# Optimal Parameter Tuning of Feedback Controllers
## with Application to Biomolecular Antithetic Integral Control

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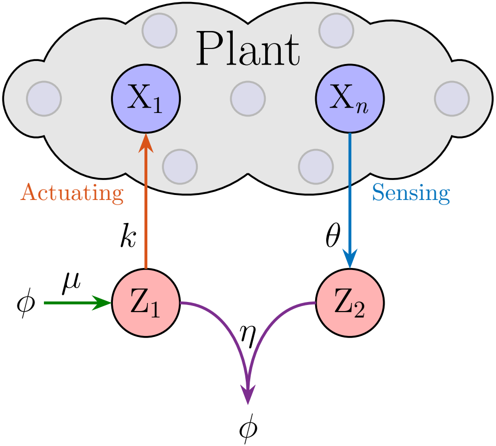
DBSSE

ETH zürich

# Motivation: transient dynamics are ALSO important

Arbitrary plant in feedback with Antithetic Integral Controller (AIC) [1]




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

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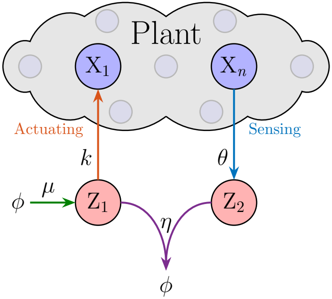


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| $\mathcal{R}_r$: Reference Reaction | $\phi \xrightarrow{\mu} Z_1$ |
| $\mathcal{R}_s$: Sensing Reaction | $X_n \xrightarrow{\theta} X_n + Z_2$ |
| $\mathcal{R}_q$: Sequestration Reaction | $Z_1 + Z_2 \xrightarrow{\eta} \phi$ |
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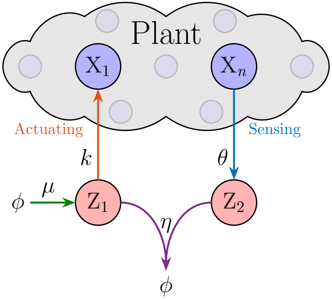


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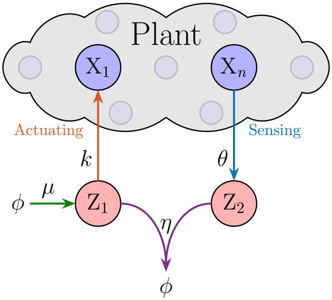


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**Deterministic Setting**

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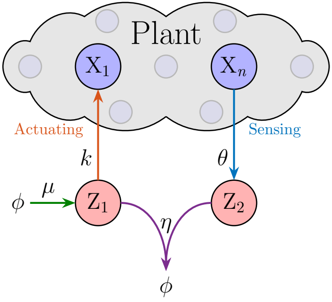


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ODE: $x_i, z_j \rightarrow$ concentrations

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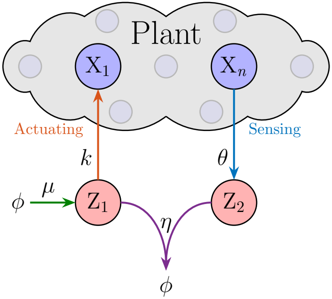


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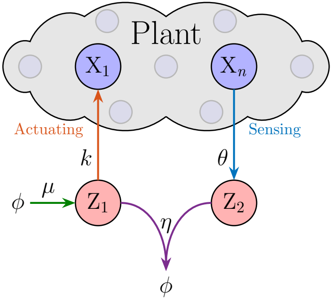


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$$\overset{\text{Stability}}{\Longrightarrow} \lim_{t\to\infty} x_n(t) = \frac{\mu}{\theta}$$

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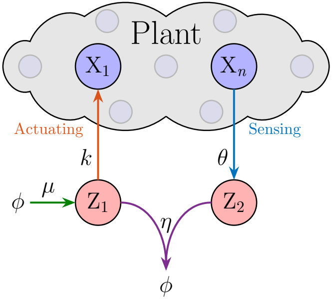


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$\overset{\text{Stability}}{\Longrightarrow} \lim_{t \to \infty} x_n(t) = \frac{\mu}{\theta}$ RPA ✓

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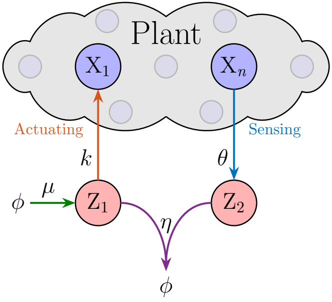


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**Stochastic Setting**

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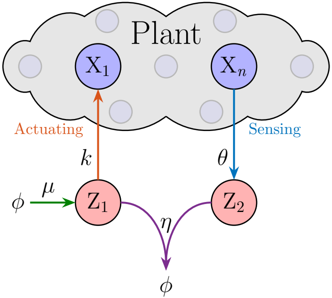


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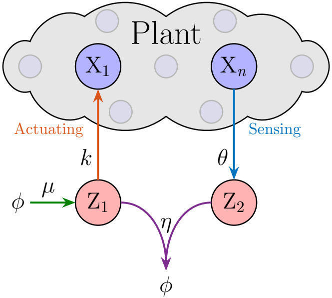
$\overset{\text{Stability}}{\Longrightarrow} \lim_{t \to \infty} x_n(t) = \frac{\mu}{\theta}$ RPA ✓

**Stochastic Setting**

CTMC: $X_i, Z_j \rightarrow$ copy #

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**Stochastic Setting**

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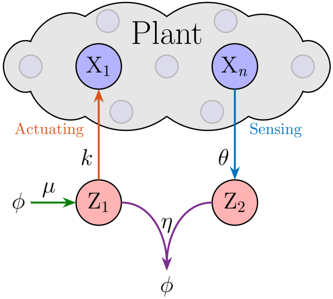


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**Stochastic Setting**

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$$\overset{\text{Ergodicity}}{\Longrightarrow} \lim_{t\to\infty} \mathbb{E}[X_n(t)] = \frac{\mu}{\theta}$$

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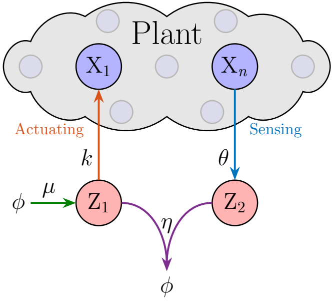


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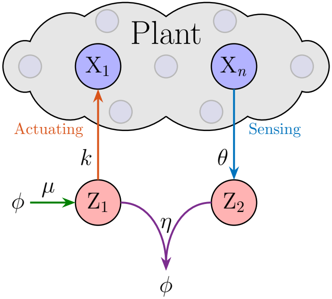
$\overset{\text{Ergodicity}}{\Longrightarrow} \lim_{t \to \infty} \mathbb{E}[X_n(t)] = \frac{\mu}{\theta}$ RPA ✓

# Motivation: transient dynamics are ALSO important




| | |
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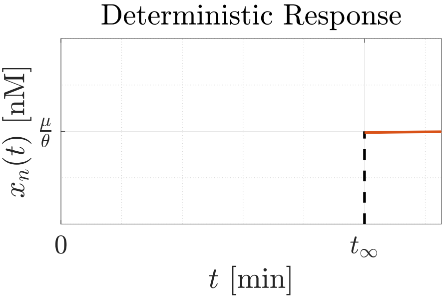

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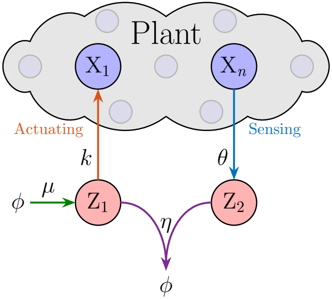


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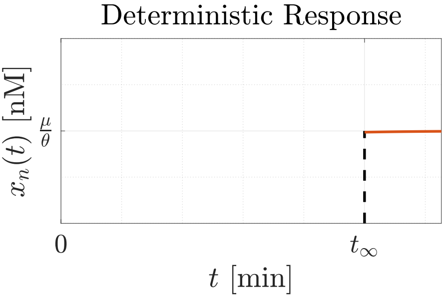

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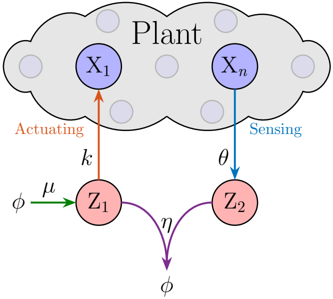


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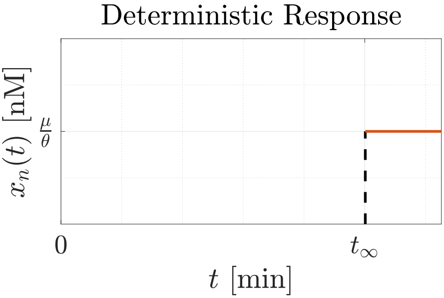

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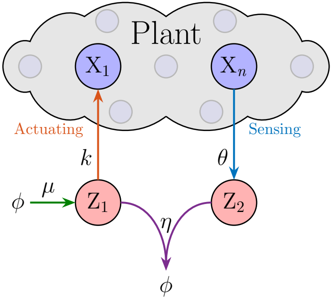


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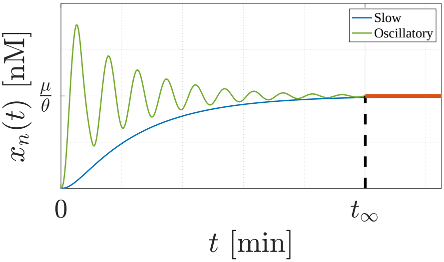
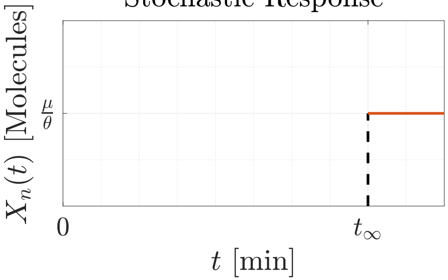
Deterministic Response




Stochastic Response



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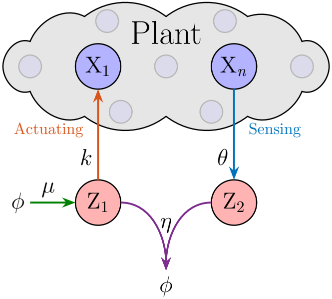


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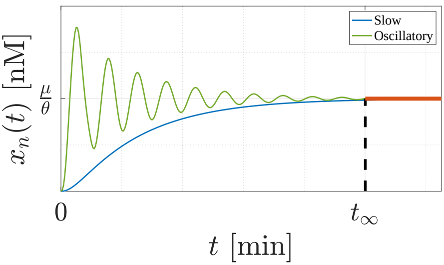


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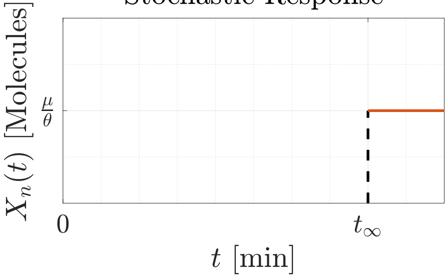

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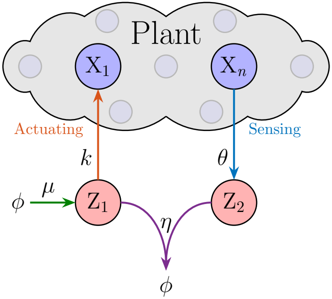


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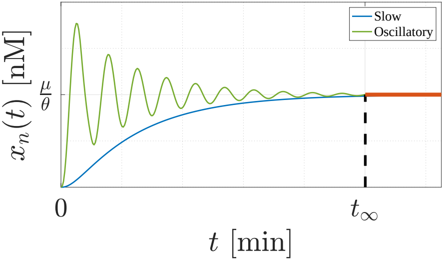
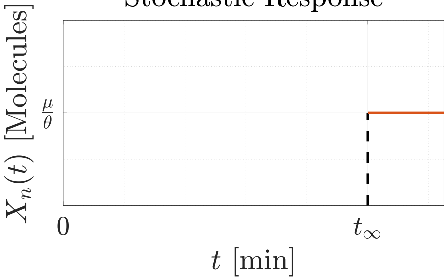



Stochastic Response



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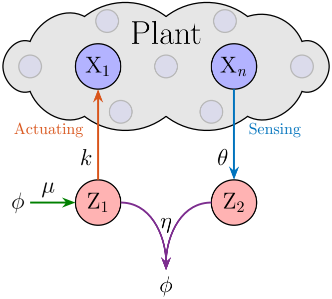


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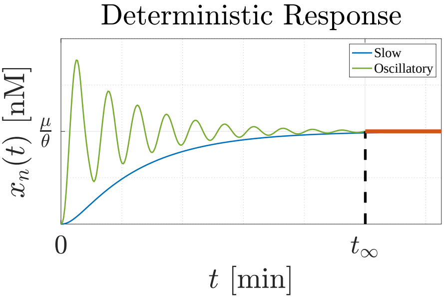


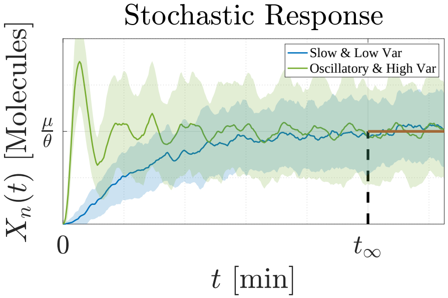

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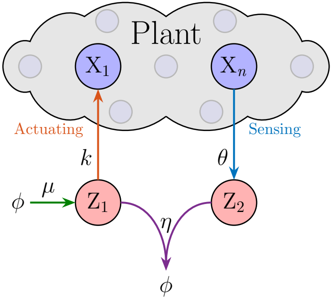
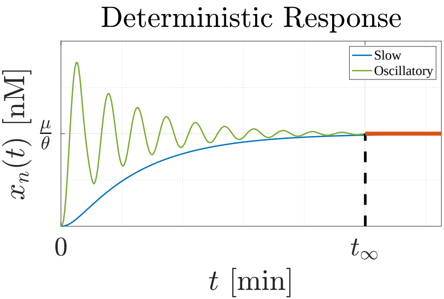
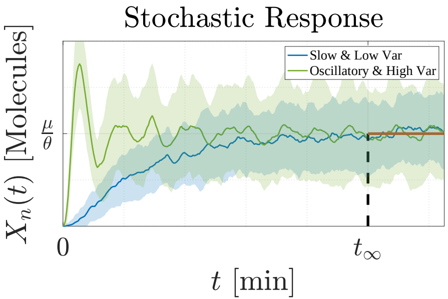



- $t_\infty$ can be very large



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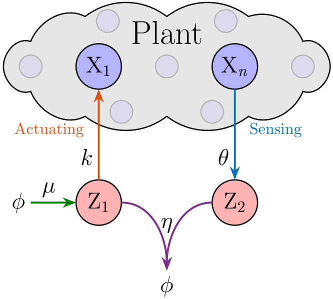
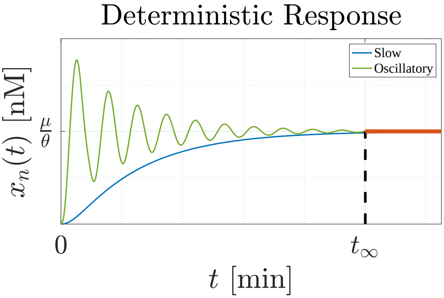
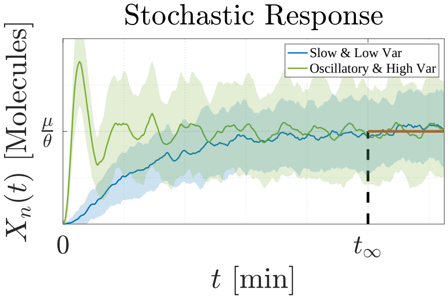



- $t_\infty$ can be very large
- Transients can be destructive



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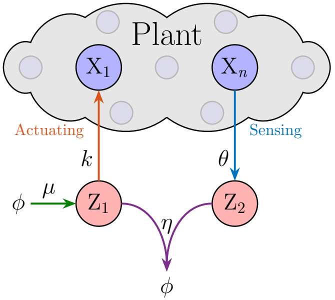
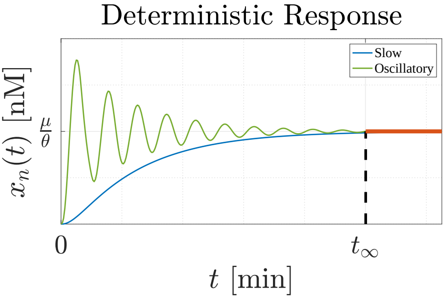
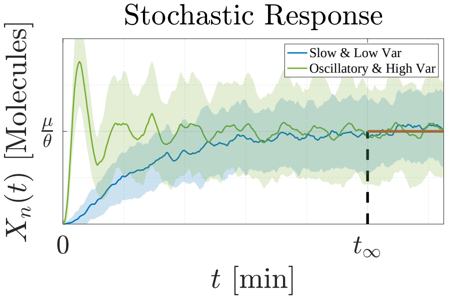



- $t_\infty$ can be very large
- Transients can be destructive
- Variance can be very large



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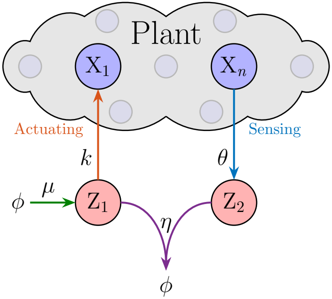
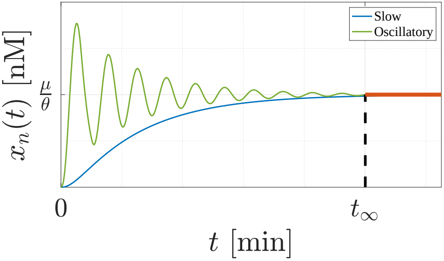


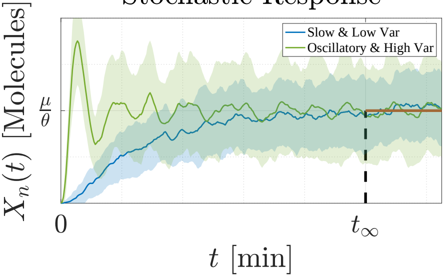

- $t_\infty$ can be very large
- Transients can be destructive
- Variance can be very large

$\Longrightarrow$ RPA practically destroyed

Deterministic Response




Stochastic Response



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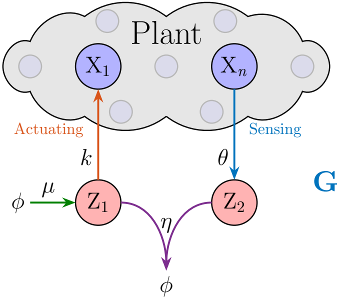


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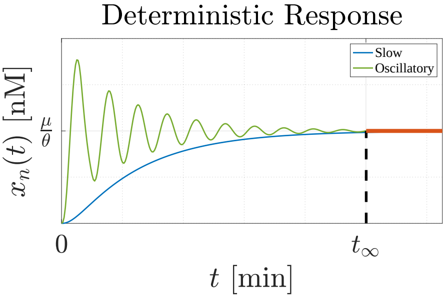
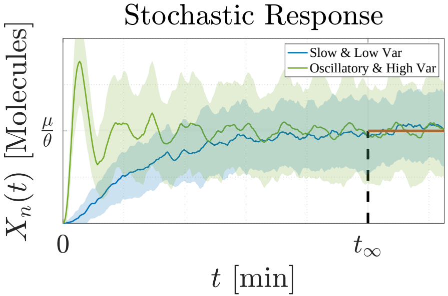
**Goal**: Attempt to fix this ...



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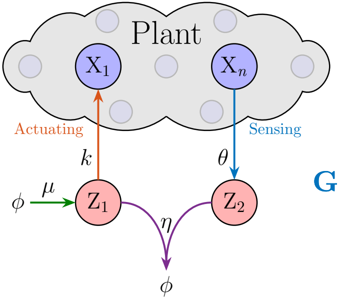


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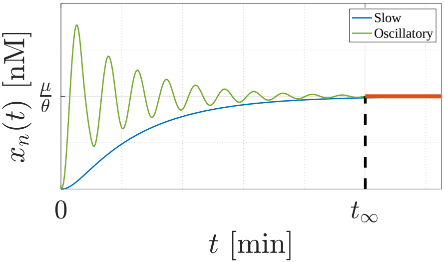
**Goal**: Attempt to fix this ...

- **Approach 1**: Optimal Parameter Tuning
- **Approach 2**: Control Architectures

Deterministic Response

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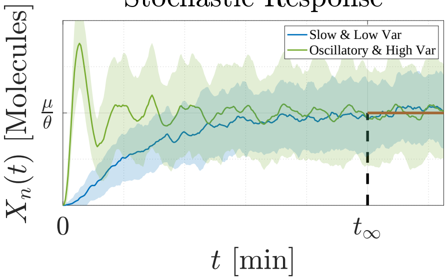
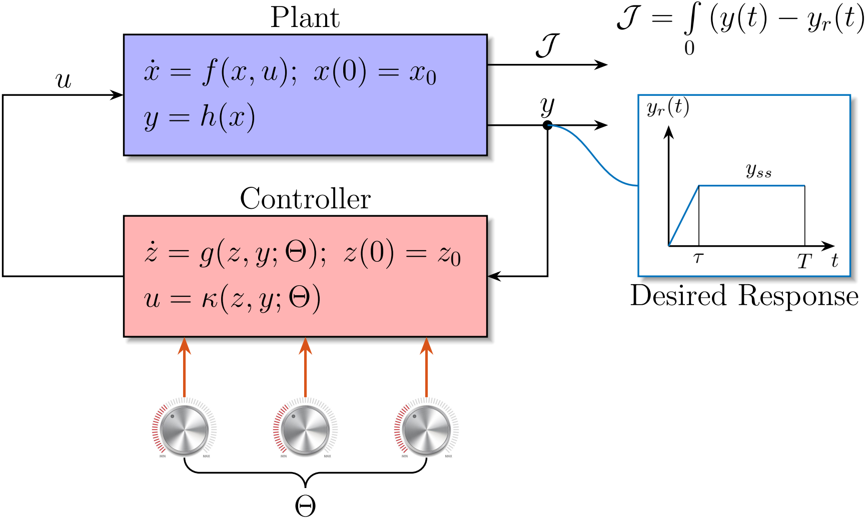


# Optimization Problem Statement

$$\mathcal{J} = \int_0^T \left(y(t) - y_r(t)\right)^2 dt$$



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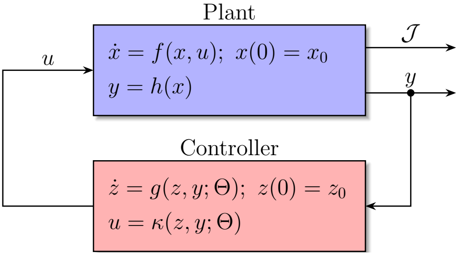



## Dynamically Constrained Optimization Problem

$$\underset{\Theta}{\text{minimize}} \quad \mathcal{J}(y;\Theta) \qquad \text{Cost Function}$$

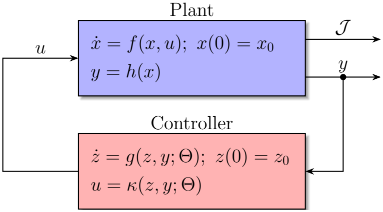
$$\text{subject to} \quad \begin{cases} \dot{x} = f(x,u,w); & x(0) = x_0 \\ y = h(x) & \text{Plant Dynamics} \\ \dot{z} = g(z,y,v;\Theta); & z(0) = z_0 \\ u = \kappa(z,y,v;\Theta) & \text{Controller Dynamics} \end{cases}$$

# Conversion to an Unconstrained Optimization Problem

## Constrained Optimization

$$\underset{\Theta}{\text{minimize}} \quad \mathcal{J}(y;\Theta)$$

$$\text{subject to} \quad \begin{cases} \dot{x} = f(x,u,w); & x(0) = x_0 \\ y = h(x) & \\ \dot{z} = g(z,y,v;\Theta); & z(0) = z_0 \\ u = \kappa(z,y,v;\Theta) & \end{cases}$$



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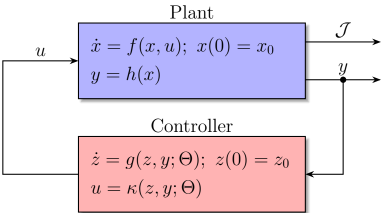
$$y = \mathcal{M}(\Theta)$$




## Nonlinear Operator

$$\mathcal{M} : \Theta \mapsto y$$

$$\begin{cases} \dot{x} = f(x,u,w); x(0) = x_0 \\ y = h(x) \\ \dot{z} = g(z,y,v;\Theta); z(0) = z_0 \\ u = \kappa(z,y,v;\Theta) \end{cases}$$

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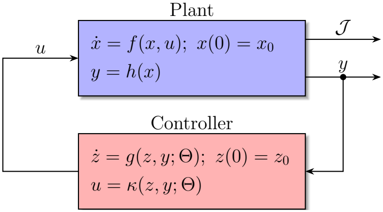
$$y = \mathcal{M}(\Theta)$$

## (Abstract) Unconstrained Optimization

$$\underset{\Theta}{\text{minimize}} \quad \mathcal{J}(\mathcal{M}(\Theta);\Theta) =: J(\Theta)$$

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# Necessary Condition of Optimality (NCO)

**(Abstract) Unconstrained Optimization**

$$\underset{\Theta \in \mathbb{R}^p}{\text{minimize}} \quad \mathcal{J}(\mathcal{M}(\Theta); \Theta) =: J(\Theta)$$

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**Abstract NCO**

$$\begin{array}{rll} \text{(Directional Derivative)} & \partial J_{\bar{\Theta}}(\tilde{\Theta}) = \langle \nabla J_{\bar{\Theta}}, \tilde{\Theta} \rangle_{\mathbb{R}^p} = 0, & \forall \tilde{\Theta} \in \mathbb{R}^p \\ \text{(Gradient)} & \nabla J_{\bar{\Theta}} = 0 & \end{array}$$

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**Chain Rule**: $\partial J_{\bar{\Theta}}(\tilde{\Theta})$

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**Chain Rule**: $\partial J_{\bar\Theta}(\tilde\Theta) = \partial_y \mathcal{J}_{(\bar y;\bar\Theta)}\left(\partial \mathcal{M}_{\bar\Theta}(\tilde\Theta)\right) + \partial_\Theta \mathcal{J}_{(\bar y;\bar\Theta)}(\tilde\Theta)$

$\left(\bar y := \mathcal{M}(\bar\Theta)\right)$

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$(\bar{y} := \mathcal{M}(\bar{\Theta}))$ $\quad = \left\langle \nabla_y \mathcal{J}_{(\bar{y};\bar{\Theta})}, \partial \mathcal{M}_{\bar{\Theta}}(\tilde{\Theta}) \right\rangle + \left\langle \nabla_\Theta \mathcal{J}_{(\bar{y};\bar{\Theta})}, \tilde{\Theta} \right\rangle_{\mathbb{R}^p}$

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$$= \left\langle \partial \mathcal{M}^*_{\bar{\Theta}}\left(\nabla_y \mathcal{J}_{(\bar{y};\bar{\Theta})}\right), \tilde{\Theta} \right\rangle_{\mathbb{R}^p} + \left\langle \nabla_\Theta \mathcal{J}_{(\bar{y};\bar{\Theta})}, \tilde{\Theta} \right\rangle_{\mathbb{R}^p}$$

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**Chain Rule**:

$(\bar{y} := \mathcal{M}(\bar{\Theta}))$

$$\begin{aligned}
\partial J_{\bar{\Theta}}(\tilde{\Theta}) &= \partial_y \mathcal{J}_{(\bar{y};\bar{\Theta})}\left(\partial \mathcal{M}_{\bar{\Theta}}(\tilde{\Theta})\right) + \partial_\Theta \mathcal{J}_{(\bar{y};\bar{\Theta})}(\tilde{\Theta}) \\
&= \left\langle \nabla_y \mathcal{J}_{(\bar{y};\bar{\Theta})}, \partial \mathcal{M}_{\bar{\Theta}}(\tilde{\Theta}) \right\rangle + \left\langle \nabla_\Theta \mathcal{J}_{(\bar{y};\bar{\Theta})}, \tilde{\Theta} \right\rangle_{\mathbb{R}^p} \\
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&= \left\langle \partial \mathcal{M}^*_{\bar{\Theta}}\left(\nabla_y \mathcal{J}_{(\bar{y};\bar{\Theta})}\right) + \nabla_\Theta \mathcal{J}_{(\bar{y};\bar{\Theta})}, \tilde{\Theta} \right\rangle_{\mathbb{R}^p}
\end{aligned}$$

# Necessary Condition of Optimality (NCO)

**(Abstract) Unconstrained Optimization**

$$\underset{\Theta\in\mathbb{R}^p}{\text{minimize}} \quad \mathcal{J}(\mathcal{M}(\Theta);\Theta) =: J(\Theta)$$

**Abstract NCO**

$$\begin{array}{ll} \text{(Directional Derivative)} & \partial J_{\bar{\Theta}}(\tilde{\Theta}) = \langle \nabla J_{\bar{\Theta}}, \tilde{\Theta}\rangle_{\mathbb{R}^p} = 0, \qquad \forall \tilde{\Theta} \in \mathbb{R}^p \\ \text{(Gradient)} & \nabla J_{\bar{\Theta}} = 0 \end{array}$$

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| | Operator Form | Differential Equations Form |
|---|---|---|
| $\mathcal{M} : \mathbb{R}^p \to \mathbb{L}^2_m[0,T]$ | $\bar{y} = \mathcal{M}(\bar{\Theta})$ | ✓Forward Nonlinear DE |
| $\partial \mathcal{M}_{\bar{\Theta}} : \mathbb{R}^p \to \mathbb{L}^2_m[0,T]$ | $\tilde{y} = \partial \mathcal{M}_{\bar{\Theta}}(\tilde{\Theta})$ | ✓Forward Linear DE |
| $\partial \mathcal{M}^*_{\bar{\Theta}} : \mathbb{L}^2_m[0,T] \to \mathbb{R}^p$ | $\hat{\Theta} = \partial \mathcal{M}^*_{\bar{\Theta}}(\hat{y})$ | ✓Backward Linear DE |

# Necessary Condition of Optimality (NCO)

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(Directional Derivative) $\partial J_{\bar{\Theta}}(\tilde{\Theta}) = \langle \nabla J_{\bar{\Theta}}, \tilde{\Theta} \rangle_{\mathbb{R}^p} = 0, \qquad \forall \tilde{\Theta} \in \mathbb{R}^p$

(Gradient) $\nabla J_{\bar{\Theta}} = 0$

$$\textbf{Gradient:} \ \nabla J_{\bar{\Theta}} = \partial \mathcal{M}^*_{\bar{\Theta}} \left( \nabla_y \mathcal{J}_{(\bar{y};\bar{\Theta})} \right) + \nabla_\Theta \mathcal{J}_{(\bar{y};\bar{\Theta})}$$

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$$\therefore \nabla J_{\bar{\Theta}} = 0 \iff \begin{cases} \dot{\chi} = F(\chi; \bar{\Theta}); & \chi(0) = \chi_0 \\ \dot{\xi} = A(\chi; \bar{\Theta})\xi + b(\chi; \bar{\Theta}); & \xi(T) = \xi_T \end{cases}$$

Parameter-Dependent TPBVP

# Gradient-Based Numerical Methods

$$\textbf{Gradient:}\ \nabla J_\Theta = \partial \mathcal{M}_\Theta^* \left(\nabla_y \mathcal{J}_{(y;\Theta)}\right) + \nabla_\Theta \mathcal{J}_{(y;\Theta)}$$

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**Iterative Numerical Method:** $\Theta_{i+1} = \Theta_i + \alpha_i d_i$

Gradient Descent: $d_i = -\nabla J_{\Theta_i}$

Conjugate Gradient Descent: $d_i = \begin{cases} -\nabla J_{\Theta_i} & i = 0 \\ -\nabla J_{\Theta_i} + \dfrac{||\nabla J_{\Theta_i}||^2}{||\nabla J_{\Theta_{i-1}}||^2} d_{i-1} & i > 0 \end{cases}$

# Gradient-Based Numerical Methods

**Algorithm 1** (Conjugate) Gradient Descent Algorithm

1: Start with an initial guess $\Theta_0 \in \mathbb{R}^p$ and set $i = 0$.
2: Compute the gradient at $\Theta_i$, $\nabla J_{\Theta_i}$:
 (a) Simulate the closed-loop dynamics with $\Theta = \Theta_i$:

$$\begin{aligned} \dot{x}_i &= f(x_i, u_i, w); & x_i(0) &= x_0 \\ \dot{z}_i &= g(z_i, y_i, v; \Theta_i); & z_i(0) &= z_0 \\ u_i &= \kappa(z_i, y_i, v; \Theta_i) & & \\ y_i &= h(x_i). & & \end{aligned}$$

 (b) Compute the time-varying Jacobians:

$$\begin{aligned} A_i &= \partial_x f_{(x_i,u_i,w)}, & B_i &= \partial_u f_{(x_i,u_i,w)} \\ C_i &= \partial h_{x_i}, & A_i^c &= \partial_z g_{(z_i,y_i,v;\Theta_i)} \\ B_i^c &= \partial_y g_{(z_i,y_i,v;\Theta_i)}, & C_i^c &= \partial_z \kappa_{(z_i,y_i,v;\Theta_i)} \\ D_i^c &= \partial_y \kappa_{(z_i,y_i,v;\Theta_i)} & B_i^\Theta &= \partial_\Theta g_{(z_i,y_i,v;\Theta_i)} \\ C_i^\Theta &= \partial_\Theta \kappa_{(z_i,y_i,v;\Theta_i)}. & & \end{aligned}$$

 (c) Solve for $\lambda_i(t)$, with $\lambda_i(T) = 0$:

$$\dot{\lambda}_i = -\begin{bmatrix} A_i + B_i D_i^c C_i & B_i C_i^c \\ B_i^c C_i & A_i^c \end{bmatrix}^T \lambda_i - \begin{bmatrix} C_i^T Q \\ 0 \end{bmatrix} (y_i - y_r).$$

 (d) Compute $\xi_i(0)$:

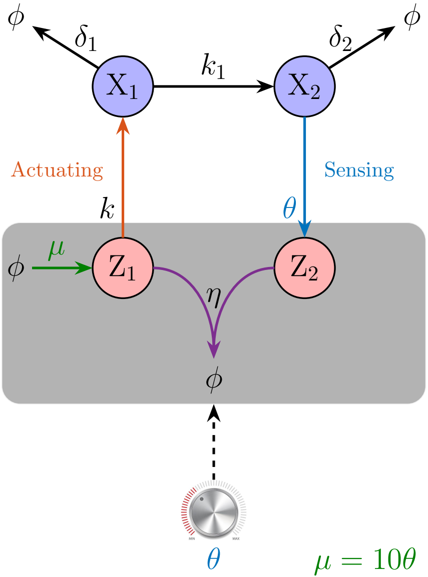
$$\dot{\xi}_i = -\begin{bmatrix} B_i C_i^\Theta \\ B_i^\Theta \end{bmatrix}^T \lambda_i; \qquad \xi_i(T) = 0.$$

 (e) $\nabla J_{\Theta_i} = \xi_i(0) + \nabla b_{\Theta_i}$.
3: Compute the update direction $s_i$:
 (a) For a Gradient Descent Method: $s_i = -\nabla J_{\Theta_i}$.
 (b) For a Conjugate Gradient Descent Method:

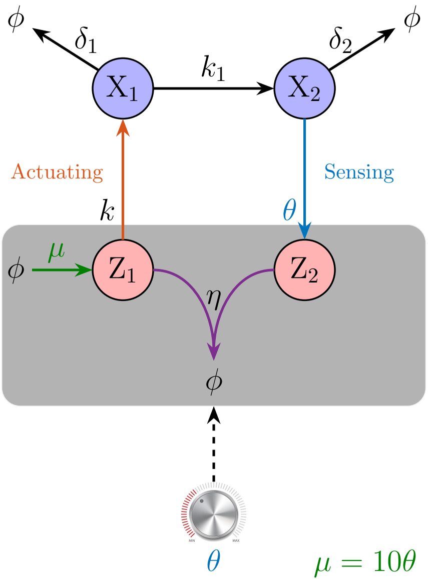
$$s_i = \begin{cases} -\nabla J_{\Theta_i} & i = 0 \\ -\nabla J_{\Theta_i} + \dfrac{||\nabla J_{\Theta_i}||^2}{||\nabla J_{\Theta_{i-1}}||^2} s_{i-1} & i > 0. \end{cases}$$

4: Pick a step size: $\alpha_i = \underset{\alpha}{\text{argmin}}\ J(\Theta_i + \alpha s_i)$.
5: Update the estimate: $\Theta_{i+1} = \Theta_i + \alpha_i s_i$.
6: Set $i = i + 1$ and go back to step 2. Repeat until convergence.

# Application to Antithetic Integral Controller, Example 1



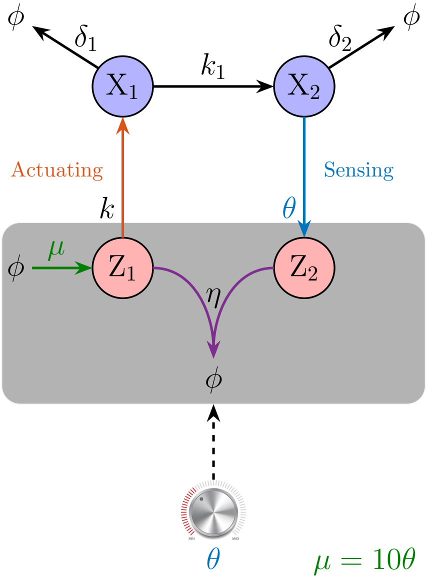

$\mu = 10\theta$




$$\lim_{t\to\infty} x_2(t) = \frac{\mu}{\theta}$$

$$\mu = 10\theta$$

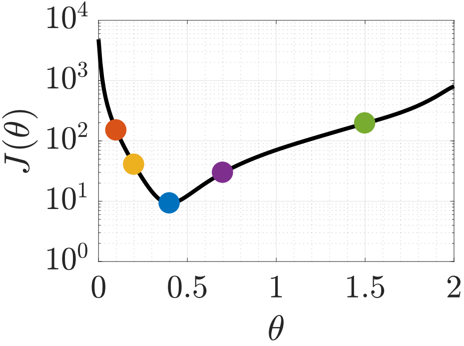
# Application to Antithetic Integral Controller, Example 1




$$\lim_{t\to\infty} x_2(t) = \frac{\mu}{\theta} = 10$$
$$\forall\theta$$

$\mu = 10\theta$

# Application to Antithetic Integral Controller, Example 1



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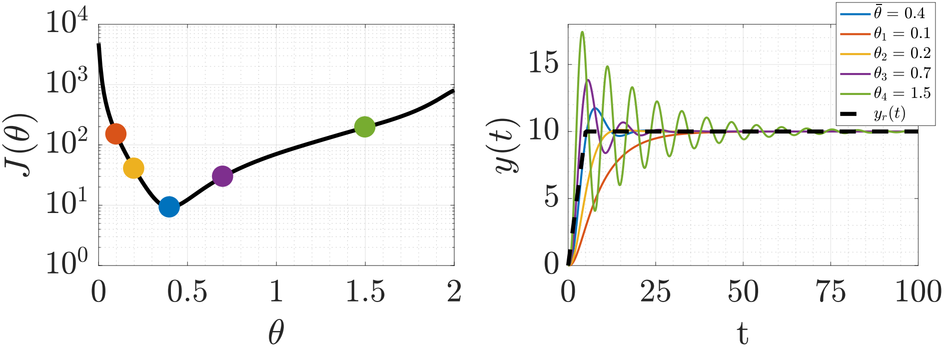
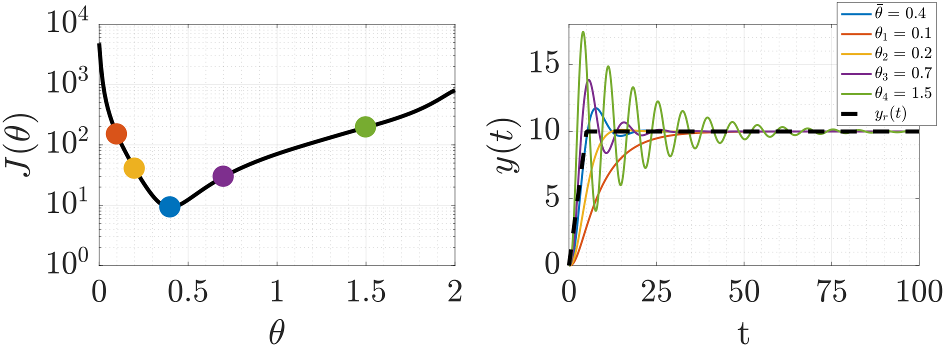
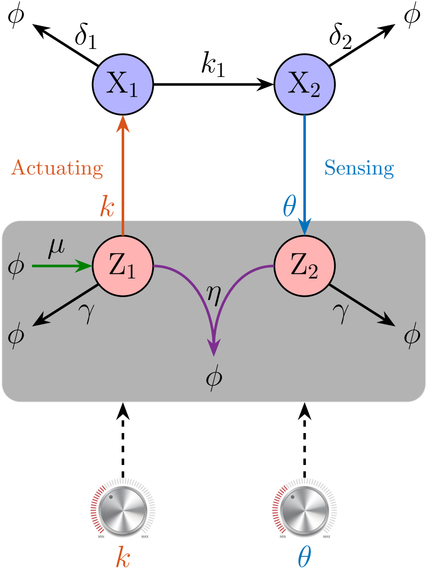





- In 1D: GD = CGD
- Convergence in 9 iterations

# Application to Antithetic Integral Controller, Example 2



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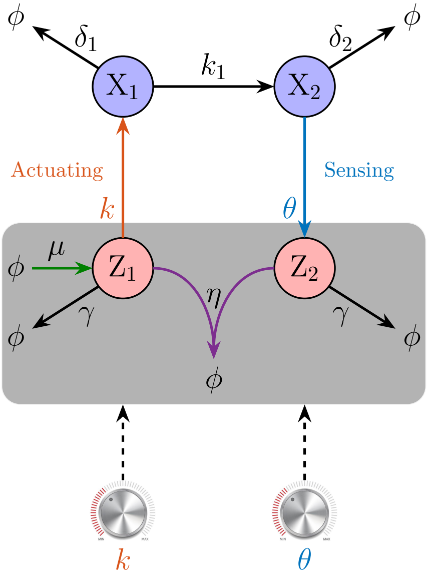
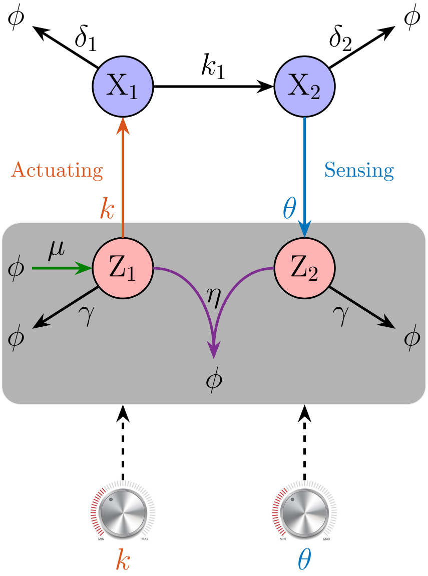


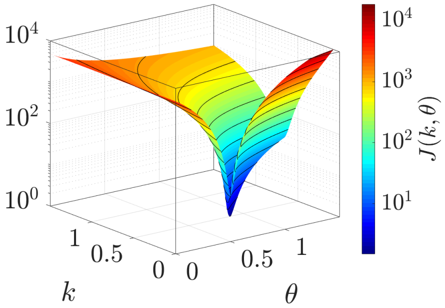

$$\lim_{t\to\infty} x_2(t) \neq \frac{\mu}{\theta}$$

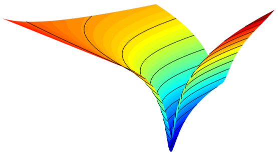
# Application to Antithetic Integral Controller, Example 2




$$\lim_{t\to\infty} x_2(t) \neq \frac{\mu}{\theta}$$
$$\approx \frac{\mu}{\theta}$$
for small $\gamma$

# Application to Antithetic Integral Controller, Example 2



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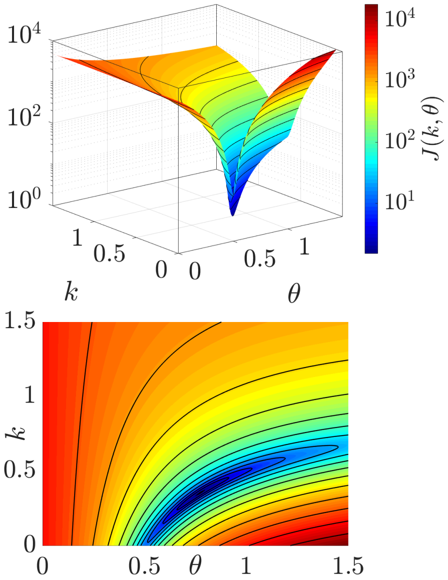

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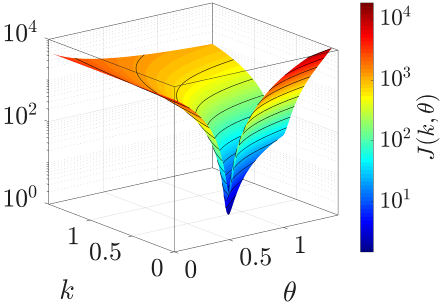
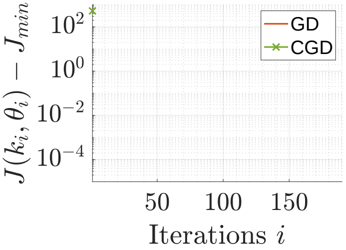
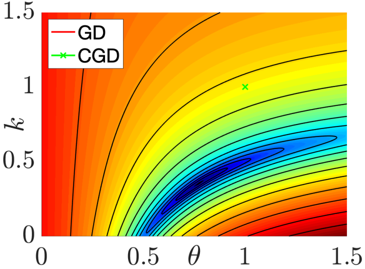
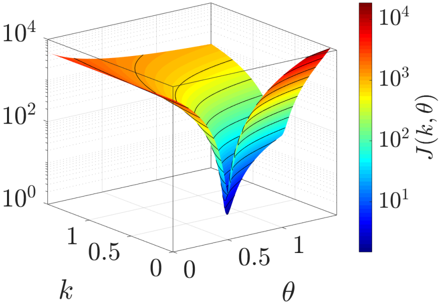
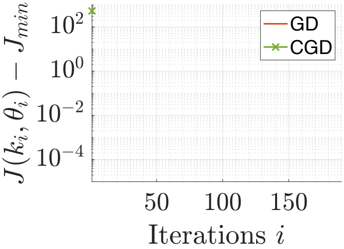


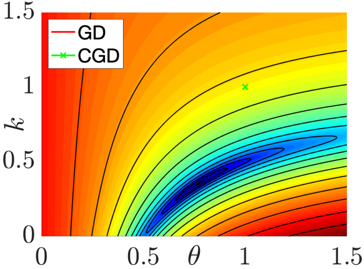





$10^4$
$10^2$
$10^0$
1
0.5
0
$k$
0
0.5
1
$\theta$
$10^4$
$10^3$
$10^2$
$10^1$
$J(k,\theta)$

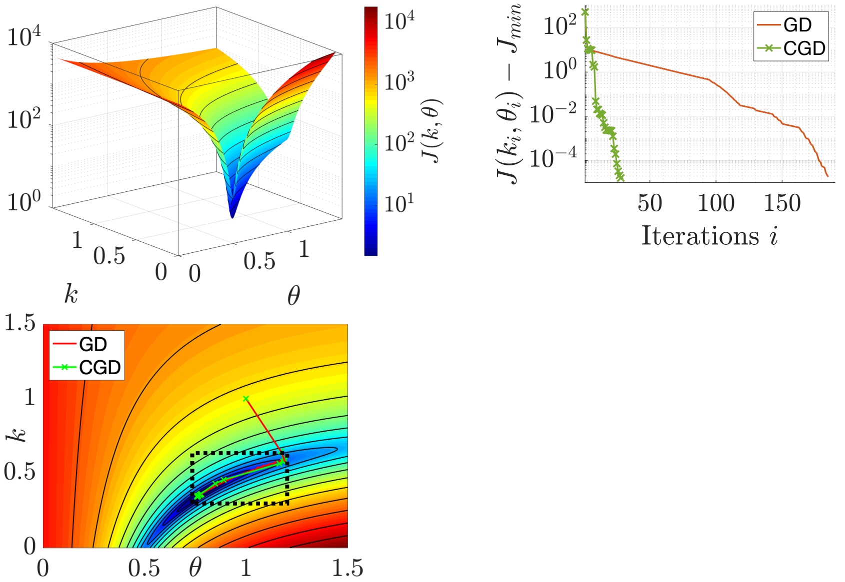



$J(k_i,\theta_i) - J_{min}$
$10^2$
$10^0$
$10^{-2}$
$10^{-4}$
50
100
150
Iterations $i$
GD
CGD

GD
CGD
1.5
1
0.5
0
$k$
0
0.5
$\theta$
1
1.5

# Application to Antithetic Integral Controller, Example 2



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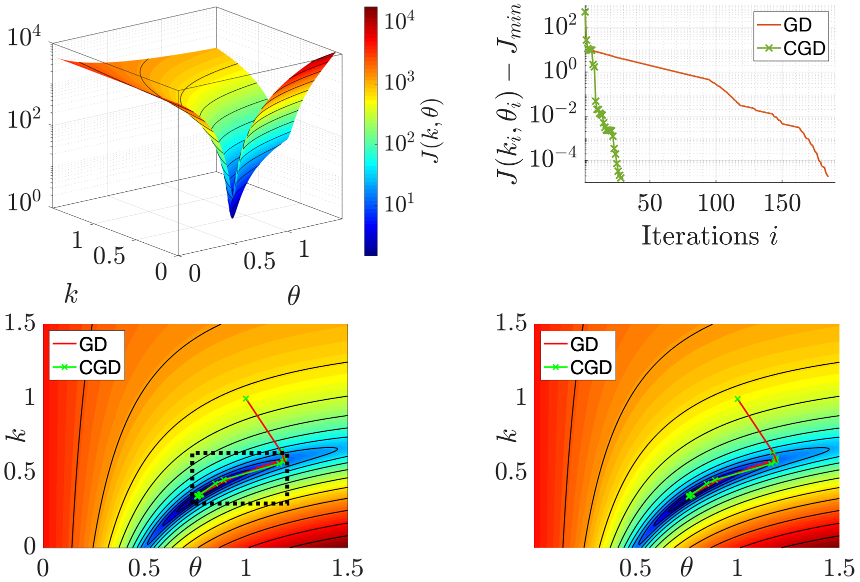

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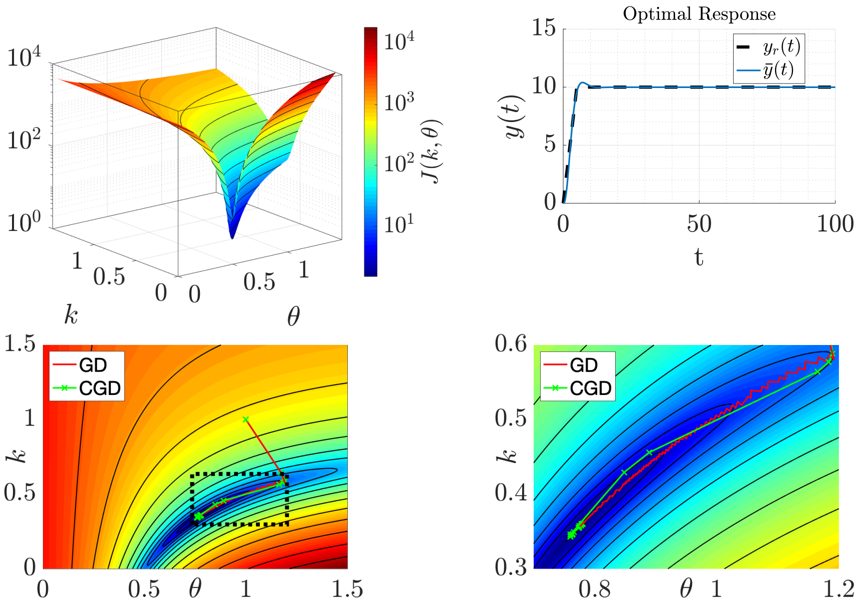

# Two Take-Home Messages

- Transient biomolecular dynamics also matter
- There is no way around proper tuning of biomolecular controllers

# Thank you!