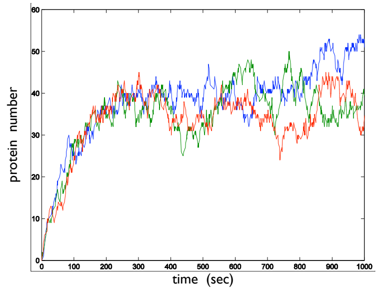
All chemical reactions are affected by thermal fluctuations and are stochastic

$$A + B \longrightarrow C$$

1. Reactants diffuse to find each other in solution
2. They must overcome the energy barrier of the reaction

Both events are randomly affected by thermal fluctuations: collisions with other molecules.

How should we quantify stochasticity?

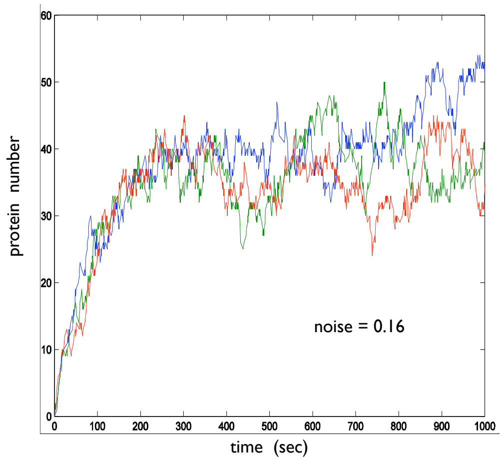


Noise is often defined as the coefficient of variation, which is the typical size of a fluctuation relative to the mean:

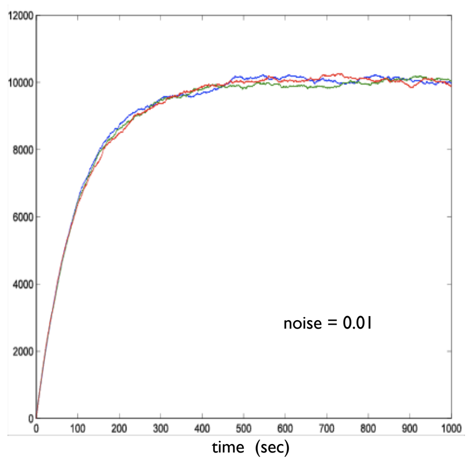
$$\text{noise} = \frac{\text{standard deviation}}{\text{mean}}$$

Stochasticity is more substantial at low numbers. Why?

mean 40



mean 10,000

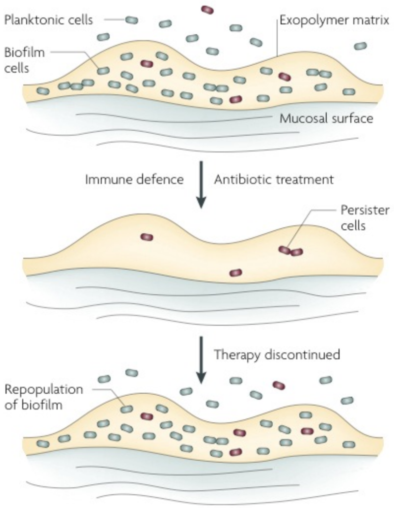


Why is stochasticity only substantial when typical numbers of molecules are low?

As a reaction only increases or decreases the number of molecules by one or two, it is only when numbers of molecules are small that stochasticity – the random timing of individual reactions – matters.

Stochasticity can be exploited: persister cells enable a population to be both invasive and tolerant to drugs

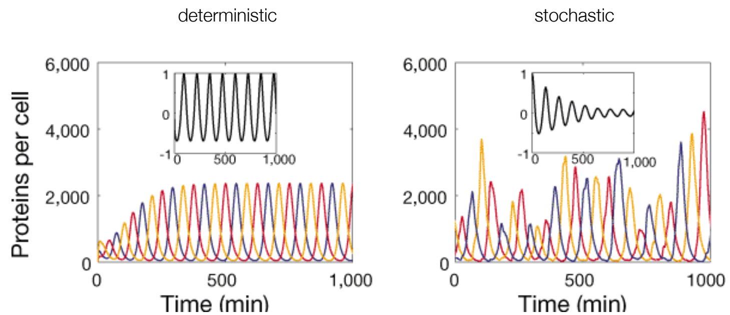
probability of being a persister is less than 10^{-5} for *E. coli*



Lewis, *Nat Rev Microbiol* 1977

Stochasticity affects the reliability of biochemical networks by affecting timing and is therefore regulated away

e.g. biological rhythms



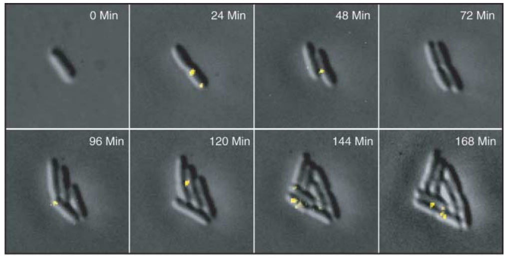
Elowitz & Leibler, *Nature* 2000
Barkai & Leibler, *Nature* 2000

Translation can occur in bursts

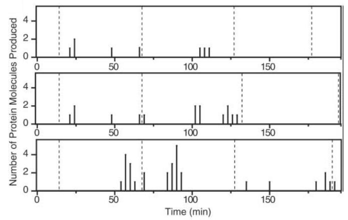
Probing Gene Expression in Live Cells, One Protein Molecule at a Time

Ji Yu,[1*] Jie Xiao,[1*] Xiaojia Ren,[1] Kaiqin Lao,[2] X. Sunney Xie[1†]

Following expression of a fluorescent membrane protein in bacteria over time.



Occasionally, one mRNA is transcribed.



Bursts of translated protein.

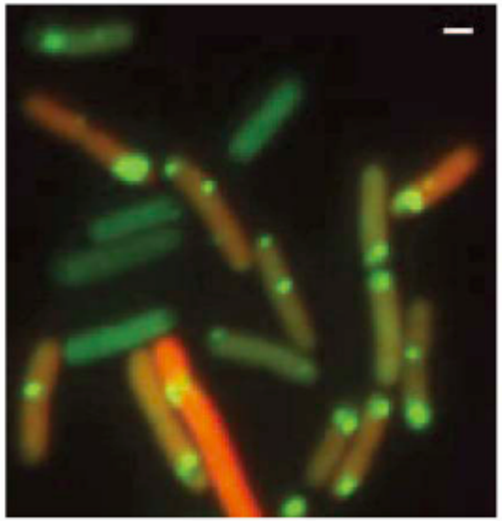
Yu *et al.*, Science (2006)

Transcription can occur in bursts

Real-Time Kinetics of Gene Activity in Individual Bacteria

Ido Golding,[1,*] Johan Paulsson,[2,3] Scott M. Zawilski,[1] and Edward C. Cox[1,*]

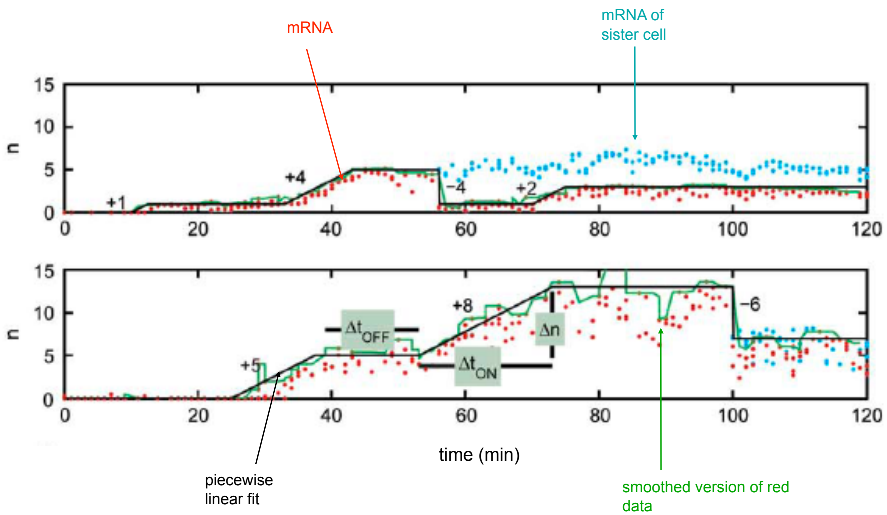
Cell *123*, 1025–1036, December 16, 2005



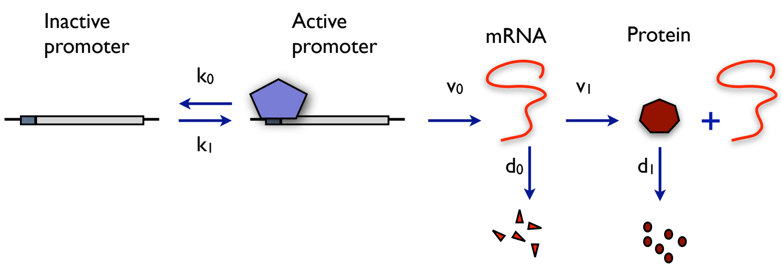
Red: protein
Green spots: mRNA

scale bar: 1 μm

Time course of mRNA numbers: mRNA is produced in bursts



The most common model of gene expression can have both bursts in transcription and translation



Kaern et al., *Nat Rev Genetics* 2005

To perform stochastic simulations, we typically use the Gillespie algorithm

Step 1: choose which reaction will occur

Step 2: choose when that reaction will occur

Example: a birth-death process with two reactions

1: $\xrightarrow{k} A$

2: $A \xrightarrow{d} \phi$

probability of a reaction in time δt

$$a_1 \delta t = k\, \delta t$$ propensity of reaction 1

$$a_2 \delta t = dA\, \delta t$$ propensity of reaction 2

probability of no reaction

$$P_0(t+\delta t) = P_0(t)\Big[1-(a_1+a_2)\delta t\Big]$$ hence $$P_0 \sim \mathrm{e}^{-(a_1+a_2)t}$$

probability of a reaction *i* at time $t+\delta t$

$$P_i(t)\delta t = P_0(t) a_i \delta t$$

Gillespie, *J Phys Chem* 1977