Introduction to Systems Biology (and why you should care)

BIOINF 524/525

3/21/2017

Module logistics

- Network analysis in systems biology (Lecture 3/21, Lab 3/23)
- High-throughput sequencing data (Lecture 3/28, Lab 3/30)
- Network inference and modeling (Lecture 4/4, Lab 4/6)
- Machine learning in systems biology (Lecture 4/11, Lab 4/13)

Module logistics

Lectures will focus on conceptual overview of goals and methods

Labs will include didactic material interspersed with exercises

Weekly homework will involve extension of lab exercises (due the day of the following lab session)

Grading is pass/fail and based on attendance and homework completion

Introduction to Systems Biology

BIOINF 524/525
3/21/2017

What is systems biology?

(and what can it do for me?)

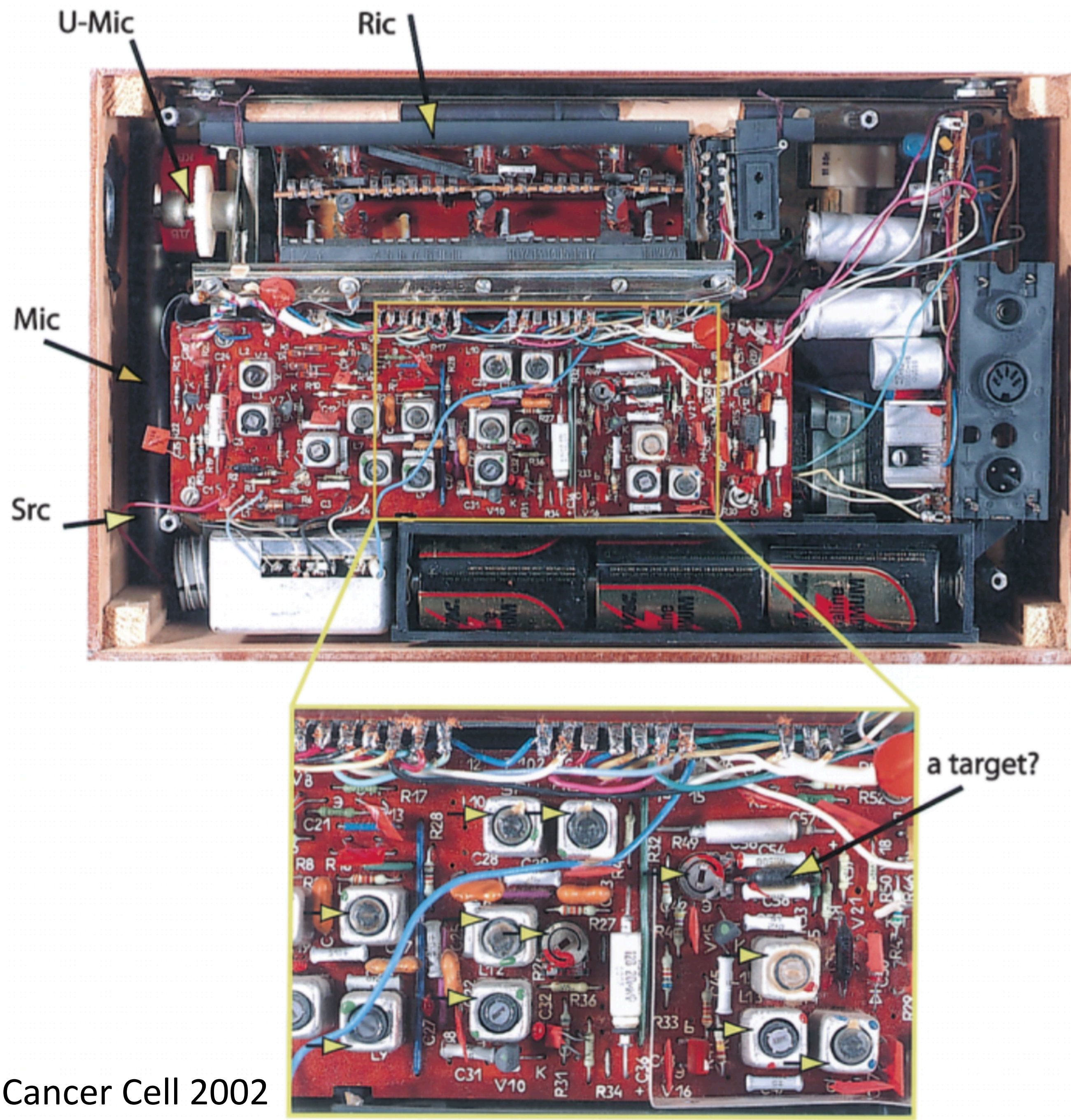
"[A]sk five biomedical researchers to define systems biology, and you'll get 10 different answers . . . or maybe more"
--Christopher Wanjek

“[A]sk five biomedical researchers to define systems biology, and you’ll get 10 different answers . . . or maybe more”
--Christopher Wanjek

“[A] scientific approach that combines the principles of engineering, mathematics, physics, and computer science with extensive experimental data to develop a quantitative as well as a deep conceptual understanding of biological phenomena, permitting prediction and accurate simulation of complex (emergent) biological behaviors.”
--Dr. Ron Germain

Can a Biologist Fix a Radio?

Lazebnik, Y. Cancer Cell 2002
(slides via Michael Wolfe)



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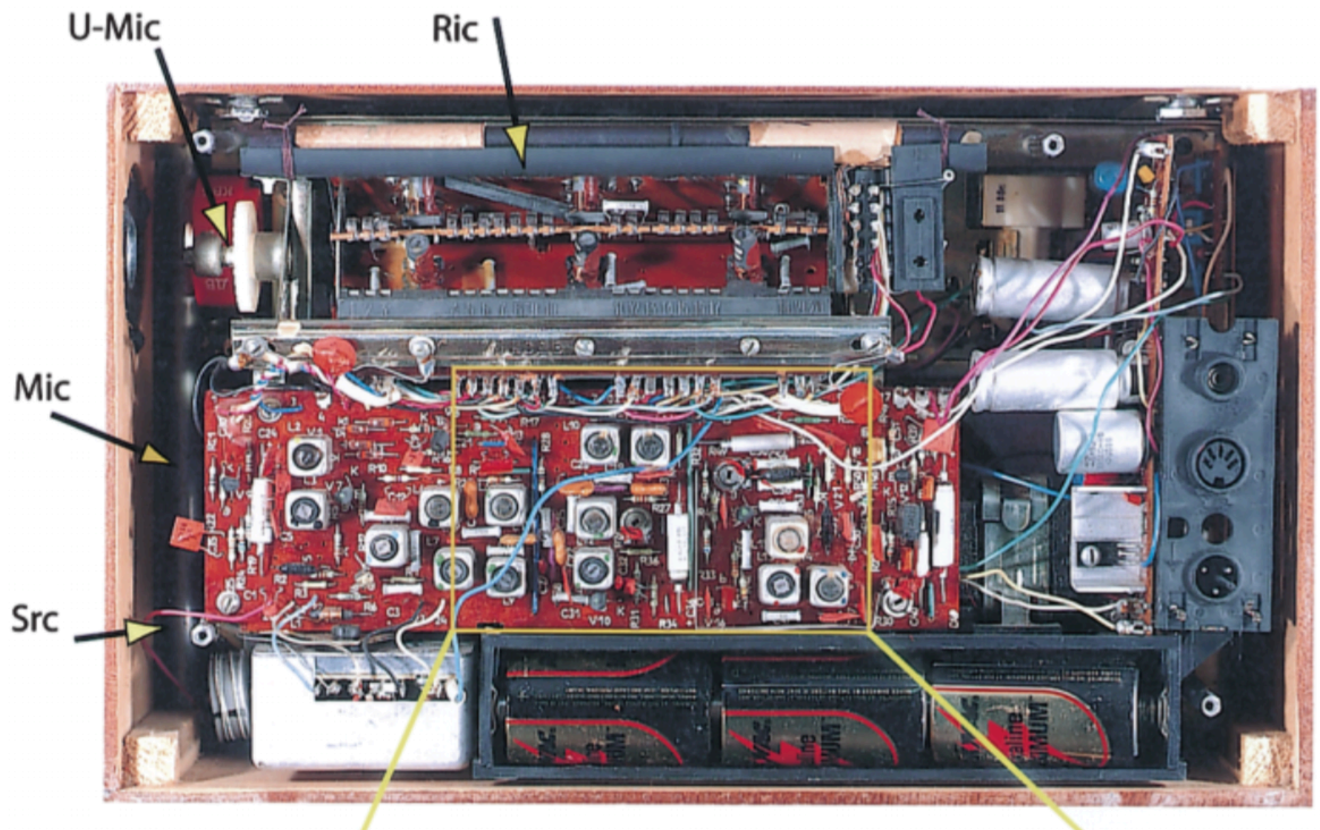
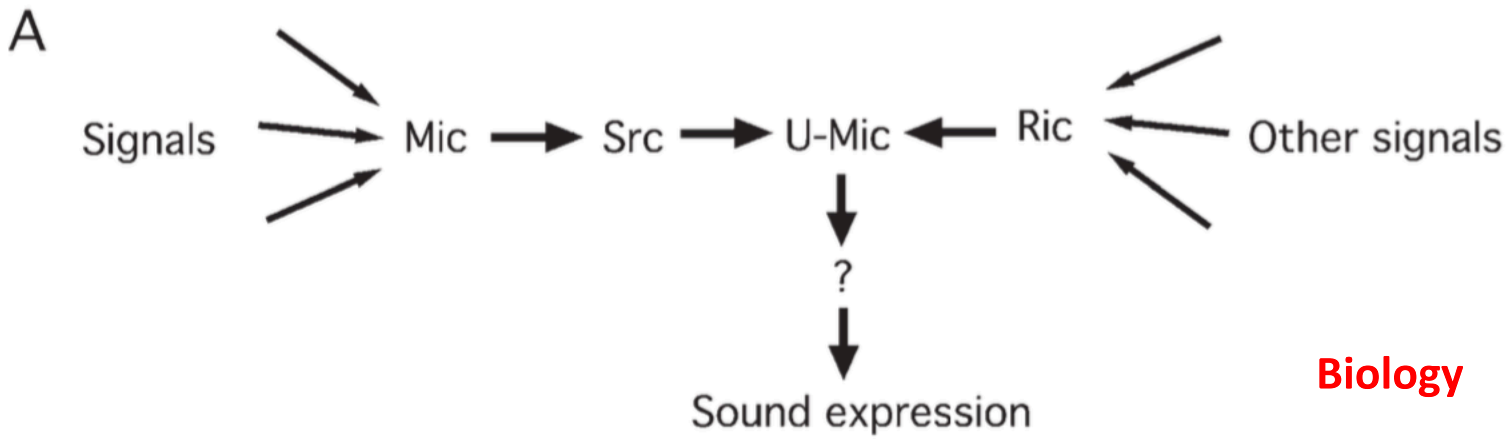


“The first thing a biochemist would do with a radio would be to stick it in a Waring blender”
-Prof. Phil Andrews

Lazebnik, Y. Cancer Cell 2002
(slides via Michael Wolfe)



Biology

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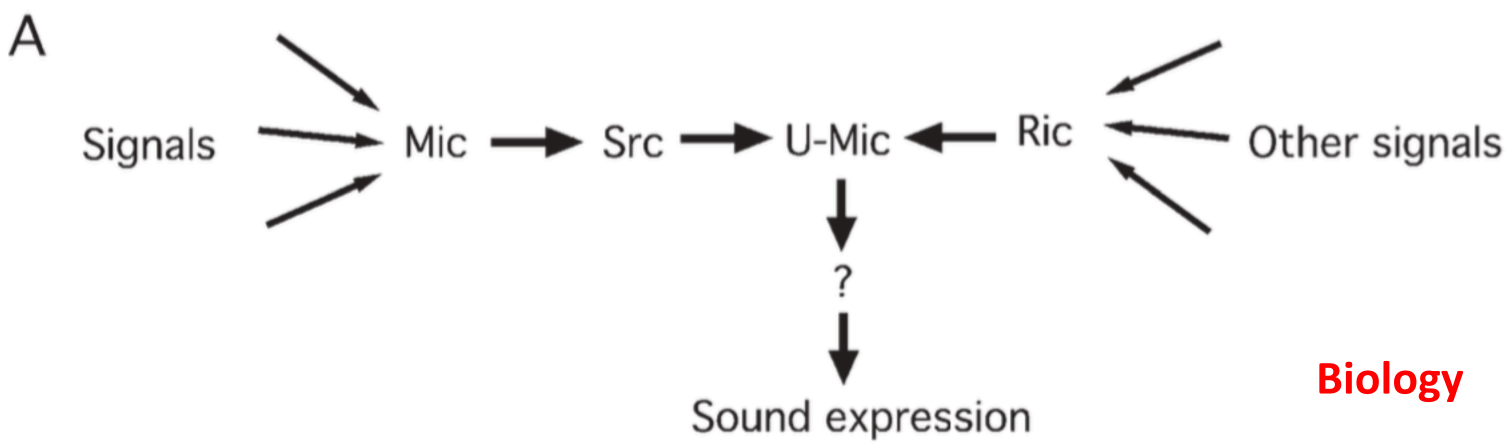
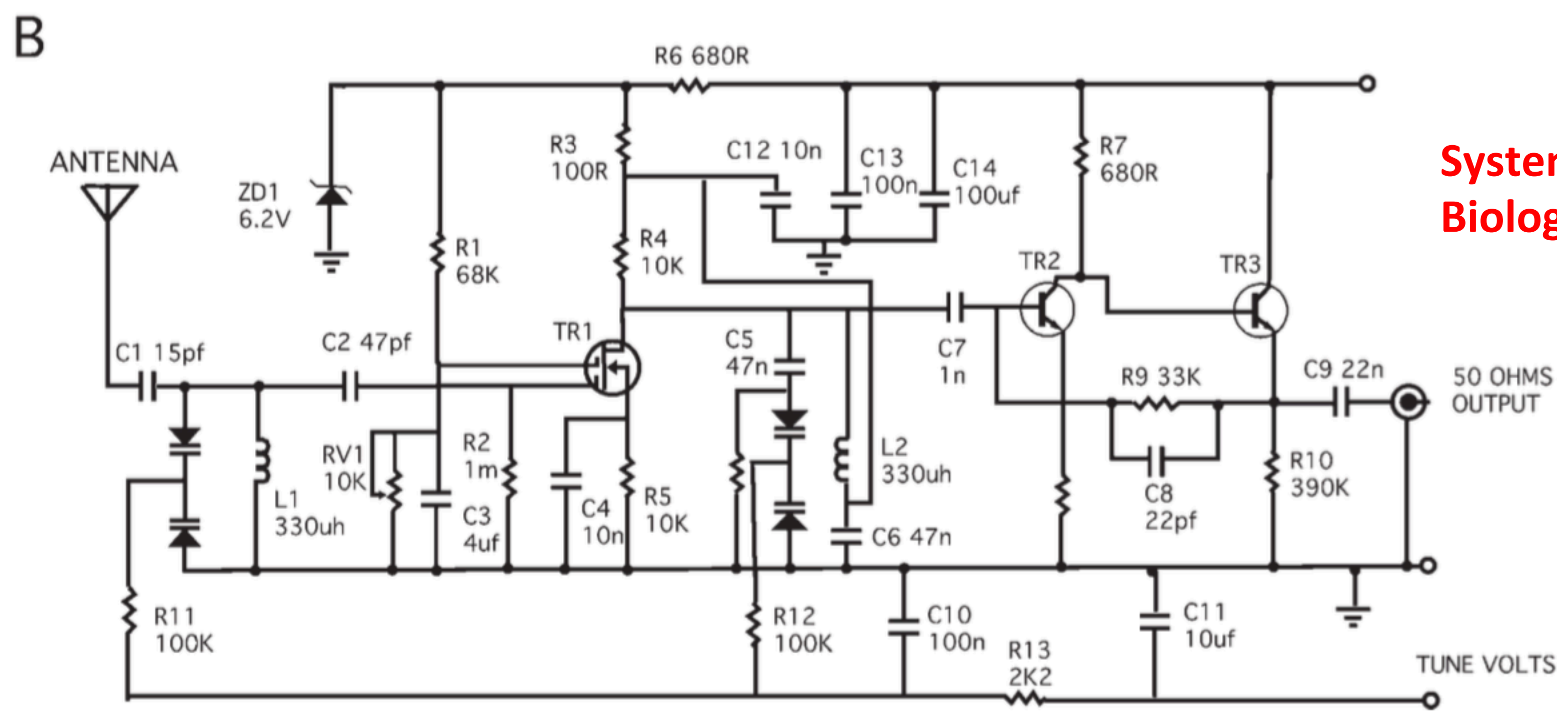


Biology



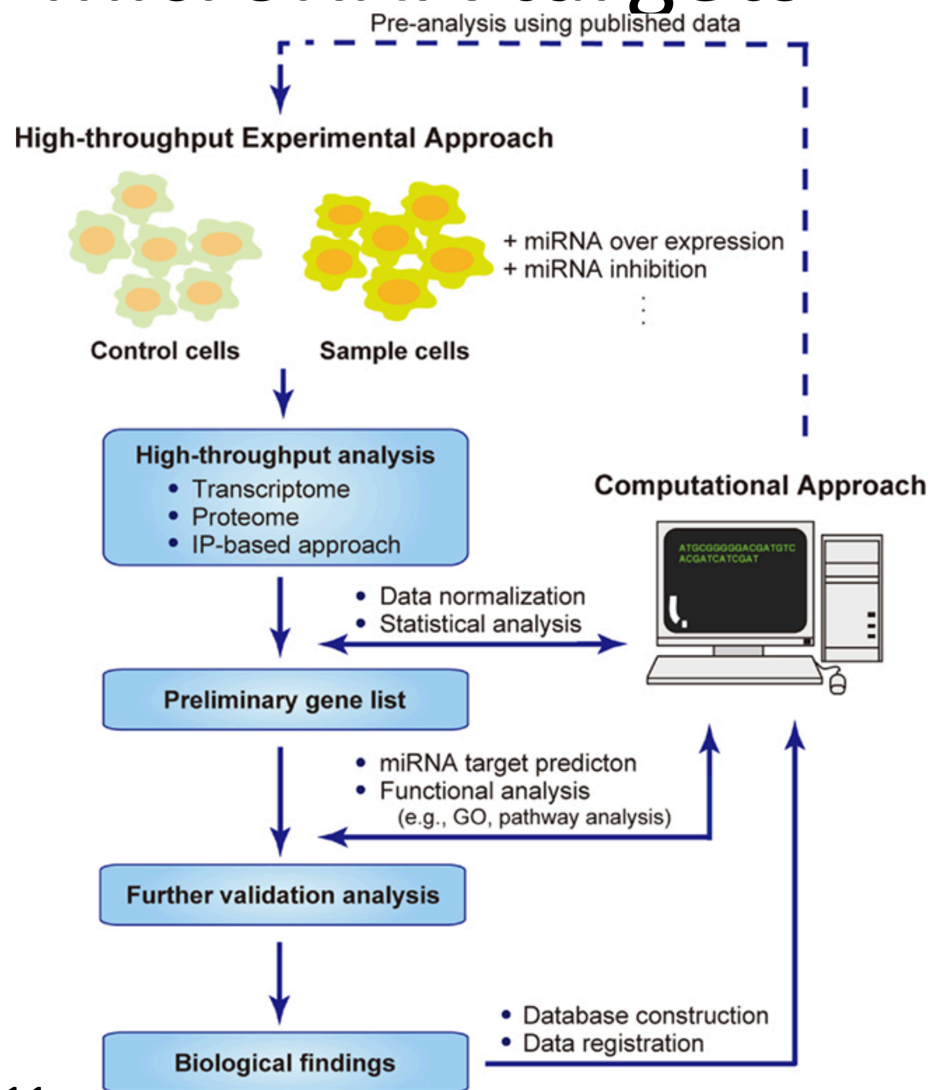
Systems Biology

Lazebnik, Y. Cancer Cell 2002
(slides via Michael Wolfe)

Guiding principles of systems biology

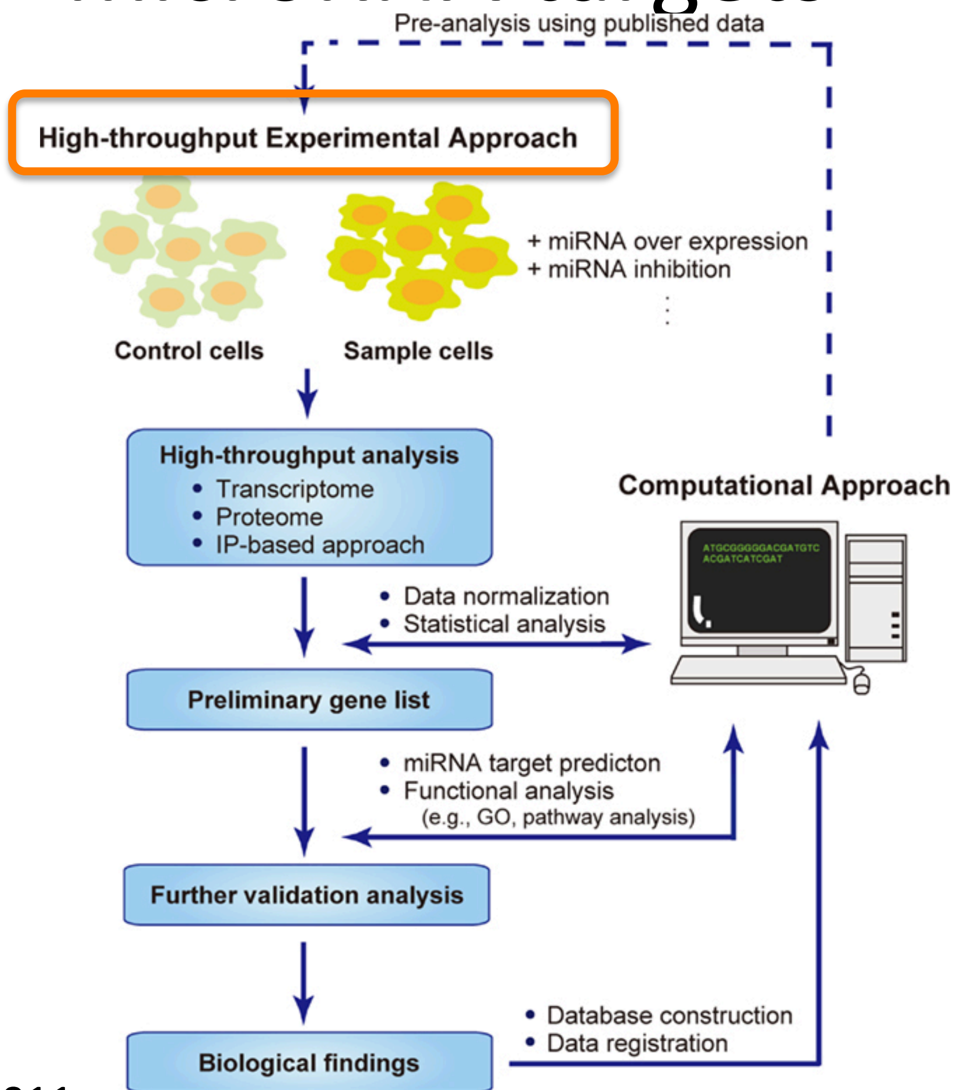
- Draw from physics and engineering to obtain quantitative descriptions
- Aim to describe and predict biological behavior
- Identify organizing principles and minimal functional examples of common biological motifs
- Emphasis on connections of components as well as their individual behavior

Example in action: discovery of microRNA targets



Watanabe and Kanai,
Front. Genet., 23 June 2011

Example in action: discovery of microRNA targets



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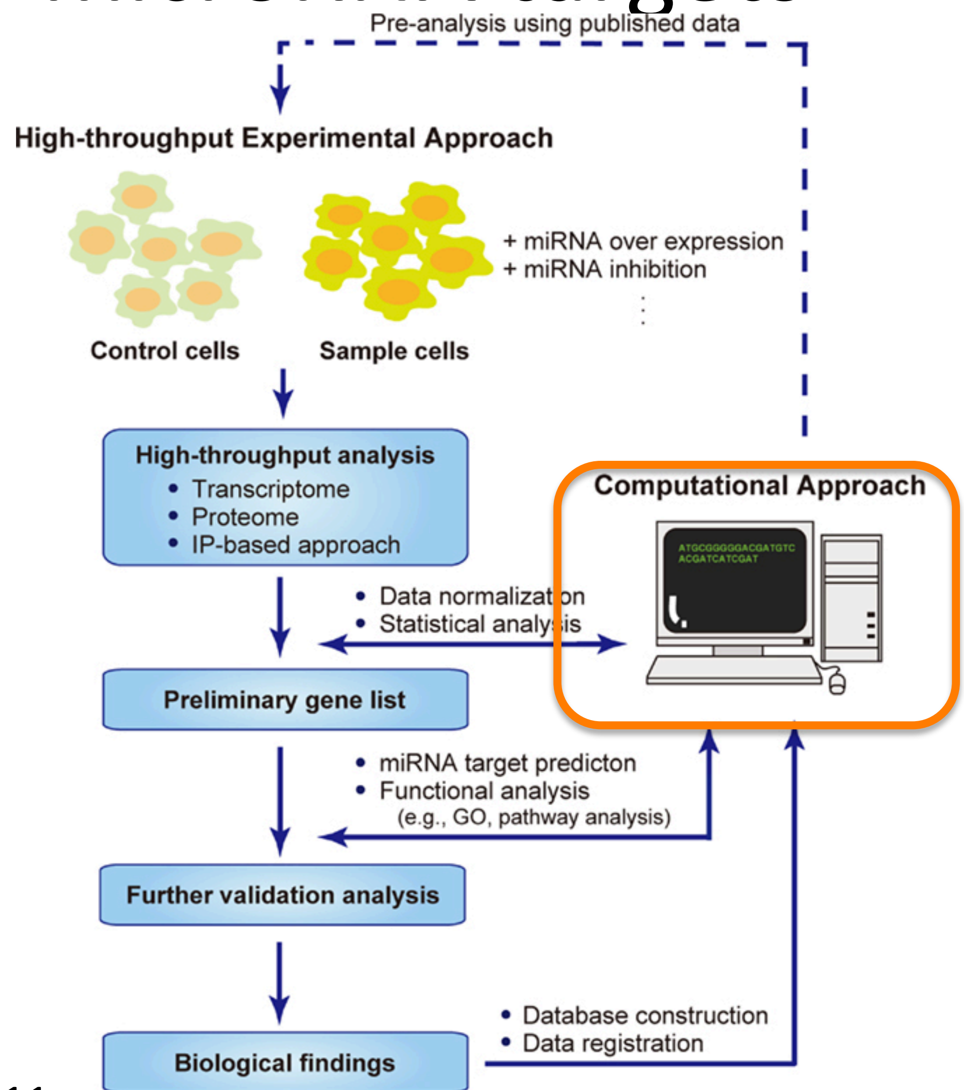

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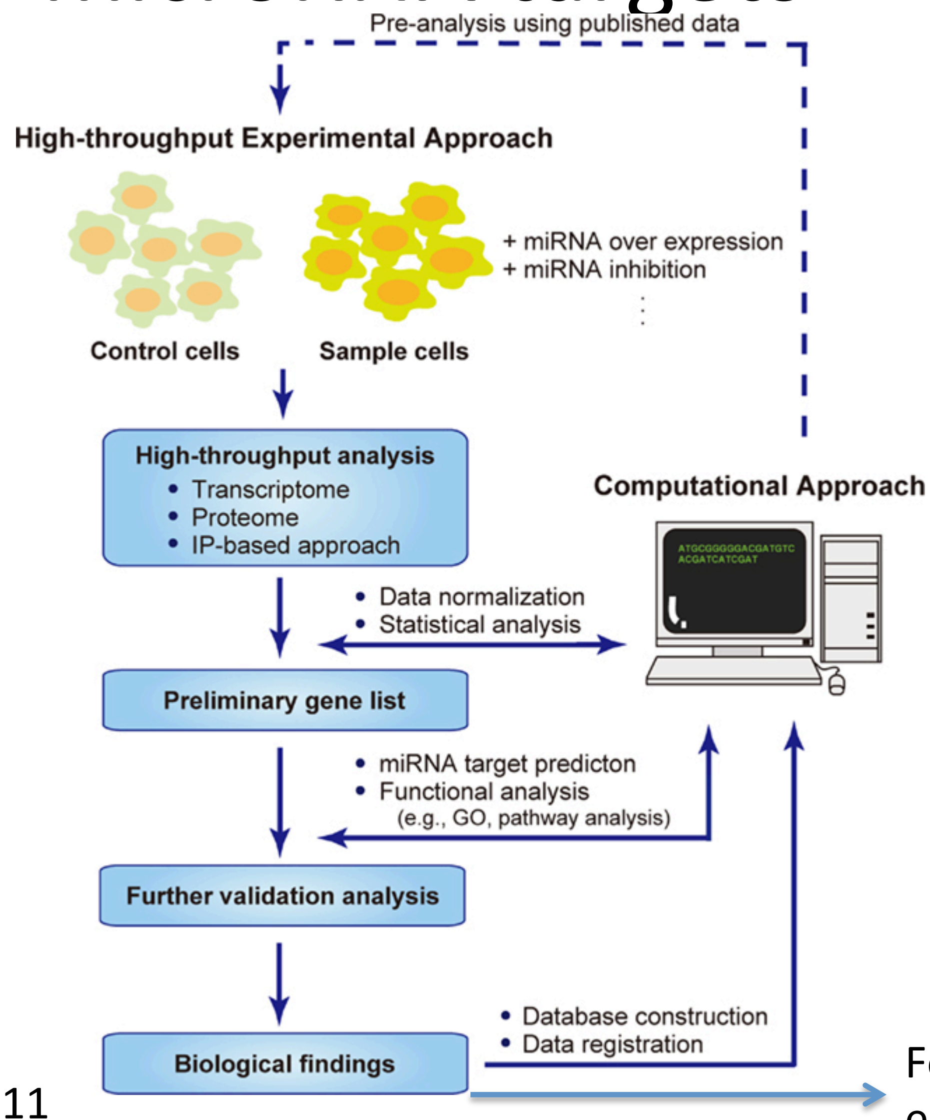


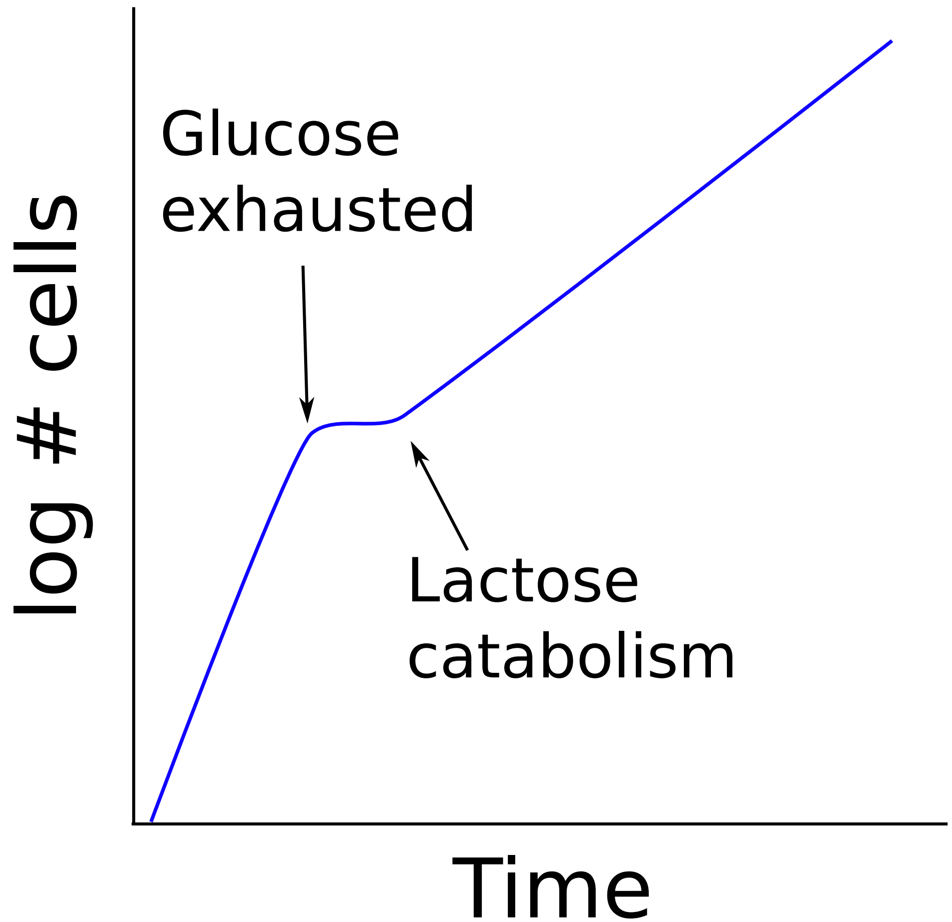
Watanabe and Kanai,
Front. Genet., 23 June 2011

Follow-up experiments

Organizing principles of biological networks

The lac operon, viewed four ways

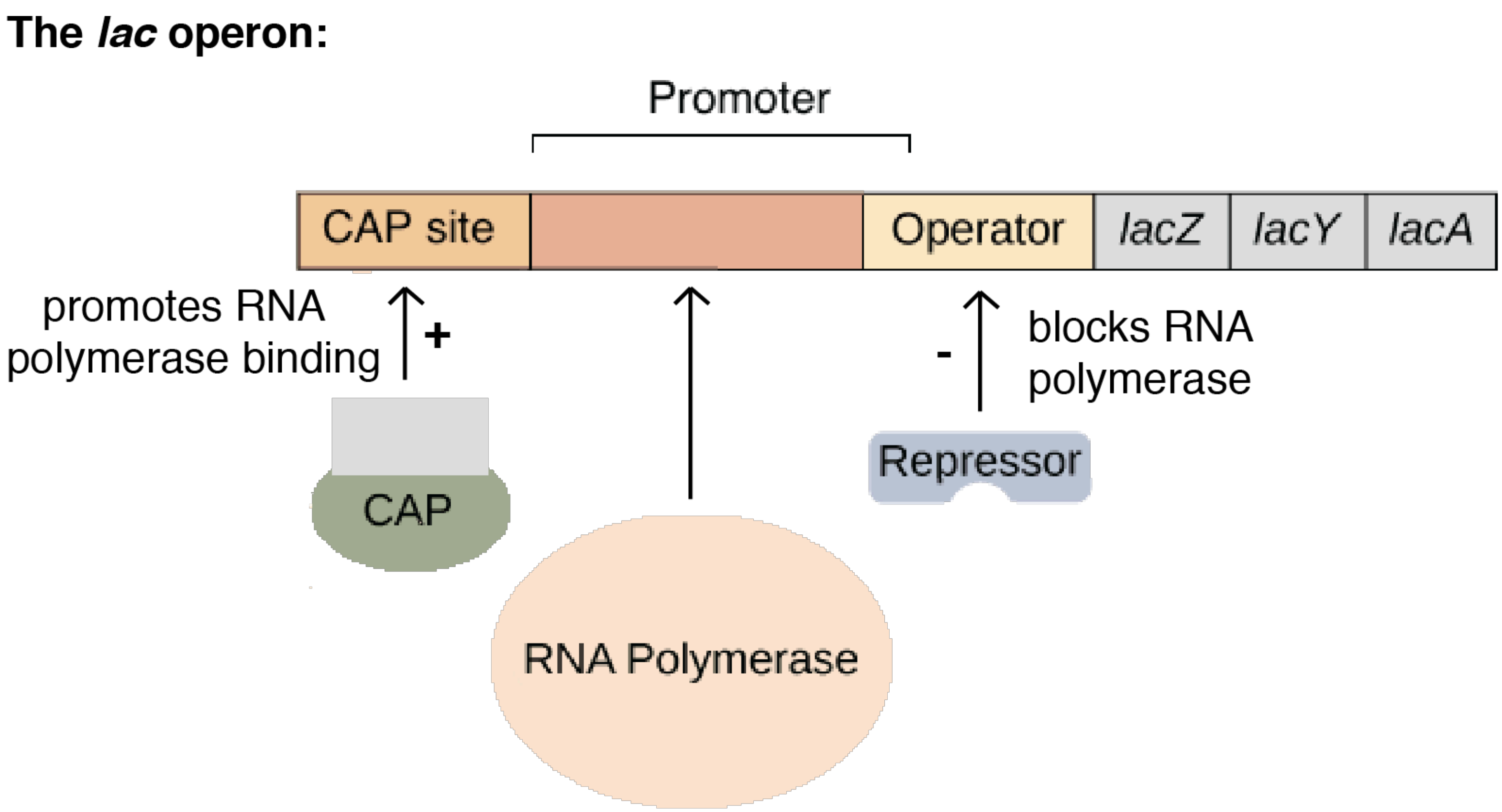
The lac operon, viewed four ways



The lac operon, viewed four ways

Genetics

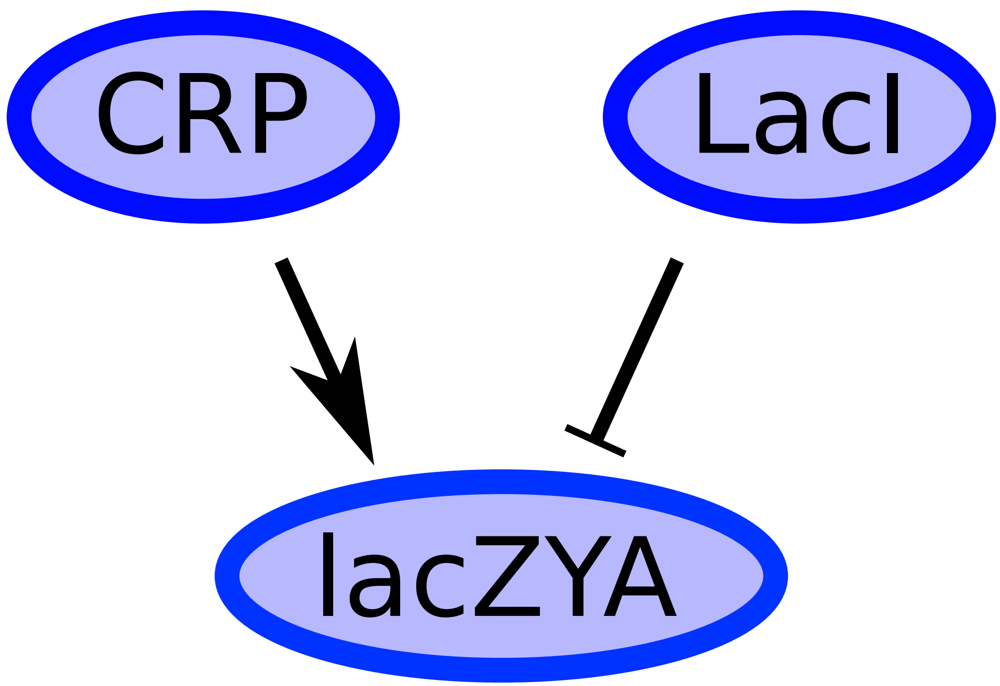
The lac operon, viewed four ways



Molecular biology

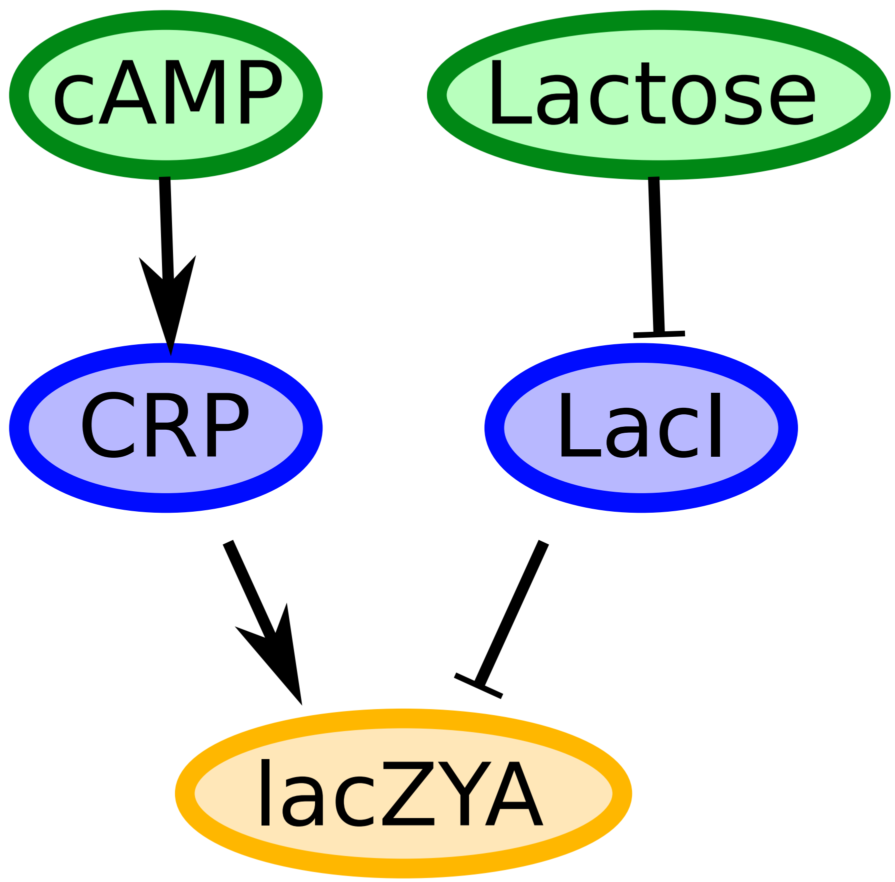
(Image from Khan Academy)

The lac operon, viewed four ways



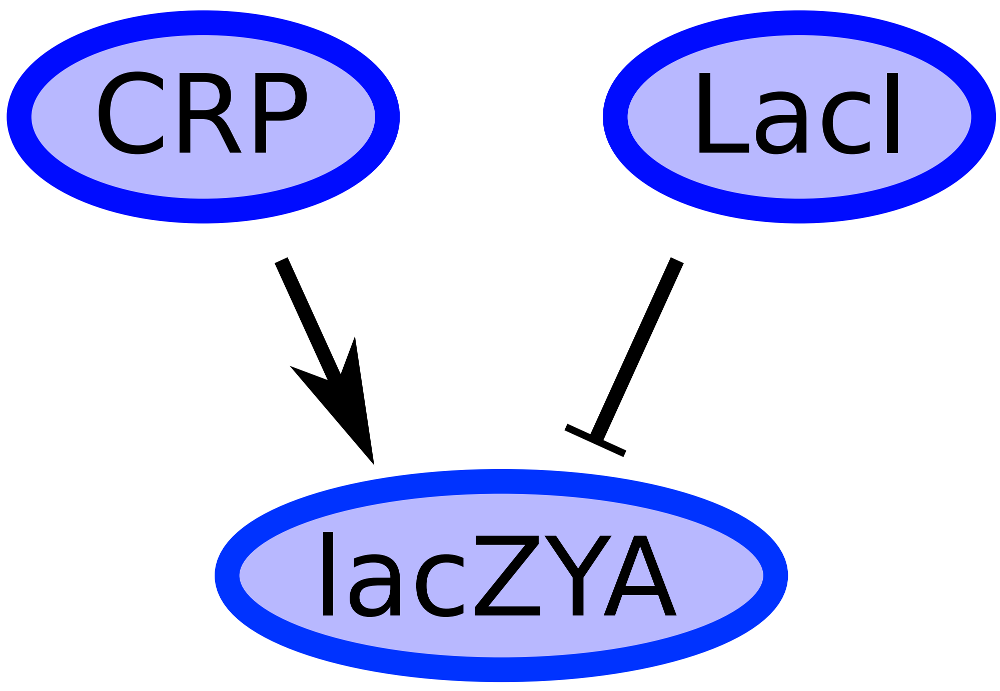
Graph theory

The lac operon, viewed four ways



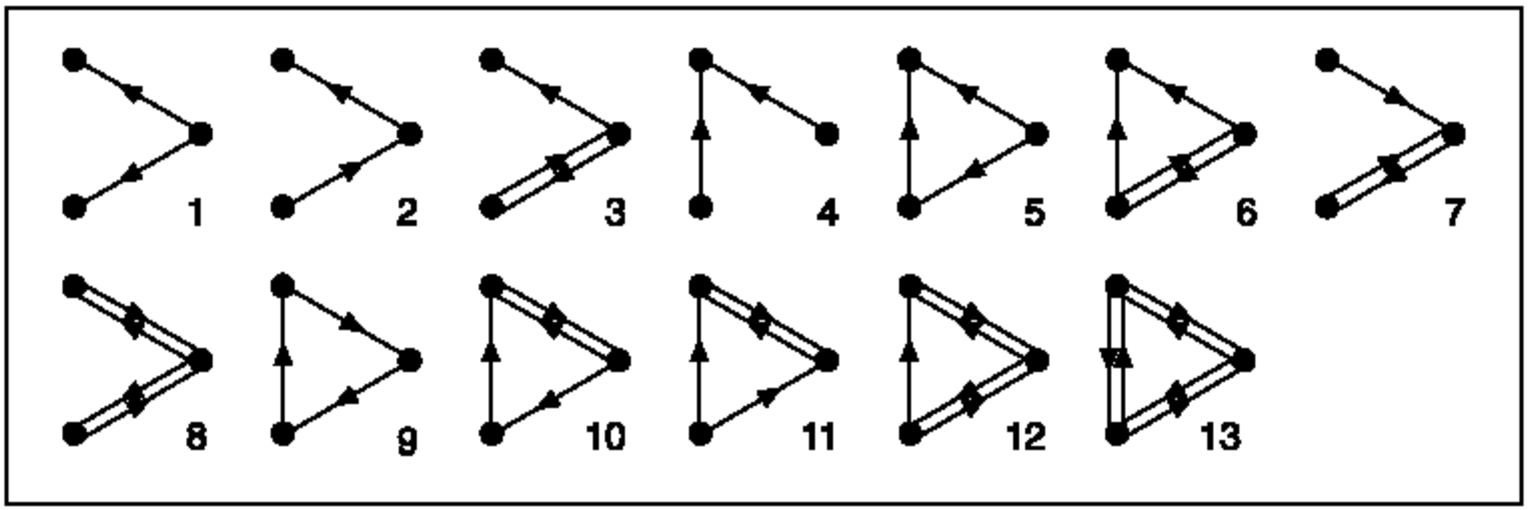
Graph theory

The lac operon, viewed four ways



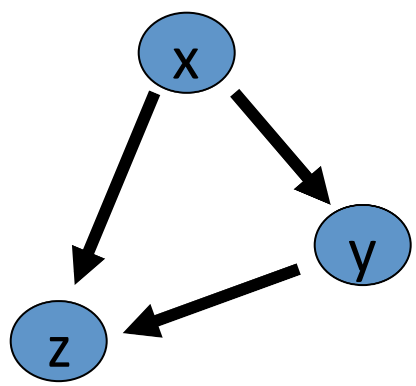
Graph theory

Network motifs yield specific biological functions

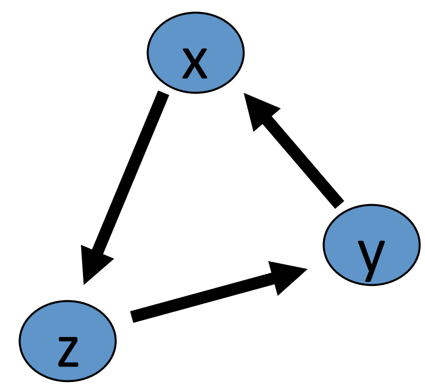


(U. Alon, *An Introduction to Systems Biology*)

Network motifs yield specific biological functions



Feed-forward loop



3-node feedback loop
(cycle)

(U. Alon, *An Introduction to Systems Biology*)

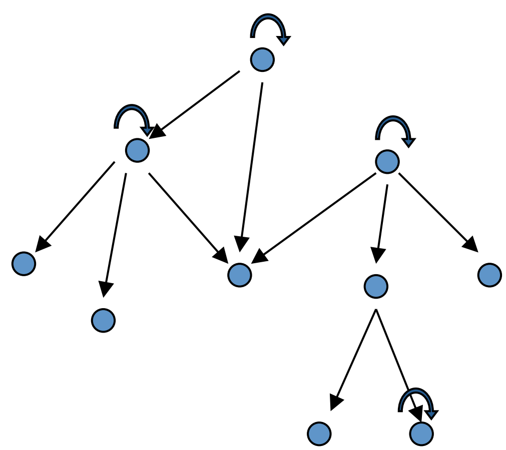
Network motifs yield specific biological functions

How do we find over-represented network motifs?

Network motifs yield specific biological functions

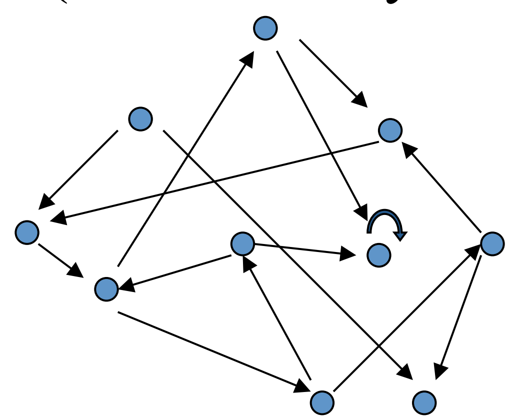
How do we find over-represented network motifs?

‘Real’ Network



N=10 nodes
E= 14 edges
Es=4 self-edges

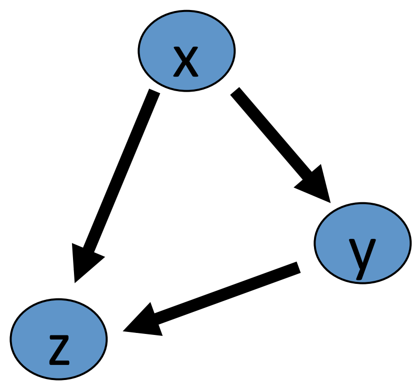
Randomized network
(Erdos – Renyi model)



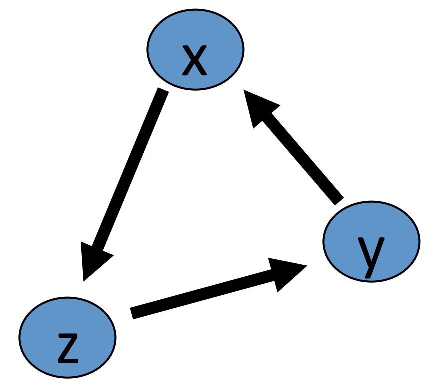
N=10 nodes
E= 14 edges
Es=1 self-edge

(U. Alon, *An Introduction to Systems Biology*)

Example: Comparison of two 3-node network motifs



Feed-forward loop



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(U. Alon, *An Introduction to Systems Biology*)

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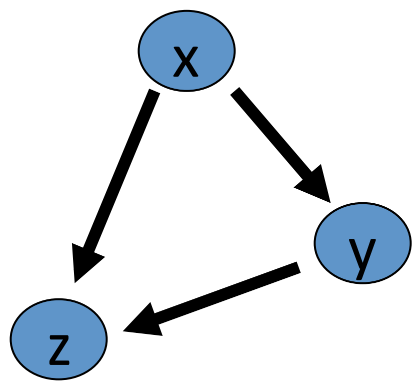
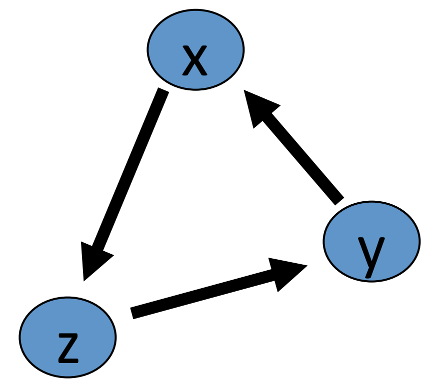


Feed-forward loop



3-node feedback loop (cycle)

	Feed-forward loop	3-node Feedback loop
E. Coli	42	0
Random network	1.7 +/- 1.3	0.6 +/- 0.8
Degree-preserving random network	7 +/- 5	0.2 +/- 0.6

(U. Alon, *An Introduction to Systems Biology*)

Different feed-forward loops implement distinct functions

(Mangan *et al.*, JMB 356:1073-1081, 2006)

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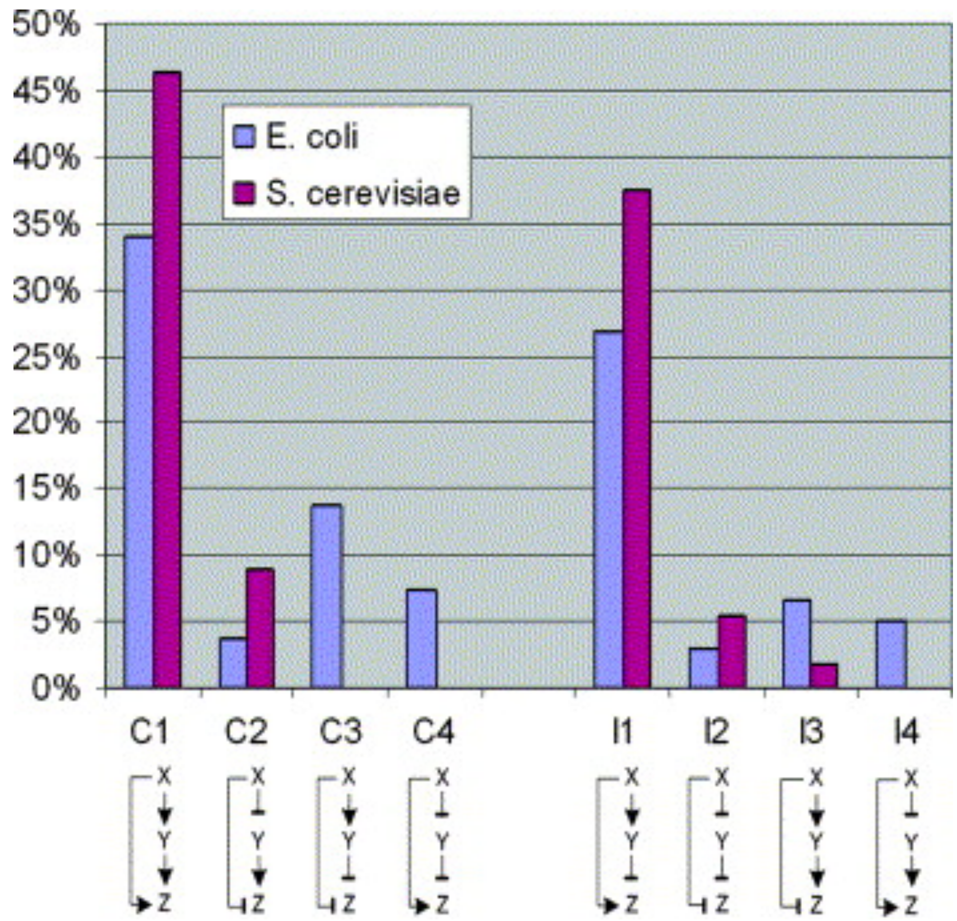

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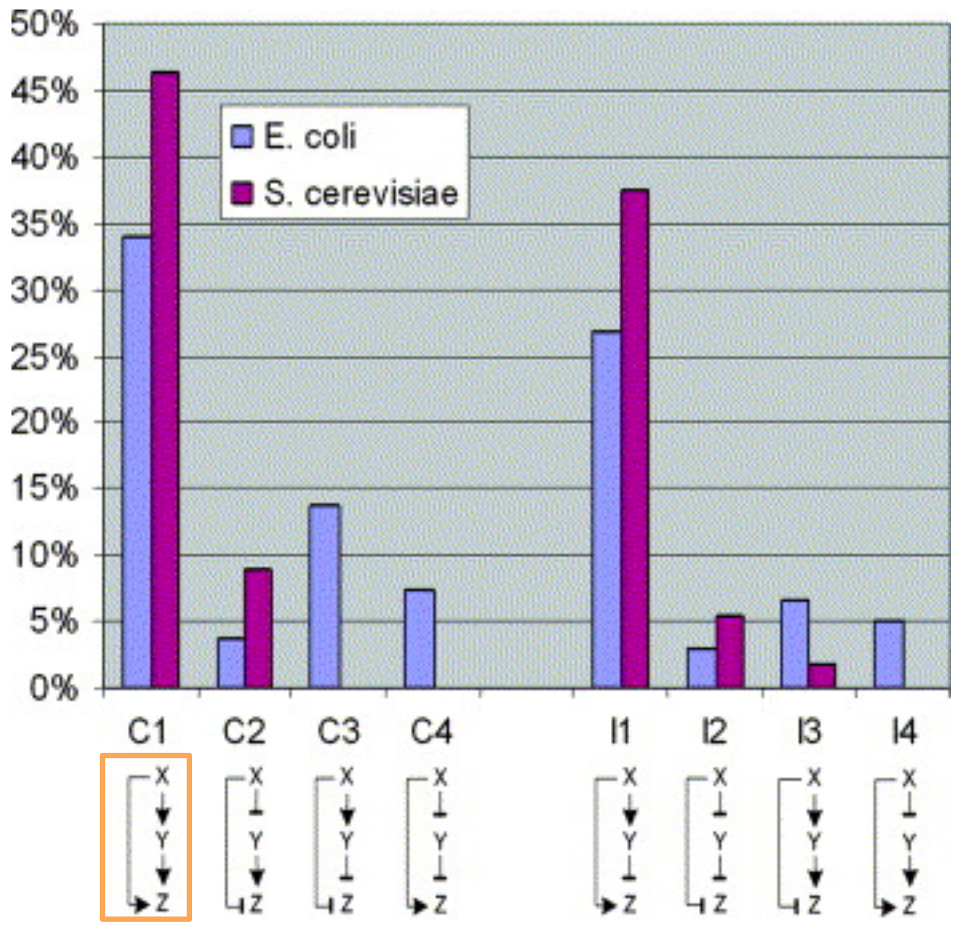

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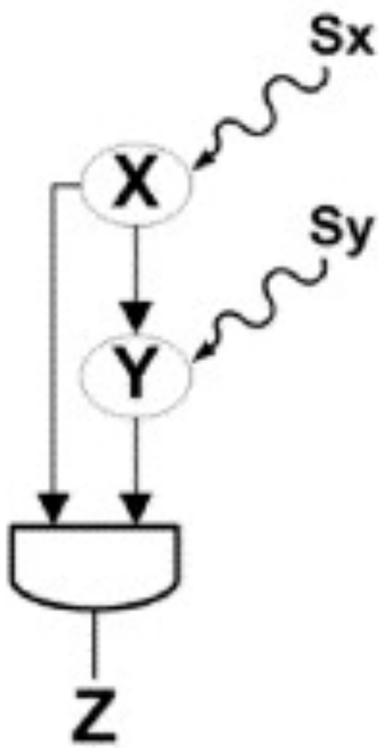
Type 1 coherent FFLs implement delays



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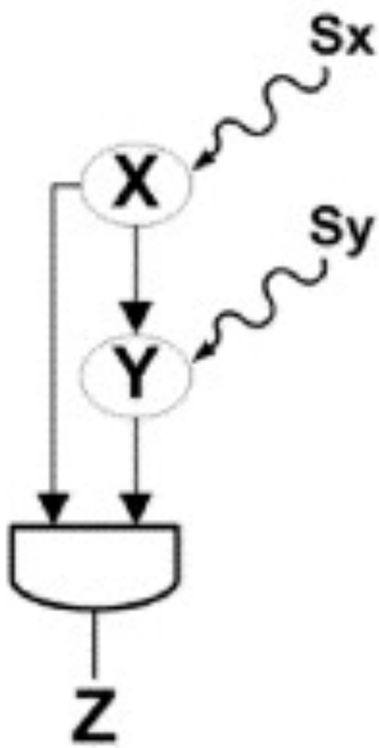

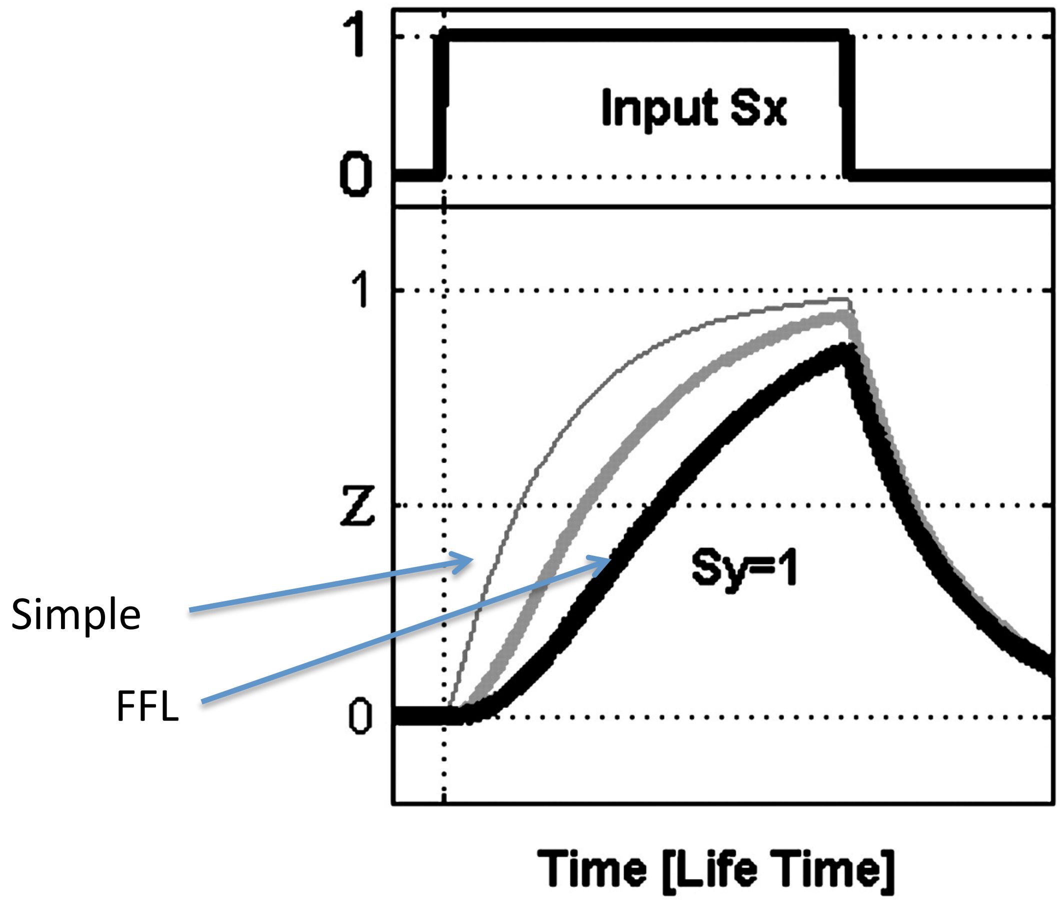

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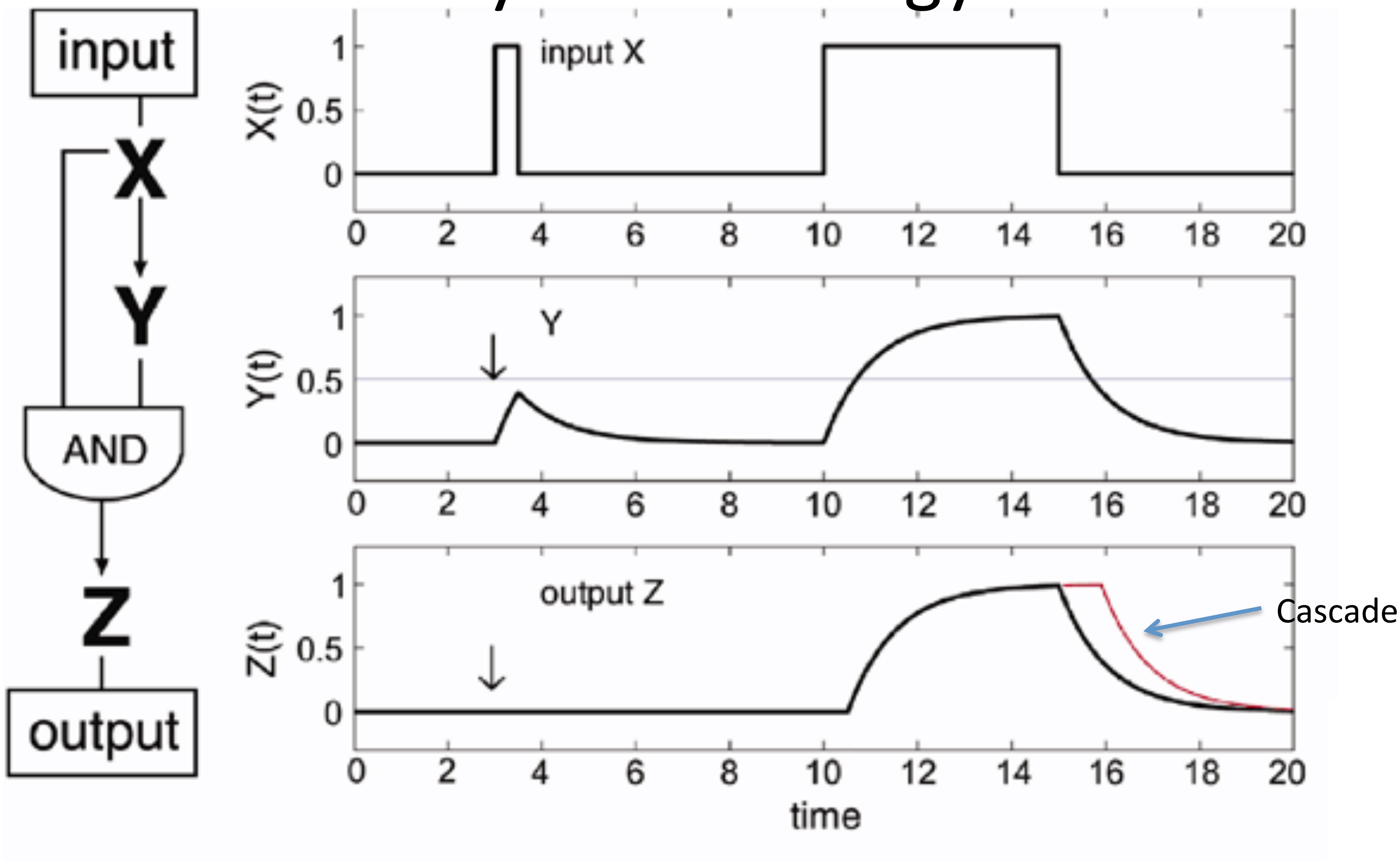
An aside: Numerical models in systems biology



(Shen-Orr *et al.*, Nat. Gen. 2002)

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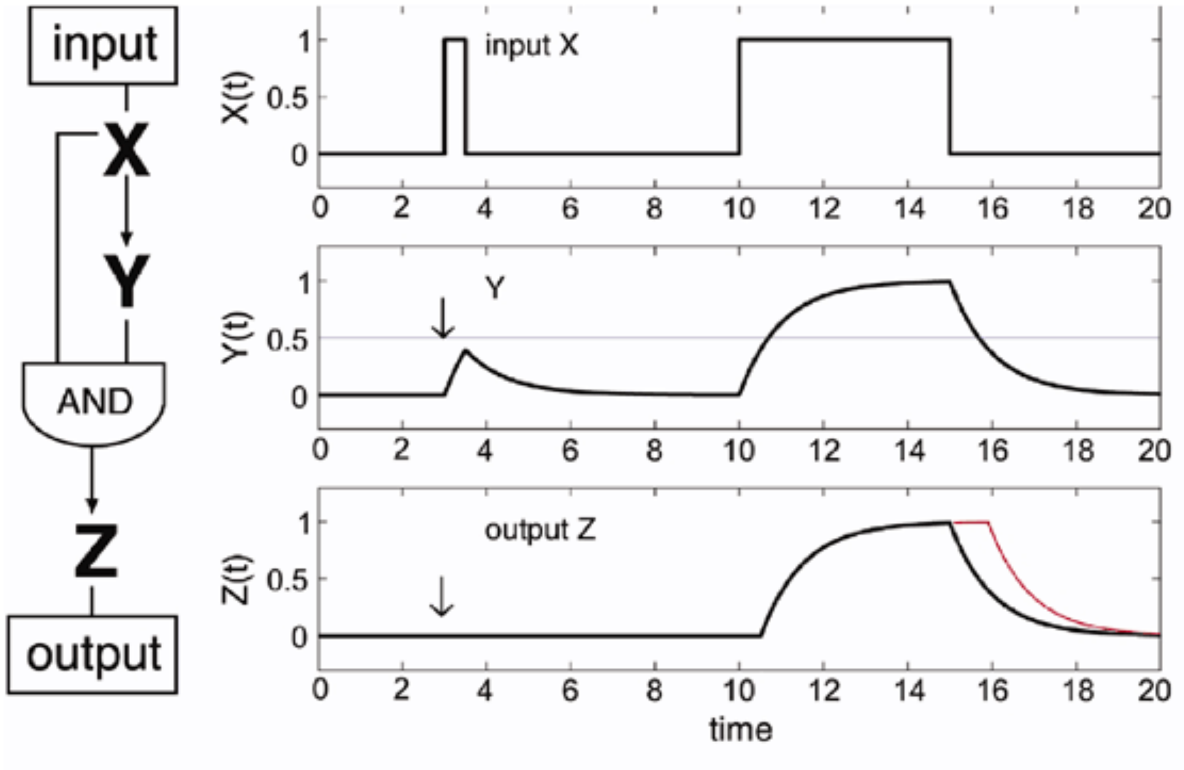

$$\frac{dY}{dt} = F(X, T_y) - \alpha Y$$

(Shen-Orr *et al.*, Nat. Gen. 2002)

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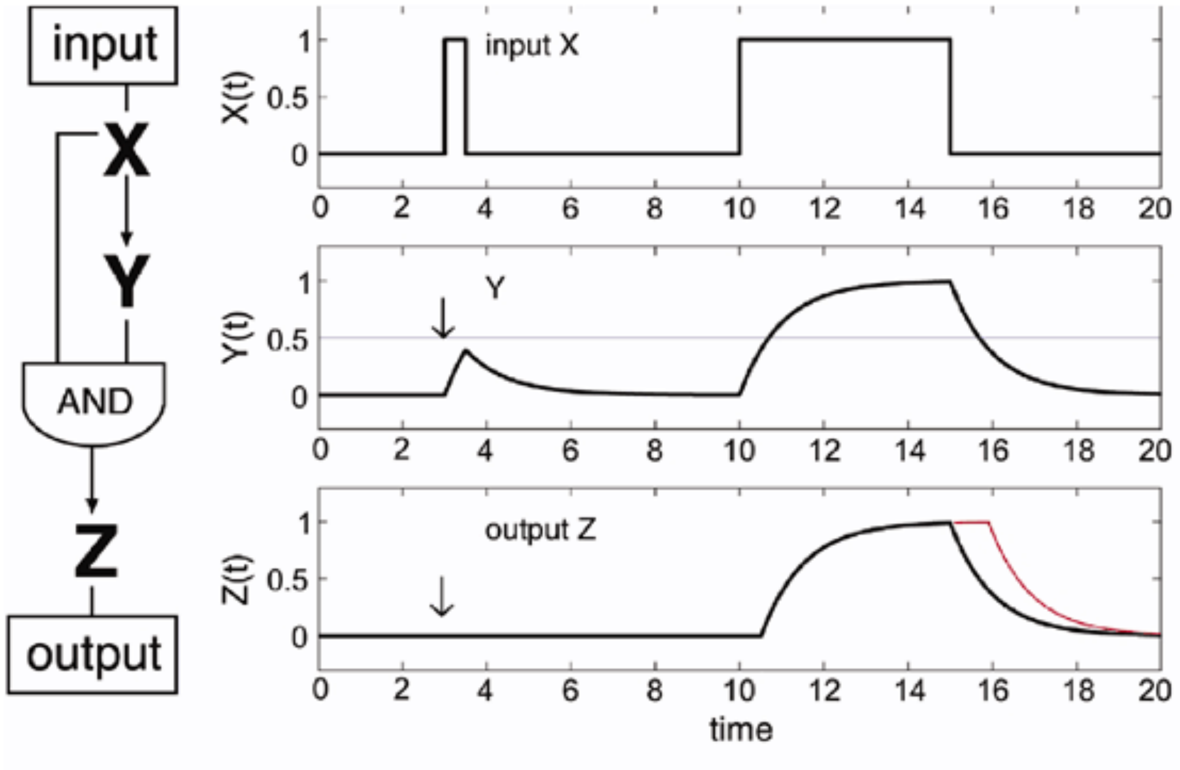


Rate of change in [Y]

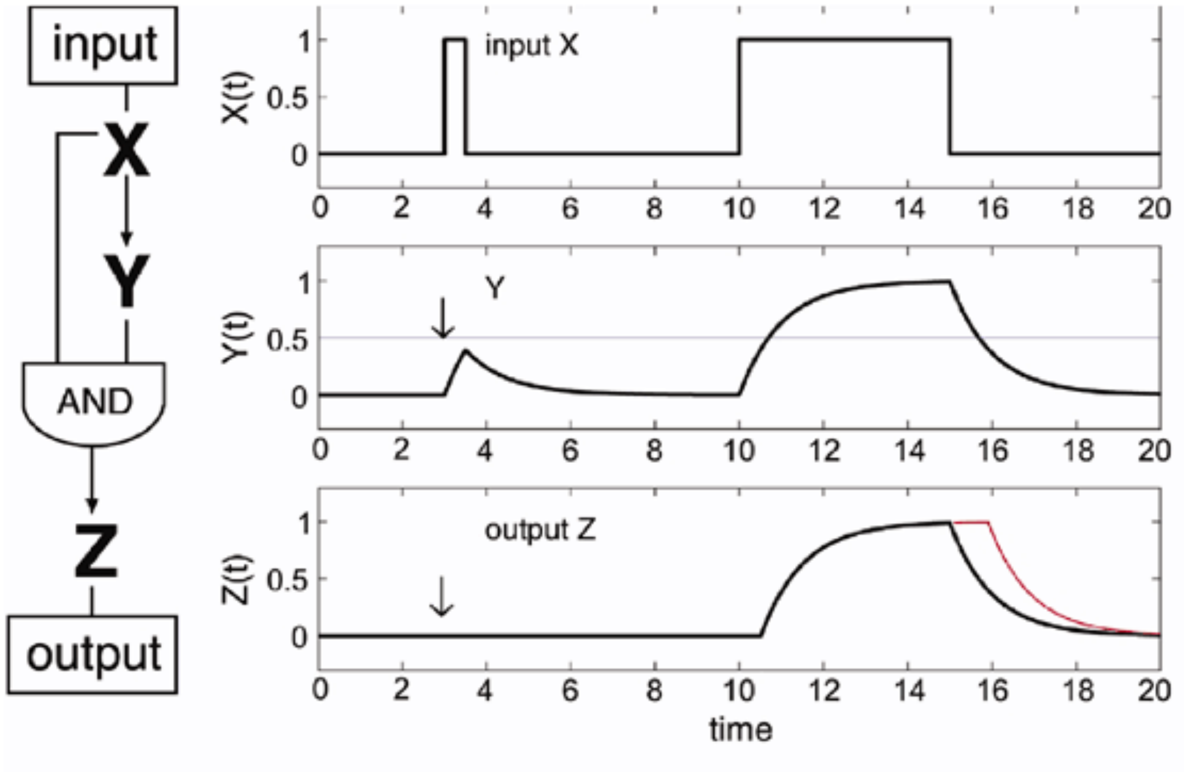
$$\frac{dY}{dt} = F(X, T_y) - \alpha Y$$

Degradation rate of Y

Threshold on X value

(Shen-Orr *et al.*, Nat. Gen. 2002)

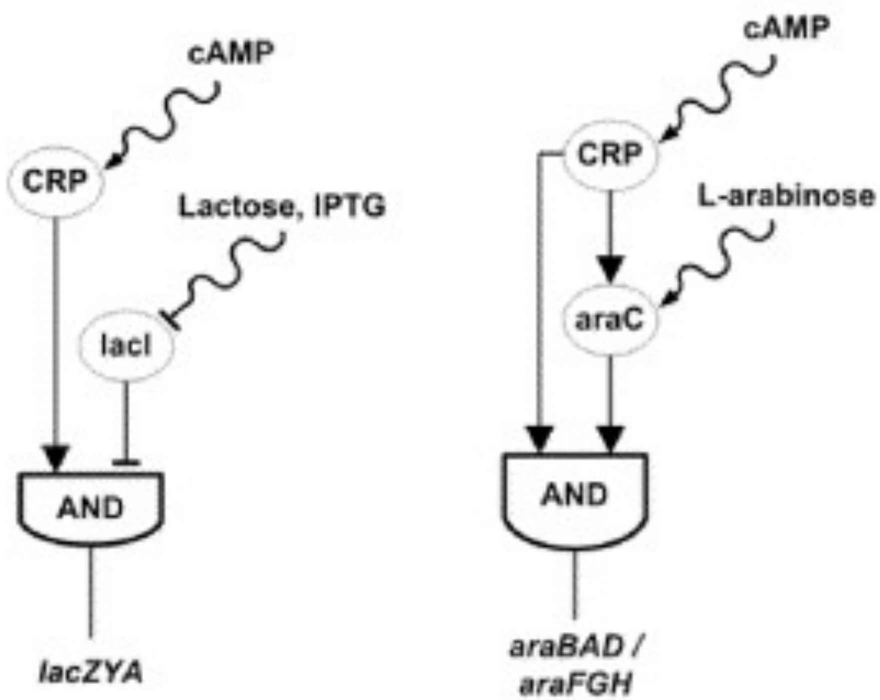
An aside: Numerical models in systems biology



$$\frac{dY}{dt} = F(X, T_y) - \alpha Y$$
$$\frac{dZ}{dt} = F(X, T_y) F(Y, T_z) - \alpha Z$$

(Shen-Orr *et al.*, Nat. Gen. 2002)

Type 1 coherent FFLs
in a real regulatory network



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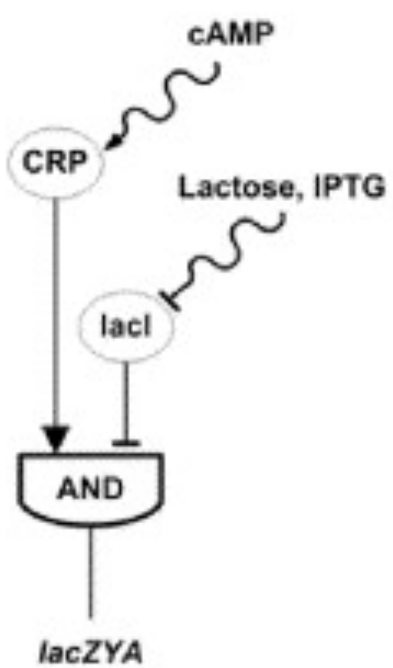

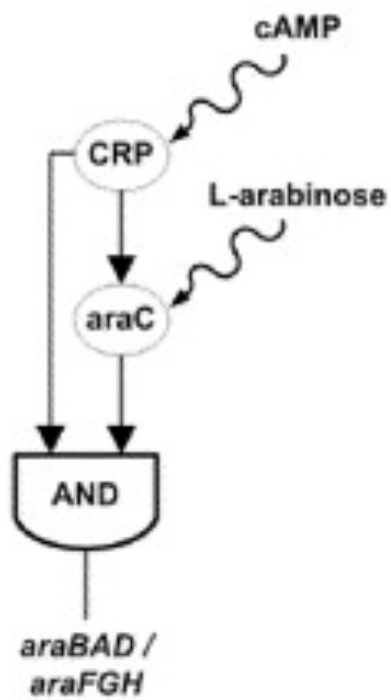

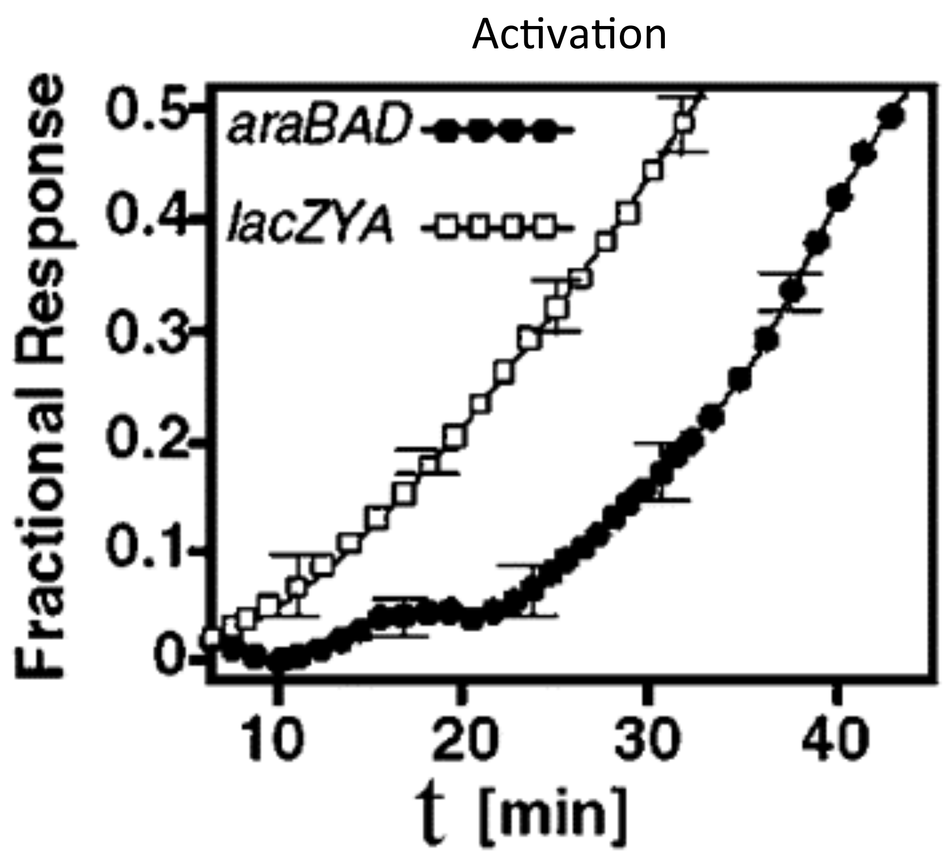

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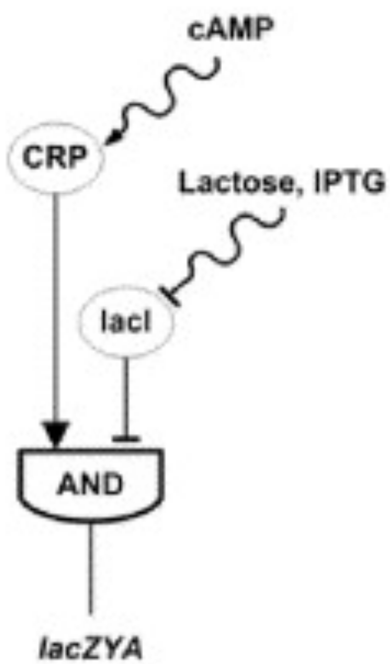
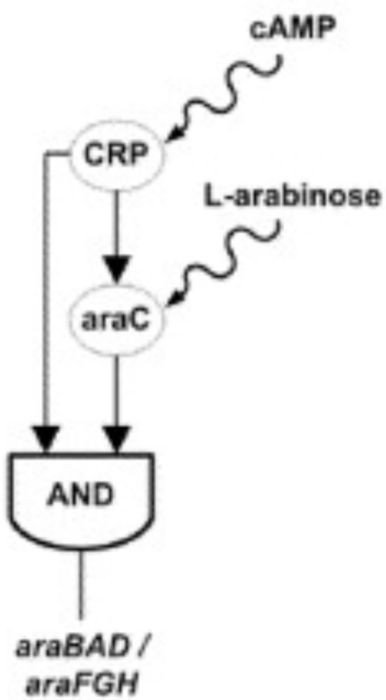
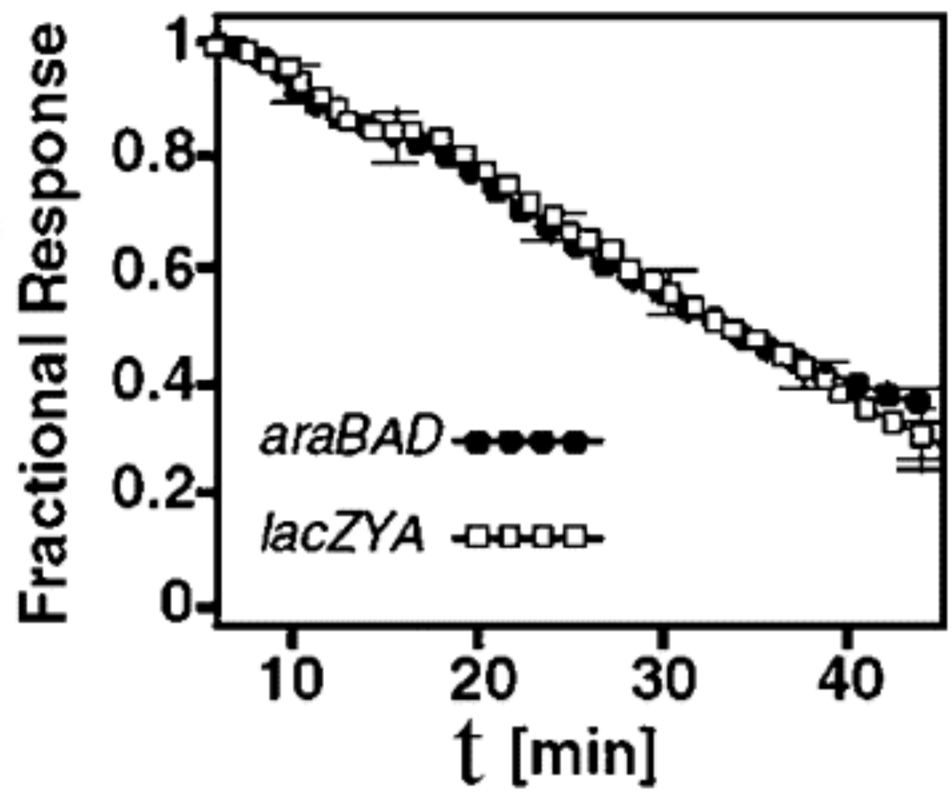




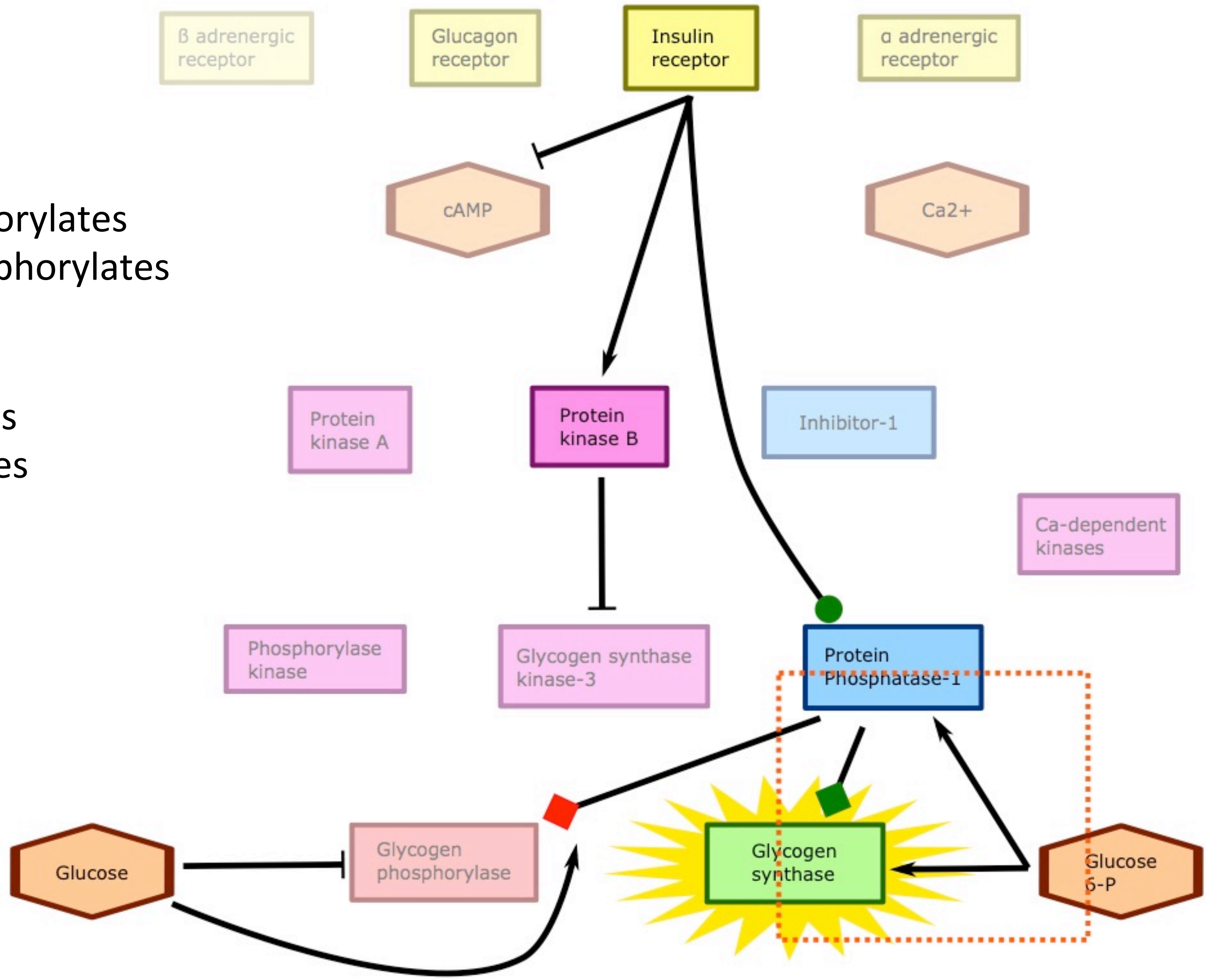
De-activation



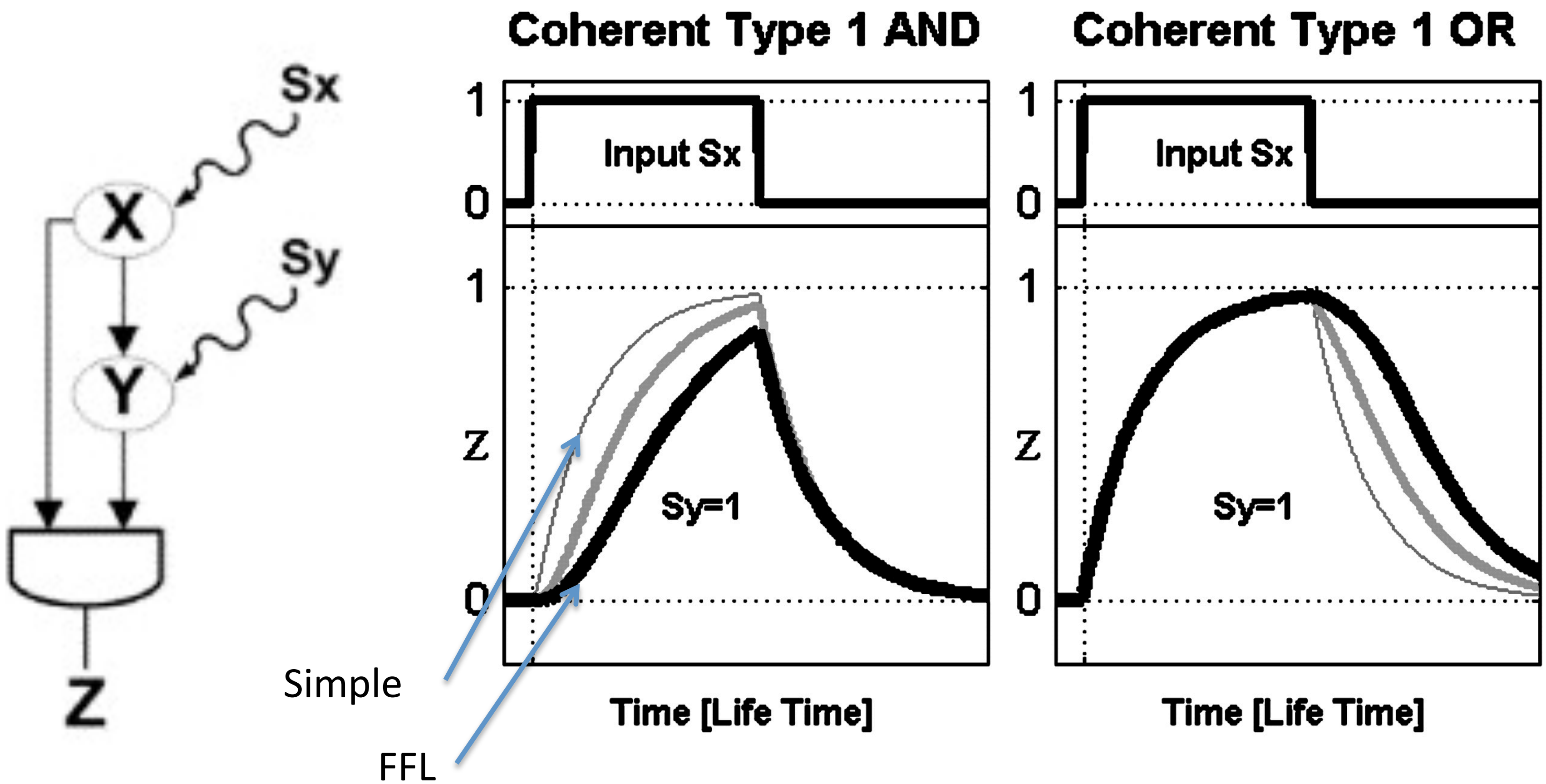
(Mangan *et al.*, JMB 2006)

FFLs in regulation of glycogen synthesis

: phosphorylates
: dephosphorylates
Activates
Represses
: activates
: represses



Changing the logic at the promoter alters behavior



(Mangan and Alon, PNAS 2003)

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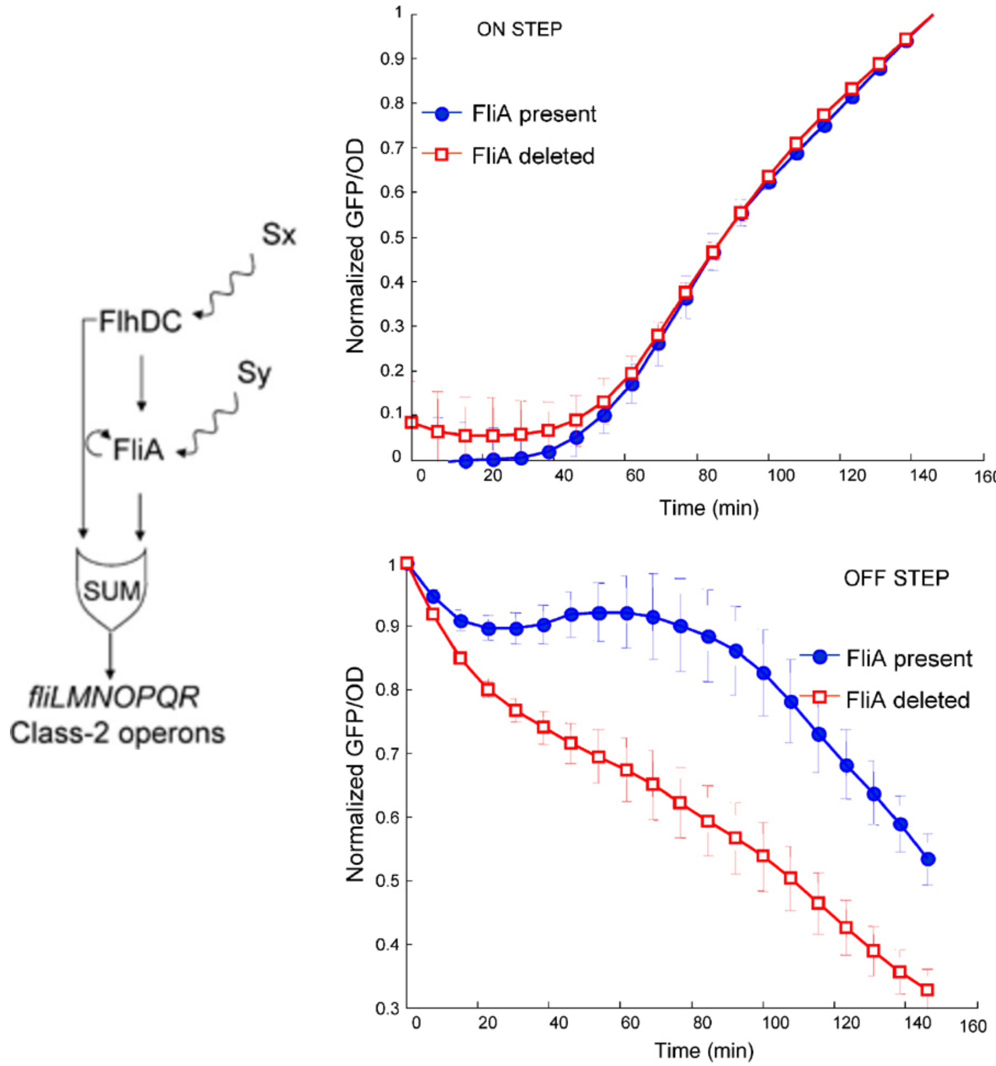
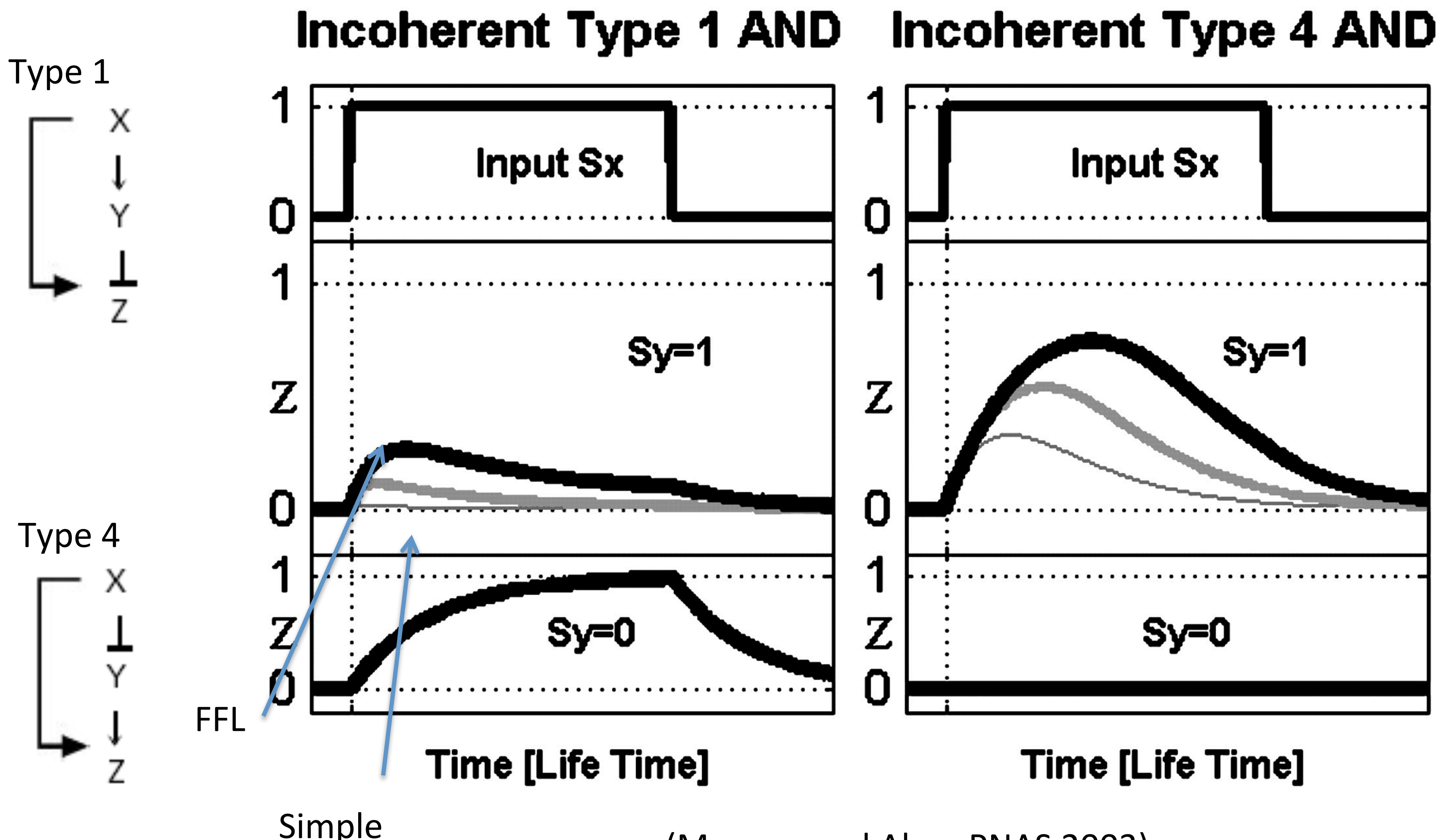


(Kalir *et al.*,
Mol. Sys. Bio. 2005)

Incoherent FFLs allow rapid response or transient bursts



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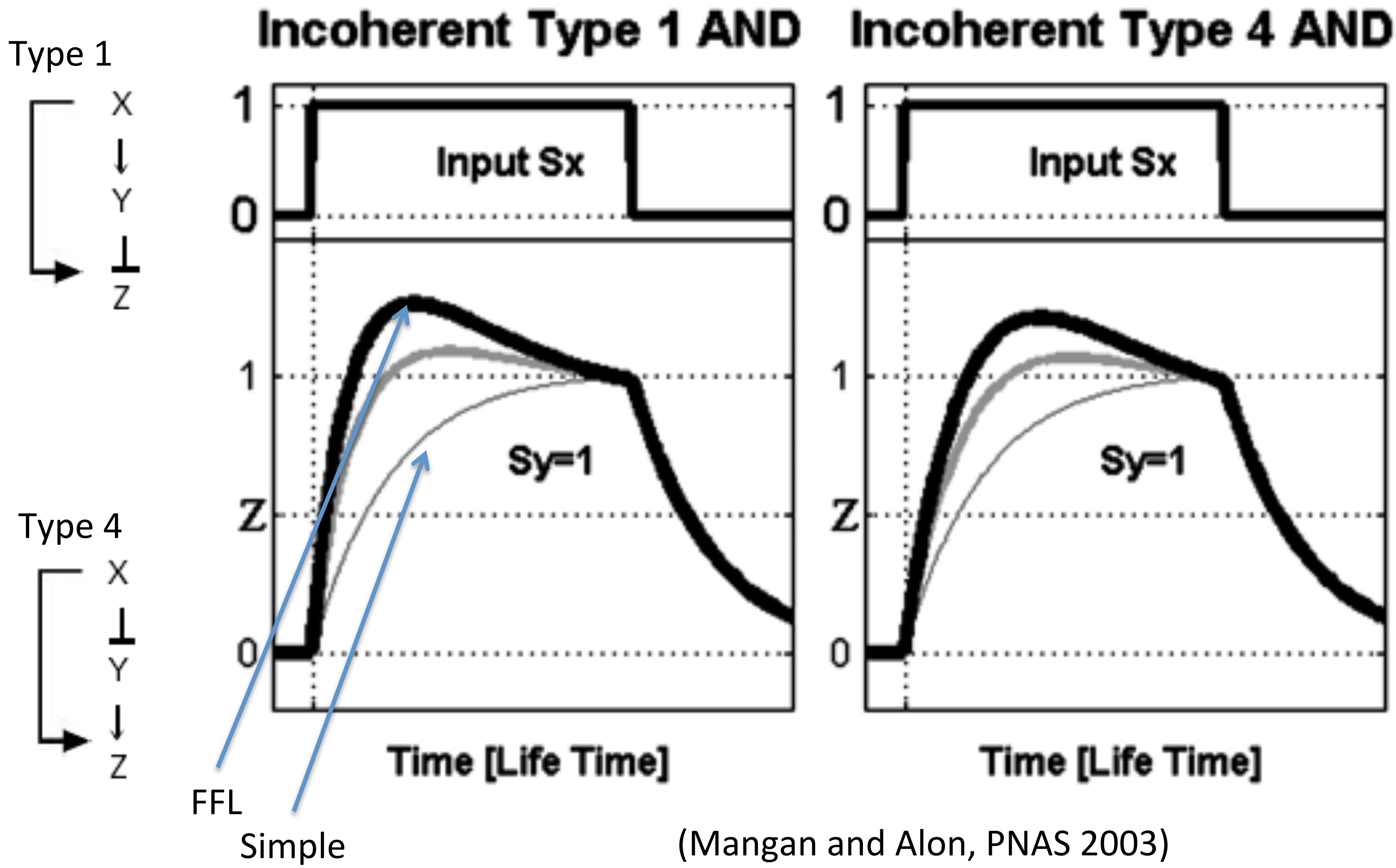
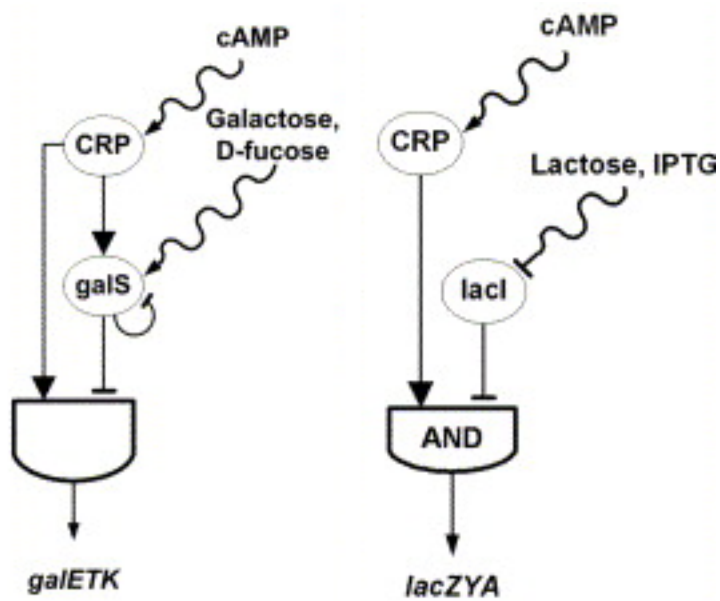
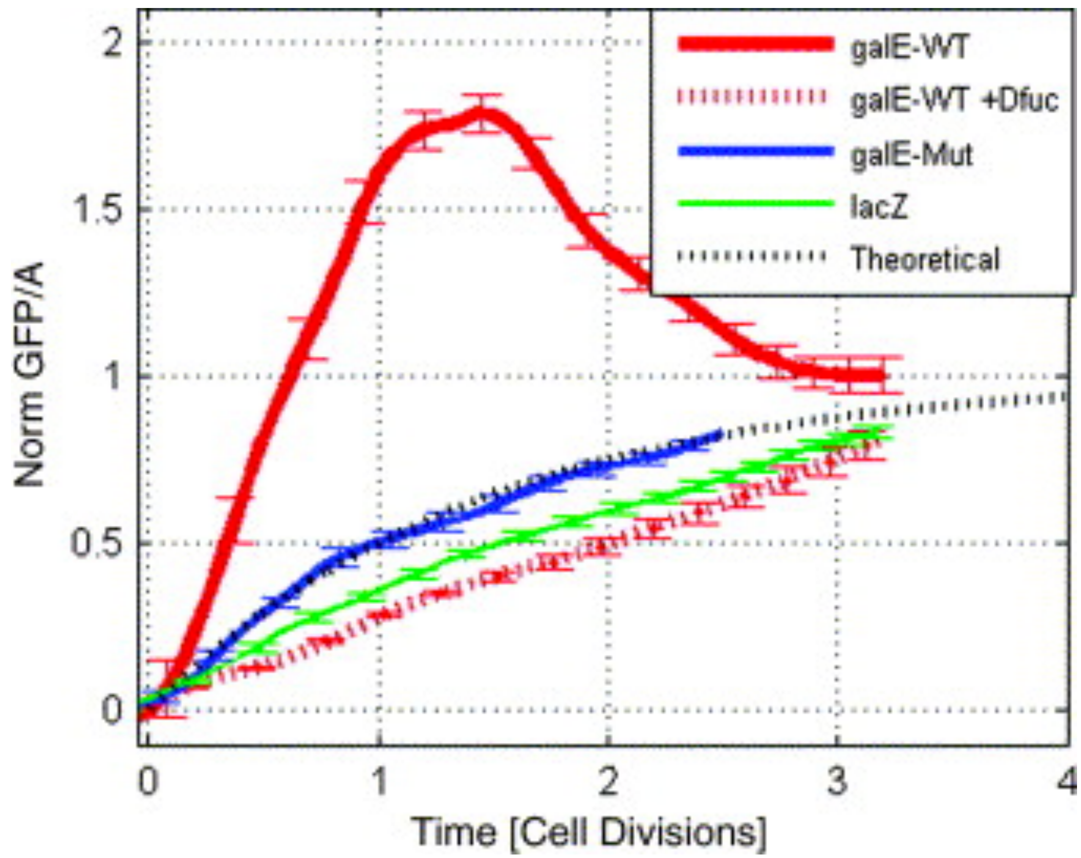


(Mangan and Alon, PNAS 2003)

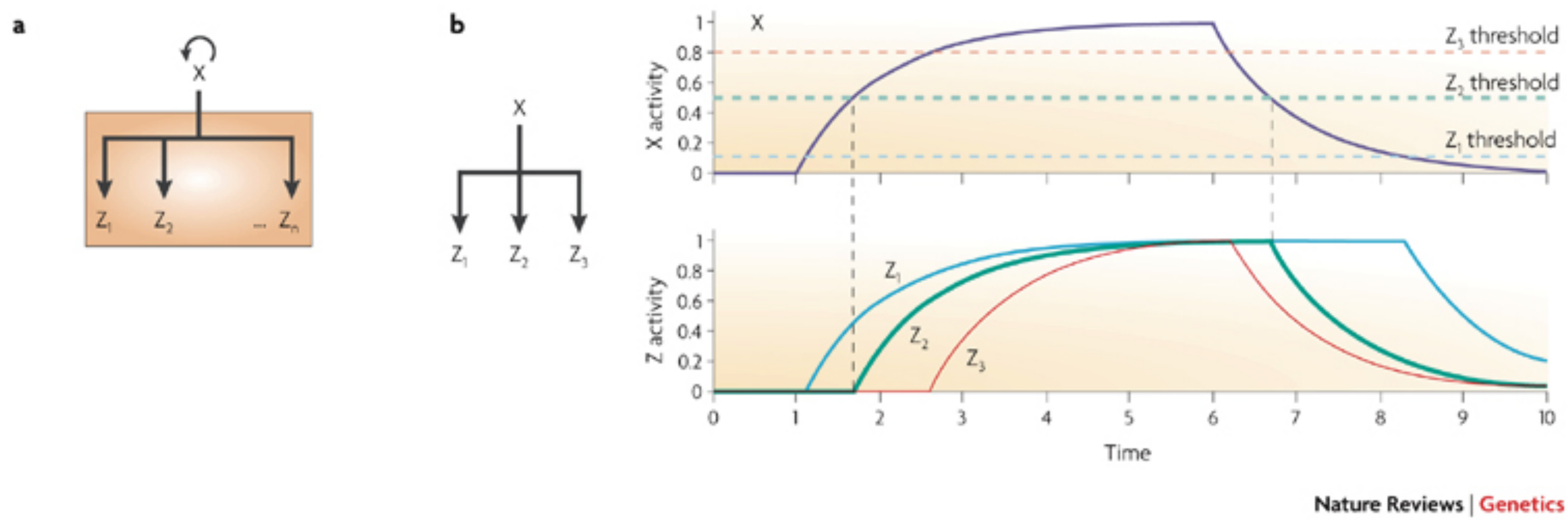
FFL-accelerated response in biological context





(Mangan *et al.*, JMB 2006)

Single-input modules (SIMs) allow coordination of large regulons



(Alon, Nat. Rev. Genet. 2007)

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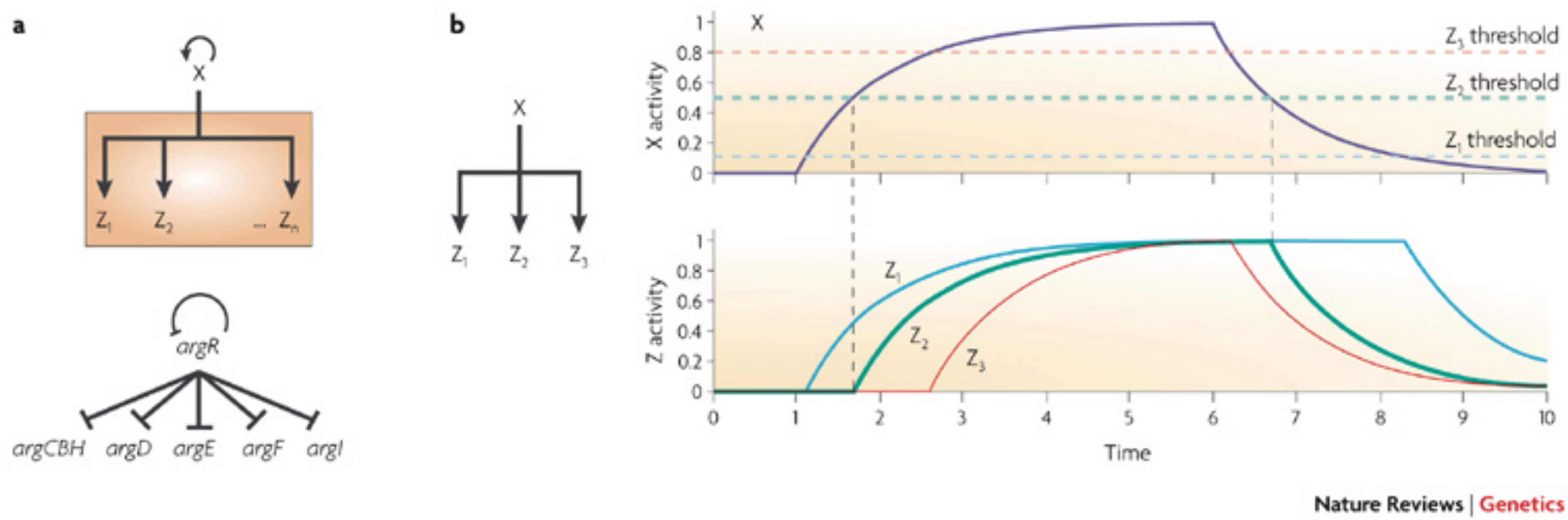

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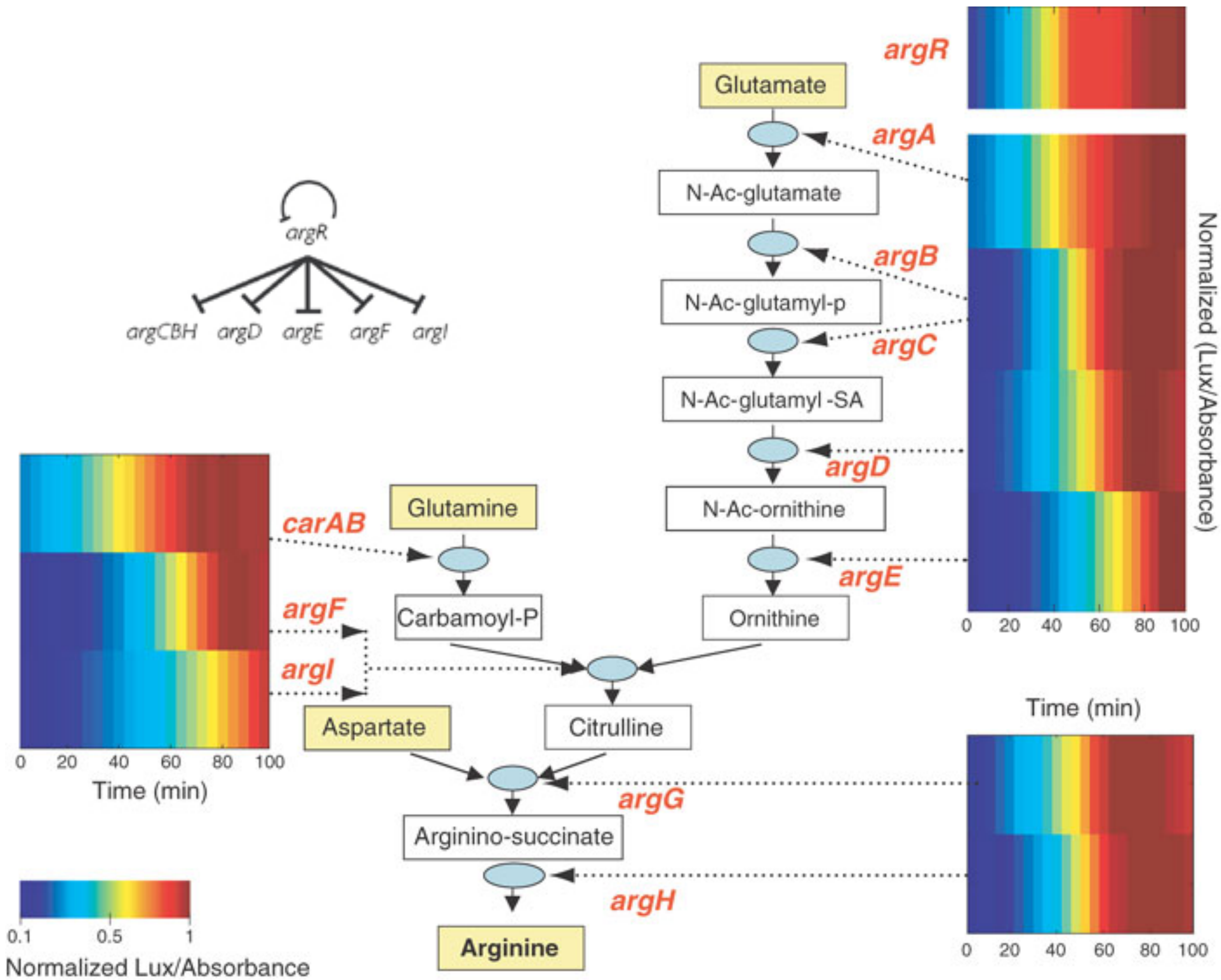
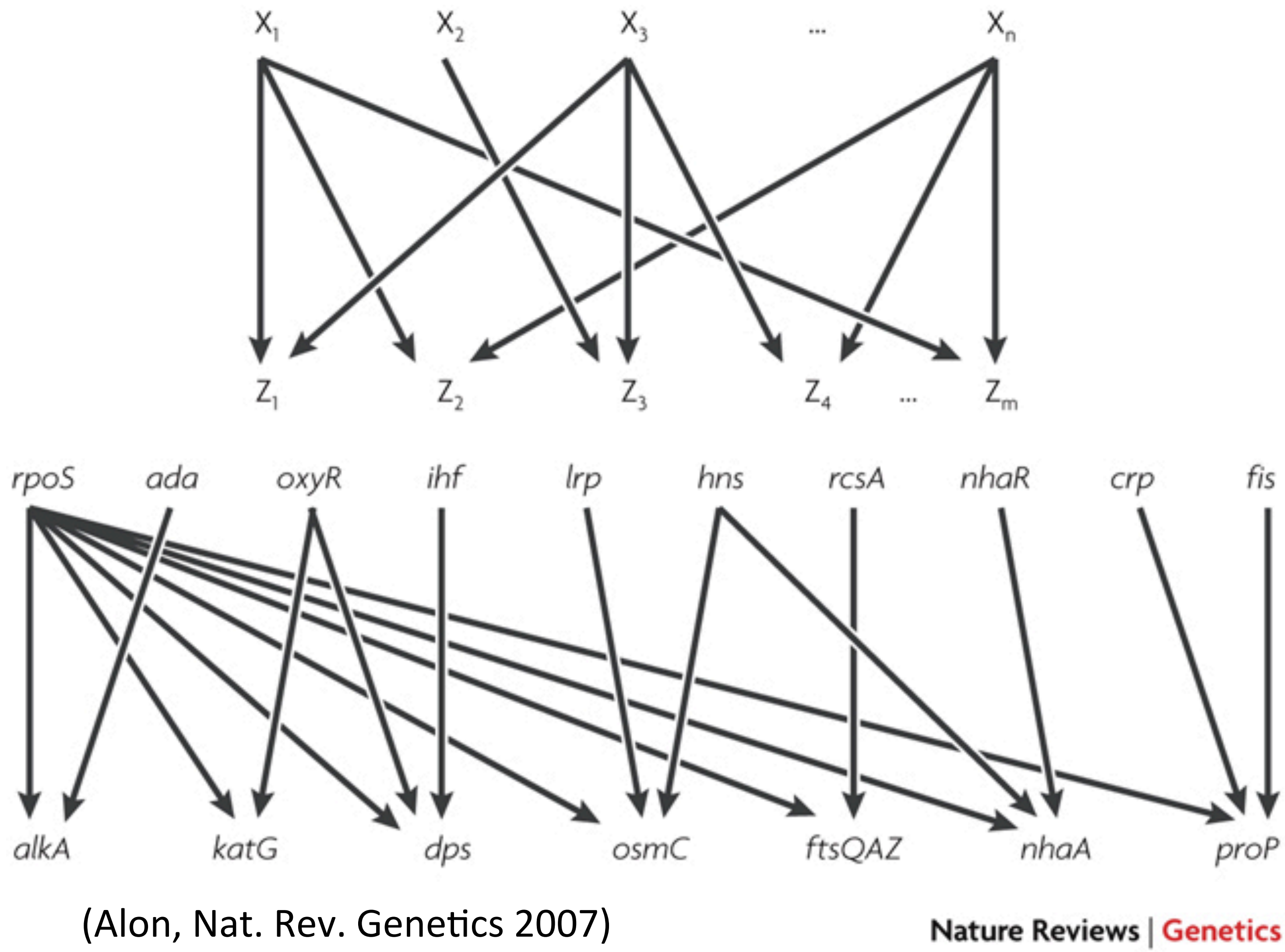


(Zaslaver *et al.*, Nat. Genet. 2004)

Dense overlapping regulons enable combinatorial control



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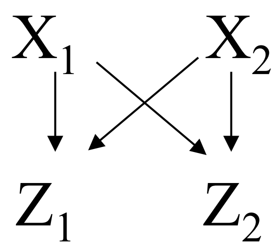
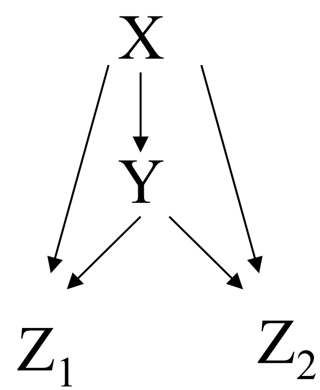


Bifan

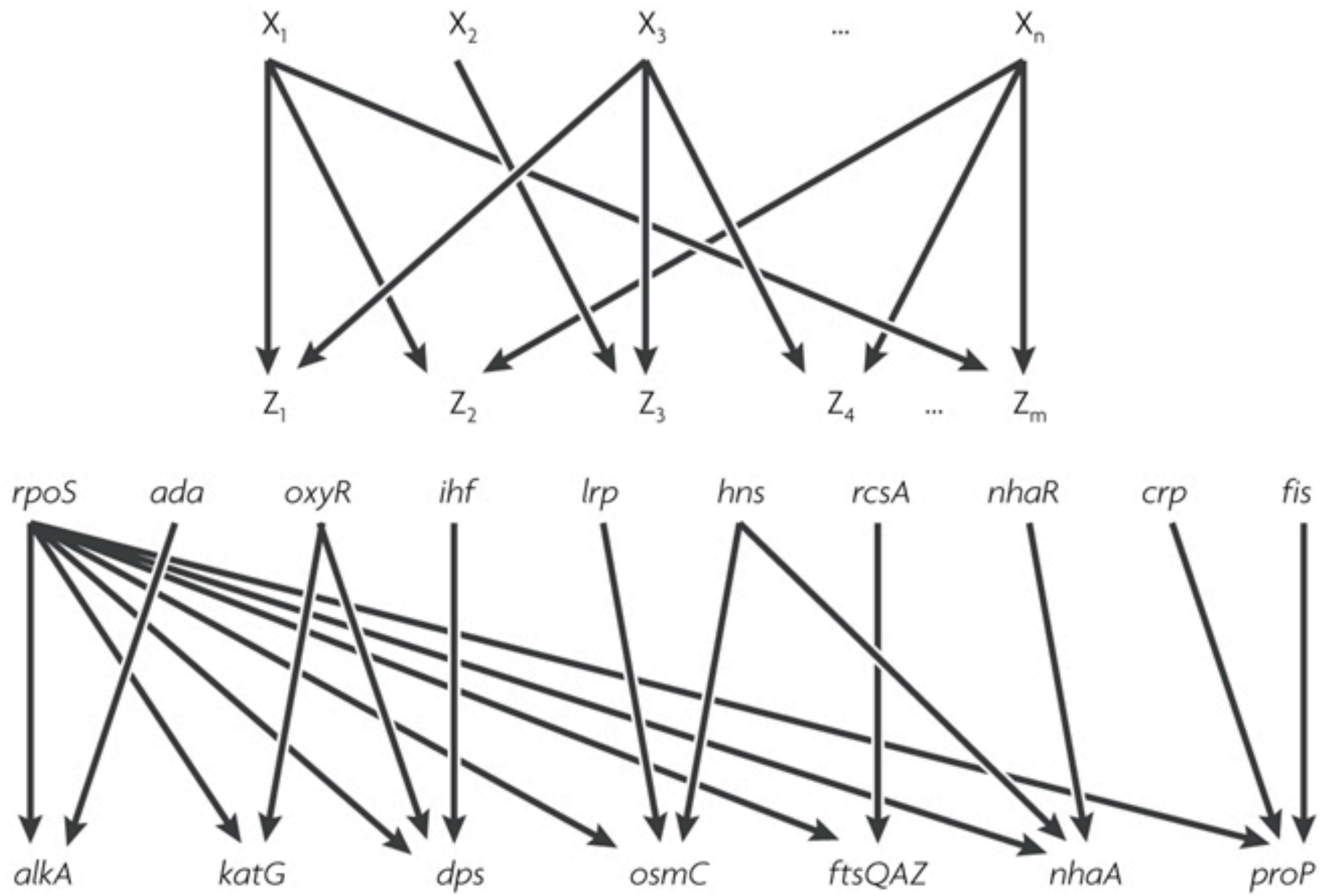


Two-output

Feed-forward loop

(U. Alon, *An Introduction to Systems Biology*)

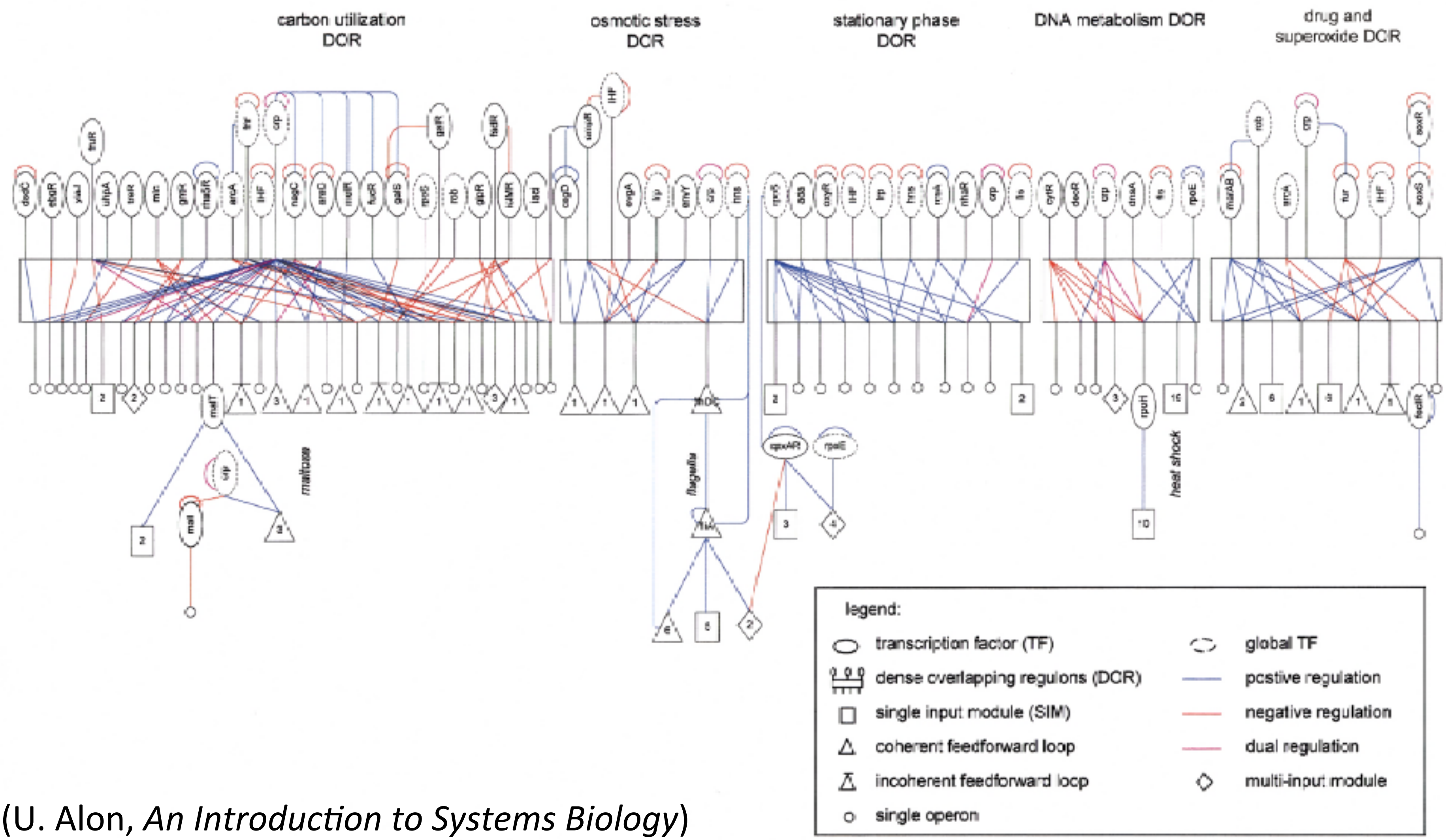
Dense overlapping regulons enable combinatorial control



(Alon, Nat. Rev. Genetics 2007)

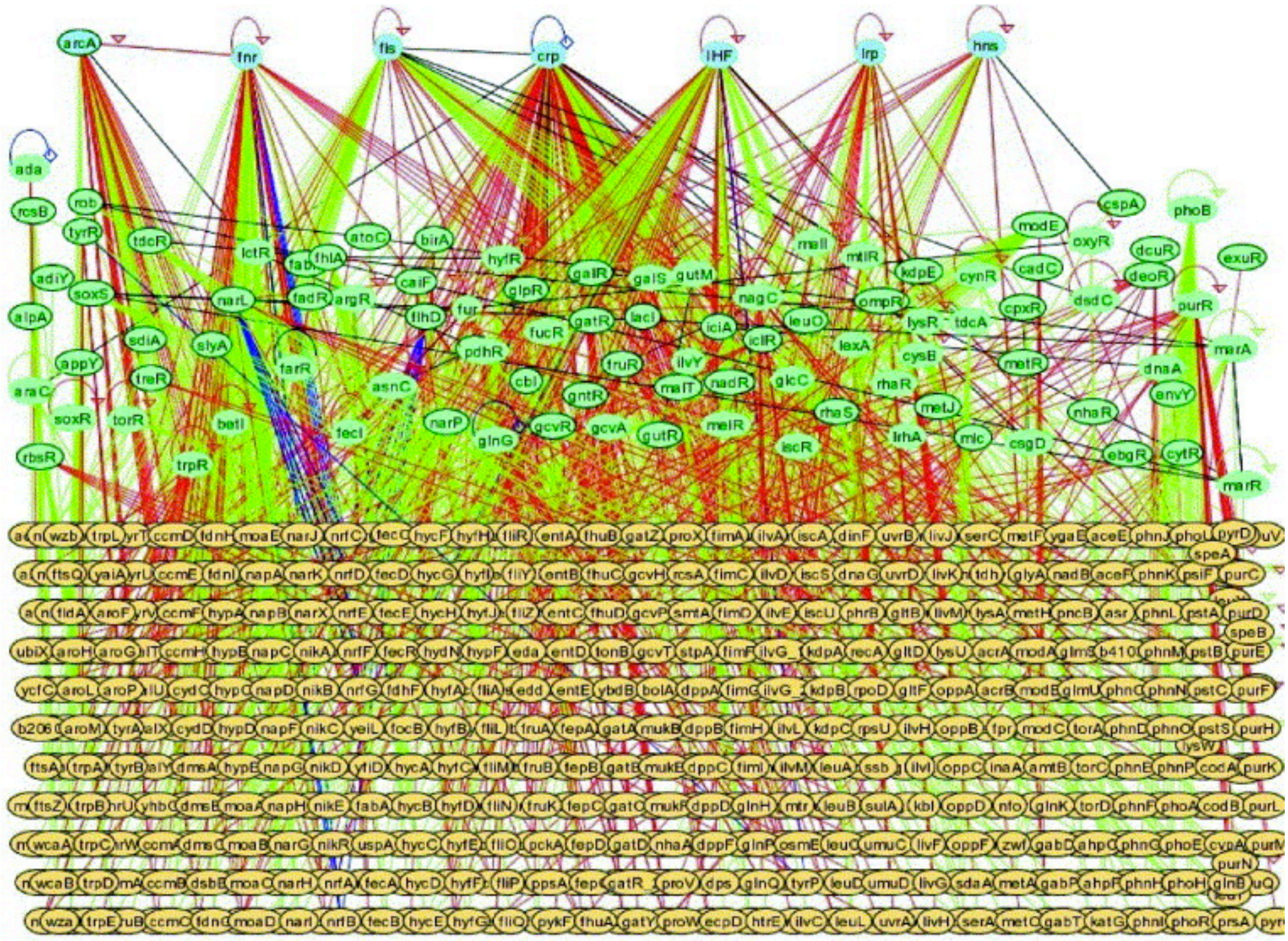
Nature Reviews | Genetics

Circuit diagram of the *E. coli* transcriptional regulatory network



(U. Alon, *An Introduction to Systems Biology*)

Standard display of the same network



(Martinez-Antonio and Collado-Vides, 2003)

Current Opinion in Microbiology

Network motifs in other biological networks

Sensory transcriptional regulatory networks:

- Coherent and incoherent FFLs
- Single-input module
- Dense overlapping regulons

Network motifs in other biological networks

Sensory transcriptional regulatory networks:

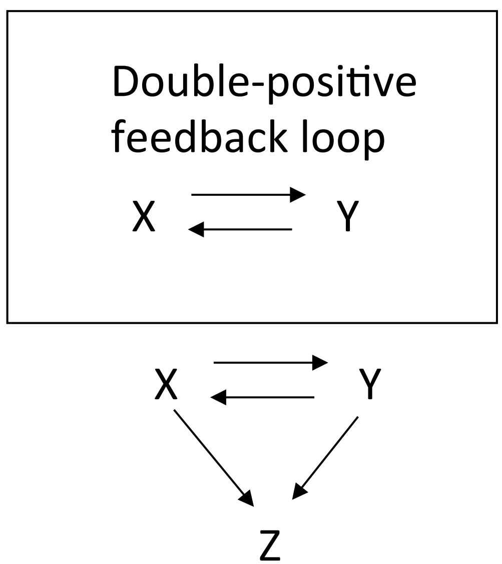
- Coherent and incoherent FFLs
- Single-input module
- Dense overlapping regulons

Additional motifs in other network types:

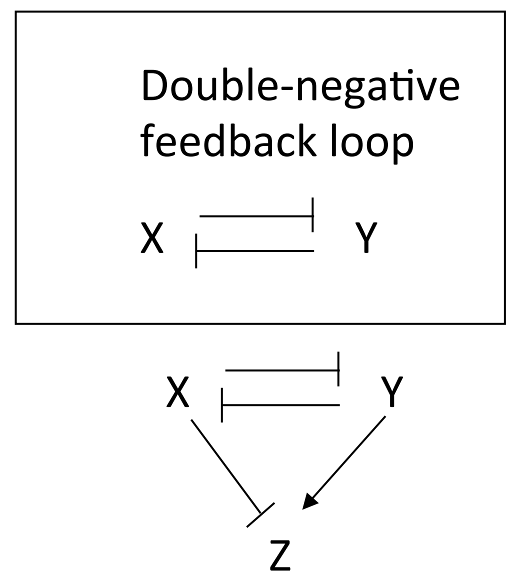
- Feedback loops
- Long signaling cascades
- Multi-input FFLs

Network motifs in other biological networks

Feedback loops



	X	Y	Z
Steady-State 1	ON	ON	ON
Steady-State 2	OFF	OFF	OFF

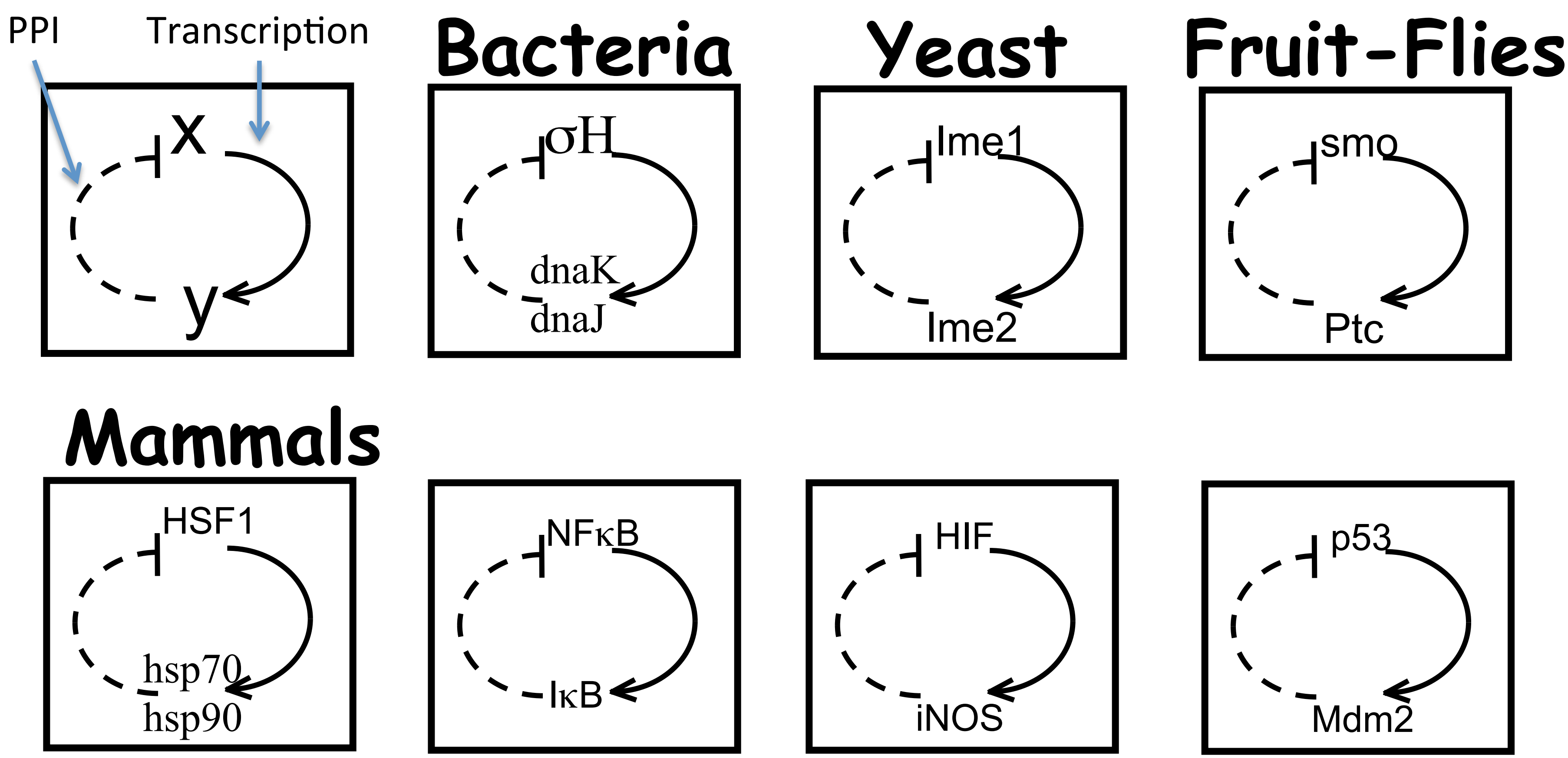


	X	Y	Z
Steady-State 1	ON	OFF	OFF
Steady-State 2	OFF	ON	ON

(U. Alon, *An Introduction to Systems Biology*)

Network motifs in other biological networks

Feedback loops



(U. Alon, *An Introduction to Systems Biology*)

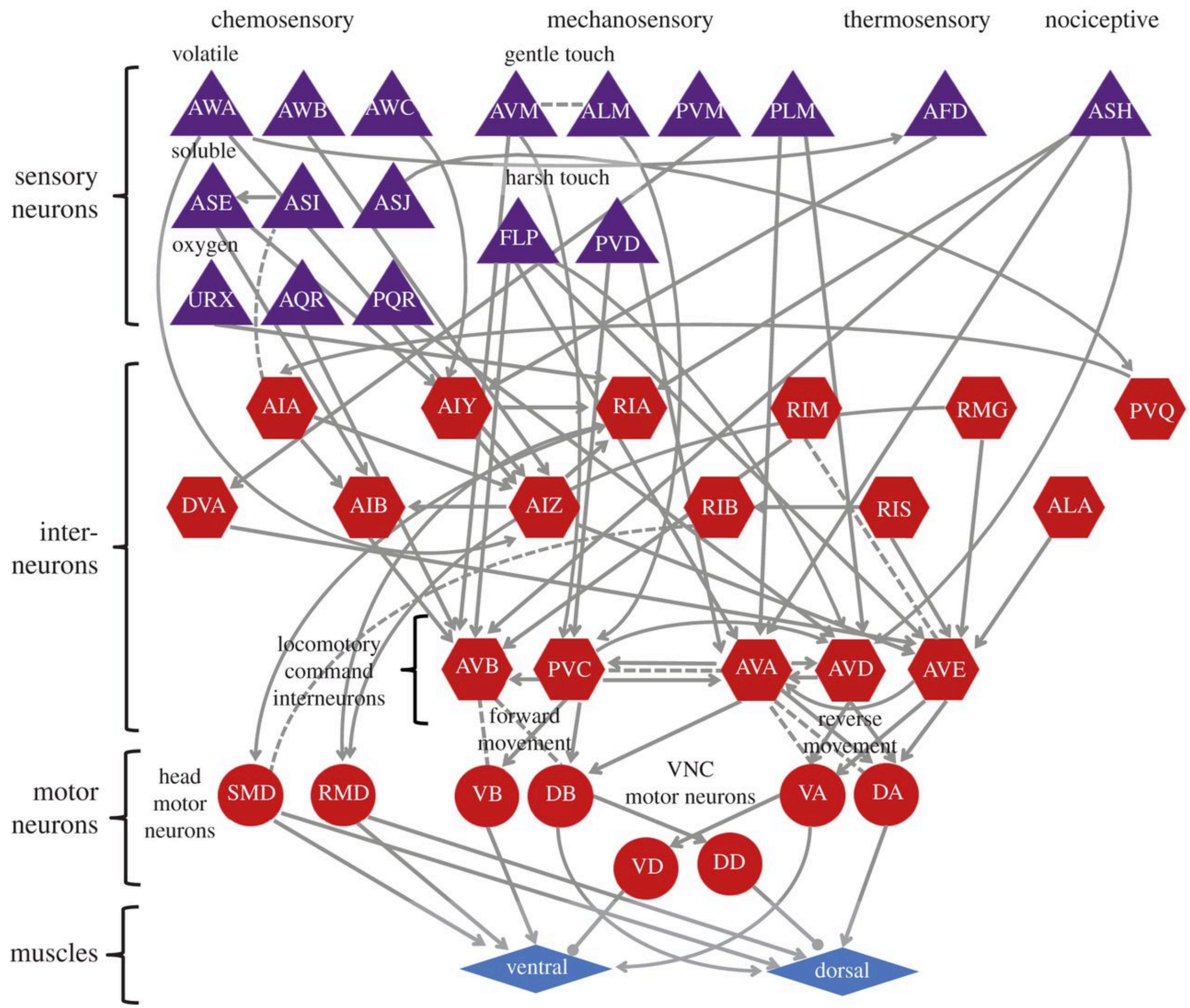
Network motifs in other biological networks

(U. Alon, *An Introduction to Systems Biology*)

Network	Nodes	Edges	N_{real}	$N_{rand} \pm SD$	Z score	N_{real}	$N_{rand} \pm SD$	Z score	N_{real}	$N_{rand} \pm SD$	Z score
Gene regulation (transcription)					**Feed-forward loop**			**Bi-fan**			
E. coli	424	519	40	7 ± 3	10	203	47 ± 12	13			
*S. cerevisiae**	685	1,052	70	11 ± 4	14	1812	300 ± 40	41			
Neurons					**Feed-forward loop**			**Bi-fan**			**Bi-parallel**
C. elegans†	252	509	125	90 ± 10	3.7	127	55 ± 13	5.3	227	35 ± 10	20
Food webs					**Three chain**			**Bi-parallel**			
Little Rock	92	984	3219	3120 ± 50	2.1	7295	2220 ± 210	25			
Ythan	83	391	1182	1020 ± 20	7.2	1357	230 ± 50	23			
St. Martin	42	205	469	450 ± 10	NS	382	130 ± 20	12			
Chesapeake	31	67	80	82 ± 4	NS	26	5 ± 2	8			
Coachella	29	243	279	235 ± 12	3.6	181	80 ± 20	5			
Skipwith	25	189	184	150 ± 7	5.5	397	80 ± 25	13			
B. Brook	25	104	181	130 ± 7	7.4	267	30 ± 7	32			
Electronic circuits (forward logic chips)					**Feed-forward loop**			**Bi-fan**			**Bi-parallel**
s15850	10,383	14,240	424	2 ± 2	285	1040	1 ± 1	1200	480	2 ± 1	335
s38584	20,717	34,204	413	10 ± 3	120	1739	6 ± 2	800	711	9 ± 2	320
s38417	23,843	33,661	612	3 ± 2	400	2404	1 ± 1	2550	531	2 ± 2	340
s9234	5,844	8,197	211	2 ± 1	140	754	1 ± 1	1050	209	1 ± 1	200
s13207	8,651	11,831	403	2 ± 1	225	4445	1 ± 1	4950	264	2 ± 1	200
Electronic circuits (digital fractional multipliers)					**Three-node feedback loop**			**Bi-fan**			**Four-node feedback loop**
s208	122	189	10	1 ± 1	9	4	1 ± 1	3.8	5	1 ± 1	5
s420	252	399	20	1 ± 1	18	10	1 ± 1	10	11	1 ± 1	11
s838‡	512	819	40	1 ± 1	38	22	1 ± 1	20	23	1 ± 1	25
World Wide Web					**Feedback with two mutual dyads**			**Fully connected triad**			**Uplinked mutual dyad**
nd.edu§	325,729	1.46e6	1.1e5	$2e3 \pm 1e2$	800	6.8e6	$5e4 \pm 4e2$	15,000	1.2e6	$1e4 \pm 2e2$	5000

Network motifs in other biological networks

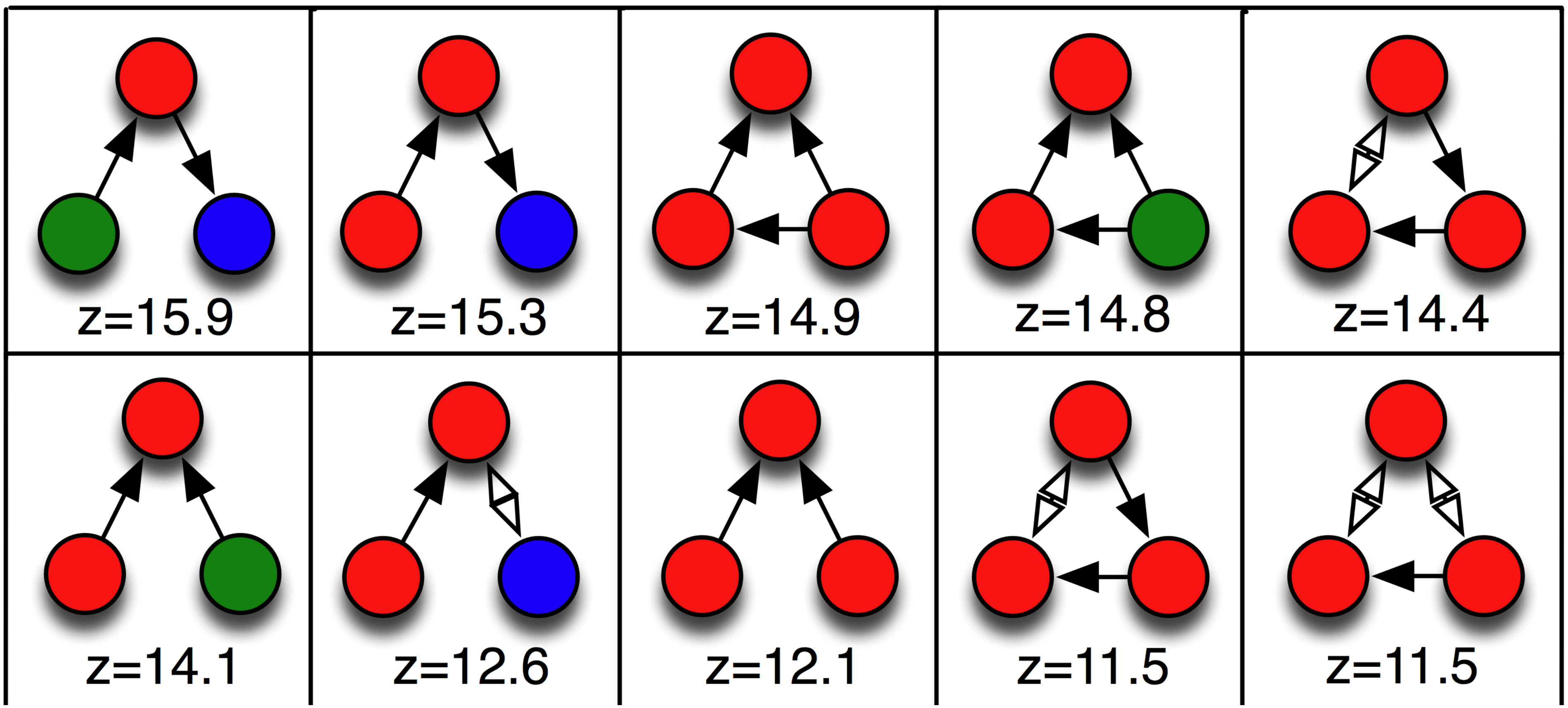
C. elegans somatic nervous system



(Fang-Yen et al., Phil. Trans. Royal Soc. B 2015)

Network motifs in other biological networks

C. elegans somatic nervous system

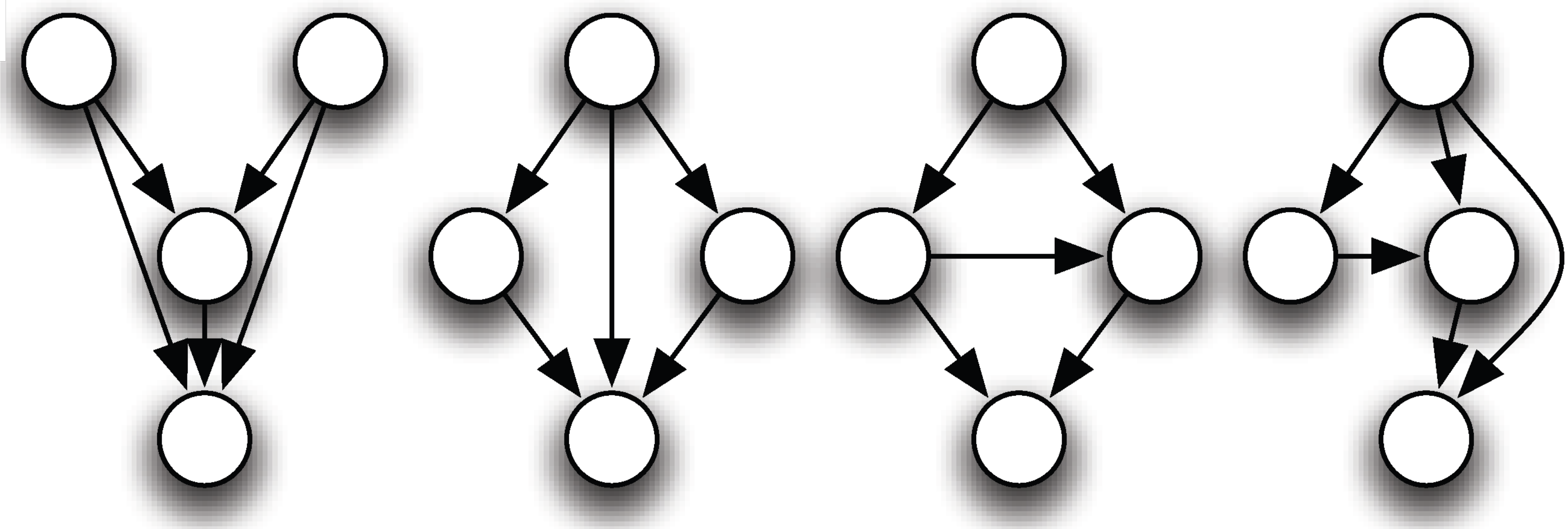


(Qian et al., PLoS One 2011)

Sensory neuron
Interneuron
Motor neuron

Network motifs in other biological networks

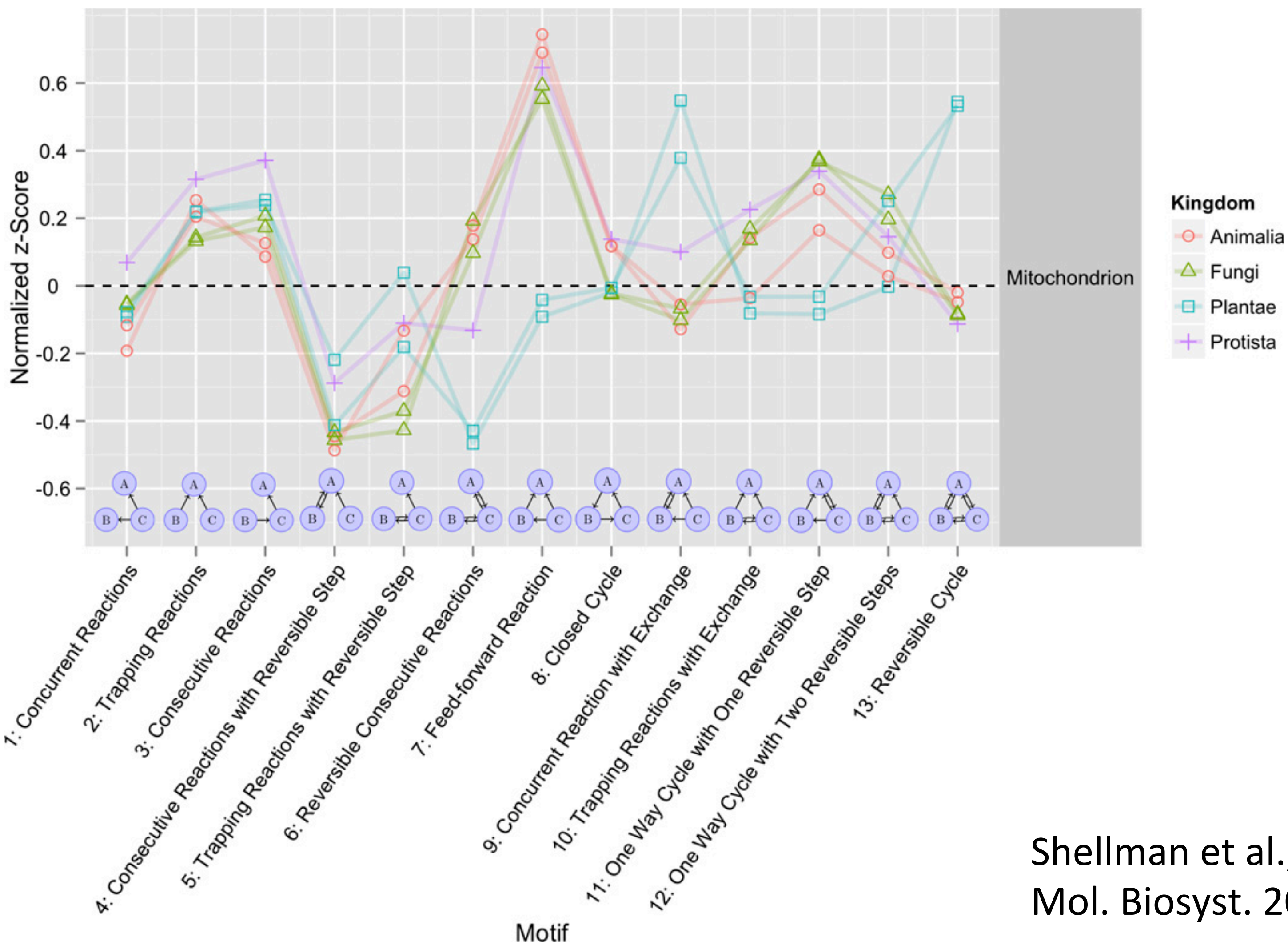
C. elegans somatic nervous system



(Qian et al., PLoS One 2011)

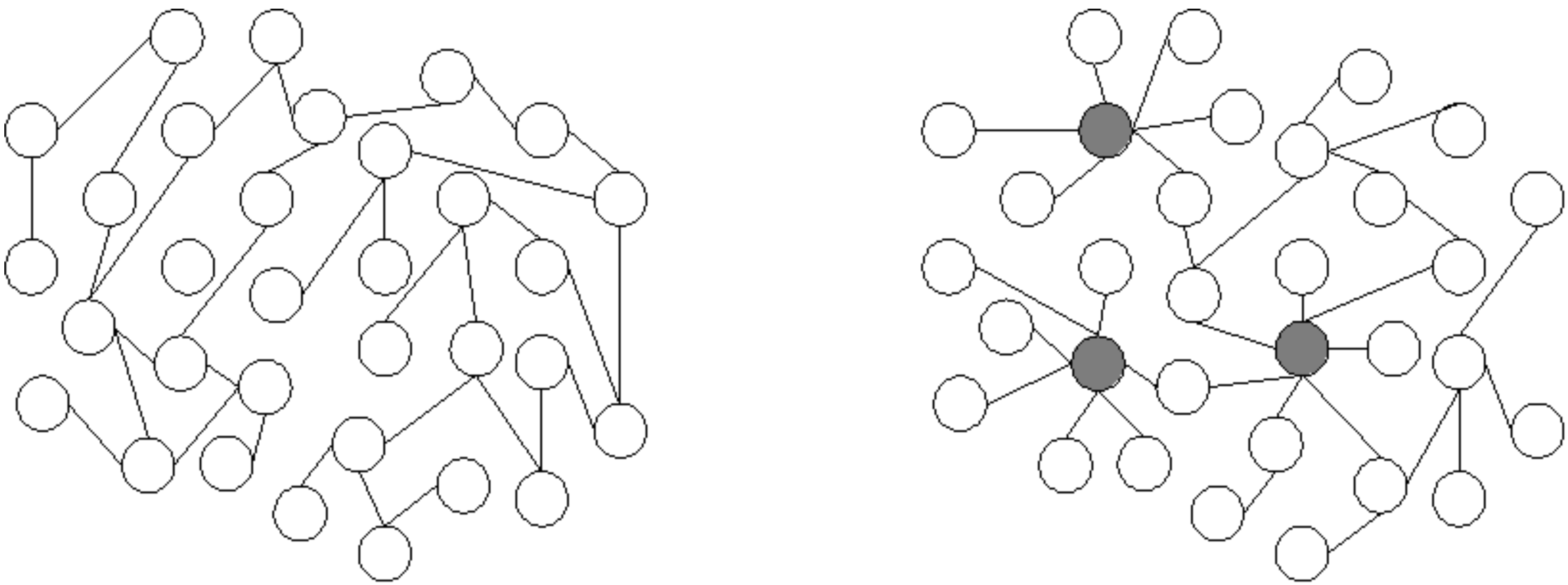
Network motifs in other biological networks

Mitochondrial metabolic networks from various eukaryotes



Shellman et al.,
Mol. Biosyst. 2013

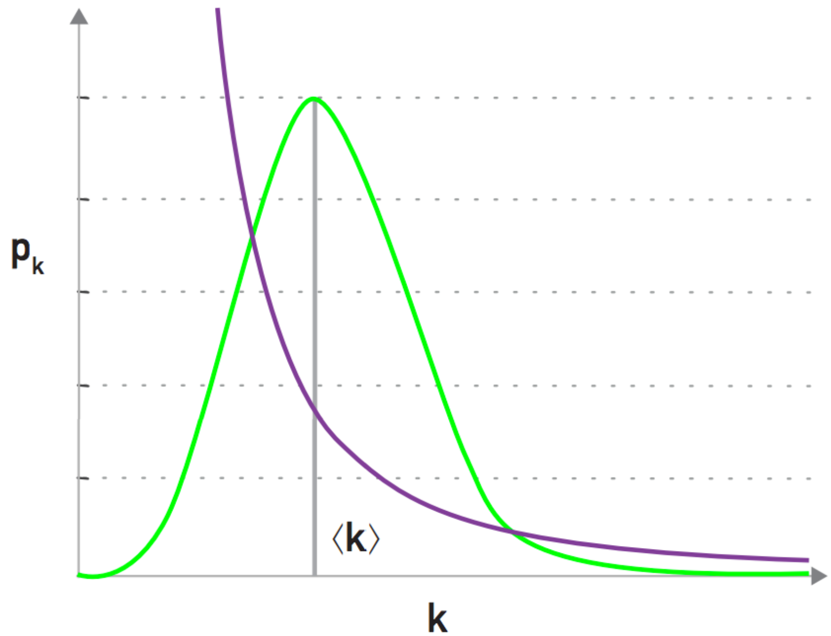
Many biological networks show **scale-free organization**



(a) Random network (b) Scale-free network

(Image from Carlos Castillo)

Many biological networks show scale-free organization



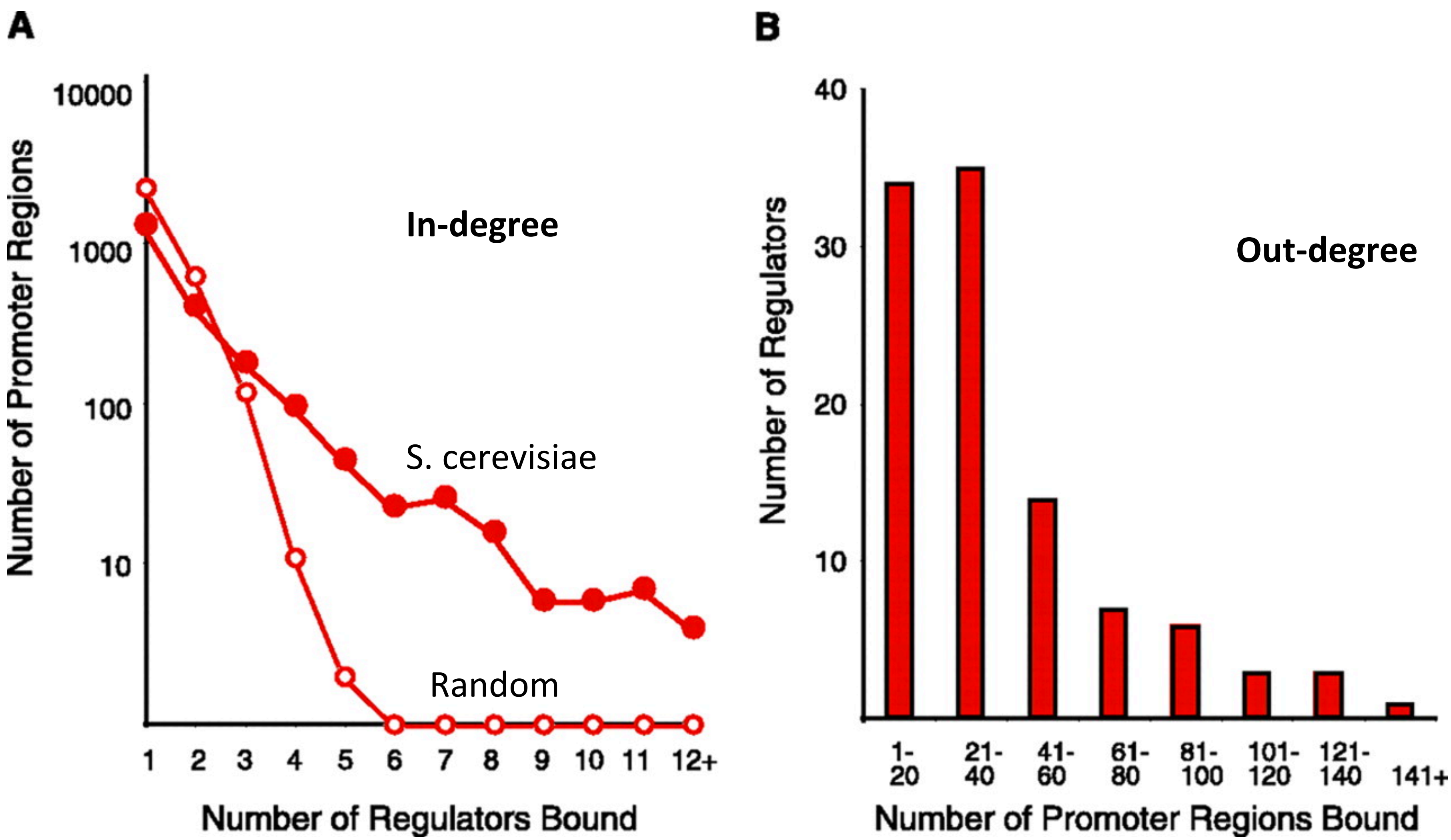
$P(k) \sim k^{-\gamma}$

Random Network
Randomly chosen node: $k = \langle k \rangle \pm \langle k \rangle^{1/2}$
Scale: $\langle k \rangle$

Scale-Free Network
Randomly chosen node: $k = \langle k \rangle \pm \infty$
Scale: none

(Albert Barabasi, *Network Science*)

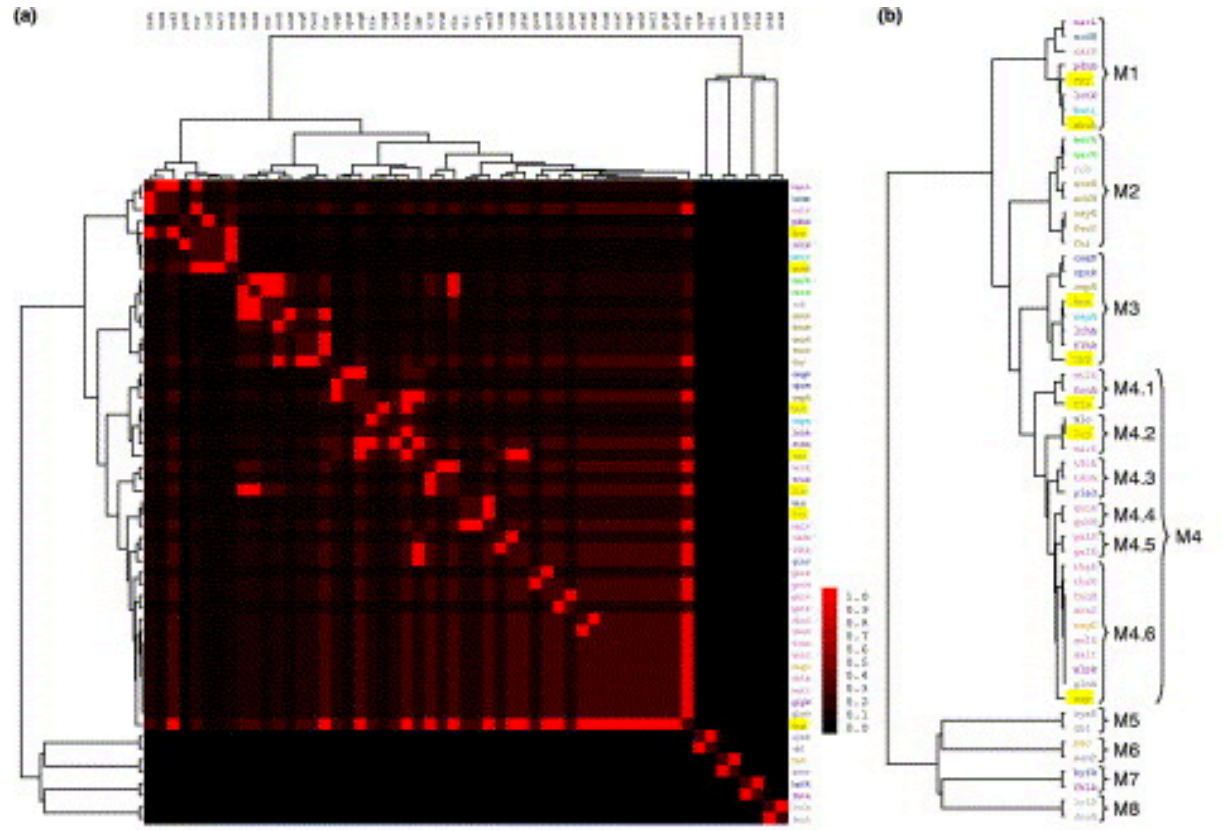
Many biological networks show scale-free organization



(Lee et al., Science 2002)

Biological networks are often **modular**

(Resendes-Antonio et al., Trend. Genet. 2005)



(c)

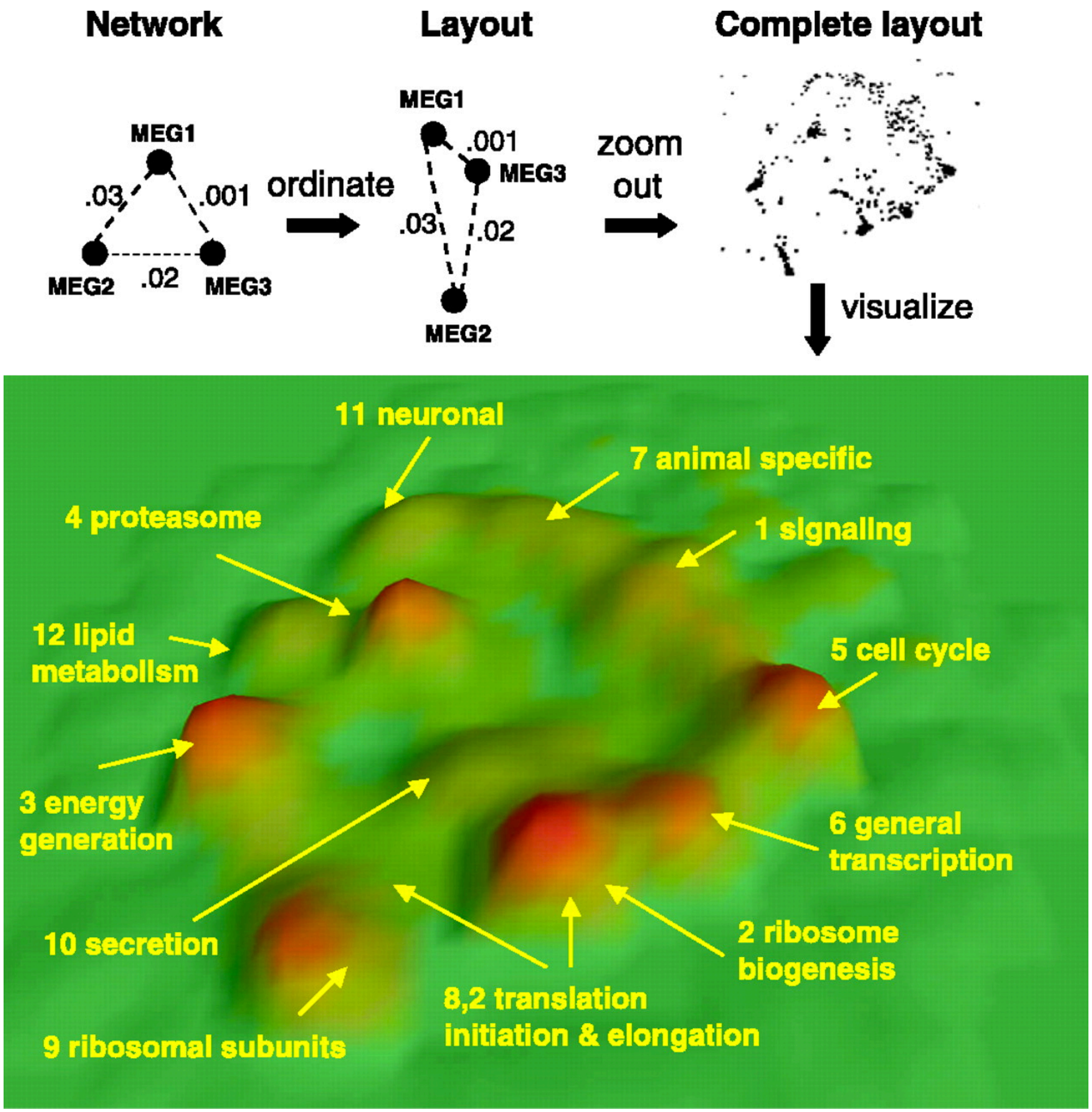
Module	Biological function
M1	Aerobic and/or anaerobic respiration forms
M2	Stress response to weak organic acids, antibiotics and oxidizing compounds
M3	Chemotaxis, motility and biofilm formation
M4	Carbon sources assimilation
M5	Sulfur assimilation
M6	Nitrogen metabolism
M7	Fermentative conditions
M8	Chromosome replication

(d)

Colour	Functional class
	0.0: Unknown proteins, no known homologs
	1.4: Protection responses
	1.5: Transport and binding proteins
	1.6: Adaptation
	2.2: Macromolecule synthesis, modification
	3.1: Amino acid biosynthesis
	3.3: Central intermediar y metabolism
	3.4: Degradation of small molecules
	3.5: Energy metabolism, carbon
	4.1: Cell envelope
	6.1: Global regulatory functions
	7.0: Some information available but genes are not classifiable

TRENDS in Genetics

Biological networks are often **modular**



(Stuart et al., Science 2003)

Biological networks are **robust**

"A biological system is robust if it continues to
function in the face of perturbation"
--Andreas Wagner, *Robustness and Evolvability in Living Systems*

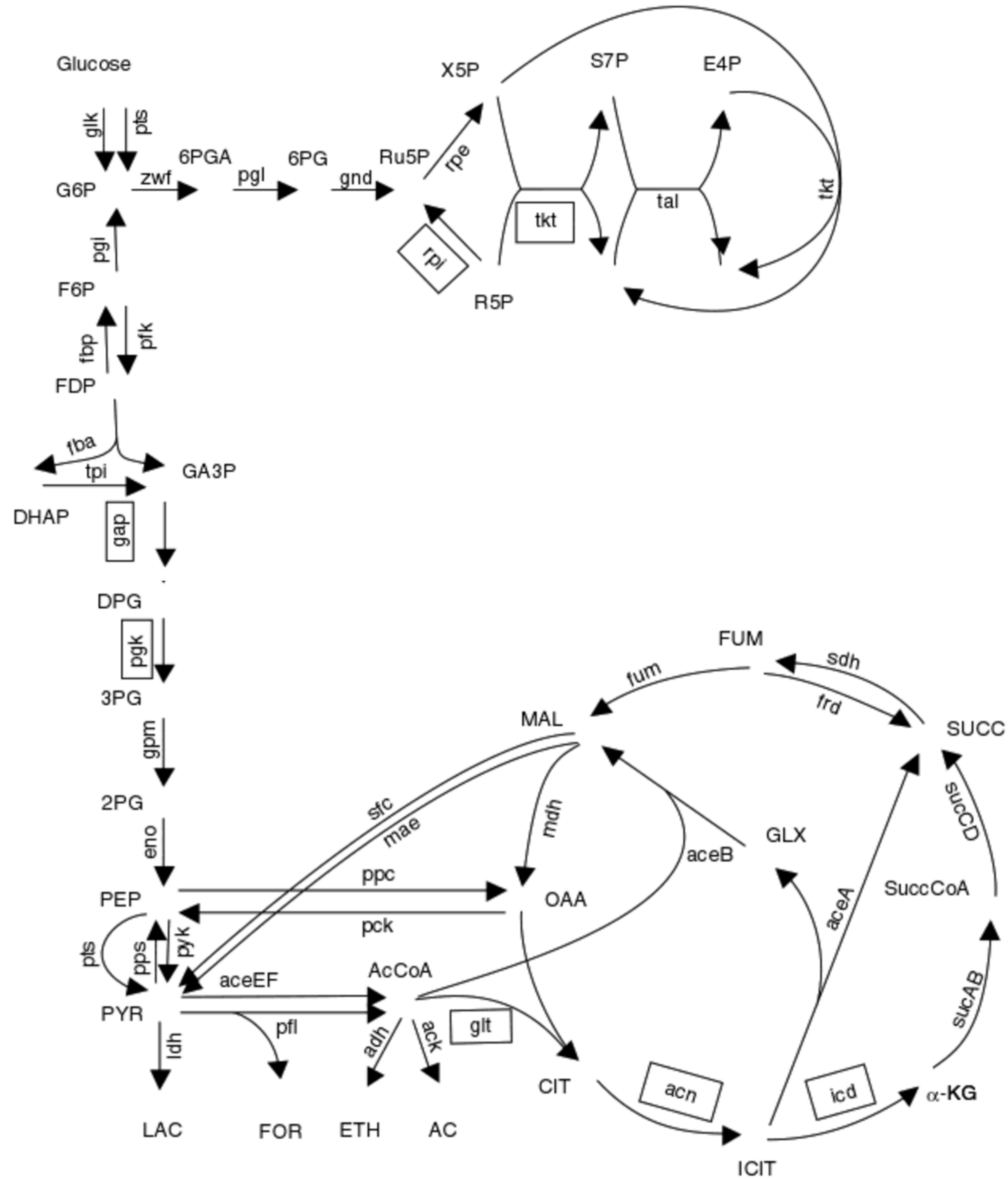
Biological networks are **robust**

	U		C		A		G	
U	UUU	Phe	UCU	Ser	UAU	Tyr	UGU	Cys
	UUC	Phe	UCC	Ser	UAC	Tyr	UGC	Cys
	UUA	Leu	UCA	Ser	**UAA**	**TER**	**UGA**	**TER**
	UUG	Leu	UCG	Ser	**UAG**	**TER**	UCG	Trp
C	CUU	Leu	CCU	Pro	CAU	His	CGU	Arg
	CUC	Leu	CCC	Pro	CAC	His	CGC	Arg
	CUA	Leu	CCA	Pro	CAA	Gln	CGA	Arg
	CUG	Leu	CCG	Pro	CAG	Gln	CGG	Arg
A	AUU	Ile	ACU	Thr	AAU	Asn	AGU	Ser
	AUC	Ile	ACC	Thr	AAC	Asn	AGC	Ser
	AUA	Ile	ACA	Thr	AAA	Lsy	AGA	Arg
	AUG	Met	ACG	Thr	AAG	Lys	AGG	Arg
G	GUU	Val	GCU	Ala	GAU	Asp	GGU	Gly
	GUC	Val	GCC	Ala	GAC	Asp	GGC	Gly
	GUA	Val	GCA	Ala	GAA	Glu	GGA	Gly
	GUG	Val	GCG	Ala	GAG	Glu	GGG	Gly

Acidic
Amide
Alkyl
Aromatic
Alkyl
Basic
Hydroxyl containing
Sulfur containing
STOP

(A. Wagner, *Robustness and Evolvability in Living Systems*)

Example: Central carbon metabolism of *E. coli*



Of 48 reactions, only 7 essential;
2/3 give less than 5% growth defect

(A. Wagner, *Robustness and Evolvability in Living Systems*)

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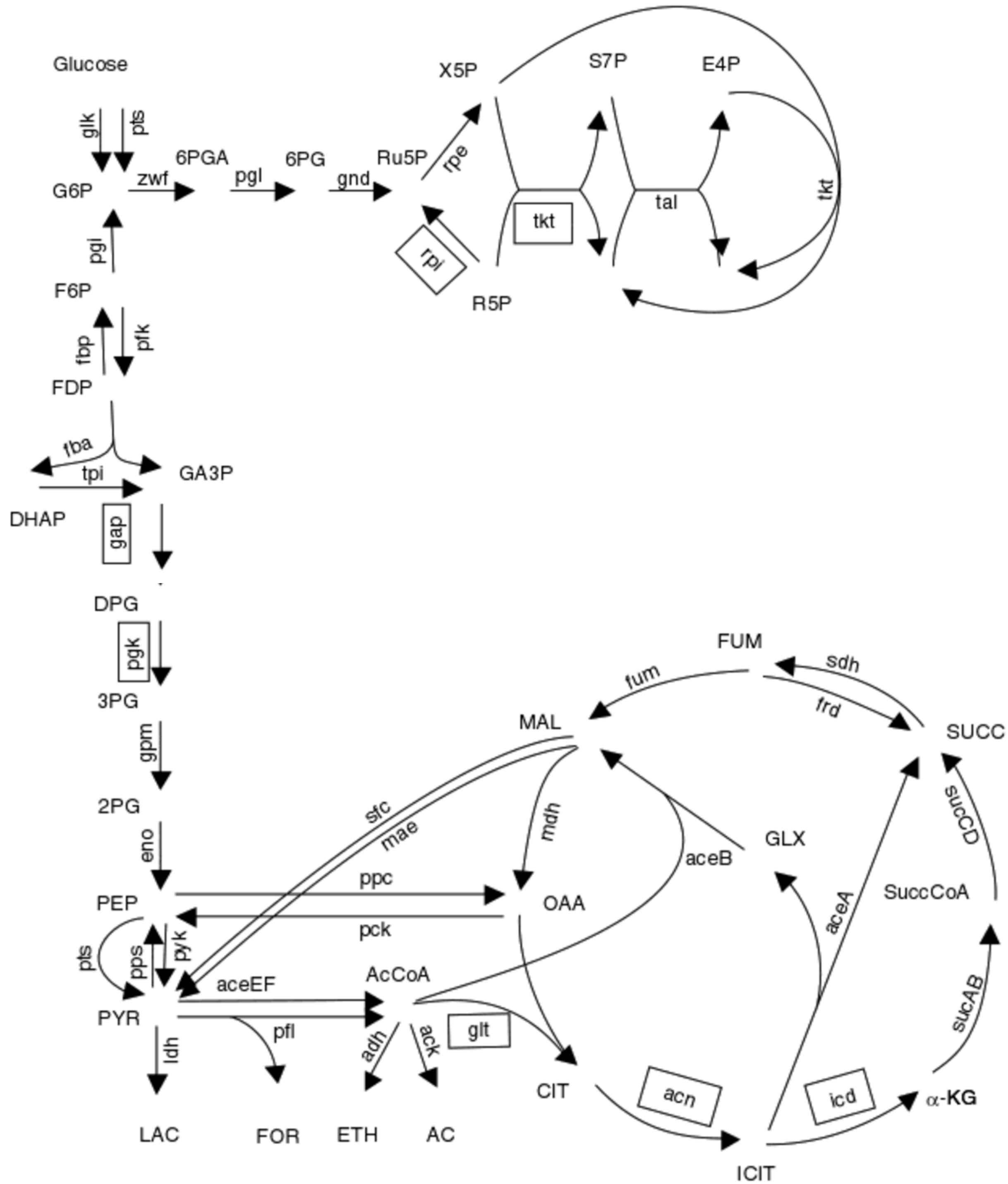

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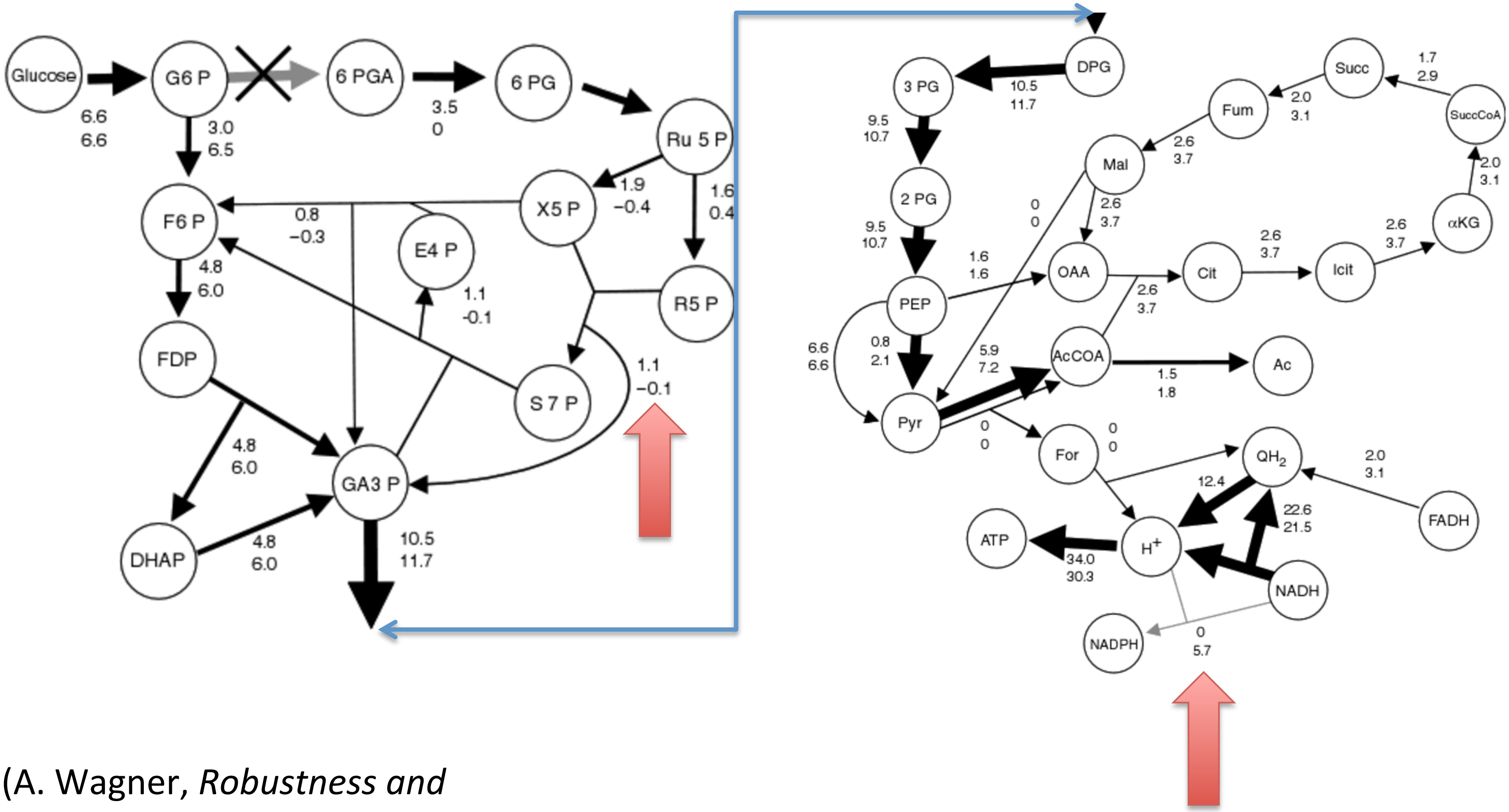
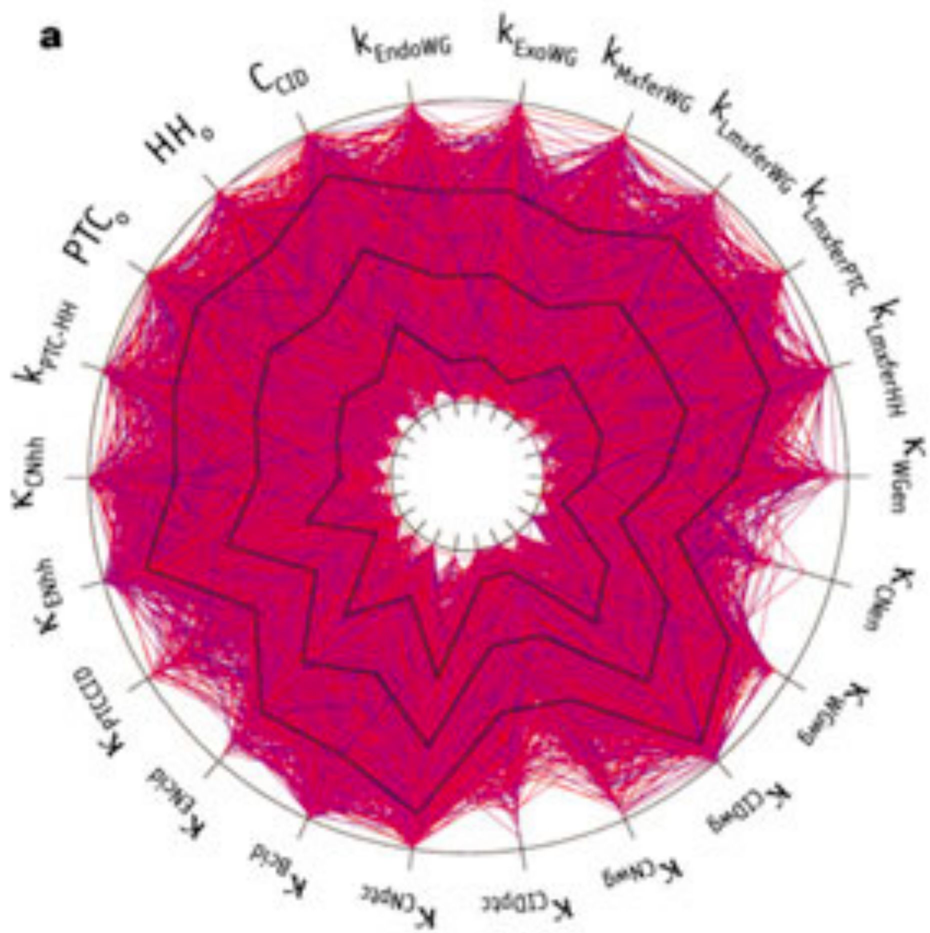


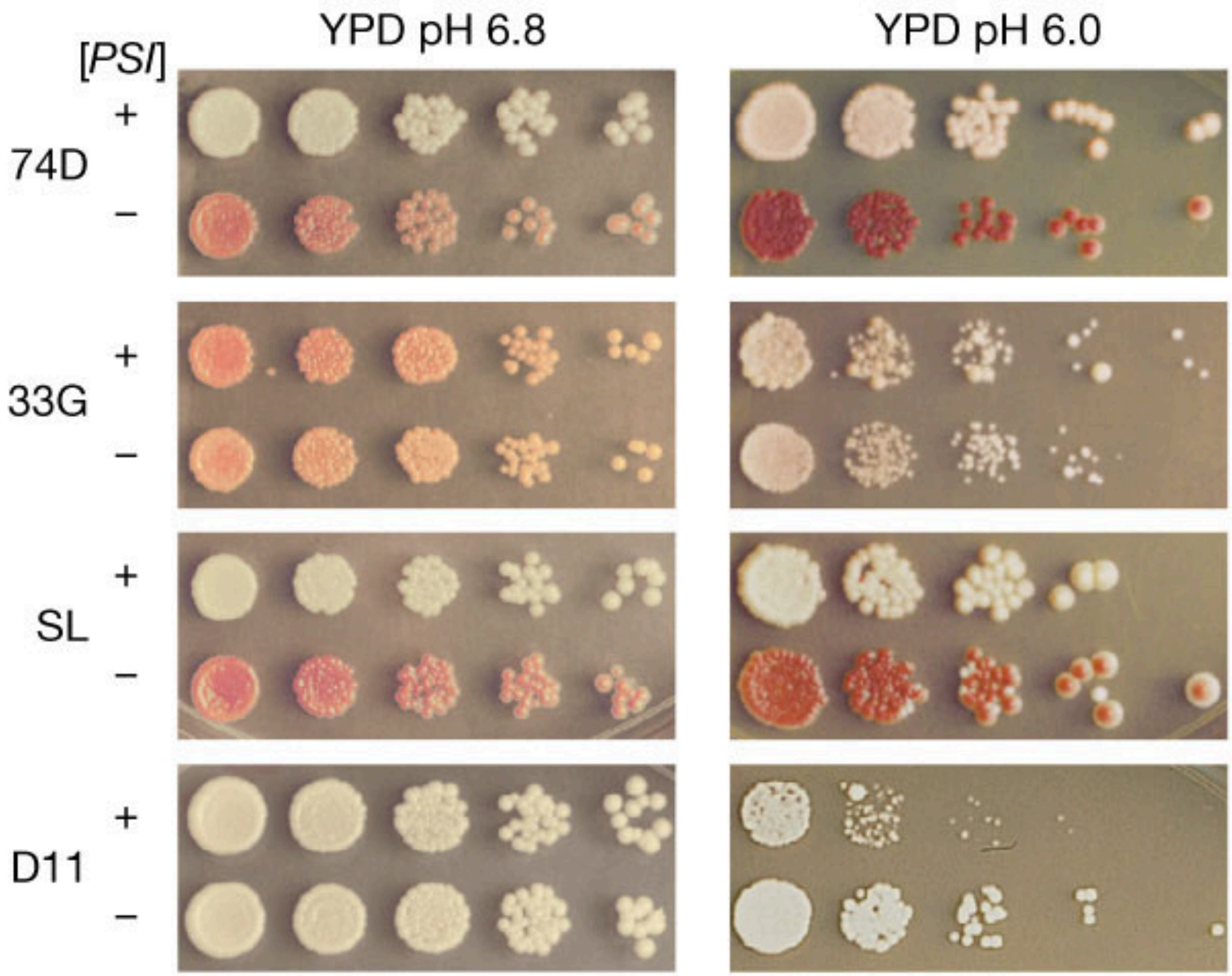
(A. Wagner, *Robustness and Evolvability in Living Systems*)

Robustness enables evolutionary capacitance



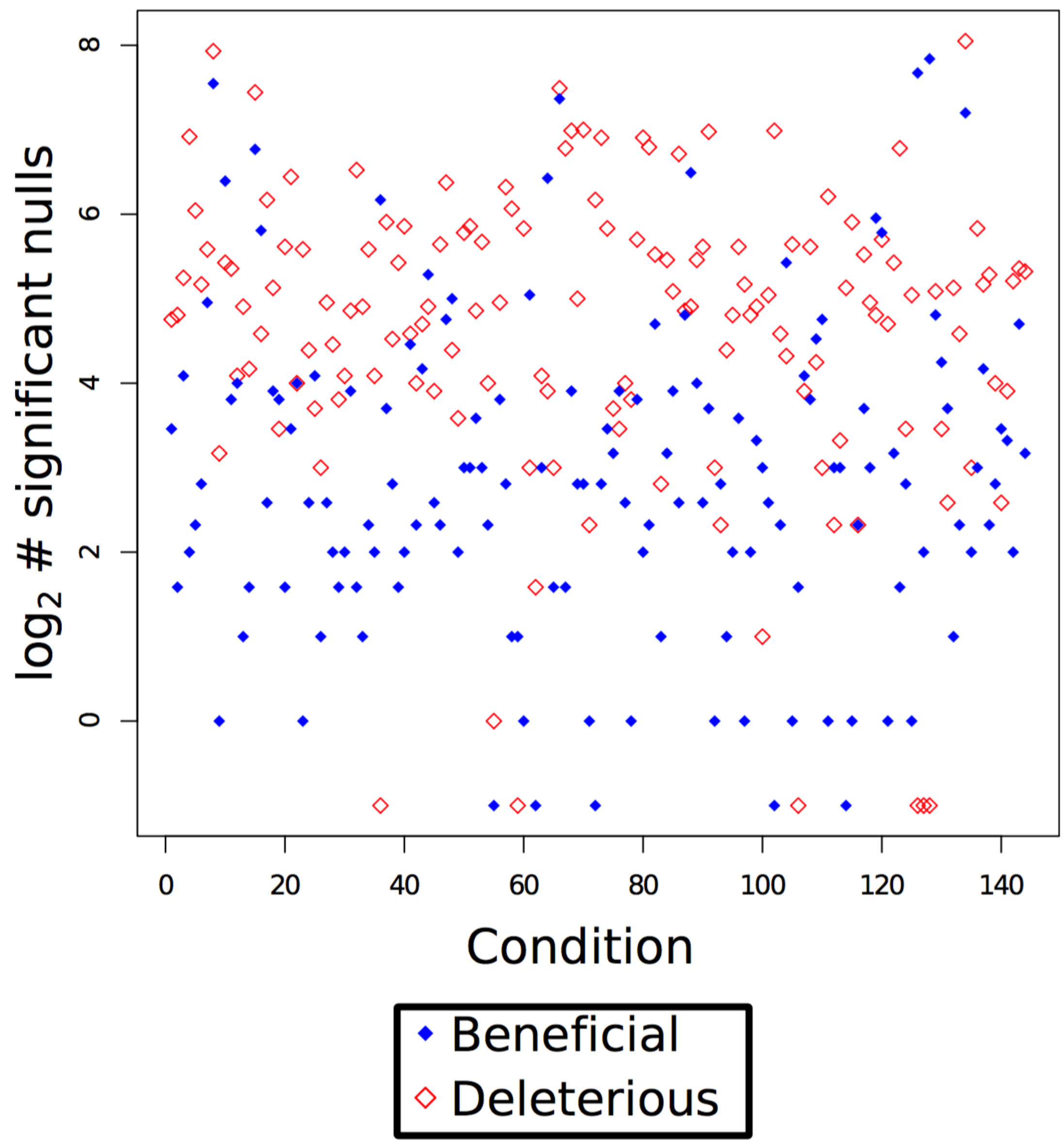
(Von Dassow *et al.*, Nature, 2000)

Robustness enables evolutionary capacitance



(True and Lindquist, Nature, 2000)

Robustness facilitates rapid evolution



Data drawn from 144 non-redundant conditions across 7 studies

Average of 19 beneficial null mutations and 42 deleterious null mutations per condition

(Hottes et al.,
PLoS Genetics 2013)

Biological networks…

- Show enriched functional motifs
- Are highly modular
- Often have scale-free organization
- Are robust to internal and external perturbation

… and we can use our understanding of the behavior of network components to understand the behavior of the whole

Additional reading

- *An Introduction to Systems Biology* – Uri Alon
- *Robustness and Evolvability in Living Systems* – Andreas Wagner
- *Physical Biology of the Cell* -- Jane Kondev, Julie Theriot, and Rob Phillips