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Delay-Induced Oscillatory Dynamics of Tumor-Immune System Interaction.

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Contents

Introduction

In the latest years, among scientific literature, many papers have been published presenting mathematical models in cancer research field. They examine different biological aspects and use different mathematical tools.

In this work we focus on deterministic models concerning tumor-immune system interaction, based on ordinary differential equations or delay differential equations. It has been done a critical reading of the existing literature drawing our attention on a special family of models that we have then generalized. From this departing point we studied how adding of a delay term can affect the system dynamics.

In biological phenomena, especially in tumor growth and development, and in the tumor-immune system interaction, delays can be due to many reasons (times of cellular division and displacement in the organism, time lags from signals sending to their reception, times of synthesis and transport of proteins, ...), but often they are neglected in mathematical models that are formulated using ordinary differential equations.

In this work, applying the theory of delay differential equations, we have analyzed models behavior both with discrete and distributed delay, aiming to stress the possibility of these systems to show an oscillatory dynamics. As far as the examined literature is concerned, oscillations experimentally observed in tumor growth are a feature hard to explain for scientists.

This research is mainly done looking for Hopf bifurcations. We use delay as bifurcating parameter, in order to study if and how the delay can influence the stability of the system and its dynamics. We proved that including a delay term may cause - under some conditions - changes in the stability of equilibrium points. Moreover, for some delay values, models can exhibit limit-cycles that are not present in systems without delay.

The study has been run both analytically and numerically: we have been dealing with different realistic examples whose parameter values, taken from literature, were fitted from data sampled in clinical experiments. The obtained results have been discussed both from a mathematical point of view and for their medical-biological meaning. Finally, some simulations have been conducted on a system to which has been added a term representing delivery of a therapy (immunotherapy).

We took in exam both constant and periodic therapy, described with dif-

ferent mathematical expressions, primarily focusing our numerical analysis on the more relevant case of boli-based therapy.

As a result, varying therapy parameters, such as administration and clearance time, we observed very interesting behaviors in model dynamics, changes in stability properties and also resonance effects.

Contents are organized into six chapters.

The first reports basic results of theory of delay differential equations and methods of analysis that are then utilized in following chapters.

In the second chapter topics of tumor-immune system interaction and mathematical modeling are introduced and some relevant models are sumarized and discussed.

In third chapter a new model of tumor-immune system interaction is presented and studied both analytically and numerically showing some biologically meaningful examples.
Then the issue of immunotherapy is taken into account adding to the system a treatment term and studying its behavior.

The fourth and fifth chapter are the core of this work. In these chapters a delay term is added to model introduced in third chapter and obtained delayed systems are studied analytically, with the aim to point out changes in stability of equilibrium points, Hopf bifurcations and periodic dynamics. Then delayed systems are studied numerically taking parameters within a range of biological significance. In fourth chapter the delay term introduced is a fixed lag delay, whereas in fifth chapter distributed delays are considered.

Finally the sixth chapter deals with immunotherapy in delayed models. A numerical analysis was carried out for systems with delay and treatment terms and many examples are showed and discussed, pointing out interesting biological and mathematical features.

Chapter 1

Basic theory of delay differential equations

In many real processes, especially in the medical/biologic field, the dynamics depends not only on the present state of the system, but also on the past history of state variables. Modeling situations in which past history is not negligible necessarily leads to the study of delay differential equations (DDE).

In this chapter we report a survey of the theory of DDE. In the first part we give some basic definitions, existence, uniqueness and stability results. Then we treat existence and stablity of periodic solutions stating the Hopf Theorem for DDE.

Finally we describe some methods to study stability of delay system. In the last chapter of this work we will deal with that again to analyze stability properties and the occurrence of Hopf bifurcations in a family of models of tumor-immune system interaction.

The following text [1] may be consulted on this topic; it exposes an exhaustive theory of delay differential equations. In [2], [3] the matter is handled paying special attention to the biological applications. Interesting sections on equation with delay can also be found in [4] and [7].

1.1 Basic properties

Let $r \geq 0$ be a real number and $C = C([-r, 0], \mathbb{R}^n)$ the Banach space of continuous functions mapping $[-r, 0]$, into $\mathbb{R}^n$ and the supremum norm. For $\sigma \in \mathbb{R}$, $A \geq 0$, $x \in C([\sigma - r, \sigma + A], \mathbb{R}^n)$, and $t \in [\sigma, \sigma + A]$, we define $x_t \in C$ as $x_t(\theta) = x(t + \theta)$, $\theta \in [-r, 0]$.
Let Ω be a subset of $\mathbb{R} \times C$, $f : \Omega \to \mathbb{R}^n$ a given function and denote the right-hand derivative by a dot: $\dot{}$.

Then we call DDE(f) (delay differential equation) on Ω an equation of

the form:

$$\dot{x}(t) = f(t, x_t). \tag{1.1}$$

A function x is said to be a solution of (1.1) on $[\sigma - r, \sigma + A)$ if there is $\sigma \in \mathbb{R}$, $x \in C([\sigma - r, \sigma + A), \mathbb{R}^n)$, $(t, x_t) \in \Omega$ and x_t satisfies (1.1) for $t \in [\sigma, \sigma + A)$. Given $\sigma \in \mathbb{R}$, $\varphi \in C$ we say that $x(\sigma, \varphi)$ is a solution of (1.1) with initial value φ in σ, or a solution through (σ, φ), if there is $A > 0$ such that $x(\sigma, \varphi)$ is a solution of (1.1) on $[\sigma, \sigma + A)$ and $x_\sigma(\sigma, \varphi) = \varphi$. According to (1.1) the right-hand derivative of the solution x at t is determined by t and by the restriction of $x(t)$ to the interval $[t - r, t]$. If the solution is unique, then for every $t \geq 0$ we can define:

$$T(t) : \varphi \to x_t(\sigma, \varphi), \tag{1.2}$$

that maps C into itself. $T(t)$ is called the *solution map* of

$$\begin{cases} \dot{x}(t) = f(t, x_t), & t \geq \sigma, \\ x_\sigma = \varphi. \end{cases} \tag{1.3}$$

We say that the equation (1.1) is *linear* if $f(t, x_t) = L(t, x_t) + h(t)$, where $L(t, x_t)$ is linear in x_t; *linear homogeneous* if $h(t) \equiv 0$ and *linar nonhomogeneous* if $h(t) \neq 0$. We say that (1.1) is *autonomous* if $f(t, x_t) = g(x_t)$ where g does not depend on t, otherwise we say that (1.1) is *nonautonomous*.

The DDE (1.1) includes many classes of equations such as ODE if $r = 0$, in fact, in this case x_t is defined on the interval consisting of the single point 0 and $x_t = x_t(0) = x(t)$. It includes also differential-difference equations of the form:

$$\dot{x}(t) = f(t, x(t), x(t - r_1), ..., x(t - r_m)) \tag{1.4}$$

where $0 \leq r_i \leq r$ for $i = 0, ..., m$. Here f is a function of $nm + 1$ real variables and we say that there are m delays in the equation, each less than r. The delays r_i may also depend on the time t. Finally, DDE (1.1) includes integro-differential equations:

$$\dot{x}(t) = \int_{-r}^{0} g(t, x(t), \theta, x_t(\theta)) d\theta \tag{1.5}$$

where g is a function of $2n + 2$ variables.

We observe that, if we assume f continuous, finding a solution of (1.1) through $(\sigma, \varphi) \in \mathbb{R} \times C$ is equivalent to solving the integral equation:

$$\begin{cases} x(t) = \varphi(0) + \int_\sigma^t f(s, x_s) ds & t \geq 0 \\ x_\sigma = \varphi \end{cases} \tag{1.6}$$

Theorems of existence and uniqueness of solutions hold and are more or less analogous to the corresponding results for ODE.

Theorem 1.1.1. *Suppose Ω is an open subset in $\mathbb{R}\times C$ and f is continuous in Ω. If $(\sigma,\varphi)\in\Omega$, then there is a solution of (1.1) through (σ,φ).*

Definition 1.1.1. *We say that $f(t,\varphi)$ is Lipschitz in φ in a compact subset K in $\mathbb{R}\times C$ if there is a constant $k>0$ such that $\forall\,(t,\varphi_i)\in K$ $(i=1,2)$*

$$|f(t,\varphi_1)-f(t,\varphi_2)|\le k|\varphi_1-\varphi_2|$$

Theorem 1.1.2. *Suppose Ω is an open subset in $\mathbb{R}\times C$, $f:\Omega\to\mathbb{R}^n$ is continuous and $f(t,\varphi)$ is Lipschitz in φ in every compact of Ω. If $(\sigma,\varphi)\in\Omega$, then there is a unique solution of (1.1) through (σ,φ).*

Also theorems about continuous dependence on initial values and on the continuation of solutions hold and are analogous to the corresponding results for ODE, but in some cases one has to assume that f is completely continuous.

Theorem 1.1.3. *Suppose $\Omega\subseteq\mathbb{R}\times C$ is open, $(\sigma,\varphi)\in\Omega$, $f\in C(\Omega,\mathbb{R}^n)$, and x is a solution of (1.1) through (σ,φ) which exists and is unique on $[\sigma-r,b]$, $b>\sigma-r$. Let $W\subseteq\Omega$ be the compact set defined by $W=\{(t,x_t):t\in[\sigma,b]\}$, and let V be a neighborhood of W on which f is bounded. If (σ^k,φ^k,f^k), k=1,2,..., satisfies $\sigma^k\to\sigma$, $\varphi^k\to\varphi$, and $|f^k-f|_V\to 0$ as $k\to\infty$, then there is a K such that for $k\ge K$ each solution $x^k=x^k(\sigma^k,\varphi^k,f^k)$ through (σ^k,φ^k) of $\dot x(t)=f^k(t,x_t)$ exists on $[\sigma^k-r,b]$ and $x^k\to x$ uniformly on $[\sigma^k-r,b]$. (Since all x^k may not be defined on $[\sigma^k-r,b]$, by $x^k\to x$ uniformly on $[\sigma^k-r,b]$ we mean that for any $\varepsilon>0$ there is a $k_1(\varepsilon)$ such that $x^k(t)$, $k\ge k_1(\varepsilon)$ is defined on $[\sigma^k-r+\varepsilon,b]$ and $x^k\to x$ uniformly on $[\sigma^k-r+\varepsilon,b]$.)*

Let x be a solution of (1.1) on the interval $[\sigma,a)$, $a>\sigma$. We say that $\hat x$ is a *continuation* of x if there is a $b>a$ such that $\hat x$ is defined on $[\sigma-r,b)$, coincides with x on $[\sigma-r,a)$, and x satisfies the equation (1.1) on $[\sigma,b)$. A solution x is said *noncontinuable* if no such continuation exists, that is the interval $[\sigma,a)$ is the maximal interval of existence of the solution x. The existence of a noncontinuable solution is a consequence of Zorn's lemma.

Theorem 1.1.4. *Suppose Ω open in $\mathbb{R}\times C$, $f:\Omega\to\mathbb{R}^n$ completely continuous and let x be a noncontinuable solution of (1.1) on $[\sigma-r,b)$. Then for any closed and bounded set $U\in\mathbb{R}\times C$, $U\subset\Omega$, there is a t_U such that $(t,x_t)\notin U$ for $t_U\le t<b$.*

The previous theorem says that solutions of equation (1.1) exist for any time $t\ge\sigma$ or become unbounded (with respect to Ω) in finite time and it gives conditions under which the trajectory (t,x) in $\mathbb{R}\times C$ of a noncontinuable solution of $[\sigma,b)$ approaches the boundary of Ω as $t\to b^-$. If the condition that f is completely continuous is not imposed, then it is conceivable that the trajectory $\{(t,x_t):\sigma\le t<b\}$ itself is a closed bounded subset

of Ω; that is the curve $(t, x(t))$ oscillates so badly as a subset of $\mathbb{R} \times \mathbb{R}^n$ that there are no limit points of (t, x_t) in $\mathbb{R} \times C$ as $t \to b^-$.

Theorem 1.1.5. *Suppose that $x : [-r, \alpha) \to \mathbb{R}^n$, $r > 0$, α finite, is an arbitrary bounded continously diffrentiable function satisfying the property that $x(t)$ does not approach a limit set as $t \to \alpha^-$. Then there is a continuous function $f : C \to \mathbb{R}^n$ such that x is a noncontinuable solution of the DDE(f) on $[-r, \alpha)$.*

The theorem on continuation of solutions states that a noncontinuable solution of a DDE(f) must leave every bounded and closed set W in the domain Ω of the equation, supposing that f is completely continuous on Ω. A continuous function on Ω is not necessarily completely continuous on Ω if $r > 0$, that is if C is infinite-dimensional.
The theorem on continuation of solutions does not hold if f is not completely continuous.

For the ode

$$\begin{cases} \dot{x}(t) = f(t, x_t) \\ x(0) = x_0 \end{cases} \tag{1.7}$$

if $f \in C^k$, $k \geq 0$ then the solution $x(t)$ of (1.7) is itself in the space C^k in its maximal interval of existence. For the equation (1.1) the same is true only for some values of t. In the Theorem 1.1.3 were given sufficient conditions to assure that the solution $x(\sigma, \varphi, f)$ of a DDE(f) depends continuously on (σ, φ, f). Here we state some results on the differentiability of solutions with respect to (σ, φ, f).

Theorem 1.1.6 (Smoothing property)**.** *Let $x(t)$ be the solution of*

$$\begin{cases} \dot{x}(t) = f(t, x_t) \\ x_\sigma = \varphi, \qquad\qquad \varphi \in C, \end{cases} \tag{1.8}$$

where $f \in C^k, k \geq 1$ and let $I = [\sigma, t_x)$ be the maximal interval of existence for $x(t)$. Then $x(t) \in C^l$ on $[\sigma + lr, t_x)$ for l=0,1,...k.

In other words $x(t)$ is even more regular increasing T. If $f \in C^1$, $\Phi \subset C$ is a bounded closed set and $T(t)\Phi \equiv \bigcup_{\varphi \in \Phi} X_t(\sigma, \varphi)$ is a bounded set for $t \geq \sigma + r$, then $T(t)\Phi$ is compact as $t \geq \sigma + r$.

If Ω is open in $\mathbb{R} \times C$, let $C^p(\Omega, \mathbb{R}^n)$, $p \geq 0$ be the space of functions mapping Ω in $\mathbb{R}^n$ and bounded continuously differentiable up to order p with respect to φ on Ω. The space $C^p(\Omega, \mathbb{R}^n)$ becomes a Banach space with the norm of supremum over all derivatives up to order p.

Next theorem follows from contraction principle in Banach spaces.

Theorem 1.1.7. *If $f \in C^p(\Omega, \mathbb{R}^n)$, $p \geq 1$, then the solution $x(\sigma, \varphi, f)(t)$ of DDE(f) through (σ, φ) is unique and continuously differentiable with respect*

to (φ, f) for t in a compact set in the domain of $x(\sigma, \varphi, f)$. Moreover, for any $t \geq \sigma$ the derivative of x with respect to φ: $D_\varphi x(\sigma, \varphi, f)(t)$ is a linear operator from C to $\mathbb{R}^n$, $D_\varphi x(\sigma, \varphi, f)(\sigma) = I$, the identity, and $D_\varphi x(\sigma, \varphi, f)\psi(t)$ for any $\psi \in C$ satisfies the linear variational equation:

$$y(t) = D_\varphi f(t, x_t(\sigma, \varphi, f))y_t.$$

Moreover, for any $t \geq \sigma$, $D_f x(\sigma, \varphi, f)(t)$ is a linear operator from $C^p(\Omega, \mathbb{R}^n)$ in $\mathbb{R}^n$, $D_f x(\sigma, \varphi, f)(\sigma) = 0$ and $D_f x(\sigma, \varphi, f)g(t)$ for $g \in C^p(\Omega, \mathbb{R}^n)$ satisfies the linear variational equation:

$$\dot{z}(t) = D_\varphi f(t, x_t(\sigma, \varphi, f))z_t + g(t, x_t(\sigma, \varphi, f)).$$

1.2 Dynamical systems and invariance

For autonomous ODEs, bounded solutions have nonempty, compact, connected an invariant Ω-limit sets. Similar results hold also for DDEs.

Definition 1.2.1 (Process)**.** *Let X be a Banach space, $u : \mathbb{R} \times X \times \mathbb{R}^+ \to X$ a given mapping and let us define $U(\sigma, t) : X \to X$ for $\sigma \in \mathbb{R}, t \in \mathbb{R}^+$ by $U(\sigma, t)x = u(\sigma, x, t)$. A process on X is a mapping $u : \mathbb{R} \times X \times \mathbb{R}^+ \to X$ satisfying the following properties:*

(i) *u is continuous;*

(ii) *$U(\sigma,0) = I$;*

(iii) *$U(\sigma+s,t)U(\sigma,s) = U(\sigma, s+t)$.*

A process u is said p-periodic, $p > 0$ if $U(\sigma+p,t)=U(\sigma,t)$ for $\sigma \in \mathbb{R}$, $t \in \mathbb{R}^+$.

Suppose $f : \mathbb{R} \times C \to \mathbb{R}^n$ is completely continuous and let $x(\sigma, \varphi)$ be the solution of DDE(f):

$$\dot{x}(t) = f(t, x_t), \quad x_\sigma = \varphi. \tag{1.9}$$

We assume that x is uniquely defined for $t \geq \sigma$. Theorem 1.1.3 implies that $x(\sigma, \varphi)(t)$ is continuous in σ, φ, t for $\sigma \in \mathbb{R}$, $\varphi \in C$ e $t \geq \sigma$. Define

$$u(\sigma, \varphi, \tau) = x_{\sigma+\tau}(\sigma, \varphi), \ (\sigma, \varphi, \tau) \in \mathbb{R} \times C \times \mathbb{R}^+,$$

then u is a process on C. Moreover, let $T(t, \sigma)$ be the solution operator for (1.9) defined by:

$$T(t, \sigma)\varphi = x_t(\sigma, \varphi);$$

then $U(\sigma, \tau) = T(\sigma + \tau, \sigma)$, where $U(\sigma, \tau)\varphi = u(\sigma, \varphi, t)$.
We will say that $u(\sigma, \varphi, \tau)$ is the process generated by the DDE(f).

If $f(\sigma + p, \varphi) = f(\sigma, \varphi)\, p > 0 \ \forall(\sigma, \varphi) \in \mathbb{R} \times C$ then the process generated by the DDE(f) is p-periodic.

Definition 1.2.2. *A process is said a (continuous) dynamical system, or an autonomous process, if $U(\sigma,t)$ is indipendent by σ; that is if*

$$T(t) = U(0,t), \qquad t \geq 0,$$

then T(t)x is continuous for $(t,x) \in \mathbb{R}^+ \times X$,

$$T(0) = I, \quad T(t+\tau) = T(t)T(\tau), \quad t,\tau \in \mathbb{R}^+.$$

We also call $T(t), t \geq 0$ a (continuous) dynamical system.

If $S : X \to X$ is a continuous map, the family $\left\{S^k, k \geq 0\right\}$ of iterates of S is said a discrete dynamical system. If u is a p-periodic process and $S = U(0,p)$, then $S^k = U(0,kp)$. We refer to this discrete dynamical system as the discrete dynamical system generated by the map of the p-periodic process.

In a process $u(\sigma,x,t)$ can be considered as the state of the system at time $\sigma + t$ when initial state at time σ is x.

Definition 1.2.3. *Suppose that u is a process in X. The trajectory $\tau^+(\sigma,x)$ through $(\sigma,x) \in \mathbb{R} \times X$ is:*

$$\tau^+(\sigma,x) = \left\{(\sigma+t, U(\sigma,t)x) : t \in \mathbb{R}^+\right\} \subset \mathbb{R} \times X.$$

The orbit $\gamma^+(\sigma,x)$ through (σ,x) is:

$$\gamma^+(\sigma,x) = \left\{U(\sigma,t)x : t \in \mathbb{R}^+\right\} \subset X.$$

If H is a subset of X, then

$$\tau^+(\sigma,H) = \bigcup_{x\in H} \tau^+(\sigma,x), \qquad \gamma^+(\sigma,H) = \bigcup_{x\in H} \gamma^+(\sigma,x).$$

A point $C \in X$ is said an equilibrium (or critical) point of a process u if $U(\sigma,t)C = C$ for $t \in \mathbb{R}^+$. If there is $\sigma \in \mathbb{R}$, $p > 0$, $x \in X$ such that $U(\sigma,t+p)x = U(\sigma,t)x$ for any $t \in \mathbb{R}^+$ then $\tau^+(\sigma,x)$ is said p-periodic.

If u is a process p-periodic on X, then the trajectory $\tau^+(\sigma+kp,x)$ for any integer $k \in \mathbb{R}$ is the traslated along reals of kp of the trajectory $\tau^+(\sigma,x)$. The orbits satisfy $\gamma^+(\sigma+kp,x) = \gamma^+(\sigma,x)$ for any integer $k \in \mathbb{R}$. If u is a dynamical system on X then $\tau^+(\sigma+s,x)$ is the traslated by s of $\tau^+(\sigma,x)$ for any $s \in \mathbb{R}$ and $\gamma^+(\sigma,x) = \gamma^+(0,x)$ for any $s \in \mathbb{R}$. In this last case we simply write $\gamma^+(x)$ for orbits.

Lemma 1.2.1. *For a continuous dynamical system, a trajectory is p-periodic if and only if the corresponding orbit is a closed curve. For a p-periodic process u, a trajectory through (σ,x) is kp-periodic for a positive integer k if and only if $T^k x = x$ where $T = U(\sigma,p)$.*

Lemma 1.2.2. *Let $\{T(t) : t \geq 0\}$ be a dynamical system on X. If there are sequences $\{x_n\} \subseteq X$, $\{\omega_n\} \subseteq (0, \infty)$ satisfying $T(\omega_n)x_n = x_n$, $\omega_n \to 0$ when $n \to \infty$ and some subsequence of $\{x_n\}$ converges to x_0, then x_0 is an equilibrium point.*

Definition 1.2.4. *Suppose that u is a process on X. A point $y \in X$ is said to be in the ω-limit set $\omega(\sigma, x)$ of an orbit $\gamma^+(\sigma, x)$ if there is a sequence $t_n \to \infty$ as $n \to \infty$ such that $U(\sigma, t_n)x \to y$ as $n \to \infty$. A point $y \in X$ is said to be in the α-limit set $\alpha(\sigma, x)$ of an orbit $\gamma^-(\sigma, x) = \bigcup_{t \leq 0} U(\sigma, t)x$ if $U(\sigma, t)$ is uniquely defined for $t \leq 0$ and there is a sequence $t_n \to -\infty$ as $n \to \infty$ such that $U(\sigma, t_n)x \to y$ as $n \to \infty$.*

Equivalently we have:

$$\omega(\sigma, x) = \bigcap_{t \geq 0} \overline{\bigcup_{\tau \geq t} U(\sigma, \tau)x}, \tag{1.10}$$

$$\alpha(\sigma, x) = \bigcap_{t \leq 0} \overline{\bigcup_{\tau \leq t} U(\sigma, \tau)x}, \tag{1.11}$$

For any subset $H \subseteq X$ we define ω- and α-limit sets of H, $\omega(\sigma, H)$, $\alpha(\sigma, H)$ by replacing x by H in (1.10), (1.11) respectively. If $\left\{T^k, k \geq 0\right\}$ is a discrete dynamical system of X, and $H \subseteq X$, then the ω-limit set of H is defined as:

$$\omega(H) = \bigcap_{j \geq 0} \overline{\bigcup_{n \geq j} T^n H},$$

and the α-limit set of H is defined as:

$$\alpha(H) = \bigcap_{j \leq 0} \overline{\bigcup_{n \leq j} T^n H},$$

provided that $T^n H$ is well defined for any $n \leq 0$.

For autonomous DDE(f),

$$\begin{cases} \dot{x}(t) = f(x_t), \\ x_\sigma = \varphi, \end{cases}$$

we have that $\omega(\sigma, x) = \omega(x)$ is independent on σ. So $y \in \omega(x)$ (resp. $\alpha(x)$) if and only if there is a sequence $t_n \to \infty$ (resp. $-\infty$) as $n \to \infty$ such that

$$\lim_{n \to \infty} x_{t_n}(\sigma, \varphi) = y. \tag{1.12}$$

Definition 1.2.5. *If u is a process on X, then an integral of the process on $\mathbb{R}$ is a continuous function $y : \mathbb{R} \to X$ such that for any $\sigma \in \mathbb{R}$, $\tau^+(\sigma, y(\sigma)) = \{(\sigma + t, y(\sigma + t)) : t \geq 0\}$. An integral y is an integral through $(\sigma, x) \in \mathbb{R} \times X$ if $y(\sigma) = x$. An integral set on $\mathbb{R}$ is a set M in $\mathbb{R} \times X$ such that for any $(\sigma, x) \in M$ there is an integral y on $\mathbb{R}$ through (σ, x) and $(s, y(s)) \in M$ for $s \in \mathbb{R}$. For any $\sigma \in \mathbb{R}$, let $M_\sigma = \{x \in X : (\sigma, x) \in M\}$.*

Definition 1.2.6. *If $\{T(t), t \leq 0\}$ is a dynamical system on X, then a set $Q \subseteq X$ is said invariant if $T(t)Q = Q$ for $t \geq 0$. This is equivalent to saying that through every point $x \in Q$ there is an integral y through $(0, x)$ such that $y(s) \in Q$, $s \in \mathbb{R}$.*

Definition 1.2.7. *If u is a dynamical system on X, then a subset $Q \subseteq X$ is said to be a positively (negatively) invariant set for u if for any point $x \in Q$, $\gamma^+(0, x) \subset Q$ (if $U(\sigma, t)$ is well defined for $t \leq 0$ and $\gamma^-(0, x) = \{U(\sigma, t)x : t \leq 0\} \subset Q$).*
Q is said an invariant set of u if $T(t)Q \equiv \bigcup_{x \in Q} T(t)x = Q$ for every $t \geq 0$.

Theorem 1.2.3. *If an autonomous DDE(f) generates a dynamical system and $\gamma^+(\varphi)$ is a bounded orbit, then $\omega(\varphi)$ is nonempty, compact, connected and invariant. If $H \subseteq C$ is connected and $\gamma^+(H)$ is bounded the same conclusion is true for $\omega(H)$.*

1.3 Stability theory

1.3.1 Stability and maximal invariant sets

Definition 1.3.1. *For a given process u on X and a given $\sigma \in \mathbb{R}$, we say a set $M \subset \mathbb{R} \times X$ attracts a set $H \subset X$ in σ if, for any $\varepsilon > 0$, there is a $t_0(\varepsilon, H, \sigma)$ such that $(\sigma + t, U(\sigma, t)H) \subset \mathcal{B}(M, \varepsilon)$ for $t \geq t_0(\varepsilon, H, \sigma)$. If M attracts a set H in σ for every $\sigma \in \mathbb{R}$, we say M attracts H.*

Definition 1.3.2. *For a given process u on X and a given $\sigma \in \mathbb{R}$, we say a set $M \subset \mathbb{R} \times X$ is stable in σ if, for any $\varepsilon > 0$, there is a $\delta(\varepsilon, \sigma) > 0$ such that $(\sigma, x) \in \mathcal{B}(M, \delta(\varepsilon, \sigma))$ implies that $(\sigma + t, U(\sigma, t)x) \in \mathcal{B}(M, \varepsilon)$ for $t \geq 0$. The set M is said stable if it is stable in σ for any $\sigma \in \mathbb{R}$. The set M is said unstable if it is not stable. The set M is said uniformly stable if it is stable and the number δ in the definition is independent on σ. The set M is said asymptotically stable in σ if it is stable in σ and there is a $\varepsilon_0(\sigma)$ such that $(\sigma + t, U(\sigma, t)) \to M$ as $t \to \infty$ for $(\sigma, x) \in \mathcal{B}(M, \varepsilon_0(\sigma))$. The set M is said uniformly asymptotically stable if it is uniformly stable and there is a $\varepsilon_0 > 0$ such that for every $\eta > 0$, there is $t_0(\eta, \varepsilon_0)$ with the property that $(\sigma + t, U(\sigma, t)) \in \mathcal{B}(M, \eta)$ for $t \geq t_0(\eta, \varepsilon_0)$ and for every x such that $(\sigma, x) \in \mathcal{B}(M, \varepsilon_0)$.*

If a process is generated by an ODE in $\mathbb{R}^n$, then $M \subset \mathbb{R} \times \mathbb{R}^n$ stable in a given $\sigma \in \mathbb{R}$ implies that M is stable in every $\sigma \in \mathbb{R}$, that is M is stable. This result does not hold for more general processes, in particular it is not true for DDE.

It is difficult to determine when stability in σ is equivalent to stability. From a practical point of view, it is not so relevant to consider systems that are stables in σ but there are not stables. Therefore this weaker concept will not be discussed in detail.

Suppose now that u is a p-periodic process, $K \subset X$ is a compact set, and that $M \subset \mathbb{R} \times K$ attracts compact sets of X. For any $\sigma \in \mathbb{R}$, let us consider the discrete dynamical system $\{U^k(\sigma, p),\ k \geq 0\}$. For this discrete system K attracts compact sets of X and we can define:

$$J_\sigma = \bigcap_{n \geq 0} U^n(\sigma, p)K, \quad \sigma \in \mathbb{R}. \tag{1.13}$$

J_σ is indipendent from K. If $\mathcal{J} \subset \mathbb{R} \times X$ is defined by:

$$\mathcal{J} = \bigcup_{\sigma \in \mathbb{R}} (\sigma, J_\sigma), \tag{1.14}$$

then $\mathcal{J}$ is an invariant set for the process u and

$$\mathcal{J}_\sigma \overset{def}{=} \{x \in X : (\sigma, x) \in \mathcal{J}\} = J_\sigma$$

is compact. $\bigcup_\sigma J_\sigma$ also is compact in X.

Theorem 1.3.1. *Suppose that u is a p-periodic process on X, and there is a compact set $K \subset X$ such that $\mathbb{R} \times K$ attracts compact sets of X, and let $\mathcal{J} \subset \mathbb{R} \times X$ be defined by (1.14). Then the following conclusion hold:*

(i) *$\mathcal{J}$ is connected;*

(ii) *$\mathcal{J}$ is independent of K, and it is a nonempty invariant set with $\mathcal{J}_\sigma$ compact, and $\mathcal{J}$ is maximal with respect to this property;*

(iii) *$\mathcal{J}$ is stable;*

(iv) *For any compact set $H \subset X$, $\mathcal{J}$ attracts H.*

Theorem 1.3.2. *For a p-periodic, linear, nonhomogeneous DDE, the existence of a bounded solution for $t \geq 0$ implies the existence of a p-periodic solution.*

Suppose $f : \mathbb{R} \times C \to \mathbb{R}^n$ continuous and consider the DDE(f) (1.1). We will suppose that function f is completely continuous and that it satifsfies sufficient conditions of regolarity to assure that solution $x(\sigma, \varphi)(t)$ through (σ, φ) is continuous in (σ, φ, t) in the domain of the function.

Definition 1.3.3. *Suppose $f(t, 0) = 0\ \forall t \in \mathbb{R}$.*

- *The solution $x = 0$ of equation (1.1) is said stable if for any $\sigma \in \mathbb{R}$, $\varepsilon > 0$,there is a $\delta = \delta(\varepsilon, \sigma)$ such that $\varphi \in \mathcal{B}(0, \delta)$ implies $x_t(\sigma, \varphi) \in \mathcal{B}(0, \varepsilon)$ for $t \geq \sigma$.*

- *The solution $x = 0$ of equation (1.1) is said asymptotically stable if it is stable and there is a $b_0 = b_0(\sigma) > 0$ such that $\varphi \in \mathcal{B}(0, b_0)$ implies $x(\sigma, \varphi)(t) \to 0$ if $t \to \infty$.*

- *Solution $x = 0$ is said uniformly asymptotically stable if the number δ in the definition is independent to σ.*

- *Finally it is said uniformly asymptotically stable if it is uniformly stable and there is a $b_0 > 0$ such that for any $\eta > 0$ there is a $t_0(\eta)$ such that $\varphi \in \mathcal{B}(0, b_0)$ implies $x_t(\sigma, \varphi) \in \mathcal{B}(0, \eta)$ for $t \geq \sigma + t_0(\eta)$ for any $\sigma \in \mathbb{R}$.*

If $y(t)$ is a generic solution of equation (1.1), then y is said to be stable if solution $z = 0$ of equation

$$\dot{z}(t) = f(t, z_t + y_t) - f(t, y_t)$$

is stable and similarly are defined other concepts.

Lemma 1.3.3. *If there is a $\omega > 0$ such that $f(t + \omega, \varphi) = f(t, \varphi)$ for every $(t, \varphi) \in \mathbb{R} \times C$, then solution $x = 0$ is stable (asymptotically stable) if and only if it is uniformly stable (uniformly asymptotically stable).*

Definition 1.3.4. *A solution $x(\sigma, \varphi)$ of a DDE(f) is bounded if there is a $\beta(\sigma, \varphi)$ such that $|x(\sigma, \varphi)(t)| < \beta(\sigma, \varphi)$ for $t \geq \sigma - r$. Solutions are uniformly bounded if for any $\alpha > 0$, there is a $\beta = \beta(\alpha) > 0$ such that for any $\sigma \in \mathbb{R}$, $\varphi \in C$ and $|\varphi| \leq \alpha$, we have $|x(\sigma, \varphi)(t)| \leq \beta(\alpha)$ for all $t \geq \sigma$.*

1.3.2 The method of Liapunov functionals

In this section we give sufficient conditions to stability and instability of solution $x = 0$ of equation (1.1) generalizing the method of Liapunov by which we may obtain stability results, and often global ones, in the context of DDE(f):

$$\dot{x}(t) = f(t, x_t), \tag{1.15}$$

where $f : \mathbb{R} \times C \to \mathbb{R}^n$ is completely continuous and $f(t, 0) = 0$.

Let $V : \mathbb{R} \times C \to \mathbb{R}^n$ be continuous and $x(\sigma, \varphi)$ be the solution of (1.15)) through (σ, φ). We denote:

$$\dot{V} = \dot{V}(t, \varphi) = \limsup_{h \geq 0^+} \frac{1}{h}[V(t + h, x_{t+h}(t, \varphi)) - V(t, \varphi)].$$

Next theorem contains general stability results of the method of Liapunov functionals.

Theorem 1.3.4. *Let u(s), v(s), w(s): $\mathbb{R}^+ \to \mathbb{R}^+$ be continuous and non-decreasing, $u(s) > 0, v(s) > 0$ for $s > 0$ and u(0)=v(0)=w(0)=0. The following statements are true:*

(i) *If there is a* $V : \mathbb{R} \times C \to \mathbb{R}$ *such that*

$$u(|\varphi(0)|) \leq V(t, \varphi) \leq v(\|\varphi\|),$$

$$\dot{V}(t, \varphi) \leq -w(|\varphi(0)|),$$

then $x = 0$ *is uniformly stable.*

(ii) *If, in addition to* ***(i)****,* $\lim_{s \to +\infty} u(s) = +\infty$*, then solutions of (1.15) are uniformly bounded (that is, for any* $\alpha > 0$*, there is a* $\beta = \beta(\alpha) > 0$ *such that, for all* $\sigma \in \mathbb{R}$*,* $\varphi \in C$*,* $\|\varphi\| \leq \alpha$ *we have* $|x(\sigma, \varphi)(t)| \leq \beta$ *for all* $t \geq \sigma$*.)*

(iii) *If, in addition to* ***(i)****,* $w(s) > 0$ *for* $s > 0$*, then x=0 is uniformly asymptotically stable.*

We say that $V : \mathbb{R} \times C \to \mathbb{R}$ is a *Liapunov functional* for equation (1.15) if it satisfies Theorem 1.3.4-(i).

Next Theorem gives sufficient conditions to instability of solution $x = 0$ of equation (1.15).

Theorem 1.3.5. *Suppose that* $V(\varphi)$ *is a scalar functional completely continuous on* C *and that there is a* $\gamma > 0$ *and an open set* U *in* C *such that:*

(i) $V(\varphi) > 0$ *on* U*,* $V(\varphi) = 0$ *on the boundary of* U*;* $0 \in U \cap \bar{B}(0, \gamma)$*;*

(ii) *zero belongs to the closure of* $U \cap B(0, \gamma)$*,*

(iii) $V(\varphi) \leq u(|\varphi(0)|)$ *on* $U \cap B(0, \gamma)$*;*

(iv) $\dot{V}_-(\varphi) \geq w(|\varphi(0)|)$ *for* $(t, \varphi) \in [0.\infty) \times U \cap B(0, \gamma)$*, where*

$$\dot{V}_- \equiv \liminf_{h \to 0^+} \frac{1}{h}[V(x_{t+h}(t, \varphi)) - V(\varphi)],$$

and where $u(s)$*,* $w(s)$ *are continuous, positive and increasing for* $s > 0$*,* $u(0) = w(0) = 0$*. Then* $x = 0$ *is unstable.*

We consider now autonomous systems:

$$\dot{x}(t) = f(x_t), \tag{1.16}$$

where $f : C \to \mathbb{R}^n$ is completely continuous and solutions of (1.16) are unique and depend continuously on initial conditions.

For autonomous ODEs Liapunov-La Salle Theorem is a very useful tool to state sufficient conditions of (global) stability of equilibrium points or of attractors.

A similar Theorem holds also in the context of DDE.

For a continuous functional $V : C \to \mathbb{R}$, we define:

$$\dot{V}(\varphi) = \limsup_{h \to 0^+} \frac{1}{h}[V(x_h(\varphi)) - V(\varphi)],$$

the derivative of V along the solution of (1.16). In order to state the Liapunov-La Salle type theorem for DDE(f) (1.16), we need the following definition:

Definition 1.3.5. *We say that $V : C \to \mathbb{R}$ is a Liapunov functional on a set G in C for equation (1.16) if it is continuous on $\bar{G}$ and $\dot{V} \leq 0$ on G. We also define*
$E = \left\{ \varphi \in \bar{G} : \dot{V}(\varphi) = 0 \right\}$,
M= the largest set in E invariant with respect to (1.16).

We state now the Liapunov-La Salle type theorem for DDE(f) (1.16).

Theorem 1.3.6. *If V is a Liapunov functional on G and $x_t(\varphi)$ is a bounded solution of (1.16) that stays in G, then $\omega(\varphi) \subset M$; that is, $x_t(\varphi) \to M$ as $t \to +\infty$.*

Corollary 1.3.7. *If V is a Liapunov functional on $U_l = \{\varphi \in C : V(\varphi) < l\}$ for equation (1.16) and there is a constant $K = K(l)$ such that φ in U_l implies that $|\varphi(0)| < K$, then for $\varphi \in U_l$, $\omega(\varphi) \subset M$.*

Corollary 1.3.8. *Suppose that $a(\cdot)$ and $b(\cdot)$ are continuous and nonnegative, that $a(0) = b(0) = 0$, and $\lim_{s \to +\infty} a(s) = +\infty$, and that $V : C \to \mathbb{R}$ is continuous and satisfies:*

$$V(\varphi) \geq a(|\varphi(0)|), \quad \dot{V}(\varphi) \leq -b(|\varphi(0)|).$$

then solution $x = 0$ of equation (1.16) is uniformly stable, and every solution is bounded. If, in addition, $b(s) > 0$ for $s > 0$, then $x = 0$ is globally asymptotically stable; that is every solution of (1.16) converges to $x = 0$ as $t \to +\infty$.

Theorem 1.3.9. *Suppose that 0 belongs to the closure of an open subset U in C and that N is an open neighborhood of 0 in C. Assume that:*

(i) *V is a Liapunov function on $G = N \cap U$.*

(ii) *$M \cap G$ is either the empty set or zero .*

(iii) *$V(\varphi) < \eta$ on G when $\varphi \neq 0$.*

(iv) *$V(0) = \eta$ and $V(\varphi) = \eta$ when $\varphi \in \partial G \cap N$.*

If N_0 is a bounded neighborhood of zero properly contained in N, then $\varphi \neq 0$ in $G \cap N_0$ implies there exists a τ such that $x_\tau(\varphi) \in \partial N_0$.

1.3.3 Razumikhin theorems

In the previous section, sufficient conditions for stability of a DDE were given in terms of the rate of change of functionals along solutions. The use of functionals is a natural generalization of the method of Liapunov for ODEs.
On the other hand, it is much simpler to handle functions than functionals, so it is natural to explore the possibility of using the rate of change of a function in $\mathbb{R}^n$ to determine sufficient conditions for stability. Results in this direction are generally referred to as theorems of Razumikhin type.

If $v : \mathbb{R}^n \to \mathbb{R}^n$ is a given positive function, continuously differentiable, then the derivative of v along a DDE(f) is given by:

$$\dot{v}(x(t)) = \frac{\partial v(x(t))}{\partial x} f(x_t). \tag{1.17}$$

In order for $\dot{v}$ to be nonpositive for all initial data, we will be forced to impose very severe restrictions on $f(\varphi)$. In fact, the point $\varphi(0)$ must play a dominant role and, therefore, the results will apply only to equations that are very similar to ODEs.

But we may see that it is not necessary to require that $\dot{v}$ is nonpositive for every initial condition in order to have stability. In fact if a solution of DDE(f) begins in a ball and is to leave this ball at some time t, then $|x_t| = |x(t)|$; that is $|x(t+\theta)| \leq |x(t)|$ for all $\theta \in [-r, 0]$. Consequently, one needs only consider initial data satisfying this latter property. This is the basic idea exploited in this section.

If $V : \mathbb{R}\times\mathbb{R}^n \to \mathbb{R}$ is a continuous function, then $\dot{V}(t, \varphi(0))$, the derivative of V along solutions of DDE(f) is defined by:

$$\dot{V}(t, \varphi(0)) = \limsup_{h\to 0^+} \frac{1}{h}[V(t+h, x(t,\varphi)(t+h)) - V(t, \varphi(0))]$$

where $x(t, \varphi)$ is the solution of DDE(f) through (t, φ).

Theorem 1.3.10. *Suppose $f : \mathbb{R} \times C \to \mathbb{R}^n$ maps $\mathbb{R}\times$(bounded sets of C) into bounded sets of $\mathbb{R}^n$ and consider the DDE(f). Suppose $u, v, w : \mathbb{R}^+ \to \mathbb{R}^+$ are continuous, nondescreasing functions $u(s)$, $v(s)$ positive for $s > 0$, $u(0) = v(0) = 0$, v strictly increasing. If there exists a continuous function $V : \mathbb{R} \times \mathbb{R}^n \to \mathbb{R}$ such that*

$$u(|x|) \leq V(t, x) \leq v(|x|), \quad t \in \mathbb{R},\ x \in \mathbb{R}^n, \tag{1.18}$$

and

$$\dot{V}(t, \varphi(0)) \leq -w(|\varphi(0)|) \quad \text{se } V(t+\theta, \varphi(\theta)) \leq V(t, \varphi(0)), \tag{1.19}$$

for $\theta \in [-r, 0]$, then solution $x = 0$ of DDE(f) is uniformly stable.

Theorem 1.3.11. *Suppose all the conditions of Theorem 1.3.10 are satisfied and in addition $w(s) > 0$ for $s > 0$. If there exists a continuous nondecreasing function $p(s) > s$ for $s > 0$ such that condition (1.18) is strengthened in:*

$$\dot{V}(t, \varphi(0)) \leq -w(|\varphi(0)|) \quad if\ V(t+\theta, \varphi(\theta)) \leq pV(t, \varphi(0)), \tag{1.20}$$

for $\theta \in [-r, 0]$, then solution $x = 0$ of DDE(f) is uniformly asymptotically stable. If $u(s) \to \infty$ as $s \to \infty$, then solution $x = 0$ is also a global attractor for DDE(f).

Theorem 1.3.12. *Suppose $f : \mathbb{R} \times C \to \mathbb{R}^n$ maps $\mathbb{R}\times$(bounded sets of C) into bounded sets of $\mathbb{R}^n$ and consider DDE(f). Suppose $u, v, w : \mathbb{R}^+ \to \mathbb{R}^+$ are continuous nonincreasing functions, $u(s) \to \infty$ as $s \to \infty$. If there is a continuous function $V : \mathbb{R} \times \mathbb{R}^n \to \mathbb{R}$ and a continuous nondecreasing function $p : \mathbb{R}^+ \to \mathbb{R}^+$, $p(s) > s$ for $s > 0$ and a constant $H \geq 0$ such that:*

$$u(|x|) \leq V(t, x) \leq v(|x|) \quad t \in \mathbb{R}, x \in \mathbb{R}^n$$

and $\dot{V}(t, \varphi) \leq -w(|\varphi(0)|)$. If $|\varphi(0)| \geq H$, $V(t+\theta, \varphi(\theta)) < p(V(t, \varphi(0)))$, $\theta \in [-r, 0]$, then solutions of DDE(f) are uniformly ultimately bounded.

1.4 Periodic solutions of autonomous equations - Hopf bifurcations.

Many observations realised that real world systems that have a stable steady state may lose the stability and begins to oscillate first with small amplitudes and then wilder as a parameter of the system (for example the delay lenght) is varied. In most cases as the amplitude of oscillation get larger these systems collapse, break down or just remain oscillatory.

The mathematical modeling of such phenomena leads to systems of differential equations depending on a parameter and having isolated equilibrium point that is stable if the parameter belongs to some interval but loses its stability as the parameter crosses the boundary of this interval. At the same time, in the neighbourhood of the critical value of the parameter where the stability of the equilibrium is lost, small amplitude periodic solutions occur. The appearance of small amplitude periodic solutions simultaneously with the loss of stability of an equilibrium is a generic phenomenon in systems depending on a parameter and having an isolated equilibrium for every parameter value. The important thing is that the linearization of the system at the equilibrium point must have a pair of complex conjugated eigenvalues (depending on the parameter), and at the critical value of the parameter this pair has to cross from the left-hand half plane to the right-hand half in the complex plane and has to do it with non-zero speed.

In this section we will indicate a procedure to determine periodic solutions of some classes of autonomous DDE. In particular we give special attention to one of the simplest methods in which nonconstant periodic solutions of autonomous equations can arise: Hopf bifurcations. As we know, even in ODE case one of the most simpler methods in which a nonconstant periodic solution can occur is via Hopf bifurcations. It happens when a real parameter α passes through a critical value α_0 and two eigenvalues cross the imaginary axis from left to right. Hopf bifurcation theorem ensures the local existence of emerging periodic solutions.

Going back to DDE theory we consider a one-parameter family of the form:

$$\dot{x}(t) = F(\alpha, x_t) \tag{1.21}$$

where $F(\alpha, \varphi)$ has continuous first and second derivatives in α, φ for $\alpha \in \mathbb{R}$, $\varphi \in C$, and $F(\alpha, 0) = 0$ for every α. We define $L : \mathbb{R} \times C \to \mathbb{R}^n$ as:

$$L(\alpha)\psi = D_\varphi F(\alpha, 0)\psi \tag{1.22}$$

where $D_\varphi F(\alpha, 0)$ is the derivative of $F(\alpha, \varphi)$ with respect to φ in $\varphi = 0$ and we define:

$$f(\alpha, \varphi) = F(\alpha, \varphi) - L(\alpha)\varphi. \tag{1.23}$$

We also suppose:

(H1) The linear DDE($L(0)$) has a simply purely imaginary characteristic root: $\lambda_0 = i\nu_0 \neq 0$ and all characteristic roots $\lambda_j \neq \lambda_0, \bar{\lambda_0}$ satisfy $\lambda_j \neq m\lambda_0$ for any integer m.

Since $L(\alpha)$ is continuously differentiable in α, there is a $\alpha_0 > 0$ and a simple characteristic root $\lambda(\alpha)$ of the DDE($L(\alpha)$) that has a continuous derivative $\lambda'(\alpha)$ in α for $|\alpha| < \alpha_0$. Suppose:

(H2) $\mathrm{Re}\lambda'(0) \neq 0$.

We will show that (H1) and (H2) imply there are nonconstant periodic solutions of equation (1.21) for α small that have period close to $2\pi/\nu_0$. Before stating this result precisely, we have to introduce some notations.

By taking a_0 sufficiently small, we may assume $\mathrm{Im}\lambda(\alpha) \neq 0$ for $|\alpha| < \alpha_0$ and obtain a function $\varphi_\alpha \in C$ that is continuously differentiable in α and that is a basis for the solutions of the DDE($L(\alpha)$) corresponding to $\lambda(\alpha)$. The functions:

$$(\mathrm{Re}\varphi_\alpha, \mathrm{Im}\varphi_\alpha) \stackrel{def}{=} \Phi_\alpha$$

form a corresponding basis for the characteristic roots $\lambda(\alpha)$, $\bar{\lambda}(\alpha)$. Similarly we obtain a basis Ψ_α for the adjoint equation with $(\Psi_\alpha, \Phi_\alpha) = I$.

If we decompose C by $(\lambda(\alpha), \bar{\lambda}(\alpha))$ as $C = P_\alpha \oplus Q_\alpha$, then Φ_α is a basis of P_α. We know that

$$\Phi_\alpha(\theta) = \Phi_\alpha(0)e^{B(\alpha)\theta}, \quad -r \leq \theta \leq 0, \tag{1.24}$$

and the eigenvalues of the 2×2 matrix $B(\alpha)$ are $\lambda(\alpha)$ and $\bar{\lambda}(\alpha)$. By a change of coordinates and redefining parameter α we may assume that:

$$B(\alpha) = v_0 B_0 + \alpha B_1(\alpha) \tag{1.25}$$

$$B_0 = \begin{bmatrix} 0 & 1 \\ -1 & 0 \end{bmatrix}, \qquad B_1(\alpha) = \begin{bmatrix} 1 & \gamma(\alpha) \\ -\gamma(\alpha) & 1 \end{bmatrix}$$

where $\gamma(\alpha)$ is continuously differentiable on $0 \leq |\alpha| < \alpha_0$

We can now state the Hopf bifurcation theorem.

Theorem 1.4.1. *Suppose $F(\alpha, \varphi)$ has continuous first and second derivatives with respect to α, φ, $F(\alpha, 0) = 0$ for all α and hypothesis (H1) and (H2) are satisfied. Then there are constants $a_0 > 0$, $\alpha_0 > 0$, $\delta_0 > 0$, functions $\alpha(a) \in \mathbb{R}$, $\omega(a) \in \mathbb{R}$, and an $\omega(a)$-periodic function $x^*(a)$, with all functions being continuously differentiable in a for $|a| < a_0$, such that $x^*(a)$ is a solution of equation (1.21) with:*

$$x_0^*(a)^{P_\alpha} = \varphi_{\alpha(a)} y^*(a), \quad x_0^*(a)^{Q_\alpha} = z_0^*(a)$$

where $y^*(a) = (a, 0)^T + o(|a|)$, $z_0^*(a) = o(|a|)$ as $|a| \to 0$. Furthermore, for $|\alpha| < \alpha_0$, $|\omega - (2\pi/\nu_0)| < \delta_0$, every ω-periodic solution of equation (1.21) with $|x_t| < \delta_0$ must be of this type except for a translation in phase.

1.5 Characteristic equation analysis

Now we have to introduce methods of analysis that will be utilised in chapters 4 and 5 of this work to study qualitative properties of a model of tumor-immune system interaction with delay. In particular we are interested to analysis of stability of equilibrium points and to possible occurrence of Hopf bifurcations and oscillatory dynamics arising from them. Therefore in this section we will see how to handle this problem both for equations with discrete delay, that is of the form:

$$\dot{x}(t) = f(t, x(t), x(t - r_1), ..., x(t - r_m)),$$

and in the case of distributed delay, that is for integro-differential equations of the form:

$$\dot{x}(t) = \int_{-\infty}^{t} k(t - \theta) G(x(\theta)) d\theta,$$

where integration kernel is choosen of a specific type to permit a strong simplification in qualitative study that otherwise may result very complicated.

Most studies on delay differential equations start from the local stability analysis of some special solutions. The standard approach is to analyze the stability of the linearized equations about the special solution. Stability of the zero solution depends on the locations of the roots of the associated characteristic equation.

If delays are finite, characteristic equations are functions to delay and so are roots of these equations. By changing the value of the delay, stability of solutions can also change. Such phenomena are often referred to as stability switches.

In this section the stability of DDE is referred to as the stability of its zero solution.

We will consider the following equation:

$$\sum_{k=0}^{n} a_k \frac{d^k}{dt^k} x(t) + \sum_{k=0}^{n} b_k \frac{d^k}{dt^k} x(t-\tau) = 0, \tag{1.26}$$

we know that if the associated characteristic equation has only roots with negative real part, and if all roots are uniformly bounded away from the imaginary axis, then the zero solution of (1.26) is uniformly asymptotically stable. So, stability analysis reduces to determine conditions under which every root of

$$\sum_{k=0}^{n} a_k \lambda^k + (\sum_{k=0}^{n} b_k \lambda^k) e^{-\lambda\tau} = 0, \tag{1.27}$$

lies in the left half of the complex plane and is uniformly bouded away from the imaginary axis. We denote:

$$P(\lambda) = \sum_{k=0}^{n} a_k \lambda^k, \quad Q(\lambda) = \sum_{k=0}^{n} b_k \lambda^k.$$

And in addition we assume, without loss of generality $a_n = 1$. It holds:

Theorem 1.5.1. *If $|b_n| > 1$, then for any $\tau > 0$, there is an infinite number of roots of*

$$P(\lambda) + Q(\lambda) e^{-\lambda\tau} = 0,$$

with positive real parts.

Consequently we have

Theorem 1.5.2. *If $|b_n| > 1$, then the trivial solution of (1.26) is unstable for every $\tau > 0$.*

Furthermore:

Theorem 1.5.3. *Let $f(\lambda,\tau)=\lambda^n+\alpha\lambda^n e^{-\lambda\tau}+g(\lambda,\tau)$, where $g(\lambda,\tau)$ is an analytic function. Assume $|\alpha|>1$, and*

$$\lim_{Re\lambda>0,\,|\lambda|\to\infty}\frac{1}{\lambda^n}g(\lambda,\tau)=0$$

Then for any $\tau>0$, there is an infinite number of roots of $f(\lambda,\tau)=0$ whose real parts are positive. In fact there is a sequence $\{\lambda_j\}$ of roots of $f(\lambda,\tau)=0$ such that $|\lambda_j|\to\infty$ and $\lim_{j\to\infty}\mathrm{Re}\lambda_j=\frac{1}{\tau}\ln|\alpha|>0$, when $\tau>0$.

Theorem 1.5.4. *Let $f(\lambda,\tau)=\lambda^n+g(\lambda,\tau)$, where $g(\lambda,\tau)$ is an analytic function. Assume*

$$\alpha=\limsup_{Re\lambda>0,\,|\lambda|\to\infty}|\lambda^{-n}g(\lambda,\tau)|<1$$

Then, as τ varies, the sum of the multiplicities of roots of $f(\lambda,\tau)=0$ in the open right half-plane can change only if a root appears on or crosses the imaginary axis.

1.5.1 Discrete delay- second order equations

Let us discuss now the case of second order equations, since for study the model that we will analyze in this work, we have to use equations of this type. The general form of equation is:

$$\frac{d^2x(t)}{dt^2}+\alpha\frac{d^2x(t-\tau)}{dt^2}+a\frac{dx(t)}{dt}+b\frac{dx(t-\tau)}{dt}+cx(t)+dx(t-\tau)=0, \quad (1.28)$$

where τ,α,a,b,c,d are real constants. The corresponding characteristic equation is:

$$\lambda^2+\alpha\lambda^2e^{-\lambda\tau}+a\lambda+b\lambda e^{-\lambda\tau}+c+de^{-\lambda\tau}=0. \quad (1.29)$$

We see that if $|\alpha|>1$ trivial solution is always unstable for $\tau>0$, therefore we will assume $|\alpha|<1$.

Suppose $\lambda=i\omega,\omega>0$ is a root of (1.29) for some τ. Assume:
(1) $c+d\neq 0$, that implies $\omega\neq 0$, we have:

$$\begin{aligned} &c-\omega^2+b\omega sin\omega\tau+(d-\alpha\omega^2)cos\omega\tau=0,\\ &a\omega+b\omega cos\omega\tau-(d-\alpha\omega^2)sin\omega\tau=0. \end{aligned} \quad (1.30)$$

Hence:

$$(1-\alpha^2)\omega^4+(a^2-b^2+2d\alpha-2c)\omega^2+c^2-d^2=0. \quad (1.31)$$

whose roots are

$$\begin{aligned} \omega_\pm^2 \;=\; &\tfrac{1}{2}(1-\alpha^2)^{-1}\left\{(b^2+2c-2d\alpha-a^2)\pm[(b^2+2c-2d\alpha-a^2)^2\right.\\ &\left.-4(1-\alpha^2)(c^2-d^2)]^{1/2}\right\}. \end{aligned} \quad (1.32)$$

If $c^2\leq d^2$, then there is only one imaginary solution $\lambda=i\omega_+$, $\omega_+>0$. if $c^2>d^2$ there are two imaginary solutions $\lambda_\pm=i\omega_\pm$ with $\omega_+>\omega_->0$, provided that the following statements hold:

1. $b^2 + 2c - 2d\alpha - a^2 > 0$;

2. $(b^2 + 2c - 2d\alpha - a^2)^2 > 4(1 - \alpha^2)(c^2 - d^2)$,

and no such solutions otherwise.

Now we have to determine the sign of the derivative of $\mathrm{Re}\lambda(\tau)$ at the points where $\lambda(\tau)$ is purely imaginary.
Assume $a^2 + b^2 + (d - \alpha c)^2 \neq 0$ which guarantees that $\lambda = i\omega$ is simple.

For convenience, we study $(d\lambda/d\tau)^{-1}$. We have:

$$(\frac{d\lambda}{d\tau})^{-1} = \frac{(2\lambda + a)e^{\lambda} + b + 2\alpha\lambda}{\lambda(\alpha\lambda^2 + b\lambda + d)} - \frac{\tau}{\lambda},$$

and

$$e^{\lambda\tau} = -\frac{\alpha\lambda^2 + b\lambda + d}{\lambda^2 + a\lambda + c}. \tag{1.33}$$

With easy calculations we obtain:

$$sign(\frac{d\mathrm{Re}}{d\lambda})_{\lambda=i\omega} = sign(a^2 + 2\alpha d - 2c - b^2 + 2\omega^2(1 - \alpha^2)).$$

And this sign is positive for ω_+^2 and negative for ω_-^2.
In the case in which $c^2 < d^2$ only one imaginary root exists $\lambda = i\omega_+$, therefore the only crossing of the imaginary axis is from left to right as τ increases and the stability of the trivial solution can be only be lost and not recovered.
In the case $c^2 > d^2$ crossing from left to right with increasing τ occurs whenever τ assumes a value corresponding to ω_+, and crossing from right to left occurs for values corresponding to ω_-. From equation (1.30) we obtain the following two sets of values of τ for which there are imaginary roots:

$$\tau_{n,1} = \frac{\theta_1}{\omega_+} + \frac{2n\pi}{\omega_+}, \tag{1.34}$$

where $0 \leq \theta_1 < 2\pi$ and

$$\begin{aligned} cos\theta_1 &= -\frac{ab\omega_+^2 + (c - \omega_+^2)(d - \alpha\omega_+^2)}{b^2\omega_+^2 + (d - \alpha\omega_+^2)^2}, \\ sen\theta_1 &= \frac{(d - \alpha\omega_+^2)a\omega_+ - b\omega_+(c - \omega_+^2)}{b^2\omega_+^2 + (d - \alpha\omega_+^2)^2}; \end{aligned} \tag{1.35}$$

and

$$\tau_{n,2} = \frac{\theta_2}{\omega_-} + \frac{2n\pi}{\omega_-}, \tag{1.36}$$

where $0 \leq \theta_2 < 2\pi$ and

$$\begin{aligned} cos\theta_2 &= -\frac{ab\omega_-^2 + (c-\omega_-^2)(d-\alpha\omega_-^2)}{b^2\omega_-^2 + (d-\alpha\omega_-^2)^2}, \\ sen\theta_2 &= \frac{(d-\alpha\omega_-^2)a\omega_- - b\omega_-(c-\omega_-^2)}{b^2\omega_-^2 + (d-\alpha\omega_-^2)^2}; \end{aligned} \tag{1.37}$$

where $n = 0, 1, 2, ...$

In the case that $c^2 < d^2$ only $\tau_{0,1}$ need to be considered, since if (1.28) is asymptotically stable for $\tau = 0$, then it remains asymptotically stable until $\tau_{0,1}$, and it is unstable thereafter. At the value of $\tau = \tau_{0,1}$, (1.29) has pure imaginary roots $\pm i\omega_+$.
In the case $c^2 > d^2$ if (1.28) is stable for $\tau = 0$, then it follows that $\tau_{0,1} < \tau_{0,2}$, since the multiplicity of roots with positive real parts cannot become negative. We observe that

$$\tau_{n+1,1} - \tau_{n,1} = \frac{2\pi}{\omega_+} < \frac{2\pi}{\omega_-} = \tau_{n+1,2} - \tau_{n,2}.$$

Therefore, there can be only a finite number of switches between stability and instability. Moreover, it is easy to see that there exist values of the parameters that realize any number of such stability switches. However there exists a value of τ, $\tau = \hat{\tau}$, such that in $\tau = \hat{\tau}$ a stability switch occurs from stable to unstable, and for $\tau > \hat{\tau}$ the solution remains unstable.
If (1.28) is unstable for $\tau = 0$, then we can argue similarly. The equation (1.28) can either be unstable for all $\tau > 0$ or exhibit any number of stability switches as in the preceding case.

As τ increases, the multiplicity of roots for which $\mathrm{Re}\lambda > 0$ is increased by two whenever τ passes through a vaue of $\tau_{n,1}$ and it is decreased by two whenever τ passes through a value of $\tau_{n,2}$.

We can summarize the analysis carried out above in a Theorem:

Theorem 1.5.5. *In (1.28), assume that $|\alpha| < 1$, $c+d \neq 0$ and $a^2+b^2+(d-\alpha c)^2 \neq 0$. The number of different imaginary roots with positive (negative) imaginary parts of (1.29) can be zero, one or two only.*

1. *If there are no such roots, then the stability of the zero solution does not change for any $\tau \geq 0$.*

2. *If there is one imaginary root with positive imaginary part, an unstable zero solution never becomes stable for $\tau \geq 0$. If the zero solution is asymptotically stable for $\tau = 0$, then it is uniformly asymptotically stable for $\tau < \tau_{0,1}$ and it becomes unstable for $\tau > \tau_{0,1}$.*

3. *If there are two imaginary roots with positive imaginary part, $i\omega_+$ and $i\omega_-$, such that $\omega_+ > \omega_- > 0$, then the stability of the zero solution can change a finite number of times at most as τ is increased, and eventually it becomes unstable.*

1.5.2 Distributed delay - Linear chain trick

Finally we see how to study a special class of systems with distributed delay. In fact, often, above all considering models of biological phenomena, it is more realistic to consider distributed delays instead of discrete ones. With a distributed delay indeed the present state of the system depends on the cumulative effects of all past history of state variable.

We will study equations of the form:

$$\dot{x}(t) + bx(t) + c\int_{-\infty}^{t} k_{a,m}(t-\theta)x(\theta)d\theta = 0 \tag{1.38}$$

where $k_{a,m}$ is of erlangian type: $k_{a,m}(\theta) = \dfrac{a^m\theta^{m-1}e^{-a\theta}}{(m-1)!}$. We can rewrite this equation by introducing m new variables:

$$\begin{aligned} &x_0(t) = x(t), \\ &x_l(t) = \textstyle\int_{-\infty}^{t} k_{a,l}(t-\theta)x(\theta)d\theta, \qquad l = 1, ..., m. \end{aligned} \tag{1.39}$$

We observe that:

$$k_{a,l}(0) = 0, \quad l > 1; \qquad k_{a,1}(0) = a; \qquad k_{a,l}(\infty) = 0;$$

hence differentiating under the integral sign we note that new variables statisfy:

$$\dot{x_0}(t) = -bx_0(t) - cx_m(t), \tag{1.40}$$

$$\dot{x_l}(t) = a[x_{l-1}(t) - x_l(t)], \quad l = 1, ..., m. \tag{1.41}$$

The original integro-differential equation (1.38) is then replaced by the ordinary differential equation (1.40) linking $x_0(t)$ and $x_m(t)$, and (1.41) constitues the linear chain, that is a sequence of variable each driven by the previous one. Then every change in $x_0(t)$ in propagated down the chain until it reaches $x_m(t)$ that affects the derivative of $x_0(t)$. So the delay is caused by intermediate processes.

In particular the characteristic equation of the system is a polynomial of order $(m+1)$:

$$(\lambda + b)(a + \lambda)^m + ca^m = 0,$$

and the study of the system can be made considering (1.40)-(1.41) and utilising classical methods of theory of ODEs, for example analysing stability with Routh-Urwitz criterion.

Exponentially fading memory The simplest example of distributed delay and the more biologically sound is obtained considering as integration kernel:

$$k_{a,1}(\theta) = ae^{-a\theta}.$$

In this way the past moments are weighted with a density function exponentially decaying, and the influence of the past is increasing with the decrease of parameter a.

To analyze the system we have to introduce only one more variable, for example the equation (1.38) with $k_{a,1}$ is equivalent to the two equations-system:

$$\dot{x_0}(t) = -bx_0(t) - cx_1(t), \tag{1.42}$$
$$\dot{x_1}(t) = a[x_0(t) - x_1(t)]. \tag{1.43}$$

We will analyze our model with an exponentially distributed delay in the section 5.1.

Memory with a hump Another possible interesting case is obtained taking as integration kernel the strong erlangian distributed one:

$$k_{a,2}(\theta) = a^2\theta e^{-a\theta}.$$

In this case we have to analyze an ODE system with two more variables. For example the equation (1.38) with $k_{a,2}$ is equivalent to the three equations-system:

$$\dot{x_0}(t) = -bx_0(t) - cx_2(t), \tag{1.44}$$
$$\dot{x_1}(t) = a[x_0(t) - x_1(t)] \tag{1.45}$$
$$\dot{x_2}(t) = a[x_1(t) - x_2(t)]. \tag{1.46}$$

We will analyze our model with a strong erlangian distributed delay in the section 5.2.

1.6 Delayed logistic equation

As an example of delay differential equation with biological meaning, and to introduce the importance of delay in biological sytem, we report here the delayed logistic equation and its derivation in the context of population dynamics; both with discrete and with distributed delay.

Without considering time delay, the *pro capite* growth rate of a population is often assumed to be logistic, that is:

$$\frac{\dot{x}(t)}{x(t)} = r\left[1 - \frac{x(t)}{K}\right]; \tag{1.47}$$

where $x(t)$ denotes the quantity of the population at time t, $K > 0$ is the carrying capacity of the environment and $r > 0$ is the intrinsic birth rate.

One of the deficiencies of single population models like (1.47) is that the birth rate is considered to act instantaneously whereas there may be a time delay to take account of the time to reach maturity, the finite gestation period and so on.

If we think the gestation period is τ, then the *pro capite* growth rate function should carry a time delay $\tau > 0$, which results in:

$$\dot{x}(t) = rx(t)\left[1 - \frac{x(t-\tau)}{K}\right]; \tag{1.48}$$

This says that the regulatory effect depends on the population at an earlier time, $t - \tau$, rather than that at t.
This equation can be viewed as a particular case of the more general one in which the delay effect is taken as an average over past populations and which results in an integrodifferential equation. Thus a more accurate model can be made considering distributed delay instead of fixed lag delay:

$$\dot{x}(t) = rx(t)\left[1 - \frac{1}{K}\int_{-\infty}^{t} k(t-s)x(s)ds\right]. \tag{1.49}$$

where $k(t)$ is the weighting function which says how much emphasis should be given to the quantity of the population at earlier times to determine the present effect on resource availability. Practically $k(t)$ will tend to zero for large negative and positive t and will probably have a maximum at some representative time T.

Regarding tha analytical study of the delayed equation with discrete delay, we notice that the character of the solutions of (1.48), and the type of boundary conditions required are quite different from those of (1.47), and in general solutions have to be found numerically. Moreover, solutions of (1.48) can exhibit stable limit cycles for a large range of values of the product $r\tau$ of the birth rate and the delay, whereas solutions of (1.47) cannot exhibit periodic dynamics.

A direct application ([2]) of the theory exposed previously in this chapter, yields that the zero solution of (1.48) is asymptotically stable for $r\tau < \frac{\pi}{2}$ and unstable for $r\tau > \frac{\pi}{2}$. Moreover, it is been proved that if

$$r\tau < \frac{37}{24}, \qquad x(0) > 0, \tag{1.50}$$

then $x(t) \to K$ as $t \to +\infty$; and if $r\tau > \frac{\pi}{2}$ then (1.48) has a nonconstant periodic solution oscillating with respect to K.

As we said above , in the classical logistic model for a population limit cycles can not arise; though oscillations are often observed in reality in single population dynamics. The addition of the delay term, leading to equation

(1.48), permits instead to explain periodic dynamics depending on the value of delay.

This can be a justification for using delay models to study the dynamics of single populations which exhibit periodic behaviour.

Chapter 2

Tumor-Immune System Interaction and Mathematical Models

This chapter aims to point out some basic facts about tumors, immune system and tumor-immune system interaction. The problem of mathematical modeling in cancer research is therefore introduced, followed by a possible mathematical approach to this issue.

2.1 Tumor, Immune system, and their interaction

Cancer is a family of high-mortality diseases each differing from the other but all characterized by a remarkable lack of symptoms and by a time course that can be classified in a broad sense as nonlinear.

The broad outlines of how cancer cells develop and act are now becoming clear thanks to the discoveries of geneticists and cell biologists that have uncovered some basic mechanisms. Cancer is a complex phenomenon consequent on the breakdown of the normal cellular interaction, control of replication and induced cellular death.

If a malignant transformation occurs in the genetic control of cellular replication and interaction it will produce highly proliferative cells that tend to invade the host organism by rapid proliferation, and subsequent vascularization and metastasis.

Normally the immune system acts as defense against these alterations and the organism tries to counteract the action of malignant cells by sending killer cells in the tumor situ. It is the outcome of competition between malignant and killer cells to decide whether the cancer is rejected or becomes dominant.

The macroscopic complexity of tumor behavior reflects the intricacy of its underlying deregulating microscopic biochemical mechanisms, as phe-

nomenal progress in the field of molecular biology has explained.

Despite these advances, however, challenges remain in detection, as treatment and management of this disease, that include multidisciplinary approaches in many circumstances.

Immune system produces undifferentiated immune stem cells in the bone marrow. These cells subsequently differentiate into B- and T- lymphocytes and are released in the organism as a whole. B and T-cells have a wide range of antigen receptors, which allow the immune system to identify foreign antigens and to distinguish cancer cells.

T-cells perform the tumor elimination, but, to do that, B-cells must activate them with the help of cytokines (protein hormones produced by activated lymphocytes which mediate both natural and specific immunity).

When an unknown tissue, an organism or cancer cells appear in the body, the immune system tries to identify them and, if it succeeds, it tries to eliminate them. Therefore, the immune system cells are the first host cells to appear within a tumor.

The immune response begins when the cancer cells are recognized as being non self and consists of two different interacting responses: the cellular response and the humoral response. The cellular response is carried out by T-lymphocytes while the humoral response is related to B-lymphocytes.

Cancer cells are caught by macrophages which can be found in all tissue of the body and circulate round in the blood stream. An immune response to specific antigens starts by intensive proliferation of lymphocytes and only after some time it is accompanied by the production of antibodies and cytotoxic activity of T-cells.

When B-cells encounter the antigen they differentiate further into large cells that proliferate and secrete chemical substances capable of neutralizing the antigen (antibodies). On the other hand, the T-cells, after further differentiation in the Thymus, regulate the action of the B-cells by both activation and inhibition. They are also involved in immune responses that are directly cell mediated.

This cytotoxic activity is shared by other cellular species of the immune system, such as macrophages. Macrophages absorb cancer cells, eat them and release series of cytokines which activate T-helper cells that coordinate the counterattack. T-helper cells can also be directly stimulated to interact with antigens.

Helper cells cannot kill cancer cells, but they send urgent biochemical signals to a special type of T-lymphocytes called Natural killers (NKs). T-cells begin to multiply and release other cytokines that further stimulate more T-cells, B-cells or NK-cells.

As the number of B-cells increases, T-helper cells send a signal to start the process of production of antibodies. Antibodies circulate in the blood and are attached to cancer cells, which implies that they are more quickly

engulfed by macrophages or killed by natural killer cells. Like all T-cells, NK cells, trained to recognize one specific type of an infected cell or a cancer cell, are lethal.

The immune system comprises many types of lymphocytes which effectively destroy foreign strange cells after activation. Some lymphocytes (NKs) even exhibit natural cytotoxicity and do not require activation.

Inflammatory cells are usually the first to be seen. Later, NK-cells, LAK, T-lymphocytes, B-lymphocytes, non immune cells and vascular system components are found in a tumor.

Each of the immune cells type is able to produce a large quantity of biologically active substances and to absorb them from a medium.

The tumor itself secrets a large number of biologically active substances, whose effect results in the initiation of leukocyte migration into the tumor. Tumor may also destroy immune cells that approach it by providing apoptotic signals.

The competitive interaction between TCs and the IS, involves a considerable number of events and molecules, and as such is extremely complex. As a consequence, the IS is not able to eliminate a neoplasm in all cases, which may escape from its control.

Of course, a dynamic equilibrium may also be established, such that the tumor may survive in a microscopic steady state which is undetectable by diagnostic equipment.

However, consider a tumor which is constrained by the IS in a microscopic state. Over a long period of time the neoplasm may develop multiple strategies to circumvent the action of the IS, which in the long term may allow it to evade immune surveillance and to recommence growing. The tumor has adapted itself to survive in a hostile environment in which anti tumor immune response is activated.

Thus, the tumor at an early developmental stage already represents a rather complex and heterogeneous tissue. These cellular elements are constantly interacting in a dynamical fashion. The dynamics of the anti-tumor immune response in vivo seems to be very complicated and is not yet well understood. Spontaneously arising tumors are known to be of low immunogenicy and usually grow out of control in a organism.

Nevertheless, at the early stages of tumor growth, the cytolytic effector cell of the immune system are able to suppress the growth or destroy the host tumor. On the other hand, tumor growth may be stimulated by some molecules and immune system cells.

The tumor-immune system interaction involves the stimulation of the immune response by tumor antigens, but also the tumor induced death of lymphocytes. When the tumor size increases, it causes a deactivation of lymphocytes that enter the tumor region. This phenomenon is known as immunodepression.

In conclusion, the responses of cancer cells to these interactions are char-

acterized by a considerable evolutionary ability and by mutations that enhance their survival in a hostile environment.

2.2 Immunotherapy

The treatment of cancer is one of the most challenging problems in modern medicine. Cancer is a main cause of death against which surgery and chemotherapy are unsuccessful in many cases. That is the reason why the principal efforts are addressed nowadays to search new treatment strategies. An ideal treatment method should fulfill two basic conditions: it should destroy cancer cells in the entire body and it should distinguish between cancerous cells and healthy ones.

Immunotherapy seems to be the method that best fulfills both of these requirements. Resulting to be an interesting therapeutic approach, it is defined as the use of the immune system and its products to prevent, treat and control cancer. It may act stimulating the immune system of a cancerous patient in order to eliminate or control the population of cancer cells and consists, as already mentioned, in stimulating the IS in order to better fight, and hopefully eradicate a cancer.

We will refer now to generic immunostimulations for example via cytokines. The use of cytokine alone to boost the immune system represents one of the most commonly used methods in immunotherapy. The stimulation of an immune system in order to provide an effective treatment of cancer diseases can be realized with the aid of vaccinations.

If the cancer is very aggressive, the immune system is unable to stop the development of the neoplasm, despite the identification of cancer cells. In this case cancer vaccine can be very useful, thus within its application we still have to deal with the activation of the immune system. The vaccine has now the character of a treatment, not that of prevention.

2.3 Mathematical Models in Cancer Research

The fight against cancer required many efforts in the last century and will require greater efforts in the future. The idea is to gain understanding of the process and to design better treatment strategies or improve existing ones to eradicate the disease or at least to improve the patient's quality of life. To be successful it is to be hoped the fullest possible cooperation among different scientists: primarily biologists, immunologists and medical doctors, but also physicists and mathematicians who can provide valuable support to research in this field.

The role of mathematics - modeling complex systems and yielding numerical simulations - stays between phenomenological observation and physical reality. Mathematical models can be good approximations of the system

which is being modeled and can contribute to heighten the understanding of reality.

Moreover, a model can be useful to decompose a very complex system into more simple elements and to reproduce some particular behaviors of these selected aspects. Different models of the same situation, with different simplifying assumptions, can provide useful complementary insights and levels of descriptions.

A good mathematical model can be useful to formulate ideas precisely in a concise language and gives the possibility to use theorems, to interpret data and to stimulate experiments. Besides, computational resources can aid to confirm or reject hypothesis, to reveal contradictions and incompleteness and to suggest the existence of new phenomena.

As a consequence, using models and simulations can reduce the cost of experiments, the investigation times and predict dynamics under untested or untestable hypothesis. Nevertheless, the interplay of different scientists in the cancer research field can also promote the development of new mathematics.

There is a sequence of increasingly sophisticated models in the literature that concern immune response to tumor (among whose models with reaction-diffusion formulation; regarding the growing tumor as a deterministic dynamical system; using kinetic-cellular theory, ...)

Referring to what has been said in the previous section, tumor-immune can be modeled in the framework of populations dynamics models following a predator-prey paradigm to describe the response of effector cells (ECs) to the growth of tumor cells (TCs), eventually adding a term describing immunotherapy. We follow this approach describing the process in terms of ODE or DDE. Many papers in literature present competition models of tumor growth and immune system interaction using both ODE and DDE and analyzing the effect of a delay term ([10], [11], [14],[17], [18], [12], [16], [21], [19], [23],[15]).

2.3.1 Some relevant models

We have made a critical study of existing literature concerning tumor-immune system interaction. For brevity we can not discuss many of the models studied, but we report in this section a description of the main features of models that we considered as the most important, both for their historical importance, and for the subsequent extensions developed in this work.

As a first example we report a brief summary of features and purposes of the model presented in [14] by Kuznetsov *et al.* which can be considered

as a point of departure for many models on the topic.

In this paper the authors analyze a model of cell mediated response to a growing cancer cell population, taking into account the possibility of infiltration of the tumor by effector cells and the possibility of effector cell inactivation.

The interaction between effector cells (EC) and tumor cells (TC) is described by the kinetic scheme:

$$E + T \rightleftharpoons C \begin{array}{l} \nearrow \; E + T^* \\ \\ \searrow \; E^* + T \end{array}$$

where E, T, C, E*, T* are the local concentrations of effector cells, tumor cells, effector cell-tumor cell conjugates, inactivated effector cells, and "lethally hit" TC cells, respectively.

Mathematically the considered model for the interaction between EC and a growing immunogenic tumor *in vivo* is:

$$\begin{cases} \dfrac{dE}{dt} = s + F(C,T) - d_1 E - k_1 ET + (k_{-1} + k_2)C, \\ \dfrac{dT}{dt} = aT(1 - bT) - k_1 ET + (k_{-1} + k_3)C, \\ \dfrac{dC}{dt} = k_1 ET - (k_{-1} + k_2 + k_3)C, \\ \dfrac{dE^*}{dt} = k_3 C - d_2 E^*, \\ \dfrac{dT^*}{dt} = k_2 C - d_3 T^*, \end{cases} \tag{2.1}$$

The parameters k_1, k_{-1}, k_2 and k_3 are non-negative kinetic constants: k_{-1} and k_1 describe the rates of binding of EC to TC and detachment of EC from TC without damaging cells; k_2 is the rate at which EC-TC interactions irreversibly program TC for lysis; and k_3 is the rate at which EC-TC interactions inactivate EC. The parameter s is the "normal" (non-enhanced by TC presence) rate of flow of mature EC into the region of TC localization; d_1, d_2 and d_3 are positive constants representing the rates of elimination of E, E* and T* cells, respectively, resulting from their destruction or migration from the TC localization area; a is a coefficient of the maximal growth of tumor and b is the environment capacity.

The function $F(C,T)$ characterizes the rate at which cytotoxic effector cells accumulate in the region of TC localization due to the presence of the

tumor and the form suggested for this function is of Michaelis-Menten type:

$$F(C,T) = \frac{fC}{g+T}, \qquad f,g > 0.$$

In fact this functional form is consistent with a model in which one assumes that the accumulation of effector cells is due to signals, such as released cytokines, generated by effector cells in conjugates. Further note that the rate of stimulated accumulation has some maximum value as T gets large. This is consistent with limitations in the rate of transport of effector cells to the tumor. The rate limitation could occur in the circulation, in the rate of exit from the circulation, or in the rate of movement through the tissue to the tumor. A function of this form also adequately describes the rate of lymphocyte accumulation into allogeneic tumor spheroids in mice when the concentration of infiltrating macrophages is constant or changes slowly.

This model is slightly simplified thanks to biological meaningful approximations. Firstly is observed that variables T* and E* have no effect on each other or on the other variables in the system. Then only the first three equations, dictating the behavior of system, are analyzed.

Then is argued that formation and dissociation of cellular conjugates C occurs on a time scale of several tens of minutes to a few hours, whereas the multiplication as well as influx of effector cells into the spleen occurs on a much slower time scale, probably tens of hours. This motivates the application of a quasi-steady-state approximation to third equation yielding the relation:

$$C \approx KET,$$

where $K = \frac{k_1}{k_2+k_3+k_{-1}}$. Finally, since experimental observations indicate that EC-TC conjugates usually comprise a small portion of the total number of effector or tumor cells, the approximation $T_{tot} \approx T$ is made.

The simplified system results:

$$\begin{cases} \dfrac{dE}{dt} = s + \dfrac{pET}{g+T} - d_1 E - mET, \\ \\ \dfrac{dT}{dt} = aT(1-bT) - nET. \end{cases} \tag{2.2}$$

where $p = fK,\ m = Kk_3,\ n = Kk_2$.

System is then non-dimensionalized by choosing an order-of-magnitude concentration scale for the E and T cell populations, E_0 and T_0, respectively. Time too is scaled relative to the rate of tumor cell deactivation: $\tilde{t} = nT_0 t$.

Non-dimensional model can be written as:

$$\begin{cases} \dfrac{dx}{d\tilde{t}} = \alpha x(1-\beta x) - xy, \\ \\ \dfrac{dy}{d\tilde{t}} = \sigma + \dfrac{\rho xy}{\eta + x} - \mu xy - \delta y; \end{cases} \tag{2.3}$$

where:

$$\begin{gathered} x = \tfrac{T}{T_0}, \quad y = \tfrac{E}{E_0}, \quad \sigma = \frac{s}{nE_0T_0}, \quad \rho = \frac{p}{nT_0}, \\ \eta = \frac{g}{T_0}, \quad \mu = \frac{m}{n}, \quad \delta = \frac{d_1}{nT_0}, \quad \alpha = \frac{a}{nT_0}, \quad \beta = bT_0. \end{gathered} \tag{2.4}$$

Then steady state are considered examining the nullclines. A disease free steady state $(0, \frac{\sigma}{\delta})$ always exists and its stability depends upon the relative values of the parameters for the system. In addition, depending upon the intersections of nullclines there may be from zero to three additional steady states for the system.

The stability of steady states and the qualitative behavior of the system is studied using techniques from bifurcation theory with the aim to analyze mechanisms of tumor dormancy and sneaking through. Tumor dormancy is a term used to describe a state in which potentially lethal tumor cells persist for a prolonged period of time with small or no increase in the tumor cell population. Sneaking through refers to a phenomenon in which low doses of cancer cells can escape immune defenses and grow into a large tumor, whereas larger doses of tumor cells are eliminated. Parameter regimes are delineated in which these behaviors can be expected: tumor dormancy, escape from immunoregulation and sneaking through. It is also proved, using the Dulac-Bendixson criterion that there are no closed orbits and that no periodic dynamics arise for the system for positive values of x and y. Moreover, no Hopf bifurcations giving rise to limit cycles occur.

The model is tested choosing parameters obtained by fitting the results of experiments on the dynamics of growth of a BCL 1 lymphoma in the spleen of chimeric mice.

The analysis made shows that a non-zero rate of effector cell inactivation is required to obtain sneaking through. Bifurcations analysis carried out for realistic values of the parameters shows that sneaking through, tumor dormancy and the immunostimulation of tumor growth, may all be related and explained by the same model in different parameter regimes.

Although limit cyles do not arise in this model, simulations show that transients in the vicinity of tumor dormancy steady state exhibit decaying oscillations; it is also interesting that the predicted time scale of such oscillations, 3 or 4 months, is in rough agreement with the time for recurrent clinical manifestations of certain human leukemias.

Furthermore, this model may be applicable to other biological processes such as the infection of T cells by HIV.

Starting from the model (2.1) of Kuznetsov *et al.* presented above ([14]), Galach in [12] have presented another model adding a delay term. One of the main features of this delayed model is that it exhibits also oscillatory dynamics.

Firstly a simplified model is studied, utilizing biological approximations made by Kuznetsov and taking F of Lotka-Volterra form instead of Michaelis-Menten form as in the model above; that is F becomes bilinear and has the form $F(C,T) = F(E,T) = \theta ET$.

The simplified, non-dimensional model is:

$$\begin{cases} \dfrac{dx}{dt} = \alpha x(1-\beta x) - xy, \\ \\ \dfrac{dy}{dt} = \sigma + \omega xy - \delta y \end{cases} \tag{2.5}$$

where x denotes the dimensionless density of the population of TCs and y stands for the dimensionless density of ECs. Parameters α, β, σ, δ are defined as in (2.4) and $\omega = \dfrac{\theta - m}{n}$.

Analyzing stability of steady states and features of this system and comparing results with the model of Kuznetsov, it is showed that the dynamics of simplified model are simpler than the dynamics of the original one.
However, solutions to both models are usually similar, it is noticed that with simplified model it is possible to describe the dormant tumor and the tumor escape under immunoregulation, but not the sneaking-through mechanism. It is also proved that there is no nonnegative periodic solution of the system, ruling out oscillatory dynamics.

Afterwards a delay term is added to the simplified model representing the time needed by immune system to develop a suitable response after the recognition of cancer cells.

The considered delayed model is then:

$$\begin{cases} \dfrac{dx}{dt} = \alpha x(1-\beta x) - xy, \\ \\ \dfrac{dy}{dt} = \sigma + \omega x(t-\tau)y(t-\tau) - \delta y, \end{cases} \tag{2.6}$$

where τ is a constant time delay.

Studying analitically this system is observed that steady states are the same as in the simplified model, but the stability or instability of these states

are more difficult to prove and equilibrium points can change their stability with respect to the case without delay.

Moreover, the behavior of solutions is also more complex than that for simplified model. In fact tumor dormancy behavior is observed with small values of delay and we note the appearence of oscillations in solutions and a state of *returning* tumor when higher values of delay are considered. Sneaking-through mechanism is not observed with this model whereas tumor escape under immunoregulation can be described depending on the parameter values.

Finally, as a last example, we will report a family of models proposed in [10] by d'Onofrio. We are very interested in this family because we will generalize this model in the next chapter and then we will add to generalized system a delay term both of discrete and distributed type (chapters 4 and 5).

This family of models is constructed drawing on precedent models. Moreover, the killing of lymphocytes is seen as a function of tumor size and the influx of lymphocytes too is taken as a function of entity of disease. Many terms are then generalized: the influx function, the interaction term, the term representing saturation in the predation, and the form of function describing tumor growth.

The system considered is:

$$\begin{aligned} x' &= x(\alpha f(x) - \phi(x)y) \\ y' &= \beta(x)y - \mu(x)y + \sigma q(x) + \theta(t) \end{aligned} \tag{2.7}$$

where:

- x and y are respectively dimensionless quantities of tumoral and immune cells;
- $0 < f(0) \leq +\infty$, $f'(x) \leq 0$; $f(x)$ summarizes different forms of growth rate of the tumor;
- $\sigma q(x)$ is such that $q(0) = 1$; this term represents the influx of immune cells in tumor situ, whose intensity may depend on the size of the tumor. More precisely it may be non increasing, or initally increasing and than decreasing; that is small tumors may stimolate the influx of immune cells, while tumors in advanced state have the opposite effect.
- $\beta(x) \geq 0, \beta(0) = 0$ e $\beta'(x) \geq 0$; $\beta(x)$ indicates the stimulating effect of tumor on immune cells proliferation;
- $\mu(x) > 0$ and $\mu'(x) > 0$; $\mu(x)$ stands for the loss factor of immune cells due to the presence of the tumor.

- $\phi(x) > 0$, $\phi(0) = 1$, $\phi'(x) > 0$ and $x\phi(x) \to l < \infty$; $x\phi(x)$ is the functional response of tumor cells.
- $\theta(t)$ represents an eventual therapy term.

Using techniques similar to those utilized in [10], in the next chapter we will study a generalized model that includes this as particular case. Then we refer to the general case for a detailed analysis of properties of the system, and here we discuss only general aspects of [10].

We point out that in the paper [10] an analysis is performed in the absence of therapy term, proving that this system always has a disease free equilirium whose stability depend on values of parameter. In fact considering different functions (in particular taking different conditions on f, $\mu - \beta$ and ϕ), it is proved that the disease free equilirium can be either locally asymptotically stable (LAS), globally asymptotically stable (GAS), or unstable.
Moreover, studying nullclines intersections, it is proved that varying the parameters the system can also have an immune free equilibrium and some equilibria with non null disease. Stability analysis of equilibria is carried out, both stating conditions to have local asymptotic stability, both proving propositions on global behavior of the system.

Concerning the possibility of periodic solutions, it is showed that with exponential growth of the tumor ($f(x) = 1$) and if $q(x) \equiv 0$ for $x > x_q$, system may admit limit cycles.
But under more general conditions: if the nullcline corresponding to the first equation ($y_c(x) = \alpha\frac{f(x)}{\phi(x)}$) is non increasing, then it is showed that Dulac-Bendixson theorem excludes the possibility of limit cycles.

The inclusion of a therapy term is also investigated. An analytical and numerical study is done for constant, periodic and impulsive therapies. Results point out that generally eradication due to immunotherapy is possible but depends on initial values. Conditions for LAS and GAS of disease free equilibrium are stated both for the case of constant therapy, both for periodic scheduling.

It is also showed that the behavior of the system does not depend on the shape of the therapy term but only on the mean value of this. Numerical simulations of immunotherapy are performed choosing parameter on the basis of the model proposed by Kuznetsov et al. [14] and realistic estimates there reported.

Chapter 3

A New Nonlinear Model of Tumor-Immune System Interaction

Let us introduce a new model describing tumor-immune system interaction, generalizing system depicted in [10] and reported in 2.3.1.

The idea behind this model is to look at tumoral and immune cells as two populations competing with each other, modifying interaction terms according to the specific biological context and adding terms such as the influx of immune cells in tumor situ, whose intensity may depend on the presence of the tumor.

Cancer cells are considered as preys of immune cells. At the same time, they stimulate proliferation of immune cells but also their loss, due to competition between the two populations.

Mathematically we will study the system:

$$\begin{aligned} x' &= x(f(x) - \Phi(x,y)) \\ y' &= \beta(x)y - \mu(x)y + \sigma q(x) + \theta(t) \end{aligned} \tag{3.1}$$

where functions satisfy the same constraints as for system (2.7) reported in the previoud chapter.

With respect to (2.7) in this model we have generalized the interaction term $\phi(x)y$ by introducing $\Phi(x,y)$ representing that the competition between populations is no more necessarily linear in y. We assume:

$$\Phi(0,y) > 0,\ \Phi(x,0) = 0, \tag{3.2}$$

the strict positivity of $\Phi(0,y) > 0$ is required to allow the possibility of immune surveillance, that is the possibility that immune system eliminates

tumors. Moreover, the interaction term is assumed decreasing in the tumor variable x and increasing in the immune variable y:

$$\frac{\partial}{\partial x}\Phi(x,y) \leq 0 \tag{3.3}$$

$$\frac{\partial}{\partial y}\Phi(x,y) > 0. \tag{3.4}$$

Finally we assume some limit conditions: the interaction term becomes zero when the tumor growths unboundendly:

$$\lim_{x\to+\infty} \Phi(x,y) = 0, \tag{3.5}$$

and

$$\lim_{y\to+\infty} \Phi(x,y) = L(x), \text{ with: } f(x) < L(x) \leq +\infty. \tag{3.6}$$

The biological meaning of constraint (3.6) is that for a large level of immune system effectors, there would be decrease of the tumor.
An example of $\Phi(x,y)$ is :

$$\Phi(x,y) = \frac{Ay}{1+Bx+Cy} \tag{3.7}$$

It will be useful to define $\psi(x) = \mu(x) - \beta(x)$ which we assume positive, or positive in $[0,x_1) \cup (x_2,+\infty)$ with $\psi(x_1) = \psi(x_2) = 0$. Moreover, we assume that $\psi(x)$ has an absolute minimum in $[0,+\infty)$ and this function will be used to classify the interaction between tumor and immune system:

- $\psi(x) > 0$ = highly aggressive tumor: the capacity of destroying immune cells is even higher than the stimulation effect of immune system.
- Variable sign of $\psi(x)$ = lowly aggressive tumor: the two effects can balance each other out.

Finally the term $\theta(t)$ represents a possible immunotherapy that may be constant or periodic. We will treat therapy in section 3.5.

3.1 Nullclines

Now we will study properties of nullclines of system without therapy.
We denote with $y_c(x)$ the nullcline obtained putting $x' = 0$ in the case $x \neq 0$, that is $y_c(x)$ is such that:

$$\Phi(x, y_c(x)) = f(x) \quad \forall x \neq 0. \tag{3.8}$$

We denote with $y_i(x)$ the nullcline obtained putting $y' = 0$, that is

$$y_i(x) = \frac{\sigma q(x)}{\mu(x) - \beta(x)}.$$

As far as the nullcline $y_c(x)$ thanks to the constraints (3.4) and (3.6), it follows that for all $x \geq 0$ the function $y_c(x)$ is monodrome. Applying implicit functions theorem to (3.8) one has that:

$$y_c'(x) = \frac{f'(x) - \partial_x \Phi(x, y_C(x))}{\partial_y \Phi(x, y_C(x))} \tag{3.9}$$

may have variable sign.
In the particular case (3.7) it is:

$$y_c(x) = \frac{f(x)}{(A - Cf(x))(1 + Bx)} \tag{3.10}$$

which is decreasing: $y_c'(x) < 0$.

3.1.1 Disease Free Equilibrium

Considering system without therapy ($\theta(t) = 0$), we initially study the disease free equilibrium:

$$DFE = (0, y_i(0)) \tag{3.11}$$

which exists for every choice of parameter values.
The linearized system at DFE is:

$$\begin{aligned} x' &= [f(0) - \Phi(0, y_i(0)))]\, x \\ y' &= [\beta'(0) y_i(0) - \mu'(0) y_i(0) + \sigma q'(0)]\, x - \mu(0) y, \end{aligned} \tag{3.12}$$

and, since $\mu(0) > 0$, the local stability condition at this point (eradication condition) is:

$$\Phi(0, y_i(0)) > f(0), \tag{3.13}$$

which, remembering the definition of $y_c(x)$, reads as follow:

$$y_i(0) > y_c(0). \tag{3.14}$$

After defining the following sets:

$$P = \{x \in \mathbb{R}_+ | y_i(x) > 0\} \tag{3.15}$$

$$Q = \left\{(x, y) \in \mathbb{R}_+^2 | y \geq MAX\left(y_c(x), 0\right)\right\} \tag{3.16}$$

let us study the Global stability of DFE:

Theorem 3.1.1. *If for $x \in P$ it holds that:*

$$y_i(x) > y_c(x) \tag{3.17}$$

then DFE is GAS in $\mathbb{R}_+^2$.

Proof. Let us start by assuming the following simple Liapunov-La Salle function:

$$L = x. \tag{3.18}$$

Then, we note that if (3.17) holds, the set Q is positively invariant for our system. In fact, the curve

$$(x, y_c(x)) \tag{3.19}$$

is the lower border of Q, and on it we have:

$$y'|_{(x,y_c(x))} > 0. \tag{3.20}$$

In fact, if $\psi(x) > 0$ then we can rewrite

$$y'|_{(x,y_c(x))} = \psi(x)\,(y_i(x) - y_c(x)) > 0, \tag{3.21}$$

if $\psi(x) = 0$ then

$$y'|_{(x,y_c(x))} = \sigma q(x) + \theta > 0, \tag{3.22}$$

and finally if $\psi(x) < 0$

$$y'|_{(x,y_c(x))} = \psi(x)\,(y_i(x) - y_c(x)) > 0, \tag{3.23}$$

since where $\psi(x) < 0$ it is $y_i(x) < 0$. Moreover, as it is easy to see, Q is also attractive.
Finally, since in Q it is

$$\frac{dL}{dt}|_{\text{our model}} = x' \leq 0, \tag{3.24}$$

then applying the LaSalle's theorem it follows that DFE is GAS. □

3.1.2 Equilibria with non null disease

The system may show multiple biologically meaningful non-eradicative equilibria given by intersections between nullclines.
Practically this means that the disease can evolve in different ways, reaching states corresponding to stable equilibrium points.

A stable equilibrium point $EQ = (x_e, y_e)$ with a small value of x_e will correspond to tumor dormancy, that is to a small tumor controlled by immune system; whereas a stable equilibrium point with a higher value x_e corresponds to a large tumor, or also, depending on the value of x_e to tumor escape under immunoregulation, probably leading to the death of host organism before equilibrium is reached.

Unstable points, instead, are not biologically meaningful, because they are not physically observable.

It is then important to state condition for local asymptotic stability of equilibria. Obviously we are interested only on points with positive coordinates.

Theorem 3.1.2. *Let be $EQ = (x_e, y_e)$ with $x_e > 0,\ y_e > 0$. If*

$$\psi(x_e) - x_e \partial_y \Phi(x_e, y_e) y_c'(x_e) > 0 \text{ AND } y_i'(x_e) > y_c'(x_e) \tag{3.25}$$

then EQ is local asymptotically stable (LAS).

Proof. Note that to have $y_e > 0$ it must be:

$$\psi(x_e) > 0.$$

The characteristic equation of the linearized system at EQ is:

$$\lambda^2 + \left(\psi(x_e) - x_e \partial_y \Phi(x_e, y_e) y_c'(x_e)\right) \lambda + x_e \partial_y \Phi(x_e, y_e) \psi(x_e) \left(y_i'(x_e) - y_c'(x_e)\right) = 0,$$

so applying Descartes's rule of sign it is easy to see that if

$$\psi(x_e) - x_e \partial_y \Phi(x_e, y_e) y_c'(x_e) > 0 \text{ AND } y_i'(x_e) > y_c'(x_e) \tag{3.26}$$

then both roots of characteristic equation have negative real parts, and the equilibrium is LAS. □

3.2 Limit cycles

This system can exhibit limit cycles. More precisely:

Theorem 3.2.1. *Let DFE be unstable, and $EQ = (x_e, y_e)$ be the unique disease equilibrium point. Let it be $y_i(x)$ bounded in $[0, \bar{x}]$, and let it be*

$$\psi(x_e) - x_e \partial_y \Phi(x_e, y_e) y_c'(x_e) < 0 \text{ AND } y_i'(x_e) > y_c'(x_e) \tag{3.27}$$

then the system has at least a LAS limit cycle.

Proof. Condition (3.27) both implies the instability of EQ and it rules out the possibility of homoclinic orbits. Moreover, the boundedness of $y_i(x)$ implies that the set:

$$BB = [0, \bar{x}] \times \left[0, Max_{x \in [0, \bar{x}]} y_i(x)\right]$$

is positively invariant for our system. These two facts, thanks to the Bendixon-Poincarè thricothomy imply the existence of at least a LAS limit cycle. □

Theorem 3.2.2. *Let DFE be unstable, and $EQ = (x_e, y_e)$ be the unique disease equilibrium point such that (3.27) holds. Moreover, let it be $y_i(x)$ unbounded and increasing in $[0, x_{as}]$, with:*

$$\widehat{x} < x_{as} < \bar{x}$$

where

$$y_c(\widehat{x}) = y_{DFE}.$$

Then the system has at least a LAS limit cycle.

Proof. In this case, it is easy to verify that the set

$$BB_1 = [0, \widehat{x}] \times [y_{DFE}, y_i(\widehat{x})]$$

is positively invariant. Thus, since (3.27) holds, it easily follows the existence of at least a LAS limit cycle. □

3.3 Unique non-DFE equilibrium

Theorem 3.3.1. *If there is a unique and LAS equilibrium point EQ, and*

$$y_c'(x) < 0 \ AND \ \psi(x) > 0$$

then EQ is GAS.

Proof. The positiveness of $\psi(x)$ implies the boundedness of $y_i(x)$ implying, in turn, that the set:

$$BB = [0, \bar{x}] \times \left[0, Max_{x \in [0,\bar{x}]} y_i(x)\right]$$

is positively invariant for our system. Moreover, since:

$$Div\left(\frac{x'}{x}, \frac{y'}{x}\right) = f'(x) - \partial_x \Phi - \frac{\psi(x)}{x} = y_c'(x) - \frac{\psi(x)}{x} < 0, \tag{3.28}$$

the GAS of EQ follows from the Bendixon-Poincare thrichothomy. □

3.4 Examples

Example 1. *As a first example we introduce a system which will be largely utilized in the rest of this work to obtain numerical results.*

We observe that taking parameters of the form:

$$\begin{aligned} f(x) = \alpha(1 - \tilde{\beta}x), \quad \Phi(x,y) = y, \quad \beta(x) = \frac{\rho x}{\eta + x}, \\ \sigma q(x) = \sigma, \quad \mu(x) = \tilde{\mu}x + \delta, \end{aligned} \tag{3.29}$$

we obtain as a particular case the adimensional model of Kuznetsov et al. reported in (2.3). Then the estimate of parameters is made referring to paper of Kuznetsov et al. [14] where values are fitted from real data obtained with experiments on chimeric mice.

We have:

$$\begin{aligned} f(x) = 1.636(1 - 0.002x), \quad \Phi(x,y) = y, \\ \beta(x) = \frac{1.131x}{20.19 + x}, \quad \sigma q(x) = 0.1181, \quad \mu(x) = 0.00311x + 0.3743, \end{aligned} \tag{3.30}$$

Since these values are calculated after adimensionalazing the system, we have $t_{real} = 9.9\, t_{adim}\, days$.

And, as regards number of cells: $(X_{real}, Y_{real}) = 10^6(x,y) cells$.

This system has 4 equilibrium points:

- *The disease free equilibrium:* $DFE = (0, 0.316)$ *which is unstable;*
- *A microscopic LAS equilibrium point:* $E_{micro} = (8.1897, 1.6092)$*;*
- *A saddle point:* $E_u = (267.798, 0.7598)$*;*
- *A macroscopic LAS equilibrium point:* $E_{macro} = (447.1342, 0.173)$.

Example 2. *A second model, that, as we will see, has different dynamical behaviors with respect to the system presented in previous example, can be obtained taking* $\Phi(x, y)$ *as in (3.7) and sligthly modifying the expression of* $f(x)$*: In particular we will take:*

$$\Phi(x, y) = \frac{y}{1 + 0.002x + 0.25y}, \quad f(x) = 1.636\,(1 - 0.00476x). \tag{3.31}$$

All the other parameters remain as above. This model too will be largely studied in the rest of this work.

This system has only two equilibrium points, both unstables:

- *The disease free equilibrium:* $DFE = (0, 0.316)$*;*
- *The point* $E_c = (9.6446, 3.0535)$.

The system with parameter taken as in [14] cannot exhibit limit cycles, whereas cycles are possible in the system with parameters taken as in (3.31), in fact all the hypothesis of above theorems hold for the equilibrium point E_c.

3.5 Therapy

In this section we add the therapy term $\theta(t)$ in the model studied in previous sections.

We will consider two different types of therapies:

- Constant therapy: $\theta(t) = \theta_m$

- Periodic therapy: $\theta(t) = \theta_m + \Omega(t)$, $\theta(t + T) = \theta(t)$

Firstly we will make a qualitative analysis of constant case proceeding as in [10] and then we will see some numerical results in the case of periodic therapy.

3.5.1 Constant therapy

In this case system becomes:

$$\begin{aligned} x' &= x(f(x) - \Phi(x, y)) \\ y' &= \beta(x)y - \mu(x)y + \sigma q(x) + \theta_m \end{aligned} \tag{3.32}$$

and substantially therapy has the effect of moving the stable equilibrium point decreasing the value of x_e.
To studying stability of new equilibrium we can carry out the same analysis done in the case without therapy, but the nullcline $y_i(x)$ becomes:

$$y_i(x; \theta) = \frac{\sigma q(x) + \theta_m}{\mu(x) - \beta(x)}. \tag{3.33}$$

In particular the LAS condition of disease free equilibrium is:

$$y_i(0; \theta) > y_c(0); \tag{3.34}$$

this condition is not global because of the presence of other equilibria; so it does not correspond to tumor eradication, but depends on initial values that are practically difficult to measure with sufficient precision.

If $\mu(x) - \beta(x) > 0$, we have that $y_i(x; \theta) > y_i(x)$, then roughly speaking, the stable equilibrium size of the cancer becomes smaller and the unstable equilibria greater, so that the basin of attraction of the unbounded solution is reduced.

In Figure 3.1 we see how constant therapy can also induce disease free equilibrium to be GAS. In this case we have taken parameters as in (2.4) and $\theta_m = 0.7$ which can be considered a very strong therapy (probably unrealistic) comparing for example this value with the constant influx of lymphocytes that is $\sigma q(x) = 0.1181$.

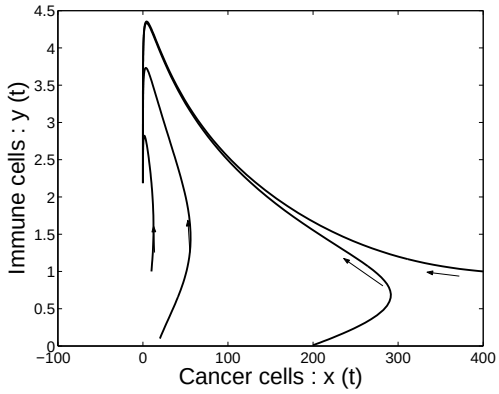

Figure 3.1: *Phase portrait in (x,y)-plane for system with parameters as in (2.4) and constant therapy* $\theta_m = 0.7$. *In this case DFE is GAS.*

3.5.2 Periodic therapy

In the case of periodic therapy we can take into account two different expressions of $\theta(t)$:

- An expression more unrealistic, but mathematically simpler, which often is utilized to describe forcing term to nonlinear systems:

$$\theta(t) = \theta_A(1 + cos(\frac{2\pi}{T}t)), \tag{3.35}$$

  where θ_A represents the maximal quantity of drug present in the organism and T is the time lag between an administration and the next.

- A more realistic expression representing a boli-based therapy with administration time T:

$$\theta(t) = \theta_A exp(-\psi Mod(t, T)), \tag{3.36}$$

  where, as above, θ_A is the maximal quantity of drug, and ψ is a measure of clearance time of drug from the host organism: $(\ln 2/\psi)$ is the half life of delivered drug.
  To have an idea of the entity of the therapy we will write the mean value:

$$M = \theta_A \frac{e^{-T\psi}\left(-1 + e^{T\psi}\right)}{T\psi}. \tag{3.37}$$

  A quite realistic example, with $T = 1$ (roughly 10 days), $\theta_A = 0.1181$, and different values of ψ can be seen in Figure 3.2.

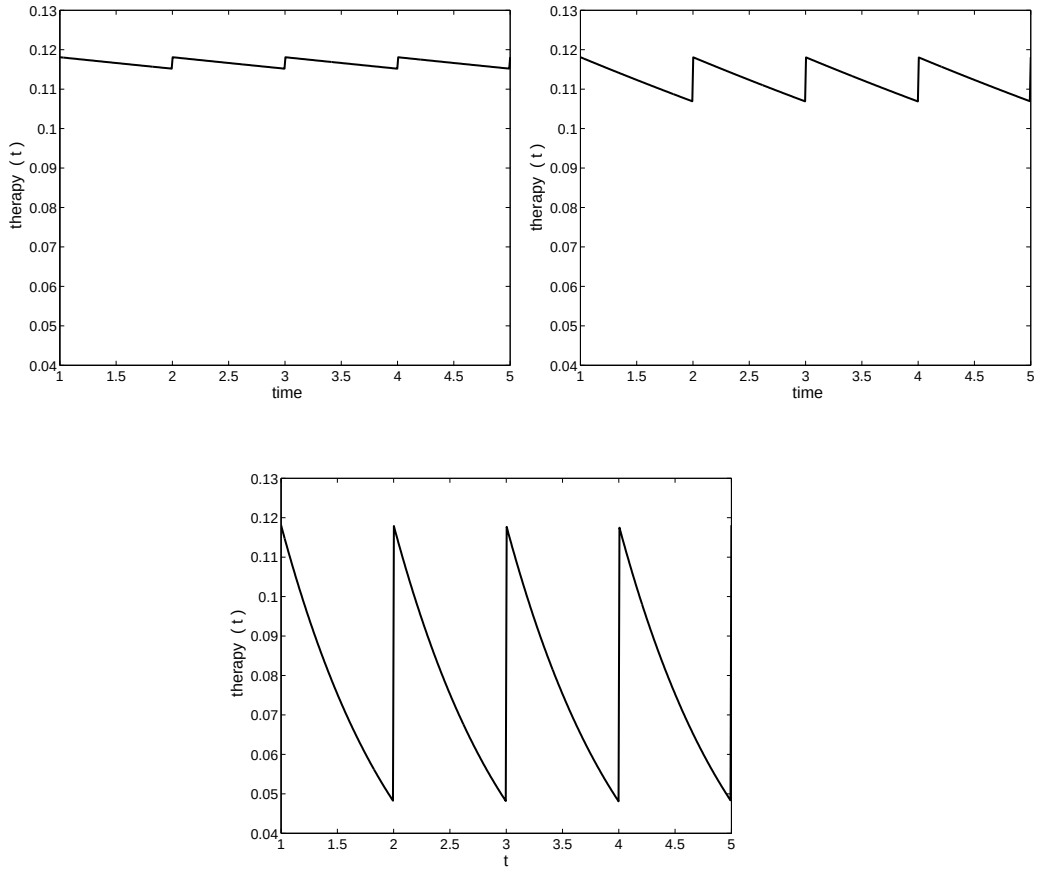

Figure 3.2: *Pattern of boli-based therapy administration with* $T = 1$, $\theta_A = 0.1181$ *and different clearance times: very slow clearance* $\psi = 0.025$, *mean value* $M = 0.1166$ *(on the left); average time of clearance* $\psi = 0.1$, *mean value* $M = 0.1124$ *(on the right); fast clearance* $\psi = 0.9$, *mean value* $M = 0.0779$ *(down). In abscissa is reported time and in ordinate is reported therapy value:* $\theta(t)$.

In numerical simulations reported below, values of T are taken either of the order of the period of limit cycle of the system without therapy (if it exists), or in a more relistic interval: $[0.1, 3]$ corresponding in dimensional terms to: [1 day, 1 month].

We will make simulations only with boli-based form of periodic therapy for its greater biological reliability.

3.5.3 Numerical results

We show some results obtained adding different periodic therapies to the system with limit cycle presented in the example 2 of the previous section:

$$\begin{cases} x' = x\left(1.636\,(1-0.00476x) - \dfrac{y}{1+0.02x+0.25y}\right) \\ \\ y' = \dfrac{1.131x}{20.19+x}y - (0.00311x + 0.3743)y + 0.1181 + \theta(t). \end{cases} \tag{3.38}$$

For $\theta = 0$ the system exhibits a limit cycle of period $P = 18$, that is roughly 180 days (figure 3.3).
We will see how the qualitatively behavior of solutions varies considering different periodic therapies.

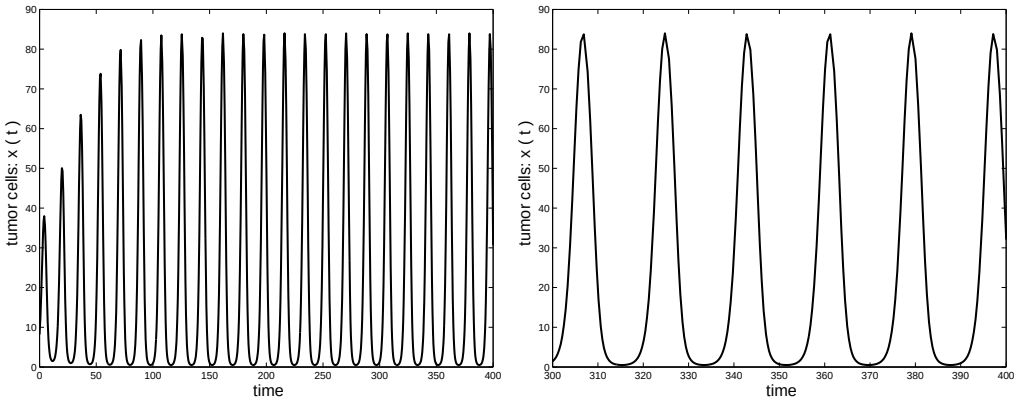

Figure 3.3: *Solution x(t) (tumor cells) of system (3.38) without therapy.*

Let us introduce a therapy of the form:

$$\theta(t) = 0.1181\,\exp(-\psi Mod(t,T)), \tag{3.39}$$

with $\theta_A = 0.1181$ and consider different values of T and of ψ.

We remark here that, as we see also in Figure 3.2, a small value of ψ indicates that the clearance is slower, so in the organism is ever present a high quantity of drug, quite constant between an administration and the next. Here we take as minimal value $\psi = 0.025$ corresponding to an half life of the drug in the organism of approximately 9 months.

If, instead, the value of ψ is higher (the maximum that we take is $\psi = 0.9$ corresponding in dimensional terms to an half life of 11 days), so the clearance is faster and the quantity of drug in the organism falls down between an administration and the next.

Obviously to decide how a therapy is enduring it is important not only the clearance time (that is, in our case, ψ) and the value of θ_A, but also the administration time T. In fact if the doses of drug are delivered very often (that is T= time between an admistration and the next, is small), then the organism will retain a high quantity of drug even if the cleareance is fast (high value of ψ).

In Figure 3.4 administration times T are considered in a realistic range (from 1 day to 1 month: $T \in (0.1, 3)$, whereas in Figure 3.5 T is of the order of P (in dimensional terms T is roughly from 5 to 8 months) which is an unrealistic value for administration times, but, as we will see, interesting mathematical phenomena occur for this values, such as resonance effects.

Values of ψ in both cases are taken as in the Figure 3.2, that is $\psi = 0.025$, $\psi = 0.1$, $\psi = 0.9$.
In simulations below, the integration is made for a very large interval of time (corresponding to roughly 15 years). Actually, a so lenghty treatment is not biologically meaningful, but here we are mainly interested to show the asymptotic behavior of solutions.

Now we report some numerical simulations of solution $x(t)$ of system (3.38) with a boli-based therapy.

In Figure 3.4 we notice that taking realistic adminstration times, we obtain almost always the convergence to the new equilibrium point (which becomes LAS in the majority of cases considered in this Figure); however, also when a limit cycle persits, the size of oscillations decreases notably, remaining in an interval in which the tumor, although with periodic dynamics, may be considered small.

In this case, in which the period of therapy and period of limit cycle are very different, there are not resonance effects that instead are present when T is of the order of P as we can see in figures 3.5 and 3.6.

It also important to remark that in this simulations eradication of tumor is never achieved, not even with stronger therapies. Therapy has the only effect to keep the tumor size in a controlled, microscopic state.

We can also observe that, since system without therapy has not LAS equilibrium point, when treatment is interrupted, tumor restarts to grow and the limit cycle will arise again.

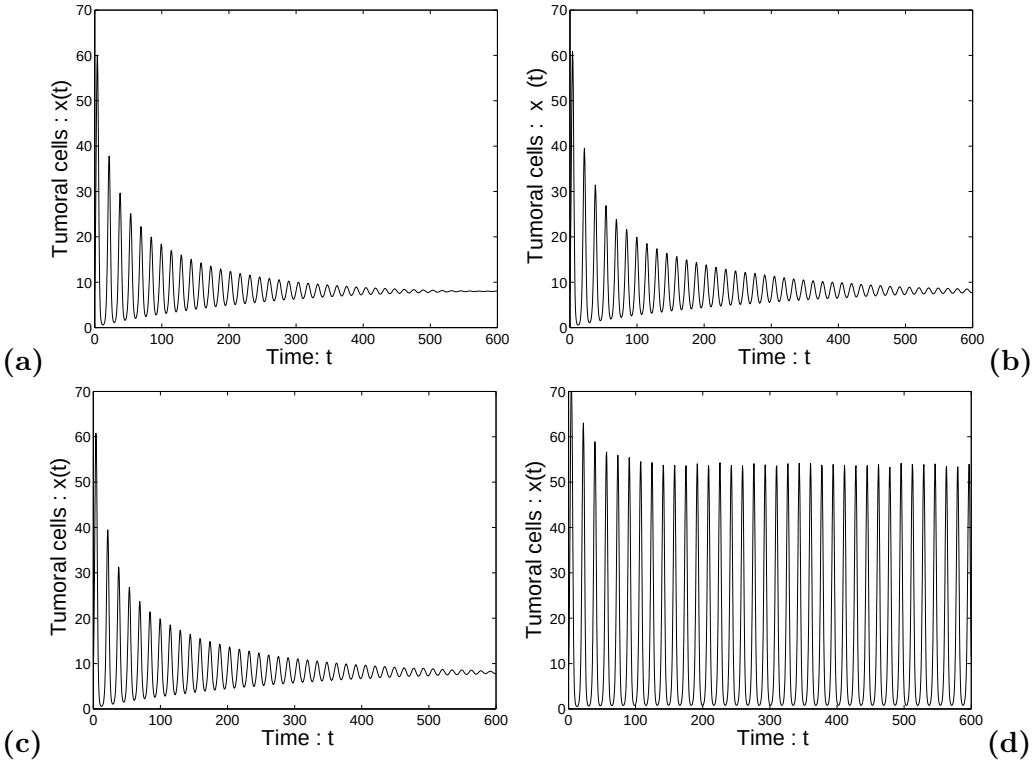

Figure 3.4: *Solutions x(t) of system (3.38) with* $\theta_A = 0.1181$ *and different value of* T *and* ψ: ***(a)*** $\psi = 0.025$, *T=0.1; M=0.1180;* ***(b)*** $\psi = 0.1$, *T=1; M=0.1124,* ***(c)*** $\psi = 0.9$, *T=0.1; M=0.1129;* ***(d)*** $\psi = 0.9$, *T=3; M=0.0408.*

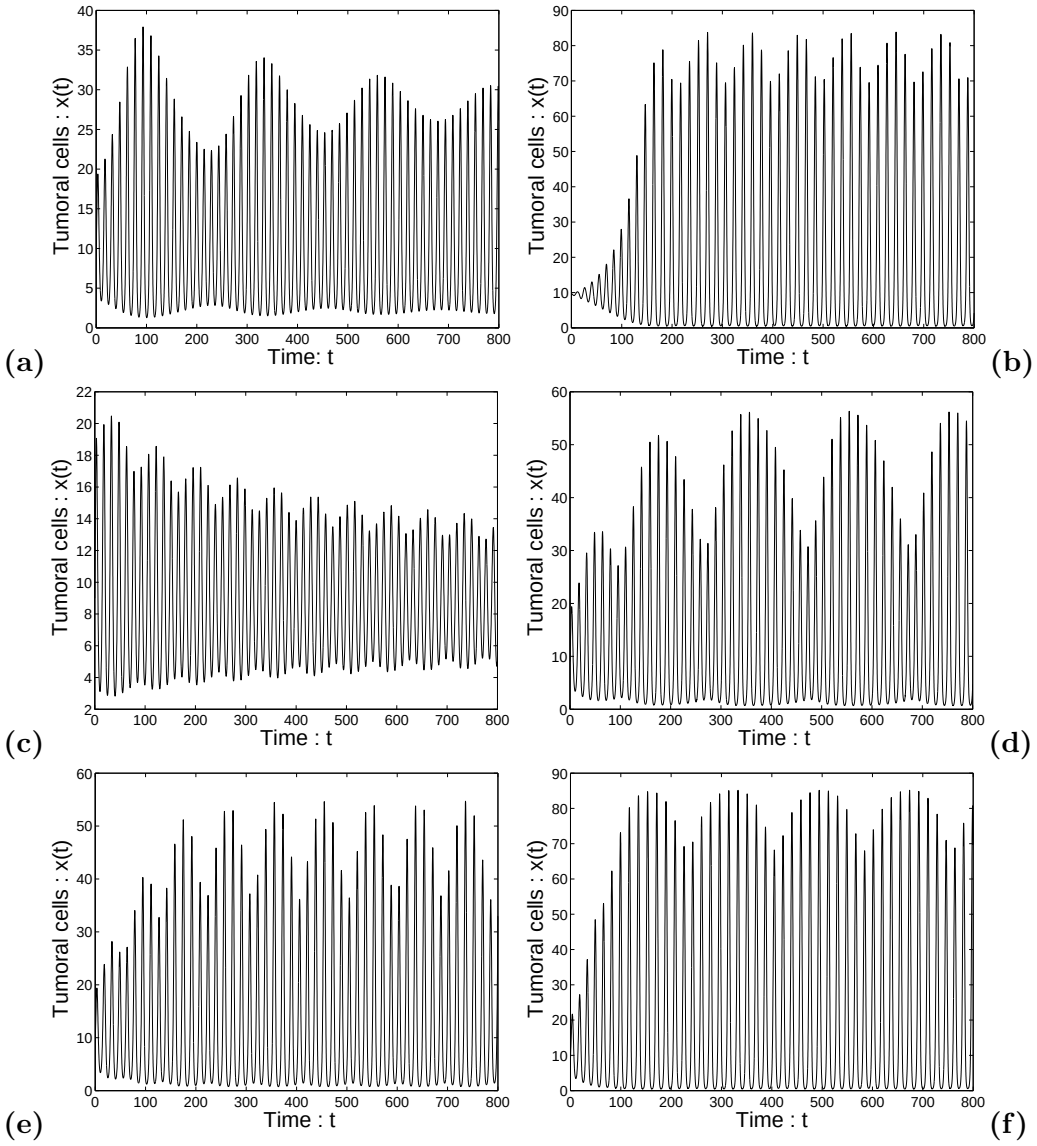

Figure 3.5: *Solution x(t) of system 3.38 with* $\theta_A = 0.1181$. ***(a)*** $\psi = 0.1$, *T=15;* ***(b)*** $\psi = 0.9$, *T=15;* ***(c)*** $\psi = 0.025$, *T=18;* ***(d)*** $\psi = 0.1$, *T=18;* ***(e)*** $\psi = 0.1$, *T=20;* ***(f)*** $\psi = 0.9$, *T=20;*

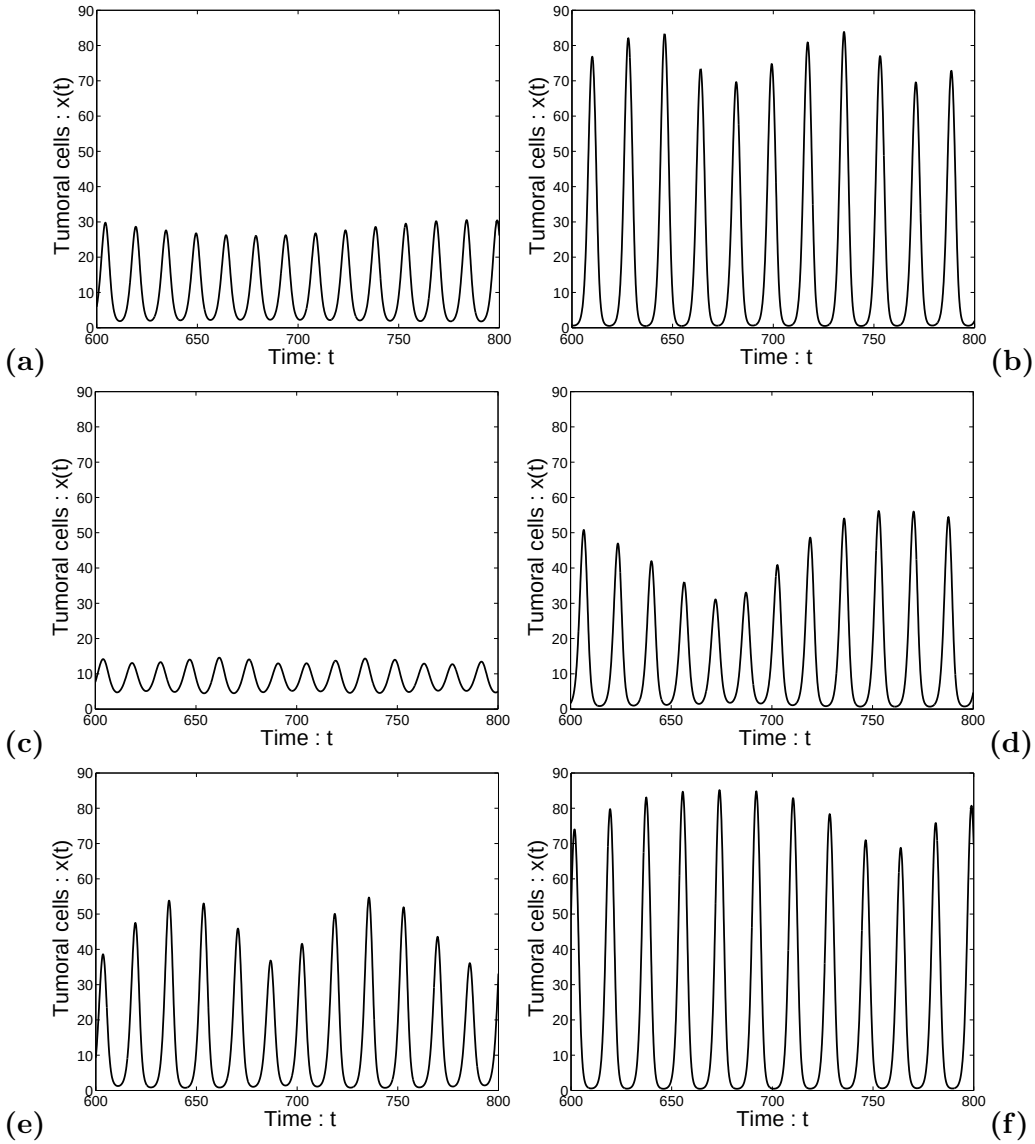

Figure 3.6: *Zoom of Figure 3.5 to highlight changes in period and amplitude of limit cycles oscillations. Time value in abscissa are taken in the interval (600,800); values of ordinate axis range in (0,90). In all graphs* $\theta_A = 0.1181$. ***(a)*** $\psi = 0.1$, *T=15;* ***(b)*** $\psi = 0.9$, *T=15;* ***(c)*** $\psi = 0.025$, *T=18;* ***(d)*** $\psi = 0.1$, *T=18;* ***(e)*** $\psi = 0.1$, *T=20;* ***(f)*** $\psi = 0.9$, *T=20;*

In Figures 3.5 and 3.6 we observe that in all cases an oscillatory dynamics persists.
On the other hand, we can make distinctions between different cases:

- for slower clearance times ($\psi = 0.025$) and smaller delivery times we see that the size of oscillations decreases in time and presumably the system will converge to the equilibrium point;

- for therapies with faster clearance times ($\psi = 0.1$ e $\psi = 0.9$), instead, we continue to see a periodic or pseudoperiodic behavior, but, with respect to oscillations in the system without therapy, we can notice a new effect of modulation or resonances caused by the overlap of the two periodic processes (the system and the therapy).

Moreover, in the Figure 3.6 we have collected some graphs where the same solutions of the Figure 3.5 are depicted, but selecting and zooming an interval of times ([600,800] rather than [0,800]) to highlight differencies not only in qualitative behavior, but also in size and period of oscillations.

Chapter 4

Mathematical analysis of the effect of delays between tumor growth and stimulation of immune cells proliferation

In this chapter we want to study what occurs to the system (3.1) adding a delay in $\beta(x)$, that is in the proliferation rate of immune system cells accounting for the presence of tumor.

The effect of time delay is taken into account in order to achieve a better compatibility with reality and to approximate missing dynamical components such as, chemical signals, B-lymphocytes-mediated maturation and activation of T-lymphocytes. In fact, immune system needs time to identify the tumor and to adequatly react with the counterattack of T lymphocytes, and this time lag - which is an organism characteristic time - can be used as control parameter of immune response.

Periodicity in tumor growth and in oncological diseases are sometimes observed in reality. Another reason to study delay models of tumor-immune system interaction is that these models can produce limit cycles that non-delayed models do not exhibit. In fact as we have seen in section 1.6 in the example of delayed logistic equation; introducing a delay term in the model can produce periodic dynamics. Then with delayed models we can explain observed periodicities.

In this work we have studied the model presented in previous chapter adding both a fixed lag delay, and distributed delays with some special integration kernels.
We have carried out an analytical study addressed particularly to changes in stability of equilibrium points via Hopf bifurcations and to possibility

of periodic solutions. We have also performed many numerical simulations taking values of parameters within the range of biological significance.

In this chapter we treat the case of discrete delay; whereas in the chapter 5 distributed delays are considered.

4.1 Fixed lag delay

Following some papers about specific models of tumor-immune system interaction ([12], [18], [21], [23]), in this chapter we add a fixed lag delay in term representing the proliferation rate of immune system cells accounting for the presence of tumor. Conversely to the approach followed by many authors in literature, we add the delay term only in the proliferative function $\beta(x)$ and not in the immune system variable y in analogy to the derivation of delayed logistic function where the delay term is introduced only in the growth rate function $F(x) = (1 - x/K)$ and not in the term $x(t)$ (see section 1.6).

We will analyze delayed system and in particular we will point out the possibility of changes in stability properties of equilibrium points via Hopf bifurcations. With the aim to study destabilizing properties of delay we will use as bifurcation parameter the delay τ.

The system with the new term $\beta(x(t-\tau))$ becomes

$$\begin{cases} x' = x(f(x) - \Phi(x, y)) \\ y' = \beta(x_\tau)y - \mu(x)y + \sigma q(x). \end{cases} \tag{4.1}$$

where $x_\tau(t) = x(t-\tau)$, $\tau \in \mathbb{R}^+$.

Equlibrium points are the same with respect to the system without delay.

With regard to disease free equilibrium we have the next simple result:

Proposition 4.1.1. *The equilibrium point disease free $DFE = (0, y_i(0))$ does not change its stability for any $\tau > 0$.*

Proof. Referring to the analysis of stability of DFE done in 3.1.1 in the nondelayed case, we only have to note that the delay does not affect the linearized equation for x:

$$x' = x(f(0) - \Phi(0, y_{DFE})) \tag{4.2}$$

then LAS condition is the same as in nondelayed case, that is:

$$\Phi(0, y_i(0)) > f(0) \tag{4.3}$$

and does not depend on the delay.

□

Now we study the equilibria with non null disease: $E = (x_e, y_e)$. To analyze the stability of these points, first of all we write the linearized system:

$$\begin{cases} \dfrac{d}{dt}u(t) = Hu(t) + Nv(t) \\ \\ \dfrac{d}{dt}v(t) = Qu(t-\tau) + Su(t) + Rv(t) \end{cases} \tag{4.4}$$

where:

$$H = x_e\left(f'(x_e) - \partial_x\Phi(x_e, y_e)\right) \tag{4.5}$$

$$N = -x_e\partial_y\Phi(x_e, y_e) < 0 \tag{4.6}$$

$$Q = y_e\beta'(x_e) \geq 0 \tag{4.7}$$

$$S = -y_e\mu'(x_e) + \sigma q'(x_e) \tag{4.8}$$

$$R = \beta(x_e) - \mu(x_e) = -\psi(x_e) < 0. \tag{4.9}$$

In this chapter we will make large use of the notations H, N, Q, R, S, so we rewrite the LAS conditions (3.25) as:

$$H + R < 0; \tag{4.10}$$

$$HR > N(Q + S). \tag{4.11}$$

With introduced notations, the characteristic equation of the system is:

$$\lambda^2 - (H + R)\lambda + (HR - NS) - NQe^{-\lambda\tau} = 0. \tag{4.12}$$

About which we want to find purely imaginary roots, that is, setting $\lambda = i\omega,\ \omega \in \mathbb{R}$ solutions of the equation:

$$-\omega^2 - i(H + R)\omega + (HR - NS) - NQ(cos\omega\tau - isen\omega\tau) = 0. \tag{4.13}$$

Separating real and imaginary part we have:

$$\begin{cases} -\omega^2 + (HR - NS) - NQcos\omega\tau = 0 \\ \\ -(H + R)\omega + NQsen\omega\tau = 0 \end{cases} \tag{4.14}$$

that is:

$$\begin{cases} cos(\omega\tau) = \dfrac{(HR - NS) - \omega^2}{NQ} \\ \\ sen(\omega\tau) = \dfrac{(H + R)\omega}{NQ} \end{cases} \tag{4.15}$$

From which we obtain the biquadratic equation in ω:

$$\omega^4 + (H^2 + R^2 + 2NS)\omega^2 + (HR - NS)^2 - (NQ)^2 = 0 \tag{4.16}$$

which we rewrite as follows:

$$\omega^4 + (H^2 + R^2 + 2NS)\omega^2 + (HR - NS - NQ)(HR - NS + NQ) = 0 \tag{4.17}$$

We will continue subdividing the analysis in all possible cases, treated according to their biologic relevance.

4.1.1 EQ is LAS and $q'(x_e) \leq 0$

This case is biologically very important because it represents a physically observable equilibrium with constant or decreasing effector influx.
In other terms, the size of tumor can be macroscopic or microscopic, but not so small to be in a range with increasing effector influx.

In this case $NS > 0$, and:

$$HR - NS - NQ > 0. \tag{4.18}$$

With the delay τ the equilibrium point EQ can remain LAS for any $\tau > 0$, or it may lose stability if the delay overcomes a critical value $\tau_{0,1}$.
More precisely we have:

Proposition 4.1.2. *Let $EQ = (x_e, y_e)$ be an equilibrium point with non null disease of system (4.1), which is LAS for $\tau = 0$ and let $q'(x_e) \leq 0$.*
If in EQ we have $(HR - NS + NQ) \geq 0$, then EQ will be LAS for any $\tau > 0$.
If in EQ we have:

$$HR - NS + NQ < 0, \tag{4.19}$$

Then there is a critical value $\tau_{0,1}$ and EQ is stable if $\tau < \tau_{0,1}$, and it is unstable if $\tau > \tau_{0,1}$. In $\tau = \tau_{0,1}$ there is a Hopf bifurcation.

Proof. To study the possibility of stability changes varying the delay τ, we have to verify conditions for which it is possible to have Hopf bifurcations; therefore we will study solutions of equation (4.17), that is, purely imaginary roots $\lambda = i\omega$ of characteristic equation.
Formally solutions of (4.17) are given by:

$$\omega_{\pm}^2 = \frac{-(H^2 + R^2 + 2NS) \pm \sqrt{\Delta}}{2} \tag{4.20}$$

where $\Delta = (H^2 - R^2)^2 + 4NS(H + R)^2 + 4N^2Q^2$.
Since $NS > 0$, we have a positive root ω_+^2 if and only if

$$(HR - NS + NQ)(HR - NS - NQ) < 0, \tag{4.21}$$

that is (4.19), remembering that EQ is LAS and therefore $(HR - NS - NQ) > 0$.

To complete the proof we have to study the sign of the derivative of $\mathrm{Re}\lambda(\tau)$ at the points where $\lambda(\tau)$ is purely imaginary. For the sake of semplicity we study the sign of inverse:

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{2\lambda - H - R + \tau NQe^{-\lambda\tau}}{-\lambda NQe^{-\lambda\tau}} = \frac{-2\lambda e^{\lambda\tau} + (H + R)e^{\lambda\tau} - \tau NQ}{\lambda NQ}$$

Setting $\lambda = i\omega_+$ and taking real part we have:

$$\mathrm{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1}|_{\lambda=i\omega_0} = \frac{-2cos\omega\tau}{NQ} + \frac{(H+R)sen\omega\tau}{\omega NQ} = \frac{-2(HR-NS)+2\omega_+^2+(H+R)^2}{(NQ)^2}$$

and this derivative is positive in ω_+^2, so there is a Hopf bifurcation with loss of stability in

$$\tau_{0,1} = \frac{\theta_1}{\omega_+} \tag{4.22}$$

where θ_1 is such that $0 \leq \theta_1 < 2\pi$ and

$$cos\theta_1 = \frac{(HR-NS)-\omega_+^2}{NQ}, \quad sen\theta_1 = \frac{(H+R)\omega_+}{NQ}. \tag{4.23}$$

□

4.1.2 EQ is LAS and $q'(x_e) > 0$ but $S < 0$

This case is mathematically equivalent to the previous one, nevertheless we distinguished it because it is biologically deeply different. In fact it corresponds to a microscopic equilibrium where the effector influx is increasing: $q'(x_e) > 0$, but it also is $q'(x_e) < y_e\mu'(x_e)$.
All the observations made in the previous section are still valid, so we have to verify the condition:

$$HR - NS + NQ < 0. \tag{4.24}$$

If this inequality holds there will be a Hopf bifurcation with loss of stability in $\tau = \tau_{0,1}$ where $\tau_{0,1}$ is calculated with (4.22)-(4.23); else, if (4.24) does not hold, the equilibrium point is stable for any $\tau > 0$.

4.1.3 EQ is LAS but $NS < 0$

This case biologically represents a microscopic equilibrium with an extremely small tumor size where the stimulation activity on the influx of effectors is so high that $q'(x_e) > y_e\mu'(x_e)$.
In this case there are many possible behaviors.
Arguing as in the previous sections we have that if $HR - NS + NQ < 0$, then the biquadratic equation (4.17) has two real roots $\pm\omega_+$ and there is a Hopf bifurcation with loss of stability in $\tau = \tau_{0,1}$ where $\tau_{0,1}$ is given by (4.22)-(4.23).

Else, if $HR - NS + NQ > 0$ and following conditions hold:

$$2NS < -H^2 - R^2, \tag{4.25}$$

$$(H^2 - R^2)^2 + 4NS(H+R)^2 + 4(NQ)^2 > 0, \tag{4.26}$$

then the biquadratic equation (4.17) has four distinct real solutions: $\pm\omega_+$, $\pm\omega_-$, where ω_+, $\omega_- > 0$ are the roots of:

$$\omega_\pm^2 = \frac{-(H^2 + R^2 + 2NS) \pm \sqrt{\Delta}}{2} \tag{4.27}$$

and $\text{Re}\left(\frac{d\lambda}{d\tau}\right)|_{\lambda=i\omega_\pm}$ is positive in ω_+ and negative in ω_-.

So, defined:

$$\tau_{n,1} = \frac{\theta_1}{\omega_+} + \frac{2n\pi}{\omega_+} \tag{4.28}$$

with $0 \leq \theta_1 < 2\pi$ and

$$cos\theta_1 = \frac{(HR - NS) - \omega_+^2}{NQ}, \quad sen\theta_1 = \frac{(H + R)\omega_+}{NQ}. \tag{4.29}$$

$$\tau_{n,2} = \frac{\theta_2}{\omega_-} + \frac{2n\pi}{\omega_-} \tag{4.30}$$

with $0 \leq \theta_2 < 2\pi$ and

$$cos\theta_2 = \frac{(HR - NS) - \omega_-^2}{NQ}, \quad sen\theta_2 = \frac{(H + R)\omega_-}{NQ}. \tag{4.31}$$

for $n = 0, 1, 2, ...$, we have:

Proposition 4.1.3. *Let $EQ = (x_e, y_e)$ be an equilibrium point for the system (4.1) with non null disease, which is LAS for $\tau = 0$, and in which we have $q'(x_e) > 0$, $S > 0$.*

If in EQ it holds:

$$HR - NS + NQ < 0, \tag{4.32}$$

then a Hopf bifurcation occurs in $\tau = \tau_{0,1}$ given by (4.22)-(4.23) and EQ in LAS for $\tau < \tau_{0,1}$, and unstable for $\tau > \tau_{0,1}$.

If in EQ we have:

$$HR - NS + NQ > 0, \tag{4.33}$$

$$2NS + H^2 + R^2 < 0, \tag{4.34}$$

$$(H^2 - R^2)^2 + 4NS(H + R)^2 + 4(NQ)^2 > 0, \tag{4.35}$$

Then EQ is LAS for $\tau < \tau_{0,1}$, and in $\tau = \tau_{0,1}$ a Hopf bifurcation occurs with loss of stability. Moreover, if $\tau_{0,2} < \tau_{1,1}$ stability is recovered in $\tau = \tau_{0,2}$ and there are a finite number of stability switches, whereas if $\tau_{0,2} < \tau_{1,1}$ stability is lost definitively.

Finally, if (4.33) holds, but (4.34) or (4.35) are not satisfied, EQ will remain stable for any $\tau > 0$.

4.1.4 EQ is unstable and there are no limit cycles

In this case in absence of delay the resulting equilibrium is not biologically observable, thus one might speculate that the introduction of a delay might stabilize it, although usually the effect of delays is unstabilizing. Our analysis shows that such stabilization does not hold.

In fact in this case two tipes of equilibrium points are summarized:

- EQ unstable; $H + R < 0$ and $HR - NS - NQ < 0$;
- EQ unstable; $H + R > 0$ and $HR - NS - NQ < 0$.

Both cases correspond to saddle points for the system without delay and adding delay does not involve any qualitative change.

4.1.5 EQ is unstable, $H + R > 0$ but $HR - NS - NQ > 0$

In this case EQ in the system without delay is unstable, but we have occurrence of limit cycles if EQ is the only equilibrium with non null disease.

Adding the delay we observe that oscillatory dynamics may overstay; but we will see that in this case, differently from the previous one, delay can have a stabilizing effect, that is, under certain assumptions, increasing the value of delay, that there may be stability switches from instability to stability. More precisely we have:

Proposition 4.1.4. *Let EQ be an unstable equilibrium point with non null disease in which $H+R > 0$ and $HR-NS-NQ > 0$. If, moreover, following conditions hold:*

$$HR - NS + NQ > 0, \tag{4.36}$$
$$2NS + H^2 + R^2 < 0, \tag{4.37}$$
$$(H^2 - R^2)^2 + 4NS(H + R)^2 + 4(NQ)^2 > 0; \tag{4.38}$$

then there may be a finite number of stability switches from instability to stability.

Proof. We first remember the biquadratic equation:

$$\omega^4 + (H^2 + R^2 + 2NS)\omega^2 + (HR - NS - NQ)(HR - NS + NQ) = 0 \tag{4.39}$$

and we observe that the condition (4.38) is equivalent to the positiveness of the determinant, and therefore there are two distinct real roots:

$$\omega_{\pm}^2 = \frac{-(H^2 + R^2 + 2NS) \pm \sqrt{\Delta}}{2} \tag{4.40}$$

whereas conditions (4.37) and (4.38) imply that both the roots are positive. Following theory of the section 1.5.1 and proceeding as in the Proposition 4.1.3 we can define:

$$\tau_{n,1} = \frac{\theta_1}{\omega_+} + \frac{2n\pi}{\omega_+} \tag{4.41}$$

and

$$\tau_{n,2} = \frac{\theta_2}{\omega_-} + \frac{2n\pi}{\omega_-} \tag{4.42}$$

where θ_1, θ_2 are such that $0 \leq \theta_1 < 2\pi$, $0 \leq \theta_2 < 2\pi$ and

$$cos\theta_1 = \frac{(HR - NS) - \omega_+^2}{NQ}, \quad sen\theta_1 = \frac{(H + R)\omega_+}{NQ}. \tag{4.43}$$

$$cos\theta_2 = \frac{(HR - NS) - \omega_-^2}{NQ}, \quad sen\theta_2 = \frac{(H + R)\omega_-}{NQ}. \tag{4.44}$$

for $n = 0, 1, 2, ...$
The molteplicity of roots with $Re\lambda > 0$ increases and decreases of two units when τ passes through $\tau_{n,1}$ or $\tau_{n,2}$ eventually leading to stability switches. □

If hypothesis of previous proposition do not hold, the system continues to have an oscillatory dynamics for any value of delay.

In the section 4.2.4 we will see, through numerical simulations, that delay has however some effect on the limit cycle which changes slightly its shape. In fact the state variable x (representing the size of tumor), assumes higher values increasing the delay. Furthermore, will see that the period of cycle also increases while τ is growing.

4.2 Numerical simulations

We will report in this section some numerical simulations with the aim to give biologically meaningful examples of different cases analyzed previously.

To estimate system parameters, at the beginning we refer to paper of Kuznetsov [14], that is we consider the system described in the example 1 of previous chapter:

$$\begin{cases} x' = x(1.636\,(1 - 0.002x) - y) \\ \\ y' = \dfrac{1.131x_\tau}{20.19 + x_\tau} y - (0.00311x + 0.3743)y + 0.1181 \end{cases} \tag{4.45}$$

We rembember here that this system has 4 equilibrium points:

- The disease free equilibrium: $DFE = (0, 0.316)$ which is unstable;
- A microscopic LAS equilibrium point: $E_{micro} = (8.1897, 1.6092)$;

- A saddle point: $E_u = (267.798, 0.7598)$;
- A macroscopic LAS equilibrium point: $E_{macro} = (447.1342, 0.173)$.

Moreover, we remember that $t_{real} = 9.9\, t_{adim}\, days$.
Next we will refer to this relation to verify the biological reliability of values of delays utilized in our numerical simulations and of critical values of τ for which bifurcations occur.

Delay considered in our analysis can be due to many factors: above all to the time lag needed by immune system to notice tumor presence and to start to produce differentiated cells ables to compete with it; secondly to proliferation time, that is division cell lenght, normally valued between 0.9 and 12 days [18], [19]; and finally to time lag that immune cells need to reach tumor situ.

In literature typical delays are estimated between 1 and 20 days [18], [21], but for critical values of delays in which Hopf bifurcations occur we find times from 1 to roughly 50 days [23].

4.2.1 EQ is LAS and $q'(x_e) \leq 0$

We can see, as a first example, the behavior of two LAS equilibrium points E_{micro}, E_{macro} of the system (4.45) with the add of a delay term.

In the section 4.1.1 we have proved that two behaviors are possibles: the equilibrium point remains LAS for any value of delay, or a Hopf bifurcation occurs with loss of stability.

With respect to two points considered, we have that in E_{micro} condition (4.19) holds and the critical bifurcation value is $\tau_{bif} = 0.2692$; whereas in E_{macro} condition (4.19) does not hold and the point remains stable.

We show the bifurcation diagram at the point E_{micro} in Figure 4.1. We see that for $\tau = \tau_{bif}$ a Hopf bifurcation occurs and dynamics is cyclic until around $\tau = 1.09$ (value obtained numerically).
After this thereshold the point E_{micro} remains unstable, but limit cycles break down and the system converge to E_{macro} that is LAS for every value of delay.

To better see different dynamics, in Figure 4.2 we showed the behavior of solutions of system (4.45) with different, increasing, values of delay taking initial conditions close to E_{micro}.
We see that for small delays the equilibrium point is still LAS (4.2-**a**), but when τ passes through τ_{bif} (figure 4.2-**b**), solutions start oscillate and the size of cycles becomes larger and larger as τ increases.
Finally (figure 4.2-**c**) for greater values of delay solutions converge to E_{macro}.

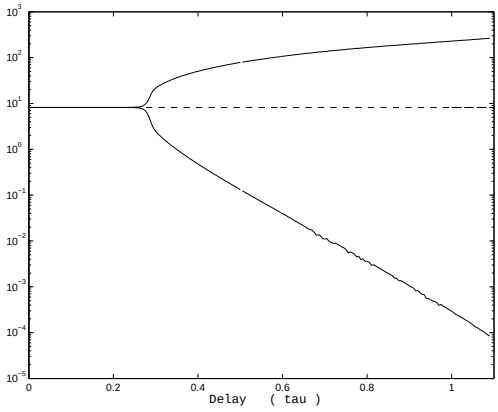

Figure 4.1: *Bifurcation diagram of system (4.45) at the equilibrium point E_{micro} plotted in logarithmic scale.*

In Figure 4.3 we summarized in a phase portrait different asymptotical dynamical behaviors of solution $x(t)$ of the system (4.45), showing how the point E_{micro} is LAS for values of delay less than τ_{bif}, and exhibits limit cycles of increasing amplitude as delay increases. Finally, when $\tau > 1.09$, limit cycles break down and we have convergence to E_{macro}.

It is interesting to note that not only amplitudes of cycle, but also periods increase as delay increases. To see this we have reported in Table 4.2.1 values of period and amplitude of limit cycles for different increasing values of τ.

This increasing trend in periods and amplitudes can be observed also in Figure 4.4 where we reported long-term time paths of solutions $x(t)$ of tumor variable for some values of those seen in Table 4.2.1.

Concerning what we said discussing about tipical and biological meaningful values of delay, we see that the critical value found for this first model:

$$\tau_{bif} = 0.2692$$

corresponds to 2.66 days, and so it lies in the range of acceptable values.

We can imagine that in an organism suffering from tumor, the effective delay in proliferation of immune system can be either less or greater than τ_{bif} depending on the individual. So, depending on the circumstances, tumor can have or not an oscillatory behavior. Moreover, it is possible that this delay varies in time for different reasons (age, environment, diseases,...) and that consequenly system passes from an oscillatory dynamics to one convergent to E_{micro} and viceversa, until variables do not lie in the attraction basin of E_{macro} that is LAS independently on delay value.

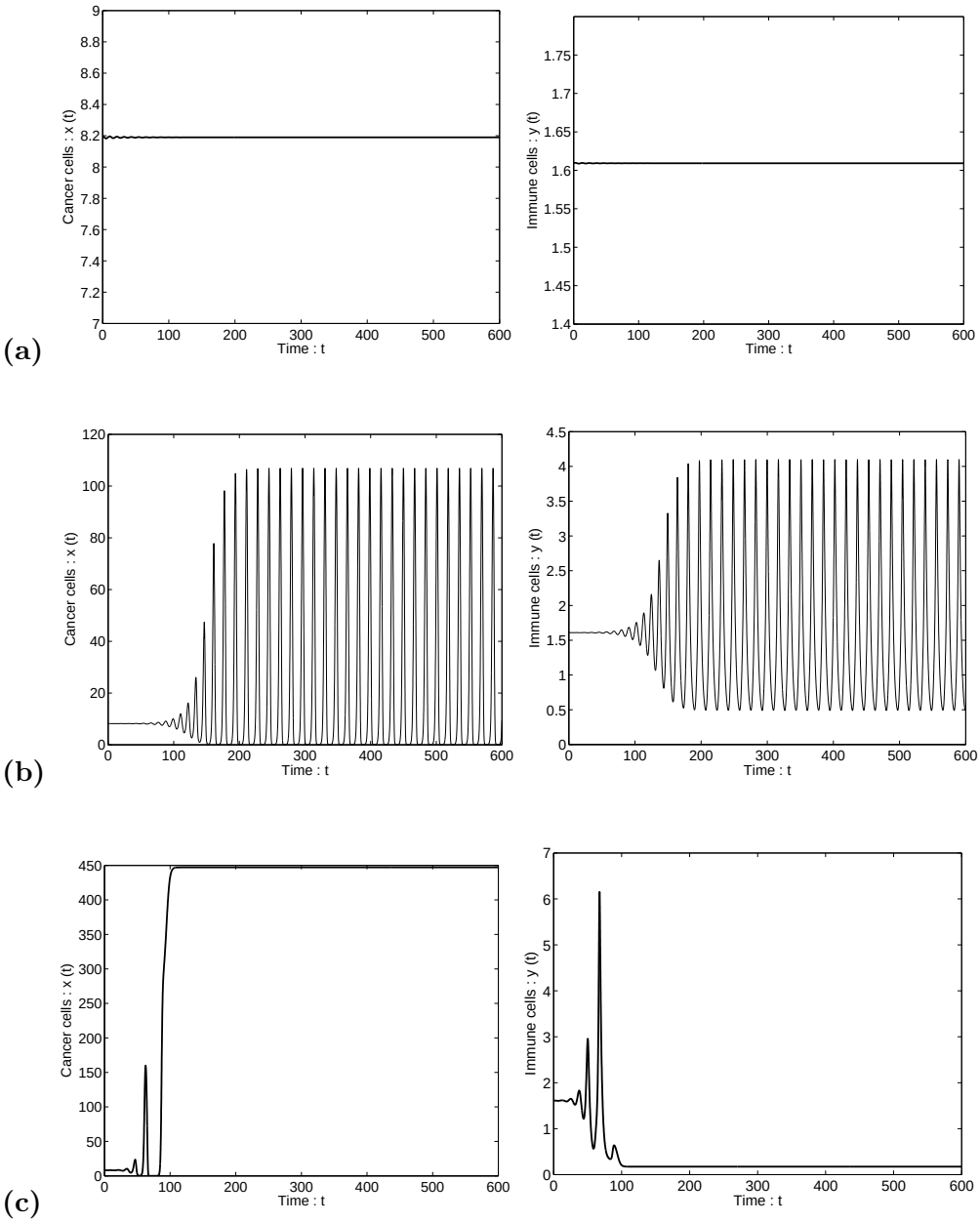

Figure 4.2: *Solutions x(t) (cancer cells) on the left and immune cells y(t) (on the right) of system (4.45) with initial conditions close to equilibrium point E_{micro}. Values of delay are:* ***(a)*** $\tau = 0.1$*;* ***(b)*** $\tau = 0.6$*;* ***(c)*** $\tau = 1.2$.

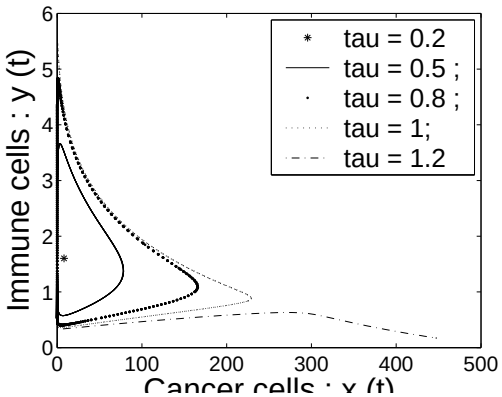

Figure 4.3: *Phase portrait in (x,y)-plane of solutions of system (4.45) for different values of delay.*

Delay (τ)	Cycle Period	Amplitude
0.3	11.6	21.8
0.35	12.5	36.4
0.4	13.5	50.3
0.45	14.5	64.3
0.5	15.3	78.4
0.55	16.3	92.5
0.6	17.2	106.9
0.65	18.1	121.3
0.7	19	135.9
0.75	20	150.6
0.8	21.2	165.6
0.85	22.3	180.8
0.9	23.7	196.4
0.95	25.1	212.3
1	27	229.1
1.05	29.9	247.3

Table 4.1: *We reported in this table periods and amplitudes of cycles of variable $x(t)$ dependent on delay. Data are referred to system (4.45) in the range of delay values when limit cycle is present. We note how both periods and amplitudes increase as τ increases.*

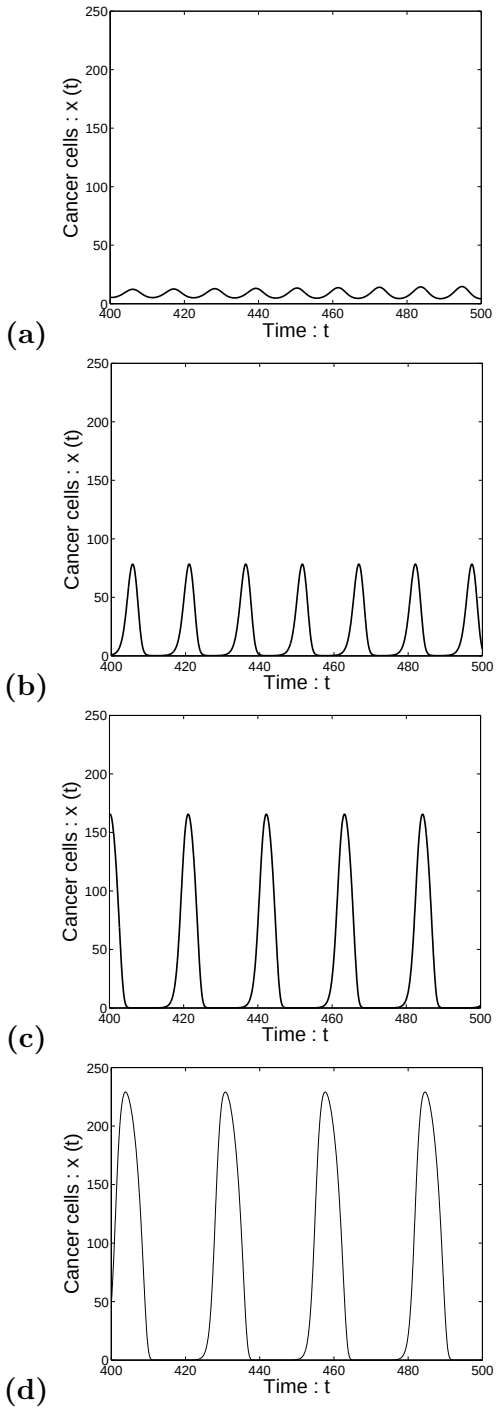

Figure 4.4: *Solutions x(t) (cancer cells) of the system (4.45) with initial conditions close to equilibrium point E_{micro}. In abscissa was taken an interval of time of lenght 100 units. We can observe differences in periods and amplitudes of cycles, and compare these graphs with data in Table 4.2.1. Values of delay are:* ***(a)*** $\tau = 0.3$*;* ***(b)*** $\tau = 0.5$*;* ***(c)*** $\tau = 0.8$*;* ***(d)*** $\tau = 1$.

4.2.2 EQ is LAS and $q'(x_e) > 0$ but $S < 0$

In this section we study an equilibrium point with non null disease in which the conditions:

1 - $EQ = (x_e, y_e)$ LAS;

2 - $q'(x_e) > 0$;

3 - $S = -y_e\mu'(x_e) + \sigma q'(x_e) < 0$

hold. To have such a point we slightly modified system (4.45), setting :

$$\Phi(x, y) = \frac{y}{1 + 0.01x + 0.5y}, \tag{4.46}$$

$$\tag{4.47}$$

$$\sigma q(x) = Min(0.01181 + 0.009\,x\,,\, 0.1181), \tag{4.48}$$

and taking other parameters as in (4.45).

This system when $\tau = 0$ has 4 equilibrium points:

- The disease free equilibrium $DFE = (0, 0.3155)$ which is unstable;

- A LAS equilibrium point $E_1 = (10.925, 8.881)$, corresponding to a microscopic tumor;

- A saddle point $E_2 = (219, 719, 5.415)$;

- Another LAS equilibrium point $E_3 = (492.662, 0.144)$ corresponding to a macroscopic tumor much bigger than E_1.

Moreover, in E_1 we have $S < 0$.

In this case again a Hopf bifurcation occurs in $\tau_h = 0.2015$ with loss of stability for E_1. In Figure 4.5 different numerical simulations are showed with increasing values of τ and with initial conditions close to E_1.

The qualitatively behavior is analogous to that discussed above for Figure 4.2 in section 4.2.1: again we can see how for delay less than bifurcation value the equilibrium point E_1 is LAS. Then, increasing τ above τ_h, we have range where dynamics is cyclic; and finally, when the delay exceeds a critical value τ_c, greater than τ_h, the cycle breaks down and solutions converge to macroscopic equilibrium point E_3.
Here we have reported only Figure 4.5 where the three possible patterns of solutions are showed.

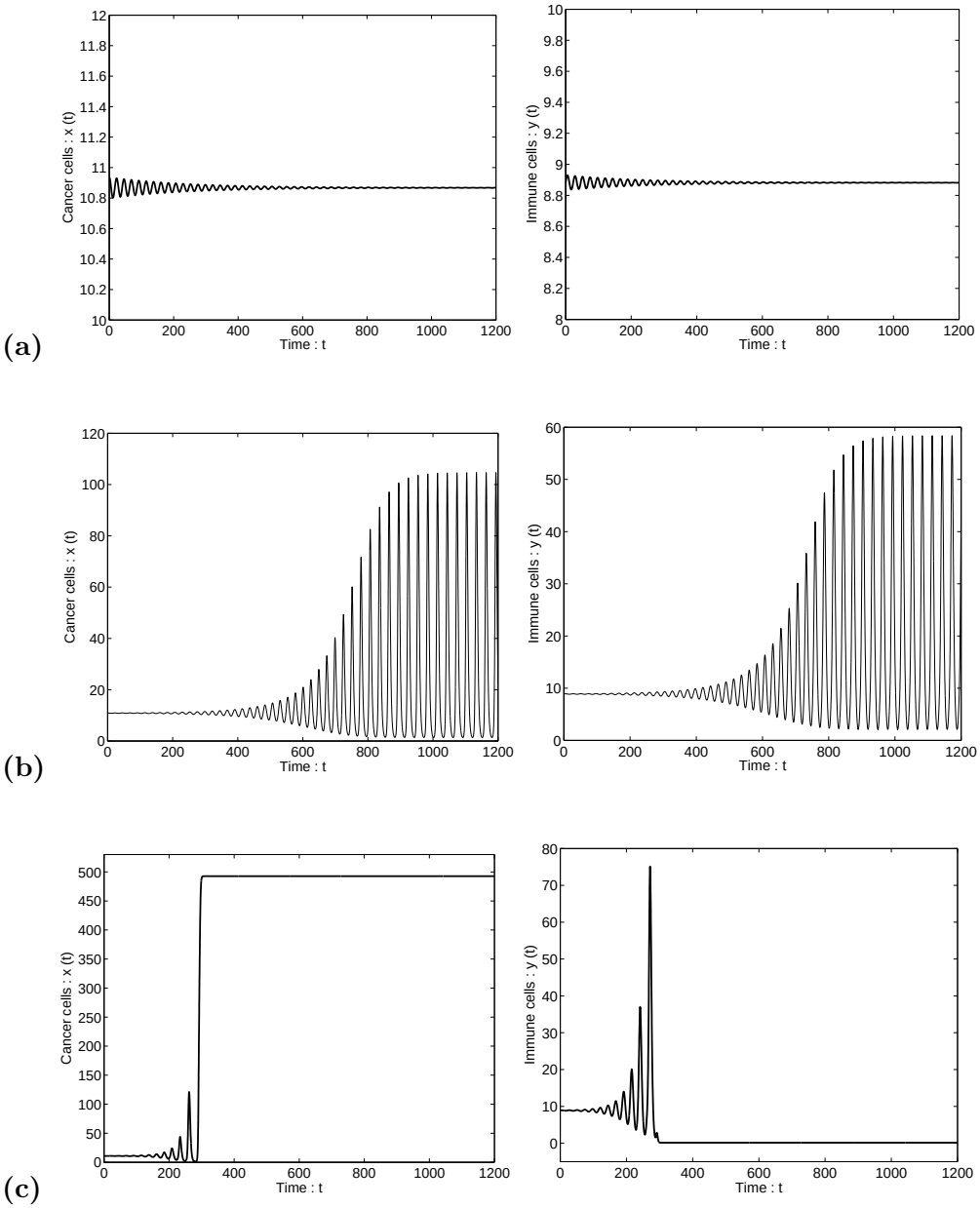

Figure 4.5: *Solutions of system described in section 4.2.2 with initial conditions close to equilibrium point E_1. x(t) (cancer cells) on the letf and y(t) (immune cells) on the right. Values of delay are varied:* ***(a)*** $\tau = 0.1$*;* ***(b)*** $\tau = 0.4$*;* ***(c)*** $\tau = 0.8$

4.2.3 EQ is LAS but $NS < 0$

In this section we show the behavior of the system which has all parameters equals to model (4.45) except for:

$$\sigma q(x) = Min(0.01181 + 0.01181\, x\, ,\, 0.1181).$$

Such a system, in fact, has an equilibrium point with non null disease $E = (8.3724, 1.6086)$ which is LAS when $\tau = 0$ and in which $NS < 0$.
The others equilibrium points of the system are:

- The disease free equilibrium $DFE = (0, 0.3155)$, unstable;
- An unstable point $U = (267.79, 0.7597)$;
- A macroscopic LAS equilibrium $E_S = (447.134, 0.173)$.

E is LAS when $\tau = 0$, but the stability is lost via Hopf bifurcation when $\tau > \tau_{bif} = 0.2564$.

Some numerical simulatons showing the behavior of solutions $x(t)$ and $y(t)$ of system with these parameters values can be seen in Figure 4.6.

Again we have reported only one example for any possible behavior and we can repeat considerations reported in section 4.2.1, that is note that when delay is small the equilibrium point E is LAS, then, increasing delay, there is a bifurcation value where Hopf bifurcation occurs and a limit cycle arises, and finally there is another critical value above which the system converge to the macroscopic LAS equilibrium E_S.

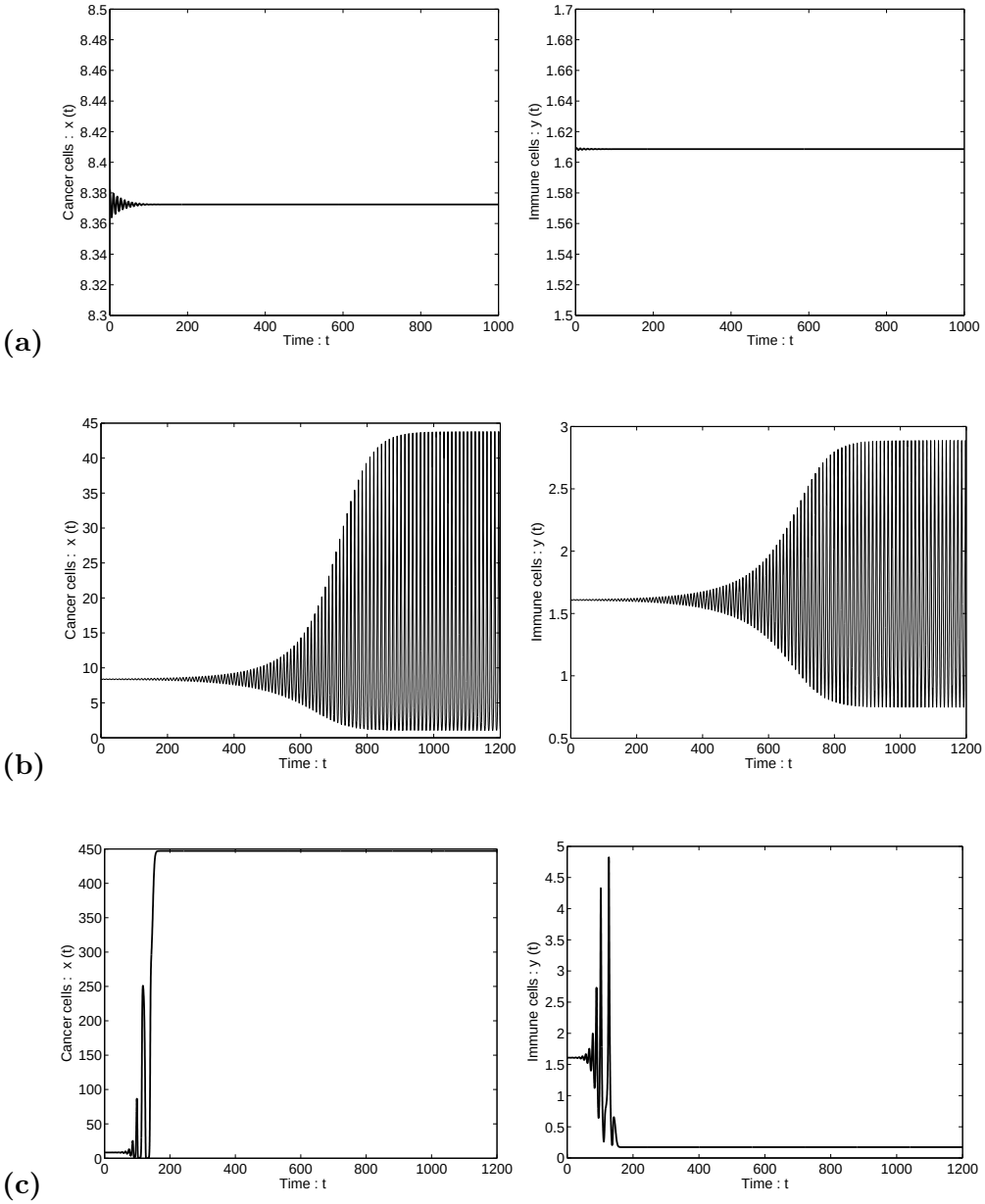

Figure 4.6: *Solutions of delayed system with parameters taken as in section 4.2.3 and initial conditions close to equilibrium point E. x(t) (cancer cells) on the letf and y(t) (immune cells) on the right. Values of delay are:* ***(a)*** $\tau = 0.1$*;* ***(b)*** $\tau = 0.3$*;* ***(c)*** $\tau = 0.8$*.*

4.2.4 EQ is unstable and there are limit cycles: $H + R > 0$ but $HR - NS - NQ > 0$

Finally let us take account of system presented in the example 2 of previous chapter:

$$\begin{cases} x' = x(1.636\,(1 - 0.00476x) - \dfrac{y}{1 + 0.02x + 0.25y}) \\ \\ y' = \dfrac{1.131x}{20.19 + x}y - (0.00311x + 0.3743)y + 0.1181 \end{cases} \tag{4.49}$$

As we have seen, this system has the unstable equilibrium DFE and a diseased unstable equilibrium point $E_c = (9.6446, 3.0535)$. Moreover, in this system limit cycles are present for $\tau = 0$.

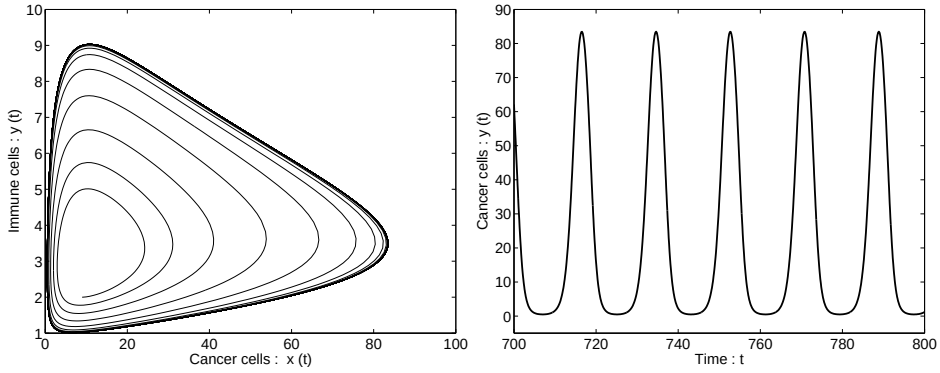

Figure 4.7: *Limit cycle in system without delay described in the section 4.2.4 with initial conditions close to equilibrium point $E_c = (9.6446, 3.0535)$. On the left phase-portait in (x,y)-plane; on the right period of solutions x(t).*

Adding the delay we see in Figure 4.9 that variables x and y assume higher values as τ increases (especially x).

Moreover, in Figure 4.8 we see also that as τ increases the period of the cycle P increases , from a value $P \simeq 20$ (that is 198 days) for $\tau = 0.1$, to $P \simeq 25$ (roughly 247 days) for $\tau = 0.8$; whereas in the system without delay the period is $P = 18$ (figure 4.7).

These periods of roughly 6-8 months are rather meaningful as oscillation times of a tumor.

To see how amplitudes of cycle, but also periods increase as delay increases we have reported in Table 4.2.4 some values of period and amplitude for different, increasing, values of τ.

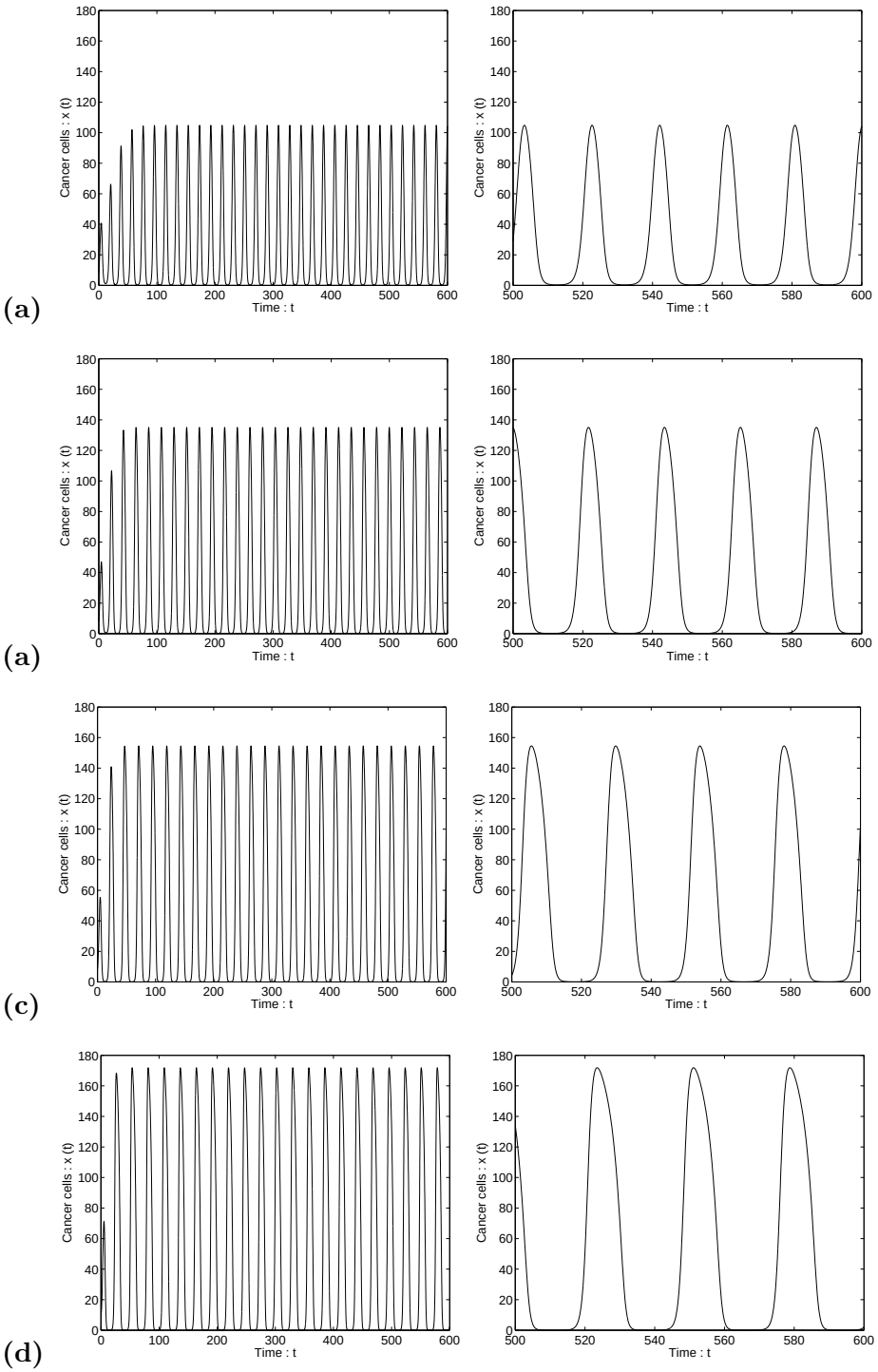

Figure 4.8: *Solutions $x(t)$ (cancer cells) of system with delay described in the section 4.2.4 with initial conditions close to equilibrium point E_c and delays: (a) $\tau = 0.1$; (b) $\tau = 0.3$; (c) $\tau = 0.5$; (d) $\tau = 0.8$. On the right we reported long-term paths of $x(t)$ and we may observe how period changes.*

Delay (τ)	cycle Period	Amplitude
0.1	19.5	104.9
0.2	20.8	121.6
0.3	21.9	135.1
0.4	23	145.8
0.5	24.3	154.5
0.6	25.5	161.5
0.7	26.6	167.2
0.8	27.6	171.9
0.9	28.8	175.7
1	29.8	178.9

Table 4.2: *We reported in this table periods and amplitudes of cycles of variable $x(t)$ dependent on delay. Data are referred to system (4.49) for which limit cycles arise also in the nondelayed case. We note how both periods and amplitudes increase as τ increases.*

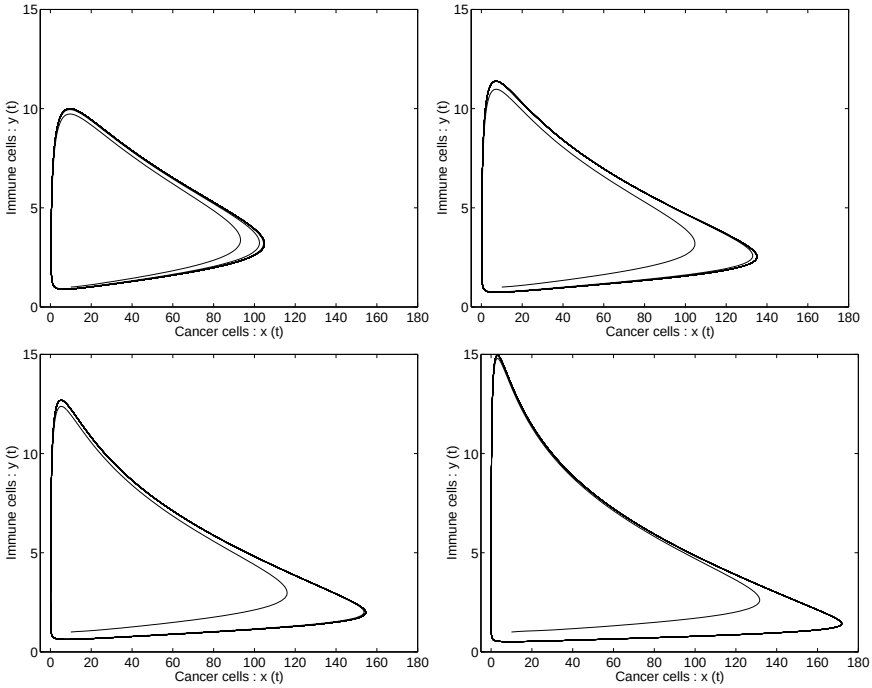

Figure 4.9: *Limit-cycles in (x(t),y(t))-plane. Solutions of delay-system described in section 4.2.4, with initial conditions close to point E_c and delays:* $\tau = 0.1$, $\tau = 0.3$, $\tau = 0.5$, $\tau = 0.8$.

Chapter 5

Distributed delay

Generally in biological phenomena, and particularly in our case, it is rather unrealistic to suppose that the time lag is a fixed one, whereas it is more meaningful to think that a delay term is due to cumulative effects of many different factors and so that is describable with a distributed delay.

As far as we know, distributed delay has not yet been considered too much in tumor-immune system models found in literature, although it is certainly reasonable to think that a delay term of this type can better approximate the response time of the immune system.

So, in this chapter, we examine models with distributed delay, that is systems of the form:

$$\begin{aligned} x' &= x(f(x) - \Phi(x,y)) && (5.1)\\ y' &= \beta(z)y - \mu(x)y + \sigma q(x) + \theta(t) && (5.2)\\ z &= \int_{-\infty}^{t} x(\tau)K(t-\tau)d\tau, && (5.3) \end{aligned}$$

Where the integration kernel K is erlangian, with probability density:

$$Erl_{n,a}(t) = \frac{a^n}{(n-1)!}t^{n-1}e^{-at} \quad t, a \in \mathbb{R}_+,\ n \in \mathbb{N}_+ \tag{5.4}$$

for which the mean delay is $T = \frac{n}{a}$ and the standard deviation is $\sigma = \frac{\sqrt{n}}{a}$.

In particular in the first section we will consider an exponential delay ($Erl_{1,a}$) whereas in the second section we will study the case $Erl_{2,a}$.

5.1 Exponentially distributed delay

Taking account of $Erl_{1,a}$, we can rewrite (5.1) as a system of 3 ODEs depending on the parameter $a > 0$:

$$\begin{aligned} x' &= x(f(x) - \Phi(x, y)) \\ y' &= \beta(z)y - \mu(x)y + \sigma q(x) \\ z' &= a\,(x - z)\,. \end{aligned} \tag{5.5}$$

An equilibrium point $EQ = (x_e, y_e, z_e)$ of this system has the same coordinates (x_e, y_e) of an equilibrium point of the system without delay and $z_e = x_e$.
We remember that in this case the value of the mean delay is $T = a^{-1}$.

In the equilibrium point disease free $DFE = (0, y_{DFE}, 0)$, there are not qualitatively changes due to delay, in particular:

Lemma 5.1.1. *The equilibrium point disease free $DFE = (0, y_{DFE}, 0)$ of system (5.1) is stable if $\Phi(0, y_{DFE}) - f(0) > 0$ and unstable otherwise.*

Proof. The matrix associated with linearized system in the equilibrium DFE is:

$$\begin{bmatrix} f(0) - \Phi(0, y_{DFE}) & 0 & 0 \\ -\mu'(0)y + \sigma q'(0) & -\mu(0) & \beta'(0)y \\ a & 0 & -a \end{bmatrix} \tag{5.6}$$

with characteristic equation:

$$(f(0) - \Phi(0, y_{DFE}) - \lambda)(-\mu(0) - \lambda)(-a - \lambda) = 0. \tag{5.7}$$

Since $\mu(0) > 0$ and $a > 0$, the eigenvalues:

$$\lambda_1 = f(0) - \Phi(0, y_{DFE}), \quad \lambda_2 = -\mu(0), \quad \lambda_3 = -a,$$

are all negative if and only if $\Phi(0, y_{DFE}) - f(0) > 0$. □

Let us consider therefore an equilibrium diseased point: $EQ = (x_e, y_e, z_e)$. It will be useful to define H, N, S, Q, R with (4.5)-(4.9) as in the section 4,

that is:

$$H = x_e \left(f'(x_e) - \partial_x \Phi(x_e, y_e) \right),$$

$$N = -x_e \partial_y \Phi(x_e, y_e) < 0,$$

$$Q = y_e \beta'(x_e) \geq 0,$$

$$S = -y_e \mu'(x_e) + \sigma q'(x_e),$$

$$R = \beta(x_e) - \mu(x_e) = -\psi(x_e) < 0.$$

And, thanks to these notations we can write the linearized system at EQ:

$$\begin{cases} X' = HX + NY \\ Y' = QZ + SX + RY \\ Z' = aX - aZ. \end{cases} \tag{5.8}$$

The characteristic equation of the system is:

$$\lambda^3 + c_2 \lambda^2 + c_1 \lambda + c_0 = 0, \tag{5.9}$$

where:

$$c_2 = a - (H + R),$$

$$c_1 = (-aH - aR + HR - NS),$$

$$c_0 = a(HR - NS - NQ).$$

In the following analysis we will use a as bifurcation parameter because equilibrium points do not depend on a and especially because a is the inverse of mean delay value and therefore it is a biological meaningful parameter. Moreover, in this way we can compare results with those obtained in previous chapter for fixed lag delays.

To studying stability of the equilibrium point EQ we will use Routh-Hurwitz rule, that is we will study the sign of the three quantities:

$$c_2, \quad c_0, \quad c_1 c_2 - c_0.$$

We know that if these quantities are positive the equilibrium point is LAS; whereas if one of them becomes negative varying a we have the loss of stability of the point.

Moreover, to see if Hopf bifurcations can occur, we suppose that there is a couple of conjugate complex roots $\lambda_H = \pm \omega_H$, with $\omega_H \in \mathbb{R}$. By substituing in characteristic equation and collecting real and imaginary part, we have:

$$\begin{cases} \omega_H^2 = \dfrac{c_0}{c_2} = \dfrac{a_H(HR - NS - NQ)}{a_H - (H + R)} \\ \\ c_1 - \dfrac{c_0}{c_2} = 0 \end{cases} \tag{5.10}$$

From these simple observations we can say that there will be a loss of stability via Hopf bifurcation when $(c_1c_2 - c_0)$ passes from positive to negative, moreover, since in Hopf points we have $\omega_H^2 = \frac{c_0}{c_2}$ we have to assume $c_0c_2 > 0$.

We can also state the following:

Lemma 5.1.2. *If $H+R < 0$ then a necessary condition to have Hopf points varying a is that EQ is LAS in the system without delay.*

Proof. This result follows immediatly from condition (5.10). In fact to have Hopf points ω_H^2 must be positive, and, since $a > 0$ and we are supposing $H + R < 0$ it follows that $HR - NS - NQ > 0$. But we remember that the two conditions $H + R < 0$, $HR - NS - NQ > 0$ imply that the point is LAS for the system without delay. □

Before studying in details stability of system by analyzing all possible cases, we want to introduce an useful notation: we define $p(a) = (c_1c_2 - c_0)$.

We have $p(a) = B_2a^2 + B_1a + B_0$, where

$$\begin{aligned} B_2 &= -H - R, \\ B_1 &= (H + R)^2 + NQ, \\ B_0 &= (-H - R)(HR - NS). \end{aligned} \tag{5.11}$$

We can now enunciate the following:

Proposition 5.1.3. *Let EQ be an equilibrium point of the system (5.5) which is stable in the non-delayed system. That is in EQ the following conditions hold:*

$$H + R < 0, \qquad HR - NS - NQ > 0.$$

(i) *If $HR - NS \leq 0$ then there is $a_h > 0$ such that if $a > a_h$ the equilibrium point is LAS, else if $0 < a < a_h$ then the point is unstable.*
In $a = a_h$ a Hopf bifurcation occurs.

(ii) *If $HR - NS > 0$ we have that if*

$$(H + R)^2 + NQ < -2(H + R)\sqrt{(HR - NS)}, \tag{5.12}$$

Then there are two values $0 < a_1 < a_2$ of the parameter a such that EQ is LAS for $a \notin [a_1, a_2]$ and unstable for $a \in (a_1, a_2)$.
In a_1, a_2 Hopf bifurcations occur.

If, instead, (5.12) does not hold, then EQ is LAS for any $a > 0$.

Proof. Firstly we remember conditions for the stability of the point:

$$c_2 = a - (H + R) > 0 \tag{5.13}$$
$$c_0 = a(HR - NS - NQ) > 0 \tag{5.14}$$
$$c_1 c_2 - c_0 = p(a) > 0. \tag{5.15}$$

The two first conditions are satisfied thanks to hypothesys of proposition, so we have to study the sign of $p(a)$ varying the parameter a. Since $p(a) = B_2 a^2 + B_1 a + B_0$ is a second order polynomial in a, we calculate the determinant:

$$\Delta = [(H + R)^2 + NQ]^2 - 4(H + R)^2(HR - NS). \tag{5.16}$$

Let us analyze now the two cases described in the proposition.

(i) In this case we have $\Delta > 0$, $B_2 > 0$ and $B_0 < 0$; $p(a)$ has a positive root a_h and a negative one, but we are interested only in positive values of the parameter a. Moreover, we can say that $p(a) > 0$, that is the point is stable if $a > a_h$, else if $0 < a < a_h$ $p(a) < 0$ the point is unstable.

(ii) In this case we have that $B_2 > 0$ e $B_0 > 0$; therefore if $B_1 \geq 0$ the point EQ will be LAS indipendently on the value of a, else if $B_1 < 0$ there will be stability switches if $p(a)$ has positive roots, that is if the determinant is positive.
Let us write

$$\Delta = (B_1 + 2\sqrt{B_0 B_2})(B_1 - 2\sqrt{B_0 B_2}),$$

since we are assuming $B_1 < 0$, we have $\Delta > 0$ if and only if $B_1 < -2\sqrt{B_0 B_2}$, that is if condition (5.12) holds. In this case roots a_1 and a_2 are both positive, $a_2 > a_1 > 0$ and $p(a)$ is positive outside the interval (a_1, a_2) and negative inside; That is the point is stable if $a \notin (a_1, a_2)$ and unstable otherwise.
Finally we verify the nonzero-speed condition noting that:

$$\frac{dp(a)}{da} \mid_{a=a_1} < 0 \tag{5.17}$$

e

$$\frac{dp(a)}{da} \mid_{a=a_2} > 0. \tag{5.18}$$

□

Finally we analyze the last case, that is the one in which the equilibrium point is unstable in the nondelayed system (when $a = +\infty$).

If $HR - NS - NQ < 0$ the point is unstable for every $a > 0$, then we consider only the case in which $HR - NS - NQ > 0$ that is the case in which $c_0 > 0$.

Proposition 5.1.4. *Let EQ be an equilibrium point of the system (5.5) in which $H + R > 0$ and $HR - NS - NQ > 0$.*

(i) *If $HR - NS \leq 0$ then there is an $a_h > 0$ such that $p(a)$ is negative if $a > a_h$ and positive if $0 < a < a_h$. If $a_h < H + R$ then the point is unstable for every $a > 0$. If $a_h > H + R$ then in $a = a_h$ a Hopf bifurcation occurs, EQ is LAS in $H + R < a < a_h$ and unstable if $a > a_h$ or $a < H + R$.*

(ii) *If $HR - NS > 0$ we have that if:*

$$(H + R)^2 + NQ > -2(H + R)\sqrt{(HR - NS)}, \tag{5.19}$$

then there are $0 < a_1 < a_2$ such that $p(a)$ is positive in (a_1, a_2) and negative otherwise. If $a_2 < H + R$ then the point is unstable for every $a > 0$. If $a_2 > H + R > a_1$ then in $a = a_2$ a Hopf bifurcation occurs, EQ is stable in $H + R < a < a_2$ and unstable if $a > a_2$ or $a < H + R$. Finally, if $a_1 > H + R$ then in $a = a_2$ and in $a = a_1$ Hopf bifurcation occurs, and EQ is stable if $a \in (a_1, a_2)$ and unstable otherwise.

If, instead, (5.19) does not hold, then EQ is unstable for any $a > 0$.

Proof. To study the sign of $p(a)$ we can proceed exactly as done in the previous proof, but now we have to check also the sign of $c_2 = a - (H + R)$. In both cases **(i)** and **(ii)** it is $B_2 < 0$.

(i) In this case $B_0 > 0$ and $\Delta > 0$ so $p(a)$ has a positive root a_h and a negative one. For $a > a_h$ it is $p(a) < 0$ and for $0 < a < a_h$ it is $p(a) > 0$. Now we have to verify the sign of $c_2 = a - (H + R)$.
If $a_h < H + R$ then $c_2 < 0$ when $p(a) > 0$ and the point is unstable for every $a > 0$.
If $a_h > H + R$ then for $H + R < a < a_h$ we have $c_2 > 0$ and $p(a) > 0$, then the point is stable if $a \in (H + R, a_h)$ and unstable otherwise.
In $a = a_h$ conditions (5.10) hold, and proceeding as in the previous proof we can prove that the nonzero-speed condition holds too; then a_h is an Hopf point. In $a = H + R$ conditions (5.10) do not hold and then $a = H + R$ is not a Hopf point.

(ii) In this case $B_0 < 0$; therefore if $B_1 < 0$ there are not positive real roots, whereas if $B_1 > 0$ there are two positive roots $a_1 < a_2$ if $\Delta = (B_1 + 2\sqrt{B_0 B_2})(B_1 - 2\sqrt{B_0 B_2}) > 0$, that is if $B_1 > 2\sqrt{B_0 B_2}$.
Then if (5.19) does not hold $p(a) < 0$ for every $a > 0$ and EQ remains unstable.

We assume now that (5.19) holds. In this case $p(a)$ is positive if a stays in (a_1, a_2) and negative otherwise.
However if $a_2 < H+R$, in (a_1, a_2) we have $c_2 < 0$ then EQ remains unstable for every $a > 0$. If $a_2 > H + R$ then for $H + R < a < a_2$ we have $c_2 > 0$ and $p(a) > 0$, then the point is stable if $a \in (H + R, a_2)$ and unstable otherwise. In $a = a_2$ a Hopf bifurcation occurs. Finally if $a_1 > H + R$ then $c_2 > 0$ in (a_1, a_2) and the point is stable for $a \in (a_1, a_2)$ and unstable otherwise. As above we can easily verify that in $a = a_2$, $a = a_1$ Hopf bifurcations occur.
□

5.1.1 Numerical results

To see an example of what we proved above, we perform numerical simulations considering the system (5.5) where parameters are the same as these in section 4.2.3.

Equilibrium points of non-delayed system are the same points reported in section 4.2.3; remembering that in this case we have a 3-dimensional system and, at equilibria $z_e = x_e$.

In $E_m = (8.3724, 1.6086, 8.3724)$ it is $HR - NS > 0$ and the condition (5.12) also holds; therefore two bifurcations occur when a passes through:

$$a_1 = 0.0155,$$

$$a_2 = 3.8067.$$

These values correspond to mean delays:

$\tau_1 = \frac{1}{a_1} = 64.51$,

$\tau_2 = \frac{1}{a_2} = 0.2627$ which is comparable to bifurcation values obtained taking into account discrete delays (in the same system with discrete delay bifurcation value is $\tau_{bif} = 0.2564$).

Since $t_{real} = 9.9\, t_{adim}$ days, we note that τ_2 corresponds to 2.6 days, a value quite realistic for a delay of this type; whereas τ_1 corresponds roughly to 37 days which, instead, is a value difficult to achieve for a delay in proliferation rate of immune cells.

In Proposition 5.1.3 we have seen that the system is stable for $a > a_2$. In $a = a_2$ a Hopf bifurcation occurs and system becomes unstable. Then, continuing decreasing the parameter there is another bifurcation when a passes through $a = a_1$ and stability is recovered.

In Figure 5.1 we note as the equilibrium point is LAS if the parameter a lies outside the interval (a_1, a_2).

Moreover, thanks to numerical simulations we see that when a stays in the interval (a_1, a_2), where system is unstable, there are two different possible behaviors. If a is less than a_2, but greater than a critical value a_c then system exhibits a limit cycle whose oscillations have amplitude increasing as a decreases (figure 5.3). In $a = a_c$ amplitude of cycle is such that the cycle is tangent to the seperatrix curve passing through the unstable equilibrium point U; therefore, diminishing again the value of a the system go into the attraction basin of the macroscopic equilibrium point E_M. In fact, from Figure 5.2 we can notice that system converges to E_M when $a < a_c$.

Decreasing further a the behavior changes again in a_1, in fact, as stated in Proposition 5.1.3 the point E_m is stable for $a < a_1$.

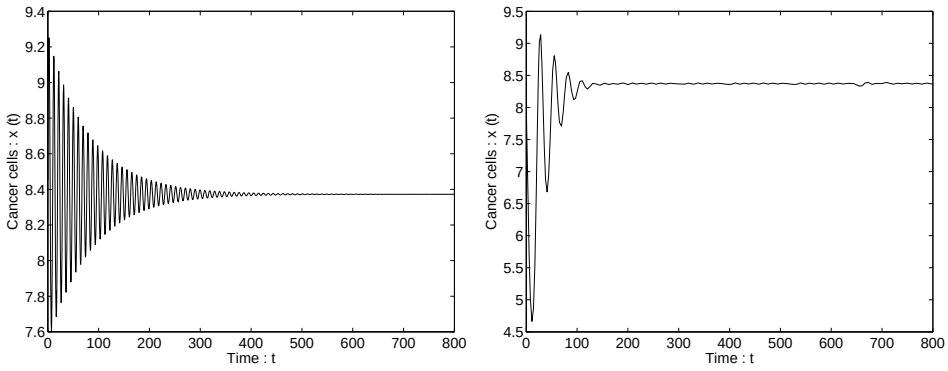

Figure 5.1: *Solutions x(t) (cancer cells) of the system with parameters as in section 5.1.1, initial conditions close to equilibrium point E_m and parameter values outside the range of instability: $a = 5 > a_2$ in the left and $a = 0.005 < a_1$ in the right.*

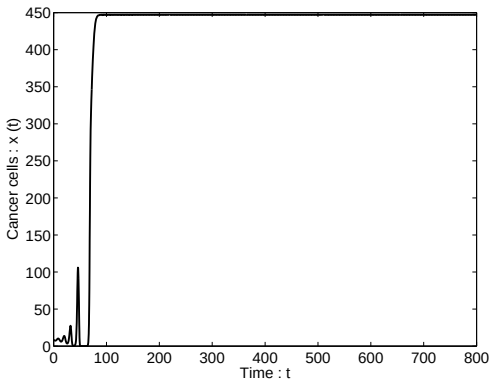

Figure 5.2: *Solutions x(t) (cancer cells) of the system with parameters as in section 5.1.1, initial conditions close to equilibrium point E_m and in which the parameter $a = 1$ lies in the instability interval and it is less than a_c.*

In Figure 5.3 are reported graphs of solutions $x(t)$ of tumor variable when the parameter a lies in the range where cyclic dynamics arise. In the right half of this figure, solutions are drawing in the final interval of time of lenght 100 units. Thanks to this magnification it is possible to see an increasing trend in periods of amplitudes of long-term time cyclic paths.
As we did in section 4.2.1 for a system with discrete delay, we show in Figure 5.4 a phase portrait that summarizes different long-term paths of solutions $x(t)$ of system (5.5). We can observe how the point E_m is LAS for values of parameter a greater than a_1, and exhibits limit cycles of increasing amplitude as delay increases (that is as a decreases). Finally, when $a < a_c$, limit cycles break down and we have convergence to the macroscopic equilibrium E_M.

Also in this case, as in the case of discrete delay we can observe how not only amplitudes of cycle, but also periods increase as delay increases. To see this we have reported in Table 5.1.1 values of period and amplitude of limit cycles for different, increasing, values of τ.

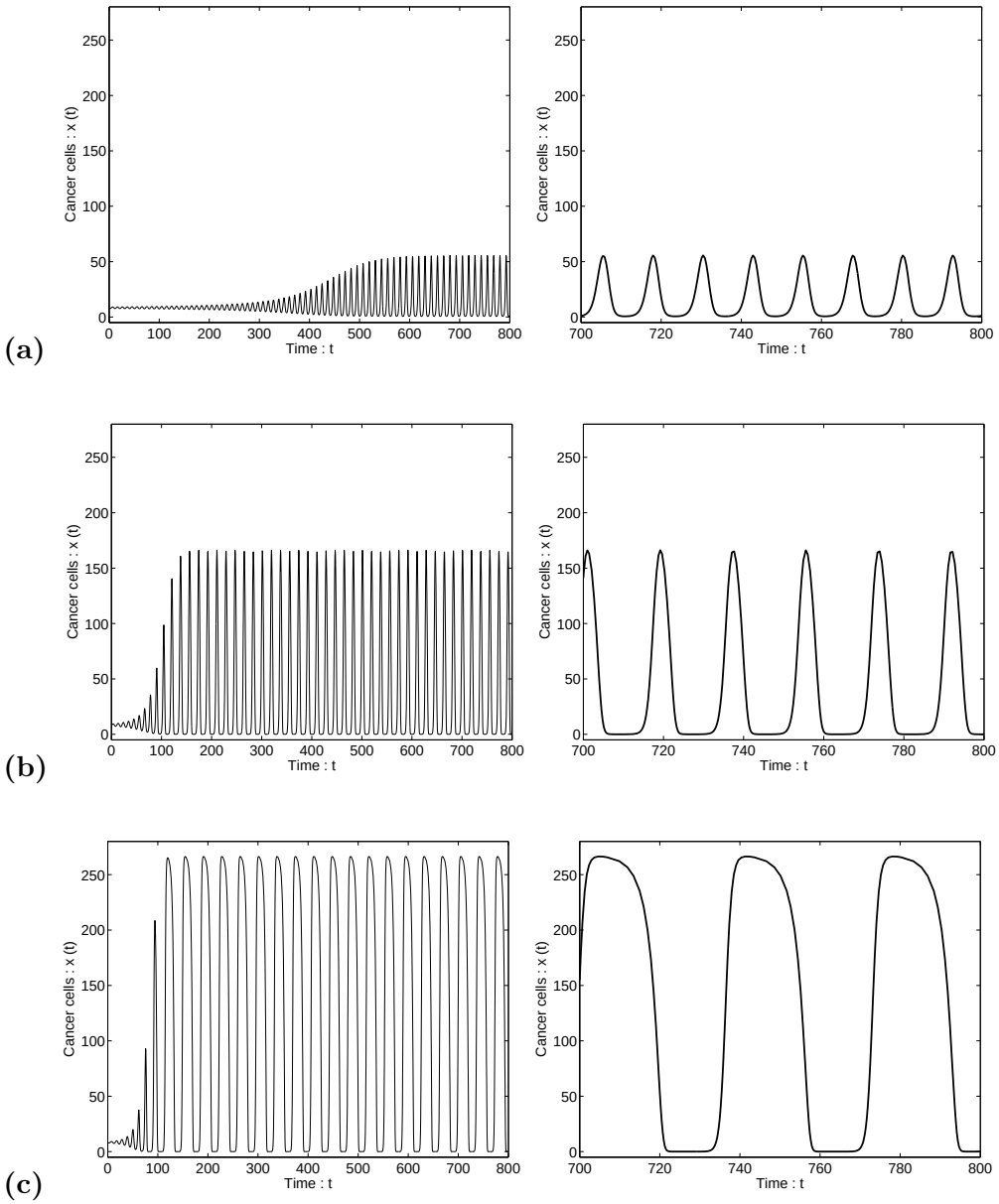

Figure 5.3: *Solutions x(t) (cancer cells) of the system with parameters as in section 5.1.1, initial conditions close to equilibrium point E_m and values of parameter: (a) $a = 3.2$; (b) $a = 2$; (c) $a = 1.5$. In the right half of figure are reported graphs where in abscissa is selected only a final interval of time of 100-units lenght.*

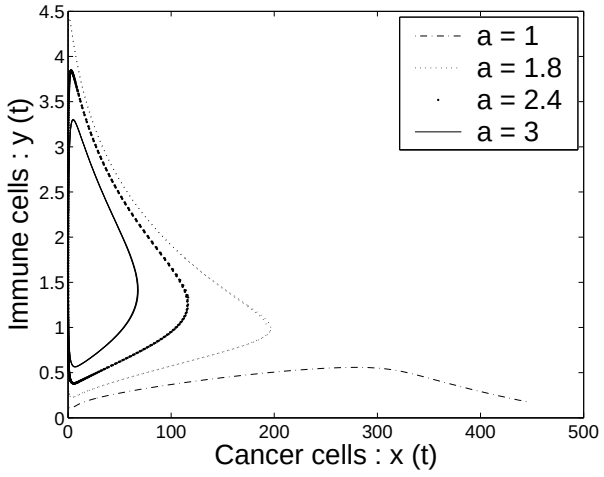

Figure 5.4: *Phase portrait in (x,y)-plane of solutions of system with parameters as in section 5.1.1 for different values of parameter a.*

Value of a	Mean delay (a^{-1})	Cycle Period	Amplitude
3.6	0.278	11.4	34.2
3.4	0.294	12	44.9
3.2	0.313	12.5	55.6
3	0.333	13.1	67.6
2.8	0.357	13.8	81.4
2.6	0.385	14.6	97
2.4	0.417	15.5	116.1
2.2	0.455	16.7	139.2
2	0.5	18.3	165.1
1.8	0.555	20.5	198.4

Table 5.1: *We reported in this table periods and amplitudes of cycles of variable $x(t)$ dependent on delay. Data are referred to system with parameters as in section 5.1.1, in the range of delay values when limit cycle is present. We note how both periods and amplitudes increase as delay increases (that is as the parameter a decreases).*

5.2 Strong Erlangian delay

We consider now a distrubuted delay with distribution $Erl_{2,a}$. System (5.1) can be rewritten in this case as a system of 4 ODEs:

$$\begin{aligned} x' &= x(f(x) - \Phi(x,y)) \\ y' &= \beta(z)y - \mu(x)y + \sigma q(x) + \theta(t) \\ u' &= a\,(x-u) \\ z' &= a\,(u-z) \end{aligned} \tag{5.20}$$

where $a \in \mathbb{R}^+$

An equilibrium point $EQ = (x_e, y_e, u_e, z_e)$ has as coordinates the coordinates (x_e, y_e) of the correspondent equilibrium in non delayed-system and $u_e = z_e = x_e$. The mean delay is given by $T = \frac{2}{a}$. So we will take a as bifurcation parameter in this section too.

In this case again, proceeding as in the previous section, we easily prove that delay does not affect stability of disease free equilibrium $DFE = (0, y_{DFE}, 0, 0)$.

Then we will consider only equilibria with non null disease
$EQ = (x_e, y_e, u_e, z_e)$, and we define:

$$H = x_e\left(f'(x_e) - \partial_x\Phi(x_e, y_e)\right) \tag{5.21}$$

$$N = -x_e\partial_y\Phi(x_e, y_e) < 0 \tag{5.22}$$

$$Q = y_e\beta'(x_e) \geq 0 \tag{5.23}$$

$$S = -y_e\mu'(x_e) + \sigma q'(x_e) \tag{5.24}$$

$$R = \beta(x_e) - \mu(x_e) = -\psi(x_e) < 0. \tag{5.25}$$

The linearized system is:

$$X' = HX + NY \tag{5.26}$$

$$y' = QZ + SX + RY \tag{5.27}$$

$$U' = aX - aU \tag{5.28}$$

$$Z' = aU - aZ \tag{5.29}$$

and the characteristic equation:

$$\lambda^4 + b_3\lambda^3 + b_2\lambda^2 + b_1\lambda + b_0 = 0, \tag{5.30}$$

where:

$$\begin{aligned} b_3 &= 2a - H - R, \\ b_2 &= a^2 - 2aH - 2aR + HR - NS, \\ b_1 &= a^2(-H - R) + 2a(HR - NS), \\ b_0 &= a^2(HR - NS - NQ). \end{aligned} \tag{5.31}$$

these coefficients are positive if two following conditions hold:

$$\begin{aligned} H + R &< 0, \\ HR - NS &> 0. \end{aligned} \tag{5.32}$$

To studying stability of system we apply Routh-Hurwitz rule. So we have to study the sign of:

$$\begin{aligned} &b_0,\ b_1,\ b_3, \\ &g(a) = (b_1 b_2 - b_3 b_0) b_3 - b_1^2; \end{aligned} \tag{5.33}$$

And we have that if these four terms are positive, so the corresponding point is LAS, else if one of them is negative, the point is unstable.

If, as an example, we consider a LAS point in non delayed-system, that is a point where

$$H + R < 0, \qquad HR - NS - NQ > 0, \tag{5.34}$$

we have that $b_0 > 0$ and $b_3 > 0$ indipendently of the value of a.

If, moreover, we take the stronger assumption: $HR - NS > 0$ we have that $b_1 > 0$ for any a. In this case we have to study how the sign of $g(a)$ varies, varying a. We can rewrite:

$$g(a) = a(B_4 a^4 + B_3 a^3 + B_2 a^2 + B_1 a + B_0), \tag{5.35}$$

where:

$$\begin{aligned} B_4 &= 2(-H - R) > 0; \\ B_3 &= 4((H + R)^2 + NQ); \\ B_2 &= -2(H + R)((H + R)^2 + 2(HR - NS + NQ)); \\ B_1 &= (H + R)^2(4(HR - NS) + NQ); \\ B_0 &= -2(H + R)(HR - NS)^2 > 0. \end{aligned} \tag{5.36}$$

If $g(a) > 0$ for any value of a the equilibrium point is always LAS, otherwise changes of stability will occur if a passes through simple roots of $g(a)$.

5.2.1 Numerical results

We consider here the system with same parameters as in the previous section, that is with parameter values introduced in section 4.2.3.

We will observe how changes the stability of the equilibrium point

$$E_m = (8.3724, 16086, 8.3724, 8.3724).$$

Solving numerically the equation $g(a) = 0$, where $g(a)$ is the function described in (5.35), we find three real roots: $a_0 = 0$, $a_1 = 0.0545$, $a_2 = 7.7217$; and in these roots the derivative $g'(a_i)$, $i = 0, 1, 2$ is non null.

Then in $a = a_1$ and in $a = a_2$ Hopf bifurcations will occur, and system passes from stability to instability in a_1 and from instability to stability in a_2.

Mean delays corresponding to these bifurcation values are:

$$T_1 = \frac{2}{a_1} = 36.7$$

$$T_2 = \frac{2}{a_2} = 0.259$$

T_1 corresponds to roughly one year, and so is surely a value too high to be biologically meaningful, whereas T_2 corresponds roughly 2.5 days, and is completely compatible with critical values found in previous sections (for example, the same system with discrete delay has as bifurcation value $\tau = 0.2564$, whereas with exponentially distributed delay the mean delay corresponding to critical value in which a Hopf bifurcaion occurs and system passes from stability to instability is $\tau_2 = 0.2627$).

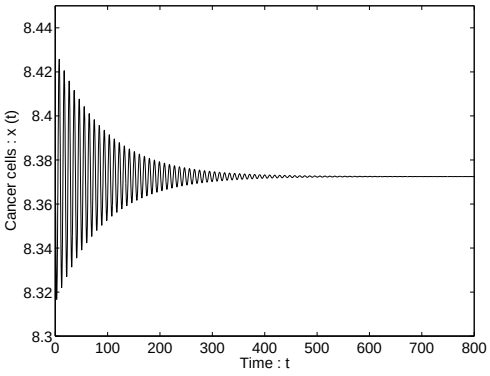

Figure 5.5: *Solutions x(t) (cancer cells) of the system with strong erlangian delay described in section 5.2.1 with initial conditions close to equilibrium point E_m and $a = 10$.*

In Figure 5.5, 5.6 and 5.7 we observe a behavior analogous to that reported in previous section for exponentially distributed delay.

For values of a greater than a_1 the equilibrium point remains LAS (figure 5.5). Between a_1 and a_2 the equilibrium point is unstable and we have a cyclic dynamics until a is greater than a value a_c (figure 5.6).

When $a < a_c$ the cycle breaks down and system converges to macroscopic equilibrium $E_M = (447.134, 0.173, 447.134, 447.134)$ that is LAS for any value of the parameter a.

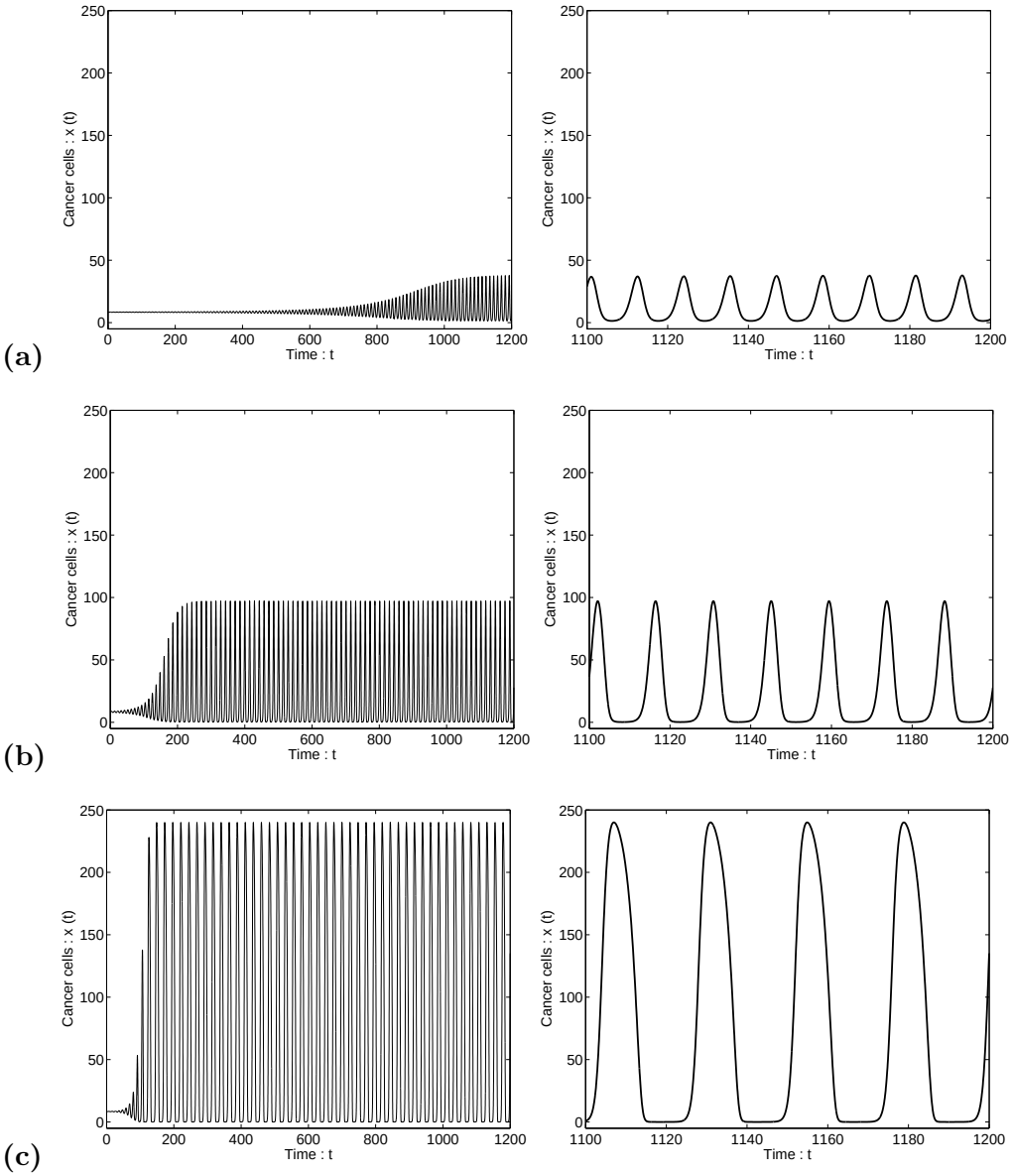

Figure 5.6: *Solutions x(t) (cancer cells) of the system of section 5.2.1 with initial conditions close to equilibrium point E_m. Values of parameter are:* ***(a)*** $a = 7$, ***(b)*** $a = 5$, ***(c)*** $a = 3$.

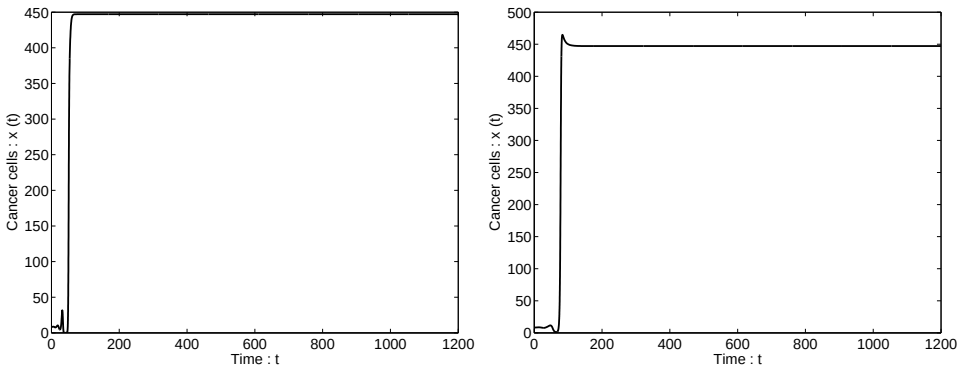

Figure 5.7: *Solutions x(t) (cancer cells) of the system of section 5.2.1 with initial conditions close to equilibrium point E_m. On the left $a = 1$, on the right $a = 0.1$.*

Chapter 6

Interactions between delay and therapy

In this chapter we will take account of models with delay and immunotherapy terms. We perform a numerical analysis taking some significant examples and we make some observations remarking both biological and mathematical interesting features.

We consider again, as we did in section 3.5, a boli-based therapy of the form:

$$\theta(t) = 0.1181 \, \exp\left(-\psi Mod(t,T)\right), \tag{6.1}$$

and then we consider different systems with delay either discrete or distributed.

Again simulations will be made by varying T and ψ to analyze any differences in therapy effects when different times of administration and different clearance time of the drug are considered.
We remember that T represents the administartion time of the therapy; ψ is a measure of the clearance time (it is proportional to the inverse of the half life of the drug in the organism); and the mean value of the therapy is:

$$M = \theta_A \, \frac{e^{-T\psi}\left(-1 + e^{T\psi}\right)}{T\psi}. \tag{6.2}$$

and we have taken $\theta_A = 0.1181$.
For further explications on parameter of boli-based therapy see section 3.5.2.

The values of T will be taken either within a biologically reasonable range ($T \in [0.1, 3]$, that is from 1 day to 1 month), or, if the system exhibit oscillatory dynamics, in the order of periods of limit cycles.

6.1 Discrete delay; no limit cycle model

As a first example we take the model presented in section 4.2:

$$\begin{cases} x' = x(1.636\,(1 - 0.002x) - y) \\ \\ y' = \dfrac{1.131x_\tau}{20.19 + x_\tau} y - (0.00311x + 0.3743)y + 0.1181 + \theta(t). \end{cases} \tag{6.3}$$

And we remember that this system without therapy term has a LAS equilibrium point $E_{micro} = (8.1897, 1.6092)$; around which limit cycles arise via Hopf bifurcations if the delay exceeds the value $\tau_{bif} = 0.2692$.

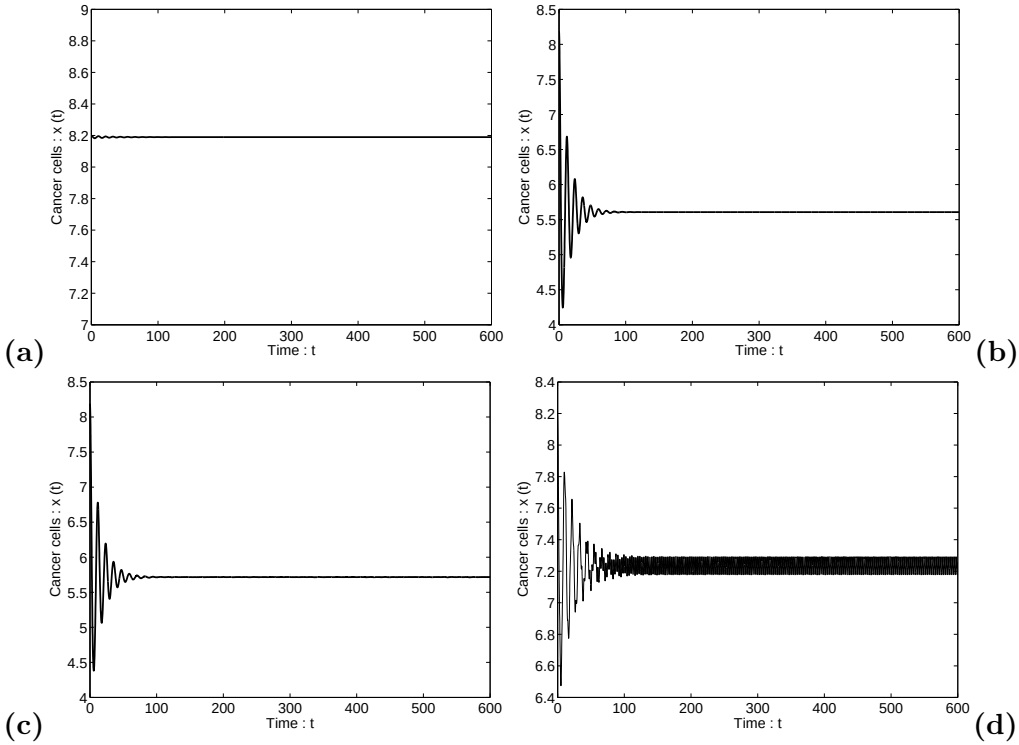

Figure 6.1: *Solutions x(t) of system (6.3) with delay $\tau = 0.1$.* ***(a)*** *system without therapy.* ***(b)*** *$\psi = 0.025$, $T = 0.1$.* ***(c)*** *$\psi = 0.1$, $T = 1$.* ***(d)*** *$\psi = 0.9$, $T = 3$. Mean values of therapy are:* ***(b)*** *M=0.1180.* ***(c)*** *M=0.1124.* ***(d)*** *M=0.0408.*

In Figure 6.1 we can see the behavior of the system (6.3) with delay $\tau = 0.1$ and initial conditions close to the point E_{micro} . We have reported the case without treatment (the equilibrium point is LAS), and cases with different therapies (various values of ψ and T).

We see that in each case the values taken by variable $x(t)$ of cancer cells decrease compared to the case without therapy; but with $\psi = 0.9$ and $T = 3$

(therapy less strong among those considered), an oscillation is produced. We also notice that tumor eradication is never reached.

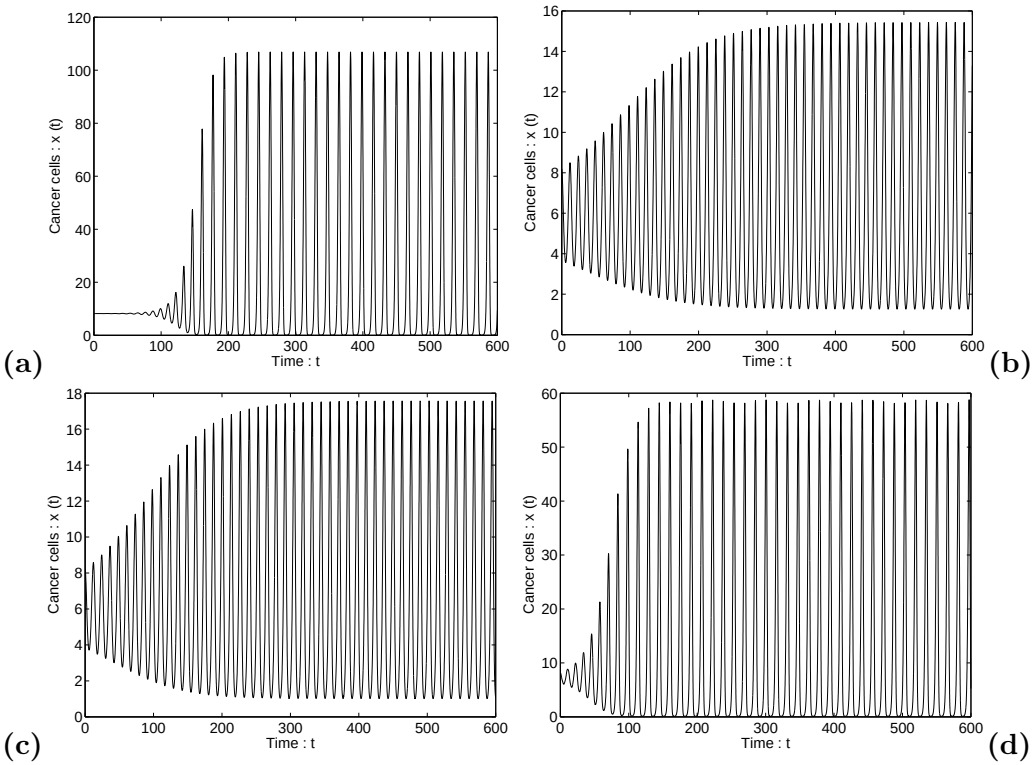

Figure 6.2: *Solutions x(t) of system with delay* $\tau = 0.6$. ***(a)*** *system without therapy.* ***(b)*** $\psi = 0.025$, $T = 0.1$. ***(c)*** $\psi = 0.1$, $T = 1$. ***(d)*** $\psi = 0.9$, $T = 3$. *Mean values of therapy are:* ***(b)*** *M=0.1180.* ***(c)*** *M=0.1124.* ***(d)*** *M=0.0408.*

In Figure 6.2 we observe behavior of solutions of the system with $\tau = 0.6$.

In this case without therapy term the model exhibits oscillatory dynamics as reported in the first graph of Figure (6.2-(a)).

We can notice as adding therapies with different, but realistic, parameters ($\psi = 0.025$ e $T = 0.1$, $\psi = 0.1$ e $T = 1$, $\psi = 0.9$, $T = 3$) we still have limit cycles , but the size of oscillations decreases as the clearance time increases (so as ψ decreases) and as T decreases (figure 6.3).

For the system with delay $\tau = 0.6$ we performed numerical simulations also choosing $T = 17$ (close to the period of oscillations of the system without therapy).

As an example in the Figure 6.4 we can see how, taking $\psi = 0.025$, resonance effects arise.

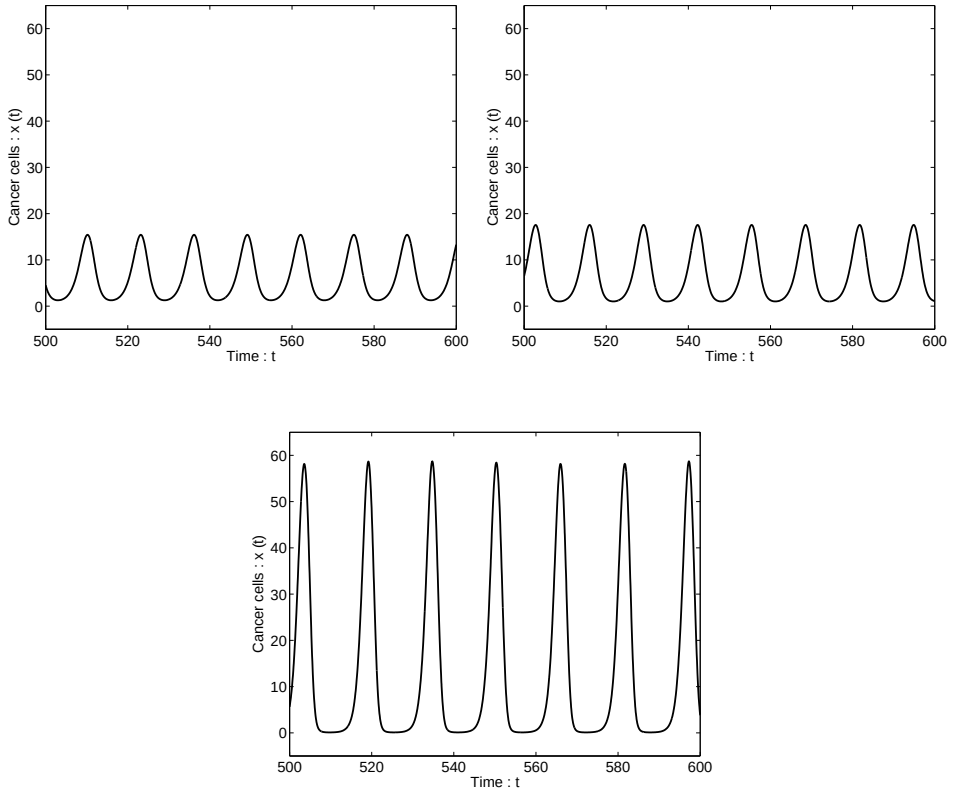

Figure 6.3: *Zoom of Figure 6.2. Periods of solutions x(t) of system with delay* $\tau = 0.6$. *On the left* $\psi = 0.025$, $T = 0.1$. *On the right* $\psi = 0.1$, $T = 1$. *Down* $\psi = 0.9$, $T = 3$.

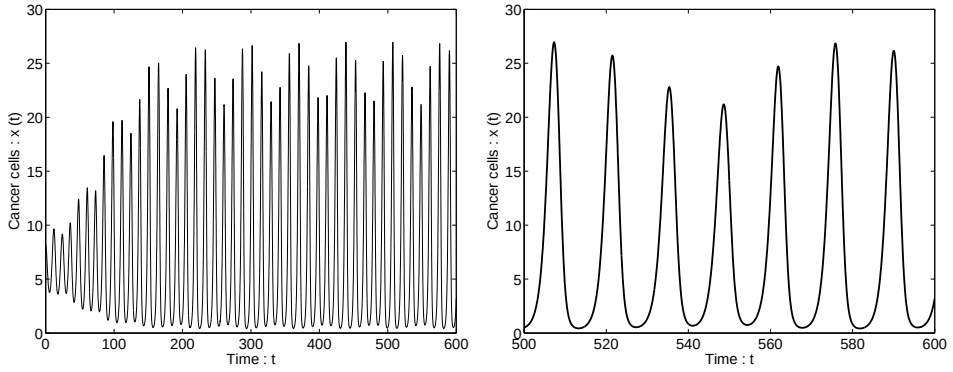

Figure 6.4: *Solutions* $x(t)$ *(on the left) and zooming (on the right) when* $\tau = 0.6$, $\psi = 0.025$, $T = 17$.

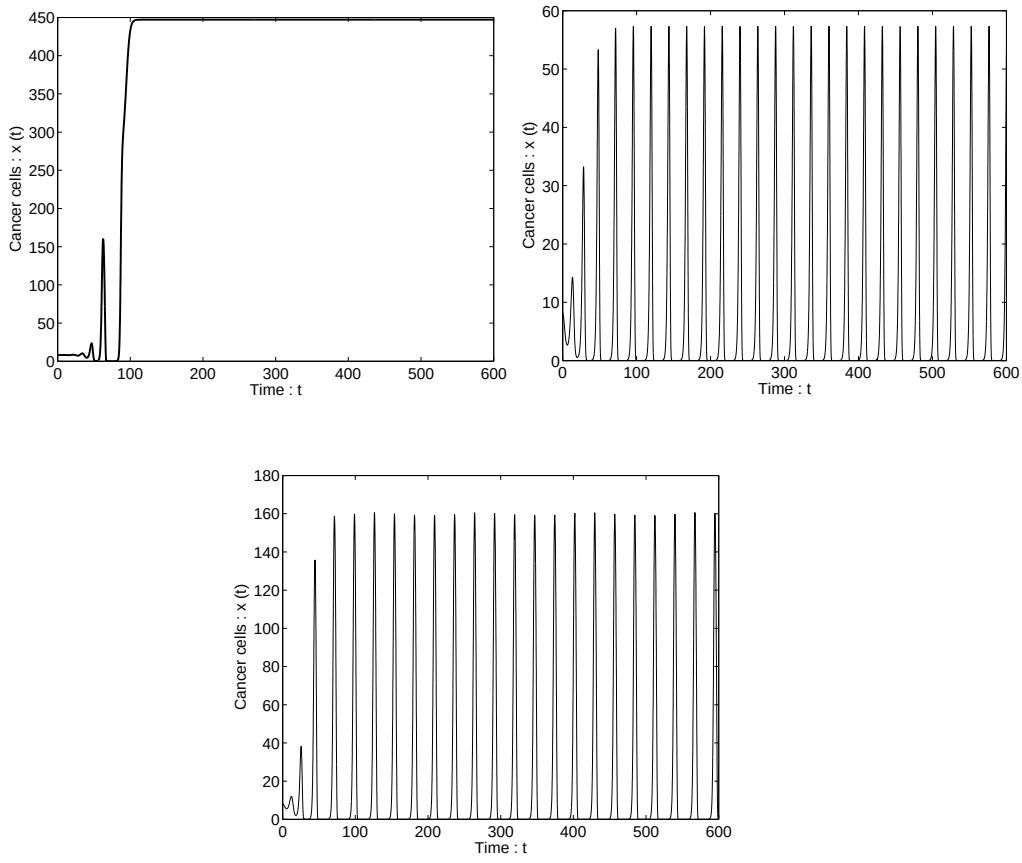

Figure 6.5: *Solutions x(t) of the system with delay* $\tau = 1.2$*. On the left system without therapy. On the right* $\psi = 0.025$*,* $T = 0.1$*. Down* $\psi = 0.9$*,* $T = 3$*.*

Finally, we considered system (6.3) with delay $\tau = 1.2$. For this value, without therapy, starting simulations with initial conditions close to E_{micro}, solutions converge to the other LAS equilibrium point: E_{macro} (first graph in the figure 6.5).

In this case we add therapy with different parameter values choosed in biological meaninguful ranges. We observe that adding these different therapies, solutions do not converge to E_{macro}, but, instead, the system show oscillatory dynamics with cycles of amplitude more or less high (figure 6.5 and 6.6).

In Figures 6.5 and 6.6 are reported only two cases with extreme parameters of therapies (in realistic intervals): $\psi = 0.025$ - $T = 0.1$ and $\psi = 0.9$ - $T = 3$

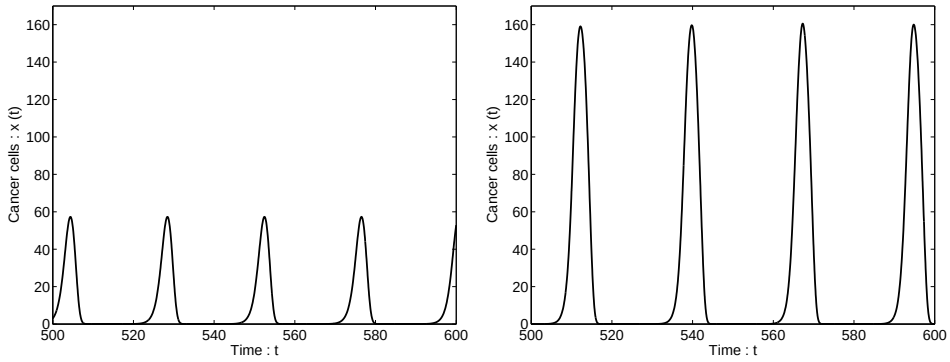

Figure 6.6: *Zoom of the Figure 6.5.Periods of solutions of system with delay* $\tau = 1.2$. *On the left* $\psi = 0.025$, $T = 0.1$. *On the right* $\psi = 0.9$, $T = 3$.

6.2 Discrete delay; limit cycle model

In this section we observe the behavior of the model presented in section 3.5, adding a therapy term.

The system we consider is then:

$$\begin{cases} x' = x(1.636\,(1 - 0.00476x) - \dfrac{y}{1 + 0.02x + 0.25y}) \\ \\ y' = \dfrac{1.131x_\tau}{20.19 + x_\tau}y - (0.00311x + 0.3743)y + 0.1181 + \theta(t) \end{cases} \tag{6.4}$$

We consider for example the case $\tau = 0.3$, in which system without therapy exhibit oscillations of period $P \simeq 22$ (see section 4.2.4).

In Figure 6.7 we note as, taking realistic parameters for therapy, dynamics qualitatively remains the same; with oscillations of lower period as slower is the clearance time of therapy.

Choosing instead times of administration close to the period P we have again resonance effects and chaos, as already seen in the previous section and in the case without delay (figure 6.8, 6.9, 6.10).

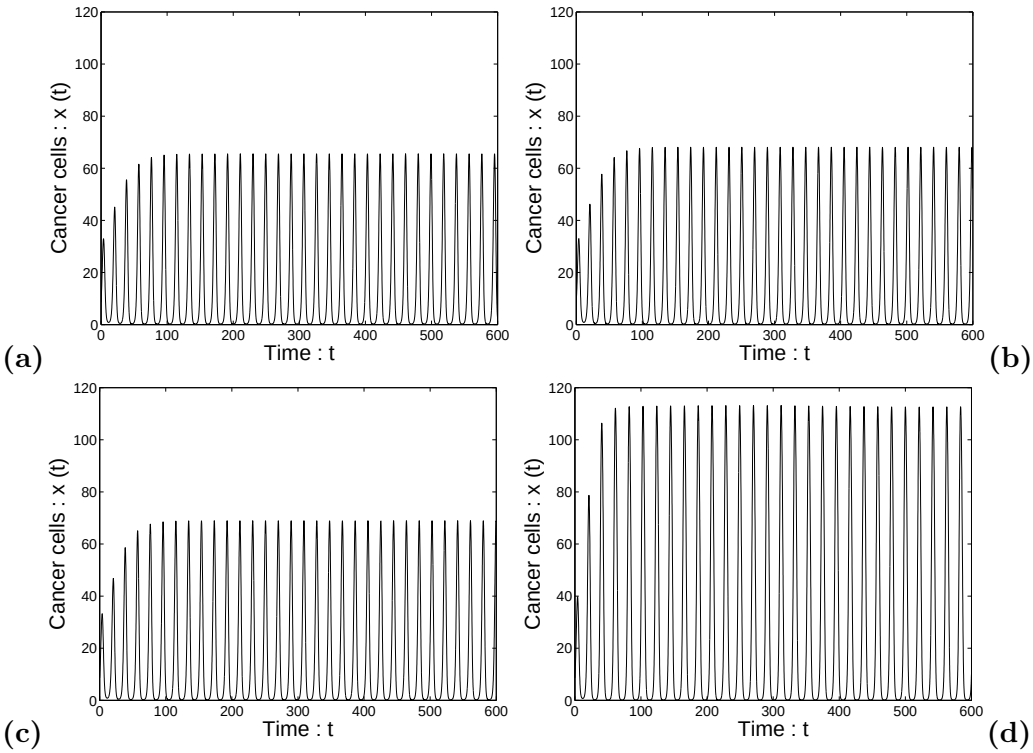

Figure 6.7: *Solutions x(t) of system (6.4) with delay* $\tau = 0.3$ ***(a)*** $\psi = 0.025$, $T = 0.1$. ***(b)*** $\psi = 0.025$, $T = 3$. ***(c)*** $\psi = 0.1$, $T = 1$. ***(d)*** $\psi = 0.9$, $T = 3$.

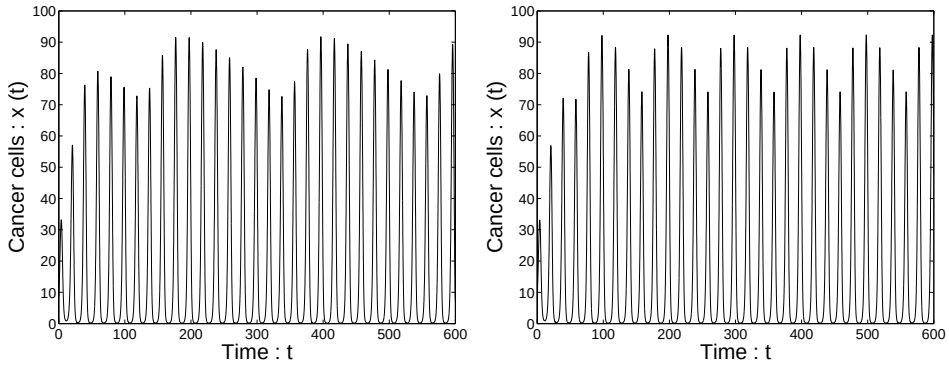

Figure 6.8: *Solutions x(t) of system (6.4) with delay* $\tau = 0.3$ $\psi = 0.025$. *On the left* $T = 22$*; on the right* $T = 25$.

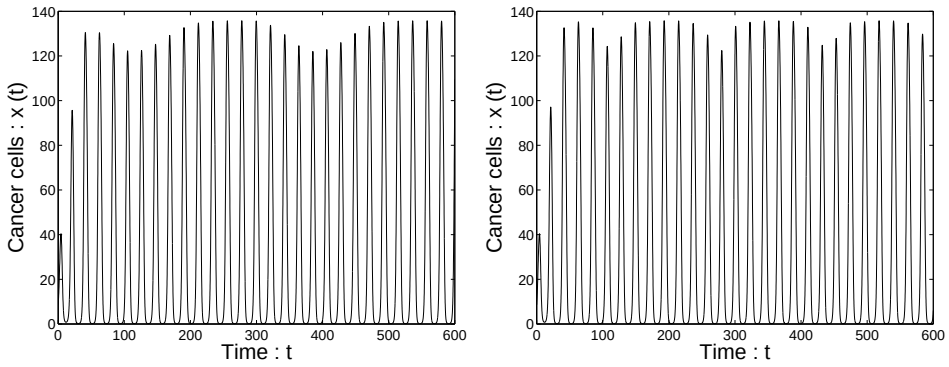

Figure 6.9: *Solutions x(t) of the system (6.4) with delay* $\tau = 0.3$, $\psi = 0.9$. *On the left* $T = 20$*; on the right* $T = 25$.

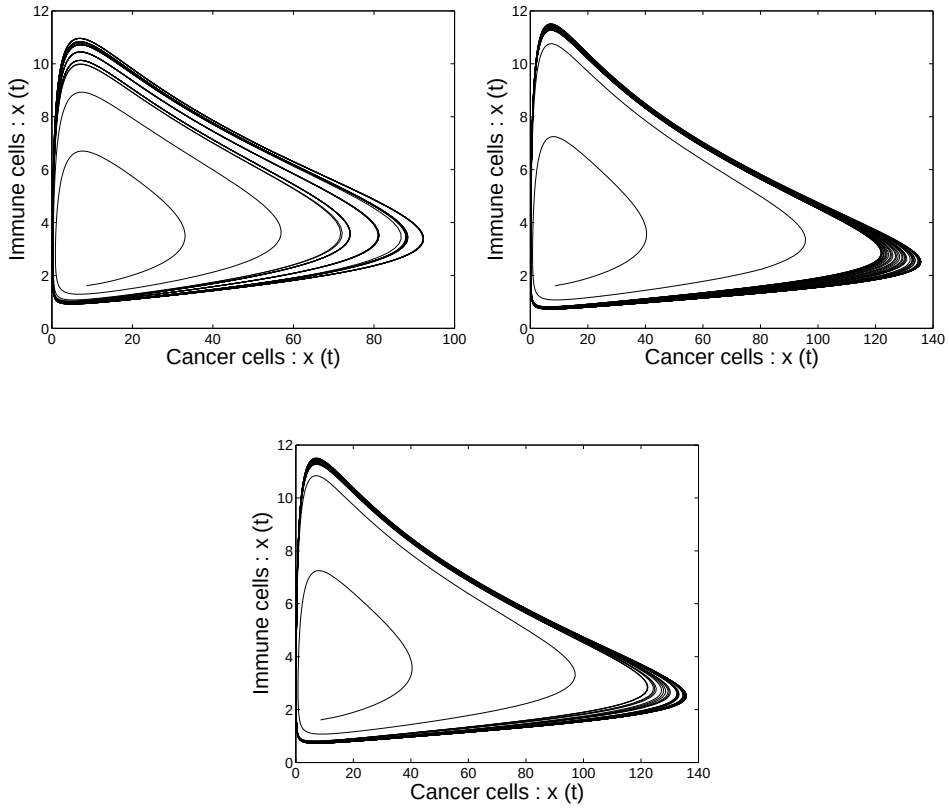

Figure 6.10: *Phase portrait in the plane (x,y). System (6.4)with delay* $\tau = 0.3$. *On the left* $\psi = 0.025$ *and* $T = 25$*; on the right* $\psi = 0.9$ *and* $T = 20$*; down* $\psi = 0.9$ *and* $T = 25$.

6.3 Exponentially distributed delay

We conclude simulations of models with therapy taking as last example the system with exponentially distributed delay studied in section 5.1.1.

We remember that with these parameters Hopf bifurcations occur at the equilibrium E_m when a passes through:

$$a_1 = 0.0155,$$

$$a_2 = 3.8067.$$

In simulations reported below initial conditions are taken close to E_m, to study possible changes of stability due to therapy term, or even resonance effects.

As a first example we take simulations with $a = 5$. For this value of parameter without therapy the equilibrium point is still LAS (figure 6.11-(a)).

In Figure 6.11 are collected some examples illustrating different therapies.

Adding a therapy term and varying its parameters taking values in biological meaningful intervals as in previous sections, we see again that equilibrium point moves (the x_e value decreases). We have nevertheless stability (**(b)** and **(c)**), or small oscillations around new equilibrium point; whose maximal amplitude is less than the value of steady state in system without therapy (figure 6.11-(d)).

We see now the case $a = 2$. Without therapy the system has oscillatory dynamics with cycles of period $P \simeq 18$ (see section 5.1). In this case we consider first therapy with different ψ and realistic administration times ($T \in [0.1, 3]$), and then T close to the period P.

In the Figure 6.12 we see as dynamics remains oscillatory, for $\psi = 0.025$ and $T = 0.1$ amplitude of oscillations increases very slowly, whereas when $\psi = 0.9$ and $T = 3$ we have immediately convergence to a limit cycle whose amplitude is less than that of system without therapy.

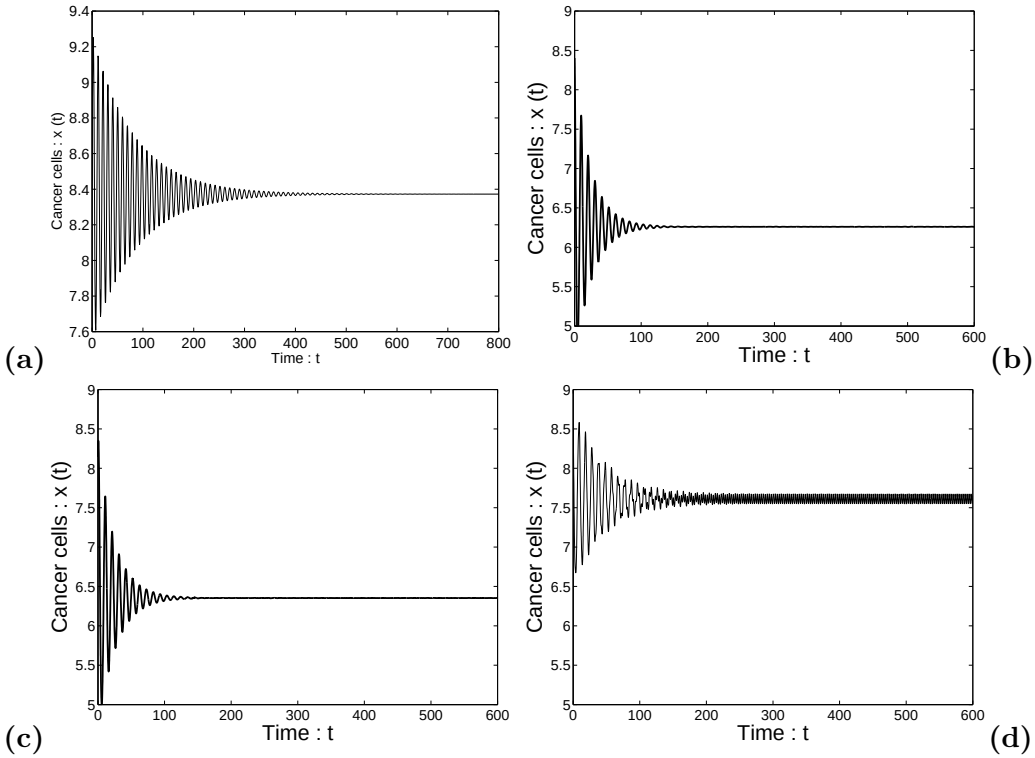

Figure 6.11: *Solutions x(t) of the system with exponential delay with parameter as in section 5.1.1, therapy term and* $a = 5$. ***(a)*** *system without therapy.* ***(b)*** $\psi = 0.025$, $T = 0.1$. ***(c)*** $\psi = 0.1$, $T = 1$. ***(d)*** $\psi = 0.9$, $T = 3$.

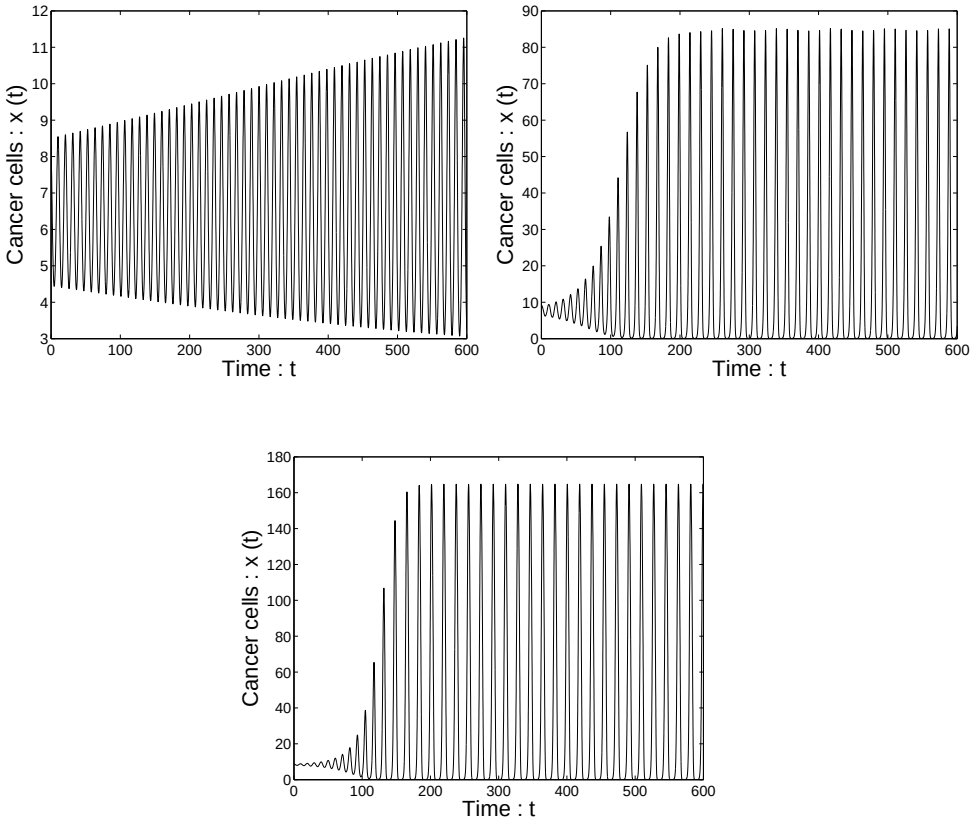

Figure 6.12: *Solutions x(t) of system with exponential delay with parameter as in section 5.1.1, therapy term and* $a = 2$. *On the left* $\psi = 0.025$, $T = 0.1$. *On the right* $\psi = 0.9$, $T = 3$. *Down system without therapy.*

In Figures 6.13 and 6.14 we observe that also in this case, taking administration times close to period of limit cycle of the system without therapy, there can occur modulation effects or resonances.

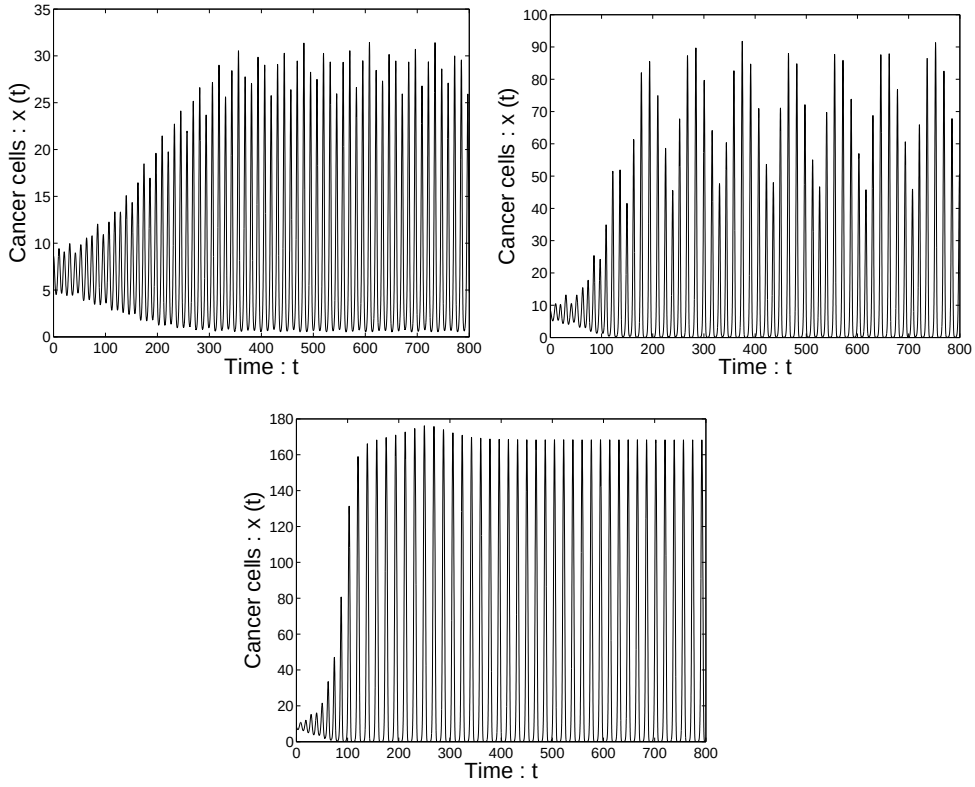

Figure 6.13: *Solutions x(t) of the system with exponential delay with parameter as in section 5.1.1, therapy term and* $a = 2$ *and* $T = 18$*. On the right* $\psi = 0.025$*; in the centre* $\psi = 0.1$*; on the right* $\psi = 0.9$*.*

Moreover, regarding figure 6.14, we can hypothesize that system is chaotic. We have then calculated the Lyapunov spectrum of this system with the software NDT (Nonlinear Dynamics Toolbox) developed by J.Reiss. We have obtained that the dominant exponent is strictly positive indicating that probably dynamics is really chaotic.

However, we remark that the administration time taken to obtain system of figure 6.14, is very unrealistic ($T = 18$, that is roughly 6 months); then this result have only a mathematical interest.

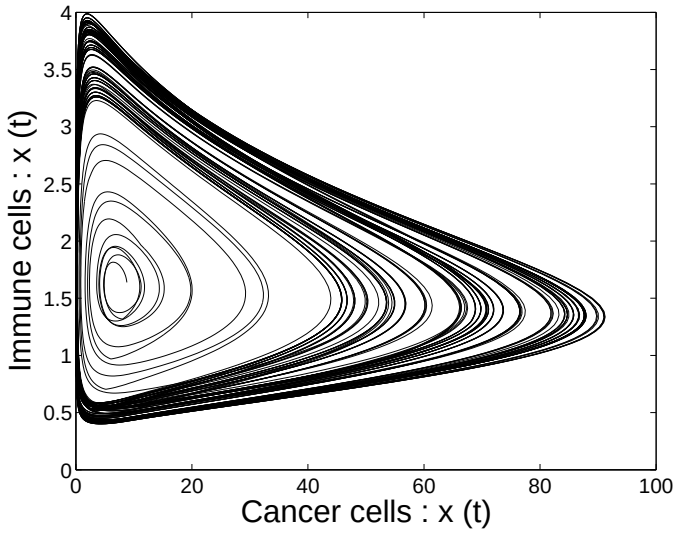

Figure 6.14: *Phase portrait in (x,y)-plane. Solutions of system with exponential delay with parameter as in section 5.1.1, therapy term and* $a = 2$. $\psi = 0.1$ *and* $T = 18$.

Finally in Figure 6.15 we have taken $a = 1$. We note as in system without therapy solutions converge to macroscopic equilibrium E_M, whereas adding different therapies system exhibit a limit cycle (and therefore the size of tumor, even if oscillating, remains smaller than in case without therapy).

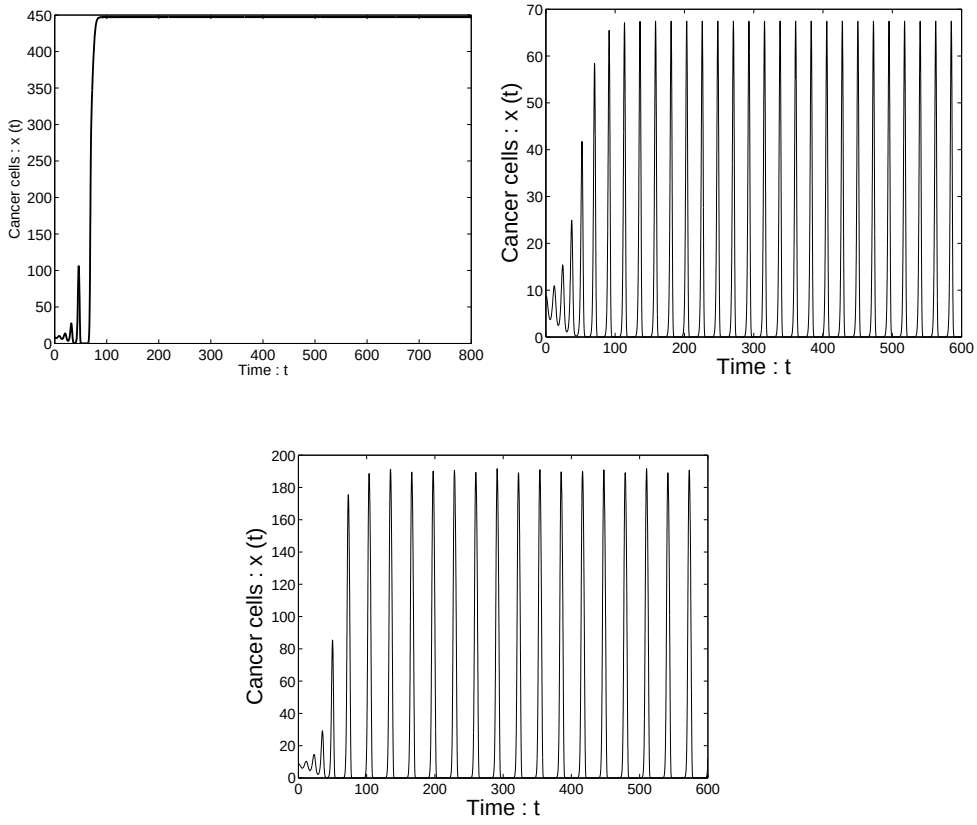

Figure 6.15: *Solutions x(t) of the system with exponential delay with parameter as in section 5.1.1, therapy term and* $a = 1$. *On the left without therapy; in the centre* $\psi = 0.025$ *and* $T = 0.1$*; on the right* $\psi = 0.9$ *and* $T = 3$.

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Numerical simulations where made using the Matlab subroutines developed by Shampine and Thompson for solving delay differential equations, dde23, available on http://www.runet.edu/ thompson/webddes/index.html.

The analysis of chaotic time series was done with NDT.exe developed by J.Reiss, available on: http://www.elec.qmul.ac.uk/people/josh/research.htm