Network motifs

part of “Graphen und Netzwerke in der Biologie”

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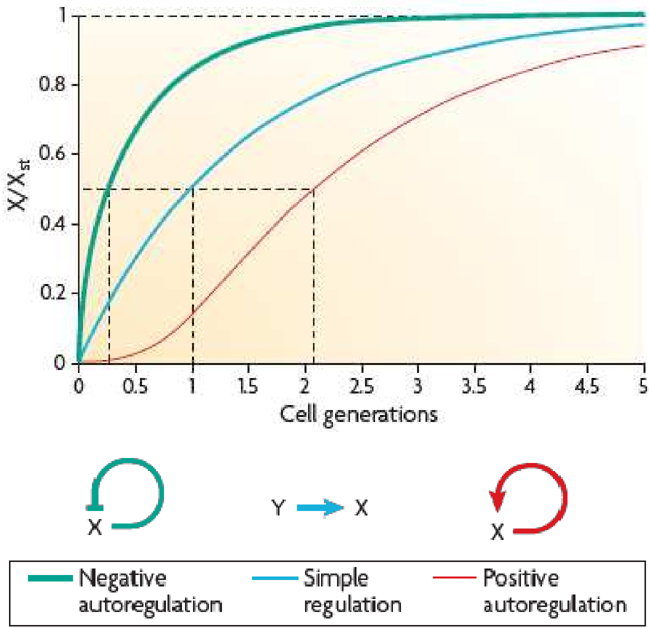
Simple regulation

- transcription factor (TF) Y regulates gene X
- no additional interactions
- Y is activated by a signal S_Y other than trascriptional (e.g. ligand binding, posttranslational modification)
- when **transcription begins**, $[X]$ rises and converges to a steady-state level X_{st}
- **steady-state level** X_{st}: is equal to the ratio of the production and degradation rate
- degradation here is active degradation and dilution (by cell growth)
- when **transcription stops**, $[X]$ decays exponentially
- $[X](t) = X_{st} 2^{-t/t_{1/2}}$ and $t_{1/2} = \ln 2/\lambda$
- the response time is the time it takes to reach $X_{st}/2$
- **response time**: is equal to the half-life $t_{1/2}$ of X
- noise causes fluctuations of $[X]$ from 10 to 20%

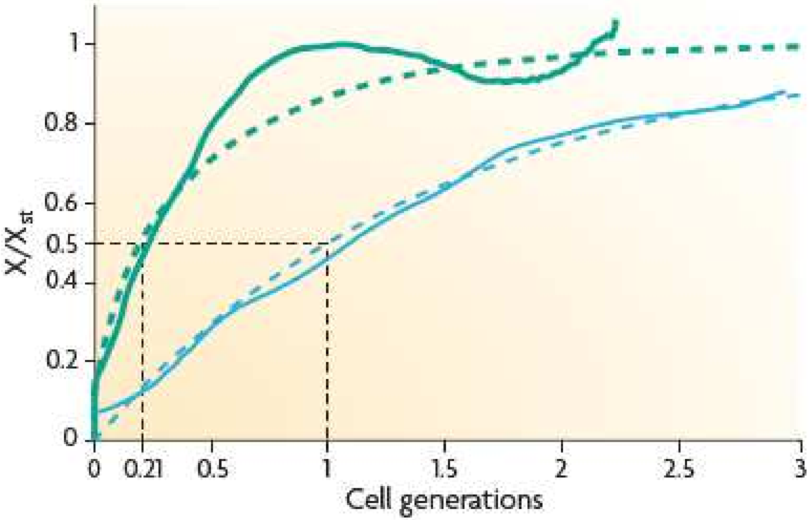


Add the decay to the simple regulation above!

Negative autoregulation (NAR)

- TF X represses its own transcription
- X has a strong promotor which leads to a rapid initial rise
- followed by a sudden locking into the steady state
- the steady state X_{st} is close to the repression threshold
- **NAR speeds up the response time**
- **NAR can reduce cell-cell variation in protein levels**
  low $[X]$ enhanced production
  high $[X]$ reduced production
  nerrower distribution of protein levels

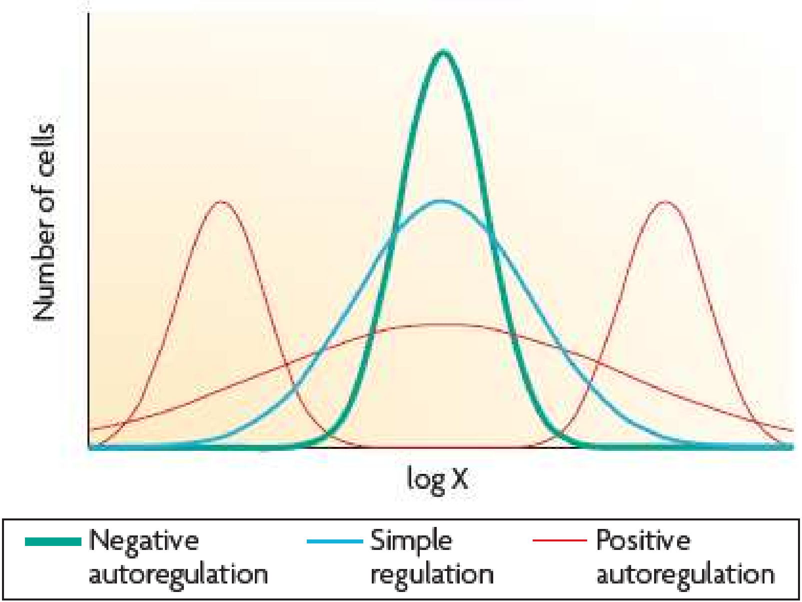
Simpel regulation and NAR in experiments



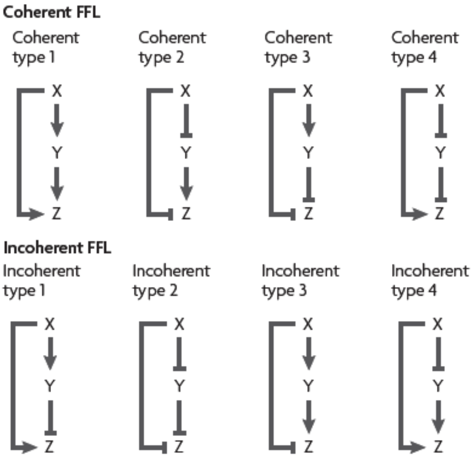
Positive autoregulation (PAR)

- TF X activates its own transcription
- S-shaped curve with inflection point
  $[X]$ lower than activation threshold below inflection point
  $[X]$ higher than activation threshold above inflection point
- **PAR slowes the response time**
- **PAR can enhance cell-cell variation in protein levels**
  low $[X]$ slow production
  high $[X]$ rapid production
- high variability in $[X]$ among cells
- can lead to **bimodal distribution**
  some cells have high $[X]$
  others have low $[X]$
- differentiation-like partitioning of cells into two populations
- helps populations to maintain a mixed phenotype and respond better to fluctuations in the environment

Variation in Cell Populations



Feedforward loops (FLL)



Eight types of loops in motifs with three genes.

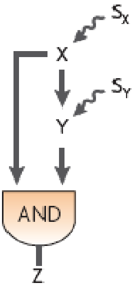
Input functions

Two inputs for Z can be integrates as:

- AND gate (requires both inputs)
- OR gate (requires either input)
- additive (inputs add up)

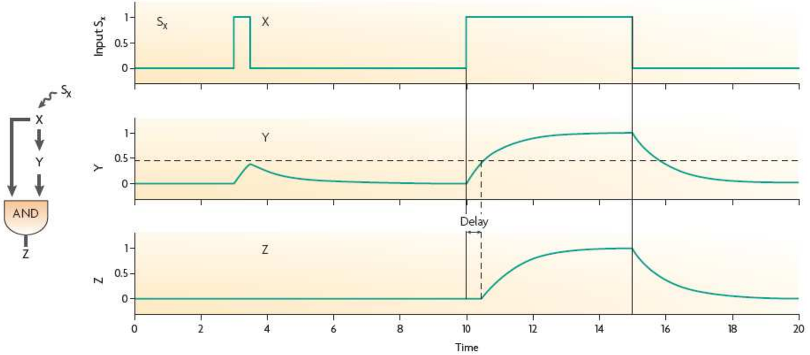
In combination with the 8 types of motif topologies this makes 8×3 different feedforward network motifs of size 3.
Input functions for transcription factor networks are usually not known.

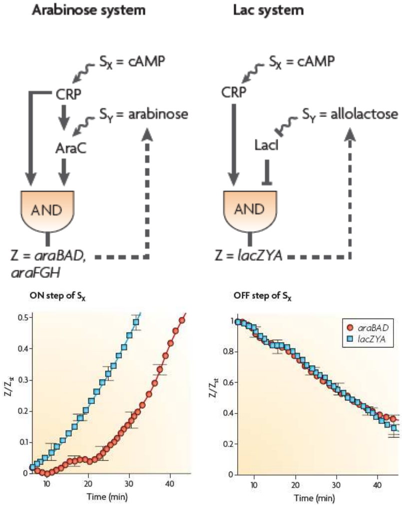
Coherent type 1 feedforward loop – AND



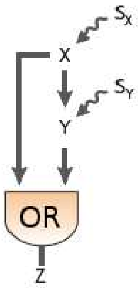
- delay after stimulation, no delay when stimulation stops
- dynamic behavior is called "**sign sensitive delay**"
  sign: elevation or reduction of stimulus S_X level
  elevation $\rightarrow$ delay
  reduction $\rightarrow$ no delay
- **persistence detector**
  the higher the activation threshold of Z by Y the longer the delay
  short stimulation does not increase Y fast enough to activate Z
  only persistent stimulation activates Z

Coherent type 1 feedforward loop – AND

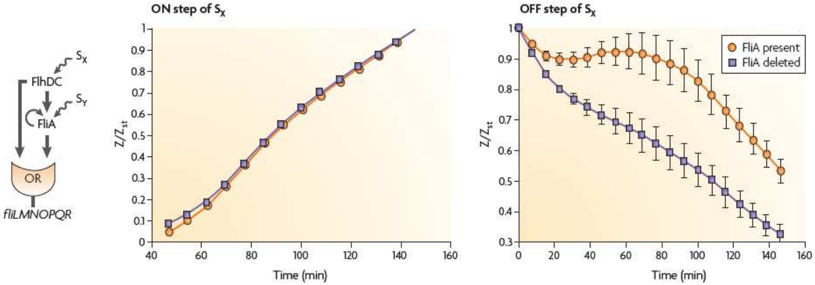



Arabinose system
Lac system
S_X = cAMP
CRP
S_Y = arabinose
AraC
AND
Z = araBAD, araFGH
S_X = cAMP
CRP
S_Y = allolactose
LacI
AND
Z = lacZYA
ON step of S_X
OFF step of S_X
Z/Z_{st}
Time (min)
araBAD
lacZYA

Coherent type 1 feedforward loop – OR

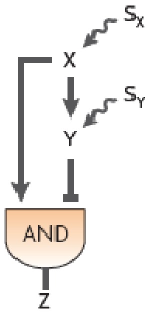


- no delay after stimulation, delay when stimulation stops
- when X is no longer active, still enough Y to activate Z
- the lower the decay rate of Y the longer the delay
- short loss of stimulation does not decrease Y fast to shut the production of Z
- smoothes the fluctuation of S_X



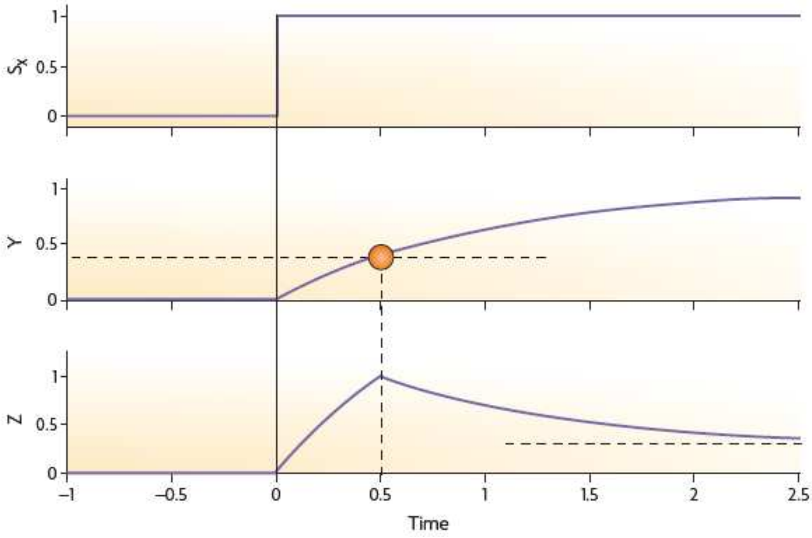
S_X
FlhDC
S_Y
FliA
OR
fliLMNOPQR
ON step of S_X
OFF step of S_X
Z/Z_st
Time (min)
FliA present
FliA deleted

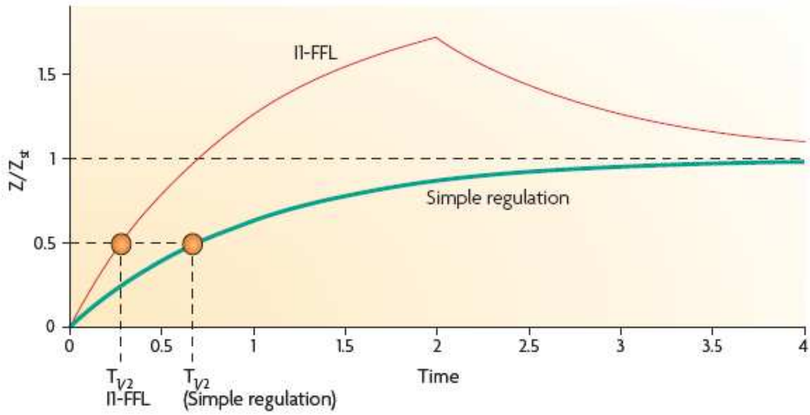
Incoherent type 1 feedforward loop



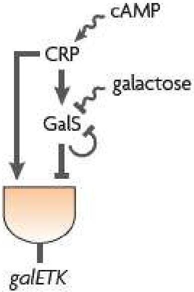
- X activates Z, but also represses Z (by activating the repressor Y)
- Z increases until Y reaches its repressor threshold
- this results in **puls-like dynamics**
- if Y does not completely repress Z
- the motif acts as a **response accelerator**
- $[Z]$ reaches a certain non-zero steady state level

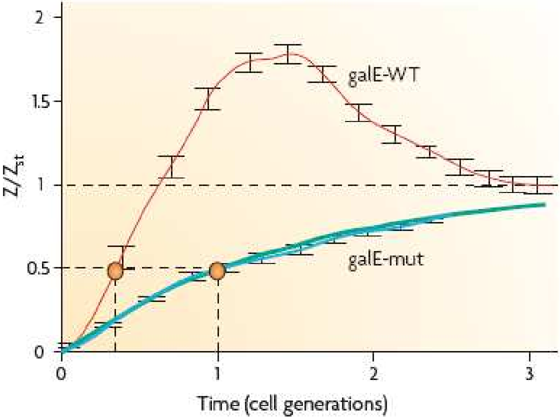
puls-like dynamics



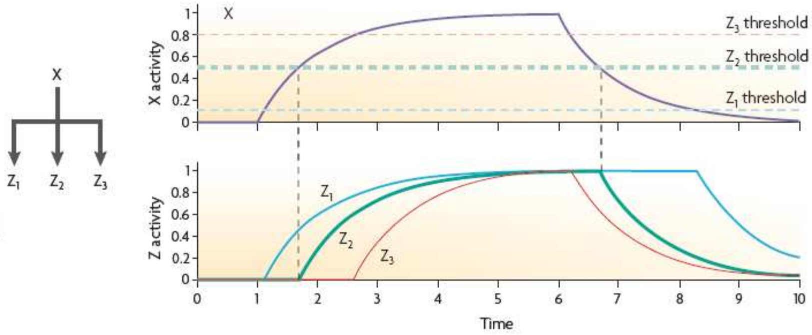


I1-FFL
1.5
1
0.5
0
Z/Z_{st}
Simple regulation
0
0.5
1
1.5
2
2.5
3
3.5
4
Time
$T_{1/2}$ I1-FFL
$T_{1/2}$ (Simple regulation)


cAMP
CRP
galactose
GalS
galETK


2
1.5
1
0.5
0
Z/Z_st
galE-WT
galE-mut
0
1
2
3
Time (cell generations)

single-input module (SIM)



- coordinated expression of a group of genes
- different activation thresholds for $Z_1, ..., Z_n$ result in a temporally ordered activation of $Z_1, ..., Z_n$, an "**expression program**"
- activation is often in functional order

dense overlapping regulon (DOR)

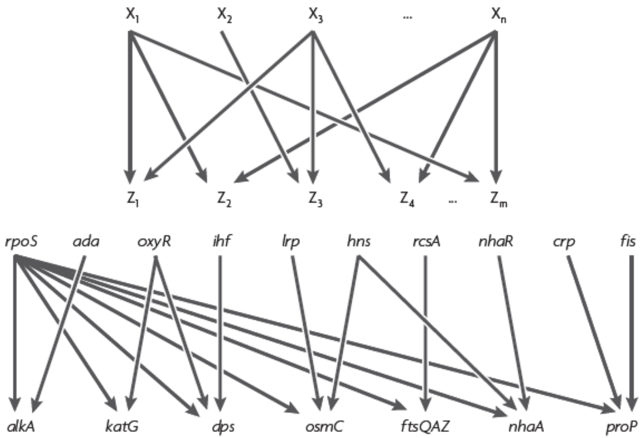
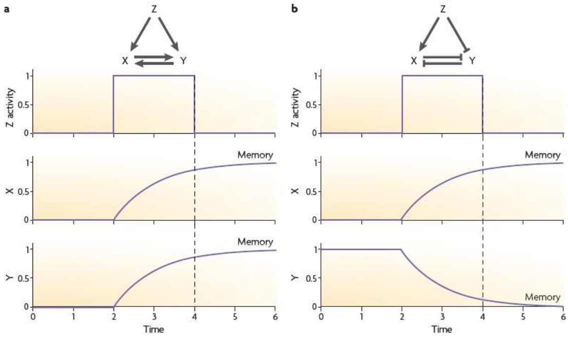


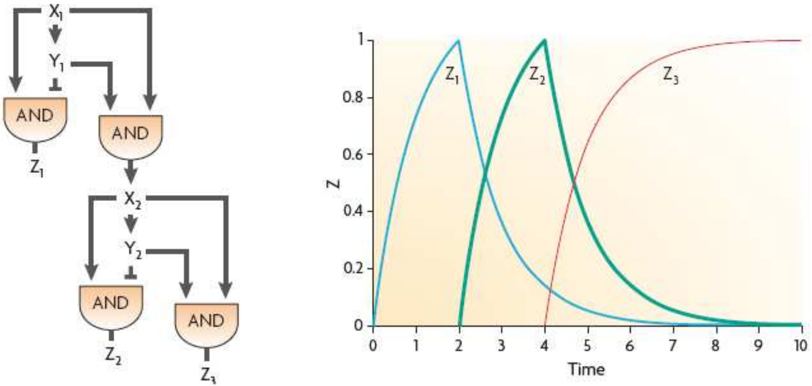
Figure 6 | **The dense overlapping regulon (DOR) network motif.** In this motif, many inputs regulate many outputs (top panel). The bottom panel shows an example from the stress-response system of *Escherichia coli*.

carry out a computation by which multiple inputs are translated into multiple outputs

Memory in transcription factor networks



- **double positive feedback loop (a)**: X and Y can remain "ON" even when activator *Z* disappears
- **double negative feedback loop (b)**: Z switches the steady state of X and Y, the state persists even after Z is deactivated



Two incoherent type-1 feedforward loops generate pulses of Z_1 and Z_2, one coherent type-1 feedforward loops generates a delayed Z_3 step

Literature

Network motifs: theory and experimental approaches. by Uri Alon; Nature Review Genetics (2007), 8, p450-461

Network motifs in integrated cellular networks of transcription-regulation and protein-protein interaction. Esti Yeger-Lotem, Shmuel Sattath, Nadav Kashtan, Shalev Itzkovitz, Ron Milo, Ron Y. Pinter and Uri Alon; PNAS (2004), 101 (16), p5934-5939