Intrinsic and extrinsic noise in gene expression

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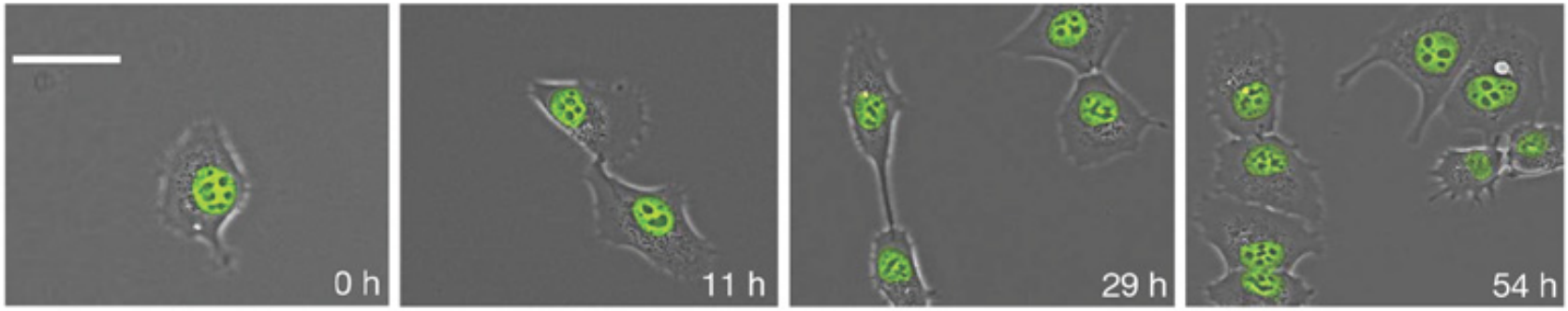
Stochastic influences on phenotype

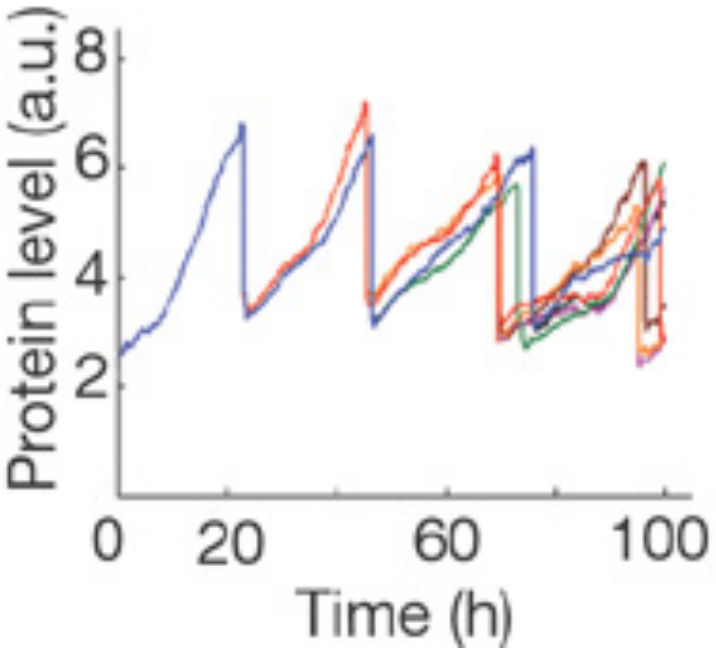
Fingerprints of identical twins

Cc the first clone cat & Rainbow, Cc's genetic mother

Raser and O'shea, Science 309, 5743 (2006)

Protein variability in human cells



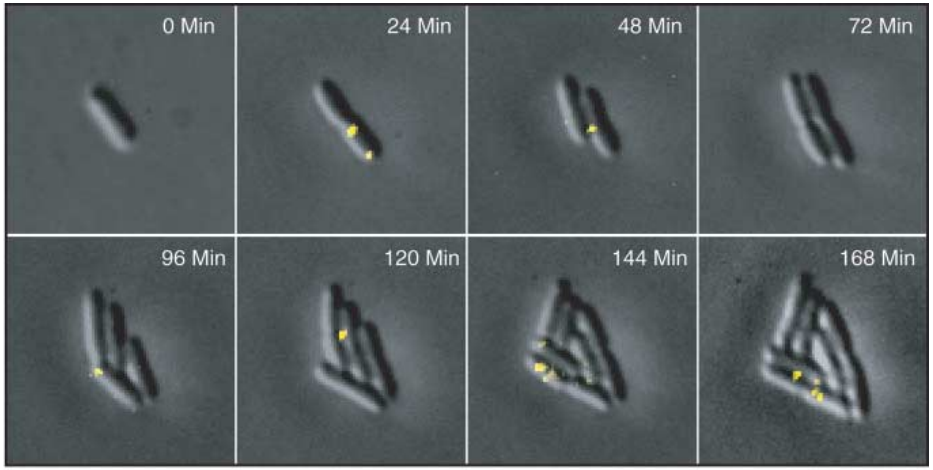


Sigal *et al.* Nature 444, 643 (2006)

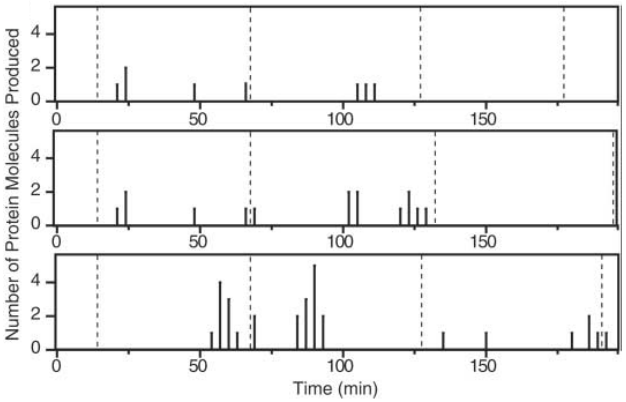
Probing Gene Expression in Live Cells, One Protein Molecule at a Time

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.



One mRNA is occasionally transcribed.



Bursts of translated protein.

Yu *et al.* (2006)

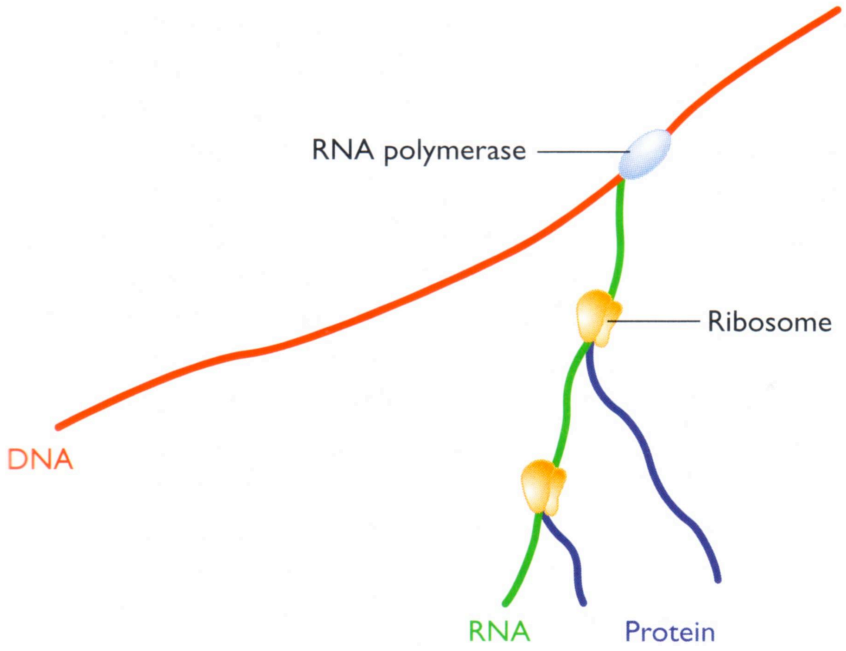
Gene expression

DNA → mRNA → protein

Promoter activation

RNA transcription

Protein translation



All chemical reactions are noisy!
Particularly, when they involve low number of molecules.

When are chemical reactions significantly stochastic?

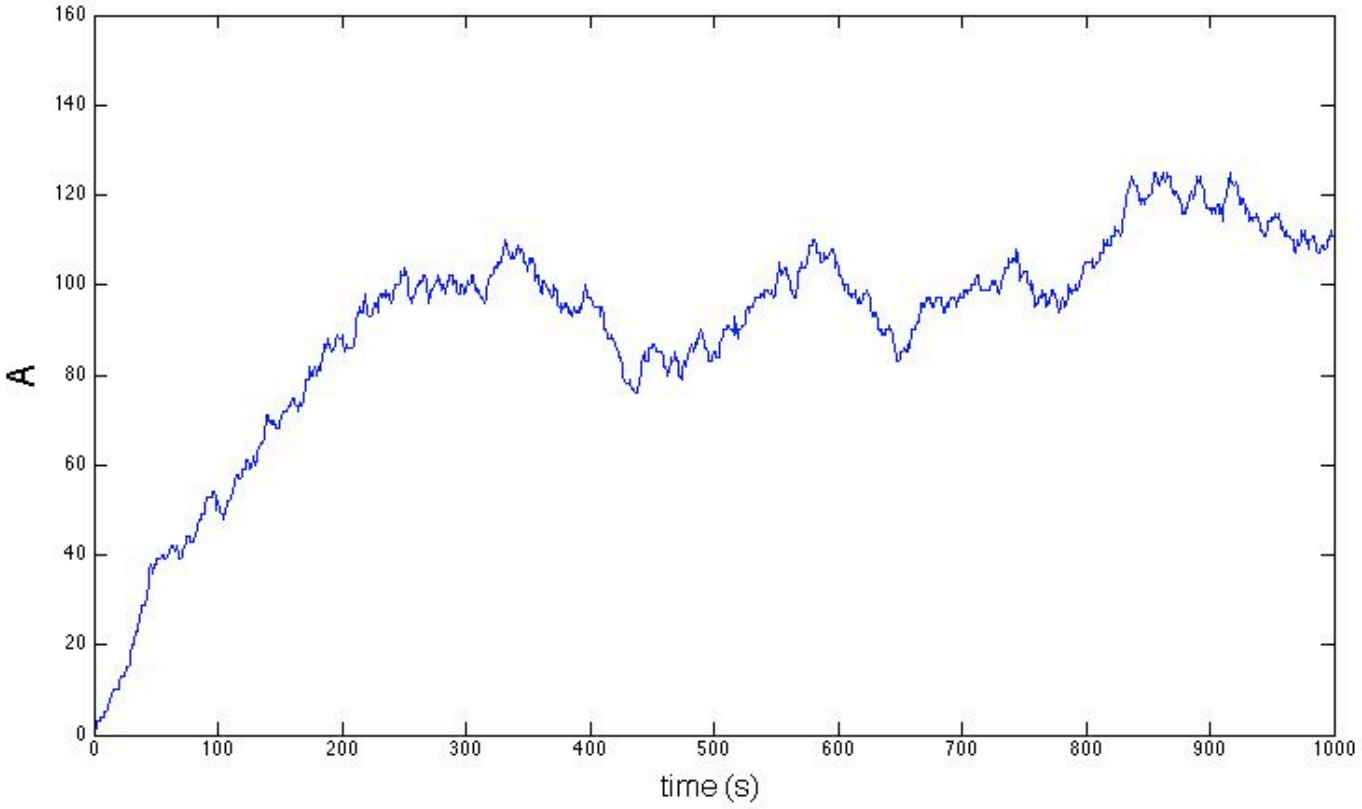
As a reaction only increases or decreases the number of molecules by one or two, it is only when numbers of molecules are small that random timing of individual reactions will matter.

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

coefficient of variation

Stochastic simulation using Gillespie method

Stochastic simulation using Gillespie method

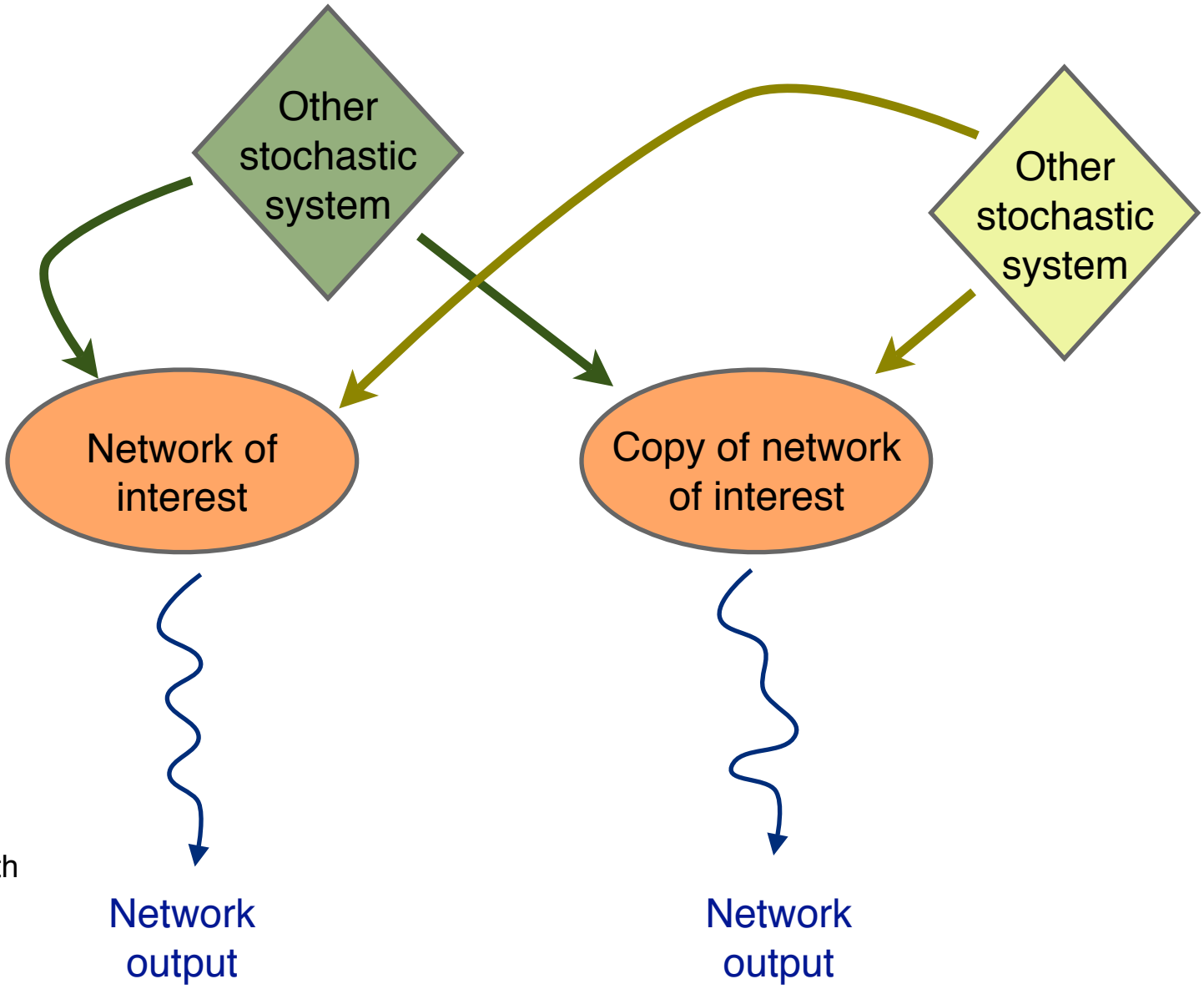


Two types of noise: intrinsic and extrinsic

Extrinsic fluctuations equally affect both network copies.

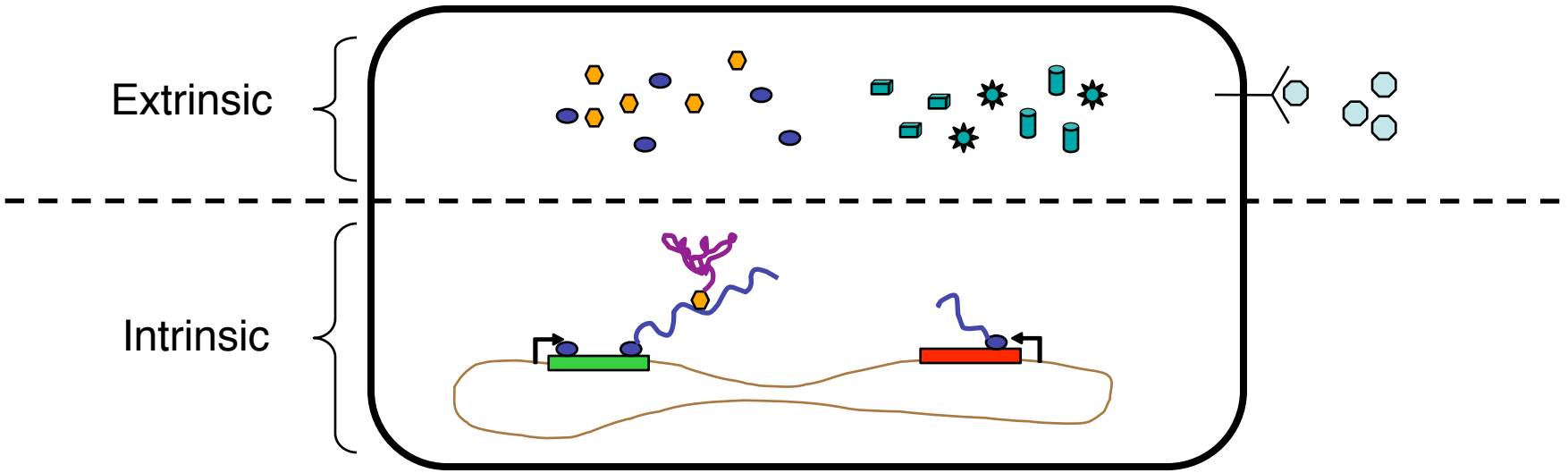
Intrinsic fluctuations differ between network copies.

Network output has both intrinsic and extrinsic fluctuations.



Measuring intrinsic and extrinsic noise in gene expression

with two copies of gene of interest



Extrinsic variables: same for each gene

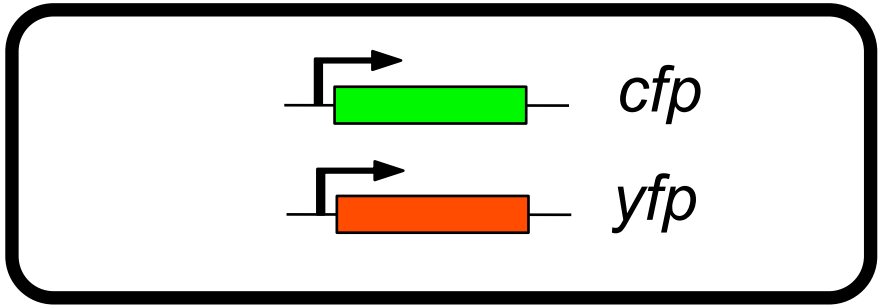
e.g. number of free RNAPs, cellular environment

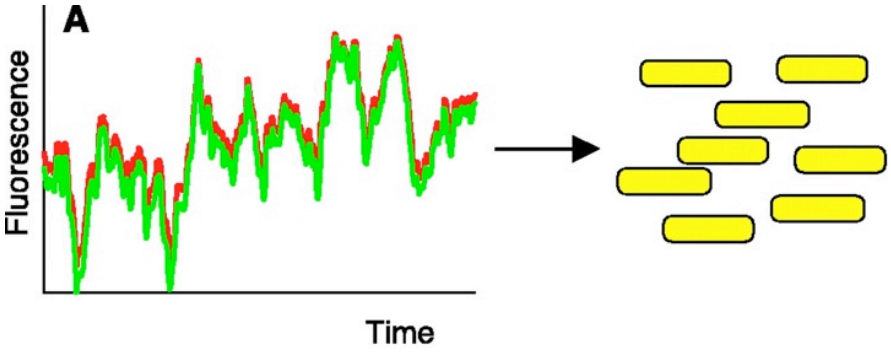
Intrinsic variables: different for each gene

e.g. number of transcribing RNAPs, number of mRNAs

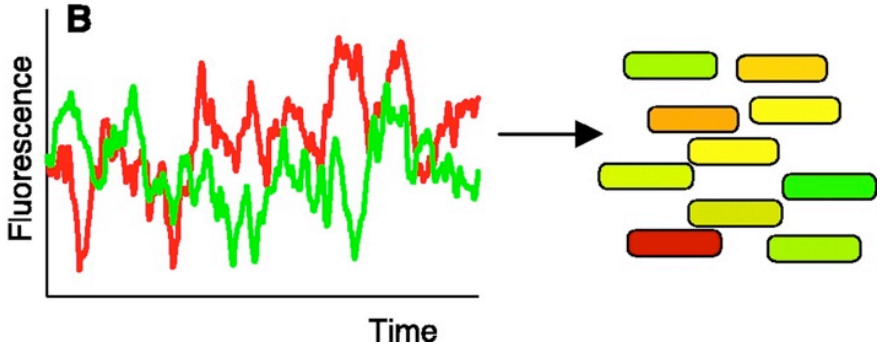
Measuring intrinsic and extrinsic noise

Two color experiments





Correlated expression
extrinsically noisy



Uncorrelated expression
intrinsically noisy

Elowitz, Levine, Siggia and Swain, Science 297, 1081 (2002)

Definitions

Define a fluctuation in an intrinsic variable, such as protein numbers, by

$$\tilde{I}(t) = I(t) - \langle I(t) \rangle$$

If I_1 is the intrinsic variable for one copy of the system and I_2 is the same intrinsic variable for the second copy, then

extrinsic noise

$$\eta_{\rm ext}^2 = \frac{\langle \tilde{I}_1 \tilde{I}_2 \rangle}{\langle I \rangle^2}$$

correlation coefficient

intrinsic noise

$$\eta_{\rm int}^2 = \frac{\left\langle (\tilde{I}_1 - \tilde{I}_2)^2 \right\rangle}{2\langle I \rangle^2}$$

normalized difference

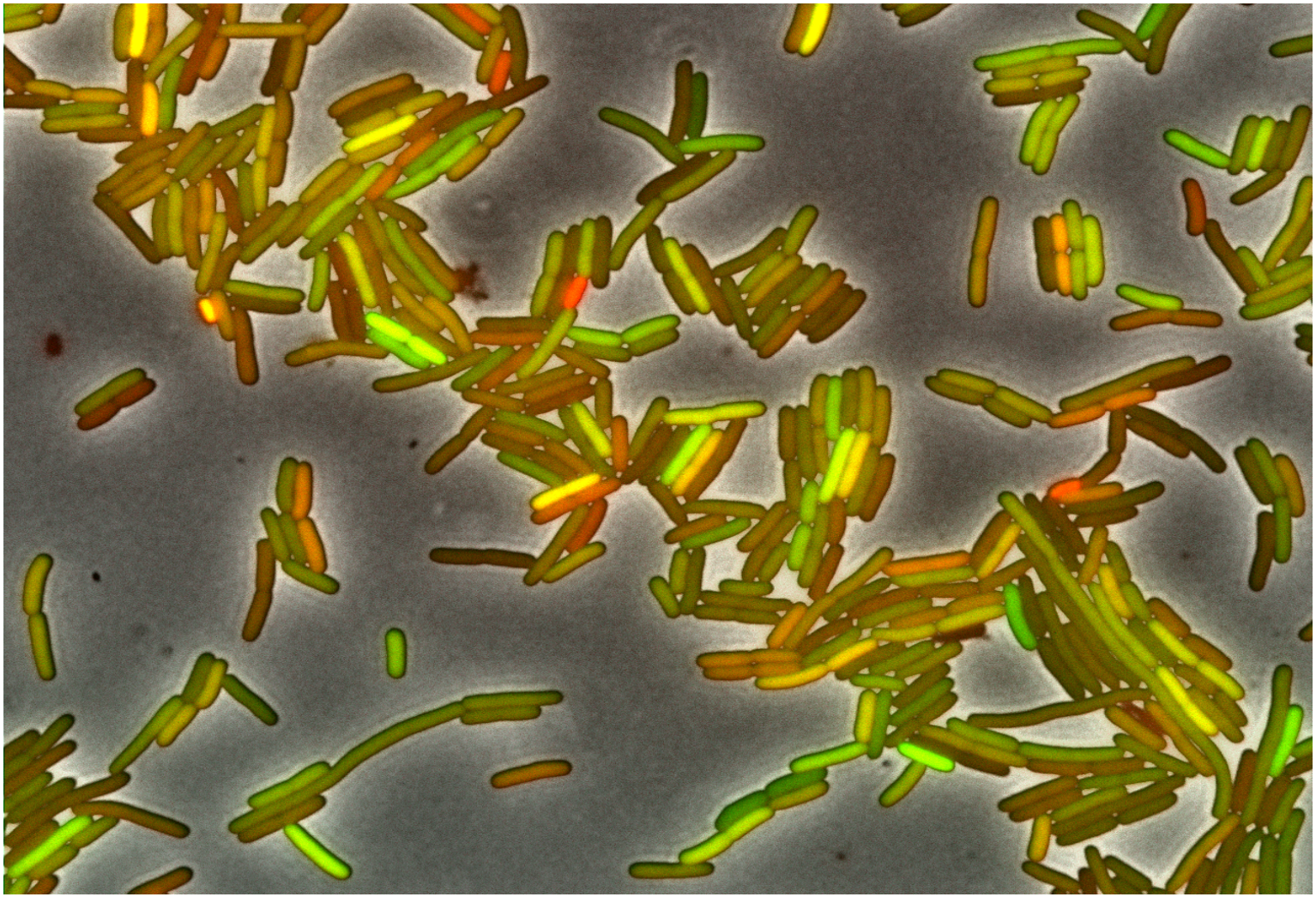
with $\eta_{\rm int}^2 + \eta_{\rm ext}^2 = \eta_{\rm tot}^2$ and

total noise

$$\eta_{\rm tot}^2 = \frac{\langle \tilde{I}^2 \rangle}{\langle I \rangle^2} = \frac{1}{2}\left(\frac{\langle \tilde{I}_1^2 \rangle}{\langle I \rangle^2} + \frac{\langle \tilde{I}_2^2 \rangle}{\langle I \rangle^2} \right).$$

coefficient of variation

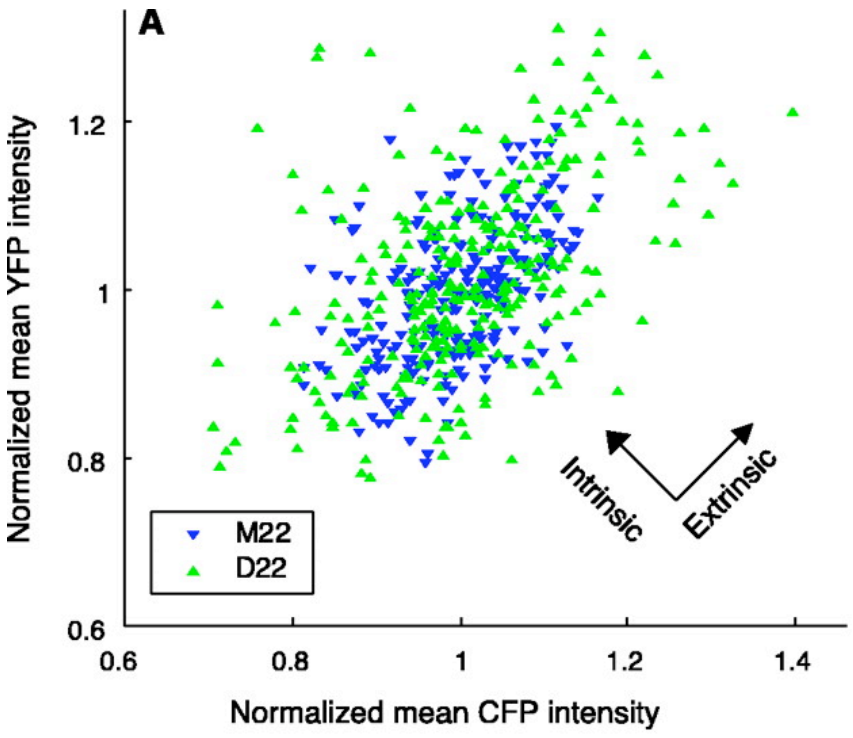
Measuring extrinsic and intrinsic noise in Bacteria
~ 50% extrinsic



Elowitz, Levine, Siggia and Swain, Science 297, 1081 (2002)

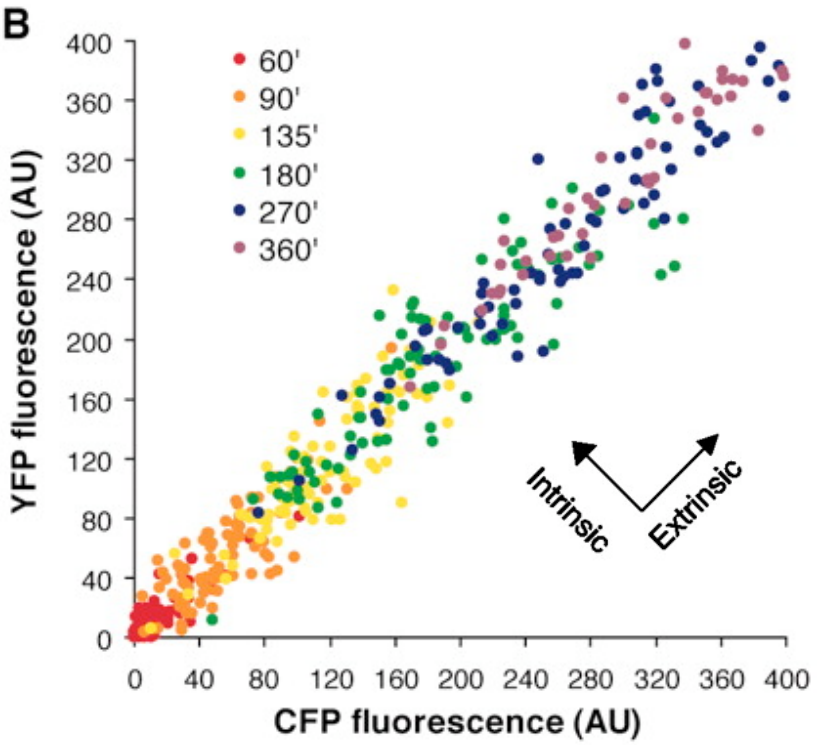
Extrinsic noise may dominate

E coli: ~ 50% extrinsic



Elowitz, Levine, Siggia and Swain,
Science 297, 1081 (2002)

Yeast: 80-98% extrinsic



Raser and O'Shea,
Science 304, 1811 (2004)

Gillespie Algorithm:
An exact method to solve chemical master equation

1. Initialize the numbers of all species. Set time t = 0.

2. Calculate the propensity for each chemical reactions (a_i for reaction i).

3. For each reaction i, generate a putative next reaction time, τ_i , according to exponential distribution $a_i \exp(-a_i \tau)$.

4. Let μ be the reaction with minimum τ_i.

5. Change the numbers of species appropriately for the occurrence of reaction μ. Change t to $t + \tau_\mu$.

6. Go to step 2.

Modeling intrinsic fluctuations:

Stochastic simulation using Gillespie method

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Stochastic simulation using Gillespie method