Optimal bang-bang control in coupled dynamical systems

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Abstract:

In many dynamical systems, the behavior can be changed or even optimized by a suitably chosen external parameter. However, the complexity of the dynamics grows significantly if coupled systems are considered. As an example we here refer to the coupled dynamics of cancer cells and healthy cells during fractionated radiation therapy. In this method the iterative sequence of radiation and breaks leads to a destruction of tumor cells while keeping the destruction in the surrounding healthy cells at a low level. Thereby one takes advantage of the fact that the healthy cells recover to a higher degree in the time interval between radiative treatments. The resulting control problem is solved using bang-bang control, i.e. the dosis rate switches between a lower and an upper bound.

Keywords: control theory, dynamical systems

1. Introduction

The physical and chemical interactions between cell systems during radiation therapy can be described on a very fundamental level using coupled differential equations. Our model is based on equations for intact cells and tumor cells. For each cell type we use two equations: a first equation to describe the dynamics of intact cells and another equation for the dynamics of affected cells. The model includes rates for the reduction due to radiation, death rates to describe the fraction of irrepairable cells leaving the system, a growth rate describing tumor growth and a recovery rate describing a partial recovery of cells hit by radiation. The recovery term coupling the equations takes into account that a part of the cells that are capable of being repaired may heal. This effect is particular important in fractionated radiation theory since the healthy cells recover with higher probability in the irradiation pause between successive treatments than the cancer cells. The problem is solved with methods of control theory using optimization to find a minimum of a suitably chosen functional. The condition to optimize such a system is a bang-bang control scheme, i.e. the control parameter represented by the dosis rate is either cero (no radiation) or maximum (radiation).
This paper is organized as follows: In section 2, the theoretical description is summarized, section 3 explains the usage of COMSOL, sections 4, 5 and 6 show simulation results in dependence on number of initial cancer cells, recovery rates and tumor growth, section 7 concludes the article.

2. Governing equations

Finding the optimum switching times in fractionated radiation theory requires a suitable numerical approach. Mathematical descriptions and simulations have been in the focus of many papers [1—5]. The sensitivity of the set of equations to parameter changes is very high leading to challenges in optimization algorithms.
We here present results of optimized control of the cancer growth on the basis of the COMSOL optimization module.
The model equations describe the dynamics of cancer cells and healthy cells (e.g. in the environment of a tumor) during radiative treatment in the linear response regime. They take into account, in particular, the partial recovery of cells affected by the radiation, a different sensitivity of tumor and healthy cells to radiation as well as a tumor growth rate and death rates. The radiation is described by a dosis rate which can be switched on (corresponding to a maximum dose) and off (corresponding to no treatment) according to fractionated radio therapy. We use the following equations

$$\begin{aligned}
\dot{x}_1^H(t) &= -a^H \cdot u(t) \cdot x_1^H(t) + c^H \cdot x_1^H(t) + \gamma^H \cdot x_2^H(t) \\
\dot{x}_2^H(t) &= a^H \cdot u(t) \cdot x_1^H(t) - b^H \cdot u(t) \cdot x_2^H(t) - \gamma^H \cdot x_2^H(t) \\
\dot{x}_1^T(t) &= -a^T \cdot u(t) \cdot x_1^T(t) + c^T \cdot x_1^T(t) + \gamma^T \cdot x_1^T(t) \\
\dot{x}_2^T(t) &= a^T \cdot u(t) \cdot x_2^T(t) - b^T \cdot u(t) \cdot x_2^T(t) - \gamma^T \cdot x_2^T(t)
\end{aligned}$$

where x_1^H and x_2^H are the number of intact (1) and affected (2) healthy cells, x_1^T and x_2^T are the

number of intact (1) and affected (2) tumor cells. a^H, a^T are damage rates, b^H, b^T death rates, c^G, c^T growth rates and γ^H, γ^T recovery rates. $u(t)$ is the dosis rate. We use the following parameters for the rates: maximum dosis rate u_{max}= 0.1 (for better visualization multiplied with a factor of 1000 in the figures), recovery rate for healthy cells $1 \cdot 10^{-3}$, recovery rate for tumor cells $3 \cdot 10^{-4}$, damage rate for healthy cells 0.2 and for tumor cells (corresponding to the higher sensitivity to radiation) 0.3, death rates for healthy cells and for tumor cells 0.03, and growth rate for the tumor $1 \cdot 10^{-3}$. Please note that any parameter set is generally possible.
We search a time plan for the dosis rate that significantly reduces the tumor cells while keeping the damage to healthy cells on a moderate level.

3. Use of COMSOL Multiphysics

We use the optimization module of COMSOL MULTIPHYSICS® to set up our coupled model equations. The functional depending on the state vector (including all cell cell types), time, and dosis rate) to be optimized is

$$F(T, x, u) := -\alpha_1 x_1^H(T_{final}) + \alpha_2 x_1^T(T_{final})$$

Without loss of generality we here set α_1 to 0,3 and α_2 to 0,7, i.e. the reduction of the cancer cells is more important than the protection (maximation) of healthy cells. Please note that any weighting of the two contributions is possible.
The simulations using the optimization module allows us to find, for a given parameter system the best time plan for radiative treatment that minimizes the damage to healthy cells by significant reducing the cancer cells, i.e. minimizing the functional given above. We here use a limit for the dosis rate leading to a dynamic switching between minimum (no radiation) and maximum dosis rate. However, other conditions such as number of switching times or boundaries for the duration of the radiative treatment can be included in a similar way.
In the following we show results of the simulations. We thereby focus on the influence of number of initial cancer cells, the influence of recovery rate and the influence of the tumor growth rate.

4. Influence of number of initial cancer cells

In the simulation we use start values for the cancer cells and the healthy cells. We thereby include two effects: We include the fact that a different number of cancer cells may be hit by the radiation and additionally we include that healthy cells surrounding the tumor may also be affected by radiation. In a first step we thus set the number of healthy cells to 300 and vary the number of cancer cells. We would like to emphasize that any ratio and any absolute value may be considered since the rates directly scale with the number of cells.

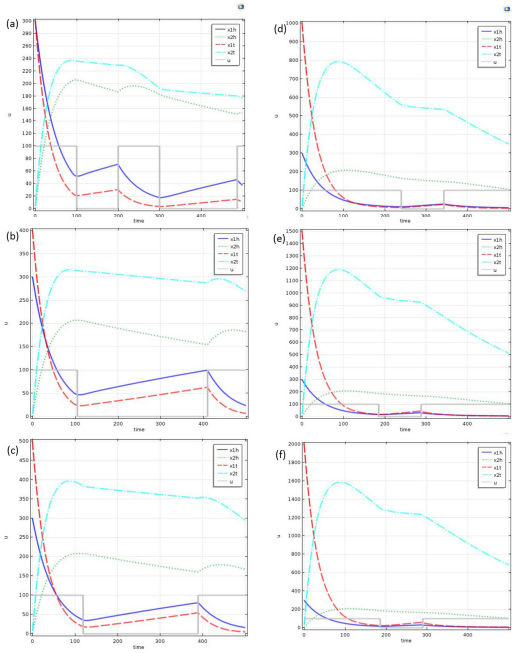

Figure 1: dynamics of cancer cells and healthy cells for an optimized radiation time plan in dependence on initial value for the cancer cells: a) 300, b) 400, c) 500, d) 1000, e) 1500, f) 2000

As can be seen in Fig. 1, an increase in the number of cancer cells (while keeping the healthy cells to a constant value) strongly affects the optimum time plan.

5. Influence of recovery rate

For a given set of parameters the difference in the capability to recover is the key to the efficiency of fractionated radiation therapy. If the difference in the recovery rate of healthy and cancer cells is large, the healthy cells can recover much faster in the breaks between successive radiative treatments. As a consequence the time interval with no radiation can be shorter leading to an improved reduction of cancer cells. Fig 2 summarizes simulation results for a recovery rate of cancer cells of $3{\cdot}10^{-4}$ and a variable recovery rate of healthy cells. The results demonstrate that the optimum time plan for the dosis rate may be different, the minimum of the functional is thus strongly dependent on the different rates.

Please note that in the given simulations the death rates for both cell types are chosen small enough so that a recovery is generally possible, i.e. a sufficiently high number of affected cells x_2^H and $x_2^T$is still available in the cell systems acting as a reservoir. For high death rates the recovery effect would be much smaller due to the reduced number of cells that can still recover.

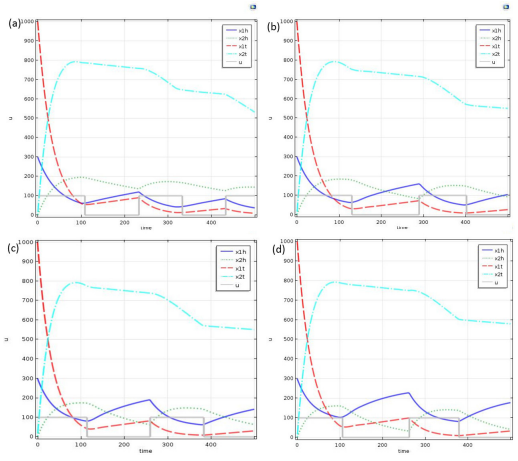

Figure 2: dynamics of cancer cells and healthy cells for an optimized radiation time plan in dependence on recovery rate for the healthy cells: a) $3{\cdot}10^{-3}$, b) $5{\cdot}10^{-3}$, c) $7{\cdot}10^{-3}$, d) $1{\cdot}10^{-2}$

6. Influence of cancer growth

For a demonstration of the influence of the cancer growth we vary the cancer growth rate keeping the remaining parameters constant. Fig. 3 visualizes the change in cell dynamics and the calculated optimum dosis rate. For the simulations depicted in the left row ((a)—(c)) the values were set to quite low values.

The results show that an optimization yields different durations of radiation exposure periods and breaks between successive treatments. The situation changes for larger values (right row, (e)—(f)). The adjustment of the dosis rate to an very high cancer growth rates is limited by the fact that the damage to the healthy cells must – as part of the functional – stay at a tolerable level. We would like to note that depending on the values and boundaries chosen for all parameters the quantitative and qualitative behavior may look different.

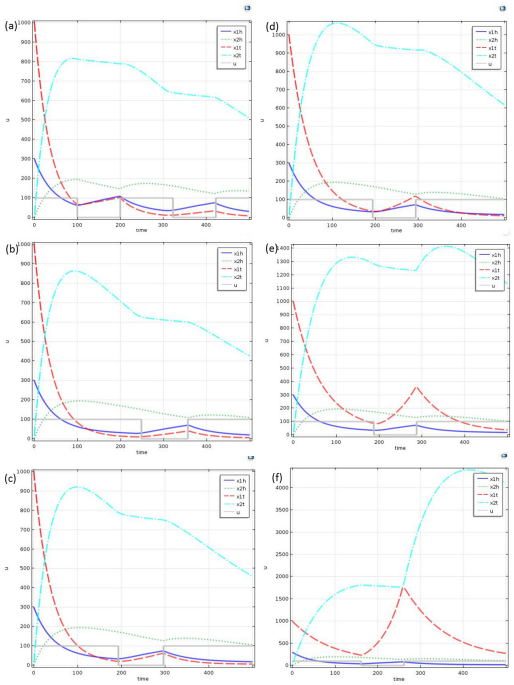

Figure 3: dynamics of cancer cells and healthy cells for an optimized radiation time plan in dependence on growth rate: a) $2{\cdot}10^{-3}$, b) $4{\cdot}10^{-3}$, c) $6{\cdot}10^{-3}$, d) $1{\cdot}10^{-2}$, e) $1.5{\cdot}10^{-2}$, f) $2{\cdot}10^{-3}$

7. Conclusions

We investigated the dynamics of cancer cells and healthy cells during fractionated radiation theory. On the basis of a bang-bang control scheme using the dosis rate as control parameter we explored for an optimized radiation time plan the dependence of the dynamics of number on cancer cells, recovery rates and cancer growth rate.
Our model description is very general and can be used for various parameter sets. Restrictions to the time plan, duration of radiation, maximum dosis rate etc. can be included by suitable boundary conditions allowing for a detailed optimization for a given situation. The model may thus be of importance for the future development of time plans in cancer treatment. An extension of the model description to consider combined therapies (i.e. radiation therapy and infusion) is also straight forward and will be considered in future investigations.

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