BE/APH161 – PHYSICAL BIOLOGY OF THE CELL

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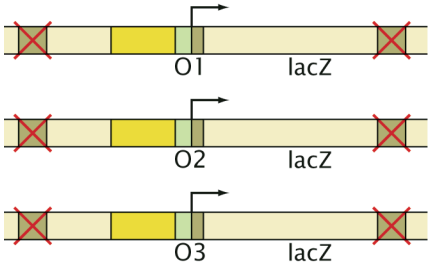
CONFRONTING THEORY AND EXPERIMENT: A SIMPLE CASE

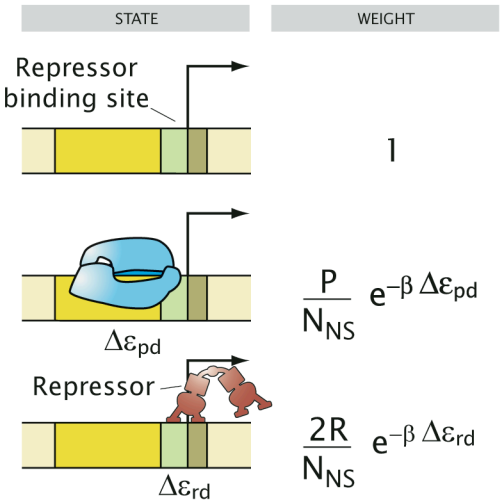
$$fold\ change = \left(1 + \frac{R}{N} e^{-\beta \Delta\varepsilon}\right)^{-1}$$

Fold-change

50 Number of repressors 900 $\Delta\varepsilon_{rd}$ (k_BT)



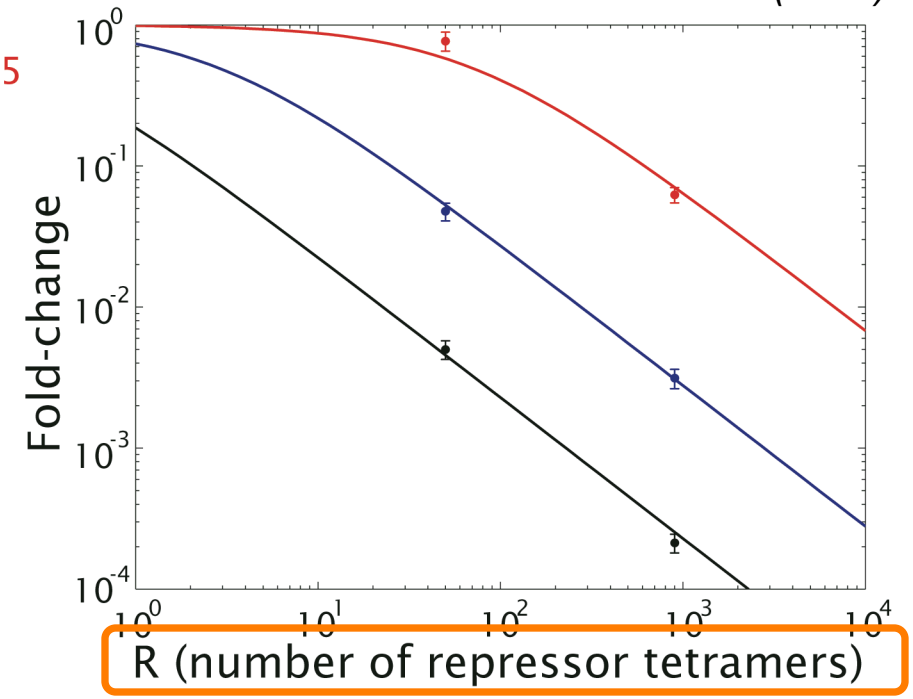
O1	5×10^{-3}	2.1×10^{-4}	-16.2
O2	0.048	3.1×10^{-3}	-13.7
O3	0.77	0.063	-10.5



Oehler et al. (1994)

Becker et al. (2005)
Vilar and Leibler (2003)

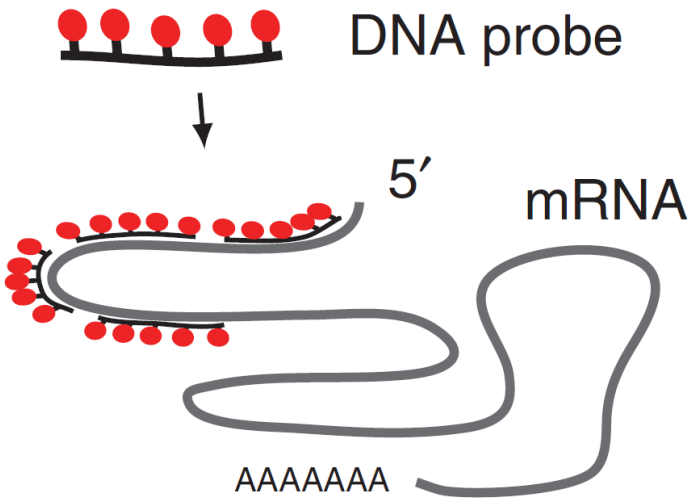
Bintu et al. (2005)

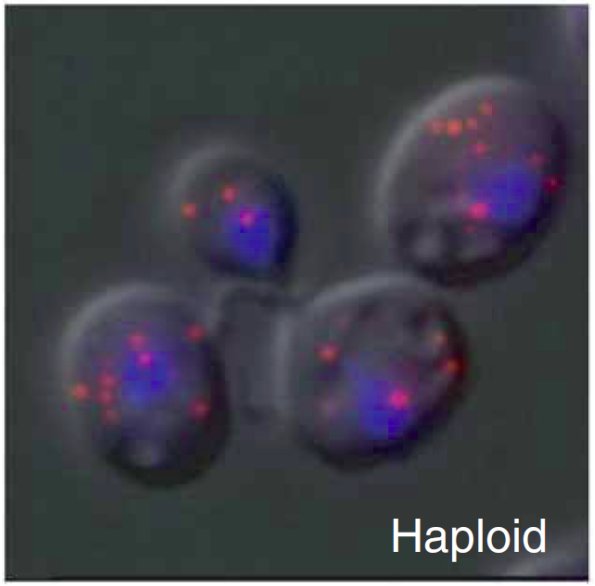


COUNTING MESSENGER RNAS IN CELLS

- *Fixed cells*

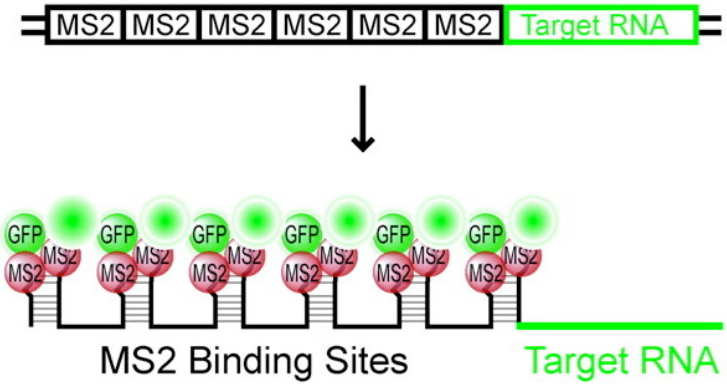
  Zenklusen et al. '08

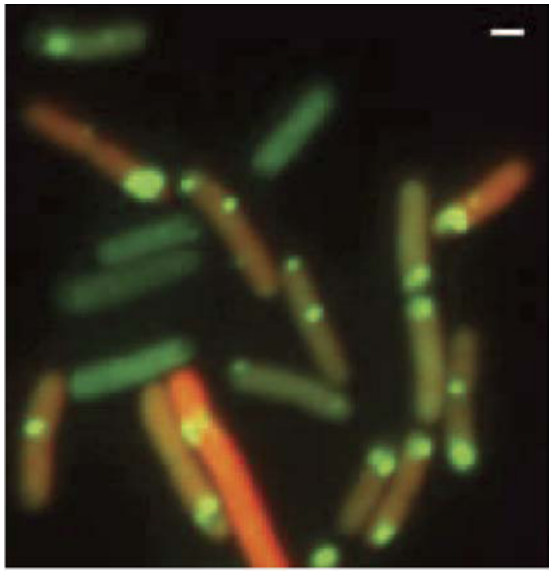




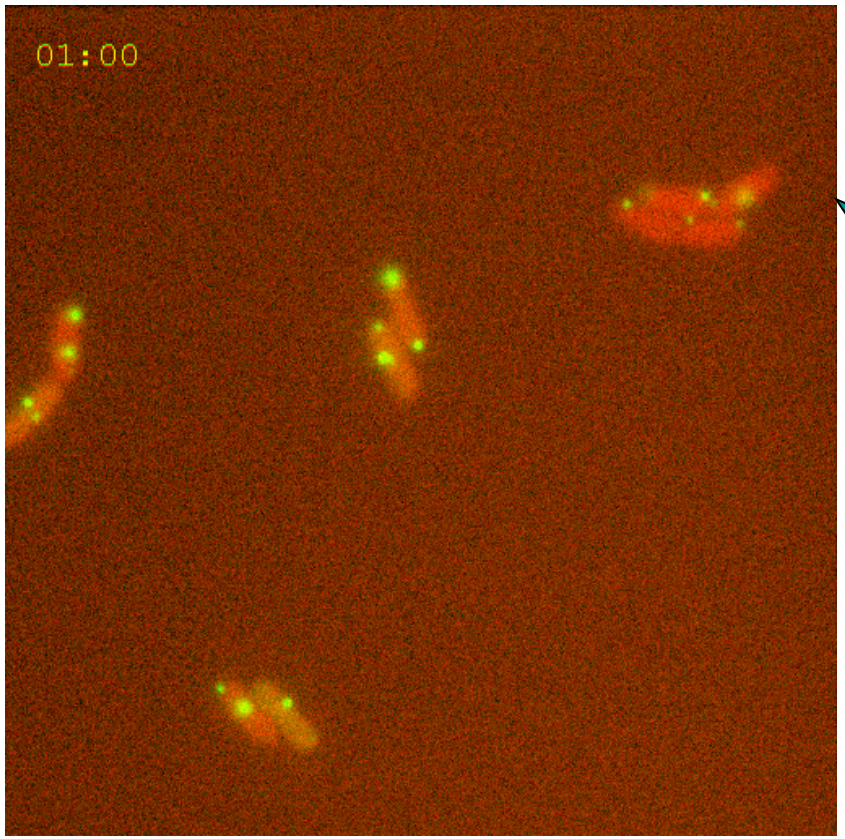
- *Live cells*

  Golding et al. '05

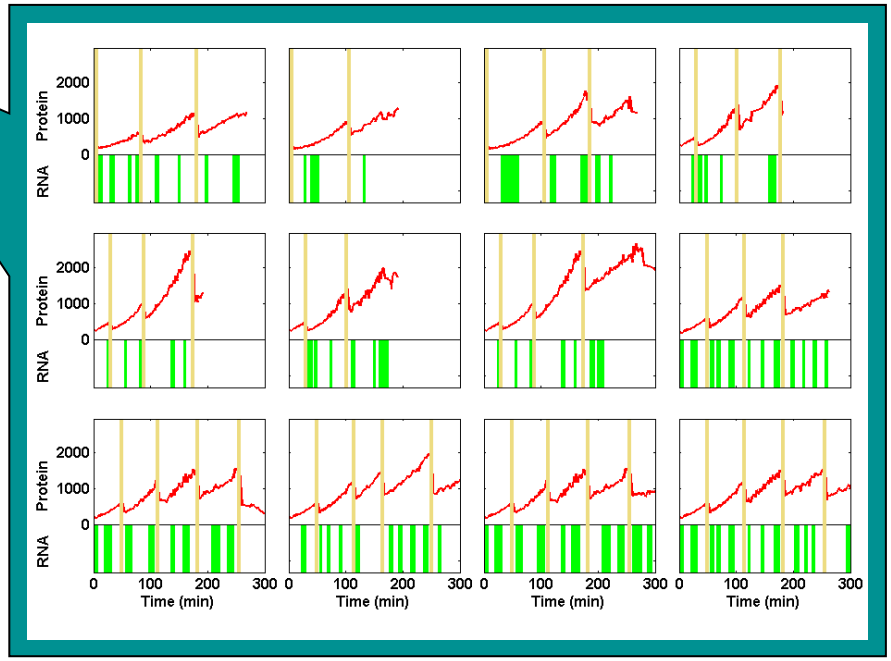




INFORMATION PROCESSING IN LIVING CELLS: BEYOND FIRST APPROXIMATIONS



Ido Golding



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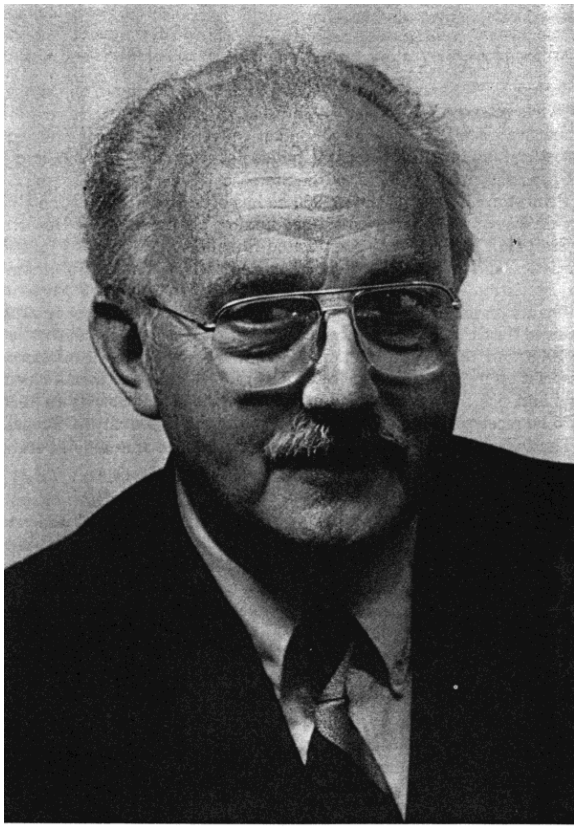
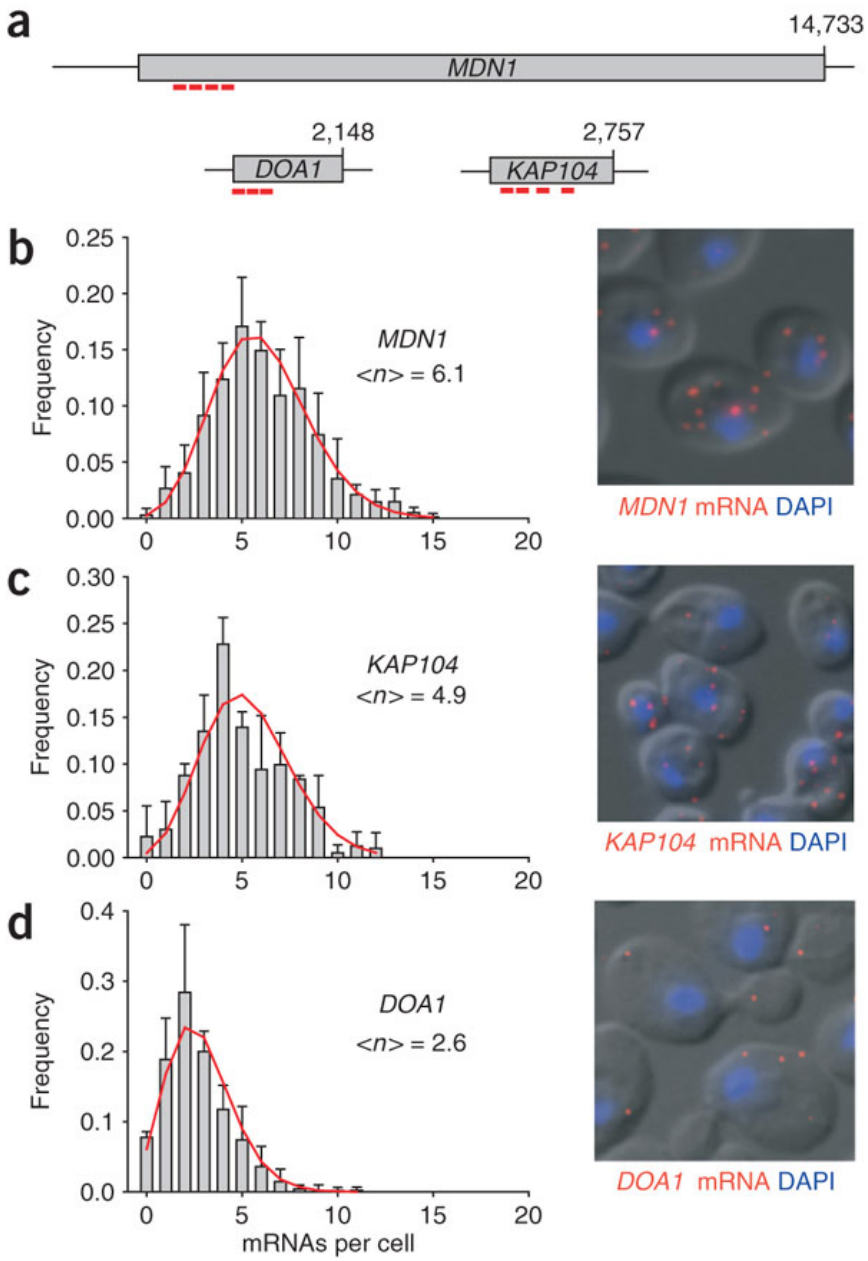


George E. P. Box

ON THE USEFULNESS OF MODELS

"It should be remembered that just as the Declaration of Independence promises the pursuit of happiness rather than happiness itself, so the iterative scientific model building process offers only the pursuit of the perfect model. For even when we feel we have carried the model building process to a conclusion, some new initiative may make further improvement possible. Fortunately to be useful a model does not have to be perfect." George Box

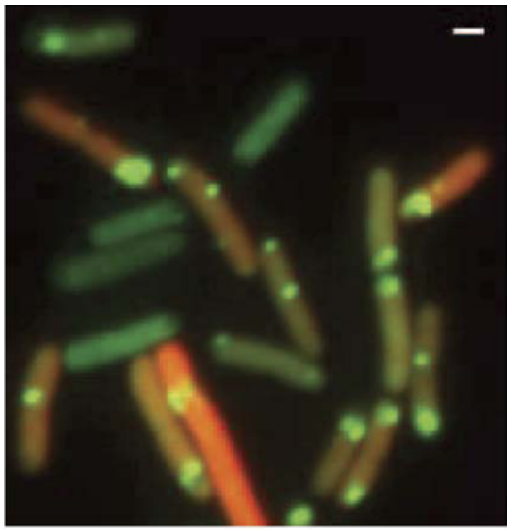
RNA DISTRIBUTION IN YEAST

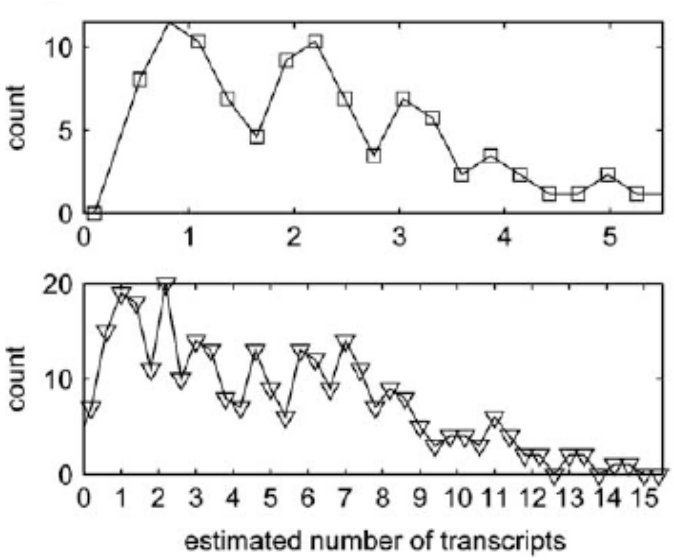


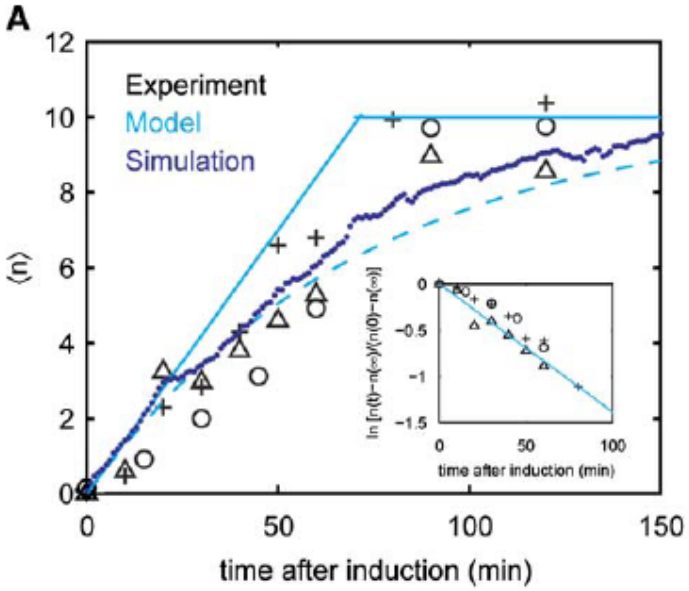
Zenklusen et al. '08

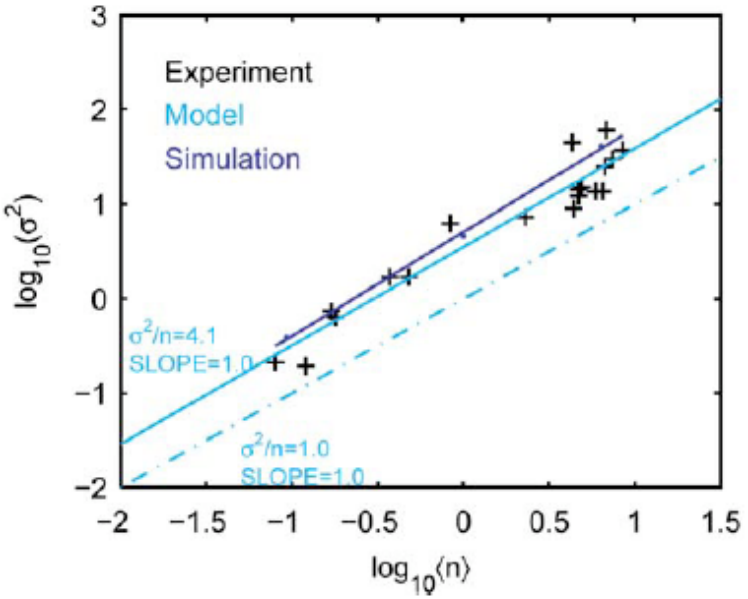
MRNA PRODUCTION IN *E.COLI*

Golding et al. '05

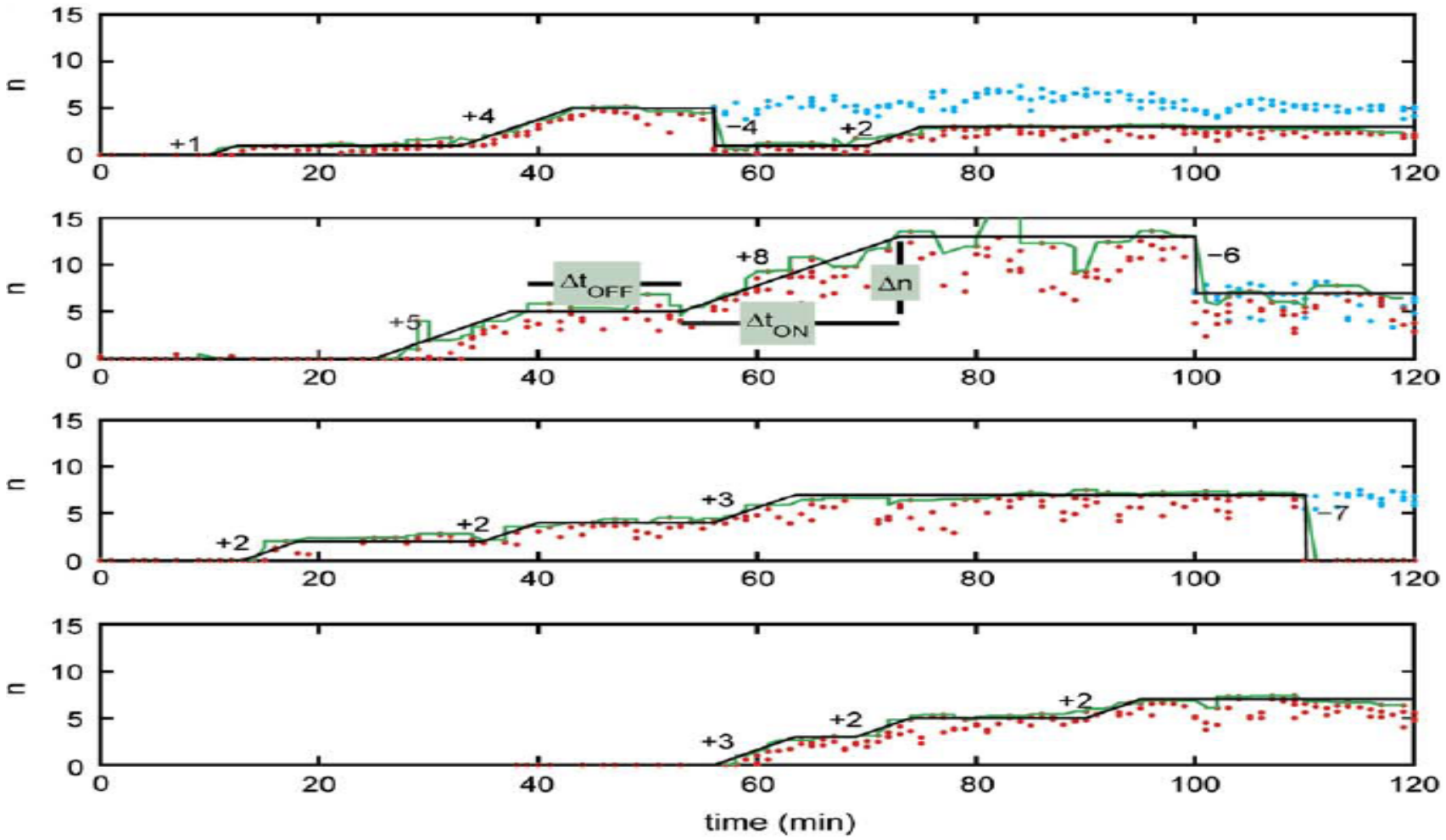




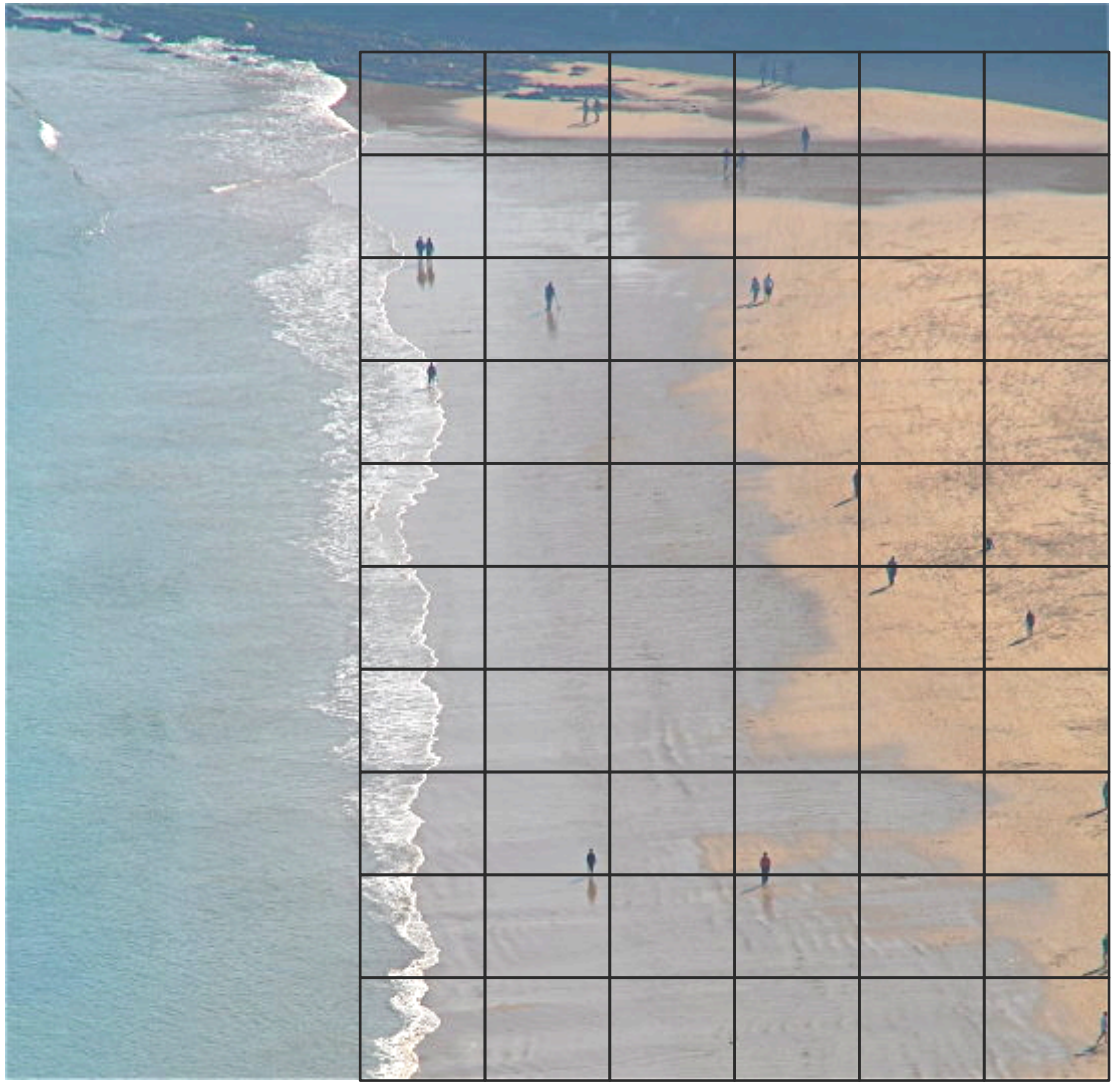




MRNA PRODUCTION HAPPENS IN BURSTS



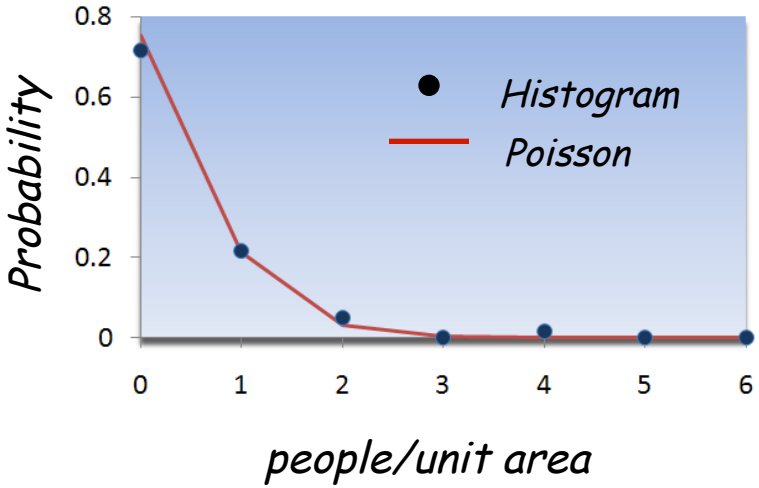
THE POISSON DISTRIBUTION



What is the distribution of people per square?

$$P(m) = \frac{e^{-\mu}\mu^{m}}{m!}$$

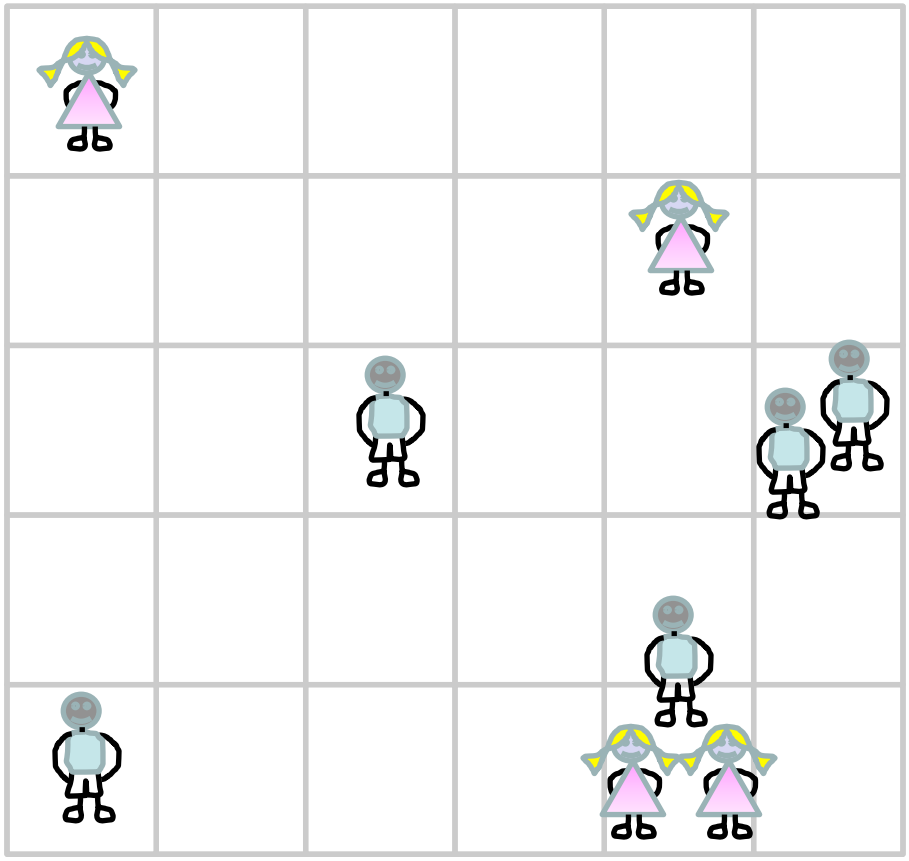
$$\mu = \frac{23 people}{60 squares} = 0.36$$



(thanks to Al Sanchez and Jane Kondev)

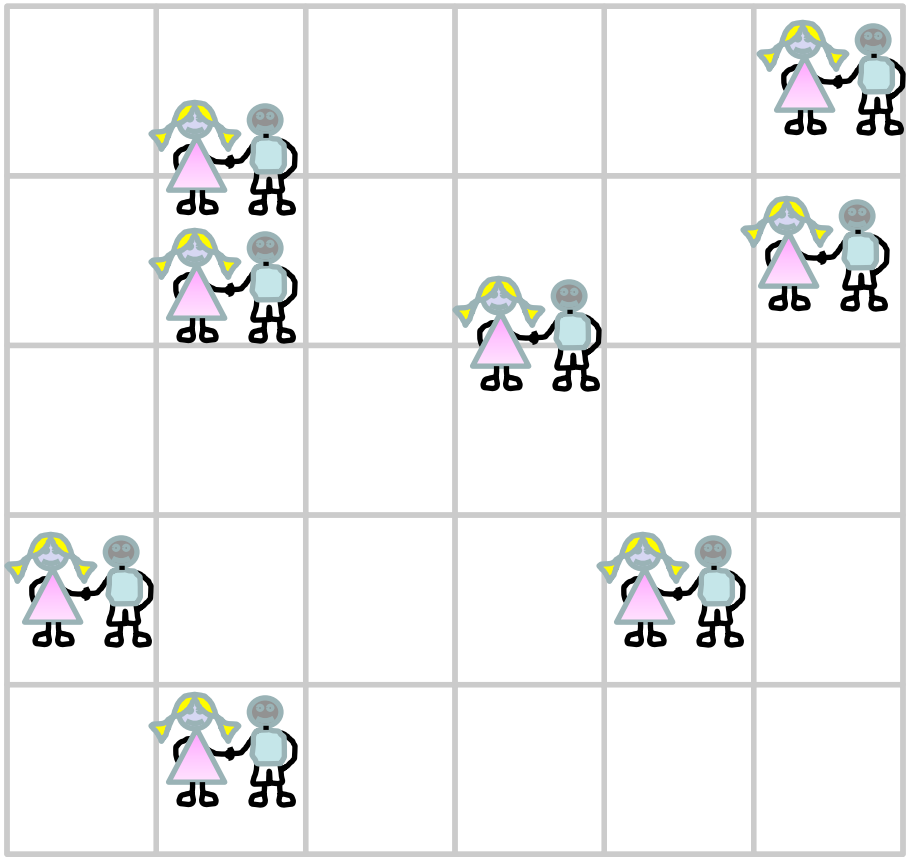
INTERACTIONS CAN CHANGE THE DISTRIBUTION

Independent singles: Poisson distribution of people



$$\mathrm{var}(P) = \langle P \rangle$$

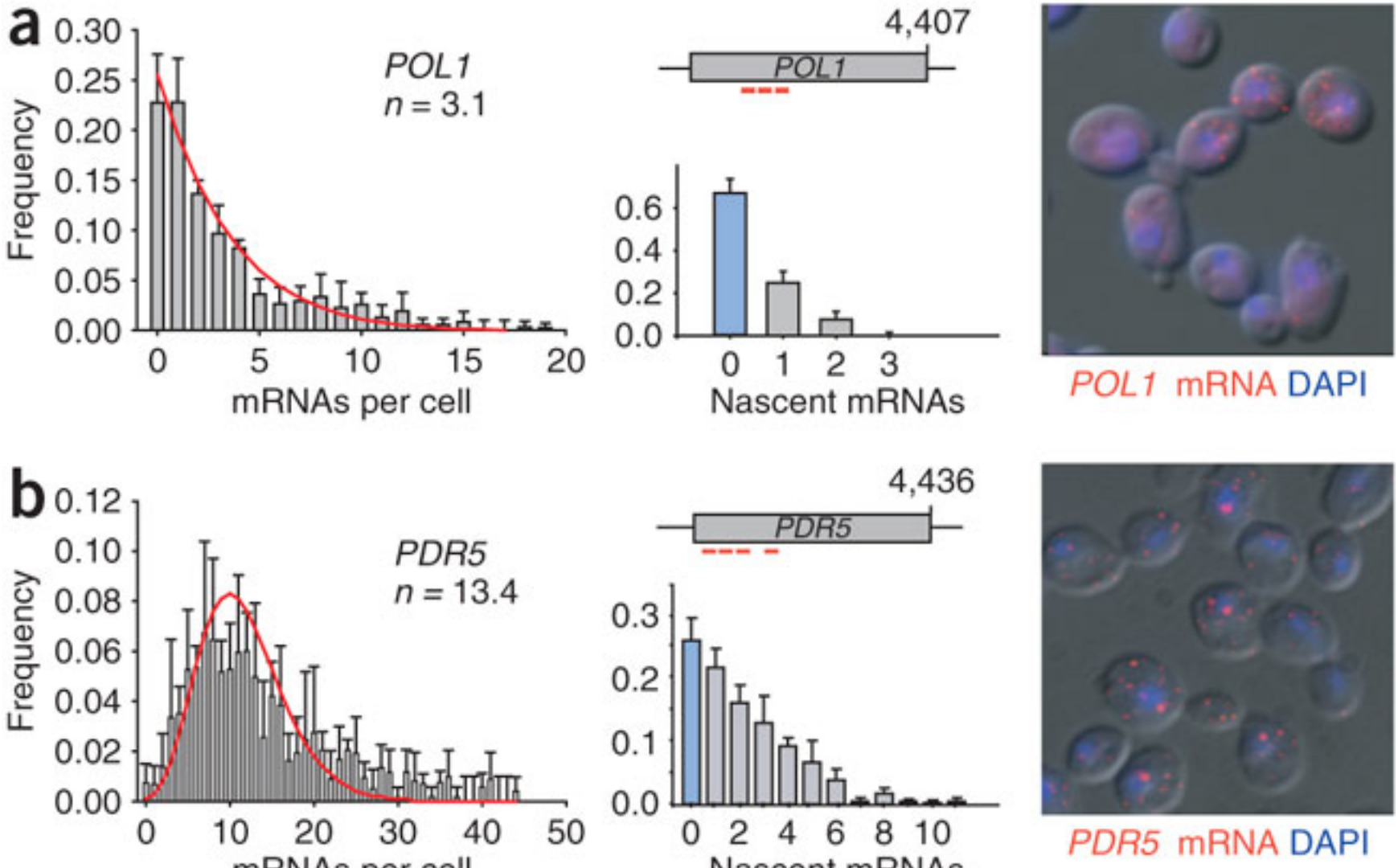
Valentine's Day: Poisson distribution of couples



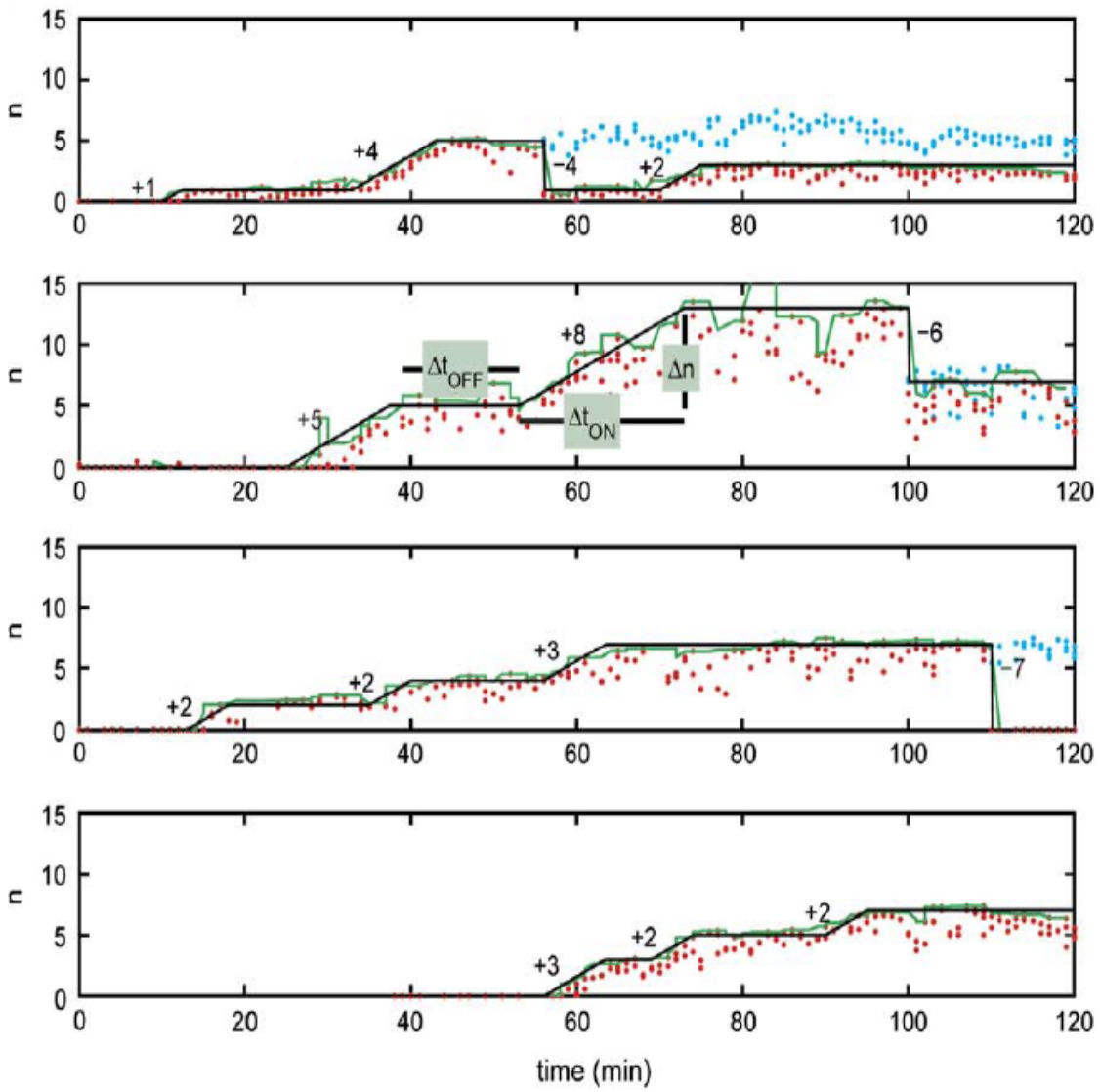
$$\mathrm{var}(P) = 2 \times \langle P \rangle$$

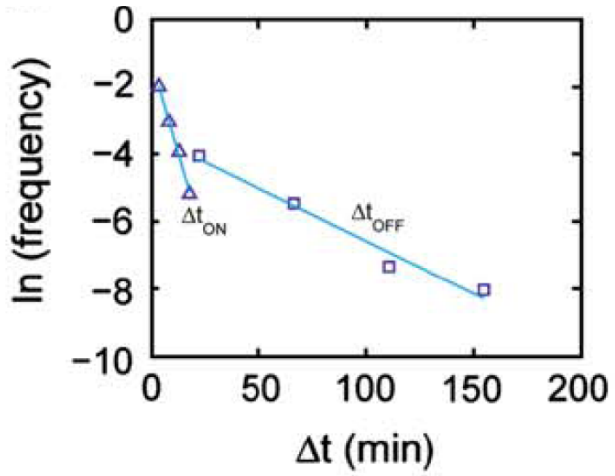
NOT POISSON

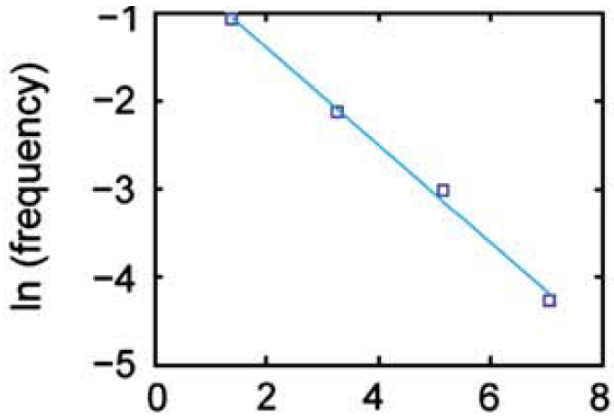
Zenklusen et al. '08



MRNA PRODUCTION OCCURS IN BURSTS

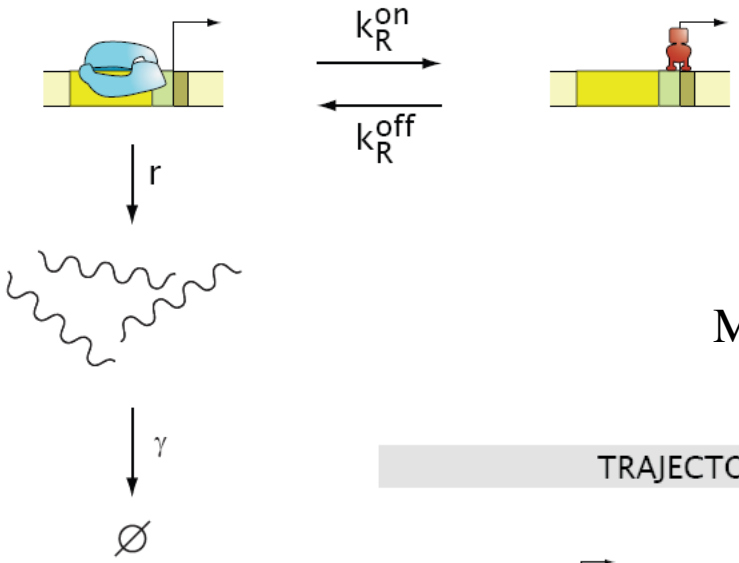




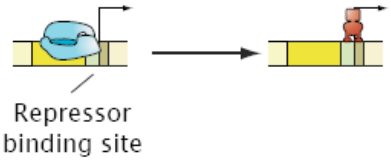
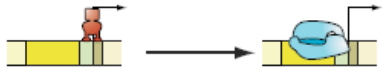
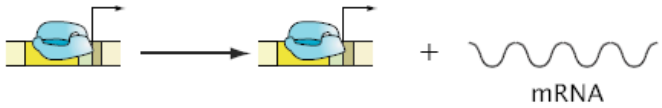
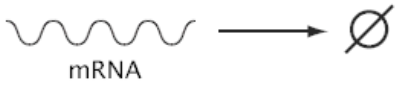


What is the origin of transcriptional bursts?

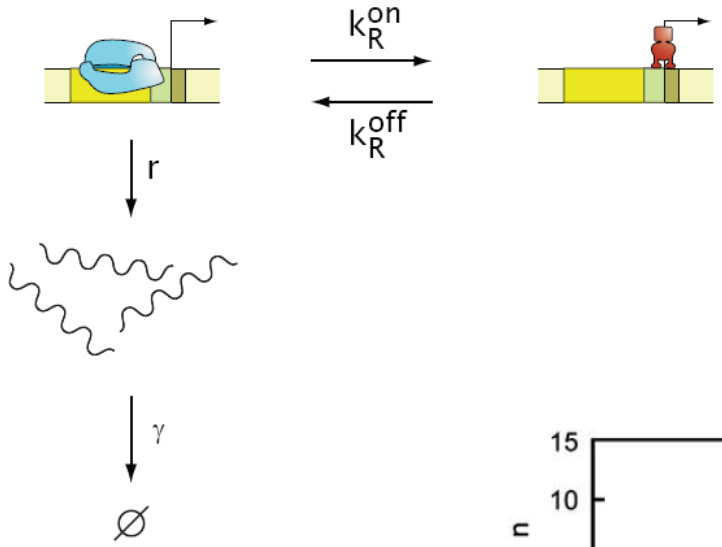
TWO-STATE PROMOTER



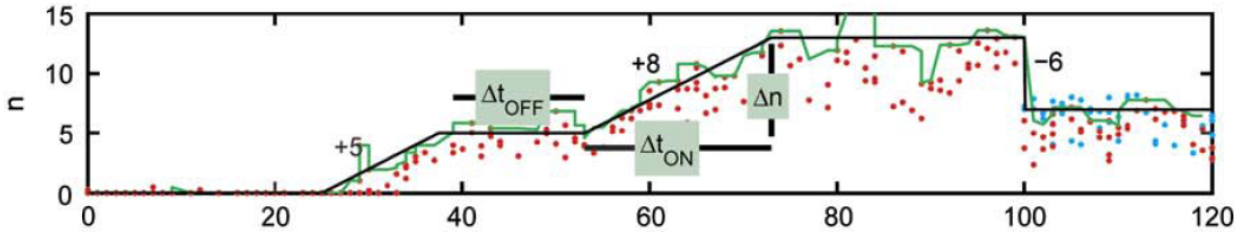
Master equation for a two state promoter

TRAJECTORY	PROMOTER STATE	mRNA STATE	WEIGHT
	1 → 2	m	$k_R^{on}\,\Delta t$
	2 → 1	m	$k_R^{off}\,\Delta t$
	2 → 1	m → m+1	$r\,\Delta t$
	1 or 2	m → m−1	$\gamma\,\Delta t$

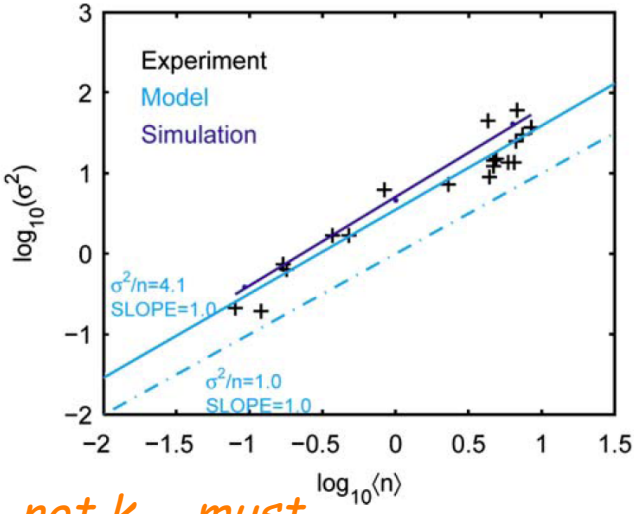
TWO-STATE PROMOTER



At full induction



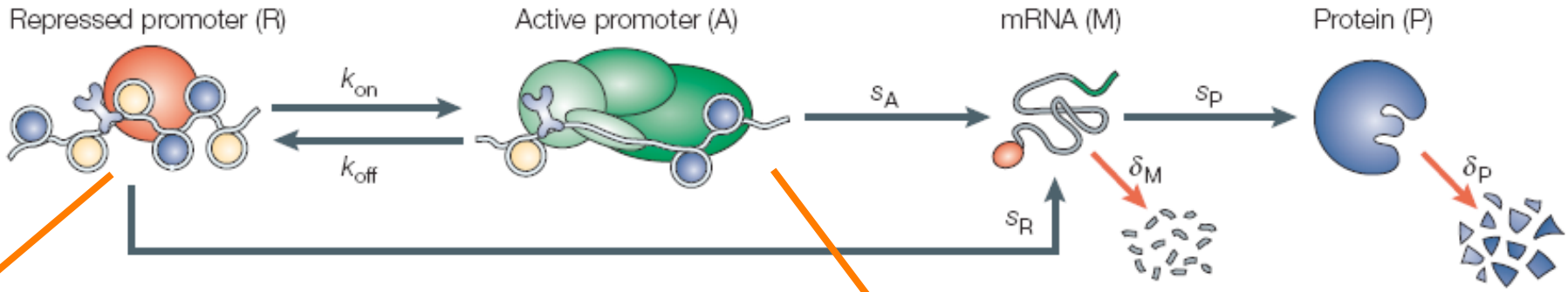
- k_{on} = 1/(6min)
- k_{off} = 1/(36 min)
- r = 1/(2.5 min}
- ° = 1/(72 min)

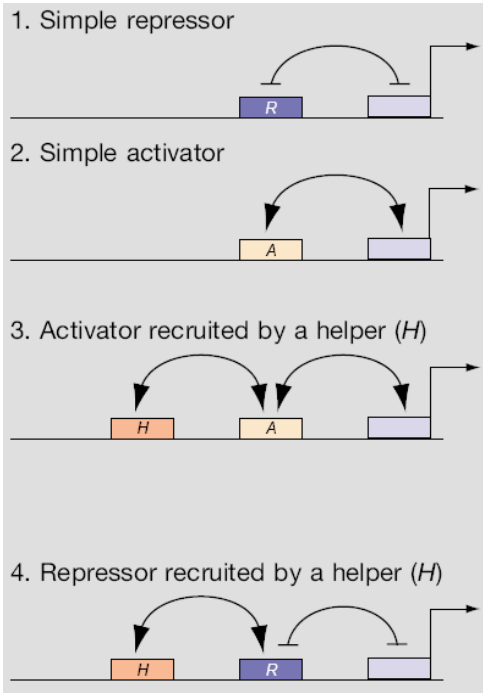


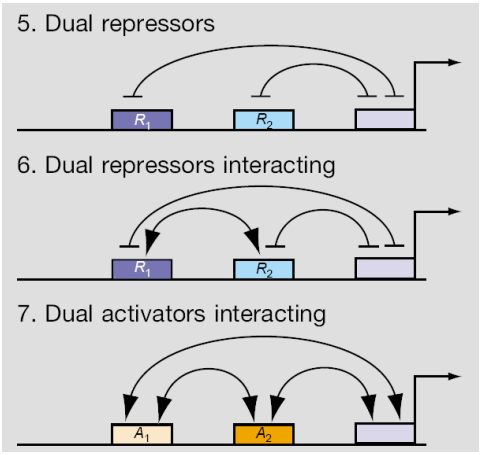
Prediction: For the scaling to hold, k_{off}, not k_{on}, must be the rate that changes with induction .

Stochastic Model of Transcription

Kepler and Elston '02



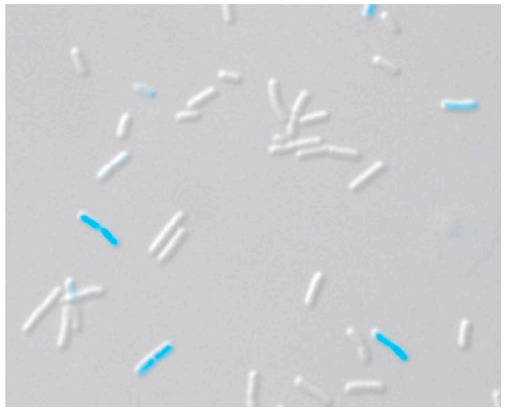




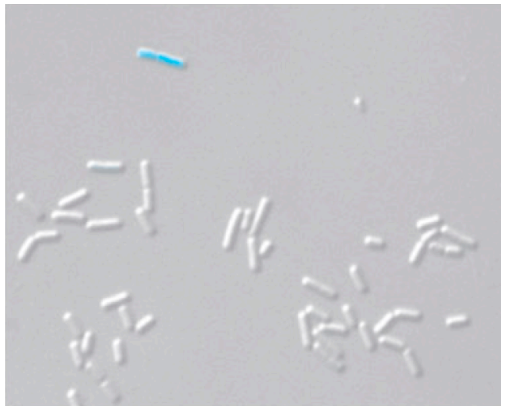
Generalize to arbitrary number of promoter states with different transcription rates.

PHENOTYPIC CONSEQUENCES OF NOISE

Maamar, Raj, and Dubnau '07

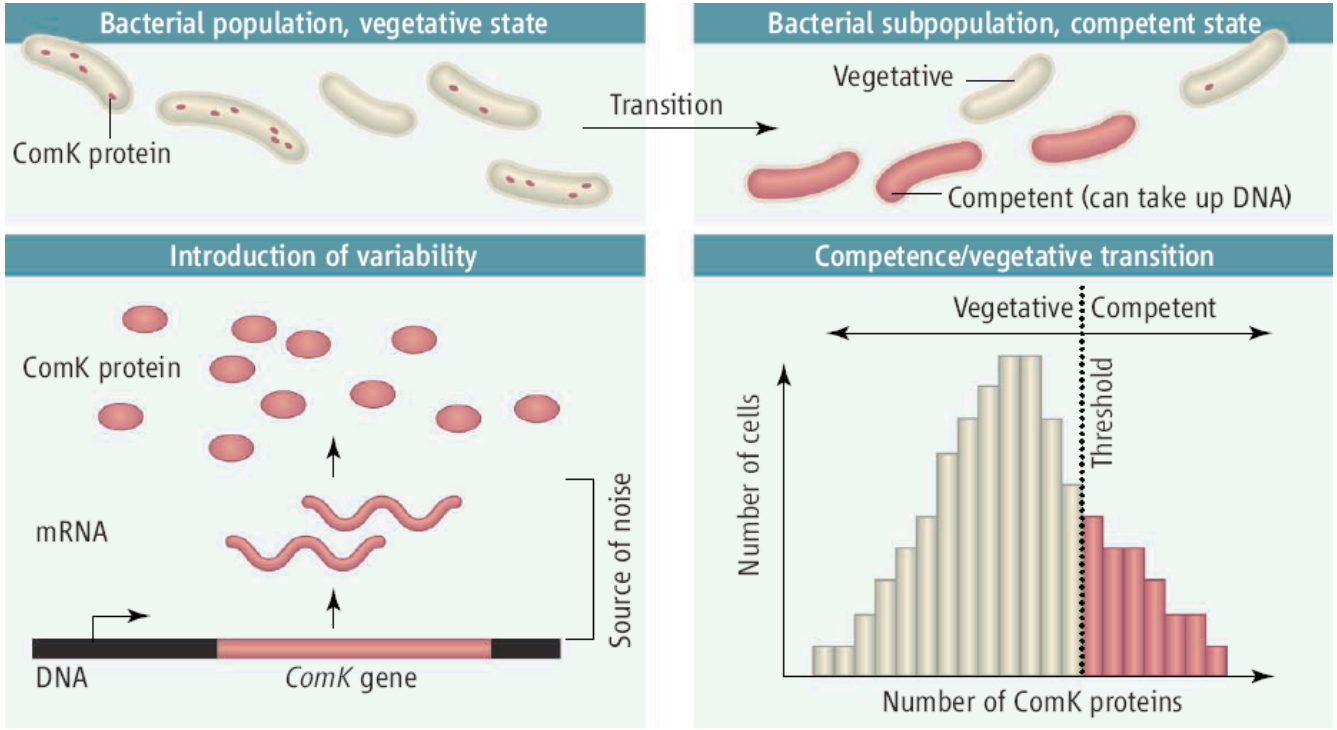


High noise



Low noise

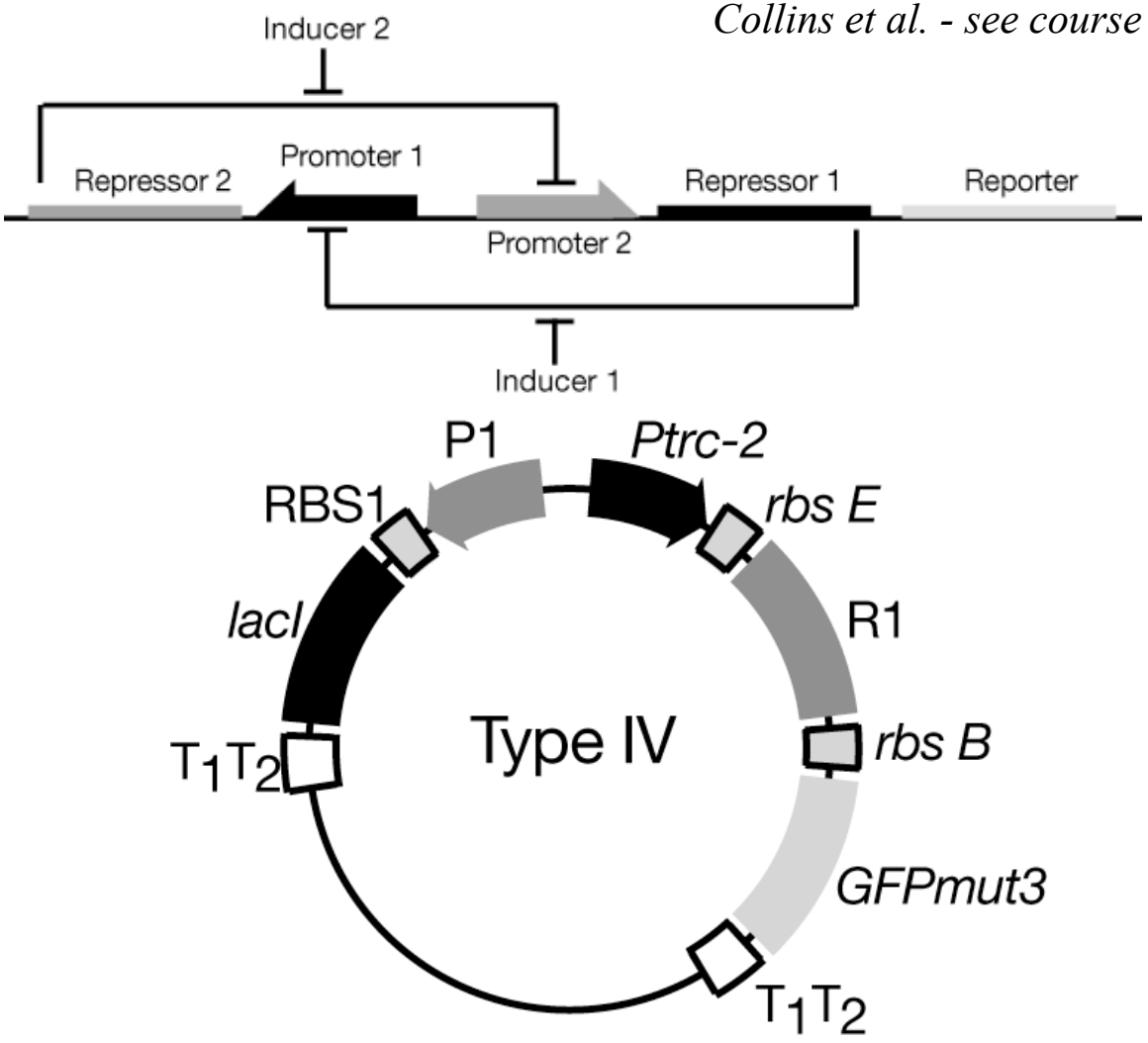
Amount of noise in expression of a single gene determines the number of competent cells in a population.



Mettetal and van Oudernaaden '07

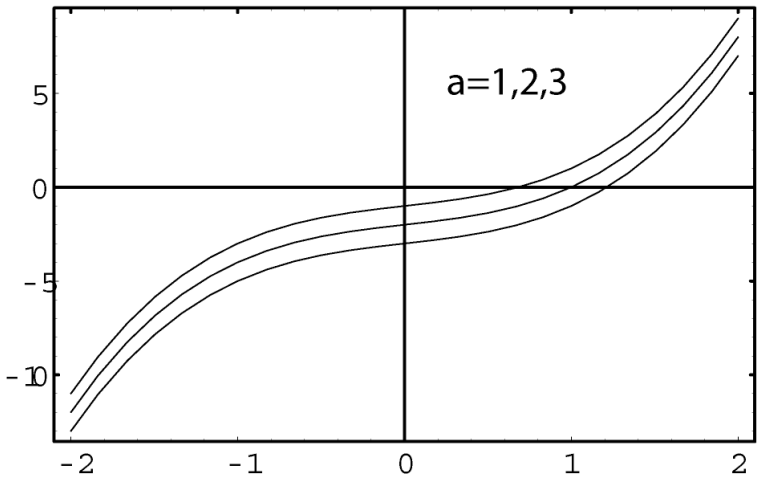
SYNTHETIC GENETIC SWITCH

Collins et al. - see course website

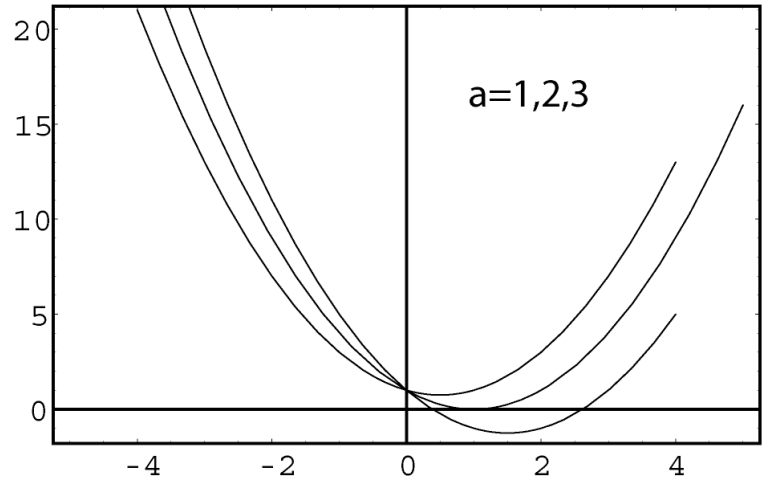


STABLE SOLUTIONS

a)

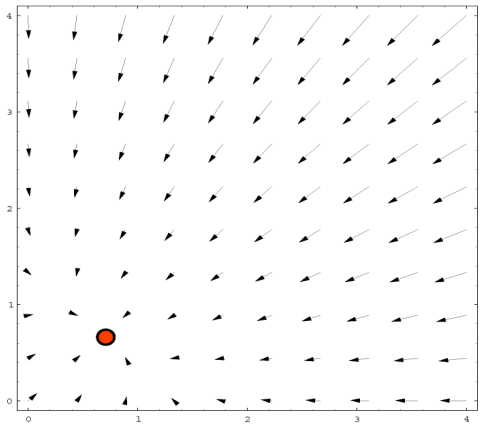


b)

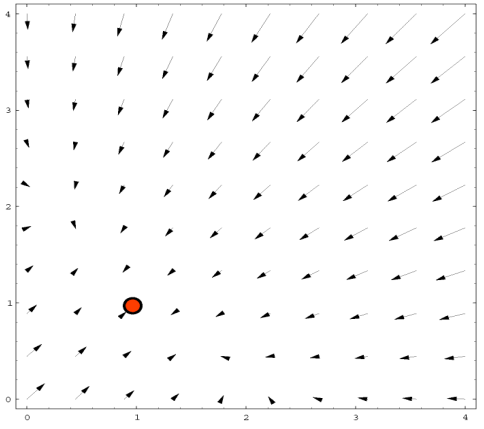


PHASE PORTRAIT FOR THE SWITCH

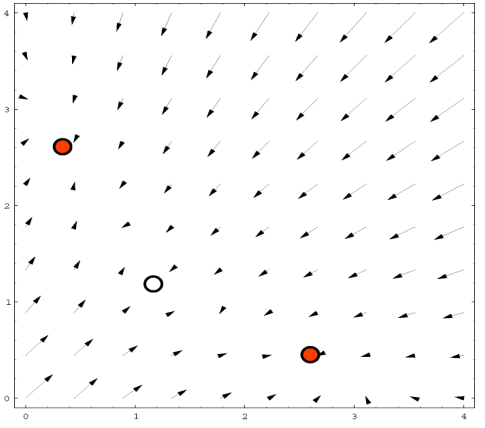
a)



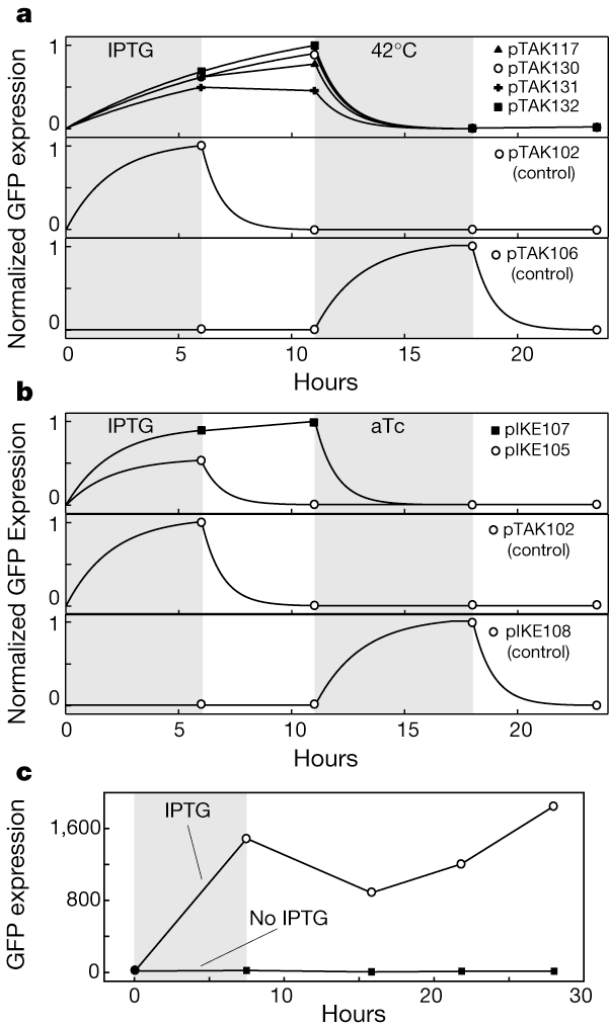
b)



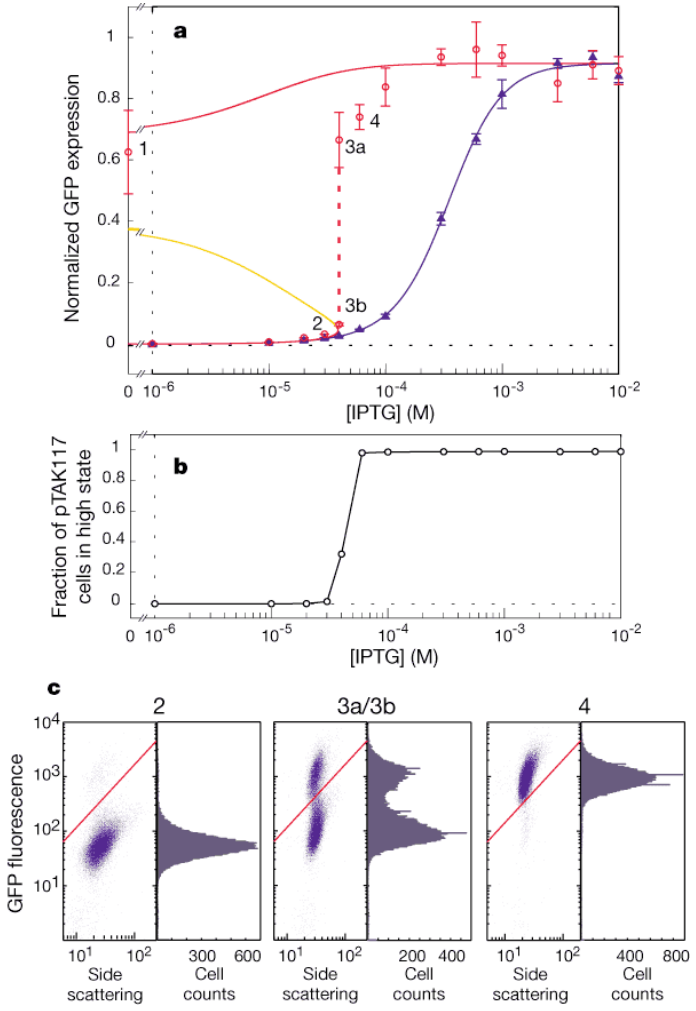
c)



SYNTHETIC GENETIC SWITCH

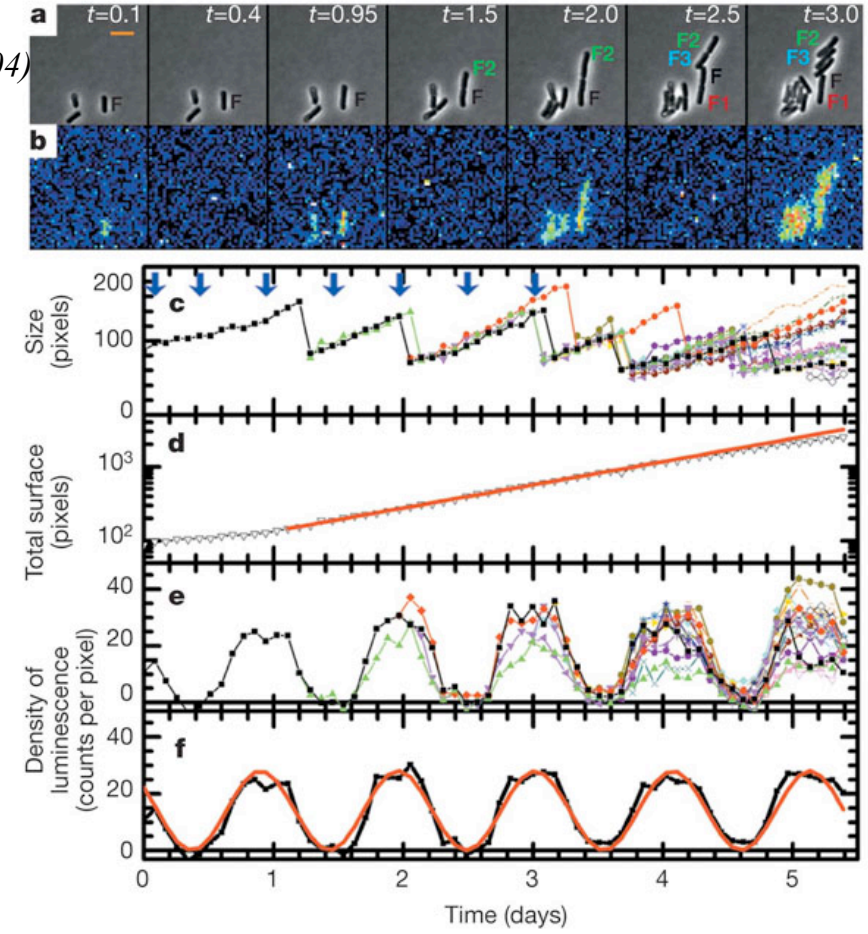


Collins et al. - see course website



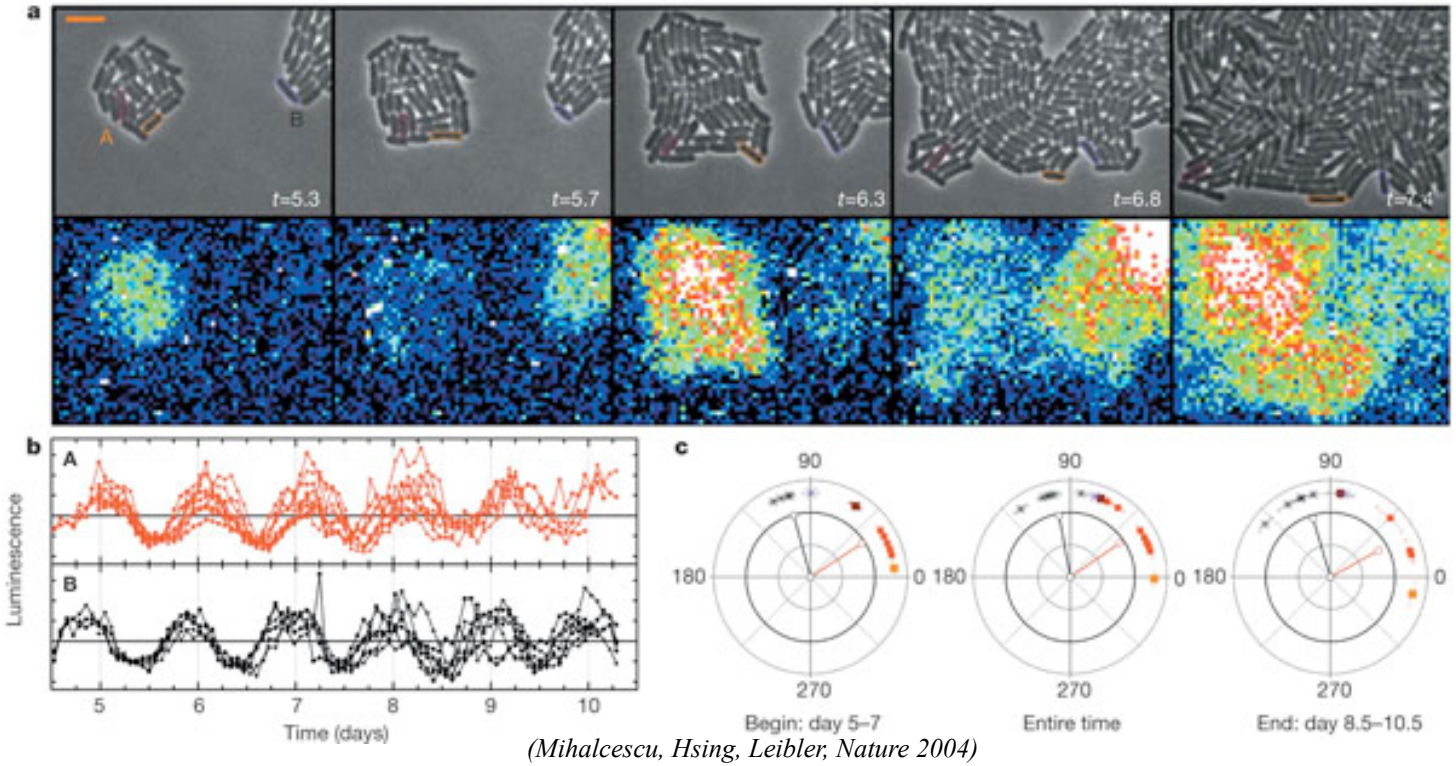
GENE EXPRESSION IN CYANOBACTERIA

(Mihalcescu, Hsing, Leibler, Nature 2004)



a, Snapshots of phase-contrast image showing cell F and its progeny and b, related bioluminescence image at different times t (given in days, a 24 h period of time) from the beginning of the measurement. Pixels in the bioluminescence images were binned 3 times 3 (pseudo-colour, where red is high signal intensity and blue is low signal intensity). Scale bar, 5 microm. c, The size of the cell F and all its progeny as a function of time measured from the phase-contrast images (non-binned pixels). The arrows point to the time where the snapshots in (a) and (b) were taken. d, The total number of pixels occupied by F and its all progeny versus time (black line) plotted in a logarithmic scale. The red line is the corresponding exponential growth fit: total size (t) = initial size times 2t/tau with tau = 23.04 plusminus 0.17 h. e, Density of bioluminescence for the same cell and all its progeny versus time. f, The average density of bioluminescence versus time (black line) and its fit (red line) with: left fenced(t)right fence = B + A cos(2pit/T0 + phi0). The resulting period is T0 = 25.4 plusminus 0.12 h, the initial phase phi0 = 52 plusminus 2.8°, the amplitude A = 12.9 plusminus 0.3 counts per pixel and the offset B = 14.8 plusminus 0.3 counts per pixel.

GENE EXPRESSION IN CYANOBACTERIA

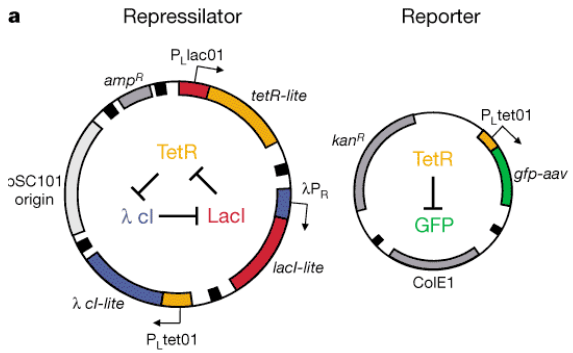


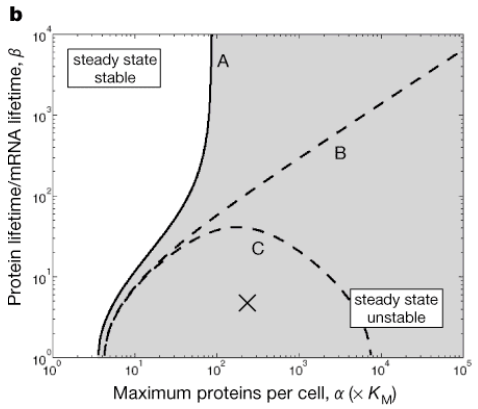
(Mihalcescu, Hsing, Leibler, Nature 2004)

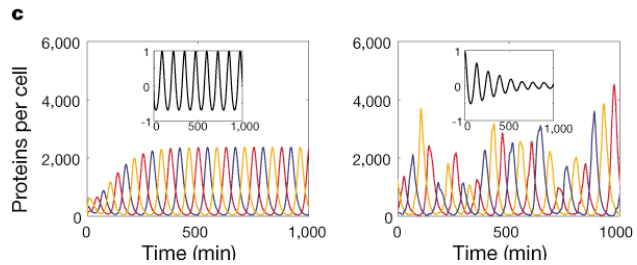
a, Upper part shows the phase-contrast snapshots of colonies A and B; lower part shows the related bioluminescence images. Scale bar, 5 microm. b, Normalized density of bioluminescence of individual cyanobacterial cells. Each colour corresponds to the progeny from one of the initial cells: red line, colony A; black line, colony B. c, Phase of individual oscillators as a function of their original colony and their evolution in time: red square, colony A; asterisk, colony B. An example of the exact location for three of the cells tracked and their phase evolution is shown, marked by the corresponding coloured lines: magenta, orange and purple. The change of the phase in time was quantified by a fit over a different period of time: the first 2 days (days 5–7), the entire time (days 5–10.5) and the last 2 days of the measurement (days 8.5–10.5). The fit function is left fenced(t)right fence = B + A cos(2pit/T0 + phi), with T0 = 24.78 h. The line segments in each graph, with corresponding colours, represent the resulting vector Pres = sumPi, where Pi is the unit vector whose orientation is the measured angle of the same colony cell i.

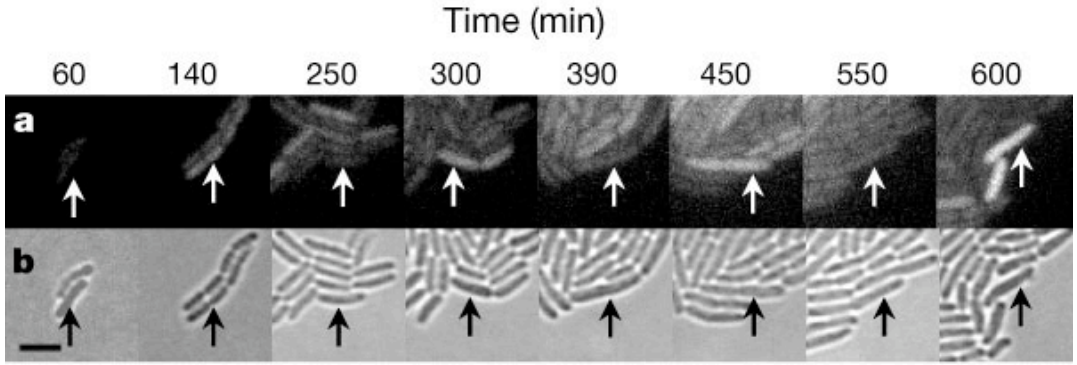
SYNTHETIC TRANSCRIPTIONAL OSCILLATOR

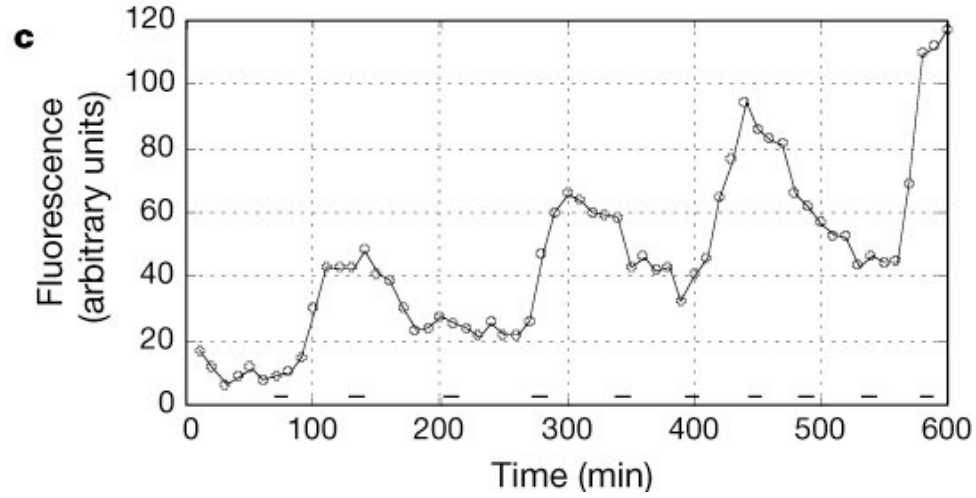
(Elowitz, Leibler, Nature 2002)











COUPLING OF GENES IN NETWORKS