

# **Robust and Circuit Design of Biochemical Networks under Stochastic Intrinsic Fluctuations and Extrinsic Noises**

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## **Abstract Submission**

Robustness is an essential property to attenuate the effects of internal fluctuation and external noise which affect the biochemical regulatory networks including genes, proteins and other regulatory molecules. In this study, several system control schemes are proposed for the robust circuit control design of nonlinear biochemical regulatory networks. If a biochemical regulatory network is not sufficiently robust to tolerate internal fluctuation and does not have enough attenuation ability to filter the external noise, how to improve the robustness and noise attenuation ability by engineered control mechanisms is also proposed via biochemical circuit design. A global linearization method is employed to avoid solving Hamilton-Jacobi inequality (HJI) but only solving a set of linear matrix inequalities (LMI) to simplify the circuit design procedure. This has potential applications for therapy and drug design.

Robustness is an essential property to attenuate the effects of internal and external noise which affect the biochemical regulatory networks including genes, proteins and others. In this study, several system control schemes are proposed for the robust control design of nonlinear biochemical regulatory networks. If a network is not sufficiently robust and has insufficient attenuation ability, how to improve these properties by engineered control mechanisms is also proposed via biochemical circuit design. A global linearization method is employed to avoid solving Hamilton-Jacobi inequality (HJI) but only solving a set of linear matrix inequalities (LMI) to simplify this procedure. This has potential applications for therapy and drug design.

### Extend Abstract

Suppose the nonlinear biochemical regulatory network is affected by the following intrinsic stochastic perturbation  $\sum_{i=1}^L f_i(X[k])p_i[k]$  and extrinsic noise  $v[k]$  simultaneously

$$\begin{aligned} X[k+1] &= f(X[k]) + \sum_{i=1}^L f_i[k]p_i[k] + B_v v[k] \\ Z[k] &= C_Z X[k] \end{aligned} \quad (1)$$

where  $f(X[k])$  denotes the nonlinear interactions among  $n$  molecules, and the intrinsic perturbation is due to different stochastic perturbative sources  $p_i$ . Then we want to discuss the robust stability and the attenuation ability from the external

disturbance to  $Z[k]$  of interested molecules, i.e.  $\frac{\|Z[k]\|_2}{\|v[k]\|_2} \leq \rho$  for some attenuate level  $\rho$ .

### Theorem 1

If the following inequality holds for a Lyapunov function  $V(X[k]) > 0$  and a prescribed noise attenuation  $\rho$

$$\begin{aligned} & \left( \frac{\partial V(X[k])}{\partial X[k]} \right)^T (f(X[k]) - X[k]) + \frac{1}{2} \left( \frac{\partial V(X[k])}{\partial X[k]} \right)^T \left( \frac{\partial V(X[k])}{\partial X[k]} \right) + \frac{1}{2} \sum_{i=1}^L f_i^T(X[k]) f_i(X[k]) \\ & + \frac{1}{2\rho^2} \left( \frac{\partial V(X[k])}{\partial X[k]} \right)^T B_v B_v^T \left( \frac{\partial V(X[k])}{\partial X[k]} \right) + \frac{1}{2} Z^T[k] Z[k] \leq 0 \end{aligned} \quad (2)$$

then the effect of external noise  $v[k]$  on  $Z[k]$  is less than  $\rho$ , i.e. the robust filtering with noise attenuation  $\rho$  is achieved for the nonlinear biochemical network.

### Remark 1

In general, it is not easy to solve the Hamilton-Jacobi inequality (HJI) in (2) for the robust noise attenuation problem. Based on the vertices of the convex hull of the

global linearization of a nonlinear system (1), i.e.  $\begin{bmatrix} f(X) \\ f_i(X) \end{bmatrix} \in \Omega \left\{ \begin{bmatrix} A_1 \\ A_{i1} \end{bmatrix}, \dots, \begin{bmatrix} A_M \\ A_{iM} \end{bmatrix} \right\}$ ,

$i = 1 \dots L$ , if there is a common solution  $P > 0$  for the following LMIs,

$$\begin{bmatrix} A_j^T P A_j - P + \sum_{i=1}^L \sigma_i^2 A_{ij}^T P A_{ij} + C_Z^T C_Z & A_j^T P B_v \\ B_v^T P A_j & B_v^T P B_v - \rho^2 I \end{bmatrix} \leq 0, j = 1 \dots M \quad (3)$$

then the robust filtering with a prescribed noise attenuation  $\rho$  could be achieved for the stochastically perturbative biochemical network. In (3), we need to solve  $M$  LMIs to replace solving the HJI in (2).

The noise attenuation ability  $\rho_0$  defined as the minimum  $\rho$  to solve HJI in a nonlinear biochemical system (1) could be achieved by minimizing  $\rho$  via the following constrained optimization problem

$$\rho_0 = \min_{P>0} \rho \quad (4)$$

subject to  $P > 0$ , (3)

For biotechnology or therapeutic design, suppose a prescribed noise attenuation ability  $\rho_p < \rho_0$  is to be designed for more efficient noise filtering in the nonlinear perturbative biochemical network (1). In this situation, the following biochemical circuit control design  $Fg(X[k])$  is proposed to improve the robust filtering to achieve the prescribed attenuation ability  $\rho_p$

$$X[k+1] = f(X[k]) + Fg(X[k]) + \sum_{i=1}^L f_i(X[k])p_i[k] + B_v v[k] \quad (5)$$

$$Z[k] = C_Z X[k]$$

By the global linearization method, we get the following robust filtering design to improve the noise attenuation ability.

### Theorem 2

Suppose control parameter matrix  $F$  is specified for a biochemical network (5) such that the following LMIs hold for a symmetric positive  $P > 0$

$$\begin{bmatrix} -P + \sum_{i=1}^L A_{ij}^T P A_{ij} + C_Z^T C_Z & (A_j + FG_j)^T P & (A_j + FG_j)^T P B_v \\ P(A_j + FG_j) & -P & 0 \\ B_Z^T P A_j & 0 & B_v^T P B_v - \rho_p^2 I \end{bmatrix} < 0, \quad j = 1 \dots M \quad (6)$$

Then the prescribed noise attenuation ability  $\rho_p$  is achieved by the biochemical circuit control design.

If the optimal robust filtering circuit design is employed for a perturbed biochemical network, then the control matrix  $F$  is specified to solve the following constrained optimization

$$\rho_0 = \min_F \rho_p \quad (7)$$

subject to  $P > 0$ , and (6).

where  $\rho_0$  in eq. (7) is the noise attenuation ability of the optimally controlled biochemical network in eq. (5).

**Remark 2**

If the control parameter  $F$  can not be separated and is contained in  $f(X[k])$  as  $f(X[k], F)$  in eq. (5), i.e.

$$\begin{aligned} X[k+1] &= f(X[k], F) + \sum_{i=1}^L f_i(X[k])p_i[k] + B_v v[k] \\ Z[k] &= C_Z X[k] \end{aligned} \quad (8)$$

then the LMIs in eq. (6) for robust filtering circuit design should be modified as follows

$$\begin{bmatrix} -P + \sum_{i=1}^L A_{ij}^T P A + C_Z^T C_Z & (P A_j(F))^T & A_j(F) P B_v \\ P A_j(F) & -P & 0 \\ B_v^T P A_j(F) & 0 & B_v^T P B_v - \rho_p^2 I \end{bmatrix} < 0 \quad (9)$$

where  $A(F)$  denotes the matrix  $A$  with control parameters  $F$  in their elements.

Similarly, the optimal robust filtering circuit design for a nonlinear biochemical control system in eq. (8) could be solved by the following constrained optimization problem

$$\rho_0 = \min_F \rho_p \quad (10)$$

subject to  $P > 0$ , and (9)

In this study, several biochemical circuit designs will be given *in-silico* to illustrate the design procedure and to confirm the performance of proposed method.