Synchronization of Goodwin’s oscillators under boundedness and nonnegativeness constraints for solutions
Proskurnikov, Anton V.; Cao, Ming

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Abstract—In the recent paper by Hamadeh et al. (2012) an elegant analytic criterion for incremental output feedback passivity (iOFP) of cyclic feedback systems (CFS) has been reported, assuming that the constituent subsystems are incrementally output strictly passive (iOSP). This criterion was used to prove that a network of identical CFS can be synchronized under sufficiently strong linear diffusive coupling. A very important class of CFS consists of biological oscillators, named after Brian Goodwin and describing self-regulated chains of enzymatic reactions, where the product of each reaction catalyzes the next reaction in the chain, however, the last product inhibits the first reaction in the chain. Goodwin’s oscillators are used to model the dynamics of genetic circadian pacemakers, hormonal cycles and some metabobolic pathways.

In this paper we show that for Goodwin’s oscillators, where the individual reactions have nonlinear (e.g. Michaelis-Menten) kinetics, the synchronization criterion, obtained by Hamadeh et al., cannot be directly applied. This criterion relies on the implicit assumption of the solution boundedness, dictated also by the chemical feasibility (the state variables stand for the concentrations of chemicals). Furthermore, to test the synchronization condition one needs to know an explicit bound for a solution, which generally cannot be guaranteed under linear coupling. At the same time, we show that these restrictions can be avoided for a nonlinear coupling protocol, where the control inputs are saturated by a special nonlinear function (belonging to a wide class), which guarantees nonnegativity of the solutions and allows to get explicit ultimate bounds for them. We prove that oscillators synchronize under such a protocol, provided that the couplings are sufficiently strong.

I. Introduction

The rhythmicity of many vital processes in living organisms, such as the cell division, blood pulse and breathing, diurnal sleep and wake cycle, are controlled by genetic and other biochemical “clocks”, or pacemakers, that are typically described by nonlinear systems of differential equations with stable limit cycles as their solutions. One of the first and most influential models of this type, describing genetic oscillators [1]–[4], metabolic pathways in a cell [5] and hormonal cycles [1], [6], [7], is known (along with its extensions) as Goodwin’s oscillator. For 50 years since Goodwin’s seminal paper [8] this model has been attracting intensive attention in applied mathematics.

A challenging problem concerned with biochemical oscillators is to study mechanisms of their synchronization via coupling. Experiments and extensive simulations (see [2]–[4] and references therein) show that the stable 24h-periodic circadian rhythm is not inherent to intracellular genetic oscillators (whose natural periods are spread from 20h to 28h) but emerges due to the coupling among them, which also facilitates the oscillations’ entrainability by the daylight and other environmental cues (“zeitgebers”).

The Goodwin oscillator is a special case of a cyclic feedback system (CFS), consisting of incrementally output passive blocks. An important step in understanding the synchronization mechanism for such systems has been done in the recent paper [9], establishing an elegant criterion for synchronization of identical CFS under sufficiently “strong” linear diffusive couplings. An ensemble of CFS gets synchronized if the algebraic connectivity of the (weighted) digraph, describing the coupling between the systems, exceeds the incremental passivity gain of the CFS. A critical observation is that this gain depends on the secant gains of the constituent subsystems.

As will be shown, the criterion from [9] not only adopts an implicit assumption of the solution’s boundedness, but in fact requires to find the bounds explicitly. In order to apply this criterion, one needs to estimate the incremental passivity (or secant) gains of the blocks constituting the CFS. Synchronization is guaranteed only when these gains are finite, except for that of the leading block, since otherwise the minimal coupling strength, required to synchronize oscillators, becomes infinite. As will be discussed in Section II-B, the chemical reactions with linear kinetics correspond to the blocks with finite secant gains. However, nonlinear (e.g. Michaelis-Menten) kinetics, typically arising in models of enzymatic and other biochemical reactions [10], [11], lead to the infinite passivity gain of the correspondent block. This gain becomes finite only for solutions, confined to some bounded set, and to estimate the gain, one has to find this set or, equivalently, explicit bound for the solution. For a linear diffusive protocol establishing such bounds is a non-trivial, and in fact open problem. This hinders application of the criterion from [9] to Goodwin’s biochemical oscillators with Michaelis-Menten nonlinearities, modeling e.g. the genetic circadian clocks [2]–[4].

In this technical note, we propose a modification of the algorithm from [9], combining the usual diffusive coupling with a nonlinear “saturating” map, which, similar to the linear protocol from [9], guarantees non-negativity of the solutions but, additionally, provides an explicit upper bound for the solutions. Under some technical assumptions, we prove that the ensemble of CFS’s synchronizes, and find explicitly the margin for the coupling strength. Unlike linear coupling protocols, the “saturated” protocol also guarantees non-negative control input which can be important when such an input stands for some chemical concentration (e.g., the models of circadian oscillators from [2]–[4] treat the input as the concentration of a neurotransmitting polypeptide in the extracellular domain).

The main contribution of the paper is twofold. First, we point out some limitations of the synchronization criterion from [9], concerned with the necessity to prove the solution boundedness and estimate the incremental passivity gains. Second, we develop the approach from [9] to address “saturated” protocols, providing synchronization of Goodwin-type oscillators with nonlinear reactions’ kinetics. Dealing with a more general class of Goodwin’s oscillators, our result inevitably inherits two basic limitations of the incremental passivity approach [9], [12] and is confined to identical oscillators and diffusive couplings (the input of each oscillator depends on the deviation between its own and neighbors’ outputs). The results of this paper can be applied e.g. to synchronization of synthetic oscillator networks (see e.g. [11] and references therein), where the individual oscillators and coupling protocols are artifically engineered.

Note that such oscillator networks as the main circadian pacemaker...
in mammal consist of heterogeneous cells that are coupled non-diffusively (being, in fact, an example of pulse-coupled network). A simplified continuous-time model for such a network, proposed in [2], [3], employs a non-diffusive mean-field coupling. Unlike the diffusive protocols, under mean-field coupling the inputs of oscillators are identical (depending on the average concentration of neurotransmitter, released by individual cells) and do not vanish as the oscillators get synchronized. Synchronization of oscillators under mean-field coupling and more complicated “nearest-neighbor” coupling rules [4] remains a non-trivial mathematical problem.

II. A CLASS OF CYCLIC FEEDBACK SYSTEMS WITH INCREMENTAL PASSIVITY PROPERTIES

We first briefly recall the central concepts of the incremental output strict and feedback passivity (iOSP and iOFP) [9]. To simplify matters, we confine ourselves to single input-single output systems. We will make use the following notations. Given a vector \( x = (x_1, \ldots, x_n)^T \in \mathbb{R}^n \), we denote \( \|x\|_\infty = \max |x_i| \). We define \( 1_N = (1, 1, \ldots, 1)^T \in \mathbb{R}^n \), and use the symbol \( I_N \) for the identity matrix. Given a matrix \( L \), let \( \|L\|_\infty = \max |L_{ij}| \) stand for its max norm; for \( z = Lx \) one has then \( \|z\|_\infty \leq \|L\|_\infty \|x\|_\infty \). Let \( \mathbb{I}^+ = (0; +\infty) \) and \( \mathbb{R}^+ = [0; \infty) \).

A. Definition of the iOFP property

**Definition 1:** A system \( \mathcal{H} \), whose dynamics obey

\[
\begin{align*}
\dot{x} &= \varphi(x, u) \\
y &= g(x, u)
\end{align*}
\]

where \( x \in \mathbb{R}^n, u \in \mathbb{R}, \) and \( y \in \mathbb{R} \) stand respectively for the state, input and output of \( \mathcal{H} \), is said to be incrementally output strictly passive with passivity (or sector) gain \( \gamma > 0 \), written \( \text{iOSP}(\gamma^{-1}) \), if a radially unbounded, positive definite function \( S: \mathbb{R}^n \to \mathbb{R} \) exists such that for any two solutions \( x_1, x_2 \) to (1), denoted respectively by \( x^+ \) associated with \( y^+, u^+ \) and \( x^{-} \) associated with \( y^-, u^- \), the increments

\[
\Delta x = x^+ - x^-, \quad \Delta y = y^+ - y^- \quad \text{and} \quad \Delta u = u^+ - u^- \quad \text{satisfy}
\]

\[
\frac{d}{dt} S(\Delta x) \leq \Delta u \Delta y - \gamma^{-1} |\Delta y|^2. \tag{2}
\]

The function \( S \) is referred to as the incremental storage function. More generally, \( \mathcal{H} \) is said to be incrementally output feedback passive, written \( \text{iOFP}(\gamma^{-1}) \), if inequality \ref{2} holds for some nonzero \( \gamma \in \mathbb{R} \cup \{\pm \infty\} \) that has been relaxed from being strictly positive.

In a degenerate case of static input-output map of \( \mathcal{H} \), taking the special form \( u \to y = g(u) \), inequality \ref{2} simplifies to the condition

\[
0 \leq \Delta u \Delta y - \gamma^{-1} |\Delta y|^2, \tag{3}
\]

i.e. \( g \) is non-decreasing and Lipschitz: \( |g(u_1) - g(u_2)| \leq \gamma |u_1 - u_2| \).

Definition 1 deals with the case when system \( \mathcal{H} \) defined globally, that is, \( x(t) \in \mathbb{R}^n \) may be arbitrary. The dynamics of biochemical systems are naturally defined in the positive orthant, and the iOFP property for such systems often can be proved in even more narrow domains. We say the inequality (2) is satisfied in a set \( G \), the property for such systems often can be proved in even more narrow domains. We say the inequality (2) is satisfied in a set \( G \).

B. An iOFP criterion for CFS

Many cyclic feedback systems (CFS), including Goodwin-type oscillators, appear to be iOSP or iOFP, provided that all of their sub-systems are iOSP. The results of [9] are concerned with CFS whose structures are described by the block diagram in Fig. 1. As illustrated, the overall system with the input \( u_{ext} \in \mathbb{R} \) and the output \( y_i \in \mathbb{R} \) consists of \( n \geq 1 \) nonlinear subsystems \( \mathcal{H}_i \), governed by

\[
\begin{align*}
\dot{x}_i &= \varphi_i(x_i, u_i), \\
y_i &= g_i(x_i, u_i), \quad i = 1, \ldots, n.
\end{align*}
\]

Here \( x_i \in \mathbb{R}^{n_i}, u_i \in \mathbb{R}, y_i \in \mathbb{R} \) are \( \mathcal{H}_i \)'s state, input and output respectively, and \( \varphi_i: \mathbb{R}^{n_i} \times \mathbb{R} \to \mathbb{R}^{n_i} \) and \( g_i: \mathbb{R}^{n_i} \times \mathbb{R} \to \mathbb{R} \) are Lipschitz.

The cascaded structure of the system imposes that

\[
\begin{align*}
\dot{u}_{ext} &= u_1 - y_n, \\
\dot{u}_2 &= u_2 - y_{n-1}, \\
&\vdots \\
\dot{u}_n &= u_n - y_1.
\end{align*}
\]

Therefore, the dynamics of the overall CFS can be described by

\[
\begin{align*}
\dot{x}_1 &= \varphi_1(x_1, u_{ext} - y_n), \\
x_2 &= \varphi_2(x_2, y_1), \\
&\vdots \\
x_n &= \varphi_n(x_n, y_{n-1}).
\end{align*}
\]

An important result of [9, Theorem 1] states that a CFS, composed of iOSP blocks \( \mathcal{H}_i \), is always iOFP with a gain, satisfying the sector condition. Namely, if each \( \mathcal{H}_i \) is iOSP(\( \gamma_i^{-1}, \mathcal{G}_i \)) with \( \gamma_i > 0 \), then CFS (6) is iOFP(\( -k_i \mathcal{G}_i \)), where \( \mathcal{G}_i \triangleq \mathcal{G}_{x_1} \times \ldots \times \mathcal{G}_{x_n} \) and

\[
k > \tilde{k} = 1 + \frac{1}{\gamma_1^2 + \gamma_2 \gamma_3 + \ldots + \gamma_n \cos \pi n}.
\]

Theorem 1 in [9] provides a constructive way to find the incremental storage function \( V(\Delta x) \) (positive and radially unbounded), such that

\[
V(\Delta x) + \alpha |\Delta y|^2 \leq k(\Delta y)^2 + \Delta y_1 u_{ext}
\]

for any two solutions staying in \( \mathcal{G}_x \). Here \( x \in [x_1, \ldots, x_n] \), \( y \in [y_1, \ldots, y_n] \) stand for the joint state and output vectors respectively. Notice that \( k < \infty \) if and only if all the gains \( \gamma_i \) are finite, except for possibly the gain \( \gamma_1 \) of the leading block. For the blocks, constituting the Goodwin-type oscillator, the gain is usually finite only in a bounded domain due to presence of the Michaelis-Menten or the Hill nonlinearity.¹ Typically, the state-space description (4) of the block \( \mathcal{H}_i \), representing a chemical reaction, is given by

\[
\dot{x}_i = -f_i(x_i) + u_i \in \mathbb{R}, \quad y_i = g_i(x_i) \in \mathbb{R}, \quad (i = 1, 2, \ldots, n)
\]

where the maps \( f_i, g_i \) are strictly increasing and Lipschitz continuous.

In the case when \( g_i \) is linear \( (g_i(x) = \text{const} > 0) \), it was proved in [9], [13] that the subsystem (9) is iOSP(\( \gamma_i^{-1} \)), where

\[
\tilde{\gamma}_i = \sup_{x_i} \frac{g_i(x_i)}{f_i(x_i)}. \tag{10}
\]

¹Formally, this theorem deals only with the case where \( \mathcal{G}_x = \mathbb{R}^n \forall i \), but its extension to CFS that are not globally iOSP is straightforward.

²The Michaelis-Menten function is the nonlinear function in the form \( f(x) = K_1 x / (K_2 + x) \), and the Hill function is the nonlinear function in the form \( f(x) = K_1 / (K_2 + x^p) \), where \( K_1, K_2, p > 0 \) are constant.

³The linearity follows implicitly from the assumption that the integral in [9, eq.(8)] is well-defined.
Claim 1: For nonlinear monotone functions \( f_i, g_i \) if \( \inf_{x_i} g'_i(x_i) > 0 \) \( \forall i \in \mathbb{N} \). The following lemma extends this result to the case where \( f_i \) is not necessarily monotone and shows that the condition \( \inf g'_i > 0 \) is critical and cannot be dropped.

**Lemma 1:** Let \( G_\epsilon \subset \mathbb{R} \) be an interval where the functions \( f_i, g_i \) are \( C^1 \)-smooth. For system (9), the following holds:

1. If \( \inf_{x_i} g'_i(x_i) > 0 \) and \( \bar{k}_i = \inf_{x_i} \frac{f'_i(x_i)}{g'_i(x_i)} > -\infty \), then (9) is iOFP (1, \( G_\epsilon \)). Hence, if \( f_i \) is non-decreasing on \( G_\epsilon \), i.e. \( \bar{k}_i \geq 0 \), then system (9) is iOFP (1, \( G_\epsilon \)) with \( \bar{k}_i \) given in (10).

The incremental storage function \( S(\Delta x) \) can be chosen quadratic.

2. Let \( G_\epsilon = (0; \infty) \), \( f_i \) be globally bounded and \( g_i(x) \sim a + b x^{-\alpha} \) as \( x \to -\infty \), where \( a, b \in \mathbb{R} \) and \( \alpha > 0 \). Then (9) can never be iOFP no matter what passivity gain is chosen.

**Proof:** We prove 1) first. For notational simplicity, we drop the subscript \( i \) in \( f_i, g_i, x_i, \bar{k}_i, \bar{g}_i \), throughout the proof by definition of \( k \), one has \( f_i(x) - \bar{k}_i g_i(x) \geq 0 \) for every \( x \in G_\epsilon \). For any pair of solutions \( z^i = \bar{x}^i(x, y^i, u^i) \) and \( \bar{z}^i = \bar{x}^i(x, y^i, u^i) \), \( x^i(t), y^i(t) \in G_\epsilon \), let \( \Delta x = (x^i - \bar{x}^i, \Delta y^i, y^i) = (x^i, \bar{x}^i) - f(x^i, \bar{x}^i) - g^i(z^i) + g^i(\bar{z}^i) \). Assuming the mean value theorem to be known, we know that \( \Delta x \cdot \Delta y \leq -\bar{k}_i \Delta x \Delta y \) for any \( \bar{k}_i \). Thus minimizing solutions \( z^i \) and \( \bar{z}^i \), the following condition is valid as \( t \to \infty \):

\[
\dot{S}(\Delta x) = \Delta x \cdot \Delta y \leq -\bar{k}_i \Delta x \Delta y = \Delta x \cdot \Delta y.
\]

**Remark 1:** Theorem 2 in [9] claims a more general result stating that synchronization is achieved without the assumption on bounded solutions; however, as discussed below, this assumption is implicitly required in its proof when appealing to the LaSalle invariance principle. For special types of oscillators, e.g. the Lur'e system with sector nonlinearity, the solution’s boundedness is ensured by the input-to-state stability property of the individual system [12]. However, in general the technique to drop it remains elusive if not impossible.

The following theorem extends Theorem 2 in [9] to the case where the iOFP property holds only in some domain; its proof, following the line of the proof from [9], demonstrates, in particular, that the boundedness assumption is essential.

**Theorem 1:** Consider a system of \( N > 1 \) identical limit-set detectable [9] CFS (6), satisfying (8) with some \( \alpha, k > 0 \) in some closed domain \( G_\epsilon \subset \mathbb{R}^{1+m+n} \). Suppose the CFS are coupled together through the protocol (11) with \( \lambda_j > k \). Then any bounded solution of the closed-loop system, such that \( x^j(t) \in G_\epsilon, \forall t \geq 0 \) for \( j = 1, \ldots, N \) and some \( t_0 \geq 0 \), asymptotically synchronizes (12).

**Proof:** As before we use \( x^j(t) \in \mathbb{R}^{1+m+n} \) to denote the state of the \( j \)-th CFS, and now let \( \xi^j = \begin{bmatrix} x^j \end{bmatrix} \in \mathbb{R}^{1+m+n} \) and \( \xi = \begin{bmatrix} x^1, \ldots, x^N \end{bmatrix} \in \mathbb{R}^{1+m+n} \) be the state and output of the overall networked system respectively. For the incremental storage function \( V \) of each individual CFS, which satisfies (8), and for \( 1 \leq j, m \leq N \), let \( V_{j,m}(\xi) = \begin{bmatrix} V(x^j - x^m) \end{bmatrix} \in \mathbb{R}^{1+m+n} \) and \( \xi^j = \begin{bmatrix} x^j \end{bmatrix} \). Substituting the solutions \( x^j(t), x^m(t) \) respectively, into (8), the following condition is valid as \( t \geq t_0 \):

\[
\dot{V}(x^j(t)) + \alpha \|x^j(t) - x^m(t)\| \leq k \|y^j(t) - y^m(t)\| + (u^j(t) - u^m(t)) \leq \|y^j(t) - y^m(t)\| + (u^j(t) - u^m(t)).
\]

Summing up these inequalities over all \( p, q \) and introducing the projector \( \Pi \in \mathbb{R}^{1+n+m} \) on \( t \leq 0 \), one arrives at (9) the following

\[
S(\xi) \leq \begin{bmatrix} \Pi \otimes I_n \|x(t)\|^2 + \|k\|I_{1+m} \Pi^T \Pi \|u(t)\|^2 \end{bmatrix} \leq \begin{bmatrix} \Pi^T \Pi \|x(t)\|^2 + \|k\|I_{1+m} \Pi^T \Pi \|u(t)\|^2 \end{bmatrix} \leq \begin{bmatrix} \Pi \otimes I_n \|x(t)\|^2 + \|k\|I_{1+m} \Pi^T \Pi \|u(t)\|^2 \end{bmatrix}.
\]

Using (11), one easily finds that \( \Pi u(t) = -\Pi \Pi^T \Pi \Pi u(t) \leq \lambda_0 \Pi \Pi^T \Pi \Pi u(t) \); therefore (13) implies that

\[
S(\xi) \leq -\alpha \|\Pi \Pi \| \|x(t)\|^2 \leq 0 \quad \forall t \geq t_0.
\]

\[
\xi(t) \text{ is a bounded solution with } x^j(t) \in G_\epsilon \text{ and } M = \begin{bmatrix} \xi = \begin{bmatrix} x^j \end{bmatrix} \in \mathbb{R}^{1+n+m} \end{bmatrix} \text{ satisfies } S(\xi(t)) \leq S(\xi(t_0)) \text{ for } t \geq 0.\text{ Due to (13) one has } \xi(t) \in M \text{ and hence the closed set } M \text{ contains the } \omega \text{- limit set of } \xi(t). \text{ Thanks to the LaSalle invariance principle, the solution } \xi(t) \text{ converges to the maximal subset of } M, \text{ where } S = 0 \text{ and hence } \xi(t) \in M \text{ for } t \in [0, \infty) \text{ and the limit-set detectability assumption entails now synchronization of the state vectors.}\n\]

Note that a widely used version of LaSalle invariance principle [14] requires the Lyapunov function \( S \), along with \( S \), to be defined on a compact invariant set \( M \), and guarantees that any solution starting in \( M \) converges to the maximal set where \( S = 0 \). However, original versions of LaSalle’s invariance principle [15], [16] are applicable to any bounded solution and guarantee that \( S \geq 0 \) on its \( \omega \)-limit set, provided that \( S \) and \( \lambda_0 \) are well defined in the vicinity. Assumption of compactness and invariance of \( M \) automatically entail the latter condition, as well as boundedness of any solution starting at \( M \). Without this assumption, LaSalle’s invariance principle can still be applied, but the extra condition of boundedness is then unavoidable.

To prove synchronization of CFS under linear balanced protocol (11), using Theorem 2 in [9] or more general Theorem 1, one has first
to establish the iOFP property in some domain $\mathcal{G}_x$. As follows from Lemma 1, the relevant passivity gains $\gamma_i$ of the subsystems $\mathbb{H}_i$ can be infinite or even undefined, unless the corresponding state variables $x_i$ are confined to some bounded domains $\mathcal{G}_{x_i}$. So the restriction $x(t) \in \mathcal{G}_x$, imposed to apply the iOFP property (8), requires to find some explicit bound for the solution. Even if $\mathcal{G}_x$ can be unbounded (like in the example from [9]), the criterion still guarantees synchronization only for bounded solutions. Using (14), deviations $x^p - x^q$ are shown to be bounded, entailing boundedness of the states $x^p(t)$ under input-to-state stability assumptions (which hold e.g. for Lur'e-type systems [12]). However, proving the solution boundedness for general CFS, coupled via a linear protocol (11), remains a non-trivial problem.

To cope with this problem, we replace the linear protocol (11) with a nonlinear one, providing sufficiently small and non-negative control inputs $u^j_\text{ext}$, that is, $0 \leq u^j_\text{ext} \leq M_0$, where $M_0$ is some known constant. Under such a constraint, one often can localize the solution in a domain where the incremental passivity gains of all the subsystems are known and finite. Relevant sufficient conditions for this, dealing with Goodwin’s oscillators, will be discussed in Section IV. In fact, the input restrictions are often dictated by the biological feasibility, e.g. in some models of coupled circadian clocks [2]-[4] the oscillators’ inputs stand for the concentrations of the neurotransmitter in extracellular media. In this technical note, we do not aim to examine the model from [2]-[4] itself, which considers mean field couplings. Instead, we propose a diffusing coupling protocol similar to (11), but employing a non-negative “saturating” nonlinearity, which guarantees the input constraint and thus entails the solution’s boundedness. Meanwhile, the protocol constructed below provides synchronization under sufficiently “strong” coupling, and the minimal sufficient strength may also be explicitly estimated.

The algorithm we propose is as follows

$$u^j_\text{ext}(t) = g_0(c,v^j(t)), \quad V(t) \triangleq [v^1, \ldots, v^N]^\top = -LY_1(t). \quad (15)$$

A constant $c$ stands for the coupling gain; here, to emphasize the effect of the coupling strength, we have intentionally added $c$ that has been implicitly incorporated into the entries of $L$ in (11) as done in [9]. The function $g_0 : \mathbb{R} \to [0, +\infty)$ is bounded, saturating the inputs at a prescribed constant $M_0 = \sup_{v \in \mathbb{R}} g_0(v)$. The auxiliary inputs $v^j(t) \in \mathbb{R}$ are introduced to emphasize the similarity between the protocols (11) and (15): in fact, the system of N CFS’s (6), coupled through the protocol (15), may be considered as a collective of appropriately modified CFS’s, coupled linearly.

Hereinafter, we assume the following assumption to be valid.

**Assumption 1:** The function $g_0(\cdot)$ is smooth, globally bounded and strictly increasing, hence $g_0'(v) > 0$, $\forall v \in \mathbb{R}$. Additionally, $\nu(s) \triangleq \inf_{v \in \mathbb{R}} g_0(v)$ decreases at infinity more slowly than linear functions, i.e. $\nu(s) \to 0$ yet $|\nu(s)| \to +\infty$ as $s \to +\infty$.

Assumption 1 is satisfied by a wide class of functions, e.g.

$$g_0(v) = \frac{M_0}{2} \left(1 + \frac{|v|^{\rho} \text{sign} v}{1 + |v|^\rho}\right), \quad \text{with } M_0 > 0, \rho \in (0,1). \quad (16)$$

Note that $M_0 = \sup_{v \in \mathbb{R}} g_0(v)$ may be chosen as small as possible.

The next result shows that the modified protocol (15) synchronizes the systems (6), provided that the coupling is sufficiently strong and the solution stays in some compact set; the crucial difference with the linear protocol (11) is that the existence of such a set attracting the solutions may often be proved by choosing $g_0(\cdot)$ sufficiently small.

**Theorem 1:** Suppose that Assumption 1, and the assumptions of Theorem 1 hold, where $\mathcal{G}_x \subset \mathbb{R}^{1+\cdots'+n}$ is a compact set and $\rho_1(x_1, u_1) = \rho_1(x_1)$. Then for sufficiently large gain $c$, any solution of the closed-loop system such that $x^p(t) \in \mathcal{G}_x, \forall t \geq t_0$ for all $p = 1, \ldots, N$ and some $t_0 \geq 0$ gets synchronized (12). Synchronization is implied by the following inequality, which holds as $c \to +\infty$

$$c v(\|L\|\bar{y}_s) \lambda_2 > k, \quad k = \max\{\rho_1(x_1) : x_1 \in \mathcal{G}_x\}. \quad (17)$$

**Proof:** Along with the original CFS (6), consider a modified system with a new input $v(t)$, which obeys (6) and the additional equation $u_\text{ext} = c g_0(c v(t))$ as shown in Fig. 2. The network of CFS (6), coupled via protocol (15), is now equivalent to the network of $N$ “augmented” systems, coupled via (11). One may easily notice that if $x^p(t) \in \mathcal{G}_x$ then $|v^p(t)| \leq y_s$ and hence $|v^p(t)| \leq \|L\|y_s$ due to (11); this implies that $0 \leq u^p_\text{ext} \leq M_0 = \max g_0$. Due to mean value theorem, for any two solutions one has $|v^p(t)| = c g_0'(c v(t)) \Delta v$, where $|\frac{\partial}{\partial v}| \leq |L\| y_s$, and thus $0 < m \leq c v(\|L\| \|y_s\|) \leq c g_0'(c v(t)) \leq M_0 \triangleq c \max g_0(v)$ and thus the right-hand side of (8) is not greater than $M(m^{-1}k|\Delta y(t)|^2 + \Delta v(t)|\Delta y(t)|)$. This ensures that the augmented CFS also satisfies (8), where $u_\text{ext}$, $\alpha$ and $k$ are to be replaced with respectively $v$, $\alpha \triangleq M^{-1} \alpha$ and $\bar{k} = k/m$. Synchronization now follows from Theorem 1 since $\lambda_2 > \bar{k}$ due to (17).

IV. APPLICATIONS IN COUPLED BIOCHEMICAL OSCILLATORS

In this section, we discuss how Theorem 2 allows to estimate the coupling strength, needed to synchronize biochemical oscillators of the Goodwin type, governed by the equations

$$x_1 = -f_1(x_1) + (u_\text{ext} - y_n), \quad y_1 = g_1(x_1), \quad \cdots$$
$$x_N = -f_N(x_N) + (u_\text{ext} - y_n), \quad y_N = g_N(x_N).$$

Therefore, the Goodwin-type oscillator is an example of the system (6) shown in Fig. 1, where the blocks $\mathbb{H}_1, \ldots, \mathbb{H}_n$ obey equations (9) with $u_1 = u_\text{ext} - y_n$, $u_2 = y_1, \ldots, u_n = y_{n-1}$, and the block $\mathbb{H}_n$ is static: $y_n(t) = g_n(u_{n}(t))$. The classical Goodwin’s model [8] corresponds to the case where $f_i$ are linear and $g_n$ is the Hill nonlinearity. We emphasize that the system operates in the positive orthant, namely $x_i > 0, 1 \leq i \leq n - 1$.

Consider now a network of $N$ identical oscillators (18), coupled via the distributed protocol (15), where $g_0$ satisfies Assumption 1. Denoting $M_0 = \max_{v \in \mathbb{R}} g_0(v)$, we adopt the following assumption.

**Assumption 2:** The functions $f_i, g_i : \mathbb{R} \to \mathbb{R}, i = 1, \ldots, n - 1$, $g_0 : \mathbb{R} \to [0, M_0], g_n : \mathbb{R} \to [-M_0, 0]$ are smooth and strictly increasing ($f_i', g_i' > 0$). Additionally, the maps $f_i$ satisfy the condition $\Phi_i(0) = -\infty$, $\Phi_i(+\infty) = +\infty$, $\Phi_i(x) \triangleq \int_1^x \frac{ds}{f_i(s)} \geq 0$. \quad (19)

Condition (19) holds, for instance, for linear functions $f_i(x) = a_i x, a_i > 0$ and Michaelis-Menten type nonlinear functions. Under Assumption 2, any solution of the cyclic feedback system with

$\begin{align*}
\begin{array}{c}
\mathbb{H}_0 \\
\mathbb{H}_1 \\
\vdots \\
\mathbb{H}_{n-1} \\
y_n
\end{array}
\end{align*}$

Fig. 2: Auxiliary cyclic feedback system with saturated input

$\begin{align*}
\begin{array}{c}
u \to u_\text{ext} \\
\rightarrow u_1 \\
\rightarrow u_2 \\
\cdots \\
\rightarrow y_{n-1} \\
y_n
\end{array}
\end{align*}$

$\begin{align*}
\begin{array}{c}
\mathbb{H}_0 \\
\mathbb{H}_1 \\
\vdots \\
\mathbb{H}_{n-1} \\
y_n
\end{array}
\end{align*}$

$\begin{align*}
\begin{array}{c}
u \to u_\text{ext} \\
\rightarrow u_1 \\
\rightarrow u_2 \\
\cdots \\
\rightarrow y_{n-1} \\
y_n
\end{array}
\end{align*}$
saturated input, starting strictly inside the positive orthant, remains positive and, under additional assumptions, is ultimately bounded.

**Lemma 2:** Let Assumption 2 hold and \( u_{ext}(t) \in [0; M_0] \) is defined for \( t \in \mathbb{R}^+ \) with \( 0 \leq u_{ext}(t) \leq M_0 \). Then for any initial condition \( x_i(t_0) \in \mathbb{R}^n \) (\( i = 1, \ldots, n \)) the solution \( x_i(t) = x_i(t_0), y_i(t), y_{ext}(t) \) exists on \( \Delta \) and remains positive \( x_i(t) \in \mathbb{R}^n \). If \( \beta = \infty \) and the functions \( h_0, \gamma_0 \) given by the recursion \( h_0 = f_{-1}^1(b_2 - f_{-1}^2(b_1)), \ldots, h_{n-1} = f_{-1}^n\bar{g}_n - \bar{g}_n - \bar{h}_n \), are well defined on \( 0; M + c_0 \), where \( M \geq M_0 + N_0 + c_0 > 0 \), the solution is ultimately bounded and

\[
\lim_{t \to \infty} x_i(t) \leq \bar{x}_i, \quad \forall t \geq 1, \ldots, n \quad \forall x_i(t_0),
\]

where \( \bar{x}_i = h_i(M) \) are independent of the initial conditions.

**Proof:** We now prove that if \( x_i(t) \) exists and is positive on \( \Delta \). Since \( x_i(0) > 0 \), by continuity of the map \( \Delta \), there exists a maximal interval \( \Delta' = [0; \beta') \subset \Delta \) such that \( x_i(t) > 0 \) for all \( t \in \Delta' \) and \( i = 1, \ldots, n \). From Assumption 2, for \( t \in \Delta' \) it always holds that \( u_i(t) \geq u_0(t) \leq 0, u_i = u_{ext} - y_i, y_i = 1, \ldots, u_n = y_{ext} \). Hence, by the definition of the upper limit, a number \( T_0 \) exists such that \( u_i(T_0) \leq \mu_i + \delta \) for all \( t \geq T_0 \). From the facts that \( x_i(T_0) \geq \mu_0 + \delta \) and \( x_i(t) = f_i(x_i(t)) > 0 \), we know the following two statements hold: (i) if \( x_i(T_0) \leq \xi \) for some \( T_0 \geq 0 \), then \( x_i(t) \leq \xi \forall t \geq T_0 \), and (ii) if \( x_i(T_0) \leq \xi \), then one can take \( x_i(T_0) = \xi \), otherwise, \( x_i(T_0) := (x_0(T_0) - \xi)^+ \) is the first time instant after \( T_0 \) at which \( x_i(T_0) = \xi \). Indeed, let \( \delta > 0 \) be small enough such that \( \mu_i + \delta < \max_{1 \leq i \leq n} f_i \). From the definition of the upper limit, a number \( T_0 \) exists such that \( u_i(T_0) \leq \mu_i + \delta \) for all \( t \geq T_0 \). From the facts that \( x_i(T_0) \geq \mu_0 + \delta \) and \( x_i(t) = f_i(x_i(t)) > 0 \), we know the following two statements hold: (i) if \( x_i(T_0) \leq \xi \) for some \( T_0 \geq 0 \), then \( x_i(t) \leq \xi \forall t \geq T_0 \), and (ii) if \( x_i(T_0) \leq \xi \), then one can take \( x_i(T_0) = \xi \), otherwise, \( x_i(T_0) := (x_0(T_0) - \xi)^+ \) is the first time instant after \( T_0 \) at which \( x_i(T_0) = \xi \). Then \( 0 \leq x_i(t) \leq \mu_i + \delta < \max_{1 \leq i \leq n} f_i \). Indeed, let \( \delta > 0 \) be small enough such that \( \mu_i + \delta < \max_{1 \leq i \leq n} f_i \). From the definition of the upper limit, a number \( T_0 \) exists such that \( u_i(T_0) \leq \mu_i + \delta \) for all \( t \geq T_0 \). From the facts that \( x_i(T_0) \geq \mu_0 + \delta \) and \( x_i(t) = f_i(x_i(t)) > 0 \), we know the following two statements hold: (i) if \( x_i(T_0) \leq \xi \) for some \( T_0 \geq 0 \), then \( x_i(t) \leq \xi \forall t \geq T_0 \), and (ii) if \( x_i(T_0) \leq \xi \), then one can take \( x_i(T_0) = \xi \), otherwise, \( x_i(T_0) := (x_0(T_0) - \xi)^+ \) is the first time instant after \( T_0 \) at which \( x_i(T_0) = \xi \). Then \( 0 \leq x_i(t) \leq \mu_i + \delta < \max_{1 \leq i \leq n} f_i \). Indeed, let \( \delta > 0 \) be small enough such that \( \mu_i + \delta < \max_{1 \leq i \leq n} f_i \). From the definition of the upper limit, a number \( T_0 \) exists such that \( u_i(T_0) \leq \mu_i + \delta \) for all \( t \geq T_0 \). From the facts that \( x_i(T_0) \geq \mu_0 + \delta \) and \( x_i(t) = f_i(x_i(t)) > 0 \), we know the following two statements hold: (i) if \( x_i(T_0) \leq \xi \) for some \( T_0 \geq 0 \), then \( x_i(t) \leq \xi \forall t \geq T_0 \), and (ii) if \( x_i(T_0) \leq \xi \), then one can take \( x_i(T_0) = \xi \), otherwise, \( x_i(T_0) := (x_0(T_0) - \xi)^+ \) is the first time instant after \( T_0 \) at which \( x_i(T_0) = \xi \). Then \( 0 \leq x_i(t) \leq \mu_i + \delta < \max_{1 \leq i \leq n} f_i \).

**Example:** Synchronization of Circadian Clocks

In this section we demonstrate our synchronization criterion for oscillators, describing the cellular circadian clocks [2], [3]. The main
circuitry pacemaker in mammal is controlled by the neurons of SCN (suprachiasmatic nucleus, a zone in hypothalamus). Within each cell (indexed 1 through N), a clock gene mRNA (X) produces a clock protein (Y) which, in turn, activates a transcriptional inhibitor (Z), closing a negative feedback loop [3]; their dynamics are given by

\[
\begin{align*}
\dot{X}_i(t) &= \nu_1 \frac{K_i}{K_i + (cZ)^n} - \frac{1}{K_4 + X_i} + u_{i,t}^e, \\
\dot{Y}_i(t) &= k_3 X_i - \frac{1}{K_4 + Y_i}, \\
\dot{Z}_i(t) &= k_5 Y_i - \frac{1}{K_6 + Z_i},
\end{align*}
\]

(25)

Here \( u_{i,t}^e \) are some external inputs. In [2]–[4] the networks with mean-field couplings are considered, where \( u_{i,t}^e = \ldots = u_{N,t}^e \) is a common input, which is positive, bounded and depend on the average concentration of neurotransmitting peptide in the extracellular domain, depending in its turn on \( X^1, \ldots, X^N \). We consider synchronization of oscillators (25) under diffusive protocol (15). Unlike the mean-field control, which remains oscillatory when the synchronization is established, under protocol (15) the inputs stabilize at the constant value \( u_{i,t}^e(t) \to \text{const} = g_0(0) \forall t \to \infty \).

It is confirmed experimentally [2] that an individual circadian clock has a stable limit cycle in the positive octant \( X, Y, Z > 0 \), and the corresponding oscillation period lies between 20 and 27 hours. This means that for realistic sets of parameters in (25) Lemma 3 and Theorem 3 work, stating that for any compact set \( K \subset \mathbb{R}_+^4 \) one can find \( M_0 = M_0(K) > 0 \) (sufficiently small) and \( c > 0 \) (sufficiently large), such that the protocol (15) synchronizes oscillators (25) starting at \( (X(0), Y(0), Z(0)) \in K \). For a special set of parameters \( n, k, K_i, \nu_i \), found in [3], Lemma 2 is applicable which gives explicit estimates for \( M_0 \) and explicit bounds for the solutions. We simulated dynamics of a more complicated model [2], where Lemma 2 is unapplicable (in the notation of Lemma 2, the function \( h_3 = f_3^{-1} \) is not defined on \( [0; M_0] \)) and \( M_0 \) can be found numerically. Note that the incremental passivity of (25) in the whole positive orthant does not follow from the criterion in [9], unlike the Goodwin oscillator in the example from [2], so synchronization of CFS (25) under strong linear couplings remains an open problem.

We simulate the dynamics of \( N = 10 \) all-to-all coupled oscillators (25) with the parameters from [2]; \( \nu_1 = 0.7nM/h; K_1 = 1nM; n = 4; \nu_2 = 0.35nM/h; K_2 = nM; K_3 = 0.7/h; \nu_3 = 0.35nM/h; K_4 = 1nM; K_5 = 0.7/h; \nu_4 = 0.35nM/h; K_6 = 1nM \), which correspond to the oscillation period \( \approx 23.5h \). We choose \( g_0(0) \) in the form (16), where \( M_0 = 0.0005 \) and \( p = 0.9 \). We simulate the dynamics for \( c = 0, c = 1, c = 10 \) and \( c = 100 \). Oscillators are not synchronous for \( c \) being small, however, the synchronization emerges as \( c \) increases, confirming thus Theorem 3.

VI. Concluding remarks

Theorem 3 of this note has shown that a similar conclusion in comparison to that of [9] holds even when the coupled biochemical oscillators are under input constraints, imposed by the requirements of biological feasibility and necessity to explicitly estimate the coupling gains. To satisfy these constraints, we combine the linear coupling protocol from [9] with a ”saturating” nonlinear block. We have proved that strong diffusive couplings can get coupled CFS-type oscillators synchronized when the saturation nonlinearity of the oscillators’ inputs belongs to the identified class. Our proof is based on the synchronization criterion from [9], extended to the systems with additional saturated block. The result may be extended to the CFS coupled through outputs \( y_n \), as considered in [20]. The techniques of quadratic constraints, used in our recent paper [21], allow to extend our results to some other types of “saturated” protocols, where not only control inputs, but also outputs (or their deviations) are saturated.

The results of our paper can be applied e.g. to networks of synthetic biochemical oscillators [11] where the couplings between the individual oscillators are artificially engineered. However, as has been reported by biochemists and biophysicists, the couplings between many natural biochemical oscillators, in particular neurons of the circadian pacemakers, are in general not diffusive [2]. Hence, we are studying models for biochemical oscillators under mean field coupling [2], [3] or more complicated nearest-neighbor coupling [4] regulated by the concentrations of neurotransmitter.

REFERENCES


