Chapter 1
Analysis of synchronizing biochemical networks via incremental dissipativity

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1.1 Introduction

Synchronization, defined in a broad sense, is the phenomenon in which communicating agents coordinate outputs. The abundance of examples of this process in nature and engineering has led to its becoming an active sub-area of research in networks theory, as evidenced by the multitude of publications on the subject (Boccaletti et al, 2006).

The aim of this chapter is to re-visit, generalize and extend earlier work in (Stan et al, 2007; Hamadeh et al, 2012, 2008), on the synchronization of interconnected control systems, in which a dissipativity approach is employed to arrive at the coupling conditions necessary to ensure the convergence of nodal outputs to a common value. The motivation for the development of these tools comes from a systems biology example, namely the modeling and analysis of synchrony in the neuronal networks that control circadian rhythms in the mammalian hypothalamus (Gonze et al, July 2005). In this context, the 'network' is composed of a set of cells (the network nodes). Each cell communicates with its neighbors by sending a biochemical output signal that reflects its internal state, and by taking as an external input, a measure of outputs of its neighboring cells.

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An assumption we make is that the internal dynamics of each cell can be modularized into a set of interconnected compartments. In (Stan et al, 2007; Hamadeh et al, 2012, 2008) these compartments were connected in a ring that is structurally similar to the Goodwin oscillator. Such a structure represents a simple yet common genetic circuit whereby DNA is transcribed to mRNA, which is then translated into a protein, which feeds back to inhibit mRNA transcription. As shown in (Sontag, 2005), in many cases the dynamics of such modules can be characterized, from an input-output perspective, as being passive in the sense of (Willems, 1972). A biochemical circuit that is formed by the interconnection of such modules thus lends itself to stability analysis by the dissipativity theory tools developed in (Vidyasagar, 1981; Arcak and Sontag, 2006; Sontag and Arcak, 2008). A particular advantage of this approach with regards to biological systems is that the internal dynamics of each module need not be known precisely.

To analyze synchronization in networks of such interconnected cells, (Stan et al, 2007; Hamadeh et al, 2012) regards synchronization as the stability of signals that represent the differences in output between two nodes. In parallel with the use of passivity theory (Arcak and Sontag, 2006) to analyze the stability of circuits composed of the interconnection of passive subsystems, the work in (Stan et al, 2007; Hamadeh et al, 2012) employs the concept of *incremental passivity*, first introduced in (Stan, March 2005; Stan and Sepulchre, 2007), to study the synchronization of cells composed of incrementally passive subsystems. Given two identical copies of a system that has an input-state-output description, the system is said to be *incrementally passive* if it is passive with respect to the *difference* between its inputs, states and outputs (termed the *incremental signals* of the system). The class of network agents we will study in this chapter is such that the compartments of each individual node are subsystems that are individually incrementally output feedback passive (Sepulchre et al, 1997). We will use measures of their incremental passivity in order to quantify the degree of shortage of incremental passivity of each node with respect to its coupling inputs and outputs. Then, in analogy with the use of strong negative feedback for purposes of stabilizing output feedback passive systems, we will show that linear static coupling that is strongly connected can similarly be used to incrementally stabilize the network nodes, thus leading to asymptotic output synchrony and asymptotic state synchrony under a zero-state detectability assumption on the *differences* between the corresponding states and outputs of network nodes. Following (Stan et al, 2007), an alternative input-output approach was developed in (Scardovi et al, 2009) to analyze the synchrony of network agents that have structures more general than the cyclic nodes studied in (Stan et al, 2007). An aim of this chapter is to show that the incrementally passifying role of coupling, which is analogous to the stabilizing role of feedback, can be used for the analysis of synchrony in networks of nodes as general as those studied in (Scardovi et al, 2009).

With respect to other synchrony analysis tools in the literature such as contraction theory (Lohmiller and Slotine, 1998; Demidovich, 1967; Pavlov et al, 2004) or incremental input-to-state stability (Angeli, 2002), the methodology we present here takes an input-output, modular approach. This results in a natural framework with which to analyze synchrony of agents composed of the interconnection of subsystems, and little knowledge of the subsystem dynamics is required. To illustrate our results, we apply them towards the analysis of synchrony in networks of the repressilator genetic (synthetic) circuit (Elowitz and Leibler, 2000; Garcia-Ojalvo et al, 2004). Genetic circuits can generally be posed in a modular form similar to that of the repressilator. For this reason we envision that the tools we present here will prove to be especially useful for the analysis of synchrony in networks of such systems.

1.2 Synchronization and incremental dissipativity

As networked systems are generally connected through their inputs and outputs, it is natural to characterize them through their input-output properties to identify sufficient synchronization conditions. This chapter considers an incremental dissipativity characterization of the network nodes that will be termed incremental output-feedback passivity (iOFP). The following section will give a brief introduction to the concepts of incremental dissipativity, first introduced in (Stan, March 2005; Stan and Sepulchre, 2007).

1.2.1 Incremental dissipativity

Consider a system Υ represented by a state-space model of the form

$$\Upsilon \begin{cases} \dot{x} = f(x,e),\ x \in \mathbb{R}^r,\ e \in \mathbb{R} \\ y = g(x), \quad\ y \in \mathbb{R} \end{cases} \tag{1.1}$$

where $e(t)$, $y(t)$, and $x(t)$ denote its input, output and state respectively and the functions $f(x,e) : \mathbb{R}^r \times \mathbb{R} \to \mathbb{R}^r$ and, $g(x) : \mathbb{R}^r \to \mathbb{R}$ are Lipschitz continuous. Let $x_a(t)$ and $x_b(t)$ be two solutions of Υ, with the corresponding input-output pairs $(e_a(t), y_a(t))$, and $(e_b(t), y_b(t))$. Denote by $\Delta x = x_a - x_b$, $\Delta e = e_a - e_b$, and $\Delta y = y_a - y_b$ the corresponding incremental variables. System (1.1) is incrementally dissipative if there exists a radially unbounded incremental storage function

$$S_\Delta : \mathbb{R}^r \to \mathbb{R}, S_\Delta\left(\Delta x\right) > 0 : \forall \Delta x \neq 0, S_\Delta(0) = 0, S_\Delta \in \mathcal{C}^1 \tag{1.2}$$

and an incremental supply rate $w\left(\Delta e, \Delta y\right)$ such that, if $S_\Delta(\Delta x)$ is at least once differentiable (i.e. $S_\Delta \in \mathcal{C}^1$)

$$\dot{S}_{\Delta}(\Delta x) \leq \mathcal{W}(\Delta e, \Delta y) \tag{1.3}$$

is satisfied for all time t and along any pair of trajectories $(x_a(t), x_b(t))$ (see (Willems, 1972) for a definition of dissipativity).

Definition 1. (Stan, March 2005; Stan and Sepulchre, 2007) System Υ in (1.1) is said to be

- *incrementally passive* when it is incrementally dissipative with incremental supply rate $\mathcal{W}(\Delta e, \Delta y) = \Delta y \Delta e$.
- *incrementally output feedback passive* (iOFP$\left(\frac{1}{\gamma}\right)$) when it is incrementally dissipative with the incremental supply rate $\mathcal{W}(\Delta e, \Delta y) = -\frac{1}{\gamma}(\Delta y)^2 + \Delta y \Delta e$ with $\gamma \in (-\infty, \infty)$.
- *incrementally output strictly passive* (iOSP) when it is incrementally dissipative with the incremental supply rate $\mathcal{W}(\Delta e, \Delta y) = -\frac{1}{\gamma}(\Delta y)^2 + \Delta y \Delta e$ and $\gamma > 0$.

When $\gamma > 0$ the system possesses an *excess of incremental passivity* of $\frac{1}{\gamma}$. On the other hand, when $\gamma < 0$ the system possesses *a shortage of incremental passivity* and $-\frac{1}{\gamma}$ quantifies the minimum gain of proportional negative incremental output feedback required to make the system incrementally passive.

Definition 2 (Incremental secant gain). Following the concept of the 'secant gain' in (Sontag, 2005; Arcak and Sontag, 2006), the smallest $\gamma > 0$ such that the iOSP dissipation inequality in Definition 1 is satisfied will be termed the *incremental secant gain* of the system.

Remark 1. (Stan, March 2005; Stan and Sepulchre, 2007) Passivity implies incremental passivity for linear systems, that is, if the quadratic storage function $S(x) = \frac{1}{2}x^* P x \geq 0$ satisfies the dissipation inequality $\dot{S} \leq yu$ then the incremental storage function $S_{\Delta}(\Delta x) = \frac{1}{2}(\Delta x)^* P \Delta x \geq 0$ satisfies the incremental dissipation inequality $\dot{S}_{\Delta} \leq \Delta y \Delta e$. Passivity also implies incremental passivity for a monotone increasing, static nonlinearity: if $\phi(\cdot)$ is monotone increasing, then $(e_a - e_b)(\phi(e_a) - \phi(e_b)) = \Delta e \Delta \phi(e) \geq 0$, $\forall \Delta e = e_a - e_b, \Delta \phi(e) = \phi(e_a) - \phi(e_b)$. Similarly, it is easy to show that for linear systems, output strict passivity implies incremental output strict passivity with the incremental secant gain equal to the secant gain.

1.2.2 Incremental output-feedback passivity and synchronization

Thus far we have seen that a system is incrementally dissipative if, given any two sets of initial conditions, input trajectories and corresponding outputs, the inequality (1.3) is satisfied. For this reason, the incremental dissipativity property, which is a property of each individual node, can be used as an analysis tool for an entire network composed of interconnected copies of such a node. The main result that will link incremental output feedback passivity of nodes of a network to (output) synchronization states that if each subsystem is iOFP and the coupling strength between nodes is large enough then all the nodes will asymptotically synchronize.

1.3 Notation

In the following sections, we consider networks composed of N coupled identical nodes, each composed of n interconnected SISO subsystems. As a general convention $j = 1, \cdots, N$ will denote the index associated to a particular node of the network whilst $i = 1, \cdots, n$ will denote the index associated to a particular subsystem in a given node. The signals to be introduced in Assumption 1 below carry the following notations and are illustrated in Figure 1.1.

- The subsystem i of node j has a state vector $x_{i_j} \in \mathbb{R}^s$, an input $e_{i_j} = u_{i_j} + w_{i_j}$ and output y_{i_j}, with $e_{i_j}, u_{i_j}, w_{i_j}, y_{i_j} \in \mathbb{R}$. The *internal input* u_{i_j} is a function of the outputs of different subsystems from the same node j. The *external input* w_{i_j} is a function of the outputs of corresponding subsystems i from the different nodes.
- The vectors of the states, inputs, internal inputs, external inputs and outputs of the j^{th} node are respectively denoted by $\mathbf{x}_j$, $\mathbf{e}_j$, $\mathbf{u}_j$, $\mathbf{w}_j$, $\mathbf{y}_j$, where $\mathbf{x}_j = [\, x_{1_j}^* \; \cdots \; x_{n_j}^* \,]^*$ and $\mathbf{e}_j$, $\mathbf{u}_j$, $\mathbf{w}_j$, $\mathbf{y}_j$ are similarly defined.
- The vectors of the i^{th} states, inputs, external inputs and outputs of each node are respectively denoted by X_i, E_i, U_i, W_i, Y_i, where $X_i = \left[\, x_{i_1}^* \; \cdots \; x_{i_N}^* \,\right]^* \in \mathbb{R}^N$ and E_i, U_i, W_i, Y_i are similarly defined.
- The vectors of all the states, inputs, internal inputs, external inputs and outputs are respectively denoted by X, E, U, W, Y, where $X = [\, X_1^* \cdots X_n^*]^*$, and the vectors E, U, W, Y are similarly defined.
- The incremental states, inputs, internal inputs, external inputs and outputs are respectively denoted by $\Delta x_{i_{j,m}}$, $\Delta e_{i_{j,m}}$, $\Delta u_{i_{j,m}}$, $\Delta w_{i_{j,m}}$, $\Delta y_{i_{j,m}}$, where $\Delta x_{i_{j,m}} \triangleq x_{i_j} - x_{i_m}$, and the signals $\Delta e_{i_{j,m}}$, $\Delta u_{i_{j,m}}$, $\Delta w_{i_{j,m}}$, $\Delta y_{i_{j,m}}$ are similarly defined.
- The vectors of incremental states, inputs, internal inputs, external inputs and outputs for two nodes j, m are respectively denoted by $\Delta\mathbf{x}_{j,m}$, $\Delta\mathbf{e}_{j,m}$, $\Delta\mathbf{u}_{j,m}$, $\Delta\mathbf{w}_{j,m}$, $\Delta\mathbf{y}_{j,m}$, where $\Delta\mathbf{x}_{j,m} \triangleq \mathbf{x}_j - \mathbf{x}_m$, and the signals $\Delta\mathbf{e}_{j,m}$, $\Delta\mathbf{u}_{j,m}$, $\Delta\mathbf{w}_{j,m}$, $\Delta\mathbf{y}_{j,m}$ are similarly defined.
- The vector in $\mathbb{R}^{NNns}$ of all incremental state vectors $\Delta x_{i_{j,m}}$ is denoted by X_Δ.

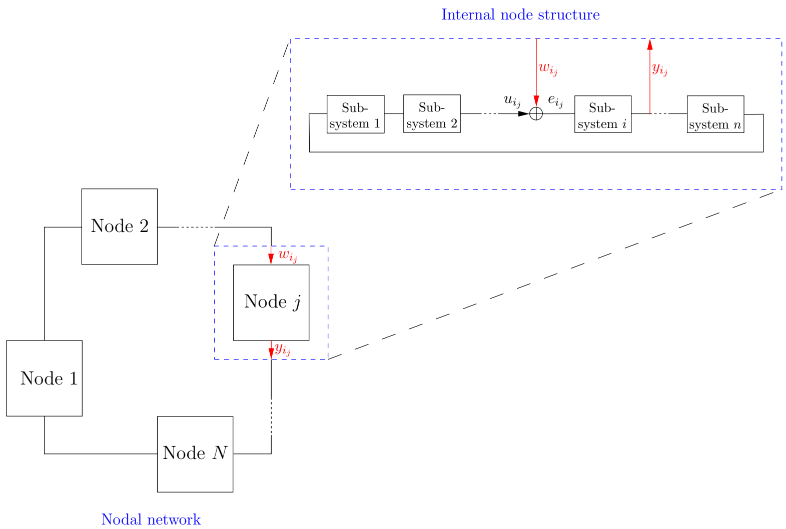

Fig. 1.1 Network of nodes and illustration of internal nodal structure. The subsystem interconnection structure can be arbitrary.

1.4 Characterization of network nodes and their dissipativity properties

The following assumption gives a formal description of the networks and nodes that we shall consider in this chapter.

Assumption 1 *Consider a network of N identical nodes. It is assumed that:*

- *Each node j is composed of n interconnected SISO subsystems of the form (1.1), and each such subsystem i has state vector, input and output x_{i_j}, e_{i_j}, y_{i_j} respectively.*
- *Each subsystem i is iOFP$\left(\frac{1}{\gamma_i}\right)$ and therefore, for any two nodes j, m there is associated with each subsystem i a function $S_{i_{j,m}}(\Delta x_{i_{j,m}})$ that satisfies (1.2) and an incremental dissipation inequality of the form (1.3), with*

$$\dot{S}_{i_{j,m}} \leq \mathcal{W}_i(\Delta e_{i_{j,m}}, \Delta y_{i_{j,m}}) = -\frac{1}{\gamma_i}(\Delta y_{i_{j,m}})^2 + \Delta e_{i_{j,m}} \Delta y_{i_{j,m}}, \quad \gamma_i \in \mathbb{R} \tag{1.4}$$

- *The input to subsystem i of node j is given by $e_{i_j} = u_{i_j} + w_{i_j}$ where u_{i_j} are inputs from within the same node j and $u_{i_j} = \sum_{\substack{\ell=1 \\ \ell \neq i}}^{n} \alpha_{i,\ell} y_{\ell_j}$, $\alpha_{i,\ell} \in \mathbb{R}$ and where w_{i_j} is an exogenous input.*

Under Assumption 1, and by linearity we have

$$\Delta e_{i_{j,m}} = \Delta w_{i_{j,m}} + \sum_{\substack{\ell=1 \\ \ell\neq i}}^{n} \alpha_{i,\ell} \Delta y_{\ell_{j,m}} \tag{1.5}$$

Combining this relation with the incremental dissipation inequality of the i^{th} subsystem yields

$$\dot{S}_{i_{j,m}} \leq -\frac{1}{\gamma_i}(\Delta y_{i_{j,m}})^2 + \Delta w_{i_{j,m}} \Delta y_{i_{j,m}} + \Delta y_{i_{j,m}} \sum_{\substack{\ell=1 \\ \ell\neq i}}^{n} \alpha_{i,\ell} \Delta y_{\ell_{j,m}} \tag{1.6}$$

Definition 3 (Interconnection matrix). For the vector of elements $\{\boldsymbol{\gamma}\} \triangleq \begin{bmatrix} \gamma_1 \cdots \gamma_n \end{bmatrix}^*$, define the *interconnection matrix* $A(\boldsymbol{\gamma})$ as

$$A(\boldsymbol{\gamma}) \triangleq \begin{bmatrix} -\frac{1}{\gamma_1} & \alpha_{1,2} & \cdots & \alpha_{1,n-1} & \alpha_{1,n} \\ \alpha_{2,1} & -\frac{1}{\gamma_2} & \alpha_{2,3} & \cdots & \alpha_{2,n} \\ \alpha_{3,1} & \alpha_{3,2} & -\frac{1}{\gamma_3} & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & \alpha_{4,n} \\ \alpha_{n,1} & \cdots & \alpha_{n,2} & \alpha_{n,n-1} & -\frac{1}{\gamma_n} \end{bmatrix}$$

which is such that

$$\sum_{i=1}^{n} \left[-\frac{1}{\gamma_i}(\Delta y_{i_{j,m}})^2 + \Delta y_{i_{j,m}} \sum_{\substack{\ell=1 \\ \ell\neq i}}^{n} \alpha_{i,\ell} \Delta y_{\ell_{j,m}} \right] = \frac{1}{2}(\Delta \mathbf{y}_{j,m})^* (A(\boldsymbol{\gamma})^* + A(\boldsymbol{\gamma})) \Delta \mathbf{y}_{j,m}$$

Lemma 1. *For an interconnection matrix $A(\boldsymbol{\gamma})$ as defined in Definition 3, there exist diagonal matrices $D > 0$, $D \in \mathbb{R}^{n\times n}$, $D = \operatorname{diag}\{d_1, \cdots, d_n\}$ and $K \geq 0$, $K \in \mathbb{R}^{n\times n}$, $K = \operatorname{diag}\{k_1, \cdots, k_n\}$ so that for all diagonal matrices $K' = \operatorname{diag}\{k'_1, \cdots, k'_n\} \in \mathbb{R}^{n\times n}$ which satisfy $K' \geq K$, there exists $\epsilon_{D,K} > 0$ which is such that*

$$\frac{1}{2}\left(A(\tilde{\boldsymbol{\gamma}})^* D + D A(\tilde{\boldsymbol{\gamma}})\right) \leq -\epsilon_{D,K} I_n, \quad \tilde{\boldsymbol{\gamma}} = \{\tilde{\gamma}_i\}, \tilde{\gamma}_i \triangleq \frac{\gamma_i}{1 + k'_i \gamma_i} \tag{1.7}$$

Proof. Since $\tilde{\gamma}_i = \frac{\gamma_i}{1+k'_i\gamma_i}$ and $\tilde{\boldsymbol{\gamma}} = \{\tilde{\gamma}_i\}$, it follows that $A(\tilde{\boldsymbol{\gamma}}) = A(\boldsymbol{\gamma}) - K'$. To prove the existence of a pair of matrices $D > 0, K \geq 0$, that satisfy (1.7), note that if $D = I_n$ then there always exists a set of elements k'_i which are individually sufficiently large in magnitude to make the diagonal elements of $A(\tilde{\boldsymbol{\gamma}})$ negative and also sufficiently large in magnitude to ensure that $A(\tilde{\boldsymbol{\gamma}})^*D + DA(\tilde{\boldsymbol{\gamma}}) = A(\tilde{\boldsymbol{\gamma}})^* + A(\tilde{\boldsymbol{\gamma}}) < 0$ by diagonal dominance[1]. Taking any such pair D, K which are such that

$$\frac{1}{2}\left((A(\boldsymbol{\gamma}) - K)^*D + D(A(\boldsymbol{\gamma}) - K)\right) \leq -\epsilon_{D,K} I_n$$

is satisfied with $\epsilon_{D,K} > 0$, then since $D(K' - K) \geq 0$, it necessarily follows that for any $K' \geq K$

$$\frac{1}{2}\left(A(\tilde{\boldsymbol{\gamma}})^*D + DA(\tilde{\boldsymbol{\gamma}})\right) \leq -\epsilon_{D,K} I_n$$

This completes the proof.

Lemma 1 proves that the diagonal stability of interconnection matrices can always be achieved by making their diagonal elements large in magnitude and negative in size. The following theorem makes use of this result to quantify the shortage of passivity of the network nodes from the degree of passivity of the individual nodal subsystems.

Theorem 1. *For a network of identical nodes that satisfy Assumption 1, there exist diagonal matrices $D > 0$, $D \in \mathbb{R}^{n\times n}$, $D = \mathrm{diag}\{d_1, \cdots, d_n\}$ and $K \geq 0$, $K \in \mathbb{R}^{n\times n}$, $K = \mathrm{diag}\{k_1, \cdots, k_n\}$ so that for the storage function $\mathbf{S}_{j,m} = \sum_{1=i}^{n} d_i S_{i_{j,m}}$ each network node is iOFP$(-K)$ and satisfies the incremental dissipation inequality*

$$\dot{\mathbf{S}}_{j,m} \leq -\epsilon_{D,K}(\Delta\mathbf{y}_{j,m})^*(\Delta\mathbf{y}_{j,m}) + (\Delta\mathbf{y}_{j,m})^* D(K\Delta\mathbf{y}_{j,m} + \Delta\mathbf{w}_{j,m}) \tag{1.8}$$

where $\epsilon_{D,K} > 0$ is such that

$$\frac{1}{2}\left(A(\tilde{\boldsymbol{\gamma}})^*D + DA(\tilde{\boldsymbol{\gamma}})\right) \leq -\epsilon_{D,K} I_n, \quad \tilde{\boldsymbol{\gamma}} = \{\tilde{\gamma}_i\}, \tilde{\gamma}_i \triangleq \frac{\gamma_i}{1 + k_i\gamma_i} \tag{1.9}$$

and where $A(\cdot)$ is as defined in Definition 3.

Proof. The first step of the proof is to add and subtract to each dissipation inequality (1.6) the term $k_i\left(\Delta y_{i_{j,m}}\right)^2$, with $k_i \geq 0$, to obtain

$$\dot{S}_{i_{j,m}} \leq -\frac{1}{\tilde{\gamma}_i}(\Delta y_{i_{j,m}})^2 + k_i(\Delta y_{i_{j,m}})^2 + \Delta y_{i_{j,m}} \sum_{\substack{\ell=1\\ \ell\neq i}}^{n} \alpha_{i,\ell}\Delta y_{\ell_{j,m}} + \Delta w_{i_{j,m}}\Delta y_{i_{j,m}} \tag{1.10}$$

where

$$\tilde{\gamma}_i = \frac{\gamma_i}{1 + k_i\gamma_i}$$

[1] Note that the choice of matrix $D = I_n$ is not unique and in most cases a matrix D can be constructed to reduce the sizes of elements k_i required to achieve negative definiteness of $A(\tilde{\boldsymbol{\gamma}})^*D + DA(\tilde{\boldsymbol{\gamma}})$.

Now, defining the incremental storage function $\mathbf{S}_{j,m}(\Delta\mathbf{x}_{j,m})$ as the linear sum $\mathbf{S}_{j,m} = \sum_{i=1}^{n} d_i S_{i_{j,m}}$, its time derivative becomes

$$\dot{\mathbf{S}}_{j,m} \leq \sum_{i=1}^{n} d_i \left(-\frac{1}{\tilde{\gamma}_i}(\Delta y_{i_{j,m}})^2 + \Delta y_{i_{j,m}} \sum_{\substack{\ell=1\\ \ell\neq i}}^{n} \alpha_{i,\ell} \Delta y_{\ell_{j,m}} + \Delta w_{i_{j,m}} \Delta y_{i_{j,m}} + k_i \left(\Delta y_{i_{j,m}}\right)^2 \right)$$

$$= \frac{1}{2}(\Delta\mathbf{y}_{j,m})^* (A(\tilde{\boldsymbol{\gamma}})^* D + DA(\tilde{\boldsymbol{\gamma}}))(\Delta\mathbf{y}_{j,m}) + \sum_{i=1}^{n} d_i \Big(\Delta w_{i_{j,m}} \Delta y_{i_{j,m}} + k_i \left(\Delta y_{i_{j,m}}\right)^2 \Big)$$

$$= \frac{1}{2}(\Delta\mathbf{y}_{j,m})^* (A(\tilde{\boldsymbol{\gamma}})^* D + DA(\tilde{\boldsymbol{\gamma}}))(\Delta\mathbf{y}_{j,m}) + (\Delta\mathbf{y}_{j,m})^* D (K\Delta\mathbf{y}_{j,m} + \Delta\mathbf{w}_{j,m})$$

where $d_i > 0$, $\forall i$, $D = \mathrm{diag}(d_1, \cdots, d_n)$, and $A(\tilde{\boldsymbol{\gamma}})$ is as defined in Definition 3 but with the vector of elements $\tilde{\boldsymbol{\gamma}} = \{\tilde{\gamma}_i\}$. The key step at this point is that, following the definition of $\tilde{\gamma}_i$, increasing k_i sufficiently can make the quantity $\tilde{\gamma}_i$ positive if γ_i is negative. In this way the subsystem i, which satisfies the incremental dissipation inequality (1.10) becomes iOFP($-k_i$).

Moreover, if each k_i is made sufficiently large, the values of $\tilde{\gamma}_i$ can be made small enough so that a diagonal matrix D can be constructed which makes

$$\frac{1}{2}\left(A(\tilde{\boldsymbol{\gamma}})^* D + DA(\tilde{\boldsymbol{\gamma}})\right) \leq -\epsilon_{D,K} I_n \tag{1.11}$$

for some $\epsilon_{D,K} > 0$, as shown in Lemma 1. Therefore if quantities k_i and d_i are chosen so that (1.11) is satisfied then

$$\dot{\mathbf{S}}_{j,m} \leq -\epsilon_{D,K}(\Delta\mathbf{y}_{j,m})^*(\Delta\mathbf{y}_{j,m}) + (\Delta\mathbf{y}_{j,m})^* D(K\Delta\mathbf{y}_{j,m} + \Delta\mathbf{w}_{j,m})$$

and the node is therefore iOFP($-K$) since a negative feedback of $\Delta\mathbf{w}_{j,m} = -K\Delta\mathbf{y}_{j,m}$ would render the node iOSP. This completes the proof.

1.4.1 Network Coupling Topology

Now consider a network composed of N identical nodes, where each node is iOFP($-K$) as shown in Theorem 1. Assume that the nodes are connected using their i^{th} subsystems through a weighted directed graph $\mathcal{G}^i$ (the graph can be different for each i) and assume that the coupling structure is restricted to a linear, static input-output interconnection, so that the i^{th} subsystem on the j^{th} node is coupled to the i^{th} subsystem on other nodes in the network through its inputs w_{i_j} and outputs y_{i_j} using the Laplacian coupling matrix $\Gamma_i \in \mathbb{R}^{N\times N}$, so that $W_i = -\Gamma_i Y_i$. The graph $\mathcal{G}^i = \{\mathcal{A}^i, \mathcal{D}^i\}$ has the following definitions.

Definition 4 (Weighted Adjacency Matrix). A weighted adjacency matrix $\mathcal{A}^i = \left\{\rho_{i_{j,l}}\right\}$, $j,l = 1, \cdots, N$, $\mathcal{A}^i \in \mathbb{R}^{N\times N}$, is a positive matrix where

$\rho_{i_{j,l}}$ represents the weight of the edge from node l to node j. It is assumed that the graph is simple, i.e. $\rho_{i_{j,l}} \geq 0$, $\forall j \neq l$ and $\rho_{i_{j,j}} = 0$, $\forall j, l$.

Definition 5 (Degree Matrix). The degree matrix $\mathcal{D}^i$ associated with the adjacency matrix $\mathcal{A}^i$ is a diagonal matrix $\mathcal{D}^i = \text{diag}\{\delta^i_j\}$, $j = 1, \cdots, N$, $\mathcal{D}^i \in \mathbb{R}^{N \times N}$ with $\delta^i_j = \sum_{\substack{l=1 \\ l \neq j}}^N \rho_{i_{j,l}}$.

Definition 6 (Laplacian Matrix). The weighted Laplacian matrix $\Gamma_i \in \mathbb{R}^{N \times N}$ associated with the adjacency matrix $\mathcal{A}^i$ is defined as $\Gamma_i = \mathcal{D}^i - \mathcal{A}^i = \left\{\Gamma_{i_{j,l}}\right\}$ for $j, l = 1, \cdots, N$ and $\Gamma_{i_{j,j}} = \delta^i_j$, $\forall j = 1, \cdots, N$ and $\Gamma_{i_{j,l}} = -\rho_{i_{j,l}}$, $\forall j \neq l$. The matrix $\tilde{\Gamma}$ is defined as

$$\tilde{\Gamma} \triangleq \text{diag}\{\Gamma_1, \cdots, \Gamma_n\}$$

The interconnection rule $W_i = -\Gamma_i Y_i$ then corresponds to the linear consensus protocol $w_{i_j} = -\sum_{l=1}^N \rho_{i_{j,l}} \left(y_{i_j} - y_{i_l}\right)$ (see (Olfati-Saber and Murray, 2004)). The following assumptions are made on Γ_i:

- (A1) $\text{rank}(\Gamma_i) = N - 1$
- (A2) $\Gamma_i + \Gamma_i^T \geq 0$
- (A3) $\Gamma_i \mathbf{1}_N = \Gamma_i^T \mathbf{1}_N = \mathbf{0}_N$

The conditions (A1)-(A3) characterize the coupling structure we consider here as *diffusive coupling* (Pogromsky and Nijmeijer, 2001). Assumption (A1) holds provided that the graph is strongly connected (see (Olfati-Saber and Murray, 2004)). Assumption (A3) holds if the graph is balanced, i.e. if $\mathcal{A}^i \mathbf{1}_N = \mathcal{A}^{i^*} \mathbf{1}_N$ (see (Cremean and Murray, 2003)). Furthermore, this latter property implies (A2) (see (Cremean and Murray, 2003), which uses Gershgorin's disk theorem to prove this fact). Note that these assumptions do not imply that Γ_i is symmetric which would be equivalent to assuming an undirected graph. We denote by λ_{k_i} the k^{th} eigenvalue of the symmetric part of the Laplacian Γ_i, which is given by $\frac{1}{2}(\Gamma_i + \Gamma_i^*)$.

The eigenvalues λ_{k_i} are such that $\lambda_{1_i} < \lambda_{2_i} \leq \cdots \leq \lambda_{N_i}$. From (A2) it follows that $\lambda_{k_i} \geq 0$ whilst from (A1) $\lambda_{1_i} = 0$. From (A3) $\lambda_{1_i} = 0$ corresponds to the eigenvector $\mathbf{1}_N$. The quantity λ_{2_i} has a special significance in graph theory and is known as the algebraic connectivity. As will be shown in Theorem 2 this quantity is a measure of the coupling strength of the network Laplacian Γ_i.

To compare each nodal output with its average over all the N nodes outputs, the projector matrix $\Pi \in \mathbb{R}^{N \times N}$, which is first defined in (Stan, March 2005; Stan and Sepulchre, 2007)

$$\Pi \triangleq I_N - \frac{1}{N} \mathbf{1}_N \mathbf{1}_N^* \tag{1.12}$$

is employed. This projector measures the instantaneous difference between a signal and its average over all nodes in the network, e.g. the j^{th} element of $\Pi Y_1(t)$ measures the difference between output $y_{1_j}(t)$, $j = 1, \cdots, N$ and the average output $\frac{1}{N}\sum_{j=1}^{N} y_{1_j}(t)$. Note that the projector has the following properties from (Stan, March 2005; Stan and Sepulchre, 2007)

- $\Pi^* \Pi = \Pi$
- $\Pi = \Pi^*$
- $\Pi \mathbf{1}_N = \mathbf{0}_N$

We also define the matrix

$$\tilde{\Pi}_r \triangleq I_r \otimes \Pi \tag{1.13}$$

which will be used to measure consensus in the concatenated signal vectors (for example the concatenated output vector Y).

1.4.2 Main result on network synchronization

Because the nodes are identical, the incremental storage function $\mathbf{S}_{j,m}$ is such that, given any two sets of initial conditions, inputs, states and outputs for any two nodes $j, m \in \{1, \cdots, N\}$, their corresponding trajectories satisfy an incremental dissipation inequality of the form (1.8). Due to Assumption 1, the incremental storage function $\mathbf{S}_{j,m}$ has the properties $\mathbf{S}_{j,m}(\Delta\mathbf{x}_{j,m}) > 0$ $\forall \Delta\mathbf{x}_{j,m} \neq \mathbf{0}_n$, $\mathbf{S}_{j,m}(\mathbf{0}_n) = 0$. As we have seen in Theorem 1, equation (1.8) can be arrived at by a suitable choice of matrices D, K.

In Theorem 2 below, the following property will be used to deduce state synchronization from output synchronization.

Definition 7 (Incremental zero-state detectability). A system of the form (1.1) is *incrementally zero-state detectable* if, $\Delta u(t) = 0$ and $\Delta y(t) = 0$, $\forall t$, implies $\lim_{t\to\infty} \Delta x = \mathbf{0}_r$.

In the following theorem, the result on global asymptotic state synchronization of network nodes is given.

Theorem 2. *(Asymptotic State Synchronization) Consider a network of N identical nodes satisfying Assumption 1, linearly coupled through the interconnection matrices Γ_i so that $W_i = -\Gamma_i Y_i$ where matrices Γ_i satisfy the assumptions (A1), (A2), and (A3). Assume that each node is incrementally zero-state detectable as in Definition 7 and is iOFP$(-K)$ as shown in Theorem 1, so that for every pair of nodes $j, m \in \{1, \cdots, N\}$ there exists a radially unbounded incremental storage function $\mathbf{S}_{j,m}$ satisfying (1.8). Assume also that the network satisfies the strong coupling assumption $L \geq K$ where $L = \mathrm{diag}\{\lambda_{2_1}, \cdots, \lambda_{2_n}\}$. Then, each bounded network solution that exists for all $t \geq 0$ is such that $\forall i = 1, \cdots, n, \forall j, l = 1, \cdots, N$: $\lim_{t\to+\infty}\left(x_{i_j}(t) - x_{i_l}(t)\right) = 0$ (global asymptotic synchronization). In addition to global asymptotic synchronization, any bounded network solution is* *such that the state solution of each node converges to the omega-limit set of the isolated node.*

Proof. Summing the storage functions $\mathbf{S}_{j,m}$ given in (1.8) for all node pairs j, m and then scaling by $\frac{1}{2N}$ gives the incremental storage function $S(X_\Delta) = \frac{1}{2N}\sum_{j=1}^{N}\sum_{m=1}^{N}\mathbf{S}_{j,m}$ for the network. From (1.8), S obeys the dissipation inequality

$$\dot{S} \leq -\epsilon_{D,K}(\tilde{\Pi}_n Y)^*(\tilde{\Pi}_n Y) + (\tilde{\Pi}_n Y)^*(D\otimes I_N)^*((K\otimes I_N)\tilde{\Pi}_n Y + \tilde{\Pi}_n W) \quad (1.14)$$

Using (A3) and the relation $W_i = -\Gamma_i Y_i$, we have $\Pi W_i = -\Pi\Gamma_i Y_i = -\Gamma_i \Pi Y_i$ and therefore $\tilde{\Pi}_n W = -\tilde{\Gamma}\tilde{\Pi}_n Y$, where $\tilde{\Gamma} = \mathrm{diag}\{\Gamma_1, \cdots, \Gamma_n\}$. From this, (1.14) becomes

$$\dot{S} \leq -\epsilon_{D,K}(\tilde{\Pi}_n Y)^*(\tilde{\Pi}_n Y) + (\tilde{\Pi}_n Y)^*(D\otimes I_N)^*((K\otimes I_N)\tilde{\Pi}_n Y - \tilde{\Gamma}\tilde{\Pi}_n Y) \quad (1.15)$$

From (A1)-(A3), $\Pi Y_i = Y_i - \left(\frac{1}{N}\mathbf{1}_N^* Y_i\right)\mathbf{1}_N = 0$ iff $Y_i \in \ker(\Gamma_i)$. Since $\ker(\Gamma_i)$ is of dimension one, it follows that

$$(\Pi Y_i)^* \, \Gamma_i \Pi Y_i \geq \lambda_{2_i} \, (\Pi Y_i)^* \, \Pi Y_i \quad (1.16)$$

Letting $L = \mathrm{diag}\{\lambda_{2_1}, \cdots, \lambda_{2_n}\}$ and substituting (1.16) in (1.15) yields

$$\dot{S} \leq -\epsilon_{D,K}(\tilde{\Pi}_n Y)^*(\tilde{\Pi}_n Y) + (\tilde{\Pi}_n Y)^*(D(K-L)\otimes I_N)^*\tilde{\Pi}_n Y$$

Noting that the diagonal matrix $D > 0$, then if, $\forall i \ \lambda_{2_i}(\Gamma_{i_s}) > k_i$ (strong coupling) then $K - L < 0$. This gives the Lyapunov inequality

$$\dot{S} \leq -\epsilon_{D,K}(\tilde{\Pi}_n Y)^*(\tilde{\Pi}_n Y) \quad (1.17)$$

If this inequality holds, then letting $S_0 = S(X_\Delta(0))$, the initial value of the incremental storage function for the whole network, we note that, since $S \geq 0$ and $\dot{S} \leq 0$, the set $\mathcal{M} = \{X_\Delta | S(X_\Delta) \leq S_0\}$ is an invariant set. Note that $\mathcal{M}$ also contains the origin $X_\Delta = \mathbf{0}_{NNns}$ which is a strict minimum of $S(X_\Delta)$ since $S(X_\Delta) > 0$ for $X_\Delta \neq \mathbf{0}_{NNns}$ and $S(\mathbf{0}_{NNns}) = 0$. Due to (1.17), this minimum is also a stable incremental equilibrium point of the network.

From (1.17), and using the LaSalle invariance principle, the incremental signal X_Δ will converge to the largest invariant subset of $\{X_\Delta \in \mathbb{R}^{NNns} | \dot{S}(X_\Delta) = 0\}$ as $t \to \infty$. Due to (1.17), $\dot{S}(X_\Delta) = 0$ only if $\tilde{\Pi}_n Y = \mathbf{0}_{Nn}$. This implies asymptotic output synchronization since $\forall i$ and for any pair $j, m \in \{1, \cdots, N\}$, $\lim_{t\to\infty}(y_{i_j}(t) - y_{i_m}(t)) = 0$. Furthermore, from the incremental zero-state detectability assumption, the condition $\tilde{\Pi}_n Y = \mathbf{0}_{Nn}$ and the fact that there is no external input to the network means that $\lim_{t\to\infty} X_\Delta = \mathbf{0}_{NNns}$. This proves that each network solution that exists for all $t \geq 0$ is, regardless of initial conditions, such that $\forall i = 1, \cdots, n, \forall j, m = 1, \cdots, N$: $\lim_{t\to+\infty}\left(x_{i_j}(t) - x_{i_m}(t)\right) = 0$.

Since $\Gamma \mathbf{1}_N = 0$, the effect of the coupling disappears when output synchrony is reached and each node in the network is then effectively isolated. Therefore, in addition to global asymptotic state synchronization, for any bounded network solution, the solution of each node converges to the omega-limit set of an isolated node. This completes the proof.

The preceding discussion has presented two main ideas, formalized in Theorems 1 and 2. In the Theorem 1 it was shown that *any* node of the form specified in (1) (that is, any node composed of an interconnection of subsystems that obey an iOFP property) is iOFP$(-K)$, where $K \geq 0$ is a diagonal matrix. In Theorem 2, it is then shown that an iOFP$(-K)$ node can be made to synchronize by sufficiently strong coupling, where the coupling strength is quantified by the eigenvalues of the diagonal matrix L (which are the algebraic connectivities of Laplacians Γ_i). In effect, the coupling acts as an incrementally stabilizing negative feedback that compensates for any shortage of incremental passivity by the nodes.

Lemma 1 and Theorem 1 show that the network nodes are iOFP$(-K)$, $K = \text{diag}\{k_1, \cdots, k_n\}$, by demonstrating that, associated with any given K is another matrix $D > 0$ such that $A(\tilde{\boldsymbol{\gamma}})^* D + DA(\tilde{\boldsymbol{\gamma}}) < 0$ where

$$\tilde{\boldsymbol{\gamma}} = \{\tilde{\gamma}_i\}, \quad \tilde{\gamma}_i = \frac{\gamma_i}{1 + k_i \gamma_i} \tag{1.18}$$

If $D = I_n$ the diagonal elements of $A(\tilde{\boldsymbol{\gamma}})^* + A(\tilde{\boldsymbol{\gamma}})$, equal $-\frac{2}{\tilde{\gamma}_i}$. By sufficiently increasing each k_i, the diagonal elements of $A(\tilde{\boldsymbol{\gamma}})^* + A(\tilde{\boldsymbol{\gamma}})$ can therefore be made negative and large enough for $A(\tilde{\boldsymbol{\gamma}})^* + A(\tilde{\boldsymbol{\gamma}})$ to become diagonally dominant and hence negative definite. However, the size of the eigenvalues of K required to achieve diagonal dominance is usually conservatively high.

Moreover, it is important to note that, for a given interconnection matrix $A(\boldsymbol{\gamma})$ the diagonal matrices D and K that make each node iOFP$(-K)$ are not unique, and there are, in fact, some choices that are 'better' than others in that some matrices D can be used to make $A^*(\tilde{\boldsymbol{\gamma}})D + DA(\tilde{\boldsymbol{\gamma}}) = (A(\boldsymbol{\gamma}) - K)^* D + D(A(\boldsymbol{\gamma}) - K) < 0$ using matrices K which are more sparse than others (by the sparsity of K we mean the number of zeros on its diagonals). The sparser the matrix K, the fewer the coupling connections that need to be made between the nodes since for every positive k_i, λ_{2_i} needs to also be positive to meet the synchronization condition of Theorem 2. If K is a positive definite diagonal matrix then all subsystems need to be coupled in order to meet the synchronization condition. This results in a conservative coupling structure.

For certain nodal structures it is possible to find conditions on the values of the elements $\tilde{\gamma}_i$ such that $A(\tilde{\boldsymbol{\gamma}})^* D + DA(\tilde{\boldsymbol{\gamma}}) < 0$ using matrices K that are only positive semi-definite. For example the work in (Stan et al, 2007; Hamadeh et al, 2012) uses the results of Arcak and Sontag (2006) to show that for nodes with a cyclic feedback structure there exists $D > 0$ such that $A(\tilde{\boldsymbol{\gamma}})^* D + DA(\tilde{\boldsymbol{\gamma}}) < 0$ if and only if the *secant condition*

$$\tilde{\gamma}_1 \cdots \tilde{\gamma}_n < \sec^n \left(\frac{\pi}{n}\right)$$

is satisfied. The value of each $\tilde{\gamma}_i$ can be made arbitrarily small (and positive) by increasing k_i. Therefore to construct a matrix $D > 0$ such that $A(\tilde{\boldsymbol{\gamma}})^* D + DA(\tilde{\boldsymbol{\gamma}}) < 0$, it is sufficient to increase the values of the elements k_i to the point where the secant condition is met. In fact, as shown in (Stan et al, 2007; Hamadeh et al, 2012), if all elements γ_i are positive, the secant condition can be met by making only a single element k_i positive and sufficiently large in magnitude.

1.4.3 Network of repressilator circuits

As an example demonstrating the methods presented in this chapter, we consider the synchronization of a network of repressilator circuits, (Elowitz and Leibler, 2000). The repressilator is a synthetic oscillating genetic circuit that was developed in *Escherichia coli* (*E. coli*), and is composed of a cyclic network of three genes and their protein products, wherein each protein inhibits the transcription of the next gene in the cycle. The circuit is illustrated schematically in Figure 1.2 and works in the following cyclic manner:

- The *E. coli* gene *lacI* expresses the protein LacI which inhibits transcription of the gene *tetR*.
- The gene *tetR* expresses the protein TetR which inhibits transcription of the gene *cI*.
- The gene *cI* expresses the protein CI which inhibits transcription of the gene *lacI*.

A dimensionless dynamical model of the repressilator is given in (1.19)-(1.24), where states $x_{1_j}, x_{3_j}, x_{5_j}$ respectively represent concentrations of the mRNA transcribed from *lacI*, *tetR* and *cI* and states $x_{2_j}, x_{4_j}, x_{6_j}$ respectively represent concentrations of the proteins LacI, TetR and CI (here, the subscript j is an index denoting the particular repressilator circuit for the network analysis which is to follow).

$$\dot{x}_{1_j} = - x_{1_j} + g(x_{6_j}) \tag{1.19}$$
$$\dot{x}_{2_j} = - x_{2_j} + x_{1_j} \tag{1.20}$$
$$\dot{x}_{3_j} = - x_{3_j} + g(x_{2_j}) \tag{1.21}$$
$$\dot{x}_{4_j} = - x_{4_j} + x_{3_j} \tag{1.22}$$
$$\dot{x}_{5_j} = - x_{5_j} + g(x_{4_j}) \tag{1.23}$$
$$\dot{x}_{6_j} = - x_{6_j} + x_{5_j} \tag{1.24}$$

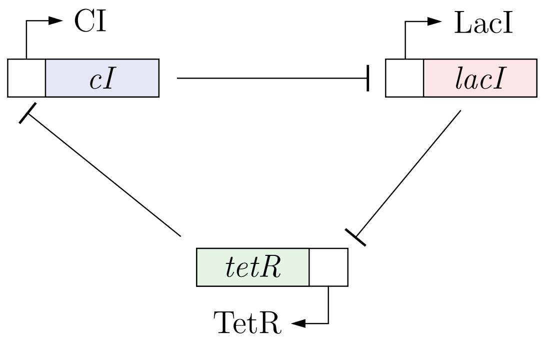

Fig. 1.2 The repressilator genetic network.

where $g(x_{i_j}) = \begin{cases} \frac{5}{1+x_{i_j}^2} & x_i \geq 0 \\ 5 & x_{i_j} \leq 0 \end{cases}$

In (Garcia-Ojalvo et al, 2004) a modification to the repressilator circuit is proposed that enables the coupling of the multiple such circuits for the purpose of building a synchronized genetic clock. The authors propose the inclusion in the repressilator of an intercellular communication mechanism found in the bacterium *Vibrio fischeri*. In this mechanism, the protein LuxI is used to synthesize an autoinducer (AI) molecule which diffuses through the cell membrane. The AI forms a complex with the protein LuxR, which in turn activates the transcription of certain genes. The authors suggest that this coupling mechanism be added to the repressilator circuit in *E. coli* in addition to an extra copy of the *lacI* gene so that the coupling functions as a feedback loop in the following way

- The LacI protein inhibits the transcription of gene *luxI* as it does *tetR*.
- The LuxR-AI complex induces the expression of the additional *lacI* gene.

The AI molecule forms the inter-cellular coupling signal for this network. The authors decompose the concentration of AI into that inside and outside the cell membrane. The authors further assume that the diffusion of AI into and out of the cell is a relatively fast process, and therefore under a quasi-steady-state assumption (as in (Dockery and Keener, 2001)) and the additional assumption that AI does not degrade outside the cell, it is possible to make the approximation that intra- and extra-cellular AI are of the same concentration, which we denote by x_{9_j}. The dimensionless dynamical model of the coupled repressilator proposed in (Garcia-Ojalvo et al, 2004) therefore modifies (1.19) to

$$\dot{x}_{1_j} = -\,x_{1_j} + g(x_{6_j}) + f(x_{9_j}) \qquad f(x_{9_j}) = \begin{cases} \frac{x_{9_j}}{1+x_{9_j}} & x_{9_j} \geq 0 \\ 0 & x_{9_j} < 0 \end{cases} \tag{1.25}$$

$$\tag{1.26}$$

and, for a network of N repressilators, (Garcia-Ojalvo et al, 2004) models the time evolution of x_{9_j} by

$$\dot{x}_{9_j} = -x_{9_j} + x_{4_j} - \frac{1}{N}\rho_9 \sum_{k=1}^{N} (x_{9_j} - x_{9_k}) \tag{1.27}$$

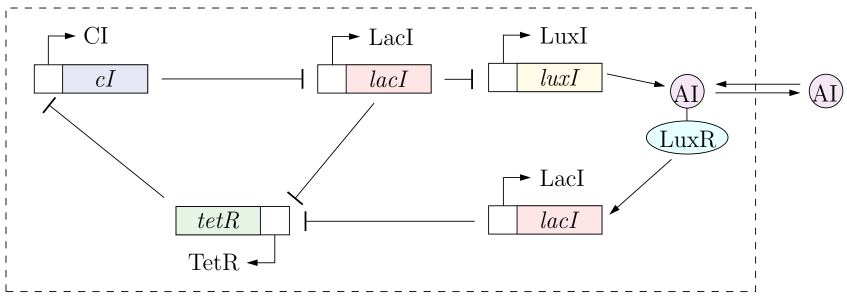

Fig. 1.3 The repressilator genetic network modified with the coupling mechanism suggested in (Garcia-Ojalvo et al, 2004). The dashed box represents the cell membrane.

For the purposes of this example, we shall slightly modify the model. In (Garcia-Ojalvo et al, 2004) it is assumed that LuxI and TetR behave identically, which is why LuxI is represented in (1.27) by x_{4_j}. We relax this assumption and assume TetR and LuxI behave independently, as do the concentrations of mRNA transcribed by *tetR* and *luxI*. The concentration of mRNA transcribed by *luxI* and the concentration of LuxI protein are denoted by x_{7_j} and x_{8_j} respectively. The revised coupled oscillator model that we shall consider is then given by the following set of ODEs

$$\dot{x}_{1_j} = -x_{1_j} + g(x_{6_j}) + f(x_{9_j}) \tag{1.28}$$
$$\dot{x}_{2_j} = -x_{2_j} + x_{1_j} \tag{1.29}$$
$$\dot{x}_{3_j} = -x_{3_j} + g(x_{2_j}) \tag{1.30}$$
$$\dot{x}_{4_j} = -x_{4_j} + x_{3_j} \tag{1.31}$$
$$\dot{x}_{5_j} = -x_{5_j} + g(x_{4_j}) \tag{1.32}$$
$$\dot{x}_{6_j} = -x_{6_j} + x_{5_j} \tag{1.33}$$
$$\dot{x}_{7_j} = -x_{7_j} + g(x_{2_j}) \tag{1.34}$$
$$\dot{x}_{8_j} = -x_{8_j} + x_{7_j} \tag{1.35}$$
$$\dot{x}_{9_j} = -x_{9_j} + x_{8_j} - \frac{1}{N}\rho_9 \sum_{k=1}^{N}(x_{9_j} - x_{9_k}) \tag{1.36}$$

Here, ρ_9 is a measure of coupling strength. The uncoupled ($\rho_9 = 0$) model (1.28)-(1.36) is illustrated in Figure 1.4, where each block represents an incrementally passive subsystem. For $i = 1, \cdots, 9$ each subsystem H_i represents the dynamic block

$$\begin{aligned} \dot{x}_{i_j} &= -x_{i_j} + e_{i_j},\ e_{i_j} = u_{i_j} + w_{i_j} \\ y_{i_j} &= x_{i_j} \end{aligned}$$

Each H_i^s represents the monotonically increasing static map

$$y_{i_j}^s = \begin{cases} -g(u_{i_j}^s),\ i = 2,4,6 \\ f(u_{i_j}^s), \quad i = 9 \end{cases}$$

Inputs u_{i_j} to each dynamic block H_i are such that

$$u_{i_j} = \begin{cases} y_{i-1_j}, & i = 2,4,6,8 \\ -y_{6_j}^s + y_{9_j}^s, & i = 1 \\ -y_{i-1_j}^s, & i = 3,5 \\ -y_{2_j}^s, & i = 7 \\ y_{8_j}, & i = 9 \end{cases}$$

Inputs $u_{i_j}^s$ to each static block H_i^s are such that

$$u_{i_j}^s = \begin{cases} y_{i-1_j},\ i = 2,4,6 \\ -y_{9_j},\ i = 9 \end{cases}$$

For blocks H_i the incremental storage function $S_i = \frac{1}{2}\Delta x_{i_{j,m}}^2$ satisfies the incremental dissipation inequality

$$\dot{S}_i = -\frac{1}{\gamma_i}(\Delta y_{i_{j,m}})^2 + \Delta y_{i_{j,m}} \Delta e_{i_{j,m}}$$

where $\gamma_i = 1$ for $i = 1, \cdots, 9$. For blocks H_i^s the incremental storage function $S_i^s = 0$ satisfies the incremental dissipation inequality

$$\dot{S}_i^s \leq -\frac{1}{\gamma_i^s}(\Delta y_{i_{j,m}})^{s^2} + \Delta y_{i_{j,m}}^s \Delta y_{i_{j,m}}$$

where

$$\gamma_i^s = \begin{cases} \sup_{x_{i_j} \in \mathbb{R}} -g'(x_{i_j}) & i = 2,4,6 \\ \sup_{x_{i_j} \in \mathbb{R}} f'(x_{i_j}) & i = 9 \end{cases}$$

Note that from the definitions of outputs y_{i_j} for this example, each node is incrementally zero-state observable since for all i and any j, m $|y_{i_j} - y_{i_m}| = 0 \Leftrightarrow |x_{i_j} - x_{i_m}| = 0$. This implies the iZSD property required in Theorem 2 to deduce asymptotic state synchronization from asymptotic output synchronization.

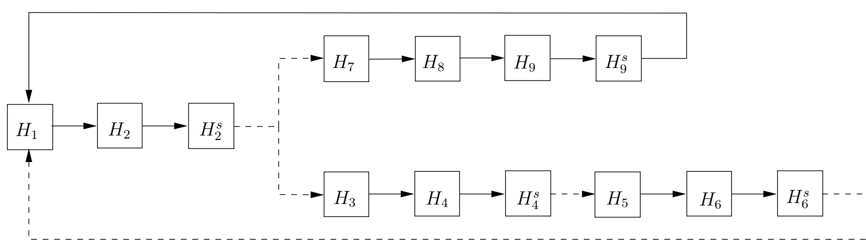

Fig. 1.4 Block diagram representation of the uncoupled repressilator genetic circuit of the model (1.28)-(1.36). Dashed lines represent inhibitory reactions.

With the above definitions of the input-output relations between the different blocks of Figure 1.4, it is now possible to construct an incremental storage function $S(X_\Delta)$ for the incremental state vector X_Δ. For the two sets $\mathcal{I} = \{1, \cdots, 9\}$ and $\mathcal{I}^s = \{2,4,6,9\}$ let

$$S(X_\Delta) = \frac{1}{2N} \sum_{j=1}^{N} \sum_{j=1}^{N} \left(\sum_{i \in \mathcal{I}} d_i S_{i_{j,m}} + \sum_{i \in \mathcal{I}^s} d_i^s S_{i_{j,m}}^s \right)$$

where $d_i, d_i^s > 0$. Defining

$$Y = \left[Y_1^* \; Y_2^* \; Y_2^{s^*} \; Y_3^* \; Y_4^* \; Y_4^{s^*} \; Y_5^* \; Y_6^* \; Y_6^{s^*} \; Y_7^* \; Y_8^* \; Y_9^* \; Y_9^{s^*} \right]^*$$

where $Y_i^s = \left[y_{i_1}^s \; \cdots \; y_{i_N}^s \right]^*$ and defining

$$K = \mathrm{diag}\{k_1, k_2, k_2^s, k_3, k_4, k_4^s, k_5, k_6, k_6^s, k_7, k_8, k_9, k_9^s\}$$

where

$$\begin{cases} k_i = 0 & i = 1, \dots, 8 \\ k_i > 0 & i = 9 \end{cases} \quad \text{and} \quad k_i^s = 0, \quad i \in \mathcal{I}^s \tag{1.37}$$

we then have the incremental dissipation inequality

$$\begin{aligned} \dot{S} &\leq Y^* \tilde{\Pi}_n^* ((A(\boldsymbol{\gamma})^* D + DA(\boldsymbol{\gamma})) \otimes I_N) \tilde{\Pi}_n Y + W_9^* \Pi^* \Pi Y_9 \\ &\leq Y^* \tilde{\Pi}_n^* ((A(\tilde{\boldsymbol{\gamma}})^* D + DA(\tilde{\boldsymbol{\gamma}})) \otimes I_N) \tilde{\Pi}_n Y + k_9 Y_9^* \Pi^* \Pi Y_9 + W_9^* \Pi^* \Pi Y_9 \end{aligned} \tag{1.38}$$

with $D = \text{diag}\{d_1, d_2, d_2^s, d_3, d_4, d_4^s, d_5, d_6, d_6^s, d_7, d_8, d_9, d_9^s\}$ and the interconnection matrix

$$A(\tilde{\boldsymbol{\gamma}}) = \begin{bmatrix} -\frac{1}{\tilde{\gamma}_1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 1 \\ 1 & -\frac{1}{\tilde{\gamma}_2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & -\frac{1}{\tilde{\gamma}_2^s} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -1 & -\frac{1}{\tilde{\gamma}_3} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & -\frac{1}{\tilde{\gamma}_4} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & -\frac{1}{\tilde{\gamma}_4^s} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -1 & -\frac{1}{\tilde{\gamma}_5} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & -\frac{1}{\tilde{\gamma}_6} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -\frac{1}{\tilde{\gamma}_6^s} & 0 & 0 & 0 & 0 \\ 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & -\frac{1}{\tilde{\gamma}_7} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -\frac{1}{\tilde{\gamma}_8} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -\frac{1}{\tilde{\gamma}_9} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -\frac{1}{\tilde{\gamma}_9^s} \end{bmatrix} \tag{1.39}$$

where

$$\tilde{\gamma}_i = \frac{\gamma_i}{1 + k_i \gamma_i} \quad \text{and} \quad \tilde{\gamma}_i{}^s = \frac{\gamma_i^s}{1 + k_i^s \gamma_i^s}$$

and where the interconnection matrix $A(\boldsymbol{\gamma})$ is of the same structure as $A(\tilde{\boldsymbol{\gamma}})$ but with $\tilde{\gamma}_i, \tilde{\gamma}_i^s$ replaced with γ_i, γ_i^s.

Theorem 1 shows that there always exists a matrix $K \geq 0$ such that (1.38) is iOSP($-K$). However in the case of this network the only state directly coupled to others in the network is the state x_{9_j}, and therefore the coupling can only compensate for a shortage of incremental passivity as in Theorem 2 if K is limited to the form (1.37) since the matrix L in Theorem 2 is constrained by the coupling to the structure

$$\begin{cases} \lambda_{2_i} = 0 & i = 1, \cdots, 8 \\ \lambda_{2_i} > 0 & i = 9 \end{cases} \quad \text{and} \quad \lambda_{2_i}^s = 0, \quad i \in \mathcal{I}^s$$

In other words, with this incremental output passification method, it will only be possible to prove asymptotic global state synchronization under strong coupling if decreasing $\tilde{\gamma}_9$ by increasing k_9 is sufficient to guarantee that there exists $D > 0$ such that $A(\tilde{\boldsymbol{\gamma}})^* D + DA(\tilde{\boldsymbol{\gamma}}_i) < -\epsilon_{D,K} I_n$ for some $\epsilon_{D,K} > 0$.

To see if this is possible, first note the branched structure of the block diagram shown in Figure 1.4. A similar branched structure was analyzed in (Sontag and Arcak, 2008), which derived a necessary and sufficient condition on the quantities $\tilde{\gamma}_i$ and $\tilde{\gamma}_i^s$ for the diagonal stability of the interconnection matrix associated with the branched structure in that reference. The nodal structure in Figure 1.4 is different to that in (Sontag and Arcak, 2008). However, similar arguments to those in (Sontag and Arcak, 2008) can be used to derive at least a necessary condition for the diagonal stability of $A(\tilde{\boldsymbol{\gamma}})$ in (1.39). The main idea in (Sontag and Arcak, 2008) concerning such structures is that a necessary condition for the diagonal stability of $A(\tilde{\boldsymbol{\gamma}})$ is that all its principal submatrices are also diagonally stable (Barker et al, 1978). For $A(\tilde{\boldsymbol{\gamma}})$, consider the principal submatrix obtained by deleting the $10^{\text{th}} - 13^{\text{th}}$ rows and columns and the principal submatrix obtained by deleting the $4^{\text{th}} - 9^{\text{th}}$ rows and columns. These are

$$A(\tilde{\boldsymbol{\gamma}})_{(10-13)} = \begin{bmatrix} -\frac{1}{\tilde{\gamma}_1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 \\ 1 & -\frac{1}{\tilde{\gamma}_2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & -\frac{1}{\tilde{\gamma}_2^s} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -1 & -\frac{1}{\tilde{\gamma}_3} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & -\frac{1}{\tilde{\gamma}_4} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & -\frac{1}{\tilde{\gamma}_4^s} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -1 & -\frac{1}{\tilde{\gamma}_5} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & -\frac{1}{\tilde{\gamma}_6} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -\frac{1}{\tilde{\gamma}_6^s} \end{bmatrix}$$

and

$$A(\tilde{\boldsymbol{\gamma}})_{(4-9)} = \begin{bmatrix} -\frac{1}{\tilde{\gamma}_1} & 0 & 0 & 0 & 0 & 0 & 1 \\ 1 & -\frac{1}{\tilde{\gamma}_2} & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & -\frac{1}{\tilde{\gamma}_2^s} & 0 & 0 & 0 & 0 \\ 0 & 0 & -1 & -\frac{1}{\tilde{\gamma}_7} & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & -\frac{1}{\tilde{\gamma}_8} & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & -\frac{1}{\tilde{\gamma}_9} & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & -\frac{1}{\tilde{\gamma}_9^s} \end{bmatrix}$$

These two principal submatrices exhibit a cyclic feedback structure (with negative feedback). As discussed above, the stability of systems with this structure was studied in (Arcak and Sontag, 2006), where it was shown that the matrix such as $A(\tilde{\boldsymbol{\gamma}})_{(10-13)}$ is diagonally stable if and only if

$$\tilde{\gamma}_1 \tilde{\gamma}_2 \tilde{\gamma}_2^s \tilde{\gamma}_3 \tilde{\gamma}_4 \tilde{\gamma}_4^s \tilde{\gamma}_5 \tilde{\gamma}_6 \tilde{\gamma}_6^s < \sec^9\left(\frac{\pi}{9}\right) \tag{1.40}$$

whilst $A(\tilde{\boldsymbol{\gamma}})_{(4-9)}$ is diagonally stable if and only if

$$\tilde{\gamma}_1\tilde{\gamma}_2\tilde{\gamma}_2^s\tilde{\gamma}_7\tilde{\gamma}_8\tilde{\gamma}_9\tilde{\gamma}_9^s < \sec^7\left(\frac{\pi}{7}\right) \tag{1.41}$$

Since $\tilde{\gamma}_9$ appears in (1.41) only, these two necessary conditions can only be met by strengthening the coupling if (1.40) is satisfied *a priori*.

If it were possible to modify the repressilator circuit so that the coupling state is x_{1_j} or x_{2_j} it could then be possible to diagonally stabilize $A(\tilde{\boldsymbol{\gamma}})$ by reducing the incremental secant gains $\tilde{\gamma}_1$, $\tilde{\gamma}_2$ or $\tilde{\gamma}_2^s$ by increasing k_1, k_2, k_2^s and then compensating for the shortage of incremental passivity with strong coupling. This is because the quantities $\tilde{\gamma}_1$, $\tilde{\gamma}_2$, $\tilde{\gamma}_2^s$ appear in both (1.40) and (1.41), and these two necessary conditions can therefore be satisfied under such a change. To see this, we propose a modification to the repressilator model wherein *lacI* is replaced with a different gene, the protein product of which behaves as LacI in inhibiting the transcription of *luxI* and *tetR*, but with the difference that the new protein product is also a coupling signal in the same manner as AI. Equation (1.29) is then modified to

$$\dot{x}_{2_j} = -x_{2_j} + x_{1_j} - \frac{1}{N}\rho_2\sum_{k=1}^{N}(x_{2_j} - x_{2_k}) \tag{1.42}$$

For this example, we consider a network of $N = 4$ nodes of the form (1.28)-(1.36) but with (1.29) replaced with (1.42). The incremental secant gains γ_i can be calculated from the model to be as follows:

$$\gamma_i = 1,\ \text{for } i = 1, \cdots, 9 \qquad \gamma_i^s = 3.25,\ \text{for } i = 2, 4, 6 \qquad \gamma_9^s = 1$$

Since the coupling is only through the states x_{2_j} and x_{9_j}, strong coupling can incrementally passify the network nodes only if $K = \text{diag}\{0, k_2, 0, \cdots, 0, k_9\}$ as L would have the same structure as K.

We set $k_2 = 12$ and $k_9 = 0$, which makes $\tilde{\gamma}_2 = 0.04$ and $\tilde{\gamma}_9 = \gamma_9 = 1$. Otherwise, $k_i = k_i^s = 0$, which leaves $\tilde{\gamma}_i = \gamma_i, \forall i \neq 2$ and $\tilde{\gamma}_i^s = \gamma_i^s$ for $i = 2, 4, 6, 9$. Without a sufficient condition on the gains $\tilde{\gamma}_i$ that guarantees the diagonal stability of $A(\tilde{\boldsymbol{\gamma}})$, it is nevertheless possible to use an LMI solver to find a matrix $D > 0$ such that $A(\tilde{\boldsymbol{\gamma}})^*D + DA(\tilde{\boldsymbol{\gamma}}) < 0$. One possible matrix D is given by

$$D = \text{diag}\{1, 17, 208, 53, 57, 19, 7, 7, 3, 17, 18, 19, 26\} \tag{1.43}$$

which is such that $A(\tilde{\boldsymbol{\gamma}})^*D + DA(\tilde{\boldsymbol{\gamma}}) < -0.0014I_n$. and therefore $S(X_\Delta)$ satisfies the incremental dissipation inequality

$$\begin{aligned}\dot{S} &\le (\tilde{\Pi}_nY)^*((A(\tilde{\boldsymbol{\gamma}})^*D + DA(\tilde{\boldsymbol{\gamma}})) \otimes I_N)\tilde{\Pi}_nY + k_2Y_2^*\Pi^*\Pi Y_2 + W_2^*\Pi^*\Pi Y_2 \\ &\le -0.0072(\tilde{\Pi}_nY)^*\tilde{\Pi}_nY + k_2Y_2^*\Pi^*\Pi Y_2 + W_2^*\Pi^*\Pi Y_2\end{aligned} \tag{1.44}$$

The coupling is given by the relation $W_2 = -\Gamma_2 Y_2$ where, from (1.42), Γ_2 has the all-to-all structure

$$\Gamma_2 = \rho_2 \left(I_N - \frac{1}{N} \mathbf{1}_{N\times N} \right)$$

and $\lambda_{2_2} = \rho_2$. From Theorem 2, we require $\lambda_{2_2} \geq k_2$ to guarantee synchronization.

This condition therefore requires $\rho_2 > 12$. The simulation in Figure (1.5) shows the synchronization of the output y_{2_j} across the network nodes as well as the asymptotic stability of the synchronization error in the output y_{2_j} under this coupling. Note that this figure also demonstrates the synchronization of state x_{2_j} since $y_{2_j} = x_{2_j}$.

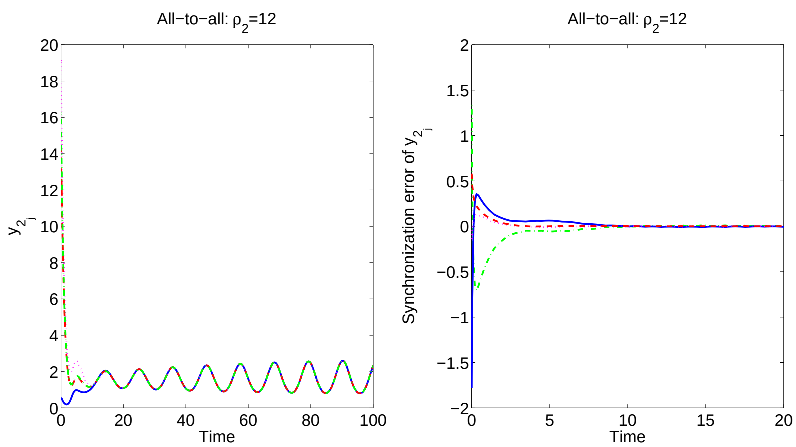

Fig. 1.5 Synchronization of four repressilator circuits. Left: Synchronization of output y_{2_j}. Right: Synchronization error of output y_{2_j}.

1.5 Discussion

This chapter has presented a constructive approach to finding sufficient conditions for global asymptotic state synchronization in networks of identical nodes. The principal assumptions are that each node is composed of iOFP subsystems, and that these subsystems are directly coupled to their corresponding subsystems on other nodes in the network using linear static coupling.

By taking advantage of the iOFP property, it was possible to quantify the degree of the shortage of incremental passivity of each node (Theorem 1).

In Theorem 2 it was shown that the nodal coupling can act as a passifying feedback and the degree of shortage of passivity was used to determine a lower bound on the minimum coupling strength required to render each node iOSP and hence guarantee asymptotic output synchronization. With an additional iZSD assumption, this also implied asymptotic state synchronization. These two theorems demonstrated that for arbitrary nodal structures satisfying Assumption 1, it was always possible to characterize the shortage of passivity and it was always possible to find a strong enough coupling topology that can eliminate this shortage and thus achieve asymptotic state synchronization.

Inequalities such as (1.4) is an incremental dissipation inequality that can be used to represent general (iOFP$\left(\frac{1}{\gamma_i}\right)$) subsystems. Therefore if a given network satisfies our sufficient conditions for synchrony and we were to replace the ith subsystem of each node in the network with another subsystem that has a shortage of passivity that is equal to or less than that of the original subsystem, the network with the new subsystem would also synchronize. This ability to modify the parameters, and indeed the structure, of the network subsystems and yet maintain synchrony lends a significant degree of robustness to the results we have presented. In the applied setting of synchronizing biochemical reaction networks such as (Gonze et al, July 2005), where biological parameters typically vary significantly, placing a biologically plausible upper bound on the quantity γ_i would allow us to analyze synchrony in such a system in a way that is robust to such parametric variations. Furthermore, the proposed methodology can also have implications for the design of synthetic circuits that synchronize upon interconnection because it can yield insight into the what system outputs could serve as network coupling signals that lead to incremental stability.

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