Transcription Regulation Motifs

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References

- **Alon U**. 2007. Network motifs: theory and experimental approaches. *Nat Rev Genet,* 8(6):450-61.
- **Krishna S., Semsey S., Sneppen K**. 2007. Combinatorics of feedback in cellular uptake and metabolism of small molecules. *PNAS,* 104(52):20815-9.

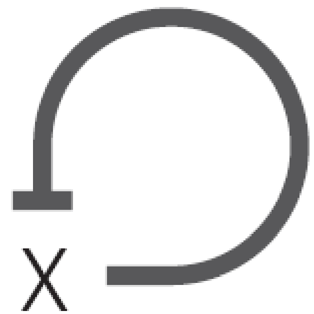
Network motifs

- To uncover structural design principles of complex networks studied across many fields of science, “network motifs”, patterns of interconnections occurring in complex networks at numbers that are significantly higher than those in randomized networks was defined.
- Network motifs can be thought of as recurring circuits of interactions from which the networks are built.
- Network motifs were first systematically defined in Transcription regulation networks of *Escherichia coli*
- The same motifs have since been found in organisms from bacteria and yeast to plants and animals.

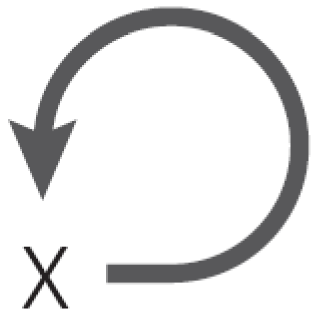
The basic building blocks

- Simple regulation

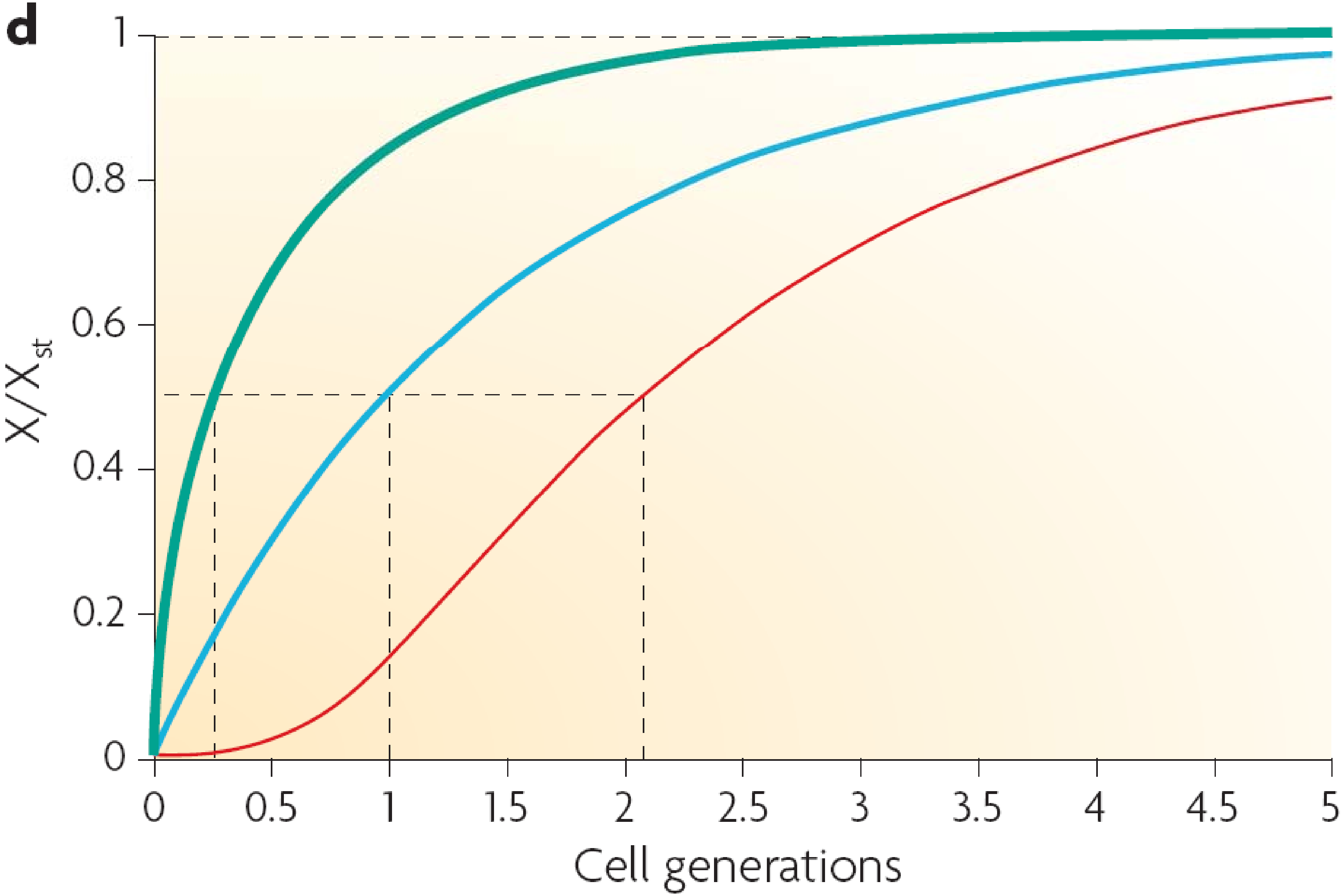
- Negative autoregulation (NAR)



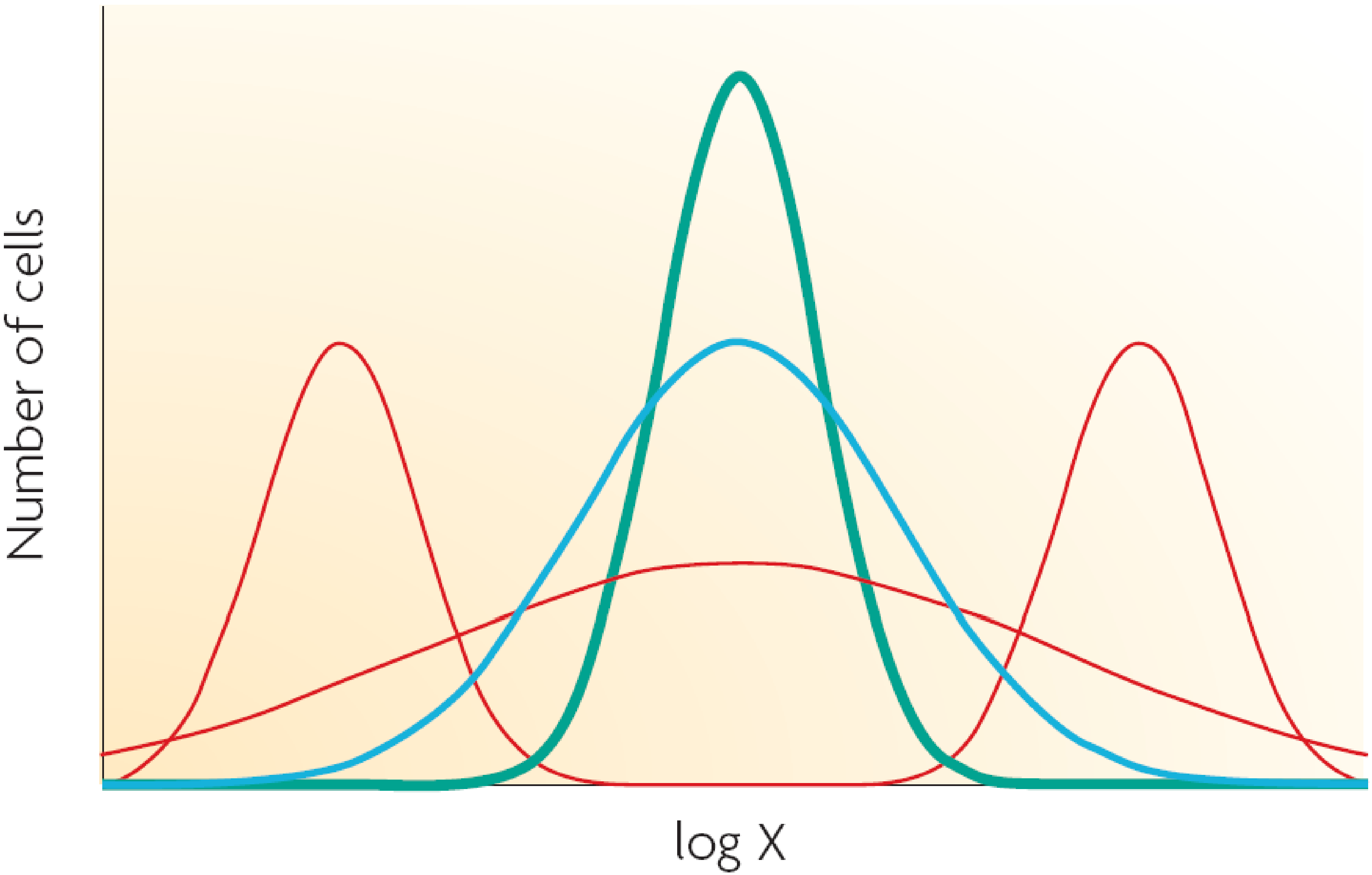
- Positive autoregulation (PAR)



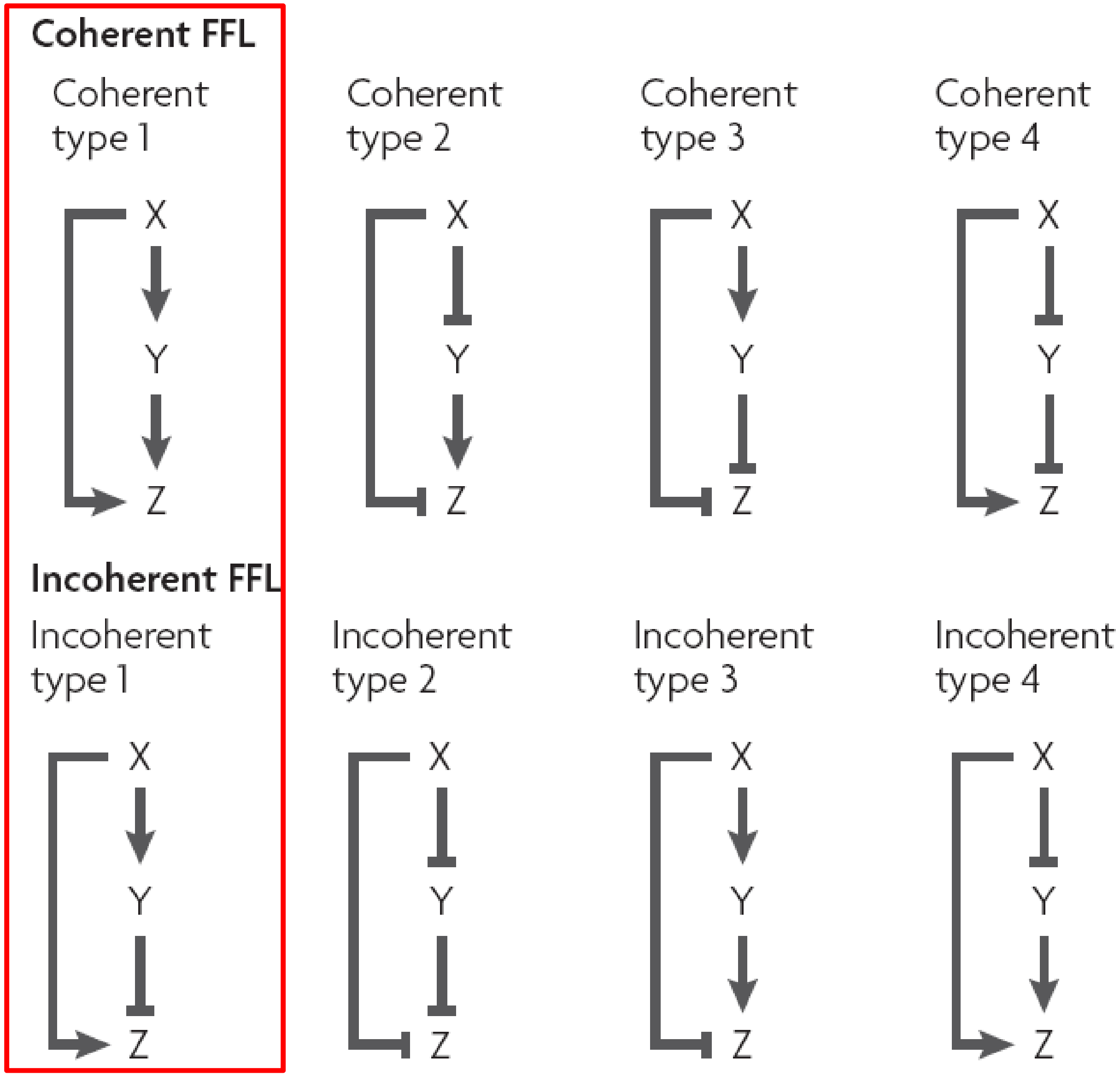
Response time of gene circuits



Cell–cell distribution of protein levels

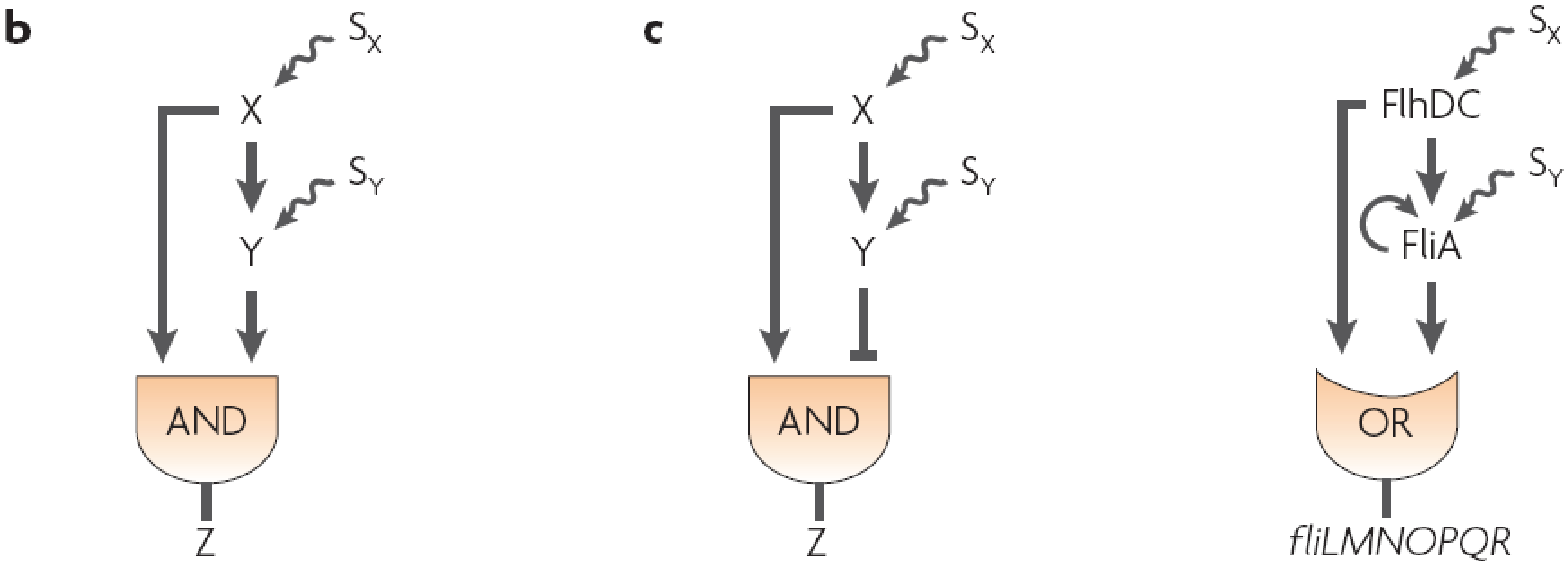


Feedforward loops (FFL)



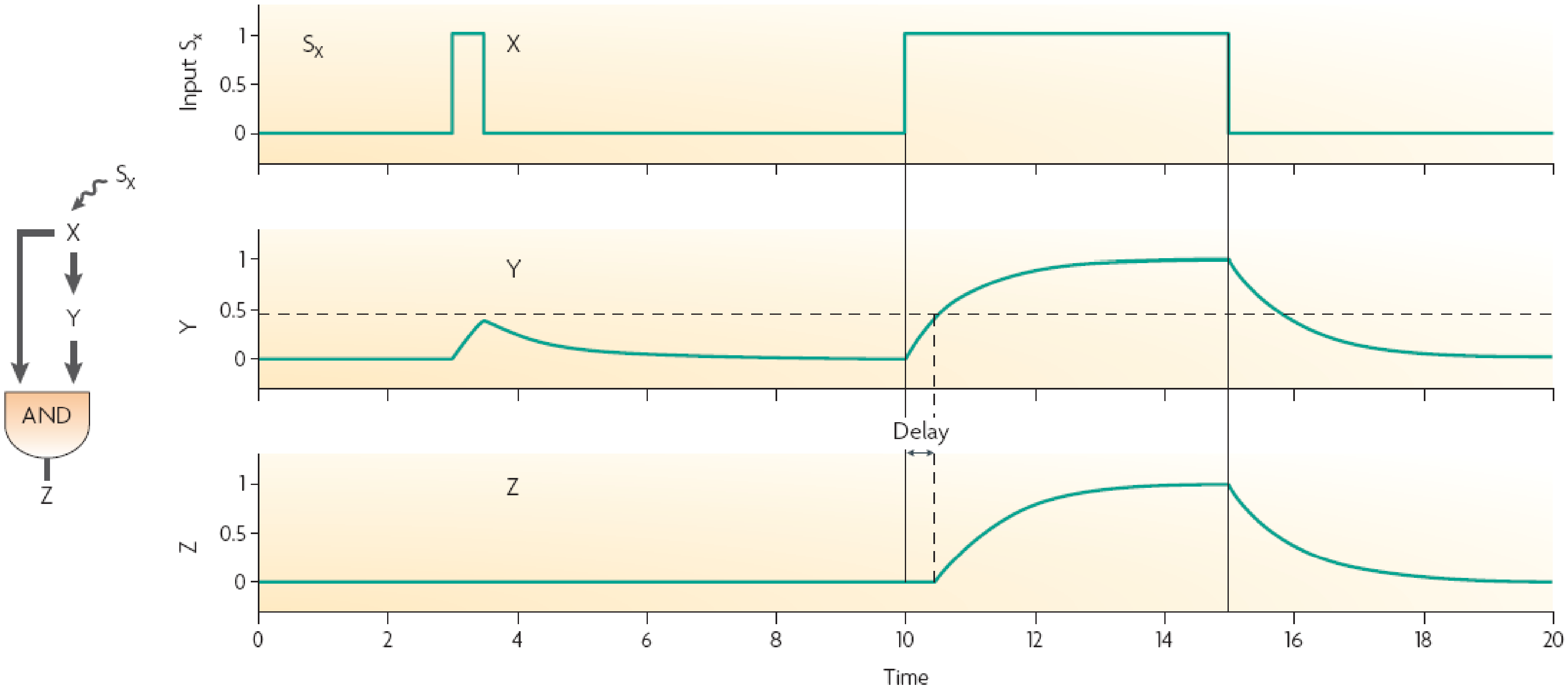
Integration of two regulators

- Much of the essential behaviour of FFLs can be understood by focusing on the stereotypical **AND** and **OR** gates.

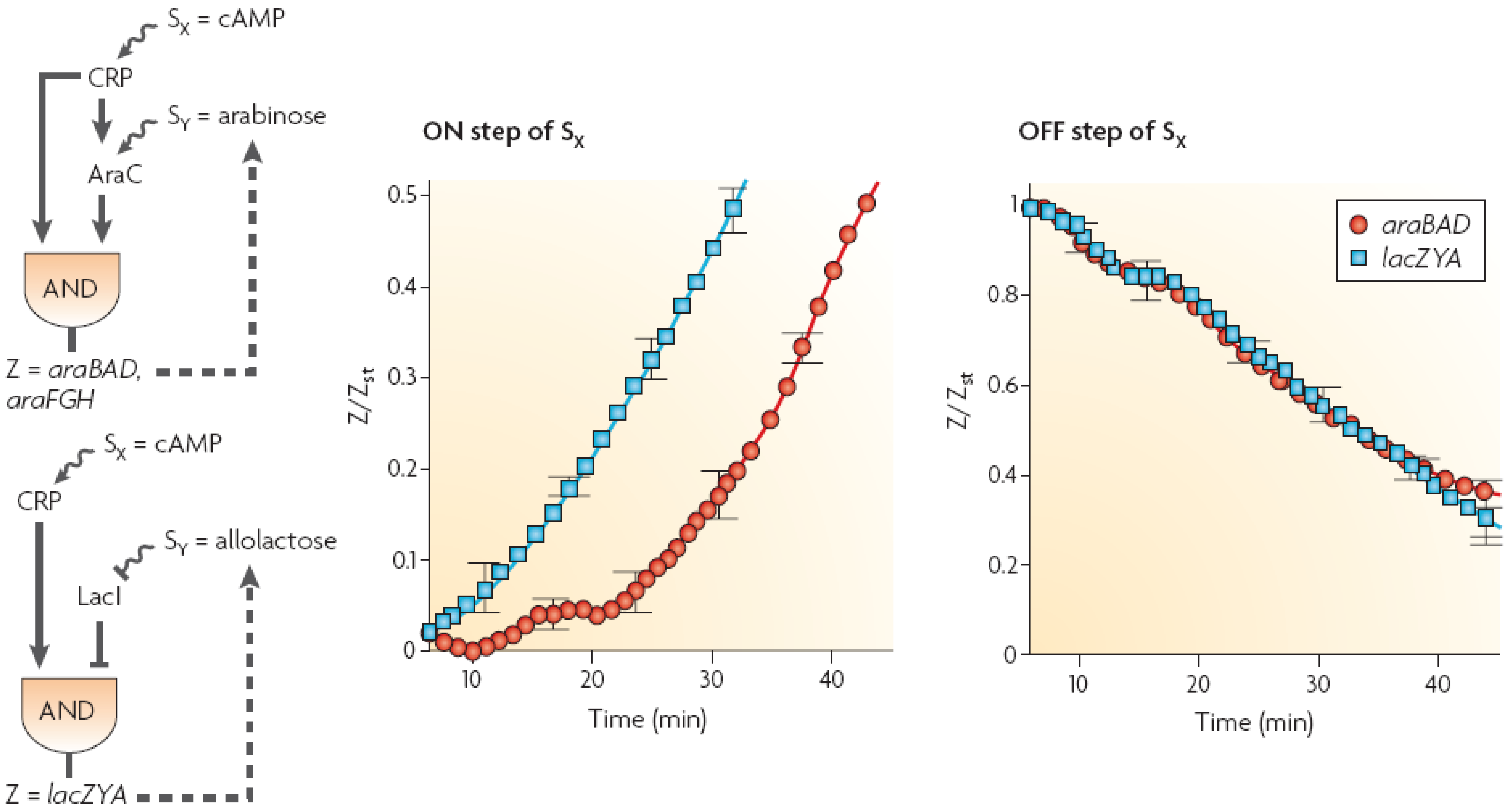


Coherent type-1 FFL (C1-FFL)

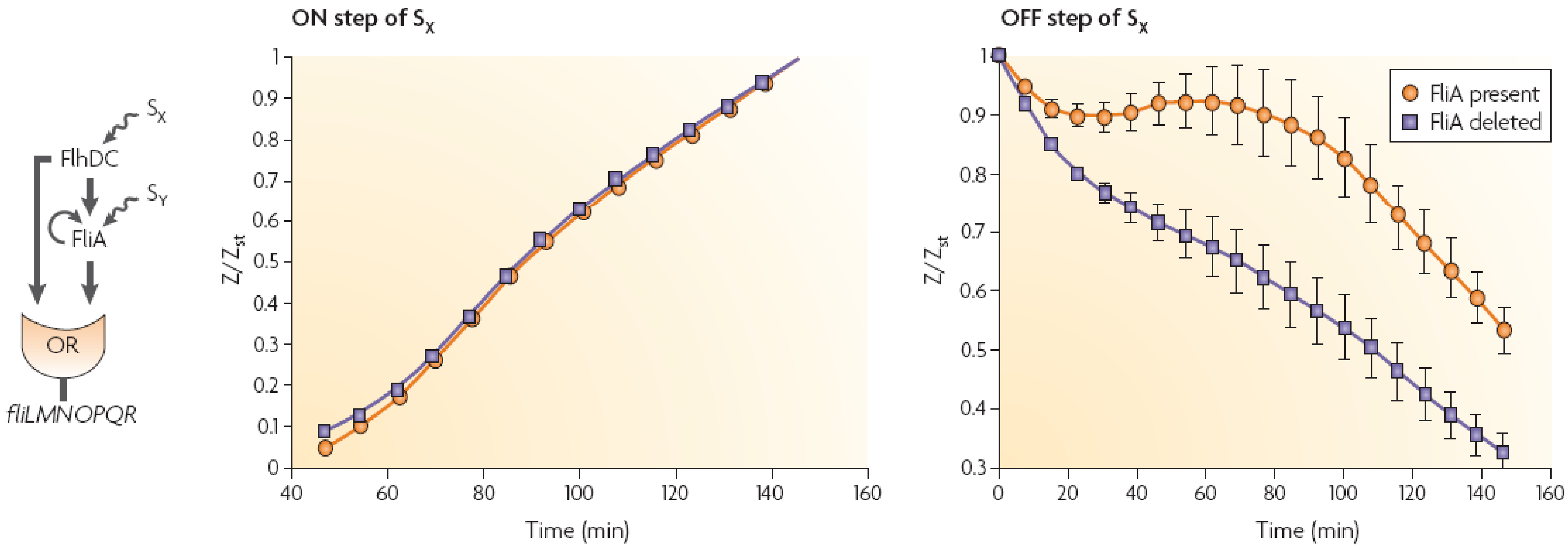
- The C1-FFL is a 'sign-sensitive delay' element and a persistence detector.



Arabinose and lactose systems

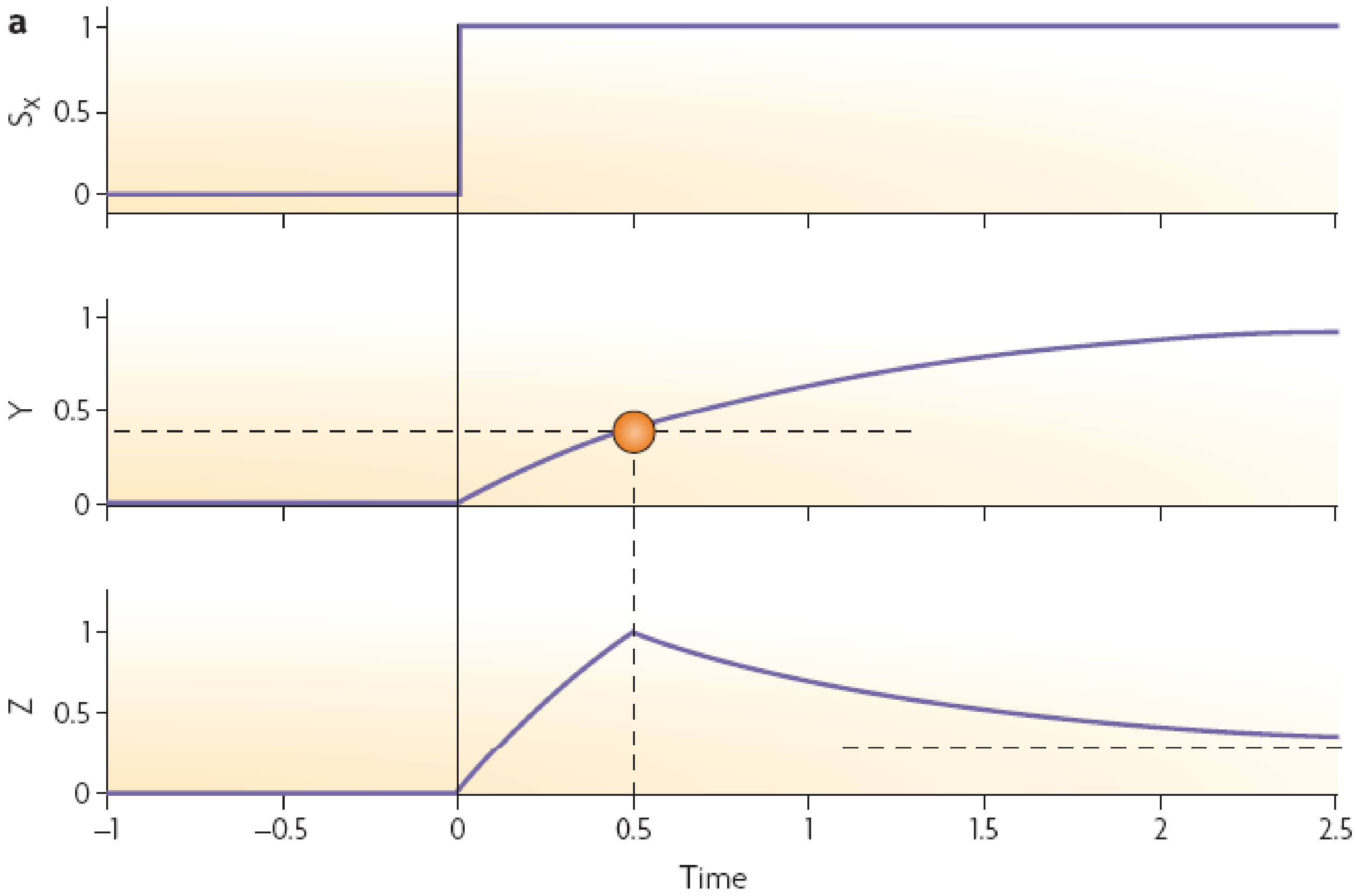


Flagella system of *E. coli*



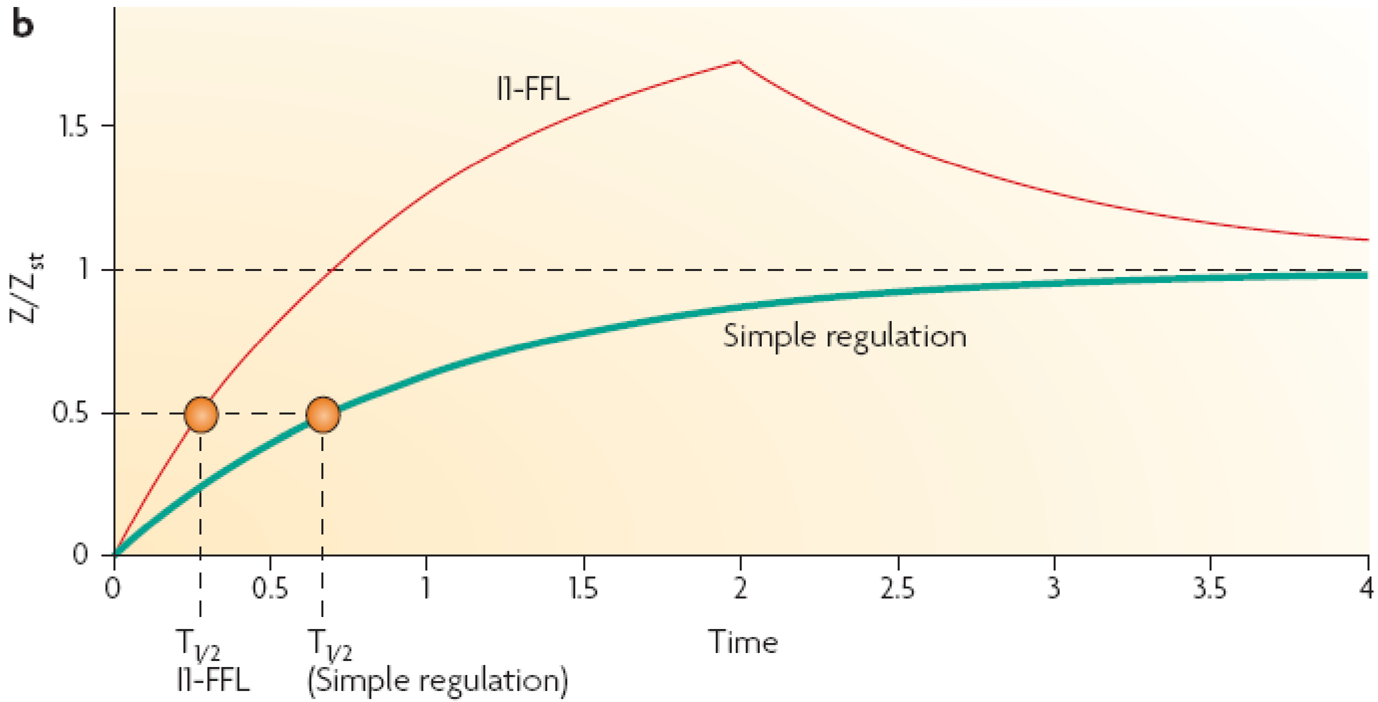
Incoherent type-1 FFL (I1-FFL)

- The I1-FFL is a pulse generator.



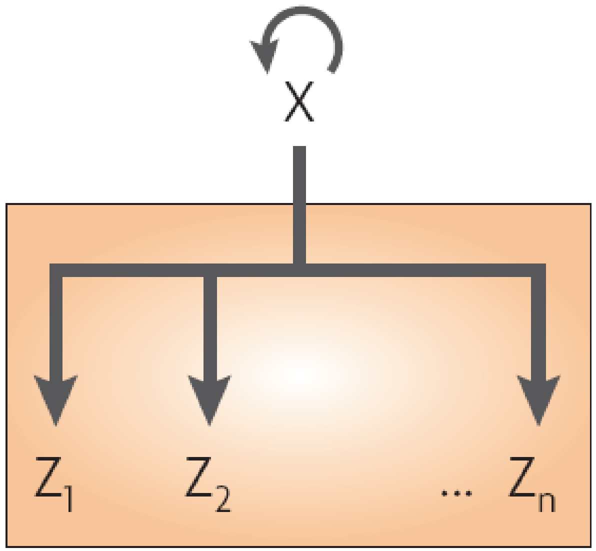
Incoherent type-1 FFL (I1-FFL)

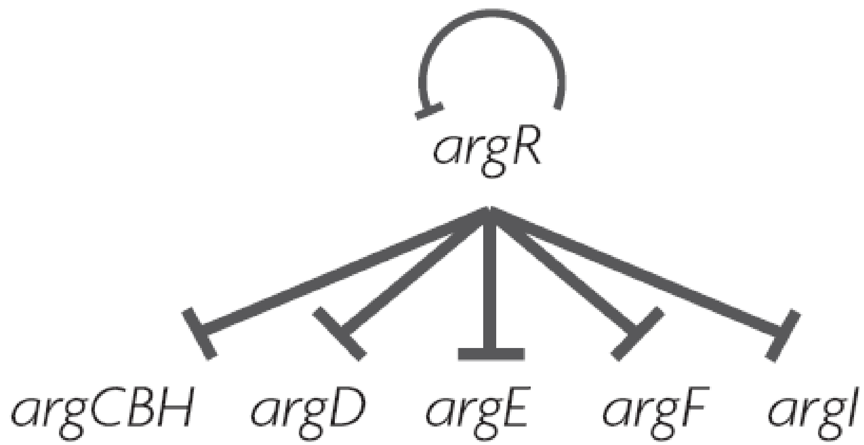
- The I1-FFL is also a response accelerator.
- NAR speeds up responses only on transcription factors whereas the I1-FFL can accelerate any target gene Z.



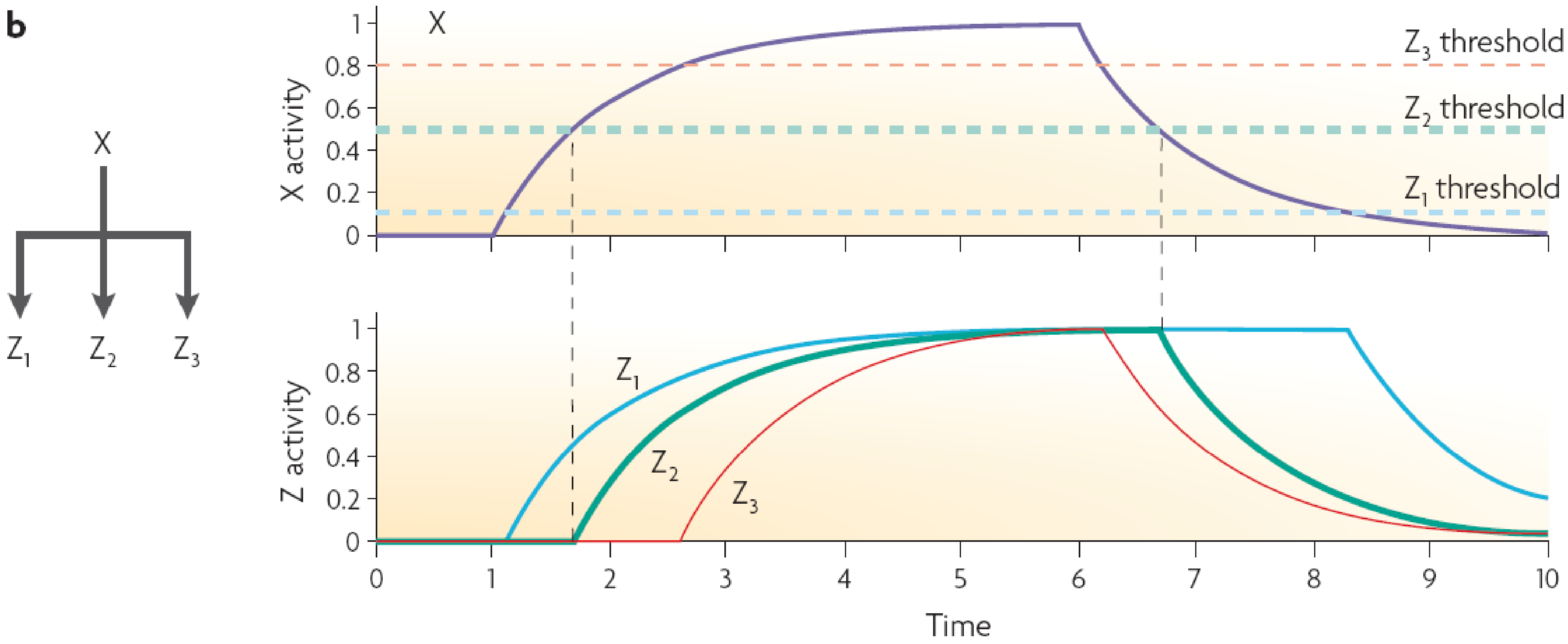
Single-input module (SIM)

- A regulator X regulates a group of target genes.
- In the purest form, no other regulator regulates any of these genes.
- X also typically regulates itself.





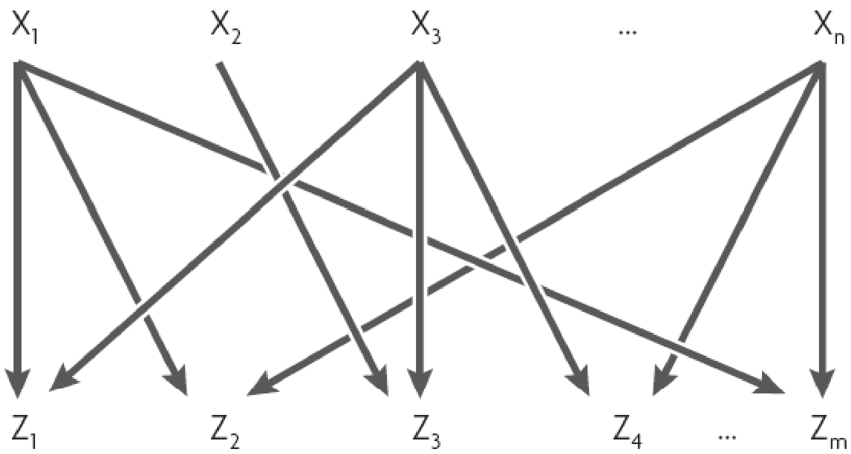
Temporal order of expression in a SIM

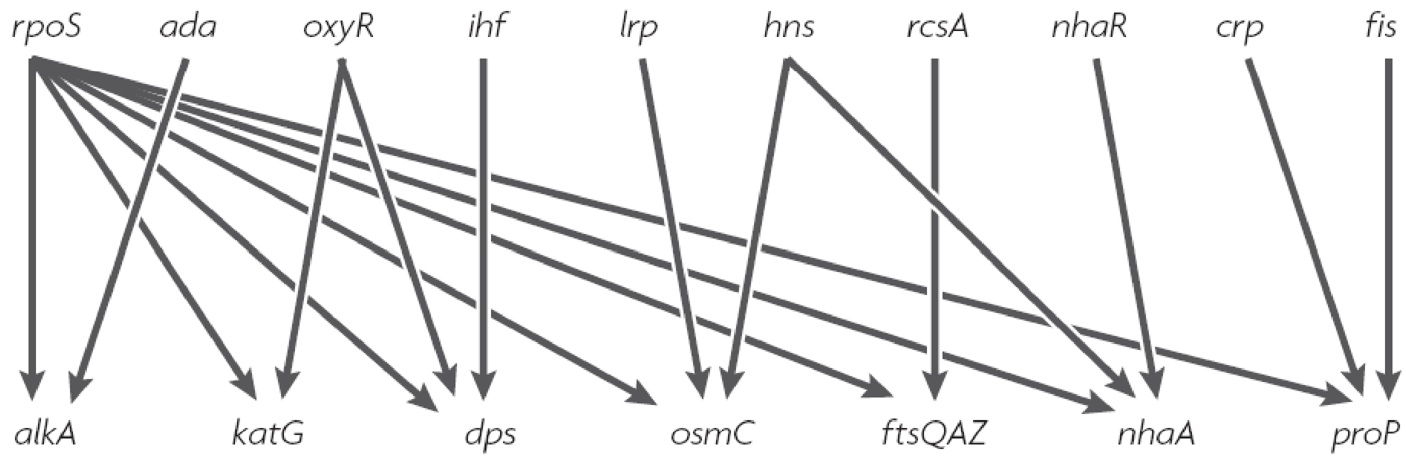


Multi-output FFLs & SIM

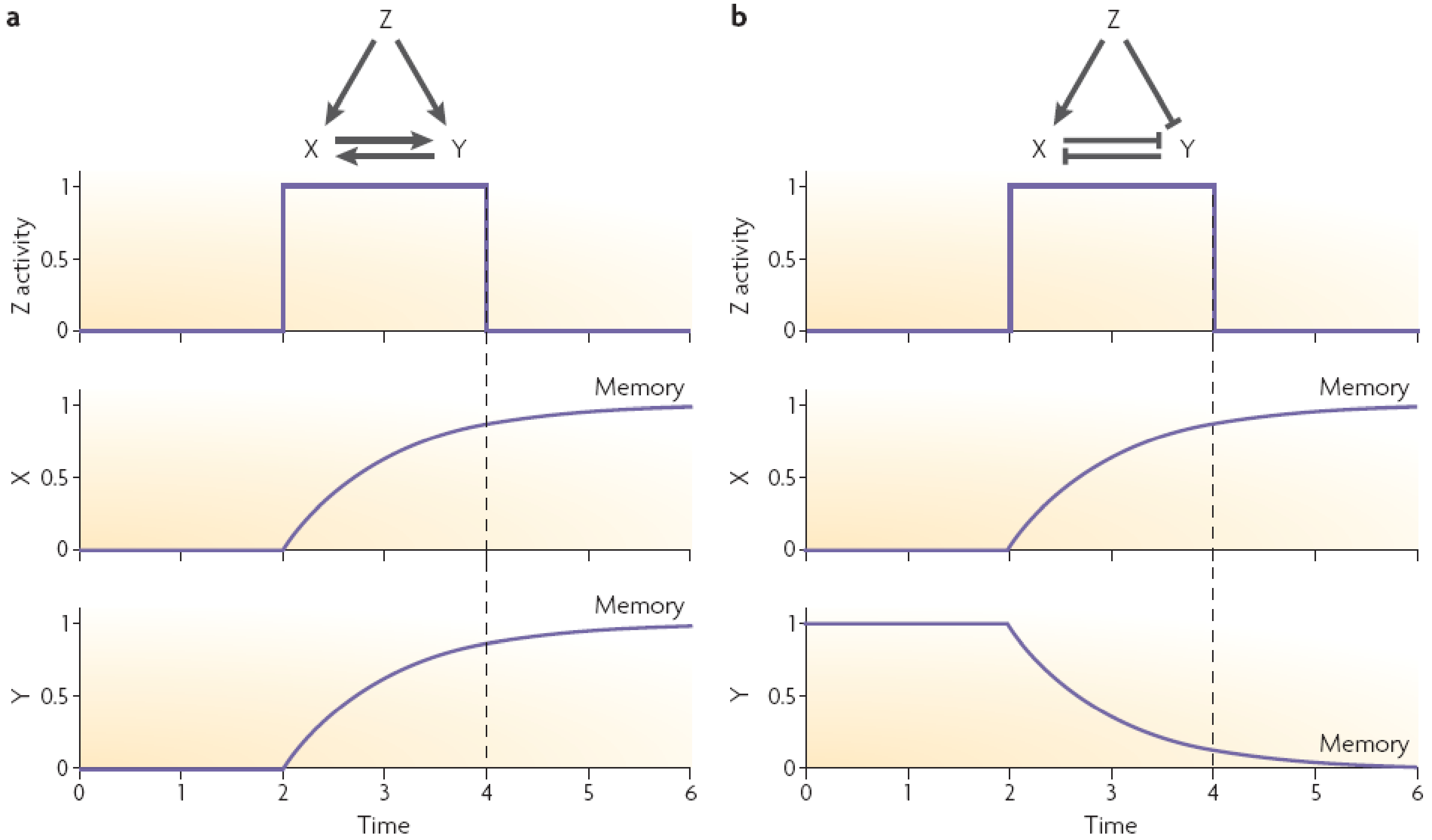
- Both can generate temporal orders of gene activation and inactivation by means of a hierarchy of regulation thresholds for the different promoters.

Dense overlapping regulon (DOR)

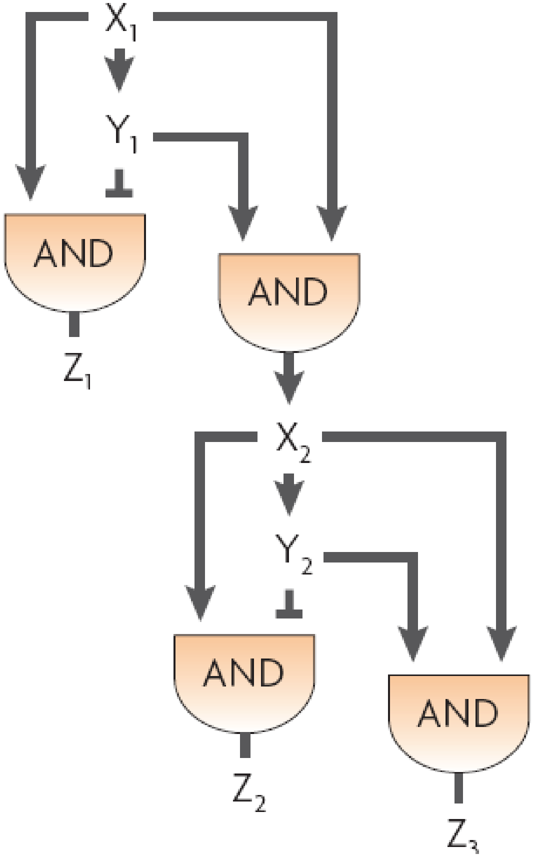


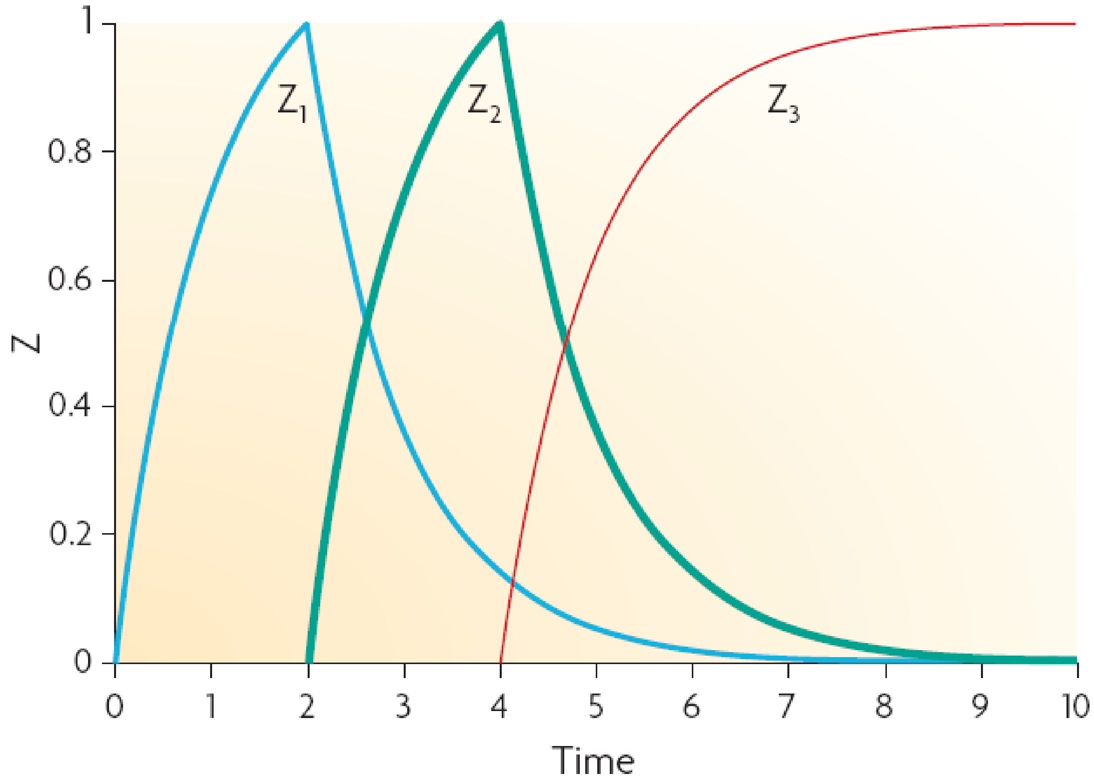


Developmental networks - 1



Developmental networks - 2



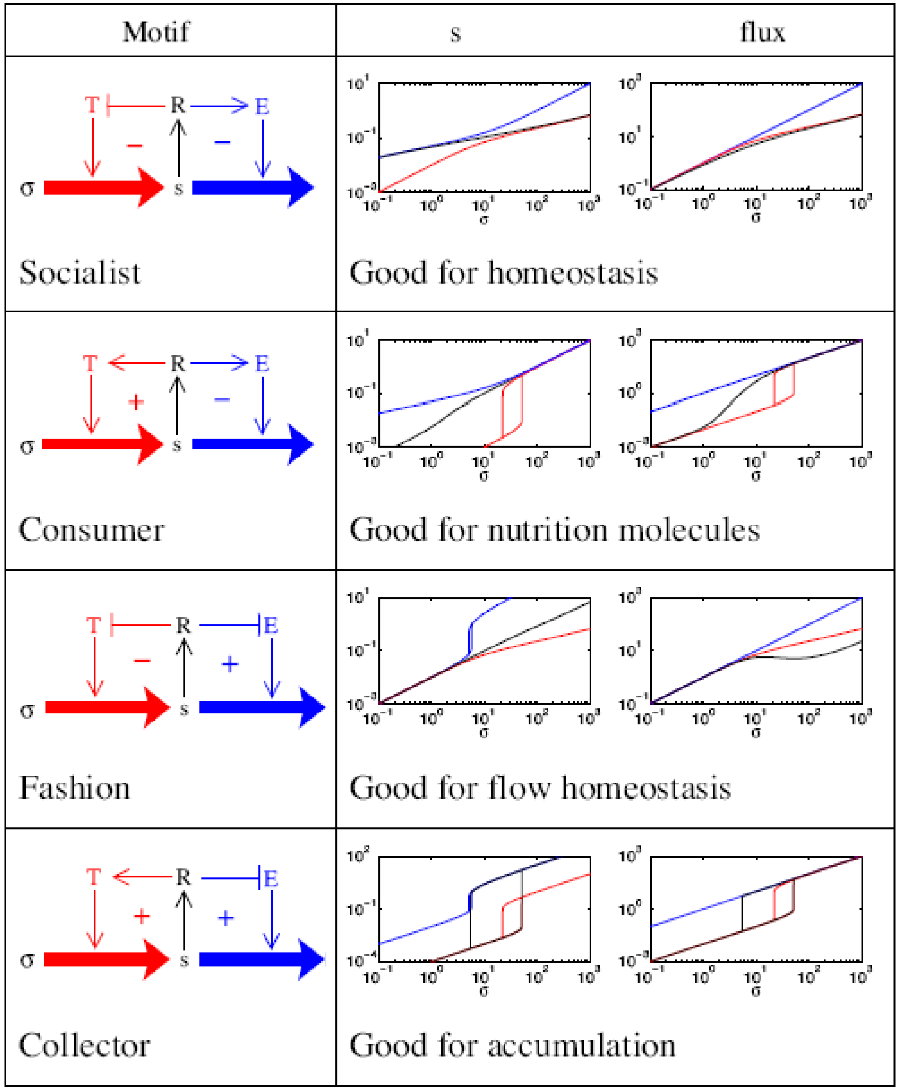


Feedback

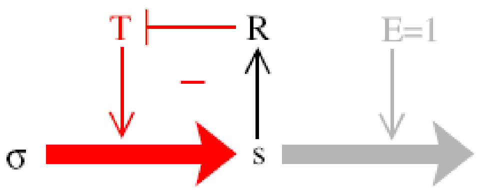
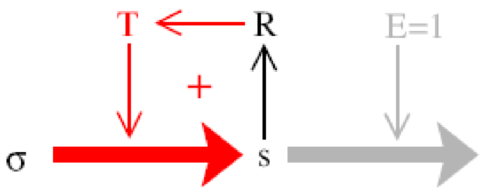
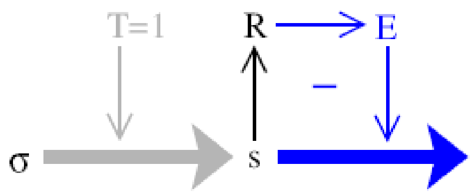
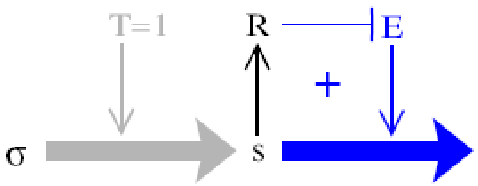
- Feedback always acts a role in biological regulation.
- Reflecting the need of the living cell to deal with changing environments;
- To generate cell to cell heterogeneity;
- And to optimize cellular metabolism to a given external condition.

Four Combinations of Transport and Metabolic Feedback

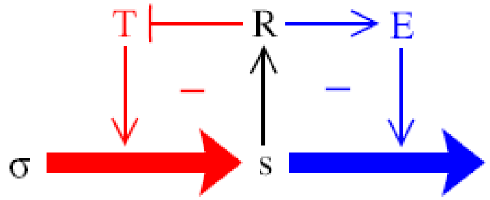
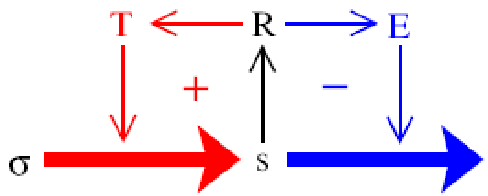
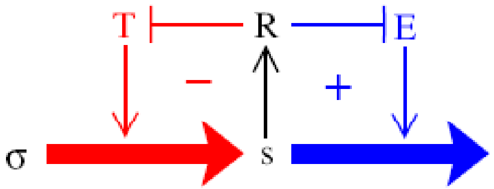
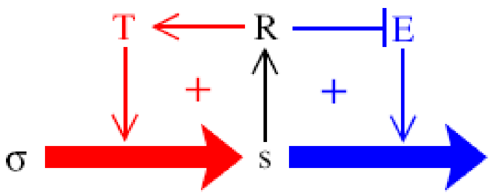
- The Socialist Motif
- The Consumer Motif
- The Fashion Motif
- The Collector Motif



The main features of single loop

Motif	s	flux
	At low σ, s grows linearly with σ At high σ prevents s from growing large	At low σ, flux grows linearly with σ At high σ prevents flux from growing large
	Causes bistability Outside the bistable range s is proportional to σ	Causes bistability Outside the bistable range flux is proportional to σ
	At high σ, s grows linearly with σ At low σ prevents s from falling too low	Flux grows linearly with σ for all values of σ
	Causes bistability Outside the bistable range s is proportional to σ	Flux grows linearly with σ for all values of σ

The main features of double loops

	s is kept within a narrow range at both low and high σ	At low σ, flux grows linearly with σ At high σ prevents flux from growing large
	No bistability s grows (almost) linearly with σ	No bistability flux has steep increase at intermediate σ
	No bistability s grows linearly with σ	flux is non–monotonic for intermediate σ outside this range it grows linearly with σ
	Bistability; s is proportional to σ Bistable range is larger than either single loop	Bistability; flux is proportional to σ Bistable range is larger than either single loop

Concluding Remarks

- Transcription networks contain a small set of recurring regulation patterns, called network motifs.
- As networks become better characterized, new motifs and new motif functions will doubtless be discovered.

Concluding Remarks (Cont'd)

- The qualitative features of two-loop motifs are robust to a weakening of one or the other loop.
- Combinations are more than the sum of their single loops.