Design patterns of biological cells

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Design patterns paper

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REVIEW

Design patterns of biological cells

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Abstract

Design patterns are generalized solutions to frequently recurring problems. They were initially developed by architects and computer scientists to create a higher level of abstraction for their designs. Here, we extend these concepts to cell biology to lend a new perspective on the evolved designs of cells' underlying reaction networks. We present a catalog of 21 design patterns divided into three categories: creational patterns describe processes that build the cell, structural patterns describe the layouts of reaction networks, and behavioral patterns describe reaction network function. Apply-

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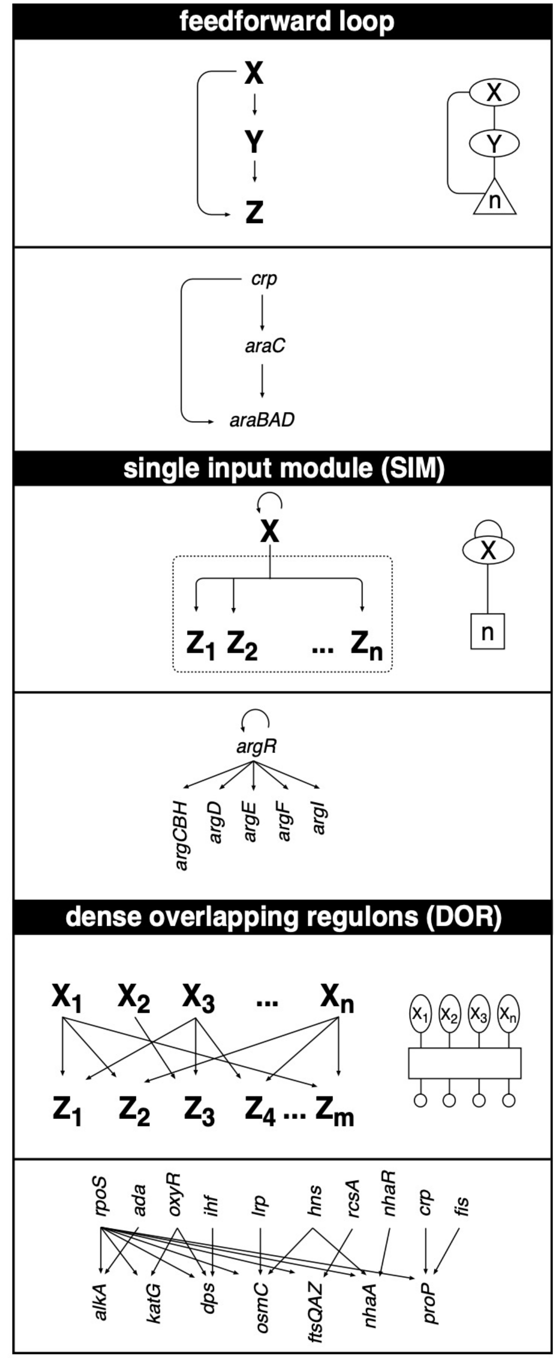
Motifs

Motifs: statistically over-represented structures

Important work in Uri Alon’s group in 2002-2004:

Milo et al., Science 298:824, 2002
Shen-Orr et al., Nature Genetics 31:64, 2002
Alon, Nature Reviews Genetics 8:450, 2007

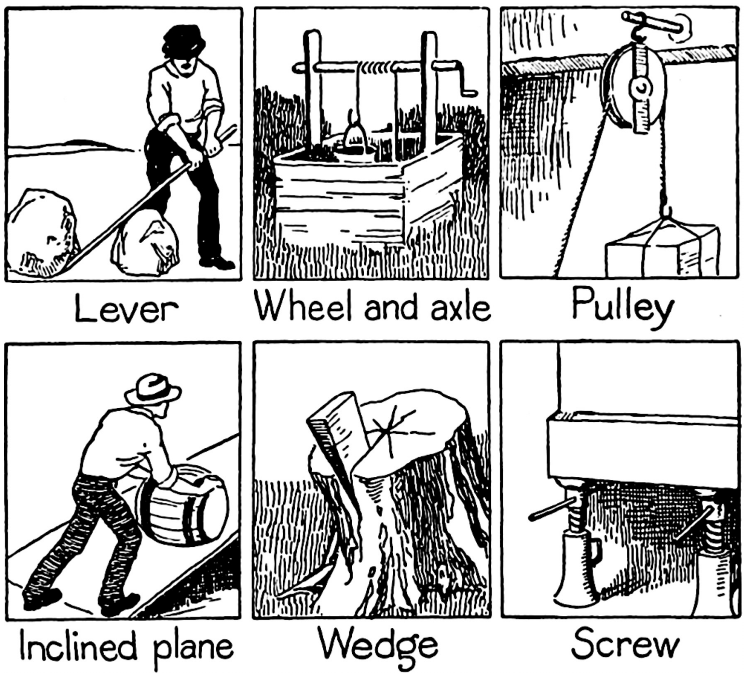
Purpose is often deduced from motifs, but is not a defining property.



Images: UW magazine; Shen-Orr et al., Nature Genetics 31:64, 2002.

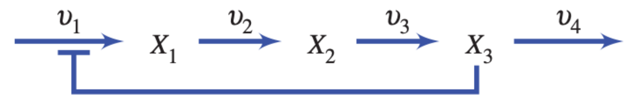
Mechanisms

Mechanism: a particular implementation

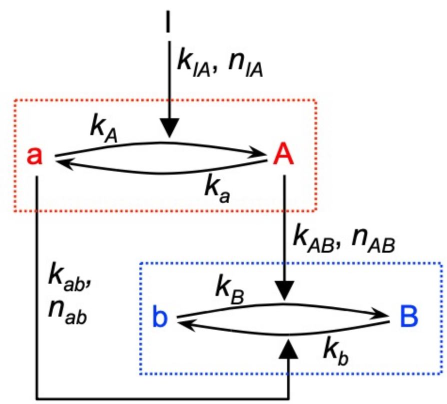


Multiple mechanisms can serve the same purpose.

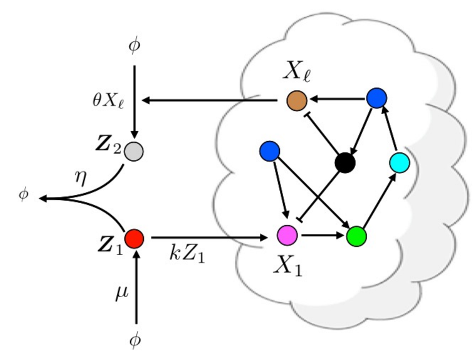
Negative feedback mechanism:



Push-pull mechanism:



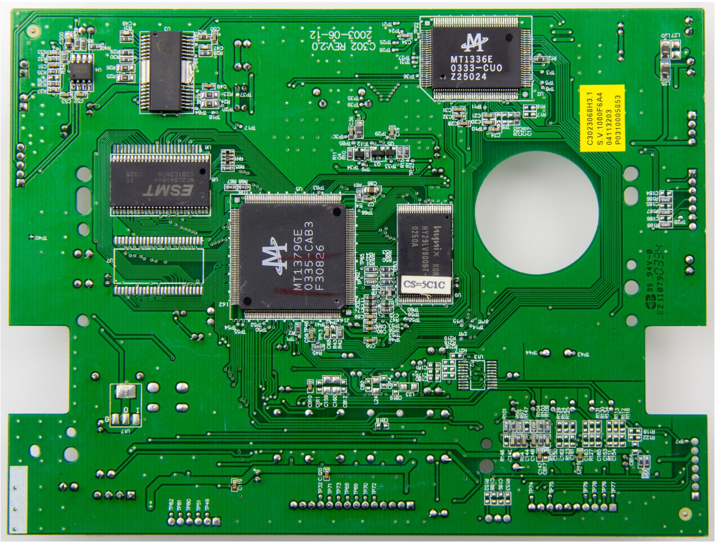
Antithetic integral control mechanism:

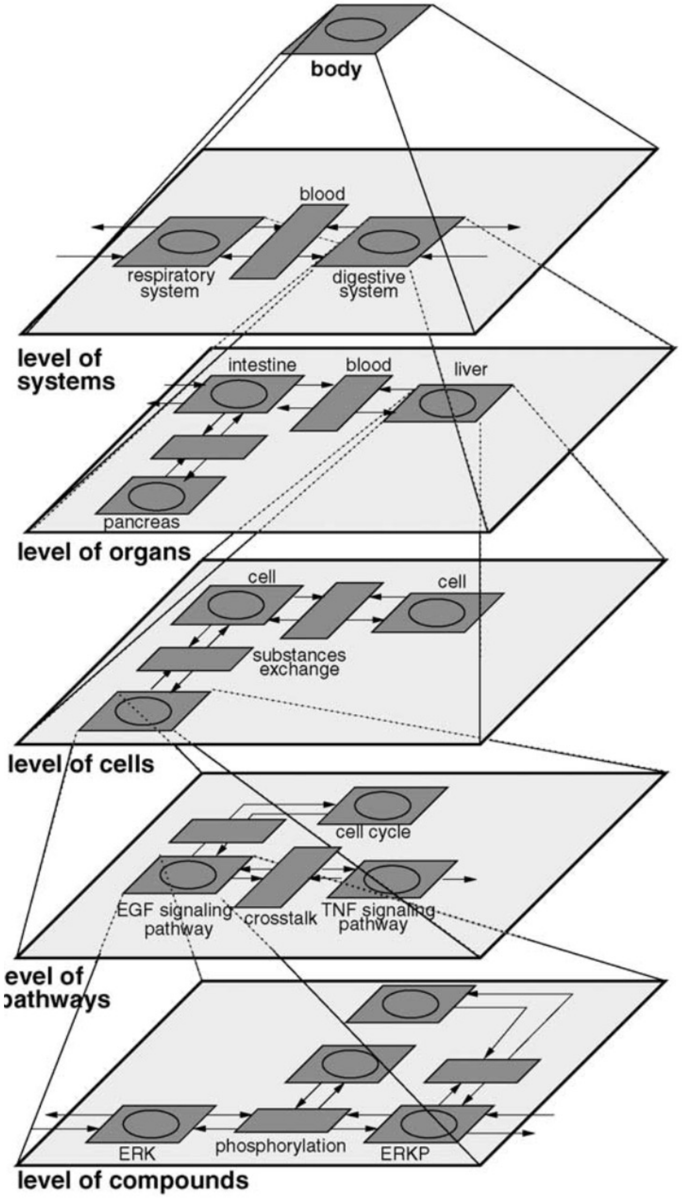


Images: Wikipedia “Simple machine”; Sauro, J. R. Soc. Interface 14:20160848, 2017; Andrews et al., Cell Systems 3:1, 2016; Briat et al., Cell Systems 2:15, 2016.

Modules

Module: a subsystem that behaves sufficiently independently that it retains its intrinsic properties irrespective of what it's connected to.





Modules have inputs and outputs. "Ideally", their inputs don't affect upstream processes, and downstream processes don't feed back to their outputs. Reality includes retroactivity.

Images: Wikipedia "Printed circuit board"; Saez-Rodriguez et al., Computers and Chem. Eng. 29:619, 2005.

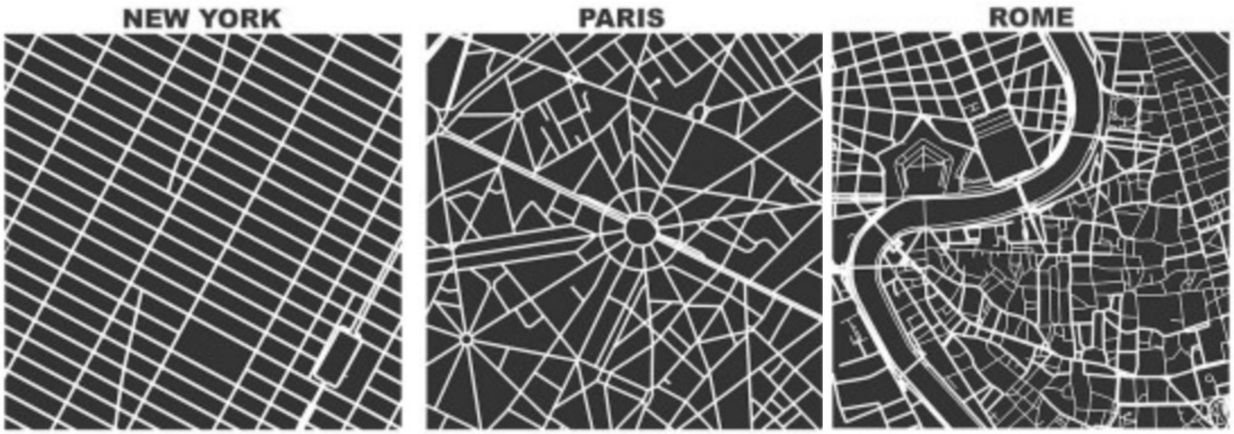
Design patterns

Design patterns: frequently used solutions to common problems.

Architecture concept from Christopher Alexander, 1966
Software concept by Gamma, Helm, Johnson, Vlissides, 1994, in influential book

problems: efficient traffic flow, livable city space

solutions:

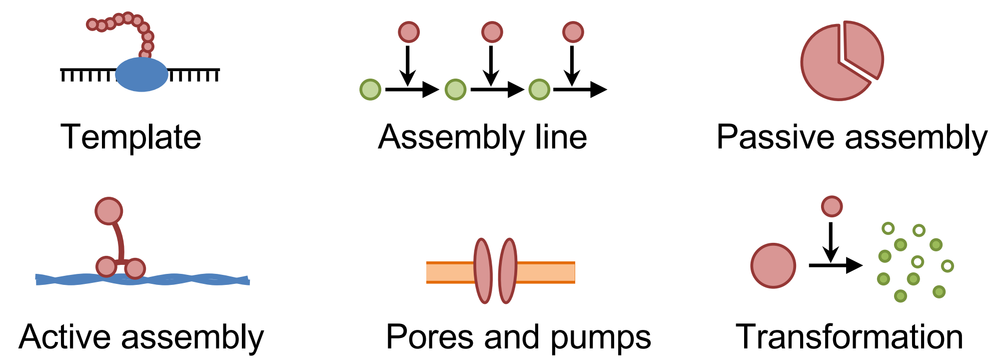


Do design pattern concepts apply to cell biology?

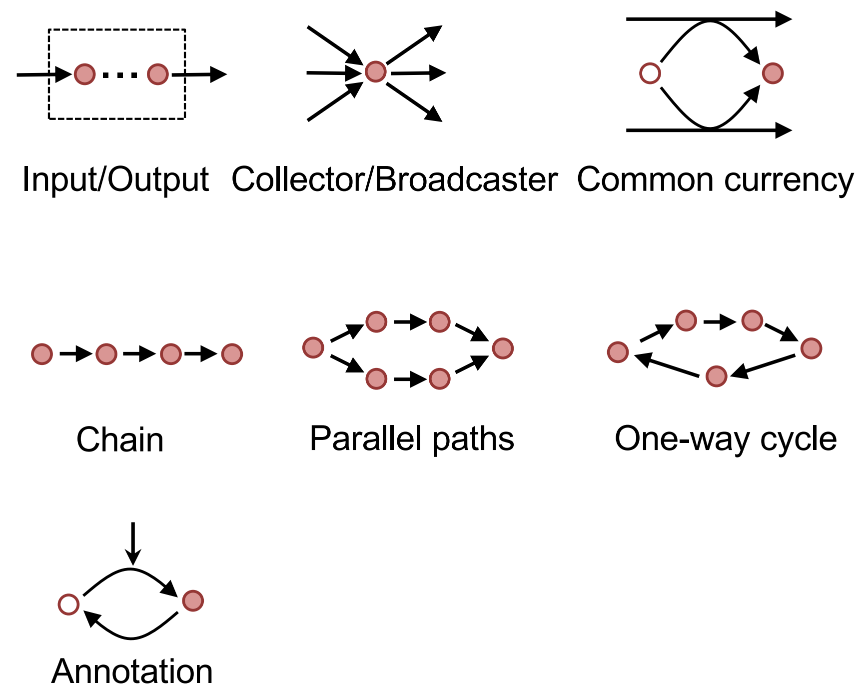
figure: https://99percentinvisible.org/article/on-the-grid-visualizing-street-network-orientations-across-50-global-cities/

Cell biology design pattern catalog

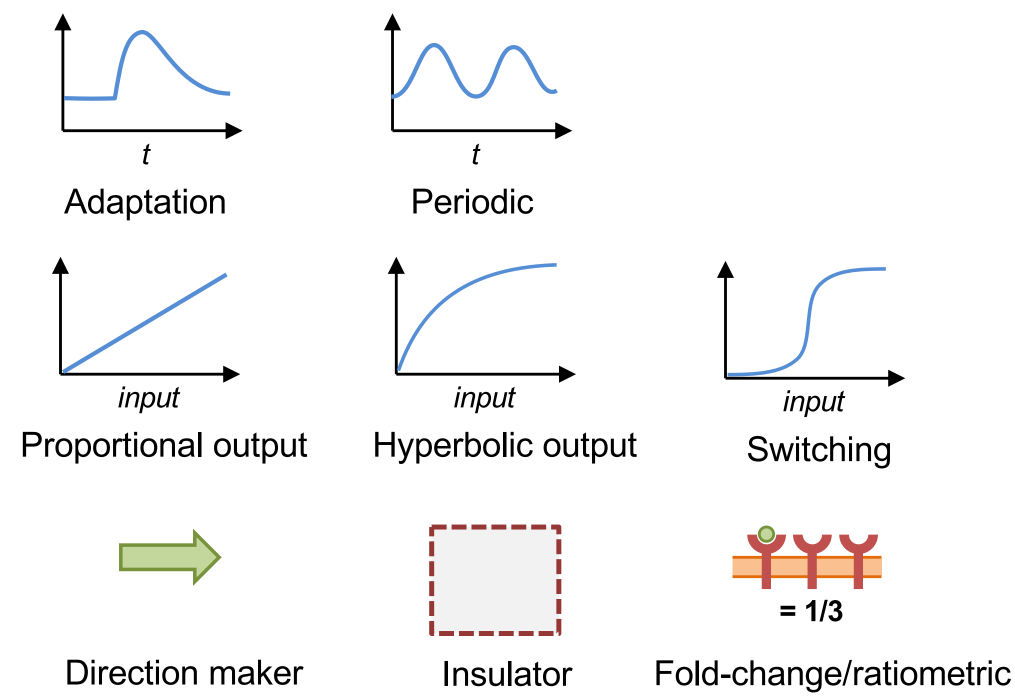
Creational patterns



Structural patterns

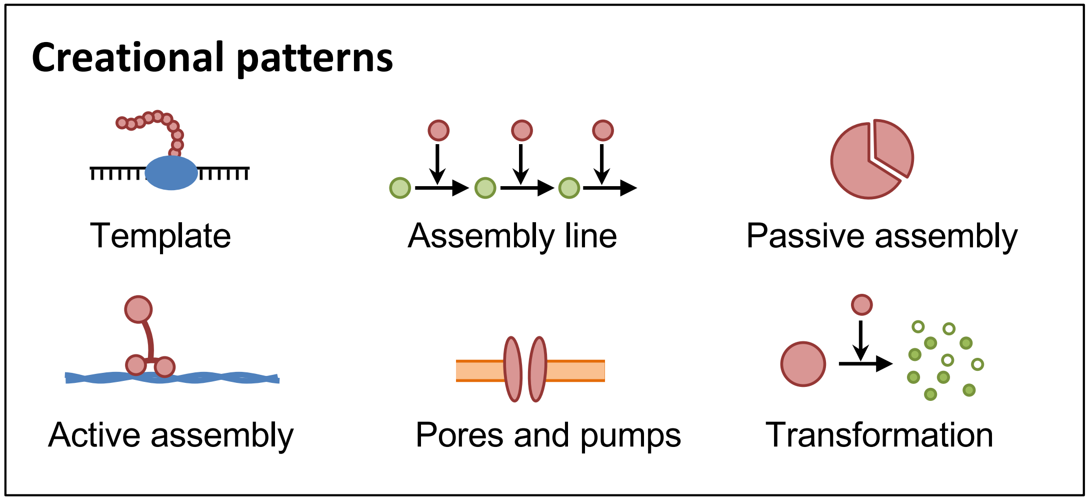


Behavioral patterns



Creational patterns

Creational patterns: how cells are assembled.



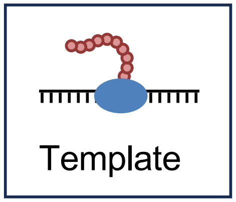
Template pattern

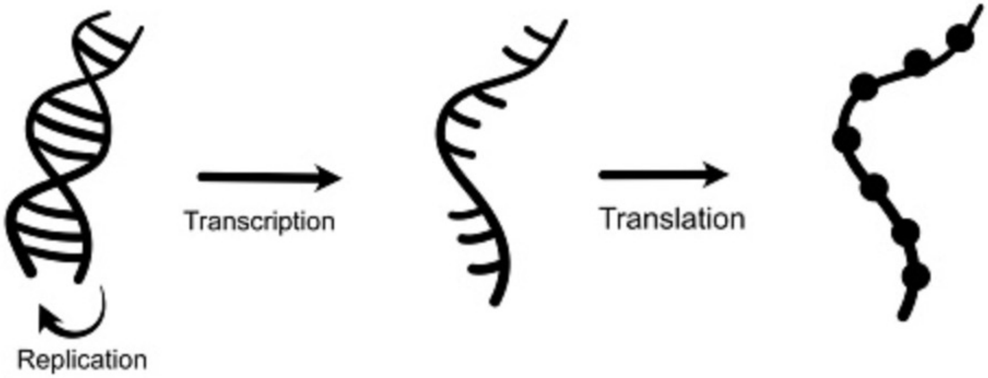
Problem: cells need molecules that are built from pre-specified designs.

Solution: biosynthesis from a master copy (i.e. transcription, translation)

This is the ***template*** pattern.

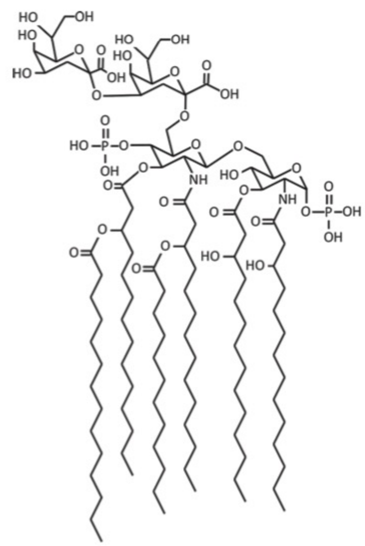
It is uniquely heritable and evolvable.





Assembly line pattern

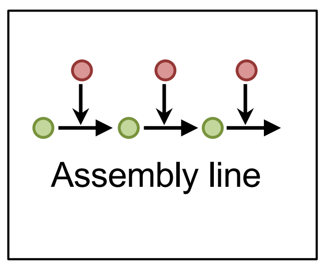
Problem: cells need functions that aren't available in proteins (e.g. lipids).



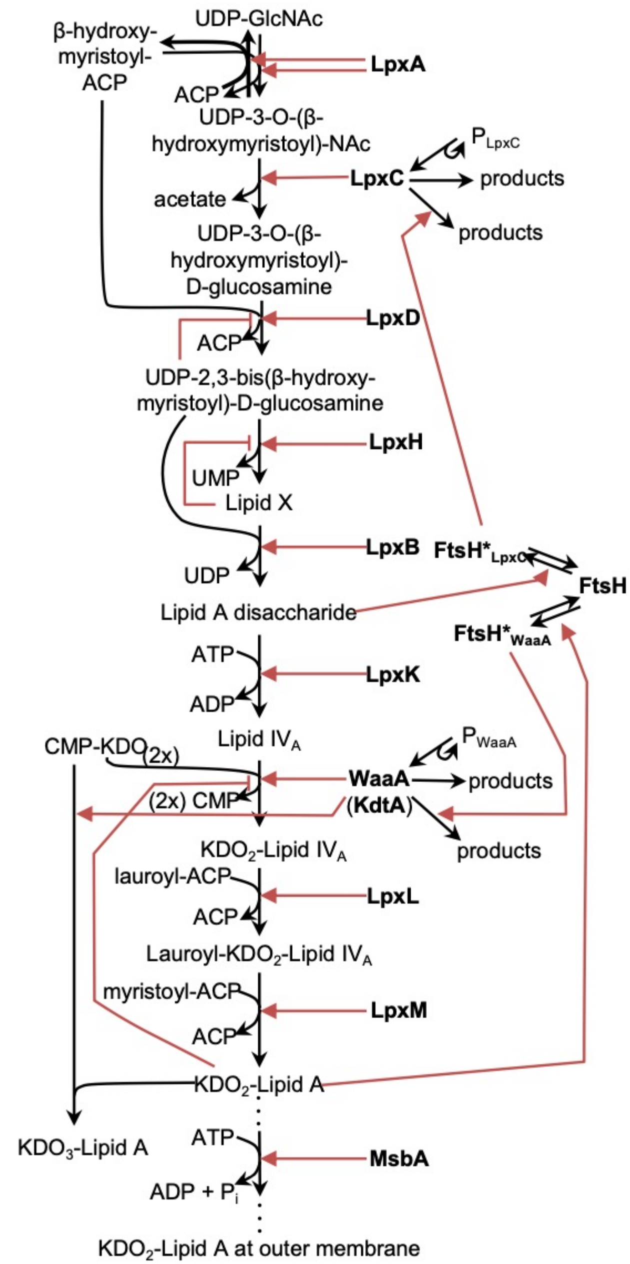
Solution: biosynthesis with a sequence of enzymes

This is the ***assembly line*** pattern

They invariably use negative feedbacks to control flux.



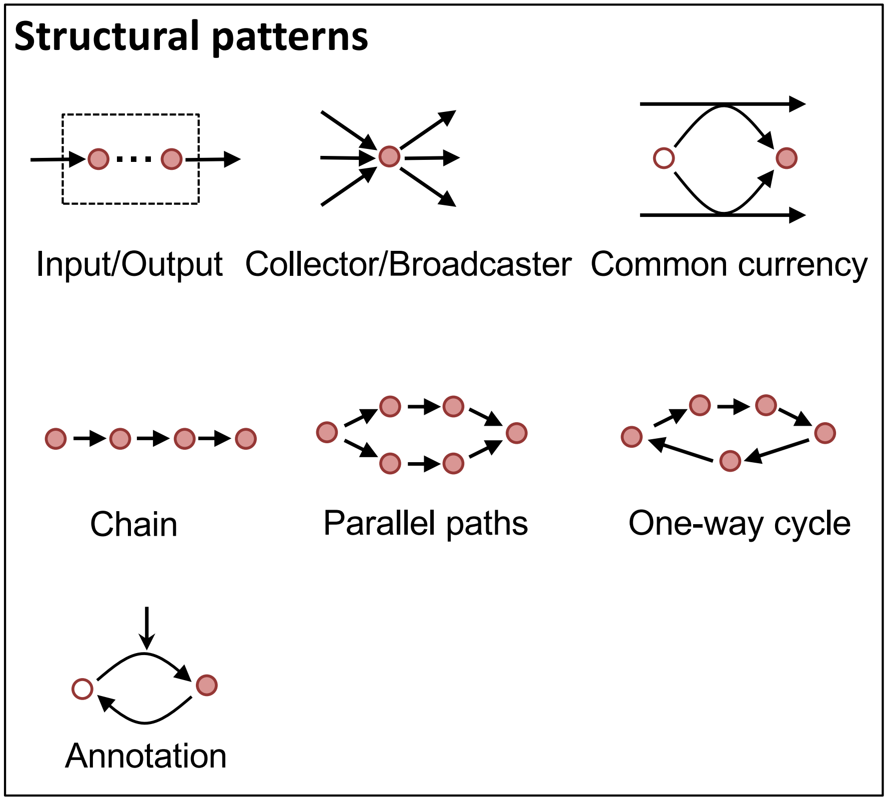
lipid synthesis assembly line



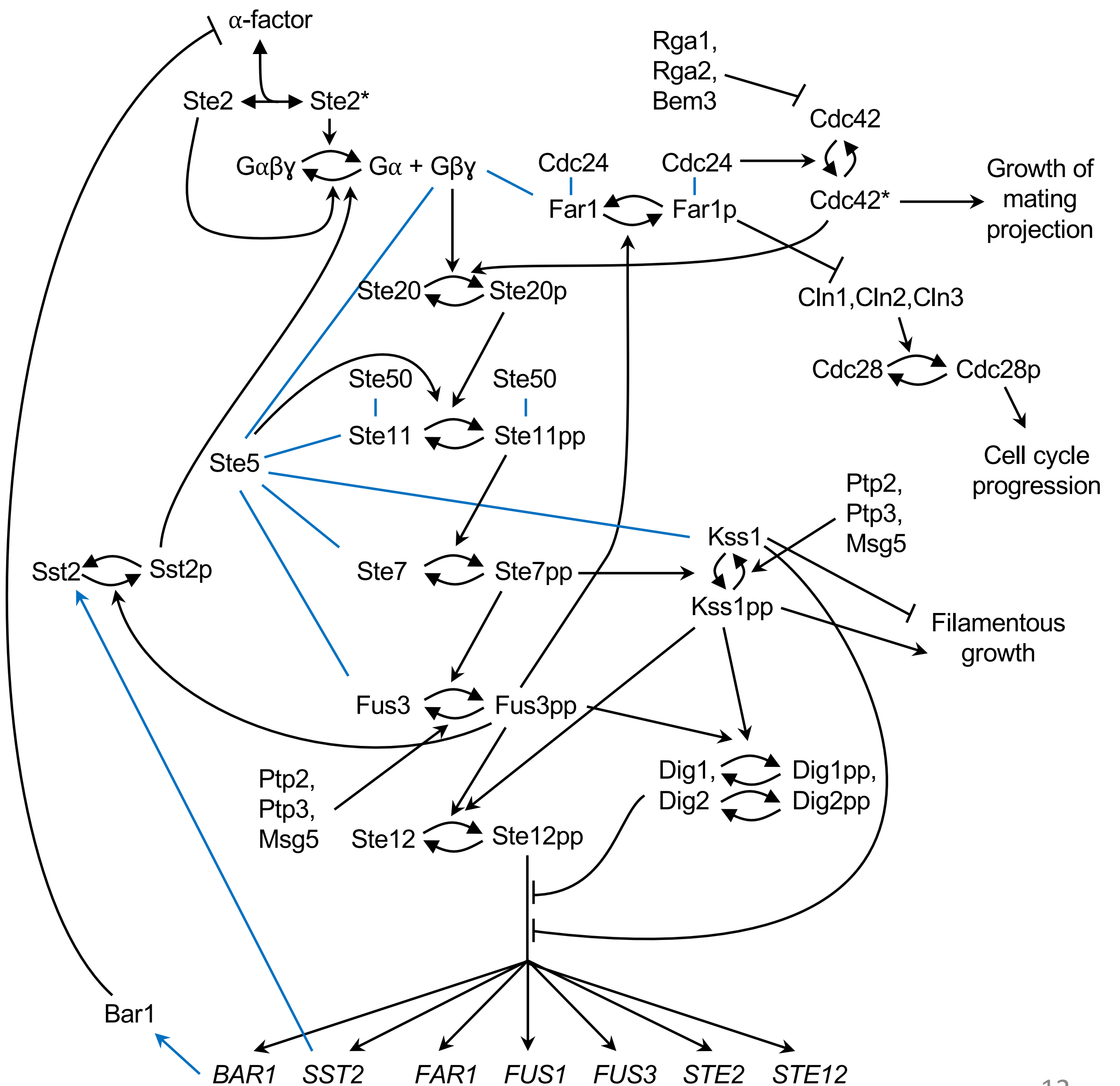
Figures: Emiola, George, Andrews, PLoS ONE 10:e0121216, 2015.

Structural patterns

Structural patterns: topological structures of chemical reaction networks



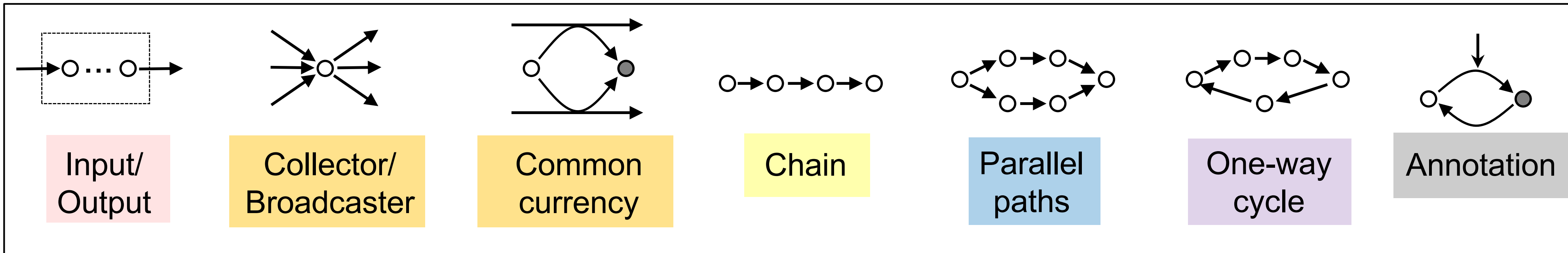
Yeast pheromone response network



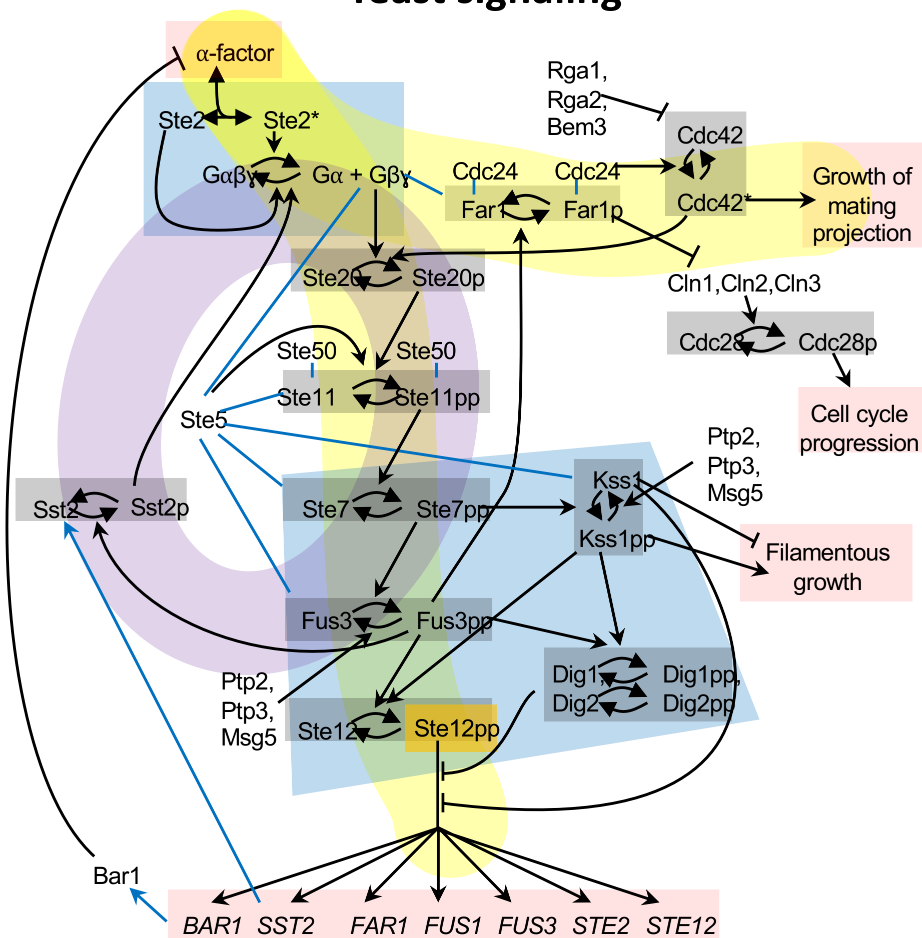
Structural patterns

What are the patterns in biochemical reaction networks?

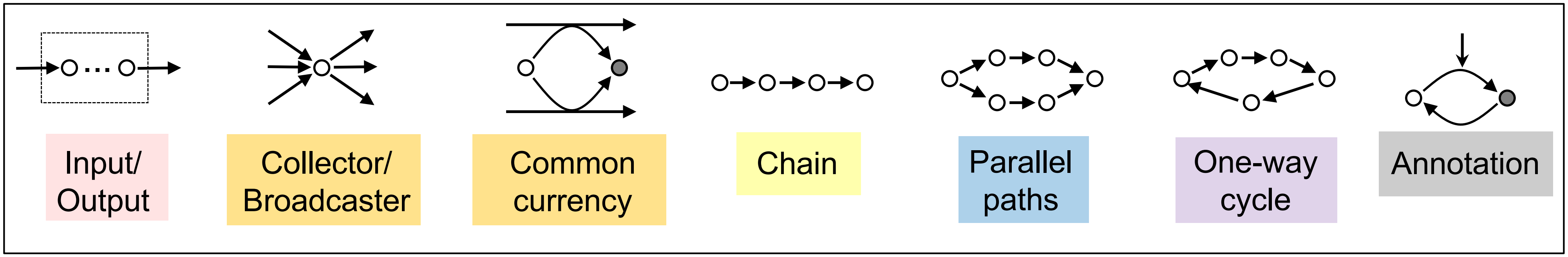
Cell biology design patterns: Structural patterns



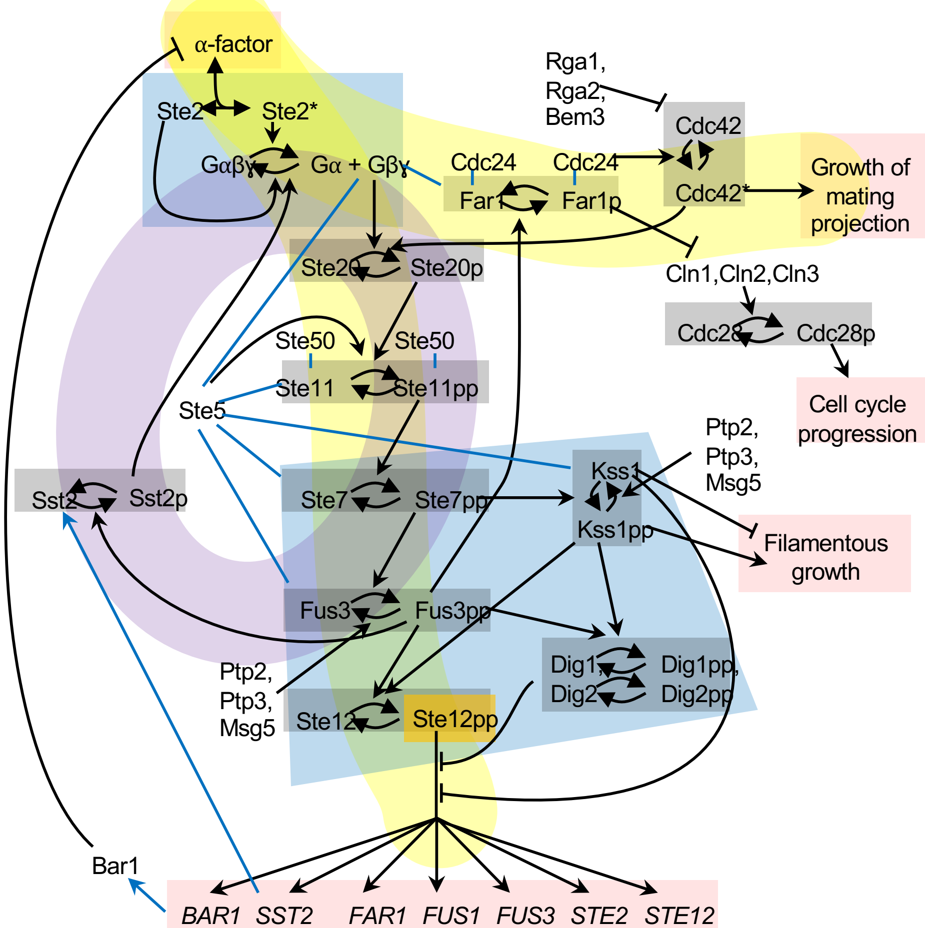
Yeast signaling



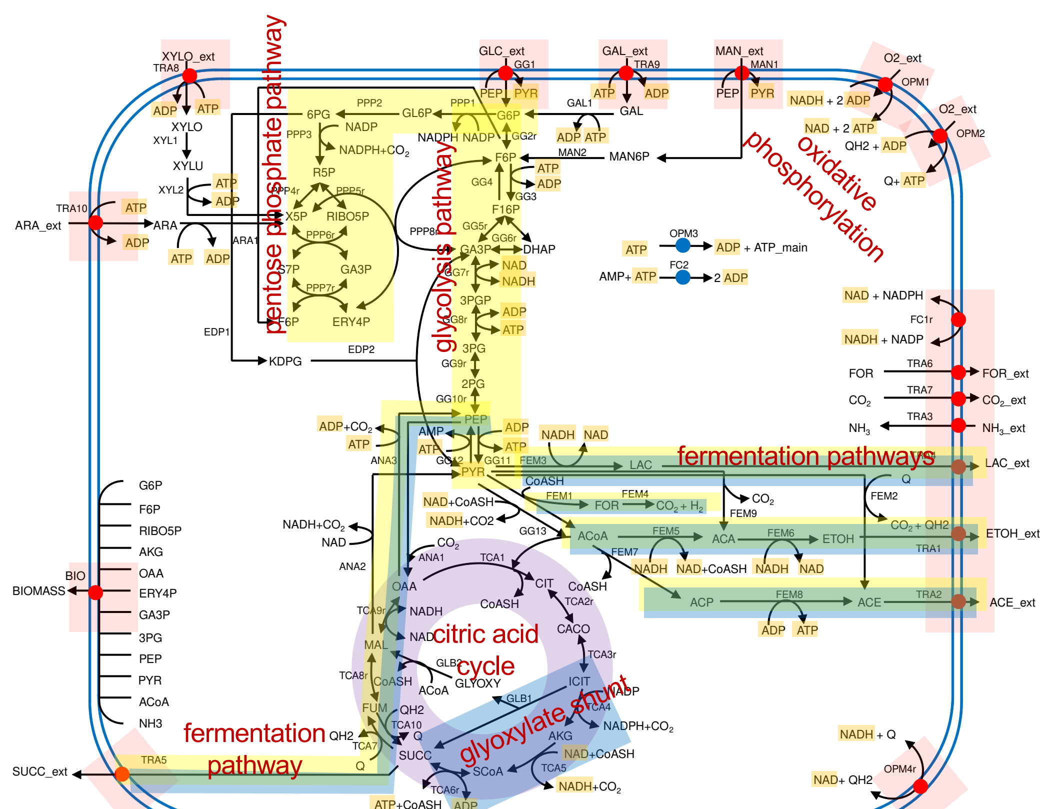
Cell biology design patterns: Structural patterns



Yeast signaling

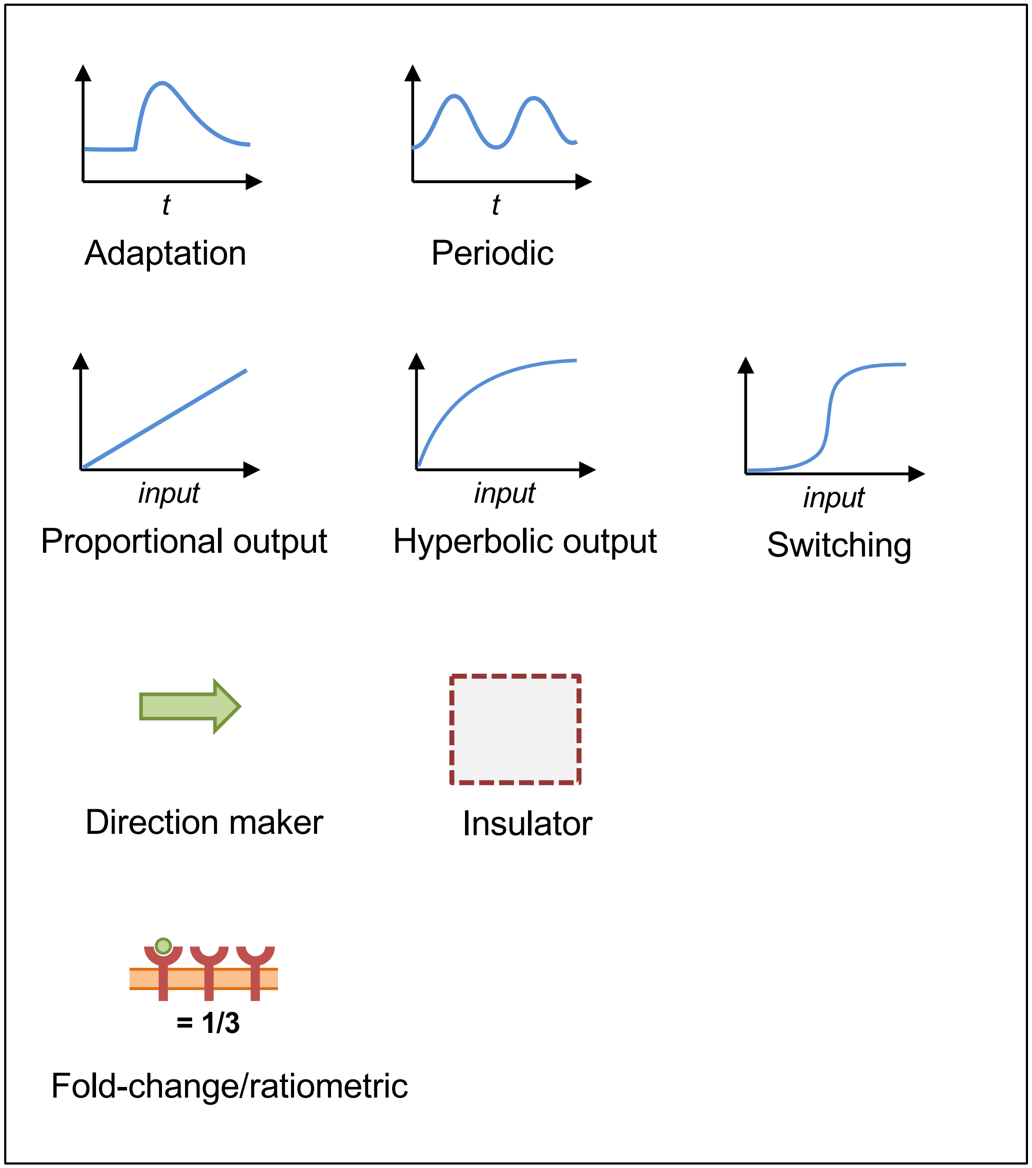


E. coli metabolism



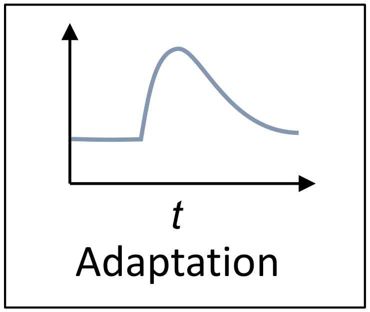
Behavioral patterns

Behavioral patterns: what a cell does



- Time-dependent behaviors
- Input/output behaviors
- Module behaviors
- Sensing behaviors

Adaptation pattern

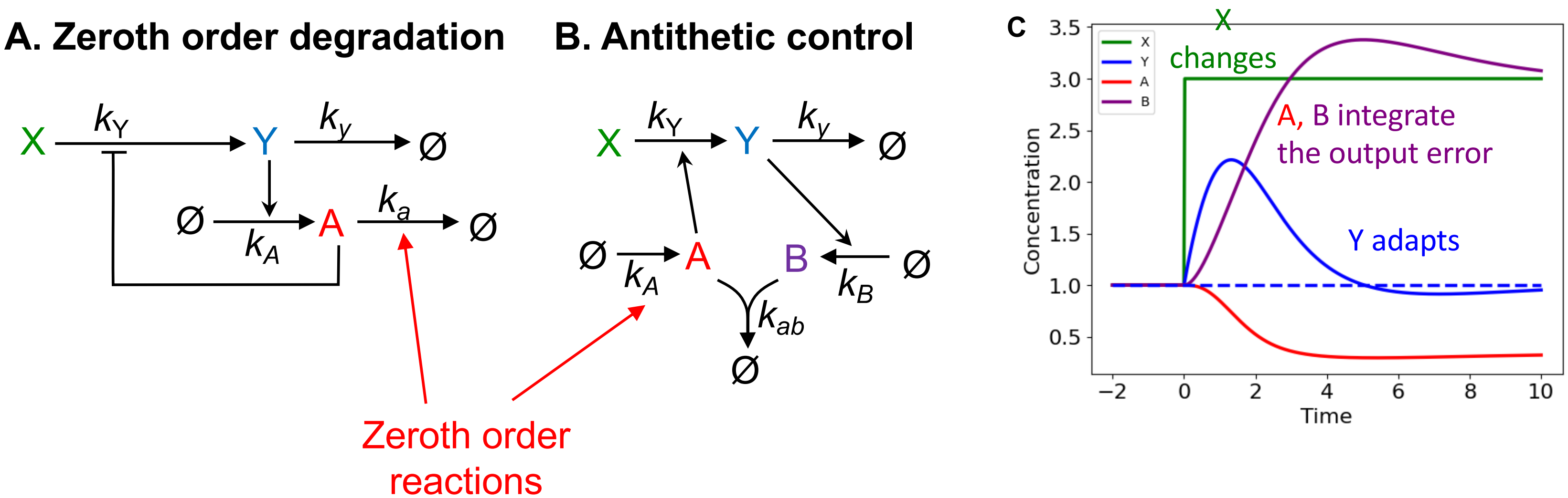


Observed in:

- endotherm temperature homeostasis
- mammalian blood glucose despite exercise
- dairy cow blood calcium despite milk production
- plant root nitrate levels despite environment
- *E. coli* swimming behavior

- Perfect adaptation *always* uses integral feedback control*.

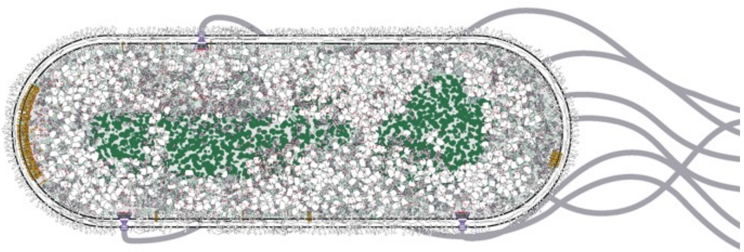
- Two known mechanisms for this:



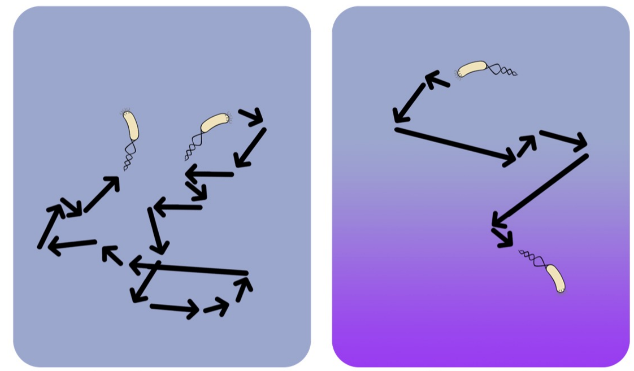
* Yi, Tau-Mu, et al. *PNAS* 97.9 (2000): 4649-4653.

Adaptation pattern example: *E. coli* chemotaxis

E. coli cell



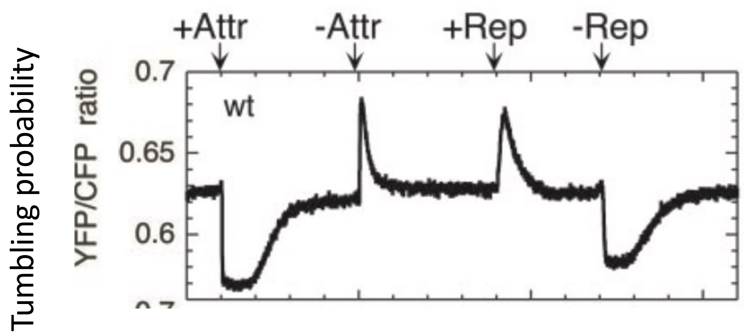
E. coli swim toward attractants (nutrients)



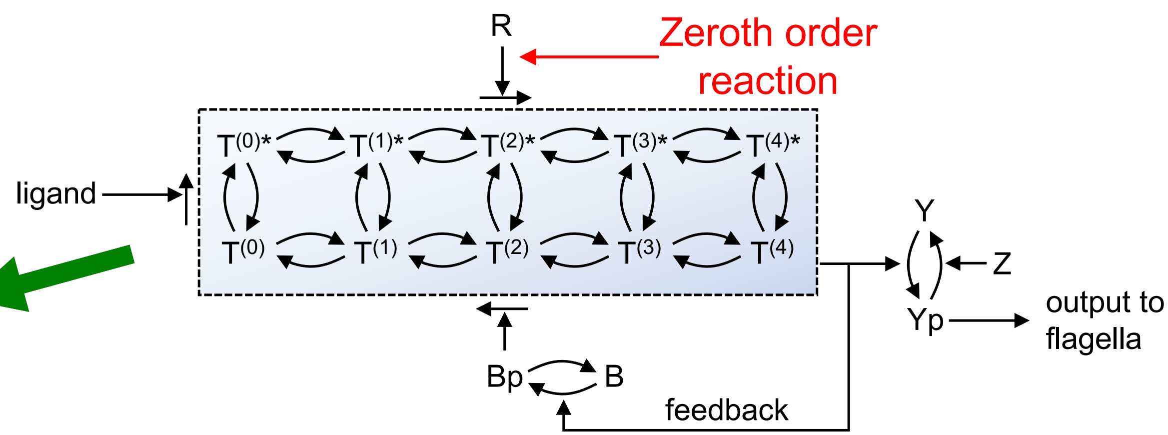
Random walk
(No stimulus)

Chemotaxis
(Positive stimuluse)

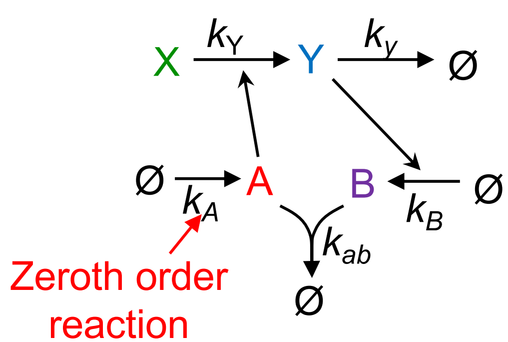
This chemotaxis relies on adaptation



Adaptation is created by the reaction network:

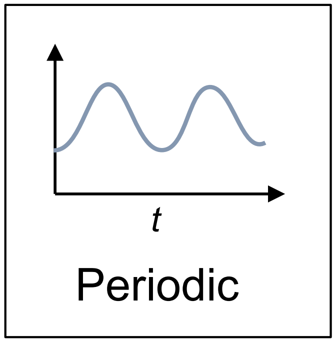


It is based on antithetic control



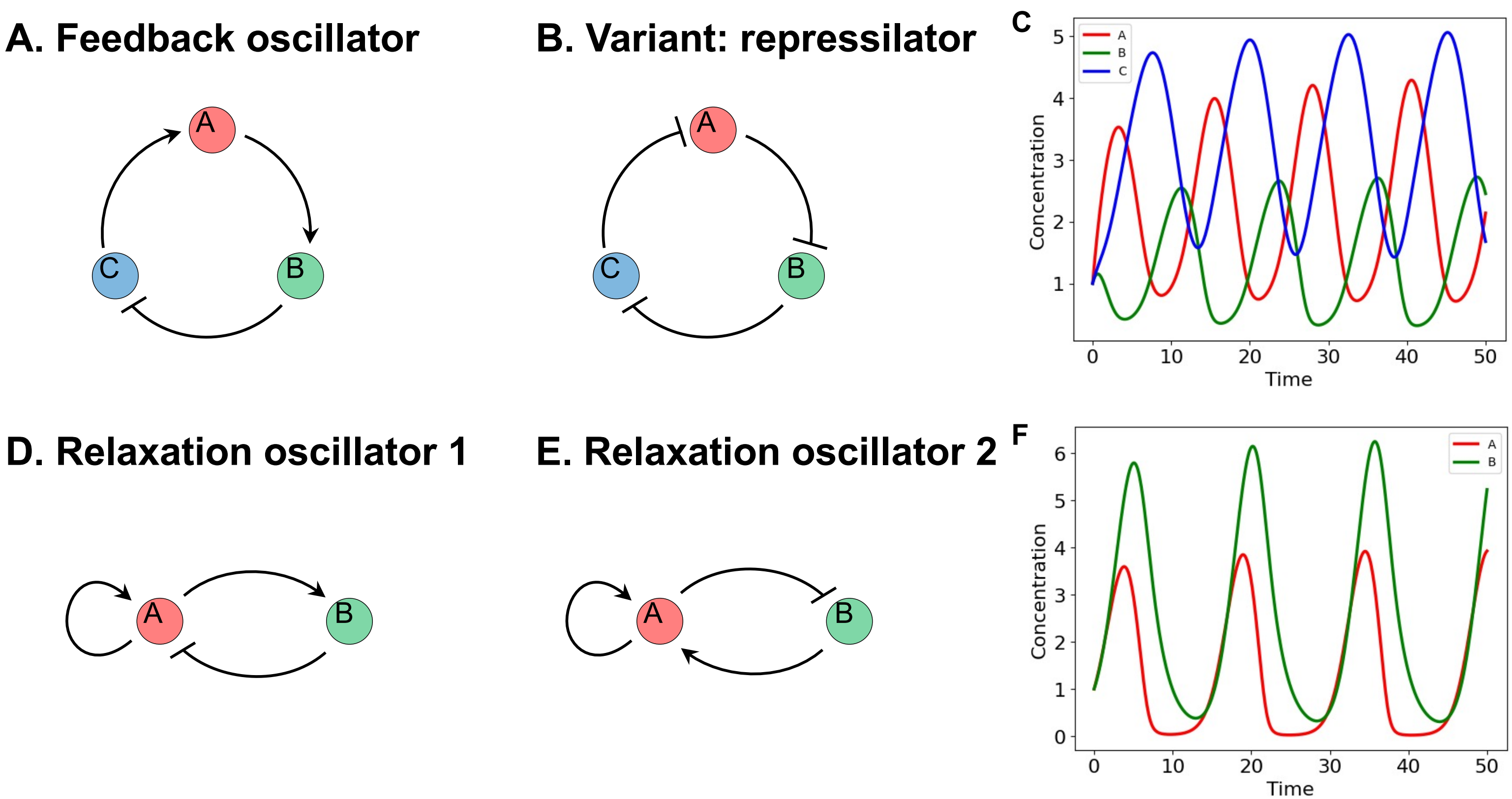
Figures: Bray, Wetware, 2009; Sourjik and Berg, *PNAS* 99.1 (2002): 123-127.

Periodic pattern

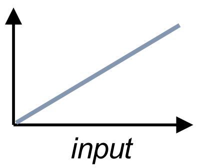


Observed in:
- circadian rhythms
- cell cycle
- engineered in the “repressilator”

Oscillators *always* use negative feedback.



Proportional output pattern

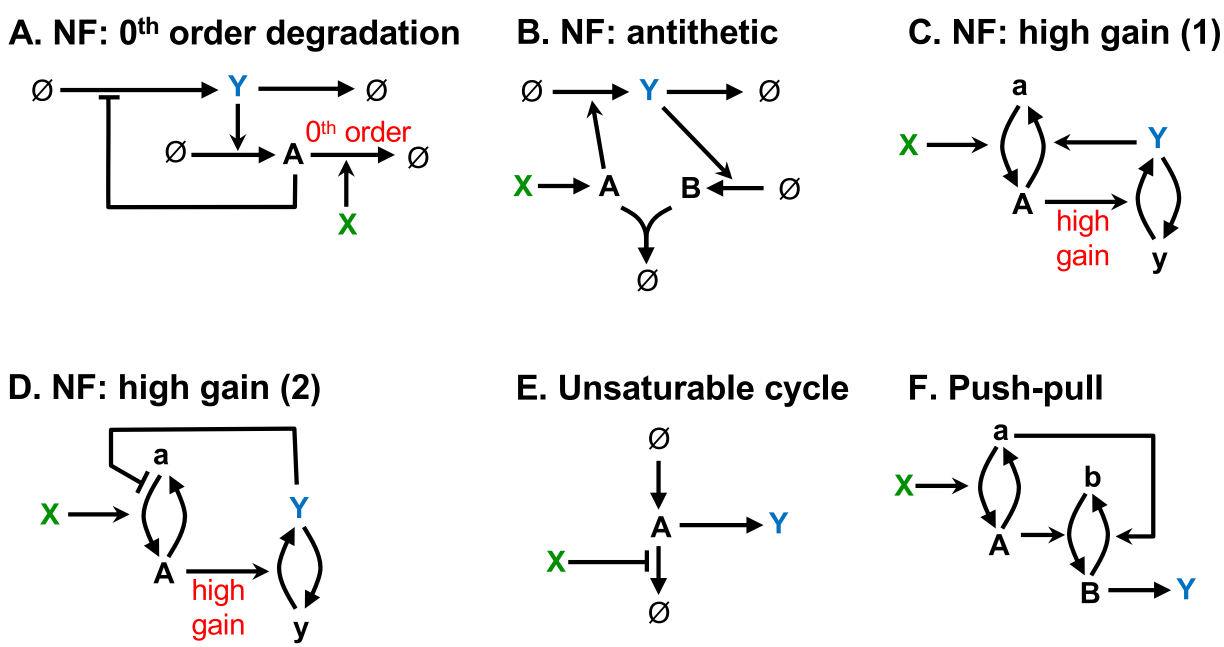


Proportional output

<u>Many signaling systems</u>

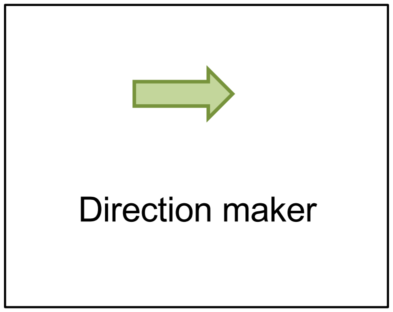
- yeast pheromone response
- EGF-ERK pathway
- Wnt pathway
- TGF-β pathway

Used for high information transmission



See also: Andrews, Brent, Balaszi, *eLife*, 7:e41894, 2018

Direction maker pattern

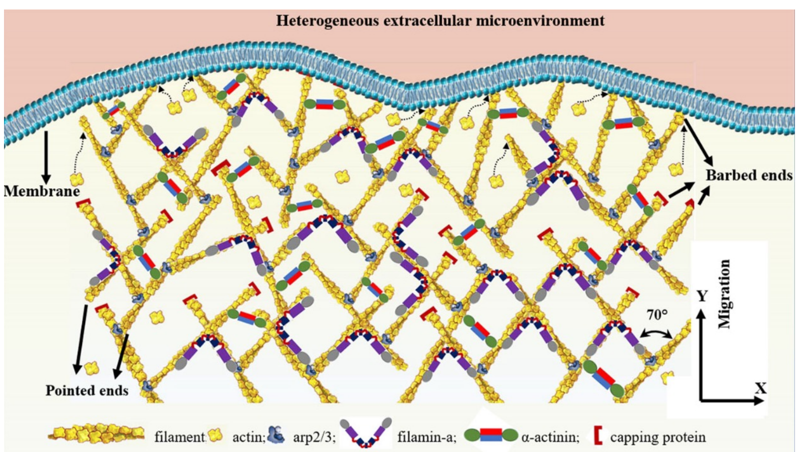


Problem: All reactions are reversible, but they often need to operate in a specific direction to be useful.

Solution: Make reactions effectively irreversible

- Large free energy decrease
- Keep reactant at a high concentration

Example: actin networks need to push on a cell membrane to create motion.



Solution is to rely on ATP.

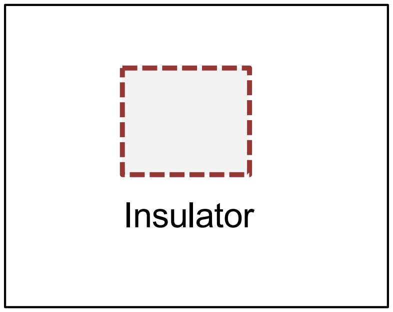
$$\mathrm{ADP} + \mathrm{P_i} \rightleftharpoons \mathrm{ATP}$$

ATP:ADP ratio is ~10^{10} times higher in cells than at equilibrium*.

Image: Chen et al., *Comm. Biol.* 3:616, 2020

* Wikipedia, “Adenosine triphosphate”

Insulator pattern

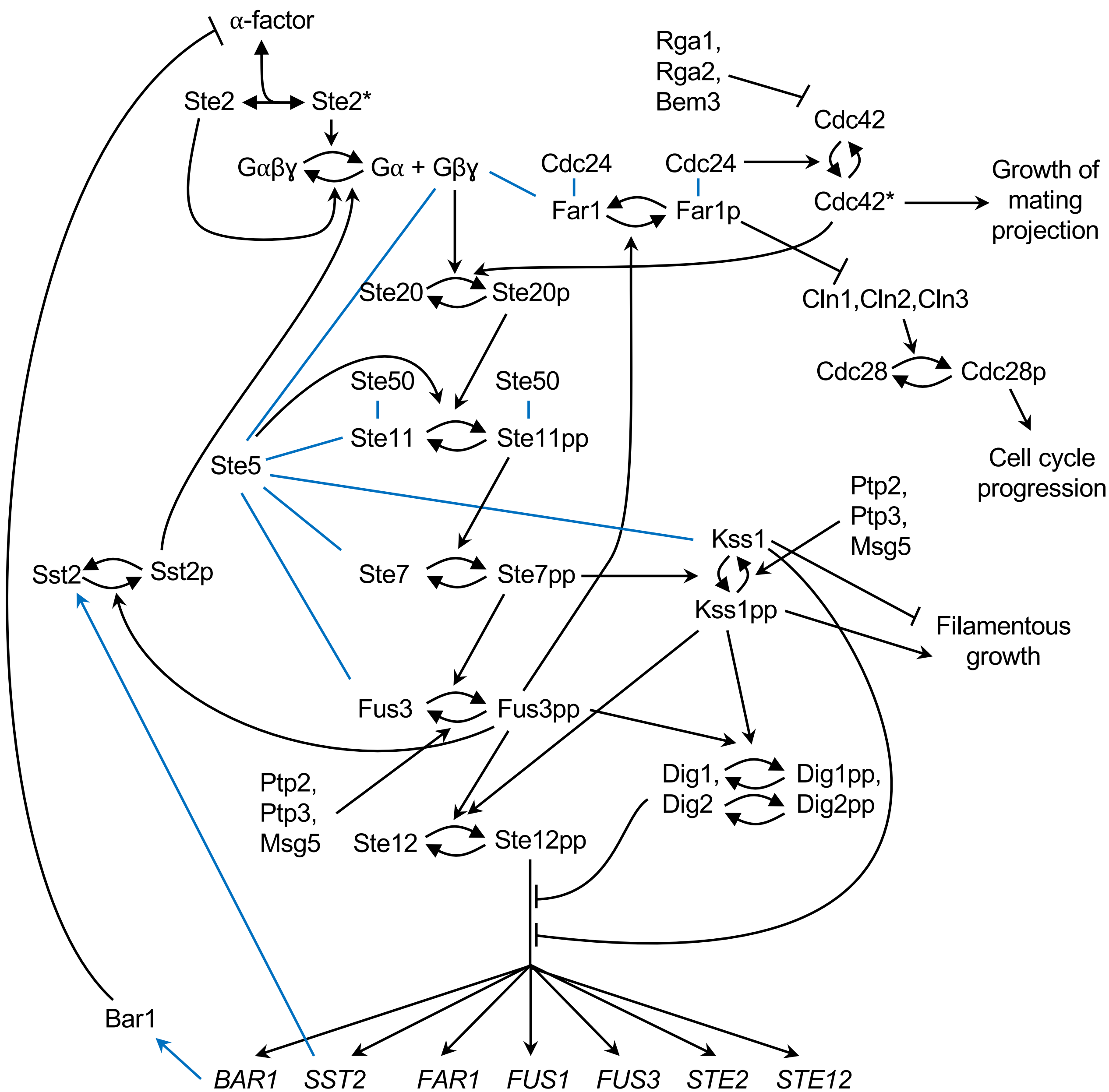


Problem: Reaction networks need to be modular to reduce crosstalk and to maintain evolvability.

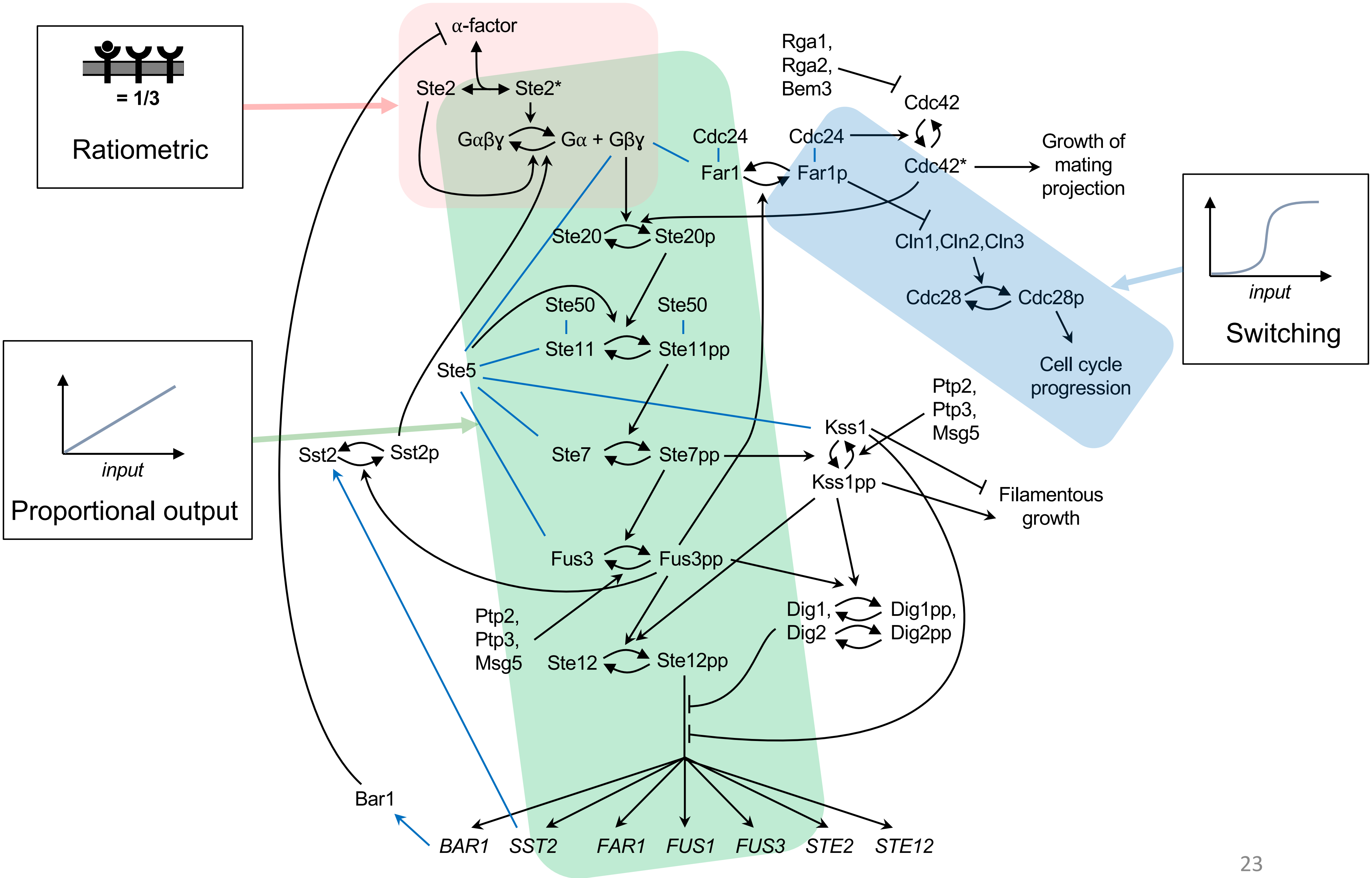
Solution: Boundaries that insulate subnetworks from each other.

- Spatial localization
- Standardized connections
- Input amplification
- Output negative feedback
- Kinetic insulation

Behavioral patterns for abstraction

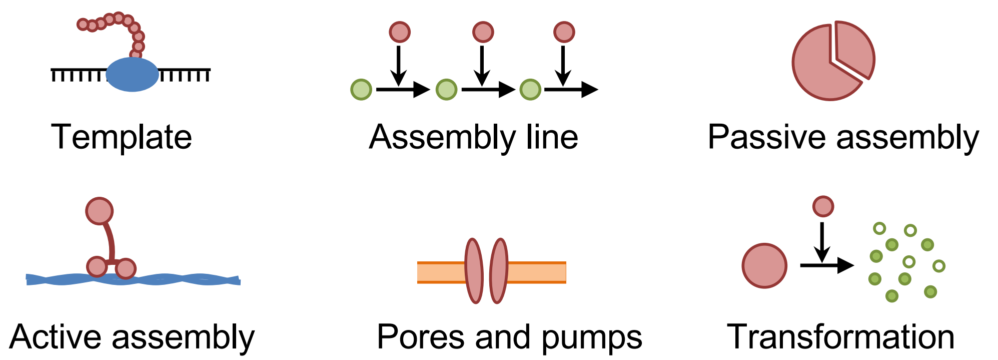


Behavioral patterns for abstraction



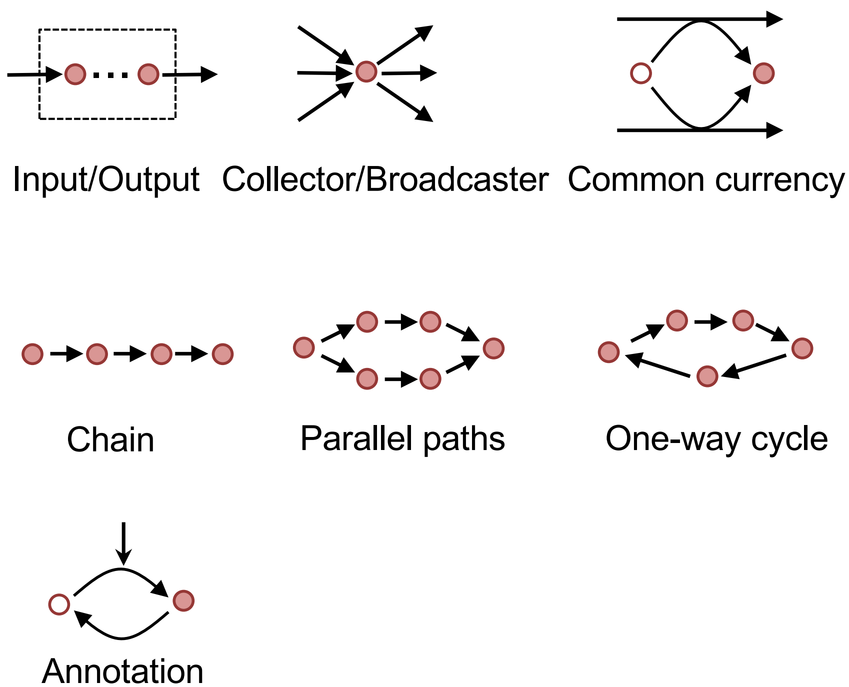
Conclusions

Creational patterns



- Each is a widely observed solution to a common problem
- They help abstract complex reaction networks.
- The same patterns would likely arise in any evolutionary history.

Structural patterns



Behavioral patterns