

Réponse à deux questions posées lors du cours précédent:

**Definitions of noise and parameterization of data.** Intrinsic noise ( $\eta_{int}$ ), extrinsic noise ( $\eta_{ext}$ ), and total variation ( $\eta_{tot}$ ) were defined as follows:

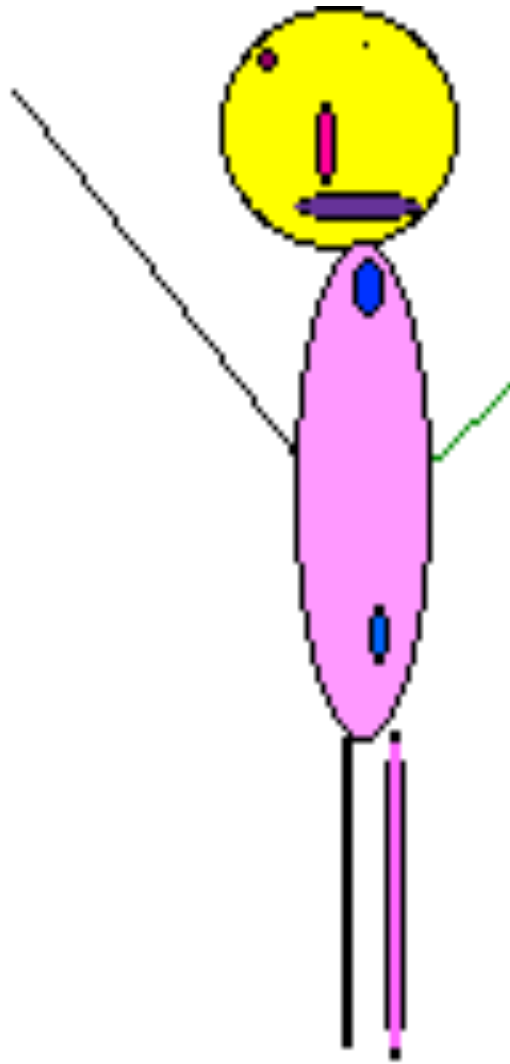
$$\eta_{int}^2 \equiv \frac{\langle (c - y)^2 \rangle}{2\langle c \rangle \langle y \rangle}; \quad \eta_{ext}^2 \equiv \frac{\langle cy \rangle - \langle c \rangle \langle y \rangle}{\langle c \rangle \langle y \rangle} \quad \eta_{tot}^2 \equiv \frac{\langle c^2 + y^2 \rangle - 2\langle c \rangle \langle y \rangle}{2\langle c \rangle \langle y \rangle}$$

Here the  $i^{\text{th}}$  element of vectors  $\mathbf{c}$  and  $\mathbf{y}$  contains the average CFP or YFP intensity, respectively, of the  $i^{\text{th}}$  cell in the sample. Angled brackets denote means over the cell population.

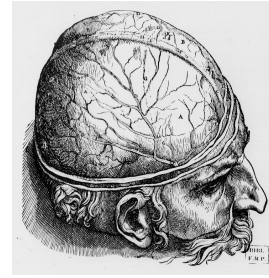
Pour la puissance de 12, si mes souvenirs sont bons, il n'y a pas vraiment de justification. Les deux (mauvaises) raisons pour lesquelles on utilise 12 sont empirique et pratique. C'est assez loin dans ma mémoire, mais je crois que des gens ont essayé de faire des simulations avec différentes formes de potentiels pour reproduire des comportements physiques connus. Et 12, ça marchait pas mal grosso modo... En fait d'autres valeurs marchent aussi, mais si tu descend trop bas, les contacts deviennent trop mous et si tu dépasses 12, ils sont trop durs... Pour le côté pratique, on a choisi 12 parce que c'est facile de calculer  $r^{12}$  quand on a déjà  $r^6$ . Et pour le coup, le terme en  $r^6$  qui représente la force de van der Waals est pleinement justifié (il se calcule comme une force dipôle-dipôle et ça donne un terme en  $r^6$ ).

Antoine Coulon

Quelques rappels sur l'expression génique et son importance biologique:



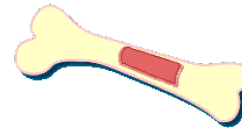
Organisme



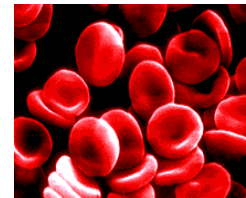
Cerveau



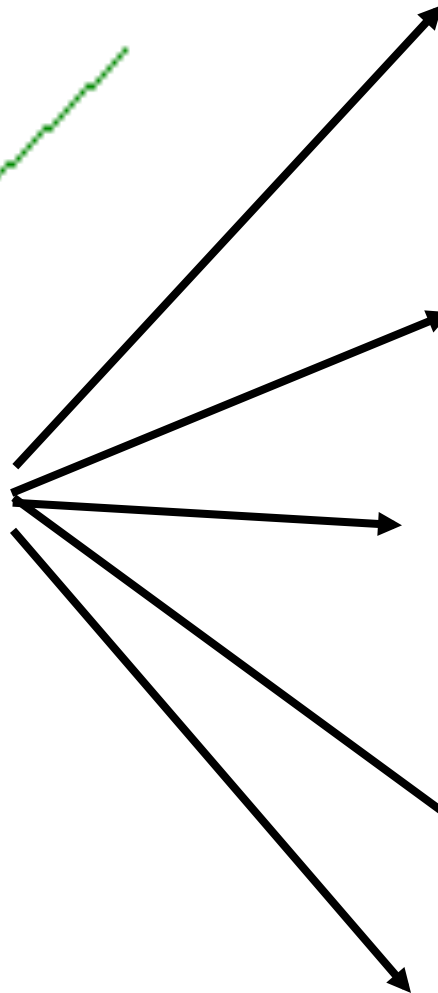
Coeur



Os

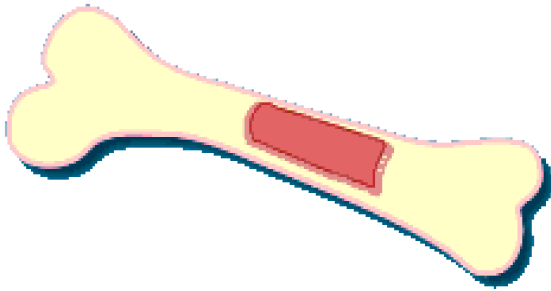


Sang



Autres...

Tissus



Cellules qui  
fabriquent l'os  
(ostéoblastes)

Cellules qui mangent  
l'os (ostéoclastes)

Moelle osseuse

Tissus

Cellules

**Il y a environ 1000 milliards**

**de cellules dans notre corps.**

**Elles sont toutes originaires d'une seule cellule:**

**l'Oeuf**

1



10000000000000

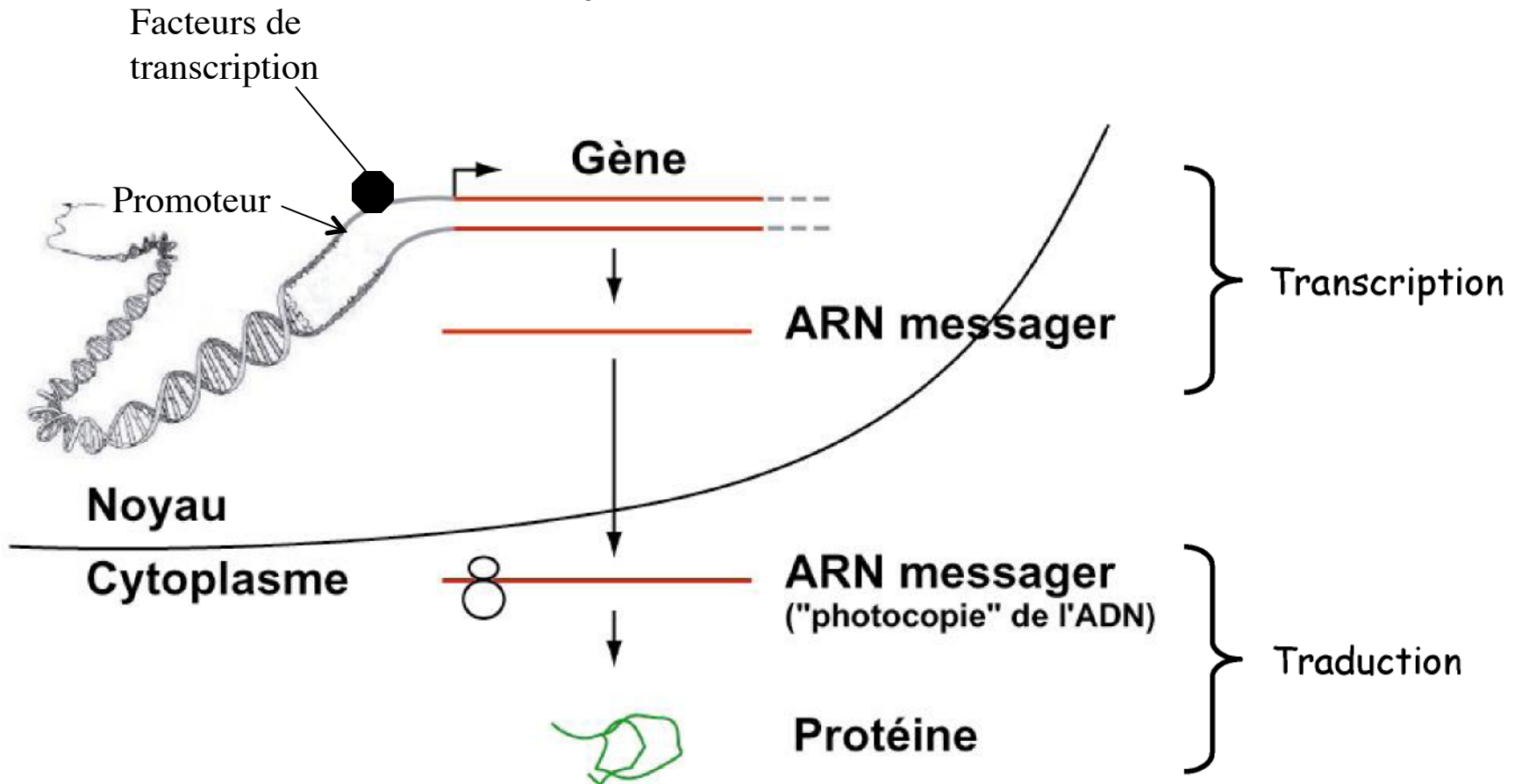
(différentes mais avec le même  
génomé)

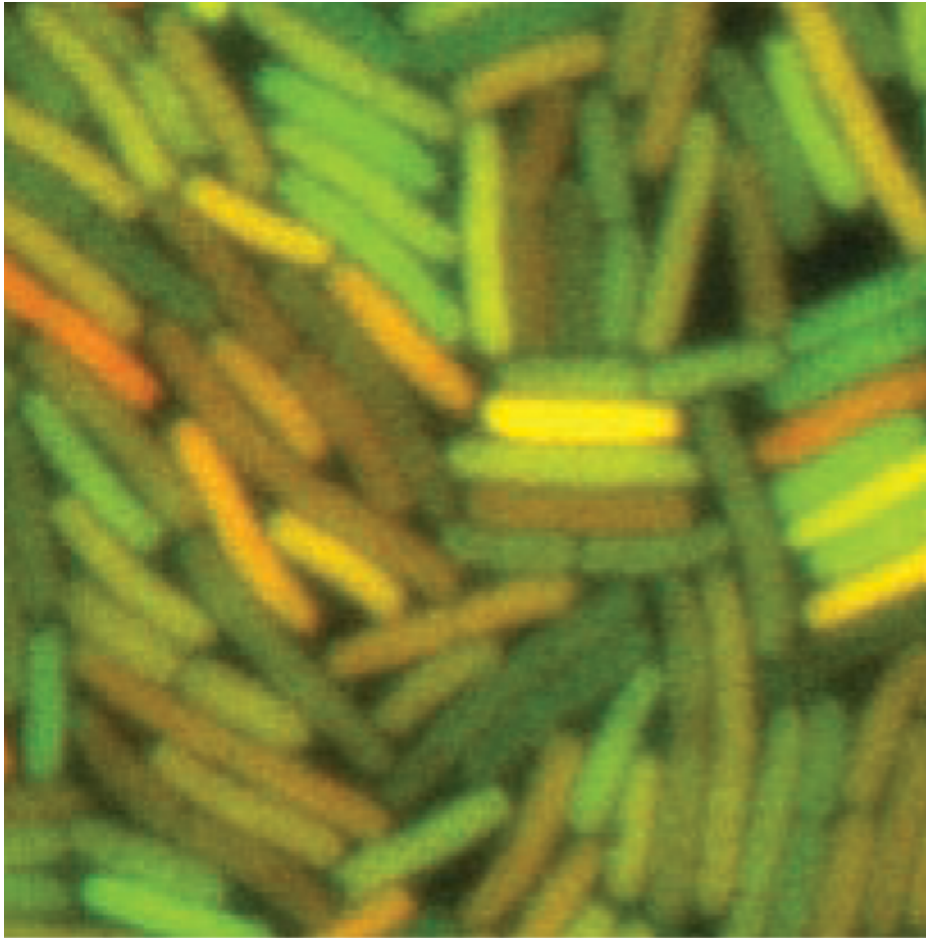
= > il faut chercher l'apparition du  
différentiel dans la modulation de  
l'expression du génome



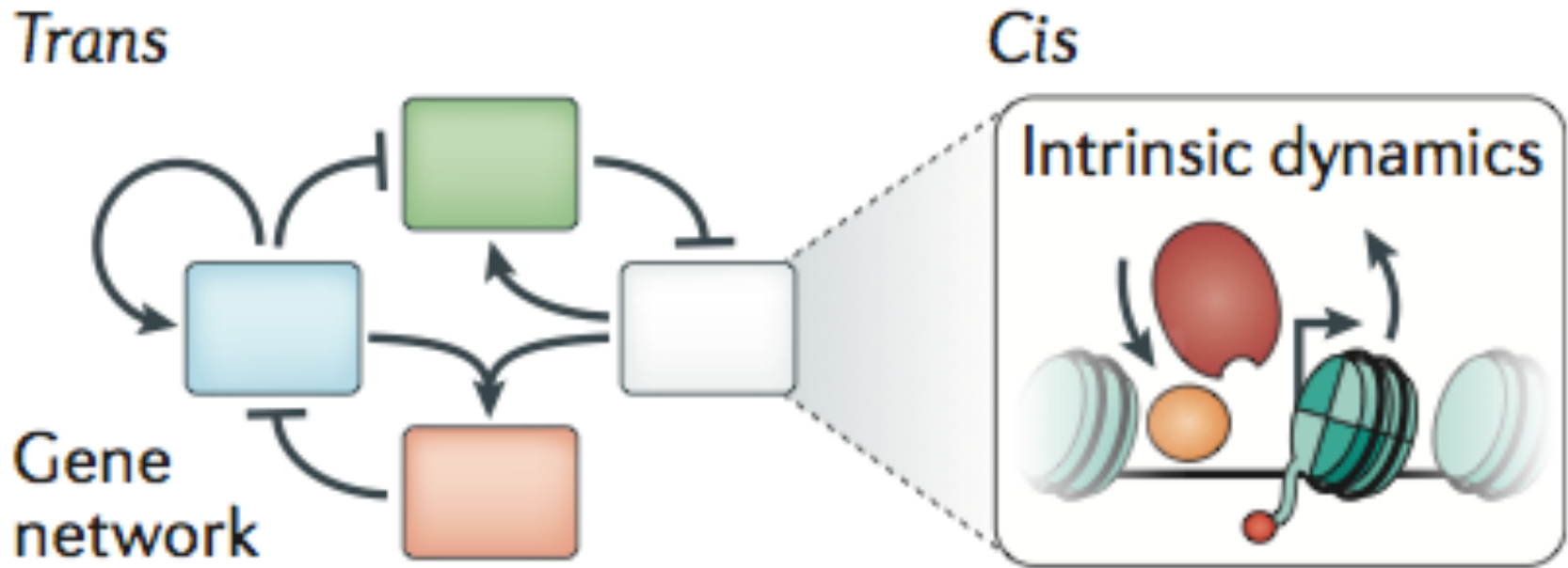
# Expression des gènes:

## Transcription et traduction

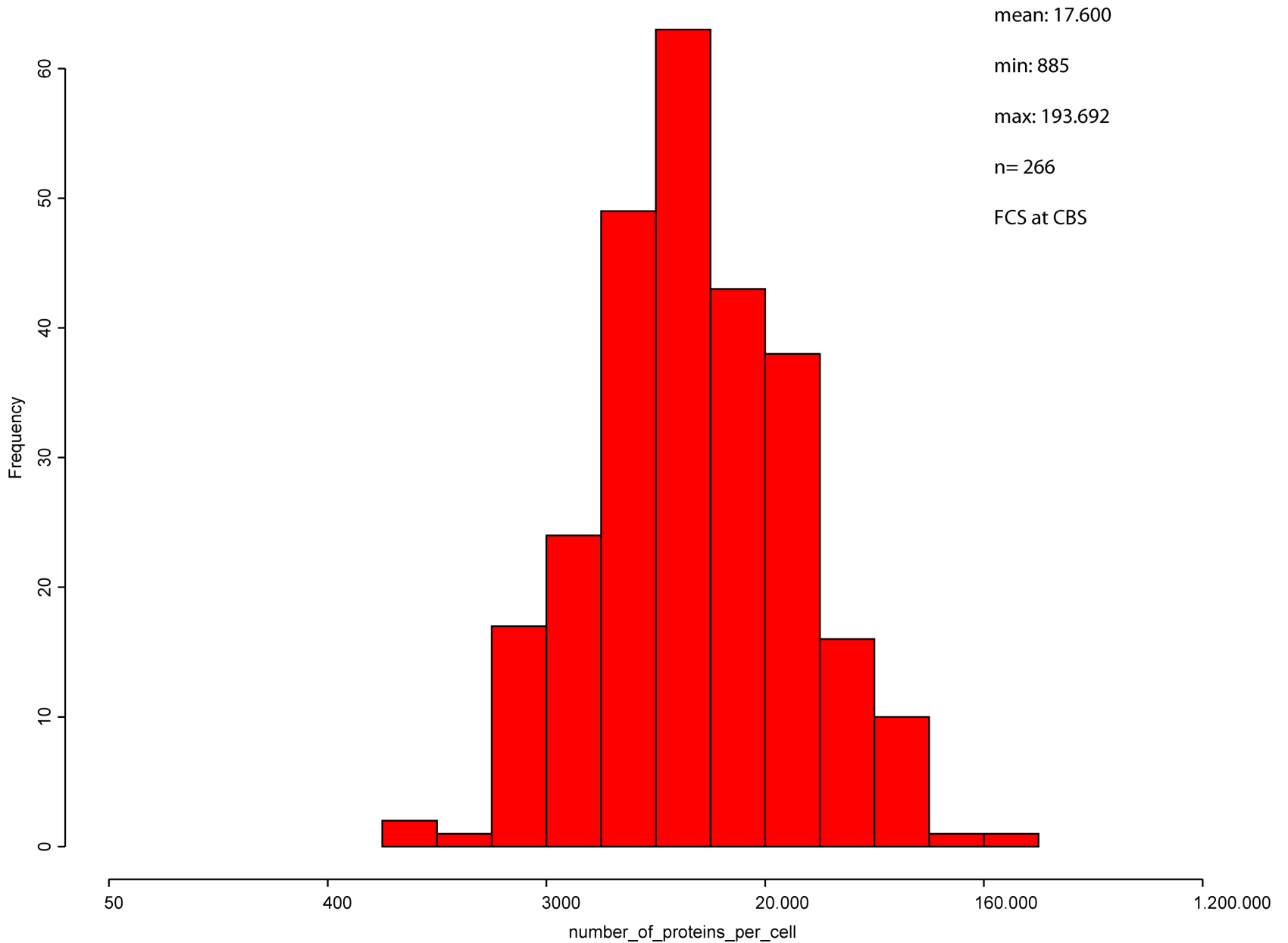




L'expression des gènes est un  
phénomène probabiliste



Il existe des influences locales ("Cis") ou plus globales ("Trans") qui contribuent à la fois à réguler le niveau moyen d'expression génique mais aussi son niveau de "bruit".



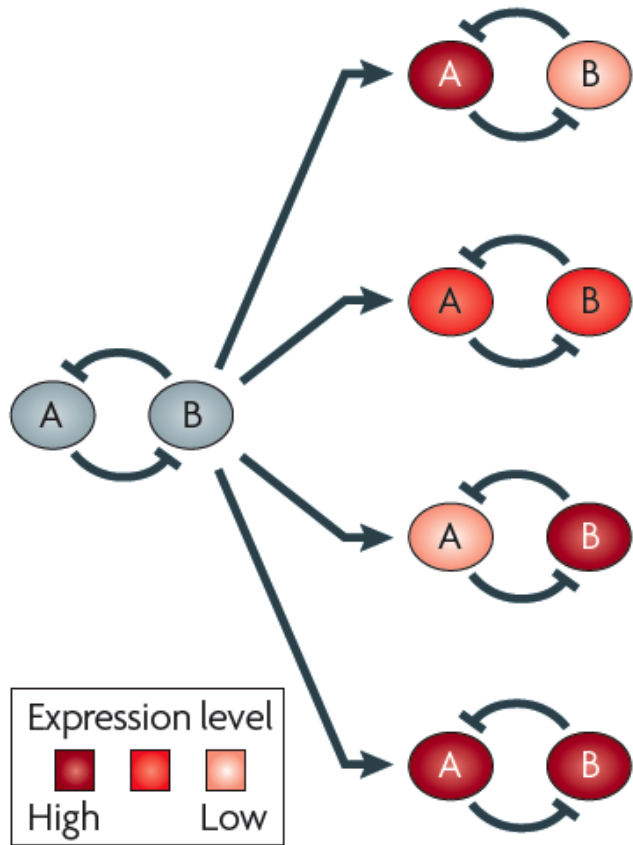
L'importance de ces fluctuations ne doit pas être sous-estimée!

## Rôles biologique du bruit

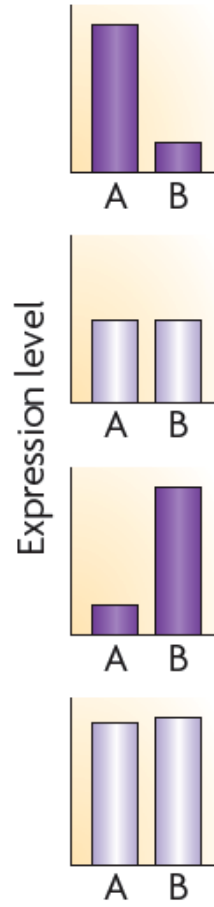
1. Rôle évolutif (bet-hedging)
2. Rôle durant les processus de différenciation cellulaires

2009: cells as dots in a state space. Brock et al. (2009). Nature Reviews Genetics

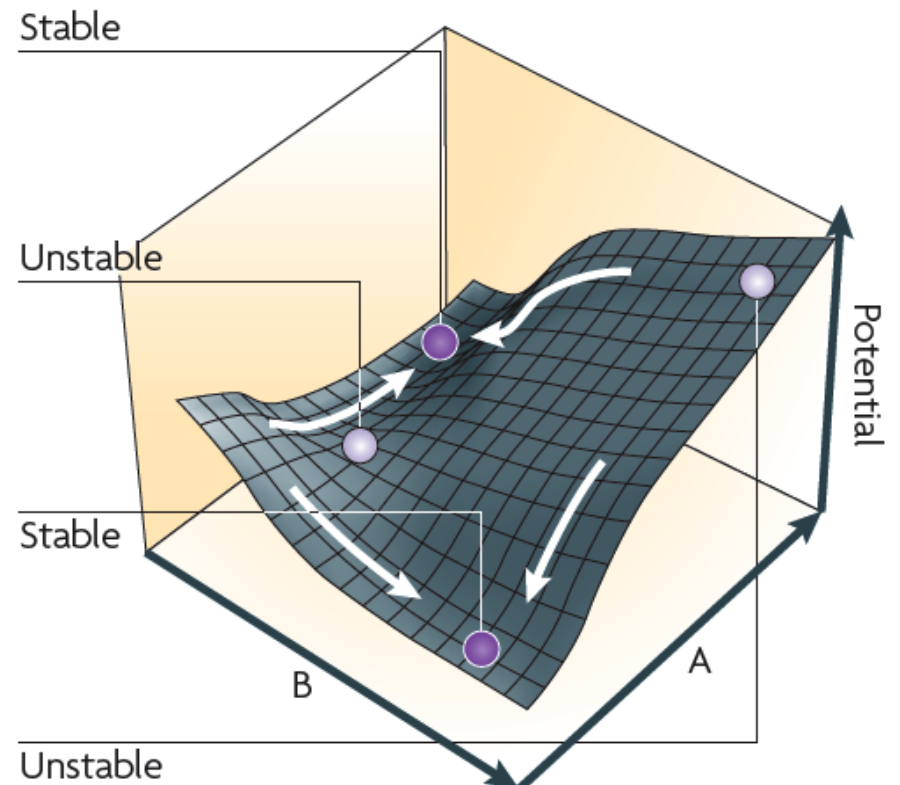
**The network**  
Two-gene genome



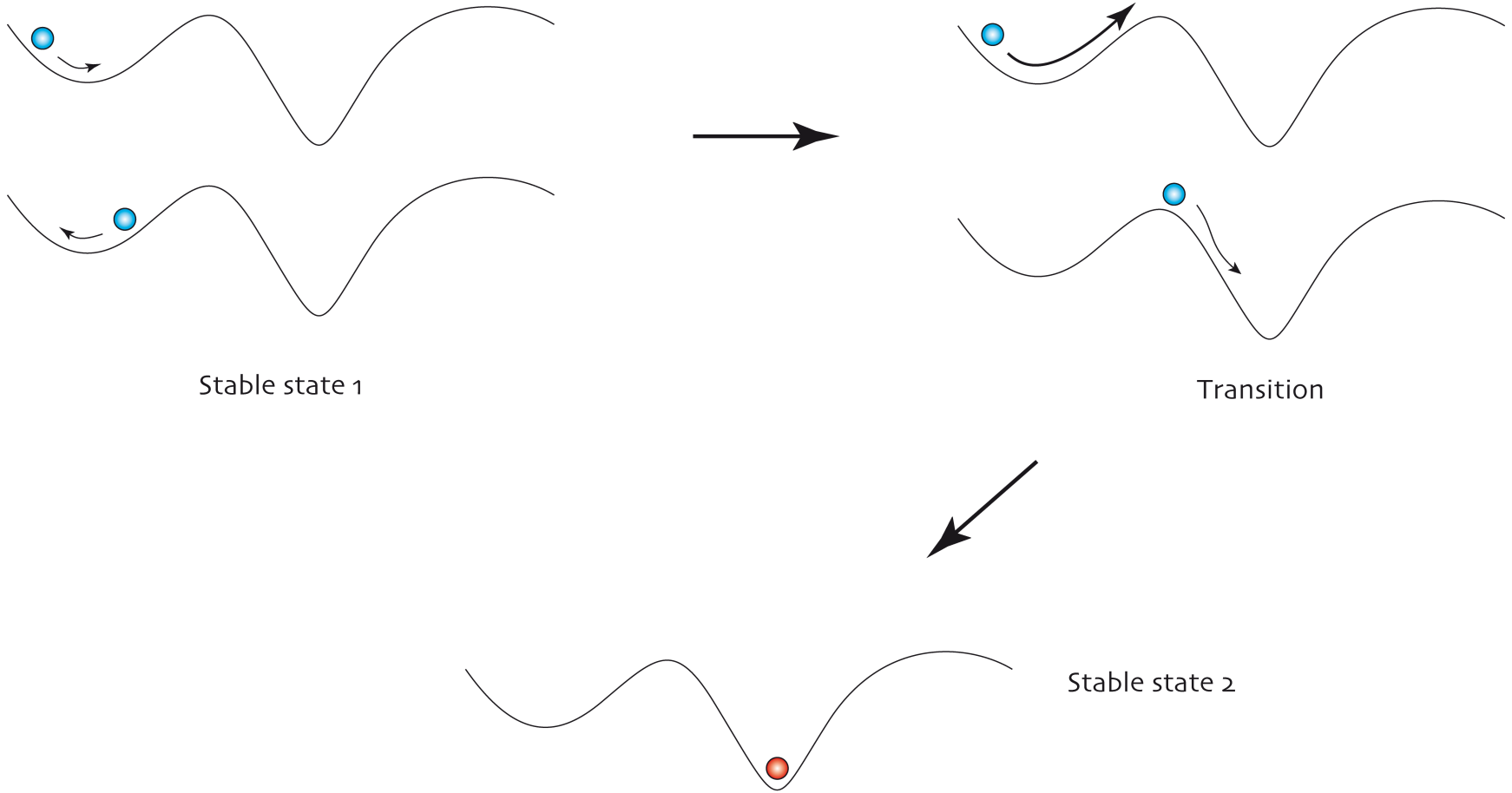
**Network states**



**State space within the epigenetic landscape**



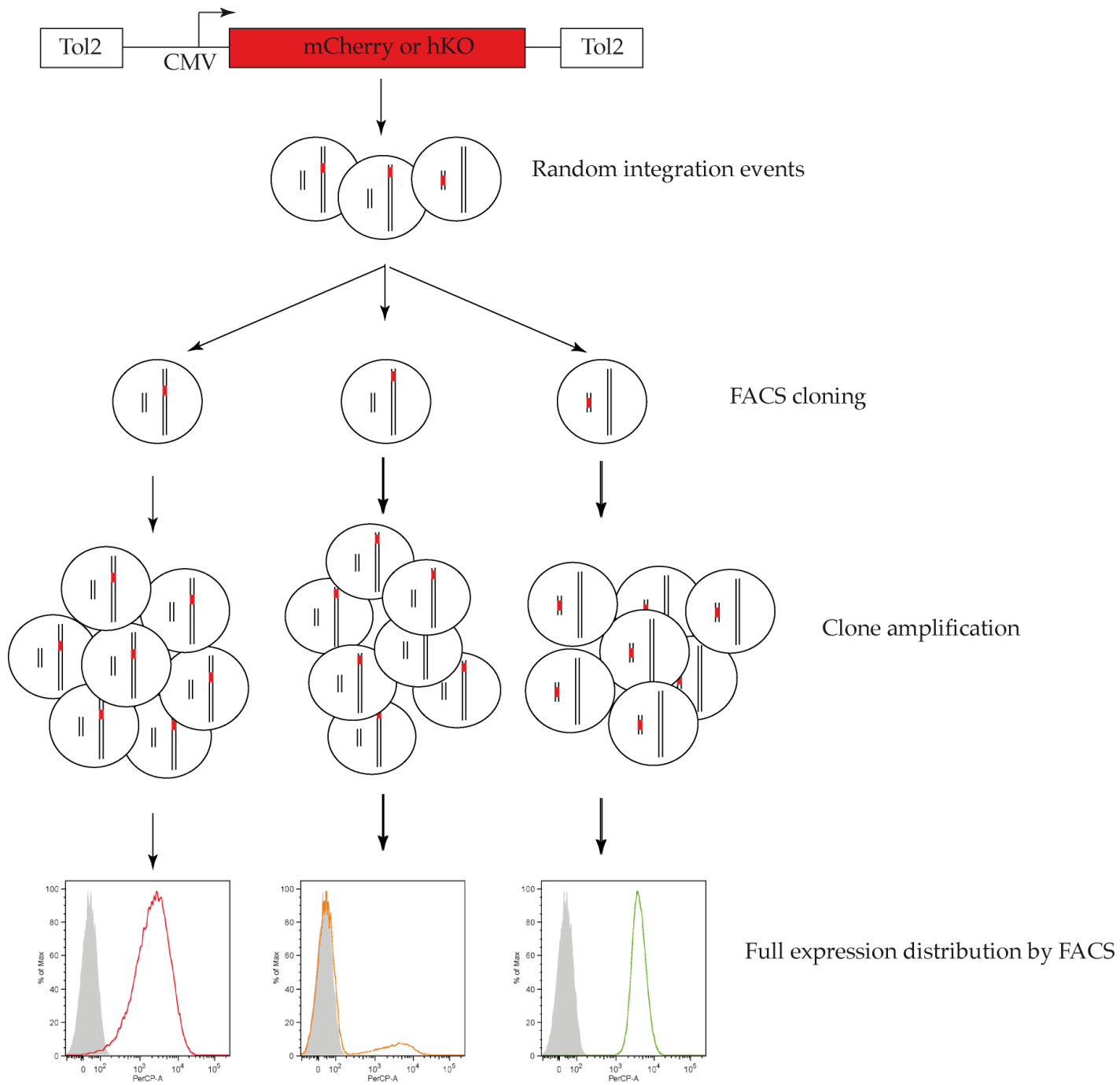
**Working hypothesis:** a regulated level of gene expression stochasticity is responsible for decision-making (viewed as change in a cell's state)



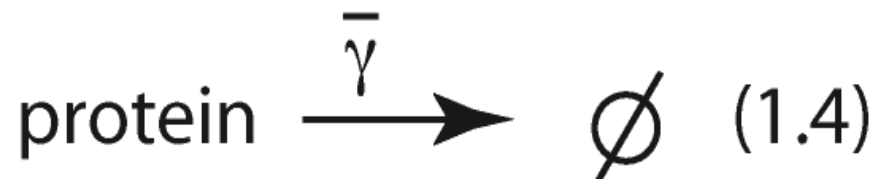
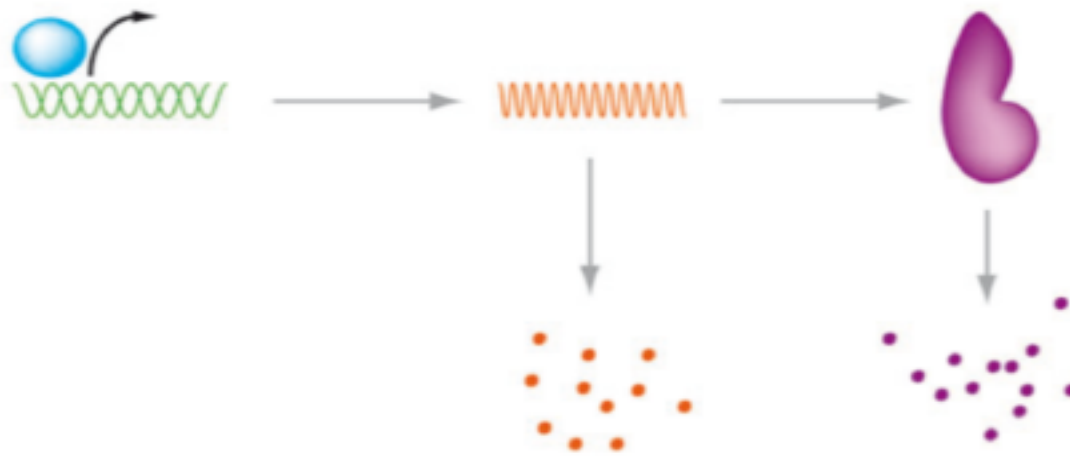
The question: can chromatin  
dynamics be an important  
noise regulator?

Strategy: generation of a clone  
cohort

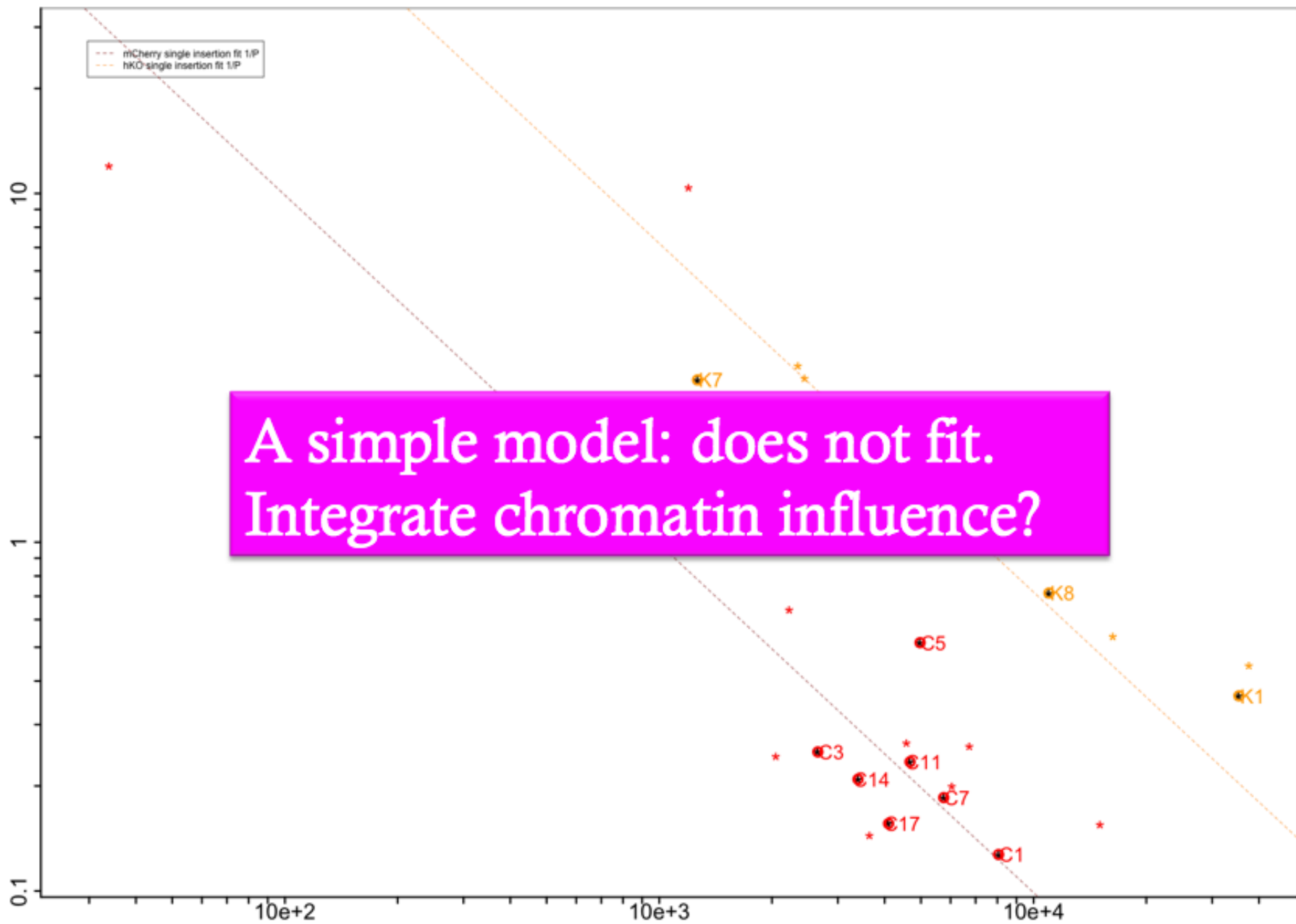




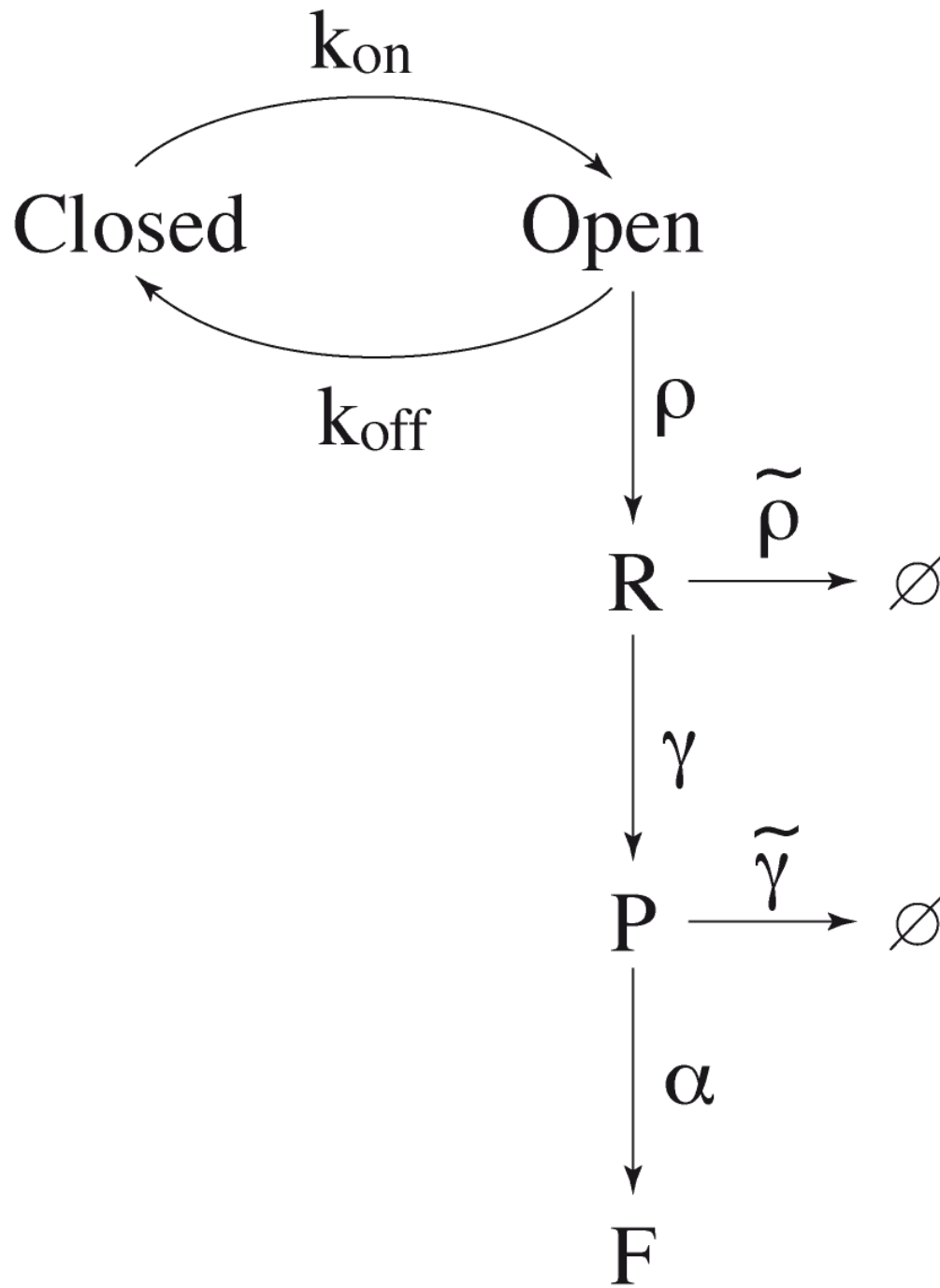




Gene Expression Normalized Variance



Gene Expression Mean



For each clone with a single insertion site, knowing:

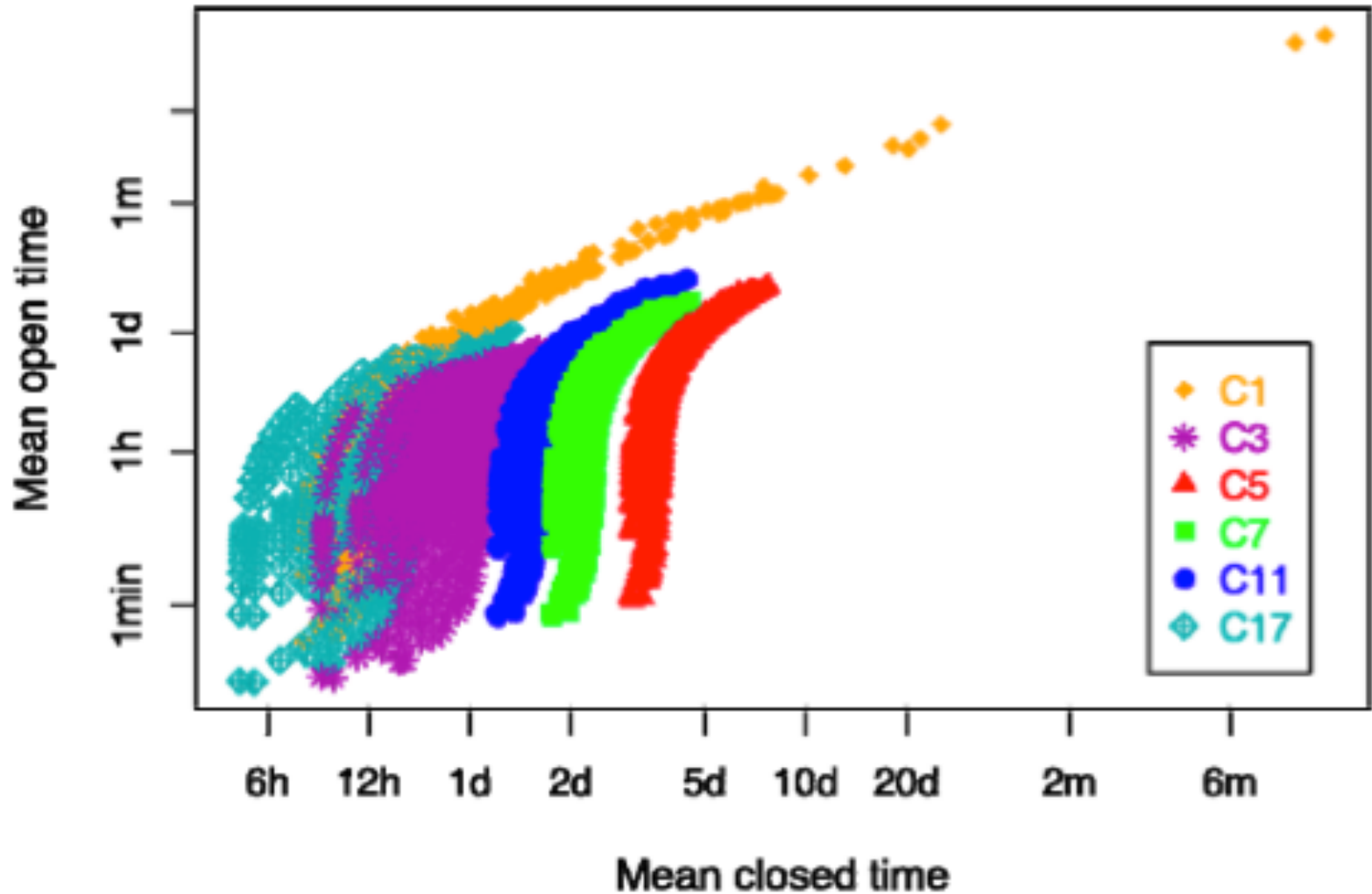
1. the mean expression level
2. the normalized variance in gene expression
3. the half-life of the cherry protein (66 hours)
4. the half-life of the mRNA (7 hours)

and by estimating the transcription and translation rates, as well as the value for  $a$ .

> one can now calculate the respective values of  $k_{off}$  and  $k_{on}$  (Paulsson, 2005)

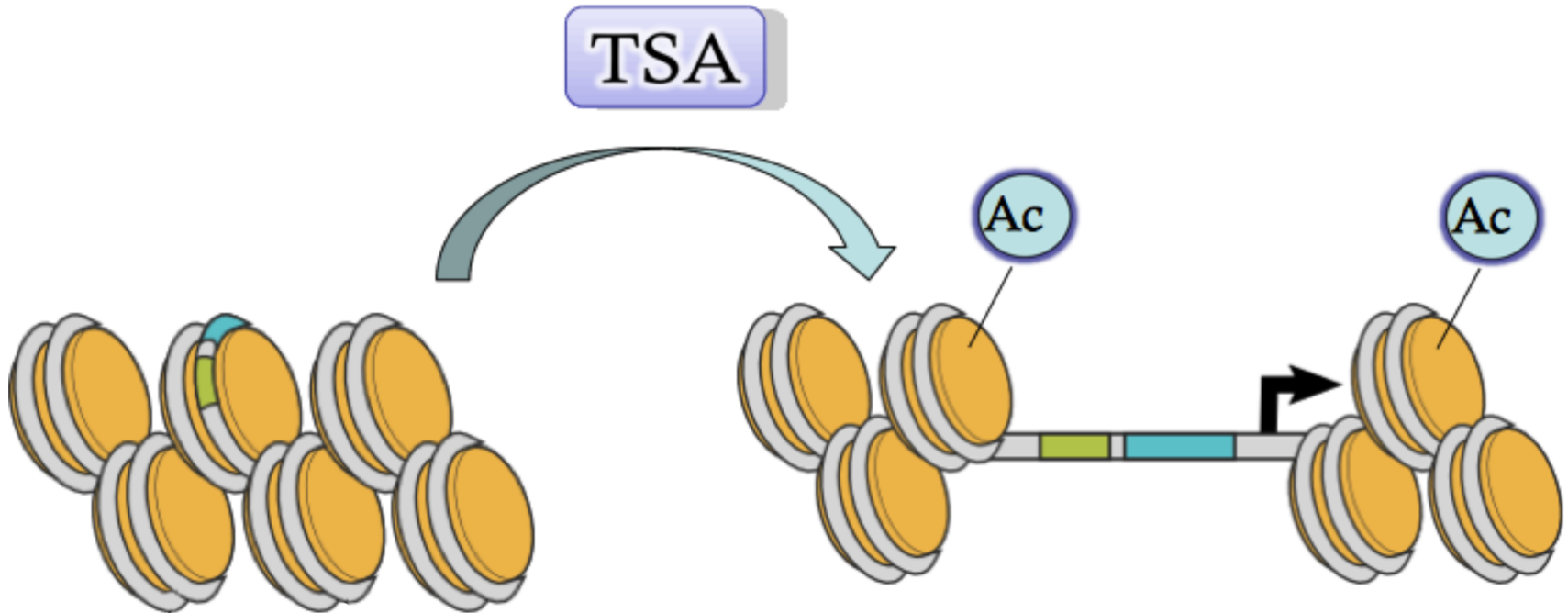
$$\left\{ \begin{array}{l} A = \left( 1 + \frac{\alpha \frac{\rho \tilde{\gamma}}{\tilde{\rho} \tilde{\gamma}} - MFI}{MFI} \right) \\ B = \frac{\left( A \left( \frac{\tilde{\rho}}{\rho} \right) \left( \frac{\tilde{\gamma}}{\gamma} + \frac{\tilde{\gamma}}{\tilde{\rho} + \tilde{\gamma}} \right) \right) - NV}{(A - 1) \frac{\tilde{\gamma}}{\tilde{\rho} + \tilde{\gamma}}} \\ 0 < (A(B(\tilde{\gamma} + \tilde{\rho}) + \tilde{\rho}))^2 - 4A^2B(\tilde{\rho}(\tilde{\rho} + \tilde{\gamma}(B + 1))) \\ k_{on} = \frac{-(A(B(\tilde{\gamma} + \tilde{\rho}) + \tilde{\rho})) - \sqrt{(A(B(\tilde{\gamma} + \tilde{\rho}) + \tilde{\rho}))^2 - 4A^2B(\tilde{\rho}(\tilde{\rho} + \tilde{\gamma}(B + 1)))}}{2A^2B} \\ k_{on} > 0 \\ k_{off} = (A - 1)k_{on} \end{array} \right.$$

By keeping only “realistic” values:”:

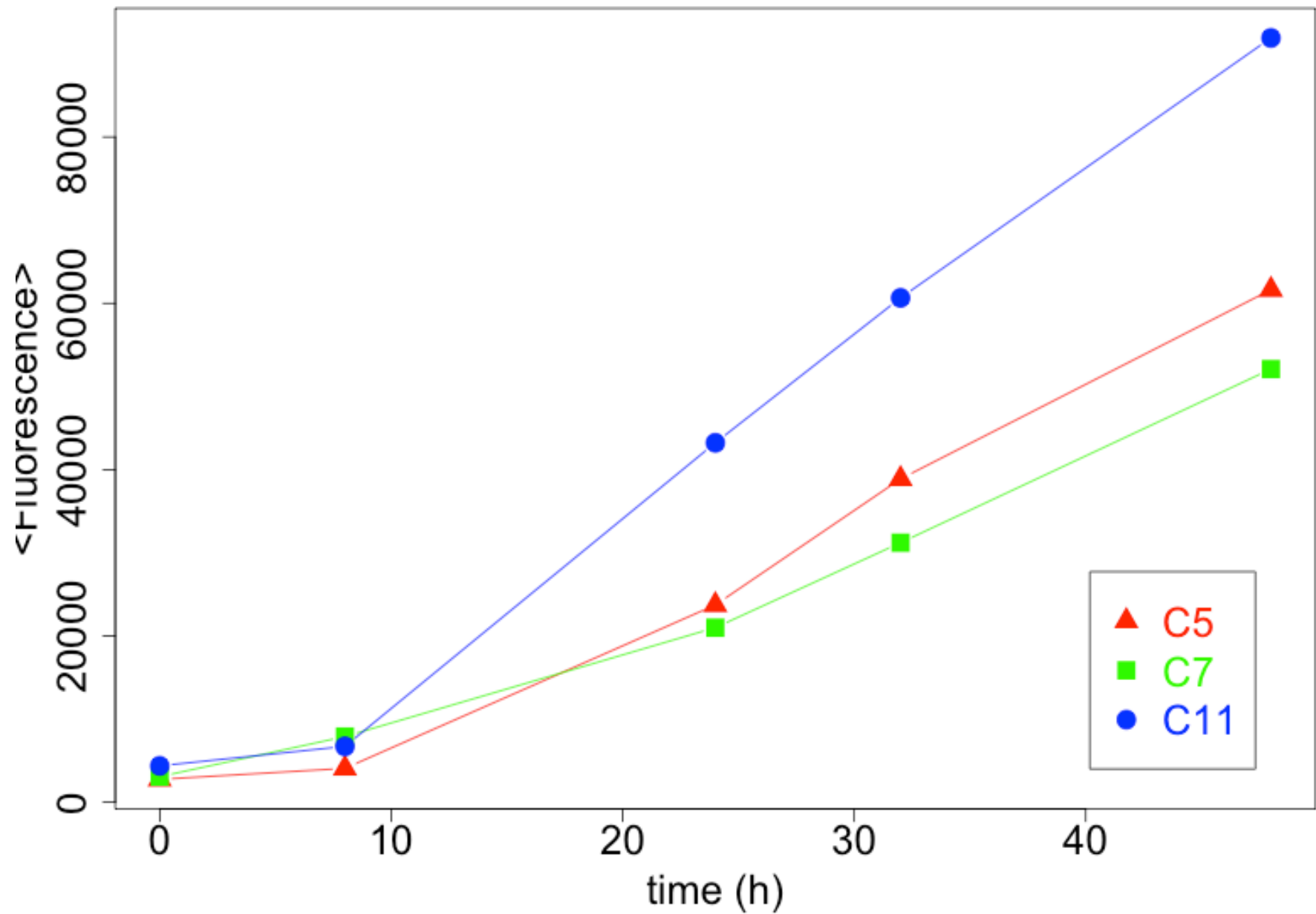


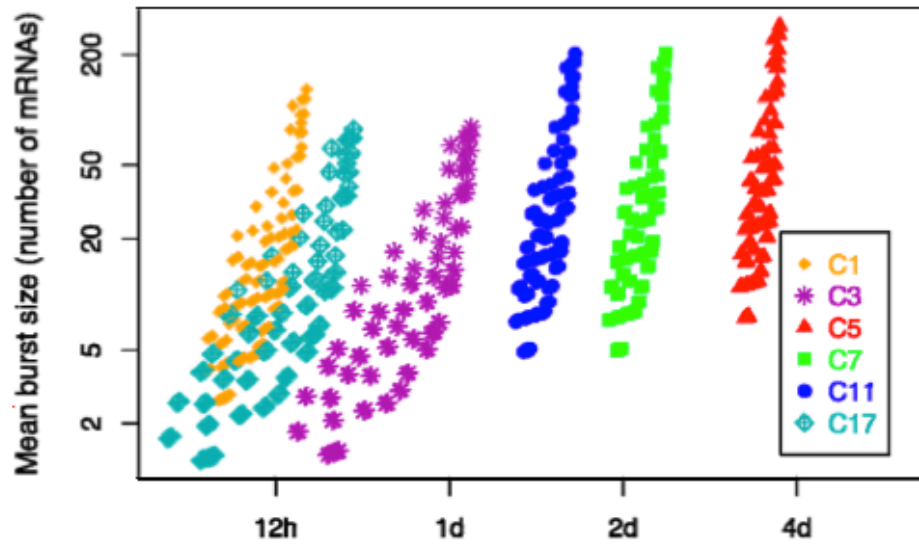
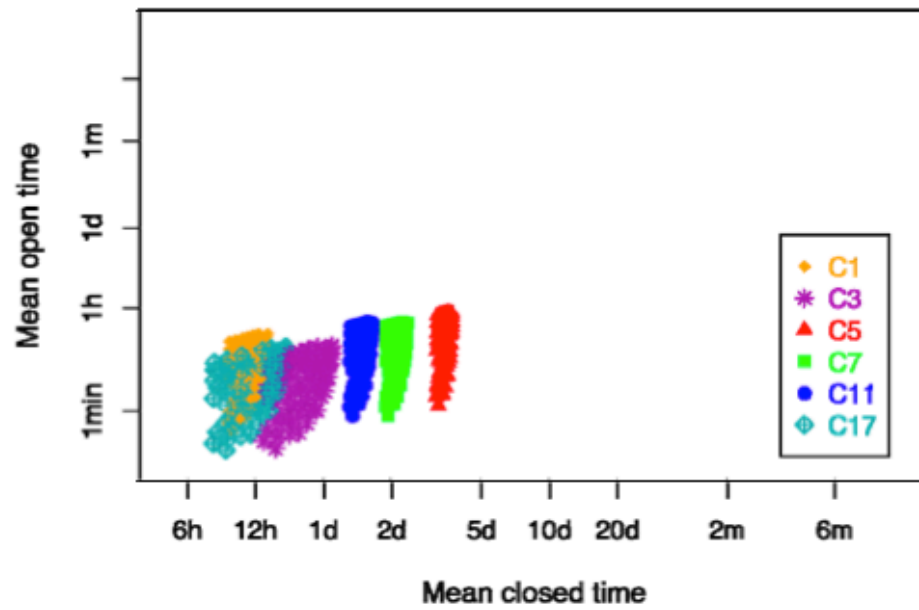
1087 parameter sets: reduce the parameter space.

# Use of a global chromatin modifier







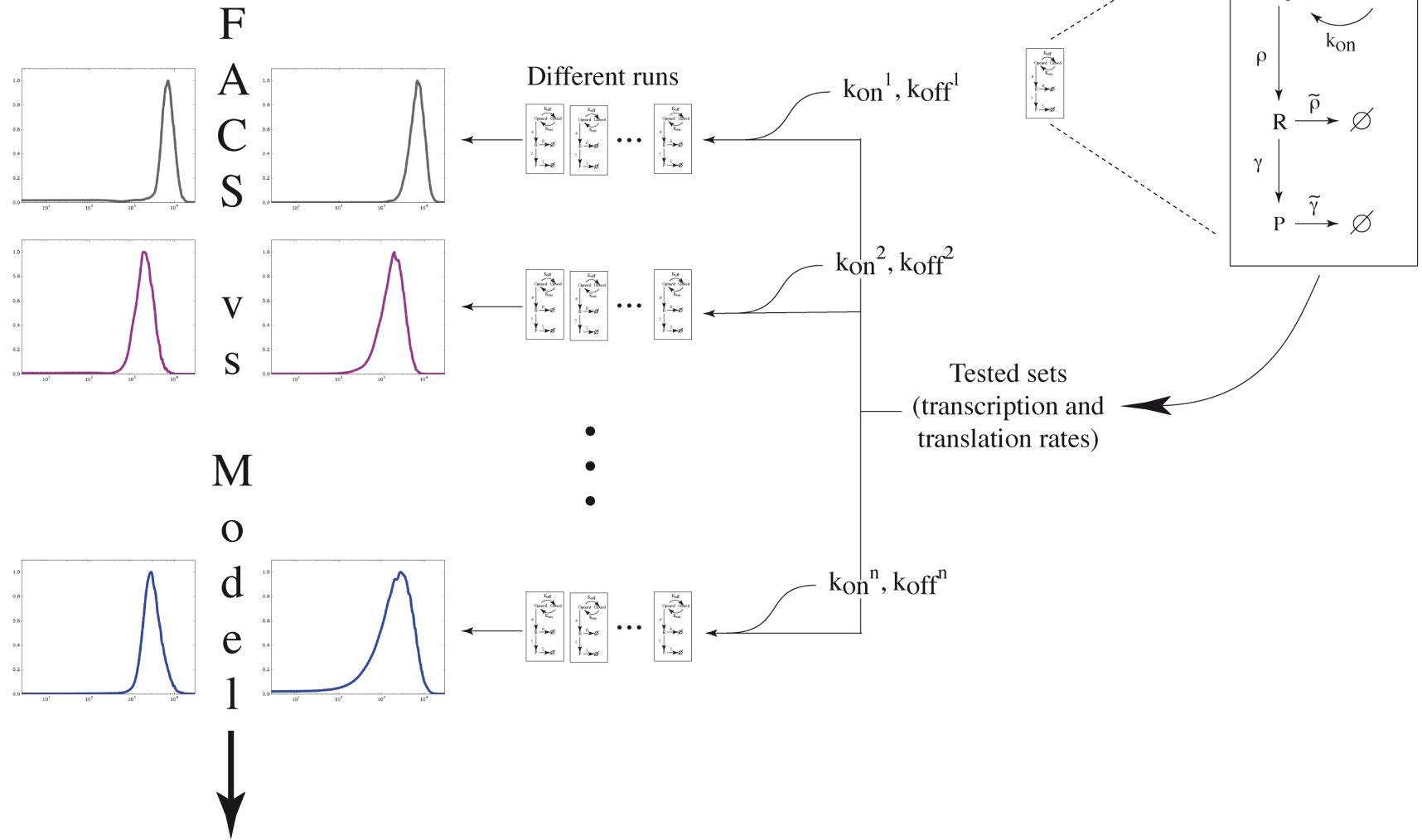


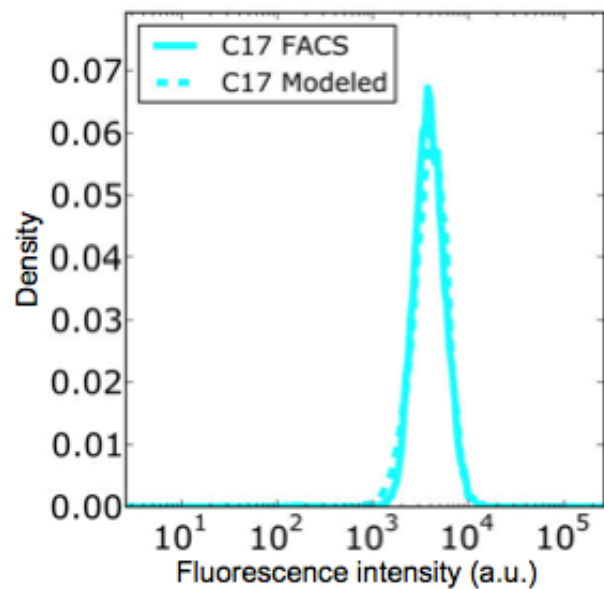
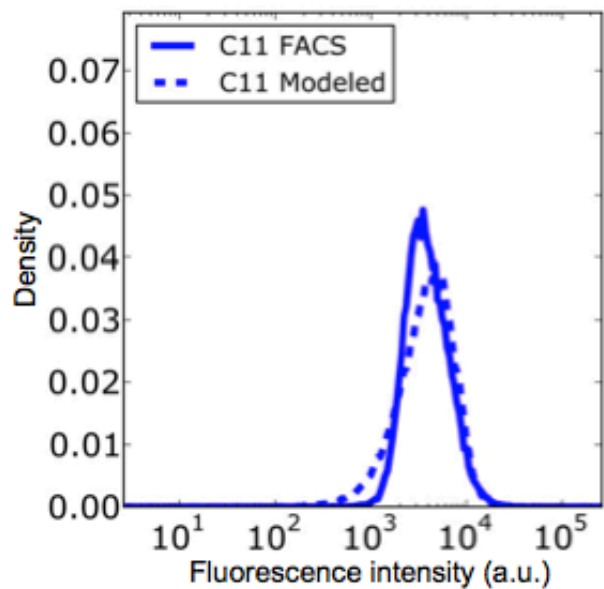
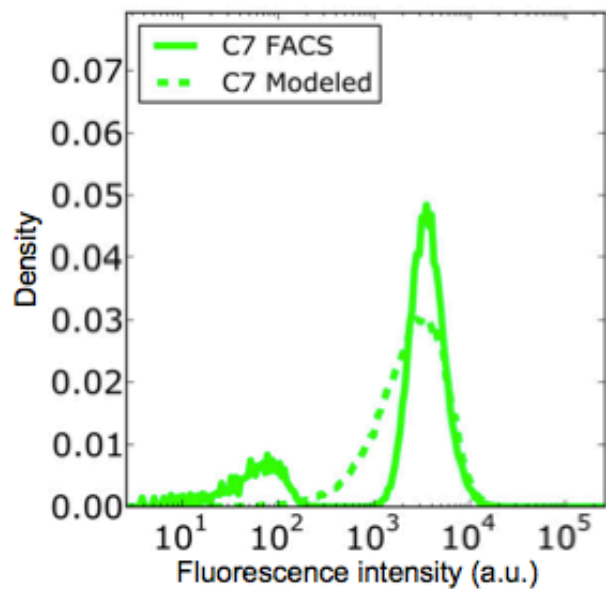
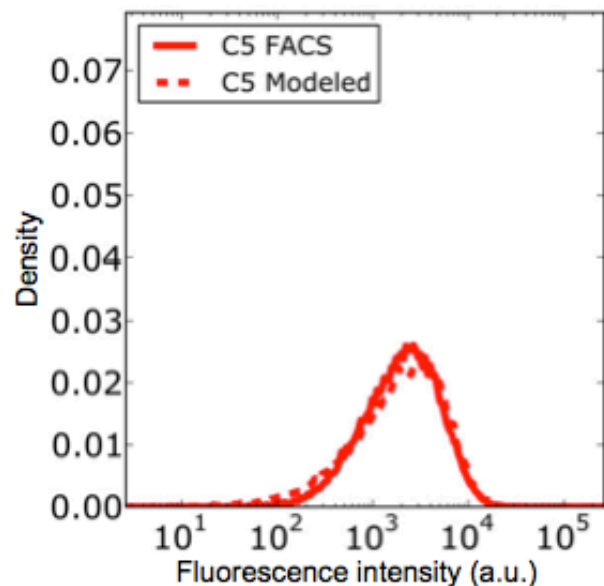
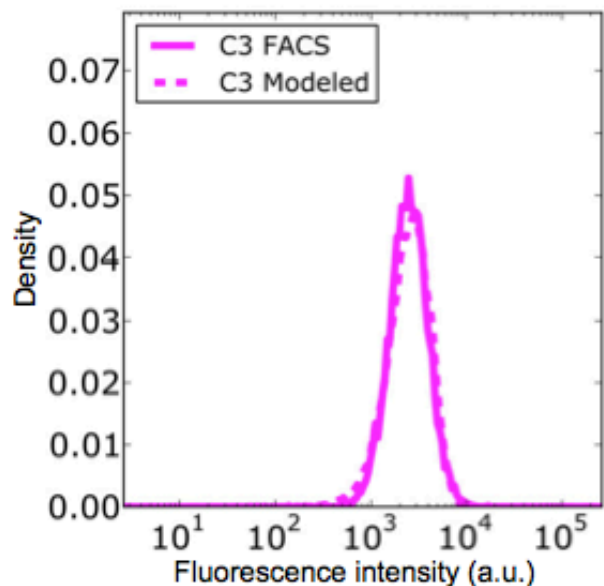
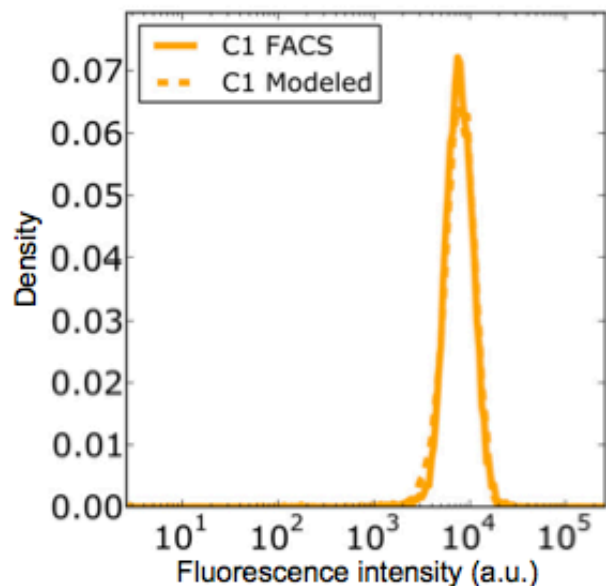
114 parameter sets: much better!

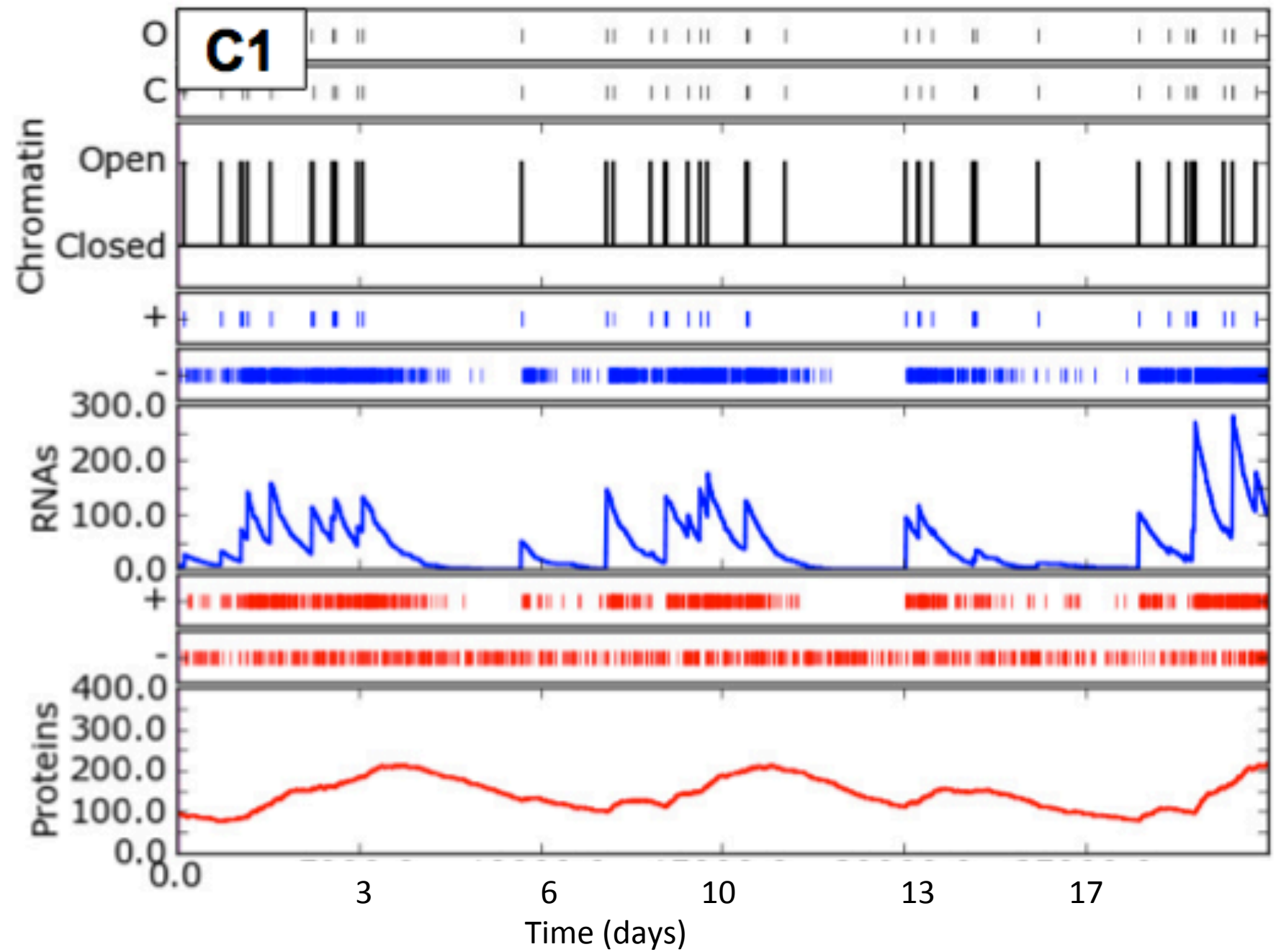
# Now let's SSA!!!!

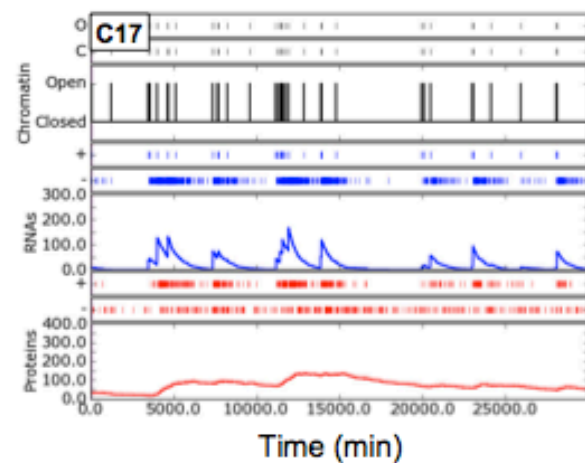
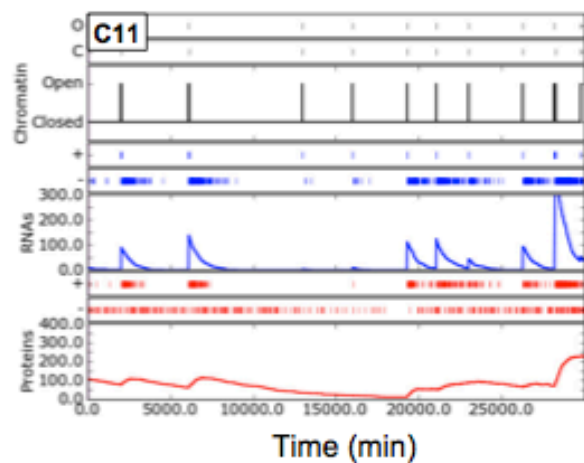
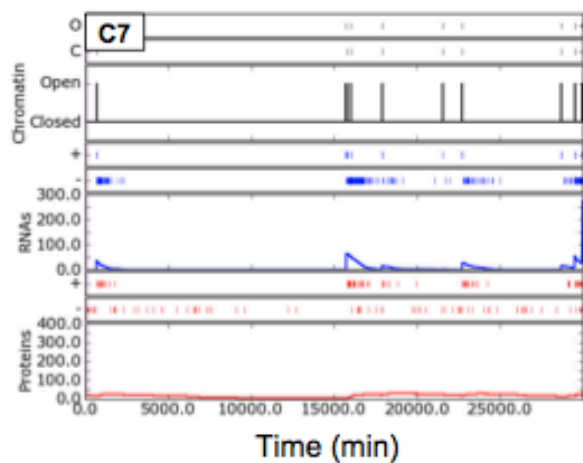
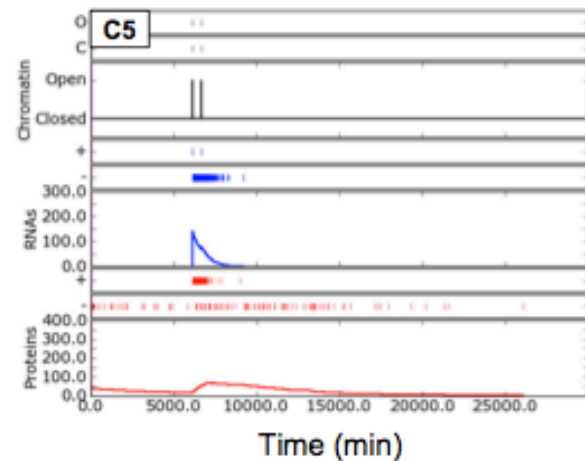
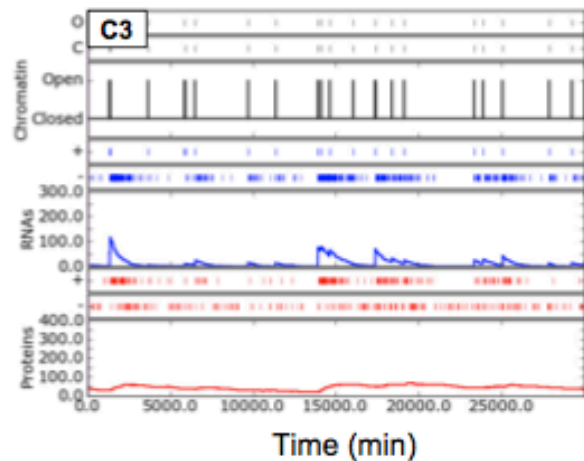
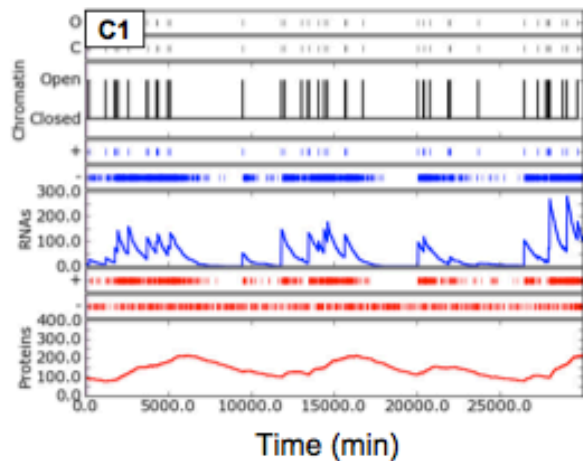
Simulated clones

Model

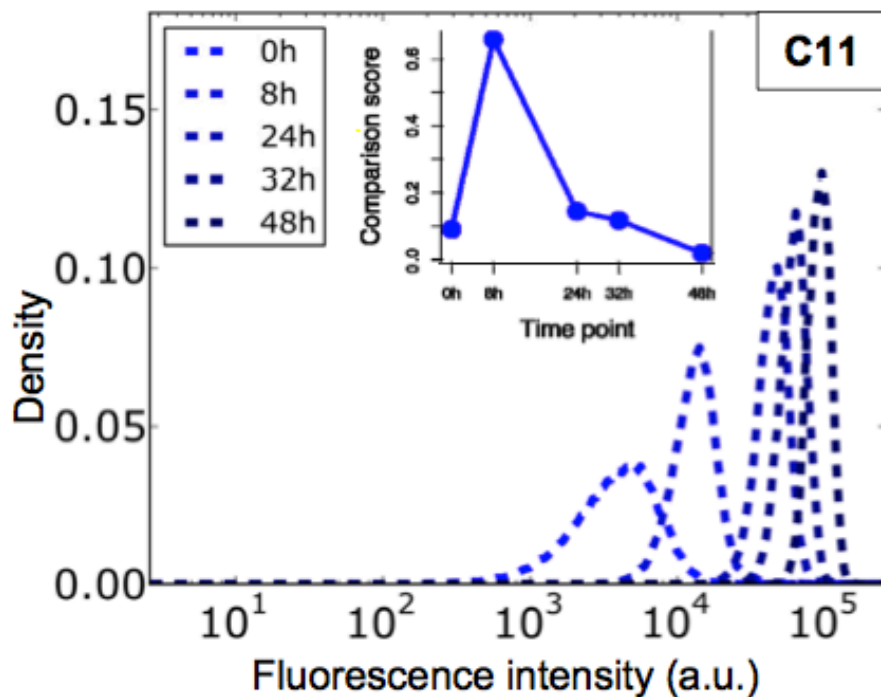
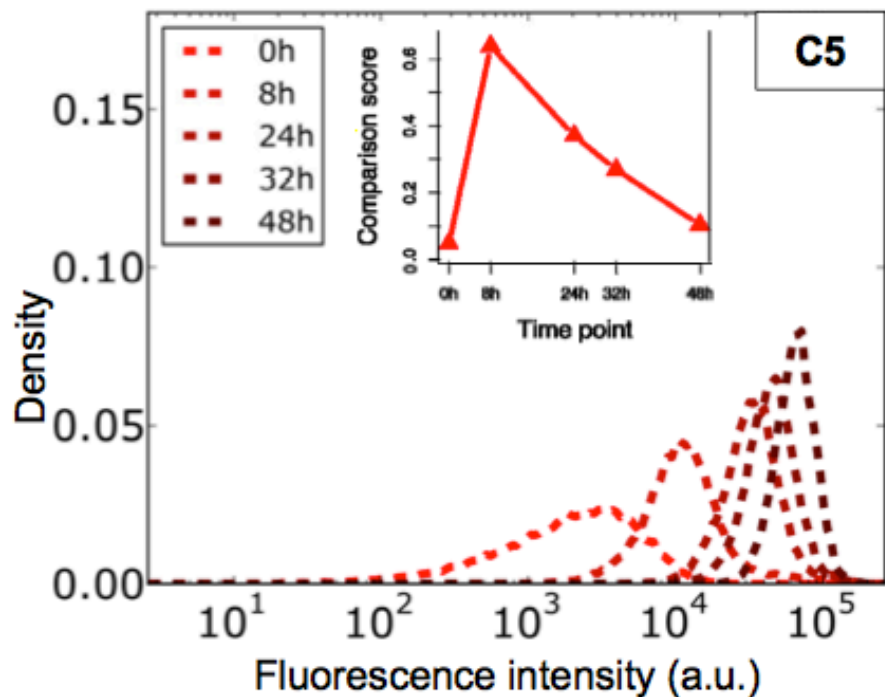
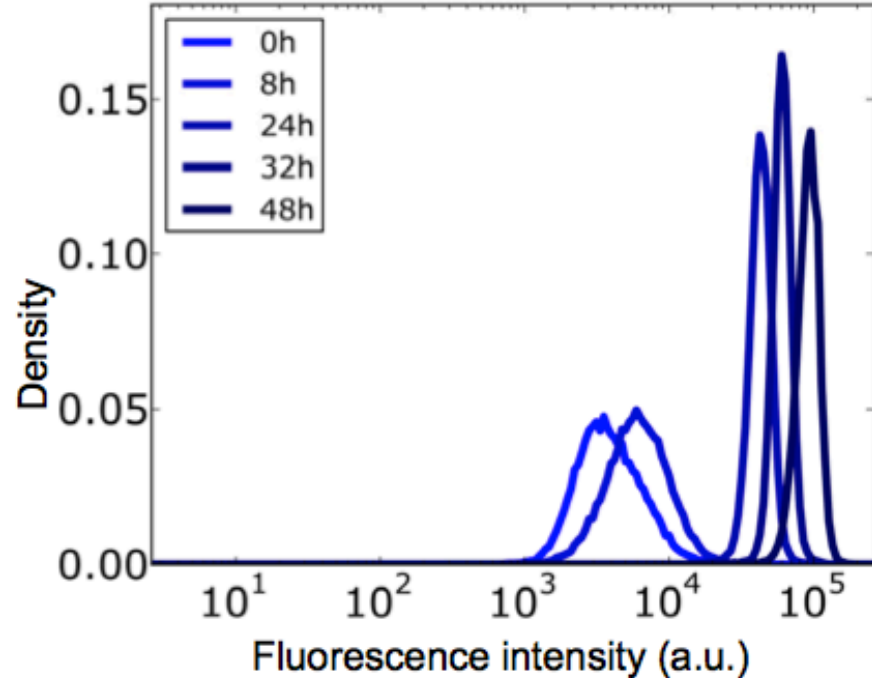
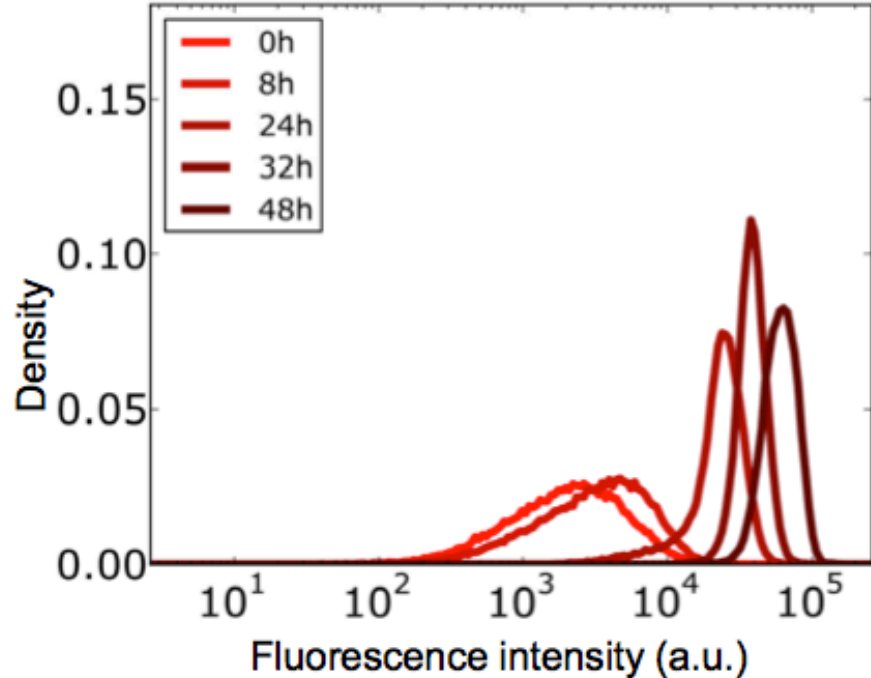




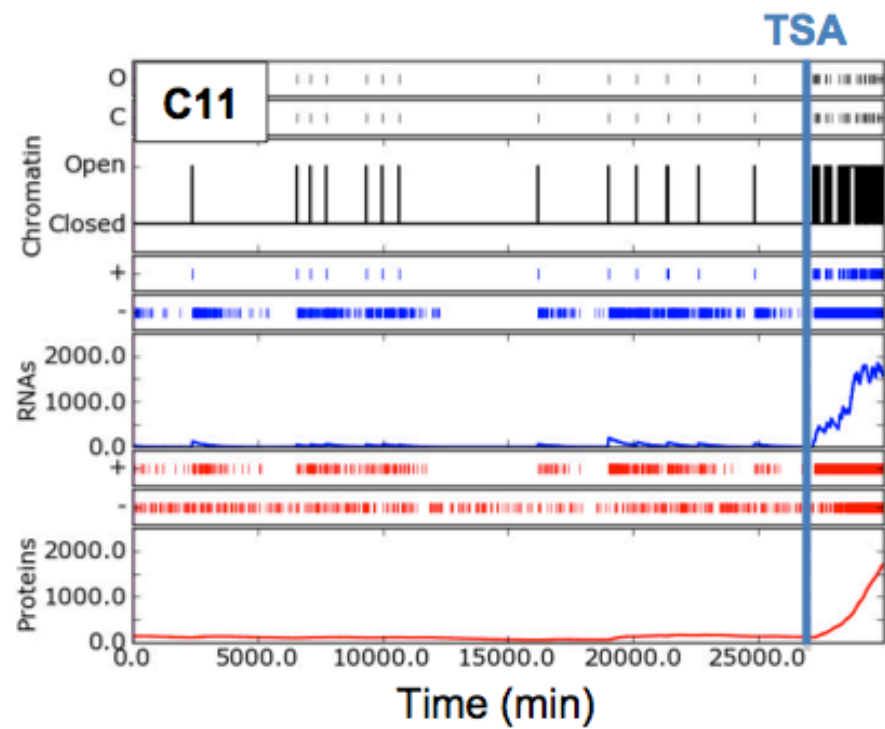
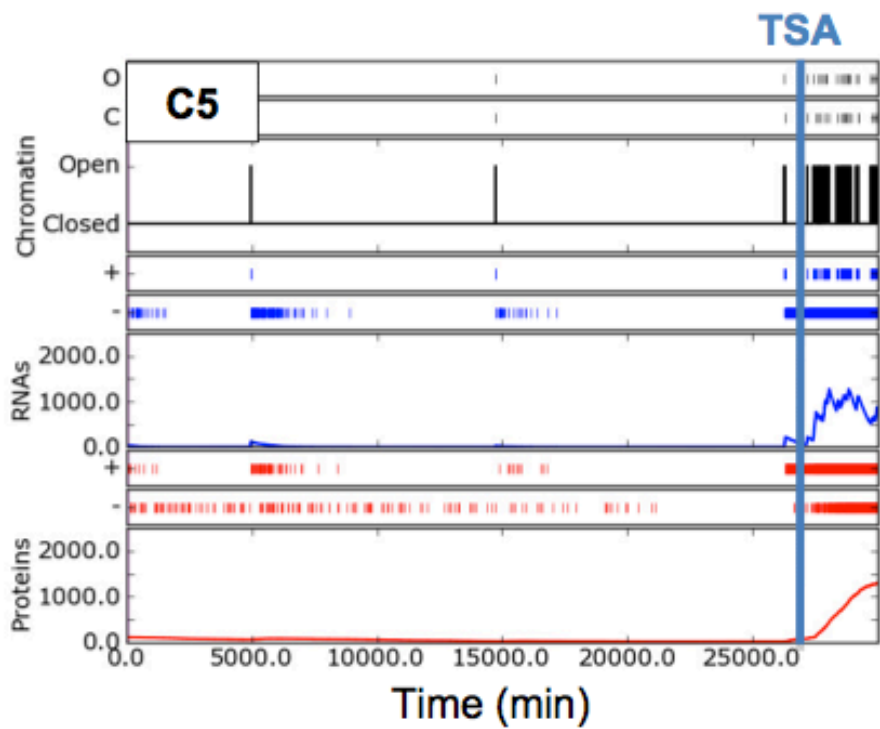




We now have a parameter set that correctly captures the steady state of the system. What about its ability to deal with perturbations? TSA treatment.







Proposer en 2-3 pages un couplage expérience  
humide/modélisation permettant d'explorer  
un des aspects de la stochasticité de  
l'expression génique.