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Zero-Hopf Bifurcation of two classes of differential systems.

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Dedication

I dedicate this humble work to:

- To my dear parents, my father " Farid " and my mother " Nadjla " for the sacrifices they made, their support and the depth of their patience throughout my studies.
- To all my sweet sister's " khadidja, Sara and Bouchra " who have supported me.
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Contents

Introduction

A dynamical system is everything that changes over time, the study of differential systems is a mathematical field that historically has been the subject of numerous types of research and which nevertheless continues to remain topical, due to the fact that it is of particular interest to disciplines such as mechanics, physics and biology. Despite people's perception that mathematics and biology are separate, there have always been models through which mathematics could explain complex biological phenomena and also to find solutions in some cases such as prediction.

In the study of dynamical systems, one often talks about solutions that repeat themselves after a certain time, hence their name of periodic orbits, which were first defined by Henri Poincaré in 1881 in his thesis" on curves defined by a differential equation ". In this study, why is there so much emphasis on the study of periodic orbits of systems instead of the other types of solutions that can be found (e.g. any closed orbit not being periodic, or other types)?
You might want to check the KAM theory, which simply states that a no-integrable system will have areas where the orbits are sustained (or in other words any sufficiently small perturbation away from an integrable system, can be studied by KAM theory using the periodic orbits[9].

Periodic solutions or orbits have remarkable significance in various domains, including physics, mathematics, engineering, and even biological biosphere systems. In the context of biological biosphere systems, a key challenge arises in assessing or investigating whether automatic oscillatory activity can persist despite encountering minor external influences. Extensive research has studied the continuation problem of periodic orbits. Despite the diverse perspectives from which these studies have been undertaken, they have all arrived at the same result.

There are several theories and methods for studying the existence, the number and stability of periodic orbits of differential systems.

Currently, the method of averaging holds significant importance in the examination of the number of periodic orbits in differential systems. The averaging theory has a lengthy history, dating back to the works of Lagrange and Laplace, who offered an intuitive explanation for the method. Fatou [10] formalized this theory for the first time in 1928. Significant practical and theoretical advancements in the field of averaging theory were achieved during the 1930's. Notable contributions were made by Bogoliubov-Krylov in the 1930s [2], followed by Bogoliubov in 1945 [1], and Bogoliubov-Mitropolsky [3] (English version published in 1961). See the book Sanders-Verhulst-Murdock [18] for a more recent discussion of the averaging theory. Many researchers have dedicated their efforts to investigating the bifurcating periodic orbit originating from a Zero-Hopf equilibrium point. Jaune Llibre has utilized first-order averaging on the Rössler system, while Pérez-Chavela and Llibre have applied second-order averaging theory to a specific class of three-dimensional autonomous quadratic polynomial differential systems of Lorenz-type.

The objective of this work is to study the Zero-Hopf bifurcation of two biological models. The first is the Malaria model and the second is Tumor Growth Cancer model.

The work of this dissertation is distributed as follows.

The first chapter is dedicated to reminders of some preliminary notions on the dynamics of systems. More precisely in the first section, we begin by defining polynomial differential systems, first integral, solution, periodic solution, and limit cycle. In the second section of this chapter, we expose the first and second order of averaging theory, we have illustrated these methods with examples and we introduce the notion of Zero-Hopf bifurcation in $\mathbb{R}^n$, we develop application namely to Rössler system.

In the second chapter, we study the Zero-Hopf bifurcation of the Malaria model. We present in it the main results for studying the number of periodic orbits which can have by applying averaging method.

In the last chapter, we study the Zero-Hopf Bifurcation of the Tumor Growth Cancer model. We put the main results for the conditions in order that the system has Zero-Hopf equilibria and by using the averaging theory for the existence and number of periodic orbits.

Chapter 1

Some Concepts and Preliminaries

In this chapter, we put some basic concepts for studying the dynamics of systems, we start with the definition of polynomial differential systems, and we will discuss the notions of a first integral, solution, periodic solution, and limit cycle. We also put main concepts and theorems related to the averaging theory. We present the averaging theory of first order for periodic orbit, we develop an application named the Van der Pol equation. We study the Zero-Hopf bifurcation in $\mathbb{R}^n$, we present application Rössler system. Finally, we define the averaging theory of second order.

1.1 Polynomial differential systems

Definition 1.1 *[8] A polynomial differential system is a differential system of the form*

$$\begin{aligned} \dot{x} &= P(x(t), y(t)), \\ \dot{y} &= Q(x(t), y(t)). \end{aligned} \tag{1.1}$$

Where the dot denotes the derivative with respect to the independent variable t, P and Q are polynomials in the variables x and y.

- *We now that $n = max(deg(P), deg(Q))$ is the degree of the polynomial system (1.1).*
- *A nonlinear differential system consists of nonlinear differential equations.*

1.2 First integral

Definition 1.2 *[8] The vector field $\mathcal{X}$ or equivalently the system (1.1) is integrable on an open subset Ω of $\mathbb{R}^n$ if there exists a non constant analytic function $H : \Omega \to \mathbb{R}^n$, called a first integral of the system on Ω, which is constant on all solution curves $(x(t), y(t))$ of $\mathcal{X}$ contained in Ω; i.e*

$$\frac{dH(x, y)}{dt} = P(x, y)\frac{\partial H(x, y)}{\partial x} + Q(x, y)\frac{\partial H(x, y)}{\partial y} = 0. \tag{1.2}$$

Moreover, $H(x, y) = c$, is the general solution of (1.2), where c is a constant.

Remark 1.1 *We say that the differential system (1.1) is integrable on an open subset Ω of $\mathbb{R}^n$ if it admits a first integral on it.*
It is well known that for differential systems defined on $\mathbb{R}^n$ the existence of the first integral determines its phase portrait.

1.3 Solution and Periodic Solution

Definition 1.3 *[12] We say that $(x(t), y(t))_{t\in\mathbb{R}}$ is a solution of system (1.1) if the vector field $\mathcal{X} = (P, Q)$ is always tangent to the trajectory representing this solution in the phase plane.*

$$P(x(t), y(t))\dot{x} + Q(x(t), y(t))\dot{y} = 0.$$

A solution $(x(t), y(t))$ of system (1.1) is periodic if there exists a real number $T > 0$ such that:

$$\forall t \in \mathbb{R}, \qquad x(t+T) = x(t), \qquad and \qquad y(t+T) = y(t).$$

- *The smallest number $T > 0$ is called the period of this solution.*

Remark 1.2 *We define the function $\Phi(., X) : \mathbb{R} \to E$, where E is an open subset of $\mathbb{R}^n$ is a closed solution curve of system (1.1).*

- *Γ is a trajectory of system (1.1) through the point X_0 at time $t = 0$ where*

$$\Gamma_{X_0} = \{X \in E \mid X = \Phi(t, X_0), t \in \mathbb{R}\}$$

1.3.1 Limit cycle

Definition 1.4 *[17] A limit cycle $\Gamma = \{(x(t), y(t)), t \in [0, T]\}$ is an isolated periodic solution in the set of all periodic solution of system (1.1).*
A periodic orbit Γ is called stable if: for each $\varepsilon > 0$ there is a neighborhood U of Γ such that for all $x \in U$ and $t > 0$ we have

$$d(\Phi(t, x), \Gamma) < \varepsilon.$$

A periodic orbit Γ is called unstable if it is not stable.

Remark 1.3 *The limit cycle appears only in non-linear differential systems.*

Example 1.1 *We consider*

$$\begin{aligned} &\dot{r} = r(1 - r^2), \qquad r \geq 0, \\ &\dot{\theta} = 1. \end{aligned} \tag{1.3}$$

We an easily prove that $r = 1$ is a stable limit cycle of system (1.3).

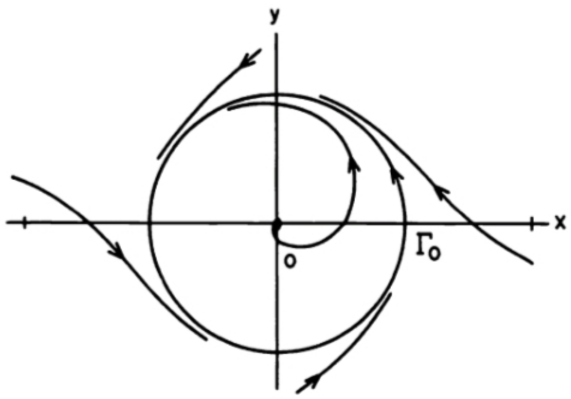

FIG 1.1: Limit Cycle.

The averaging method is a classical tool allowing us to study the dynamics of non-linear differential systems under periodic forcing. Many authors have used it to study the bifurcating periodic orbits from a Zero-Hopf equilibrium point. Castellanos et al. (Castellanos, 2013), Llibre et al. (Llibre, 2015) have used the averaging theory of first order to study the possible periodic orbits bifurcating from the Zero-Hopf equilibrium points of the tritrophic food chain model, the Rössler system and the Chen-Wang differential system respectively. In these studies, two periodic orbits were the maximum number. The second order of averaging theory is applied to study the existence of periodic orbits to a quadratic polynomial differential system in $\mathbb{R}^3$, a class of three-dimensional autonomous quadratic polynomial differential systems of Lorenz-type by Llibre et al. (Llibre, 2009) and Llibre and Pérez-Chavela (Llibre, 2014) respectively. In their work, the maximum number of periodic orbits was three.

1.4 The averaging theory of first order

[15] We consider the differential system

$$\dot{x} = \varepsilon F_1(t, x) + \varepsilon^2 R(t, x, \varepsilon), \tag{1.4}$$

with $x \in D \subset \mathbb{R}^n$, D a bounded domain, and $t \geq 0$. Moreover we assume that $F(t, x)$ and $R(t, x, \varepsilon)$ are T-periodic in t.
The averaged system associated to the system (1.4) is defined by

$$\dot{y} = \varepsilon f^0(y), \tag{1.5}$$

where

$$f^0(y) = \frac{1}{T}\int_0^T F(s, y)ds. \tag{1.6}$$

The next theorem says under what conditions the singular points of the averaged system (1.5) provide T -periodic orbits for the system (1.4).

Theorem 1.1 *[15] We consider system (1.4) and assume that the vector functions F, R, D_xF, D_x^2F and D_xR are continuous and bounded by a constant M (independent of ε) in $[0, \infty) \times D$,* *with* $-\varepsilon_0 < \varepsilon < \varepsilon_0$. *Moreover, we suppose that* F *and* R *are T-periodic in t, with* T *independent of* ε.

(i) If $p \in D$ *is a singular point of the averaged system* (1.5) *such that*

$$det(D_x f^0(p)) \neq 0 \tag{1.7}$$

then, for $|\ \varepsilon\ |> 0$ *sufficiently small, there exists a T-periodic solution* $x(t, \varepsilon)$ *of system* (1.4) *such that* $x(0, \varepsilon) \to p$ *as* $\varepsilon \to 0$.

(ii) If the singular point $y = p$ *of the averaged system* (1.5) *has all its eigenvalues with negative real part then, for* $|\varepsilon| > 0$ *sufficiently small, the corresponding periodic solution* $x(t, \varepsilon)$ *of system* (1.4) *is asymptotically stable and, if one of the eigenvalues has positive real part* $x(t, \varepsilon)$, *it is unstable.*

1.5 Application

We recall that a limit cycle of a differential system is a periodic orbit isolated in the set of all periodic orbits of the system.

1.5.1 The van der Pol differential equation

[18] Consider the van der Pol differential equation

$$\ddot{x} + x = \varepsilon(1 - x^2)\dot{x},$$

which can be written as the differential system

$$\begin{aligned} \dot{x} &= y, \\ \dot{y} &= -x + \varepsilon(1 - x^2)y. \end{aligned} \tag{1.8}$$

In polar coordinates (r, θ), where $x = r\cos\theta$, $y = r\sin\theta$, this system becomes

$$\begin{aligned} \dot{r} &= \varepsilon r(1 - r^2\cos^2\theta)\sin^2\theta, \\ \dot{\theta} &= -1 + \varepsilon\cos\theta(1 - r^2\cos^2\theta)\sin\theta. \end{aligned} \tag{1.9}$$

Or equivalently

$$\frac{dr}{d\theta} = -\varepsilon r(1 - r^2\cos^2\theta)\sin^2\theta + O(\varepsilon^2).$$

Note that the previous differential system is in the normal form (1.4) for applying the averaging theory described in theorem 1.1 if we take $x = r$, $t = \theta$, $T = 2\pi$ and
$F(t, x) = -r(1 - r^2\cos^2\theta)\sin^2\theta$.
From (1.6) we get that

$$f^0(r) = -\frac{1}{2\pi}\int_0^{2\pi} r(1 - r^2\cos^2\theta)\sin^2\theta d\theta = \frac{1}{8}r(r^2 - 4).$$

The unique positive root of $f_0(r)$ is $r = 2$. Since $\left| \dfrac{df^0}{dr}(2) \right| = 1$, by statement (i) of theorem 1.1, it follows that system (1.8) has, for $|\varepsilon| \neq 0$ sufficiently small, a limit cycle bifurcating from the periodic orbit of radius 2 of the unperturbed system (1.8) with $\varepsilon = 0$. Moreover, since $(\dfrac{df^0}{dr})(2) = 1 > 0$, by statement (ii) of theorem 1.1, this limit cycle is unstable. For more examples see the book "Asymptotic Methods in the Theory of nonlinear oscillations".

In this part we introduce the notion of Zero-Hopf bifurcation in $\mathbb{R}^n$.

1.6 Zero-Hopf Bifurcation in $\mathbb{R}^n$

[15] In this application, we study a Zero-Hopf bifurcation of C^3 differential systems in $\mathbb{R}^n$ with $n \geq 3$.

We assume that these systems have a singularity at the origin, whose linear part has eigenvalues $\varepsilon a \pm bi$, with $b \neq 0$ and εC_k for $k = 3, \cdots, n$, where ε is a small parameter. Since the eigenvalues of the linearization at the origin when $\varepsilon = 0$ are $\pm bi \neq 0$ and 0 with multiplicity $n - 2$, if an infinitesimal periodic orbit bifurcates from the origin when $\varepsilon = 0$, we call such kind of bifurcation a Zero-Hopf bifurcation.

Such systems can be written into the form

$$\begin{aligned} \dot{x} &= \varepsilon a x - by + \textstyle\sum_{i_1,\ldots,i_n=2} a_{i_1,\ldots,n} x^{i_1} y^{i_2} z_3^{i_3} \cdots z_n^{i_n} + A, \\ \dot{y} &= bx + \varepsilon a y + \textstyle\sum_{i_1,\ldots,i_n=2} b_{i_1,\ldots,n} x^{i_1} y^{i_2} z_3^{i_3} \cdots z_n^{i_n} + B, \\ \dot{z}_k &= \varepsilon c_k z_k + \textstyle\sum_{i_1,\ldots,i_n=2} c^{(k)}_{i_1,\ldots,n} x^{i_1} y^{i_2} z_3^{i_3} \cdots z_n^{i_n} + C_k. \quad k = 3, \ldots, n. \end{aligned} \tag{1.10}$$

Where $a_{i_1,\ldots,n}$, $b_{i_1,\ldots,n}$, $c^{(k)}_{i_1,\ldots,n}$, a, b and c_k are real parameters, $ab \neq 0$ and A, B and C_k are the Lagrange expression of the error function of third order in the expansion of the functions of the system in Taylor series.

Theorem 1.2 *[15] There exist C^3 systems (1.10) for which $l \in \{0, 1, \ldots, 2^{n-3}\}$ limit cycles bifurcate from the origin at $\varepsilon = 0$, i.e., for ε sufficiently small the system has exactly l limit cycles in a neighborhood of the origin, and these limit cycles tend to the origin when $\varepsilon \searrow 0$.*

Corollaire 1.1 *[15] There exist quadratic polynomial differential systems (1.10) (i.e.,with$A = B = C_k = 0$) for which $l \in \{0, 1, \ldots, 2^{n-3}\}$ limit cycles bifurcate from the origin at $\varepsilon = 0$, i.e., for ε sufficiently small the system has exactly l limit cycles in a neighborhood of the origin and these limit cycles tend to the origin when $\varepsilon \searrow 0$.*

1.7 Application

In this part we shall develop an application of Zero-Hopf bifurcation in $\mathbb{R}^n$.

1.7.1 Rössler System

Rössler System has been studied by different authors. They are mainly interested in the existence of periodic solutions, in their stability, bifurcation, etc.
Rössler invented a series of systems, the most famous is probably

$$\begin{aligned} \dot{x} &= -y - z, \\ \dot{y} &= x + ay, \\ \dot{z} &= bx - cz + xz. \end{aligned} \tag{1.11}$$

Where a, b and c are real parameters.
This system was studied by Jaune Llibre in the paper [13].
Their results were improved in [13] by Jaune Llibre, we present a part of these improvements here.
Instead of working with the Rössler System (1.11) we shall work with the equivalent differential system

$$\begin{aligned} \dot{x} &= -y - z, \\ \dot{y} &= x + ay, \\ \dot{z} &= b - cz + xz. \end{aligned} \tag{1.12}$$

Proposition 1.1 *There are two one-parameter families of Rössler systems for which the origin of coordinates is a Zero-Hopf equilibrium point. Namely:*

(i) $a = c \in (-\sqrt{2}, \sqrt{2})$ *and b=1; and*

(ii) $a = c = 0$ *and* $b \in (-1, \infty)$.

The proof of the Proposition 1.1 is due to [13].

Theorem 1.3 *Let* $(a, b, c) = (\overline{a} + \varepsilon\alpha, 1 + \varepsilon\beta, \overline{a} + \varepsilon\gamma)$ *be with* $\overline{a} \in (-\sqrt{2}, \sqrt{2}) \setminus \{0\}$ *and* ε *a sufficiently small parameter. If*

$$(-\alpha + a(1 - a^2)\beta + \gamma)((a^2 - 1)\alpha + a\beta + (1 - a^2\gamma) < 0,$$

and

$$\alpha + a\beta - \gamma \neq 0.$$

Then the Rössler system (1.11) has a Zero-Hopf bifurcation at the equilibrium point localized at the origin of coordinates, and a periodic orbit borns at this equilibrium when $\varepsilon = 0$, *and it exists for* $\varepsilon > 0$ *sufficiently small. Moreover, the stability or instability of this periodic orbit is given by the eigenvalues*

$$\frac{A \pm \sqrt{B}}{2a^2(2 - a^2)^{3/2}}, \tag{1.13}$$

where
$A = (2 - a^2)(\alpha - a\beta - \gamma)$,
$B = (3a^4 - 4)\alpha^2 + 2a(2a^6 - 3a^4 + 4)\alpha\beta - 2(3a^4 - 4)\alpha\gamma + a^2(3a^4 - 4)\beta^2 - 2a(2a^6 - 3a^4 + 4)\beta\gamma + (3a^4 - 4)\gamma^2$.

Proof of theorem 1.3. If $(a, b, c) = (\overline{a}+\varepsilon\alpha, 1+\varepsilon\beta, \overline{a}+\varepsilon\gamma)$, where $\varepsilon \neq 0$ is a small parameter, then the Rössler system becomes

$$\begin{aligned}\dot{x} &= -y - z,\\ \dot{y} &= x + (\overline{a} + \varepsilon\alpha)y,\\ \dot{z} &= (1 + \varepsilon\beta)x - (\overline{a} + \varepsilon\gamma)z + xz.\end{aligned} \tag{1.14}$$

Doing the rescaling of the variables $(x, y, z) = (\varepsilon X, \varepsilon Y, \varepsilon Z)$ system (1.14) in the new variables (X, Y, Z) writes

$$\begin{aligned}\dot{X} &= -Y - Z,\\ \dot{Y} &= X + \overline{a}Y + \varepsilon\alpha Y,\\ \dot{Z} &= X - \overline{a}Z + \varepsilon(\beta X - \gamma Z + XZ).\end{aligned} \tag{1.15}$$

And we write the linear part at the origin of the differential system (1.15) when $\varepsilon = 0$ with the Jacobian determinant not equal to zero, then we consider the change of variables $(X, Y, Z) \to (u, v, w)$ given by

$$\begin{aligned}X &= \frac{(\overline{a}^2 - 2)v - \overline{a}(\sqrt{2 - a^2}u + w)}{\overline{a}^2 - 2},\\ Y &= \frac{\sqrt{2 - \overline{a}^2}u + w}{\overline{a}^2 - 2},\\ Z &= -\frac{\overline{a}(2 - \overline{a}^2)v + \sqrt{2 - \overline{a}^2}(\overline{a}^2 - 1)u + w}{\overline{a}^2 - 2}.\end{aligned} \tag{1.16}$$

And by the new variables (u, v, w) written the differential system (1.15). Now we write the differential system in cylindrical coordinates (r, θ, w) defined by u = r $\cos\theta$, v = r $\sin\theta$ and $w = w$, we obtain

$$\begin{aligned}\frac{dr}{d\theta} &= \varepsilon F_1(\theta, r, w) + O(\varepsilon^2),\\ \frac{dw}{d\theta} &= \varepsilon F_2(\theta, r, w) + O(\varepsilon^2).\end{aligned} \tag{1.17}$$

Such that

$$\begin{aligned}F_1(\theta, r, w) = \;& \frac{1}{\sqrt{2 - \overline{a}^2}} r(\frac{1}{\overline{a}^2}(\alpha\overline{a}\sqrt{2 - \overline{a}^2}r^2\cos\theta\sin\theta) + \frac{1}{\overline{a}^2 - 2}(\alpha\overline{a}rw\sin\theta)\\ &+ \frac{1}{(2 - \overline{a}^2)^{3/2}}(r\cos\theta)(\alpha(1 - \overline{a}^2)(w + \sqrt{2 - \overline{a}^2}r\cos\theta) + (\beta\\ &- \frac{1}{\overline{a}^2 - 2}w + \frac{1}{\sqrt{2 - \overline{a}^2}}((\overline{a}^2 - 1)r\cos\theta) + \overline{a}r\sin\theta)(-\overline{a}w\\ &- \overline{a}\sqrt{2 - \overline{a}^2}r\cos\theta + (\overline{a}^2 - 2)r\sin\theta) + \gamma(w + \sqrt{2 - \overline{a}^2}\\ &(\overline{a}^2 - 1)r\cos\theta - \overline{a}(\overline{a}^2 - 2)r\sin\theta)))),\\ F_2(\theta, r, w) = \;& \frac{1}{\sqrt{2 - \overline{a}^2}(\overline{a}^2 - 2)}(-\alpha(w + \sqrt{2 - \overline{a}^2}r\cos\theta) + (\beta - \frac{w}{\overline{a}^2 - 2}\\ &+ \frac{(\overline{a}^2 - 1)r\cos\theta}{\sqrt{2 - \overline{a}^2}}\overline{a}r\sin\theta)(-\overline{a}w - \overline{a}\sqrt{2 - \overline{a}^2}r\cos\theta + (\overline{a}^2 - 2)r\\ &\sin\theta) + \gamma(w + \sqrt{2 - \overline{a}^2}(\overline{a}^2 - 1)r\cos\theta - \overline{a}(\overline{a}^2 - 2)r\sin\theta)).\end{aligned}$$

We shall apply the averging theory to the differential system (1.17), we considering $t = \theta$, $T = 2\pi$ and $X = (r, w)^T$.

We obtain the average function of first order

$$\begin{aligned}
f_1(r,w) &= \frac{1}{2\pi}\int_0^{2\pi} F_1(\theta,r,w)d\theta \\
&= \frac{r(2(\alpha-\gamma)+\overline{a}(\overline{a}(-3\alpha+\overline{a}(-w+\beta+\overline{a}(\alpha-\gamma))+3\gamma)-2\beta))}{2(2-\overline{a}^2)^{5/2}}, \\
f_2(r,w) &= \frac{1}{2\pi}\int_0^{2\pi} F_2(\theta,r,w)d\theta \\
&= \frac{2w(\gamma-\alpha)\overline{a}^2+2(r^2+w(w+2\beta))\overline{a}+4w(\alpha-\gamma)-(r^2+2w\beta)\overline{a}^3}{2(2-\overline{a}^2)^{5/2}}.
\end{aligned}$$

The system $f_1(r,w)=f_2(r,w)=0$ has unique solution (r^*,w^*) with $r^*>0$ namely

$$r^* = \frac{\sqrt{2(\overline{a}^2-2)(-\alpha+\overline{a}(1-\overline{a}^2)\beta+\gamma)((\overline{a}^2-1)\alpha+\overline{a}\beta+(1-\overline{a}^2)\gamma)}}{\overline{a}^3},$$

$$w^* = \frac{(a^2-2)((\overline{a}^2-1)\alpha+\overline{a}\beta+(1-\overline{a}^2)\gamma)}{\overline{a}^3}.$$

Moreover, the eigenvalues of the Jacobian matrix are given in 1.13. So one periodic orbit bifurcates from the Zero-Hopf equilibrium localized at the origin of coordinates. ❐

1.8 The averaging theory of second order

[15] In this section, we present a second-order averaging method for periodic orbits. Consider the differential system

$$\dot{x}(t) = \varepsilon F_1(t,x) + \varepsilon^2 F_2(t,x) + \varepsilon^3 R(t,x,\varepsilon), \tag{1.18}$$

where $F_1, F_2 : \mathbb{R}\times D \to \mathbb{R}^n$ and $R : \mathbb{R}\times D\times(-\varepsilon_f,\varepsilon_f) \to \mathbb{R}^n$ are continuous functions, T-periodic in the first variable, and where D is an open subset of $\mathbb{R}^n$. We define the following functions $F_K : \mathbb{R}\times D \to \mathbb{R}^n$ for $k=1,2$ as

$$\begin{aligned}
f_1(z) &= \int_0^T F_1(t,z)dt, \\
f_2(z) &= \int_0^T (F_2(t,z) + D_z F_1(t,z) y_1(t,z))dt,
\end{aligned}$$

where $y_1(t,z) = \int_0^t F_1(s,z)ds.$

The averaging theory for a differential system (1.18) works as follows
If the average function $f_1(z)$ is not the zero function, every simple zero of $f_1(z)$ provides a limit cycle of the differential system (1.18).
If $f_1(z) \equiv 0$ but $f_2(z) \neq 0$, then every simple zero of $f_2(z)$ provides a limit cycle of the differential system (1.18). For more detail see the book " Averaging Methods in Nonlinear Dynamical Systems".

Chapter 2

Zero-Hopf Bifurcation in Malaria model

In this chapter, we study the Zero-Hopf bifurcation of the Malaria model. More precisely, we will study the conditions for the existence of Zero-Hopf equilibrium points, and the averaging theory of the first and second order is also applied to prove the existence of periodic orbit bifurcating from the Zero-Hopf equilibrium points.

2.1 Malaria model

Malaria is one of the most mortifying infections in the world which is caused by mosquitoes. Mathematical models have been used to give an adequate study to understand the transmission of Malaria in human population for ever 100 years, see [4]. Many researchers studied the role of transgenic mosquitoes in order to reduce the transmission of the Malaria. One of the most and remarkable models is the one where the authors examined the possibility to replacing wild mosquitoes by transgenic ones, in which they established a model of Malaria transmission, and by using Floquet theory [6] they studied the existence and stability of the disease-free equilibrium points.

Based on Kermack and Mckendrick assumptions of the model given in [16] and the epidemic model given in [5, 11], Liu et al. studied the behaviors and the numerical simulations of Malaria dynamic models with transgenic mosquitoes, such model depends on eight parameters. These authors provided the conditions for which the equilibrium points of these models are asymptotically stable.

First, they considered the model

$$\begin{aligned} \dot{x} &= \beta(1-x)y - \gamma x, \\ \dot{y} &= \alpha x(1-a-y)-z) - \mu y - cay. \end{aligned} \tag{2.1}$$

At a fixed proportion a with $0 \leq a < 1$. After they studied this model at a changeable proportion, i.e.

$$\begin{aligned} \dot{x} &= \beta(1-x)y - \gamma x, \\ \dot{y} &= \alpha x(1-y-z) - \mu y - cyz, \\ \dot{z} &= \delta_1 yz + \delta_2 z(1-y-z) - \omega z. \end{aligned} \tag{2.2}$$

Where α, β, γ, μ, ω, a, c, δ_1 and δ_2 are positive constants. The description of these parameters in systems (2.1) and (2.2) is shown in Table 3.1.

Parameter	Description
β	Incidence rate of malaria due to biting
α	Efficiency of infection in mosquitoes by biting patients
μ	Death rate of anopheles
γ	Recovery rate of patients
c	Decrement rate of anopheles due to transgenic mosquitoes bred by transgenic mosquitoes and anopheles
ω	Death rate of transgenic mosquitoes
δ_1	Birth rate of transgenic mosquitoes bred by transgenic mosquitoes and wild anopheles
δ_2	Birth rate of transgenic mosquitoes bred by transgenic mosquitoes and wild susceptible mosquitoes
$x(t)$	Proportion of patients at t time
$y(t)$	Proportion of anopheles at t time
$z(t)$	Proportion of transgenic mosquitoes released at time t

TABLEAU 2.1: Descriptions of the parameters in system (2.2).

2.2 Statement of the main results

At the beginning, we try to study the conditions of Zero-Hopf equilibrium point of Malaria model. We consider the Malaria system written as

$$\begin{aligned} \dot{x} &= \beta(1-x)y - \gamma x, \\ \dot{y} &= \alpha x(1-y-z) - \mu y - cyz, \\ \dot{z} &= \delta_1 yz + \delta_2 z(1-y-z) - \omega z. \end{aligned} \tag{2.3}$$

This system has five equilibrium points given as follows

$p_1 = (0,0,0)$, $p_2 = \Big(0,0,1-\dfrac{\omega}{\delta_2}\Big)$, $p_3 = \Big(\dfrac{1}{\alpha\beta+\alpha\gamma}(\alpha\beta-\gamma\mu), \dfrac{1}{\alpha\beta+\beta\mu}(\alpha\beta - \gamma\mu), 0\Big)$.

Due to the fact that the expressions of p_4 and p_5 are big we will omit them, and we will study only two equilibrium points $p_1 = (0,0,0)$ and $p_2 = \Big(0,0,1-\dfrac{\omega}{\delta_2}\Big)$.

In the following proposition, we will give sufficient conditions in order that system (2.3) has Zero-Hopf equilibria.

Proposition 2.1 *The differential system (2.3) has simultaneously two Zero-Hopf equilibria located at the points $p_1 = (0,0,0)$ and $p_2 = \Big(0,0,1-\dfrac{\omega}{\delta_2}\Big)$, if the parameters of the system satisfy $\beta = -\dfrac{(\gamma^2+k^2)}{\alpha}$, $\mu = -\gamma$ and $\omega = \delta_2$.*

In the following theorems, we study the periodic orbits bifurcating from the Zero-Hopf equilibria of Proposition 2.1.

Theorem 2.1 *Let* $(\omega, \delta_2, \mu, \gamma) = (\omega_0+\varepsilon\omega_1+\varepsilon^2\omega_2, \omega_0+\varepsilon\delta_{21}+\varepsilon^2\delta_{22}, -\gamma_0+\varepsilon\mu_1+\varepsilon^2\mu_2, \gamma_0+\varepsilon\gamma_1+\varepsilon^2\gamma_2) \neq 0$*, where* $\varepsilon \neq 0$ *is a small parameter. If* $(\delta_{21}-\omega_1)(c(\delta_{21}-\omega_1)+\omega_0(\gamma_1+\mu_1)) \neq 0$*, then system* (2.3) *has a periodic orbit bifurcates from the Zero-hopf equilibrium point* p_1 *when* $\varepsilon = 0$*. Moreover, the stability or the unstability of this periodic orbit is given by the sign of the eigenvalues*

$$\frac{\omega_1 - \delta_{21}}{k}, \quad and \quad -\frac{c(\delta_{21} - \omega_1) + \omega_0(\gamma_1 + \mu_1)}{2k\omega_0}.$$

Where K is defined through $\beta = -\dfrac{(\gamma - \mu)^2 + 4k^2}{4\alpha}$.
We note that if the two eigenvalues are negative then the periodic orbit, which bifurcates from the equilibrium point p_1 *is stable, i.e, it is a local attractor. But if one of these eigenvalues is positive, then such periodic orbit is unstable.*

It is interesting to see the averaging of second order provides more periodic solutions bifurcating from the Zero-Hopf equilibrium localized at the origin of coordinates.

Theorem 2.2 *If* $|\ \varepsilon\ |$ *is a sufficient small parameter, the differential system* (2.3) *has three limit cycles bifurcating from the Zero-Hopf equilibrium point* p_1 *when* $\gamma_0(\gamma_2 + \mu_2)(\alpha^2 - \gamma_0^2 - k^2) > 0$*. Moreover, the stability or the unstability of the first periodic orbit is given by the sign of the eigenvalues* λ_1 *and* λ_2*.*
And also the stability or the unstability of the second periodic orbit is given by the sign of the eigenvalues λ_1 *and* $-\lambda_2$ *where*

$$\begin{aligned}\lambda_1 = \frac{\gamma_2 + \mu_2}{k}, \quad and \quad \lambda_2 = {} & \frac{1}{2\gamma_0 k(\gamma_0^2 + k^2)(-\alpha^2 + \gamma_0^2 + k^2)}(\gamma_0^2(\alpha - \gamma_0) \\ & (\alpha(2\gamma_0(\delta_{22} - \omega_2) + 3\delta_1(\gamma_2 + \mu_2)) + 2\gamma_0^2(\delta_{22} - \omega_2)) \\ & +2\gamma_0 k^4(\omega_2 - \delta_{22}) + k^2(\alpha^2(2\gamma_0(\delta_{22} - \omega_2) + \delta_1(\gamma_2 \\ & +\mu_2)) - 3\alpha\gamma_0\delta_1(\gamma_2 + \mu_2) + 4\gamma_0^3(\omega_2 - \delta_{22}))).\end{aligned}$$

We note that if the two eigenvalues are negative then the periodic orbit, which bifurcates from the equilibrium point p_1 *is stable, i.e, it is a local attractor. But if one of these eigenvalues is positive, then such periodic orbit is unstable.*

To apply the averaging theory of first order for the point p_2 we must translate it to the origin of coordinates, then we obtain system

$$\begin{aligned}\dot{x} = {} & -\gamma x - \beta xy + \beta y, \\ \dot{y} = {} & \frac{1}{\delta_2}(c\omega y) - cyz - cy + \frac{1}{\delta_2}(\alpha x\omega) - \alpha xy - \alpha xz - \mu y, \\ \dot{z} = {} & -\frac{1}{\delta_2}(\delta_1 y\omega) + \delta_1 y - \delta_2 y + y\omega + \delta_1 yz - \delta_2 yz - \delta_2 z^2 - \delta_2 z + \omega z.\end{aligned} \tag{2.4}$$

Theorem 2.3 *Let* $(\omega, \delta_2, \mu, \gamma) = (\delta_{20} + \varepsilon\omega_1, \delta_{20} + \varepsilon\delta_{21}, -\gamma_0 + \varepsilon\mu_1, \gamma_0 + \varepsilon\gamma_1)$*, where* ε *is a sufficiently small parameter. If* $\delta_{21} \neq \omega_1$*, then system* (2.4) *has a periodic orbit bifurcates from* *the Zero-hopf equilibrium point p_2 when $\varepsilon = 0$. Moreover, the stability or the unstability of this periodic orbit is given by the sign of the eigenvalues*

$$-\frac{\gamma_1 + \mu_1}{2k}, \quad and \quad \frac{\delta_{21} - \omega_1}{k}.$$

Where K is defined through $\beta = -\dfrac{(\gamma - \mu)^2 + 4k^2}{4\alpha}$.

2.3 Proof of the main results

Proof of Proposition 2.1. The characteristic polynomial of the linear part of the Malaria model at $(0,0,0)$ is

$$\begin{aligned} p(\lambda) = \; & -\frac{1}{\delta_2}(\lambda(-\alpha\beta\omega + c\gamma\delta_2 - c\gamma\omega + c\delta_2^2 + \gamma\delta_2^2 + \gamma\delta_2\mu - 2c\delta_2\omega - \gamma\delta_2\omega + c\omega^2 \\ & +\delta_2^2\mu - \delta_2\mu\omega)) - ((\delta_2 - \omega)(-\alpha\beta\omega + c\gamma\delta_2 - c\gamma\omega + \gamma\delta_2\mu)) - (\lambda^2(c\delta_2 \\ & +\gamma\delta_2 - c\omega + \delta_2^2 + \delta_2\mu - \delta_2\omega) - \delta_2\lambda^3. \end{aligned}$$

Assume $p(\lambda) = \lambda(k^2 + \lambda^2)$, we obtain $\beta = -\dfrac{(\gamma^2 + k^2)}{\alpha}$, $\mu = -\gamma$ and $\omega = \delta_2$. Then proposition 2.1 holds. ❐

Proof of Theorem 2.1. If $(\omega, \delta_2, \mu, \gamma) = (\omega_0 + \varepsilon\omega_1 + \varepsilon^2\omega_2, \omega_0 + \varepsilon\delta_{21} + \varepsilon^2\delta_{22}, -\gamma_0 + \varepsilon\mu_1 + \varepsilon^2\mu_2, \gamma_0 + \varepsilon\gamma_1 + \varepsilon^2\gamma_2)$, where $\varepsilon \neq 0$ is a small parameter, then the Malaria system becomes

$$\begin{aligned} \dot{x} = \; & \frac{1}{\alpha}\Big((x-1)y\left(\gamma_0^2 + k^2\right)\Big) - \gamma_0 x + \varepsilon\left(\frac{1}{\alpha}(\gamma_0 y(x-1)(\delta_1 - \mu_1) - \gamma_1 x\right) \\ & +\frac{1}{4\alpha}(\varepsilon^2((x-1)y(4\gamma_0(\gamma_2 - \mu_2) + (\gamma_1 - \mu_1)^2) - 4\alpha\gamma_2 x)), \\ \dot{y} = \; & -cyz - \alpha x(y + z - 1) + \gamma_0 y - \mu_1 y\varepsilon - \mu_2 y\varepsilon^2, \\ \dot{z} = \; & \delta_1 yz - z\varepsilon(\delta_{21}(y + z - 1) + \omega_1) - \omega_0 z(y+z) - z\varepsilon^2(\delta_{22} \\ & (y + z - 1) + \omega_2). \end{aligned} \tag{2.5}$$

Doing the rescaling of the variables $(x, y, z) = (\varepsilon X, \varepsilon Y, \varepsilon Z)$ system (2.5) in the new variables (X, Y, Z) writes

$$\begin{aligned} \dot{X} = \; & \frac{1}{\alpha}(\varepsilon(k^2XY - \alpha\gamma_1 X + \gamma_0^2 XY - \gamma_0\gamma_1 Y + \gamma_0\mu_1 Y)) - \frac{1}{\alpha}(k^2 Y \\ & +\alpha\gamma_0 X + \gamma_0^2 Y) + \frac{1}{4\alpha}(XY\varepsilon^3(4\gamma_0\gamma_2 - 4\gamma_0\mu_2 + \gamma_1^2 - 2\gamma_1\mu_1 + \mu_1^2)) \\ & +\frac{1}{4\alpha}(\varepsilon^2(-4\alpha\gamma_2 X + 4\gamma_0\gamma_1 XY - 4\gamma_0\mu_1 XY - 4\gamma_0\gamma_2 Y + 4\gamma_0\mu_2 Y \\ & +\gamma_1^2(-Y) + 2\gamma_1\mu_1 Y - \mu_1^2 Y)), \\ \dot{Y} = \; & \varepsilon(-cYZ - \alpha XY - \alpha XZ - \mu_1 Y) + \alpha X + \gamma_0 - \mu_2 Y\varepsilon^2, \\ \dot{Z} = \; & Z\varepsilon(\delta_{21} + \delta_1 Y - Y\omega_0 - \omega_1 - \omega_0 Z) - Z\varepsilon^2(Y\delta_{21} + Z\delta_{21} - \delta_{22} + \omega_2) \\ & -\delta_{22} Z\varepsilon^3(Y + Z). \end{aligned} \tag{2.6}$$

We want to write M the Jacobian matrix of system (2.6) in the Jordan form

$$J = \begin{pmatrix} 0 & -k & 0 \\ k & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

Then we consider the following equation $A.M - J.A = 0$ where

$$A = \begin{pmatrix} y_1 & y_2 & y_3 \\ y_4 & y_5 & y_6 \\ y_7 & y_8 & y_9 \end{pmatrix}.$$

With the Jacobian determinant $| A | \neq 0$ we obtain

$$A = \begin{pmatrix} 0 & 1 & 0 \\ \frac{\gamma_0 y_1}{k} - \frac{\alpha y_2}{k} & -\frac{y_1 \left(\gamma_0^2 - k^2\right)}{\alpha k} - \frac{\gamma_0 y_2}{k} & 0 \\ 0 & 0 & \alpha k \end{pmatrix}.$$

Now we consider the change of variables $(X, Y, Z) \to (u, v, w)$ given by

$$X = -\frac{kv + \gamma_0 u}{\alpha}, Y = u, Z = \frac{w}{\alpha k}. \tag{2.7}$$

In the new variables (u, v, w) the differential system (2.6) becomes

$$\begin{aligned} \dot{u} = {} & \varepsilon(\frac{1}{\alpha k}(uw(\gamma_0 - c)) + kuv + u(\gamma_0 u - \mu_1) + \frac{vw}{\alpha}) - kv - \mu_2 u\varepsilon^2, \\ \dot{v} = {} & \frac{1}{\alpha k^2}(\varepsilon(\gamma_0 uw(c - \gamma_0) + k^4 uv + \gamma_0 k^3 u^2 - k^2 v(\alpha\gamma_1 + \gamma_0 u(\alpha - \gamma_0)) \\ & -\gamma_0 k(\gamma_0 u^2(\alpha - \gamma_0) + vw))) + \frac{1}{4\alpha k}(\varepsilon^2(u(\gamma_1 - \mu_1)(\alpha(\gamma_1 - \mu_1) \\ & +4\gamma_0^2 u) - 4kv(\alpha\gamma_2 + \gamma_0 u(\mu_1 - \gamma_1)))) + \frac{1}{4\alpha k}(u\varepsilon^3(kv + \gamma_0 u) \\ & (4\gamma_0(\gamma_2 - \mu_2) + \gamma_1^2 - 2\gamma_1\mu_1 + \mu_1^2)) + ku, \\ \dot{w} = {} & -w\varepsilon^2(\frac{w\delta_{21}}{\alpha k} + u\delta_{21} - \delta_{22} + \omega_2) - w\varepsilon(-\delta_{21} + \frac{w\omega_0}{\alpha k} + u(\omega_0 - \delta_1) \\ & +\omega_1) - \delta_{22} w\varepsilon^3(\frac{w}{\alpha k} + u). \end{aligned} \tag{2.8}$$

Now we write the differential system (2.8) in cylindrical coordinates (r, θ, w) defined by u = r cos θ, v = r sin θ and $w = w$, we obtain

$$\begin{aligned} \frac{dr}{d\theta} = {} & \frac{1}{\alpha k^3}(r\varepsilon(\sin\theta\cos\theta(w(\gamma_0(c - \gamma_0) + k^2) + kr\cos\theta(\gamma_0^2(\gamma_0 - \alpha) \\ & +k^2(\alpha + \gamma_0))) + k\cos^2\theta(-cw - \alpha k\mu_1 + \alpha\gamma_0 kr\cos\theta + \gamma_0 w) \\ & +k\sin^2\theta(kr\cos\theta(\gamma_0(\gamma_0 - \alpha) + k^2) - \alpha\gamma_1 k + \gamma_0(-w)))) \\ & +\frac{1}{4\alpha^2 k^6}(r\varepsilon^2(4(-k\sin\theta\cos\theta(cw + kr\cos\theta(\gamma_0(\gamma_0 - 2\alpha) + k^2) \\ & +\alpha k(\mu_1 - \gamma_1) - 2\gamma_0 w) + \gamma_0\cos^2\theta(w(\gamma_0 - c) - kr\cos\theta(\gamma_0(\gamma_0 \\ & -\alpha) + k^2)) + k^2\sin^2\theta(\alpha kr\cos\theta + w))(\sin\theta\cos\theta(w(\gamma_0(c - \gamma_0) \\ & +k^2) + kr\cos\theta(\gamma_0^2(\gamma_0 - \alpha) + k^2(\alpha + \gamma_0))) + k\cos^2\theta(-cw - \alpha \\ & k\mu_1 + \alpha\gamma_0 kr\cos\theta + \gamma_0 w) + k\sin^2\theta(kr\cos\theta(\gamma_0(\gamma_0 - \alpha) + k^2) \\ & -\alpha\gamma_1 k + \gamma_0(-w))) + \alpha k^4(-4\alpha k\mu_2\cos^2\theta - 4k\sin^2\theta(\alpha\gamma_2 + \gamma_0 \\ & r(\mu_1 - \gamma_1)\cos\theta) + (\gamma_1 - \mu_1)\sin\theta\cos\theta(\alpha(\gamma_1 - \mu_1) + 4\gamma_0^2 r\cos\theta)), \\ \frac{dw}{d\theta} = {} & \frac{1}{\alpha^2 k^5}(w\varepsilon^2((\alpha k(\omega_1 - \delta_{21}) + \alpha kr(\omega_0 - \delta_1)\cos\theta + w\omega_0)(k\sin\theta \\ & \cos\theta(cw + kr\cos\theta(\gamma_0(\gamma_0 - 2\alpha) + k^2) + \alpha k(\mu_1 - \gamma_1) - 2\gamma_0 w) \\ & +\gamma_0\cos^2\theta(w(c - \gamma_0) + kr\cos\theta(\gamma_0(\gamma_0 - \alpha) + k^2)) - k^2\sin^2\theta \\ & (\alpha kr\cos\theta + w)) - \alpha k^3(\alpha k(\omega_2 - \delta_{22}) + \alpha\delta_{21} kr\cos\theta + \delta_{21} w)) \end{aligned} \tag{2.9}$$

$$-\frac{1}{\alpha k^2}(w\varepsilon(\alpha k(\omega_1-\delta_{21})+\alpha kr(\omega_0-\delta_1)\cos\theta+w\omega_0)).$$

This system can be written as

$$\begin{aligned}\frac{dr}{d\theta}&=\varepsilon F_{11}(\theta,r,w)+\varepsilon^2F_{21}(\theta,r,w)+O(\varepsilon^3),\\ \frac{dw}{d\theta}&=\varepsilon F_{12}(\theta,r,w)+\varepsilon^2F_{22}(\theta,r,w)+O(\varepsilon^3).\end{aligned}\tag{2.10}$$

We shall apply the averaging theory to the differential system (2.10).
We considering $t=\theta, T=2\pi$, $X=(r,w)^T$ and

$$F_1(\theta,r,w)=\begin{pmatrix}F_{11}(\theta,r,w)\\ F_{12}(\theta,r,w)\end{pmatrix},$$

such that

$$\begin{aligned}F_{11}(\theta,r,w)=&\ \frac{1}{\alpha k^3}(r\varepsilon(\sin\theta\cos\theta(w(\gamma_0(c-\gamma_0)+k^2)+kr\cos\theta(\gamma_0^2(\gamma_0-\alpha)\\ &+k^2(\alpha+\gamma_0)))+k\cos^2\theta(-cw-\alpha k\mu_1+\alpha\gamma_0kr\cos\theta+\gamma_0w)\\ &+k\sin^2\theta(kr\cos\theta(\gamma_0(\gamma_0-\alpha)+k^2)-\alpha\gamma_1k+\gamma_0(-w)))),\\ F_{12}(\theta,r,w)=&\ -\frac{1}{\alpha k^2}(w(\alpha k(\omega_1-\delta_{21})+\alpha kr(\omega_0-\delta_1)\cos\theta+w\omega_0).\end{aligned}$$

We have the average function of first order

$$\begin{aligned}f_{11}(r,w)&=\frac{1}{2\pi}\int_0^{2\pi}F_{11}(\theta,r,w)d\theta=-\frac{1}{2\alpha k^2}(r(cw+\alpha k(\gamma_1+\mu_1))),\\ f_{12}(r,w)&=\frac{1}{2\pi}\int_0^{2\pi}F_{12}(\theta,r,w)d\theta=-\frac{1}{\alpha k^2}(w(\alpha k(\omega_1-\delta_{21})+w\omega_0)).\end{aligned}$$

The system $f_{11}(r,w)=f_{12}(r,w)=0$ has two solutions (r^*,w^*) with $r^*>0$ where

$$(r^*,w^*)\in\{(0,0),(0,\frac{\alpha\delta_{21}k-\alpha k\omega_1}{\omega_0})\}$$

The first solution is not good because it provides an equilibrium point, but the second solution is good, and since the Jacobian matrix of the function (f_{11},f_{12}) is not zero at that solution it provides a periodic solution of the differential system.

The jacobian determinant at $(r^*,w^*)=(0,\dfrac{\alpha\delta_{21}k-\alpha k\omega_1}{\omega_0})$ is given by

$$\Delta=\frac{(\delta_{21}-\omega_1)(c(\delta_{21}-\omega_1)+\omega_0(\gamma_1+\mu_1))}{2k^2\omega_0}.$$

Moreover the eigenvalues of the Jacobian matrix

$$\frac{\partial(f_{11},f_{12})}{\partial(r,w)}\ |_{(r,w)=(r^*,w^*)}$$

are given as follows

$$\frac{\omega_1 - \delta_{21}}{k}, \quad and \quad -\frac{c(\delta_{21} - \omega_1) + \omega_0(\gamma_1 + \mu_1)}{2k\omega_0}.$$

So one periodic orbit bifurcates from the Zero-Hopf equilibrium localized at the origin of coordinates. ❒

Proof of Theorem 2.2. To compute the averaging of second order we must do averaging of first order identically zero.

From first averaging function

$$f_1(r,w) = \begin{pmatrix} f_{11}(r,w) \\ f_{12}(r,w) \end{pmatrix},$$

and we considering $\Big(c = 0, \mu_1 = -\gamma_1, \omega_0 = 0, \delta_{21} = \omega_1\Big)$,
we know that

$$f_1(r,w) \equiv (0,0).$$

The second averaging function f_2 is given by

$$f_2(r,w) = \int_0^{2\pi} [D_{r,w}F_1(\theta,r,w).y_1(\theta,r,w) + F_2(\theta,r,w)]d\theta, \tag{2.11}$$

where

$$y_1(\theta,r,w) = \textstyle\int_0^\theta F_1(\theta,r,w)d\theta.$$

We have

$$F_2(\theta,r,w) = \begin{pmatrix} F_{21}(\theta,r,w) \\ F_{22}(\theta,r,w) \end{pmatrix},$$

such that

$$\begin{aligned} F_{21}(\theta,r,w) = \; & \frac{1}{4\alpha^2k^6}(r(4(-k\sin\theta\cos\theta(cw + kr\cos\theta(\gamma_0(\gamma_0 - 2\alpha) + k^2) \\ & +\alpha k(\mu_1 - \gamma_1) - 2\gamma_0 w) + \gamma_0\cos^2\theta(w(\gamma_0 - c) - kr\cos\theta(\gamma_0 \\ & (\gamma_0 - \alpha) + k^2)) + k^2\sin^2\theta(\alpha kr\cos\theta + w))(\sin\theta\cos\theta(w(\gamma_0 \\ & (c - \gamma_0) + k^2) + kr\cos\theta(\gamma_0^2(\gamma_0 - \alpha) + k^2(\alpha + \gamma_0))) + k\cos^2\theta \\ & (-cw - \alpha k\mu_1 + \alpha\gamma_0 kr\cos\theta + \gamma_0 w) + k\sin^2\theta(kr\cos\theta(\gamma_0 \\ & (\gamma_0 - \alpha) + k^2) - \alpha\gamma_1 k + \gamma_0(-w))) + \alpha k^4(-4\alpha k\mu_2\cos^2\theta \\ & -4k\sin^2\theta(\alpha\gamma_2 + \gamma_0 r(\mu_1 - \gamma_1)\cos\theta) + (\gamma_1 - \mu_1)\sin\theta\cos\theta \\ & (\alpha(\gamma_1 - \mu_1) + 4\gamma_0^2 r\cos\theta)))), \\ F_{22}(\theta,r,w) = \; & \frac{1}{\alpha^2k^5}(w((\alpha k(\omega_1 - \delta_{21}) + \alpha kr(\omega_0 - \delta_1)\cos\theta + w\omega_0)(k\sin\theta\cos\theta \\ & (cw + kr\cos\theta(\gamma_0(\gamma_0 - 2\alpha) + k^2) + \alpha k(\mu_1 - \gamma_1) - 2\gamma_0 w) + \gamma_0 \\ & \cos^2\theta(w(c - \gamma_0) + kr\cos\theta(\gamma_0(\gamma_0 - \alpha) + k^2)) - k^2\sin^2\theta(\alpha kr \\ & \cos\theta + w)) - \alpha k^3(\alpha k(\omega_2 - \delta_{22}) + \alpha\delta_{21}kr\cos\theta + \delta_{21}w)). \end{aligned}$$

We can now calculate the function (2.11), and we obtain

$$f_2(r,w) = -\frac{1}{8\alpha^2k^3}(r(\gamma_0k^4r^2 + 4\alpha^2\gamma_2k^2 + 4\alpha^2k^2\mu_2 - \alpha^2\gamma_0k^2r^2 + 2\gamma_0^3k^2r^2 - \alpha^2\gamma_0^3r^2 + \gamma_0^5r^2)), \frac{1}{8\alpha k^3}(w(8\alpha\delta_{22}k^2 - 8\alpha k^2\omega_2 + \alpha\delta_1k^2r^2 - 3\gamma_0 \delta_1k^2r^2 - 8kw\omega_1 + 3\alpha\gamma_0^2\delta_1r^2 - 3\gamma_0^3\delta_1r^2)).$$

We have to find the zeros (r^*, w^*) of the function (2.11), and to check that the Jacobian determinant

$$\mid D_{r,w}f_2(r^*, w^*) \mid \neq 0.$$

Solving the equation $f_2(r,w) = 0$, we obtain six solutions (r^*, w^*) with $r^* > 0$.
If $\gamma_0(\gamma_2 + \mu_2)\left(\alpha^2 - \gamma_0^2 - k^2\right) > 0$, then system (2.3) has a two solutions with $r^* > 0$.

$$(r_{11}, w_{11}) = \Big(\frac{2\alpha k\sqrt{\gamma_2 + \mu_2}}{\sqrt{\gamma_0(\gamma_0^2 + k^2)(-\alpha^2 + \gamma_0^2 + k^2)}}, \frac{1}{2\gamma_0\omega_1(\gamma_0^2 + k^2)(-\alpha^2 + \gamma_0^2 + k^2)} (\alpha k(\gamma_0^2(\gamma_0 - \alpha)(\alpha(2\gamma_0\delta_{22} + 3\delta_1(\gamma_2 + \mu_2)) + 2\gamma_0^2\delta_{22}) + 2\gamma_0\delta_{22}k^4 - k^2(\alpha^2(2\gamma_0\delta_{22} + \delta_1(\gamma_2 + \mu_2)) - 3\alpha\gamma_0\delta_1(\gamma_2 + \mu_2) - 4\gamma_0^3\delta_{22}) - 2\gamma_0 \omega_2(\gamma_0^2 + k^2)(-\alpha^2 + \gamma_0^2 + k^2)))\Big),$$

and the second solution is

$$(r_{21}, w_{21}) = \Big(\frac{2\alpha k\sqrt{\gamma_2 + \mu_2}}{\sqrt{\gamma_0(\gamma_0^2 + k^2)(-\alpha^2 + \gamma_0^2 + k^2)}}, 0\Big),$$

and the third solution

$$(r_{31}, w_{31}) = \Big(0, \frac{1}{\omega_1}(\alpha k(\delta_{22} - \omega_2))\Big).$$

This provide three limit cycles bifurcating from the Zero-Hopf equilibrium point p_1 when

$$\delta_2 = \omega,\ \mu = -\gamma \text{ and } 4\alpha\beta + (\gamma - \mu)^2 = -4k^2.$$

If the Jacobian determinant is equal to zero, then the periodic orbit does not exist, and if it is not equal to zero, then the periodic orbit does exist.

The Jacobian determinant of the first solution is

$$\Delta_1 = \frac{1}{32\alpha^3k^4(\gamma_2 + \mu_2)(\gamma_0^2(\alpha - \gamma_0) + \alpha(\delta_1(\gamma_2 + \mu_2) + (2\gamma_0(\delta_{22} - \omega_2) - (4\gamma_0^3(\omega_2 - \delta_{22})))}(\gamma_0(\gamma_0^2 + k^2)(-\alpha^2 + \gamma_0^2 + k^2)(3\gamma_0k^4r^2 + k^2(4\alpha^2(\gamma_2 + \mu_2) + r^2(6\gamma_0^3 - 3\alpha^2\gamma_0)) + 3\gamma_0^3r^2(\gamma_0^2 - \alpha^2))(k^2(8\alpha(\omega_2 - \delta_{22}) - \delta_1r^2(\alpha - 3\gamma_0)) + 16kw\omega_1 + 3\gamma_0^2\delta_1r^2(\gamma_0 - \alpha))).$$

Then the first solution exists.

The Jacobian determinant of the second solution is

$$\Delta_2 = -\frac{1}{2\gamma_0k^2(\gamma^2 + k^2)(-\alpha^2 + \gamma_0^2 + k^2)}((\gamma_2 + \mu_2)(\gamma_0^2(\alpha - \gamma_0)(\alpha(2\gamma_0(\delta_{22} - \omega_2) + 3\delta_1(\gamma_2 + \mu_2)) + 2\gamma_0^2(\delta_{22} - \omega_2)) + 2\gamma_0k^4(\omega_2 - \delta_{22}) + k^2(\alpha^2(2\gamma_0(\delta_{22} - \omega_2) + \delta_1(\gamma_2 + \mu_2)) - 3\alpha\gamma_0\delta_1(\gamma_2 + \mu_2) + 4\gamma_0^3(\omega_2 - \delta_{22})))).$$

Then the second solution exists.

And for the third solution, the determinant of the Jacobian at this solution is equal to

$$\Delta_3 = \frac{(\gamma_2+\mu_2)(\delta_{22}-\omega_2)}{2k^2}.$$

Then the third solution exists.

Moreover, the stability or the unstability of the first periodic orbit is given by the sign of the eigenvalues λ_1 and λ_2.
And also the stability or the unstability of the second periodic orbit is given by the sign of the eigenvalues λ_1 and $-\lambda_2$ where

$$\begin{aligned}\lambda_1 = \frac{\gamma_2+\mu_2}{k}, \quad and \quad \lambda_2 = & \frac{1}{2\gamma_0 k(\gamma_0^2+k^2)(-\alpha^2+\gamma_0^2+k^2)}(\gamma_0^2(\alpha-\gamma_0)\\ & (\alpha(2\gamma_0(\delta_{22}-\omega_2)+3\delta_1(\gamma_2+\mu_2))+2\gamma_0^2(\delta_{22}-\omega_2))\\ & +2\gamma_0 k^4(\omega_2-\delta_{22})+k^2(\alpha^2(2\gamma_0(\delta_{22}-\omega_2)+\delta_1(\gamma_2\\ & +\mu_2))-3\alpha\gamma_0\delta_1(\gamma_2+\mu_2)+4\gamma_0^3(\omega_2-\delta_{22}))).\end{aligned}$$

We note that if the two eigenvalues are negative then the periodic orbit, which bifurcates from the equilibrium point p_1 is stable, i.e, it is a local attractor. But if one of these eigenvalues is positive, then such periodic orbit is unstable. ❒

Proof of Theorem 2.3. If $(\omega,\delta_2,\mu,\gamma) = (\delta_{20}+\varepsilon\omega_1, \delta_{20}+\varepsilon\delta_{21}, -\gamma_0+\varepsilon\mu_1, \gamma_0+\varepsilon\gamma_1)$, where $\varepsilon \neq 0$ is a small parameter, then the Malaria system becomes

$$\begin{aligned}\dot{x} = & \frac{1}{\alpha}(k^2(x-1)y+\gamma_0(\gamma_0(x-1)y-\alpha x)) - \frac{1}{\alpha}(\gamma_1\varepsilon(\alpha x-2\gamma_0(x-1)y))\\ & +\frac{1}{\alpha}(\gamma_1^2(x-1)y\varepsilon^2),\\ \dot{y} = & \frac{1}{\delta_{20}^2}(\delta_{21}\varepsilon^2(\delta_{21}-\omega_1)(cy+\alpha x)) + \frac{1}{\delta_{20}}(\varepsilon(cy(\omega_1-\delta_{21})+\alpha x(\omega_1-\delta_{21})\\ & +\delta_{20}\mu_1(-y))) - cyz - \alpha x(y+z-1)+\gamma_0 y,\\ \dot{z} = & \frac{1}{\delta_{20}^2}(\delta_1\delta_{21}y\varepsilon^2(\omega_1-\delta_{21})+\delta_1 yz-\delta_{20}z(y+z)+\frac{1}{\delta_{20}^2}(\varepsilon(y(\delta_1(\delta_{21}-\omega_1)\\ & +\delta_{20}(\omega_1-\delta_{21}(z+1)))-\delta_{20}z(\delta_{21}-\omega_1+\delta_{21}z))).\end{aligned} \tag{2.12}$$

Doing the rescaling of the variables $(x,y,z) = (\varepsilon X, \varepsilon Y, \varepsilon Z)$ the system (2.12) in the new variables $(X,Y,Z$ writes

$$\begin{aligned}\dot{X} = & \frac{1}{\alpha}(\varepsilon(XY(\gamma_0^2+k^2)-\gamma_1(\alpha X+2\gamma_0 Y))) - \frac{1}{\alpha}(Y(\gamma_0^2+k^2)+\alpha\gamma_0 X)\\ & +\frac{1}{\alpha}(\gamma_1 Y\varepsilon^2(2\gamma_0 X-\gamma_1)),\end{aligned}$$

$$\begin{aligned}\dot{Y} = & \frac{1}{\delta_{20}^2}(\delta_{21}\varepsilon^2(\delta_{21}-\omega_1)(cY+\alpha X))+\alpha X+\gamma_0 Y - \frac{1}{\delta_{20}}(\varepsilon(cY(\delta_{21}\\ & -\omega_1+\delta_{20}Z)+\alpha X(\delta_{21}+\delta_{20}(Y+Z)-\omega_1)+\delta_{20}\mu_1 Y)),\\ \dot{Z} = & \frac{1}{\delta_{20}}(\varepsilon(\delta_1 Y-\delta_{20}(Y+Z))(\delta_{21}-\omega_1+\delta_{20}Z)) - \frac{1}{\delta_{20}^2}(\delta_{21}\varepsilon^2(Y(\delta_1(\delta_{21}\\ & -\omega_1)+\delta_{20}^2 Z)+\delta_{20}^2 Z^2).\end{aligned} \tag{2.13}$$

We want to write M the Jacobian matrix of system (2.13) in the Jordan form

$$J = \begin{pmatrix} 0 & -k & 0 \\ k & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

Then we consider the following equation $A.M - J.A = 0$ where

$$A = \begin{pmatrix} y_1 & y_2 & y_3 \\ y_4 & y_5 & y_6 \\ y_7 & y_8 & y_9 \end{pmatrix}.$$

With the Jacobian determinant $\mid A \mid \neq 0$ we obtain

$$A = \begin{pmatrix} 1 & 0 & 0 \\ \dfrac{\gamma_0}{k} & \dfrac{\gamma_0^2 + k^2}{\alpha k} & 0 \\ 0 & 0 & \alpha k \end{pmatrix}.$$

Now we consider the change of variables $(X, Y, Z) \to (u, v, w)$ given by

$$X = u, Y = \frac{1}{\gamma_0^2 + k^2}(\alpha(kv - \gamma_0 u)), Z = \frac{w}{\alpha k}. \tag{2.14}$$

In the new variables (u, v, w) the differential system (2.13) becomes

$$\begin{aligned}
\dot{u} = \;& \frac{1}{\gamma_0^2 + k^2}(\gamma_1 \varepsilon^2(2\gamma_0 u - \gamma_1)(kv - \gamma_0 u)) + \varepsilon(\frac{1}{\gamma_0^2 + k^2}(\gamma_1(-k^2 u \\
& -2\gamma_0 kv + \gamma_0^2 u)) + u(kv - \gamma_0 u)) - kv, \\
\dot{v} = \;& \frac{1}{k(\gamma_0^2 + k^2)}(\varepsilon^2(\frac{1}{\delta_{20}^2}(\delta_{21}(\delta_{21} - \omega_1)(\gamma_0^2 + k^2)(ckv + \gamma_0 u(\gamma_0 - c) \\
& +k^2 u)) + \gamma_0\gamma_1(2\gamma_0 u - \gamma_1)(kv - \gamma_0 u))) + \frac{1}{\alpha k}(\varepsilon(\frac{1}{\delta_{20} k}(-k^2(\alpha v \\
& (c\delta_{21} - c\omega_1 + \delta_{20}\mu_1) + \delta_{20} u(\alpha^2 v + w)) + k(\alpha\gamma_0 u(-\gamma_0\delta_{21} + \gamma_0 \\
& \omega_1 + \delta_{20}\mu_1 + \alpha\delta_{20} u) - c(\alpha\gamma_0 u(\omega_1 - \delta_{21}) + \delta_{20} vw)) + \gamma_0\delta_{20} uw \\
& (c - \gamma_0) + \alpha k^3 u\omega_1 - \delta_{21})) + \gamma_0(\alpha u(kv - \gamma_0 u) - \alpha\gamma_1(\frac{1}{\gamma_0^2 + k^2} \\
& (2\gamma_0(kv - \gamma_0 u)) + u)))) + ku, \\
\dot{w} = \;& -\frac{1}{\delta_{20}^2 k}(\alpha\delta_{21}\varepsilon^2(\frac{1}{\gamma_0^2 + k^2}(k(kv - \gamma_0 u)(\alpha\delta_1 k(\delta_{21} - \omega_1) + \delta_{20}^2 w)) \\
& \frac{\delta_{20}^2 w^2}{\alpha^2})) - \frac{1}{\alpha\delta_{20} k(\gamma_0^2 + k^2)}(\varepsilon(\alpha k(\delta_{21} - \omega_1) + \delta_{20} w)(k^2(\alpha^2 v \\
& (\delta_{20} - \delta_1) + \delta_{20} w) + \alpha^2\gamma_0 ku(\delta_1 - \delta_{20}) + \gamma_0^2\delta_{20} w)).
\end{aligned} \tag{2.15}$$

Now we write the differential system (2.15) in cylindrical coordinates (r, θ, w) defined by u = r cos θ, v = r sin θ and $w = w$, we obtain

$$\begin{aligned}
\frac{dr}{d\theta} = \;& \frac{1}{k(k^2 + \gamma_0^2)}(\frac{1}{k}((\frac{1}{\delta_{20}^2}(r(k^2 + \gamma_0^2)\delta_{21}(\delta_{21} - \omega_1)((k^2 + \gamma_0(\gamma_0 - c)) \\
& \cos\theta + ck\sin\theta)) + r\gamma_0\gamma_1(\gamma_1 - 2r\gamma_0\cos\theta)(\gamma_0\cos\theta - k\sin\theta)) \\
& \sin\theta) + r\gamma_1\cos\theta(\gamma_1 - 2r\gamma_0\cos\theta)(\gamma_0\cos\theta - k\sin\theta)) + \frac{1}{kr}
\end{aligned}$$

$$
\begin{aligned}
&((-\frac{1}{k^2(k^2+\gamma_0^2)}(\gamma_1\cos^2\theta\gamma_0^3)+\frac{1}{k^2}(r\cos^3\theta\gamma_0^2)+\frac{1}{k^2\delta_{20}}(\delta_{21}\cos^2\theta\\
&\gamma_0^2)+\frac{1}{k^3\alpha}(w\cos^2\theta\gamma_0^2)+\frac{1}{k(k^2+\gamma_0^2)}(3\gamma_1\cos\theta\sin\theta\gamma_0^2)-\frac{1}{k^2\delta_{20}}\\
&(\omega_1\cos^2\theta\gamma_0^2)+\frac{1}{k^2+\gamma_0^2}(\gamma_1\cos^2\theta\gamma_0)+\frac{1}{k^2\delta_{20}}(c\omega_1\cos^2\theta\gamma_0)-\frac{1}{k}\\
&(2r\cos^2\theta\sin\theta\gamma_0)-\frac{1}{k^2}(r\alpha\cos^3\theta\gamma_0)-\frac{1}{k^2}(\mu_1\cos^2\theta\gamma_0)-\frac{1}{k^3\alpha}\\
&(cw\cos^2\theta\gamma_0-\frac{1}{k^2+\gamma_0^2}(2\gamma_1\sin^2\theta\gamma_0)-\frac{1}{k^2\delta_{20}}(c\delta_{21}\cos^2\theta\gamma_0)+\frac{1}{\delta_{20}}\\
&(\delta_{21}\cos^2\theta)+\frac{1}{k\alpha}(w\cos^2\theta)+r\cos\theta\sin^2\theta+\frac{1}{k}(r\alpha\cos^2\theta\sin\theta)\\
&+\frac{1}{k\delta_{20}}(c\delta_{21}\cos\theta\sin\theta)+\frac{1}{k}(\mu_1\cos\theta\sin\theta)+\frac{1}{k^2\alpha}(cw\cos\theta\sin\theta)\\
&-\frac{1}{k^2+\gamma_0^2}(k\gamma_1\cos\theta\sin\theta)-\frac{1}{\delta_{20}}(\omega_1\cos^2\theta)-\frac{1}{k\delta_{20}}(c\omega_1\cos\theta\sin\theta))\\
&(r(r\cos\theta(kr\sin\theta-r\gamma_0\cos\theta)+\frac{1}{k^2+\gamma_0^2}(r\gamma_1((\gamma_0^2-k^2)\cos\theta\\
&-2k\gamma_0\sin\theta)))\cos\theta+\frac{1}{k\alpha}(r\sin\theta(r\alpha\gamma_0(r\cos\theta(k\sin\theta-\gamma_0\cos\theta)\\
&+\frac{1}{k^2+\gamma_0^2}(\gamma_1((\gamma_0^2-k^2)\cos\theta-2k\gamma_0\sin\theta)))+\frac{1}{k\delta_{20}}(r\cos\theta(\alpha\\
&(\omega_1-\delta_{21})k^3+\alpha\gamma_0(\delta_{20}\mu_1+(c-\gamma_0)(\delta_{21}-\omega_1))k+r\alpha^2\gamma_0\delta_{20}\\
&\cos\theta k-k^2w\delta_{20}+w(c-\gamma_0)\gamma_0\delta_{20})-kr(kr\delta_{20}\cos\theta\alpha^2+k\delta_{20}\\
&\mu_1\alpha+c(w\delta_{20}+k\alpha(\delta_{21}-\omega_1)))\sin\theta)))))\varepsilon^2+\frac{1}{kr}(\epsilon(r(r\cos\theta\\
&(kr\sin\theta-r\gamma_0\cos\theta)+\frac{1}{k^2+\gamma_0^2}(r\gamma_1((\gamma_0^2-k^2)\cos\theta-2k\gamma_0\\
&\sin\theta)))\cos\theta+\frac{1}{k\alpha}(r\sin\theta(r\alpha\gamma_0(r\cos\theta(k\sin\theta-\gamma_0\cos\theta)\\
&+\frac{1}{k^2+\gamma_0^2}(\gamma_1((\gamma_0^2-k^2)\cos\theta-2k\gamma_0\sin\theta)))+\frac{1}{k\delta_{20}}(r\cos\theta\\
&(\alpha(\omega_1-\delta_{21})k^3+\alpha\gamma_0(\delta_{20}\mu_1+(c-\gamma_0)(\delta_{21}-\omega_1))k+r\alpha^2\\
&\gamma_0\delta_{20}\cos(\theta k-k^2w\delta_{20}+w(c-\gamma_0)\gamma_0\delta_{20})-kr(kr\delta_{20}\cos\theta\alpha^2\\
&+k\delta_{20}\mu_1\alpha+c(w\delta_{20}+k\alpha(\delta_{21}-\omega_1)))\sin\theta)))),
\end{aligned}
\tag{2.16}
$$

$$
\begin{aligned}
\frac{dw}{d\theta} = \;&\varepsilon^2(\frac{1}{\alpha\delta_{20}k^2(\gamma_0^2+k^2)}((\alpha k(\delta_{21}-\omega_1)+\delta_{20}w)(\delta_{20}w(\gamma_0^2+k^2)\\
&+\alpha^2kr(\delta_1-\delta_{20})(\gamma_0\cos\theta-k\sin\theta))(-\frac{1}{\alpha k^3}(c\gamma_0w\cos^2\theta-\frac{1}{\delta_{20}k^2}\\
&(c\gamma_0\delta_{21}\cos^2\theta)\frac{1}{\delta_{20}k^2}(c\gamma_0\omega_1\cos^2\theta)+\frac{1}{\alpha k^2}(cw\sin\theta\cos\theta)+\frac{1}{\delta_{20}k}\\
&(c\delta_{21}\sin\theta\cos\theta)-\frac{1}{\delta_{20}k}(c\omega_1\sin\theta\cos\theta)+\frac{1}{\delta_{20}}(\delta_{21}\cos^2\theta)-\frac{1}{\delta_{20}}\\
&(\omega_1\cos^2\theta)+\frac{1}{\alpha k^3}(\gamma_0^2w\cos^2\theta)-\frac{1}{\gamma_0^2+k^2}(2\gamma_0\gamma_1\sin^2\theta)+\frac{1}{\gamma_0^2+k^2}\\
&(\gamma_0\gamma 1\cos^2\theta)+\frac{1}{k(\gamma_0^2+k^2)}(3\gamma_0^2\gamma_1\sin\theta\cos\theta)-\frac{1}{\gamma_0^2+k^2}(\gamma_1k\sin\theta\\
&\cos\theta)+\frac{1}{\delta_{20}k^2}(\gamma_0^2\delta_{21}\cos^2\theta)-\frac{1}{\delta_{20}k^2}(\gamma_0^2\omega_1\cos^2\theta)-\frac{1}{k^2(\gamma_0^2+k^2)}\\
&(\gamma_0^3\gamma_1\cos^2\theta)-\frac{1}{k^2}(\gamma_0\mu_1\cos^2\theta)-\frac{1}{k^2}(\alpha\gamma_0r\cos^3\theta)+\frac{1}{k^2}(\gamma_0^2r\cos^3\theta)
\end{aligned}
$$

$$+\frac{1}{k}(\mu_1\sin\theta\cos\theta)+\frac{1}{k}(\alpha r\sin\theta\cos^2\theta)-\frac{1}{k}(2\gamma_0 r\sin\theta\cos^2\theta)+\frac{1}{\alpha k}$$
$$(w\cos^2\theta)+r\sin^2\theta\cos\theta))-\frac{1}{\delta_{20}^2k^2}(\alpha\delta_{21}(\frac{1}{\gamma_0^2+k^2}kr(k\sin\theta-\gamma_0\cos\theta)$$
$$(\alpha\delta_1k(\delta_{21}-\omega_1)+\delta_{20}^2w))+\frac{1}{\alpha^2}(\delta_{20}^2w^2))))-\frac{1}{\alpha\delta_{20}k^2(\gamma_0^2+k^2)}(\varepsilon(\alpha k(\delta_{21}$$
$$-\omega_1)+\delta_{20}w)(\delta_{20}w(\gamma_0^2+k^2)+\alpha^2kr(\delta_1-\delta_{20})(\gamma_0\cos\theta-k\sin\theta))).$$

This system can be written as

$$\begin{aligned}\frac{dr}{d\theta}&=\varepsilon F_{11}(\theta,r,w)+\varepsilon^2F_{21}(\theta,r,w)+O(\varepsilon^3),\\ \frac{dw}{d\theta}&=\varepsilon F_{12}(\theta,r,w)+\varepsilon^2F_{22}(\theta,r,w)+O(\varepsilon^3).\end{aligned}\tag{2.17}$$

We shall apply the averaging theory to the differential system (2.17).
We considering $t=\theta$, $T=2\pi$, $X=(r,w)^T$ and

$$F_1(\theta,r,w)=\begin{pmatrix}F_{11}(\theta,r,w)\\ F_{12}(\theta,r,w)\end{pmatrix},$$

such that

$$\begin{aligned}F_{11}(\theta,r,w)=\ &\frac{1}{k(k^2+\gamma_0^2)}(\frac{1}{k}((\frac{1}{\delta_{20}^2}(r(k^2+\gamma_0^2)\delta_{21}(\delta_{21}-\omega_1)((k^2+\gamma_0(\gamma_0-c))\\
&\cos\theta+ck\sin\theta))+r\gamma_0\gamma_1(\gamma_1-2r\gamma_0\cos\theta)(\gamma_0\cos\theta-k\sin\theta))\\
&\sin\theta)+r\gamma_1\cos\theta(\gamma_1-2r\gamma_0\cos\theta)(\gamma_0\cos\theta-k\sin\theta))+\frac{1}{kr}\\
&((-\frac{1}{k^2(k^2+\gamma_0^2)}(\gamma_1\cos^2\theta\gamma_0^3)+\frac{1}{k^2}(r\cos^3\theta\gamma_0^2)+\frac{1}{k^2\delta_{20}}(\delta_{21}\\
&\cos^2\theta\gamma_0^2)+\frac{1}{k^3\alpha}(w\cos^2\theta\gamma_0^2)+\frac{1}{k(k^2+\gamma_0^2)}(3\gamma_1\cos\theta\sin\theta\gamma_0^2)\\
&-\frac{1}{k^2\delta_{20}}(\omega_1\cos^2\theta\gamma_0^2)+\frac{1}{k^2+\gamma_0^2}(\gamma_1\cos^2\theta\gamma_0)+\frac{1}{k^2\delta_{20}}(c\omega_1\cos^2\theta\\
&\gamma_0)-\frac{1}{k}(2r\cos^2\theta\sin\theta\gamma_0)-\frac{1}{k^2}(r\alpha\cos^3\theta\gamma_0)-\frac{1}{k^2}(\mu_1\cos^2\theta\gamma_0)\\
&-\frac{1}{k^3\alpha}(cw\cos^2\theta\gamma_0)-\frac{1}{k^2+\gamma_0^2}(2\gamma_1\sin^2\theta\gamma_0)-\frac{1}{k^2\delta_{20}}(c\delta_{21}\cos^2\theta\\
&\gamma_0)+\frac{1}{\delta_{20}}(\delta_{21}\cos^2\theta)+\frac{1}{k\alpha}(w\cos^2\theta)+r\cos\theta\sin^2\theta+\frac{1}{k}(r\alpha\\
&\cos^2\theta\sin\theta)+\frac{1}{k\delta_{20}}(c\delta_{21}\cos\theta\sin\theta)+\frac{1}{k}(\mu_1\cos\theta\sin\theta)+\frac{1}{k^2\alpha}\\
&(cw\cos\theta\sin\theta)-\frac{1}{k^2+\gamma_0^2}(k\gamma_1\cos\theta\sin\theta)-\frac{1}{\delta_{20}}(\omega_1\cos^2\theta)-\\
&\frac{1}{k\delta_{20}}(c\omega_1\cos\theta\sin\theta))(r(r\cos\theta(kr\sin\theta-r\gamma_0\cos\theta)+\frac{1}{k^2+\gamma_0^2}\\
&(r\gamma_1((\gamma_0^2-k^2)\cos\theta-2k\gamma_0\sin\theta)))\cos\theta+\frac{1}{k\alpha}(r\sin\theta(r\alpha\gamma_0(r\\
&\cos\theta(k\sin\theta-\gamma_0\cos\theta)+\frac{1}{k^2+\gamma_0^2}(\gamma_1((\gamma_0^2-k^2)\cos\theta-2k\gamma_0\\
&\sin\theta)))+\frac{1}{k\delta_{20}}(r\cos\theta(\alpha(\omega_1-\delta_{21})k^3+\alpha\gamma_0(\delta_{20}\mu_1+(c-\gamma_0)\end{aligned}$$

$$
\begin{aligned}
& (\delta_{21}-\omega_1))k + r\alpha^2\gamma_0\delta_{20}\cos\theta k - k^2 w\delta_{20} + w(c-\gamma_0)\gamma_0\delta_{20}) \\
& -kr(kr\delta_{20}\cos\theta\alpha^2 + k\delta_{20}\mu_1\alpha + c(w\delta_{20} + k\alpha(\delta_{21}-\omega_1))) \\
& \sin\theta)))))) + \frac{1}{kr}((r(r\cos\theta(kr\sin\theta - r\gamma_0\cos\theta) + \frac{1}{k^2+\gamma_0^2} \\
& (r\gamma_1((\gamma_0^2-k^2)\cos\theta - 2k\gamma_0\sin\theta)))\cos\theta + \frac{1}{k\alpha}(r\sin\theta(r\alpha\gamma_0 \\
& (r\cos\theta(k\sin\theta - \gamma_0\cos\theta) + \frac{1}{k^2+\gamma_0^2}(\gamma_1((\gamma_0^2-k^2)\cos\theta \\
& -2k\gamma_0\sin\theta)), \\
F_{12}(\theta,r,w) = & \frac{1}{\alpha\delta_{20}k^2(\gamma_0^2+k^2)}((\alpha k(\delta_{21}-\omega_1) + \delta_{20}w)(\delta_{20}w(\gamma_0^2+k^2) \\
& +\alpha^2 kr(\delta_1-\delta_{20})(\gamma_0\cos\theta - k\sin\theta).
\end{aligned}
$$

We have the average function of first order

$$
\begin{aligned}
f_{11}(r,w) &= \frac{1}{2\pi}\int_0^{2\pi} F_{11}(\theta,r,w)d\theta = -\frac{r(c(\alpha k(\delta_{21}-\omega_1)+\delta_{20}w) + \alpha\delta_{20}k(\gamma_1+\mu_1))}{2\alpha\delta_{20}k^2}, \\
f_{12}(r,w) &= \frac{1}{2\pi}\int_0^{2\pi} F_{12}(\theta,r,w)d\theta = -\frac{w(\alpha k(\delta_{21}-\omega_1)+\delta_{20}w)}{\alpha k^2}.
\end{aligned}
$$

The system $f_{11}(r,w) = f_{12}(r,w) = 0$ has two solutions (r^*, w^*) with $r^* > 0$ where

$$
(r^*, w^*) \in \{(0,0), (0, \frac{\alpha k\omega_1 - \alpha\delta_{21}k}{\delta_{20}})\}
$$

The first solution is not good because provides an equilibrium point, but the second solution is good, and since the Jacobian matrix of the function (f_{11}, f_{12}) is not zero at that solution it provides a periodic solution of the differential system

The jacobian determinant at $(r^*, w^*) = (0, \frac{1}{\delta_{20}}(\alpha k\omega_1 - \alpha\delta_{21}k))$ is given by

$$
\Delta = -\frac{(\gamma_1+\mu_1)(\delta_{21}-\omega_1)}{2k^2}.
$$

Moreover the eigenvalues of the Jacobian matrix

$$
\frac{\partial(f_{11}, f_{12})}{\partial(r,w)}\ |_{(r,w)=(r^*,w^*)}
$$

are given as follows

$$
-\frac{\gamma_1+\mu_1}{2k}, \quad and \quad \frac{\delta_{21}-\omega_1}{k}.
$$

So one periodic orbit bifurcates from the Zero-Hopf equilibrium localized at the origin of coordinates. ❐

Chapter 3

Zero-Hopf Bifurcation in Tumor Growth Cancer model

In this chapter, we study the Zero-Hopf bifurcation of the Tumor Growth Cancer model. More precisely, we will study the conditions for the existence of Zero-Hopf equilibrium points, and the averaging theory of the first and second order is also applied to prove the existence of periodic orbit bifurcating from the Zero-Hopf equilibrium points.

3.1 Tumor Growth Cancer model

In this section we consider a deterministic mathematical model for the growth of tumor and incorporated the stochastic environmental perturbation with white noise on the system. The preys are the tumor cells that are attacked and destroyed by the immune cells. The predator has two states viz, hunting and resting cells which destroy the prey. The resting predator cells can interact with antigens. These resting cells cannot kill tumor cells but they are converting into a special type of T-lymphocyte cells which is called natural killer or hunting cells and begin to multiply which releases other cytokines simulating more resting cells. This conversion between hunting and resting cells results in a degradation of the resting cells undergoing natural growth and an activation of hunting cells. The required mathematical model assumes that the tumor cells are being destroyed at a rate proportional to the tumor cell densities according to the law of mass action like prey-predator interaction. It is also assumed that the resting predator cells are converted into the hunting cells either by direct contact with them or by contact with a fast diffusing substance produced by hunting cells. We consider that once a cell has been converted, it will never return to the resting stage, and active cells which die out at a constant probability per unit time. For more detail see [7].
The dynamical system can be described by the following set of non-linear differential equations

$$\begin{aligned} \dot{x} &= a_1(1-x)x - k_1xy - k_2x + 1, \\ \dot{y} &= a_2yz - a_3y - k_3xy, \\ \dot{z} &= a_4(1-z)z - a_5yz - a_6z - k_4xz. \end{aligned} \tag{3.1}$$

Where a_1, a_2, a_3, a_4, a_5, a_6, k_1, k_2, k_3 and k_4 are constants. The description of these parameters in system (3.1) is shown in Table 3.1.

Parameter	Description
a_1	is the growth rate of tumor cells
a_2	represents the conversion rate of the resulting cells to hunting predator cells
a_3	is the specific loss rates of hunting predator cells
a_4	represents the growth rate of resting cells
a_5	is the conversion rate of resting cells to hunting predator cells
a_6	is the specific loss rates of the resting cells
k_1	is the rate of killing of tumor cells by hunting cells
k_2	is the specific loss rates of tumor cells
k_3	represents the rate of killing of hunting predator cells by tumor cells
k_4	represents the rate of killing of resting cells by tumor cells
$x(t)$	represents the density of tumor cells at time t
$y(t)$	represents density of hunting predator cells at time t
$z(t)$	represents density of resulting cells at time t

TABLEAU 3.1: Descriptions of the parameters in system (3.1).

3.2 Statement of the main results

Firstly, we shall study the conditions for the existence of Zero-Hopf equilibrium point of Tumor Growth Cancer model. We consider the Tumor Growth Cancer system written as

$$\begin{aligned} \dot{x} &= a_1(1-x)x - k_1xy - k_2x + 1, \\ \dot{y} &= a_2yz - a_3y - k_3xy, \\ \dot{z} &= a_4(1-z)z - a_5yz - a_6z - k_4xz. \end{aligned} \tag{3.2}$$

This system has seven equilibrium points given as follows

$p_1 = \Big(\dfrac{1}{2a_1}(\sqrt{-2a_1k_2 + a_1(a_1+4) + k_2^2} - a_1 + k_2), 0, 0\Big)$,

$p_2 = \Big(\dfrac{1}{2a_1}(\sqrt{-2a_1k_2 + a_1(a_1+4) + k_2^2} + a_1 - k_2), 0, 0\Big)$,

$p_5 = \Big(-\dfrac{a_3}{k_3}, \dfrac{1}{a_3k_1k_3}(a_1a_3(a_3+k_3) - k_3(a_3k_2+k_3)), 0\Big)$.

Due to the fact that the expressions of p_3, p_4, p_6 and p_7 are big we will omit them, and we will study only one equilibrium point $p_5 = \Big(-\dfrac{a_3}{k_3}, \dfrac{1}{a_3k_1k_3}(a_1a_3(a_3+k_3) - k_3(a_3k_2+k_3)), 0\Big)$.

To Find the sufficient conditions in order that system (3.1) has Zero-Hopf equilibria we must translate p_5 to the origin of coordinates, then we obtain the following system

$$\begin{aligned} \dot{x} =& \ \frac{1}{k_3}(a_1a_3x) - a_1x^2 + \frac{1}{k_3}(a_3k_1y) + \frac{1}{a_3}(k_3x) - k_1xy, \\ \dot{y} =& \ \frac{1}{k_1k_3}(a_1a_2a_3z) + \frac{1}{k_1}(a_1a_2z) - \frac{1}{k_1}(a_1a_3x) - \frac{1}{k_1}(a_1k_3x) - \frac{1}{a_3k_1} \\ & (a_2k_3z) - \frac{1}{k_1}(a_2k_2z) + a_2yz + \frac{k_3^2x}{a_3k_1} + \frac{k_2k_3x}{k_1} - k_3xy, \\ \dot{z} =& -\frac{1}{k_1k_3}(a_1a_3a_5z) - \frac{a_1a_5z}{k_1} + \frac{1}{a_3k_1}(a_5k_3z) + \frac{1}{k_3}(a_3k_4z) - a_4z^2 \\ & + a_4z + \frac{1}{k_1}(a_5k_2z - a_5yz - a_6z - k_4xz. \end{aligned} \tag{3.3}$$

The results considering the existence of Zero-Hopf equilibria of system (3.3) is given in the following proposition.

Proposition 3.1 *The differential system* (3.3) *has Zero-Hopf equilibria located at the point* $p_5 = \left(-\frac{a_3}{k_3}, \frac{1}{a_3k_1k_3}(a_1a_3(a_3+k_3) - k_3(a_3k_2+k_3)), 0\right)$, *if the parameters of the system satisfy* $a_1 = -\frac{k_3^2}{a_3^2}$, $k_2 = \frac{-a_3k^2 - 2a_3k_3 - k_3^2}{a_3^2}$ *and* $k_4 = \frac{-a_3a_4k_1k_3 + a_3a_6k_1k_3 + a_5k^2k_3}{a_3^2k_1}$.

In the following theorem, we study the periodic orbits bifurcating from the Zero-Hopf equilibrium point p_5 of proposition using the averaging theory.

Theorem 3.1 *(i) If* $a_{50} \neq 0$, $\left(a_{11}a_{30}^3 + a_{11}a_{30}^2k_{30} - a_{30}^2k_{21}k_{30} + a_{31}k^2k_{30}\right) \neq 0$ *and* $F \neq 0$, *then the differential system* (3.3) *has a periodic orbit bifurcates from the Zero-Hopf equilibrium point* p_5 *for* $\varepsilon \neq 0$ *a small parameter.*

(ii) The stability or the unstability of this periodic orbit is given by the sign of the eigenvalues

$$-\frac{1}{a_{30}k_1(a_{20}(a_{60}-a_{40}) + a_{30}a_{40}) + a_{20}a_{50}k^2}(a_{20}a_{50}(a_{11}a_{30}^2(a_{30}+k_{30}) + k_{30}(a_{31}k^2 - a_{30}^2k_{21}))(k_1(a_{30}(a_{60}-a_{40}) + 2k_{30}) + a_{50}k^2))) + \frac{1}{2a_{30}^2kk_1k_{30}}((k_1(a_{11}a_{30}^3 + 2k_{30}(a_{30}k_{31} - a_{31}k_{30})), \quad and \quad -\frac{1}{a_{30}^2kk_1k_{30}}(a_{50}(a_{11}a_{30}^2(a_{30}+k_{30}) + k_{30}(a_{31}k^2 - a_{30}^2k_{21}))).$$

Where K is defined through $k_2 = \frac{-a_3k^2 - 2a_3k_3 - k_3^2}{a_3^2}$.

Where

$$F = a_{11}a_{30}^2(a_{20}(a_{50}k_{30}(a_{30}k_1(-a_{40}+a_{60}+2) + a_{50}k^2) + a_{30}(a_{50}-k_1)(a_{30}k_1(a_{60}-a_{40}) + a_{50}k^2) + 2a_{50}k_1k_{30}^2) - a_{30}^3a_{40}k_1^2) + k_{30}(a_{20}(a_{31}(a_{50}k^2k_1(a_{30}(a_{60}-a_{40}) + 4k_{30}) + 2a_{30}k_1^2k_{30}(a_{60}-a_{40}) + a_{50}^2k^4) + a_{30}(a_{30}a_{50}k_{21}(k_1(a_{30}(a_{40}-a_{60}) - 2k_{30}) - a_{50}k^2) - 2k_1k_{31}(a_{30}k_1(a_{60}-a_{40}) + a_{50}k^2))) + 2a_{30}^2a_{40}k_1^2(a_{31}k_{30} - a_{30}k_{31}),$$

and

$$a_1 = -\frac{k_{30}^2}{a_{30}^2} + \varepsilon a_{11} + \varepsilon^2 a_{12} + \varepsilon^3 a_{13}, \qquad a_2 = a_{20} + \varepsilon a_{21} + \varepsilon^2 a_{22} + \varepsilon^3 a_{23},$$
$$a_3 = a_{30} + \varepsilon a_{31} + \varepsilon^2 a_{32} + \varepsilon^3 a_{33}, \qquad a_4 = a_{40} + \varepsilon a_{41} + \varepsilon^2 a_{42} + \varepsilon^3 a_{43},$$
$$a_5 = a_{50} + \varepsilon a_{51} + \varepsilon^2 a_{52} + \varepsilon^3 a_{53}, \qquad a_6 = a_{60} + \varepsilon a_{61} + \varepsilon^2 a_{62} + \varepsilon^3 a_{63},$$
$$k_3 = k_{30} + \varepsilon k_{31} + \varepsilon^2 k_{32} + \varepsilon^3 k_{33}, \qquad k_4 = \frac{-a_3a_4k_1k_3 + a_3a_6k_1k_3 + a_5k^2k_3}{a_3^2k_1},$$
$$k_2 = \frac{1}{a_{30}^2}(-a_{30}k^2 - 2a_{30}k_{30} - k_{30}^2) + \varepsilon k_{21} + \varepsilon^2 k_{22} + \varepsilon^3 k_{23}, \quad \textit{with } a_{30} \neq 0.$$

Moreover, we note that if the two eigenvalues are negative then the periodic orbit, which bifurcates from the equilibrium point p_5 is stable, i.e, it is a local attractor. But if one of these eigenvalues is positive then, such periodic orbit is unstable.

It is interesting to see the averaging of second order provides more periodic solutions bifurcating from the Zero-Hopf equilibrium localized at the origin of coordinates.

Theorem 3.2 *For* $\mid \varepsilon \mid$ *is a sufficiently small parameter. If* $k_1 \in \Big(-\infty, -4/10\Big) \cup \Big(0, +\infty\Big)$, *the differential system* (3.3) *has two limit cycles bifurcating from the Zero-Hopf equilibrium point* p_5 *with* $a_{30} \neq 0$ *and* $-k_1\Big(1 + 4k_1 \pm \sqrt{6k_1^2 + 4k_1 + 1}\Big) > 0$. *Moreover, the stability or the unstability of the first periodic orbit is given by the sign of the eigenvalues*

$$\lambda_1 = \frac{1}{k_1}\Big(-1 - 4k_1 + \sqrt{6k_1^2 + 4k_1 + 1}\Big), \quad and \quad \lambda_2 = \frac{1}{k_1^2}\Big(2k_1\Big(-2 - 3k_1 + \sqrt{6k_1^2 + 4k_1 + 1}\Big) - 1 + \sqrt{6k_1^2 + 4k_1 + 1}\Big).$$

And also the stability or the unstability of the second periodic orbit is given by the sign of the eigenvalues

$$\lambda_1 = \frac{2\sqrt{6k_1^2 + 4k_1 + 1}}{1 + 2k_1 - \sqrt{6k_1^2 + 4k_1 + 1}}, \quad and \quad \lambda_2 = -\frac{1}{k_1}\Big(1 + 4k_1 + \sqrt{6k_1^2 + 4k_1 + 1}\Big).$$

We note that if the two eigenvalues are negative then the periodic orbit, which bifurcates from the equilibrium point p_5 *is stable, i.e, it is a local attractor. But if one of these eigenvalues is positive, then such periodic orbit is unstable.*

3.3 Proof of the main results

Proof of Proposition 3.1. The characteristic polynomial of the linear part of the Tumor Growth Cancer model at ($(0,0,0)$ is

$$\begin{aligned}p(\lambda) = \; & \frac{1}{a_3^2 k_1 k_3^2}(\lambda(a_1^2 a_3^4 a_5 + a_1^2 a_3^3 a_5 k_3 - a_1 a_3^4 k_1 k_3 - a_1 a_3^4 k_1 k_4 - a_1 a_3^3 a_4 k_1 k_3 \\ & - a_1 a_3^3 a_5 k_2 k_3 + a_1 a_3^3 a_6 k_1 k_3 - a_1 a_3^3 k_1 k_3^2 + a_1 a_3 a_5 k_3^3 + a_3^3 k_1 k_2 k_3^2 + a_3^2 \\ & k_1 k_3^3 - a_3^2 k_1 k_3^2 k_4 - a_3 a_4 k_1 k_3^3 - a_3 a_5 k_2 k_3^3 + a_3 a_6 k_1 k_3^3 - a_5 k_3^4)) + \frac{1}{a_3 k_1 k_3} \\ & (\lambda^2(-a_1 a_3^2 a_5 + a_1 a_3^2 k_1 - a_1 a_3 a_5 k_3 + a_3^2 k_1 k_4 + a_3 a_4 k_1 k_3 + a_3 a_5 k_2 k_3 \\ & - a_3 a_6 k_1 k_3 + a_5 k_3^2 + k_1 k_3^2)) - \frac{1}{a_3 k_1 k_3^2}((a_1 a_3^2 + a_1 a_3 k_3 - a_3 k_2 k_3 - k_3^2) \\ & (a_1 a_3^2 a_5 + a_1 a_3 a_5 k_3 - a_3^2 k_1 k_4 - a_3 a_4 k_1 k_3 - a_3 a_5 k_2 k_3 + a_3 a_6 k_1 k_3 - a_5 \\ & k_3^2)) - \lambda^3.\end{aligned}$$

Assume $p(\lambda) = \lambda\,(k^2 + \lambda^2)$, we obtain $a_1 = -\dfrac{k_3^2}{a_3^2}$, $k_2 = \dfrac{-a_3 k^2 - 2a_3 k_3 - k_3^2}{a_3^2}$ and $k_4 = \dfrac{-a_3 a_4 k_1 k_3 + a_3 a_6 k_1 k_3 + a_5 k^2 k_3}{a_3^2 k_1}$. Then proposition 3.1 holds. ❐

Proof of Theorem 3.1. By considering the following perturbation $\Big(a_1, a_2, a_3, a_4, a_5, a_6, k_2, k_3, k_4\Big) = \Big(-\dfrac{k_{30}^2}{a_{30}^2} + \varepsilon a_{11} + \varepsilon^2 a_{12} + \varepsilon^3 a_{13}, a_{20} + \varepsilon a_{21} + \varepsilon^2 a_{22} + \varepsilon^3 a_{23}, a_{30} + \varepsilon a_{31} + \varepsilon^2 a_{32} + \varepsilon^3 a_{33}, a_{40} + \varepsilon a_{41} + \varepsilon^2 a_{42} + \varepsilon^3 a_{43}, a_{50} + \varepsilon a_{51} + \varepsilon^2 a_{52} + \varepsilon^3 a_{53}, a_{60} + \varepsilon a_{61} + \varepsilon^2 a_{62} + \varepsilon^3 a_{63}, \dfrac{1}{a_{30}^2}(-a_{30} k^2 - 2a_{30} k_{30} - k_{30}^2) + \varepsilon k_{21} + \varepsilon^2 k_{22} + \varepsilon^3 k_{23}, k_{30} + \varepsilon k_{31} + \varepsilon^2 k_{32} + \varepsilon^3 k_{33}, \dfrac{1}{a_3^2 k_1}(-a_3 a_4 k_1 k_3 + a_3 a_6 k_1 k_3 + a_5 k^2 k_3)\Big)$, where $\varepsilon \neq 0$

is a small parameter, then the Tumor Growth Cancer system becomes

$$
\begin{aligned}
\dot{x} = {} & \frac{1}{a_{30}^3 k_{30}^3}(\varepsilon^2(k_{30}x(a_{11}a_{30}^3(a_{31}k_{30}-a_{30}k_{31})+a_{12}a_{30}^3k_{30}(a_{30}-k_{30}x) \\
& +k_{30}(a_{30}(2a_{30}k_{30}k_{32}-a_{30}k_{31}^2-2a_{32}k_{30}^2)+a_{31}^2k_{30}^2))+a_{30}^3k_1y(a_{30} \\
& (k_{31}^2-k_{30}k_{32})-a_{31}k_{30}k_{31}+a_{32}k_{30}^2)))+\frac{1}{a_{30}^2k_{30}^2}(\varepsilon(a_{11}a_{30}^2k_{30}x(a_{30} \\
& -k_{30}x)-(a_{31}k_{30}-a_{30}k_{31})(2k_{30}^2x-a_{30}^2k_1y)))+\frac{1}{a_{30}^2}(k_{30}^2x^2)+\frac{1}{k_{30}} \\
& (a_{30}k_1y)-k_1xy, \\
\dot{y} = {} & \frac{1}{a_{30}^3k_1k_{30}^2}(\varepsilon^2(z(a_{11}a_{30}^3(a_{20}(a_{31}k_{30}-a_{30}k_{31})+a_{21}k_{30}(a_{30}+k_{30}))- \\
& k_{30}(k_{30}(a_{30}^3(a_{20}k_{22}+a_{21}k_{21})+a_{20}a_{31}^2k_{30})+a_{20}a_{30}^2k_{31}^2-2a_{20}a_{30}a_{31} \\
& k_{30}k_{31}-a_{22}a_{30}^2k_{30}(a_{30}k_1y+k^2)))+k_{30}^2x(-a_{11}a_{30}^3(a_{31}+k_{31})+a_{30}^3 \\
& (-k_1k_{32}y+k_{21}k_{31}+k_{22}k_{30})+a_{30}^2(k_{31}^2-k^2k_{32})-2a_{30}a_{31}k_{30}k_{31}+ \\
& a_{31}^2k_{30}^2)-a_{12}a_{30}^3k_{30}(a_{30}+k_{30})(k_{30}x-a_{20}z)))+\frac{1}{a_{30}k_1k_{30}}(\varepsilon(z(a_{11} \\
& a_{20}a_{30}(a_{30}+k_{30})+k_{30}(a_{21}(a_{30}k_1y+k^2)-a_{20}a_{30}k_{21}))-k_{30}x(a_{11} \\
& a_{30}(a_{30}+k_{30})+a_{30}k_1k_{31}y-a_{30}k_{21}k_{30}+k^2k_{31})))-\frac{1}{a_{30}k_1}((k_{30}x \\
& -a_{20}z)(a_{30}k_1y+k^2)), \\
\dot{z} = {} & -\frac{1}{a_{30}^4k_1k_{30}^2}(z\varepsilon^2(a_{11}a_{30}^4(-a_{30}a_{50}k_{31}+a_{51}k_{30}(a_{30}+k_{30})+a_{31}a_{50}k_{30}) \\
& +a_{12}a_{30}^4a_{50}k_{30}(a_{30}+k_{30})+k_{30}(a_{30}^4k_{30}(a_{42}k_1z-a_{50}k_{22}-a_{51}k_{21}+ \\
& a_{52}k_1y)+a_{30}^3(k_1k_{30}x(-a_{40}k_{32}-a_{41}k_{31}a_{42}k_{30}+a_{60}k_{32}+a_{61}k_{31}+ \\
& a_{62}k_{30})-a_{50}k_{31}^2)+a_{30}^2k_{30}(a_{31}(k_1x(a_{40}k_{31}+a_{41}k_{30}-a_{60}k_{31}-a_{61} \\
& k_{30})+2a_{50}k_{31}+a_{51}k^2)+a_{32}k_1k_{30}x(a_{40}-a_{60})+a_{32}a_{50}k^2+k^2x \\
& (a_{50}k_{32}+a_{51}k_{31}+a_{52}k_{30}))+a_{30}k_{30}(a_{31}^2(-(k_1k_{30}x(a_{40}-a_{60})+a_{50} \\
& (k^2+k_{30})))-2a_{31}k^2x(a_{50}k_{31}+a_{51}k_{30})-2a_{32}a_{50}k^2k_{30}x)+3a_{31}^2 \\
& a_{50}k^2k_{30}^2x)))-\frac{1}{a_{30}^3k_1k_{30}}(z\varepsilon(a_{11}a_{30}^3a_{50}(a_{30}+k_{30})+k_{30}(a_{30}^3(a_{41}k_1z \\
& -a_{50}k_{21}+a_{51}k_1y)+a_{30}^2k_1x(k_{31}(a_{60}-a_{40})-a_{41}k_{30}+a_{61}k_{30})+a_{30} \\
& (a_{31}k_1k_{30}x(a_{40}-a_{60})+a_{31}a_{50}k^2+k^2x(a_{50}k_{31}+a_{51}k_{30}))-2a_{31} \\
& a_{50}k^2k_{30}x)))-\frac{1}{a_{30}^2\,k_1}(z(a_{50}(a_{30}^2k_1y+k^2k_{30}x)+a_{30}k_1(a_{30}a_{40}z- \\
& a_{40}k_{30}x+a_{60}k_{30}x))).
\end{aligned}
\tag{3.4}
$$

Doing the rescaling of the variables $(x, y, z) = (\varepsilon X, \varepsilon Y, \varepsilon Z)$ system (3.4) in the new variables (X, Y, Z) writes

$$
\begin{aligned}
\dot{X} = {} & \frac{1}{30^3k_{30}^3}(\varepsilon^2(k_{30}X(-a_{11}a_{30}^3(a_{30}k_{31}-a_{31}k_{30}+k_{30}^2X)+a_{12}a_{30}^4k_{30}+ \\
& k_{30}(a_{30}(2a_{30}k_{30}k_{32}-a_{30}k_{31}^2-2a_{32}k_{30}^2)+a_{31}^2k_{30}^2))+a_{30}^3k_1Y(a_{30} \\
& (k_{31}^2-k_{30}k_{32})-a_{31}k_{30}k_{31}+a_{32}k_{30}^2)))+\varepsilon(\frac{1}{k_{30}}(a_{11}a_{30}X)+\frac{1}{a_{30}^2}(X \\
& (2a_{30}k_{31}-2a_{31}k_{30}+k_{30}^2X))+\frac{1}{k_{30}^2}(k_1Y(k_{30}(a_{31}-k_{30}X)-a_{30}k_{31})))
\end{aligned}
$$

$$+\frac{1}{k_{30}}(a_{30}k_1Y),$$

$$\begin{aligned}
\dot{Y} = \;& \frac{1}{a_{30}^3k_1k_{30}^2}(\varepsilon^2(a_{11}a_{30}^3(Z(a_{20}(a_{31}k_{30}-a_{30}k_{31})+a_{21}k_{30}(a_{30}+k_{30}))\\
& -k_{30}^2X(a_{31}+k_{31}))-a_{12}a_{30}^3k_{30}(a_{30}+k_{30})(k_{30}X-a_{20}Z)+k_{30}\\
& (a_{30}^3k_{30}(k_{22}(k_{30}X-a_{20}Z)+(k_{21}-k_1Y)(k_{31}X-a_{21}Z))+a_{30}^2\\
& (k_{30}(k^2(a_{22}Z-k_{32}X)+k_{31}^2X)-a_{20}k_{31}^2Z)+2a_{30}a_{31}k_{30}k_{31}(a_{20}\\
& Z-k_{30}X)+a_{31}^2k_{30}^2(k_{30}X-a_{20}Z))))+\frac{1}{a_{30}k_1k_{30}}(\varepsilon(k_{30}(a_{30}(k_{21}\\
& -k_1Y)(k_{30}X-a_{20}Z)+k^2(a_{21}Z-k_{31}X))-a_{11}a_{30}(a_{30}+k_{30})\\
& (k_{30}X-a_{20}Z)))+\frac{1}{a_{30}k_1}(k^2(a_{20}Z-k_{30}X)),\\
\dot{Z} = \;& -\frac{1}{a_{30}^3k_1k_{30}^2}(Z\varepsilon^2(a_{11}a_{30}^3(-a_{30}a_{50}k_{31}+a_{51}k_{30}(a_{30}+k_{30})+a_{31}a_{50}\\
& k_{30})+a_{12}a_{30}^3a_{50}k_{30}(a_{30}+k_{30})+k_{30}(a_{30}(a_{30}^2k_{30}(a_{41}k_1Z-a_{50}k_{22}\\
& +a_{51}k_1Y-a_{51}k_{21})+a_{30}k_1k_{30}X(-a_{40}k_{31}-a_{41}k_{30}+a_{60}k_{31}+a_{61}\\
& k_{30})-a_{30}a_{50}k_{31}^2+a_{32}a_{50}k^2k_{30}+k^2k_{30}X(a_{50}k_{31}+a_{51}k_{30}))+a_{31}\\
& k_{30}(a_{30}(k_1k_{30}X(a_{40}-a_{60})+2a_{50}k_{31}+a_{51}k^2)-2a_{50}k^2k_{30}X)-\\
& a_{31}^2a_{50}k_{30}(k^2+k_{30}))))-\frac{1}{a_{30}^2k_1k_{30}}(Z\varepsilon(a_{11}a_{30}^2a_{50}(a_{30}+k_{30})+k_{30}\\
& (a_{30}^2(a_{40}k_1Z+a_{50}k_1Y-a_{50}k_{21})+a_{30}k_1k_{30}X(a_{60}-a_{40})+a_{31}a_{50}\\
& k^2+a_{50}k^2k_{30}X))).
\end{aligned} \tag{3.5}$$

We want to write M the Jacobian matrix of system (3.5) in the Jordan form

$$J=\begin{pmatrix} 0 & -k & 0\\ k & 0 & 0\\ 0 & 0 & 0\end{pmatrix}.$$

Then we consider the following equation $A.M-J.A=0$ where

$$A=\begin{pmatrix} y_1 & y_2 & y_3\\ y_4 & y_5 & y_6\\ y_7 & y_8 & y_9\end{pmatrix}.$$

With the Jacobian determinant $\mid A\mid\neq 0$ we obtain

$$A=\begin{pmatrix} 0 & 1 & 0\\ \dfrac{kk_{30}}{a_{30}k_1} & 0 & -\dfrac{a_{20}k}{a_{30}k_1}\\ 0 & 0 & a_{30}kk_1k_{30}\end{pmatrix}.$$

Now we consider the change of variables $(X,Y,Z)\rightarrow(u,v,w)$ given by

$$(X,Y,Z)\rightarrow\left(\frac{a_{20}w+a_{30}^2k_1^2k_{30}v}{a_{30}kk_1k_{30}^2},u,\frac{w}{a_{30}kk_1k_{30}}\right). \tag{3.6}$$

In the new variables (u, v, w) the differential system (3.5) becomes

$$
\begin{aligned}
\dot{u} = \;& \frac{1}{a_{30}^2 k k_1^2 k_{30}^3}(\varepsilon^2(-a_{11}a_{30}(a_{30}(a_{20}k_{31}w - a_{21}k_{30}w) + k_{30}w(a_{20}k_{31}- \\
& a_{21}k_{30}) + a_{30}^2k_1^2k_{30}^2v(a_{31}+k_{31})) - a_{12}a_{30}^3k_1^2k_{30}^2v(a_{30}+k_{30}) + k_{30} \\
& (a_{30}(-w(k_{21}-k_1u)(a_{21}k_{30}-a_{20}k_{31}) - 2a_{31}k_1^2k_{30}^2k_{31}v) + k^2w(a_{22} \\
& k_{30} - a_{20}k_{32}) + a_{30}^3k_1^2k_{30}v(k_{31}(k_{21}-k_1u) + k_{22}k_{30}) + a_{30}^2k_1^2k_{30}v(k_{31}^2 \\
& -k^2k_{32}) + a_{31}^2k_1^2k_{30}^3v))) + \frac{1}{a_{30}^2kk_1^2k_{30}^2}(\varepsilon(-a_{11}a_{30}^3k_1^2k_{30}v(a_{30}+k_{30}) \\
& +k^2w(a_{21}k_{30}-a_{20}k_{31}) + a_{30}^3k_1^2k_{30}^2v(k_{21}-k_1u) - a_{30}^2k^2k_1^2k_{30}k_{31}v)) \\
& -kv, \\
\dot{v} = \;& \frac{1}{a_{30}^5k_1^3k_{30}^3}(\varepsilon^2(a_{20}w(a_{11}a_{30}^3(-a_{30}a_{50}k_{31} + a_{51}k_{30}(a_{30}+k_{30}) + a_{31}a_{50} \\
& k_{30}) + a_{12}a_{30}^3a_{50}k_{30}(a_{30}+k_{30}) + k_{30}(a_{30}(\frac{1}{kk_{30}}((a_{20}w + a_{30}^2k_1^2k_{30}v) \\
& (k_{31}(a_{60}-a_{40}) - a_{41}k_{30} + a_{61}k_{30})) + \frac{1}{a_{30}k_1k_{30}}(k(a_{50}k_{31}+a_{51}k_{30}) \\
& (a_{20}w + a_{30}^2k_1^2k_{30}v)) - \frac{1}{k}(a_{30}(a_{30}kk_{30}(a_{50}k_{22} + a_{51}(k_{21}-k_1u))- \\
& a_{41}w)) - a_{30}a_{50}k_{31}^2 + a_{32}a_{50}k^2k_{30}) + \frac{1}{a_{30}kk_1}(a_{31}(a_{20}a_{30}k_1w(a_{40} \\
& -a_{60}) - 2a_{20}a_{50}k^2w + a_{30}^3k_1^3k_{30}v(a_{40}-a_{60}) + a_{30}^2kk_1k_{30}(2a_{50}(k_{31} \\
& -kk_1v) + a_{51}k^2))) - a_{31}^2a_{50}k_{30}(k^2+k_{30}))) + a_{30}kk_1^2k_{30}(a_{30}^3k_1u \\
& (a_{30}(k_{31}^2 - k_{30}k_{32}) - a_{31}k_{30}k_{31} + a_{32}k_{30}^2) - \frac{1}{a_{30}k^2k_1^2k_{30}}((a_{20}w \\
& +a_{30}^2k_1^2k_{30}v)(a_{11}a_{30}^2(a_{20}w + a_{30}^2k_1(kk_{31}+k_1k_{30}v) - a_{30}a_{31}kk_1k_{30} \\
&) - a_{12}a_{30}^4kk_1k_{30} + kk_1k_{30}(a_{30}(-2a_{30}k_{30}k_{32} + a_{30}k_{31}^2 + 2a_{32}k_{30}^2) \\
& -a_{31}^2k_{30}^2)))))) + \frac{1}{a_{30}^5kk_1^4k_{30}^2}(\varepsilon(a_{30}^4k_1(k(a_{11}a_{20}a_{50}w + a_{11}a_{20}k_1w+ \\
& 2k_1^3k_{30}^2k_{31}v) + a_{31}k^2k_1^3k_{30}^2u + k_1^4k_{30}^3v^2) + a_{30}^3k_1k_{30}(a_{20}w(a_{11}a_{50}k \\
& +k_1^2(-(v(a_{40}-a_{60}) + ku)) + a_{50}k(k_1u - k_{21})) - 2a_{31}kk_1^3k_{30}^2v) \\
& +a_{11}a_{30}^6kk_1^4k_{30}v + a_{20}^2w^2(a_{50}k^2 + k_1k_{30}) + a_{20}a_{30}^2k_1w(a_{40}w + a_{50} \\
& k^2k_1k_{30}v + 2kk_1k_{30}k_{31} + 2k_1^2k_{30}^2v) + a_{20}a_{30}k_1w(a_{20}w(a_{60}-a_{40}) \\
& +a_{31}kk_{30}(a_{50}k^2 - 2k_1k_{30})) - a_{30}^5kk_1^4k_{30}u(kk_{31} + k_1k_{30}v))) + ku, \\
\dot{w} = \;& -\frac{1}{a_{30}^3k_1k_{30}^2}(w\varepsilon^2(a_{11}a_{30}^3(-a_{30}a_{50}k_{31} + a_{51}k_{30}(a_{30}+k_{30}) + a_{31}a_{50} \\
& k_{30}) + a_{12}a_{30}^3a_{50}k_{30}(a_{30}+k_{30}) + k_{30}(a_{30}(\frac{1}{kk_{30}}((a_{20}w + a_{30}^2k_1^2k_{30}v) \\
& (k_{31}(a_{60}-a_{40}) - a_{41}k_{30} + a_{61}k_{30})) + \frac{1}{a_{30}k_1k_{30}}(k(a_{50}k_{31}+a_{51}k_{30}) \\
& (a_{20}w + a_{30}^2k_1^2k_{30}v)) - \frac{1}{k}(a_{30}(a_{30}kk_{30}(a_{50}k_{22} + a_{51}(k_{21}-k_1u))- \\
& a_{41}w)) - a_{30}a_{50}k_{31}^2 + a_{32}a_{50}k^2k_{30}) + \frac{1}{a_{30}kk_1}(a_{31}(a_{20}a_{30}k_1w(a_{40}- \\
& a_{60}) - 2a_{20}a_{50}k^2w + a_{30}^3k_1^3k_{30}v(a_{40}-a_{60}) + a_{30}^2kk_1k_{30}(2a_{50}(k_{31}- \\
& kk_1v) + a_{51}k^2))) - a_{31}^2a_{50}k_{30}(k^2+k_{30})))) - \frac{1}{a_{30}^3kk_1^2k_{30}}(w\varepsilon(a_{11}a_{30}^3 \\
& a_{50}kk_1(a_{30}+k_{30}) + a_{30}k_1(a_{20}w(a_{60}-a_{40}) + a_{31}a_{50}k^3k_{30}) + a_{20}a_{50}
\end{aligned}
\tag{3.7}
$$

$$k^2w + a_{30}^3k_1k_{30}(k_1^2v(a_{60} - a_{40}) + a_{50}k(k_1u - k_{21})) + a_{30}^2k_1(a_{40}w+ a_{50}k^2k_1k_{30}v))).$$

Now we write the differential system (3.7) in cylindrical coordinates (r, θ, w) defined by u = r $\cos\theta$, v = r $\sin\theta$ and $w = w$, we obtain

$$\begin{aligned}
\frac{dr}{d\theta} = {} & \frac{1}{r(k\sin^2\theta + k\cos^2\theta)}(\varepsilon(\frac{1}{a_{30}^5kk_1^4k_{30}^2}(r\sin\theta(a_{30}^4k_1(k(a_{11}a_{20}a_{50}\sin\theta) - (a_{11}\\
& a_{20}k_1w + 2k_1^3k_{30}^2k_{31}r\sin\theta) + a_{31}k^2k_1^3k_{30}^2r\cos\theta + k_1^4k_{30}^3r^2\sin^2\theta) + a_{30}^3k_1\\
& k_{30}(a_{20}w(a_{11}a_{50}k + k_1^2(-(r(a_{40} - a_{60})\sin\theta + kr\cos\theta)) + a_{50}k(k_1r\cos\theta\\
& -k_{21})) - 2a_{31}kk_1^3k_{30}^2r\sin\theta) + a_{11}a_{30}^6kk_1^4k_{30}r\sin\theta + a_{20}^2w^2(a_{50}k^2 + k_1k_{30})\\
& +a_{20}a_{30}^2k_1w(a_{40}w + a_{50}k^2k_1k_{30}r\sin\theta + 2kk_1k_{30}k_{31} + 2k_1^2k_{30}^2r\sin\theta) + a_{20}\\
& a_{30}k_1w(a_{20}w(a_{60} - a_{40}) + a_{31}kk_{30}(a_{50}k^2 - 2k_1k_{30})) - a_{30}^5kk_1^4k_{30}r\cos\theta(k\\
& k_{31} + k_1k_{30}r\sin\theta))) + r\cos\theta(-\frac{1}{kk_{30}}(a_{11}a_{30}^2r\sin\theta) - \frac{1}{k}(a_{11}a_{30}r\sin\theta)-\\
& \frac{1}{a_{30}^2k_1^2k_{30}^2}(a_{20}kk_{31}w) + \frac{1}{a_{30}^2k_1^2k_{30}}(a_{21}kw) - \frac{1}{k}(a_{30}k_1r^2\sin\theta\cos\theta) + \frac{1}{k}(a_{30}\\
& k_{21}r\sin\theta) - \frac{1}{k_{30}}(kk_{31}r\sin\theta)))) + \varepsilon^2(\frac{1}{r(k\cos^2\theta + k\sin^2\theta)}(\frac{1}{a_{30}^2kk_1^2k_{30}^3}(r\\
& \cos\theta(-a_{12}k_1^2k_{30}^2(a_{30} + k_{30})r\sin\theta a_{30}^3 - a_{11}(a_{30}^2k_1^2(a_{31} + k_{31})r\sin\theta k_{30}^2+\\
& (a_{20}k_{31} - a_{21}k_{30})wk_{30} + a_{30}(a_{20}k_{31}w - a_{21}k_{30}w))a_{30} + k_{30}(k_1^2k_{30}r(k_{22}k_{30}\\
& +k_{31}(k_{21} - k_1r\cos\theta))\sin\theta a_{30}^3 + k_1^2k_{30}(k_{31}^2 - k^2k_{32})r\sin\theta a_{30}^2 + (-2a_{31}k_1^2\\
& k_{31}r\sin\theta k_{30}^2 - (a_{21}k_{30} - a_{20}k_{31})w(k_{21} - k_1r\cos\theta))a_{30} + k^2(a_{22}k_{30} - a_{20}\\
& k_{32})w + a_{31}^2k_1^2k_{30}^3r\sin\theta))) + \frac{1}{a_{30}^5k_1^3k_{30}^3}(r\sin\theta(a_{30}kk_{30}(a_{30}^3k_1(a_{32}k_{30}^2 - a_{31}\\
& k_{31}k_{30} + a_{30}(k_{31}^2 - k_{30}k_{32}))r\cos\theta - \frac{1}{a_{30}k^2k_1^2k_{30}}((a_{30}^2k_{30}r\sin\theta k_1^2 + a_{20}w)\\
& (-a_{12}kk_1k_{30}a_{30}^4 + a_{11}(k_1(kk_{31} + k_1k_{30}r\sin\theta)a_{30}^2 - a_{30}a_{31}kk_1k_{30} + a_{20}w)\\
& a_{30}^2 + kk_1k_{30}(a_{30}(2a_{32}k_{30}^2 - 2a_{30}k_{32}k_{30} + a_{30}k_{31}^2) - a_{31}^2k_{30}^2))))k_1^2 + a_{20}w\\
& (a_{12}a_{50}k_{30}(a_{30} + k_{30})a_{30}^3 + a_{11}(a_{31}a_{50}k_{30} + a_{51}(a_{30} + k_{30})k_{30} - a_{30}a_{50}k_{31})\\
& a_{30}^3 + k_{30}(-a_{31}^2a_{50}k_{30}(k^2 + k_{30}) + a_{30}(a_{32}a_{50}k_{30}k^2 + \frac{1}{a_{30}k_1k_{30}}((a_{51}k_{30} + a_{50}\\
& k_{31})(a_{30}^2k_{30}r\sin\theta k_1^2 + a_{20}w)k) - a_{30}a_{50}k_{31}^2 + \frac{1}{kk_{30}}((-a_{41}k_{30} + a_{61}k_{30} + (a_{60}\\
& -a_{40})k_{31})(a_{30}^2k_{30}r\sin\theta k_1^2 + a_{20}w)) - \frac{1}{k}(a_{30}(a_{30}kk_{30}(a_{50}k_{22} + a_{51}(k_{21} - k_1r\\
& \cos\theta)) - a_{41}w))) + \frac{1}{a_{30}kk_1}(a_{31}(a_{30}^3(a_{40} - a_{60})k_{30}r\sin\theta k_1^3 + a_{20}a_{30}(a_{40}-\\
& a_{60})wk_1 + a_{30}^2kk_{30}(a_{51}k^2 + 2a_{50}(k_{31} - kk_1r\sin\theta))k_1 - 2a_{20}a_{50}k^2w))))))\\
& -\frac{1}{r^3(k\cos^2\theta + k\sin^2\theta)^2}((((\frac{1}{kk_{30}}(a_{11}r\sin\theta a_{30}^2) + \frac{1}{k}(a_{11}r\sin\theta a_{30}) + \frac{1}{k}(k_1\\
& r^2\cos\theta\sin\theta a_{30}) - \frac{1}{k}(k_{21}r\sin\theta a_{30}) + \frac{1}{a_{30}^2k_1^2k_{30}^2}(a_{20}kk_{31}w) + \frac{1}{k_{30}}(kk_{31}r\\
& \sin\theta) - \frac{a_{21}kw}{a_{30}^2k_1^2k_{30}})r\sin\theta + \frac{1}{a_{30}^5kk_1^4k_{30}^2}(r\cos\theta(a_{11}kk_1^4k_{30}r\sin\theta a_{30}^6 - kk_1^4k_{30}\\
& r\cos\theta(kk_{31} + k_1k_{30}r\sin\theta)a_{30}^5 + k_1(k_{30}^3r^2\sin^2\theta k_1^4 + a_{31}k^2k_{30}^2r\cos\theta k_1^3 + k
\end{aligned}$$

$$(2k_{30}^2k_{31}r\sin\theta k_1^3 + a_{11}a_{20}wk_1 + a_{11}a_{20}a_{50}w))a_{30}^4 + k_1k_{30}(a_{20}w(-(kr \cos\theta + (a_{40}-a_{60})r\sin\theta k_1^2 + a_{11}a_{50}k + a_{50}k(k_1r\cos\theta - k_{21})) - 2a_{31} kk_1^3k_{30}^2r\sin\theta)a_{30}^3 + a_{20}k_1w(a_{50}k_1k_{30}r\sin\theta k^2 + 2k_1k_{30}k_{31}k + a_{40}w+ 2k_1^2k_{30}^2r\sin\theta)a_{30}^2 + a_{20}k_1w(a_{31}kk_{30}(a_{50}k^2 - 2k_1k_{30}) + a_{20}(a_{60}-a_{40})w) a_{30} + a_{20}^2(a_{50}k^2 + k_1k_{30})w^2)))((-\frac{1}{kk_{30}}(a_{11}r\sin\theta a_{30}^2) + \frac{1}{k}(k_{21}r\sin\theta a_{30}) -\frac{1}{k}(a_{11}r\sin\theta a_{30}) - \frac{1}{k}(k_1r^2\cos\theta\sin\theta a_{30}) + \frac{1}{a_{30}^2k_1^2k_{30}}(a_{21}kw) - \frac{1}{k_{30}}(kk_{31} r\sin\theta) - \frac{1}{a_{30}^2k_1^2k_{30}^2}(a_{20}kk_{31}w)r\cos\theta + \frac{1}{a_{30}^5kk_1^4k_{30}^2}(r\sin\theta(a_{11}kk_1^4k_{30}r\sin\theta a_{30}^6 - kk_1^4k_{30}r\cos\theta(kk_{31} + k_1k_{30}r\sin\theta)a_{30}^5 + k_1(k_{30}^3r^2\sin^2\theta k_1^4 + a_{31}k^2k_{30}^2 r\cos\theta k_1^3 + k(2k_{30}^2k_{31}r\sin\theta k_1^3 + a_{11}a_{20}wk_1 + a_{11}a_{20}a_{50}w))a_{30}^4 + k_1k_{30}(a_{20} w(-(kr\cos\theta + (a_{40}-a_{60})r\sin\theta)k_1^2 + a_{11}a_{50}k + a_{50}k(k_1r\cos\theta - k_{21}))- 2a_{31}kk_1^3k_{30}^2r\sin\theta)a_{30}^3 + a_{20}k_1w(a_{50}k_1k_{30}r\sin\theta k^2 + 2k_1k_{30}k_{31}k + a_{40}w+ 2k_1^2k_{30}^2r\sin\theta)a_{30}^2 + a_{20}k_1w(a_{31}kk_{30}(a_{50}k^2 - 2k_1k_{30}) + a_{20}(a_{60}-a_{40})w)a_{30} +a_{20}^2(a_{50}k^2 + k_1k_{30})w^2))))),$$

$$\frac{dw}{d\theta} = -\frac{1}{a_{30}^3kk_1^2k_{30}(k\sin^2\theta + k\cos^2\theta)}(w\varepsilon(a_{11}a_{30}^3a_{50}kk_1(a_{30}+k_{30}) + a_{30}k_1 (a_{20}w(a_{60}-a_{40}) + a_{31}a_{50}k^3k_{30}) + a_{20}a_{50}k^2w + a_{30}^3k_1k_{30}(k_1^2r(a_{60}- a_{40})\sin\theta + a_{50}k(k_1r\cos\theta - k_{21})) + a_{30}^2k_1(a_{40}w + a_{50}k^2k_1k_{30}r\sin\theta))) +\varepsilon^2(\frac{1}{a_{30}^3kk_1^2k_{30}r^2(k\sin^2\theta + k\cos^2\theta)^2}(w(a_{11}a_{30}^3a_{50}kk_1(a_{30}+k_{30}) + a_{30}k_1 (a_{20}w(a_{60}-a_{40}) + a_{31}a_{50}k^3k_{30}) + a_{20}a_{50}k^2w + a_{30}^3k_1k_{30}(k_1^2r(a_{60}-a_{40}) \sin\theta + a_{50}k(k_1r\cos\theta - k_{21})) + a_{30}^2k_1(a_{40}w + a_{50}k^2k_1k_{30}r\sin\theta))(\frac{1}{a_{30}^5kk_1^4k_{30}^2} (r\cos\theta(a_{30}^4k_1(k(a_{11}a_{20}a_{50}w + a_{11}a_{20}k_1w + 2k_1^3k_{30}^2k_{31}r\sin\theta) + a_{31}k^2k_1^3 k_{30}^2r\cos\theta + k_1^4k_{30}^3r^2\sin^2\theta) + a_{30}^3k_1k_{30}(a_{20}w(a_{11}a_{50}k + k_1^2(-(r(a_{40}-a_{60})\sin\theta + kr\cos\theta)) + a_{50}k(k_1r\cos\theta - k_{21})) - 2a_{31}kk_1^3k_{30}^2r\sin\theta) + a_{11}a_{30}^6 kk_1^4k_{30}r\sin\theta + a_{20}^2w^2(a_{50}k^2 + k_1k_{30}) + a_{20}a_{30}^2k_1w(a_{40}w + a_{50}k^2k_1k_{30}r\sin \theta + 2kk_1k_{30}k_{31} + 2k_1^2k_{30}^2r\sin\theta) + a_{20}a_{30}k_1w(a_{20}w(a_{60}-a_{40}) + a_{31}kk_{30}(a_{50} k^2 - 2k_1k_{30})) - a_{30}^5kk_1^4k_{30}r\cos\theta(kk_{31} + k_1k_{30}r\sin\theta))) + r\sin\theta(\frac{1}{kk_{30}}(a_{11} a_{30}^2r\sin\theta) + \frac{1}{k}(a_{11}a_{30}r\sin\theta) + \frac{1}{a_{30}^2k_1^2k_{30}^2}(a_{20}kk_{31}w) - \frac{1}{a_{30}^2k_1^2k_{30}}(a_{21}kw)+ \frac{1}{k}(a_{30}k_1r^2\sin\theta\cos\theta) - \frac{1}{k}(a_{30}k_{21}r\sin\theta) + \frac{1}{k_{30}}(kk_{31}r\sin\theta))))- \frac{1}{a_{30}^3k_1k_{30}^2(k\sin^2\theta + k\cos^2\theta)}(w(a_{11}a_{30}^3(-a_{30}a_{50}k_{31} + a_{51}k_{30}(a_{30}+k_{30})+ a_{31}a_{50}k_{30}) + a_{12}a_{30}^3a_{50}k_{30}(a_{30}+k_{30}) + k_{30}(a_{30}(\frac{1}{kk_{30}}((k_{31}(a_{60}-a_{40}) - a_{41} k_{30} + a_{61}k_{30})(a_{20}w + a_{30}^2k_1^2k_{30}r\sin\theta)) + \frac{1}{a_{30}k_1k_{30}}(k(a_{50}k_{31} + a_{51}k_{30})(a_{20} w + a_{30}^2k_1^2k_{30}r\sin\theta)) - \frac{1}{k}(a_{30}(a_{30}kk_{30}(a_{50}k_{22} + a_{51}(k_{21} - k_1r\cos\theta)) - a_{41} w)) - a_{30}a_{50}k_{31}^2 + a_{32}a_{50}k^2k_{30}) + \frac{1}{a_{30}kk_1}(a_{31}(a_{20}a_{30}k_1w(a_{40}-a_{60}) - 2a_{20} a_{50}k^2w + a_{30}^3k_1^3k_{30}r(a_{40}-a_{60})\sin\theta + a_{30}^2kk_1k_{30}(2a_{50}(k_{31} - kk_1r\sin\theta)+$$

$$a_{51}k^2))) - a_{31}^2 a_{50} k_{30}(k^2 + k_{30}))))).$$

This system can be written as

$$\begin{aligned} \frac{dr}{d\theta} &= \varepsilon F_{11}(\theta, r, w) + \varepsilon^2 F_{21}(\theta, r, w) + O(\varepsilon^3), \\ \frac{dw}{d\theta} &= \varepsilon F_{12}(\theta, r, w) + \varepsilon^2 F_{22}(\theta, r, w) + O(\varepsilon^3). \end{aligned} \tag{3.8}$$

We shall apply the averaging theory to the differential system (3.8).
We considering $t = \theta, T = 2\pi$, $X = (r, w)^T$ and we get the normal form is given by

$$\frac{dX}{d\theta} = \varepsilon F_1(\theta, X) + \varepsilon^2 F_2(\theta, X) + \varepsilon^3 R(\varepsilon, \theta, X),$$

where

$$F_1(\theta, X) = \begin{pmatrix} F_{11}(\theta, X) \\ F_{12}(\theta, X) \end{pmatrix},$$

such that

$$\begin{aligned} F_{11}(\theta, r, w) = \ & \frac{1}{r(k \sin^2\theta + k \cos^2\theta)}\Big(\Big(\frac{1}{a_{30}^5 k k_1^4 k_{30}^2}(r \sin\theta(a_{30}^4 k_1(k(a_{11}a_{20}a_{50}w \\ & + a_{11}a_{20}k_1 w + 2k_1^3 k_{30}^2 k_{31} r \sin\theta) + a_{31}k^2 k_1^3 k_{30}^2 r \cos\theta + k_1^4 k_{30}^3 r^2 \\ & \sin^2\theta) + a_{30}^3 k_1 k_{30}(a_{20}w(a_{11}a_{50}k + k_1^2(-(r(a_{40} - a_{60})\sin\theta + k \\ & r\cos\theta)) + a_{50}k(k_1 r\cos\theta - k_{21})) - 2a_{31}kk_1^3 k_{30}^2 r \sin\theta) + a_{11}a_{30}^6 \\ & kk_1^4 k_{30} r \sin\theta + a_{20}^2 w^2(a_{50}k^2 + k_1 k_{30}) + a_{20}a_{30}^2 k_1 w(a_{40}w + a_{50}k^2 \\ & k_1 k_{30} r \sin\theta + 2kk_1 k_{30} k_{31} + 2k_1^2 k_{30}^2 r \sin\theta) + a_{20}a_{30}k_1 w(a_{20}w(a_{60} \\ & -a_{40}) + a_{31}kk_{30}(a_{50}k^2 - 2k_1 k_{30})) - a_{30}^5 kk_1^4 k_{30} r \cos\theta(kk_{31} + k_1 \\ & k_{30} r \sin\theta))) + r\cos\theta\Big(-\frac{1}{kk_{30}}(a_{11}a_{30}^2 r \sin\theta) - \frac{1}{k}(a_{11}a_{30} r \sin\theta) - \\ & \frac{1}{a_{30}^2 k_1^2 k_{30}^2}(a_{20}kk_{31}w) + \frac{1}{a_{30}^2 k_1^2 k_{30}}(a_{21}kw) - \frac{1}{k}(a_{30}k_1 r^2 \sin\theta\cos\theta) \\ & + \frac{1}{k}(a_{30}k_{21} r \sin\theta) - \frac{1}{k_{30}}(kk_{31} r \sin\theta)\Big)\Big)\Big), \\ F_{12}(\theta, r, w) = \ & -\frac{1}{a_{30}^3 kk_1^2 k_{30}(k\sin^2\theta + k\cos^2\theta)}(w(a_{11}a_{30}^3 a_{50}kk_1(a_{30} + k_{30}) + a_{30} \\ & k_1(a_{20}w(a_{60} - a_{40}) + a_{31}a_{50}k^3 k_{30}) + a_{20}a_{50}k^2 w + a_{30}^3 k_1 k_{30}(k_1^2 r \\ & (a_{60} - a_{40})\sin\theta + a_{50}k(k_1 r\cos\theta - k_{21})) + a_{30}^2 k_1(a_{40}w + a_{50}k^2 k_1 \\ & k_{30} r \sin\theta))). \end{aligned}$$

And

$$F_2(\theta, X) = \begin{pmatrix} F_{21}(\theta, X) \\ F_{22}(\theta, X) \end{pmatrix},$$

such that the explicit expression of F_{21} and F_{22} are given in the appendix.

We have the average function of first order $f_1(r, w) = (f_{11}(r, w), f_{12}(r, w))$, where

$$\begin{aligned}
f_{11}(r,w) &= \frac{1}{2\pi}\int_0^{2\pi} F_{11}(\theta,r,w)d\theta\\
&= \frac{1}{2a_{30}^3k^2k_1^2k_{30}}(r(a_{30}kk_1^2(a_{11}a_{30}^3+2k_{30}(a_{30}k_{31}-a_{31}k_{30}))+a_{20}w\\
&\quad (k_1(a_{30}(a_{60}-a_{40})+2k_{30})+a_{50}k^2))),\\
f_{12}(r,w) &= \frac{1}{2\pi}\int_0^{2\pi} F_{12}(\theta,r,w)d\theta\\
&= -\frac{1}{a_{30}^3k^2k_1^2k_{30}}(w(a_{30}a_{50}kk_1(a_{11}a_{30}^2(a_{30}+k_{30})+k_{30}(a_{31}k^2-a_{30}^2\\
&\quad k_{21}))+w(a_{30}k_1(a_{20}(a_{60}-a_{40})+a_{30}a_{40})+a_{20}a_{50}k^2))).
\end{aligned}$$

The system $f_{11}(r,w)=f_{12}(r,w)=0$ has two solutions $(r^*,\ w^*)$, where the first solution $(r^*,w^*)=(0,0)$ is not good because it provides an equilibrium point, but the second solution $(r^*,w^*)=\left(0,\dfrac{-a_{11}a_{30}^4a_{50}kk_1-a_{11}a_{30}^3a_{50}kk_1k_{30}+a_{30}^3a_{50}kk_1k_{21}k_{30}-a_{30}a_{31}a_{50}k^3k_1k_{30}}{-a_{20}a_{30}a_{40}k_1+a_{20}a_{30}a_{60}k_1+a_{20}a_{50}k^2+a_{30}^2a_{40}k_1}\right)$ is good, and since the Jacobian matrix of the function (f_{11},f_{12}) is not zero at this solution it provides a periodic solution of the differential system.

The Jacobian determinant at the second solution is given by

$$\begin{aligned}
\Delta = \ & \frac{1}{2a_{30}^4k^2k_1^2k_{30}^2(a_{30}k_1(a_{20}(a_{60}-a_{40})+a_{30}a_{40})+a_{20}a_{50}k^2)}(a_{50}(a_{11}a_{30}^2(a_{30}\\
&+k_{30})+k_{30}(a_{31}k^2-a_{30}^2k_{21}))(a_{11}a_{30}^2(a_{20}(-a_{50}k_{30}(a_{30}k_1(-a_{40}+a_{60}+2)\\
&+a_{50}k^2)+a_{30}(a_{50}-k_1)(a_{30}k_1(a_{40}-a_{60})-a_{50}k^2)-2a_{50}k_1k_{30}^2)+a_{30}^3a_{40}\\
&k_1^2)+k_{30}(a_{20}(2a_{31}k_1k_{30}(a_{30}k_1(a_{40}-a_{60})-2a_{50}k^2)-a_{31}a_{50}k^2(a_{30}k_1(a_{60}\\
&-a_{40})+a_{50}k^2)+a_{30}(a_{30}a_{50}k_{21}(-a_{30}a_{40}k_1+a_{30}a_{60}k_1+a_{50}k^2+2k_1k_{30})\\
&+2k_1k_{31}(a_{30}k_1(a_{60}-a_{40})+a_{50}k^2)))+2a_{30}^2a_{40}k_1^2(a_{30}k_{31}-a_{31}k_{30})))).
\end{aligned}$$

Moreover, the eigenvalues of the Jacobian matrix

$$\frac{\partial(f_{11},f_{12})}{\partial(r,w)}\ |_{(r,w)=(r^*,w^*)}$$

are given as follows

$$\begin{aligned}
&-\frac{1}{a_{30}k_1(a_{20}(a_{60}-a_{40})+a_{30}a_{40})+a_{20}a_{50}k^2}(a_{20}a_{50}(a_{11}a_{30}^2(a_{30}+k_{30})+k_{30}\\
&(a_{31}k^2-a_{30}^2k_{21}))(k_1(a_{30}(a_{60}-a_{40})+2k_{30})+a_{50}k^2)))+\frac{1}{2a_{30}^2kk_1k_{30}}((k_1(a_{11}\\
&a_{30}^3+2k_{30}(a_{30}k_{31}-a_{31}k_{30})),\quad and\quad -\frac{1}{a_{30}^2kk_1k_{30}}(a_{50}(a_{11}a_{30}^2(a_{30}+k_{30})+\\
&k_{30}(a_{31}k^2-a_{30}^2k_{21}))).
\end{aligned}$$

So one periodic orbit bifurcates from the Zero-Hopf equilibria localized at the origin of coordinates. ❐

Proof of Theorem 3.2. To compute the averaging function of second order we must make the first averaging function identically zero.

From the first averaging function $f_1(r,w)=(f_{11}(r,w),f_{12}(r,w))$, and by considering

$$a_{31} = \frac{a_{30}(a_{30}^2 k_{21} + 2a_{30}k_{31} + 2k_{30}k_{31})}{a_{30}k^2 + 2a_{30}k_{30} + 2k_{30}^2}, \qquad a_{11} = \frac{2(a_{30}k_{21}k_{30}^2 - k^2 k_{30}k_{31})}{a_{30}(a_{30}k^2 + 2a_{30}k_{30} + 2k_{30}^2)},$$
$$a_{50} = -\frac{-2a_{20}k_1k_{30} + a_{30}^2 a_{60}k_1 + 2a_{30}k_1k_{30}}{a_{30}k^2}, \qquad a_{40} = \frac{2a_{20}k_{30}}{a_{30}^2}, \text{ where } a_{30} \neq 0,$$

we know that $f_1(r,w) \equiv (0,0)$.

The second averaging function $f_2(r,w) = (f_{11}(r,w), f_{12}(r,w))$ is given by

$$f_{21}(r,w) = \int_0^{2\pi} [D_{r,w}F_{11}(\theta,r,w).y_1(\theta,r,w) + F_{21}(\theta,r,w)]d\theta,$$

and

$$f_{22}(r,w) = \int_0^{2\pi} [D_{r,w}F_{12}(\theta,r,w).y_1(\theta,r,w) + F_{22}(\theta,r,w)]d\theta,$$

where $y_1(\theta,r,w) = \int_0^{\theta} F_1(\theta,r,w)d\theta.$

After an exhausting calculation we get the function $f_2(r,w)$ writes as follows

$$f_2(r,w) = \ (A_1 + A_2r^2 + A_3w + A_4w^2, B_1 + B_2r^2 + B_3w + B_4w^2).$$

The explicit expression of A_i and B_i, with $i = 1,\ldots,4$ are given in the appendix.

Solving $f_2(r,w) = 0$ is equivalently solving the system

$$\begin{aligned} A_1 + A_2r^2 + A_3w + A_4w^2 &= 0, \\ B_1 + B_2r^2 + B_3w + B_4w^2 &= 0. \end{aligned} \tag{3.9}$$

We know that system (3.9) has four solutions (r_i^*, w_i^*) where $i = 1,\ldots,4$, but only two of them are accepted and satisfying $\mid D_{r,w}f_2(r^*,w^*) \mid \neq 0$, and the two remaining solutions have $r^* < 0$.

Due to the fact that the expressions of the two accepted solutions are big, we will not give them. Now we will give an example to illustrate our results.

Example 3.1 *We consider* $a_{12} = a_{20} = a_{21} = a_{30} = a_{32} = a_{41} = a_{51} = a_{60} = a_{61} = k_{32} = k_{21} = k_{22} = k_{30} = k_{31} = k = 1$. *Then the differential system* (3.8) *becomes*

$$\begin{aligned}
\frac{dr}{d\theta} &= \varepsilon^2 \frac{1}{\sin^2\theta + \cos^2\theta}\Big(\frac{1}{k_1^2}(a_{22}w\cos\theta) + \frac{1}{k_1^4}(w^2\sin\theta) + \frac{1}{k_1^3}(2w^2\sin\theta) + \frac{1}{k_1^2}(rw \\
&\quad \sin^2\theta) + \frac{1}{k_1^2}(rw\sin\theta\cos\theta) - \frac{1}{k_1^2}(w\cos\theta) - k_1r^2\sin\theta\cos^2\theta + \frac{1}{k_1}(rw\sin^2\theta) \\
&\quad + r\sin^2\theta - r\sin\theta\cos\theta) + \frac{1}{k_1^3 r(\sin^2\theta + \cos^2\theta)^2}(k_1^4r^2\sin\theta\cos^2\theta - 2k_1^4r^2 \\
&\quad \sin^2\theta\cos\theta + 2k_1^2rw\cos^2\theta - w^2\cos\theta)\frac{w^2\sin\theta}{k_1^3} + k_1r^2\sin^3\theta - k_1r^2\sin\theta\cos^2\theta \\
&\quad - k_1r^2\sin^2\theta\cos\theta - \frac{1}{k_1}(2rw\sin(\theta)\cos(\theta))))) + \frac{1}{\sin^2\theta + \cos^2\theta}\Big(\varepsilon\Big(\frac{1}{k_1^3}(w^2\sin\theta)) \\
&\quad + k_1r^2\sin^3\theta - k_1r^2\sin\theta\cos^2\theta - k_1r^2\sin^2\theta\cos\theta - \frac{1}{k_1}(2rw\sin\theta\cos\theta))),
\end{aligned}$$

$$\begin{aligned}
\frac{dw}{d\theta} &= \varepsilon^2\Big(\frac{1}{\sin^2\theta + \cos^2\theta}\Big(-\frac{w^2}{k_1^2} - k_1rw\sin\theta - \frac{2w^2}{k_1} - rw\sin\theta - rw\cos\theta + w) + \\
&\quad \frac{1}{k_1^3 r(\sin^2\theta + \cos^2\theta)^2}((2k_1rw\sin\theta + k_1rw\cos\theta)(k_1^4r^2\sin\theta\cos^2\theta - 2k_1^4r^2 \\
&\quad \sin^2\theta\cos\theta + 2k_1^2rw\cos^2\theta - w^2\cos\theta))) + \frac{1}{\sin^2\theta + \cos^2\theta}(\varepsilon(2k_1rw\sin\theta + \\
&\quad k_1rw\cos\theta)).
\end{aligned}$$

We compute the averaging function of first order we get $f_1(r,\theta) \equiv (0,0)$.
The second averaging function is $f_2(r,\theta) = (f_{21}(r,\theta), f_{22}(r,\theta))$*, where*

$$f_{21}(r,w) = (\frac{1}{200k_1^2}(r25k_1^4r^2 + 100k_1^2 + 100k_1w + 50w^2 + 100w),$$

$$f_{22}(r,w) = \frac{1}{200k_1^2}(w200k_1^2 - 400k_1w - 100w^2 - 200w)).$$

For $-k_1\Big(1+4k_1 \pm \sqrt{6k_1^2+4k_1+1}\Big) > 0$*, with* $k_1 \in \Big(-\infty, -4/10\Big) \cup \Big(0, +\infty\Big)$*, the solutions of* $f_2(r,w) = (0,0)$ *are*

$$(r_{11}, w_{11}) = \quad \Big((2\sqrt{-k_1\Big(1+4k_1-\sqrt{6k_1^2+4k_1+1}\Big)})/\sqrt{k_1^4}, -1-2k_1+\sqrt{6k_1^2+4k_1+1}\Big),$$

and

$$(r_{21}, w_{21}) = \quad \Big((2\sqrt{-k_1\Big(1+4k_1+\sqrt{6k_1^2+4k_1+1}\Big)})/\sqrt{k_1^4}, -1-2k_1-\sqrt{6k_1^2+4k_1+1}\Big).$$

The determinant of the Jacobian matrix at the first solution is

$$\Delta_1 = \frac{1}{k_1^3}\Big(\Big(-1-4k_1+\sqrt{6k_1^2+4k_1+1}\Big)\Big(2k_1\Big(-2-3k_1+\sqrt{6k_1^2+4k_1+1}\Big) -1+\sqrt{6k_1^2+4k_1+1}\Big)\Big).$$

Then the first solution exists.

And for the second solution, the determinant of the Jacobian at this solution is equal to

$$\Delta_2 = \frac{1}{k_1^3}\Big(\Big(1+4k_1+\sqrt{6k_1^2+4k_1+1}\Big)\Big(2k_1\Big(2+3k_1+\sqrt{6k_1^2+4k_1+1}\Big)+1 +\sqrt{6k_1^2+4k_1+1}\Big)\Big).$$

Then the second solution exists.

Moreover, the stability or the unstability of the first periodic orbit is given by the sign of the eigenvalues

$$\lambda_1 = \frac{1}{k_1}\Big(-1-4k_1+\sqrt{6k_1^2+4k_1+1}\Big), \quad and \quad \lambda_2 = \frac{1}{k_1^2}\Big(2k_1\Big(-2-3k_1+ \sqrt{6k_1^2+4k_1+1}\Big)-1+\sqrt{6k_1^2+4k_1+1}\Big).$$

And also the stability or the unstability of the second periodic orbit is given by the sign of the eigenvalues

$$\lambda_1 = \frac{2\sqrt{6k_1^2+4k_1+1}}{1+2k_1-\sqrt{6k_1^2+4k_1+1}}, \quad and \quad \lambda_2 = -\frac{1}{k_1}\Big(1+4k_1+\sqrt{6k_1^2+4k_1+1}\Big).$$

We note that if the two eigenvalues are negative then the periodic orbit, which bifurcates from the equilibrium point p_5 *is stable, i.e, it is a local attractor. But if one of these eigenvalues is positive, then such periodic orbit is unstable.*

❒

Conclusion

In this work, we present the Zero-Hopf bifurcation of two biological models. The first one is Malaria model, we provide sufficient conditions in order that Malaria system has Zero-Hopf equilibria and we applied the first and second averaging theory to prove the existence of periodic orbits. Then, for the first order, we conclude that the number of periodic orbits is one and for the second order the Malaria system has three limit cycles. The second model is Tumor Growth Cancer model we did the same work as the first system and we conclude that the system has one limit cycle for the first order and for the second order two limit cycles.

Appendices

Appendix

Here we provide the values A_1, A_2, A_3, A_4, B_1, B_2, B_3 and B_4 of averaging function f_2.

$$
\begin{aligned}
A_1 = \;& 4a_{12}a_{30}^8k^6k_1^2k_{30} + 16a_{12}a_{30}^8k^4k_1^2k_{30}^2 + 16a_{12}a_{30}^8k^2k_1^2k_{30}^3 + 16a_{12}a_{30}^7k^4k_1^2k_{30}^3 \\
& +32a_{12}a_{30}^7k^2k_1^2k_{30}^4 + 16a_{12}a_{30}^6k^2k_1^2k_{30}^5 + 12a_{30}^8k^2k_1^2k_{21}k_{30}^3 - 16a_{30}^7k^4k_1^2k_{21} \\
& k_{30}^2k_{31} + 16a_{30}^7k^2k_1^2k_{21}k_{30}^3k_{31} + 8a_{30}^6k^6k_1^2k_{30}^2k_{32} + 4a_{30}^6k^6k_1^2k_{30}k_{31}^2 + 32a_{30}^6 \\
& k^4k_1^2k_{30}^3k_{32} - 16a_{30}^6k^4k_1^2k_{30}^2k_{31}^2 + 16a_{30}^6k^2k_1^2k_{21}k_{30}^4k_{31} + 32a_{30}^6k^2k_1^2k_{30}^4k_{32} \\
& -8a_{30}^5a_{32}k^6k_1^2k_{30}^3 - 32a_{30}^5a_{32}k^4k_1^2k_{30}^4 - 32a_{30}^5a_{32}k^2k_1^2k_{30}^5 + 32a_{30}^5k^4k_1^2k_{30}^4 \\
& k_{32} - 16a_{30}^5k^4k_1^2k_{30}^3k_{31}^2 + 64a_{30}^5k^2k_1^2k_{30}^5k_{32} - 32a_{30}^4a_{32}k^4k_1^2k_{30}^5 - 64a_{30}^4a_{32} \\
& k^2k_1^2k_{30}^6 + 32a_{30}^4k^2k_1^2k_{30}^6k_{32} - 32a_{30}^3a_{32}k^2k_1^2k_{30}^7. \\
A_2 = \;& a_{30}^6k^4k_1^4k_{30}^3 + 4a_{30}^6k^2k_1^4k_{30}^4 + 4a_{30}^6k_1^4k_{30}^5 + 4a_{30}^5k^2k_1^4k_{30}^5 + 8a_{30}^5k_1^4k_{30}^6 + 4a_{30}^4 \\
& k_1^4k_{30}^7). \\
A_3 = \;& -8a_{20}^2a_{30}^4k^3k_1k_{21}k_{30}^2 - 16a_{20}^2a_{30}^4kk_1k_{21}k_{30}^3 - 16a_{20}^2a_{30}^3k^3k_1k_{30}^2k_{31} - 16a_{20}^2 \\
& a_{30}^3kk_1k_{21}k_{30}^4 - 32a_{20}^2a_{30}^3kk_1k_{30}^3k_{31} - 16a_{20}^2a_{30}^2k^3k_1k_{30}^3k_{31} - 64a_{20}^2a_{30}^2kk_1 \\
& k_{30}^4k_{31} - 32a_{20}^2a_{30}kk_1k_{30}^5k_{31} + 4a_{20}a_{30}^6a_{60}k^3k_1k_{21}k_{30} + 8a_{20}a_{30}^6a_{60}kk_1k_{21} \\
& k_{30}^2 - 2a_{20}a_{30}^6k^5k_1k_{31} - 8a_{20}a_{30}^6k^3k_1k_{30}k_{31} - 8a_{20}a_{30}^6kk_1k_{30}^2k_{31} - 4a_{20}a_{30}^5 \\
& a_{41}k^5k_1k_{30} - 16a_{20}a_{30}^5a_{41}k^3k_1k_{30}^2 - 16a_{20}a_{30}^5a_{41}kk_1k_{30}^3 + 8a_{20}a_{30}^5a_{60}k^3k_1 \\
& k_{30}k_{31} + 8a_{20}a_{30}^5a_{60}kk_1k_{21}k_{30}^3 + 16a_{20}a_{30}^5a_{60}kk_1k_{30}^2k_{31} + 4a_{20}a_{30}^5a_{61}k^5k_1 \\
& k_{30} + 16a_{20}a_{30}^5a_{61}k^3k_1k_{30}^2 + 16a_{20}a_{30}^5a_{61}kk_1k_{30}^3 - 8a_{20}a_{30}^5k^3k_1k_{30}^2k_{31} - 16 \\
& a_{20}a_{30}^5kk_1k_{30}^3k_{31} - 16a_{20}a_{30}^4a_{41}k^3k_1k_{30}^3 - 32a_{20}a_{30}^4a_{41}kk_1k_{30}^4 + 4a_{20}a_{30}^4a_{51} \\
& k^7k_{30} + 16a_{20}a_{30}^4a_{51}k^5k_{30}^2 + 16a_{20}a_{30}^4a_{51}k^3k_{30}^3 + 8a_{20}a_{30}^4a_{60}k^3k_1k_{30}^2k_{31}+ \\
& 32a_{20}a_{30}^4a_{60}kk_1k_{30}^3k_{31} + 16a_{20}a_{30}^4a_{61}k^3k_1k_{30}^3 + 32a_{20}a_{30}^4a_{61}kk_1k_{30}^4 + 6a_{20} \\
& a_{30}^4k^5k_1k_{30}k_{31} + 24a_{20}a_{30}^4k^3k_1k_{30}^2k_{31} - 8a_{20}a_{30}^4kk_1k_{30}^4k_{31} + 24a_{20}a_{30}^4kk_1k_{30}^3 \\
& k_{31} - 16a_{20}a_{30}^3a_{41}kk_1k_{30}^5 + 16a_{20}a_{30}^3a_{51}k^5k_{30}^3 + 32a_{20}a_{30}^3a_{51}k^3k_{30}^4 + 16a_{20} \\
& a_{30}^3a_{60}kk_1k_{30}^4k_{31} + 16a_{20}a_{30}^3a_{61}kk_1k_{30}^5 + 24a_{20}a_{30}^3k^3k_1k_{30}^3k_{31} + 48a_{20}a_{30}^3k \\
& k_1k_{30}^4k_{31} + 16a_{20}a_{30}^2a_{51}k^3k_{30}^5 + 24a_{20}a_{30}^2kk_1k_{30}^5k_{31} + 2a_{21}a_{30}^6k^5k_1k_{30} + 8 \\
& a_{21}a_{30}^6k^3k_1k_{30}^2 + 8a_{21}a_{30}^6kk_1k_{30}^3 + 8a_{21}a_{30}^5k^3k_1k_{30}^3 + 16a_{21}a_{30}^5kk_1k_{30}^4 + 2a_{21} \\
& a_{30}^4k^5k_1k_{30}^2 + 8a_{21}a_{30}^4k^3k_1k_{30}^3 + 8a_{21}a_{30}^4kk_1k_{30}^5 + 8a_{21}a_{30}^4kk_1k_{30}^4 + 8a_{21}a_{30}^3 \\
& k^3k_1k_{30}^4 + 16a_{21}a_{30}^3kk_1k_{30}^5 + 8a_{21}a_{30}^2kk_1k_{30}^6. \\
A_4 = \;& 2a_{20}^2a_{30}^2k^4k_{30} + 8a_{20}^2a_{30}^2k^2k_{30}^2 + 8a_{20}^2a_{30}^2k_{30}^3 + 8a_{20}^2a_{30}k^2k_{30}^3 + 16a_{20}^2a_{30}k_{30}^4+ \\
& 8a_{20}^2k_{30}^5. \\
B_1 = \;& 8a_{12}a_{30}^{10}a_{60}k^6k_1^2 + 32a_{12}a_{30}^{10}a_{60}k^4k_1^2k_{30} - 16a_{12}a_{20}a_{30}^8k^6k_1^2k_{30} + 16a_{12}a_{30}^9k^6 \\
& k_1^2k_{30} + 8a_{12}a_{30}^9a_{60}k^6k_1^2k_{30} + 8a_{30}^7a_{32}a_{60}k^8k_1^2k_{30} - 8a_{30}^{10}a_{60}k^4k_1^2k_{21}^2k_{30} - 8 \\
& a_{30}^9a_{60}k^6k_1^2k_{22}k_{30} + 32a_{12}a_{30}^{10}a_{60}k^2k_1^2k_{30}^2 - 64a_{12}a_{20}a_{30}^8k^4k_1^2k_{30}^2 + 64a_{12}a_{30}^9 \\
& k^4k_1^2k_{30}^2 + 64a_{12}a_{30}^9a_{60}k^4k_1^2k_{30}^2 - 16a_{12}a_{20}a_{30}^7k^6k_1^2k_{30}^2 + 16a_{12}a_{30}^8k^6k_1^2k_{30}^2+ \\
& 32a_{30}^7a_{32}a_{60}k^6k_1^2k_{30}^2 - 16a_{20}a_{30}^5a_{32}k^8k_1^2k_{30}^2 + 16a_{30}^6a_{32}k^8k_1^2k_{30}^2 + 8a_{30}^{10}a_{60}k^2 \\
& k_1^2k_{21}^2k_{30}^2 + 16a_{20}a_{30}^8k^4k_1^2k_{21}^2k_{30}^2 - 16a_{30}^9k^4k_1^2k_{21}^2k_{30}^2 - 32a_{30}^9a_{60}k^4k_1^2k_{22}k_{30}^2+ \\
& 16a_{20}a_{30}^7k^6k_1^2k_{22}k_{30}^2 - 16a_{30}^8k^6k_1^2k_{22}k_{30}^2 - 64a_{12}a_{20}a_{30}^8k^2k_1^2k_{30}^3 + 64a_{12}a_{30}^9k^2 \\
& k_1^2k_{30}^3 + 96a_{12}a_{30}^9a_{60}k^2k_1^2k_{30}^3 - 128a_{12}a_{20}a_{30}^7k^4k_1^2k_{30}^3 + 128a_{12}a_{30}^8k^4k_1^2k_{30}^3+ \\
& 32a_{12}a_{30}^8a_{60}k^4k_1^2k_{30}^3 + 32a_{30}^7a_{32}a_{60}k^4k_1^2k_{30}^3 - 64a_{20}a_{30}^5a_{32}k^6k_1^2k_{30}^3 + 64a_{30}^6 \\
& a_{32}k^6k_1^2k_{30}^3 + 32a_{30}^6a_{32}a_{60}k^6k_1^2k_{30}^3 - 16a_{20}a_{30}^8k^2k_1^2k_{21}^2k_{30}^3 + 16a_{30}^9k^2k_1^2k_{21}^2
\end{aligned}
$$

$$
\begin{aligned}
& k_{30}^3 - 32a_{30}^9 a_{60}k^2k_1^2k_{22}k_{30}^3 + 64a_{20}a_{30}^7k^4k_1^2k_{22}k_{30}^3 - 64a_{30}^8k^4k_1^2k_{22}k_{30}^3 - 32\\
& a_{30}^8a_{60}k^4k_1^2k_{22}k_{30}^3 - 192a_{12}a_{20}a_{30}^7k^2k_1^2k_{30}^4 + 192a_{12}a_{30}^8k^2k_1^2k_{30}^4 + 96a_{12}a_{30}^8\\
& a_{60}k^2k_1^2k_{30}^4 - 64a_{12}a_{20}a_{30}^6k^4k_1^2k_{30}^4 + 64a_{12}a_{30}^7k^4k_1^2k_{30}^4 - 64a_{20}a_{30}^5a_{32}k^4k_1^2\\
& k_{30}^4 + 64a_{30}^6a_{32}k^4k_1^2k_{30}^4 + 64a_{30}^6a_{32}a_{60}k^4k_1^2k_{30}^4 - 64a_{20}a_{30}^4a_{32}k^6k_1^2k_{30}^4 + 64\\
& a_{30}^5a_{32}k^6k_1^2k_{30}^4 + 64a_{20}a_{30}^7k^2k_1^2k_{22}k_{30}^4 - 64a_{30}^8k^2k_1^2k_{22}k_{30}^4 - 64a_{30}^8a_{60}k^2k_1^2\\
& k_{22}k_{30}^4 + 64a_{20}a_{30}^6k^4k_1^2k_{22}k_{30}^4 - 64a_{30}^7k^4k_1^2k_{22}k_{30}^4 - 192a_{12}a_{20}a_{30}^6k^2k_1^2k_{30}^5 +\\
& 192a_{12}a_{30}^7k^2k_1^2k_{30}^5 + 32a_{12}a_{30}^7a_{60}k^2k_1^2k_{30}^5 - 128a_{20}a_{30}^4a_{32}k^4k_1^2k_{30}^5 + 128a_{30}^5\\
& a_{32}k^4k_1^2k_{30}^5 + 32a_{30}^5a_{32}a_{60}k^4k_1^2k_{30}^5 + 128a_{20}a_{30}^6k^2k_1^2k_{22}k_{30}^5 - 128a_{30}^7k^2k_1^2\\
& k_{22}k_{30}^5 - 32a_{30}^7a_{60}k^2k_1^2k_{22}k_{30}^5 - 64a_{12}a_{20}a_{30}^5k^2k_1^2k_{30}^6 + 64a_{12}a_{30}^6k^2k_1^2k_{30}^6 -\\
& 64a_{20}a_{30}^3a_{32}k^4k_1^2k_{30}^6 + 64a_{30}^4a_{32}k^4k_1^2k_{30}^6 + 64a_{20}a_{30}^5k^2k_1^2k_{22}k_{30}^6 - 64a_{30}^6k^2k_1^2\\
& k_{22}k_{30}^6 - 48a_{30}^9a_{60}k^4k_1^2k_{21}k_{30}k_{31} + 96a_{20}a_{30}^7k^4k_1^2k_{21}k_{30}^2k_{31} - 96a_{30}^8k^4k_1^2k_{21}\\
& k_{30}^2k_{31} - 32a_{30}^8a_{60}k^4k_1^2k_{21}k_{30}^2k_{31} + 64a_{20}a_{30}^6k^4k_1^2k_{21}k_{30}^3k_{31} - 64a_{30}^7k^4k_1^2k_{21}\\
& k_{30}^3k_{31} + 8a_{30}^8a_{60}k^6k_1^2k_{31}^2 - 32a_{30}^8a_{60}k^4k_1^2k_{30}k_{31}^2 - 16a_{20}a_{30}^6k^6k_1^2k_{30}k_{31}^2 + 16\\
& a_{30}^7k^6k_1^2k_{30}k_{31}^2 + 64a_{20}a_{30}^6k^4k_1^2k_{30}^2k_{31}^2 - 64a_{30}^7k^4k_1^2k_{30}^2k_{31}^2 - 64a_{30}^7a_{60}k^4k_1^2k_{30}^2\\
& k_{31}^2 + 128a_{20}a_{30}^5k^4k_1^2k_{30}^3k_{31}^2 - 128a_{30}^6k^4k_1^2k_{30}^3k_{31}^2 - 32a_{30}^6a_{60}k^4k_1^2k_{30}^3k_{31}^2 + 64\\
& a_{20}a_{30}^4k^4k_1^2k_{30}^4k_{31}^2 - 64a_{30}^5k^4k_1^2k_{30}^4k_{31}^2.
\end{aligned}
$$

$$
\begin{aligned}
B_2 = \; & 2a_{20}a_{30}^8k^4k_1^4k_{30}^2 + 8a_{20}a_{30}^8k^2k_1^4k_{30}^3 + 8a_{20}a_{30}^8k_1^4k_{30}^4 + 8a_{20}a_{30}^7k^2k_1^4k_{30}^4 + 16\\
& a_{20}a_{30}^7k_1^4k_{30}^5 + 2a_{20}a_{30}^6k^4k_1^4k_{30}^3 + 8a_{20}a_{30}^6k^2k_1^4k_{30}^4 + 8a_{20}a_{30}^6k_1^4k_{30}^6 + 8a_{20}a_{30}^6\\
& k_1^4k_{30}^5 + 8a_{20}a_{30}^5k^2k_1^4k_{30}^5 + 16a_{20}a_{30}^5k_1^4k_{30}^6 + 8a_{20}a_{30}^4k_1^4k_{30}^7 - a_{30}^{10}a_{60}k^4k_1^4k_{30}\\
& -4a_{30}^{10}a_{60}k^2k_1^4k_{30}^2 - 4a_{30}^{10}a_{60}k_1^4k_{30}^3 - 4a_{30}^9a_{60}k^2k_1^4k_{30}^3 - 8a_{30}^9a_{60}k_1^4k_{30}^4 - 2a_{30}^9\\
& k^4k_1^4k_{30}^2 - 8a_{30}^9k^2k_1^4k_{30}^3 - 8a_{30}^9k_1^4k_{30}^4 - a_{30}^8a_{60}k^4k_1^4k_{30}^2 - 4a_{30}^8a_{60}k^2k_1^4k_{30}^3 - 4\\
& a_{30}^8a_{60}k_1^4k_{30}^5 - 4a_{30}^8a_{60}k_1^4k_{30}^4 - 8a_{30}^8k^2k_1^4k_{30}^4 - 16a_{30}^8k_1^4k_{30}^5 - 4a_{30}^7a_{60}k^2k_1^4k_{30}^4\\
& -8a_{30}^7a_{60}k_1^4k_{30}^5 + 2a_{30}^7k^6k_1^4k_{30}^2 + 6a_{30}^7k^4k_1^4k_{30}^3 - 8a_{30}^7k_1^4k_{30}^6 - 8a_{30}^7k_1^4k_{30}^5 - 4\\
& a_{30}^6a_{60}k_1^4k_{30}^6 + 8a_{30}^6k^4k_1^4k_{30}^4 + 8a_{30}^6k^2k_1^4k_{30}^5 - 16a_{30}^6k_1^4k_{30}^6 + 8a_{30}^5k^2k_1^4k_{30}^6 - 8\\
& a_{30}^5k_1^4k_{30}^7.
\end{aligned}
$$

$$
\begin{aligned}
B_3 = \; & -8a_{20}a_{30}^5a_{51}k^9 - 32a_{20}a_{30}^4a_{51}k_{30}^2k^7 - 8a_{30}^7a_{41}k_1k^7 + 8a_{20}a_{30}^6a_{41}k_1k^7 - 8a_{20}\\
& a_{30}^6a_{61}k_1k^7 - 32a_{20}a_{30}^5a_{51}k_{30}k^7 + 8a_{21}a_{30}^5k_1k_{30}k^7 + 8a_{20}a_{30}^5k_1k_{31}k^7 - 32a_{20}\\
& a_{30}^3a_{51}k_{30}^4k^5 - 64a_{20}a_{30}^4a_{51}k_{30}^3k^5 + 32a_{21}a_{30}^4k_1k_{30}^3k^5 - 32a_{20}a_{30}^5a_{51}k_{30}^2k^5 +\\
& 32a_{21}a_{30}^5k_1k_{30}^2k^5 - 32a_{30}^6a_{41}k_1k_{30}^2k^5 + 32a_{20}a_{30}^5a_{41}k_1k_{30}^2k^5 - 32a_{20}a_{30}^5a_{61}k_1\\
& k_{30}^2k^5 - 8a_{20}a_{30}^7a_{60}k_1k_{21}k^5 - 32a_{30}^7a_{41}k_1k_{30}k^5 + 32a_{20}a_{30}^6a_{41}k_1k_{30}k^5 - 32\\
& a_{20}a_{30}^6a_{61}k_1k_{30}k^5 - 32a_{20}a_{30}^6k_1k_{21}k_{30}k^5 + 16a_{20}^2a_{30}^5k_1k_{21}k_{30}k^5 - 32a_{20}a_{30}^4\\
& k_1k_{30}^2k_{31}k^5 + 32a_{20}^2a_{30}^3k_1k_{30}^2k_{31}k^5 - 16a_{20}a_{30}^6a_{60}k_1k_{31}k^5 - 32a_{20}a_{30}^5k_1k_{30}\\
& k_{31}k^5 + 32a_{20}^2a_{30}^4k_1k_{30}k_{31}k^5 - 16a_{20}a_{30}^5a_{60}k_1k_{30}k_{31}k^5 + 32a_{21}a_{30}^3k_1k_{30}^5k^3 +\\
& 64a_{21}a_{30}^4k_1k_{30}^4k^3 - 32a_{30}^5a_{41}k_1k_{30}^4k^3 + 32a_{20}a_{30}^4a_{41}k_1k_{30}^4k^3 - 32a_{20}a_{30}^4a_{61}\\
& k_1k_{30}^4k^3 + 32a_{21}a_{30}^5k_1k_{30}^3k^3 - 64a_{30}^6a_{41}k_1k_{30}^3k^3 + 64a_{20}a_{30}^5a_{41}k_1k_{30}^3k^3 - 64\\
& a_{20}a_{30}^5a_{61}k_1k_{30}^3k^3 - 64a_{20}a_{30}^5k_1k_{21}k_{30}^3k^3 + 32a_{20}^2a_{30}^4k_1k_{21}k_{30}^3k^3 - 32a_{30}^7a_{41}\\
& k_1k_{30}^2k^3 + 32a_{20}a_{30}^6a_{41}k_1k_{30}^2k^3 - 32a_{20}a_{30}^6a_{61}k_1k_{30}^2k^3 - 64a_{20}a_{30}^6k_1k_{21}k_{30}^2k^3\\
& +32a_{20}^2a_{30}^5k_1k_{21}k_{30}^2k^3 - 16a_{20}a_{30}^6a_{60}k_1k_{21}k_{30}^2k^3 - 16a_{20}a_{30}^7a_{60}k_1k_{21}k_{30}k^3\\
& -96a_{20}a_{30}^3k_1k_{30}^4k_{31}k^3 + 64a_{20}^2a_{30}^2k_1k_{30}^4k_{31}k^3 - 192a_{20}a_{30}^4k_1k_{30}^3k_{31}k^3 + 128\\
& a_{20}^2a_{30}^3k_1k_{30}^3k_{31}k^3 - 32a_{20}a_{30}^4a_{60}k_1k_{30}^3k_{31}k^3 - 96a_{20}a_{30}^5k_1k_{30}^2k_{31}k^3 + 64\\
& a_{20}^2a_{30}^4k_1k_{30}^2k_{31}k^3 - 64a_{20}a_{30}^5a_{60}k_1k_{30}^2k_{31}k^3 - 32a_{20}a_{30}^6a_{60}k_1k_{30}k_{31}k^3.
\end{aligned}
$$

$$B_4 = 8a_{20}^3a_{30}^2k^4k_{30} + 32a_{20}^3a_{30}^2k^2k_{30}^2 + 32a_{20}^3a_{30}^2k_{30}^3 + 32a_{20}^3a_{30}k^2k_{30}^3 + 64a_{20}^3 a_{30}k_{30}^4 + 32a_{20}^3k_{30}^5 - 4a_{20}^2a_{30}^4a_{60}k^4 - 16a_{20}^2a_{30}^4a_{60}k^2k_{30} - 16a_{20}^2a_{30}^4a_{60} k_{30}^2 - 16a_{20}^2a_{30}^3a_{60}k^2k_{30}^2 - 32a_{20}^2a_{30}^3a_{60}k_{30}^3 - 8a_{20}^2a_{30}^3k^4k_{30} - 32a_{20}^2a_{30}^3 k^2k_{30}^2 - 32a_{20}^2a_{30}^3k_{30}^3 - 16a_{20}^2a_{30}^2a_{60}k_{30}^4 - 32a_{20}^2a_{30}^2k^2k_{30}^3 - 64a_{20}^2a_{30}^2k_{30}^4 -32a_{20}^2a_{30}k_{30}^5.$$

Here we provide the values of the functions F_{21} and F_{22} that appear in the proof of theorem 3.1.

$$F_{21}(\theta, r, w) = \frac{1}{r(k\cos^2\theta + k\sin^2\theta)}(\frac{1}{a_{30}^2kk_1^2k_{30}^3}(r\cos\theta(-a_{12}k_1^2k_{30}^2(a_{30}+k_{30}) r\sin\theta a_{30}^3 - a_{11}(a_{30}^2k_1^2(a_{31}+k_{31})r\sin\theta k_{30}^2 + (a_{20}k_{31} - a_{21}k_{30}) wk_{30} + a_{30}(a_{20}k_{31}w - a_{21}k_{30}w))a_{30} + k_{30}(k_1^2k_{30}r(k_{22}k_{30} + k_{31} (k_{21} - k_1r\cos\theta))\sin\theta a_{30}^3 + k_1^2k_{30}(k_{31}^2 - k^2k_{32})r\sin\theta a_{30}^2 + (-2 a_{31}k_1^2k_{31}r\sin\theta k_{30}^2 - (a_{21}k_{30} - a_{20}k_{31})w(k_{21} - k_1r\cos\theta))a_{30} +k^2(a_{22}k_{30} - a_{20}k_{32})w + a_{31}^2k_1^2k_{30}^3r\sin\theta))) + \frac{1}{a_{30}^5k_1^3k_{30}^3}(r\sin\theta (a_{30}kk_{30}(a_{30}^3k_1(a_{32}k_{30}^2 - a_{31}k_{31}k_{30} + +a_{30}(k_{31}^2 - k_{30}k_{32}))r\cos\theta -\frac{1}{a_{30}k^2k_1^2k_{30}}((a_{30}^2k_{30}r\sin\theta k_1^2 + a_{20}w)(-a_{12}kk_1k_{30}a_{30}^4 + a_{11}(k_1 (kk_{31} + k_1k_{30}r\sin\theta)a_{30}^2 - a_{30}a_{31}kk_1k_{30} + a_{20}w)a_{30}^2 + kk_1k_{30} (a_{30}(2a_{32}k_{30}^2 - 2a_{30}k_{32}k_{30} + a_{30}k_{31}^2) - a_{31}^2k_{30}^2))))k_1^2 + a_{20}w(a_{12} a_{50}k_{30}(a_{30}+k_{30})a_{30}^3 + a_{11}(a_{31}a_{50}k_{30} + a_{51}(a_{30}+k_{30})k_{30} - a_{30} a_{50}k_{31})a_{30}^3 + k_{30}(-a_{31}^2a_{50}k_{30}(k^2+k_{30}) + a_{30}(a_{32}a_{50}k_{30}k^2 + \frac{1}{a_{30}k_1k_{30}} ((a_{51}k_{30} + a_{50}k_{31})(a_{30}^2k_{30}r\sin\theta k_1^2 + a_{20}w)k) - a_{30}a_{50}k_{31}^2 + \frac{1}{kk_{30}} ((-a_{41}k_{30} + a_{61}k_{30} + (a_{60} - a_{40})k_{31})(a_{30}^2k_{30}r\sin\theta k_1^2 + a_{20}w)) -\frac{1}{k}(a_{30}(a_{30}kk_{30}(a_{50}k_{22} + a_{51}(k_{21} - k_1r\cos\theta)) - a_{41}w))) + \frac{1}{a_{30}kk_1} (a_{31}(a_{30}^3(a_{40} - a_{60})k_{30}r\sin\theta k_1^3 + a_{20}a_{30}(a_{40} - a_{60})wk_1 + a_{30}^2k k_{30}(a_{51}k^2 + 2a_{50}(k_{31} - kk_1r\sin\theta))k_1 - 2a_{20}a_{50}k^2w)))))))- \frac{1}{r^3(k\cos^2\theta + k\sin^2\theta)^2}(((\frac{1}{kk_{30}}(a_{11}r\sin\theta a_{30}^2) + \frac{1}{k}(a_{11}r\sin\theta a_{30}) +\frac{1}{k}(k_1r^2\cos\theta\sin\theta a_{30}) - \frac{1}{k}(k_{21}r\sin\theta a_{30}) + \frac{1}{a_{30}^2k_1^2k_{30}^2}(a_{20}kk_{31}w) +\frac{1}{k_{30}}(kk_{31}r\sin\theta) - \frac{a_{21}kw}{a_{30}^2k_1^2k_{30}})r\sin\theta + \frac{1}{a_{30}^5kk_1^4k_{30}^2}(r\cos\theta(a_{11}kk_1^4 k_{30}r\sin\theta a_{30}^6 - kk_1^4k_{30}r\cos\theta(kk_{31} + k_1k_{30}r\sin\theta)a_{30}^5 + k_1(k_{30}^3r^2 \sin^2\theta k_1^4 + a_{31}k^2k_{30}^2r\cos\theta k_1^3 + k(2k_{30}^2k_{31}r\sin\theta k_1^3 + a_{11}a_{20}wk_1 + a_{11}a_{20}a_{50}w))a_{30}^4 + k_1k_{30}(a_{20}w(-(kr\cos\theta + (a_{40} - a_{60})r\sin\theta k_1^2 +a_{11}a_{50}k + a_{50}k(k_1r\cos\theta - k_{21})) - 2a_{31}kk_1^3k_{30}^2r\sin\theta)a_{30}^3 + a_{20} k_1w(a_{50}k_1k_{30}r\sin\theta k^2 + 2k_1k_{30}k_{31}k + a_{40}w + 2k_1^2k_{30}^2r\sin\theta)a_{30}^2 +a_{20}k_1w(a_{31}kk_{30}(a_{50}k^2 - 2k_1k_{30}) + a_{20}(a_{60} - a_{40})w)a_{30} + a_{20}^2 (a_{50}k^2 + k_1k_{30})w^2)))((-\frac{1}{kk_{30}}(a_{11}r\sin\theta a_{30}^2) + \frac{1}{k}(k_{21}r\sin\theta a_{30})- \frac{1}{k}(a_{11}r\sin\theta a_{30}) - \frac{1}{k}(k_1r^2\cos\theta\sin\theta a_{30}) + \frac{1}{a_{30}^2k_1^2k_{30}}(a_{21}kw)-$$

$$
\begin{aligned}
& \frac{1}{k_{30}}(kk_{31}r\sin\theta) - \frac{1}{a_{30}^2k_1^2k_{30}^2}(a_{20}kk_{31}w)r\cos\theta + \frac{1}{a_{30}^5kk_1^4k_{30}^2}(r\sin \\
& \theta(a_{11}kk_1^4k_{30}r\sin\theta a_{30}^6 - kk_1^4k_{30}r\cos\theta(kk_{31} + k_1k_{30}r\sin\theta)a_{30}^5 + \\
& k_1(k_{30}^3r^2\sin^2\theta k_1^4 + a_{31}k^2k_{30}^2r\cos\theta k_1^3 + k(2k_{30}^2k_{31}r\sin\theta k_1^3 + a_{11} \\
& a_{20}wk_1 + a_{11}a_{20}a_{50}w))a_{30}^4 + k_1k_{30}(a_{20}w(-(kr\cos\theta + (a_{40} - a_{60}) \\
& r\sin\theta)k_1^2 + a_{11}a_{50}k + a_{50}k(k_1r\cos\theta - k_{21})) - 2a_{31}kk_1^3k_{30}^2r\sin\theta) \\
& a_{30}^3 + a_{20}k_1w(a_{50}k_1k_{30}r\sin\theta k^2 + 2k_1k_{30}k_{31}k + a_{40}w + 2k_1^2k_{30}^2r \\
& \sin\theta)a_{30}^2 + a_{20}k_1w(a_{31}kk_{30}(a_{50}k^2 - 2k_1k_{30}) + a_{20}(a_{60} - a_{40})w) \\
& a_{30} + a_{20}^2(a_{50}k^2 + k_1k_{30})w^2))))), \\
F_{22}(\theta, r, w) = {} & \frac{1}{a_{30}^3kk_1^2k_{30}r^2(k\sin^2\theta + k\cos^2\theta)^2}(w(a_{11}a_{30}^3a_{50}kk_1(a_{30} + k_{30}) + a_{30} \\
& k_1(a_{20}w(a_{60} - a_{40}) + a_{31}a_{50}k^3k_{30}) + a_{20}a_{50}k^2w + a_{30}^3k_1k_{30}(k_1^2r \\
& (a_{60} - a_{40})\sin\theta + a_{50}k(k_1r\cos\theta - k_{21})) + a_{30}^2k_1(a_{40}w + a_{50}k^2k_1 \\
& k_{30}r\sin\theta))(\frac{1}{a_{30}^5kk_1^4k_{30}^2}(r\cos\theta(a_{30}^4k_1(k(a_{11}a_{20}a_{50}w + a_{11}a_{20}k_1w + \\
& 2k_1^3k_{30}^2k_{31}r\sin\theta) + a_{31}k^2k_1^3k_{30}^2r\cos\theta + k_1^4k_{30}^3r^2\sin^2\theta) + a_{30}^3k_1k_{30} \\
& (a_{20}w(a_{11}a_{50}k + k_1^2(-(r(a_{40} - a_{60})\sin\theta + kr\cos\theta)) + a_{50}k(k_1r \\
& \cos\theta - k_{21})) - 2a_{31}kk_1^3k_{30}^2r\sin\theta) + a_{11}a_{30}^6kk_1^4k_{30}r\sin\theta + a_{20}^2w^2 \\
& (a_{50}k^2 + k_1k_{30}) + a_{20}a_{30}^2k_1w(a_{40}w + a_{50}k^2k_1k_{30}r\sin\theta + 2kk_1k_{30} \\
& k_{31} + 2k_1^2k_{30}^2r\sin\theta) + a_{20}a_{30}k_1w(a_{20}w(a_{60} - a_{40}) + a_{31}kk_{30}(a_{50}k^2 \\
& -2k_1k_{30})) - a_{30}^5kk_1^4k_{30}r\cos\theta(kk_{31} + k_1k_{30}r\sin\theta))) + r\sin\theta(\frac{1}{kk_{30}} \\
& (a_{11}a_{30}^2r\sin\theta) + \frac{1}{k}(a_{11}a_{30}r\sin\theta) + \frac{1}{a_{30}^2k_1^2k_{30}^2}(a_{20}kk_{31}w) - \frac{1}{a_{30}^2k_1^2k_{30}} \\
& (a_{21}kw) + \frac{1}{k}(a_{30}k_1r^2\sin\theta\cos\theta) - \frac{1}{k}(a_{30}k_{21}r\sin\theta) + \frac{1}{k_{30}}(kk_{31}r \\
& \sin\theta)))) - \frac{1}{a_{30}^3k_1k_{30}^2(k\sin^2\theta + k\cos^2\theta)}(w(a_{11}a_{30}^3(-a_{30}a_{50}k_{31} + a_{51} \\
& k_{30}(a_{30} + k_{30}) + a_{31}a_{50}k_{30}) + a_{12}a_{30}^3a_{50}k_{30}(a_{30} + k_{30}) + k_{30}(a_{30} \\
& (\frac{1}{kk_{30}}((k_{31}(a_{60} - a_{40}) - a_{41}k_{30} + a_{61}k_{30})(a_{20}w + a_{30}^2k_1^2k_{30}r\sin\theta)) \\
& +\frac{1}{a_{30}k_1k_{30}}(k(a_{50}k_{31} + a_{51}k_{30})(a_{20}w + a_{30}^2k_1^2k_{30}r\sin\theta)) - \frac{1}{k}(a_{30} \\
& (a_{30}kk_{30}(a_{50}k_{22} + a_{51}(k_{21} - k_1r\cos\theta)) - a_{41}w)) - a_{30}a_{50}k_{31}^2 + \\
& a_{32}a_{50}k^2k_{30}) + \frac{1}{a_{30}kk_1}(a_{31}(a_{20}a_{30}k_1w(a_{40} - a_{60}) - 2a_{20}a_{50}k^2w + \\
& a_{30}^3k_1^3k_{30}r(a_{40} - a_{60})\sin\theta + a_{30}^2kk_1k_{30}(2a_{50}(k_{31} - kk_1r\sin\theta) + \\
& a_{51}k^2))) - a_{31}^2a_{50}k_{30}(k^2 + k_{30}))))).
\end{aligned}
$$

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- **الملخص:**

الهدف من هذه المذكرة هو دراسة تشعبات هوبف الصفرية لنوعين من النماذج البيولوجية، حيث ركزنا على ايجاد عدد الحلول الدورية المعزولة لهذه الانظمة التفاضلية باستخدام نظرية المتوسط من الرتبة الاولى والثانية.

- **الكلمات المفتاحية:**

نقطة التوازن، نموذج الملاريا، نموذج نمو الورم السرطاني، نظرية حساب المتوسط.

- **Abstract:**

The objective of this memory is to study the Zero-Hopf Bifurcation of two types of biological models, where we focus on finding the number of isolated periodic solutions for there corresponding differential systems by using the averaging theory of first and second order.

- **Keywords:**

Equilibrium point, Malaria model, Tumor Growth Cancer model, Averaging theory.

- **Résumé :**

L'objectif de ce mémoire est d'étudier la Bifurcation Zéro-Hopf de deux types de modèles biologiques, ou nous sommes intéressé sur la recherche du nombre de solutions périodiques isolées pour les systèmes différentiels correspondants en utilisant la méthode de moyennisation du premier et du second degré.

- **Mots clés :**

Point d'équilibre, Modèle de Malaria, Modèle du Cancer de la croissance tumorale, Théorie de la moyennisation.