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Periodic solutions for a model of tumor volume with anti-angiogenic periodic treatment

Soluciones periódicas para un modelo del volumen de un tumor con tratamiento periódico

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Abstract. In this work, we consider the dynamics of a model for tumor volume growth under a drug periodic treatment targeting the process of angiogenesis within the vascularized cancer tissue. We give sufficient conditions for the existence and uniqueness of a global attractor consisting of a periodic solution. This conditions happen to be satisfied by values of the parameters tested for realistic experimental data. Numerical simulations are provided illustrating our findings.

Key words and phrases. Cancer treatment modelling, cooperative systems, periodic orbits, tumor development, angiogenesis.

2020 Mathematics Subject Classification. 92C50, 34C25, 34C12.

Resumen. En este trabajo, consideramos la dinámica de un modelo para el crecimiento del volumen de un tumor bajo un tratamiento periódico de medicamentos dirigido al proceso de angiogénesis dentro del tejido vascularizado del cáncer. Damos condiciones suficientes para la existencia y la unicidad de una solución periódica la cual es globalmente atractora. Estas condiciones se cumplen con los valores de los parámetros probados en datos experimentales reales. Se proporcionan simulaciones numéricas que ilustran nuestros resultados.

Palabras y frases clave. Angiogénesis, Modelos de tratamiento de tumores de cancer, sistemas cooperativos, órbitas periódicas.

1. Introduction

Once tumor spheroids reach the blood stream, the process of vascularization called angiogenesis begins, see [3]. This stage of tumor development has major importance for the process of metastasis. Under this condition the *volume (population)*, $V > 0$, of tumor cells, as well as its *maximal capacity*, $K > 0$, are both dynamical variables. The treatment strategy called angiogenic therapy is a chemical therapy by inhibitors targeting this process, see [5]. It has been successfully modeled by standard pharmacokynetic in [4], for certain inhibitor such as TNP-470, Angiostatin and Endostatin. This model consists of the following system of differential equations:

$$\dot{V} = -\alpha V \ln(V/K), \tag{1a}$$

$$\dot{K} = -\lambda K + bV - dKV^{2/3} - eKg(t). \tag{1b}$$

Here $g(t) > 0$ is a T-periodic continuous function that represents the concentration of inhibitors administered at a given time, whose maxima and minima are denoted as $g^*, g_* \geq 0$, respectively. In realistic descriptions, $\lambda > 0$ is negligible meaning that constitutive endothelial spontaneous vasculature loss does not play a major role. The parameter $e > 0$ stands for the vascular inactivation rate. The impact depends directly on the vasculature K and due to volume dimensions carries an exponent $V^{2/3}$ while $d > 0$ is the linear rate of this impact. Finally $b > 0$ is the rate of stimulation of cell proliferation induced by inhibitors. The seminal model [2] was biologically validated by fitting it to experimental data. For practical applications the search of an 'optimal' solution under a treatment cost function is useful, although these problems require the tools of optimal control approach, see for instance [7, 8]. Notice that the final treatment outcome according to this model leaves a small oscillating tumor as time flows. This does not imply the desired elimination of cancer cells. Nevertheless the value of this treatment is to bound the size of the tumor by reducing vascularization. See further discussions on heuristics and interpretations for both experimental and modeling work in [1], where it is also important the use of a periodic treatment simulations for medication.

We extend results presented in [4], proving the existence of periodic dynamics for periodical continuous drug dose under certain conditions on the parameters. One generalization due to d'Onofrio and Gandolfi, [2], differs a little bit of the original Hahnfeldt et al. model [4]. Namely [2] considers the proliferative term bK instead of bV as in [4]. Moreover, although [2] considers periodic treatment, it does not provide general results of existence of periodic solutions. The tools we use to prove our result arise directly from the Theory of Cooperative Systems, see [6, 9]. Our aim is to give an analytical justification for the existence of such solutions.

2. Results

For the reader's convenience we first recall some basic facts about cooperative systems that will be used for proving our results.

For two points $u, v \in \mathbb{R}^n$ denote the partial order $u \leq v$ defined by $u_i \leq v_i$ for each i, also denote $u < v$ if $u \leq v$ and $u \neq v$. Consider a system

$$\begin{aligned} \dot{x} &= \mathrm{f}(t, x(t), y(t)), \\ \dot{y} &= \mathrm{g}(t, x(t), y(t)), \end{aligned} \tag{2}$$

where f, g are C^1 in an open $D \subset \mathbb{R}^2$ and continuous T-periodic functions on t. Recall that (2) is said to be a *cooperative system* in $\mathbb{R} \times D$ if

$$\mathrm{f}_y(t, x, y) \geq 0, \text{ and } \mathrm{g}_x(t, x, y) \geq 0, \ \forall\, t \in \mathbb{R}, (x, y) \in D. \tag{3}$$

Cooperative systems have very important properties, for a brief introduction to cooperative systems see [9].

We say that a pair of T-periodic differentiable functions $(a(t), b(t))$ is a *sub-solution pair* of (2) if

$$\begin{aligned} \dot{a} &\leq \mathrm{f}(t, a(t), b(t)), \\ \dot{b} &\leq \mathrm{g}(t, a(t), b(t)), \text{ for all } t. \end{aligned} \tag{4}$$

Analogously a pair of T-periodic differentiable functions $(A(t), B(t))$ is a *super-solution pair* if

$$\begin{aligned} \dot{A} &\geq \mathrm{f}(t, A(t), B(t)), \\ \dot{B} &\geq \mathrm{g}(t, A(t), B(t)), \text{ for all } t. \end{aligned} \tag{5}$$

We say that sub- and super-solution pairs are ordered if for all t we have $a(t) < A(t)$ and $b(t) < B(t)$.

An important feature for cooperative system (2) related to periodic orbits was established in [6], Theorem 2.1.

Theorem 2.1 (Korman (2016))**.** *Assume that the system* (2) *is cooperative and has ordered sub- and super-solution pairs* $(a(t), b(t))$ *and* $(A(t), B(t))$*. Then the system has a* T*-periodic solution* $(x(t), y(t))$*, satisfying* $a(t) < x(t) < A(t)$, $b(t) < y(t) < B(t)$, *for all* t*. Furthermore, any solution of* (2)*, with initial condition* $(x(0), y(0))$ *satisfying* $a(0) < x(0) < A(0)$ *and* $b(0) < y(0) < B(0)$*, converges to the product of the strips*

$$(\check{x}(t), \hat{x}(t)) \times (\check{y}(t), \hat{y}(t)),$$

where $(\check{x}(t), \check{y}(t)), (\hat{x}(t), \hat{y}(t))$ *are the minimal, maximal* T*-periodic solution, respectively.*

Lemma 2.2. *Any solution of* (1) *starting in the positive quadrant* $\mathbb{R}^2_+$ *either approach, enter, or remain in the subset defined by*

$$D := \{(V,K) \in \mathbb{R}^2 : 0 < V,\ 0 < K \leq \frac{3b}{2d} V^{\frac{1}{3}}\}.$$

Proof. Indeed, for any initial condition $(V(0), K(0))$ in the region

$$K > \frac{2b}{3d} V^{1/3},\ V > 0,$$

K is decreasing while V is increasing, thus any solution with initial conditions in $\mathbb{R}^2_+$ remains or eventually enters into region D. ☑

Thus, it suffices to consider solutions in the region D. The following result gives sufficient conditions for the existence of periodic orbits in D. It is expected that the periodicity of the medication g of period T induces a periodic orbit of the same period T, whenever such periodic orbits exists. There is a bounded behavior of the system which yields a periodic orbit. This follows from the positive invariance of D under the flow. Thus the existence claim stated in Theorem 2.3 below, asserts that for a suitable choice of the parameter, the resulting drug treatment is provided with at least one periodic limit orbit which is not merely a fixed point. The other non-trivial fact, stated in Theorem 2.4 is that the periodic orbit is a global attractor, i.e., that the limiting orbit is stable and there is no dependence of the initial conditions that are chosen.

Theorem 2.3 (Existence)**.** *Assume* $\alpha, \lambda, b, d, e > 0$ *and* $g(t)$ *is a non negative, non constant continuous* T*-periodic function. If*

$$b > \lambda + eg^*, \tag{6}$$

then there exists at least one T*-periodic solution* $(V(t), K(t))$ *of* (1) *whose components are positive.*

Proof. We consider the positively invariant region D defined in the previous Lemma. In this domain (1) describes a cooperative system.

For a super-solution pair take the fixed point solution,

$$\dot{A} = 0, \qquad A(0) = M, \tag{7a}$$

$$\dot{B} = 0, \qquad B(0) = M, \tag{7b}$$

with $M > 0$ to be chosen; replacing in (5) we can see that the first equation in (5) is clearly satisfied. For the second relation we need

$$\dot{B}(t) = 0 \geq M(-\lambda + b - dM^{2/3} - eg(t)). \tag{8}$$

We choose M with $\left(\frac{b}{d}\right)^{3/2} \leq M \leq V_0 := \left(\frac{3b}{2d}\right)^{3/2}$ then inequality (8) is satisfied. We immediately have that these functions satisfy the inequalities in (5). Therefore they constitute a super-solution pair in D.

For constructing a sub-solution pair $(a(t), b(t))$ in D, we take

$$\dot{a} = 0, \qquad a(0) = m, \tag{9a}$$

$$\dot{b} = 0, \qquad b(0) = m. \tag{9b}$$

In order to satisfy both inequalities in (4), we choose $0 < m < M$ sufficiently small so that the following inequality holds

$$0 < m < \left(\frac{b - \lambda - eg^*}{d}\right)^{3/2}.$$

Consequently, $(a(t), b(t))$ form a sub-solution pair.

Therefore Theorem 2.1 applies, so there exists at least one T-periodic solution for system (1), which proves the result. ☑

We say that a solution $(u(t), w(t))$ of (2) is globally attracting on a positively invariant set $\Omega \subseteq \mathbb{R}^2$ if all solutions $(x(t), y(t))$ with $(x(0), y(0)) \in \Omega$ satisfy

$$(x(t), y(t)) - (u(t), w(t)) \to 0,\ t \to \infty.$$

We consider the region

$$R := \left\{ (V, K) \in D : 0 < V < V_0 := \left(\frac{3b}{2d}\right)^{3/2},\ 0 < K \leq \frac{3b}{2d} V^{\frac{1}{3}} \right\}.$$

Notice that R remains positively invariant under the system (1). The following result establishes the uniqueness of the periodic orbit as well as that it is a global attractor.

Theorem 2.4 (Uniqueness)**.** *Under the same conditions as in Theorem 2.3, there exists a unique T-periodic solution of* (1) *in $\mathbb{R}^2_+$ which attracts all other positive solutions, when $t \to \infty$.*

Proof. Given any $T-$periodic solution we can chose $0 < m < M \leq V_0$ and a solution of (7) with $A(0) = M = B(0)$ large enough, and $a(0) = m = b(0)$ small enough so that we can consider the periodic solution as dominated by this super-solution and simultaneously dominating its sub-solution. According to Theorem 2.1, the set of periodic solutions of (1) is ordered, i.e., we can take the maximal periodic solution, $(\hat{V}(t), \hat{K}(t))$, as well as the minimal periodic solution, $(\check{V}(t), \check{K}(t))$, so that for any other periodic solution, $(V(t), K(t))$, we have $\check{V}(t) \leq V(t) \leq \hat{V}(t)$ and $\check{K}(t) \leq K(t) \leq \hat{K}(t)$. Our strategy is to prove that we actually have $(\hat{V}(t), \hat{K}(t)) = (\check{V}(t), \check{K}(t))$.

Under the change of coordinates $p = VK, q = V/K$, the system (1) becomes

$$\begin{aligned}\left(\frac{p+q}{2}\right)' &= -\alpha \ln q,\\ \left(\frac{p-q}{2}\right)' &= \lambda + bq - d(pq)^{1/3} - eg(t).\end{aligned} \tag{10}$$

Substitute $\hat{q} = \hat{V}/\hat{K}, \check{q} = \check{V}/\check{K}$ and $\hat{p} = \hat{V}\hat{K}, \check{p} = \check{V}\check{K}$ in the first equation of (10). Integrating over $[0, T]$ we get

$$0 = \int_0^T \ln \hat{q} - \ln \check{q}\, ds = \int_0^T \ln \frac{\hat{q}}{\check{q}} ds.$$

Since by its very definition we have $\hat{q}/\check{q} \geq 1$, then $\hat{q} = \check{q}$.

Now, integrating over $[0, T]$ the second equation of (10) we get

$$0 = \int_0^T \left(\hat{p}^{1/3} - \check{p}^{1/3}\right) \hat{q}^{1/3}\, ds.$$

Since $\hat{p} \geq \check{p}$, hence $\hat{p} = \check{p}$. This proves the uniqueness of periodic solutions for initial conditions in $R \subseteq D \subseteq \mathbb{R}^2_+$.

For the rest of the domain D, we just observe that V is decreasing for any $V(0) \geq V_0$ and $K(0) \leq \frac{2b}{3d} V^{1/3}$. Therefore R is attracting for any solution in D, by Lemma 2.2 any solution with initial conditions in $\mathbb{R}^2_+$ eventually enters region D and consequently to R. This concludes the proof. ☑

3. Applications

In the previous section, we analyzed the existence of periodic solutions model (1) for a tumor's volume growth. The object of this section is to show numerical evidence of the existence of periodic solutions, we numerically solved these equations using Mathematica. We will use the estimated parameters given in [4].

Example. Consider the system

$$\dot{V} = -\alpha V \ln(V/K), \tag{11a}$$

$$\dot{K} = -\lambda K + bV - dKV^{2/3} - eKg(t). \tag{11b}$$

The parameter values for the angiogenic inhibitors Angiostatin are as in [4], which are given by $\alpha = 0.192$/day, $b = 5.85$/day, $d = 0.0087/(\text{day vol}^{-\frac{2}{3}})$ and $e = 0.15/(\text{day conc})$ where conc $\equiv mg/kg$ and vol $\equiv mm^3$, since λ is negligible we consider $\lambda = 0.001$/day. The concentration of inhibitors function is determined by $g(t) = 5 + \sin(2\pi t)$. Notice that $b > \lambda + eg^*$ so by Theorems 2.3 and 2.4 the system has a periodic solution which is globally attractive. To

illustrate this fact, we consider different initial conditions for the system (11) and we observe that the corresponding solutions (the components K) tend the corresponding numerical approximation of the periodic orbit. See Figure 1. Recall that biologically forbidden initial conditions arise from the region, $V_0 > K_0$.

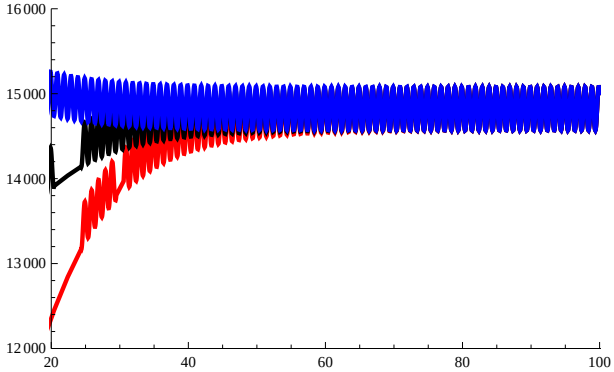

FIGURE 1. Plots for the solutions (V, K) of model (11), with different initial conditions (V_0, K_0) such as $(12000, 12000)$ in blue, $(15000, 15000)$ in red and $(14250, 13000)$ in green. We observed that the corresponding numerical approximation of the periodic orbit behaves like a globally attractive orbit.

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