Gliederung

- -Was sind feedforward loops (FFL)
- -Struktur/Verschaltung
- -Mathematisches Modell
    - -Ecoli L-arabinose FFL
    - -Ecoli Flagellensystem
- -Übersicht kohärente FFL
- -Übersicht inkohärente FFL
- -Zusammenfassung/Diskussion

Transkriptionsnetzwerke

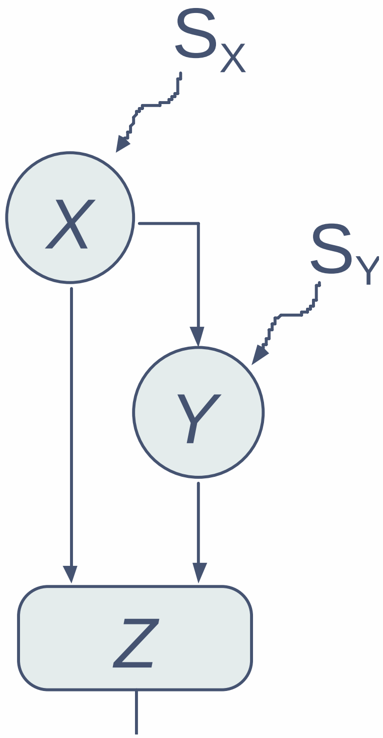
-Informationsverarbeitende Prozesse

- Input
- Veränderte Transkriptionsaktivität
- Bindung an spezifische Gene
- Repression/Aktivierung (Inputfunktion)
- Zellantwort

- Verbildlichung als gerichteter Graph

Was sind FFL

Feed-Forward-Loop ⟷ Simples Regulationsmodell



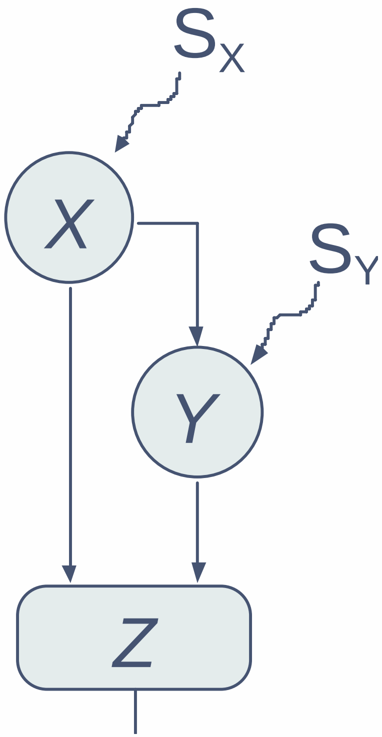
X,Y Transkriptionsfaktoren

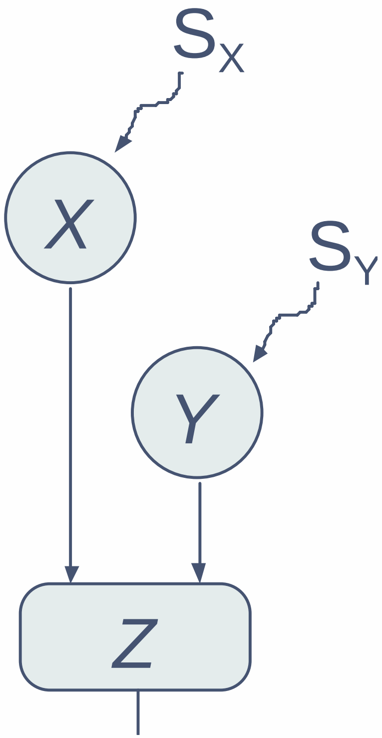
S_x,S_y Inducer

Z (Target-) Gen

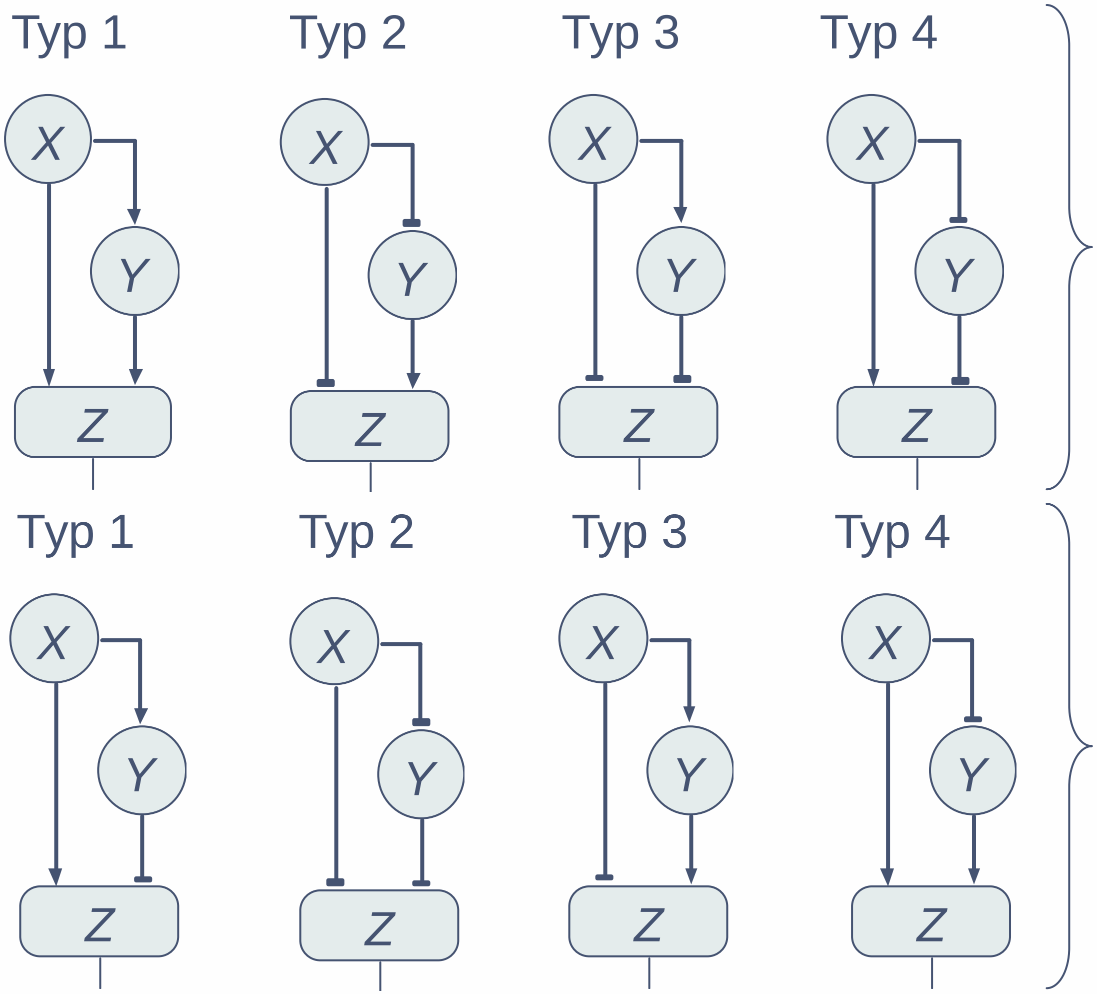
Was sind FFL

Feed-Forward-Loop ⟷ Simples Regulationsmodell





Struktur



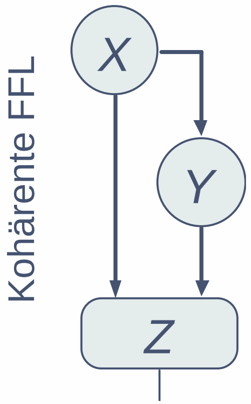
Kohärente
FLL

Inkohärente

FFL

Inputfunktion von Z

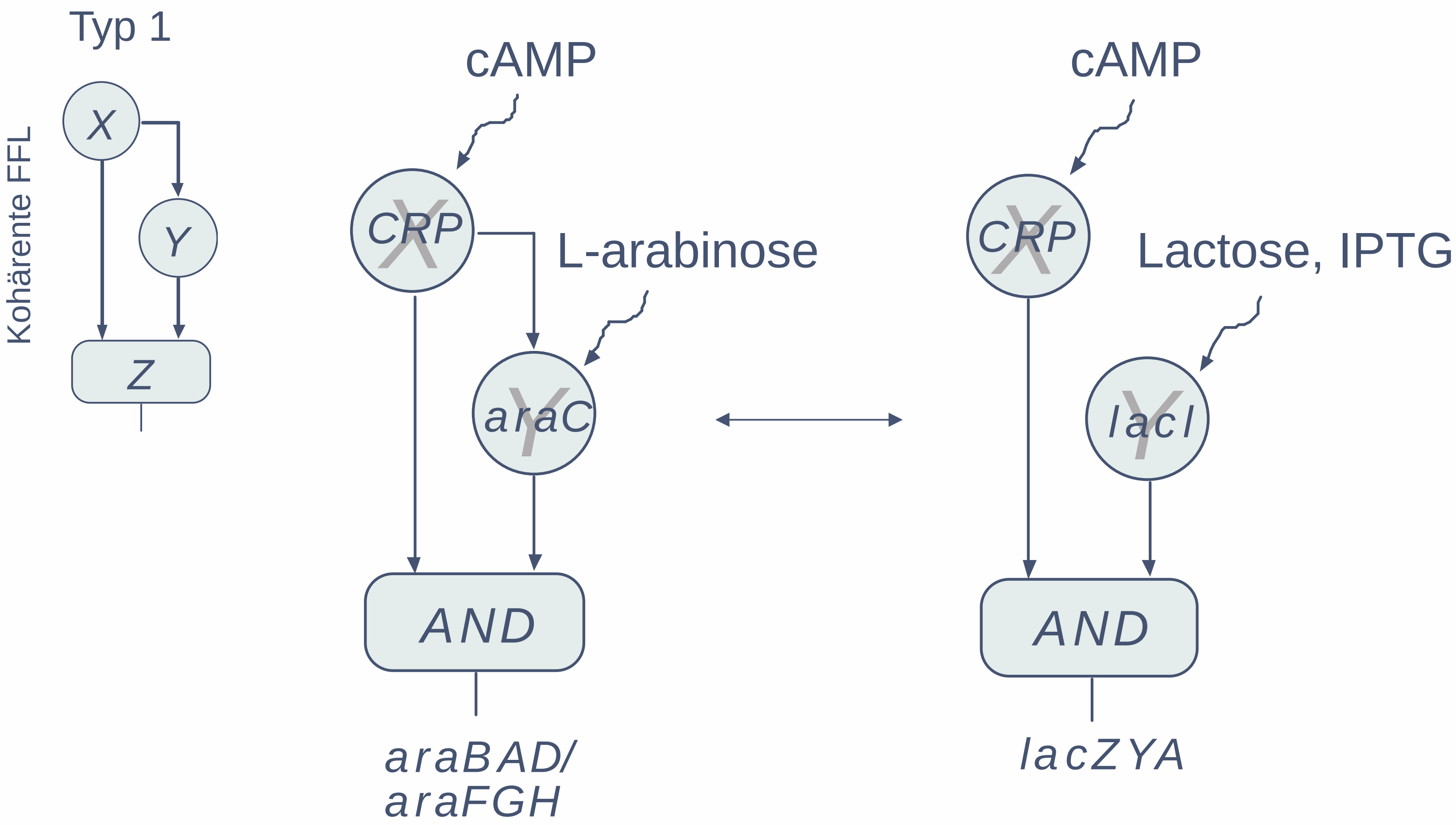
Typ 1



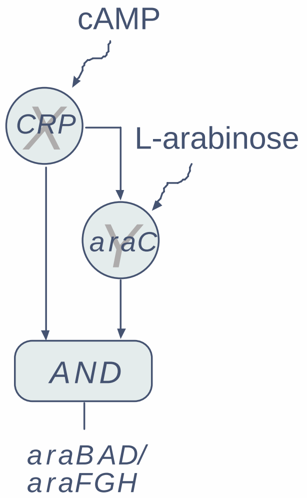
AND-Gatter : X und Y benötigt, um Z zu aktivieren

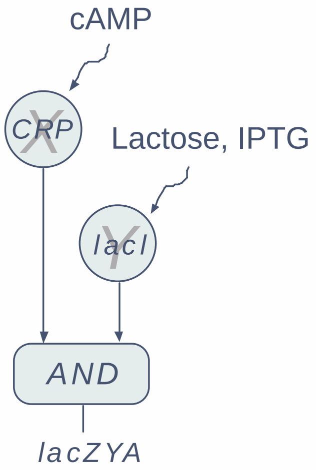
OR-Gatter : X oder Y reicht für Z-Aktivierung aus

Typ1 kohärente FFL in E.coli mit AND-Gatter



Mathematisches Modell



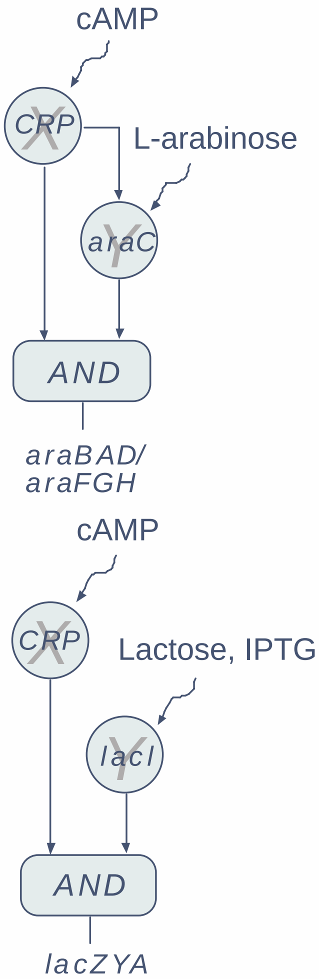


Differentialgleichungen:

$$\boxed{\frac{dY}{dt} = B_Y + \beta_Y f\left(X^*, K_{XY}\right) - \alpha_Y Y} \qquad (1)$$

$$\boxed{\frac{dZ}{dt} = B_Z + \beta_Z G\left(X^*, K_{XZ}, Y^*, K_{YZ}\right) - \alpha_Z Z} \qquad (2)$$

Mathematisches Modell (cont)



Differentialgleichung:

$$\boxed{\frac{dY}{dt} = B_Y + \beta_Y f\left(X^*, K_{XY}\right) - \alpha_Y Y} \qquad (1)$$

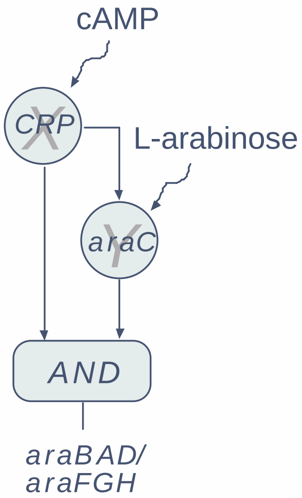
Aktivator:

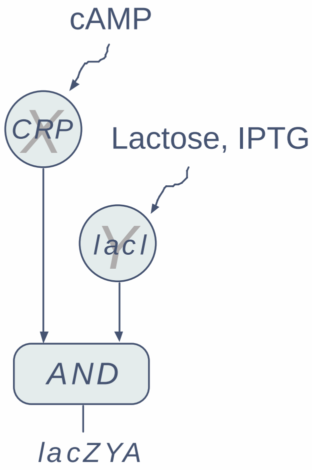
$$\boxed{f\left(u,K\right) = \frac{\left(\frac{u}{K}\right)^H}{1+\left(\frac{u}{K}\right)^H}}$$

Repressor:

$$\boxed{f\left(u,K\right) = \frac{1}{1+\left(\frac{u}{K}\right)^H}}$$

Mathematisches Modell (cont)



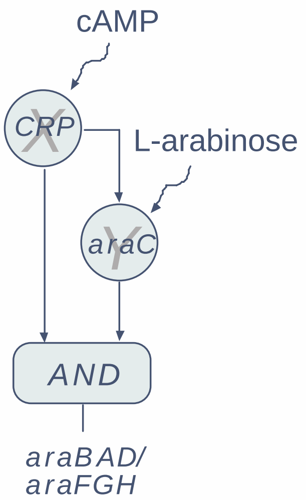


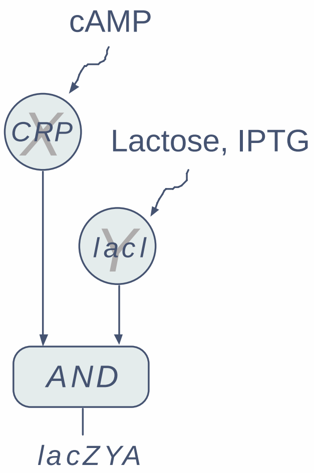
Differentialgleichung:

$$\boxed{\frac{dZ}{dt} = B_Z + \beta_Z G\left(X^*, K_{XZ}, Y^*, K_{YZ}\right) - \alpha_Z Z} \qquad (2)$$

AND-Gatefunktion:

$$\boxed{G_Z = f\left(X^*, K_{XZ}\right) f\left(Y^*, K_{YZ}\right)}$$





Synthese von Y

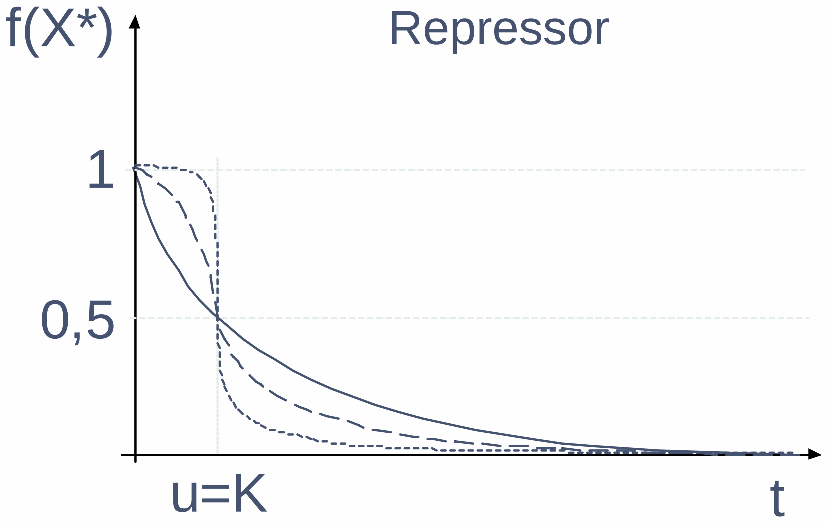
X=CRP und S_X=cAMP

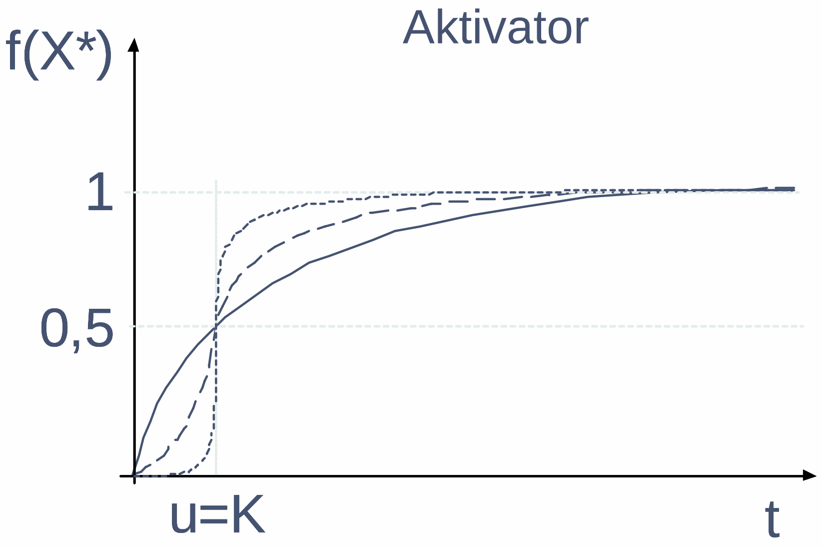
X = inaktiv, falls $S_x = 0$

X*= aktiv, falls $S_x = 1$

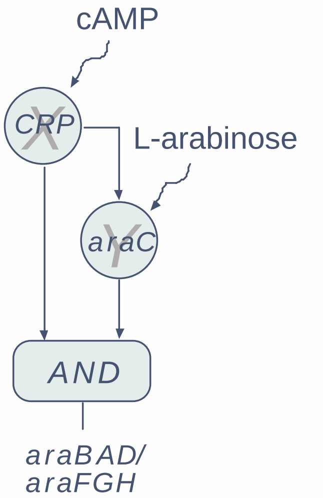
<u>Synthese von Y:</u>

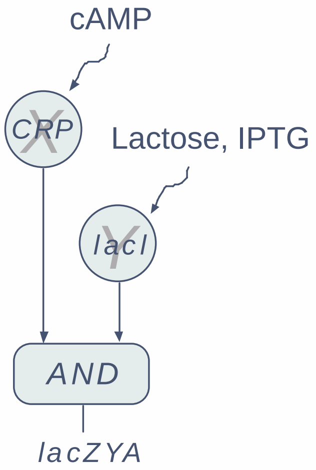
$$f\left(u,K\right)=\frac{\left(\frac{u}{K}\right)^{H}}{1+\left(\frac{u}{K}\right)^{H}}$$

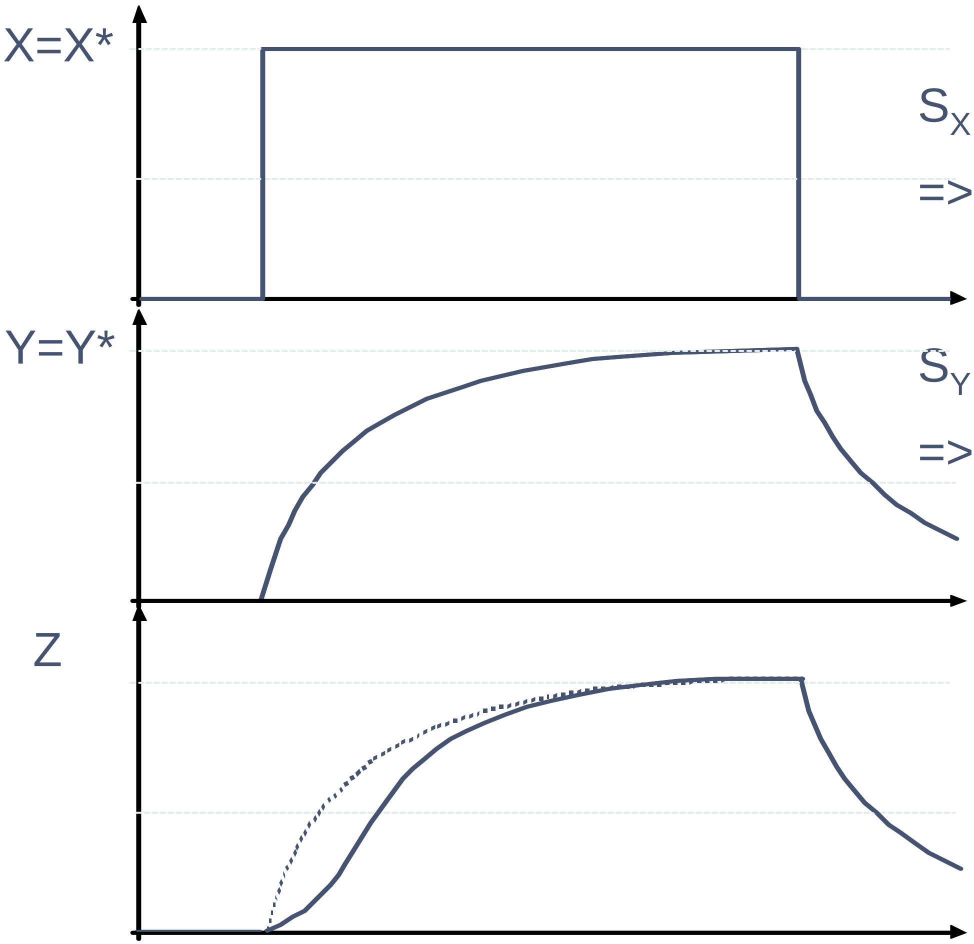




Synthese von Z







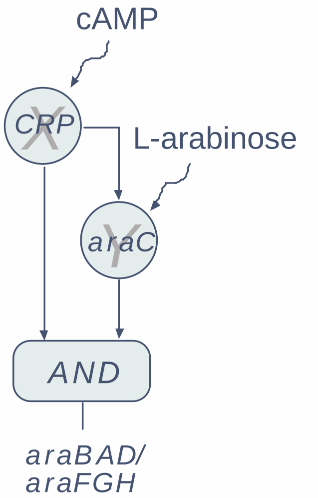
$S_X(\text{cAMP}) = 1$

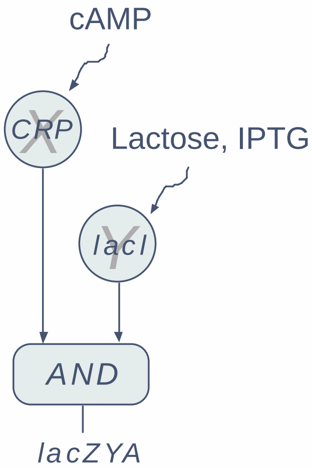
$\Rightarrow X \longrightarrow X^*$

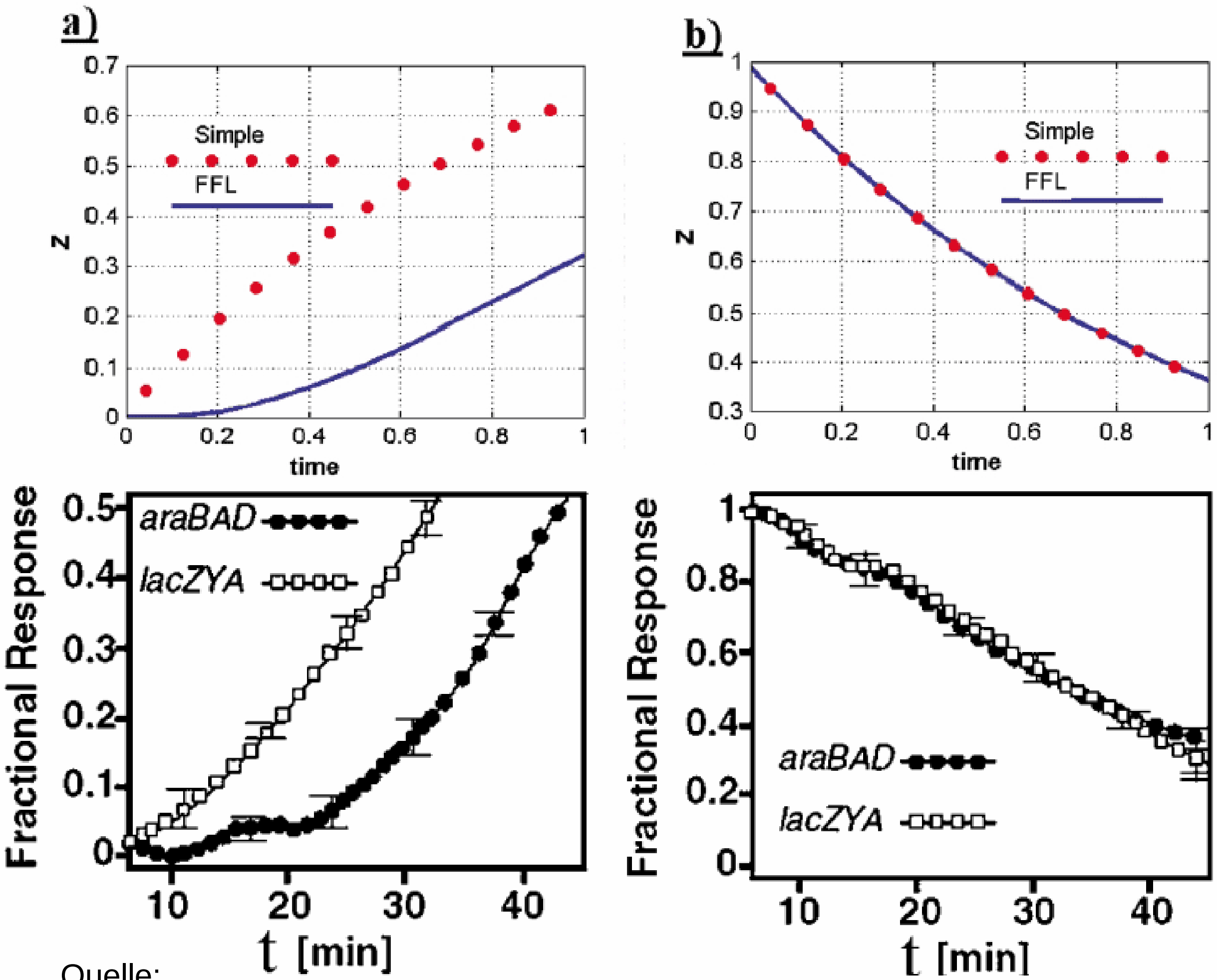
$S_Y(\text{L-arabinose}|\text{Lactose}) = 1$

$\Rightarrow Y \longrightarrow Y^*$

Simulation vs Experiment

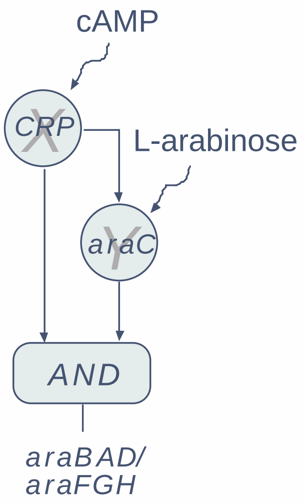


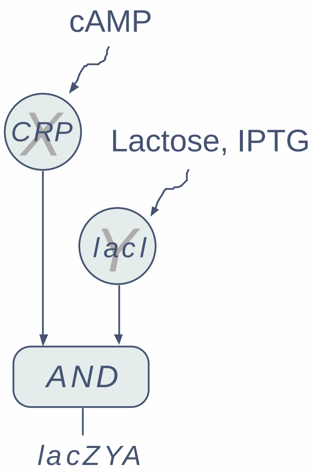




Quelle:
The Coherent Feedforward Loop Serves as a Signsensitive Delay Element in Transcription Networks

Diskussion / biologischer Hintergrund



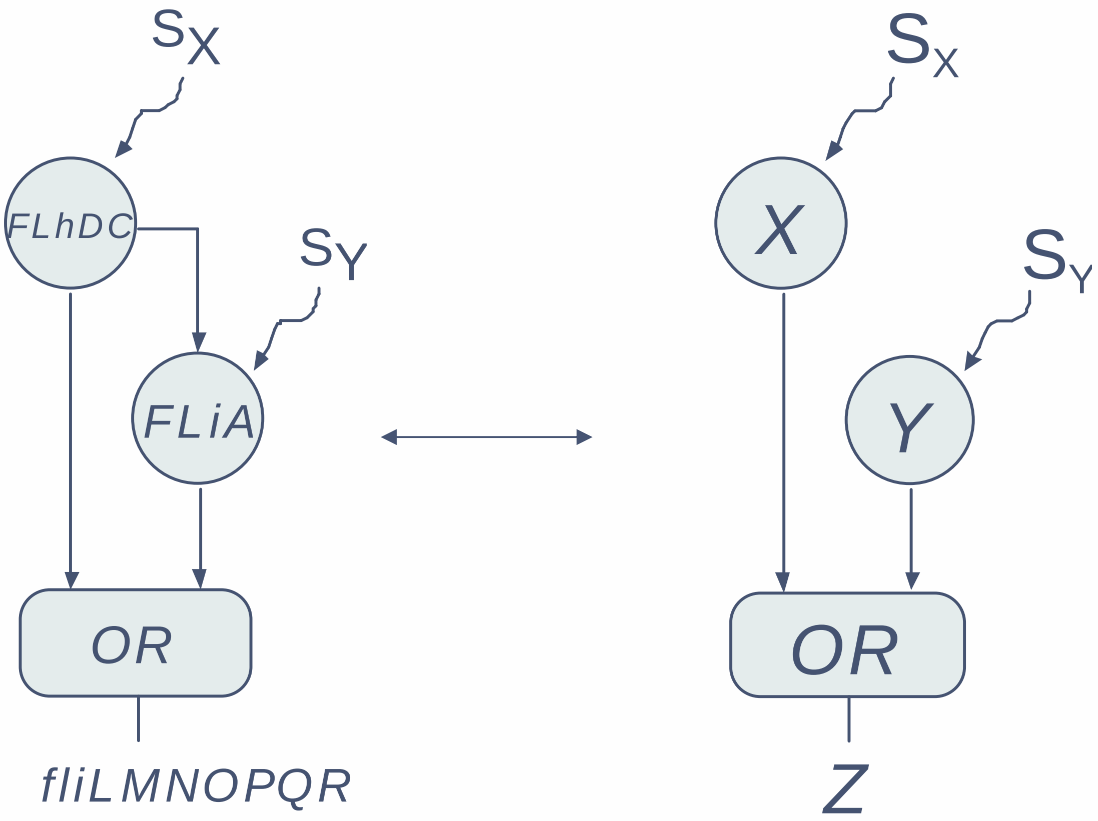


Welchen Vorteil bringt die asymmetrische Antwort auf cAMP-Präsenz?

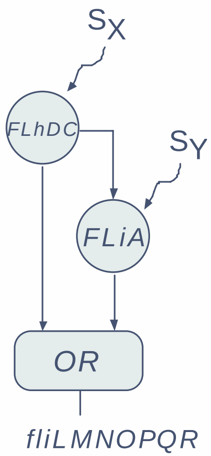
- zwei E.coli Lebenszyklen (im/außerhalb des Wirts)
- Im Wirt: reiche Zuckervorkommen / nur kurze Glucosepulse
- araSystem arbeitet, wenn beide Inducer präsent
- Glucosevorkommen vorhanden

  > araSystem schnell abgeschalten (Ressourcen sparen)
- Glucose von Wirt und E.coli rasch erschöpft
- Tolerierbare Verzögerung der Aktivierung des araSystems spart Ressourcen
- Persistenz-Detektor

Typ1 kohärente FFL in E.coli mit OR-Gatter



Mathematisches Modell



Differentialgleichungen:

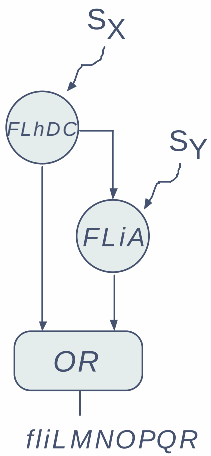
$$\frac{dY}{dt} = B_Y + \beta_Y f\left(X^*, K_{XY}\right) - \alpha_Y Y$$

$$\frac{dZ}{dt} = B_Z + \beta_Z G\left(X^*, K_{XZ}, Y^*, K_{YZ}\right) - \alpha_Z Z$$

Gatefunktion:

$$G = f_c\left(X^*, K_{XZ}, K_{YZ}, Y^*\right) + f_c\left(Y^*, K_{YZ}, K_{XZ}, X^*\right)$$

Mathematisches Modell (cont)

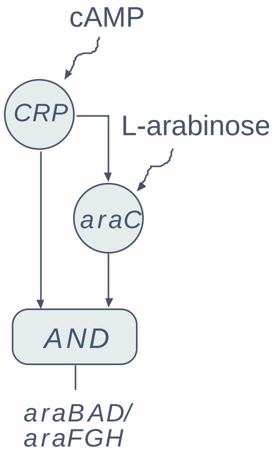


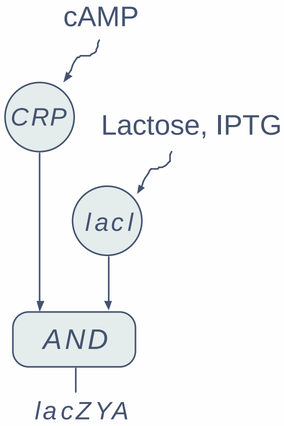
Gatefunktion:

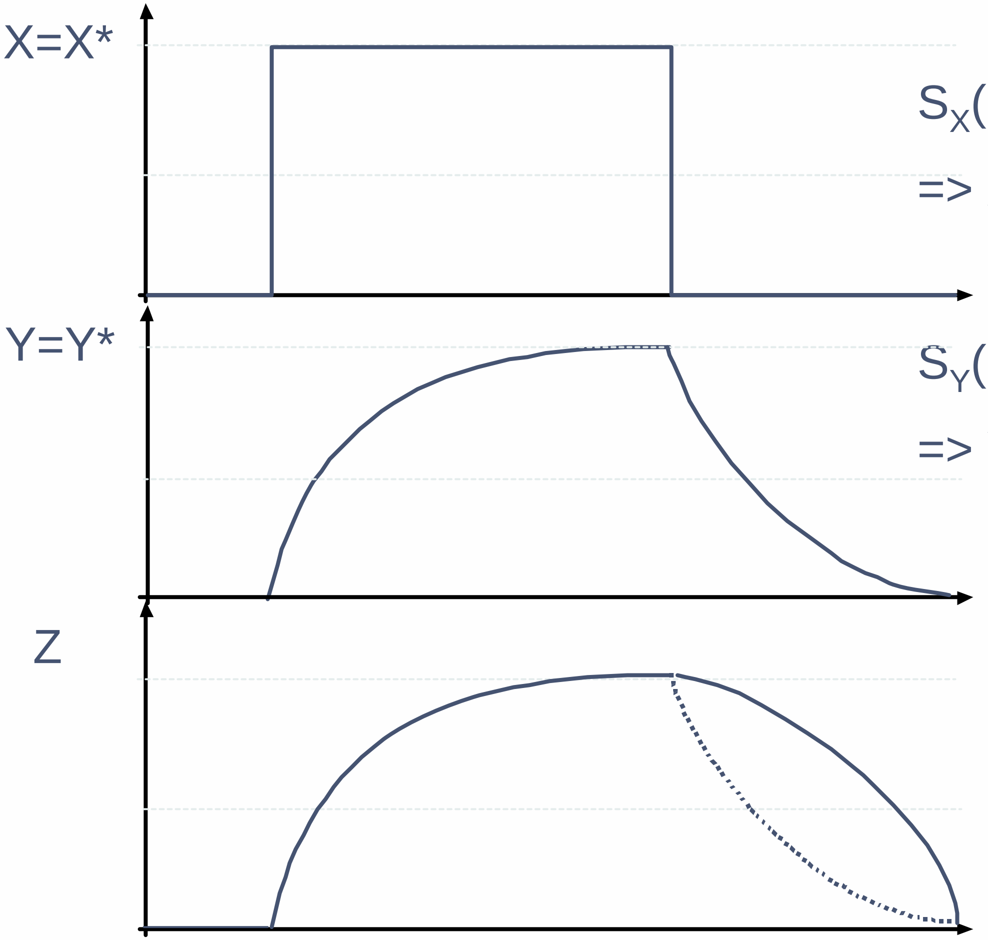
$$\boxed{G_Z = f_c\left(X^*, K_{XZ}, K_{YZ}, Y^*\right) + f_c\left(Y^*, K_{YZ}, K_{XZ}, X^*\right)}$$

$$\boxed{f_c\left(u, K_u, K_v, v\right) = \frac{\left(\frac{u}{K_u}\right)^H}{1 + \left(\frac{u}{K_u}\right)^H + \left(\frac{v}{K_v}\right)^H}}$$

Synthese von Z







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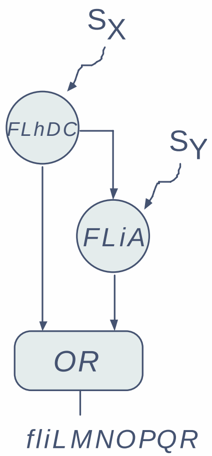
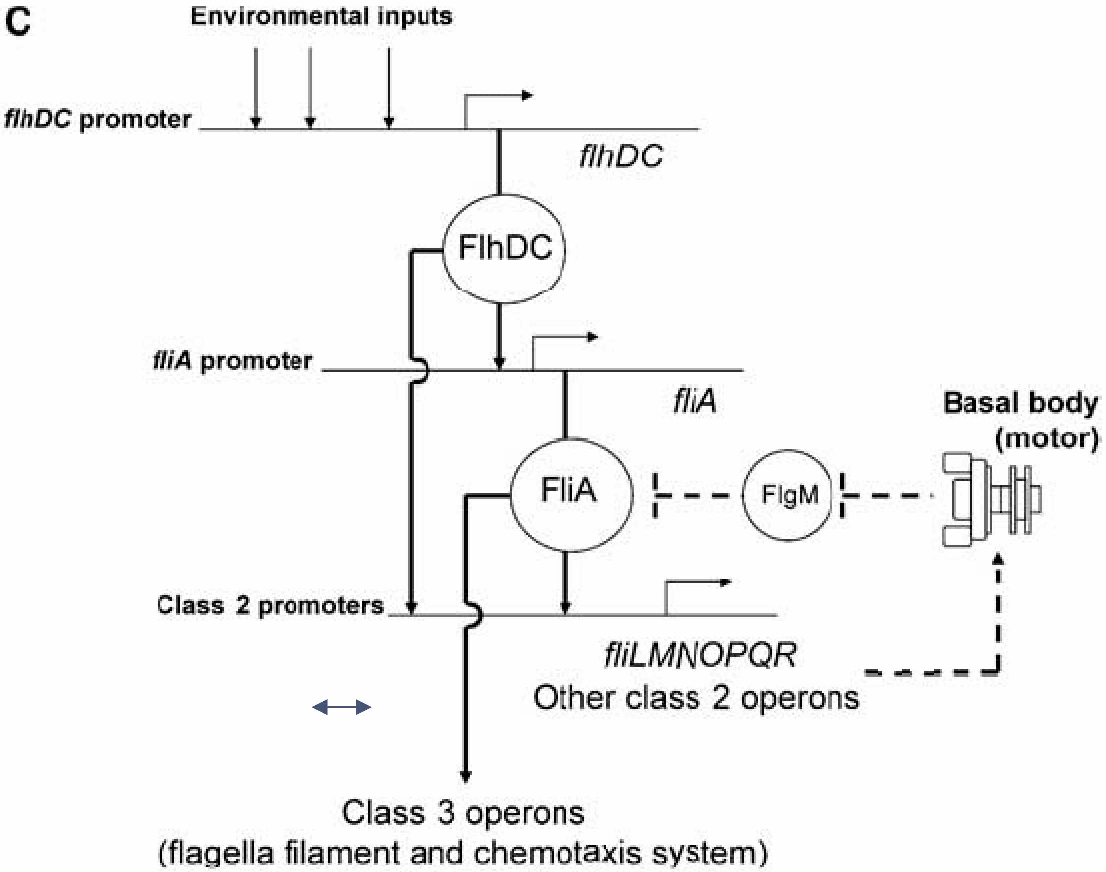
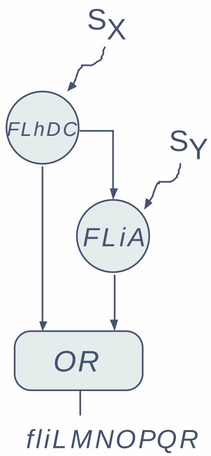
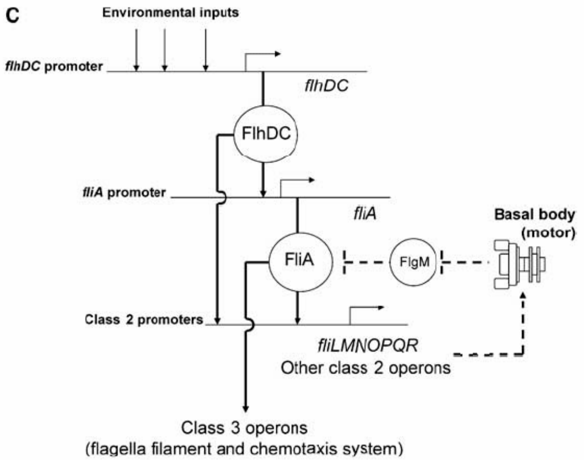


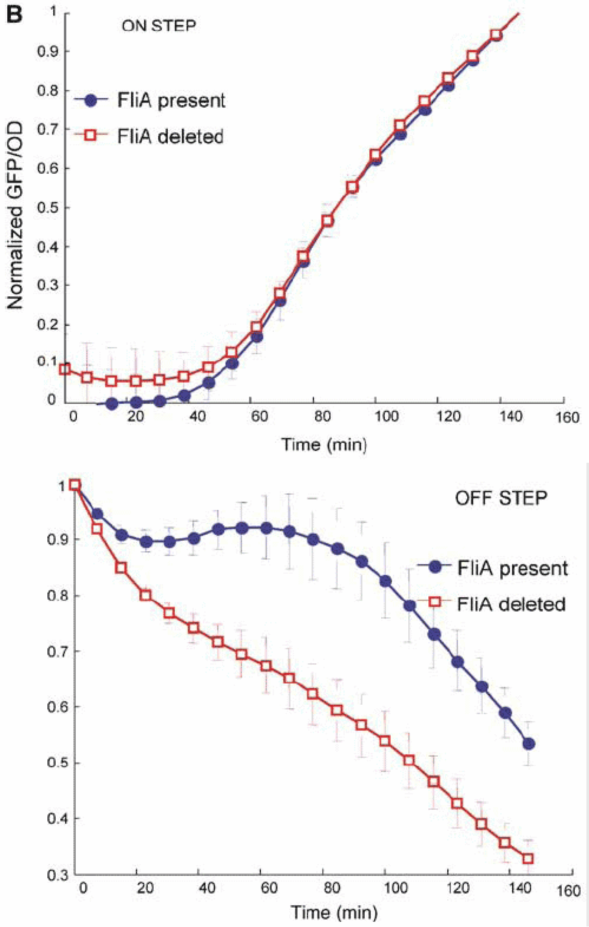


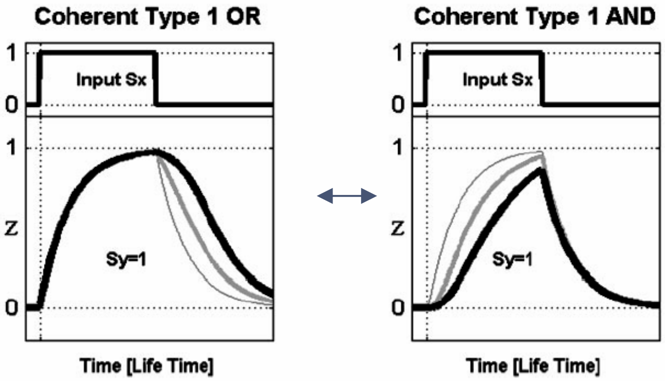
Quelle:
A coherent feed-forward loop with a SUM input function prolongs flagella expression in Escherichia coli

Synthese von Z



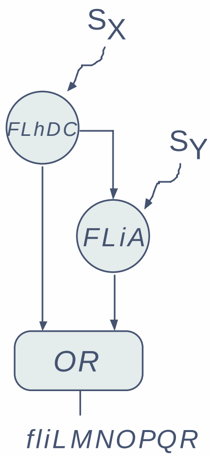






Quelle:
A coherent feed-forward loop with a SUM input function prolongs flagella expression in Escherichia coli

Diskussion / biologischer Hintergrund



Warum verlängerte Z-expression nachdem Abschaltung von Master-Aktivator?

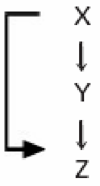
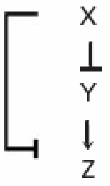
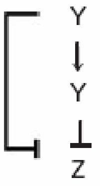
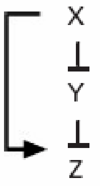
-Master-Aktivator von Vielzahl externer Parameter beeinflußt (Temperatur, Nährstoffe…)

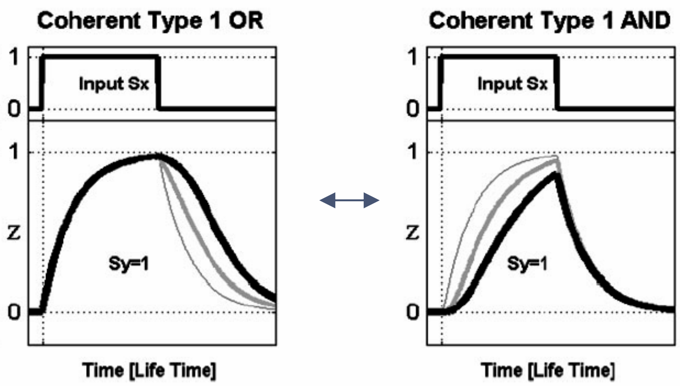
-Parameter ändern sich, wenn E.coli schwimmt

➢Flagellensytem unsensibel bei kurzzeitiger Inaktivierung von X

➢Flagellensytem erst deaktiviert, bei langfristig guten Konditionen

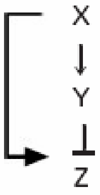
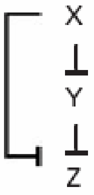
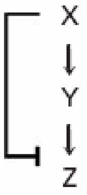
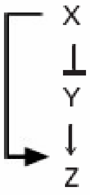
Übersicht kohärente FFL (Verzögerung)

	Coherent type 1		Coherent type 2		Coherent type 3		Coherent type 4	
Species	Structure	Abundance	Structure	Abundance	Structure	Abundance	Structure	Abundance
E. coli		28		2		4		1
S. cerevisiae		26		5		0		0
Z Logic→	AND	OR	AND	OR	AND	OR	AND	OR
Steady-state Z(Sx,Sy)	$S_x \wedge S_y$	S_x	$\bar{S}_x \wedge S_y$	$\bar{S}_x$	$\bar{S}_x$	$\bar{S}_x \wedge \bar{S}_y$	S_x	$S_x \vee \bar{S}_y$
Response delay								
Sx on step	Delay	—	—	Delay	—	—	Delay	Delay
Sx off step	—	Delay	Delay	—	Delay	Delay	—	—
Inverted out	No	No	Yes	Yes	Yes	Yes	No	No



Quelle:
Structure and function of the feed-forward loop network motif

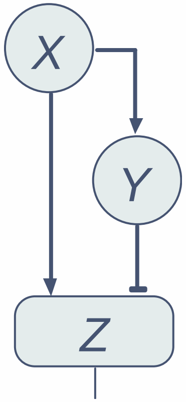
Übersicht Inkohärente FFL (Beschleunigung, Puls)

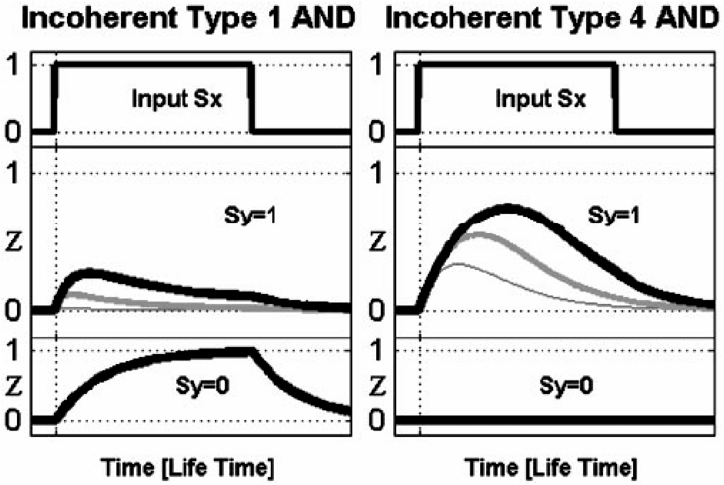
	Incoherent type 1		Incoherent type 2		Incoherent type 3		Incoherent type 4	
Species	Structure	Abundance	Structure	Abundance	Structure	Abundance	Structure	Abundance
E. coli		5		0		1		1
S. cerevisiae		21		3		1		0
Z logic →	AND		AND		AND		AND	
Steady-state								
Z(Sx,Sy)	$S_x \wedge \bar{S}_y$		$\bar{S}_x \wedge \bar{S}_y$		0		0	
Pulse								
Sx on step	Weak		—		—		Strong	
Sx off step	—		Weak		Strong		—	
Sy effect	Destroy		Destroy		Enable		Enable	
Response acceleration								
Sx on step	Accelerate		—		—		Accelerate	
Sx off step	—		Accelerate		Accelerate		—	

Quelle:
Structure and function of the feed-forward loop network motif

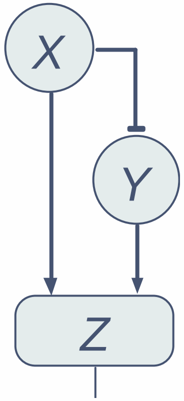
Inkohärente FFL - Pulsgeber

Typ 1

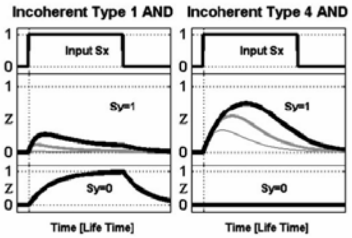


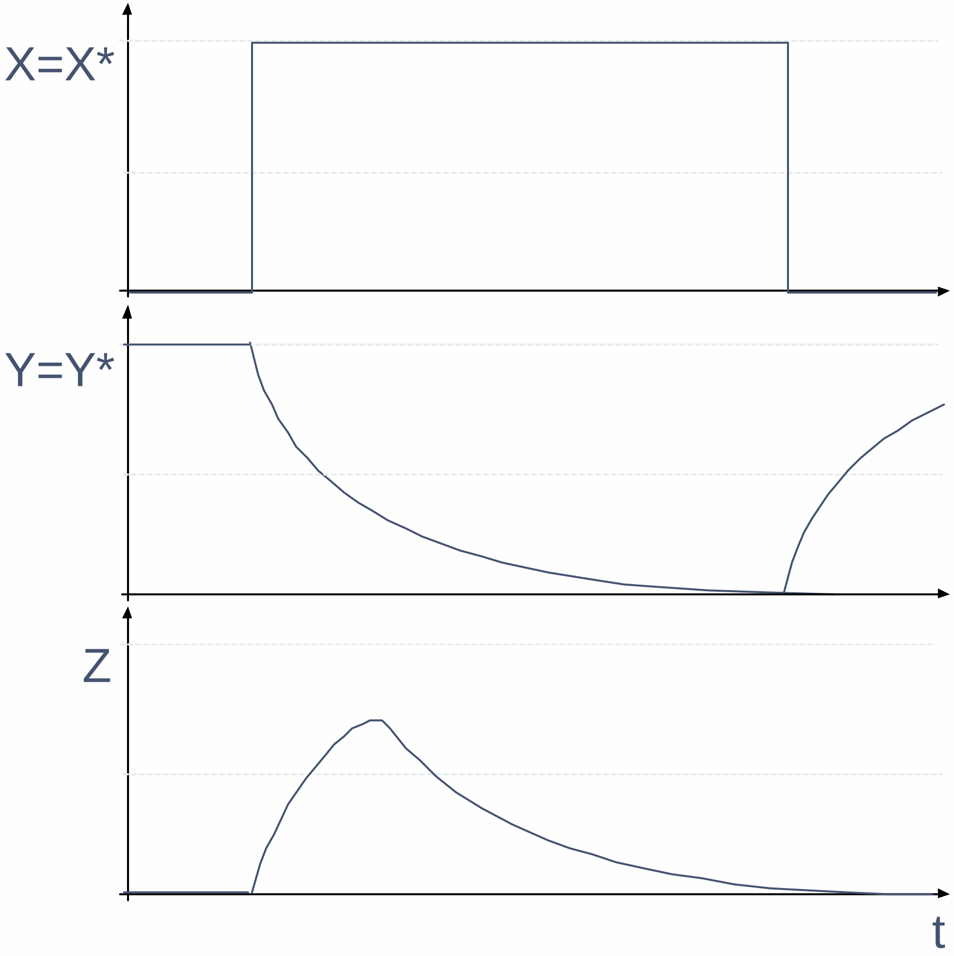


Typ 4

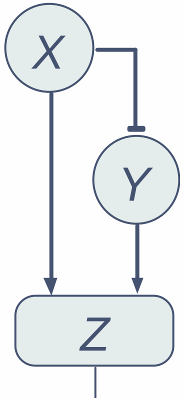


Inkohärente FFL - Pulsgeber



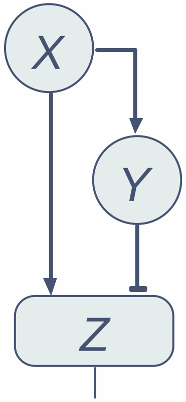


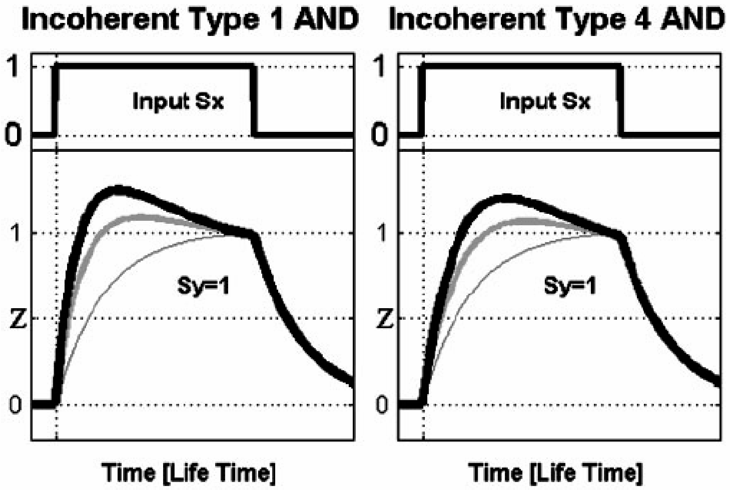
Typ 4



Inkohärente FFL - Beschleunigung

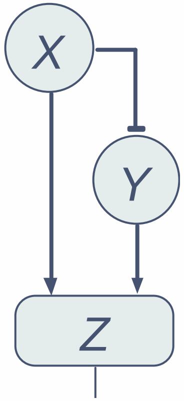
Typ 1



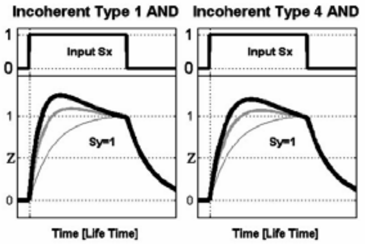

Incoherent Type 1 AND

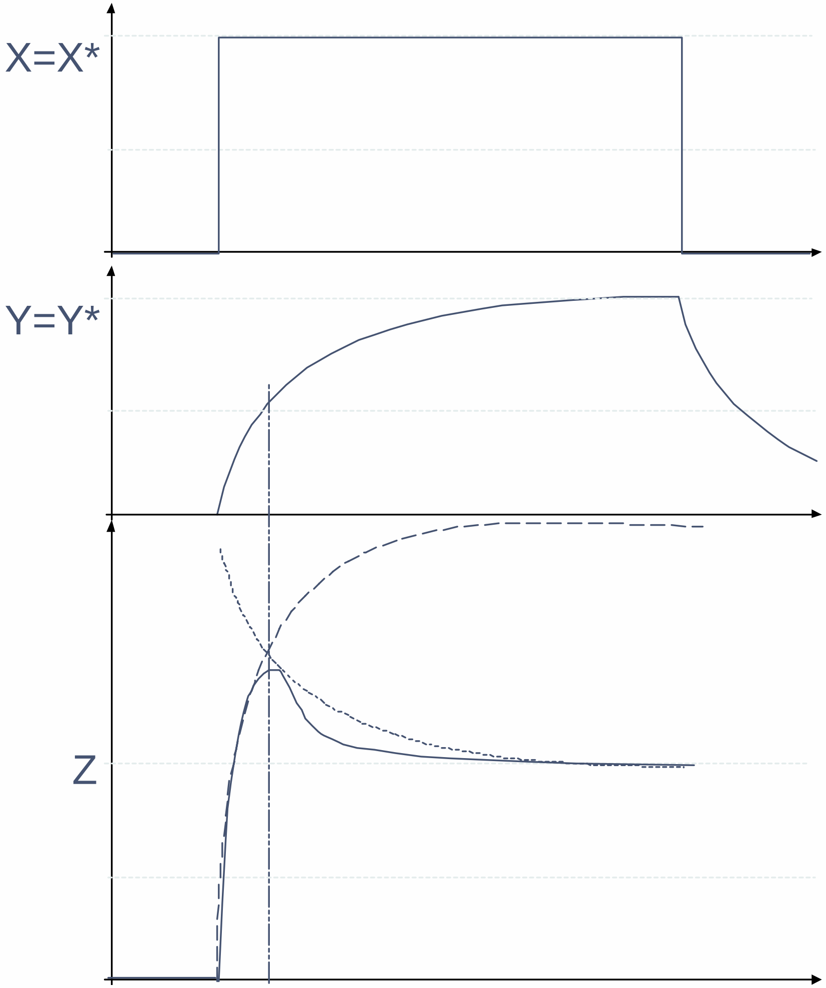
Incoherent Type 4 AND

Typ 4

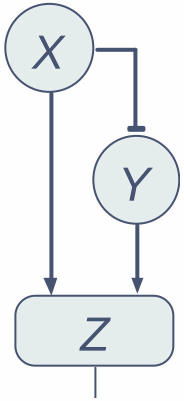


Inkohärente FFL - Beschleunigung





Typ 4



Zusammenfassung / Diskussion

- kohärente FFL verzögern Zielgen-Antwort
- Inkohärente FFL beschleunigen Zielgen-Antwort oder pulsieren
- FFL vorzeichensensitiv
- AND / OR Logic
- Kohärente Typ1 FFL am häufigsten (E.coli & Hefe)

  => arbeitet mit Kooperativität
- Persistenz-Detektor

Papers

1. A coherent feed-forward loop with a SUM input function prolongs flagella expression in Escherichia coli
   [Shiraz Kalir, Shmoolik Mangan and Uri Alon*]

2. The Coherent Feedforward Loop Serves as a SignsensitiveDelay Element in Transcription Networks
   [S. Mangan, A. Zaslaver and U. Alon*]

3. Structure and function of the feed-forward loop network motif
   [S. Mangan and U. Alon†]