



**qbio**  
quantitative  
biology

# INTRODUCTION TO QUANTITATIVE BIOLOGY

An overview - with flashbacks

25<sup>TH</sup> NOVEMBER 2025

Luca Ciandrini ([luca.ciandrini@umontpellier.fr](mailto:luca.ciandrini@umontpellier.fr))

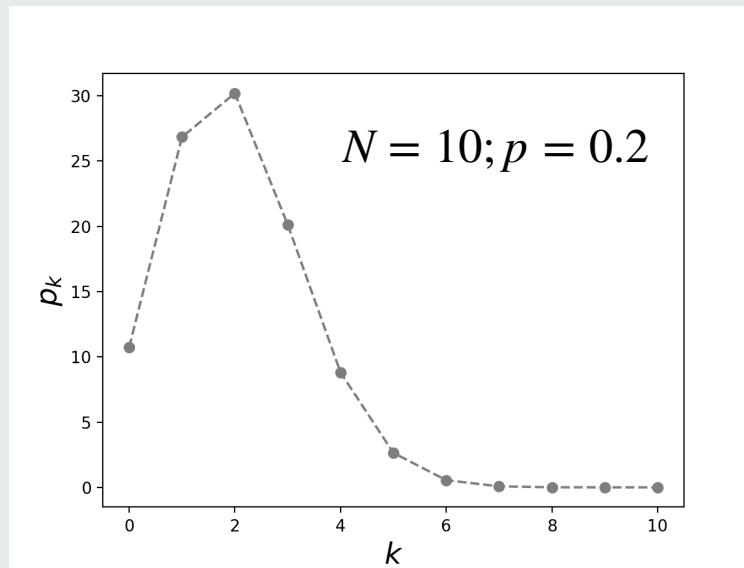
# TOSSING COINS



# BINOMIAL DISTRIBUTION



$$b(k, N, p) = \binom{N}{k} p^k (1-p)^{N-k}$$



$$\mu = Np \qquad \sigma^2 = Np(1-p)$$

# PROTEIN PARTITIONING



Ex: Cell-to-cell variability

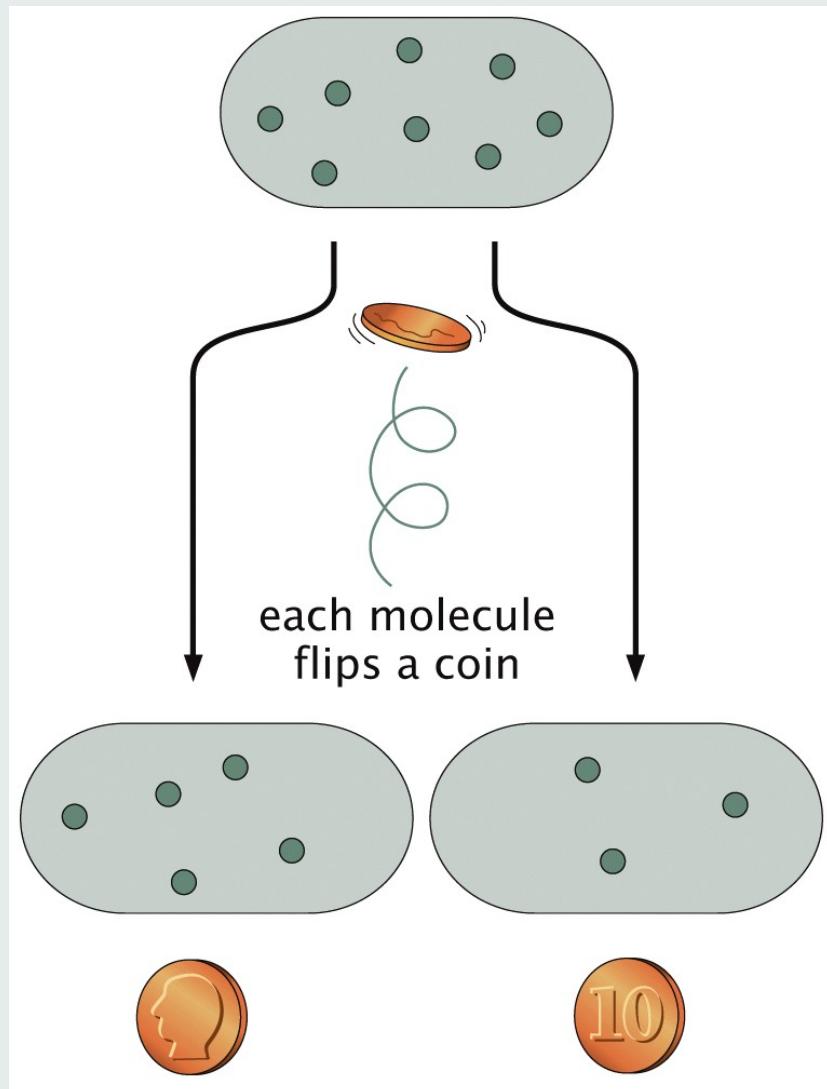


Figure 2.7a Physical Biology of the Cell, 2ed. (© Garland Science 2013)

# PROTEIN PARTITIONING



Ex: Cell-to-cell variability

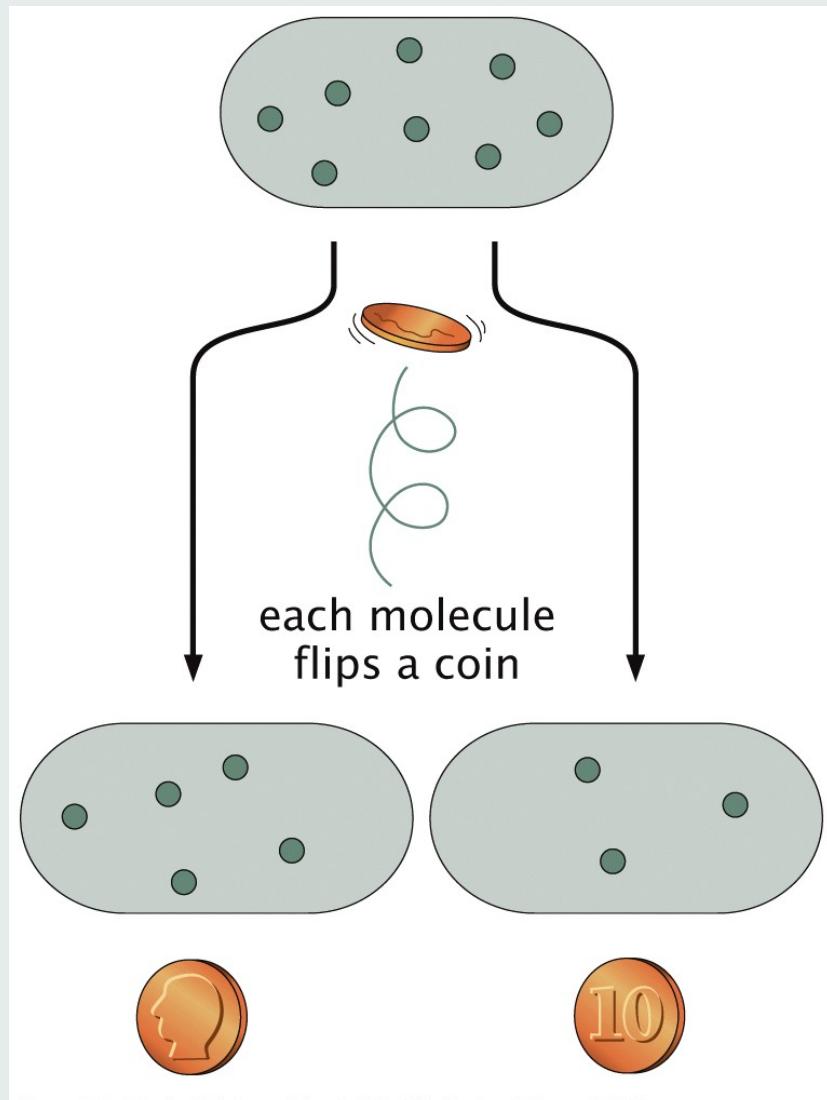
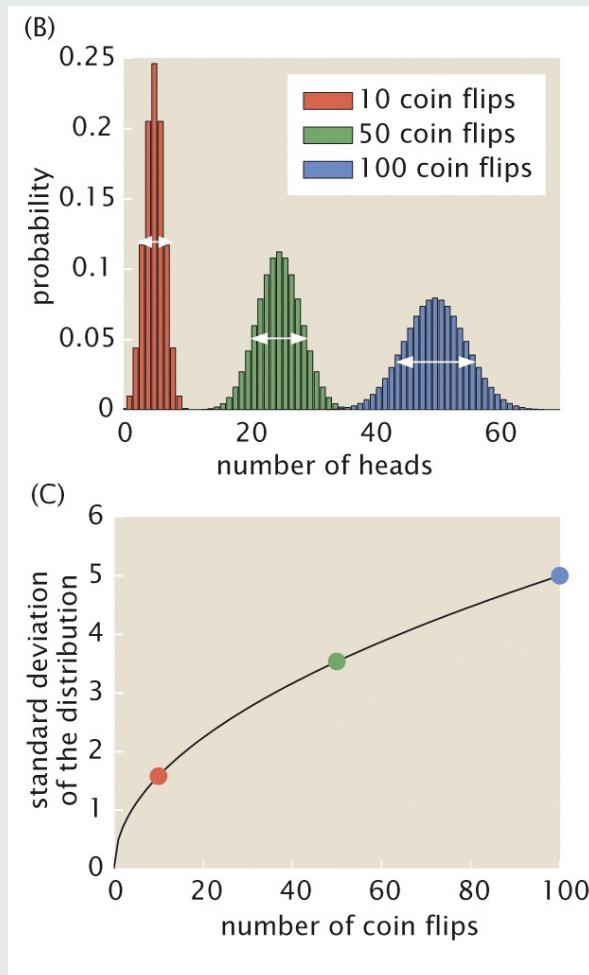


Figure 2.7a Physical Biology of the Cell, 2ed. (© Garland Science 2013)



Science 2005

# Gene Regulation at the Single-Cell Level

Nitzan Rosenfeld,<sup>1\*</sup> Jonathan W. Young,<sup>3</sup> Uri Alon,<sup>1</sup>

Peter S. Swain,<sup>2\*</sup> Michael B. Elowitz<sup>3†</sup>

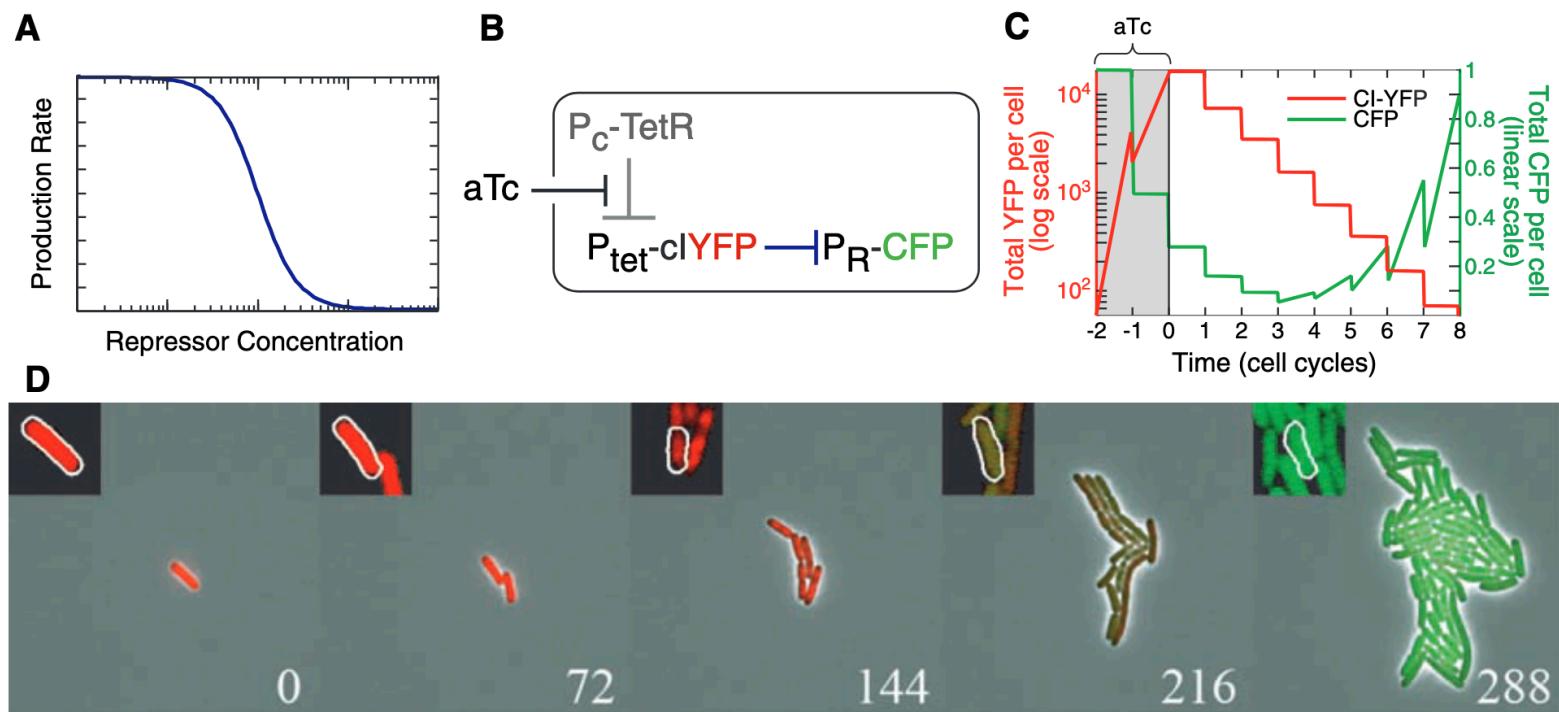
The quantitative relation between transcription factor concentrations and the rate of protein production from downstream genes is central to the function of genetic networks. Here we show that this relation, which we call the gene regulation function (GRF), fluctuates dynamically in individual living cells, thereby limiting the accuracy with which transcriptional genetic circuits can

# PROTEIN PARTITIONING



Science 2005

**Fig. 1.** Measuring a gene regulation function (GRF) in individual *E. coli* cell lineages. (A) The GRF is the dependence of the production rate of a target promoter ( $y$  axis) on the concentration of one (or more) transcription factors ( $x$  axis). (B) In the  $\lambda$ -cascade strains (16) of *E. coli*, CI-YFP is expressed from a tetracycline promoter in a TetR+ background and can be induced by anhydro-tetracycline (aTc). CI-YFP represses production of CFP from the  $P_R$  promoter. (C) The regulator dilution experiment (schematic): Cells are transiently induced to express CI-YFP and then observed in time-lapse microscopy as repressor dilutes out during cell growth (red line). When CI-YFP levels decrease sufficiently, expression of the *cfp* target gene begins (green line). (D) Snapshots of a typical regulator dilution



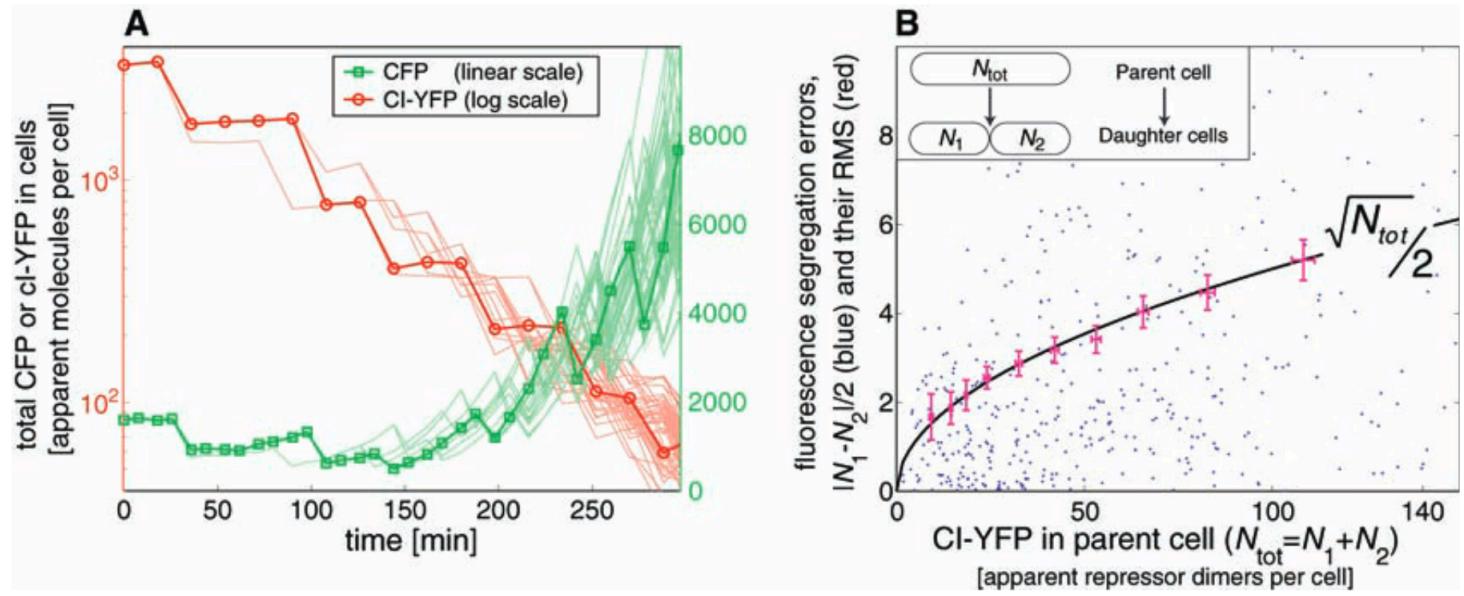
experiment using the  $O_R^{2*}$ - $\lambda$ -cascade strain (see fig. S3) (16). CI-YFP protein is shown in red and CFP is shown in green. Times, in minutes, are indicated on snapshots. (Insets) Selected cell lineage (outlined in white). Greater time resolution is provided in fig. S1.

# PROTEIN PARTITIONING



Science 2005

**Fig. 2.** Data and calibration. (A) Fluorescence intensities of individual cells are plotted over time for the experiment of Fig. 1D. Red indicates CI-YFP, which is plotted on a logarithmic y axis to highlight its exponential dilution: As CI-YFP is not produced, each division event causes a reduction of about twofold in total CI-YFP fluorescence. Green indicates CFP, which is plotted on a linear y axis to emphasize its increasing slope, showing that CFP production rate increases as the CI-YFP levels decrease. A selected cell lineage is highlighted (also outlined in Fig. 1D). (B) Analysis of binomial errors in protein partitioning to find  $v_y$ , the apparent fluorescence intensity of one independently segregating fluorescent particle (16). Cells containing  $N_{tot}$  copies of a fluorescent particle (total fluorescence  $Y_{tot} = v_y \cdot N_{tot}$ ) undergo division (inset). If each particle segregates independently,  $N_1$  and  $N_2$ , the number of copies received by the two daughter cells, are distributed binomially, and satisfy



$\sqrt{\left\langle \left(\frac{N_1 - N_2}{2}\right)^2 \right\rangle} = \sqrt{N_{tot}/2}$ . A single-parameter fit thus determines the value of  $v_y$ . Here we plot  $|N_1 - N_2|/2$  (in numbers of apparent molecule dimers) versus  $N_{tot} = N_1 + N_2$ . Blue dots show the scatter of individual division events. Crosses (red) show the root-mean-square (RMS) error in protein partitioning and its standard error. The expected binomial standard deviation is shown in black.



## Stochastic modelling for quantitative description of heterogeneous biological systems

*Darren J. Wilkinson*

**Abstract** | Two related developments are currently changing traditional approaches to computational systems biology modelling. First, stochastic models are being used increasingly in preference to deterministic models to describe biochemical network dynamics at the single-cell level. Second, sophisticated statistical methods and algorithms are being used to fit both deterministic and stochastic models to time course and other experimental data. Both frameworks are needed to adequately describe observed noise, variability and heterogeneity of biological systems over a range of scales of biological organization.

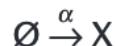


## Stochastic modelling for quantitative description of heterogeneous biological systems

*Darren J. Wilkinson*

### Box 1 | A simple model for protein production and degradation

Consider the following artificial model for production and degradation of a single protein,  $X$ : the protein is produced at a constant rate  $\alpha$ , and each protein molecule is independently degraded at a constant rate  $\mu$ . This can be written using chemical reaction notation as:



Let the number of molecules at time  $t$  be denoted  $X_t$ , and assume that there are initially no protein molecules, so that  $X_0 = 0$ . The plots show the case  $\alpha = 1$ ,  $\mu = 0.1$ . The parameters are purely illustrative and not intended to model any real biological system.

# A SIMPLE MODEL OF GENE EXPRESSION



Continuous deterministic model (RRE):

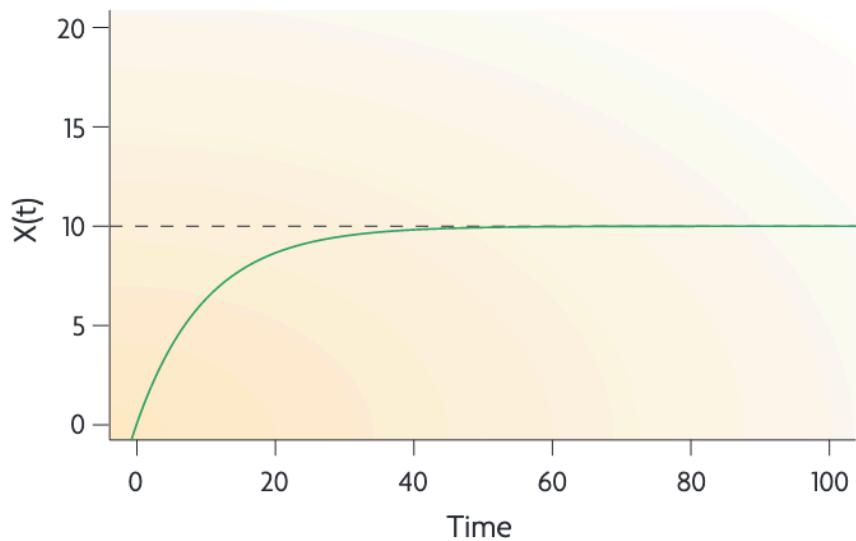
$$\frac{dX}{dt} = \alpha - \mu X$$

Solution:

$$X_t = \frac{\alpha}{\mu} (1 - e^{-\mu t})$$

Equilibrium:

$$X_{\infty} = \alpha/\mu$$



We revised ODEs, analytical solution and **numerical solution**.

# A SIMPLE MODEL OF GENE EXPRESSION



Discrete stochastic model:

$$\Pr(X_{t+dt} = x + 1 | X_t = x) = \alpha dt$$

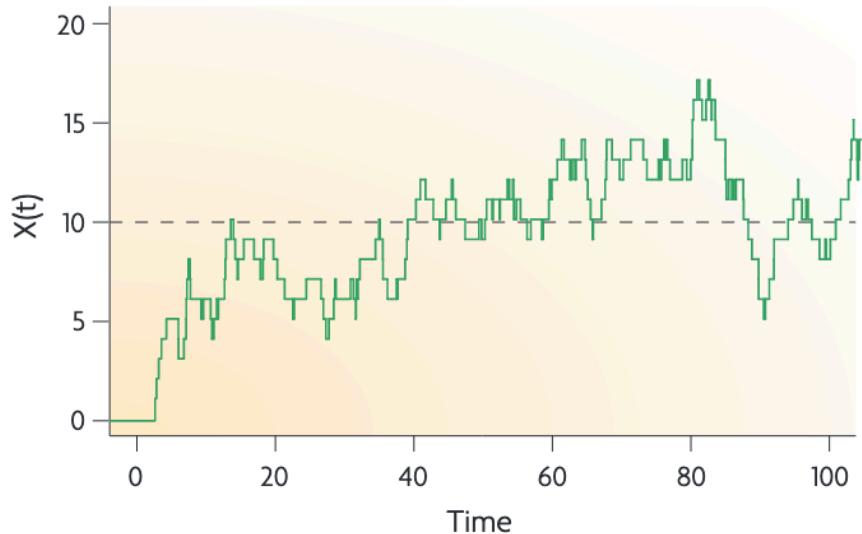
$$\Pr(X_{t+dt} = x - 1 | X_t = x) = \mu x dt$$

Solution:

$$X_t \sim \text{Poisson} \left( \frac{\alpha}{\mu} [1 - e^{-\mu t}] \right)$$

Equilibrium distribution:  $X_\infty \sim \text{Poisson} (\alpha/\mu)$

$$E(X_\infty) = \text{Var}(X_\infty) = \alpha/\mu$$



# A SIMPLE MODEL OF GENE EXPRESSION



**Discrete stochastic model:**

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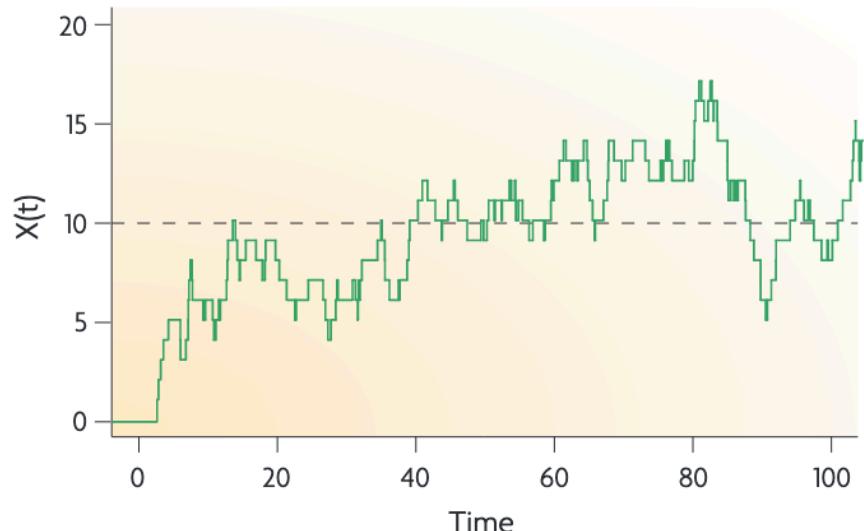
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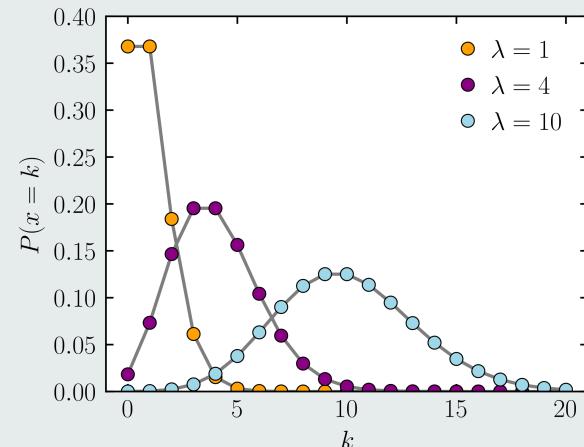


Poisson    If  $N \gg 1$  and  $p \ll 1$  the binomial can be approximated as

$$\lambda = Np$$

$$\sigma^2 = Np = \lambda$$

$$p(k, \lambda) = \frac{\lambda^k}{k!} e^{-\lambda}$$



source: wiki

# A SIMPLE MODEL OF GENE EXPRESSION



Gillespie algorithm.

# A SIMPLE MODEL OF GENE EXPRESSION

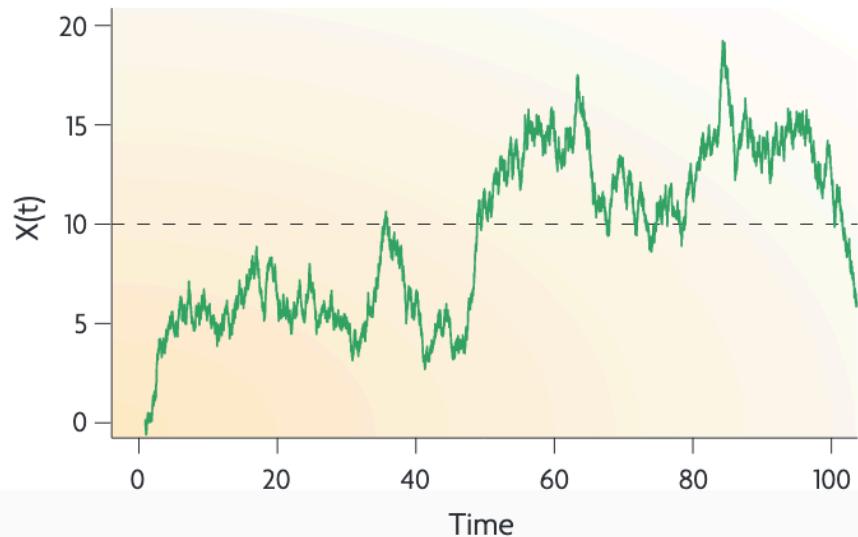


Continuous stochastic model (CLE):

$$dX_t = (\alpha - \mu X_t) dt + \sqrt{\alpha + \mu X_t} dW_t$$

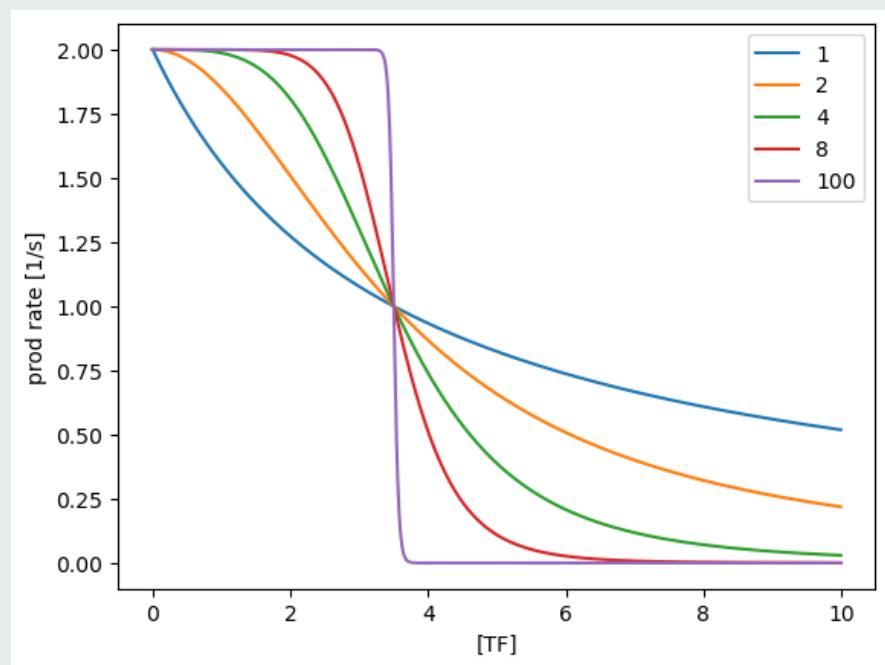
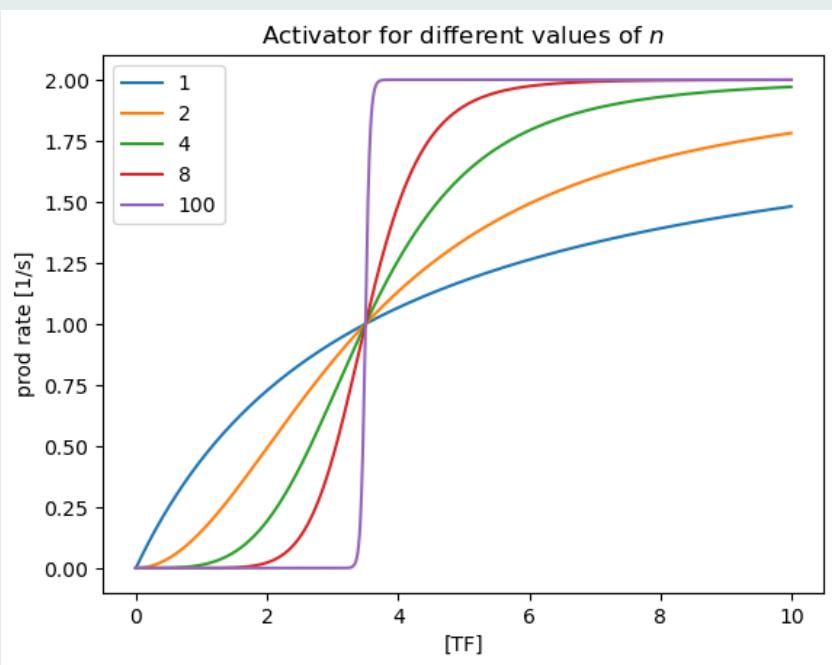
At equilibrium:

$$E(X_\infty) = \text{Var}(X_\infty) = \alpha/\mu$$



Gillespie algorithm.

# ACTIVATORS AND REPRESSORS

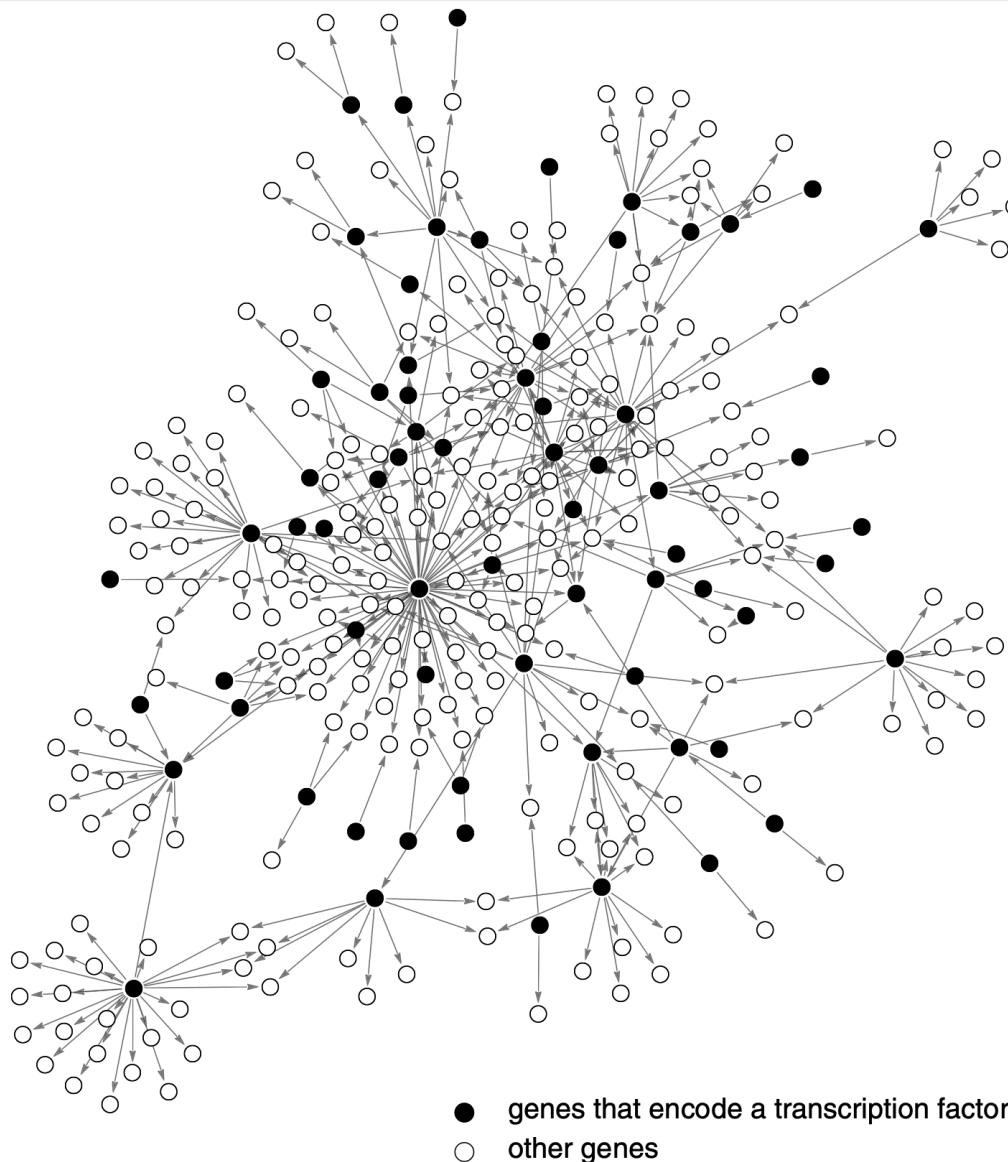


RESEARCH ARTICLE

# Effect of transcription factor resource sharing on gene expression noise

Dipjyoti Das<sup>1</sup>✉, Supravat Dey<sup>2</sup>✉, Robert C. Brewster<sup>3,4†\*</sup>, Sandeep Choube<sup>5,6†\*</sup>

# GENE REGULATORY NETWORKS



# Network Motifs: Simple Building Blocks of Complex Networks

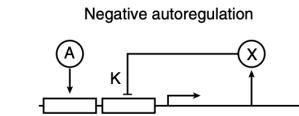
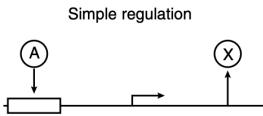
R. Milo,<sup>1</sup> S. Shen-Orr,<sup>1</sup> S. Itzkovitz,<sup>1</sup> N. Kashtan,<sup>1</sup> D. Chklovskii,<sup>2</sup>  
U. Alon<sup>1\*</sup>

Complex networks are studied across many fields of science. To uncover their structural design principles, we defined "network motifs," patterns of interconnections occurring in complex networks at numbers that are significantly higher than those in randomized networks. We found such motifs in networks from biochemistry, neurobiology, ecology, and engineering. The motifs shared by ecological food webs were distinct from the motifs shared by the genetic networks of *Escherichia coli* and *Saccharomyces cerevisiae* or from those found in the World Wide Web. Similar motifs were found in networks that perform information processing, even though they describe elements as different as biomolecules within a cell and synaptic connections between neurons in *Cae-norhabditis elegans*. Motifs may thus define universal classes of networks. This approach may uncover the basic building blocks of most networks.

[www.sciencemag.org](http://www.sciencemag.org) SCIENCE VOL 298 25 OCTOBER 2002

Network	Nodes	Edges	$N_{\text{real}}$	$N_{\text{rand}} \pm \text{SD}$	Z score
<b>Gene regulation (transcription)</b>			X ↓ Y ↓ → Z		Feed-forward loop
<i>E. coli</i>	424	519	40	7 ± 3	10
<i>S. cerevisiae</i> *	685	1,052	70	11 ± 4	14

# NEGATIVE AUTOREGULATION



doi:10.1016/S0022-2836(02)00994-4 available online at <http://www.idealibrary.com> on IDEAL®

J. Mol. Biol. (2002) 323, 785–793

JMB



## Negative Autoregulation Speeds the Response Times of Transcription Networks

Nitzan Rosenfeld<sup>1</sup>, Michael B. Elowitz<sup>2</sup> and Uri Alon<sup>1\*</sup>

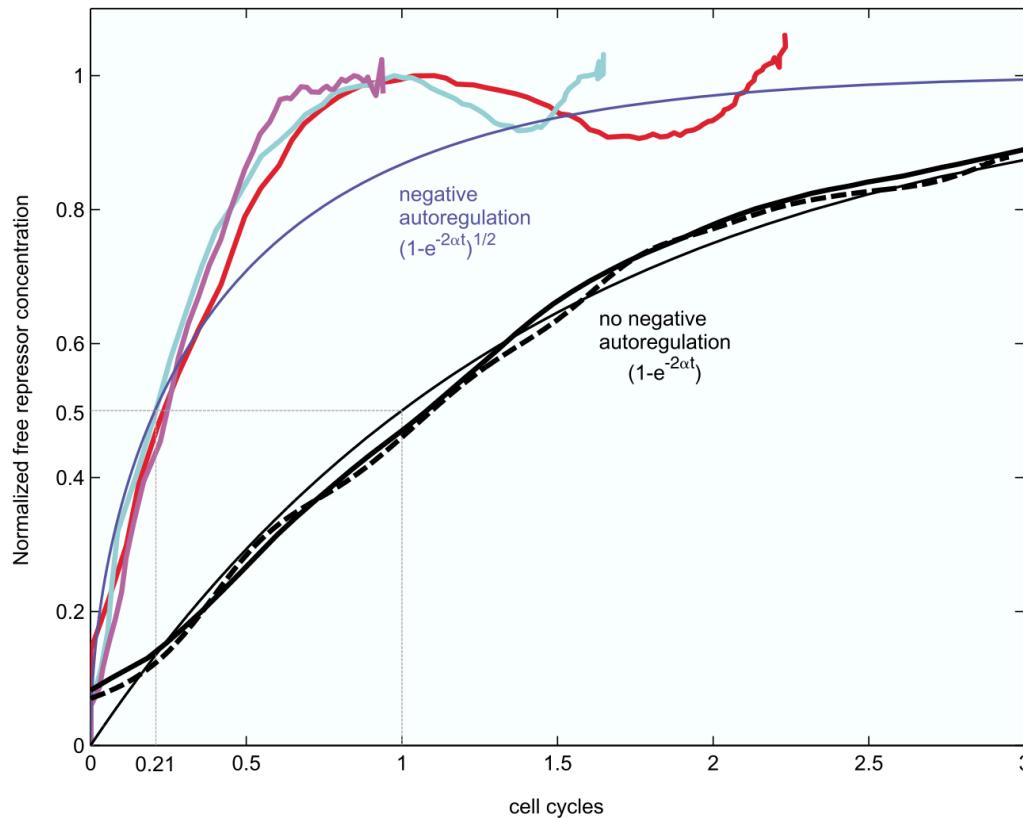
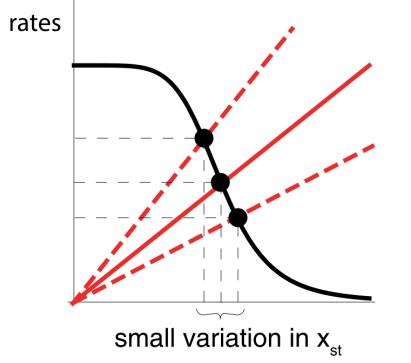
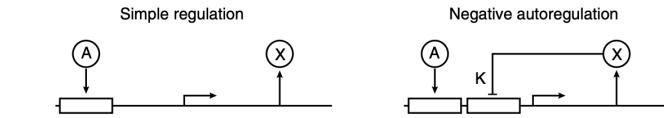


Plate reader

# NEGATIVE AUTOREGULATION

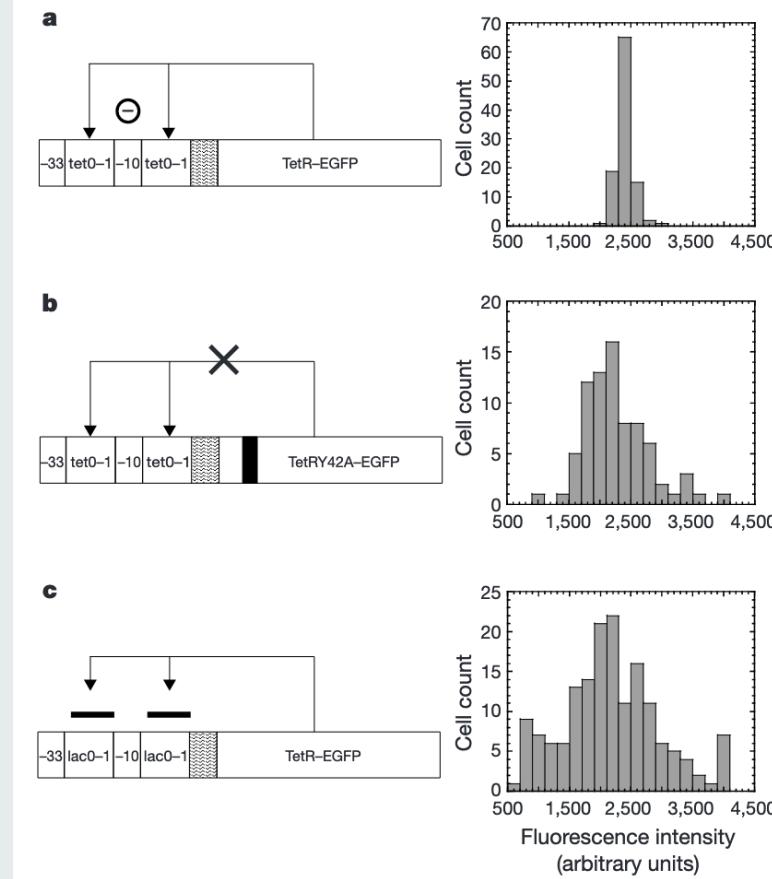


## Engineering stability in gene networks by autoregulation

Attila Becskei & Luis Serrano

EMBL, Structures & Biocomputing, Meyerhofstrasse 1, Heidelberg D-69012, Germany

The genetic and biochemical networks which underlie such things as homeostasis in metabolism and the developmental programs of living cells, must withstand considerable variations and random perturbations of biochemical parameters<sup>1-3</sup>. These occur as transient changes in, for example, transcription, translation, and RNA and protein degradation. The intensity and duration of these perturbations differ between cells in a population<sup>4</sup>. The unique state of cells, and thus the diversity in a population, is owing to the different environmental stimuli the individual cells experience and the inherent stochastic nature of biochemical processes (for example, refs 5 and 6). It has been proposed, but not



**Figure 2** Gene circuits and corresponding typical distributions of fluorescence intensities. Each circuit consists of the following units: operator at position V, -33 hexamer, operator at position IV, -10 hexamer, untranslated region, fusion protein. GFP fluorescence intensity is denoted by arbitrary units in the histograms which corresponds to intensities of a 12-bit (4,096 grey level) image. The mean values of the three systems were normalized from different exposure times. Relative mean values (r.m.v.) are given for each distribution. **a**, Autoregulatory system in DH5 $\alpha$  cells; r.m.v. = 1. **b**, The repressor was mutated (Y42A) in the DNA-binding domain to obtain the unregulated system in DH5 $\alpha$  cells; r.m.v. = 38. **c**, Unregulated system obtained by operator replacement in DH5 $\alpha$ Z1 cells. Sample is taken after induction by IPTG; r.m.v. = 14.

# MORE COMPLEX CIRCUITS



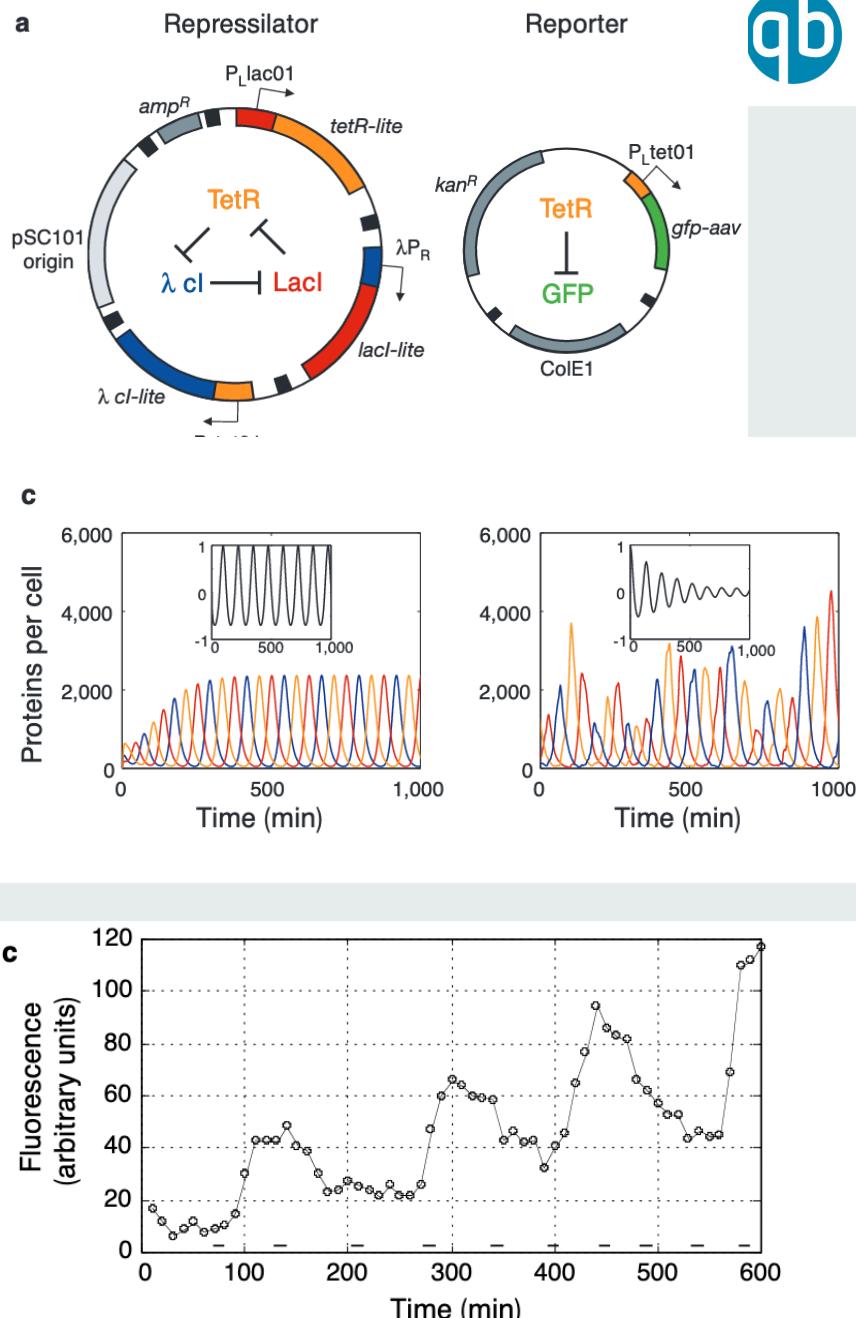
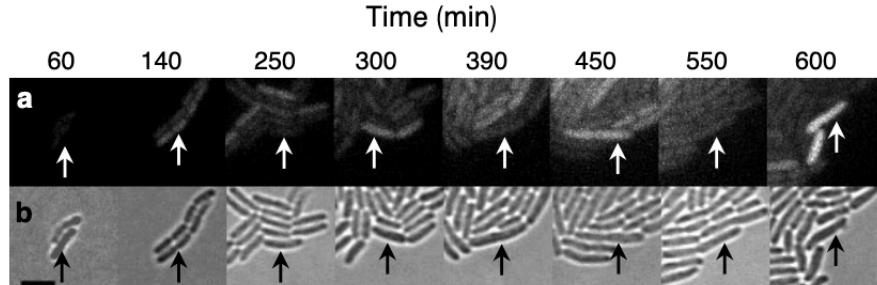
## A synthetic oscillatory network of transcriptional regulators

Michael B. Elowitz & Stanislas Leibler

Departments of Molecular Biology and Physics, Princeton University, Princeton, New Jersey 08544, USA

Networks of interacting biomolecules carry out many essential functions in living cells<sup>1</sup>, but the ‘design principles’ underlying the functioning of such intracellular networks remain poorly understood, despite intensive efforts including quantitative analysis of relatively simple systems<sup>2</sup>. Here we present a complementary approach to this problem: the design and construction of a synthetic network to implement a particular function. We used three transcriptional repressor systems that are not part of any natural biological clock<sup>3–5</sup> to build an oscillating network, termed

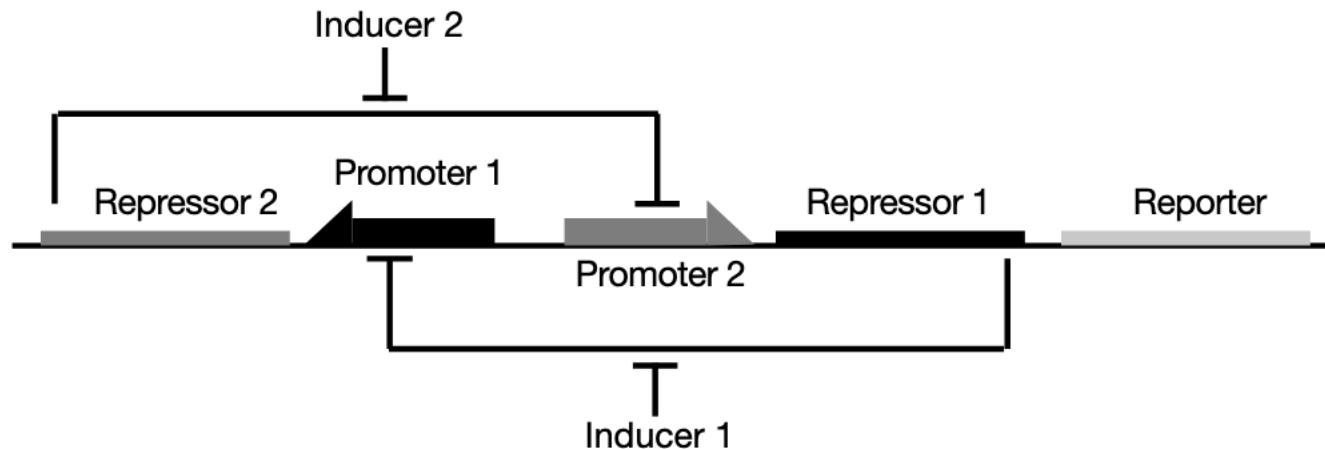
NATURE | VOL 403 | 20 JANUARY 2000 | www.nature.com



## ..... **Construction of a genetic toggle switch in *Escherichia coli***

**Timothy S. Gardner\*†, Charles R. Cantor\* & James J. Collins\*†**

\* Department of Biomedical Engineering, † Center for BioDynamics and ‡ Center for Advanced Biotechnology, Boston University, 44 Cummings Street, Boston, Massachusetts 02215, USA





# Stochastic Gene Expression in a Single Cell

Michael B. Elowitz,<sup>1,2\*</sup> Arnold J. Levine,<sup>1</sup> Eric D. Siggia,<sup>2</sup>  
Peter S. Swain<sup>2</sup>

www.sciencemag.org SCIENCE VOL 297 16 AUGUST 2002

The amount of protein produced by a particular gene varies from cell to cell.

The **noise** (defined as the standard deviation divided by the mean) in this distribution is often called coefficient of variation (CV) and can be divided into two components.

# EXTRINSIC AND INTRINSIC NOISE



*“Because expression of each gene is controlled by the concentrations, states, and locations of molecules such as regulatory proteins and polymerases, fluctuations in the amount or activity of these molecules cause corresponding fluctuations in the output of the gene.” —> **Extrinsic noise***

*“On the other hand, consider a population of cells identical not just genetically but also in the concentrations and states of their cellular components. Even in such a (hypothetical) population, the rate of expression of a particular gene would still vary from cell to cell because of the random microscopic events that govern which reactions occur and in what order.” —> **Intrinsic noise***

Intrinsic noise is “*that remaining part of the total noise arising from the discrete nature of the biochemical process of gene expression. No matter how accurately the levels of regulatory proteins are controlled, intrinsic noise fundamentally limits the precision of gene regulation.*”

## EXPERIMENTAL DESIGN

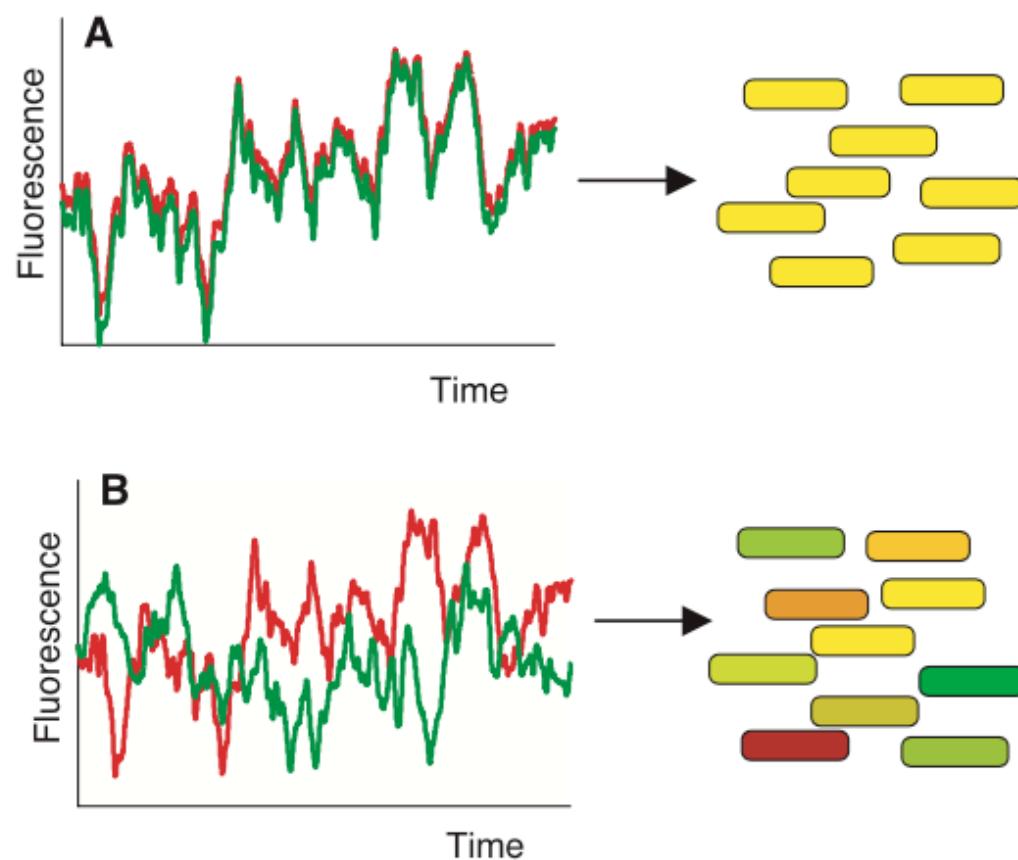


Operationally, intrinsic noise for a given gene may be defined as the extent to which the activities of two identical copies of that gene, in the same intracellular environment, fail to correlate (Fig. 1, A and B). Therefore, we built strains of *Escherichia coli*, incorporating the distinguishable cyan (*cfp*) and yellow (*yfp*) alleles of green fluorescent protein in the chromosome. In each strain, the two reporter genes were controlled by identical promoters. To avoid systematic differences in copy number, we integrated the genes at loci equidistant from, and on opposite sides of, the origin of replication (fig. S1). The two fluorescent proteins exhibited statistically equivalent intensity distributions and thus displayed the necessary independence and equivalence to detect noise (7).

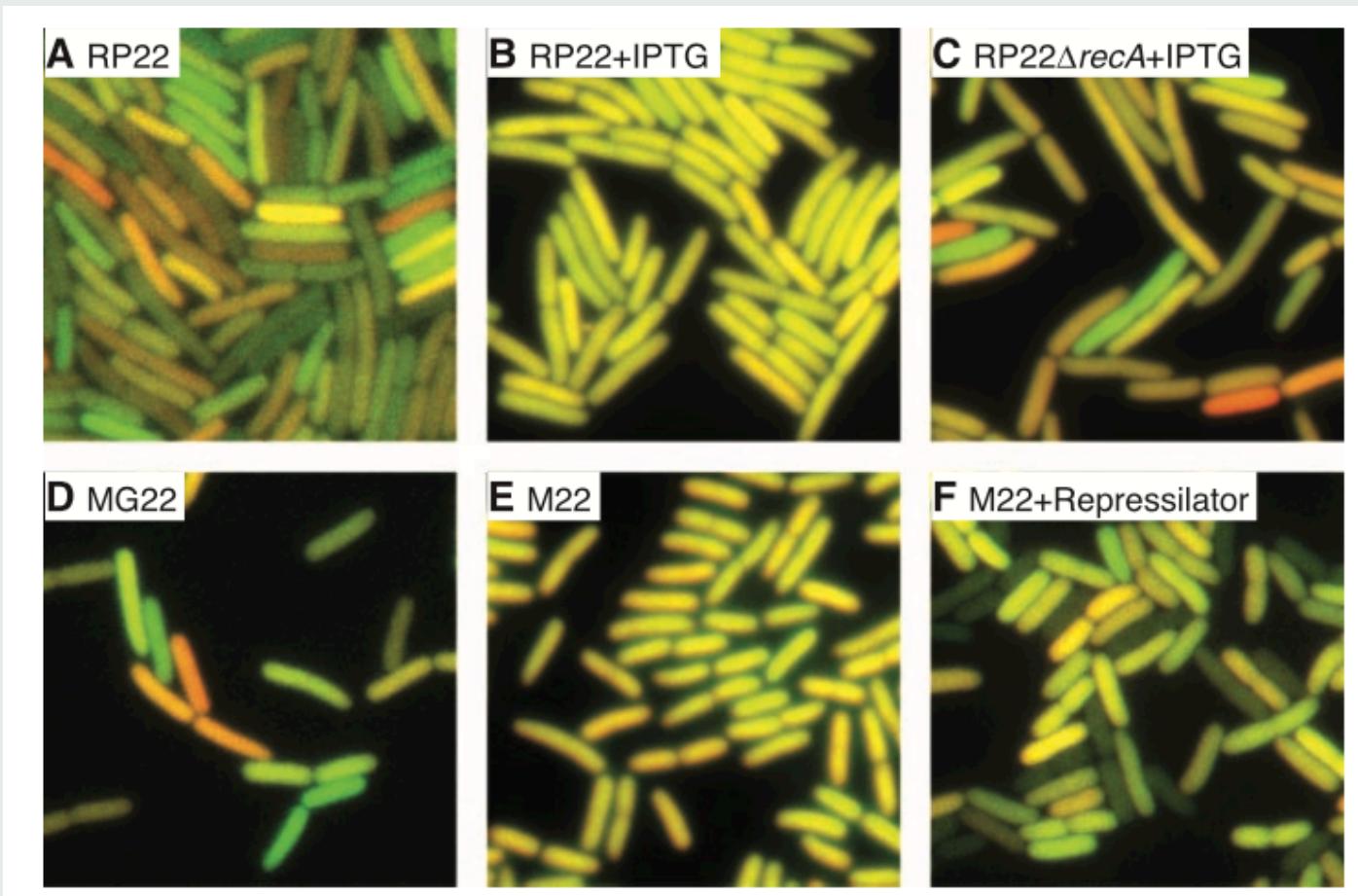
# RESULTS



**Fig. 1.** Intrinsic and extrinsic noise can be measured and distinguished with two genes (*cfp*, shown in green; *yfp*, shown in red) controlled by identical regulatory sequences. Cells with the same amount of each protein appear yellow, whereas cells expressing more of one fluorescent protein than the other appear red or green. (A) In the absence of intrinsic noise, the two fluorescent proteins fluctuate in a correlated fashion over time in a single cell (left). Thus, in a population, each cell will have the same amount of both proteins, although that amount will differ from cell to cell because of extrinsic noise (right). (B) Expression of the two genes may become uncorrelated in individual cells because of intrinsic noise (left), giving rise to a population in which some cells express more of one fluorescent protein than the other.

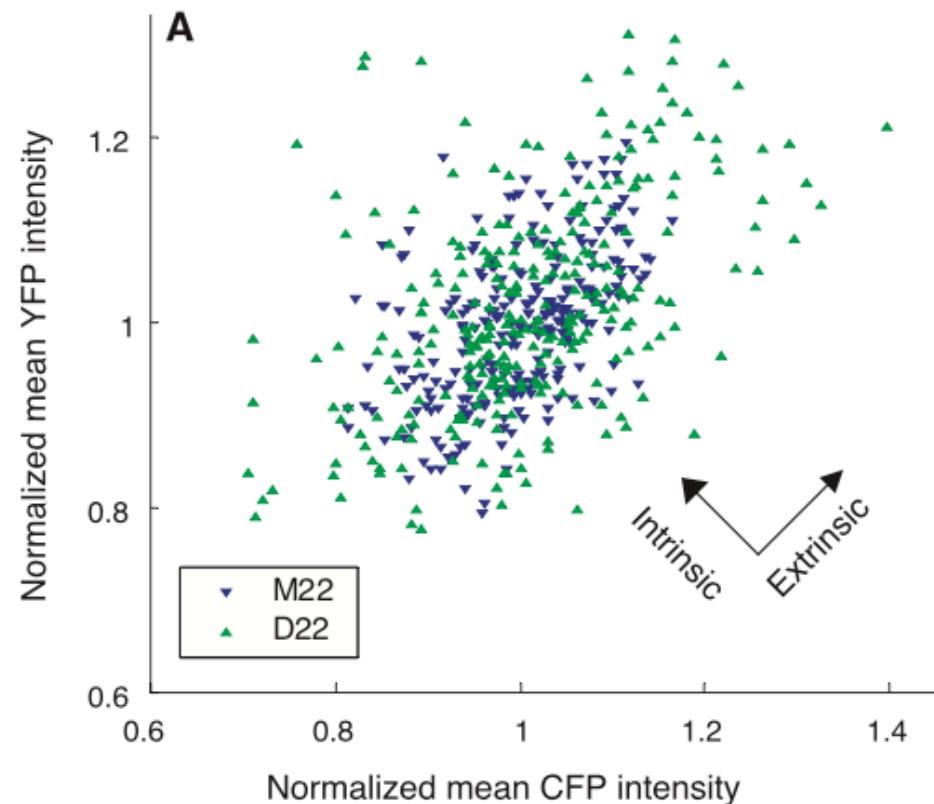


# EXPERIMENTS



...cells were grown in LB medium and photographed through cfp and yfp fluorescence filter sets and in phase contrast.

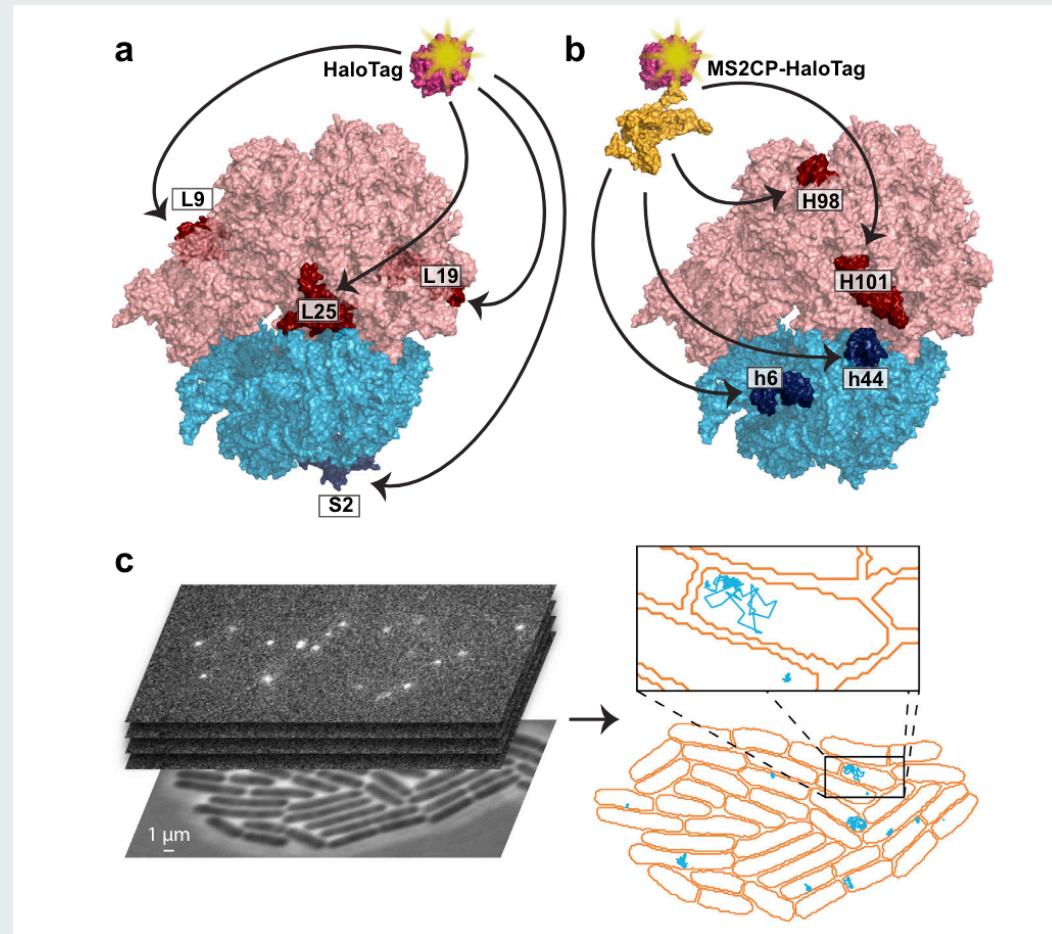
# EXPERIMENTS



**Fig. 3.** Quantification of noise. (A) Plot of fluorescence in two strains: one quiet (M22) and one noisy (D22). Each point represents the mean fluorescence intensities from one cell. Spread of points perpendicular to the diagonal line on which CFP and YFP intensities are equal corresponds to intrinsic noise, whereas spread parallel to this line is increased by extrinsic noise.

# Direct measurements of mRNA translation kinetics in living cells

Mikhail Metelev <sup>1</sup>, Erik Lundin <sup>1</sup>, Ivan L. Volkov <sup>1</sup>, Arvid H. Gynnå <sup>1</sup>, Johan Elf <sup>1</sup> & Magnus Johansson <sup>1</sup>✉



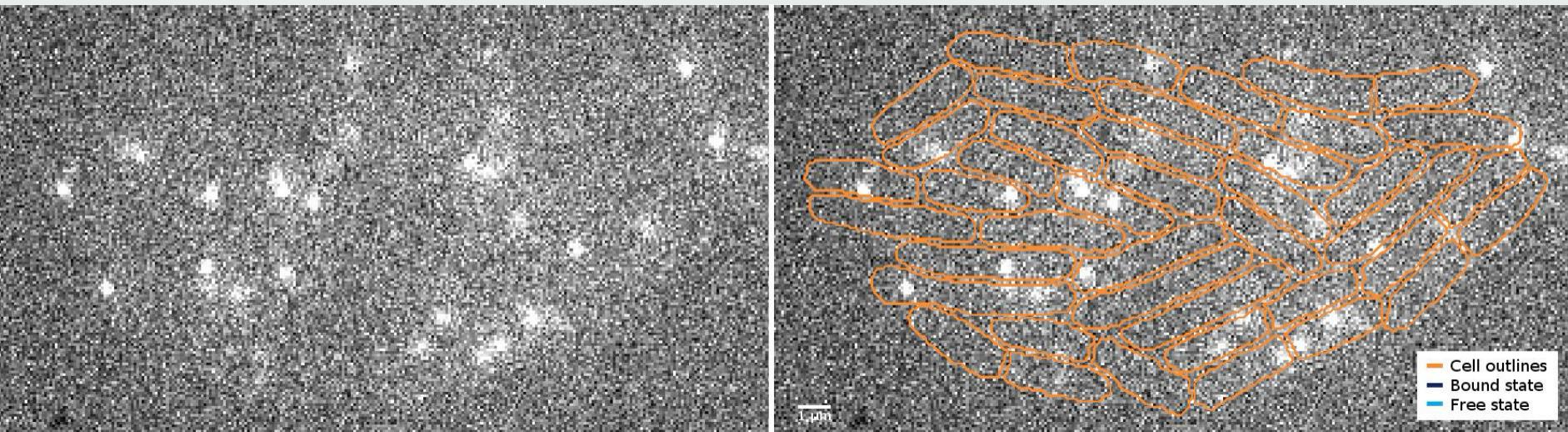
<https://doi.org/10.1038/s41467-022-29515-x>

OPEN



# Direct measurements of mRNA translation kinetics in living cells

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