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Stability Analysis for a Prostate Cancer Model with Distributed Delay ⋆

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Abstract: Some mathematical models of infectious diseases or cancer use time delays to consider the influence of past states in their evolution, models that include distributed delays are more realistic since they take into account all the states in a time interval in the past. In cancer models it is convenient to know the parameter ranges for which the model is stable in the presence of a tumour. We use tools like an stability criterion depending on the delay Lyapunov matrix and a computational program to determine the roots of the characteristic equation of the linearized model.

Keywords: Delay systems, Stability of delay systems, Stability analysis, Time domain analysis, Lyapunov methods, Systems biology.

1. INTRODUCTION

Mathematical models are used in all branches of science and engineering as they are a resource that allows simulations of economic, physical, chemical and biological phenomena in different scenarios and without the need for specialized equipment. Mathematical models allow evaluating and understanding the behavior of the modeled phenomena as well as assessing the complexity of the systems through the study of the effect produced by changes in the model and to discard hypotheses before executing experiments in a laboratory. In biological systems, models help to understand the interactions and behavior of biological entities such as cells, tissues, organs and organisms. For example, the responses of the immune system and the evolution of diseases within an organism by studying populations of viruses, bacteria or malicious cells to the host, another approach is the study of the spread of infectious diseases such as measles, chicken pox, mumps, influenza and other viral diseases within a population.

Thanks to mathematical modeling and computation, it has become possible to simulate biological systems that are considered particularly complex because of the large number of variables involved and the need to recalculate the responses repeatedly during the simulation time (Dagasso et al., 2021).

One equation employed for the modelling of diseases is the classical logistic equation introduced by the Belgian mathematician Pierre Verhulst to study population growth. In this model the population is neither allowed to grow out of control nor grow or decay constantly (Abell and Braselton, 2014).

The lag between an individual gets infected and the reaction of the immune system varies and can impact in the evolution of the disease in the host (Dagasso et al., 2021).

The introduction of a delay into the classical logistic equation results in:

$$\dot{u}(t) = m\left(1 - au(t-\tau)\right)u(t), \tag{1}$$

where a characterizes the resistance to the external environment, m is called the Malthusian coefficient which is the intrinsic population growth and τ is the delay that describe the time it takes for pathogens to start to multiply. This equation describes the population dynamics (Kashchenko, 2021; Kuang, 1993).

The model (1) is useful to describe oscillations in the dynamics in the case where a single species is studied without the presence of predators. However, integro-differential equations like the logistic equation with distributed delay defined in (2) allows describing the evolution of the population size in a way closer to reality.

$$\dot{y}(t) = py(t)\left(1 - \frac{1}{K}\int_{t-\tau}^{t} y(s)G(t-s)ds\right),\ t \geqslant t_0. \tag{2}$$

In this case, the state derivative depends on all the states of $y(t)$ after the initial moment t_0, p is the intrinsic growth of the population and K is the environmental carrying capacity which is defined as the species' average population size in a particular habitat considering the necessary elements to support the species. The delay is continuously distributed between t and $t-\tau$, this means that model (2) has a fixed time lag or finite memory (Rihan, 2021).

Our goal is to use the tools developed for the stability analysis of time delay systems in the analysis of a particular model of prostate cancer involving distributed delays and thus obtain parameter vales for which the disease remains in a tumour-dormancy state. We illustrate our results through examples where we obtain stability maps in the space of the selected parameters. As cancer is

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a complex disease, this kind of analysis can be useful for understanding the effect of parameter changes and their relation with tumour-dormancy states, which can be used for designing administration protocols for medical treatments that allow driving the disease to a desirable stable state and attempt to eliminate tumor cells.

2. DELAY EQUATIONS MODELLING CANCER

The immune system is a network of cells and signals that respond to the presence of pathogens and protect the body from cancer cells. It monitors substances normally found in the body, if the system detects an unrecognized new substance then proceed to attack it. The substances that cause a response of the immune system are called *antigens*. The mission of the immune system is to destroy everything containing antigens, in fact, it considers any foreign substance as an antigen. The immune system is better at recognizing and attacking pathogens than cancer cells. Pathogens are easily detectable due to certain types of proteins on their outer surfaces that normally are not found in the human body. In contrast, cancer cells and normal cells show fewer differences even though they also have unusual substances on their outer surfaces (Rihan et al., 2014b).

Several mathematical models have been obtained and used to estimate important biological parameters, to understand certain behaviours both of tumours and of the immune response. These models also have been used to make predictions, however, the dynamics of the immune response to tumours *in vivo* is complex and some reactions are difficult to predict and understand. The reasons of the capabilities of new tumours of being able to hide from the immune system and grown out of control are still unknown Kuznetsov et al. (1994). Mathematical models, using ordinary, partial, and delay differential equations, play an important role to understand how immune cells and cancerous cells evolve and interact over time (Rihan et al., 2014b,a).

Cancer is one of the most challenging problems of modern medicine and is a disease with high mortality rates worldwide. Some studies of cancer are focused on understand the interactions between tumor cells and the immune system. Treatments for cancer include chemotherapy, surgery, radiation and immunotherapy. Chemotherapy kills both the cancerous and healthy cells making the patient susceptible to opportunistic infections. Combination of chemotherapy and immunotherapy protects the patient from infections, as well as boost their immune system to fight cancer (Rihan et al., 2014a).

The called *tumour-dormancy* is a state in which potentially lethal tumor cells persist for a long period of time with little or no increasing population. It is assumed that the population does not increase due to the absence of some growth factor or that the fast-growing cells are eliminated at a rate equal to the rate at which they were generated (Kuznetsov et al., 1994).

3. PROSTATE CANCER MODEL

Some research groups focus on a particular cancer type to develop and improve mathematical models. We focus in a prostate cancer model including distributed delays since with this type of delays all states from a point in the past to the present time are considered, this property is more realistic than punctual delays, were certain states in the past are taken. In Turner et al. (2021), a nonlinear model for prostate cancer with distributed delay is presented:

$$\begin{aligned}
\dot{A} &= \gamma(A_{\max} - A) - \mu_A(A - A_{\min}) + \kappa N, \\
\dot{L} &= (1 - k_p\alpha(A))F(A)L\left(1 - \int_{-\tau}^{0} L(t+\theta)\frac{\omega(\theta)}{\eta_k}d\theta\right) \\
&\quad - \delta_L L - k_t\alpha(A)L, \\
\dot{N} &= k_p\alpha(A)F(A)L\left(1 - \int_{-\tau}^{0} L(t+\theta)\frac{\omega(\theta)}{\eta_k}d\theta\right) \\
&\quad + k_t\alpha(A)L - \delta_N N^2 - \mu_N N,
\end{aligned} \tag{3}$$

here $\omega(\theta)$ is the delay kernel or delay distribution which is usually taken as a constant or an exponential function. For simplicity, the time dependency of variables $A(t)$, $L(t)$, $N(t)$ and their derivatives is omitted. The model considers the androgen concentration in the environment A, the androgen dependent **L**ymph **N**ode **Ca**rcinoma of the **P**rostate (LNCaP) cells L, and the neuroendocrine androgen independent cells N. They study the androgen concentration because it has been observed that this hormone stimulates the prostate tumour growth. It has also been observed that some LNCaP cells change (transdifferentiate) to neuroendocrine cells, possibly caused by low androgen levels. This change is aimed at secreting androgens or other anabolic hormones to promote tumor growth.

The first equation of (3) represents the dynamics of androgen, $A_{\min}$ is the minimum androgen concentration for tumour growth, $A_{\max}$ is the maximum androgen concentration of the system and satisfies $A_{\max} > A_{\min}$. The model considers that androgen can be produced from endocrine glands like adrenal glands and kidneys, with production rate γ. The depletion of androgen depends on μ_A which is the maximum depletion rate and assumes a minimum threshold of androgen to sustain the cancer. The equation also considers androgen secretion by N cells with secretion rate κ.

The second equation of (3) describes the dynamics of L cells, assumes asymmetric cell division, apoptosis at rate δ_L, transdifferentiation into N cells at maximum rate k_p during growth and maximum rate k_t when they are mature. Transdifferentiation depends on the androgen concentration through function $\alpha(A) = rAe^{-aA}$ with gradient of the differentiation increase r and inverse of the maximum differentiation rate a. Proliferation of L cells is governed through

$$F(A) = \beta_p\left(1 - \frac{A_{\min}}{A}\right),$$

here β_p is the maximum proliferation rate of L, the growth of L is limited by the population density and distributed over a past time interval τ. The term $L(t+\theta)$ is the delay term for L cells, and η_k is the carrying capacity of the environment.

Finally, in the third equation of (3), the growth of N cells depends on the production by asymmetrical cell division and transdifferentiation of L cells. The death

rate has a linear term for apoptosis with maximum rate μ_N and a quadratic term that represents the intraspecific competition for space and resources at rate δ_N.

For biological representation, all parameters are considered to be positive and initial conditions are positive continuous functions defined for $\theta \in [-\tau, 0]$ as

$$\varphi(\theta) = [\varphi_1(\theta),\ \varphi_2(\theta),\ \varphi_3(\theta)]^T = [A(\theta),\ L(\theta),\ N(\theta)]^T.$$

The proportion of L cells produced by asymmetric division must satisfy $0 < 1 - k_p\alpha(A) \leqslant 1 \quad \forall A$, and $\alpha_{\max} = re^{-1}/a$, thus, we have the condition $k_p\alpha_{\max} \leqslant 1$.

3.1 Equilibrium points

In Turner et al. (2021), two equilibrium points of system (3) were detected; A tumour-free equilibrium point E_1, and a tumour-present equilibrium point $E^\star$ which can be considered a *tumour-dormancy* state. The study of the equilibrium points of system (3) and their stability led to the following result.

Theorem 1. (Turner et al. (2021)). System (3) always admits a tumour-free equilibrium E_1 at

$$E_1 = (A_1, L_1, N_1) = \left(\frac{\gamma A_{\max} + \mu_A A_{\min}}{\gamma + \mu_A}, 0, 0\right),$$

and if the conditions

$$R_0 = \frac{A_1\left(\delta_L + k_t\alpha(A_1)\right)}{\beta_p\left(A_1 - A_{\min}\right)\left(1 - k_t\alpha(A_1)\right)} \leqslant 1, \quad A_1 \geqslant \frac{1}{a},$$

are satisfied, then system (3) admits a tumour-present equilibrium $E^\star = (A^\star, L^\star, N^\star)$ with coordinates given by the solution for $A^\star > A_1$ of the nonlinear equation:

$$\begin{aligned}\frac{\delta_N}{\kappa^2}\Bigg(&\left((\gamma+\mu_A)A^\star - (\gamma A_{\max} + \mu_A A_{\min})\right)^2 \\ &+ \frac{\kappa\mu_N}{\delta_N}\left((\gamma+\mu_A)A^\star - (\gamma A_{\max} + \mu_A A_{\min})\right)\Bigg) \\ &- \frac{\eta_k}{\Delta}\left(1 - \frac{A^\star\left(\delta_L + k_t\alpha(A^\star)\right)}{\beta_p\left(A^\star - A_{\min}\right)\left(1 - k_t\alpha(A^\star)\right)}\right) \\ &\times \left(\frac{\delta_L + k_t\alpha(A^\star)}{1 - k_p\alpha(A^\star)} - \delta_L\right) = 0,\end{aligned}$$

and

$$L^\star = \frac{\eta_k}{\Delta}\left(1 - \frac{A^\star\left(\delta_L + k_t\alpha(A^\star)\right)}{\beta_p\left(A^\star - A_{\min}\right)\left(1 - k_t\alpha(A^\star)\right)}\right),$$

$$N^\star = \frac{\left(\gamma+\mu_A\right)A^\star - \left(\gamma A_{\max} + \mu_A A_{\min}\right)}{\kappa},$$

with $\Delta = \int_{-\tau}^{0}\omega(\theta)d\theta$.

3.2 Linearized model

Since system (3) is nonlinear it is necessary to linearize it to apply some standard methods for the analysis of its stability, for example, frequency strategies. The linearized version of (3) is analyzed around a generic equilibrium $\bar{E} = \left(\bar{A}, \bar{L}, \bar{L}\right)$. Using the change of variables $x_1(t) = A - \bar{A}$, $x_2(t) = L - \bar{L}$, $x_3(t) = N - \bar{N}$ and the truncated Taylor expansion around $(0, 0, 0)$, the following linearized system is obtained (Turner et al., 2021):

$$\begin{aligned}\dot{x_1}(t) &= -\left(\gamma + \mu_A\right)x_1(t) + \kappa x_3(t), \\ \dot{x_2}(t) &= b_1 x_1(t) + b_2 x_2(t) - c_1\int_{-\tau}^{0} x_2(t+\theta)\omega(\theta)d\theta, \\ \dot{x_3}(t) &= b_3 x_1(t) + b_4 x_2(t) - \left(2\delta_N\bar{N} + \mu_N\right)x_3(t) \\ &\quad - c_2\int_{-\tau}^{0} x_2(t+\theta)\omega(\theta)d\theta.\end{aligned}$$

where,

$$\begin{aligned}b_1 &= -k_p\alpha'(\bar{A})F(\bar{A})\bar{L}\left(1 - \frac{\bar{L}\Delta}{\eta_k}\right) \\ &\quad + F'(\bar{A})\left(1 - k_p\alpha(\bar{A})\right)\bar{L}\left(1 - \frac{\bar{L}\Delta}{\eta_k}\right) - k_t\alpha'(\bar{A})\bar{L}, \\ b_2 &= \left(1 - k_p\alpha(\bar{A})\right)F(\bar{A})\left(1 - \frac{\bar{L}\Delta}{\eta_k}\right) - \left(\delta_L + k_t\alpha(\bar{A})\right), \\ b_3 &= k_p\alpha(\bar{A})F'(\bar{A})\bar{L}\left(1 - \frac{\bar{L}\Delta}{\eta_k}\right) \\ &\quad + k_t\alpha'(\bar{A})\bar{L} + k_p\alpha'(\bar{A})F(\bar{A})\bar{L}\left(1 - \frac{\bar{L}\Delta}{\eta_k}\right), \\ b_4 &= k_p\alpha(\bar{A})F(\bar{A})\left(1 - \frac{\bar{L}\Delta}{\eta_k}\right) + k_t\alpha(\bar{A}),\end{aligned}$$

and

$$\begin{aligned}c_1 &= \frac{1}{\eta_k}\left(1 - k_p\alpha(\bar{A})\right)F(\bar{A})\bar{L}, \\ c_2 &= \frac{1}{\eta_k}k_p\alpha(\bar{A})F(\bar{A})\bar{L}.\end{aligned}$$

Which is rewritten as

$$\dot{x}(t) = Bx(t) + \int_{-\tau}^{0} C\omega(\theta)x(t+\theta)d\theta, \tag{4}$$

with $x(t) = [x_1(t),\ x_2(t),\ x_3(t)]^T$ and matrices

$$B = \begin{bmatrix} -\left(\gamma+\mu_A\right) & 0 & \kappa \\ b_1 & b_2 & 0 \\ b_3 & b_4 & -\left(2\delta_N\bar{N} + \mu_N\right) \end{bmatrix},\ C = \begin{bmatrix} 0 & 0 & 0 \\ 0 & -c_1 & 0 \\ 0 & -c_2 & 0 \end{bmatrix}.$$

3.3 Delay distribution

The distributed delay works similarly to a memory, it considers all the past states contained between a time span defined by the delay value. The delay distribution assigns weights to the history. If it is a constant on the time span, it is uniform and assigns the same importance to all the history, but if it is a function that varies in the same time range, then it gives different weights to the history, possibly giving more importance to the closest states to the present time. For the delay distribution $\omega(\theta)$ of equation (4), in Turner et al. (2021) two cases are considered:

- Uniform distribution (constant case)

$$\omega(\theta) = \begin{cases} \dfrac{1}{\tau}, & \theta \in [-\tau, 0], \\ 0, & \theta \notin [-\tau, 0], \end{cases} \tag{5}$$

  which gives equal weight to all of the history incorporated by the distributed delay.
- Exponential distribution

$$\omega(\theta) = \zeta e^{\psi\theta},$$

  which is the most used distribution in the literature. In this case, is assumed that the history of L cells have a much greater weight close to the present time.

4. STABILITY OF TIME DELAY SYSTEMS WITH DISTRIBUTED DELAY

Linear delay systems are usually analyzed by classical frequency methods like those involving the analysis of the roots of the characteristic equation of the system. It is known that delay equations have an infinite number of roots (Bellman and Cooke, 1963), with the help of computational tools like the QPmR root finder software (Vyhlídal and Zítek, 2003), it is possible to observe a slice of the spectrum of the characteristic equation. Other tool is the D-Subdivisions method in which the stability borders in a space of parameters are determined by detecting the zero crossing of the roots of the system (Neimark, 1949). An alternative to the frequency methods are the temporal ones like those involving Lyapunov functions (Razumikhin, 1956) and functionals (Krasovskii, 1963).

4.1 Stability criterion

In this contribution, we focus on the stability analysis of linear delay equations with distributed delay in the temporal approach by means of Lyapunov matrices and functionals (Kharitonov, 2013). Next, we introduce the Lyapunov matrices for pointwise and distributed time-delay systems. Consider equations of the form

$$\dot{x}(t) = A_0 x(t) + A_1 x(t-\tau) + \int_{-\tau}^{0} G(\theta) x(t+\theta) d\theta, \quad (6)$$

where $\tau > 0$, $A_0, A_1 \in \mathbb{R}^{n\times n}$ and $G(\theta)$ is a real piecewise continuous matrix function of dimension $n \times n$ defined on $\theta \in [-\tau, 0]$. The *characteristic equation* of (6) is given by

$$\det\left(sI - A_0 - A_1 e^{-s\tau} - \int_{-\tau}^{0} G(\theta) e^{s\theta} d\theta \right) = 0. \quad (7)$$

It is said that equation (6) satisfies the *Lyapunov condition* if the characteristic equation (7) has no symmetric solutions s_1 and s_2 with respect to zero i.e. $s_1 = -s_2$.

The delay Lyapunov matrix $U(t)$, $t \in \mathbb{R}$ of (6) associated to matrix $W \in \mathbb{R}^{n\times n}$ is a matrix function satisfying the following properties (Cuvas and Mondié, 2016):

- Continuity property:
$$U \in \mathcal{C}\left(\mathbb{R}, \mathbb{R}^{n\times n}\right).$$
- Dynamic property, for $t > 0$:
$$\dot{U}(t) = U(t) A_0 + U(t-\tau) A_1 + \int_{-\tau}^{0} U(t+\theta) G(\theta) d\theta.$$
- Symmetry property:
$$U(t) = U^T(-t), \quad t \in \mathbb{R}.$$
- Algebraic property:
$$\begin{aligned} -W =& A_0^T U^T(0) + U(0) A_0 \\ &+ A_1^T U^T(-\tau) + U(-\tau) A_1 \\ &+ \int_{-\tau}^{0} \left[G^T(\theta) U^T(\theta) + U(\theta) G(\theta) \right] d\theta. \end{aligned}$$

In Kharitonov (2013) and Aliseyko (2017), it was shown that the Lyapunov matrix exists and is unique if equation (6) satisfies the Lyapunov condition.

To present the stability criterion, first let us introduce the following block matrices:

$$\mathcal{K}_1 = U(0),$$
$$\mathcal{K}_2 = \begin{bmatrix} U(0) & U(\tau) \\ * & U(0) \end{bmatrix},$$
$$\mathcal{K}_3 = \begin{bmatrix} U(0) & U(\tau/2) & U(\tau) \\ * & U(0) & U(\tau/2) \\ * & * & U(0) \end{bmatrix},$$

and so on. Since block matrices $\mathcal{K}_r$ are symmetric, the blocks denoted by $*$ represent the transpose of the corresponding block. In general, for $r = 2, 3, \ldots$

$$\mathcal{K}_r = \left[U\left(\frac{(j-i)\tau}{r-1} \right) \right]_{i,j=1}^{r}.$$

Theorem 2. (Egorov et al. (2017)). System (6) is exponentially stable if and only if the Lyapunov condition is satisfied and, for every natural number r, $\mathcal{K}_r > 0$ is satisfied. Moreover, if the Lyapunov condition is satisfied and system (6) is unstable, then there exist a natural number r such that $\mathcal{K}_r \ngeq 0$.

4.2 Construction of the delay Lyapunov matrix

One important task to determine the stability of systems of the form defined by (6) is the computation of the delay Lyapunov matrix in order to construct the block matrices $\mathcal{K}_r$ and test their positivity. The path followed to compute the delay Lyapunov matrix of (6) is to use the semi-analytic method described in Aliseyko (2017), where function $G(\theta)$ is defined as

$$G(\theta) = \sum_{i=1}^{m} \eta_i(\theta) B_i,$$

here $B_i \in \mathbb{R}^{n\times n}$, and $\eta_i(\theta)$ are scalar functions satisfying

$$\eta_i'(\theta) = \sum_{j=1}^{m} \alpha_{ij} \eta_j(\theta), \quad \alpha_{ij} \in \mathbb{R},$$

in general $\eta'(\theta) = A\eta(\theta)$ with

$$\eta(\theta) = \begin{bmatrix} \eta_1(\theta) \\ \eta_2(\theta) \\ \vdots \\ \eta_m(\theta) \end{bmatrix}, \quad A = \begin{bmatrix} \alpha_{11} & \alpha_{12} & \cdots & \alpha_{1m} \\ \alpha_{21} & \alpha_{22} & \cdots & \alpha_{2m} \\ \vdots & \vdots & \ddots & \vdots \\ \alpha_{m1} & \alpha_{m2} & \cdots & \alpha_{mm} \end{bmatrix}.$$

5. RESULTS

We analyze the stability of the linearized model (4) around the tumour-present equilibrium $E^\star$ defined in Theorem 1, equivalently, we analyze the stability of equation (6) with $A_0 = B$, $A_1 = 0_3$ (zero matrix in $\mathbb{R}^{3\times 3}$) and $G(\theta) = C\omega(\theta)$. As we argued in Section 3, the delay distribution can be uniform or exponential. Observe that if we take $\psi = 0$ and $\zeta = 1/\tau$ in the exponential distribution $\omega(\theta) = \zeta e^{\psi\theta}$, we recover exactly the uniform distribution $\omega(\theta) = 1/\tau$ therefore, we do not need to compute the delay Lyapunov matrix for both cases, it is enough if we consider just the exponential case.

We seek to determine the parameter values for what the tumour-present equilibrium is stable in a tumour-dormancy state. For the analysis, we take the parameter values defined in Turner et al. (2021) and summarized in Table 1 unless we specify the contrary and except for the pair of parameters object of our stability analysis. In the

analysis we take a pair of parameters of interest (p_1, p_2) and define a range of values for which we will carry out the analysis and set the rest of parameters according to the values in Table 1. Next we grid the space of parameters (p_1, p_2) in a mesh of 80×80 points, we compute the tumour-free equilibrium which always exists and is stable and verify if the conditions for the existence of the tumour-present equilibrium $E^\star$ are satisfied at each point with coordinates (p_{1x}, p_{2y}), as described in Theorem 1. For those points where conditions are satisfied, we proceed to compute $E^\star$ and the rest are discarded. For not discarded points, we use the stability criteria in Theorem 2 to test the stability of system (4) with the values of the point (p_{1x}, p_{2y}) around the equilibrium $E^\star$. Since sometimes for small values of r we obtain outer estimates of the stable zone, we start the analysis with $r = 1$, save the obtained candidate stability region and increase the value of r, we analyze the points of the candidate stability area with the new r value until the number of stable points remains the same for two consecutive values of r. For comparison purposes we use the QPmR root finder software to determine the unstable roots of the characteristic equation of (4) defined in expression (7) with the values of (p_{1x}, p_{2y}) around $E^\star$ at each point where $E^\star$ exists, it is worth mentioning that the result gives us values were the cancer is present but in a tumour-dormancy state. It is evident that the stability region obtained by Theorem 2 matches the coordinates where there are no roots in the right-hand-side of the complex plane. Notice that with the selection of a pair of parameters (p_1, p_2) the stability analysis leads to a two-dimensional stability map, we choose this option for simplicity and to reduce computational cost however, it is also possible to take a triplet (p_1, p_2, p_3) leading to a three-dimensional stability map.

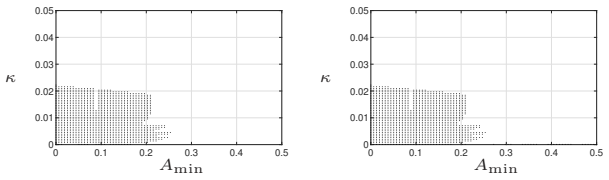
The integral term in (4) corresponds to the rate of appearance of new cancer cells at time t due to the cells that appeared at all previous times since $t - \tau$. Next we present some examples where we consider that function $\omega(\theta)$ is a constant or an exponential function.

5.1 Uniform distribution

In this case $\omega(\theta)$ is defined by (5), which gives equal relevance to the history of cancer cells in the integral term, this distribution is typically used when there is no information about the behaviour of the delay (Turner et al., 2021). For the computation of the Lyapunov matrix, as described in the previous section, we consider $\omega(\theta) = \zeta e^{\psi\theta}$ with $\zeta = 1/\tau$ and $\psi = 0$.

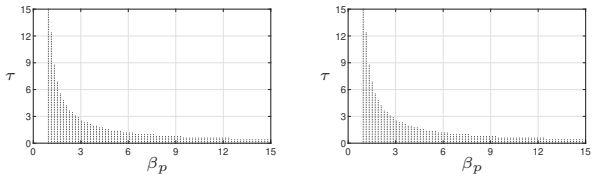
Example 1. In this example we take the parameters of interest $A_{\min}$ which is the minimum concentration of androgen for tumour growth and κ that is the androgen secretion rate from N cells that transdifferentiate with the aim at helping L cells to multiply. Fig. 1 shows the stability region of equation (4) in the space of parameters $(A_{\min}, \kappa)$.

Example 2. We analyze equation (4) in the space of parameters of the maximum proliferation rate β_p of L cells and the length of the history considered in the distributed delay τ, (β_p, τ). Fig. 2 depicts the obtained stability region.



(a) (b)

Fig. 1. Stability region of (4). (a) Using Theorem 2, reached for $r = 2$. (b) Using the QPmR software.



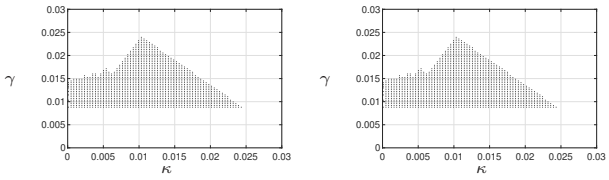
(a) (b)

Fig. 2. Stability region of (4). (a) Using Theorem 2 reached for $r = 3$. (b) Analysing the eigenvalues with QPmR.

5.2 Exponential distribution

We consider the exponential distribution $\omega(\theta) = \zeta e^{\psi\theta}$ which is the most used distribution in the literature due to its more realistic behaviour. This distribution assumes that the production of new cancer cells at time t has a greater influence of the history of recently produced cells than those produced near time $t - \tau$ (Turner et al., 2021).

Example 3. We consider system (4) with the parameter values of Table 1 and considering the exponential distribution $\omega(\theta) = \zeta e^{\psi\theta}$, with the values ζ and ψ defined in Table 1, the analysis is carried out in the space of parameters (κ, γ), both parameters are androgen production rates; production from N cells (κ) and from the endocrine glands (γ).



(a) (b)

Fig. 3. Stability region of (4) with $\omega(\theta) = \zeta e^{\psi\theta}$. (a) Using Theorem 2, reached for $r = 1$. (b) Analyzing the number of unstable roots with the QPmR software.

6. DISCUSSION

In this contribution we analyze the stability of the prostate cancer model with distributed delay (4) by means of a stability criterion based on the delay Lyapunov matrix and with a software which computes the roots of the characteristic equation of (4). We consider these tools as an alternative for the stability analysis of

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Table 1. Values of the parameters taken from Turner et al. (2021) for the analysis of (4).

Parameter	Value	Units	Parameter	Value	Units
γ	0.013	day^{-1}	r	3.67	-
$A_{\max}$	6	%	a	1.5	-
$A_{\min}$	0.1	%	β_p	1.4	day^{-1}
μ_A	0.08	day^{-1}	δ_N	0.013	day^{-1}
κ	0.009	day^{-1}	μ_N	0.08	day^{-1}
k_p	0.41	day^{-1}	τ	1.42	day
k_t	0.52	day^{-1}	ψ	1	-
δ_L	0.013	day^{-1}	ζ	1.318	-
η_k	3	$\times 10^6$cells/l	-	-	-

the model studied in Turner et al. (2021) where they make an analytical study to determine the stability of the system (3). For the case of the uniform distribution $\omega(\theta) = 1/\tau$ they make a frequency analysis to obtain stability conditions. However, for the case of the exponential distribution $\omega(\theta) = \zeta e^{\psi\theta}$ it was not possible to obtain analytical results to conclude about the stability properties of the system, instead several numerical simulation were programmed to explore the dynamics of the system.

For the cases where the analysis of the characteristic equation is hard because of the big dependency of the parameters that do not allow to develop classical analysis, like D-Partitions, the stability criterion described in Theorem 2 gives an interesting alternative for the stability analysis of systems with distributed delay. In this case, it is useful to find the parameter values for which the linearized system (4) around a tumour-present equilibrium (according to Theorem 1) is exponentially stable. The criterion is simple and for some value r we obtain necessary and sufficient stability conditions that in practice is reached with really small values of r as is illustrated in the examples above.

The stability regions shown in Figs. 1-3, allow identifying the system parameter values that correspond to a tumour-dormancy state. For instance, for the case depicted in Fig. 3 since the model considers that androgen stimulates tumour growth is interesting to know the stability area in order to define possible values to be reached with some treatment for example, with androgen deprivation therapy.

7. CONCLUSION

Mathematical models of biological phenomena to make computational simulations help researchers to experiment and understand the relations of the different elements involved and the effects when parameters vary. When the goal of the investigation is to get parameter ranges where the system is stable, simple stability criteria like the one described in Theorem 2 are particularly useful as it is not necessary to run simulations and observe the system response for each value in the range considered.

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