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Global Stability for Monotone Tridiagonal Systems with Negative Feedback

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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 equilibrium is asymptotically stable, and if one can rule out periodic orbits, then the steady state is globally asymptotically stable. Different approaches are discussed to rule out period orbits. One is based on direct linearization, while the other uses the theory of second additive compound matrices. Among the examples that will illustrate our main theoretical results is the classical Goldbeter model of the circadian rhythm.**

I. 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". 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 control 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. 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 [3]. In all such examples, it is of interest to find conditions that characterize oscillatory versus non-oscillatory regimes.

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.

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II. PRELIMINARIES

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 $A_{ij}\le B_{ij}$ for all i,j, then we denote this by $A\le B$. For an arbitrary real $n\times n$ matrix A we let $|A|$ be the $n\times n$ matrix defined by

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

Consider a general ordinary differential equation

$$\dot{y} = G(y), \quad y\in U, \tag{1}$$

where U is an open set in $\mathbb{R}^n$, and the vector field G is of class C^1. Suppose that system (1) has a periodic solution $p(t)$.

Definition 1: The periodic solution $p(t)$ is said to be orbitally (Lyapunov) stable if for an arbitrarily small neighborhood W of $p(t)$, all forward trajectories which start in a sufficiently small neighborhood of $p(t)$ do not emerge from W.

Definition 2: The periodic solution $p(t)$ is said to be orbitally asymptotically stable (OAS) if it is orbitally Lyapunov stable and if all the phase curves with initial condition sufficiently close to the orbit of $p(t)$ approach $p(t)$ asymptotically as $t\to+\infty$.

Definition 3: A set K is called absorbing in U for (1) if any solution $y(t)$ with initial condition in K_1 stays in K for each compact set $K_1\subset U$ and t sufficiently large.

III. MONOTONE TRIDIAGONAL SYSTEMS WITH NEGATIVE FEEDBACK

A tridiagonal system with feedback has the form:

$$\begin{aligned} \dot{x}_i &= f_i(x_{i-1},x_i,x_{i+1}), \quad i=1,\ldots,n-1 \\ \dot{x}_n &= f_n(x_{n-1},x_n), \end{aligned} \tag{2}$$

where x_0 is identified with x_n, and the vector field $F=(f_1,\ldots,f_n)$ is defined on an open set U. In typical applications, the variables x_i represent nonnegative physical quantities, such as concentrations of chemical species. In such cases, the equations describing the system are initially only specified for vectors x belonging to the nonnegative orthant $\mathbb{R}^n_{\ge 0}$. However, in most cases, one may restrict the system to the interior of $\mathbb{R}^n_{\geq 0}$, or one may also view any such system as a system defined on a slightly larger open set U. This is done by appropriately extending the functions f_i to a neighborhood of the orthant.

Definition 4: System (2) is called a tridiagonal feedback system if there exist scalars $\delta_i \in \{+1, -1\}$, $i = 1, \ldots, n$, such that for all $1 \leq i \leq n-1$,

$$\delta_i \frac{\partial f_i(x_{i-1}, x_i, x_{i+1})}{\partial x_{i-1}} > 0, \text{ and } \frac{\partial f_i(x_{i-1}, x_i, x_{i+1})}{\partial x_{i+1}} \geq 0, \quad (3)$$

for all $x \in U$, and

$$\delta_n \frac{\partial f_n(x_{n-1}, x_n)}{\partial x_{n-1}} > 0 \text{ for all } x \in U. \quad (4)$$

Monotone tridiagonal feedback systems are known to have the Poincaré-Bendixson property ([11]), that is, any compact omega limit set that contains no equilibrium is a periodic orbit. There are two types of tridiagonal feedback systems depending on the sign of the product $\delta_1 \cdots \delta_n$. If the sign is positive (negative), then system (2) is called a tridiagonal system with positive (negative) feedback. In this paper, we focus on the negative feedback case, and from now on we assume without loss of generality (after suitable rescaling of the state components with scaling factor $+1$ or -1) that system (2) satisfies conditions (3) and (4) with

$$\delta_1 = -1 \text{ and } \delta_i = +1, \text{ for } i = 2, \ldots, n. \quad (5)$$

For a system with the Poincaré-Bendixson property, if the system has an 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. To achieve this, the following argument is used [7]. One assumes that every periodic orbit is OAS. Then the boundary of the region of attraction of x^* must contain a periodic orbit since it is invariant. 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 1: (Theorem 2.2 in [10]) For a general ordinary differential equation system (1) with 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.

IV. Ruling out periodic orbits

In this section, we consider two approaches to showing that all periodic orbits are OAS. One is to consider directly the linearization of system (2) at a periodic orbit. The other is to use the theory of second compound matrices, as done in the work of Sanchez [16] 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 (2).

A. Linearization

Using a linearization approach, and Lemma 13 in the Appendix, we have the following fact:

Theorem 2: Let system (2) have a compact absorbing set K in U, and assume that there is a unique equilibrium x^*. If for all $x \in K$, $|DF(x)| \leq B$ for some quasi-monotone and Hurwitz matrix B, then x^* is globally asymptotically stable for (2) with respect to initial conditions in U.

Proof: System (2) has the Poincaré-Bendixson property, so we can apply Theorem 1. The first condition is trivial. The second condition holds because $|DF(x^*)| \leq B$, as a result $DF(x^*)$ must be Hurwitz. To check the third condition, notice that the inequality $|DF(x)| \leq B$ for $x \in K$ implies (using Lemma 13 in Appendix) that every periodic solution is exponentially stable, and hence asymptotically stable, and in particular property 3 holds. The conclusion now follows from an application of Theorem 1. ∎

This theorem can also be proved without appealing to Theorem 1, simply by noticing that all periodic orbits are ruled out: the linearization of an autonomous system along a periodic solution can never be asymptotically stable, because two points on such a solution do not approach each other.

The bounding matrix B can always be assumed to have a special structure, namely that it is the sum of a tridiagonal quasi-monotone matrix, and a matrix with a single nonzero positive entry in the last position of the first row. If B has positive entries on both sub-and superdiagonal, we can give a necessary condition and a sufficient condition such that B is Hurwitz. To see this, let $B = T + F$, where T is tridiagonal and quasi-monotone, and $T_{ii+1}, T_{i+1i} > 0$ for all $i = 1, \ldots, n-1$, and $F_{1n} = f > 0$ while $F_{ij} = 0$ when $(i, j) \neq (1, n)$. Define a diagonal matrix D with positive diagonal entries such that

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

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

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

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, $D^{-1}FD := \tilde{F}$ is given by

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

where

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

Thus, since B is similar to $S + \tilde{F}$, and since the dominant Perron-Frobenius eigenvalues ([2]) of the quasi-monotone matrices S and B are related as follows:

$$\lambda_{PF}(S) \leq \lambda_{PF}(S + \tilde{F}) = \lambda_{PF}(B),$$

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

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

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

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

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

alternate in sign starting with $m_1 < 0$. 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, nonnegative row vector d:

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

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

Then by direct computation,

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

where

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

We claim that if

$$\lambda + \alpha f < 0,$$

then $S + \tilde{F}$ and therefore also B is Hurwitz. To see this, notice first that $S + \tilde{F}$ is irreducible and quasi-monotone, hence it has a unique positive (right) eigenvector ζ associated to its real dominant Perron-Frobenius eigenvalue r [2]. We need to show that $r < 0$. But this is immediate from

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

since $c\zeta > 0$ and $d\zeta > 0$. Summarizing, assuming that $S = S^T$ is negative definite, and using the definitions for α and λ in terms of the entries of T, the matrix B is Hurwitz if

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

B. Second Additive Compound Matrix Approach

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

Definition 5: 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:

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

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 [6].

Lemma 6: Let the eigenvalues of a real $n \times n$ matrix A be denoted by λ_i, $i = 1, \ldots, n$. Then the eigenvalues of $A^{[2]}$ are given by $\lambda_i + \lambda_j$ for $i < j$ with $i = 1, \ldots, n-1$ and $j = 2, \ldots, n$.

Let us denote by $DF(x)$ the Jacobian of system (2). The following observation is crucial to our proof.

Lemma 7: 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 $DF(x)_{ii-1} > 0, DF(x)_{ii+1} \ge 0$ for $i = 2, \ldots, n-1$, $DF(x)_{12} \ge 0$, $DF(x)_{nn-1} > 0$, and $DF(x)_{1n} < 0$. 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. ■

Second additive compound matrices can be used to study the stability of periodic orbits. The following lemma states a result by Muldowney ([8], [13]), also used in [10], [15], [16].

Lemma 8: A given nontrivial periodic solution $p(t)$ of (1) is orbitally asymptotically stable provided the linear system

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

is asymptotically stable.

By Lemma 7 we know that for system (2) the matrix $DF^{[2]}(p(t))$ is quasi-monotone for all times. In this case, it turns out that to establish asymptotic stability for

$$\dot{z} = DF^{[2]}(p(t))z, \tag{8}$$

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 [15]. An alternative proof based on Lemma 13 in the Appendix is provided here.

The following result provides an alternative to Theorem 2:

Theorem 3: Assume that the first two conditions in Theorem 1 hold, and that there exists a quasi-monotone Hurwitz matrix M such that $M \ge DF^{[2]}(x)$ for all $x \in K$. Then x^* is globally asymptotically stable for system (2).

Proof: 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 that there exist componentwise positive vectors c and d such that $Md \le -c$ by Theorem 15.1.1 in [5]. Since for all t, we have that $M - DF^{[2]}(p(t)) \ge 0$ and thus that $\left(M - DF^{[2]}(p(t))\right) d \ge 0$.

Since $DF^{[2]}(p(t))$ is quasi-monotone for all t, and hence $|DF^{[2]}(p(t))| = DF^{[2]}(p(t))$, it follows that for all t,

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

which by Lemma 13 in the Appendix yields that (8) is asymptotically stable. Thus $p(t)$ is OAS for system (2). The conclusion now follows from an application of Theorem 1. ■

V. Applications

A. Linear Monotone Tridiagonal Systems with Nonlinear Negative Feedback

We restrict our attention to systems of the form:

$$\begin{aligned} \dot{x}_1 &= -d_1 x_1 + \beta_1 x_2 + g(x_n) \\ \dot{x}_i &= \alpha_i x_{i-1} - d_i x_i + \beta_i x_{i+1}, \quad i = 2, \ldots, n-1 \\ \dot{x}_n &= \alpha_n x_{n-1} - d_n x_n. \end{aligned} \tag{9}$$

We denote by $F = (f_1, \ldots, f_n)$ the vector field of system (9). The following assumptions are made about system (9).

A1 d_i, α_j, and β_k are positive numbers.

A2 The function $g : \mathbb{R}_{\ge 0} \to \mathbb{R}_{\ge 0}$ is smooth and strictly decreasing with $g(0) > 0$.

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 (9) is a monotone tridiagonal system with negative feedback on the interior of $\mathbb{R}^n_{\ge 0}$. Moreover, the nonnegative orthant is forward invariant for system (9).

Lemma 9: Under assumptions **A1** to **A3**, system (9) has a unique steady state $x^* \in \mathbb{R}^n_{>0}$.

Proof: The steady state x^* satisfies $Tx^* + G(x^*_n) = 0$. Let us start from solving the nth equation of $T\bar{x}^* + G(x^*_n) = 0$, which gives $\alpha_n \bar{x}^*_{n-1} = d_n \bar{x}^*_n$, that is, $\bar{x}^*_{n-1} = \frac{d_n}{\alpha_n}\bar{x}^*_n$. Substituting $\bar{x}^*_{n-1} = d_n \bar{x}^*_n/\alpha_n$ in 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 $T_{i_1,\ldots,i_k,i_1,\ldots,i_k}$ 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

$$x^*_j = \frac{1}{\prod_{i=j+1}^n \alpha_i}(-1)^{n-j}\det(T_{j+1,\ldots,n,j+1,\ldots,n})x^*_n, \tag{10}$$

for all $j = 1, \ldots, n-1$. The coefficient in front of $\bar{x}^*_n$ in equation (10) is positive for each j since the matrix T is Hurwitz (assumption **A3**). By substituting (10) to the equation $d_1 x^*_1 - \beta_1 x^*_2 = g(x^*_n)$, we obtain

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

Under assumption **A3**, the left-hand side is a linear increasing function in x^*_n. The right hand side is a decreasing function with $g(0) > 0$. So there is a unique root x^*_n in $(0, \infty)$. The other components are also positive and unique because of (10). ■

Define a vector function $G(x_n) = (g(x_n)\ 0\ \ldots\ 0)^T$. System (9) can be rewritten as

$$\dot{x} = Tx + G(x_n).$$

Lemma 10: Under assumptions **A1** to **A3**, system (9) has a compact absorbing set $K \subset \mathbb{R}^n_{>0}$, defined as

$$K = \{x \,|\, \underline{x} - \delta \le x \le \bar{x} + \delta\},$$

where $\bar{x} = (\bar{x}_1, \ldots, \bar{x}_n) = -T^{-1}G(0)$, $\underline{x} = (\underline{x}_1, \ldots, \underline{x}_n) = -T^{-1}G(\bar{x}_n)$, and δ is a positive vector such that $\underline{x} - \delta > 0$.

Proof: By a similar argument as in the proof of Lemma 9, it is easy to see that $\bar{x}$ and $\underline{x}$ are both in the interior of $\mathbb{R}^n_{\ge 0}$. As a result, there exists a positive vector δ such that $\underline{x} - \delta > 0$. We pick such a δ from now on.

Let K_1 be any compact subset of $\mathbb{R}^n_{>0}$ and $x(t)$ be the solution to system (9) with an arbitrary initial condition $x_0 \in K_1$. We first show that $x(t)$ is bounded from above by the constant $\bar{x}$ for large enough t.

Consider the following system:

$$\dot{u} = Tu + G(0). \tag{11}$$

Let $u(t)$ be the solution of (11) with the initial condition $u(0) = x_0$. The point $\bar{x}$ is the steady state of the linear system (11), and it is globally asymptotically stable.

On the other hand, since $g(x_n)$ is strictly decreasing in x_n on $[0, +\infty)$, we have $\dot{x} \le Tx + G(0)$. By the comparison principle for monotone systems ([17]), it follows that the solution $x(t)$ of (9) is bounded from above by $u(t)$ for all $t \ge 0$, that is, $x(t) \le u(t)$ for all $t \ge 0$. As a result,

$$\limsup_{t \ge 0} x(t) \le \lim_{t \to 0} u(t) = \bar{x},$$

which implies that there exists a positive constant t_0 such that $x(t) \le \bar{x} + \delta$ for all $t > t_0$. This t_0 can be chosen uniformly for all $x_0 \in K_1$.

Similarly, we can consider the system

$$\dot{v} = Tv + G(\bar{x}_n), \tag{12}$$

and let $v(t)$ be the solution of (12) with an arbitrary initial condition $x_0 \in K_1$. Since $g(x_n)$ is strictly decreasing in x_n, and $x_n(t)$ is bounded from above by $\bar{x}_n$ for all $t > t_0$, as a result we have $\dot{x} \ge Tx + G(\bar{x}_n)$ for all $t > t_0$. Applying again the comparison principle for monotone systems, we get $x(t) \ge v(t)$ for all $t > t_0$. It thus follows that

$$\liminf_{t > t_0} x(t) \ge \lim_{t \to 0} y(t) = \underline{x}.$$

That is, there exists a positive constant $t_1 > t_0$ such that $x(t) \ge \underline{x} - \delta$ for all $t > t_1$.

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

$$\underline{x} - \delta \le x(t) \le \bar{x} + \delta$$

holds for all $t > t_1$. Therefore K is an absorbing set in $\mathbb{R}^n_{>0}$. ■

Remark 11: Using this result, the existence of the steady states of system (9) can be derived directly from the fact that K is homeomorphic to a ball. However, the algebraic approach given in the proof of Lemma 9 guarantees both existence and uniqueness.

The Jacobian matrix of system (9) 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 $B := T + F$, where $F_{1n} = \max_{x\in K} |g'(x_n)|$ while $F_{ij} = 0$ when $(i, j) \neq (1, n)$. Then Theorem 2 yields:

Theorem 4: Under assumptions **A1** to **A3**, x^* is globally asymptotically stable for system (9) provided B is Hurwitz.

Recall from the discussion following Theorem 2 that B is Hurwitz if (6) and (7) hold. Condition (6) holds because matrices T and S are similar, and T is Hurwitz. The condition that B is Hurwitz can be rephrased here as follows:

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

It is remarkable that, when restricted to this special case, one basically recovers the classical small-gain theorem. Indeed, for a monotone system such as $\dot{x} = Tx + (1, 0, \ldots, 0)'u$ with output x_n, the H_∞ gain is the same as the DC gain. Now, the transfer function of this system is

$$W(s) = \frac{\prod_{i=2}^n \alpha_i}{\prod_{i=1}^n (s - \lambda_i)}$$

where the λ_i are the (real) eigenvalues of T (see for instance Lemma 6.1 in [1]). Therefore

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

and the above condition becomes the small-gain theorem.

Let us also consider the approach based on the second compound matrix. We define the matrix $D := T - F$. Based on the proof of Lemma 7, it is easy to see that $DF^{[2]}(x) \leq D^{[2]}$, for all $x \in K$. Notice in particular that if D is Hurwitz, then so is $D^{[2]}$ by Lemma 6. Moreover, if $D^{[2]}$ is Hurwitz, then so is $DF^{[2]}(x^*)$ because $\lambda_{PF}(DF^{[2]}(x^*)) \leq \lambda_{PF}(D^{[2]})$, see [2].

Finally, in order to apply Theorem 3, we need the condition that the steady state x^* is asymptotically stable, which is guaranteed if $DF(x^*)$ is Hurwitz. It follows from Lemma 6 that this will be the case if $DF^{[2]}(x^*)$ is Hurwitz, provided that the determinant of $DF(x^*)$ has sign $(-1)^n$. Indeed, this is true under the condition that the matrix T is Hurwitz. To see this, we compute $\det(DF(x^*))$, which equals

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

Therefore, $\det(DF(x^*))$ has the sign of $(-1)^n$. In summary, we have established the following:

Theorem 5: Under assumptions **A1** to **A3**, x^* is globally asymptotically stable for system (9) provided D is Hurwitz.

B. Goldbeter Model

In this section, we consider one of the simplest and classical models of circadian rhythm s by Goldbeter ([3], [4]), 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:

$$\begin{aligned} \dot{M} &= \frac{v_s K_I^n}{K_I^n + P_N^n} - \frac{v_m M}{k_m + M} \\ \dot{P}_0 &= k_s M - \frac{V_1 P_0}{K_1 + P_0} + \frac{V_2 P_1}{K_2 + P_1} \\ \dot{P}_1 &= \frac{V_1 P_0}{K_1 + P_0} - \frac{V_2 P_1}{K_2 + P_1} - \frac{V_3 P_1}{K_3 + P_1} + \frac{V_4 P_2}{K_4 + P_2} \\ \dot{P}_2 &= \frac{V_3 P_1}{K_3 + P_1} - \frac{V_4 P_2}{K_4 + P_2} - k_1 P_2 + k_2 P_N - \frac{v_d P_2}{k_d + P_2} \\ \dot{P}_N &= k_1 P_2 - k_2 P_N. \end{aligned} \tag{13}$$

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 (13) considered on a slightly larger open set U containing $\mathbb{R}^n_{\geq 0}$ is a tridiagonal system with a negative feedback from P_N to M. It clearly satisfies conditions (3) and (4) with values of the δ_i as in (5). We next state a result from [1] for this system:

Lemma 12: 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 (13) has a compact absorbing set C in U, where

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

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

Observe that the vector field of (13) contains functions of Michaelis-Menten form, that is,

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

Thus, $h'(y) = \frac{vK}{(K+y)^2} > 0$. 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 $D^{[2]}$. Here D is the sum of a diagonal matrix $\mathrm{diag}\{-\frac{v_m k_m}{(k_m+\bar{M})^2}, -\frac{V_1 K_1}{(K_1+\bar{P}_0)^2}, -\frac{V_2 K_2}{(K_2+\bar{P}_1)^2} - \frac{V_3 K_3}{(K_3+\bar{P}_1)^2}, -\frac{V_4 K_4}{(K_4+\bar{P}_2)^2} - \frac{v_d k_d}{(k_d+\bar{P}_2)^2} - k_1, -k_2\}$ and the matrix

$$\begin{pmatrix} 0 & 0 & 0 & 0 & \bar{g} \\ k_s & 0 & \frac{V_2}{K_2} & 0 & 0 \\ 0 & \frac{V_1}{K_1} & 0 & \frac{V_4}{K_4} & 0 \\ 0 & 0 & \frac{V_3}{K_3} & 0 & k_2 \\ 0 & 0 & 0 & k_1 & 0 \end{pmatrix},$$

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 $[0,\infty)$.

Applying Theorem 3, we obtain:

Theorem 6: Suppose that the assumptions in Lemma 12 hold and that the matrix D is Hurwitz. If the sign of $\det(DF(x^*))$ is -1, then x^* is globally asymptotically stable.

This result provides conditions under which oscillations will be blocked. On the other hand, when there is a oscillation, conditions in Theorem 6 fail to hold for that set of kinetic parameters.

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VII. APPENDIX

We will state a stability result for general time-varying systems which may be of interest in itself. Its proof requires the use of Dini derivatives. For Dini derivatives used for Lyapunov functions, see [14]. 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 13: Let $\dot{x} = A(t)x$ be a linear time-varying system where $A(t)$ is a continuous 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

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

Taking the maximum over all i we get

$$\begin{aligned}
\max_i \frac{|x_i(t+h)|}{hd_i} &\le \frac{1}{h}V(x(t)) \\
&+ \max_i \frac{1}{d_i}\left[a_{ii}(t)d_i + \sum_{j\neq 1}^n |a_{ij}(t)|d_j\right] \\
&\times V(x(t)) + |O_i(h)|. \qquad (14)
\end{aligned}$$

Plugging (14) into the expression for $D^+V(x(t))$ above, we obtain that:

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

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

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