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Conditions for global stability of monotone tridiagonal systems with negative feedback

Liming Wang [a], Patrick De Leenheer [b], Eduardo D. Sontag [c,*]

[a] Department of Mathematics, UC Irvine, United States
[b] Department of Mathematics, University of Florida, United States
[c] Department of Mathematics, Rutgers University, 8854 Piscataway, NJ, United States

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ABSTRACT

This paper studies monotone tridiagonal systems with negative feedback. These systems possess the Poincaré–Bendixson property, which implies that, if orbits are bounded, if there is a unique steady state and this unique steady state is asymptotically stable, and if one can rule out periodic orbits, then the steady state is globally asymptotically stable. Two different approaches are discussed to rule out period orbits, one based on direct linearization and another one based on the theory of second additive compound matrices. Among the examples that illustrate the theoretical results is the classical Goldbeter model of the circadian rhythm.

1. Introduction

Tridiagonal systems are those in which each of the state variables $x_1, \ldots, x_n$ is only allowed to interact with its "neighbors", see Fig. 1. Such systems arise in one-dimensional formations of vehicles with local communication (x_i denotes the position of the ith vehicle), as well as in many models in biology. In the latter field, x_i denotes the size of the population of the ith species in ecology models, or the concentration of the ith chemical in cell biology models. Ecological examples include those in which species are arranged in physical layers (altitude in air, depth in water) and competition or cooperation occurs with individuals in adjoining zones. Cell biology examples include those in which a set of genes g_i controls the production of proteins P_i, each of which acts as a transcription factor for the next gene g_{i+1} (binding and unbinding to the promoter region of g_{i+1} affects the concentration of free protein P_i as well as the transcription rate of g_{i+1}). Somewhat different, though mathematically similar, biological examples arise from sequences of protein post-translational modifications such as phosphorylations and (providing the backward interaction) dephosphorylations.

Especially in biology, it is usual to find situations involving feedback from the last to the first component, see Fig. 2. A very common situation involves negative (repressive) feedback, which allows set-point regulation of protein levels, or which enables the generation of oscillations. A specific and classical instance of this is the Goldbeter model for circadian oscillations in the *Drosophila* PER ("period") protein [1]. In all such examples, it is of interest to find conditions that characterize oscillatory versus non-oscillatory regimes.

Fig. 1. The schematic diagram of a tridiagonal system of size n.

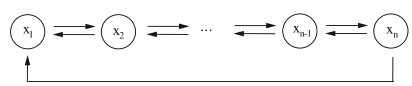

Fig. 2. The schematic diagram of a tridiagonal system of size n with feedback.

In this paper, we provide sufficient conditions for global asymptotic stability of tridiagonal systems with negative feedback. Of course, when negated, we also have then necessary conditions on parameters that must hold in order for oscillations to exist.

1.1. *Monotone tridiagonal systems with negative feedback*

A tridiagonal system with feedback has the form:

$$\dot{x}_i = f_i(x_{i-1}, x_i, x_{i+1}), \quad i = 1, \ldots, n-1 \tag{1}$$
$$\dot{x}_n = f_n(x_{n-1}, x_n),$$

* Corresponding author. Tel.: +1 732 445 2390x3072.
E-mail addresses: limingwang.math@gmail.com (L. Wang), deleenhe@math.ufl.edu (P. De Leenheer), sontag@math.rutgers.edu (E.D. Sontag).

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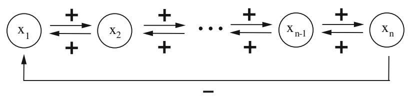

Fig. 3. The schematic diagram of a monotone tridiagonal system of size n with negative feedback.

where x_0 is identified with x_n, and the C^1 vector field $F = (f_1, \ldots, f_n)$ is defined on an open set U. Often in applications, the variables x_i evolve in a set C which is not open. For example, C may be the non-negative orthant $\mathbb{R}^n_{\geq 0}$, as is the case when the variables x_i represent non-negative physical quantities such as concentrations of chemical species. If C is the closure of its interior, then one may study the equations in the set U equal to the interior; alternatively, often it is easy to extend the equations to a slightly larger open set U which contains C, by an appropriate extension of the functions f_i. Thus, for the purposes of the results in the paper, the assumption that the set U is open is not very restrictive.

Definition 1. System (1) is called a tridiagonal feedback system if there exist scalars $\delta_i \in \{+1, -1\}$, $i = 1, \ldots, n$, such that for all $1 \leq i \leq n - 1$,

$$\delta_i \frac{\partial f_{i+1}(x_i, x_{i+1}, x_{i+2})}{\partial x_i} > 0, \quad \text{and} \quad \delta_i \frac{\partial f_i(x_{i-1}, x_i, x_{i+1})}{\partial x_{i+1}} \geq 0, \qquad (2)$$

for all $x \in U$, and

$$\delta_n \frac{\partial f_1(x_n, x_1, x_2)}{\partial x_n} > 0 \quad \text{for all } x \in U. \qquad (3)$$

Monotone tridiagonal feedback systems are known to have the Poincaré–Bendixson property [2], that is, any compact omega limit set that contains no equilibrium is a periodic orbit. There are two types of monotone tridiagonal feedback system depending on the sign of the product $\delta_1 \cdots \delta_n$. If the sign is positive (negative), then system (1) is called a monotone tridiagonal system with positive (negative) feedback.

Monotone tridiagonal systems with positive feedback (or systems that have no feedback at all, i.e. the derivative in (3) is zero) are in particular *monotone systems* in the usual sense of [3], and hence the results in this paper trivially apply to them (unique equilibria and boundedness of solutions implies convergence, at least if the set U satisfies appropriate geometric assumptions, see [3,4] for example). Thus, in this paper we focus exclusively on the negative feedback case. (The terminology "monotone tridiagonal system with negative feedback" is standard but unfortunate, since such systems are not monotone in the usual sense of [3]).

Without loss of generality, we will assume that

$$\delta_i = +1, \qquad \delta_n = -1, \qquad (4)$$

for $i = 1, \ldots, n-1$ (Fig. 3). This is justified because, for arbitrary δ_i with $\delta_1 \cdots \delta_n = -1$, we can introduce new variables

$$x_i^* = \mu_i x_i, \quad 1 \leq i \leq n,$$

where $\mu_1 = 1$, $\mu_{i+1} = \delta_i \mu_i$. Then

$$f_i^*(x_{i-1}^*, x_i^*, x_{i+1}^*) = \dot{x}_i^* = \mu_i \dot{x}_i = \mu_i f_i\left(\frac{x_{i-1}^*}{\mu_{i-1}}, \frac{x_i^*}{\mu_i}, \frac{x_{i+1}^*}{\mu_{i+1}}\right).$$

Thus, for $i = 1, \ldots, n-1$,

$$\frac{\partial f_{i+1}^*}{\partial x_i^*} = \frac{\mu_{i+1}}{\mu_i} \frac{\partial f_{i+1}}{\partial x_i} = \delta_i \frac{\partial f_{i+1}}{\partial x_i} > 0.$$

Similarly, $\frac{\partial f_i^*}{\partial x_{i+1}^*} \geq 0$. To check (3):

$$\frac{\partial f_1^*}{\partial x_n^*} = \frac{\mu_1}{\mu_n} \frac{\partial f_1}{\partial x_n} = -\delta_n \frac{\partial f_1}{\partial x_n} < 0.$$

The last equality uses the condition that $\delta_1 \cdots \delta_n = -1$. From now on, we assume that system (1) satisfies conditions (2)–(4).

1.2. Statements of main results

We now state our main results; their proofs are given in Sections 3.1 and 5.1 respectively. The first of the results is based on a direct linearization argument, and is included here for completeness and comparison with the second one, which is based on compound matrices and tends to give better estimates.

We say that a square matrix is quasi-monotone (Metzler) if it has non-negative off-diagonal entries. A real vector is called non-negative (positive) if all its components are non-negative (positive). If A and B are $n \times n$ such that $A_{ij} \leq B_{ij}$ for all i, j, then we denote this by $A \leq B$. For an arbitrary real $n \times n$ matrix A we let $|A|$ be the $n \times n$ matrix defined by

$$|A_{ij}| = \begin{cases} A_{ij}, & \text{if } i = j \\ |A_{ij}|, & \text{if } i \neq j. \end{cases}$$

Note that $A \leq |A|$.

A set K is said to be absorbing in U, with respect to the system (1), if for each compact set $K_1 \subset U$ there is a $t_0 = t_0(K_1)$ so that every solution $y(t)$ that starts in K_1 has the property that $y(t) \in K$ for all $t \geq t_0$.

Theorem 1. *Let system (1) have a compact absorbing set K in U, and assume that there is a unique equilibrium x^*. Suppose that there exists a quasi-monotone and Hurwitz matrix B such that*

$$|DF(x)| \leq B \quad \text{for all } x \in K.$$

Then x^* is globally asymptotically stable for (1) with respect to initial conditions in U.

Theorem 2. *Let system (1) have a compact absorbing set K in U, and assume that there is a unique equilibrium x^*. Suppose that there exists a quasi-monotone and Hurwitz matrix M such that*

$$DF^{[2]}(x) \leq M \quad \text{for all } x \in K$$

and that x^* is locally asymptotically stable. Then x^* is globally asymptotically stable for (1) with respect to initial conditions in U.

The notation "$^{[2]}$" in the above theorem refers to second compound matrices, which are introduced in Section 4. By a "Hurwitz" matrix, we mean one with the property that the real parts of all its eigenvalues are negative.

2. Preliminaries

We first make remarks that apply to any system of ordinary differential equations

$$\dot{y} = G(y), \quad y \in U, \qquad (5)$$

where U is an open set in $\mathbb{R}^n$, and the vector field G is of class C^1, with special structure.

Definition 2. Let $p(t)$ be a periodic solution of system (5), and denote by Ω the corresponding orbit, $\Omega = \{x = p(t), t \geq 0\}$. The solution $p(t)$ is said to be

1. orbitally (Lyapunov) stable if for any neighborhood W of Ω, all forward trajectories which start in a sufficiently small neighborhood of Ω do not emerge from W;
2. orbitally asymptotically stable (OAS) if it is orbitally Lyapunov stable and if all the solutions with initial condition sufficiently close to Ω approach Ω asymptotically as $t \to +\infty$.

Observe that OAS is the only reasonable notion of "asymptotic stability" for periodic solutions, since a (non-constant) periodic solution can never be asymptotically stable in the usual sense, as solutions with initial conditions at different points of the cycle do not approach one another as $t \to +\infty$.

The key idea for the proofs is as follows. For a system with the Poincaré–Bendixson property, if the system has a compact absorbing set K and a unique equilibrium x^*, which is asymptotically stable, we can obtain global stability of x^*, by ruling out the existence of periodic orbits, as long as one knows that that every periodic orbit is OAS. The intuitive idea [5,6] is that the boundary of the region of attraction of x^*, denoted by ∂U, is compact and invariant. Thus, ∂U must contain a periodic orbit since the equilibrium x^* is unique and $x \notin \partial U$. But then there exist points in the region of attraction of x^* whose orbit converges to the periodic orbit, which is impossible. More precisely:

Theorem 3 (*Theorem 2.2 in [6]*). *For a general ordinary differential equation system (5) with the Poincaré–Bendixson property, if the following assumptions hold:*

1. *There exists a compact absorbing set $K \subset U$.*
2. *There is a unique equilibrium point x^*, and it is locally asymptotically stable.*
3. *Each periodic orbit is orbitally asymptotically stable.*

Then x^* is globally asymptotically stable in U.

In this paper, we consider two different approaches to showing that all periodic orbits are OAS. One is to consider directly the linearization of system (1) at a periodic orbit. The other one relies upon the theory of second compound matrices. This latter approach was followed by Sanchez in [7], for the special case of cyclic systems. Cyclic systems are those for which

$$\frac{\partial f_i(x_{i-1}, x_i, x_{i+1})}{\partial x_{i+1}} \equiv 0 \quad \text{for all } x \in U,\ i = 1, \ldots, n$$

in (1).

3. Linearization approach

We consider here an approach based on direct linearization.

3.1. Proof of Theorem 1

From Lemma 17 in the Appendix, it follows that for some positive vector d, the vector Bd and hence also the vector $|DF(x^*)|d$, are negative vectors. Then Lemma 16 with $A(t) = DF(x^*)$ implies that $DF(x^*)$ must be Hurwitz, and thus x^* is locally asymptotically stable.

By the Poincaré–Bendixson property, it is suffices to show that system (1) has no nontrivial periodic solutions. To see this, assume that $p(t)$ is a nontrivial periodic solution of (1). Then $F(p(t))$ is a nontrivial and periodic solution of the first variational equation:

$$\dot{z} = DF(p(t))z.$$

But by Lemma 16 and since $|DF(p(t))|d \le Bd = -c$ for some positive vector c, it follows that $z = 0$ is asymptotically stable for this equation, and thus we have a contradiction, because 1 is always a Floquet multiplier. ∎

Remark 3. An alternative proof of Theorem 1 could be based on the notion of "infinitesimally contracting" systems. These are systems for which some matrix measure of the Jacobian is uniformly negative on the state space. Specifically, the property that, for some positive d it holds that $|DF(x^*)|d$ is negative for all x, amounts to the requirement of contractivity with respect to the matrix measure corresponding to the weighted L^∞ norm $|x|_d = \max\{d_1|x_1|, \ldots, d_n|x_n|\}$. If such a property holds, then all solutions approach each other, which, in particular, implies asymptotic stability if there is a unique equilibrium. See for instance [8,9].

3.2. When can one find a matrix B as required in the theorem?

Because of the form of the Jacobian, it is reasonable to look for a bounding matrix B with a special structure, namely the sum of a tridiagonal quasi-monotone matrix plus a matrix with a single nonzero positive entry in the last position of the first row. When B has positive entries on both sub-and super-diagonal entries, we next provide a simple necessary condition and a simple sufficient condition for such a matrix B to be Hurwitz.

We start by writing B in the form $B = T + N$, where T is tridiagonal and quasi-monotone, and $T_{ii+1}, T_{i+1i} > 0$ for all $i = 1, \ldots, n-1$, and $N_{1n} = f > 0$ while $N_{ij} = 0$ when $(i,j) \ne (1,n)$. We first make the matrix T symmetric, using a change of coordinates as also done for example in [10]. Define a diagonal matrix D with positive diagonal entries such that:

$$D_{i+1i+1}/D_{ii} = \sqrt{T_{i+1i}/T_{ii+1}}, \quad i = 1, \ldots, n-1.$$

Then by direct computation, $D^{-1}TD =: S$ is tridiagonal, quasi-monotone and *symmetric* ($S = S^T$), with

$$S_{ii} = T_{ii}, \quad i = 1, \ldots, n \quad \text{and} \quad S_{ii+1} = \sqrt{T_{ii+1}T_{i+1i}}, \quad i = 1, \ldots, n-1.$$

In other words, S is obtained from T by replacing the sub- and superdiagonal entries by the geometric means of each pair of entries. Also, $D^{-1}ND := \tilde{N}$ is given by

$$\tilde{N}_{1n} = \alpha f, \quad \text{and} \quad \tilde{N}_{ij} = 0 \quad \text{if } (i,j) \ne (1,n),$$

where

$$\alpha := \sqrt{\prod_{i=1}^{n-1} \frac{T_{i+1i}}{T_{ii+1}}}.$$

Thus, since B is similar to $S + \tilde{N}$, and since the dominant Perron–Frobenius eigenvalues [11] of the quasi-monotone matrices S and B are related as follows:

$$\lambda_{PF}(S) \le \lambda_{PF}(S + \tilde{N}) = \lambda_{PF}(B),$$

because $\tilde{N}$ has non-negative entries, it follows that B is Hurwitz only if S is Hurwitz, i.e.

$$S = S^T \quad \text{is negative definite.} \tag{6}$$

Recall that (6) holds if and only if the leading principal minors of S,

$$m_1 := T_{11}, \qquad m_2 := \det\begin{pmatrix} T_{11} & \sqrt{T_{12}T_{21}} \\ \sqrt{T_{12}T_{21}} & T_{22} \end{pmatrix},$$

$$m_3 := \det\begin{pmatrix} T_{11} & \sqrt{T_{12}T_{21}} & 0 \\ \sqrt{T_{12}T_{21}} & T_{22} & \sqrt{T_{23}T_{32}} \\ 0 & \sqrt{T_{23}T_{32}} & T_{33} \end{pmatrix}, \ldots$$

alternate in sign starting with $m_1 < 0$. In summary, we have the following necessary condition:

Proposition 4. *If the matrix B is Hurwitz, then $(-1)^i m_i > 0$ for $i = 1, \ldots, n$.*

To obtain a sufficient condition that B is Hurwitz, we assume henceforth that S is negative definite. Define a positive row vector c, and a nonzero, non-negative row vector d, as follows:

$$c_1 = 1, \qquad c_i = \frac{(-1)^{i-1} m_{i-1}}{\prod_{j=1}^{i-1} S_{jj+1}}, \quad i = 2, \ldots, n.$$

$$d_i = 0, \quad i = 1, \ldots, n-1, \qquad d_n = 1.$$

Then by direct computation,

$$c(S + \tilde{N}) = cS + \alpha f d = (\lambda + \alpha f)d,$$

where

$$\lambda := -\frac{(-1)^n m_n}{\prod_{i=1}^{n-1} S_{ii+1}} = -\frac{(-1)^n \det T}{\sqrt{\prod_{i=1}^{n-1} T_{ii+1}T_{i+1i}}}.$$

Observe that $\lambda < 0$. We claim that under the assumption that S is negative definite, the matrix $S + \tilde{N}$, and therefore also the matrix B are Hurwitz if and only if:

$\lambda + \alpha f < 0$.

To see this, notice first that $S + \tilde{N}$ is irreducible and quasi-monotone, hence it has a unique positive (right) eigenvector ζ associated to its real dominant Perron–Frobenius eigenvalue r [11]. We need to show that $r < 0$ if and only if $\lambda + \alpha f < 0$ holds. But this is immediate from

$c(S + \tilde{N})\zeta = rc\zeta = (\lambda + \alpha f)d\zeta$

since $c\zeta > 0$ and $d\zeta > 0$.

In summary, using the definitions for α and λ in terms of the entries of T, we have the following sufficient condition:

Proposition 5. *Suppose that $S = S^T$ is negative definite. Then, the matrix B is Hurwitz if and only if*

$$f < \frac{(-1)^n \det T}{\prod_{i=1}^{n-1} T_{i+1i}}. \tag{7}$$

Remark 6. Proposition 5 amounts to a small-gain theorem. Indeed, consider the following system with scalar input u and scalar output y:

$$\dot{x} = Tx + bu \tag{8}$$

$$y = cx \tag{9}$$

with $b = \mathrm{col}\,(1, 0, 0, \dots, 0)$ and $c = (0, \dots, 0, 1)$ and note that the system of interest, $\dot{x} = Bx$, is obtained by substituting the feedback law $u = fx$ into (8). Since T is stable (this is equivalent to the assumption that S is negative definite), the linear system (8) has a well-defined characteristic, in the sense of [12]. Thus, the small-gain theorem given in that paper (or, equivalently, since the H_∞ norm in this case coincides with the DC gain, the classical small gain theorem for induced L^2 norms) says that B will be Hurwitz provided that $W(0)f < 1$. Now, Lemma 6.1 of [10] establishes that the transfer function $W(s)$ of this system is:

$$W(s) = \frac{\prod_{i=2}^{n} T_{i+1,i}}{q(s)}$$

where $q(s)$ is the characteristic polynomial of T. In particular, then,

$$W(0) = \frac{\prod_{i=2}^{n} T_{i+1,i}}{(-1)^n \det T}.$$

4. Second additive compound matrices

Recall the definition of the second additive compound matrix [13]:

Definition 7. Let A be a matrix of order n. The second compound matrix $A^{[2]}$ is a matrix of order $\binom{n}{2}$ which is defined as follows:

$$A^{[2]}_{(i)(j)} = \begin{cases} A_{i_1 i_1} + A_{i_2 i_2}, & \text{if } (i) = (j), \\ (-1)^{r+s} A_{i_r j_s} & \text{if exactly one entry } i_r \text{ of } (i) \text{ does not occur in } (j) \text{ and } j_s \text{ does not occur in } (i), \text{ for some } r, s \in \{1, 2\}, \\ 0 & \text{if } (i) \text{ differs from } (j) \text{ in both entries.} \end{cases}$$

Here, $(i) = (i_1, i_2)$ is the ith member of the lexicographic order of integer pairs for which $1 \le i_1 < i_2 \le n$.

For future reference, we state the following well-known fact from the theory of second compound matrices, see [14].

Lemma 8. *Let the eigenvalues of a real $n \times n$ matrix A be denoted by λ_i, $i = 1, \dots, n$. Then the eigenvalues of $A^{[2]}$ are given by $\lambda_i + \lambda_j$ for $i < j$ with $i = 1, \dots, n-1$ and $j = 2, \dots, n$.*

Lemma 9. *A matrix A of order n is Hurwitz if and only if $A^{[2]}$ is Hurwitz and the sign of $\det(A)$ is $(-1)^n$.*

Let us denote by $DF(x)$ the Jacobian of system (1). The following observation is crucial to our proof.

Lemma 10. *The second additive compound matrix $DF^{[2]}(x)$ is quasi-monotone for any $x \in U$.*

Proof. Recall that the only non-zero off-diagonal entries of $DF(x)$ are

$$DF(x)_{ii-1} > 0, \quad DF(x)_{ii+1} \ge 0, \quad \text{for } i = 2, \dots, n-1,$$
$$DF(x)_{12} \ge 0, \quad DF(x)_{nn-1} > 0, \quad DF(x)_{1n} < 0.$$

Thus the off-diagonal entries of $DF^{[2]}(x)$ are non-zero only when one of the following five cases happens:

1. The pairs $i = (i_1, i_2), j = (i_1, i_2 - 1)$ for some $i_2 > i_1 + 1$. In this case $DF^{[2]}_{ij}(x) = (-1)^{2+2} DF(x)_{i_2 i_2 - 1} > 0$.
2. The pairs $i = (i_1, i_2), j = (i_1, i_2 + 1)$ for some $i_2 > i_1$. In this case $DF^{[2]}_{ij}(x) = (-1)^{2+2} DF(x)_{i_2 i_2 + 1} \ge 0$.
3. The pairs $i = (i_1, i_2), j = (i_1 - 1, i_2)$ for some $i_2 > i_1$. In this case $DF^{[2]}_{ij}(x) = (-1)^{1+1} DF(x)_{i_1 i_1 - 1} > 0$.
4. The pairs $i = (i_1, i_2), j = (i_1 + 1, i_2)$ for some $i_2 > i_1 + 1$. In this case $DF^{[2]}_{ij}(x) = (-1)^{1+1} DF(x)_{i_1 i_1 + 1} \ge 0$.
5. The pairs $i = (1, i_2), j = (i_2, n)$ for some $1 < i_2 < n$. In this case $DF^{[2]}_{ij}(x) = (-1)^{1+2} DF(x)_{1n} > 0$.

Therefore, the second additive compound matrix $DF^{[2]}(x)$ has only non-negative off-diagonal entries. ■

See [15] for a full characterization of the class of matrices whose second additive compound matrices are quasi-monotone.

5. Compound matrices approach

Second additive compound matrices can be used to study the stability of periodic orbits. The following lemma states a result by Muldowney [16,13], also used in [6,17,7].

Lemma 11. *A given nontrivial periodic solution $p(t)$ of (5) is orbitally asymptotically stable provided the linear system*

$$\dot{z} = DG^{[2]}(p(t))z$$

is asymptotically stable.

By Lemma 10 we know that for system (1) the matrix $DF^{[2]}(p(t))$ is quasi-monotone for all times. In this case, it turns out that to establish asymptotic stability for

$$\dot{z} = DF^{[2]}(p(t))z, \tag{10}$$

it is enough to check that for all t, the matrix $DF^{[2]}(p(t))$ is bounded above (in the same sense as when talking about the Jacobian of F) by a quasi-monotone and Hurwitz matrix B. This follows for instance from Proposition 3 in [17] or proofs based on quadratic Lyapunov functions [18–20]. Here, we use Lemma 16 provided in the Appendix.

5.1. Proof of Theorem 2

Let us assume that $p(t)$ is a nontrivial periodic solution and show that it must be OAS. Since M is quasi-monotone and Hurwitz, it follows from Lemma 17 that there exist componentwise positive vectors c and d such that $Md = -c$. Notice that for all t, we have $M - DF^{[2]}(p(t)) \ge 0$ and thus $\left(M - DF^{[2]}(p(t))\right) d \ge 0$. Moreover,

$DF^{[2]}(p(t)) \geq 0$, for all t, implies $|DF^{[2]}(p(t))| = DF^{[2]}(p(t))$. It thus follows that for all t,

$$|DF^{[2]}(p(t))|d \leq Md = -c,$$

which by Lemma 16 in the Appendix yields that (10) is asymptotically stable. Therefore, $p(t)$ is OAS for system (1). The conclusion now follows from an application of Theorem 3. ■

6. Applications

6.1. Linear monotone tridiagonal systems with nonlinear negative feedback

We restrict our attention to systems of the form:

$$\begin{aligned}\dot{x}_1 &= -d_1x_1 + \beta_1x_2 + g(x_n)\\ \dot{x}_i &= \alpha_ix_{i-1} - d_ix_i + \beta_ix_{i+1}, \quad i = 2, \dots, n-1 \\ \dot{x}_n &= \alpha_nx_{n-1} - d_nx_n.\end{aligned} \tag{11}$$

We denote by $F = (f_1, \dots, f_n)$ the vector field of system (11). The following assumptions are made about system (11).

A1 d_i, α_j, and β_k are positive numbers.
A2 The function $g : \mathbb{R}_{\geq 0} \to \mathbb{R}_{>0}$ is smooth and strictly decreasing.
A3 The matrix T is Hurwitz:

$$T = \begin{pmatrix} -d_1 & \beta_1 & 0 & \cdots & 0 \\ \alpha_2 & -d_2 & \beta_2 & \cdots & 0 \\ \cdots & \cdots & \cdots & \cdots & \cdots \\ 0 & \cdots & 0 & \alpha_n & -d_n \end{pmatrix}.$$

It is clear from assumptions A1 and A2 that system (11) is a monotone tridiagonal system with negative feedback. Moreover, the non-negative orthant is forward invariant for system (11).

Lemma 12. *Under assumptions* A1 *to* A3*, system* (11) *has a unique steady state* $x^* \in \mathbb{R}^n_{>0}$.

Proof. Every steady state x^* satisfies $Tx^* + G(x_n^*) = 0$, with $G(x_n) = (g(x_n), 0, \dots, 0)^T$. Let us start from solving the nth equation of $T\bar{x}^* + G(x_n^*) = 0$, i.e., $\alpha_n\bar{x}^*_{n-1} = d_n\bar{x}^*_n$, which yields $\bar{x}^*_{n-1} = \frac{d_n}{\alpha_n}\bar{x}^*_n$. Substituting $\bar{x}^*_{n-1} = d_n\bar{x}^*_n/\alpha_n$ into the $(n-1)$th equation, we obtain

$$\bar{x}^*_{n-2} = \frac{1}{\alpha_{n-1}\alpha_n}\det(T_{n-1\ n,n-1\ n})\bar{x}^*_n.$$

Here $T_{i_1,\dots,i_k,i_1,\dots,i_k}$ denote the $k \times k$ submatrix of T consisting of rows and columns from i_1 to i_k. Repeating this procedure for other equations of $T\bar{x}^* + G(x_n^*) = 0$ in backward order, we have

$$x_j^* = \frac{1}{\prod_{i=j+1}^{n}\alpha_i}(-1)^{n-j}\det(T_{j+1,\dots,n,j+1,\dots,n})x_n^*, \tag{12}$$

for all $j = 1, \dots, n-1$. We claim that all x_j^* are positive.

To see this we recall from Theorem 15.5.1 in [21] that a quasi-monotone matrix is Hurwitz if and only if its leading principal minors alternate in sign, and the first one (the diagonal entry in the upper left corner) is negative. We can apply this result to the matrix obtained from T by performing the permutation which reverses the order of the state components by transforming $(x_1, x_2, \dots, x_n)$ into $(x_n, x_{n-1}, \dots, x_1)$. This matrix is Hurwitz since it is similar to T, and it is also quasi-monotone, and thus by the result from [21] we just mentioned, its leading principal minors alternate in sign. But these are precisely the determinants appearing in (12), implying that each x_j^* is positive.

By substituting (12) into the equation $d_1x_1^* - \beta_1x_2^* = g(x_n^*)$, we obtain

$$\frac{1}{\prod_{i=2}^{n}\alpha_i}(-1)^n\det(T)x_n^* = g(x_n^*). \tag{13}$$

Under assumption A3, the left-hand side of (13) is a linear increasing function in x_n^*. The right-hand side of (13) is a decreasing function with $g(0) > 0$. So there is a unique root x_n^* on $(0, \infty)$. The other coordinates at the steady state are also positive and unique because of (12). ■

Lemma 13. *Under assumptions* A1 *to* A3*, system* (11) *has a compact absorbing set* $K \subset \mathbb{R}^n_{>0}$*, defined as*

$$K = \{x \mid \underline{x} \leq x \leq \bar{x}\},$$

for some positive vectors $\underline{x}$ *and* $\bar{x}$.

Proof. Fix any compact subset K_1 of $\mathbb{R}^n_{>0}$. Denote the solution to system (11) with arbitrary initial condition x_0 by $x(t, x_0)$.

We will first show that there is some $t_0 \geq 0$ and $\bar{x} \in \mathbb{R}^n_{>0}$ such that

$$x(t, x_0) \leq \bar{x}, \quad \forall\, t \geq t_0 \text{ and } x_0 \in K_1. \tag{14}$$

By A2 it follows that

$$\dot{x} = Tx + G(x_n) \leq Tx + G(0),$$

and then the comparison principle for monotone systems [3] implies that

$$x(t, x_0) \leq u(t, x_0), \quad \forall\, t \geq 0, \tag{15}$$

where $u(t, x_0)$ solves the linear system $\dot{u} = Tu + G(0)$. The latter system has a globally asymptotically stable equilibrium $\bar{u} := -T^{-1}G(0)$ ($\bar{u} \in \mathbb{R}^n_{>0}$ since T is Hurwitz and irreducible and $G(0)$ is a nonzero, non-negative vector), and therefore:

$$|u(t, x_0) - \bar{u}| \leq M_0|x_0|\mathrm{e}^{-a_0t}, \quad \forall\, x_0 \in \mathbb{R}^n, \tag{16}$$

for some $a_0, M_0 > 0$. Using (15) and (16) we can find some $t_0 > 0$ and some $\bar{x} \in \mathbb{R}^n_{>0}$ such that (14) holds.

With similar arguments we can establish the existence of a lower bound $\underline{x}$ for solutions starting in K_1. Specifically, we can find $T_0 \geq t_0$ and $\underline{x} \in \mathbb{R}^n_{>0}$ such that

$$\underline{x} \leq x(t, x_0), \quad \forall\, t \geq T_0 \text{ and } x_0 \in K_1. \tag{17}$$

Using (14), we have, in particular, that $x_n \leq \bar{x}_n$. As G is a decreasing function, $G(x_n) \geq G(\bar{x}_n)$ for all $t \geq t_0$ and all $x_0 \in K_1$. Thus,

$$\dot{x} = Tx + G(x_n) \geq Tx + G(\bar{x}_n), \quad \forall\, t \geq t_0$$

and then the comparison principle for monotone systems [3] implies that

$$x(t, x_0) \geq v(t, x(t_0)), \quad \forall\, t \geq t_0, \tag{18}$$

where $v(t, x(t_0))$ denotes the solution starting in $x(t_0)$ at time t_0 of the linear system $\dot{v} = Tv + G(\bar{x}_n)$. The latter system has a globally asymptotically stable equilibrium $\underline{v} := -T^{-1}G(\bar{x}_n)$ ($\underline{v} \in \mathbb{R}^n_{>0}$ since T is Hurwitz and irreducible and $G(\bar{x}_n)$ is a nonzero, non-negative vector), and therefore:

$$|v(t, x(t_0)) - \underline{v}| \leq M_1|x(t_0)|\mathrm{e}^{-a_1(t-t_0)}, \quad \forall\, x(t_0) \in \mathbb{R}^n \text{ and } t \geq t_0, \tag{19}$$

for some $a_1, M_1 > 0$. Using (18) and (19) we can find some $T_0 \geq t_0$ and some $\underline{x} \in \mathbb{R}^n_{>0}$ such that (17) holds.

To summarize, we have established that for any initial condition $x_0 \in K_1$, the following inequality

$$\underline{x} \le x(t) \le \bar{x}$$

holds for all $t \ge T_0$, where T_0 is uniform for all $x_0 \in K_1$. Therefore K is an absorbing set in $\mathbb{R}^n_{>0}$. ■

Remark 14. Using this result, the existence of the steady states of system (11) can be derived directly from the fact that K is homeomorphic to a ball. However, the algebraic approach given in the proof of Lemma 12 guarantees both existence and uniqueness.

The Jacobian matrix of system (11) is

$$DF(x) = \begin{pmatrix} -d_1 & \beta_1 & 0 & \cdots & g'(x_n) \\ \alpha_2 & -d_2 & \beta_2 & \cdots & 0 \\ \cdots & \cdots & \cdots & \cdots & \cdots \\ 0 & \cdots & 0 & \alpha_n & -d_n \end{pmatrix}.$$

Using the approach based on direct linearization we define the matrix $B := T + N$, where $N_{1n} = \max_{x \in K} |g'(x_n)|$ while $N_{ij} = 0$ when $(i, j) \neq (1, n)$. Then Theorem 1 yields:

Theorem 4. *Under assumptions* A1 *to* A3*, x^* is globally asymptotically stable for system* (11) *provided B is Hurwitz.*

Recall from the discussion following Theorem 1 that under the assumption that (6) holds, the matrix B is Hurwitz if and only if (7) holds. Condition (6) holds because matrices T and S are similar, and T is Hurwitz. Thus, B is Hurwitz if and only if:

$$\max_{x \in K} |g'(x_n)| < \frac{(-1)^n \det(T)}{\prod_{i=2}^{n} \alpha_i}. \tag{20}$$

Let us also consider the approach based on the second compound matrix. The existence of a compact absorbing set is proved in Lemma 13. The existence and uniqueness of the equilibrium is shown in Lemma 12. It remains to show that x^* is locally asymptotically stable and to find a quasi-monotone Hurwitz matrix M such that $M \ge DF^{[2]}(x)$ for all $x \in K$.

Consider the matrix $A := T - N$, and let $M = A^{[2]}$. Based on the proof of Lemma 10, it is easy to see that M is quasi-monotone and $M \ge DF^{[2]}(x)$ for all $x \in K$. If we further assume that A is Hurwitz, then so is M (Lemma 9). On the other hand, if M is Hurwitz, then $DF^{[2]}(x^*)$ is Hurwitz because $\lambda_{PF}(DF^{[2]}(x^*)) \le \lambda_{PF}(M)$ [11]. In order to get local asymptotical stability of x^*, $DF(x^*)$ needs to be Hurwitz, which is true by Lemma 9 provided that the determinant of $DF(x^*)$ has the sign of $(-1)^n$. The determinant of $DF(x^*)$ equals

$$(-1)^n(-g'(x_n^*))\alpha_2\alpha_3\cdots\alpha_n + \det(T).$$

Since T is Hurwitz and g is strictly decreasing, the sign of $\det(DF(x^*))$ is $(-1)^n$. In summary, we have established the following:

Theorem 5. *Under assumptions* A1 *to* A3*, x^* is globally asymptotically stable for system* (11) *provided A is Hurwitz.*

Let us now compare the conditions for global stability based on the linearization approach (Theorem 4) to those based on the second compound matrices approach (Theorem 5). We claim that the condition "B is Hurwitz" from the former implies the condition "A is Hurwitz" from the latter (By means of a numerical example below we will see that the converse is not necessarily true). In other words, the condition based on the linearization approach is at least as strong as the condition based on the second compound matrices approach. On the other hand, verifying that B is Hurwitz amounts to checking the single inequality (20) which might be easier to do in practice than verifying that the matrix A (which is not quasi-monotone) is Hurwitz.

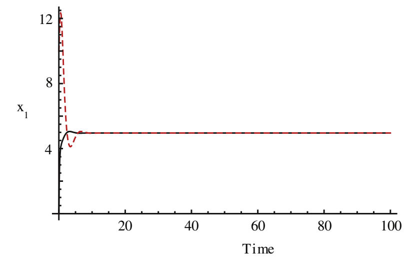

Fig. 4. The time evolution of the x_1-coordinate of two solutions of system (21) when $\gamma = 1$. The red dashed curve corresponds to the one with initial condition (10, 0, 0, 0), and the black solid curve represents the solution with initial condition (0, 0, 3, 0).

To prove the claim, we note that if B, a quasi-monotone matrix, is Hurwitz, then by Lemma 17 in the Appendix, there exist positive vectors c and d, such that $Bd = -c$. But $B = |A|$, hence it follows from Lemma 16 in the Appendix that A is Hurwitz as well.

To illustrate the results in Theorem 5, consider the following example of a system of type (11):

$$\begin{aligned} \dot{x}_1 &= -2x_1 + x_2 + 10e^{-\gamma(x_4-1)} \\ \dot{x}_2 &= x_1 - 4x_2 + x_3 \\ \dot{x}_3 &= x_2 - 3x_3 + x_4 \\ \dot{x}_4 &= 2x_3 - 1.5x_4. \end{aligned} \tag{21}$$

Here, $\gamma > 0$ and $g(x_4) = 10e^{-\gamma(x_4-1)}$ is a strictly decreasing function with $g(0) = 10e^{\gamma}$ and $g'(x_4) = -10\gamma e^{-\gamma(x_4-1)}$. The matrix

$$T = \begin{pmatrix} -2 & 1 & 0 & 0 \\ 1 & -4 & 1 & 0 \\ 0 & 1 & -3 & 1 \\ 0 & 0 & 2 & -1.5 \end{pmatrix}$$

is Hurwitz. The matrix N by definition has $N_{1n} = 10\gamma e^{\gamma}$ and $N_{ij} = 0$ when $(i, j) \neq (1, n)$. Therefore,

$$A = T - F = \begin{pmatrix} -2 & 1 & 0 & -10\gamma e^{\gamma} \\ 1 & -4 & 1 & 0 \\ 0 & 1 & -3 & 1 \\ 0 & 0 & 2 & -1.5 \end{pmatrix}.$$

When $\gamma = 1$, A is Hurwitz, and thus all conditions in Theorem 5 are satisfied. We expect that all solutions converge to the unique steady state, see Fig. 4. When $\gamma = 10$, A is not Hurwitz. The simulation result shows oscillations, see Fig. 5. In fact, in the case $\gamma = 10$, the unique equilibrium is unstable, and the existence of limit cycles follows from the Poincaré–Bendixson property.

Theorem 4 requires the matrix

$$B = \begin{pmatrix} -2 & 1 & 0 & 10\gamma e^{\gamma} \\ 1 & -4 & 1 & 0 \\ 0 & 1 & -3 & 1 \\ 0 & 0 & 2 & -1.5 \end{pmatrix}$$

to be Hurwitz, which by condition (20) is equivalent to:

$$\gamma e^{\gamma} < 0.725.$$

Using the Routh–Hurwitz criterion, the condition that A is Hurwitz in Theorem 5 is equivalent to

$$\gamma e^{\gamma} < 5.7055,$$

which is a more relaxed condition that that in Theorem 4, the inequality $\gamma e^{\gamma} < 0.725$.

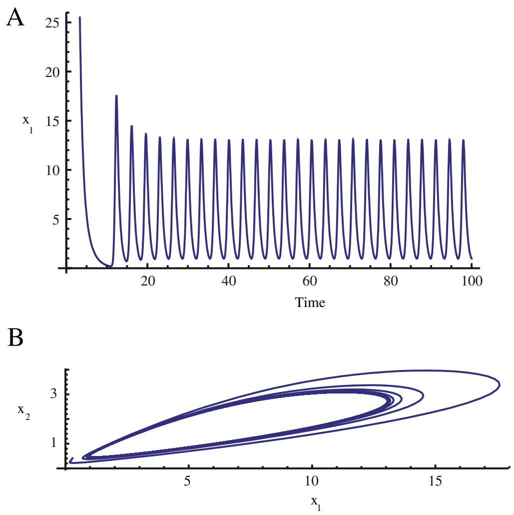

Fig. 5. Oscillation appears in system (21) when $\gamma = 10$. A the x_1-coordinate of the solution with initial condition (0, 0, 3, 0). B the projection of the same solution to the x_1, x_2-plane starting at $t = 10$.

6.2. The Goldbeter model

In this section, we consider one of the simplest and classical models of circadian rhythms, the one proposed by Goldbeter [1,22], and present conditions under which the rhythm is disrupted, more precisely, there is a globally asymptotically stable steady state. The model is given as follows:

$$\begin{aligned}\dot{M} &= \frac{v_s K_I^n}{K_I^n + P_N^n} - \frac{v_m M}{k_m + M}\\ \dot{P_0} &= k_s M - \frac{V_1 P_0}{K_1 + P_0} + \frac{V_2 P_1}{K_2 + P_1}\\ \dot{P_1} &= \frac{V_1 P_0}{K_1 + P_0} - \frac{V_2 P_1}{K_2 + P_1} - \frac{V_3 P_1}{K_3 + P_1} + \frac{V_4 P_2}{K_4 + P_2}\\ \dot{P_2} &= \frac{V_3 P_1}{K_3 + P_1} - \frac{V_4 P_2}{K_4 + P_2} - k_1 P_2 + k_2 P_N - \frac{v_d P_2}{k_d + P_2}\\ \dot{P_N} &= k_1 P_2 - k_2 P_N.\end{aligned} \tag{22}$$

Here, all the parameters are positive, and all variables are non-negative. The variable M represents the mRNA concentration of PER; P_0, P_1, and P_2 represent the concentrations of PER in the cytoplasm with no phosphate group, one phosphate group, and two phosphate groups, respectively; P_N denotes the concentration of PER in the nucleus.

System (22) considered on a slightly larger open set U containing $\mathbb{R}^n_{\geq 0}$ is a tridiagonal system with negative feedback from P_N to M. It clearly satisfies conditions (2) and (3) with values of the δ_i as in (4). We next state a result from [10] for this system.

Lemma 15. *Assume the following conditions hold:*

- $0 < \frac{v_s k_m}{v_m - v_s} < \frac{v_d}{k_s}$;
- $v_d + V_2 < V_1$;
- $V_1 + V_4 < V_2 + V_3$;
- $V_4 + v_d < V_3$.

Then there exists positive numbers $\bar{M}, \bar{P}_0, \bar{P}_1, \bar{P}_2, \bar{P}_N$ such that system (22) has a compact absorbing set C in U, where

$$C := \{x \mid 0 \leq M \leq \bar{M}, 0 \leq P_0 \leq \bar{P}_0, 0 \leq P_1 \leq \bar{P}_1, 0 \leq P_2 \leq \bar{P}_2, 0 \leq P_N \leq \bar{P}_N\}.$$

Moreover, there is a unique steady state x^* inside C.

Table 1
Parameter values used in simulations of system (22).

Parameter	Value	Parameter	Value
k_2	1.3	k_1	1.9
V_1	3.2	V_2	1.58
V_3	5	V_4	2.5
v_m	0.65	k_m	0.5
k_s	0.38	v_d	0.95
k_d	0.2	n	4
K_1	2	K_2	2
K_3	2	K_4	2
K_I	1		

Observe that the nonlinear terms in vector field of (22) are all functions of Michaelis–Menten form, that is, of the type:

$$h(y) = \frac{vy}{K + y}, \quad y \in [0, \bar{y}].$$

For such a function, $h'(y) = \frac{vK}{(K+y)^2} > 0$. As a result, the maximum and minimum of $h'(x)$ on $[0, \bar{y}]$ are $h'(0)$ and $h'(\bar{y})$, respectively. Based on this observation, it is easy to see that the second additive compound matrix $DF^{[2]}(x)$ is bounded by the matrix $A^{[2]}$. Here,

$$\begin{aligned}A = \operatorname{diag}\Big\{&-\frac{v_m k_m}{(k_m + \bar{M})^2}, -\frac{V_1 K_1}{(K_1 + \bar{P}_0)^2}, -\frac{V_2 K_2}{(K_2 + \bar{P}_1)^2}\\ &-\frac{V_3 K_3}{(K_3 + \bar{P}_1)^2}, -\frac{V_4 K_4}{(K_4 + \bar{P}_2)^2} - \frac{v_d k_d}{(k_d + \bar{P}_2)^2} - k_1, -k_2\Big\}\\ &+ \begin{pmatrix} 0 & 0 & 0 & 0 & \bar{g}\\ k_s & 0 & \frac{V_2}{K_2} & 0 & 0\\ 0 & \frac{V_1}{K_1} & 0 & \frac{V_4}{K_4} & 0\\ 0 & 0 & \frac{V_3}{K_3} & 0 & k_2\\ 0 & 0 & 0 & k_1 & 0 \end{pmatrix},\end{aligned}$$

where $\bar{g} = -\frac{v_s (n-1)^{\frac{n-1}{n}} (n+1)^{\frac{n+1}{n}}}{4nK_I}$ is the minimum of $v_s K_I^n/(K_I^n + P_N^n)$ on $[0, \infty)$.

Theorem 6. *Suppose that the assumptions in Lemma 15 hold and that the matrix A is Hurwitz. If the sign of $\det(DF(x^*))$ is -1, then x^* is globally asymptotically stable.*

Proof. Lemma 15 guarantees the existence of an absorbing set C and the uniqueness of the steady state x^*. We pick the quasi-monotone matrix M (in Theorem 2) as $A^{[2]}$. It thus follows from our previous observations (derivatives of the Michaelis–Menten functions are positive) that $A^{[2]} \geq DF^{[2]}(x)$ for all $x \in C$. It remains to show that x^* is asymptotically stable, which is equivalent to $DF(x^*)$ being Hurwitz. The condition, A is Hurwitz, implies that $A^{[2]}$ is Hurwitz, and so does $DF(x^*)^{[2]}$. Since the sign of $\det(DF(x^*))$ is negative, by Lemma 9, $DF(x^*)$ is Hurwitz. ∎

This result provides conditions under which oscillations will be blocked. On the other hand, when there are oscillations, the conditions in Theorem 6 fail to hold for that set of kinetic parameters. To simulate system (22), we take the set of parameters used by Goldbeter in [1] (see Table 1) and vary v_s to switch between global convergence and oscillations. When $v_s = 0.4$, all conditions in Lemma 15 hold and the matrix A is Hurwitz. Applying Theorem 6, all solutions converge to a unique steady state (Fig. 6). On the other hand, when $v_s = 0.76$, oscillation appears (Fig. 7). Checking conditions in Theorem 6, we see that the condition $0 < \frac{v_s k_m}{v_m - v_s}$ is violated, and in addition, the Jacobian matrix at the unique steady state is unstable.

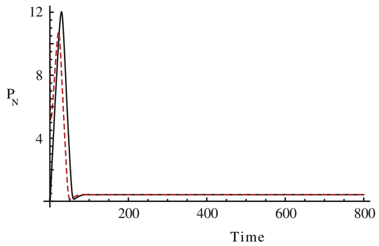

Fig. 6. The P_N-coordinate of two solutions of system (21) when $v_s = 0.4$. The red dashed curve corresponds to the one with initial condition (10, 0, 0, 0, 10), and the black solid curve represents the solution with initial condition (10, 10, 0, 0, 0).

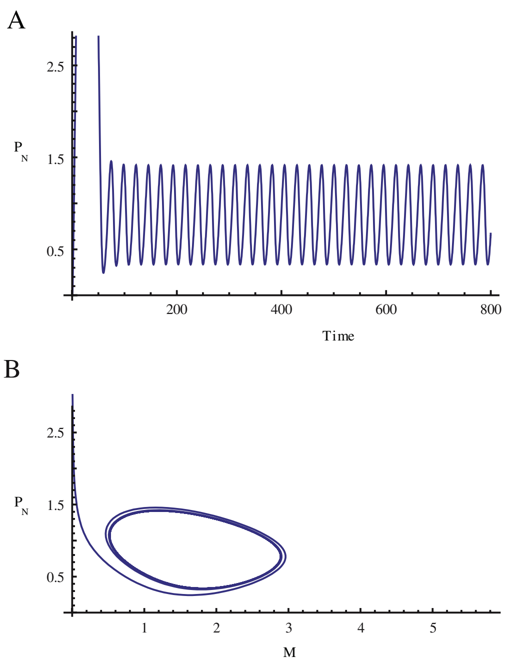

Fig. 7. Oscillation appears when $v_s = 0.76$ in system (21). A the P_N-coordinate of the solution with initial condition (10, 1, 0, 0, 0). B the projection of the same solution to the M, P_N-plane.

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Appendix

We will state a stability result for general time-varying systems which may be of interest in itself. This result may be proved by means of the theory of contractive systems, using a weighted L^∞ norm as described in Remark 3. We choose to give instead an alternative proof based on the use of Dini derivatives.

For Dini derivatives used for Lyapunov functions, see [23]. Recall that if f is a scalar real-valued function, then we denote the (right upper) Dini derivative at x as:

$$D^+ f(x) = \limsup_{h\to 0+} \frac{f(x+h) - f(x)}{h},$$

whenever it exists.

Lemma 16. *Let $\dot{x} = A(t)x$ be a linear time-varying system where $A(t)$ is a continuous matrix function. If there are (componentwise) positive vectors $c, d > 0$ such that $|A(t)|d \le -c$ for all t, then $x = 0$ is asymptotically stable.*

Proof. We will prove that $V(x) = \max_i |x_i|/d_i$ is a Lyapunov function for the system $\dot{x} = A(t)x$, by showing that $D^+V(x(t))$ is negative for every nontrivial solution $x(t)$. There holds that

$$\begin{aligned} D^+V(x(t)) &= \limsup_{h\to 0+} \frac{\max_i \frac{|x_i(t+h)|}{d_i} - \max_i \frac{|x_i(t)|}{d_i}}{h} \\ &= \limsup_{h\to 0+} \left[\max_i \frac{|x_i(t+h)|}{hd_i} - \max_i \frac{|x_i(t)|}{hd_i} \right]. \end{aligned}$$

Now for every i and all $h > 0$ small enough, there holds

$$\begin{aligned} \frac{|x_i(t+h)|}{hd_i} &= \left| \frac{x_i(t)}{hd_i} + \frac{h}{hd_i} \sum_{j=1}^n a_{ij}(t)x_j(t) + \frac{o_i(h)}{hd_i} \right| \\ &\le \frac{(1+ha_{ii}(t))}{h} \frac{|x_i(t)|}{d_i} + \frac{1}{d_i} \sum_{j\ne i}^n |a_{ij}(t)| d_j \frac{|x_j(t)|}{d_j} + \frac{|o_i(h)|}{hd_i} \\ &\le \frac{(1+ha_{ii}(t))}{h} V(x(t)) + \frac{1}{d_i} \sum_{j\ne i}^n |a_{ij}(t)| d_j V(x(t)) + \frac{|o_i(h)|}{hd_i} \\ &= \frac{1}{h} V(x(t)) + \frac{1}{d_i} \left[a_{ii}(t)d_i + \sum_{j\ne i}^n |a_{ij}(t)| d_j \right] V(x(t)) + \frac{|o_i(h)|}{hd_i}. \end{aligned}$$

Taking the maximum over all i we get

$$\begin{aligned} \max_i \frac{|x_i(t+h)|}{hd_i} \le \frac{1}{h} V(x(t)) + \max_i \frac{1}{d_i} \Bigg[a_{ii}(t)d_i \\ + \sum_{j\ne 1}^n |a_{ij}(t)| d_j \Bigg] V(x(t)) + \frac{|o(h)|}{hd_i}. \end{aligned} \tag{23}$$

Plugging (23) into the expression for $D^+V(x(t))$ above, we obtain that,

$$\begin{aligned} D^+V(x(t)) &\le \limsup_{h\to 0+} \Bigg[\max_i \frac{1}{d_i} \Bigg[a_{ii}(t)d_i \\ &\quad + \sum_{j\ne 1}^n |a_{ij}(t)| d_j \Bigg] V(x(t)) + \frac{|o(h)|}{hd_i} \Bigg] \\ &= \max_i \frac{1}{d_i} \left[a_{ii}(t)d_i + \sum_{j\ne 1}^n |a_{ij}(t)| d_j \right] V(x(t)) \\ &\le -V(x(t)) \min_i \left(\frac{c_i}{d_i} \right) < 0, \end{aligned}$$

since $x(t) \ne 0$. This concludes the proof. ■

For convenience we state part of Theorem 15.1.1 in [21]:

Lemma 17. *Let A be quasi-monotone. Then A is Hurwitz if and only if there exist componentwise positive vectors c and d such that $Ad = -c$.*

Notice in particular that the sufficiency part of Lemma 17 can be proved by applying Lemma 16 with $A(t) = A$ since in this case $|A(t)| = A$.

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