GLOBAL ASYMPTOTIC STABILITY OF THE GOODWIN SYSTEM WITH REPRESSION

LUIS A. SANCHEZ

Abstract. We give a global asymptotic stability result for the classical Goodwin system. The proof follows from a combination of the Poincaré-Bendixson property enjoyed by the monotone cyclic feedback systems, the theory of compound matrices and comparisons techniques from the theory of monotone systems.

1. Introduction

The Goodwin system with repression is the differential system

$$(1) \qquad \begin{cases} \dot{x}_1 = -\alpha_1 x_1 + g(x_n) \\ \dot{x}_i = x_{i-1} - \alpha_i x_i \qquad i = 2, \ldots, n \end{cases}$$

where $\alpha_i > 0$ and g is a C^1 function with strictly negative derivative.

This system was introduced in the sixties as a model of the synthesis of an enzyme X_n from an initial protein X_1 (usually $mRNA$), through a cascade of reactions involving some intermediate enzymes X_i. Each function $x_i(t)$ represents the concentration of the reactive X_i, and the equations in (1) account for the interaction between them: every X_i induces the synthesis of X_{i+1} for $i = 1, \ldots, n-1$, and the end product X_n close the cycle by repressing the reaction of X_1.

Biologists have extensively studied the Goodwin model through experimentation and computer simulation, and some mathematicians have attempted to provide a rigorous explanation of the observed behavior by means of analytical tools. The first work to be mentioned is that of Tyson and Othmer [13], where classical techniques were used to provide results on local and global stability of equilibria, existence of small and large amplitude periodic oscillations, influence of the presence of delays and diffusion terms, etc.

Many of the subsequent works on the Goodwin system have been devoted to the problem of the global asymptotic stability of equilibria (see for example [1],[2],[3],[4] and [11]). The reason for that is not only the mathematical tractability of this question, but also its importance from the biological

2000 *Mathematics Subject Classification.* 34D23, 34C12.

Key words and phrases. Goodwin system, global asymptotic stability, compound matrices, monotone systems.

Supported by MTM2005-03483 and 00675/PI/04.

point of view: it seems desirable that the synthesis process reaches rapidly a steady state independent of the initial conditions.

In this paper we give a new global asymptotic stability criterion for system (1) that improves in some cases the previously mentioned ones. To give a slight idea of our result, recall that the local asymptotic stability of an equilibrium of a nonlinear system follows from the asymptotic stability of the linearization of the vector field at that equilibrium. It is usually untrue that requiring this last condition on every point one could assert the global asymptotic stability of the equilibrium. However we shall prove that this idea actually works for Goodwin system.

To do that we shall strongly use that system (1) belongs to the class of monotone cyclic feedback systems, which by the results of Mallet-Paret and Smith in [8] are known to satisfy the Poincaré-Bendixson property. This allows us in section 2, following an idea of Li in [7], to reduce the problem of the global asymptotic stability of equilibria to that of the local orbital stability of the possible existing closed orbits.

This last issue is treated in section 3 by means of the theory of second additive compound matrices. The key observation that we make is that second additive compound matrices defined by monotone cyclic negative feedback system are cooperative, and then the theory of monotone systems can be straightforwardly applied to estimate the characteristic multipliers of closed orbits. This allows us to establish a global asymptotic stability criterion based on the induced linearized systems.

Finally in section 4 we apply that criterion to Goodwin system and compare to the previous works.

2. Some facts on monotone cyclic negative feedback systems

Cyclic feedback systems have the form

$$\dot{x}_i = f_i(x_{i-1}, x_i) \qquad i = 1, \ldots, n \tag{2}$$

where variables x_0 and x_n are identified. The vector field $F = (f_1, \ldots, f_n)$ is defined in an open set O, and we call O_i to the orthogonal projection of O into the $x_{i-1}x_i$ plane.

A monotone cyclic feedback system is a cyclic feedback system as (2) such that F is C^1 in O and verifies that

$$\delta_i \frac{\partial f_i(x_{i-1}, x_i)}{\partial x_{i-1}} > 0 \quad \text{for all} \quad (x_{i-1}, x_i) \in O_i \quad \text{and} \quad \delta_i \in \{-1, 1\}. \tag{3}$$

In [8] Mallet-Paret and Smith carried out a thorough study of these class of systems and proved its main property:

Poincaré-Bendixson property: Given a monotone cyclic feedback system, any compact omega-limit set of it that contains no equilibrium is a closed orbit.

Remark 1. *This fact was proved under the technical condition of each O_i being convex, which we assume henceforth.*

Monotone cyclic feedback systems are classified according to the value of the number $\Delta = \delta_1\delta_2\ldots\delta_n$. If $\Delta = 1$ (positive feedback), then the flow induced by the system is monotone with respect to an orthant of $\mathbb{R}^n$. In consequence its solutions have a strong tendency to converge to equilibria and no attracting closed orbits can occur (see [12]).

If $\Delta = -1$ (negative feedback), the system is no longer monotone in that sense and observable periodic oscillations can arise. In order to prevent the appearance of such oscillations we intend to give conditions ensuring the existence of globally attracting equilibria.

Then from now on we assume that system (2) satisfies conditions (3). Furthermore we also assume that

$$\delta_i = 1, \quad i = 1, \ldots, n-1 \quad \text{and} \quad \delta_n = -1, \tag{4}$$

since this can be easily achieved through a change of variables of the form $y_i = \mu_i x_i$ with $\mu_i \in \{-1, 1\}$.

To establish our result on global stability we shall exploit the same ideas developed by M. Li in [7]. In that paper it is shown that when dealing with systems having the Poincaré-Bendixson property, the global asymptotic stability of equilibria can be deduced from the local orbital stability of the possible existing closed orbits. Concretely theorem 2.2 of [7] can be applied in our setting and leads to:

Theorem 1. *Let us assume that system (2) satisfies:*

1. *It has a compact global attractor K in O.*
2. *There is a unique equilibrium point $\bar{x}$, and it is locally asymptotically stable.*
3. *Each periodic orbit is orbitally asymptotically stable.*

Then $\bar{x}$ is globally asymptotically stable.

The approach of M. Li to the hypothesis (3) of the theorem was based on the theory of compound matrices. Next section is devoted to show how that theory can be applied to system (2) in a very simple manner.

3. Compound matrices and global asymptotic stability of monotone cyclic negative feedback systems

Let $A = (a_{i,j})$ be of order n. The second additive compound of A is the matrix $A^{[2]} = (b_{i,j})$ of order $\binom{n}{2}$ defined as follows:

For $i = 1, \dots, \binom{n}{2}$, let $(i) = (i_1, i_2)$ be the ith member in the lexicographic ordering of integer pairs (i_1, i_2) such that $1 \le i_1 < i_2 \le n$. Then

$$b_{i,j} = \begin{cases} a_{i_1,i_1} + a_{i_2,i_2} & \text{if } (i) = (j) \\ (-1)^{r+s} a_{i_r,i_s} & \text{if exactly one entry } i_r \text{ of } (i) \text{ does not occur} \\ & \text{in } (j) \text{ and } j_s \text{ does not occur in } (i) \\ 0 & \text{if neither entry from } (i) \text{ occurs in } (j) \end{cases}$$

The relation between compound matrices and the stability properties of closed orbits was pointed out by Muldowney in [9]. Consider a general system

$$\dot{x} = G(x) \tag{5}$$

where G is a C^1 vector field in an open set $\Omega \subset \mathbb{R}^n$.

Theorem 2 (Theorem 4.2 in [9])**.** *A sufficient condition for a closed orbit $\gamma = \{p(t) : 0 \le t \le T\}$ of (5) to be orbitally asymptotically stable is that the linear system*

$$\dot{y} = DG(p(t))^{[2]} y \tag{6}$$

is asymptotically stable.

The key of our work will be next lemma:

Lemma 1. *If $\gamma = \{p(t) : 0 \le t \le T\}$ is a closed orbit of system (2), then $DF(p(t))^{[2]}$ has nonnegative off-diagonal coefficients.*

Proof: The only nonzero off-diagonal elements of $DF(x)$ are $a_{k,k-1} > 0$ with $k = 2, \dots, n$ and $a_{1,n} < 0$. Hence we can assert that the only nonzero off-diagonal coefficients of $DF(x)^{[2]}$ are the $b_{i,j}$'s with (i) and (j) satisfying one of the following conditions:

(1) $(i) = (i_1, i_2)$, $(j) = (i_1, i_2 - 1)$ and $i_2 = 2, \dots, n$
(2) $(i) = (i_1, i_2)$, $(j) = (i_1 - 1, i_2)$ and $i_1 = 2, \dots, n$
(3) $(i) = (1, i_2)$, $(j) = (i_2, n)$

In case (1) we have that $b_{i,j} = (-1)^{2+2} a_{i_2,i_2-1} > 0$. In case (2) we also have that $b_{i,j} = (-1)^{1+1} a_{i_1,i_1-1} > 0$. Finally in case (3) we have that $b_{i,j} = (-1)^{1+2} a_{1,n} > 0$. This proves the lemma.

This lemma will allow us to use the theory of monotone systems. Let us recall briefly some terminology on that subject.

First the set of $d \times d$ matrices can be ordered according to the following definition:

$$A = (a_{i,j}) \le B = (b_{i,j}) \qquad \text{if and only if} \qquad a_{i,j} \le b_{i,j} \quad \text{for all } i, j.$$

Matrices A verifying $0 \le A$ are called nonnegative matrices. Given a linear system $\dot{x} = L(t)x$, a necessary and sufficient condition for its fundamental matrix to be nonnegative is that $L(t)$ has nonnegative off-diagonal coefficients. In such a case the linear system is said cooperative. For short we shall also say that matrices $L(t)$ are cooperative.

Lemma 1 then means that the linearizations of system (2) are cooperative linear systems. Perron-Frobenius theory and comparison of solutions yields the following result:

Proposition 1. *Let $\dot{Y} = A_i(t)Y$, $i = 1, 2$ be two linear periodic cooperative systems (with the same period) such that $A_1(t) \leq A_2(t)$ for all t. Then the asymptotic stability of $\dot{Y} = A_2(t)Y$ implies the asymptotic stability of $\dot{Y} = A_1(t)Y$.*

Proof: This proposition is just proposition 3 of [10]. We only observe that the irreducibility hypothesis required there can be easily removed.

We are now ready to state the main theorem of this section. First we recall that a Hurwitzian matrix is a matrix whose eigenvalues have all negative real parts.

Theorem 3. *Suppose that system (2) has a compact global attractor K and a unique equilibrium point $\bar{x}$ that is locally asymptotically stable. Suppose also that there exists a cooperative Hurwitzian matrix U verifying*

$$DF(x)^{[2]} \leq U \quad \textit{for all } x \in K.$$

Then $\bar{x}$ is globally asymptotically stable.

Proof: To prove this theorem we only have to check hypothesis (3) of theorem 1. Let $\gamma = \{p(t) : 0 \leq t \leq T\}$ be a closed orbit of (2). By lemma 1 the matrices $DF(p(t))^{[2]}$ are cooperative and by hypothesis $DF(p(t))^{[2]} \leq U$. Then we can apply proposition 1 with $A_2(t) = U$ and $A_1(t) = DF(p(t))^{[2]}$ to deduce that system $\dot{y} = DF(p(t))^{[2]}y$ is asymptotically stable and hence γ is orbitally asymptotically stable.

Next section is devoted to prove that for Goodwin system this theorem can be reformulated in terms of the Jacobian matrices themselves.

4. The Goodwin equation with negative feedback

Let us consider

$$\begin{cases} \dot{x}_1 = -\alpha_1 x_1 + g(x_n) \\ \dot{x}_i = x_{i-1} - \alpha_i x_i \qquad i = 2, \dots, n \end{cases} \tag{7}$$

where $\alpha_i > 0$ and $g : [0, +\infty[\to]0, +\infty[$ is C^1 and $g'(x_n) < 0$.

This system is obviously monotone cyclic with negative feedback. It has a compact attractor K in the box

$$B = \{(x_1, \dots, x_n) \in \mathbb{R}^n : 0 \leq x_i \leq g(0)(\alpha_1 \dots \alpha_i)^{-1}\},$$

and there is a unique equilibrium $\bar{x} = (\bar{x}_1, \dots, \bar{x}_n)$ therein (see [8]).

The matrix $DF(x)$ depends solely on the variable x_n, then we denote

$$J(x_n) = DF(x_1, \dots, x_n) = \begin{pmatrix} -\alpha_1 & 0 & \dots & \dots & g'(x_n) \\ 1 & -\alpha_2 & \dots & \dots & 0 \\ \dots & \dots & \dots & \dots & \dots \\ \dots & \dots & \dots & 1 & -\alpha_n \end{pmatrix}.$$

All the non-displayed coefficients are zero. We shall prove:

Theorem 4. *Let $g'(\xi) = \min\{g'(x_n) : 0 \leq x_n \leq g(0)(\alpha_1 \dots \alpha_n)^{-1}\}$. Then if the matrix $J(\xi)$ is Hurwitzian then the equilibrium $\bar{x}$ is globally asymptotically stable.*

Remark 2. *In the proof of this theorem we shall get that $J(\xi)$ is Hurwitzian if and only if every $J(x_n)$ is so. Therefore, as asserted in the introduction, we can say that the global asymptotic stability of $\bar{x}$ follows from the asymptotic stability of every induced linearization of (7).*

Before proving the theorem we state a result given in [6] that will be repeatedly used in that proof.

Theorem 5. *A matrix A of order n is Hurwitzian if and only if $A^{[2]}$ is Hurwitzian and* $\text{sign}(\text{Det } A) = (-1)^n$.

Proof of theorem 4 Consider the compact segments of matrices

$$S = \{J(x_n) : 0 \leq x_n \leq g(0)(\alpha_1 \dots \alpha_n)^{-1}\}$$

and

$$S^{[2]} = \{J(x_n)^{[2]} : 0 \leq x_n \leq g(0)(\alpha_1 \dots \alpha_n)^{-1}\}.$$

The segment $S^{[2]}$ consists of cooperative matrices by lemma 1, and it is clear from the definition of ξ that

$$J(x_n)^{[2]} \leq J(\xi)^{[2]} \quad \text{for all } x_n \in [0, g(0)(\alpha_1 \dots \alpha_n)^{-1}]$$

Moreover, since $J(\xi)$ is Hurwitzian, theorem 5 implies that $J(\xi)^{[2]}$ also is. If we prove that $\bar{x}$ is locally asymptotically stable we can apply theorem 3 and that will finish the proof.

Again Proposition 1 implies that every matrix in $S^{[2]}$ is Hurwitzian, in particular $J(\bar{x})^{[2]}$ is so. On the other hand

$$\text{Det } J(x_n) = (-1)^n(\alpha_1 \dots \alpha_n - g'(x)),$$

whose sign is obviously $(-1)^n$ by the negativeness of g'. Again theorem 5 shows that $J(\bar{x})$ is Hurwitzian and so $\bar{x}$ is locally asymptotically stable.

To finish the paper we relate theorem 4 and the one obtained in [4] . In that paper next theorem is proved

Theorem 6. *Define the function $k : [0, g(0)] \to [0, g(0)]$ by*

$$k(x_n) = g((\alpha_1 \dots \alpha_n)^{-1} x_n).$$

Then the equilibrium $\bar{x}$ is globally asymptotically stable if k has no two-periodic point other than $\bar{x}_n$.

We shall see that theorems 4 and 6 are independent. Let us consider the case $\alpha_i = 1$ for all $i = 1, \ldots, n$ so that $k(x_n) = g(x_n)$.

Take a function $g : \mathbb{R}_+ \to \mathbb{R}_+$ verifying $-1 \leq g'(x_n) < 0$ and coinciding with the function $h(x_n) = -x_n + 1$ in a neighborhood of $x_n = 1/2$. The equilibrium is $\bar{x} = (1/2, \ldots, 1/2)$. The equation $g \circ g(x_n) = x_n$ has a continuum of solutions near $x_n = 1/2$, then theorem 6 cannot be applied. The matrix $J(\xi)$ in theorem 4 is just $J(\bar{x})$ and its characteristic polynomial is $P(\lambda) = (-1)^n((1+\lambda)^n+1))$. Their roots are of the form $\lambda_k = -1+z_k$ where $\{z_k : k = 1, \ldots, n\}$ are the nth roots of -1. If $n > 1$ each λ_k has negative real part. Then theorem 4 implies that $\bar{x}$ is globally asymptotically stable.

On the contrary let us consider a function $g(x_n)$ verifying:

(1) $g(0) = 1$.
(2) $g'(0)$ large enough so that 3 does not hold.
(3) $g'(x_n) > -1$ in an interval of the form $[\epsilon, +\infty[$.
(4) $g^{-1}(I) \cap g(I) = \emptyset$.

Notice that condition (4) will hold due to condition (1) by taking $\epsilon > 0$ sufficiently small.

Condition (2) implies that theorem 4 cannot be applied. Nevertheless if we check that $g(x_n)$ does not have two periodic points then theorem 6 implies the global asymptotic stability.

Firstly by (3) there cannot be a nontrivial two-periodic point contained in $[\epsilon, +\infty[$ (the Mean Value Theorem would imply that $g'(y) = -1$ for some y in the interval defined by the two-periodic orbit) . Secondly condition (4) prevents that any two-periodic point intersects the interval $[0, \epsilon]$. So we are done.

References

[1] D. J. Allwright, *A Global stability criterion for simple control loops*, Journal of Mathematical Biology 4 (1977), 363-373.

[2] H. T. Banks, J. M. Mahaffy, *Stability of cyclic gene models for systems involving repression*, Journal of Theoretical Biology 74 (1978), 323-334.

[3] H. T. Banks, J. M. Mahaffy, *Global asymptotic stability of certain models for protein synthesis and repression*, Quaterly of Applied Mathematics 36 (1978), 209-221.

[4] B.A. Enciso, H. L. Smith, E. D. Sontag, *Non-monotone systems decomposable into monotone systems with negative feedbacks*, to appear in Journal of Differential Equations.

[5] S. P. Hastings, J. Tyson, D. Webster, *Existence of periodic solutions for negative feedback cellular control systems*, Journal of Differential Equations 25 (1977), 39-64.

[6] M. Y. Li, L. Wang, *A criterion for stability of matrices*, Journal of Mathematical Analysis and Applications 225 (1998), 249-264.

[7] M. Y. Li, L. Wang, *Global stability in some SEIR epidemic models*, IMA Vol. Math. Appl. 126, 295-311, Springer, New York, 2000.

[8] J. Mallet-Paret, H. L. Smith, *The Poincaré-Bendixson theorem for monotone feedback systems*, Journal of Dynamics and Differential Equations 2 (1990), 367-421.

[9] J. Muldowney, *Compound matrices and ordinary differential equations*, Rocky Mountain Journal of Mathematics 20 (1990), 857-872.

[10] L. A. Sanchez, *Dynamics of the modified Michaelis-Menten system*, Journal of Mathematical Analysis and Applications 317 (2006), 71-79.
[11] H. L. Smith, *Oscillations and multiple steady states in a cyclic gene model with repression*, Journal of Mathematical Biology 25, (1987), 169-190.
[12] H. L. Smith, *Monotone Dynamical Systems*, American Mathematical Society, Providence, 1995.
[13] J. J. Tyson, H. G. Othmer, *The dynamics of feedback control circuits in biochemical pathways*, Progress in Theoretical Biology 5, Academic Press, New York (1978), 1-62.

E-mail address: `luis.sanchez@upct.es`

Departamento de Matemática Aplicada y Estadística, Escuela Universitaria de Ingeniería Técnica Civil, Universidad Politécnica de Cartagena, 30203, Cartagena (Murcia), Spain