

Regions of Attraction Estimation for Tumor Immune Dynamical Systems

Tutorial session: Modeling and Treatment of Cancer

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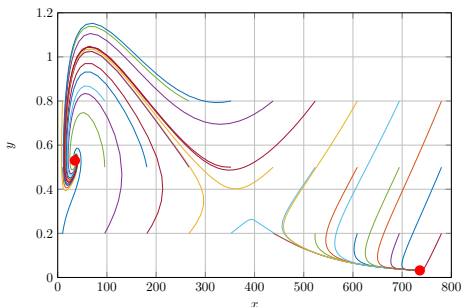
² Univ. Grenoble Alpes, CNRS, Grenoble INP, GIPSA-lab, 38000 Grenoble, France

Cancer growth modeling

- ▶ Modeling **cancer dynamics** using (**ODE's, PDE's...**)
- ▶ **Compartmental modeling** of cancer dynamics
- ▶ **Experimental tests** for cancer are highly expensive
- ▶ Modeling cancer dynamics helps to:
 1. **Analyze** the different involved mechanisms
 2. **Predict** the cancer behavior
 3. Provide systematic approaches for **cancer drug scheduling**

Region of attraction (RoA) estimation for cancer models

- ▶ RoA is the set of **all initial conditions** for which there exists a control such that the state trajectory is driven to a **stable equilibrium**
- ▶ It is highly important in the context of cancer dynamics to find the set of initial **health indicators** that can be **healed**



- ▶ x : The number of tumor cells
- ▶ y : The density of immune cells

Outline

- 1 Modeling cancer immune interactions
- 2 Probabilistically certified region of attraction of a cancer model
- 3 Take-away messages & perspectives

Classical cancer-immune interactions model

$$\dot{x}_1 =$$

$$\dot{x}_2 =$$

x_2 : density of immune cells

x_1 : number of tumor cells



Immune cells x_2



Tumor x_1

A. d'Onofrio, U. Ledzewicz, H. Schättler, *On the Dynamics of Tumor-Immune System Interactions and Combined Chemo- and Immunotherapy*, New Challenges for Cancer Systems Biomedicine, Springer, 2012

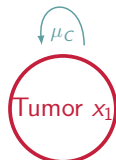
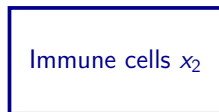
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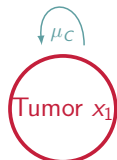
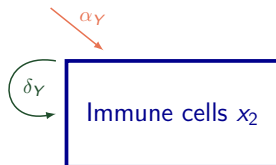
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$$\dot{x}_1 = \mu_C x_1 \left(1 - \frac{x_1}{x_\infty}\right)$$

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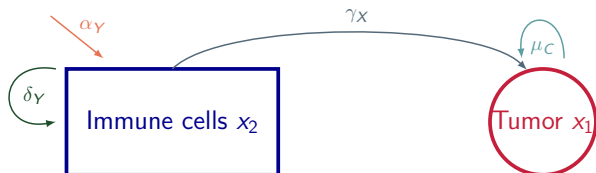
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$$\dot{x}_1 = \mu_C x_1 \left(1 - \frac{x_1}{x_\infty} \right) - \gamma_X x_1 x_2$$

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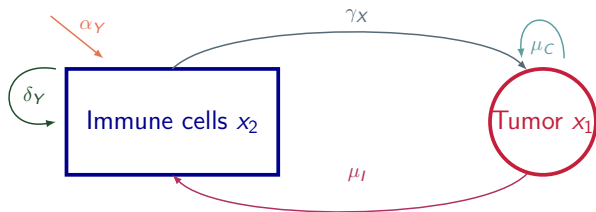
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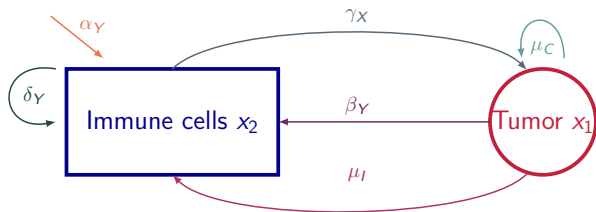
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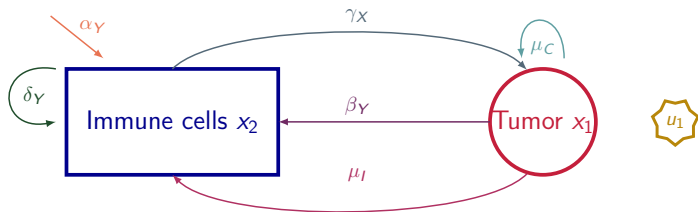
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u_1 : cytotoxic agent



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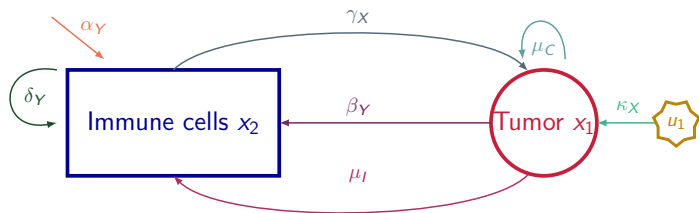
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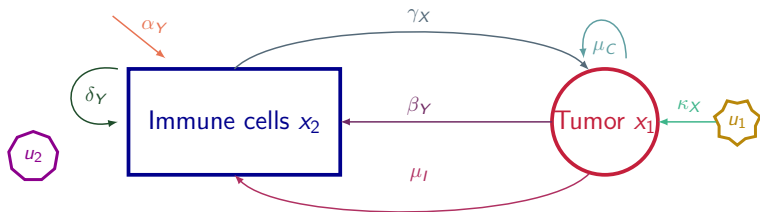
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u_2 : immune stimulation agent

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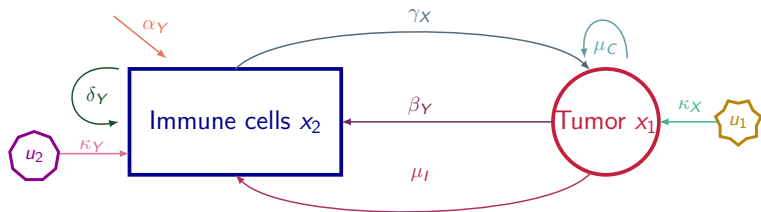
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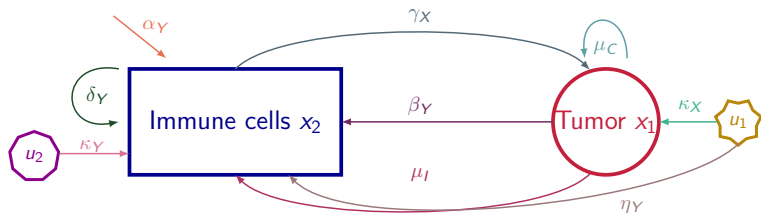
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Chance-constrained optimization problems

Robust optimization problem

$$\min_{\theta \in \Theta} J(\theta)$$

$$\text{s.t.} \quad \forall p \quad g_c(\theta, p) = 0$$

$$g_c(\theta, p) := \begin{cases} 0 & \text{if all the constraints} \\ & \text{are satisfied} \\ 1 & \text{otherwise} \end{cases}$$

- ▶ θ is the decision variable
- ▶ g_c is an indicator function on the constraints violation

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- ▶ η is the **precision**

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Simplified optimization problem

$$\begin{aligned} \min_{\theta \in \Theta} \quad & J(\theta) \\ \text{s.t.} \quad & \frac{\sum_{i=1}^N g_c(\theta, p^{(i)})}{N} \leq \frac{m}{N} \end{aligned} \quad (2)$$

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- ▶ m is the number of **violations**
- ▶ Choosing N s.t. (1) is satisfied with **confidence** δ

Validation guaranties

- ▶ $\theta \in \Theta$ is the **decision** variable with cardinality n_Θ
- ▶ m is the number of **violations**
- ▶ $\{\rho^{(j)}\}_{j=1}^N$ are i.i.d following \mathcal{P}
- ▶ $\delta \in (0, 1)$ is the **confidence**

Theorem [Álamo, 2015]

Take N satisfying

$$N \geq \frac{1}{\eta} \left(m + \ln \left(\frac{n_\Theta}{\delta} \right) + \left(2m \ln \left(\frac{n_\Theta}{\delta} \right) \right)^{\frac{1}{2}} \right)$$

then any solution of (2) satisfies $\Pr_{\mathcal{P}} \{g_c(\theta, \rho) = 1\} \leq \eta$ with a probability $\geq 1 - \delta$

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n_Θ	$\eta = 0.1$	$\eta = 0.01$	$\eta = 0.001$
10	146	1451	14503
100	174	1732	17312
1000	201	2008	20073
10000	228	2280	22796

for $m = 1$ and $\delta = 0.001$

Pharmacokinetics/ Pharmacodynamics

$$\dot{x}_1 = \mu_C \left(1 - \frac{x_1}{x_{\infty}}\right) x_1 - \gamma_X x_1 x_2 - \kappa_X \left(\frac{x_4^{\gamma_C}}{x_4^{\gamma_C} + C_{50C}^{\gamma_C}} \right) x_1$$

$$\dot{x}_2 = \mu_I (1 - \beta x_1) x_1 x_2 + \alpha_Y - \delta_Y x_2 - \eta_Y x_2 x_3 + \kappa_Y \left(\frac{x_5^{\gamma_I}}{x_5^{\gamma_I} + C_{50I}^{\gamma_I}} \right) x_2$$

$$\dot{x}_3 = -(k_1 + k_2) x_3 + s_1 \frac{u_1}{V_1}$$

$$\dot{x}_4 = k_{12} \frac{V_1}{V_2} x_3 - k_2 x_4$$

$$\dot{x}_5 = -c_i x_5 + s_2 u_2$$

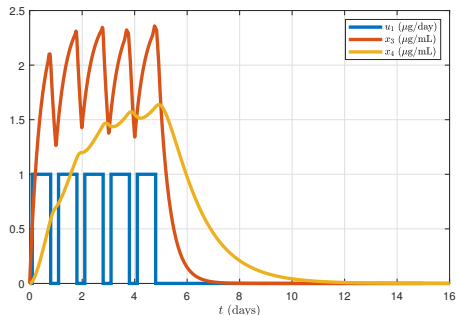
u_1 : Chemo. infusion rate

≠

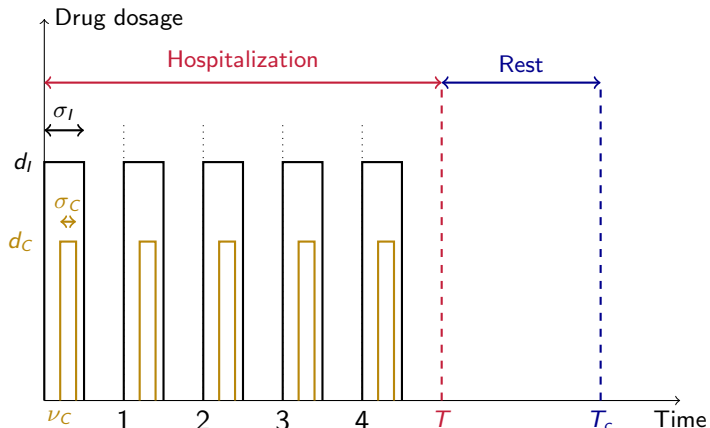
x_3 : Chemo. concentration in the plasma

≠

x_4 : Chemo. concentration in the tumor effect-site



Treatment protocol & decision variable



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

Probabilistically certified RoA framework

$$\dot{x}(t) = F(x(t), u(t), p), x(0) = x_0$$

$$x \in \mathbb{X}, \quad u \in \mathbb{U}, \quad x(T) \in \Omega$$

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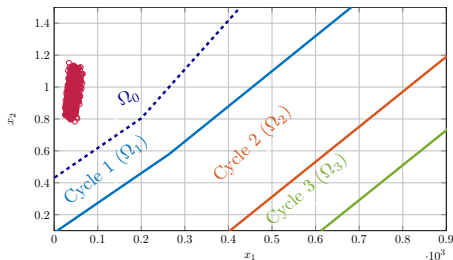
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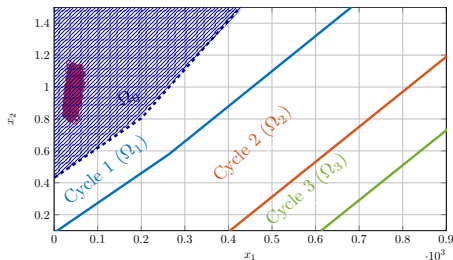
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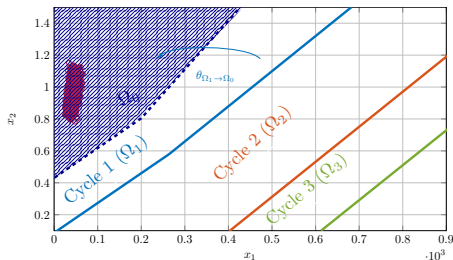
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- Ω_0 is the certified safe region
- We derive a sequence $\{\Omega_k\}_{k=1}^{N_C}$
- $x_0 \sim \mathcal{U}(\Omega_k)$

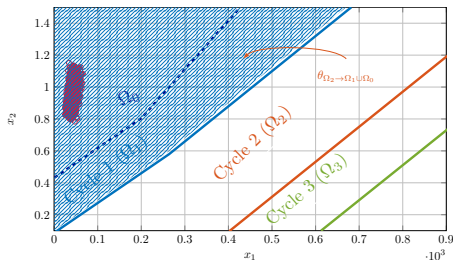
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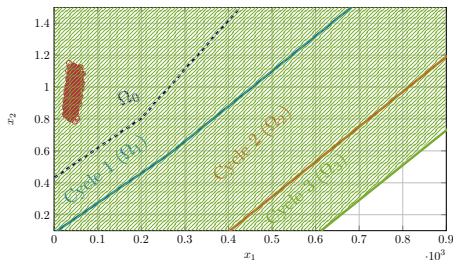
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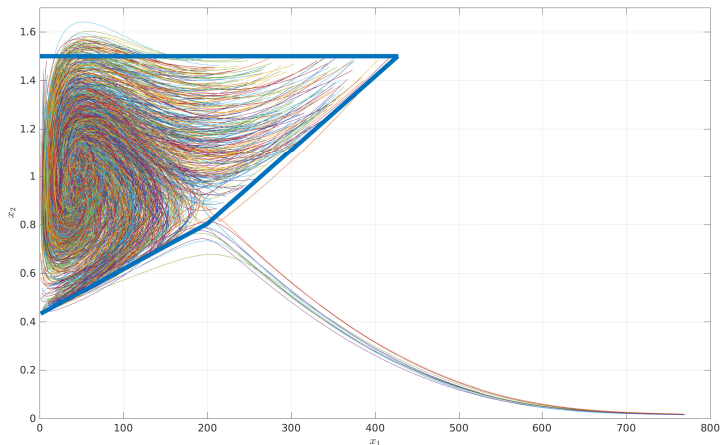
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- ▶ $\Omega_C = \bigcup_{i=0}^{N_C} \Omega_i$

Validation of the certified target set Ω_0 without control

- ▶ 5000 Monte-Carlo tests were performed



Problem setup

Constraints:

$$x_2(t) \geq c, \text{ with } c \in \mathbb{R}_+$$

$$0 \leq u_1(t) \leq 1$$

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Failure indicator:

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

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- ▶ The number of control protocols is $n_\Theta = 300$
- ▶ **Accepted failures** $m = 1$
- ▶ **Precision** parameter $\eta = 10^{-2}$
- ▶ **Confidence** parameter $\delta = 10^{-3}$
- ▶ Number of **scenarios** $N \geq 1863$
- ▶ $N_{sim} = N \cdot n_\Theta = 558900$

Probabilistically certified RoA

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

- ▶ d_C, d_I : concentration of chemo- and immunotherapy
- ▶ σ_I : duration of immunotherapy

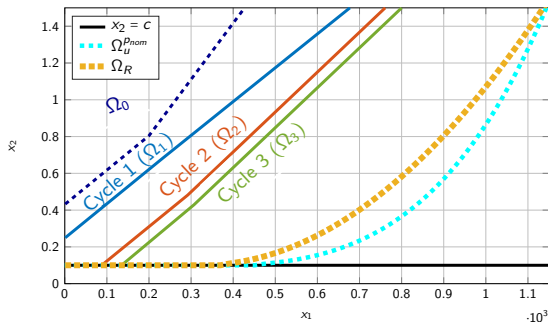
$$\left\{ \begin{array}{l} \sigma_I \in \{0, 0.16, 0.32, 0.48, 0.64, 0.8\}, \\ \sigma_C = 0.5, \quad \nu_C = 0.2, \\ d_I \in \{0, 0.25, 0.5, 0.75, 1\}, \\ d_C \in \{0, 0.11, 0.22, 0.33, \\ \quad 0.44, 0.56, 0.67, 0.78, 0.89, 1\}. \end{array} \right.$$

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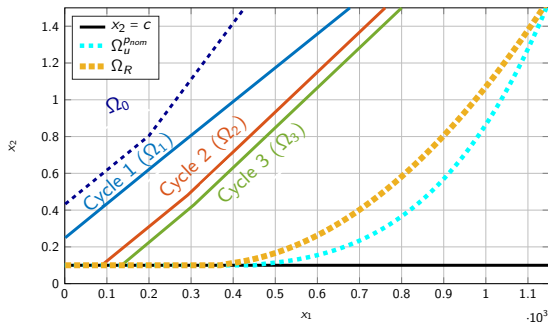


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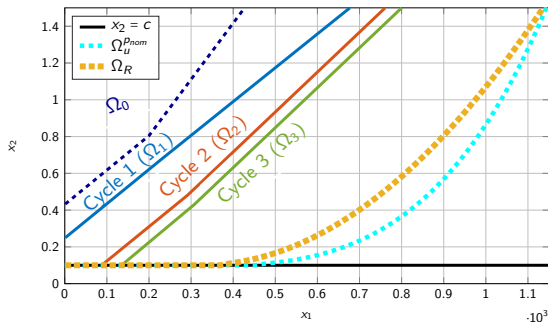
$$\theta_{\Omega_1 \rightarrow \Omega_0} = (0.2, 0.5, 0, 0.64, 0.25)$$

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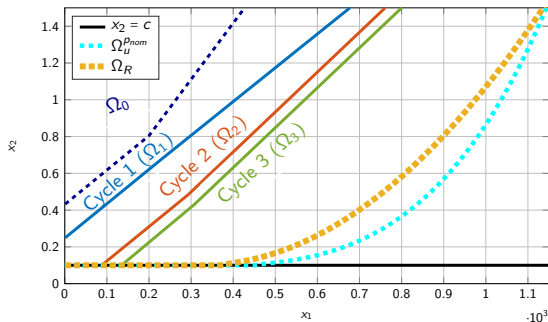
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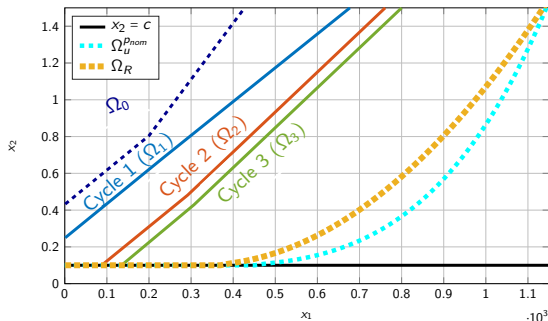
$$\theta_{\Omega_1 \rightarrow \Omega_0} = (0.2, 0.5, 0, \mathbf{0.64}, \mathbf{0.25})$$

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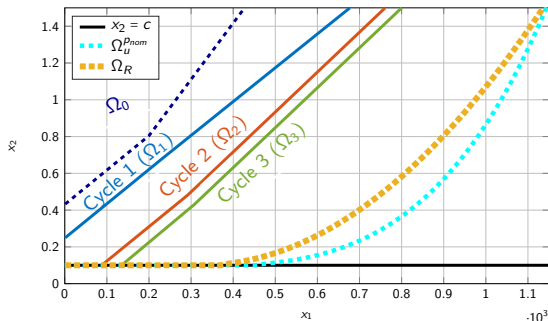
$$\begin{aligned} \theta_{\Omega_1 \rightarrow \Omega_0} &= (0.2, 0.5, 0, 0.64, 0.25) \\ \theta_{\Omega_2 \rightarrow \Omega_1 \cup \Omega_0} &= (0.2, 0.5, 0.67, 0.64, 1) \end{aligned}$$

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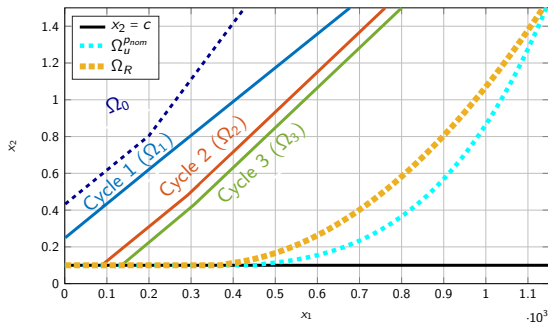
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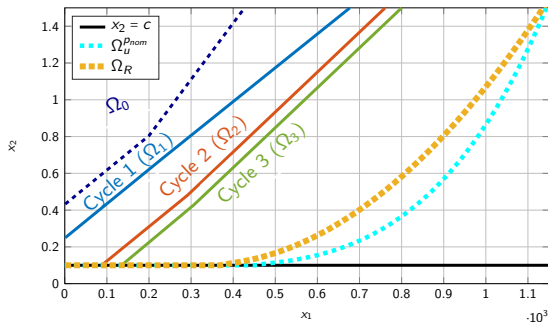
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$$\theta_{\Omega_1 \rightarrow \Omega_0} = (0.2, 0.5, 0, 0.64, 0.25)$$

$$\theta_{\Omega_2 \rightarrow \Omega_1 \cup \Omega_0} = (0.2, 0.5, 0.67, 0.64, 1)$$

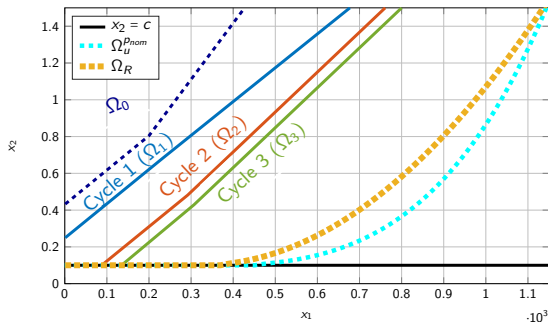
$$\theta_{\Omega_3 \rightarrow \Omega_2 \cup \Omega_1 \cup \Omega_0} = (0.2, 0.5, 0.56, 0.8, 0.5)$$

Probabilistically certified RoA

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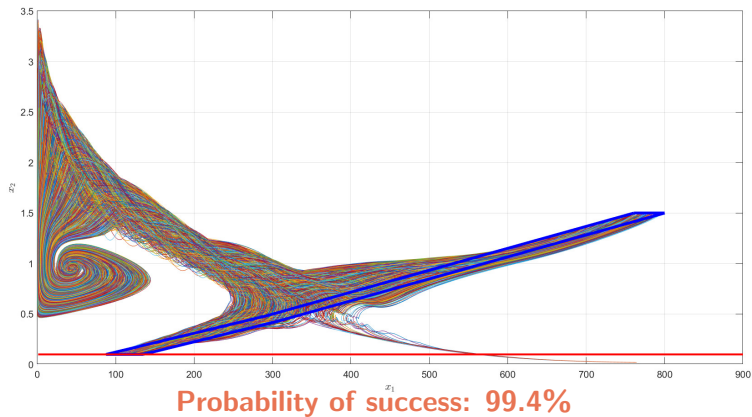


$$\begin{aligned} \theta_{\Omega_1 \rightarrow \Omega_0} &= (0.2, 0.5, 0, 0.64, 0.25) \\ \theta_{\Omega_2 \rightarrow \Omega_1 \cup \Omega_0} &= (0.2, 0.5, 0.67, 0.64, 1) \\ \theta_{\Omega_3 \rightarrow \Omega_2 \cup \Omega_1 \cup \Omega_0} &= (0.2, 0.5, 0.56, 0.8, 0.5) \end{aligned}$$

$$\Omega_C = \Omega_0 \cup \Omega_1 \cup \Omega_2 \cup \Omega_3$$

Validation of the estimation of Ω_C

- ▶ 5000 Monte-Carlo tests were performed



Outline

- 1 Modeling cancer immune interactions
- 2 Probabilistically certified region of attraction of a cancer model
- 3 Take-away messages & perspectives

Take-away messages & perspectives

- ▶ A framework of **probabilistic certification** for **RoA**
 - + Avoid **conservatism**
 - + Provide the **certified control law**
 - Might be **computationally expensive**
 - use **Matlab Coder** or parallel computing
 - use **iterative** algorithms to avoid enumeration

Future perspectives:

Take-away messages & perspectives

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Take-away messages & perspectives

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Future perspectives:

- ▶ Application of the probabilistic framework to **other models**
- ▶ Other types of **set generators** in the RoA probabilistic certification
- ▶ Derive formal **bounds** on the final convergence probability

Thank you for your attention!