Computer control of gene expression: Robust setpoint tracking of protein mean and variance using integral feedback

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Outline

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Introduction

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Stochastic chemical reaction network

Variables

- N molecular species $S_1, \ldots, S_N$
- M reactions $R_1, \ldots, R_M$
- Population of each species: random variables $X_1(t), \ldots, X_N(t)$

Chemical Master Equation

$$\dot{P}(\varkappa, t) = \sum_{k=1}^{M} [w_k(\varkappa - s_k)P(\varkappa - s_k, t) - w_k(\varkappa)P(\varkappa, t)] \quad (1)$$

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

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Moments expression

General case

$$\begin{aligned}\frac{dE[X]}{dt} &= SE[w(X)],\\ \frac{dE[XX^T]}{dt} &= SE[w(X)X^T] + E[w(X)X^T]^T S^T + S\,\mathrm{diag}\{E[w(X)]\}S^T\end{aligned} \quad (2)$$

- $S := \begin{bmatrix} s_1 & \ldots & s_M \end{bmatrix} \in \mathbb{R}^{N\times M}$: stoichiometry matrix.
- $w(X) := \begin{bmatrix} w_1^T & \ldots & w_M^T \end{bmatrix}^T \in \mathbb{R}^M$: propensity vector.

Affine propensity case $w(X) = WX + w_0$

$$\begin{aligned}\frac{dE[X]}{dt} &= SWE[X] + Sw_0,\\ \frac{d\Sigma}{dt} &= SW\Sigma + (SW\Sigma)^T + S\,\mathrm{diag}(WE[X] + w_0)S^T\end{aligned} \quad (3)$$

- Σ: covariance matrix
- Linear equations

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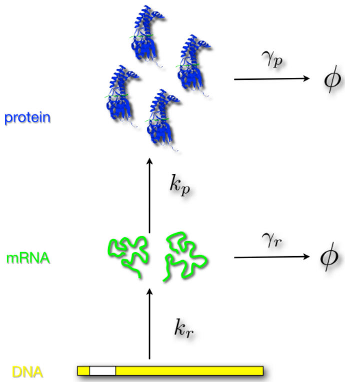
Gene expression circuit



$$R_1 \quad : \quad \phi \xrightarrow{k_r} \text{mRNA}$$
$$R_2 \quad : \quad \text{mRNA} \xrightarrow{\gamma_r} \phi$$
$$R_3 \quad : \quad \text{mRNA} \xrightarrow{k_p} \text{protein+mRNA}$$
$$R_4 \quad : \quad \text{protein} \xrightarrow{\gamma_p} \phi$$

$$S = \begin{bmatrix} 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{bmatrix} \qquad w(X) = \begin{bmatrix} k_r & \gamma_r X_1 & k_p X_1 & \gamma_p X_2 \end{bmatrix}^T$$

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Moments dynamics

$$\dot{x}(t) = \left[\begin{array}{cc|ccc} -\gamma_r & 0 & 0 & 0 & 0 \\ k_p & -\gamma_p & 0 & 0 & 0 \\ \hline \gamma_r & 0 & -2\gamma_r & 0 & 0 \\ 0 & 0 & k_p & -(\gamma_r+\gamma_p) & 0 \\ k_p & \gamma_p & 0 & 2k_p & -2\gamma_p \end{array}\right] x(t) + \left[\begin{array}{c} 1 \\ 0 \\ \hline 1 \\ 0 \\ 0 \end{array}\right] k_r$$

where the state variables are defined as

$$\begin{bmatrix} x_1 \\ x_2 \end{bmatrix} := E[X] \text{ and } \begin{bmatrix} x_3 & x_4 \\ x_4 & x_5 \end{bmatrix} := \Sigma$$

- Asymptotically stable system with equilibrium point

$$x_1^* = \frac{k_r}{\gamma_r}, \quad x_2^* = \frac{k_p k_r}{\gamma_p \gamma_r}, \quad x_3^* = \frac{k_r}{\gamma_r}, \quad x_4^* = \frac{k_p k_r}{\gamma_r(\gamma_p+\gamma_r)}, \quad x_5^* = \frac{k_p k_r(\gamma_p + k_p + \gamma_r)}{\gamma_p\gamma_r(\gamma_p+\gamma_r)}.$$

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Mean Control

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Problem statement

Mean dynamics

$$\begin{bmatrix} \dot{x}_1(t) \\ \dot{x}_2(t) \end{bmatrix} = \begin{bmatrix} -\gamma_r & 0 \\ k_p & -\gamma_p \end{bmatrix} \begin{bmatrix} x_1(t) \\ x_2(t) \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \end{bmatrix} u(t) \quad (4)$$

- Control input: transcription rate k_r.
- Controlled variable: mean number of proteins x_2, [Klavins, 2010], [Milias-Argeitis et al. 2011]

Positive PI Controller

$$u(t) = \varphi\left(k_1(\mu_* - x_2(t)) + k_2 \int_0^t [\mu_* - x_2(s)]ds\right) \quad (5)$$

- μ^*: desired mean value.
- k_1, k_2: gains of the PI controller
- $\varphi(u) := \max\{0, u\}$: nonnegativity constraint on the control input.

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Global stability analysis

Equilibrium point

Given any $\mu_* \geq 0$, the equilibrium point of the closed-loop system is given by

$$x_1^* = \frac{\mu_* \gamma_p}{k_p}, \; x_2^* = \mu_*, \; u^* = \frac{\mu_* \gamma_p \gamma_r}{k_p}, \; I^* = \frac{u^*}{k_2} \tag{6}$$

where I^* is the equilibrium value of the integral term.

Theorem - Global asymptotic stability

Given system parameters $k_p, \gamma_p, \gamma_r > 0$ and assume that

$$k_1 \quad > \quad \frac{k_2}{\gamma_p} \quad \text{and} \quad k_2 \quad > \quad 0. \tag{7}$$

then the unique equilibrium point of the controlled system is globally asymptotically stable.

- Straightforward extension to the robust case.

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Proof sketch

- LTI system + static nonlinearity in the sector $[0, 1]$
- Popov criterion can be used to infer stability of the closed-loop system:
- Globally asymptotically stable if there exists $q \geq 0$ such that

$$\Re\left[(1 + qj\omega)H(j\omega)\right] > -1 \tag{8}$$

holds for all $\omega \in \mathbb{R}$ and where

$$H(s) = \frac{k_p(k_1 s + k_2)}{s(s + \gamma_r)(s + \gamma_p)}. \tag{9}$$

- Equivalent to the positivity problem

$$N_0(\omega) + qN_1(\omega) + D(\omega) > 0 \tag{10}$$

- Descartes' rule of signs yields the result.
- Exact conditions can be obtained using Sturm series.

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Mean and variance control

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Fundamental limitations

Mean vs. variance

$$\sigma_*^2 = \left(1 + \frac{k_p}{\gamma_p + \gamma_r}\right)\mu_*, \qquad \mu_* = \frac{k_p u_1^*}{\gamma_p \gamma_r} \tag{11}$$

- Need of a second control input $\rightarrow u_2 \equiv \gamma_r$

Property

The set of admissible reference values (μ_*, σ_*^2) *is given by*

$$\mathcal{A} := \left\{(x, y) \in \mathbb{R}_{>0}^2 : \; x < y < \left(1 + \frac{k_p}{\gamma_p}\right)x\right\} \tag{12}$$

where $k_p, \gamma_p > 0$.

Independent of the controller !

Sketch

- Lower bound $\leftarrow C_\nu := \sigma_*/\mu_*$.
- Upper bound $\leftarrow$ nonnegativity of the control inputs.

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System formulation

Mean and variance dynamics

$$\begin{aligned}\dot{x}_1 &= -u_2 x_1 + u_1\\ \dot{x}_2 &= k_p x_1 - \gamma_p x_2\\ \dot{x}_3 &= u_2 x_1 - 2u_2 x_3 + u_1\\ \dot{x}_4 &= k_p x_3 - \gamma_p x_4 - u_2 x_4\\ \dot{x}_5 &= k_p x_1 + \gamma_p x_2 + 2k_p x_4 - 2\gamma_p x_5\\ \dot{I}_1 &= \mu_* - x_2\\ \dot{I}_2 &= \sigma_*^2 - x_5\end{aligned} \tag{13}$$

- Bilinear system.

Controller

$$\begin{aligned}u_1 &= \varphi\left(k_1(\mu_* - x_2) + k_2 I_1 + k_3(\sigma_*^2 - x_5) + k_4 I_2\right)\\ u_2 &= \varphi\left(k_5(\mu_* - x_2) + k_6 I_1 + k_7(\sigma_*^2 - x_5) + k_8 I_2\right)\\ \varphi(u) &= \max\{u, 0\}\end{aligned} \tag{14}$$

- Multivariable positive PI controller.

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Equilibrium Point

Equilibrium point is unique

Assume that $k_2k_8 - k_4k_6 \neq 0$, then the equilibrium point of the closed-loop system is unique and given by

$$\begin{array}{rclrclrcl} x_1^* & = & \dfrac{\gamma_p}{k_p}\mu_* = x_3^*, & x_2^* & = & \mu_*, & x_5^* & = & \sigma_*^2, \\ x_4^* & = & \dfrac{\gamma_p}{\gamma_p + u_2^*}\mu_*, & u_1^* & = & \dfrac{\gamma_p}{k_p}\mu_* u_2^*, & u_2^* & = & -\gamma_p + \dfrac{k_p\mu_*}{\sigma_*^2 - \mu_*} \end{array}$$

and

$$\begin{bmatrix} I_1^* \\ I_2^* \end{bmatrix} = \begin{bmatrix} k_2 & k_4 \\ k_6 & k_8 \end{bmatrix}^{-1} \begin{bmatrix} u_1^* \\ u_2^* \end{bmatrix}.$$

Set of equilibrium points

$$\mathcal{X}^* := \left\{(x^*, I^*) \in \mathbb{R}^7 : \ (y_*, \sigma_*^2) \in \mathcal{A}\right\}$$

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Semiglobal stabilizability

Theorem

Given any $k_p, \gamma_p > 0$, the mean/variance bilinear system is locally exponentially stabilizable around any equilibrium point in $\mathcal{X}^*$ using the PI control law.

Moreover, there exists a PI control law that simultaneously locally exponentially stabilizes the mean/variance system around all the equilibrium points in $\mathcal{X}^*$.

Proof sketch

- Open-loop system marginally stable
- Two integrators (controller)
- Difficulties: system large and structured controller.
- Eigenvalue perturbation argument

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Examples

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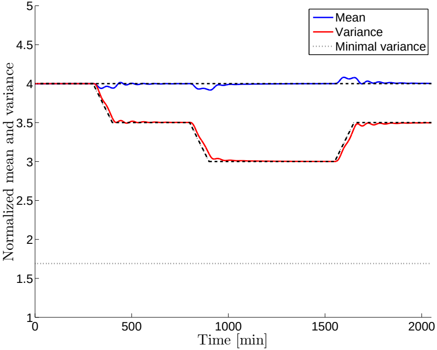
Variance control

- Model parameters taken from [Milias-Argeitis et al. 2011].
- PI controller gains $k_1 = 1$, $k_2 = 0.007$, $k_7 = -0.2$ and $k_8 = -0.0014$.



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Conclusion

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Conclusion and Future Works

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Conclusion

- PI controller sufficient for mean and variance control.
- PI control globally and simultaneously stabilizes the mean around any desired equilibrium point.
- PI control locally and simultaneously stabilizes the mean and variance around any admissible equilibrium point.

Future Works

- Implementation.
- Generalization to more general networks (moment closure problem)

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Thank you for your attention