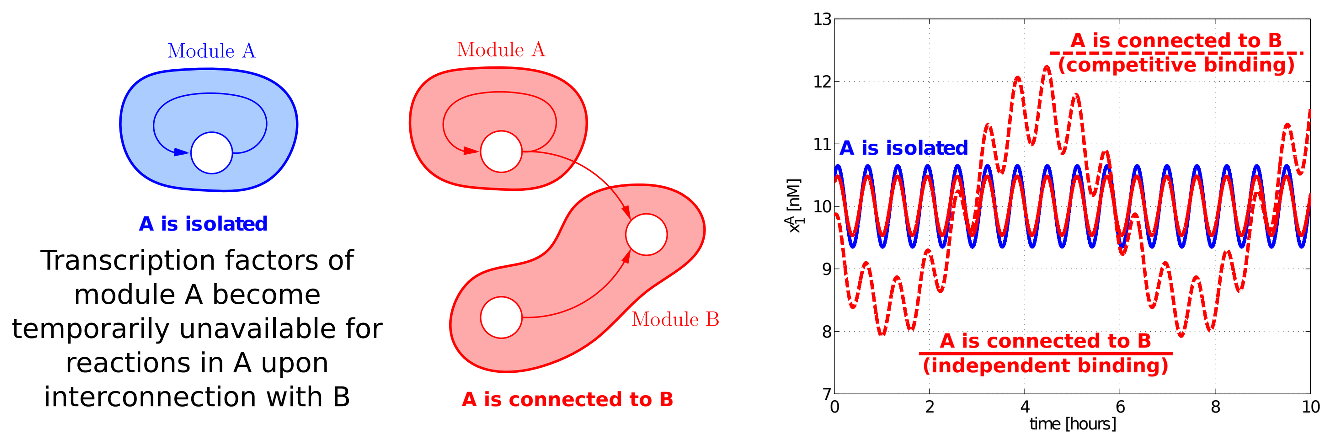
Modular Composition of Gene Transcription Networks

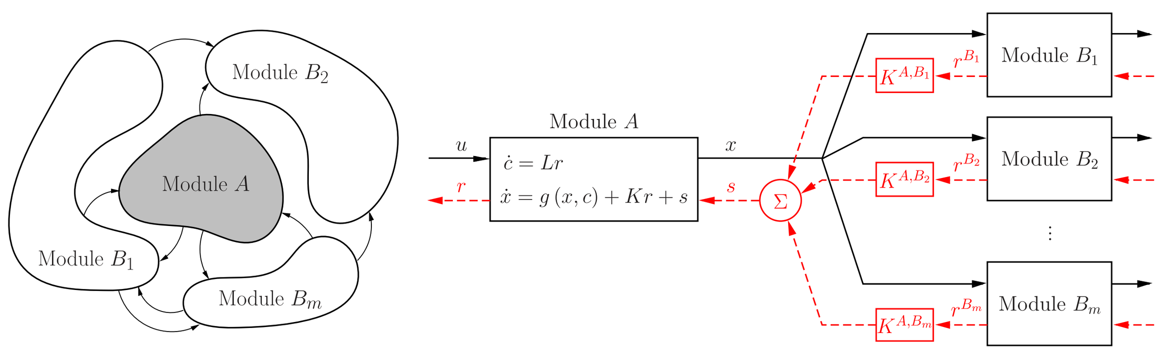
Andras Gyorgy (gyorgy@mit.edu) and Domitilla Del Vecchio (ddv@mit.edu)
Massachusetts Institute of Technology

Retroactivity Causes Context-Dependence

The output of Module A changes upon interconnection with Module B



The output of an upstream module (Module A) changes by adding downstream modules (Module B_i)



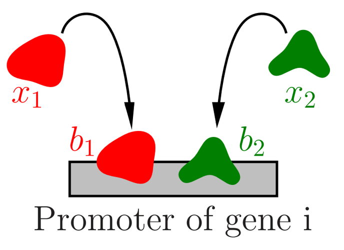
How to describe the salient properties of a module that are relevant to interconnections?

How do the dynamics of connected modules change compared to those in isolation?

To what extent the connected dynamics change and how to minimize this effect?

Retroactivities that Determine the Salient Properties of Modules

Retroactivity of a promoter



$$R_i = \begin{bmatrix} \frac{\partial b_1}{\partial x_1} & \frac{\partial b_1}{\partial x_2} \\ \frac{\partial b_2}{\partial x_1} & \frac{\partial b_2}{\partial x_2} \end{bmatrix}$$

Independent binding	Competitive binding	Cooperative binding
off-diagonals are zero (no effect)	off-diagonals are negative (obstruction)	off-diagonals are positive (promotion)

Internal retroactivity of a module

Scaling retroactivity of a module

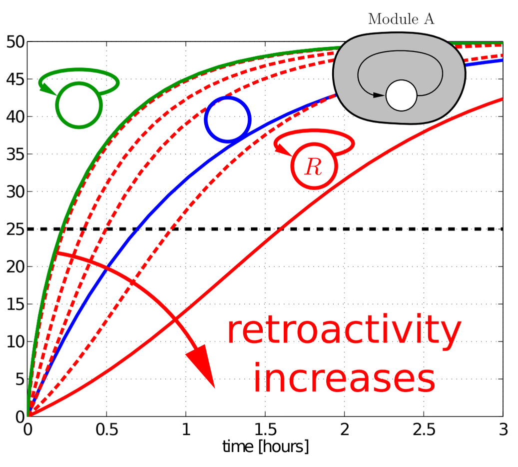
Mixing retroactivity of a module

physical properties

$$R = \sum V_i' R_i V_i \qquad S = \sum (D_i T_i)' R_i D_i T_i \qquad M = \sum (D_i T_i)' R_i V_i$$

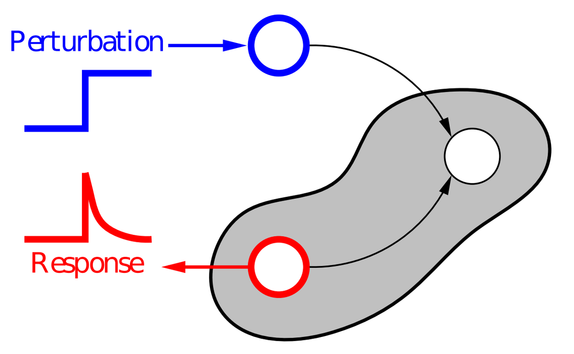
interconnection topology

Autorepression can make the response of a gene slower



How do the dynamics of module A (upstream) change due to interconnection with module B (downstream)?

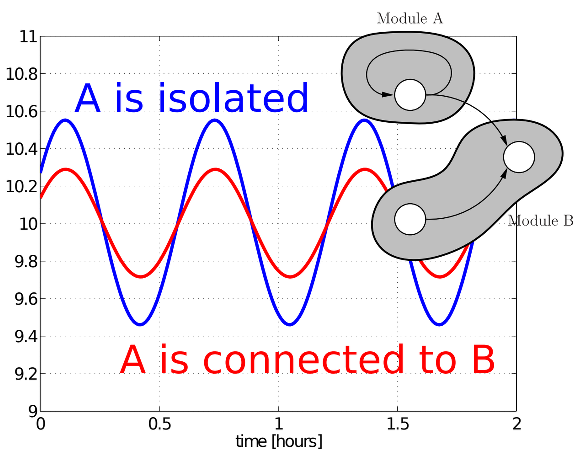
$$\dot{x}^A = \left[I + (I+R^A)^{-1} S^B\right]^{-1} \overbrace{f^A\left(x^A, T^A x^B, T^A \dot{x}^B\right)}^{\text{isolated dynamics of A}} - \left(I + R^A + S^B\right)^{-1} M^B \underbrace{f^B\left(x^B, T^B x^A, T^B \dot{x}^A\right)}_{\text{isolated dynamics of B}}$$



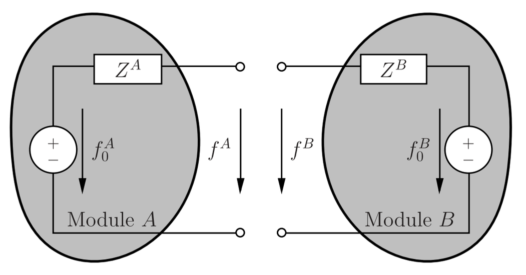
Introduces virtual regulatory linkages when employing perturbation based network identification techniques

Effect of scaling retroactivity

The dynamics of A are scaled due to the extra load presented by module B (independent binding)



Analogy with electrical systems and impedance

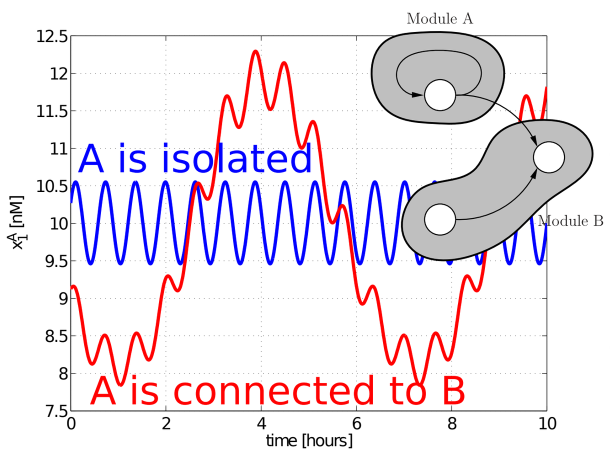


$$f^A = \frac{1}{1+Z^A/Z^B} f_0^A + \frac{1}{1+Z^B/Z^A} f_0^B$$

Module A is robust to interconnection with B if

$$Z^A \ll Z^B \qquad \|S^B\|, \|M^B\| \ll \|I + R^A\|$$

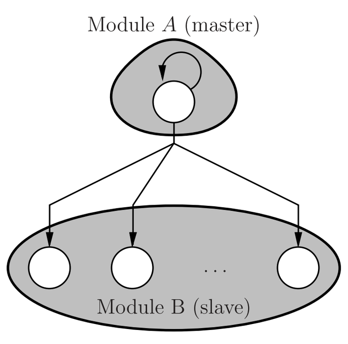
Effect of mixing retroactivity

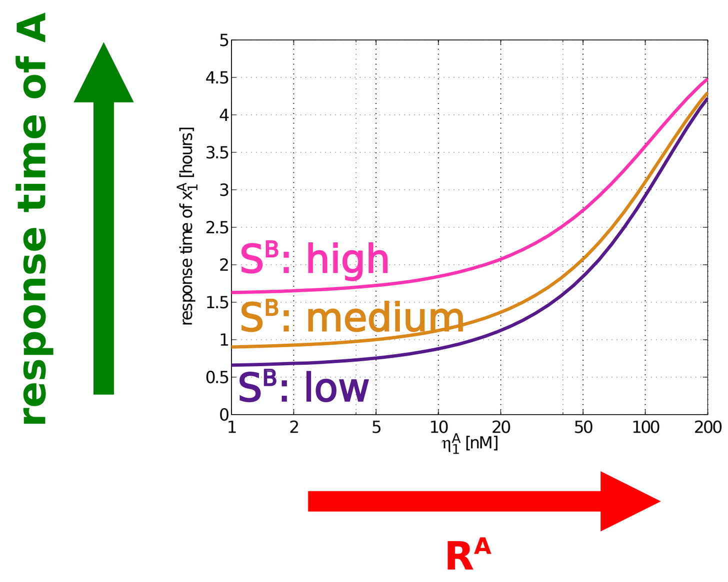


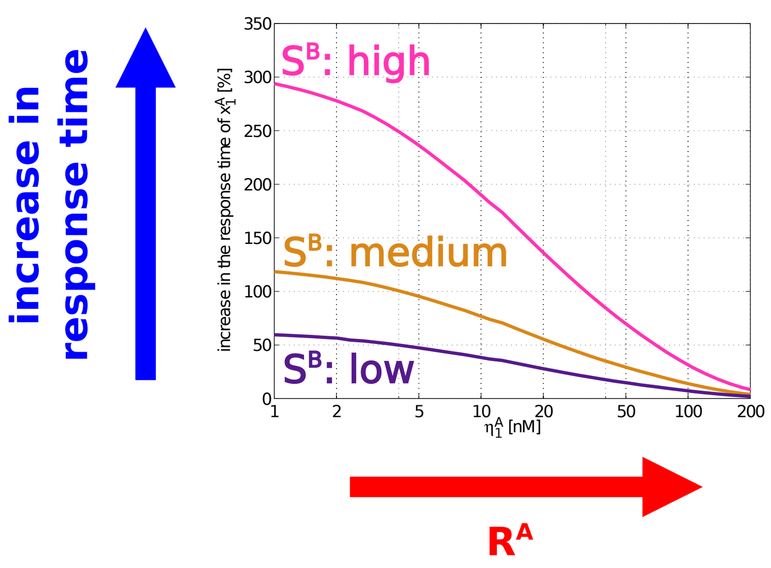
The dynamics of B appear in the dynamics of A as TFs of B force TFs of A to bind and unbind (nonindependent binding)

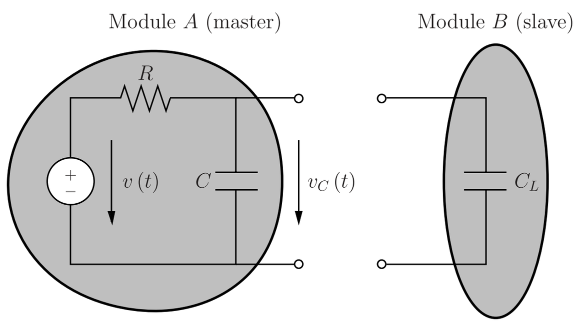
Trade-off Between Performance and Robustness & Network Partitioning

As performance measured by speed increases, robustness to interconnection decreases





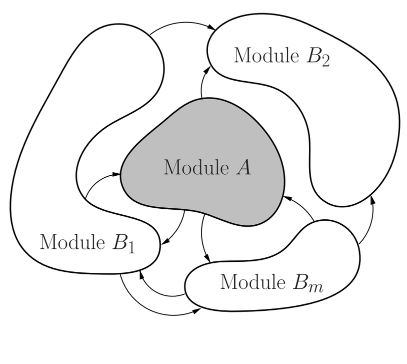




R^A can be interpreted as the capacitance C of the electric circuit A

S^B can be interpreted as the capacitance C_L of the electric circuit B

Metric of robustness to interconnection is defined using the retroactivity matrices



$$\|\text{Behavior (A isolated)} - \text{Behavior (A connected to B)}\| \propto \|(I+R^A)^{-1} S^B\|$$

(1) Find a group of nodes with large R such that the rest of the network has small S and zero M.

(2) Partition the network to such robust modules (divide-and-conquer).

(3) Analyze their behavior by themselves in isolation to understand the behavior of the complex network.

This work was supported by AFOSR grant #FA9550-10-1-0242 and by DARPA grant # W911NF-12-1-0540.