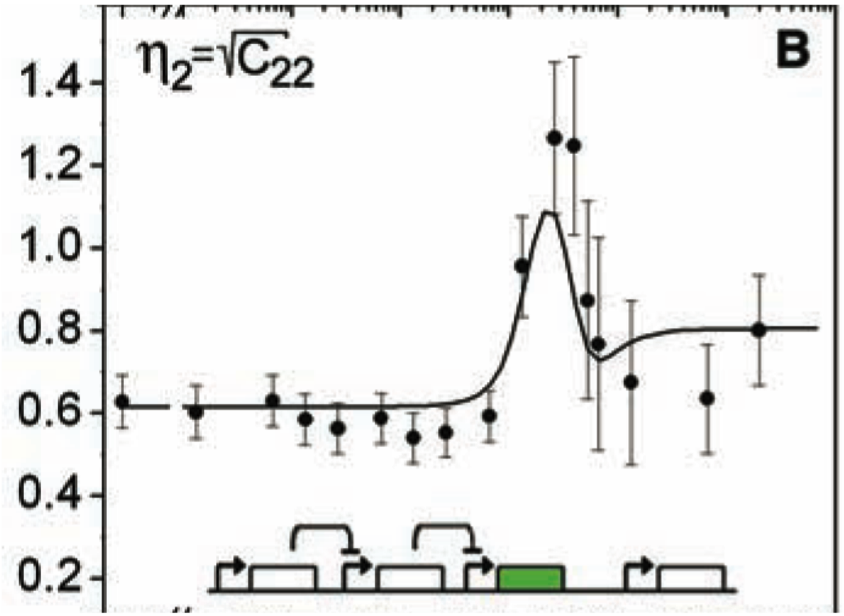
Modèle de Bruit:

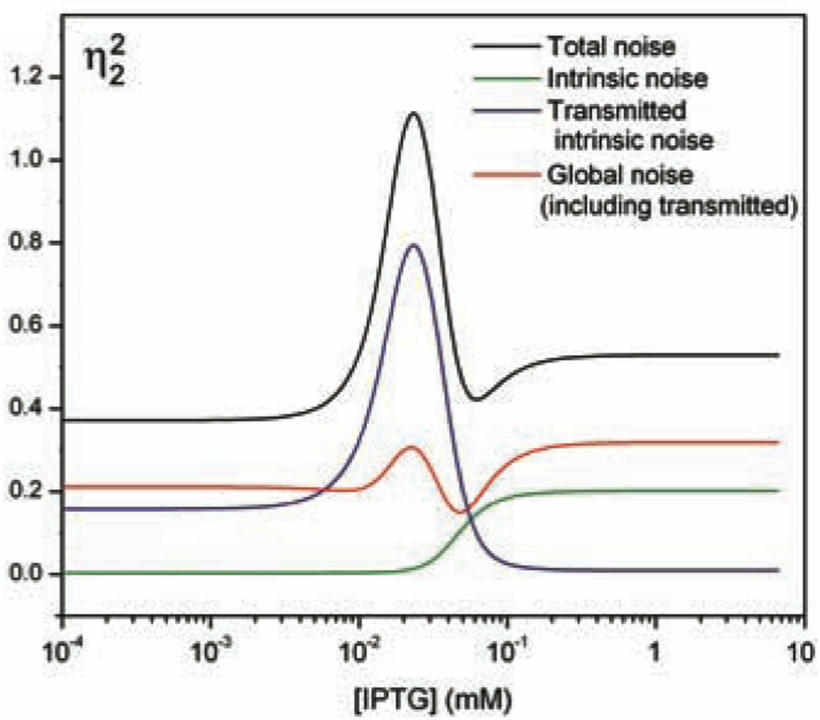


Modèle mathématique basé sur l'approche Langevin: ODE + composant stochastique

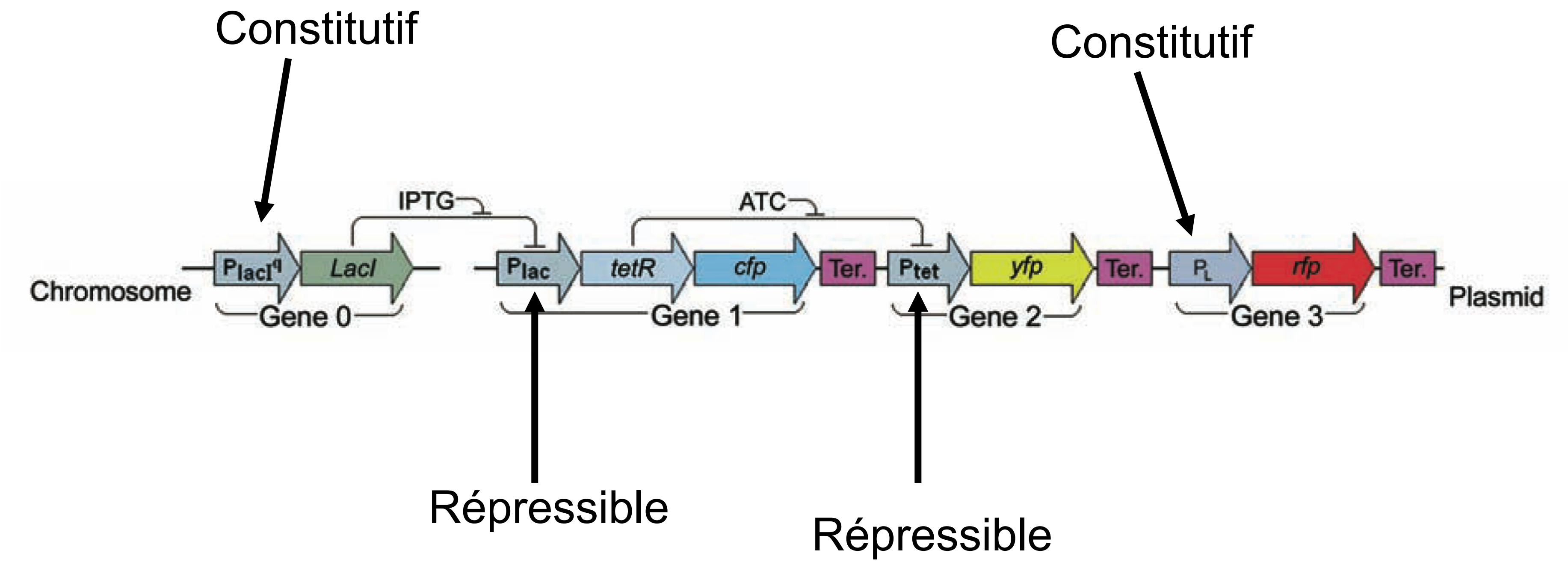
Observé

Prédit (et décomposé)

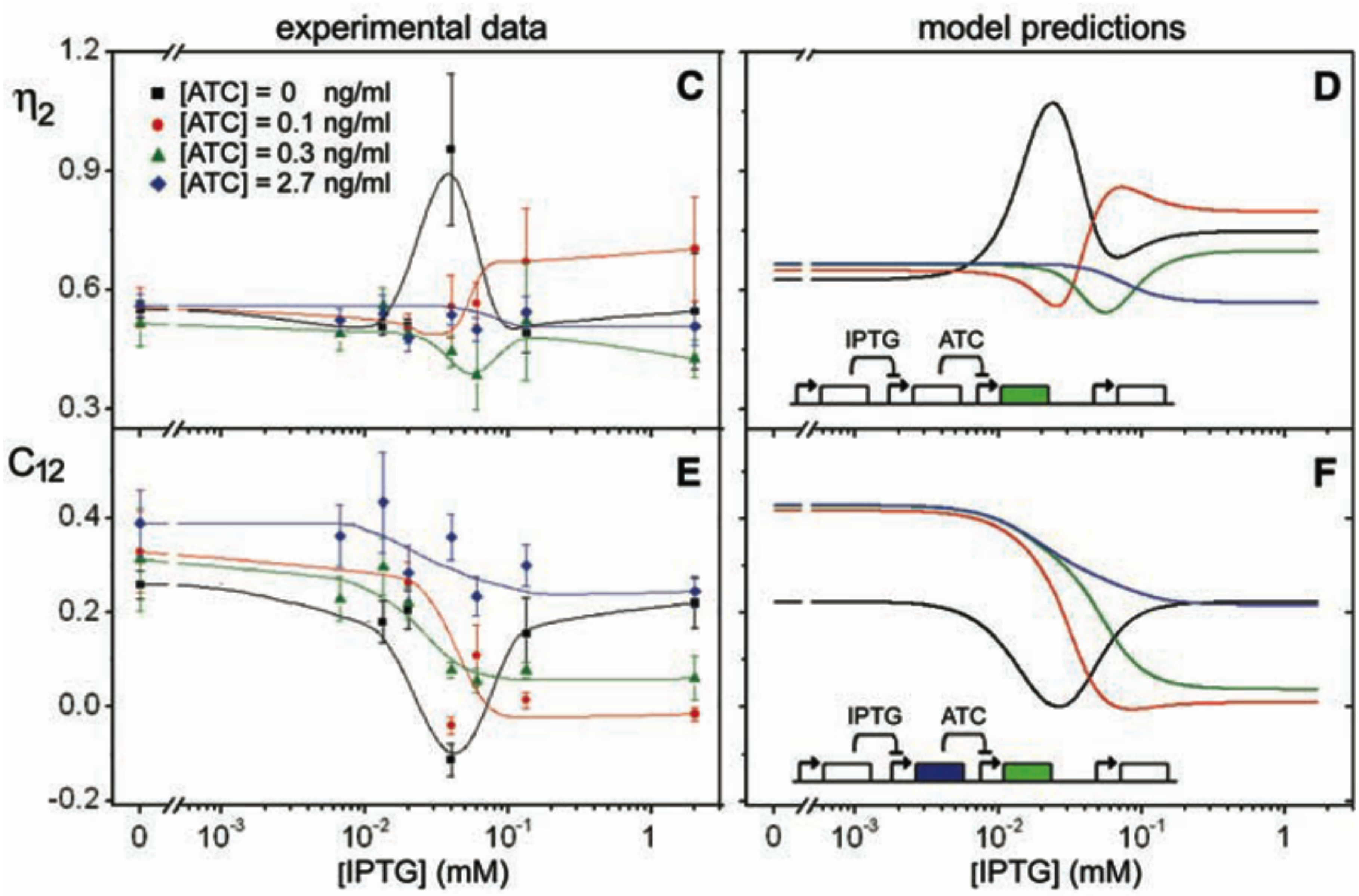




The main features of the noise in this gene are determined by the network interactions, rather than by its own intrinsic noise characteristics.

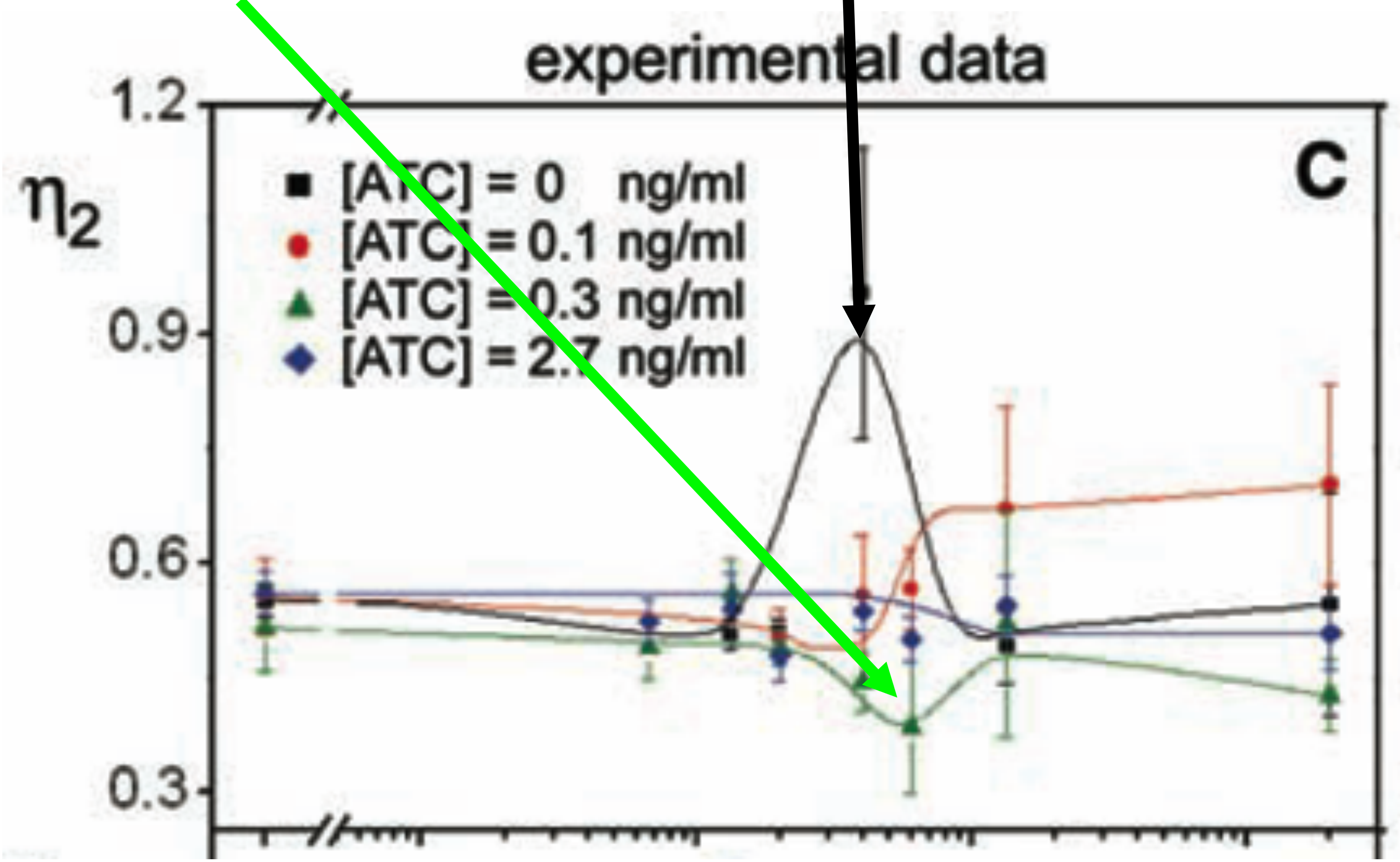


Que se passe-t-il quand on augmente la concentration d’ATC?



experimental data
model predictions
η2
C12
C
D
E
F
[ATC] = 0 ng/ml
[ATC] = 0.1 ng/ml
[ATC] = 0.3 ng/ml
[ATC] = 2.7 ng/ml
1.2
0.9
0.6
0.3
0.4
0.2
0.0
-0.2
IPTG
ATC
0
10-3
10-2
10-1
1
[IPTG] (mM)

Une petite différence dans la concentration de l'inducteur transforme un maximum en un minimum.



« Our results highlight the importance of including stochastic effects in the study of regulatory networks. »

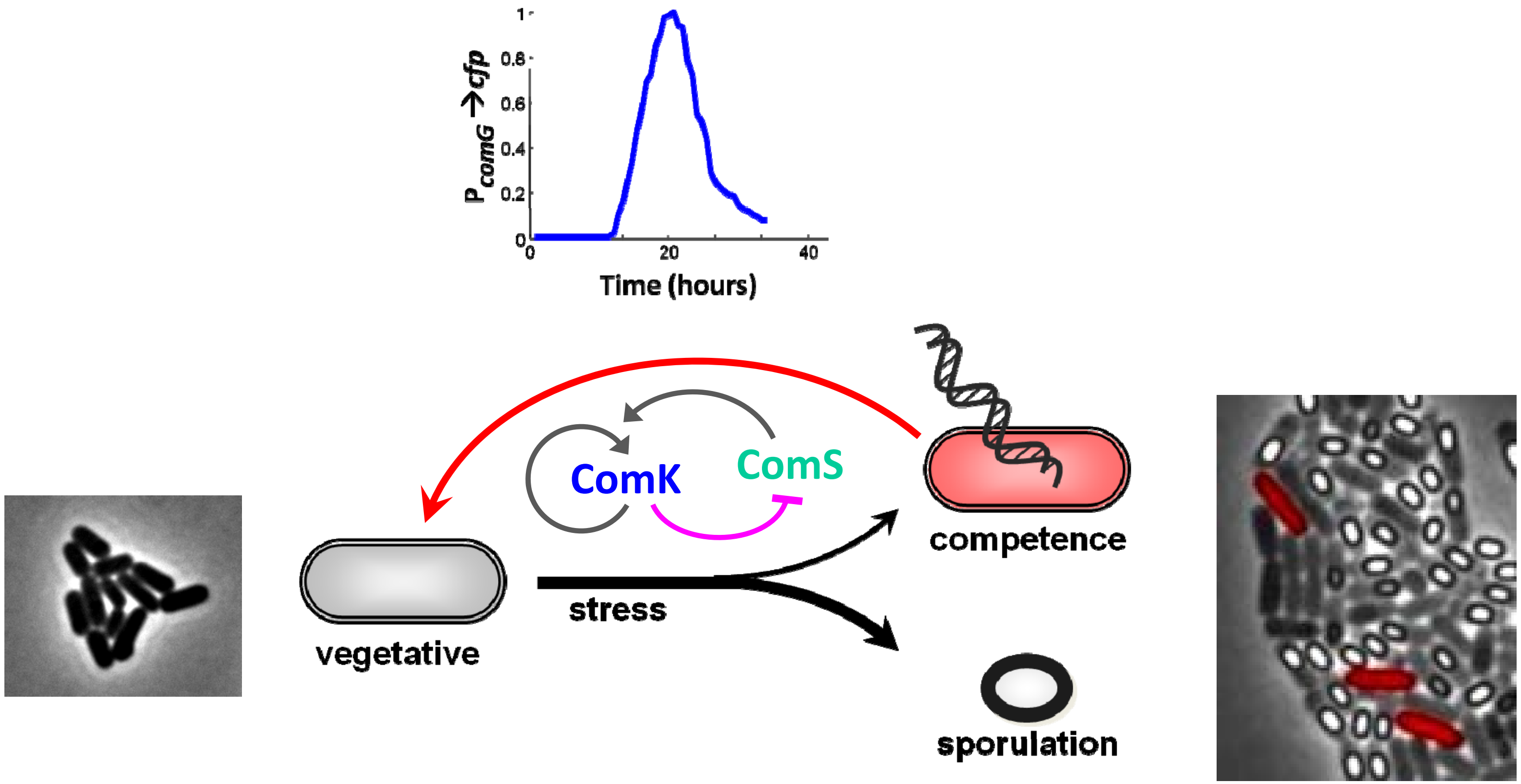
Quel peut être le sens biologique de ce bruit?

Cell

Architecture-Dependent Noise Discriminates Functionally Analogous Differentiation Circuits

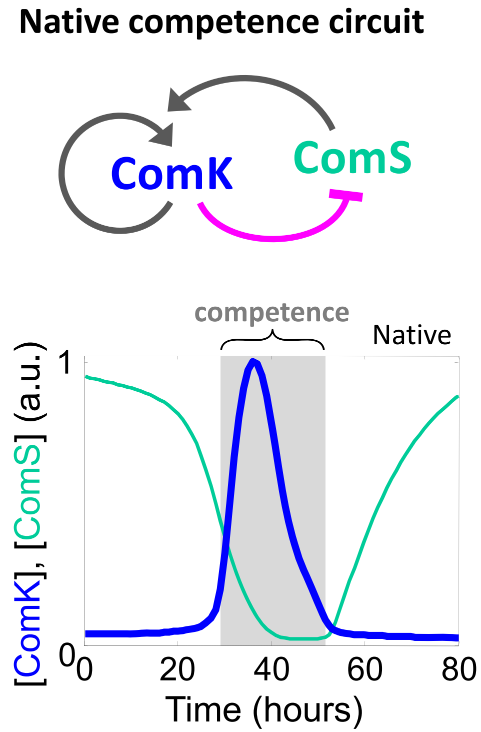
Tolga Çağatay,[1,2] Marc Turcotte,[2] Michael B. Elowitz,[3] Jordi Garcia-Ojalvo,[4] and Gürol M. Süel[1,2,*]
[1]Green Center for Systems Biology
[2]Department of Pharmacology
University of Texas Southwestern Medical Center, Dallas, TX 75390, USA
[3]Division of Biology and Department of Applied Physics, California Institute of Technology, Pasadena, CA 91125, USA
[4]Departament de Física i Enginyeria Nuclear, Universitat Politècnica de Catalunya, Colom 11, E-08222 Terrassa, Spain
*Correspondence: gurol.suel@utsouthwestern.edu
DOI 10.1016/j.cell.2009.07.046

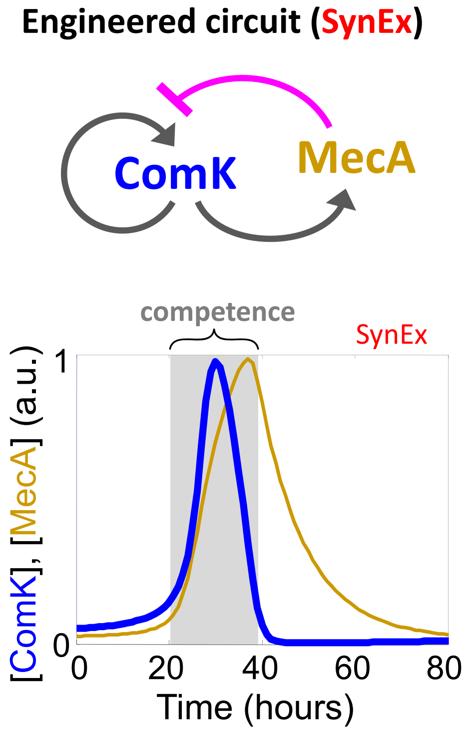
Function, architecture and dynamics of the competence circuit



Süel *et al*. Science, 2007, Volume 315, number 5818
Süel *et al*. Nature, 2006, volume 440, number 7083

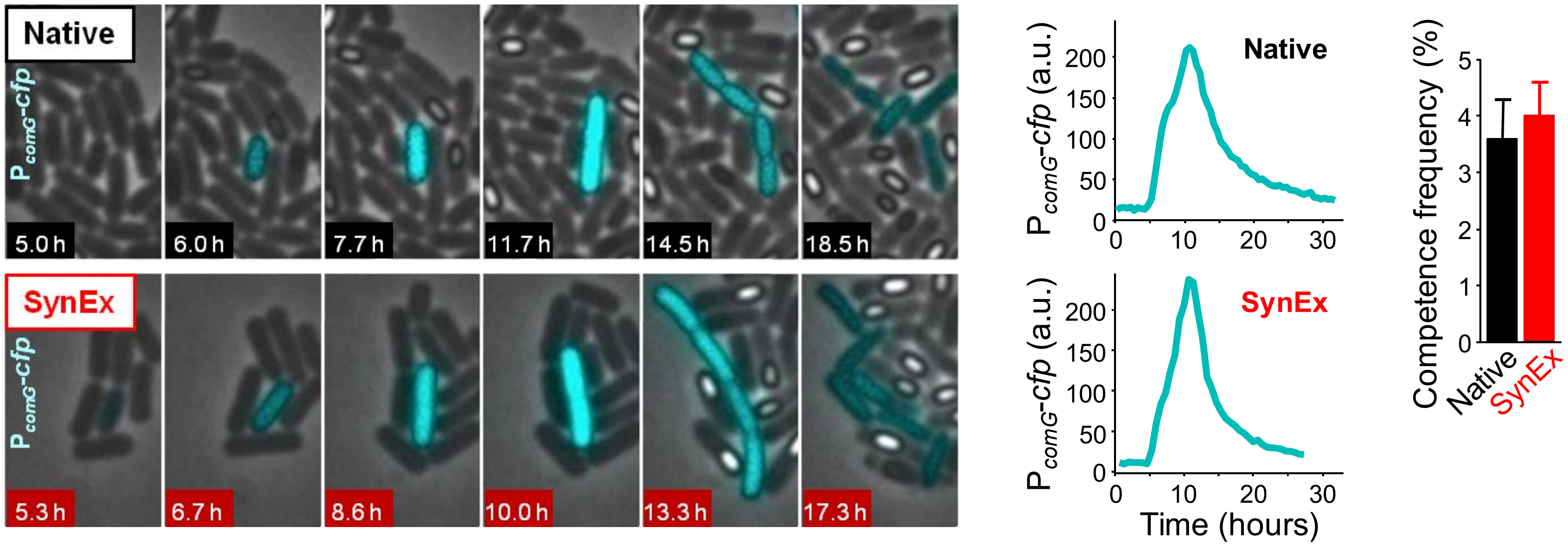
The native competence circuit architecture is not an exclusive solution for excitability





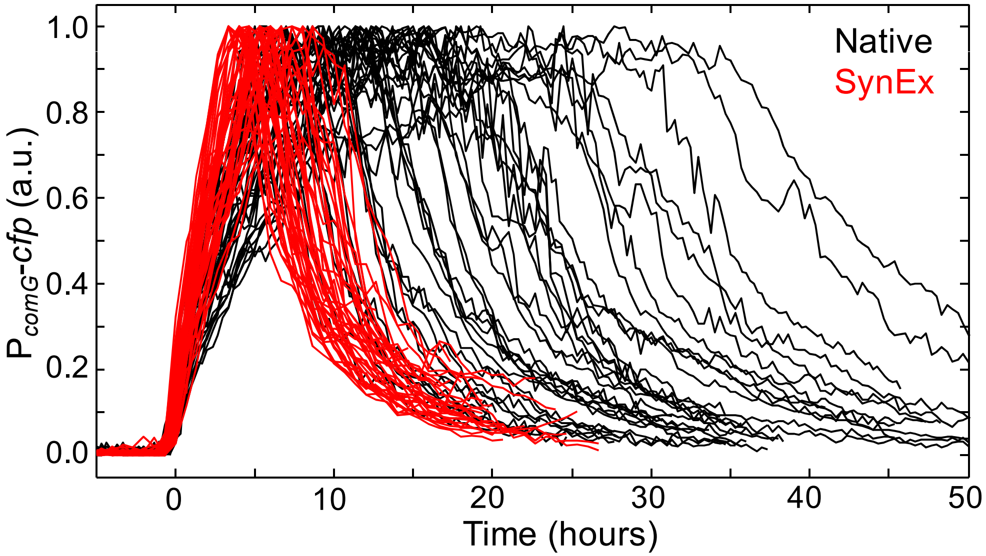
Turcotte M., G-Ojalvo J. and Süel G.M.; *PNAS* (2008)

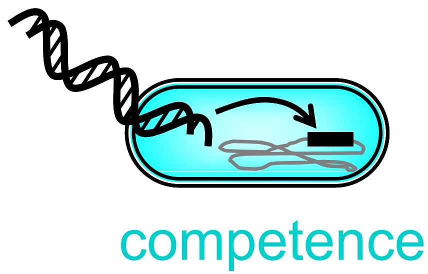
SynEx generates same frequency of competent cells

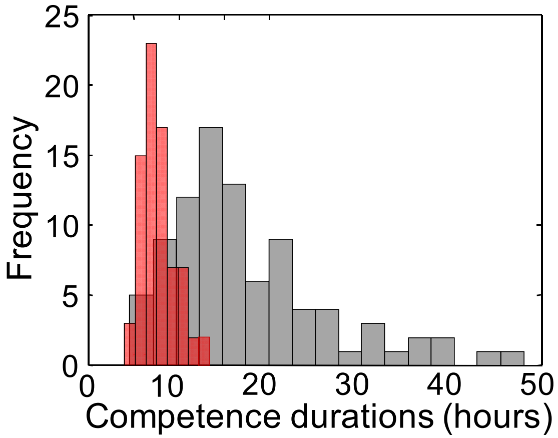


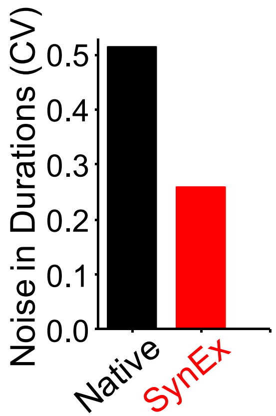
Cell 139, 512–522, October 30, 2009

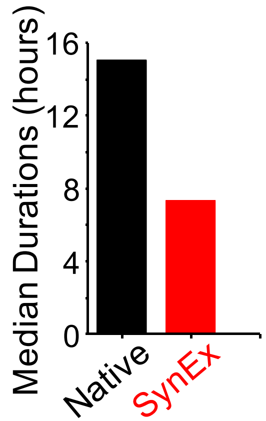
Differences between SynEx and Native competence events

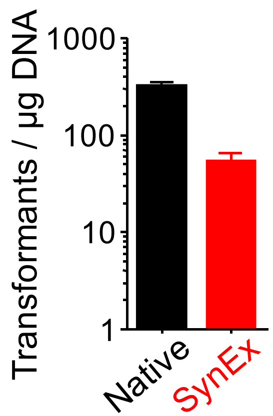












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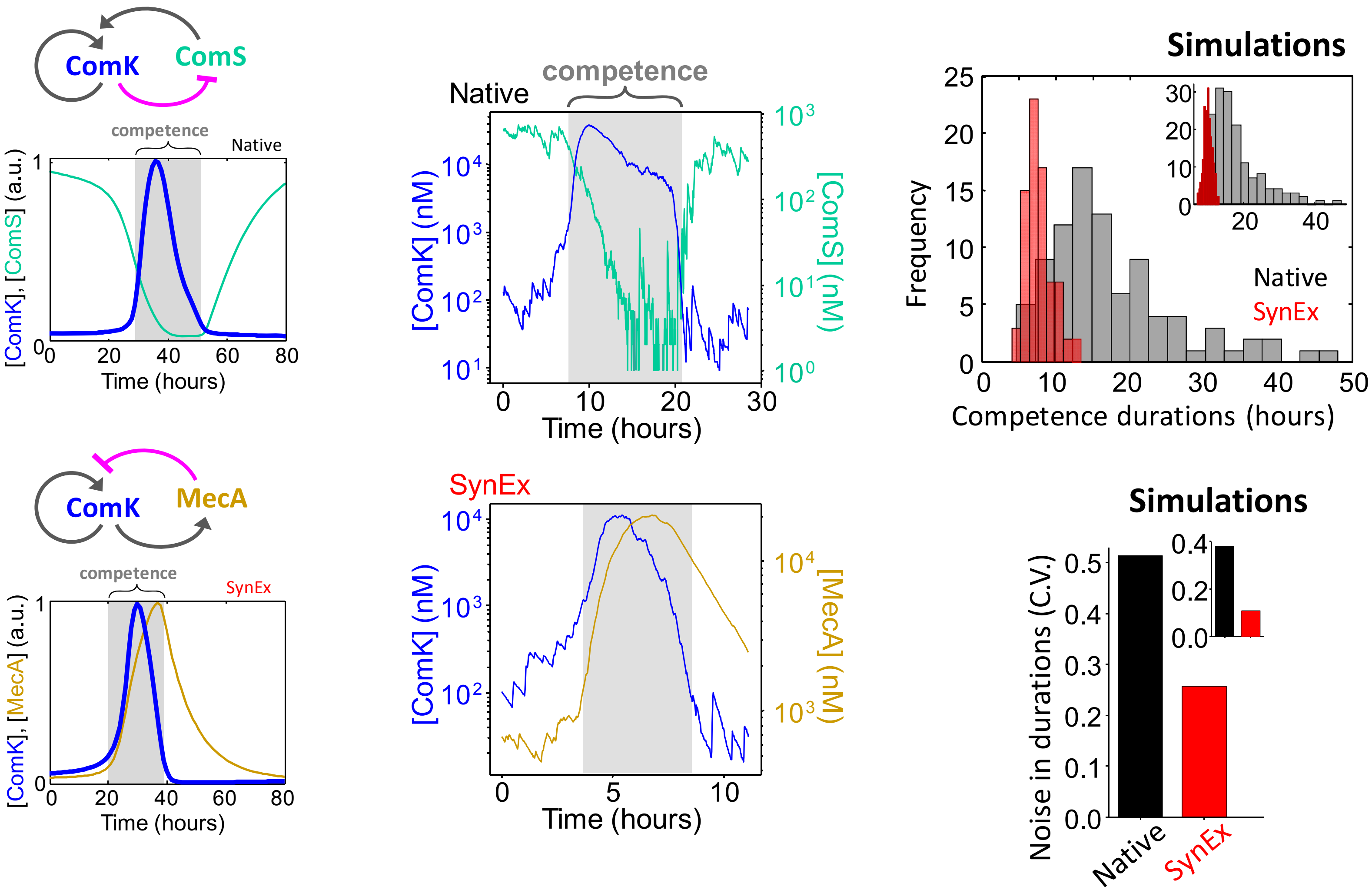
Precision of SynEx is due to its architecture



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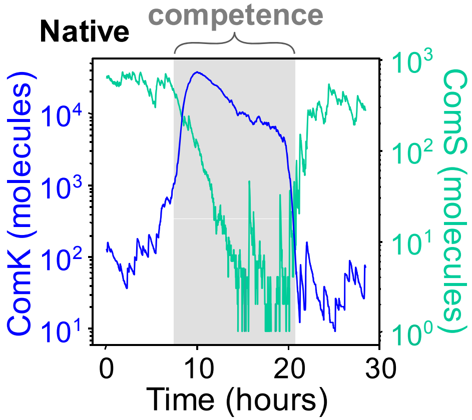
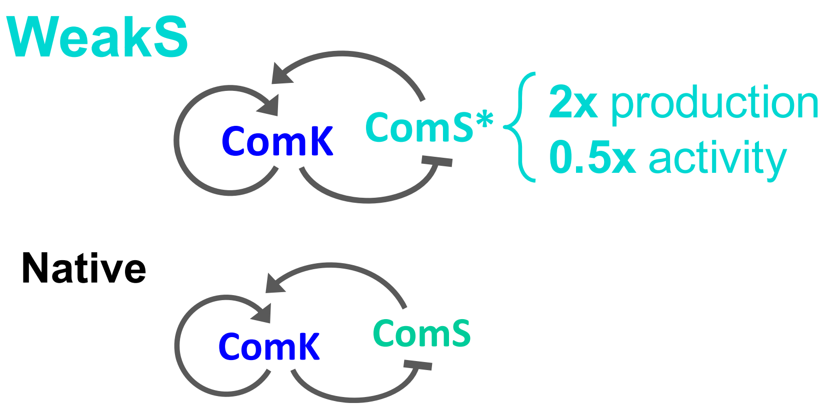
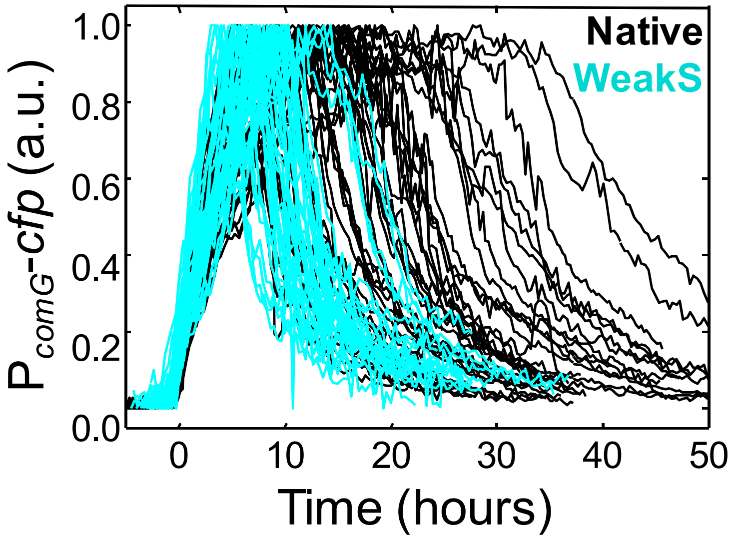
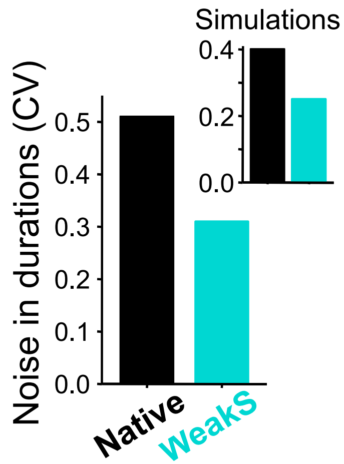
ComS regulation in the native circuit is the noise source









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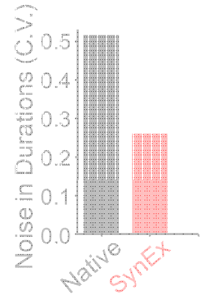
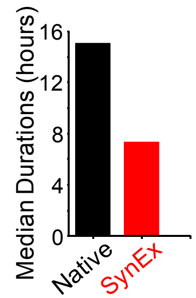
Understanding the differences between SynEx and Native:

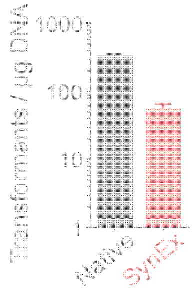
Variability in competence durations (noise)



Mean length of competence durations



Efficiency in transformations



Engineer SynEx with same mean durations as Native

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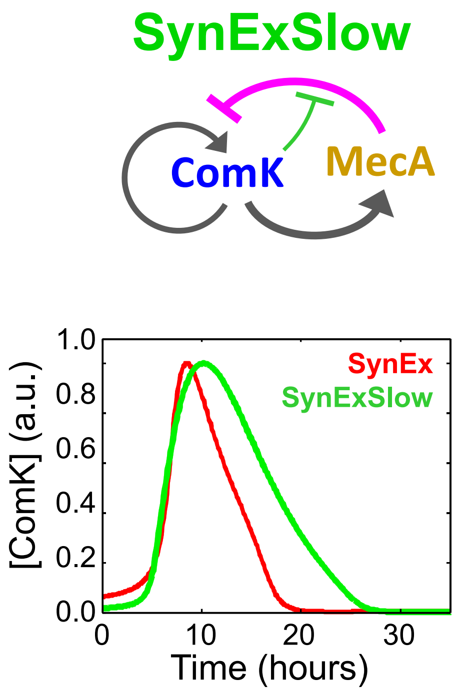
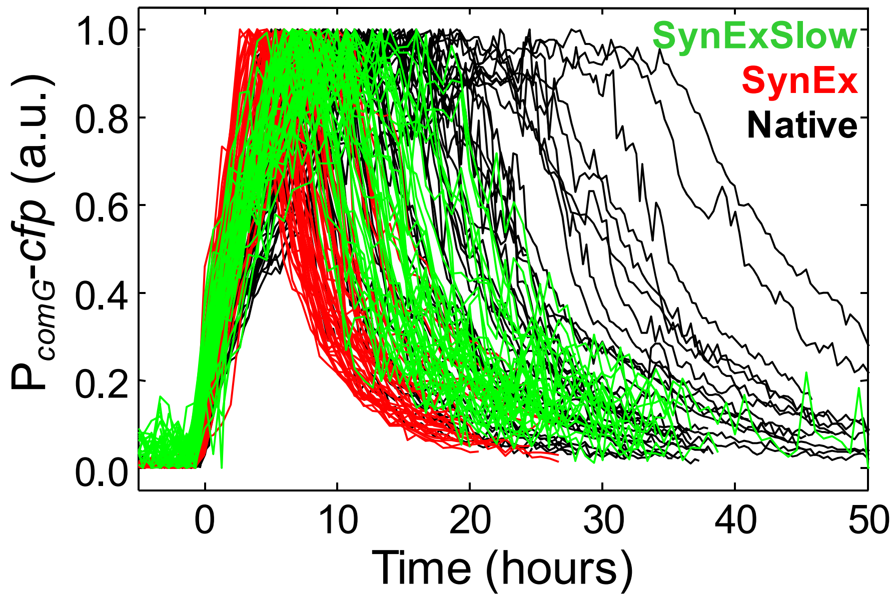
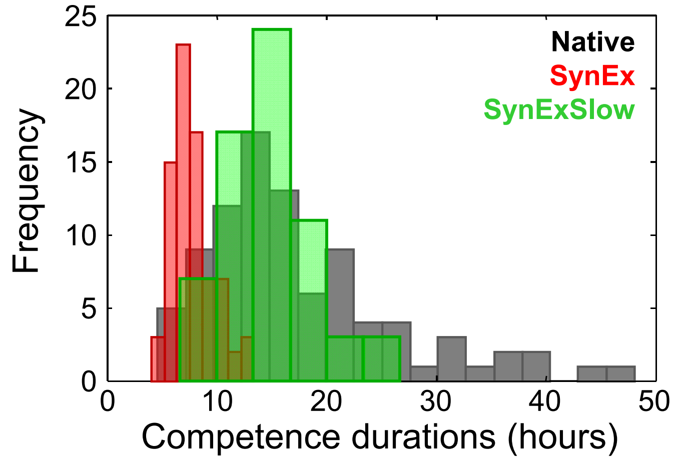
SynExSlow : SynEx with slower competence durations







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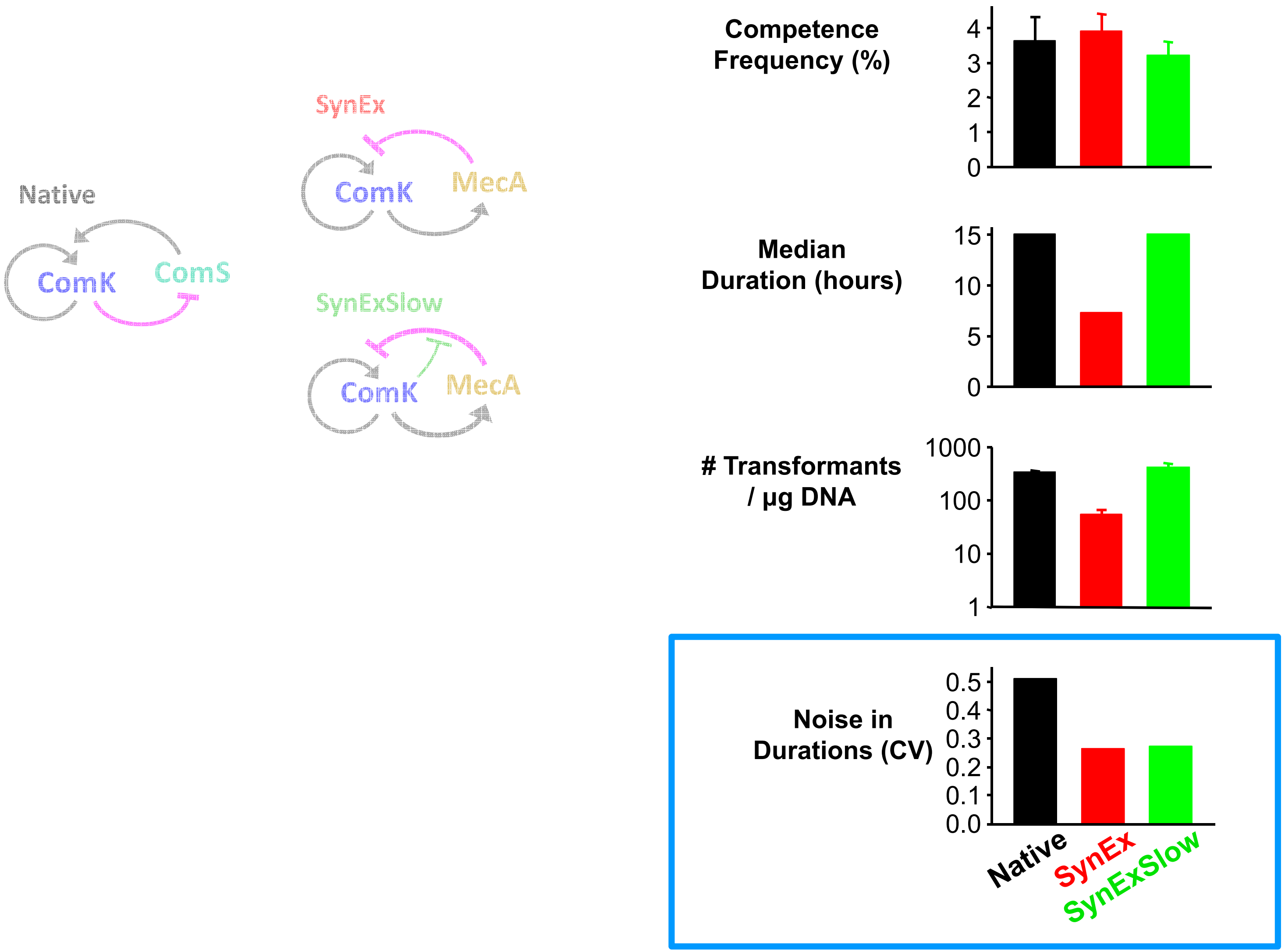
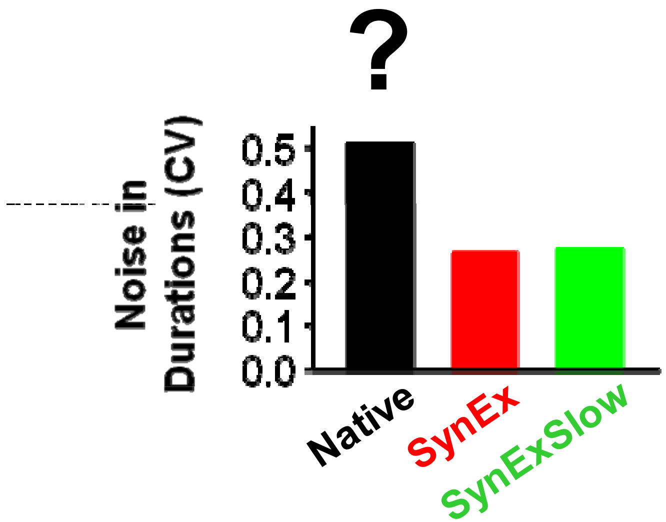
SynExSlow differs from Native ***exclusively*** in noise of durations



Cell *139*, 512–522, October 30, 2009

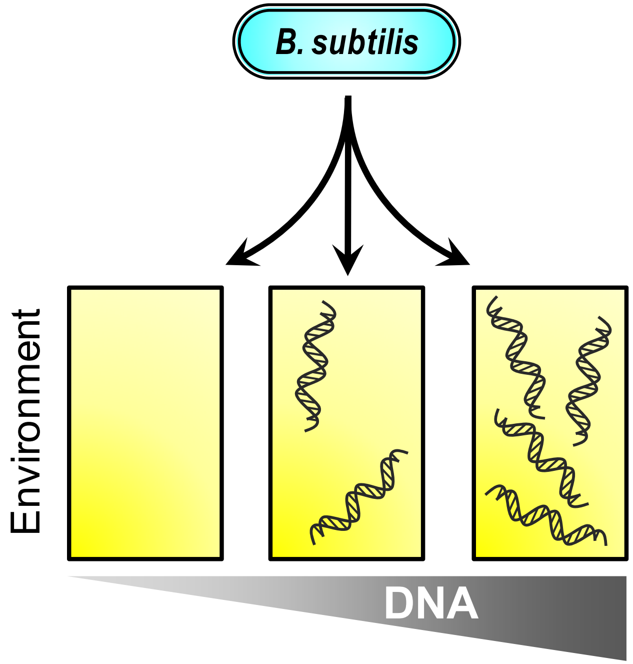
Does higher noise in competence durations provide a biological advantage for *B. subtilis*?



Cell *139*, 512–522, October 30, 2009

Constraints to consider…

1) DNA concentration in the environment can **vary**



Cell *139*, 512–522, October 30, 2009

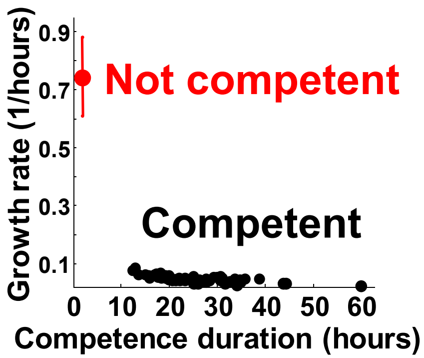
Constraints to consider…

1) DNA concentration in the environment can **vary**

2) **Benefit** and **Cost** of competence durations to *B. subtilis*

Benefit:
Longer durations → Higher DNA uptake probability

Cost:
Longer durations → Reduced growth rate



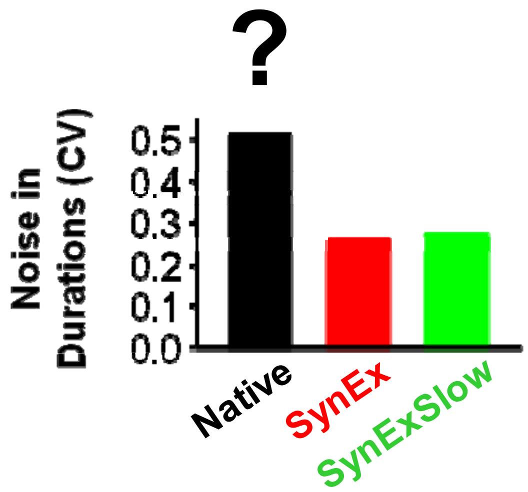
Cell 139, 512–522, October 30, 2009

What is the optimal duration for competence ?

1) DNA concentration in the environment can vary

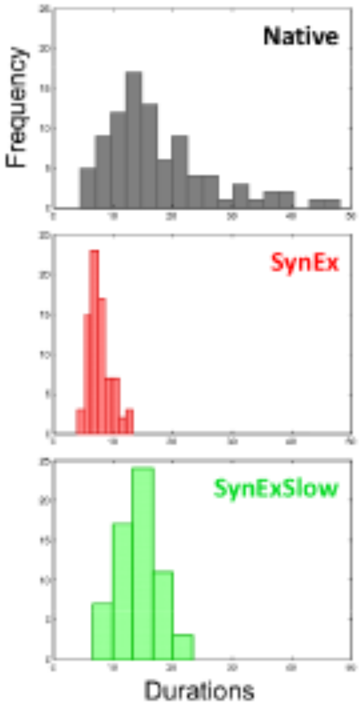
2) Benefit and Cost of competence durations to *B. subtilis*

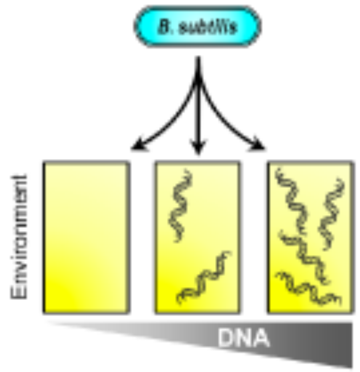
... using Noise as a bet-hedging strategy ?

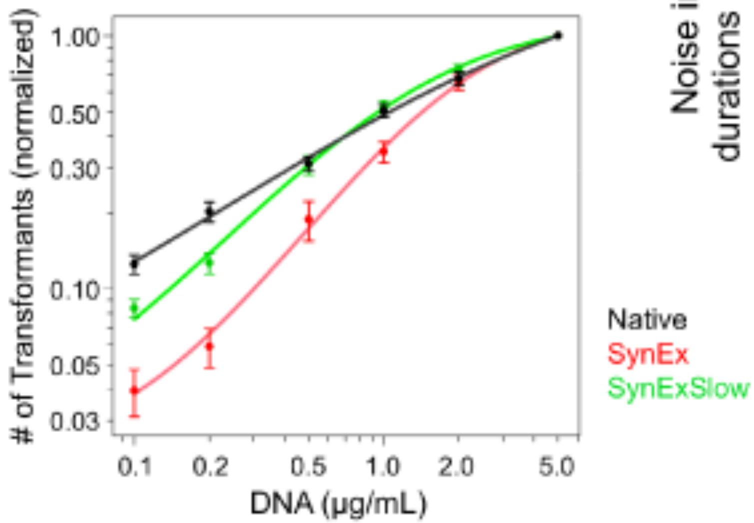


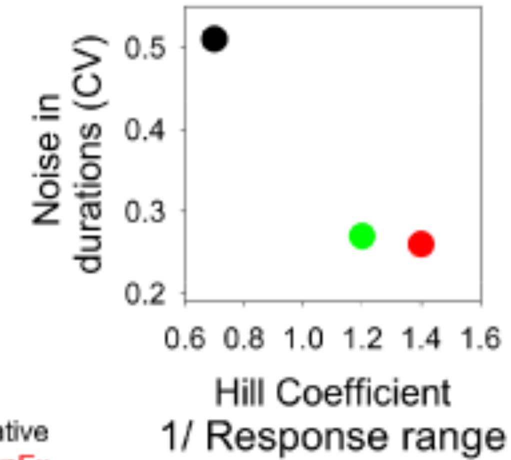
Cell *139*, 512–522, October 30, 2009

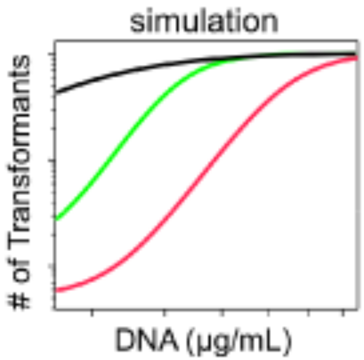
Noise in competence durations increases response range to [DNA]







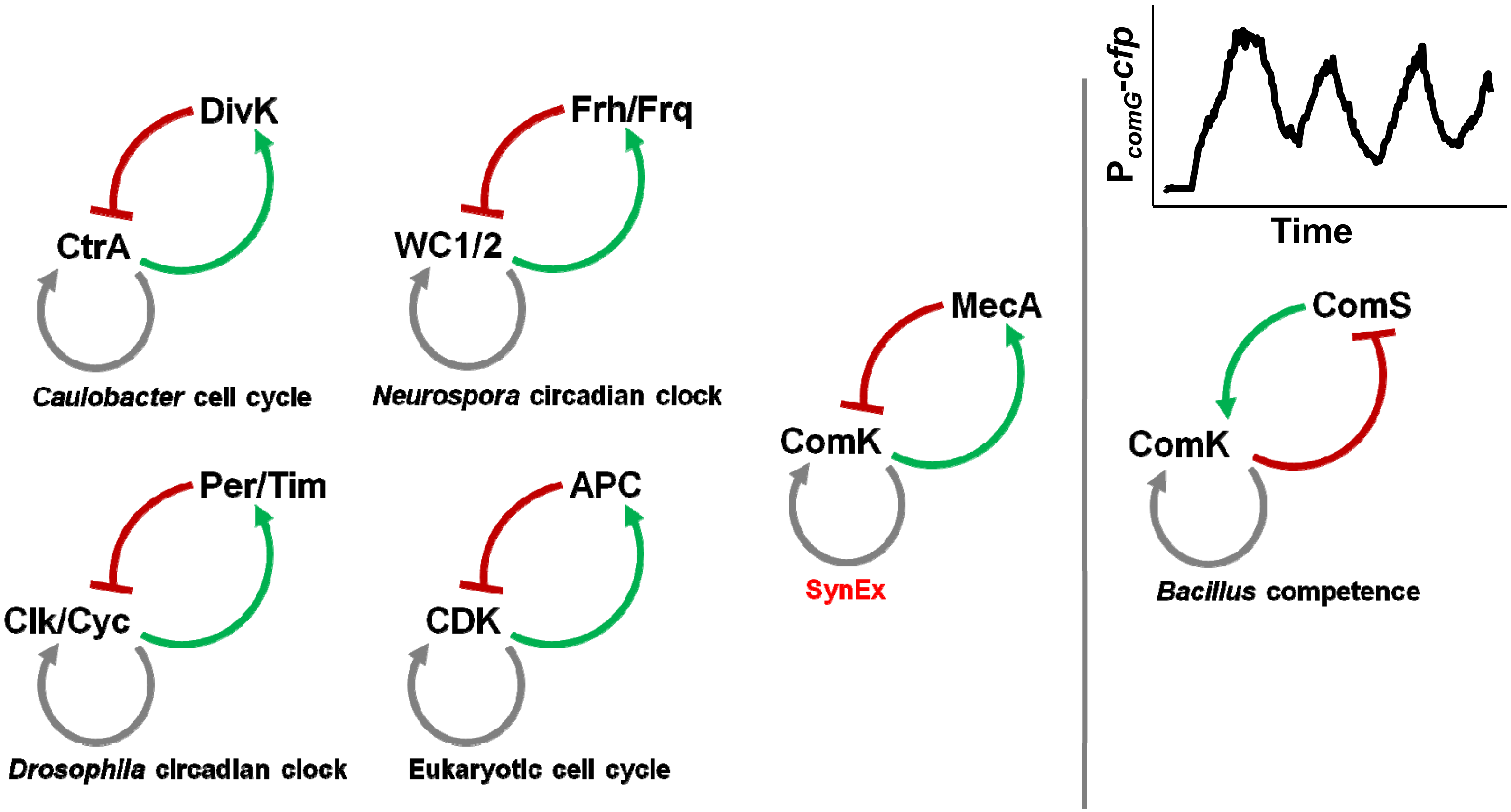




Cell *139*, 512–522, October 30, 2009

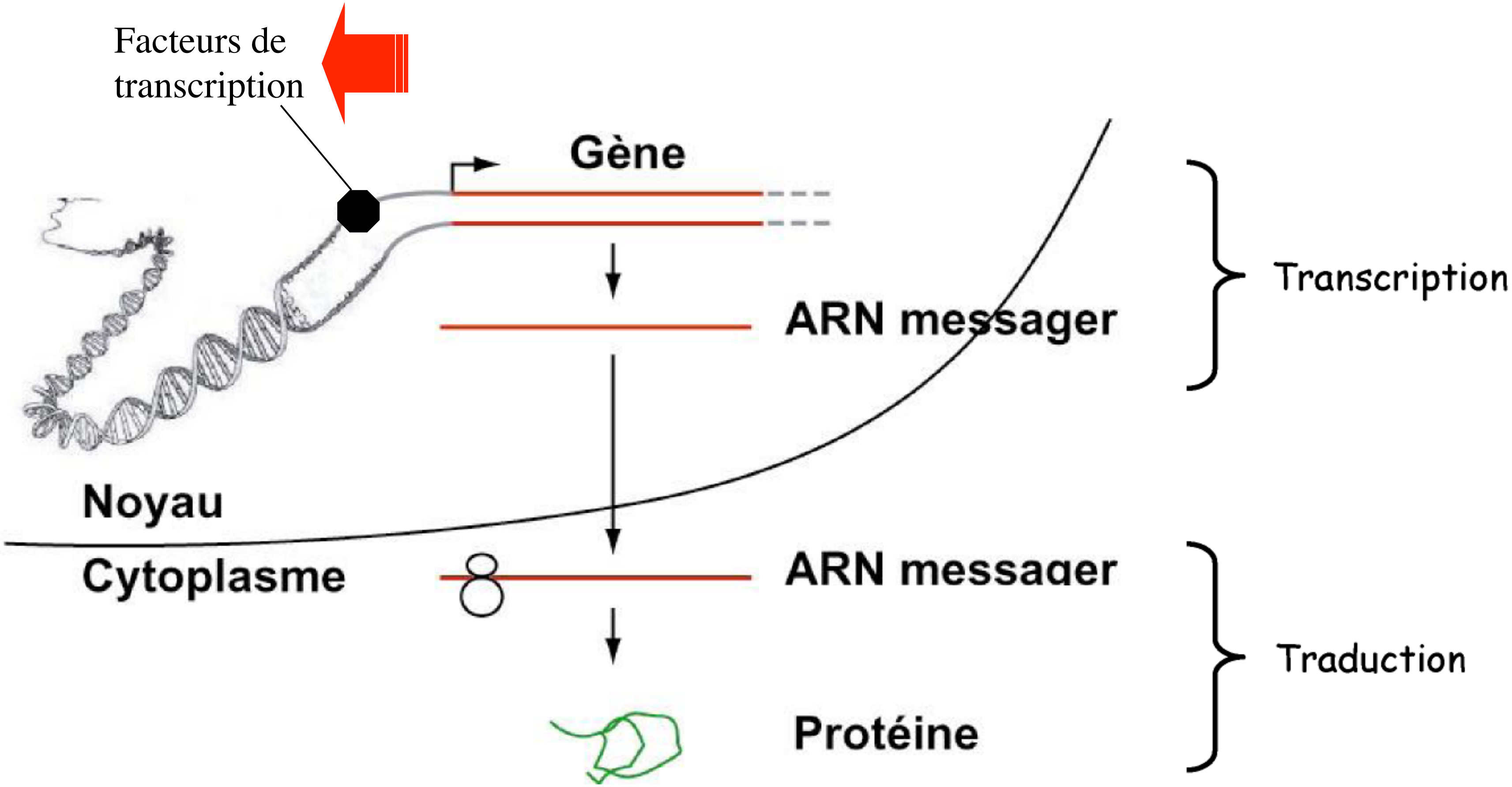
Conclusions:

- Circuit architecture dictates noise which dictates physiological response range
- Circuit architecture as an internal model of environmental constraints
- Different circuit architectures for different biological requirements

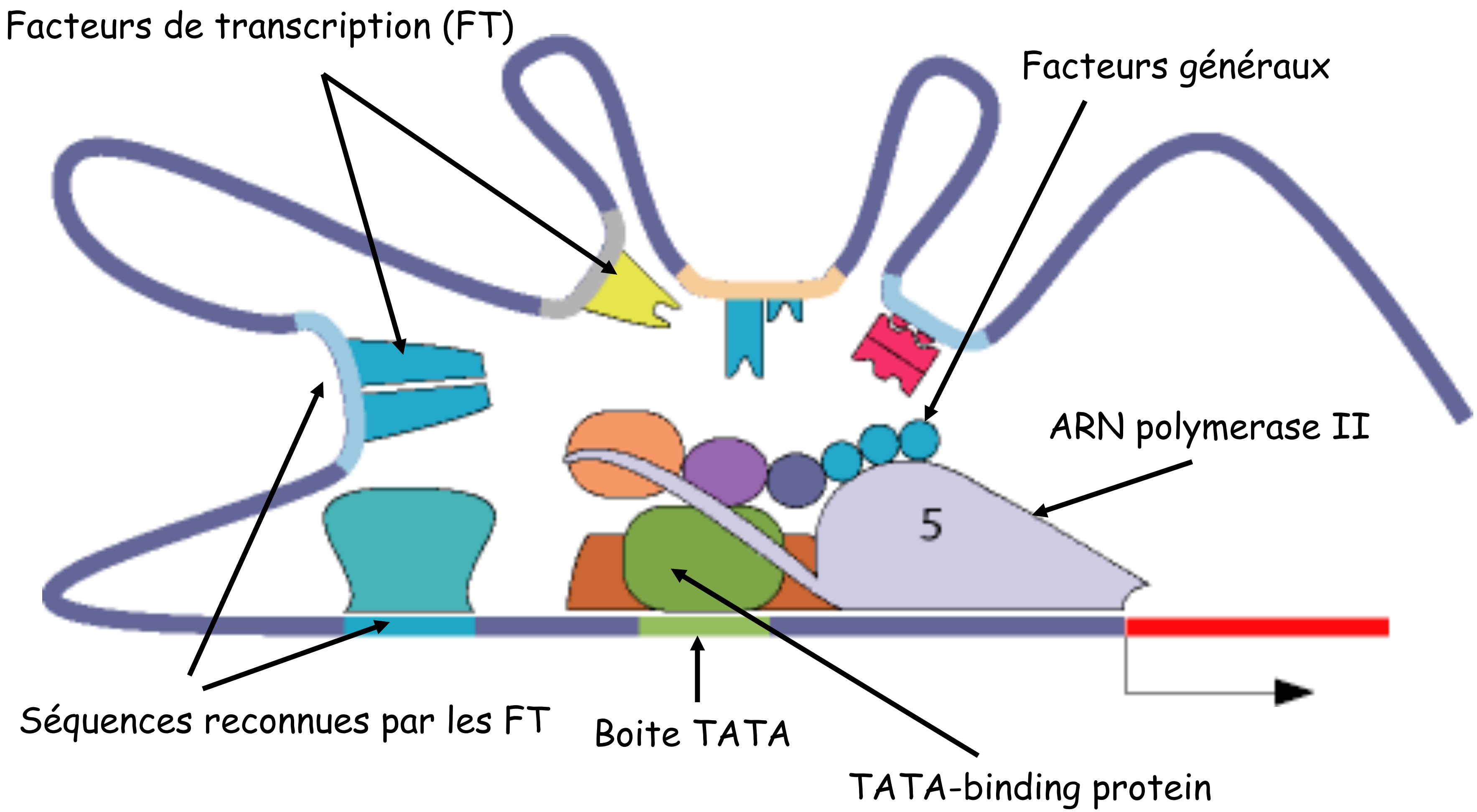


Süel *etal* .Science, 2007, Volume 315, number 5818

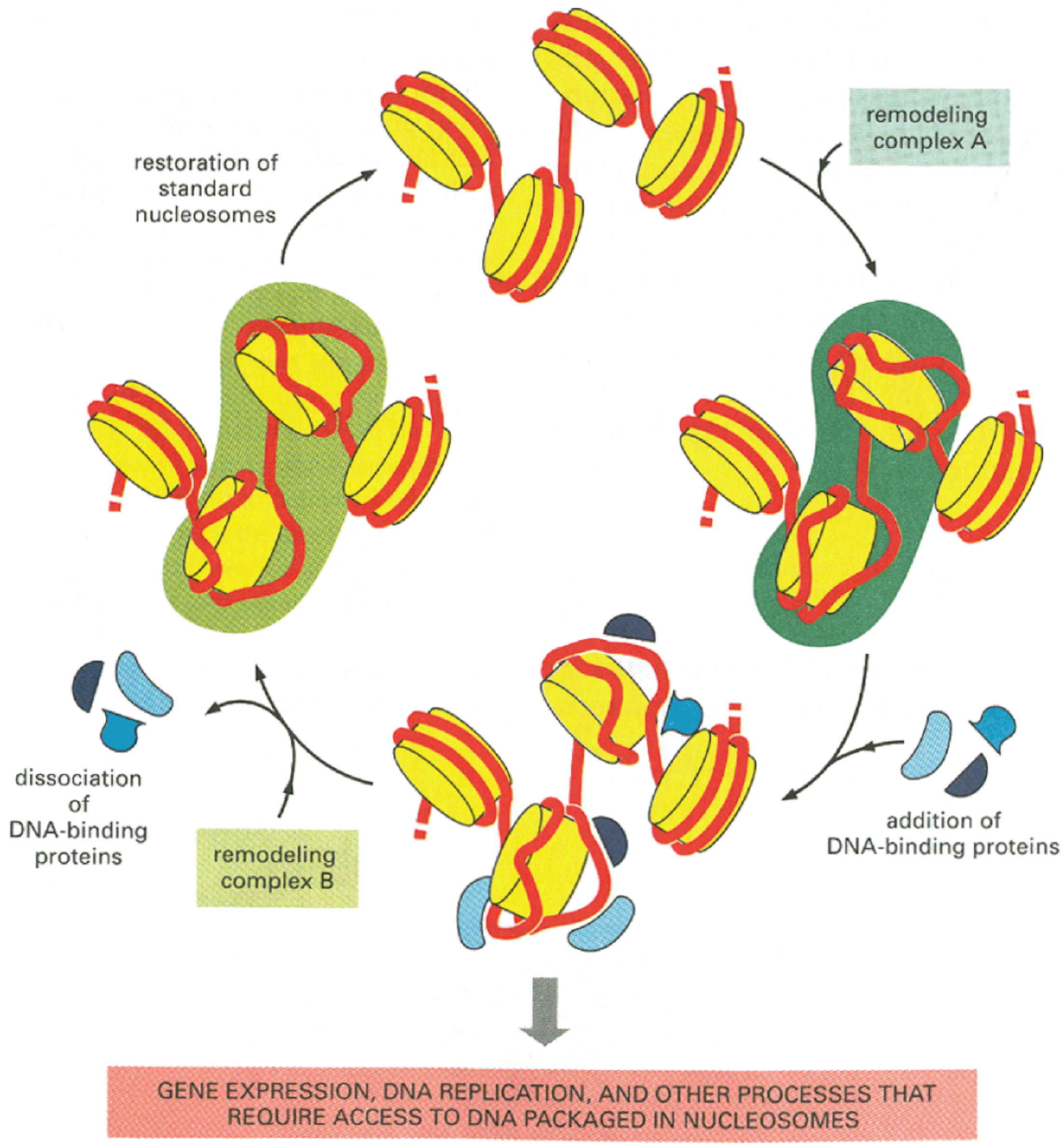
Oblige à se poser la question de la réalité physique des phénomènes….



3. the essentially dynamic nature of protein-protein interactions {Coulon, 2010};

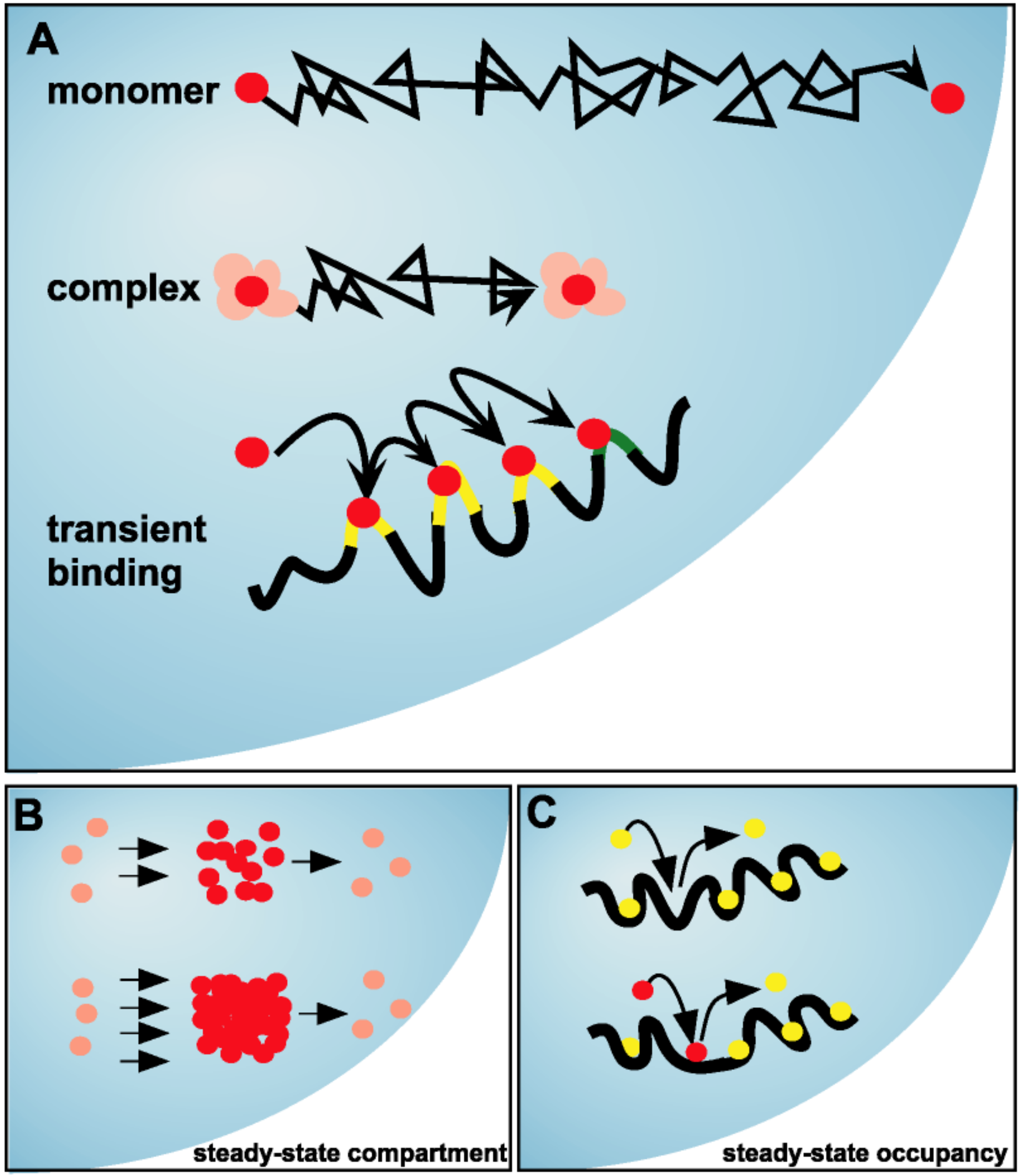


L' initiation de la transcription: une vision statique



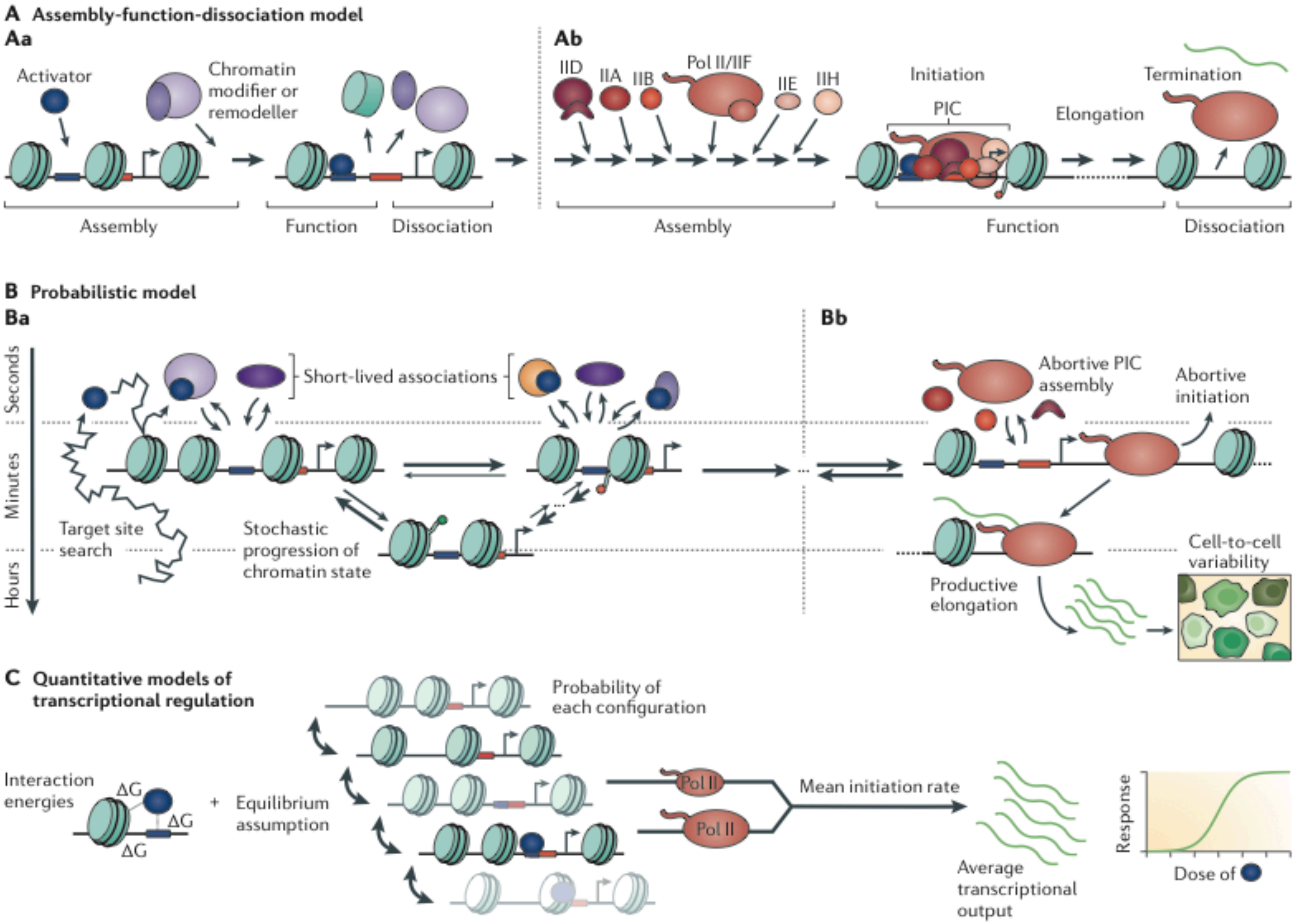
En pratique:

Des phénomènes hautement complexes (la structure de la chromatine joue un rôle essentiel)



En pratique:

Des phénomènes hautement dynamiques



Coulon et al. (2013). *Nature Reviews Genetics*

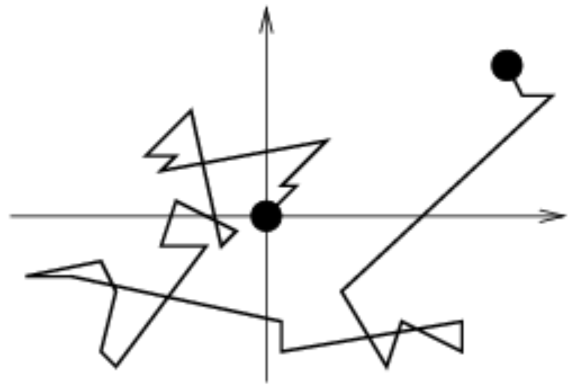
Comment étudier la stochasticité générée par la dynamique des déplacements moléculaires?

Utilisation d'un système multi-agents moléculaire: 3DSpi

Antoine Coulon, Guillaume Beslon, Olivier Gandrillon **(2008). Large Multiprotein Structures Modeling and Simulation: The Need for Mesoscopic Models.** Functional Proteomics Methods in Molecular Biology Volume 484, pp 537-558)

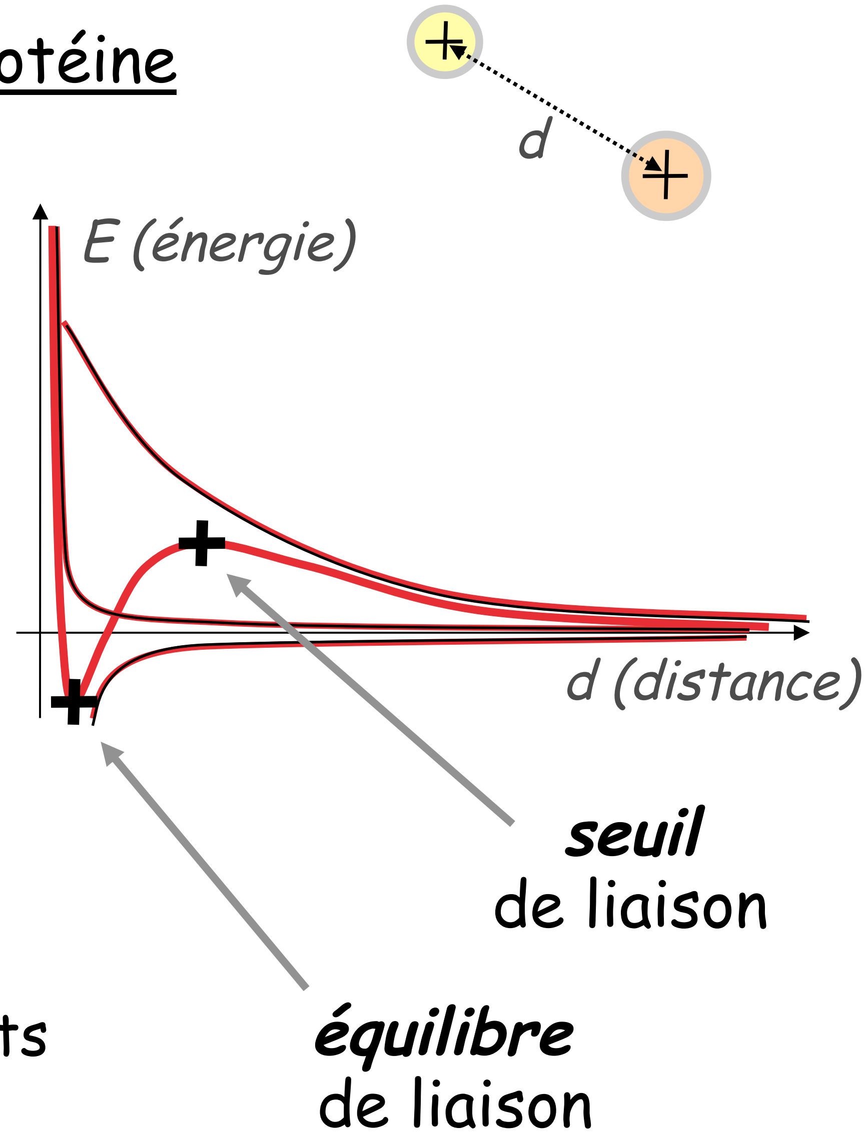
3DSpi.v3.0

- Dynamique “non-newtonienne”
  - La viscosité prime la masse
- Modèle brownien “vrai”
  - Trajectoires fractales



Champs d'énergie

- Défini pour chaque paire de protéine



- 3 composantes :
  - énergie de Born
  - énergie de van der Waals
  - énergie de Coulomb

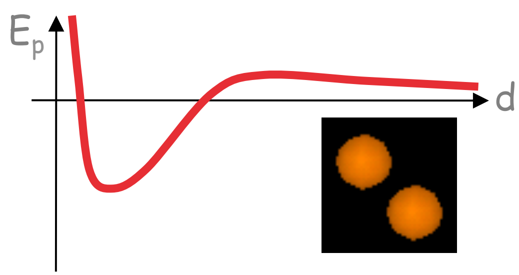
$$E = \frac{A}{d^{12}}$$

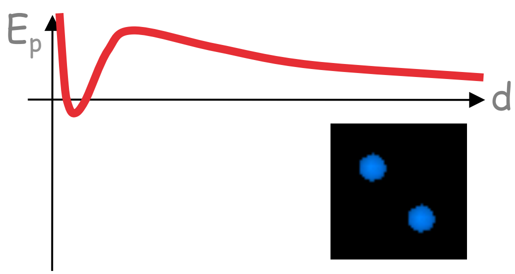
- Force = dérivé de l'énergie
  ➔ ***minimisation de l'énergie***

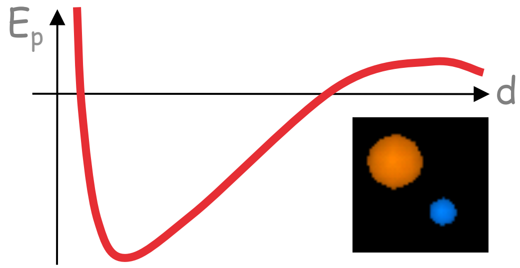
- Paramétrage : position des 2 points

◆ <u>Exemple 1</u> : formation de structures auto-organisées

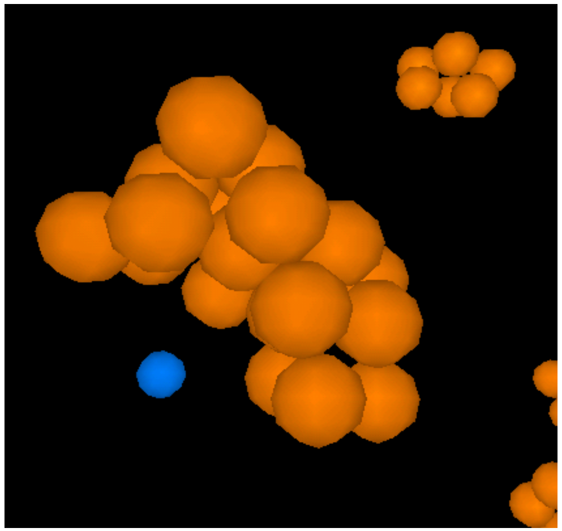
- 2 espèces de protéines



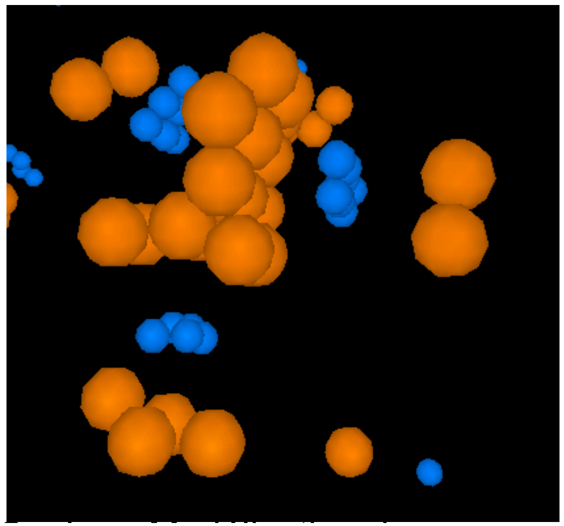


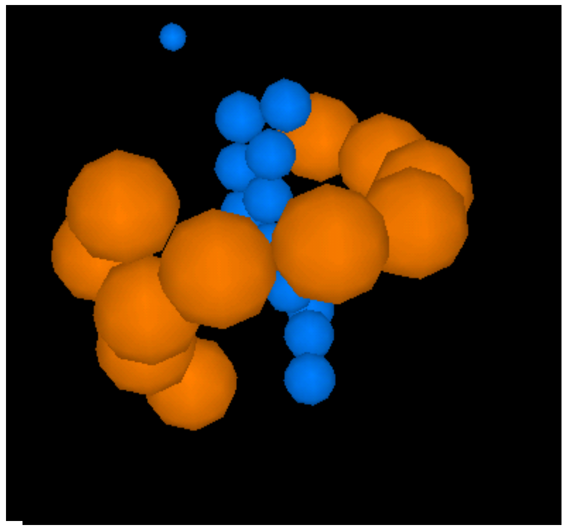


96% vs 4%

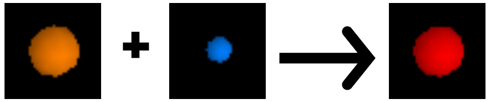
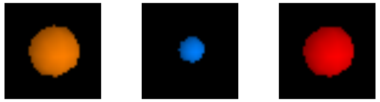


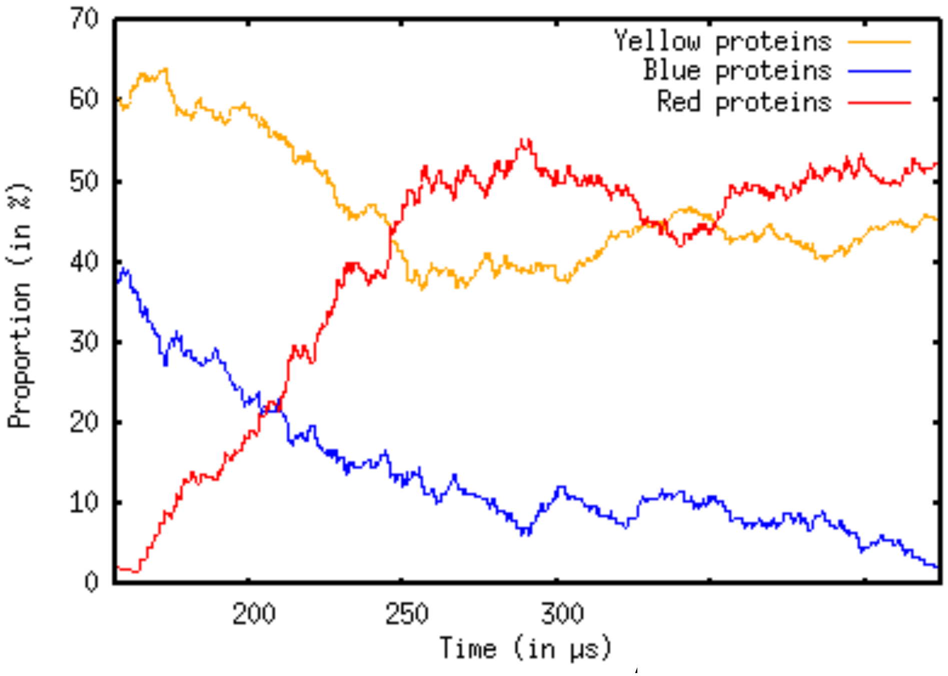
50% vs 50%

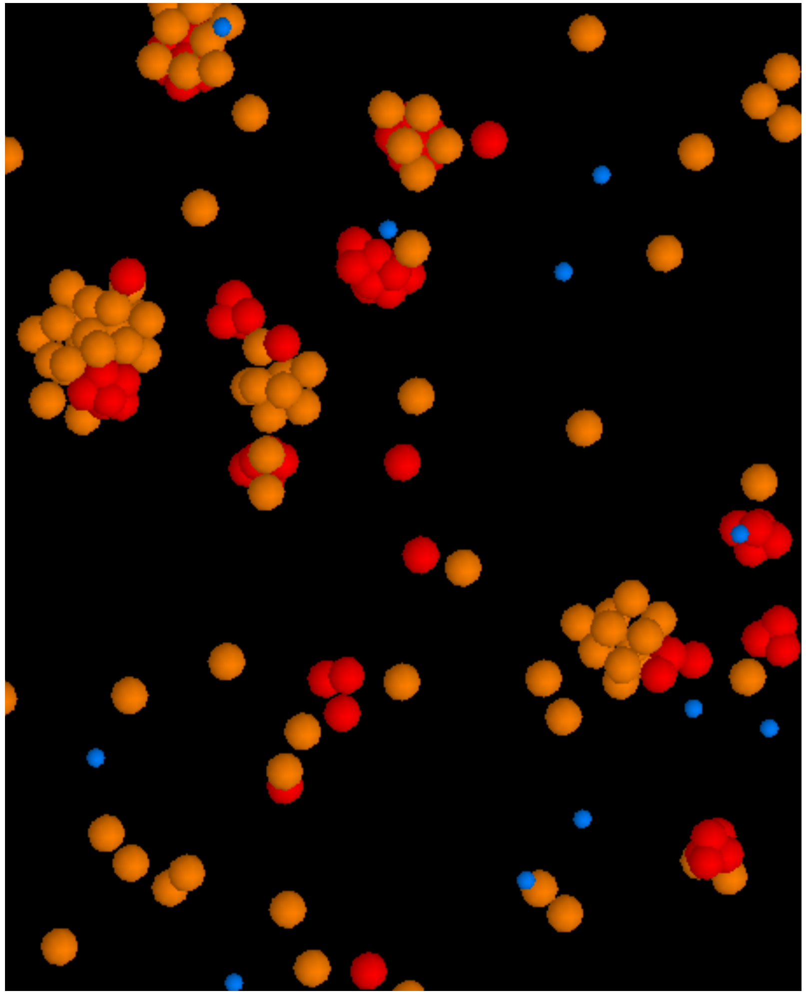




◆ <u>Exemple 2</u> : cinétique de réaction en milieu hétérogène

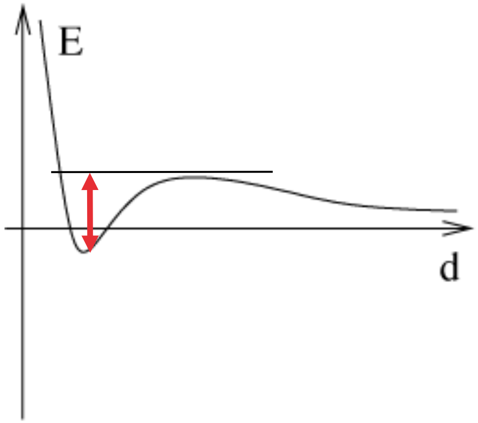
- Entrées : 
- Réaction : 
- Sorties : 



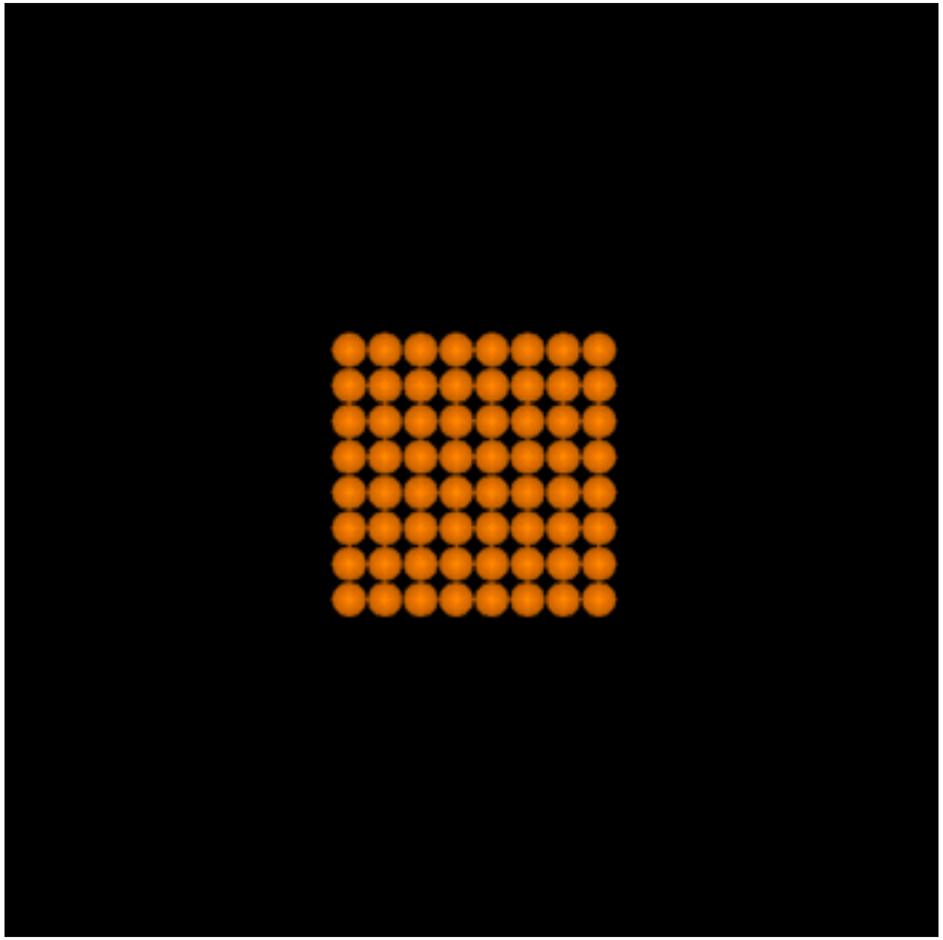


Comportements de base du modèle

- **Exemple 3** : disruption d'une structure multiprotéique



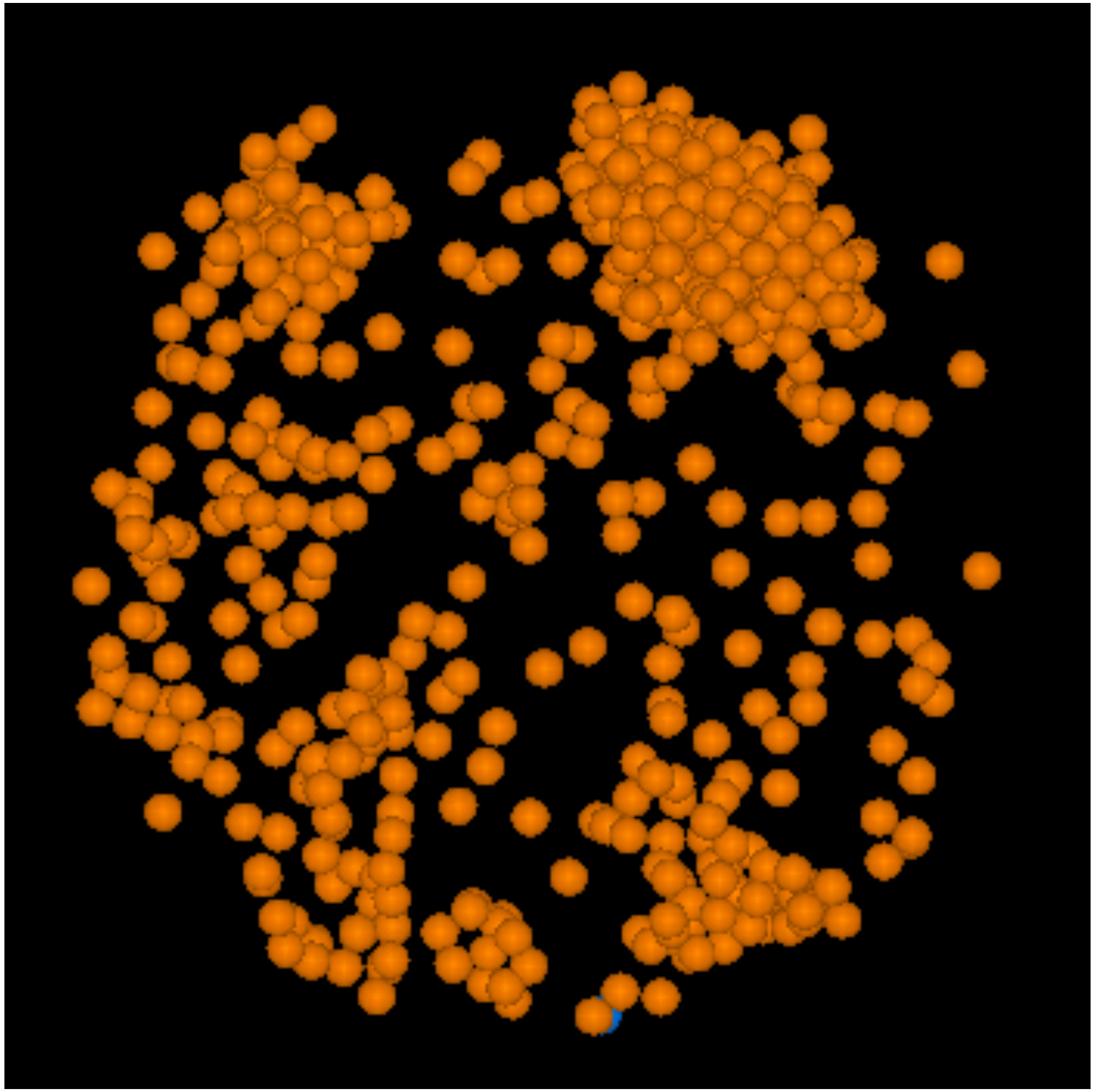
a. Agrégats dynamiques



Movie_2

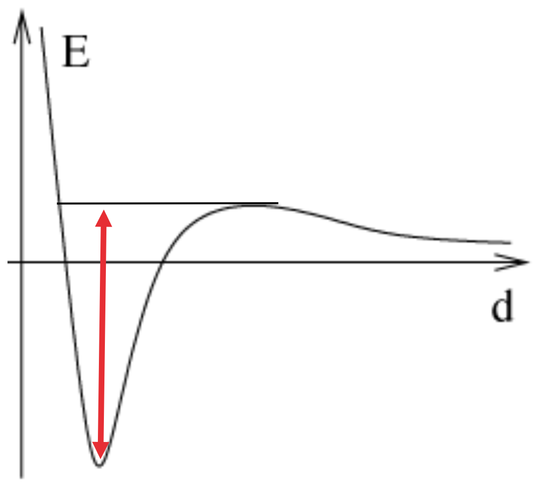
Comportements de base du modèle

- <u>Exemple 3</u> : disruption d'une structure multiprotéique

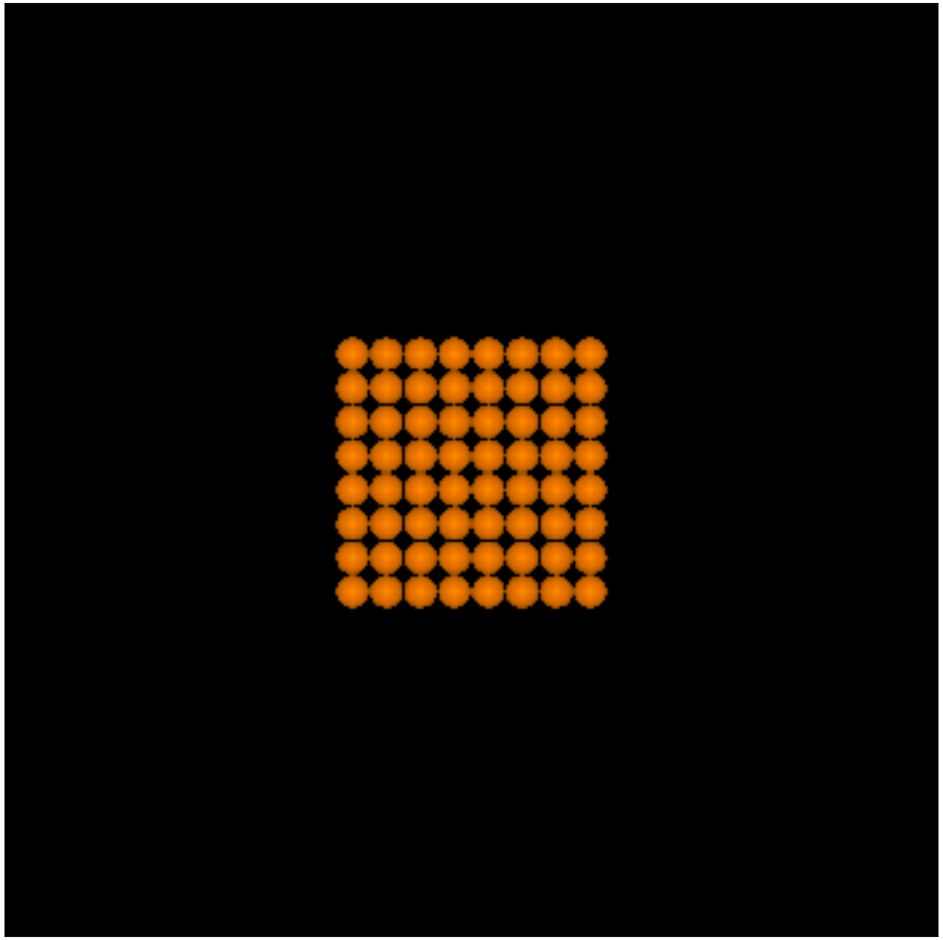


Comportements de base du modèle

- **Exemple 3** : disruption d'une structure multiprotéique



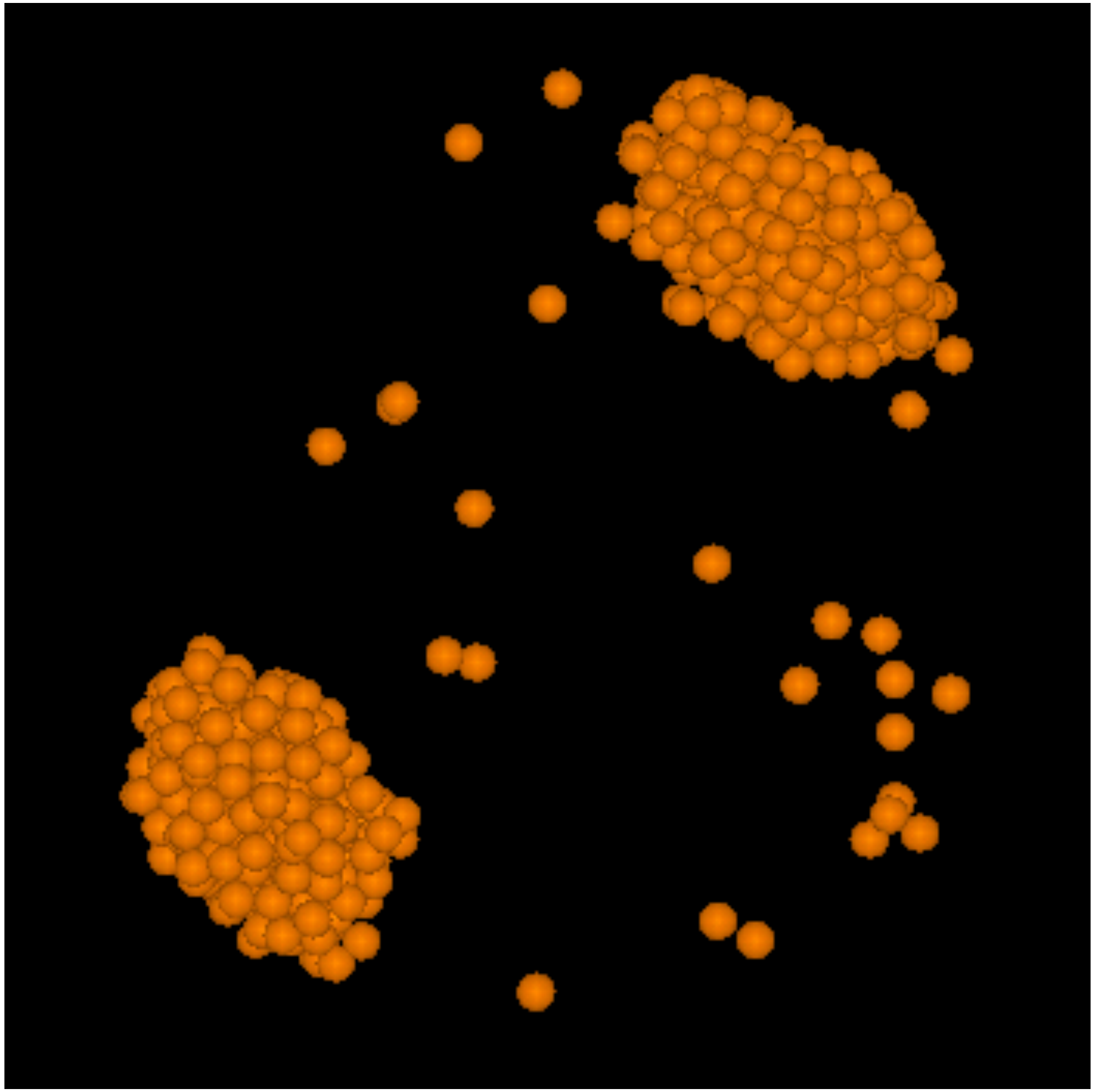
b. Agrégats peu dynamiques

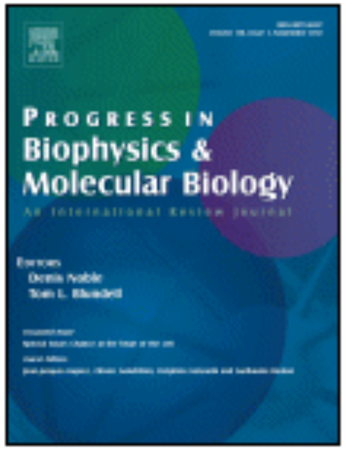


Movie_3

Comportements de base du modèle

- Exemple 3 : disruption d'une structure multiprotéique





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Volume 110, Issue 1, Pages 1-150 (September 2012)

Special Issue: Chance at the heart of the cell

Edited by Jean-Jacques Kupiec, Olivier Gandrillon, Delphine Kolesnik and Guillaume Beslon


"That's all Folks!"
Cartoon Songs From
MERRIE MELODIES & LOONEY TUNES