ETH zürich

Robust tracking and perfect adaptation in antithetic integral control of stochastic biochemical reaction networks

Corentin Briat & Mustafa Khammash
Department of Biosystems Science and Engineering, ETH-Zürich

55th IEEE Conference on Decision and Control, Las Vegas, USA

Contents

1 Stochastic reaction networks and antithetic integral control

2 Robust tracking and perfect adaptation

3 Example

Contents

1 Stochastic reaction networks and antithetic integral control

2 Robust tracking and perfect adaptation

3 Example

Stochastic reaction networks

A stochastic reaction network consists of...

- A set of d distinct species $\boldsymbol{X} = \{\boldsymbol{X_1}, \ldots, \boldsymbol{X_d}\} \rightarrow$ state
- A set of K reactions $\mathcal{R} = \{\mathcal{R}_1, \ldots, \mathcal{R}_K\}$ involving the species in $\boldsymbol{X} \rightarrow$ dynamics
  - Stoichiometric vector ζ_k; i.e. if $\mathcal{R}_k$ fires, then $x \rightarrow x + \zeta_k$
  - Propensity function $\lambda_k(x)$; i.e. the "strength" of the reaction $\mathcal{R}_k$

Stochastic reaction networks

A stochastic reaction network consists of...

- A set of d distinct species $\boldsymbol{X} = \{\boldsymbol{X_1}, \ldots, \boldsymbol{X_d}\} \rightarrow$ state
- A set of K reactions $\mathcal{R} = \{\mathcal{R}_1, \ldots, \mathcal{R}_K\}$ involving the species in $\boldsymbol{X} \rightarrow$ dynamics
  - Stoichiometric vector ζ_k; i.e. if $\mathcal{R}_k$ fires, then $x \rightarrow x + \zeta_k$
  - Propensity function $\lambda_k(x)$; i.e. the "strength" of the reaction $\mathcal{R}_k$

Examples

- (Bio)chemistry: $\boldsymbol{X} = \{$distinct molecular species$\}$ and $\mathcal{R} = \{$reaction rules$\}$
- Ecology:
  - $\boldsymbol{X} = \{$animal/vegetal species and resources$\}$
  - $\mathcal{R} = \{$predation and reproduction rules$\}$
- Epidemiology:
  - $\boldsymbol{X} = \{$illness state of individuals$\}$
  - $\mathcal{R} = \{$disease propagation and recovery rules$\}$

Antithetic integral feedback

Open-loop network

- A reaction network $(\boldsymbol{X}, \mathcal{R})$
- $\boldsymbol{X_1}$ is the **actuated species**
- $\boldsymbol{Y} = \boldsymbol{X_\ell}$ is the **controlled species**

Antithetic integral feedback

Open-loop network

- A reaction network $(\boldsymbol{X}, \mathcal{R})$
- $\boldsymbol{X_1}$ is the **actuated species**
- $\boldsymbol{Y} = \boldsymbol{X_\ell}$ is the **controlled species**

Control objective (roughly)

Find a set of additional species $\boldsymbol{Z}$ and additional reactions $\mathcal{R}^c$ that acts on the actuated species $\boldsymbol{X_1}$ in a way that the mean value of the controlled species $\boldsymbol{Y}$ robustly tracks a desired set-point μ/θ and ensures perfect adaptation for the controlled species at the mean level.

Antithetic integral feedback

Open-loop network

- A reaction network $(\boldsymbol{X}, \mathcal{R})$
- $\boldsymbol{X_1}$ is the **actuated species**
- $\boldsymbol{Y} = \boldsymbol{X_\ell}$ is the **controlled species**

Control objective (roughly)

Find a set of additional species $\boldsymbol{Z}$ and additional reactions $\mathcal{R}^c$ that acts on the actuated species $\boldsymbol{X_1}$ in a way that the mean value of the controlled species $\boldsymbol{Y}$ robustly tracks a desired set-point μ/θ and ensures perfect adaptation for the controlled species at the mean level.

Antithetic integral controller [Briat, Gupta & Khammash]

$$
\begin{aligned}
\mathcal{R}_1^c &: \quad \boldsymbol{Y} \xrightarrow{\theta} \boldsymbol{Y} + \boldsymbol{Z_2} && \text{(Measurement reaction)} \\
\mathcal{R}_2^c &: \quad \boldsymbol{\phi} \xrightarrow{\mu} \boldsymbol{Z_1} && \text{(Reference reaction)} \\
\mathcal{R}_3^c &: \quad \boldsymbol{Z_1} \xrightarrow{k} \boldsymbol{Z_1} + \boldsymbol{X_1} && \text{(Actuation reaction)} \\
\mathcal{R}_4^c &: \quad \boldsymbol{Z_1} + \boldsymbol{Z_2} \xrightarrow{\eta} \boldsymbol{\phi} && \text{(Comparison reaction)}
\end{aligned}
$$

where $\theta, \mu, \eta, k > 0$ are the controller parameters.

Unimolecular case

Propensities

In the unimolecular case (no 0-th order reactions), we can write

$$\lambda(x) = W(\rho)x$$

where $W(\rho) \in \mathbb{R}_{\geq 0}^{K \times d}$ and $\rho \in \mathbb{R}_{>0}^{n_\rho}$ is the positive vector of reaction rates

Unimolecular case

Propensities

In the unimolecular case (no 0-th order reactions), we can write

$$\lambda(x) = W(\rho)x$$

where $W(\rho) \in \mathbb{R}_{\geq 0}^{K \times d}$ and $\rho \in \mathbb{R}_{>0}^{n_\rho}$ is the positive vector of reaction rates

Characteristic matrix

The *characteristic matrix* $A(\rho)$ of a unimolecular reaction network $(\boldsymbol{X}, \mathcal{R})$ is defined as

$$A(\rho) := SW(\rho).$$

Unimolecular case

Propensities

In the unimolecular case (no 0-th order reactions), we can write

$$\lambda(x) = W(\rho)x$$

where $W(\rho) \in \mathbb{R}_{\geq 0}^{K \times d}$ and $\rho \in \mathbb{R}_{>0}^{n_\rho}$ is the positive vector of reaction rates

Characteristic matrix

The *characteristic matrix* $A(\rho)$ of a unimolecular reaction network $(\boldsymbol{X}, \mathcal{R})$ is defined as

$$A(\rho) := SW(\rho).$$

First-order moments dynamics

$$\begin{aligned} \frac{\mathrm{d}\mathbb{E}[X(t)]}{\mathrm{d}t} &= A(\rho)\mathbb{E}[X(t)] + e_1 u(t) \\ y(t) &= e_\ell^T \mathbb{E}[X(t)] \end{aligned}$$

where e_i is a vector with entry i equal to 1 and 0 everywhere else.

Main result

Theorem (Briat, Gupta & Khammash)

Assume that the state-space of the closed-loop reaction network is irreducible and that the vector of reaction rates ρ is fixed and equal to ρ_0. Assume further that there exist vectors $v \in \mathbb{R}^d_{>0}$, $w \in \mathbb{R}^d_{\geq 0}$, $w_1 > 0$, such that

$$v^T A(\rho_0) < 0 \quad \text{and} \quad w^T A(\rho_0) + e_\ell^T = 0.$$

Main result

Theorem (Briat, Gupta & Khammash)

Assume that the state-space of the closed-loop reaction network is irreducible and that the vector of reaction rates ρ is fixed and equal to ρ_0. Assume further that there exist vectors $v \in \mathbb{R}^d_{>0}$, $w \in \mathbb{R}^d_{\geq 0}$, $w_1 > 0$, such that

$$v^T A(\rho_0) < 0 \quad \text{and } w^T A(\rho_0) + e_\ell^T = 0.$$

Then, for any values for the controller rate parameters $\eta, k, \mu, \theta > 0$, the mean of the controlled species satisfies $\mathbb{E}[X_\ell(t)] \to \mu/\theta$ as $t \to \infty$.

Main result

Theorem (Briat, Gupta & Khammash)

Assume that the state-space of the closed-loop reaction network is irreducible and that the vector of reaction rates ρ is fixed and equal to ρ_0. Assume further that there exist vectors $v \in \mathbb{R}^d_{>0}$, $w \in \mathbb{R}^d_{\geq 0}$, $w_1 > 0$, such that

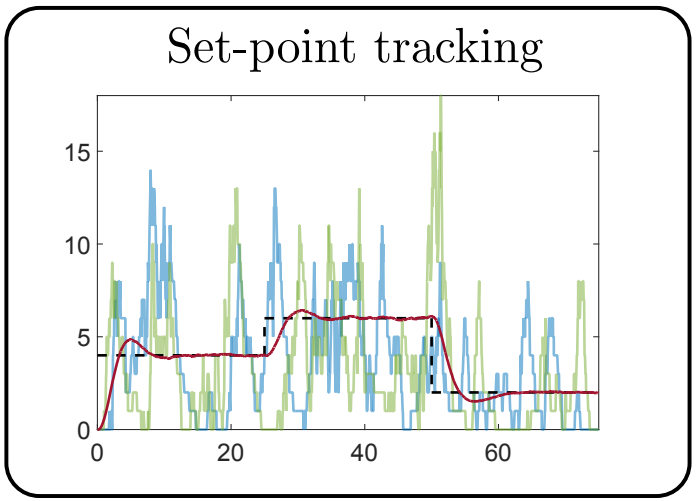
$$v^T A(\rho_0) < 0 \quad \text{and } w^T A(\rho_0) + e_\ell^T = 0.$$

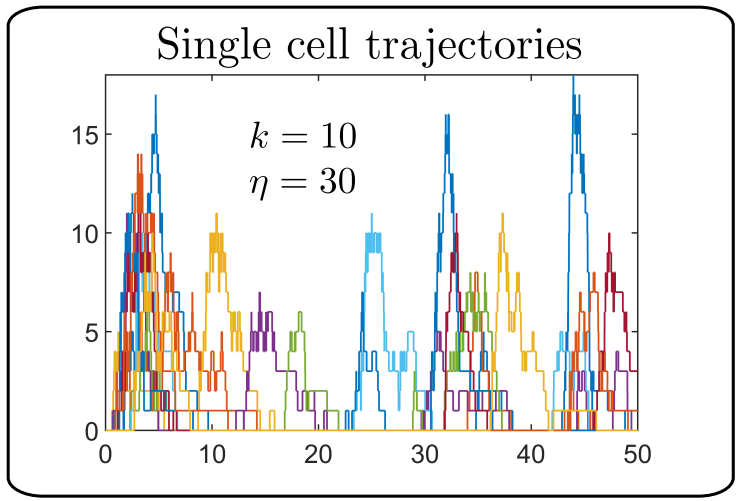
Then, for any values for the controller rate parameters $\eta, k, \mu, \theta > 0$, the mean of the controlled species satisfies $\mathbb{E}[X_\ell(t)] \to \mu/\theta$ as $t \to \infty$.

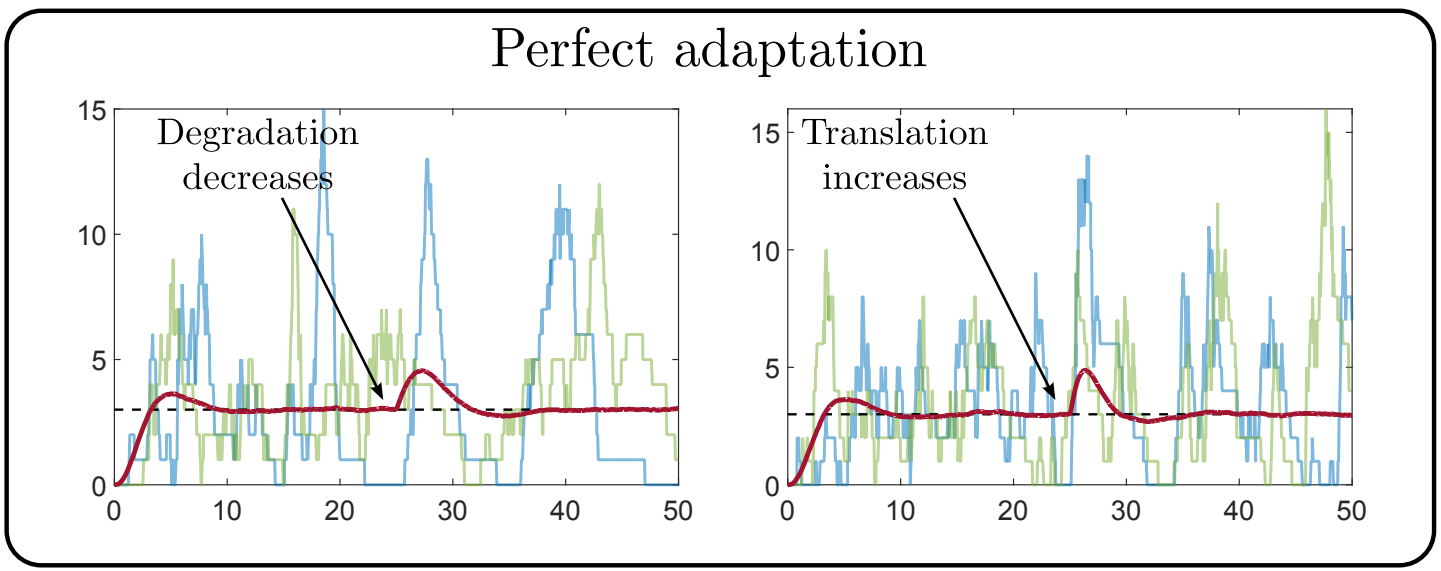
Remarks

- States conditions on the open-loop network regarding closed-loop dynamics
- Equivalent to the stability of $A(\rho_0)$ and the output controllability of $(A(\rho_0), e_1, e_\ell^T)$
- Linear programming conditions
- Independent of the controller parameters $k, \eta, \mu, \theta > 0$
- Can be extended to include 0th order reactions $\to$ conditions on μ, θ

Antithetic control of gene expression







Contents

1 Stochastic reaction networks and antithetic integral control

2 Robust tracking and perfect adaptation

3 Example

Interval matrices

- We assume now that $\rho \in \mathcal{P}$ where $\mathcal{P}$ is the compact set containing all the possible values for the rate parameters.

Interval matrices

- We assume now that $\rho \in \mathcal{P}$ where $\mathcal{P}$ is the compact set containing all the possible values for the rate parameters.
- The set of all the matrices $A(\rho)$ is given by

$$\mathcal{A}_{exact} := \{A(\rho) : \rho \in \mathcal{P}\}$$

Interval matrices

- We assume now that $\rho \in \mathcal{P}$ where $\mathcal{P}$ is the compact set containing all the possible values for the rate parameters.
- The set of all the matrices $A(\rho)$ is given by

$$\mathcal{A}_{exact} := \{A(\rho) : \rho \in \mathcal{P}\}$$

- Since $\mathcal{P}$ is compact, then there exist matrices $A^- \leq A^+$ such that

$$A^- \leq A(\rho) \leq A^+$$

holds for all $\rho \in \mathcal{P} \subset \mathbb{R}^K_{>0}$. Inequalities are componentwise here.

Interval matrices

- We assume now that $\rho \in \mathcal{P}$ where $\mathcal{P}$ is the compact set containing all the possible values for the rate parameters.
- The set of all the matrices $A(\rho)$ is given by

$$\mathcal{A}_{exact} := \{A(\rho) : \rho \in \mathcal{P}\}$$

- Since $\mathcal{P}$ is compact, then there exist matrices $A^- \leq A^+$ such that

$$A^- \leq A(\rho) \leq A^+$$

  holds for all $\rho \in \mathcal{P} \subset \mathbb{R}^K_{>0}$. Inequalities are componentwise here.
- We then define

$$\mathcal{A} := \left\{ M \in \mathbb{R}^{d \times d} : \ A^- \leq M \leq A^+ \right\} \supseteq \mathcal{A}_{exact}$$

- May be conservative because we may lose the true parameter dependence
- Still it is useful because it is simple

Robust stability and robust output controllability

Proposition (Berman & Plemmons)

The following statements are equivalent:

(a) *All the matrices in $\mathcal{A}$ are Hurwitz stable;*

(b) *The matrix A^+ is Hurwitz stable.*

(c) *There exists a vector $v_+ \in \mathbb{R}^d_{>0}$ such that $v_+^T A^+ < 0$.*

Robust stability and robust output controllability

Proposition (Berman & Plemmons)

The following statements are equivalent:

(a) *All the matrices in $\mathcal{A}$ are Hurwitz stable;*

(b) *The matrix A^+ is Hurwitz stable.*

(c) *There exists a vector $v_+ \in \mathbb{R}^d_{>0}$ such that $v_+^T A^+ < 0$.*

Proposition

The following statements are equivalent:

(a) *For all $A \in \mathcal{A}$, the system (A, e_1, e_ℓ^T) is output controllable.*

(b) *The system (A^-, e_1, e_ℓ^T) is output controllable.*

If, moreover, A^+ is Hurwitz stable, then the above statement are also equivalent to

(c) *There exists a vector $w_- \in \mathbb{R}^d_{\geq 0}$ such that $w_-^T e_1 > 0$ and $w_-^T A^- + e_\ell^T = 0$.*

Main result

Theorem

Let us consider a unimolecular reaction network $(\boldsymbol{X}, \mathcal{R})$ with characteristic matrix A in $\mathcal{A}$. Assume also that the state-space of the closed-loop reaction network is irreducible. Then, the following statements are equivalent:

(a) *For all $A \in \mathcal{A}$, there exist $v \in \mathbb{R}^d_{>0}$, $w \in \mathbb{R}^d_{\geq 0}$ such that $v^T A < 0$, $w^T e_1 > 0$ and $w^T A + e_\ell^T = 0$.*

(b) *There exist two vectors $v_+ \in \mathbb{R}^d_{>0}$, $w_- \in \mathbb{R}^d_{\geq 0}$ such that $v_+^T A^+ < 0$, $w_-^T e_1 > 0$ and $w_-^T A^- + e_\ell^T = 0$.*

Moreover, when one of the above statements holds, then for any values for the controller rate parameters $\eta, k, \mu, \theta > 0$ and any network with characteristic matrix in $\mathcal{A}$, the mean of the controlled species satisfies $\mathbb{E}[X_\ell(t)] \to \mu/\theta$ as $t \to \infty$.

- LP with same complexity as in the nominal case

Contents

1 Stochastic reaction networks and antithetic integral control

2 Robust tracking and perfect adaptation

3 Example

Open-loop network

Table: Modified stochastic switch of Gardner, Cantor and Collins

	Reaction	Propensity
$\mathcal{R}_1$	$\emptyset \longrightarrow \boldsymbol{X_1}$	$\alpha_1 + k_{21} X_2 + \delta_1$
$\mathcal{R}_2$	$\boldsymbol{X_1} \longrightarrow \emptyset$	$\gamma_1 X_1$
$\mathcal{R}_3$	$\emptyset \longrightarrow \boldsymbol{X_2}$	$\alpha_2 + \beta_2/(1 + X_1)$
$\mathcal{R}_4$	$\boldsymbol{X_2} \longrightarrow \emptyset$	$\gamma_2 X_2$

- We also assume that $\alpha_1, \alpha_2, \gamma_1, \gamma_2 > 0$, which implies that the state-space of the open-loop network is irreducible.
- The other parameters are nonnegative.
- Our goal is to control the mean population of $\boldsymbol{X_2}$ by actuating $\boldsymbol{X_1}$.

Analysis

- Assume that $\gamma_1 \in [1,2]$, $\gamma_2 \in [3,4]$, $k_{12} \in [k_{12}^-, 2]$ and $k_{21} = [0, k_{21}^+]$, where $0 \leq k_{12}^- \leq 2$ and $k_{21}^+ \geq 0$.
- Hence, we have

$$\begin{bmatrix} -2 & 0 \\ k_{12}^- & -4 \end{bmatrix} = A^- \leq A \leq A^+ = \begin{bmatrix} -1 & k_{21}^+ \\ 2 & -3 \end{bmatrix}.$$

- A Hurwitz stable if and only if A^+ is Hurwitz stable; equivalently, $k_{21}^+ < 2/3$.
- (A, e_1, e_2^T) output controllable if and only if (A^-, e_1, e_2^T); equivalently, $k_{12}^- > 0$
- Alternatively, we can check the LP conditions

Concluding statements

Results

- Extensions of the conditions to uncertain systems
- Robust analysis (interval matrices) $\rightarrow$ Linear Program
- Structural analysis (sign-matrices) $\rightarrow$ Linear Program
- The conditions remain easily solvable

Issues

- The use of interval matrices can be conservative when entries are not independent
- Same problem with sign-matrices
- Results are only valid for unimolecular networks
- Some of these issues are solved in our submitted IFAC World Congress paper

Thank you for your attention