Chaotic Modeling and Simulation (CMSIM) 2: 237–248, 2018

Chaos in a delay mathematical model for AIDS-related cancer

Carla M.A. Pinto[1] and Ana R.M. Carvalho[2]

[1] School of Engineering, Polytechnic of Porto,
Rua Dr. António Bernardino de Almeida, 431, 4200-072 Porto, Portugal
(E-mail: cap@isep.ipp.pt)
[2] Faculty of Sciences, University of Porto,
Rua do Campo Alegre s/n, 4440-452 Porto, Portugal
(E-mail: up200802541@fc.up.pt)

Abstract. We study a delay mathematical model for the dynamics of AIDS-related cancer. Cancer is a major burden in HIV infected patients, and as such, is extremely important to understand the epidemiology and the mechanisms behind it. Our model consists of four classes, the cancer cells, the healthy cells, the infected cells and the virus. We show numerically the existence of periodic orbits arising from a Hopf bifurcation from an endemic state. Moreover, we observe the appearance of chaos, due to a cascade of period doubling bifurcations.

1 Introduction

In the last few decades, several mathematical models have been proposed to describe the interaction of the immune system with the human immunodeficiency virus (HIV) [6,4]. HIV deteriorates the immune system, attacking, in particular, the $CD4^+$ T cells. When the immune system's level of defence decreases below a given threshold, the individual enters an immunodeficiency state. Individuals with acquired immune deficiency syndrome (AIDS) are more vulnerable to the emergence of various types of cancer, such as Kaposi sarcoma, non-Hodgkin lymphoma (NHL) of high-grade pathologic type and of B cell or unknown immunologic phenotype, and invasive cervical carcinoma. These are known as AIDS-related malignancies, which means that an HIV infected person with one of these cancers has officially AIDS. Death attributed to these cancers in HIV infected patients is high. The non-Hodgkin lymphoma (NHL) has been associated with an immunocompromised status, with individuals infected with HIV being $\geq$76 times more likely to develop NHL, than non-infected individuals. Current findings suggest that viral supression is extremely important to prevent AIDS-related lymphomas, independently of CD4 cell count. Sustained periods of HIV replication can induce irreversible damage in the immune system, namely lymphoid fibrosis, thymic destruction, etc [2,9]. Thus, it

Received: 22 March 2017 / Accepted: 14 March 2018

ISSN 2241-0503

is epidemiological defiant and valuable to better understand the mechanisms behind the development of neoplasia in HIV infected patients.

In 1993, Lund et al [7] developed a model for the interaction of HIV with the immune system. The authors find that oscillations are seen in both $CD4^+$ T cells and the virus particles. This type of solutions interfere negatively in the prediction of the spread of HIV. Moreover, the study shows that the model can present chaotic behaviour. The later could explain the distinct dynamics of HIV in different individuals. Later on, in 2007, Lou et al [4] investigate how the 'incubation' periods of $CD4^+$ T cells and quiescent memory T cells, after being infected by HIV, affect cancer development. Memory T cells have higher incubation periods. The authors find that the longer the 'incubation' period, the smaller is the needed reproducing capacity of cancer cells to evolve to AIDS. Thus, increased numbers of infected quiescent memory T cells promote worse scenarios for HIV infected patients. Lou et al [5] propose a model for the dynamics of HIV in the presence of cancer. The authors show that HIV boosts the growth of cancer. Moreover, the authors find Hopf bifurcations leading to periodic solutions, sequences of period doubling bifurcations and the appearance of chaos. In 2014, Starkov et al [8] study further the model created by Lou et al [5]. The authors derive sufficient conditions for cancer free behaviour in the model.

Following the aforementioned ideas, in this paper, we propose a model for AIDS-related cancer dynamics. In Section 2, we introduce the model. In Section 3, we compte the equilibria of the model and the corresponding stability. In Section 4, we show and discuss the results of the simulations of the model. In Section 5 we conclude our work and shed light on future research.

2 The Model

The model is composed by the concentrations of cancer cells, $C(t)$, of healthy cells, $T(t)$, of infected cells, $I(t)$ and of virus, $V(t)$.

In the model, we assume that the cancer is caused by one single cell, due to gene mutation, being r_1 their uncontrolled proliferation rate. Cancer cells are killed by the immune system at rate k_1. The healthy T cells grow at a rate r_2. The maximum carrying capacity is m. The healthy cells die, due to the effect of the cancer cells at rate p, and are infected by HIV at rate k_2. There exists an 'incubation' period after healthy cells infection and the production of virus, it is denoted by τ. The infected cells die at a rate μ_I. The virus are produced by the infected $CD4^+$ T cells, with bursting size N_s, and die at a rate c. The nonlinear system of delay differential equations, describing the dynamics of the model, is given by:

$$\begin{aligned}
\dot{C}(t) &= C(t)\left[r_1\left(1-\tfrac{C(t)+T(t)+I(t)}{m}\right)-k_1T(t)\right]\\
\dot{T}(t) &= T(t)\left[r_2\left(1-\tfrac{C(t)+T(t)+I(t)}{m}\right)-pk_1C(t)-k_2V(t)\right]\\
\dot{I}(t) &= k_2T(t-\tau)V(t-\tau)-\mu_II(t)\\
\dot{V}(t) &= N_s\mu_II(t)-cV(t)
\end{aligned} \tag{1}$$

We assume constant initial conditions: $C(\theta) = C_0$, $T(\theta) = T_0$, $I(\theta) = I_0$, $V(\theta) = V_0$, $\forall\theta \in [\tau, 0]$.

3 Equilibria and stability analysis

Model (1) has several equilibria:

- The trivial equilibrium: $P_0 = (0, 0, 0, 0)$
- The cancer equilibrium: $P_1 = (m, 0, 0, 0)$
- The healthy equilibrium: $P_2 = (0, m, 0, 0)$
- The cancer-healthy equilibrium:

$$P_3 = (\bar{C}, \bar{T}, 0, 0) = \left(\frac{mr_2}{r_2 + p(r_1 + k_1m)}, \frac{mr_1p}{r_2 + p(r_1 + k_1m)}, 0, 0\right)$$

- The HIV-healthy equilibrium:

$$P_4 = \left(0, \hat{T}, \hat{I}, \hat{V}\right) = \left(0, \frac{c}{N_sk_2}, \frac{cr_2(N_sk_2m - c)}{N_sk_2(r_2c + k_2N_s\mu_Im)}, \frac{r_2\mu_I(N_sk_2m - c)}{k_2(r_2c + k_2N_s\mu_Im)}\right)$$

- The cancer-HIV-healthy equilibrium:

$$P_5 = (C^\star, T^\star, I^\star, V^\star) = \left(\frac{c^2k_1r_2 + N_sk_2\mu_I(r_1c + k_1cm - r_1mN_sk_2)}{N_sk_2r_1(pk_1c - k_2N_s\mu_I)}, \frac{c}{N_sk_2}, \frac{k_1c\,[pmN_sk_2r_1 - c(r_2 + pr_1 + pk_1m)]}{N_sk_2r_1(pk_1c - k_2N_s\mu_I)}, \frac{k_1\mu_I\,[pmN_sk_2r_1 - c(r_2 + pr_1 + pk_1m)]}{k_2r_1(pk_1c - k_2N_s\mu_I)}\right)$$

We first discuss the stability of the cancer equilibrium, P_0. The matrix of the linearization of model (1) around the trivial equilibrium, P_0, is:

$$M = \begin{pmatrix} r_1 & 0 & 0 & 0\\ 0 & r_2 & 0 & 0\\ 0 & 0 & -\mu_I & 0\\ 0 & 0 & N_s\mu_I & -c \end{pmatrix}$$

The eigenvalues are easily obtained: r_1, r_2, $-\mu_I$ and $-c$. Since the eigenvalues r_1 and r_2 are positive, this equilibrium is unstable.

Following, we compute the stability of the cancer equilibrium, P_1. The matrix of the linearization of model (1) around the cancer equilibrium, P_1, is written as:

$$M_1 = \begin{pmatrix} -r_1 & -r_1 - k_1m & -r_1 & 0\\ 0 & -pk_1m & 0 & 0\\ 0 & 0 & -\mu_I & 0\\ 0 & 0 & N_s\mu_I & -c \end{pmatrix}$$

The eigenvalues are easily obtained: $-r_1$, $-pk_1m$, $-\mu_I$ and $-c$. Since they are all negative, this equilibrium is locally stable.

We proceed with the discussion of the stability of the healthy equilibrium, P_2. The corresponding characteristic equation is given by:

$$\begin{vmatrix} -k_1m-\lambda & 0 & 0 & 0 \\ -r_2-pk_1m & -r_2-\lambda & -r_2 & -k_2m \\ 0 & 0 & -\mu_I-\lambda & k_2me^{-\lambda\tau} \\ 0 & 0 & N_s\mu_I & -c-\lambda \end{vmatrix} = 0 \tag{2}$$

The following eigenvalues are easily obtained: $-k_1m$ and $-r_2$. The remaining eigenvalues are the roots of the following characteristic equation:

$$\begin{vmatrix} -\mu_I-\lambda & k_2me^{-\lambda\tau} \\ N_s\mu_I & -c-\lambda \end{vmatrix} = 0 \tag{3}$$

which is equivalent to:

$$\lambda^2+(c+\mu_I)\lambda+\mu_Ic-N_s\mu_Ik_2me^{-\lambda\tau}=0 \tag{4}$$

When $\tau=0$, the characteristic equation reduces to $\lambda^2+(c+\mu_I)\lambda+\mu_Ic-N_s\mu_Ik_2m=0$. By the Routh-Hurwitz criteria, the two roots of the characteristic equation $\lambda^2+a_1\lambda+a_2=0$ have negative real parts if and only if $a_1>0$ and $a_2>0$. It is easy to show that $a_1=c+\mu_I>0$. We prove below that $a_2>0$ if $R_0<1$.

$$a_2=\mu_Ic-N_s\mu_Ik_2m>0 \Leftrightarrow \frac{N_sk_2m}{c}<1 \Leftrightarrow R_0<1 \tag{5}$$

Consider now the case $\tau>0$. In order to show that the eigenvalues have also negative real parts, we prove that the characteristic equation does not have a purely imaginary root. This means, that the real parts don't change signs. By a way of contradiction, we consider that there is some $\omega>0$ such that $\lambda=i\omega$ is an eigenvalue of the characteristic equation, that is:

$$-\omega^2+(c+\mu_I)\omega i+\mu_Ic-N_s\mu_Ik_2me^{-\omega i\tau}=0 \tag{6}$$

Thus

$$\omega^4+(c+\mu_I)\omega^2+(\mu_Ic)^2=(N_s\mu_Ik_2m)^2|e^{-\omega i\tau}|^2\leq(N_s\mu_Ik_2m)^2 \tag{7}$$

therefore, if $R_0=\frac{N_sk_2m}{c}<1$, the characteristic equation has no purely imaginary roots. We conclude that the healthy equilibrium is locally stable for $R_0<1$, when $\tau\geq0$.

The study of the local stability of the cancer-healthy equilibrium, P_3, is as follows. The characteristic equation of system (1) for the cancer-healthy equilibrium P_3, is given by:

$$\begin{vmatrix} -\frac{r_1 r_2}{r_2+p(r_1+k_1 m)} - \lambda & -\frac{r_2(r_1+k_1 m)}{r_2+p(r_1+k_1 m)} & -\frac{r_1 r_2}{r_2+p(r_1+k_1 m)} & 0 \\ -\frac{r_1 p(r_2+pk_1 m)}{r_2+p(r_1+k_1 m)} & -\frac{r_1 r_2 p}{r_2+p(r_1+k_1 m)} - \lambda & -\frac{r_1 r_2 p}{r_2+p(r_1+k_1 m)} & -\frac{k_2 m r_1 p}{r_2+p(r_1+k_1 m)} \\ 0 & 0 & -\mu_I - \lambda & \frac{k_2 m r_1 p}{r_2+p(r_1+k_1 m)} e^{-\lambda\tau} \\ 0 & 0 & N_s \mu_I & -c-\lambda \end{vmatrix} = 0 \tag{8}$$

The last equation is equivalent to:

$$\left[\left(-\frac{r_1 r_2}{A} - \lambda\right)\left(-\frac{r_1 r_2 p}{A} - \lambda\right) - \frac{r_1 r_2 p(r_2+pk_1 m)(r_1+k_1 m)}{A^2}\right]\left[(\mu_I+\lambda)(c+\lambda) - \frac{N_s \mu_I k_2 m r_1 p}{A} e^{-\lambda\tau}\right] = 0 \tag{9}$$

where $A = r_2 + p(r_1 + k_1 m)$. The first term of the last equation is equivalent to:

$$\lambda^2 + \frac{r_1 r_2 + r_1 r_2 p}{A}\lambda + \frac{r_1^2 r_2^2 p}{A^2} - \frac{r_1 r_2 p(r_2+pk_1 m)(r_1+k_1 m)}{A^2} = 0$$

By the Routh-Hurwitz criteria, the two roots of the last equation $\lambda^2 + a_1\lambda + a_2 = 0$ have negative real parts if and only if $a_1 > 0$ and $a_2 > 0$. It is easily verified that $a_1 = \frac{r_1 r_2 + r_1 r_2 p}{A} > 0$. The proof of $a_2 > 0$ leads to an impossibility.

$$\begin{aligned} a_2 &= \frac{r_1^2 r_2^2 p}{A^2} - \frac{r_1 r_2 p(r_2+pk_1 m)(r_1+k_1 m)}{A^2} \\ &= \frac{r_1^2 r_2^2 p - r_1 r_2 p(r_1 r_2 + r_2 k_1 m + r_1 p k_1 m + p k_1^2 m^2)}{A^2} \\ &= -\frac{r_1 r_2 p(r_2 k_1 m + r_1 p k_1 m + p k_1^2 m^2)}{A^2} < 0 \end{aligned} \tag{10}$$

Since $a_2 < 0$, the Routh-Hurwitz criteria is not verified, thus we conclude that the cancer-healthy equilibrium is unstable.

The local stability of the HIV-healthy equilibrium, P_4, follows. The characteristic equation of system (1) for the HIV-healthy equilibrium P_4, is given by:

$$\begin{vmatrix} r_1\left(1-\frac{\hat{T}+\hat{I}}{m}\right) - k_1\hat{T} - \lambda & 0 & 0 & 0 \\ -\frac{\hat{T}r_2}{m} - pk_1\hat{T} & r_2\left(1-\frac{\hat{T}+\hat{I}}{m}\right) - k_2\hat{V} - \frac{\hat{T}r_2}{m} - \lambda & -\frac{\hat{T}r_2}{m} & -k_2\hat{T} \\ 0 & k_2\hat{V}e^{-\lambda\tau} & -\mu_I - \lambda & k_2\hat{T}e^{-\lambda\tau} \\ 0 & 0 & N_s\mu_I & -c-\lambda \end{vmatrix} = 0 \tag{11}$$

The following eigenvalue is easily obtained: $r_1\left(1-\frac{\hat{T}+\hat{I}}{m}\right)-k_1\hat{T}=-\frac{k_1c}{N_sk_2}+\frac{r_1\mu_I(N_sk_2m-c)}{r_2c+N_sk_2\mu_Im}$. This eigenvalue is negative if $R_1=\frac{N_sk_2r_1\mu_I(R_0-1)}{k_1(r_2c+N_sk_2\mu_Im)}<1$. The remaining eigenvalues are the roots of the following characteristic equation:

$$\begin{vmatrix} r_2\left(1-\frac{\hat{T}+\hat{I}}{m}\right)-k_2\hat{V}-\frac{\hat{T}r_2}{m}-\lambda & -\frac{\hat{T}r_2}{m} & -k_2\hat{T} \\ k_2\hat{V}e^{-\lambda\tau} & -\mu_I-\lambda & k_2\hat{T}e^{-\lambda\tau} \\ 0 & N_s\mu_I & -c-\lambda \end{vmatrix}=0 \tag{12}$$

which may be written in the form:

$$P(\lambda)+Q(\lambda)e^{-\lambda\tau}=0 \tag{13}$$

where $P(\lambda)=\lambda^3+b_1\lambda^2+b_2\lambda+b_3$ and $Q(\lambda)=b_4\lambda+b_5$ and

$$b_1=c+\mu_I+\tfrac{r_2c}{mN_sk_2},\qquad b_2=\mu_Ic+\tfrac{r_2c}{mN_sk_2}(c+\mu_I),\qquad b_3=\tfrac{r_2c^2\mu_I}{mN_sk_2},$$
$$b_4=\tfrac{cr_2^2\mu_I(N_sk_2m-c)}{N_sk_2m(r_2c+k_2N_s\mu_Im)}-\mu_Ic,\ b_5=\tfrac{r_2^2c^2\mu_IN_sk_2m-2r_2^2c^3\mu_I-r_2c\mu_I^2N_s^2k_2^2m^2}{mN_sk_2(r_2c+k_2N_s\mu_Im)} \tag{14}$$

When $\tau=0$, the characteristic equation reduces to $\lambda^3+B_1\lambda^2+B_2\lambda+B_3=0$, where

$$B_1=b_1>0,\ B_2=b_2+b_4=\tfrac{r_2^2c^3+r_2ck_2N_s\mu_Im(c+\mu_I+r_2)}{mN_sk_2(r_2c+k_2N_s\mu_Im)}>0, \tag{15}$$

$$B_3=b_3+b_5=\tfrac{r_2c^2\mu_I\left[\mu_ImN_sk_2\left(1-\frac{k_2m}{c}\right)+r_2c(R_0-1)\right]}{mN_sk_2(r_2c+k_2N_s\mu_Im)} \tag{16}$$

By the Routh-Hurwitz criteria, the three roots of the characteristic equation $\lambda^3+B_1\lambda^2+B_2\lambda+B_3=0$ have negative real parts if and only if $B_1>0$, $B_3>0$ and $B_1B_2>B_3$. We have shown that $B_1>0$. We proceed with the proof of $B_3>0$.

$$B_3=\tfrac{r_2c^2\mu_I\left[\mu_ImN_sk_2\left(1-\frac{k_2m}{c}\right)+r_2c(R_0-1)\right]}{mN_sk_2(r_2c+k_2N_s\mu_Im)}>0\Leftrightarrow\mu_ImN_sk_2\left(1-\tfrac{k_2m}{c}\right)+r_2c(R_0-1)=$$
$$=\mu_Imk_2\left(N_s-R_0\right)+r_2c(R_0-1)>0\Leftrightarrow 1<R_0<N_s \tag{17}$$

By some algebraic manipulation we also prove that $B_1B_2>B_3$. Thus, if $\tau=0$, the HIV-healthy equilibrium, P_4 is locally stable if $R_1<1$ and $1<R_0<N_s$. Let now $\tau>0$. The equilibrium P_4 is unstable if there is at least one root λ_i with $Re(\lambda_i)>0$ and is stable if $Re(\lambda_i)<0$ for all λ_i. That is to say, the stability of solutions depends on the location of the zeros of the associated characteristic equation. By Theorem 1 [3], we obtain the following lemma.

Lemma 1. *Consider the transcendental equation (13), where P and Q are analytic functions in a right half-plane $Re(\lambda) > -\sigma$, $\sigma > 0$, which satisfy the following conditions:*

1. *$P(\lambda)$ and $Q(\lambda)$ have no common imaginary zero.*
2. *$\overline{P(-i\omega)} = P(i\omega)$, $\overline{Q(-i\omega)} = Q(i\omega)$ for real ω.*
3. *$P(0) + Q(0) \neq 0$.*
4. *when $\tau = 0$ there are at most a finite number of roots of (13) in the right half-plane.*
5. *$F(\omega) = |P(i\omega)|^2 - |Q(i\omega)|^2$ for real ω, has at most a finite number of real zeroes.*

   Under these conditions, the following statements are true:
   - *Suppose that the equation $F(\omega) = 0$ has no positive roots. Then if (13) is stable $\tau = 0$ it remains stable for all $\tau \geq 0$, whereas if it is unstable at $\tau = 0$ it remains unstable for all $\tau \geq 0$.*
   - *Suppose that the equation $F(\omega) = 0$ has the least one positive root and that each positive root is simple. As τ increases, stability switches may occur. There exists a positive number $\tau^\star$ such that (13) is unstable for all $\tau > \tau^\star$. As τ varies from 0 to $\tau^\star$, at most a finite number of stability switches may occur.*

Lemma 2. *If the conditions of the Lemma 1 are verified for system (1), then:*

- *if $\tau \in [0, \tau^\star[$, then the HIV-healthy equilibrium P_4 is locally asymptotically stable;*
- *if $\tau > \tau^\star$, then the HIV-healthy equilibrium P_4 is unstable and system (1) undergoes a Hopf bifurcation at P_4 when $\tau = \tau^\star$.*

where $\tau^\star = \frac{1}{\omega_0} \arccos\left(\frac{b_4\omega_0^4 + (b_1b_5 - b_2b_4)\omega_0^2 - b_3b_5}{b_4^2\omega_0^2 + b_5^2}\right)$

Finally, we study the stability of the cancer-HIV-healthy equilibrium, P_5. This equilibrium exists only if $R_2 = \frac{r_1 p(R_0-1)}{r_2 + pk_1 m} < 1$. The characteristic equation of system (1) for the cancer-HIV-healthy equilibrium P_5, is given by:

$$\begin{vmatrix} r_1\left(1 - \frac{C^\star+T^\star+I^\star}{m}\right) - k_1T^\star - \frac{r_1C^\star}{m} - \lambda & -\frac{r_1C^\star}{m} - k_1C^\star & -\frac{r_1C^\star}{m} & 0 \\ -\frac{r_2T^\star}{m} - pk_1T^\star & r_2\left(1 - \frac{C^\star+T^\star+I^\star}{m}\right) - pk_1C^\star - k_2V^\star - \frac{r_2T^\star}{m} - \lambda & -\frac{r_2T^\star}{m} & -k_2T^\star \\ 0 & k_2V^\star e^{-\lambda\tau} & -\mu_I - \lambda & k_2T^\star e^{-\lambda\tau} \\ 0 & 0 & N_s\mu_I & -c - \lambda \end{vmatrix} = 0 \tag{18}$$

Lemma 3. *If the conditions of the Lemma 1 are verified for system (1), then:*

- *if $\tau \in [0, \hat{\tau}[$, then the cancer-HIV-healthy equilibrium P_5 is locally asymptotically stable;*
- *if $\tau > \hat{\tau}$, then the cancer-HIV-healthy equilibrium P_5 is unstable and system (1) undergoes a Hopf bifurcation at P_5 when $\tau = \hat{\tau}$.*

where $\hat{\tau} = \frac{1}{\omega_0} \arccos\left(\frac{b_5\omega_0^6+(b_1b_6-b_2b_5-b_7)\omega_0^4+(b_2b_7+b_4b_5-b_3b_6)\omega_0^2-b_4b_7}{b_5^2\omega_0^4+(b_6^2-2b_5b_7)\omega_0^2+b_7^2}\right)$

Lemma 4. *Let* $R_0 = \frac{N_s k_2 m}{c}$, $R_1 = \frac{N_s k_2 r_1 \mu_I (R_0-1)}{k_1(r_2 c + N_s k_2 \mu_I m)}$, *and* $R_2 = \frac{r_1 p (R_0-1)}{r_2 + m p k_1}$. *For system (1), we have:*

1. *P_0 and P_3 are unstable for all $\tau \geq 0$;*
2. *The cancer equilibrium P_1 is locally stable for all $\tau \geq 0$;*
3. *When $R_0 < 1$, the healthy equilibrium P_2 is locally stable for all $\tau \geq 0$.*
4. *When $R_0 > 1$, the healthy equilibrium P_2 is unstable for all $\tau \geq 0$ and P_4 exists.*
   - *When $R_1 < 1$ and $1 < R_0 < N_s$ then P_4 is asymptotically stable for $\tau < \tau^\star$, and unstable when $\tau > \tau^\star$, where*

$$\tau^\star = \frac{1}{\omega_0} \arccos\left(\frac{b_4\omega_0^4 + (b_1b_5 - b_2b_4)\omega_0^2 - b_3b_5}{b_4^2\omega_0^2 + b_5^2}\right) \tag{19}$$

   When $\tau = \tau^\star$, a Hopf bifurcation occurs; that is, a family of periodic solutions bifurcates from P_4 as τ passes through the critical value $\tau^\star$.
   - *When $R_1 > 1$, P_4 is unstable for all $\tau \geq 0$. When $R_2 < 1$, P_5 exists. Suppose that the Routh-Hurwitz criteria is verified, then the cancer-HIV-healthy equilibrium, P_5, is asymptotically stable when $\tau < \hat{\tau}$ and unstable when $\tau > \hat{\tau}$, where*

$$\hat{\tau} = \frac{1}{\omega_0} \arccos\left(\frac{b_5\omega_0^6 + (b_1b_6 - b_2b_5 - b_7)\omega_0^4 + (b_2b_7 + b_4b_5 - b_3b_6)\omega_0^2 - b_4b_7}{b_5^2\omega_0^4 + (b_6^2 - 2b_5b_7)\omega_0^2 + b_7^2}\right) \tag{20}$$

   When $\tau = \hat{\tau}$, a Hopf bifurcation occurs; that is, a family of periodic solutions bifurcates from P_5 as τ passes through the criticial value $\hat{\tau}$.

4 Numerical Results

In this section, we simulate the model (1). The parameters used in the simulations are $r_1 = 0.11$ day^{-1}, $m = 1500$ mm^{-3}, $k_1 = 1 \times 10^4$ mm^{-3} day^{-1}, $r_2 = 0.03$ day^{-1}, $p = 0.1$, $k_2 = 2.5 \times 10^{-5}$ mm^{-3} day^{-1}, $\tau = 9.75$ day, $\mu_I = 0.3$ day^{-1}, $N_s = 200$, $c = 3$ day^{-1}. The initial conditions are set to $C(0) = 1$ mm^{-3}, $T(0) = 800$ mm^{-3}, and all other variables are set to 10 mm^{-3}.
We consider r_1, the uncontrolled proliferation rate of the cancer cells, a bifurcation parameter. We start from the cancer-HIV-healthy (CHH) equilibrium of model (1), for $r = 0.11$, in Figure 1. As r_1 is increased, a Hopf bifurcation takes place and a periodic solution appears (see Fig. 2). Further bifurcations occur in which this periodic orbit doubles its period repeatedly. Thus, we can observe period 4, period 8, and period 16 orbits. This numerically observed period-doubling bifurcation leads to the appearance of chaotic behaviour in Figure 7.

Biologically, these results may be explained as follows. We know that if the proliferation rate of cancer cells, r_1, increases then cancer and HIV coexist in the organism. After a given threshold thus, the cancer structure will evolve and

this could mean the beginning of the AIDS stage in the HIV infected patient. This phase is characterized by a deterioration of the health status of the HIV infected patient which leads to death.

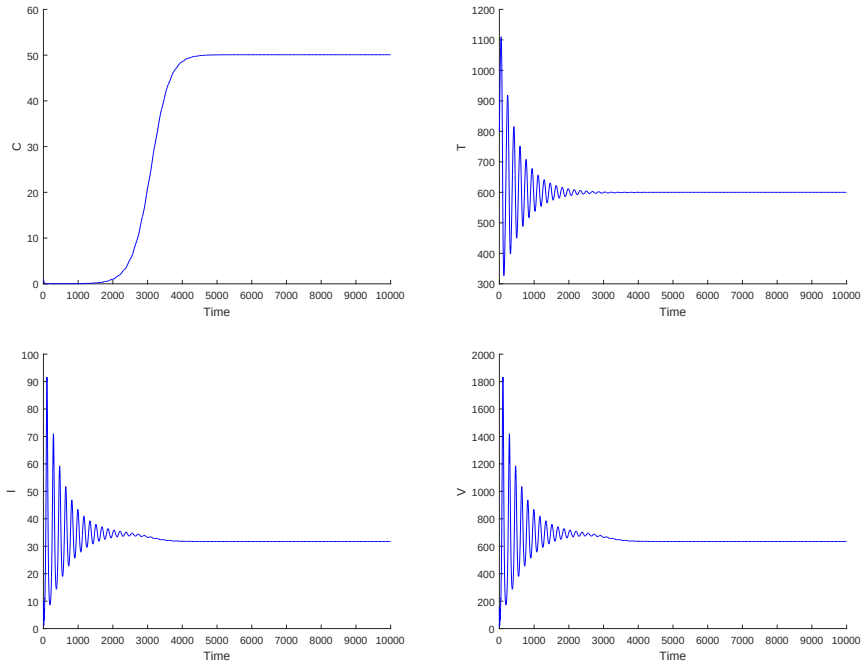

Fig. 1. Cancer-HIV-healthy equilibrium of the model (1), for parameter values and initial conditions given in the text.

5 Conclusions

We propose a delay mathematical model for the dynamics of AIDS-related cancer. The model exhibits equilibria, periodic solutions and chaos, for some regions of the parameter values. Chaos has been found in biological models, namely in the throbs of the ventricular cells of a chicken heart, or in the human brain activity. Biologically, the appearance of chaos in our model means that the HIV infected patient has developed neoplasia, and is 'officially' at the AIDS-stage, which means he will die. Thus, understanding the mechanisms behind the development of neoplasia in HIV infected patients is a defiant challenge. Future work will consider the effect of cell-to-cell transmission in the severity of AIDS-related cancers.

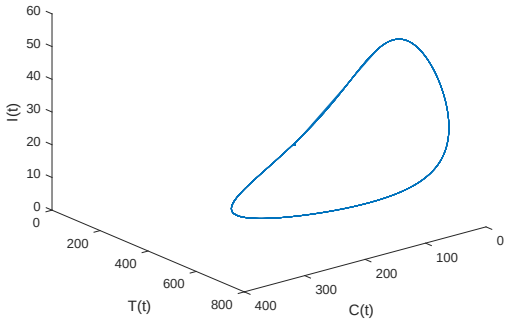

Fig. 2. Periodic solution of the model (1) of period 1, for parameter values (except $r_1 = 0.13$) and initial conditions given in the text.

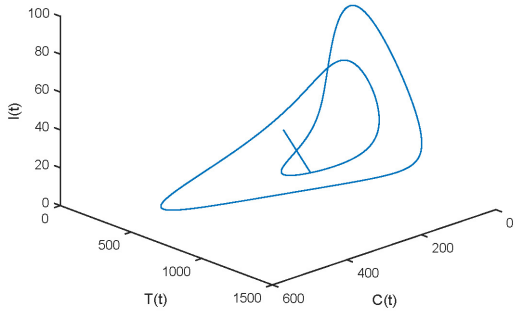

Fig. 3. Periodic solution of the model (1) of period 2, for parameter values (except $r_1 = 0.0.14$) and initial conditions given in the text.

Acknowledgments

Authors wish to thank the Polytechnic of Porto, through the PAPRE Programa de Apoio à Publicação em Revistas Científicas de Elevada Qualidade for financial support. The authors were partially funded by the European Regional Development Fund through the program COMPETE and by the Portuguese Government through the FCT - Fundação para a Ciência e a Tecnologia under the project PEst-C/MAT/UI0144/2013. The research of AC was partially supported by a FCT grant with reference SFRH/BD/96816/2013.

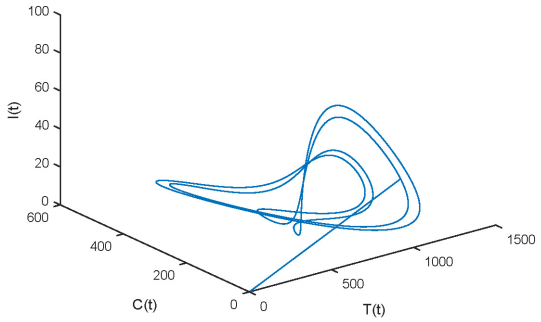

Fig. 4. Periodic solution of the model (1) of period 4, for parameter values (except $r_1 = 0.141$) and initial conditions given in the text.

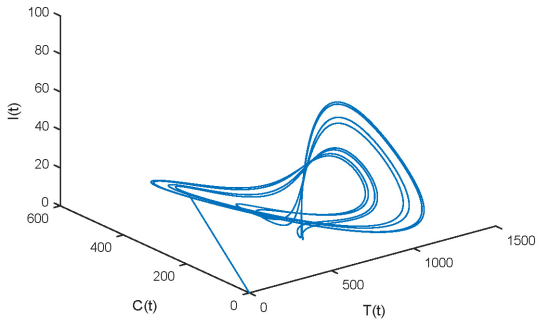

Fig. 5. Periodic solution of the model (1) of period 8, for parameter values (except $r_1 = 0.1416$) and initial conditions given in the text.

References

1. M. Bodnar, U. Forys and Z. Szymanska. Model of AIDS-related tumour with time delay. *XXI Congress of Differential Equations and Applications and XI Congress of Applied Mathematics*, Ciudad Real, 21-25 September, 2009.
2. M. Bower, M. Fisher, T. Hill, I. Reeves, J. Walsh, C. Orkin, *et al.* CD4 counts and the risk of systemic non-Hodgkin's lymphoma in individuals with HIV in the UK. *Haematologica*, 94, 875–880, 2009.
3. K.L. Cooke and P. Driessche. On zeros of some transcendental equations. Funkcialaj Ekvacioj, 29, 77–90, 1986.
4. J. Lou and T. Ruggeri. A time delay model about AIDS-related cancer: equilibria, cycles and chaotic behavior. *Ricerche di Matematica*, 56, 195–208, 2007.
5. J. Lou, T. Ruggeri and Z. Ma. Cycles and Chaotic Behavior in an AIDS-related cancer dynamic model in vivo. *Journal of Biological Systems*, 15, 2, 149–168, 2007.

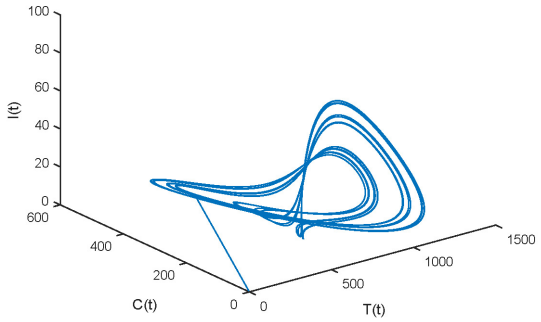

Fig. 6. Periodic solution of the model (1) of period 16, for parameter values (except for $r_1 = 0.14165$) and initial conditions given in the text.

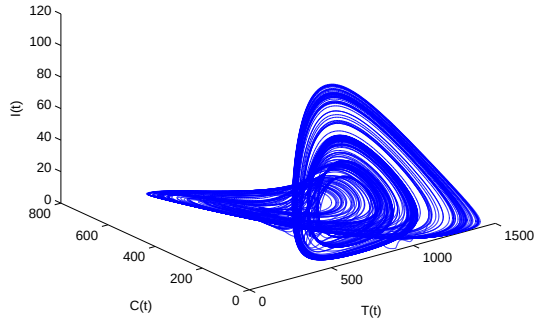

Fig. 7. Chaotic behaviour of the model (1) for parameter values (except for $r_1 = 0.14812244897959$) and initial conditions given in the text.

6. J. Lou, T. Ruggeri and C. Tebaldi. Modeling cancer in HIV-1 infected individuals: equilibria, cycles and chaotic behavior. *Mathematical Biosciences and Engineering*, 3, 2, 313–324, 2006.
7. O. Lund, E. Mosekilde and J. Hansen. Period doubling route to chaos in a model of HIV infection of the immune system - A comment on the Anderson-May model. *Simulation Practice and Theory*, 1, 49–55, 1993.
8. K.E. Starkov and C. Plata-Ante. On the global dynamics of the cancer AIDS-related mathematical model. *Kybernetika*, 50, 4, 563–579, 2014.
9. A. Zoufaly, H.-J. Stellbrink, M. an der Heiden, C. Kollan, C. Hoffmann, J. van Lunzen, O. Hamouda. Cumulative HIV Viremia during Highly Active Antiretroviral Therapy Is a Strong Predictor of AIDS-Related Lymphoma. *The Journal of Infectious Diseases*, 200, 79–87, 2009.