On a numerical construction of viability sets in the problems of chemotherapy of malignant tumors

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Notations

m be quantity of malignant cells,
h be quantity of drug,
$f(h)$ be a therapy function describing the effect of drug on tumor cells,
$u(t)$ be a restricted control,
T be the given final instance,
M be the maximum quantity of malignant cells in the body compatible with life,
L be the maximum quantity of drug in the body,
Q be the maximum quantity of drug injected into the tumor per unit time.

Mathematical model

The process of interaction between tumor cells and drugs is described by the following model, where time varies within $t \in [0, T]$:

$$\begin{cases} \dfrac{dm}{dt} = g(m) - \gamma m f(h), \quad m(t_0) = m_0, \ \gamma - const > 0, \\ \\ \dfrac{dh}{dt} = -\alpha h + u(t), \quad h(t_0) = h_0, \ \alpha - const > 0. \end{cases} \tag{1}$$

Mathematical model

The tumor can grow according to the following laws:

1. $g(m) = rm - \theta m \ln(m)$ — Gompertz law, r, θ — const > 0,
2. $g(m) = rm\left[1 - \left(\frac{m}{\theta}\right)^{\beta}\right]$ — generalized logistic law, r, θ, β — const > 0.

Restrictions

The set of starting points in the model is considered with the following restrictions:

$$t_0 \in [0, T], \quad 0 < m_0 < M, \quad 0 \leq h_0 \leq L.$$

Let us consider piecewise constant functions as admissible controls:

$$u(\cdot) : [t_0, T] \mapsto [0, Q].$$

It is assumed that the amount of drug introduced into the tumor per unit time is restricted:

$$0 \leq u(t) \leq Q. \tag{2}$$

Therapy function

Consider a piecewise monotone, continuously differentiable therapy function $f(h)$ with the following properties:

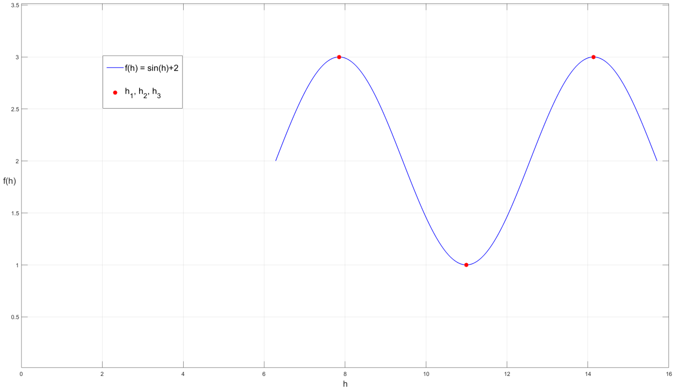
$A1$. The function $f(h)$ is positive definite on $[0, L]$,

$A2$. The function $f(h)$ has two maximum points $\hat{h}_1$ and $\hat{h}_3$ and one minimum point $\hat{h}_2$ such that

$$0 < \hat{h}_1 < \hat{h}_2 < \hat{h}_3 < L, \quad F = \max_{h \in [0,L]} f(h) = f(\hat{h}_1) = f(\hat{h}_3).$$

$A3$. The condition is valid: $0 < \alpha \hat{h}_i < Q, \quad i = 1, 2, 3.$

Example of therapy function



Statement of the problem

The problem of optimal control is to construct an admissible control that minimizes the terminal cost function

1. for Gompertz law:

$$\sigma_1(m(T)) = m^2(T; t_0, m_0, h_0, u(\cdot)) \to \inf_{u(\cdot)}, \tag{3}$$

2. for the generalized logistic law:

$$\sigma_2(m(T)) = m^\beta(T; t_0, m_0, h_0, u(\cdot)) \to \inf_{u(\cdot)}. \tag{4}$$

where $m(t) = m(t; t_0, m_0, h_0, u(\cdot))$, $t \in [t_0, T]$ – solution of the system (1) with initial conditions (t_0, m_0, h_0), generated by the influence of admissible control $u(t)$.

Value function

We introduce the value function in the considered problem, which to each initial state of the system $(t_0, m_0, h_0) \in [t_0, T] \times [0, M] \times [0, L]$ sets the optimal result $Val_i(t_0, m_0, h_0)$ according to (3) and (4).
The value function is as follows

1. for Gompertz law:

$$Val_1(t_0, h_0, m_0) = m_0^{e^{-2\theta(t-t_0)}} exp\left[\frac{2r}{\theta}(e^{-\theta(t-t_0)} - 1) - 2\gamma V(t_0, h_0)\right],$$

2. for the generalized logistic law:

$$Val_2(t_0, h_0, m_0) = \frac{\theta^\beta m_0^\beta e^{-\beta\gamma V(t_0, h_0)}}{\theta^\beta e^{-\beta r(T - t_0)} + \beta m_0^\beta r \int_{t_0}^{T} exp\left[-\beta(r(\tau - t_0) + \gamma V(\tau, h^0(\tau)))d\tau\right]}.$$

Value function

Where $V(t, h)$ there is an optimal result in the following reduced optimal control problem:

$$\frac{dh}{dt} = -\alpha h + u(t), \quad u \in [0, Q], \quad h(t_0) = h_0,$$

$$J_{t_0,h_0}(u(\cdot)) = \int_{t_0}^{T} f(h(t; t_0, h_0, u(\cdot)))dt \to \sup_{u(\cdot)},$$

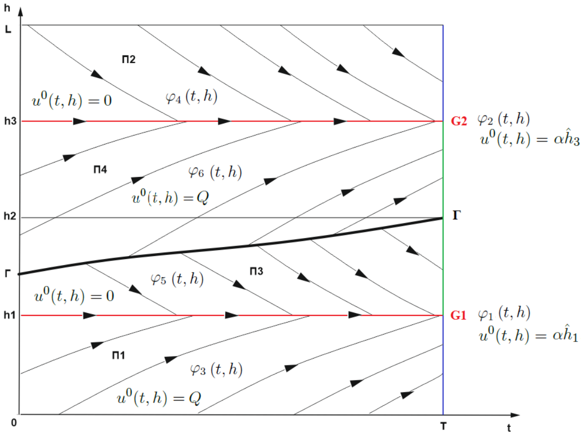
$$(t, h) \mapsto V(t, h) = \sup_{u(\cdot)} J_{t_0,h_0}(u(\cdot)).$$

Optimal synthesis

The optimal synthesis in the considered problem (1), (3) and (1), (4) has the form:

$$u^0(t,h) = \begin{cases} \alpha \hat{h}_1, & (t,h) \in G_1, \\ \alpha \hat{h}_3, & (t,h) \in G_2, \\ Q, & (t,h) \in \Pi_1, \\ 0, & (t,h) \in \Pi_2, \\ 0, & (t,h) \in \Pi_3, \\ Q, & (t,h) \in \Pi_4 \setminus \Gamma. \end{cases}$$

Optimal synthesis



Solvability set

Consider viability sets W_i:

1. In the problem (1), (3) the viability set has the form

$$W_1 = \left\{ (t_0, m_0, h_0) \in [0, T] \times [0, M] \times [0, L] : \mathrm{Val}_1(t_0, m_0, h_0) \leq M^2 \right\},$$

$$M = e^{\dfrac{r - \gamma F}{\theta}},$$

2. In the problem (1), (4) the viability set has the form

$$W_2 = \left\{ (t_0, m_0, h_0) \in [0, T] \times [0, M] \times [0, L] : \mathrm{Val}_2(t_0, m_0, h_0) \leq M^\beta \right\},$$

$$M = \theta \left(1 - \frac{\gamma F}{r} \right)^{\dfrac{1}{\beta}}.$$

Theorem

For $W \in \{W_1, W_2\}$ the following statements are true:
1. For any points $(t_0, m_0, h_0) \in W$ it is true that $m_0 \leq M$.
2. The set W is weakly invariant with respect to the differential inclusion $\dot{w} \in Y(w)$, where

$$w = (t, m, h) \mapsto Y(w) = \Big(1,\ g(m) - \gamma m f(h),\ -\alpha h + [0, Q]\Big).$$

3. For any point $w_0 = (t_0, m_0, h_0) \notin W$ and for any measurable function $u(\cdot) : [t_0, T] \mapsto [0, Q]$ there is such a point in time $t_* \in (t_0, T)$, that the inequality holds:

$$m(t_*; t_0, h_0, m_0, u(\cdot)) > M.$$

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THANKS FOR ATTENTION!