Genetic Circuit Engineering Meets Control Theory

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A journey towards modular composition

Engineering biology: Why and how

Modular composition: A grand challenge

Inter-module loads and the *load driver*

Disturbance attenuation via time scale separation

Resource loading and the *resource decoupler*

Disturbance rejection despite leaky integral actions

Decentralized implementation

Outlook

Engineering biology: historical view

Jacob and Monod
Arber
Mullis…

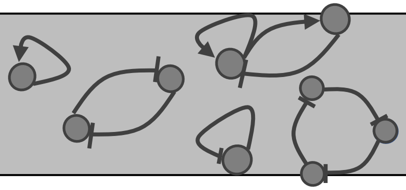
Genetic Engineering

2000

Synthetic Biology

understanding biology

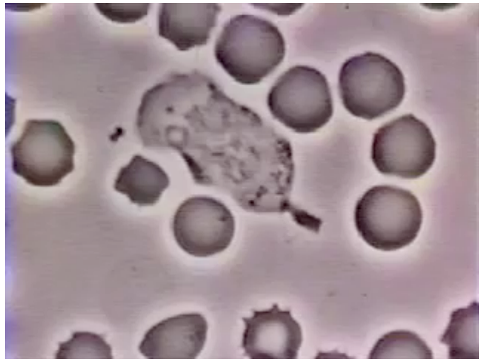
Motifs era



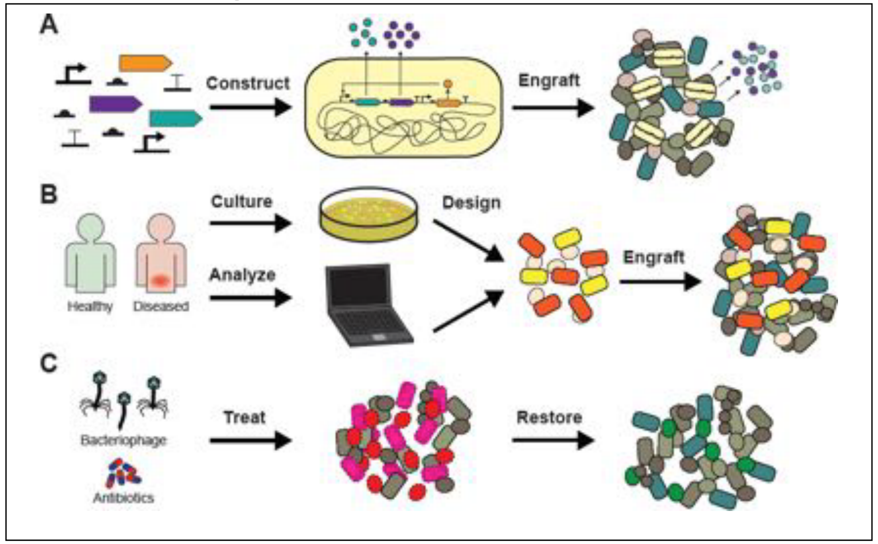
201X

programming cells with useful decision-making

Systems era



engineered microbiome

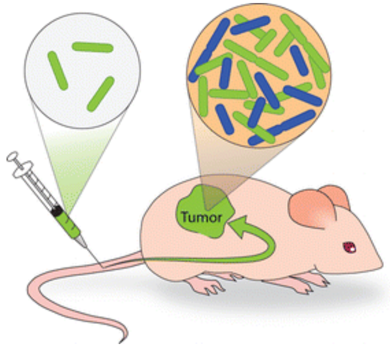


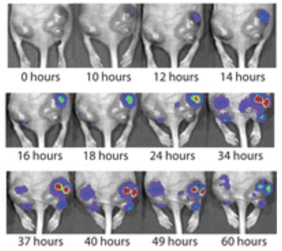
human performance enhancement

regenerative medicine

control of cell fate

curing disease



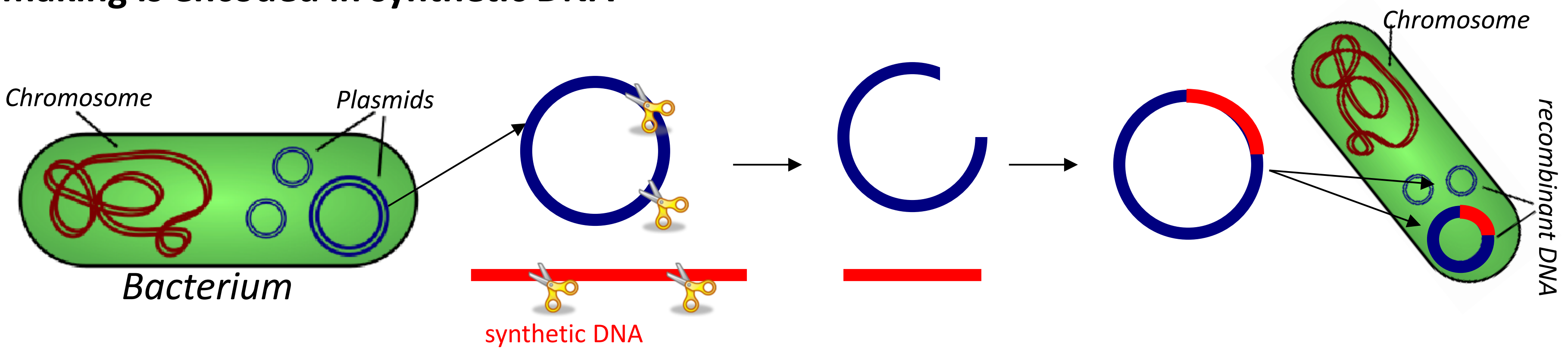


Courtesy of Tal Danino

tracking, recognizing, killing cancer cells

How do we engineer cells with *de novo* decision making

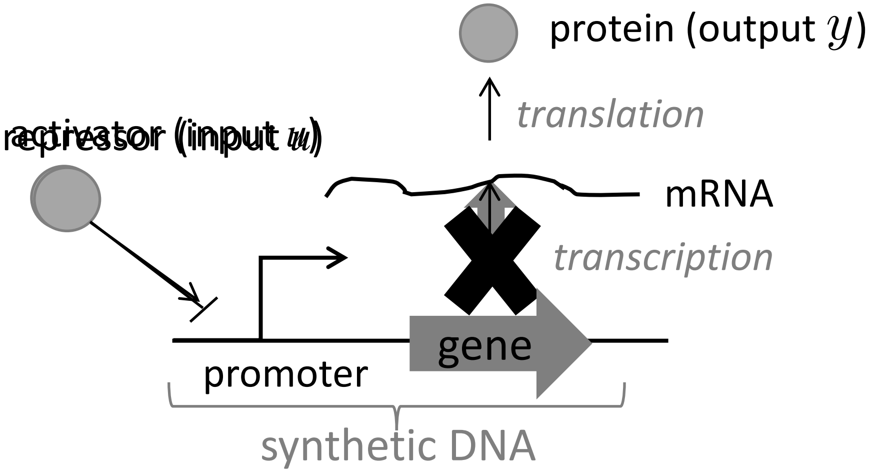
Decision making is encoded in synthetic DNA



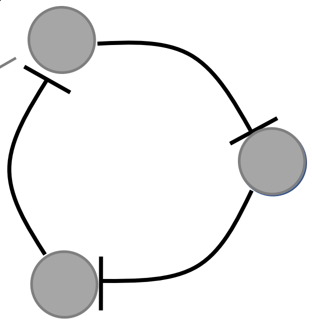
Synthetic DNA encodes genes that express proteins regulating expression of other genes (synthetic/endogenous)

- **regulatory interactions create circuits**
- **interactions can be externally controlled by chemical signals**

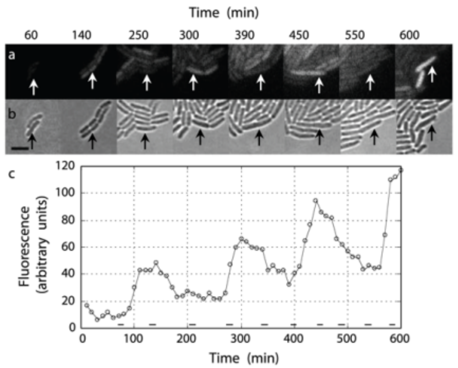
genetic module



$$\dot{x} = f(x, u, \theta)$$
$$y = h(x)$$



A biomolecular oscillator



(Elowitz and Leibler, *Nature* 2000)

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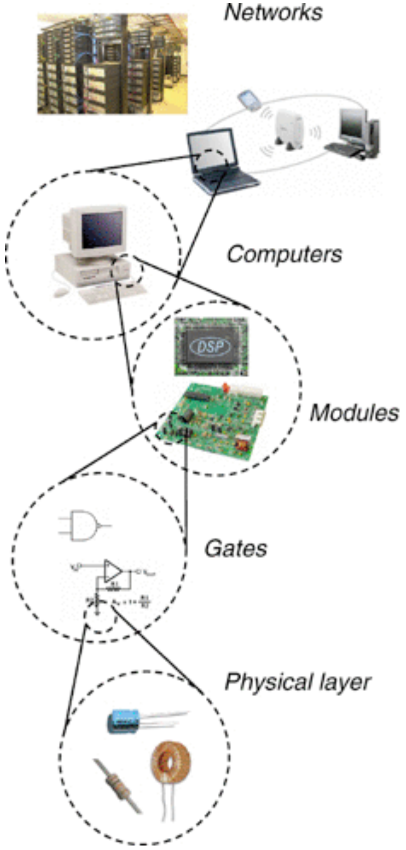
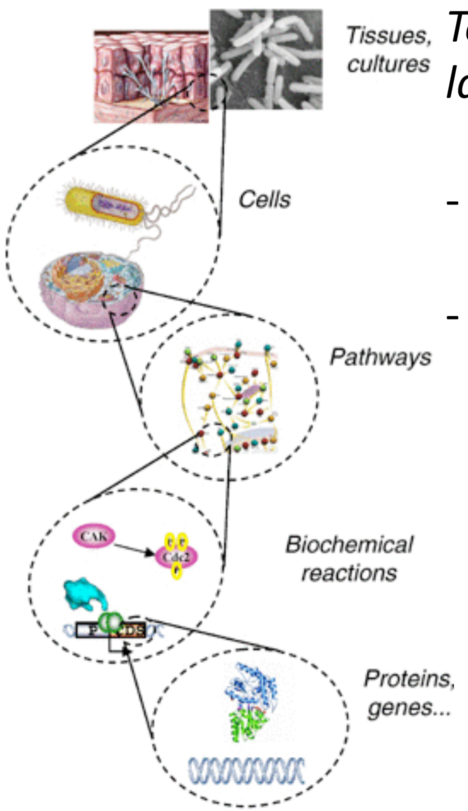
Modular design in engineering biology



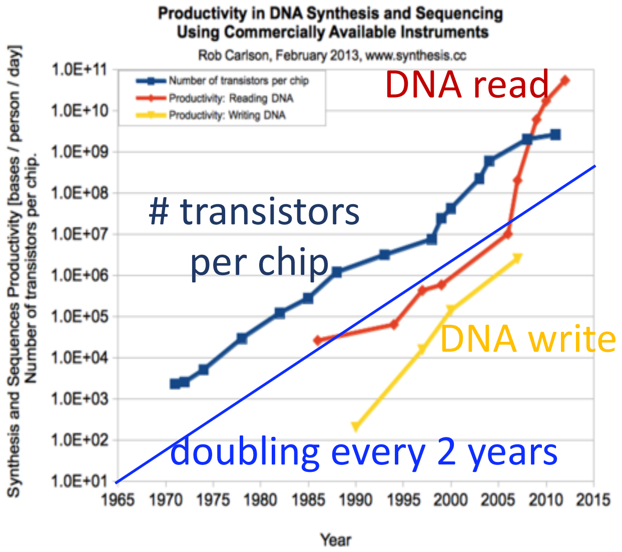
Describing a sophisticated system as the composition of simpler subsystems helps overcoming the complexity of design:

- we "forget" the details within subsystems when we compose them
- feedback can maintain I/O properties providing simplified abstractions for layered design



Tempting in engineering biology: layered and modular composition

- we have large libraries of genetic parts
- we can synthesize DNA very quickly



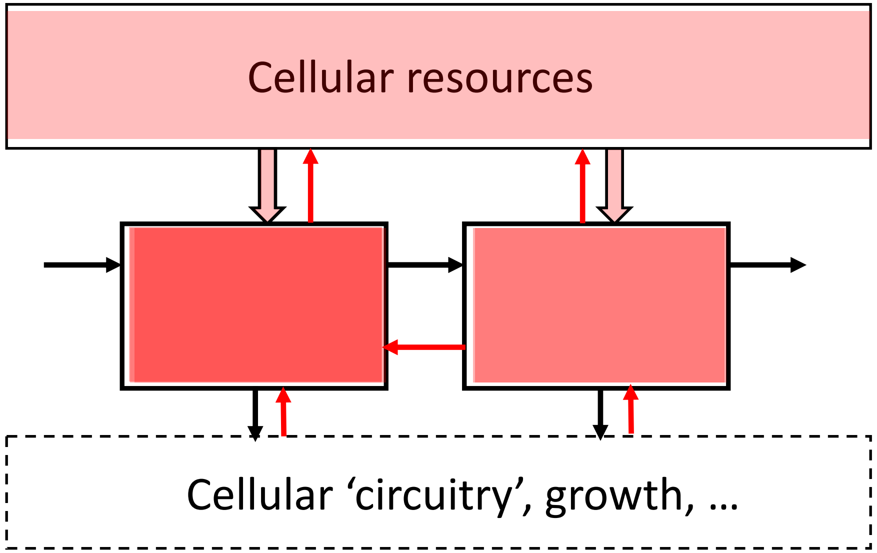
increased scale is becoming possible

modularity is critical to manage complexity/time
the I/O behavior of a "module" should not change upon composition

in practice, modularity fails
a system's I/O properties are affected by surrounding systems
→ need to re-design "modules" after composition

for a circuit with 11 genes it takes one PhD thesis of 5-6 years

Some reasons why modularity is a challenge



Loads applied by downstream modules change the behavior of upstream systems
(Del Vecchio, Hespanha, Klavins, Papachristodoulou, Sontag, …)

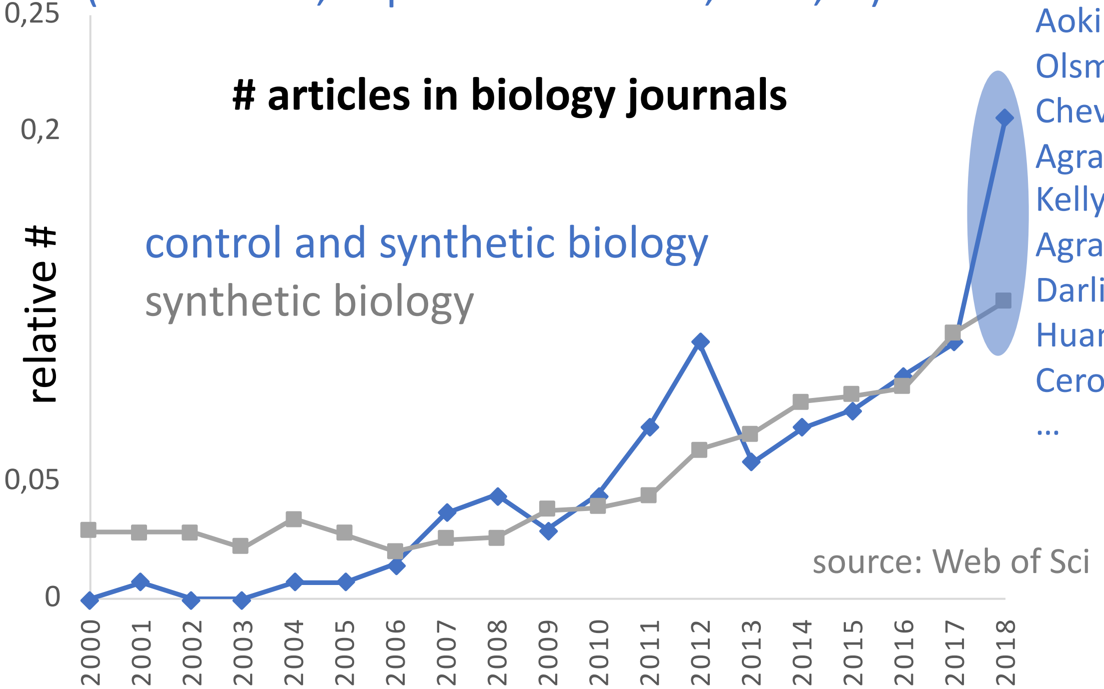
Modules apply a load the cellular resources: creates subtle couplings
(Bates, Del Vecchio, Murray, Stan,…)

Modules often have "off-target" interactions, affect growth rate, and this, in turn, has global effects on a module's dynamics
(Khammash, Papachristodoulou, Stan, …)

these issues can be viewed as *lack of robustness* to perturbations

can we "insulate" desired I/O behaviors from these perturbations?

→ **this is a Control System Design problem**



Aoki et al. *Nature* 2019
Olsman et al. *Cell Systems* 2019
Chevalier et al. *Cell Systems* 2019
Agrawal et al. *Nat Comm* 2019
Kelly et al. *NAR* 2018
Agrawal et al. *ACS Syn Bio* 2018
Darlington et al. *Nat Comm* 2018
Huang et al. *Nat Comm* 2018
Ceroni et al. *Nat Methods* 2018
…

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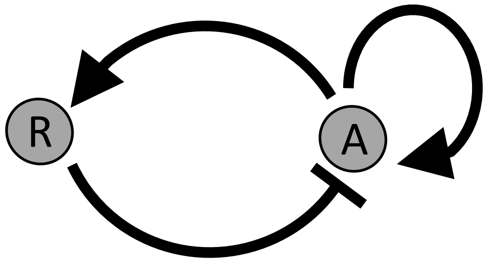
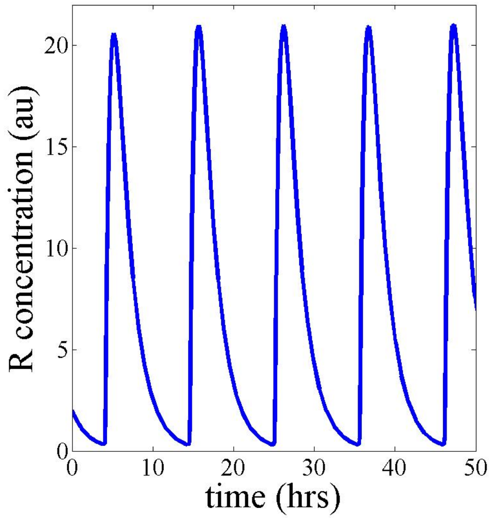
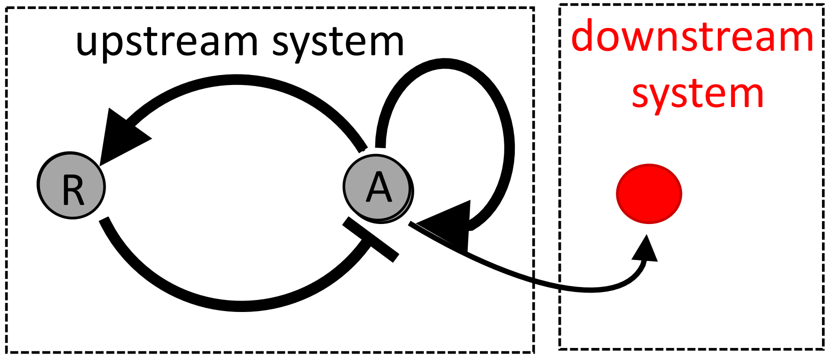
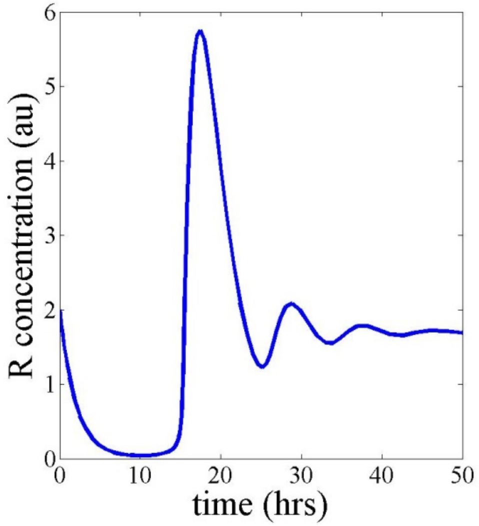
Inter-module loading changes upstream system's dynamics

(Atkinson et al, *Cell* 2003)



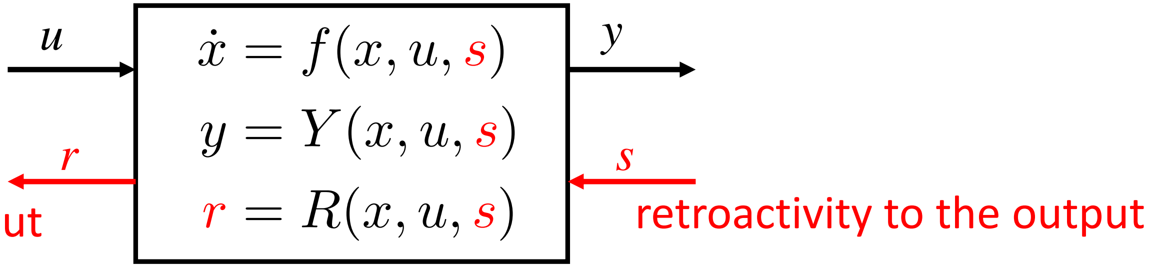






loads change the behavior of the upstream system **→ we fail to transmit the signal to the downstream system**

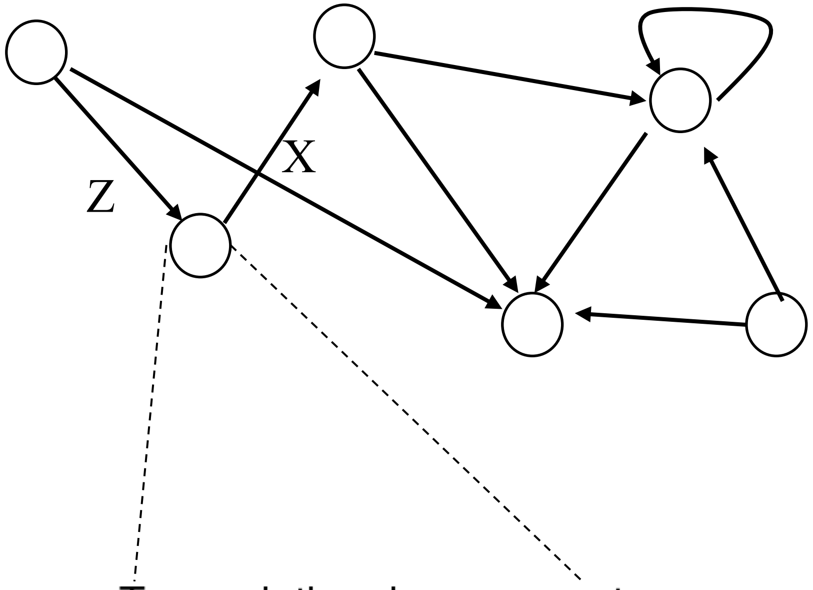
systems & signals representation of loads: **retroactivity**

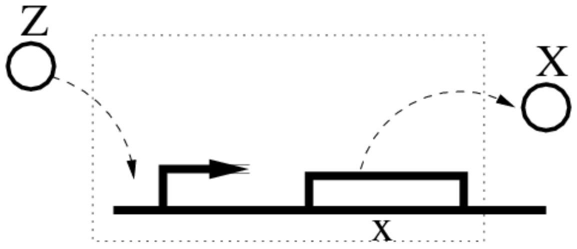


the I/O model of the **isolated system** is obtained when s=0

Del Vecchio et al, *MSB* 2008

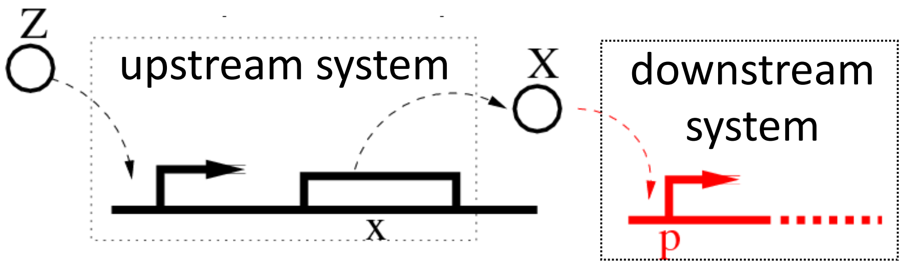
Retroactivity is a reaction flux affecting upstream system's output





isolated

$$\frac{dX}{dt} = k(t) - \delta X$$



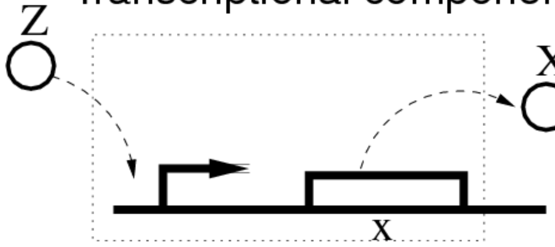
connected

s

$$\frac{dX}{dt} = k(t) - \delta X + k_{\mathrm{off}}C - k_{\mathrm{on}}pX$$

$$\frac{dC}{dt} = -k_{\mathrm{off}}C + k_{\mathrm{on}}pX$$

Transcriptional component

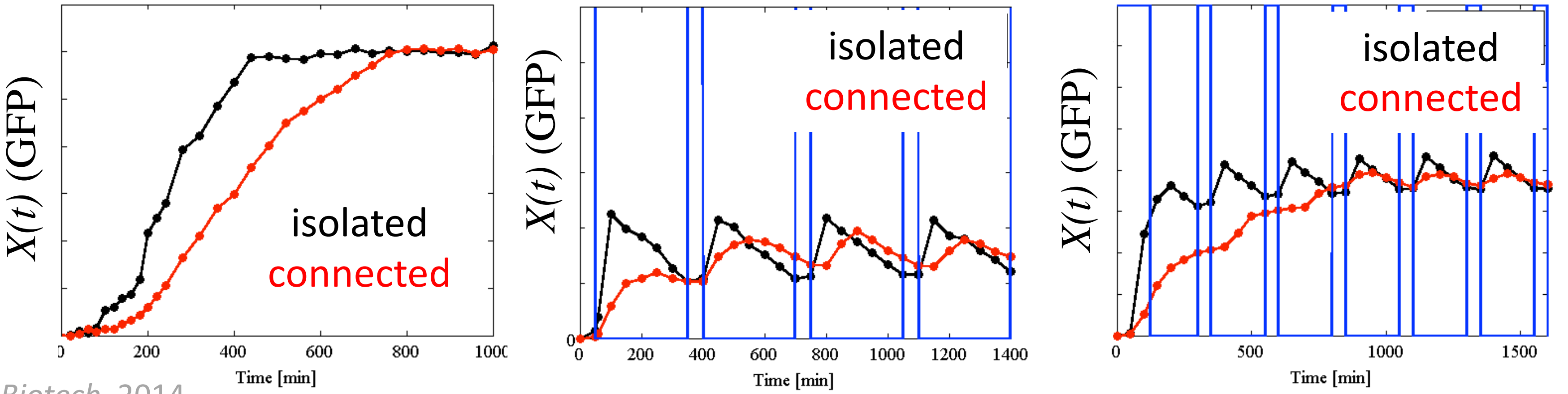


a transcriptional component is an input/output module

how does its input/output response change upon interconnection?

experiments in transcriptional components in yeast

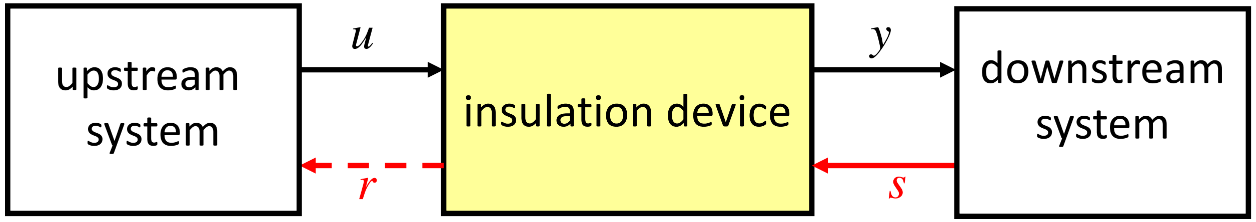
retroactivity reduces bandwidth of upstream system



Jayanthi et al. *ACS Syn Bio* 2013; Mishra et al, *Nat. Biotech,* 2014

Insulation devices to mitigate retroactivity

consider retroactivity as a state-dependent disturbance



1. **r≈0**
2. **s is attenuated**

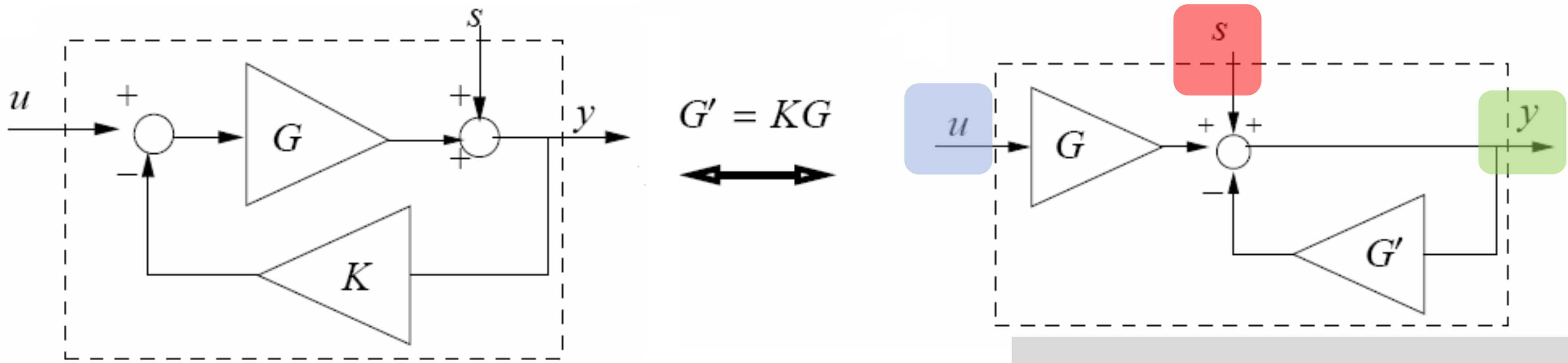
Principle 1
high-gain feedback

requires an explicit negative feedback

Principle 2
time scale separation

no explicit feedback required

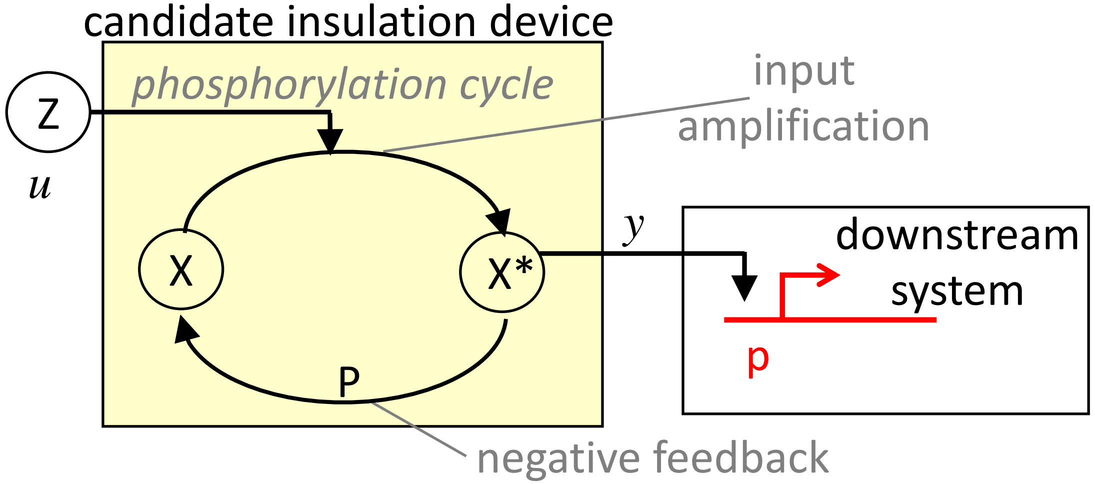
From high-gain feedback to time-scale separation



large input amplification
and a large negative feedback

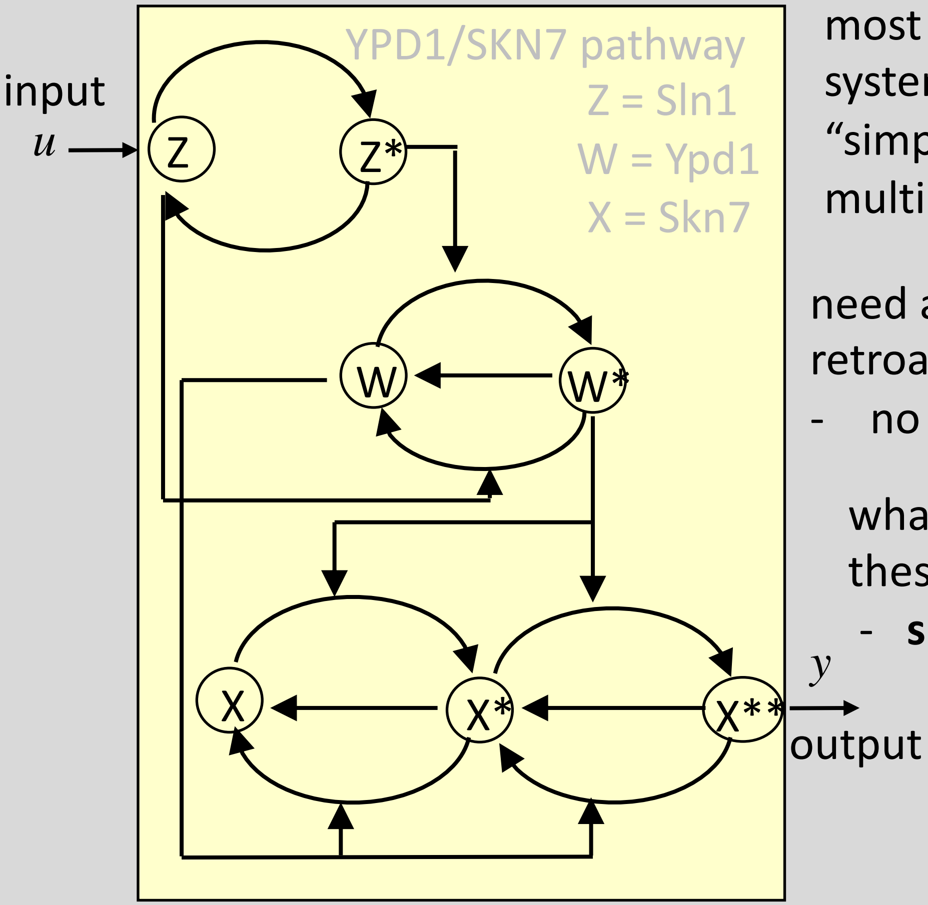
what biomolecular systems
can realize it?

$$y = u\frac{G}{1+KG} + \frac{s}{1+KG} \quad G \to \infty \quad \to 0$$



$$\frac{dX^*}{dt} = k_1 X_{tot}\left(1 - \frac{X^*}{X_{tot}}\right) Z(t) - k_2 P X^* - k_{on} X^* p + k_{off} C$$

G (naturally large), u, G', y, s



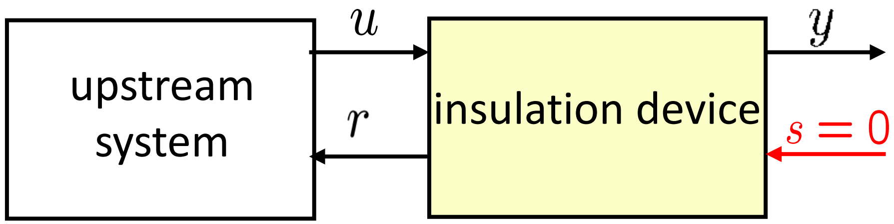
most naturally-occurring systems are not that "simple" and involve multiple modifications

need a different scheme for retroactivity attenuation:
- no explicit feedback

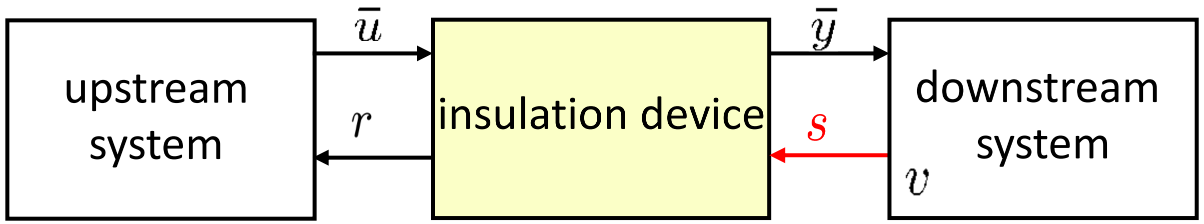
what is common between these two systems?
- **speed**

Retroactivity attenuation via time-scale separation

isolated system



connected system



upstream system $\dot{u} = f_0(u,t) + r(u,y)$

insulation device $\dot{y} = G_1 f_1(u,y)$

large $G_1 \gg 1$

upstream system $\dot{\bar{u}} = f_0(\bar{u},t) + r(\bar{u},\bar{y})$

insulation device $\dot{\bar{y}} = G_1 f_1(\bar{u},\bar{y}) + G_2 M s(\bar{y},v)$

downstream system $\dot{v} = -G_2 N s(\bar{y},v)$

very large rates $G_2 \gg G_1$

Fact: There are a matrix T and a non-singular matrix P such that $P \cdot M - T \cdot N = 0$ (closed system)

Theorem: If $\left.\frac{\partial f_1(u,y)}{\partial y}\right|_{y=h(u)}$ is Hurwitz with $y = h(u) \;\Rightarrow\; f_1(u,y) = 0,$ then:

$$\|y(t) - \bar{y}(t)\| = \mathcal{O}(1/G_1), \quad \forall t \in [t_b, t_f]$$ independent of $G_2 M s$

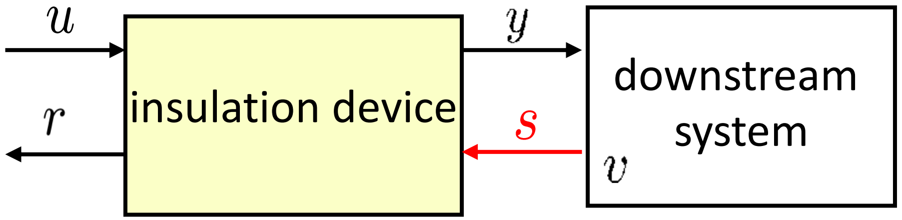
Proof: use singular perturbation and nested application of Tikhonov's theorem

change of cords: $x = Py + Tv$

$$\left.\begin{array}{l} \epsilon_1 \dot{\bar{x}} = P f_1(\bar{u},\bar{y}), \quad \epsilon_1 = 1/G_1 \\ \epsilon_2 \dot{v} = -s(\bar{y},v), \quad \epsilon_2 = 1/G_2 \end{array}\right\} \quad \epsilon_1 = 0 \Rightarrow \bar{y} = h(\bar{u})$$

Jayanthi and Del Vecchio, *IEEE TAC*, 2011; Del Vecchio and Slotine, *IEEE TAC*, 2013

Application to signal transduction networks

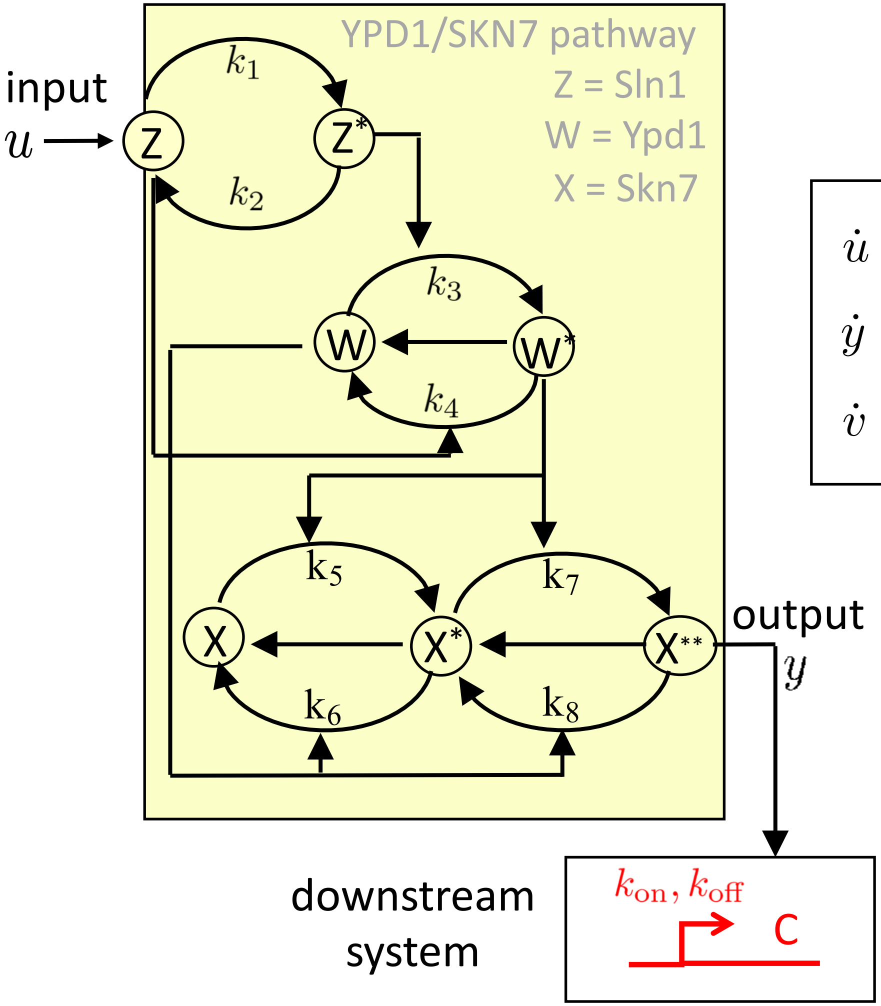


$\delta \in [0.001, 0.01]\ \mathrm{min}^{-1}$
$k_i W_T \in [1, 100]\ \mathrm{min}^{-1}$
$k_{\mathrm{off}} \in [0.1, 10^4]\mathrm{min}^{-1}$

Z: gene expression time scale
W/X: time scale of signal transduction
C: time scale of reversible binding to DNA

$G_1 = (k_i W_T)/\delta \gg 1$

$G_2 = k_{\mathrm{off}}/\delta \gg 1$



$$\dot{u} = f_0(u,t) + r(u,y)$$
$$\dot{y} = G_1 f_1(u,y) + G_2 M s(y,v)$$
$$\dot{v} = -G_2 N s(y,v)$$

$$\dot{z}_T = k(t) - \delta(z_T - Z^*) \qquad z_T := Z + Z^*$$

$$\dot{Z}^* = G_1\delta\Big(-c_1 Z^*(1 - \frac{W^*}{W_T}) + c_2\frac{W^*}{W_T}(z_T - Z^*) + c_p(z_T - Z^*) - c_p' Z^* - \frac{\delta}{G_1} Z^*\Big)$$

$$\dot{W}^* = G_1\delta\Big(c_1 Z^*(1 - \frac{W^*}{W_T}) - c_2\frac{W^*}{W_T}(z_T - Z^*) + c_4 X^*(1 - \frac{W^*}{W_T}) - c_3\left(X_T - X^* - X^{**} - C\right)\frac{W^*}{W_T} - c_3 X^*\frac{W^*}{W_T} + c_4 X^{**}(1 - \frac{W^*}{W_T}) - c_7\frac{W^*}{W_T}\Big)$$

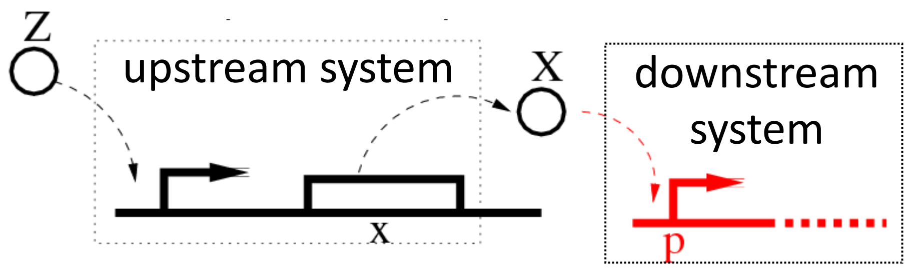
$$\dot{X}^* = G_1\delta\Big(c_3\left(X_T - X^* - X^{**} - C\right)\frac{W^*}{W_T} - c_4 X^*(1 - \frac{W^*}{W_T}) - c_3 X^*\frac{W^*}{W_T} + c_4 X^{**}(1 - \frac{W^*}{W_T}) - c_5 X^* + c_6 X^{**}\Big)$$

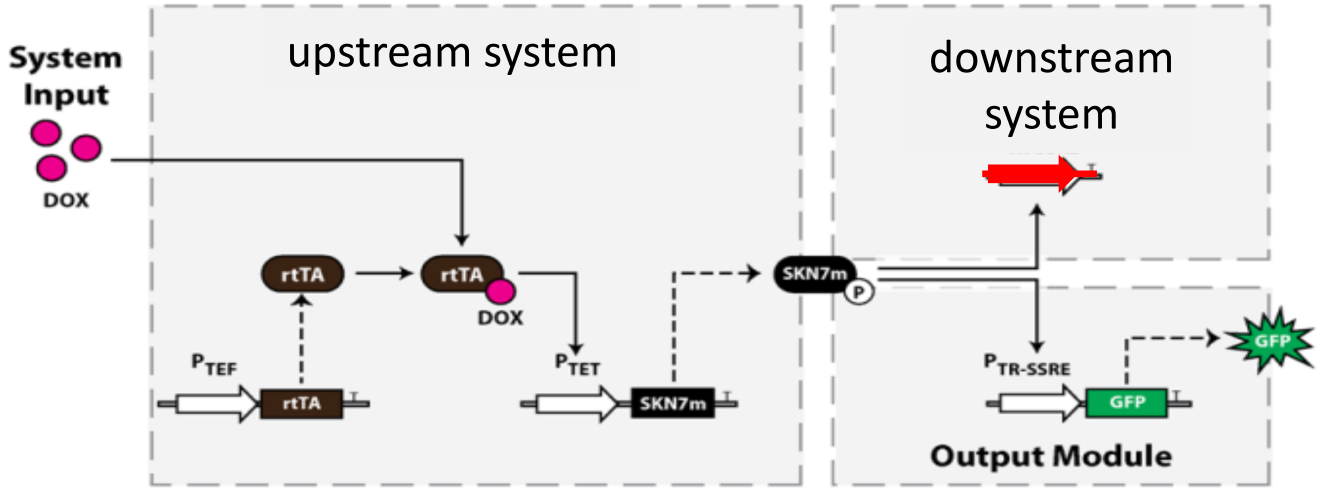
$$\dot{X}^{**} = G_1\delta\Big(c_3 X^*\frac{W^*}{W_T} - c_4 X^{**}(1 - \frac{W^*}{W_T}) - c_6 X^{**}\Big) + G_2\Big(\delta C - \frac{\delta}{K_d} X^{**}(p_T - C)\Big)$$

$$\dot{C} = -G_2\Big(\delta C - \frac{\delta}{K_d} X^{**}(p_T - C)\Big)$$

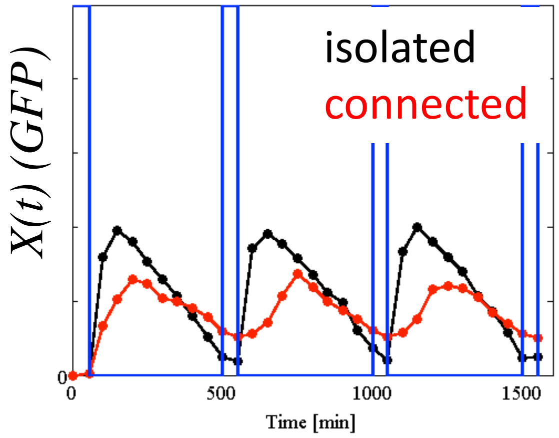
The *Load Driver*: Insulation by time scale separation

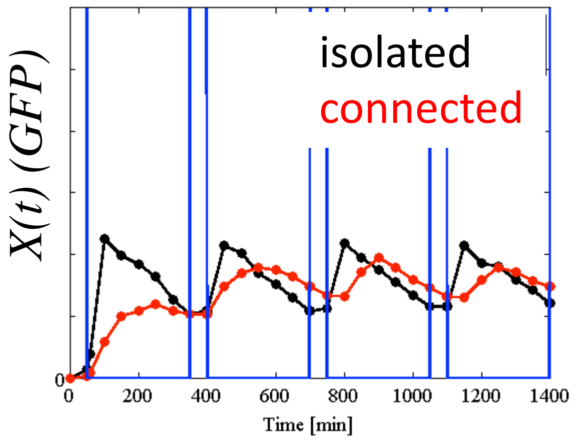
recall

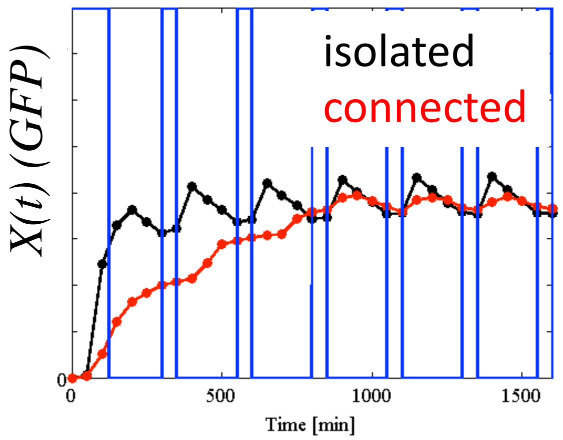




directly connecting the downstream system to the upstream system



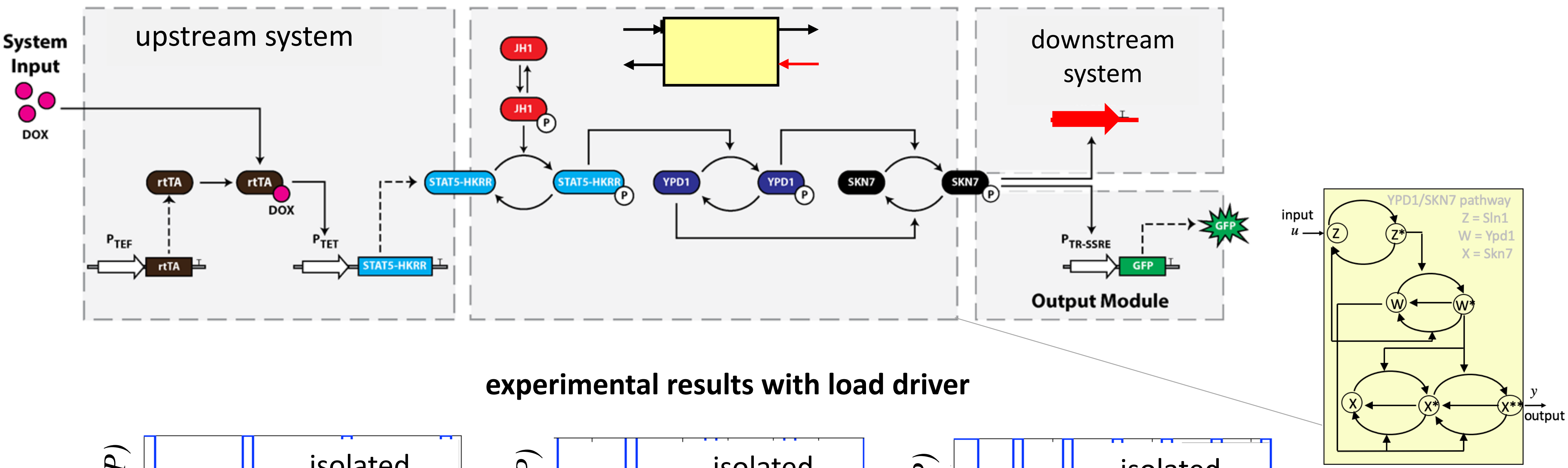




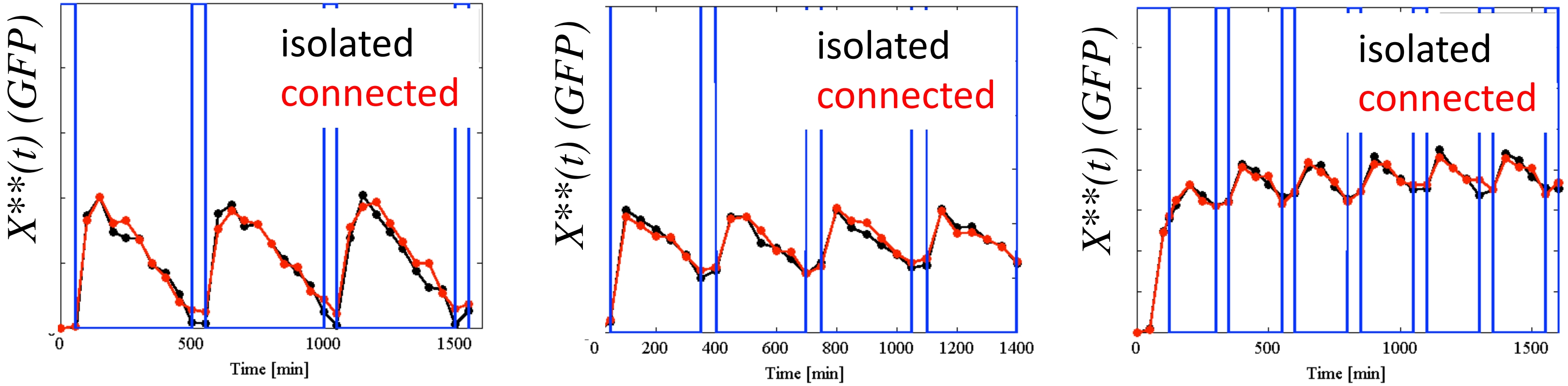
Mishra et al., *Nat. Biotech* 2014

The *Load Driver*: Insulation by time scale separation

Load driver



experimental results with load driver

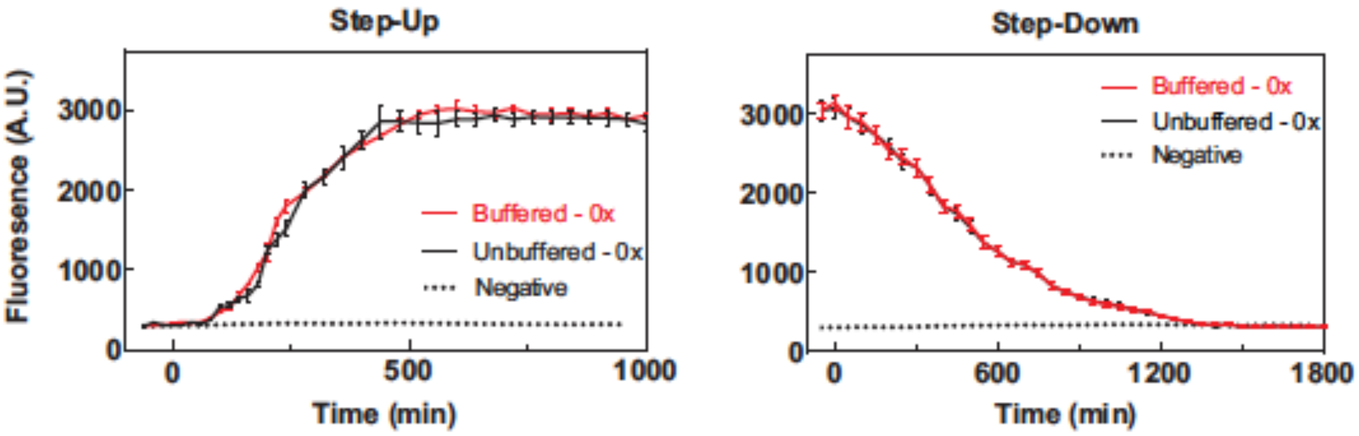


Mishra et al., *Nat. Biotech* 2014

The *Load Driver*: Insulation by time scale separation

Experiments with fast time scales

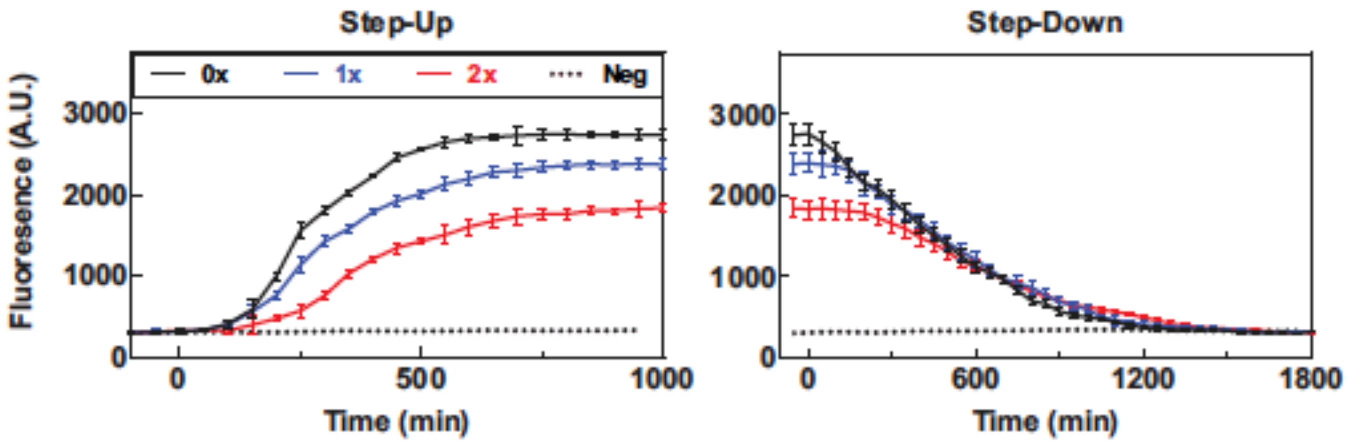
(endogenous amounts of YPD1 and SKN7)



Experiments with slow time scales

(reduced amounts of YPD1 and SKN7 obtained through weaker constitutive promoters)

insulation property is lost



Slow/fast/slow pattern allow to reliably transmit signals to large loads: the ***synergy between slow transcription and fast signal transduction is likely to be used by natural systems to insulate signals from downstream loads***

Mishra et al., *Nat. Biotech* 2014

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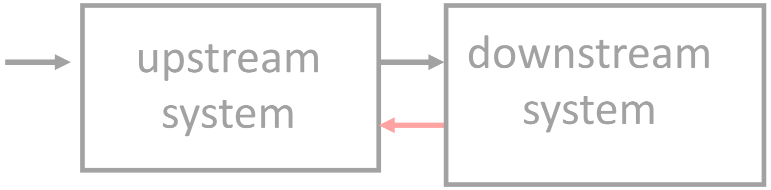
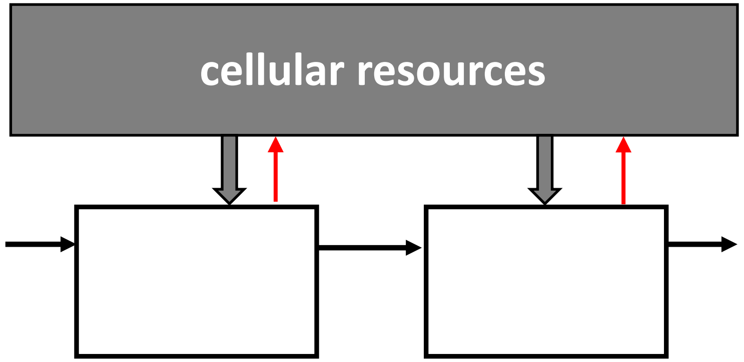


Resource loading and the *resource decoupler*

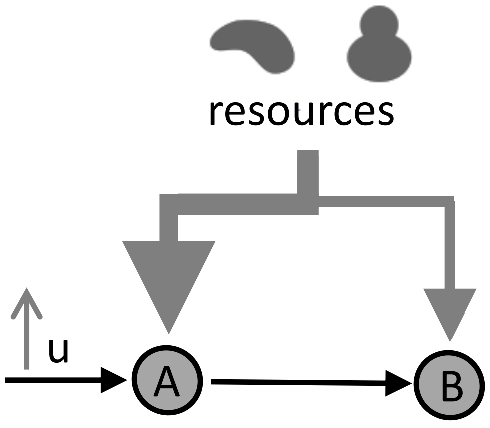
Disturbance rejection despite leaky integral actions

Decentralized implementation

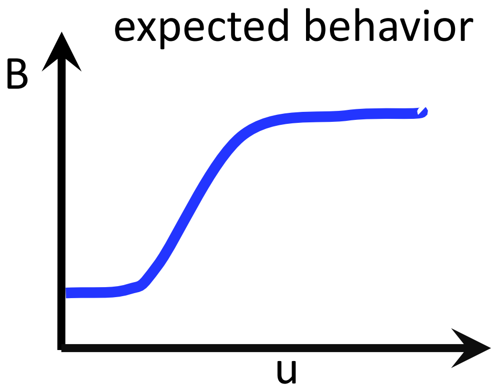


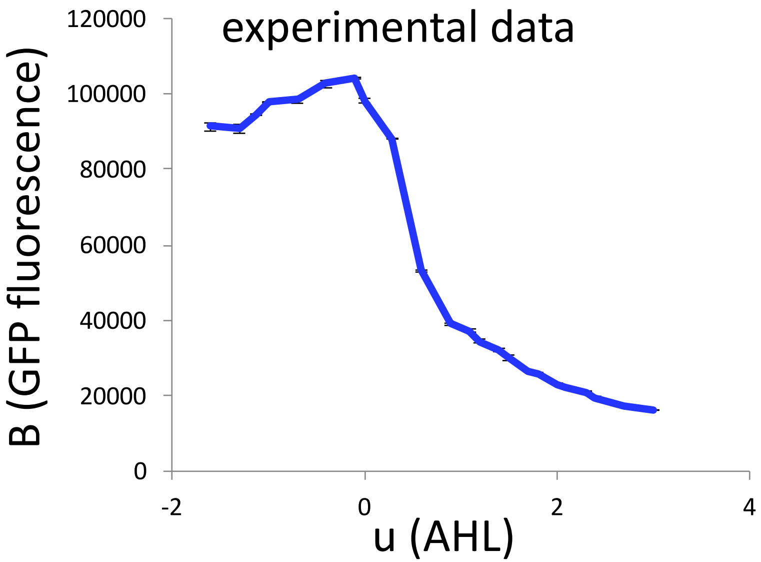
Outlook

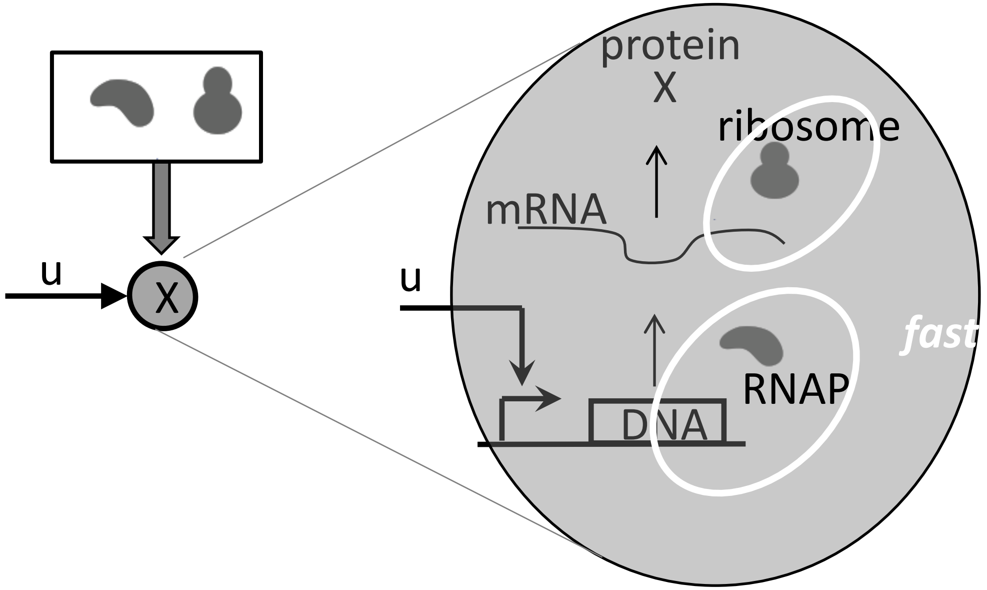
Modules become coupled by loading cellular resources



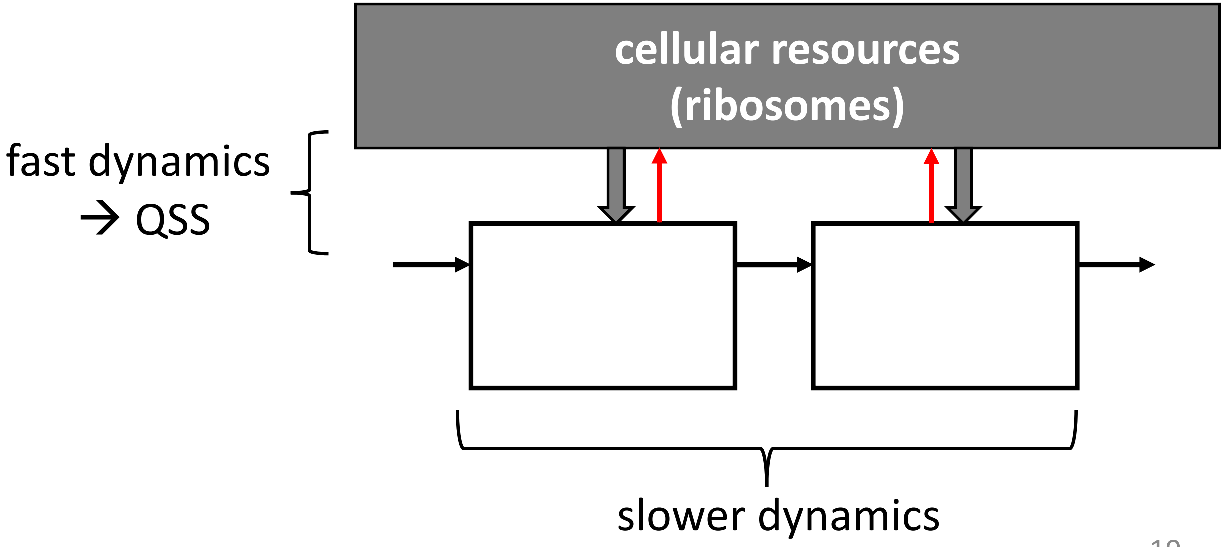
activation cascade



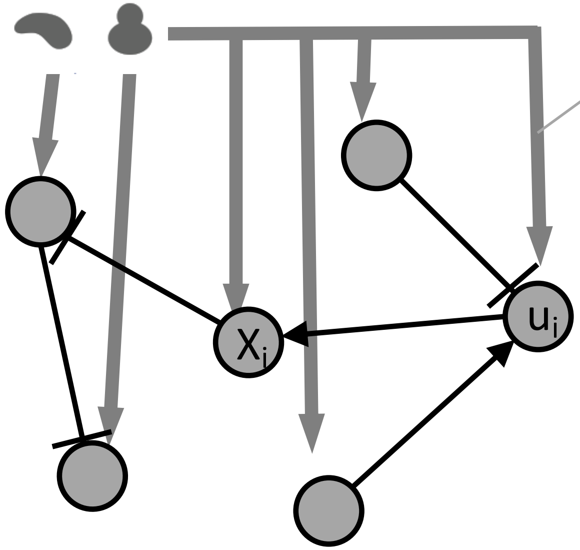




genetic module

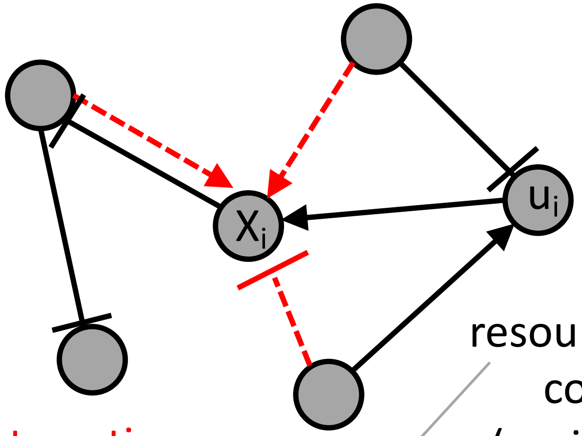


Coupling can be mathematically captured by “hidden” graphs



use time scale separation and conservation of resources

=



resource demand coefficient (easily tunable)

hidden interactions

$$\dot{X}_i = F_i(u_i) - \delta X_i$$

intended regulatory function

$$\dot{X}_i = \frac{F_i(u_i)}{1 + \sum_k J_k F_k(u_k)} - \delta X_i$$

$H_i(u)$ effective regulatory function

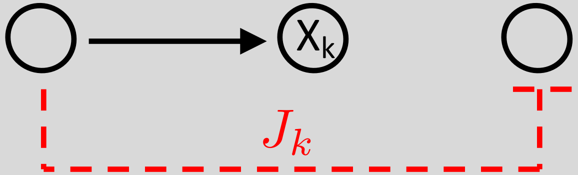
effective interaction graph

$$\frac{\partial H_i(u)}{\partial u} = \frac{\partial F_i / \partial u}{(1 + \sum_j J_j F_j)^2} - \frac{F_i \sum_j J_j \partial F_j / \partial u}{(1 + \sum_j J_j F_j)^2}$$

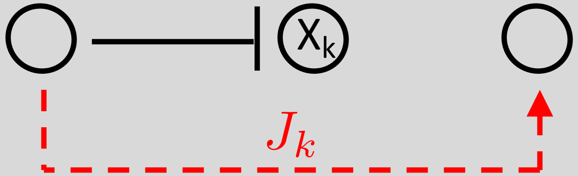
re-scaling of intended regulatory links

“hidden” interaction graph

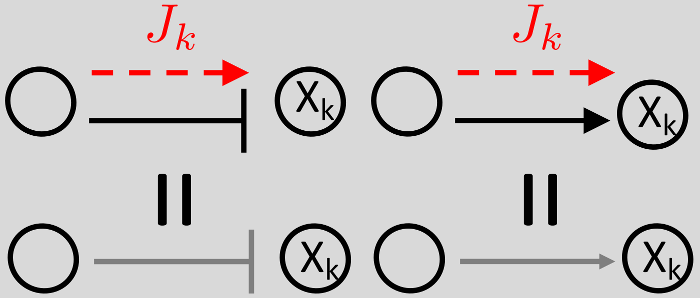
rules to draw hidden interactions



activators become “effective repressors” for non-target nodes



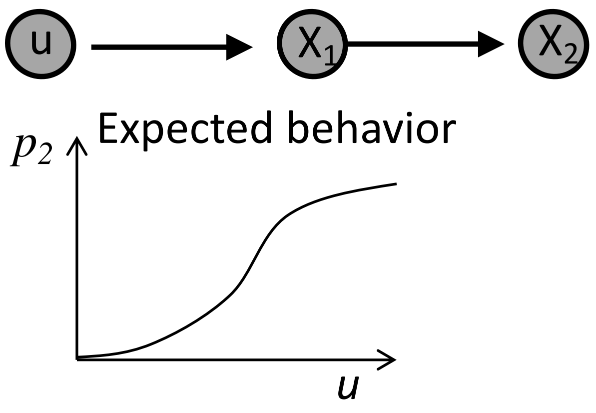
repressors become “effective activators” for non-target nodes



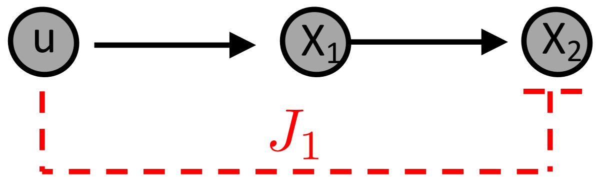
the effect on target nodes is weaker

Qian et al. *ACS Syn Bio*, 2017

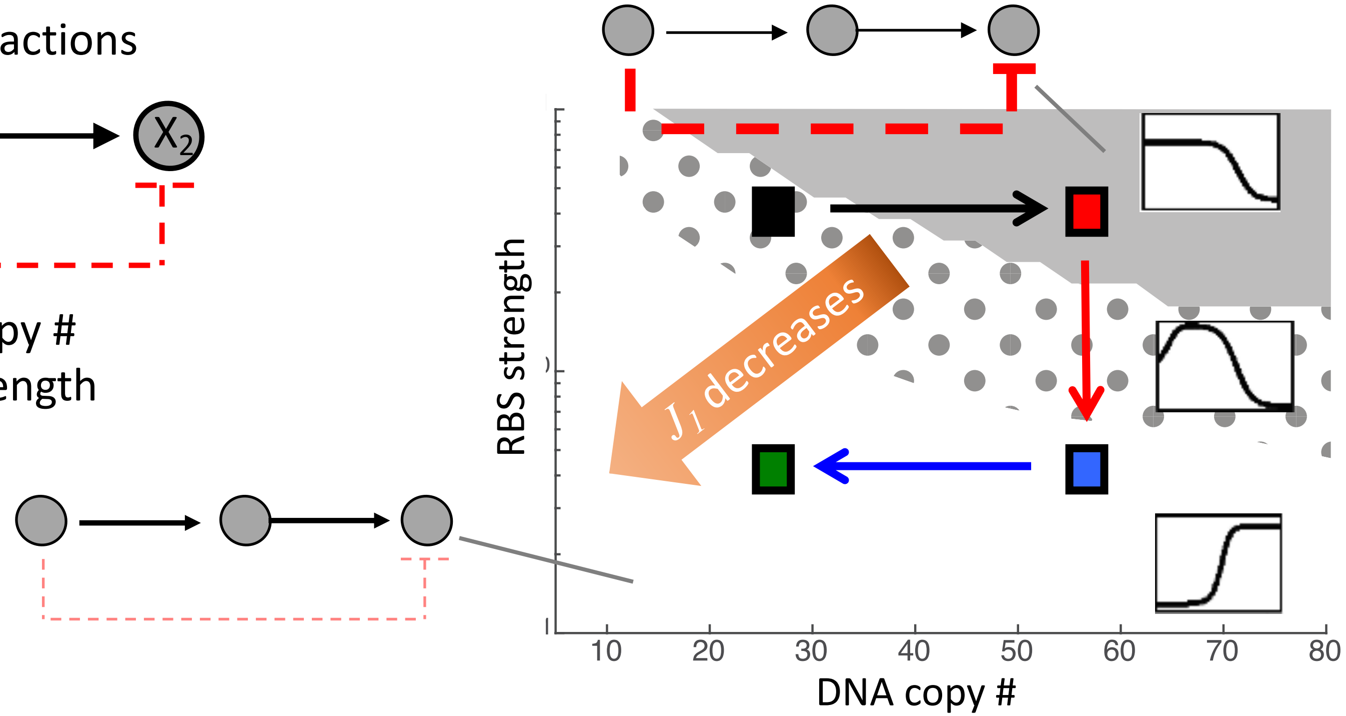
The effective interaction graph of an activation cascade is an iFFL

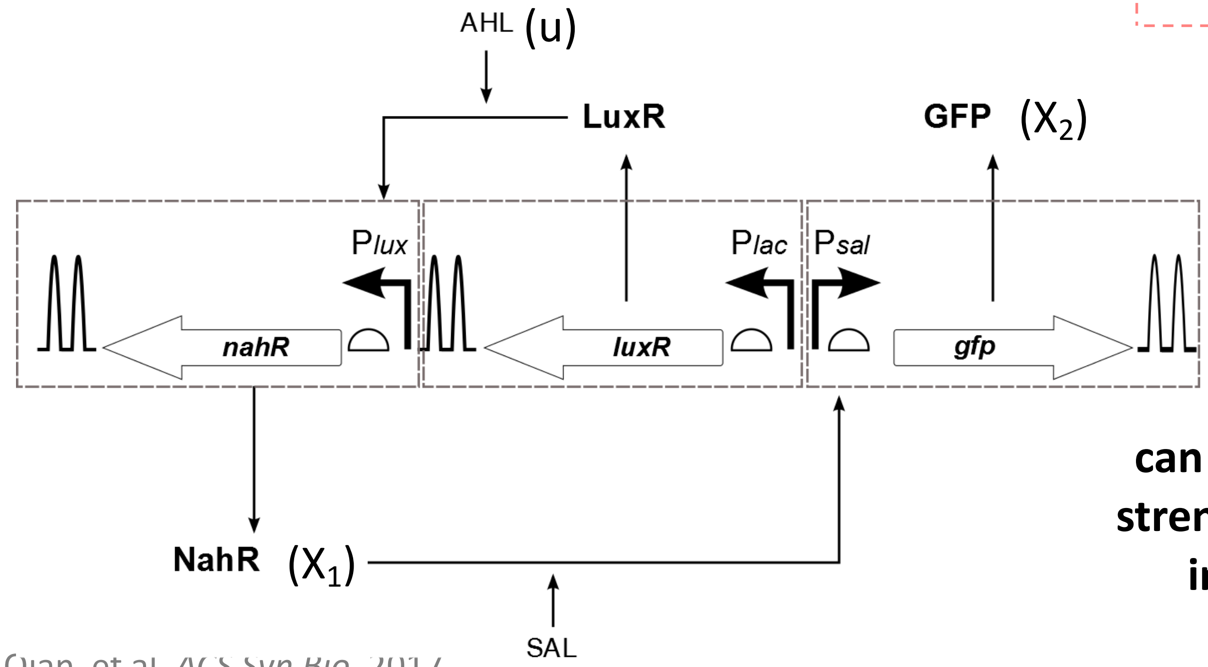


with hidden interactions

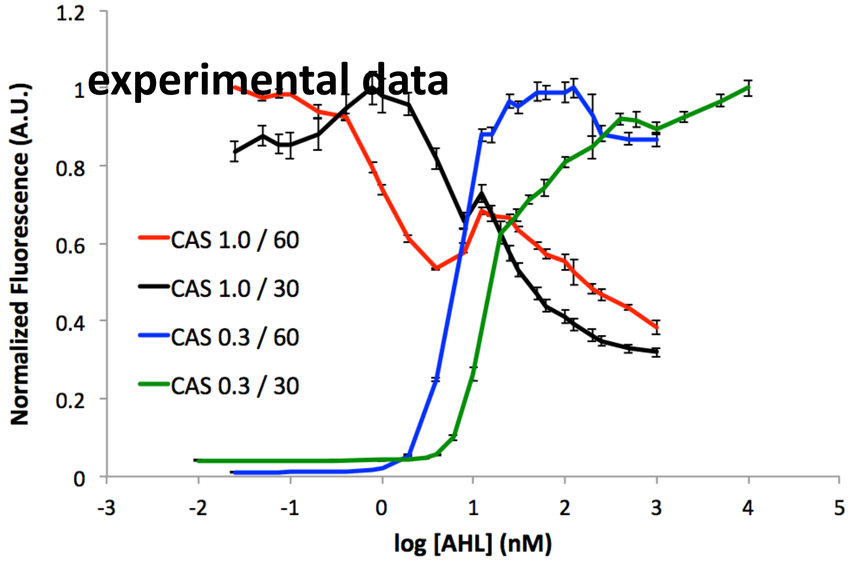


$J_1 \propto$ DNA copy #, RBS strength





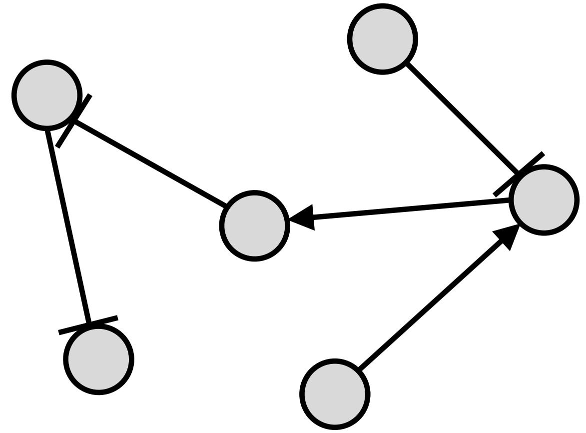
can use J to tune strength of hidden interactions



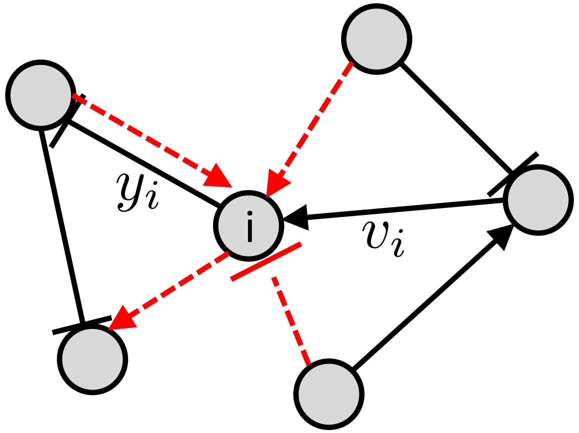
Qian et al. *ACS Syn Bio*, 2017

Network disturbance attenuation

system without hidden interactions

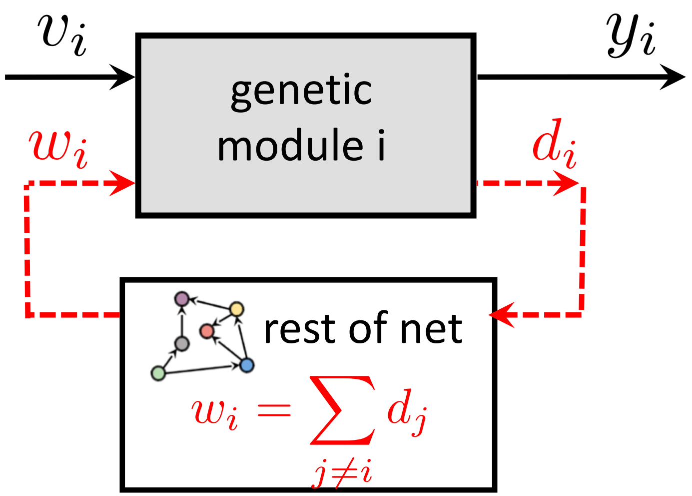


system with hidden interactions



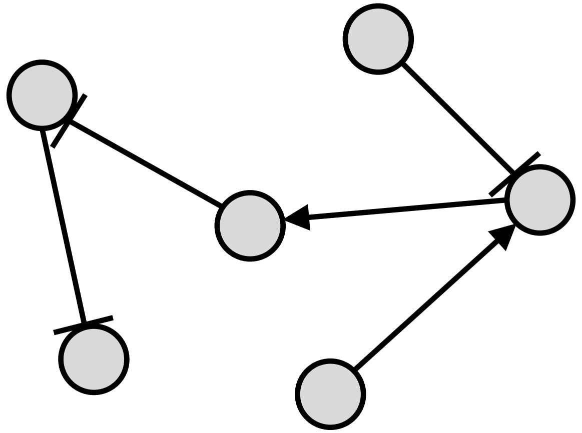
$d_i \propto J_i$
resource demand
at node i

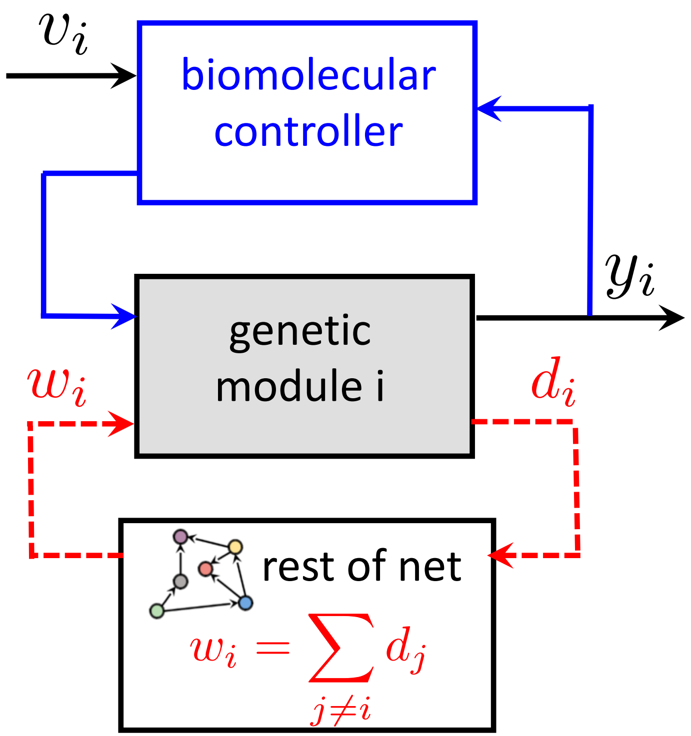
$$w_i = \sum_{j \neq i} d_j$$



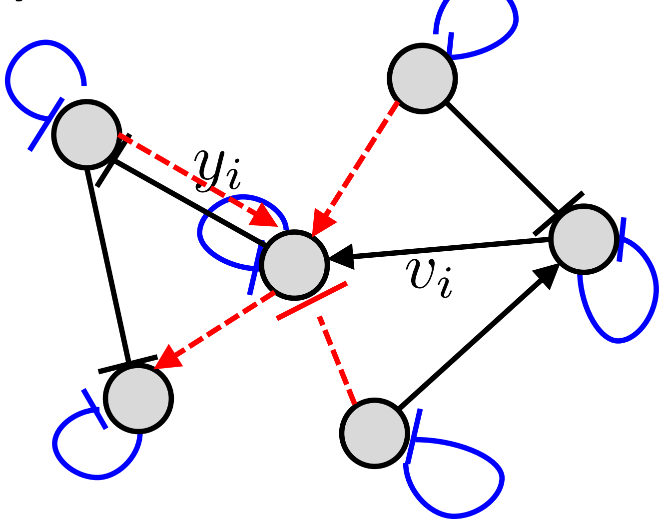
Network disturbance attenuation

system without hidden interactions





system with hidden interactions

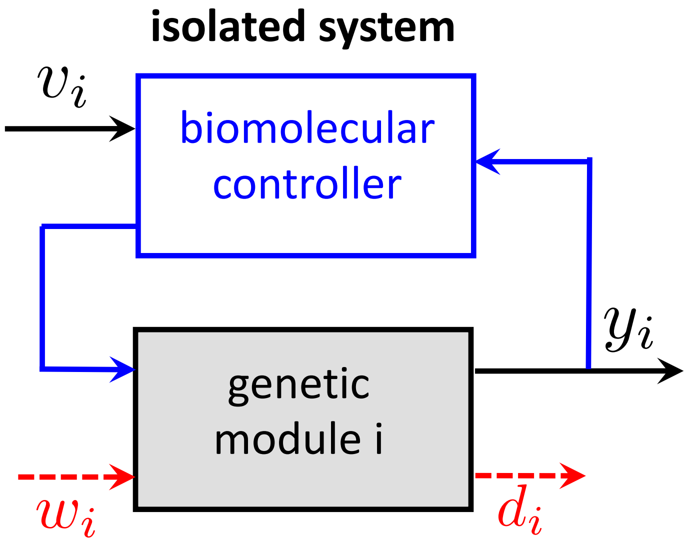


$d_i \propto J_i$
resource demand at node i

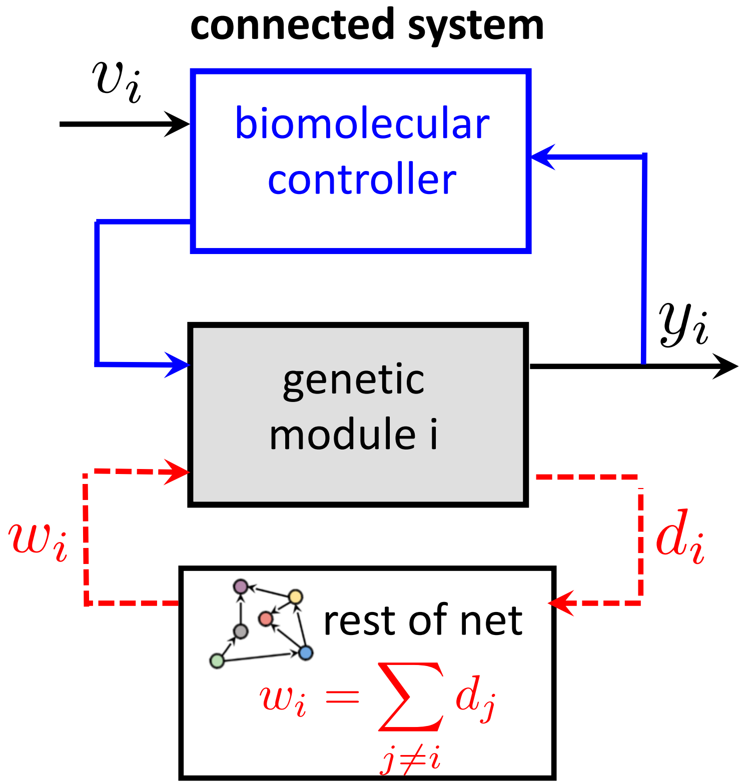
$$w_i = \sum_{j \neq i} d_j$$

Problem: Design a local feedback controller such that y_i depends only on v_i and it is independent of w_i

Network disturbance attenuation

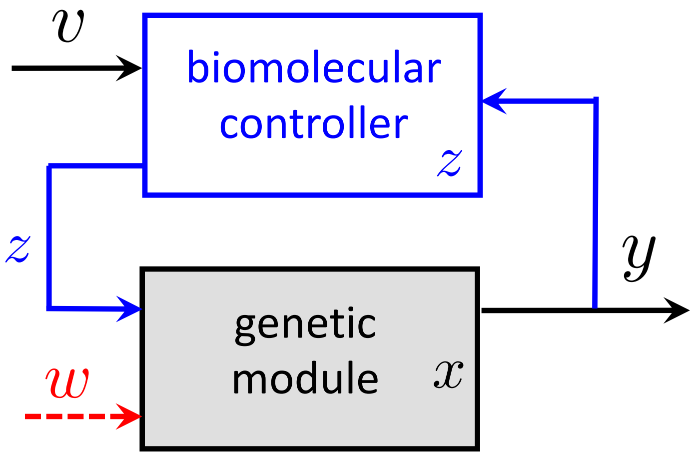


Problem 1: Design a biomolecular controller such that the input/output response v_i to y_i is independent of w_i



Problem 2: Determine conditions such that the biomolecular controller can still attenuate the effect of w_i on y_i (i.e., ensure network stability)

Disturbance rejection despite leaky integrators



Approach: For v and w constants, use integral control, e.g.

$$\dot{x} = f(x, v, z, w), \qquad y = g(x)$$
$$\dot{z} = k(v - y)$$

under stability conditions, y is independent of w at steady state

Challenge: molecular decay is unavoidable *in vivo* due to cell growth → integrator leakiness

$$\dot{x} = f(x, z, w), \quad y = g(x)$$
$$\dot{z} = k(v - y) - \gamma z$$

cannot send growth to zero
→ increase speed of
all controller's reactions

$$\dot{x} = f(x, z, w), \quad y = g(x)$$
$$\dot{z} = \frac{1}{\epsilon}(v - y) - \gamma z$$

quasi-integral control (QIC) structure

Theorem:

$$\dot{x} = f(x, z, w)$$
$$\dot{z}_1 = \frac{1}{\epsilon} h(v, z, y) - \gamma z_1$$
$$\dot{z}_2 = \frac{k}{\epsilon}(v - y) - \gamma z_2$$
$$y = g(x)$$

If this closed loop system with $\gamma = 0$ is LES for small $\epsilon > 0$

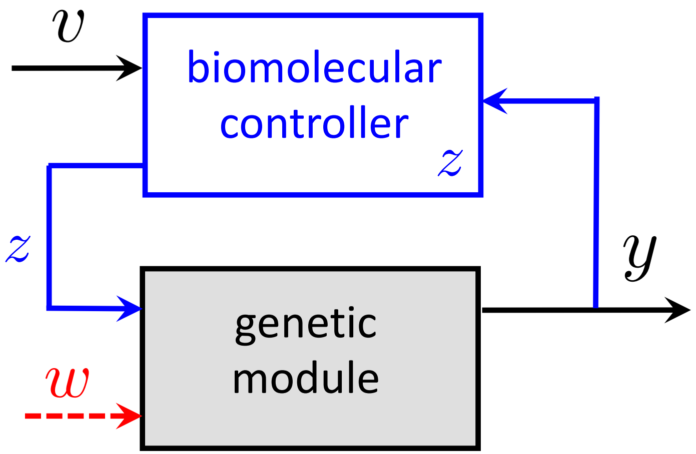
Then: $y(\epsilon) \to v \text{ as } \epsilon \to 0$ *independent of* w

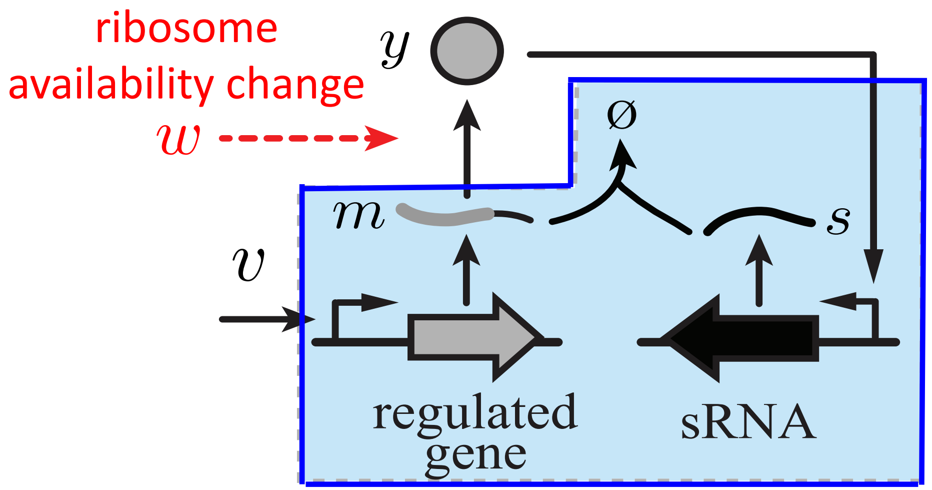
biomolecular implementation:

all fast controller reactions compute the difference and integrate

Qian and Del Vecchio. *J. Royal Society Interface,* 2018

Quasi-integral control implementation via sRNA silencing





$$\dot{y} = R(w)m - \delta y$$

$$\dot{m} = \frac{v}{\epsilon} - \frac{\theta}{\epsilon}ms - \gamma m$$

$$\dot{s} = \frac{y}{\epsilon} - \frac{\theta}{\epsilon}ms - \gamma s$$

fast RNA interactions

(for "free")

high RNA transcription rates

(we can tune)

$$z = m - s$$

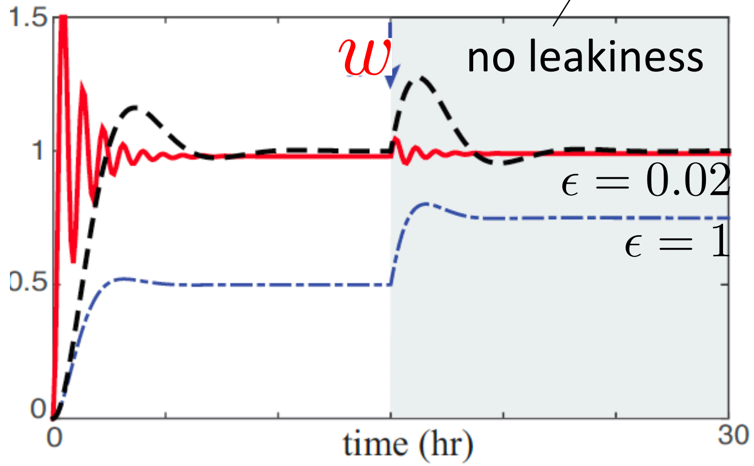
$$\epsilon\dot{z} = (v - y) - \epsilon\gamma z \quad \text{(QIC)}$$

closed loop system when $\gamma = 0$ is LES

then $y(\epsilon) \to v \text{ as } \epsilon \to 0$

independent of disturbance

Briat et al. (2016) sequestration-based feedback



Qian and Del Vecchio. *J. Royal Society Interface*, 2018

Tracking performance of quasi-integral control: a SSP problem

Problem: With time-varying inputs, can we still attenuate effect of disturbance as timescale separation between controller and plant increases ($\epsilon \to 0$) ?

Not obvious - tempting observation:

$$\dot{y} = R(w)m - \delta y$$
$$\epsilon \dot{m} = v(t) - \theta m s - \epsilon \gamma m$$
$$\epsilon \dot{s} = y - \theta m s - \epsilon \gamma s$$

$\epsilon = 0 \Rightarrow y(t) = v(t)$

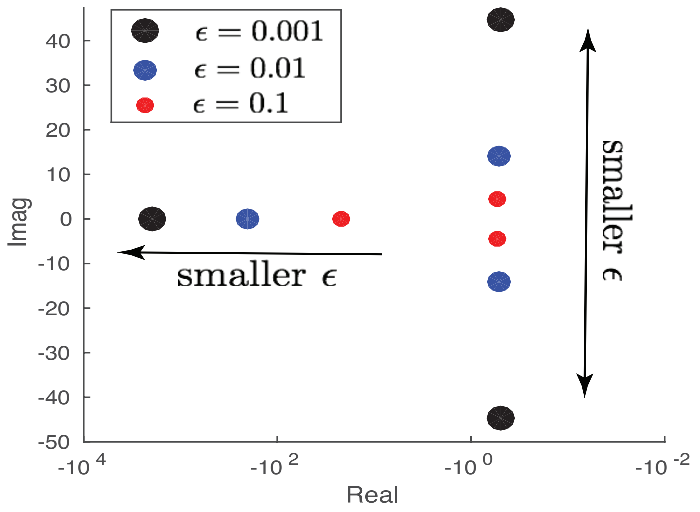
independent of w

Boundary layer dynamics

$$m' = v(t) - \theta m s$$
$$s' = y - \theta m s$$

Jacobian is singular everywhere

e-values of linearization



→ **Singular singular perturbation (SSP) problem**

$$\dot{y} = f(y, x, t), \;\; y \in \mathbb{R}^q$$
$$\epsilon \dot{x} = g(y, x, \epsilon), \;\; x \in \mathbb{R}^p$$

$$y' = \epsilon f(y, x, t)$$
$$x' = g(y, x, \epsilon)$$

$$J = \begin{pmatrix} 0 & 0 \\ \frac{\partial g}{\partial y} & \frac{\partial g}{\partial x} \end{pmatrix}\Bigg|_{\epsilon=0}$$

J has more than q zero e-values

If zero e-value of J has algebraic multiciplity (am) = geometric multiciplity (gm) → system can be taken to standard SP form by ϵ-independent coordinate change with less than p fast variables (Gu, Nefedov and O'Malley (1989); Sobolev (2005))

- *not applicable here since gm=1 and am=2 (am<gm)*
- *Marino & Kokotovic (1988): there is no* ϵ-independent diffeomorphism to standard SP form

Asymptotic expansion (with fractional exponents) can address some SSP problems assuming a limiting solution exists as $\epsilon \to 0$ (O'Malley & Jameson (1975); O'Malley (1979))

- not applicable – no limiting solution exists as $\epsilon \to 0$

Qian and Del Vecchio, *IEEE Control Systems Letters, CDC*, 2018

Solving the SSP problem

$$\dot y = A_1 \begin{bmatrix} y \\ x \end{bmatrix} + B_1 w(t), \; y \in \mathbb{R}^q$$

$$\epsilon \dot x = A_2{}^{\epsilon} \begin{bmatrix} y \\ x \end{bmatrix} + B_2 v(t), \; x \in \mathbb{R}^p$$

assume $J = \begin{pmatrix} 0 & 0 \\ A_{21}^0 & A_{22}^0 \end{pmatrix}$

- zero e-value has am = $q+1$ and gm= q
- all other e-values have negative real part

→ There is an **ϵ**-independent coordinate change with S Hurwitz

$$\dot y = A_1 \begin{bmatrix} y \\ x \end{bmatrix} + B_1 w(t)$$ *slow*

$$\epsilon \dot z_1 = Ry + B_2 v(t) + \epsilon Dz$$ one-dimensional

$$\epsilon \dot z_2 = Sz_2 + B + 3v(t) + \epsilon E \begin{bmatrix} y \\ z_1 \end{bmatrix}$$ *fast*

→ set $\epsilon = 0$ in the fast dynamics

ϵ-dependent reduced system

$$\dot{\bar y} = \bar A_{11} \bar y + \bar A_{12} \bar z_1 + \bar B_1 w(t) + \bar B_4 v(t)$$

$$\epsilon \dot{\bar z}_1 = R \bar y + \bar B_2 v(t) + \epsilon \bar D \bar z_1$$

Theorem (SSP): Assume that:

A1. inputs and their first derivatives bounded

A2. the reduced system is such that $\bar D < 0, \; (\bar A_{11}, \bar A_{12})$ controllable, $R \bar A_{12} > 0$

Then: $\limsup_{t \to \infty} \|y(t) - \bar y(t)\| = \mathcal{O}(\sqrt{\epsilon})$

Proof : - decompose the error system into a slow and a fast subsystem

- S Hurwitz → fast subsystem is ISS with gain $\mathcal{O}(\epsilon)$
- A2. → slow subsystem is ISS with gain $\mathcal{O}(1/\sqrt{\epsilon})$

result follows from ISS small gain theorem for ϵ sufficiently small

Qian and Del Vecchio, *IEEE Control Systems Letters, CDC*, 2018

Solving the robust tracking problem

original system

$$\dot{y} = A_1 \begin{bmatrix} y \\ x \end{bmatrix} + B_1 w(t), \; y \in \mathbb{R}^q$$

$$\epsilon \dot{x} = A_2{}^{\epsilon} \begin{bmatrix} y \\ x \end{bmatrix} + B_2 v(t), \; x \in \mathbb{R}^p$$

ϵ-dependent reduced system

$$\dot{\bar{y}} = \bar{A}_{11}\bar{y} + \bar{A}_{12}\bar{z}_1 + \bar{B}_1 w(t) + \bar{B}_4 v(t)$$

$$\epsilon \dot{\bar{z}}_1 = R\bar{y} + \bar{B}_2 v(t) + \epsilon \bar{D}\bar{z}_1$$

$$\limsup_{t\to\infty} \|y(t) - \bar{y}(t)\| = \mathcal{O}(\sqrt{\epsilon})$$

Theorem (robust tracking for reduced system):

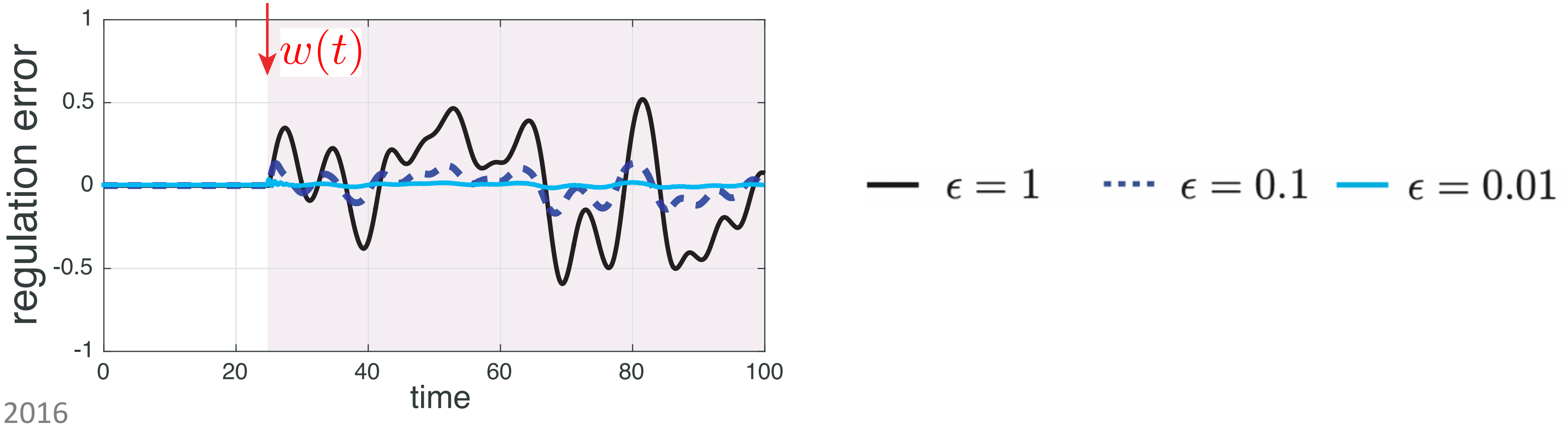
If, in addition, all input derivatives are bounded, then $\limsup_{t\to\infty} \|R\bar{y}(t) + \bar{B}_2 v(t)\| = \mathcal{O}(\sqrt{\epsilon})$

→ $\limsup_{t\to\infty} \|y(t) + R^{-1}\bar{B}_2 v(t)\| = \mathcal{O}(\sqrt{\epsilon})$ → $y(t)$ independent of $w(t)$ as $\epsilon \to 0$

$$\dot{y} = R(w)m - \delta y$$

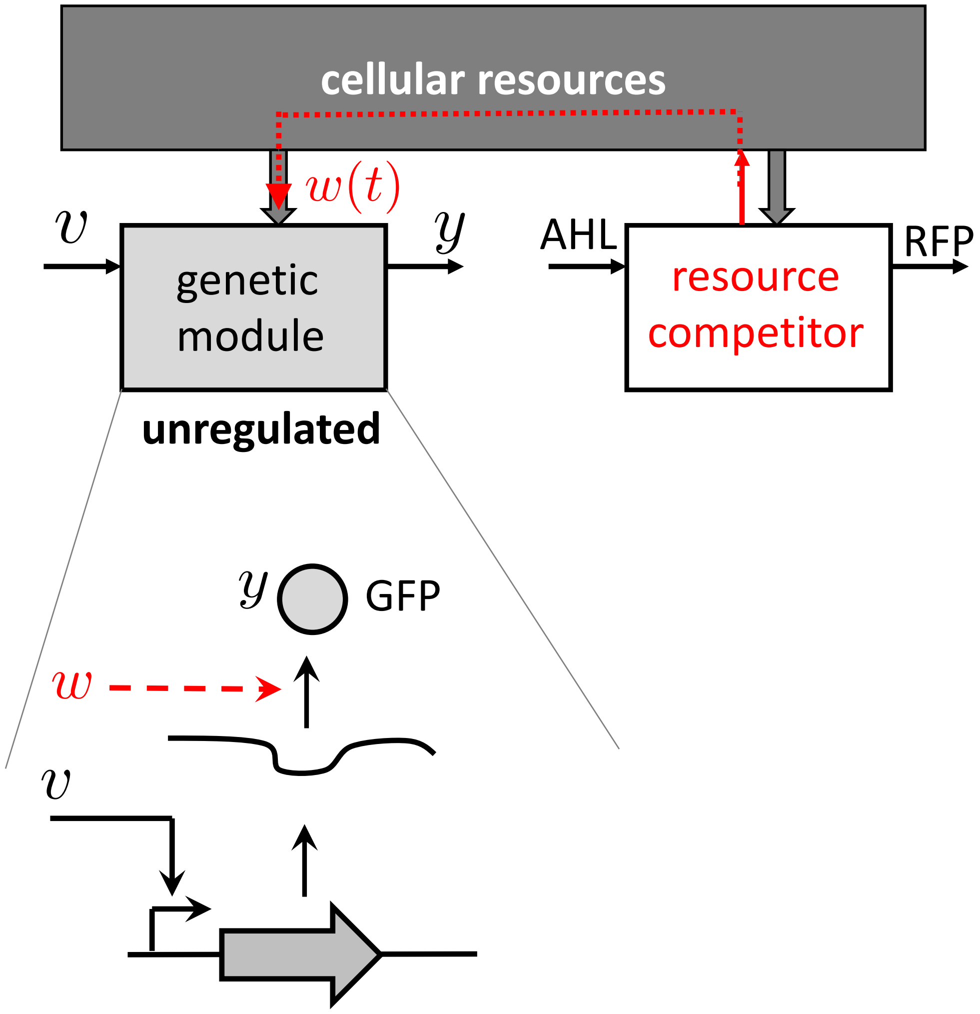
$$\epsilon \dot{m} = v(t) - \theta m s - \epsilon \gamma m$$

$$\epsilon \dot{s} = y - \theta m s - \epsilon \gamma s$$

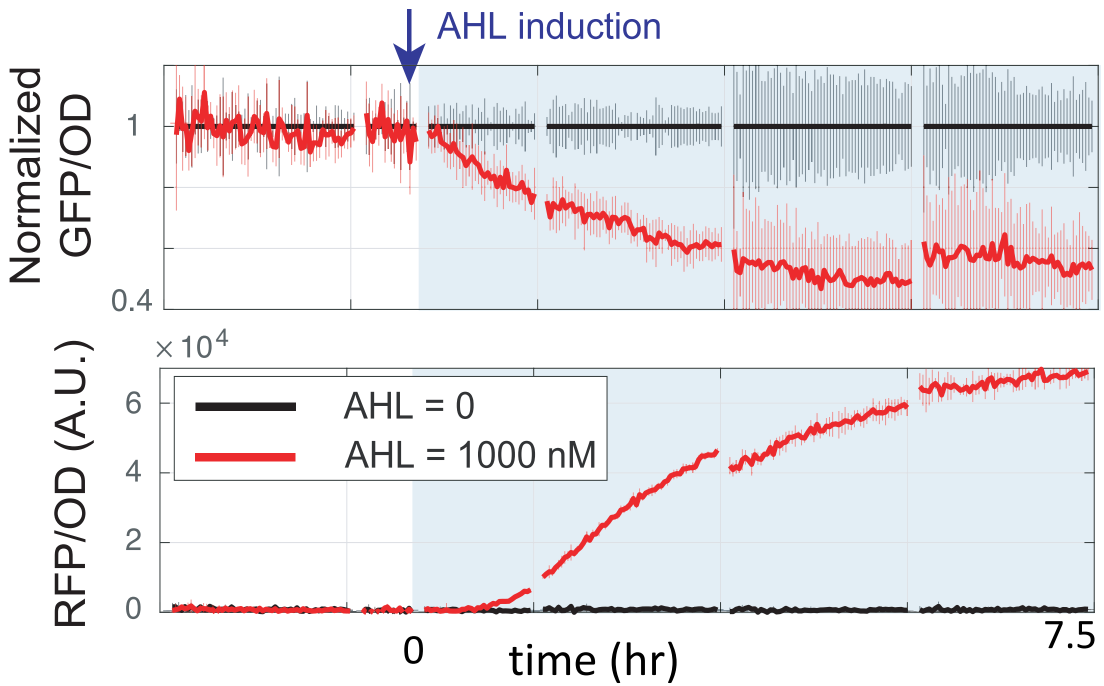


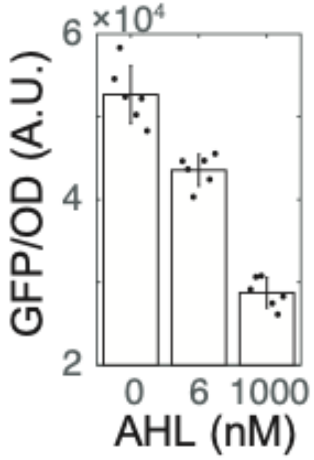
Hamadeh, Sontag and Del Vecchio, *IEEE CDC* 2016

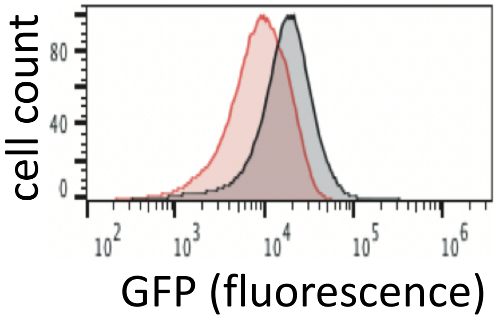
The *Resource Decoupler*: insulation via fast quasi-integral control



experimental data



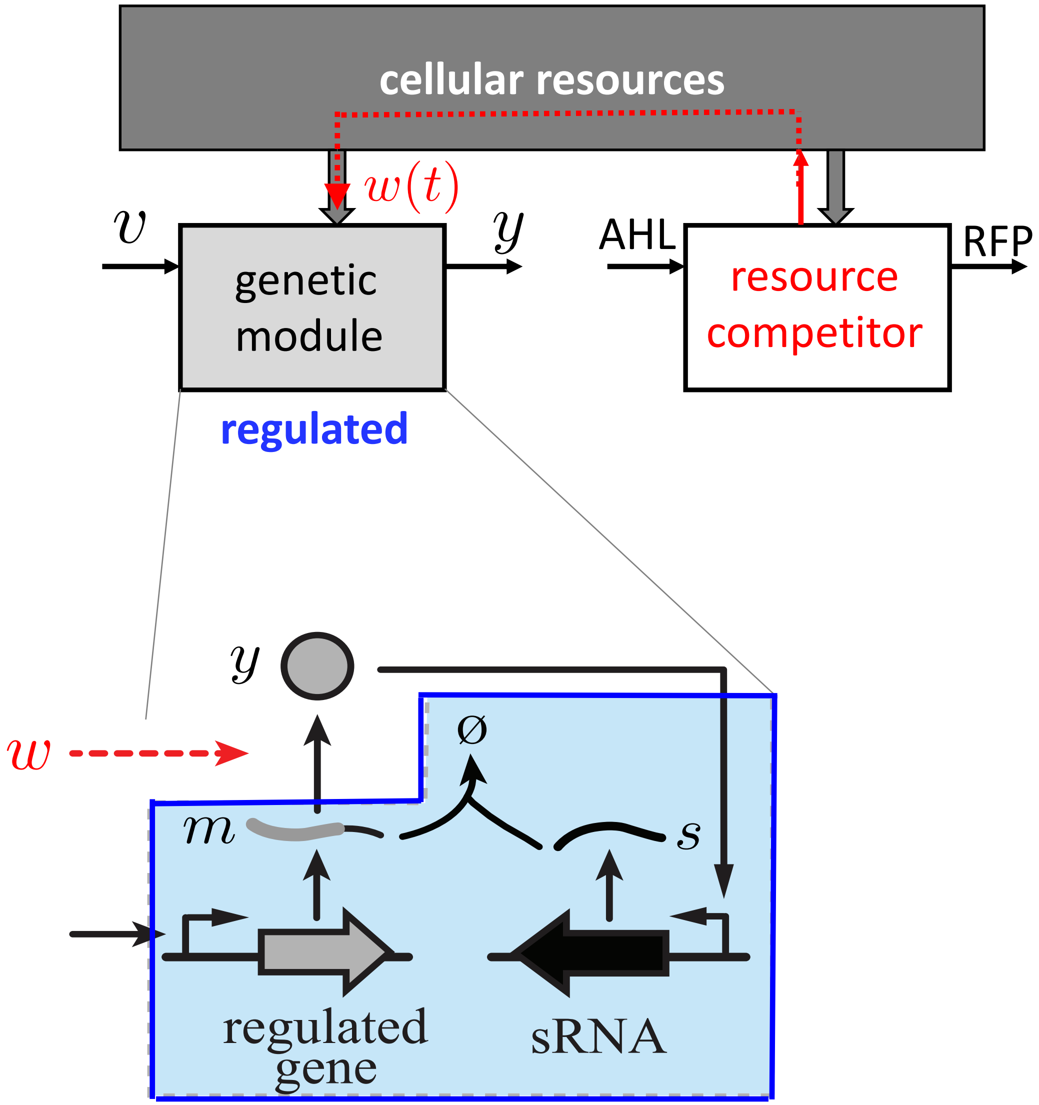




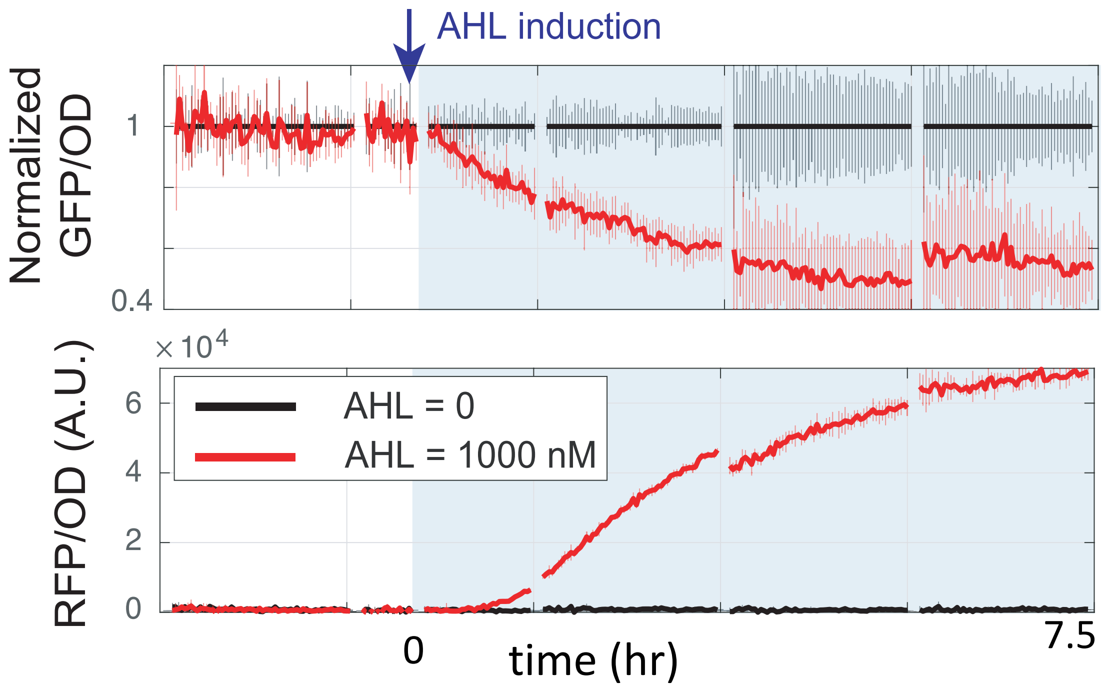
AHL=0
AHL=1000nM

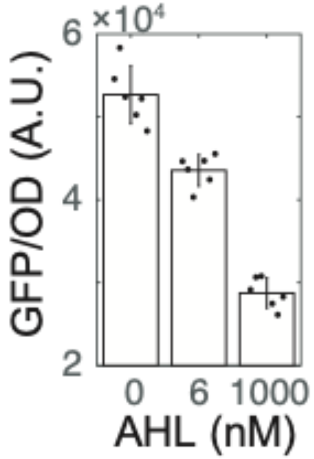
Huang, Qian, and Del Vecchio. *Nat. Comm.*, December 2018

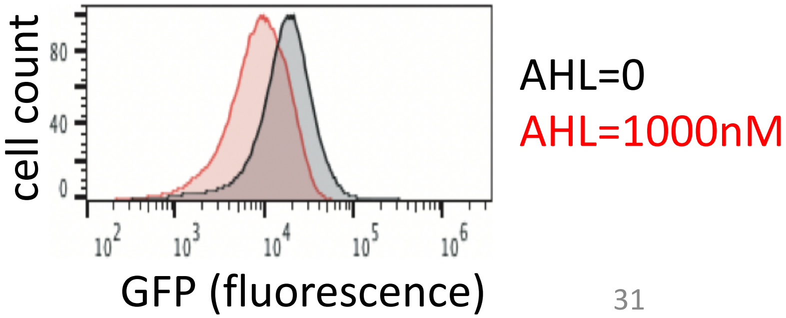
The *Resource Decoupler*: insulation via fast quasi-integral control



experimental data







Huang, Qian, and Del Vecchio. *Nat. Comm.*, December 2018

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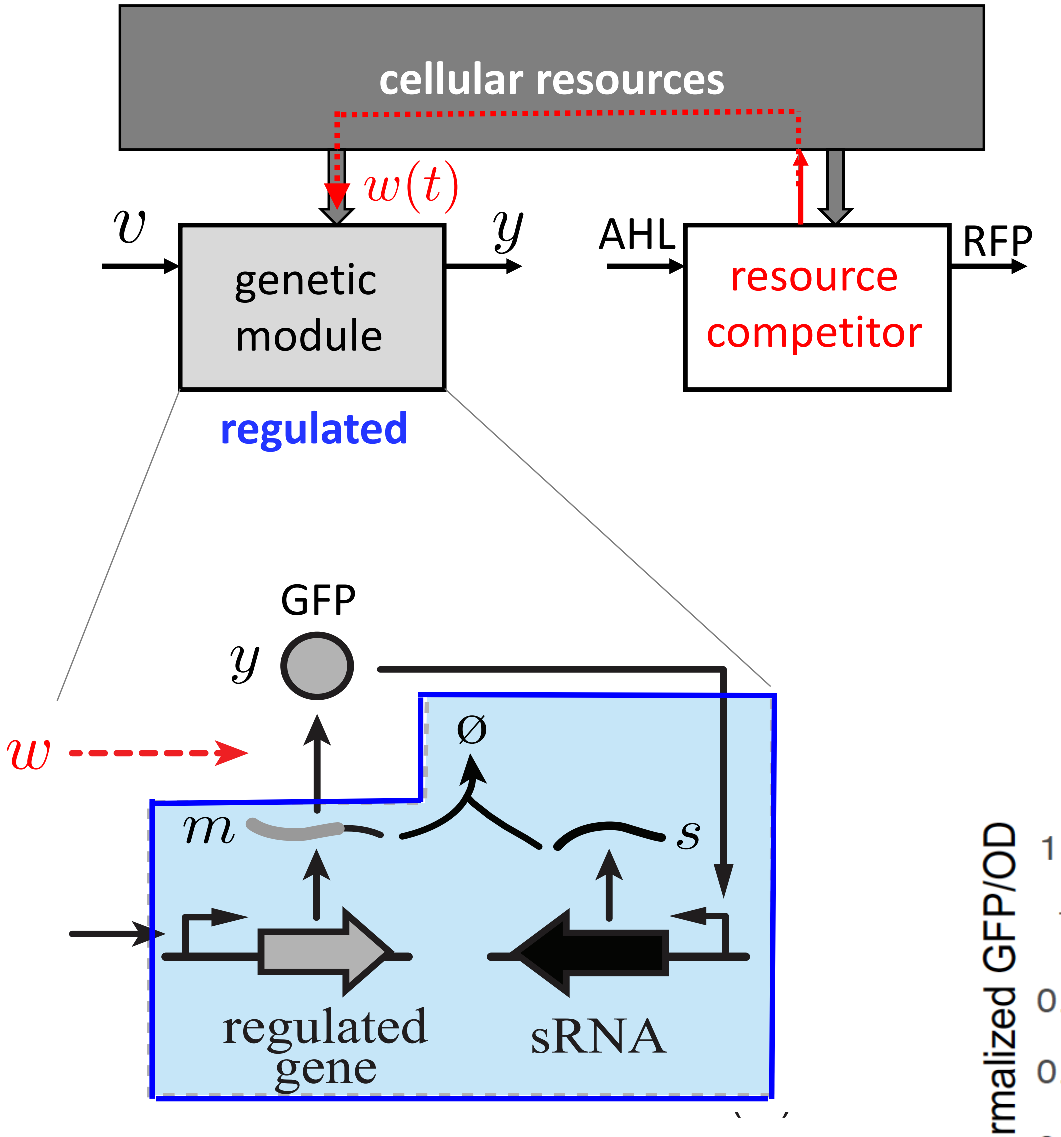
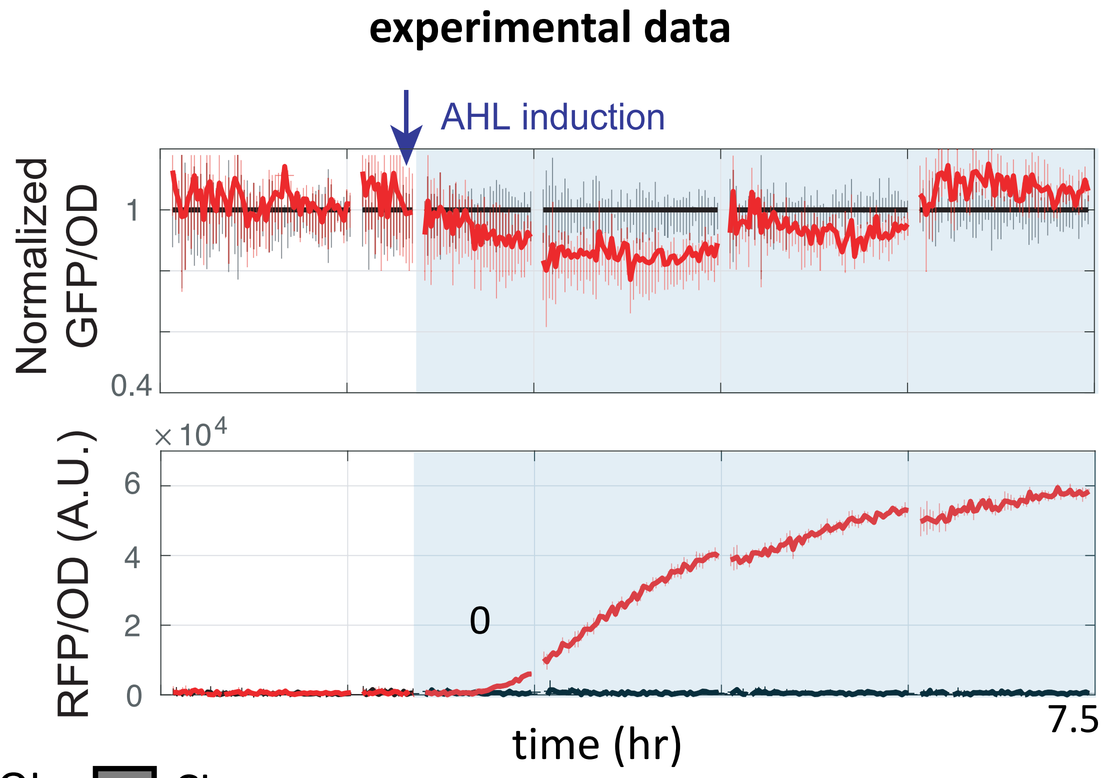
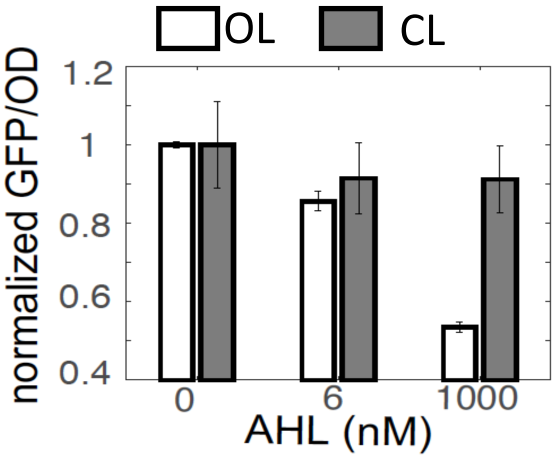
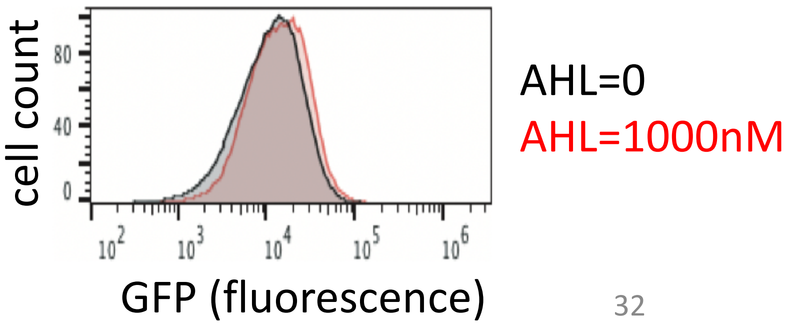


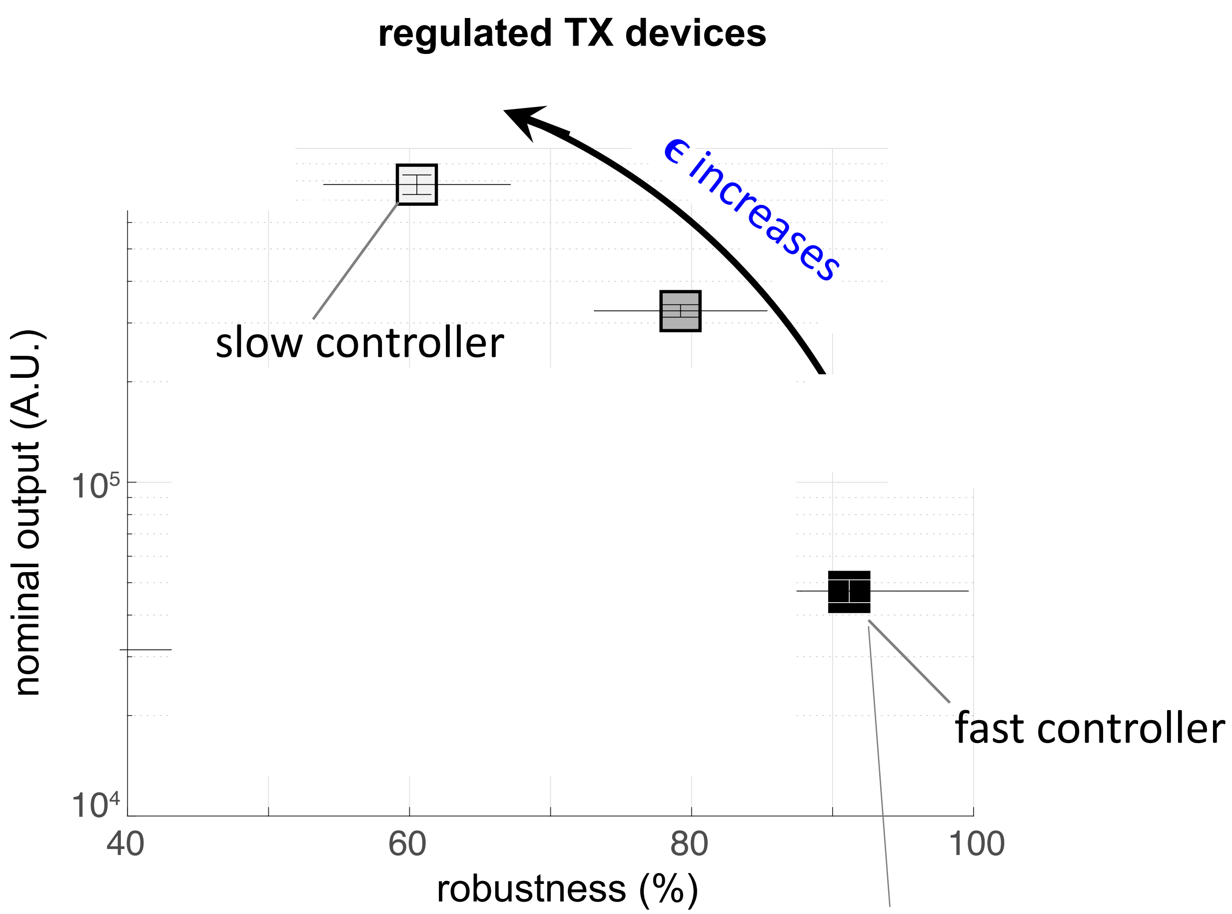




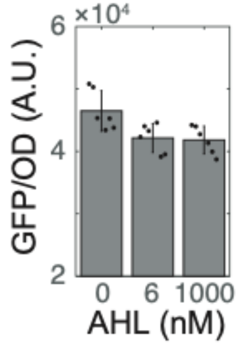


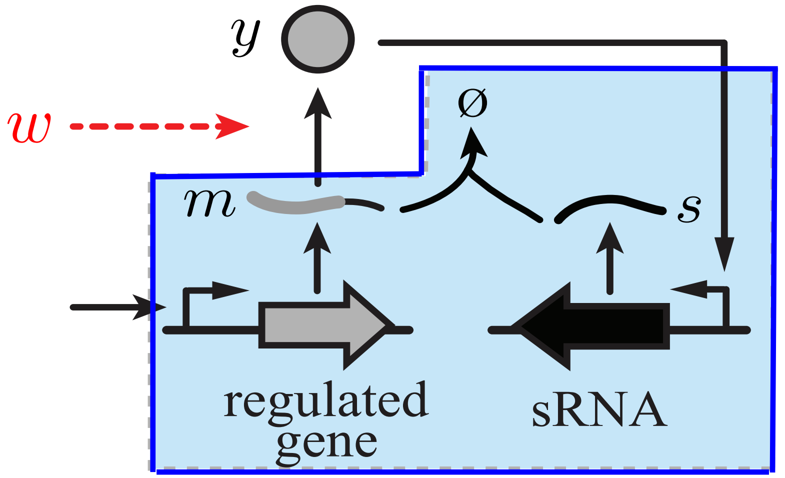
Huang, Qian, and Del Vecchio. *Nat. Comm.*, December 2018

The *Resource Decoupler*: insulation via fast quasi-integral control



(1-relative change) x100%





$$\dot{y} = R(w)m - \delta y$$

$$\dot{m} = T_m \cdot v - \frac{\theta}{\epsilon} ms - \gamma m$$

$$\dot{s} = T_s \cdot y - \frac{\theta}{\epsilon} ms - \gamma s$$

fast RNA interactions "free"

high RNA TX rates

T_s easily tunable by sRNA promoter

T_m GFP promoter strength

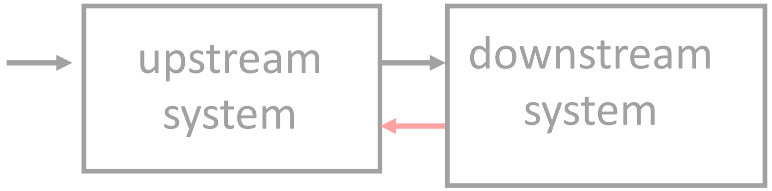
A journey towards modular composition

Engineering biology: Why and how

Modular composition: A grand challenge

Inter-module loads and the *load driver*

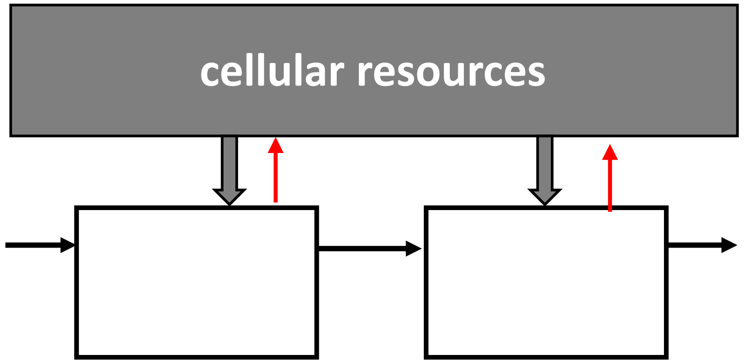
Disturbance attenuation via time scale separation



Resource loading and the *resource decoupler*

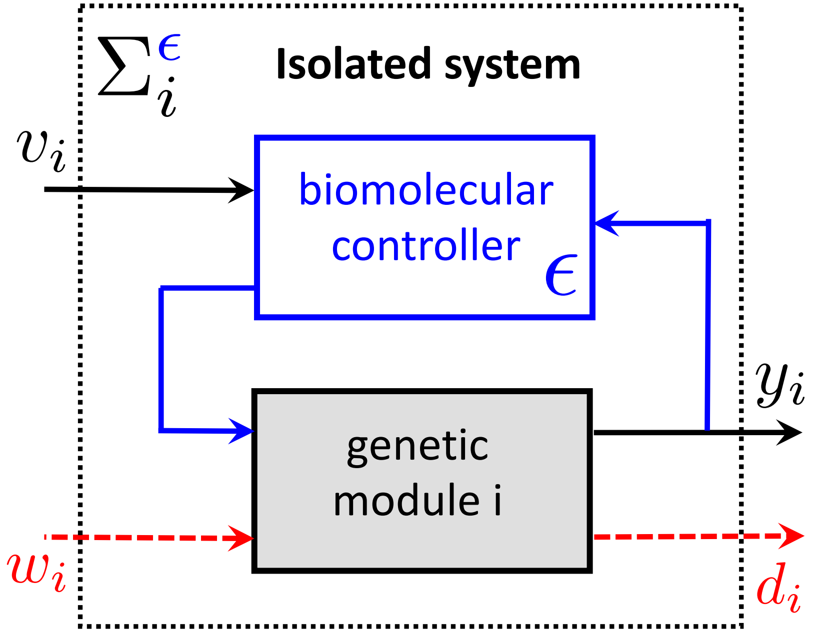
Disturbance rejection despite leaky integral actions

Decentralized implementation



Outlook

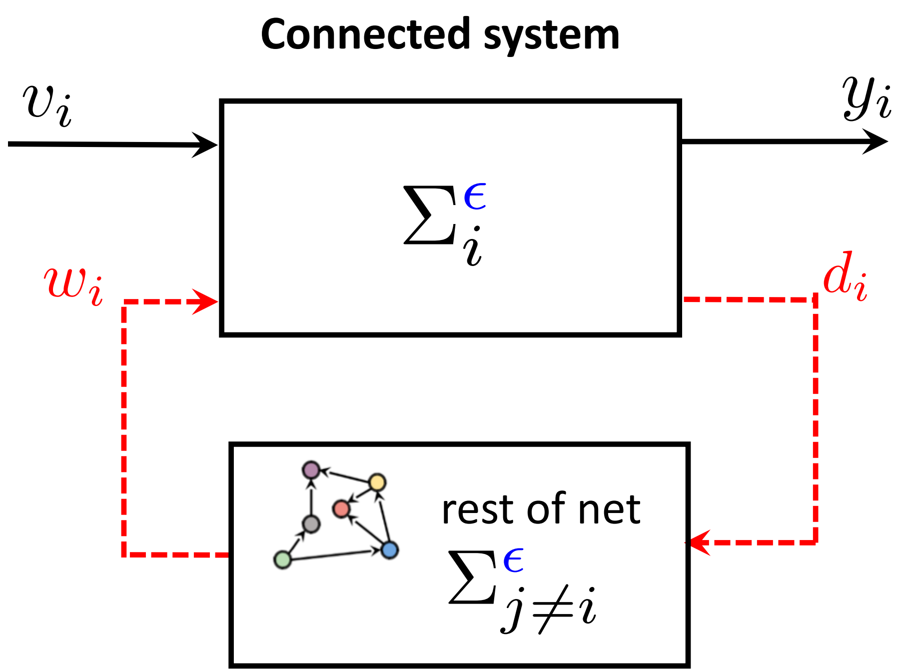
Network disturbance attenuation



We have: for constant w_i bounded independent of ϵ

$$\lim_{t\to\infty} \|y_i(t) - h(v_i)\| = \mathcal{O}(\sqrt{\epsilon})\|w_i\|$$

→ y_i independent of w_i



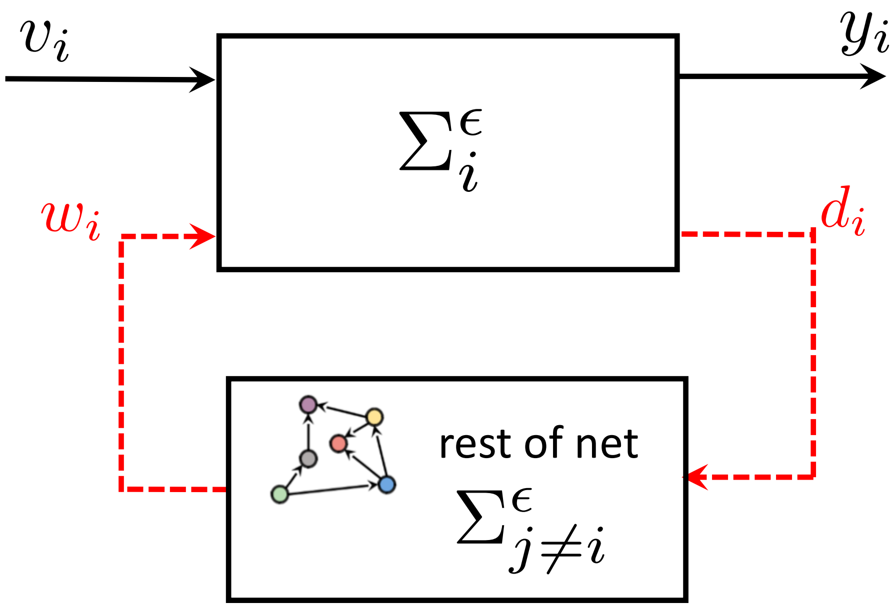
Problem: Can we guarantee that

$$\lim_{t\to\infty} \|y_i(t) - h(v_i)\| = \mathcal{O}(\sqrt{\epsilon})$$

- ensure that w_i steady state has ϵ-independent bound
- ensure closed loop system approaches steady state

Network disturbance attenuation

ensure that w_i has an ϵ -independent steady state bound



physics leads to steady state relationships:

(i) system i $\quad d_i = g_i(v_i) + \hat{g}_i(v_i) \cdot w_i + \tilde{g}_i(w_i) \cdot O(\epsilon)$

linear term in w_i $\quad$ HOT in w_i

(ii) interconnection $\quad w_i = \sum_{j \neq i} d_j$

(iii) system $\quad$ (i)+(ii)→ $A(v) \cdot w = g(v) + \tilde{g}(w)\mathcal{O}(\epsilon)$

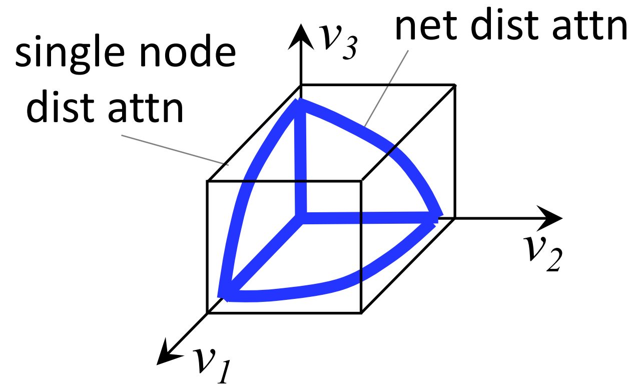
$$A(v) = \begin{bmatrix} 1 & -\hat{g}_2 & \cdot & \cdot & -\hat{g}_n \\ -\hat{g}_1 & 1 & -\hat{g}_2 & \cdot & -\hat{g}_n \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ -\hat{g}_1 & -\hat{g}_2 & \cdot & -\hat{g}_{n-1} & 1 \end{bmatrix}$$

→ If $A(v)$ is invertible, then w has ϵ -independent bound

sufficient check: diagonal dominance $\quad \sum_{j \neq i} \hat{g}_j(v_j) < 1, \quad \forall\, i$

$\hat{g}_j(v_j)$ increasing function of v_j

↓

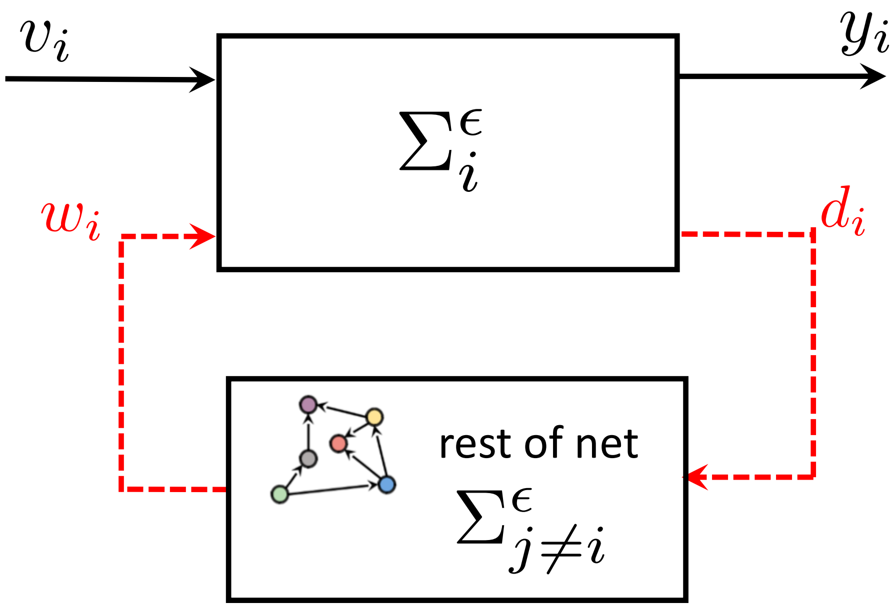


obtain constraints on tunable parameters as a function of the number of nodes

Qian and Del Vecchio, *Proc. IEEE CDC* 2016

Network disturbance attenuation

ensure closed loop system approaches steady state



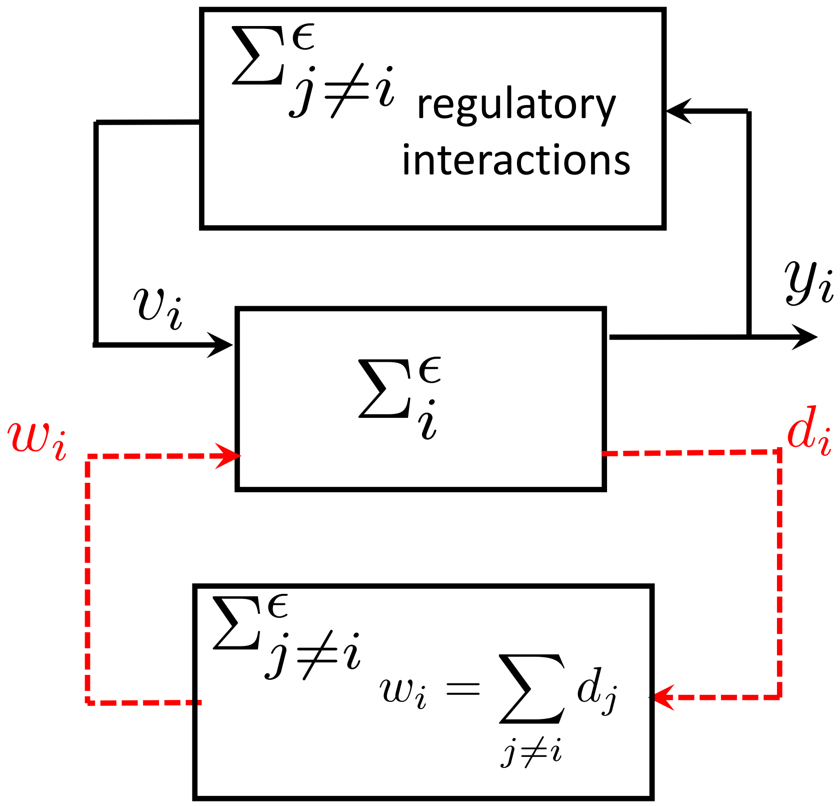
Assumption: Σ_i^ϵ is input-to-state/output monotone

→ use Small Gain Theorem for Monotone Systems
(Angeli & Sontag, *IEEE TAC* 2003)

$A(v)$ diagonally dominant →unique/globally attractive equilibrium

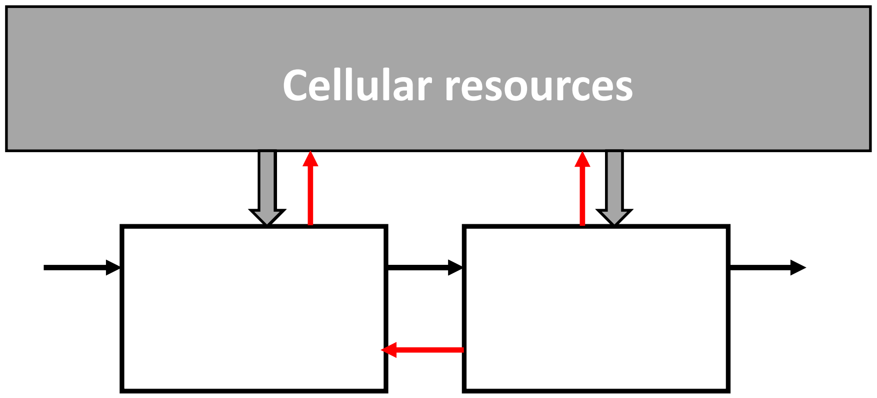
Note: we can prove the controller makes Σ_i^ϵ SP - monotone
if its dynamics are much faster than the plant
(Grunberg and Del Vecchio, *IEEE CDC* 2019)

on-going: time-varying inputs and regulatory interactions



In preparation – ingredients:
small-gain theorem for singularly perturbed monotone systems (Christofides & Teel, *IEEE TAC* 1995; Angeli & Sontag, *IEEE TAC* 2003)

Summary

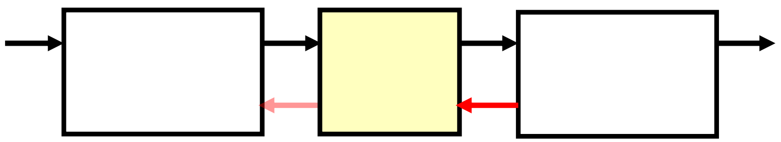


Loads applied by downstream modules change the behavior of upstream systems

Loads that modules apply to cellular resources cause subtle couplings among theoretically independent modules

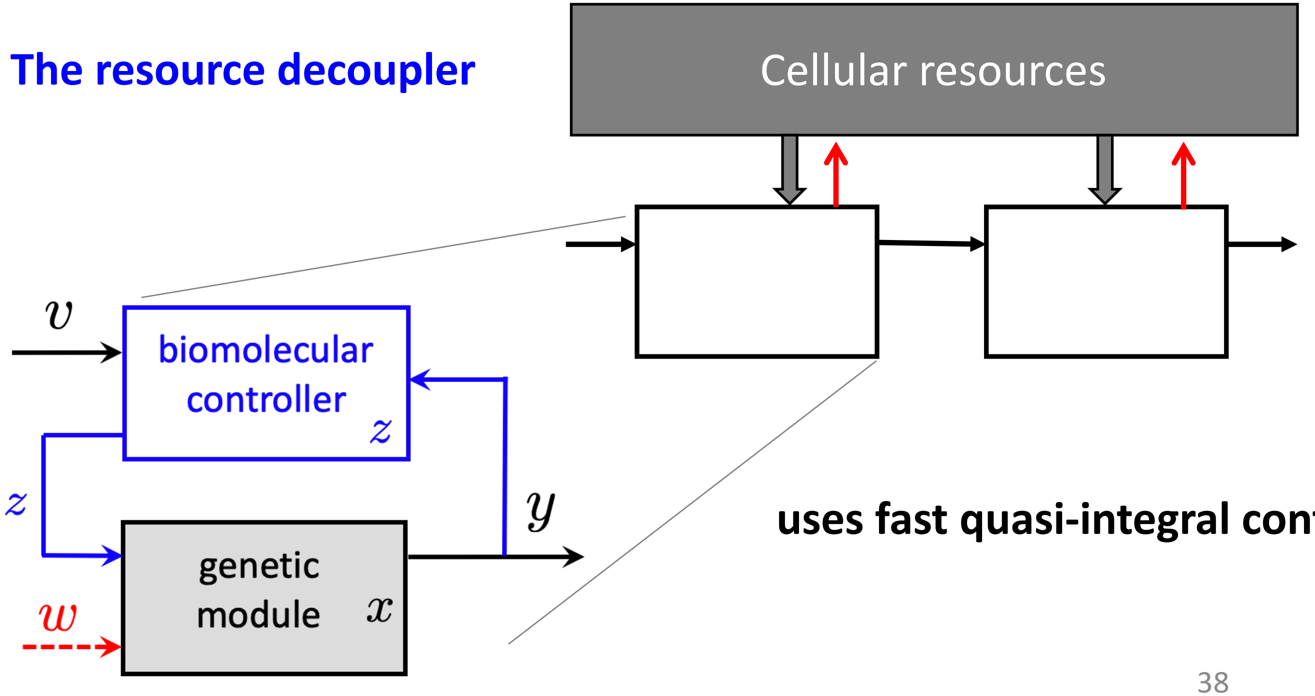
An engineering framework for insulating genetic modules from perturbations

The load driver



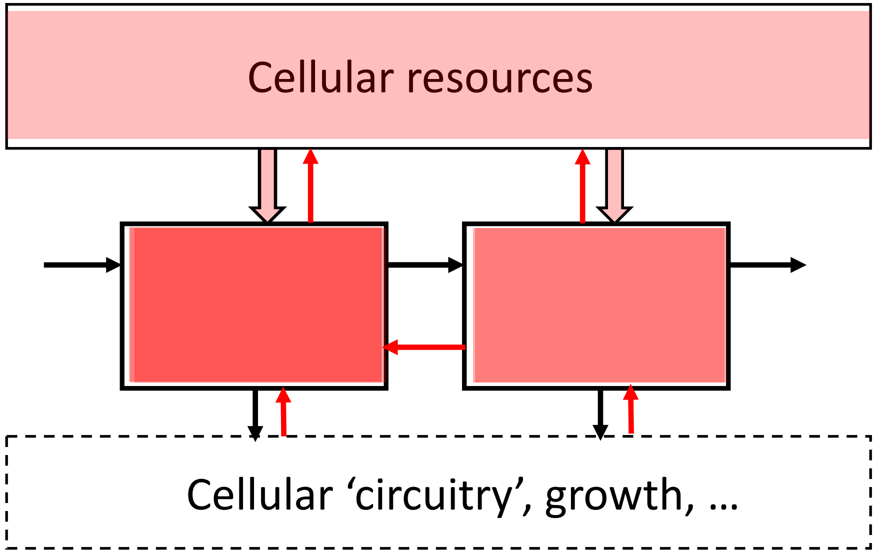
uses time scale separation in place of high-gain negative feedback

The resource decoupler



uses fast quasi-integral control

Some reasons why modularity is a challenge



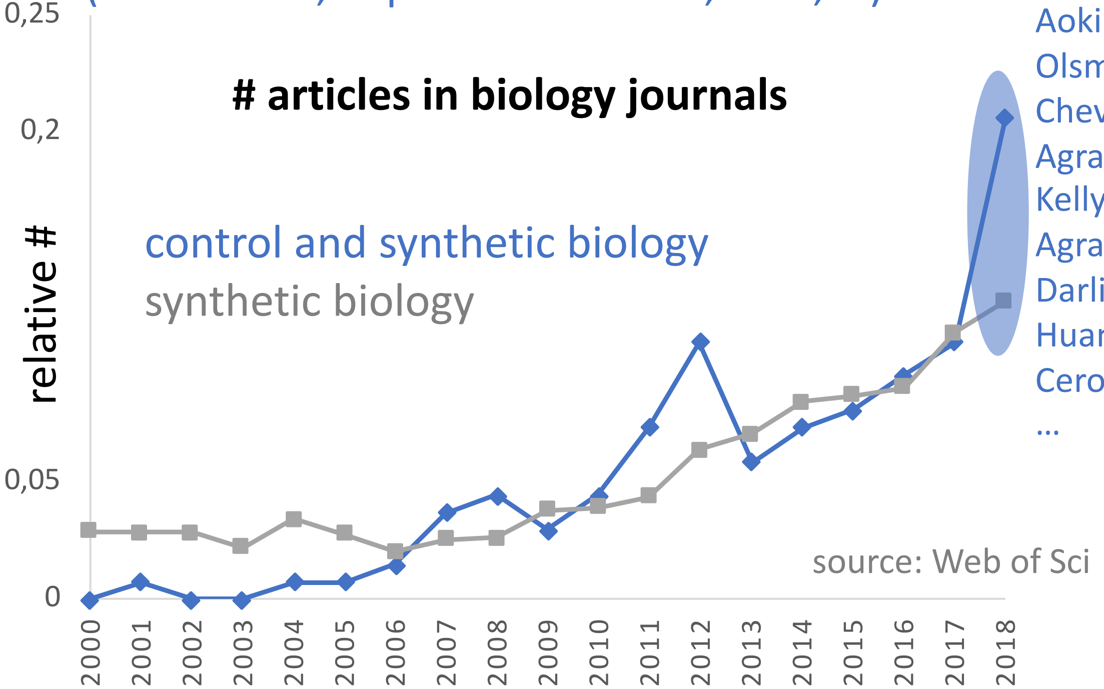
Loads applied by downstream modules change the behavior of upstream systems
(Del Vecchio, Hespanha, Klavins, Papachristodoulou, Sontag, …)

Modules apply a load the cellular resources: creates subtle couplings
(Bates, Del Vecchio, Murray, Stan,…)

Modules often have "off-target" interactions, affect growth rate, and this, in turn, has global effects on a module's dynamics
(Khammash, Papachristodoulou, Stan, …)

and many more…

- **lab conditions:** temperature, nutrients, Ph,…
- **cell type/strain**
- **growth phase**
- **mutations**



Aoki et al. *Nature* 2019
Olsman et al. *Cell Systems* 2019
Chevalier et al. *Cell Systems* 2019
Agrawal et al. *Nat Comm* 2019
Kelly et al. *NAR* 2018
Agrawal et al. *ACS Syn Bio* 2018
Darlington et al. *Nat Comm* 2018
Huang et al. *Nat Comm* 2018
Ceroni et al. *Nat Methods* 2018
…

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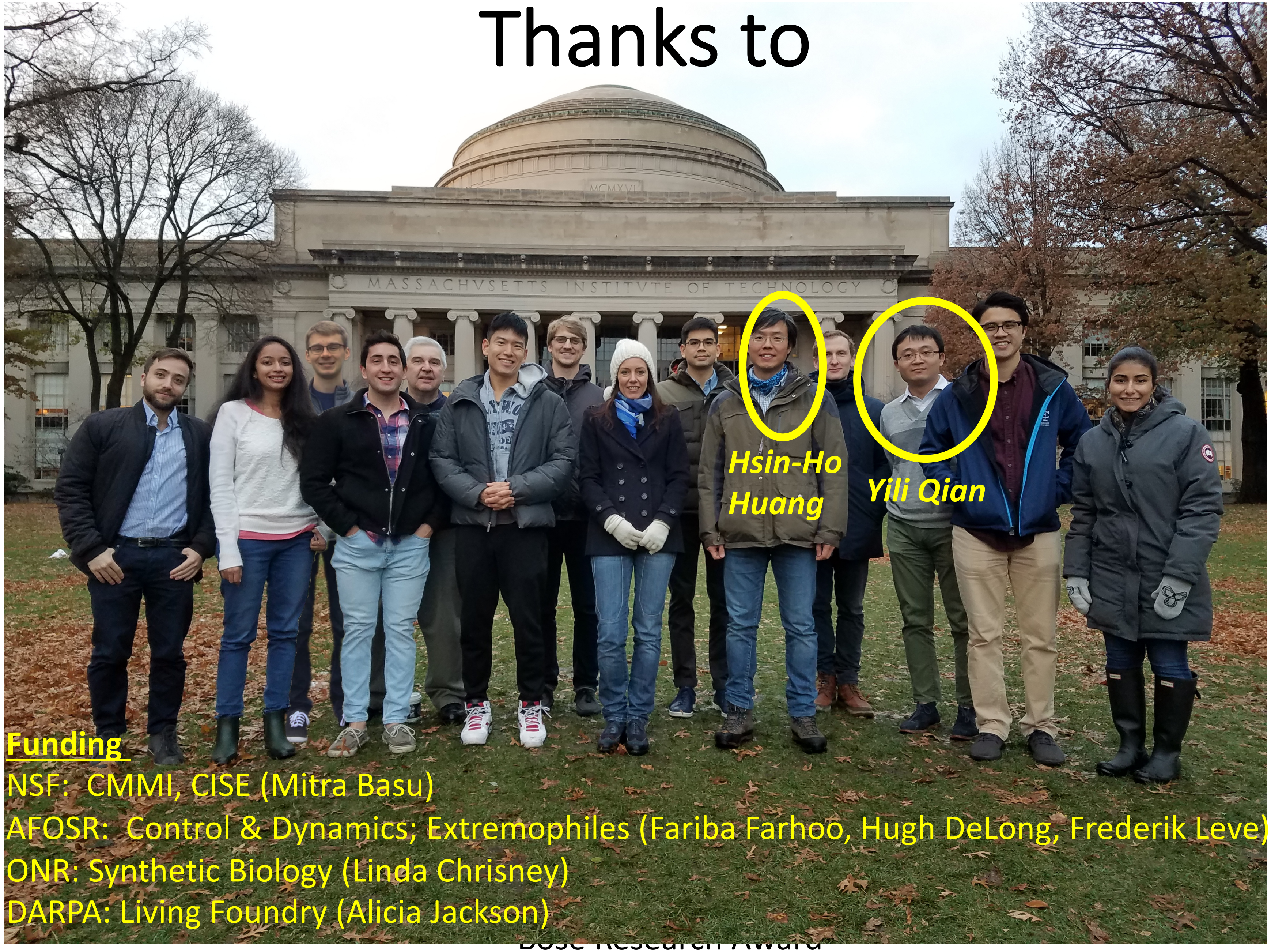

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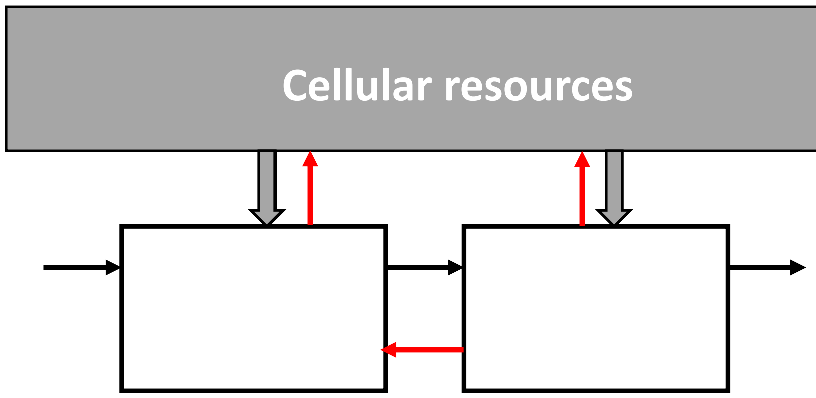
Summary



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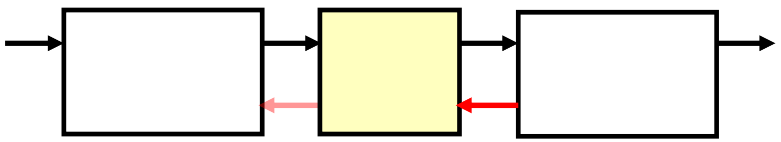

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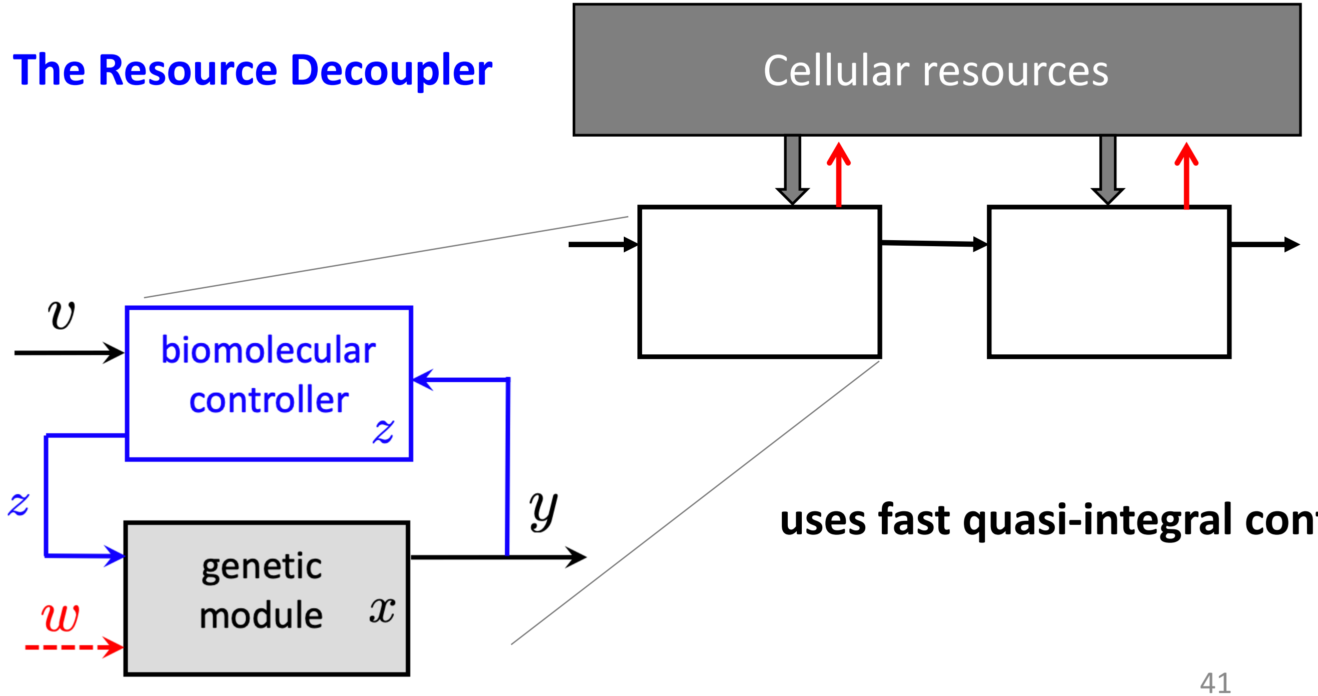

uses fast quasi-integral control