Modularity in Complex Gene Transcription Networks

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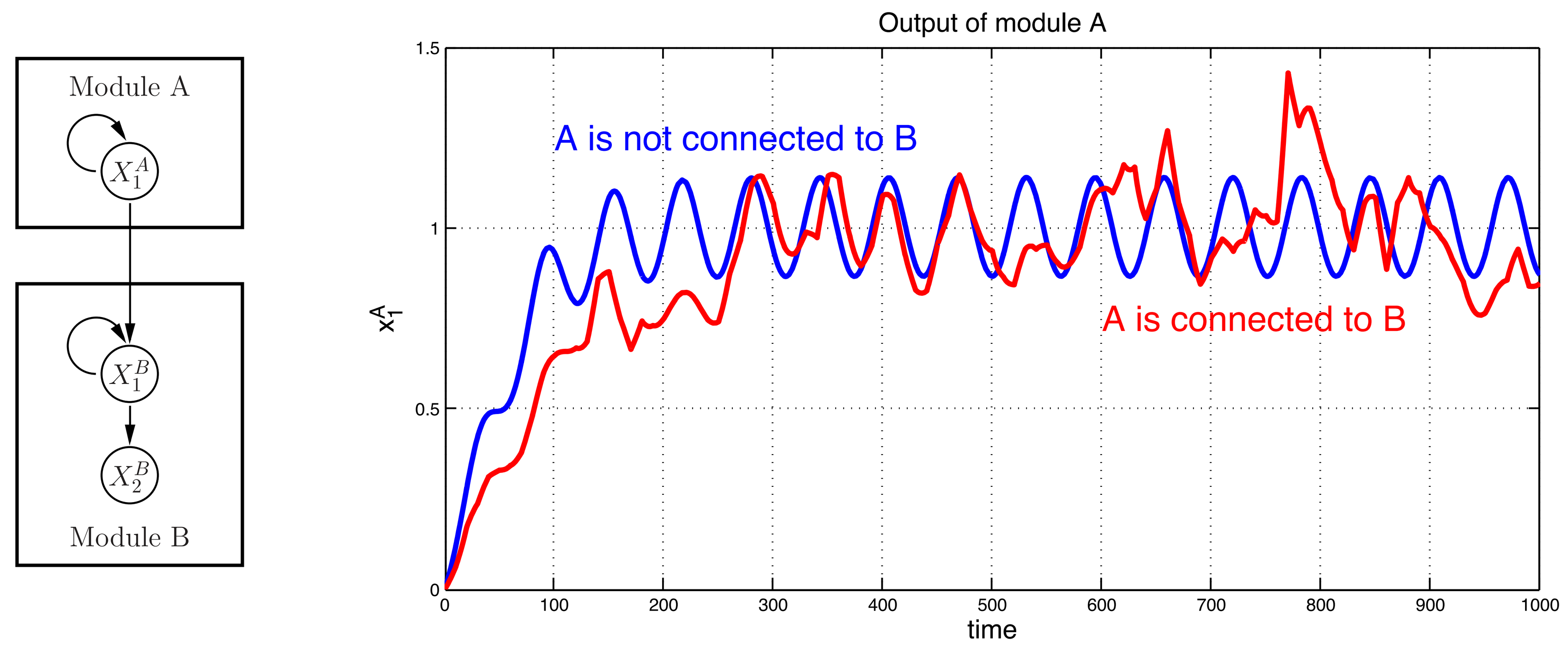
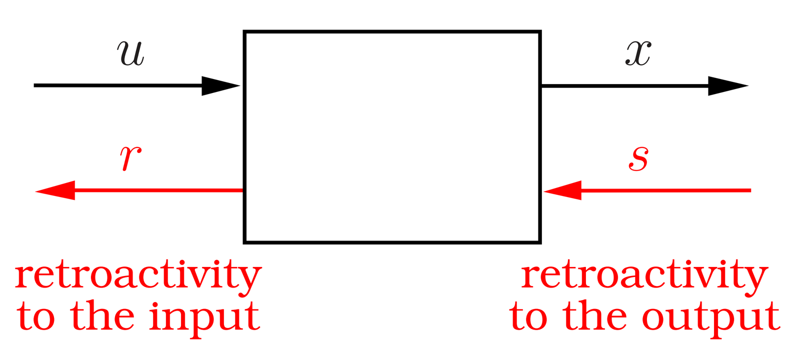
Motivation

In order to build large, complex systems of DNA, one needs to be able to compose small pieces in a modular fashion. But can we design biomolecular systems modularly?



Unfortunately, the behavior of a module changes once connected in a network due to retroactivity effects [1],[2]. Retroactivity arises whenever two molecules bind describing the effect that these molecules become unavailable for other reactions.

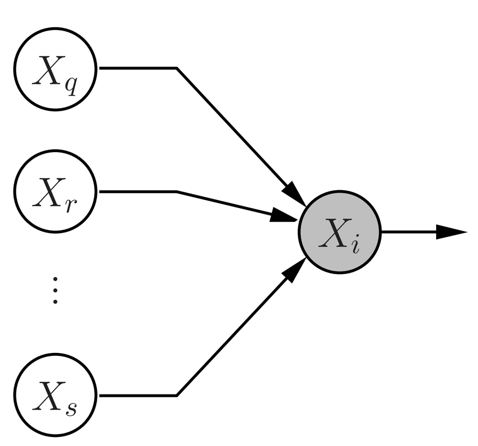


Research questions

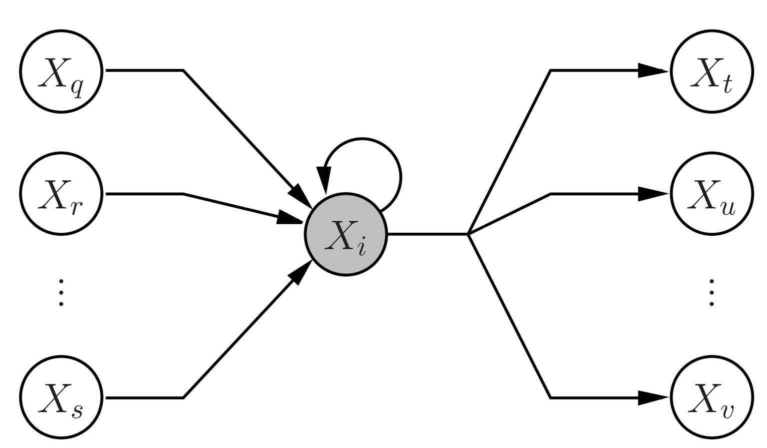
Question #1

How do the dynamics of isolated nodes change once connected?

Isolated node X_i



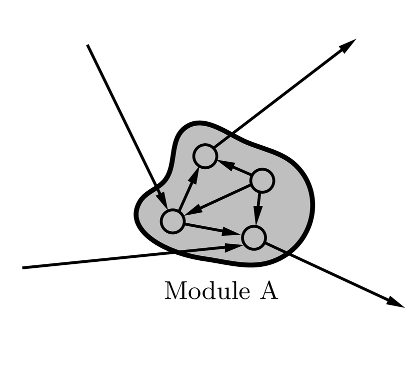
Connected node X_i



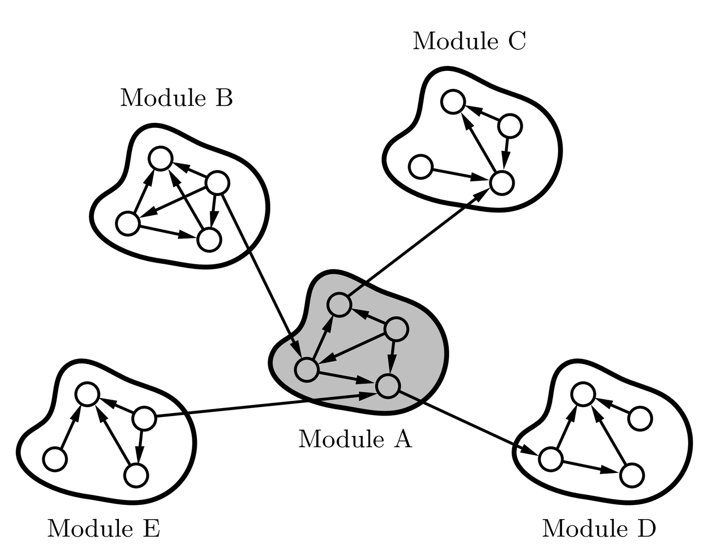
Question #2

How do the dynamics of isolated modules change once connected?

Isolated module A



Connected module A



Restoring modular composition

Effective retroactivity to the input of node i

$$R_i\left(p_i\right) = \frac{\partial\,[\text{bound parents of } X_i]}{\partial\,[\text{free parents of } X_i]}$$

Property of the promoter, describes the loading effect the node has on its parents. Function of measurable biochemical parameters, independent of network topology.

Internal retroactivity of module A

$$R^A\left(x^A,u^A\right) = \sum_{i\in A} \underbrace{V_i}_{\text{binary matrix describing network topology}} \overbrace{R_i\left(p_i\right)}^{\text{physical property of node}} V_i^T$$

Property of module A, captures loading effects due to intramodular binding reactions.

Answer #1

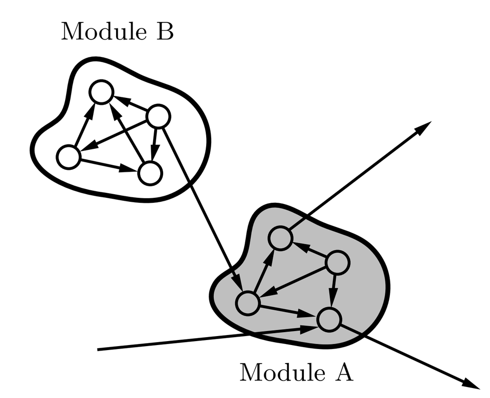
$$\left[\begin{array}{c}\text{connected}\\\text{node dynamics}\end{array}\right] = \left[I + R^A\left(x^A,u^A\right)\right]^{-1}\left[\begin{array}{c}\text{isolated}\\\text{node dynamics}\end{array}\right]$$

$\left\|R^A\left(x^A,u^A\right)\right\|_2 \approx 0$ ⟶ the connected nodes behave as if they were isolated

Effective retroactivity to the input of module A to B

$$\Delta R_B^A\left(x^A,u^A\right) = \sum_{i\in A} \underbrace{W_i}_{\text{binary matrix describing network topology}} \overbrace{R_i\left(p_i\right)}^{\text{physical property of node}} W_i^T$$

Property of module A, captures loading effects due to intermodular binding reactions.



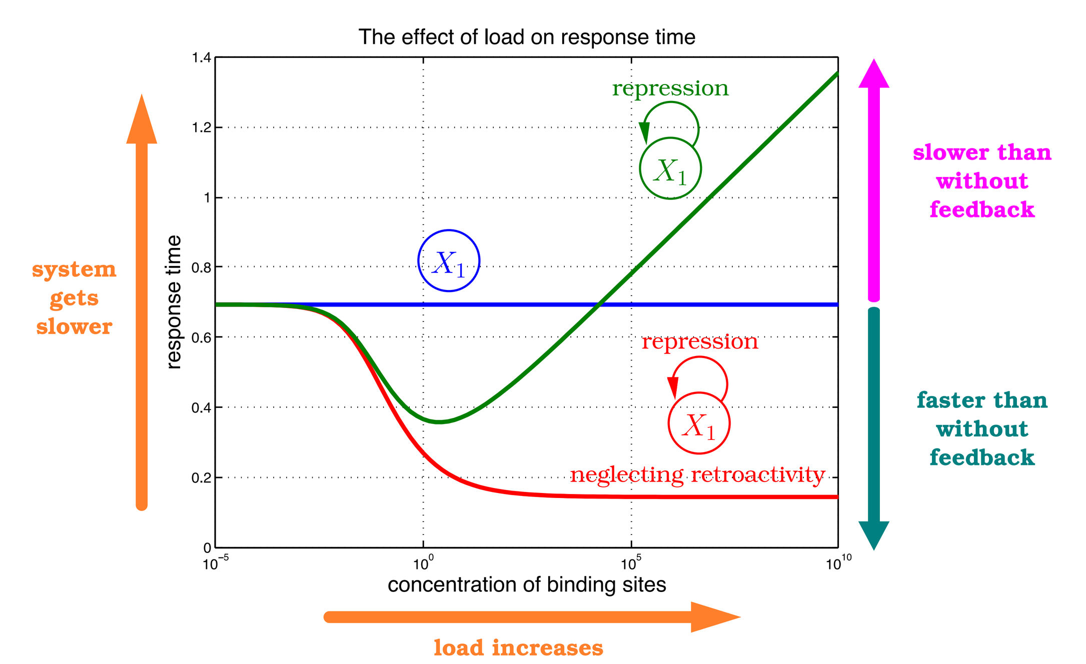
$\left\|\Delta R_B^A\left(x^A,u^A\right)\right\|_2 \approx 0$ ⟶ the connected modules behave as if they were isolated

Answer #2

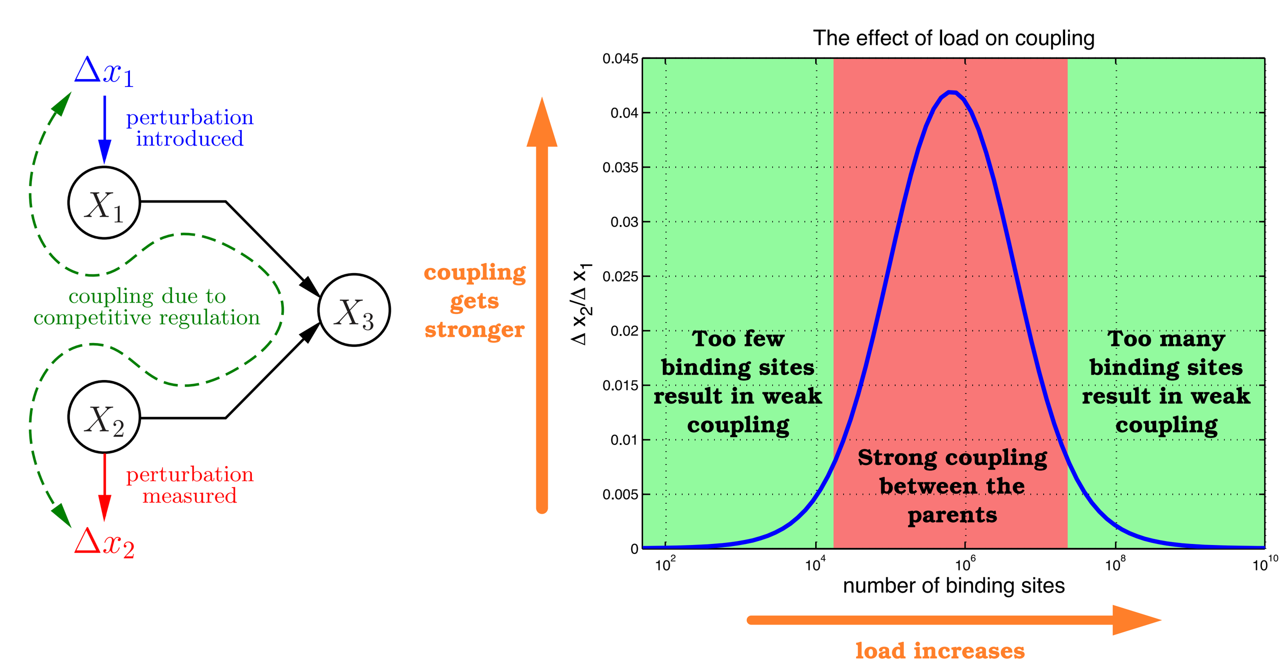
$$\left[\begin{array}{c}\text{connected}\\\text{module dynamics}\end{array}\right] = \left[I + \left[\begin{array}{cc} I + R^A\left(x^A,u^A\right) & 0\\ 0 & I + R^B\left(x^B,u^B\right)\end{array}\right]^{-1}\Delta R_B^A\left(x^A,u^A\right)\right]^{-1}\left[\begin{array}{c}\text{isolated}\\\text{module dynamics}\end{array}\right]$$

Modules are described by: (i) isolated dynamics, (ii) internal retroactivity and (iii) input retroactivity. Now one can combine transcriptional modules modularly by explicitly accounting for loading effects.

Implications about autorepression and competitive regulation



Negative feedback can slow down the dynamics



Competitive binding couples the dynamics of regulator transcription factors

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[1] D. Del Vecchio, A. Ninfa, and E. Sontag (2008) Modular Cell Biology: Retroactivity and insulation. MSB 4:161.

[2] P. Jiang, A. Ventura, E. Sontag, S. Merajver, A. Ninfa, and D. Del Vecchio (2011) Load-induced modulation of signal transduction networks. Science Signaling 4(194):ra67.