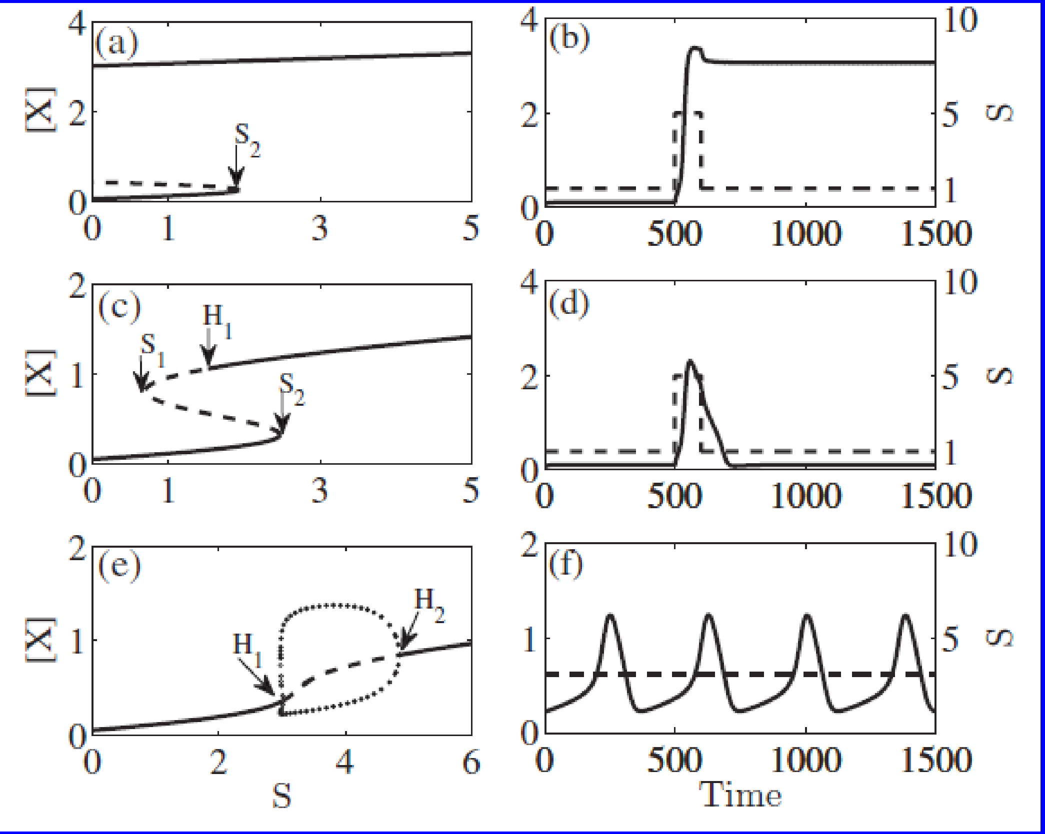
Review

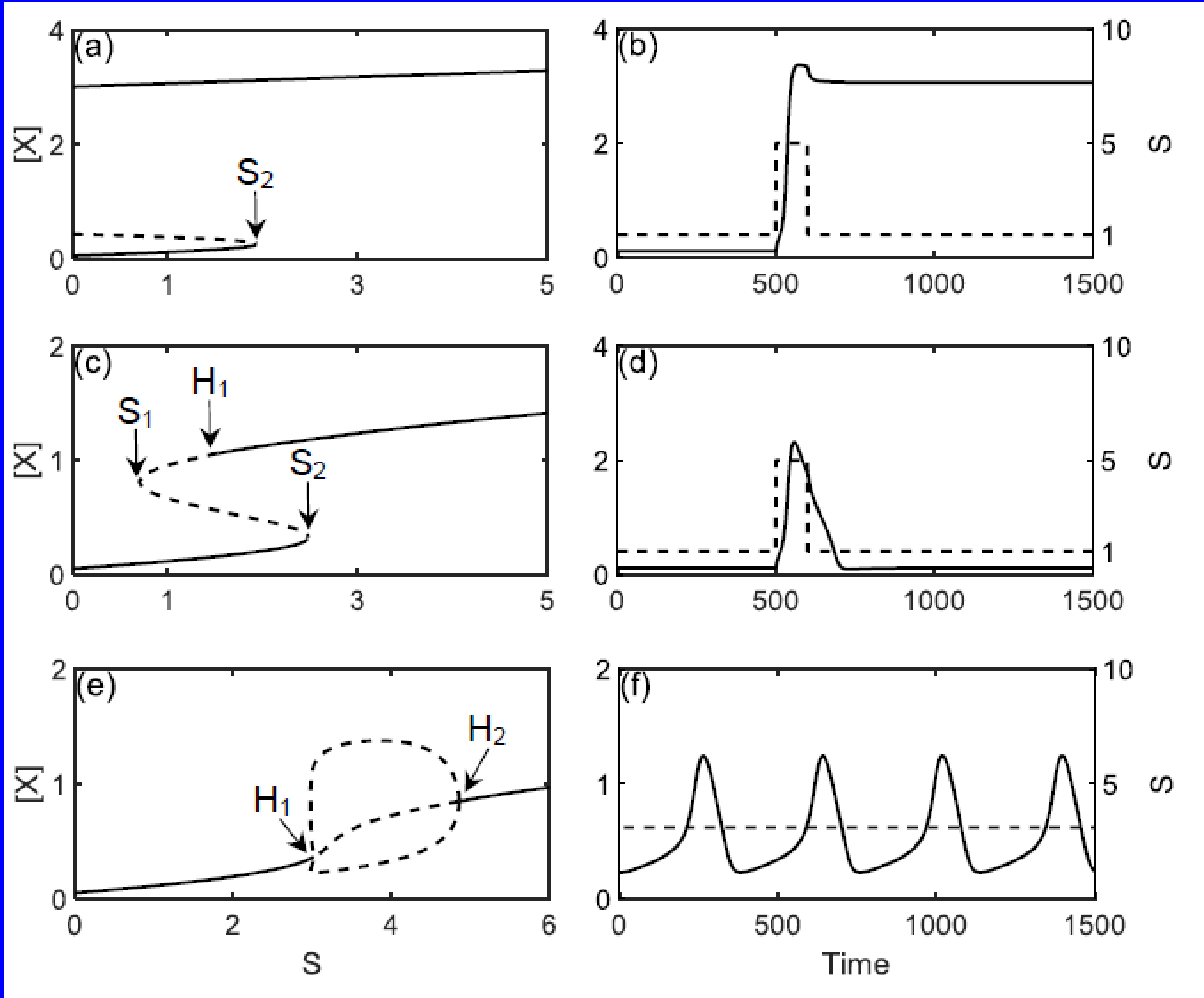
- Interlinked positive and negative feedback loops produces robust, tunable oscillations.
- Interlinking positive and negative feedback loops creates a tunable motif in gene regulatory networks.
- Modulation of dynamic modes by interplay between positive and negative feedback loops

Assignment 7

Reproducing Figures 5 in the literature:

Tian, X.-J., X.-P. Zhang, et al. (2009). Physical Review E **80**(1): 011926-011928.





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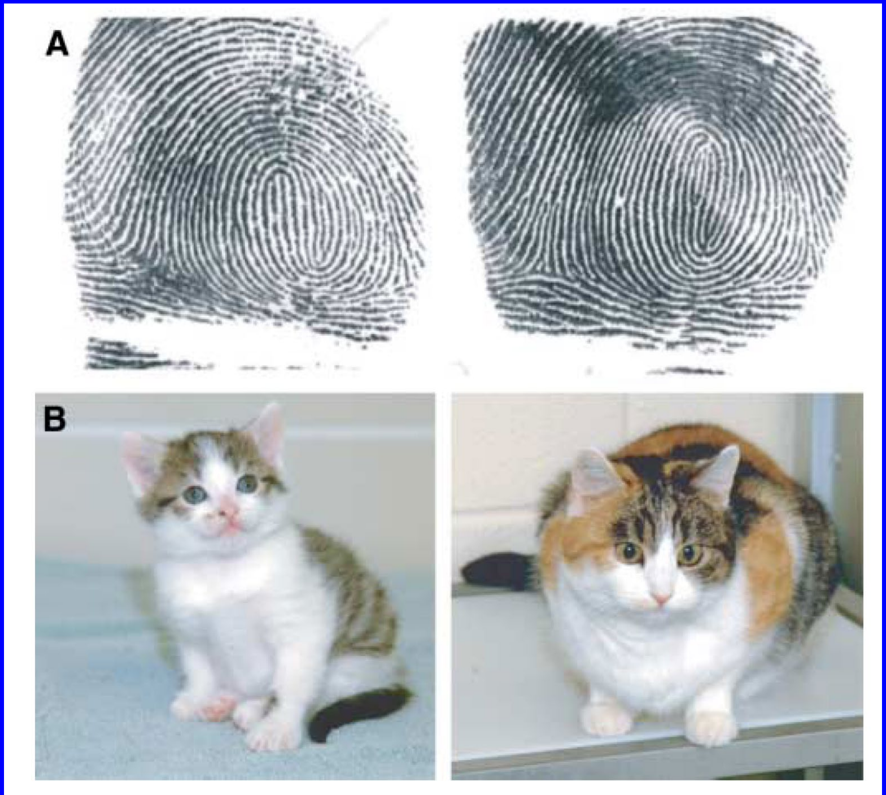
Chap4 Noise in Biological network

Outline

- Origin, consequences, and control.
- The effects of noise on the function of biological network.

Chap4-1 Origins, Consequences, and Control of Biological Noise



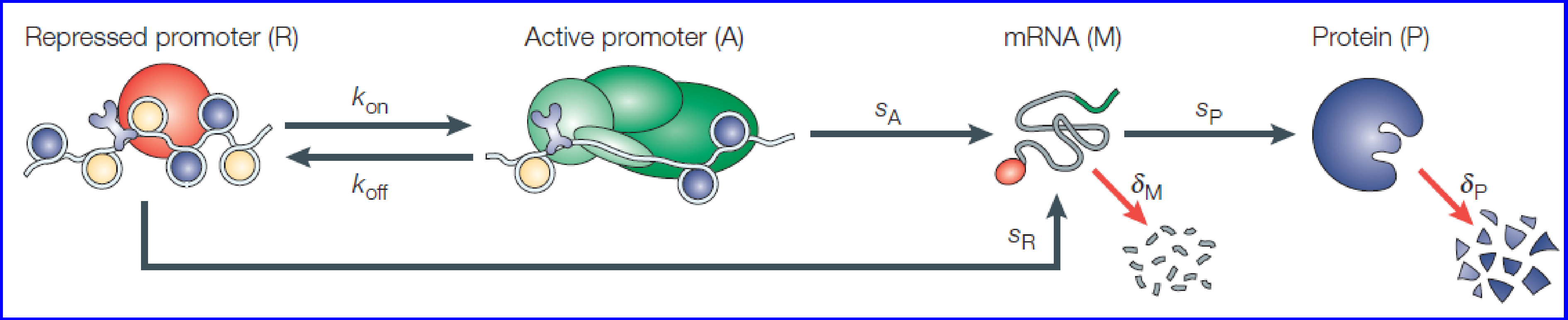
Genetically identical cells and organisms exhibit remarkable diversity.

Noise, or variation, in the process of gene expression may contribute to this phenotypic variability.

Examples of possible stochastic influences on phenotype.

Raser JM, O'Shea EK. Science. 2005; **309**(5743): 2010-3.

A model of the expression of a single gene



Each step represents several biochemical reactions, which are associated with mRNA and protein production, transitions between promoter states and the decay of mRNA and protein.

Kaern, M., T. C. Elston, et al. (2005). Nat Rev Genet **6**(6): 451-464.

Origins of noise in gene expression

Four potential sources of noise in gene expression:

(i) the inherent stochasticity of biochemical processes involving small numbers of molecules;

(ii) variation in gene expression owing to differences in the internal states of a population of cells

(iii) subtle environmental differences, such as morphogen gradients in multicellular development;

(iv) ongoing genetic mutation, either random or directed.

Raser JM, O'Shea EK. Science. 2005; **309**(5743): 2010-3.

Noise Terminology

Coefficient of variation

$$\eta=\frac{\sigma}{\mu},\quad \mu=\frac{1}{N}\sum_{i=1}^{N}x_i,\sigma=\sqrt{\frac{1}{N}\sum_{i=1}^{N}(\mu-x_i)^2}$$

Normalized variation

$$\eta'=\frac{\sigma^2}{\mu^2}$$

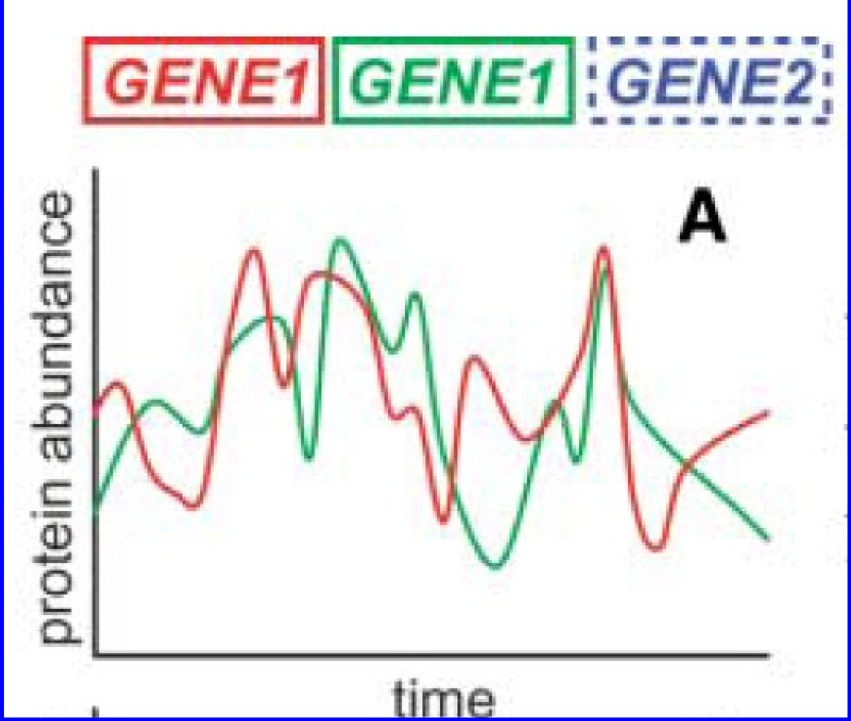
Noise strength

$$\mathrm{D}=\frac{\sigma^2}{\mu}$$

Types of biological noise

The *intrinsic noise* is defined as noise that creates differences in two identical reporters of gene expression contained within the same cell.

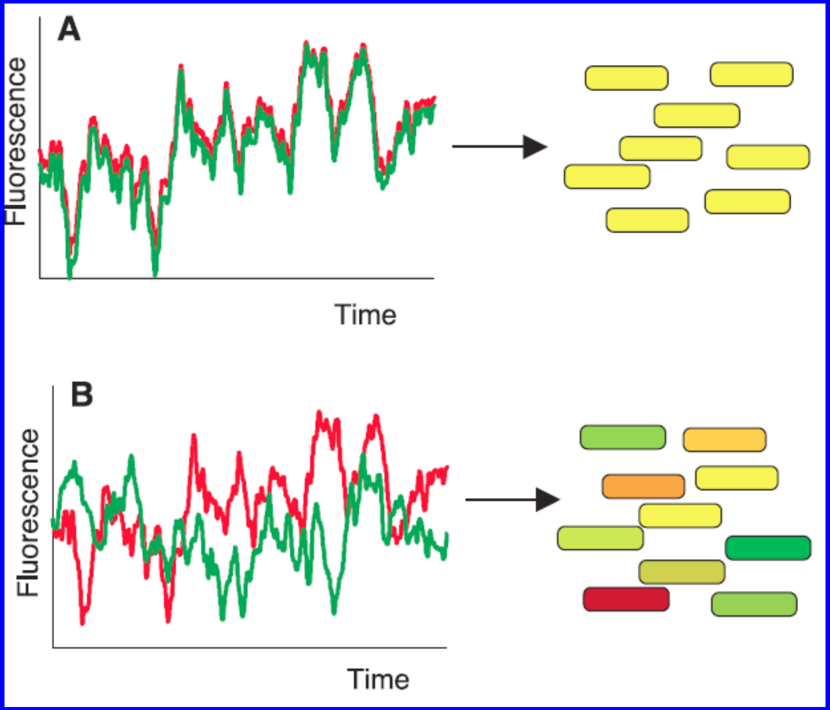
(A) Intrinsic noise results in differences between two reporters of the same gene in a single cell.

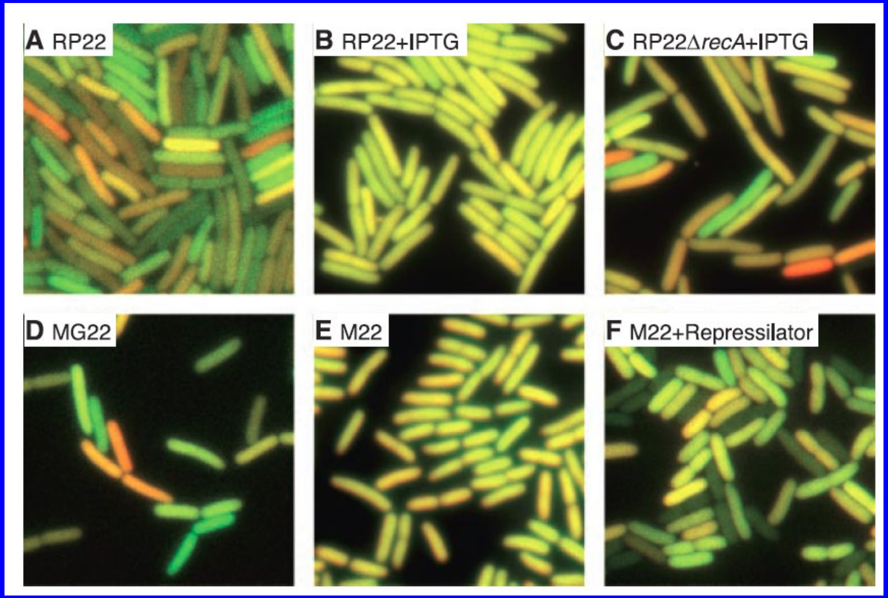


Stochastic Gene Expression in a Single Cell

Without intrinsic noise

Different intrinsic noise





With intrinsic noise

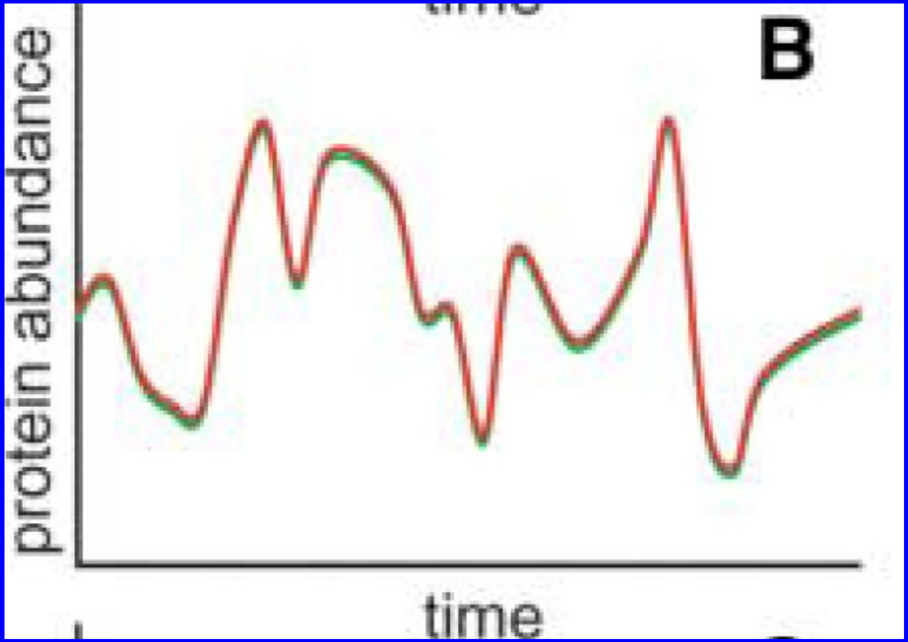
Elowitz, M. B., A. J. Levine, et al. (2002). Science **297**(5584): 1183-1186.

Intrinsic noise may be attributed to any stochastic event during gene expression, from the level of promoter-binding events, to mRNA splicing, to translation, to partitioning of proteins during cell division. Intrinsic noise may also arise from differences in reporter copy number or gene replication timing.

Extrinsic Noise

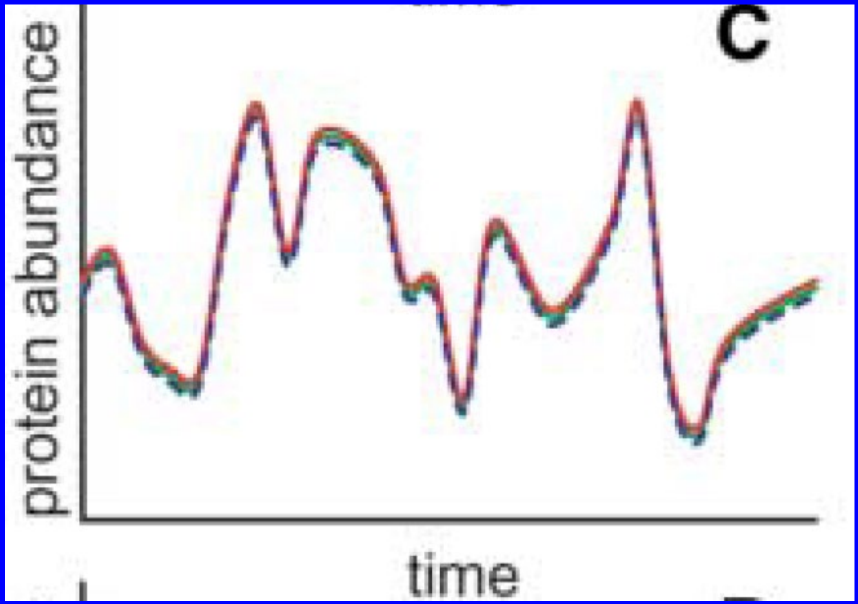
Extrinsic noise affects two identical reporters of gene expression within a given cell equally, but generates differences in reporter expression among cells

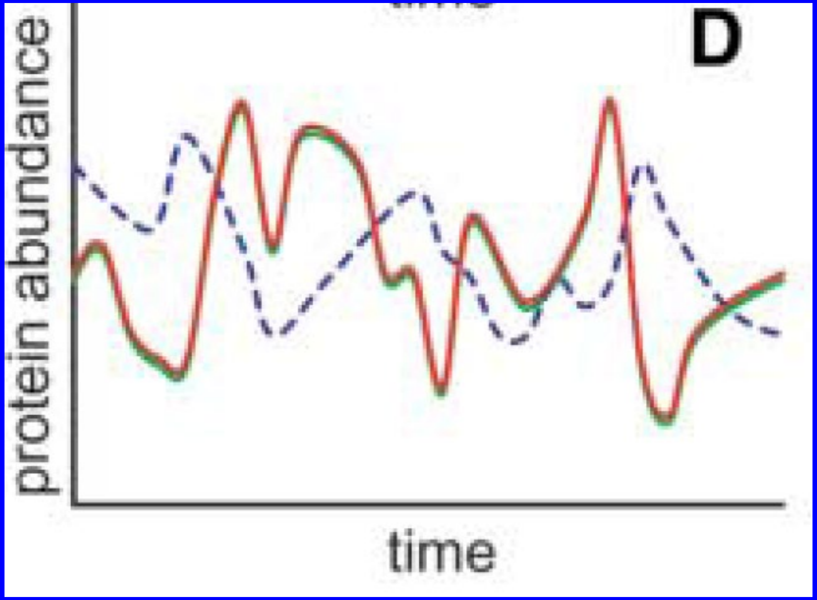
(B) Extrinsic noise affects two reporters of the same gene equally in a single cell but causes differences from cell to cell or in a single cell over time.



Extrinsic Noise

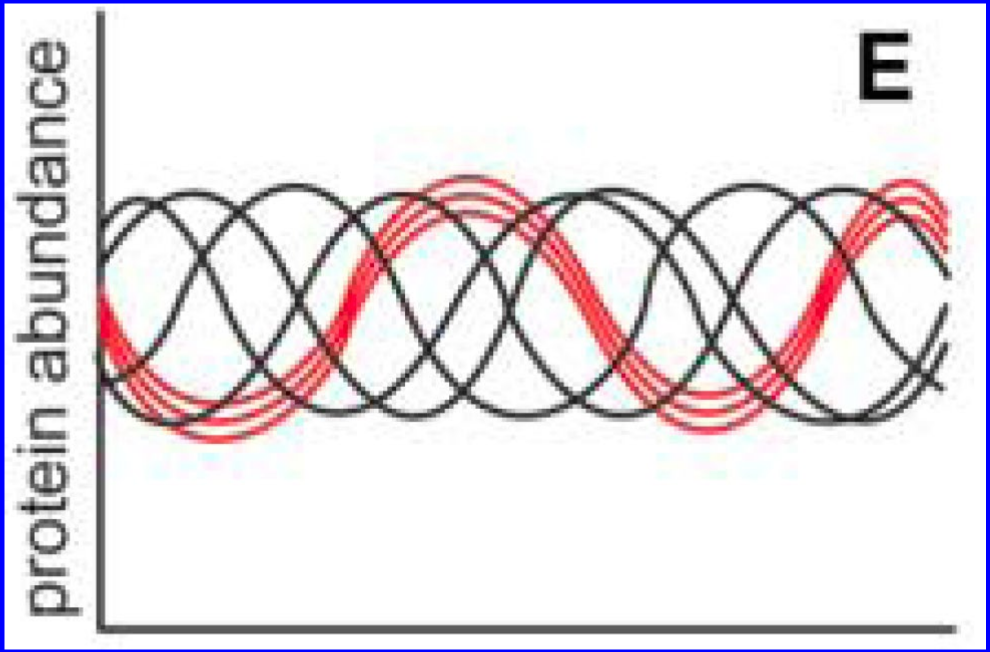
Extrinsic noise should be further subdivided into two categories: global noise, or fluctuations in the rates of the basic reactions that affect expression of all genes , and gene or pathway-specific extrinsic noise.



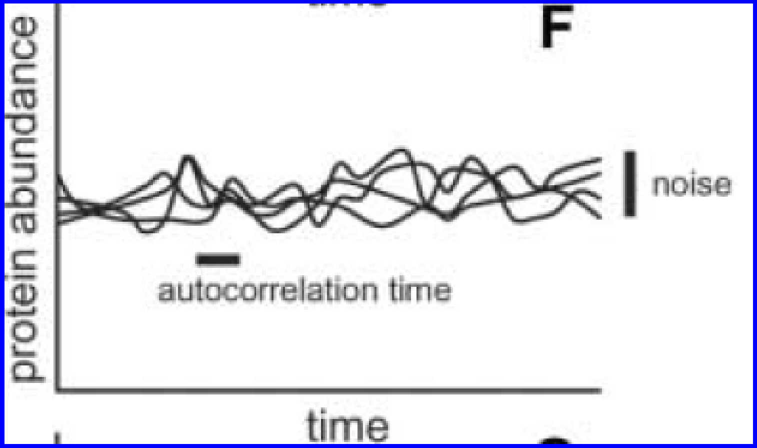


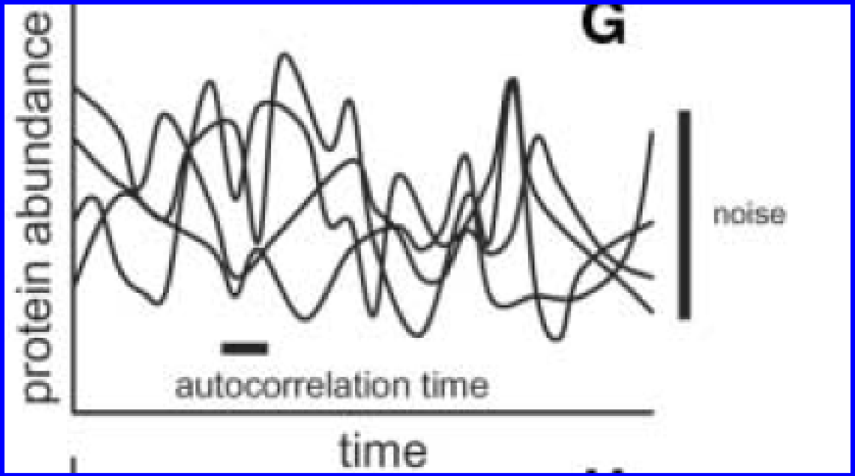
Manipulable extrinsic noise

In a synchronized population of cells, cell cycle progression results in predictable changes in protein abundance over time (red lines); when the cells grow asynchronously, the population displays variability (black lines).



Relative amplitude and time scales of intrinsic and extrinsic noise

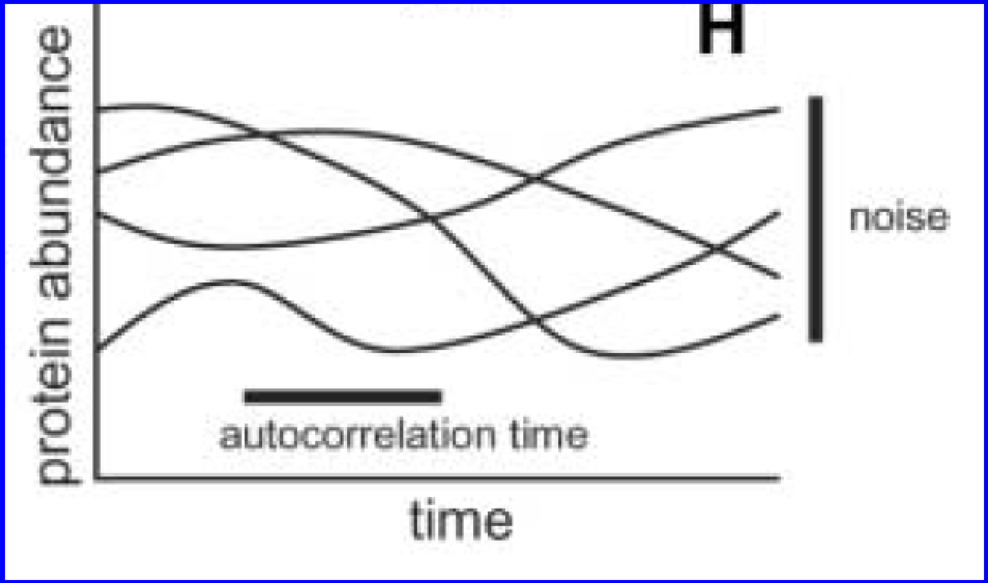




(F) Noise of low magnitude and short autocorrelation time.
(G) Noise of high magnitude and short autocorrelation time.

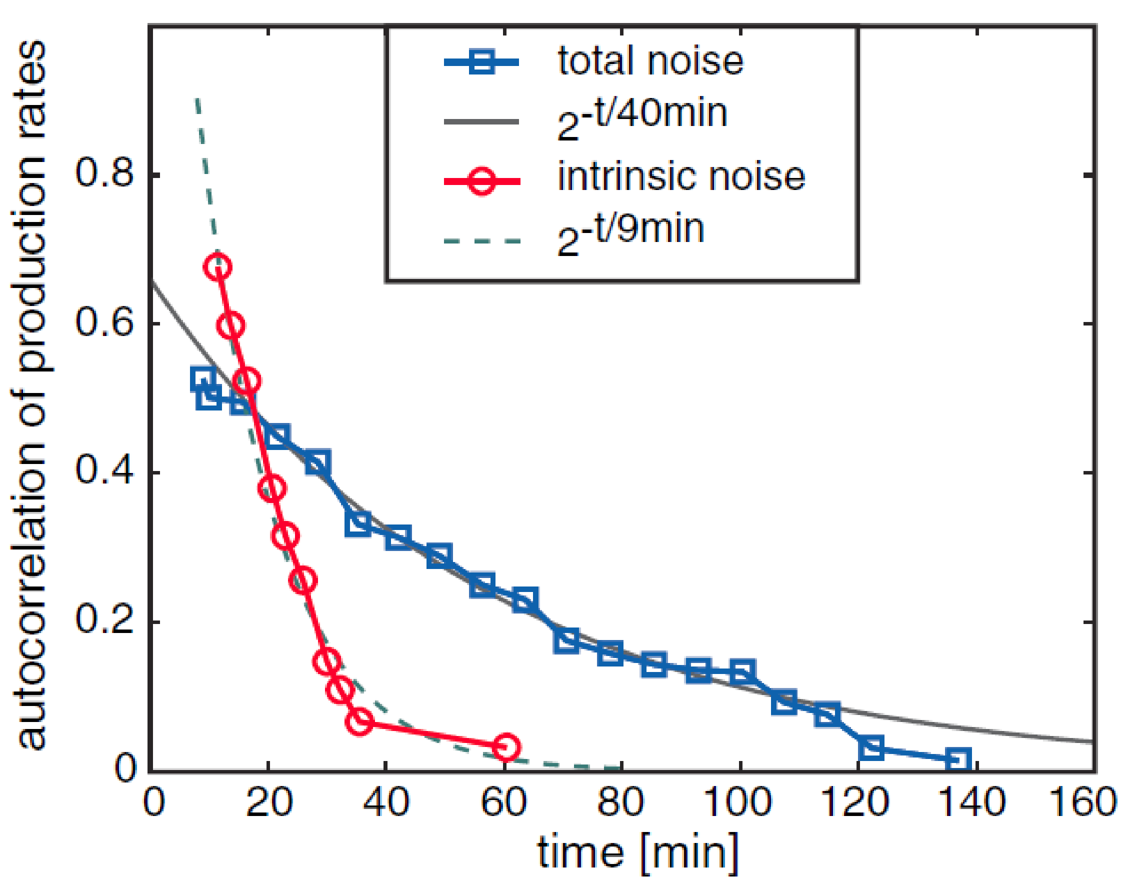
The autocorrelation time for intrinsic noise is <= 10 min.

Rosenfeld, N., J. W. Young, et al. (2005). "Science **307**(5717): 1962-1965.



(H) Noise of high magnitude and long autocorrelation time.

The autocorrelation time for global noise factors in protein production rate is <=40 min, similar to the observed cell cycle length, which suggests that whatever factors result in global noise persist on average for about one cell cycle.



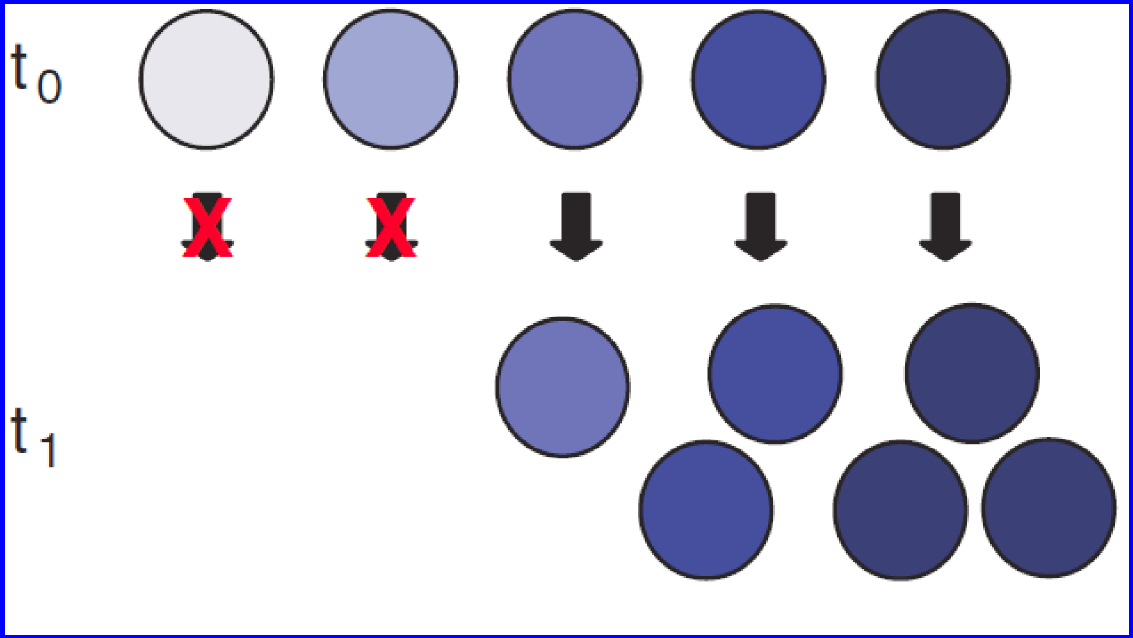
Rosenfeld, N., J. W. Young, et al. (2005). Science **307**(5717): 1962-1965.

Consequences of Noise in Gene Expression

Small changes in protein abundance may have dramatic effects on fitness if they persist long enough, whereas large fluctuations in abundance may not have any effect if they occur too frequently to affect a cellular process.

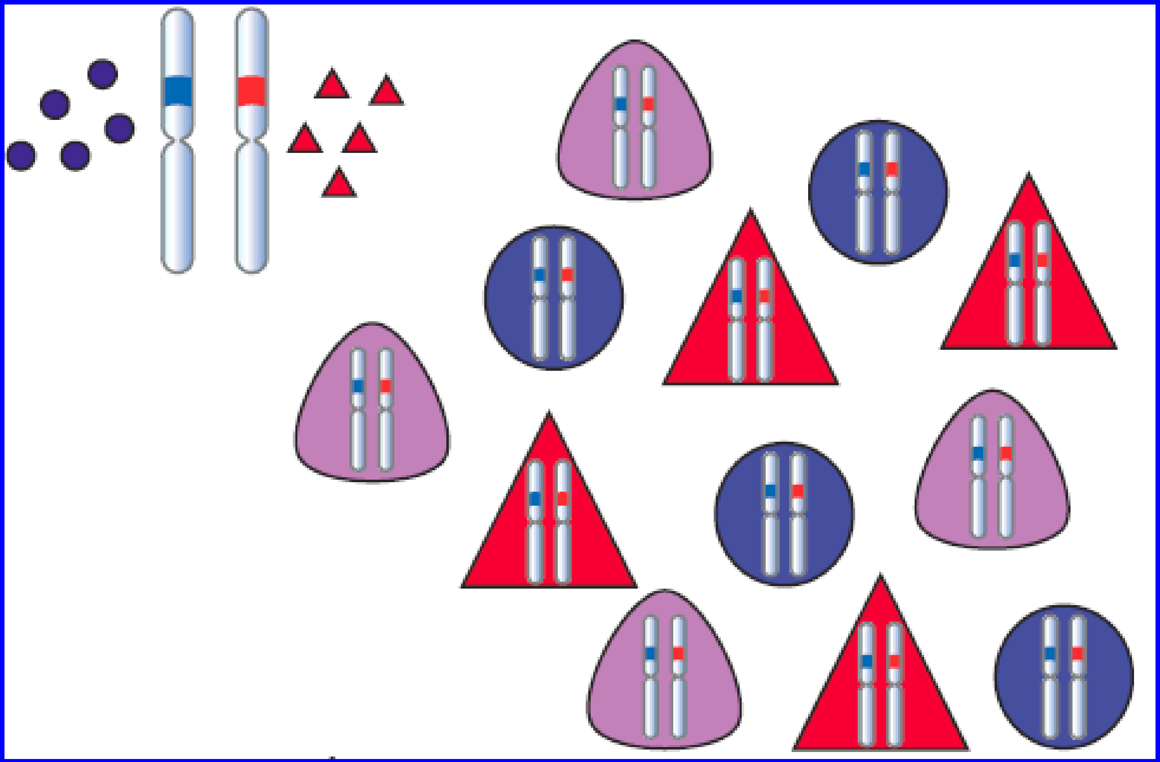
The observation that the time scale for intrinsic noise fluctuations is much shorter than that for extrinsic noise suggests that extrinsic noise may affect cellular phenotypes more strongly than intrinsic noise.

Raser JM, O'Shea EK. Science. 2005; **309**(5743): 2010-3.

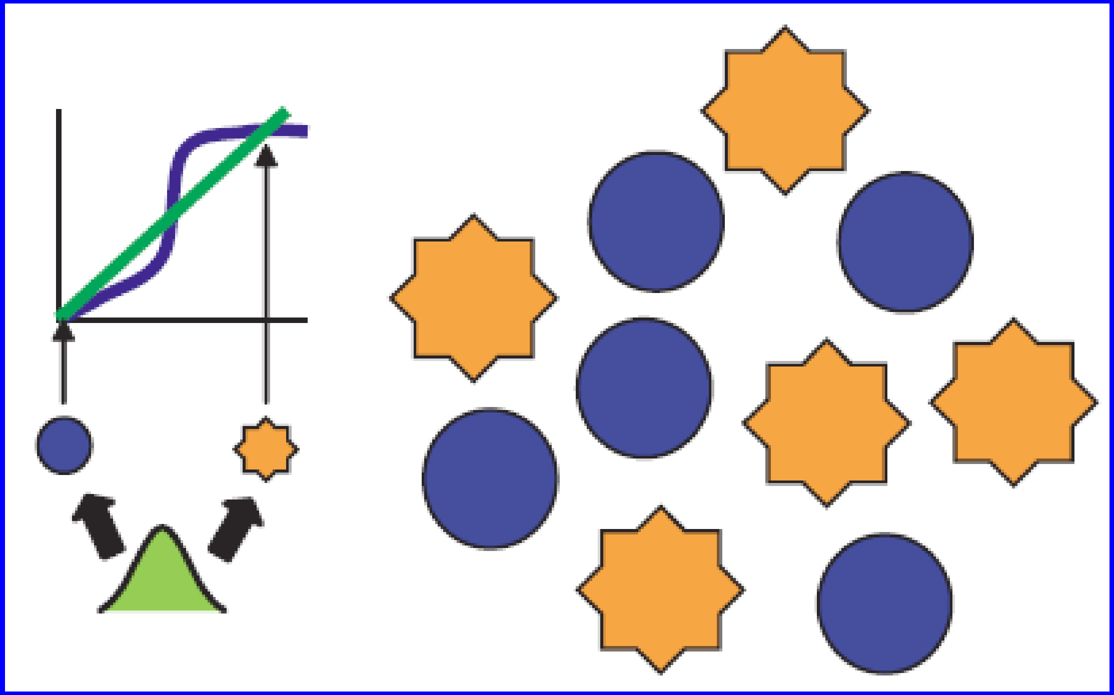


Small differences in gene product abundance affect reproductive fitness.

Raser JM, O'Shea EK. Science. 2005; **309**(5743): 2010-3.

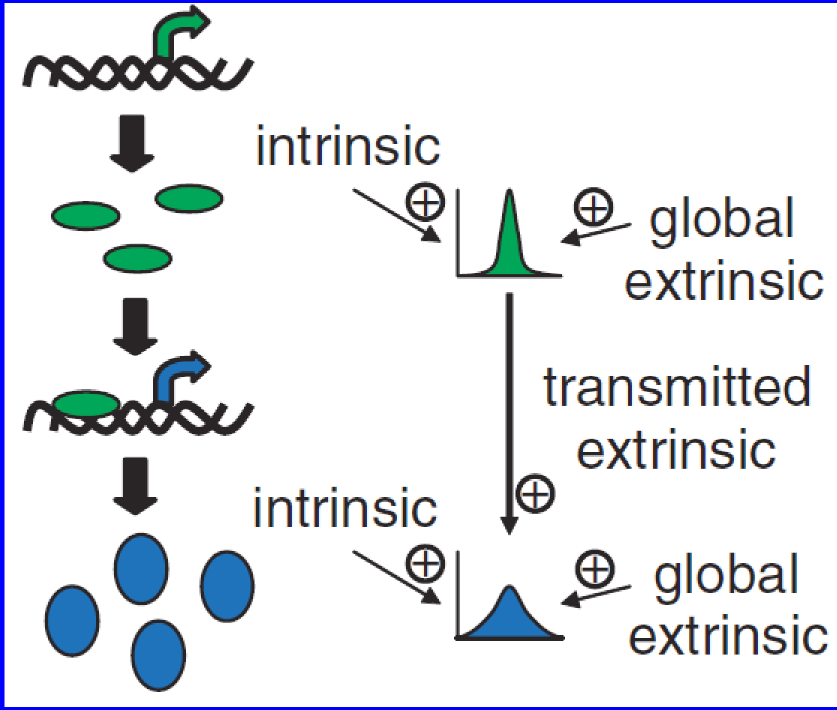


In a heterozygous diploid population, cells display the phenotypes associated with each homozygote as well as the heterozygote.



Noise allows simultaneous achievement of multiple steady-state phenotypes in a population.

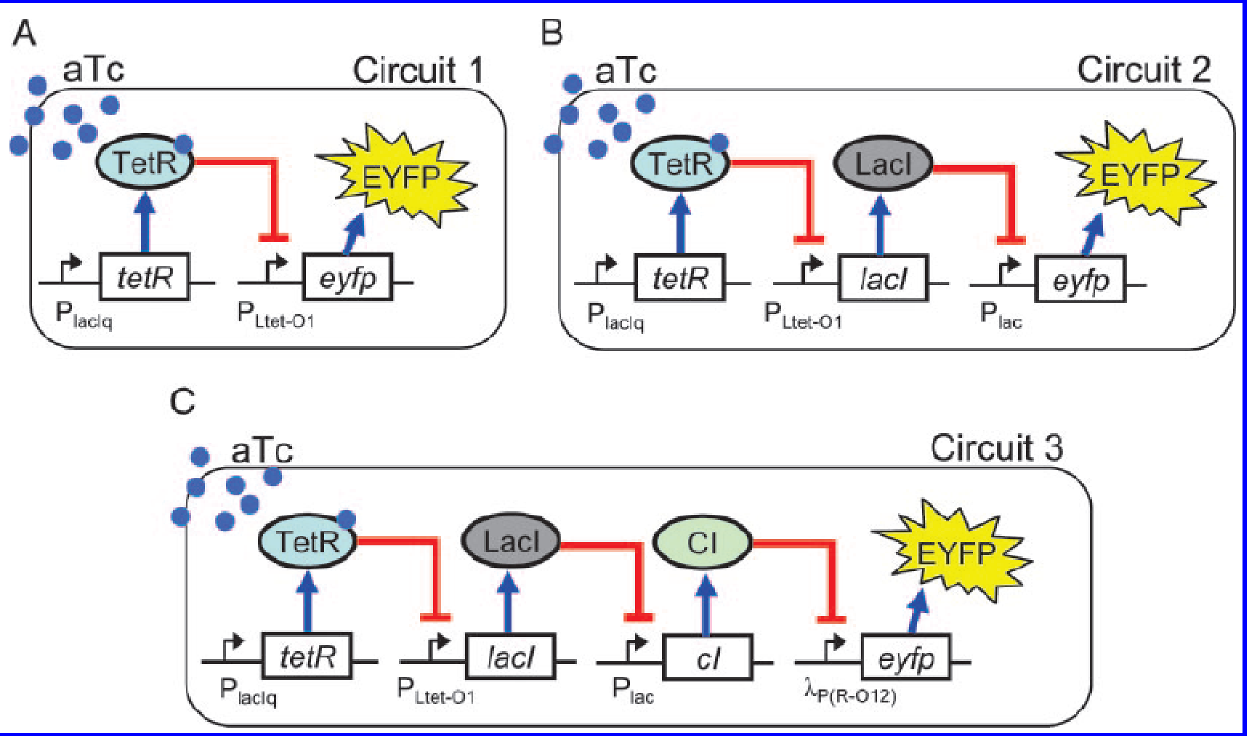
Noise can be transmitted from one gene, in this case a transcription factor, to a downstream target. The intrinsic and global extrinsic noise of the transcription factor can cause extrinsic noise in the downstream gene.



Global fluctuations in the repressor counteract the effects of global fluctuations in the expression of the downstream gene, which global fluctuations in a transcriptional activator will exacerbate the noise in the target gene.

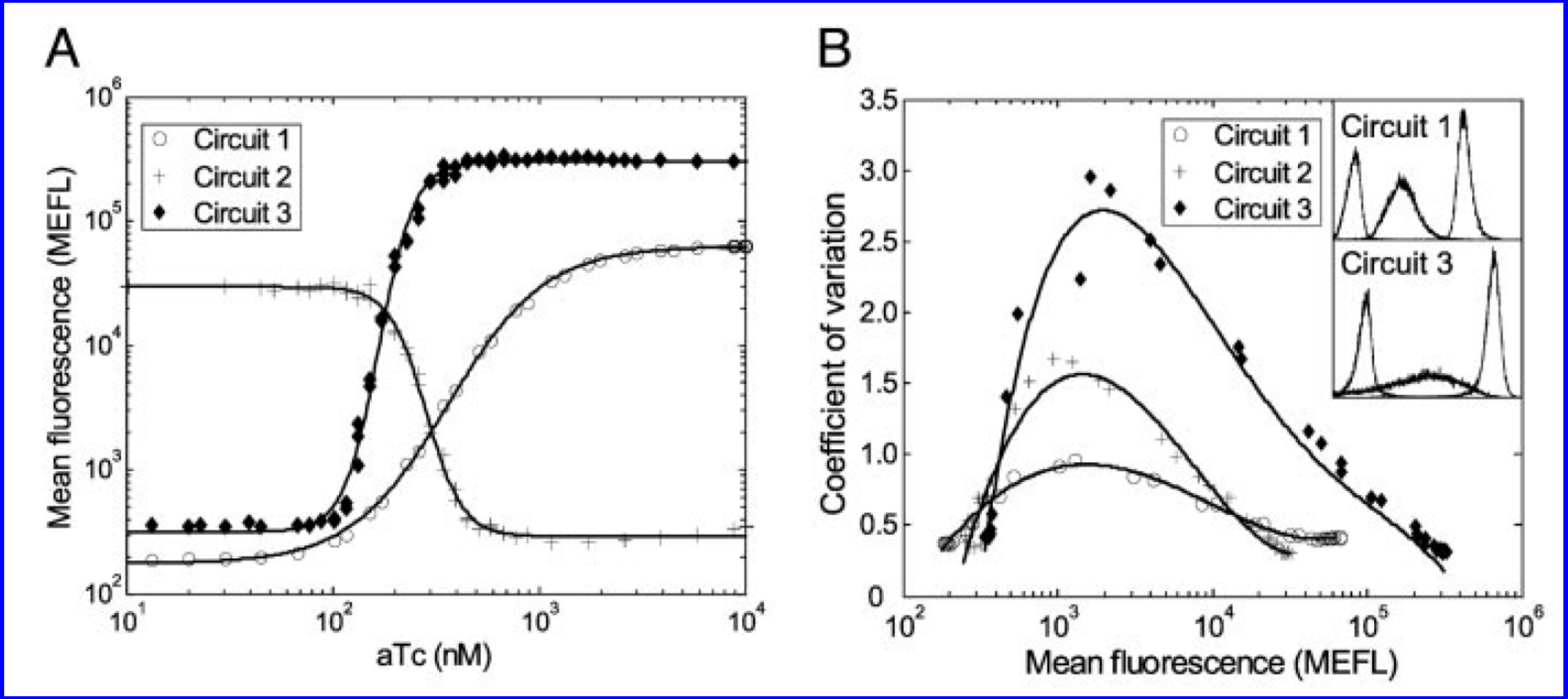
Raser JM, O'Shea EK. Science. 2005; **309**(5743): 2010-3.

Ultrasensitivity and noise propagation in a synthetic transcriptional cascade



Hooshangi Sara, Thiberge Stephan, Weiss Ron. PNAS 102:3581 (2005)

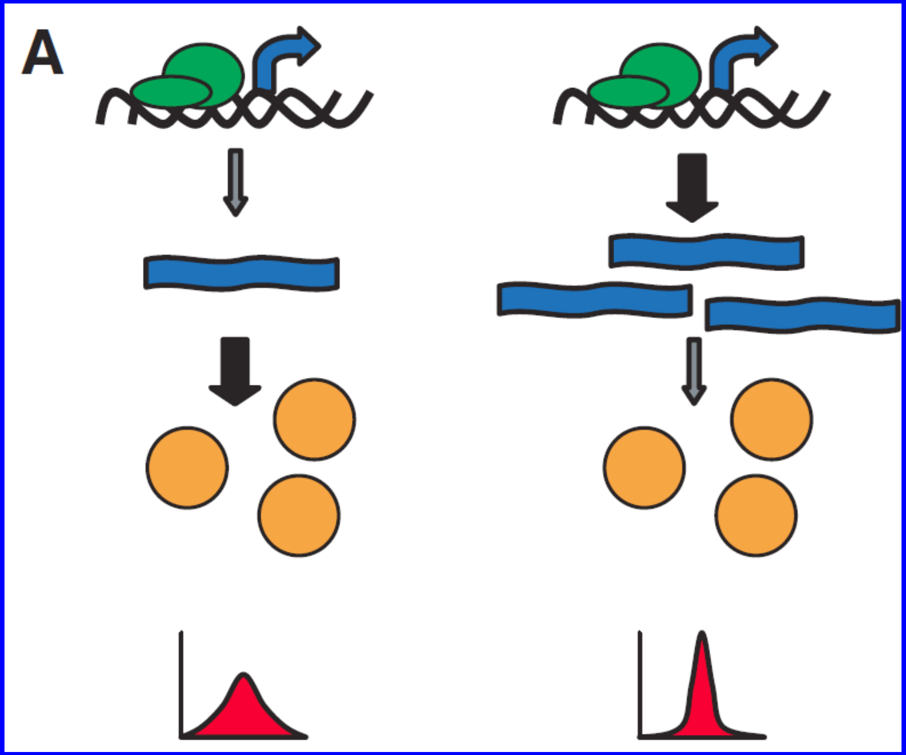
Ultrasensitivity and noise propagation in a synthetic transcriptional cascade



Hooshangi Sara, Thiberge Stephan, Weiss Ron. PNAS 102:3581 (2005)

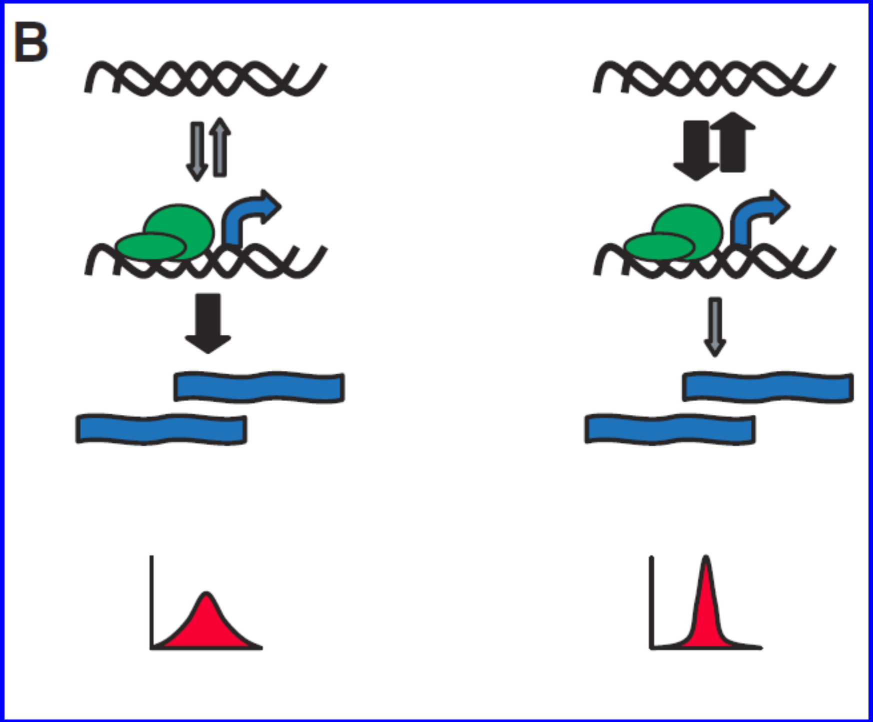
Control of noise in gene expression

Infrequent transcription followed by efficient translation results in high intrinsic noise in protein levels (left); frequent transcription and inefficient translation results in low intrinsic noise (right).



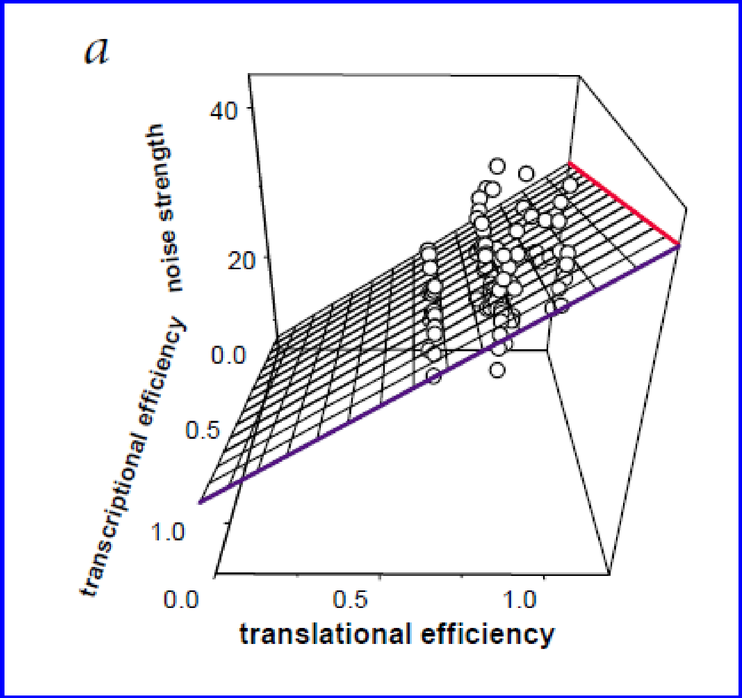
Raser JM, O'Shea EK. Science. 2005; **309**(5743): 2010-3.

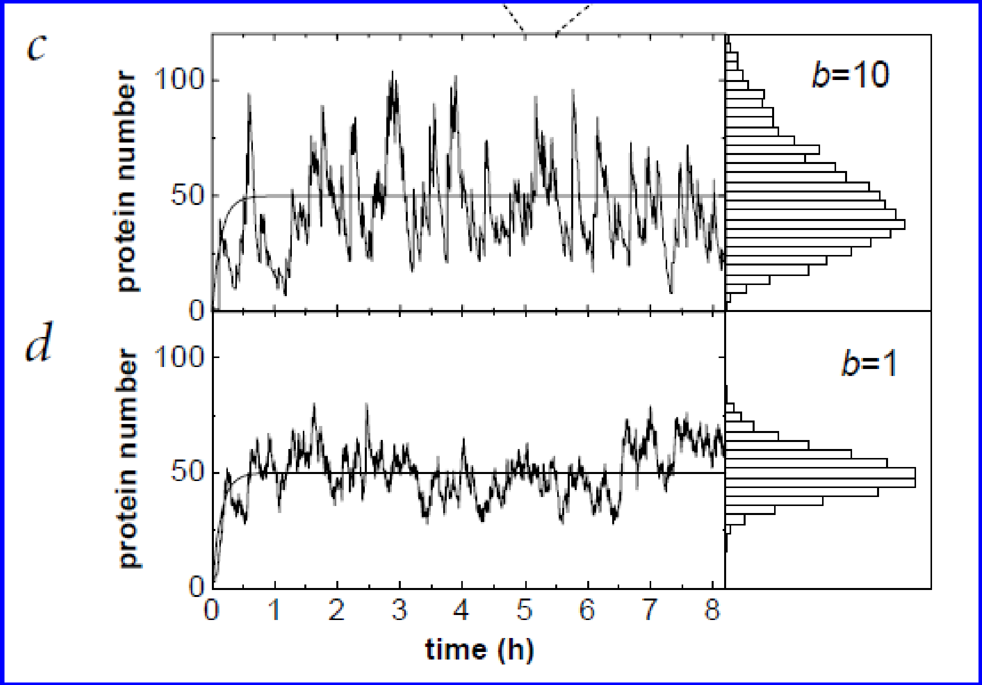
Infrequent promoter transitions between inactive and active states followed by efficient transcription result in high intrinsic noise in mRNA levels (left); frequent promoter transitions followed by inefficient transcription result in low intrinsic noise (right).



Raser JM, O'Shea EK. Science. 2005; **309**(5743): 2010-3.

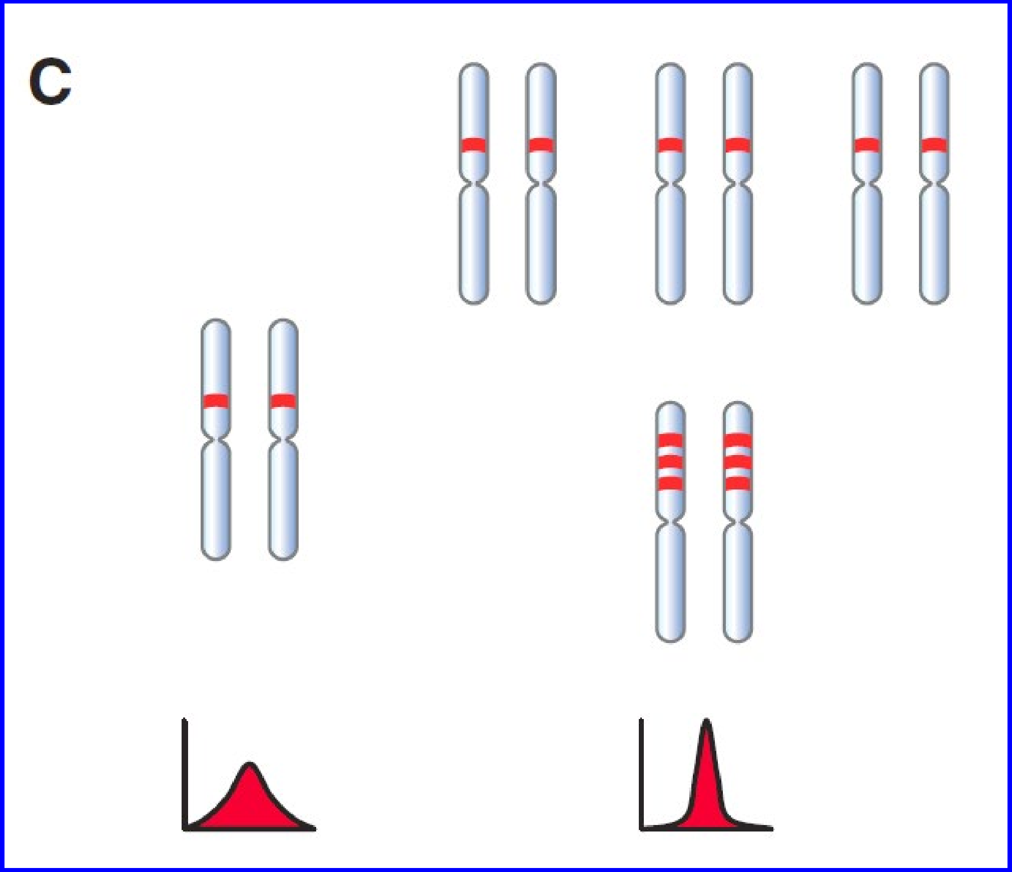
The phenotypic noise strength shows a strong positive correlation with translational efficiency.





Ozbudak, E. M., M. Thattai, et al. (2002). Nat Genet **31**(1): 69-73.

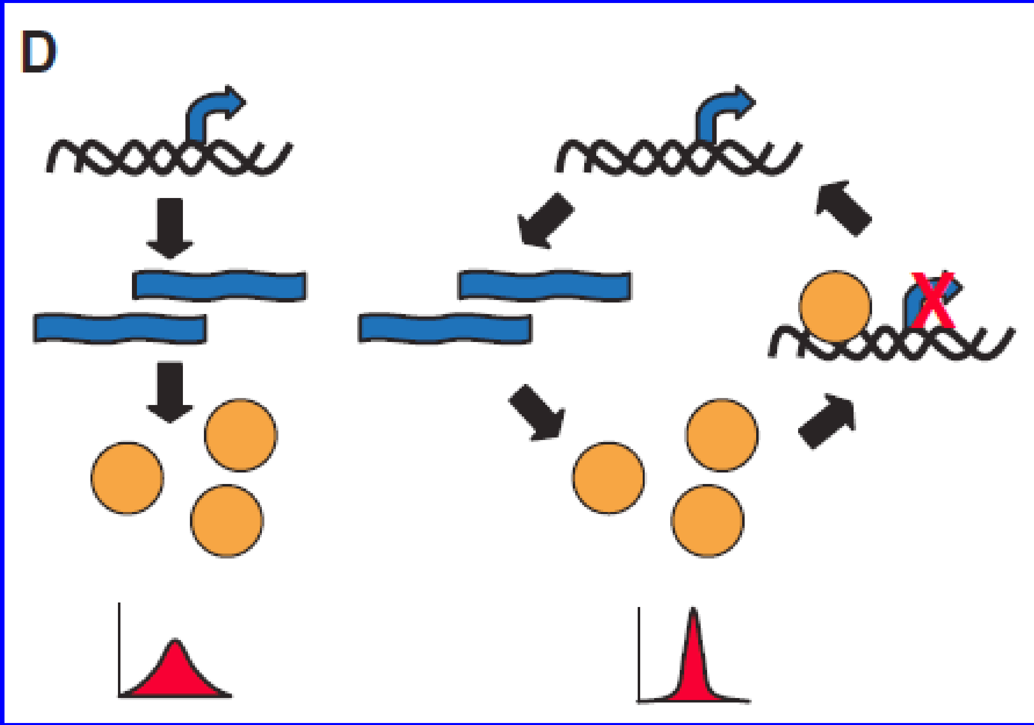
Increases in gene copy number through polyploidy (top right) or gene duplication (bottom right) result in decreased intrinsic noise relative to a single gene copy (left)



Raser JM, O'Shea EK. Science. 2005; **309**(5743): 2010-3.

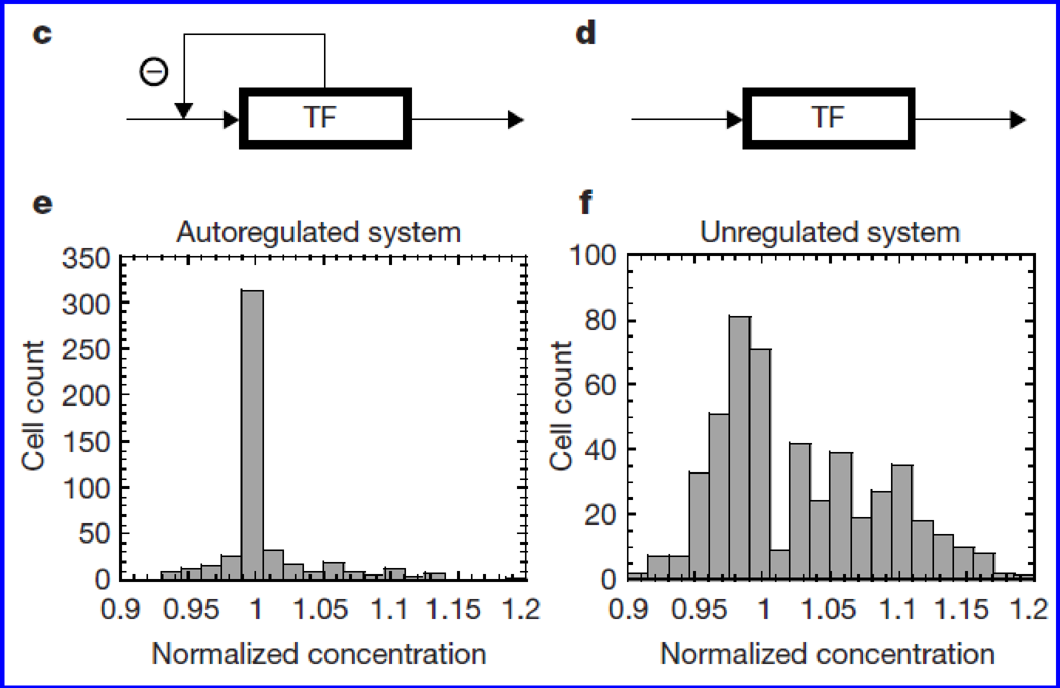
Negative feedback represses noise

Negative feedback, as when a transcription factor represses its own transcription (right), results in decreased noise relative to a linear pathway (left)



Becskei, A. and L. Serrano (2000). Nature **405**(6786): 590-593.

Negative feedback loops in gene circuits provide stability, thereby limiting the range over which the concentrations of network components fluctuate.



Becskei, A. and L. Serrano (2000). Nature **405**(6786): 590-593.

Positive feedback produces a bimodal distribution in population

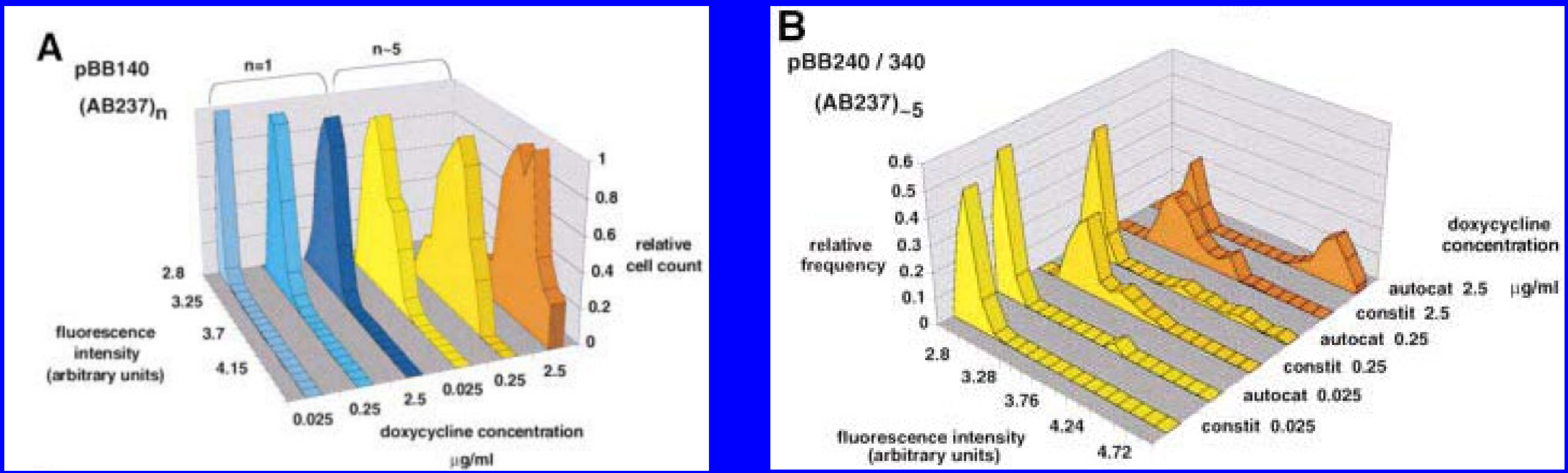


Fig. 2. Distribution of cell fluorescence intensities in chromosomal reporter systems. (**A**) The constitutive plasmid pBB140 (CMV

Becskei, A., B. Séraphin, et al. (2001). EMBO J, 20,2528-2535

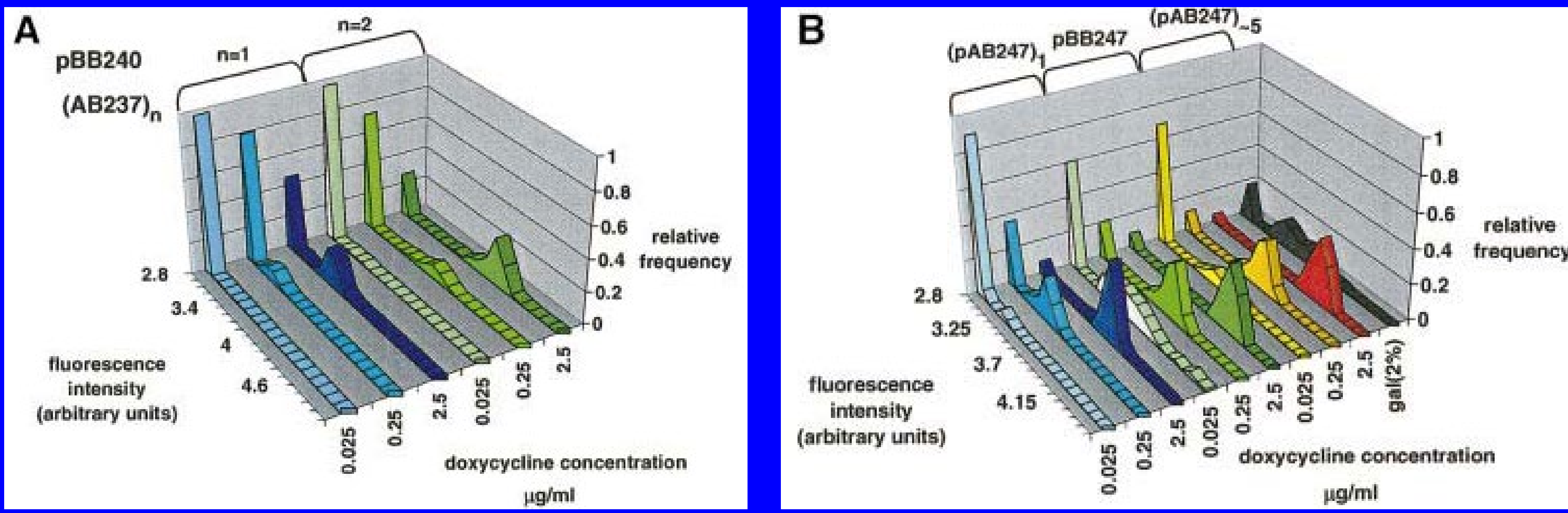


Fig. 4. Fluorescence level distributions in the autocatalytic systems.

Becskei, A., B. Séraphin, et al. (2001). EMBO J, 20,2528-2535

Assignment 8

Reproducing Fig2C-G (stochastic case) in the following paper: Brandman, O., J. E. Ferrell, Jr., et al. (2005). Science **310**(5747): 496-498.

1) One loop

$$\frac{dOUT}{dt} = k_{out\_on} * A * (1 - OUT) - k_{out\_off} * OUT + k_{out\_min}$$

$$\frac{dA}{dt} = [stimulus * \frac{OUT^n}{OUT^n + ec_{50}^n} * (1 - A) - A + k_{min}] * \tau_A$$

2) Two loops

$$\frac{dOUT}{dt} = k_{out\_on} * (A + B) * (1 - OUT) - k_{out\_off} * OUT + k_{out\_min}$$

$$\frac{dA}{dt} = [stimulus * \frac{OUT^n}{OUT^n + ec_{50}^n} * (1 - A) - A + k_{min}] * \tau_A$$

$$\frac{dB}{dt} = [stimulus * \frac{OUT^n}{OUT^n + ec_{50}^n} * (1 - B) - B + k_{min}] * \tau_B$$