

Networks, noise and survival in stress

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**The Microsoft Research - University of Trento
Centre for Computational and Systems Biology
Computational and Systems Biology Course at CoSBI**

Wednesday, February 19, 2008



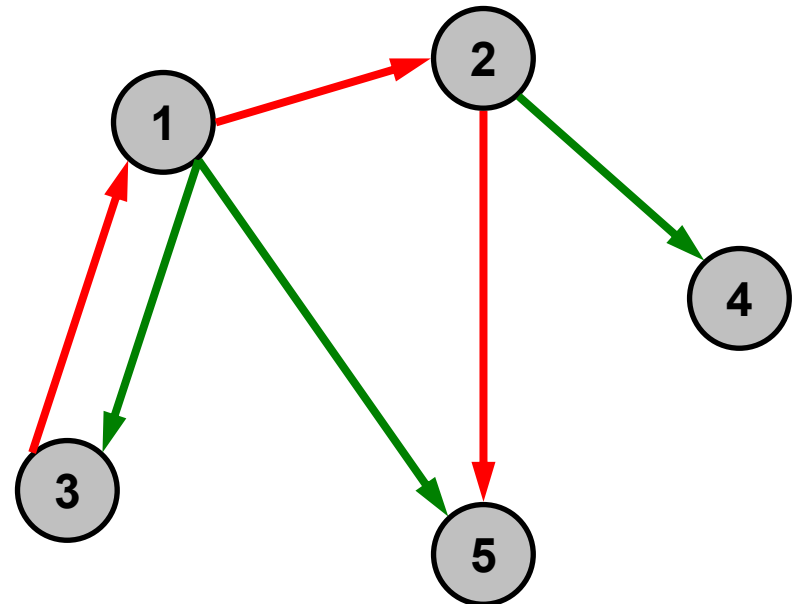
Networks (Graphs)

- A **network (graph)** is a system of interconnected objects
- Components of a network:

- **Nodes (vertices)**

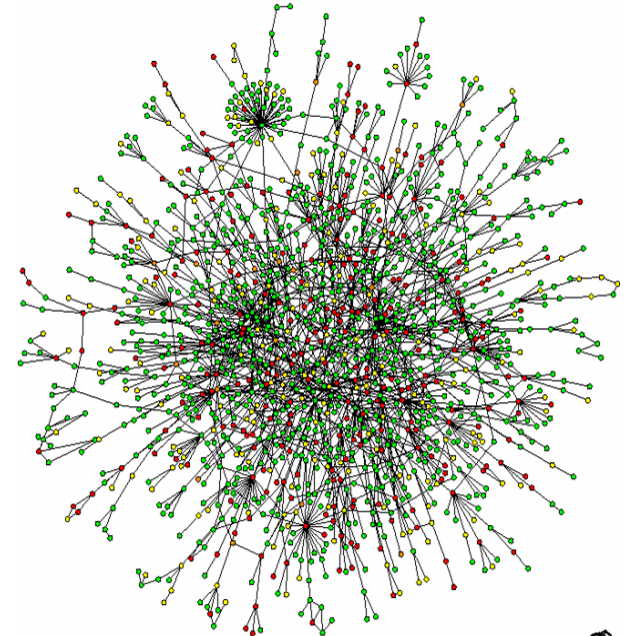
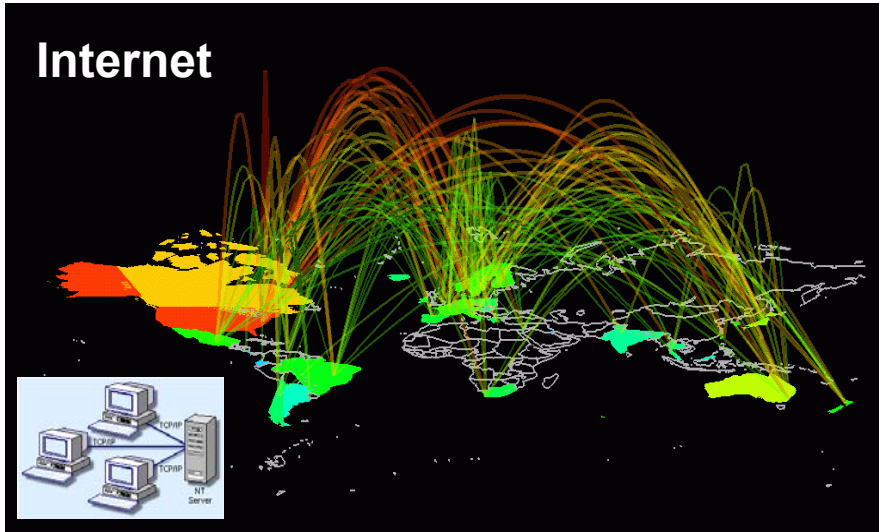
- **Links (edges) can be:**

- Directed
- Undirected

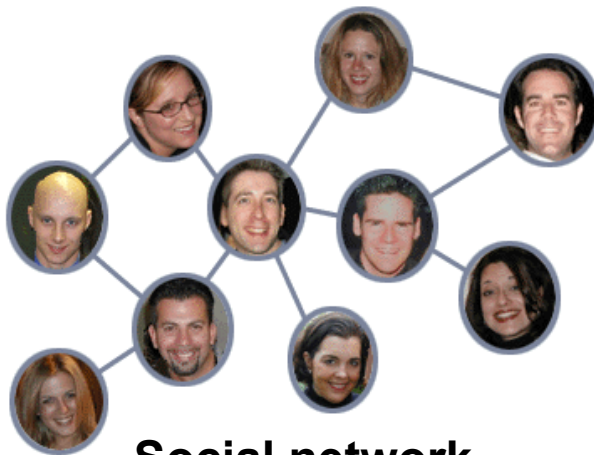


Examples of networks

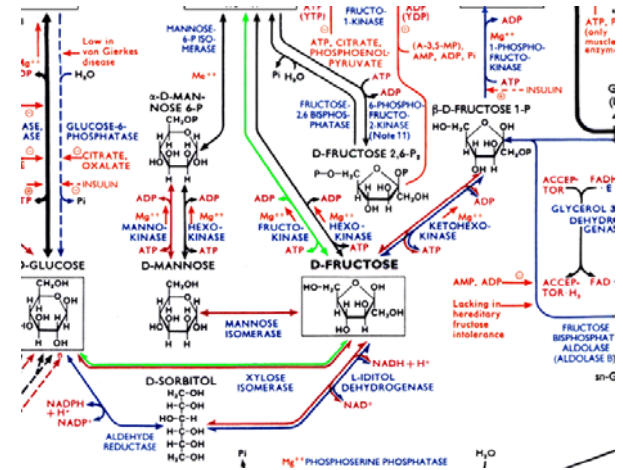
Internet



Protein-protein interaction network



Social network



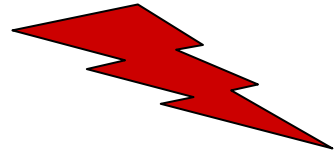
Metabolic network

Network topology: A large-scale perspective (Part I)



Gene expression

Environment



Cytoplasm

protein

protein

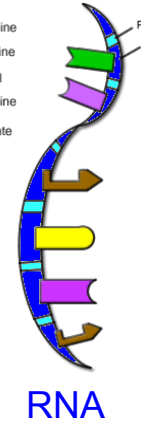


Thymine
Adenine
Guanine
Cytosine
D = Deoxyribose (sugar)
P = Phosphate
*** Hydrogen Bond

Adenine
Guanine
Uracil
Cytosine
P= phosphate
R= Ribose



Adenine
Guanine
Uracil
Cytosine
P= phosphate
R= Ribose



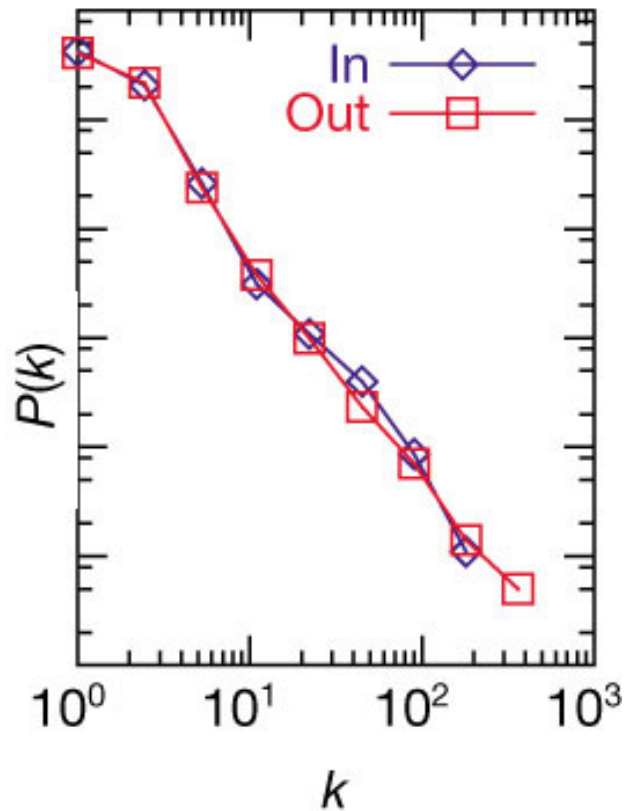
Nucleus

Membrane

- **Protein:**
 - Determines phenotype
- **DNA:**
 - Determines genotype

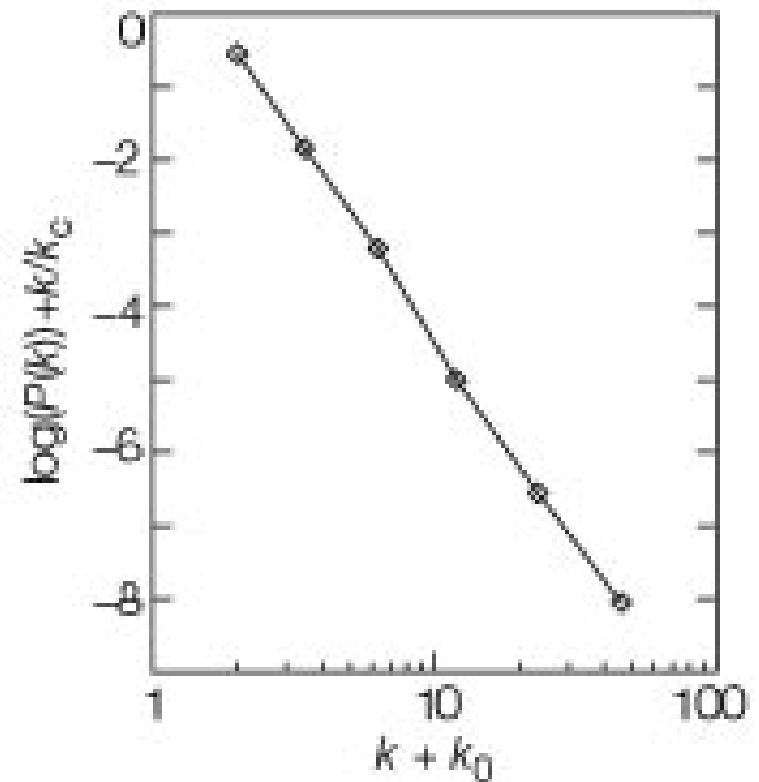
Connectivity distribution

METABOLIC



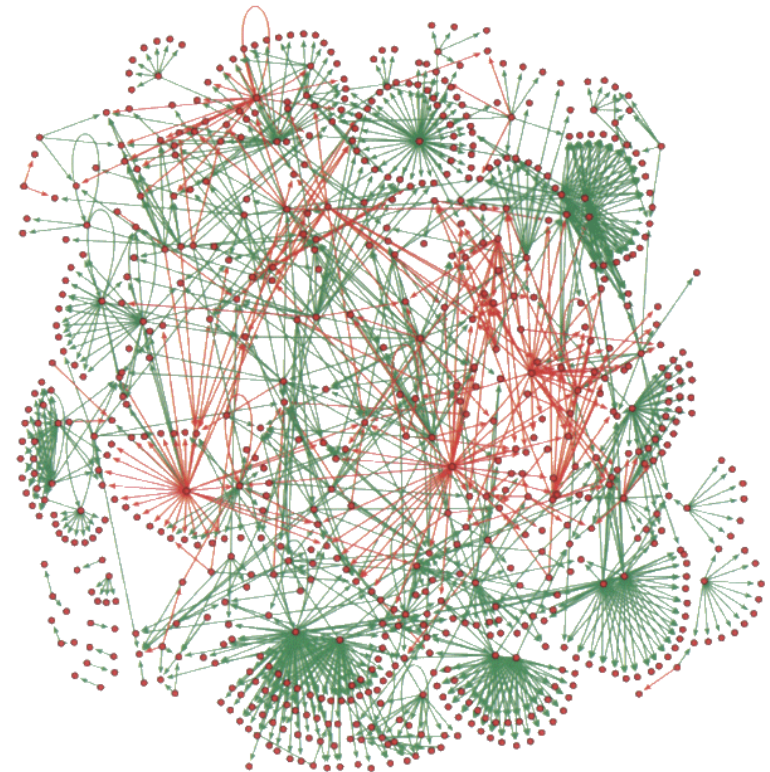
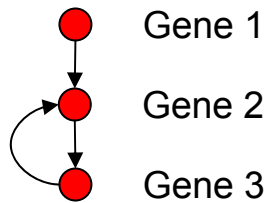
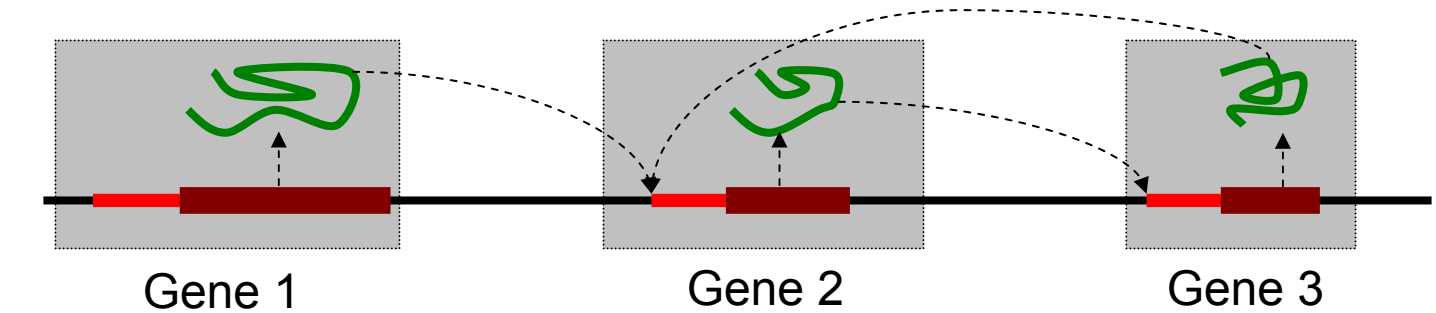
Jeong et al., *Nature* **407**, 651 (2000);

PPI



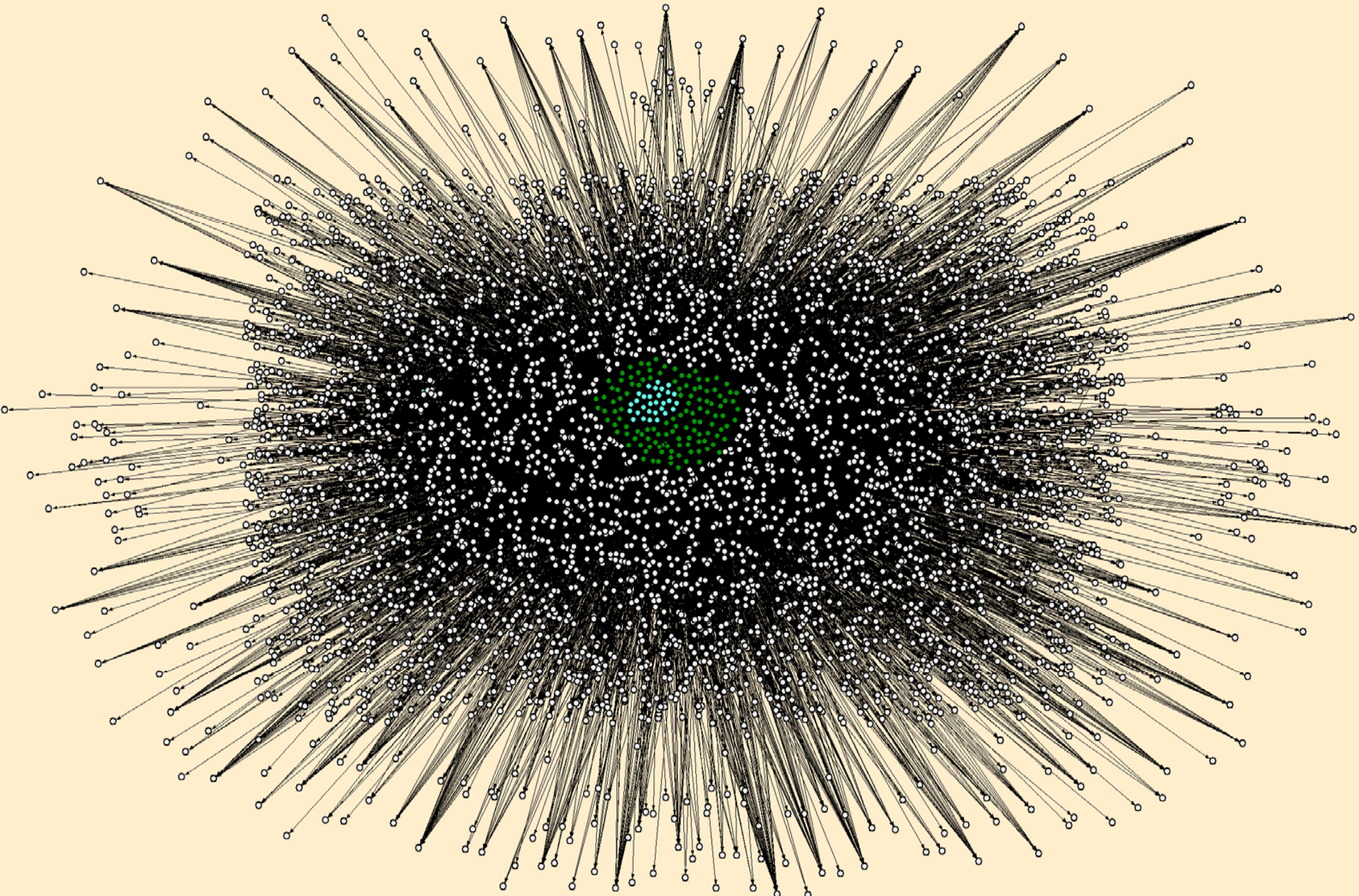
Jeong et al., *Nature* **411**, 41 (2001)

Transcriptional regulatory (TR) networks



Maslov & Sneppen, Phys. Biol. 2005

The yeast TR network

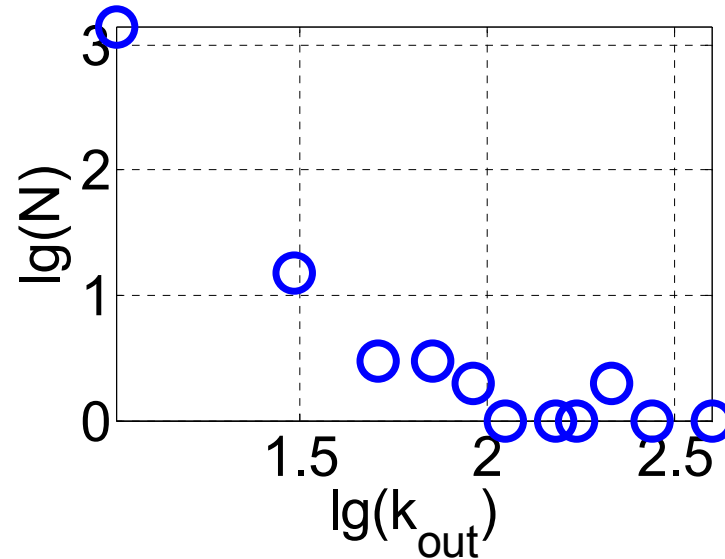
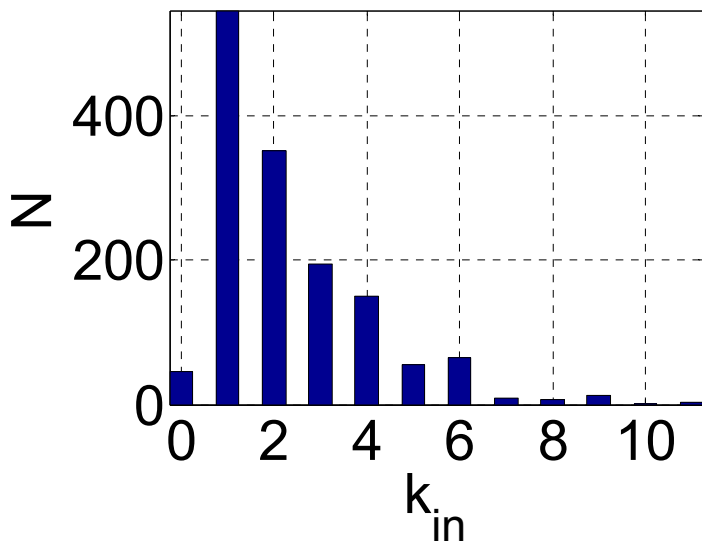


Connectivity distribution of TR networks

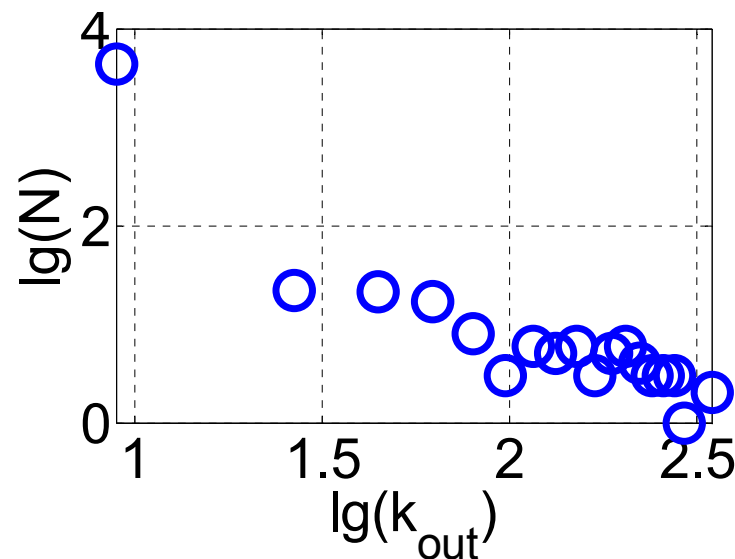
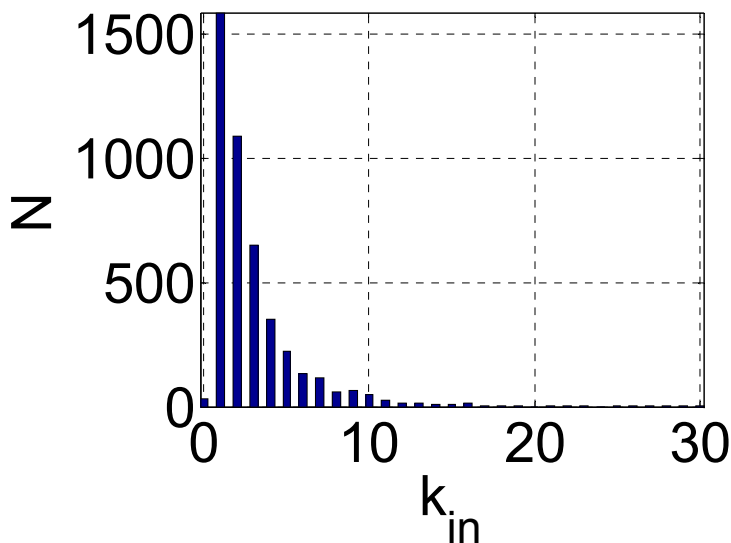
In-degree

Out-degree

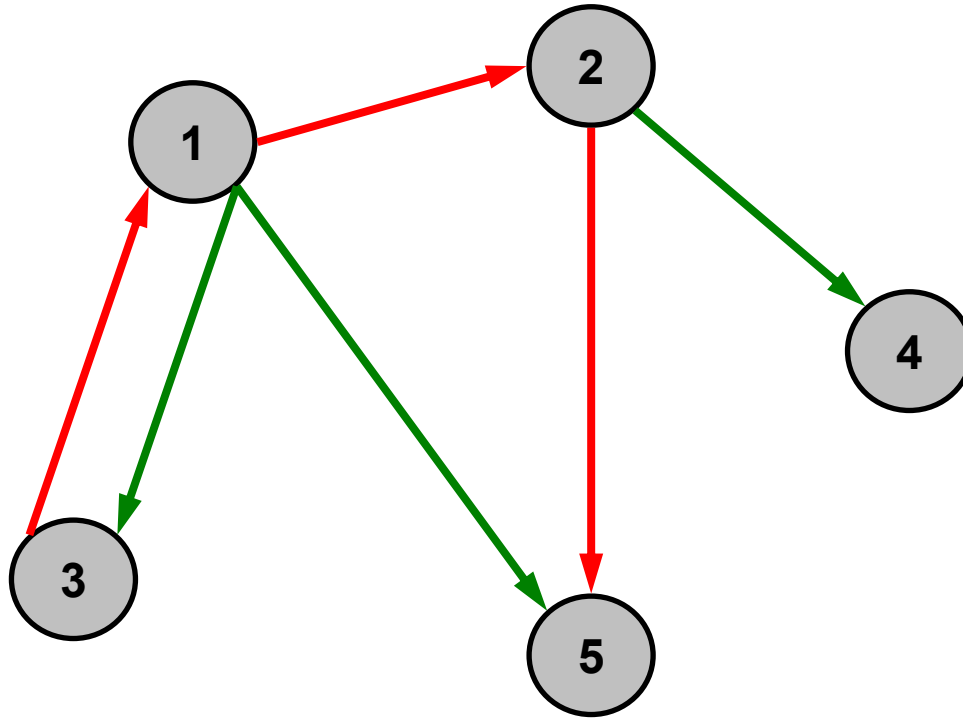
E. coli



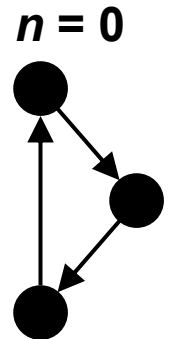
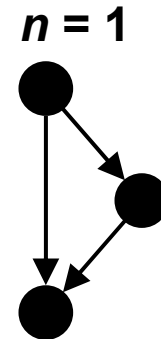
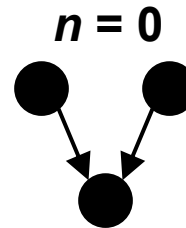
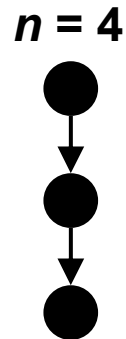
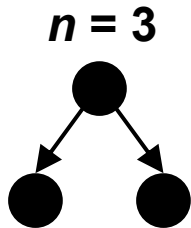
Yeast



Subgraphs



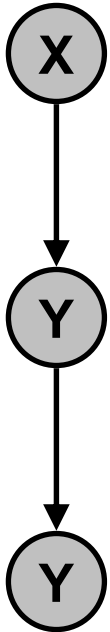
Abundance of
3-node
subgraphs



Subgraphs: some examples

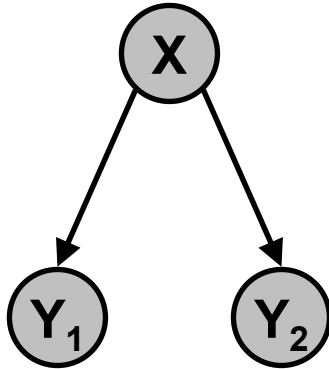
CAS

(Cascade)



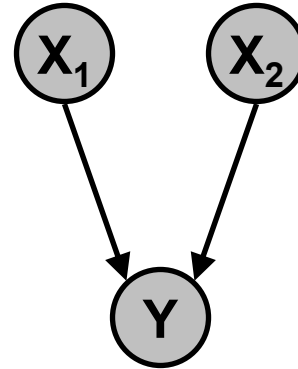
DIV

(Divergence)



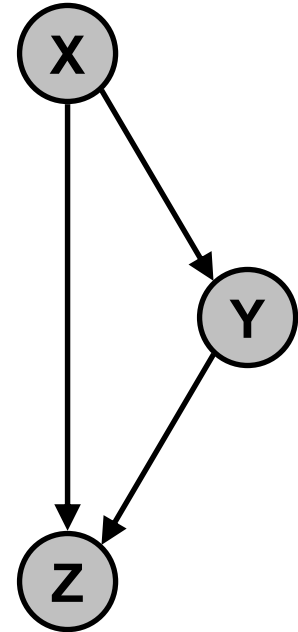
CNV

(Convergence)



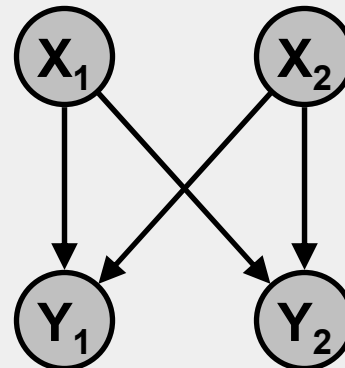
FFL

(Feed-forward loop)



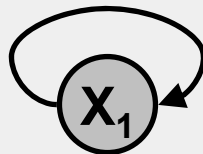
BFM

(Bi-fan motif)








ARL





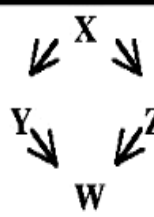
(Autoregulatory loop)



Subgraph abundance in the *E. coli* TR network

Subgraph	CON 	DIV 	CAS 	FFL 	BFM 
Abundance in <i>E. coli</i> network	227	4777	160	42	209
Abundance in randomized network	231.92 ± 8.05	4339.3 ± 132.0	186.69 ± 7.08	9.50 ± 4.17	74.78 ± 16.36
Z-score	0.6114	3.3149	3.7682	7.7909	8.2052

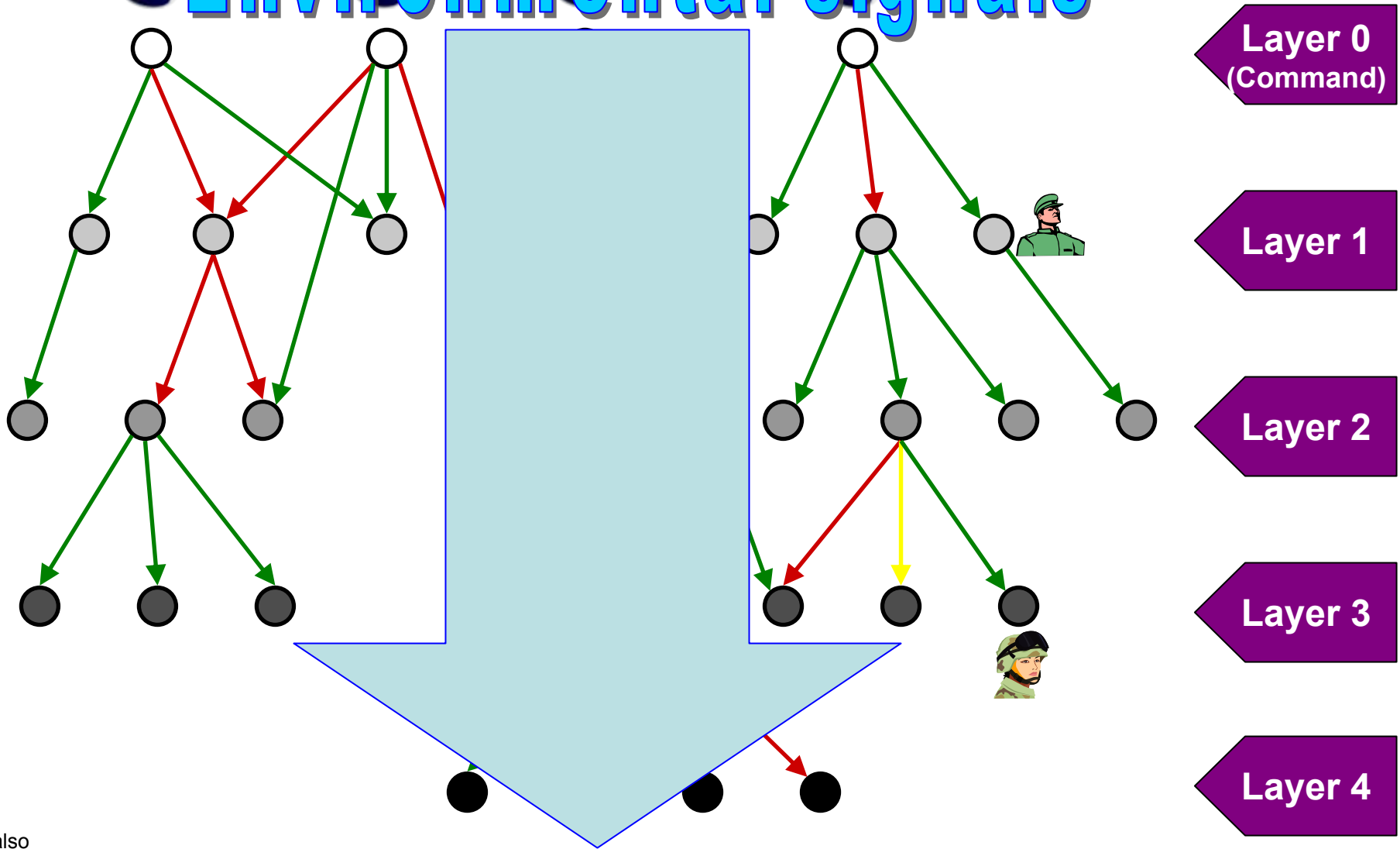
Motifs in information-processing networks

Network	Nodes	Edges	N_{real}	$N_{\text{rand}} \pm \text{SD}$	Z score	N_{real}	$N_{\text{rand}} \pm \text{SD}$	Z score	N_{real}	$N_{\text{rand}} \pm \text{SD}$	Z score
Gene regulation (transcription)				Feed-forward loop			Bi-fan				
<i>E. coli</i>	424	519	40	7 ± 3	10	203	47 ± 12	13			
<i>S. cerevisiae</i> *	685	1,052	70	11 ± 4	14	1812	300 ± 40	41			
Neurons				Feed-forward loop			Bi-fan			Bi-parallel	
<i>C. elegans</i> †	252	509	125	90 ± 10	3.7	127	55 ± 13	5.3	227	35 ± 10	20

R Milo et al., *Science* **298**, 824-827 (2002).

Hierarchical TR network topology

Environmental signals



Layer 0
(Command)

Layer 1

Layer 2

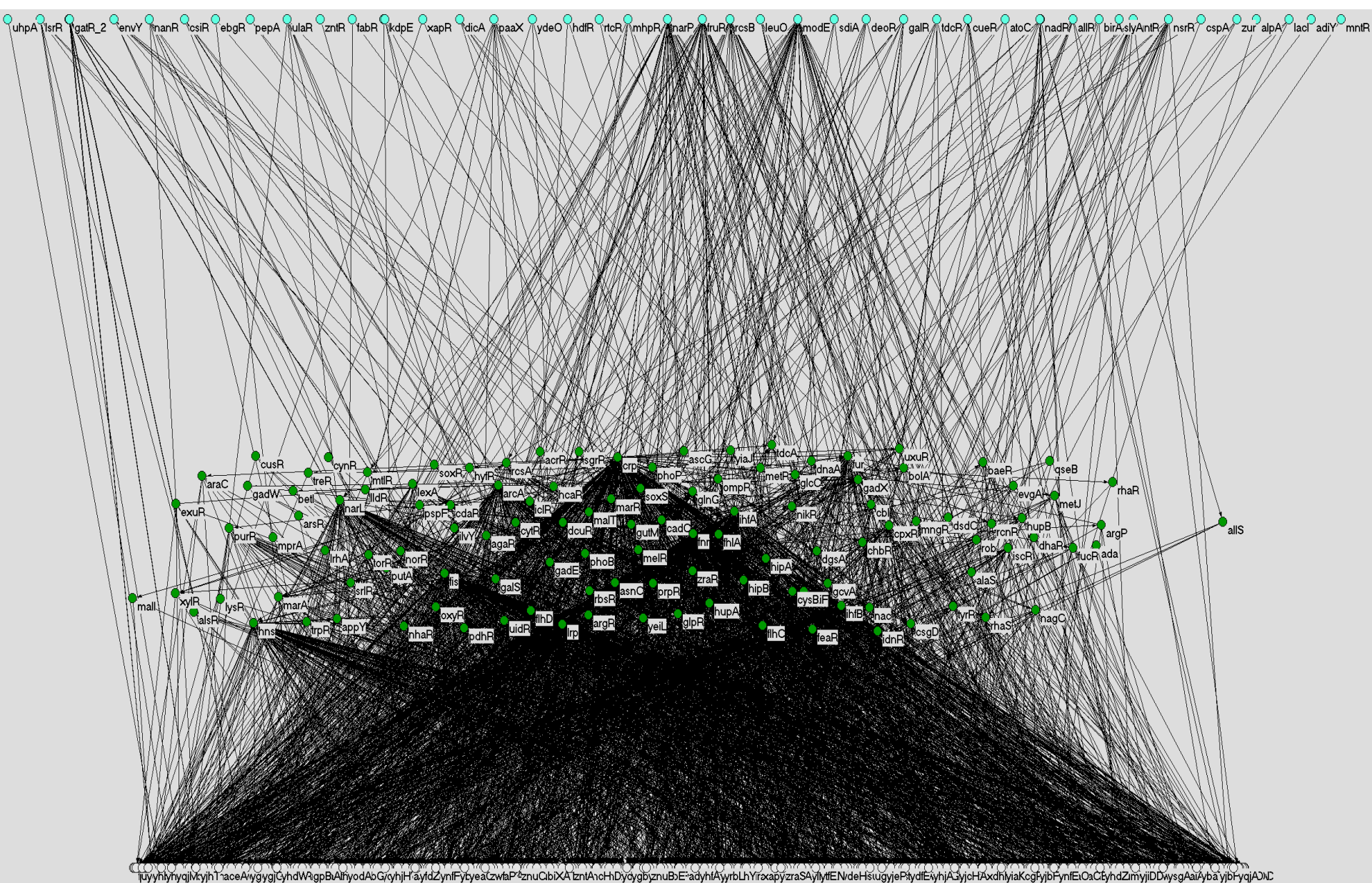
Layer 3

Layer 4

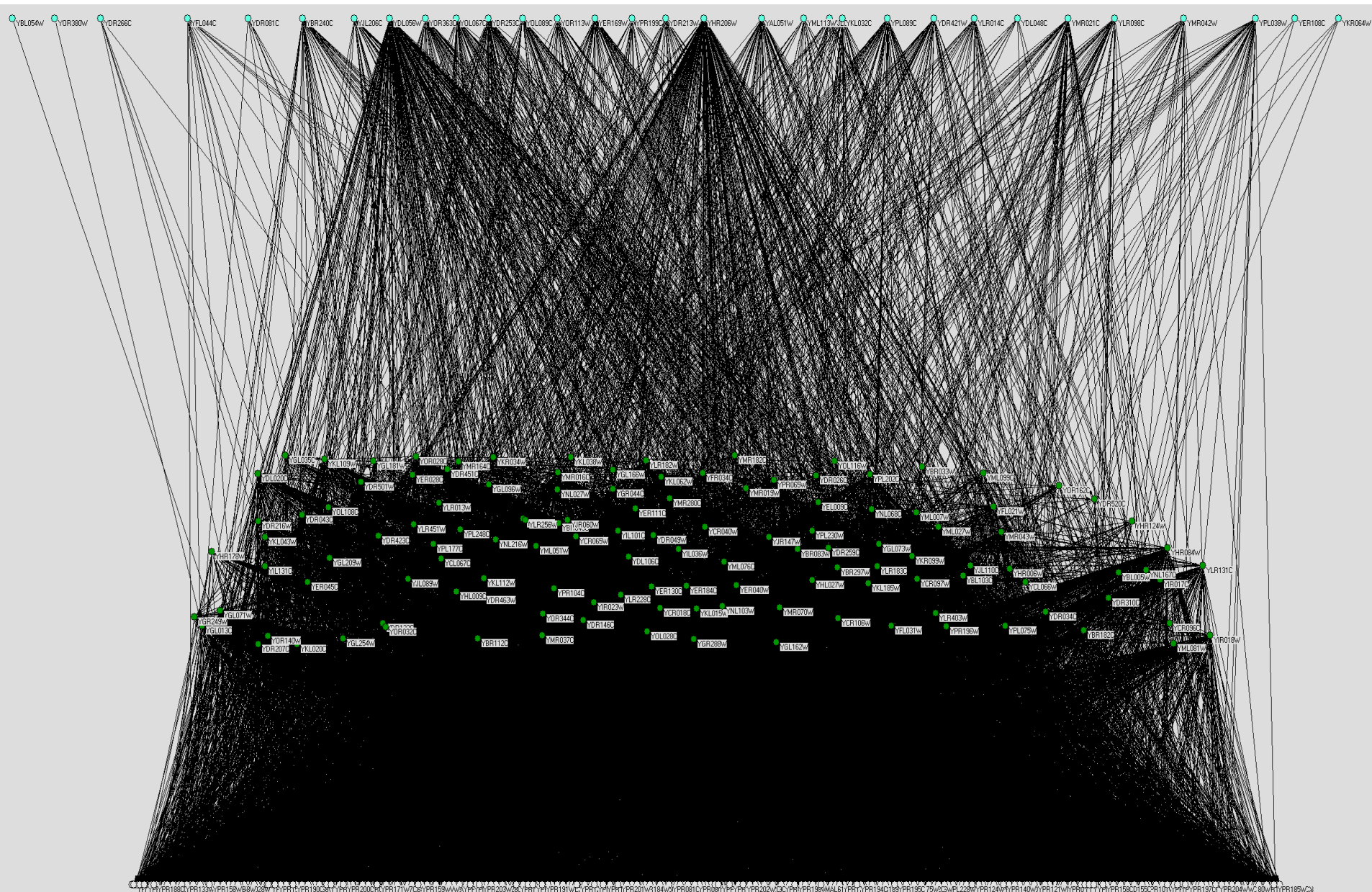
See also
Ma et al., *BMC Bioinformatics* **5**, 199 (2004)
Yu and Gerstein, *PNAS* **103**, 14724 (2006).

Balázsi G, Barabási A.-L., Oltvai ZN, *PNAS* **102**, 7841-6 (2005)

The *E. coli* TR network



The yeast TR network



YPR188C, YPR133W, YPR158W, YB6W, YJ29W, YPR190C, YPR191W, YPR192C, YPR193W, YPR194W, YPR195W, YPR196W, YPR197W, YPR198W, YPR199W, YPR200W, YPR201W, YPR202W, YPR203W, YPR204W, YPR205W, YPR206W, YPR207W, YPR208W, YPR209W, YPR210W, YPR211W, YPR212W, YPR213W, YPR214W, YPR215W, YPR216W, YPR217W, YPR218W, YPR219W, YPR220W, YPR221W, YPR222W, YPR223W, YPR224W, YPR225W, YPR226W, YPR227W, YPR228W, YPR229W, YPR230W, YPR231W, YPR232W, YPR233W, YPR234W, YPR235W, YPR236W, YPR237W, YPR238W, YPR239W, YPR240W, YPR241W, YPR242W, YPR243W, YPR244W, YPR245W, YPR246W, YPR247W, YPR248W, YPR249W, YPR250W, YPR251W, YPR252W, YPR253W, YPR254W, YPR255W, YPR256W, YPR257W, YPR258W, YPR259W, YPR260W, YPR261W, YPR262W, YPR263W, YPR264W, YPR265W, YPR266W, YPR267W, YPR268W, YPR269W, YPR270W, YPR271W, YPR272W, YPR273W, YPR274W, YPR275W, YPR276W, YPR277W, YPR278W, YPR279W, YPR280W, YPR281W, YPR282W, YPR283W, YPR284W, YPR285W, YPR286W, YPR287W, YPR288W, YPR289W, YPR290W, YPR291W, YPR292W, YPR293W, YPR294W, YPR295W, 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Types of genes: Commander, Intermediate, Executor



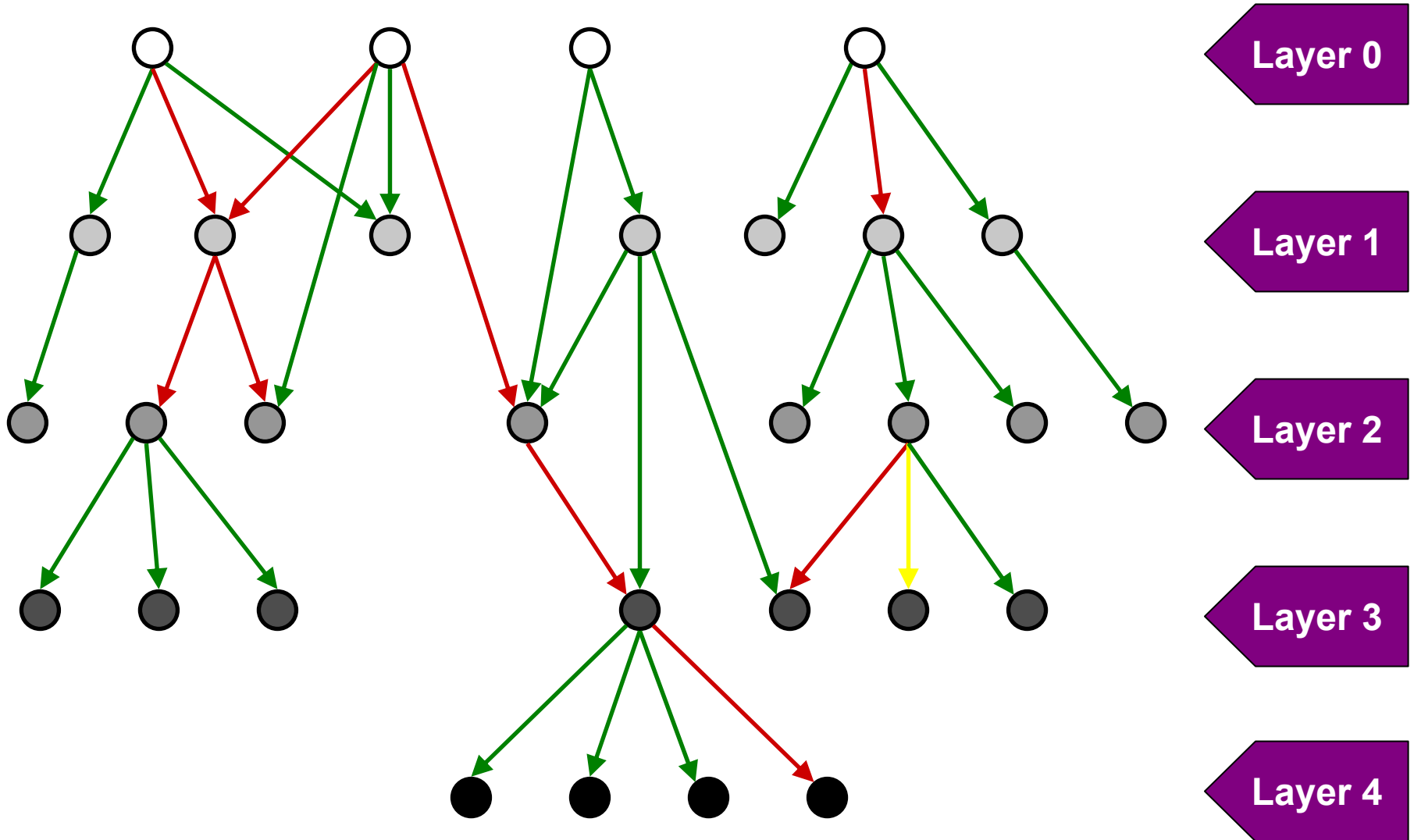
$82 + 78 + 1273 = 1433$	Commander	Intermediate	Executor	Total
Number of genes	82	78	1273	1433
<i>Escherichia coli</i>				

$31 + 126 + 4284 = 4441$	Commander	Intermediate	Executor	Total
Number of genes	31	126	4284	4441
<i>Saccharomyces cerevisiae</i>				

$34 + 11 + 735 = 780$	Commander	Intermediate	Executor	Total
Number of genes	34	11	735	780
<i>Mycobacterium tuberculosis</i>				

Are all three gene types equally responsive and/or noisy?

Definition of origons

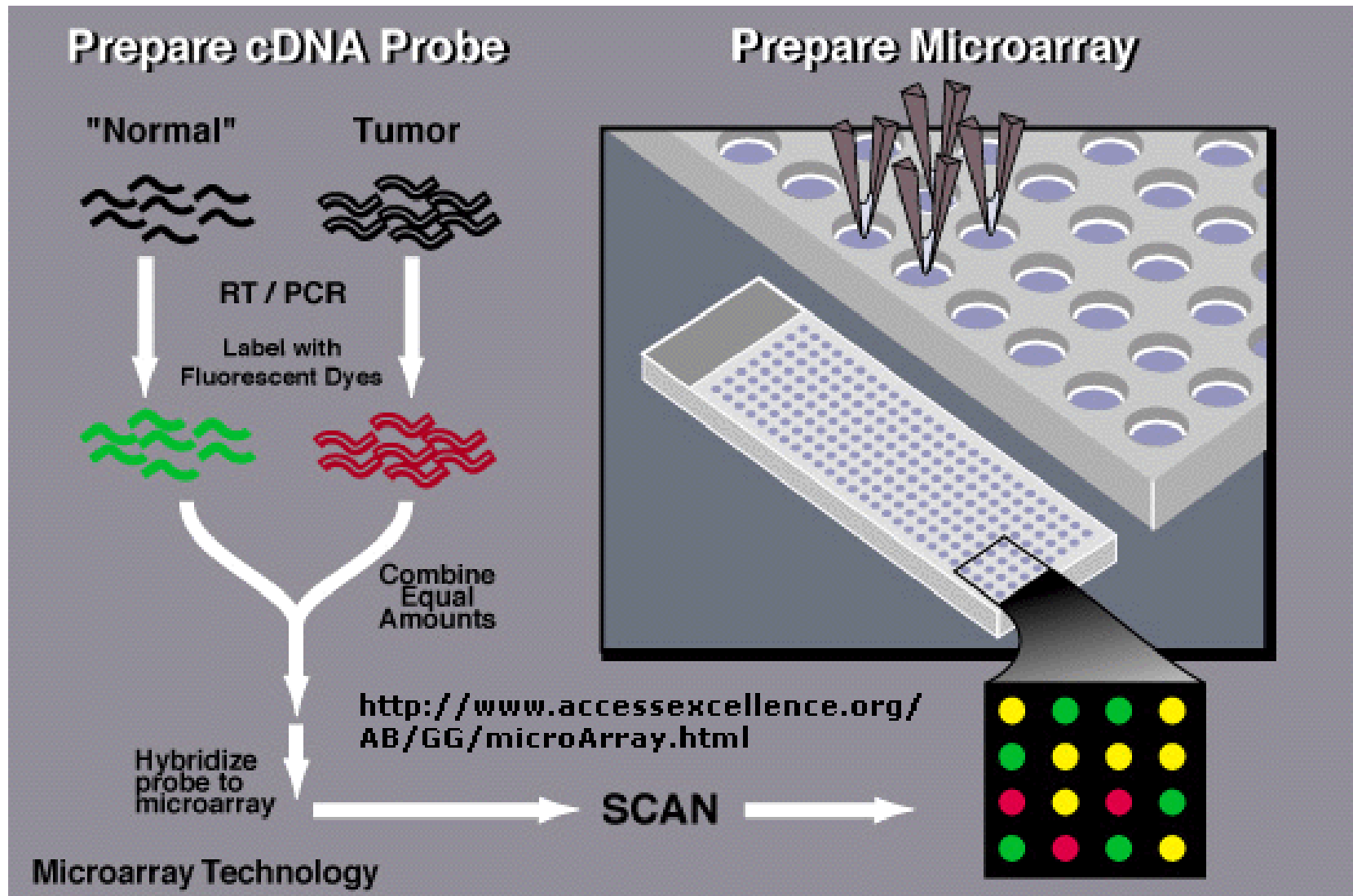


Origons in the *E. coli* regulatory network

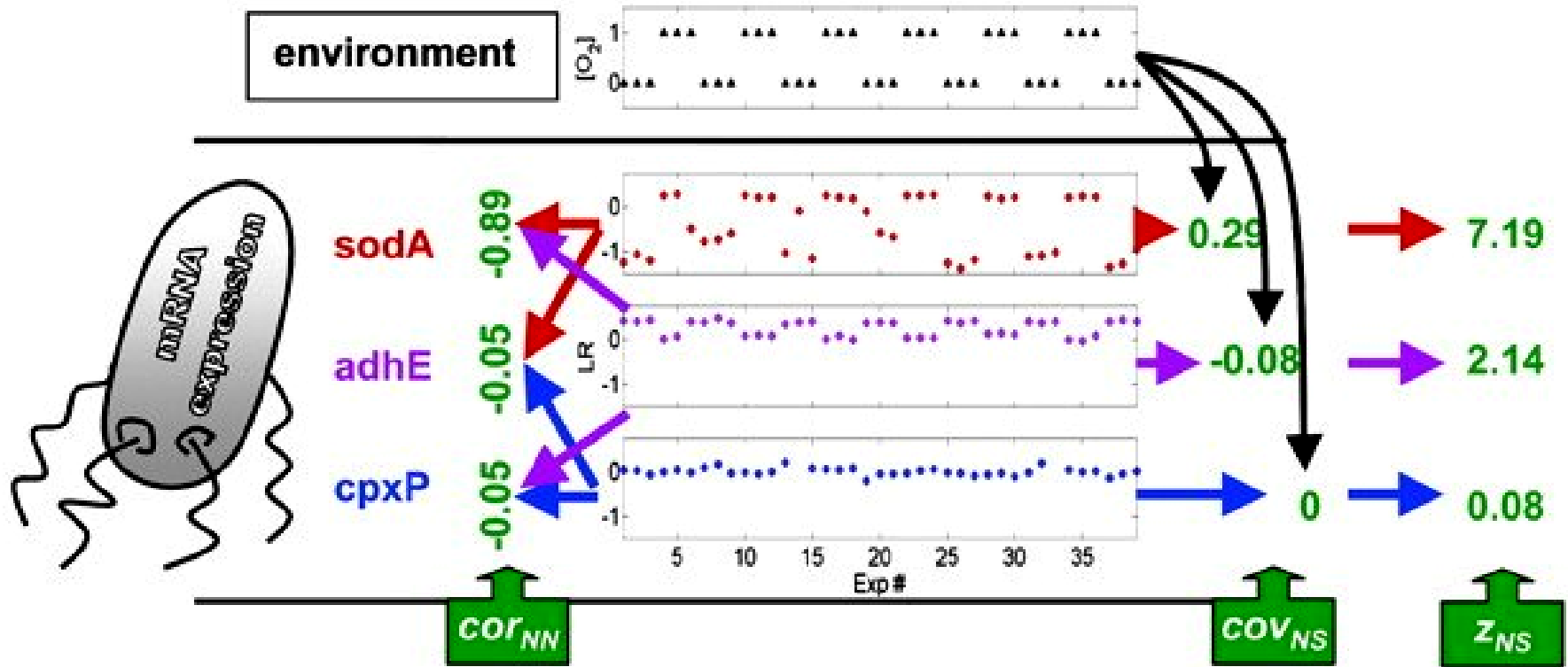
Why are origons important?

- Many nodes serve as **sensors**, monitoring environmental changes. The information captured by the sensor TFs percolate into their origons.
- If we suppose it is possible to perturb only one node in the *E. coli* TR network (i.e., by altering input gene expression or the activity of a transcription factor), primarily the nodes **within the origon** are expected to change their expression levels due to transcriptional regulation.
- If most of the network is unaffected, **only the origon of the perturbed input node** remains to be analyzed, **reducing network complexity**.
- Origons are more complex than **modulons**, but less complex than **stimulons**
- If **specific** origons respond to **specific** stimuli, then origons are the **topological units of dynamical network utilization**.

Microarray data



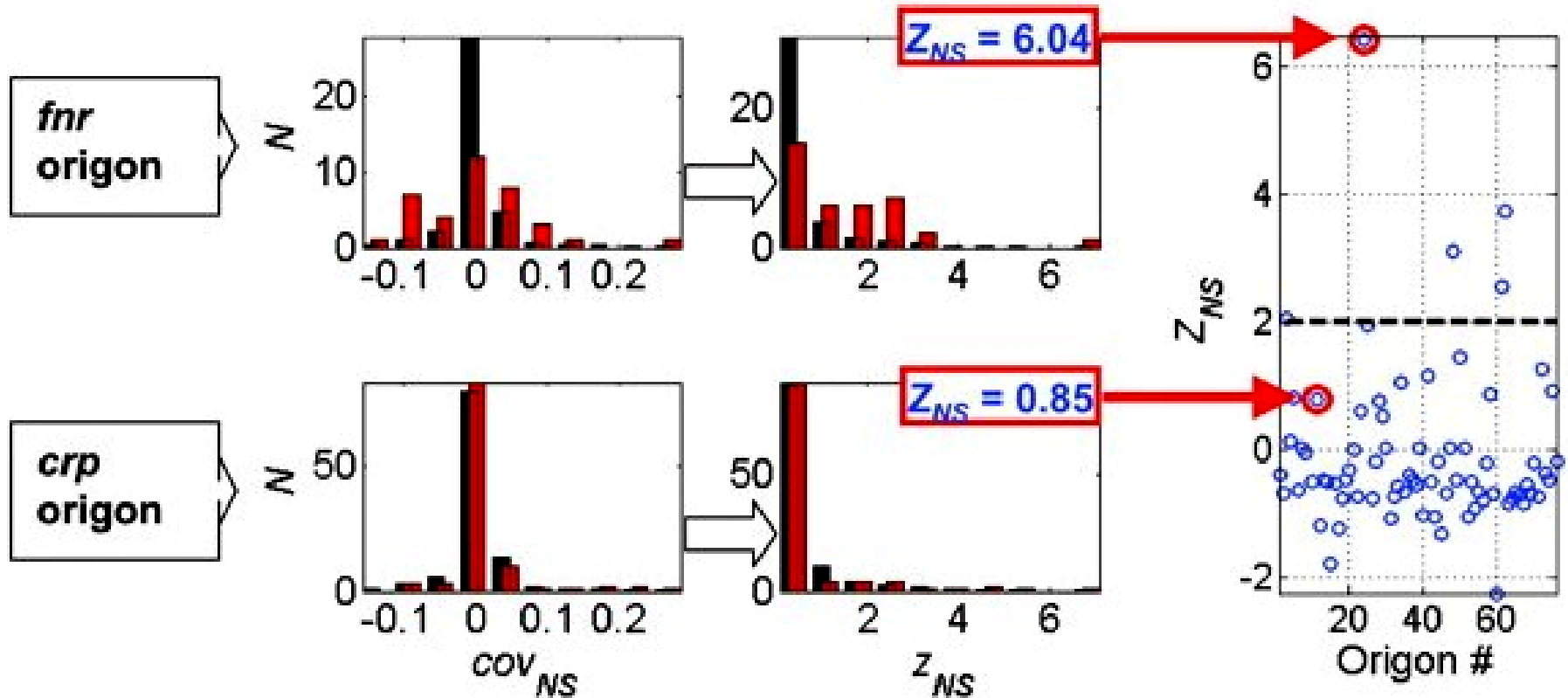
Response to extracellular oxygen



$$COR_{i,j} = \left\langle \frac{\sum_{c=1}^{N_c} LR_{r,c} LR_{r',c}}{\sigma_r \sigma_{r'}} \right\rangle_{r \in I, r' \in J}$$

$$COV_i = \left\langle \sum_{c=1}^{N_c} LR_{r,c} S_c \right\rangle_{r \in I}$$

Significantly affected origons



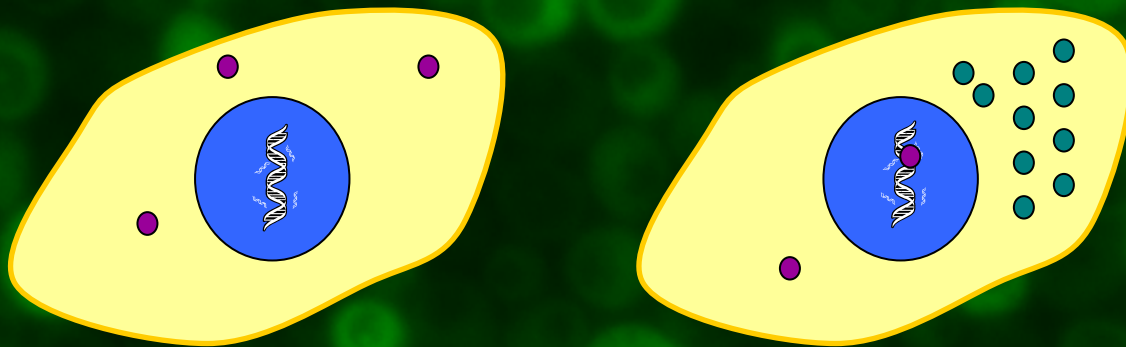
$$z_{NS}(n) = \frac{|\text{COV}_{NS}(n) - \mu_{NS}|}{\sigma_{NS}}$$

$$\mu_O = \langle z_{NS} \rangle_O$$

$$Z_{NS} = \frac{\mu_O - \mu_R}{\sigma_R}$$

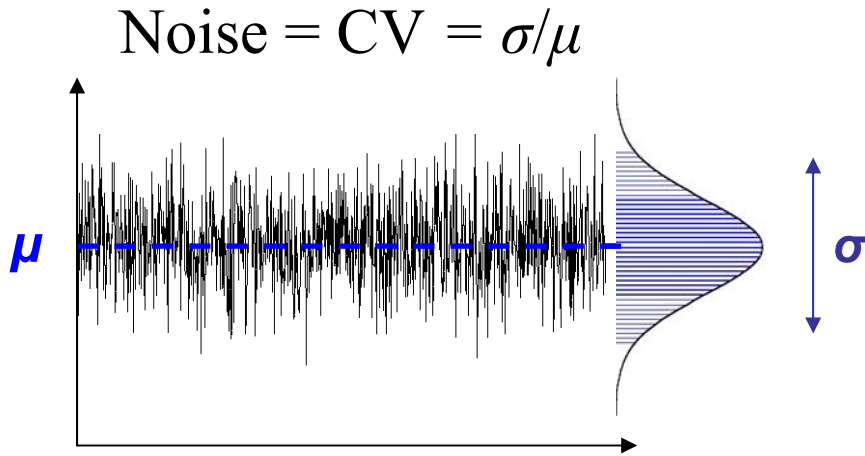
Significantly affected origons: **fnr, soxR, narL, rpoN, adiA-adiY**

Gene Expression Noise (Part II)



Genetically identical yeast cells
Expressing a fluorescent reporter
Photo by Kevin F. Murphy (Boston U)

Measuring noise



Noise = $\frac{\sigma}{\mu}$

Coeff. of variation = $\frac{\sigma}{\mu}$

CVR = $\frac{\sigma}{\mu}$

STD/mean

Elowitz et al., *Science* **297**, 1183 (2002)

Becskei et al., *Nat. Gen.* **37**, 937 (2005)

Colman-Lerner et al., *Nature* **437**, 699 (2005)

Noise strength = $\frac{\sigma^2}{\mu}$

Fano factor = $\frac{\sigma^2}{\mu}$

$f = \frac{\sigma^2}{\mu}$

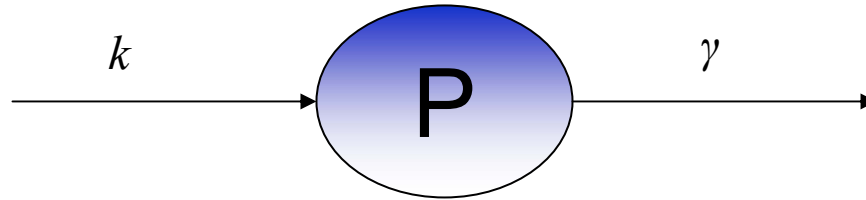
Var/mean

Ozbudak et al., *Nat. Gen.* **31**, 69 (2002)

Blake et al., *Nature* **422**, 633 (2003)

Raser & O'Shea, *Science* **304**, 1811 (2004)

A simple example: birth-death process



$$\gamma = \ln(2)/\tau$$

τ : half-life

$$\frac{dP_N}{dt} = kP_{N-1} + \gamma(N+1)P_{N+1} - (k + \gamma N)P_N; \quad N \neq 0, P_{-1} = 0$$

Master equation

$$\frac{d\langle N \rangle}{dt} = k - \gamma\langle N \rangle \Rightarrow \mu(t) = \frac{k}{\gamma}(1 - e^{-\gamma t})$$

Time evolution: **mean**

$$\frac{d\langle N^2 \rangle}{dt} = -2\gamma\langle N^2 \rangle + (\gamma + 2k)\langle N \rangle + k \Rightarrow \sigma^2(t) = \frac{k}{\gamma}(1 - e^{-\gamma t})$$

Time evolution: **variance**

$$CV = \frac{\sigma(t)}{\mu(t)} = \frac{1}{\sqrt{\frac{k}{\gamma}(1 - e^{-\gamma t})}}$$

CV = Coefficient of Variation

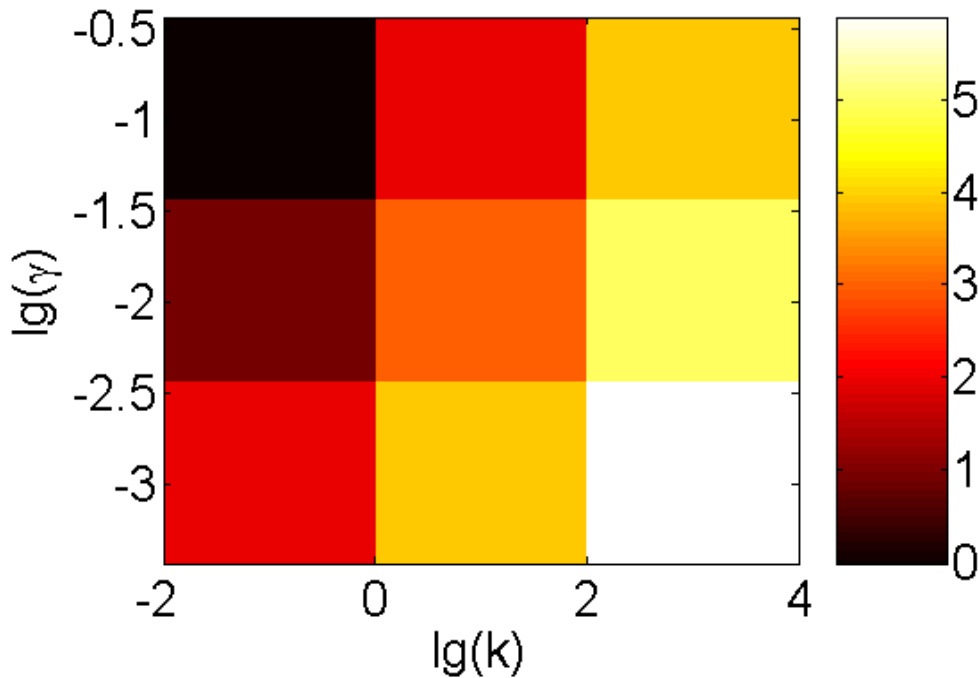
Time evolution: **noise**

Steady-state: birth-death process

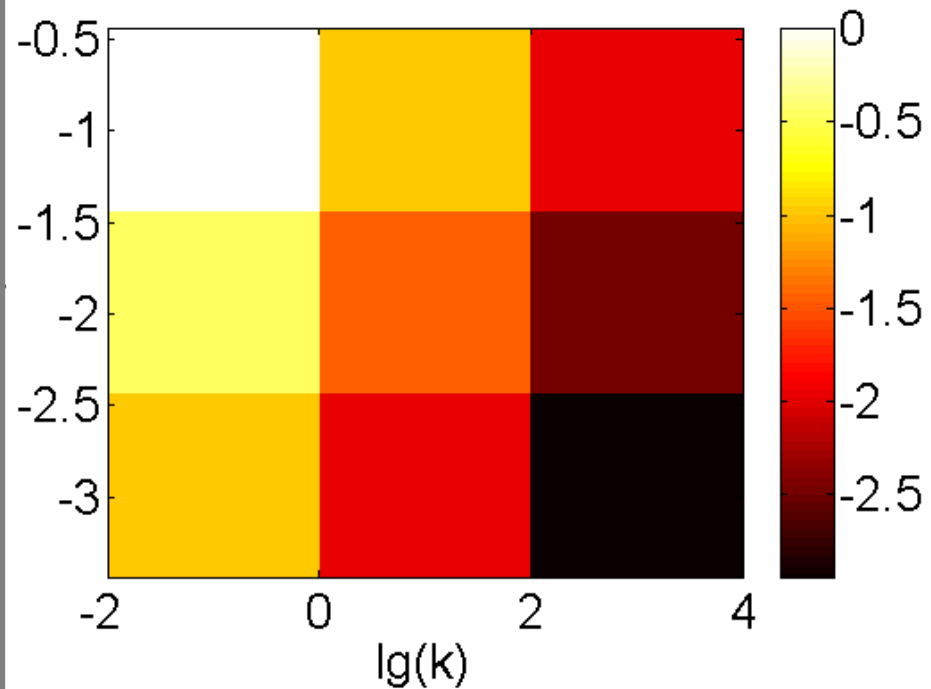
$$\mu_{SS} = \sigma_{SS}^2 = \frac{k}{\gamma}$$

$$CV_{SS} = \frac{\sigma_{SS}}{\mu_{SS}} = \sqrt{\frac{\gamma}{k}}$$

$\lg(\mu) = \lg(\sigma^2)$



$\lg(CV)$



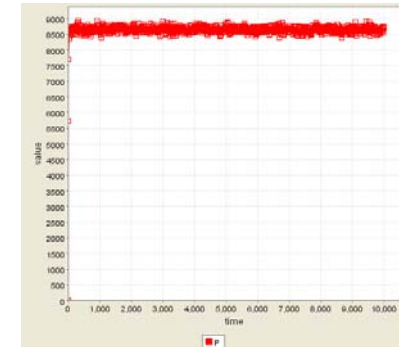
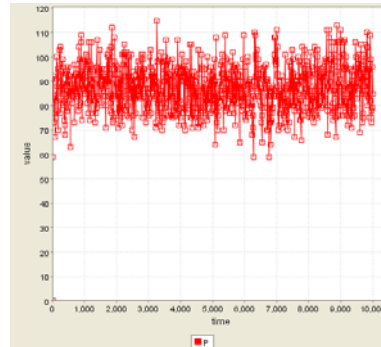
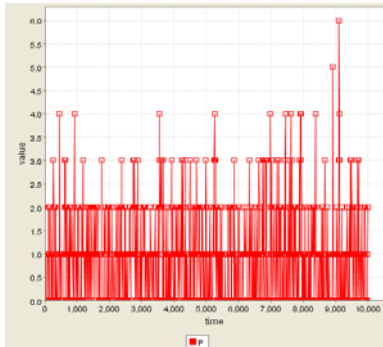
Stochastic simulation: birth-death process

$k=0.1$

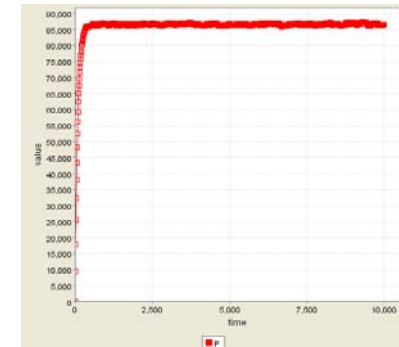
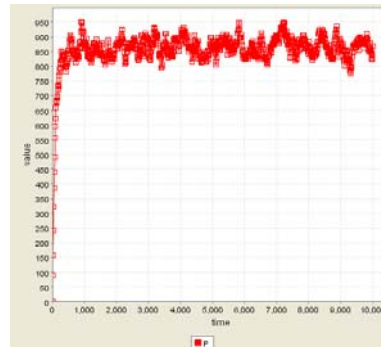
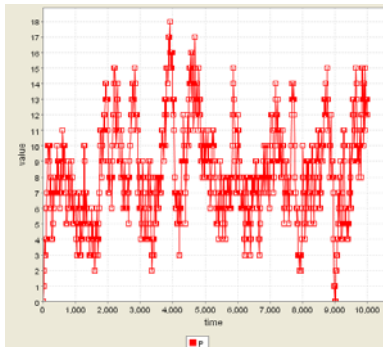
$k=10$

$k=1000$

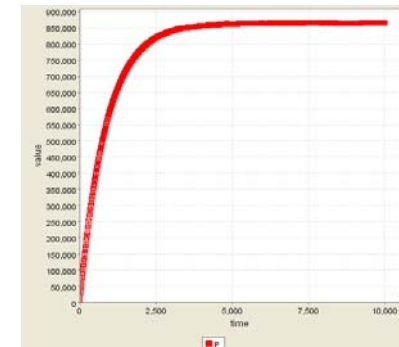
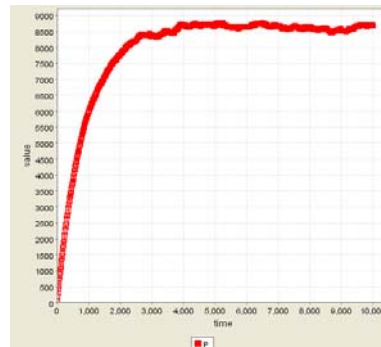
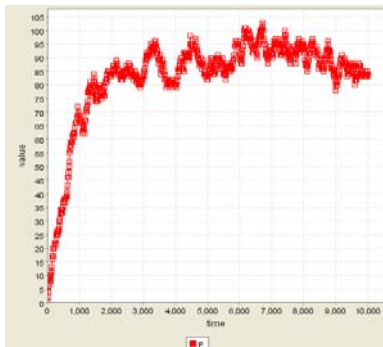
$\gamma = \ln(2)/6$



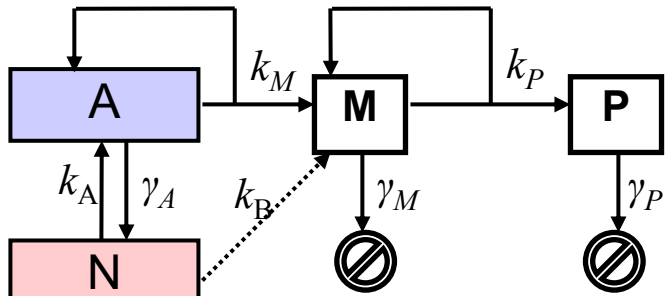
$\gamma = \ln(2)/60$



$\gamma = \ln(2)/600$



Gene expression models



Kærn et al. *Nat. Rev. Genet.*
6, 451-464 (2005)

Dynamics:

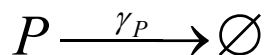
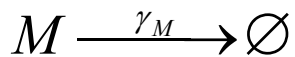
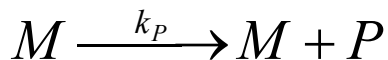
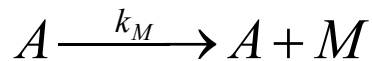
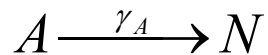
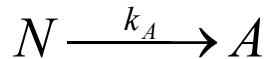
$$\dot{N} = -k_A N + \gamma_A A$$

$$\dot{A} = k_A N - \gamma_A A$$

$$\dot{M} = k_M A - \gamma_M M$$

$$\dot{P} = k_P M - \gamma_P P$$

Reactions:



Steady state:

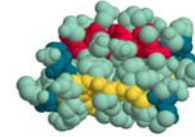
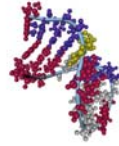
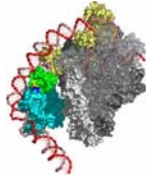
$$A_{SS} = \frac{k_A}{k_A + \gamma_A}$$

$$M_{SS} = \frac{k_M}{\gamma_M} \frac{k_A}{k_A + \gamma_A}$$

$$N_{SS} = \frac{\gamma_A}{k_A + \gamma_A}$$

$$P_{SS} = \frac{k_P}{\gamma_P} \frac{k_M}{\gamma_M} \frac{k_A}{k_A + \gamma_A}$$

Sources of noise



Process #1:
Promoter binding
(DNA)

Process #2:
Transcription
(mRNA)

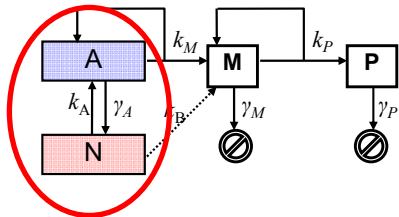
Process #3:
Translation
(Protein)

$$\frac{\sigma_1^2}{\langle n_1 \rangle^2} = \frac{\lambda_1^-}{\lambda_1^+} = \frac{\gamma_A}{k_A}$$

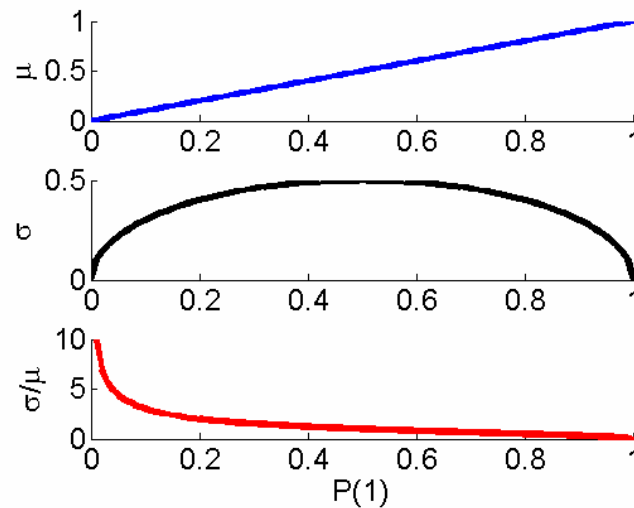
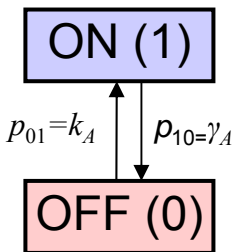
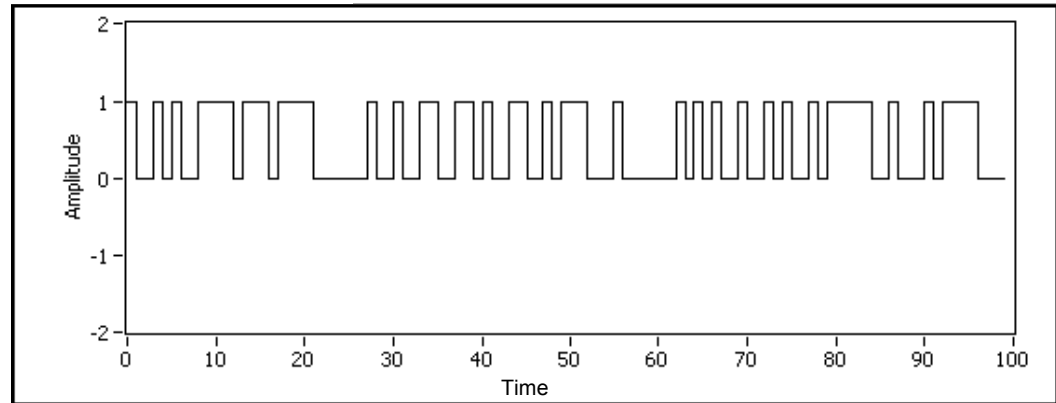
$$\frac{\sigma_2^2}{\langle n_2 \rangle^2} = \frac{1}{\langle n_2 \rangle} + \frac{\lambda_1^-}{\lambda_1^+} \frac{\tau_1}{\tau_2 + \tau_1}$$

$$\frac{\text{Total protein noise}}{\langle n_3 \rangle^2} = \underbrace{\frac{1}{\langle n_3 \rangle}}_{\text{Poisson}} + \underbrace{\frac{1}{\langle n_2 \rangle}}_{\text{Poisson}} \underbrace{\frac{\tau_2}{\tau_3 + \tau_2}}_{\text{One-step time-averaging}} + \underbrace{\frac{1 - P_{\text{on}}}{\langle n_1 \rangle}}_{\text{Binomial}} \underbrace{\frac{\tau_2}{\tau_2 + \tau_3} \frac{\tau_1}{\tau_1 + \tau_3} \frac{\tau_1 + \tau_3 + \tau_1 \tau_3 / \tau_2}{\tau_1 + \tau_2}}_{\text{Two-step time-averaging}}$$

Noise at the promoter: Random Telegraph Process



$$A + N = \text{const} = 1$$

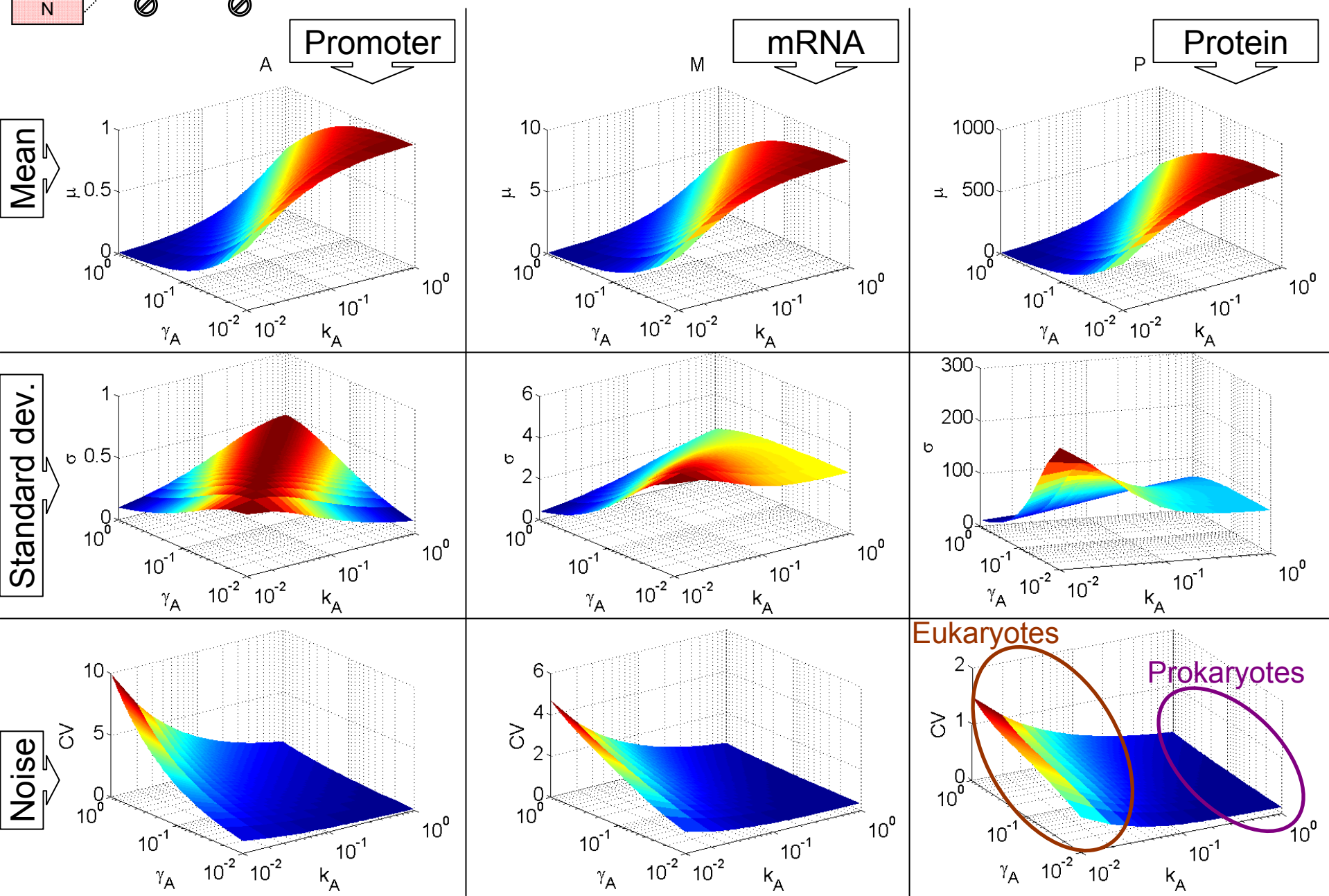
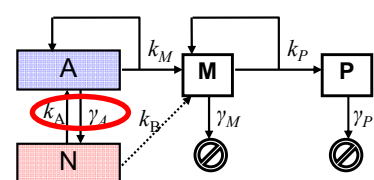


$$\mu = \frac{p_{01}}{p_{01} + p_{10}}$$

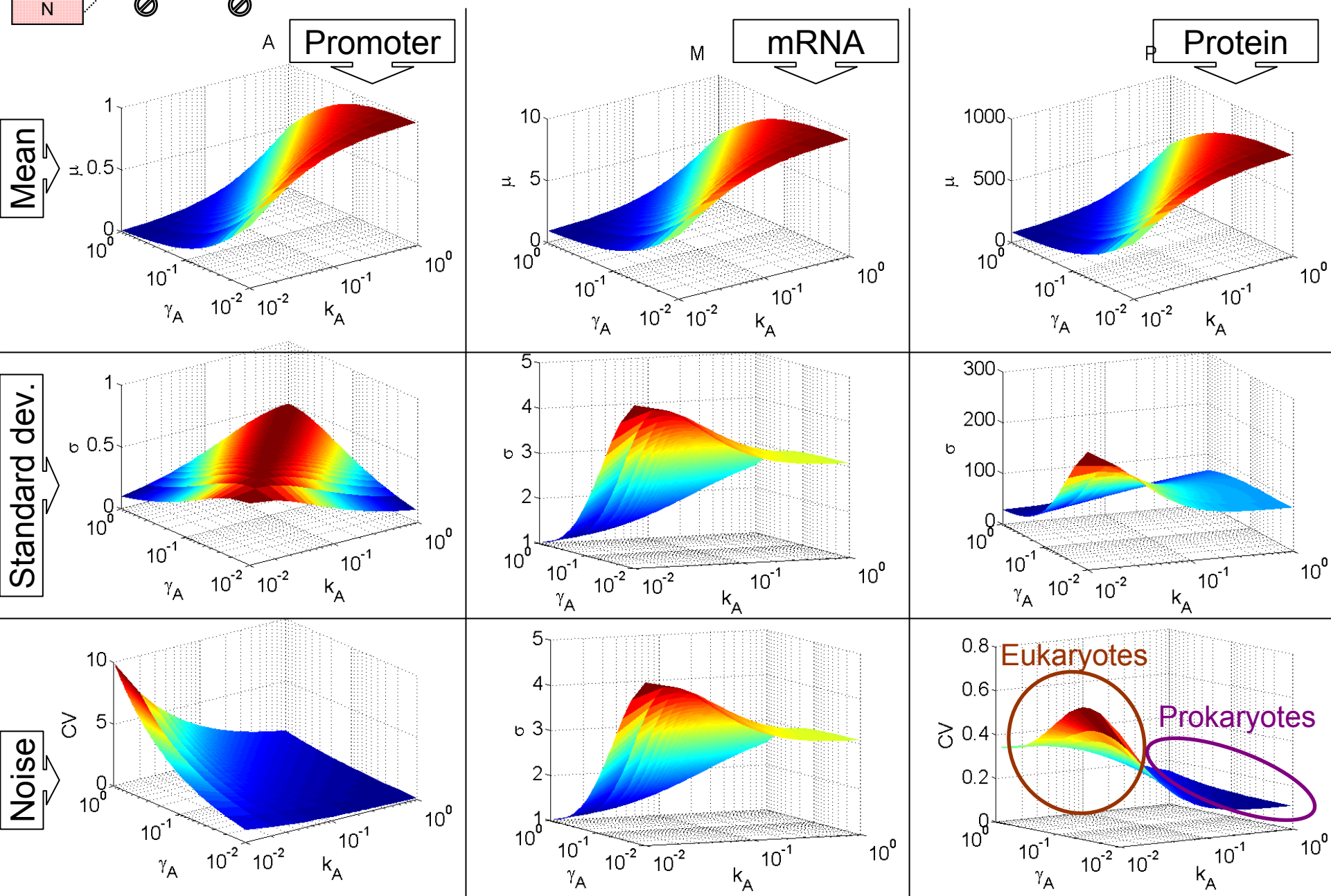
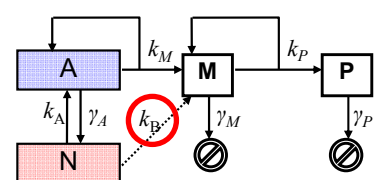
$$\sigma = \frac{\sqrt{p_{01}p_{10}}}{p_{01} + p_{10}}$$

$$\frac{\sigma}{\mu} = \sqrt{\frac{p_{10}}{p_{01}}}$$

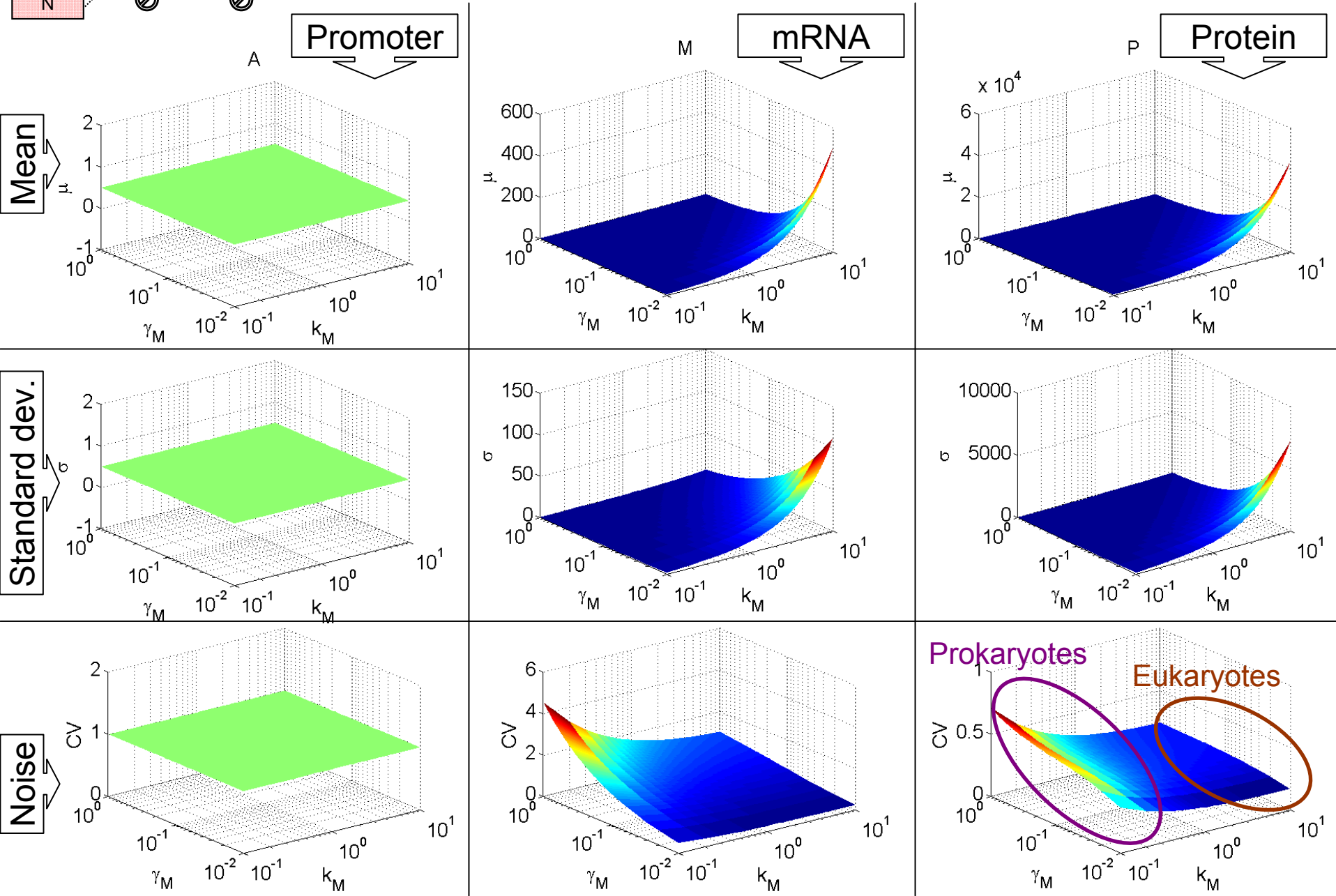
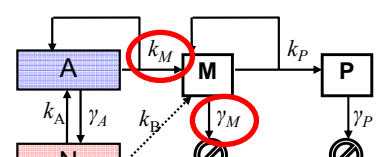
Promoter dynamics affects noise



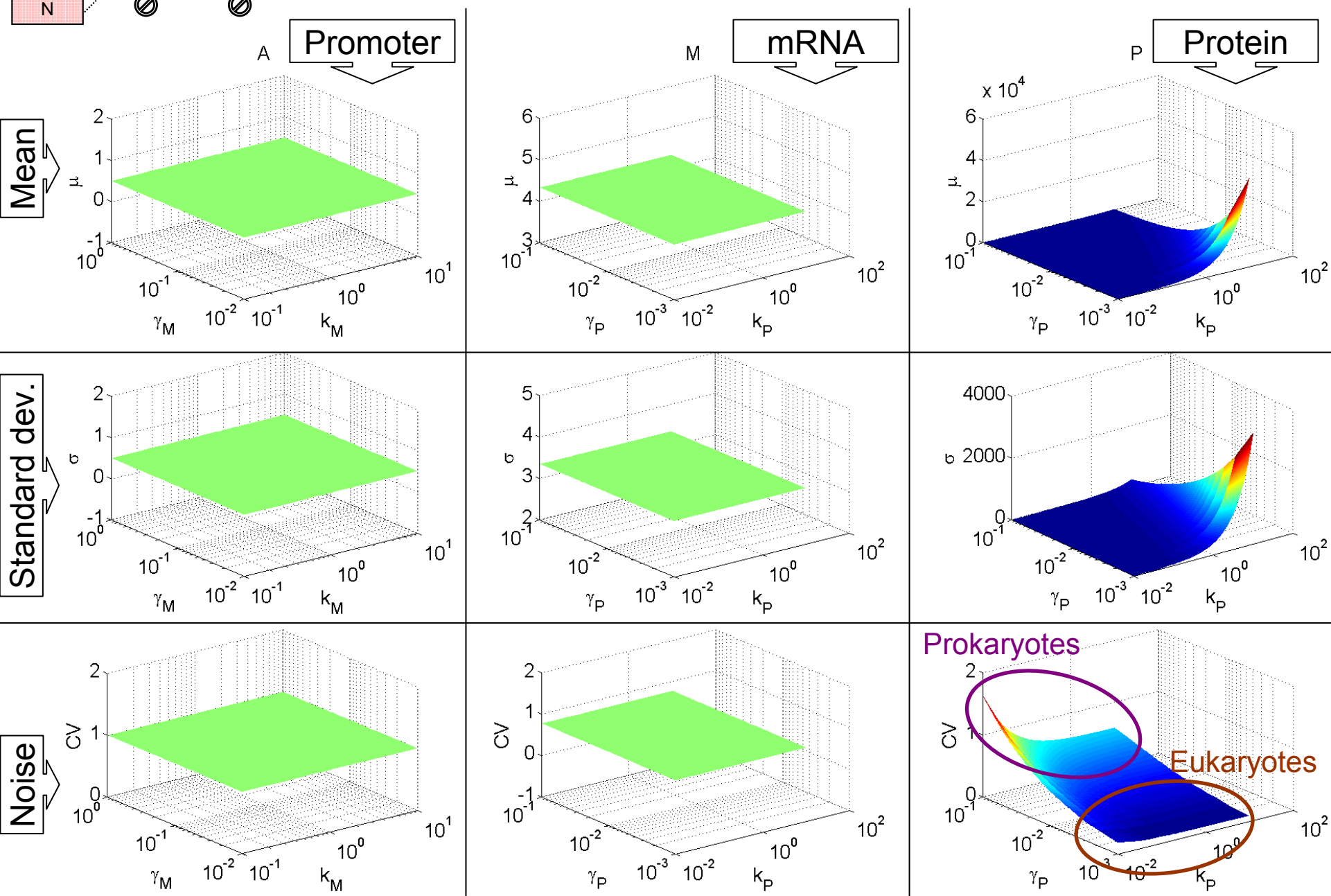
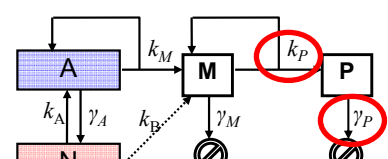
Basal expression affects noise



mRNA birth/death affects noise

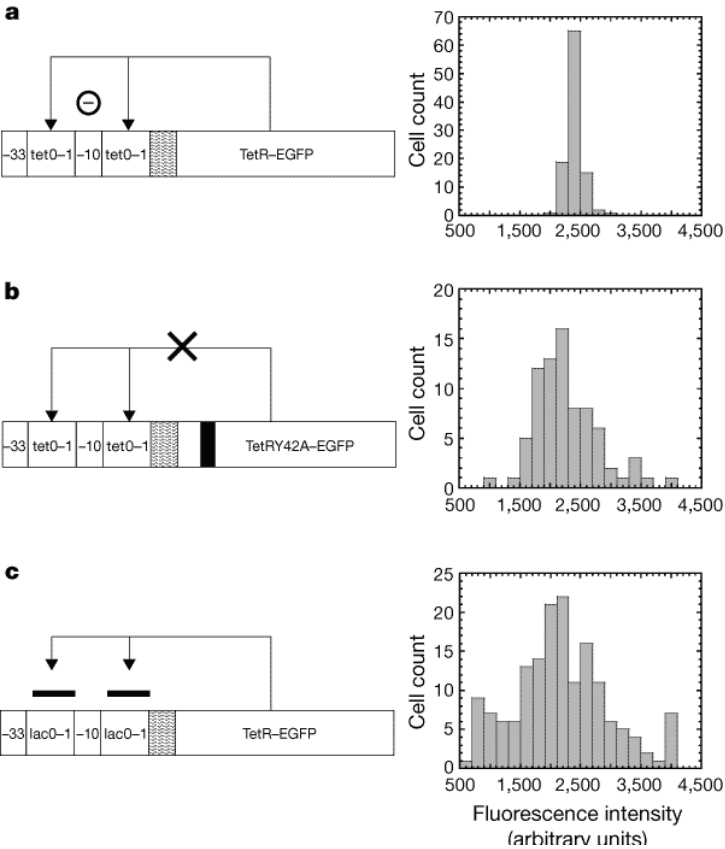
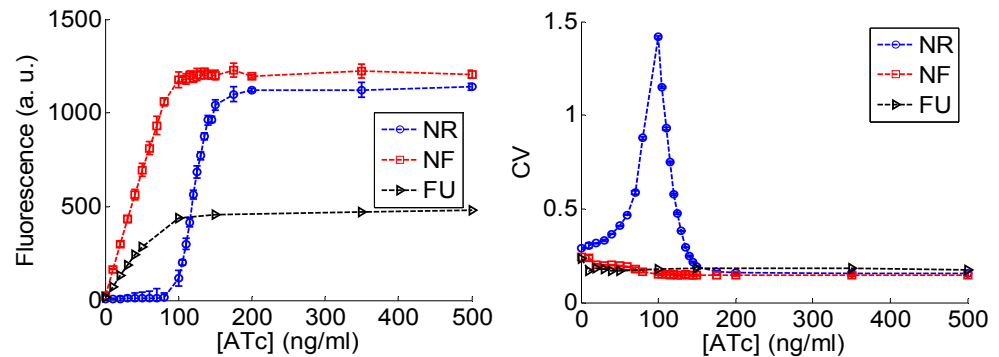
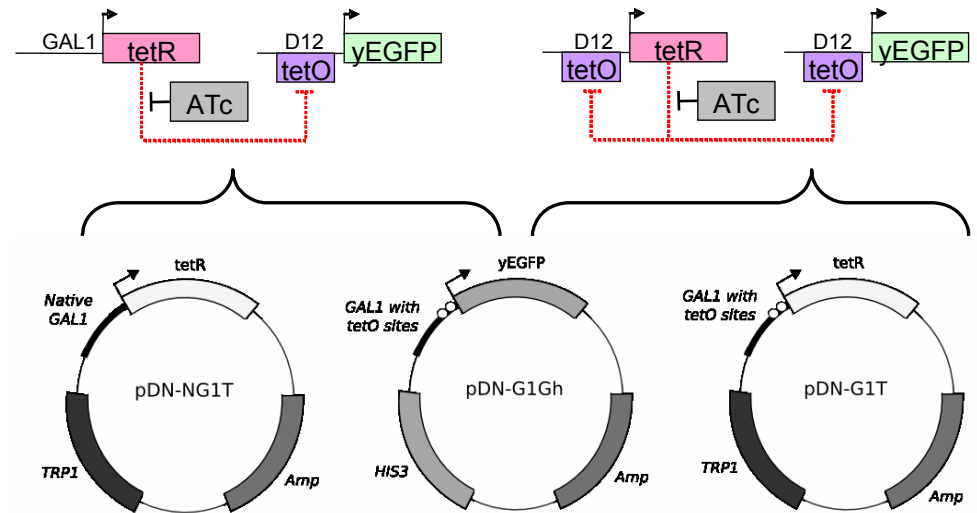


Protein birth/death affects noise



Noise and negative feedback

Negative Regulation (NR) Negative Feedback (NF)

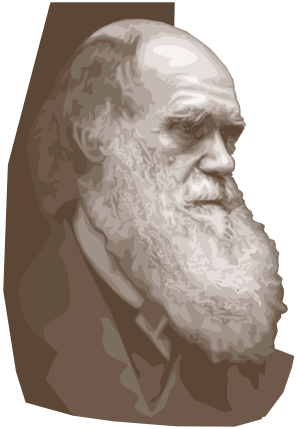


Becskei et al., *Nature* **405**, 590 (2000).

Survival and evolution in a changing environment (Part III)

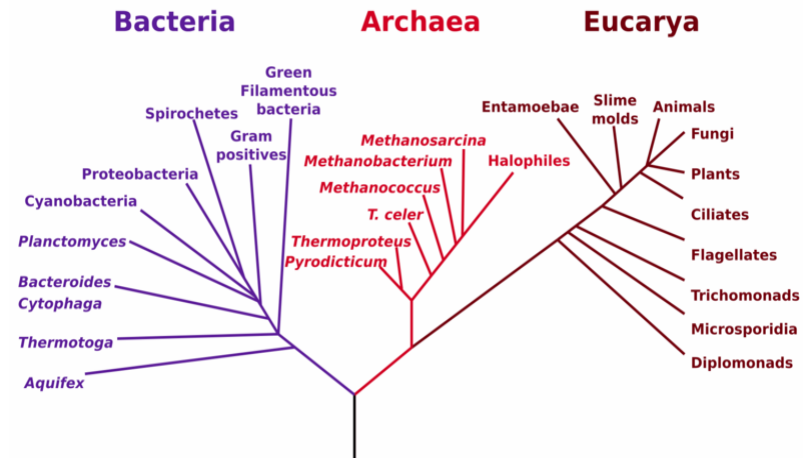


Evolutionary theory



- Evolution is the process through which the heritable traits of a biological population change from one generation to the next.

Phylogenetic Tree of Life



- Charles Darwin: The Origin of Species (1859)
- Gregor Mendel: Experiments on Plant Hybridization (1866)
- Population Genetics (1900-1930)
- Modern Synthesis: Fisher, Haldane, Wright, Huxley, Mayr (1930-1950)
- Neutral Theory: M. Kimura (1960-1980)

Requirements for evolution under selection

1. Variation:

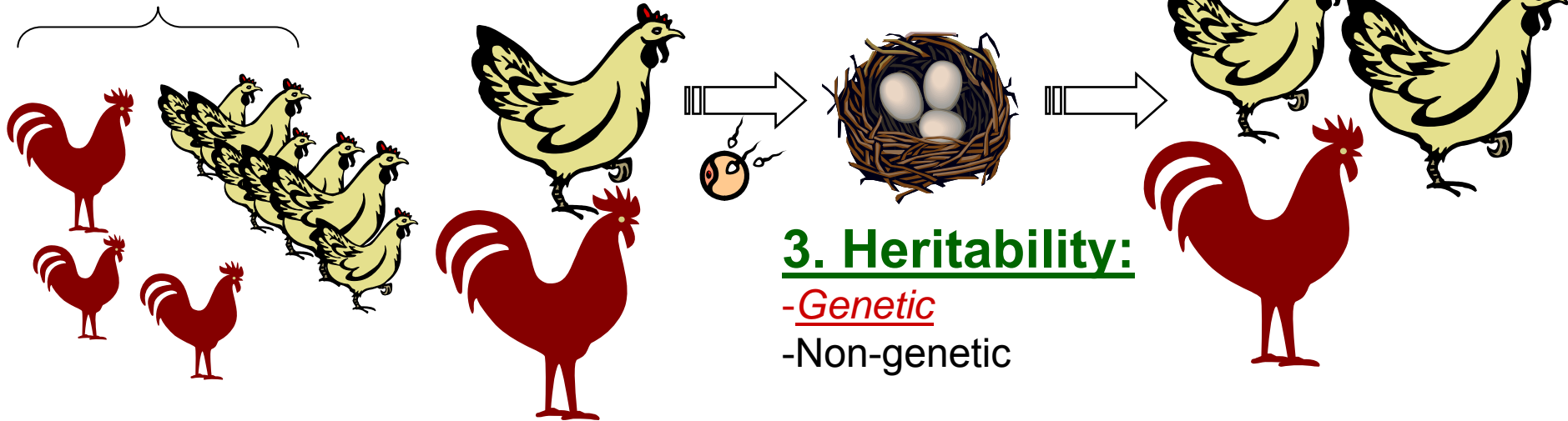
-Genetic

-Non-genetic

2. Selection:

-Fitness + Competition

-Survival



This is the **textbook-understanding**, focusing on **multicellular species**.

• **Phenotype:**

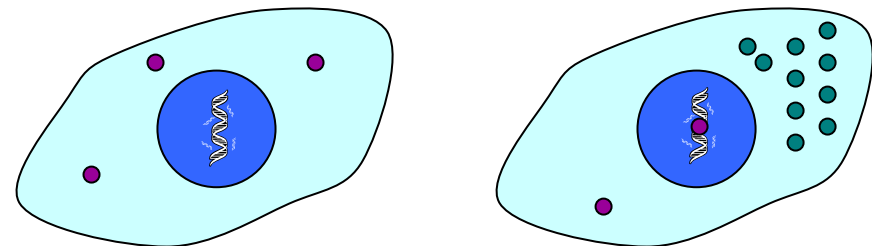
- Observed quality (size, color, shape, ...)
- Subject to selection

• **Genotype:**

- DNA sequence
- Not directly selected
- Makes phenotypes heritable

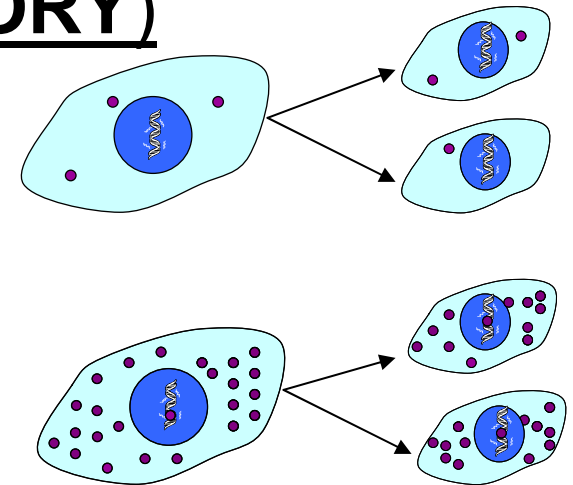
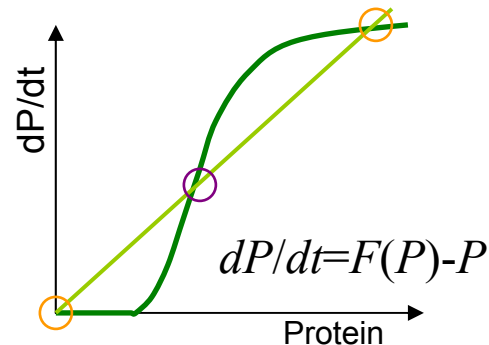
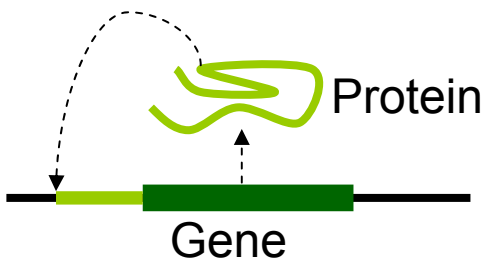
Sources of cell-cell variation

- Variation is required for evolution
- The source of phenotypic variation can be:
 - Genetic
 - Gene mutations (amplifications, deletions, insertions,...)
 - Epigenetic
 - DNA methylation
 - Chromatin modification
 - Non-genetic (**NOISE**)
 - Low intracellular concentrations



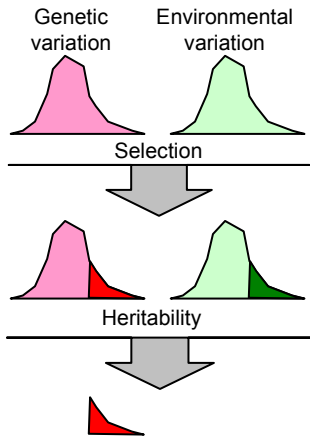
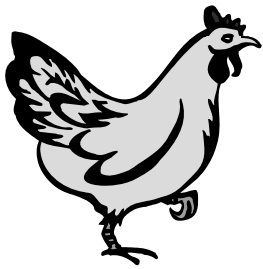
Heritability of cellular phenotypes

- Heritability is required for evolution
- The source of heritability can be:
 - Genetic
 - Gene mutations (amplifications, deletions, insertions,...)
 - Epigenetic
 - DNA methylation
 - Chromatin modification
 - Non-genetic (CELLULAR MEMORY)
 - Positive feedback

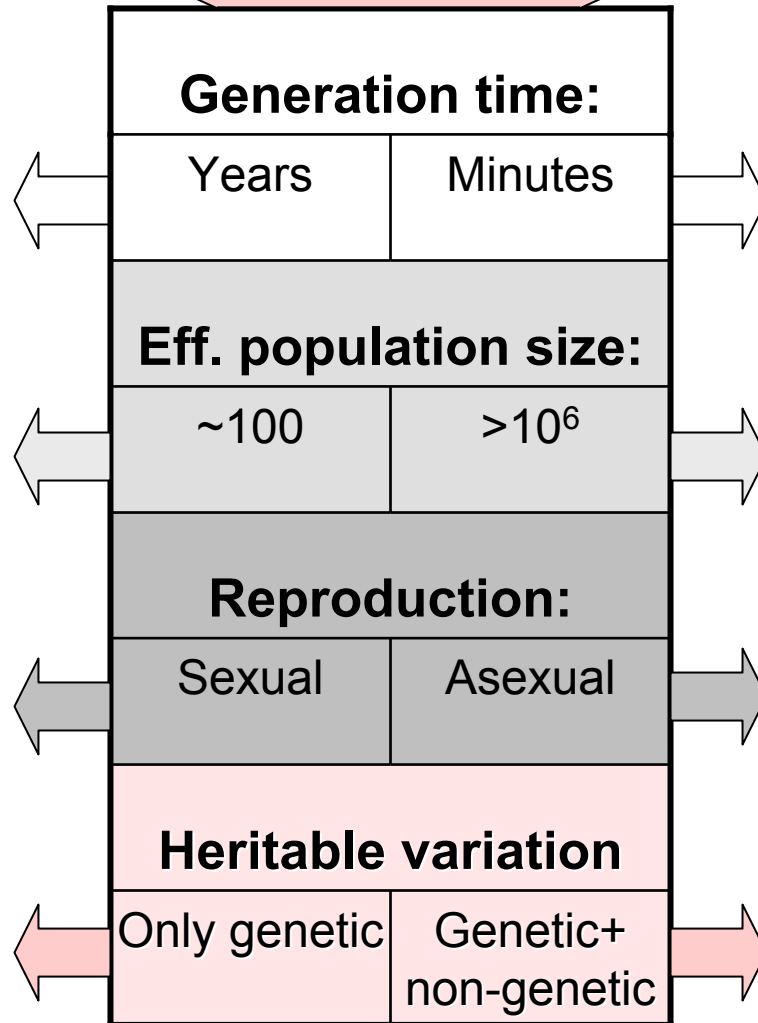


Evolution at the single-cell level

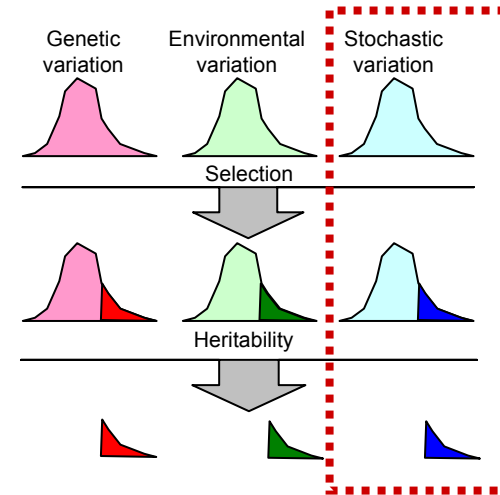
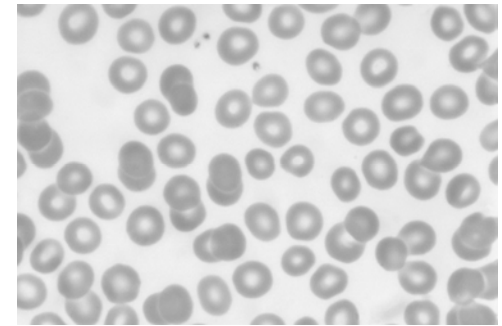
Multicellular organisms



Differences

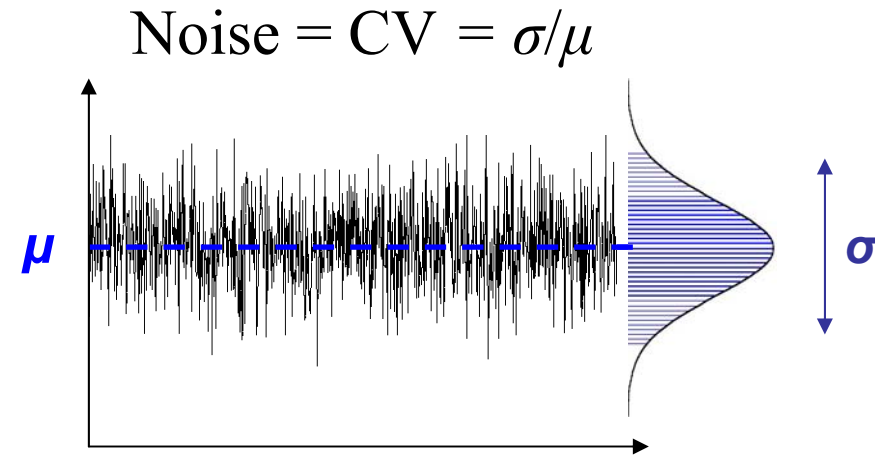
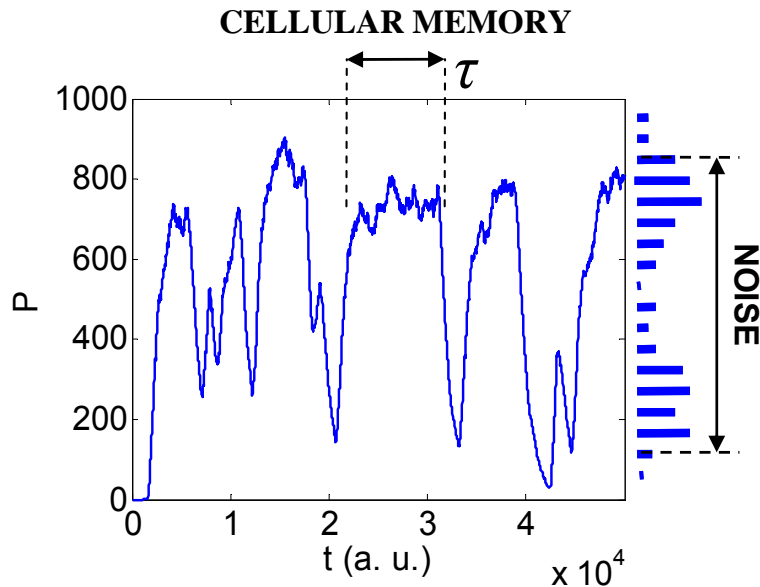


Single cells



-Genome-scale data available (yeast & *E. coli*)
 -Easy to manipulate genetically

CELLULAR MEMORY and NOISE



Noise:

- Quantifies non-genetic deviations from the population mean
- Measured by the Coefficient of Variation (CV, standard deviation / mean)

Cellular memory:

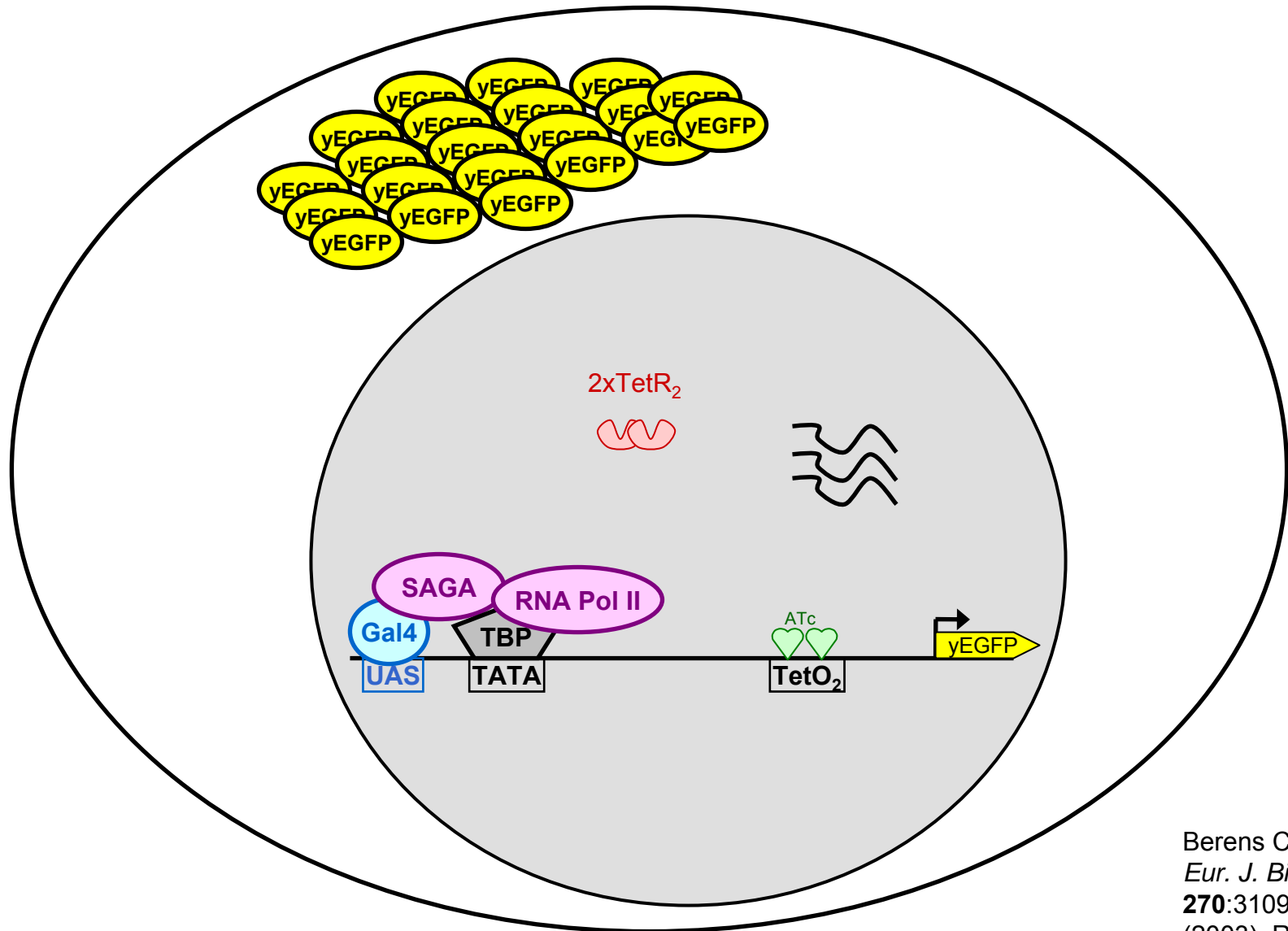
- The capacity of cell lineages to maintain deviant states non-genetically over time.
- It is the inverse of the rate of switching between phenotypic states ($1/\tau$)

How do they affect survival and evolution at the single cell level?

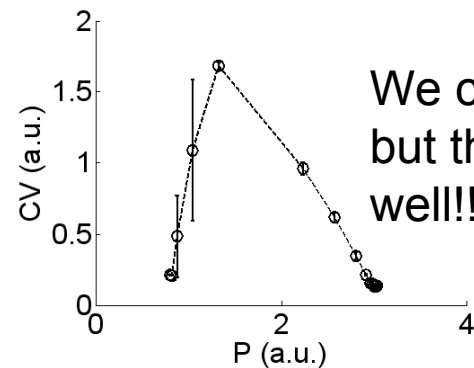
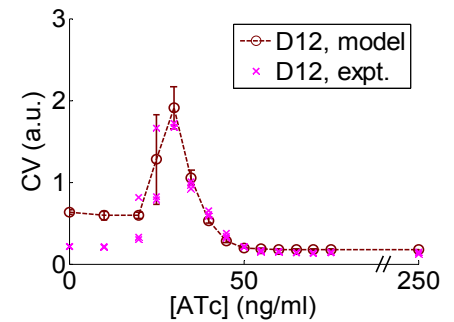
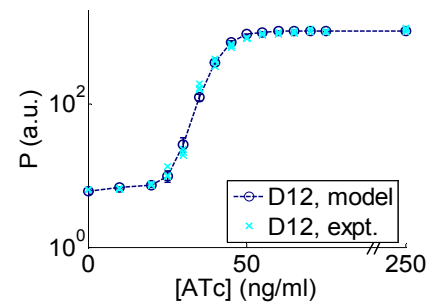
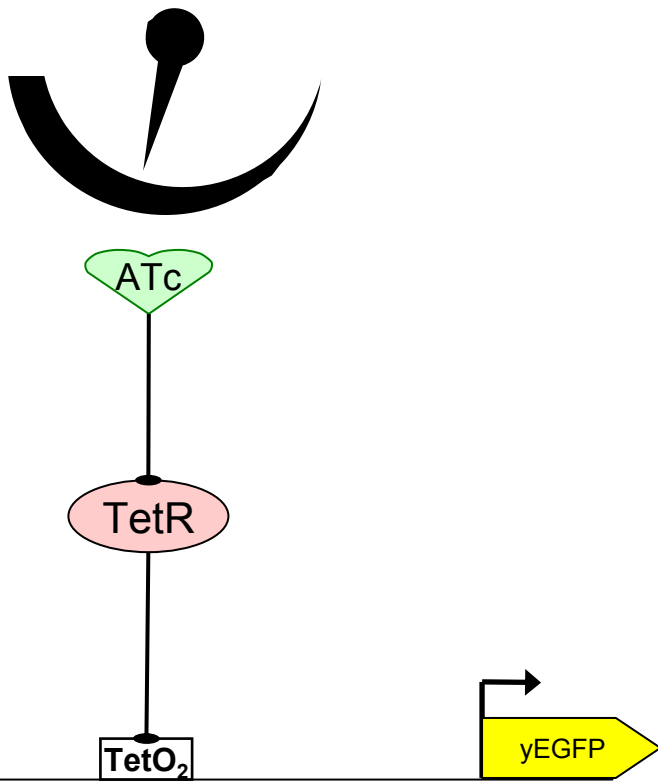
Noise and phenotype

- To study the phenotypic effect of noise, we need to control it experimentally
- Controlling noise also affects other cellular properties (e.g., gene expression mean)
- Therefore, we need to uncouple the control of noise from the control of mean

The TetR-repressible GAL1 promoter

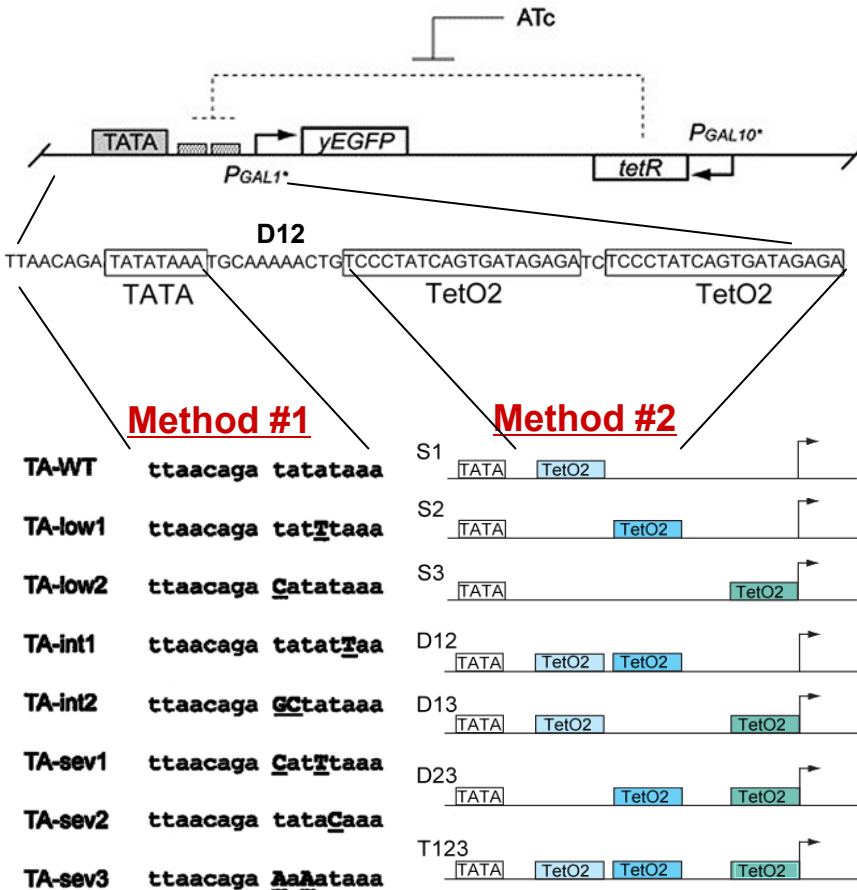


Changing noise affects the mean



We can change the noise...
but the mean changes as
well!!!

Uncoupling the noise and the mean

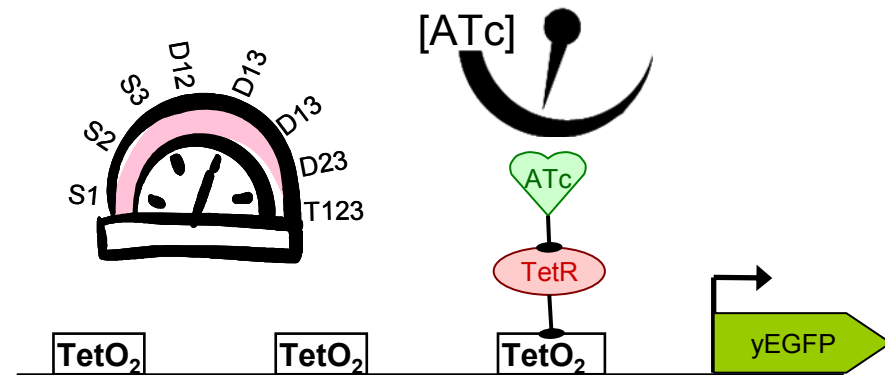


-The goal of these methods is to establish different dependence of the noise on the mean

-Method #1 consists of mutating the TATA box, decreasing the rate of promoter inactivation

-Method #2 consists of changing the number of repressor binding sites

-Mathematical models accompany both methods



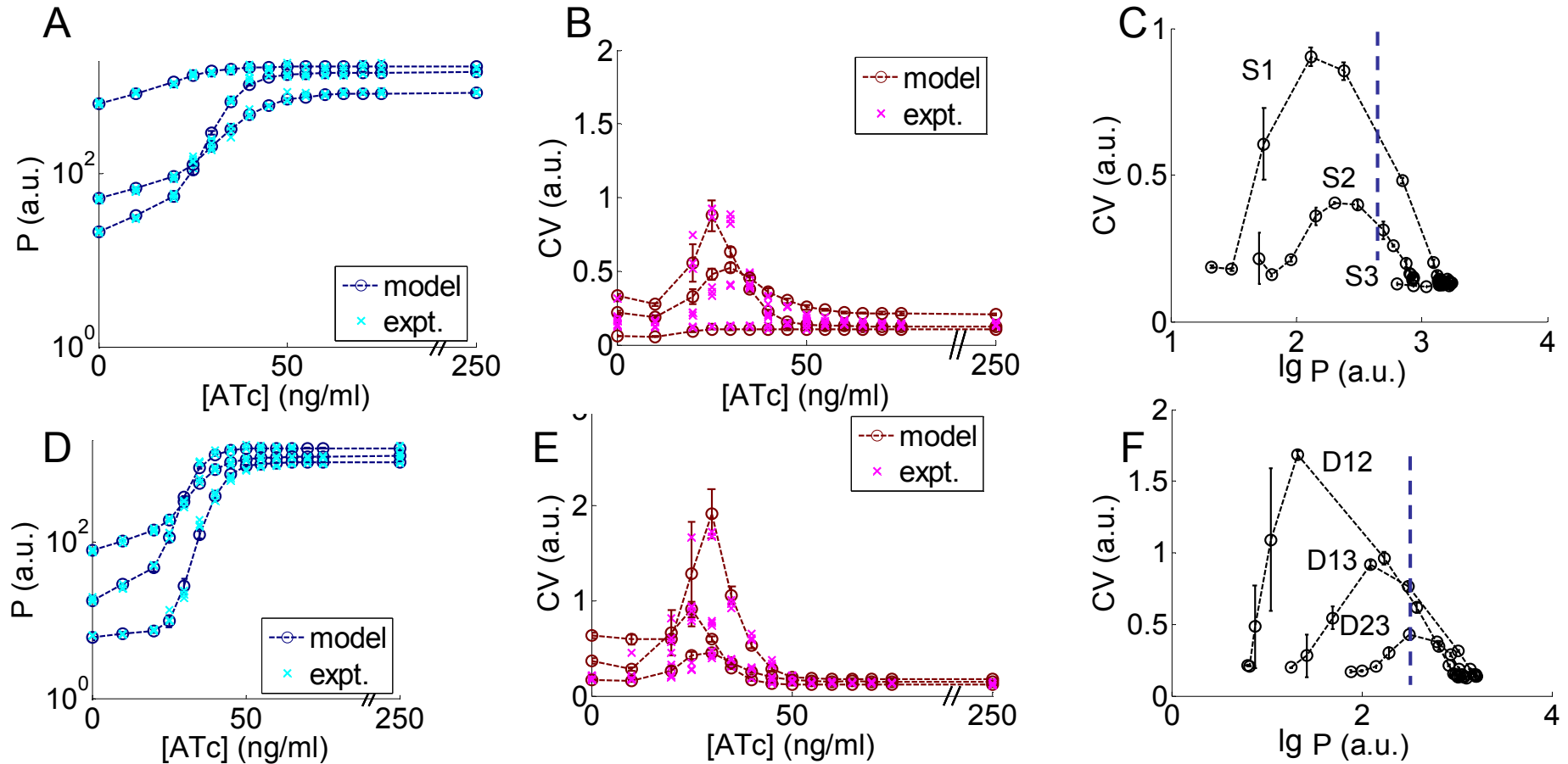
See also:

-Smith, Sumner & Avery, *Mol. Microb.* 2007

-Maamar, Raj & Dubnau, *Science* 2007

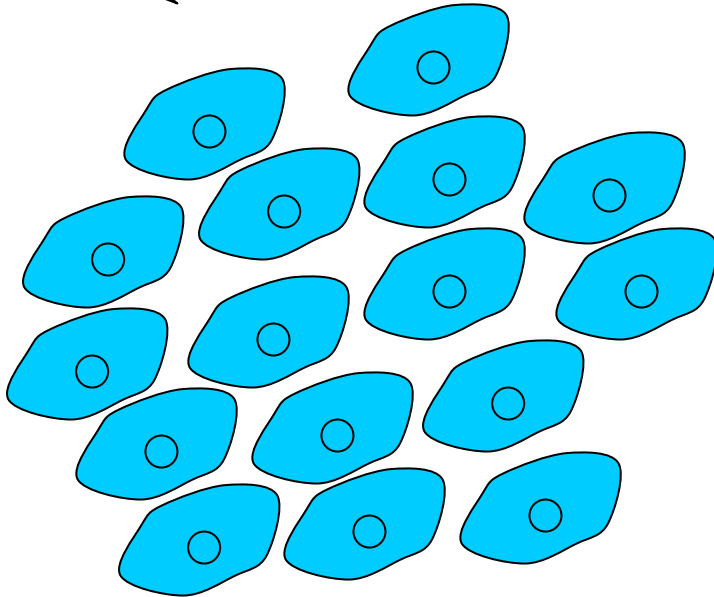
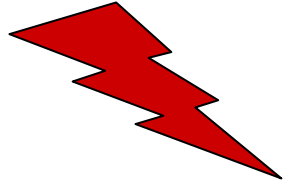
-Süel et al., *Science* 2007

Independent control of the noise and the mean

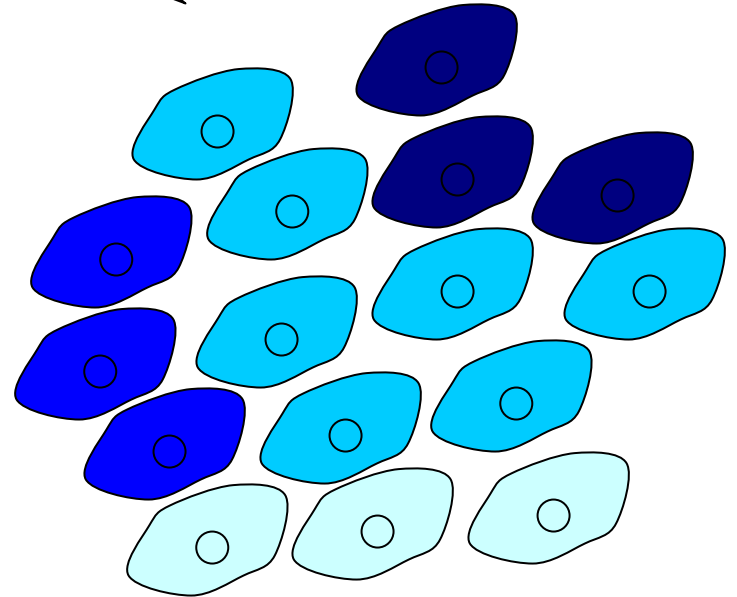
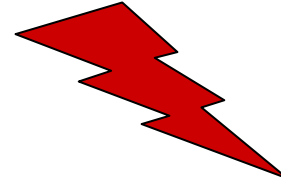


Noise and drug resistance

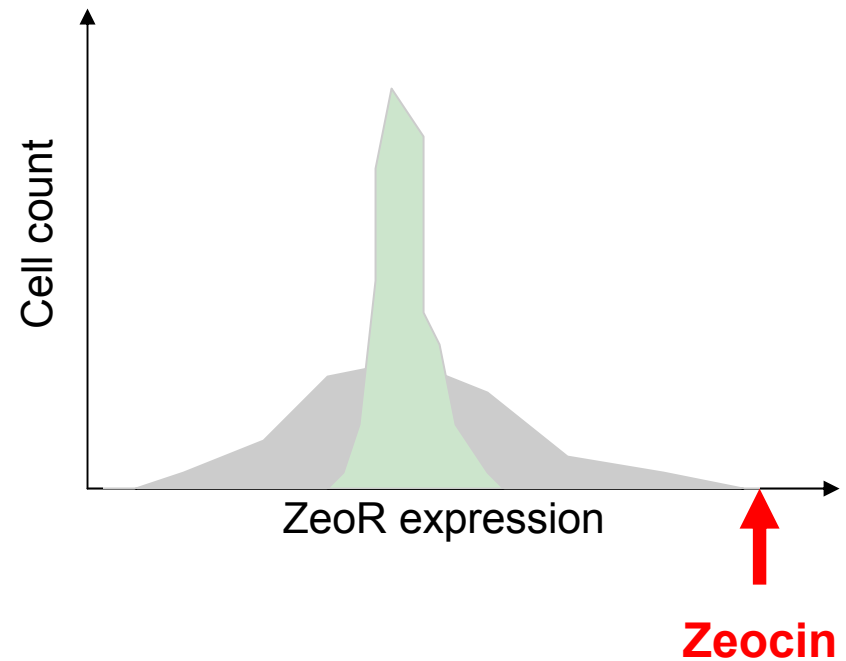
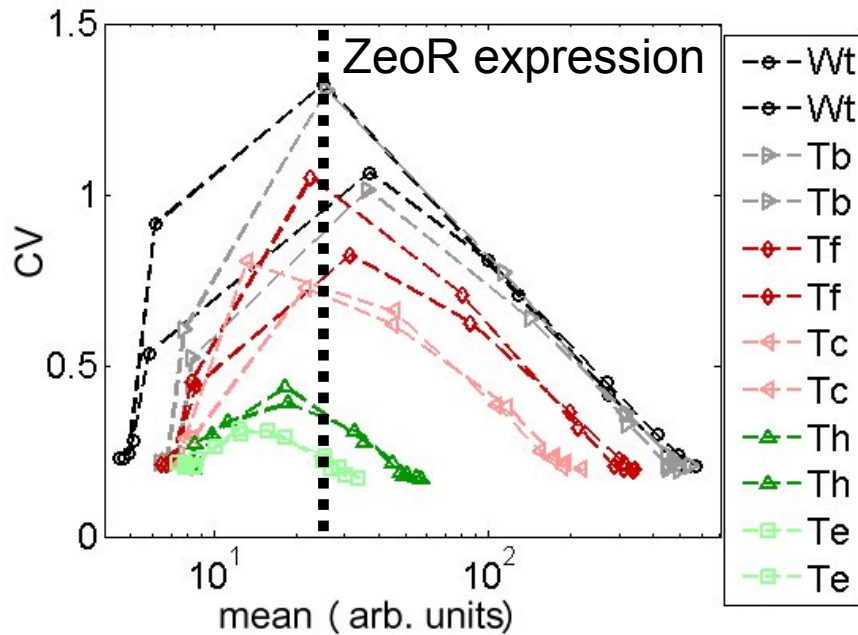
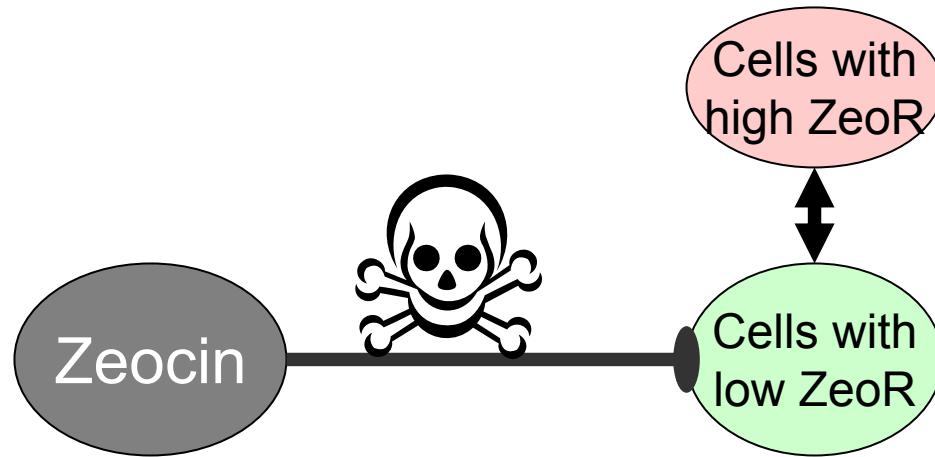
Drug



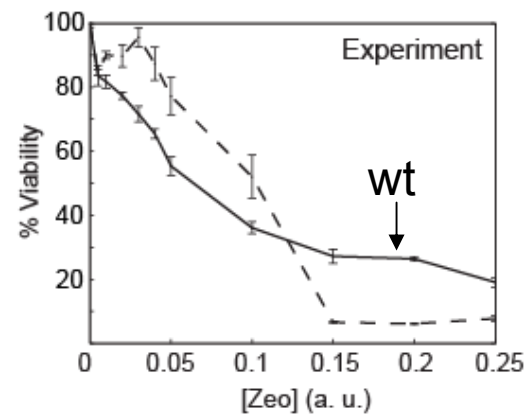
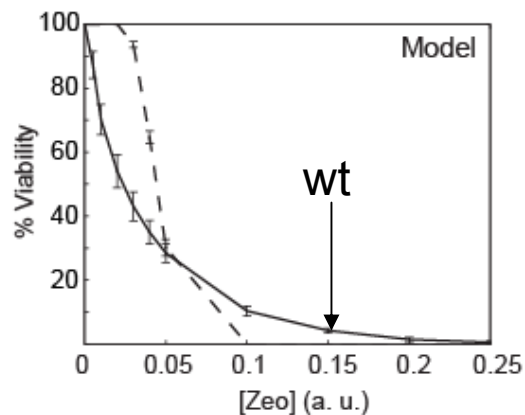
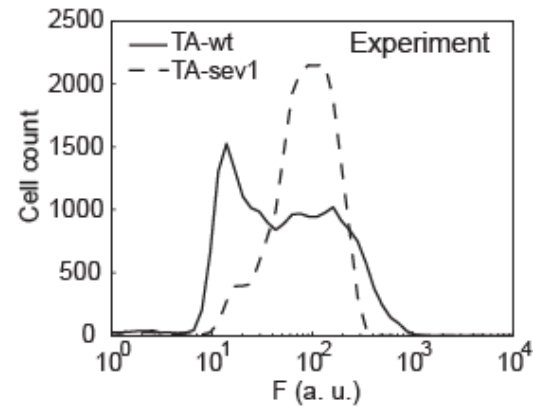
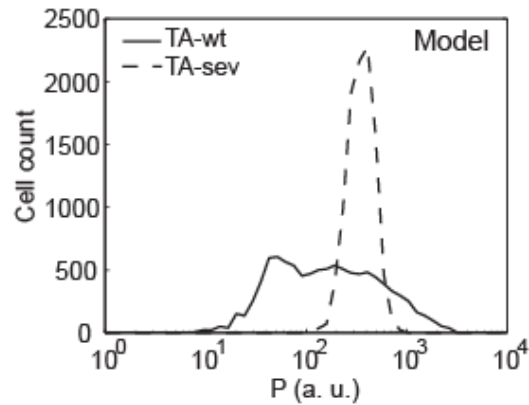
Drug



Controlling drug resistance noise



Noise aids survival during drug treatment



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Vinícius
Bonato

Allison
Heath



Thank you!

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- **Albert-László Barabási**

