Probabilistically Certified Region of Attraction of a Tumor Growth Model with Combined Chemo- and Immunotherapy

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Abstract—This paper deals with the estimation of regions of attraction (RoAs) under parametric uncertainties for a cancer growth model with combined therapies. We propose a framework of probabilistic certification, based on the randomized methods, in order to derive probabilistically certified RoAs of a cancer growth model. The model that we consider in this paper describes the interaction between tumor and immune system in presence of a combined chemo- and immunotherapy. Furthermore, we model the concentration of the chemotherapy agent in the body via a pharmacokinetic equation.

I. INTRODUCTION

The last decades witnessed a considerable progress in experimental and clinical immunology [8] as well as in modeling the immune system dynamics.

The progress in cancer dynamics modeling motivated researchers to apply control approaches in order to schedule cancer treatments using optimal control strategies. We can find in the literature many works regarding the application of optimal control approaches on cancer treatment problems. For instance [6], where optimal protocols for anti-angiogenic therapy were investigated, or [5] where linear controls were designed for a tumor-immune interactions model with chemotherapy delivery. However, only few works addressed the problem of handling parametric uncertainties. One can cite for example, [1] where a robust feedback scheme is proposed to schedule antiangiogenic treatment combined with chemotherapy, [9] where an $H_{\infty}$-based robust control was applied to the same model and [2] where a general framework for probabilistic certification of cancer therapies was proposed.

The estimation of the region of attraction for cancer models is an interesting problem since it provides a set of possible initial conditions (tumor volume and immune density for example) that can be driven to a desired target set (benign region). This problem becomes complex when dealing with nonlinear systems and even more challenging for uncertain systems. There are some works which dealt with the problem of estimating the RoA for cancer models but only few of them considered model uncertainties. In particular, in [12], an iterative method to estimate the robust RoA was presented. However, robust RoA estimation is based on the worst-case scenario analysis leading to very pessimistic design. This is because the worst case is considered no matter how small its probability of occurrence is.

In this paper, we propose a framework to probabilistically certify the existence of a control structure that drives the states corresponding to tumor cells and immune density from an initial state set to a certified target set. This probabilistic certification framework is based on the randomized methods proposed in [3] and [4], which, unlike the robust classical design, avoids focusing on few unlikely very bad scenarios allowing to overcome the conservatism of the robust RoA design. The methodology that we propose in this paper consists mainly of two steps. Firstly, we derive an ordered sequence of sets and a control strategy over each of them such that the states can be driven from a set to the previous with a certain probabilistic guarantee. The appropriate choice of the first set allows to insure that the union of the sets is a probabilistically certified approximation of the RoA. The second step consists of providing a global certification on the probability of convergence to the initial certified target set.

This paper is organized as follows: In Section II, the dynamical cancer model and the problem of RoA probabilistic certification are introduced. In Section III, a framework for RoA probabilistic certification is proposed, based on the randomized methods presented in [3] and [4]. In Section IV, the proposed RoA probabilistic certification framework is applied to the considered cancer model. Finally, Section V summarizes the contribution and gives some hints for further investigation.

II. PROBLEM STATEMENT

The following nonlinear dynamical system describes the interaction between tumor and immune system in presence of chemotherapy and immunotherapy drugs:

$$\begin{align*}
\dot{x}_1 &= \mu_C x_1 - \frac{\mu C}{x_\infty} x_1^2 - \gamma x_1 x_2 - \alpha x_1 x_3, \\
\dot{x}_2 &= \mu_1 x_1 x_2 - \beta x_1^2 x_2 - \chi x_2 + \lambda x_2 - \sigma x_3 x_2 + \alpha, \\
\dot{x}_3 &= -ax_3 + bu_1, \\
x(0) &= (x_1(0), x_2(0), x_3(0)) = x_0,
\end{align*}$$

(1)

where $x_1$, $x_2$ and $x_3$ denote, respectively, the number of tumor cells, the density of effector immune cells (ECs) and the concentration of chemotherapy in the body, $u_1$ and $u_2$ are, respectively, the dosages of a cytotoxic agent and an immuno-stimulator. This model gives the
advantage of a low dimensional system that nevertheless includes the main aspects of cancer-immune interactions.

In many models it is assumed that the drug concentration is equal to its dosage which is an oversimplification. Therefore, we revisited the model proposed in [7] by adding a pharmacokinetic (PK) equation that allows to model the concentration of chemotherapy in the body. This equation is a classical PK model with an exponential growth/decay of the drug concentration.

Fig. 1 presents a scheme describing the different interactions between the tumor and the immune system. Table I summarizes the definitions of the model parameters and their numerical values. We slightly tuned the values of some parameters since with the previous set of parameters values (used in [11] and [10]), the domain of attraction of the benign equilibrium for the uncontrolled system (1) (for \( u_1 = 0 \) and \( u_2 = 0 \)) was unrealistically big, this allows us to solve a more challenging and seemingly realistic problem. Moreover, we properly chose the parameters \( a \) and \( b \) of the PK dynamics, such that the drug concentration reaches its maximum in 4.8h and starts decreasing towards a negligible value after a period of 15 days. Nevertheless, it is worth emphasizing that in this paper, we focus on the assessment of a methodology that remains applicable for different nominal and PK parameters values.

Let’s denote by \( x = (x_1, x_2, x_3) \) and \( u = (u_1, u_2) \) respectively, the state and the control input vectors. In this paper, we consider a cycle-based treatment, where the drugs are injected following \( N_C \) therapeutic cycles, each cycle has two phases, a hospitalization period where the drugs are injected for 5 consecutive days and a rest period where the patient recovers. Fig. 2 shows a typical temporal combined control structure where the time unit is in days, \( \sigma_1 \) and \( d_1 \) stand for the duration and the concentration level of the immunotherapy injection, respectively. The chemotherapy is assumed to be delayed from the immunotherapy by \( \nu_C \) and is injected for \( \sigma_C \) days with a concentration \( d_C \). \( T \) stands for the time of the hospitalization period while \( T_e \) denotes the cycle duration. Therefore, for a given treatment cycle, the therapeutic profile considered in this paper is completely defined by the following control parametrization \( \theta \):

\[
\theta = [\nu_C, \sigma_C, d_C, \sigma_I, d_I].
\]

In cancer treatment design, we usually have many constraints to satisfy, they can be defined either on the states or on the control inputs. These constraints enable to prevent from drug toxicity and immune weakening. Therefore, we consider the following constraints:

\[
\begin{align*}
& x_2(t) \geq c, \quad \forall t \in [0, T] \quad \text{with} \quad c, T \in \mathbb{R}^+, \\
& 0 \leq x_3(t) \leq 1, \quad 0 \leq u_2(t) \leq 1,
\end{align*}
\]

where the first constraint is a health constraint on the minimal density of immune cells. The constraints on \( x_3(t) \) and \( u_2(t) \) for all \( t \), are drug toxicity constraints. The constraint on \( x_3 \) can be satisfied by properly choosing a constraint on \( u_1 \), given the PK parameters \( (a \text{ and } b) \) since these two variables are linked through a simple first order dynamics. Fig. 3 shows a typical PK curve, where 5 consecutive doses of chemotherapy are injected, at a rate of 1 dose per day, each dose last 4.8h. We can notice that thanks to a proper choice of the constraint on \( u_1 \), the

![Fig. 1: Schematic representation of the different interactions in model (1), between tumor, immune system and drug dosages.](image)

![Fig. 2: Temporal open-loop control structure for each cycle, in black and yellow, respectively, the immunotherapy and the chemotherapy profiles.](image)

![Fig. 3: Typical PK curve.](image)
constraint on \( x_3 \) is satisfied even for successive drug doses injections. Furthermore, the constraints on the control inputs, \( u_1 \) and \( u_2 \), can be satisfied by properly choosing the parametrization \( \theta \) of the control input \( u \). Therefore, we will consider only the first constraint on \( x_2 \), since the satisfaction of the other constraints can be monitored by a proper choice of \( \theta \).

![Fig. 3: A typical PK curve for chemotherapy, where \( u_1 \) represents 5 consecutive doses of 4.8h, during the 5 first days of the therapy period, at a rate of one dose per day.](image)

III. RoA PROBABILISTIC CERTIFICATION USING RANDOMIZED METHODS

In this section, we will establish a framework of RoA probabilistic certification, based on the randomized methods presented in \([3]\) and \([4]\). Therefore, we will briefly recall the main key-points of the randomized approaches that are important for our RoA certification framework. The Randomized methodology had been used to certify feedback control strategies in \([2]\) for a combined cancer therapy model. In this paper, we propose to use this general framework in order to probabilistically certify the existence of a control structure which allows to drive initial states from a given set to a target set under parametric uncertainties.

Let’s rewrite system \( \mathbf{1} \) into the following form:

\[
\dot{x} = f(x, u, p),
\]

where \( p \) is the vector of parameters that model \( \mathbf{1} \) involves. Furthermore, we consider that the variables of system \( \mathbf{1} \) are subject to the following constraints:

\[
x \in X, \quad x(T) \in \Omega, \quad u \in U.
\]

In this paper, we are interested in specific control structures, since in cancer treatment, control inputs cannot be free real variables. They are usually defined by specific cyclic protocols, as illustrated in the subsequent section. Furthermore, in order to solve the optimization problem that we will define in the sequel, using the randomized methods, we need to consider that the control inputs are parametrized by a vector \( \theta \) which lies in a discrete set \( \Theta \) with cardinality \( n_\Theta \in \mathbb{N} \). However, this choice of \( \theta \) remains interesting in the case of cancer therapy design, since some of the parameters involved in the treatment scheduling are naturally quantified.

We consider that the parameters vector \( p \) is a random variable following the probability distribution \( \mathcal{P} \) that we denote \( p \sim \mathcal{P} \). Given a set \( \Gamma \subseteq \mathbb{R}^n \) (to be more precise, \( \Gamma \) must belong to the \( \sigma \)-algebra defined on \( \mathbb{R}^n \)) and a parameterization of the input \( \theta \in \Theta \), let’s consider the following optimization problem:

\[
\min_{\theta \in \Theta} J(\theta) \quad \text{s.t.} \quad \forall (x_0, p) \in (\Gamma \times \mathcal{P}) \quad g(\theta, x_0, p) = 0,
\]

where \( J(\theta) \) is a cost function to be minimized. In terms of cancer treatment design, this function can be a combination of many objectives that one seeks to achieve, for example reducing the quantity of injected drugs, to prevent from toxicity, or reducing the duty cycle in order to reduce the hospitalization duration. Whereas \( g \) is the failure indicator function, defined on the state trajectories of \( \mathbf{1} \). The function \( g \), in particular, is a deterministic function that, for given initial state, input parameter \( \theta \) and model parameter \( p \in \mathcal{P} \), has value equal to one if constraints \( \mathbf{5} \) are violated, zero otherwise. Problem \( \mathbf{4} \), then, aims at selecting the optimal control strategy such that no specification violation occurs.
The randomized method consists of replacing the original problem in (6) by the following chance-constrained problem allowing some violations:
\[
\min_{\theta \in \Theta} J(\theta) \quad \text{s.t.} \quad \text{Pr}_{x_0(\Gamma) \times \mathcal{P}} \{g(\theta, x_0, p) = 1\} \leq \eta,
\tag{7}
\]
where the constraint is on the probability of constraints violation, with respect to the distribution of \(x_0\) on \(\Gamma\), that we denote \(x_0(\Gamma)\), and \(p \sim \mathcal{P}\). This problem gives therefore a chance constrained formulation in the sense that we can accept a vector \(\theta\) which minimizes the cost \(J\), even if the specifications are violated for some realizations of \((x_0, p)\), provided that the probability of these violations is lower than \(\eta\) hence small enough.

Since problem (7) is hard to solve, it can be simplified into the following problem, employing the empirical mean instead of the probability of the constraints violations.
\[
\min_{\theta \in \Theta} J(\theta) \quad \text{s.t.} \quad \sum_{i=1}^{N} g \left( \theta, x_0(i), p(i) \right) \leq m,
\]
\[
(x_0, p)(i) \sim (x_0(\Gamma) \times \mathcal{P}), \quad \forall i = 1, \ldots, N,
\tag{8}
\]
where \(m\) is the maximum number of constraints violation.

**Theorem 1**: For given \(\Gamma \subseteq \mathbb{R}^n\), let \(m \in \mathbb{N}\) be any integer, let \(\delta \in (0, 1)\) be a targeted precision parameter, and suppose that problem (8) has a solution, that we denote \(\hat{\theta}\), for \(N\) i.i.d. samples of \((x_0, p)\), with \(N\) satisfying the following condition from [4]:
\[
N \geq \frac{1}{\eta} \left( m + \ln \left( \frac{n_0}{\delta} \right) + \left( 2 m \ln \left( \frac{n_0}{\delta} \right) \right)^{\frac{1}{2}} \right)
\]
Then the solution \(\hat{\theta}\) satisfies the constraint in problem (7) with a probability higher than \(1 - \delta\).

It is interesting to notice that the bound on \(N\) in Theorem 1 provided by [4] does not depend on the dimension of the vector \((x_0, p)\) which is useful when having many uncertain parameters and initial states in the certification problem. Furthermore, the confidence parameter \(\delta\) affects the bound with a logarithmic term which means that we can have a highly confident certification with a tractable number of random samples.

Therefore, the iterative resolution of problems of the type (8) allows one to generate a sequence of sets \(\{\Omega_k\}_{k=1}^{N_C}\) such that the constraints violation on passing from \(\Omega_{k+1}\) to \(\bigcup_{j=0}^{k} \Omega_j\) is smaller than \(\eta\) with a certain desired confidence probability \(1 - \delta\).

**A. Algorithm for RoA estimation**

Given a target set \(\Omega\), let’s suppose that our objective is to certify that the set \(\Gamma\) is such that there exists a control parametrization \(\theta\), for which at least \(100 \cdot (1 - \eta)\)% of the trajectories of (4), generated by the distributions of the initial states \(x_0 \in \Gamma\) and the uncertain parameters \(p\), converge to \(\Omega\) at time \(T\), while satisfying constraints \([\delta]\), with a probability of confidence higher than \(1 - \delta\). Any solution of \([\delta]\) defines a local control strategy that satisfies the constraints while minimizing the cost \(J(\theta)\).

**\(\Gamma\) generator**: we suppose that we have a generator of sets \(\Gamma\) with a parametrized geometry providing a family of nested potential geometry, then we can compute the biggest one that is probabilistically certified through \([\delta]\).

Therefore, starting from \(\Omega_0\) which is known to be in the region of attraction of the desired equilibrium, an iterative procedure can be designed to generate the sequence \(\{\Omega_k\}_{k=0}^{N_C}\) such that the trajectories starting in \(\Omega_{k+1}\) end in \(\bigcup_{j=0}^{k} \Omega_j\) with the desired probability and without violating the constraints. In particular, we will consider sequences of sets such that \(\Omega_k \cap \Omega_{k+1} = \emptyset\). Then we keep doing this certification process until, given \(\Omega_{k-1}\), the set \(\Omega_k\) is empty. Once the RoA probabilistic certification algorithm terminates, the probabilistically certified RoA is the set \(\Omega_C = \bigcup_{i=1}^{N_C} \Omega_i\).

Note that, if \(x_0 \in \Omega_k\) for \(k = 1, \ldots, N_C\), this means that the trajectory of length \(T\) will end in \(\bigcup_{j=0}^{k-1} \Omega_j\) without violating the constraint with a certain probability, but no direct probabilistic guarantee is given regarding the convergence to the set \(\Omega_0\). It is not straightforward to derive a probabilistic bound on driving the states directly from the last set of the sequence \(\Omega_{N_C}\) to \(\Omega_0\). This because it involves the accuracy and confidence parameters, \(\eta\) and \(\delta\), but also since there is no guarantee that, given the initial state distribution \(x_0(\Omega_0)\), the distribution of the state at the end of the \(k\)-th therapeutic cycle is \(x_0(\Omega_{k-1})\), for which the probabilistic validation is performed. However, after deriving the sequence of certified sets, we can approximate the probability of driving the states from \(\Omega_{N_C}\) to \(\Omega_0\), with the derived certified control strategy, using Monte-Carlo simulations.

**Algorithm 1** Sequence of probabilistically certified sets

**Input**: \(\Omega_0\)

\[k \leftarrow 0\]

**while** \(\Omega_k \neq \emptyset\) **do**

\[\Omega \leftarrow \bigcup_{j=0}^{k} \Omega_j\]

**repeat**

\[\text{Generate } \Gamma\]

**until** \([\delta]\) is unfeasible for \(\Gamma\)

\[k \leftarrow k + 1\]

\[\Omega_k \leftarrow \Gamma\]

**end while**

\[N_C \leftarrow k - 1\]

**Output**: \(\Omega_C = \bigcup_{i=1}^{N_C} \Omega_i\)
Finally, by using Algorithm 1 we can obtain a sequence of certified sets, such that the output is the probabilistically certified RoA $\Omega_C$.

IV. PROBABILITYALLY CERTIFIED ROA FOR CANCER MODEL

In cancer treatment, therapies are usually injected following many successive cycles with specific periods of hospitalization and rest. This makes the certification framework presented in the previous section suitable to certify RoAs for a cancer model. Hence, considering $N_C$ treatment cycles, our objective consists of estimating the probabilistically certified RoA of model (1) that we denote $\Omega_C$. To this end, we certify a sequence of successive disjoint sets such that their union is the probabilistically certified RoA. Moreover, the temporal control profiles that we consider correspond only to the hospitalization period (see Fig. 2), meaning that the rest period is not included in the decision variable $\theta$ defined in Section II, since we assume that this parameter can be estimated afterwards depending on the health conditions of the patient.

The initial condition $x_0$ is assumed to be uniformly distributed in the set $\Gamma$ while the parameters of model (1) are assumed to be normally distributed in the intervals $[0.9p_{nom},1.1p_{nom}]$, where $p_{nom}$ is the nominal value of each parameter and the variance of these distributions is 0.01. The parameter $x_{\infty}$ is supposed to be known and doesn’t follow any distribution.

The failure indicator function, which indicates whether the constraints (11) are satisfied or not, is defined on $x(t|x_0,p,\theta)$ which is the state trajectory of (1) for a given control parametrization $\theta$ and a random sample of $x_0$ and $p$. We denote by $x(T|x_0,p,\theta)$ the state trajectory $x$ evaluated at the end of the hospitalization period. Therefore, the failure indicator is defined as:

$$
g(\theta,x_0,p,\Omega) := \begin{cases} 
0 & \text{if } x_2(t|x_0,p,\theta) \geq c \ \forall t \text{ and } x(T|x_0,p,\theta) \in \Omega \ \\
1 & \text{otherwise}
\end{cases}
$$

where $\Omega$ is a probabilistically certified target set which can be seen as the safe region. Using Algorithm 1 we can derive a sequence of probabilistically certified sets providing the probabilistically certified RoA. Firstly, we need to derive an initial target set $\Omega_0$, in order to initialize the certification algorithm.

A. Probabilistically certified initial target set $\Omega_0$

We define the probabilistically certified initial target set $\Omega_0$ as being the uncontrolled probabilistically certified region of attraction of many locally asymptotically stable equilibriums. Therefore, given $p \in \mathcal{P}$ (drawn according to the probability distribution $\mathcal{P}$) and $x_0$ following a uniform distribution on $\Omega_0$, that we denote $\mathcal{U}(\Omega_0)$, we certify that:

$$
\mathbb{P}_{t \in [\Omega_0]} x_{2}(t|x_0,p) \geq c, \ \forall t > 0 \ \land \ x(T|x_0,p) \in \Omega_{eq} > 1 - \eta, \tag{9}
$$

for a given time $T$. We denote by $\Omega_{eq}$ a certified set in a neighborhood of benign equilibriums of (1), generated by the realizations of $p$ according to the probability distribution $\mathcal{P}$. Therefore $\Omega_{eq}$ is derived such that:

$$
\mathbb{P}_{t \in [\Omega_{eq}]} x_{2}(t|x_0,p) \geq c, \ \forall t > 0 \ \land \ x(T|x_0,p) \in \Omega_{eq} > 1 - \eta, \tag{10}
$$

Note that $\Omega_{eq}$ is slightly different than a probabilistically certified invariant set, since we don’t require that the trajectories starting in $\Omega_{eq}$ stay in it, rather require that these trajectories satisfy the constraints (3) and converge to $\Omega_{eq}$ after some time $T$. Moreover, the set $\Omega_{eq}$ is derived in order to be used as a target set for the determination of $\Omega_0$.

In order to find $\Omega_{eq}$, we draw the distribution of the benign equilibriums of model (1) when it is subjected to parametric uncertainties. Then, we choose a geometry for $\Omega_{eq}$ surrounding the benign equilibriums of the sample shown in Fig. 4. Finally, we expand this set until (10) is not satisfied. Fig. 4 shows the probabilistically certified RoA of benign equilibriums $\Omega_{eq}$, the estimated uncontrolled nominal region of attraction $\Omega_N$ and the initial probabilistically certified target set $\Omega_0$ for different $T$.

Using the phase-portrait of system (1) with $u = 0$ and considering nominal parameters (in Table I), we give an estimate of the nominal region of attraction of the benign equilibrium for system (1) without control, denoted $\Omega_N$, see Fig. 4. After finding a proper geometry for the set $\Omega_{eq}$ such that it satisfies (10), we use the transition between (11) and (12) provided by the randomized methods, in order to certify the set $\Omega_0$. Note that in this case $\lambda_0(\Gamma)$ corresponds to $\mathcal{U}(\Omega_0)$ since we assume that $x_0$ is uniformly distributed on $\Omega_0$, and the target set for the states at time $T$ denoted $\Omega$ in the definition of $g$ corresponds to $\Omega_{eq}$. Furthermore, since we deal with an uncontrolled problem, we have that $\theta = 0$, therefore, (12) turns out to be a feasibility problem, where we need only to guarantee the probability condition in (11) by using the empirical mean over $g$ for $N$ i.i.d. samples of $(x_0,p)$ mentioned in (13), with $\theta = 0$ and $n_\theta = 1$, the bound $N$ is then given by Theorem 1.

Therefore, we assume that the set $\Omega_0$ to be certified has the same geometry as the estimated nominal uncontrolled region of attraction $\Omega_N$ that we shrink until (10) is not satisfied given the confidence probability $1 - \delta$. There
is clearly no guarantee that the set $\Omega_0$ that we obtain is the biggest possible certified set, however, in this case, proving the existence of a set $\Omega_0$ satisfying $\mathcal{Q}$ is enough, since $\Omega_0$ is only used as a target set for the Algorithm I allowing therefore to compute the sequence of certified sets.

B. Probabilistically certified region of attraction $\Omega_C$

We denote by $\Omega_C$ the probabilistically certified region of attraction of system $[1]$. We initialize Algorithm I with $\Omega_0$ in order to derive the sequence of probabilistically certified sets providing the certified RoA for model $[1]$.

We consider that the decision variable $\theta$ is defined by the following variables:

$$\begin{align*}
\sigma_I &\in \{0, 0.16, 0.32, 0.48, 0.64, 0.8\}, \\
\sigma_C &\in \{0.2, 0.25, 0.5, 0.75, 1\}, \\
d_I &\in \{0, 0.22, 0.33, 0.44, 0.56, 0.67, 0.78, 0.89, 1\},
\end{align*}$$

where $\tilde{d}_C$ denotes the maximal desired concentration of $x_3$ allowing to monitor $d_C$. Therefore, the cardinality of $\Theta$ is $n_\Theta = 300$ giving the bound $N \geq 1863$ according to Theorem 1, for $\eta = 10^{-2}$ and $\delta = 10^{-3}$. The number of simulations to be performed for each set certification is $N_{\text{sim}} = N \cdot n_\Theta = 558900$. The required computational time to perform $N_{\text{sim}}$ simulations is around $5.79\text{mn}$ using Matlab coder toolbox, therefore, 1 simulation requires around $621\mu\text{s}$ on an hp EliteBook 2.60GHz Intel Core i7.

Fig. 5 shows the 3 certified cycles for $T = 5$ obtained using Algorithm I nominal and robust RoAs that have been estimated using a sliding-mode-based method, where bang-bang feedback control is considered. We can see that, as the number of cycles increases, the certified RoA gets closer to the robust controlled one. Furthermore, it is interesting to notice that there is a small region of $\Omega_2$, which is probabilistically certified but does not belong to the robust RoA, although the control structure in the robust case is less restrictive. This is potentially due to the fact that the probabilistic method is less conservative than the robust one. Furthermore, we approximated the probability of driving the states from $\Omega_3$ to $\Omega_0$ using 5000 Monte-Carlo simulations. We obtained that 99.6% of the trajectories of $[1]$ having initial conditions in $\Omega_4$ converge to $\Omega_0$ using the probabilistic certified control strategies that we derived.

V. Conclusion

In this paper, we presented a framework of probabilistic certification for regions of attraction. This framework is based on the randomized methods which allow to overcome the conservatism of worst-case robust approaches by proposing a tractable problem with probabilistic constraints. The framework of region of attraction certification can be seen as a tool to tune the several parameters of treatment protocols by properly choosing the model parameters and their distributions, the geometry of the regions of attraction to be certified and the control parametrization. An interesting perspective for future work would be to apply this methodology to other systems describing cancer dynamics.

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