Modular Composition of Complex Gene Transcription Networks

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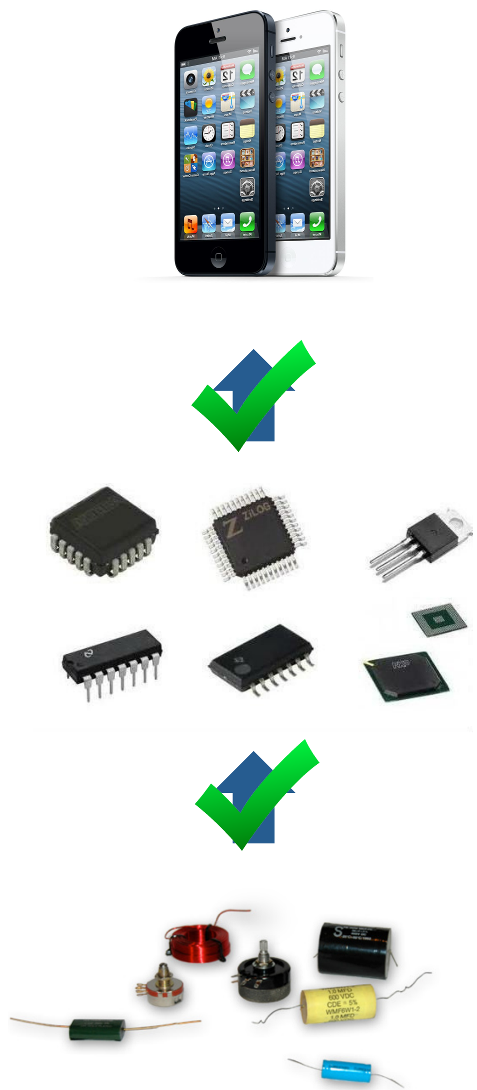
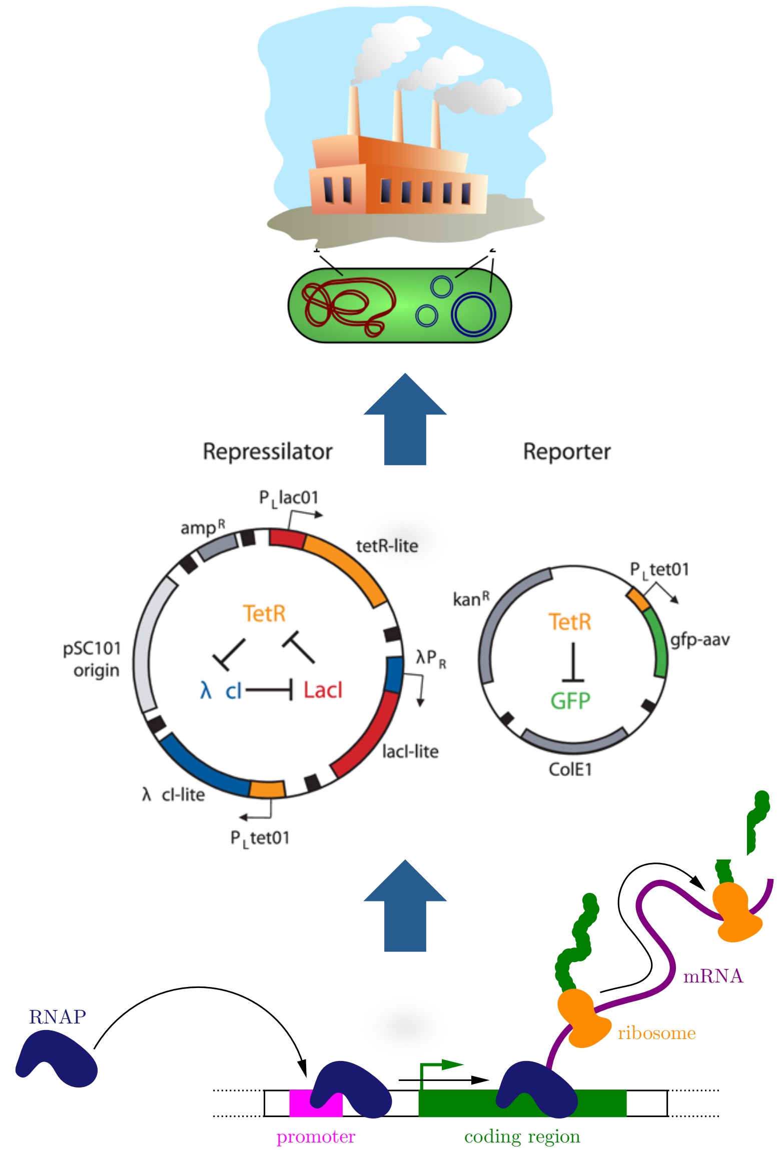
January 28, 2013

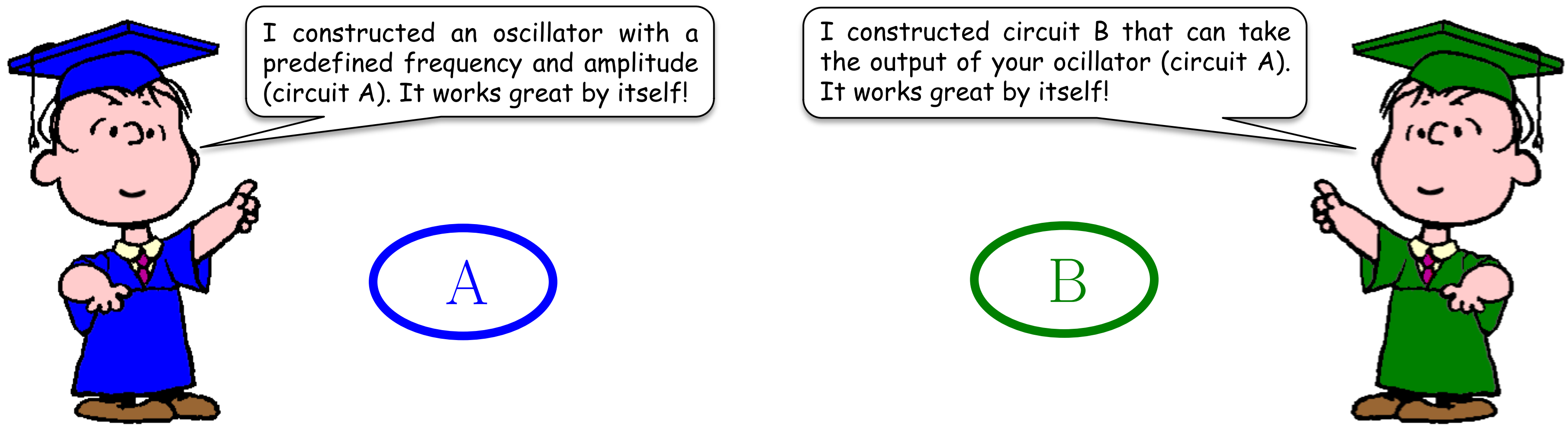
Grant #FA9550-10-1-0242

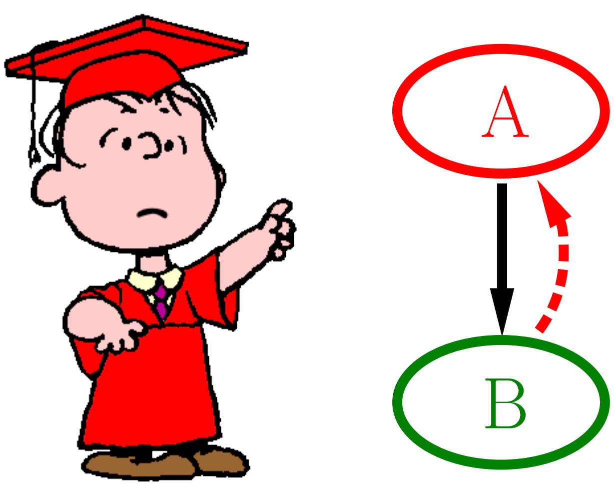
The future of synthetic biology is via modular design

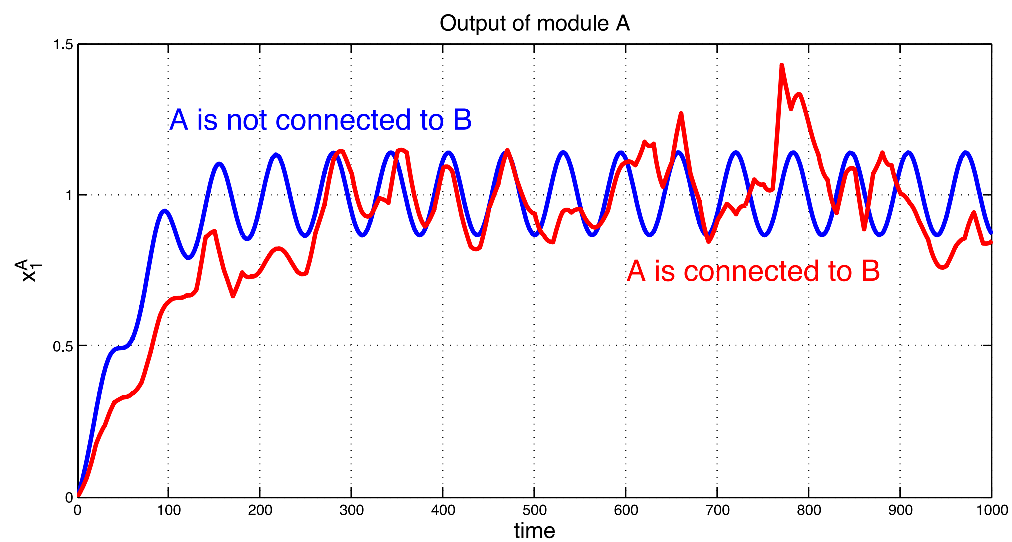




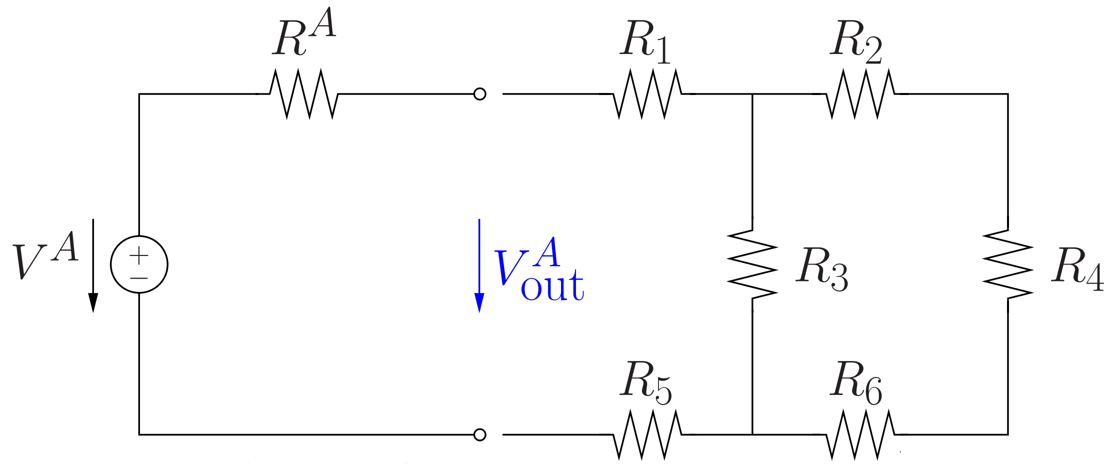
We are not designing systems modularly (yet)



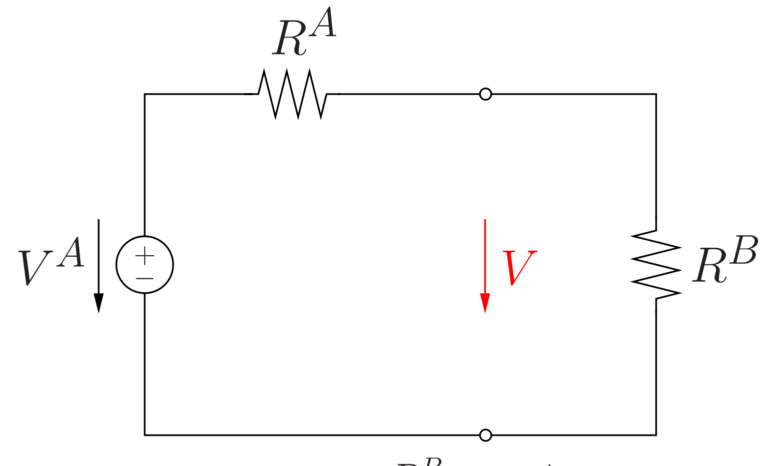




This is a known effect in electrical systems: loading



$V^A_{out} \neq V^A$



$V = \frac{R^B}{R^A+R^B}V^A$

Question #1

Can we obtain a simple, equivalent description of a complex transcription network? If so, can we predict how the dynamics of the upstream module change by considering only the equivalent description of the downstream?

Question #2

How to design modules so that their input-output behavior is robust to interconnections? What are the design principles resulting in modular composition?

(1) **Model of a transcription network**

(2) **Restoring modular composition by appending the description of a module with retroactivities**

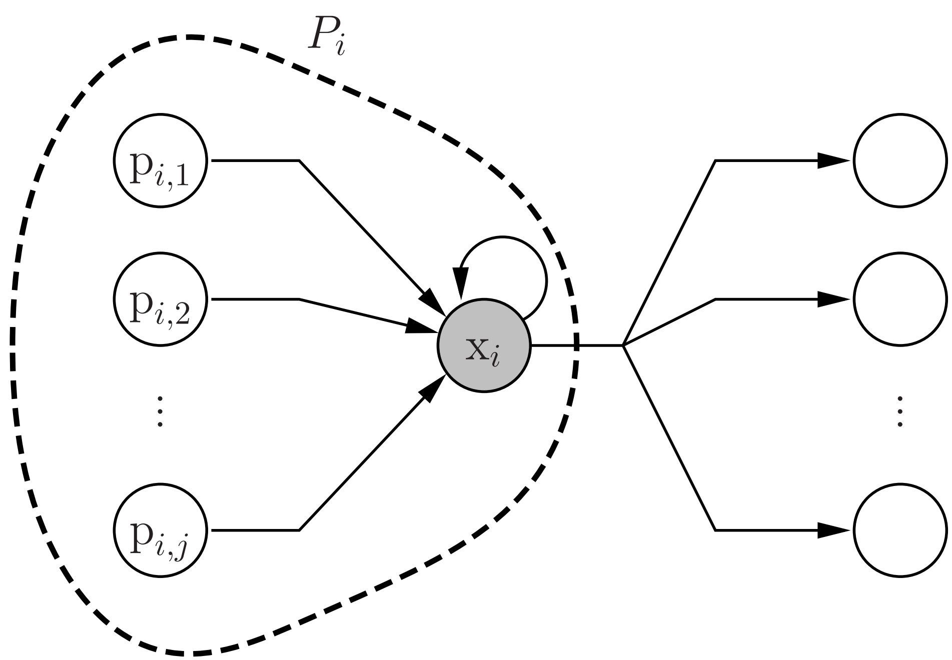
(3) **Quantifying the difference in dynamics and trajectory of the upstream system**

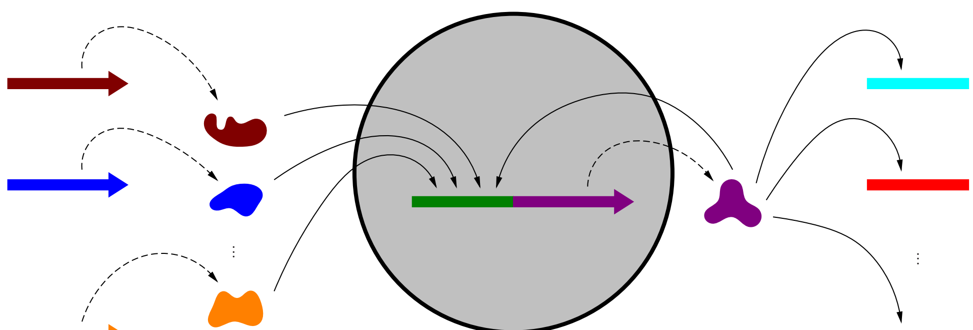
(1) Model of a transcription network

(2) Restoring modular composition by appending the description of a module with retroactivities

(3) Quantifying the difference in dynamics and trajectory of the upstream system

Building blocks are transcription components





Binding and unbinding of parents to form promoter complexes

$$c_{i,j} + p_{i,l} \underset{\alpha_{i,k,j}}{\overset{\alpha_{i,j,k}}{\rightleftharpoons}} c_{i,k}$$

Protein production and decay

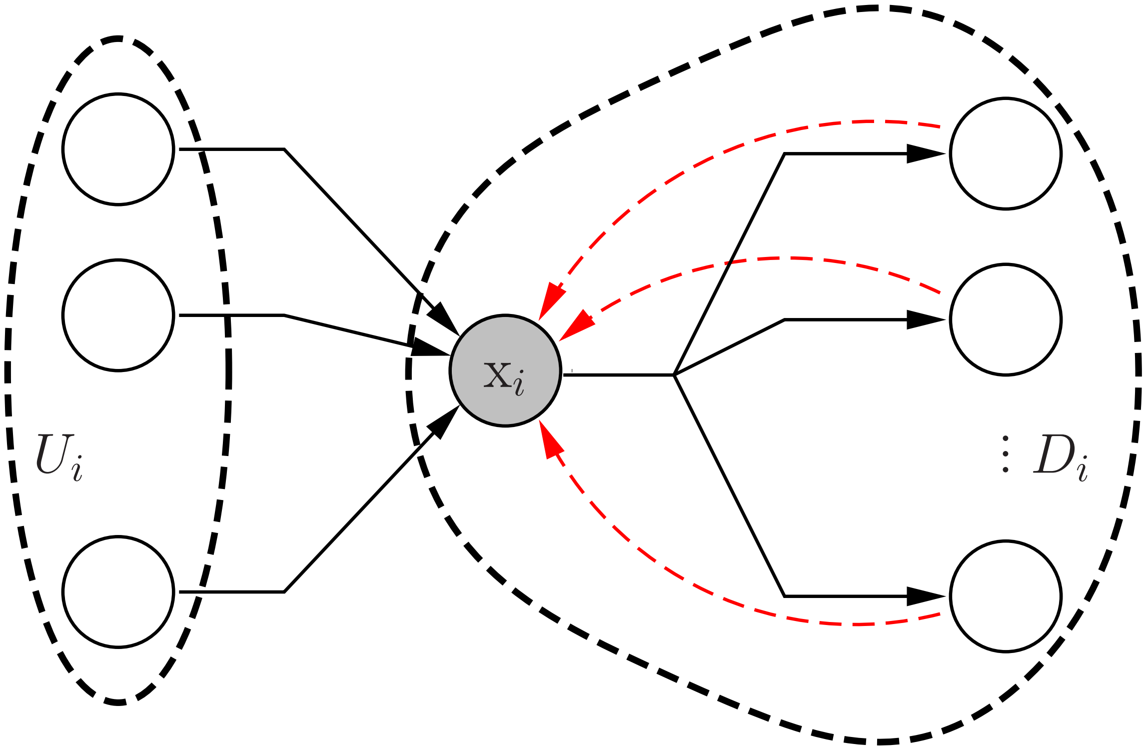
$$c_{i,j} \xrightarrow{\pi_{i,j}} c_{i,j} + x_i$$

$$\emptyset \underset{\delta_i}{\overset{\nu_i(t)}{\rightleftharpoons}} x_i$$

Conservation law for promoter

$$\eta_i = \sum_{j=0}^{\chi_i} c_{i,j}$$

Descendants change the dynamics of parents



u_i x_i

$$\dot{c}_i = L_i \overbrace{r_i\left(x_i, c_i, u_i\right)}^{\text{retroactivity to the input of node } i}$$

$$\dot{x}_i = \nu_i - \delta_i x_i + \sum_{j=0}^{\chi_i} \pi_{i,j} c_{i,j} + \underbrace{\sum_{\{j \mid x_j \in D_i\}} K_{i,j} r_j\left(x_j, c_j, u_j\right)}_{\text{retroactivity to the output of node } i:\ s_i}$$

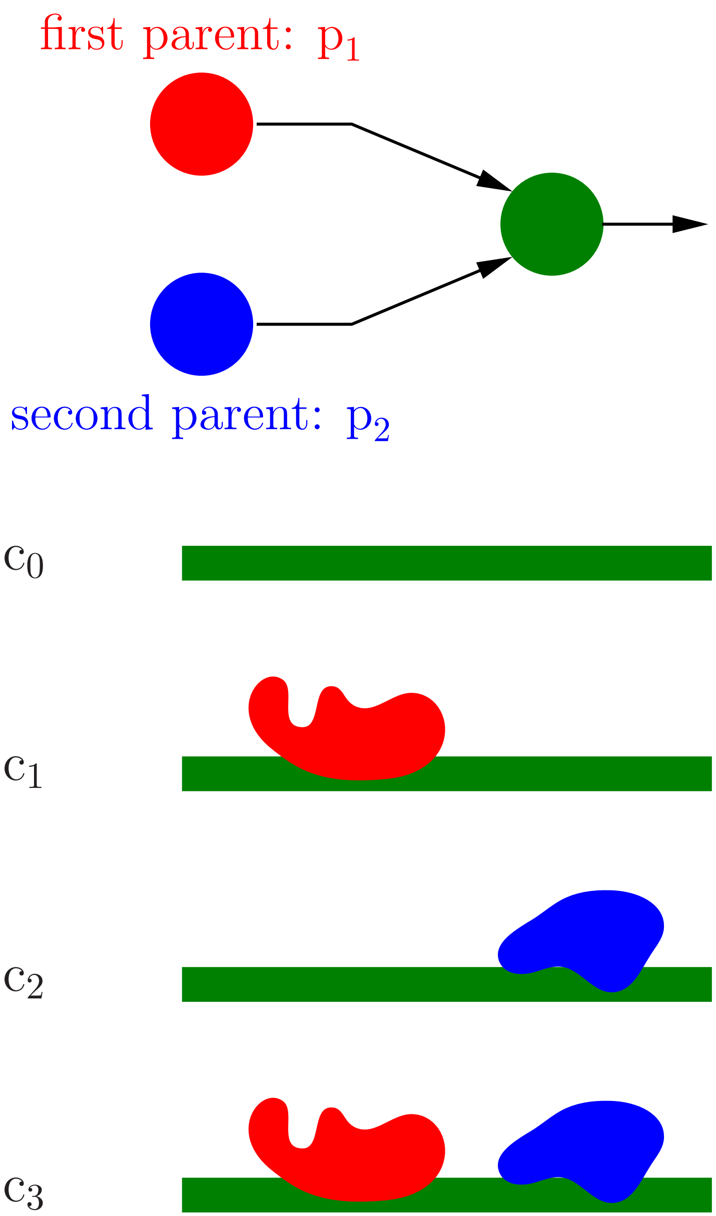
r_i s_i

(1) Model of a transcription network

(2) **Restoring modular composition by appending the description of a module with retroactivities**

(3) Quantifying the difference in dynamics and trajectory of the upstream system

Retroactivity of a node makes a node stiff



Concentration of bound first parent:

$$b_1 = c_1 + c_3$$

Concentration of bound second parent:

$$b_2 = c_2 + c_3$$

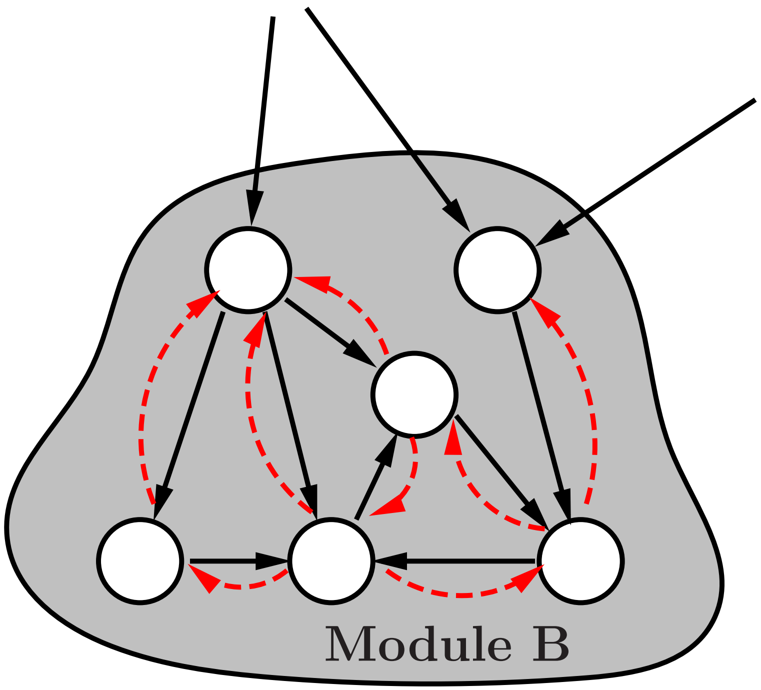
$$R = \frac{\partial b}{\partial p} = \begin{bmatrix} \frac{\partial b_1}{\partial p_1} & \frac{\partial b_1}{\partial p_2} \\ \frac{\partial b_2}{\partial p_1} & \frac{\partial b_2}{\partial p_2} \end{bmatrix}$$

TOPOLOGY INDEPENDENT

Independent binding:
off-diagonals are zero

Competitive binding:
off-diagonals are negative

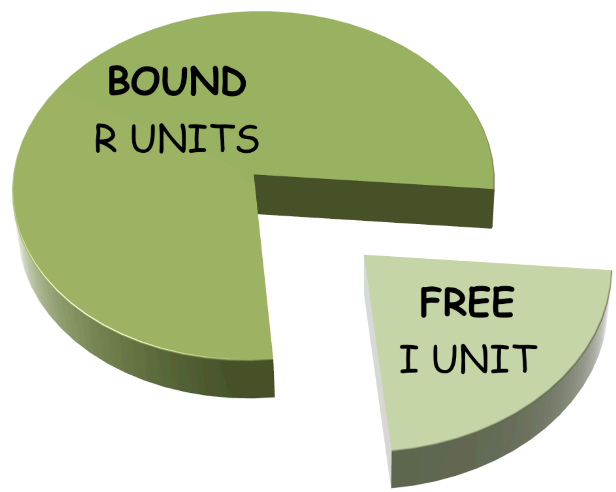
Internal retroactivity makes the module stiff



Internal retroactivity of a module

$$R(x,u) = \sum_{i \in \Phi} V_i R_i V_i'$$

Change of free and bound TFs

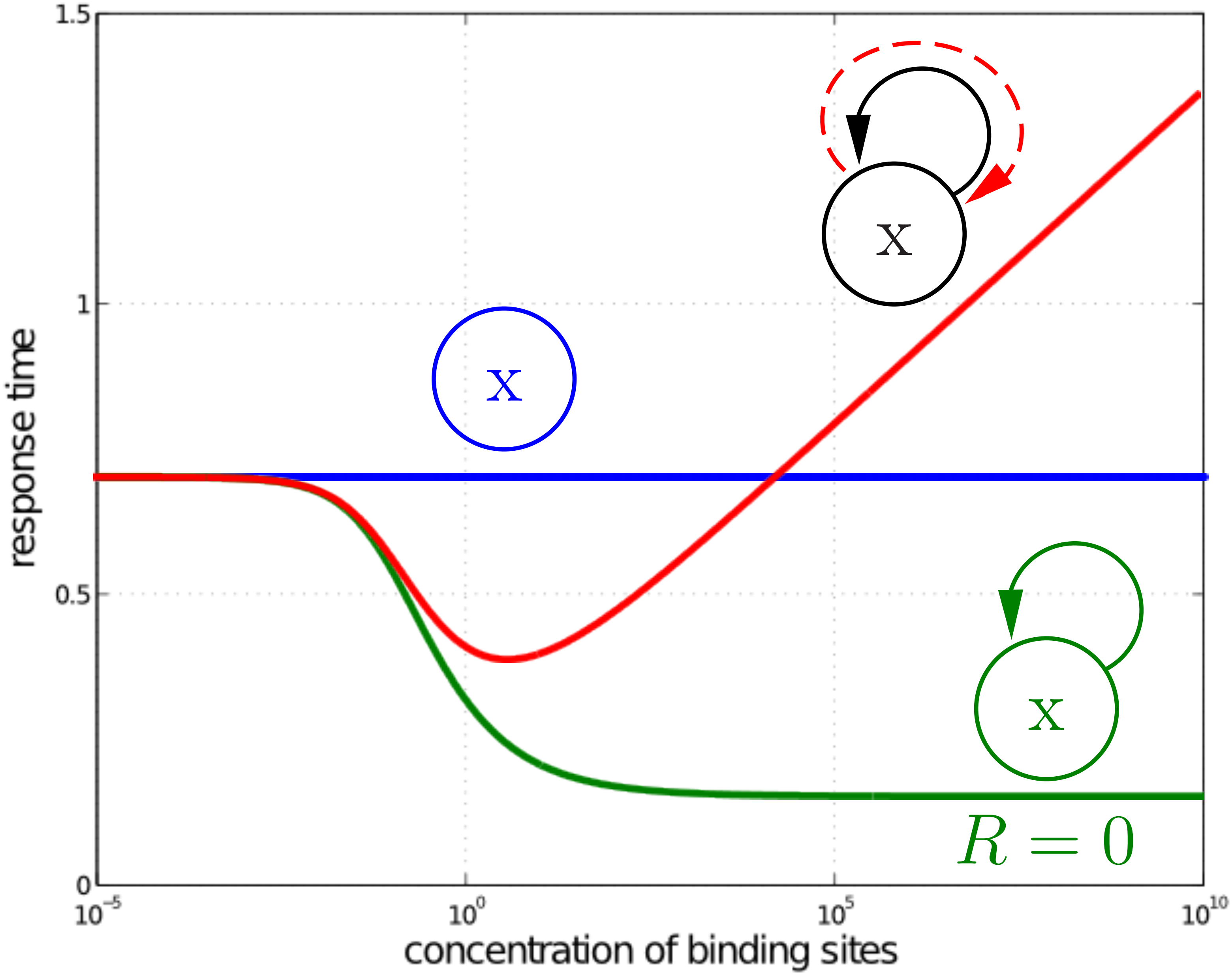


Reduced order model of an isolated module

$$\dot{x} = [I + R]^{-1} \underbrace{g\left(x, \gamma(x,u)\right)}_{\text{rate of change of free+bound TFs}}$$

The greater the internal retroactivity, the stiffer the module

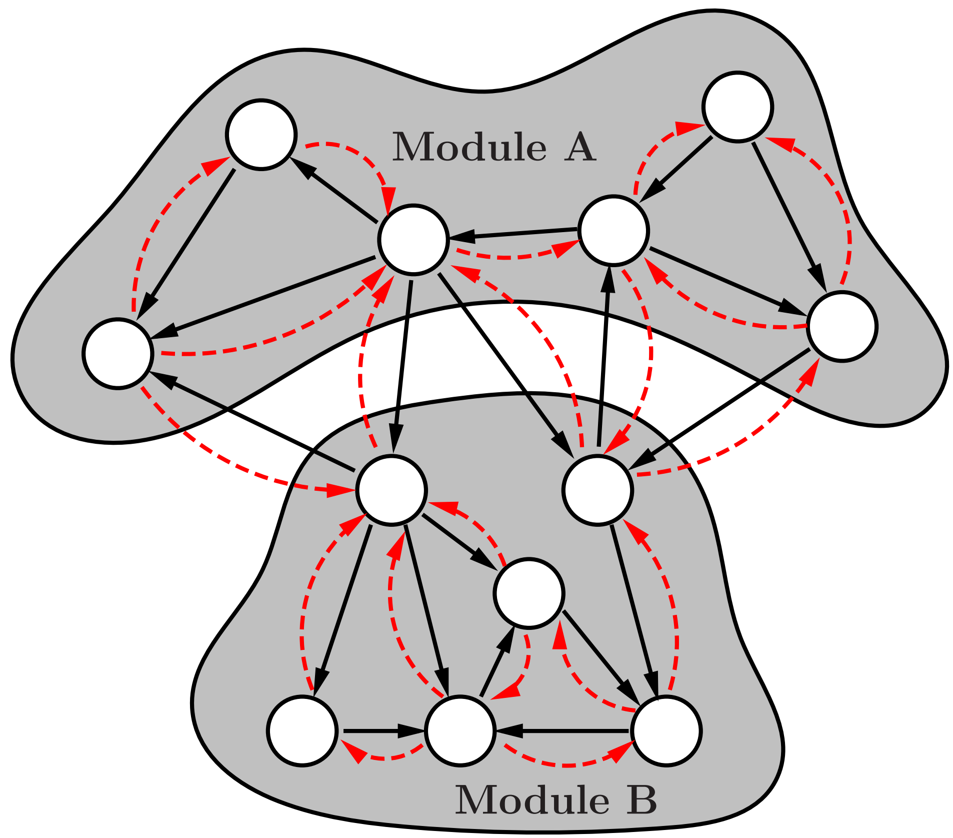
Negative feedback can make the system slower



Effect of intermodular connections

Modules A and B are not connected:

$$\begin{bmatrix} \dot{x}^A \\ \dot{x}^B \end{bmatrix} = \begin{bmatrix} f^A\left(x^A, u^A\right) \\ f^B\left(x^B, u^B\right) \end{bmatrix}$$



Input retroactivity of B to A

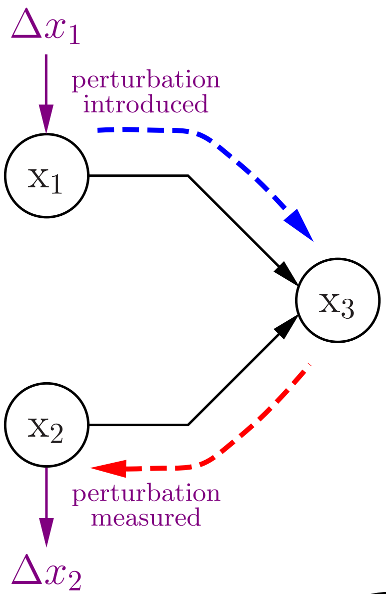
$$\Delta R_A^B\left(x^B, u^B\right) = \sum_{i \in \Phi_A^B} \begin{bmatrix} V_i R_i^B V_i' & W_i R_i^B W_i' \\ W_i R_i^B V_i' & 0 \end{bmatrix}$$

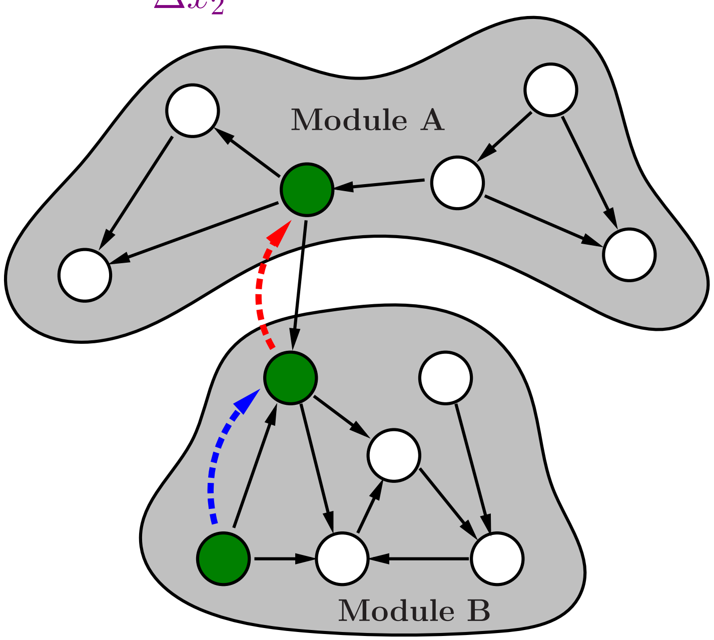
Connected modules

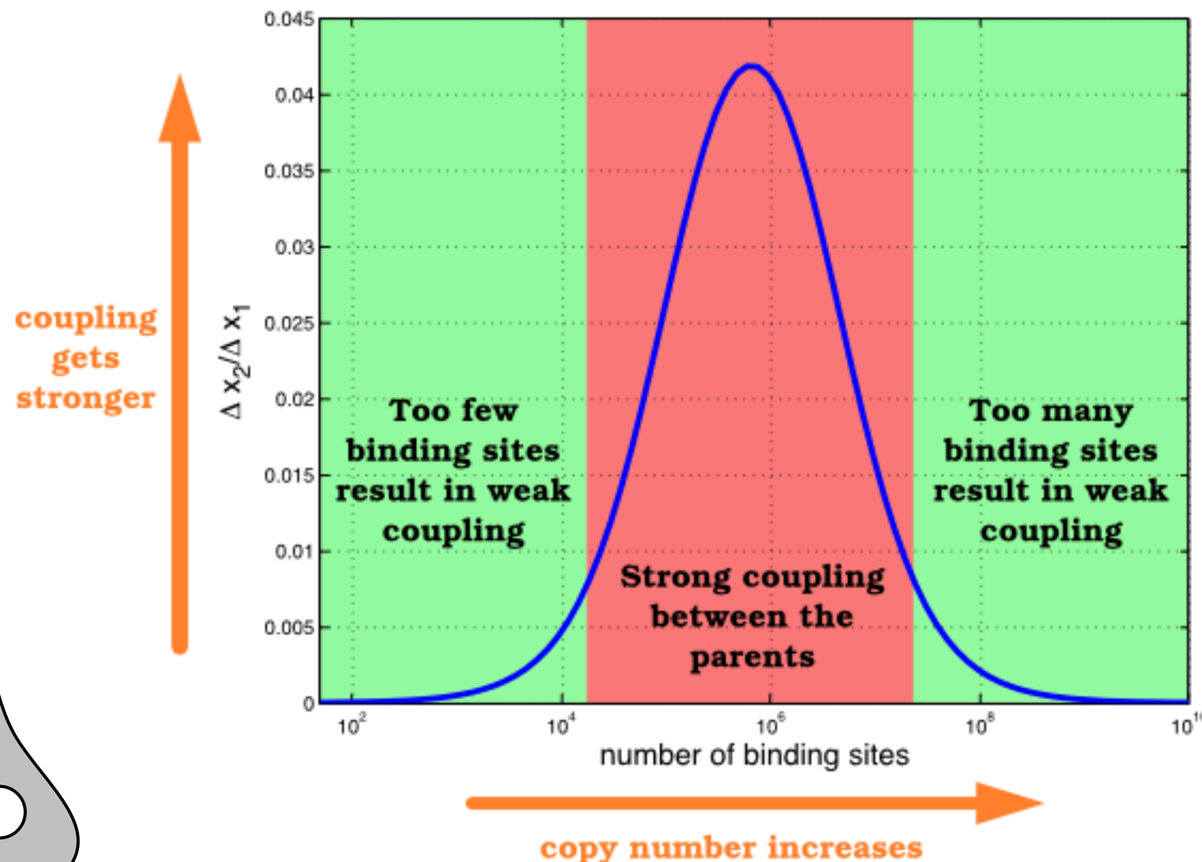
$$\begin{bmatrix} \dot{x}^A \\ \dot{x}^B \end{bmatrix} = \left[I + G\left(\Delta R_A^B + \Delta R_B^A\right)\right]^{-1} \underbrace{\begin{bmatrix} f^A\left(x^A, u^A\right) \\ f^B\left(x^B, u^B\right) \end{bmatrix}}_{\text{isolated modules}}$$

$$G = \begin{bmatrix} \left(I + R^A\right)^{-1} & 0 \\ 0 & \left(I + R^B\right)^{-1} \end{bmatrix}$$

Mixed parents can cause unwanted couplings







$$\dot{x}^A = M_1 \underbrace{f^A\left(x^A, u^A\right)}_{\text{isolated A}} + M_2 \underbrace{f^B\left(x^B, u^B\right)}_{\text{isolated B}}$$

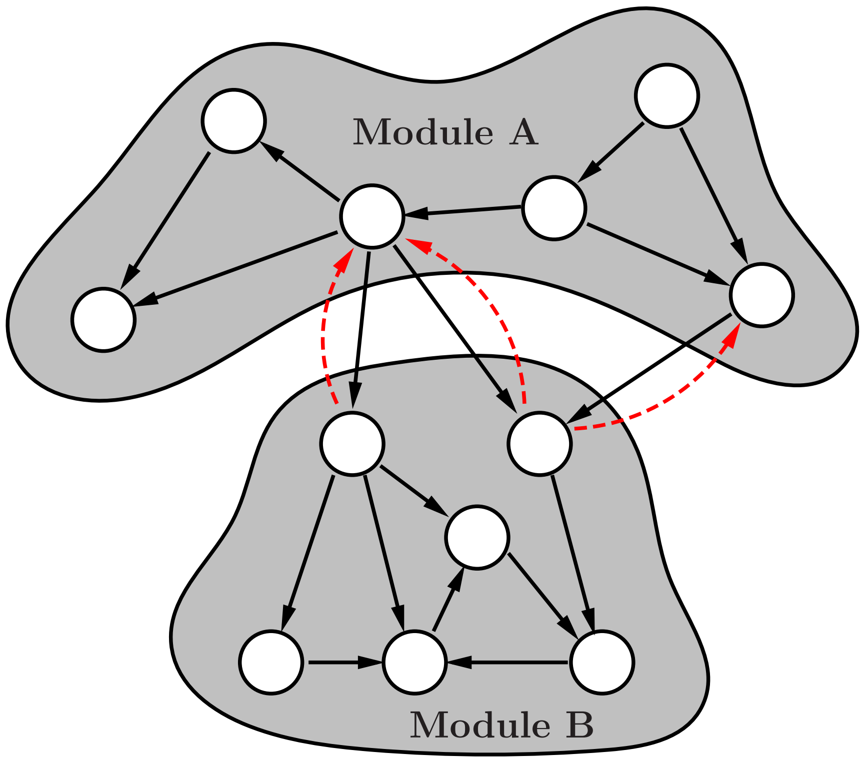
In the following we assume that parents are not mixed

(1) Model of a transcription network

(2) Restoring modular composition by appending the description of a module with retroactivities

(3) Quantifying the difference in dynamics and trajectory of the upstream system

Quantifying the effect of downstream on upstream



$$\begin{bmatrix} \dot{x}^A \\ \dot{x}^B \end{bmatrix} = [I + G\Delta]^{-1} \underbrace{\begin{bmatrix} f^A(x^A, u^A) \\ f^B(x^B, u^B) \end{bmatrix}}_{\text{isolated modules}}$$

$$\Delta = \Delta R_A^B = \begin{bmatrix} \delta R_A^B & 0 \\ 0 & 0 \end{bmatrix}$$

Percentage change in dynamics of A

$$\sigma \leq \frac{\left\| \left(I + R^A\right)^{-1} \delta R_A^B \right\|_2}{1 - \left\| \left(I + R^A\right)^{-1} \delta R_A^B \right\|_2}$$

Difference in trajectories can also be upper bounded by σ

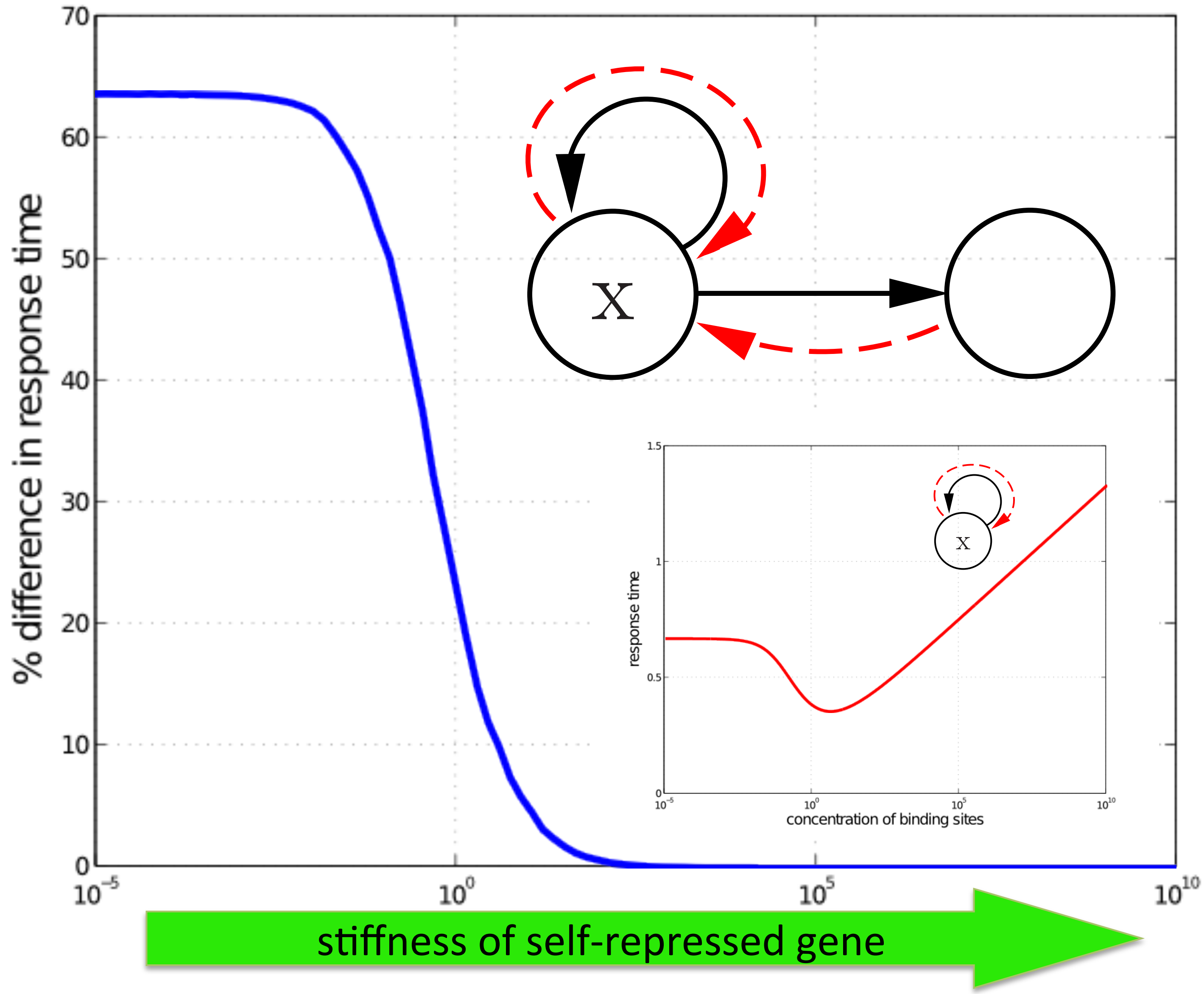
Upstream module is robust if

Strong internal retroactivity: R^A "large"

Weak retroactivity in between: δR_A^B "small"

The upstream module should be stiff

The upstream module better be stiff



Conclusion: modular composition is restored, and more

Module A

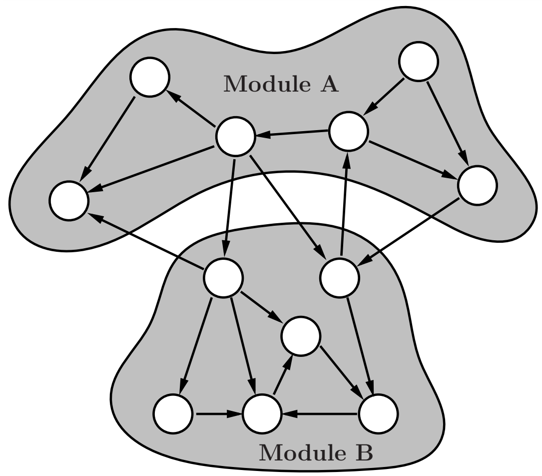
$$\dot{x}^A = f^A\left(x^A, u^A\right)$$

$$R^A \quad \Delta R^A_B$$

Connected modules

$$\begin{bmatrix} \dot{x}^A \\ \dot{x}^B \end{bmatrix} = [I + G\Delta]^{-1} \begin{bmatrix} f^A\left(x^A, u^A\right) \\ f^B\left(x^B, u^B\right) \end{bmatrix} \qquad G = \begin{bmatrix} \left(I + R^A\right)^{-1} & 0 \\ 0 & \left(I + R^B\right)^{-1} \end{bmatrix}$$

$$\Delta = \Delta R^A_B + \Delta R^B_A$$



Avoid mixing parents from different modules

Otherwise downstream dynamics appears in upstream system

Module B

$$\dot{x}^B = f^B\left(x^B, u^B\right)$$

$$R^B \quad \Delta R^B_A$$

Upstream module is robust if

Strong internal and weak intramodular retroactivity

Quantify difference in dynamics and trajectory