On Viable Therapy Strategy for a Mathematical Spatial Cancer Model Describing the Dynamics of the Malignant and Healthy Cells

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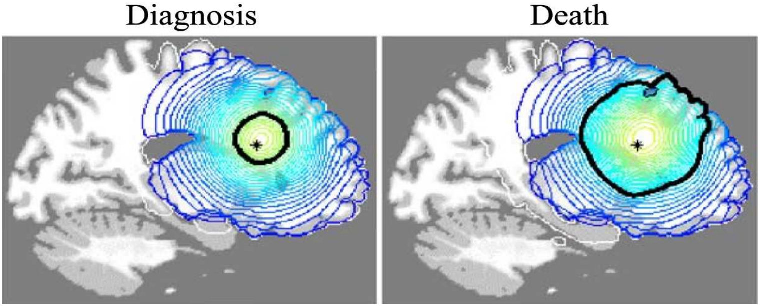
Motivation



K.Swanson et al., Virtual and real brain tumors: using mathematical modeling to quantify glioma growth and invasion, 2003

Usual Actors in Mathematical Cancer Modelling

- $c(x,t)$ or $c(t)$ the density of cancer cells ,
- $n(x,t)$ or $n(t)$ the density of normal cells,
- $h(x,t)$ or $h(t)$ the concentration of the drug
  (in dependence on the position and time or only time)

Usual optimization aim: To minimize c

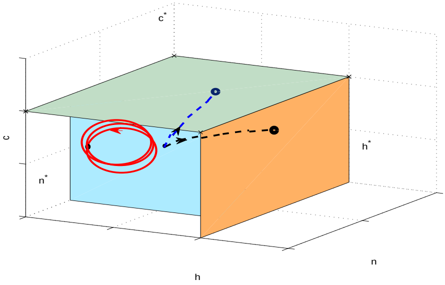
What is in Fact Important?

To keep the patient alive for a maximal long period of time!
To define the Viable Domain V:

$$c \leqslant c^*, \; n \geqslant n^*, \; h \leqslant h^*.$$

and for the total amount of the drug $\leqslant Q$.

Possible Strategy



To find cyclic (or quasi cyclic) trajectories in domain V means potential possibility to control the illness applying a regular treatment therapy

Statement of the Control Problem

To find such therapy strategy from some set S

- which maximizes the total response time of trajectory of the system in the viable domain

$$T_V \longrightarrow \max$$

- provided realization of the restriction on total amount of the drug (or maximal concentration)

The Control Problem Considered

R.Gatenby, A change of strategy in the war on cancer, Nature, 2009

Consider a usual ODE-Model for Cancer

$$\begin{aligned}\frac{dc(t)}{dt} &= f_1(c(t)) - k_1 c(t) g(h),\\ \frac{dn(t)}{dt} &= f_2(n(t)) - k_2 n(t) g(h) - l_1 \varphi(c,n),\\ \frac{dh(t)}{dt} &= -\gamma_h h(t) - (\varepsilon_1 c(t) + \varepsilon_2 n(t)) h(t) + u(t).\end{aligned}$$

with the initial conditions

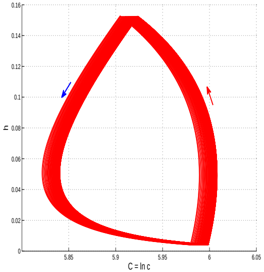
$$c(0) = c_0,\ n(0) = n_0,\ h(0) = h_0;$$

and the constraint

$$\int_0^{T_V} h(t)\, dt \leqslant Q.$$

An Almost Periodical Treatment Strategy in the Case of the ODE-Model

Рис. : **An 'almost periodical' strategy with a small declination in** $\overline{c} = \ln c$**.** $k_1 = 0.105;\ k_2 = 0.054;\ q = 0.07;\ \tau_1 = 3.4;\ \tau_2 = 12.$



Description of the Model

- Let $D \subset \mathbb{R}^m$, $m = 2, 3$, $t \geqslant 0$ be a bounded domain of area (or volume) S with a smooth boundary Γ, ν be the outer normal unit vector to Γ,
- $c(x, t)$ denotes the density of cancer cells,
- $n(x, t)$ denotes the density of normal cells,
- $h(x, t)$ denotes the concentration of the drug in dependence of the position and time, respectively,
- $$d_c(x) = \begin{cases} d_g, & \text{if } x \text{ belongs to grey matter,} \\ d_w, & \text{if } x \text{ belongs to white matter} \end{cases}$$

  with $d_g, d_w \in \mathbb{R}^{>0}$ denotes the diffusion coefficient of cancer cells
- d_n, d_h are the diffusion coefficients of normal cells and the medicine, respectively,
- γ_h is the dissipation rate of the therapeutic agent

Mathematical Model of Glioma

$$
\begin{aligned}
\frac{\partial c(x,t)}{\partial t} &= f_1(c(x,t)) + \nabla\left(d_c(x)\nabla c(x,t)\right) - k_1 c(x,t)g(h),\\
\frac{\partial n(x,t)}{\partial t} &= f_2(n(x,t)) + d_n\Delta n(x,t) - k_2 n(x,t)g(h) - \alpha\varphi(c,n),\\
\frac{\partial h(x,t)}{\partial t} &= -\gamma_h h(x,t) + d_h\Delta h(x,t) + u(x,t).
\end{aligned}
$$

Initial Conditions:

$$c(x,0) = c_0(x) > 0,\ n(x,0) = n_0(x),\ h(x,0) = h_0(x);$$

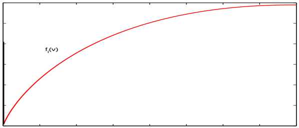
Boundary Conditions:

$$\left.\frac{\partial c(x,t)}{\partial \nu}\right|_\Gamma = 0,\ \left.\frac{\partial n(x,t)}{\partial \nu}\right|_\Gamma = 0,\ \left.\frac{\partial h(x,t)}{\partial \nu}\right|_\Gamma = 0;$$

Possible Descriptions of Proliferation Laws

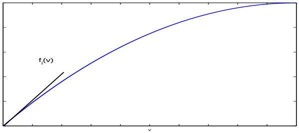
- The Gompertz's Law:

$$f_i(v) = \rho_i v(1 - \beta_i \ln v), \ \ v \geqslant 0$$



- The Logistic Law:

$$f_i(v) = \rho_i v(1 - \beta_i v), \ \ v \geqslant 0$$



Description of the Therapy, Damage and Competition Functions

- The Therapy Function for Cancer Cells and the Damage Function to Normal Cells:

$$g(h) = \frac{h}{a_0 + h}, \; a_0 > 0$$

- The Competition Function:

$$\varphi(c, h) = \frac{cn}{b_0 + c}, \; b_0 > 0$$

Values of Parameters of the Model Considered

parameter	notation	value
diffusion of cancer cells	d_g	1.3×10^{-3} cm^2/day
diffusion of cancer cells	d_w	5×10^{-3} cm^2/day
diffusion of drug	d_h	0.386×10^{-2} cm^2/day
diffusion of normal cells	d_n	1.0×10^{-3} cm^2/day
drug dissipation	γ_h	0.0347
proliferation of cancer cells	ρ_1	0.012 day^{-1}
saturation of cancer cells	β_1	0.0819
proliferation of normal cells	ρ_2	0.006 day^{-1}
saturation of normal cells	β_2	0.0869
cancer domain area	S_D	6×6 cm^2

Definition of the Viable Domain

$$\overline{n(t)} = \int\limits_D \ln n(x,t)\,dx,\ \ \overline{c(t)} = \int\limits_D \ln c(x,t)\,dx. \tag{1}$$

$c^* > 0$ denotes the restriction on the total number of malignant cells (upper limit),
$n^* > 0$ the restriction on the total number of normal cells (lower limit)

Definition

If the solutions $n(x,t)$, $c(x,t)$ of the PDE system considered satisfy for all t the following integral inequalities:

$$\overline{n(t)} \geqslant n^*,\ \ \overline{c(t)} \leqslant c^*. \tag{2}$$

then we say that the numbers of malignant and normal cells are in the viable domain V bounded by the parameters n^* and c^*.

The Class of Simple Therapy Strategies

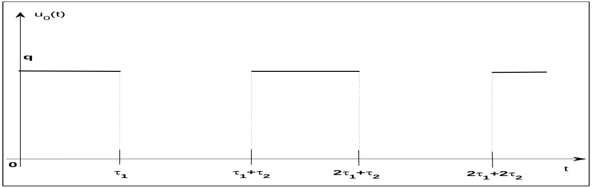
Definition

Let $D_0 \subseteq D, q > 0, \tau_1 > 0, \tau_2 > 0$. We will say that a control function $u(x,t)$ belongs to the class of simple therapy strategies ($\mathbf{S}$) if it has the form

$$u(x,t) = \chi(x)u_0(t),$$

where

$$u_0(t) = \begin{cases} q, & 0 \leqslant t \leqslant \tau_1; \\ 0, & \tau_1 \leqslant t \leqslant \tau_1 + \tau_2; \end{cases} \quad \chi(x) = \begin{cases} 1, & x \in D_0; \\ 0, & x \notin D_0; \end{cases}$$



Statement of the Control Problem

To find the control function $u(x,t)$ in the class of simple tharapy strategies such that response time T in the viable domain V bounded by the parameters n^* and c^* (survival time) will be maximal under the restriction on cumulative amount of chemotherapeutic agent during the whole therapy process:

$$\int_0^T \int_D h(x,t)\,dx \leqslant Q. \tag{3}$$

where $Q > 0$

Existence of Viable Therapy Strategies

Let $C(t)$ and $N(t)$ be positive functions defined by

$$C(t) := \frac{\sigma_c}{\rho_1\beta_1}\left(1 - e^{-\rho_1\beta_1 t}\right) + e^{-\rho_1\beta_1 t}\overline{c(0)}, \; N(t) := \frac{\sigma_n}{\rho_2\beta_2}\left(1 - e^{-\rho_2\beta_2 t}\right) + e^{-\rho_2\beta_2 t}\overline{n(0)}$$

where $\sigma_c, \sigma_n, \rho_1, \beta_1, \rho_2, \beta_2, \overline{c(0)}, \overline{n(0)}$ some positive constants which can be found from the PDE-system considered.

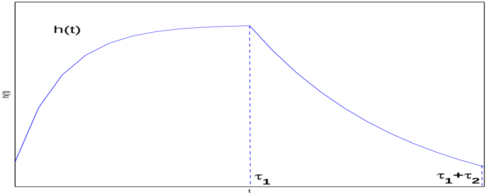
1. If for some $t \geqslant 0$ and some $c^* > 0$ the inequality $C(t) > c^*$ takes place then there is no treatment strategy $u(x,t) \in \Sigma$ that can supply the fulfillment of the viable restriction $\overline{c(t)} \leqslant c^*$.
2. If for any $t > 0$ and some $n^* > 0$ the inequality $N(t) > n^*$ takes place then for any treatment strategy from the set Σ the viable restriction $\overline{n(t)} \geqslant n^*$ is fulfilled.

Explanation of the Property of Inertion

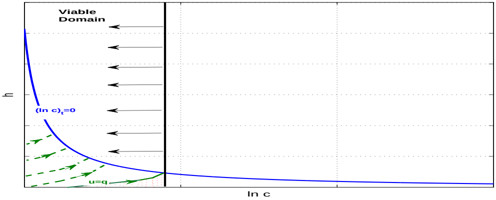
In the case of ODE with

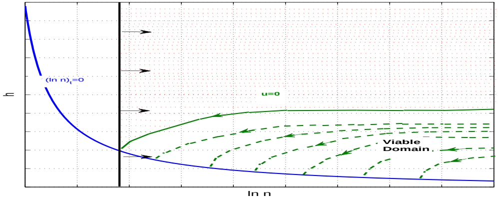
$$u(t) = \begin{cases} q, & 0 \leqslant t \leqslant \tau_1,\ \tau_1 > 0 \\ 0, & \tau_1 \leqslant t \leqslant \tau_1 + \tau_2,\ \tau_2 > 0 \end{cases}$$

we have

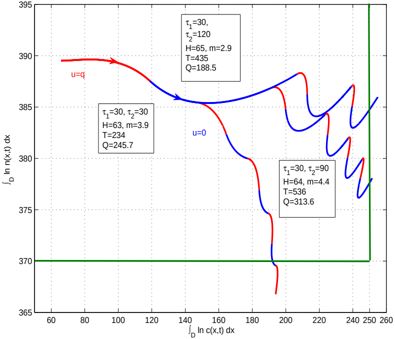


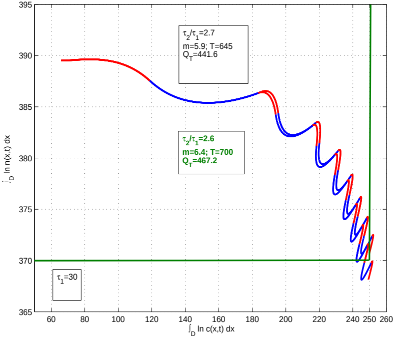
Correction of the Viable Domain due to the Property of Inertion



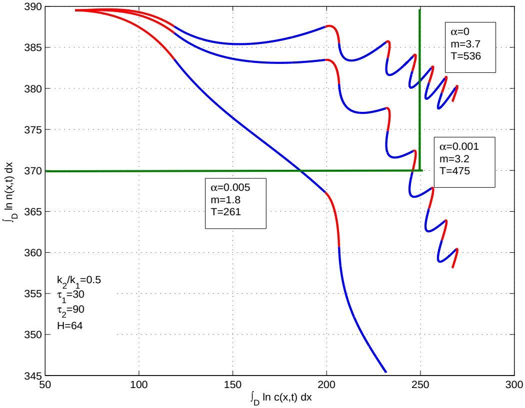


Search $\frac{\tau_2}{\tau_1}$. $Q = \int\limits_D \int\limits_0^T h(x,t)\, dx \leqslant 500$; $\frac{k_2}{k_1} = 0.5$, $\alpha = 0$, $q = 0.002$.





Search α. $\frac{k_2}{k_1} = 0.5$, $\tau_1 = 30$, $\tau_2 = 90$, $q = 0.002$.



For $q = 0.002$ the optimal ratio is $\frac{\tau 2}{\tau 1} = 2.6$

- τ_1 be the time during that $u = q$ takes place ('active control time') and
- τ_2 be the 'passive control time' (i.e. with $u = 0$)

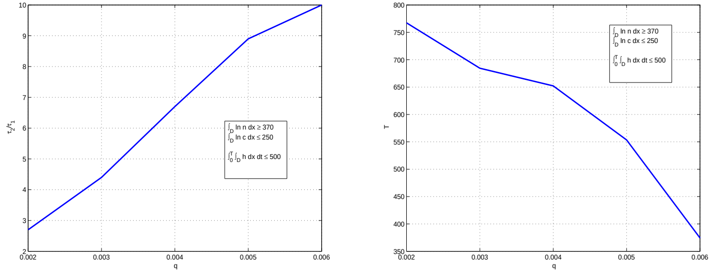
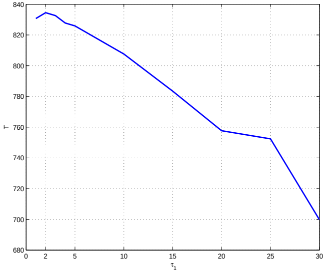


Рис. : For every q the maximum viable time is $T(q)$ (on the right fig.) and it is reached with $\frac{\tau_2}{\tau_1}(q)$ (on the left fig.)

Optimal value $\tau_1 = 2, \ \tau_2 = 5.2 \ (\frac{\tau 2}{\tau 1} = 2.6)$ for $q = 0.002$



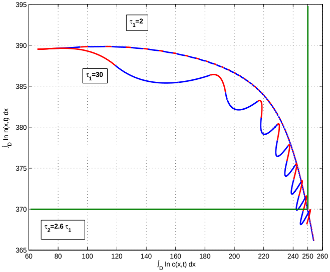
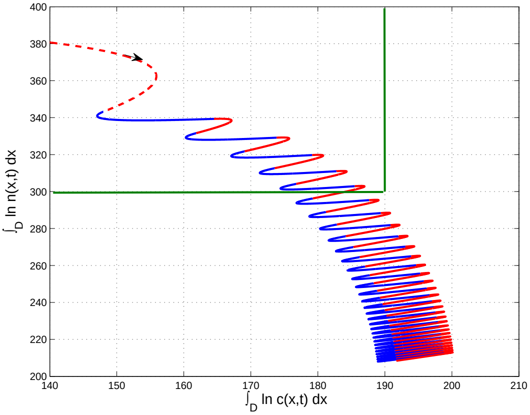


Рис. : For every τ_1 the maximum viable time is $T(\tau_1)$ (on the left fig.)

Existence of Periodical Treatment Strategy Outside of the Viable Domain



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