Instability of equilibrium and convergence to periodic orbits in strongly 2-cooperative systems

Rami Katz^a Giulia Giordano ^a Michael Margaliot ^b

^aDepartment of Industrial Engineering, University of Trento, Italy.

^bSchool of Electrical Engineering, Tel Aviv University, Israel.

Abstract

We consider time-invariant nonlinear n-dimensional strongly 2-cooperative systems, that is, systems that map the set of vectors with up to weak sign variation to its interior. Strongly 2-cooperative systems enjoy a strong Poincaré-Bendixson property: bounded solutions that maintain a positive distance from the set of equilibria converge to a periodic solution. For strongly 2-cooperative systems whose trajectories evolve in a bounded and invariant set that contains a single unstable equilibrium, we provide a simple criterion for the existence of periodic trajectories. Moreover, we explicitly characterize a positive-measure set of initial conditions which yield solutions that asymptotically converge to a periodic trajectory. We demonstrate our theoretical results using two models from systems biology, the n-dimensional Goodwin oscillator and a 4-dimensional biomolecular oscillator with RNA-mediated regulation, and provide numerical simulations that verify the theoretical results.

Key words: Asymptotic analysis, compound matrices, sign variations, cones of rank k, biological oscillators.

1 Introduction

Oscillations, as well as periodic behaviors, rhythms and regular patterns, are among the most widespread behavioral motifs in nature (Goldbeter et al., 2012), but they are still not entirely understood. Biological clocks and oscillators are frequently encountered at various scales. Single-molecule clocks (Johnson-Buck and Shih, 2017) include the segmentation clock (Uriu et al., 2009, 2010), which rules pattern generation in vertebrate embryonic development. The regulation of cell life cycle and metabolism hinges upon biomolecular oscillators (Ferrell et al., 2011). An internal biological clock regulates the physiological processes of living beings on Earth, including plants, animals and humans, according to circadian rhythms (Doyle et al., 2006), i.e. almost daily (circadies) fluctuations that are almost exactly synchronized with the 24-hour rotation period of the

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planet; this biological clock regularly oscillates even when the organism faces constant darkness, or constant light, and is entrained by the alternating daylight and darkness. The circadian clock thus allows living organisms to effectively adapt their physiology to the periodic rhythms of sunlight and darkness, and regulates e.g. hormone secretion, body temperature and metabolic functions. Jeffrey C. Hall, Michael Rosbash and Michael W. Young received the 2017 Nobel Prize in Physiology or Medicine "for their discoveries of molecular mechanisms controlling the circadian rhythm" in fruit flies. Also in synthetic biology, building biomolecular computing systems requires oscillators with a timekeeping function; several design principles and architectures have been proposed so far (Novák and Tyson, 2008; Panghalia and Singh, 2020), but constructing reliable biomolecular oscillators with tunable amplitude and phase is still an open challenge.

Mathematical control theory (Sontag, 1998) offers powerful methodologies to regulate dynamical systems, but the synthesis and analysis of biological oscillators that exhibit periodic behaviors is still a major challenge. This type of questions is significant not only in the life sciences, but also in numerous applications in engineering, including vibrational mechanics (Blekhman, 2000) and power electronics (Schubert and Kim, 2016).

In general, it is important to provide sufficient conditions guaranteeing that a bounded solution of an *n*-dimensional nonlinear system converges to a periodic orbit, thereby allowing for oscillatory behavior of solutions. Determining whether a set of nonlinear ODEs admits a periodic orbit, and if so, what is the set of initial conditions yielding convergence to a periodic orbit is a highly non-trivial problem (Farkas, 1994).

We focus on a specific class of nonlinear dynamical systems that are strongly 2-cooperative. These systems are known to satisfy a strong Poincaré-Bendixson property: if the ω -limit set of a bounded solution contains no equilibrium points, then it is a periodic orbit (Weiss and Margaliot, 2021).

Here, we consider an n-dimensional strongly 2-cooperative system evolving in a convex, invariant and bounded state space Ω , which admits a unique equilibrium $e \in \Omega$, such that the Jacobian of the vector field computed at e admits at least two unstable eigenvalues. Our main result shows that the system admits an explicit set of initial conditions of positive measure, such that every solution emanating from this set converges to a periodic orbit. Our result generalizes recent work on the particular case of 3-dimensional strongly 2-cooperative systems (Katz et al., 2024). The generalization to the n-dimensional case requires several additional tools from the theory of cones of rank k (Sanchez, 2009a), the spectral theory of totally positive matrices (see, e.g. (Fallat and Johnson, 2011; Margaliot and Sontag, 2019)), and a generalization of the Perron-Frobenius theorem to cones of rank k (Fusco and Oliva, 1991).

To demonstrate the usefulness of the theoretical result, we consider two important examples from systems biology: the well-known *n*-dimensional Goodwin system (Goodwin, 1965), and a four-dimensional biomolecular oscillator with RNA-mediated regulation proposed by (Blanchini et al., 2014a). We rigorously analyze the oscillatory behavior of both systems, characterizing a set of initial conditions from which the trajectories converge to a periodic orbit, and we provide numerical simulations that validate our theoretical results.

The remainder of this paper is organized as follows. The next section reviews known definitions and results that are used throughout the paper. Section 3 presents our main result. The proof of

our main result is given in Section 4. Section 5 describes two applications from systems biology. The concluding section elaborates on possible directions for future research.

2 Notations and Preliminary results

Given an integer $n \geq 1$, let $[n] := \{1, \ldots, n\}$. The cardinality of a set S is denoted by $\operatorname{card}(S)$. For a set $S \subseteq \mathbb{R}^n$, we denote by $\operatorname{int}(S)$ and $\operatorname{clos}(S)$ its interior and closure, respectively. For two sets $S_1, S_2 \subseteq \mathbb{R}^n$ and a scalar $c \in \mathbb{R}$, we denote by $S_1 + S_2 = \{s_1 + s_2 \mid s_i \in S_i, i = 1, 2\}$ and $cS_1 = \{cs_1 \mid s_1 \in S_1\}$ the usual set addition and scalar-set multiplication. We denote vectors and matrices by lowercase and uppercase letters, respectively. For $\varepsilon > 0$ and $y \in \mathbb{R}^n$, let $B(y, \varepsilon)$ denotes the open Euclidean ball centered at y with radius ε . The non-negative orthant in \mathbb{R}^n is $\mathbb{R}^n_{\geq 0} := \{x \in \mathbb{R}^n \mid x_i \geq 0, i \in [n]\}$, and the non-positive orthant is $\mathbb{R}^n_{\leq 0} := -\mathbb{R}^n_{\geq 0}$. The transpose, spectrum and determinant of a matrix A are denoted by A^{\top} , spec(A) and $\det(A)$, respectively. I_n is the $n \times n$ identity matrix. Given matrices $A_j \in \mathbb{R}^{n_j \times n_j}$, $j \in [m]$, we denote by $\operatorname{diag}(A_1, \ldots, A_m)$ the block diagonal matrix with diagonal elements A_j . A square matrix A is Hurwitz if all its eigenvalues have a negative real part, unstable if it admits an eigenvalue with a positive real part, and Metzler if all its off-diagonal entries are non-negative.

A matrix \bar{A} is a sign matrix if every entry of \bar{A} is either * ("don't care"), ≤ 0 , 0, or ≥ 0 . A time-varying matrix A(t) has the sign pattern \bar{A} if the following three properties hold at all times $t \geq 0$:

- (1) $a_{ij}(t) \leq 0$ for all indices i, j such that \bar{a}_{ij} is ≤ 0 ,
- (2) $a_{ij}(t) = 0$ for all indices i, j such that \bar{a}_{ij} is 0,
- (3) $a_{ij}(t) \ge 0$ for all indices i, j such that \bar{a}_{ij} is ≥ 0 ,

with no restriction imposed on $a_{ij}(t)$ when \bar{a}_{ij} is *.

2.1 From cooperative to k-cooperative systems

The flow of cooperative systems (Smith, 1995) maps the non-negative orthant $\mathbb{R}^n_{\geq 0}$ to itself, and also the non-positive orthant $\mathbb{R}^n_{\leq 0}$ to itself. In other words, the flow maps the set of vectors whose entries exhibit no sign changes (zero sign variations) to itself. Cooperative systems have many special asymptotic properties: Hirsch's quasi-convergence theorem asserts that in a strongly cooperative system with bounded solutions all initial conditions outside of a zero-measure set give rise to solutions that converge to an equilibrium.

Cooperative systems and cooperative control systems (Angeli and Sontag, 2003), which allow to study interconnections of cooperative systems, have found numerous applications in various fields, including social dynamics (Shi et al., 2019), dynamic neural networks (Smith, 1991), chemistry and systems biology (Angeli et al., 2004; Blanchini and Giordano, 2021; Donnell et al., 2009; Leenheer et al., 2007; Margaliot and Tuller, 2012; Raveh et al., 2016; Sontag, 2007). However, since a strongly cooperative system cannot admit an *attracting* periodic orbit (Smith, 1995), cooperative systems theory is not suitable to support the study of systems that admit periodic solutions.

The theory of k-cooperative systems provides a generalization of cooperative systems (Weiss and Margaliot, 2021). The flow of a k-cooperative system maps the set of vectors with up to k-1 weak sign variations to itself. In particular, 1-cooperative systems are cooperative systems. Also, (n-1)-cooperative systems, where n is the dimension of the system, are, up to a coordinate transformation, compet-

itive systems (Weiss and Margaliot, 2021). The property of k-cooperativity depends on the sign structure (also called sign pattern) of the system Jacobian, and hence it can be assessed without knowing the exact values of various system parameters. Below, we recall the formal definitions of these concepts.

2.2 Sign variations in a vector

Definition 1 Given the vector $x \in \mathbb{R}^n$ with $\prod_{i=1}^n x_i \neq 0$, the number of sign variations in x is denoted by

$$\sigma(x) := \operatorname{card} (\{i \in [n-1] \mid x_i x_{i+1} < 0\}).$$

For example,
$$\sigma\left(\left[2\pi - 3.3\sqrt{2}\right]^{\top}\right) = 2.$$

Two useful generalizations of $\sigma(\cdot)$ to vectors that may contain zero entries are offered by the theory of totally positive matrices (see, e.g., Fallat and Johnson (2011); Gantmacher and Krein (2002); Pinkus (2010)).

Definition 2 Given $x \in \mathbb{R}^n \setminus \{0\}$, let x^d denote the vector obtained from x by deleting all its zero entries. The weak number of sign variations in x is

$$s^-(x) := \sigma(x^d).$$

Let $S_x \subseteq \mathbb{R}^n$ denote the set of all vectors obtained from x by replacing each of its zero entries by either +1 or -1. The strong number of sign variations in x is

$$s^+(x) := \max_{z \in \mathcal{S}_x} \sigma(z).$$

Finally, for $0 \in \mathbb{R}^n$, we set $s^-(0) := 0$ and $s^+(0) := n - 1$.

For example, for $x = [-3 \ 0 \ 0 \ 3 \ 4]^{\top}$, we have $s^{-}(x) = \sigma \left([-3 \ 3 \ 4]^{\top} \right) = 1$, whereas $s^{+}(x) = \sigma \left([-3 \ 1 \ -1 \ 3 \ 4]^{\top} \right) = 3$.

By defintion,

$$0 < s^{-}(x) < s^{+}(x) < n-1 \text{ for all } x \in \mathbb{R}^{n}.$$
 (1)

Throughout the paper we will employ the following lower semi-continuity property of s^- .

Lemma 1 (Pinkus, 2010, Lemma 3.2) The function $s^-: \mathbb{R}^n \to \mathbb{R}$ is lower semi-continuous.

The notions of weak and strong (number of) sign variations, respectively s^- and s^+ , yield the following special sets.

Definition 3 Given $k \in [n]$, we define the set $P_-^k := \{x \in \mathbb{R}^n \mid s^-(x) \leq k-1\}$ (respectively, $P_+^k := \{x \in \mathbb{R}^n \mid s^+(x) \leq k-1\}$) of vectors with up to k-1 weak (respectively, strong) sign variations.

For example, for k = 1 we have $P_-^1 = \mathbb{R}^n_{\geq 0} \cup \mathbb{R}^n_{\leq 0}$ and $P_+^1 = \operatorname{int}(\mathbb{R}^n_{\geq 0} \cup \mathbb{R}^n_{\leq 0})$.

We list here several properties of the sets P_{-}^{k} and P_{+}^{k} that hold for any $k \in [n]$; the proofs can be found in Weiss and Margaliot (2021).

- **(P1)** P_-^k is closed, P_+^k is open, and $P_+^k = \operatorname{int}(P_-^k)$.
- **(P2)** If $y \in P_{-}^{k}$, then $\alpha y \in P_{-}^{k}$ for any $\alpha \in \mathbb{R}$; in particular, P_{-}^{k} is a closed cone. If $y \in P_{+}^{k}$, then $\alpha y \in P_{+}^{k}$ for any $\alpha \in \mathbb{R} \setminus \{0\}$.

The set P_-^k is a closed cone, but unlike $\mathbb{R}^n_{\geq 0}$, it is not a convex cone. For example, for n=3, $y^1:=\begin{bmatrix}-5 \ 1 \ 1\end{bmatrix}^\top$, and $y^2:=\begin{bmatrix}1 \ 1 \ -5\end{bmatrix}^\top$, we have $s^-(y^1)=s^-(y^2)=1$, and hence $y^1,y^2\in P_-^2$, but their convex combination $\frac{1}{2}y^1+\frac{1}{2}y^2=\begin{bmatrix}-2 \ 1 \ -2\end{bmatrix}^\top\not\in P_-^2$.

In order to state two more properties of P_-^k , recall that a set $S \subseteq \mathbb{R}^n$ is called a cone of rank k if: (i) S is closed; (ii) $x \in S$ implies that $\alpha x \in S$ for all $\alpha \in \mathbb{R}$; and (iii) S contains a linear subspace of dimension k, and no linear subspace of dimension larger than k. A cone of rank k is called k-solid if there exists a linear subspace V of dimension k such that $V \setminus \{0\} \subseteq \text{int}(S)$ (see Krasnoselśkii et al. (1989); Sanchez (2009a)).

- **(P3)** P_{-}^{k} is a cone of rank k.
- (P4) P_{-}^{k} is k-solid.

Fix a matrix $A \in \mathbb{R}^{n \times n}$ with positive entries. By the Perron-Frobenius theory (see, e.g., Horn and Johnson (2013)), A has special spectral properties. For example, A admits a positive eigenvector v and thus maps the one-dimensional linear subspace $W^1 := \operatorname{span}(v)$ to itself. The matrix A also maps the cone of rank one P^1_- to itself, and maps $P^1_- \setminus \{0\}$ to $P^1_+ = \operatorname{int}(P^1_-)$. More generally, linear operators that map a cone of rank k to its interior induce a decomposition of \mathbb{R}^n into a direct sum of invariant subspaces of prescribed dimension, and satisfy a spectral gap condition, as shown by the next theorem.

Theorem 1 (Fusco and Oliva, 1991) Let $S \subseteq \mathbb{R}^n$ be a cone of rank k with a non-empty interior, and suppose that the matrix $A \in \mathbb{R}^{n \times n}$ maps $S \setminus \{0\}$ to int(S). Then, there exist unique linear subspaces $W^1, W^2 \subset \mathbb{R}^n$ such that:

- (1) $W^1 \cap W^2 = \{0\}, W^1 \setminus \{0\} \subseteq \operatorname{int}(S), W^2 \cap S = \{0\};$
- (2) $\dim(W^1) = k$, $\dim(W^2) = n k$;
- (3) $AW^1 \subseteq W^1$ and $AW^2 \subseteq W^2$.

Furthermore, consider the restriction of the linear operator A to the subspace W^i , denoted as $A|_{W^i}$, for i = 1, 2. Any $\lambda \in \sigma_1(A)$ and $\mu \in \sigma_2(A)$, where $\sigma_i(A)$ is the spectrum of $A|_{W^i}$, satisfy the spectral gap condition $|\lambda| > |\mu|$.

The next example demonstrates that Theorem 1 is a generalization of the Perron-Frobenius theorem.

Example 1 Fix a matrix $A \in \mathbb{R}^{n \times n}$ with positive entries. Let $S := P^1_- \subset \mathbb{R}^n$. This is a cone of rank 1 with a non-empty interior, and A maps $S \setminus \{0\}$ to $int(S) = P^1_+$. Applying Theorem 1 implies

that \mathbb{R}^n can be partitioned into a one-dimensional subspace W^1 , such that $W^1 \setminus \{0\} \subseteq P_+^1$, and an (n-1)-dimensional subspace W^2 . Hence, $W^1 = \operatorname{span}(v)$, where v is a vector whose entries are all positive. Furthermore, since A maps W^1 to W^1 , we have that $Av = \lambda v$ with $\lambda > 0$, and the spectral gap condition in Theorem 1 implies that $\lambda > |\mu|$ for any other eigenvalue μ of A. The fact that $W^1 = \operatorname{span}(v)$ is unique implies that the eigenvector v is unique, up to multiplication by a scalar. This recovers the Perron theorem. Now, if A is an irreducible matrix with non-negative entries, then $\exp(A)$ is a matrix with positive entries and the analysis can be extended to this case as well.

2.3 k-positive linear ODE systems

Let us recall the notion of (strong) k-positivity for linear time-varying ordinary-differential-equation (ODE) systems.

Definition 4 The linear time-varying (LTV) system

$$\dot{x}(t) = A(t)x(t),$$

$$x(t_0) = x_0,$$
(2)

with fundamental solution matrix $T(t,t_0)$, is called k-positive if $T(t,t_0)P_-^k \subseteq P_-^k$ for all $t \ge t_0$, namely, the flow induced by (2) maps P_-^k to itself. The system is called strongly k-positive if $T(t,t_0)\left(P_-^k\setminus\{0\}\right)\subseteq P_+^k$ for all $t>t_0$, namely, the flow induced by (2) maps $P_-^k\setminus\{0\}$ to $P_+^k=\inf(P_-^k)$.

Suppose that A(t) in (2) is piecewise continuous. Then the conditions for k-positivity of the LTV system (2) depend only on the sign structure of A(t). More precisely, the system (2) is k-positive, with k = 1, 2, if and only if, for all $t \ge t_0$, A(t) has the sign pattern \bar{A}_k , where

$$\bar{A}_{1} := \begin{bmatrix} * & \geq 0 \geq 0 \dots \geq 0 \geq 0 \\ \geq 0 & * & \geq 0 \dots \geq 0 \geq 0 \\ \geq 0 \geq 0 & * \dots \geq 0 \geq 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ \geq 0 \geq 0 \geq 0 \dots & * \geq 0 \\ \geq 0 \geq 0 \geq 0 \dots \geq 0 & * \end{bmatrix} \quad \text{and} \quad \bar{A}_{2} := \begin{bmatrix} * & \geq 0 & 0 & \dots & 0 & \leq 0 \\ \geq 0 & * & \geq 0 & \dots & 0 & 0 \\ 0 & \geq 0 & * & \dots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \dots & * \geq 0 \\ \leq 0 & 0 & 0 & \dots & \geq 0 & * \end{bmatrix}. \tag{3}$$

System (2) is strongly 2-positive if, in addition, matrix A(t) is irreducible almost everywhere (Weiss and Margaliot 2021) (see also (Ge and Arcak, 2009)).

The sign pattern \bar{A}_1 corresponds to a Metzler matrix, while a matrix with sign pattern \bar{A}_2 is not Metzler in general. A sign pattern similar to \bar{A}_2 in (3) appears in the seminal work of Mallet-Paret and Smith (1990) on monotone cyclic feedback systems (see also (Ben Avraham et al., 2020; Feng et al., 2021; Wang et al., 2022), and the references therein for more recent results).

Remark 1 Systems of the form $\dot{x}(t) = Ax(t)$ with $A \in \bar{A}_2$ often arise in the field of multi-agent systems (Wooldridge, 2009), where the agents $\{x_i\}_{i=1}^n$ are interconnected through a ring topology with

bidirectional links. Each agent x_i , $i \in \{2, ..., n-1\}$ receives arbitrarily signed feedback from itself, and non-negative feedback from its two neighbors x_{i-1} and x_{i+1} . Agent x_1 receives arbitrary signed feedback from itself, non-negative feedback from its right neighbor x_2 and non-positive feedback from its "cyclic left" neighbor x_n . Agent x_n receives arbitrary signed feedback from itself, non-negative feedback from its left neighbor x_{n-1} and non-positive feedback from its "cyclic right" neighbor x_1 . Since A may include negative off-diagonal entries, the system $\dot{x} = Ax$ is in general not cooperative.

We note in passing that the analysis of sign patterns guaranteeing k-positivity relies on the theory of compound matrices (see, e.g., (Bar-Shalom et al., 2023)), a fundamental tool also for k-contractive (Wu et al., 2022a), α -contractive (Wu et al., 2022b), and totally positive differential systems (Margaliot and Sontag, 2019).

2.4 k-cooperative nonlinear ODE systems

Consider the time-invariant nonlinear ODE system

$$\dot{x} = f(x), \quad t \ge 0, \tag{4}$$

and assume that its solutions evolve on a convex state space $\Omega \subseteq \mathbb{R}^n$. Assume also that there exists a $\varepsilon > 0$ such that $f \in C^1(\Omega_{\varepsilon})$, where $\Omega_{\varepsilon} := \Omega + B(0, \varepsilon)$, is an ε -neighborhood of Ω , and that for all initial conditions $a \in \Omega$ the system admits a unique solution $x(t, a) \in \Omega$ for all $t \geq 0$. Denote the Jacobian of the vector field by $J_f(x) := \frac{\partial}{\partial x} f(x)$.

Given two initial conditions $a, b \in \Omega$, let z(t) := x(t, a) - x(t, b). Then

$$\dot{z}(t) = M_{a,b}(t)z(t),\tag{5}$$

where

$$M_{a,b}(t) := \int_0^1 J_f(rx(t,a) + (1-r)x(t,b)) dr.$$

The linear time-varying (LTV) system (5) is the variational equation associated with system (4). If $J_f(x)$ has a given sign pattern for all $x \in \Omega$, then $M_{a,b}(t)$ has the same sign pattern for all $t \ge 0$ and for all $a, b \in \Omega$, because sign patterns are preserved under summation and thus integration.

Definition 5 (Weiss and Margaliot, 2021) The nonlinear system (4) is called (strongly) k-cooperative if the associated variational equation (5) is (strongly) k-positive for all $a, b \in \Omega$ and all $t \geq 0$.

For example, the nonlinear system (4) is 1-cooperative if the variational equation (5) is 1-positive, i.e., if $J_f(x)$ is Metzler for all $x \in \Omega$. Thus, 1-cooperativity is exactly cooperativity.

Remark 2 Suppose that the system (4) is strongly k-cooperative, and that $0 \in \Omega$ is an equilibrium of (4). Fix an initial condition $a \in \Omega \setminus \{0\}$, and let z(t) := x(t,a) - x(t,0) = x(t,a). Considering equation (5), Definitions 4 and 5 imply that if $s^-(x(t,a)) \le k-1$ at some time $t \ge 0$, then $s^+(x(\tau,a)) \le k-1$ for all $\tau > t$. In particular, P_-^k , which is a cone of rank k, is invariant under the dynamics of the nonlinear system (4).

For an initial condition $a \in \Omega$, let $\omega(a)$ denote the ω -limit set of a, namely, the set of all points $y \in \Omega$ for which there exists a sequence of times $0 \le t_1 < t_2 < \ldots$, with $\lim_{n\to\infty} t_n = +\infty$, such that $\lim_{n\to\infty} x(t_n, a) = y$; see e.g. (Teschl, 2012, p. 193). This concept is fundamental when defining the

Poincaré-Bendixson property.

Definition 6 Consider the dynamical system (4) and let \mathcal{E} denote its set of equilibria. System (4) satisfies the strong Poincaré-Bendixson property if, for any bounded solution x(t, a), with $a \in \Omega$, it holds that

$$\omega(a) \cap \mathcal{E} = \emptyset \implies \omega(a)$$
 is a periodic orbit.

This property is well known to hold for autonomous planar dynamical systems. Also strongly 2-cooperative systems satisfy the strong Poincaré-Bendixson property (Weiss and Margaliot, 2021); therefore, establishing strong 2-cooperativity provides important information on the asymptotic behavior of the nonlinear system (4).

3 Main result

We provide a sufficient condition for the existence of at least one (non-trivial) periodic orbit for strongly 2-cooperative nonlinear systems. Furthermore, we explicitly characterize a positive-measure set of initial conditions such that all solutions emanating from this set converge to a (non-trivial) periodic orbit.

Theorem 2 Consider a strongly 2-cooperative nonlinear time-invariant system

$$\dot{x} = f(x), \quad t > 0, \tag{6}$$

with $f: \mathbb{R}^n \to \mathbb{R}^n$. Let $\Omega \subset \mathbb{R}^n$ be an open, bounded and convex such that $f \in C^2(\Omega_{\varepsilon})$, and such that for any initial condition $a \in \Omega$ the system admits a unique solution $x(t, a) \in \Omega$ for all $t \geq 0$. Suppose that $0 \in \Omega$ is a unique equilibrium of (6) in Ω , and that $J_f(0) = \frac{\partial}{\partial x} f(0)$ has at least two eigenvalues with a positive real part. Partition Ω as the disjoint union

$$\Omega = \Omega_{<1} \uplus \Omega_{>2},$$

where

$$\Omega_{\leq 1} := \Omega \cap P_{-}^{2} \text{ and } \Omega_{\geq 2} := \Omega \setminus P_{-}^{2}. \tag{7}$$

Then, for any $a \in \Omega_{\leq 1} \setminus \{0\}$, the solution x(t,a) of (6) converges to a (non-trivial) periodic orbit as $t \to \infty$.

Intuitively speaking, $\Omega_{\leq 1} = \Omega \cap P_-^2$ is the part of Ω with a "small" number of sign variations, whereas $\Omega_{\geq 2} := \Omega \setminus P_-^2$ is the part with a "large" number of sign variations. The proof of Theorem 2 is based on showing that solutions emanating from $\Omega_{\leq 1}$ do not converge to the (unique) equilibrium, whence are guaranteed to converge to a periodic orbit, due to the strong Poincaré-Bendixson property.

The assumption that the equilibrium e is at the origin is not restrictive, and can be achieved by a coordinate shift. If $e \neq 0$, the statement of Theorem 2 becomes:

Suppose that $e \in \Omega$, $e \neq 0$, is a unique equilibrium of (6) in Ω , and that $J_f(e) := \frac{\partial}{\partial x} f(e)$ has at least two eigenvalues with a positive real part. Then, for any $a \in \Omega \setminus \{e\}$ such that $s^-(a-e) \leq 1$, the solution x(t,a) of (6) converges to a (non-trivial) periodic orbit as $t \to \infty$.

It is important to emphasize that Theorem 2 offers an *explicit description*, in terms of sign variations, of initial conditions yielding convergence to a (non-trivial) periodic orbit.

4 Proof of Theorem 2

The proof requires an auxiliary result describing some spectral properties of strongly 2-cooperative matrices that may be of independent interest.

Proposition 3 Assume that the system $\dot{x} = Ax$, with $A \in \mathbb{R}^{n \times n}$ and $n \geq 3$, is strongly 2-positive. Then there exist unique subspaces $W^1, W^2 \subset \mathbb{R}^n$ such that:

(1)
$$W^1 \cap W^2 = \{0\}, W^1 \setminus \{0\} \subseteq P_+^2, W^2 \cap P_-^2 = \{0\};$$

(2)
$$\dim(W^1) = 2$$
, $\dim(W^2) = n - 2$;

(3)
$$AW^1 \subseteq W^1$$
 and $AW^2 \subseteq W^2$.

Furthermore, order the eigenvalues of A such that complex conjugate eigenvalues appear consecutively (including multiplicities), and

$$\operatorname{Re}(\lambda_1) \ge \dots \ge \operatorname{Re}(\lambda_n).$$
 (8)

Then

$$\operatorname{Re}(\lambda_2) > \operatorname{Re}(\lambda_3),$$
 (9)

and $\sigma(A|_{W^1}) = \{\lambda_1, \lambda_2\}.$

PROOF. Fix s > 0. The eigenvalues of the matrix $B_s := \exp(As)$ are $\exp(\lambda_i s)$, $i \in [n]$, and (8) implies that

$$|\exp(\lambda_1 s)| \ge |\exp(\lambda_2 s)| \ge \dots \ge |\exp(\lambda_n s)|,$$
 (10)

with complex conjugate eigenvalues appearing in consecutive pairs. Since $\dot{x} = Ax$ is strongly 2-positive, the matrix B_s (which is the fundamental solution matrix of $\dot{x} = Ax$) maps $P_-^2 \setminus \{0\}$ to $\operatorname{int}(P_-^2) = P_+^2$. Since P_-^2 is a cone of rank 2, applying Theorem 1 yields two unique linear subspaces $W^i(s)$, i = 1, 2, which satisfy properties (1) and (2) stated in the theorem. Furthermore, $B_sW^i(s) \subseteq W^i(s)$, i = 1, 2, and we have the spectral gap condition

$$\exp(\operatorname{Re}(\lambda_2)s) = |\exp(\lambda_2 s)| > |\exp(\lambda_3 s)| = \exp(\operatorname{Re}(\lambda_3)s), \tag{11}$$

therefore (9) holds.

We now show that the linear subspaces $W^i(s)$, i = 1, 2, do not depend on s. It is enough to prove this for $W^1(s)$, as the proof for $W^2(s)$ is identical. Define the sequence $T_n := 2^{-n}$, n = 1, 2, ..., and let $W_n^1 := W^1(T_n)$, denote the corresponding linear subspace. For any $n \ge 1$, we have

$$\exp(AT_n)W_{n+1}^1 = \exp(2AT_{n+1})W_{n+1}^1 = \exp(AT_{n+1})\exp(AT_{n+1})W_{n+1}^1 \subseteq W_{n+1}^1,$$

where we used the fact that $\exp(AT_{n+1})W_{n+1}^1 \subseteq W_{n+1}^1$. Since W_{n+1}^i , i = 1, 2, also satisfy conditions (1) and (2) in the proposition, the uniqueness of W_n^1 implies that $W_n^1 = W_{n+1}^1$, for all $n \ge 1$, so we can simply write $W^1 := W_n^1$.

Fix T > 0 and $\zeta \in W^1$. For any $\epsilon > 0$, there exists a finite sum of elements of $\{T_n \mid n = 1, 2, ...\}$ (with possible repetitions) in the form $\sum_{n=1}^{N(\epsilon)} a(\epsilon, n) T_n$, where $a(\epsilon, n)$ are integers, such that

$$\left| T - \sum_{n=1}^{N(\epsilon)} a(\epsilon, n) T_n \right| < \epsilon.$$

Then, by the previous step,

$$\exp\left(A\left(\sum_{n=1}^{N(\epsilon)}a(\epsilon,n)T_n\right)\right)\zeta = \left(\prod_{n=1}^{N(\epsilon)}\left(\exp(AT_n)\right)^{a(\epsilon,n)}\right)\zeta \in W^1.$$

Employing continuity of the mapping $t \mapsto \exp(At)\zeta$, we conclude that $\exp(AT)\zeta \in W^1$, so $\exp(AT)W^1 \subseteq W^1$. Using again uniqueness of the subspaces decomposing \mathbb{R}^n into a direct sum, and the fact that T is arbitrary, we conclude that the subspaces W^1, W^2 do not depend on T.

Fix h > 0. By the previous arguments, $\exp(Ah)\zeta \in W^1$ and, since W^1 is a linear subspace,

$$h^{-1}\left(e^{Ah}\zeta - \zeta\right) \in W^1.$$

Taking the limit as $h \downarrow 0$, we conclude that $\dot{\zeta} = A\zeta \in W^1$, whence W^1 is A-invariant; a similar argument shows that W^2 is also A-invariant. In particular, \mathbb{R}^n can be decomposed as the direct sum of A-invariant subspaces $W^1 \bigoplus W^2$, whence A can be represented as $A = \operatorname{diag}(A|_{W^1}, A|_{W^2})$. Recalling (8) and (9), we must have $\lambda_1, \lambda_2 \in \sigma(A|_{W^1})$. Indeed, the representation of A yields $\sigma(A) = \sigma(A|_{W^1}) \bigcup \sigma(A|_{W^2})$. If, for some i = 1, 2, it holds that $\lambda_i \in \sigma(A|_{W^2})$, then $\exp(\lambda_i s) \in \sigma(B_s|_{W^2})$ for s > 0, which contradicts the spectral gap condition for B_s in (10) and (11). Since $\dim(W^1) = 2$, we conclude that $\sigma(A|_{W^1}) = \{\lambda_1, \lambda_2\}$, and this completes the proof of Proposition 3.

The next result follows from Proposition 3.

Corollary 1 Under the assumptions of Proposition 3, there exists a non-singular matrix $S \in \mathbb{R}^{n \times n}$ such that

$$SAS^{-1} = \operatorname{diag}(\Lambda, \Psi), \qquad (12)$$

where $\Lambda \in \mathbb{R}^{2 \times 2}$ is the real Jordan form of $A|_{W^1}$, and $\Psi \in \mathbb{R}^{(n-2) \times (n-2)}$. Furthermore, Λ has one of

the following three forms:

$$(i) \ \Lambda = \begin{bmatrix} u_1 & 0 \\ 0 & u_2 \end{bmatrix}, \ u_1, u_2 \in \mathbb{R}, \ with \ u_1 \ge u_2;$$

$$(ii) \ \Lambda = \begin{bmatrix} u & -v \\ v & u \end{bmatrix}, \ u, v \in \mathbb{R}, \ with \ v \ne 0;$$

$$(iii) \ \Lambda = \begin{bmatrix} u & 1 \\ 0 & u \end{bmatrix}, \ u \in \mathbb{R}.$$

The three possible forms in the corollary correspond to the cases: (i) $\lambda_1 = u_1$ and $\lambda_2 = u_2$ are real and distinct eigenvalues and each has geometric multiplicity 1, or $\lambda_1 = \lambda_2$ and has geometric multiplicity 2; (ii) $\lambda_1 = u + iv$ and $\lambda_2 = \overline{\lambda_1}$ are two complex conjugate eigenvalues; and (iii) $\lambda_1 = \lambda_2 = u$ is a real eigenvalue of algebraic multiplicity 2 and geometric multiplicity 1.

We can now prove Theorem 2.

PROOF. Since the system (6) is strongly 2-cooperative, we have that

$$x(t,a) \in P_-^2 \setminus \{0\} \text{ for some } t \ge 0 \Rightarrow x(\tau,a) \in P_+^2 = \operatorname{int}(P_-^2) \text{ for all } \tau > t.$$
 (13)

Combining this with the assumed invariance of Ω implies that $\Omega_{\leq 1}$ is also invariant. Note that $0 \in \Omega_{\leq 1}$. To prove the theorem we use the strong Poincaré-Bendixon property of strongly 2-cooperative systems, the instability of $J_f(0)$ and the spectral properties of strongly 2-positive systems in Proposition 3 to show that, for all $a \in \Omega_{\leq 1} \setminus \{0\}$, the solution x(t, a) does not converge to 0 and thus it must converge to a periodic solution. The proof includes several steps.

Step 1: A change of variables.

Let $A := J_f(0)$. Since the system (6) is strongly 2-cooperative, the linear system $\dot{y} = Ay$ is strongly 2-positive. Let $S \in \mathbb{R}^{n \times n}$ be the invertible matrix in Corollary 1. For $\delta > 0$, let

$$S_{\delta} := \begin{bmatrix} 1 & 0 & \mathbf{0} \\ 0 & \delta & \mathbf{0} \\ \hline \mathbf{0} & I_{n-2} \end{bmatrix} S, \tag{14}$$

where **0** denotes an all-zero matrix of the appropriate size. Then S_{δ} is invertible. Introduce the change of coordinates $q(t) := S_{\delta}x(t)$. Then

$$\dot{q} = g(q), \text{ with } g(q) := S_{\delta} f(S_{\delta}^{-1} q).$$

$$\tag{15}$$

The state-space of this system is the open, bounded and convex set $\tilde{\Omega} := S_{\delta}\Omega$. Let $\tilde{\Omega}_{\leq 1} := S_{\delta}\Omega_{\leq 1}$

and $\tilde{\Omega}_{\geq 2} := S_{\delta}\Omega_{\geq 2}$. Then $\tilde{\Omega} = \tilde{\Omega}_{\leq 1} \uplus \tilde{\Omega}_{\geq 2}$, with $\tilde{\Omega}_{\leq 1}$ being invariant under (15). In these new coordinates, we have

$$\tilde{W}^1 := S_{\delta} W^1 = \operatorname{span} \{e^1, e^2\}, \quad \tilde{W}^2 := S_{\delta} W^2 = \operatorname{span} \{e^3, \dots, e^n\},$$
 (16)

where $\{e^i\}_{i=1}^n$ is the standard basis in \mathbb{R}^n . Also,

(1)
$$\tilde{W}^1 \cap \tilde{W}^2 = \{0\}, \ \tilde{W}^1 \setminus \{0\} \subseteq S_{\delta}P_+^2, \ \tilde{W}^2 \cap S_{\delta}P_-^2 = \{0\};$$

(2)
$$\dim(\tilde{W}^1) = 2$$
, $\dim(\tilde{W}^2) = n - 2$.

The origin is an equilibrium of the system (15), and its Jacobian is

$$J_g(z) = S_{\delta} J_f(S_{\delta}^{-1} z) S_{\delta}^{-1}.$$

Using (12), (14), and the assumption that $J_f(0)$ has at least two eigenvalues with a positive real part gives

$$\tilde{A}_{\delta} := J_g(0) = S_{\delta} A S_{\delta}^{-1} = \begin{bmatrix} \tilde{\Lambda}_{\delta} & 0 \\ 0 & \Psi \end{bmatrix}, \tag{17}$$

with

$$\tilde{\Lambda}_{\delta} := \operatorname{diag}(1, \delta) \Lambda \operatorname{diag}(1, \delta^{-1}),$$

and $\tilde{\Lambda}_{\delta}$ has one of the following three forms (see Corollary 1):

$$(i) \tilde{\Lambda}_{\delta} = \begin{bmatrix} u_1 & 0 \\ 0 & u_2 \end{bmatrix}, \ u_1, u_2 > 0; \quad (ii) \tilde{\Lambda}_{\delta} = \begin{bmatrix} u & -\delta^{-1}v \\ \delta v & u \end{bmatrix}, \ u > 0, v \neq 0; \quad (iii) \tilde{\Lambda}_{\delta} = \begin{bmatrix} u & \delta^{-1} \\ 0 & u \end{bmatrix}, \ u > 0.$$

$$(18)$$

Let $\tilde{P}_{\delta} := (\tilde{\Lambda}_{\delta} + \tilde{\Lambda}_{\delta}^{\top})/2$. If case (i) holds then \tilde{P}_{δ} is in fact independent of δ and is positive-definite. If case (ii) holds then \tilde{P}_{δ} is positive-definite for $\delta = 1$. If case (iii) holds then $\tilde{\Lambda}_{\delta}$ is positive-definite for any $\delta > 0$ sufficiently large. Summarizing, we can always choose $\delta > 0$ such that \tilde{P}_{δ} is positive-definite.

Step 2: Derivation of an appropriate conic neighborhood around \tilde{W}^2 .

Recall that $\tilde{W}^2 \cap S_{\delta}P_-^2 = \{0\}$. Hence, $\tilde{W}^2 \cap \tilde{\Omega} \subseteq \tilde{\Omega}_{\geq 2}$, with $\tilde{\Omega}_{\geq 2}$ being an open set. For any $\xi \in \mathbb{R}^n \setminus \{0\}$, define

$$p(\xi) := \frac{\sqrt{\sum_{i=3}^n \xi_i^2}}{|\xi|},$$

that is, $p(\xi)$ is the ratio between the norm of the projection of ξ on \tilde{W}^2 and the norm of ξ . By definition, p is a homogeneous function of degree zero, that is,

$$p(\alpha \xi) = p(\xi) \text{ for any } \alpha \in \mathbb{R} \setminus \{0\},$$
 (19)

and also $p(\xi) \in [0,1]$ for all $\xi \in \mathbb{R}^n \setminus \{0\}$. By (16), for any $\xi \in \mathbb{R}^n \setminus \{0\}$ we have

$$p(\xi) = 1 \text{ if and only if } \xi \in \tilde{W}^2 \setminus \{0\}.$$
 (20)

The following lemma shows that there is a conic neighborhood around $\tilde{W}^2 \setminus \{0\}$, whose intersection with $\tilde{\Omega}$ lies entirely in $\tilde{\Omega}_{\geq 2}$.

Lemma 2 There exists $\tilde{\varepsilon} \in (0,1)$ such that, for any $\xi \in \tilde{\Omega} \setminus \{0\}$, we have that

$$p(\xi) > 1 - \tilde{\varepsilon} \Rightarrow \xi \in \tilde{\Omega}_{\geq 2}.$$

PROOF. We prove the statement by contradiction. Assume that the claim does not hold. Then there exist sequences $\{\xi^{\ell}\}_{\ell=1}^{\infty} \subseteq \tilde{\Omega} \setminus \{0\}$ and $\{\varepsilon_{\ell}\}_{\ell=1}^{\infty} \subseteq (0,1)$ such that

$$\lim_{\ell \to \infty} \varepsilon_{\ell} = 0, \qquad p\left(\xi^{\ell}\right) > 1 - \varepsilon_{\ell}, \qquad \xi^{\ell} \in \tilde{\Omega}_{\leq 1}, \tag{21}$$

where we used the fact that $\tilde{\Omega} = \tilde{\Omega}_{\leq 1} \uplus \tilde{\Omega}_{\geq 2}$. Let $\mu > 0$ be such that $B(0, \mu) \subseteq \tilde{\Omega}$. Using the fact that p is homogeneous of degree zero and $S_{\delta}P_{-}^{2}$ is scaling invariant (see Property (**P2**) in Section 2.2), we can scale the vectors $\{\xi_{\ell}\}_{\ell=1}^{\infty}$ to $\partial B(0, \mu)$, while preserving (21), to obtain

$$\lim_{\ell \to \infty} \varepsilon_{\ell} = 0, \qquad p\left(\mu \frac{\xi^{\ell}}{|\xi^{\ell}|}\right) > 1 - \varepsilon_{\ell}, \qquad \mu \frac{\xi^{\ell}}{|\xi^{\ell}|} \in \tilde{\Omega}_{\leq 1}. \tag{22}$$

Passing to a sub-sequence, if needed, we may assume that $\mu \frac{\xi^{\ell}}{|\xi^{\ell}|}$ converges to a limit ξ , with $|\xi| = \mu > 0$, and $p(\xi) \ge 1$, so $p(\xi) = 1$, whence $\xi \in \tilde{W}^2 \setminus \{0\}$ in view of (20). Since P_-^2 is closed and S_{δ} is invertible, $S_{\delta}P_-^2$ is closed, so (22) implies that $\xi \in S_{\delta}P_-^2$. Using (20) gives

$$\xi \in (S_{\delta}P_{-}^{2}) \cap (\tilde{W}^{2} \setminus \{0\}).$$

However, the intersection of these two sets is empty. This contradiction completes the proof of Lemma 2.

Corollary 2 There exists $\tilde{\theta} > 0$ such that

$$\xi \in \tilde{\Omega}_{\leq 1} \setminus \{0\} \implies |\xi|^2 \leq (\xi_1^2 + \xi_2^2) \,\tilde{\theta}.$$
 (23)

PROOF. Let $\tilde{\epsilon} \in (0,1)$ be as in Lemma 2, and define $\tilde{q} := (1-\tilde{\epsilon})^2$, so $\tilde{q} \in (0,1)$. Fix $\xi \in \tilde{\Omega}_{\leq 1} \setminus \{0\}$. Then Lemma 2 gives $(p(\xi))^2 \leq (1-\tilde{\epsilon})^2 = \tilde{q}$, that is, $\sum_{i=3}^n \xi_i^2 \leq \tilde{q} \sum_{i=1}^n \xi_i^2$, so $(1-\tilde{q}) \sum_{i=3}^n \xi_i^2 \leq \tilde{q} (\xi_1^2 + \xi_2^2)$. Thus,

$$|\xi|^2 = \xi_1^2 + \xi_2^2 + \sum_{i=3}^n \xi_i^2 \le \left(1 + \frac{\tilde{q}}{1 - \tilde{q}}\right) \left(\xi_1^2 + \xi_2^2\right) = \frac{1}{1 - \tilde{q}} \left(\xi_1^2 + \xi_2^2\right),$$

and (23) holds for $\tilde{\theta} := \frac{1}{1-\tilde{a}} > 0$.

Step 3: Local Lyapunov analysis.

We now show that for any $a \in \tilde{\Omega}_{\leq 1} \setminus \{0\}$ the solution q(t, a) of (15) remains bounded away from the unique equilibrium $0 \in \tilde{\Omega}$ of (15). Applying a Taylor expansion to the right-hand side of (15) gives

$$\dot{q} = \tilde{A}q + h(q). \tag{24}$$

Since we assume that f is C^2 on a convex neighborhood that includes the closure of Ω (and this carries over to g and $\tilde{\Omega}$), there exists M>0 such that the nonlinear terms in (24) satisfy

$$|h_i(q)| \le M|q|^2 \text{ for all } q \in \tilde{\Omega}, \ i \in [n].$$
 (25)

Let

$$V(q) := \frac{1}{2} \left(q_1^2 + q_2^2 \right). \tag{26}$$

Intuitively, the value $(2V(q))^{1/2} = (q_1^2 + q_2^2)^{1/2}$ is the norm of the projection of q on the dominant unstable directions (eigenvectors) of \tilde{A}_{δ} in (17).

For any $\eta > 0$, let

$$H_{\eta} := \tilde{\Omega}_{\leq 1} \cap \{ q \in \mathbb{R}^n \mid V(q) \geq \eta \}. \tag{27}$$

Note further that $0 \notin H_{\eta}$. Recalling that $\tilde{\Omega}_{\leq 1}$ is invariant for (24), our next goal is to show that there exists a value $\eta_0 > 0$ such that H_{η} is an invariant set of (24) for any $0 < \eta < \eta_0$. For this purpose, we evaluate the Lyapunov derivative $\dot{V}(q)$ for $q \in \mathcal{H}_{\eta}$ and show that there exists $\eta_0 > 0$ such that, if $0 < \eta < \eta_0$, then

$$V(q) = \eta \Longrightarrow \dot{V}(q) > 0.$$

The latter implies, in particular, that if q(t, a) is a solution of (24) with $V(a) \ge \eta$, where $0 < \eta < \eta_0$, then $\inf_{t>0} V(q(t, a)) \ge \eta$.

The Lyapunov derivative is

$$\dot{V}(q) = q_1 \dot{q}_1 + q_2 \dot{q}_2 = \begin{bmatrix} q_1 & q_2 \end{bmatrix} \tilde{\Lambda}_{\delta} \begin{bmatrix} q_1 \\ q_2 \end{bmatrix} + \begin{bmatrix} q_1 & q_2 \end{bmatrix} \begin{bmatrix} h_1(q) \\ h_2(q) \end{bmatrix}.$$

Recall that we can always choose $\delta > 0$ such that $(\tilde{\Lambda}_{\delta} + \tilde{\Lambda}_{\delta}^{\top})/2$ is positive-definite, so there exists $\alpha > 0$ such that

$$\dot{V}(q) \ge \alpha \left| \left[q_1 \ q_2 \right]^\top \right|^2 + \left[q_1 \ q_2 \right] \left[\begin{matrix} h_1(q) \\ h_2(q) \end{matrix} \right]. \tag{28}$$

To bound the second term in the sum, note that

$$\left| \begin{bmatrix} q_1 & q_2 \end{bmatrix} \begin{bmatrix} h_1(q) \\ h_2(q) \end{bmatrix} \right| \le \left| \begin{bmatrix} q_1 & q_2 \end{bmatrix}^\top \right| \left| \begin{bmatrix} h_1(q) \\ h_2(q) \end{bmatrix} \right| \le \left| \begin{bmatrix} q_1 & q_2 \end{bmatrix}^\top \right| 2M|q|^2 \le 2M\tilde{\theta} \left| \begin{bmatrix} q_1 & q_2 \end{bmatrix}^\top \right|^3,$$

where the first inequality follows from the Cauchy-Schwarz inequality, the second inequality uses (25),

and the third inequality follows from Corollary 2. Thus,

$$\dot{V}(q) \ge 2\alpha V(q) - 2M\tilde{\theta} \left(2V(q)\right)^{3/2} = 2V(q) \left(\alpha - M\tilde{\theta}V(q)^{\frac{1}{2}}\right).$$

This implies that there exists a sufficiently small $\eta_0 > 0$ such that if $V(q) = \eta$, where $0 < \eta < \eta_0$, then $\dot{V}(q) > 0$, so H_{η} is an invariant set of (24).

Step 4: Completing the proof of Theorem 2.

Consider the nonlinear system (7). Fix an initial condition $a \in \Omega_{\leq 1} \setminus \{0\}$. Let $\tilde{a} := S_{\delta} a \neq 0$ (where $\delta > 0$ is chosen so that \tilde{P}_{δ} is positive-definite). Then $\tilde{a} = (\tilde{a}_1, \dots, \tilde{a}_n)^{\top} \in \tilde{\Omega}_{\leq 1} \setminus \{0\}$. If $\tilde{a}_1 = \tilde{a}_2 = 0$ then

$$0 \neq \tilde{a} \in \tilde{W}^2 \cap \tilde{\Omega}_{\leq 1} \subseteq \tilde{W}^2 \cap S_{\delta} P_-^2$$

which is a contradiction. We conclude that $\tilde{a}_1^2 + \tilde{a}_2^2 \neq 0$, so there is some $\eta \in (0, \eta_0)$ such that $\tilde{a} \in H_{\eta}$. By Step 3, the solution q(t, a) of (15) remains in H_{η} and is thus bounded away from $0 \in \tilde{\Omega}$. This implies that x(t, a) is bounded away from $0 \in \Omega$, which is the only equilibrium of (2) in Ω . Since the system is strongly 2-cooperative, it satisfies the strong Poincaré-Bendixson property in Definition 6. As $0 \notin \omega(a)$, we conclude that $\omega(a)$ is a periodic orbit and x(t, a) converges to $\omega(a)$ as $t \to \infty$. This completes the proof of Theorem 2.

5 Applications

We describe two applications of Theorem 2 to models from systems biology.

5.1 Convergence to periodic orbits in the n-dimensional Goodwin model

The Goodwin model captures a classical biochemical circuit design where enzyme or protein synthesis are regulated by incorporating a negative-feedback of the end product (Goodwin, 1965). This has become a touchstone circuit in systems biology, see the recent survey paper by Gonze and Ruoff (2021) and the many references therein. The model includes n first-order differential equations:

$$\begin{cases} \dot{x}_{1} &= -\alpha_{1}x_{1} + \frac{1}{1+x_{n}^{m}}, \\ \dot{x}_{2} &= -\alpha_{2}x_{2} + x_{1}, \\ \dot{x}_{3} &= -\alpha_{3}x_{3} + x_{2}, \\ &\vdots \\ \dot{x}_{n} &= -\alpha_{n}x_{n} + x_{n-1}, \end{cases}$$
(29)

where $\alpha_i > 0$ for all i = 1, ..., n, and $m \in \mathbb{N}$. Denote by $\alpha := \alpha_1 \alpha_2 \alpha_3 \cdots \alpha_n$ the product of all the dissipation gains in the system.

The state space of (29) is $\Omega := \mathbb{R}^n_{\geq 0}$. Furthermore, all trajectories are bounded. In fact, any trajectory emanating from Ω eventually enters into the closed box $\mathcal{B}_G := \{x \in \mathbb{R}^n_{\geq 0} \mid x_1 \leq \alpha_1^{-1}, x_2 \leq (\alpha_1 \alpha_2)^{-1}, \ldots, x_n \leq (\alpha_1 \ldots \alpha_n)^{-1}\}$. Moreover, since on $\partial \mathcal{B}_G$ the vector field of (29) points into $\operatorname{int}(\mathcal{B}_G)$, the solutions eventually enter $\operatorname{int}(\mathcal{B}_G)$.

Since \mathcal{B}_G is a compact, convex, and invariant set, $\operatorname{int}(\mathcal{B}_G)$ is also an invariant set (see Angeli and Sontag (2003)), and there exists at least one equilibrium point $e \in \operatorname{int}(\mathcal{B}_G)$. By computing the equilibria

of system (29) we can see that e_n is a real and positive root of the polynomial

$$Q(s) := \alpha s^{m+1} + \alpha s - 1, \tag{30}$$

and, in view of Descartes' rule of signs, there is a unique such e_n . Then

$$e_j = \left(\prod_{k \ge j+1} \alpha_k\right) e_n, \text{ for all } j \in [n-1], \tag{31}$$

and hence $e \in \text{int}(\mathcal{B}_G)$ is unique.

Several studies (see e.g. Sanchez (2009b) and the references therein) derived conditions guaranteeing that the equilibrium $e \in \text{int}(\mathcal{B}_G)$ is globally asymptotically stable. Tyson (1975) analyzed the special case of (29) with n=3. He noted that if e is locally asymptotically stable, then one may expect that all solutions converge to e, and proved that system (29) admits a periodic solution whenever e is unstable. For n=3, the model can also be studied using the theory of competitive dynamical systems (Smith, 1995). The case n=3 has also been analyzed using the theory of Hopf bifurcations (Woller et al., 2014). For a general n, the analysis using Hopf bifurcations becomes highly non-trivial and results exist only for special cases, e. g. under the additional assumption that all the α_i 's are equal, see Invernizzi and Treu (1991). Hastings et al. (1977) studied the general n-dimensional case and proved that, if the Jacobian of the vector field at the equilibrium has no repeated eigenvalues and at least one eigenvalue with a positive real part, then the system admits a non-trivial periodic orbit; the proof relies on the Brouwer fixed point theorem.

Our Theorem 2 allows us to prove the following result.

Corollary 3 Consider the n-dimensional Goodwin model (29) with $n \geq 3$, and let e denote the unique equilibrium in int (\mathcal{B}_G) . Let $J: \mathbb{R}^n_{\geq 0} \to \mathbb{R}^{n \times n}$ denote the Jacobian of the vector field of the Goodwin model. Suppose that J(e) has at least one eigenvalue with a positive real part. Then, for any initial condition $a \in \mathbb{R}^n_{\geq 0} \setminus \{e\}$ such that $s^-(a-e) \leq 1$, the solution x(t,a) of (29) converges to a (non-trivial) periodic orbit as $t \to \infty$.

PROOF.

The Jacobian of (29)

$$J(x) = \begin{bmatrix} -\alpha_1 & 0 & 0 & \dots & 0 & -\frac{mx_n^{m-1}}{(1+x_n^m)^2} \\ 1 & -\alpha_2 & 0 & \dots & 0 & 0 \\ 0 & 1 & -\alpha_3 & \dots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \dots & -\alpha_{n-1} & 0 \\ 0 & 0 & 0 & \dots & 1 & -\alpha_n \end{bmatrix}$$

has the sign pattern \bar{A}_2 in (3) for all $x \in \mathbb{R}^n_{\geq 0}$, hence the system is 2-cooperative on $\mathbb{R}^n_{\geq 0}$. We

now show that the system is strongly 2-cooperative on $\mathbb{R}^n_{\geq 0}$. If x(t,a) is a solution of (29) with initial condition $a \in \mathbb{R}^n_{\geq 0}$ and $x_n(t_0,a) = 0$ at some time $t_0 \geq 0$, then there exists some $\delta > 0$ such that $t \in (t_0,t_0+\delta) \implies x_n(t,a) > 0$. In particular, the set $\{t \geq 0 \mid x_n(t,a) = 0\}$ is at most countable, and this implies that the time-varying matrix M(t) in the variational equation (5), which is obtained from integrating J(x(t)), is irreducible for almost all t. As a result, the system is strongly 2-cooperative on $\mathbb{R}^n_{\geq 0}$ and the set $\{x \in \mathbb{R}^n_{\geq 0} \mid s^-(x-e) \leq 1\}$ is forward invariant (see Remark 2).

To analyze the eigenvalues of J(e), consider the matrix

$$A := \begin{bmatrix} -\alpha_1 & 0 & 0 & \dots & 0 & -\beta_n \\ \beta_1 & -\alpha_2 & 0 & \dots & 0 & 0 \\ 0 & \beta_2 & -\alpha_3 & \dots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \dots & -\alpha_{n-1} & 0 \\ 0 & 0 & 0 & \dots & \beta_{n-1} & -\alpha_n \end{bmatrix},$$

$$(32)$$

with $n \geq 3$, and $\alpha_i, \beta_j > 0$ for all $i, j \in [n]$. Let $\beta := \prod_{j=1}^n \beta_j$. The characteristic polynomial of A is

$$p_A(s) := \beta + \prod_{j=1}^n (s + \alpha_j) = s^n + a_{n-1}s^{n-1} + \dots + a_1s + a_0,$$
(33)

and since the α_i 's and β_j 's are all positive, the coefficients of $p_A(s)$ satisfy $a_i > 0$ for all i. This implies that $p_A(s)$ cannot have a real positive zero. Since we assume that J(e) has an unstable eigenvalue λ_1 , we conclude that λ_1 is not real, and therefore its complex conjugate $\bar{\lambda}_1$ is another eigenvalue of J(e) with a positive real part, so J(e) has at least two unstable eigenvalues.

Take now $a \in \mathbb{R}^n_{\geq 0}$ such that $s^-(a-e) \leq 1$ and consider x(t,a). There exists a time T(a) > 0 such that $x(T(a),a) \in \operatorname{int}(\mathcal{B}_G)$. Furthermore, as the set $\{x \in \mathbb{R}^n_{\geq 0} \mid s^-(x-e) \leq 1\}$ is forward invariant, we also have $s^-(x(T(a),a)-e) \leq 1$. Since $\omega(a) = \omega(x(T(a),a))$, applying Theorem 2 in int (\mathcal{B}_G) completes the proof of Corollary 3.

The next numerical example demonstrates Corollary 3.

Example 2 Consider system (29) with n = 4, $\alpha_1 = \alpha_2 = \alpha_3 = \alpha_4 = 1/2$, and m = 10. Then

$$\mathcal{B}_G = \{x \in \mathbb{R}^4_{>0} \mid x_1 \le 2, \ x_2 \le 4, \ x_3 \le 8, \ x_4 \le 16\},\$$

and the polynomial in (30) becomes

$$Q(s) = \frac{1}{16}s^{11} + \frac{1}{16}s - 1.$$

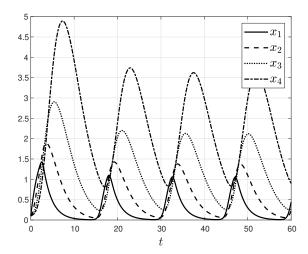


Fig. 1. Solution to the Goodwin system in Example 2 emanating from $x(0) = \begin{bmatrix} 0.1 & 0.1 & 0.1 & 0.1 \end{bmatrix}^{\top}$.

The unique real and positive root of this polynomial is $e_4 \approx 1.2770$, and

$$e = \begin{bmatrix} e_4/8 & e_4/4 & e_4/2 & e_4 \end{bmatrix}^{\top} \approx \begin{bmatrix} 0.1596 & 0.3192 & 0.6385 & 1.2770 \end{bmatrix}^{\top}.$$

The characteristic polynomial of J(e) is

$$\det(sI_4 - J(e)) = s^4 + 2s^3 + 1.5s^2 + 0.5s + 0.6376.$$

As expected, all the coefficients in this polynomial are positive. Applying the Routh stability criterion reveals that e is unstable. Indeed, the eigenvalues of J(e) are

$$0.1158 + 0.6158j, \ \ 0.1158 - 0.6158j, \ \ -1.1158 + 0.6158j, \ \ -1.1158 - 0.6158j,$$

so J(e) has two unstable eigenvalues. Fig. 1 depicts the solution x(t,a) of (29) emanating from the initial condition $a = \begin{bmatrix} 0.1 & 0.1 & 0.1 \end{bmatrix}^{\top}$ as a function of time. Note that $s^{-}(a-e) = 0$. As predicted by our result, the trajectory x(t,a) converges to a periodic orbit.

5.2 Convergence to periodic orbits in a biomolecular oscillator model.

Blanchini et al. (2014a) proposed the following mathematical model for a biological oscillator based on RNA-mediated regulation:

$$\begin{cases}
\dot{x}_{1} = \kappa_{1}x_{2} - \delta_{1}x_{1} - \gamma_{2}x_{4}x_{1}, \\
\dot{x}_{2} = -\beta_{1}x_{2} + \gamma_{1}(x_{2}^{tot} - x_{2})x_{3}, \\
\dot{x}_{3} = \kappa_{2}x_{4} - \delta_{2}x_{3} - \gamma_{1}(x_{2}^{tot} - x_{2})x_{3}, \\
\dot{x}_{4} = \beta_{2}(x_{4}^{tot} - x_{4}) - \gamma_{2}x_{4}x_{1},
\end{cases} (34)$$

where κ_i , β_i , δ_i and γ_i , as well as x_2^{tot} and x_4^{tot} , are positive parameters, and proved that there exist $x_1^{tot}, x_3^{tot} > 0$ such that the closed set $\mathcal{B}_O := [0, x_1^{tot}] \times \cdots \times [0, x_4^{tot}]$ is an invariant set of

the dynamics, and that \mathcal{B}_O includes a unique equilibrium $e \in \operatorname{int}(\mathcal{B}_O)$. They also showed that, up to a coordinate transformation, the system (34) is the negative feedback interconnection of two cooperative systems, and hence it is structurally a strong candidate oscillator according to the classification introduced by Blanchini et al. (2014b, 2015), namely, local instability can only occur due to a complex pair of unstable poles crossing the imaginary axis. For such an interconnection there exists a sufficient condition for the global asymptotic stability of e (Angeli and Sontag, 2003). Blanchini et al. (2014a) suggested that, when this condition does not hold, the system may admit a non-trivial periodic solution, and can thus serve as a biological oscillator. This was motivated by the analysis of the linearization of (34) around the equilibrium e, which demonstrated that, for some choices of κ_i , β_i , δ_i and γ_i , the eigenvalues of J(e) do cross the imaginary axis in the complex plane. The appearance of oscillations was also confirmed using extensive simulations. Applying Theorem 2 provides more precise information of a global nature.

Corollary 4 Consider the 4-dimensional oscillator model (34) and let e denote the unique equilibrium in int (\mathcal{B}_O) . Let $J: \mathbb{R}^n_{\geq 0} \to \mathbb{R}^{n \times n}$ denote the Jacobian of the vector field of system (34). Suppose that J(e) admits at least two eigenvalues with a positive real part. Then for any initial condition $x_0 \in \text{int}(\mathcal{B}_O)$ such that $s^-(x_0 - e) \leq 1$ the solution $x(t, x_0)$ of (34) converges to a (non-trivial) periodic orbit as $t \to \infty$.

PROOF. Since the closed set \mathcal{B}_O is an invariant set of the dynamics, so is the open set int(\mathcal{B}_O) (see, e.g., Angeli and Sontag (2003)). The Jacobian of the vector field in (34) is

$$J(x) = \begin{bmatrix} -\delta_1 - \gamma_2 x_4 & \kappa_1 & 0 & -\gamma_2 x_1 \\ 0 & -\beta_1 - \gamma_1 x_3 & \gamma_1 \left(x_2^{tot} - x_2 \right) & 0 \\ 0 & \gamma_1 x_3 & -\delta_2 - \gamma_1 \left(x_2^{tot} - x_2 \right) & \kappa_2 \\ -\gamma_2 x_4 & 0 & 0 & -\beta_2 - \gamma_2 x_1 \end{bmatrix},$$
(35)

and hence the system is strongly 2-cooperative on $int(\mathcal{B}_0)$. Applying Theorem 2 completes the proof.

Example 3 Consider the system (34) with the (arbitrarily chosen) parameter values: $\beta_1 = 0.2$, $\beta_2 = 0.5$, $\kappa_1 = 15$, $\kappa_2 = 1$, $\delta_1 = 0.01$, $\delta_2 = 0.1$, $\gamma_1 = 0.1$, $\gamma_2 = 20$, $x_2^{tot} = 15$, and $x_4^{tot} = 20$. A numerical calculation shows that in this case $e = \begin{bmatrix} 3.4932 & 0.6643 & 0.0927 & 0.1421 \end{bmatrix}^{\mathsf{T}}$, and J(e) admits two unstable eigenvalues. Let $x_0 = 0$, and note that $s^{\mathsf{T}}(e - x_0) = 0$. Fig. 2 depicts $x(t, x_0)$ as a function of time and shows that it converges to a periodic orbit.

6 Discussion

Strongly 2-cooperative systems enjoy an important asymptotic property, called the strong Poincaré-Bendixon property: any bounded solution that keeps a positive distance from the set of equilibria converges to a periodic orbit. For a general system satisfying the strong Poincaré-Bendixon property, it is possible that all bounded solutions converge to an equilibrium, so that the system does not exhibit oscillatory behaviors. Therefore, it is important to find sufficient conditions that guarantee convergence to a non-trivial periodic orbit.

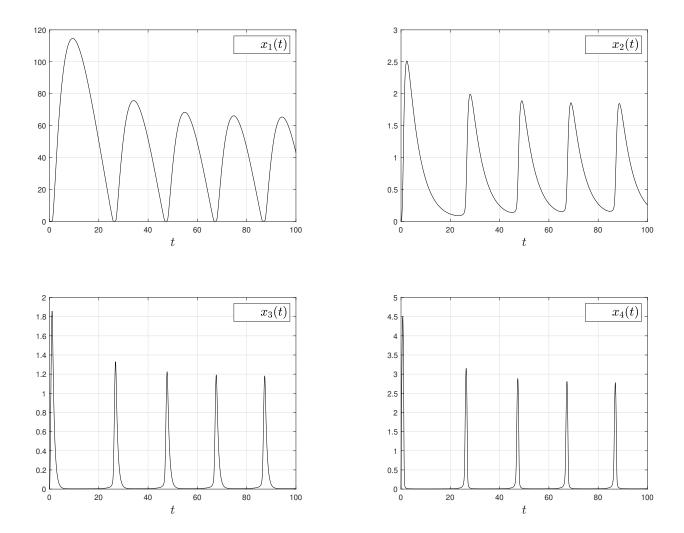


Fig. 2. Solution $x_i(t)$, i = 1, ..., 4, to the oscillator model in Example 3 emanating from x(0) = 0.

For a strongly 2-cooperative system defined on a bounded and convex invariant set with a single equilibrium point, we derived a simple condition that guarantees the existence of periodic trajectories. Moreover, we explicitly characterized a positive measure set of initial conditions such that any bounded solution emanating from this set must converge to a periodic orbit. The proof relies on the special asymptotic and spectral properties of strongly 2-cooperative systems. We demonstrated our theoretical results using two models from systems biology: the *n*-dimensional Goodwin model and a 4-dimensional biomolecular oscillator.

An interesting topic for further research is to find conditions that guarantee uniqueness of the periodic orbit (see, e.g. the survey paper Li (1981)). Then, our results would imply that the periodic orbit is a global attractor for solutions emanating from an invariant set that includes no equilibrium points. Another research direction may be applying the theory to the systemic design of synthetic biological oscillators (see, e.g. (Blanchini et al., 2014a; Novák and Tyson, 2008; Panghalia and Singh, 2020)).

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