Analysis and control of stochastic reaction networks – Applications to biology

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joint work with A. Gupta and M. Khammash

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Introduction

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Reaction networks

A reaction network is. . .

- A set of d distinct species $\boldsymbol{X_1}, \ldots, \boldsymbol{X_d}$
- A set of K reactions $R_1, \ldots, R_K$ specifying how species interact with each other and for each reaction we have
  - A stoichiometric vector $\zeta_k \in \mathbb{Z}^d$ describing how reactions change the state value
  - A propensity function $\lambda_k \in \mathbb{R}_{\geq 0}$ describing the "strength" of the reaction

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Example - SIR model

$$\begin{array}{lcrcl} R_1 & : & \boldsymbol{S}+\boldsymbol{I} & \xrightarrow{\beta} & 2\boldsymbol{I} \\ R_2 & : & \boldsymbol{I} & \xrightarrow{\gamma} & \boldsymbol{R} \\ R_3 & : & \boldsymbol{R} & \xrightarrow{\alpha} & \boldsymbol{S} \end{array} \qquad \begin{array}{lcl} \boldsymbol{X_1} & \equiv & \boldsymbol{S} \\ \boldsymbol{X_2} & \equiv & \boldsymbol{I} \\ \boldsymbol{X_3} & \equiv & \boldsymbol{R} \end{array}$$

Stoichiometries and propensities

$$\begin{array}{lcllcl} \zeta_1 & = & (-1,1,0), & \lambda_1(x) & = & \beta x_1 x_2 \\ \zeta_2 & = & (0,-1,1), & \lambda_2(x) & = & \gamma x_2 \\ \zeta_3 & = & (1,0,-1), & \lambda_3(x) & = & \alpha x_3 \end{array}$$

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Deterministic networks

- Large populations (concentrations are well-defined), e.g. as in chemistry
- Lots of analytical tools, e.g. reaction network theory, dynamical systems theory, Lyapunov theory of stability, nonlinear control theory, etc.

Stochastic networks

- Low populations (concentrations are NOT well defined)
- Biological processes where key molecules are in low copy number (mRNA $\simeq$10 copies per cell)
- No well-established theory for biology, “analysis" often based on simulations. . .
- No well-established control theory

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Chemical master equation

State and dynamics

- The state $X \in \mathbb{N}_0^d$ is vector of random variables representing molecules count
- The dynamics of the process is described by a jump Markov process $(X(t))_{t\geq 0}$

Chemical Master Equation (Forward Kolmogorov equation)

$$\dot{p}_{x_0}(x,t) = \sum_{k=1}^{K} \lambda_k(x-\zeta_k)p_{x_0}(x-\zeta_k,t) - \lambda_k(x)p_{x_0}(x,t),\ x \in \mathbb{N}_0^d$$

where $p_{x_0}(x,t) = \mathbb{P}[X(t)=x|X(0)=x_0]$, i.e. $p_{x_0}(x,0) = \delta_{x_0}(x)$.

Solving the CME

- Infinite countable number of linear time-invariant ODEs
- Exactly solvable only in very simple cases
- Some numerical schemes are available (FSP, QTT, etc) but limited by the curse of dimensionality; if $X \in \{0,\dots,\bar{x}-1\}^d$, then we have $\bar{x}^d$ states

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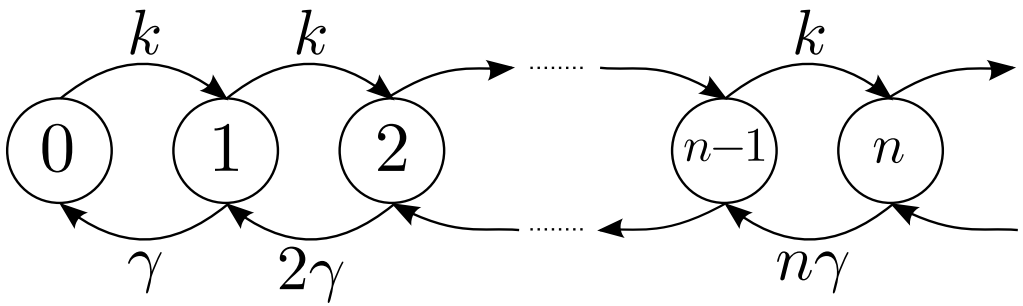
Birth-death process

Process ($X(t) \in \mathbb{N}_0$, $d = 1$, $K = 2$)



- Birth reaction: $\zeta_1 = 1$ and $\lambda_1(x) = k$
- Death reaction: $\zeta_2 = -1$ and $\lambda_2(x) = \gamma x$

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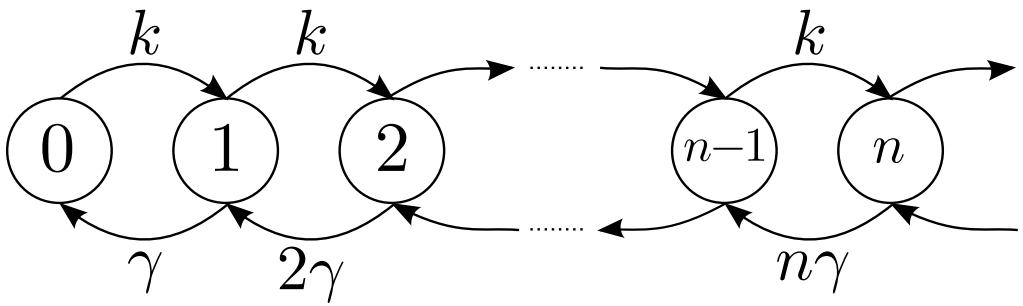

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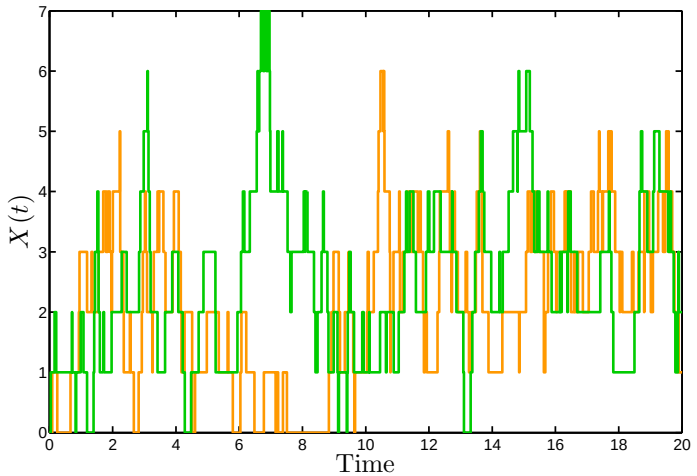
Two sample-paths with $X(0) = 0$, $k = 3$ and $\gamma = 1$



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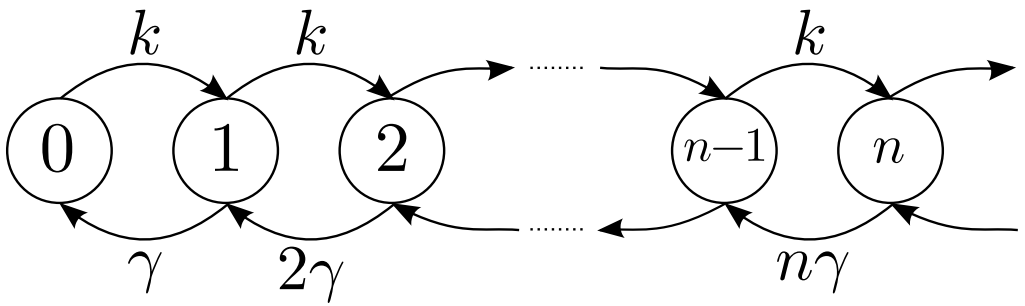

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- Death reaction: $\zeta_2 = -1$ and $\lambda_2(x) = \gamma x$

Solution of the CME for $p(x, 0) = \delta_0(x)$

- $p(x,t) = \dfrac{\sigma(t)^x}{x!} e^{-\sigma(t)}$ where $\sigma(t) := \dfrac{k}{\gamma}\left(1 - e^{-\gamma t}\right),\ x \in \mathbb{N}_0$
- $p(x,t) \xrightarrow{t\to\infty} \dfrac{k^x}{\gamma^x x!} e^{-\frac{k}{\gamma}}$

Exponentially converges to a unique stationary Poisson distribution with parameter $\bar{\sigma}$
(true for any initial condition $p(x, 0)$)

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Problems

Stability of stochastic reaction networks

- How to define stability?
- How to characterize global stability?

Control of stochastic reaction networks

- What control problems can we actually define?
- What controllers can we use?
- How to implement them?

Analysis of stochastic reaction networks

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Ergodicity

A given stochastic reaction network is ergodic if there is a probability distribution π such that for all $x_0 \in \mathbb{N}_0^d$, we have that $p_{x_0}(x,t) \to \pi$ as $t \to \infty$.

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Theorem (Condition for ergodicity[1])

Assume that

(a) *the state-space of the network is irreducible; and*

(b) *there exists a norm-like function $V(x)$ such that the **drift condition***

$$\sum_{i=1}^{K} \lambda_i(x)[V(x+\zeta_i) - V(x)] \leq c_1 - c_2 V(x)$$

holds for some $c_1, c_2 > 0$ and for all $x \in \mathbb{N}_0^d$.

[1] S. P. Meyn and R. L. Tweedie. Stability of Markovian processes III: Foster-Lyapunov criteria for continuous-time processes, *Adv. Appl. Prob.* , 1993

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holds for some $c_1, c_2 > 0$ and for all $x \in \mathbb{N}_0^d$.

Then, the stochastic reaction network is (exponentially) ergodic.

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Ergodicity of unimolecular networks

Unimolecular network ($\lambda(x)$ affine)

$$\emptyset \longrightarrow X_1, \quad X_1 \longrightarrow \emptyset, \quad X_1 \longrightarrow X_2, \quad X_1 \longrightarrow X_1 + X_2$$

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Theorem ([1])

Let us consider $V(x) = \langle v, x \rangle$, $v \in \mathbb{R}^d_{>0}$ and a given irreducible reaction network. The drift condition is given by

$$\langle v, Ax + b \rangle \leq c_1 - c_2 \langle v, x \rangle \text{ for all } x \in \mathbb{N}_0^d$$

where A is a Metzler matrix and b is a nonnegative vector obtained from the reactions.

[1] A. Gupta, C. Briat, and M. Khammash. A scalable computational framework for establishing long-term behavior of stochastic reaction networks, *PLOS Computational Biology*, 2014

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Assume that A is nonsingular, then the following statements are equivalent:

(a) *There exists $v \in \mathbb{R}^d_{>0}$ such that $v^T A < 0$ (LP problem); i.e. A is Hurwitz stable.*

(b) *The Markov process is ergodic and all the moments are bounded and globally converging*

[1] A. Gupta, C. Briat, and M. Khammash. A scalable computational framework for establishing long-term behavior of stochastic reaction networks, *PLOS Computational Biology*, 2014

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Ergodicity of bimolecular networks

Bimolecular network ($\lambda(x)$ quadratic)

unimolecular reactions and $\boldsymbol{X_1} + \boldsymbol{X_1} \longrightarrow \times, \quad \boldsymbol{X_1} + \boldsymbol{X_2} \longrightarrow \times$

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Let us consider $V(x) = \langle v, x \rangle$, $v \in \mathbb{R}^d_{>0}$ and a given irreducible reaction network. The drift condition is given by

$$\begin{bmatrix} 1 \\ x \end{bmatrix}^T M(v) \begin{bmatrix} 1 \\ x \end{bmatrix} + \langle v, Ax + b \rangle \leq c_1 - c_2 \langle v, x \rangle \text{ for all } x \in \mathbb{N}_0^d$$

where A and b are related to unimolecular reactions and $M(v)$ to bimolecular reactions.

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- *A is nonsingular*
- *there exists a $v \in \mathcal{N}_q := \left\{ \theta \in \mathbb{R}^d_{>0} : \ M(\theta) = 0 \right\}$ such that $v^T A < 0$.*

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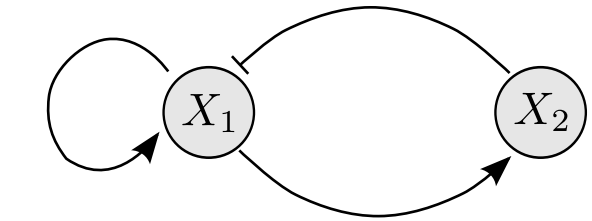
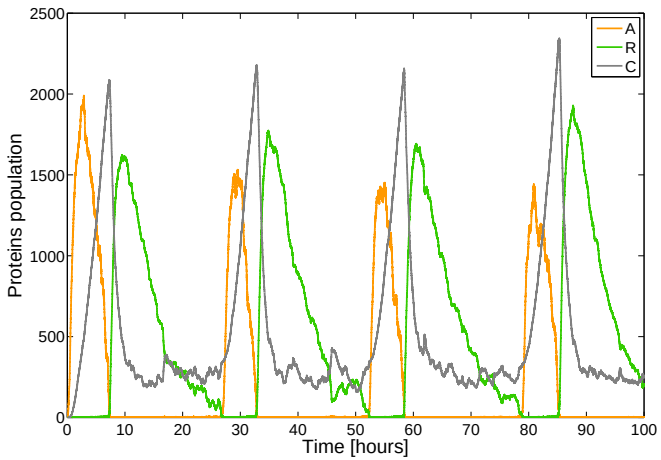
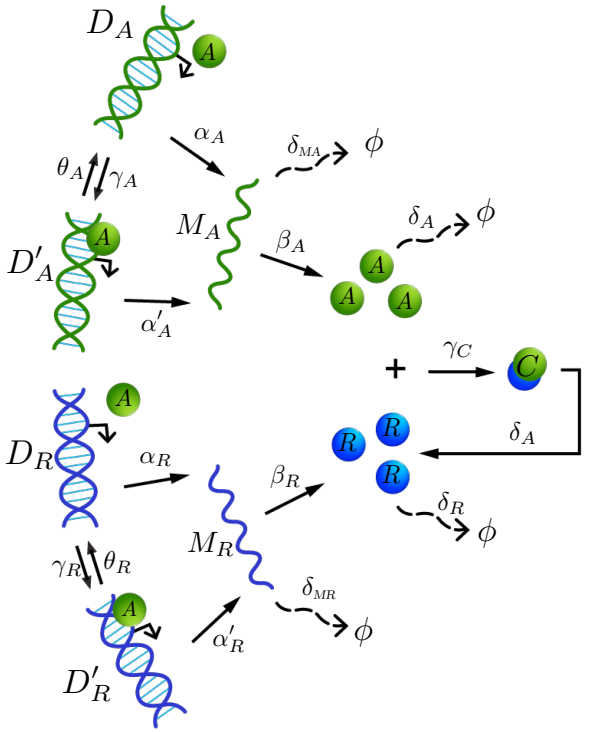
Circadian clock[1,2] $d = 9$, $K = 16$







1 J. M. G. Vilar, et al. Mechanisms of noise-resistance in genetic oscillator, *Proc. Natl. Acad. Sci.*, 2002

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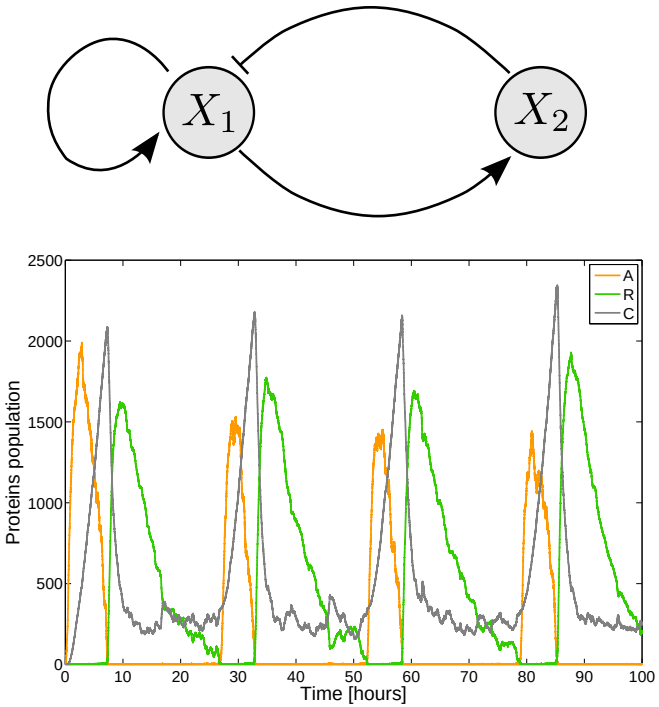

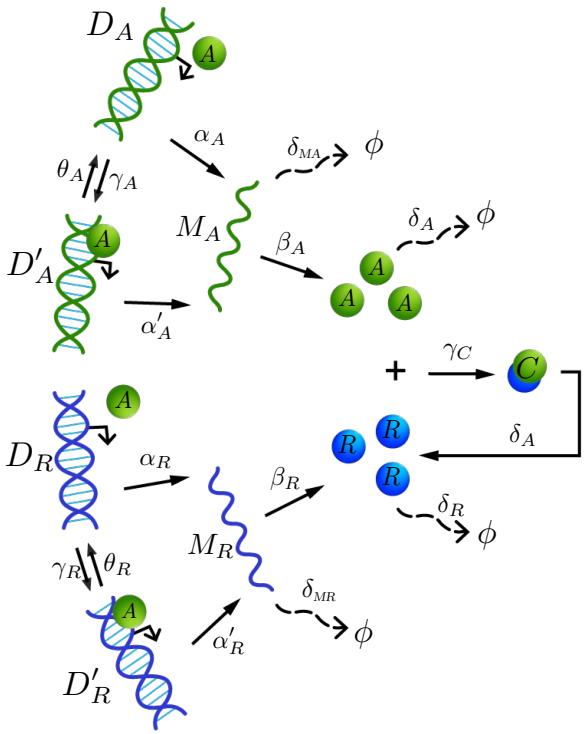

Theorem

For any values of the rate parameters, the circadian clock model is ergodic and has all its moments bounded and converging.

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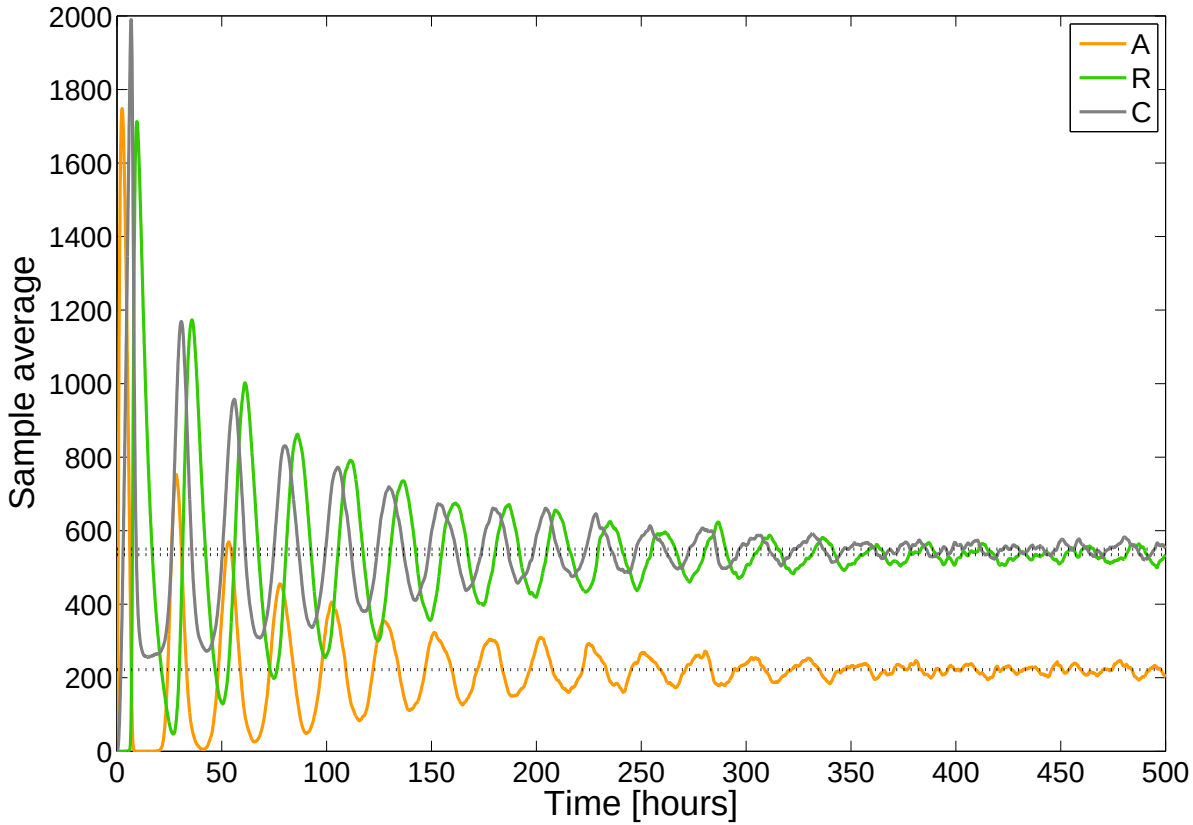
Circadian clock - Population and time averages



- The ensemble averages (plain) converge to the their stationary values, which coincide with the asymptotic time-averages (black dotted), i.e.

$$\lim_{t\to\infty} \mathbb{E}[X(t)] = \sum_{x\in\mathbb{N}_0^d} x\pi(x) = \lim_{t\to\infty} \frac{1}{t}\int_0^t X(s)ds \text{ a.s.} \qquad (1)$$

In-vivo population control

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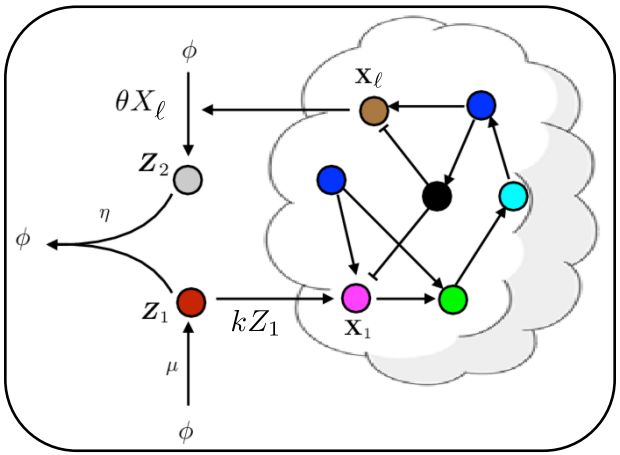
Setup[1]

Open-loop reaction network

- d molecular species: $\boldsymbol{X_1, \ldots, X_d}$
- $\boldsymbol{X_1}$ is the actuated species: $\emptyset \xrightarrow{u} \boldsymbol{X_1}$
- Measured/controlled species: $\boldsymbol{Y = X_\ell}$



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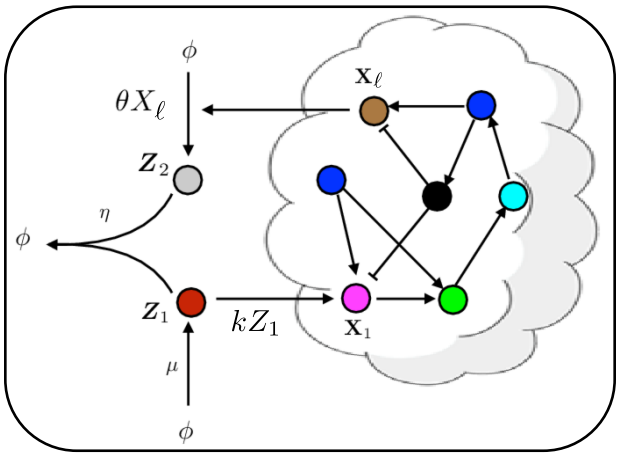

Problem

Find a controller such that the closed-loop network is ergodic and such that we have $\mathbb{E}[Y(t)] \to \mu^*$ as $t \to \infty$ for some reference value μ^* as $t \to \infty$

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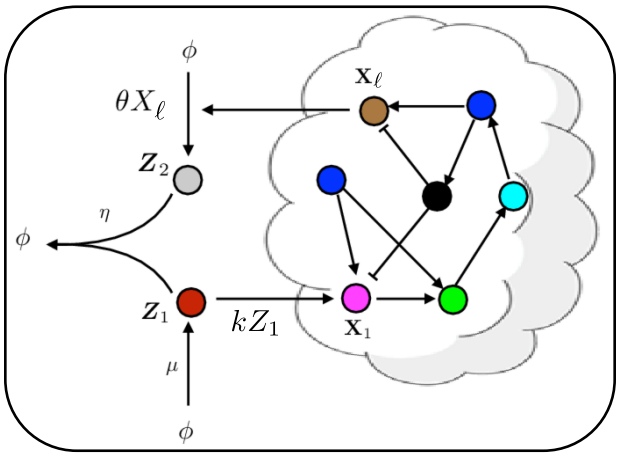

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Antithetic integral controller

- Two species $\boldsymbol{Z_1}$ and $\boldsymbol{Z_2}$.

$$\underbrace{\emptyset \xrightarrow{\mu} \boldsymbol{Z_1}}_{\text{reference}}, \quad \underbrace{\emptyset \xrightarrow{\theta Y} \boldsymbol{Z_2}}_{\text{measurement}}, \quad \underbrace{\boldsymbol{Z_1 + Z_2} \xrightarrow{\eta} \emptyset}_{\text{comparison}}, \quad \underbrace{\emptyset \xrightarrow{kZ_1} \boldsymbol{X_1}}_{\text{actuation}}.$$

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

[1] C. Briat, A. Gupta, and M. Khammash. A new motif for robust perfect adaptation in noisy biomolecular networks, *accepted in Cell Systems*, 2015

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The hidden integral action[1]

Moments equations

$$\begin{aligned}\frac{d}{dt}\mathbb{E}[Z_1(t)] &= \mu - \eta\mathbb{E}[Z_1(t)Z_2(t)] \\ \frac{d}{dt}\mathbb{E}[Z_2(t)] &= \theta\mathbb{E}[Y(t)] - \eta\mathbb{E}[Z_1(t)Z_2(t)].\end{aligned}$$

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[1] K. Oishi and E. Klavins. Biomolecular implementation of linear I/O systems, *IET Systems Biology*, 2010

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Integral action

- We have that
$$\frac{d}{dt}\mathbb{E}[Z_1(t) - Z_2(t)] = \mu - \theta\mathbb{E}[Y(t)],$$
so we have an integral action on the mean and we have that $\mu^* = \mu/\theta$
- No need for solving moments equations $\rightarrow$ no moment closure :)

[1] K. Oishi and E. Klavins. Biomolecular implementation of linear I/O systems, *IET Systems Biology*, 2010

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General stabilization result

Theorem

Let $V(x) = \langle v, x \rangle$ with $v \in \mathbb{R}^d_{>0}$ and $W(x) = \langle w, x \rangle$ with $w \in \mathbb{R}^d_{\geq 0}$, $w_1, w_\ell > 0$. Assume that

(a) *the state-space of the open-loop reaction network is irreducible; and*

(b) *there exist $c_2 > 0$ and $c_3, c_4 \geq 0$ such that*

$$\begin{aligned} \sum_{k=1}^{K} \lambda_k(x)[V(x+\zeta_k) - V(x)] &\leq -c_2 V(x), \\ \sum_{k=1}^{K} \lambda_k(x)[W(x+\zeta_k) - W(x)] &\geq -c_3 - c_4 x_\ell, \end{aligned} \tag{2}$$

hold for all $x \in \mathbb{N}^d_0$ (together with some other dreadful conditions).

Then, the closed-loop network is ergodic and we have that $\mathbb{E}[Y(t)] \to \mu/\theta$ as $t \to \infty$.

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Unimolecular networks

Theorem

Let us consider a unimolecular reaction network with irreducible state-space. Assume that its first-order moment system

$$\begin{aligned} \frac{d}{dt}\mathbb{E}[X(t)] &= A\mathbb{E}[X(t)] + e_1 u(t) \\ y(t) &= e_\ell^T \mathbb{E}[X(t)] \end{aligned} \tag{3}$$

is

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Theorem

Let us consider a unimolecular reaction network with irreducible state-space. Assume that its first-order moment system

$$\begin{aligned} \frac{d}{dt}\mathbb{E}[X(t)] &= A\mathbb{E}[X(t)] + e_1 u(t) \\ y(t) &= e_\ell^T \mathbb{E}[X(t)] \end{aligned} \tag{3}$$

is

(a) *asymptotically stable, i.e* A *Hurwitz stable (LP)*

(b) *output controllable, i.e.* $\operatorname{rank}\begin{bmatrix} e_\ell^T e_1 & e_\ell^T A e_1 & \dots e_\ell^T A^{d-1} e_1 \end{bmatrix} = 1$ *(LP)*

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Unimolecular networks

Theorem

Let us consider a unimolecular reaction network with irreducible state-space. Assume that its first-order moment system

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Then, for all control parameters $k, \eta > 0$*,*

(a) *the closed-loop reaction network (system + controller) is ergodic*

(b) *all the first and second order moments of the random variables* $X_1, \dots, X_d$ *are uniformly bounded and globally converging*

(c) $\mathbb{E}[Y(t)] \to \mu/\theta$ *as* $t \to \infty$*.*

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Properties

Closed-loop system

- Robust ergodicity, tracking and disturbance rejection
- Population control is achieved

Controller

- Innocuous: open-loop ergodic & output controllable $\Rightarrow$ closed-loop ergodic
- Decentralized: use only local information (single-cell control)
- Implementable: small number of (elementary) reactions
- Low metabolic cost: the energy consumption is proportional to μ, not μ/θ

Additional remarks

- No moment closure problem
- Expected to work on a wide class of networks (even though the theory is not there yet)

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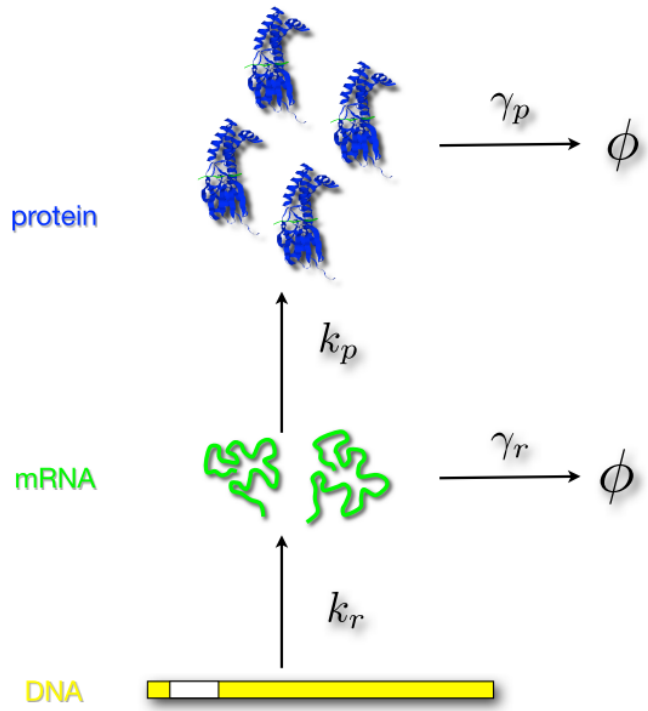
Gene expression network $d = 2$, $K = 4$



$$R_1 : \emptyset \xrightarrow{k_r} \text{mRNA } (\boldsymbol{X_1})$$
$$R_2 : \text{mRNA} \xrightarrow{\gamma_r} \emptyset$$
$$R_3 : \text{mRNA} \xrightarrow{k_p} \text{mRNA+protein } (\boldsymbol{X_1} + \boldsymbol{X_2})$$
$$R_4 : \text{protein} \xrightarrow{\gamma_p} \emptyset$$

$$S = \begin{bmatrix} \zeta_1 & \zeta_2 & \zeta_3 & \zeta_4 \end{bmatrix} = \begin{bmatrix} 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{bmatrix}$$

$$\lambda(x) = \begin{bmatrix} \lambda_1(x) & \lambda_2(x) & \lambda_3(x) & \lambda_4(x) \end{bmatrix}^T = \begin{bmatrix} k_r & \gamma_r x_1 & k_p x_1 & \gamma_p x_2 \end{bmatrix}^T$$

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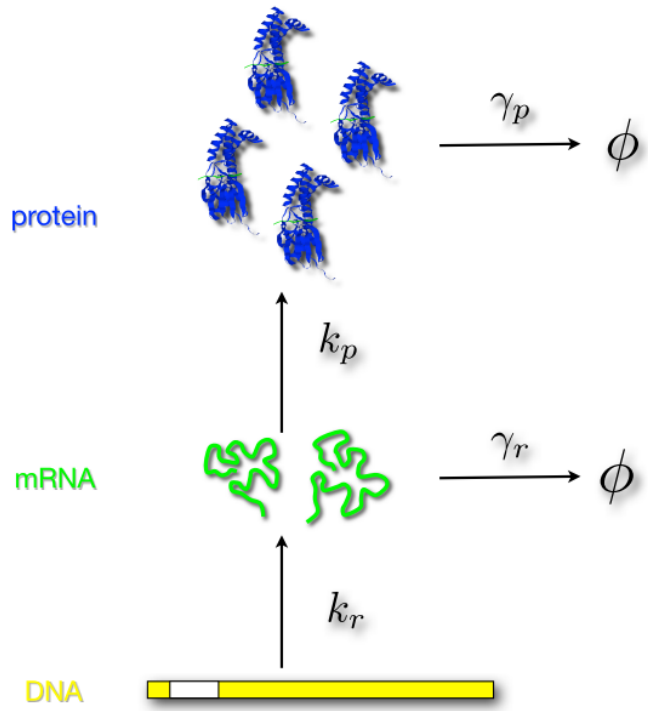
Gene expression network $d = 2$, $K = 4$



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We want to control the average number of proteins by suitably acting on the transcription rate k_r

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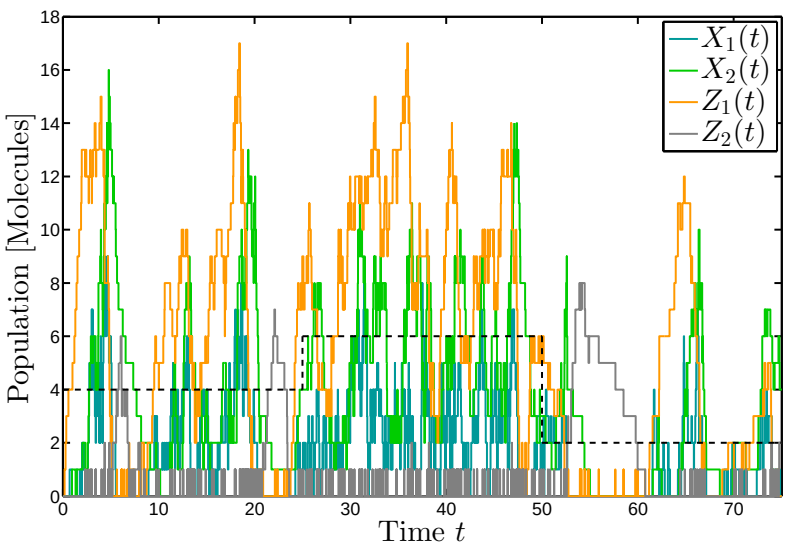
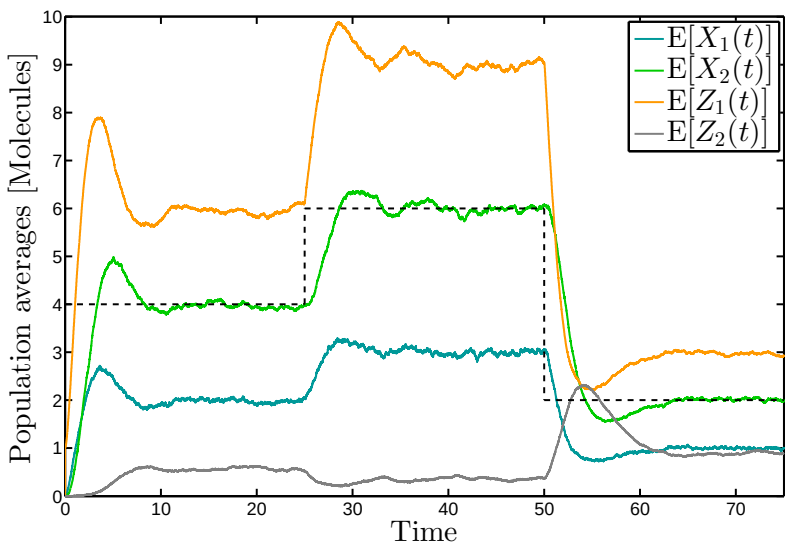
Gene expression control

Theorem

For any values of the system parameters $k_p, \gamma_r, \gamma_p > 0$ and the control parameters $\mu, \theta, k, \eta > 0$, the closed-loop network is ergodic and we have that $\mathbb{E}[X_2(t)] \to \mu/\theta$ as $t \to \infty$ globally.





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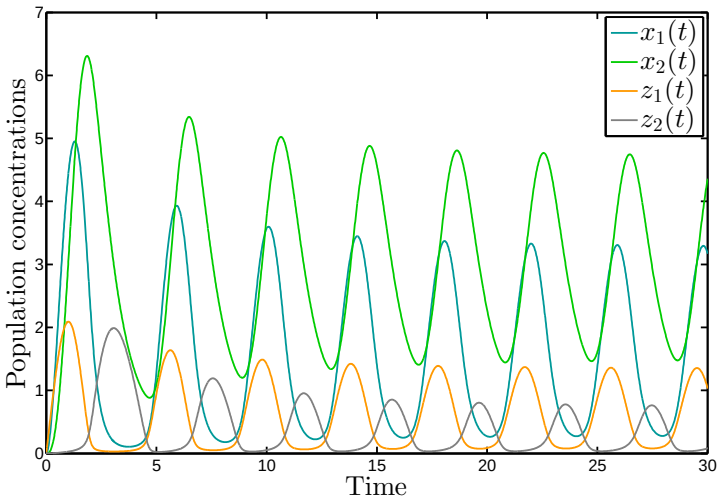
Deterministic vs. stochastic populations

Deterministic cell population

$$
\begin{aligned}
\dot{x}_1 &= k z_1 - \gamma_r x_1 \\
\dot{x}_2 &= k_p x_1 - \gamma_p x_2 \\
\dot{z}_1 &= \mu - \eta z_1 z_2 \\
\dot{z}_2 &= \theta x_2 - \eta z_1 z_2
\end{aligned}
$$



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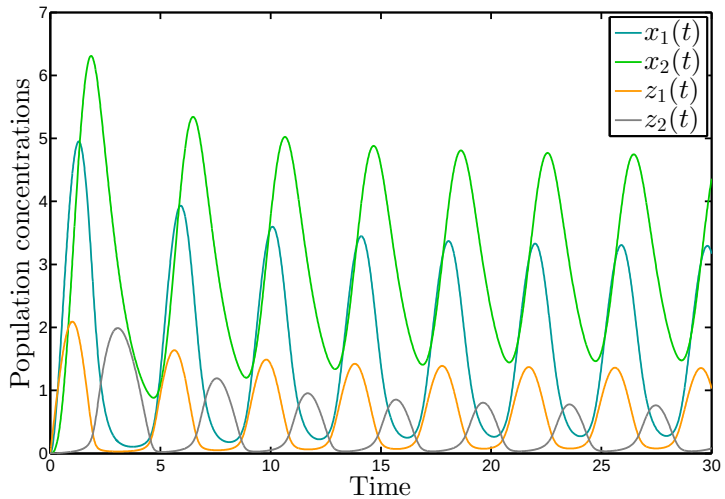
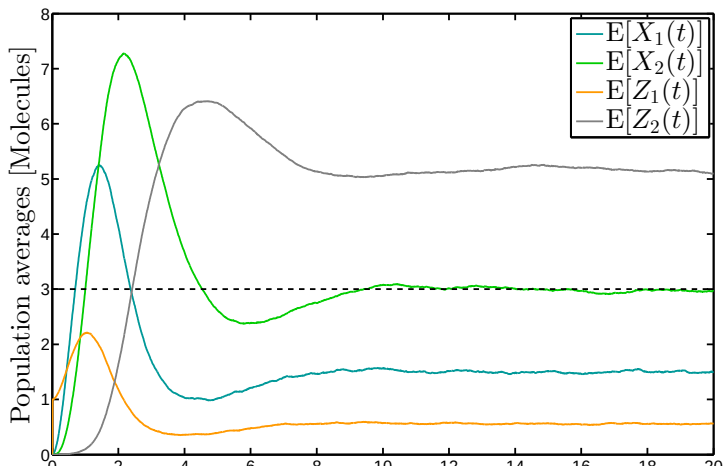


Stochastic cell population

$$
\begin{aligned}
\dot{\mathbb{E}}[X_1] &= k\mathbb{E}[Z_1] - \gamma_r \mathbb{E}[X_1] \\
\dot{\mathbb{E}}[X_2] &= k_p \mathbb{E}[X_1] - \gamma_p \mathbb{E}[X_2] \\
\dot{\mathbb{E}}[Z_1] &= \mu - \eta \mathbb{E}[Z_1]\mathbb{E}[Z_2] \\
&\quad -\eta V(Z_1, Z_2) \\
\dot{\mathbb{E}}[Z_2] &= \theta \mathbb{E}[X_2] - \eta \mathbb{E}[Z_1]\mathbb{E}[Z_2] \\
&\quad -\eta V(Z_1, Z_2)
\end{aligned}
$$



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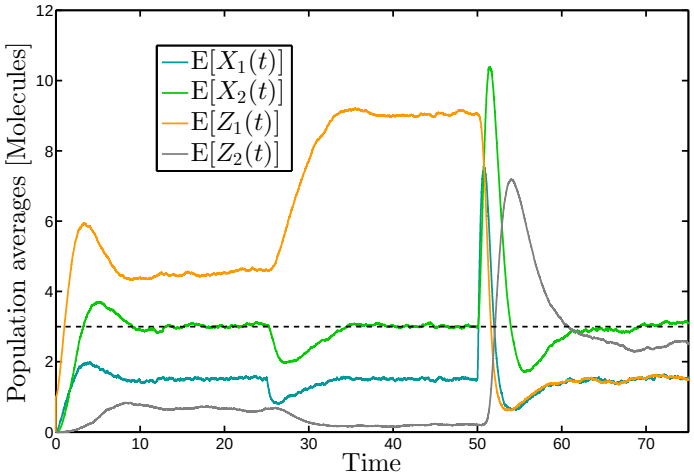
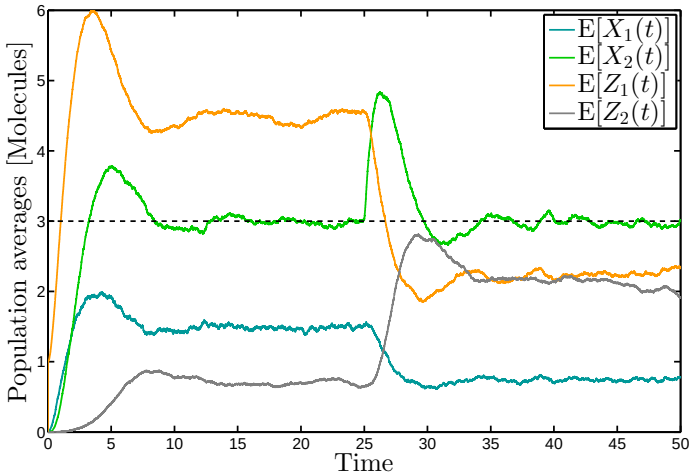
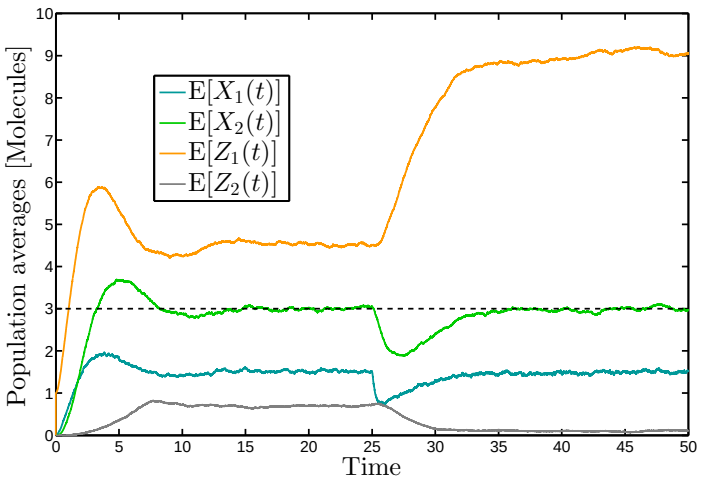
Robustness - Perfect adaptation



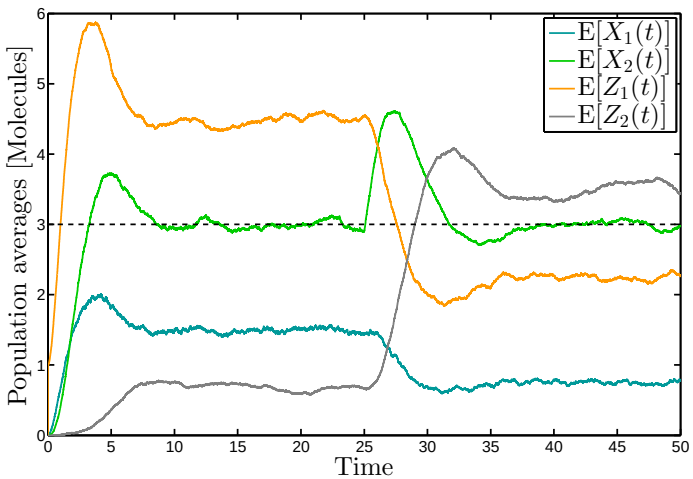
(a) Perturbation of the controller gain k



(b) Perturbation of the translation rate k_p



(c) Perturbation of the mRNA degradation rate



(d) Perturbation of the protein degradation rate

Concluding statements

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Concluding statements

Analysis - Still a lot of work

- Other types of Lyapunov functions
- Optimization methods have to be developed routines
- Some other stuffs can be done for ergodicity analysis; i.e. non-Lyapunov methods

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Concluding statements

Analysis - Still a lot of work

- Other types of Lyapunov functions
- Optimization methods have to be developed routines
- Some other stuffs can be done for ergodicity analysis; i.e. non-Lyapunov methods

Control - Even more work...

- In-vivo (integral) control seems promising (closure problem does not exist)
- Extension to bimolecular networks, multiple inputs/outputs, different controllers $\rightarrow$ biomolecular control theory - Cybergenetics
- Implementation?

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Thank you for your attention

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Computational results

Theorem

The following statements are equivalent:

(a) *The matrix A is Hurwitz and the triplet (A, e_1, e_ℓ^T) is output-controllable.*

(b) *There exist $v \in \mathbb{R}^d_{>0}$ and $w \in \mathbb{R}^d_{\geq 0}$ with $w^T e_1 > 0$, $w^T e_\ell > 0$, such that*

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

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Computational results

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

Comments

- Linear program
- Can be robustified $\rightarrow$ if $A \in [A^-, A^+]$, then $v_+^T A^+ < 0$ and $w_-^T A^- + e_\ell^T = 0$.
- Can be made structural $\rightarrow$ $A \in \{\ominus, 0, \oplus\}^{d \times d}$

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Implementation