Systems of Delay Differential Equations: Analysis of a model with feedback

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Abstract

Using topological degree theory, we prove the existence of positive $T$-periodic solutions of a system of delay differential equations for models with feedback arising on regulatory mechanisms in which self-regulation is relevant, e.g. in cell physiology.

Keywords: Differential equations with delay; Periodic solutions; Models with feedback; Topological degree.

1 Introduction

Self-regulatory models are common in nature, as described e.g. in (\cite{4}), (\cite{6}) and (\cite{8}). Let us consider a system made up of a number of glands as a motivation. Each gland secretes a hormone that allows secretion in the next gland, which successively generates another hormone to stimulate the next one and so on. In the end, a final hormone is released which, by increasing its concentration, will inhibit the secretion of previous hormones that allowed the production process. This generates the decay of this hormone to a minimum threshold that re-activates the cycle again.

This behavior can be seen in other biochemical processes, such as enzymatic or bacterial models. Topological degree is a useful tool to find stable equilibria in a wide variety of models with constant parameters and, furthermore, allows to deduce the existence of periodic solutions when the constant parameters are replaced by periodic functions.

In this work, we study the existence of solutions for a more general model, namely the following system of delay differential equations:

Figure 1: A system with feedback
The following continuation theorem can be easily deduced from the standard topological degree methods (see e.g. (1)).

with the subset of constant functions of \( L u \) that is:

\[
\begin{align*}
\frac{dx_0}{dt} &= F(t, x_n(t - \tau_0)) - b_0(x_0(t)), \\
\frac{dx_j}{dt} &= G_j(t, x_{j-1}(t - \varepsilon_j), x_n(t - \tau_j)) - b_j(x_j(t)), \quad 1 \leq j \leq n - 1, \\
\frac{dx_n}{dt} &= H(t, x_{n-1}(t - \varepsilon_n)) - b_n(x_n(t))
\end{align*}
\]

Here \( \tau_i \) and \( \varepsilon_j \), with \( 0 \leq i \leq n - 1 \) and \( 1 \leq j \leq n \) are fixed positive delays in time.

The features of the model read as follows.

1. \( F, H : \mathbb{R} \times [0, +\infty) \to [0, \infty) \) and \( G_j : \mathbb{R}^3 \to [0, \infty) \) are continuous and \( T \)-periodic in the first coordinate for some fixed period \( T > 0 \).
2. \( b_i : [0, +\infty) \to [0, +\infty) \) is a strictly increasing function with \( b_i(0) = 0 \) for \( i = 0, \ldots, n \).
3. \( F \) is nonincreasing in its second coordinate and \( F(t, x) > 0 \) for all \( x > 0 \) and \( \text{Im}(F) \subseteq \text{Im}(b_0) \).
4. \( H \) is nondecreasing in its second coordinate and \( H(t, x) > 0 \) for all \( x > 0 \) and \( \text{Im}(H) \subseteq \text{Im}(b_n) \).
5. \( G_j \) is nondecreasing in its second coordinate and \( G_j(t, x, y) > 0 \) for \( x > 0 \) and \( \text{Im}(G_j) \subseteq \text{Im}(b_j) \), for \( j = 1, \ldots, n - 1 \).

We shall prove the existence of positive \( T \)-periodic solutions for (1), more precisely:

**Theorem 1.** Assume that the previous conditions 1-5 hold. Then problem (1) has at least one \( T \)-periodic solution \( u = (x_0, x_1, \ldots, x_n) \) such that \( x_k(t) > 0 \) for all \( t \) and all \( k \).

### 2 Existence of positive periodic solutions

We shall apply the continuation method in the the positive cone

\[
\mathcal{K} := \{ u \in C_T : x_0, x_1, \ldots, x_n > 0 \}
\]

of the Banach space of continuous periodic functions

\[
C_T := \{ u \in C(\mathbb{R}, \mathbb{R}^{n+1}) : u(t) = u(t + T) \text{ for all } t \}
\]

equipped with the standard uniform norm. Consider the linear operator \( L : C^1 \cap C_T \to C \) given by \( Lu := u' \) and the nonlinear operator \( N : \mathcal{K} \to C_T \) defined as the right-hand side of system (1).

For convenience, the average of a function \( u \) shall be denoted by \( \overline{u} \), namely \( \overline{u} := \frac{1}{T} \int_0^T u(t) \, dt \). Also, identifying \( \mathbb{R}^{n+1} \) with the subset of constant functions of \( C_T \), we may define the function \( \phi : [0, +\infty)^{n+1} \to \mathbb{R}^{n+1} \) given by \( \phi(x) := \overline{Nx} \), that is:

\[
\phi(x_0, x_1, \ldots, x_n) = \left( \frac{1}{T} \int_0^T F(t, x_n) \, dt - b_0(x_0), \frac{1}{T} \int_0^T G_1(t, x_1, x_n) \, dt - b_1(x_1), \ldots, \frac{1}{T} \int_0^T H(t, x_{n-1}) \, dt - b_n(x_n) \right).
\]

The following continuation theorem can be easily deduced from the standard topological degree methods (see e.g. (1)).

**Theorem 2.** Assume there exists \( \Omega \subset \mathcal{K}^\circ \) open and bounded such that:

a) The problem \( Lu = \lambda Nu \) has no solutions on \( \partial \Omega \) for \( 0 < \lambda < 1 \).

b) \( \phi(u) \neq 0 \) for all \( u \in \partial \Omega \cap \mathbb{R}^{n+1} \).

c) \( \text{deg}(\phi, \Omega \cap \mathbb{R}^{n+1}, 0) \neq 0 \), where ‘deg’ denotes the Brouwer degree.

Then (1) has at least one solution in \( \overline{\Omega} \).

In order to apply Theorem 2 to our problem, let us assume that \( u = (x_0, x_1, \ldots, x_n) \in \mathcal{K} \) is a solution of the system \( Lu = \lambda Nu \) for some \( \lambda \in (0, 1) \). We shall obtain bounds that will yield an appropriate choice of the subset \( \Omega \).

In the first place, suppose that \( x_0 \) achieves its absolute maximum \( M_0 \) at some value \( t^* \), then \( x_0(t^*) = 0 \) and hence

\[
b_0(M_0) = F(t^*, x_n(t^* - \tau_0)) \leq F(t^*, 0).
\]
Fixing a constant $\mathcal{M}_0 > \max_{t \in \mathbb{R}} b_{-1}^{-1}(F(t, 0))$, we conclude that $x_0(t^*) < \mathcal{M}_0$. Next, observe that if $x_1$ achieves its absolute maximum $M_1$ at some $t^*$, then

$$b_1(M_1) = G_1(t^*, x_0(t^* - \varepsilon_1), x_n(t^* - \tau_1)) \leq G_1(t^*, M_0, 0) \leq G_1(t^*, M_0, 0).$$

Thus, we may fix a constant $M_1 > \max_{t \in \mathbb{R}} b_{-1}^{-1}(G_1(t, M_0, 0))$ and hence $\varepsilon_1 < M_1$. In the same way, for $j = 2, \ldots, n-1$ we fix constants $M_j > \max_{t \in \mathbb{R}} b_{-1}^{-1}(G_j(t, M_{j-1}, 0))$ so $x_j(t) < M_j$ for all $t$. For the last equation, we suppose $x_n$ achieves its absolute maximum $M_n$ for some $t^*$, then

$$b_n(M_n) = H(t^*, x_{n-1}(t^* - \varepsilon_n)) \leq H(t^*, M_{n-1}).$$

Thus we may fix a constant $M_n > \max_{t \in \mathbb{R}} b_{-1}^{-1}(H(t, M_{n-1}))$ and conclude that $x_n(t^*) < M_n$.

In order to obtain lower bounds, assume firstly that $x_0$ achieves its absolute minimum $m_0$ at some $t_*$, then

$$b_0(m_0) = F(t_*, x_0(t_* - \tau_0)) \geq F(t_*, M_n) > 0.$$ 

Then, choosing a positive constant $m_0 < \min_{t \in \mathbb{R}} b_{-1}^{-1}(F(t, M_0))$, it is seen that $m_0 > m_0$. In the same way, we fix $m_j > 0$ is such that $m_j < b_{-1}^{-1}(F_j(t, M_{j-1}, 0))$ for all $t$ and conclude that then $x_j(t) > m_j$ for all $t$ and $1 \leq j \leq n - 1$.

Finally, fix a positive constant $m_n$ such that $m_n < b_{-1}^{-1}(H(t, M_{n-1}))$ for all $t$, then $x_n(t) > m_n$ for all $t$.

In other words, the first condition of the continuation theorem is satisfied on

$$\Omega := \{(x_0, x_1, \ldots, x_n) \in C_T : m_0 < x_0(t) < M_0, \ldots, m_j < x_j(t) < M_j, \ldots, m_n < x_n(t) < M_n \text{ for all } t, 1 \leq j \leq n - 1\}.$$ 

On the other hand, observe that $Q := \Omega \cap \mathbb{R}^{n+1} = (m_0, M_0) \times \ldots \times (m_n, M_n)$, so we shall study the behavior of the mapping $\phi$ over the faces of $Q$.

Let $x \in Q$ and suppose $x_0 = m_0$, then for some $\tilde{t}$

$$\frac{1}{T} \int_0^T F(t, x_n) dt - b_0(m_0) = F(\tilde{t}, x_n) - b_0(m_0) > F(\tilde{t}, x_n) - F(\tilde{t}, M_n) \geq 0.$$ 

Now suppose $x_0 = M_0$, then

$$\frac{1}{T} \int_0^T F(t, x_n) dt - b_0(M_0) = F(\tilde{t}, x_n) - b_0(M_0) < F(\tilde{t}, x_n) - F(\tilde{t}, 0) \leq 0.$$ 

In the same way, for all $j = 1, \ldots, n - 1$ it is seen that

$$\frac{1}{T} \int_0^T G_j(t, x_{j-1}, x_n) dt - b_j(m_j) = G_j(\tilde{t}, x_{j-1}, x_n) - b_j(m_j) \geq G(\tilde{t}, m_{j-1}, M_n) - b_j(m_j) > 0,$$

and

$$\frac{1}{T} \int_0^T H(t, x_{n-1}) dt - b_n(m_n) = H(\tilde{t}, x_{n-1}) - b_n(m_n) \geq H(\tilde{t}, m_{n-1}) - b_n(m_n) > 0.$$ 

We deduce that the second condition of the continuation theorem is fulfilled. Moreover, if we consider the homotopy $h : \overline{Q} \times [0, 1] \rightarrow \mathbb{R}^{n+1}$ given by

$$h(x, \lambda) := (1 - \lambda)(p - x) + \lambda \phi(x)$$

where

$$p := \left(\frac{M_0 + m_0}{2}, \ldots, \frac{M_n + m_n}{2}\right)$$

then $h \neq 0$ on $\partial Q \times [0, 1]$. Indeed, if $h(x, \lambda) = 0$ for some $x = (x_0, x_1, \ldots, x_n) \in \partial Q$, then we may suppose for example that $x_0 = M_0$ and hence

$$0 = h_1(x, \lambda) = (1 - \lambda)(\frac{m_0 - M_0}{2} + \lambda \phi_1(M_0, x_1, \ldots, x_n)) < 0,$$

a contradiction. The other cases follow similarly. By the homotopy invariance of the Brouwer degree, we conclude that

$$\deg(\phi, Q, 0) = \deg(p - \text{Id}, Q, 0) = (-1)^{n+1}$$

and the proof is complete.
3 Examples

3.1 Model of Testosterone Secretion

The following system is mentioned in [4] and [2], which is based on a model proposed by Smith [9] and gave rise to the general model developed in this work.

Let us consider the model shown in Figure 2 for the cycle of the Testosterone hormone (see [4]), where the different variables denote the concentrations at time \( t \) of the Luteinising Hormone (LH), which is represented by \( R(t) \), from Hypothalamus, Luteinising Hormone Releasing Hormone (LHRH), represented by \( L(t) \), from Pituitary gland and Testosterone Hormone (TH) from Testes in man, represented by \( X(t) \).

A general autonomous model describing the biochemical interaction of the hormones LH, LHRH and TH in the male is presented.

The model structure consists of a negative feedback system of three delay differential equations.

**Remark 1.** It is seen from the model that high levels of \( X \) affect the concentration of \( R \) and \( L \).

\[
\begin{align*}
\frac{dR}{dt} &= F(t, X(t - \tau_1)) - b_1(R(t)), \\
\frac{dL}{dt} &= g_1(R(t - \tau_2)) - b_2(L(t)), \\
\frac{dX}{dt} &= g_2(L(t - \tau_3)) - b_3(X(t))
\end{align*}
\]

(2)

This model has the form of (1) and conditions 1-5 are satisfied if \( b_i(x) \) and \( g_j(x) \) are positive increasing functions for \( i = 1, 2, 3 \) and \( j = 1, 2 \), the delays \( \tau_i \geq 0 \) are constant (at least one of them different from zero) and \( F \) is positive, \( T \)-periodic in \( t \) and strictly decreasing in \( X \).

With this structure, Murray [4] proposed in 1989 a simpler (autonomous) system, with:

\[
\begin{align*}
b_i(x) &= \beta_i x, \quad \beta_i > 0, \\
g_j(x) &= \alpha_j x, \quad \alpha_j > 0, \\
F(x) &= \frac{\kappa_1}{\kappa_2 + x^m}, \quad m \in \mathbb{N}, \quad \tau_1 = \tau_2 = 0
\end{align*}
\]

where \( \kappa_j > 0 \) are constants.

The functions \( g_j \) represent the rates for productions of \( L \) and \( X \), \( b_i \) are the respective decay rates in the blood stream. It is assumed that each of these hormones is cleared from blood stream according to first order kinetics. (See Das et al [2])

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