LECTURE 4: NETWORK MOTIFS AND AUTOREGULATION

Introduction to cellular system modelling

Daniel Georgiev

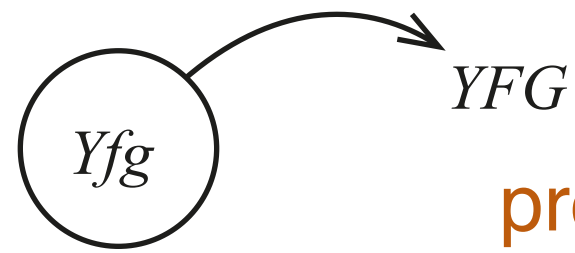
Summer 2015

OUTLINE

- Network motif concept
- Simple gene expression revisited
- Cell growth and protein degradation
- Simple gene expression limitations
- Single node motifs
- Negative autoregulation
- Properties of negative autoregulation
- Positive autoregulation
- Properties of positive autoregulation

GENE EXPRESSION - MODELLING

constitutive GENE

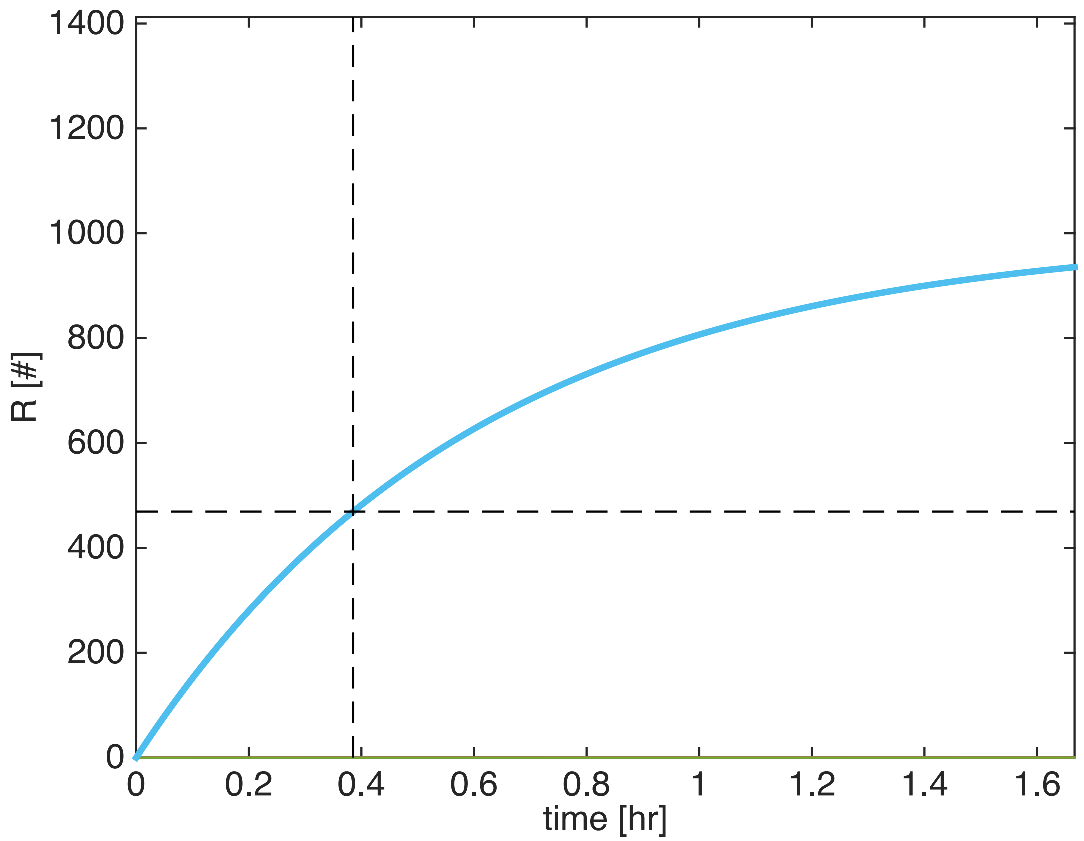


product

SOURCE

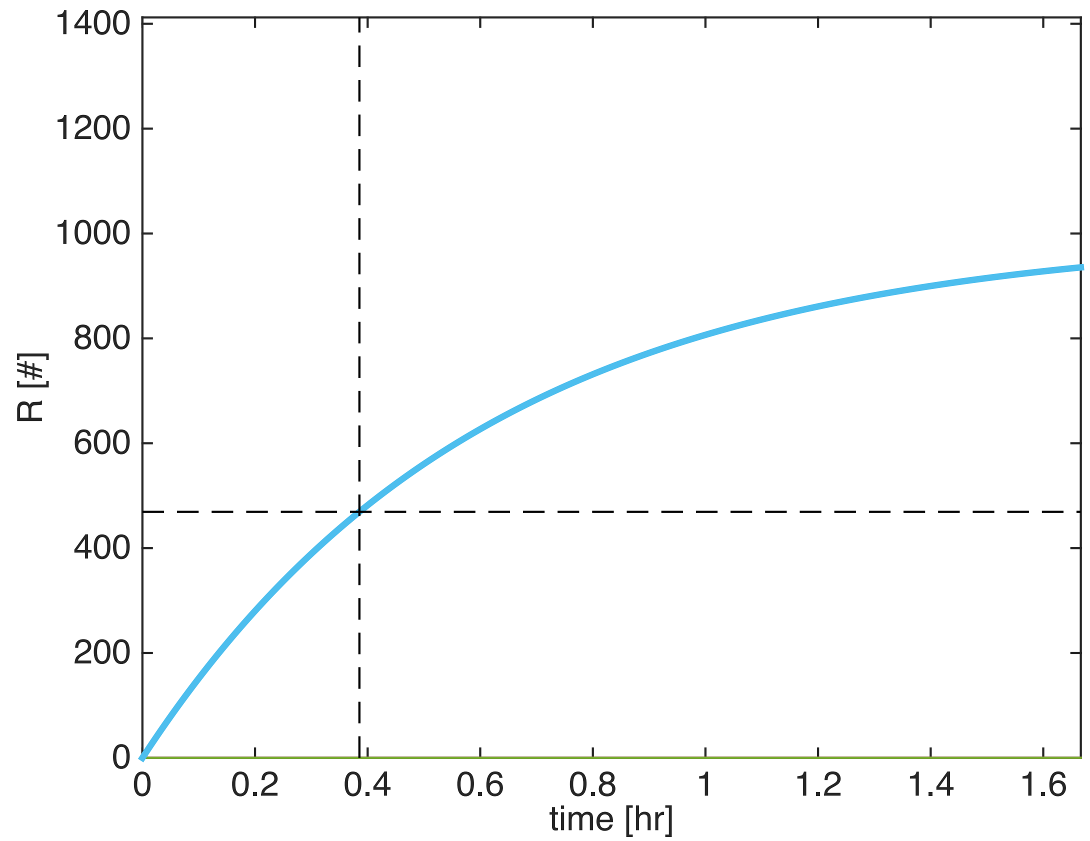
$$\emptyset \underset{k^-}{\overset{k^+}{\rightleftharpoons}} \mathrm{YFG} \qquad \frac{d\,\mathrm{YFG}}{dt} = k^+ - k^-\,\mathrm{YFG}$$

GENE EXPRESSION - MODELLING



$$\emptyset \underset{k^-}{\overset{k^+}{\rightleftharpoons}} \mathrm{YFG} \qquad \frac{d\,\mathrm{YFG}}{dt} = k^+ - k^- \,\mathrm{YFG}$$

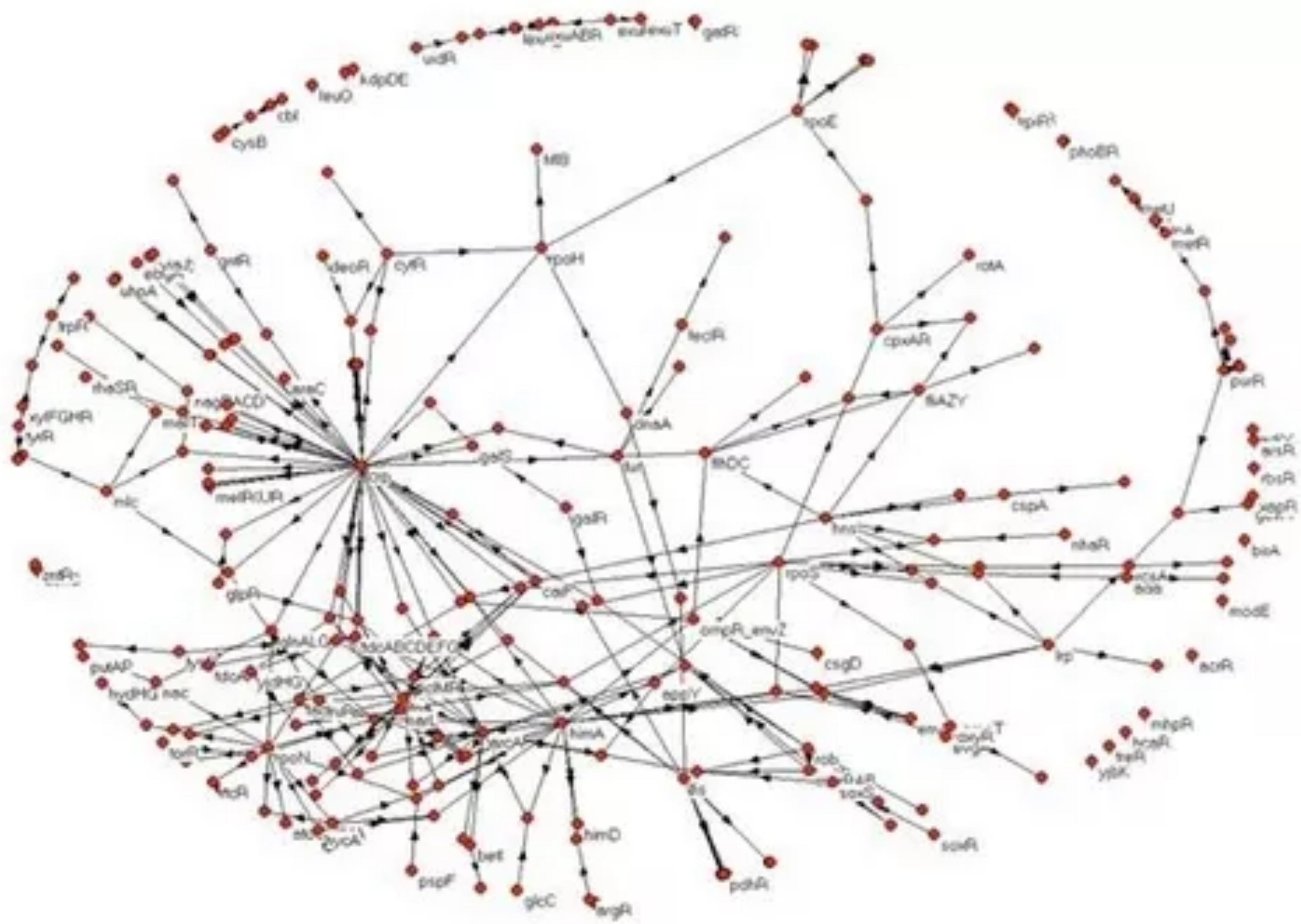
GENE EXPRESSION - MODELLING



$$\emptyset \underset{k^-}{\overset{k^+}{\rightleftharpoons}} \mathrm{YFG} \qquad \frac{d\,\mathrm{YFG}}{dt} = k^+ - k^-\,\mathrm{YFG}$$

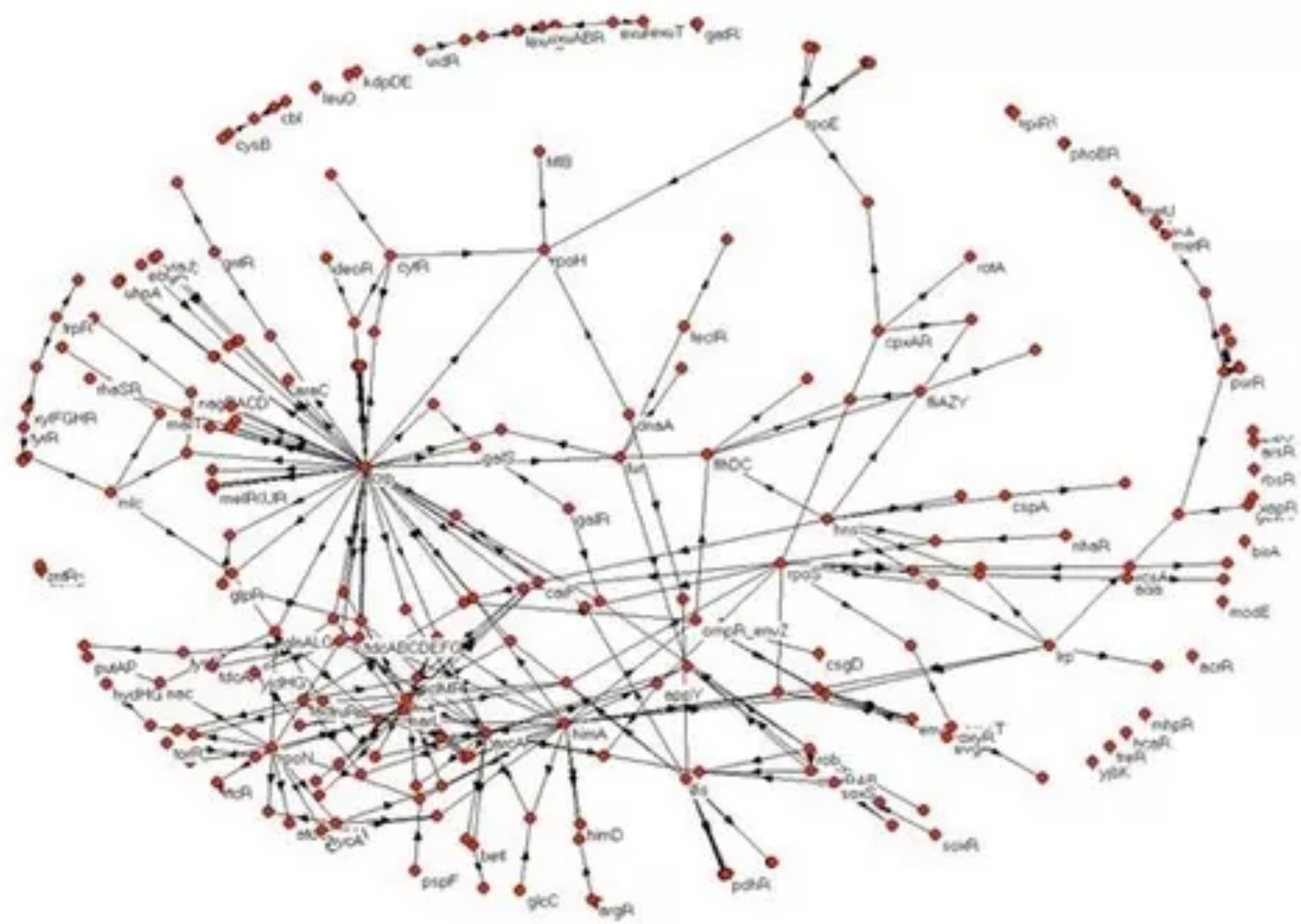
$$\mathrm{YFG}\,(t) = Y_{st}\,\mathrm{e}^{-k^-t} \qquad \mathrm{YFG}\,(t) = Y_{st}\left(1 - \mathrm{e}^{-k^-t}\right)$$

NETWORK MOTIFS



What devices do bacteria use?
420 nodes, 520 edges

NETWORK MOTIFS



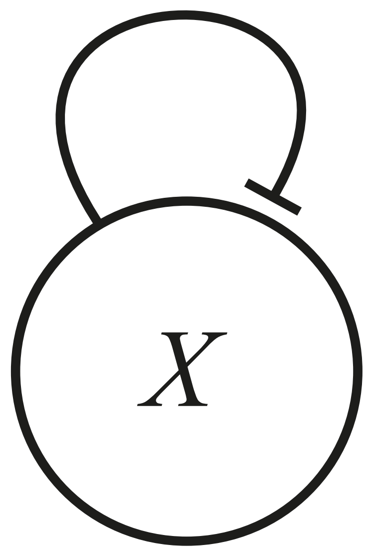
What devices do bacteria use?
420 nodes, 520 edges
40 self edges

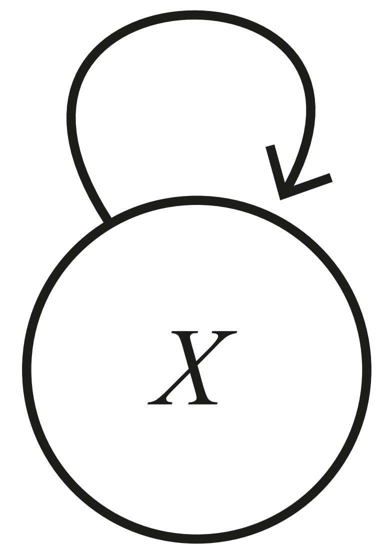
1 NODE MOTIFS

random network of N nodes includes N^2 edges
for 420 nodes and 520 edges, the expected number of self edges is approx.1
approximating biniomial distribution of self edges by the Poisson distribution implies the std is approx. 1

in a similar sized network in bacteria, the number of self edges = 40, i.e., approx. 40X the std deviation above the mean

1 NODE MOTIFS





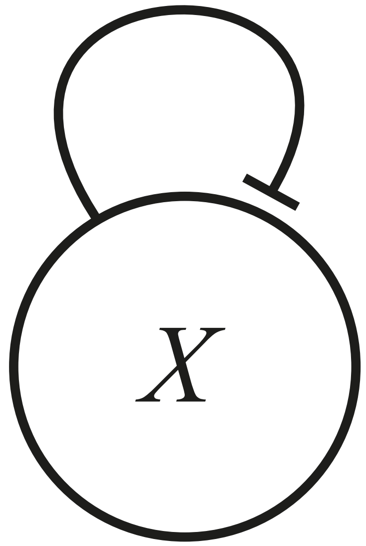
36 negative autoregulation motifs

Examples: TetR, LacI

4 negative autoregulation motifs

Examples: AraC, CRP

NAR MOTIF



$$\frac{dX}{dt} = f(X) - k^{-}X$$

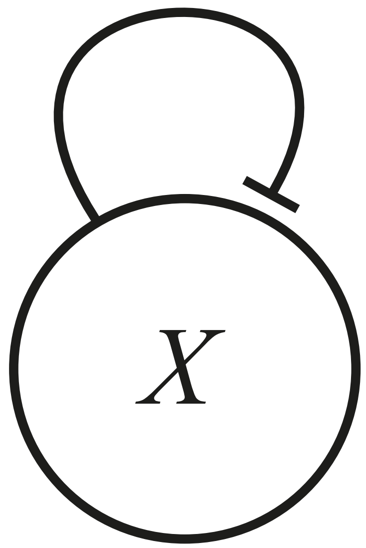
$$\frac{dX}{dt} \approx k^{+}G_T \; (X < K)$$

$$X(t) \approx k^{+}G_T t$$

$$T_{st} \approx K$$

$$T_K \approx \frac{K}{k^{+}G_T}$$

NAR MOTIF



$$\frac{dX}{dt} = f(X) - k^- X$$

$$\frac{dX}{dt} \approx k^+ G_T \; (X < K)$$

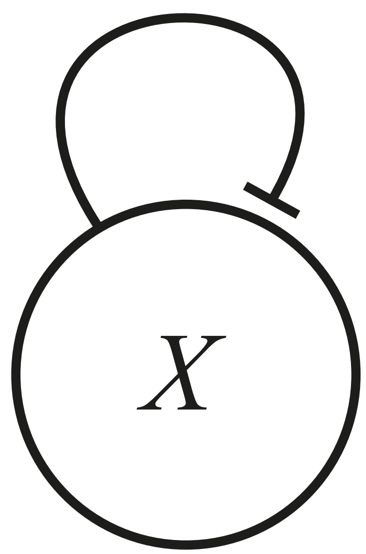
$$X(t) \approx k^+ G_T t$$

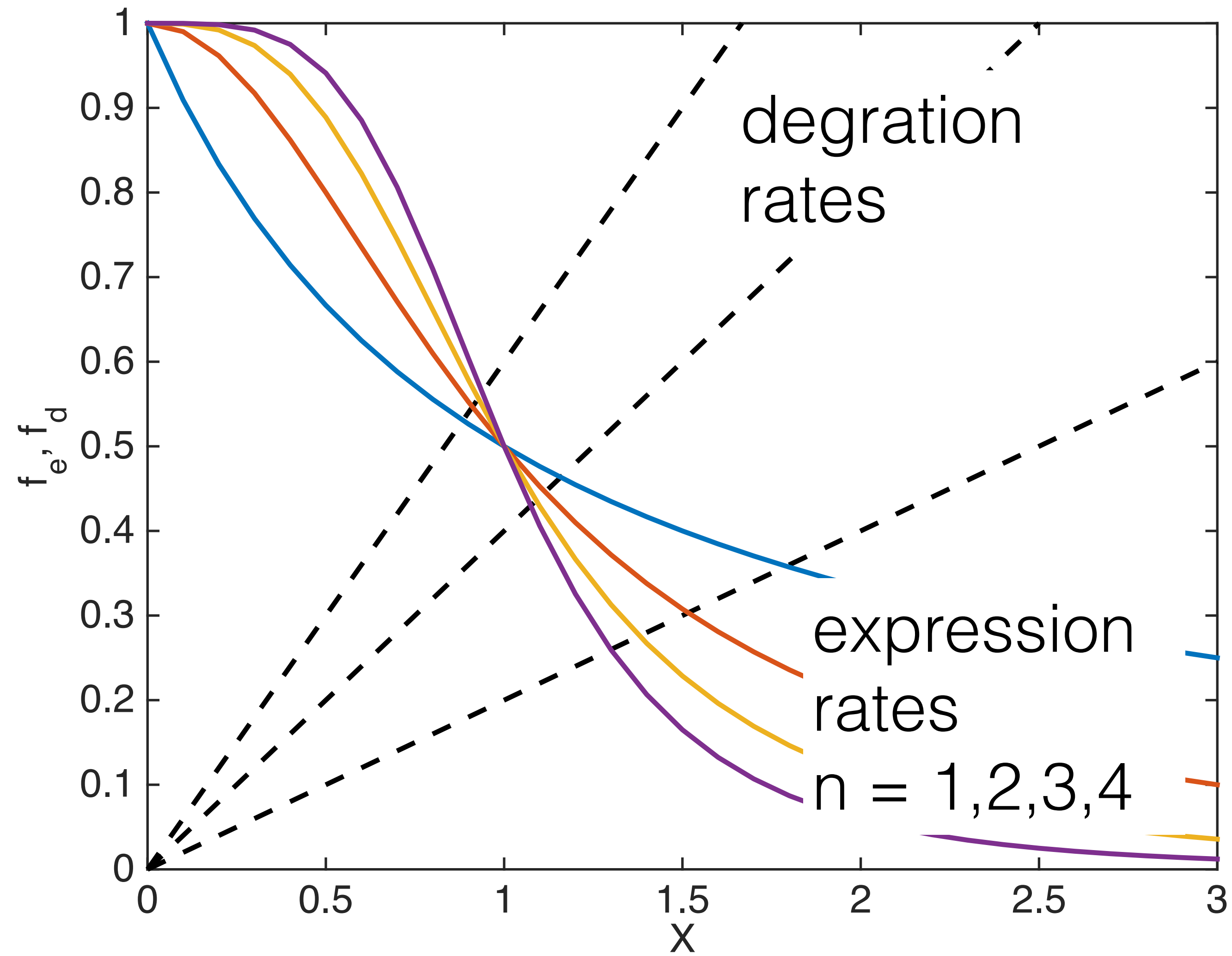
$$T_{st} \approx K$$

$$T_K \approx \frac{K}{k^+ G_T}$$

NAR allows for independent adjustment of rise time and steady state value.
NAR is used to speed up expression. Degradation remains the same.

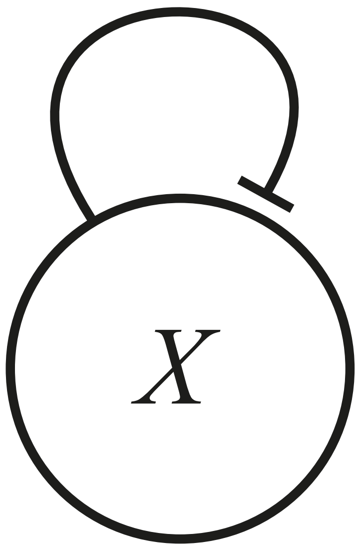
NAR MOTIF

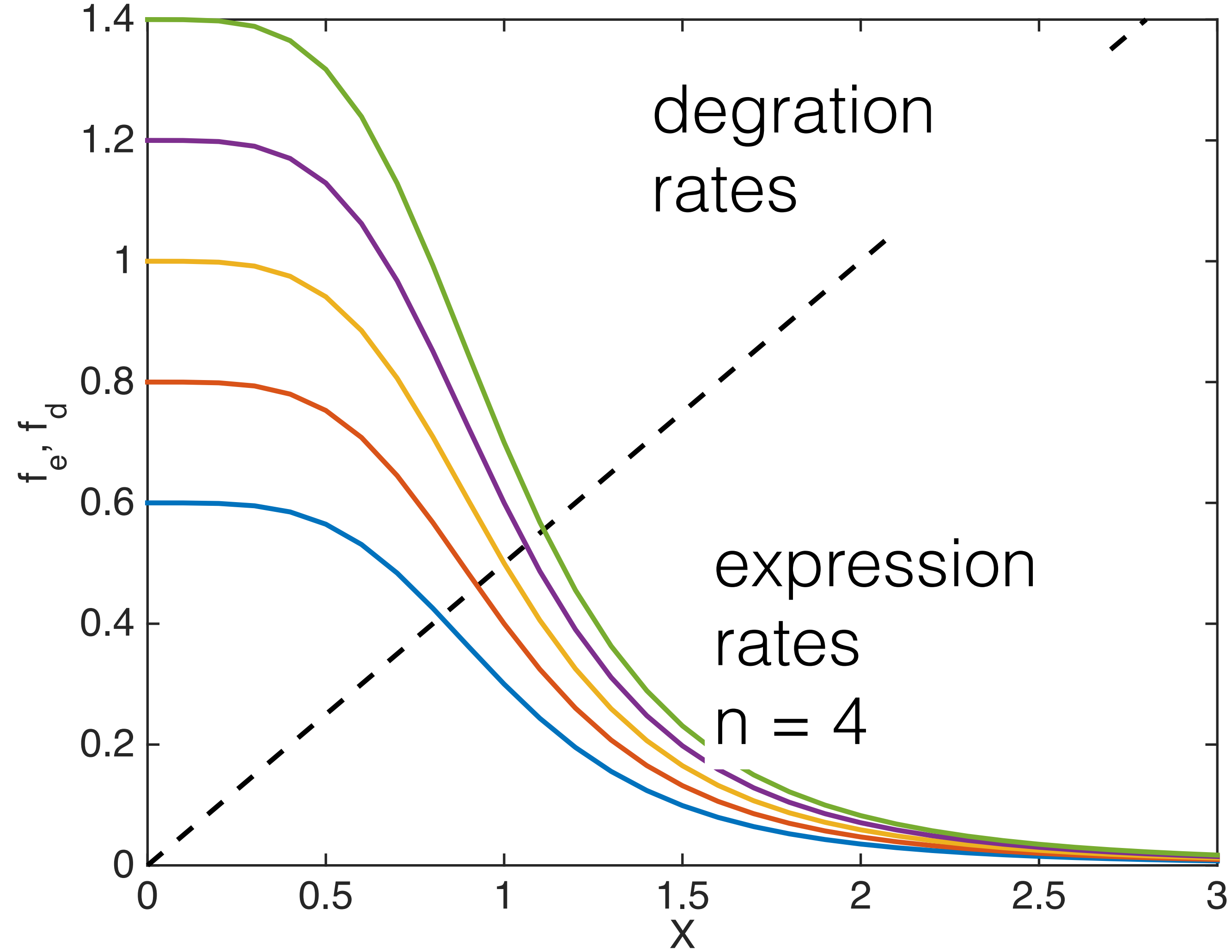




NAR also increases robustness of the steady state to perturbations in degradation rates.

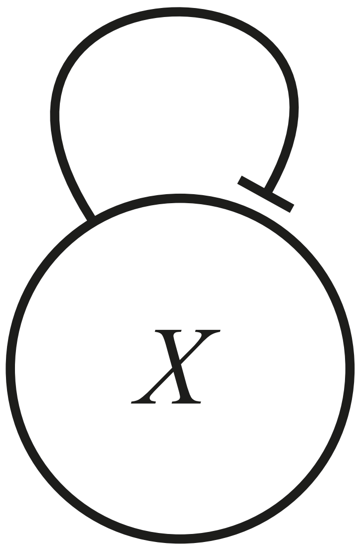
NAR MOTIF

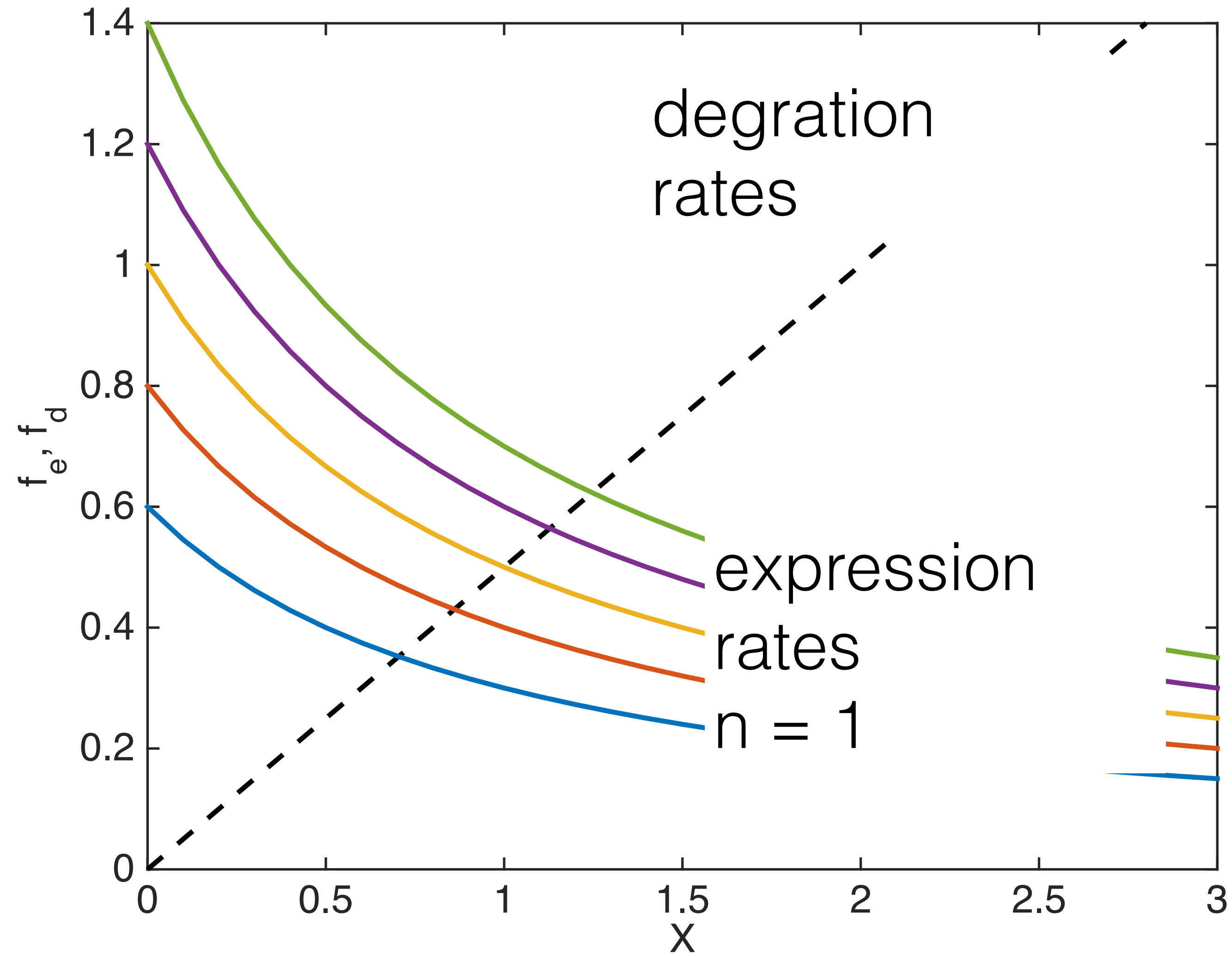




NAR also increases robustness of the steady state to perturbations in expression rates.

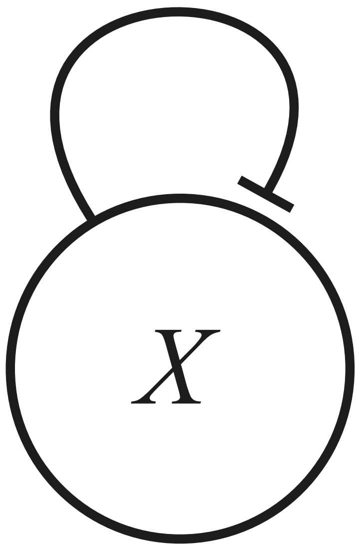
NAR MOTIF

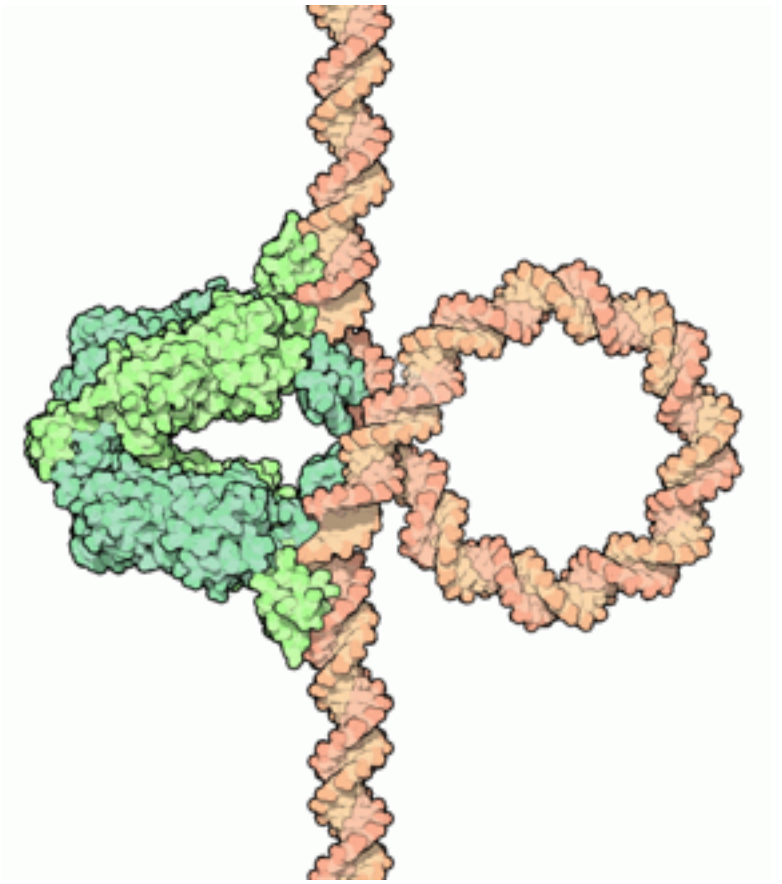




NAR also increases robustness of the steady state to perturbations in expression rates.

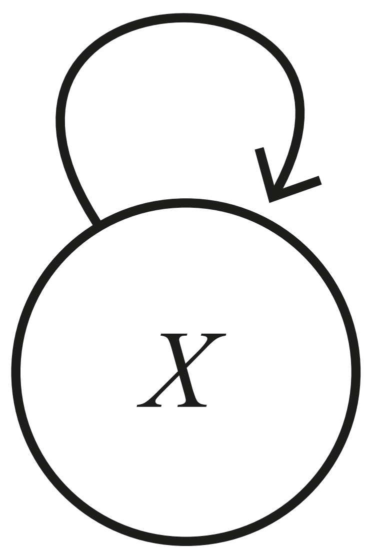
NAR MOTIF

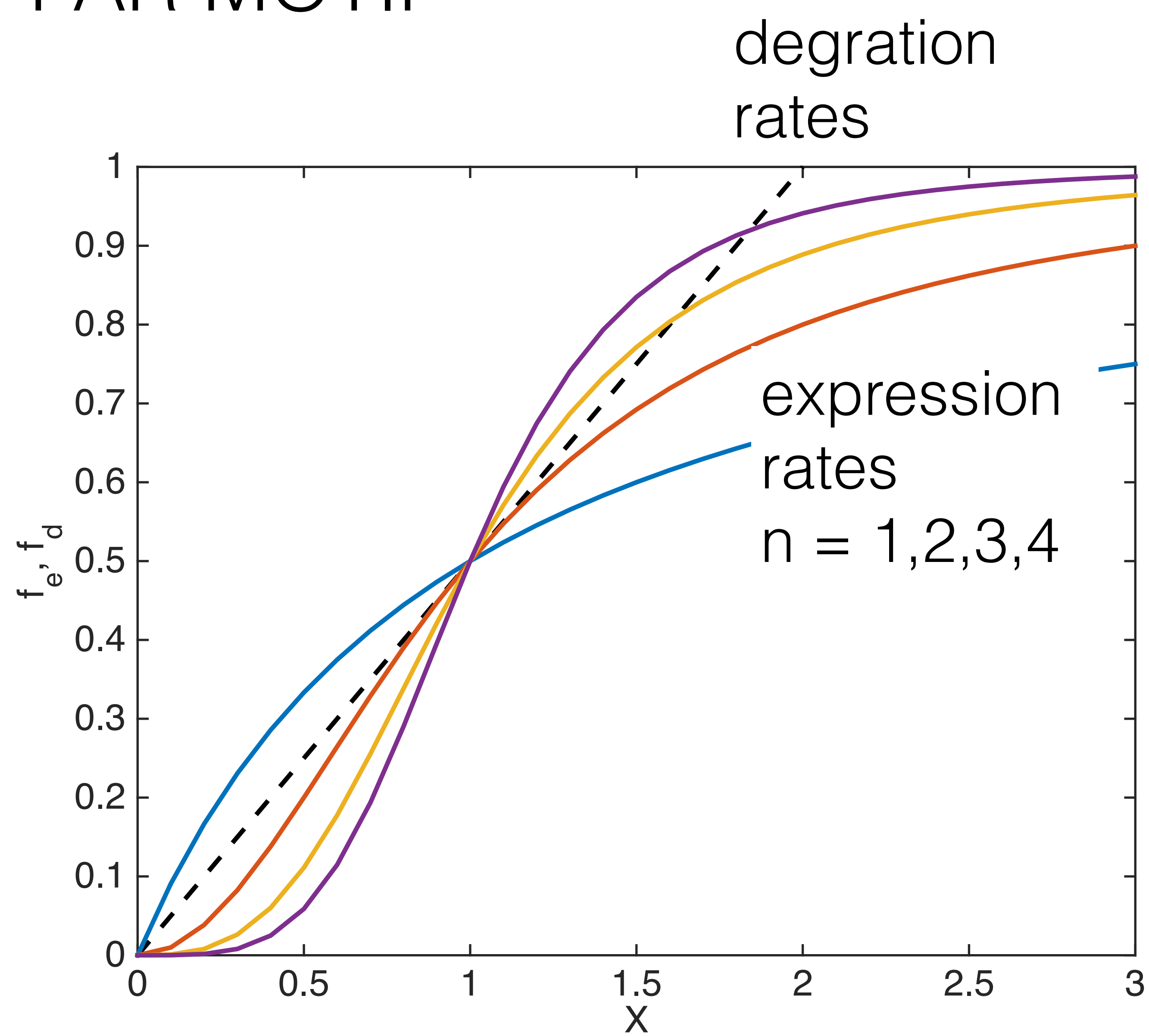




Lac inhibitor is a regulator of the Lac Operon, encoding lactose transporters and cleavage enzymes. Lac inhibitor is repressed by allolactose, a derivative of the disaccharide lactose. It binds DNA as a dimer. Two dimers form a stable tetramer to initiate and stabilise DNA looping.

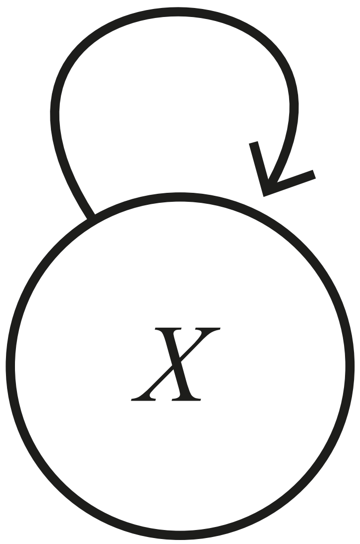
PAR MOTIF

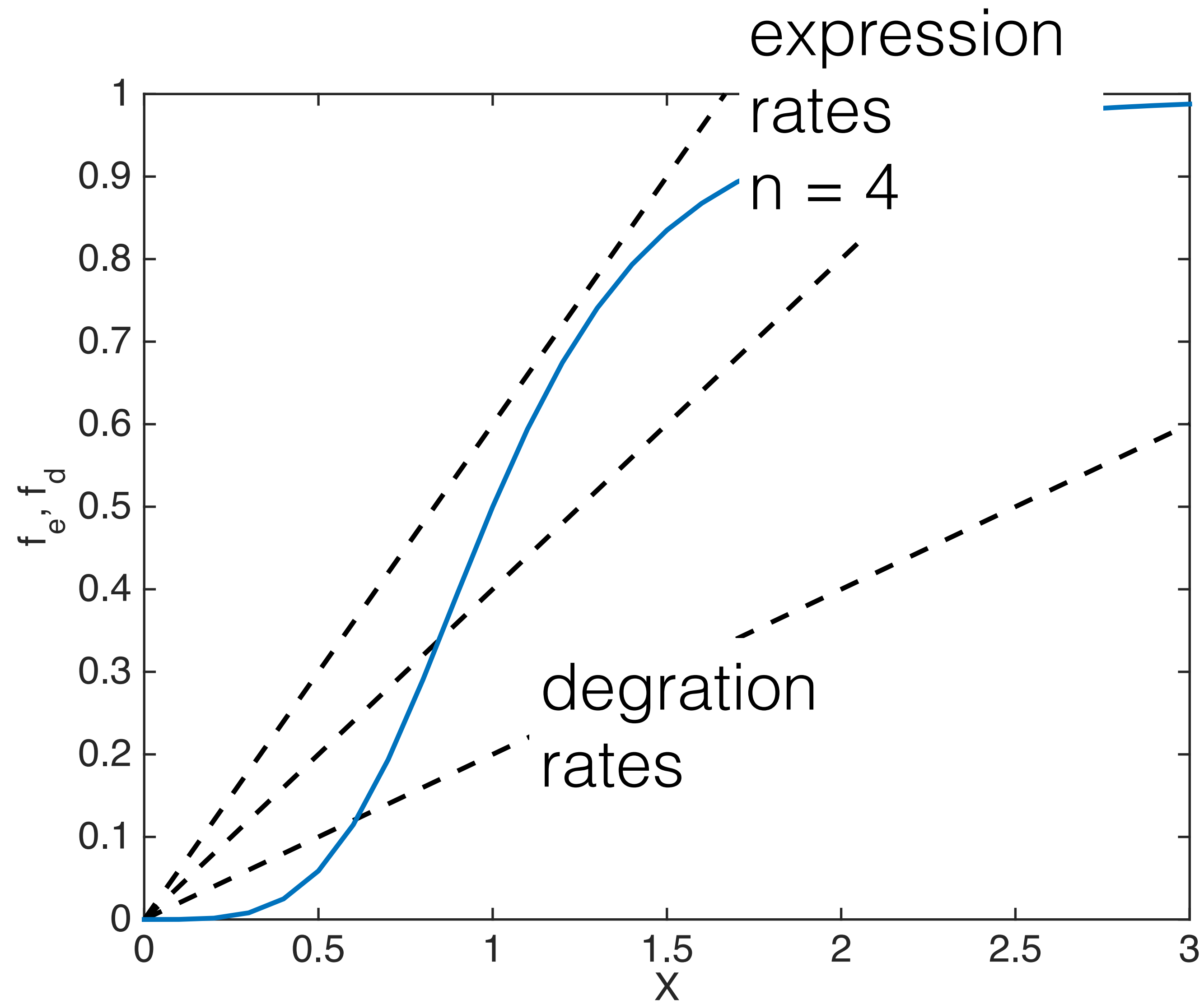




PAR generates bistability for higher cooperation rates.
PAR for a one-way bistable switch.

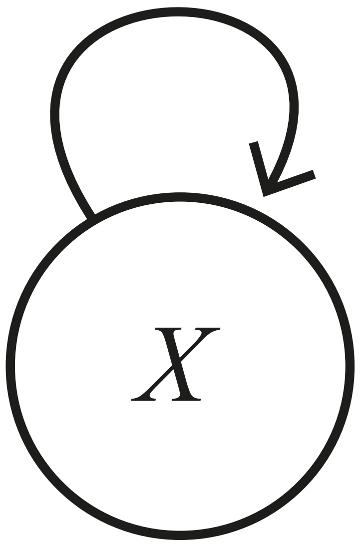
PAR MOTIF

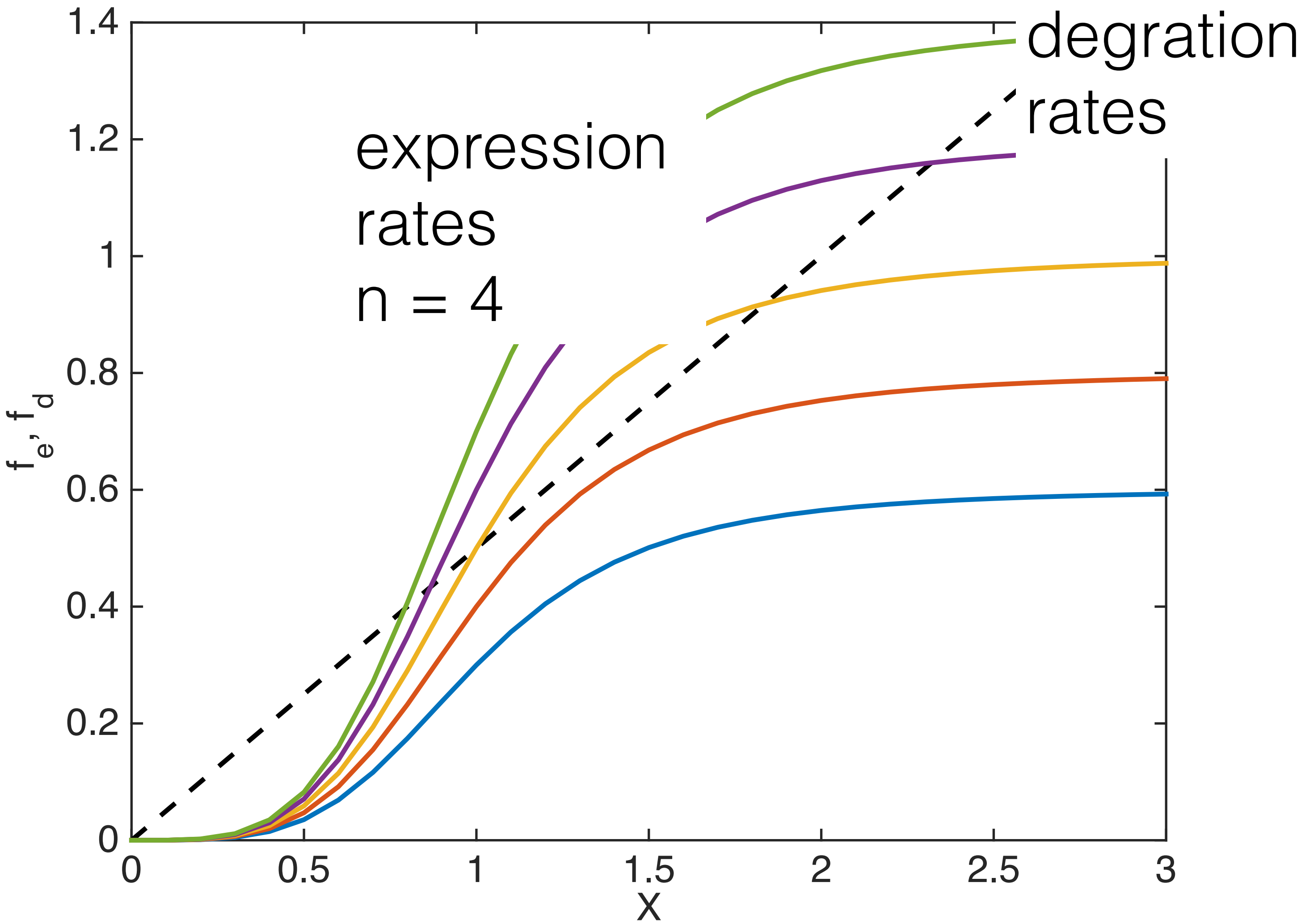




PAR increases sensitivity.

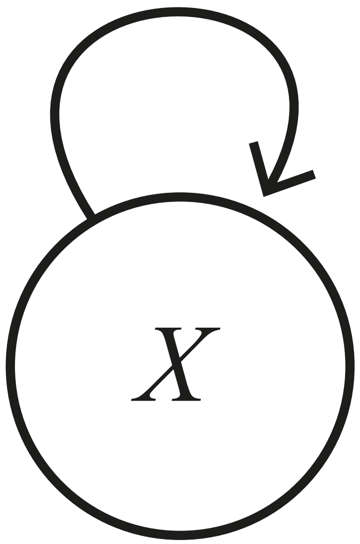
PAR MOTIF

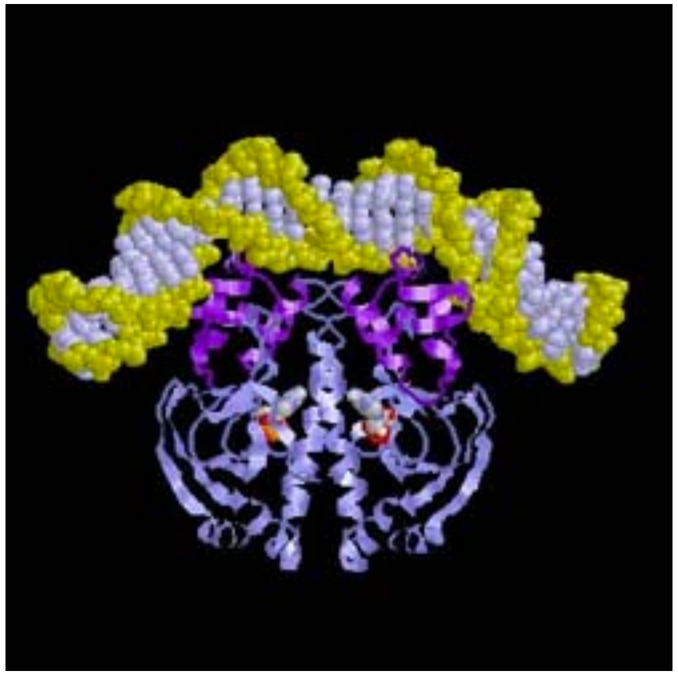




PAR increases sensitivity.

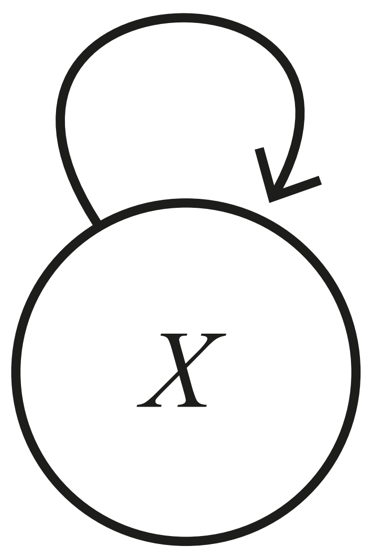
PAR MOTIF

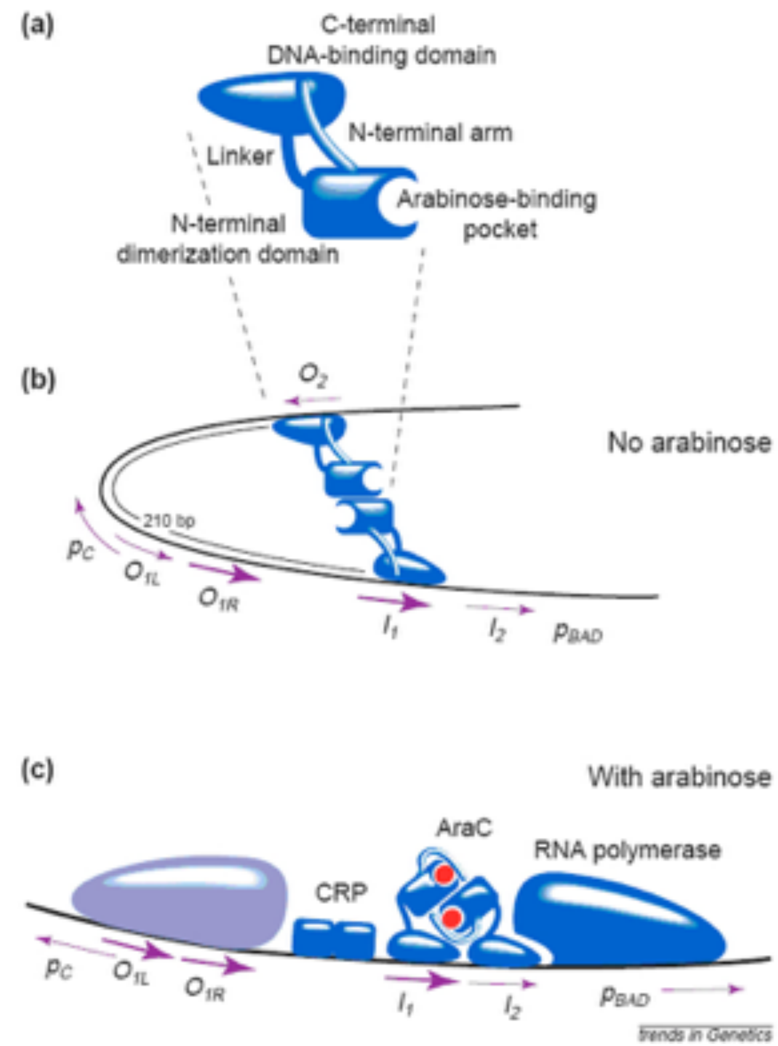




CRP, cAMP responsive protein, is activated by cyclic adenosine mono phosphate (ATP that has lost two of its phosphates). This happens when the cell is starved.

PAR MOTIF





CRP can cooperate with other activators, such as AraC to turn on metabolism of particular sugars. AraC is activated by arabinose, a monosaccharide found in cell walls of plants. AraC is special in that it can act as a repressor as well as an activator.