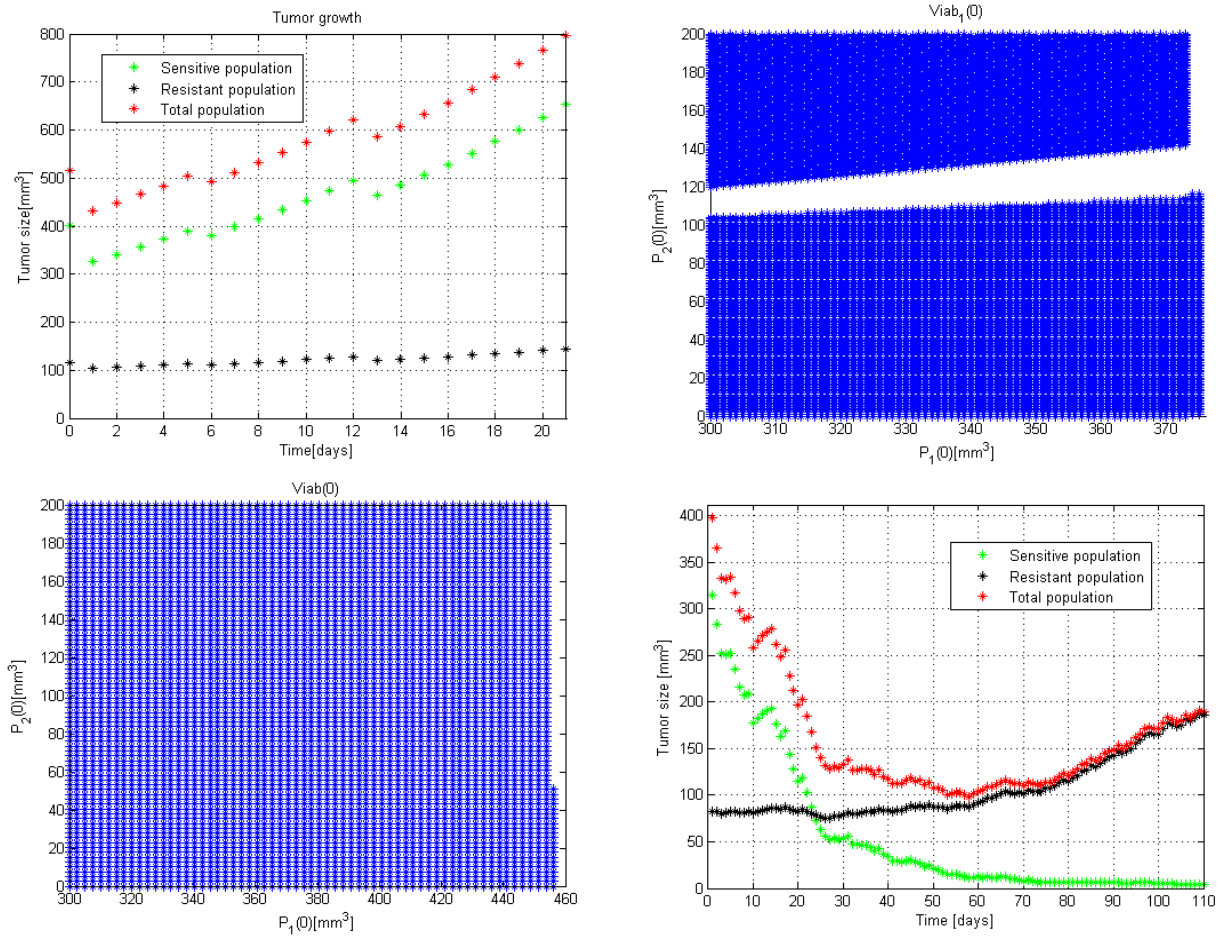

Sustainable Chemotherapy Schedules

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Abstract— **We used a discrete time version of viability theory in order to study the sustainable therapies against the cancer. We assume that the tumor is composed of two subpopulations, one resistant and the another sensitive. We consider a discrete model in order to simulate the response of this tumor to therapy, and we apply the Bellman equation within the viable control framework for calculating viability kernel, so as to determine the existence of a therapy that maintain the cell population bounded. Both theoretical and numerical results are presented.**

Keywords— **Cancer, Chemotherapy, Bellman, Tumor, Viability.**

Introduction

Systematic administration of cytotoxic drugs is the primary treatment strategy for patients with disseminated cancer. Whereas a wide range of treatment regimens are used in clinical practice, their fundamental goal is typically to induce lethal toxicity in the largest possible number of tumoral cells. Thus, most research efforts in chemotherapy are focused on discovery of agents and combinations of agents, doses, and dose schedules that maximize the killing of the tumoral cells, while minimizing the toxicity for the host. In most clinical therapies, patient's tolerance is the primary factor that bounds the dose of cytotoxic agents.

Is necessary to mention, that patients with cancer are usually treated near the maximum tolerated dose, with implicit intent to eradicate (cure) the tumor, even when such an outcome, based on the extensive clinical experience, indicates that this is highly improbable [2, 7].

A number of mathematical approaches have been developed to optimize the chemotherapy, as well as to limit the development of resistance. For instance, the Norton-Simon model [8], found the treatment with the highest possible dose over the shortest period of time (maximum dose density). High dose density is designed to produce the maximal tumoral cells' death, and to minimize the evolutionary potential of the resistant clones. So, each patient typically receives

chemotherapeutic doses, near the side effects tolerable limit. Generally, high-density chemotherapy has improved survival, but only in rare cases the cure is achieve, just for the most common epithelial tumors. It is because of the great heterogeneity in space and time of the tumor micro-environment, usually modeling through two or more subpopulations of cells [7]. One of these populations is sensitive to the therapy, whereas the other is resistant. The resistant populations are typically found in small numbers, because they fit less than the sensitive populations. Sensitive cells have a higher rate of replication. The traditional therapy looks for the elimination of the maximum possible quantity, of malignant cells; but when this happens, the sensitive ones die and the resistant population, can proliferate freely because of the absence of competition (see Fig.1).

We proposed an alternative approach to this methodology, and we found therapies that maintain bounded the sensitive population; and in this way we prevent the growth of the resistant cells, allowing that the overall tumor burden, remains stable. This corresponds with new medical vision of the cancer, as a chronical disease, and which one the patient can live with.

Using the mathematical concept of viability kernel, we examined the model in order to find these therapies and the set of all viable states,i.e. for which there exists a control policy maintaining them within a set of constraints.

Section 2 we present the mathematical model for the chemotherapy problem. In Section 3 we present the main results of the viability theory in a discrete time version. Section 4 is devoted to presented numerical results. Finally, we provide the conclusions, and the future work.

Fig Treatment designed to kill maximum numers of cancer cells.

TUMOR DYNAMICS WITH CHEMOTHERAPY SCHEDULES

For free growth of heterogeneous tumor each subpopulation P_i within the tumor grows according to following dynamic [7]:

$$P_i(t+1) = P_i(t)\left(1+\gamma_i G\right),$$

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where γ_i represents the replication rate of each subpopulation P_i, and G represents the competition for resources among different populations. G is given by the following equation:

$$G = \frac{\gamma_T \Sigma_j P_j}{\Sigma_j P_j}.$$

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Finally, γ_T is the maximum theorical replication rate of the entire tumor.

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If the therapy is administered, the tumor growth dynamics (1) become in the following dynamic [7]:

$$P_i(t+1) = P_i(t)\left(1+\gamma_i G\right)\left(1-a(t)\sigma_i \beta(t)\right),$$

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where σ_i is the phenotypic sensitivity of the population i to
the therapy, $a(t)$ is the therapy to time t, and

$$\beta(t) = 1 + \frac{t}{t+\tau_S}.$$

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Equation (4) represent the environmental sensitivity to time t, τ_S is the time required for the environmental sensitivity to increase from 1 to 1.5. We assume that $0 \leq a(t) \leq 1$, $0 \leq \beta(t) \leq 2$ and $0 \leq \sigma_i \leq 1$.

VIABILITY THEORY

The viability problem relies on the consistency between a controlled dynamic and acceptability constraints applying both to states and decisions of the system [6]. Such a problem is frequent in biology, bioeconomics, ecology, robotics and sustainability sciences in general. The main concepts of this theory are as follows.

Dynamical systems are mathematical objects used to model physical phenomena whose state (or instantaneous description) changes over time. These models are used in financial and economic forecasting, environmental modeling, medical diagnosis, industrial equipment diagnosis, and a host of other applications.

In mathematical language, we write a discrete dynamical system as follows:

$$\begin{cases} x(t+1) = F(t, x(t), u(t)) \\ x(t_0) = x_0. \end{cases}$$

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for $t = t_0, t_0 + 1, \ldots, T$. Where t is the time index and belonging to the set of natural numbers $\mathbb{N}$, which runs from initial time t_0 to horizon time, T. On the other hand $x(t) = (x_1(t), \ldots, x_n(t))$ is the state of the dynamical system, $u(t) = (u_1(t), \ldots, u_p(t))$ is the control or decision and function $F(t, x(t), u(t))$ represents the system evolution.

A. *Decision constraints*

We consider the conditions:

$$u(t) \in B(t, u(t)), \quad \forall t = t_0, \ldots, T.$$

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Where $B(t,x(t))$ is the set of admissible decisions. Generally, these constraints are associated with equality and nequality requirement, which have the following form $b^d(t,x(t), u(t)) \leq 0$ and $b^i(t,x(t), u(t)) = 0$.

B. *State constraint*

We require that

$$x(t) \in A(t), \quad \forall t = t_0,...,T.$$

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The usual window $A(t)$ concerns equality and inequality constraints $a^d(t, x(t)) \leq 0$ and $a^i(t,x(t)) = 0$. For the time horizon we require

$$x(t) \in A(T).$$

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A state trayectory is any sequence $x(\cdot) = (x(t_0),...,x(T))$ and similary a control trayectory is any sequence of decisions $u(\cdot) = (u(t_0),...,u(T-1))$.

VIABILITY KERNELS

Definition 1: The viability kernel at time $s \in \{t_0, ... ,T\}$ for dynamical system (5) and constraints (6), (7) and (8) is the set, $Viab(s)$, defined by every x such that $\exists\ u(\cdot)$ and $x(\cdot)$ that starting from x at time s satisfies (5), (6), (7) and (8), $\forall\ t \in \{s,...,T\}$.

From the definition 1 we have that $Viab(s) \subset A(s)$. In the following proposition we show a framework in order to calculate the viability kernel, $Viab(t_0)$, through backward induction.

Proposition 1: if $T < \infty$, then $Viab(t)$ satisfies the backward induction, where t runs from $T-1$ to t_0,

$$Viab(t) = \{x \in A(t) | \exists u \in B(t,x), F(t,x,u) \in Viab(t+1)\}$$

and for the time horizon $Viab(T) = A(T)$.
This last equation is known as the Bellman's equation in the framework of viability.

When the control trayectories depending only on time, $u: t \rightarrow u(t)$, we can compute the state of system by the dynamics: $x(t+1) = F(t,x(t),u(t))$; its the deterministic case. But under uncertainty the control rule is $\boldsymbol{u} : (t,x) \rightarrow u(t, x)$, and we can compute the control and state trajectories by the following relations: $u(t) = \boldsymbol{u}(t,x(t))$, and $x(t+1) = F(t,x(t), u(t),w(t))$, where $w(t)$ represent the uncertain variable. We assume that $w(t) \in S(t)$, so that the sequences $w(\cdot) = (w(t_0),...,w(T))$ belonging to $\Omega = (S(t_0),..., S(T))$ capture the idea of possible scenarios for the problem. Probabilistic assumptions on the uncertainty $w(\cdot)$ may also be added. In such framework we define the robust viability kernel.

Definition 2: the robust viability kernel at time t_0 is the set, $Viab_1(s)$, defined by every x such that $\exists\ u(\cdot)$ such that $\forall\ w(\cdot) \in \Omega$, $x(t) \in A(t)$, for $t = t_0,...,T$.

In this framework we have that the robust viability kernel satisfy the backward induction, where t runs from $T-1$ down to t_0.

Proposition 2: if $T < \infty$, then $Viab(t)$ satisfies the backward induction, where t runs from $T-1$ to t_0,

$$Viab_1(t) = \{x \in A(t) | \exists u \in B(t,x), \text{ such that } \forall\ w \in S(t), F(t,x(t),u(t),w(t)) \in Viab_1(t+1)\}$$

and for the time horion $Viab_1(T) = A(T)$.

This equation is called the Bellman's equation in the robust viability framework.

COMPUTATIONAL ASPECTS

We program bellman equations in MATLAB R2009a. The main limitation of the viability approach is its computational complexity. The arithmetic operations that a computer performs on these numbers are called floating-point or flops. In the viability approach algorithm to model (3), for each $t = t_0,...,T-1$ we have a outer loop will be executed M_1 times. On each of these pasees, the inner loop is executed M_2 times. Were M_1 and M_2 are the grids of populations P_1 and P_2 respectively. For each of these iterations we have M_3 iterations corresponding to the control grid and for this last loops we have two more loops, each of M_1 and M_2 iterations respectively

NUMERICAL RESULTS

We used the Bellmann equation within the viable control framework to dynamical system (3) with two populations. We denote the sensitive and resistant cells by $P_1(t)$ and $P_2(t)$ respectively. The unit of measurement for $P_i(t)$ is mm^3, and for $a(t)$ is [mg/kg].

We considered a treatment of 21 days. In table I, we show the values assigned to the parameters γ_1, γ_2, σ_1 and σ_2, which are estimated (We use the method of least squares) from experiment performed in [8]. We consider the following contraints in order to mantain the system such that $P_1(t) \in [300, 600]mm^3$, $P_2(t) \in [0, 200]mm^3$ and therapy $a(t) \in [0,50]$mg, $\forall\ t \in [0, 21]$. Evidently here $t_0 = 0$ and $T = 21$.

Table Parameters tumor

γ_1	γ_2	σ_1	σ_2
0.052	0.027	0.0055	0.0028

Now we consider two different cases.

A. *The deterministic case*

We find $Viab(t_0)$ through proposition 1 using a grid of size 300×200. In figure 2 we observe the approximation obtained.

Fig : Viability kernel approximation.

B. *The uncertainty case*

As the carcinogenic cells population increases, it is reasonable to assume that the accumulation of random mutations and heterogeneous blood flow, may cause significantly variation on the sensitivity's levels, in the therapy that might be applied, at that moment. Then we assume $\sigma_1 \in \{0.0035, 0.0055\}$. For example: if P_1 could mutate with some probability $\boldsymbol{P}$ and we apply a therapy

found through $Viab(t_0)$, so may occur that $P(t)$ does not belong to $A(t)$ for some $t \in [0, T]$ (See Fig. 4). This evidences that we must find $Viab_1(t_0)$ what is done, through the Bellman's equation, over the robust viable framework. Figure 3 show the approximation of the robust viability kernel using a grid of size 600 × 400.

Fig Approximation of the robust viability kernel.

Conclusions

We apply the viability theory to dynamics of heterogeneous tumor with chemotherapy. We want to emphasize that calculating $Viab(t_0)$, we can know the set of initial conditions, $P(t_0) = (P_1(t_0),P_2(t_0))$, with at least a therapy, therapy which satisfy the corresponding constraints. We can also calculate therapy (control) if there. We can say that in the presence of a tumor, approximate Viab(t0) allows us to know in advance whether or not of therapy, $a(t)$, satisfying $P(t) \in A(t)$, $t = t_0,...,T$ and $a(t) \in U(t)$. The same comment is valid for the robust viability kernel $Viab_1(t_0)$.

As future work, we propose to study more long therapies than previous therapy, and we will use a SVM to approximate $Viab(t_0)$ and $Viab_1(t_0)$ [4, 5].

Fig Dynamic of tumor with mutation under a therapy obtained from $Viab(t_0)$.

Conflict of Interest

The authors declare that they have no conflict of interest.

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