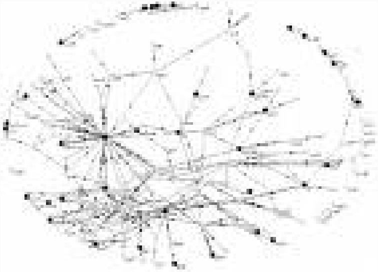
The Feed-Forward Loop Network Motif

2IF35 Formal Modelling in Cell Biology

Technische Universiteit Eindhoven

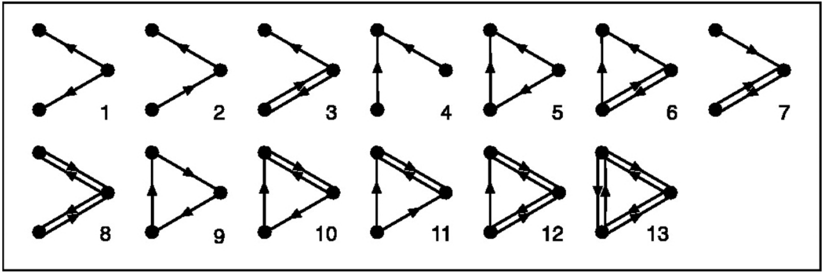
November 20, 2012

feed forward loops

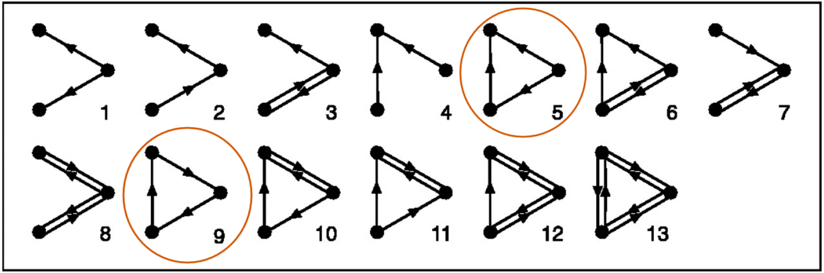


feed-forward loops in *E. coli* transcription network

connected 3-node graphs



all 13 connected 3-node graphs



feed-forward loop (nr. 5) and feedback loop (nr. 9)

real vs. random graphs

graph G of N nodes and E edges
subgraph g of n nodes and e edges with s symmetries

probability for specific edge $p = E/N^2$
expected subgraph frequency $[N_g] \approx \frac{1}{s} N^n p^e$

mean connectivity $\lambda = E/N$
thus $p = \lambda/N$ and $[\,N_g\,] \approx \frac{1}{s} N^{n-e} \lambda^e$

scaling relation $[\,N_g\,] \sim N^{n-e}$ (fixed λ)

V-shape	$3 - 2 = 1$	$[\,N_g\,] \sim N$
full 3-clique	$3 - 6 = -3$	$[\,N_g\,] \sim N^{-3}$

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V-shape	$3-2=1$	$[\,N_g\,] \sim N$
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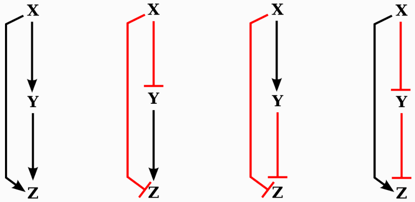
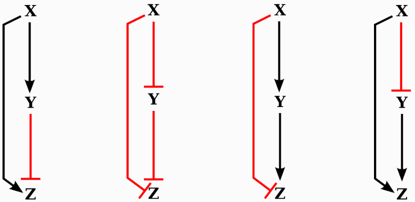
constant expectations

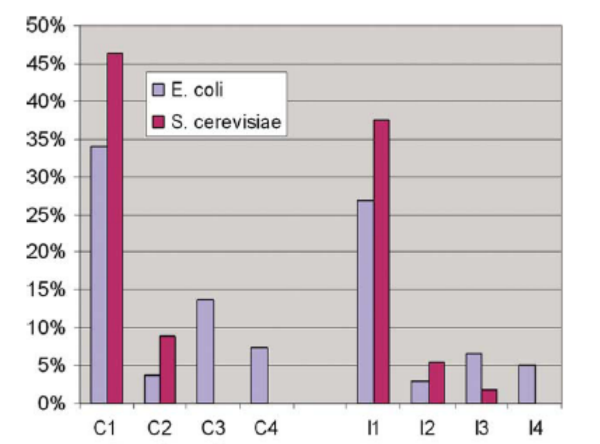
$[\,N_{FFL}\,] = \frac{1}{1}\lambda^3 N^0 = \lambda^3$ and $[\,N_{3loop}\,] = \frac{1}{3}\lambda^3 N^0 = \lambda^3$

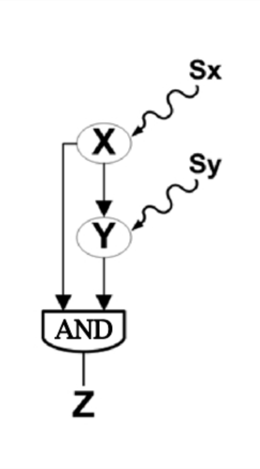
FFL is a network motif

	Feed-Forward Loop		Feedback Loop
E. coli	42		0
Erdös-Reyni random	1.7 ± 1.3	(Z=31)	0.6 ± 0.8
degree-preserving random	7 ± 5	(Z=7)	0.2 ± 0.6

coherent FFL	C1-FFL	C2-FFL	C3-FFL	C4-FFL
				
incoherent FFL	I1-FFL	I2-FFL	I3-FFL	I4-FFL
				

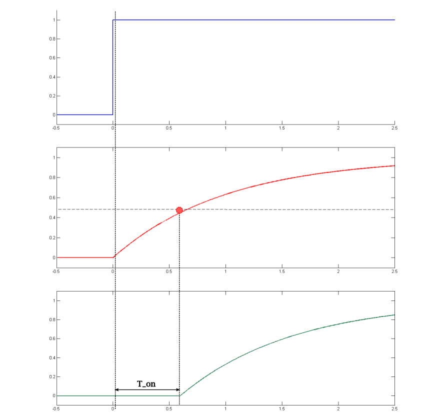
relative frequency of FFL types





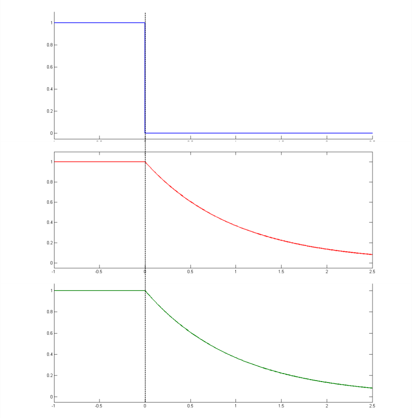
C1-FFL with AND logic

C1-FFL as sign-sensitive delay element



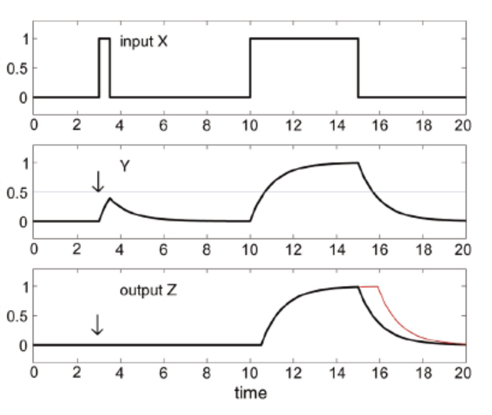
$$\frac{dY}{dt} = \beta_Y \theta(X^* > K_{XY}) - \alpha_Y Y \quad \text{and} \quad \frac{dZ}{dt} = \beta_Z \theta(X^* > K_{XZ}) \theta(Y^* > K_{YZ}) - \alpha_Z Z$$

C1-FFL as sign-sensitive delay element (cont.)

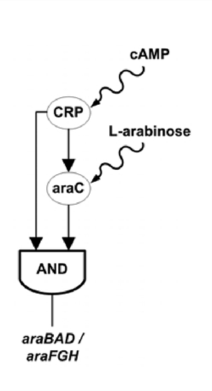


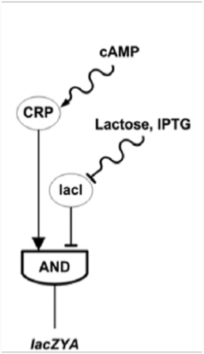
dynamics of C1-FFL following an OFF step

C1-FFL as sign-sensitive delay element (cont.)

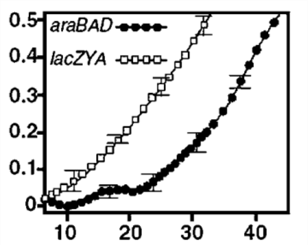


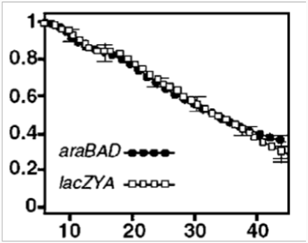
persistence detector: protection against brief input fluctuations





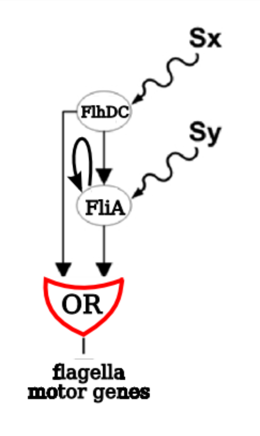
C1-FFL compared to simple regulation





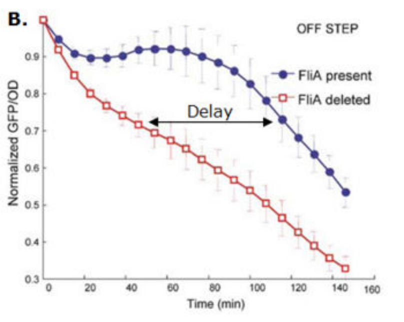
C1-FFL compared to simple regulation

C1-FFL with OR logic



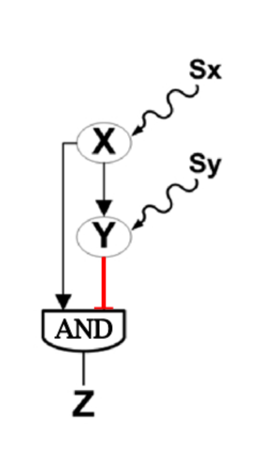
sign-sensitive delay for OFF steps

C1-FFL with OR logic



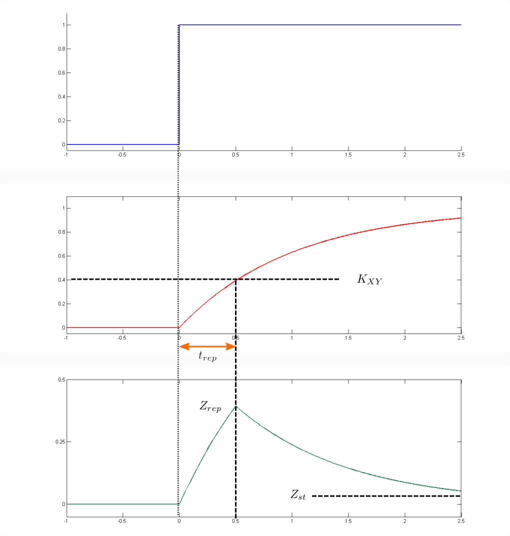
sign-sensitive delay for OFF steps

type-1 incoherent FFL



two parallel antagonistic paths

type-1 incoherent FFL (cont.)



dynamics of I1-FFL

type-1 incoherent FFL (cont.)

production of Y

$$\frac{dY}{dt} = \beta_Y - \alpha_Y Y$$

$$Y(t) = Y_{st}(1 - e^{-\alpha_Y t}) \qquad Y_{st} = \frac{\beta_Y}{\alpha_Y}$$

production of Z while $Y < K_{XY}$

$$\frac{dZ}{dt} = \beta_Z - \alpha_Z Z$$

$$Z(t) = Z_m(1 - e^{-\alpha_Z t}) \qquad Z_m = \frac{\beta_Z}{\alpha_Z}$$

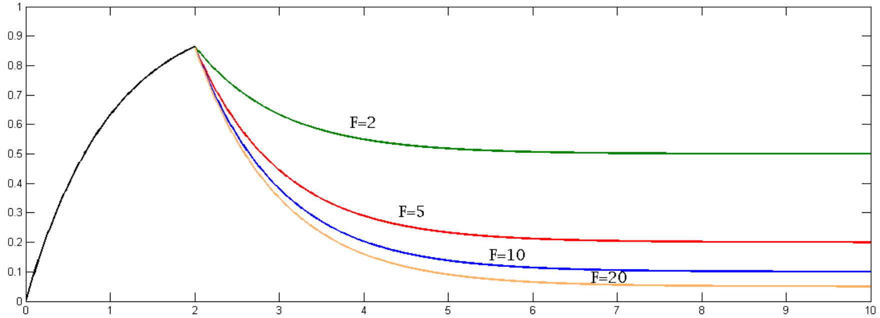
production of Z once $Y \geqslant K_{XY}$

$$\frac{dZ}{dt} = \beta'_Z - \alpha_Z Z$$

$$Z(t_{rep}) = Z_{rep} \qquad Y(t_{rep}) = K_{YX} \qquad Z_{st} = \frac{\beta'_Z}{\alpha_Z}$$

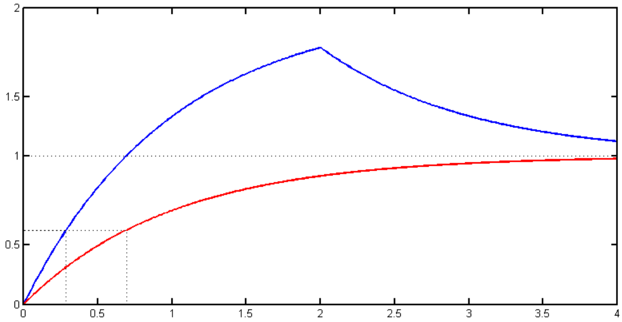
$$Z(t) = Z_{st} + (Z_{rep} - Z_{st})e^{-\alpha_Z(t - t_{rep})}$$

I1-FFL as pulse generator



repression factor $F = \frac{\beta_Z}{\beta'_Z}$

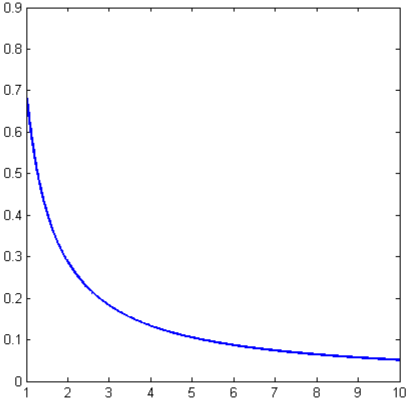
I1-FFL shortens response time



I1-FFL vs. simple regulation

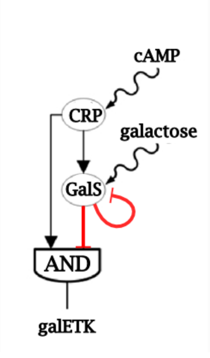
speed-up of initial reduction with equal steady state value

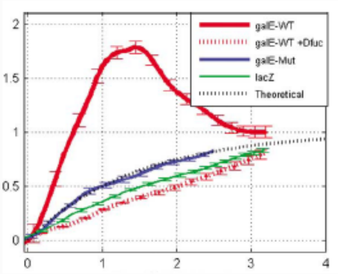
I1-FFL shortens response time (cont.)



response time $T_{1/2}$ vs. repression factor F

solving $\frac{\beta_Z}{\alpha_Z}(1 - e^{-\alpha_Z T_{1/2}}) = \frac{1}{2}\frac{\beta'_Z}{\alpha_z}$ yields $T_{1/2} = \log(\frac{2F}{2F-1})$





I1-FFL dynamics in *E. coli* galactose system