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Existence of Solutions for a Biological Model Using Topological Degree Theory

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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; drosophila; circadian cycle.*

Mathematics Subject Classification (2010): 34K13, 92B05.

1 Introduction

The study of cellular control has been developed in many papers on mathematical analysis to determine the existence of stable oscillations in mRNA regulatory processes, see [5] and to understand circadian cycles and, in particular, of the cellular machinery that produces them, see [7].

In all cases, search for conditions on the parameters of the proposed systems has been carried out with the purpose of determining conditions for the existence of stable cycles and the cycles when the system solution may be even chaotic.

Let us consider a model proposed by Goldbeter [3], who showed the variation on PER: the period of *messenger of Ribo-Nucleic Acid (mRNA)* in Drosophila (often called "fruit flies") related to circadian rhythms. Our model does not consider temperature variation as shown in [6]. 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 (see [1] and [2]). 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.

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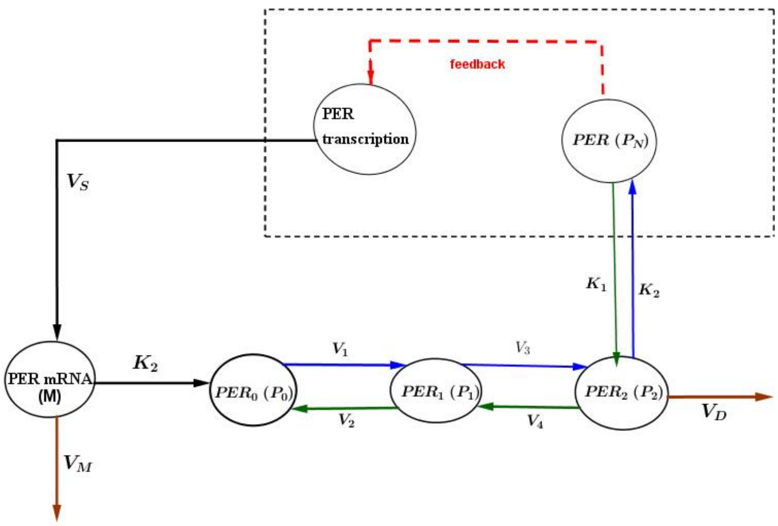

Figure 1: Model for the circadian variation in PER.

2 The Model

The following simplified model was proposed in [3]. Some more complex alternative models have been studied with light interaction and timeless (TIM) proteins (see [4]).

2.1 General features

1. This negative feedback will be described by an equation of Hill type in which n denotes the degree of cooperativity, and $K(t)$ is the threshold repression function.
2. To simplify the model, we consider that P_N behaves directly as a repressor.
3. The constants K_s, K_i and V_j denote the maximum rate and Michaelis constant of the kinase(s) and the phosphatase(s) involved in the reversible phosphorylation of P_0 into P_1, and of P_1 into P_2 are not negative.
4. Maximum accumulation rate of cytosol is denoted by V_s.
5. Cytosol is degraded enzymically, in a Michaelian manner, at a maximum rate V_m.
6. 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.

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

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

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

With this in mind, our non-autonomous version of Goldbeter's system reads:

$$
\begin{aligned}
\frac{dM}{dt} &= \frac{V_S(t)K_1(t)^n}{K_1^n(t)+P_N(t)^n} - \frac{V_m(t)M(t)}{K_{m_1}(t)+M(t)},\\
\frac{dP_0}{dt} &= K_s(t)M(t) + \frac{V_2(t)P_1(t)}{K_2(t)+P_1(t)} - \frac{V_1(t)P_0(t)}{K_1(t)+P_0(t)},\\
\frac{dP_1}{dt} &= \frac{V_1(t)P_0(t)}{K_1(t)+P_0(t)} + \frac{V_4(t)P_2(t)}{K_4(t)+P_2(t)} - P_1(t)\left(\frac{V_2(t)}{K_2(t)+P_1(t)} + \frac{V_3(t)}{K_3(t)+P_1(t)}\right),\\
\frac{dP_2}{dt} &= \frac{V_3(t)P_1(t)}{K_3(t)+P_1(t)} + k_2(t)P_N(t) - P_2(t)\left(k_1(t) + \frac{V_4(t)}{K_4(t)+P_2(t)} + \frac{V_d(t)}{K_d(t)+P_2(t)}\right),\\
\frac{dP_N}{dt} &= k_1(t)P_2(t) - k_2(t)P_N(t),
\end{aligned}
\tag{1}
$$

where $K_i,\ i=1,2,3,4,d,m_1,s,\ k_1,\ k_2$ 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 (1), 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

$$\mathcal{K} := \{u \in C_T : u_j \geq 0, j = 1,\dots,5\}.$$

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 $\phi(x) := \overline{Nx}$.

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 $F : \overline{\Omega} \to E$, 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 $\mathrm{Im}(K)$. If $deg_{LS}(F, \Omega, 0)$ is different from 0, then F vanishes in Ω; moreover, the degree is invariant over a continuous homotopy $F_\lambda := I - K_\lambda$ with K_λ being compact and $F_\lambda \neq 0$ over $\partial\Omega$. Finally, we recall that if $\Delta : \mathbb{R}^n \to \mathbb{R}^n$ is a diffeomorphism and $0 \in \Delta(A)$ for some open bounded $A \subset \mathbb{R}^n$, then $deg_B(\Delta, A, 0)$ is just the sign of the Jacobian determinant of Δ at the (unique) pre-image of 0. The following continuation theorem is a direct consequence of the standard topological degree methods (see e.g. [1]).

Theorem 3.1 *Assume there exists $\Omega \subset \mathcal{K}^\circ$ being 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 $u \in \partial\Omega \cap \mathbb{R}^5$.

c) $deg_B(\phi, \Omega \cap \mathbb{R}^5, 0) \neq 0$.

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

3.1 A priori bounds

Firstly, 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

$$0 < v_i \leq V_i(t) \leq \mathcal{V}_i,\ 0 < \kappa_j \leq K_j(t) \leq \mathcal{K}_j,\ 0 < \hat{k}_l \leq k_l(t) \leq \Bbbk_l,\ \forall\ i,\ j,\ l.$$

Now assume that $u \in \mathcal{K}^\circ$ satisfies $Lu = \lambda Nu$ for some $0 < \lambda < 1$. Let us firstly consider a value t^* at which M achieves an absolute maximum, then $M'(t^*) = 0$ and hence

$$\frac{V_S(t^*)K_1(t^*)^n}{K_1^n(t^*) + P_N(t^*)^n} = \frac{V_m(t^*)M(t^*)}{K_{m_1}(t^*) + M(t^*)} \geq \frac{v_m M(t^*)}{\mathcal{K}_{m_1} + M(t^*)} := b_M(M(t^*)),$$

where the increasing function

$$b_M(x) := \frac{v_m x}{\mathcal{K}_{m_1} + x}$$

has inverse such that

$$b_M^{-1}(y) := \frac{\mathcal{K}_{m_1} y}{v_m - y}.$$

If

Hypothesis 3.1

$$v_m > \mathcal{V}_S,$$

then

$$M(t^*) = b_M^{-1}\left(\frac{V_S(t^*)K_1(t^*)^n}{K_1^n(t^*) + P_N(t^*)^n}\right) < b_M^{-1}\left(V_S(t^*)\right) \leq \frac{\mathcal{V}_S \mathcal{K}_{m_1}}{v_M - \mathcal{V}_S} := \mathcal{M}.$$

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

$$K_s(t^*)M(t^*) + \frac{V_2(t^*)P_1(t^*)}{K_2(t^*) + P_1(t^*)} = \frac{V_1(t^*)P_0(t^*)}{K_1(t^*) + P_0(t^*)} \geq \frac{v_1 P_0(t^*)}{\mathcal{K}_1 + P_0(t^*)} := b_0(P_0(t^*)).$$

Again, we define an increasing and invertible function:

$$b_0(x) := \frac{v_1 x}{\mathcal{K}_1 + x} \to b_0^{-1}(y) := \frac{\mathcal{K}_1 y}{v_1 - y}.$$

Thus, under the condition

Hypothesis 3.2

$$\mathcal{K}_S \mathcal{M} + \mathcal{V}_2 < v_1$$

we deduce that

$$P_0(t^*) = b_0^{-1}\left(K_s(t^*)M(t^*) + \frac{V_2(t^*)P_1(t^*)}{K_2(t^*) + P_1(t^*)}\right) < \frac{\mathcal{K}_S\mathcal{M} + \mathcal{V}_2}{v_1 - (\mathcal{K}_S\mathcal{M} + \mathcal{V}_2)}\mathcal{K}_1 := \mathcal{P}_0.$$

Next, an upper bound $\mathcal{P}_1$ for P_1 is readily obtained in the following way. Let us denote again by t^* a value at which P_1 achieves its absolute maximum, then

$$\frac{V_1(t^*)P_0(t^*)}{K_1(t^*) + P_0(t^*)} + \frac{V_4(t^*)P_2(t^*)}{K_4(t^*) + P_2(t^*)} = P_1(t^*)\left(\frac{V_2(t^*)}{K_2(t^*) + P_1(t^*)} + \frac{V_3(t^*)}{K_3(t^*) + P_1(t^*)}\right).$$

When $P_1(t^*) \gg 0$, the right-hand side gets close to $V_2(t^*) + V_3(t^*)$, while the left-hand side is always less than or equal to $\frac{\mathcal{V}_1\mathcal{P}_0}{\kappa_1 + \mathcal{P}_0} + \mathcal{V}_4$ because $\frac{P_2}{K_4(t^*)+P_4} \leq 1$ and $\frac{x}{\kappa_1 + x}$ increase when $x = \mathcal{P}_0$.

Thus, the existence of $\mathcal{P}_1$ is guaranteed by the condition

Hypothesis 3.3

$$\frac{\mathcal{V}_1\mathcal{P}_0}{\kappa_1 + \mathcal{P}_0} + \mathcal{V}_4 < \min_{t\in\mathbb{R}}\{V_2(t) + V_3(t)\}.$$

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:

$$\frac{dQ}{dt} = \frac{V_3(t)P_1(t)}{K_3(t) + P_1(t)} - P_2(t)\left(\frac{V_4(t)}{K_4(t) + P_2(t)} + \frac{V_d(t)}{K_d(t) + P_2(t)}\right).$$

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

$$\frac{\mathcal{V}_3\mathcal{P}_1}{\kappa_3 + \mathcal{P}_1} \geq \frac{V_3(t^*)P_1(t^*)}{K_3(t^*) + P_1(t^*)} - P_2(t^*)\left(\frac{V_4(t^*)}{K_4(t^*) + P_2(t^*)} + \frac{V_d(t^*)}{K_d(t^*) + P_2(t^*)}\right).$$

As before, if the condition

Hypothesis 3.4

$$\frac{\mathcal{V}_3\mathcal{P}_1}{\kappa_3 + \mathcal{P}_1} < \min_{t\in\mathbb{R}}(V_4(t) + V_d(t))$$

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 $\dfrac{dP_2}{dt} \geq -CP_2(t)$. Hence we obtain, for all t, that $P_2(t) \leq e^{CT}\tilde{P} := \mathcal{P}_2$. Then $Q'(t)$ is bounded. Besides, there exist $\hat{t}$ critical point of $\mathcal{P}_N$, in consequence

$$k_1(\hat{t})P_2(\hat{t}) = k_2(\hat{t})P_N(\hat{t}),$$

then $P_N(\hat{t})$ verifies:

$$P_N(\hat{t}) \leq \frac{k_1^*}{k_{2*}}\mathcal{P}_2,$$

thus

$$Q(\hat{t}) = P_N(\hat{t}) + P_2(\hat{t}) \leq \mathfrak{Q}_0 := \left(\frac{k_1^*}{k_{2*}} + 1\right)\mathcal{P}_2.$$

In this way, knowing that $Q' \leq \mathfrak{Q}_1$, by integrating up to a certain t in the interval $\mathcal{J} := [\hat{t}, \hat{t}+T]$ follows:

$$Q(t) = Q(\hat{t}) + \int_{\hat{t}}^{t} Q'(t) \leq \mathfrak{Q}_0 + \mathfrak{Q}_1 \underbrace{(t-\hat{t})}_{\leq T},\ t \in \mathcal{J}$$

in this way, there is also a $\mathcal{P}_N$ of $P_N(t)$, then

$$P_N(t) \leq Q(t) \leq \mathfrak{Q}_0 + \mathfrak{Q}_1 T := \mathcal{P}_N.$$

After upper bounds are established, we proceed with the lower bounds as follows. Assume that M achieves its absolute minimum at some t_*, then we use again the fact that $M'(t_*) = 0$ to obtain:

$$\frac{V_m(t_*)M(t_*)}{K_{m_1}(t_*) + M(t_*)} = \frac{V_S(t_*)K_1(t_*)^n}{K_1^n(t_*) + P_N(t_*)^n} \geq \frac{v_S \kappa_1^n}{\kappa_1^n + \mathcal{P}_N^n}.$$

As we did before:

$$\frac{V_m(t_*)M(t_*)}{K_{m_1}(t_*) + M(t_*)} \geq \frac{v_m M(t_*)}{\kappa_{m_1} + M(t_*)}$$

lets define the increasing and bijective function

$$\hat{b}_M(x) := \frac{v_m x}{\kappa_{m_1} + x},\ \hat{b}_M^{-1}(y) := \frac{\kappa_{m_1} y}{v_m - y}$$

this inverse is increasing too, thus:

$$M(t_*) \geq \hat{b}_M^{-1}\left(\frac{v_S \kappa_1^n}{\mathcal{K}_1^n + \mathcal{P}_N^n}\right) := \mathfrak{m}.$$

This shows that $M_1(t) \geq \mathfrak{m}$ for some positive constant $\mathfrak{m}$. In the same way, we find a lower bound $\mathfrak{p}_0$ for P_0 using the fact that

$$\frac{V_1(t_*)P_0(t_*)}{K_1(t_*) + P_0(t_*)} = K_s(t_*)M(t_*) + \frac{V_2(t_*)P_1(t_*)}{K_2(t_*) + P_1(t_*)} \geq \kappa_s \mathfrak{m}.$$

We know that

$$\frac{V_1(t_*)P_0(t_*)}{K_1(t_*) + P_0(t_*)} \geq \frac{v_1 P_0(t_*)}{\kappa_1 + P_0(t_*)},$$

this function is increasing and its inverse is also increasing:

$$\hat{b}_1(x) := \frac{v_1 x}{\kappa_1 + x} \to \hat{b}_1^{-1}(y) := \frac{\kappa_1 y}{v_1 - y},$$

therefore, it is defined $\mathfrak{p}_0 := \hat{b}_1^{-1}(\kappa_s \mathfrak{m})$.

Next, suppose that P_1 achieves its absolute minimum at t_*, then

$$P_1(t_*)\left(\frac{V_2(t_*)}{K_2(t_*)+P_1(t_*)}+\frac{V_3(t_*)}{K_3(t_*)+P_1(t_*)}\right) > \frac{V_1(t_*)P_0(t^*)}{K_1(t_*)+P_0(t_*)} \geq \frac{v_1\mathfrak{p}_0}{\mathcal{K}_1+\mathfrak{p}_0} > 0$$

which yields the existence of a positive lower bound $\mathfrak{p}_1 := \frac{v_1\mathfrak{p}_0}{\mathcal{K}_1+\mathfrak{p}_0}$. 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_*, then

$$P_2(t_*)\left(\frac{V_4(t_*)}{K_4(t_*)+P_2(t_*)}+\frac{V_d(t_*)}{K_d(t_*)+P_2(t_*)}\right) \geq \frac{v_3\mathfrak{p}_1}{\mathcal{K}_3+\mathfrak{p}_1}$$

and we deduce that $P_2(t_*)$ 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 $\mathfrak{p}_N > 0$ for P_N.

4 Main Theorem

We are already in conditions of defining the open set $\Omega \subset \mathcal{K}^\circ$ as

$$\Omega := \{(M, P_0, P_1, P_2, P_N) \in C_T : \mathfrak{m} < M(t) < \mathcal{M}, \mathfrak{p}_0 < P_0(t) < \mathcal{P}_0,$$
$$\mathfrak{p}_1 < P_1(t) < \mathcal{P}_1, \mathfrak{p}_2 < P_2(t) < \mathcal{P}_2, \mathfrak{p}_N < P_N(t) < \mathcal{P}_N\}.$$

Theorem 4.1 *Assume that the previous conditions (3.1), (3.2), (3.3) and (3.4) hold. Then problem (1) has at least one positive $T-$periodic solution.*

Proof. 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 $\mathcal{Q} := \Omega \cap \mathbb{R}^5$ and recall that the function $\phi : \overline{\mathcal{Q}} \to \mathbb{R}^5$ is defined by $\phi(x) = \overline{Nx}$. We claim that each coordinate ϕ_j has different signs at the corresponding opposite faces of $\mathcal{Q}$.

Indeed, compute for example $\phi_1(\mathcal{M}, P_0, P_1, P_2, P_N)$ and $\phi_1(\mathfrak{m}, P_0, P_1, P_2, P_N)$ for $\mathfrak{p}_j \leq P_j \leq \mathcal{P}_j$:

$$\phi_1(\mathcal{M}, P_0, P_1, P_2, P_N) = \frac{1}{T}\int_0^T \left(\frac{V_S(t)K_1(t)^n}{K_1^n(t)+P_N} - \frac{V_m(t)\mathcal{M}}{K_{m_1}(t)+\mathcal{M}}\right) dt$$
$$< \mathcal{V}_S - \frac{v_m\mathcal{M}}{\mathcal{K}_{m_1}+\mathcal{M}} = 0,$$
$$\phi_1(\mathfrak{m}, P_0, P_1, P_2, P_N) = \frac{1}{T}\int_0^T \left(\frac{V_S(t)K_1(t)^n}{K_1^n(t)+P_N} - \frac{V_m(t)\mathfrak{m}}{K_{m_1}(t)+\mathfrak{m}}\right) dt$$
$$> \frac{v_S\kappa_1^n}{\mathcal{K}_1^n+\mathcal{P}_N^n} - \frac{\mathcal{V}_m\mathfrak{m}}{\kappa_{m_1}+\mathfrak{m}} \geq 0$$

provided that $\mathfrak{m}$ is small enough. In the same way, making the lower bounds smaller if necessary, we deduce that

$$\phi_2(M, \mathcal{P}_0, P_1, P_2, P_N) < 0 < \phi_2(M, \mathfrak{p}_0, P_1, P_2, P_N),$$

$$\phi_3(M, P_0, \mathcal{P}_1, P_2, P_N) < 0 < \phi_3(M, p_0, \mathfrak{p}_1, P_2, P_N),$$

$$\phi_4(M, P_0, P_1, \mathcal{P}_2, P_N) < 0 < \phi_4(M, p_0, p_1, \mathfrak{p}_2, P_N),$$
$$\phi_5(M, P_0, P_1, P_2, \mathcal{P}_N) < 0 < \phi_5(M, p_0, p_1, p_2, \mathfrak{p}_N).$$

Thus, condition $b)$ of the continuation theorem is verified. Moreover, we may define a homotopy as follows. Consider the center of $\mathcal{Q}$ given by

$$\wp := \left(\frac{\mathcal{M}+\mathfrak{m}}{2}, \frac{\mathcal{P}_0+\mathfrak{p}_0}{2}, \frac{\mathcal{P}_1+\mathfrak{p}_1}{2}, \frac{\mathcal{P}_2+\mathfrak{p}_2}{2}, \frac{\mathcal{P}_N+\mathfrak{p}_N}{2}\right)$$

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

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

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

$$0 = \mathcal{H}_1(\mathcal{M}, \hat{\lambda}) = (1-\hat{\lambda}) \underbrace{\left(\frac{\mathcal{M}+\mathfrak{m}}{2} - \mathcal{M}\right)}_{<0} + \hat{\lambda} \underbrace{\phi_1(\mathcal{M}, P_0, P_1, P_2, P_N)}_{<0} < 0,$$

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

$$deg_B(\phi, \mathcal{Q}, 0) = deg_B(\wp - I, \mathcal{Q}, 0) = (-1)^5 \neq 0.$$

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

5 Conclusion

Topological degree was used for proving existence of stable equilibrium in a generic model of circadian cycle. This theory allowed to demonstrate the existence of positive periodic solutions when parameters are replaced by fixed periodic functions. The relevance of finding periodic solutions in biological models relies mainly on the fact that periodic functions represent natural cycles, such as hormonal processes.

We show that topological degree can be successfully applied to find positive periodic orbits for some of these models in the non-autonomous case. It is worthy mentioning that, for diverse biological cycles, the behaviour is characterized by models with periodic parameters; thus, the present paper provides a useful mathematical tool to understand such models.

For future work, it would be interesting to consider a more general situation, in which the parameters are not periodic but almost-periodic functions, which attracted the attention of many researchers in the last decades. Here, the topological degree cannot be used anymore because of the lack of compactness of the associated operator; thus, a different approach is required, such as the use of fixed points in cones under monotonicity conditions that avoid the compactness assumption.

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