Model Predictive Control for Optimal Treatment
in a Spatial Cancer Game*

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Abstract— This work focuses on modeling tumorigenesis as a spatial evolutionary game and on finding optimal cancer treatment using a model predictive control approach. Extending a nonspatial cancer game from the literature into a spatial setting, we consider a solid tumor composed of cells of two different types: proliferative and motile. In our agent-based spatial game, cells represent vertices of an undirected dynamic graph where a link between any two cells indicates that these cells can interact with each other. A focal cell can reproduce only if it interacts with another cell, where the proliferation probabilities are given by the fitness matrix of the original nonspatial game. Without treatment, the cancer cells grow exponentially. Subsequently, we use nonlinear model predictive control to find an optimal time-varying treatment, with an objective representing a trade-off between minimization of the tumor mass and treatment toxicity. As for example androgen-deprivation treatment in metastatic castrate-resistant prostate cancer, this treatment is assumed to decrease the chances for interaction between the cancer cells and hereby decrease cells' proliferation rate. In case studies, we show that the optimal treatment often leads to a decrease of the tumor mass. This suggests that model predictive control has a high potential in designing cancer treatments.

Keywords: cancer modeling and treatment, spatial evolutionary game theory, nonlinear model predictive control, dynamic graphs.

I. INTRODUCTION

Tumor is a complex ecosystem containing cancer cells, normal cells, blood vasculature, inter-cellular spaces, and various nutrients [1]–[4]. Within this ecosystem, cancer cells interact with each other, in order to proliferate and survive [5]. While tumors are often modeled non-spatially, biopsies, histological samples and magnetic resonance images provide all spatial information on tumor characteristics [6]. Pathologists often measure and score spatial distributions of cancer cell types, vasculature, immune cells, and other tumor properties. Cancer biologists often study spatial heterogeneity within tumors [7]–[9]. This heterogeneity likely has significance for tumor progression, metastases and patient prospects.

Spatial models of cancer may take the form of diffusion processes framed as partial differential equations models [10], or the models may be agent based [1], [8], [11]–[14]. As each cancer cell's proliferation is influenced by its type and the types of other cancer cells, the evolutionary dynamics of cancer is game theoretic [15]. *Evolutionary game theory* (EGT) provides an excellent modeling tool for analysis of complex tumors that include several interacting cancer cell types. When there are a finite number of different possible strategies among the cancer cells, then the evolutionary dynamics can be modeled using *replicator dynamics* (RD) [16], [17]. While RD is non-spatial, recent research has focused on its extension into spatially explicit scenarios [1], [18]–[21]. Both the evolutionary dynamics and subsequent equilibria may change dramatically when space is made explicit [1], [22]–[26].

Inspired by the added realism when moving a known nonspatial game into space, in this paper we extend an evolutionary game between two different cancer types (proliferative and motile) from [27] into a spatial agent-based game. We use a dynamic graph to model the interaction and proliferation of cancer cells. All cells connected to a focal cell belong to its neighborhood (microenvironment) and can be interacted with. The probability for a cancer cell to proliferate when interacting with its neighbor of any type is given by a fitness matrix from [27]. If the focal cell proliferates, it produces a daughter cell of the same type, which is then placed into the field and connected to all existing cells in this field.

Moreover, for this newly developed model we seek an optimal treatment using a model predictive control (MPC) approach [28]–[30]. MPC has become the accepted standard for complex constrained multivariable control problems [28], [29]. The treatment is assumed to decrease cells' ability to interact with their neighbors as it removes a portion of links between cells of certain types. In fact, it is believed that some of androgen-deprivation therapies in metastatic castrate-resistant prostate cancer have this effect [31], [32]. MPC is a promising strategy for finding optimal cancer treatment as shown in other recents works [33]–[35]. Here we present a combination of modeling the tumorigenesis as an evolutionary game over a dynamic graph and finding its treatment using MPC. To the best of our knowledge, there is no existing research combining these two elements.

The remainder of this paper is organized as follows. In Section II, the cancer game played over the dynamic graph and the treatment vector are introduced. In Section III, a nonlinear MPC for finding the optimal treatment is presented. In Section IV, the MPC approach is tested on case studies

differing in the prespecified maximal tolerable treatment dose. Finally, the conclusions of this work and possible future steps are discussed in Section V.

II. PROBLEM DESCRIPTION

Consider a population of cancer cells that evolve in time $\mathcal{N}(k) = \{1, 2, \ldots, N(k)\}$, which is composed of two different cell types: *proliferative* and *motile*, and denoted by $\mathcal{P}(k) = \{1, 2, \ldots, P(k)\}$ and $\mathcal{M}(k) = \{1, 2, \ldots, M(k)\}$, respectively, with $\mathcal{P}(k) \cup \mathcal{M}(k) = \mathcal{N}(k)$, $\mathcal{P}(k) \cap \mathcal{M}(k) = \emptyset$. Each cell $i \in \mathcal{N}(k)$ belongs to either $\mathcal{P}(k)$ or $\mathcal{M}(k)$. For detailed characteristics of each of the two groups of cells, see [27]. The probability of proliferation of types $\mathcal{P}$ and $\mathcal{M}$ is given by the following time-constant fitness matrix $\mathbf{A} = [a_{rs}] \in \mathbb{R}^{2\times 2}$, which is taken from [27] and defined as

$$\begin{array}{cc} & \mathcal{P} \quad\;\; \mathcal{M} \\ \begin{array}{c} \mathcal{P} \\ \mathcal{M} \end{array} & \left[\begin{array}{cc} \frac{b}{2} & b \\ b-c & b-\frac{c}{2} \end{array} \right]. \end{array} \tag{1}$$

Here a_{rs} defines the probability for a focal cell of type r to produce a daughter cell of the same type after interacting with a cell of type s from its microenvironment. The following inequalities (also from [27]) have to be satisfied:

$$0 \le b \le 1, \qquad 2(b-1) \le c \le b. \tag{2}$$

Depending on the values of b and c, *evolutionary stable strategies* (ESSs [36]) for the fitness matrix given by (1) will fit into one of the three following cases:

1) If $b < 2c$ and $c > 0$, we have a pure-strategy ESS with only proliferative cells.
2) If $b > 2c$ and $c < 0$, we have a pure-strategy ESS with only motile cells.
3) If $b > 2c$ and $c > 0$, we have a mixed-strategy ESS at $\left(\frac{c}{b-c}, \frac{b-2c}{b-c} \right)$.

While in [27] the game was analyzed as a nonspatial evolutionary game, we will extend this standard case into a spatial agent-based game with cancer treatment.

Example 1 *For the particular case of $b = 0.8$, $c = 0.2$, matrix $\mathbf{A}$ is given by*

$$\mathbf{A} = \begin{bmatrix} a_{PP} & a_{PM} \\ a_{MP} & a_{MM} \end{bmatrix} = \begin{bmatrix} 0.4 & 0.8 \\ 0.6 & 0.7 \end{bmatrix}, \tag{3}$$

and the corresponding matrix game has an ESS at $\left(\frac{1}{3}, \frac{2}{3} \right)$.

A. Modeling tumor growth and treatment

In this work, we will model the interactions and proliferation of cancer cells as a spatial game on a dynamic graph. The tumor at time step k is represented by an undirected graph $(\mathcal{N}(k), \mathcal{E}(k))$, where $\mathcal{N}(k)$ and $\mathcal{E}(k) \subseteq \mathcal{E}^{\mathcal{N}}(k) = \mathcal{N}(k) \times \mathcal{N}(k)$ are the set of cancer cells in the system and the set of links between these cells, respectively, at time k. Only if there is a link between cells i and j, these cells belong to each other's neighborhood (microenvironment) and can therefore interact with each other. A set $\mathcal{E}_{rs}(k)$ of links connecting cells of type r with cells of type s at time s, where $r, s \in \{\mathcal{P}, \mathcal{M}\}$, satisfies $\bigcup_{\forall rs} \mathcal{E}_{rs}(k) = \mathcal{E}(k)$. Therefore, $\mathcal{E}(k) = \mathcal{E}_{\text{PP}}(k) \cup \mathcal{E}_{\text{PM}}(k) \cup \mathcal{E}_{\text{MM}}(k)$.

B. Interaction between cancer cells

We specify rules regarding cell death, interaction, and proliferation, which occur in generations. During one generation all alive cells are selected in a random order as focal cells to undergo the following steps:

1) A focal cell survives with probability ξ. If the cell dies, it will not undergo any further actions.
2) A focal cell interacts with a random neighbor connected to it in the graph $(\mathcal{N}(k), \mathcal{E}(k))$. The probability that the cell of type i will produce a daughter cell of the same type when interacting with e neighbor of type j is given by element a_{ij} of the fitness matrix (1).

Once all cells have been selected as focal cells, all dead cells are removed from the field, together with all their links, and all daughter cells will be placed into the field and connected to all alive cells. The next generation, corresponding to the next time step, begins.

C. Treatment

Inspired by androgen deprivation therapy in metastatic castrate-resistant prostate cancer and other therapies targeting ability of cancer cells to profit from interactions with other types of cancer cells [31], [32], [37], [38], we assume that a treatment at time k removes a subset of links in $\mathcal{E}(k)$, leaving only their subset $\Lambda(k) \subseteq \mathcal{E}(k)$ in the system. We assume that the treatment is applied only inbetween generations and that it affects the tumor immediately. The final cancer network configuration at the end of time step k is therefore given by $(\mathcal{N}(k), \Lambda(k))$. It is impossible to target interaction ability of specific cancer cells and, therefore, the treatment will be defined by vector

$$\mathbf{t}(k) = [t_{\text{PP}}(k), t_{\text{PM}}(k), t_{\text{MM}}(k)]^{\text{T}}, \tag{4}$$

where each component $t_{rs}(k)$ refers to the percentage of links of type rs being removed at time step k. Therefore,

$$|\Lambda_{rs}(k)| = t_{rs}|\mathcal{E}_{rs}(k)|. \tag{5}$$

We assume that these links are removed at random. Additionally, once a link is removed, it cannot be reconnected. In Section III, we will explain how the time-varying treatment will be optimized subject to certain constraints, using MPC.

Example 2 *Consider the population of cancer cells $\mathcal{N}(\hat{k}) = \{1, 2, 3, 4, 5\}$ at time step $k = \hat{k}$, with the first three cells being proliferate and the latter two being motile. Let $\mathcal{E}(\hat{k}) = \{\text{I}, \text{II}, \text{III}, \text{IV}, \text{V}, \text{VI}\}$, as shown in Fig. 1a, with $|\mathcal{E}_{\text{PP}}| = 2$, $|\mathcal{E}_{\text{PM}}| = 3$, $|\mathcal{E}_{\text{MM}}| = 1$. Let the treatment vector be chosen as $\mathbf{t}(\hat{k}) = \left[\frac{1}{2}, \frac{1}{3}, 0 \right]^{\text{T}}$.*

After applying the treatment, network $(\mathcal{N}(\hat{k}), \mathcal{E}(\hat{k}))$ is reduced to $(\mathcal{N}(\hat{k}), \Lambda(\hat{k}))$, with $\Lambda(\hat{k})$ being any topology that verifies (5), i.e.,

$$|\Lambda_{\text{PP}}| = 1, \quad |\Lambda_{\text{PM}}| = 1, \quad |\Lambda_{\text{MM}}| = 1. \tag{6}$$

From 64 *possible topologies that can be obtained from* $\mathcal{E}(\hat{k})$, *the only six topologies that satisfy* (6) *are shown in Fig. 1b (in lexicographical order). Note that we will consider all these topologies equivalent from the control viewpoint.*
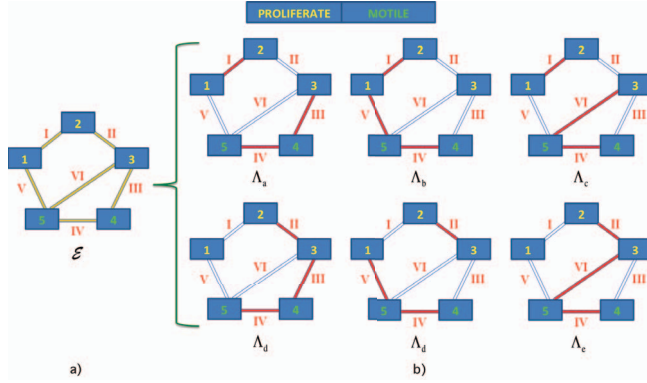

Fig. 1.   Topologies that correspond to the treatment in Example 2

III. MODEL PREDICTIVE CONTROL

Model predictive control (MPC) uses an explicit process model to predict this process future evolution starting from the current system state along a pre-specified prediction horizon N_{p}. This way, at each time instant, an optimal control problem is solved to calculate an optimal input sequence over the horizon. Only the first element of the input sequence, which corresponds to the current time step, is applied and the rest of the elements is discarded. This is repeated at each time step following a receding horizon strategy.

In this section, a nonlinear centralized MPC controller is considered to calculate the optimal treatment. Fig. 2 illustrates the MPC algorithm.
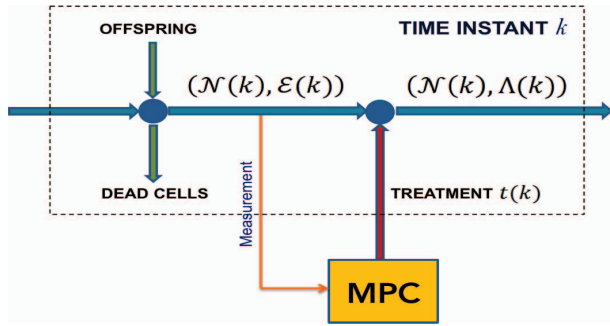

Fig. 2.   Control scheme for finding optimal treatment at time step k

A. Macroscopic cancer model

In this section, we introduce a model for the process of interaction among cells described in Section II. The following matrix captures the decrease of the probability of reproduction of fitness matrix $\mathbf{A}$ given by (1), as a consequence of the treatment:

$$
\begin{aligned}
\mathbf{A}_\Lambda(k) &= \begin{bmatrix} a_{\mathrm{PP}}^\Lambda(k) & a_{\mathrm{PM}}^\Lambda(k) \\ a_{\mathrm{MP}}^\Lambda(k) & a_{\mathrm{MM}}^\Lambda(k) \end{bmatrix} \\
&= \begin{bmatrix} a_{\mathrm{PP}}(1 - t_{\mathrm{PP}}(k)) & a_{\mathrm{PM}}(1 - t_{\mathrm{PM}}(k)) \\ a_{\mathrm{MP}}(1 - t_{\mathrm{PM}}(k)) & a_{\mathrm{MM}}(1 - t_{\mathrm{MM}}(k)) \end{bmatrix}.
\end{aligned}
\tag{7}
$$

Here each element $a_{rs}^\Lambda(k)$ refers to the proliferation probability of a cell of type r when interacting with a cell of type s after the treatment is applied. Without the treatment all the links stay available and, consequently, $\Lambda(k) = \mathcal{E}(k)$, and $\mathbf{A}_\Lambda(k) = \mathbf{A}, \forall k$.

Considering (7), the following population macroscopic nonlinear model is used by the controller to estimate the number of cells of each type:

$$
\begin{aligned}
P(k + 1) &= \xi\left(P(k) + N(k)\left[\frac{P^2(k)}{N^2(k)} a_{\mathrm{PP}}^\Lambda(k) + \frac{P(k)M(k)}{N^2(k)} a_{\mathrm{PM}}^\Lambda(k) \right] \right), \\
M(k + 1) &= \xi\left(M(k) + N(k)\left[\frac{M^2(k)}{N^2(k)} a_{\mathrm{MM}}^\Lambda(k) + \frac{P(k)M(k)}{N^2(k)} a_{\mathrm{MP}}^\Lambda(k) \right] \right),
\end{aligned}
\tag{8}
$$

with $P(k) + M(k) = N(k)$, where a_{rs}^Λ is given by $\mathbf{A}_\Lambda$ in (7), and with ξ being a scalar constant that refers to the portion of cells that survive in each generation.

Note that model (8) is calculated by making a probabilistic forecast based on the process described in Section II.

Remark 1 *Alternatively, the evolution of the system can be modeled by the well-known replicator dynamics [17], [39]. A generalization of the discrete-time replicator equation that considers the treatment is given by*

$$
\mathbf{x}(k+1) = \mathbf{x}(k) + \mathbf{x}(k) \circ (\mathbf{A}_\Lambda \mathbf{x}(k) - \mathbf{e}\, \mathbf{x}^{\mathrm{T}}(k)\mathbf{A}_\Lambda \mathbf{x}(k)), \tag{9}
$$

where $\mathbf{x}(k) = \left[\frac{P(k)}{N(k)}, \frac{M(k)}{N(k)} \right]^{\mathrm{T}}$, $\mathbf{e} = [1, 1]^{\mathrm{T}}$, *with operator* $\circ$ *denoting the Hadamard or element-wise product, and with* $\mathbf{A}_\Lambda$ *given by* (7).

Naturally, the macroscopic model could be also replaced by patient's data on cancer progression.

B. Cumulated treatment model

We also consider an additional state in the system model, which is decoupled from the dynamics of cancer cells. In particular, we assume that the treatment $\mathbf{t}(k)$ applied at each time step has a cumulative (toxic) effect on the patient, which has to be taken into account for safety reasons. The cumulated treatment is modeled as follows:

$$
t_{\mathrm{cum}}(k + 1) = \alpha_1 t_{\mathrm{cum}}(k) + \alpha_2\big(t_{\mathrm{PP}}(k) + t_{\mathrm{PM}}(k) + t_{\mathrm{MM}}(k)\big),
\tag{10}
$$

where $0 \leq \alpha_1, \alpha_2 \leq 1$ are scalar constants.

C. Optimization problem

The controller has the following goals:

1) Minimize the number of cancer cells
2) Keep the proportion of both types of cells intact: an abrupt change of the proportions can have fatal consequences for the patient. The so-called adaptive treatment focuses on keeping the proportion of different cell types under control to avoid evolution of resistance to treatment [1], [4].
3) To keep the cumulated treatment $t_{\mathrm{cum}}(k)$ below a pre-specified maximal tolerable dose, as large amounts of treatment are toxic for the patient.

We will solve the following optimization problem over the prediction horizon N_p:

$$\min_{\mathbf{t}[k:k+N_p-1]} \sum_{h=0}^{N_p-1} \left(\mathbf{y}(k+h) - \mathbf{y}_{\text{ref}}(k+h)\right)^{\text{T}}$$
$$\mathbf{Q}(k+h)\left(\mathbf{y}(k+h) - \mathbf{y}_{\text{ref}}(k+h)\right)$$
$$+\mathbf{t}^{\text{T}}(k+h)\mathbf{R}(k+h)\mathbf{t}(k+h), \quad (11)$$

where $\mathbf{t}[k : k + N_p - 1] = (\mathbf{t}(k), \ldots, \mathbf{t}(k + N_p - 1))$, with $\mathbf{y}(k) = [P(k), M(k), t_{\text{cum}}(k)]^{\text{T}}$, where $\mathbf{Q}(k), \mathbf{R}(k)$ are weighting matrices, and where $\mathbf{y}_{\text{ref}}(k)$ represents a dynamic reference. Problem (11) is solved subject to the following constraints:

- The model dynamics, which is given by (8) for the cancer cells and by (10) for the cumulated treatment.
- Treatment vector $\mathbf{t}(k)$ refers to proportions of links to be removed, thus

$$0 \le t_{rs}(k+h) \le 1, \quad \forall h \in \{0, \ldots, N_p - 1\}. \quad (12)$$

- Likewise, the cumulated treatment $t_{\text{cum}}(k)$ is required to satisfy the following:

$$\sum_{h=0}^{N_p-1} \sum_{\forall rs} t_{rs}(k+h) \le \gamma(t_{\text{cum}}^{\text{max}} - t_{\text{cum}}(k)), \quad (13)$$

with $\gamma \in \mathbb{R}^+, \gamma > 1$ being a constant scalar, and where $t_{\text{cum}}^{\text{max}}$ is the maximum tolerable dose of treatment at each time instant. Using constraint (13) we impose a limit on the dose of drug that can be administrated to the patient during the horizon. The maximum of this limit is achieved at $\gamma t_{\text{cum}}^{\text{max}}$, which happens when $t_{\text{cum}}(k) = 0$.

- The initial conditions $\mathbf{y}(k)$ for the optimization problem, which may be estimated by means of clinical measurements.

We denote an argument solving problem (11) by $\mathbf{t}^*[k : k+N_p-1]$. Only the first element $\mathbf{t}^*(k)$ of $\mathbf{t}^*[k : k+N_p-1]$ is actually applied, the rest is discarded. The horizon is shifted to the next time step, when the problem is solved again, applying only the first element of the argument. This process is repeated in a receding horizon fashion. The problem (11) is a nonlinear MPC problem due to the nonlinear nature of the model (8).

IV. CASE STUDIES

The case studies presented in this work have been simulated by using the Matlab® solver fmincom to calculate the optimal treatment, in a 2.7 GHz quad-core Intel Core® i5, 4 GB RAM computer. The initial tumor conditions are $P(0) = 17$, $M(0) = 33$ and the configuration is shown in Fig. 7 (top left). The controller receives an estimate of the cancer cells population and the cumulated treatment, which is provided by an unbiased estimator with an error bounded to the 2% of the actual value. The fitness matrix $\mathbf{A}$ is given by (3). The rest of the parameters is set as follows:

$$T_{\text{sim}} = 15, \xi = 0.95, \ \alpha_1 = 0.9, \ \alpha_2 = 0.05,$$
$$N_p = 5, \ \mathbf{y}_{\text{ref}}(k) = N(k) \left[\tfrac{1}{3}, \tfrac{2}{3}, 0\right]^{\text{T}}, \ t_{\text{cum}}^{\text{max}} = 1,$$
$$\mathbf{Q} = \begin{bmatrix} 0.95^{(k-1)} & 0 & 0 \\ 0 & 0.95^{(k-1)} & 0 \\ 0 & 0 & 0 \end{bmatrix}, \quad (14)$$
$$\mathbf{R} = \begin{bmatrix} 10 \cdot 0.95^{(k-1)} & 0 \\ 0 & 10 \cdot 0.95^{(k-1)} \end{bmatrix}.$$

Note that, if we set $t_{\text{cum}}^{\text{max}} = 1$, the maximum tolerable dose of treatment along N_p is simply given by $\gamma t_{\text{cum}}^{\text{max}} = \gamma$. We have considered the following three scenarios: (i) no treatment, i.e., $\mathbf{t}(k) = 0$, $\forall k$, (ii) applied treatment with $\gamma = 5$, (iii) applied treatment with $\gamma = 20$.

A. Scenario I

With no treatment, each cell in network $(\mathcal{N}(k), \mathcal{E}(k))$ can always interact with any other cell in the entire population, as there no links removed and hence $\Lambda(k) = \mathcal{E}(k)$, $\forall k$. This way, the probability of reproduction given by the fitness matrix (3) does not change. The frequencies of the two types of cells coincide with the ESS of this matrix, as shown in Fig. 3. The tumor increases rapidly as both cell populations grow exponentially.
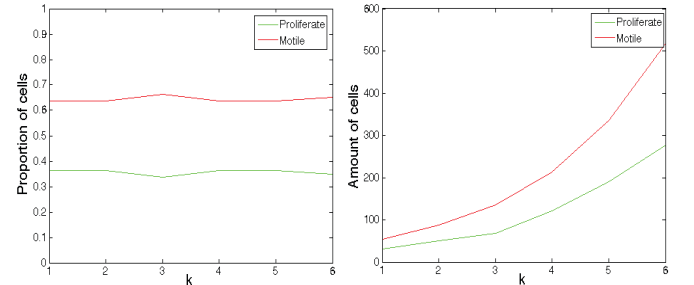

Fig. 3. Scenario I. No treatment applied: (left) Cell proportions stay close to ESS $\left(\tfrac{1}{3}, \tfrac{2}{3}\right)$; (right) Populations of cells. The simulation length in this scenario was reduced to $T_{\text{sim}} = 6$, due to combinatorial issues caused by the exponential growth in cancer cells.

B. Scenario II

In this scenario, we consider a treatment with $\gamma = 5$. This value represents a strict upper bound on the applied treatment during the prediction horizon. For this reason, the cumulated treatment at each instant k is always kept under 0.45, much lower than the maximal tolerable dose $t_{\text{cum}}^{\text{max}} = 1$. When applying this treatment, some links are removed which causes a lower reproduction rate in comparison with Scenario I. Therefore, the population growth of cancer cells is slower, while the proportions of the two cell types are close to their ESS proportions. Nevertheless, the treatment dose is not sufficient to kill the tumor. All the results provided by this scenario are shown in Fig. 4.
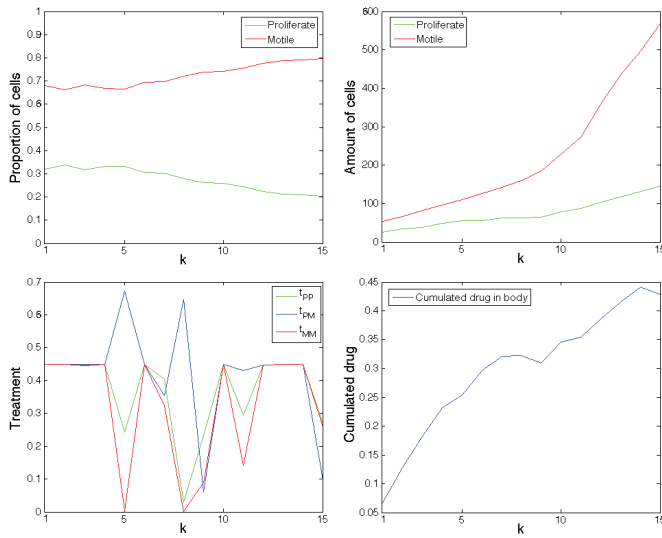
Fig. 4. Scenario II. Treatment with $\gamma = 5$: (top left) Cell proportions are close to their ESS proportions; (top right) The speed of population growth has been reduced; (down left) Optimal treatment; (down right) Cumulated treatment.

C. Scenario III

In the last scenario we consider a treatment with $\gamma = 20$. In this case, a higher maximal tolerable treatment dose is permitted. Subsequently, the cumulated amount of drug at each instant k is higher than in Scenario II, but it is always below $t_{\text{cum}}^{\max}$. The frequencies of cancer cell types are also similar to their ESS frequencies. This treatment stops the tumor growth, as it can be seen in Fig. 5.

Finally, Fig. 6 shows a networked overview of the initial cells and their evolution in the three proposed scenarios. Note that for the initial population and the case without treatment the number of links $|\mathcal{E}(k)|$ corresponds to the complete-network case, i.e., $|\mathcal{N}(k)||\mathcal{N}(k) - 1|/2$, since there are no links removed by the treatment.
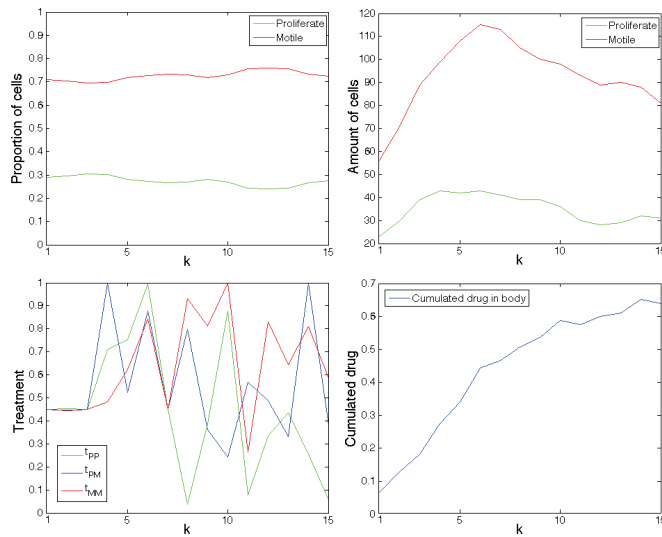

Fig. 5. Scenario III. Treatment with $\gamma = 20$: (top left) Cell proportions are similar to their ESS proportions; (top right) The population of cells has been reduced and decreased; (down left) Optimal treatment; (down right) Cumulated treatment.
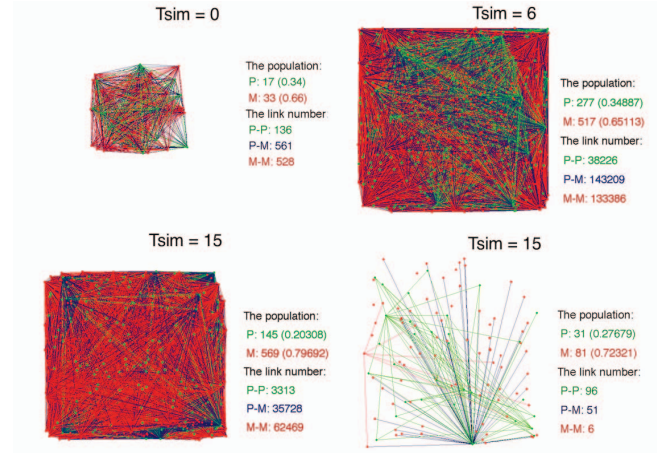

Fig. 6. Visualization of the tumor growth in the different scenarios: (top left) Initial tumor; (top right) Tumor in Scenario I, $T_{\text{sim}} = 6$; (down left) Tumor in Scenario II, $T_{\text{sim}} = 15$; (down right) Tumor in Scenario III, $T_{\text{sim}} = 15$.

V. CONCLUSIONS

We have developed a spatial game played over a dynamic undirected graph to model tumorigenesis. The nodes of this graph represent cancer cells and the cell types represent cells' strategies, while links determine who is allowed to interact with whom. An optimal cancer treatment disconnecting proportion of the links among specific cell types and hereby reducing cancer cells' proliferation rate has been found using a nonlinear MPC controller. Here a nonspatial RD model was used to estimate the cells' number at each time step of the MPC, while the total amount of treatment was bounded by its a priori decided maximal tolerable dose.

We have considered three scenarios: the first one corresponds to the tumor progression without treatment. Here cancer cells show exponential growth. In the second scenario with a very low maximal tolerable dose the speed of cancer growth is substantially decreased. The third scenario with a higher maximal tolerable treatment dose leads to the complete elimination of the cancer cells.

In this work, we have demonstrated that the MPC approach has a high potential for designing cancer treatment. However, as an initial step, we assumed an ideal setting in which it is possible to obtain measurement regarding the state of the tumor and directly manipulate the corresponding variables of interest. How to obtain the measurements and apply the drugs are topics beyond the scope of this paper since it would lead to a higher complexity of the models considered. As a consequence, the MPC policy can be seen as a top layer controller that receives estimates of the state of the tumor and provides actions that will be translated into inputs on the patients body, e.g., androgen deprivation therapy doses. Both the estimation and the drug application procedures are ignored here for the sake of simplicity. More realism could be added to the model also on the treatment side: Instead of focusing on a single treatment, we could think of finding the best combination of multiple treatments. Some of these

treatments may attack the carrying capacity of certain cancer cells' type instead of their proliferative capabilities. In order to model such treatments as well, we will need to convert the RD model into a Lotka-Volterra competition model, which includes carrying capacities of different cancer types and which we can then manipulate.

One of the biggest challenges of finding the appropriate cancer treatment is the evolution of resistance in cancer cells. Similarly as it is done in pest management when pests evolve resistance to pest control, the treatment-resistant type of cancer cells needs to be controlled to increase the chances for a successful treatment [40]. Future work should therefore include treatment-resistant type into our spatial model, similarly as it was done in [1].

Finally, the ultimate objective of our efforts should be to validate our treatment predictions with real patients' data.

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