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IMPULSIVE CONTROLABILITY OF TUMOR GROWTH

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ABSTRACT: In this article we introduce some impulsive models of tumor growth based on classical models as inhibition model, Piantadosi model, and autostimulation model. The basic goal is to describe the medical interventions during the treatment of the cancer process.

The used technique is based on the theory of impulsive differential equations.

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1. INTRODUCTION: SPHEROID MODEL OF TUMOR GROWTH

To develop a model, it is natural to postulate some assumptions of the mechanism of tumor growth. In general, we assume that the cells are elementary units in multicellular tumor system and moreover the geometry of tumor system is sphere. Many mathematical models in oncology are based on considered below multicellular tumor spheroid model (MTSM), see for example [9], [15], [20], [23], and also the bibliography therein. The geometry of MTSM is ploted on Figure 1; the dynamics of MTSM (based on the results in [17]) is presented on Figure 2.

Following the investigations in [20], [10], the following *general hypotheses* will be used:

(GH.1) The number of cells is large enough. Therefore we may present the volume of biomass as a smooth function of time.

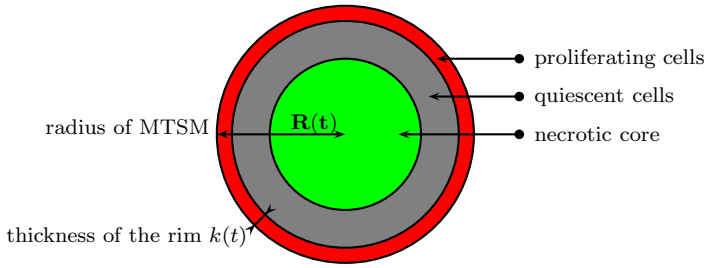

Figure 1: Multicellular tumor spheroid model (MTSM)

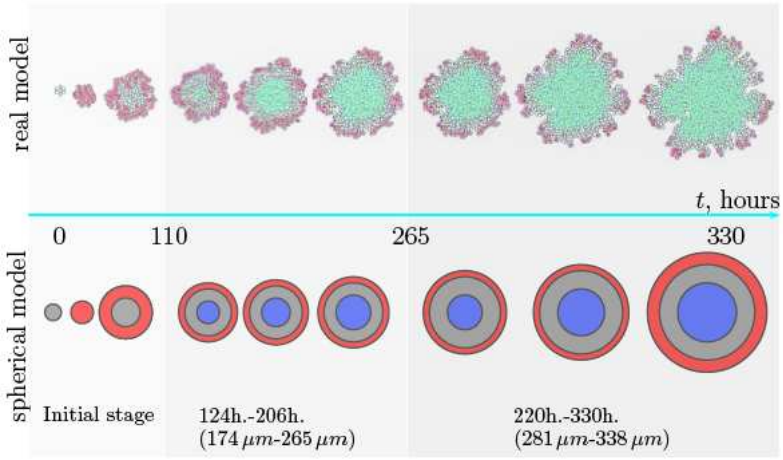

Figure 2: Real and idealized spheroid model of tumor growth. The dynamics is based on results in [17]

(GH.2) Spheroid volume is proportional to the number of cells.

(GH.3) Spheroid is ideal sphere and it contains 3 layers: necrotic core (assumed to be an ideal sphere), quiescent cells (assumed to be an ideal layer around the core), and proliferating cells (assumed to be an ideal sphere layer around the rim of quiescent cells), see Figure 1.

Also the following four natural assumptions to develop the *dynamics* of spheroid model of tumor growth will be used:

(DH.1) Let $N = N(t)$ be the size of biomass containing only:

(a) the proliferating subpopulation of the size $P = P(t)$,

(b) the quiescent subpopulation and subpopulation in necrotic core of the size $Q = Q(t)$.

(DH.2) The growth rate is characterized by the rate constant α and is proportional to the size of the reproducing subpopulation.

(DH.3) Cells in quiescent subpopulation reenter the reproducing subpopulation at the time-dependent rate $g = g(t)$.

(DH.4) Dying of cells in both subpopulations is a first order process characterized by the rate ω.

Our additional assumptions are based on *external human activities* (radiation therapy, local hyperthermia, cancer nanobots, and many others, but not like surgery) during evolution (i.e. tumor vitality) of the process:

(HA.6) It is possible to affect on cells in 3-rd layer only: proliferating cells, i.e. we may wipe-up (or add-in) proliferating cells only.

(HA.7) The time period of any single external medical action is negligible with respect to time interval $[0, T]$ of tumor vitality.

(HA.8) It is not possible to wipe-up all proliferating cells at once, i.e. there exists a number d such that in any medical treatment, we may affect on maximum volume $d_{\max}$.

Using the assumptions above:

$$\text{from (DH.1):} \quad N(t) = P(t) + Q(t), \tag{1}$$

$$\text{from (DH.2)-(DH.4):} \quad \dot{P}(t) = g(t)Q(t) + \alpha P(t) - \omega P(t), \tag{2}$$

$$\text{from (DH.2)-(DH.4):} \quad \dot{Q}(t) = -g(t)Q(t) - \omega Q(t), \tag{3}$$

$$\text{from (HA.6)-(HA.7):} \quad P(\tau_i + 0) = P(\tau_i) - d_i,\ i = 1, \ldots, p. \tag{4}$$

$$\text{from (HA.8):} \quad 0 \le d_i \le d_{\max} < P(\tau_i),\ i = 1, \ldots, p. \tag{5}$$

Here: τ_i are the moments of external medical actions; d_i are the number of destroyed proliferating cells, $i = 1, \ldots, p$; p is the number of medical actions; $P(\tau_i) = P(\tau_i - 0) = \lim_{t \to \tau_i, t \le \tau_i} P(t)$ is the volume of reproducing subpopulation before i-th external action and $P(\tau_i + 0) = \lim_{t \to \tau_i, t > \tau_i} P(t)$ is the volume of reproducing subpopulation after this moment.

Adding equations (2) and (3)

$$\dot{P}(t) + \dot{Q}(t) = \alpha P(t) - \omega \left(P(t) + Q(t)\right)$$

and using (1), we obtain

$$\dot{N}(t) = \alpha F(t)N(t) - \omega N(t), \tag{6}$$

where

$$F^*(t) = \frac{P(t)}{N(t)} \leq 1, \quad t \in [0, T]. \tag{7}$$

Usually $F^*(t)$ is called *growth fraction*.

According to (GH.1) and (GH.2), we may substitute the biomass size $N(t)$ with volume of tumor $V(t)$. Therefore, we may rewrite the equation (6) in the form

$$\dot{V}(t) = \alpha F^*(t)V(t) - \omega V(t), \tag{8}$$

Let $R(t)$ be the radius of idealized spheroidal tumor at the moment t and let $k(t)$ be the thickness of the ring of proliferating cells. Then

$$\begin{aligned} V(t) =& \frac{4}{3}\pi R^3(t), \\ V_P(t) =& V_N(t) - V_{QC}(t) = \frac{4}{3}\pi R^3(t) - \frac{4}{3}\pi \left(R(t) - k(t)\right)^3, \end{aligned}$$

where $V_P(t)$ and V_{QC} are the volumes of proliferating cells and quiescent cells (including the necrotic core), respectively. Hence

$$\begin{aligned} F^*(t) =& \frac{V_P(t)}{V(t)} = \frac{R^3(t) - \left(R(t) - k(t)\right)^3}{R^3(t)} = 1 - \left(1 - \frac{k(t)}{R(t)}\right)^3 \\ =& 3\frac{k(t)}{R(t)} - 3\left(\frac{k(t)}{R(t)}\right)^2 + \left(\frac{k(t)}{R(t)}\right)^3. \end{aligned}$$

Substituting in (8), we receive

$$\frac{4}{3}\pi 3R^2(t)\dot{R}(t) = \alpha \frac{3R^2(t)k(t) - 3R(t)k^2(t) + k^3(t)}{R^3(t)} \frac{4}{3}\pi R^3(t) - \omega \frac{4}{3}\pi R^3(t)$$

or we may replace the equation (8) with the next one

$$\dot{R}(t) = \frac{\alpha}{3}F(R)R(t) - \frac{\omega}{3}R(t). \tag{9}$$

Indeed:

1. Assuming $\lim\limits_{t\to\infty} \frac{k(t)}{R(t)} = \beta$, i.e. $k \approx R$, as $R \to \infty$, then we have $\lim\limits_{t\to\infty} F^*(R(t)) = \beta^3$, or we have to set $F(R) = \beta^3$. In such a case, we have received *simple spheroid model*, see [2], [24], [25].

   We have the same situation in the initial stage (see Figure 2) of tumor growth: all cells are in reproducting subpopulation, i.e. the growth fraction is equal to one, see [11].

2. Assuming $\lim\limits_{t\to\infty}\frac{k(t)}{R(t)}=0$, i.e. $k=o(R)$, as $R\to\infty$, we have

$$\lim_{t\to\infty}F^*(R(t))=0 \quad \text{but} \quad \lim_{t\to\infty}(F^*(R(t))-F(R(t)))=+0,$$

where the growth fraction $F(R)$ has the following forms:

$$F(R)=\begin{cases}\dfrac{1}{1+\beta R}, & \textit{inhibition model}, \text{ see [2], [24], } \beta>0 \text{ is a constant;}\\ \dfrac{1}{(1+\beta R^{\gamma})^{\frac{1}{\gamma}}}, & \textit{Piantadosi model}; \gamma>0 \text{ is a constant, see [16];}\\ \dfrac{1+S}{1+\beta R}, & \textit{autostimulation model,} \text{ where } S'=\alpha R-\beta S^2, \text{ see [12].}\end{cases}$$

Let us consider some moment τ_i of medical treatment, $i=1,\dots,p$. The radius $R(t)$ of spheroidal tumor in the moment τ_i is $R(\tau_i)$. It is obvious that $\lim\limits_{t\to\tau_i-0}R(t)=R(\tau_i)$. After the impulsive effect at the moment τ_i, we have

$$R(\tau_i+0)=R(\tau_i)-d_i.$$

Hence we obtain the following discontinuous dynamical model:

1. From the initial moment t_0 to the first moment of medical action τ_1, we have the following continuous model

$$\begin{aligned}\dot{R}(t)=&\frac{\alpha}{3}F(R(t))R(t)-\omega R(t),\\ R(t_0)=&R_0,\end{aligned}\tag{10}$$

where $R(t_0)$ is the initial radius of the tumor.

2. At the first moment τ_1, we have

$$R(\tau_1+0)=R(\tau_1)-d_1,\tag{11}$$

3. In the time interval $(\tau_1,\tau_2]$ (after the first medical treatment but before the second medical treatment), we have

$$\begin{aligned}\dot{R}(t)&=\frac{\alpha}{3}F(R(t))R(t)-\omega R(t),\\ R(\tau_1+0)&=R(\tau_1)-d_1,\end{aligned}\tag{12}$$

4. At the moment τ_2 of second medical treatment we have to use the similar arguments to extend the model, and so on.

Therefore, we receive the following inhibition impulsive model

$$\dot{R}(t)=\frac{\alpha}{3}F(R(t))R(t)-\omega R(t),\tag{13}$$

$$R(\tau_i+0)=R(\tau_i)-d_i,\ i=1,\dots,p.\tag{14}$$

In general, we have to analyze the following two elements of the system (13), (14):

1. The continuous term $\frac{\alpha}{3}F(R)R-\omega R(t)$. In Section 2 we will consider a model for gioblastoma tumor growth to show how to estimate inhibition model parameters α and ω using a nonlinear optimization method.

2. General structure of the system. In Section 3 we will present the used mathematical techniques to analyze obtained impulsive systems.

2. EXAMPLE: GLIOBLASTOMA MODEL

Consider the data given in [22] for U-87 MG glioblastoma (one of the most aggressive cancer) growth in the time period 4–21 days, see Table 1.

days	4	7	10	12	14	17	19	21
volume ($\mu m^3 \times 10^8$)	0.3	2.1	4.2	5.6	7.1	7.6	8	9.2

Table 1: U-87 MG spheroid growth, see [22, Figure 2].

Our goal in this section is to estimate the coefficients α, β and ω.

Following [1], the better known and a statistically more valid approach is to construct a numerical solution $u(t)$ of the continuous model (13). As a second step, we have to minimize the least squares error

$$E(\alpha,\omega)=\sum_{i=1}^{8}\left(u(t_i)-R(t_i)\right)^2. \tag{15}$$

We will use *Maple* codes to construct the numerical solution and solve the minimization problem.

Initialization:

```
restart: Digits:=20:
with(plots): with(Optimization):
with(LinearAlgebra): with(DEtools):

Sd:=[4,7,10,12,14,17,19,21]: N:=nops(Sd):
SV:=[0.3,2.1,4.2,5.6,7.1,7.6,8,9.2]:
f:=j->root[3]((3/4)*SV[j]/Pi):
SR:=Vector(N,f):

ode:=
```

```
diff(R(t),t)=(1/3)*alpha*R(t)/(1+betta*R(t))-omega*R(t);
ic:=R(4)=SR[1]:
```

First step: Numerical computation of (15). Here (and in the next step) we will use a slight modification of a procedure suggested by [18]:

```
myNSol := proc (a, b, c)
  local F, V;
  if not type([a, b, c], [numeric,numeric,numeric])
    then return ('myNSol')(a, b, c)
  elif a < 0 or b < 0 or c < 0 then return 0
  end if;

  F := dsolve(eval({ic, ode},
    {:-alpha = a, :-beta = c, :-omega = b}),
    R(t), numeric, output = Array(Sd));
    V := convert(Column(F[2, 1], 2), Vector);
    Norm(V-convert(SR, Vector), 2)
end proc
```

Second step: Minimizing the least squares error (nonlinear method: *sqp* – Sequential Quadratic Programming):

```
Gl_sol := GlobalOptimization:-GlobalSolve(
  'myNSol'(a, b, c),a = 0 .. 10,b = 0 .. 10,c = 0 .. 10);
```

The approximate results of calculations are $\alpha = 4.095$, $\omega = 0.2693$, $\beta = 3.1272$. The least squares error is

$$E(\alpha, \omega) = 0.0451. \tag{16}$$

Therefore, the continuous inhibition model is

$$\begin{aligned} \dot{R}(t) =& 1.365 \frac{1}{1 + 3.1272\, R(t)} R(t) - 0.2693\, R(t), \\ R(0) =& 0.0321. \end{aligned} \tag{17}$$

Table 2 contains the initial data and numerically obtained data. Figure 3 shows the graph of the numerical solution of the inhibition initial value problem, with the point graph of initial data.

3. SUCCESSIVE AND NONSUCCESSIVE TREATMENTS

Let $T > 0$; p be a fixed integer; $\mathcal{D}$ be an open interval in $\mathbb{R}$; $f \in [0, T] \times \overline{\mathcal{D}} \to \mathbb{R}$ be a continuous function;

t	4	7	10	12	14	17	19	21
$R(t)$	0.415	0.794	1.001	1.102	1.192	1.22	1.241	1.3
num. solution	0.415	0.764	1.014	1.116	1.182	1.237	1.256	1.267

Table 2: Experimental data and numerical solution.

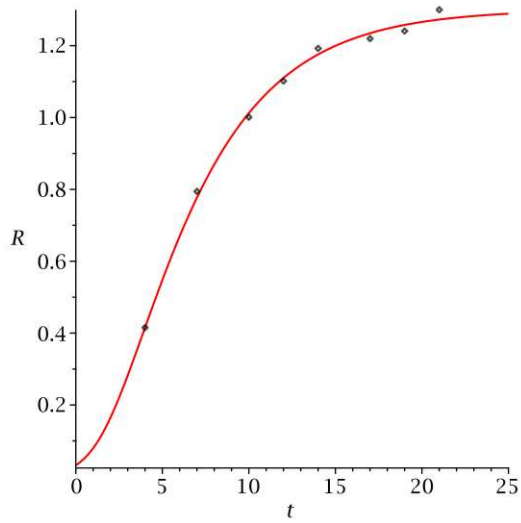

Figure 3: Numerical solution of the inhibition initial value problem and initial data-points.

$$\mathcal{T} = \Big\{ \boldsymbol{\tau} = \{\tau_0 = 0, \tau_1, \ldots, \tau_p = T\} : \\ \boldsymbol{\tau} \text{ is a finite increasing sequence, i.e., } 0 < \tau_1 < \cdots < \tau_{p-1} < T \Big\};$$

and let $\Phi \in C^0((0,T] \times \overline{\mathcal{D}}, \overline{\mathcal{D}})$. The system

$$\dot{x} = f(t,x), \qquad t \in [\tau_i, \tau_{i+1}),\ i = 0, \ldots, p-1 \tag{18}$$

$$x(\tau_i + 0) = \Phi(\tau_i, x), \quad i = 1, \ldots, p. \tag{19}$$

is called *impulsive system of differential equations with fixed moments* (see [3] and references therein).

We will use the following assumptions (A):

(A.1) $\overline{\mathcal{D}}$ is invariant set with respect to (18).

(A.2) Let $f \in C^0([0,T] \times \overline{\mathcal{D}}, \mathbb{R})$ and let f be a Lipschitz-continuous function with respect to its second argument in $\mathcal{D}$.

The function $x = x(t, x_0)$ is a *solution* of (18), (19) with initial condition

$$x(0) = x_0, \tag{20}$$

if:

1. $x(0, x_0) = x_0$;
2. The function $x(t, x_0)$ is differentiable in $\bigcup_{i=0}^{p-1} (\tau_i, \tau_{i+1}]$;
3. The equality (18) is valid for each $t \in [0,T] \setminus \boldsymbol{\tau}$;
4. For any $i = 1, \ldots, p$, we have $x(\tau_i - 0, x_0) = x(\tau, x_0)$ and $x(\tau_i + 0, x_0) = \Phi(t, x(\tau_i, x_0))$.

Based on the introduced above cancer models, it is natural to use the following definitions: Let p be an integer, $\tau_{\min}, d_{\max}$ are given positive numbers, $0 < \tau_{\min} < T$, $0 < d_{\max}$; $\Phi(x, \tau_i) = x - d_i$; $\boldsymbol{d} = \{d_1, \ldots, d_p\}$.

1. The triple $(p, \boldsymbol{\tau}, \boldsymbol{d})$ will be called *treatment*. Here: $\boldsymbol{\tau} = \{\tau_0 = 0, \tau_1, \ldots, \tau_p = T\}$, $\tau_{\min} \leq \tau_{i+1} - \tau_i \leq$ and $0 \leq d_i \leq d_{\max}$.
2. The treatment $(p, \boldsymbol{\tau}, d)$ is *nonsuccessive*, if

$$x(\tau_p) - d_{\max} > 0.$$

3. The treatment $(p, \boldsymbol{\tau}, d)$ is *successive*, if

$$x(\tau_p) - d_{\max} \leq 0.$$

Wrongly speaking the treatment is successive, if at the p-th impulsive moment, we are in position to destroy all the cancer biomass under natural assumptions: the time interval between two treatments is more than $\tau_{\min}$ and the magnitudes of impulsive effects are less than $d_{\max}$.

Example 1 (Continuation of examined gioblastoma model)**.** Consider the inhibition model

$$\begin{aligned} \dot{x} &= 1.365 \, \frac{1}{1 + 3.1272\, x} x - 0.2693\, x, \\ x(0) &= 0.0321. \end{aligned} \tag{21}$$

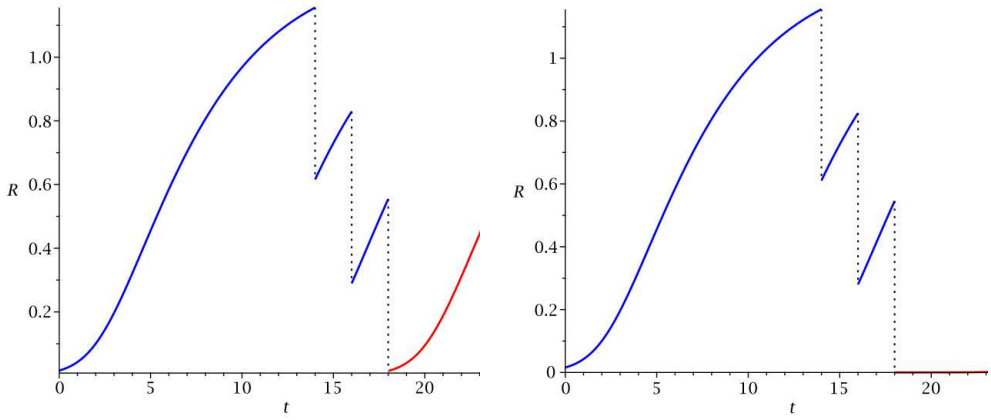

Figure 4: Example 1 – impulsive orbits of nonsuccessive and successive treatment, respectively

and treatment

$$(p = 3, \boldsymbol{\tau} = \{14, 16, 18\}, \boldsymbol{d} = \{0.54, 0.54, 0.54\})$$

for the model (21). This treatment is nonsuccessive.

Indeed, it is not hard to solve the initial value problem (21) numerically in the time interval $[0, 14]$ and to receive $x(14) = 1.176$ (in the example, we rounded to three digits after decimal point). At $\tau_1 = 14$, we have $x(\tau_1 + 0) = 1.176 - 0.54 = 0.636$. In the interval $[14, 16]$, we have the initial value problem

$$\begin{aligned} \dot{x}(t) =& 1.365F(x(t))x(t) - 0.2693x(t), \\ x(14) =& 0.636, \end{aligned}$$

with $x(18) = 0.569$. Hence $x(16 + 0) = 0.569 - 0.45 = 0.304$ and in the interval $[16, 18]$, we receive the problem

$$\begin{aligned} \dot{x}(t) =& 1.365F(x(t))x(t) - 0.2693x(t), \\ x(16) =& 0.304. \end{aligned}$$

At the end, we obtain $x(18) = 0.569 > 0.54$. Therefore, the treatment is nonsuccessive, see Figure 4.

Using similar arguments, the treatment

$$(p = 3, \boldsymbol{\tau} = \{14, 16, 18\}, \boldsymbol{d} = \{0.56, 0.56, 0.56\})$$

is successive for the same inhibition model, see Figure 4.

Bellow, we will find some sufficient conditions for nonsuccessive and successive treatment for the inhibition model $F(x) = 1/(1 + \beta x)$. Let us remark that some basic

properties of treatments follow from the qualitative theory of impulsive differential equations. For example, it follows from [3, Theorem 1.2 (Continuous dependence on initial data and impulses)] that biomass sizes depend continuously on treatments.

Lemma 2. *Let the following conditions hold true:*

1. $\alpha, \beta, \omega > 0$, $\alpha - 3\omega > 0$, $x_0 \in \left(0, \dfrac{\alpha - 3\omega}{3\beta\omega}\right)$.
2. $x = x(t, t_0, x_0)$, $t_0 \geq 0$ *be the solution of initial value problem*
$$\dot{x} = f(x) = \frac{\alpha}{3}\frac{x}{1+\beta x} - \omega x, \quad x(t_0) = x_0. \tag{22}$$
3. $\underline{x}_0, \overline{x}_0 \in \left[0, \dfrac{\alpha - 3\omega}{3\beta\omega}\right]$ *and* $\underline{x}_0 \leq x_0 \leq \overline{x}_0$.

Then:

1. *The right maximal extension interval of solution* $x(t, t_0, x_0)$ *is* $[t_0, \infty)$.
2. $\lim\limits_{t\to\infty} x(t, t_0, x_0) = \dfrac{\alpha - 3\omega}{3\beta\omega}$.
3. *The following inequalities*
$$\frac{(\alpha - 3\omega)\underline{x}_0}{3\beta\omega\underline{x}_0 + (\alpha - 3(\beta\underline{x}_0 + 1)\omega)e^{\frac{\alpha-3\omega}{3}(t_0 - t)}} < x(t, t_0, x_0) < \frac{(\alpha - 3\omega)\overline{x}_0}{3\beta\omega\overline{x}_0 + (\alpha - 3(\beta\overline{x}_0 + 1)\omega)e^{\frac{\omega(\alpha-3\omega)}{\alpha}(t_0 - t)}},$$
are valid for all $t \in [t_0, +\infty)$.

Proof. We will prove the lemma in several steps.

Step 1. Let us set $h(x) = -x^2 + \dfrac{\alpha - 3\omega}{3\beta\omega}x$. Then:

1. The equation $h(x) = 0$ has two real roots 0 and $\dfrac{\alpha - 3\omega}{3\beta\omega} > 0$.
2. For all $x \in \left[0, \dfrac{\alpha - 3\omega}{3\beta\omega}\right]$, we have:
$$\begin{aligned}\omega\beta h(x) - f(x) =& -\frac{\beta\left(\beta\omega x - \frac{\alpha}{3} + \omega\right)x^2}{\beta x + 1}\\ \geq& 0.\end{aligned}$$
Indeed, it follows from $\beta > 0$ and $\omega > 0$ that $\beta\omega x - \frac{\alpha}{3} + \omega \leq 0$ for all $x \in \left[0, \dfrac{\alpha - 3\omega}{3\beta\omega}\right]$.

Moreover, if $x \geq 0$, then

$$f(x) - \frac{3\omega^2\beta}{\alpha}h(x) = \frac{x(3x\beta\omega - \alpha + 3\omega)^2}{3\alpha(1+\beta x)} \geq 0.$$

In general

$$\frac{3\omega^2\beta}{\alpha}h(x) < f(x) < \omega\beta h(x), \quad x \in \left(0, \frac{\alpha - 3\omega}{3\beta\omega}\right) \tag{23}$$

and $h(x) = f(x) = 0$, iff $x = 0$ or $x = \dfrac{\alpha - 3\omega}{3\beta\omega}$.

Step 2. In this step, we consider the following two initial value problems

$$\dot{\underline{x}} = \frac{3\omega^2\beta}{\alpha}h(\underline{x}), \quad x(t_0) = \underline{x}_0 \tag{24}$$

and

$$\dot{\overline{x}} = \omega\beta h(\overline{x}), \quad x(t_0) = \overline{x}_0. \tag{25}$$

Here $\underline{x}_0, \overline{x}_0 \in \left[0, \dfrac{\alpha - 3\omega}{3\beta\omega}\right]$ and $\underline{x}_0 \leq x_0 \leq \overline{x}_0$.

Let the solutions of (24) (resp. (25)) be $\underline{x} = \underline{x}(t; t_0, \underline{x}_0)$ (resp. $\overline{x} = \overline{x}(t; t_0, \overline{x}_0)$).

Hence, the inequalities $\underline{x}_0 \leq x_0 \leq \overline{x}_0$ and (23) imply

$$\underline{x}(t; t_0, \underline{x}_0) \leq x(t, t_0, x_0) \leq \overline{x}(t; t_0, \overline{x}_0), \quad t \in [t_0, \infty). \tag{26}$$

Also, let us mark that the solutions of (24) and (25) are:

$$\begin{aligned} \underline{x}(t; t_0, \underline{x}_0) &= \frac{(\alpha - 3\omega)\underline{x}_0}{3\beta\omega\underline{x}_0 + (\alpha - 3(\beta\underline{x}_0 + 1)\omega)e^{\frac{\alpha - 3\omega}{3}(t_0 - t)}}, \\ \overline{x}(t; t_0, \overline{x}_0) &= \frac{(\alpha - 3\omega)\overline{x}_0}{3\beta\omega\overline{x}_0 + (\alpha - 3(\beta\overline{x}_0 + 1)\omega)e^{\frac{\omega(\alpha - 3\omega)}{\alpha}(t_0 - t)}}. \end{aligned} \tag{27}$$

Step 3. If we suppose that the solution $x(t, t_0, x_0)$ is defined in an interval $J \subset \mathbb{R}$ bounded from above by $t^* < \infty$, then it must leave any compact $K \subset \mathbb{R}^2$ at some finite time $t' < t^*$, see [8, Chapter 2, Theorem 3.1]. This does not hold true for the compact K bounded from $t = t_0$, $t = t^*$ and curves $\overline{x}(t; t_0, x_0)$ and $\underline{x}(t; t_0, x_0)$, $t \in [t_0, t^*]$, because $\underline{x}(t'; t_0, \underline{x}_0) \leq x(t', t_0, x_0) \leq \overline{x}(t'; t_0, \overline{x}_0)$, i.e. $x(t', t_0, x_0) \in K$. Therefore, the maximal extension interval of solution $x(t, t_0, x_0)$ is $[t_0, \infty)$.

It follows from (27) that

$$\lim_{t\to\infty} \underline{x}(t; t_0, x_0) = \lim_{t\to\infty} \overline{x}(t; t_0, x_0) = \frac{\alpha - 3\omega}{3\beta\omega}.$$

Hence $\lim\limits_{t\to\infty} x(t; t_0, x_0) = \frac{\alpha - 3\omega}{3\omega}$.

The proof of (3) follows directly from (26) and (27). □

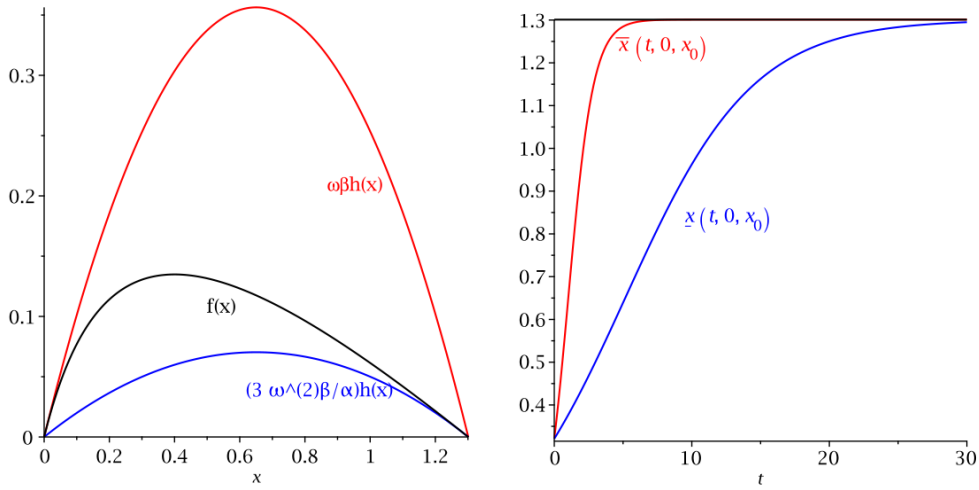

Figure 5: Example 3 – The graphics of functions $\omega\beta h(x)$ (in red), $\frac{3\omega^2\beta}{\alpha}h(x)$ (in blue), $f(x)$ (in black) and solutions $\underline{x}(t;0,x_0)$ (in blue) and $\overline{x}(t;0,x_0)$ (in red), respectively

Example 3 (Continuation of examined gioblastoma model, Example 1)**.** Let $\alpha = 4.095$, $\omega = 0.2693$, $\beta = 3.1272$, $x_0 = 0.0321$. The graphics of functions $\omega\beta h(x)$, (in red) $\frac{3\omega^2\beta}{\alpha}h(x)$ (in blue), $f(x)$ (in black) and coresponding solutions $\underline{x}(t;0,x_0)$ (in blue) and $\overline{x}(t;0,x_0)$ (in red) are plotted on Figure 5.

Now, let us consider the impulsive inhibition initial value problem

$$\dot{x} = f(x) = \frac{\alpha}{3}\frac{x}{1+\beta x} - \omega x, \quad t \in [\tau_i, \tau_{i+1}),\ i = 0, \dots, p-1 \tag{28}$$

$$x(\tau_i + 0) = x(\tau_i) - d_i, \qquad i = 1, \dots, p, \tag{29}$$

$$x(t_0) = x_0, \qquad x_0 \in \left(0, \frac{\alpha - 3\omega}{3\omega}\right), \tag{30}$$

and corresponding lower and upper problems

$$\dot{\underline{x}} = \frac{3\omega^2\beta}{\alpha}h(\underline{x}), \qquad t \in [\tau_i, \tau_{i+1}),\ i = 0, \dots, p-1 \tag{31}$$

$$\underline{x}(\tau_i + 0) = \underline{x}(\tau_i) - d_i, \quad i = 1, \dots, p, \tag{32}$$

$$\underline{x}(t_0) = x_0, \tag{33}$$

and

$$\dot{\overline{x}} = \omega\beta h(\overline{x}), \qquad t \in [\tau_i, \tau_{i+1}),\ i = 0, \dots, p-1 \tag{34}$$

$$\overline{x}(\tau_i + 0) = \overline{x}(\tau_i) - d_i, \quad i = 1, \dots, p, \tag{35}$$

$$\overline{x}(t_0) = x_0, \qquad x_0 \in \left(0, \frac{\alpha - 3\omega}{3\omega}\right), \tag{36}$$

Let $x = x(t, t_0, x_0)$ (resp. $\underline{x} = \underline{x}(t; t_0, \underline{x}_0)$ and $\overline{x} = \overline{x}(t; t_0, \overline{x}_0)$) be the solution of (22) (resp. (24) and (25)).

The following result is obvious and we omit its proof.

Lemma 4. *Let the conditions of Lemma 2 be valid.*

Then:

1. *If $(p, \boldsymbol{\tau}, \boldsymbol{d})$ is a successive treatment for the impulsive system* (34)-(36)*, then the same triple is successive for* (28)-(30)*, too.*

2. *If $(p, \boldsymbol{\tau}, \boldsymbol{d})$ is a nonsuccessive treatment for the impulsive system* (31)-(33)*, then the same triple is nonsuccessive for* (28)-(30)*, too.*

Combining the previous results, it is easy to find some criteria for successfull treatment, because we have the implicit solutions of upper and lower system for inhibition model.

Indeed let $(p, \boldsymbol{\tau}, \boldsymbol{d})$ be a treatment. Let us define:

$$\begin{aligned}
\underline{x}_1 &= \underline{x}(\tau_1, 0, x_0), & \overline{x}_1 &= \overline{x}(\tau_1, 0, x_0),\\
\underline{x}_2 &= \underline{x}(\tau_2, \tau_1, \underline{x}_1 - d_1), & \overline{x}_2 &= \overline{x}(\tau_2, \tau_1, \overline{x}_1 - d_1),\\
&\vdots & &\vdots\\
\underline{x}_p &= \underline{x}(\tau_p, \tau_{p-1}, \underline{x}_{p-1} - d_{p-1}), & \overline{x}_p &= \overline{x}(\tau_p, \tau_{p-1}, \overline{x}_{p-1} - d_{p-1}),
\end{aligned}$$

where $\underline{x}(t, t_0, x_0)$ and $\overline{x}(t, t_0, x_0)$ are defined by (27).

Theorem 5. *Let the conditions of Lemma 2 be valid.*

The treatment $(p, \boldsymbol{\tau}, \boldsymbol{d})$ is successive if $\overline{x}_p \le d_{\max}$.

The treatment $(p, \boldsymbol{\tau}, \boldsymbol{d})$ is nonsuccessive if $\underline{x}_p > d_{\max}$.

Example 6. Continuing the previous example, it is not hard to prove that the treatment

$$(3, \boldsymbol{\tau} = \{14, 16, 18\}, \boldsymbol{d} = \{0.85, 0.85, 0.85\})$$

is successive.

Indeed:

$$\begin{aligned}
\overline{x}_1 &= \overline{x}(14, 0, 0.0321) = 1.3011,\\
\overline{x}_2 &= \overline{x}(16, 14, 1.3011 - 0.85) = 1.0747,\\
\overline{x}_3 &= \overline{x}(18, 16, 1.0747 - 0.85) = 0.8474 < 0.85.
\end{aligned}$$

Obviosly, more aggressive treatment leads to "biger" dmax but destroys olso healt cells and damage the tissue . Its natural to find "small" enough $d_{\min}$ which ensures gentle successive treatment, but increases the number of treatments. For example, it is not hard to prove that the treatment

$$(7, \boldsymbol{\tau} = \{i : i = 14, \ldots, 20\}, \boldsymbol{d} = \{0.46 : i = 1, \ldots, 7\})$$

is successive too.

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