Existence of periodic and almost periodic solutions in a resonant model on stem cell dynamics

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Abstract

This work deals with the existence of almost periodic solutions in a biological model, the model proposed by VG Nazarenko and E.E. Sel'kov of stem cell dynamics. This article demonstrates the existence of almost periodic solutions, for this purpose, the constant parameters of the system were changed to almost periodic functions which allows greater adaptability in biological cases such as this. This kind of changes have already been raised in other biological systems. In this case we will use the implicit function theorem to prove the existence of periodic solutions.

KEYWORDS: existence and uniqueness of almost periodic solutions; non-linear nonautonomous delay differential equations; implicit function theorem; resonant problem, cellular dynamics

MSC Classification 2010; 92C37; 34K14

1 Introduction

Fixed Point methods are a widely used tool to analyze the existence of nonlinear differential equation solutions. There are classical methods, for example those that appeal to the use of contractions and those that use the Schauder Theorem (see [3, 9]).
Unfortunately, the latter cannot be used to analyze the existence of almost periodic solutions because it requires the compactness of the associated operator K, a characteristic that in $AP(\mathbb{R}, \mathbb{X})$ cannot be verified; therefore, a different approach is required, such as the use of fixed points in cones under monotonicity conditions (see [4]) that avoid the assumption of compactness.

Almost periodic functions attracted the attention of many researchers in recent decades. Almost periodic solutions of systems of differential equations of biological models have been studied in various works, for example in the SIR type models of infectious disease dynamics such as Córdova Lepe et al [7] where the authors study the stability of an epidemic model with seasonal cyclic pulses, and under what conditions new endemic equilibrium are observed; Xiao et al [14] who analyze the existence of almost periodic solutions in a model of migrant workers with periodic almost periodic coefficients. In relation to cellular dynamics, which is more similar to the subject of study of this article. Several

recent studies have analyzed the existence and stability of almost periodic solutions in different models of hematopoiesis (cell production) such as Amster and Balderrama [3] who proved for a model with several delays and an oscillating circulation loss rate existence and uniqueness of positive almost periodic solutions by using a fixed point theorem in abstract cones or Ding et al [6] who have established results of existence and stability of almost periodic solutions. Existence of almost periodic dynamics in a hematopoiesis model with mixed discontinuous harvesting terms with delay can be seen in Nieto et al [12]. Recently Kong et al [11] have proved stability, uniqueness and global exponential stability of almost periodic solutions of a discontinuous bi-directional associative memory (BAM) neural network model.
In nature the perfect periodic cycles are a rarity, as we have already mentioned, the lack of periodicity is attributable to the adaptability of the system to changes in its environment, which is why almost periodic functions are better suited to these cyclic processes.

For this reason, we point out that the introduction of almost periodic functions are far from being an artificial assumption without biological meaning, indeed we think that its mean value properties provides a natural framework to describe some cyclic processes with behavior more complex than periodicity.

In particular, in our work we focus on giving a different approach to the population dynamics model of stem cells originally proposed by Nazarenko and Sel'kov [13] and then taken up by Hastings et al [10]. In these previous works the almost periodicity of the solutions had not been tested.

1.1 A model to represent the stem cell cycle

Stem cells have the ability to divide through mitosis and their study is of wide scientific interest since they can be differentiated not only in stem cells, but in numerous other types of specialized cells.
All multicellular organisms have stem cells, which can be classified according to their potency, which determines the number of different cell types in which these stem cells can differentiate.
The medical interest in the study of these cells lies in the possibility of using them for the recovery of tissues damaged by diseases or accidents.

The process to study is reflected in the following scheme G is the mass of undifferentiated stem cells, the differentiated cells D_j have different phases (or *ages*) until they reach a I inhibitory stage or phase, the concentration of these cells (aged n) inhibits the mitotic process of differentiation. In this model there is also a loop on G that reflects a duplication (according to [13]) of these undifferentiated stem cells.

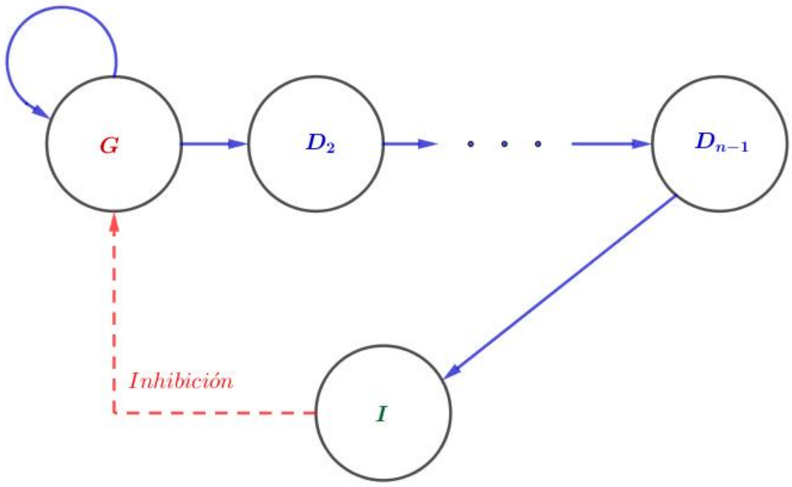

Figure 1: A generalized scheme of the stem cell cycle.

Nazarenko-Sel'kov's model is as follows:

$$
\begin{aligned}
\frac{dG}{dt} &= \frac{r(t)G(t)}{K(t)+I(t-\tau)^p} - k_1(t)G(t),\\
\frac{dD_2}{dt} &= k_1(t)G(t-\tau) - k_2(t)D_2(t),\\
\frac{dD_j}{dt} &= k_{j-1}(t)D_{j-1}(t-\tau) - k_j(t)D_j(t), \quad 3 \le j \le n-1\\
\frac{dI}{dt} &= k_{n-1}(t)D_{n-1}(t-\tau) - k_n(t)I(t)
\end{aligned} \tag{1}
$$

where $r(t),\ K(t),\ k_i(t)$ for all i, are positives functions and the delay $\tau \ge 0$.

Let us observe that the first equation fits into the type of differential equations that are called resonants, in this case we will use a classic result: the Implicit Function Theorem.

Theorem 1 (Implicit Function)**.** *Lets $\mathbb{X}$, $\mathbb{Y}$ and $\mathbb{W}$ Banach spaces, let $U \subset \mathbb{X}$, $V \subset \mathbb{Y}$ be open sets and let $f : U \times V \to \mathbb{W}$ be a C^k mapping. Furthermore, assume that $f(x_0, y_0) = 0$ and that $\frac{\partial f}{\partial y}(x_0, y_0) : \mathbb{Y} \to \mathbb{W}$ is an isomorphism. Then there exists a U_0 neighbourhood of x_0 and an unique C^k function $\phi : U_0 \to V$ such that $\phi(x_0) = y_0$ and $f(x, \phi(x)) = 0\ \forall\ x \in U_0$.*

1.2 Preliminaires

For convenience, we introduce some notations. Set $AP(\mathbb{R}, \mathbb{X}) = \{x(t)\ :\ x(t) \in C(\mathbb{R}, \mathbb{R}_+,\ x(t)$ is almost periodic function.

Definition 1. *A set $A \in \mathbb{R}$ is relatively dense in $\mathbb{R}$ if there exists a number $\ell > 0$ such that any interval of lenght ℓ has a non empty intersection with A.*

Definition 2 (Bohr)**.** *For any bounded function f and $\varepsilon > 0$, we define*

$$T(f,\varepsilon) = \{x : \ |f(x+t) - f(x)| < \varepsilon \ \forall \ t\}$$

$T(f,\varepsilon)$ is called the $\varepsilon-$translation set of f.

Definition 3 (Bohr)**.** *A function $f : \mathbb{R} \to \mathbb{X}$ is called almost periodic if for every $\varepsilon > 0$, $T(f,\varepsilon)$ is relatively dense.*

Theorem 2 (Open Map)**.** *Lets $\mathbb{X}$, $\mathbb{Y}$ Banach spaces and $T : \mathbb{X} \to \mathbb{Y}$ a linear, surjective and continuous map, then T is open.*

Lemma 1. *If $T : \mathbb{X} \to \mathbb{Y}$ is linear, bijective and continuous, spaces $\mathbb{X}$, $\mathbb{Y}$ as open map theorem 2, then $T^{-1} : \mathbb{Y} \to \mathbb{X}$ is continuous.*

Theorem 3 (Fink [8], 5.11)**.** *Consider the system*

$$x'(t) = Ax(t) + f(t) \tag{2}$$

where $f \in AP(\mathbb{R}, \mathbb{R}^n_+)$. Suppose that $|\mu - i\epsilon_n| \geq \rho > 0$ for all eigenvalues μ of matrix A and $\epsilon_n \in exp(f)$.
Then there is a unique almost periodic solution $x(f)$ of (2) with $exp(x(f)) \subset exp(f)$.
There exists a polynomial P of degree $\leq n$ with no constant term depending only on the matrix A and an absolute constant C , so that the mapping $f \mapsto x(f)$, defined on

$$\mathcal{N}_\rho = \{f \ : \ f \in CP(\mathbb{R}, \mathbb{R}^n_+), \ |\mu - i\epsilon_n| \geq \rho > 0\}$$

is a linear mapping withcon norm less than $P(C\rho^{-1})$.

2 The periodic Nazarenko-Sel'kov model

Lets suppose that functions $r(t)$, $K(t)$, $k_i(t)$ are $T-$periodic for all i.

Theorem 4. *Assume that the following conditions hold*

- *(sufficiency) For all $t \in \mathbb{R}$*

$$\frac{r(t)}{K(t)} > k_1(t) \tag{3}$$

- *(necessity)*

$$\frac{1}{T}\int_0^T \frac{r(t)}{K(t)}dt > \frac{1}{T}\int_0^T k_1(t)dt \tag{4}$$

Then problem (1) has at least one $T-$periodic solution $u = (G, D_1, ..., D_{n-1}, I)$ such that $u_k(t) > 0$ for all t and all k.

We shall apply the continuation method in the the positive cone

$$\mathcal{K} := \{u \in C_T : x_0, x_1, ..., x_n \geq 0\}$$

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

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

Theorem 5. *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) $deg(\phi, \Omega \cap \mathbb{R}^{n+1}, 0) \neq 0$, where 'deg' denotes the Brouwer degree.

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

In order to apply Theorem 5 to our problem, let us assume that $u = (x_0, x_1, ..., x_n) \in \mathcal{K}$ 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 Ω.

Theorem 6. *Homotopy ϕ vanishes at a single point within an open set $\mathcal{Q} \subset \mathbb{R}^{n+1}$*

Proof.

$$\phi(z) = \mathbf{0}$$

which is equivalent to the non-linear model $A(z_n) \cdot z = \mathbf{0}$:

$$\begin{pmatrix} \overline{\frac{r}{K+z_n^p}} - \overline{k_1} & 0 & 0 & 0 & \dots & 0 \\ \overline{k_1} & -\overline{k_2} & 0 & 0 & \dots & 0 \\ 0 & \overline{k_2} & -\overline{k_3} & 0 & \dots & 0 \\ 0 & 0 & \overline{k_3} & -\overline{k_4} & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \ddots & \vdots \\ 0 & 0 & \dots & 0 & \overline{k_{n-1}} & -\overline{k_n} \end{pmatrix} \cdot \begin{pmatrix} z_1 \\ z_2 \\ \vdots \\ z_n \end{pmatrix} = \mathbf{0} \qquad (5)$$

Obviously a solution is the trivial $z = \mathbf{0}$ that does not interest us.

For there to be another solution, we need

$$det(A(z_n)) = 0 \Leftrightarrow \overline{\frac{r}{K + z_n^p}} = \overline{k_1}$$

this value z_n is unique because the average is strictly decreasing as a function of z_n.
Solving the system, a non-trivial solution can be written in $\mathcal{Q}$ in this way

$$z = (z_1, z_2, ..., z_{n-1}, z_n) = \left(\frac{\overline{k_n}}{\overline{k_1}} z_n, \frac{\overline{k_n}}{\overline{k_2}} z_n, ..., \frac{\overline{k_n}}{\overline{k_{n-1}}} z_n, z_n\right) = \overline{k_n} z_n \left(\frac{1}{\overline{k_1}}, \frac{1}{\overline{k_2}}, ..., \frac{1}{\overline{k_{n-1}}}, \frac{1}{\overline{k_n}}\right)$$

In this way we prove that ϕ vanishes once inside $\mathcal{Q} \subset \mathbb{R}^n$ and by degree theory it is concluded that there is a unique solution in $\Omega \subset C_T$. $\square$

3 The almost periodic Nazarenko-Sel'kov model

For the following, we will use the Implicit Function Theorem to prove the existence of almost periodic solutions.

4 Main Results

We consider the notation:

$$\Lambda(t) := (r(t), K(t), k_1(t), k_2(t), ..., k_n(t)) \in (AP(\mathbb{R}, \mathbb{R}_+))^{n+2}$$

$$\Lambda_0 = (\alpha_r, \alpha_K, \lambda_1, \lambda_2, \lambda_3, ..., \lambda_{n-1}, \lambda_n) := (r, K, k_1, k_2, ..., k_n) \in \mathbb{R}^{n+2}$$

$$Y = (y_1, y_2, y_3, ..., y_{n-1}, y_n) := (G, D_2, D_3, ..., D_{n-1}, I).$$

We will deduce that for almost periodic positive functions that take values near certain positive constants (the components of Λ_0), then (1) has a positive almost periodic solution.
Now be $F(\Lambda, Y)$ the operator $F : AP(\mathbb{R}, \mathbb{R}_+)^{n+2}\, x AP^1(\mathbb{R}, \mathbb{R}_+)^n \to AP(\mathbb{R}, \mathbb{R}_+)^n$ defined by:

$$F(\Lambda, Y) = \frac{dY}{dt} - N(\Lambda, Y)$$

where

$$N(\Lambda, Y) := \left(\frac{\alpha_r y_1}{\alpha_K + y_n^p} - \lambda_1 y_1,\ \lambda_1 y_1 - \lambda_2 y_2,\ , ...,\ \lambda_{n-1} y_{n-1} - \lambda_n y_n\right). \qquad (6)$$

We will set constant parameters $r,\ K,\ k_j > 0$ and determine conditions for a positive balance of the resulting system. Be $(\Lambda_0, Y_0) \in \mathbb{R}^{n+2}_{>0} \times \mathbb{R}^n_{>0}$ such that $F(\Lambda_0, Y_0) = 0$, lets see what conditions should be met for the existence of Λ_0 y de Y_0:

$$\begin{aligned}
&\frac{r y_1^{eq}}{K + (y_n^{eq})^p} - \lambda_1 y_1^{eq} = 0 \Leftrightarrow y_n^{eq} = \sqrt[p]{\frac{r - K\lambda_1}{\lambda_1}}, \\
&\lambda_1 y_1^{eq} = \lambda_2 y_2^{eq} \Rightarrow y_1^{eq} = \frac{\lambda_2 y_2^{eq}}{\lambda_1}, \\
&\lambda_{j-1} y_{j-1}^{eq} = \lambda_j y_j^{eq} \Rightarrow y_{j-1}^{eq} = \frac{\lambda_j y_j^{eq}}{\lambda_{j-1}}, \quad 3 \le j \le n-1 \\
&\lambda_{n-1} y_{n-1}^{eq} = \lambda_n y_n^{eq} \Rightarrow y_{n-1}^{eq} = \frac{\lambda_n y_n^{eq}}{\lambda_{n-1}} = \frac{\lambda_n}{\lambda_{n-1}} \sqrt[p]{\frac{r - K\lambda_1}{\lambda_1}}.
\end{aligned} \qquad (7)$$

Given the characteristics of the model (1), each equilibrium coordinate can be written like this:

$$y_j^{eq} = \frac{\lambda_n}{\lambda_j} \sqrt[p]{\frac{\alpha_r - \alpha_K \lambda_1}{\lambda_1}},\ 1 \leq j \leq n.$$

The differential is defined: $L := D_y F(\Lambda_0, Y_0) : (CP^1(\mathbb{R}, \mathbb{R}^+))^n \to (CP(\mathbb{R}, \mathbb{R}^+))^n$ of function $F(\Lambda, Y)$ considering the derivatives with respect to Y in the sense of Fréchet:

$$L\varphi = D_Y F(\Lambda_0, Y_0)(\varphi) = \varphi' - \underbrace{\frac{\partial N}{\partial y_k}(\Lambda_0, Y_0)}_{:=A} \varphi. \tag{8}$$

Be also the differential matrix (that is, $D_Y N(\Lambda_0, Y_0)$) A of the nonlinear operator

$$A := \begin{pmatrix} \frac{r}{K+(y_n^{eq})^p} - k_1 & k_1 & 0 & \cdots & 0 & 0 \\ 0 & -k_2 & k_2 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \cdots & \vdots & \vdots \\ -\frac{y_1^{eq} k_1^2 p (y_n^{eq})^{p-1}}{r} & 0 & 0 & \dots & 0 & -k_n \end{pmatrix} = \begin{pmatrix} 0 & \lambda_1 & 0 & \cdots & 0 & 0 \\ 0 & -\lambda_2 & \lambda_2 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \cdots & \vdots & \vdots \\ -\eta & 0 & 0 & \dots & 0 & -\lambda_n \end{pmatrix}, \tag{9}$$

where

$$\eta := \frac{\lambda_n}{\lambda_1} \left(\frac{\alpha_r - \alpha_K \lambda_1}{\lambda_1} \right)^{2-\frac{1}{p}}.$$

To prove the main statement, we will need the Theorem 3.

Theorem 7. *Lets be $r,\ K,\ k_j \in (0, +\infty)$ such that $r - Kk_1 > 0$, we fix Λ_0 as before.*

Besides, suppose the following polynomial

$$Q(x) = 1 + \frac{x + \lambda_n}{\eta} \frac{x}{\lambda_1} \prod_{k=2}^{n-1} \frac{x + \lambda_k}{\lambda_k}$$

has no pure imaginary roots.

Then there is a $\varepsilon > 0$ such that for every

$$\|\Lambda(t) - \Lambda_0\| < \varepsilon,$$

there is a positive almost periodic solution of (1).

To prove the theorem 7 we will use the following results.

Proposition 1. *If polynomial Q does not have pure imaginary roots, all A eigenvalues have a non-zero real part.*

Proof. Suppose there is a vector $v \in \mathbb{C}^n_{\neq 0}$ such that for certain $\epsilon \in \mathbb{R}$:

$$Av = i\epsilon v.$$

Now we proceed as follows:

$$\begin{pmatrix} 0 & \lambda_1 & 0 & \cdots & 0 & 0 \\ 0 & -\lambda_2 & \lambda_2 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \cdots & \vdots & \vdots \\ -\eta & 0 & 0 & \dots & 0 & -\lambda_n \end{pmatrix} \begin{pmatrix} v_1 \\ v_2 \\ \vdots \\ v_n \end{pmatrix} = \begin{pmatrix} i\epsilon v_1 \\ i\epsilon v_2 \\ \vdots \\ i\epsilon v_n \end{pmatrix} \tag{10}$$

This follows:

$$v_2 = \frac{i\epsilon}{\lambda_1} v_1$$

$$v_3 = \frac{i\epsilon + \lambda_2}{\lambda_2} \frac{i\epsilon}{\lambda_1} v_1$$

$$v_4 = \frac{i\epsilon + \lambda_3}{\lambda_3} v_3 = \frac{i\epsilon + \lambda_3}{\lambda_3} \frac{i\epsilon + \lambda_2}{\lambda_2} \frac{i\epsilon}{\lambda_1} v_1$$

$$v_5 = \frac{i\epsilon + \lambda_4}{\lambda_4} v_4 = \frac{i\epsilon + \lambda_4}{\lambda_4} \frac{i\epsilon + \lambda_3}{\lambda_3} \frac{i\epsilon + \lambda_2}{\lambda_2} \frac{i\epsilon}{\lambda_1} v_1$$

$$\vdots$$

$$v_n = \frac{i\epsilon + \lambda_{n-1}}{\lambda_{n-1}} v_{n-1} = \frac{\epsilon}{\lambda_1}(i\lambda_2 - \epsilon) v_1 \prod_{k=3}^{n-1} \frac{i\epsilon + \lambda_k}{\lambda_k}$$

and finally:

$$v_1 = -\frac{i\epsilon + \lambda_n}{\eta} v_n = -\frac{i\epsilon + \lambda_n}{\eta} \frac{i\epsilon}{\lambda_1} v_1 \prod_{k=2}^{n-1} \frac{i\epsilon + \lambda_k}{\lambda_k}.$$

From the latter it follows that either $v_1 = 0$ (which concludes the proof) or the term:

$$-\frac{i\epsilon + \lambda_n}{\eta} \frac{i\epsilon}{\lambda_1} \prod_{k=2}^{n-1} \frac{i\epsilon + \lambda_k}{\lambda_k} = 1,$$

but this is equivalent to the following,

$$1 + \frac{i\epsilon + \lambda_n}{\eta} \frac{i\epsilon}{\lambda_1} \prod_{k=2}^{n-1} \frac{i\epsilon + \lambda_k}{\lambda_k} = 0 \Longleftrightarrow Q(i\epsilon) = 0, \ \epsilon \in \mathbb{R},$$

That is not supposed to happen. □

Now we have what we need to prove the result we are looking for.

Proposition 2. *Under the conditions of Theorem 7, the linear operator L is an isomorphism.*

Proof. Under the proposal 1 we have $det(A) = -\eta \prod_{k=1}^{n} \lambda_k \neq 0$; furthermore, it is known from the same proposition that the A eigenvalues have a real part other than 0 accordingly, from Theorem 3 it follows that L is bijective.

Besides $L : (CP^1(\mathbb{R}, \mathbb{R}^+))^n \to (CP(\mathbb{R}, \mathbb{R}^+))^n$, it is continuous then

$$||L\varphi||_\infty \leq ||\varphi'||_\infty + ||A||||\varphi||_\infty \leq C||\varphi||_{CP^1}$$

where $C = 1 + ||A||$ y $||\varphi||_{CP^1} = ||\varphi'||_\infty + ||\varphi||_\infty$.

By Theorem 2, L has continuous inverse. Then, L is an isomorphism that was what we wanted to prove. □

Finally, let's prove the Theorem 7.

By the Implicit Function Theorem, there exists $U_0 \subset (CP(\mathbb{R}, \mathbb{R}^+))^{n+2}$ an environment of Λ_0, $V_0 \subset (CP^1(\mathbb{R}, \mathbb{R}_+))^n$ an environment of Y_0 and an unique function $\phi : U_0 \to V_0$ such that $F(\Lambda, \phi(\Lambda)) = 0$, therefore there is some almost periodic solution of (1).

5 Discussion

Almost periodic solutions have a meaning applied to models of differential equations representative of various biological dynamics. Given its degree of adaptability, these types of solutions have aroused much interest in the study of biological mathematics. In this work the existence of almost periodic positive solutions (with biological sense) in a resonant problem was demonstrated. These two characteristics make it difficult to use nonlinear topological analysis tools such as topological degree theory. In our case, we successfully use a classic result such as the implicit function theorem. In future studies we intend to use techniques similar to the one observed here for systems of differential equations with and without delay and circumstantially resonant.

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