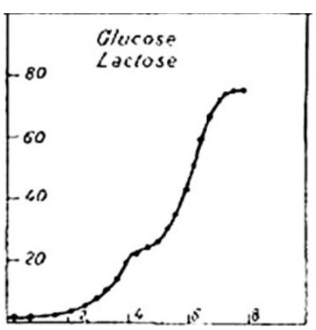
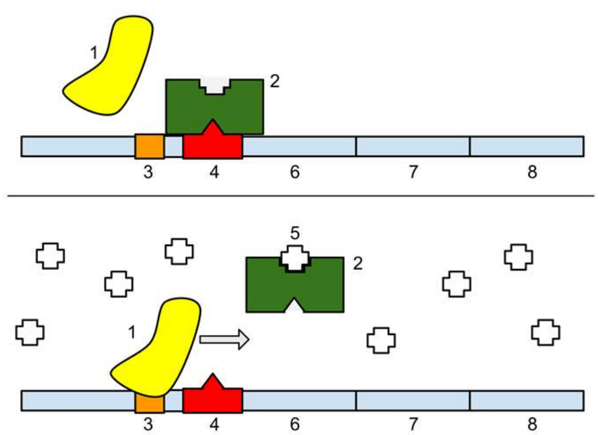
Quantitative principles in biological systems

5. Gene regulation and statistical mechanics

Spring 2026

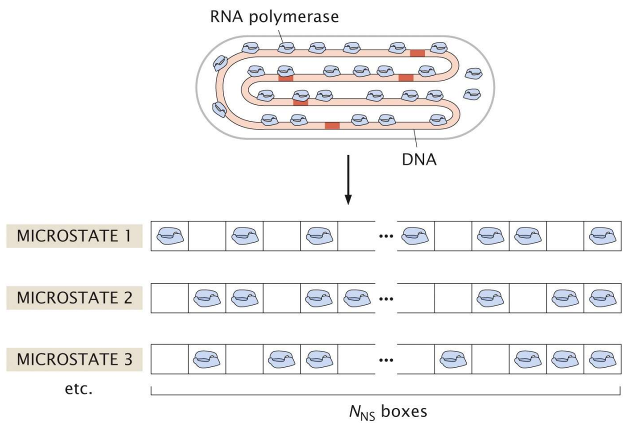
The *lac* operon will be our model system for gene regulation.





Monod (1942)
Wikipedia

Crash course on stat mech



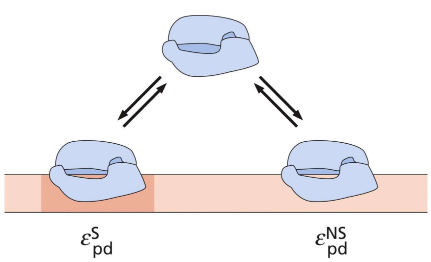
Fundamental principle

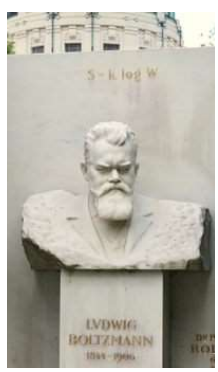
At equilibrium, all microstates occur with equal probability.

$$p = \frac{1}{W}$$

Phillips et al

The probability of a microstate is given by the Boltzmann distribution.





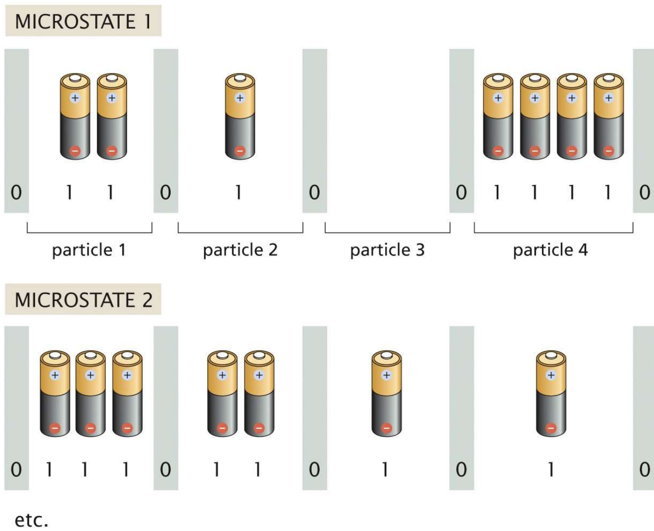
Boltzmann distribution

The probability of a state with energy E is:

$$p(E) = \frac{1}{Z} e^{-\frac{E}{kT}}$$

Phillips et al

The probability of a microstate is given by the Boltzmann distribution.



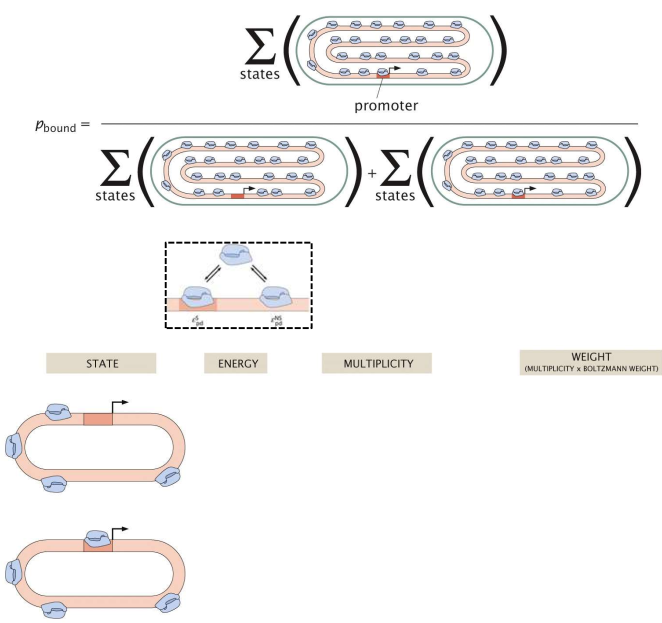
<u>Boltzmann distribution</u>

The probability of a state with energy E is:

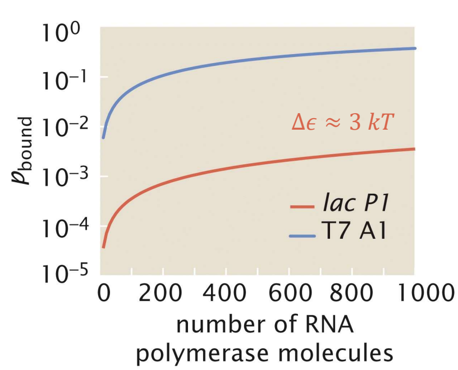
$$p(E) = \frac{1}{Z} e^{-\frac{E}{kT}}$$

Phillips et al

The Boltzmann distribution allows us to write down binding probabilities.



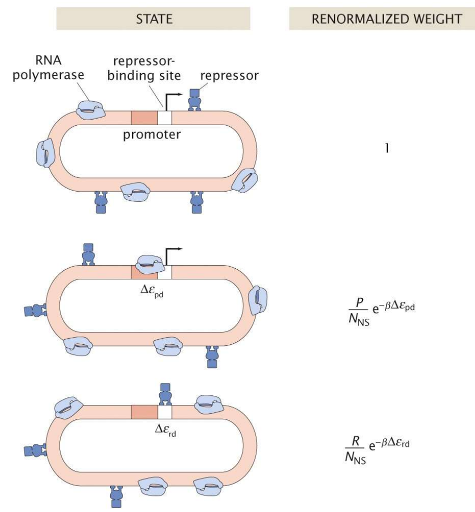
$$\boxed{p_{bound} = \frac{1}{1 + \frac{N_{NS}}{P} e^{\frac{-\Delta\epsilon}{kT}}}}$$



Phillips et al

Parameter-free predictions of Lac repression.

$$p_{\text{bound}} = \frac{1}{1 + \frac{N_{NS}}{P} e^{\frac{-\Delta\epsilon_{pd}}{kT}} \left(1 + \frac{R}{N_{NS}} e^{\frac{-\Delta\epsilon_{rd}}{kT}}\right)}$$



Phillips et al

Parameter-free predictions of Lac repression.

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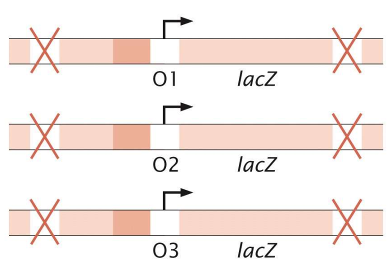
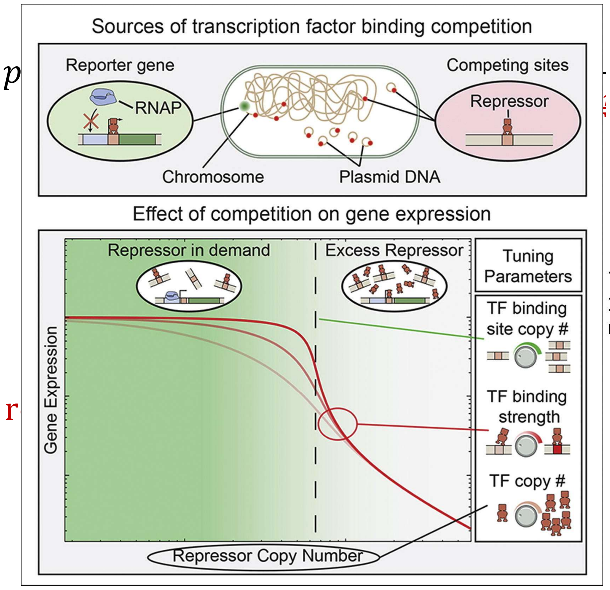
$$\text{repression} = \frac{p_{\text{bound}}(R = 0)}{p_{\text{bound}}(R \neq 0)}$$

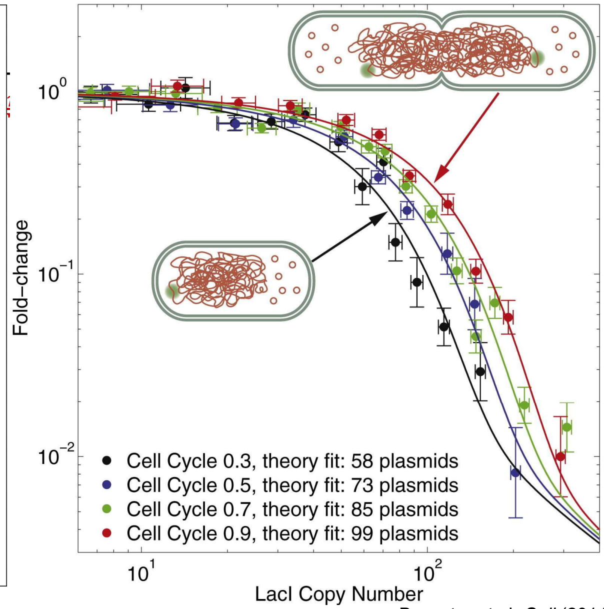


repression		
50	number of repressors	900
200		4700
21		320
1.3		16

Oehler et al. *EMBO J* (1994)
Phillips et al

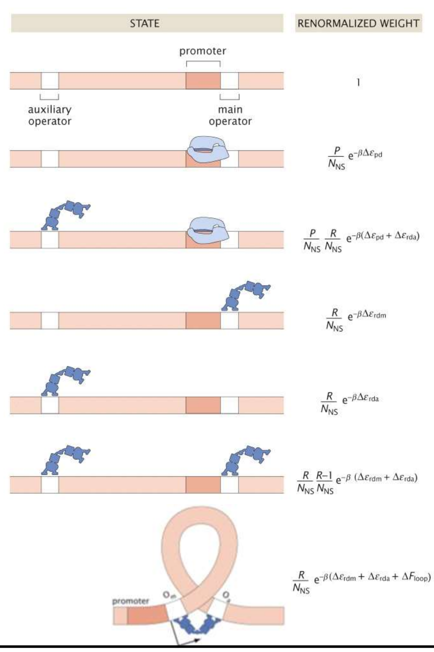
Parameter-free predictions of Lac repression.

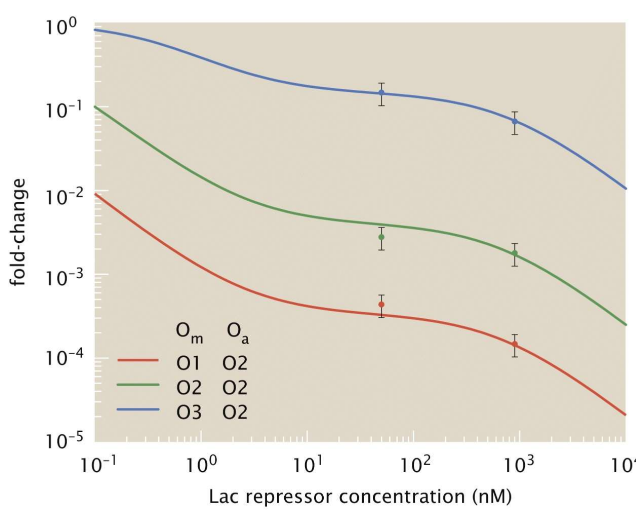




Brewster et al. *Cell* (2014)

Parameter-free predictions of Lac repression.





Oehler et al. *EMBO J* (1994)
Phillips et al

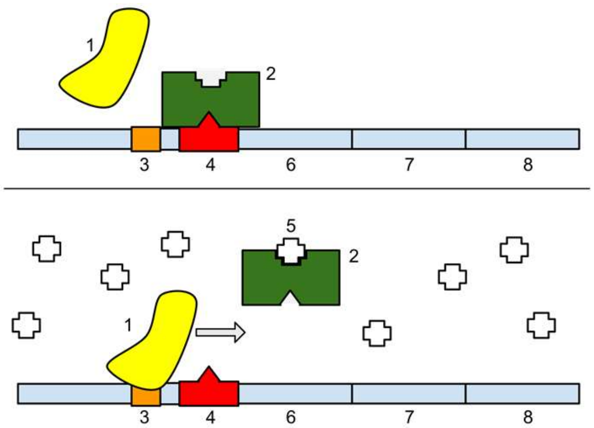
The *lac* operon forms a positive feedback circuit.

$$\dot{X} = Y - \gamma X + \xi$$

inducer: X; import: Y; degradation: γX; supply: ξ

$$\dot{Y} = \frac{X^2}{1+X^2} - Y$$

transporter: Y; induction: $\frac{X^2}{1+X^2}$



Bingkan Xue

The *lac* operon forms a positive feedback circuit.

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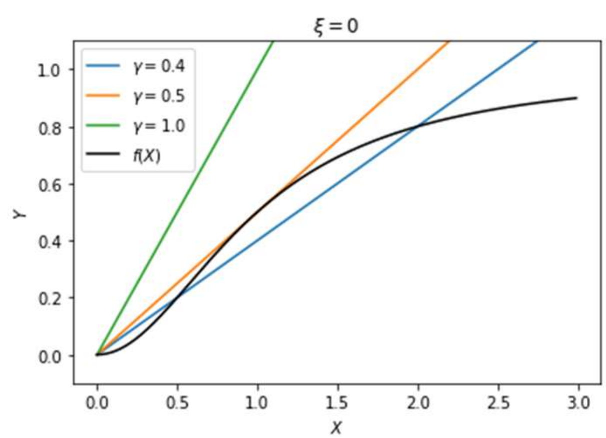
$$\dot{Y} = \frac{X^2}{1+X^2} - Y$$

transporter: Y; induction $f(x)$: $\frac{X^2}{1+X^2}$



Bingkan Xue

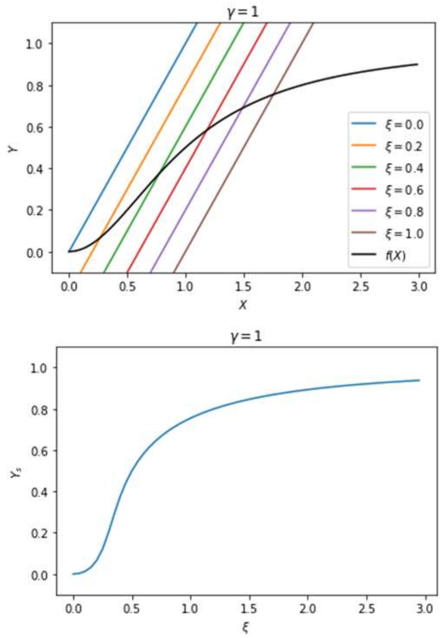
The *lac* operon forms a positive feedback circuit.

inducer, import, degradation, supply

$$\dot{X} = Y - {\color{red}\gamma} X + {\color{red}\xi}$$

$$\dot{Y} = \frac{X^2}{1 + X^2} - Y$$

transporter, induction $f(x)$



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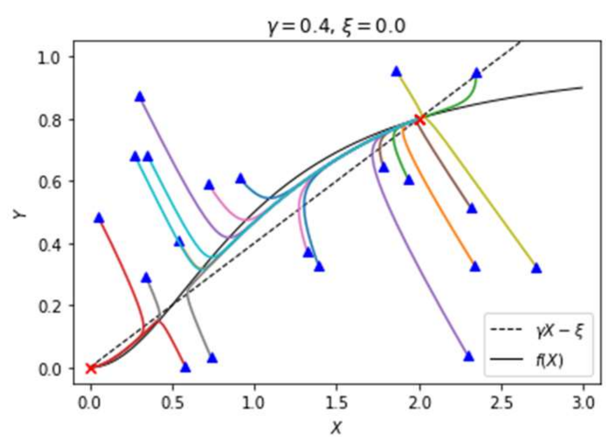

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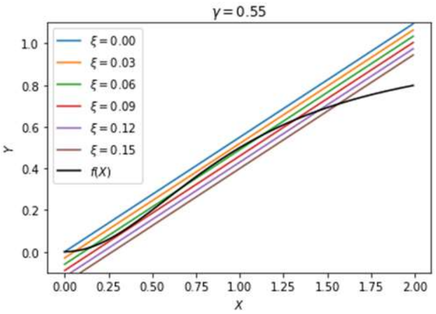

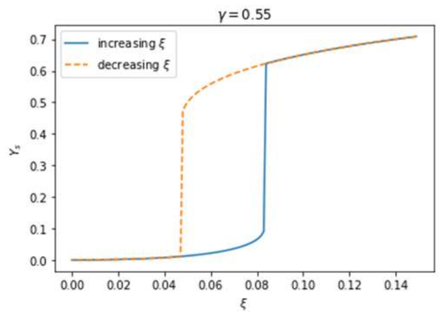

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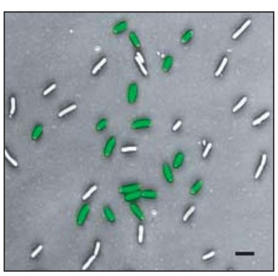
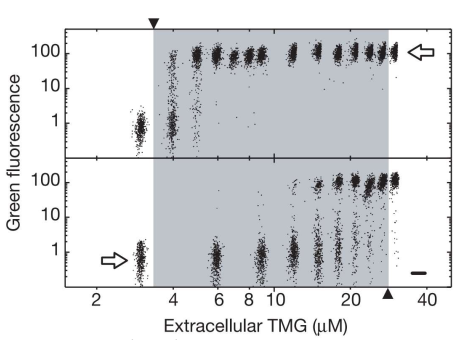
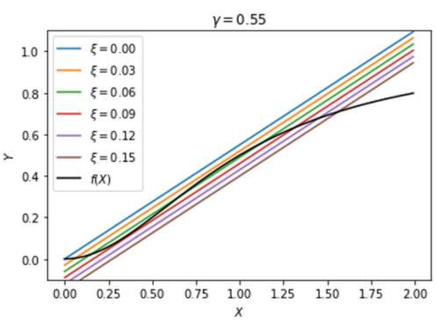
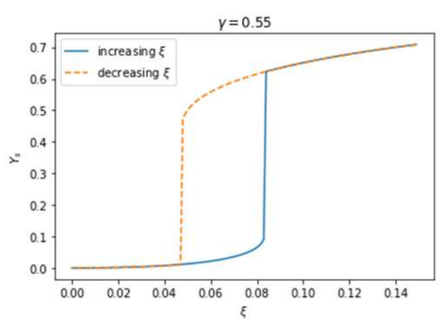




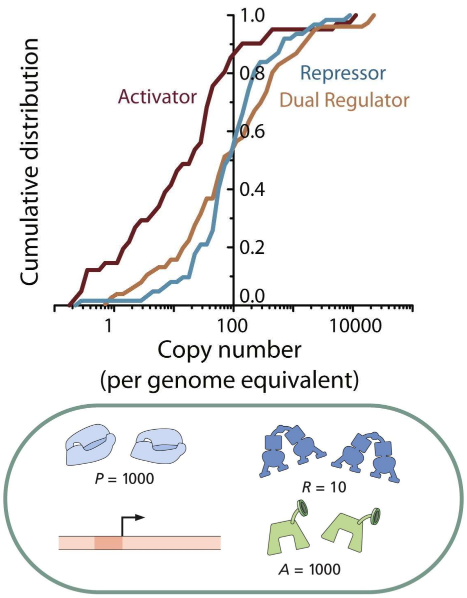


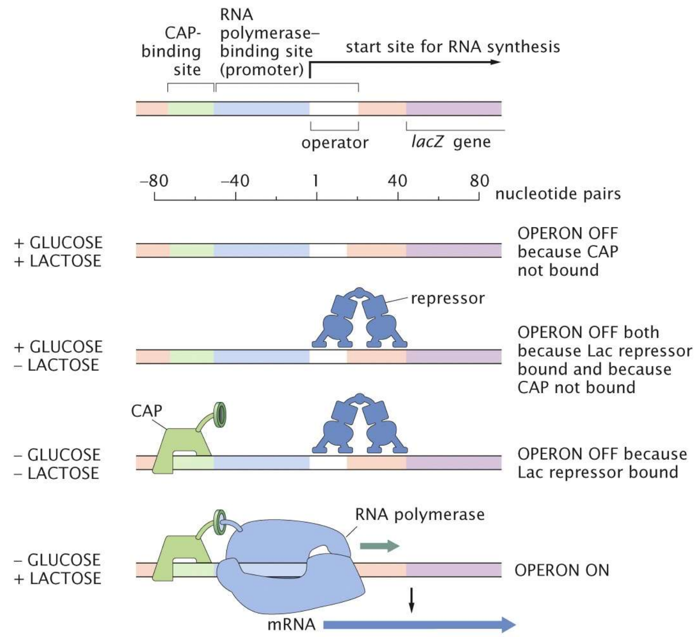


Ozbudak et al. *Nature* (2004)

Bingkan Xue

Activate or repress?

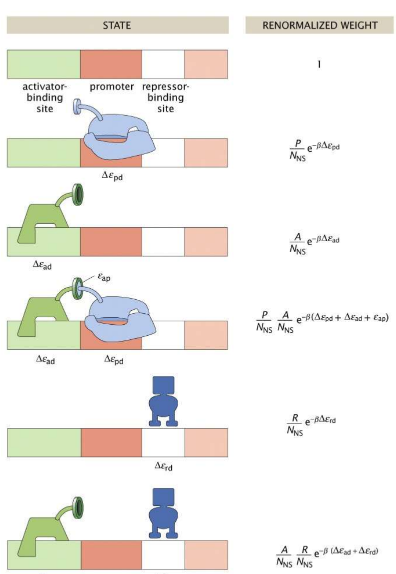


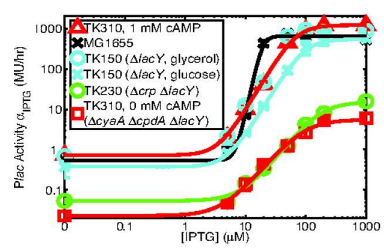


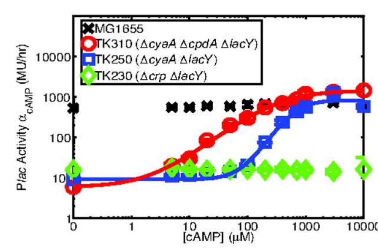
Gene-Wei Li et al. *Cell* (2014)

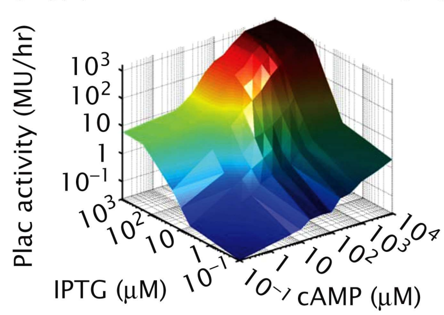
Phillips et al

The *lac* operon is regulated by both a repressor and an activator.





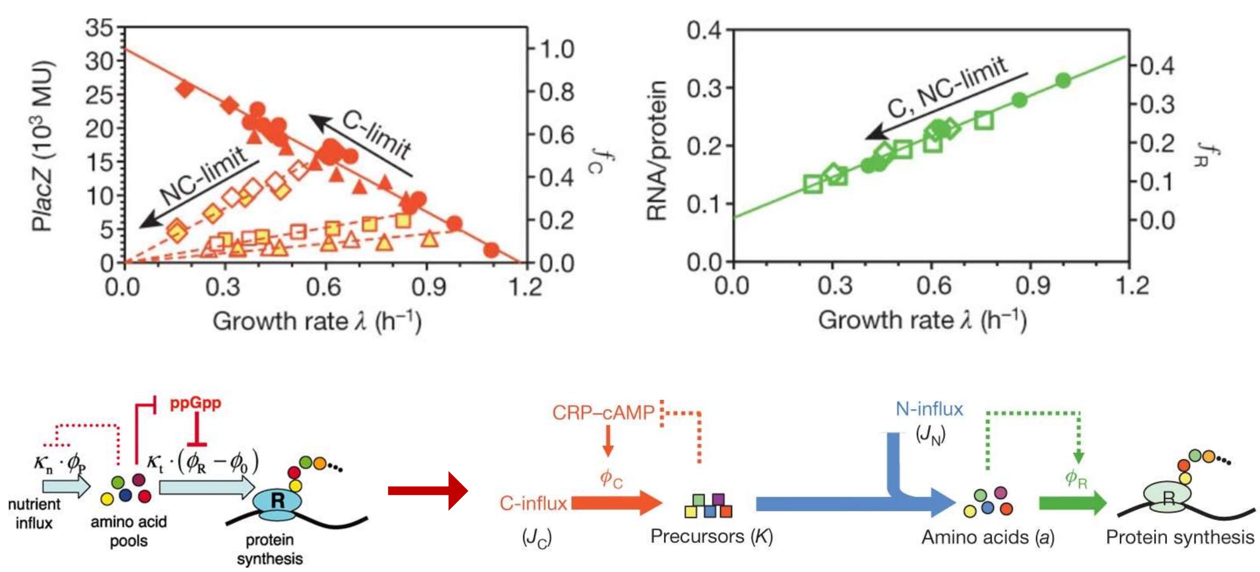




Gerland et al. *PNAS* (2007)

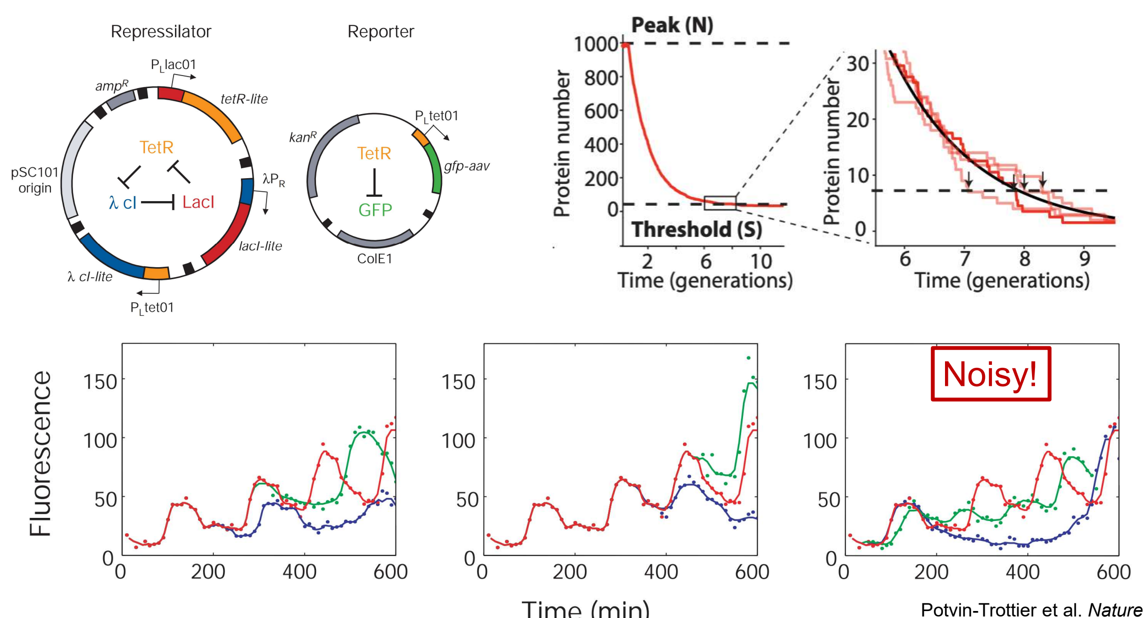
Phillips et al

New growth laws emerge from CAP regulation.



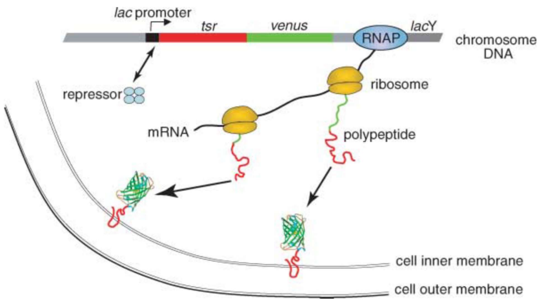
You et al. *Nature* (2013)

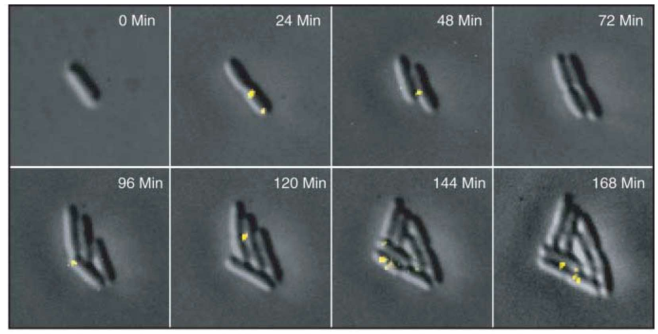
Synthetic transcriptional networks



Potvin-Trottier et al. *Nature* (2016)
Elowitz and Leibler. *Nature* (2000)

Measuring noise





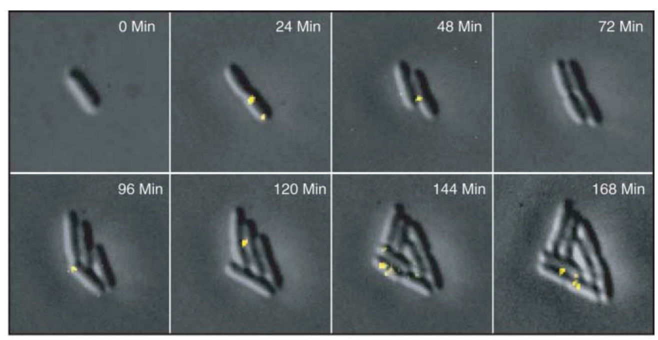
Ji Yu et al. *Science* (2006)

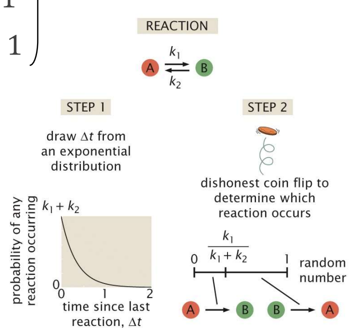
Measuring noise

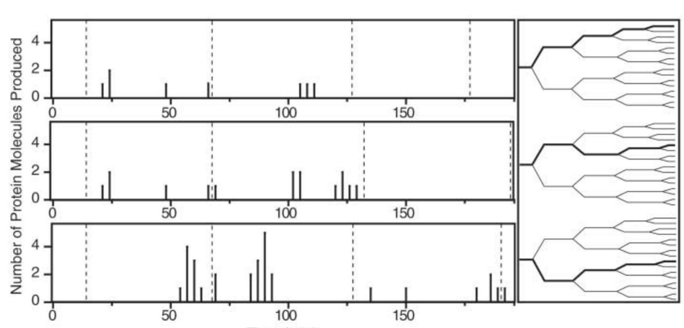
$$\mathrm{DNA} \xrightarrow{k_1} \mathrm{mRNA} \xrightarrow{k_2} \mathrm{Protein}$$
$$\gamma_1 \downarrow \varnothing \qquad \gamma_2 \downarrow \varnothing$$

$$\left.\begin{aligned} M &\xrightarrow{k_1} M+1 \\ M &\xrightarrow{\gamma_1 M} M-1 \\ P &\xrightarrow{k_2} P+1 \\ P &\xrightarrow{\gamma_2 P} P-1 \end{aligned}\right\}$$

Can simulate via the Gillespie algorithm.







Ji Yu et al. *Science* (2006)

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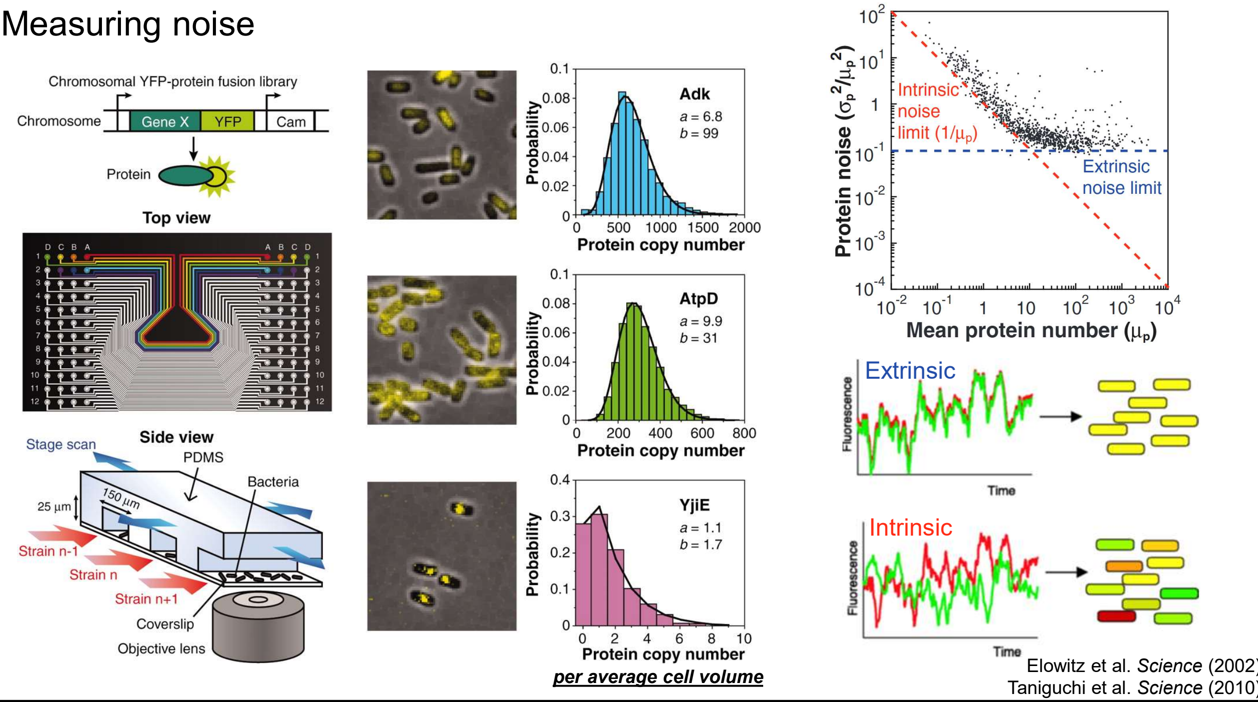
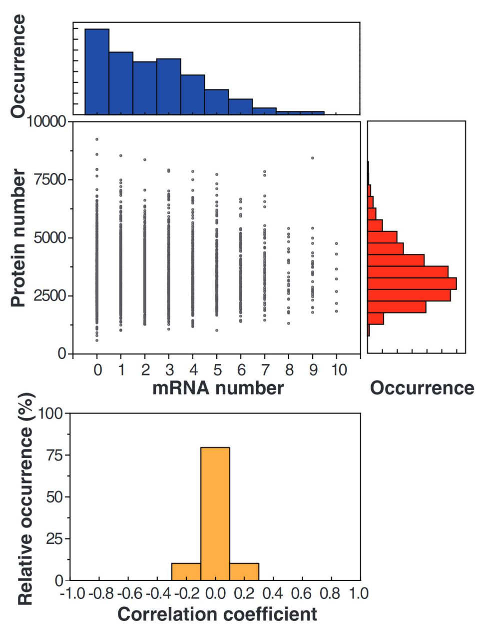


Elowitz et al. *Science* (2002)
Taniguchi et al. *Science* (2010)

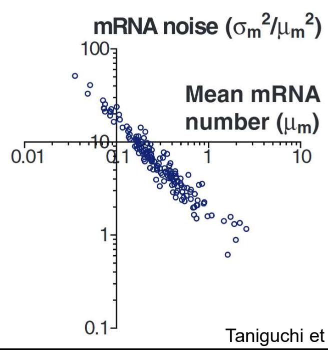
Measuring noise



Quantifying *E. coli* Proteome and Transcriptome with Single-Molecule Sensitivity in Single Cells

Yuichi Taniguchi,[1*] Paul J. Choi,[1*] Gene-Wei Li,[1,2*] Huiyi Chen,[1,3*] Mohan Babu,[4] Jeremy Hearn,[1] Andrew Emili,[4,5] X. Sunney Xie[1]†

Protein and messenger RNA (mRNA) copy numbers vary from cell to cell in isogenic bacterial populations. However, these molecules often exist in low copy numbers and are difficult to detect in single cells. We carried out quantitative system-wide analyses of protein and mRNA expression in individual cells with single-molecule sensitivity using a newly constructed yellow fluorescent protein fusion library for *Escherichia coli*. We found that almost all protein number distributions can be described by the gamma distribution with two fitting parameters which, at low expression levels, have clear physical interpretations as the transcription rate and protein burst size. At high expression levels, the distributions are dominated by extrinsic noise. We found that a single cell's protein and mRNA copy numbers for any given gene are uncorrelated.



Taniguchi et al. *Science* (2010)

Summary

- Transcriptional regulation is a stochastic process that can be quantitatively understood and controlled.

- Toolbox for modeling biological systems: stochastic processes, chemical reaction networks, coarse-grained models, … and more to come!