Research Article

On the System Entropy and Energy Dissipativity of Stochastic Systems and Their Application in Biological Systems

Bor-Sen Chen ^{1,2} **Xiangyun Lin** ³ **Weihai Zhang** ⁴ and **Tianshou Zhou** ⁵

¹Department of Electrical Engineering, National Tsing Hua University, Hsinchu 30013, Taiwan

²Department of Electrical Engineering, Yuan Ze University, Chung-Li, 32003, Taiwan

³College of Mathematics and Systems, Shandong University of Science and Technology, Qingdao 266590, China

⁴College of Electrical Engineering and Automation, Shandong University of Science and Technology, Qingdao 266590, China

⁵School of Mathematics and Computational Science, Sun Yat-Sen University, Guangzhou 510275, China

Correspondence should be addressed to Xiangyun Lin; lxy9393@sina.com

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This study discusses the relationship between the entropy and the dissipativity of stochastic systems under the background of biological systems. First, measurement methods of the system entropy and energy dissipativity of linear stochastic biological systems are introduced. We found that the system entropy is negatively proportional to the energy dissipativity in logarithmic scale. Some opposite effects between system entropy and energy dissipativity are also discussed and compared based on their measured values to get insight into the understanding of the system mechanisms and the system characteristics. We found that the intrinsic random fluctuation and the enhancement of the system robust stability both can increase the system entropy but decrease the system dissipativity. The system entropy and the energy dissipativity of nonlinear stochastic biological systems are also discussed and compared based on a global linearization method. Computation methods are also provided. Finally, two numerical examples are demonstrated to verify theoretical prediction.

1. Introduction

In general, entropy is considered as a measurement of randomness of thermodynamic systems [1–4]. According to the second law of thermodynamics, entropy is used to describe the dispersion of energy and the natural tendency of spontaneous change toward states with higher entropy in a thermally isolated system [5–8]. Since biological systems can exchange material and energy with their environment to maintain life, they are open systems, i.e., their entropy can be maintained through exchanging material and energy with their environment [9–15]. Recently, system entropy of biological system has been introduced as the net signal entropy between input signal entropy and output signal entropy [9, 10]. Further, biological systems need energy consumption to maintain their mechanisms [16–22]. The power dissipation denotes the power exhaustion of biological system [23–26]. Nonnegative dissipation corresponds to the passivity

of biological system, and negative dissipation corresponds to the activity of biological system [23, 26]. In general, a biological system is passive (nonnegative dissipation), if the biological system has more energy dissipation (heat output) due to passive components than energy generation due to active components (i.e., net energy dissipation [26]). A biological system is with negative dissipation (i.e., active) if the biological system has more energy generation than energy dissipation (i.e., net energy generation) [13, 14, 26]. The largest dissipation of the biological system is called dissipativity [1, 26]. Obviously, there is some relationship between system entropy and dissipativity of biology systems, which is valuable to investigate from the systematic perspective.

In this study, we first measure the system entropy and energy dissipativity of a more general linear biological system. We could obtain system entropy by solving a linear matrix inequality (LMI), constrained minimization problem and energy dissipativity by solving a LMI, constrained

maximization problem. We found that both system entropy and energy dissipativity are both system characteristics dependent on system parameters of biological system. By comparing two LMI constraints for system entropy and energy dissipativity and their corresponding Riccati-like inequalities, we found that system randomness r and system energy dissipativity η^* are approximately related by $r = h - 2\eta^*$ for some constant h and system entropy s and system energy dissipativity η^* are related by $s = \log(h - 2\eta^*)$ as shown in Figure 1. We found that a more stable (with eigenvalues in the far left s-domain) biological system is with smaller system randomness and entropy, and with a nonnegative dissipativity. However, when biological system is less stable, the system randomness and entropy become larger and the energy dissipativity becomes negative dissipation (energy generation). When the coupling matrices between the biological system and external environment become weaker, the system randomness, system entropy, and system energy dissipation become smaller and vice versa. In nonlinear biological system, we need to solve two Hamilton Jacobi inequalities (HJI), constrained optimization problems for calculating system entropy and energy dissipativity, respectively [27]. In general it is very difficult to solve these two HJI-constrained optimization problems for system entropy and energy dissipativity of nonlinear biological systems except very simple systems [28–34]. Moreover, such difficulties still exist in nonlinear system's stability theories [35–37] and other topics [38–41]. In this study, the global linearization method is introduced to interpolate several linearized local biological systems to approximate the nonlinear biological system [23, 42]. In this way, the nonlinear HJI could be interpolated by a set of LMIs. In this situation, the HJI-constrained optimization problems for solving the system entropy and energy dissipativity of nonlinear biological system could be replaced by the corresponding LMI-constrained optimization problems, which could be efficiently solved with help of LMI toolbox in Matlab [23, 43–45]. Based on those techniques, the relationship between system entropy and energy dissipativity can be easily investigated and discussed.

The contributions of this paper are described as follows: we investigate the relationship between two important systematic characters, i.e., system entropy and dissipativity of stochastic system. We found that the system entropy is negatively proportional to the energy dissipativity in logarithmic scale. In order to overcome the difficulty of the measurement of the system entropy and energy dissipativity of nonlinear biological systems given by the HJI-constrained optimization method, the global linearization technique is also employed to interpolate a nonlinear system by a set of local linearized systems such that system entropy and energy dissipativity could be measured by the LMIs-constrained optimization method. Then the relationship between system entropy and energy dissipativity could be also investigated by solving the corresponding LMIs. Finally, two in silico examples of a phosphorelay biological system and a predator-prey ecological system are given to illustrate how to measure the system entropy and energy dissipativity and to confirm their relationship investigated by the proposed method.

2. Systems Entropy and Energy Dissipativity of Linear Biological Systems

In this section, we consider a more general linear biological system with the following stoichiometric equation [9, 26]:

$$\begin{aligned}\dot{x}(t) &= Ax(t) + Bv(t) \\ y(t) &= Cx(t) + Dv(t)\end{aligned}\quad (1)$$

where $x(t) = [x_1(t) \cdots x_n(t)]^T \in \mathbb{R}^n$ denotes the state vector of biological system with n species, the random signal $v(t) = [v_1(t) \cdots v_m(t)]^T \in \mathbb{R}^m$ denotes the system input which can be drawn from any distribution with zero moment $\mathbb{E}[v(t)] = 0$ and finite variance $\mathbb{E}\{\int_0^{T_f} v^T(t)v(t)dt\} < \infty$ for every $T_f > 0$, and $y(t) = [y_1(t) \cdots y_l(t)]^T \in \mathbb{R}^l$ denotes the system output. $A \in \mathbb{R}^{n \times n}$, $B \in \mathbb{R}^{n \times m}$, $C \in \mathbb{R}^{l \times n}$, and $D \in \mathbb{R}^{l \times m}$, respectively, denote the system interaction matrix, input state coupling matrix, state/output coupling matrix, and input/output coupling matrix of the linear biological system as follows:

$$\begin{aligned}A &= \begin{bmatrix} a_{11} & \cdots & a_{1n} \\ \vdots & & \vdots \\ a_{n1} & \cdots & a_{nn} \end{bmatrix}, \\ B &= \begin{bmatrix} b_{11} & \cdots & b_{1m} \\ \vdots & & \vdots \\ b_{n1} & \cdots & b_{nm} \end{bmatrix}, \\ C &= \begin{bmatrix} c_{11} & \cdots & c_{1n} \\ \vdots & & \vdots \\ c_{l1} & \cdots & c_{ln} \end{bmatrix}, \\ D &= \begin{bmatrix} d_{11} & \cdots & d_{1m} \\ \vdots & & \vdots \\ d_{l1} & \cdots & d_{lm} \end{bmatrix}\end{aligned}\quad (2)$$

2.1. System Entropy of Linear Biological System. The randomness of output and input signals can be considered as the dispersion of random signals; i.e., the randomness of input signal is represented by [9, 10]

$$r_i = \mathbb{E} \left\{ \frac{1}{T_f} \int_0^{T_f} v^T(t)v(t)dt \right\} \quad (3)$$

when the randomness of output signal is represented by [9, 10]

$$r_o = \mathbb{E} \left\{ \frac{1}{T_f} \int_0^{T_f} y^T(t)y(t)dt \right\} \quad (4)$$

where $\mathbb{E}\{\cdot\}$ denotes the expectation of $\cdot$ and T_f denotes the period of the corresponding signal for trajectories $x(t)$ with

FIGURE 1: The relationships between system randomness r , system entropy s , and energy dissipativity η^* . When energy dissipativity $\eta^* = h/2$, the system entropy $s = -\infty$. As the energy dissipativity decreases to $\eta^* = (h-1)/2$, the system entropy increases to $s = 0$. As η^* continuously decreases to $-\infty$, the system entropy s increases in the logarithmic scale. (a) The relationship between r and η^* of linear biological system in (1); as the energy dissipativity decreases from $h/2$, the system randomness increases linearly. (b) The relationship between s and η^* of the linear biological system in (1).

$x(0) = 0$ and $T_f > 0$. The randomness in (3) and (4) is an estimator of the variance of random signal.

The entropy of input signal $v(t)$ is denoted as [9–11]

$$S_i = -\log \mathbb{E} \left\{ \frac{1}{T_f} \int_0^{T_f} v^T(t) v(t) dt \right\} \quad (5)$$

and the entropy of output signal $y(t)$ is denoted as [9–11]

$$S_o = -\log \mathbb{E} \left\{ \frac{1}{T_f} \int_0^{T_f} y^T(t) y(t) dt \right\} \quad (6)$$

Then the system entropy s of linear biological network in (1) is defined as the difference between input signal entropy and output signal entropy with zero initial state condition $x(0) = 0$, i.e., the net signal entropy [9, 10]

$$s = S_i - S_o = \log \frac{\mathbb{E} \left\{ \int_0^{T_f} y^T(t) y(t) dt \right\}}{\mathbb{E} \left\{ \int_0^{T_f} v^T(t) v(t) dt \right\}} \quad (7)$$

The system entropy s denotes the entropy increment between input signals and output signals. In this process, by the second law of thermodynamics, the dynamical system (1) should provide/absorb enough energy to achieve such transformation [4–6]. Similarly, when system entropy s decreases/increases, the systems should absorb/release energy from/to the environment to maintain the system entropy s at a steady state. For the biological systems, these processes are achieved by exchanging energy with external environment.

Let us denote the system randomness r as [9, 10]

$$r = \frac{\mathbb{E} \left\{ \int_0^{T_f} y^T(t) y(t) dt \right\}}{\mathbb{E} \left\{ \int_0^{T_f} v^T(t) v(t) dt \right\}} \quad (8)$$

Then the system entropy of linear biological system in (1) is the logarithm of the system randomness as [9, 10]

$$s = \log r \quad (9)$$

2.2. System Dissipativity of Linear Biological System. Suppose the dimensions of v and y are equivalent. The linear stochastic biological system in (1) is said to have energy dissipation η if [23, 26]

$$\mathbb{E} \int_0^{T_f} (v^T(t) y(t) - \eta v^T(t) v(t)) dt \geq 0 \quad (10)$$

holds for every stochastic input $v(t)$ and the corresponding process $x(t)$ with $x(0) = 0$ and all $T_f \geq 0$.

The energy dissipation denotes the energy exhaustion of biological system. The largest dissipation of the biological system, i.e., the largest number η such that (10) holds, will be called its dissipativity η^* .

Remark 1. The biological system in (1) is said to be passive if energy solution $x(t)$ with $x(0) = 0$ satisfies [23, 26]

$$\mathbb{E} \int_0^{T_f} v^T(t) y(t) dt \geq 0 \quad (11)$$

i.e., passivity corresponds to nonnegative dissipation (i.e., $\eta \geq 0$ in (10)). The nonnegative dissipation ($\eta \geq 0$) corresponds to the passivity of the biological system, and negative dissipation ($\eta < 0$) corresponds to the activity of the biological system. In general, a biological system is passive ($\eta \geq 0$) if the biological system has more energy dissipation due to passive components than energy generation due to active components (net energy dissipation). On the other hand, biological system is of negative dissipation ($\eta < 0$) if the biological system has energy generation than energy dissipation (net energy generation). Obviously, there is some relationship between system entropy and dissipativity needful to be investigated for biological systems.

2.3. Measurement of System Entropy and Energy Dissipativity of Linear Biological Systems. From fractional functions in (7)–(9), it is difficult to calculate the system entropy for the linear biological system in (1) directly. An indirect method is proposed to measure system entropy s in (9) through system

matrices A, B, C , and D of the biological system. Let us denote the upper bound $\bar{r}$ of system randomness as follows:

$$r = \frac{\mathbb{E} \left\{ \int_0^{T_f} y^T(t) y(t) dt \right\}}{\mathbb{E} \left\{ \int_0^{T_f} v^T(t) v(t) dt \right\}} \leq \bar{r} \quad (12)$$

or equivalently

$$\mathbb{E} \left\{ \int_0^{T_f} y^T(t) y(t) dt \right\} \leq \bar{r} \mathbb{E} \left\{ \int_0^{T_f} v^T(t) v(t) dt \right\} \quad (13)$$

We will first estimate the upper bound $\bar{r}$ of system randomness in (12) and then decrease $\bar{r}$ as small as possible to approach the system randomness r of biological system.

Proposition 2. *If the linear matrix inequality (LMI) has a positive definite solution $P = P^T > 0$*

$$\begin{bmatrix} A^T P + PA + C^T C & PB + C^T D \\ B^T P + D^T C & D^T D - \bar{r} I \end{bmatrix} \leq 0 \quad (14)$$

then the system randomness r of linear biological system has an upper bound $\bar{r}$.

Proof. See Appendix A. $\square$

Based on Proposition 2, the system randomness of biological system (1) could be estimated by solving the following LMI-constrained optimization problem:

$$r = \min_{P > 0} \bar{r} \quad (15)$$

subject to LMI in (14)

The above LMI-constrained optimization problem for system randomness could be easily solved by decreasing $\bar{r}$ in (14) until there exists no positive definite symmetric $P > 0$, which is easily performed with the LMI toolbox available in Matlab software package. For further discussion, we prefer to reference [23]. After solving r from (15), we could obtain system entropy $s = \log r$ from (9).

For the energy dissipation η in (10), we get the following result.

Proposition 3. *If the LMI has a positive definite solution $P = P^T > 0$*

$$\begin{bmatrix} A^T P + PA & PB - C^T \\ B^T P - C & 2\eta I - (D^T + D) \end{bmatrix} \leq 0 \quad (16)$$

then the biological system in (1) has energy dissipation η as shown in (10).

Proof. See Appendix B. $\square$

Since the energy dissipativity η^* is the largest number of energy dissipation η [23, 26], the energy dissipativity η^*

of linear biological system in (1) is measured by solving the following LMI-constrained optimization problem:

$$\eta^* = \max_{P > 0} \eta \quad (17)$$

subject to LMI in (16)

In the constrained maximization of η , to obtain energy dissipativity η^* in (17), we could increase η until there exists no $P > 0$ in the LMI of (16), and we could obtain η^* . The LMI-constrained maximization in (17) could be also solved with the help of LMI toolbox in Matlab software package.

Remark 4. (i) In the case of strict linear biological system (i.e., without direct coupling matrix D) [9]

$$\begin{aligned} \dot{x}(t) &= Ax(t) + Bv(t) \\ y(t) &= Cx(t) \end{aligned} \quad (18)$$

the LMI of system randomness of biological system in (18) is reduced from (14) to the following LMI [9]:

$$\begin{bmatrix} A^T P + PA + C^T C & PB \\ B^T P & -\bar{r} I \end{bmatrix} \leq 0 \quad (19)$$

In this situation, the system randomness of biological system in (18) is solved as follows [9]:

$$r = \min_{P > 0} \bar{r} \quad (20)$$

subject to LMI in (19)

Similarly, the LMI of energy dissipativity of biological system in (18) is reduced from (16) to the following LMI:

$$\begin{bmatrix} A^T P + PA & PB - C^T \\ B^T P - C & 2\eta I \end{bmatrix} \leq 0 \quad (21)$$

In this situation, the system energy dissipativity of biological system in (18) is solved as

$$\eta^* = \max_{P > 0} \eta \quad (22)$$

subject to LMI in (21)

(ii) After solving r from (15), by the Schur complement, the LMI of system randomness in (14) of biological system in (1) is equivalent to

$$\begin{aligned} & A^T P + PA + C^T C \\ & + (PB + C^T D)(rI - D^T D)^{-1}(B^T P + D^T C) \end{aligned} \quad (23)$$

≤ 0

Similarly, after solving η^* from (17), the LMI of system dissipativity in (16) of biological system (1) is equivalent to

$$\begin{aligned} & A^T P + PA \\ & + (PB - C^T)[-2\eta^* I + D^T + D]^{-1}(B^T P - C) \end{aligned} \quad (24)$$

≤ 0

In the case of strict biological system in (18), the inequality of system randomness in (24) is reduced to [9]

$$A^T P + PA + C^T C + \frac{1}{r} P B B^T P \leq 0 \quad (25)$$

and the inequality of energy dissipativity in (24) is reduced to

$$A^T P + PA - \frac{1}{2\eta^*} (PB - C^T) (B^T P - C) \leq 0 \quad (26)$$

From the analysis in Remark 4, it is seen that the relationship between the system randomness and the energy dissipativity has the following proportion approximately:

$$r \propto -2\eta^* \quad (27)$$

or

$$r = h - 2\eta^* \quad (28)$$

for some constant h .

According to (9), the relationship between system entropy s and the energy dissipativity η^* is approximately given by

$$s = \log(h - 2\eta^*) \quad (29)$$

for some constant h .

Remark 5. (i) In Proposition 2, in order to guarantee the negative definite of LMI in (14) all the diagonal components should be negative definite. In this situation, the lower bound of system randomness of the biological system in (1) is given by

$$rI \geq D^T D \geq 0 \quad (30)$$

Therefore the constant h has the following lower bound

$$hI \geq 2\eta^* I + D^T D \quad (31)$$

(ii) In Proposition 3, in order to guarantee the negative definite of LMI in (16), the upper bound of system dissipativity η^* of the biological system in (1) is given by

$$\eta^* I \leq \frac{1}{2} (D^T + D) \quad (32)$$

(iii) Since there are some extra-terms in the left hand side of (26) which do not appear in (25), the relation in (27) or (28) holds only if the equalities of (30) and (31) are satisfied for some positively definite matrix P .

3. System Entropy and Energy Dissipativity of Nonlinear Biological Systems

Biological systems are always nonlinear stochastic systems. Therefore, the biological dynamical system in (1) should be modified as the following nonlinear stochastic system

$$\begin{aligned} \dot{x}(t) &= f(x(t)) + g(x(t))v(t) \\ y(t) &= h(x(t)) + d(x(t))v(t) \end{aligned} \quad (33)$$

FIGURE 2: The nonlinear biological system of (33) with the phenotype at the equilibrium point x_e is of interest.

where $f(x) = [f_1(x) \cdots f_n(x)]^T$ denotes the nonlinear interaction vector among n species within the biological system, $g(x) = [g_1(x) \cdots g_m(x)]^T$ denotes the nonlinear coupling vector between the biological dynamic system and environmental disturbance $v(t)$, $h(x) = [h_1(x) \cdots h_l(x)]^T$ denotes l nonlinear outputs, and $d(x) = [d_1(x) \cdots d_l(x)]^T$ denotes the direct coupling vector from $v(t)$ to $y(t)$.

3.1. System Entropy of Nonlinear Biological Systems. We assume the equilibrium point x_e of interest (i.e., the phenotype to be discussed) of nonlinear biological system in (33) is at $x(t) \equiv 0$, i.e. $x_e = 0$. If the equilibrium point $x_e \neq 0$ is of interest (see Figure 2), the origin of nonlinear biological system must be shifted to x_e for the convenience of analysis. Based on the above assumptions, we get the following result of system randomness in (12) for nonlinear biological system in (33).

Proposition 6. *The system randomness of nonlinear biological system in (33) has an upper bound $\bar{r}$ if the following Hamilton Jacobi Inequality (HJI) has a positive Lyapunov solution $V(x) > 0$ ($x \neq 0$)*

$$\begin{aligned} & \left(\frac{\partial V(x)}{\partial x} \right)^T f(x) + \left(\frac{\partial V(x)}{\partial x} \right)^T g(x) v(t) \\ & + (h(x) + d(x)v(t))^T (h(x) + d(x)v) \\ & - \bar{r} v^T(t) v(t) \leq 0 \end{aligned} \quad (34)$$

Proof. See Appendix C. $\square$

Based on the result of Proposition 6, the system randomness of nonlinear biological system in (33) could be estimated by solving the following HJI-constrained optimization problem

$$\begin{aligned} r &= \min_{V(x)>0} \bar{r} \\ \text{subject to} & \text{ HJI in (34)} \end{aligned} \quad (35)$$

After measuring system randomness r from solving the above HJI-constrained optimization problem, we could estimate system entropy $s = \log r$ for the nonlinear biological system in (33).

3.2. Energy Dissipativity of Nonlinear Biological Systems. For the energy dissipation η in (10) of nonlinear biological system in (33), we get the following result.

Proposition 7. *If the HJI has a positive solution $V(x) > 0$*

$$\begin{aligned} & \left(\frac{\partial V(x)}{\partial x} \right)^T f(x) + \left(\frac{\partial V(x)}{\partial x} \right)^T d(x) v(t) \\ & + 2\eta v^T(t) v(t) - 2[h(x) + d(x)v(t)]^T v(t) \end{aligned} \quad (36)$$

$$\leq 0$$

then the nonlinear biological system in (33) has energy dissipation η as shown in (10).

Proof. See Appendix D. $\square$

Since the energy dissipativity η^* is the largest number of energy dissipation η , the energy dissipativity η^* of nonlinear biological system in (33) could be measured by solving the following HJI-constrained optimization problem:

$$\begin{aligned} \eta^* &= \max_{V(x)>0} \eta \\ \text{subject to} \quad & \text{HJI in (36)} \end{aligned} \quad (37)$$

Remark 8. (i) After solving the system randomness r of nonlinear biological system (33) from (35), then the HJI of system randomness in (34) should be modified as follows:

$$\begin{aligned} & \left(\frac{\partial V(x)}{\partial x} \right)^T f(x) + \left(\frac{\partial V(x)}{\partial x} \right)^T g(x) v(t) \\ & + [h(x) + d(x)v(t)]^T [h(x) + d(x)v] \\ & - rv^T(t) v(t) \leq 0 \end{aligned} \quad (38)$$

Similarly, after solving the energy dissipativity η^* of nonlinear biological system (33) from (37), the HJI of energy dissipativity in (36) should be modified as follows:

$$\begin{aligned} & \left(\frac{\partial V(x)}{\partial x} \right)^T f(x) + \left(\frac{\partial V(x)}{\partial x} \right)^T d(x) v(t) \\ & + 2\eta^* v^T(t) v(t) - 2[h(x) + d(x)v(t)]^T v(t) \end{aligned} \quad (39)$$

$$\leq 0$$

(ii) By comparing two HJIs of system randomness and energy dissipativity in (38) and (39), we found that the relationships among system randomness, system entropy, and energy dissipativity in (27), (28), and (29) are still approximately true near the equilibrium point x_e .

(iii) If the nonlinear biological system is more stable at the equilibrium x_e in Figure 2 (i.e., the basin of the equilibrium

point x_e is more deep and sharp), in this situation, the term $(\partial V(x)/\partial x)^T f(x)$ in (38) is more negative and r could be smaller to maintain in the negative inequality of (38), i.e., a more stable nonlinear biological system is with a smaller system randomness. Further large couplings $g(x)$, $h(x)$, and $d(x)$ in (38) will lead to large system randomness r and vice versa.

(iv) From the inequality of energy dissipativity in (39), if nonlinear biological system is more stable at x_e (i.e., the basin of x_e in Figure 2 is more deep and sharp and $(\partial V(x)/\partial x)^T f(x)$ is more negative at x_e), the energy dissipativity η^* is more nonnegative. When the biological system is less stable at x_e , the energy dissipativity η^* become less nonnegative or positive (i.e., active with energy generation).

3.3. Measurement of System Entropy and Energy Dissipativity of Nonlinear Biological Systems. In general, it is very difficult to solve the HJI-constrained optimization problems in (35) and (37) for system randomness r and energy dissipativity η^* of nonlinear biological system in (33), respectively. In this study, the global linearization technique will be employed to interpolate several local biological systems to approximate a nonlinear biological system so that the HJI in (34) or (36) could be interpolated by a set of LMIs to simplify the solution of HJI-constrained optimization problem in (30) or (37).

If the global linearized systems of nonlinear biological system in (33) are bounded by a polytope consisting of the M vertices [23, 42]

$$\begin{bmatrix} \frac{\partial f(x)}{\partial x} \\ \frac{\partial g(x)}{\partial x} \\ \frac{\partial h(x)}{\partial x} \\ \frac{\partial d(x)}{\partial x} \end{bmatrix} \in C_0 \left(\begin{bmatrix} A_1 \\ B_1 \\ C_1 \\ D_1 \end{bmatrix} \dots \begin{bmatrix} A_i \\ B_i \\ C_i \\ D_i \end{bmatrix} \dots \begin{bmatrix} A_M \\ B_M \\ C_M \\ D_M \end{bmatrix} \right), \quad (40)$$

$$\forall x(t)$$

then the state trajectory $x(t)$ of nonlinear biological system in (33) can be represented by the convex combination of state trajectories of the following M local linearized biological systems derived from the vertices of the polytope in (40):

$$\begin{aligned} \dot{x}(t) &= A_i x(t) + B_i v(t) \\ y(t) &= C_i x(t) + D_i v(t), \quad i = 1, 2, \dots, M \end{aligned} \quad (41)$$

According to the global linearization theory in [23, 42], every trajectory $x(t)$ of the nonlinear biological system in (33) can be interpolated by the following M local linearized biological systems:

$$\begin{aligned} \dot{x}(t) &= \sum_{i=1}^M \alpha_i(x) [A_i x(t) + B_i v(t)] \\ y(t) &= \sum_{i=1}^M \alpha_i(x) [C_i x(t) + D_i v(t)] \end{aligned} \quad (42)$$

where the interpolation functions

$$\alpha_i(x(t)) = \begin{cases} \frac{(1/\|x_i(t) - x(t)\|_2^2)}{\left[\sum_{j=1}^M (1/\|x_j(t) - x(t)\|_2^2)\right]}, & \text{if } x(t) \neq x_i(t) \\ 1, & \text{if } x(t) = x_i(t) \end{cases} \quad (43)$$

with interpolation nodes $x_j \in \mathbb{R}^n$, $j = 1, 2, \dots, M$, satisfy $0 \leq \alpha_i(x) \leq 1$ and $\sum_{i=1}^M \alpha_i(x) = 1$.

Remark 9. The linear biological system in (1) could be considered as a special linearization case of nonlinear biological system (33) at the origin $x = 0$. Therefore the trajectories of the nonlinear biological system in (33) can be represented by the global linearization biological system in (42), i.e., the convex combination of M local linearized biological systems at the vertices of polytope in (40).

After the nonlinear biological system in (33) is represented by the global linearization system in (42), we get following results for nonlinear biological system in (33) or (42).

Proposition 10. *If the linear matrix inequalities (LMIs) have a positive definite solution $P = P^T > 0$*

$$\begin{bmatrix} A_i^T P + PA_i + C_i^T C_i & PB_i + C_i^T D_i \\ B_i^T P + D_i^T C_i & D_i^T D_i - \bar{r}I \end{bmatrix} \leq 0 \quad (44)$$

$i = 1, \dots, M$

then the system randomness r of nonlinear biological system in (42) or (33) has an upper bound $\bar{r}$.

Proof. See Appendix E. $\square$

Therefore, according to Proposition 10, the system randomness of nonlinear biological system in (42) or (33) could be calculated by solving the following LMIs-constrained optimization problem:

$$r = \min_{P>0} \bar{r} \quad (45)$$

subject to LMIs in (44)

Similarly, a systematic characteristic of energy dissipativity η in (10) of nonlinear biological system in (33) is derived as follows.

Proposition 11. *If the LMIs have a positive definite solution $P > 0$*

$$\begin{bmatrix} A_i^T P + PA_i & PB_i - C_i^T \\ B_i^T P - C_i & 2\eta I - (D_i^T + D_i) \end{bmatrix} \leq 0 \quad (46)$$

$i = 1, 2, \dots, M$

then the nonlinear biological system in (33) or (42) has energy dissipation η .

Proof. See Appendix F. $\square$

Therefore, the energy dissipativity of nonlinear biological system in (33) or (42) could be calculated by solving the following LMIs-constrained optimization method:

$$\eta^* = \max_{P>0} \eta \quad (47)$$

subject to LMIs in (46)

After solving the LMIs-constrained optimization problems in (45) and (47) for system randomness r and energy dissipativity η^* for nonlinear biological system in (33) or (42), LMIs in (44) for system randomness and LMIs in (46) for energy dissipativity are given in the following, respectively:

$$\begin{bmatrix} A_i^T P + PA_i + C_i^T C_i & PB_i + C_i^T D_i \\ B_i^T P + D_i^T C_i & D_i^T D_i - rI \end{bmatrix} \leq 0 \quad (48)$$

$i = 1, \dots, M$,

$$\begin{bmatrix} A_i^T P + PA_i & PB_i - C_i^T \\ B_i^T P - C_i & 2\eta I - (D_i^T + D_i) \end{bmatrix} \leq 0 \quad (49)$$

$i = 1, 2, \dots, M$

which are equivalent to the following Riccati-like inequalities, respectively,

$$\begin{aligned} & A_i^T P + PA_i + C_i^T C_i + (PB_i + C_i^T D_i) \\ & \times (rI - D_i^T D_i)^{-1} (B_i^T P + D_i^T C_i) \leq 0 \quad (50) \end{aligned}$$

$i = 1, 2, \dots, M$,

$$\begin{aligned} & A_i^T P + PA_i + (PB_i - C_i^T) [-2\eta^* I + D_i^T + D_i]^{-1} \\ & \times (B_i^T P - C_i) \leq 0 \quad i = 1, 2, \dots, M \end{aligned} \quad (51)$$

which could be considered as M local linearizations of the HJIs in (34) and (36), respectively; i.e., the interpolation of M local Riccati-like inequalities in (50) and (51) could approach HJIs in (34) and (36), respectively.

Remark 12. (i) Comparing (48) and (50) with (14) and (24), it is seen that the system randomness r of nonlinear biological system in (33) or (42) should satisfy M LMIs (48) or M Riccati-like inequalities (50) of M local linearized biological systems in (40) or (42). Similarly, comparing (49) and (51) with (24) and (24), the energy dissipativity η^* of nonlinear biological system in (33) or (42) should satisfy M LMIs in (49) and M Riccati-like inequalities in (51) of M local linear biological systems in (40) or (42).

(ii) Comparing (48) and (50) with (49) and (51), it is seen that the relationships between system random, system entropy, and energy dissipativity in (27), (28), and (29) are also true near the equilibrium point x_e .

FIGURE 3: A scheme representation of phosphorelay system in Example 1 consisting of Sln1-branch of high osmolarity glycerol (HOG) pathway in yeast [9].

4. Example of Calculating System Entropy and Energy Dissipativity of Biological Networks

In this section two examples of calculating the system entropy and the energy dissipativity of biological networks are given to illustrate the relationships between them.

4.1. Example 1: The System Entropy and Energy Dissipativity of a Phosphorelay System. A phosphorelay system from high osmolarity glycerol (HOG) signal transduction pathway in yeast is shown in Figure 3. This signal transduction pathway involves a transmembrane protein Sln1, which is a dimmer. Under normal conditions, the signal transduction pathway is active due to continuous autophosphorylation at a histidine residue, sln1H-p, under the consumption of ATP. Then, this phosphate group is transferred to an aspartate group of Sln1, i.e., Sln1D-p, consequently to a histidine residue of Ypd1, and to an aspartate residue of Ssk1. Finally, the Ssk1-p is continuously dephosphorylated by phosphatase in the signal transduction pathway [20].

Let us denote the state vector $x(t)$ of the signal transduction pathway as

$$x(t) = \begin{bmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \\ x_4(t) \\ x_5(t) \\ x_6(t) \\ x_7(t) \end{bmatrix} = \begin{bmatrix} \text{Sln1}(t) \\ \text{Sln1H-P}(t) \\ \text{Sln1D-P}(t) \\ \text{Ypd1}(t) \\ \text{Ypd1-P}(t) \\ \text{Ssk1}(t) \\ \text{Ssk1-P}(t) \end{bmatrix} \quad (52)$$

Then the dynamic system of the Sln1-phosphorelay signal pathway in yeast can be represented by the following dynamic equation:

$$\begin{aligned} \dot{x}_1(t) &= -k_1 x_1(t) + k_3 x_3(t) x_4(t) + k_0 v(t) \\ \dot{x}_2(t) &= k_1 x_1(t) - k_2 x_2(t) \\ \dot{x}_3(t) &= k_2 x_2(t) - k_3 x_3(t) x_4(t) \\ \dot{x}_4(t) &= k_4 x_5(t) x_6(t) - k_3 x_3(t) x_4(t) + k_0 v(t) \\ \dot{x}_5(t) &= -k_4 x_5(t) x_6(t) + k_3 x_3(t) x_4(t) + k_4 x_4(t) v(t) \\ \dot{x}_6(t) &= k_5 x_7(t) - k_4 x_4(t) x_5(t) x_6(t) + k_0 v(t) \\ \dot{x}_7(t) &= -k_5 x_7(t) + k_4 x_4(t) x_5(t) x_6(t) \\ y(t) &= x_6(t) + 0.2v(t) \end{aligned} \quad (53)$$

where $v(t)$ is input signal, i.e., high osmolarity.

In order to investigate the relationship between system entropy and energy dissipativity of the phosphorelay system in (28) and (29), the following three systematic characteristics around the equilibrium point are considered to measure their system entropy and dissipativity:

- (a) Case 1: $k_0 = 0.125$, $k_1 = 0.1$, $k_2 = 0.025$, $k_3 = 12.5$, $k_4 = 12.5$, and $k_5 = 0.125$;
- (b) Case 2: $k_0 = 0.25$, $k_1 = 0.2$, $k_2 = 0.05$, $k_3 = 25$, $k_4 = 25$, and $k_5 = 0.25$;
- (c) Case 3: $k_0 = 0.375$, $k_1 = 0.3$, $k_2 = 0.075$, $k_3 = 37.5$, $k_4 = 37.5$, and $k_5 = 0.375$.

The temporal profiles of the phosphorelay system at the above three systematic characteristic cases are given in Figure 4.

Based on the proposed calculation procedure, we could measure the system entropy and energy dissipativity of the phosphorelay system. According to the global linearization

FIGURE 4: Temporal profiles of the state variables of Sln-1-phosphorelay system in (53) at three systematic characteristic cases: (a) $k_0 = 0.125$, $k_1 = 0.1$, $k_2 = 0.025$, $k_3 = 12.5$, $k_4 = 12.5$, and $k_5 = 0.125$; (b) $k_0 = 0.25$, $k_1 = 0.2$, $k_2 = 0.05$, $k_3 = 25$, $k_4 = 25$, and $k_5 = 0.25$; (c) $k_0 = 0.375$, $k_1 = 0.3$, $k_2 = 0.075$, $k_3 = 37.5$, $k_4 = 37.5$, and $k_5 = 0.375$, with $v(t) \sim N(0, ((1 + t^2)/(2 + t^2)) \times 10^{-6})$.

in (42), the phosphorelay system in (53) could be represented by the following global linearization system:

$$\begin{aligned} \dot{X}(t) &= \sum_{i=1}^{27} \alpha_i(X(t)) [A_i X(t) + B_i v(t)] \\ y(t) &= Cx(t) + Dv(t) \end{aligned} \quad (54)$$

where the local linearized system matrices A_i and B_i , $i = 1, \dots, 27$ for Case 1, Case 2, and Case 3 are given in Appendix G.

By solving the LMI-constrained optimization problem in (45) at the above three system characteristic cases with $P_1^{(r)}, P_2^{(r)}, P_3^{(r)}$

$$\begin{aligned} P_1^{(r)} &= \begin{bmatrix} 0.5215 & -2.0233 & -1.7648 & 0.0718 & 0.4512 & 1.5876 & 1.5876 \\ -2.0233 & -1.1725 & -2.1575 & 0.0729 & 0.329 & 1.5876 & 1.5876 \\ -1.7648 & -2.1575 & -1.3297 & 0.0763 & 0.0332 & 1.5876 & 1.5876 \\ 0.0718 & 0.0729 & 0.0763 & -0.001 & -0.0028 & 0 & 0 \\ 0.4512 & 0.329 & 0.0332 & -0.0028 & 0.4438 & 0 & 0 \\ 1.5876 & 1.5876 & 1.5876 & 0 & 0 & -1.5876 & -1.5876 \\ 1.5876 & 1.5876 & 1.5876 & 0 & 0 & -1.5876 & -1.5876 \end{bmatrix} \times 10^5, \\ P_2^{(r)} &= \begin{bmatrix} 0.5691 & -2.0605 & -1.1532 & 0.033 & 0.4562 & 1.4314 & 1.4314 \\ -2.0605 & -1.2311 & -2.0099 & 0.0349 & 0.1048 & 1.4314 & 1.4314 \\ -1.1532 & -2.0099 & -0.476 & 0.0355 & -0.038 & 1.4314 & 1.4314 \\ 0.033 & 0.0349 & 0.0355 & -0.0004 & -0.0015 & 0 & 0 \\ 0.4562 & 0.1048 & -0.038 & -0.0015 & 0.5459 & 0 & 0 \\ 1.4314 & 1.4314 & 1.4314 & 0 & 0 & -1.4314 & -1.4314 \\ 1.4314 & 1.4314 & 1.4314 & 0 & 0 & -1.4314 & -1.4314 \end{bmatrix} \times 10^5, \\ P_3^{(r)} &= \begin{bmatrix} 1.9341 & -2.3316 & 1.3606 & 0.0185 & 0.0797 & 1.1428 & 1.1428 \\ -2.3316 & -1.0656 & -2.2795 & 0.0212 & 0.0256 & 1.1428 & 1.1428 \\ 1.3606 & -2.2795 & 2.4259 & 0.0201 & -0.1057 & 1.1428 & 1.1428 \\ 0.0185 & 0.0212 & 0.0201 & -0.0006 & -0.0009 & 0 & 0 \\ 0.0797 & 0.0256 & -0.1057 & -0.0009 & 0.4012 & 0 & 0 \\ 1.1428 & 1.1428 & 1.1428 & 0 & 0 & -1.1428 & -1.1428 \\ 1.1428 & 1.1428 & 1.1428 & 0 & 0 & -1.1428 & -1.1428 \end{bmatrix} \times 10^5, \end{aligned} \quad (55)$$

we could obtain the system randomness r and the corresponding system entropy s at three systematic characteristic cases as follows:

$$\begin{aligned} r_1 &= 1.2942 \times 10^6, \\ r_2 &= 1.1618 \times 10^6, \\ r_3 &= 9.9235 \times 10^5 \\ s_1 &= 14.0734, \\ s_2 &= 13.9654, \\ s_3 &= 13.8078, \end{aligned} \quad (56)$$

Similarly, by solving the LMIs-constrained optimization problem in (47) at three system characteristic cases with $P_1^{(\eta^*)}, P_2^{(\eta^*)}, P_3^{(\eta^*)}$

$$\begin{aligned} &P_1^{(\eta^*)} \\ &= \begin{bmatrix} 1.3015 & 1.3015 & 1.3015 & 0 & 0 & -1.3015 & -1.3015 \\ 1.3015 & 1.3015 & 1.3015 & 0 & 0 & -1.3015 & -1.3015 \\ 1.3015 & 1.3015 & 1.3015 & 0 & 0 & -1.3015 & -1.3015 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -1.3015 & -1.3015 & -1.3015 & 0 & 0 & 1.3015 & 1.3015 \\ -1.3015 & -1.3015 & -1.3015 & 0 & 0 & 1.3015 & 1.3015 \end{bmatrix} \\ &\quad \times 10^8, \\ &P_2^{(\eta^*)} \\ &= \begin{bmatrix} 2.5907 & 2.5907 & 2.5907 & 0 & 0 & -2.5907 & -2.5908 \\ 2.5907 & 2.5907 & 2.5907 & 0 & 0 & -2.5907 & -2.5907 \\ 2.5907 & 2.5907 & 2.5907 & 0 & 0 & -2.5907 & -2.5907 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -2.5907 & -2.5907 & -2.5907 & 0 & 0 & 2.5911 & 2.5911 \\ -2.5908 & -2.5907 & -2.5907 & 0 & 0 & 2.5911 & 2.6013 \end{bmatrix} \\ &\quad \times 10^4, \\ &P_3^{(\eta^*)} \\ &= \begin{bmatrix} 2.2688 & 2.2688 & 2.2688 & 0 & 0 & -2.2688 & -2.2688 \\ 2.2688 & 2.2688 & 2.2688 & 0 & 0 & -2.2688 & -2.2688 \\ 2.2688 & 2.2688 & 2.2688 & 0 & 0 & -2.2688 & -2.2688 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -2.2688 & -2.2688 & -2.2688 & 0 & 0 & 2.2688 & 2.2688 \\ -2.2688 & -2.2688 & -2.2688 & 0 & 0 & 2.2688 & 2.2689 \end{bmatrix} \\ &\quad \times 10^6, \end{aligned} \quad (57)$$

FIGURE 5: The relationship between of system entropy and system energy dissipativity of the phosphorelay system based on three systematic characteristic cases.

we could obtain the system energy dissipativity at three systematic characteristic cases as follows:

$$\begin{aligned} \eta_1^* &= 0.1277, \\ \eta_2^* &= 0.1647, \\ \eta_3^* &= 0.1660. \end{aligned} \quad (58)$$

According to the above measurement results of system entropy and energy dissipativity at three systematic characteristic cases, with some interpolation technique, the relationship between of system entropy and system energy dissipativity of the phosphorelay system in Equation (53) is shown in Figure 5 which could confirm the relationship in Figure 1(b) between the system entropy s and the energy dissipativity η^* near the equilibrium state of nonlinear biological system. The simulations of the output y for Case 1, Case 2, and Case 3 are shown in Figure 6. Obviously, the measurements of phosphorelay system can confirm the predicted relationship of system entropy and system energy dissipativity of biological system in (29) and in Figure 1.

4.2. Example 2: The System Entropy and Energy Dissipativity of Predator-Prey Ecological System. In the predator-prey ecological system [21, 46–49]

$$\begin{aligned} \dot{x}_1(t) &= -kx_1(t) + kx_1(t)x_2(t)v_2(t) + 0.8v_1(t) \\ \dot{x}_2(t) &= kx_2(t) - kx_1(t)x_2(t) + 0.6v_2(t) \end{aligned} \quad (59)$$

$$y = \begin{bmatrix} x_1(t) + 0.1v_1(t) \\ x_2(t) + 0.2v_2(t) \end{bmatrix}$$

where $v_1(t)$ and $v_2(t)$ are external inputs, from (42), the nonlinear predator-prey system in (59) was approximated by the following global linearization system:

$$\dot{X}(t) = \sum_{i=1}^{12} \alpha_i(X(t)) (A_i X(t) + B_i v(t)) \quad (60)$$

FIGURE 6: Simulations of the output y of Sln1-phosphorelay system in (53) for three systematic characteristics at Case 1, Case 2, and Case 3, with $v(t) \sim N(0, ((1 + t^2)/(2 + t^2)) \times 10^{-6})$.

where A_i and B_i , $i = 1, 2, \dots, 12$, for three systematic characteristic cases of $k = 0.01, 0.013$, and 0.015 given in Appendix H. The simulations of the predatory-prey ecological system in (59) with three systematic characteristic cases are shown in Figure 7, solving the LMIs-constrained optimization problems in (45) and in (47) with

$$\begin{aligned}
 P_1^{(r)} &= \begin{bmatrix} 15326.9841 & -74.8895 \\ -74.8895 & 905.0034 \end{bmatrix}, \\
 P_2^{(r)} &= \begin{bmatrix} 13284.8144 & -82.9125 \\ -82.9125 & 768.9035 \end{bmatrix}, \\
 P_3^{(r)} &= \begin{bmatrix} 11383.7755 & -63.6299 \\ -63.6299 & 663.2808 \end{bmatrix}, \\
 P_1^{(\eta^*)} &= \begin{bmatrix} 1.254 & -0.0015 \\ -0.0015 & 1.6596 \end{bmatrix}, \\
 P_2^{(\eta^*)} &= \begin{bmatrix} 1.2531 & -0.0008 \\ -0.0008 & 1.6577 \end{bmatrix}, \\
 P_3^{(\eta^*)} &= \begin{bmatrix} 1.253 & -0.0009 \\ -0.0009 & 1.6578 \end{bmatrix}
 \end{aligned} \tag{61}$$

The system entropy and energy dissipativity of predatory-prey ecological system in (59) at the three systematic characteristic cases of $k = 0.01, 0.013$, and 0.015 are obtained, respectively,

$$\begin{aligned}
 s_1 &= 13.6308, \\
 s_2 &= 13.2975, \\
 s_3 &= 13.0128, \\
 \eta_1^* &= 0.0314, \\
 \eta_2^* &= 0.0525, \\
 \eta_3^* &= 0.0659,
 \end{aligned} \tag{62}$$

The relationship between system entropy and dissipativity based on three systematic characteristic cases is shown in Figure 8 which could also confirm the relationship in Figure 1(b) between the system entropy s and the energy dissipativity η^* near the equilibrium state x_e of biological system. The simulations of the first component y_1 of the output y for three systematic characteristic cases $k = 0.01, 0.013$, and 0.015 are shown in Figure 9. Obviously the measured results of predator-prey ecological system can also confirm the predicted relationship of system entropy and system energy dissipativity of biological system in (29) and Figure 1.

5. Conclusion

In this study, the measurement methods of system entropy and energy dissipativity of more general biological system are introduced and the relationship between system entropy s and energy dissipativity η^* is also investigated by $s = \log(h - 2\eta^*)$ as shown in Figure 1(b). In the nonlinear biological systems, based on the global linearization technique, we could find that the same relationship between system entropy and energy dissipativity is also maintained at the phenotype near the equilibrium point x_e . From the two simulation results, the relationship between the system entropy and energy dissipativity is confirmed by two nonlinear biological systems. Our theories verify that when biological systems exchange material and energy with their environment to maintain life, their entropy and energy dissipativity can be maintained through exchanging material and energy with their environment. Since the evolution of biological system is also related to the intrinsic genetic variations and environmental disturbances, our future work will be to investigate the relationship between the system entropy and evolution of biological systems. Furthermore, the experimental results in literature for the validation of the proposed theories are also important which also can be considered in the future studies.

Appendix

A. Proof of Proposition 2

Proof. From (13), we get

$$\begin{aligned}
 &\mathbb{E} \left\{ \int_0^{T_f} y^T(t) y(t) dt \right\} \\
 &= \mathbb{E} \left\{ \int_0^{T_f} \left[x^T(t) C^T + v^T(t) D^T \right] \right. \\
 &\quad \cdot [Cx(t) + Dx(t)] dt \Big\} \leq \overline{r} \mathbb{E} \left\{ \int_0^{T_f} v^T(t) \right. \\
 &\quad \cdot v(t) dt \Big\}
 \end{aligned} \tag{A.1}$$

FIGURE 7: Temporal profiles of the state variables of predator-prey system in (53) at the three systematic characteristic cases: (a) $k = 0.01$, (b) $k = 0.013$, and (c) $k = 0.015$, with $v(t) \sim N(0, (1 + t^2)/(2 + t^2))$.

FIGURE 8: The relationship between of system entropy and system energy dissipativity of the predator-prey ecological system based on three systematic characteristic cases: $k = 0.01, 0.013$, and 0.015 .

or equivalently

$$\begin{aligned} & \mathbb{E} \{V(x(0))\} - \mathbb{E} \{V(x(T_f))\} \\ & + \mathbb{E} \left\{ \int_0^{T_f} \left[x^T(t) C^T + v^T(t) D^T \right] \right. \\ & \cdot [Cx(t) + Dx(t)] + \frac{d}{dt} V(x(t)) \left. \right\} dt \quad (A.2) \\ & \leq \bar{r} \mathbb{E} \left\{ \int_0^{T_f} v^T(t) v(t) dt \right\} \end{aligned}$$

where the Lyapunov function $V(x(t)) = x^T(t)Px(t)$ for some positive symmetric matrix $P > 0$. Since we assume $x(0) = 0$ and $V(x(T_f)) = x^T(T_f)Px(T_f) \geq 0$, the following inequality implies (A.1) and (A.2):

$$\begin{aligned} & \mathbb{E} \left\{ \int_0^{T_f} \left[x^T(t) C^T Cx(t) + x^T(t) C^T Dv(t) \right. \right. \\ & + v^T(t) D^T Cx(t) + v^T(t) D^T Dv(t) \\ & + \dot{x}^T(t) Px(t) + x^T(t) P\dot{x}(t) \left. \right\} dt \quad (A.3) \\ & \leq \bar{r} \mathbb{E} \left\{ \int_0^{T_f} v^T(t) v(t) dt \right\} \end{aligned}$$

FIGURE 9: Simulation of the first component y_1 of the output y of predatory-prey system in (59) for $k = 0.01, 0.013, 0.015$, with $v(t) \sim N(0, (1 + t^2)/(2 + t^2))$.

By $\dot{x}(t) = Ax(t) + Bv(t)$ in (1), we get

$$\begin{aligned} & \mathbb{E} \left\{ \int_0^{T_f} \left[x^T(t), v^T(t) \right] \right. \\ & \cdot \begin{bmatrix} A^T P + PA + C^T C & PB + C^T D \\ B^T P + D^T C & -\bar{r}I + D^T D \end{bmatrix} \begin{bmatrix} x(t) \\ v(t) \end{bmatrix} dt \left. \right\} \quad (A.4) \\ & \leq 0 \end{aligned}$$

Therefore, if the LMI in (14) holds, then the inequality (A.4) holds and (A.1) also holds. $\square$

B. Proof of Proposition 3

Proof. From (10), we get

$$\mathbb{E} \left\{ \int_0^{T_f} \left[2\eta v^T(t) v(t) - 2v^T(t) y(t) \right] dt \right\} \leq 0 \quad (B.1)$$

or equivalently

$$\begin{aligned} & \mathbb{E} \{V(x(0))\} - \mathbb{E} \{V(x(T_f))\} \\ & + \mathbb{E} \left\{ \int_0^{T_f} \left[2\eta v^T(t) v(t) - 2v^T(t) y(t) \right. \right. \\ & \left. \left. + \frac{d}{dt} V(x(t)) \right] dt \right\} \leq 0 \end{aligned} \quad (\text{B.2})$$

By the fact $x(0) = 0$ and $V(x(0)) = x^T(0)Px^T(0) = 0$ and $V(x(T_f)) = x^T(T_f)Px(T_f) \geq 0$, the following inequality implies the inequality in (B.2):

$$\begin{aligned} & \mathbb{E} \left\{ \int_0^{T_f} \left[2\eta v^T(t) v(t) - 2v^T(t) (Cx(t) + Dv(t)) \right. \right. \\ & \left. \left. + \dot{x}^T(t) Px(t) + x^T(t) P\dot{x}(t) \right] dt \right\} \leq 0 \end{aligned} \quad (\text{B.3})$$

By the fact $\dot{x}(t) = Ax(t) + Bv(t)$ in (1), we get

$$\begin{aligned} & \mathbb{E} \left\{ \int_0^{T_f} \left[2\eta v^T(t) v(t) - 2v^T(t) Cx(t) \right. \right. \\ & - 2v^T(t) Dv(t) + \dot{x}^T(t) A^T Px(t) \\ & + v^T(t) B^T Px(t) + x^T(t) PAx(t) \\ & \left. \left. + x^T(t) PBv(t) \right] dt \right\} \leq 0 \end{aligned} \quad (\text{B.4})$$

By the fact $v^T(t)Cx(t) = x^T(t)C^T v(t)$ and $v^T(t)Dv(t) = v^T(t)D^T v(t)$, (B.4) is equivalent to

$$\begin{aligned} & \mathbb{E} \left\{ \int_0^{T_f} \left[x^T(t), v^T(t) \right] \right. \\ & \cdot \begin{bmatrix} A^T P + PA & PB - C^T \\ B^T P - C & 2\eta I - (D^T + D) \end{bmatrix} \begin{bmatrix} x(t) \\ v(t) \end{bmatrix} dt \left. \right\} \leq 0 \end{aligned} \quad (\text{B.5})$$

Therefore, the LMI in (16) implies (B.5) and (B.1). $\square$

C. Proof of Proposition 6

Proof. From (12), we get

$$\begin{aligned} & \mathbb{E} \left\{ \int_0^{T_f} y^T(t) y(t) dt \right\} \\ & = \mathbb{E} \left\{ \int_0^{T_f} [h(x(t)) + d(x(t))v(t)]^T \right. \end{aligned}$$

$$\begin{aligned} & \cdot [h(x(t)) + d(x(t))v(t)] dt \leq \bar{r} \mathbb{E} \left\{ \int_0^{T_f} v^T(t) \right. \\ & \cdot v(t) dt \left. \right\} \end{aligned} \quad (\text{C.1})$$

or equivalently, for some Lyapunov energy function $V(0) = 0$, $V(x(t)) > 0$ when $x(t) \neq 0$

$$\begin{aligned} & \mathbb{E} \{V(x(0)) - V(x(T_f))\} \\ & + \mathbb{E} \left\{ \int_0^{T_f} \left\{ [h(x(t)) + d(x(t))v(t)]^T \right. \right. \\ & \cdot [h(x(t)) + d(x(t))v(t)] + \frac{d}{dt} V(x(t)) \left. \right\} dt \left. \right\} \end{aligned} \quad (\text{C.2})$$

$$\leq \bar{r} \mathbb{E} \left\{ \int_0^{T_f} v^T(t) v(t) dt \right\}$$

By the fact $x(0) = 0$, $V(0) = 0$ and $V(x(T_f)) \geq 0$, the following inequality implies (C.2):

$$\begin{aligned} & \mathbb{E} \left\{ \int_0^{T_f} \left\{ [h(x(t)) + d(x(t))v(t)]^T \right. \right. \\ & \cdot [h(x(t)) + d(x(t))v(t)] + \left(\frac{\partial V(x(t))}{\partial x} \right)^T \\ & \cdot [f(x(t)) + g(x)v(t)] \left. \right\} dt \left. \right\} \\ & - \bar{r} \mathbb{E} \left\{ \int_0^{T_f} v^T(t) v(t) dt \right\} \leq 0 \end{aligned} \quad (\text{C.3})$$

Therefore, the HJI in (34) implies (C.3), and (C.3) implies (C.1); i.e., HJI in (34) implies that the system randomness of nonlinear biological system in (33) has an upper bound $\bar{r}$ in (12). $\square$

D. Proof of Proposition 7

Proof. From (10), we get

$$\mathbb{E} \left\{ \int_0^{T_f} \left[2\eta v^T(t) v(t) - 2v^T(t) y(t) \right] dt \right\} \leq 0 \quad (\text{D.1})$$

or equivalently, for some Lyapunov energy function $V(0) = 0$, $V(x(t)) > 0$ when $x(t) \neq 0$

$$\begin{aligned} & \mathbb{E} \{V(x(0))\} - \mathbb{E} \{V(x(T_f))\} \\ & + \mathbb{E} \left\{ \int_0^{T_f} \left[2\eta v^T(t) v(t) - 2v^T(t) y(t) \right. \right. \\ & \left. \left. + \frac{d}{dt} V(x(t)) \right] dt \right\} \leq 0 \end{aligned} \quad (\text{D.2})$$

By the fact $x(0) = 0$ and $V(x(0)) = V(0) = 0$ and $V(x(T_f)) \geq 0$, the following inequality implies the inequality in (D.2) or (D.1):

$$\begin{aligned}
& \mathbb{E} \left\{ \int_0^{T_f} \left\{ 2\eta v^T(t) v(t) \right. \right. \\
& \quad - v^T(t) [h(x(t)) + d(x(t)) v(t)] \\
& \quad - [h(x(t)) + d(x(t)) v(t)]^T v(t) \\
& \quad + \left(\frac{\partial V(x(t))}{\partial x} \right)^T \times f(x(t)) \\
& \quad \left. \left. + \left(\frac{\partial V(x(t))}{\partial x} \right)^T d(x) v(t) \right\} dt \right\} \leq 0
\end{aligned} \tag{D.3}$$

The HJI in (36) could imply the inequality in (D.3) and then implies (D.2) and (D.1). Therefore the HJI in (36) implies the energy dissipation η in (10). $\square$

E. Proof of Proposition 10

Proof. From (13), we get

$$\begin{aligned}
& \mathbb{E} \left\{ \int_0^{T_f} y^T(t) y(t) dt \right\} \\
& = \mathbb{E} \left\{ \int_0^{T_f} \left\{ [x^T(t) C^T + v^T(t) D^T] \right. \right. \\
& \quad \cdot [Cx(t) + Dx(t)] \left. \right\} dt \right\} \leq \bar{r} \mathbb{E} \left\{ \int_0^{T_f} v^T(t) \right. \\
& \quad \left. \cdot v(t) dt \right\}
\end{aligned} \tag{E.1}$$

$$\begin{aligned}
& \mathbb{E} \left\{ \int_0^{T_f} \sum_{i=1}^M \alpha_i(x(t)) \right. \\
& \quad \cdot [x^T(t) C^T Cx(t) + x^T(t) C^T Dv(t) + v^T(t) D^T Cx(t) + v^T(t) D^T Dv(t) + x^T(t) A_i^T Px(t) + v^T(t) B_i^T Px(t) + x^T(t) PA_i x(t) + x_i^T(t) PBv(t) - \bar{r} v^T(t) v(t)] dt \left. \right\} \\
& \leq 0
\end{aligned} \tag{E.4}$$

or

$$\begin{aligned}
& \mathbb{E} \left\{ \int_0^{T_f} \sum_{i=1}^M \alpha_i(x(t)) \left[x^T(t), v^T(t) \right] \right. \\
& \quad \cdot \begin{bmatrix} A_i^T P + PA_i + C^T C & PB_i + C^T D \\ B_i^T P + D^T C & -\bar{r} I + D^T D \end{bmatrix} \begin{bmatrix} x(t) \\ v(t) \end{bmatrix} dt \left. \right\} \\
& \leq 0
\end{aligned} \tag{E.5}$$

Therefore, if the LMI in (44) holds, then the inequality (E.5) holds and (E.1) also holds. $\square$

F. Proof of Proposition 11

Proof. From (10), there exists

$$\mathbb{E} \left\{ \int_0^{T_f} [2\eta v^T(t) v(t) - 2v^T(t) y(t)] dt \right\} \leq 0 \tag{F.1}$$

or equivalently

$$\begin{aligned}
& \mathbb{E} \{V(x(0))\} - \mathbb{E} \{V(x(T_f))\} \\
& + \mathbb{E} \left\{ \int_0^{T_f} \left\{ [x^T(t) C^T + v^T(t) D^T] \right. \right. \\
& \quad \cdot [Cx(t) + Dx(t)] + \frac{d}{dt} V(x(t)) \left. \right\} dt \left. \right\} \\
& \leq \bar{r} \mathbb{E} \left\{ \int_0^{T_f} v^T(t) v(t) dt \right\}
\end{aligned} \tag{E.2}$$

where the Lyapunov function $V(x(t)) = x^T(t)Px(t)$ for some positive symmetric matrix $P > 0$ satisfying LMIs (46). Since $x(0) = 0$ and $V(x(T_f)) = x^T(T_f)Px(T_f) \geq 0$, the following inequality implies (E.1) and (E.2):

$$\begin{aligned}
& \mathbb{E} \left\{ \int_0^{T_f} \left\{ x^T(t) C^T Cx(t) + x^T(t) C^T Dv(t) \right. \right. \\
& \quad + v^T(t) D^T Cx(t) + v^T(t) D^T Dv(t) \\
& \quad + \dot{x}^T(t) Px(t) + x^T(t) P\dot{x}(t) \left. \right\} dt \left. \right\} \\
& \leq \bar{r} \mathbb{E} \left\{ \int_0^{T_f} v^T(t) v(t) dt \right\}
\end{aligned} \tag{E.3}$$

Keeping (42) in mind, we get

or equivalently

$$\begin{aligned}
& \mathbb{E} \{V(x(0))\} - \mathbb{E} \{V(x(T_f))\} \\
& + \mathbb{E} \left\{ \int_0^{T_f} \left\{ 2\eta v^T(t) v(t) - 2v^T(t) y(t) \right. \right. \\
& \quad \left. \left. + \frac{d}{dt} V(x(t)) \right\} dt \right\} \leq 0
\end{aligned} \tag{E.2}$$

Taking $V(x) = x^T Px$ and by the fact $x(0) = 0$ and $V(x(0)) = x^T(0)Px(0) = 0$ and $V(x(T_f)) = x^T(T_f)Px(T_f) \geq 0$, the following inequality implies the inequality in (E.2):

$$\begin{aligned}
& \mathbb{E} \left\{ \int_0^{T_f} \left\{ 2\eta v^T(t) v(t) - 2v^T(t) (Cx(t) + Dv(t)) \right. \right. \\
& \quad \left. \left. + \dot{x}^T(t) Px(t) + x^T(t) P\dot{x}(t) \right\} dt \right\} \leq 0
\end{aligned} \tag{E.3}$$

By (42), we get

$$\mathbb{E} \left\{ \int_0^{T_f} \sum_{i=1}^M \alpha_i(x(t)) \cdot \left[2\eta v^T(t) v(t) - 2v^T(t) Cx(t) - 2v^T(t) + x^T(t) A_i^T P x(t) + v^T(t) B_i^T P x(t) + x^T(t) P A_i x(t) + x^T(t) P B_i v(t) \right] dt \right\} \leq 0 \quad (\text{F.4})$$

By the fact $v^T(t)Cx(t) = x^T(t)C^T v(t)$ and $v^T(t)Dv(t) = v^T(t)D^T v(t)$, (F.4) is equivalent to

$$\mathbb{E} \left\{ \int_0^{T_f} \sum_{i=1}^M \alpha_i(x(t)) \left[x^T(t), v^T(t) \right] \cdot \begin{bmatrix} A^T P + PA & PB - C^T \\ B^T P - C & 2\eta I - (D^T + D) \end{bmatrix} \begin{bmatrix} x(t) \\ v(t) \end{bmatrix} dt \right\} \leq 0 \quad (\text{F.5})$$

Therefore, the LMI in (46) implies (F.5) and (F.1). $\square$

G. System Matrices A_i and B_i of Local Linearized Systems in (40) Used in Example 1

In system (53), the corresponding nonlinear coefficients $f(x)$ and $g(x)$ are presented as

$$f(x) = \begin{bmatrix} -k_1 x_1(t) + k_3 x_3(t) x_4(t) \\ k_1 x_1(t) - k_2 x_2(t) \\ k_2 x_2(t) - k_3 x_3(t) x_4(t) \\ k_4 x_5(t) x_6(t) - k_3 x_3(t) x_4(t) \\ k_3 x_3(t) x_4(t) - k_4 x_5(t) x_6(t) \\ k_5 x_7(t) - k_4 x_4(t) x_5(t) x_6(t) \\ -k_5 x_7(t) + k_4 x_4(t) x_5(t) x_6(t) \end{bmatrix}, \quad (\text{G.1})$$

$$g(x) = \begin{bmatrix} k_0 \\ 0 \\ 0 \\ k_0 \\ k_4 x_4(t) \\ k_0 \\ 0 \end{bmatrix}.$$

In order to linearize system (53), let $\zeta_1 = x_4$, $\zeta_2 = x_6$ and $\zeta_3 = x_4 x_5$ as the approximation variables. Denote

$$A(\zeta) = \begin{bmatrix} -k_1 & 0 & k_3 \zeta_1 & 0 & 0 & 0 & 0 \\ k_1 & -k_2 & 0 & 0 & 0 & 0 & 0 \\ 0 & k_2 & -k_3 \zeta_1 & 0 & 0 & 0 & 0 \\ 0 & 0 & -k_3 \zeta_1 & 0 & k_4 \zeta_2 & 0 & 0 \\ 0 & 0 & k_3 \zeta_1 & 0 & -k_4 \zeta_2 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -k_4 \zeta_3 & k_5 \\ 0 & 0 & 0 & 0 & 0 & k_4 \zeta_3 & k_5 \end{bmatrix}, \quad (\text{G.2})$$

$$B(\zeta) = \begin{bmatrix} k_0 \\ 0 \\ 0 \\ k_0 \\ k_4 \zeta_1 \\ k_0 \\ 0 \end{bmatrix}.$$

Then $f(x) \approx A(\zeta)x$ with $x = [x_1, x_2, x_3, x_4, x_5, x_6, x_7]^T$ and $g(x) \approx B$ when $\zeta = [\zeta_1, \zeta_2, \zeta_3]$ takes the fixed approximating values.

The matrices A_i and B_i for Case 1, Case 2, and Case 3 in Example 1 are calculated based on (G.2) where ζ takes values in $\{0.001, 0.005, 0.009\} \times \{0.001, 0.0025, 0.0065\} \times \{0.000003, 0.000011, 0.000022\}$, $\{0.003, 0.008, 0.016\} \times \{0.003, 0.007, 0.015\} \times \{0.00003, 0.00008, 0.0002\}$, and $\{0.015, 0.05, 0.12\} \times \{0.022, 0.07, 0.13\} \times \{0.000030, 0.000120, 0.00023\}$, respectively, $i = 1, 2, \dots, 27$.

H. System Matrices A_i and B_i of Local Linearized Systems in (40) Used in Example 2

In system (59), the corresponding nonlinear coefficients $f(x)$ and $g(x)$ are presented as

FIGURE 10: Relationships between $\alpha_{ij}(X(t))$ and $z(t)$ with different $\zeta^{(ij)} = [\zeta_1^{(i)}(t), \zeta_2^{(j)}(t)]$.

$$\begin{aligned} f(x) &= \begin{bmatrix} -kx_1(t) \\ kx_1(t) - kx_1(t)x_2(t) \end{bmatrix}, \\ g(x) &= \begin{bmatrix} kx_1(t)x_2(t) & 0.8 \\ 0 & 0.6 \end{bmatrix}. \end{aligned} \quad (\text{H.1})$$

In order to linearize system (59), let $\zeta_1 = x_1$ and $\zeta_2 = x_1x_2$ as the approximation variables. Denote

$$\begin{aligned} A(\zeta) &= \begin{bmatrix} -k & 0 \\ k & -k\zeta_1 \end{bmatrix}, \\ B(\zeta) &= \begin{bmatrix} 0.8 & k\zeta_2 \\ 0 & 0.6 \end{bmatrix}. \end{aligned} \quad (\text{H.2})$$

Then $f(x) \approx A(\zeta)x$ with $x = [x_1, x_2]^T$ and $g(x) \approx B$ when $\zeta = [\zeta_1, \zeta_2]$ takes the fixed approximating values. The matrices A_i and B_i for $k = 0.01, k = 0.013$, and $k = 0.015$ used in Example 2 are calculated based on (H.2), where ζ takes values in $\{0.1, 0.3, 0.7, 1.5\} \times \{0.1, 0.2, 0.7\}$, $i = 1, 2, \dots, 12$.

Denote $z_1(t) = x_1(t)$, $z_2 = x_1(t)x_2(t)$, and $z(t) = [z_1(t), z_2(t)]$, and let

$$\alpha_{ij}(X(t)) = \begin{cases} \frac{(1/\|\zeta^{(ij)}(t) - z(t)\|_2^2)}{\left[\sum_{k=1}^4 \sum_{l=1}^3 (1/\|\zeta^{(kl)}(t) - z(t)\|_2^2)\right]}, & \text{if } z(t) \neq \zeta^{(ij)}(t) \\ 1, & \text{if } z(t) = \zeta^{(ij)}(t) \end{cases} \quad (\text{H.3})$$

where $\zeta^{(ij)}(t) = [\zeta_1^{(i)}(t), \zeta_2^{(j)}(t)]$ and $\zeta_1^{(i)}(t)$ takes values in $\{0.1, 0.3, 0.7, 1.5\}$ with $i = 1, 2, 3, 4$, $\zeta_2^{(j)}(t)$ takes values in

FIGURE 11: The positional relationship among α_{ij} .

$\{0.1, 0.2, 0.7\}$ with $j = 1, 2, 3$. Then the global linearization system (60) for the nonlinear system (59) is presented as

$$\dot{X}(t) = \sum_{i=1}^{12} \alpha_{ij}(X(t)) (A(\zeta^{(ij)}) X(t) + B(\zeta^{(ij)}) v(t)) \quad (\text{H.4})$$

Figure 10 illustrates the relationships between $\alpha_{ij}(X(t))$ and $z(t)$ with different $\zeta^{(ij)}$, $i = 1, 2, 3, 4$; $j = 1, 2, 3$; i.e., α_{ij} can also be seen as the function of z (t is omitted) and is also written as $\alpha_{ij}(z)$. It shows that, for each i, j , the closer the distance between z and $\zeta^{(ij)}$ the bigger the values of α_{ij} are, inversely, the further the distance between z and $\zeta^{(ij)}$ the smaller the values of α_{ij} are.

Figure 11 illustrates the positional relationships among $\{\alpha_{ij}, i = 1, 2, 3, 4; j = 1, 2, 3\}$. It shows that for every given $z = [z_1, z_2]$ there exist several $\alpha_{ij}(z)$ with different values corresponding with it and, by (H.3), they also satisfy $\sum_{i=1}^4 \sum_{j=1}^3 \alpha_{ij}(z) = 1$.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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