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Oscillations in networks composed of Cyclic Negative Feedback systems (CNF systems) are widely used to mimic many periodic phenomena occurring in systems biology. In particular, the possible coexistence of different attractors permits to suitably describe the differentiating processes arising in living cells. The aim of the manuscript is to characterize, through a spectral based technique, the complex global dynamical behaviors emerging in arrays of diffusively coupled CNF systems.

Keywords: regulatory genetic networks, bioinspired systems, discrete breathers

1. Introduction

Cyclic Negative Feedback systems (CNF systems) are one of the most applied paradigms to model many phenomena arising in systems biology: from gene regulation systems [Tyson & Othmer, 1978; de Jong, 2002] to metabolic [Morales & McKay, 1967] and cellular signal pathways [Kholodenko, 2000; Liu, 2002; Wang *et al.*, 2008]. CNF systems have the interesting property of admitting coexisting periodic solutions. This property has been exploited to build models of circadian rhythms and developmental clocks during morphogenesis [Sontag, 2005].

As shown in [Mallet-Paret & Smith, 1990], the Poincaré-Bendixson theorem holds for monotone CNF systems. As a consequence, only equilibria, limit cycles, heteroclinic or homoclinic loops are admissible as omega-limit sets of any bounded orbit. Hence, collections of CNF systems (and more generally nonlinear oscillatory network models) with coexisting stable states allow physiologists to accurately model the cell differentiation processes. The most interesting case, that goes by the name of *hard excitation* [Liu, 2002], is when there is the concurrence between oscillatory and non-oscillatory states [Minorsky, 1974; Jovanic

et al., 2008].

The study of the dynamical behavior of networks composed of CNF systems may be extremely important to interpret several biological phenomena. Numerical simulations based on time-domain methods are not suitable for detecting global dynamic behavior of complex networks with a large number of coexisting attractors. Recently, an approach based on the Lyapunov function method, and more in general on control theories, has been proposed in order to analyze the different attractors of gene regulatory networks that can be represented as Lur'e systems [Wang *et al.*, 2008]. Furthermore, some spectral techniques have been successfully applied to unfold the global dynamical behavior of oscillatory networks [Gilli *et al.*, 2004, 2005; Lanza *et al.*, 2008].

In this manuscript we focus on networks of diffusively coupled *CNF systems*. In the following such structures are referred to as 'CNF arrays'.

We aim at studying the global dynamics of CNF arrays due to the couplings. In particular, under the assumption of weak couplings we derive the global dynamical properties from the characteristics of the single system's attractors.

As first step, we show that CNF arrays with diffusive couplings that are constant and local (i.e. they involve only the two nearest neighbors of each CNF system) are potentially equivalent to nonlinear networks whose elements are fully connected (i.e. each subsystem is linked to all the others).

Furthermore, we consider the simplest CNF array composed of two compartments that interact through diffusive couplings. By assuming that each uncoupled subsystem presents the coexistence of limit cycles and equilibrium points, the following cases are possible depending on the basin of attraction where the initial conditions are chosen:

(a) both uncoupled subsystems do not oscillate, i.e. the initial condition for each uncoupled subsystem is chosen in such a way that both subsystems settle;
(b) both uncoupled subsystems oscillate, i.e. the initial condition for each uncoupled subsystem is chosen in such a way that both subsystems oscillate;
(c) one uncoupled subsystem oscillates and the other does not oscillate, i.e. the initial condition for each uncoupled subsystem is chosen in such a way that one subsystem converges toward an equilibrium point and the other toward a limit cycle.

The effect of the coupling is pointed out when the two-compartment system is in the cases (a)-(c).

Finally, a describing function based technique is proposed to investigate CNF arrays with a large number of elements and the spatial localized patterns that can occur due to the coupling.

2. Local and global coupling in one-dimensional array of CNF systems

Cyclic Negative Feedback systems (CNF systems) are described by the following set of nonlinear differential equations [Tyson & Othmer, 1978; Arcak & Sontag, 2006, 2008]:

$$\begin{aligned} \dot{x}_1 &= -a_1\, x_1 + f(x_n) \\ \dot{x}_k &= -a_k\, x_k + b_{k-1}\, x_{k-1}, \qquad 2 \le k \le n \end{aligned} \tag{1}$$

where x_k assumes only nonnegative values (hereinafter the index k, with $k = 1, \ldots, n$, is used to label each state variable of a single CNF system) and $f'(x_n) < 0$. Systems as (1) arise in a variety of mathematical models of biological systems. For instance, the variables x_k represent the concentrations of certain molecules in the cells composing cellular control systems. In addition, the function $f(\cdot)$ suitably represents the inhibition of x_1 by the product x_n (see Figure 1). The mitogen activated protein kinase (MAPK) cascade model [Kholodenko, 2000] is a significant example of such type of systems. It can be proved [Arcak & Sontag, 2008] that system (1) exhibits a global asymptotic stable equilibrium $\mathbf{x}^* = (x_1^*, \ldots, x_n^*)$ under the condition (secant criterion)

$$\frac{b_1 \cdots b_{n-1} f'(x_n^*)}{a_1 \cdots a_n} < \sec(\pi/n)^n.$$

Furthermore, for these type of systems the Poincaré-Bendixson Theorem holds [Mallet-Paret & Smith, 1990], that is the coexistence between stable equilibria and periodic orbits is allowed.

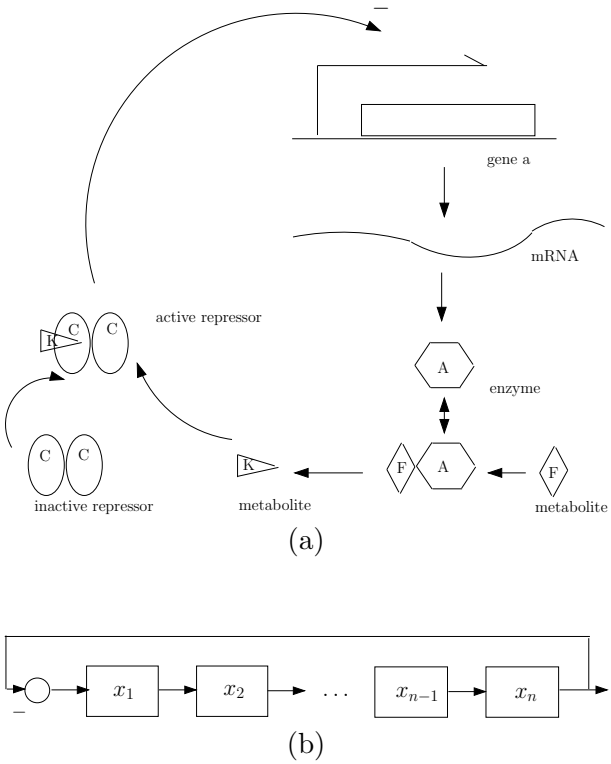

Fig. 1. *(a) Example of a genetic regulatory network that can be modeled as a third order Cyclic Negative Feedback system, where the variables are the concentrations of mRNA a, protein A, and metabolite K (representation adapted from [de Jong, 2002]). (b) Block diagram of a n-th order CNF system. Each variable $x_k(t)$ is activated by its previous neighbor $x_{k-1}(t)$, except for $x_1(t)$ that is repressed by $x_n(t)$.*

However, experimental observations reveal that some cellular reactions occur in specific locations inside the cell, while the exchange of different chemical species is realized by diffusion through the common extracellular medium. Such mechanisms are suitably modeled by the following set of reaction diffusion equations:

$$\begin{aligned} \dot{x}_1^i &= -a_1 x_1^i + f(x_n^i) + T_1 \Delta x_1^i \\ \dot{x}_k^i &= -a_k x_k^i + b_{k-1} x_{k-1}^i + T_k \Delta x_k^i, \qquad 2 \le k \le n \end{aligned} \tag{2}$$

where the index i, with $i = 1, \ldots, M$, denotes the i-th compartment (i.e. the single CNF system described by (1)), T_k ($k = 1, \ldots, n$) is the positive diffusion coefficient associated with the state variable x_k^i and Δx_k^i denotes the discretized Laplacian operator in $\boldsymbol{R}$:

$$\Delta x_k^i = x_k^{i-1} + x_k^{i+1} - 2x_k^i.$$

Generally, in this context, Neumann (i.e. zero-flux) boundary conditions are considered.

In the sequel we investigate (2) in order to study the emergence of complex dynamical phenomena under the assumption that the extracellular medium is weakly diffusive (i.e. $T_k = \varepsilon \ll 1 \; \forall \, k$).

In particular, the following subsection is devoted to show that each element of the CNF array interacts through dynamical links (i.e. the couplings are defined through dynamic operators) not only with its two nearest neighbors, despite the diffusive couplings in (2) involve only the two nearest neighbors and are constant.

2.1. *Arrays composed of n^{th}-order CNF systems*

By introducing the vector $\mathbf{X}_k = [x_k^1, \ldots x_k^M]^T$ ($[\,\cdot\,]^T$ is the transpose vector) the following relations can be derived from (2):

$$\mathbf{X}_{k-1} = \frac{1}{b_{k-1}}\mathbf{M}_{k-1}\mathbf{X}_k, \qquad 2 \le k \le n, \tag{3}$$

where $\mathbf{M}_{k-1} \in \mathbf{R}^{M,M}$ is defined as follows by taking into account the Neumann boundary conditions:

$$\mathbf{M}_{k-1} = (D + a_k)\mathbf{I} - \varepsilon\mathbf{P}, \tag{4}$$

where $D = d/dt$ is the first-order time derivative and

$$\mathbf{P} = \begin{pmatrix} -1 & 1 & 0 & \cdots & 0 \\ 1 & -2 & 1 & \ddots & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & \ddots & 1 & -2 & 1 \\ 0 & \cdots & 0 & 1 & -1 \end{pmatrix}. \tag{5}$$

Therefore, we get recursively

$$\mathbf{X}_{k-1} = \prod_{j=k-1}^{n-1} \frac{1}{b_j}\mathbf{M}_j\mathbf{X}_n, \qquad 2 \le k \le n. \tag{6}$$

By substituting these relations into the first equation of (2), after some algebraic manipulation, we obtain the following vector equation for the sole variable $\mathbf{X}_n = [x_n^1, \ldots x_n^M]^T$:

$$\mathbf{M}_0 \left(\prod_{j=1}^{n-1} \frac{1}{b_j} \cdot \mathbf{M}_j \right) \mathbf{X}_n = \mathbf{f}(\mathbf{X}_n), \tag{7}$$

where $\mathbf{f}(\mathbf{X}_n) = [f(x_n^1), \ldots, f(x_n^M)]^T$ and $\mathbf{M}_0$ is given by (4) with $k = 1$.

Equation (7) can be interpreted as the Lur'e representation of (2) in terms of the sole variables $\mathbf{X}_n$. By using such representation, it is possible to show that the couplings among the Lur'e variables $\mathbf{X}_n$ involve not only the two nearest neighbors and are in general dynamical, i.e. they concern the time derivative operator D.

For this purpose and without any loss of generality, let us consider $a_p = 1$ for all $p = 1, \ldots, n$, and $b_q = 1$ for all $q = 1, \ldots, n-1$:

$$\begin{aligned} \dot{x}_1^i &= -x_1^i + f(x_n^i) + \varepsilon(x_1^{i+1} + x_1^{i-1} - 2x_1^i) \\ \dot{x}_k^i &= -x_k^i + x_{k-1}^i + \varepsilon(x_k^{i+1} + x_k^{i-1} - 2x_k^i) \qquad 2 \le k \le n. \end{aligned} \tag{8}$$

It follows that relation (6) simplifies and reduces to $\mathbf{X}_k = \mathbf{M}^{n-k}\mathbf{X}_n$, $1 \le k \le n-1$, where

$$\mathbf{M} = (D + 1)\mathbf{I} - \varepsilon\mathbf{P}; \tag{9}$$

therefore, the Lur'e form of (8) results to be:

$$\mathbf{M}^n\mathbf{X}_n = \mathbf{f}(\mathbf{X}_n). \tag{10}$$

In order to derive the properties of (10) we need to understand the structure of matrix $\mathbf{M}^n$.

Lemma 1. *Let $\mathbf{M}$ be a $m \times m$ tridiagonal matrix. Then, for $k < m-1$, $\mathbf{M}^k$ is a band matrix with bandwidth $2k+1$. For $k \ge m-1$, $\mathbf{M}^k$ is a dense matrix.*

Proof. For the sake of simplicity, let us consider tridiagonal matrices whose elements on the superdiagonal and on the subdiagonal are constants, i.e. $\mathbf{M} = a\mathbf{U} + b\mathbf{L} + \mathbf{\Lambda}$ where $\mathbf{\Lambda} \in \mathbf{R}^{m,m}$ is a diagonal matrix, $\mathbf{L} = \mathbf{U}^T$ and $\mathbf{U} \in \mathbf{R}^{m,m}$ is an upper shift matrix defined as $\mathbf{U}_{ij} = \delta_{i+1,j}$.

Exploiting the results in [Andrews, 1990], it follows that:

$$\mathbf{M}^k = (a\mathbf{U} + b\mathbf{L} + \mathbf{\Lambda})^k = \sum_{\substack{k_1,k_2,k_3\geq 0 \\ k_1+k_2+k_3=k}} \frac{k!}{k_1!k_2!k_3!}(a\mathbf{U})^{k_1}(b\mathbf{L})^{k_2}\mathbf{\Lambda}^{k_3}$$
$$= a^k\mathbf{U}^k + b^k\mathbf{L}^k + \mathbf{\Lambda}^k + \cdots \tag{11}$$

By noting that $\mathbf{U}^k_{ij} = \delta_{i+k,j}$ and $\mathbf{L}^k_{ij} = \delta_{i,j+k}$, we can conclude that $\mathbf{M}^k$ is a band matrix with bandwidth $2k+1$ for $k < m-1$. On the other hand, $\mathbf{M}^k$ is a dense matrix for $k \geq m-1$ since $\mathbf{U}^{m-1}_{ij} = \delta_{i+m-1,j}$, $\mathbf{L}^{m-1}_{ij} = \delta_{i,j+m-1}$, and $\mathbf{U}^m = \mathbf{L}^m = 0$. ■

Proposition 1. *Let us consider the array, described by* (8)*, composed of M CNF systems of order n. Then, the each system is coupled at most with $2n+1$ other elements of the network. Furthermore, if $M \leq n+1$, then the CNF array is fully connected (i.e. each system is linked to all the others).*

Proof. By applying the previous Lemma to the matrix $\mathbf{M}$ defined in (9), we get that $\mathbf{M}^n$ is a band matrix with bandwidth $2n+1$. Furthermore, for $n \geq M-1$, $\mathbf{M}^n$ is a dense matrix, that is each equation of (10) involve all the variables $\mathbf{X}_n = [x^1_n, \ldots x^M_n]^T$. It follows that the array is fully connected (each CNF system is linked to all the others). ■

Corollary 2.1. *Let us consider an array of M CNF systems of order n, such as* (8)*. Then, the sphere of influence of each system is composed of at most $2n+1$ systems.*

Remark 2.1. It is worth recalling that (2) and (8) can be seen as the spatial discretization of reaction-diffusion partial differential equations

$$\frac{\partial \mathbf{u}(x,t)}{\partial t} = g(\mathbf{u}(x,t)) + \varepsilon\Delta\mathbf{u}(x,t), \;\; t \in \mathbf{R}^+, \; x \in I \subset \mathbf{R}.$$

Proposition 1 states that, although the coupling in (2) and (8) is local and it involves only the two nearest neighbors, actually it concerns $2n+1$ elements of the network (where n is the order of the dynamical system). This means that, although we use a finite difference scheme on three nodes for the Laplacian operator, nevertheless the discretization globally involves $2n+1$ nodes.

Remark 2.2. The results shown previously can be naturally extended to the study of a bidimensional equation of reaction-diffusion. Also in this case it is possible to derive matricial relations such as (7) and (10), where the matrices involved take into account the possible different boundary conditions (Dirichlet, Neumann or periodic ones). Therefore, it is possible to show that also in a bidimensional array, although the coupling is constant and concerns only the four nearest neighbors, nevertheless it globally links more nodes and involves dynamic operators.

2.2. *Case-study: Arrays composed of 3^{rd}-order CNF systems*

Let us consider the following simple third order cyclic negative feedback system [Jovanic *et al.*, 2008]:

$$\begin{aligned} \dot{x}_1 &= -x_1 + f(x_3) \\ \dot{x}_2 &= -x_2 + x_1 \\ \dot{x}_3 &= -x_3 + x_2 \end{aligned} \tag{12}$$

where

$$f(x) = \mathrm{e}^{-10(x-1)} + 0.1\mathrm{sgn}\{25(x-1)\}\min\{1, |25(x-1)|\}.$$

It is easy to see that (12) has $x_1 = x_2 = x_3 = 1$ as equilibrium point. Furthermore, since $f'(1) = -7.5$, the secant criterion permits us to conclude that the equilibrium is asymptotically stable. In addition, as

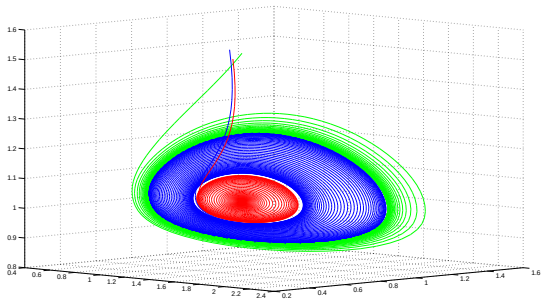

Fig. 2. *Single CNF system attractors. The stable limit cycle attracts the trajectories shown in green and blue. The stable equilibrium point* $(1, 1, 1)$ *attracts the trajectory depicted in red. The saddle limit cycle is located between the trajectories shown in blue and red.*

it can be seen in Fig. 2, a stable periodic orbit coexists with the equilibrium point $(1, 1, 1)$, and they are separated by a saddle limit cycle [Jovanic *et al.*, 2008].

System (12) can be easily recast in a Lur'e form

$$L(D)x_3(t) = f[x_3(t)] \tag{13}$$

where $L(D) = (D + 1)^3$. In addition, the following linear relations among the variables hold:

$$x_1(t) = L_1(D)x_3(t) \tag{14}$$
$$x_2(t) = L_2(D)x_3(t), \tag{15}$$

with $L_1(D) = (D + 1)^2$ and $L_2(D) = (D + 1)$. From (8) and (10), we know that arrays of M CNF systems admit the following Lur'e description

$$\mathbf{M}^3\mathbf{X}_3 = \mathbf{f}(\mathbf{X}_3), \tag{16}$$

where $\mathbf{M} \in \boldsymbol{R}^{M,M}$ is defined in (9). In this section, we are interested in explicitly evaluate $\mathbf{M}^3$ in order to characterize the couplings in (16).

From the expression for matrix $\mathbf{M}$ given in (9) and with $\mathbf{P}$ previously defined in (5), it easily follows that

$$\begin{aligned}\mathbf{M}^3 &= (D + 1)^3\mathbf{I} - 3(D + 1)^2\varepsilon\mathbf{P} + 3(D + 1)\varepsilon^2\mathbf{P}^2 - \varepsilon^3\mathbf{P}^3 \\ &= L(D)\mathbf{I} - 3L_1(D)\varepsilon\mathbf{P} + 3L_2(D)\varepsilon^2\mathbf{P}^2 - \varepsilon^3\mathbf{P}^3.\end{aligned} \tag{17}$$

The application of Proposition 1 permits us to conclude that each CNF system is coupled with at most 7 other systems. Furthermore, such couplings are dynamical due to the presence of the operators $L_1(D)$ and $L_2(D)$.

3. Dynamical behaviors due to the interactions among CNF systems

Many complex spatio-temporal phenomena arising in biological systems, modeled as a collection of cyclic negative feedback systems (CNF systems), can be interpreted by pointing out the effects of the interactions among the constituent elements. The first part of this section is devoted to study the simplest array composed of only two 3^{rd}-order CNF systems. In the second part a describing function based technique is proposed to investigate one-dimensional array with an arbitrary number of 3^{rd}-order CNF systems.

3.1. *Dynamics of two interacting 3rd-order CNF systems*

We are interested in studying the following two-compartment version of system (12) (i.e. two-element network):

$$\begin{aligned}
\dot{x}_1 &= -x_1 + f(x_3) + \varepsilon(y_1 - x_1) \\
\dot{x}_2 &= -x_2 + x_1 + \varepsilon(y_2 - x_2) \\
\dot{x}_3 &= -x_3 + x_2 + \varepsilon(y_3 - x_3) \\
\dot{y}_1 &= -y_1 + f(y_3) + \varepsilon(x_1 - y_1) \\
\dot{y}_2 &= -y_2 + y_1 + \varepsilon(x_2 - y_2) \\
\dot{y}_3 &= -y_3 + y_2 + \varepsilon(x_3 - y_3),
\end{aligned} \tag{18}$$

where the couplings are supposed to be weak ($\varepsilon = 10^{-4}$ [Jovanic *et al.*, 2008]). It is worth observing that (18) can be written as

$$\begin{aligned}
\dot{X} &= F(X) + \varepsilon G(X, Y) \\
\dot{Y} &= F(Y) + \varepsilon G(Y, X)
\end{aligned}$$

where $X = (x_1, x_2, x_3)^T$, $Y = (y_1, y_2, y_3)^T$,

$$F(X) = \begin{pmatrix} -x_1 + f(x_3) \\ -x_2 + x_1 \\ -x_3 + x_2 \end{pmatrix} \quad \text{and} \quad G(X, Y) = \begin{pmatrix} y_1 - x_1 \\ y_2 - x_2 \\ y_3 - x_3 \end{pmatrix}. \tag{19}$$

With simple algebraic calculations, the Lur'e expression for (18) can be derived:

$$L(D)x_3(t) = f[x_3(t)] + H(D)(y_3(t) - x_3(t)) \tag{20}$$
$$L(D)y_3(t) = f[y_3(t)] + H(D)(x_3(t) - y_3(t)) \tag{21}$$

with

$$L(D) = (D + 1)^3 \tag{22}$$
$$H(D) = \varepsilon[3(D + 1 + \varepsilon)^2 + \varepsilon^2]. \tag{23}$$

Each uncoupled CNF system ($\varepsilon = 0$) of the two-elements network described by (20)-(21) can converge toward the equilibrium point $(1, 1, 1)$ or the stable limit cycle by choosing appropriately the initial conditions. In the following subsections, by exploiting spectral techniques, we will study the effect of the coupling in the following cases: (a) the two uncoupled systems are in the equilibrium point; (b) the two uncoupled systems are both oscillating; (c) the uncoupled system (20) oscillates while the uncoupled system (21) is in the equilibrium point.

3.1.1. *Non-oscillating CNF systems*

It is easy to see that the configuration where each element of (20)-(21) is in the equilibrium point $P = (1, 1, 1)$ is still a steady state for the global system. We are now interested in studying its stability depending on the coupling strength ε.

The evaluation in the equilibrium point of the Jacobian matrix for system (18) yields:

$$\mathbf{J} = \begin{pmatrix}
-1-\varepsilon & 0 & f'(1) & \varepsilon & 0 & 0 \\
1 & -1-\varepsilon & 0 & 0 & \varepsilon & 0 \\
0 & 1 & -1-\varepsilon & 0 & 0 & \varepsilon \\
\varepsilon & 0 & 0 & -1-\varepsilon & 0 & f'(1) \\
0 & \varepsilon & 0 & 1 & -1-\varepsilon & 0 \\
0 & 0 & \varepsilon & 0 & 1 & -1-\varepsilon
\end{pmatrix} \tag{24}$$

where $f'(1) = -7.5$. It is worth noting that the characteristic polynomial of the Jacobian matrix $\mathbf{J}$ can be represented as:

$$\det(\mathbf{J} - \lambda\mathbf{I}) = P(\lambda)Q(\lambda, \varepsilon), \tag{25}$$

where

$$P(\lambda) = 1 - f'(1) + 3\lambda + 3\lambda^2 + \lambda^3 \tag{26}$$

is the characteristic polynomial of the Jacobian matrix for the uncoupled system (12) and

$$Q(\lambda, \varepsilon) = 1 - f'(1) + 6\varepsilon + 12\varepsilon^2 + 8\varepsilon^3 + 3(1 + 4\varepsilon + 4\varepsilon^2)\lambda + 3(1 + 2\varepsilon)\lambda^2 + \lambda^3. \tag{27}$$

The application of the Routh-Hurwitz criterion to $Q(\lambda, \varepsilon)$ permits us to conclude that the stability of the equilibrium point for the coupled system (18) depends only on the stability of the equilibrium in the uncoupled one (12), and not on the coupling itself. Hence, from the analysis of $P(\lambda)$ it follows that the equilibrium point is always stable. The explicit calculations can be found in the appendix.

3.1.2. *Oscillating CNF systems*

In order to study the two-elements network when the uncoupled systems are in the oscillatory regime, we exploit the method based on the joint application of the Malkin's theorem and the describing function technique [Gilli *et al.*, 2005]. Such method allows us to derive the dynamical evolution of the phase variables (i.e. the equation that describes the phase variation of each oscillator, due to the weak coupling). The steps of the procedure proposed in [Gilli *et al.*, 2005] for obtaining the phase equations are summarized below:

a) The hyperbolic limit cycle of each uncoupled system is approximated up to the first harmonic term (i.e. describing function approach). If we focus on (20) (with $\varepsilon = 0$) we get:

$$x_3(t) \approx \hat{x}_3(t) = A + B\sin(\omega t) \tag{28}$$

where A denotes the bias, ω and B the angular frequency and the amplitude of the first harmonic, respectively. It follows that the approximated limit cycle is:

$$\gamma_I(t) \approx \hat{\gamma}_I(t) = \begin{pmatrix} \hat{x}_1(t) \\ \hat{x}_2(t) \\ \hat{x}_3(t) \end{pmatrix} = \begin{pmatrix} L_1(D)\,\hat{x}_3(t) \\ L_2(D)\,\hat{x}_3(t) \\ \hat{x}_3(t) \end{pmatrix} = \begin{pmatrix} (D+1)^2\hat{x}_3(t) \\ (D+1)\hat{x}_3(t) \\ \hat{x}_3(t) \end{pmatrix} \tag{29}$$

where

$$\begin{aligned} \hat{x}_1(t) &= (D+1)^2\hat{x}_3(t) = (D+1)^2[A + B\sin(\omega t)] = A + B(1-\omega^2)\sin(\omega t) + 2B\omega\cos(\omega t) \\ \hat{x}_2(t) &= (D+1)\hat{x}_3(t) = (D+1)[A + B\sin(\omega t)] = A + B\sin(\omega t) + B\omega\cos(\omega t), \end{aligned}$$

having reminded that $D = d/dt$ is the time-derivative operator.
It is worth noting that since the oscillators are assumed to be identical, the limit cycle trajectory $\hat{\gamma}_{II}$ of the system (21) (with $\varepsilon = 0$) is also identical.
The parameters A, B and ω are the solution of the following describing function system:

$$\begin{aligned} L(0)A &= F^A(A; B) \\ \mathrm{Re}\,[L(j\omega)]B &= F^B(A; B) \\ \mathrm{Im}\,[L(j\omega)] &= 0, \end{aligned} \tag{30}$$

where the output of the nonlinear function $f\,[x_3(t)]$ is approximated up to the first harmonic as well, as follows:

$$f[\hat{x}_3(t)] \approx F^A(A; B) + F^B(A; B)\sin(\omega t).$$

In particular, from the expression of $L(D)$ in (22) we easily deduce

$$L(j\omega) = (j\omega + 1)^3 = 1 - 3\omega^2 + j\omega(3 - \omega^2)$$

and from the last condition of (30) we obtain

$$\mathrm{Im}\,[L(j\omega)] = \omega(3-\omega^2) = 0.$$

It follows that the approximated angular frequency of the limit cycles $\hat{\gamma}_I$ and $\hat{\gamma}_{II}$ is

$$\omega = \sqrt{3}. \tag{31}$$

b) According to [Hoppensteadt & Izhikevich, 1997], the phase equation can be derived by solving the adjoint problem related to (12). Let us denote with $Q(t) = (q_1(t), q_2(t), q_3(t))^T$ the solution of the adjoint problem

$$\dot{Q}(t) = -[DF(\gamma(t))]^T Q(t) \tag{32}$$

$$Q^T(0)F(\gamma(0)) = 1. \tag{33}$$

The idea of [Gilli *et al.*, 2005] is to approximate this quantity up to the first harmonic as well, via the describing function approximation.
In order to determine $Q(t)$ the Jacobian matrix $DF(\gamma(t))$ needs to be evaluated. From (12) it is easy to see that

$$DF(\gamma(t)) = \begin{pmatrix} -1 & 0 & f'[x_3(t)] \\ 1 & -1 & 0 \\ 0 & 1 & -1 \end{pmatrix}. \tag{34}$$

Exploiting the expression of the operator $L(D)$ and (34), after some algebraic manipulations, it is possible to see that the following Lur'e variational equation holds for $q_1(t)$:

$$L(-D)q_1(t) = f'[x_3(t)]q_1(t), \tag{35}$$

while for the other variables the following linear relationships hold:

$$\begin{aligned} q_2(t) &= (1-D)q_1(t) \\ q_3(t) &= (1-D)^2 q_1(t). \end{aligned} \tag{36}$$

The results obtained in [Gilli *et al.*, 2005] permit us to conclude that the first harmonic approximation for $q_1(t)$ presents only the term in cosine: $q_1(t) \approx \hat{q}_1(t) = \delta_1 \cos(\omega t)$.
Furthermore, from (36), for the other variables we get the following approximated expression

$$\begin{aligned} q_2(t) &\approx \hat{q}_2(t) = \delta_1 \omega \sin(\omega t) + \delta_1 \cos(\omega t) \\ q_3(t) &\approx \hat{q}_3(t) = 2\delta_1 \omega \sin(\omega t) + \delta_1(1-\omega^2)\cos(\omega t). \end{aligned}$$

The coefficient δ_1 is derived using the normalization condition in (33). Taking into account the first harmonic approximations for the functions $x_i(t)$ and $q_i(t)$ achieved before, it yields

$$\begin{aligned} \hat{Q}^T(0)F(\hat{\gamma}(0)) &= (\hat{q}_1(0), \hat{q}_2(0), \hat{q}_3(0)) \begin{pmatrix} -\hat{x}_1(0) + \hat{f}[\hat{x}_3(0)] \\ -\hat{x}_2(0) + \hat{x}_1(0) \\ -\hat{x}_3(0) + \hat{x}_2(0) \end{pmatrix} \\ &= (\delta_1, \delta_1, \delta_1(1-\omega^2))(-A - 2B\omega + F_A, B\omega, B\omega)^T \\ &= -\delta_1 \omega^3 B = 1; \end{aligned}$$

therefore, we obtain

$$\delta_1 = -\frac{1}{B\omega^3}, \tag{37}$$

having exploited from the describing function technique that $L(0)A = F_A$ and $L(0) = 1$.

c) Finally, an approximated analytical expression of the phase equations is obtained (see [Hoppensteadt & Izhikevich, 1997; Gilli *et al.*, 2005] for more details):

$$\begin{aligned}
\phi_I' &\approx \frac{\omega}{2\pi}\int_0^{\frac{2\pi}{\omega}} Q(t)^T G\left(\gamma\left(t+\frac{\phi-\phi_I}{\omega}\right)\right)\,dt \\
&= \frac{\omega}{2\pi}\int_0^{\frac{2\pi}{\omega}} \sum_{i=1}^{3}\hat{q}_i(t)\left[\hat{y}_i\left(t+\frac{\phi_{II}-\phi_I}{\omega}\right)-\hat{x}_i\left(t\right)\right]dt \\
&= \frac{3}{2}\delta_1(1-\omega^2)B\sin(\phi_{II}-\phi_I)+3\delta_1\omega B(\cos(\phi_{II}-\phi_I)-1) \qquad (38)\\
\phi_{II}' &\approx \frac{\omega}{2\pi}\int_0^{\frac{2\pi}{\omega}} Q(t)^T G\left(\gamma\left(t+\frac{\phi-\phi_{II}}{\omega}\right)\right)\,dt \\
&= \frac{\omega}{2\pi}\int_0^{\frac{2\pi}{\omega}} \sum_{i=1}^{3}\hat{q}_i(t)\left[\hat{x}_i\left(t+\frac{\phi_I-\phi_{II}}{\omega}\right)-\hat{y}_i\left(t\right)\right]dt \\
&= \frac{3}{2}\delta_1(1-\omega^2)B\sin(\phi_I-\phi_{II})+3\delta_1\omega B(\cos(\phi_I-\phi_{II})-1). \qquad (39)
\end{aligned}$$

Introducing the phase shift between the two oscillators as a new variable $\chi = \phi_I - \phi_{II}$, system (38)-(39) can be easily recast as follows:

$$\chi' = -3\delta_1(1-\omega^2)B\sin\chi. \qquad (40)$$

It is worth observing that this equation admits as equilibrium configurations only $\chi = \phi_I - \phi_{II} = \{0, \pi\}$. Therefore, the two oscillators can oscillate only in-phase or anti-phase. Furthermore, being $\omega^2 = 3$ and $\delta_1 < 0$, we can conclude that $\chi = 0$ is the unique stable steady state for these phase equations.

3.1.3. *Interaction between one oscillating CNF system and a non-oscillating one*

Let us consider the case in which the two CNF systems start from initial conditions belonging to different basins of attraction (namely, (20) converges toward a limit cycle while (21) converges toward an equilibrium point). Under the assumption that the coupling is sufficiently weak, it is possible to observe that (21) develops new oscillations, with equal period but very different amplitude with respect to the limit cycle of the other system.

For studying such case it is not possible to apply the method exploited in the previous subsection because the Malkin's theorem holds only if *all* the uncoupled systems are oscillating with commensurable frequencies. The global dynamical behavior of the two-compartments network (20)-(21) can be approximately investigated by applying the describing function technique.

The states of the two CNF systems are represented through a bias term and a single harmonic with a suitable phase:

$$\begin{aligned}
x_3(t) &\approx \hat{x}_3(t) = A_1 + B_1\sin(\omega t) \\
y_3(t) &\approx \hat{y}_3(t) = A_2 + B_2\sin(\omega t+\psi) \qquad (41)
\end{aligned}$$

where A_i are the bias terms, ω is the angular frequency, B_i are the amplitudes of the harmonic terms, and ψ denotes the phase shift between $x_3(t)$ and $y_3(t)$.

The output of the nonlinear function can be represented by a Fourier series truncated to the first harmonic as well:

$$\begin{aligned}
f[x_3(t)] &\approx F_1^A(A_1;B_1) + F_1^B(A_1;B_1)\sin(\omega t) \\
f[y_3(t)] &\approx F_2^A(A_2;B_2) + F_2^B(A_2;B_2)\sin(\omega t+\psi). \qquad (42)
\end{aligned}$$

By substituting the approximated expressions (41) and (42) in (20)-(21), and equating the terms of the same harmonic order we get the following set of nonlinear algebraic equations:

$$L(0)A_1 = F_1^A(A_1; B_1) + H(0)(A_2 - A_1) \tag{43}$$
$$\mathrm{Re}\,[L(j\omega)]B_1 = F_1^B(A_1; B_1) + \mathrm{Re}\,[H(j\omega)]B_2\cos\psi - \mathrm{Im}\,[H(j\omega)]B_2\sin\psi - \mathrm{Re}\,[H(j\omega)]B_1 \tag{44}$$
$$\mathrm{Im}\,[L(j\omega)]B_1 = \mathrm{Im}\,[H(j\omega)]B_2\cos\psi + \mathrm{Re}\,[H(j\omega)]B_2\sin\psi - \mathrm{Im}\,[H(j\omega)]B_1 \tag{45}$$
$$L(0)A_2 = F_2^A(A_2; B_2) + H(0)(A_1 - A_2) \tag{46}$$
$$\mathrm{Re}\,[L(j\omega)]B_2 = F_2^B(A_2; B_2) + \mathrm{Re}\,[H(j\omega)]B_1\cos\psi + \mathrm{Im}\,[H(j\omega)]B_1\sin\psi - \mathrm{Re}\,[H(j\omega)]B_2 \tag{47}$$
$$\mathrm{Im}\,[L(j\omega)]B_2 = \mathrm{Im}\,[H(j\omega)]B_1\cos\psi - \mathrm{Re}\,[H(j\omega)]B_1\sin\psi - \mathrm{Im}\,[H(j\omega)]B_2. \tag{48}$$

It is worth noting from (23) that for weak coupling ($\varepsilon << 1$) it yields

$$H(0) = \varepsilon(3(1+\varepsilon)^2 + \varepsilon^2) \sim 3\varepsilon \tag{49}$$
$$\mathrm{Re}\,[H(j\omega)] = \varepsilon(3(1+\varepsilon^2) + \varepsilon^2 - 3\omega^2) \sim 3\varepsilon(1-\omega^2) \tag{50}$$
$$\mathrm{Im}\,[H(j\omega)] = 6\varepsilon(1+\varepsilon)\omega \sim 6\varepsilon\omega. \tag{51}$$

Under the assumption that $\varepsilon = 10^{-4}$ [Jovanic *et al.*, 2008], it is reasonable to assume $B_2 \approx \varepsilon$ and $B_1 \approx \bar{B}_1$, where $\bar{B}_1$ denotes the amplitude of the limit cycle of the uncoupled system obtained by solving (30). As a consequence, by substituting (50)-(51) in (45) and neglecting the terms of order higher than ε, we obtain $\omega(3-\omega^2)\bar{B}_1 \approx -6\varepsilon\omega\bar{B}_1$, i.e., the approximated frequency of the limit cycle is: $\omega \approx \sqrt{3+6\varepsilon}$. The same procedure provides the phase shift ψ from equation (48)

$$\tan\psi \approx \frac{2\omega}{1-\omega^2} = -\sqrt{3}\frac{\sqrt{1+2\varepsilon}}{1+3\varepsilon}. \tag{52}$$

Notice that the remaining unknowns $A_1 = A_1(\varepsilon)$ and $A_2 = A_2(\varepsilon)$ can be found simply solving equations (43) and (46).

Table 1 shows that the numerical solution of the algebraic nonlinear system (43)-(48) and the solution under the assumption $B_2 \approx \varepsilon$ and $B_1 \approx \bar{B}_1$ are very close. In addition, it is worth observing that the two systems oscillate out-of-phase, i.e. ψ is not 0 or π. Similar results hold by increasing ε up to a critical value after which the two systems oscillate in-phase, i.e. the two-compartment network converges toward the global oscillation described in the previous subsection.

Hypothesis $B_2 \approx \varepsilon$ and $B_1 \approx \overline{B_1}$	Solution of (43)-(48)
$A_1 = 1.0901$	$A_1 = 1.0902$
$B_1 = 0.2347$	$B_1 = 0.2344$
$A_2 = 0.9912$	$A_2 = 0.9913$
$B_2 = 10^{-4}$	$B_2 = 9.67 \cdot 10^{-5}$
$\omega = 1.7322$	$\omega = 1.7322$
$\psi = -1.0471$	$\psi = -1.0476$

3.2. *Arrays with a large number of 3^{th}-order CNF systems*

The methodology proposed in the previous subsection is not suitable for analyzing the dynamics in arrays with a large number of CNF systems, because it would require to exploit a DF representation like (41) for each state variable x_n^i defined in (8). By focusing on one-dimensional arrays composed of 3^{th}-order M CNF systems, we have to investigate the following Lur'e equation:

$$\mathbf{M}^3\mathbf{X} = \mathbf{f}(\mathbf{X}), \tag{53}$$

where, with respect to expression (16), we have dropped the subscripts for simplicity of notation. The assumption of weak couplings allows us to write the solution of (53) as

$$\mathbf{X} = \overline{\mathbf{X}} + \varepsilon\tilde{\mathbf{X}}, \tag{54}$$

where $\overline{\mathbf{X}}$ is a stable attractor (either equilibrium point or limit cycle) of the uncoupled system ($\varepsilon = 0$). Furthermore, in order to emphasize the contributions of the couplings, we can represent (17) as $\mathbf{M}^3 = L(D)\mathbf{I} + \varepsilon\tilde{\mathbf{M}}(D)$, as well. Therefore, equation (53) becomes:

$$(L(D)\mathbf{I} + \varepsilon\tilde{\mathbf{M}}(D))(\overline{\mathbf{X}} + \varepsilon\tilde{\mathbf{X}}) = \mathbf{f}(\overline{\mathbf{X}} + \varepsilon\tilde{\mathbf{X}}), \tag{55}$$

with

$$\tilde{\mathbf{M}}(D) = -3(D+1)^2\mathbf{P} + 3(D+1)\varepsilon\mathbf{P}^2 - \varepsilon^2\mathbf{P}^3. \tag{56}$$

Linearizing $\mathbf{f}(\cdot)$ in a neighborhood of $\overline{\mathbf{X}} = [\overline{x}_1, \ldots, \overline{x}_M]^T$ and neglecting the terms of order greater than ε, we obtain the following set of variational equations in the unknowns $\tilde{\mathbf{X}} = [\tilde{x}_1, \ldots, \tilde{x}_M]^T$:

$$L(D)\tilde{x}_i - f'(\overline{x}_i)\tilde{x}_i = -(\tilde{\mathbf{M}}(D)\overline{\mathbf{X}})_i \;\; i = 1, \ldots, M, \tag{57}$$

where

$$(\tilde{\mathbf{M}}(D)\overline{\mathbf{X}})_i = \sum_{k \in N_i} \tilde{M}_{i,k}(D)\overline{x}_k,$$

where with $N_i = \{\max(1, i-3), \ldots, \min(i+3, M)\}$ we denote the sphere of influence of system i. Notice that N_i is composed of at most seven systems, since Lemma 1 implies that $\tilde{\mathbf{M}}$ is at most eptadiagonal.

Depending on the choice of the initial conditions for each subsystem (i.e. in the basin of attraction of the equilibrium point or in the limit cycle one), different complex dynamics can arise. For example, it is known that a CNF system near the equilibrium point, if sufficiently close to a system that oscillates, is able to develop a small amplitude limit cycle. On the other hand, if a system starts from the same basin of attraction of the neighbors of its sphere of influence, then it will not change its dynamics (except for an initial phase shift when they are all oscillating, due to the different choice of the initial conditions for each system). This behavior can be explicitly derived exploiting a spectral approach, as follows.

By exploiting the describing function technique [Mees, 1981], each variable of $\overline{\mathbf{X}}$, solution to (53) when $\varepsilon = 0$, can be represented up to the first harmonic as

$$\overline{x}_i = \sum_{r=-1}^{1} Q_i^{(r)} \mathrm{e}^{jr\omega_i t}. \tag{58}$$

More specifically, since for each compartment ($i = 1, \ldots, M$) we have a coexistence of two attractors (namely, the equilibrium point and the limit cycle), then ω_i is equal either to zero or to $\overline{\omega}$, being $\overline{\omega}$ the angular frequency of the periodic solution. Consequently,

$$f'(\overline{x}_i) = \sum_{r=-1}^{1} S_i^{(r)} \mathrm{e}^{jr\omega_i t}. \tag{59}$$

Since the right-hand side of equation (57) can be viewed as an external forcing term, the perturbation $\tilde{x}_i$ will assume the form

$$\tilde{x}_i = \sum_{r=-1}^{1} R_i^{(r)} \mathrm{e}^{jr\omega_p t} \tag{60}$$

with $\omega_p = \overline{\omega}$ if at least one of its neighbors or itself is chosen in the basin of attraction of the limit cycle, $\omega_p = 0$ otherwise.

Proposition 2. *Let us consider an array of M diffusively coupled CNF systems. Thus, for each system i, with $1 \leq i \leq M$, we have the following results:*

(i) if all the systems in its neighborhood (i.e., all $k \in N_i$) are sufficiently close to the same attractor (namely, either equilibrium point or limit cycle) before the coupling, then $\tilde{x}_i \equiv 0$;

(ii) otherwise, if at least one of its neighbors or itself is on a different attractor, then $\tilde{x}_i \neq 0$.

Proof. It is easy to notice that when $\omega_p = 0$, i.e. when all the systems in the neighborhood are on the equilibrium point, then equation (57) simply becomes:

$$L(0)R_i^{(0)} - S_i^{(0)}R_i^{(0)} = -\sum_{k\in N_i} \tilde{M}_{i,k}(0)Q_k^{(0)}, \tag{61}$$

with $Q_k^{(0)} = \bar{x}_k(0) = 1 \; \forall\, k \in N_i$ and $\tilde{M}_{i,k}(0) = -3L_1(0)P_{ik} + 3\varepsilon L_2(0)P_{ik}^2 - \varepsilon^2 P_{ik}^3$; therefore, we get

$$R_i^{(0)} = -\frac{1}{L(0) - S_i^{(0)}} \sum_{k\in N_i} \tilde{M}_{i,k}(0). \tag{62}$$

Since the sum of entries of any row of matrices $\mathbf{P}$, $\mathbf{P}^2$ and $\mathbf{P}^3$ is zero, from (62) we obtain $R_i^{(0)} = 0$, that is $x_i(t) = \bar{x}_i(t) = 1$. This means that the system does not change its dynamics due to the coupling.

On the other hand, when $\omega_p = \overline{\omega}$, following the notation exploited in [Corinto *et al.*, 2008], equation (57) can be recast in the following form:

$$\mathbf{1}^T L(D)\mathbf{E}(t)\mathbf{R}_i - \overline{\mathbf{1}}^T\overline{\mathbf{E}}(t)\mathbf{S}_i * \mathbf{R}_i = -\mathbf{1}^T \sum_{k\in N_i:\omega_k=\overline{\omega}} \tilde{M}_{i,k}(D)\mathbf{E}(t)\mathbf{Q}_k - \sum_{k\in N_i:\omega_k=0} \tilde{M}_{i,k}(0)Q_k^{(0)}, \tag{63}$$

where

$$\begin{aligned}
\mathbf{1} &= [1,1,1]^T \\
\overline{\mathbf{1}} &= [1,1,1,1,1]^T \\
\mathbf{Q}_i &= [Q_i^{(-1)}, Q_i^{(0)}, Q_i^{(1)}]^T \in \boldsymbol{C}^3 \\
\mathbf{R}_i &= [R_i^{(-1)}, R_i^{(0)}, R_i^{(1)}]^T \in \boldsymbol{C}^3 \\
\mathbf{S}_i &= [S_i^{(-1)}, S_i^{(0)}, S_i^{(1)}]^T \in \boldsymbol{C}^3 \\
\mathbf{E}(t) &= \mathrm{diag}[\mathrm{e}^{-j\overline{\omega}t}, 1, \mathrm{e}^{j\overline{\omega}t}] \in \boldsymbol{C}^{3,3} \\
\overline{\mathbf{E}}(t) &= \mathrm{diag}[\mathrm{e}^{-2j\overline{\omega}t}, \mathrm{e}^{-j\overline{\omega}t}, 1, \mathrm{e}^{j\overline{\omega}t}, \mathrm{e}^{2j\overline{\omega}t}] \in \boldsymbol{C}^{5,5}
\end{aligned}$$

and $\mathbf{S}_i * \mathbf{R}_i \in \boldsymbol{C}^5$ is the convolution of $\mathbf{S}_i$ and $\mathbf{R}_i$. Since the harmonics with order higher than one are not taken into account, such convolution product can be approximated in terms of the Hermitian Toeplitz matrix:

$$\mathbf{T}_i = \begin{pmatrix} S_i^{(0)} & S_i^{(-1)} & 0 \\ S_i^{(1)} & S_i^{(0)} & S_i^{(-1)} \\ 0 & S_i^{(1)} & S_i^{(0)} \end{pmatrix},$$

where $\mathbf{T}_i = \mathbf{T}_i^\dagger$ with $\mathbf{T}_i^\dagger$ the conjugate transpose matrix. As a consequence we obtain

$$f'(\overline{x}_i)\tilde{x}_i = \overline{\mathbf{1}}^T\overline{\mathbf{E}}(t)\mathbf{S}_i * \mathbf{R}_i \cong \mathbf{1}^T\mathbf{E}(t)\mathbf{T}_i^\dagger\mathbf{R}_i.$$

It is worth noting that the expression of matrix $\mathbf{T}_i$ depends on the different attractor where the i-th uncoupled system is. For instance, if it is on the equilibrium point, then $\mathbf{T}_i$ reduces to a diagonal matrix, since $S_i^{(-1)} = S_i^{(1)} = 0$.

Finally, recalling that a linear operator $G(D)$ applied to $\mathbf{E}(t)$ yields the following matrix

$$G(D)\mathbf{E}(t) = \boldsymbol{\Omega}(\overline{\omega})\mathbf{E}(t) = \mathbf{E}(t)\boldsymbol{\Omega}(\overline{\omega})$$

with $\boldsymbol{\Omega}(\overline{\omega}) = \mathrm{diag}[G(-j\overline{\omega}), G(0), G(j\overline{\omega})] \in \boldsymbol{C}^{3,3}$, equation (63) becomes

$$\mathbf{1}^T\boldsymbol{\Omega}^{(L)}(\overline{\omega})\mathbf{E}(t)\mathbf{R}_i - \mathbf{1}^T\mathbf{E}(t)\mathbf{T}_i^\dagger\mathbf{R}_i = -\mathbf{1}^T \sum_{k\in N_i:\omega_k=\overline{\omega}} \boldsymbol{\Omega}_{i,k}^{(M)}(\overline{\omega})\mathbf{E}(t)\mathbf{Q}_k - \sum_{k\in N_i:\omega_k=0} \tilde{M}_{i,k}(0)Q_k^{(0)}, \tag{64}$$

where $\mathbf{\Omega}^{(L)}(\overline{\omega}) = \mathrm{diag}[L(-j\overline{\omega}), L(0), L(j\overline{\omega})]$ and $\mathbf{\Omega}^{(M)}_{i,k}(\overline{\omega}) = \mathrm{diag}[\tilde{M}_{i,k}(-j\overline{\omega}), \tilde{M}_{i,k}(0), \tilde{M}_{i,k}(j\overline{\omega})]$. Exploiting the property that $\mathbf{Q}_k = [0, Q_k^{(0)}, 0]^T$ for k such that $\omega_k = 0$, and regarding that the determinant of the matrix $\mathbf{\Omega}^{(L)}(\overline{\omega}) - \mathbf{T}_i^{\dagger}$ is not zero, the set of algebraic equations (64) in the unknown $\mathbf{R}_i$ can be readily solved:

$$\mathbf{R}_i = -(\mathbf{\Omega}^{(L)}(\overline{\omega}) - \mathbf{T}_i^{\dagger})^{-1} \sum_{k \in N_i} \mathbf{\Omega}^{(M)}_{i,k}(\overline{\omega}) \mathbf{Q}_k \qquad i = 1, \ldots, M. \tag{65}$$

If we assume that $\mathbf{Q}_k = \mathbf{Q}$ for all $k \in N_i$, that is if we suppose that all the systems in the sphere of influence of the i-th one are on the limit cycle, then

$$\begin{aligned} \sum_{k \in N_i} \mathbf{\Omega}^{(M)}_{i,k}(\overline{\omega}) \mathbf{Q}_k &= \left(\sum_{k \in N_i} \mathbf{\Omega}^{(M)}_{i,k}(\overline{\omega}) \right) \mathbf{Q} \\ &= \left[-3\mathbf{\Omega}^{(L_1)}(\overline{\omega}) \sum_{k \in N_i} P_{ik} + 3\mathbf{\Omega}^{(L_2)}(\overline{\omega}) \varepsilon \sum_{k \in N_i} P_{ik}^2 - \varepsilon^2 \sum_{k \in N_i} P_{ik}^3 \right] \mathbf{Q}, \end{aligned} \tag{66}$$

where $\mathbf{\Omega}^{(L_1)}(\overline{\omega}) = \mathrm{diag}[L_1(-j\overline{\omega}), L_1(0), L_1(j\overline{\omega})]$ and $\mathbf{\Omega}^{(L_2)}(\overline{\omega}) = \mathrm{diag}[L_2(-j\overline{\omega}), L_2(0), L_2(j\overline{\omega})]$. Again, recalling the properties of matrix $\mathbf{P}$, we can conclude that $\mathbf{R}_i = 0$, that is $x_i(t) \equiv \bar{x}_i(t)$. Thus, in this case, the coupling does not produce evident changes in the dynamics of system i. On the other hand, if there exists at least one $\mathbf{Q}_k$ ($k \in N_i$) different from the others, then $\mathbf{R}_i \neq 0$ and we will get a contribution from the dynamics of the neighbors. ■

By exploiting this technique, it is possible to investigate the complex dynamical behaviors that take place in an array of CNF systems. In fact, once set the basin of attraction of each subsystem, by solving (65) for every $i = 1, \ldots, M$, we are able to detect all the small amplitude limit cycles that might arise. Furthermore, we can determine the order (in terms of ε) of the perturbations due to the coupling.

It is worth noting that in an array of M diffusively coupled CNF systems the number of possible choices of the basin of attraction for the initial conditions of each system is $\mathcal{M} = 2^M$. However, this number can be reduced due to the symmetry properties of the coupling. It is possible to prove [Gilli *et al.*, 2004] that the maximum number of independent choices is

$$\mathcal{M} = \begin{cases} 2^{M/2} + \dfrac{2^M - 2^{M/2}}{2} & \text{if } M \text{ is even} \\ \dfrac{2^{(M+1)/2}}{2} + \dfrac{2^M - 2^{(M+1)/2}}{2} & \text{if } M \text{ is odd.} \end{cases}$$

Among these, two cases are trivial. If all the CNF systems in the array are in the equilibrium point, then they will not change their dynamics, since this configuration is stable for the global system (as we have seen in Section 3.1). Furthermore, if all the CNF systems are in the basin of attraction of the limit cycle, exploiting the Malkin's theorem we are able to derive the phase equation for the entire system. In all the other conditions, the brute application of the describing function technique to the entire array is numerically too onerous, but the approach we have proposed before gives good results.

From all the possible $\mathcal{M}$ choices for the initial conditions, let us suppose that all the subsystems are in the equilibrium point, before the coupling, except the central one that is oscillating. This is an interesting case since it leads to remarkable spatio-temporal patterns. As we have seen above, we expect that the subsystems in the neighborhood of the central one will develop a small amplitude limit cycle. Moreover, the amplitude of this new oscillation will depend on the distance from the active system. Once we apply the describing function technique to the uncoupled system, it is straight forward to calculate the vectors $\mathbf{R}_i$ exploiting (65), and therefore to obtain an expression for (54). In Figure 3 the amplitudes of the different elements in an array of $M = 11$ third order CNF systems of the form (12) are represented. The elements that are close to the central one that is oscillating develop small-amplitude limit cycles. In Figure 4 it is

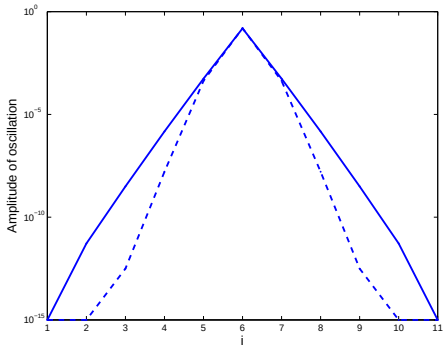

Fig. 3. *Amplitudes of each of the 11 nodes in the array, from the simulations in the time-domain (solid line) and the approximations exploiting* (65) *(dashed line). The coupling here is chosen as* $\varepsilon = 10^{-4}$.

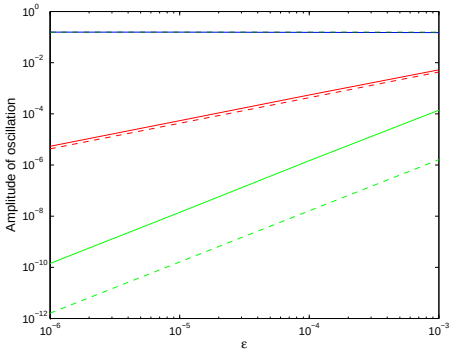

Fig. 4. *Amplitudes for the oscillating central node and the two nearest-neighbors on its left side at different values of the coupling strength* ε *(simulations in the time-domain in solid line, approximations exploiting* (65) *in dashed line).*

possible to observe the amplitude value as function of the coupling parameter ε for the oscillating element, and for the two nearest-neighbors on its left side. The different order of magnitude between the time-domain simulations and the solutions of (65) is mainly due to the describing function approximation. Moreover, the error produced by this approximation up to the first harmonic is propagated along the chain because of the action of the operator $\tilde{M}(D)$. Better results might be obtained with an harmonic balance approach. Nevertheless, the qualitative behavior of the decreasing amplitudes has been adeguately detected.

It is interesting to observe that the configuration in Figure 3 has an analogy with the discrete breathers observed in many reaction-diffusion systems [Flach & Gorbach, 2008]. In fact, as in that type of patterns, we recognize time-periodic spatial-localized solutions, with oscillations that show a rapid spatial decay of the amplitudes along the chain.

Formally, a discrete breather solution in a finite chain of M-systems can be represented in Fourier series as [Flach & Gorbach, 2008]

$$X_l(t) = \sum_k A_{kl} \mathrm{e}^{jk\Omega_b t} \qquad \forall\ l \in [0, M] \tag{67}$$

with the property $A_{k,l\to 0} = A_{k,l\to M} \to 0$, since the oscillation is localized in space. By evaluating the coefficients $\mathbf{R}_i$ in (65), it is possible to prove that this precisely holds for the stationary solution of the configuration we are considering. Let us suppose to denote with the index $c = (M+1)/2$ the central vertex of the array that is in the oscillatory regime with angular frequency equal to $\overline{\omega}$, and let us represent our solution $x_i(t)$ as

$$x_i(t) = \sum_{r=-1}^{1} V_i^{(r)} \mathrm{e}^{jr\overline{\omega}t}. \tag{68}$$

Exploiting (54), (58) and (60), it follows that $V_i^{(r)} = Q_i^{(r)} + \varepsilon R_i^{(r)}\ \forall r \in \{-1, 0, 1\}$. Furthermore, let us introduce the correspondent vector $\mathbf{V}_i = [V_i^{(-1)}, V_i^{(0)}, V_i^{(1)}]^T \in \boldsymbol{C}^3$.

Thus, we will have $Q_k^{(-1)} = Q_k^{(1)} = 0$ and $Q_k^{(0)} = 1$, for all $k \neq c$. It is easy to show that in this case $V_{c\pm1}^{(\pm1)} \sim \varepsilon$, $V_{c\pm2}^{(\pm1)} \sim \varepsilon^2$, $V_{c\pm3}^{(\pm1)} \sim \varepsilon^3$, while from Proposition 2 we have that $V_{c\pm l}^{(\pm1)} \equiv 0$ for $l > 3$. As example, let us evaluate in details $\mathbf{R}_{c+3}$, and therefore the order of magnitude (in term of ε) of $\mathbf{V}_{c+3}$. Exploiting (5) and (56), we get:

$$\begin{aligned}
\mathbf{R}_{c+3} &= (\boldsymbol{\Omega}^L(\overline{\omega}) - \mathbf{T}_c^{\dagger})^{-1} \sum_{k=c}^{c+6} \begin{pmatrix} \tilde{M}_{c+3,k}(-j\bar{\omega}) Q_k^{(-1)} \\ \tilde{M}_{c+3,k}(0) Q_k^{(0)} \\ \tilde{M}_{c+3,k}(j\bar{\omega}) Q_k^{(1)} \end{pmatrix} \\
&= (\boldsymbol{\Omega}^L(\overline{\omega}) - \mathbf{T}_c^{\dagger})^{-1} \begin{pmatrix} \tilde{M}_{c+3,c}(-j\bar{\omega}) Q_c^{(-1)} \\ \sum_{c+1}^{c+6} \tilde{M}_{c+3,k}(0) + \tilde{M}_{c+3,c}(0) Q_c^{(0)} \\ \tilde{M}_{c+3,c}(j\bar{\omega}) Q_c^{(1)} \end{pmatrix} \\
&= (\boldsymbol{\Omega}^L(\overline{\omega}) - \mathbf{T}_c^{\dagger})^{-1} \begin{pmatrix} -\varepsilon^2 Q_c^{(-1)} \\ \varepsilon^2 - \varepsilon^2 Q_c^{(0)} \\ -\varepsilon^2 Q_c^{(1)}. \end{pmatrix}
\end{aligned}$$

Thus, from (54) we conclude that $V_{c+3}^{(\pm1)} \sim \varepsilon^3$.

4. Conclusion

We have considered arrays composed of diffusively coupled Cyclic Negative Feedback systems. Under the suitable conditions each uncoupled system exhibits the coexistence of different stable states, namely equilibrium points and periodic orbits. We have investigated the effect of coupling on the global dynamics. In particular, under the assumption of weak coupling we have derived the global dynamical properties from the single system's attractors.

First of all, we have shown that CNF arrays with diffusive couplings that are constant and local (i.e. they involve only the two nearest neighbors of each CNF system) are potentially equivalent to nonlinear networks whose elements are fully connected (i.e. each system is linked to all the others). Secondly, we have considered the simplest CNF array composed of two subystems. We have shown that if both systems are in the steady state before coupling, then this configuration remains stable for any value of coupling. On the other hand, if the two systems are both in the same oscillatory state and the coupling is sufficiently weak, then they remain in the basin of attraction of the oscillatory state. Instead, if the two uncoupled CNF systems are in two different attractors (i.e. system I is in an oscillatory regime while system II in the stable equilibrium point), under the assumption of weak coupling, system I remains oscillatory while system II develops a small amplitude limit cycle. In order to detect the two different limit cycles of system I and II, a describing function technique approach for the global system has been proposed.

Finally, a methodology based on the perturbation of the solution given by the describing function technique has been developed to investigate the global dynamical behavior in CNF arrays with a large number of systems.

The proposed analysis can be extremely useful to interpret biological phenomena in bio-inspired networks composed of a large number of CNF elements.

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Appendix. Application of the Routh-Hurwitz criterion for two non-oscillating CNF systems

Let us consider two coupled third order CNF systems as in (18). In order to study the stability of the configuration where both the CNF systems are on the equilibrium point $P = (1, 1, 1)$, we have to analyze the characteristic polynomial of the Jacobian matrix, whose expression can be found in (25).

Let us write the polynomial $Q(\lambda, \varepsilon)$ in (27) in the following way:

$$Q(\lambda, \varepsilon) = \lambda^3 + c_1\lambda^2 + c_2\lambda + c_3$$

where $c_1 = 3(1 + 2\varepsilon), c_2 = 3(1 + 4\varepsilon + 4\varepsilon^2)$ and $c_3 = 8\varepsilon^3 + 12\varepsilon^2 + 6\varepsilon - f'(1) + 1$.
The application of the Routh-Hurwitz criterion [Gradshteyn *et al.*, 2000] to polynomial $Q(\lambda, \varepsilon)$ leads to:

$$\begin{aligned}
\Delta_1 &= c_1 = 3(1 + 2\varepsilon) > 0 \\
\Delta_2 &= \begin{vmatrix} c_1 & 1 \\ c_3 & c_2 \end{vmatrix} = 64\varepsilon^3 + 96\varepsilon^2 + 48\varepsilon + 8 + f'(1) \\
\Delta_3 &= \begin{vmatrix} c_1 & 1 & 0 \\ c_3 & c_2 & c_1 \\ 0 & 0 & c_3 \end{vmatrix} = c_3\Delta_2.
\end{aligned}$$

Since $f'(1) = -7.5$, we have $\Delta_2 > 0$ and $\Delta_3 > 0$. It is worth noting that this result is independent of the value of the coupling strength ε although the polynomial coefficients are function of ε. Since all the coefficients Δ_i are strictly positive, we can conclude that the polynomial $Q(\lambda, \varepsilon)$ has only roots with negative real part.

Exploiting the same criterion to the polynomial $P(\lambda)$, where

$$P(\lambda) = \lambda^3 + c_1\lambda^2 + c_2\lambda + c_3$$

with $c_1 = 3, c_2 = 3$ and $c_3 = -f'(1) + 1$, we get:

$$\begin{aligned}
\Delta_1 &= c_1 = 3 > 0 \\
\Delta_2 &= \begin{vmatrix} c_1 & 1 \\ c_3 & c_2 \end{vmatrix} = \begin{vmatrix} 3 & 1 \\ -f'(1) + 1 & 3 \end{vmatrix} = 8 + f'(1) > 0 \\
\Delta_3 &= c_3\Delta_2 > 0;
\end{aligned}$$

therefore we can conclude that also this polynomial admits only roots with negative real part. Thus, the configuration of two non-oscillating CNF systems is always stable.

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