Research Article

Entrained Collective Rhythms of Multicellular Systems: Partial Impulsive Control Strategy

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This paper is concerned with the study of entrained collective rhythms of multicellular systems by using partial impulsive control strategy. The objective is to design an impulsive controller based on only those partially available cell states, so that the entrained collective rhythms are guaranteed for the multicellular systems with cell-to-cell communication mechanism. By using the newly developed impulsive integrodifferential inequality, the sufficient conditions are derived to achieve the entrained collective rhythms of multicellular systems. A synthetic multicellular system with simulation results is finally given to illustrate the usefulness of the developed results.

1. Introduction

Complex physiological rhythms are ubiquitous in living organisms, which are central to life, such as our daily cycle of waking and sleeping and the beating of our hearts. Collective rhythms are normally generated by thousands of divers clock cells which manage to function in a coherent oscillatory state [1, 2]. In fields ranging from circadian biology to endocrinology, however, it remains an exciting challenge to understand how collective rhythms emerge in multicellular structures [3–7].

Elucidating the collective dynamics of multicellular systems not only is essential for the understanding of the rhythmic phenomena of living organisms at both molecular and cellular levels but also has many potential applications in bioengineering areas. For example, in cancer chemotherapy, treatments could be based on the circadian rhythm of cell division [8]. Over the past decade or so, many researchers have paid a great deal of attention to study the collective dynamics of multicellular systems. For instance, in [9–12], the authors considered stability of genetic networks and neural networks. In [3], the authors pointed out that intercell signaling mechanism does lead to synchronous behavior across a population of cells. In [13], after making real-time analysis of the gene expression, the authors showed the synchronized rhythms of clock gene transcription across hundreds of neurons within the mammalian suprachiasmatic nucleus (SCN) in organotypic slice culture. In addition, based on the Lyapunov stability theory, the collective rhythms of multicellular systems were further studied in [14]. For the other relevant results, please see [15–17].

Although there are significant advances on elucidating the collective behaviors of biological organisms in recent years, the essential mechanisms from which the collective rhythms arise remain to be fully understood. It is well known that coupling among cells is not sufficient to achieve collective rhythms. In fact, the collective rhythms of multicellular systems are far away from being well understood and warrant further and insightful study.

On the other hand, experimental results have already shown that external stimuli play an important role in achieving the collective rhythms. In [18], physiological rhythms were induced by regular or periodic inputs occurring in the context of medical devices. In [19], an external voltage

was applied to enhance the synchronization of electronic synthetic genetic networks. In [20], it was shown that a specific collective behavior could be realized by changing the frequency and amplitude of the periodic stimuli. Another well-known example is that organisms usually display a circadian rhythm, where the key processes show a 24-hour periodicity entrained to the light-dark cycle [21]. In [22], the authors studied the rhythmic process of the circadian oscillators under the effect of the daily light-dark cycle. Furthermore, from the view of impulsive control systems, collective behaviors of coupled systems were investigated and some interesting results have been obtained in [23–27], and, for the other relevant results, please refer to [28–32] and the references therein.

However, in the above-mentioned results, one basic assumption is that the external stimuli are applied to all the cells in the community, that is very expensive or unrealistic in practice. Actually, in many practical medical cases, only partial specific cells could be detected and utilized. In these situations, the external stimuli are applied to only those cells in the community. To the best of our knowledge, there are few results in the open literature on the entrained collective rhythms of multicellular systems by applying impulsive control based on the partially available cell states.

This paper is to study the entrained collective rhythms of multicellular systems with only partially available cell states. By using the newly developed impulsive integrod-ifferential inequality, a new criterion is derived to ensure the entrained collective rhythms of multicellular systems. It is shown that when the spontaneous synchrony cannot be achieved, an appropriate periodic stimulus could achieve a collective rhythm even only with partially available cell states. It is noted that the proposed partial impulsive control method can be also easily extended to study other complex systems.

The rest of the paper is organized as follows. Section 2 formulates the problem of the entrained collective rhythms and provides some useful lemmas. Section 3 presents the main results for entrained collective rhythms of multicellular systems. A synthetic multicellular system will be employed to illustrate the effectiveness of the developed results in Section 4, which is followed by conclusions in Section 5.

2. Model Description and Problem Formulation

To make it easy for the readers, let us start from a single cell model of the form

$$\dot{x}(t) = -Ax(t) + f(x(t)), \qquad (1)$$

where $x(t) \in \mathbb{R}^{n+}$ represents the concentrations of proteins, RNAs, and other chemical complexes, A is the positive diagonal matrix denoting the degradation and dilution rate, and $f(x(t))$ is the complex regulatory function, which usually is of the Michaelis-Menten or Hill form.

Remark 1. It is known that many biological models can be represented by (1), such as the Goodwin model [33] and the toggle switch [34]. Furthermore, the regulatory function $f(x)$ in model (1) is usually monotonically increasing or decreasing.

Without loss of generality, the regulatory function is always assumed to satisfy the following assumption.

Assumption 2. The regulatory function $f(x)$ in (1) satisfies

$$(f_i(a) - f_i(b))[f_i(a) - f_i(b) - l_i(a - b)] \le 0, \qquad (2)$$

for all $a, b \in R$, $a \ne b$, and $l_i > 0$.

Consider multicellular systems with cell-to-cell communication mechanism described as follows:

$$\dot{x}_i(t) = -Ax_i(t) + f(x_i(t))$$
$$+ c \sum_{j=1}^{N} G_{ij} \Gamma x_j(t), \quad i = 1, \dots, N, \qquad (3)$$

where $x_i(t) \in \mathbb{R}^{n+}$ is the state of the ith cell, denoting the concentrations of chemical complexes in this cell, and N is the total cell number of the entire community. The third term in model (3) describes the capability of cells to communicate with each other in order to coordinate the behavior of the entire community. $G = (G_{ij})_{N \times N}$ is the coupling structure matrix that represents the communications between different cells, and Γ is the inner coupling structure that represents the connections of different chemical complexes in one cell. G satisfies the diffusive coupling condition

$$G_{ij} \ge 0, \quad \text{for } i \ne j,$$
$$G_{ii} = -\sum_{j=1, j \ne i}^{N} G_{ij}, \quad i = 1, 2, \dots, N. \qquad (4)$$

It can be noted that such coupling is biologically plausible in many biological systems, such as the quorum sensing mechanism in bacteria [2, 35].

Suppose only l cell states in the community are measurable for the multicellular systems (3). Consider the following linear impulsive controller based on those l measurable cell states:

$$u_i = \sum_{k=1}^{\infty} E_{ik}(x_i - x)\delta(t - t_k), \quad i = 1, 2, \dots, l, \ k \in \mathbb{N}, \quad (5)$$

where x is the state of the isolated cell described in (1), l is the number of the measurable cell states, E_{ik} is the gain matrix, and $\delta(t - t_k)$ is the Dirac impulse function with discontinuity points $t_1 < t_2 < \cdots < t_k < \cdots$, $\lim_{k \to \infty} t_k = \infty$.

Then the impulsive-controlled multicellular systems with partial states can be described by the following impulsive differential equation:

$$\dot{x}_i(t) = -Ax_i(t) + f(x_i(t))$$

$$+ c\sum_{j=1}^{N} G_{ij}\Gamma x_j(t), \quad t \in (t_{k-1}, t_k],$$

$$\Delta x_i(t_k) = x_i(t_k^+) - x_i(t_k^-) = E_{ik}(x_i - x),$$

$$k = 1, 2, \ldots, \quad t = t_k, \quad (6)$$

$$i = 1, \ldots, l,$$

$$\dot{x}_i(t) = -Ax_i(t) + f(x_i(t))$$

$$+ c\sum_{j=1}^{N} G_{ij}\Gamma x_j(t), \quad i = l+1, \ldots, N.$$

Defining $e_i(t) = x_i(t) - x(t)$, one can obtain the following error system:

$$\dot{e}_i(t) = -Ae_i(t) + f(x_i(t)) - f(x(t))$$

$$+ c\sum_{j=1}^{N} G_{ij}\Gamma e_j(t), \quad t \in (t_{k-1}, t_k],$$

$$e_i(t_k^+) = (I + E_{ik})e_i(t_k), \quad k = 1, 2, \ldots, \quad (7)$$

$$t = t_k, \quad i = 1, \ldots, l,$$

$$\dot{e}_i(t) = -Ae_i(t) + f(x_i(t)) - f(x(t))$$

$$+ c\sum_{j=1}^{N} G_{ij}\Gamma e_j(t), \quad i = l+1, \ldots, N.$$

Then the problem of entrained collective rhythms is to design the partial impulsive controller (5) such that the stability of the error system (7) is guaranteed. Before presenting the main results, some useful lemmas are introduced in advance.

Lemma 3 (see [36]). *If $P \in \mathbb{R}^{n \times n}$ is a positive definite matrix and $Q \in \mathbb{R}^{n \times n}$ is a symmetric matrix, then*

$$\lambda_{\min}\left(P^{-1}Q\right)x^\top Px \leq x^\top Qx$$

$$\leq \lambda_{\max}\left(P^{-1}Q\right)x^\top Px, \quad \forall x \in \mathbb{R}^n, \quad (8)$$

where $\lambda_{\min}(\cdot)$ and $\lambda_{\max}(\cdot)$ are the minimum and maximum eigenvalues of the matrix, respectively.

Lemma 4. *For positive scalars $\delta > 0$, $\mu > 0$, and $\rho > 0$, if $u(t)$ satisfies*

$$\dot{u}(t) \leq h(t, u(t)) + \delta \int_0^t e^{-\rho(t-s)}u(s)\,ds, \quad t \neq t_k,$$

$$u(t_k^+) \leq \mu u(t_k), \quad t = t_k, \quad (9)$$

$$u(0) \leq u_0,$$

where $h(t, u(t))$ is a continuous function, then one has $u(t) \leq u_\epsilon(t)$, $t \geq 0$ for $\epsilon \geq 0$, where $u_\epsilon(t)$ is the solution to the following impulsive integrodifferential equation:

$$\dot{u}_\epsilon(t) = h(t, u_\epsilon(t)) + \delta \int_0^t e^{-\rho(t-s)}u_\epsilon(s)\,ds + \epsilon, \quad t \neq t_k,$$

$$u_\epsilon(t_k^+) = \mu u_\epsilon(t_k), \quad t = t_k, \quad (10)$$

$$u_\epsilon(0) = u_0.$$

Proof. Firstly, we prove

$$u(t) \leq u_\epsilon(t), \quad t \in (0, t_1]. \quad (11)$$

If argument (11) is not right, then there exists $\tilde{t} \in (0, t_1)$ such that

$$u(\tilde{t}) > u_\epsilon(\tilde{t}). \quad (12)$$

Considering the continuity of $u(t)$, $u_\epsilon(t)$ on $(0, t_1]$, there must exist $t^* \in (0, \tilde{t})$ such that

$$u(t^*) = u_\epsilon(t^*), \quad \dot{u}(t^*) \geq \dot{u}_\epsilon(t^*),$$

$$u(t) \leq u_\epsilon(t), \quad \forall t \leq t^*; \quad (13)$$

then it yields

$$\dot{u}(t^*) \leq h(t^*, u(t^*)) + \delta \int_0^{t^*} e^{-\rho(t^*-s)}u(s)\,ds$$

$$< h(t^*, u_\epsilon(t^*)) + \delta \int_0^{t^*} e^{-\rho(t^*-s)}u_\epsilon(s)\,ds + \epsilon \quad (14)$$

$$= \dot{u}_\epsilon(t^*),$$

which contradicts the condition $\dot{u}(t^*) \geq \dot{u}_\epsilon(t^*)$, so (11) holds.

Suppose $u(t) \leq u_\epsilon(t)$, for all $t \in (0, t_k]$; then by $u(t_k^+) = \mu u(t_k) \leq \mu u_\epsilon(t_k) = u_\epsilon(t_k^+)$, similarly, one has $u(t) \leq u_\epsilon(t)$, for all $t \in (t_k, t_{k+1}]$. By using the mathematical induction method, one can conclude $u(t) \leq u_\epsilon(t)$, for all $t \in (0, t_k]$ for any positive integer k. The proof is thus complete. $\square$

Lemma 5 (Grownwall-Bellman Inequality [37]). *Let $\alpha(t)$ be a real value continuous function and $\beta(t)$ a nonnegative continuous function on $[a, b]$. If a continuous function $u(t)$ has the property that*

$$u(t) \leq \alpha(t) + \int_a^t \beta(s)u(s)\,ds, \quad a \leq t \leq b, \quad (15)$$

then on $[a, b]$ one has

$$u(t) \leq \alpha(t) + \int_a^t \alpha(s)\beta(s)\exp\left(\int_s^t \beta(r)\,dr\right)ds. \quad (16)$$

Definition 6. The multicellular system (6) is said to achieve collective rhythms with the designed partial impulsive controller, if there exist scalars $\rho > 0$ and $M > 0$ such that

$$\lim_{t \to \infty} \|X(t)\|^2 \leq Me^{-\rho t}\|X(0)\|^2, \quad (17)$$

where $X(t) = [x_1^T - x^T, \ldots, x_N^T - x^T]^T$ and $X(0)$ is the initial condition.

3. Main Results

In this section, by using the proposed impulsive integrod-ifferential inequality, a sufficient condition guaranteeing the entrained collective rhythms of multicellular systems is derived.

Theorem 7. *For a given scalar $\mu \in (0, 1)$, if there exist matrices $P_i > 0$, $i = 1, 2, \ldots, l$, $Q_i > 0$, $i = l + 1, \ldots, N$, scalars $\lambda_i > 0$, $\mu_i > 0$, $i = 1, 2, \ldots, l$, $\eta_i > 0$, $i = l + 1, \ldots, N$, and positive scalars ϵ_1, ϵ_2, δ_1, and δ_2 such that*

$$
\left(-A^T P_i - P_i A\right) + \lambda_{\max}(P_i)\left(\epsilon_1 I + \epsilon_1^{-1} L^T L + c\delta_1 \sum_{j=1}^{N}\left|G_{ij}\right|\right)
$$

$$
+ c\delta_1^{-1}\sum_{j=1}^{l}\lambda_{\max}(P_j)\left|G_{ji}\right|\Gamma^T\Gamma \le \lambda_i P_i,
$$

(18)

$$
\left(I + E_{ik}\right)^T P_i \left(I + E_{ik}\right) \le \mu_i P_i,
$$

(19)

for $i = 1, \ldots, l$, and

$$
\left(-A^T Q_i - Q_i A\right) + \lambda_{\max}(Q_i)\left(\epsilon_2 I + \epsilon_2^{-1} L^T L + c\delta_2 \sum_{j=1}^{N}\left|G_{ij}\right|\right)
$$

$$
+ c\delta_2^{-1}\sum_{j=l+1}^{N}\lambda_{\max}(Q_j)\left|G_{ji}\right|\Gamma^T\Gamma \le -\eta_i Q_i,
$$

(20)

for $i = l + 1, \ldots, N$, and, for any impulsive time sequence $\{t_k\}$ satisfying

$$
\delta := \sup_k \{t_{k+1} - t_k\} < \frac{\ln(1/\mu)}{\eta + \lambda + (\beta\gamma)/(\eta\mu)},
$$

(21)

for $k = 0, 1, 2, \ldots$, where $\mu = \max(\mu_i)$, $\lambda = \max(\lambda_i)$, $i = 1, \ldots, l$, and $\eta = \min(\eta_i)$, $i = l + 1, \ldots, N$, then the entrained collective rhythms of multicellular systems (6) *are achieved.*

Proof. Consider the following Lyapunov function:

$$
V(t) = V_1(t) + V_2(t),
$$

(22)

where

$$
V_1(t) := \sum_{i=1}^{l} e_i^T(t) P_i e_i(t),
$$

$$
V_2(t) := \sum_{i=l+1}^{N} e_i^T(t) Q_i e_i(t),
$$

(23)

where P_i, $i = 1, 2, \ldots, l$ and Q_i, $i = l + 1, \ldots, N$ are positive definite matrices to be determined.

For any $t \in (t_k, t_{k+1}]$, $k \in \mathbb{N}$, taking the Dini derivative along the trajectories of (7), we have

$$
D^+ V_1(t) = \sum_{i=1}^{l}\left(\dot{e}_i^T(t) P_i e_i(t) + e_i^T(t) P_i \dot{e}_i(t)\right)
$$

$$
= \sum_{i=1}^{l}\left(e_i^T(t)\left(-A^T P_i - P_i A\right) e_i(t)\right.
$$

$$
+ 2e_i^T(t) P_i\left(f(x_i(t)) - f(x(t))\right)
$$

$$
\left. + 2c\sum_{j=1}^{N} e_i^T(t) P_i G_{ij}\Gamma e_j(t)\right).
$$

(24)

It follows from Assumption 2 that

$$
2e_i^T(t) P_i\left(f(x_i(t)) - f(x(t))\right)
$$

$$
\le \lambda_{\max}(P_i)\left(\epsilon_1 e_i^T(t) e_i(t) + \epsilon_1^{-1} e_i^T(t) L^T L e_i(t)\right),
$$

$$
2c\sum_{j=1}^{N} e_i^T(t) P_i G_{ij}\Gamma e_j(t)
$$

$$
\le c\lambda_{\max}(P_i)\sum_{j=1}^{N}\left|G_{ij}\right|
$$

$$
\times\left(\delta_1 e_i^T(t) e_i(t) + \delta_1^{-1} e_j^T(t)\Gamma^T\Gamma e_j(t)\right),
$$

(25)

where $\epsilon_1 > 0$, $\delta_1 > 0$ and $L = \text{diag}(l_1, \ldots, l_n)$. One also has

$$
c\delta_1^{-1}\sum_{i=1}^{l}\sum_{j=1}^{N}\lambda_{\max}(P_i)\left|G_{ij}\right| e_j^T(t)\Gamma^T\Gamma e_j(t)
$$

$$
= c\delta_1^{-1}\sum_{i=1}^{N}\sum_{j=1}^{l}\lambda_{\max}(P_j)\left|G_{ji}\right| e_i^T(t)\Gamma^T\Gamma e_i(t)
$$

$$
= c\delta_1^{-1}\sum_{i=1}^{l}\sum_{j=1}^{l}\lambda_{\max}(P_j)\left|G_{ji}\right| e_i^T(t)\Gamma^T\Gamma e_i(t)
$$

$$
+ c\delta_1^{-1}\sum_{i=l+1}^{N}\sum_{j=1}^{l}\lambda_{\max}(P_j)\left|G_{ji}\right| e_i^T(t)\Gamma^T\Gamma e_i(t).
$$

(26)

Substituting (25)–(26) into (24) yields

$$D^+ V_1(t) \leq \sum_{i=1}^{l} \left(e_i^{\mathrm{T}}(t) \left(-A^{\mathrm{T}} P_i - P_i A \right) e_i(t) + \lambda_{\max}(P_i) e_i^{\mathrm{T}}(t) \right.$$

$$\times \left(\epsilon_1 I + \epsilon_1^{-1} L^{\mathrm{T}} L + c\delta_1 \sum_{j=1}^{N} \left| G_{ij} \right| \right) e_i(t)$$

$$\left. + c\delta_1^{-1} \sum_{i=1}^{l} \sum_{j=1}^{l} \lambda_{\max}(P_j) \left| G_{ji} \right| e_i^{\mathrm{T}}(t) \Gamma^{\mathrm{T}} \Gamma e_i(t) \right)$$

$$+ c\delta_1^{-1} \sum_{i=l+1}^{N} \sum_{j=1}^{l} \lambda_{\max}(P_j) \left| G_{ji} \right| e_i^{\mathrm{T}}(t) \Gamma^{\mathrm{T}} \Gamma e_i(t)$$

$$= \sum_{i=1}^{l} e_i^{\mathrm{T}}(t) \left(\left(-A^{\mathrm{T}} P_i - P_i A \right) + \lambda_{\max}(P_i) \right.$$

$$\times \left(\epsilon_1 I + \epsilon_1^{-1} L^{\mathrm{T}} L + c\delta_1 \sum_{j=1}^{N} \left| G_{ij} \right| \right)$$

$$\left. + c\delta_1^{-1} \sum_{j=1}^{l} \lambda_{\max}(P_j) \left| G_{ji} \right| \Gamma^{\mathrm{T}} \Gamma \right) e_i(t)$$

$$+ c\delta_1^{-1} \sum_{i=l+1}^{N} \sum_{j=1}^{l} \lambda_{\max}(P_j) \left| G_{ji} \right| e_i^{\mathrm{T}}(t) \Gamma^{\mathrm{T}} \Gamma e_i(t). \tag{27}$$

Define $\beta_i = c\delta_1^{-1} \sum_{j=1}^{l} \lambda_{\max}(P_j)|G_{ji}|$. Then it follows from condition (18) and Lemma 3 that

$$D^+ V_1(t) \leq \sum_{i=1}^{l} e_i^{\mathrm{T}}(t) \lambda_i P_i e_i(t) + \sum_{i=l+1}^{N} \beta_i e_i^{\mathrm{T}}(t) e_i(t) \tag{28}$$

$$\leq \lambda V_1(t) + \beta V_2(t),$$

where $\lambda = \max(\lambda_i)$ and $\beta = \max(\beta_i \lambda_{\max}(Q_i^{-1}))$.
Furthermore, for any $t \geq 0$, one can also get

$$D^+ V_2(t) = \sum_{i=l+1}^{N} \left(\dot{e}_i^{\mathrm{T}}(t) Q_i e_i(t) + e_i^{\mathrm{T}}(t) Q_i \dot{e}_i(t) \right)$$

$$= \sum_{i=l+1}^{N} \left(e_i^{\mathrm{T}}(t) \left(-A^{\mathrm{T}} Q_i - Q_i A \right) e_i(t) \right.$$

$$+ 2 e_i^{\mathrm{T}}(t) Q_i \left(f(x_i(t)) - f(x(t)) \right)$$

$$\left. + 2c \sum_{j=1}^{N} e_i^{\mathrm{T}}(t) Q_i G_{ij} \Gamma e_j(t) \right)$$

$$\leq \sum_{i=l+1}^{N} \left(e_i^{\mathrm{T}}(t) \left(-A^{\mathrm{T}} Q_i - Q_i A \right) e_i(t) \right.$$

$$+ \lambda_{\max}(Q_i) e_i^{\mathrm{T}}(t)$$

$$\times \left(\epsilon_2 I + \epsilon_2^{-1} L^{\mathrm{T}} L + c\delta_2 \sum_{j=1}^{N} \left| G_{ij} \right| \right) e_i(t)$$

$$\left. + c\delta_2^{-1} \sum_{j=l+1}^{N} \lambda_{\max}(Q_j) \left| G_{ji} \right| e_i^{\mathrm{T}}(t) \Gamma^{\mathrm{T}} \Gamma e_i(t) \right)$$

$$+ c\delta_2^{-1} \sum_{i=1}^{l} \sum_{j=l+1}^{N} \lambda_{\max}(Q_j) \left| G_{ji} \right| e_i^{\mathrm{T}}(t) \Gamma^{\mathrm{T}} \Gamma e_i(t)$$

$$= \sum_{i=l+1}^{N} e_i^{\mathrm{T}}(t)$$

$$\times \left(\left(-A^{\mathrm{T}} Q_i - Q_i A \right) + \lambda_{\max}(Q_i) \right.$$

$$\times \left(\epsilon_2 I + \epsilon_2^{-1} L^{\mathrm{T}} L + c\delta_2 \sum_{j=1}^{N} \left| G_{ij} \right| \right)$$

$$\left. + c\delta_2^{-1} \sum_{j=l+1}^{N} \lambda_{\max}(Q_j) \left| G_{ji} \right| \Gamma^{\mathrm{T}} \Gamma \right) e_i(t)$$

$$+ c\delta_2^{-1} \sum_{i=1}^{l} \sum_{j=l+1}^{N} \lambda_{\max}(Q_j) \left| G_{ji} \right| e_i^{\mathrm{T}}(t) \Gamma^{\mathrm{T}} \Gamma e_i(t), \tag{29}$$

where $\epsilon_2 > 0$, $\delta_2 > 0$.

Defining $\gamma_i = c\delta_2^{-1} \sum_{j=l+1}^{N} \lambda_{\max}(Q_j)|G_{ji}|$, it follows from (20) and (29) that

$$D^+ V_2(t) \leq -\sum_{i=l+1}^{N} \eta_i e_i^{\mathrm{T}}(t) Q_i e_i(t)$$

$$+ \sum_{i=1}^{l} \gamma_i e_i^{\mathrm{T}}(t) e_i(t) \tag{30}$$

$$\leq -\eta V_2(t) + \gamma V_1(t),$$

where $\eta = \min(\eta_i)$ and $\gamma = \max(\gamma_i \lambda_{\max}(P_i^{-1}))$, which implies

$$V_2(t) \leq e^{-\eta t} V_2(0) + \gamma \int_0^t e^{-\eta(t-\alpha)} V_1(\alpha) \, d\alpha. \tag{31}$$

Then substituting (31) into (28) yields

$$D^+ V_1(t) \leq \lambda V_1(t) + \beta e^{-\eta t} V_2(0)$$

$$+ \beta\gamma \int_0^t e^{-\eta(t-\alpha)} V_1(\alpha) \, d\alpha, \quad t \in (t_k, t_{k+1}]. \tag{32}$$

On the other hand, when $t = t_k^+$, it follows from (19) that

$$
\begin{aligned}
V_1\left(t_k^+\right) &= \sum_{i=1}^{l} e_i^{\mathrm{T}}\left(t_k\right)\left(I + E_{ik}\right)^{\mathrm{T}} P_i\left(I + E_{ik}\right) e_i\left(t_k\right) \\
&\leq \sum_{i=1}^{l} e_i^{\mathrm{T}}\left(t_k\right) \mu_i P_i e_i\left(t_k\right) \\
&\leq \mu V_1\left(t_k\right),
\end{aligned}
\tag{33}
$$

where $\mu = \max(\mu_i)$, $i = 1, \ldots, l$.

For any scalar $\epsilon > 0$, define the following impulsive integrodifferential equation:

$$
\begin{aligned}
\dot{V}_\epsilon(t) &= \lambda V_\epsilon(t) + \beta e^{-\eta t} V_2(0) \\
&\quad + \beta\gamma \int_0^t e^{-\eta(t-\alpha)} V_\epsilon(\alpha)\, d\alpha \\
&\quad + \epsilon, \quad t \in \left(t_{k-1}, t_k\right], \\
V_\epsilon\left(t_k^+\right) &= \mu V_\epsilon\left(t_k\right), \quad t = t_k, \\
V_\epsilon(0) &= V_1(0).
\end{aligned}
\tag{34}
$$

It then follows from Lemma 4 that $V_1(t) \leq V_\epsilon(t)$, for all $t \in (0, t_k]$.

The solution to (34) can be expressed as follows:

$$
\begin{aligned}
V_\epsilon(t) &= W(t, 0) V_\epsilon(0) + \int_0^t W(t, s) \\
&\quad \times \left\{ \epsilon + \beta e^{-\eta s} V_2(0) \right. \\
&\quad \left. + \beta\gamma \int_0^s e^{-\eta(s-\alpha)} V_\epsilon(\alpha)\, d\alpha \right\} ds,
\end{aligned}
\tag{35}
$$

where $W(t, s)$ $(t, s \geq 0)$ is the Cauchy matrix of the linear impulsive system

$$
\begin{aligned}
\dot{u}(t) &= \lambda u(t), \quad t \in \left(t_{k-1}, t_k\right], \\
u\left(t_k^+\right) &= \mu u\left(t_k\right), \quad k = 1, 2, \ldots, \ t = t_k.
\end{aligned}
\tag{36}
$$

Furthermore, noting that $\mu < 1$ and $t_{k+1} - t_k \leq \delta$, it follows from condition (21) that $W(t, s)$ could be estimated as

$$
\begin{aligned}
W(t, s) &= e^{\lambda(t-s)} \prod_{s < t_k \leq t} \mu \leq e^{\lambda(t-s)} \mu^{((t-s)/\delta)-1} \\
&= \frac{1}{\mu} e^{-((1/\delta)\ln(1/\mu)-\lambda)(t-s)}.
\end{aligned}
\tag{37}
$$

Defining $\widehat{\lambda} = (1/\delta)\ln(1/\mu) - \lambda$, one has

$$
\begin{aligned}
V_\epsilon(t) &\leq \frac{1}{\mu} e^{-\widehat{\lambda}t} V_\epsilon(0) \\
&\quad + \frac{1}{\mu} \int_0^t e^{-\widehat{\lambda}(t-s)}\left(\epsilon + \beta e^{-\eta s} V_2(0)\right) ds \\
&\quad + \frac{\beta\gamma}{\mu} \int_0^t e^{-\widehat{\lambda}(t-s)} \int_0^s e^{-\eta(s-\alpha)} V_\epsilon(\alpha)\, d\alpha\, ds \\
&= \frac{1}{\mu} e^{-\widehat{\lambda}t} V_\epsilon(0) + \frac{\epsilon}{\mu\widehat{\lambda}}\left(1 - e^{-\widehat{\lambda}t}\right) \\
&\quad + \frac{\beta V_2(0)}{\mu\left(\widehat{\lambda} - \eta\right)}\left(e^{-\eta t} - e^{-\widehat{\lambda}t}\right) \\
&\quad + \frac{\beta\gamma}{\mu} \int_0^t \int_\alpha^t e^{-\widehat{\lambda}(t-s)} e^{-\eta(s-\alpha)} V_\epsilon(\alpha)\, ds\, d\alpha \\
&= \frac{1}{\mu} e^{-\widehat{\lambda}t} V_\epsilon(0) + \frac{\epsilon}{\mu\widehat{\lambda}}\left(1 - e^{-\widehat{\lambda}t}\right) \\
&\quad + \frac{\beta V_2(0)}{\mu\left(\widehat{\lambda} - \eta\right)}\left(e^{-\eta t} - e^{-\widehat{\lambda}t}\right) + \frac{\beta\gamma}{\mu\left(\widehat{\lambda} - \eta\right)} \\
&\quad \times \int_0^t \left(e^{-\eta(t-\alpha)} - e^{-\widehat{\lambda}(t-\alpha)}\right) V_\epsilon(\alpha)\, d\alpha.
\end{aligned}
\tag{38}
$$

Noting from condition (21) that $\widehat{\lambda} > \eta$, then one gets

$$
\begin{aligned}
V_\epsilon(t) &\leq \frac{1}{\mu} e^{-\widehat{\lambda}t} V_\epsilon(0) + \frac{\epsilon}{\mu\widehat{\lambda}} + \frac{\beta V_2(0)}{\mu\left(\widehat{\lambda} - \eta\right)} e^{-\eta t} \\
&\quad + \frac{\beta\gamma}{\mu\left(\widehat{\lambda} - \eta\right)} \int_0^t e^{-\eta(t-\alpha)} V_\epsilon(\alpha)\, d\alpha.
\end{aligned}
\tag{39}
$$

Defining $u(t) = e^{\eta t} V_\epsilon(t)$, $\alpha(t) = (V_\epsilon(0)/\mu) + (\beta V_2(0)/\mu(\widehat{\lambda} - \eta)) + (\epsilon/\mu\widehat{\lambda})e^{\eta t}$, and $\beta(t) = (\beta\gamma/\mu(\widehat{\lambda} - \eta)) = \rho$, one obtains

$$
u(t) \leq \alpha(t) + \int_0^t \beta(s) u(s)\, ds, \quad t \geq 0.
\tag{40}
$$

Then by using Lemma 5, it is easy to get

$$
u(t) \leq \left(\frac{V_\epsilon(0)}{\mu} + \frac{\beta V_2(0)}{\mu\left(\widehat{\lambda} - \eta\right)}\right) e^{\rho t} + \frac{\epsilon\eta}{\mu\widehat{\lambda}(\eta - \rho)} e^{\eta t}, \quad t \geq 0,
\tag{41}
$$

which implies

$$
V_\epsilon(t) \leq \left(\frac{V_\epsilon(0)}{\mu} + \frac{\beta V_2(0)}{\mu\left(\widehat{\lambda} - \eta\right)}\right) e^{-(\eta-\rho)t} + \frac{\epsilon\eta}{\mu\widehat{\lambda}(\eta - \rho)},
\tag{42}
$$

$$
t \geq 0.
$$

Let $\epsilon \to 0^+$, one can get

$$
V_1(t) \leq e^{-(\eta-\rho)t}\left(\frac{V_1(0)}{\mu} + \frac{\beta V_2(0)}{\mu\left(\widehat{\lambda} - \eta\right)}\right).
\tag{43}
$$

Then it follows from (31) that

$$V_2(t) \le e^{-\eta t} V_2(0) + e^{-(\eta-\rho)t} \left(\frac{V_1(0)}{\mu} + \frac{\beta V_2(0)}{\mu(\tilde{\lambda}-\eta)} \right) \frac{\gamma}{\rho}. \quad (44)$$

Furthermore, it follows from condition (21) that $\eta > \rho$. Therefore together with (43) and (44), one can conclude that condition (17) is satisfied; that is, the entrained collective rhythms of multicellular systems (6) are achieved. The proof is thus completed. □

Remark 8. The obtained result not only provides a new prospective to understand the interactions between the external stimuli and intrinsic physiological rhythms but also is potentially useful for the development of some medical devices. The result presented here is more effective in comparison with those in [38–41], where it is assumed that all the states are available for feedback purpose.

As a special case, if the positive matrices P_i and Q_i in the Lyapunov function (22) are chosen as the identity matrix, the following simplified result could be readily obtained.

Corollary 9. *For a given scalar $\mu \in (0, 1)$, if there exist scalars $\lambda_i > 0$, $\mu_i > 0$, $i = 1, 2, \ldots, l$, $\eta_i > 0$, $i = l + 1, \ldots, N$, and positive scalars ϵ_1, ϵ_2, δ_1, and δ_2 such that*

$$-A^T - A + \epsilon_1 I + \epsilon_1^{-1} L^T L + c\delta_1 \sum_{j=1}^{N} |G_{ij}|$$
$$+ c\delta_1^{-1} \sum_{j=1}^{l} |G_{ji}| \Gamma^T \Gamma \le \lambda_i, \quad (45)$$

$$(I + E_{ik})^T (I + E_{ik}) \le \mu_i,$$

for $i = 1, \ldots, l$ and

$$-A^T - A + \epsilon_2 I + \epsilon_2^{-1} L^T L + c\delta_2 \sum_{j=1}^{N} |G_{ij}|$$
$$+ c\delta_2^{-1} \sum_{j=l+1}^{N} |G_{ji}| \Gamma^T \Gamma \le -\eta_i, \quad (46)$$

for $i = l + 1, \ldots, N$, and, for any impulsive time sequence $\{t_k\}$ satisfying

$$\delta := \sup_k \{t_{k+1} - t_k\} < \frac{\ln(1/\mu)}{\eta + \lambda + (\beta\gamma)/(\eta\mu)}, \quad (47)$$

for $k = 0, 1, 2, \ldots$, where $\mu = \max(\mu_i)$, $\lambda = \max(\lambda_i)$, $i = 1, \ldots, l$, and $\eta = \min(\eta_i)$, $i = l + 1, \ldots, N$, then the entrained collective rhythms of multicellular systems (6) are achieved.

4. Numerical Example

In this section, a synthetic multicellular system composed of N Goodwin oscillators [33] is employed to illustrate the effectiveness of the proposed control strategy.
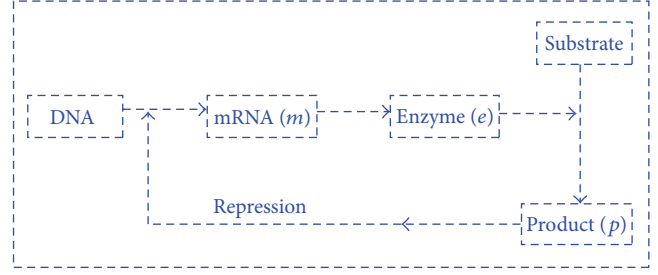

FIGURE 1: Regulatory scheme of the Goodwin oscillator.

4.1. Goodwin Oscillators. The Goodwin oscillator is a genetic network with negative feedback formed in a cyclic way [33], where metabolites repress the enzymes which are essential for their own synthesis by inhibiting the transcription of the molecule DNA to messenger RNA (mRNA) (see [42] for more details). The regulatory scheme of the Goodwin oscillator can be shown in Figure 1.

A modified model reflecting the above regulation process is given by

$$\frac{dm}{dt} = \frac{u}{k_1 + p^\alpha} - am,$$
$$\frac{de}{dt} = vm - be, \quad (48)$$
$$\frac{dp}{dt} = we - \frac{cp}{k_2 + p},$$

where m, e, and p are the concentrations of mRNA, the enzyme, and the product of the reaction of the enzyme and a substrate, respectively. a, b, and c are the degradation rates of each component, respectively. u, v, and w denote the rates of transcription, translation, and catalysis, respectively. k_1 and k_2 are two positive constants. α is the Hill coefficient denoting the cooperativity of the end product repression. It should be pointed out that model (46) is slightly different from the model in [33]. By changing the linear degradation form of the product to Michaelis-Menten form, the limit cycle oscillations can occur for a lower value of the Hill coefficient α (see [42] for details).

The parameters are chosen as $a = b = c = v = w = 0.1$, $u = 1$, and $k_1 = k_2 = 0.1$, and the Hill coefficient α is taken as $\alpha = 4$. Given 4 random initial conditions, the simulation results are recorded in Figures 2 and 3. Figure 2 shows the time response of every products, and Figure 3 shows the limit cycle of the oscillators in phase space.

4.2. Multicellular System Model. Without loss of generality, we perform the simulation study on the scale-free network structure, which is assumed to obey the scale-free distribution of the Barabási-Albert (BA) model [43]. The parameters are given as $m_0 = m = 5$ and $N = 60$. Figure 4 is the generated BA network graph.

The inner coupling matrix Γ is given by $\Gamma = \text{diag}(1, 1.2, 1)$, and the regulation function in Michaelis-Menten form satisfies condition (2). Assume that only the first 20 nodes are
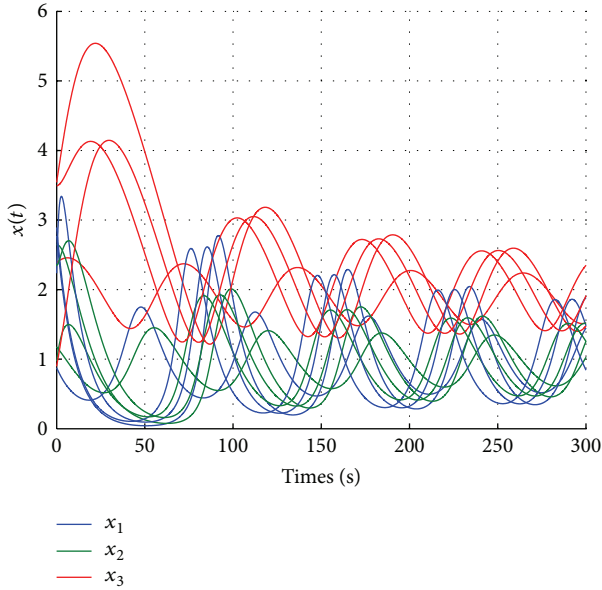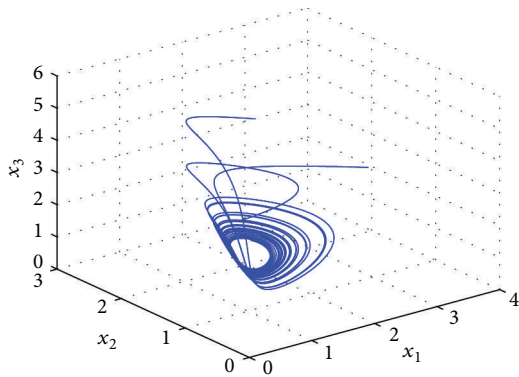
FIGURE 2: Time response of four oscillators.

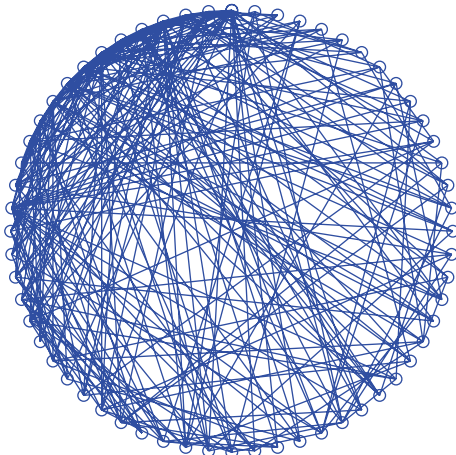FIGURE 3: Limit cycle of the oscillators in phase space.
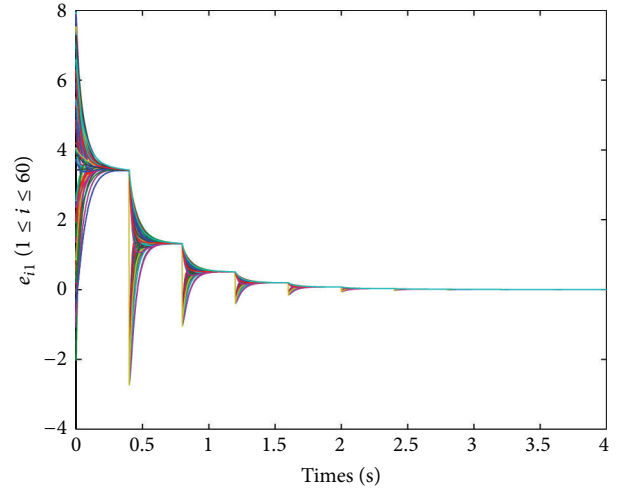

FIGURE 4: BA scale-free network graph.

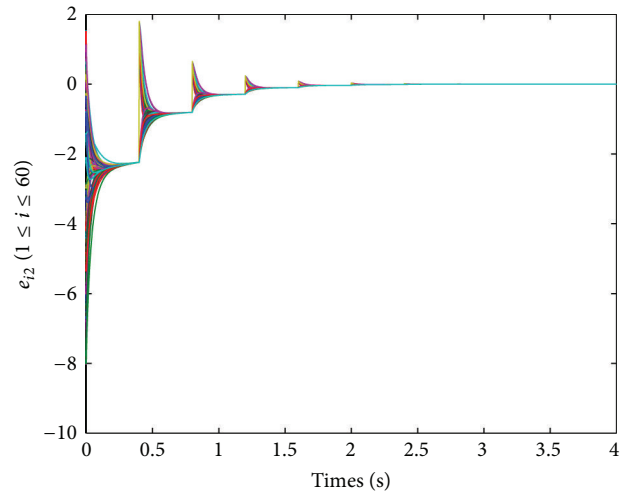FIGURE 5: Rhythmic errors e_{i1} in BA network.

FIGURE 6: Rhythmic errors e_{i2} in BA network.

able to accept the external inputs. The parameters are chosen as $c = 4$, $\epsilon_1 = 0.03$, and $\epsilon_2 = 0.01$. The impulse magnitude is given as $E_{ik} = -1.8$, and impulse interval is chosen as $\delta = 0.4$. It follows from Corollary 9 that the entrained collective behaviors can be achieved. Figures 5, 6, and 7 show the rhythmic errors of the multicellular systems.

It is noted that since only 20 measurable cells in the network are subject to the external stimuli, the approaches in [38–41], which need the information of all the states, cannot be applied in this case.

5. Conclusion

In this paper, the entrained collective rhythms of multicellular systems have been investigated. It is shown that the entrained collective behavior can be achieved via impulsive control even when only partial states of multicellular systems are available. With the help of the newly developed impulsive integrod-ifferential inequality, the sufficient conditions are derived
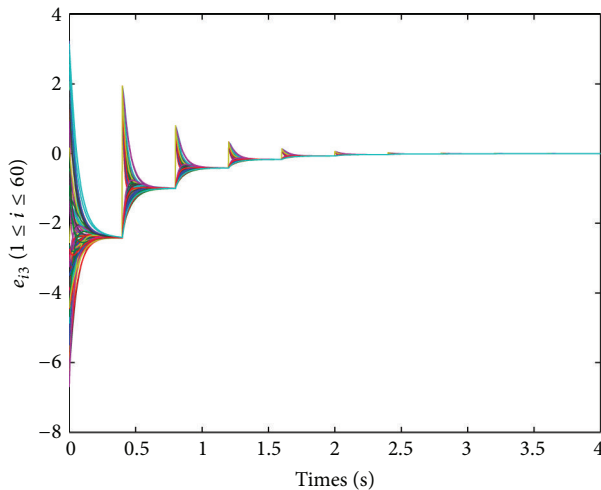
FIGURE 7: Rhythmic errors e_{i3} in BA network.

to ensure the entrained collective rhythms of multicellular systems. A synthetic multicellular system is finally used to illustrate the effectiveness of the developed impulsive control strategy.

Acknowledgments

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