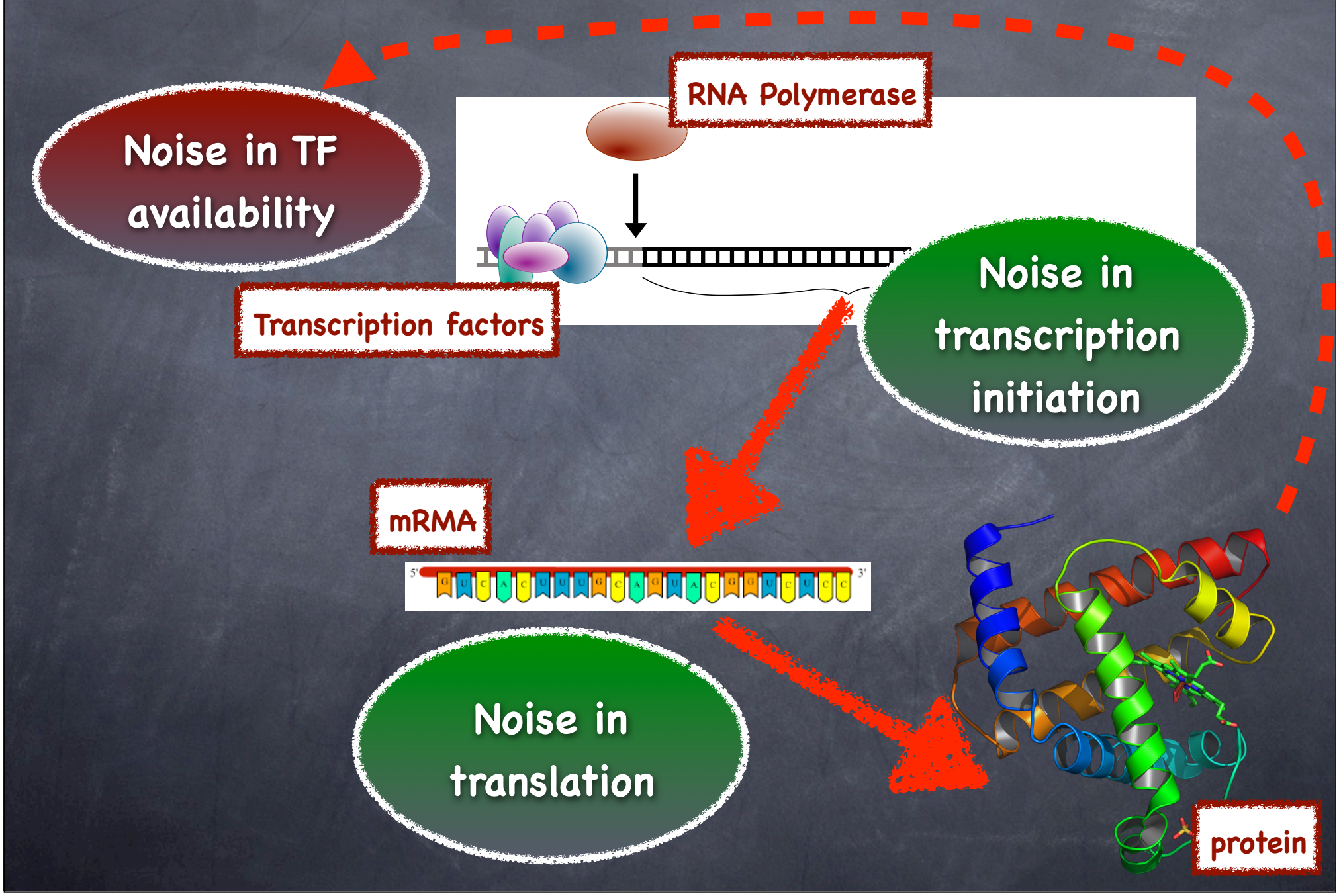
The complexity of cellular networks

Warning: Statistical physics.
It only works on average.

http://regan.med.harvard.edu/CVBR-course.php

3. Noise in genetic regulation



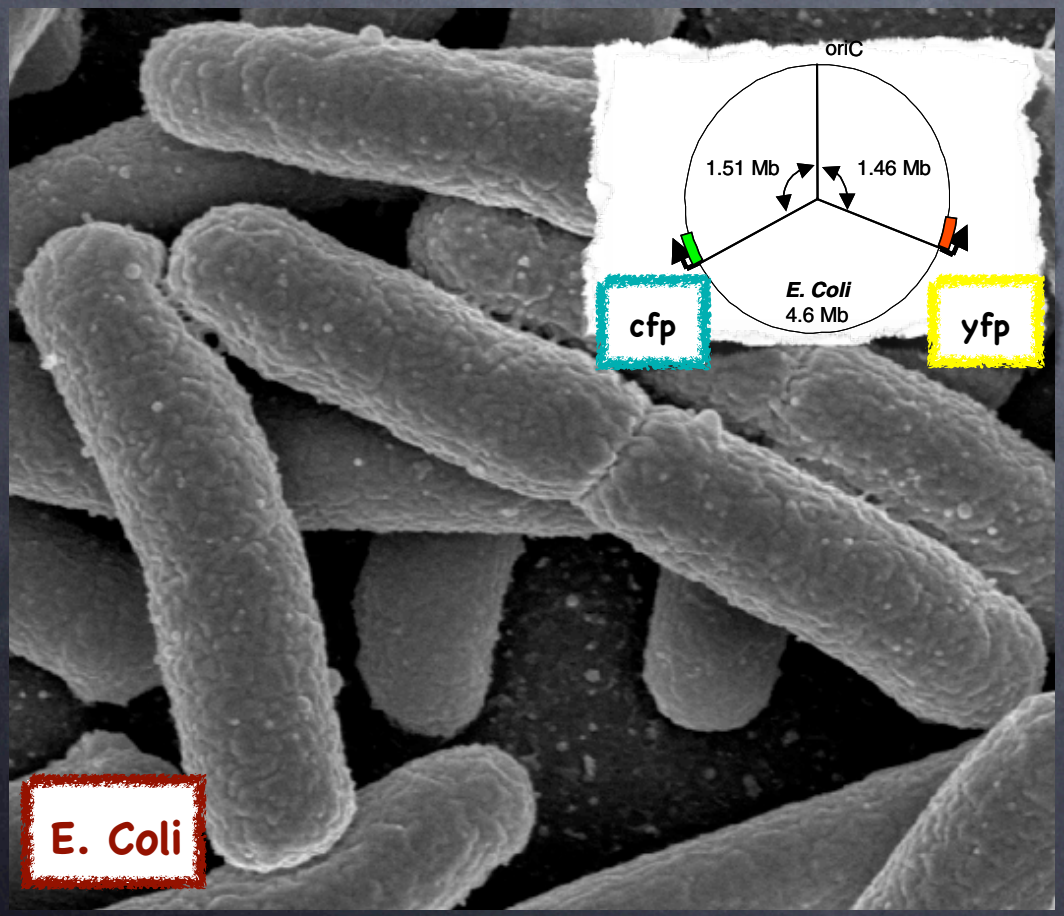
- Where does noise come from? -

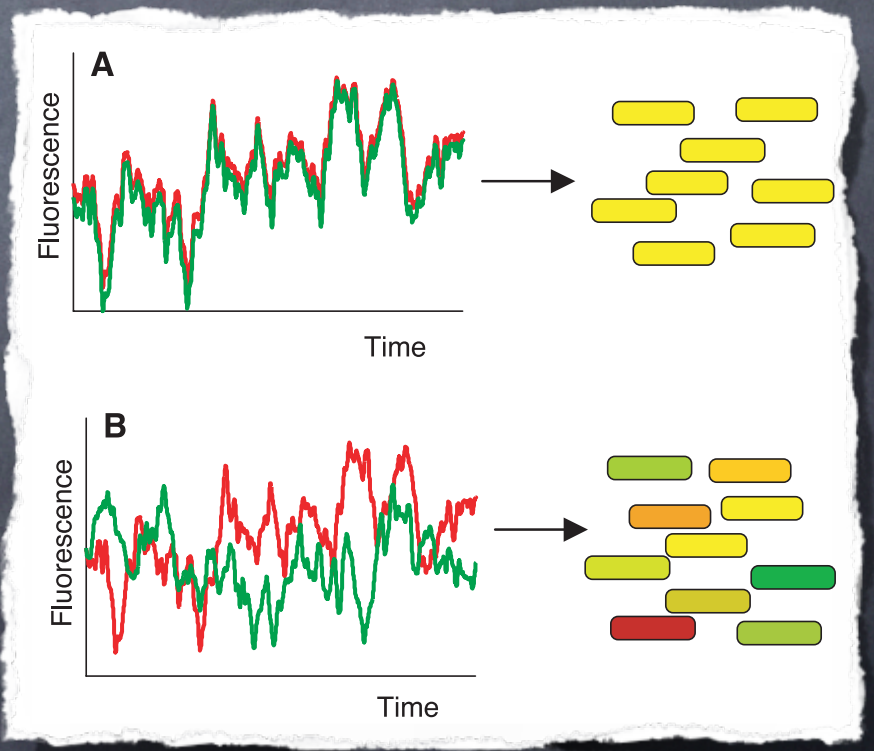
Extrinsic noise

- global to 1 cell
- variable among cells

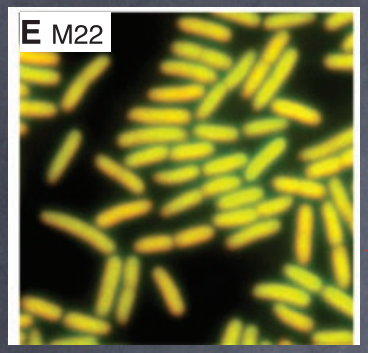
Intrinsic noise

- inherent stochasticity of regulation



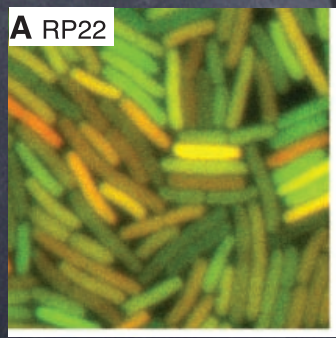


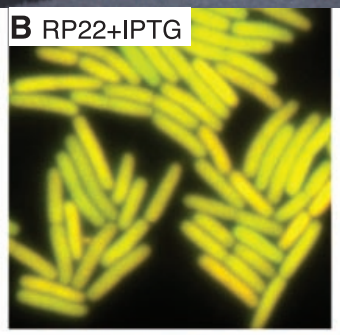
- Noise in E. Coli -

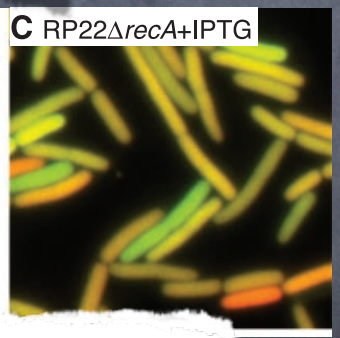


- very strong promoter
- scilenced repressor

- weak promoter
- WT repressor



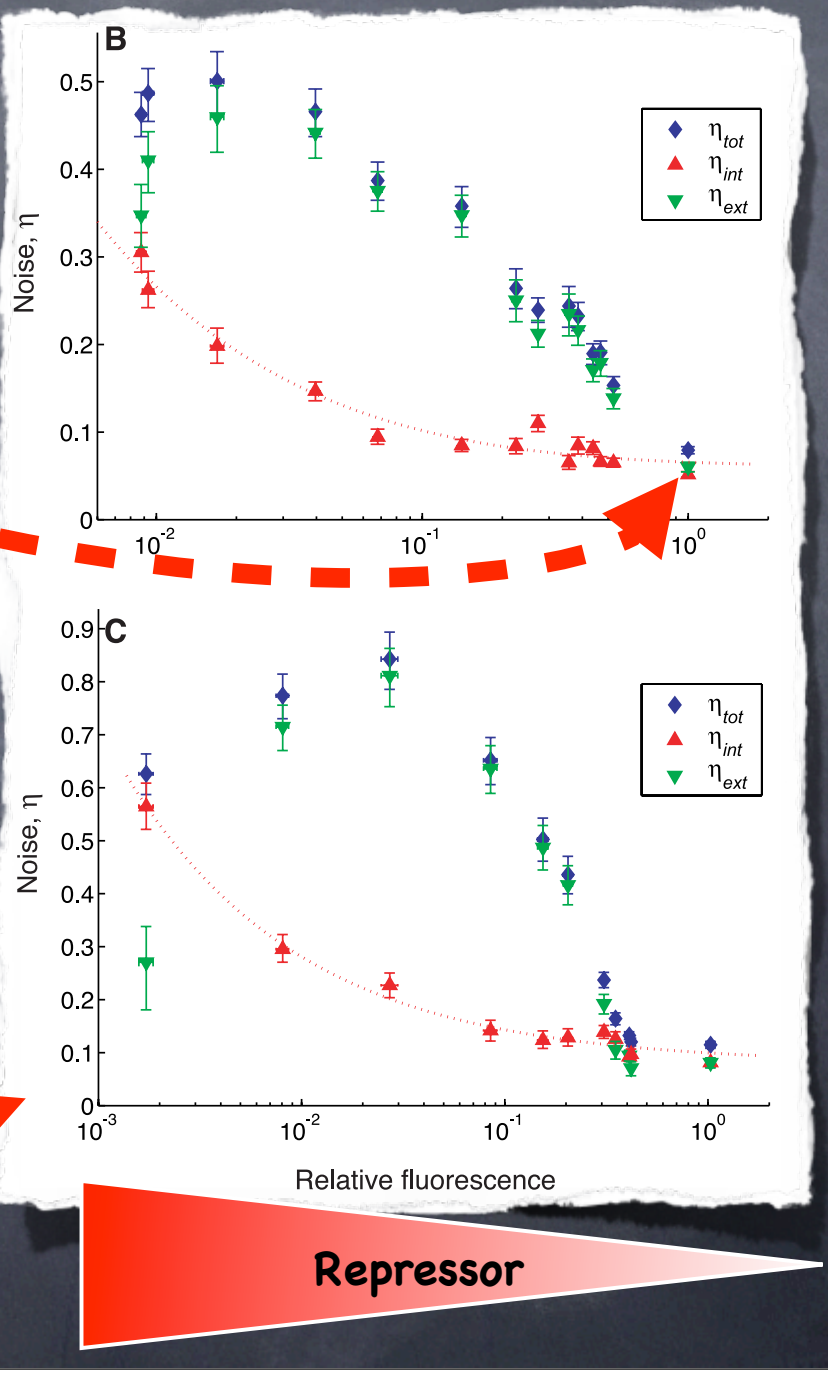




- high inducer levels

recA null strain: very noisy!

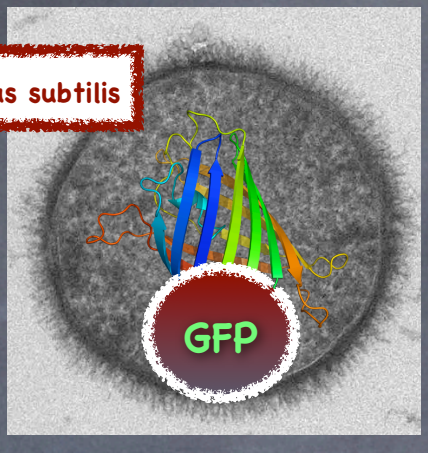
(recA rescues stalled replication forks)



- Dissecting intrinsic noise -

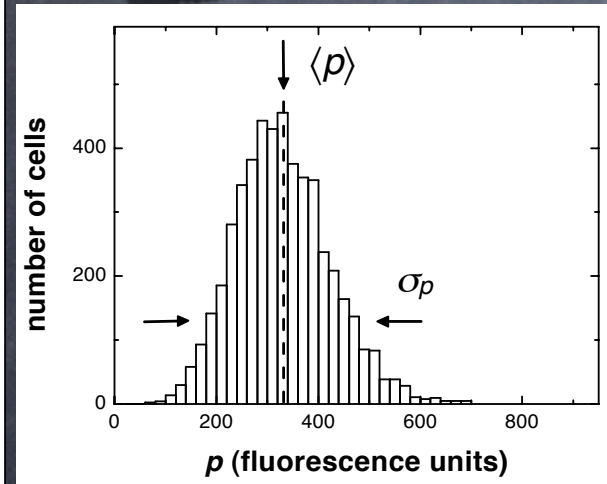
Noise in transcription initiation

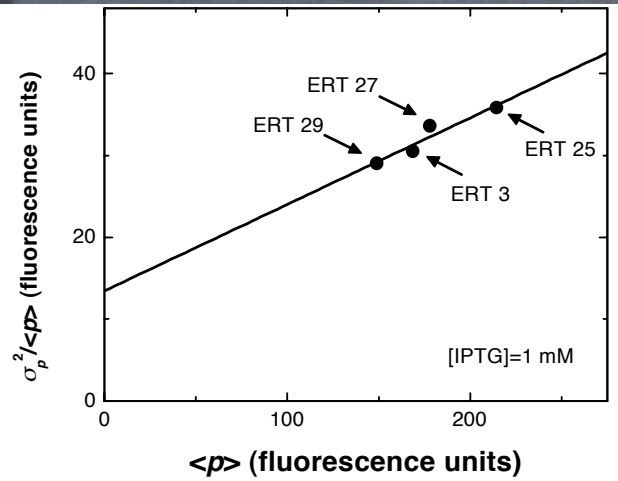
- varying levels of inducer
- mutations in promoter regions

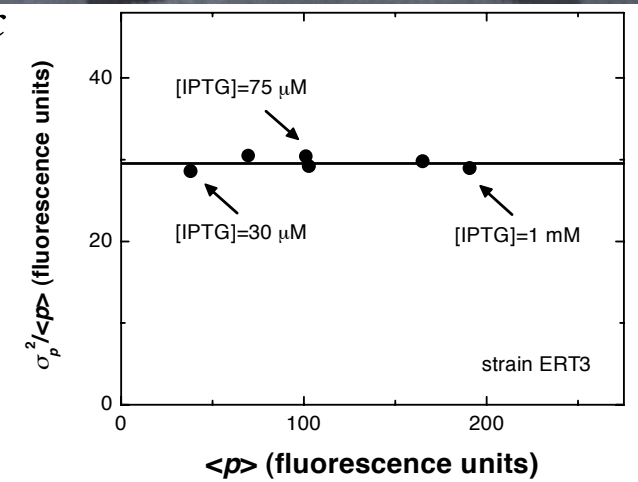


Noise in translation

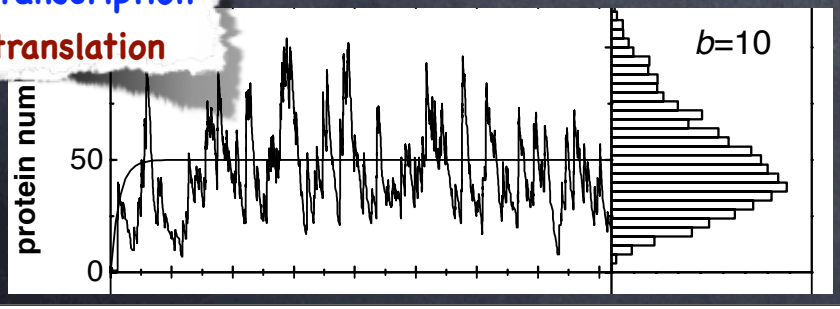
- mutations in ribosome binding sites
- changes in start codons





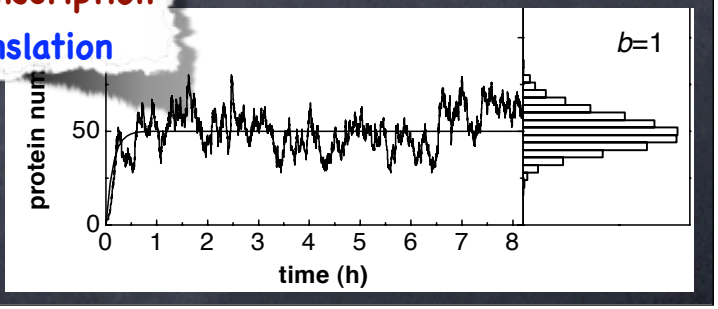


- LOW transcription
- HIGH translation



Model

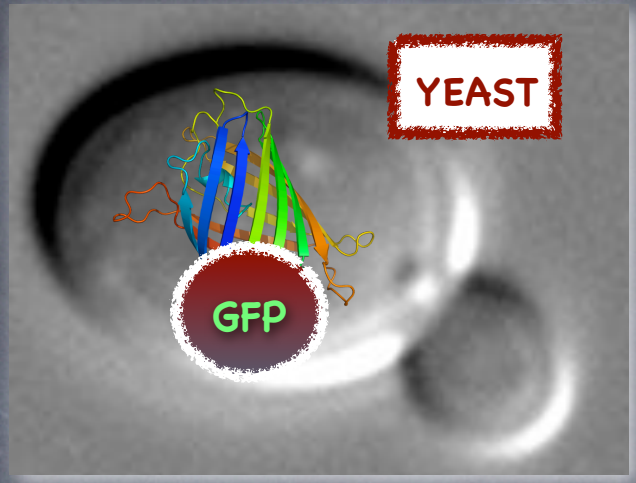
- HIGH transcription
- LOW translation



- Not so fast with the conclusions! -

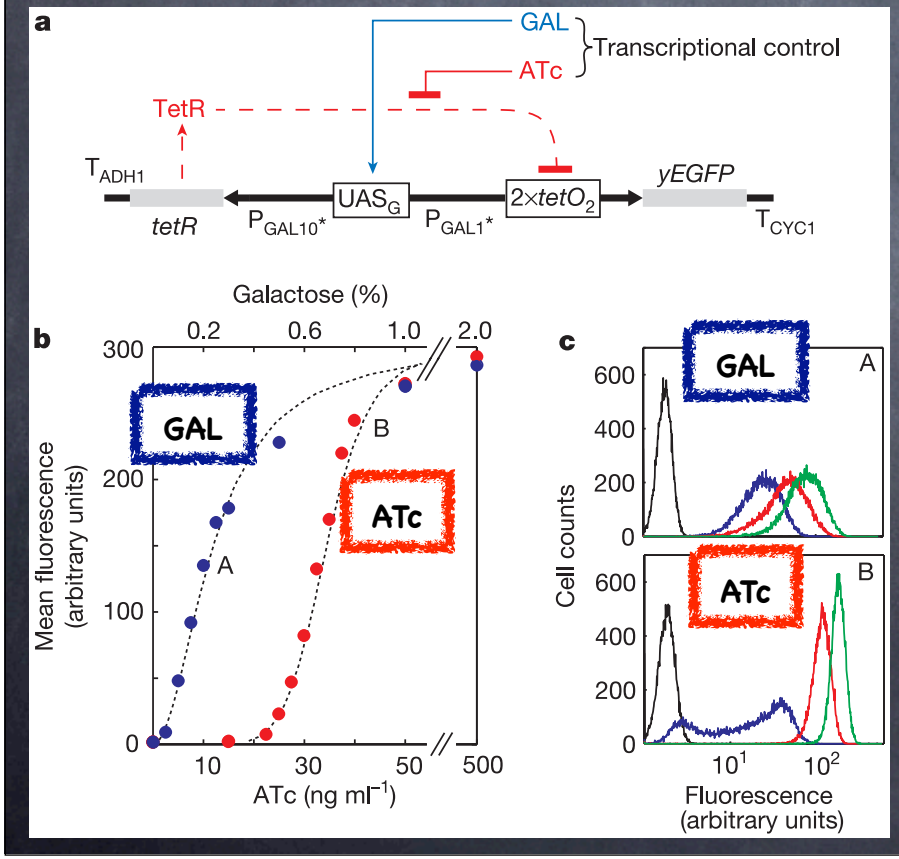
Noise in transcription initiation

- varying levels of inducer
- mutations in promoter regions

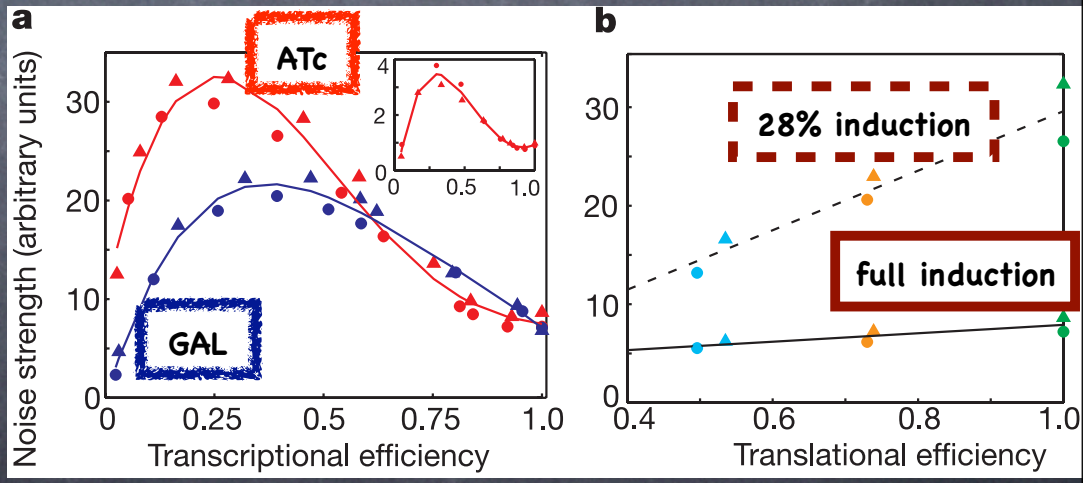


Noise in translation

- mutations in ribosome binding sites
- changes in start codons



$$\text{Noise strength} = \frac{\text{Variance}}{\text{Mean}}$$

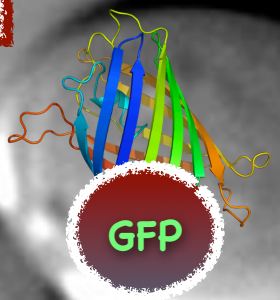


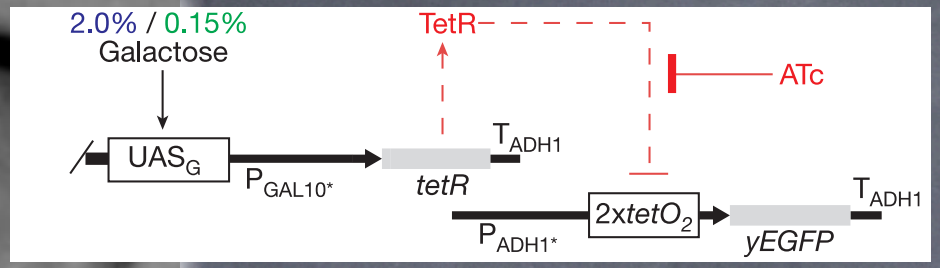
Bursty re-initiation!

Amplification of transcriptional noise

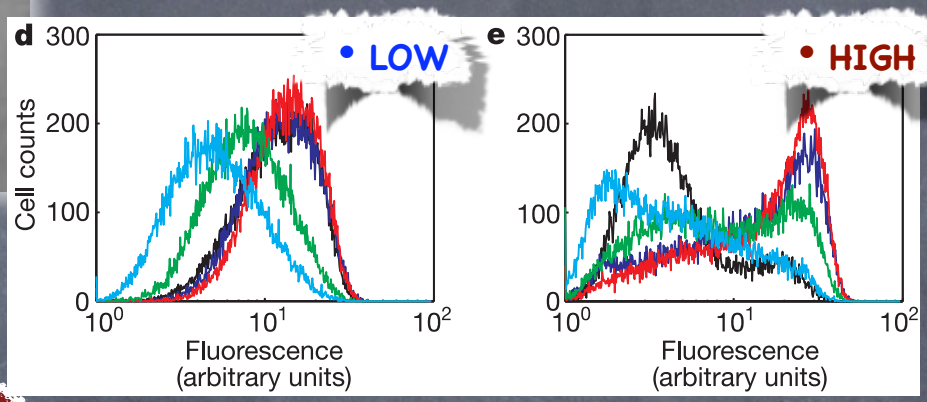
- Cascading noise and phenotypes -

YEAST



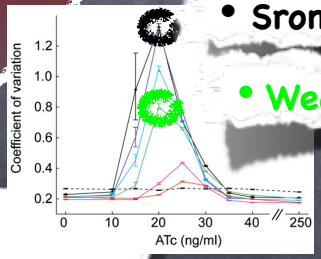


Noise in TF levels

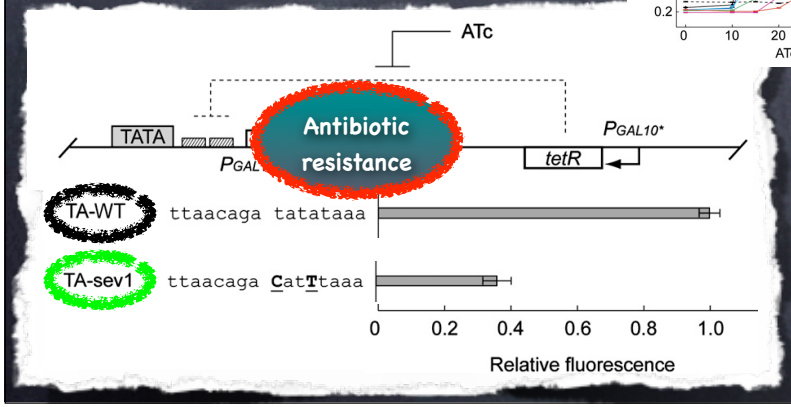


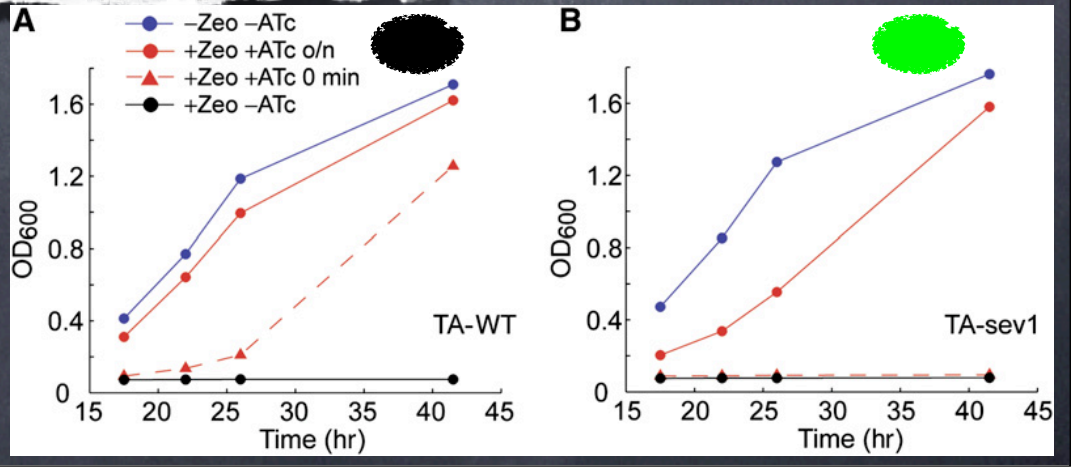
Switching appears!

Does the YEAST care?

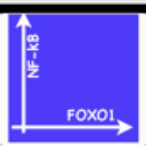
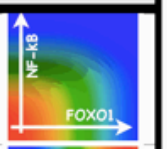
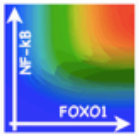
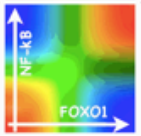
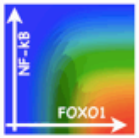
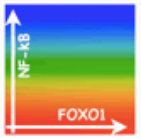
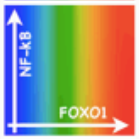
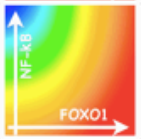
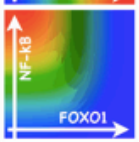
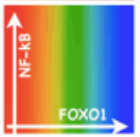
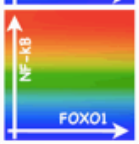
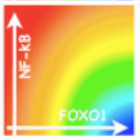
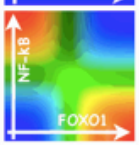
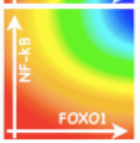
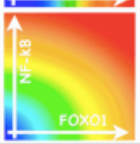


- Sronger, noisy: bursts
- Weaker, steady: few bursts

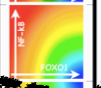


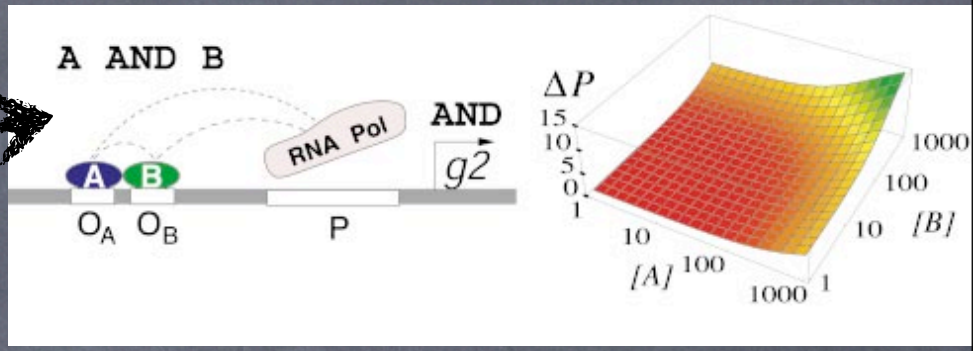


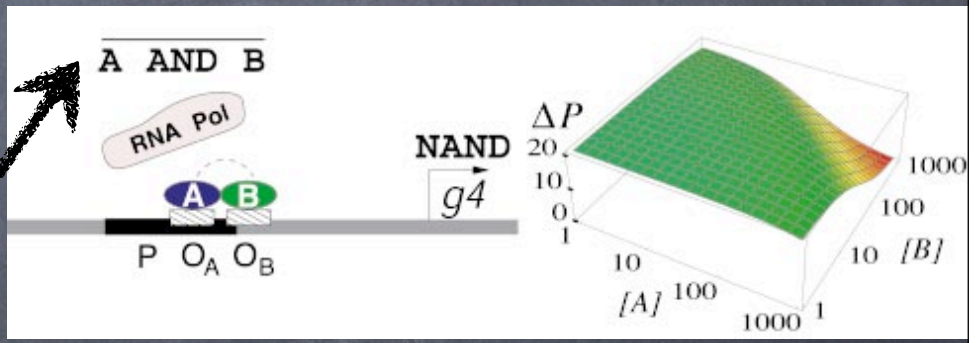
4. The logic of genetic regulation

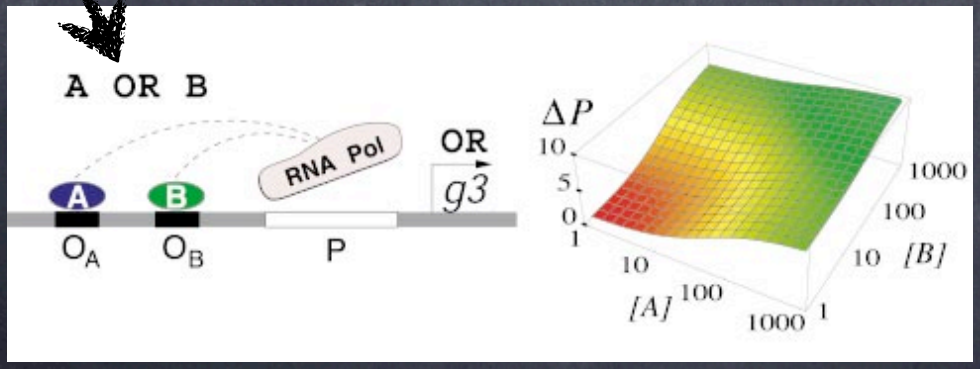
FOXO1	LOW	LOW	HIGH	HIGH	Logic gate	Expression heatmap	FOXO1	LOW	LOW	HIGH	HIGH	Logic gate	Expression heatmap
NFkB	LOW	HIGH	LOW	HIGH			NFkB	LOW	HIGH	LOW	HIGH		
G1	LOW	LOW	LOW	LOW	Indifferent to both		G9	HIGH	LOW	LOW	LOW	NOT (FOXO1 OR NFkB)	
G2	LOW	LOW	LOW	HIGH	FOXO1 AND NFkB		G10	HIGH	LOW	LOW	HIGH	FOXO1 XOR (NOT NFkB)	
G3	LOW	LOW	HIGH	LOW	FOXO1 AND (NOT NFkB)		G11	HIGH	LOW	HIGH	LOW	NOT NFkB	
G4	LOW	LOW	HIGH	HIGH	FOXO1		G12	HIGH	LOW	HIGH	HIGH	FOXO1 OR (NOT NFkB)	
G5	LOW	HIGH	LOW	LOW	(NOT FOXO1) AND NFkB		G13	HIGH	HIGH	LOW	LOW	NOT FOXO1	
G6	LOW	HIGH	LOW	HIGH	NFkB		G14	HIGH	HIGH	LOW	HIGH	(NOT FOXO1) OR NFkB	
G7	LOW	HIGH	HIGH	LOW	FOXO1 XOR NFkB		G15	HIGH	HIGH	HIGH	LOW	NOT (FOXO1 AND NFkB)	
G8	LOW	HIGH	HIGH	HIGH	FOXO1 OR NFkB		G16	HIGH	HIGH	HIGH	HIGH	Indifferent to both	

- Boolean logic from cooperative binding -

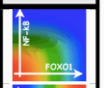
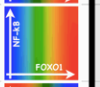
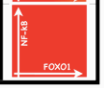
FOXO1	LOW	LOW	HIGH	HIGH	Logic gate	Expression heatmap	FOXO1	LOW	LOW	HIGH	HIGH	Logic gate	Expression heatmap
NFkB	LOW	HIGH	LOW	HIGH			NFkB	LOW	HIGH	LOW	HIGH		
G1	LOW	LOW	LOW	LOW	Indifferent to both		G9	HIGH	LOW	LOW	LOW	NOT (FOXO1 OR NFkB)	
G2	LOW	LOW	LOW	HIGH	FOXO1 AND NFkB		G10	HIGH	LOW	LOW	HIGH	FOXO1 XOR (NOT NFkB)	
G3	LOW	LOW	HIGH	LOW	FOXO1 AND (NOT NFkB)		G11	HIGH	LOW	HIGH	LOW	NOT NFkB	
G4	LOW	LOW	HIGH	HIGH	FOXO1		G12	HIGH	LOW	HIGH	HIGH	FOXO1 OR (NOT NFkB)	
G5	LOW	HIGH	LOW	LOW	(NOT FOXO1) AND NFkB		G13	HIGH	HIGH	LOW	LOW	NOT FOXO1	
G6	LOW	HIGH	LOW	HIGH	NFkB		G14	HIGH	HIGH	LOW	HIGH	(NOT FOXO1) OR NFkB	
G7	LOW	HIGH	HIGH	LOW	FOXO1 XOR NFkB		G15	HIGH	HIGH	HIGH	LOW	NOT (FOXO1 AND NFkB)	
G8	LOW	HIGH	HIGH	HIGH	FOXO1 OR NFkB		G16	HIGH	HIGH	HIGH	HIGH	Indifferent to both	

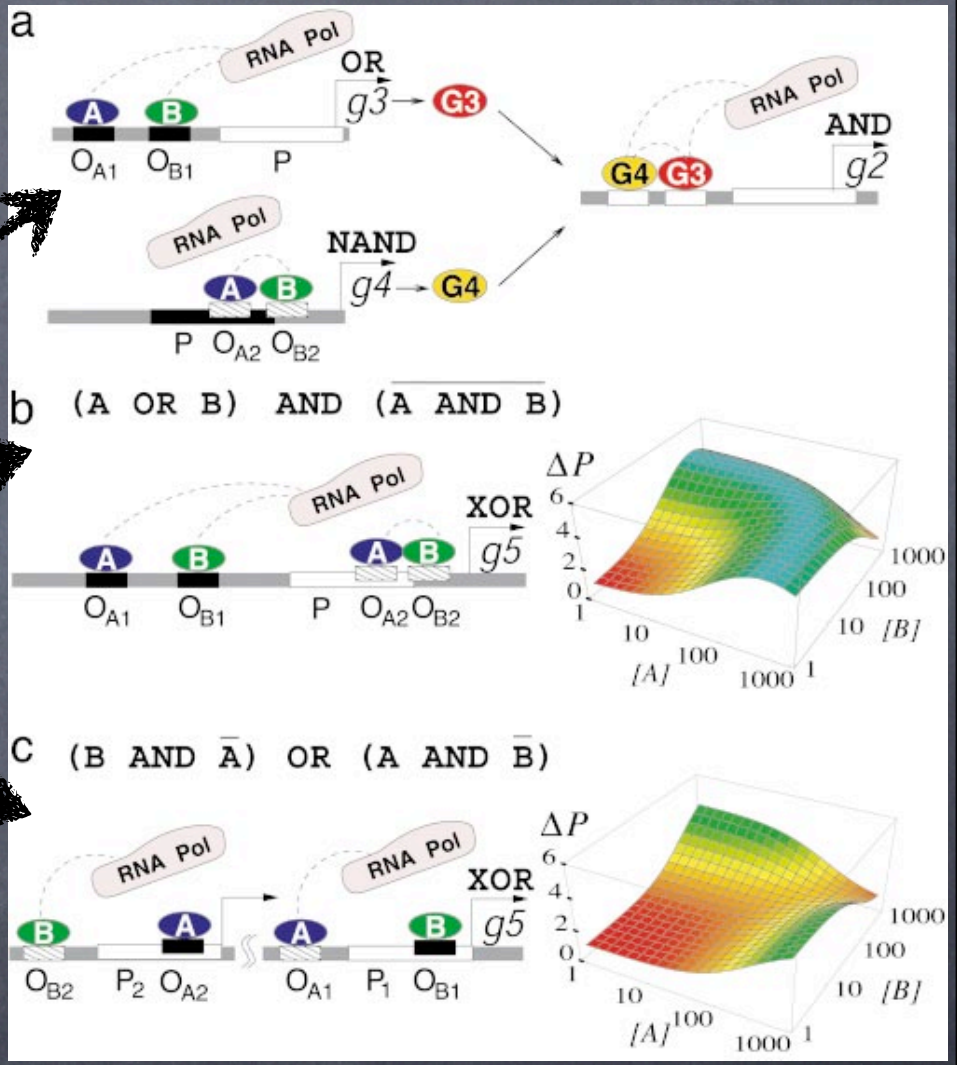






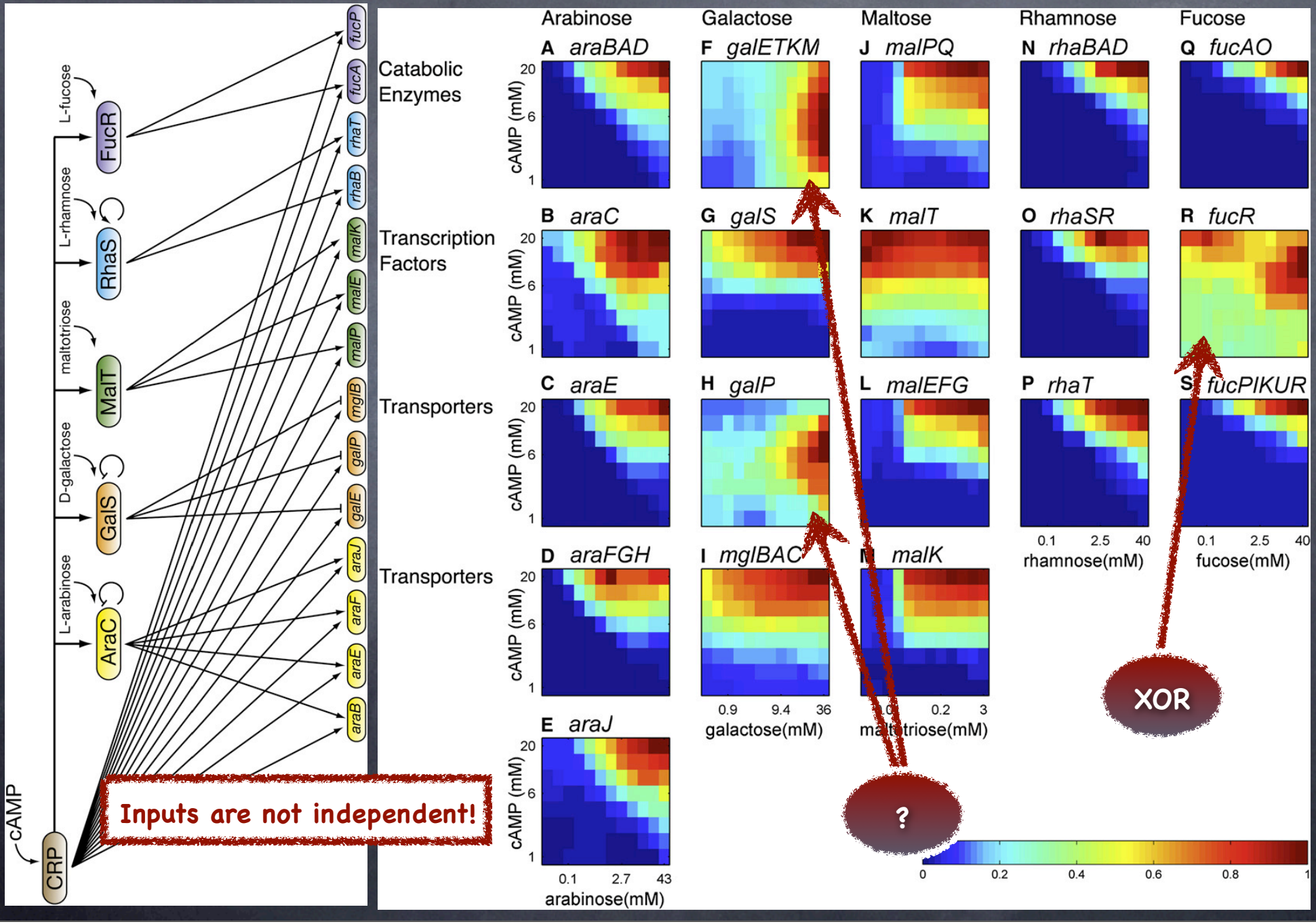
- XOR is hard! -

FOXO1	LOW	LOW	HIGH	HIGH	Logic gate	Expression heatmap	FOXO1	LOW	LOW	HIGH	HIGH	Logic gate	Expression heatmap
NFkB	LOW	HIGH	LOW	HIGH			NFkB	LOW	HIGH	LOW	HIGH		
G1	LOW	LOW	LOW	LOW	Indifferent to both		G9	HIGH	LOW	LOW	LOW	NOT (FOXO1 OR NFkB)	
G2	LOW	LOW	LOW	HIGH	FOXO1 AND NFkB		G10	HIGH	LOW	LOW	HIGH	FOXO1 XOR (NOT NFkB)	
G3	LOW	LOW	HIGH	LOW	FOXO1 AND (NOT NFkB)		G11	HIGH	LOW	HIGH	LOW	NOT NFkB	
G4	LOW	LOW	HIGH	HIGH	FOXO1		G12	HIGH	LOW	HIGH	HIGH	FOXO1 OR (NOT NFkB)	
G5	LOW	HIGH	LOW	LOW	(NOT FOXO1) AND NFkB		G13	HIGH	HIGH	LOW	LOW	NOT FOXO1	
G6	LOW	HIGH	LOW	HIGH	NFkB		G14	HIGH	HIGH	LOW	HIGH	(NOT FOXO1) OR NFkB	
G7	LOW	HIGH	HIGH	LOW	FOXO1 XOR NFkB		G15	HIGH	HIGH	HIGH	LOW	NOT (FOXO1 AND NFkB)	
G8	LOW	HIGH	HIGH	HIGH	FOXO1 OR NFkB		G16	HIGH	HIGH	HIGH	HIGH	Indifferent to both	

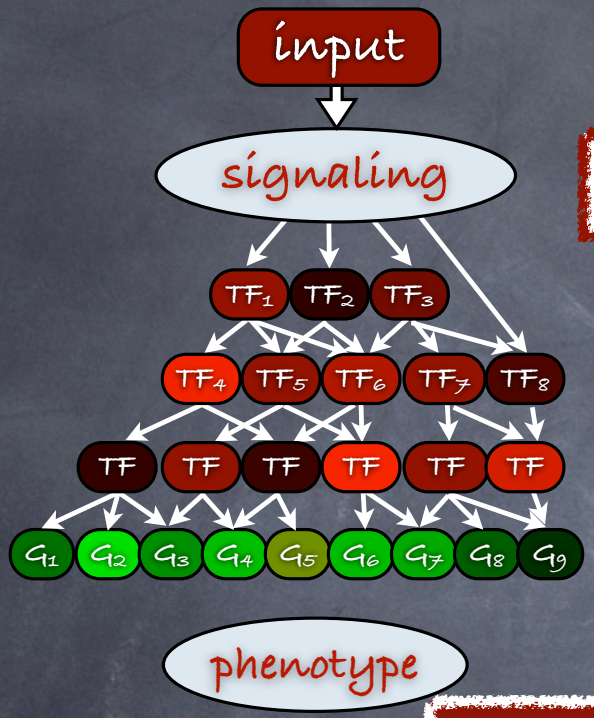


Any exprimental evidence?

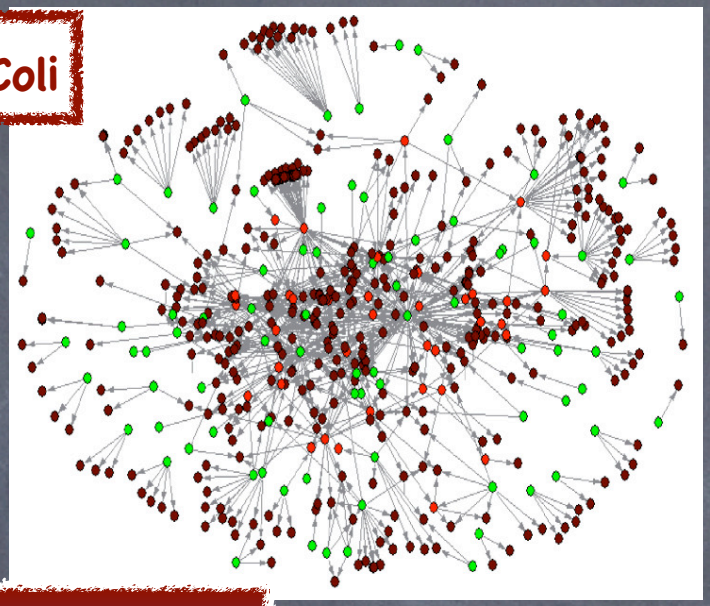
- Gates of the E. Coli sugar genes -



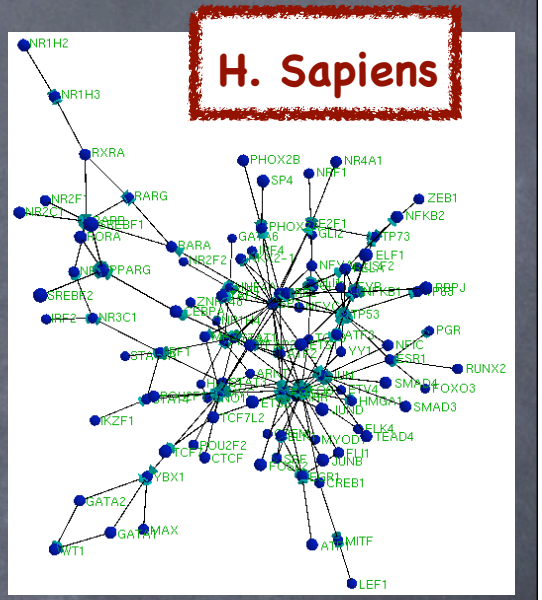
- How are regulatory signals intertwined? -



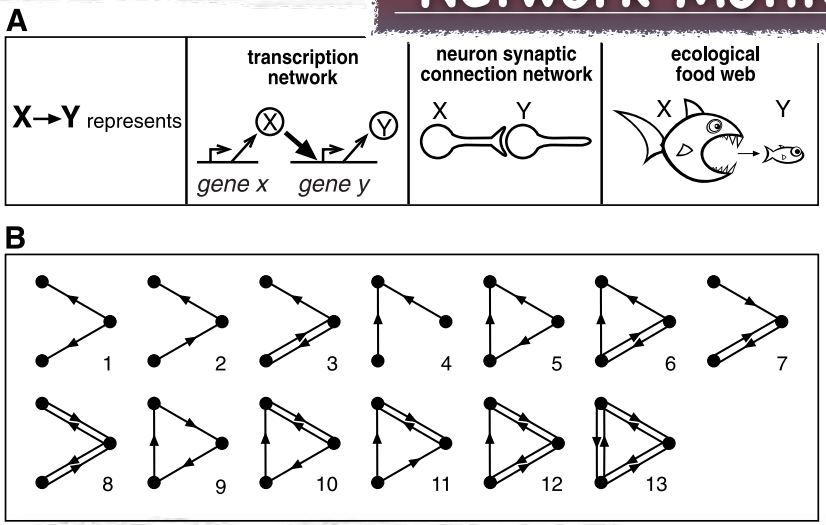
E. Coli



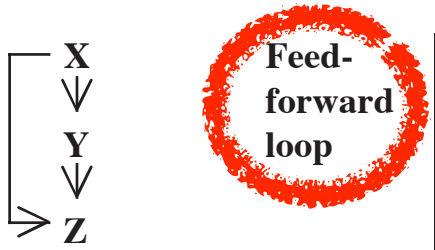
H. Sapiens



Network Motifs:

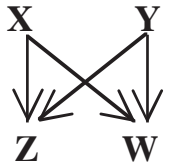


Transctiptional regulation:



Feed-forward loop

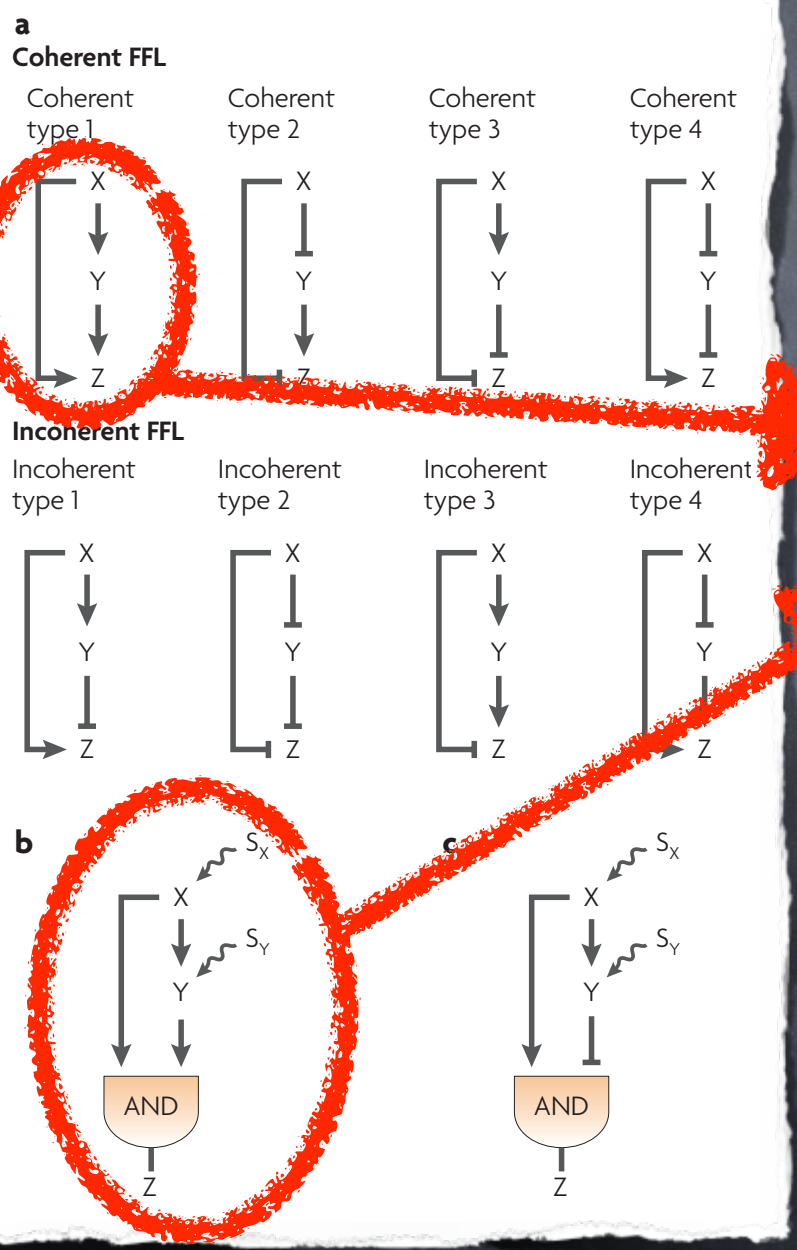
40	7 ± 3	10
70	11 ± 4	14



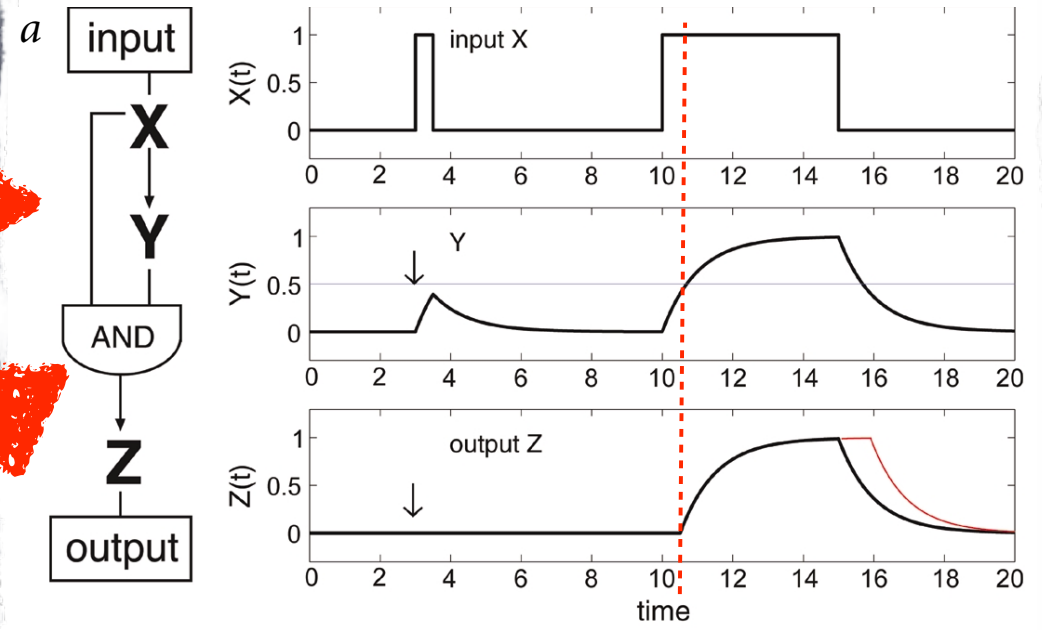
Bi-fan

203	47 ± 12	13
1812	300 ± 40	41

- The feed forward loop -



Coherent Type 1 FFL

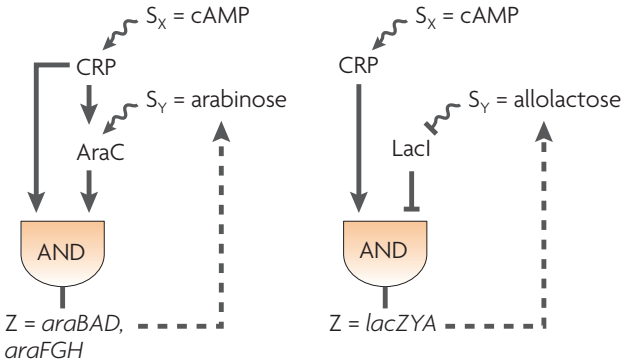


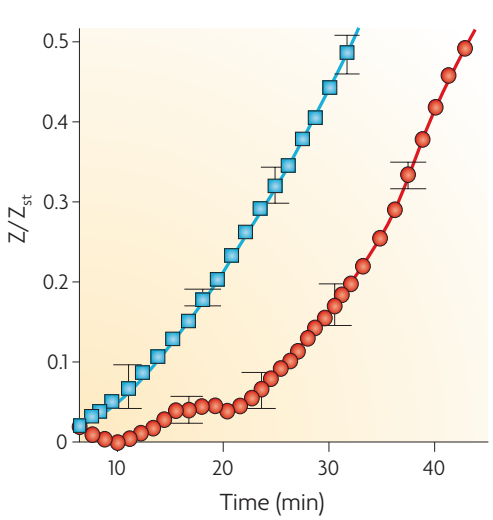
- filters transient signals
- delayed turn-on
- immediate shutdown

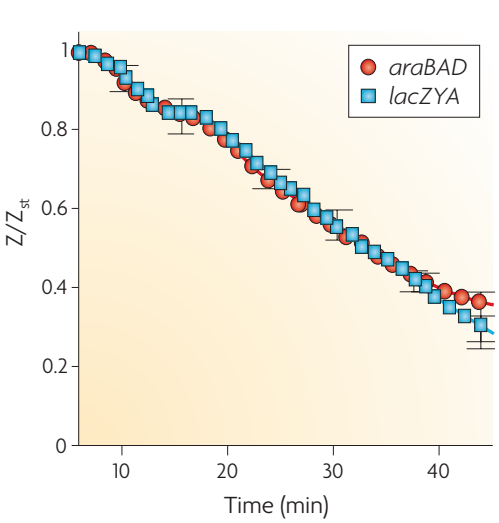
Sign-sensitive delay

- Coherent feed forward loops in E. Coli -

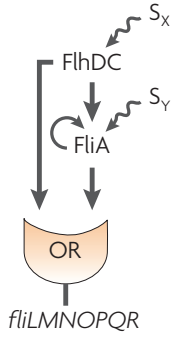
AND

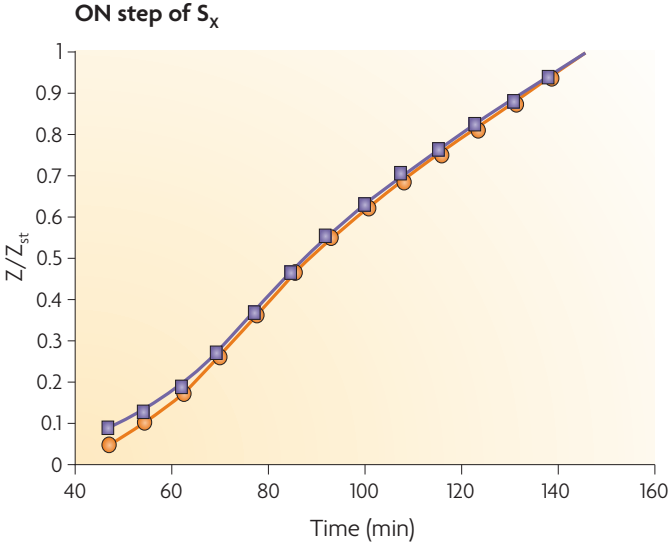


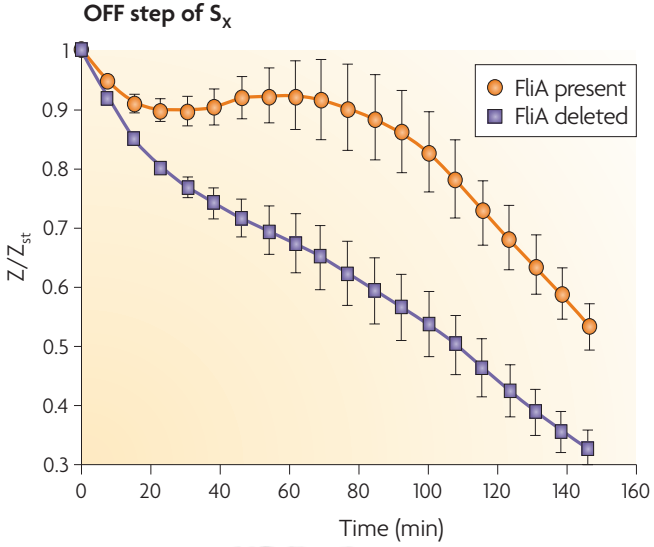




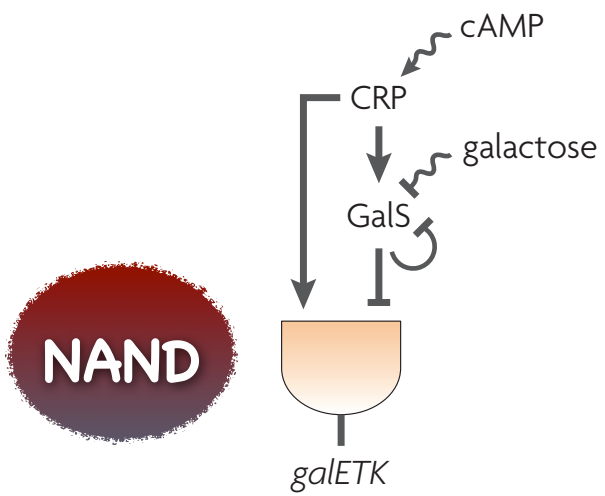
OR

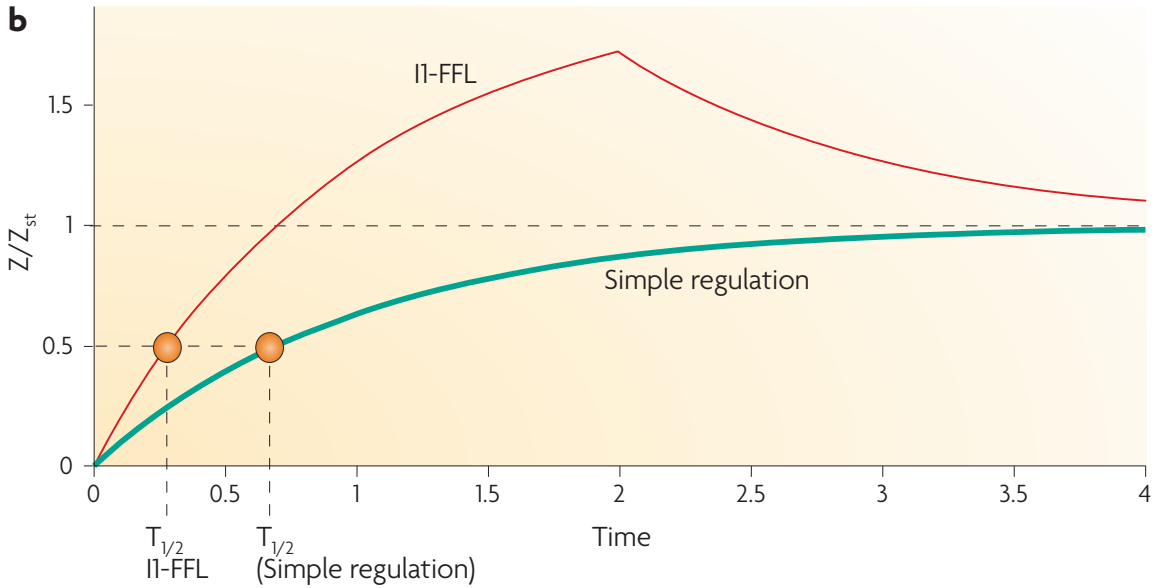




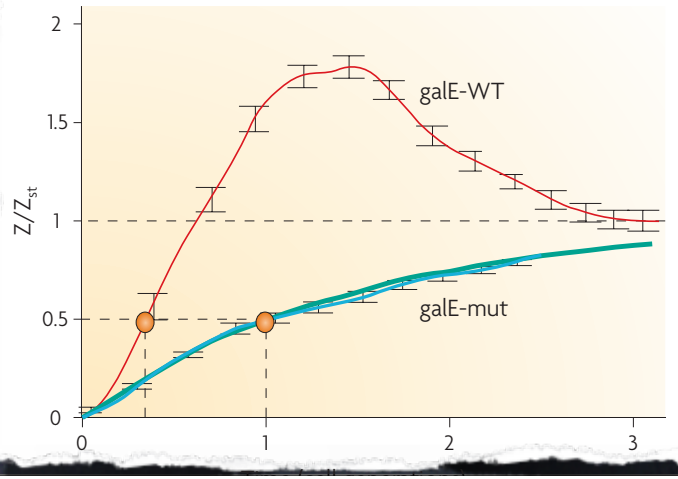


- Incoherent feed forward loops in E. Coli -

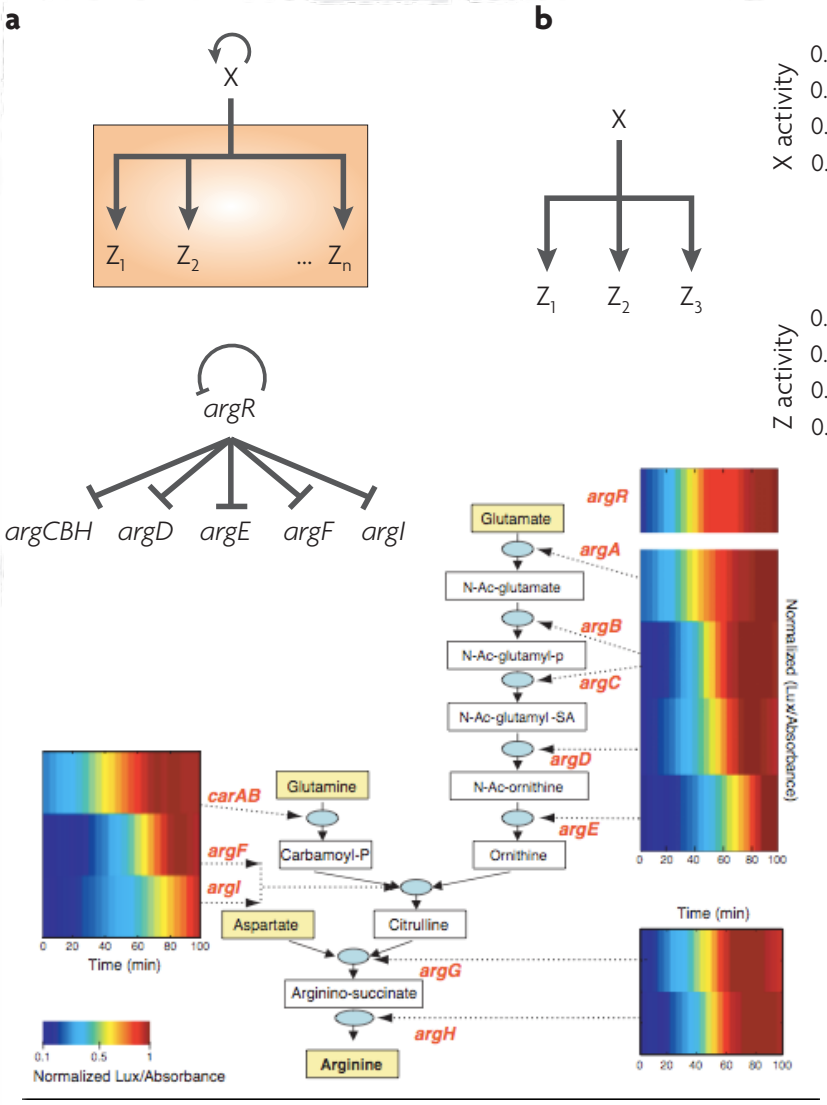


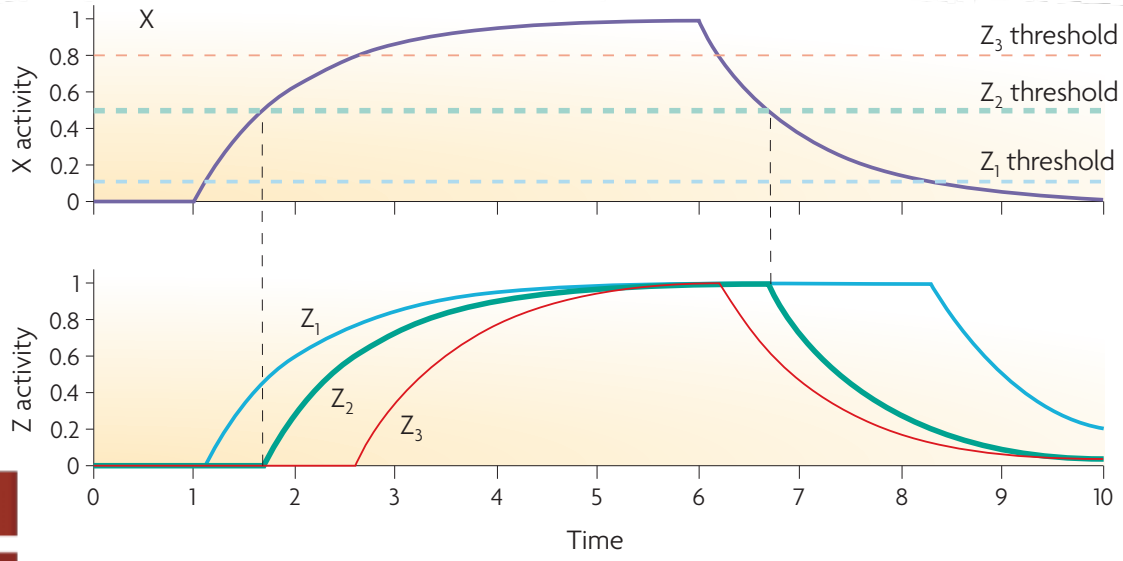


- **pulse generation**
- **response time acceleration**



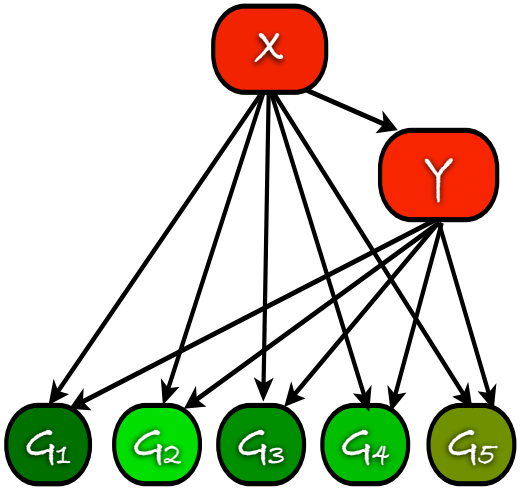
- Ordering in multiple output modules -





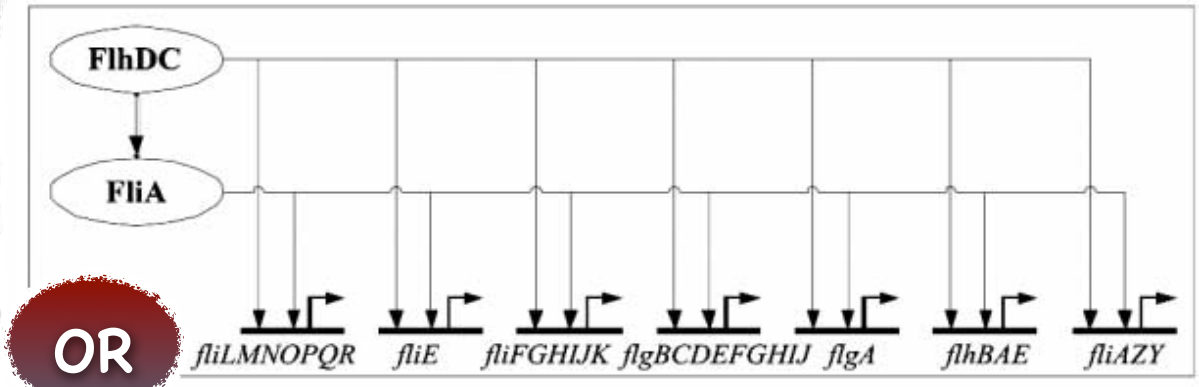
LIFO logic:
Last In, First Out

- Multi-output Feed Forward Loop -

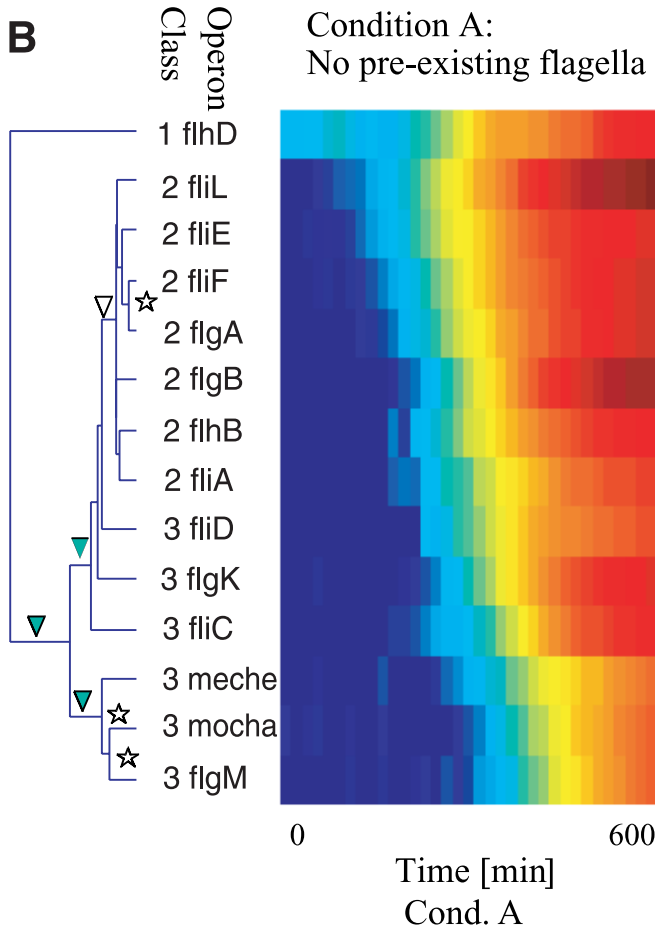


E. Coli flagellum

- Class 1 flhDC — Master regulator
- Class 2 fliL
- Class 2 fliE
- Class 2 fliF
- Class 2 flgA
- Class 2 flgB
- Class 2 flhB
- Class 2 fliA — Activator of class 3
- Class 3 fliD
- Class 3 flgK
- Class 3 fliC
- Class 3 meche
- Class 3 mocha
- Class 3 flgM



OR



FIFO logic:
First In, First Out

Slides and organized citations: on line by next week...
(conference interfering)

Slight change in plan:

Regulatory models that mimic phenotype and dynamics

THEN Transcriptional regulation from microarray data

5. Regulatory models that mimic phenotype and dynamics 1

Jun 8

12 PM