Iterative method for estimating the robust domains of attraction of non-linear systems: Application to cancer chemotherapy model with parametric uncertainties

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Abstract

In this paper, we present an iterative procedure method for estimating the robust domains of attraction of non-linear systems. This method is based on the approximation of the uncertain non-linear system with a parameters-dependent Convex Difference Inclusions (CDI) system and the classical iterative methods for linear systems, which are introduced in this paper. A robust one-step operator computing a sequence of convex sets is derived, and the polyhedral case is discussed. An algorithm summarizing the iterative procedure based on the robust one-step operator is given, which is the theoretical contribution of this paper. This method is applied to cancer chemotherapy model considering parametric uncertainties and it is shown that drastic reduction of the robust domain of attraction of the cancer chemotherapy model has happened and this is caused by the parametric uncertainties. It is also proved that the chemotherapy aggressive is not the effective treatment for all the patients.

Keywords: Robust domains of attraction, parametric uncertainties, invariance, parameters-dependent CDI system, cancer chemotherapy model.

1. Introduction

Approximating the region of attraction of non-linear systems is an important task in model analysis and controlled design/evaluation, and several works have been devoted to this issue [1]. These regions of attraction have the property of invariance. The importance of invariant sets in control and analysis of dynamical systems is due to the implicit stability and robustness properties of these regions of the state space. Many results regarding invariance and related topics have been provided in the literature: see, for instance, the notable pioneering contribution [2], the works [3, 4], concerning the maximal invariant set, and [5] regarding the minimal one. The problem of obtaining invariant sets for discrete-time non-linear systems is dealt with using ellipsoids in [6] and polytopes in [7, 8]. For a recent monograph on the subject, reader can consult [9]. The mathematical theory that may be used to address these issues is the viability theory, see [10] for more details.

According to our knowledges, there are few contributions for estimating the region of attraction of non-linear systems using set-theoretic methods. An important result in this field is the theoretical and computational methods for a wide class of non-linear systems and the corresponding iterative procedures to approximate them given in [11, 8]. In [12], invariant sets computation for Convex Difference Inclusions (CDI) systems are investigated. In [13], CDI systems and set-valued maps are discussed for systems control purposes. In [14], the estimation of the region of attraction of non-linear system is based on the approximation of the non-linear system with CDI system as well as the classical set-theoretic methods of linear systems. This technique is motivated by the fact that the use of linear matrix inequalities (LMI) and iterative procedures for linear systems has become very popular due to their advantageous properties and the availability of efficient numerical tools to solve LMI problems.

In numerous control applications the parameters of the dynamical models are considered unknown but belong to known intervals. Approximating the robust region of attraction of such models are important in model analysis and controlled design/evaluation. Based on the results of [11, 8, 14], in this work we present computational method for estimating the robust domain of attraction of non-linear systems. This method is based on the robust one-step operator of the parameters-dependent CDI system that approximates the uncertain non-linear system. This is the theoretical contribution of the paper.

Mathematical models for tumor growth have appeared in the last decades and several scientific researchers have been interested by this topic [15, 16, 17, 18]. These models have been used for control-based tumoral therapy design, applying optimal control [19, 20] or feedback control [21, 22, 23]. Some of them are based on the evolution of the different populations of cells [24, 25, 26, 18, 17] and may incorporate the effects of external drugs on the tumor growth, for instance chemotherapy and immunotherapy drugs or their combination.

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Several objectives for control-based tumoral chemotherapy design were posed in the literature. In some cases, the main goal was to minimize the amount of chemotherapy drug, with the constraint that the tumor size does not exceed the prescribed level at the end of the treatment period. In other cases, the objective was to minimize the number of tumor cells in a fixed therapy period under some constraints [18, 21, 20, 23, 27]. Minimize the amount of the therapy drug and the number of tumor cells at the end of the treatment period simultaneously is also considered in [22]. As a healthy condition, maintaining a normal cells population above a given level is often used [18, 28].

In this paper, the model based on the works done in [24, 25, 18, 15] is adopted to reproduce the behaviour of the normal cells population levels in presence of tumor cells and under the effect of chemotherapy drugs. It was given in form of a system of ordinary differential equations. This model originally was used to represent the evolution of acute myeloblastic leukemia (AML) and in [18] it has been used to simulate the tumor growth. The normal cells represent a part of the innate immune system and can be interpreted as the aggregation of NK cells, CD8+ cells and a circulating lymphocytes (or white blood cells) as in [21]. In this model, Gompertzian functions are employed to describe the tumor and normal cells growths and some assumptions are introduced in order to maintain sufficient simplicity to admit analysis.

The practical contribution of this paper, whose preliminary version is [29], consists in the development of numerical tool for cancer chemotherapy model considering parametric uncertainties. According to the literature, this assumption is crucial since in general the chemotherapy cancer models involve many unknown and dynamically varying set of parameters [22]. The presence of these uncertainties is important since, in practice, the model parameters can vary from patient to patient and are usually not exactly known. On the other hand, uncertainties might make the analysis problem much more complex. The practical contribution is done by applying the computational method that will be developed in the first part of this paper, which is based on the properties of invariant sets of parameters-dependent CDI systems.

This numerical tool compute the robust domain of attraction of the uncertain cancer chemotherapy model. It contains all the normal and tumor cells states for which a set of appropriate chemotherapy drug administration profiles exist. These profiles drive the states of this region to the safe region. The safe region is defined to be the set for which the number of tumor cells population is small enough and the normal cells population is higher than the minimal admitted level. A minimal level is imposed as a healthy condition for the patients.

In this paper, it will be shown that considering parameters uncertainties in the cancer chemotherapy models is crucial in order to achieve a good tumor contraction without killing the normal cells. It will be proved using simulations that for some patients the chemotherapy aggressive is not the efficiency chemotherapy drug administration. A comparative study between several drug strategies is provided. The characterization of all the robust domains of attraction for each chemotherapy drug administration profile is given, and the suitable strategy for each patient can be inferred by analyzing the different robust domains of attraction.

The paper is organized as follows: In Section II, the problem statement and the theoretic contribution of the paper, which is a computational method to estimate the robust domain of attraction of non-linear systems, are given. In Section III, the mathematical cancer chemotherapy model is first given then the numerical tool for approximating the robust domains of attraction of this model is developed. Simulations results for cancer chemotherapy analysis are illustrated in Section IV. Section V ends the paper by providing conclusions and giving hints for future investigations.

Notation 1. *Given $n \in \mathbb{N}$, define $\mathbb{N}_n = \{m \in \mathbb{N} : 1 \leq m \leq n\}$. Given $A \in \mathbb{R}^{n\times m}$, A_i with $i \in \mathbb{N}_n$ denotes its i-th row, $A_{i,j}$ with $i \in \mathbb{N}_n$ and $j \in \mathbb{N}_m$ a value that corresponds to the i-th row and the j-th column.*

2. Robust domains of attraction of non-linear systems

In this section the problem statement and the theoretic contribution of the paper are stated.

We consider discrete-time uncertain non-linear systems of the form

$$x^+ = f_P(x, u), \quad \forall x \in \mathcal{X},\ \forall u \in \mathcal{U},\ P \in \Sigma, \tag{1}$$

where x is the state vector, x^+ is the successor, u is the control input, and P is the vector of uncertain parameters. The function f_P is a parameters-dependent non-linear function. Furthermore, the sets $\mathcal{X}$ and $\mathcal{U}$ are intended to be, hereafter, respectively the set of state constraints and the set of admissible control inputs, and Σ is the bounding set of the parameters vector P. They are assumed to be known convex regions.

The set of all initial conditions from which the trajectories of (1) converge to the safe region (it can be just a point) regardless the parametric uncertainties is called the *robust domain of attraction*. In this paper, the main goal is to propose an algorithm to compute this domain using set-theoretic methods.

According to set-theoretic methods, the robust domain of attraction of the uncertain non-linear system (1) is the maximal robust invariant set. Since in set-theoretic methods the convexity property of sets is often considered, this domain is convex. In order to compute this domain an algorithm, which is a part of the contributions of this paper, is based on the following procedures:

1. Approximation of the uncertain non-linear system (1) with a parameters-dependent CDI system;
2. Characterization of the robust domain of attraction of the parameters-dependent CDI system using set-theoretic methods.

The CDI systems are characterized by a particular class of set-valued maps as dynamic functions. In particular, the set-valued map determining a CDI system is such that, given a point in the state space, its image through the map is a convex and compact set, for more details about CDI systems, see [11].

The approximation of a non-linear system with a CDI system is useful in order to apply the set-theoretic methods. In cancer chemotherapy analysis, that will be given in the next section, it will be shown that this algorithm can compute the exact robust domain of attraction of cancer chemotherapy model.

In order to approximate a non-linear system, one defines a CDI system which is characterized by a set-valued map whose graph contains the graph of the function determining the non-linear system. Indeed, an invariant (contractive) set for the CDI system is also invariant (contractive) for the non-linear system. Thus due to the particular properties of the CDI systems, convexity is preserved by the one-step operator and then the numerical methods proper for linear systems are also valid for CDI systems.

Now in order to approximate the uncertain non-linear system (1), which is defined by the parameters-dependent function f_P, it is sufficient to determine a parameters-dependent set-valued map that bounds the parameters-dependent function f_P. Therefore a robust invariant (contractive) set for the parameters-dependent CDI system, which is defined by a parameters-dependent set-valued map, is also invariant (contractive) for the uncertain non-linear system (1).

Now let us introduce some useful tools to deal with convex closed sets and CDI systems. First consider the parameters-dependent difference inclusions systems

$$x^+ \in \mathcal{F}_P(x,u), \tag{2}$$

where $x \in \mathcal{X} \subseteq \mathbb{R}^n$ is the state, x^+ is the successor, $u \in \mathcal{U} \subseteq \mathbb{R}^m$ is the control input, $P \in \Sigma \subseteq \mathbb{R}^r$ is the vector of parameters and $\mathcal{F}_P(\cdot,\cdot)$ is a parameters-dependent set-valued map on $\mathbb{R}^n$. $\mathcal{F}_P(x,u)$ represents a function which relates a set to every point $(x,u,P) \in \mathbb{R}^n \times \mathbb{R}^m \times \mathbb{R}^r$, i.e. $\mathcal{F}_P(x,u) \subseteq \mathbb{R}^n$ for all $x \in \mathbb{R}^n$, $u \in \mathbb{R}^m$ and $P \in \mathbb{R}^r$.

We consider that the parameters-dependent difference inclusions system (2) is used to approximate the uncertain non-linear system (1), i.e.

$$f_P(x,u) \in \mathcal{F}_P(x,u), \quad \forall x \in \mathcal{X}, \quad \forall u \in \mathcal{U}, \quad \text{and } P \in \Sigma.$$

The parameters-dependent difference inclusions system could be obtained by bounding the dynamics of the uncertain non-linear system (1) and this can be done by bounding the parameters-dependent function $f_P(\cdot,\cdot)$.

Hereafter, the second step to compute the robust domain of attraction of the uncertain non-linear system (1) is given. First, an important tool to deal with convex closed sets is the support function, it is defined as follows.

Definition 1. *Given a set $\Omega \subseteq \mathbb{R}^n$, the support function of Ω evaluated at $\eta \in \mathbb{R}^n$ is given by $\phi_\Omega(\eta)$ such that*

$$\phi_\Omega(\eta) = \sup_{x \in \Omega} \eta^T x.$$

Geometrically the support function of Ω at η is the signed "distance" of the point of the closure of Ω farthest from the origin, along the direction η. See [30] for some properties of support functions. Using the support function is helpful to transform a set-inclusion condition in terms of linear inequalities, see [30] for instance. From the definition of the support function, we get this property.

Property 1. *[31] Given the closed convex set $\Omega \subseteq \mathbb{R}^n$ and the set $\Gamma \subseteq \mathbb{R}^n$ then $x \in \Omega$ if and only if $\eta^T x \leq \phi_\Omega(\eta)$ for all $\eta \in \mathbb{R}^n$, and $\Gamma \subseteq \Omega$ if and only if $\phi_\Gamma(\eta) \leq \phi_\Omega(\eta)$ for all $\eta \in \mathbb{R}^n$.*

Before giving the definition of a controlled robust invariant set let us introduce the following assumption.

Assumption 1. *Assume that the parameters-dependent set-valued map $\mathcal{F}_P$ determining the system dynamics (2) is, such that $\mathcal{F}_P(x,u)$ for all $P \in \Sigma$ is compact and convex for all $(x\ u)^T \in \mathbb{R}^n \times \mathbb{R}^m$ and for every $\eta \in \mathbb{R}^n$ and $P \in \Sigma$ the function $F_P(x,u,\eta) : \mathbb{R}^n \times \mathbb{R}^m \times \mathbb{R}^n \longrightarrow \mathbb{R}$ defined as*

$$F_P(x,u,\eta) = \phi_{\mathcal{F}_P(x,u)}(\eta) = \sup_{z \in \mathcal{F}_P(x,u)} \eta^T z, \tag{3}$$

is convex with respect to $(x\ u)^T$ on $\mathcal{X} \times \mathcal{U}$.

Thus, in practice, given $P \in \Sigma$, $F_P(x,u,\eta)$ is the support function of the set $\mathcal{F}_P(x,u)$ evaluated at $\eta \in \mathbb{R}^n$ and then

$$\mathcal{F}_P(x,u) = \left\{ z \in \mathbb{R}^n : \quad \eta^T z \leq F_P(x,u,\eta), \quad \forall \eta \in \mathbb{R}^n \right\}, \tag{4}$$

and it is convex in $(x\ u)^T$.

The dynamical system (2) for which Assumption 1 holds are tightly related to the CDI systems defined in [11, 12]. In fact, given a known parameters vector $P \in \Sigma$ then the system (1) can be approximated by the parameters-dependent CDI system (2), i.e.

$$f_P(x,u) \in \mathcal{F}_P(x,u), \quad \forall x \in \mathcal{X}, \quad \text{and } \forall u \in \mathcal{U}.$$

However, when the parameters vector P is unknown and is assumed to belong to the known set Σ the parameters-dependent function $f_P(\cdot,\cdot)$ has to be approximated by the union of $\mathcal{F}_P(\cdot,\cdot)$ for all $P \in \Sigma$. Therefore, the uncertain non-linear system (1) can be approximated by the following parameters-dependent CDI system

$$x^+ \in \bigcup_{P \in \Sigma} \mathcal{F}_P(x,u), \tag{5}$$

where $\mathcal{F}_P(\cdot,\cdot)$ is a parameters-dependent set-valued map on $\mathbb{R}^n$ defined above.

Now let us introduce the standard definition of the controlled robust invariant set for the generic non-linear system, adapted here to the sets that do not necessarily contain the origin and the parameters-dependent set-valued maps.

Definition 2. *[9] The closed convex set $\Omega \subseteq \mathbb{R}^n$ is a controlled robust invariant set for the system (1) with $P \in \Sigma$ if for all $x \in \Omega$ there exists $u \in \mathcal{U}$ such that $f_P(x,u) \in \Omega$ for all $P \in \Sigma$. It is controlled robust invariant for the system (5) if for all $x \in \Omega$ there exists $u \in \mathcal{U}$ such that $\mathcal{F}_P(x,u) \subseteq \Omega$ for all $P \in \Sigma$.*

For every trajectory starting in a controlled robust invariant set Ω there exists a control input such that this trajectory remains inside Ω regardless of the parametric uncertainties. For the system (5), the controlled robust one-step operator is employed to check the controlled robust invariance of $\Omega \subseteq \mathcal{X}$. It is defined hereafter.

Definition 3. *Consider the closed convex set Ω and assume that Assumption 1 holds for the parameters-dependent set-valued map $\mathcal{F}_P(\cdot,\cdot)$ determining the dynamic system (5). The controlled robust one-step operator is defined as follows*

$$Q(\Omega,\mathcal{U},\mathcal{X}) = \left\{ x \in \mathcal{X} \mid \exists u \in \mathcal{U} : \quad \bigcup_{P\in\Sigma} \mathcal{F}_P(x,u) \subseteq \Omega \right\}. \quad (6)$$

Notice that obtaining the controlled robust one-step operator (6) requires sweeping the parameter vector P in the set Σ which might be computationally very demanding. Hence in order to solve this issue one focuses on the vertices of the bounding set Σ. Finally let us introduce the following proposition.

Proposition 1. *Consider the closed convex set Ω and assume that Assumption 1 holds for the parameters-dependent set-valued map $\mathcal{F}_P(\cdot,\cdot)$ determining the dynamic system (5). Given a polytope Σ and the set $\mathcal{V}$ of its vertices, assume that the support function $F_P(x,u,\eta)$ of the set $\mathcal{F}_P(x,u)$ is convex with respect to P, then the controlled robust one step-operator given by (6) is equivalent to*

$$Q(\Omega,\mathcal{U},\mathcal{X}) = \left\{ x \in \mathcal{X} \mid \exists u \in \mathcal{U} : \quad \mathcal{F}_P(x,u) \subseteq \Omega, \quad \forall P \in \mathcal{V} \right\}. \quad (7)$$

Before giving the proof the following property that is helpful for the proof is introduced, see [32] for the demonstration and for other details.

Property 2. *[32] Let C be a closed convex subset of $\mathbb{R}^n$ that has at least one extreme point. A convex function $f : C \mapsto \mathbb{R}^n$ that attains a maximum over C attains the maximum at some extreme point of C.*

Proof 1. *Applying Property 1, the inclusion $\bigcup_{P\in\Sigma} \mathcal{F}_P(x,u) \subseteq \Omega$ in Eq.(6) is equivalent to*

$$\phi_{\bigcup_{P\in\Sigma}\mathcal{F}_P(x,u)}(\eta) \leq \phi_\Omega(\eta), \qquad \forall \eta \in \mathbb{R}^n.$$

By using the properties of the support function, see [30], the latter condition is equivalent to

$$\phi_{\bigcup_{P\in\Sigma}\mathcal{F}_P(x,u)}(\eta) = \max_{P\in\Sigma} \phi_{\mathcal{F}_P(x,u)}(\eta) = \max_{P\in\Sigma} F_P(x,u,\eta) \leq \phi_\Omega(\eta), \quad \forall \eta \in \mathbb{R}^n, \quad (8)$$

since $F_P(x,u,\eta)$ for $\eta \in \mathbb{R}^n$ is the support function of $\mathcal{F}_P(x,u)$ defined in Assumption 1.

Similarly, applying Property 1 and using the definition of the support function, the inclusion $\mathcal{F}_P(x,u) \subseteq \Omega, \forall P \in \mathcal{V}$ in Eq.(7) is equivalent to

$$F_P(x,u,\eta) \leq \phi_\Omega(\eta), \quad \forall P \in \mathcal{V}, \quad \forall \eta \in \mathbb{R}^n,$$

where $\mathcal{V}$ is the set of vertices of the set Σ, such condition is also equivalent to

$$\max_{P\in\mathcal{V}} F_P(x,u,\eta) \leq \phi_\Omega(\eta), \quad \forall \eta \in \mathbb{R}^n. \quad (9)$$

Now one proves that the inequality in Eq.(8) is equivalent to the inequality in Eq.(9). Necessity is due to $\mathcal{V} \subseteq \Sigma$ since Σ is a polytope. To prove sufficiency, one have to prove that

$$\max_{P\in\Sigma} F_P(x,u,\eta) \leq \max_{P\in\mathcal{V}} F_P(x,u,\eta), \quad \forall \eta \in \mathbb{R}^n. \quad (10)$$

Since (10) would mean that $\max_{P\in\mathcal{V}} F_P(x,u,\eta) \leq \phi_\Omega(\eta)$ implies that

$$\max_{P\in\Sigma} F_P(x,u,\eta) \leq \phi_\Omega(\eta) \quad \forall \eta \in \mathbb{R}^n,$$

resonating by contradiction will be applied and this by supposing that there exists $\eta \in \mathbb{R}^n$ such that $\max_{P\in\Sigma} F_P(x,u,\eta) > \max_{P\in\mathcal{V}} F_P(x,u,\eta)$.

By hypothesis, for a given $(x,u,\eta) \in \mathcal{X}\times\mathcal{U}\times\mathbb{R}^n$, the function $F_P(x,u,\eta) : \Sigma \mapsto \mathbb{R}^n$ is convex with respect to $P \in \Sigma$, and Σ is compact. Thus the function $F_P(x,u,\eta)$ attains his maximum with respect to P over the set Σ.

Therefore, according to the Property 2 the function $F_P(x,u,\eta)$ attains his maximum at some extreme point of Σ. Hence this is a contradiction and the supposition is false then the condition given in (10) is true and the sufficiency is proved. Consequently, the condition (8) is equivalent to (9) and the robust one-step operator given in Definition 3 is equivalent to that given in Proposition 1.

The controlled robust one-step operator associates to every set Ω the set of points for which there exists a set of admissible controls $u \in \mathcal{U}$ such that these points will be mapped inside Ω through $\bigcup_{P\in\mathcal{V}} \mathcal{F}_P(x,u)$.

The one-step operator will be used to compute an increasing sequences of nested controlled robust invariant sets, as for linear or non-linear systems. In fact, Algorithm 1, standard for generating increasing controlled robust invariant approximations of the robust domain of attraction, see [9], can be also applied in this context.

Algorithm 1 Increasing sequences of controlled robust invariant sets for (5)

Input: Initial convex closed controlled robust invariant set $\Omega_0 \subseteq \mathcal{X}$.

1: **for** $k \in \mathbb{N}_N$ **do**
2: Compute $\Omega_{k+1} = Q(\Omega_k,\mathcal{U},\mathcal{X}) \cap \mathcal{X}$
3: **if** $\Omega_{k+1} = \Omega_k$ **then** $\Omega_{max} = \Omega_k$ **return**
4: **end if**
5: **end for**

Thus $\Omega_k,\ k \in \mathbb{N}_N$ are the controlled robust invariant sets that converge to the robust domain of attraction of the parameters-dependent CDI system (5), and hence of all the non-linear systems approximated by (5). Since in this paper the robust domain of attraction is needed to be calculated in polyhedral form, the following proposition is introduced, analogous to [11], which is functional for this purpose.

Proposition 2. *Given the parameters-dependent set-valued map $\mathcal{F}_P(x,u)$ determining the system dynamics (5), its support function $F_P(x,u,\eta)$ which is assumed to be convex with respect to P, and the state constraints set $\mathcal{X}$; given also a polytope $\Omega = \left\{x \in \mathbb{R}^n : \quad Hx \leq h\right\}$ with $H \in \mathbb{R}^{n_h \times n}$; given also a polytope Σ and $\mathcal{V}$ its vertices, the controlled robust one-step operator is given as follows*

$$\mathcal{Q}(\Omega,\mathcal{U},\mathcal{X}) = \left\{x \in \mathcal{X} \mid \exists u \in \mathcal{U} : \quad F_P(x,u,{H_i}^T) \leq h_i, \quad \forall i \in \mathbb{N}_{n_h}, \quad \forall P \in \mathcal{V}\right\}. \tag{11}$$

Notice that for every polytope Ω and admissible control polyhedral set $\mathcal{U}$ the set $\mathcal{Q}(\Omega,\mathcal{U},\mathcal{X})$ is closed and convex, as proved in [11]. Moreover, if $F_P(\cdot,\cdot,\eta)$ are piecewise affine functions of $(x\ u)^T$ then $\mathcal{Q}(\Omega,\mathcal{U},\mathcal{X})$ is a polyhedron, which is the intersection of a finite number of halfspaces for every polytope (or polyhedron) Ω.

The Algorithm 1 is suitable to compute the robust domain of attraction of the parameters-dependent CDI system (5) which is an approximation of the robust domain of attraction of the uncertain non-linear system (1). A meaningful application of the method developed in this section will be given in the rest of the paper.

In practice, these domains are the stability/save regions of the non-linear systems. In the second part of this paper, this algorithm will be applied for a cancer chemotherapy analysis.

3. Application to cancer chemotherapy model

3.1. Mathematical cancer model under chemotherapy drugs

3.1.1. State variables

The mathematical model considered in [18, 24, 25] to describe the behaviour of the cells populations in the presence of tumor and under the chemotherapy treatment is used in this paper. This model involves the following cells populations:

- L, tumor cells population;
- N, normal cells population. These cells are part of the innate immune system and in [24, 25] it represents the neutrophil cells population.

3.1.2. Modelling assumptions

The model given below is based on the following assumptions taken from [18, 24, 25]:

1. The growth dynamics of both tumor and normal cells populations are the same anywhere in the body;
2. The tumor and normal cells populations follow a process of Gompertzian growth;
3. The chemotherapy drug kills both tumor and normal cells;
4. The chemotherapy drug affects tumor cells more than normal cells;
5. The tumor cells exhibit a negative and inhibiting effect on the growth and development of the normal cells;
6. The drug spreads instantaneously within the body.

3.1.3. Dynamic model of a cancer under chemotherapy drugs

The assumptions given above lead to the following model, for cells populations dynamics, in presence of tumor cells and under chemotherapy drug administration:

$$\dot{L} = \alpha L \ln\frac{\theta_L}{L} - \Pi_1(u)L, \qquad L(0) = L_0,$$
$$\dot{N} = \beta N \ln\frac{\theta_N}{N} - \Xi(L)N - \Pi_2(u)N, \quad N(0) = N_0,$$

where α and β are the tumor and normal growth rates respectively, θ_L and θ_N are the greatest size of tumor cells population and the normal size of normal cells population respectively.

The terms $\alpha L \ln\frac{\theta_L}{L}$ and $\beta N \ln\frac{\theta_N}{N}$ represent the Gompertzian growth of both tumor and normal cells populations respectively, and the term $-\Xi(L)N$ represents the negative effect of the tumor on the normal cells.

The variable u stands for the concentration of the chemotherapy drug, and $\Pi_1(u)$ and $\Pi_2(u)$ represent loss functions for both cells populations due to chemotherapy effects.

According to the works [18, 24, 25], we adopt the following approximations:

- The function $\Xi(L)$ is taken to be linear as in [24] (i.e. $\Xi(L) = \gamma L$, where γ is a given parameter);
- The loss function $\Pi_1(u)$ is considered to be linear, taking into account the saturation phenomena, i.e, $\Pi_1(u) = ku$, k is the fraction of tumor cells that are killed due to the chemotherapy drugs;
- The loss function $\Pi_2(u)$ is also considered linear, i.e, $\Pi_2(u) = lu$, l is the fraction of the normal cells that are destroyed by the effects of the chemotherapy drugs (it is assumed that $l < k$);
- The parameters of the model are uncertain and bounded within known intervals. This leads to a polytopic parametric uncertain model.

Thus the resulting model becomes:

$$\begin{aligned} &\dot{L} = \alpha L \ln\frac{\theta_L}{L} - kuL, \qquad L(0) = L_0, \\ &\dot{N} = \beta N \ln\frac{\theta_N}{N} - \gamma LN - luN, \qquad N(0) = N_0 \\ &P_{LN} = \begin{pmatrix}\alpha & \beta & \gamma & \theta_N & \theta_L & k & l\end{pmatrix}^T \in \Sigma_{LN}, \end{aligned} \tag{12}$$

where P_{LN} is a vector of the parameters of the uncertain model, and Σ_{LN} is the polytopic bounding set. Since Σ_{LN} is a polytope, then it can be represented as the convex hull of its vertices, i.e.

$$\Sigma_{LN} = Co\left\{P_{LN}(1), ..., P_{LN}(Z)\right\},$$

where Co denotes a convex hull, $P_{LN}(z), z = 1,\ldots,Z$ are vertices of the polytope Σ_{LN}. Notice that, for any $P_{LN} \in \Sigma_{LN}$, there exist non-negative coefficients λ_z satisfying

$$\sum_{z=1}^{Z} \lambda_z = 1, \quad P_{LN} = \sum_{z=1}^{Z} \lambda_z P_{LN}(z).$$

Table 1: Parameters of the cancer chemotherapy model (12)

param	value	param	value
α	$3.96 \times 10^{-4}\ day^{-1}$	β	$3.33 \times 10^{-2}\ day^{-1}$
θ_N	$1.4 \times 10^{8}\ cells$	θ_L	$3 \times 10^{8}\ cells$
k	8×10^{-2}	l	15×10^{-3}
γ	$10^{-9}\ (cells.day)^{-1}$		

Notice that the non-linear model (12) involves two state variables L, N, one manipulated variable u, and $n_P = 7$ uncertain parameters. The consistent nominal values for these parameters are inferred from [24, 18], then modified to reproduce the cells evolutions given in [24] and summarized in Table 1.

As proposed in [18], we introduce the change of variables $x_1 = \ln \frac{\theta_L}{L}$ and $x_2 = \ln \frac{\theta_N}{N}$, and we get the equivalent system

$$\begin{aligned} \dot{x_1} &= -\alpha x_1 + ku,\ x_1(0) = x_{10}, \\ \dot{x_2} &= -\beta x_2 + \gamma \theta_L e^{-x_1} + lu,\ x_2(0) = x_{20}, \\ P &= \begin{pmatrix} \alpha & \beta & \gamma & \theta_L & k & l \end{pmatrix}^T \in \Sigma, \end{aligned} \tag{13}$$

where P, Σ are derived directly from (12), x_{10} and x_{20} are the initial conditions.

The discrete-time system modelling the cancer evolution is obtained by sampling the continuous-time system (13), with numerical integration schemes using Euler's method and sampling time of $T_s = 1\ day$. It results in

$$\begin{aligned} x_1^+ &= (1 - T_s\alpha)x_1 + T_s ku = f_{P1}(x, u),\ x_1(0) = x_{10}, \\ x_2^+ &= (1 - T_s\beta)x_2 + T_s\gamma\theta_L e^{-x_1} + T_s lu = f_{P2}(x, u),\ x_2(0) = x_{20}, \\ P &= \begin{pmatrix} \alpha & \beta & \gamma & \theta_L & k & l \end{pmatrix}^T \in \Sigma. \end{aligned} \tag{14}$$

We notice that this model is more suitable to apply the iterative methods for invariant set computation.

3.2. Control problem and constraints

In cancer chemotherapy the main objective is to contract the tumor cells population L while maintaining the normal cells population N above a prescribed level [21, 17]. The number of the normal cells population N is considered as a measure of the patient health [18].

In this section, the objective is to apply the algorithm developed in the first part of the paper in order to develop a numerical tool for cancer chemotherapy analysis. This numerical tool leads to determine all the initial tumor and normal states for which there exist appropriate drug injection profiles. These profiles must lead to a substantial regression of the tumor size while avoiding that the health measure reaches dangerous values for the patient. Thus, the substantial regression of the tumor size must be ensured without knowing the values of the parameters of the cancer chemotherapy model.

Explicitly the numerical tool provides the set of the initial points (L, N), such that the dynamics of the model (12) converge to the safe region, when an admissible chemotherapy drug profile is applied. The safe region is defined as the set in the state space L, N, where L is small enough and $N \geq N_{min}$, with N_{min} denoting the minimal admitted value of the normal cells population.

Similarly in the domain of coordinates x_1 and x_2, this numerical tool provides the set of the initial points (x_1, x_2), such that the dynamics of the model (14) can be driven to the safe region, by applying admissible chemotherapy drug profiles. The safe region in the state space x_1, x_2 is defined by x_1 high enough and $x_2 \leq x_{2max}$, where $x_{2max} = \ln \frac{\theta_N}{N_{min}}$ denotes the maximal admitted value of x_2.

These initial tumor and normal states are represented by the robust domain of attraction of the cancer chemotherapy model (14). Its calculation is substantially based on the properties of robust positively invariant sets and convex inclusions that are introduced in the first part of this paper.

3.3. Robust domain of attraction of cancer chemotherapy model

The robust domain of attraction of the cancer chemotherapy model (12) can be computed by following these procedures:

1. Approximating the discrete-time non-linear cancer model (14) by a parameters-dependent CDI system (5);
2. Applying Algorithm 1 for the parameters-dependent CDI system (5) that approximates the model (14); The principal task is to compute the controlled robust one-step operator (11). The result of this procedure is the robust domain of attraction in the state space (x_1, x_2);
3. Computing the robust domain of attraction in the state space (L, N) by using change of variables.

3.3.1. Controlled robust one-step operator for cancer chemotherapy model

Here the controlled robust one-step operator for the cancer chemotherapy model in the state space (x_1, x_2) (14) is determined by using the approximations and considerations given in Section 2.

Firstly, it is necessary to determine the bounding functions $F_P(x, u, \eta)$ for all $\eta \in \mathbb{R}^n$ that is convex with respect to $(x\ u)^T$. Its associated parameters-dependent set-valued maps $\mathcal{F}_P(x, u)$, that defines the parameters-dependent CDI system (5) must satisfy the following inclusion

$$f_P(x, u) \in \mathcal{F}_P(x, u), \quad \forall (x\ u)^T \in \mathcal{X} \times \mathcal{U},$$

with $f_P(x, u)$ defines the cancer model (14), and $\mathcal{F}_P(x, u)$ is defined by the bounding functions $F_P(x, u, \eta)$ as it is given by the equation (4).

Thus, according to Property 1, the functions $F_P(x, u, \eta)$ must satisfy the following inequality

$$\eta^T f_P(x, u) \leq F_P(x, u, \eta), \quad \forall \eta \in \mathbb{R}^n.$$

Moreover, since the non-linearity in (14) involves only $f_{P2}(x, u)$ then the bounding functions of $\eta^T f_P(x, u)$ are related only to η_2, since the dynamics of x_1 is linear. Thus a possible choice is

- if $\eta_2 \geq 0$: $F_P(x,u,\eta) = \eta^T f_P(x,u)$,
  since $F_P(x,u,\eta)$ is already convex in this case;
- if $\eta_2 < 0$:

$$\begin{aligned} F_P(x,u,\eta) = \quad & \eta_1\Big((1-T_s\alpha)x_1 + T_sku\Big) \\ & +\eta_2\Big((1-T_s\beta)x_2 + T_s\gamma\theta_L(ax_1+b) + T_slu\Big), \end{aligned} \tag{15}$$

  with a and b such that $(ax_1 + b) \leq e^{-x_1}$, obtained for instance as the tangent to the graph of e^{-x_1} at one point;

for all $\eta \in \mathbb{R}^2$.

Remark 1. *Notice that, if the non-linear function $\Xi(L)$ in (3.1.3) can be taken strictly increasing, convex and $\Xi(0) = 0$ as in [18], the convexity is preserved and in this case, the convex bounding function of $\eta^T f_P(x,u)$ is also easily obtainable.*

We are interested in convex piecewise affine bounding functions for computational purposes. For this it is sufficient to replace e^{-x_1} with a convex piecewise affine upper bound, which is easily obtainable, for the case of $\eta_2 \geq 0$. In fact, it is sufficient to choose a set of $q \in \mathbb{N}$ parameters $c_i \in \mathbb{R}$, $d_i \in \mathbb{R}$, with $i \in \mathbb{N}_q$, such that, $e^{-x_1} \leq \max\limits_{i\in\mathbb{N}_q}\{c_ix_1 + d_i\}$, for all $x_1 \in \mathbb{R}$. To obtain those parameters, it is sufficient to define z_i with $i \in \mathbb{N}_{q+1}$ such that $z_i < z_{i+1}$ and then

$$c_i = \frac{e^{-z_{i+1}} - e^{-z_i}}{z_{i+1} - z_i}, \qquad d_i = \frac{z_{i+1}e^{-z_i} - z_ie^{-z_{i+1}}}{z_{i+1} - z_i},$$

is the affine function such that $e^{-x_1} \leq c_ix_1 + d_i$ for every $x_1 \in [z_i,\ z_{i+1}]$ and $e^{-z_i} = c_iz_i + d_i$ for all $i \in \mathbb{N}_q$. Figure 1 illustrates this approximation.

Remark 2. *Notice that, in order to increase the precision, the number of parameters q can be taken as big as desired. Hence, arbitrary precision can be attained.*

Concerning the case of $\eta_2 < 0$, no modification is required with respect to (15), since the function (15) is already piecewise affine function. Then, we obtain

$$F_P(x,u,\eta) = \begin{cases} \eta_1\Big((1-T_s\alpha)x_1 + T_sku\Big) + \eta_2\Big((1-T_s\beta)x_2 \\ \qquad +T_s\gamma\theta_L \max\limits_{i\in\mathbb{N}_q}\{c_ix_1 + d_i\} + T_slu\Big) & \textbf{if } \eta_2 \geq 0, \\ F_P(x,u,\eta) \textit{as in (15)} & \textbf{if } \eta_2 < 0. \end{cases} \tag{16}$$

Figure 1 shows the convex upper bound and the concave lower bound of e^{-x_1} implicitly used to determine $F_P(x,u,\eta)$.

Notice that the bounding functions $F_P(x,u,\eta)$ are convex upper bounds of $\eta^T f_P(x,u)$, for all $(x\ u)^T \in \mathcal{X} \times \mathcal{U}$ and for all $\eta \in \mathbb{R}^n$. Once convex upper bounds of $\eta^T f_P(x,u)$ are determined, the controlled robust one-step operator is given by using the Proposition 2.

Since in (16) we have the term $\gamma\theta_L$ then this function is not convex with respect to the vector of model parameters P, and the Proposition 2 can not be applied directly.

In order to derive a representation of $F_P(x,u,\eta)$ with convex functions, we use the following change of variable $\delta = \gamma\theta_L$. Thus the new vector of model parameters $\bar{P}$ is equal to $\begin{pmatrix}\alpha & \beta & \delta & k & l\end{pmatrix}^T \in \bar{\Sigma}$, where $\bar{\Sigma}$ is determined from Σ by using the change of variable given above. Now the function given by (16) with this change of variable becomes

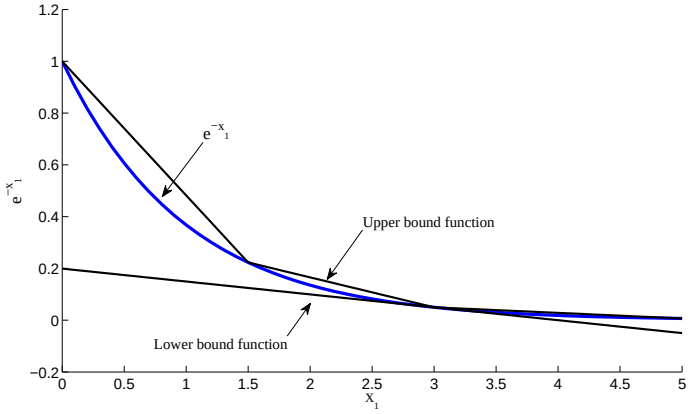

Figure 1: Bounds of the exponential function

$$F_{\bar{P}}(x,u,\eta) = \begin{cases} \eta_1\Big((1-T_s\alpha)x_1 + T_sku\Big) + \eta_2\Big((1-T_s\beta)x_2 \\ \qquad +T_s\delta \max\limits_{i\in\mathbb{N}_q}\{c_ix_1 + d_i\} + T_slu\Big) & \textbf{if } \eta_2 \geq 0, \\ \eta_1\Big((1-T_s\alpha)x_1 + T_sku\Big) + \eta_2\Big((1-T_s\beta)x_2 \\ \qquad +T_s\delta(ax_1+b) + T_slu\Big) & \textbf{if } \eta_2 < 0, \end{cases} \tag{17}$$

and is convex with respect to $\bar{P}$, since it is the sum of convex functions.

Now let us assume that the polytope $\Omega = \{x \in \mathbb{R}^n : Hx \leq h\}$ with $H \in \mathbb{R}^{n_h \times n}$, the polyhedron $\mathcal{X} = \{x \in \mathbb{R}^n : x_1 \geq 0; 0 \leq x_2 \leq x_{2max}\}$, with x_{2max} represents the maximal admitted value of x_2 and the polytope $\mathcal{U} = \{u \in \mathbb{R}^m : u_{min} \leq u \leq u_{max}\}$ with u_{max} and u_{min} are respectively the maximal and the minimal value of the chemotherapy drug, are given for the cancer chemotherapy analysis.

Then considering that the polytope $\bar{\Sigma}$ is also given, the controlled robust one-step operator, introduced in Proposition 2, is defined by using the upper bounds of $\eta^T f_P(x,u)$ given by (17). Finally, Algorithm 1 is applied in order to compute the maximal robust invariant polyhedral set for cancer chemotherapy model since $F_{\bar{P}}(x,u,\eta)$ is piecewise affine function.

Remark 3. *By applying Algorithm 1, we have found that the sequence of polytopes $\Omega_k = \{x \in \mathbb{R}^n : H^kx \leq h^k\}$ generated by the controlled robust one-step operator have never a facet determined by $H^k{}_i$ with $H^k{}_{i,2} < 0$ except the case related to the trivial constraints $x_2 \leq 0$ which can be neglected in the computation, then the lower bound of e^{-x_1} is never used. This would mean that the sequence of polytopes obtained and the robust domain of attraction are affected only by the mismatches between e^{-x_1} and the piecewise function $\max\limits_{i\in\mathbb{N}_q}\{c_ix_1 + d_i\}$, mismatch that can be done arbitrarily small, as notice in Remark 2. Hence the desired precision can be achieved by employing sufficiently close piecewise approximations of e^{-x_1}. Consequently,*

the conservatism introduced by approximating the uncertain non-linear cancer model (14) by a parameters-dependent CDI system (5) can be reduced increasing the precision as indicated in Remark 2.

Thus according to Remark 3, the piecewise affine bound function of $\eta^T f_P(x,u)$ to be employed is that given for $\eta_2 \geq 0$. Therefore the related controlled robust one-step operator for the cancer model (14) is given as follow:

$$\begin{aligned} Q(\Omega,\mathcal{U},\mathcal{X}) = \Big\{ & x \in \mathcal{X} : \exists\, u \in \mathcal{U} : \forall i \in \mathbb{N}_{n_h}, \forall j \in \mathbb{N}_q,\ \forall \bar{P} \in \bar{\mathcal{V}}, \\ & \Big(H_{i,1}(1-T_s\alpha) + H_{i,2}T_s\delta c_j\Big)x_1 + H_{i,2}\Big(1-T_s\beta\Big)x_2 \\ & \leq h_i - H_{i,2}T_s\delta d_j - \Big(H_{i,1}T_s k + H_{i,2}T_s l\Big)u \Big\}, \end{aligned} \tag{18}$$

where $\bar{\mathcal{V}}$ is the set of vertices of $\bar{\Sigma}$. Then $Q(\Omega,\mathcal{U},\mathcal{X})$ maps polytopes in polytopes and Algorithm 1 generates a sequence of polytopes.

Therefore this one-step operator can be used in Algorithm 1 to compute the robust domain of attraction of the uncertain cancer chemotherapy model (14). This domain is given in state space (x_1, x_2).

3.3.2. Tumor-normal cells robust domain of attraction

Once the robust domain of attraction Ω_{max} for the cancer chemotherapy model (14) has been obtained by applying Algorithm 1 with the one-step operator (18), the tumor-normal cells robust domain of attraction of the cancer chemotherapy model (12) can be determined using change of variables.

Now we assume that $\Omega_{max} = \{x \in \mathbb{R}^n : Hx \geq h\}$ with $H \in \mathbb{R}^{n_h \times n}$. Thus by using the change of variables $x_1 = \ln\dfrac{\theta_L}{L}$ and $x_2 = \ln\dfrac{\theta_N}{N}$ the robust domain of attraction in the state space (L,N) is given by the following equation

$$\Upsilon = \left\{ (L\,N)^T \in \mathbb{R}^2 : N \geq \max_{i\in N_{n_h}} \left\{ \left(\frac{\theta_N{}^{|H_{i,2}|}}{\theta_L{}^{|H_{i,1}|}} e^{-h_i} \right)^{\frac{1}{|H_{i,2}|}} L^{\frac{|H_{i,1}|}{|H_{i,2}|}} \right\} \right\}. \tag{19}$$

Since the Eq.(19) depends on the parameters θ_N and θ_L, and these parameters are fixed but unknown, i.e. $\theta_N \in [\underline{\theta}_N \quad \overline{\theta}_N]$ and $\theta_L \in [\underline{\theta}_L \quad \overline{\theta}_L]$, then the tumor-normal cells robust domain of attraction defined by Eq.(19) becomes

$$\begin{aligned} \bar{\Upsilon} = \Big\{ & (L\,N)^T \in \mathbb{R}^2 : N \geq \max_{i\in N_{n_h}} \left\{ \left(\frac{\theta_N{}^{|H_{i,2}|}}{\theta_L{}^{|H_{i,1}|}} e^{-h_i} \right)^{\frac{1}{|H_{i,2}|}} L^{\frac{|H_{i,1}|}{|H_{i,2}|}} \right\}, \\ & \forall \theta_N \in [\underline{\theta}_N \quad \overline{\theta}_N], \quad \forall \theta_L \in [\underline{\theta}_L \quad \overline{\theta}_L] \Big\}. \end{aligned} \tag{20}$$

In Eq.(20), we have to maximize the term $\left\{ \left(\dfrac{\theta_N{}^{|H_{i,2}|}}{\theta_L{}^{|H_{i,1}|}} e^{-h_i} \right)^{\frac{1}{|H_{i,2}|}} L^{\frac{|H_{i,1}|}{|H_{i,2}|}} \right\}$, $\forall i \in N_{n_h}$, $\forall \theta_N \in [\underline{\theta}_N \quad \overline{\theta}_N]$ and $\forall \theta_L \in [\underline{\theta}_L \quad \overline{\theta}_L]$. Hence it is equivalent to consider only the terms $\left(\dfrac{\overline{\theta}_N{}^{|H_{i,2}|}}{\underline{\theta}_L{}^{|H_{i,1}|}} e^{-h_i} \right)^{\frac{1}{|H_{i,2}|}} L^{\frac{|H_{i,1}|}{|H_{i,2}|}}$ for all $i \in N_{n_h}$ and Eq.(20) is equivalent to

$$\bar{\Upsilon} = \left\{ (L\,N)^T \in \mathbb{R}^2 : N \geq \max_{i\in N_{n_h}} \left\{ \left(\frac{\overline{\theta}_N{}^{|H_{i,2}|}}{\underline{\theta}_L{}^{|H_{i,1}|}} e^{-h_i} \right)^{\frac{1}{|H_{i,2}|}} L^{\frac{|H_{i,1}|}{|H_{i,2}|}} \right\} \right\}. \tag{21}$$

Consequently the set $\bar{\Upsilon}$ is the maximal non-convex robust domain of attraction of the cancer chemotherapy model (12) in the state space (L,N).

4. Simulation results

In this section, the method for the computation of the robust domain of attraction that is developed in Section 2 is applied to analyse the cancer chemotherapy model given in Section 3. The parameters of this model are considered unknown but assumed to belong into known intervals. According to our knowledge, this assumption is consistent and maybe it is the suitable manner to address the problem of variability of the parameters of cancer models.

For simulation the chemotherapy drug profile is constrained to take value between $u_{min} = 0$ and $u_{max} = 1$. The minimal admitted level of the normal cells population is $N_{min} = 0.1\theta_N Cells$, which implies that $x_{2max} = 2.30$ by using change of variable defined in the previous sections. Since the exact values of the model parameters are not available in the literature the value of N_{min} is also taken approximately as others parameters described and noted in Section 2.

Once the set of state constraints $\mathcal{X}$ and the initial robust invariant set Ω_0 are selected, Algorithm 1 is fully automatic and no parameters are needed to be selected.

4.1. Robust domains of attraction versus uncertainty degree of model parameters

Applying Algorithm 1 with the controlled robust one-step operator (18), by starting with an initial controlled robust invariant set Ω_0, a sequence of controlled robust invariant sets is computed. This sequence of sets converge to the controlled robust invariant set of the cancer chemotherapy model (14), in the state space (x_1, x_2).

For the model considered in this paper the set $\Omega_0 = \{x \in \mathcal{X} : x_1 \geq a\}$ with a big enough, for which the invariance condition $\Omega_0 \subseteq Q(\Omega_0,\mathcal{X},\mathcal{U})$ holds, is used as an initial controlled robust invariant set. The controlled robust one-step operator (20) is to be used to check the robust invariance of sets.

In order to illustrate the use of the method developed in the paper, let us assume that the parameters of the cancer chemotherapy model (12) can have variations of 30% around their nominal values.

Figure 2 shows a sequence of nested controlled robust invariant sets that converge to the maximal controlled robust invariant set. This sequence of sets is depicted in black line. Notice that Ω_{k+1} is defined as the set that contains all the states for which there exist a set of admissible chemotherapy drug such that these states can be mapped in Ω_k in one step regardless of the parametric uncertainties. In the same figure, the maximal controlled invariant set of the cancer chemotherapy model

(14) computed taking the nominal values of the parameters is depicted in blue line.

By applying (21) to the sets given in Figure 2, one gets the tumor-normal cells robust domains of attraction of the cancer chemotherapy model (12). These domains are depicted in Figure 3. In black line, the robust domain of attraction of the cancer chemotherapy model (12) is showed. This domain contains all the tumor and normal cells states that can be driven to the set of healthy states considering that the parameters of the cancer chemotherapy model are uncertain. In blue line the domain of attraction of the cancer chemotherapy model (12) is shown for comparison purpose.

According to simulation results given in this section, we remark drastic reduction of the domain of attraction and we conclude that this reduction is caused by model parameters uncertainties. Therefore, in order to achieve a successful chemotherapy treatment, the identification of the real values of the model parameters or the assumption that the model parameters are unknown but belong to given known intervals are crucial.

The robust domain of attraction, with arbitrary precision, is the exact domain of all the initial tumor and normal cells states for which there exist appropriate administration chemotherapy profiles. These administration profiles lead to tumor cells contraction without violating the healthy condition of the patients. Consequently, given a patient state one could infer on the existence of successful chemotherapy treatment. Furthermore, the amount of drugs that should be delivered and the therapy length can also be calculated following the method of this paper.

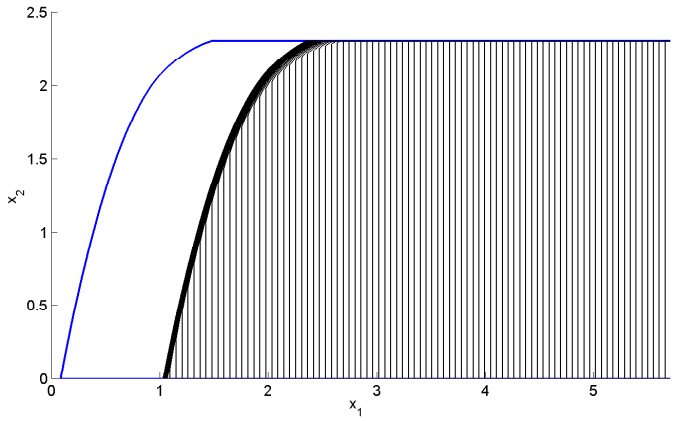

Figure 2: Comparison between the maximal controlled invariant set (blue line) and the maximal controlled robust invariant set computed by considering parameters variations of 30% around their nominal values (black line). The admitted level of x_2 is equivalent to the admitted level of the normal cells, which is $0.1\theta_N$ Cells. The chemotherapy drugs are constrained to take values between $u_{max} = 1$ and $u_{min} = 0$

Figure 4 and Figure 5 show the controlled robust invariant sets of the cancer chemotherapy model (14) in the state space (x_1, x_2), and the robust domains of attraction of the cancer chemotherapy model (12), computed by considering parameters variations of $0\%, 10\%, 20\%, 30\%, 40\%$ and 50% around their nominal values. From these figures, we conclude that the more important the parameters variations around their nominal values are, the more the reductions of domains of attraction of the cancer chemotherapy model (12) are drastic.

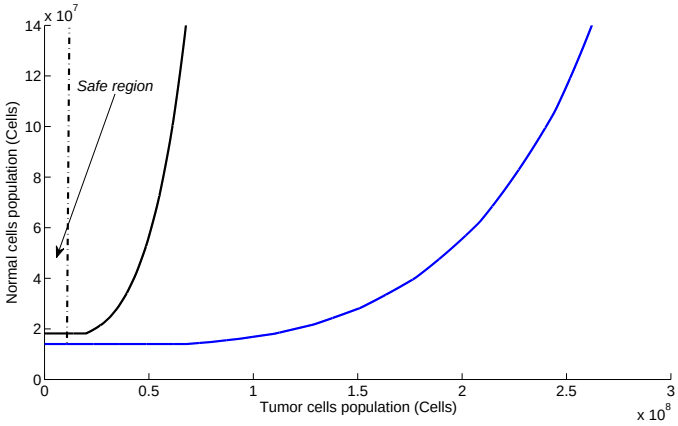

Figure 3: Comparison between the domain of attraction (blue line) and the robust domain of attraction (black line), computed considering parameters variations of 30% around their nominal values, of the cancer model (12). The admitted level of the normal cells is $0.1\theta_N$ Cells. The chemotherapy drugs are constrained to take values between $u_{max} = 1$ and $u_{min} = 0$

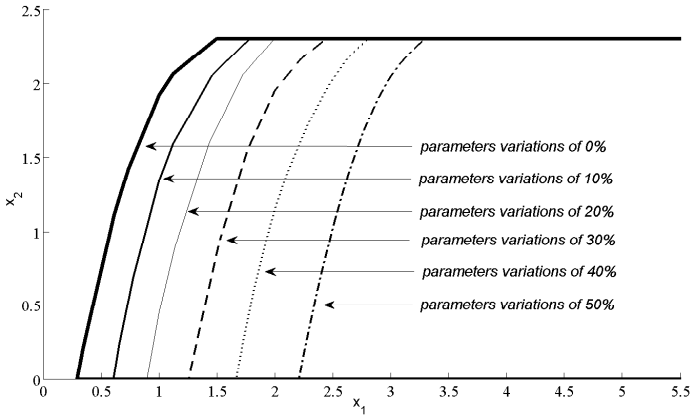

Figure 4: Controlled robust invariant sets, computed by considering parameters variations of $0\%, 10\%, 20\%, 30\%, 40\%$ and 50% around their nominal values, of the cancer chemotherapy model (14) in the state space (x_1, x_2). The admitted level of x_2 is equivalent to the admitted level of the normal cells population, which is $0.1\theta_N$ Cells. The chemotherapy drugs are constrained to take values between $u_{max} = 1$ and $u_{min} = 0$

4.2. Analysis of different chemotherapy drug administration profiles

For a given chemotherapy drug administration profile the related robust one-step operator can be determined by composing (18). For instance, the robust one-step operator for the profile given by one sampling period of full drug injection and one period of null chemotherapy drug is given by the following composition $Q\Big(Q(\Omega, \{0\}, \mathcal{X}), \{u_{max}\}, \mathcal{X}\Big)$.

In order to analyse and compare the robust domains of attraction of appropriate drug administration strategies, three profiles of chemotherapy drugs are taken into account, which are:

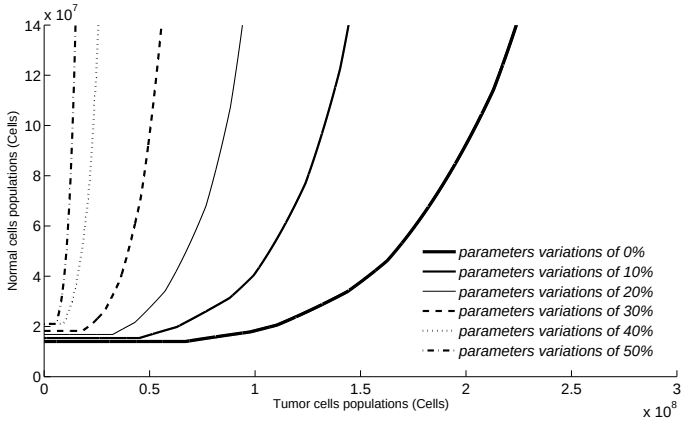

Figure 5: Robust domains of attraction, computed considering parameters variations of $0\%, 10\%, 20\%, 30\%, 40\%$ and 50% around their nominal values, of the cancer chemotherapy model (12). The admitted level of the normal cells population is $0.1\theta_N$ Cells. The chemotherapy drugs are constrained to take values between $u_{max} = 1$ and $u_{min} = 0$

- **chemotherapy drug administration profile 1**: Heavy doses of drugs are applied all the time (chemotherapy aggressive);
- **chemotherapy drug administration profile 2**: Heavy doses of drugs are applied for 12 *days* then no doses are applied for 12 *days*;
- **chemotherapy drug administration profile 3**: Heavy doses of drugs are applied for 4 *days* then no doses are applied for 4 *days*.

Model parameters variations of 30% around their nominal values are considered in the cancer chemotherapy model (12).

Now applying Algorithm 1, Figure 6 shows the robust domains of attraction of the cancer chemotherapy model (12) related to the different chemotherapy drug administration profiles given below. By analyzing the robust domains, one can notice that there are tumor and normal cells populations states that cannot be cured by the chemotherapy drug administration profile 3, whereas they can be healed by applying the chemotherapy drug administration profile 2 and there are tumor and normal cells populations states that can not be cured by chemotherapy drug administration profile 2, however they can be healed by applying the chemotherapy drug administration profile 1. Notice that both profiles 2 and 3 have the same drug delivery rate, i.e. $0.5u_{max}/day$. Consequently, it is more beneficial to attack the tumor cells population for long period then release, than for small period then release.

In Figure 6, the robust domain of attraction computed using the controlled robust one-step operator (18) is depicted in solid line. The chemotherapy drug administration profile is constrained to take value between u_{max} and u_{min}. We remark that this domain is the maximal domain of attraction of the cancer chemotherapy model (12). Consequently, the aggressive chemotherapy is not the recommended chemotherapy treatment for all the patients, and an appropriate treatment for each patient is more beneficial.

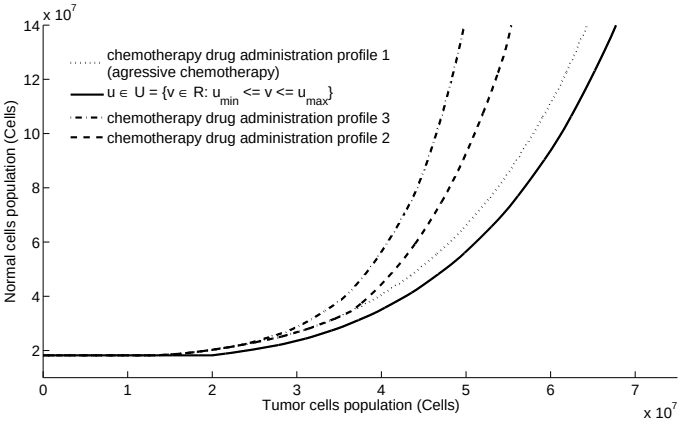

Figure 6: Robust domains of attraction of the cancer chemotherapy model (12) related to different chemotherapy drug administration profile considering parameters variations of 30% around their nominal values. The admitted level of the normal cells population is $0.1\theta_N$ cells

5. Conclusion

In this paper we develop an iterative procedure method to approximate the robust domains of attraction of non-linear systems.This procedure is based on set-theoretic methods and parameters-dependent CDI systems which is used to approximate the uncertain non-linear systems. The good approximation allows us to find the maximal robust domain of attraction as it is shown in the application. In the second part of this paper, we apply the method developed for uncertain non-linear systems to cancer chemotherapy model considering parametric uncertainties and saturation constraints which limit the chemotherapy drug injections.

Thus we have developed numerical tool that leads to compute the robust domain of attraction of cancer chemotherapy model. This domain contains all the initial tumor and normal cells states for which there exists a set of admissible chemotherapy drug administration profiles. It is shown that in order to achieve a successful chemotherapy treatment, either the identification of the real values of the model parameters or the awareness during the treatment synthesis that the parameters of the cancer model are not well known, is crucial.

In future work, alternative modelling frameworks could be employed and other methods for estimating the robust domains of attraction of non-linear systems could follow the work done in this paper.

Acknowledgements

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