Noises and dynamics in cells: Mathematical modeling in systems biology

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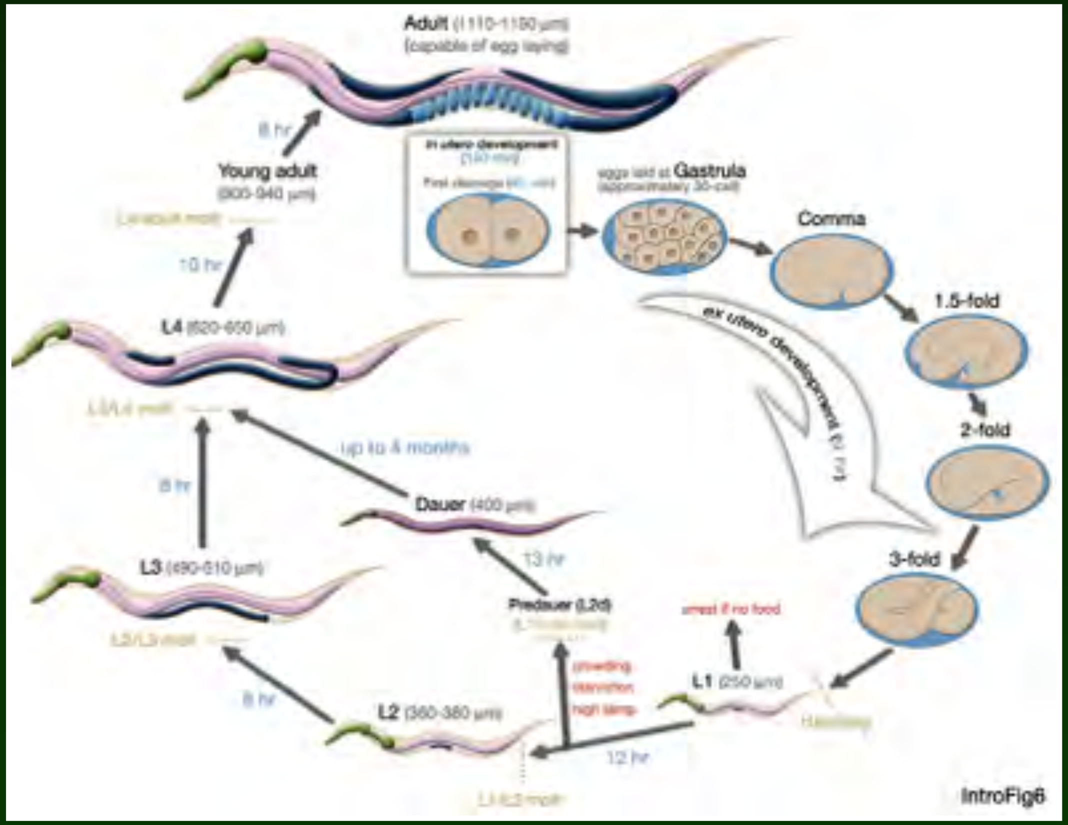
Webinar
Philippine Genome Center
May 23, 2016




South Korea
Yellow Sea
Nagoya
名古屋
Japan
Tokyo
東京
Osaka
大阪
China
Shanghai
上海
East China Sea
Library, Institute of Information Science...
Academia Sinica
Myanmar (Burma)
Laos
Hong Kong
香港
Thailand
Vietnam
South China Sea
Luzon
Bangkok
กรุงเทพมหานคร
Cambodia
Philippines
Andaman Sea
Ho Chi Minh City
Visayas

Where am I?

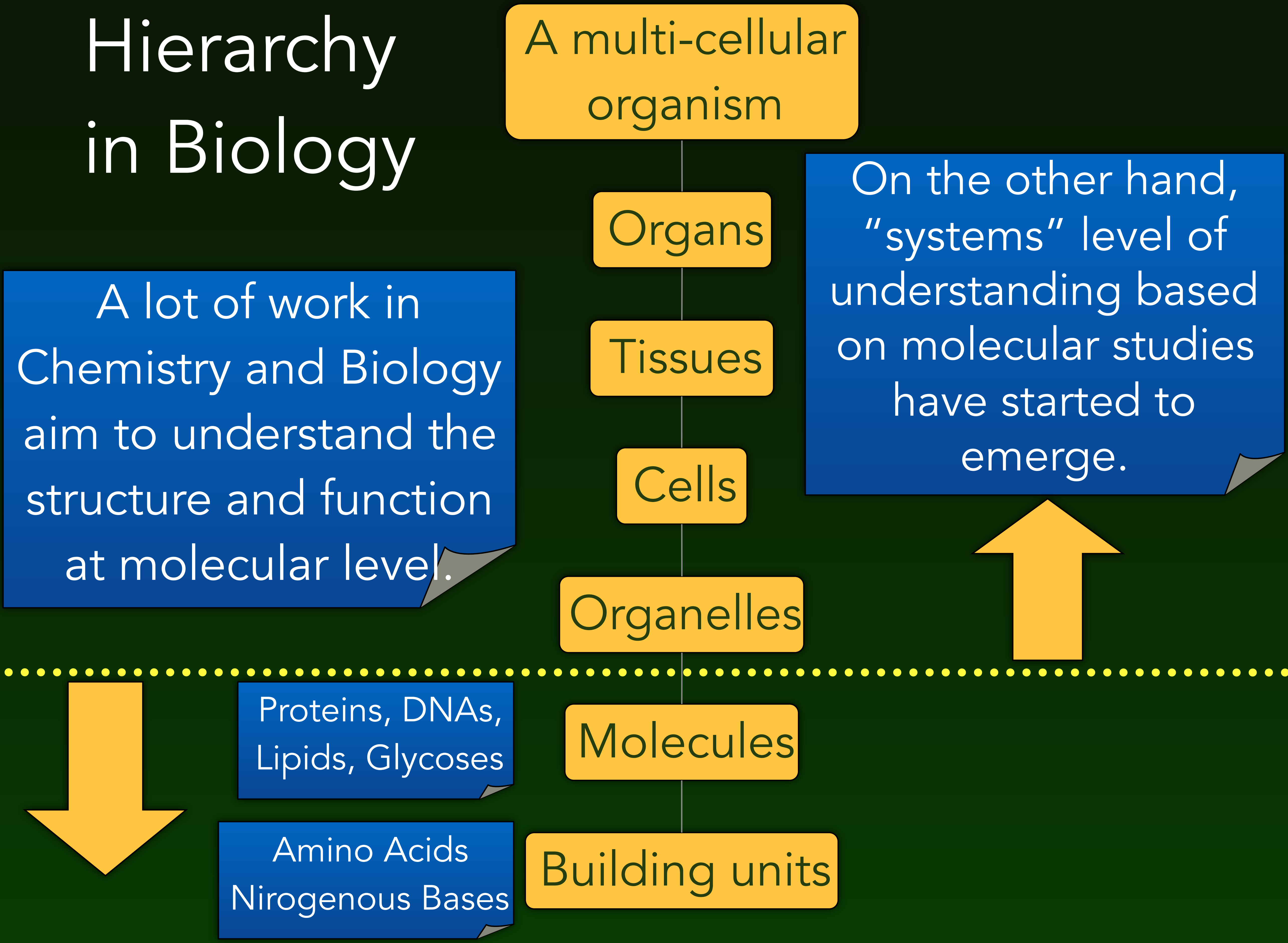
Academia Sinica is located to the East of Taipei City

Institute of Chemistry
Academia Sinica

My research interests

- Electron and energy transfer problems.
  - In quantum chemistry.
  - With an application to photosynthesis.
  - most of our application are in Materials.
- Dynamical modeling in Biology.

Hierarchy in Biology



A multi-cellular organism

Organs

Tissues

Cells

Organelles

Molecules

Building units

A lot of work in Chemistry and Biology aim to understand the structure and function at molecular level.

On the other hand, "systems" level of understanding based on molecular studies have started to emerge.

Proteins, DNAs, Lipids, Glycoses

Amino Acids Nirogenous Bases

We are interested in

- Dynamic Description of Biological systems.
  - What is really going on in a living system?
    - How the desired outputs are generated.
    - What may be the factors that contribute to the special properties of such dynamics.
    - …

In the framework of biological observations

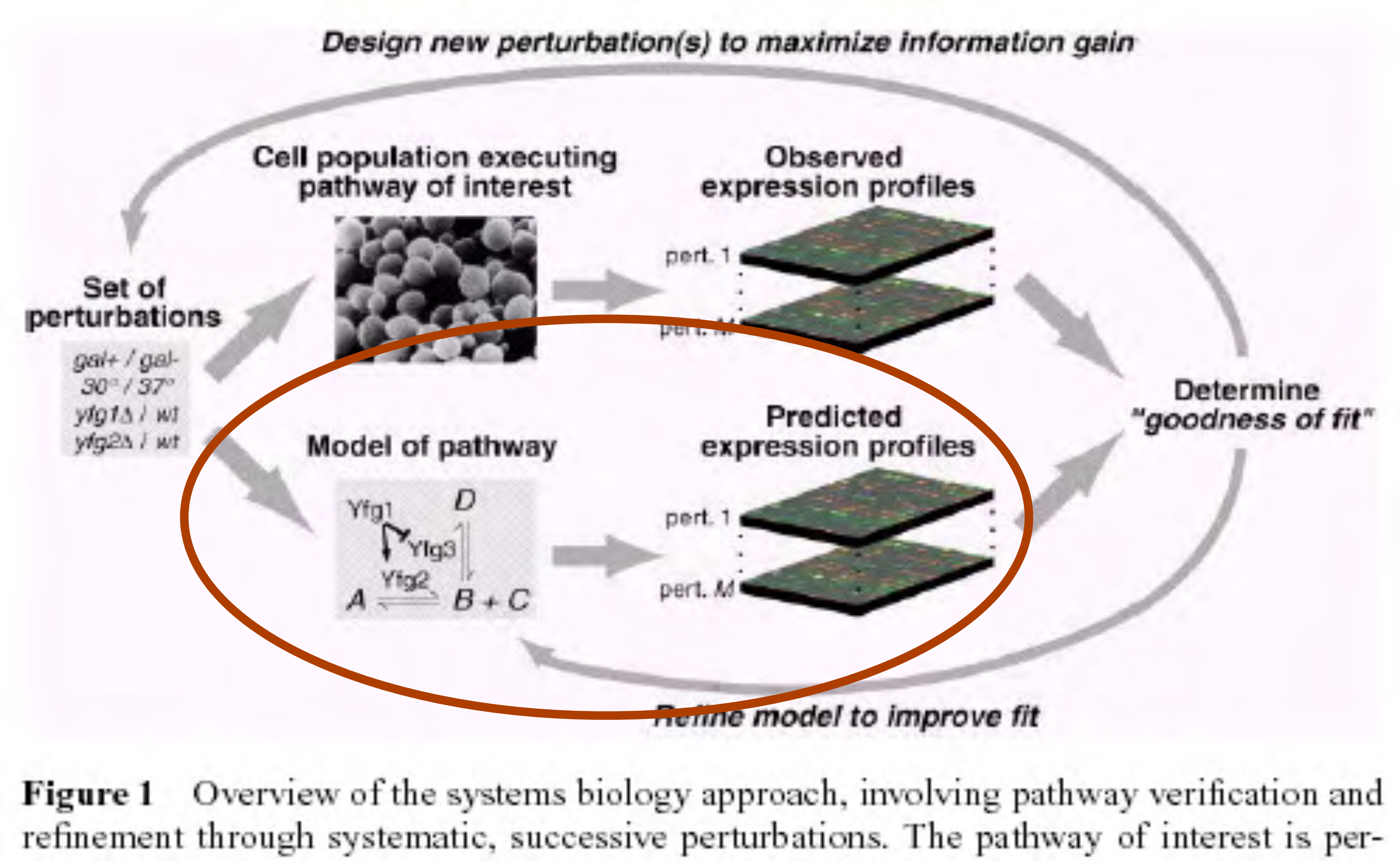
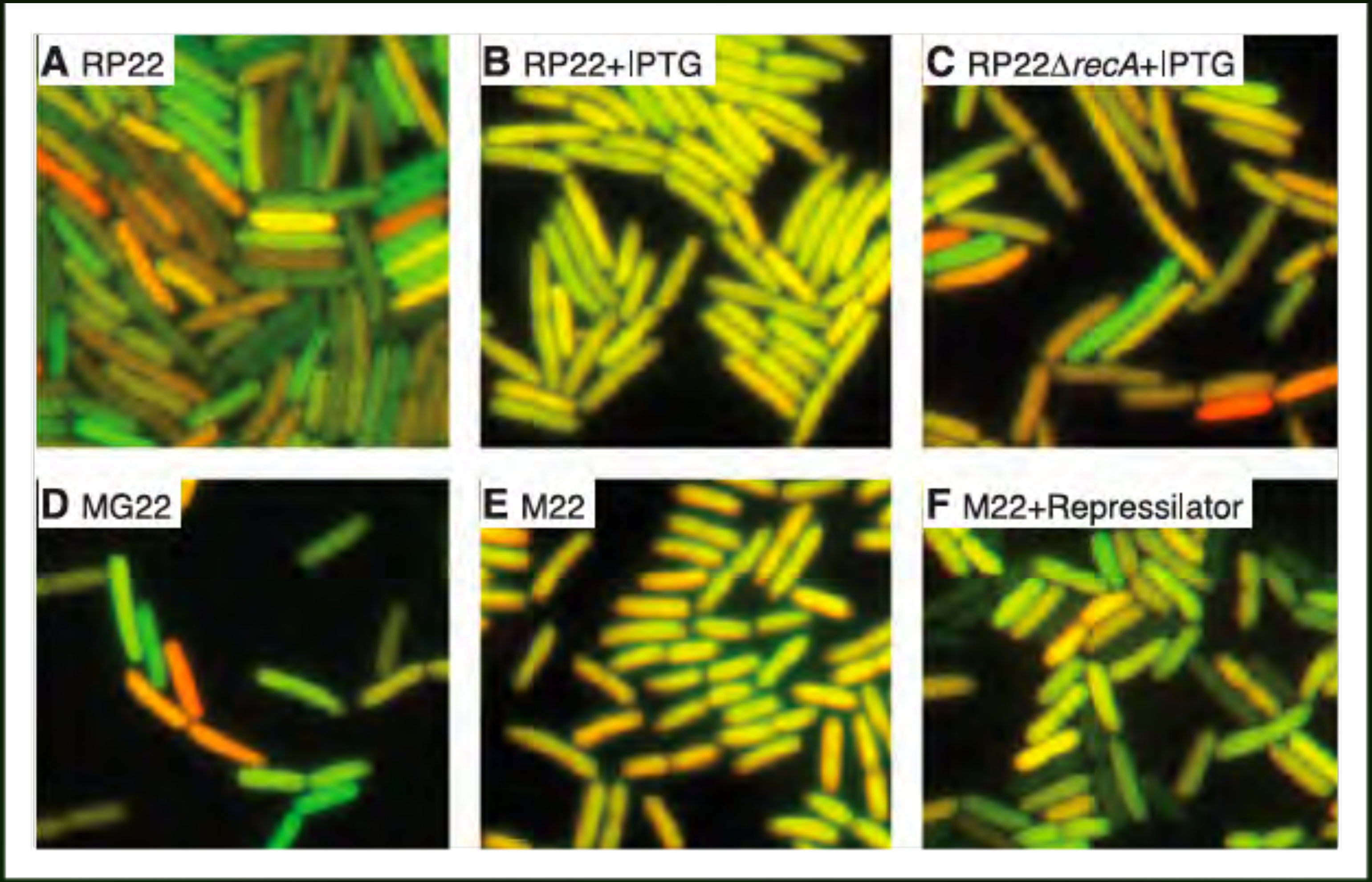


Figure 1 Overview of the systems biology approach, involving pathway verification and refinement through systematic, successive perturbations. The pathway of interest is per-

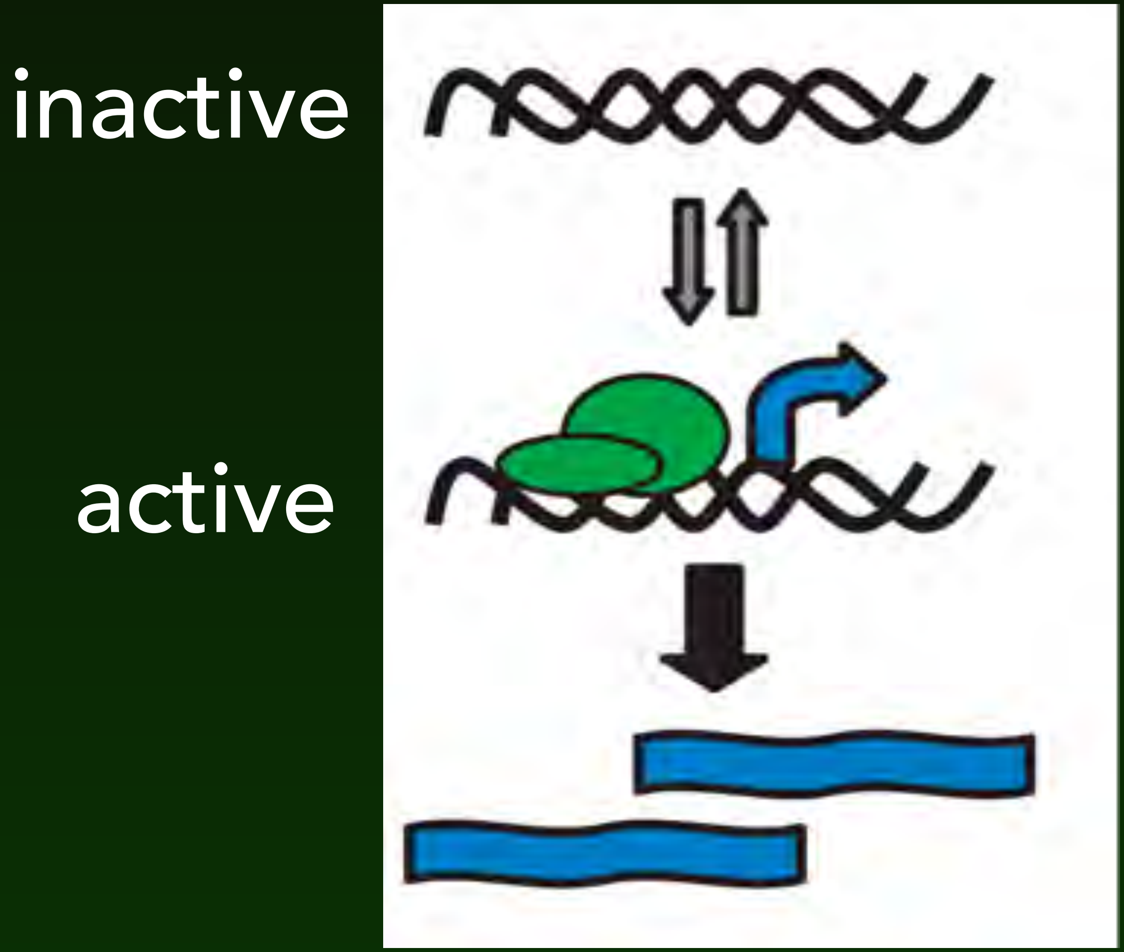
T. Ideker et al. Annu. Rev. Genomics Hum. Genet. (2001)



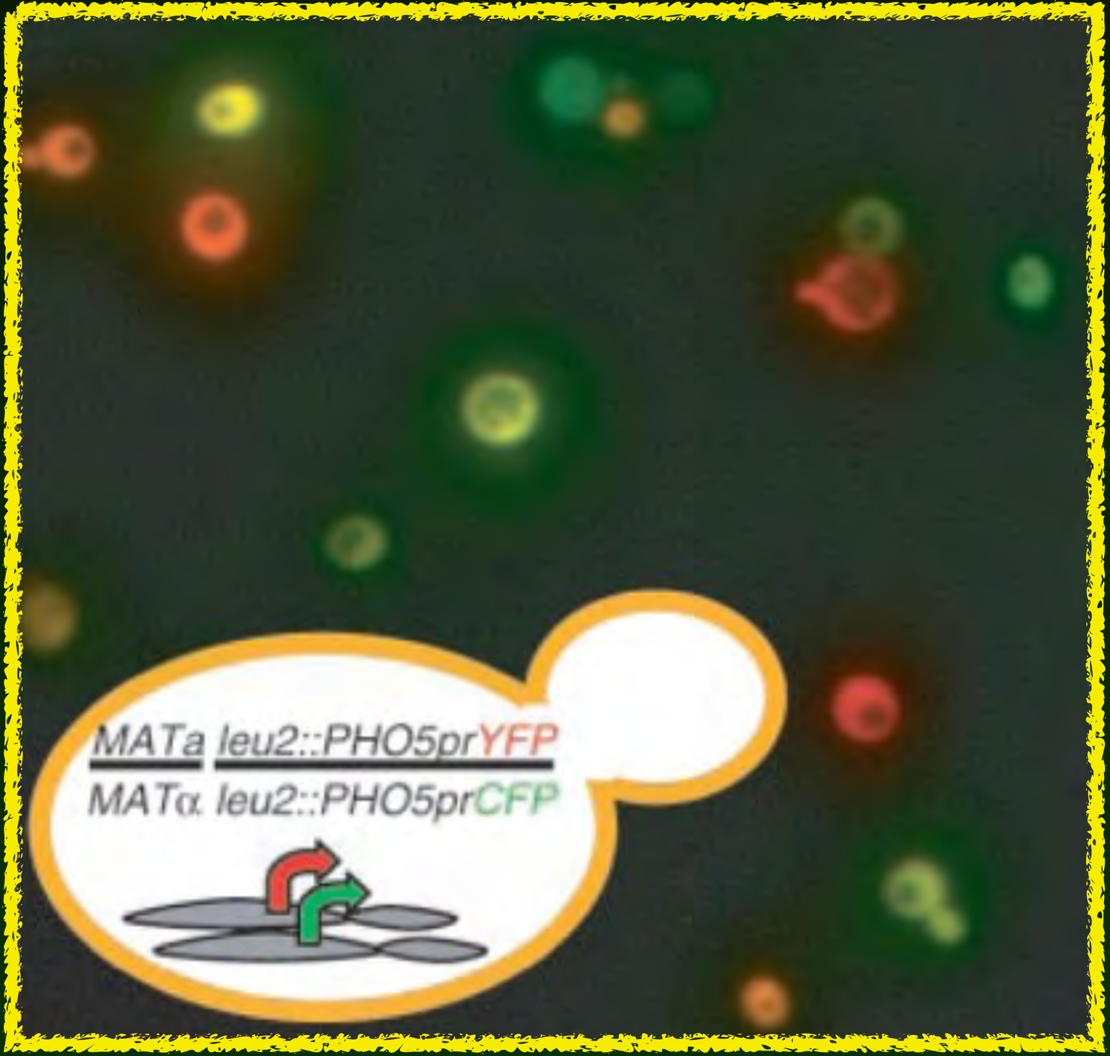
Elowitz, 2002

Dynamics in stochastic biological processes — “noisy cells”

Gene expression is "noisy"



Gene transitions randomly between active and inactive states



Cell to cell variability in a population

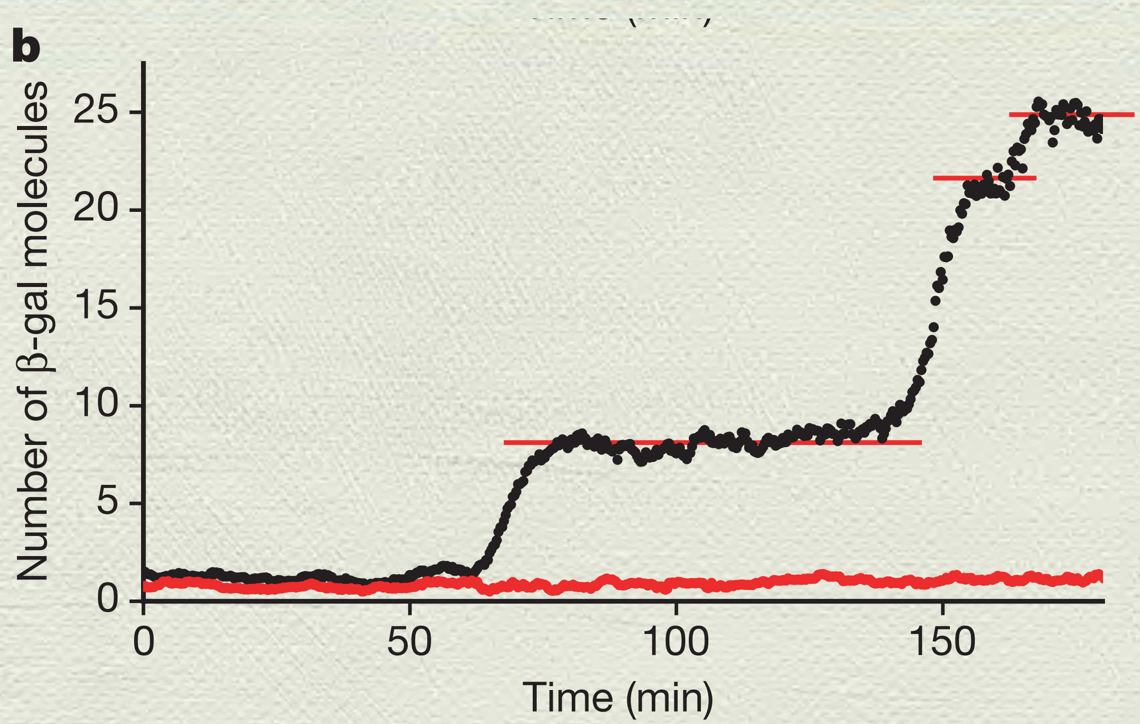
Science 309, 2010-2013 (2009)
Science 304, 1811-1814 (2004)

two genes (cfp, -green; yfp, -red) controlled by identical promoters, integrated at the same locus on homologous chromosomes.

Today’s talk includes

1. Theoretical Development for fluctuation and dynamics in a cell.
2. An account for gene expression noises.
   - for computer simulation.
3. An application project in C. elegans development.

Genes express in bursts. The production is noisy.



L. Cai, N. Friedman and X. S. Xie
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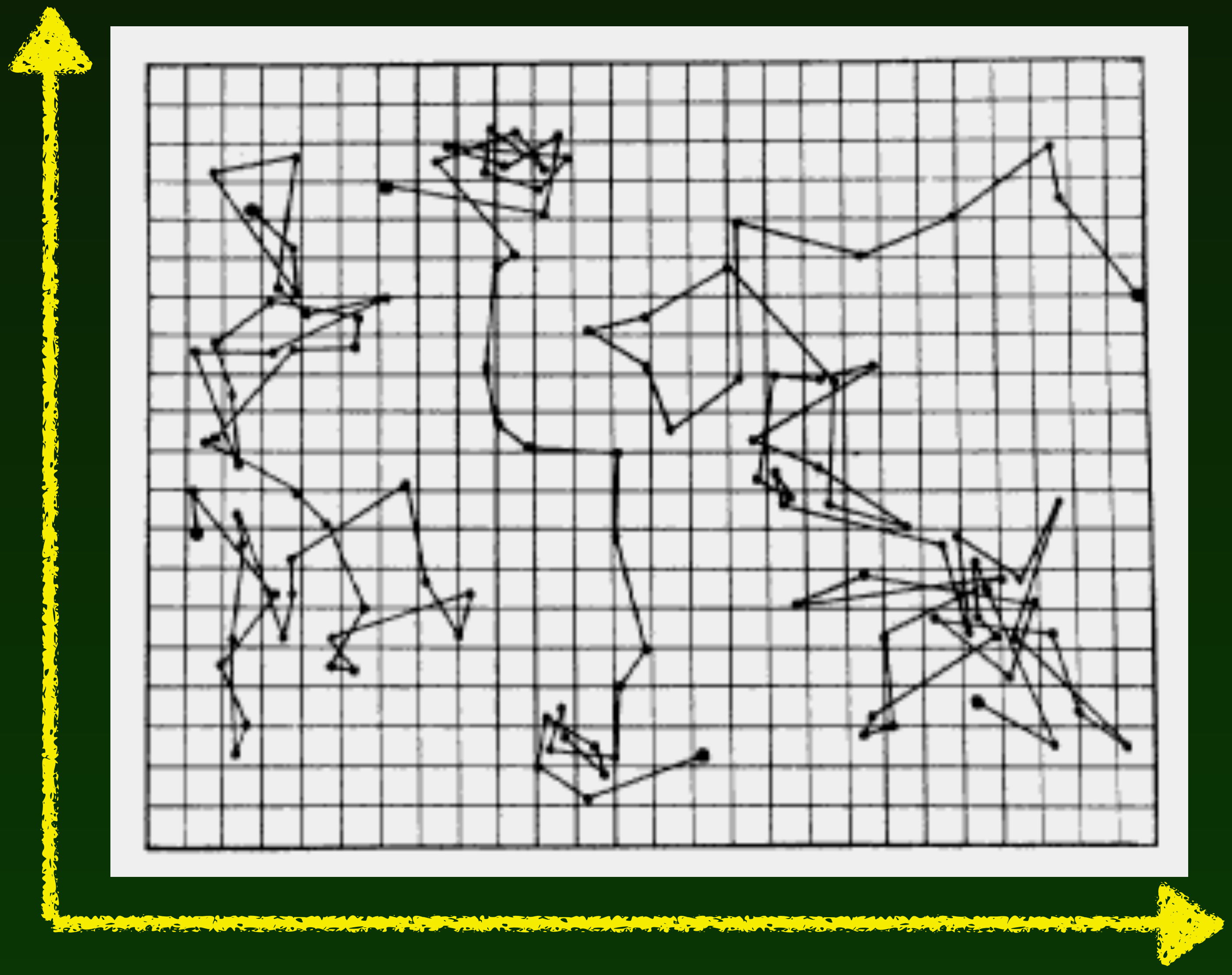
Brownian motion



Coordinate of the particle

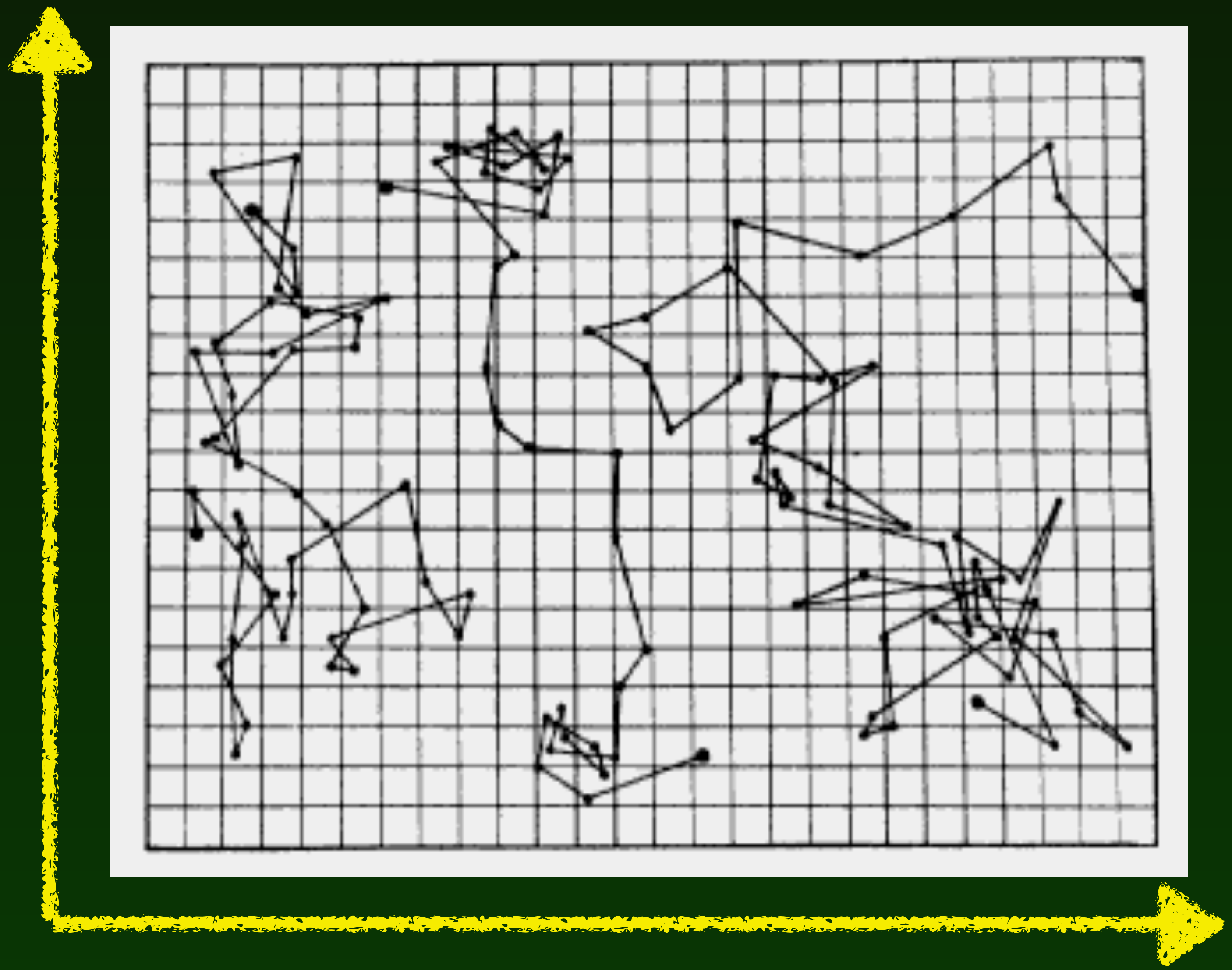
Coordinate of the particle

- Each step is:
  - A random "kick" from the solvent

Brownian motion vs. a noisy cell

Coordinate of the particle

Number of molecules (B)



- Each step is:
  - A random "kick" from the solvent
  - A chemical reaction

Coordinate of the particle

Number of molecules (A)

Measurment of cells' response in an oscillatory purturbation

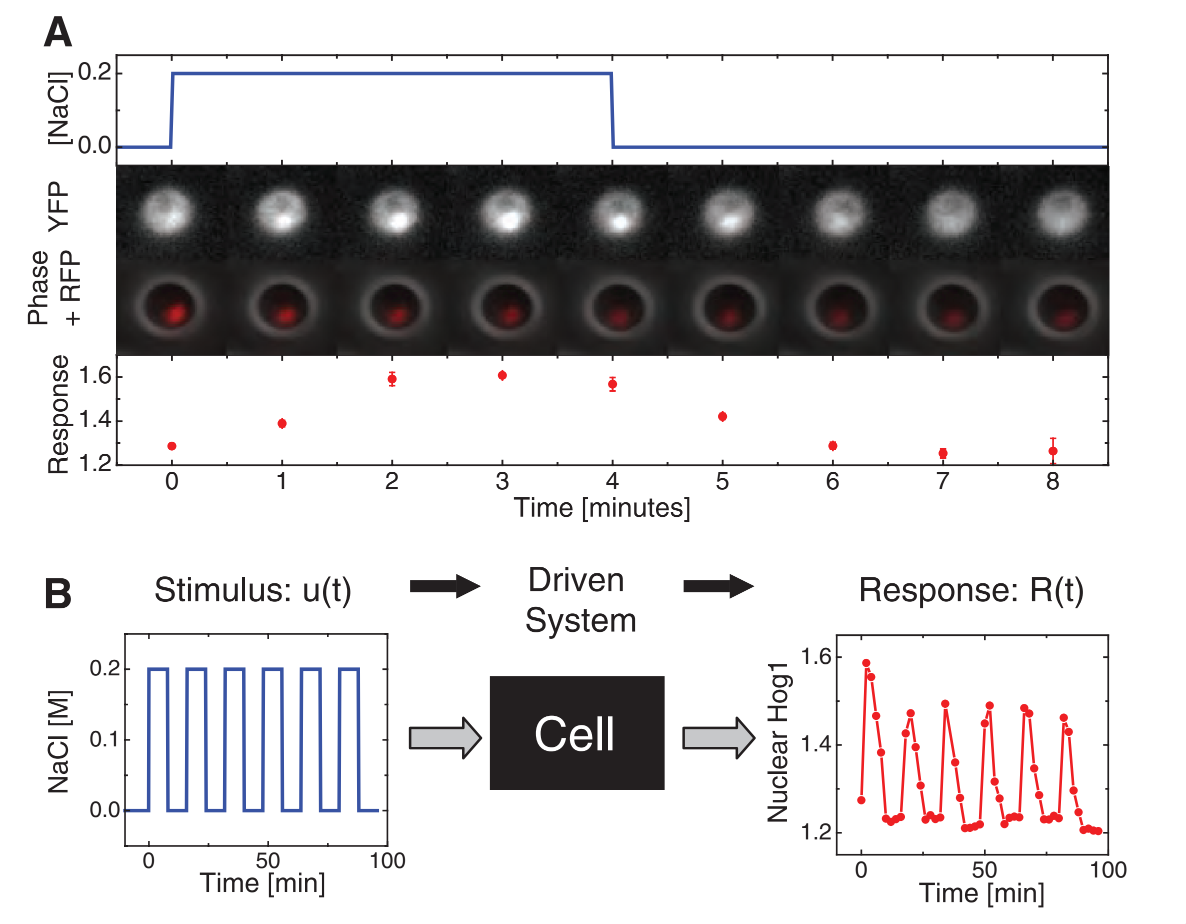
REPORTS

The Frequency Dependence of Osmo-Adaptation in *Saccharomyces cerevisiae*

Jerome T. Mettetal,[1] Dale Muzzey,[1,2] Carlos Gómez-Uribe,[1,3] Alexander van Oudenaarden[1*]

Metabolic gene regulation in a dynamically changing environment

Matthew R. Bennett[1,2*], Wyming Lee Pang[1*†], Natalie A. Ostroff[1], Bridget L. Baumgartner[1], Sujata Nayak[1], Lev S. Tsimring[2] & Jeff Hasty[1,2]



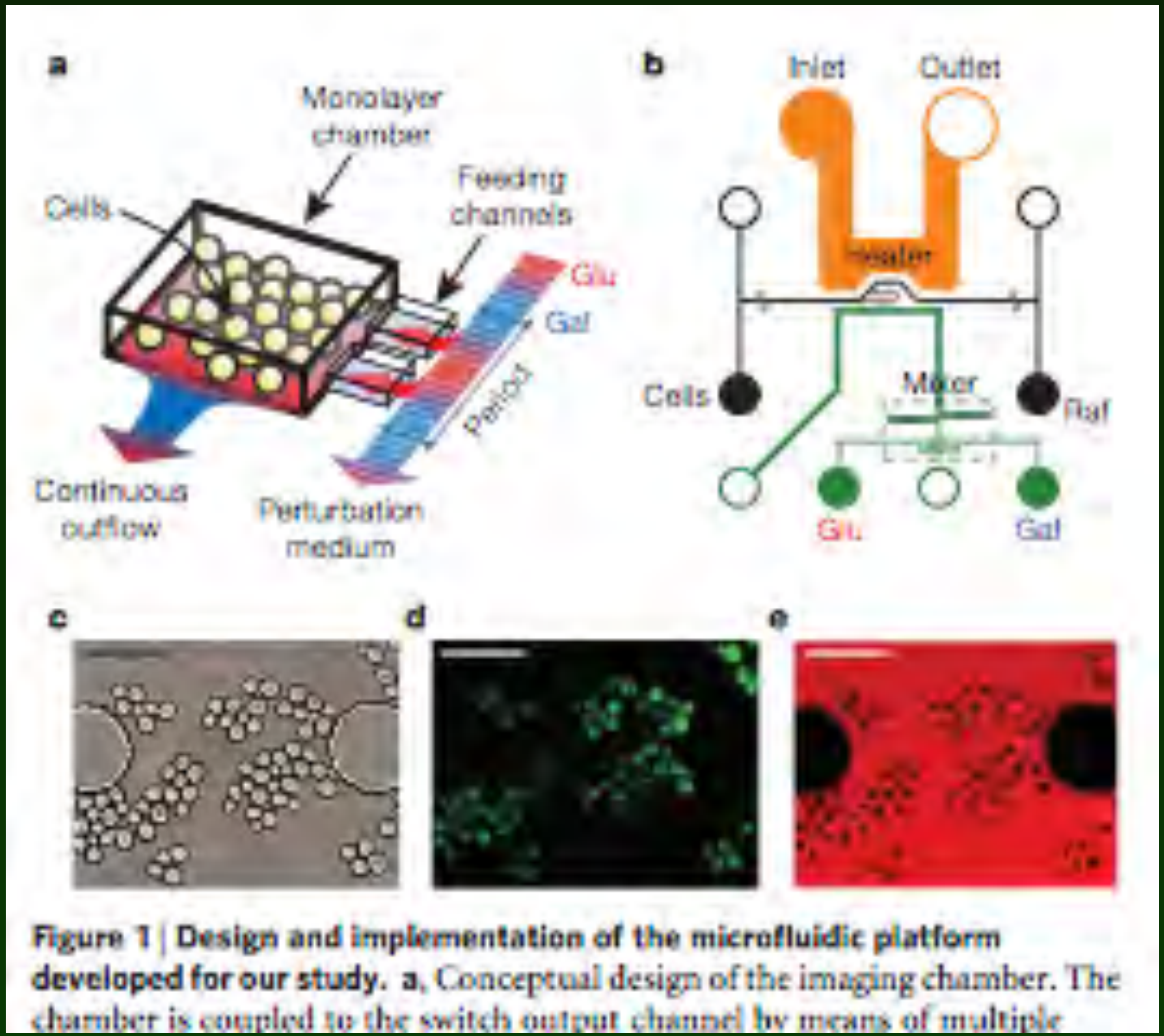
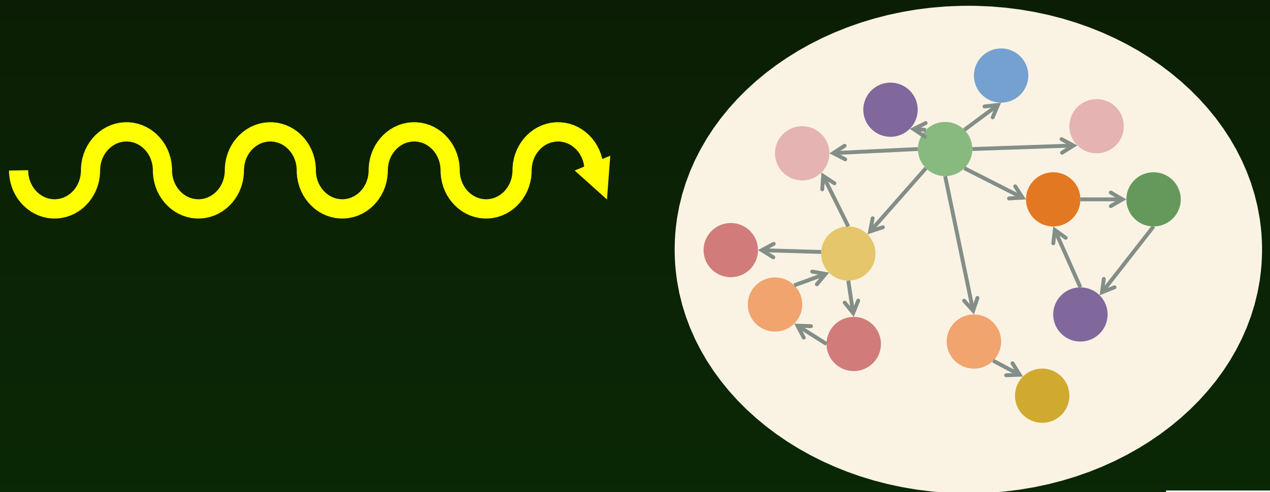
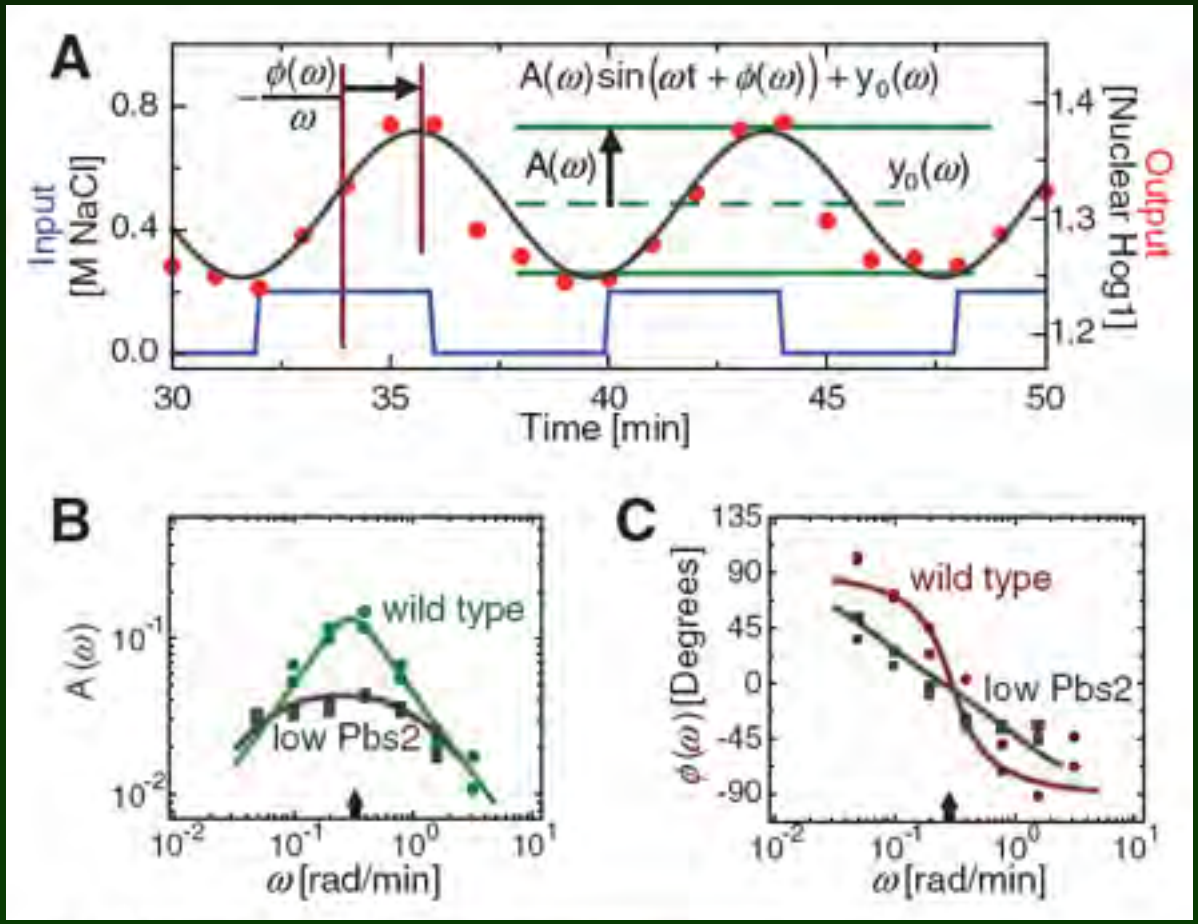
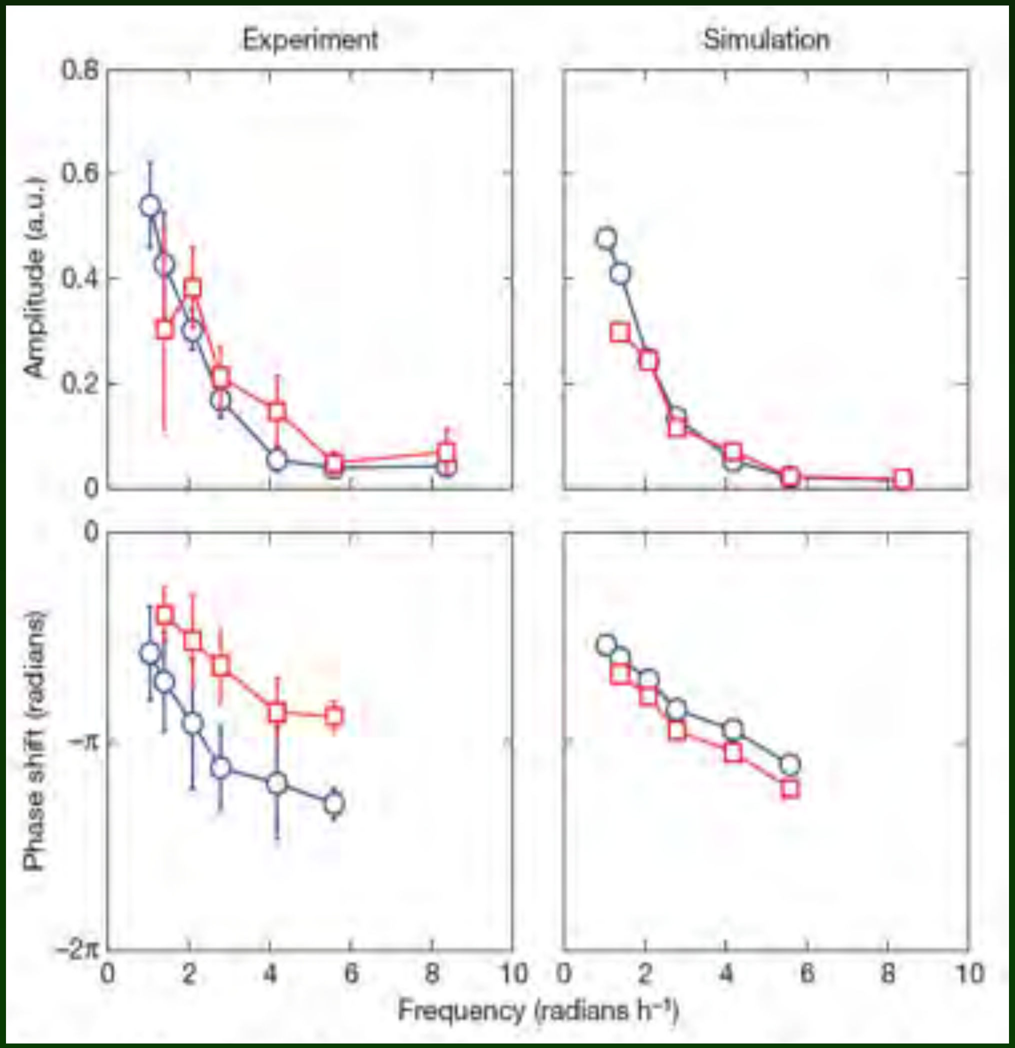


Figure 1 | Design and implementation of the microfluidic platform developed for our study. **a**, Conceptual design of the imaging chamber. The chamber is coupled to the switch output channel by means of multiple

“Spectroscopy” for a cell?

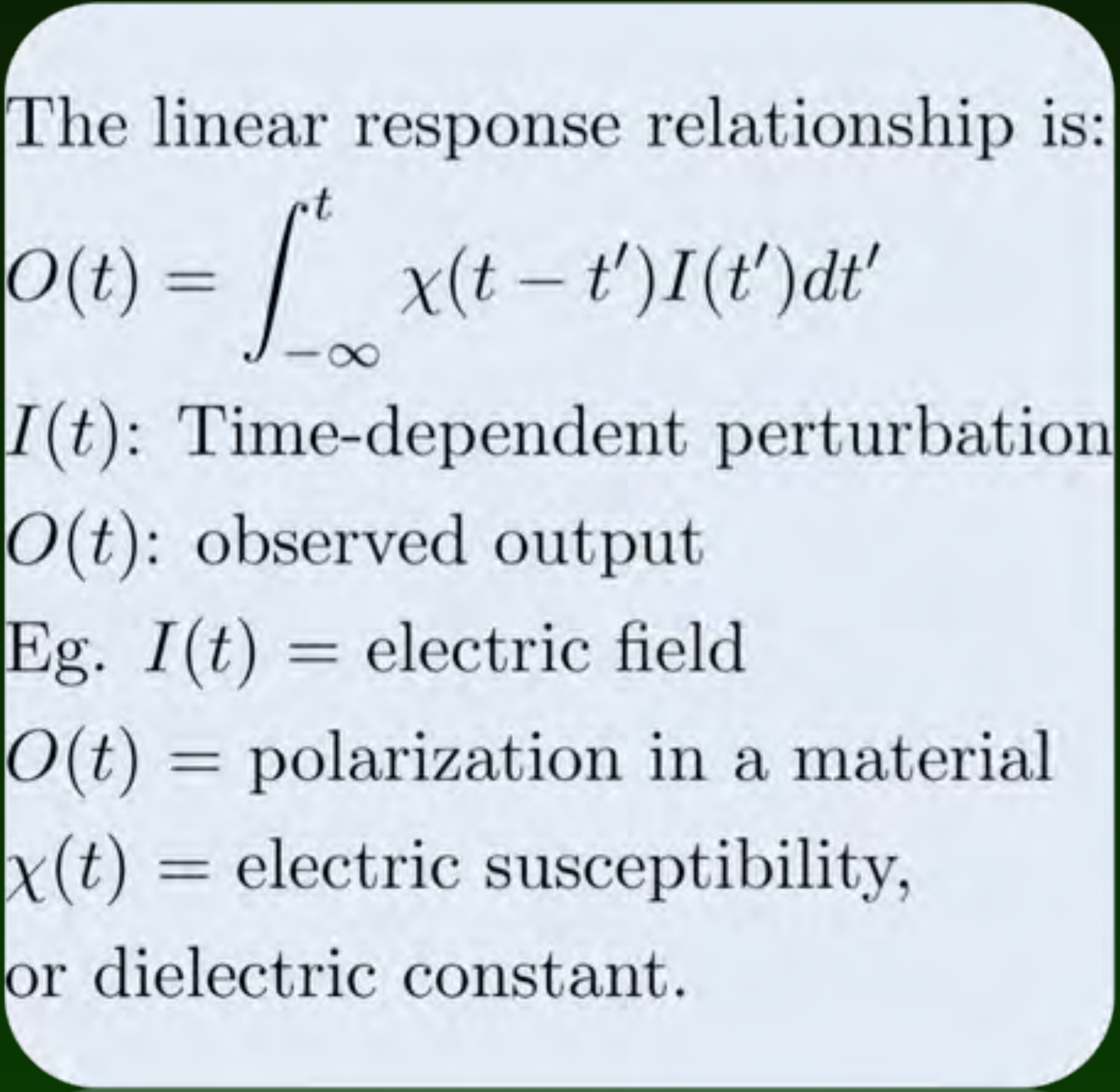






Linear response function

Time domain



The linear response relationship is:

$O(t) = \int_{-\infty}^{t} \chi(t-t')I(t')dt'$

$I(t)$: Time-dependent perturbation

$O(t)$: observed output

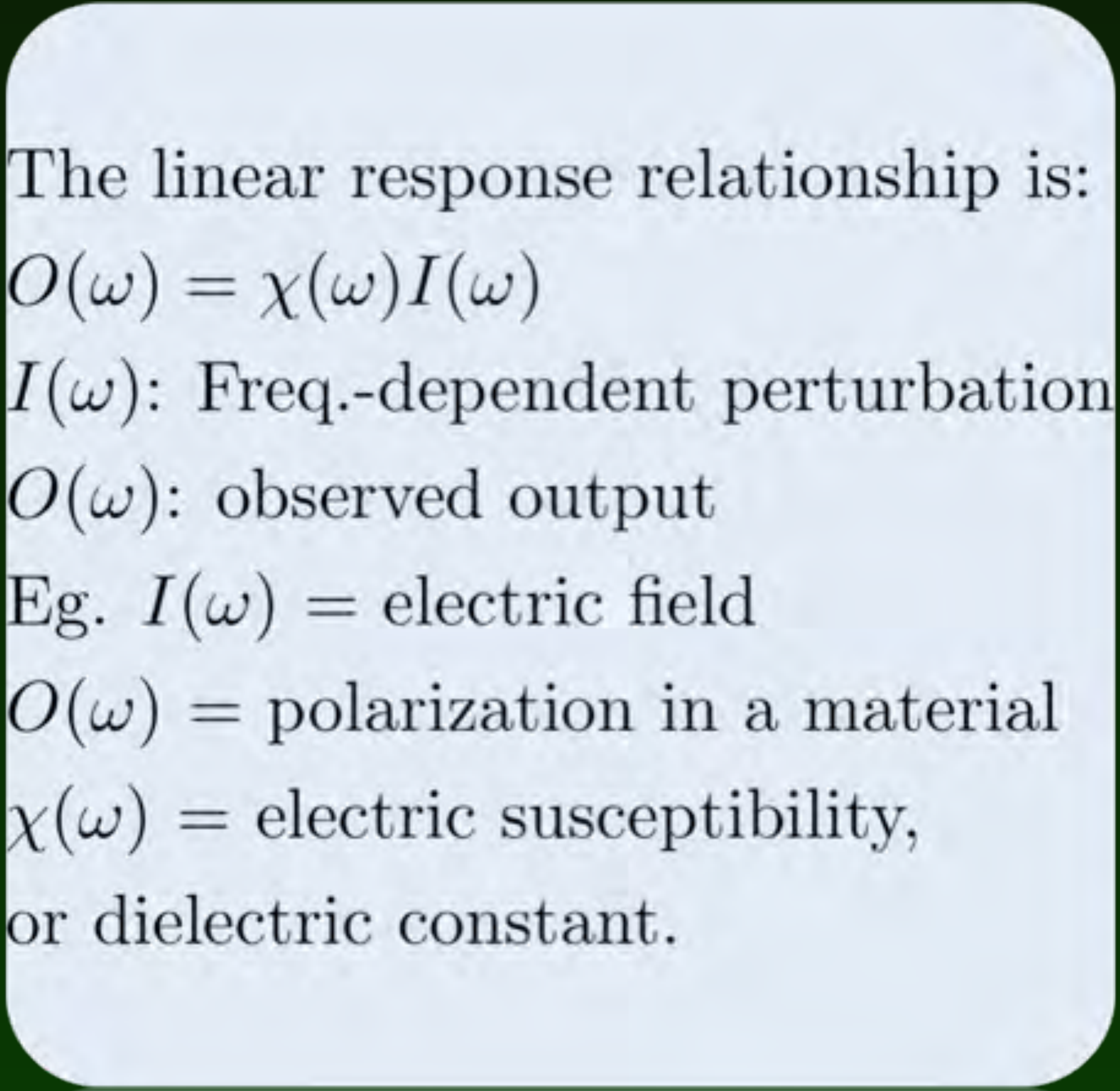
Eg. $I(t)$ = electric field

$O(t)$ = polarization in a material

$\chi(t)$ = electric susceptibility,

or dielectric constant.

Frequency domain



The linear response relationship is:

$O(\omega) = \chi(\omega)I(\omega)$

$I(\omega)$: Freq.-dependent perturbation

$O(\omega)$: observed output

Eg. $I(\omega)$ = electric field

$O(\omega)$ = polarization in a material

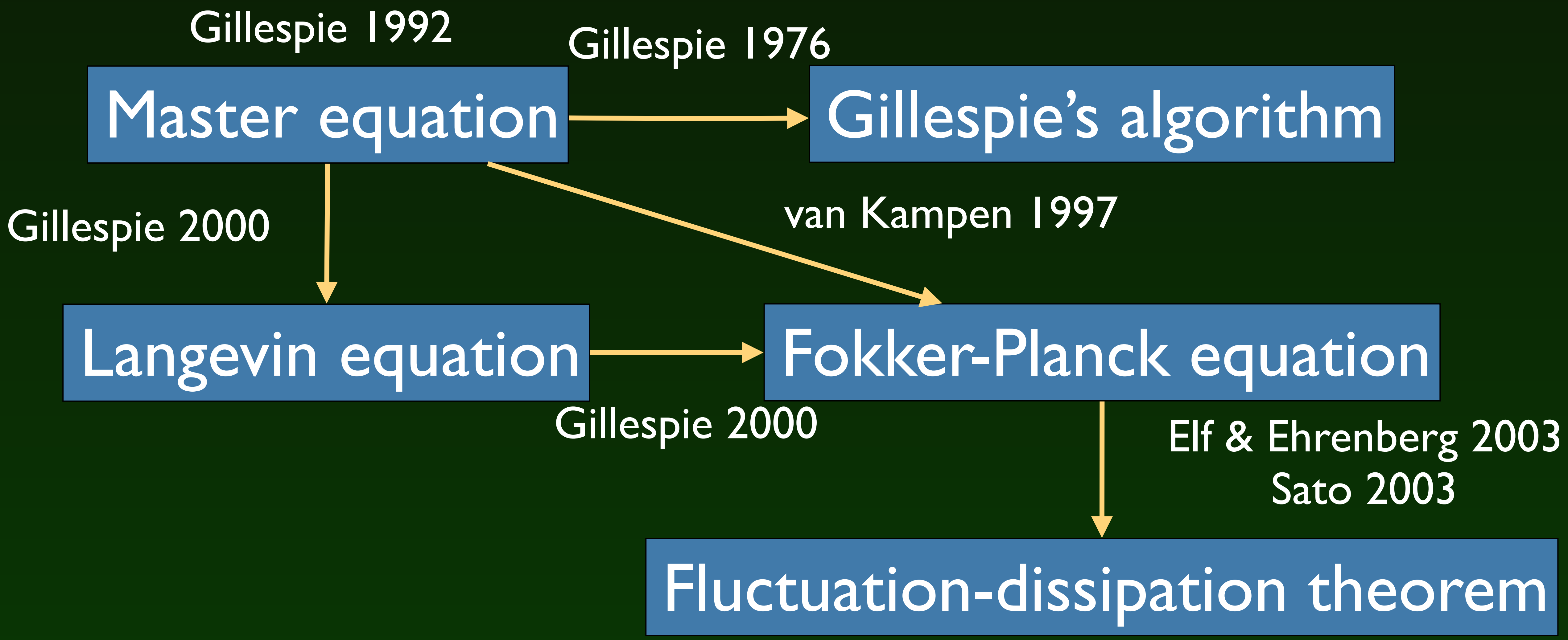
$\chi(\omega)$ = electric susceptibility,

or dielectric constant.

Linear Response theory in cells?

Possibility of Fluctuation-Dissipation theorem?

Is it possible to adapt the previously developed theories/equations (in mechanics)?



Gillespie 1992

Master equation

Gillespie 1976

Gillespie's algorithm

Gillespie 2000

van Kampen 1997

Langevin equation

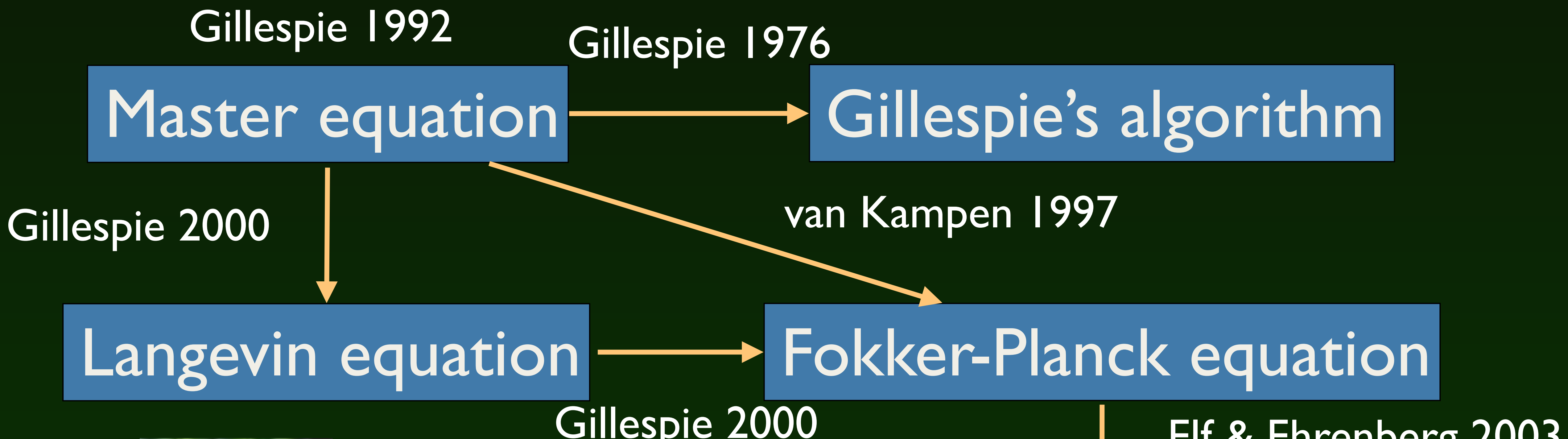
Fokker-Planck equation

Gillespie 2000

Elf & Ehrenberg 2003
Sato 2003

Fluctuation-dissipation theorem

“Dynamic” version of Fluctuation-Dissipation Theorem exists



Gillespie 1992

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Gillespie’s algorithm

Gillespie 2000

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Langevin equation

Fokker-Planck equation

Gillespie 2000

Elf & Ehrenberg 2003
Sato 2003

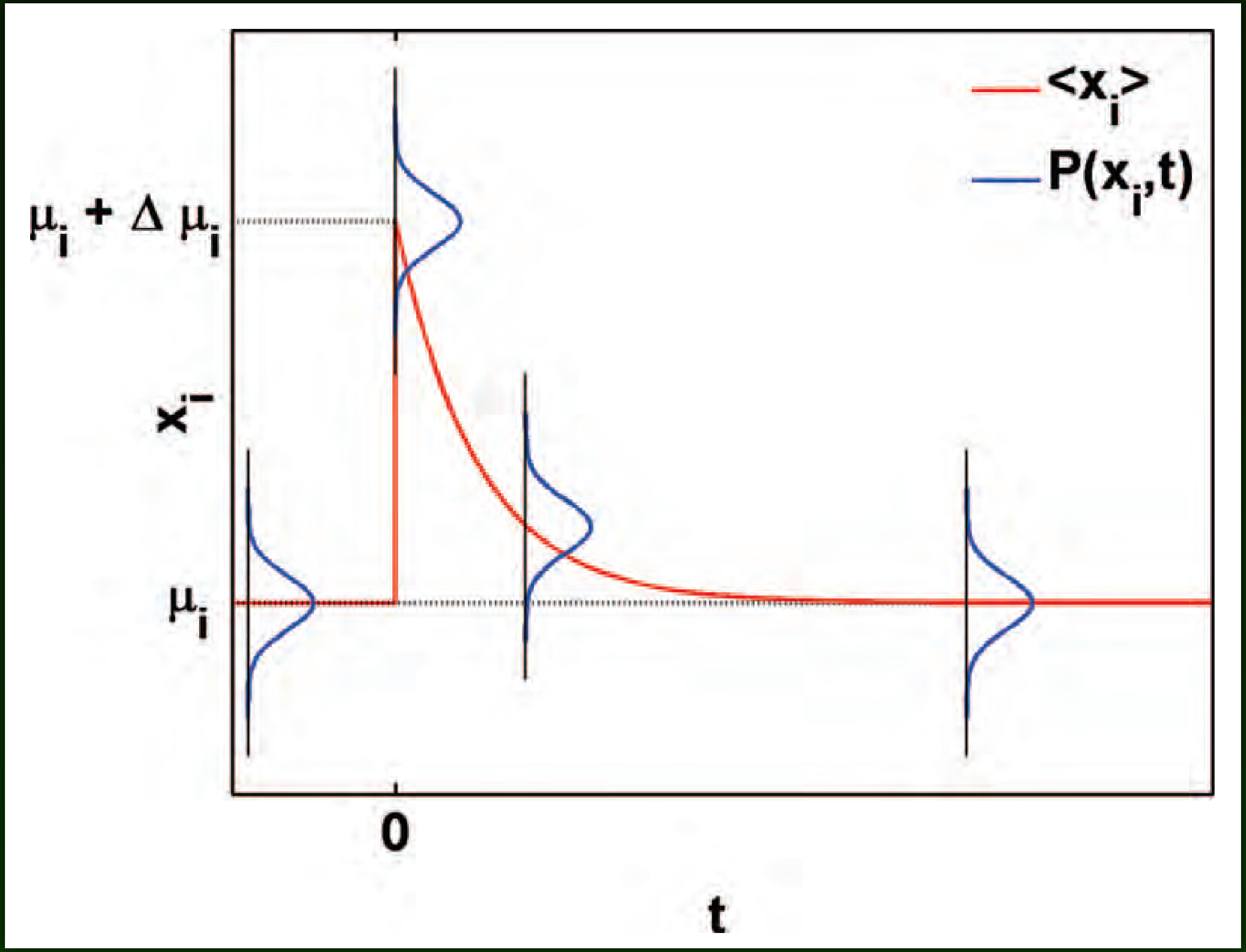
Fluctuation-dissipation theorem

Fluctuation-dissipation theorem (dynamic)

顏濤哲
Sanders Yan

Yan and Hsu, J. Chem. Phys. 2013

"Dissipation": back to steady state



Can be simulated directly.

Can we "predict" it with FDT (i.e. with correlation function)?

Derivation for FDT

- Suppose a perturbation is applied at t=0: (I.e. increase or decrease the particle number in a reaction system) $\Delta\mu$
- Gaussian probability distribution assumed.
- The time-dependent change in the averaged $x(t)$ is:

$$\langle \Delta x_j(t) \rangle = \langle x_j(t) - \mu_j \rangle = \int (x_j - \mu_j) P\left(\mathbf{x}, t\right) d\mathbf{x}$$

Dynamic Fluctuation-Dissipation Theorem for biochemical kinetics

$$\bar{x}(t) - \mu_0 = \frac{\Delta\mu}{\Sigma^2}\langle \delta x(0)\delta x(t)\rangle$$

where $x(t)$ = the particle number for the observed species

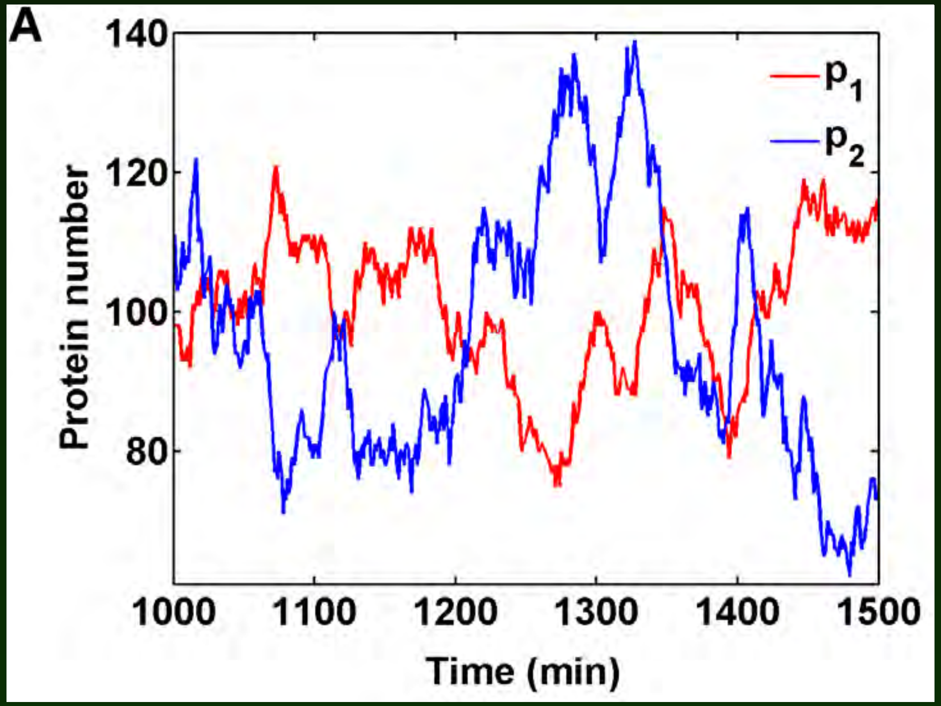
μ_0 = equilibrium average for x

Σ^2 = equilibirum variance for x

$\delta x(t)$ = instantaneous fluctuation for x

- LHS: How *x*(*t*) comes back to the equilibrium, after a perturbation. A non-equilibrium quantity.
- RHS: The correlation function is the characteristic of fluctuation in *x*(*t*). An equilibrium quantity.
- A linear response theory is provided.
- Can be generalized to multiple component systems.

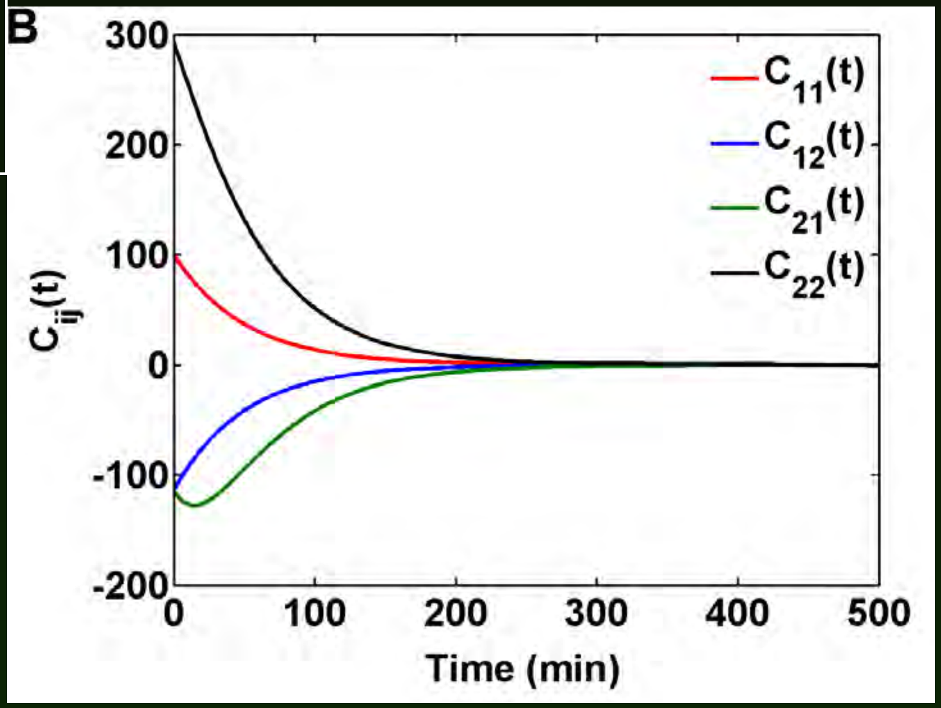
Protein 1 (p_1) ⊣ Protein 2 (p_2)



One stochastic trajectory obtained in the steady state.

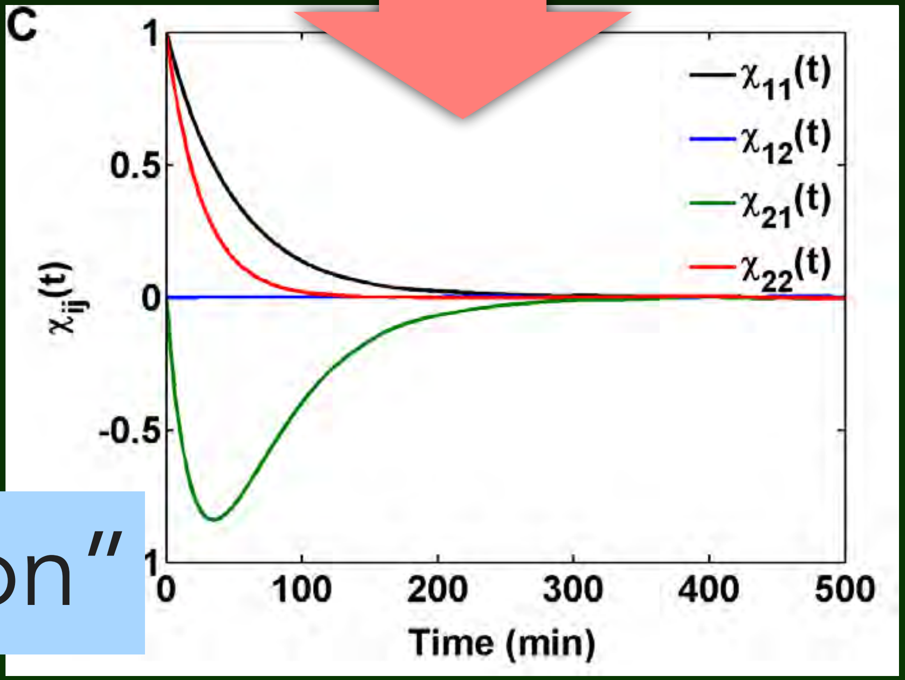
"Fluctuation"

Calculate



Correlation Functions

FDT

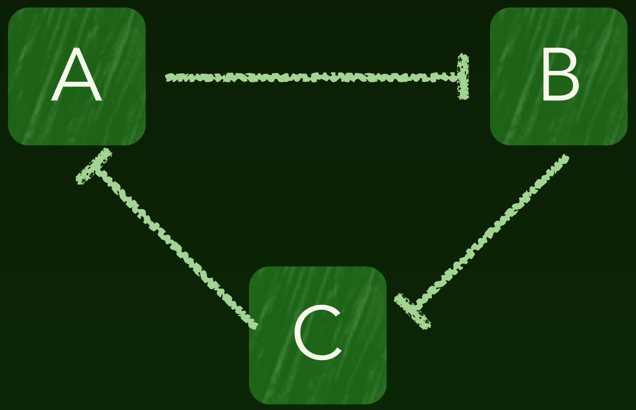


"Dissipation"

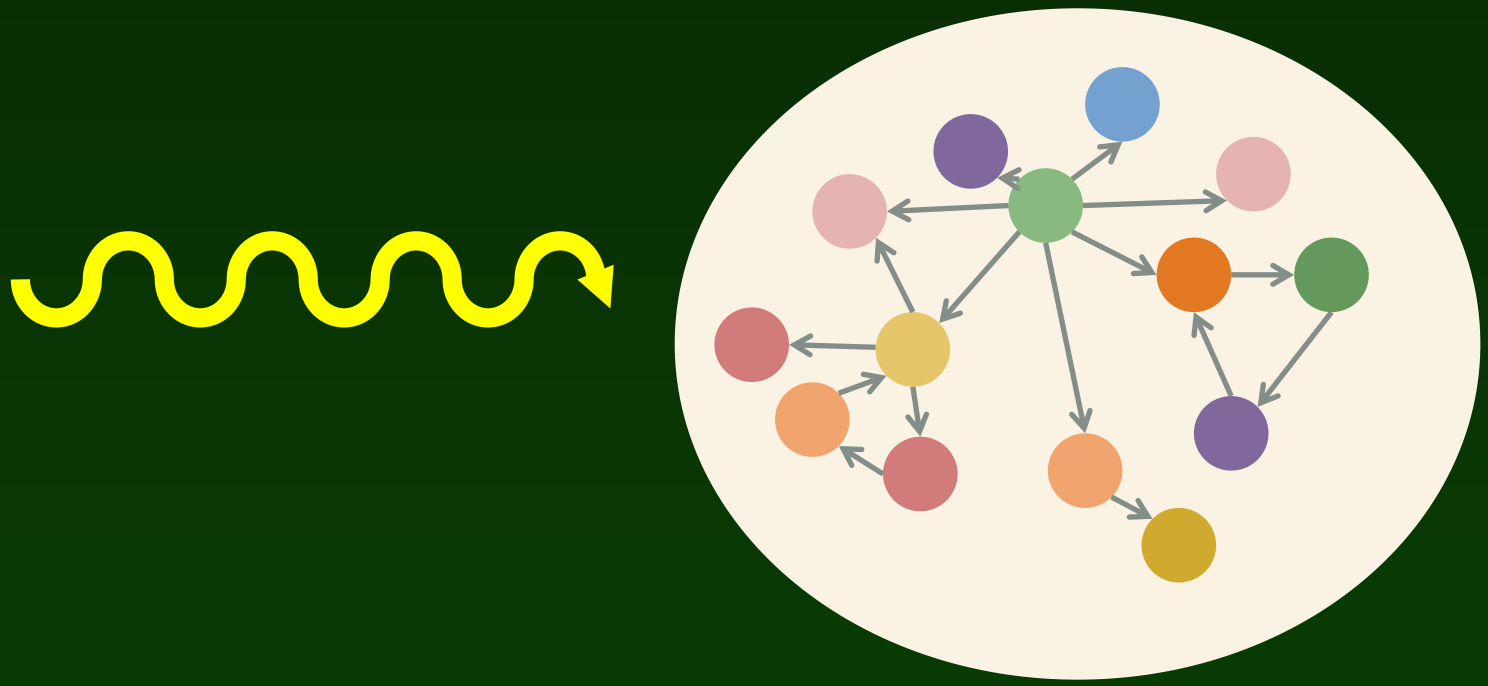
Predict the response after a perturbation.

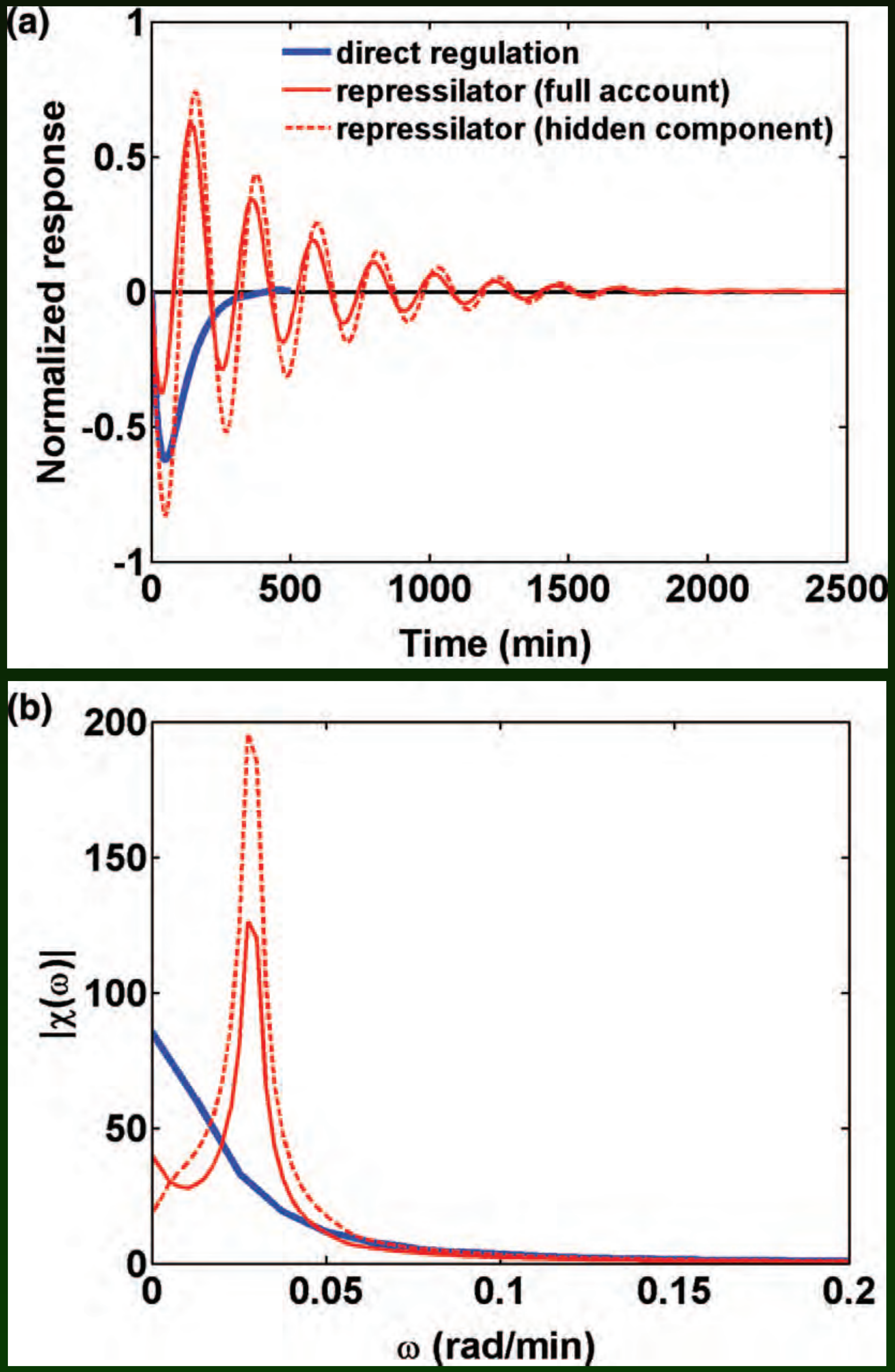
"Spectroscopy" for a cell?

Repressilator: a model with intrinsic oscillation

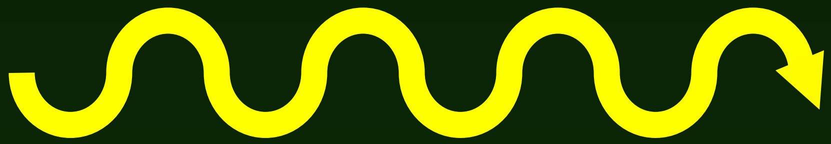


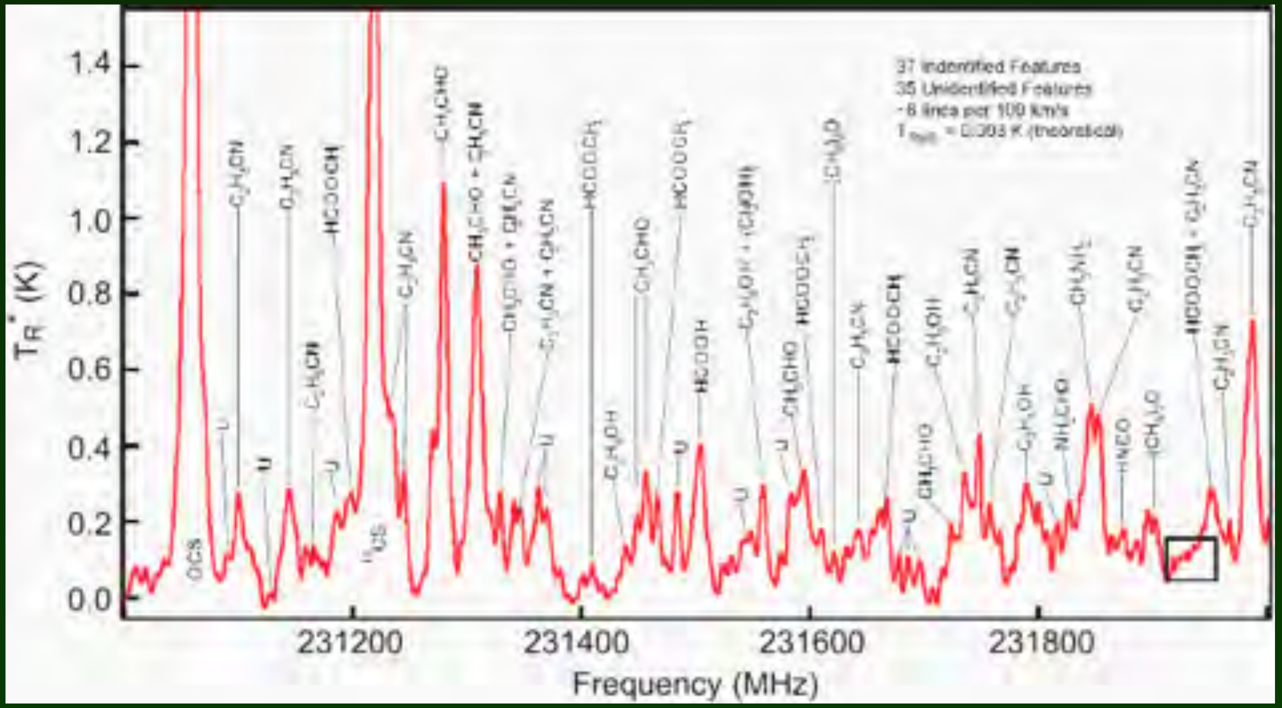
- A "resonance" is seen with periodic perturbation.
- Probing oscillators in a cell.

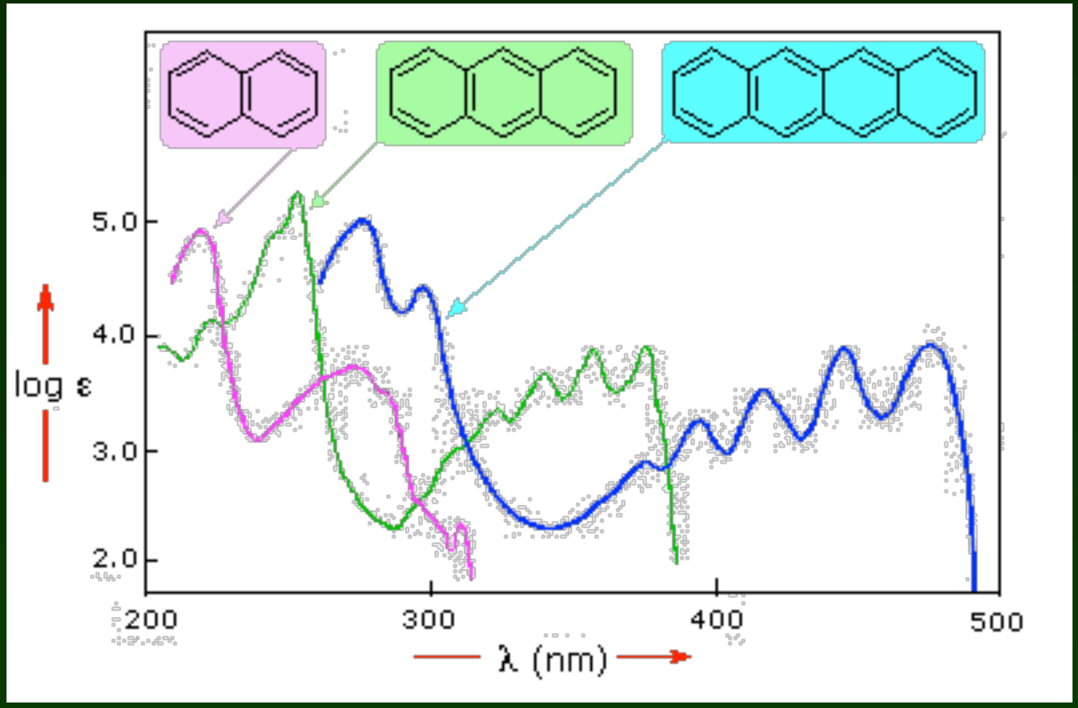




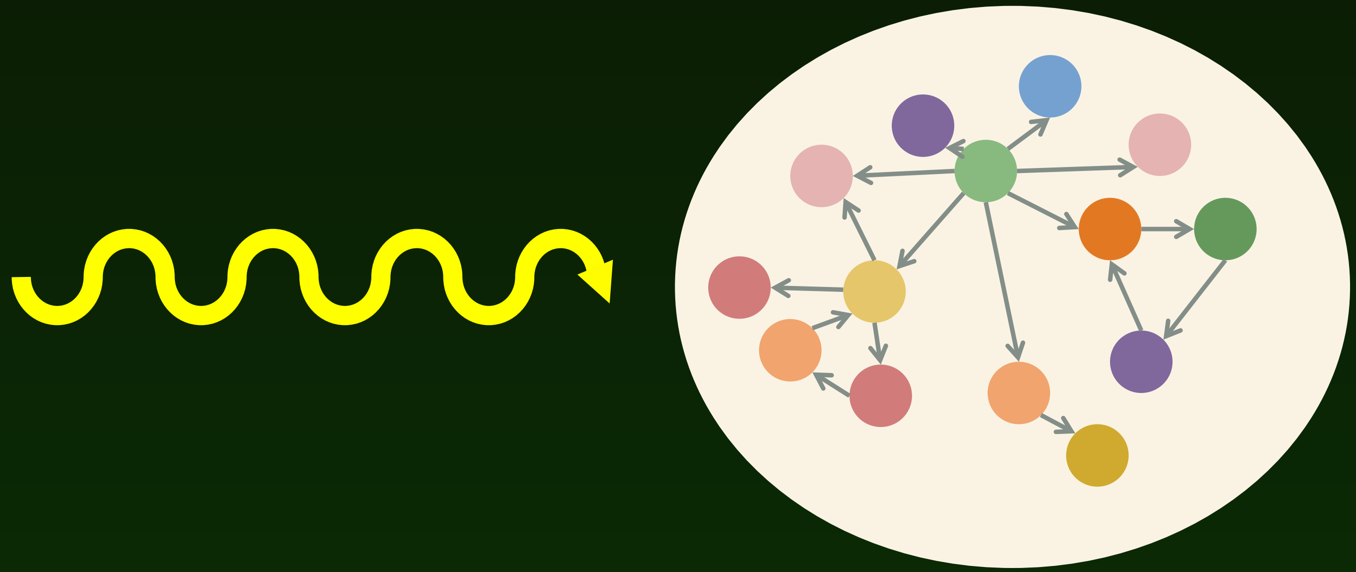
Spectroscopy for molecules

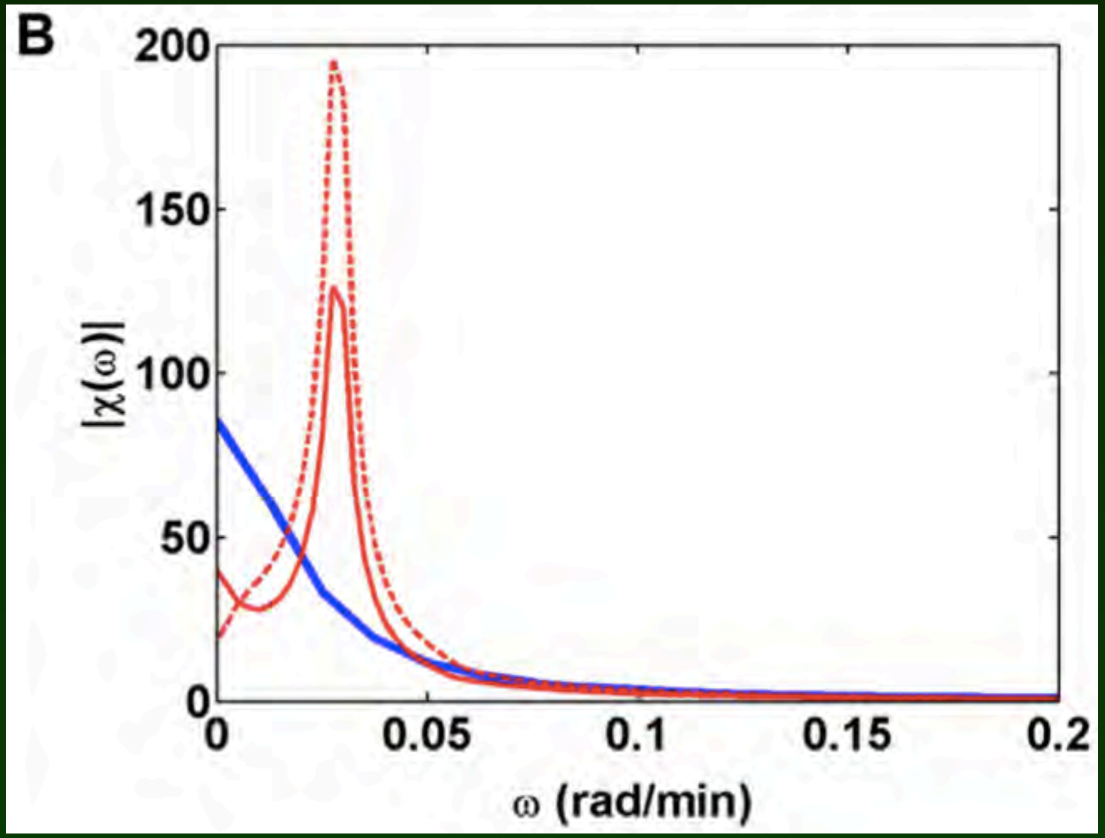






“Spectroscopy” for a cell?



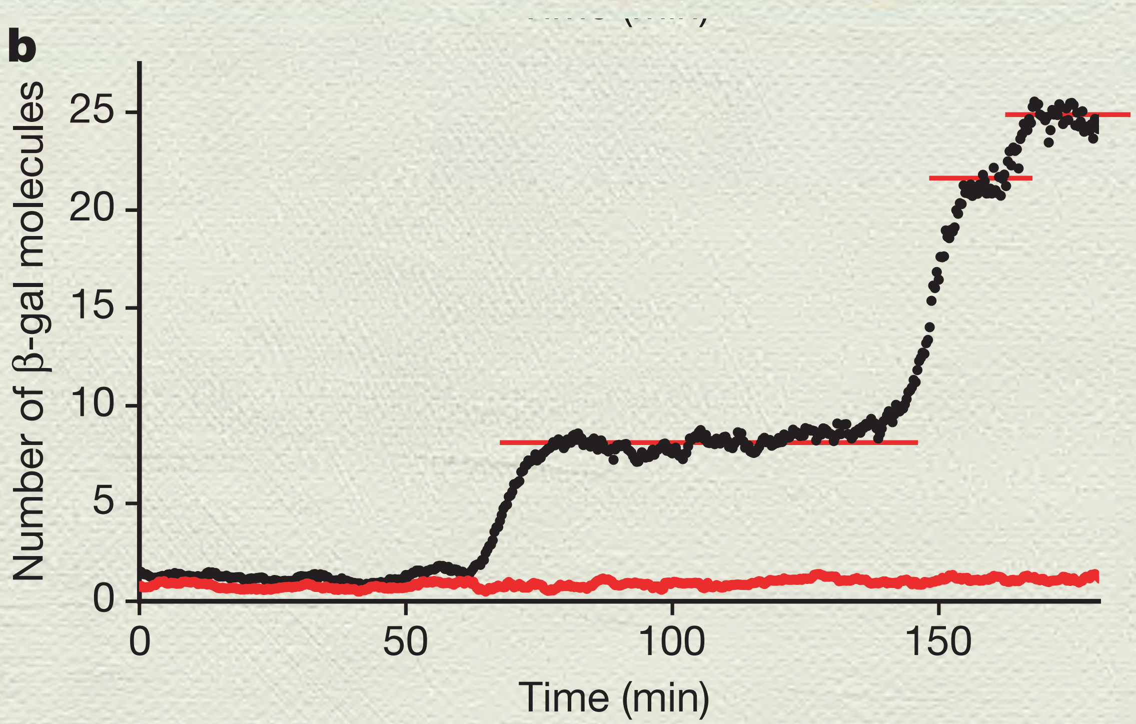


- Time scale separation?
- Not quite. Observable oscillation are mostly in 10^0-10^3 minutes.
- Relaxation (and dilution due to cell div.), also in 10^1-10^3 minutes.

Summary

- FDT — it is possible use correlation functions to compose the response function.
- To predict response from fluctuation, linear response is necessary.
- There is a limited range for linear response.
- (data not shown) It is possible to construct the response function for missing component situation.
- Limited data sampling is not a big problem either.

Genes express in bursts. The production is noisy.



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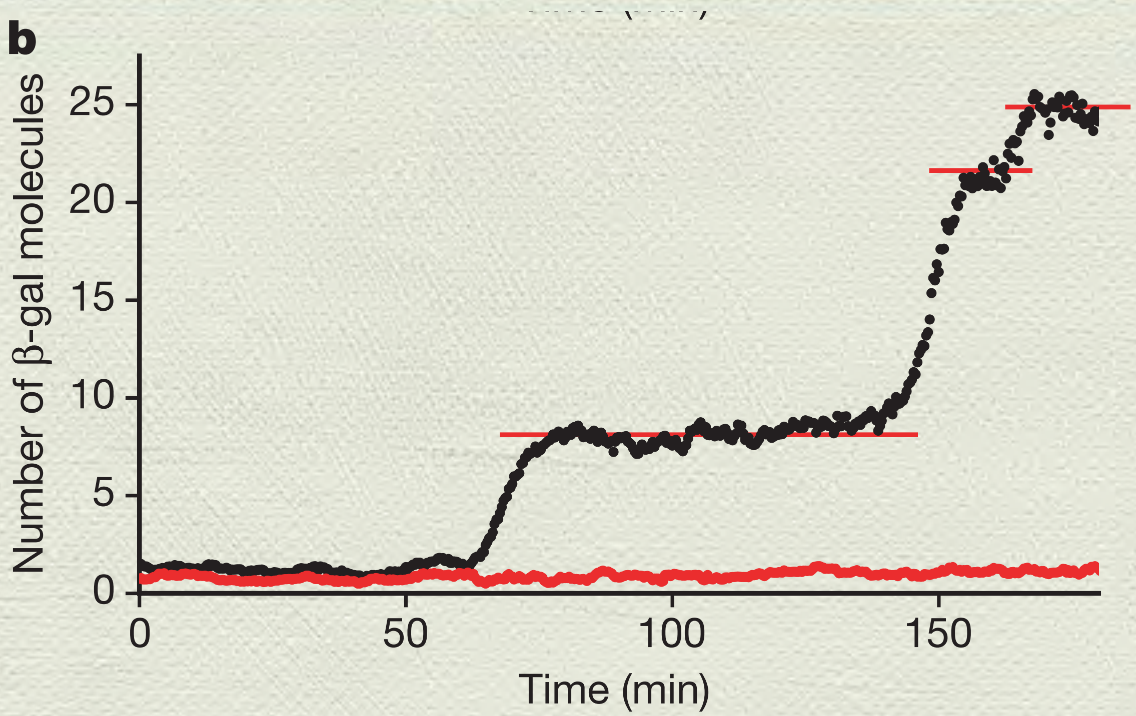

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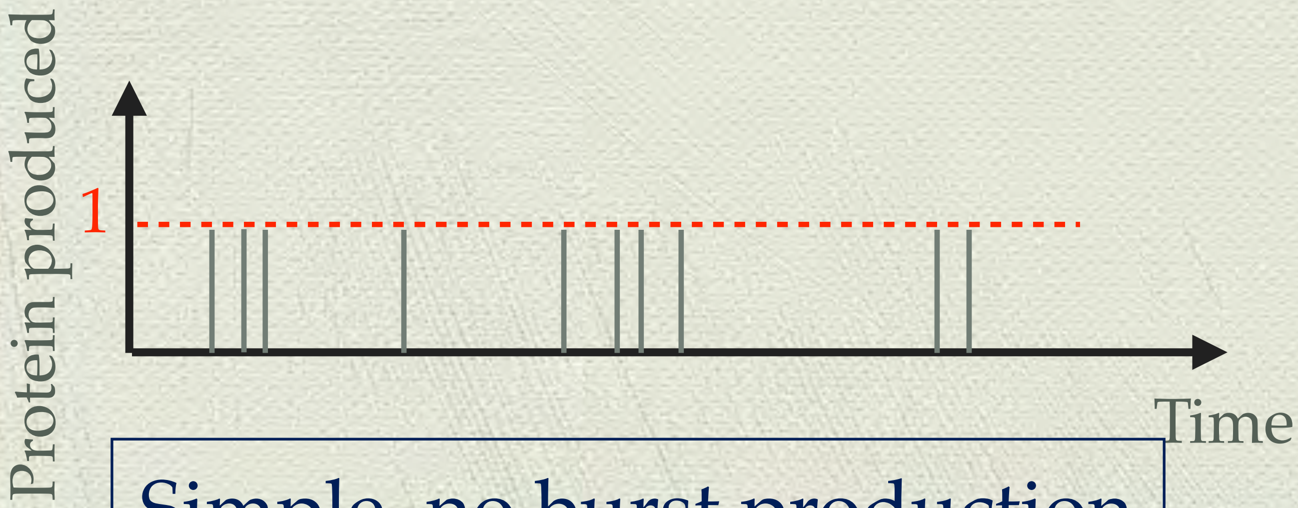
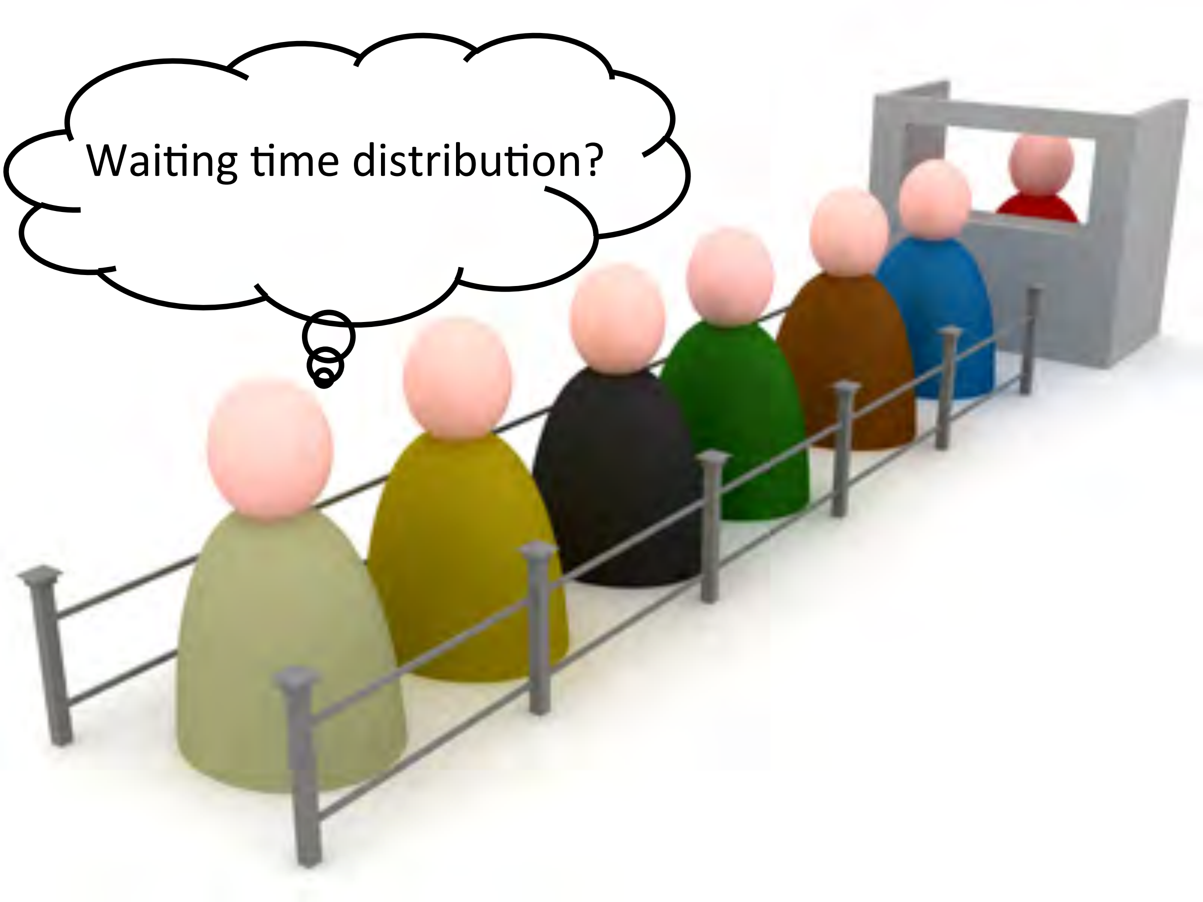


Simple, no burst production

Burst production: noiser

The distribution of protein expressed



- Number of people in front of you ~ Poisson distribution. (Number of bursts)
- Time each person spend ~ exponential distribution (Sunney Xie's result: burst size distribution).
- Total waiting time (total protein produced) distribution?

Figure from:
http://chaaidaani.wordpress.com/2012/05/02/good-mannered-when-abroad-bad-mannered-in-pakistan/

Langevin's equation

Protein burst model

- $dm/dt = k_m - \gamma_m m$
- $dp/dt = k_p m - \gamma_p p$

A Gaussian random number

$$p(t+\tau) = p(t) + \left[k_p m\tau + (k_p m\tau)^{1/2}\boxed{N(0,1)}\right] - \left[\underline{\gamma_p p\tau + (\gamma_p p\tau)}^{1/2}\boxed{N(0,1)}\right]$$

Regular reaction channels: Poisson statistics

Langevin's equation, without having to model *m* (=mRNA)

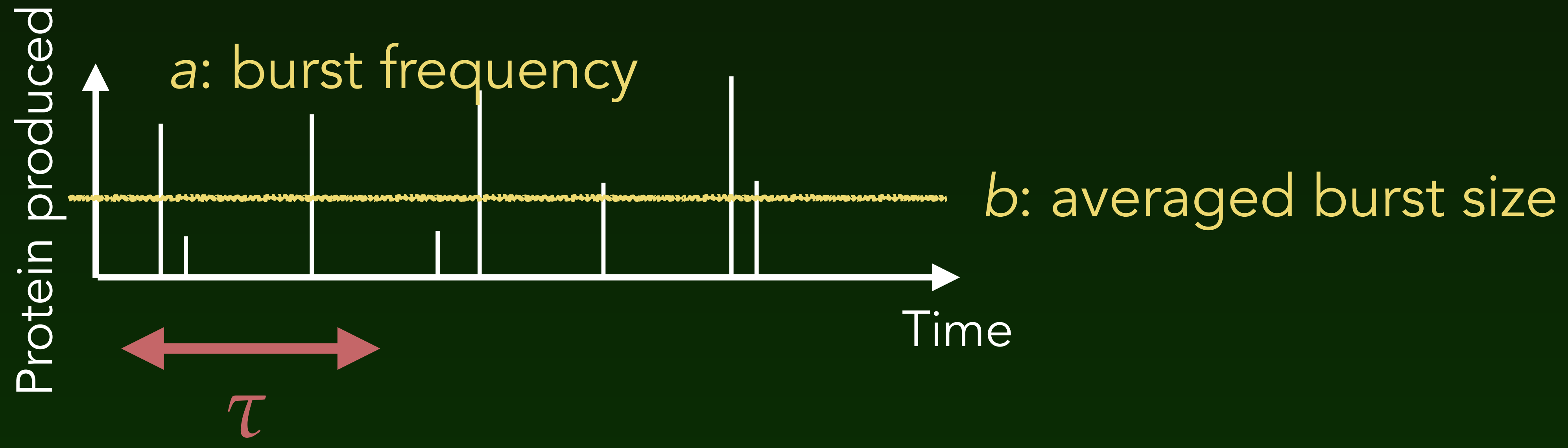
Burst channel

$$p\left(t+\tau\right) = p\left(t\right) + \boxed{\sum_{i=1}^{n_e} x_i} \qquad \boxed{\Rightarrow \mu_p + \sigma_p \, N(0,1)}$$

$$- \left[\gamma_p p \tau + \left(\gamma_p p \tau\right)^{1/2} N\left(0,1\right)\right]$$

Non-burst, "normal" channels

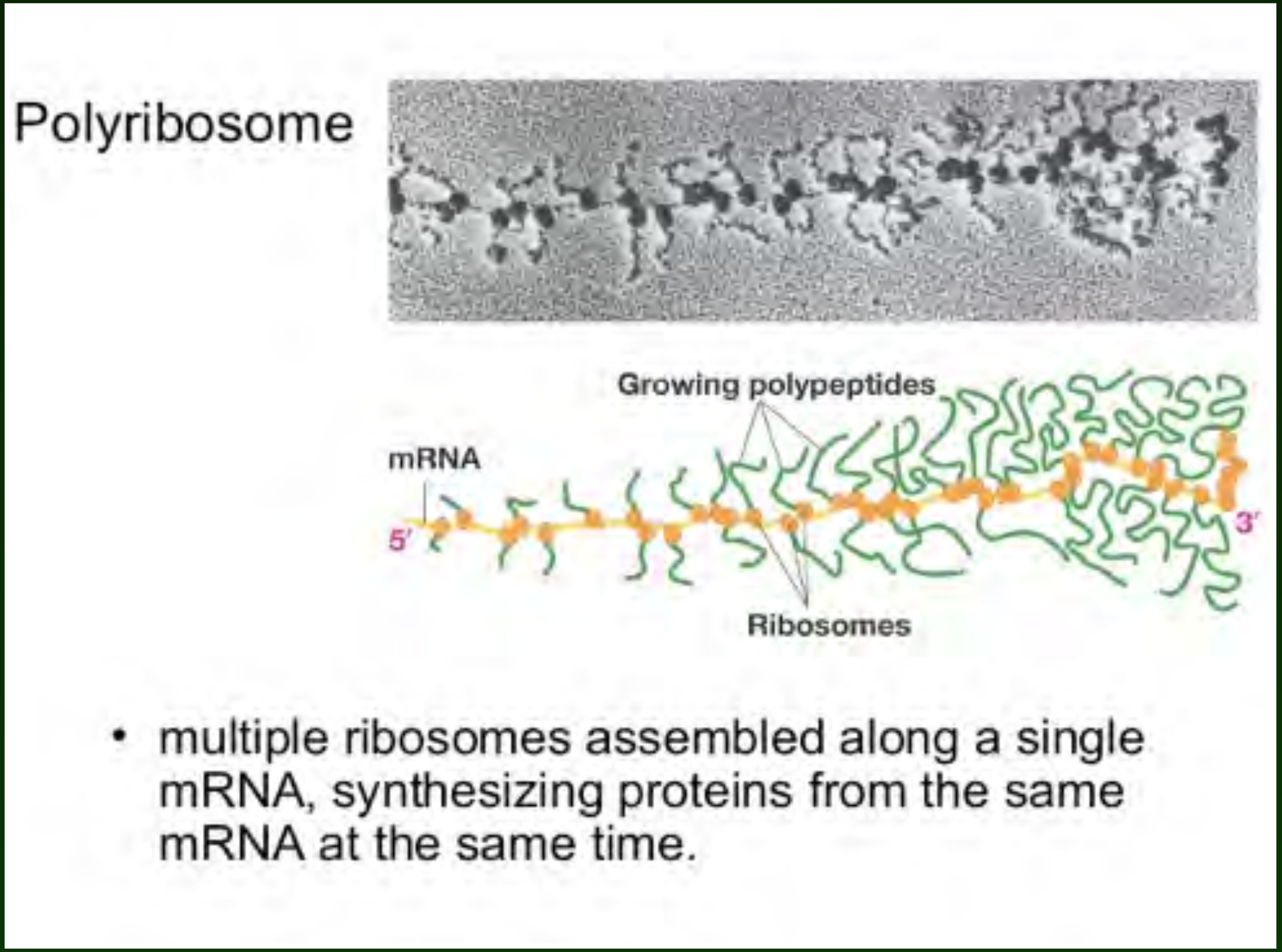
How many protein is produced in time τ?



- in time τ, on the avg, $a\tau$ bursts.
- Total: $a\tau b$ protein on the average.
- What is the variance of this total # of protein?

Some Basics

- Protein burst model
  - $dm/dt = k_m - \gamma_m m$
  - $dp/dt = k_p m - \gamma_p p$
- mRNA degrades fast: $\gamma_m >> \gamma_p$
- mRNA production is slow: $k_m << k_p$
- 1 mRNA ≈ 1 burst protein production.



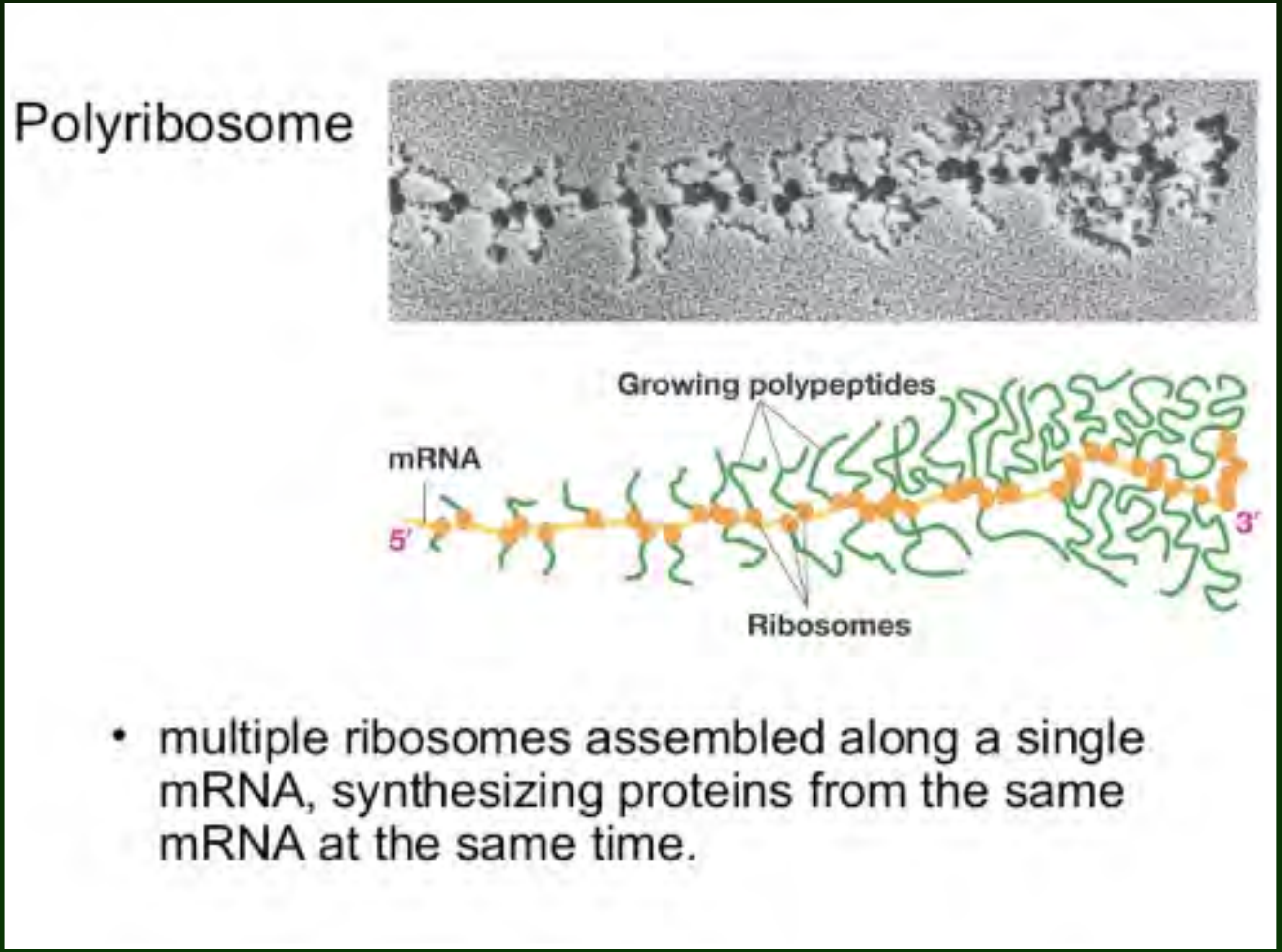
- multiple ribosomes assembled along a single mRNA, synthesizing proteins from the same mRNA at the same time.

http://www.slideshare.net/aftonchase/27-28-105-fa13-transcription-and-translation-skel

Some Basics

- Protein burst model
  - $dm/dt = k_m - \gamma_m m$
  - $dp/dt = k_p m - \gamma_p p$

- Protein production rate
  $= k_p m = k_p k_m/\gamma_m$
  $= k_m (k_p/\gamma_m)$
- $a = k_m$
- $b = k_p/\gamma_m$
- each mRNA produces k_p/γ_m protein. This # is exp. in distribution.



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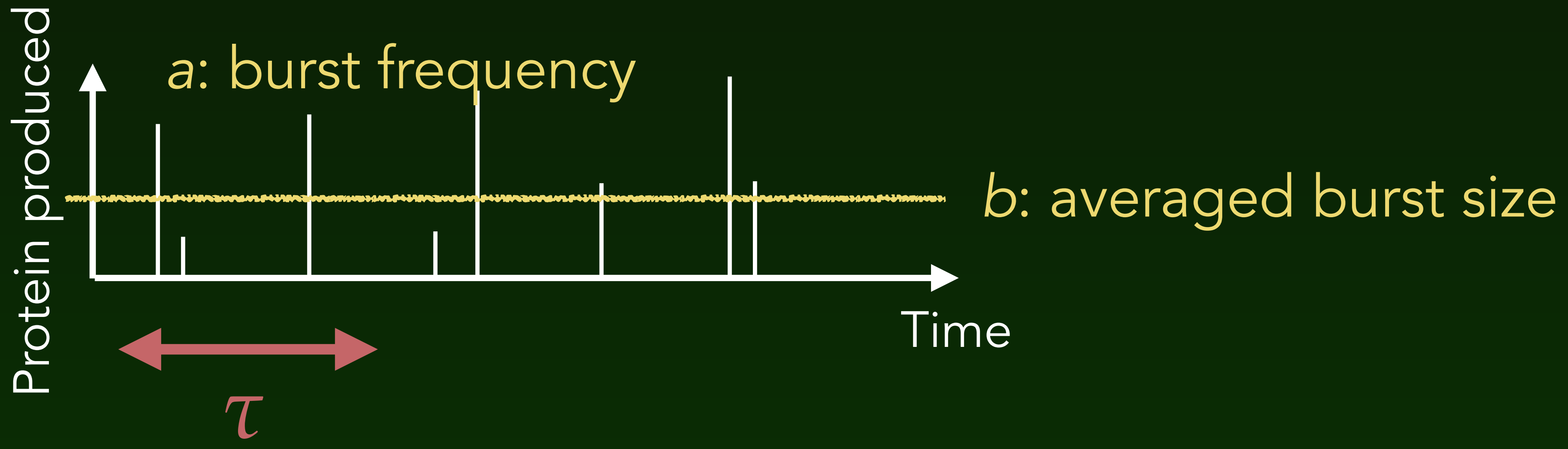


- in time τ, on the avg, $a\tau$ bursts.
- Total: $a\tau b$ protein on the average. $a\tau b$
- What is the variance of this total # of protein? $2a\tau b^2$

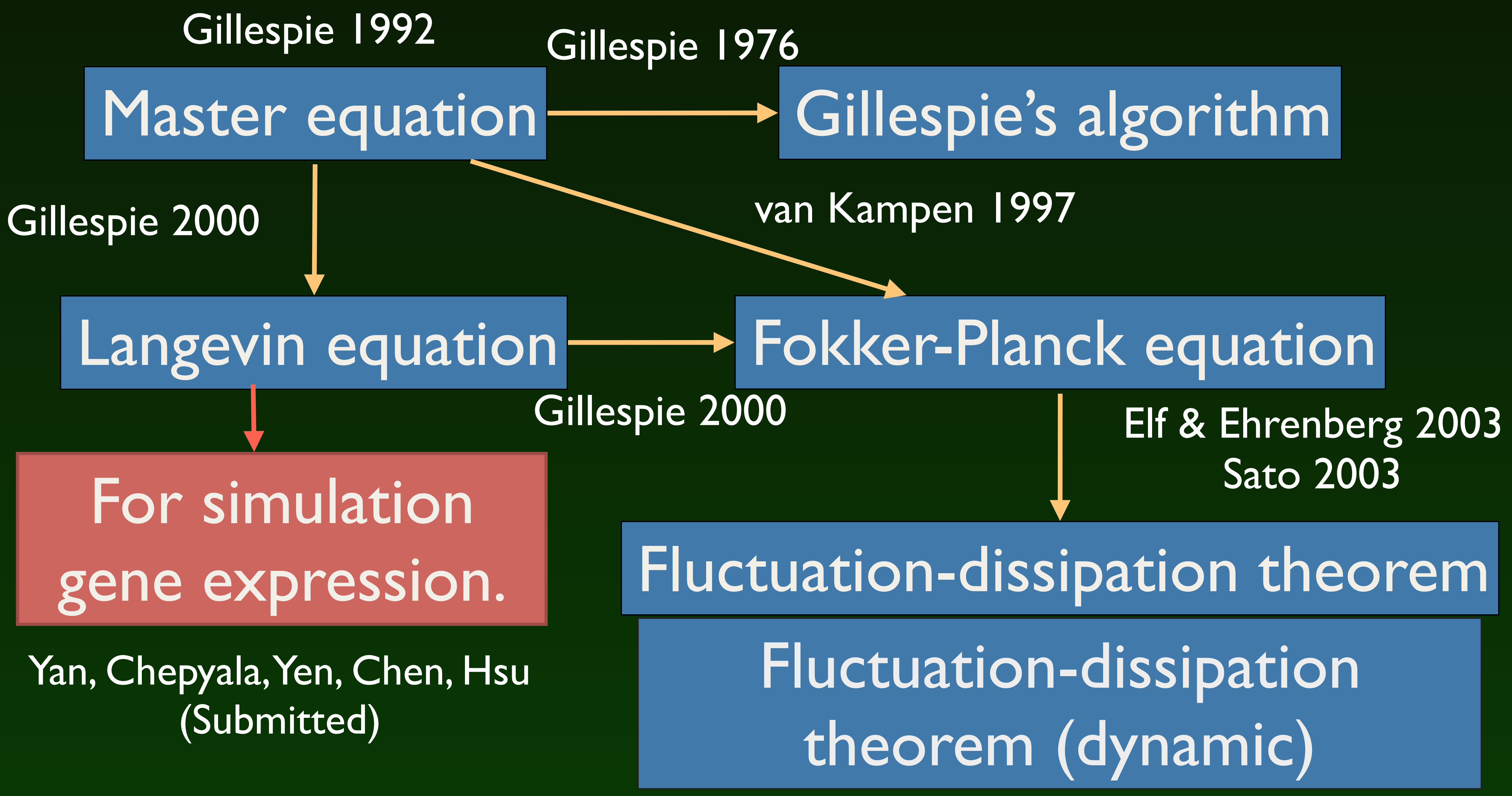
Langevin's equation can be formulated

Burst channel

$$
\begin{aligned}
p\left(t+\tau\right) = p\left(t\right) &+ \left(a\tau b_p + \left(a\tau b_p\left(2b_p+1\right)\right)^{1/2} N(0,1)\right) \\
&- \left(\gamma_p p\tau + \left(\gamma_p p\tau\right)^{1/2} N(0,1)\right),
\end{aligned}
$$

Non-burst, "normal" channels

The noise of a bursting gene production is $\sqrt{2}$ times the no-burst (1 copy at a time) noise.



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Master equation

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Langevin equation

Fokker-Planck equation

Gillespie 2000

Elf & Ehrenberg 2003
Sato 2003

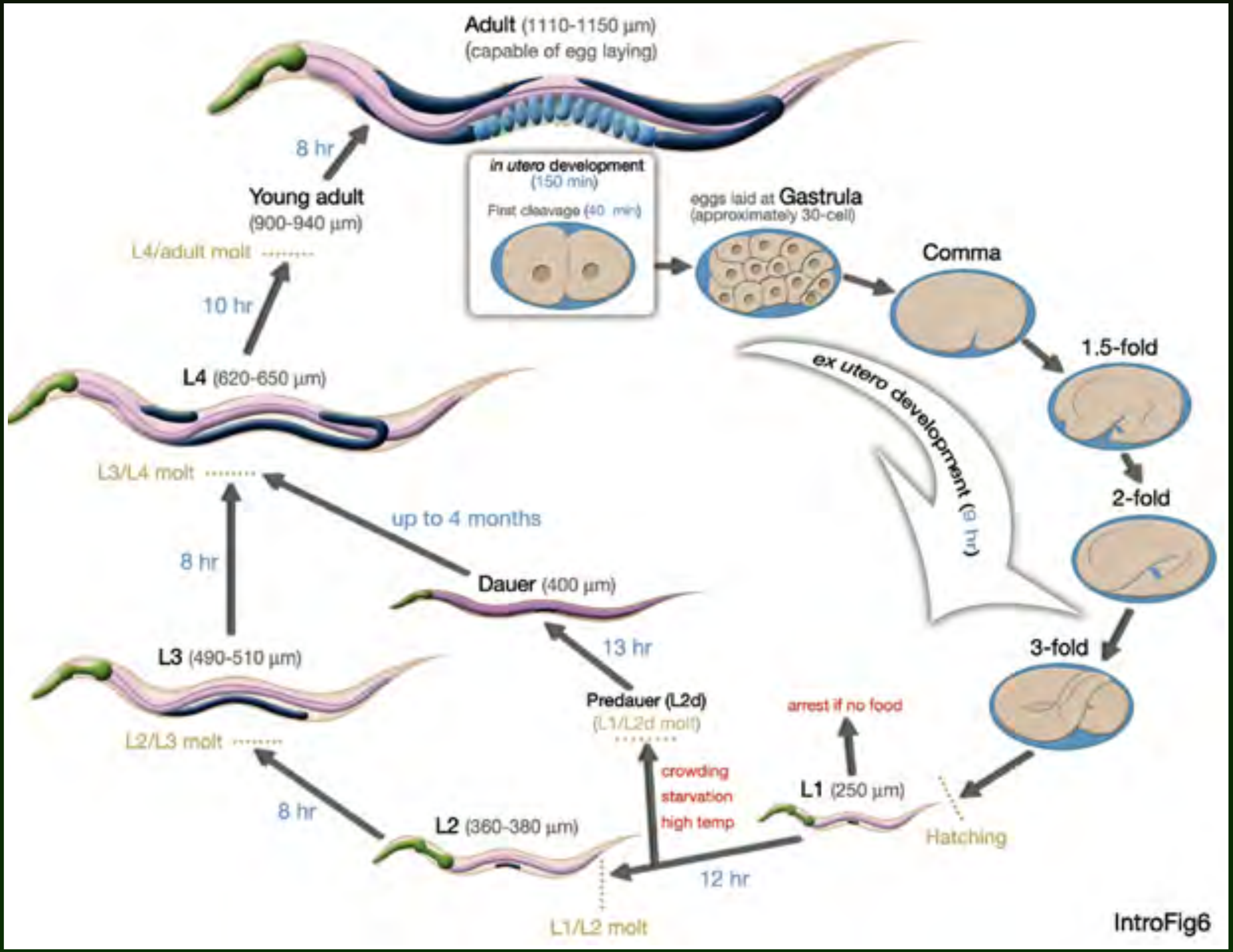
For simulation gene expression.

Yan, Chepyala, Yen, Chen, Hsu
(Submitted)

Fluctuation-dissipation theorem

Fluctuation-dissipation theorem (dynamic)

Yan and Hsu, J. Chem. Phys. 2013

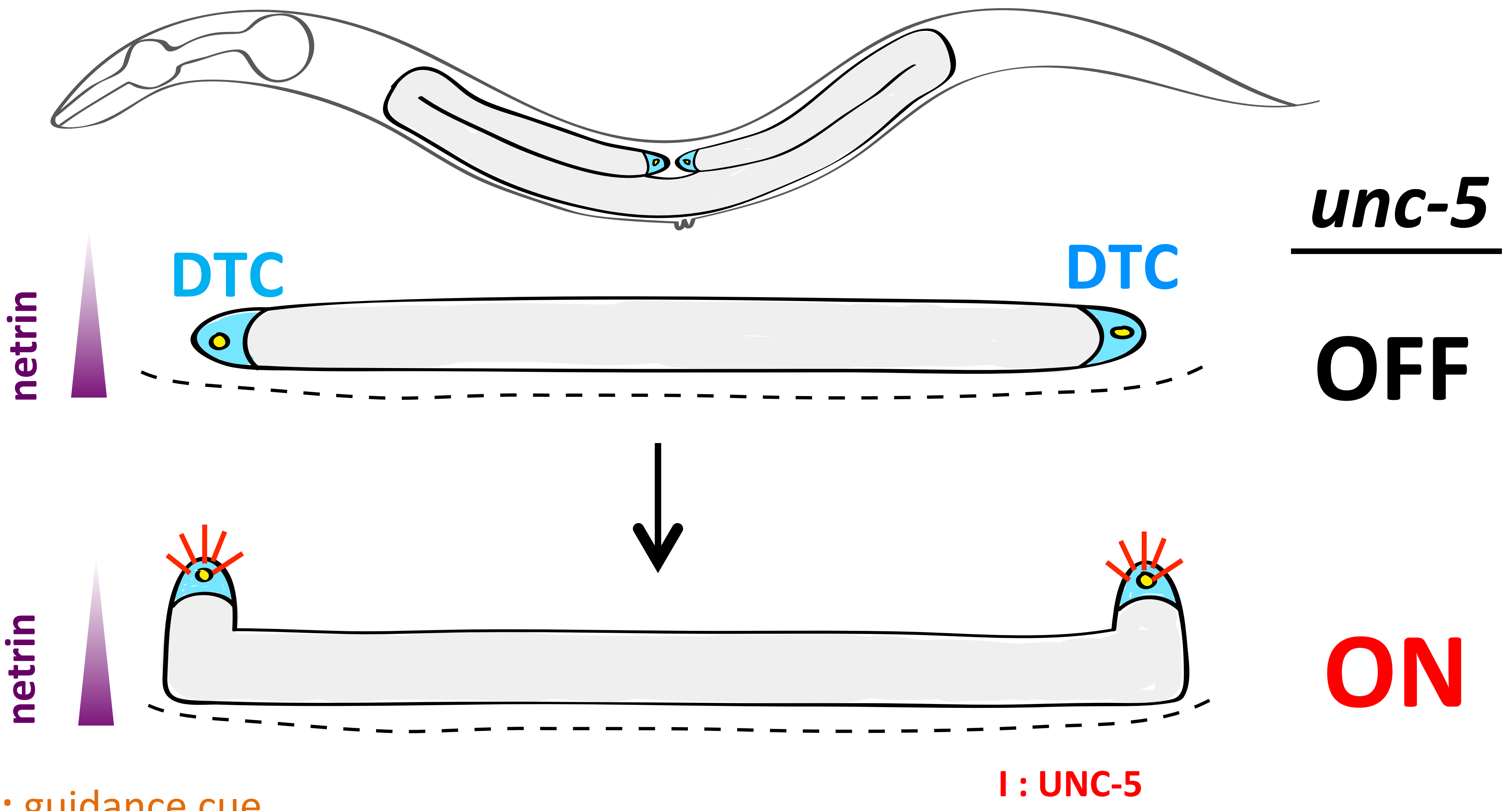


Collaboration project with NTU 吳益群教授

Noises in the development of worms (C. elegans)

Surendhar Reddy + Yi-Chen Chen 陳奕丞

The timing of gonad turn (unc5 expression) is tightly



netrin: guidance cue
UNC-5: a netrin receptor

Genes Dev. 14, 2486-2500 (2000)

Development 127, 585-594 (2000)

Picture by courtesy of Yi-Ting Cheng

Is noise buffered by the gene regulation network?

Phenotype: Dorsal turn timing (and shape) %

GENOTYPE	WILD TYPE	PRECOCIOUS	RETARDED
blmp-1(s71)	7	93	0
lin-29(n546)	100	0	0
lin-29(RNAi)	100	0	0
dre-1(dh99)	100	0	0
daf-12(rh61rh411)	100	0	0
lin-29(n546);dre-1(dh99)	0	0	100
lin-29(n546);daf-12(rh61rh411)	0	0	97
dre-1(dh99);daf-12(rh61rh411)	0	0	98
blmp-1(s71);daf-12(rh61rh411)	43	47	10
blmp-1(s71);lin-29(RNAi)	30	54	16
blmp-1(RNAi);lin-29(n546);dre-1(dh99)	22	43	35
blmp-1(s71);dre-1(dh99);daf-12(rh61rh411)	12	73	15

Is there a noise-filtering mechanism?

Lost of "noise-filtering" function?

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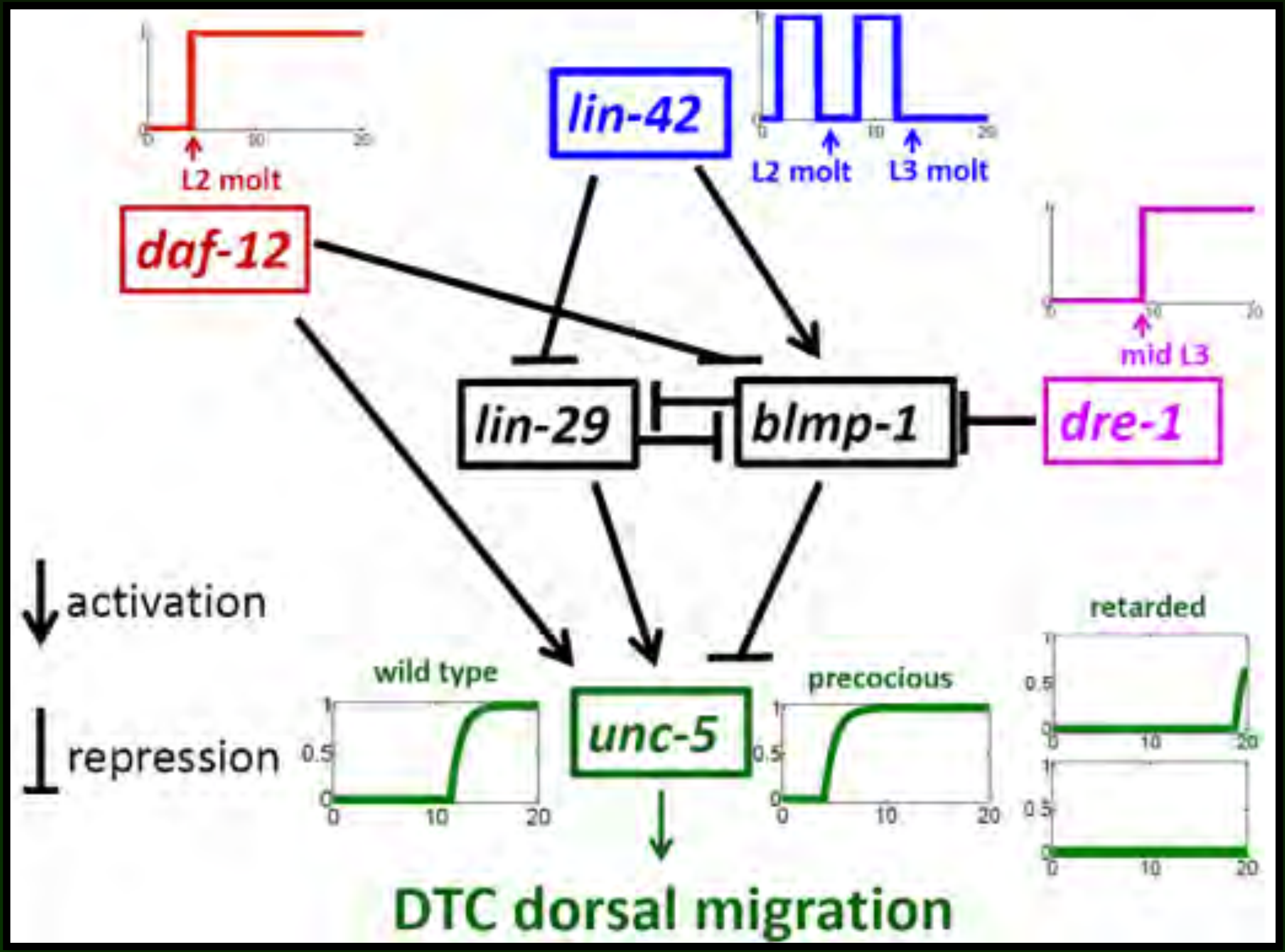
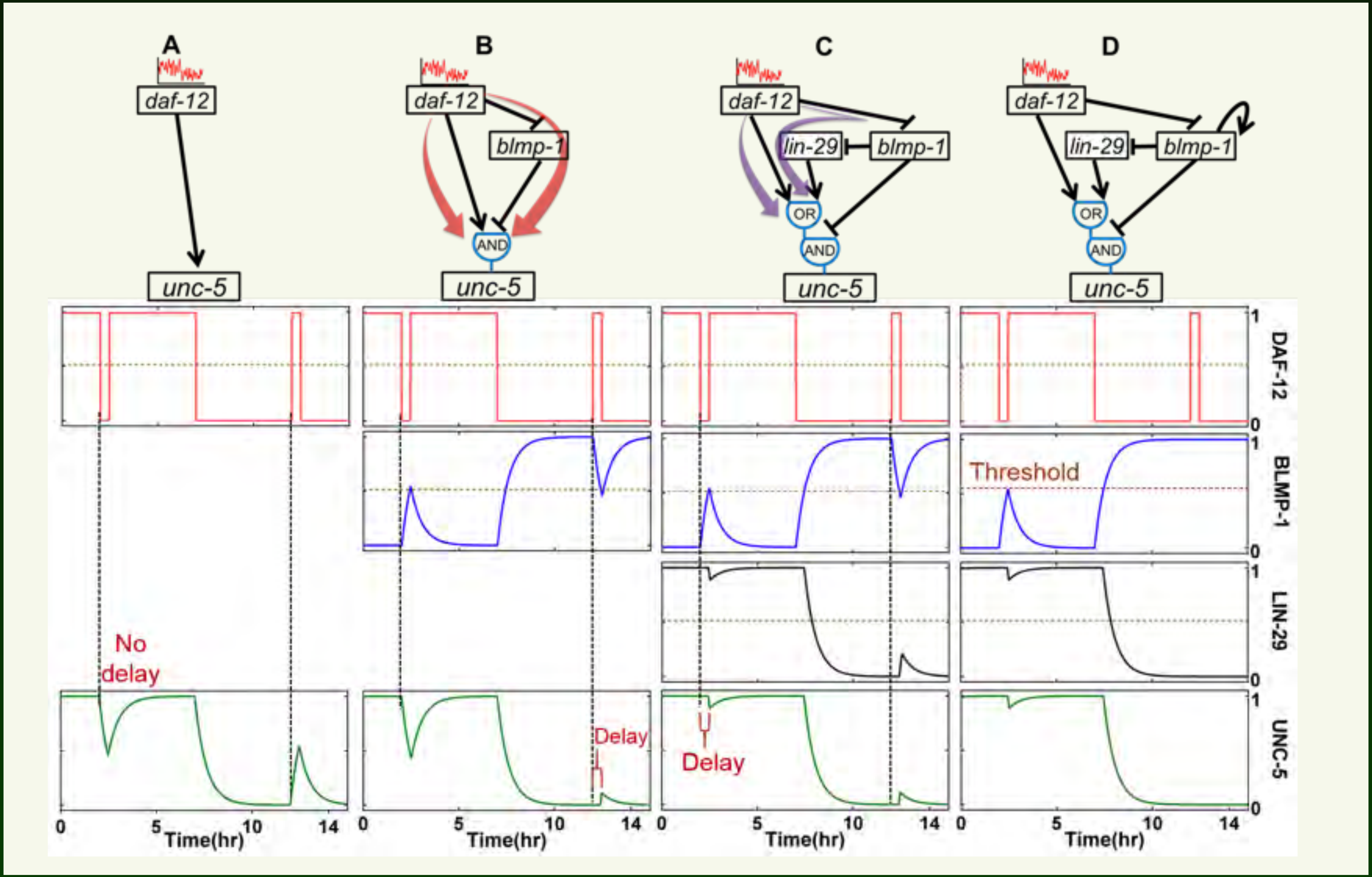
We built a model that generates almost all experimental mutant phenotypes.



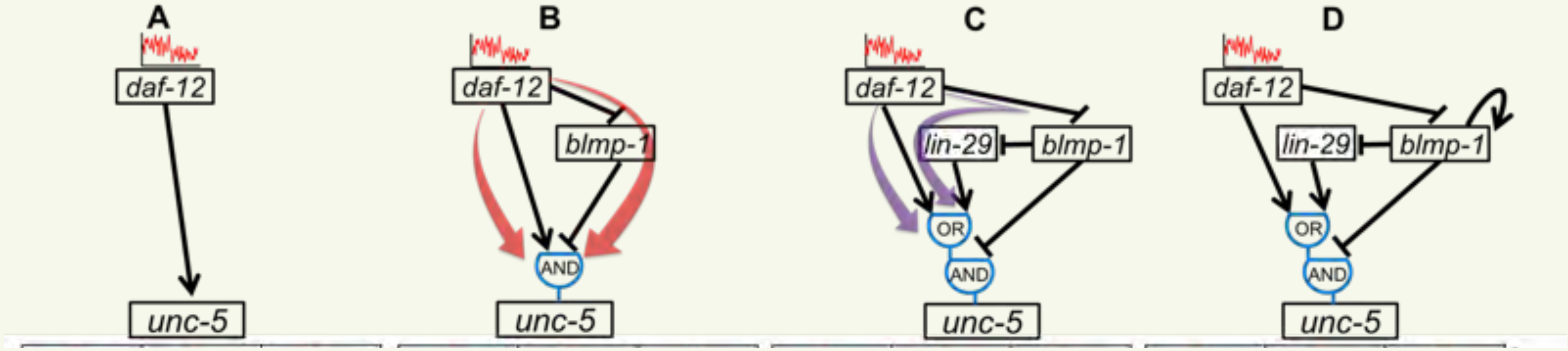
Node	Regulatory Logic
lin-29	*lin-29**= not *lin-42* and not *blmp-1*
blmp-1	*blmp-1**= (*lin-42* and not *lin-29* and not *daf-12*) or *blmp-1*
unc-5	*unc5** = (*lin-29* or *daf-12*) and not *blmp-1*

Interlinked FFL filters upstream noises



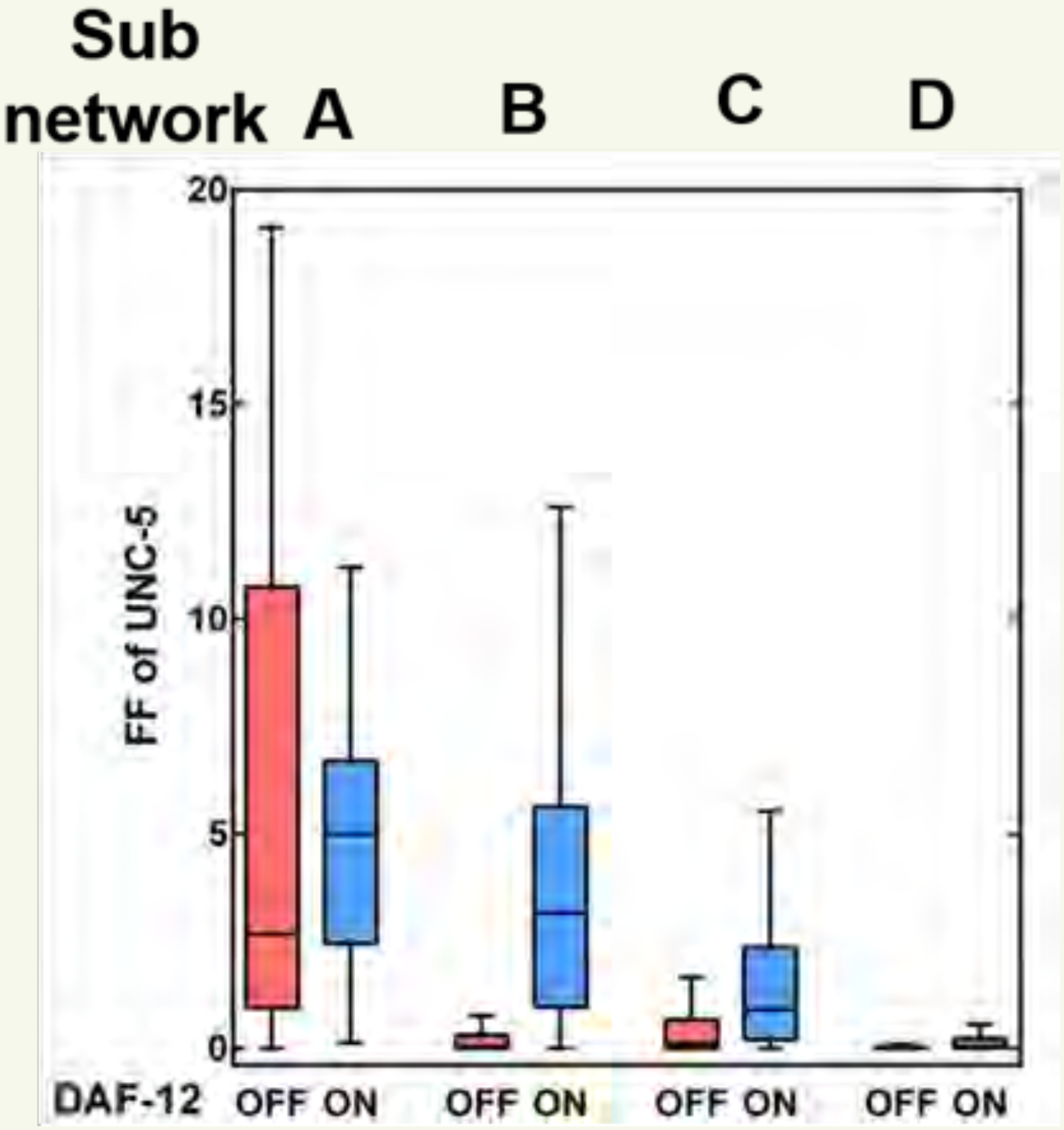
Adding noise in simulation

- Langevin’s equation: Noise can be easily added and removed.
- All genes have “intrinsic” noises — the Gaussian noise in their production and degradation.
  - Production: burst noise considered.
- Regulated genes have propagated noise.
- Other noises (not considered) — Global noise.

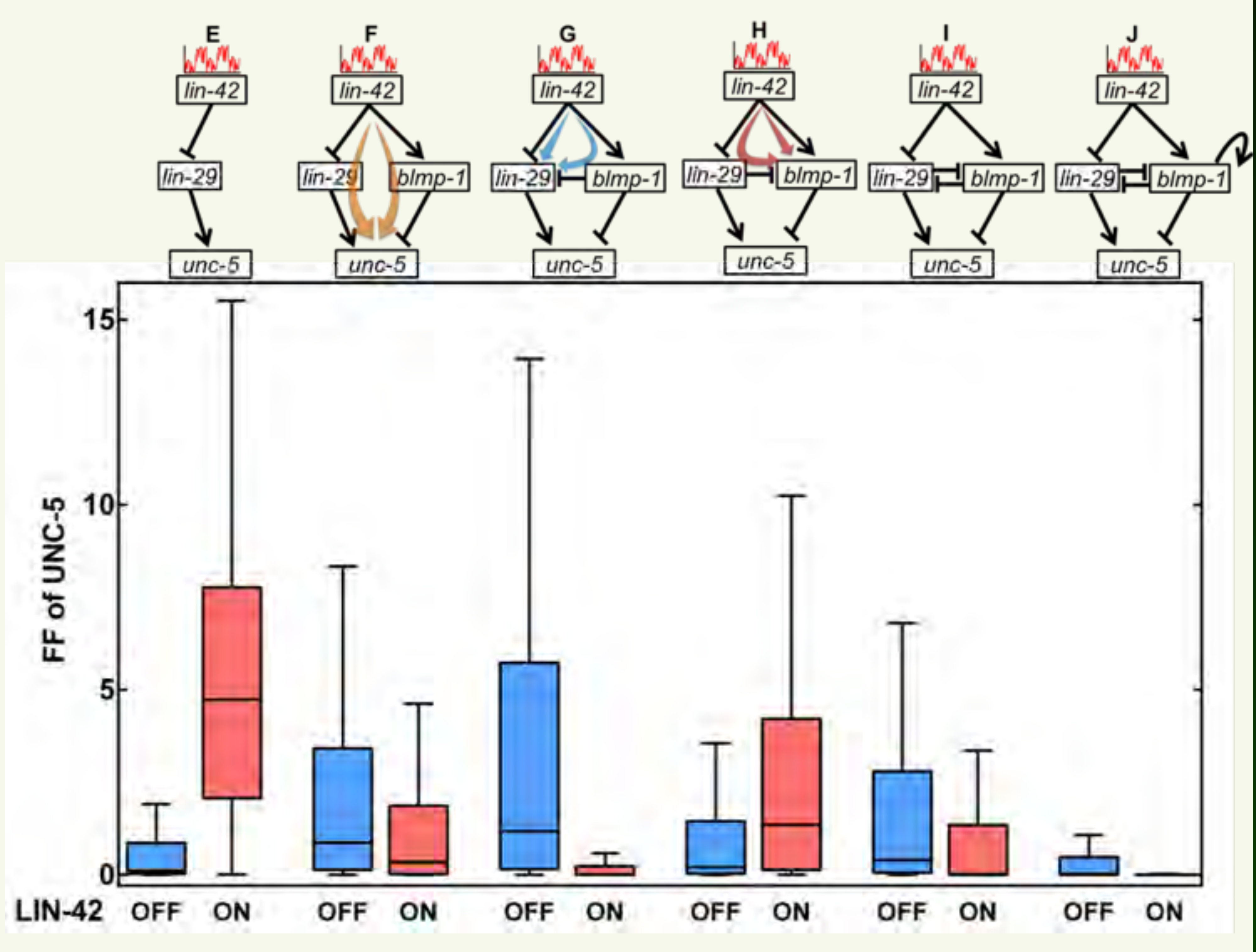


Fano Factor (FF)
=Variance/Mean

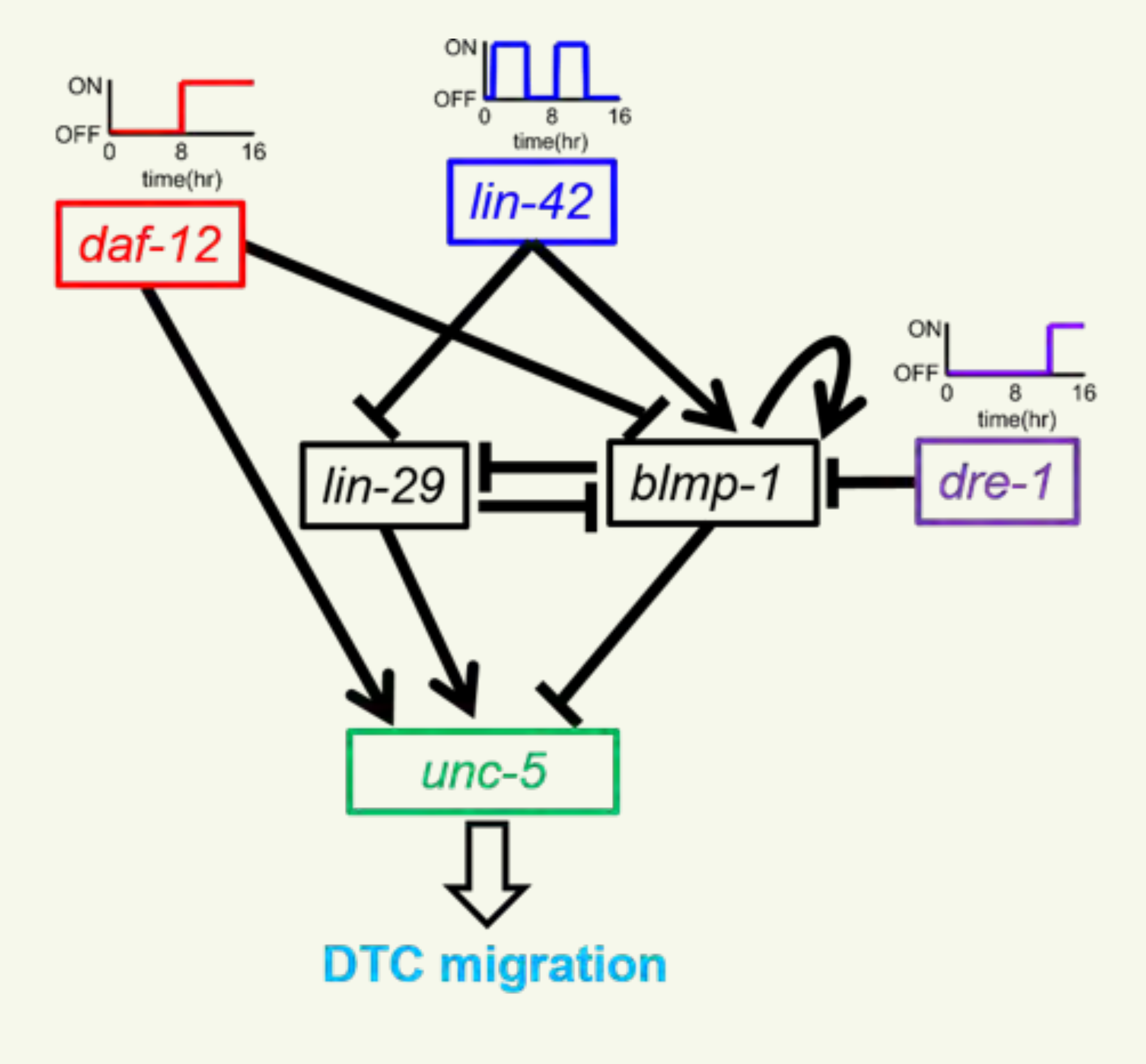
Results from 1000 randomly selected parameter sets that can produce wild type phenotype.

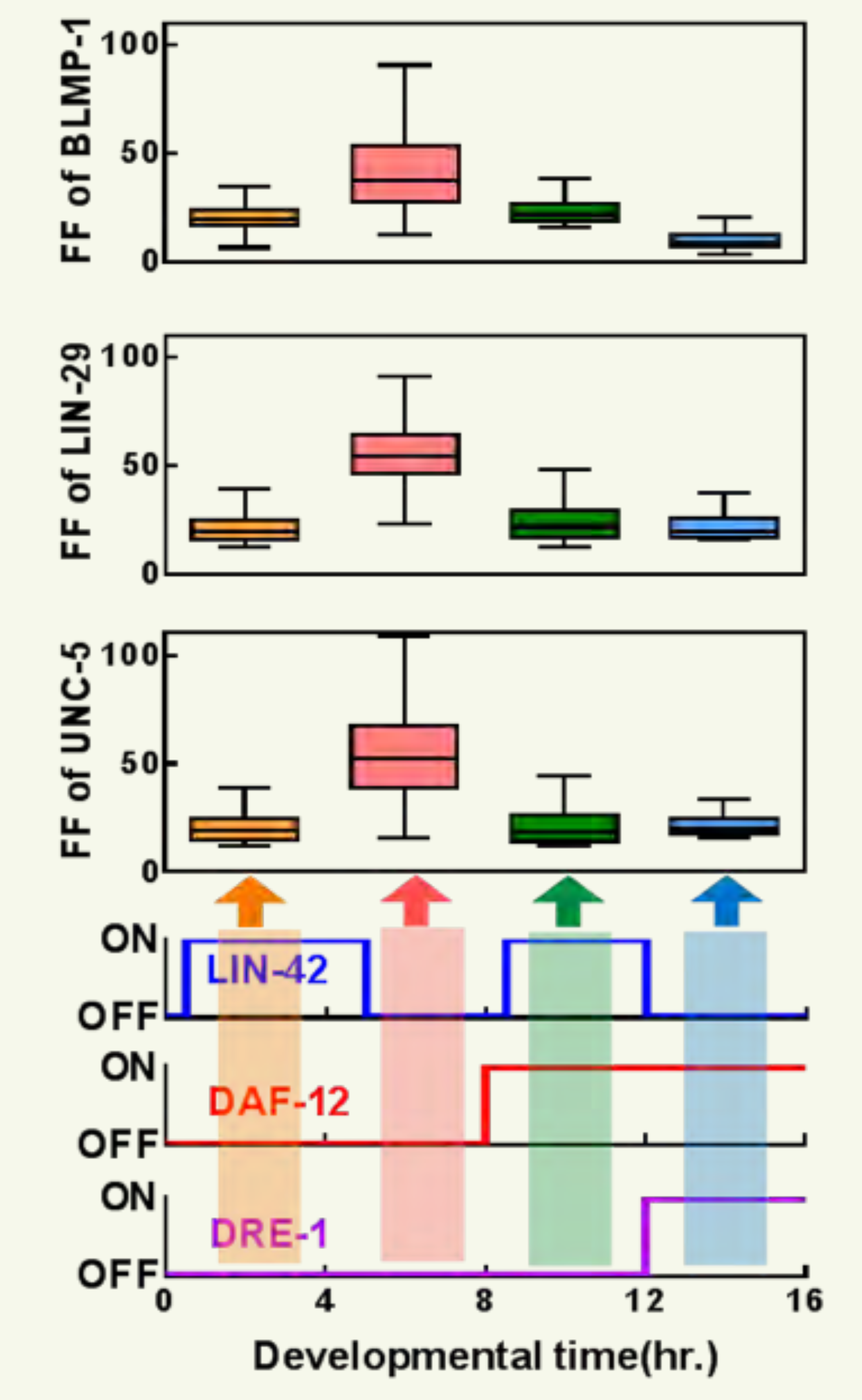


Another set of IFFL



All noise added & propagated





Is noise buffered by the gene regulation network?

Phenotype: Dorsal turn timing (and shape) %

GENOTYPE	WILD TYPE	PRECOCIOUS	RETARDED
blmp-1(s71)	7	93	0
lin-29(n546)	100	0	0
lin-29(RNAi)	100	0	0
dre-1(dh99)	100	0	0
daf-12(rh61rh411)	100	0	0
lin-29(n546);dre-1(dh99)	0	0	100
lin-29(n546);daf-12(rh61rh411)	0	0	97
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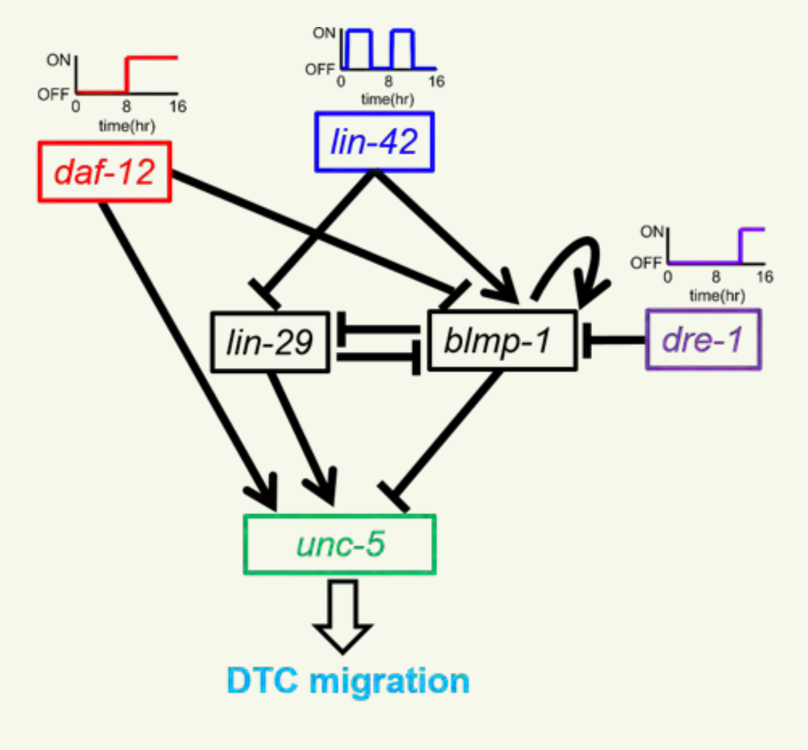
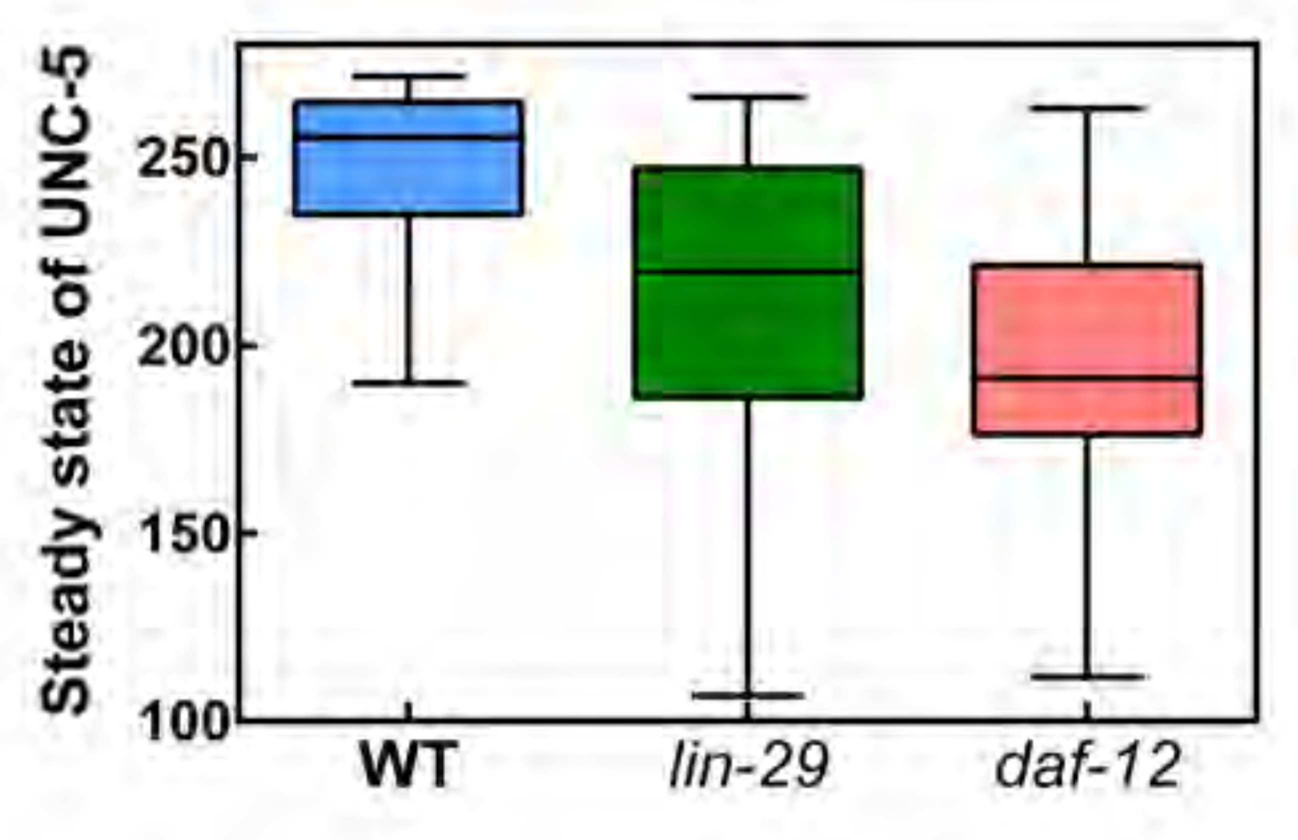
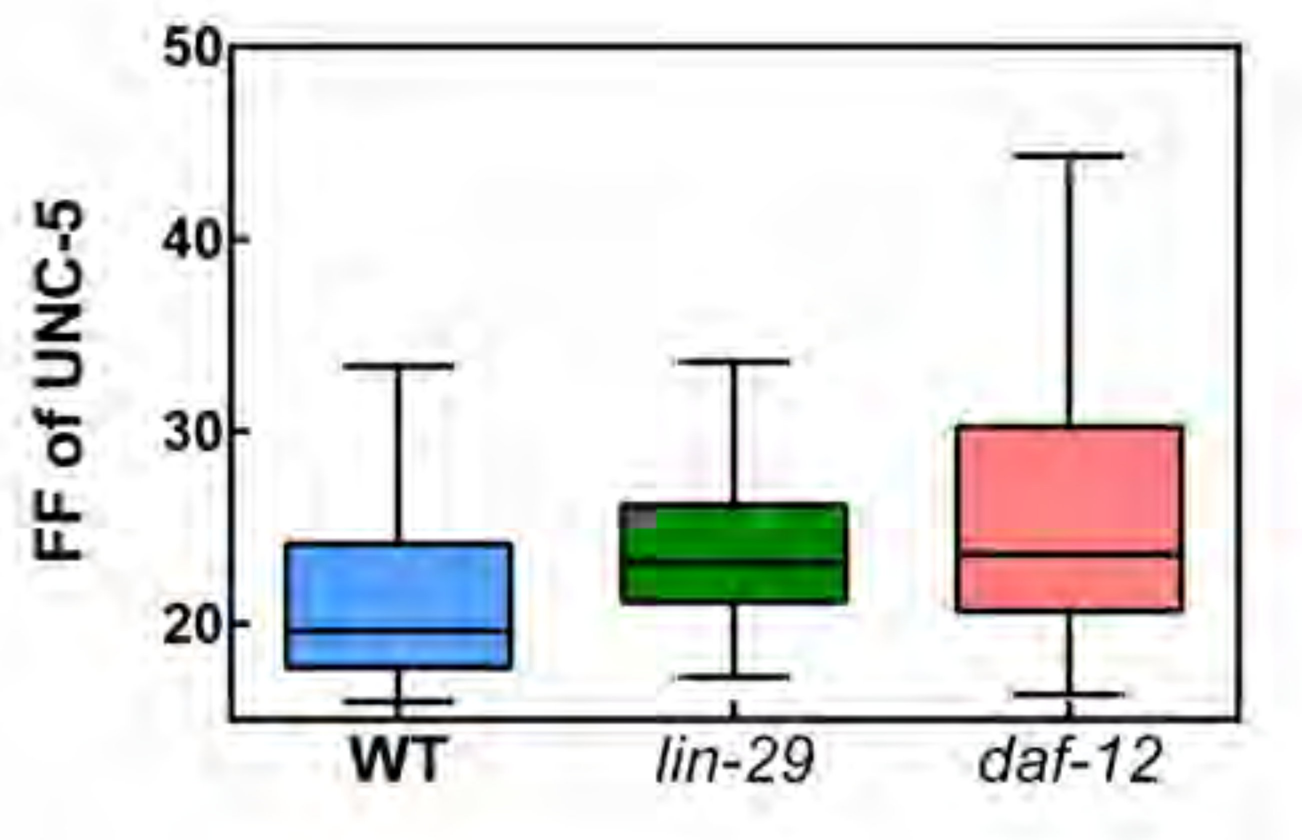
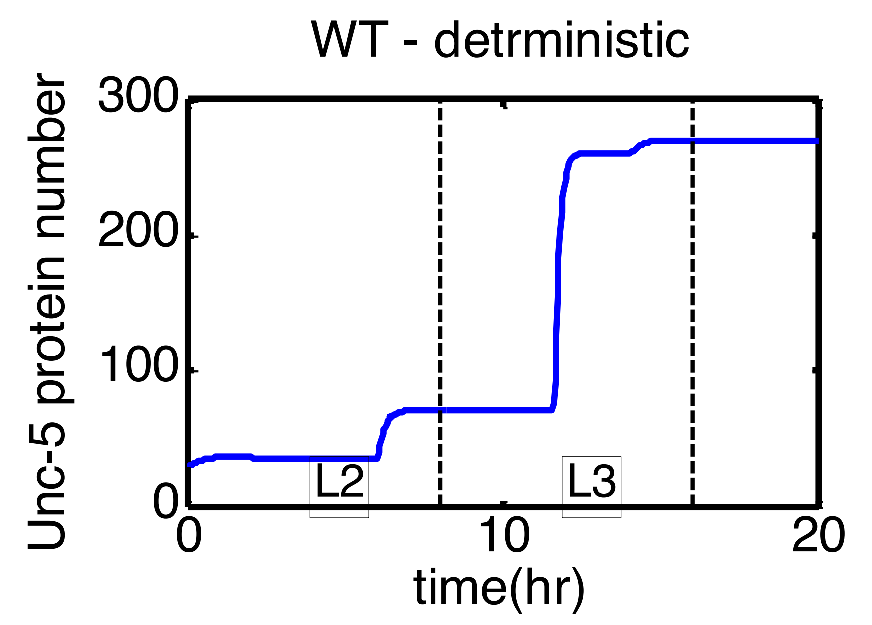
WT and Mutant behavior



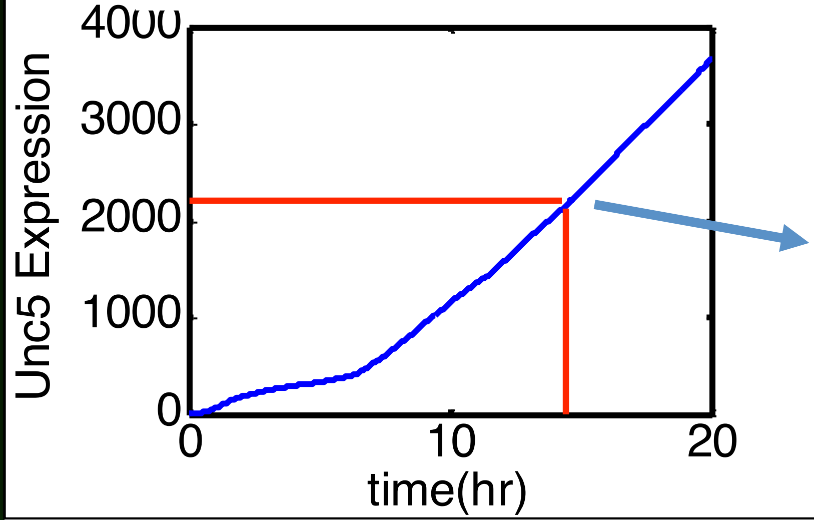




How shall we determine phenotype?

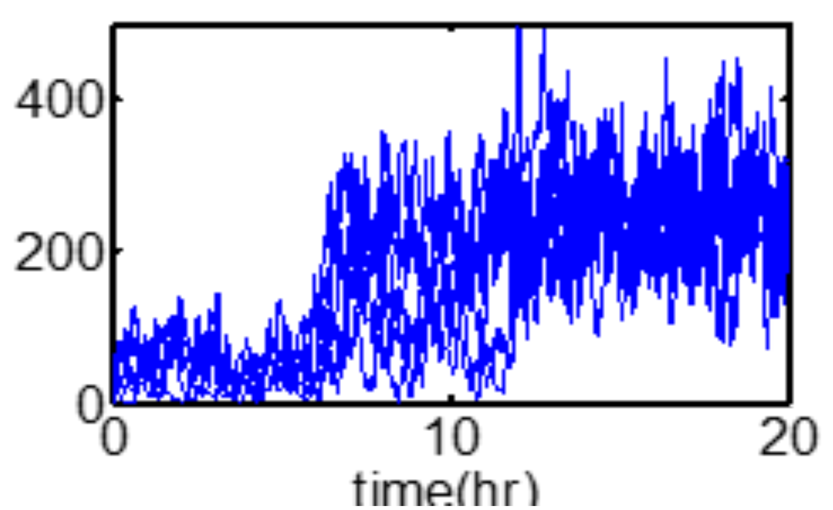


Unc-5 accumulation

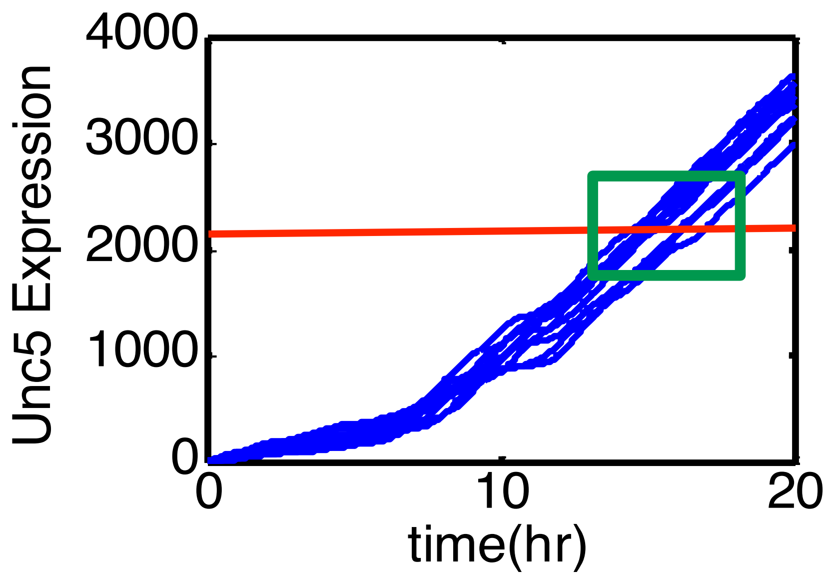


Unc5 expression level at 14 hr.

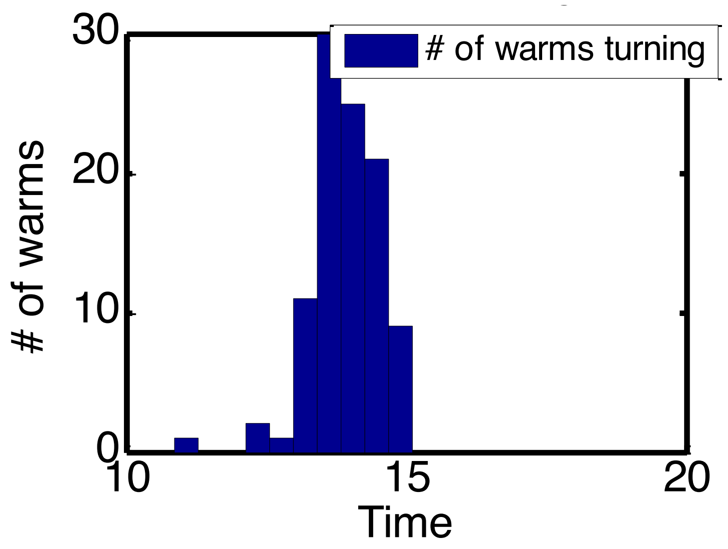
Stochastic unc-5 expression



Accumulated unc-5 signal



Time pass threshold



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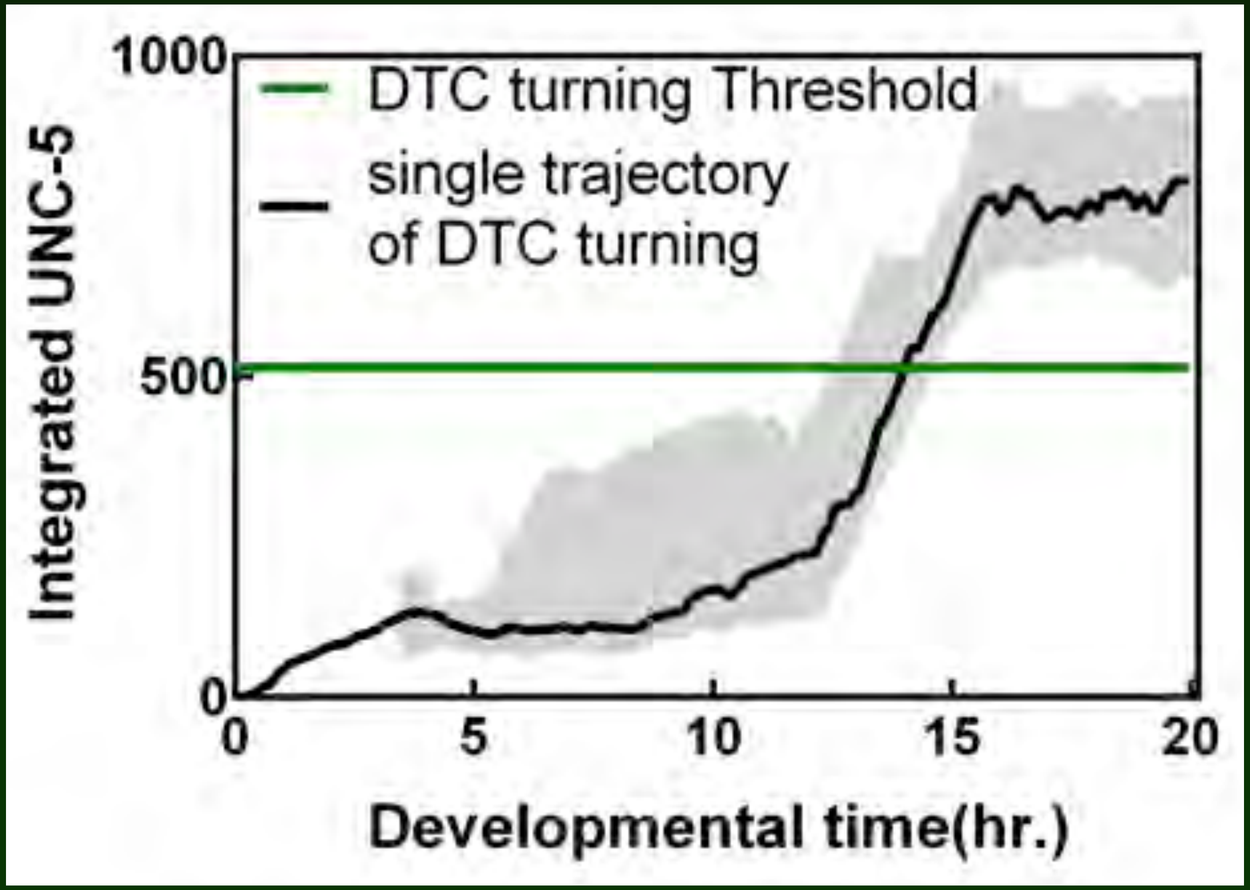
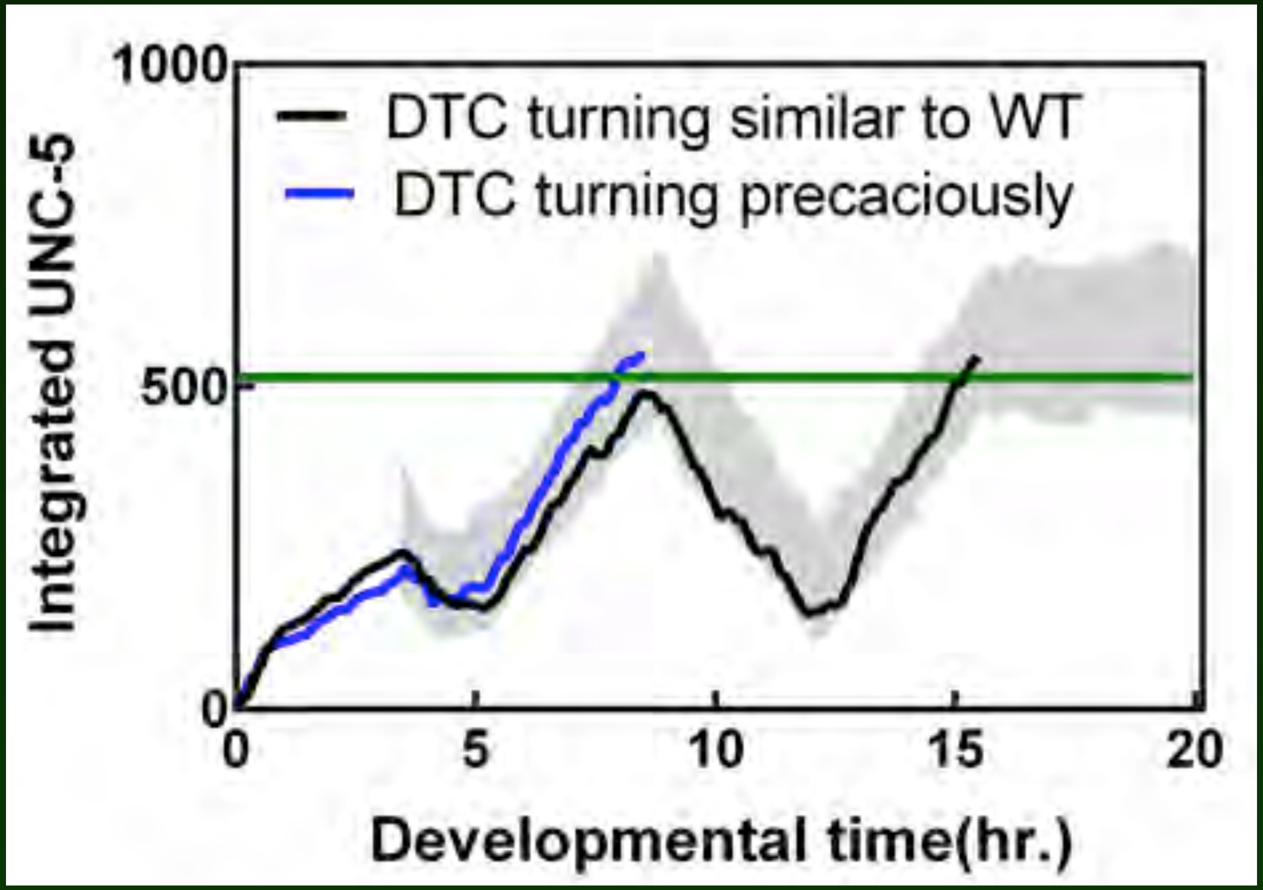
Simulating phenotypes

Wild type



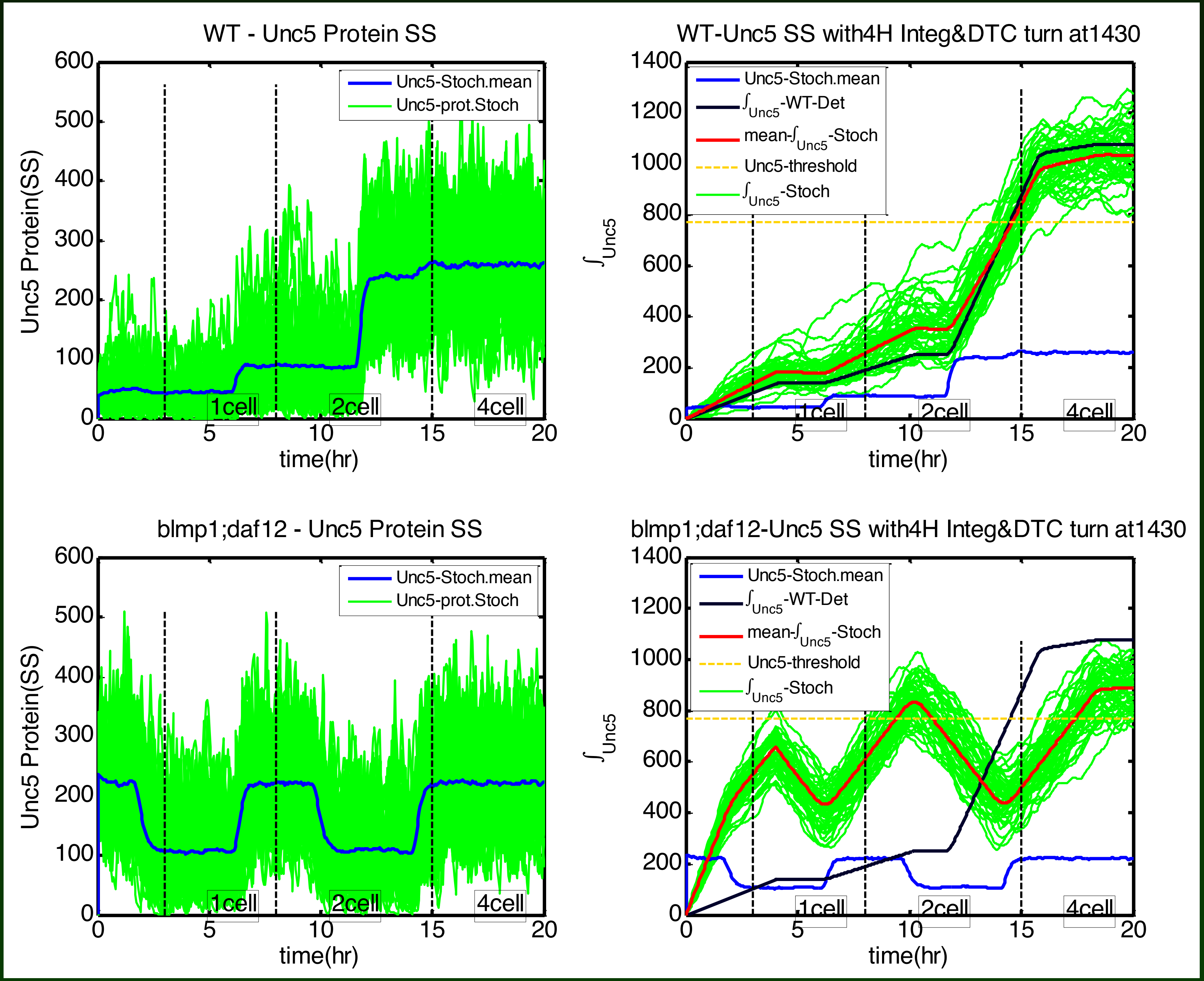
blmp-1 daf-12



Computer modeling helps us see why/how

WT

Mutant: blimp1,daf12



Phenotype diversity

- Most previous work: gene expression noises ⇒diverse phenotypes.
- Our result does not support such a link.
  - unc5 expression uncertainty does not directly correlate with DTC turning phenotypes.
- It is [Dynamics + noises]
  - WT: stay low. Even with noisy expression phenotype remains uniform.
  - mutant: unc5 expression goes up and down.

Many thanks to...

- Funding:

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科技部 Ministry of Science and Technology

- Excellent collaborators and students.