Robust Stability Analysis and Design Under Consideration of Multiple Feedback Loops in the Tryptophan Regulatory Network of *E. coli*

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Abstract—The tryptophan operon of *E. coli* represents an important regulatory unit consisting of multiple feedback loops. The role of these loops is crucial to understand the dynamics of tryptophan biosynthesis. We analyze the robust stability of this system by splitting its state into fast (mRNA concentration) and slow (anthranilate synthase and tryptophan concentrations) variables, under consideration of nonlinear uncertainties. In addition, we analyze the role of these feedback loops as key design components, responsible for the physiological performance of this regulatory unit. The range of allowed parameter perturbations and the conditions that ensure the existence of asymptotically stable equilibria for the perturbed system are determined. We also analyze two important alternate regulatory designs for the tryptophan synthesis pathway and derive the corresponding stability conditions.

Keywords: Tryptophan operon; Robust stability; Biological regulators; Singularly perturbed system

1. Introduction

Biological systems regularly exhibit more complex regulatory mechanisms than those required to ensure a nominal functionality. One possible explanation for this is the necessity of biological systems to operate robustly in the phase of a constantly changing environment. The tryptophan operon of *E. coli* represents one of the best-known molecular systems, and so it is an excellent candidate for dynamical modeling and analysis. The genes in the tryptophan operon (trp) of *E. coli* code for the enzymes that are needed to synthesize tryptophan (an essential amino acid) from chorismate. If tryptophan is available, *E. coli* consumes it and the trp operon is switched off. This process is accomplished based on three different regulatory mechanisms: repression, feedback enzyme inhibition, and transcription attenuation.

Several mathematical models have been formulated (based on the available experimental data) for the tryptophan operon [5], [6], [1]. In [6], the role of the three known regulatory mechanisms was assessed by carrying out both parameter and structure perturbations. The results based on numerical simulations showed that this system is highly robust to parameter perturbations, yet vulnerable to structural perturbations [1].

In this paper, we present a general robust stability analysis for the tryptophan operon. To do this we split the system state into fast (mRNA concentration) and slow (anthranilate synthase and tryptophan concentrations) variables, under consideration of nonlinear uncertainties. We analyze the mathematical system as an uncertain two-time scale system and show that maximal bounds for fluctuating operating parameters [3] can be obtained. As shown in [6], the regulation of tryptophan is achieved based on a feedback system consisting of three loops with different tasks. Namely: repression, transcription attenuation, and enzyme inhibition. We mathematically analyze the role of these multiple feedback loops on the overall dynamics of this system and improve the results obtained in [1] by giving a quantitative evaluation of the robustness domain.

2. Robust Stability Analysis

The objective of this study is to discuss the robust properties of the gene regulatory pathway of *E. coli*’s tryptophan operon. The analysis is based on a mathematical model and a rigorous analytic standpoint.

The mathematical description of a general regulatory pathway is given by [2]

\[
\begin{align*}
\dot{x} &= F(u, y) - \alpha x \\
\dot{y} &= G(x, y) - \beta y \\
\dot{u} &= H(s, u, y) - \gamma u \\
\dot{s} &= K(e, u, s) - \delta s
\end{align*}
\]

where \(x = [x_1, x_2, \ldots, x_{n_x}]^T\), \(y = [y_1, y_2, \ldots, y_{n_y}]^T\), \(e = [e_1, e_2, \ldots, e_{n_e}]^T\), \(s = [s_1, s_2, \ldots, s_{n_s}]^T\), and \(u = [u_1, u_2, \ldots, u_{n_u}]^T\) respectively represent the concentrations of mRNA (messenger RNA), produced proteins, external changes, second messengers, and regulator molecules, while \(\alpha, \beta, \gamma, \) and \(\delta\) represent the degradation (and dilution) rates for \(x, y, u\) and \(s\), respectively. Functions \(F, G, H\) and \(K\) describe the production rates of \(x, y, s\) and \(e\), respectively, and are rational functions of the arguments.
A block diagram of the gene regulatory pathway is shown in Figure 1. The main part of this unit represents the operon which, from the point of view of Control Theory, is the process under control. The external change variable $e$ acts as an input to the system and the second messenger concentration $s$, regulatory molecule concentration $u$, mRNA concentration $x$, and the translated protein concentration $y$ are other variables. The translated protein concentration $y$ is the output variable. It may affect the control system by feeding back and affecting the second messenger ($s$) and the regulatory molecule ($u$) concentrations. The goal of this feedback is the reduction of the influence of external changes and the achievement of a desired output.

An specific model for the regulatory pathway of $E. coli$’s tryptophan operon is given below [5]. The equations in this model respectively describe the dynamics of the transcription, translation and tryptophan biosynthesis processes.

\[
\dot{M} = k_M O \Phi(T) \Psi(T) - (\gamma_M + \mu) M, \quad (4)
\]
\[
\dot{E} = \frac{1}{2} k_E M - (\gamma_E + \mu) E, \quad (5)
\]
\[
\dot{T} = E R_T(T) - \rho \frac{T}{T + K_\rho} - \mu T. \quad (6)
\]

In the above equations $M$ represents the intracellular concentration of $trpE$ mRNA, while $E$ and $T$ denote the concentrations of the anthranilate synthase enzyme and of tryptophan, respectively. Parameters $k_M$ and $k_E$ respectively represent the synthesis rates for $M$ and $E$, while $\rho$, $\mu$, and $\gamma_M$ represent the total operator site concentration, the growth rate of $E. coli$, and the mRNA degradation rate. The values of all these parameter are given in Table 1.

The three regulatory mechanisms in the $trp$ operon are taken into account in the model by functions $\Phi(T)$, $\Psi(T)$, and $R_T(T)$. They model repression, transcription attenuation and enzyme inhibition, respectively, and are given by

\[
\Phi(T) = \frac{\mu}{1 + \frac{\mu}{k_F} + \frac{\mu}{k_R} (\frac{T}{T + K_T})^2},
\]
\[
\Psi(T) = \frac{1 + 2 \alpha \frac{T}{T + K_T}}{\left(1 + \frac{T}{K_G + T}\right)^2},
\]
\[
R_T(T) = k_T \left(\frac{K_I}{K_I + T}\right)^2.
\]

A block diagram for the tryptophan metabolism regulatory pathway is given in Figure 2. The main component of this pathway is the operon itself, which corresponds to the plant under control. As an input to this system we have the external changes as well as other variables, such as second messenger concentration being the internal tryptophan, regulatory molecule concentration such as charged tRNA and TrpR-tryptophan, mRNA concentration and finally the translated protein concentration.

A better visualization of the feedback mechanisms is illustrated in the block diagram derived from [6] shown in Figure 3.

We define new variables $\tilde{M}$, $\tilde{E}$ and $\tilde{T}$ by shifting the old variables $M, E, T$ by their equilibrium values $M^*, E^*$ and $T^*$ and obtain thus a new system:

\[
\dot{\tilde{M}} = \frac{\mu}{\gamma_M + \mu} \left(k_M O \Phi(\tilde{T} + T^*) \Psi(\tilde{T} + T^*) - k_M O \Phi(T^*) \Psi(T^*)\right) - \tilde{M},
\]
\[
\dot{\tilde{E}} = \frac{1}{2} k_E \tilde{M} - (\gamma_E + \mu) \tilde{E},
\]
\[
\dot{\tilde{T}} = (\tilde{E} + E^*) R_T(\tilde{T} + T^*) - E^* R_T(T^*) - \rho \frac{\tilde{T} + T^*}{\tilde{T} + T^* + K_\rho} + \rho \frac{T^*}{\tilde{T} + T^* + K_\rho} - \mu \tilde{T}.
\]

Table 1: Parameter values for the tryptophan model as estimated in [5].

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$</td>
<td>0.01 min$^{-1}$</td>
</tr>
<tr>
<td>$R$</td>
<td>0.8 $\mu$M</td>
</tr>
<tr>
<td>$K_F$</td>
<td>4.5 $\times 10^{-2}$ $\mu$M</td>
</tr>
<tr>
<td>$K_I$</td>
<td>4.1 $\mu$M</td>
</tr>
<tr>
<td>$\rho$</td>
<td>240 $\mu$M min$^{-1}$</td>
</tr>
<tr>
<td>$K_\rho$</td>
<td>3.1 min$^{-1}$</td>
</tr>
<tr>
<td>$K_T$</td>
<td>330 $\mu$M</td>
</tr>
<tr>
<td>$K_E$</td>
<td>40 $\mu$M</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>18.5</td>
</tr>
<tr>
<td>$\gamma_M$</td>
<td>0.69 min$^{-1}$</td>
</tr>
<tr>
<td>$K_\rho$</td>
<td>10 $\mu$M</td>
</tr>
<tr>
<td>$k_E$</td>
<td>30 min$^{-1}$</td>
</tr>
<tr>
<td>$O$</td>
<td>4 $\mu$M</td>
</tr>
<tr>
<td>$K_R$</td>
<td>2 $\times 10^{-4}$ $\mu$M</td>
</tr>
<tr>
<td>$K_G$</td>
<td>5 $\mu$M</td>
</tr>
<tr>
<td>$\gamma_E$</td>
<td>0 min$^{-1}$</td>
</tr>
<tr>
<td>$k_T$</td>
<td>7.3 $\times 10^4$ $\mu$M</td>
</tr>
</tbody>
</table>
Furthermore, we have

\[ \dot{x} = f(x) + g(x)u + \epsilon \nu \]

where

\[ f(x) = \begin{bmatrix} A_1 \end{bmatrix} x + \begin{bmatrix} b \end{bmatrix} u \]

and

\[ g(x) = \begin{bmatrix} c \end{bmatrix} \]

The above system can be transformed into a new system composed of a slow and a fast subsystems. Indeed, this new system is a superposition of a linear nominal system and perturbation terms. In more general terms, we can rewrite our system in the following form by using the notation: \( \dot{x} = [\dot{E}, \dot{T}] \) and \( x_{\text{fast}} = [M] \):

\[ \dot{x}_{\text{slow}} = A_{11} x_{\text{slow}} + A_{12} x_{\text{fast}} + f_{\text{slow}}(x_{\text{slow}}, x_{\text{fast}}) \]

\[ \dot{x}_{\text{fast}} = A_{21} x_{\text{slow}} + A_{22} x_{\text{fast}} + f_{\text{fast}}(x_{\text{slow}}, x_{\text{fast}}) \]

where

\[ \epsilon = \frac{\mu}{\gamma M + \mu} \]

\[ A_{12} = \left( \begin{array}{c} \frac{k_E}{m} \\ 0 \end{array} \right), A_{22} = -\mu, A_{21} = \left( \begin{array}{c} 0 \\ 0 \end{array} \right) \]

and

\[ A_{11} = \left( \begin{array}{cc} -\mu & 0 \\ 0 & -\mu \end{array} \right) \]

Furthermore, we have

\[ f_{\text{slow}} = \begin{bmatrix} 0 \end{bmatrix} \]

with

\[ f_{\text{slow}}(\dot{E}, T) = \begin{bmatrix} \dot{E} + E^* \end{bmatrix} R_{\dot{T} + T^*} (T + T^*) - E^* R_{T^*} (T^*) - \rho_{T + T^* + K_{\rho}} \rho_{T^* + K_{\rho}} \] and

\[ f_{\text{fast}} = k_M O \Phi(T + T^*) \Psi(T + T^*) - k_M O \Phi(T^*) \Psi(T^*) \]

The nonlinear uncertainties are bounded by

\[ ||f_{\text{slow}}(x_{\text{slow}}, x_{\text{fast}})|| \leq \alpha_1 ||x_{\text{slow}}|| + \beta_1 ||x_{\text{fast}}|| \]

\[ ||f_{\text{fast}}(x_{\text{slow}}, x_{\text{fast}})|| \leq \alpha_2 ||x_{\text{slow}}|| + \beta_2 ||x_{\text{fast}}|| \]

where \( \alpha_1, \alpha_2, \beta_1, \beta_2 \) are positive constants and \( ||f|| \) is the norm of the perturbed terms.

The linear nominal subsystem of the above system is given by

\[ \dot{x}_{\text{slow}}(t) = A_{11} x_{\text{slow}}(t) + A_{12} x_{\text{fast}}(t) \]

\[ \epsilon \dot{x}_{\text{fast}}(t) = A_{21} x_{\text{slow}}(t) + A_{22} x_{\text{fast}}(t) \]

and its stability is guaranteed by the following lemma.

**Lemma 1** [7, 4]: If \( A_{22} \) is nonsingular and both \( A_{22} \) and \( A_0 = A_{11} - A_{12} A_{22}^{-1} A_{21} \) are Hurwitz matrices, then there exists an \( \epsilon^* > 0 \) such that the system (10) is asymptotically stable for all \( \epsilon \in [0, \epsilon^*] \).

We need now to determine the upper bounds \( \alpha_i, \beta_i \) and \( \epsilon^* \) such that the system (4) is asymptotically stable, assuming that \( A_{22} \) and \( A_0 \) are Hurwitz. Let us define the following state transformation

\[ \begin{bmatrix} x_{\text{slow}}(t) \\ x_{\text{fast}}(t) \end{bmatrix} = \begin{bmatrix} 1 & 0 & -\frac{1}{2} k_E \epsilon \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} \zeta(t) \\ \eta(t) \end{bmatrix} \]

where

\[ \zeta(t) = \begin{bmatrix} \dot{x}_{\text{slow}}(t) \\ \dot{x}_{\text{fast}}(t) \end{bmatrix} \]

\[ \eta(t) = \begin{bmatrix} x_{\text{fast}}(t) \end{bmatrix} \]
with \( H = \left( \begin{array}{c} -\frac{k_R}{\mu} \\ 0 \end{array} \right) \). We thus obtain

\[
\begin{bmatrix}
\zeta(t) \\
\eta(t)
\end{bmatrix} = \begin{bmatrix}
1 & 0 & \frac{k_R}{\mu} \\
0 & 1 & 0 \\
0 & 0 & 1
\end{bmatrix} \begin{bmatrix} x_{\text{slow}}(t) \\
x_{\text{fast}}(t) \end{bmatrix}.
\]

(12)

By using the above transformation we can derive a new transformed system:

\[
\begin{align*}
\zeta(t) &= A_{11}\zeta(t) - cA_{12} \cdot A_{22}^{-1}\eta(t) + \tilde{f}_1(\zeta(t), \eta(t)), \\
c\eta(t) &= -A_{22}\eta(t) + f_2(\zeta(t), \eta(t)),
\end{align*}
\]

(13)

where the transformed nonlinear uncertainties are given by

\[
\begin{align*}
\tilde{f}_1(\zeta(t), \eta(t)) &= f_1(\zeta(t) + cH\eta, \eta(t)) - Hf_2(\zeta(t) + cH\eta, \eta(t)), \\
\tilde{f}_2(\zeta(t), \eta(t)) &= f_2(\zeta(t) + cH\eta, \eta(t)).
\end{align*}
\]

(14)

The above nonlinear uncertainty can be estimated as

\[
\|\tilde{f}_1(\zeta(t), \eta(t))\| \leq \tilde{\alpha}_1\|\zeta(t)\| + \tilde{\beta}_1\|\eta(t)\|,
\]

with \( \tilde{\alpha}_1 = \alpha_1 + \alpha_2\|H\| \), \( \tilde{\beta}_1 = \epsilon(\alpha_1 + \alpha_2\|H\|\|H\|)\|H\| \), \( \tilde{\alpha}_2 = \epsilon\alpha_2 \) and \( \tilde{\beta}_2 = \epsilon\alpha_2\|H\|. \) The stability of the transformed system (13) is equivalent to the stability of the original system (4).

**Theorem:** The system (4) is asymptotically stable for \( 0 < \epsilon < \epsilon^* \), where \( \epsilon^* = \min(\epsilon_1^*, \epsilon_2^*) \) is given by equation (23) and for any \( \gamma > 0 \) if the following inequalities hold

\[
a = 2 - \frac{2\tilde{\alpha}_1}{\mu} - \gamma \left( \frac{\|\alpha_{12}\|}{\mu} + \frac{\tilde{\beta}_1}{\mu} + \frac{\tilde{\alpha}_2}{\mu} \right) \geq 0,
\]

(16)

\[
b = 2 - \frac{2\tilde{\beta}_2}{\mu} - \gamma \left( \frac{\|\alpha_{12}\|}{\mu} + \frac{\tilde{\beta}_1}{\mu} + \frac{\tilde{\alpha}_2}{\mu} \right) \geq 0,
\]

(17)

with \( \|\alpha_{12}\| = \frac{1}{2}k_E, \) \( \tilde{\alpha}_1 = \alpha_1 + \alpha_2\|H\| \), \( \tilde{\beta}_1 = \epsilon\alpha_1 + \alpha_2\|H\|\|H\| \), \( \tilde{\alpha}_2 = \epsilon\alpha_2 \) and \( \tilde{\beta}_2 = \epsilon\alpha_2\|H\|. \) As parametric conditions for the tryptophan network resulting from the asymptotic stability, we obtain

\[
1 - \alpha_1 - \alpha_2\|H\| > 0,
\]

(18)

and

\[
4\mu(1 - \alpha_1 - \alpha_2\|H\|) > \alpha_2^2.
\]

(19)

**Proof:** We choose \( V(\zeta(t), \eta(t)) = \zeta^TP\zeta + c\eta^TR\eta \) as a Lyapunov function for the new transformed system. In this definition, \( P, R \) are the solutions of the Lyapunov equations

\[
\begin{align*}
A_1^TP + PA_1 &= -2QP, \\
A_2^TR + RA_2 &= -2QR.
\end{align*}
\]

(19)

Choosing \( Q_P = Q_R = I \) we obtain \( P = -A_{11}^{-1} \) and \( R = -A_{22}^{-1} \). From equations (13) and (19) the derivative of the Lyapunov function is

\[
\begin{align*}
\dot{V}(\zeta(t), \eta(t)) &\leq \zeta^TP\zeta + \epsilon\eta^TR\eta + c\eta^TR\eta + \epsilon\eta^TP\zeta + \epsilon\eta^TR\eta \\
&= -2\zeta^TP\zeta - 2\eta^T\eta + 2\zeta^TP\tilde{f}_1 + 2\zeta^T\epsilon\|H\|\|H\|\|H\| + 2\eta^T\tilde{f}_2.
\end{align*}
\]

(21)

Table 2: Stability conditions for the tryptophan synthesis pathway.

<table>
<thead>
<tr>
<th>Stability conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>( 1 - \alpha_1 - \alpha_2|H| &gt; 0 )</td>
</tr>
<tr>
<td>( 4\mu(1 - \alpha_1 - \alpha_2|H|) &gt; \alpha_2^2 )</td>
</tr>
</tbody>
</table>

We make use now of the inequality \( 2\|\zeta\|\|\eta\| \leq \gamma\|\zeta\|^2 + \frac{1}{2}\|\eta\|^2 \), valid for any \( \gamma > 0 \) in our Lyapunov function and, thus obtain

\[
\begin{align*}
\dot{V}(\zeta, \eta) &\leq -\left( 2 - \frac{2\tilde{\alpha}_1}{\mu} - \gamma \left( \frac{\|\alpha_{12}\|}{\mu} + \frac{\tilde{\beta}_1}{\mu} + \frac{\tilde{\alpha}_2}{\mu} \right) \right) \|\zeta\|^2 \\
&- \left( 2 - \frac{2\tilde{\beta}_2}{\mu} - \gamma \left( \frac{\|\alpha_{12}\|}{\mu} + \frac{\tilde{\beta}_1}{\mu} + \frac{\tilde{\alpha}_2}{\mu} \right) \right) \|\eta\|^2.
\end{align*}
\]

(22)

We see from the equation above that \( \dot{V}(\zeta, \eta) \leq 0 \) means that \( a, b \geq 0 \) with \( a = 2 - \frac{2\tilde{\alpha}_1}{\mu} - \gamma \left( \frac{\|\alpha_{12}\|}{\mu} + \frac{\tilde{\beta}_1}{\mu} + \frac{\tilde{\alpha}_2}{\mu} \right) \geq 0 \) and \( b = 2 - \frac{2\tilde{\beta}_2}{\mu} - \gamma \left( \frac{\|\alpha_{12}\|}{\mu} + \frac{\tilde{\beta}_1}{\mu} + \frac{\tilde{\alpha}_2}{\mu} \right) \geq 0 \) is a sufficient condition for \( \dot{V}(\zeta, \eta) \leq 0 \). We thus obtain two equations for \( \epsilon \)

\[
0 \leq \epsilon \leq \epsilon^* = \frac{E - \gamma N}{O\gamma}, \quad 0 \leq \epsilon \leq \epsilon^* = \frac{M\gamma - N}{D\gamma + O}\gamma.
\]

(23)

with \( M = 2\mu, N = \alpha_2, O = \frac{k_{Ne}}{\mu} + \alpha_1\|H\| + \alpha_2\|H\|^2, D = 2\alpha_2\|H\|^2 \) and \( E = 2 - 2(\alpha_1 + \alpha_2\|H\|) \). Since \( \epsilon^* \) is strictly decreasing and continuous on \( \gamma > 0 \) and \( \epsilon^* \) is strictly increasing and continuous on \( \gamma > 0 \), there is a unique \( \gamma^* > 0 \) such that \( \epsilon^*(\gamma^*) = \epsilon^*_2(\gamma^*) \). This represents the value of \( \gamma > 0 \) for which \( \epsilon^* = \max_{\gamma > 0}(\min(\epsilon_1^*, \epsilon_2^*)) \). By equating \( \epsilon^*_1 \) and \( \epsilon^*_2 \), we obtain from the quadratic polynomial \( (MO + ND)\gamma^2 - DE\gamma - O\gamma = 0 \) the maximum value of \( \epsilon^* \). This quadratic polynomial has one positive real solution \( \gamma^*_\epsilon > 0 \) given by

\[
\gamma^*_\epsilon = \frac{DE + \sqrt{(DE)^2 + 4OE(MO + ND)}}{2(MO + ND)}.
\]

(24)

By substituting the above expression into \( \epsilon^* \), we obtain

\[
\max_{\gamma > 0} \epsilon^* = \frac{M\gamma^* - N}{O + D\gamma^*} = \frac{E - \gamma^* N}{O\gamma^*}.
\]

(24)

As a consequence of the fact that \( \epsilon^* > 0 \), we get the following stability conditions to be fulfilled, as depicted in Table 2.

Following [5] we consider two distinct alternate regulatory designs for the tryptophan synthesis pathway: (1) a mutant lacking the transcription attenuation regulatory pathway (we mimic this mutant by substituting the function \( R_T(T) \) by \( R_T(T^*) \)) and (2) a mutant lacking enzyme inhibition (this mutant is simulated by substituting function \( \Psi(T) \) by \( \Psi(T^*) \)). The derived theoretical concepts are illustrated in two different examples derived from Figure 3.
**Example 1:** Let us consider an alternate regulatory design lacking transcription attenuation and let \( \alpha_1 = 0.5, \alpha_2 = 5.8 \cdot 10^{-8} \) for the system described by equation (4). Using equation (24), we obtain \( \gamma^* = 7.05 \). The optimized \( \epsilon^* \) is given as \( \epsilon^* = 1.7 \cdot 10^{-4} \). So the system is asymptotically stable for \( 0 \leq \epsilon \leq 1.7 \cdot 10^{-4} \).

**Example 2:** We consider again the above system but this time in the absence of the enzyme inhibition mechanisms. Using equation (24), we obtain \( \gamma^* = 9.48 \). The optimized \( \epsilon^* \) is given as \( \epsilon^* = 1.15 \cdot 10^{-3} \). So the system is asymptotically stable for \( 0 \leq \epsilon \leq 1.15 \cdot 10^{-3} \).

In summary, we have shown that the regulatory pathway of the wild-type and of both mutant strains have a single steady state which is asymptotically stable.

### 3. Conclusion

We analyzed and identified the relationship between the design of the tryptophan regulatory unit and its physiological function. This robust design of the regulatory mechanism is needed in order to deal with uncertainties while ensuring a stable operating point. We used concepts from the theory of uncertain singularly perturbed systems and applied these results to study robustness properties of the tryptophan system in *E. coli*. This system represents an important control system where three processes, transcription, translation and tryptophan synthesis, are in series and describe negative feedback loops corresponding to transcription repression, transcription attenuation, and enzyme inhibition. In addition, this is a multiple time-scale system combining a coupled nonlinear fast and slow dynamics. In this sense we established robustness stability results for the reduced-order model and determined the conditions that ensure the existence of asymptotically stable equilibria of this model. A sufficient condition for the nonnegative singular perturbation parameter, representing in our context the sum of the specific growth rate of *E. coli* and the degradation rate constant for mRNA, is derived for the uncertain reduced-order model under the condition that the nonlinear uncertainties are bounded.

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### References


