Noise in gene expression

Tie Koide, 14 jun 2012

“Life is a study in contrasts between randomness and determinism:
from the chaos of biomolecular interactions to the precise coordination of development, living organisms are able to resolve these two seemingly contradictory aspects of their internal workings”

Raj & van Oudernaarden
Cell 2008

Photo credit, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University.

Raser & O'Shea, Science 2005

When large numbers of molecules are present,
chemical reactions may proceed in a predictable manner.

However, when only a few molecules of a specific type
exist in a cell, ***stochastic*** effects can become prominent.

Raser & O'Shea, Science 2005

Stochastic (from the Greek στόχος for aim or guess) is an adjective that refers to *systems whose behavior is intrinsically non-deterministic*, sporadic and categorically not intermittent.

A stochastic process is one whose behavior is non-deterministic, in that a system's subsequent state is determined both by the process's predictable actions and by a random element.

From Wikipedia

Why is gene expression considered a *stochastic process*???

“Noise” in gene expression
refer to the measured level of variation in gene expression among cells, regardless of source, within a supposedly identical population

$\eta = \sigma/\mu$ coefficient of variation
Estimate of overall population variability

Raser & O'Shea, 2005

Sources of variation in gene expression:

1. *inherent stochasticity of biochemical processes* that are dependent on infrequent molecular events involving small numbers of molecules

2. *variation in gene expression* owing to differences in the internal states of a population of cells, either from predictable processes or from a random process

3. *subtle environmental differences*, such as morphogen gradients in multicellular development

4. *ongoing genetic mutation*, either random or directed

Raser & O'Shea, 2005

Gene expression vary from cell to cell

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INDUCED SYNTHESIS OF ENZYMES IN BACTERIA ANALYZED AT THE CELLULAR LEVEL

by

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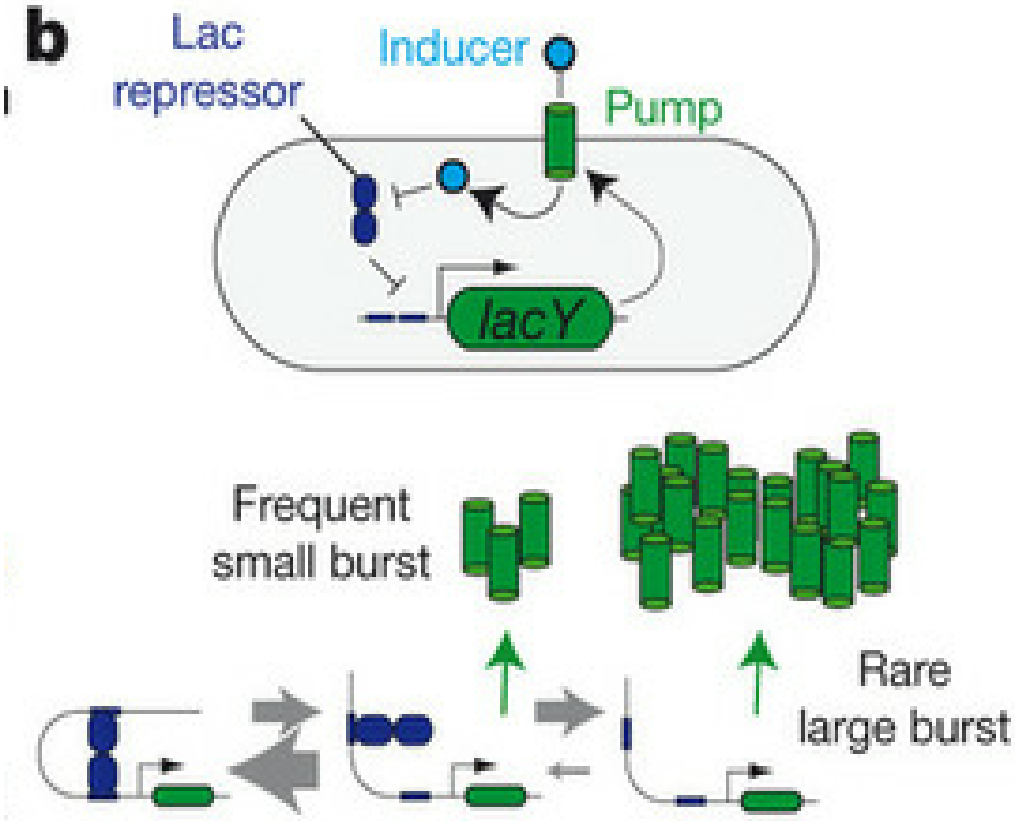
INTRODUCTION

The kinetics of the induced synthesis of enzymes ("enzymic adaptation") in micro-organisms is usually studied by measurements upon cultures containing large numbers of cells; an inducing substance is added and the consequent appearance of enzyme in the culture is followed. Such measurements of the overall activity of the culture do not reveal whether or not all cells participate equally and simultaneously in the synthesis of enzyme. A knowledge of this factor is critical, however, for the proper interpretation of the kinetics of enzyme formation.

Consider, for example, that a given cell might synthesize its maximum amount of enzyme in an abrupt fashion, this transition occurring at random times for particular cells. In such a case, the average measurement on the culture, indicating a gradual rise in enzyme level, would bear little relation to the events in the enzyme-forming system of each cell. One is not authorized to extrapolate the average kinetics to the cellular level unless a uniform behavior of the population can be demonstrated[3,13,11,10].

In this paper, a method is described for determining the cellular distribution of an enzyme in a population of bacteria. This method is based upon the special relationship between a bacteriophage and its (individual) host cell, which permits the use of phage as a discriminating device. Application of this technique to the induced synthesis of β-D-galactosidase in *E. coli* reveals that, under certain conditions, synthesis of this enzyme proceeds uniformly in all the cells of a culture and therefore the average kinetics applies at the cellular level. Under other commonly employed conditions, however, a high degree of heterogeneity occurs, so that the average kinetics does not represent the course of enzyme synthesis within individual cells.

Gene expression vary from cell to cell



Beta-galactosidase production in individual cells: highly variable and random
Induction: increase the proportion of cells expressing the enzyme
(not every cell expression level)

Novick and Weiner, PNAS **1957**

*ENZYME INDUCTION AS AN ALL-OR-NONE PHENOMENON**

By Aaron Novick and Milton Weiner

DEPARTMENT OF MICROBIOLOGY AND COMMITTEE ON BIOPHYSICS, UNIVERSITY OF CHICAGO

Communicated by W. H. Taliaferro, April 21, 1957

" (…) In any event, the existence of induced inheritable changes of the kind described here raises the possibility that some differences which arise in a clone of organisms may be the result of changes in cellular systems other than the primary genetic endowment of the cell"

Novick and Weiner, PNAS **1957**

Gene expression vary from cell to cell

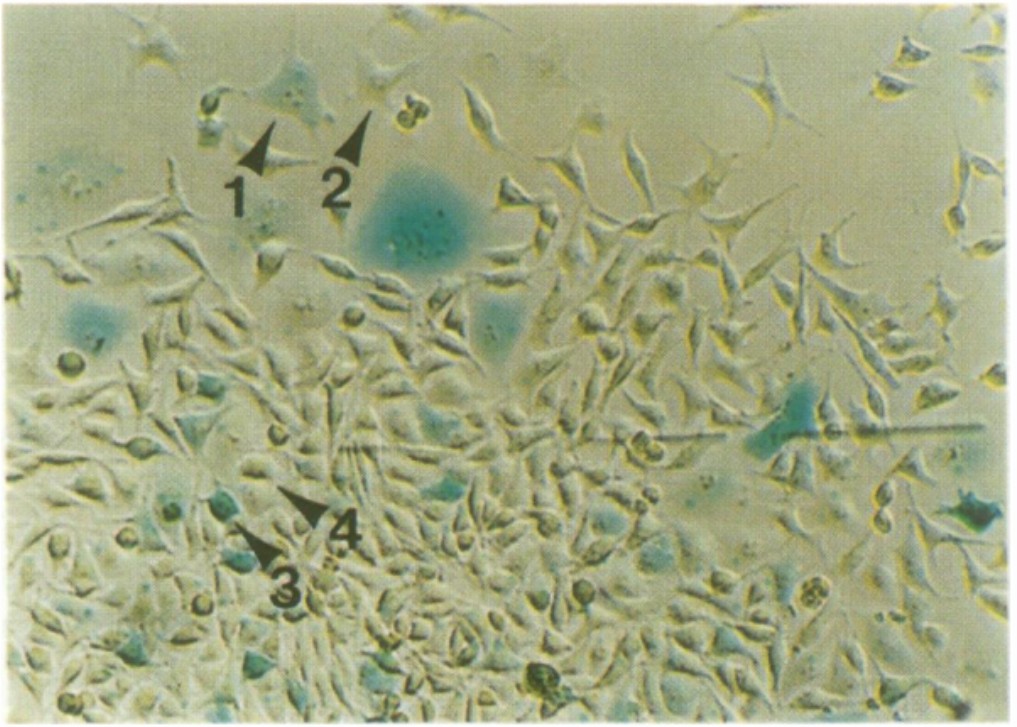
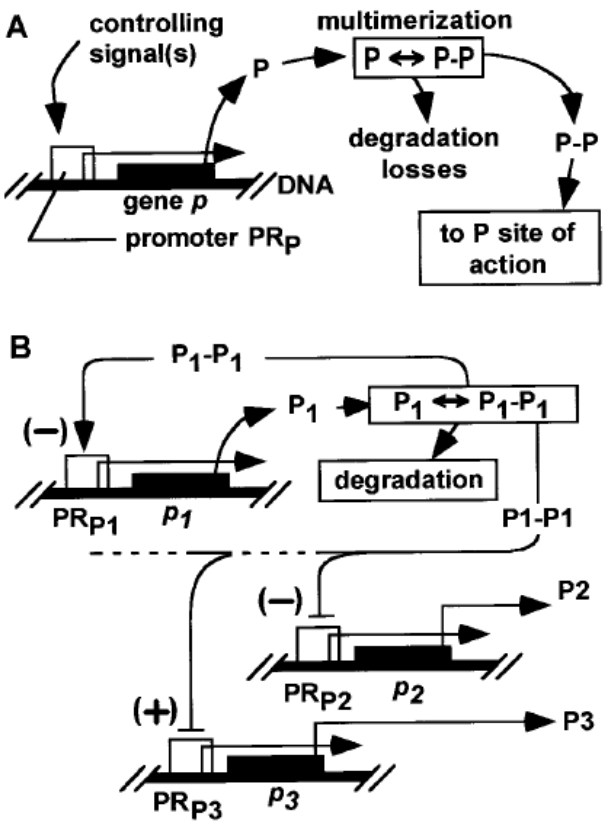


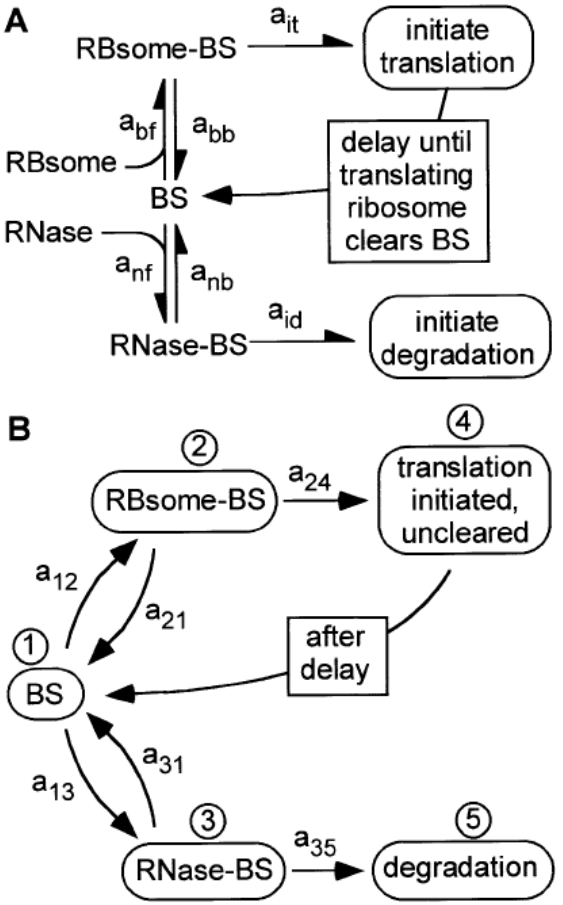
Fig. 8. A magnified view of GL27 cells (10^{-7} M dexamethasone) in the colony formation assay. The two upper arrows point to morphologically flat cells, one of which (arrow 1) produces β-galactosidase after induction with dexamethasone and the other (arrow 2) does not. The two lower arrows point to spindle shaped cells, one (arrow 3) produces β-galactosidase after induction with dexamethasone and the other (arrow 4) does not.

Ko et al, Cell 1990

Theoretical work

Model gene expression using stochastic formulation





Protein numbers – flutuate within individual cells
Lytic-lysogenic cycles of phage lambda – stochastic effects

McAdams & Arkin, 1997
Arkin, 1998

Characterization of stochastic gene expression: started with synthetic biology experiments

Synthetic Biology is

A) the design and construction of new biological parts, devices, and systems, and

B) the re-design of existing, natural biological systems for useful purposes.

http://syntheticbiology.org/

Registry of Standard Biological Parts

Go Search

page discussion view source history Log in / create account

Welcome to the Registry of Standard Biological Parts.

The Registry is a continuously growing collection of genetic parts that can be mixed and matched to build synthetic biology devices and systems. Founded in 2003 at MIT, the Registry is part of the Synthetic Biology community's efforts to make biology easier to engineer. It provides a resource of available genetic parts to iGEM teams and academic labs. You can register a new lab here.

The Registry is based on the principle of "get some, give some". Registry users benefit from using the parts and information available from the Registry in designing their engineered biological systems. In exchange, the expectation is that Registry users will, in turn, contribute back information and data on existing parts and new parts that they make to grow and improve this community resource.

Catalog of parts & devices

Help

Users & groups

DNA repositories

Registry tools

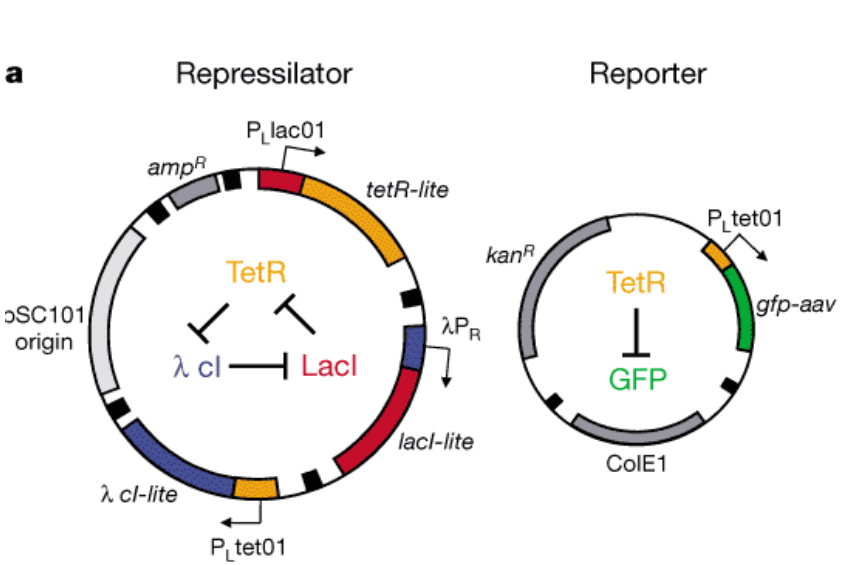
- Search parts (?)
- Add a part
- Request a part
- Send parts to the Registry
- Sequence analysis

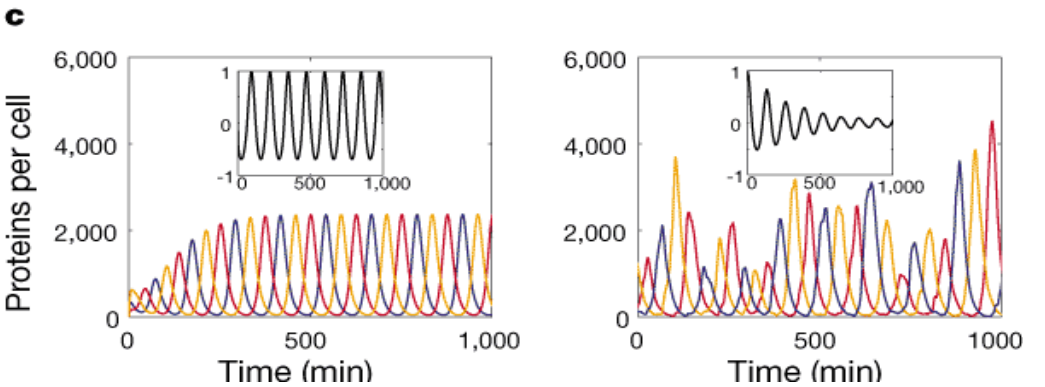
You'll notice some significant changes to the Registry recently. In particular, the Registry catalog of parts has been entirely redesigned to allow for easier browsing of the available parts and devices. You can now browse parts and devices by type, by function, by chassis and by standard. You'll also notice that the documentation and help pages for each class of parts have been greatly enhanced.

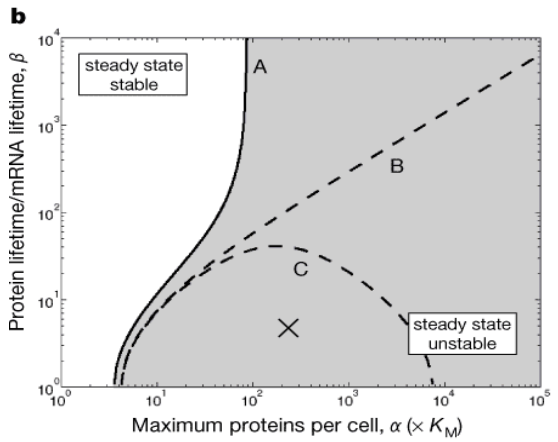
The Registry of Standard Biological Parts is *always* a work in progress. Please browse the new catalog and let us know what you think, or feel free to edit and improve the pages further.

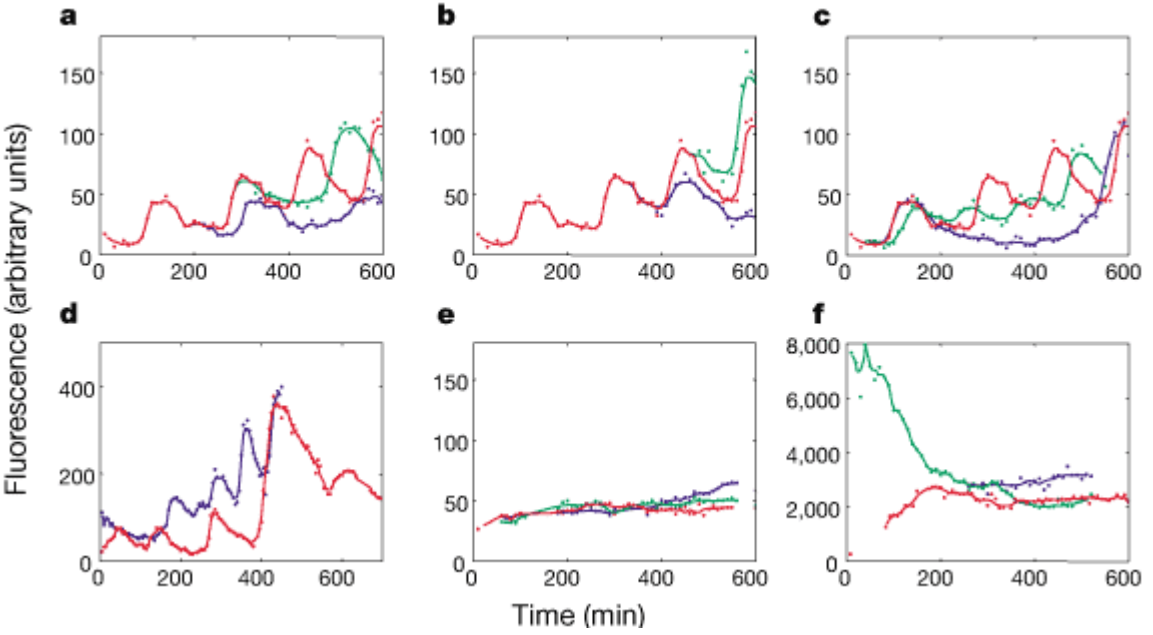
http://partsregistry.org/Main_Page

Repressilator: artificial clock





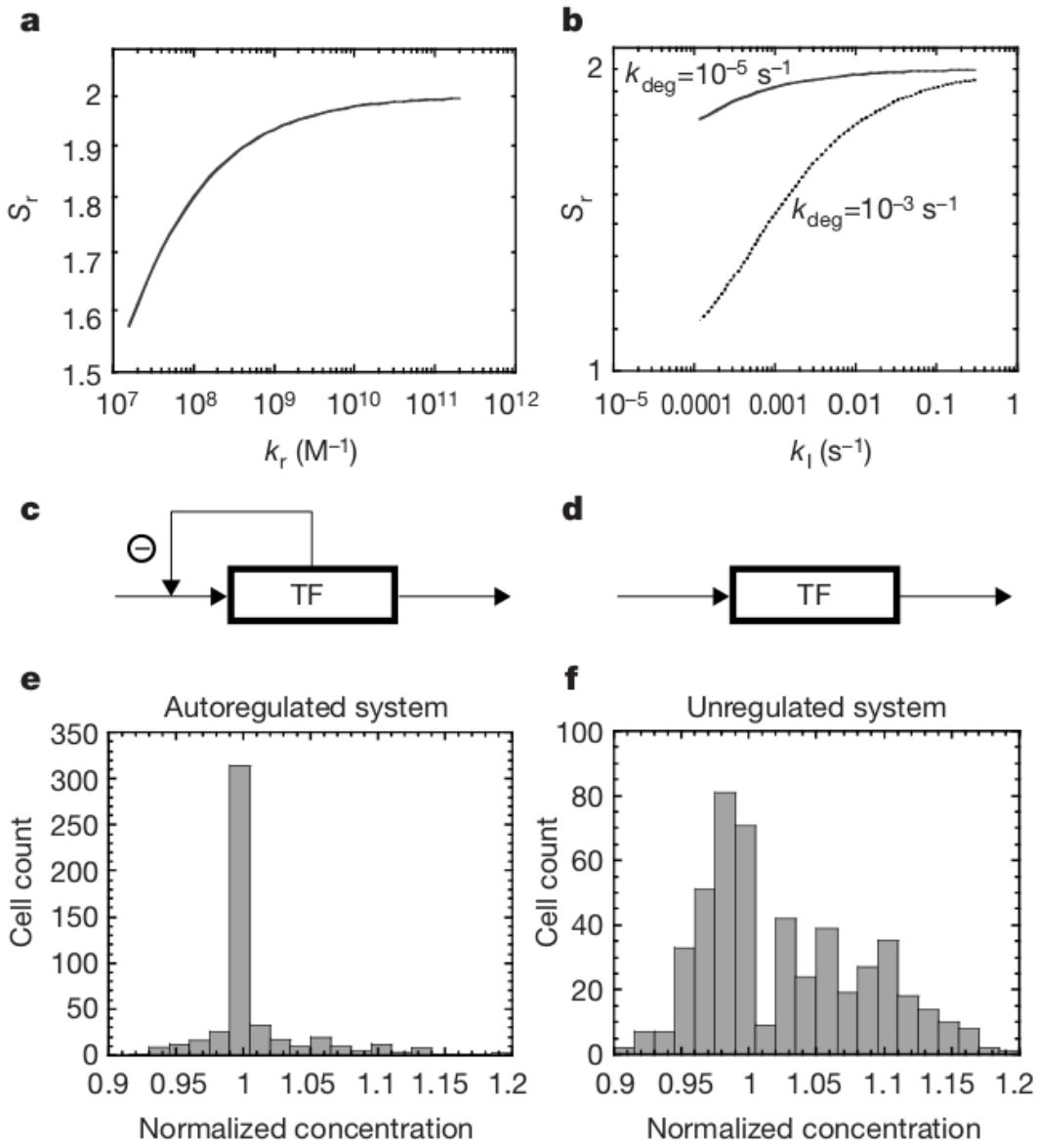




Elowitz & Leibler, Nature 2000

Engineering stability

Negative feedback
loops to control noise



Becskei & Serrano, Nature 2000

How can we study the “noise” in gene expression?

Can we count the total number of molecules in a single cell?

Experimental developments: single molecule view of gene expression

Protein levels

GFP (and other fluorescent probes)
FACS – Fluorescent Activated Cell Sorting
Live cell microscopy

mRNA levels

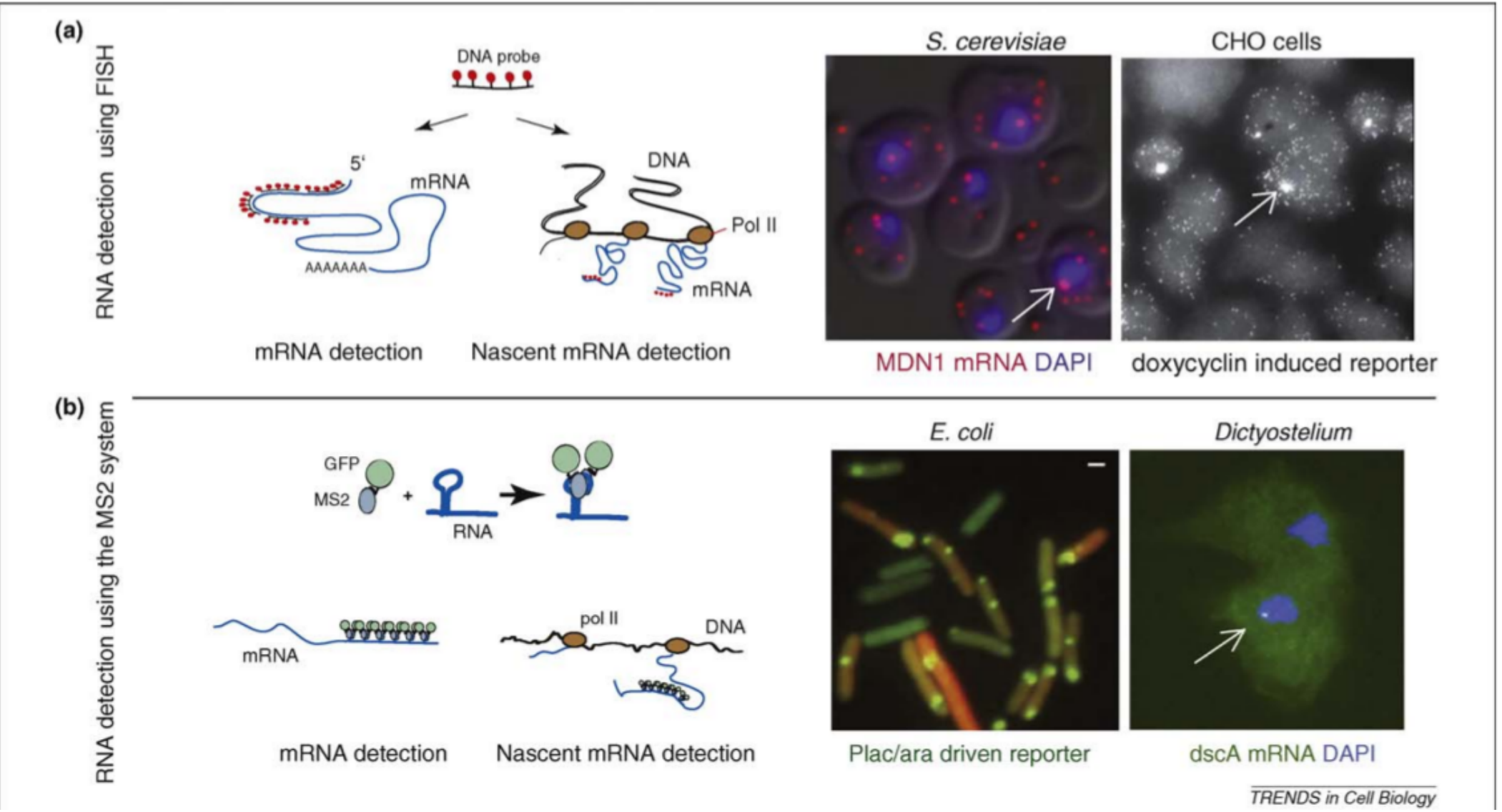
Single cell quantitative PCR
Single cell microarrays
In situ fluorescent PCR
FISH – Fluorescent in situ hybridization
MS2

Microfluidics

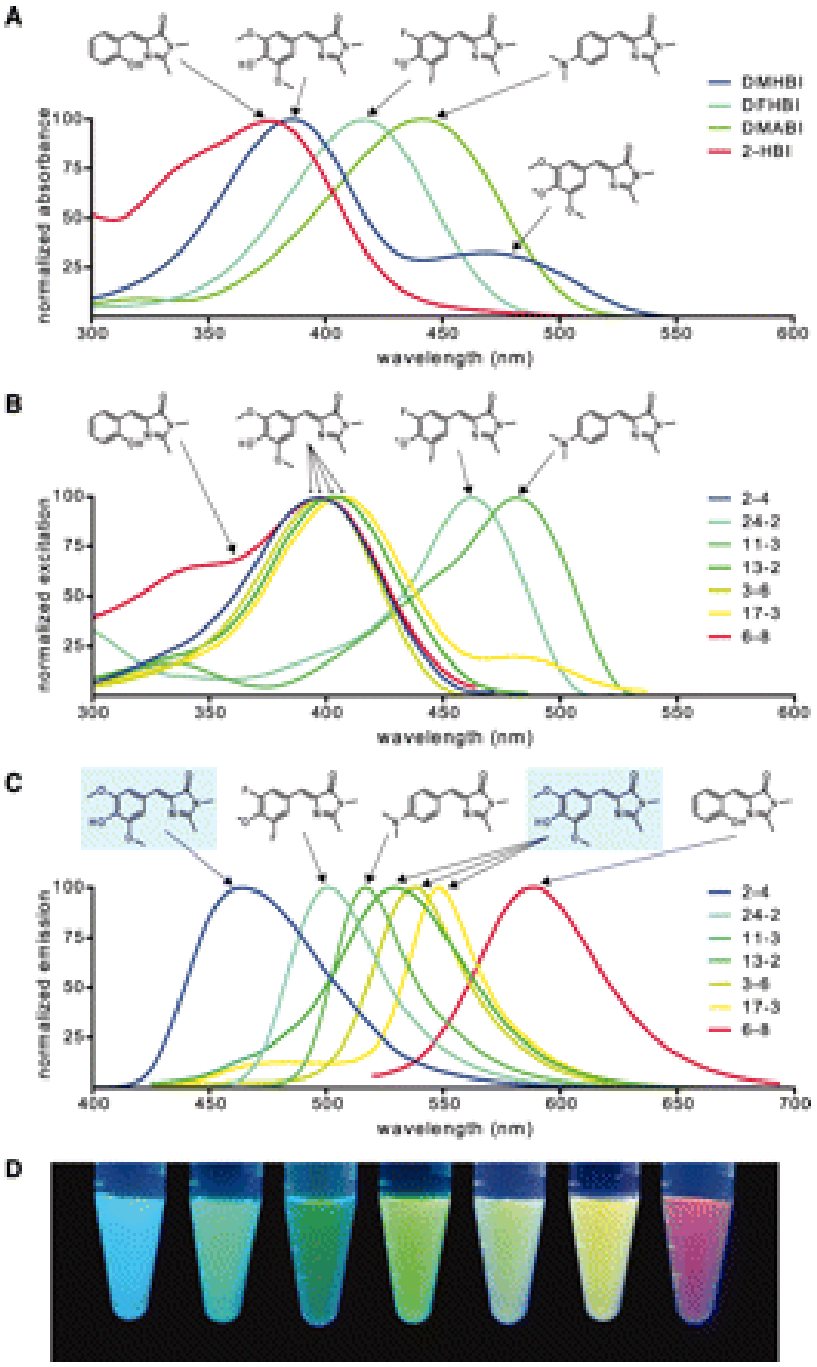
Table 1. Summary of the most common methods for mRNA quantification and transcription analysis

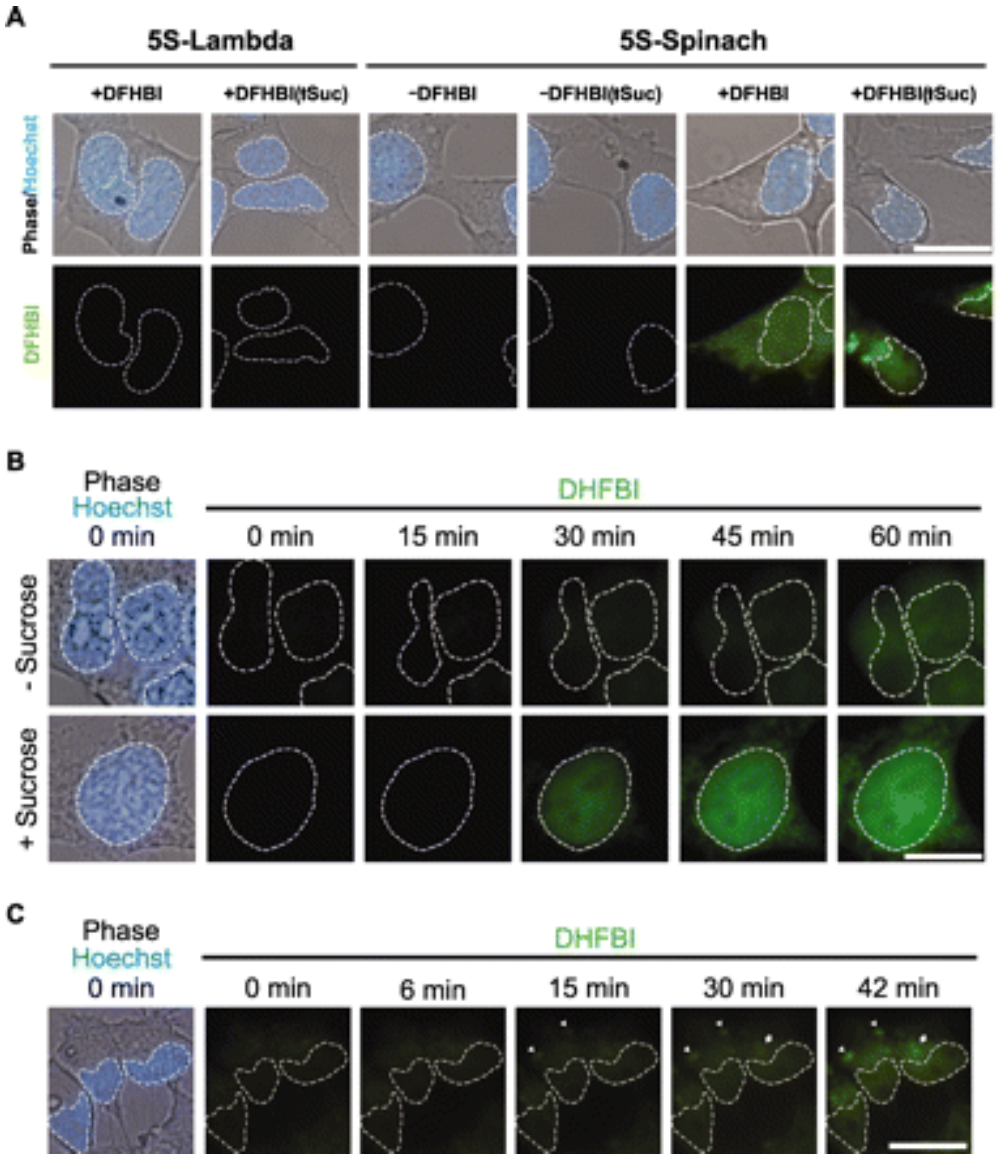
	Northern	Microarray	Real-time PCR	RNA seq	ChIP-ChIP	FISH	MS2
	Ensemble	Ensemble	Ensemble	Ensemble	Ensemble	Single cell	Single cell
Determining mRNA expression							
Measuring	Total mRNA	Total mRNA	Total mRNA	Total mRNA		Total mRNA	Total mRNA
Detection method	Blotting to membrane/ hybridization with synthetic probe	RNA labeling/ hybridization to array	Reverse transcription/ PCR	mRNA fragmentation/ adaptor ligation/ amplification/ sequencing		Hybridization using fluorescent probes	Insertion of repeats/binding of fluorescent protein
mRNA quantification	Relative intensity	Relative intensity	Absolute numbers requires standard	Single-molecule counting		Single-molecule counting	Single-molecule counting
Number of genes	Multiple	Genome wide	Many	Genome wide		1–3 per cell	1 per cell
Measuring transcription							
Measuring					Polymerase association	Nascent mRNAs	Nascent mRNAs
Detection method					Fragmentation/ IP/amplification/ hybridization to array	Hybridization using fluorescent probes	Insertion of repeats/Binding of fluorescent protein
Quantification					Relative changes in polymerase loading	Counting of nascent mRNAs	Relative intensity of mRNA signal
Number of genes					Genome wide	1–3 per cell	1 per cell

Larson et al, Trends in Cell Biology 2009



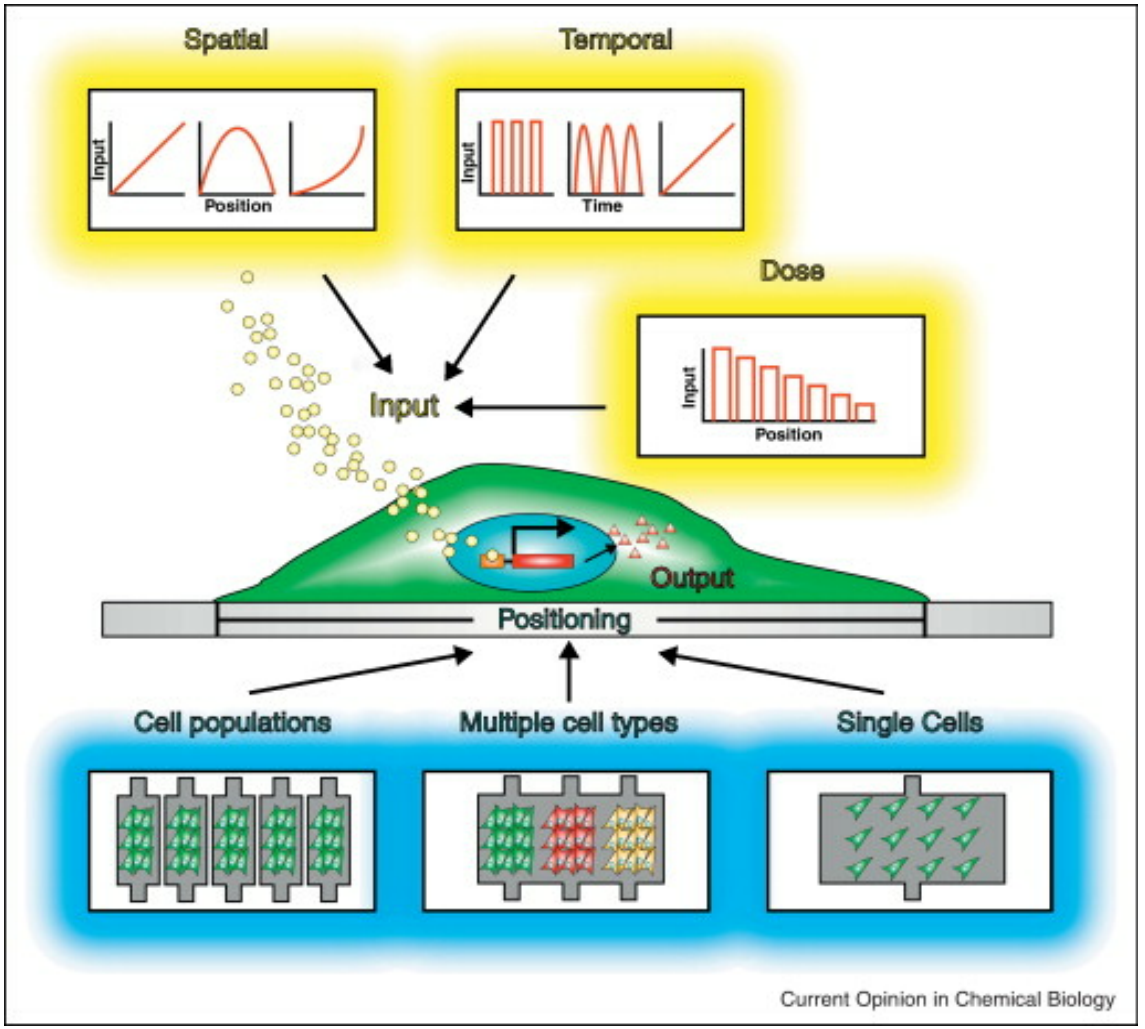
Larson et al, 2009



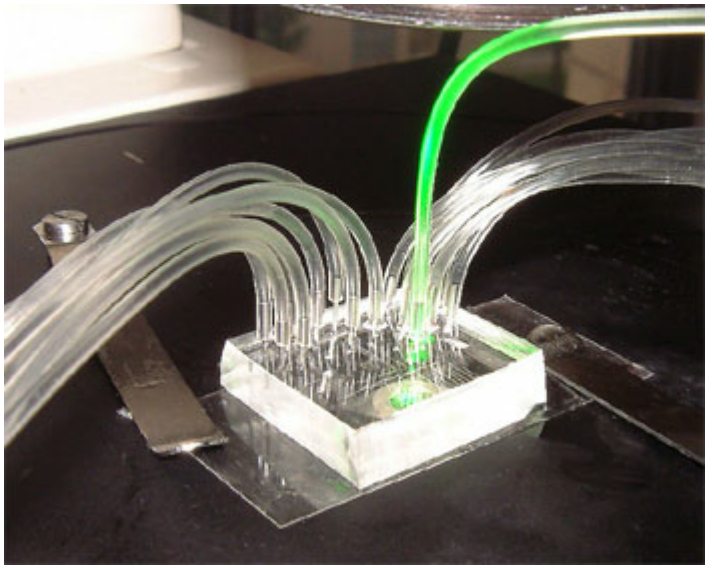


RNA mimics of GFP
Paige et al, Science 2011

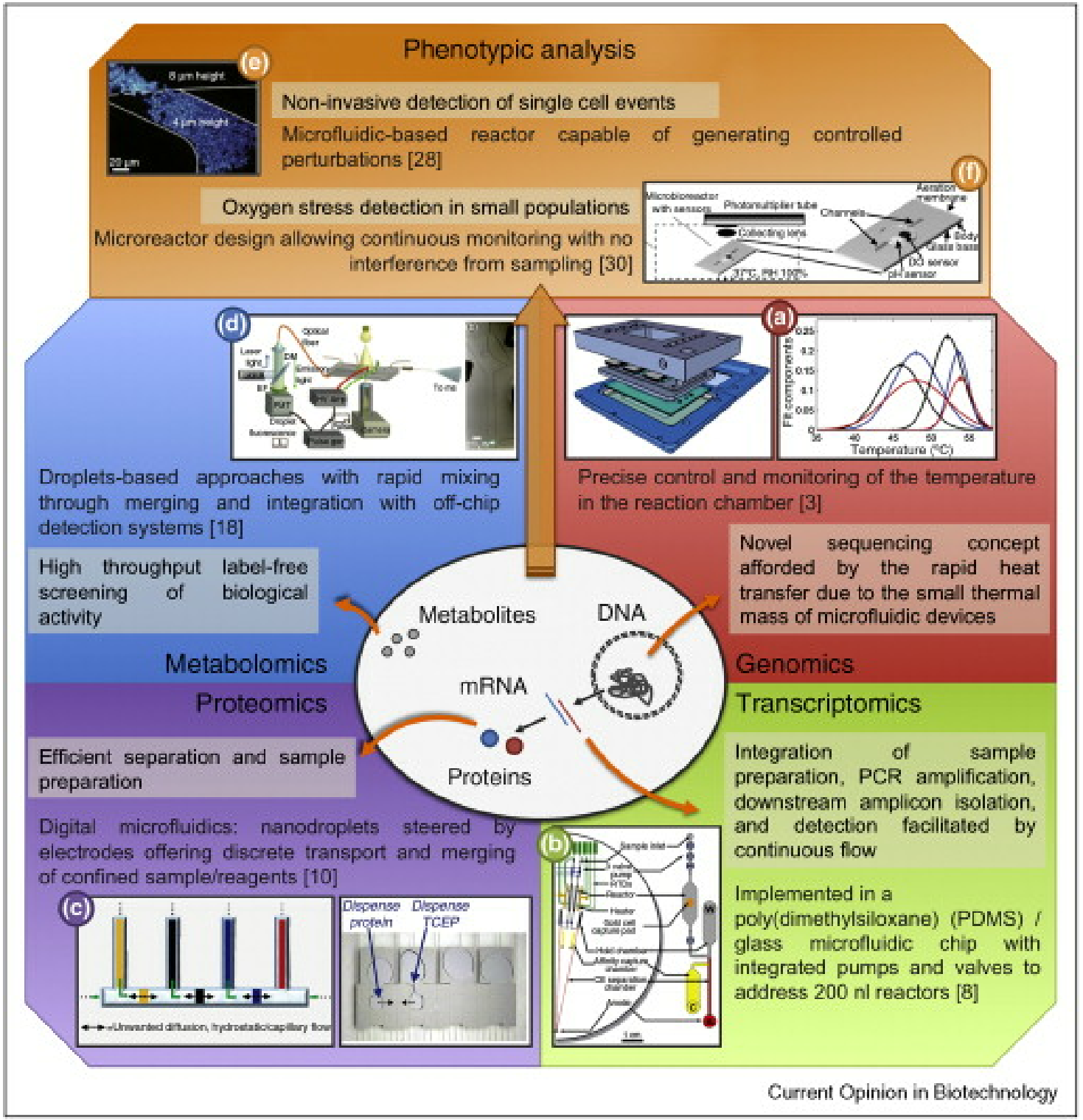
Microfluidics



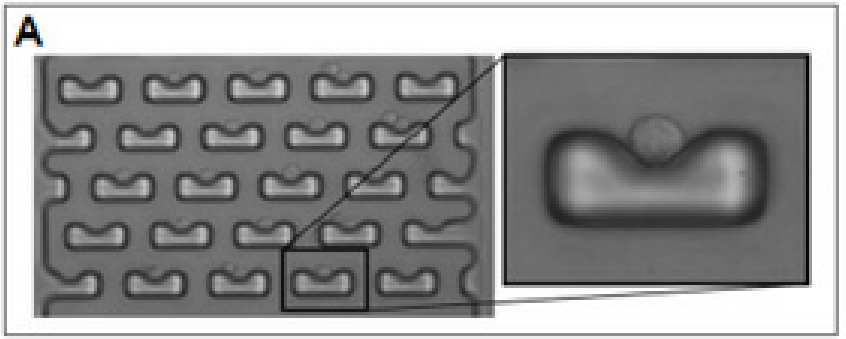
Lin & Levchenko, 2012

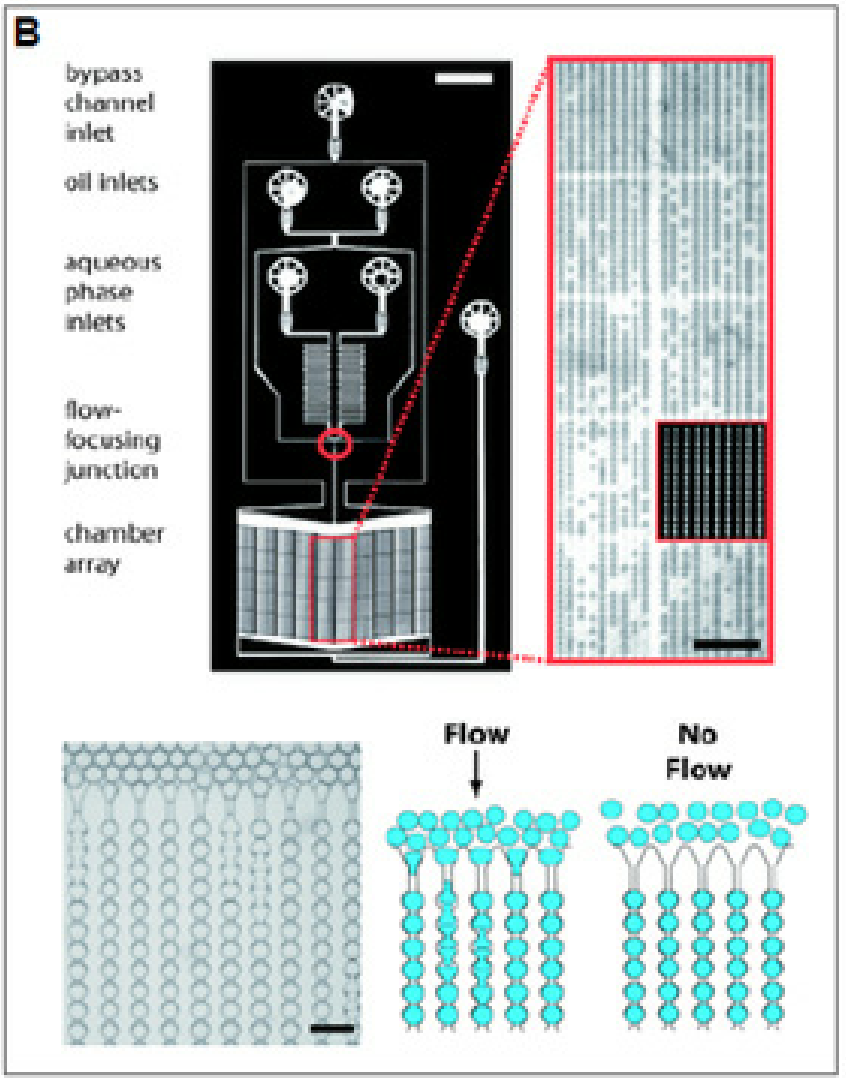


http://groups.csail.mit.edu/cag/biostream/



Szita et al, 2010



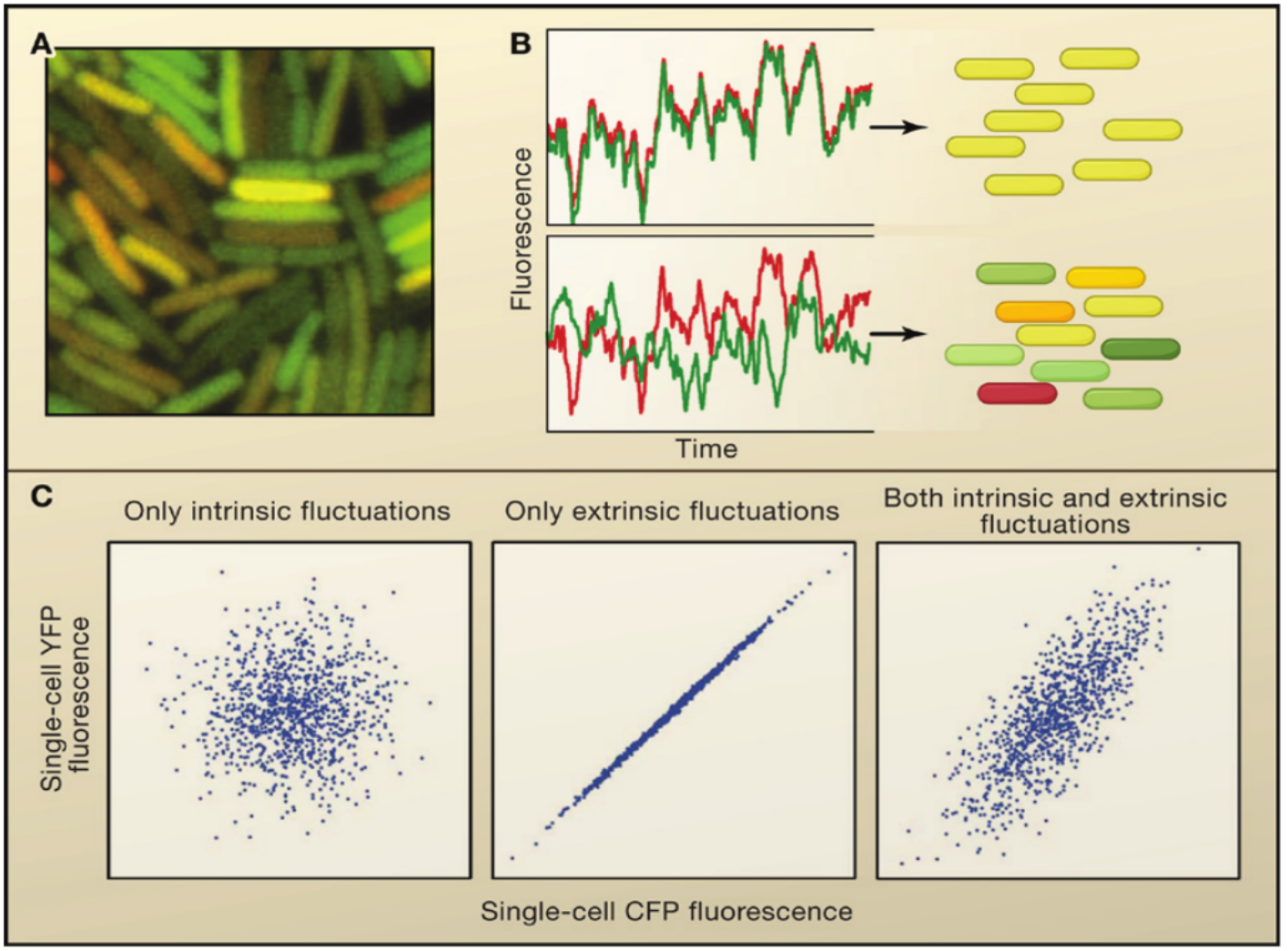


http://www.elveflow.com/microfluidic-reviews-and-tutorials/review-microfluidic-for-cell-biology

So far, we know that noise exists, can be detected and even engineered to be controlled.

...but what are the causes of stochastic gene expression?

Causes of stochastic gene expression???



Elowitz et al, Science 2002

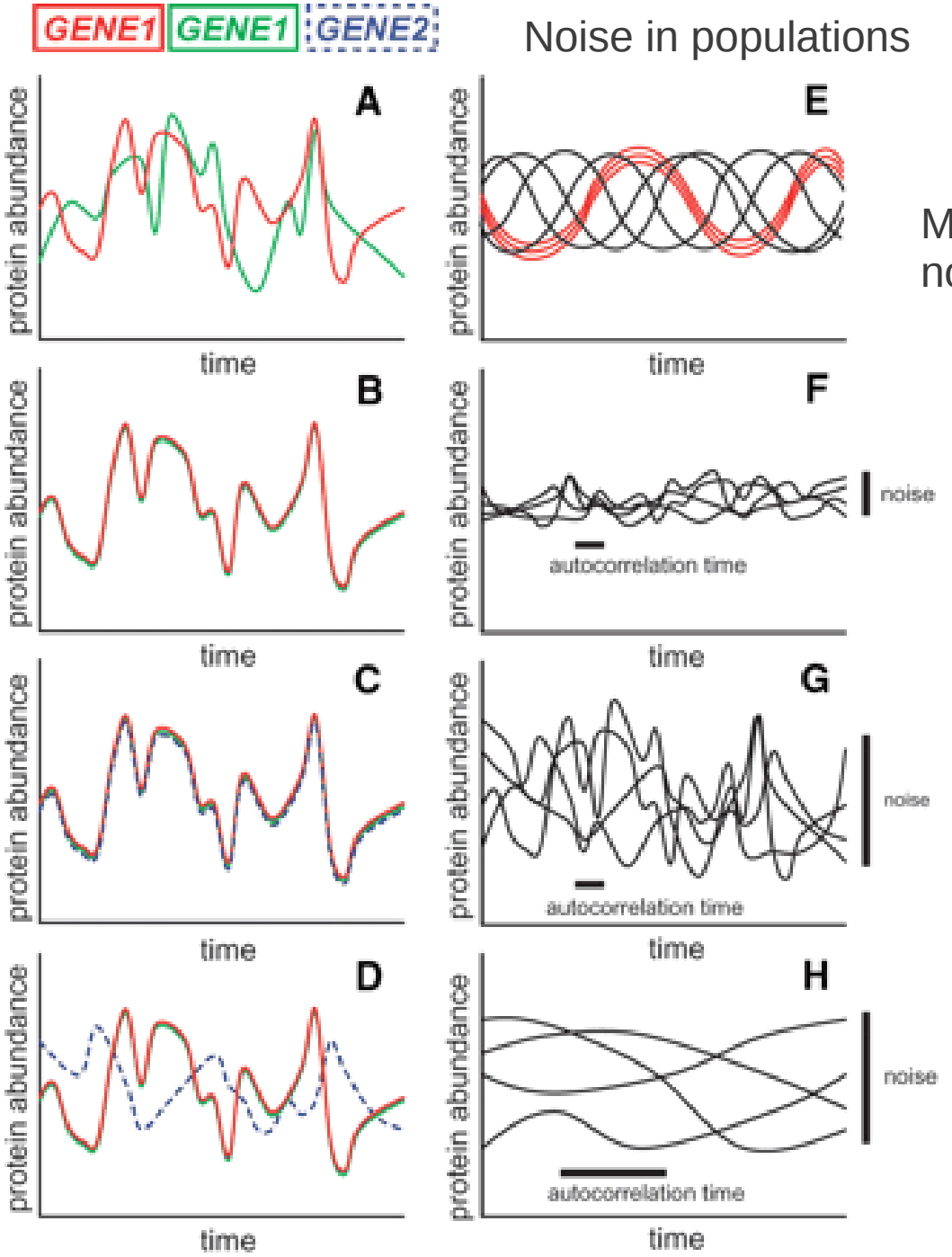
Noise in populations

Intrinsic noise

Extrinsic noise

Global noise

Gene or pathway specific noise



Manipulable extrinsic noise

Noise of low magnitude and short autocorrelation time

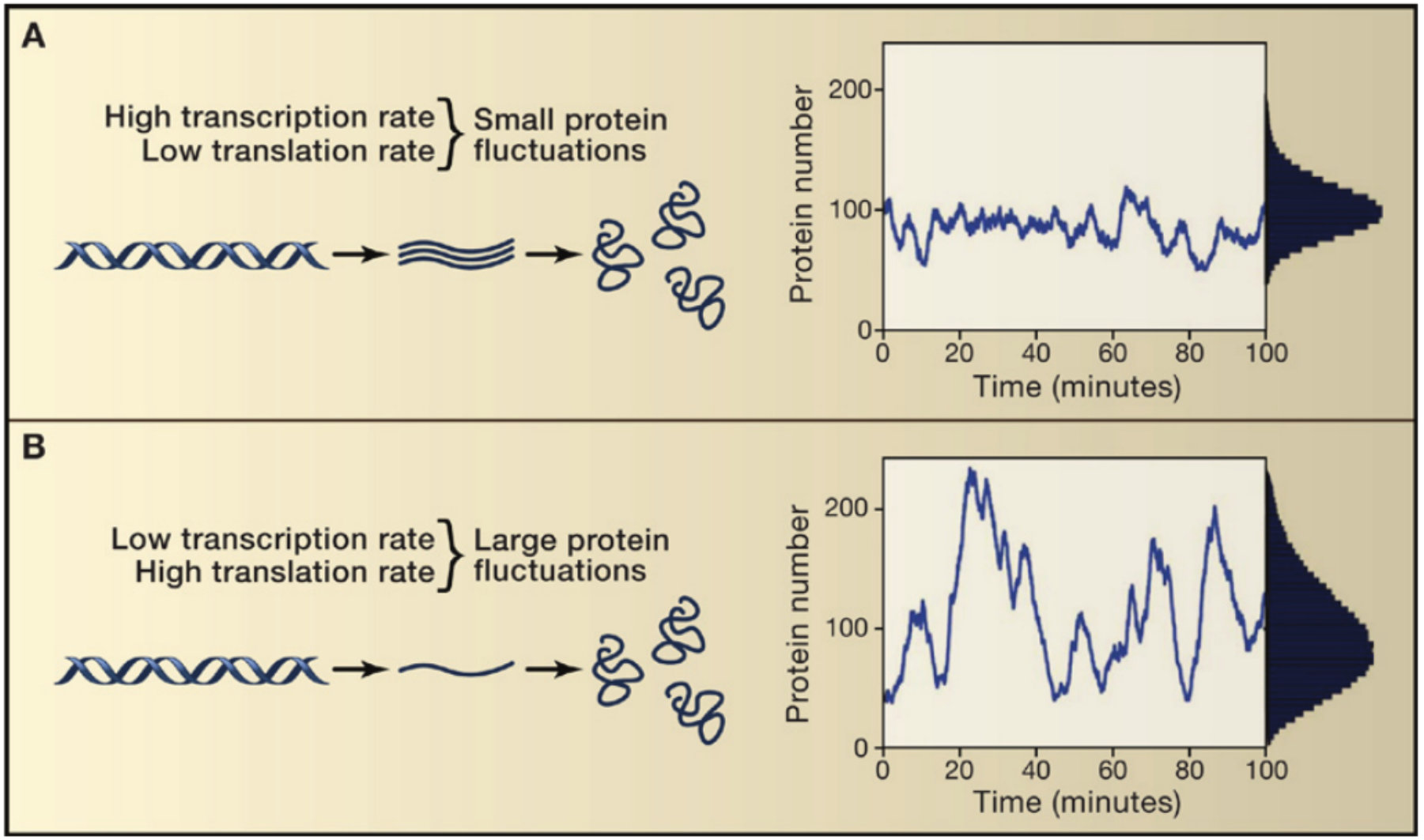
Noise of high magnitude and short autocorrelation time

Noise of high magnitude and long autocorrelation time

Autocorr. Time = time scale over which the protein production rate fluctuates in any given cell

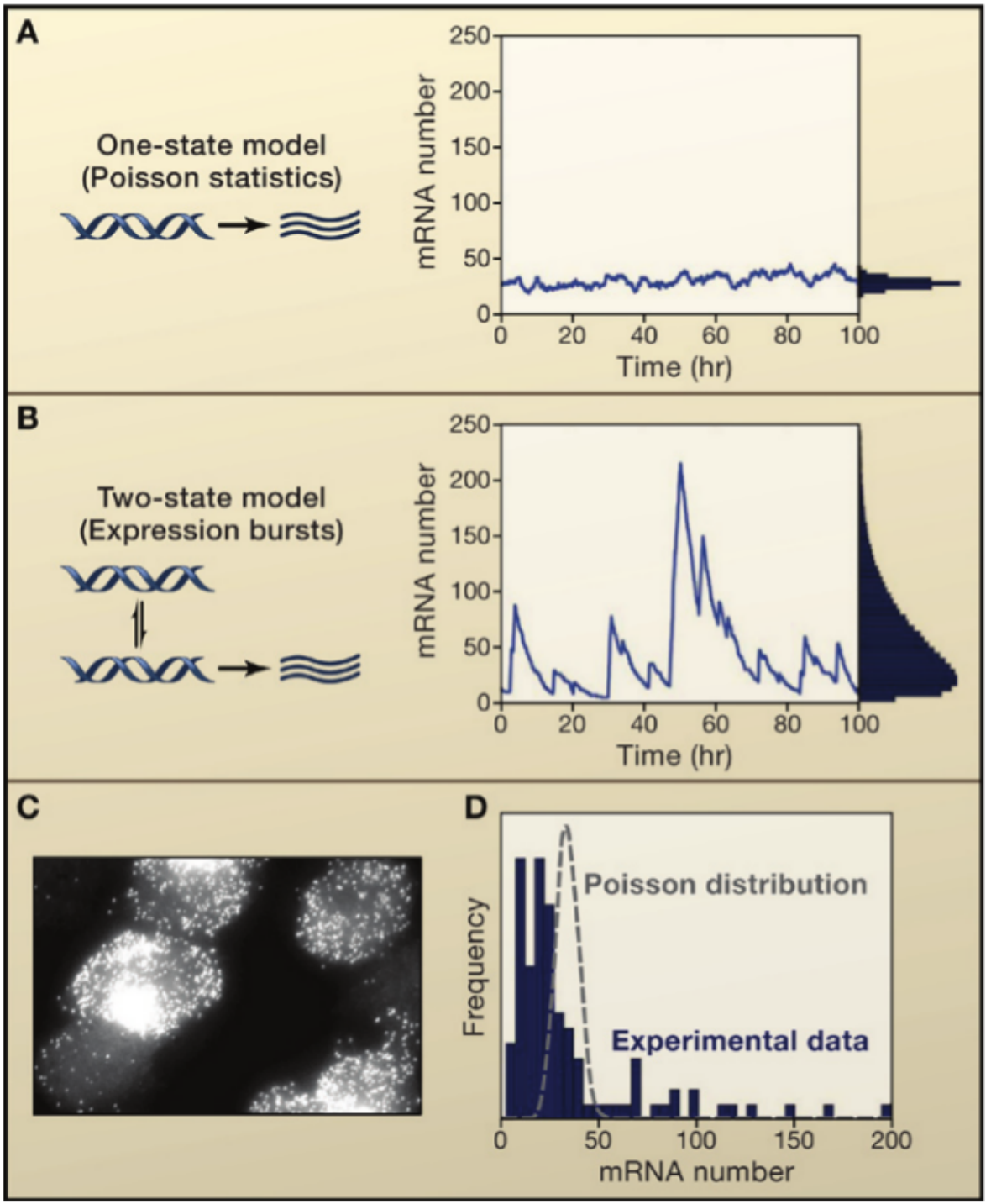
Raser & O'Shea, Science 2005

Noise in prokaryotic gene expression



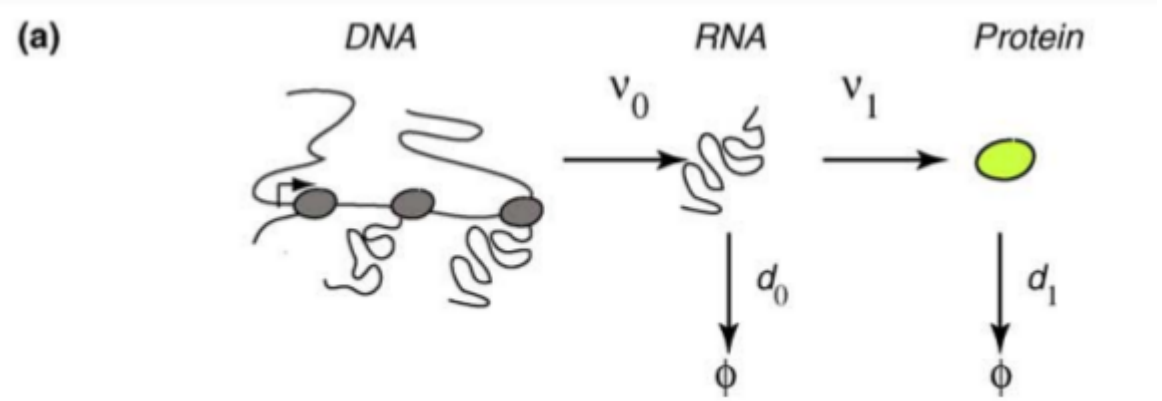
Raj & van Oudenaarden, 2008

Transcriptional bursts and cell to cell variability



Raj & van Oudenaarden, 2008

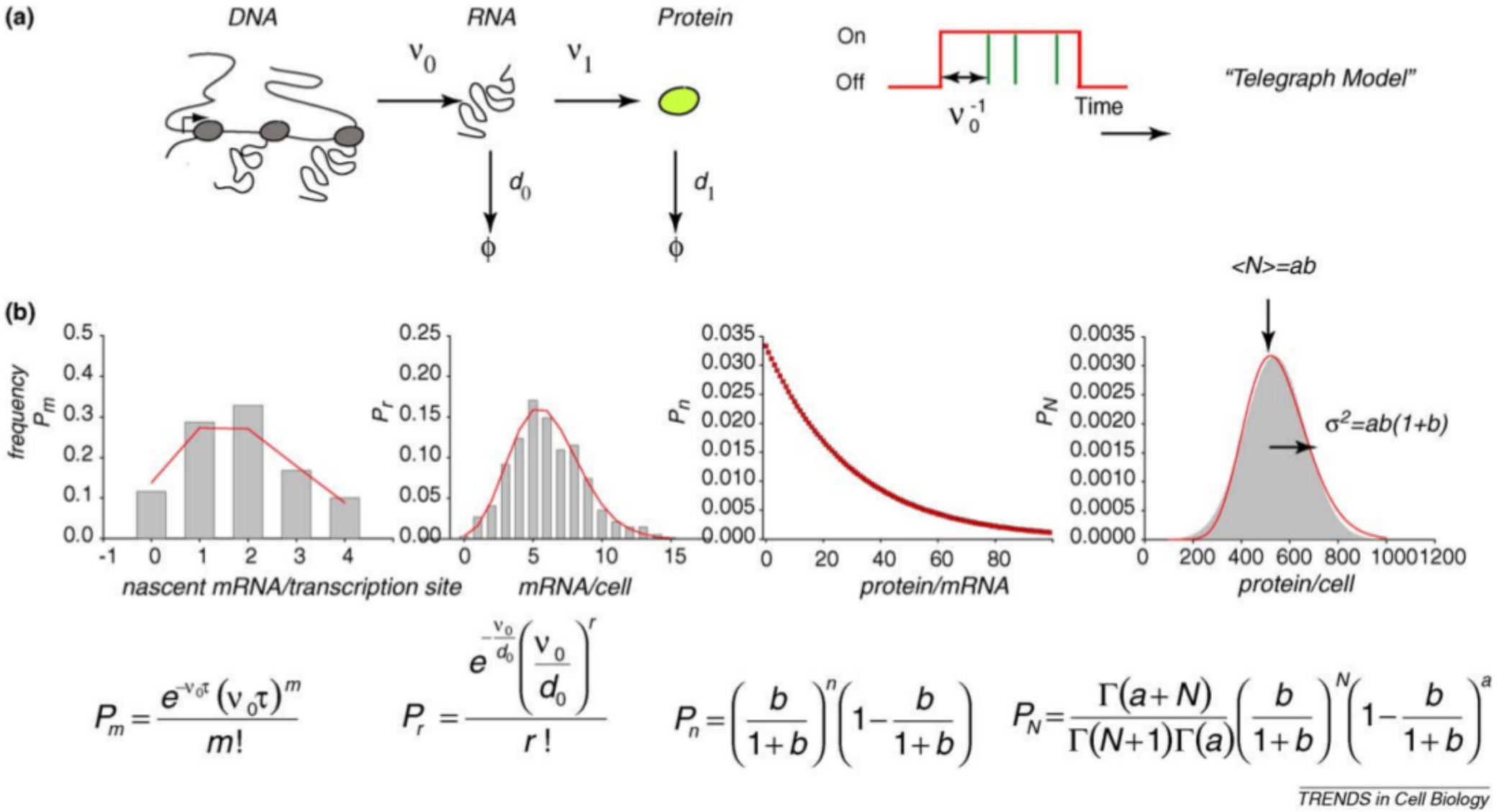
Advantage of couting molecules



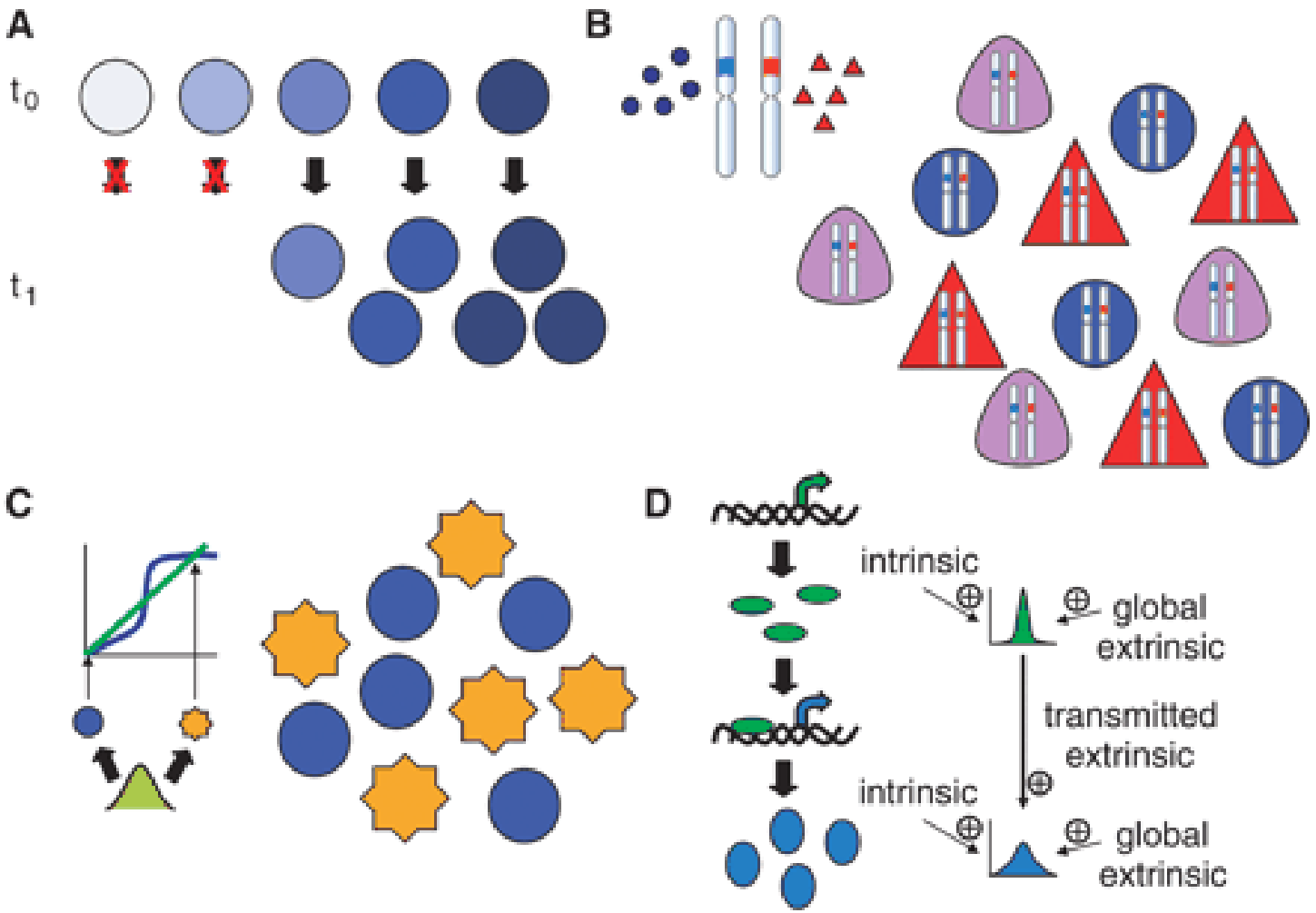
Probability distribution of molecules corresponding to each stage of the central dogma, for a single gene

Larson et al, 2009

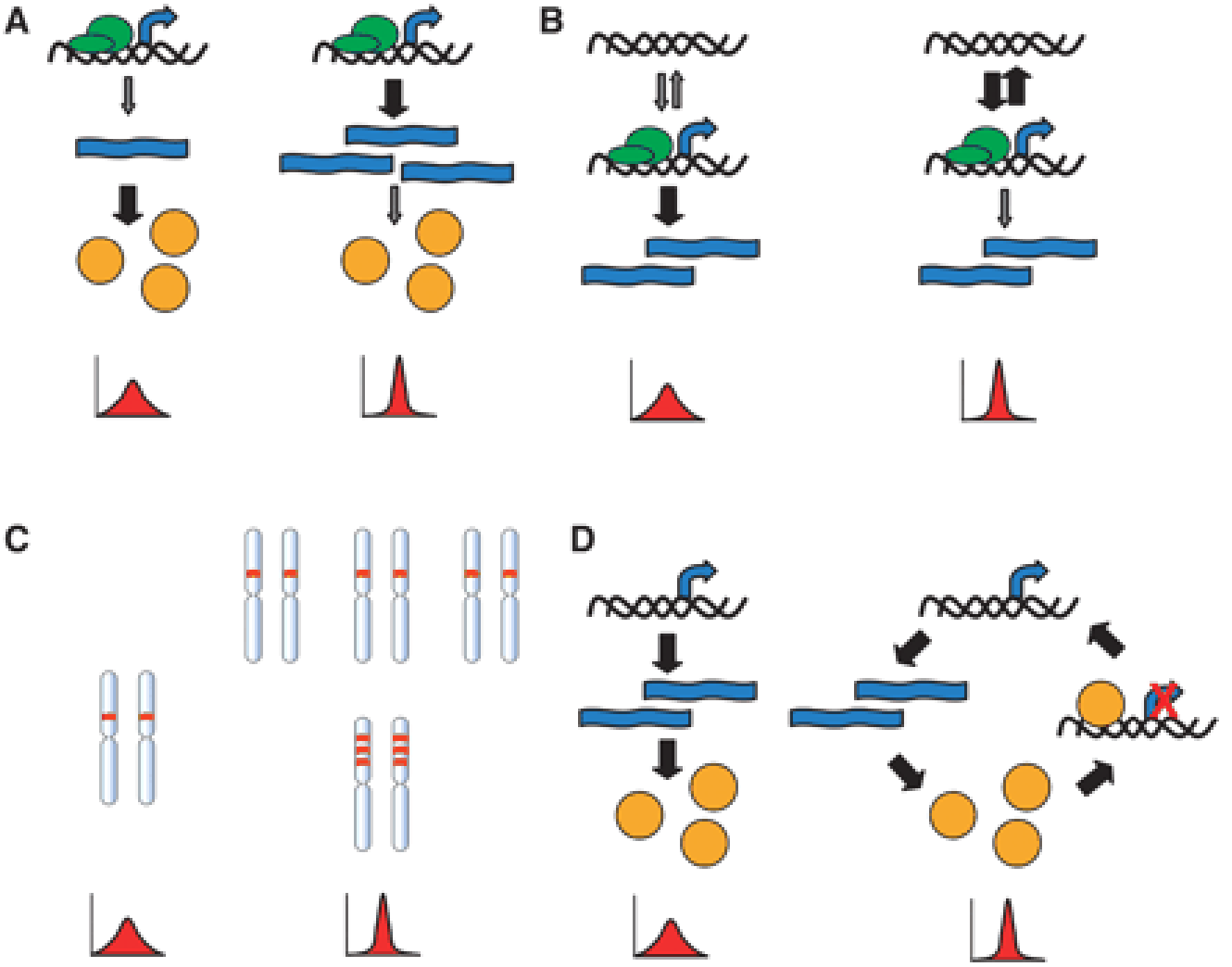
Theoretical models



Consequences of noise in gene expression



Control of noise



Afternoon discussion:

Functional roles for noise in genetic circuits

Eldar & Elowitz, Nature, 2010

Figure 1: Gene expression noise is ubiquitous, and affects diverse systems at several levels.

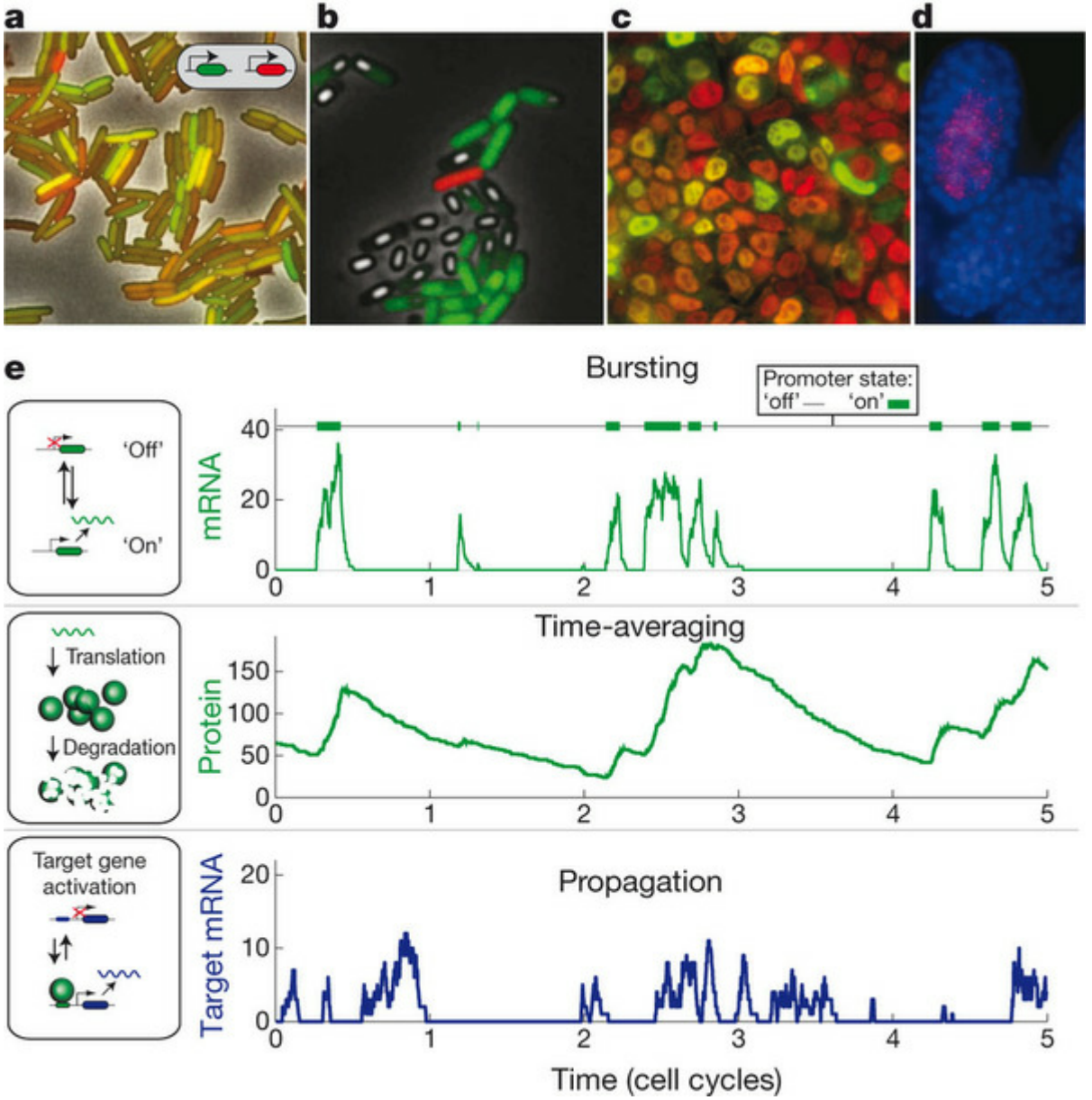


Figure 2: Frequency modulation of stochastic nuclear localization bursts enables coordination of gene regulation.

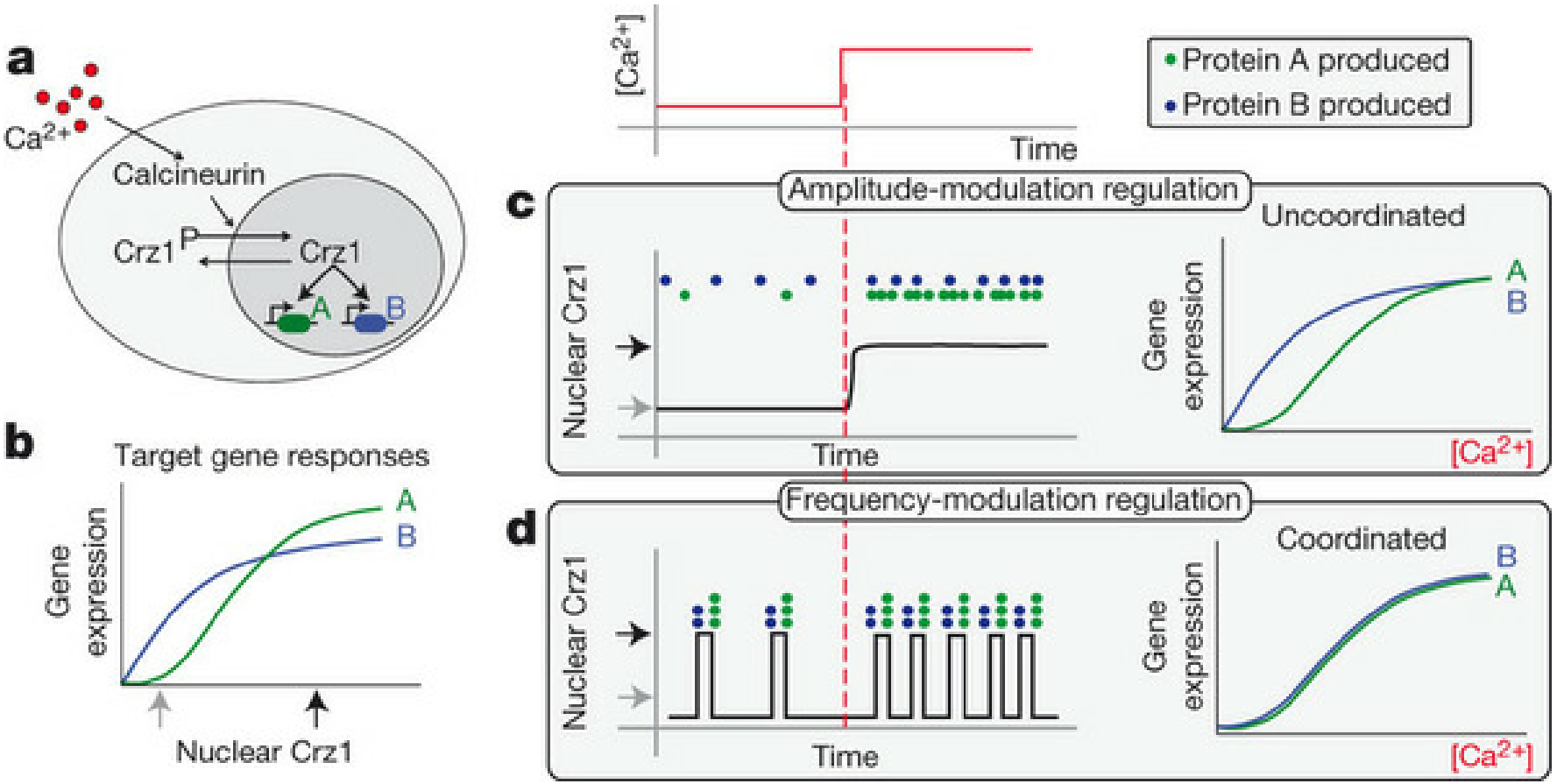


Figure 3: Probabilistic differentiation.

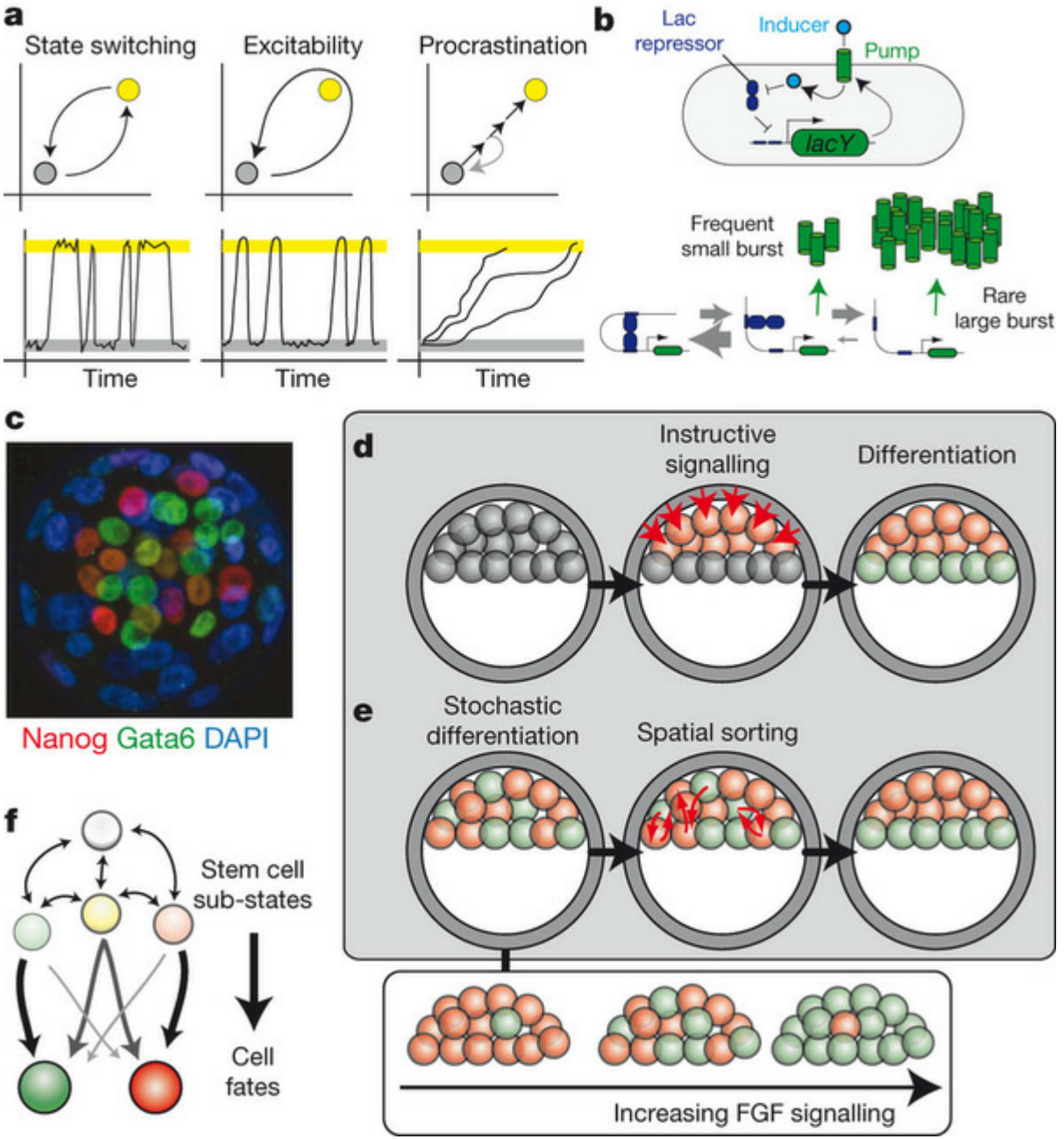


Figure 4: Roles of noise in evolution.