Exploiting the Nonlinear Structure of the Antithetic Integral Controller to Enhance Dynamic Performance

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Department of Biosystems Science and Engineering, ETHz

December 6, 2022

DBSSE

ETH zürich

European Research Council
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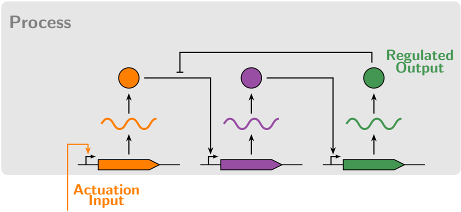
Robust Perfect Adaptation (RPA)



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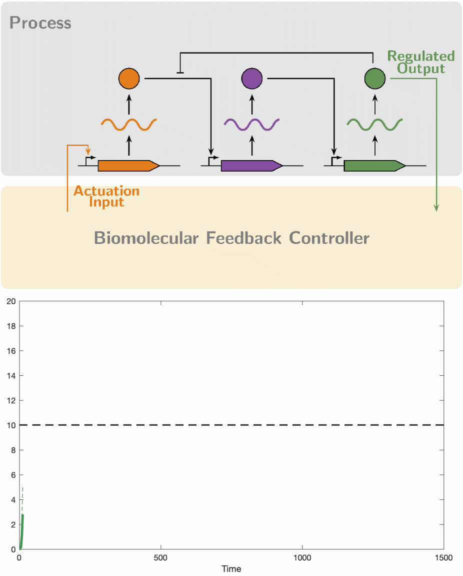
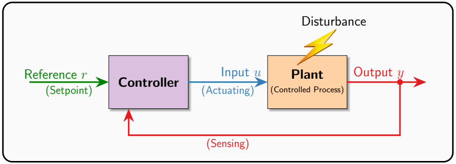
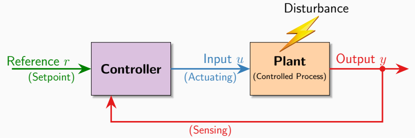


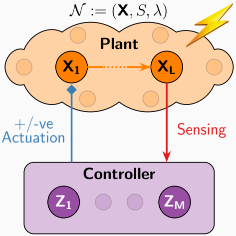
Robust Steady-State Tracking or RPA in biology

Framework for Biomolecular Feedback Control



Framework for Biomolecular Feedback Control

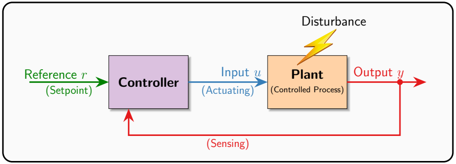


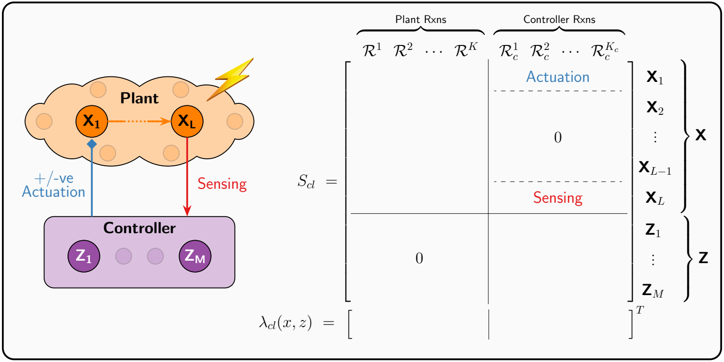


$$S_{cl} = \begin{bmatrix} \\ \end{bmatrix}$$

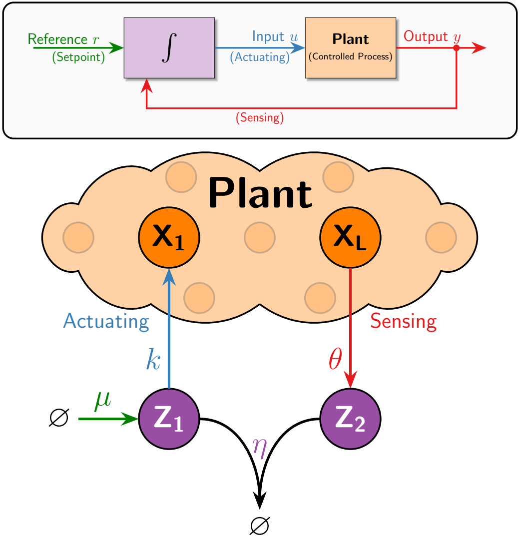
$$\lambda_{cl}(x, z) = \begin{bmatrix} \end{bmatrix}^T$$

Framework for Biomolecular Feedback Control



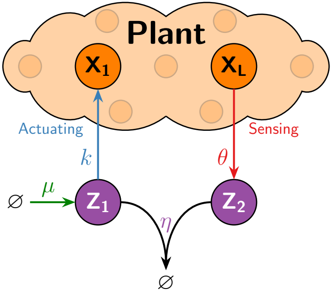


RPA $\iff$ Antithetic Integral Feedback (AIF) Control



Briat, C., Gupta, A., & Khammash, M. (2016). Antithetic integral feedback ensures robust perfect adaptation in noisy biomolecular networks. Cell systems, 2(1), 15-26.

RPA $\iff$ Antithetic Integral Feedback (AIF) Control



$\mathcal{R}_r$: Reference Reaction	$\varnothing \xrightarrow{\mu} Z_1$
$\mathcal{R}_s$: Sensing Reaction	$X_L \xrightarrow{\theta} X_L + Z_2$
$\mathcal{R}_q$: Sequestration Reaction	$Z_1 + Z_2 \xrightarrow{\eta} \varnothing$
$\mathcal{R}_a$: Actuation Reaction	$Z_1 \xrightarrow{k} Z_1 + X_1$

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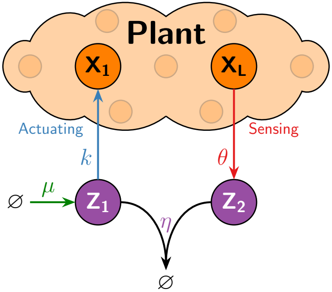

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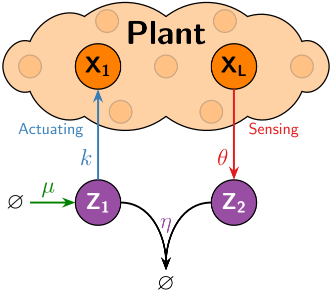
Deterministic Setting

RPA $\iff$ Antithetic Integral Feedback (AIF) Control



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Deterministic Setting

ODE: $x_i, z_j \rightarrow$ concentrations

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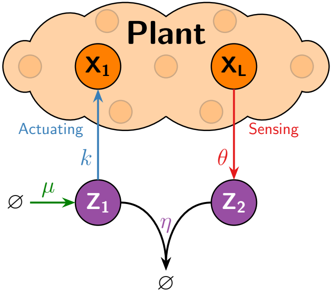

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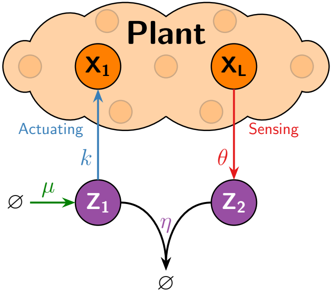
Deterministic Setting

ODE: $x_i, z_j \rightarrow$ concentrations

$$\frac{d}{dt} z_1 = \mu - \eta z_1 z_2$$

$$\frac{d}{dt} z_2 = \theta x_L - \eta z_1 z_2$$

RPA $\iff$ Antithetic Integral Feedback (AIF) Control



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Deterministic Setting

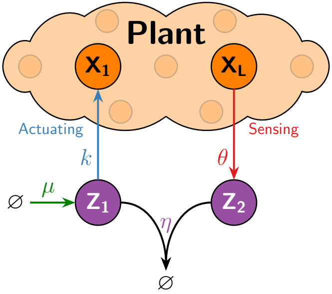
ODE: $x_i, z_j \rightarrow$ concentrations

$$\frac{d}{dt}z_1 = \mu - \eta z_1 z_2$$

$$\frac{d}{dt}z_2 = \theta x_L - \eta z_1 z_2$$

$\overset{\text{Stability}}{\Longrightarrow} \lim_{t\to\infty} x_L(t) = \frac{\mu}{\theta}$ RPA ✓

RPA $\iff$ Antithetic Integral Feedback (AIF) Control



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Deterministic Setting

ODE: $x_i, z_j \to$ concentrations

$$\frac{d}{dt}z_1 = \mu - \eta z_1 z_2$$

$$\frac{d}{dt}z_2 = \theta x_L - \eta z_1 z_2$$

Stability $\Longrightarrow$ $\lim_{t\to\infty} x_L(t) = \frac{\mu}{\theta}$ RPA ✓

Stochastic Setting

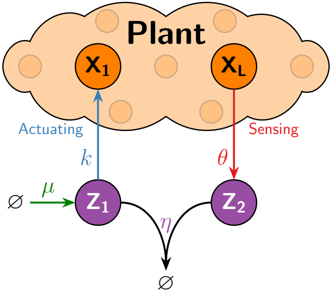
CTMC: $X_i, Z_j \to$ copy #

$$\frac{d}{dt}\mathbb{E}[Z_1] = \mu - \eta\mathbb{E}[Z_1 Z_2]$$

$$\frac{d}{dt}\mathbb{E}[Z_2] = \theta\mathbb{E}[X_L] - \eta\mathbb{E}[Z_1 Z_2]$$

Ergodicity $\Longrightarrow$ $\lim_{t\to\infty} \mathbb{E}[X_L(t)] = \frac{\mu}{\theta}$ RPA ✓

RPA $\iff$ Antithetic Integral Feedback (AIF) Control



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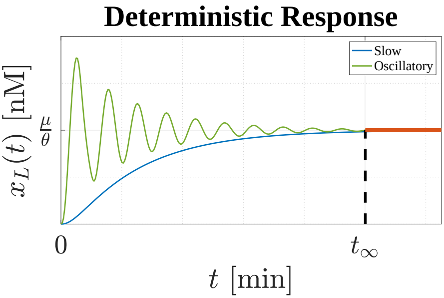
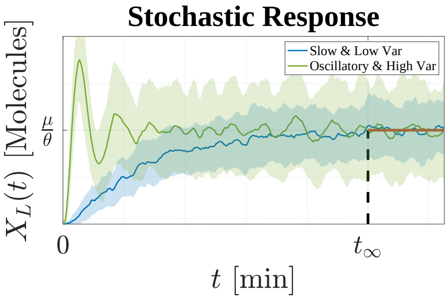
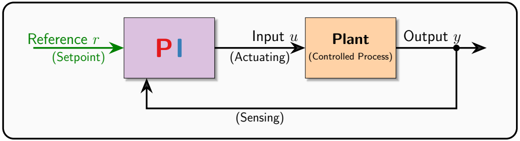
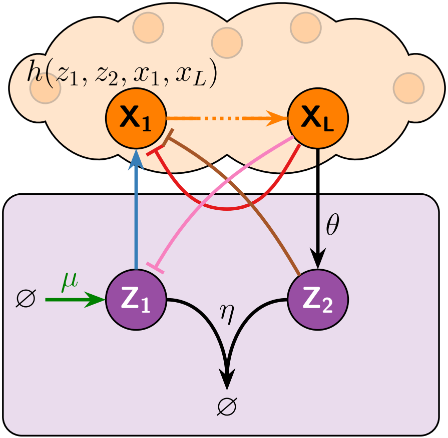




Biomolecular PI Controllers





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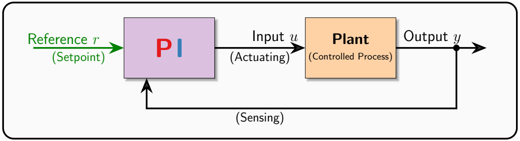

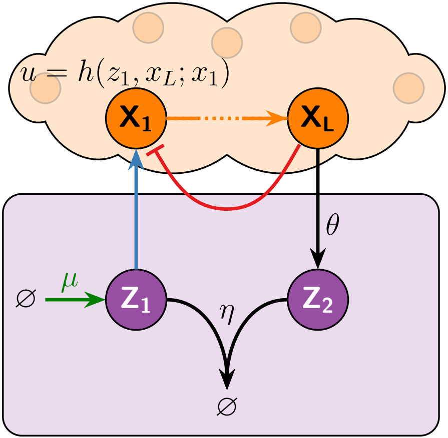

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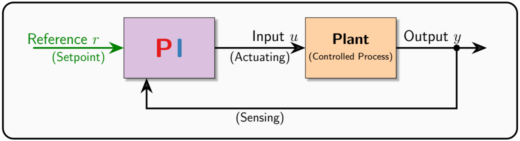
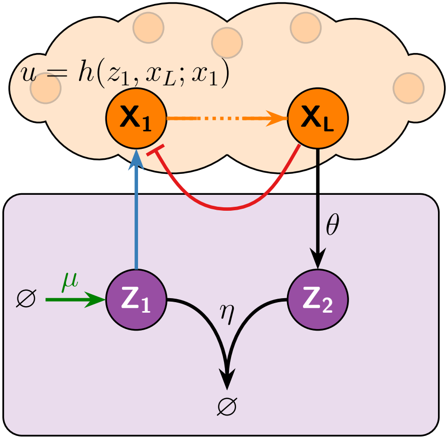
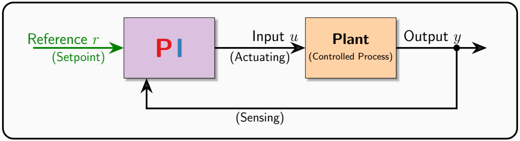
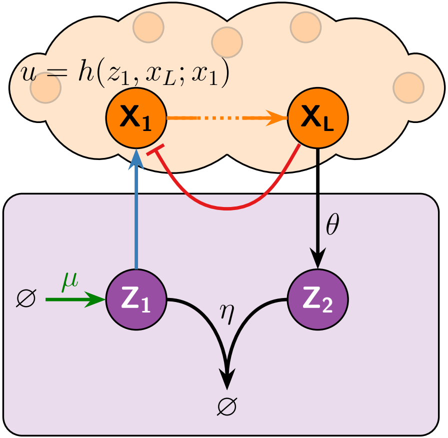




Actuation Mechanisms

Biomolecular PI Controllers





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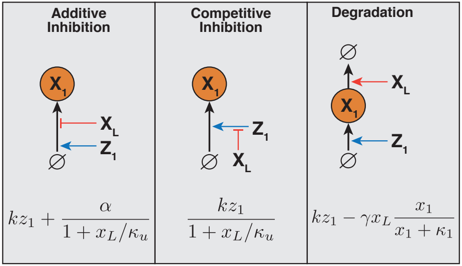

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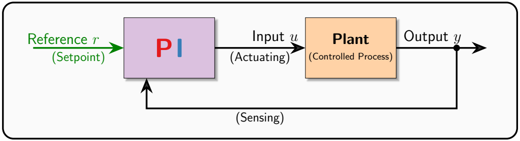

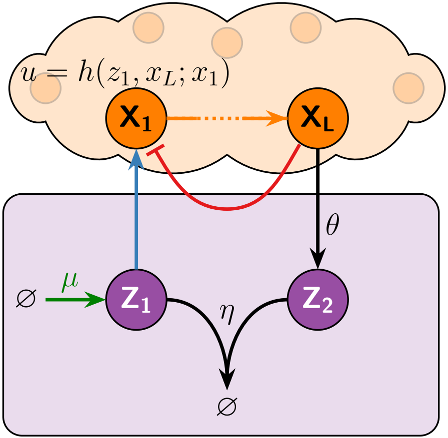

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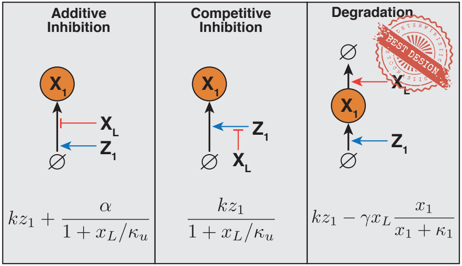
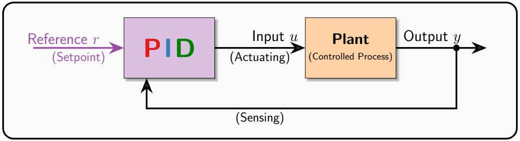
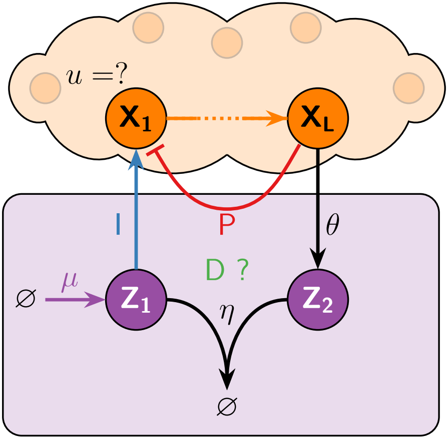


Biomolecular PID Controllers





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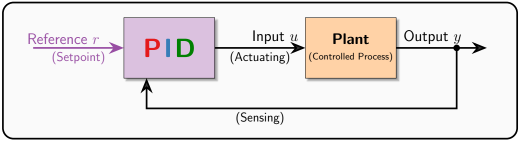

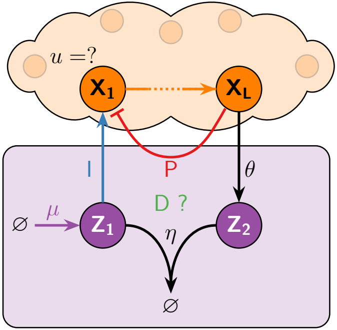

Chevalier, Michael, et al. "Design and analysis of a proportional-integral-derivative controller with biological molecules." Cell systems

Alexis, Emmanouil, et al. "Biomolecular mechanisms for signal differentiation." Iscience

Modi, Saurabh, et al. "Noise suppression in stochastic genetic circuits using pid controllers. "PLoS Computational Biology

Whitby, Max, et al. "PID control of biochemical reaction networks." IEEE Transactions on Automatic Control

Paulino, Nuno MG, et al. "PID and state feedback controllers using DNA strand displacement reactions." IEEE Control Systems Letters

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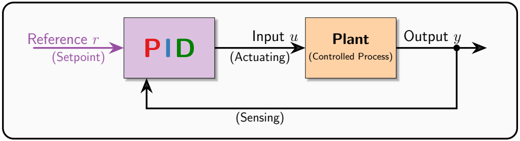

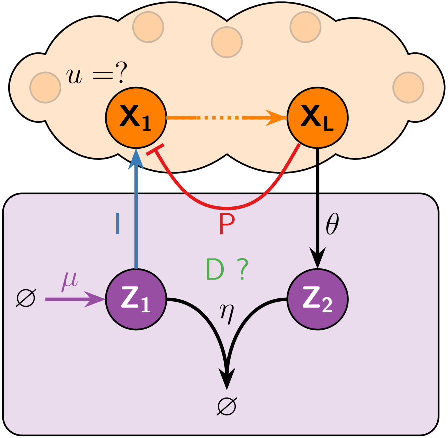

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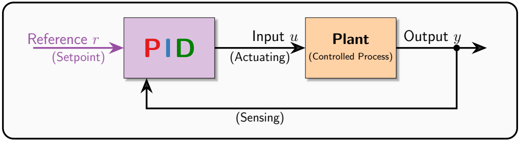
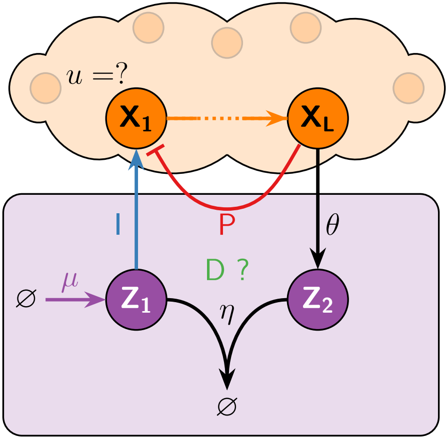
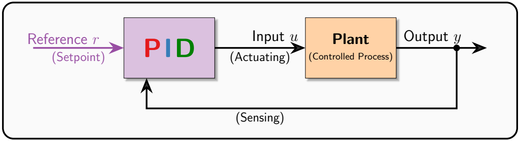
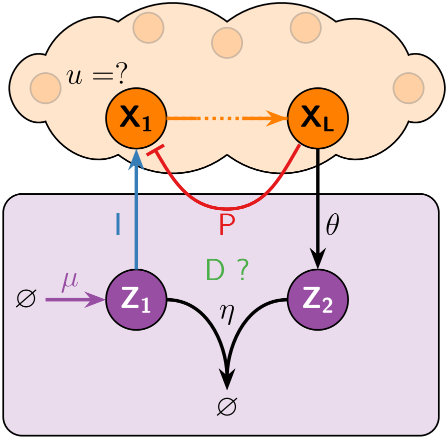




2 Approaches to Realize the D:

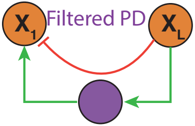
Biomolecular PID Controllers





2 Approaches to Realize the D:

1. Incoherent FeedForward Loop



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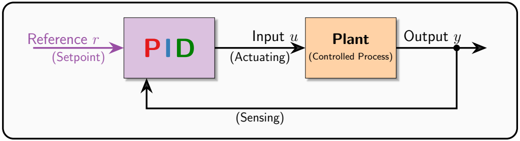

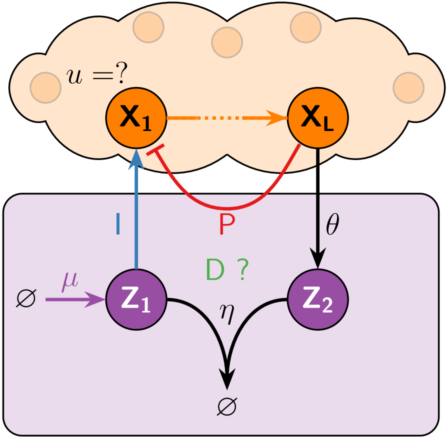

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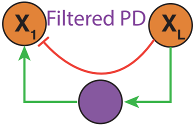
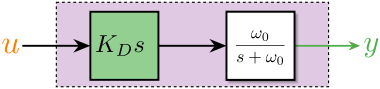
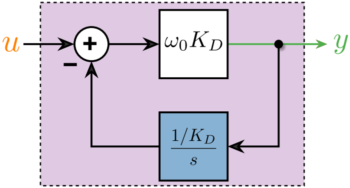


2. Integrators in Feedback

Filtered Derivative

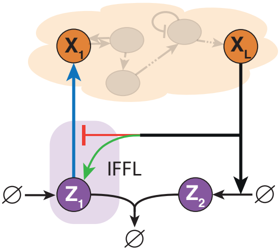


$$\frac{y(s)}{u(s)} = K_D s \frac{\omega_0}{s+\omega_0}$$



A Hierarchy of Biomolecular PID Controllers

2nd-order
IFFL-based PID



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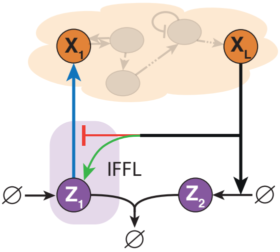
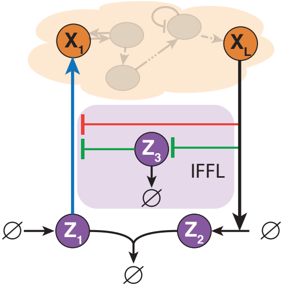


3^{rd}-order
IFFL-based PID



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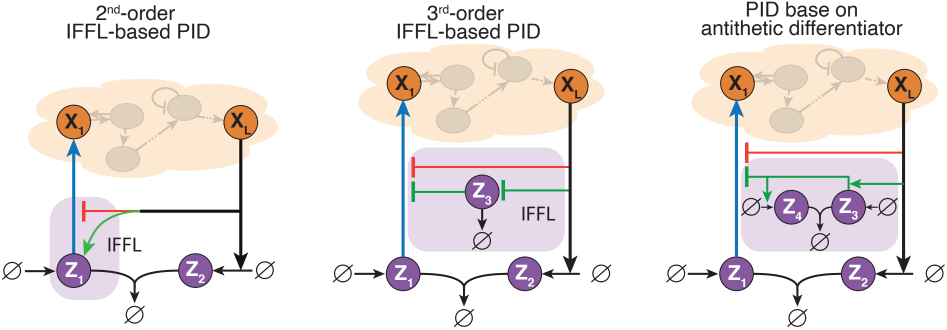

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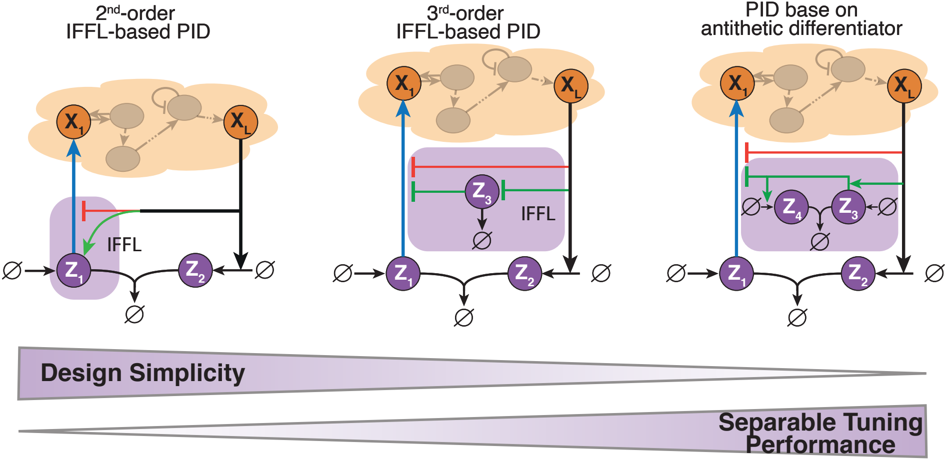
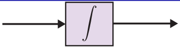
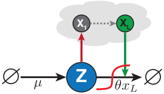


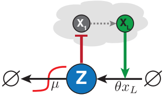
Filo, M., Kumar, S., & Khammash, M. (2022). A hierarchy of biomolecular proportional-integral-derivative feedback controllers for robust perfect adaptation and dynamic performance. Nature communications, 13(1), 1-19.

Alternative PIDs based on Different Integrators





outflow
zero-order



inflow
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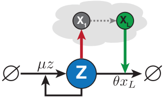

auto-catalytic

Ni, X. Y., Drengstig, T., & Ruoff, P. (2009). The control of the controller: molecular mechanisms for robust perfect adaptation and temperature compensation. Biophysical journal

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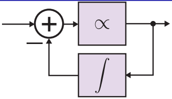
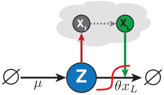
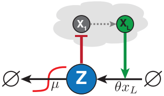
Alternative PIDs based on Different Integrators





outflow
zero-order



inflow
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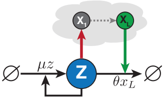
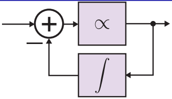
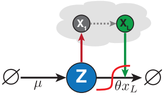


auto-catalytic

Alternative PIDs based on Different Integrators





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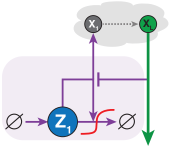

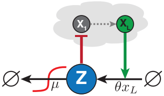

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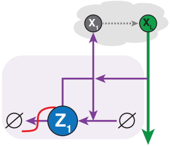

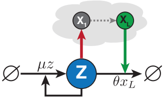

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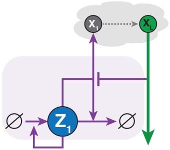

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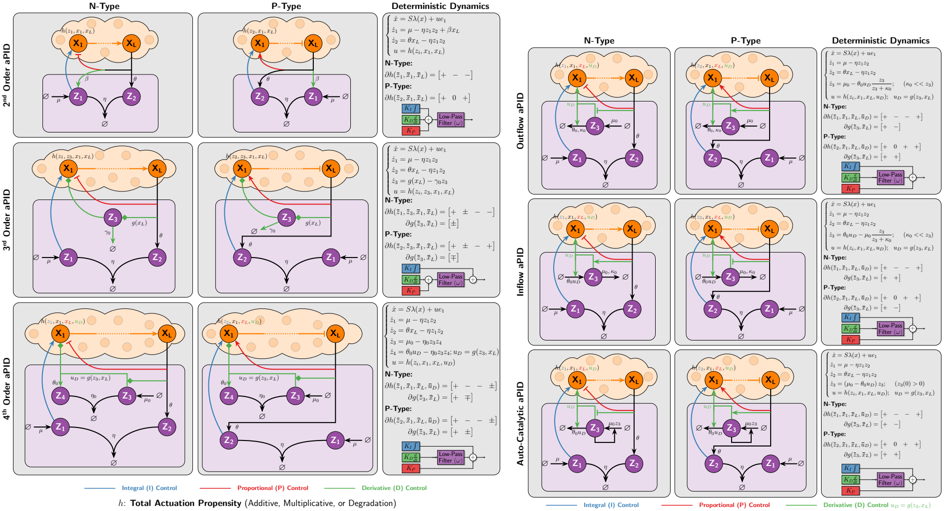
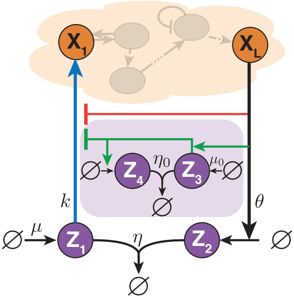
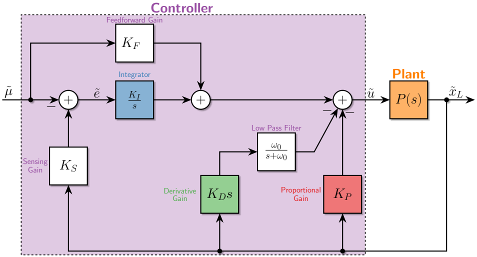


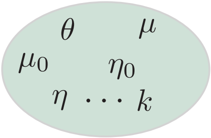
Filo, M., Kumar, S., & Khammash, M. (2022). A hierarchy of biomolecular proportional-integral-derivative feedback controllers for robust perfect adaptation and dynamic performance. Nature communications, 13(1), 1-19.

PID Coverage

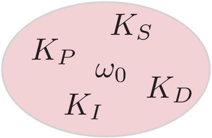




Biomolecular Parameters



PID Parameters



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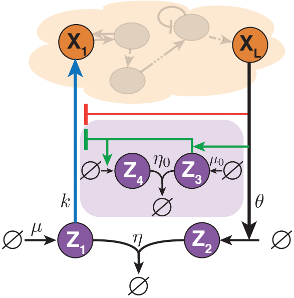

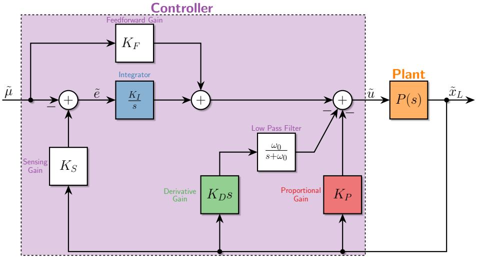

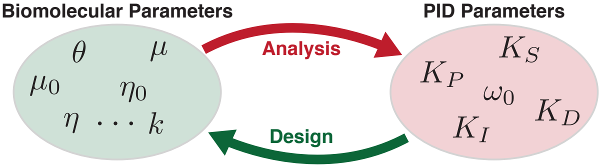

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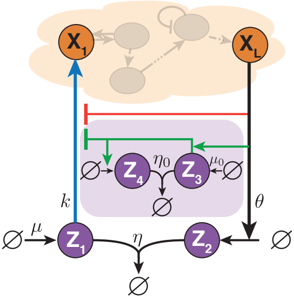

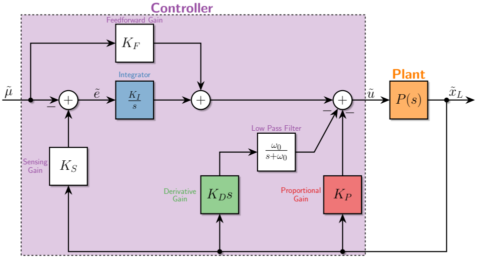

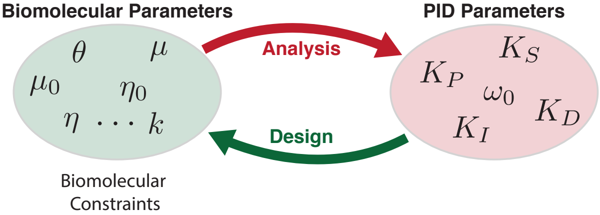

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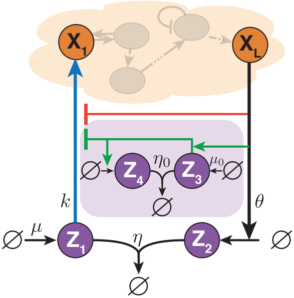
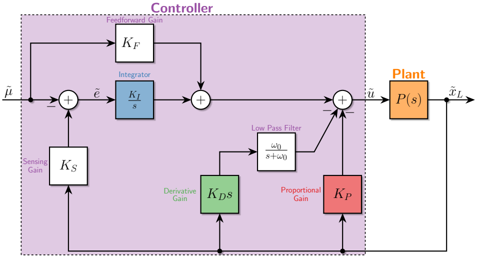
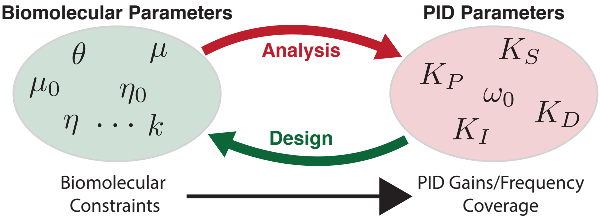






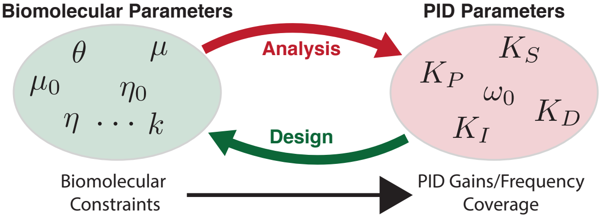
PID Coverage

2nd Order PID:

3rd Order PID:

4th Order PID:

$\mathcal{S}_4 = \left\{ (K_P, K_I, K_D, \omega_0) \in \mathbb{R}^4 : \ K_P, K_I, K_D, \omega_0 \geq 0 \right\}$



PID Coverage

2nd Order PID:

3rd Order PID:
$\mathcal{S}_3 = \left\{(K_P, K_I, K_D, \omega_0) \in \mathbb{R}^4 : \ K_P \leq K_D\omega_0, \ K_I, K_D, \omega_0 \geq 0\right\}$

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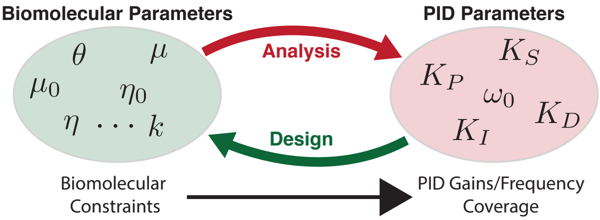

PID Coverage

2nd Order PID:

$$\mathcal{S}_2 = \left\{(K_P, K_I, K_D, \omega_c) \in \mathbb{R}^4 : \ K_P \leq K_D\omega_c, \ 0 \leq K_I \leq \frac{\omega_c}{4\mu}\frac{(\bar{u} + rK_P)^2}{\bar{u} + rK_D\omega_c}, \ K_D, \omega_c \geq 0\right\}$$

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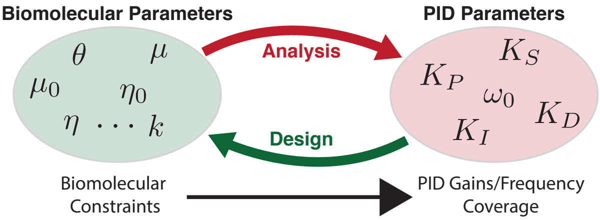

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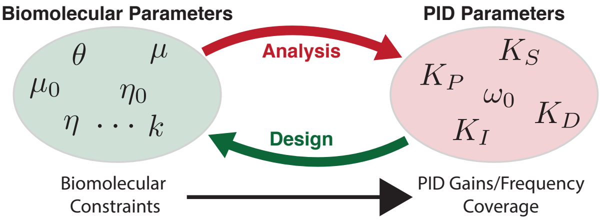
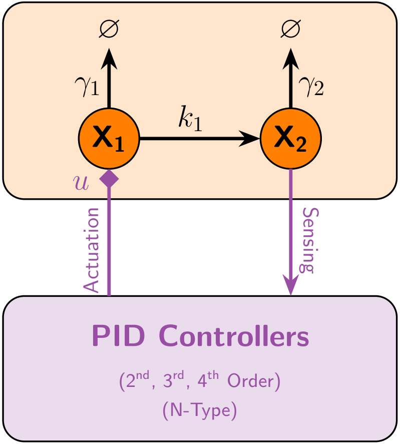
$$\Longrightarrow \quad \text{Over } \mathbb{R}_+^4 :\ \mathcal{S}_2 \subset \mathcal{S}_3 \subset \mathcal{S}_4$$



Dynamic Performance



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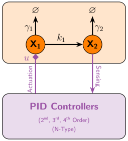
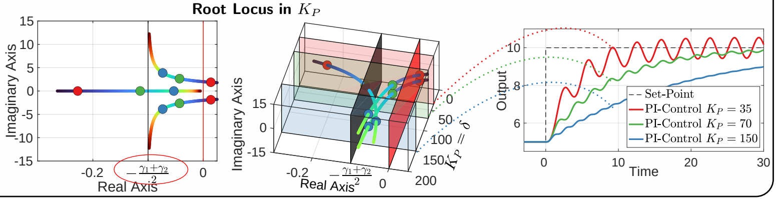


Performance Limitation of PI Controllers



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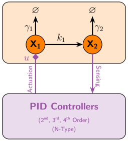

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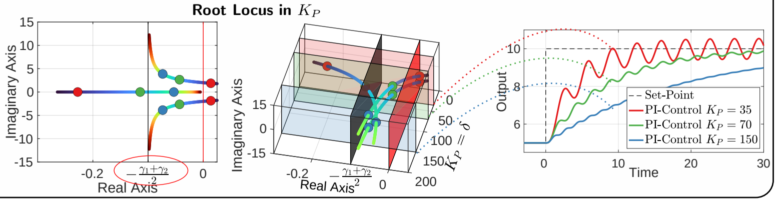
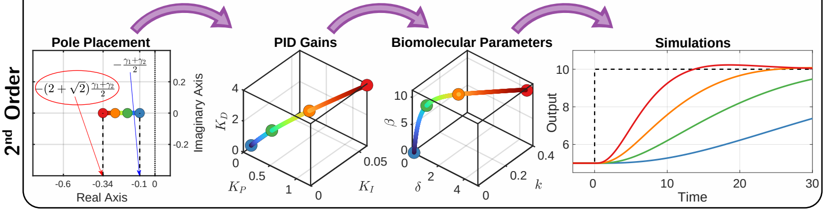
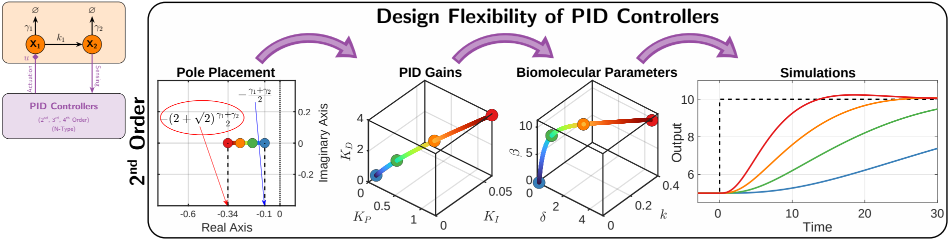


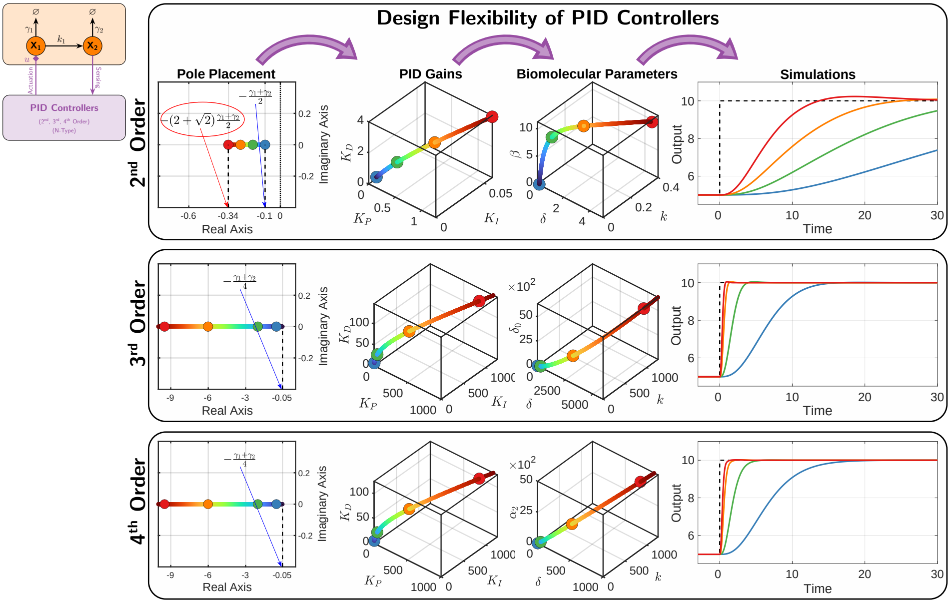
Design Flexibility of PID Controllers



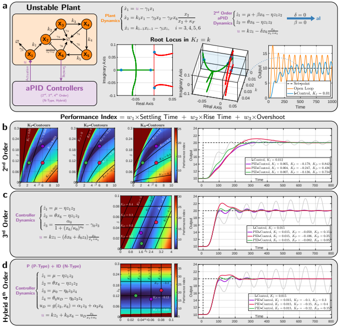
Dynamic Performance

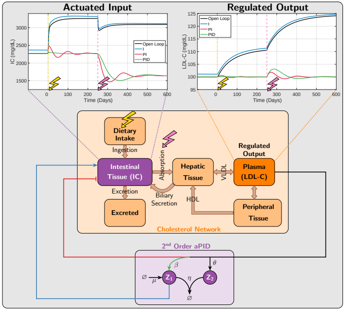


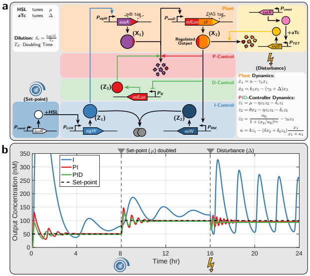
Dynamic Performance



Higher Dimensional Plants & Genetic Designs







Stochastic Setting & Cyberloop Experiments

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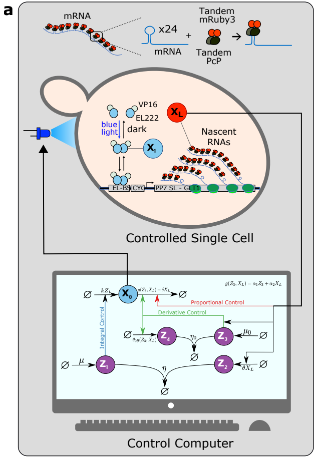

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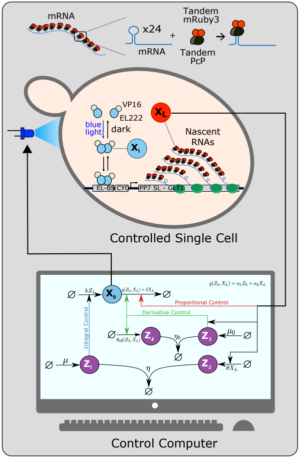
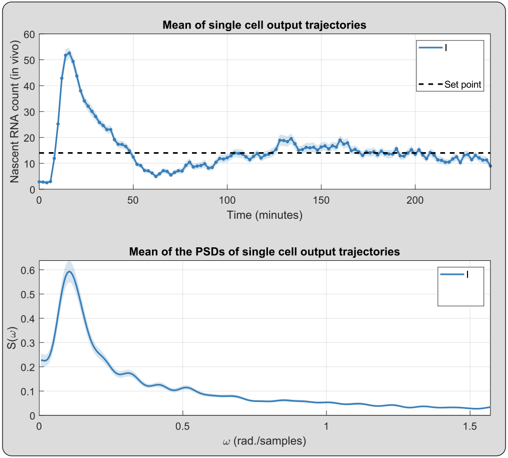
a



b



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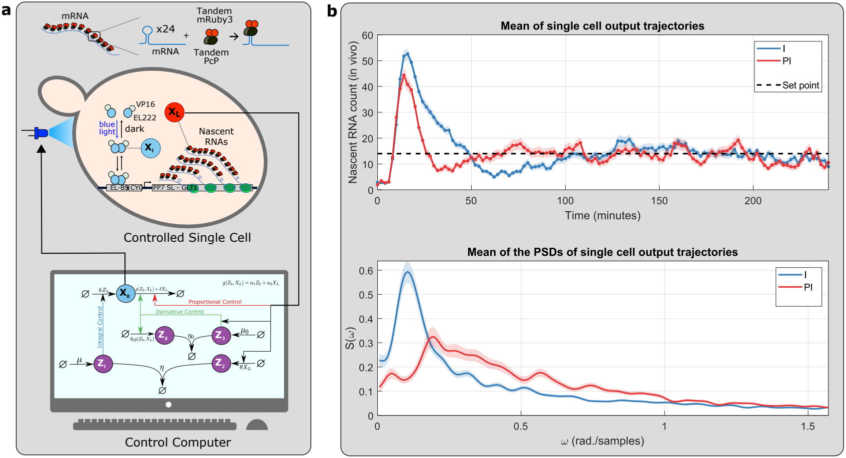

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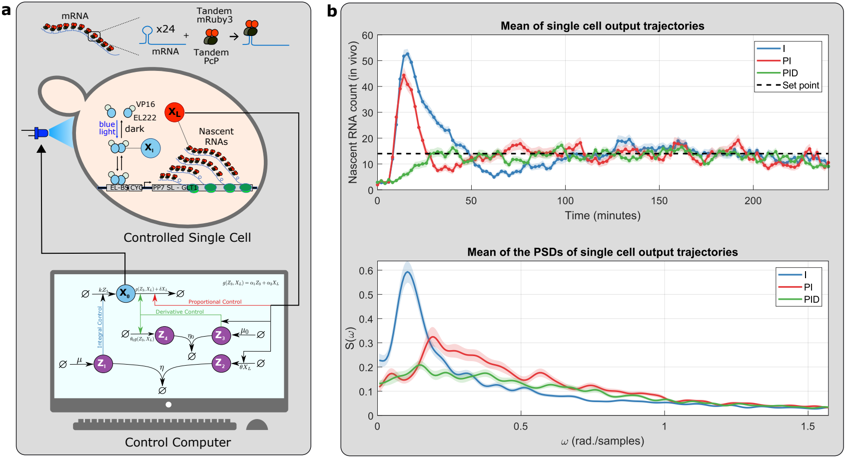
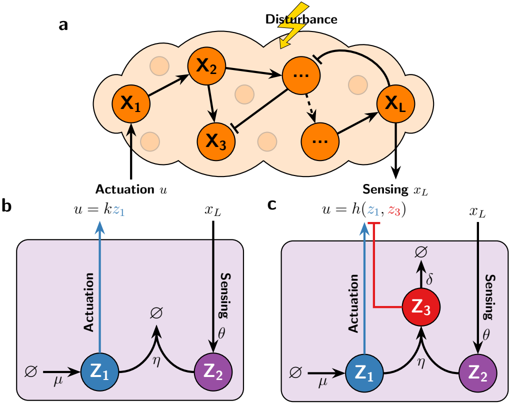


Exploiting the Nonlinearity of the Antithetic Motif



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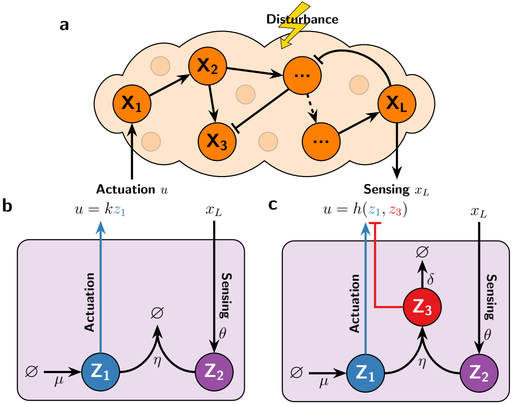
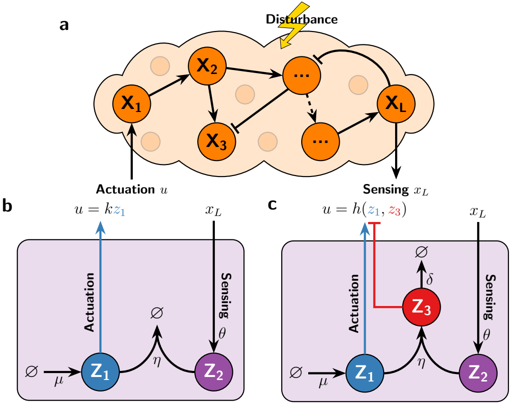


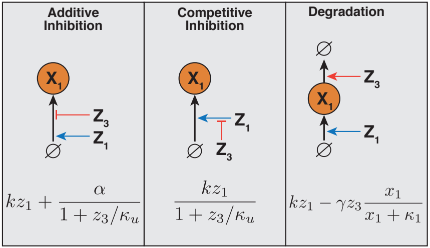
$$\dot{x} = f(x) + ue_1$$

$$\begin{cases} \dot{z}_1 = \mu - \eta z_1 z_2 \\ \dot{z}_2 = \theta x_L - \eta z_1 z_2 \end{cases} \qquad \begin{cases} \dot{z}_1 = \mu - \eta z_1 z_2 \\ \dot{z}_2 = \theta x_L - \eta z_1 z_2 \\ \dot{z}_3 = \eta z_1 z_2 - \delta z_3 \end{cases}$$

$$u = kz_1 \qquad u = h\left(z_1, z_3; x_1\right)$$



Actuation Mechanisms



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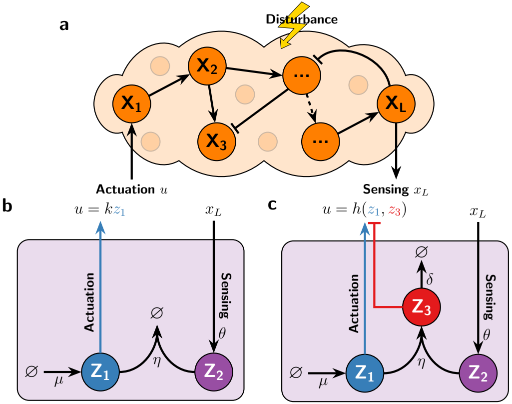
Exploiting the Nonlinearity of the Antithetic Motif



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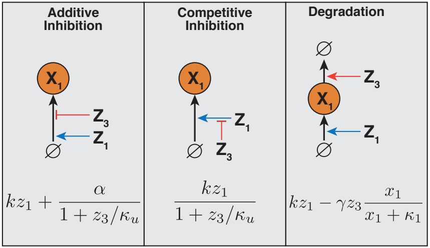
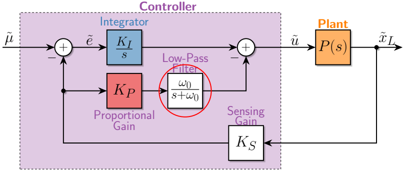
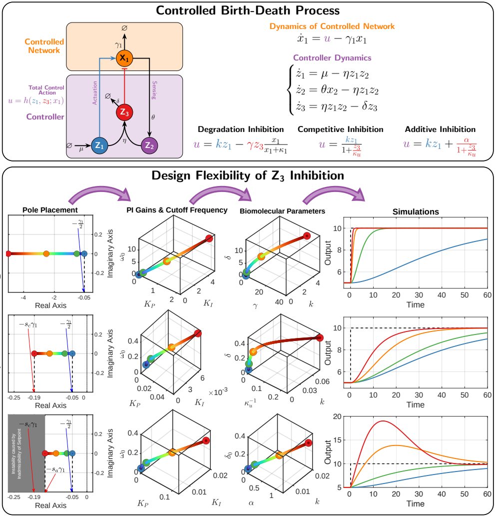


Underlying Controller Structure



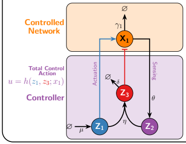
Filtered PI Controller

Sequestration Complex Enhances Dynamic Performance



Sequestration Complex Enhances Dynamic Performance

Controlled Birth-Death Process



Dynamics of Controlled Network

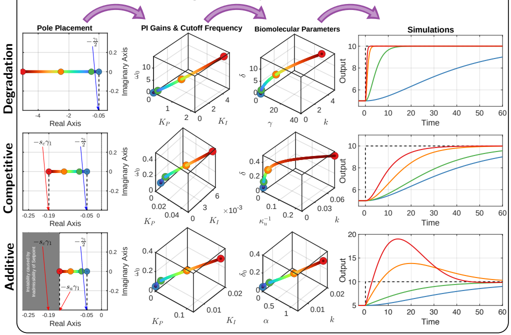
$$\dot{x}_1 = u - \gamma_1 x_1$$

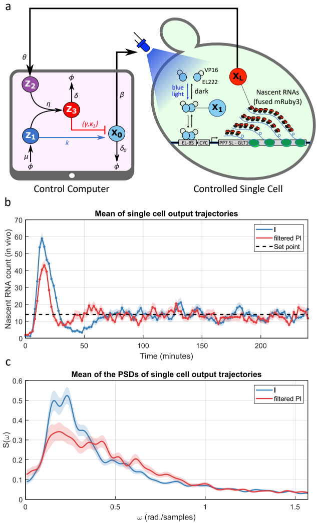
Controller Dynamics

$$\begin{cases} \dot{z}_1 = \mu - \eta z_1 z_2 \\ \dot{z}_2 = \theta x_2 - \eta z_1 z_2 \\ \dot{z}_3 = \eta z_1 z_2 - \delta z_3 \end{cases}$$

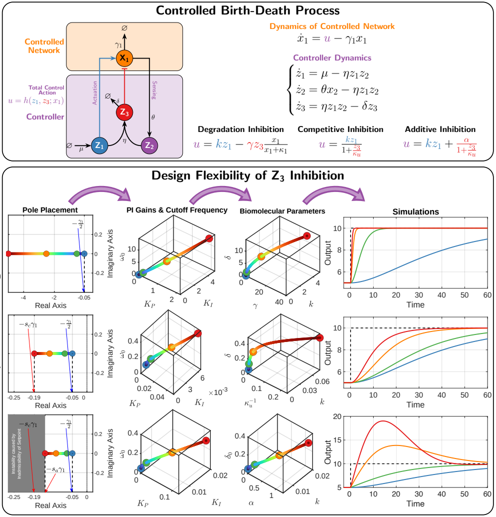
Degradation Inhibition	Competitive Inhibition	Additive Inhibition
$u = kz_1 - \gamma z_3 \frac{x_1}{x_1+\kappa_1}$	$u = \frac{kz_1}{1+\frac{z_3}{\kappa_u}}$	$u = kz_1 + \frac{\alpha}{1+\frac{z_3}{\kappa_u}}$

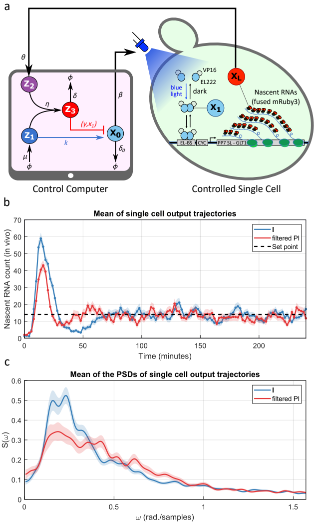
Design Flexibility of Z_3 Inhibition





Sequestration Complex Enhances Dynamic Performance





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