Probabilistic Certification

though the cancer example . . .

Mazen Alamir

CNRS-Grenoble

Objective

Probabilitic Certification:

A general framework to face high uncertainties and still have something to guarantee with an explicit (hopefully high) probability.

THIS TALK

Explain the framework of **Probabilistic Certification** through the example of combined therapy of cancer using **highly uncertain** population models.

Outline

- Cancer problem
- Proposed solution
- Results
- Take away message

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On probabilistic certification of combined cancer therapies using strongly uncertain models

Mazen Alamir *

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Model

$$
\begin{aligned}
\dot{x}_1 &= ax_1(1 - bx_1) - c_1 x_4 x_1 - k_3 x_3 x_1 \\
\dot{x}_2 &= -\delta x_2 - k_2 x_3 x_2 + s_2 \\
\dot{x}_3 &= -\gamma_0 x_3 + u_2 \\
\dot{x}_4 &= g\frac{x_1}{h + x_1} x_4 - r x_4 - p_0 x_4 x_1 - k_1 x_4 x_3 + s_1 u_1 \\
\dot{x}_5 &= u_1 \quad ; \quad x_5(0) = 0 \\
\dot{x}_6 &= u_2 \quad ; \quad x_6(0) = 0 \\
\dot{x}_7 &= -1 \quad ; \quad x_5(0) = T
\end{aligned}
$$

x_1	tumor cell population
x_2	circulating lymphocytes population
x_3	chemotherapy drug concentration
x_4	effector immune cell population
x_5	quantity of already delivered chemo drug
x_6	quantity of already delivered immuno drug
x_7	remaining time for therapy
u_1	rate of introduction of immune cells
u_2	rate of introduction of chemotherapy

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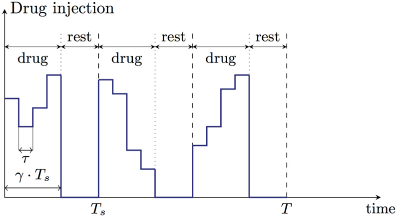

Time structure of the drug's delivery

- duty ratio $\gamma \in [0, 1]$
- updating period τ

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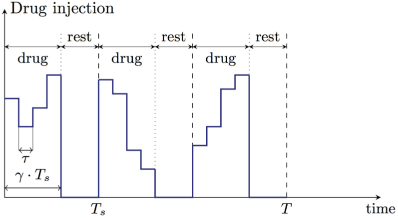

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Problem Design a feedback that contracts the tumor (x_1) while keeping the health (x_2) above above some threshold x_2^{min}

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Version 1

Reduce Hospitalization

Version 2

Reduce Drug's use

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Despite the **very bad** knowledge of the parameters

param	value	param	value	param	value
a	4.31×10^{-3} day^{-1}	b	1.02×10^{-14} $cell^{-1}$	c_1	3.41×10^{-10} $(cell \cdot day)^{-1}$
f	4.12×10^{-2} day^{-1}	g	1.5×10^{-2} day^{-1}	h	2.02×10^{1} $cell^{2}$
k_2, k_3	6×10^{-1} day^{-1}	k_1	8×10^{-1} day^{-1}	p_0	2×10^{-11} $(cell \cdot day)^{-1}$
s_1	1.2×10^{4} $cell \cdot day^{-1}$	s_2	7.5×10^{8} $cell \cdot day^{-1}$	δ	1.2×10^{-2} day^{-1}
γ	0×10^{-1} day^{-1}				

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γ	$0 \times 10^{-1}\ day^{-1}$				

p: patient-dependent parameter

Assume that a θ_c-parametrized controller has been designed:

$$u(k\tau+t) = K(x(k\tau), \theta_c) \quad t \in [0, \tau]$$

$$\theta_c := (\beta, r, \alpha)$$

Consider the protocol parameters:

$$\theta_p := (N_T, \gamma, \gamma_c, D_1, D_2)$$

N_T	Number of periods
γ	The duty ratio
γ_c	The contraction factor
D_1	Available quantity of drug 1
D_2	Available quantity of drug 2

$$\theta = (\theta_c, \theta_p)$$ Design parameter

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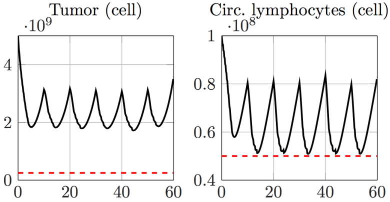

Results with
$D_i = 75\%$ (of available)
$\alpha = 0.5$
$\gamma = 0.4$

Assume that a θ_c-parametrized controller has been designed:

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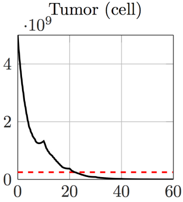

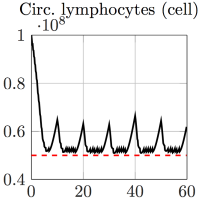

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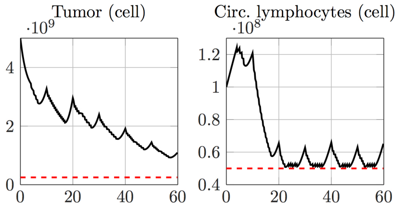

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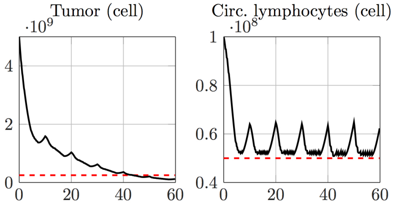

Results with
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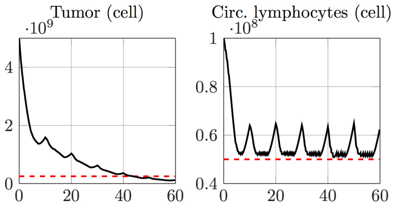
p-dependent results !!!



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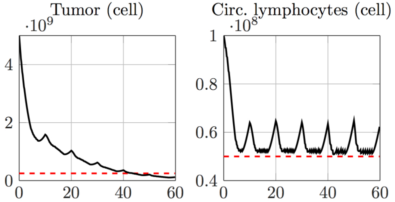
$$\theta = (\theta_c, \theta_p)$$

Design parameter

How to certify that $\forall p \in \mathbb{P}$:

$$x_1(T|\theta,p) - \gamma_c x_1(0) \leq 0$$
$$\max_t \left[x_2^{min} - x_2(t|\theta,p)\right] \leq 0$$



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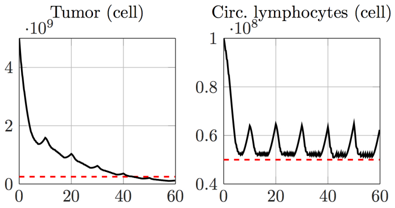
Design parameter

How to find θ such that we can certify that:

$$(\forall p \in \mathbb{P}) \qquad g(\theta, p) \leq 0$$



Results with

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θ satisfying the constraints may not be unique

$$\Downarrow$$

Optimal Robust constraints satisfaction problem

$$\min_{\theta \in \Theta} J(\theta) \qquad \text{s.t} \qquad (\forall p \in \mathbb{P}) \quad g(\theta, p) \leq 0$$

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Version 1: $J(\theta) = \gamma$
Version 2: $J(\theta) = \alpha_1 D_1 + \alpha_2 D_2$

$$\downarrow$$

$$J(\theta) = C\theta$$

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- Extremely hard to solve
- Uselessly conservative
  - worst case analysis
  - even extremely rare bad configurations are accommodated for

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Relaxed formulations $\Rightarrow$ Probabilistic certification

Define the constraints violation indicator:

$$I(\theta, p) := \begin{cases} 0 & \text{if } g(p,\theta) \le 0 \\ 1 & \text{otherwise (constraints are violated)} \end{cases}$$

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Robust constraint: $(\forall p \in \mathbb{P}) \quad g(\theta, p) \leq 0$

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First Relaxation (R_1): $\mathrm{Pr}\Big\{I(\theta, p) = 1\Big\} \leq \eta$

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Second Relaxation ($R_2(N)$): $$\frac{1}{N}\sum_{i=1}^{N}\big[I(\theta,p^{(i)})\big] \leq \frac{m}{N} \leq \eta$$

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For any given m, N must be sufficiently high yo get:

$$N \geq m/\eta$$
$$\Pr\big\{(R_2(N)) \cap (!R_1)\big\} \leq \delta$$

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(η,δ)=(precision,confidence)

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So how much for N?

When the admissible set Θ is discrete with cardinality n_Θ

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

m	positive integer ($m = 1, 5, 10$ etc.)
n_Θ	card(Θ)
η	Precision ($\eta = 10^{-2}, 10^{-3}$)
δ	Confidence parameter ($\delta \leq 10^{-3}$)

n_Θ	$\eta = 0.1$	$\eta = 0.05$	$\eta = 0.01$	$\eta = 0.001$
1	132	264	1317	13164
5	154	308	1536	15354
10	163	326	1628	16280
100	193	386	1930	19299
1000	223	445	2225	22249
10000	252	503	2515	25148

NOTA

- dim(p) does not matter !!!!
- $(n_\Theta, \delta) \rightarrow$ logarithmically !!

Application / cancer problem:

- Precision $\eta = 10^{-2}$
- Confidence $\delta = 10^{-1}$
- $m = 1$
- $n_{\Theta} = 576$

$\rightarrow N = 2155$

$\rightarrow \#$ simulations $= 1,241,280$

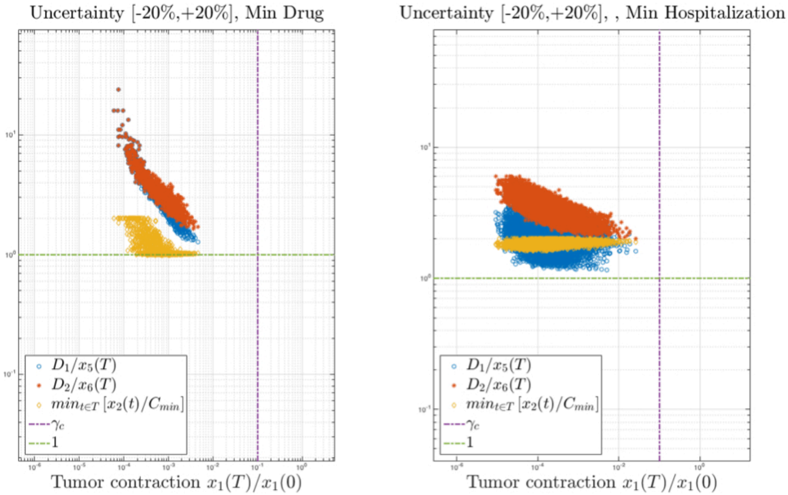
Application / cancer problem:

- Precision $\eta = 10^{-2}$
- Confidence $\delta = 10^{-1}$
- $m = 1$
- $n_\Theta = 576$

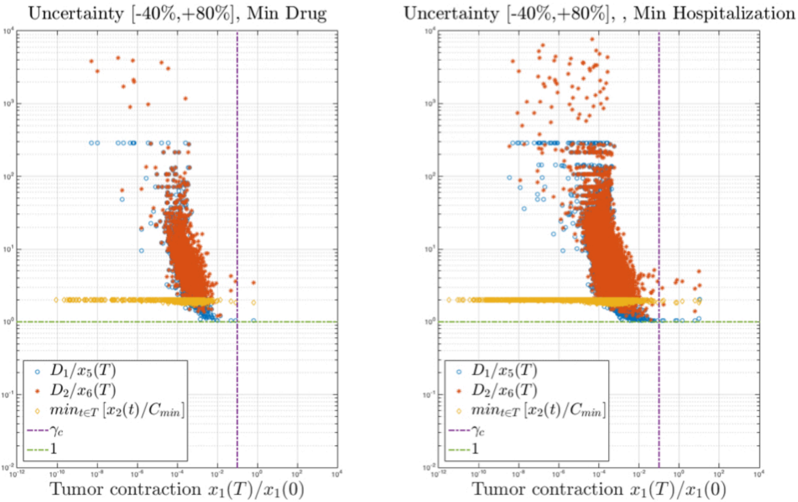
$\rightarrow N = 2155$

$\rightarrow$ # simulations $= 1,241,280$

Uncertainties	Min drug	Min Hospitalization
$[-10\%, +10\%]$	$\beta = 1.05$, $r = 0.25$, $\alpha = 0.5$, $\gamma = 0.8$, $N_T = 4$, $\mathbf{d = 0.25}$	$\beta = 1.05$, $r = 0.5$, $\alpha = 0.8$, $\boldsymbol{\gamma = 0.3}$, $N_T = 4$, $d = 0.75$
$[-20\%, +20\%]$	$\beta = 1.05$, $r = 0.25$, $\alpha = 0.5$, $\gamma = 0.8$, $N_T = 4$, $\mathbf{d = 0.5}$	$\beta = 2$, $r = 0.5$, $\alpha = 0.5$, $\boldsymbol{\gamma = 0.3}$, $N_T = 4$, $d = 0.75$
$[-40\%, +80\%]$	$\beta = 2$, $r = 0.05$, $\alpha = 0.5$, $\gamma = 0.8$, $N_T = 6$, $\mathbf{d = 0.5}$	$\beta = 2$, $r = 0.25$, $\alpha = 0.5$, $\boldsymbol{\gamma = 0.5}$, $N_T = 6$, $d = 1$



(b) Uncertainty $[-20\%, +20\%]$



(a) Uncertainty $[-40\%, +80\%]$

Successful use on

- Cancer treatment
- Anesthesia (up to 600% of parameter variation)
- EV charging station in smart district

- It is the ends of **robust** control in traditional sense
- All Market assessments are based on probabilities
- As everybody knows: the 0-risk is not of this world !
- **The knowledge of statistic of p underlines everything**
- Maybe some preliminary research on this has to be done
- **Good news**: In your case, data is available !!!