Integral population control of a quadratic dimerization process

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Outline

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- Setup
- Modeling and analysis of reaction networks
- Mean control of a dimerization process
- Example
- Conclusion

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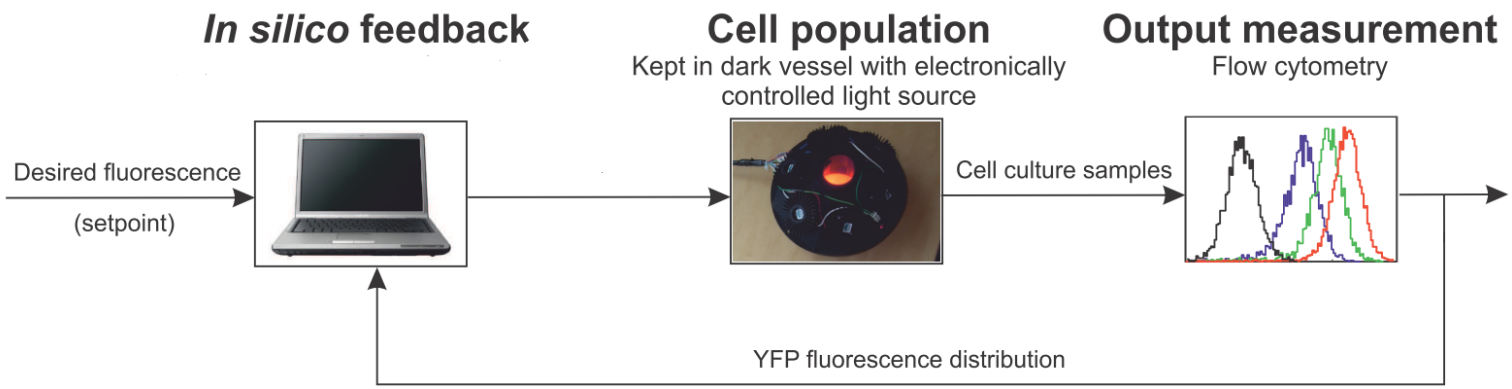
Setup



- Considered in the gene expression context
- Mean control[1] and mean+variance control in [2]

1 A. Milias-Argeitis, et al. In silico feedback for in vivo regulation of a gene expression circuit, *Nature Biotechnology*, 2011

2 C. Briat et al. Computer control of gene expression: Robust setpoint tracking of protein mean and variance using integral feedback, *51st IEEE Conference on Decision and Control*, 2012

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Modeling and analysis of reaction networks

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Modeling biochemical networks

Variables

- N molecular species $S_1, \ldots, S_N$
- M reactions $R_1, \ldots, R_M$

$$\phi \xrightarrow{k} S_1, \quad S_1 \xrightarrow{\gamma} \phi, \quad S_1 + S_2 \xrightarrow{k_b} S_3$$

Dynamics

- Deterministic (ODEs) $\rightarrow$ concentrations $x(t) \in \mathbb{R}^N_{\geq 0}$
- Stochastic (jump processes) $\rightarrow$ molecule counts $X(t) \in \mathbb{N}^N_0$

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Stochastic chemical reaction network

Randomness in biology[1]

- Intrinsic noise (variability inside a cell)
- Extrinsic noise (cell-to-cell variability)
- External noise (environment)

Chemical Master Equation

$$\dot{P}(\varkappa, t) = \sum_{k=1}^{M} [\lambda_k(\varkappa - \zeta_k)P(\varkappa - \zeta_k, t) - \lambda_k(\varkappa)P(\varkappa, t)] \tag{1}$$

- $P(\varkappa, t)$: probability to be in state $\varkappa$ at time t.
- ζ_k: stoichiometry vector associated to reaction R_k.
- λ_k: propensity function capturing the rate of the reaction R_k.

1 M. B. Elowitz, et al. Stochastic gene expression in a single cell, *Science*, 2002

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Moments expression

General case

$$\begin{aligned} \frac{\mathrm{d}E[X]}{\mathrm{d}t} &= SE[\lambda(X)], \\ \frac{\mathrm{d}E[XX^\intercal]}{\mathrm{d}t} &= SE[\lambda(X)X^\intercal] + E[\lambda(X)X^\intercal]^\intercal S^\intercal + S\,\mathrm{diag}\{E[\lambda(X)]\}S^\intercal \end{aligned} \tag{2}$$

- $S := \begin{bmatrix} \zeta_1 & \dots & \zeta_M \end{bmatrix} \in \mathbb{R}^{N\times M}$: stoichiometry matrix.
- $\lambda(X) := \begin{bmatrix} \lambda_1^\intercal & \dots & \lambda_M^\intercal \end{bmatrix}^\intercal \in \mathbb{R}^M$: propensity vector.

Affine propensity case $\lambda(X) = WX + \lambda_0$

$$\begin{aligned} \frac{dE[X]}{dt} &= SWE[X] + S\lambda_0, \\ \frac{d\Sigma}{dt} &= SW\Sigma + (SW\Sigma)^\intercal + S\,\mathrm{diag}(WE[X] + \lambda_0)S^\intercal \end{aligned} \tag{3}$$

- Σ: covariance matrix
- Linear equations

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Polynomial propensity case

- Moment closure problem $\rightarrow$ first-order moments depend on the second-order ones, and so forth...
- Infinite set of linear ODEs (unstructured, non-necessarily Metzler...)
- Closure methods

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Dimerization process

Process

$$\begin{array}{lllll} R_1 & : & \phi & \xrightarrow{k_1} & S_1 \\ R_3 & : & S_1 & \xrightarrow{\gamma_1} & \phi \end{array} \qquad \begin{array}{lllll} R_2 & : & S_1+S_1 & \xrightarrow{b} & S_2 \\ R_4 & : & S_2 & \xrightarrow{\gamma_2} & \phi \end{array}$$

- Stoichiometry matrix:

$$S = \begin{bmatrix} 1 & -2 & -1 & 0 \\ 0 & 1 & 0 & -1 \end{bmatrix}$$

- Propensity function:

$$\lambda(X) = \begin{bmatrix} k_1 & \frac{b}{2}X_1(X_1-1) & \gamma_1 X_1 & \gamma_2 X_2 \end{bmatrix}^{\intercal}.$$

Motivations

- Goes beyond the affine case (e.g. gene expression[1]) and introduce dimerization
- Check whether the moments equations framework still applicable (closure problem)

[1] C. Briat et al. Computer control of gene expression: Robust setpoint tracking of protein mean and variance using integral feedback, *51st IEEE Conference on Decision and Control*, 2012

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Moments equations

Dynamical model

$$\begin{aligned}\dot{x}_1(t) &= k_1 + (b-\gamma_1)x_1(t) - bx_1(t)^2 - bv(t)\\ \dot{x}_2(t) &= -\frac{b}{2}x_1(t) - \gamma_2 x_2(t) + \frac{b}{2}x_1(t)^2 + \frac{b}{2}v(t)\end{aligned}$$

where

- $x_i(t) := \mathbb{E}[X_i(t)]$, $i = 1, 2$,
- $v(t) := V(X_1(t))$ is the variance of the random variable $X_1(t)$.

Difficulties

- Nonlinear system (as opposed to linear for networks with affine propensities)
- Unknown "input" variance $v(t) := V(X_1(t))$ (closure problem). Is it bounded? Is it converging?
- If $v \to v^*$, we have an infinite number of non-isolated equilibrium points (model artefact since the first-order moments may have a unique stationary value)

$$v^* \to \begin{bmatrix} x_1^* \\ x_2^* \end{bmatrix} \text{ locally continuous}$$

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Statement of the problem

Objective

Find k_c such that the integral control law

$$\begin{aligned} \dot{I}(t) &= \mu - \mathbb{E}[X_2(t)] \\ u(t) &= k_c \cdot \max\{I(t), 0\} \end{aligned} \tag{3}$$

locally steers $\mathbb{E}[X_2(t)]$ to μ (stability and attractivity of the corresponding equilibrium point).

Subproblems

- Are the moments bounded and converging for some parameter values? (stability)
- Choose a control input that can drive $E[X_2]$ to μ asymptotically
- Find conditions on the controller gain k_c such that we have local asymptotic stability of the first order moments.

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Ergodicity of the dimerization process

Reaction network

$$\begin{array}{lllll} R_1 & : & \phi & \xrightarrow{k_1} & S_1 \\ R_3 & : & S_1 & \xrightarrow{\gamma_1} & \phi \end{array} \qquad \begin{array}{lllll} R_2 & : & S_1+S_1 & \xrightarrow{b} & S_2 \\ R_4 & : & S_2 & \xrightarrow{\gamma_2} & \phi \end{array}$$

Theorem

For any positive value of the network parameters k_1, b, γ_1 and γ_2, the dimerization process is ergodic and has all its moments bounded and converging.

$$\Rightarrow (x_1(t), x_2(t), v(t)) \to (x_1^*, x_2^*, v^*) \text{ globally and exponentially}$$

- Proof relying on an ergodicity result developed in the paper[1]

[1] C. Briat, A. Gupta and M. Khammash, "*A scalable computational framework for establishing long-term behavior of stochastic reaction networks*", submitted to PLOS computational biology

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Control of the mean population

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Choice of the control input

Assumption

The function $S^* := x_1^{*2} - x_1^* + v^*$, where x_1^* is the unique equilibrium solution for x_1 and v^* is the equilibrium variance, verifying the equation

$$k_1 - \gamma x_1^* - bS^* = 0, \tag{4}$$

is a continuous function of k_1.

Proposition

For any $\mu > 0$, there exists a constant $k_1 > 0$ such that $x_2(t) \to \mu$.

- The birth rate k_1 can then be chosen as control input
- Good for us, this is also the simplest case!
- Other rates could have been also chosen

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Nominal stabilization

Theorem

For any finite positive constants $\gamma_1, \gamma_2, b, \mu$ and any controller gain k_c satisfying

$$0 < k_c < 2\gamma_2 \left(2\gamma_1 + \gamma_2 + 2\sqrt{\gamma_1(\gamma_1 + \gamma_2)}\right), \tag{5}$$

the closed-loop system has a unique locally stable equilibrium point (x_1^*, x_2^*, I^*) in the positive orthant such that $x_2^* = \mu$.
The equilibrium variance moreover satisfies

$$v^* \in \left(0, \frac{2\gamma_2\mu}{b} + \frac{1}{4}\right]. \tag{6}$$

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Proof (sketch)

- We have that

$$\begin{aligned} k_c I^* - \gamma_1 x_1^* - 2\gamma_2 \mu &= 0 \\ x_1^{*2} - x_1^* + v^* - \frac{\gamma_2 \mu}{b} &= 0 \end{aligned} \tag{7}$$

- Study the eigenvalues of the Jacobian system from the characteristic polynomial
- Four different scenarios according to the value v^*
  - two positive equilibrium points: one is stable for some $k_c > 0$, the other is structurally unstable
  - one positive and one zero equilibrium point: the positive one is stable for some $k_c > 0$, the other is structurally unstable
  - one positive and one negative equilibrium point: the positive one is stable for some $k_c > 0$.
  - two complex equilibrium points: this case can not occur (existence of unique equilibrium point)
- The existence of an equilibrium point induces a condition on v^*
- Intersection of the conditions on k_c gives the result

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Robust stabilization

Uncertainty set

$$\mathcal{P} := [\gamma_1^-, \gamma_1^+] \times [\gamma_2^-, \gamma_2^+] \times [b^-, b^+] \tag{8}$$

defined for some appropriate positive real numbers $\gamma_1^- < \gamma_1^+$, $\gamma_2^- < \gamma_2^+$ and $b^- < b^+$.

We get the following robustification:

Theorem

Assume the controller gain k_c verifies

$$0 < k_c < 2\gamma_2^- \left(2\gamma_1^- + \gamma_2^- + 2\sqrt{\gamma_1^-(\gamma_1^- + \gamma_2^-)}\right). \tag{9}$$

Then, for all $(\gamma_1, \gamma_2, b) \in \mathcal{P}$, the closed-loop system has a unique locally stable equilibrium point (x_1^*, x_2^*, I^*) in the positive orthant such that $x_2^* = \mu$. The equilibrium variance v^*, moreover, satisfies

$$v^* \in \left(0, \frac{2\gamma_2^+ \mu}{b^-} + \frac{1}{4}\right] \tag{10}$$

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Example

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Example

- Parameters: $b = 3$, $\gamma_1 = 2$ and $\gamma_2 = 1$
- Closed-loop stability and tracking ensured if $0 < k_c < 19.798$
- Choose $k_c = 1$, $\mu = 5$, $T_s = 10$ms, $I(0) = 0$, $N = 2000$, x_0^i picked randomly in $\{0, 1\}^2$, $i = 1, \ldots, N$

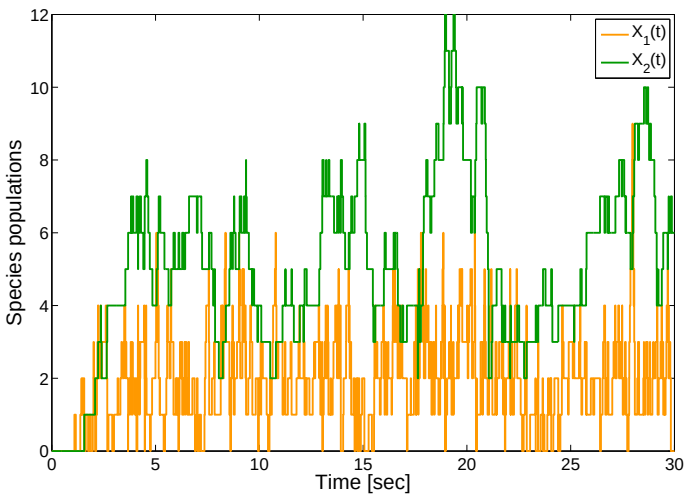

Figure: Evolution of proteins populations in a single cell.

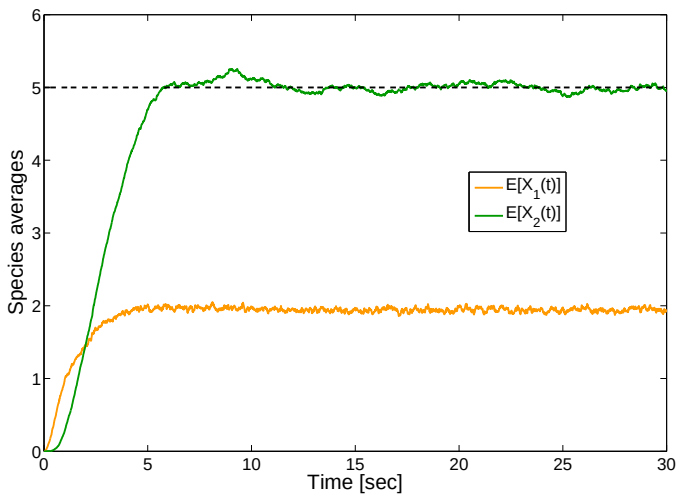

Figure: Evolution of the proteins averages in a population of 2000 cells.

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Example

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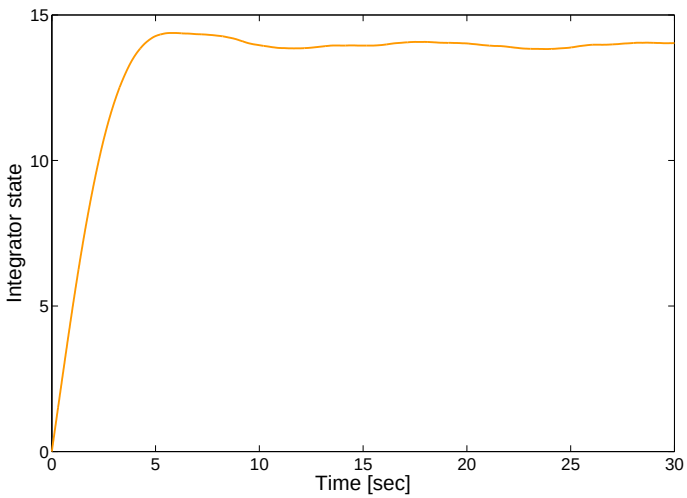

Figure: State of the integrator.

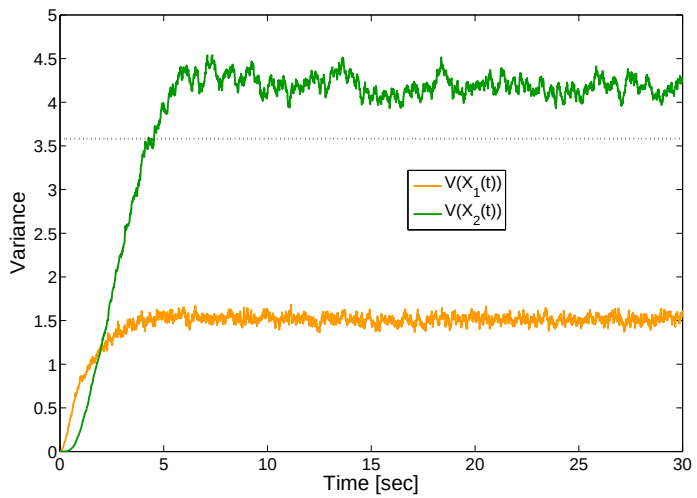

Figure: Evolution of the variances.

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Approximate simulation algorithm

Require: $T_s, \mu, k_c, T > 0$, $N, N_p \in \mathbb{N}$, $\{x_0^1, \ldots, x_0^N\} \in \left(\mathbb{N}_0^2\right)^N$, $I_0 \in \mathbb{R}$ and $p \in \mathbb{R}_{>0}^{N_p}$

1: Create array t of time instants from 0 to T with time-step T_s.
2: $N_s = \text{length}(t)$
3: Initialize: $i \leftarrow 1$, $y \leftarrow \text{mean}(dimer\ population)$, $I \leftarrow I_0$
4: **for** $i < N_s$ **do**
5: Update control input: $u \leftarrow k_c \cdot \max\{0, I\}$
6: Update controller state: $I \leftarrow I + T_s(\mu - y)$
7: Simulation of N cells from time $t[i]$ to $t[i+1]$ with control input u and network parameters p
8: Update output: $y \leftarrow \text{mean}(dimer\ population)$
9: $i \leftarrow i + 1$
10: **end for**

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Conclusion

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Conclusion and Future Works

Conclusion

- Local integral control of a simple quadratic reaction network
- Moment closure problem can be circumvented
- So the moments framework seems to be still applicable for small systems
- The complexity, however, grows quite fast and shows limits for the moments equations

Possible follow-ups

- Extensions to more general families of networks
- Good thing: reactions may be considered as worst-case quadratic for mass action kinetics
- Other types of control laws and models can be explored

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Thank you for your attention