Existence of solutions for a biological model using topological degree theory

Existencia de soluciones para un modelo biológico empeñando la teoría de grado topológico

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Abstract

Topological degree theory is a useful tool for studying systems of differential equations. In this work, a biological model is considered. Specifically, we prove the existence of positive $T$-periodic solutions of a system of delay differential equations for a model with feedback arising on Circadian oscillations in the Drosophila period gene protein.

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

Resumen

La teoría de grado topológico es una herramienta útil para estudiar sistemas de ecuaciones diferenciales. En este trabajo analizamos un modelo biológico; específicamente, probamos la existencia de soluciones positivas $T$-periódicas de un sistema de ecuaciones diferenciales con retardo basado en el modelo auto-regulado de los ciclos Circadianos de proteínas a nivel genético de la mosca de la fruta (Drosophila).

Palabras Clave: Ecuaciones diferenciales con retardo; Soluciones periódicas, Modelos auto-regulados; Grado topológico.

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1 Introduction

Let us consider a model proposed by Goldbeter [1], who showed the variation on PER: Period of messenger of Ribonucleic Acid (mRNA) in Drosophila (often called “fruit flies”) related to circadian rhythms. Here, a nonautonomous version of the model is considered with the aim of proving the existence of periodic solutions by means of a powerful topological tool: the Leray-Schauder degree. In the original model, the existence of a positive steady state can be shown, under appropriate conditions, by the use of the Brouwer degree. As we shall see, when the parameters are replaced by periodic functions, essentially the same conditions yield the existence of positive periodic solutions.
2 The model

2.1 General features

I) This negative feedback will be described by an equation of Hill type in which \( n \) denotes the degree of cooperativity, and \( K(t) \), the threshold repression function.

II) To simplify the model, we consider that \( P_N \) behaves directly as a repressor.

III) The constants \( K, K_i \) and \( V_j \) denote the maximum rate and Michaelis constant of the kinase(s) and phosphatase(s) involved in the reversible phosphorylation of \( P_0 \), into \( P_1 \), and of \( P_1 \), into \( P_2 \) are not negative.

IV) Maximum accumulation rate of cytosol is denoted by \( V_s \).

V) Cytosol is degraded enzymically, in a Michaelian manner, at a maximum rate \( V_m \).

VI) Functions of this system are:

(a) Cytosolic concentration is denoted by \( M \).

(b) We consider only three states of the protein: unphosphorylated (\( P_0 \)), monophosphorylated (\( P_1 \)) and bisphosphorylated (\( P_2 \)).

(c) Fully phosphorylated form of PER (\( P_2 \)) is degraded in a Michaelian manner, at a maximum rate \( V_d \) and also transported into the nucleus, at a rate characterized by the apparent first-order rate constant \( k_1 \).

VII) The rate of synthesis of PER, proportional to \( M \), is characterized by an apparent first-order rate constant \( K_s \).

VIII) Transport of the nuclear, bisphosphorylated form of PER (\( P_N \)) into the cytosol is characterized by the apparent first-order rate constant \( k_2 \).

IX) The model could be readily extended to include a larger number of phosphorylated residues.

Figure 1: The model for the circadian variation in PER.
With this in mind, our non-autonomous version of Goldbeter’s system reads:

\[
\begin{align*}
\frac{dM}{dt} &= \frac{V_2(t)K_1(t)^n}{K_1(t) + P_N(t)} - \frac{V_m(t)M(t)}{K_m(t) + M(t)}, \\
\frac{dP_0}{dt} &= K_4(t)M(t) + \frac{V_2(t)P_1(t)}{K_2(t) + P_1(t)} - \frac{V_4(t)P_0(t)}{K_4(t) + P_0(t)}, \\
\frac{dP_1}{dt} &= \frac{V_3(t)P_0(t)}{K_1(t) + P_0(t)} + \frac{V_3(t)P_2(t)}{K_4(t) + P_2(t)} - P_1(t) \left( \frac{V_2(t)}{K_2(t) + P_1(t)} + \frac{V_4(t)}{K_4(t) + P_1(t)} \right), \\
\frac{dP_2}{dt} &= \frac{V_3(t)P_0(t)}{K_3(t) + P_1(t)} + k_2(t)P_N(t) - P_2(t) \left( k_1(t) + \frac{V_2(t)}{K_2(t) + P_2(t)} + \frac{V_4(t)}{K_4(t) + P_2(t)} \right), \\
\frac{dP_N}{dt} &= k_1(t)P_2(t) - k_2(t)P_N(t)
\end{align*}
\]

(1)

where \(K_i, \ i = 1, 2, 3, 4, d, m_1, k_1, k_2 \) and \(V_j, \ j = 1, 2, 3, 4, S, m, d \) are strictly positive, continuous \(T\)-periodic functions. We shall prove that, under accurate assumptions to be specified below, the system admits at least one positive \(T\)-periodic solution.

### 3 Existence of positive periodic solutions

In order to apply the topological degree method to problem (2), let us consider the space of continuous \(T\)-periodic vector functions

\[C_T := \{ u \in C(\mathbb{R}, \mathbb{R}^5) : u(t) = u(t + T) \ \text{for all} \ t \},\]

equipped with the standard uniform norm, and the positive cone

\[\mathcal{K} := \{ u \in C_T : u_j \geq 0, j = 1, \ldots, 5 \}.\]

Thus, the original problem can be written as \(Lu = Nu\), where \(L : C^1 \cap C_T \to C\) is given by \(Lu := u'\) and the nonlinear operator \(N : \mathcal{K} \to C_T\) is 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 \(\mathbb{R}^5\) with the subset of constant functions of \(C_T\), we may define the function \(\phi : [0, +\infty)^5 \to \mathbb{R}^5\) given by \(\phi(x) := x\mathcal{K}\).

For the reader’s convenience, let us summarize the basic properties of the Leray-Schauder degree which, roughly speaking, can be regarded as an algebraic count of the zeros of a mapping \(F : \Omega \to E\), where \(E\) is a Banach space and \(\Omega \subset E\) is open and bounded. In more precise terms, assume that \(F = I - K\), where \(K\) is compact and \(F \neq 0\) on \(\partial \Omega\). The degree \(deg_{LS}(F; \Omega, 0)\) is defined as the Brouwer degree \(deg_B\) of its restriction \(F|_V : \Omega \cap V \to V\), where \(V\) is an accurate finite-dimensional subspace of \(E\). In particular, if the range of \(K\) is finite dimensional, then one may take \(V\) as the subspace spanned by \(\text{Im}(K)\). If \(deg_{LS}(F; \Omega, 0)\) is different from 0, then \(F\) vanishes in \(\Omega\); moreover, the degree is invariant over a continuous homotopy \(F_\lambda := I - \lambda K\) with \(K\) compact and \(F_\lambda \neq 0\) on \(\partial \Omega\). Finally, we recall that if \(T : \mathbb{R}^n \to \mathbb{R}^n\) is a diffeomorphism and \(0 \in T(A)\) for some open bounded \(A \subset \mathbb{R}^n\), then \(deg_B(T, A, 0)\) is just the sign of the Jacobian determinant of \(T\) at the (unique) pre-image of 0. The following continuation theorem is a direct consequence of the standard topological degree methods (see e.g. [2]).

**Theorem 1** Assume there exists \(\Omega \subset \mathcal{K}^5\) 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 \(u \in \partial \Omega \cap \mathbb{R}^5\).
3.1 A priori bounds

In this section, we shall find appropriate bounds for the solution of the problem $Lu = \lambda Nu$ with $\lambda \in (0, 1)$. For convenience, let us fix the following notation for the minima and maxima of all the functions involved in the model, namely:

$$0 < v_0 \leq V_i(t) \leq V_\ell, \quad 0 < \kappa_j \leq K_j(t) \leq K_j, \quad 0 < k_i(t) \leq k_i, \quad \forall \ i, \ j, \ l.$$ 

Now assume that $u \in C^3$ satisfies $Lu = \lambda Nu$ for some $0 < \lambda < 1$.

Let us firstly consider a value $t^*$ where $M$ achieves an absolute maximum, then $M'(t^*) = 0$ and hence

$$\frac{V_\ell(t^*)K_1(t^*)}{K_1(t^*) + P_N(t^*)} = \frac{V_{m_1}(t^*)M(t^*)}{K_{m_1}(t^*) + M(t^*)} \geq \frac{v_{m_0}M(t^*)}{K_{m_0} + M(t^*)} := b_M(M(t^*)).$$

If $v_{m_0} > V_\ell$, then

$$M(t^*) = b_M \left( \frac{V_\ell(t^*)K_1(t^*)}{K_1(t^*) + P_N(t^*)} \right) < b_M \left( V_\ell(t^*) \right) \leq \frac{V_{m_1}K_{m_1}}{v_{m_0} - V_\ell} := M$$

Next, suppose that $P_0$ achieves its absolute maximum at some point, denoted again $t^*$, then

$$K_2(t^*)M(t^*) + \frac{V_2(t^*)P_1(t^*)}{K_2(t^*) + P_1(t^*)} = \frac{V_1(t^*)P_0(t^*)}{K_1(t^*) + P_0(t^*)} \geq \frac{v_1P_0(t^*)}{K_1 + P_0(t^*)} := b_0(P_0(t^*)).$$

Thus, under the condition

$$K_3M + V_2 < v_1,$$

we deduce that

$$P_0(t^*) = b_0^{-1} \left( K_2M(t^*) + \frac{V_2(t^*)P_1(t^*)}{K_2(t^*) + P_1(t^*)} \right) < \frac{K_3M + V_2}{v_1 - (K_3M + V_2)} < 1.$$  

Next, an upper bound $P_1$ for $P_1$ is readily obtained in the following way. Let us denote again by $t^*$ a value where $P_1$ achieves its absolute maximum, then

$$\frac{V_1(t^*)P_0(t^*)}{K_1(t^*) + P_0(t^*)} + \frac{V_2(t^*)P_2(t^*)}{K_2(t^*) + P_2(t^*)} = P_1(t^*) \left( \frac{V_2(t^*)}{K_2(t^*) + P_1(t^*)} + \frac{V_3(t^*)}{K_3(t^*) + P_1(t^*)} \right).$$

When $P_1(t^*) \geq 0$, the right-hand side gets close to $V_2(t^*) + V_3(t^*)$, while the left-hand side is always less or equal than $\frac{V_1P_0}{v_1 + P_0} + V_4$. Thus, the existence of $P_1$ is guaranteed by the condition

$$\frac{V_1P_0}{v_1 + P_0} + V_4 < \min_{t \in [0, 1]} \{V_2(t) + V_3(t)\}.$$  

The remaining upper bounds are obtained as follows. In the first place, define a new variable $Q := P_N + P_2$, which satisfies the equation:

$$\frac{dQ}{dt} = \frac{V_4(t)P_2(t)}{K_4(t) + P_2(t)} - P_2(t) \left( \frac{V_4(t)}{K_4(t) + P_2(t)} - \frac{V_3(t)}{K_3(t) + P_2(t)} \right).$$

If $Q$ achieves its absolute maximum at $t^*$, then

$$\frac{V_3P_1}{K_3 + P_1} \geq \frac{V_4(t^*)P_2(t^*)}{K_4(t^*) + P_2(t^*)} - \frac{P_1(t^*)}{K_4(t^*) + P_2(t^*)} \left( \frac{V_4(t^*)}{K_4(t^*) + P_2(t^*)} + \frac{V_3(t^*)}{K_3(t^*) + P_2(t^*)} \right).$$
As before, if the condition
\[
\frac{V_3P_1}{\kappa_3 + P_1} < \min_{t \in \mathbb{R}}(V_4(t) + V_d(t))
\]
is assumed, then \(P_2(t^*) \leq \tilde{P}\) for some \(\tilde{P}\). Moreover, from the fourth equation of the system we deduce the existence of a constant \(C\) such that \(\frac{dP_2}{dt} \geq -CP_2(t)\). Hence we obtain, for all \(t\), that \(P_2(t) \leq e^{CT} \tilde{P} := P_2\). This provides also an upper bound for \(Q(t)\) and, consequently, an upper bound \(P_N\) for \(P_N(t)\).

After upper bounds are established, we proceed with the lower bounds as follows. Assume that \(M\) achieves its absolute minimum at some \(t_s\), then we use again the fact that \(M'(t_s) = 0\) to obtain:
\[
\frac{V_m(t_s)M(t_s)}{K_{m1}(t_s) + M(t_s)} = \frac{V_2(t_s)K_1(t_s)^n}{K_1^n(t_s) + P_N(t_s)^n} \geq \frac{v_M^m}{\kappa_1^n + P_N^n}.
\]
This shows that \(M(t) \geq m\) for some positive constant \(m\). In the same way, we find a lower bound \(p_0\) for \(P_0\) using the fact that
\[
\frac{V_1(t_s)p_0(t_s)}{K_1(t_s) + P_1(t_s)} = K_1(t_s)M(t_s) + \frac{V_2(t_s)p_1(t_s)}{K_2(t_s) + P_1(t_s)} \geq \kappa_m p_0.
\]
Next, suppose that \(P_1\) achieves its absolute minimum at \(t_s\), then
\[
P_2(t_s) \left( \frac{V_2(t_s)}{K_2(t_s) + P_2(t_s)} + \frac{V_3(t_s)}{K_3(t_s) + P_1(t_s)} \right) \geq \frac{V_1(t_s)p_0(t_s)}{K_1(t_s) + P_0(t_s)} \geq \frac{v_1p_0}{\kappa_1 + p_0} > 0
\]
which yields the existence of a positive lower bound \(p_1\). Finally, positive lower bounds for \(P_2\) and \(P_N\) are obtained by means of the function \(Q = P_2 + P_N\). Indeed, if \(Q\) achieves its absolute minimum at some \(t_s\), then
\[
P_2(t_s) \left( \frac{V_4(t_s)}{K_4(t_s) + P_2(t_s)} + \frac{V_5(t_s)}{K_5(t_s) + P_2(t_s)} \right) \geq \frac{v_3p_1}{\kappa_3 + p_1}
\]
and we deduce that \(P_2(t_s)\) cannot be arbitrarily small. As before, using the fact that \(P_2 \geq -CP_2\) it is seen that \(P_2(t) \geq e^{-CT}P_2(t)\) and the conclusion follows. This, in turn, yields a lower bound \(p_N > 0\) for \(P_N\).

We are already in conditions of defining the open set \(\Omega \subset \mathbb{R}^5\) as
\[
\Omega := \{(M, P_0, P_1, P_2, P_N) \in C_T : m < M(t) < M, P_0 < P_2(t) < P_0, P_1 < P_1(t) < P_1, p_2 < P_2(t) < P_2, p_N < P_N(t) < P_N\}
\]
and

**Theorem 2** Assume that the previous conditions \([3], [3], [4]\) and \([5]\) hold. Then problem \([4]\) has at least one positive \(T\)-periodic solution.

### 3.2 Degree computation

In the previous section, the first condition of the continuation theorem was verified. It remains to prove that \(b)\) and \(c)\) are fulfilled as well. With this aim, set \(Q := \Omega \cap \mathbb{R}^5\) and recall that the function \(\phi : \Omega \to \mathbb{R}^5\) is defined by \(\phi(x) = \overline{N}\overline{x}\). We claim that each coordinate \(\phi_j\) has different signs at the corresponding opposite faces of \(Q\).

Indeed, compute for example \(\phi_1(M, P_0, P_1, P_2, P_N)\) and \(\phi_1(m, P_0, P_1, P_2, P_N)\) for \(p_j \leq P_j < P_j\):
\[
\phi_1(M, P_0, P_1, P_2, P_N) = \frac{1}{T} \int_0^T \left( \frac{V_5(t)K_1(t)^n}{K_1^n(t) + P_N} - \frac{V_m(t)M}{K_{m1}(t) + M} \right) dt
\]
\[ V_S - \frac{v_m M}{K_{m_1} + M} = 0, \]
\[
\phi_1(m, P_0, P_1, P_2, P_N) = \frac{1}{T} \int_0^T \left( V_S(t) K_1(t)^n - \frac{V_m(t)m}{K_{m_1}(t) + m} \right) dt > 0
\]
provided that \( m \) is small enough. In the same way, making the lower bounds smaller if necessary, we deduce that

\[ \phi_2(M, P_0, P_1, P_2, P_N) < 0 < \phi_2(M, p_0, P_1, P_2, P_N) \]
\[ \phi_3(M, P_0, P_1, P_2, P_N) < 0 < \phi_2(M, p_0, p_1, P_2, P_N) \]
\[ \phi_4(M, P_0, P_1, P_2, P_N) < 0 < \phi_2(M, p_0, p_1, p_2, P_N) \]
\[ \phi_5(M, P_0, P_1, P_2, P_N) < 0 < \phi_2(M, p_0, p_1, p_2, p_N) \]

Thus, condition b) of Continuation Theorem is verified. Moreover, we may define a homotopy as follows. Consider the center of \( Q \) given by

\[ \mathcal{P} := \left( \frac{M + m}{2}, \frac{P_0 + p_0}{2}, \frac{P_1 + p_1}{2}, \frac{P_2 + p_2}{2}, \frac{P_N + p_N}{2} \right) \]

and the function \( \mathcal{H} : \overline{Q} \times [0; 1] \to \mathbb{R}^5 \) given by

\[ \mathcal{H}(x, \lambda) = (1 - \lambda)(\phi - x) + \lambda \phi. \]

We need to verify that \( \mathcal{H} \) does not vanish at \( \partial Q \). To this end, suppose for example that \( \mathcal{H}(M, P_0, P_1, P_2, P_N) = 0 \) for some \( \lambda \in [0; 1] \), then

\[ 0 = \mathcal{H}_1(M, \lambda) = (1 - \lambda) \left( \frac{M + m}{2} - M \right) + \lambda \phi_1(M, P_0, P_1, P_2, P_N) < 0, \]

a contradiction. All the remaining cases follow in an analogous way. By the homotopy invariance of the Brouwer degree, it follows that

\[ \text{deg}_B(\phi, Q, 0) = \text{deg}_B(\phi - I, Q, 0) = (-1)^5 \neq 0. \]

This proves the third condition of the continuation theorem and, therefore, the existence of a \( T \)-periodic solution is deduced. \( \square \)

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