PERIODIC SOLUTIONS OF A TUMOR-IMMUNE SYSTEM INTERACTION UNDER A PERIODIC IMMUNOTHERAPY

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ABSTRACT. In this paper, we consider a mathematical model of a tumor-immune system interaction when a periodic immunotherapy treatment is applied. We give sufficient conditions, using averaging theory, for the existence and stability of periodic solutions in such system as a function of the six parameters associated to this problem. Finally, we provide examples where our results are applied.

1. Introduction and statements of the main result. Cancer is one of the leading causes of death. There are several treatments such as radiotherapy, chemotherapy, immunotherapy and surgery. Radiation therapy (also called radiotherapy) is a cancer treatment that uses high doses of radiation to kill cancer cells and shrink tumors [6]. Chemotherapy treatment is a systematic therapy that fights and kills both the residual cancer cells in a tumor site and the migrated tumor cells in other parts of the body [4]. Immunotherapy consists of stimulating the immune system to fight better and hopefully eradicate cancer [3]. In this work we focus on the mathematical model be considering immunotherapy treatment.

In [7], Sotolongo-Costa et al. proposed the following model for the interaction between malignant cells \( x(t) \) and lymphocyte cells \( y(t) \),

\[
\begin{align*}
\dot{x} &= ax - bxy, \\
\dot{y} &= dxy - fy - \kappa x + u + F \cos^2(\omega t).
\end{align*}
\]  

(1)

For the malignant cells, it is assumed a growth rate proportional to \( x \) and the rate of death is proportional to the interaction rate between the malignant cells and the lymphocytes. The growth rate of lymphocytes is proportional to the interaction with malignant cells and also to the flux per unit time of lymphocytes to the place of interaction. This last term characterizes the diffusion process of lymphocytes that takes place in the surroundings of the tumor assuming a constant lymphocytes flux. The decrease rate depends on two factors, natural death and growth of malignant cells related to the effective area of tumor interacting directly with the lymphocytes. In order to introduce the effects produced by the treatment with cytokines...
(a type of immunotherapy) in the process of activation of the immune system, a periodic function is added which imitates the periodic dosage. For this purpose it is proposed the function \( F \cos^2(\omega t) \), where \( \omega \) is the frequency of the periodic behavior for cytokines inside the body.

Inspired by the previous model and other models, A. d’Onofrio suggested in [2] a general family of models including this consideration (a general influx function in the immune system), and other biologically reasonable models based on

\[
\begin{align*}
\dot{x} &= x(\xi(x) - \phi(x)y), \\
\dot{y} &= \beta(x)y - \mu(x)y + \sigma g(x) + \theta(\omega t),
\end{align*}
\]

(2)

where \( x \) and \( y \) are variables interpreted as in the Sotolongo model. The biological meaning of the functions appearing are summarized in Table 1. Depending on the function \( \Psi(x) = \mu(x) - \beta(x) \), a cancer can be classified by its degree of aggressiveness against the immune system (see [3, p. 616]): if \( \Psi(x) > 0 \) the cancer is considered highly aggressive; otherwise, if \( \Psi(x) \) changes of sign, it is lowly aggressive.

The objective of this paper is to study the existence of periodic solutions in the particular case of (2) associated to the model

\[
\begin{align*}
\dot{x} &= ax - bxy, \\
\dot{y} &= dxy - f y - \kappa xy + \sigma g(x) + \theta(\omega t),
\end{align*}
\]

(3)

where \( \theta(\omega t) \) is a \( T \)-periodic therapy (that is, \( \theta(\omega t) \) represents the effect produced by the periodic dosage of immunotherapy) and \( g : [0, +\infty) \rightarrow (0, +\infty) \) is a decreasing function satisfying

\[
g(0) = 1, \quad \lim_{x \rightarrow +\infty} g(x) = 0.
\]

(4)

In this model it is assumed that the function \( g(x) \) satisfies \( g'(x) < 0 \) (so it is decreasing) because when the tumor grows the influx of immune cells decreases.

The parameters and their biological meaning of system (3) are summarized in Table 2.

| Functions | Biological meaning |
|-----------|-------------------|
| \( \xi(x) \) | Growth rate of the tumor |
| \( \phi(x)y \) | Functional response |
| \( g(x) \) | External inflow of effector cells |
| \( \beta(x) \) | Tumor-stimulated proliferation rate of effector cells |
| \( \mu(x) \) | Tumor-induced loss of effector cells |
| \( \sigma g(x) \) | Influx of effector cells |
| \( \theta(\omega t) \) | Immunotherapy |

Table 1. Definition of the parameters in model (2).
Table 2. Definition of the parameters in model (3).

| Parameter | Biological meaning |
|-----------|---------------------|
| \(a\)    | Intrinsic growth rate of the tumor |
| \(b\)    | Death malignant cells rate due to interaction with lymphocyte cells |
| \(d\)    | Increased lymphocyte rate due to interaction with malignant cells |
| \(f\)    | Death rate of the lymphocytes |
| \(\kappa\) | Immunosuppression coefficient |
| \(\sigma g(x)\) | Influx external of effector cells |
| \(\omega\) | Immunotherapy dosage frequency |

A summary of the averaging theory of first order which are necessary in order to get our results are given in the Appendix. Taking into account Theorem 5.1 of the Appendix, the stability or instability of the periodic orbits found in Theorems 2.1, 2.2, 2.3, 2.4, 2.5 and 2.6 can be determined by studying the eigenvalues of a convenient matrix which appears in the proof of both theorems.

2. Statement of the main results. First, we perform the following general rescaling of variables, parameters and function \(\theta\), as follows

\[
\begin{align*}
X &= \epsilon^{-m_1} x, \quad Y = \epsilon^{-m_2} y, \quad A = \epsilon^{-n_1} a, \quad B = \epsilon^{-n_2} b, \quad D = \epsilon^{-n_3} d, \\
K &= \epsilon^{-n_4} \kappa, \quad F = \epsilon^{-n_5} f, \quad S = \epsilon^{-n_7} \sigma, \quad \beta(t) = \epsilon^{-n_6} \theta(\omega t),
\end{align*}
\]

where \(m_1, m_2, n_1, n_2, n_3, n_4, n_5, \text{ and } n_6\) are integers that will be conveniently chosen, while \(\epsilon\) is a positive small parameter. The differential system (3) in the new variables \((X, Y)\) can be written as

\[
\begin{align*}
\dot{X} &= \epsilon (\epsilon^{n_1-1} AX - \epsilon^{n_2+m_2-1} BXY), \\
\dot{Y} &= \epsilon (-\epsilon^{n_5-1} FY + \epsilon^{n_3+m_1-1} DXY - \epsilon^{n_4+m_1-1} KXY + \\
&\quad \epsilon^{n_7-m_2-1} S g(\epsilon^{m_1} X) + \epsilon^{n_6-m_2-1} \beta(t)).
\end{align*}
\]

We must assume that \(n_1 - 1 \geq 0, n_2 + m_2 - 1 \geq 0, n_5 - 1 \geq 0, n_3 + m_1 - 1 \geq 0, n_4 + m_1 - 1 \geq 0, n_7 - m_2 - 1 \geq 0 \text{ and } n_6 - m_2 - 1 \geq 0.\)
Next, let $\overline{\theta}$, $\overline{\beta}$ be the averaged values of functions $\theta(\omega t)$ and $\beta(t)$, respectively, i.e.,
\[
\overline{\theta} = \frac{1}{T} \int_{0}^{T} \theta(\omega t) dt \quad \text{and} \quad \overline{\beta} = \frac{1}{T} \int_{0}^{T} \beta(t) dt.
\]
Now, we are in position to apply the Averaging Theorem of first order to the system (6).

Before formulating our main results, we introduce the real function
\[
\delta(t) = \frac{a}{b} - \frac{1}{T} \int_{0}^{T} \int_{s}^{t} (\theta(\omega r) - \overline{\theta}) dr ds + \int_{0}^{t} (\theta(\omega s) - \overline{\theta}) ds, \quad t > 0.
\]
Throughout this paper, we assume that $\delta(t) \geq 0$, for all $t > 0$.

**Theorem 2.1.** Assume that $d - \kappa > \frac{b}{a} \sigma g'(x_*)$, $0 < \frac{\sigma}{\kappa} - \frac{b}{a} < 1$, where $x_*$ satisfies $g(x_*) = \frac{a}{b} x_* - \frac{b}{a} f(x_*)$ and $(a, b, d, f, \kappa, \sigma, \theta(\omega t)) = (\epsilon A, \epsilon^2 B, \epsilon^2 D, \epsilon F, \epsilon^2 K, \beta(t))$, then for $\epsilon > 0$ sufficiently small, the model (3) has one unstable $T$–periodic solution $(x(t, \epsilon), y(t, \epsilon))$ such that
\[
\begin{align*}
x(t, \epsilon) &= \left(1 + \frac{(\kappa - d)a}{b \sigma g'(x_*)}\right) x_* + O(\epsilon^2), \\
y(t, \epsilon) &= \delta(t) + O(\epsilon).
\end{align*}
\]

In this theorem we have the necessary condition $d - \kappa > \frac{b}{a} \sigma g'(x_*)$ for the existence of the periodic solution. If $d - \kappa > 0$ (the effector cell growth rate must exceed the death rate) the previous condition is automatically satisfied.

**Theorem 2.2.** Assume that $0 < \frac{\sigma}{\kappa} x_* - \frac{b}{a} < 1$, $g'(x_*) < \frac{\sigma}{\kappa} + \frac{a}{b \sigma x_*} (dx_* - f)$, where $x_*$ satisfies $g(x_*) = \frac{a}{b} x_* - \frac{b}{a} f(x_*)$ and $(a, b, d, f, \kappa, \sigma, \theta(\omega t)) = (\epsilon A, \epsilon^2 B, \epsilon^2 D, \epsilon F, \epsilon^2 K, \beta(t))$, then for $\epsilon > 0$ sufficiently small, the model (3) has one unstable $T$–periodic solution $(x(t, \epsilon), y(t, \epsilon))$ such that
\[
\begin{align*}
x(t, \epsilon) &= x_* + \frac{a(dx_* - f)}{\kappa a - b \sigma g'(x_*)} + O(\epsilon^2), \\
y(t, \epsilon) &= \delta(t) + O(\epsilon).
\end{align*}
\]

We point out that Theorem 2.2 does not have the conditions on $d - \kappa$ as Theorem 2.1.

**Theorem 2.3.** Assume that $-\frac{\kappa a}{b^2} x_* < \frac{af}{b^2} - \frac{b}{a} < 1 - \frac{\kappa a}{b^2} x_*$, where $x_*$ is such that $g(x_*) = \frac{a}{b} x_* + \frac{af}{b^2} - \frac{b}{a} f(x_*)$ and $(a, b, d, f, \kappa, \sigma, \theta(\omega t)) = (\epsilon A, \epsilon^2 B, \epsilon^2 D, \epsilon F, \epsilon^2 K, \beta(t))$, then for $\epsilon > 0$ sufficiently small, the model (3) has one unstable $T$–periodic solution $(x(t, \epsilon), y(t, \epsilon))$ such that
\[
\begin{align*}
x(t, \epsilon) &= x_* + \frac{adx_*}{\kappa a - b \sigma g'(x_*)} + O(\epsilon^2), \\
y(t, \epsilon) &= \delta(t) + O(\epsilon).
\end{align*}
\]

A next result is as follows.
Theorem 2.4. Assume that $0 < \max \left\{ \frac{b\sigma + \frac{f}{a}}{a\sigma - \frac{\theta}{\sigma}}, \frac{b\sigma}{a\sigma - \frac{\theta}{\sigma}} \right\} < \kappa - d < \frac{b\sigma}{a\sigma - \frac{\theta}{\sigma}}(1 + \frac{\gamma}{\sigma})$, where $x_*$ satisfies $g(x_*) = \frac{a\sigma}{a\sigma - \frac{\theta}{\sigma}}(\kappa - d)x_* - \frac{\theta}{\sigma}$ and $(a, b, d, f, \kappa, \sigma, \theta(\omega t)) = (eA, \epsilon^2B, \epsilon D, \epsilon^2F, \epsilon K, S, \beta(t))$, then for $\epsilon > 0$ sufficiently small, the model (3) has one unstable $T$-periodic solution $(x(t, \epsilon), y(t, \epsilon))$ such that
\[
x(t, \epsilon) = x_* + \frac{af}{a(d - \kappa) + b\sigma g'(x_*)} + O(\epsilon^2),
\]
\[
y(t, \epsilon) = \delta(t) + O(\epsilon),
\] (11)

In the previous theorem we observe that the condition $d - \kappa < 0$ is necessary for the existence of the periodic solution, that is, the effector cell growth rate must not exceed the death rate.

Theorem 2.5. i) If $\frac{b\sigma}{a\sigma - \frac{\theta}{\sigma}}(\frac{a\sigma}{a\sigma - \frac{\theta}{\sigma}} - \frac{d}{\sigma}) < d - \kappa < 0$, where $x_*$ satisfies $g(x_*) = (\kappa - d)(\frac{a\sigma}{a\sigma - \frac{\theta}{\sigma}}x_* + \frac{\theta}{\sigma}) - \frac{\theta}{\sigma}$ and $(a, b, d, f, \kappa, \sigma, \theta(\omega t)) = (eA, \epsilon^2B, \epsilon D, \epsilon^2F, \epsilon K, S, \beta(t))$, then for $\epsilon > 0$ sufficiently small, the model (3) has one unstable $T$-periodic solution $(x(t, \epsilon), y(t, \epsilon))$ such that
\[
x(t, \epsilon) = x_* + O(\epsilon^2),
\]
\[
y(t, \epsilon) = \delta(t) + O(\epsilon).
\] (12)

ii) If $0 < \frac{b\sigma}{a\sigma - \frac{\theta}{\sigma}}(\frac{a\sigma}{a\sigma - \frac{\theta}{\sigma}} - \frac{d}{\sigma}) < d - \kappa < \min\left\{ \frac{b\sigma}{a\sigma - \frac{\theta}{\sigma}}(\frac{a\sigma}{a\sigma - \frac{\theta}{\sigma}} - \frac{\theta}{\sigma}), -\frac{b\sigma g'(x_*)}{\sigma} \right\}$, where $x_*$ satisfies $g(x_*) = (\kappa - d)(\frac{a\sigma}{a\sigma - \frac{\theta}{\sigma}}x_* + \frac{\theta}{\sigma}) - \frac{\theta}{\sigma}$ and $(a, b, d, f, \kappa, \sigma, \theta(\omega t)) = (eA, \epsilon^2B, \epsilon D, \epsilon^2F, \epsilon K, S, \beta(t))$, then for $\epsilon > 0$ sufficiently small, the model (3) has one asymptotically stable $T$-periodic solution $(x(t, \epsilon), y(t, \epsilon))$ such that
\[
x(t, \epsilon) = x_* + O(\epsilon^2),
\]
\[
y(t, \epsilon) = \delta(t) + O(\epsilon).
\] (13)

iii) If $-\frac{b\sigma g'(x_2)}{\sigma} > d - \kappa < \min\left\{ -\frac{b\sigma g'(x_1)}{\sigma}, \frac{b\sigma}{a\sigma - \frac{\theta}{\sigma}}(\frac{a\sigma}{a\sigma - \frac{\theta}{\sigma}} - \frac{\theta}{\sigma}) \right\}$, $0 < \frac{a\sigma}{a\sigma - \frac{\theta}{\sigma}} < 1$, where $x_1$ and $x_2$ satisfies $g(x_{1,2}) = (\kappa - d)(\frac{a\sigma}{a\sigma - \frac{\theta}{\sigma}}x_{1,2} + \frac{\theta}{\sigma}) - \frac{\theta}{\sigma}$ and $(a, b, d, f, \kappa, \sigma, \theta(\omega t)) = (eA, \epsilon^2B, \epsilon D, \epsilon^2F, \epsilon K, S, \beta(t))$, then for $\epsilon > 0$ sufficiently small, the model (3) has two $T$-periodic solutions; the first one $(x_1(t, \epsilon), y_1(t, \epsilon))$ is unstable and has the form
\[
x_1(t, \epsilon) = x_1 + O(\epsilon^2),
\]
\[
y_1(t, \epsilon) = \delta(t) + O(\epsilon).
\] (14)
The second solution $(x_2(t, \epsilon), y_2(t, \epsilon))$ is asymptotically stable and has the form
\[
x_2(t, \epsilon) = x_2 + O(\epsilon^2),
\]
\[
y_2(t, \epsilon) = \delta(t) + O(\epsilon).
\] (15)

Another result is the following.

Theorem 2.6. i) If $0 < \frac{\Delta}{b_0}x_* < \frac{a\sigma}{a\sigma - \frac{\theta}{\sigma}} < 1 + \frac{a\sigma}{a\sigma - \frac{\theta}{\sigma}}x_* < \frac{a\sigma}{a\sigma - \frac{\theta}{\sigma}}(1 + \frac{\gamma}{\sigma})$, where $x_*$ satisfies $g(x_*) = -\frac{b\sigma}{a\sigma - \frac{\theta}{\sigma}}x_* + \frac{\theta}{\sigma}$ and $(a, b, d, f, \kappa, \sigma, \theta(\omega t)) = (eA, \epsilon^2B, \epsilon D, \epsilon^2F, \epsilon K, S, \beta(t))$, then for $\epsilon > 0$ sufficiently small, the model (3) has one asymptotically stable $T$-periodic solution $(x(t, \epsilon), y(t, \epsilon))$ such that
\[
x(t, \epsilon) = \left(1 + \frac{\sigma g'(x_*)}{a\sigma + \frac{b\sigma g'(x_*)}{a\sigma + \theta}}\right)x_* + O(\epsilon^2),
\]
\[
y(t, \epsilon) = \delta(t) + O(\epsilon).
\] (16)
ii) If \( \max\{\frac{da}{bσ}x_{1,2}, 1\} < \frac{af}{bσ} - \frac{b}{σ} < 1 + \frac{da}{bσ}x_{1,2}, g'(x_1) < -\frac{ad}{bσ} < g'(x_2) < -\frac{ad}{bσ} + \frac{(\epsilon f + da)x_2^2}{4bσx_1} \) where \( x_1 \) and \( x_2 \) satisfies \( g(x_{1,2}) = -\frac{da}{bσ}x_{1,2} + \frac{af}{bσ} - \frac{b}{σ} \) and \((a, b, d, f, κ, σ, \theta(ωt)) = (ϵA, ϵ^2B, ϵD, ϵF, ϵ^2K, S, β(t))\), then for \( ϵ > 0 \) sufficiently small, the model (3) has two \( T \)-periodic solutions; the first one \((x_1(τ, ϵ), y_1(τ, ϵ))\) is unstable and has the form

\[
\begin{align*}
x_1(τ, ϵ) &= \left(1 + \frac{αn}{ad + bσg'(x_2)}\right)x_1 + O(ϵ^2), \\
y_1(τ, ϵ) &= δ(t) + O(ϵ).
\end{align*}
\]

The second solution \((x_2(τ, ϵ), y_2(τ, ϵ))\) is asymptotically stable and has the form

\[
\begin{align*}
x_2(τ, ϵ) &= \left(1 + \frac{αn}{ad + bσg'(x_2)}\right)x_2 + O(ϵ^2), \\
y_2(τ, ϵ) &= δ(t) + O(ϵ).
\end{align*}
\]

3. Proofs of theorems.

Proof of Theorem 2.1 Here we take \( m_1 = 0, m_2 = -1, n_1 = 1, n_2 = 2, n_3 = 2, n_4 = 2, n_5 = 1, n_6 = 0 \) and \( n_7 = 0 \). Then the system (3) in the new variables \((X, Y)\) becomes

\[
\begin{align*}
\dot{X} &= ϵ(A - BY)X, \\
\dot{Y} &= ϵ(-FY + Sg(X) + β(t)) + ϵ^2(D - K)XY.
\end{align*}
\]

Note that the system (19) is in the formal form for applying the averaging theory of first order (see Appendix). The averaged system of the system (19) is

\[
\begin{align*}
\dot{X} &= ϵf_{11}(X, Y) = ϵ(A - BY)X, \\
\dot{Y} &= ϵf_{12}(X, Y) = ϵ(-FY + Sg(X) + β).
\end{align*}
\]

This system has one equilibrium point, namely \((X_*, Y_*)\), with \( Y_* = \frac{A}{B} \) and \( X_* \) is such that \( g(X_*) = \frac{F}{B} - \frac{ω}{σ} \), which exists by the assumptions.

To guarantee the existence of periodic solutions associated to this equilibrium point \((X_*, Y_*)\) for the system (19), using Theorem 5.1, we need that the Jacobian of \( f_0 = (f_{11}, f_{12}) \) at \((X_*, Y_*)\) is nonzero. In this case it is verified that

\[
J = \begin{pmatrix}
0 & -BX_* \\
Sg'(X_*) & -F
\end{pmatrix},
\]

then

\[
\det J = BSX_*g'(X_*) \neq 0.
\]

Since the eigenvalues of \( J \) are

\[
λ_± = \frac{-F ± \sqrt{F^2 - 4BSX_*g'(X_*)}}{2},
\]

and \( g'(X) < 0 \) it easily follows that the eigenvalues are real and have different signs. Therefore, for \( ϵ \) sufficiently small, the system (19) has one unstable \( T \)-periodic solution \((X(τ, ϵ), Y(τ, ϵ))\) such that \((X(0, ϵ), Y(0, ϵ)) = (X_*, Y_*) + O(ϵ)\).

Next, we are going to go back through the rescaling (5). In fact, first we observe that

\[
(x(τ, ϵ) = X(τ, ϵ), \quad y(τ, ϵ) = \frac{1}{ϵ}Y(τ, ϵ)),
\]

for \( ϵ > 0 \). Obviously, it is a \( T \)-periodic solution of (3) with parameters \( a = ϵA, b = ϵ^2B, d = ϵ^2D, κ = ϵ^2K, f = ϵF \) and \( σ = S \).

Now, our objective is to verify that the previous periodic solution is in the first quadrant, for all \( t ∈ ℝ \), for \( ϵ > 0 \) sufficiently small. For this purpose, we need to get
a sharp approximation of this periodic solution, which will be obtained by using the analysis done in the Appendix, more precisely, we use the approximation described in (57). First, we need to compute the functions \( f_0(X, Y) \), \( \omega_0(t, (X, Y)) \), \( f_1(X, Y) \) and \( \eta_1 \).

It is clear that \( f_0 = (f_{11}, f_{12}) \) is defined as in (20), and using (49) we get
\[
\omega_0(t, (X, Y)) = \left( 0, \int_0^t (\beta(s) - \beta)ds \right),
\]
so \( \omega_0(t, (X, Y)) = \omega_0(t, (X, Y)) \).

To determine \( f_1(X, Y) \), we compute first \( \rho \) by using (51) we obtain
\[
\rho(t, (X, Y)) = \left( -BX \int_0^t (\beta(s) - \beta)ds, -F \int_0^t (\beta(s) - \beta)ds + (D - K)XY \right).
\]
Thus, considering equation (50) we arrive to
\[
f_1(X, Y) = \left( -\frac{BX}{T} \int_0^T \int_0^t (\beta(r) - \beta)drds, -\frac{F}{T} \int_0^T \int_0^t (\beta(r) - \beta)drds + (D - K)XY \right).
\]
Now, using equation (56) and substituting the involved functions, we obtain that
\[
\eta_1 = \left( \frac{-(D - K)AX_*}{BSg'(X_*)}, \frac{1}{T} \int_0^T \int_0^t (\beta(r) - \beta)drds \right).
\]
Substituting all the previous computations in (57) we have
\[
X(t, \epsilon) = X_* + \epsilon \left[ \frac{-(D - K)AX_*}{BSg'(X_*)} \right] + O(\epsilon^2),
\]
\[
Y(t, \epsilon) = Y_* + \epsilon \left[ -\frac{1}{T} \int_0^T \int_0^t (\beta(r) - \beta)drds + \int_0^t (\beta(s) - \beta)ds \right] + O(\epsilon^2),
\]
and coming back, we obtain the following approximation of the \( T \)-periodic solution of the system (3),
\[
x(t, \epsilon) = \left( 1 + \frac{(\kappa - d)\alpha}{\beta g'(\alpha)} \right) x_* + O(\epsilon^2),
\]
\[
y(t, \epsilon) = \frac{\alpha}{b} - \frac{1}{T} \int_0^T \int_0^t (\theta(ws) - \beta)drds + \int_0^t (\theta(ws) - \beta)ds + O(\epsilon).
\]
Therefore, by hypotheses we conclude that, for \( \epsilon > 0 \) sufficiently small, \( x(t, \epsilon) > 0 \) and \( y(t, \epsilon) > 0 \), and we conclude the proof.

\( \square \)

**Proof of Theorem 2.2.** Here we take \( m_1 = 0, m_2 = -1, n_1 = 1, n_2 = 2, n_3 = 2, n_4 = 1, n_5 = 2, n_6 = 0 \) and \( n_7 = 0 \). Then the system (3) in the new variables \((X, Y)\) becomes
\[
\dot{X} = \epsilon(A - BY)X,
\]
\[
\dot{Y} = \epsilon(-KXY + Sg(X) + \beta(t)) + \epsilon^2(DX - F)Y.
\]
The system (21) is in the formal form for applying the averaging theory of first order (see the Appendix). The averaged system of the system (21) is
\[
\dot{X} = \epsilon f_{11}(X, Y) = \epsilon(A - BY)X,
\]
\[
\dot{Y} = \epsilon f_{12}(X, Y) = \epsilon(-KXY + Sg(X) + \beta).
\]
This system has one equilibrium point, namely \((X_*, Y_*)\), with \( Y_* = \frac{b}{\beta} \) and \( X_* \) is such that \( g(X_*) = \frac{KA}{BS}X_* - \frac{\beta}{\beta} \) (see Figure 1), which exists by the assumptions. For the existence of periodic solutions associated to the equilibrium point \((X_*, Y_*)\) of system
(21), according Theorem 5.1, we must have that the Jacobian of $f_0 = (f_{11}, f_{12})$ at $(X_*, Y_*)$ is nonzero. In fact, it is verified that

$$J = \begin{pmatrix} 0 & -BX_* \\ S g'(X_*) - \frac{KA}{B} & -K X_* \end{pmatrix},$$

then

$$\det J = X_* (BS g'(X_*) - KA) \neq 0.$$ 

The eigenvalues of $J$ are

$$\lambda_{\pm} = \frac{-K X_* \pm \sqrt{(K X_*)^2 - 4X_* (BS g'(X_*) - KA)}}{2},$$

and since $BS g'(X_*) - KA < 0$ it easily follows that the eigenvalues are real and have different signs. Therefore, for $\epsilon$ sufficiently small, the system (21) has one unstable $T$-periodic solution $(X(t, \epsilon), Y(t, \epsilon))$ such that $(X(0, \epsilon), Y(0, \epsilon)) = (X_*, Y_*) + O(\epsilon)$.

Next, we go back through the rescaling (5). In fact, first we observe that

$$x(t, \epsilon) = X(t, \epsilon), \quad y(t, \epsilon) = \frac{1}{\epsilon} Y(t, \epsilon)$$

for $\epsilon > 0$. Obviously, it is a $T-$periodic solution of (3) with parameters $a = \epsilon A, b = \epsilon^2 B, d = \epsilon^2 D, \kappa = \epsilon K, f = \epsilon^2 F$ and $\sigma = S$.

Now, our objective is to verify that the previous periodic solution is in the first quadrant, for all $t \in \mathbb{R}$, for $\epsilon > 0$ sufficiently small. For this purpose, we need to get a sharp approximation of this periodic solution, which will be obtained by using the analysis done in the Appendix, more precisely, we use the approximation described in (57). First, we need to compute the functions $f_0(X, Y), w_0(t, (X, Y)), f_1(X, Y)$ and $\eta_1$.

In this case $f_0 = (f_{11}, f_{12})$ is defined by (22), and considering (49) we have

$$w_0(t, (X, Y)) = \left(0, \int_0^t (\beta(s) - \overline{\beta}) ds\right),$$

and $w_0(t, (X_*, Y_*)) = w_0(t, (X_*, Y_*))$.

To determine $f_1(X, Y)$, we compute first $\rho$ by using (51) and so

$$\rho(t, (X, Y)) = \left(-BX \int_0^t (\beta(s) - \overline{\beta}) ds, -K X \int_0^t (\beta(s) - \overline{\beta}) ds + (DX - F) Y\right).$$
Thus, considering the equation (50) we arrive to
\[
f_1(X, Y) = \left( -\frac{BX}{T} \int_0^T \int_0^\epsilon (\beta(r) - \overline{\beta}) dr ds, -\frac{KX}{T} \int_0^T \int_0^\epsilon (\beta(r) - \overline{\beta}) dr ds + (DX - F) Y \right)
\]

Now, using equation (56) and substituting the involved functions, we obtain that
\[
\eta = \left( -\frac{A(DX_\ast - F)}{KA - BSg'(X_\ast)}, -\frac{1}{T} \int_0^T \int_0^\epsilon (\beta(r) - \overline{\beta}) dr ds \right).
\]
Substituting all the previous computations in (57) we have
\[
X(t, \epsilon) = X_\ast + \epsilon \left[ -\frac{A(DX_\ast - F)}{KA - BSg'(X_\ast)} \right] + O(\epsilon^2),
\]
\[
Y(t, \epsilon) = Y_\ast + \epsilon \left[ -\frac{1}{T} \int_0^T \int_0^\epsilon (\beta(r) - \overline{\beta}) dr ds + \int_0^t (\beta(s) - \overline{\beta}) ds \right] + O(\epsilon^2),
\]
and coming back, we obtain the following approximation of the \(T\)-periodic solution of the system (3)
\[
x(t, \epsilon) = x_\ast + \frac{a(dx_\ast - f)}{\kappa a - bs g'(x_\ast)} + O(\epsilon^2),
\]
\[
y(t, \epsilon) = \frac{a}{b} - \frac{1}{T} \int_0^T \int_0^\epsilon (\theta(\omega r) - \overline{\theta}) dr ds + \int_0^t (\theta(\omega s) - \overline{\theta}) ds + O(\epsilon).
\]
Therefore, by hypotheses we conclude that for \(\epsilon > 0\) sufficiently small, \(x(t, \epsilon) > 0\) and \(y(t, \epsilon) > 0\), and we conclude the proof.

**Proof of Theorem 2.3.** Here we take \(m_1 = 0, m_2 = -1, n_1 = 1, n_2 = 2, n_3 = 2, n_4 = 1, n_5 = 1, n_6 = 0\) and \(n_7 = 0\). Then the system (3) in the new variables \((X, Y)\) becomes
\[
\dot{X} = \epsilon (A - BY) X,
\]
\[
\dot{Y} = \epsilon (-FY - KXY + Sg(X) + \beta(t)) + \epsilon^2 (DXY).
\]  

(24)

The system (24) is in the formal form for applying the averaging theory of first order (see the Appendix). The averaged system of the system (24) is
\[
\dot{X} = \epsilon f_{11}(X, Y) = \epsilon (A - BY) X,
\]
\[
\dot{Y} = \epsilon f_{12}(X, Y) = \epsilon (-FY - KXY + Sg(X) + \overline{\beta}).
\]  

(25)

This system has one equilibrium point, namely \((X_\ast, Y_\ast)\), with \(Y_\ast = \frac{A}{B}\) and \(X_\ast\) is such that \(g(X_\ast) = \frac{KA}{BS} X_\ast + \frac{FA}{BS} - \frac{\overline{\beta}}{B}\) (see Figure 2), which exists by assumptions. As previously, the equilibrium point \((X_\ast, Y_\ast)\) gives rise to a periodic solution if the Jacobian of \(f_0 = (f_{11}, f_{12})\) at \((X_\ast, Y_\ast)\) is nonzero. In this case we have
\[
\begin{pmatrix}
0 & -BX_\ast \\
Sg'(X_\ast) - \frac{KA}{B} & -F - KX_\ast
\end{pmatrix},
\]  

(26)

consequently,
\[
J = X_\ast (BSg'(X_\ast) - KA) \neq 0.
\]

The eigenvalues of \(J\) are can be easily calculated and are
\[
\lambda_{\pm} = \frac{-F - KX_\ast \pm \sqrt{(-F - KX_\ast)^2 - 4X_\ast (BSg'(X_\ast) - KA)}}{2}
\]
and since \(BSg'(X_\ast) - KA < 0\), the eigenvalues are real and have different signs. Therefore, for \(\epsilon\) sufficiently small, the system (24) has one unstable \(T\)-periodic solution \((X(t, \epsilon), Y(t, \epsilon))\) such that \((X(0, \epsilon), Y(0, \epsilon)) = (X_\ast, Y_\ast) + O(\epsilon)\).
Next, we go back through the rescaling (5). In fact, first we observe that

\[(x(t, \epsilon) = X(t, \epsilon), \quad y(t, \epsilon) = \frac{1}{\epsilon} Y(t, \epsilon))\]

for \( \epsilon > 0 \). Obviously, it is a \( T \)-periodic solution of (3) with parameters \( a = \epsilon A \), \( b = \epsilon^2 B \), \( d = \epsilon^2 D \), \( \kappa = \epsilon K \), \( f = \epsilon F \) and \( \sigma = S \).

Now, we need to get a sharp approximation of this periodic solution, which will be obtained by using the analysis done in the Appendix, more precisely, we use the approximation described in (57). First, we need to compute the functions \( f_0(X,Y), w_0(t,(X,Y)), f_1(X,Y) \) and \( \eta_1 \).

Since \( f_0(X,Y) = (f_{11},f_{12}) \) is as in (25), by (49) we get

\[ w_0(t,(X,Y)) = \left(0, \int_0^t (\beta(s) - \overline{\beta}) ds\right) \]

so \( w_0(t,(X_*,Y_*)) = w_0(t,(X_*,Y_*)) \).

To determine \( f_1(X,Y) \), we compute first \( \rho \) by using (51) and so

\[ \rho(t,(X,Y)) = \left(-BX \int_0^t (\beta(s) - \overline{\beta}) ds, -(F + KX) \int_0^t (\beta(s) - \overline{\beta}) ds + DXY\right). \]

Thus, by considering the equation (50) we arrive to

\[ f_1(X,Y) = \left(-BX \int_0^T \int_0^s (\beta(r) - \overline{\beta}) dr ds, -(F + KX) \int_0^T \int_0^s (\beta(r) - \overline{\beta}) dr ds + DXY\right). \]

Now, using equation (56) and substituting the involved functions, we obtain that

\[ \eta_1 = \left(\frac{ADX_*}{KA - BSg'(X_*)} - \frac{1}{T} \int_0^T \int_0^s (\beta(r) - \overline{\beta}) dr ds\right). \]

Substituting all the previous computations in (57) we have

\[ X(t, \epsilon) = X_* + \epsilon \left[\frac{ADX_*}{KA - BSg'(X_*)}\right] + O(\epsilon^2), \]

\[ Y(t, \epsilon) = Y_* + \epsilon \left[-\frac{1}{T} \int_0^T \int_0^s (\beta(r) - \overline{\beta}) dr ds + \int_0^t (\beta(s) - \overline{\beta}) ds\right] + O(\epsilon^2), \]

and coming back, we obtain the following approximation of the \( T \)-periodic solution of the system (3).
\[ x(t, \epsilon) = x_* + \frac{adx_*}{\kappa a - bg'(x_*)} + O(\epsilon^2), \]
\[ y(t, \epsilon) = \frac{a}{b} - \frac{1}{T} \int_0^T \int_0^s (\theta(\omega r) - \bar{\theta}) dr ds + \int_0^t (\theta(\omega s) - \bar{\theta}) ds + O(\epsilon). \]

Therefore, by hypotheses we conclude that, for \( \epsilon > 0 \) sufficiently small, \( x(t, \epsilon) > 0 \) and \( y(t, \epsilon) > 0 \), and we conclude the proof.

**Proof of Theorem 2.4.** Here we take \( m_1 = 0, m_2 = -1, n_1 = 1, n_2 = 2, n_3 = 1, n_4 = 1, n_5 = 2, n_6 = 0 \) and \( n_7 = 0 \). Then the system (3) in the new variables \((X, Y)\) becomes

\[
\begin{align*}
\dot{X} &= \epsilon (A - BY)X, \\
\dot{Y} &= \epsilon (DXY - KXY + S g(X) + \beta(t)) + \epsilon^2 (FY).
\end{align*}
\] (27)

The system (27) is in the formal form for applying the averaging theory of first order (see the Appendix). The averaged system of the system (27) is

\[
\begin{align*}
\dot{X} &= \epsilon f_{11}(X, Y) = \epsilon (AX - BXY), \\
\dot{Y} &= \epsilon f_{12}(X, Y) = \epsilon (DXY - KXY + S g(X) + \beta).
\end{align*}
\] (28)

This system has one equilibrium point, namely \((X_*, Y_*)\) with \( Y_* = \frac{A}{B} \) and \( X_* \) is such that \( g(X_*) = (K - D) \frac{A}{B S} X_* - \frac{3}{S} \) (see Figure 3), which exists by the assumptions. To guarantee for the system (27) the existence of periodic solutions associated to

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure3.png}
\caption{Intersection between the graph of the function \( g(X) \) and the line \( l_2 : Y = (K - D) \frac{A}{B S} X - \frac{3}{S} \), when \( K - D > 0 \).}
\end{figure}

the equilibrium point \((X_*, Y_*)\), using Theorem 5.1 we need that the Jacobian of \( f_0 = (f_{11}, f_{12}) \) at \((X_*, Y_*)\) is nonzero, and this is the case because it is verified that

\[
J = \begin{pmatrix}
0 & -BX_* \\
S g'(X_*) + (D - K) \frac{A}{B} & (D - K) X_*
\end{pmatrix},
\] (29)

thus

\[ J = X_* (BS g'(X_*) + (D - K) A) \neq 0. \]

Since the eigenvalues of \( J \) are

\[ \lambda_{\pm} = \frac{(D - K) X_* \pm \sqrt{((D - K) X_*)^2 - 4X_* (BS g'(X_*) + (D - K) A)}}{2}, \]
and \( g'(X_*) + (D - K)\frac{A}{12} \beta < 0 \) it easily follows that the eigenvalues are real and have different signs. Therefore, for \( \epsilon \) sufficiently small, the system (27) has one unstable \( T \)-periodic solution \((X(t, \epsilon), Y(t, \epsilon))\) such that \((X(0, \epsilon), Y(0, \epsilon)) = (X_*, Y_*) + O(\epsilon)\).

Next, we are going to go back through the rescaling (5). In fact, first we observe that

\[
(x(t, \epsilon) = X(t, \epsilon), \quad y(t, \epsilon) = \frac{1}{\epsilon} Y(t, \epsilon))
\]

for \( \epsilon > 0 \). Obviously, it is a \( T \)-periodic solution of (3) with parameters \( a = \epsilon A, b = \epsilon^2 B, d = \epsilon D, \kappa = \epsilon K, f = \epsilon^2 F, \sigma = S \).

Now, as in the proofs of the previous theorems, we will give the approximation of the periodic solution. For this we consider the function \( f_0 = (f_{11}, f_{12}) \), the equations (49), (51), (50) and (56), which allow us to calculate \( w_0, \rho, f_1 \) and \( \eta_1 \), the which are given by

\[
w_0(t, (X, Y)) = \left(0, \int_0^t (\beta(s) - \overline{\beta}) ds\right),
\]

so \( w_0(t, (X_*, Y_*)) = w_0(t, (X, Y)) \),

\[
\rho(t, (X, Y)) = \left(-BX \int_0^t (\beta(s) - \overline{\beta}) ds, (D - K)X \int_0^t (\beta(s) - \overline{\beta}) ds - FY\right).
\]

Next, we are going to go back through the rescaling (5). In fact, first we observe

Substituting all the previous computations in (57) we have

\[
X(t, \epsilon) = X_* + \epsilon \left(\frac{FA}{A(D - K) + BSg'(X_*)}\right) + O(\epsilon^2),
\]

\[
Y(t, \epsilon) = Y_* + \epsilon \left[-\frac{1}{T} \int_0^T \int_0^s (\beta(r) - \overline{\beta}) dr ds + \int_0^t (\beta(s) - \overline{\beta}) ds\right] + O(\epsilon^2),
\]

and coming back, we obtain the following approximation of the \( T \)-periodic solution of the system (3)

\[
x(t, \epsilon) = x_* + \frac{af}{a(d - \kappa) + b\sigma g'(x_*)} + O(\epsilon^2),
\]

\[
y(t, \epsilon) = \frac{a}{b} \left( -\frac{1}{T} \int_0^T \int_0^s (\theta(\omega r) - \overline{\theta}) dr ds + \int_0^t (\theta(\omega s) - \overline{\theta}) ds\right) + O(\epsilon).
\]

Therefore, by hypotheses we conclude that, for \( \epsilon > 0 \) sufficiently small, \( x(t, \epsilon) > 0 \) and \( y(t, \epsilon) > 0 \), and we conclude the proof.

**Proof of Theorem 2.5.** Here we take \( m_1 = 0, m_2 = -1, n_1 = 1, n_2 = 2, n_3 = 1, n_4 = 1, n_5 = 1, n_6 = 0 \) and \( n_7 = 0 \). Then the system (3) in the new variables \((X, Y)\) becomes

\[
\dot{X} = \epsilon (A - BY) X,
\]

\[
\dot{Y} = \epsilon (DXY - FY - KXY + Sg(X) + \beta(t)).
\]

Note that system (30) is in the formal form for applying the averaging theory of first order (see the Appendix). The averaged system of the system (30) is

\[
\dot{X} = \epsilon f_{11}(X, Y) = \epsilon (AX - BXY),
\]

\[
\dot{Y} = \epsilon f_{12}(X, Y) = \epsilon (DXY - FY - KXY + Sg(X) + \overline{\beta}).
\]
i) If \( K - D > 0 \) and \( \frac{FA}{BS} - \frac{\beta}{S} < 1 \).

This system has one equilibrium, namely \((X_*, Y_*)\), with \( Y_* = \frac{A}{B} \) and \( X_* \) is such that \( g(X_*) = (K - D)\frac{A}{BS}X_* + \frac{FA}{BS} - \frac{\beta}{S} \) (see Figure 4), which exists by the assumptions. To ensure the existence of periodic solutions for the system (30)

![Figure 4. Intersection between the graph of the function \( g(X) \) and the line \( l_2 : Y = (K - D)\frac{A}{BS}X + \frac{FA}{BS} - \frac{\beta}{S} \) when \( 0 < \frac{FA}{BS} - \frac{\beta}{S} < 1 \) and \( \frac{FA}{BS} - \frac{\beta}{S} < 0 \).

associated to the equilibrium point \((X_*, Y_*)\), according to Theorem 5.1 we need that the Jacobian of \( f_0 = (f_{11}, f_{12}) \) at the equilibrium point \((X_*, Y_*)\) be nonzero. In this case, it is verified that

\[
J = \begin{pmatrix}
0 & -BX_* \\
Sg'(X_*) + (D - K)\frac{A}{B} & -F + (D - K)X_*
\end{pmatrix},
\]

then

\[\det J = X_* (BSg'(X_*) + (D - K)A) \neq 0.\]

Since the eigenvalues of \( J \) are

\[
\lambda_{\pm} = \frac{-F + (D - K)X_* \pm \sqrt{(-F + (D - K)X_*)^2 - 4X_* (BSg'(X_*) + (D - K)A)}}{2},
\]

and \( g'(X_*) + (D - K)\frac{A}{BS} < 0 \), the eigenvalues are real and have different signs. Therefore, for \( \epsilon \) sufficiently small, the system (30) has one unstable \( T \)-periodic solution \((X(t, \epsilon), Y(t, \epsilon))\) such that \((X(0, \epsilon), Y(0, \epsilon)) = (X_*, Y_*) + O(\epsilon)\).

Next, we go back through the rescaling (5). In fact, first we observe that

\[
x(t, \epsilon) = x(t, \epsilon), \quad y(t, \epsilon) = \frac{1}{\epsilon} Y(t, \epsilon),
\]

for \( \epsilon > 0 \). Obviously, it is a \( T \)-periodic solution of (3) with parameters \( a = \epsilon A, b = \epsilon^2 B, d = \epsilon D, \kappa = \epsilon K, f = \epsilon F \) and \( \sigma = S \).

Proceeding similarly to the proofs of the previous theorems, we obtain that the approximation of the \( T \)-periodic solution of the system (3) is given by

\[
x(t, \epsilon) = x_* + O(\epsilon^2), \quad \frac{a}{b} = \frac{1}{T} \int_0^T \int_0^s (\theta(wr) - \overline{\theta}) dr ds + \int_0^T (\theta(\omega s) - \overline{\theta}) ds + O(\epsilon),
\]

\[
y(t, \epsilon) = \frac{a}{b} - \frac{1}{T} \int_0^T \int_0^s (\theta(wr) - \overline{\theta}) dr ds + \int_0^T (\theta(\omega s) - \overline{\theta}) ds + O(\epsilon).
\]
Therefore, by hypotheses we conclude that for $\epsilon > 0$ sufficiently small, $x(t, \epsilon) > 0$ and $y(t, \epsilon) > 0$.

ii) If $K - D < 0$, $\frac{EA}{BS} - \frac{7}{5} \geq 1$ and $BSg'(X_*) > (K - D)A$.
This system has one equilibrium point, namely $(X_*, Y_*)$, with $Y_* = \frac{A}{D}$ and $X_*$ is such that $g(X_*) = (K - D)\frac{A}{BS}X_* + \frac{EA}{BS} - \frac{7}{5}$, which exists by the assumptions. In order to have periodic solutions associated to the equilibrium point $(X_*, Y_*)$, by the Theorem 5.1 we need to verify that the Jacobian of $f_0 = (f_{11}, f_{12})$ at the equilibrium point $(X_*, Y_*)$ is nonzero. In this situation we have

$$J = \begin{pmatrix} 0 & -BX_* \\ Sg'(X_*) + (D - K)\frac{A}{BS} & -F + (D - K)X_* \end{pmatrix}, \quad (33)$$

then

$$\det J = X_* (BSg'(X_*) + (D - K)A) \neq 0.$$ 

Since the eigenvalues of $J$ are

$$\lambda_{\pm} = \frac{-F + (D - K)X_* \pm \sqrt{(-F + (D - K)X_*)^2 - 4X_* (BSg'(X_*) + (D - K)A)}}{2}.$$ 

and $BSg'(X_*) + (D - K)A > 0$ it easily follows that if $(-F + (D - K)X_*)^2 - 4X_* (BSg'(X_*) + (D - K)A) > 0$, the eigenvalues are real and negative. Therefore, for $\epsilon$ sufficiently small, the system (30) has one asymptotically stable $T$-periodic solution $(X(t, \epsilon), Y(t, \epsilon))$ such that $(X(0, \epsilon), Y(0, \epsilon)) = (X_*, Y_*) + O(\epsilon)$.

Next, we are going back through the rescaling (5). In fact, first we observe that

$$(x(t, \epsilon) = X(t, \epsilon), \quad y(t, \epsilon) = \frac{1}{\epsilon} Y(t, \epsilon),$$

for $\epsilon > 0$. Obviously, it is a $T$-periodic solution of (3) with parameters $a = \epsilon A$, $b = \epsilon^2 B$, $d = \epsilon D$, $\kappa = \epsilon K$, $f = \epsilon F$ and $\sigma = S$.

Now, we need to get a sharp approximation of this periodic solution, which will be obtained by using the analysis done in the Appendix, more precisely, we use the approximation described in (57). We obtain the following approximation of the $T$-periodic solution of the system (3)

$$x(t, \epsilon) = x_* + O(\epsilon^2),$$
$$y(t, \epsilon) = \frac{a}{b} - \frac{1}{T} - \int_0^T \int_0^s (\theta(\omega r) - \bar{\theta}) dr ds + \int_0^T (\theta(\omega s) - \bar{\theta}) ds + O(\epsilon).$$

Therefore, by hypotheses we conclude that, for $\epsilon > 0$ sufficiently small, $x(t, \epsilon) > 0$ and $y(t, \epsilon) > 0$.

iii) If $K - D < 0$, $0 < \frac{EA}{BS} - \frac{7}{5} < 1$ and $BSg'(X) \neq (K - D)A$.
This system has two equilibria, namely $(X_1, Y_1)$ and $(X_2, Y_2)$, with $Y_* = \frac{A}{D}$ and $X_*$ is such that $g(X_i) = (K - D)\frac{A}{BS}X_i + \frac{EA}{BS} - \frac{7}{5}$, $i \in \{1, 2\}$ (see Figure 5), which exists by the assumptions.

Here we verify that the Jacobian of $f_0 = (f_{11}, f_{12})$ at the equilibrium point $(X_1, Y_*)$ is nonzero,

$$J = \begin{pmatrix} 0 & -BX_1 \\ Sg'(X_1) + (D - K)\frac{A}{BS} & -F + (D - K)X_1 \end{pmatrix}, \quad (34)$$

then

$$\det J = X_1 (BSg'(X_1) + (D - K)A) \neq 0.$$
Since the eigenvalues of $J$ are
\[ \lambda_{\pm} = \frac{-F + (D - K)X_1 \pm \sqrt{(-F + (D - K)X_1)^2 - 4X_1(BSg'(X_1) + (D - K)A)}}{2}, \]
and $BSg'(X_1) + (D - K)A < 0$, it easily follows that the eigenvalues are real and have different signs. Therefore, for $\epsilon$ sufficiently small, the system (30) has one unstable $T$-periodic solution $(X_1(t, \epsilon), Y_1(t, \epsilon))$ such that $(X_1(0, \epsilon), Y_1(0, \epsilon)) = (X_1, Y_*) + O(\epsilon)$.

Next, we go back through the rescaling (5). In fact, first we observe that
\[ (x_1(t, \epsilon) = X_1(t, \epsilon), \quad y_1(t, \epsilon) = \frac{1}{\epsilon}Y_1(t, \epsilon)), \]
for $\epsilon > 0$. Obviously it is a $T$-periodic solution of (3) with parameters $a = \epsilon A$, $b = \epsilon^2 B$, $d = \epsilon D$, $\kappa = \epsilon K$, $f = \epsilon F$ and $\sigma = S$.

As in the previous case, to guarantee the existence of periodic solutions associated to the equilibrium point $(X_2, Y_*)$, using Theorem 5.1 we need that the Jacobian of $f_0 = (f_{11}, f_{12})$ at the equilibrium point $(X_2, Y_*)$ is nonzero. In this case it is verified that
\[ J = \begin{pmatrix} 0 & -BX_2 \\ BSg'(X_2) + (D - K)A & -F + (D - K)X_2 \end{pmatrix}, \]
then
\[ \det J = X_2(BSg'(X_2) + (D - K)A) \neq 0. \]
Since the eigenvalues of $J$ are
\[ \lambda_{\pm} = \frac{-F + (D - K)X_2 \pm \sqrt{(-F + (D - K)X_2)^2 - 4X_2(BSg'(X_2) + (D - K)A)}}{2}, \]
and $BSg'(X_2) + (D - K)A > 0$, it easily follows that if $(-F + (D - K)X_2)^2 - 4X_2(BSg'(X_2) + (D - K)A) > 0$, the eigenvalues are real and negative. Therefore, for $\epsilon$ sufficiently small, the system (30) has one asymptotically stable $T$-periodic solution $(X_2(t, \epsilon), Y_2(t, \epsilon))$ such that $(X_2(0, \epsilon), Y_2(0, \epsilon)) = (X_2, Y_*) + O(\epsilon)$.

Next, we are going to go back through the rescaling (5). In fact, first we observe that
\[ (x_2(t, \epsilon) = X_2(t, \epsilon), \quad y_2(t, \epsilon) = \frac{1}{\epsilon}Y_2(t, \epsilon)), \]
for $\epsilon > 0$. Obviously it is a $T$-periodic solution of (3) with parameters $a = \epsilon A$, $b = \epsilon^2 B$, $d = \epsilon D$, $\kappa = \epsilon K$, $f = \epsilon F$ and $\sigma = S$.\[ \text{Figure 5. Intersection between the graph of the function } g(X) \text{ and the line } l_2: Y = (K - D)\frac{\epsilon A}{BS}X + \frac{\epsilon A}{BS} - \frac{\epsilon A}{S}. \]
Carrying out an identical analysis of the previous item, we obtain the following approximations of the $T$-periodic solutions of the system (3)

\[
\begin{align*}
x_1(t, \epsilon) &= x_1 + O(\epsilon^2), \\
y_1(t, \epsilon) &= \frac{a}{b} - \frac{1}{T} \int_0^T \int_0^s (\theta(\omega t) - \bar{\theta})drds + \int_0^t (\theta(\omega s) - \bar{\theta})ds + O(\epsilon),
\end{align*}
\]

and

\[
\begin{align*}
x_2(t, \epsilon) &= x_2 + O(\epsilon^2), \\
y_2(t, \epsilon) &= \frac{a}{b} - \frac{1}{T} \int_0^T \int_0^s (\theta(\omega t) - \bar{\theta})drds + \int_0^t (\theta(\omega s) - \bar{\theta})ds + O(\epsilon).
\end{align*}
\]

Therefore, by hypotheses we conclude that, for $\epsilon > 0$ sufficiently small, $x_{1,2}(t, \epsilon) > 0$ and $y_{1,2}(t, \epsilon) > 0$, and we conclude the proof.

\[\square\]

**Proof of Theorem 2.6.** We take $m_1 = 0$, $m_2 = -1$, $n_1 = 1$, $n_2 = 2$, $n_3 = 1$, $n_4 = 2$, $n_5 = 1$, $n_6 = 0$ and $n_7 = 0$. Then the system (3) in the new variables $(X, Y)$ becomes

\[
\begin{align*}
\dot{X} &= \epsilon(A - BY)X, \\
\dot{Y} &= \epsilon(DXY - FY + Sg(X) + \beta(t)) + \epsilon^2(-KXY).
\end{align*}
\]

The system (36) is in the formal form for applying the averaging theory of first order (see the Appendix). The averaged system of the system (36) is

\[
\begin{align*}
\dot{X} &= \epsilon f_1(X, Y) = \epsilon(AX - BXY), \\
\dot{Y} &= \epsilon f_2(X, Y) = \epsilon(DXY - FY + Sg(X) + \bar{\theta}) + \epsilon^2(-KXY).
\end{align*}
\]

i) If $\frac{kA}{B^2} - \frac{3}{8} \geq 1$ and $DA + BSg(X_s) > 0$.

This system has one equilibrium point, namely $(X_s, Y_s)$, with $Y_s = \frac{A}{B}$ and $X_s$ is such that $g(X_s) = -\frac{DA}{2B} X_s + \frac{kA}{B^2} - \frac{3}{8}$, which exists by the assumptions.

To guarantee, for system (36), the existence of periodic solutions associated to the equilibrium point $(X_s, Y_s)$, using Theorem 5.1 we need that the Jacobian of $f_0 = (f_{11}, f_{12})$ at the equilibrium point $(X_s, Y_s)$ is nonzero. In this case it is verified that

\[
J = \begin{pmatrix}
0 & -BX_s \\
Sg'(X_s) + \frac{DA}{B} & DX_s - F
\end{pmatrix},
\]

thus

\[
\det J = X_s (BSg'(X_s) + DA) \neq 0.
\]

As the eigenvalues of $J$ are

\[
\lambda_{\pm} = -F + DX_s \pm \sqrt{(-F + DX_s)^2 - 4X_s (BSg'(X_s) + DA)},
\]

and $BSg'(X_s) + DA > 0$, it easily follows that if $(-F + DX_s)^2 - 4X_s (BSg'(X_s) + DA) > 0$, the eigenvalues are real and negative. Therefore, for $\epsilon$ sufficiently small, the system (36) has one asymptotically stable $T$-periodic solution $(X(t, \epsilon), Y(t, \epsilon))$ such that $(X(0, \epsilon), Y(0, \epsilon)) = (X_s, Y_s) + O(\epsilon)$.

Next, we go back through the rescaling (5). In fact, first we observe that

\[
(x(t, \epsilon) = X(t, \epsilon), \quad y(t, \epsilon) = \frac{1}{\epsilon} Y(t, \epsilon)),
\]

for $\epsilon > 0$. Obviously, it is a $T$-periodic solution of (3) with parameters $a = \epsilon A$, $b = \epsilon^2 B$, $d = \epsilon D$, $\kappa = \epsilon^2 K$, $f = \epsilon F$ and $\sigma = S$. 

\[\square\]
Carrying out an identical analysis of the previous item, we obtain the following approximations of the $T$-periodic solution of the system (3)

$$x(t, \epsilon) = \left(1 + \frac{ak}{ad + b\sigma g'(x_*)}\right)x_* + O(\epsilon^2),$$

$$y(t, \epsilon) = \frac{a}{b} - \frac{1}{T} \int_0^T \int_0^s (\theta(\omega r) - \overline{\theta}) dr ds + \int_0^t (\theta(\omega s) - \overline{\theta}) ds + O(\epsilon).$$

Therefore, by hypotheses we conclude that, for $\epsilon > 0$ sufficiently small, $x(t, \epsilon) > 0$ and $y(t, \epsilon) > 0$.

ii) If $0 < \frac{FA}{BS} - \frac{3}{5} < 1$ and $BSg'(X) \neq -DA$.
This system has two equilibria, namely $(X_1, Y_1)$ and $(X_2, Y_2)$, with $Y_* = \frac{A}{B}$ and $X_i$ is such that $g(X_i) = -\frac{DA}{BS}X_i + \frac{FA}{BS} - \frac{3}{5}; i \in \{1, 2\}$ (see Figure 6), which exist by assumptions. Next, we verify that the Jacobian of $f_0 = (f_{11}, f_{12})$ at the equilibrium

$$J = \begin{pmatrix} 0 & -BX_1 \\ Sg'(X_1) + \frac{DA}{B} & -F + DX_1 \end{pmatrix},$$

then

$$\det J = X_1 (BSg'(X_1) + DA) \neq 0.$$ 

Since the eigenvalues of $J$ are

$$\lambda_{\pm} = \frac{-F + DX_1 \pm \sqrt{(-F + DX_1)^2 - 4X_1 (BSg'(X_1) + DA)}}{2},$$

and $BSg'(X_1) + DA < 0$, it easily follows that the eigenvalues are real and have different signs. Therefore, for $\epsilon$ sufficiently small, the system (36) has one unstable $T$-periodic solution $(X_1(t, \epsilon), Y_1(t, \epsilon))$ such that $(X_1(0, \epsilon), Y_1(0, \epsilon)) = (X_1, Y_*) + O(\epsilon)$.

Next, we are going to go back through the rescaling (5). In fact, first we observe

$$x_1(t, \epsilon) = X_1(t, \epsilon), \quad y_1(t, \epsilon) = \frac{1}{\epsilon} Y_1(t, \epsilon),$$

for $\epsilon > 0$. Obviously, it is a $T$-periodic solution of (3) with parameters $a = \epsilon A, b = \epsilon^2 B, d = \epsilon D, \kappa = \epsilon^2 K, f = \epsilon F$ and $\sigma = S$.

\[ \text{Figure 6. Intersection between the graph of the function } g(X) \text{ and the line } l_2: Y = -\frac{DA}{BS} X + \frac{FA}{BS} - \frac{3}{5}. \]
To ensure the existence of periodic solutions of system (36), associated to the equilibrium point \((X_2, Y_2)\), we need that the Jacobian of \(f_0 = (f_{11}, f_{12})\) at the equilibrium point \((X_2, Y_2)\) is nonzero. In this case it is verified that

\[
J = \begin{pmatrix}
0 & -BX_2 \\
S g'(X_2) + \frac{DA}{\theta} & -F + DX_2
\end{pmatrix},
\]

then

\[
\det J = X_2(BSg'(X_2) + DA) \neq 0.
\]

Since the eigenvalues of \(J\) are

\[
\lambda_{\pm} = \frac{-F + DX_2 \pm \sqrt{(-F + DX_2)^2 - 4X_2(BSg'(X_2) + DA)}}{2},
\]

and \(BSg'(X_2) + DA > 0\), it easily follows that if \((-F + DX_2)^2 - 4X_2(BSg'(X_2) + DA) > 0\), the eigenvalues are real and negative signs. Therefore, for \(\epsilon\) sufficiently small, the system (36) has one asymptotically stable \(T\)-periodic solution \((X_2(t, \epsilon), Y_2(t, \epsilon))\) such that \((X_2(0, \epsilon), Y_2(0, \epsilon)) = (X_2, Y_2) + O(\epsilon)\).

Next, we are going to go back through the rescaling (5). In fact, first we observe

\[
(x_2(t, \epsilon) = X_2(t, \epsilon), \quad y_2(t, \epsilon) = \frac{1}{\epsilon}Y_2(t, \epsilon)),
\]

for \(\epsilon > 0\). Obviously, it is a \(T\)-periodic solution of (3) with parameters \(a = \epsilon A\), \(b = \epsilon^2 B\), \(d = \epsilon D\), \(\kappa = \epsilon^2 K\), \(f = \epsilon F\) and \(\sigma = S\).

In this case, using the same ideas as the previous item, we have the approximations of the \(T\)-periodic solutions of the system (3)

\[
x_1(t, \epsilon) = \left(1 + \frac{ak}{ad + b\sigma g'(x_1)}\right) x_1 + O(\epsilon^2),
\]

\[
y_1(t, \epsilon) = \frac{a}{b} - \frac{\gamma}{T} \int_0^T \int_0^T (\theta wr - \bar{\theta}) dr ds + \int_0^T (\theta \omega s - \bar{\theta}) ds + O(\epsilon),
\]

and

\[
x_2(t, \epsilon) = \left(1 + \frac{ak}{ad + b\sigma g'(x_2)}\right) x_2 + O(\epsilon^2),
\]

\[
y_2(t, \epsilon) = \frac{a}{b} - \frac{\gamma}{T} \int_0^T \int_0^T (\theta wr - \bar{\theta}) dr ds + \int_0^T (\theta \omega s - \bar{\theta}) ds + O(\epsilon).
\]

Therefore, by hypotheses we conclude that, for \(\epsilon > 0\) sufficiently small, \(x_{1,2}(t, \epsilon) > 0\) and \(y_{1,2}(t, \epsilon) > 0\), and the proof is complete.

4. Examples. In this section we exhibit one example of applicability of each of our theorems. Moreover, with the help of Mathematica we find appropriate initial conditions such that the solution is periodic. In these examples we take periodic immunotherapy as in [7, 2, 3].

Example 1. In order to apply Theorem 2.1, we consider \(\theta(t) = \gamma \cos^2 t\) with \(\gamma > 0\). It is verified that \(\bar{\theta} = \frac{\gamma}{2}\) and \(\delta(t) = \frac{\gamma}{2} - \frac{\gamma}{2} \sin(2t)\). If we consider \(g(x) = \frac{1}{1+x}\), then \(x_* = \frac{-2of + 2b + 2\sigma}{2af + b}\). We observe that taking \(a = 10^{-3}\), \(b = 10^{-8}\), \(d = 2 \cdot 10^{-8}\), \(f = 10^{-4}\), \(\sigma = 10^{-8}\), \(\gamma = 10\) and \(\gamma = 1\), the hypotheses of Theorem 2.1 are satisfied. Then, for \(\epsilon = 10^{-4}\) the model (3) has one unstable \(2\pi\)-periodic solution (see Figure 7).
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Figure 7. Malignant cells $x(t)$ and Lymphocyte Cells $y(t)$ for the periodic solution of Theorem 2.1, with initial conditions $x_0 = 1/19 + 10^{-40}$ and $y_0 = 100000 + 10^{-40}$.

Example 2. To apply Theorem 2.2, we take $\theta(t) = \gamma \cos^2 t$ with $\gamma > 0$. It is verified that $\bar{\theta} = \frac{\gamma}{2}$ and $\delta(t) = \frac{a}{b} - \frac{\gamma}{2} \sin(2t)$. If we consider $g(x) = \frac{1}{1+x}$ then $x_* = -\frac{2a\gamma + b\gamma^2 + 2b\gamma}{4a\gamma + 3b\gamma^2}$. We observe that taking $a = 8 \cdot 10^{-4}$, $b = 10^{-8}$, $f = 10^{-8}$, $\kappa = 10^{-4}$, $\sigma = 12$ and $\gamma = 1$, the hypotheses of Theorem 2.2 are satisfied. Then, for $\epsilon = 10^{-4}$ the model (3) has one unstable $2\pi$-periodic solution (see Figure 8).

Figure 8. Malignant cells $x(t)$ and Lymphocyte Cells $y(t)$ for the periodic solution of Theorem 2.2, with initial conditions $x_0 = 5/32(-3 + \sqrt{73}) + 10^{-40}$ and $y_0 = 80000 + 10^{-40}$.

Example 3. In the case of Theorem 2.3, we consider $\theta(t) = \gamma \cos^2 t$ with $\gamma > 0$ and $g(x) = \frac{1}{1+x}$. We observe that taking $a = 10^{-3}$, $b = 2 \cdot 10^{-8}$, $d = 0.9 \cdot 10^{-8}$, $f = 2 \cdot 10^{-4}$, $\kappa = 3 \cdot 10^{-4}$, $\sigma = 12$ and $\gamma = 3$, the hypotheses of Theorem 2.3 are satisfied. Then, for $\epsilon = 10^{-4}$ the model (3) has one unstable $2\pi$-periodic solution (see Figure 9).

Example 4. For the Theorem 2.4, we assume that $\theta(t) = \gamma(1 + m \cos(\omega t))$ with $\gamma > 0$ and $g(x) = e^{-x}$. We observe that taking $a = 5 \cdot 10^{-4}$, $b = 2 \cdot 10^{-8}$, $d = 10^{-4}$, $f = 2 \cdot 10^{-4}$, $\kappa = 3 \cdot 10^{-4}$, $\sigma = 7$, $\omega = 1/8$, $m = 1/2$ and $\gamma = 5/2$, the hypotheses of Theorem 2.4 are satisfied. Then, for $\epsilon = 10^{-4}$ the model (3) has one unstable $16\pi$-periodic solution (see Figure 10).

Example 5. In order to apply Theorem 2.5, we consider $\theta(t) = \gamma(1 + m \cos(\omega t))$ with $\gamma > 0$ and $g(x) = e^{-x}$. We observe that taking $a = 5 \cdot 10^{-4}$, $b = 2 \cdot 10^{-8}$,
Figure 9. Malignant cells $x(t)$ and Lymphocyte Cells $y(t)$ for the periodic solution of Theorem 2.3, with initial conditions $x_0 = 1/60(-27 + \sqrt{1009}) + 10^{-40}$ and $y_0 = 50000 + 10^{-40}$.

Figure 10. Malignant cells $x(t)$ and Lymphocyte Cells $y(t)$ for the periodic solution of Theorem 2.4, with initial conditions $x_0 = 1.0099381 + 10^{-40}$ and $y_0 = 25000 + 10^{-40}$.

Figure 11. Malignant cells $x(t)$ and Lymphocyte Cells $y(t)$ for the periodic solution of Theorem 2.5, with initial conditions $x_0 = 1.15201 + 10^{-40}$ and $y_0 = 25000 + 10^{-40}$.

Example 6. In order to apply Theorem 2.6, we consider $\theta(t) = \gamma(1 + m \cos(\omega t))$ with $\gamma > 0$ and $g(x) = e^{-x}$. We observe that taking $a = 5 \cdot 10^{-4}$, $b = 2 \cdot 10^{-8}$,
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Figure 12. Malignant cells \( x(t) \) and Lymphocyte Cells \( y(t) \) for the periodic solution of Theorem 2.5, with initial conditions \( x_0 = 9.99870 + 10^{-40} \) and \( y_0 = 25000 + 10^{-40} \).

\[ d = 10^{-2}, \quad f = 5 \cdot 10^{-4}, \quad \kappa = 2 \cdot 10^{-12}, \quad \sigma = 7, \quad \omega = 1/8, \quad m = 1/2 \text{ and } \gamma = 5/2, \] the hypotheses of Theorem 2.6 are satisfied. Then, for \( \epsilon = 10^{-4} \) the model (3) has one asymptotically stable \( 16\pi \)-periodic solution (see Figure 13).

Figure 13. Malignant cells \( x(t) \) and Lymphocyte Cells \( y(t) \) for the periodic solution of Theorem 2.6, with initial conditions \( x_0 = 0.0123435 + 10^{-40} \) and \( y_0 = 25000 + 10^{-40} \).

5. Appendix: Averaging theory of first order. We shall present the basic results from averaging theory that we need in order to prove the results of this paper.

Consider the differential equation

\[ \dot{x} = \epsilon F_0(t, x) + \epsilon^2 F_1(t, x) + \epsilon^3 R(t, x, \epsilon), \quad x(0) = x_0 \quad (41) \]

with \( x \in D \), where \( D \) is an open subset of \( \mathbb{R}^n \), \( t \geq 0 \). Moreover, we assume that both \( F_0(t, x) \), \( F_1(t, x) \) and \( R(t, x, \epsilon) \) are \( T \)-periodic in \( t \). We also consider in \( D \) the averaged differential equation

\[ \dot{y} = \epsilon f_0(y), \quad y(0) = x_0, \quad (42) \]

where

\[ f_0(y) = \frac{1}{T} \int_0^T F_0(t, y)dt. \]

Under certain conditions, equilibrium solutions of the averaged equation turn out to correspond with \( T \)-periodic solutions of equation (41).
Theorem 5.1. Consider the two initial value problems (41) and (42). Suppose:

(i) $F_0$, its Jacobian $\partial F_0/\partial x$, its Hessian $\partial^2 F_0/\partial x^2$, $F_1$ and its Jacobian $\partial F_1/\partial x$ are defined, continuous and bounded by a constant independent of $\varepsilon$ in $[0, \infty) \times D$ and $\varepsilon \in (0, \varepsilon_0]$.

(ii) $F_0$ and $F_1$ are $T$-periodic in $t$ ($T$ independent of $\varepsilon$).

Then the following statements hold:

(a) If $p$ is an equilibrium point of the averaged equation (42) and

$$\det \left( \frac{\partial f_0}{\partial y} \right) \bigg|_{y=p} \neq 0,$$

then there exists a $T$-periodic solution $\varphi(t, \varepsilon)$ of equation (41) such that $\varphi(0, \varepsilon) \to p$ as $\varepsilon \to 0$.

(b) The stability or instability of the limit cycle $\varphi(t, \varepsilon)$ is given by the stability or instability of the equilibrium point $p$ of the averaged system (42). In fact, the singular point $p$ has the stability behavior of the Poincaré map associated to the limit cycle $\varphi(t, \varepsilon)$.

For the proof see Theorems 11.5 and 11.6 of Verhulst [8].

5.1. Approximation of the periodic solutions obtained in theorem 5.1.

Initially we introduce the following change of coordinates

$$x = y + \varepsilon w(t, y, \varepsilon) = y + \varepsilon w_0(t, y) + \varepsilon^2 w_1(t, y) + O(\varepsilon^3),$$

where $w$ is a $T$-periodic function. Substituting (44) in $F_0$ and expanding in a Taylor series around $\varepsilon = 0$,

$$F_0(t, x) = F_0(t, y + \varepsilon w_0(t, y))$$

$$= F_0(t, y) + \varepsilon D_x F_0(t, y) w_0(t, y) + \varepsilon^2 \left[ 2D_x F_0(t, y) w_1(t, y) + w_0(t, y)^T Hess F_0(t, y) w_0(t, y) \right] + O(\varepsilon^3).$$

Analogously,

$$F_1(t, x) = F_1(t, y + \varepsilon w_0(t, y) + \varepsilon^2 w_1(t, y) + O(\varepsilon^3))$$

$$= F_1(t, y) + \varepsilon \frac{\partial w_0}{\partial t}(t, y) w_0(t, y) + O(\varepsilon^2).$$

Next, differentiating (44) with respect to $t$, we get

$$\dot{x} = \left( I + \varepsilon \frac{\partial w_0}{\partial y}(t, y) + \varepsilon^2 \frac{\partial w_1}{\partial y}(t, y) \right) \dot{y} + \varepsilon \frac{\partial w_0}{\partial t}(t, y) + \varepsilon^2 \frac{\partial w_1}{\partial t}(t, y) + O(\varepsilon^3).$$

Using (45) and (46) we obtain

$$\dot{y} = \left( I + \varepsilon \frac{\partial w_0}{\partial y}(t, y) + \varepsilon^2 \frac{\partial w_1}{\partial y}(t, y) \right)^{-1} \left( \varepsilon F_0(t, y) + \varepsilon^2 F_1(t, y) \right)$$

$$- \varepsilon \frac{\partial w_0}{\partial t}(t, y) - \varepsilon^2 \frac{\partial w_1}{\partial t}(t, y) + O(\varepsilon^3)$$

$$= \left[ \varepsilon \left( F_0(t, y) - \frac{\partial w_0}{\partial t}(t, y) \right) + O(\varepsilon^2) \right]$$

$$+ \varepsilon^2 \left( D_x F_0(t, y) w_0(t, y) + F_1(t, y) - \frac{\partial w_0}{\partial t}(t, y) \right) + O(\varepsilon^3)$$

$$= \varepsilon f_0(y) + \varepsilon^2 f_1(t, y) + O(\varepsilon^3),$$
Remark 2. If we assume that
\[ f_0(y) = F_0(t, y) - \frac{\partial w_0}{\partial t}(t, y), \]
\[ f_1(t, y) = D_x F_0(t, y) w_0(t, y) + F_1(t, y) - \frac{\partial w_1}{\partial t}(t, y) - \frac{\partial w_0}{\partial y}(t, y) f_0(y). \]  \hfill (48)

Remark 1. From the first equation in (48), we have
\[ \frac{\partial w_0}{\partial t}(t, y) = F_0(t, y) - f_0(y), \]
thus,
\[ w_0(t, y) = \int_0^t F_0(s, y) ds - f_0(y)t = \int_0^t F_0(s, y) ds - \frac{t}{T} \int_0^T F_0(s, y) ds. \]  \hfill (49)

Remark 2. From the second equation in (48), we have,
\[ f_1(t, y) = D_x F_0(t, y) w_0(t, y) + F_1(t, y) - \frac{\partial w_1}{\partial t}(t, y) - \frac{\partial w_0}{\partial y}(t, y) f_0(y). \]  \hfill (50)

Now, we define the following auxiliary function
\[ \rho(t, y) = D_x F_0(t, y) w_0(t, y) + F_1(t, y) - \frac{\partial w_0}{\partial y}(t, y) f_0(y). \]  \hfill (51)

If we assume that \( f_1(t, y) = f_1(y) \) is a function that depends only on \( y \), we have that
\[ f_1(y) = \frac{1}{T} \int_0^T \rho(t, y) dt, \]
and so
\[ \frac{\partial w_1}{\partial t}(t, y) = \rho(t, y) - f_1(y). \]
Therefore,
\[ w_1(t, y) = \int_0^t \rho(s, y) ds - f_1(y)t. \]

Let
\[ x(t, \xi, \epsilon) = x_0(t) + \epsilon x_1(t) + O(\epsilon^2), \]  \hfill (52)
be the general solution of (41) with initial condition \( \xi \), and let
\[ y(t, \eta, \epsilon) = y_0(t) + \epsilon y_1(t) + \epsilon^2 y_2(t) + O(\epsilon^3), \]  \hfill (53)
be the general solution of (47) with initial condition \( \eta \). Then, it follows that
\[ \eta = y(0, \eta, \epsilon) = y_0(0) + \epsilon y_1(0) + \epsilon^2 y_2(0) + O(\epsilon^3), \]
and by (47) and using a Taylor series around \( \epsilon = 0 \),
\[ \dot{y}_0(t) + \epsilon y_1(t) + \epsilon^2 y_2(t) + O(\epsilon^3) = \dot{y} = \epsilon f_0(y) + \epsilon^2 f_1(y) + O(\epsilon^3) = \epsilon f_0(y_0(t) + \epsilon y_1(t) + O(\epsilon^2)) + \epsilon^2 f_1(y_0(t) + \epsilon y_1(t) + O(\epsilon^2)) + O(\epsilon^3) = \epsilon f_0(y_0) + \epsilon^2 (D_y f_0(y_0) y_1 + f_1(y_0)) + O(\epsilon^2). \]
Thus,
\[ \dot{y}_0(t) = 0, \quad \dot{y}_1(t) = f_0(y_0), \quad \dot{y}_2(t) = D_y f_0(y_0) y_1 + f_1(y_0), \]
and it follows that
\[ y_0(t) = z, \]
\[ y_1(t) = f_0(z) t, \]
\[ y_2(t) = \frac{\epsilon^2}{2} D_y f_0(z) f_0(z) + f_1(z) t, \]
then the general solution (53) is written as

\[
y(t, \eta, \epsilon) = \eta + \epsilon f_0(\eta)t + \epsilon^2 \left( \frac{t^2}{2} D_y f_0(\eta) f_0(\eta) + f_1(\eta) t \right) + O(\epsilon^3)
\] (54)

Next, we assume that \(y(t, \eta, \epsilon)\) is a particular \(T\)-periodic solution of the system (47) with the initial condition

\[
\eta = \eta(\epsilon) = p + \epsilon \eta_1 + \epsilon^2 \eta_2 + O(\epsilon^3),
\] (55)

where \(p\) satisfies \(f_0(p) = 0\) and \(D_y f_0(p)\) is nondegenerate.

Now, we consider the \(T\)-periodic solution \(y(t, \eta(\epsilon), \epsilon)\) obtained by Theorem 5.1 of the system (47). Our next aim is to describe the approximation of this family of initial conditions, that is, we are going to characterize \(\eta_1\).

Because of the periodicity of the solution \(y(t, \eta(\epsilon), \epsilon)\) and using (54), we must have

\[
0 = \begin{array}{l}
y(T, \eta(\epsilon), \epsilon) - \eta(\epsilon) \\
= cT f_0(\eta(\epsilon)) + \epsilon^2 \left[ \frac{T^2}{2} D_y f_0(\eta(\epsilon)) f_0(\eta(\epsilon)) + f_1(\eta(\epsilon)) T \right] + O(\epsilon^3).
\end{array}
\]

Next, developing in Taylor series the previous expression around \(\epsilon = 0\), we get

\[
0 = f_0(\eta(\epsilon)) + \epsilon \left[ \frac{T}{2} D_y f_0(\eta(\epsilon)) f_0(\eta(\epsilon)) + f_1(\eta(\epsilon)) \right] + O(\epsilon^2)
= f_0(p + \epsilon \eta_1 + \epsilon^2 \eta_2 + O(\epsilon^3)) + \\
\quad + \epsilon \left[ \frac{T}{2} D_y f_0(p + \epsilon \eta_1 + \epsilon^2 \eta_2 + O(\epsilon^3)) f_0(p + \epsilon \eta_1 + \epsilon^2 \eta_2 + O(\epsilon^3)) \right] + f_1(p + \epsilon \eta_1 + \epsilon^2 \eta_2 + O(\epsilon^3)) + O(\epsilon^2)
= f_0(p) + \epsilon \left[ D_y f_0(p) \eta_1 + \frac{T}{2} D_y f_0(p) f_0(p) + f_1(p) \right] + O(\epsilon^2),
\]

so

\[
\eta_1 = -[D_y f_0(p)]^{-1} f_1(p).
\] (56)

Coming back to the associated \(T\)-periodic solution \(x(t, \eta(\epsilon), \epsilon)\) of the system (41), we arrive to

\[
x(t, \eta(\epsilon), \epsilon) = \begin{array}{l}
y(t, \eta(\epsilon), \epsilon) + \epsilon w_0(t, y(t, \eta(\epsilon), \epsilon)) + O(\epsilon^2) \\
= \eta(\epsilon) + \epsilon f_0(\eta(\epsilon)) t + \epsilon^2 \left( \frac{t^2}{2} D_y f_0(\eta(\epsilon)) f_0(\eta(\epsilon)) + f_1(\eta(\epsilon)) t \right) \\
\quad + \epsilon w_0(t, \eta(\epsilon) + \epsilon f_0(\eta(\epsilon)) t + \epsilon^2 \left( \frac{t^2}{2} D_y f_0(\eta(\epsilon)) f_0(\eta(\epsilon)) \right) + f_1(\eta(\epsilon)) t + O(\epsilon^3)) + O(\epsilon^2)
\end{array}
\]
\[
= p + \epsilon \eta_1 + O(\epsilon^2) + \epsilon f_0(\eta(\epsilon)) t \\
\quad + \epsilon^2 \left( \frac{t^2}{2} D_y f_0(\eta(\epsilon)) f_0(\eta(\epsilon)) + f_1(\eta(\epsilon)) t \right) + O(\epsilon^3)
\quad + \epsilon w_0(t, p + \epsilon \eta_1 + O(\epsilon^2) + \epsilon f_0(\eta(\epsilon)) t)
\quad + \epsilon^2 \left( \frac{t^2}{2} D_y f_0(\eta(\epsilon)) f_0(\eta(\epsilon)) + f_1(\eta(\epsilon)) t \right) + O(\epsilon^3))
\]
\[
= p + \epsilon \left[ -[D_y f_0(p)]^{-1} f_1(p) + w_0(t, p) \right] + O(\epsilon^2).
\] (57)

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