Analysing Optimal Control Problems for the Gompertz Model in Chemotherapy

Mathematical Perspectives in the Biology and Therapeutics of Cancer
Workshop in CIRM Marseille, France
July 9-13, 2018

L. A. Fernández, C. Pola

lafernandez@unican.es, polac@unican.es

Dpto. Matemáticas, Estadística y Computación,
Universidad de Cantabria,
Santander, Spain

Outline

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Introduction

• Catalog of the optimal controls ⇐ log-kill hypothesis
in cancer chemotherapy for the Gompertz model
depending on PK/PD and the integral constraint,
Discrete Contin. Dyn. Syst. Ser. B, 19 (2014), 1563–1588.

• Optimal control problems for the Gompertz model
under Norton-Simon hypothesis in chemotherapy,
Discrete Contin. Dyn. Syst. Ser. B (in press).

OPTIONS:

- A PK equation for the drug concentration.
- PD: SKIPPER (linear) model or EMAX model
- The side effects as constraints or through a penalty term

The influence of all these variants is analysed.
We've characterized the optimal solutions for all the problems.
We've got some unexpected results.

References: Skipper et al (1964), Norton and Simon (1977), Swan (1990), Fister and Panetta (2003), Swierniak et al (2009), Clairambault (2009), Ledzewicz and Schättler (2015)), Benzekry et al (2014-2015),. . . .

Mathematical models for PK/PD

$V(t)$ Tumor volume (or tumor size)
$G(V,u)$ Growth-inhibitory influence of the therapy (KILL TERM)
$L(t)$ Level of therapy
$u(t)$ Infusion rate of the drug

$$V'(t) = \psi(V(t)) - G(V(t), u(t)) \Leftarrow \text{PD term}$$

$$\psi(V) = \xi \log\left(\frac{\theta}{V}\right) V \quad \textit{Gompertz}$$

$G(V,u) = L(u)\, V, \quad \Leftarrow$ log-kill

$G(V,u) = L(u)\, \psi(V) \quad \Leftarrow$ Norton-Simon

SENSITIVITY TO THERAPY

$$L_1(u) = \quad k_1 u \quad \text{or} \quad k_1 c \qquad \text{Skipper model}$$

$$L_2(u) = \frac{k_1 u}{k_2 + u} \quad \text{or} \quad \frac{k_1 c}{k_2 + c} \qquad E_{max} \text{ model}$$

where $c'(t) = -\lambda c(t) + u(t), \quad c(0) = 0$ PK equation

Optimal control problems - Introduction

$$(OP_i) \begin{cases} \min J(u) = V(T) \\ u \in U_{ad}^i \end{cases} \quad , \quad i = 1, 2, 3$$

Problem	Characteristics
	Part I **log-kill** constraint
	$\int_0^T u(t)dt \leq y_{max}$
	$\int_0^T c(t)\, dt \leq y_{max}$

u infusion rate of the drug

c drug concentration

Optimal control problems - Introduction

$$(OP_i)\begin{cases} \min J(u) = V(T) \\ u \in U^i_{ad} \end{cases} \quad , \quad i = 1, 2, 3$$

Problem	Characteristics
	Part I **log-kill** constraint Part II **Norton-Simon**
	$\int_0^T u(t)dt \leq y_{max}$
	$\int_0^T$ c(t) $dt \leq y_{max}$

u infusion rate of the drug

c drug concentration

Optimal control problems - Introduction

$$(OP_i)\begin{cases} \min J(u) = V(T) + \alpha PT, & i = 1,2,3 \\ u \in U^i_{ad} \end{cases}$$

Problem	Characteristics	
	Part I **log-kill** constraint $(\alpha = 0)$	Part II **Norton-Simon** Penalty Term $(\alpha > 0)$
	$\int_0^T u(t)dt \leq y_{max}$	$\int_0^T u(t)dt$
	$\int_0^T$ c(t) $dt \leq y_{max}$	$\int_0^T$ c(t) dt

u infusion rate of the drug

c drug concentration

Optimal control problems - Introduction

$$(OP_i)\begin{cases} \min J(u) = V(T) + \alpha PT, & i = 1,2,3 \\ u \in U^i_{ad} \end{cases}$$

Problem	Characteristics		
		Part I **log-kill** constraint ($\alpha = 0$)	Part II **Norton-Simon** Penalty Term ($\alpha > 0$)
(OP_1)	$u = c$	$\int_0^T u(t)dt \le y_{max}$	$\int_0^T u(t)dt$
(OP_2)	$c'(t) = -\lambda c(t) + u(t)$	$\int_0^T \mathrm{u(t)}\, dt \le y_{max}$	$\int_0^T \mathrm{u(t)}\, dt$
(OP_3)	$c'(t) = -\lambda c(t) + u(t)$	$\int_0^T \mathrm{c(t)}\, dt \le y_{max}$	$\int_0^T \mathrm{c(t)}\, dt$

u infusion rate of the drug

c drug concentration

Admisible control sets, U^i_{ad}

for problems with an integral constraint

$$\{u \in L^\infty(0,T) : 0 \le u(t) \le u_{max}, \ a.e. \ t \in (0,T), \int_0^T u(t)dt \le y_{max}\}, \quad \text{for } i = 1,2.$$

$$\{u \in L^\infty(0,T) : 0 \le u(t) \le u_{max}, \ a.e. \ t \in (0,T), \int_0^T c(t)dt \le y_{max}\}, \quad \text{for } i = 3.$$

ASSUMPTION for avoiding the trivial solution $\bar{u} \equiv u_{max}$:

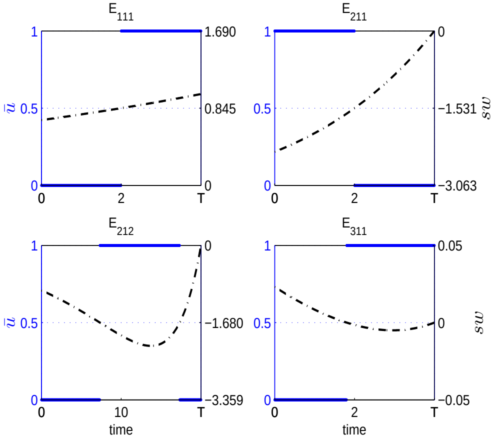
$$Tu_{max} > y_{max}, \qquad \text{for } i = 1,2$$

$$(\lambda T + \exp(-\lambda T) - 1)u_{max} > \lambda^2 y_{max}, \quad \text{for } i = 3.$$

for problems with a penalty term

$$\{u \in L^\infty(0,T) : 0 \le u(t) \le u_{max}, \ a.e. \ t \in (0,T)\}.$$

Optimal controls for LOG-KILL and Skipper PD model



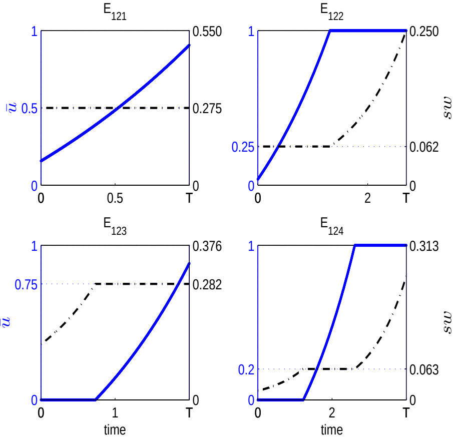
$$V'(t) = \psi(V(t)) - \boxed{L_1(u(t))V(t)}$$

$$0 \le u(t) \le u_{max}$$

	$L_1(u)$	Constraint
(OP_1):	$k_1 u$	$\int_0^T u(t)dt \le y_{max}$
(OP_2):	$k_1 c$	$\int_0^T u(t)dt \le y_{max}$
(OP_3):	$k_1 c$	$\int_0^T c(t)\, dt \le y_{max}$

Problem	Examples	Optimal controls	
(OP_1)	E_{111}	$0/u_{max}$	
(OP_2)	E_{211}, E_{212}	$u_{max}/0$	$0/u_{max}/0$
(OP_3)	E_{311}	$0/u_{max}$	

Optimal controls for LOG-KILL, E_{max} PD model with (OP_1)



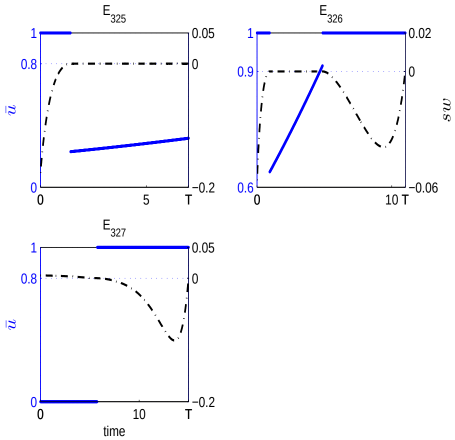
$$V'(t) = \psi(V(t)) - \boxed{L_2(u(t))V(t)}$$

$$0 \leq u(t) \leq u_{max}$$

	$L_2(u)$	Constraint
(OP_1):	$\dfrac{k_1\, u}{k_2 + u}$	$\int_0^T u(t)\, dt \leq y_{max}$

Problem	Optimal controls			
(OP_1)	u_{sin}	u_{sin}/u_{max}	$0/u_{sin}$	$0/u_{sin}/u_{max}$

Optimal controls for LOG-KILL, E_{max} PD model with (OP_3)



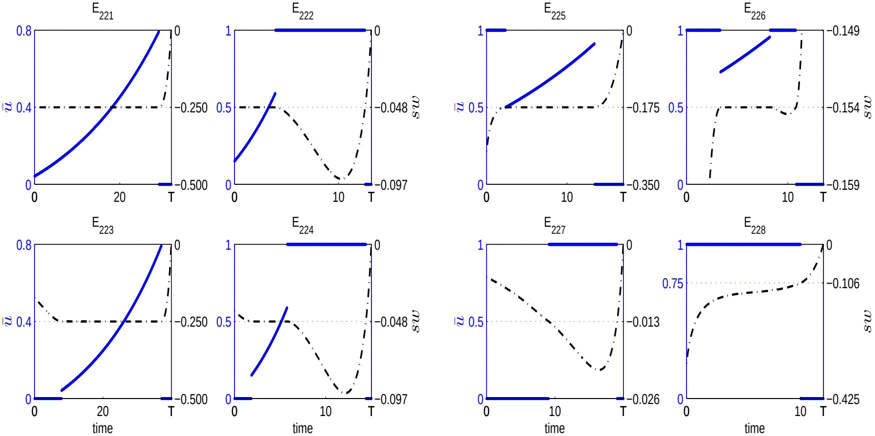
$$V'(t) = \psi(V(t)) - \boxed{L_2(u(t))V(t)}$$

$$0 \leq u(t) \leq u_{max}$$

	$L_2(u)$	Constraint
(OP_3):	$\dfrac{k_1\, c}{k_2 + c}$	$\int_0^T c(t)\, dt \leq y_{max}$

Problem	Optimal controls			
(OP_1)	u_{sin}	u_{sin}/u_{max}	$0/u_{sin}$	$0/u_{sin}/u_{max}$
(OP_3)	u_{sin} u_{max}/u_{sin}	u_{sin}/u_{max} $u_{max}/u_{sin}/u_{max}$	$0/u_{sin}$ $0/u_{max}$	$0/u_{sin}/u_{max}$

Optimal controls for LOG-KILL, E_{max} PD model with (OP_2)



Problem	Optimal controls			
(OP_2)	$u_{sin}/0$	$u_{sin}/u_{max}/0$	$0/u_{sin}/0$	$0/u_{sin}/u_{max}/0$
	$u_{max}/u_{sin}/0$	$u_{max}/u_{sin}/u_{max}/0$	$0/u_{max}/0$	$u_{max}/0$

$$L_2(u) = \frac{k_1\, c}{k_2 + c}, \qquad \int_0^T u(t)\, dt \le y_{max}$$

Optimal control problems - EDOs with NORTON-SIMON -I

$$(OP_i) \begin{cases} \min J(u) = V(T) \\ u \in U_{ad}^i \end{cases}, \quad \text{for} \quad i = 1, 2, 3$$

$$V'(t) = \psi(V(t)) - L(u(t))\psi(V(t)), \quad t \in [0, T],$$

$$V(0) = V_0, \qquad \psi(V(t)) = \xi \log\left(\frac{\theta}{V(t)}\right) V(t)$$

Admissible controls U_{ad}^i

$$\{u \in L^\infty(0, T) : 0 \le u(t) \le u_{max}, \ a.e. \ t \in (0, T), \int_0^T u(t)dt \le y_{max}\},$$

for $i = 1, 2.$

$$\{u \in L^\infty(0, T) : 0 \le u(t) \le u_{max}, \ a.e. \ t \in (0, T), \int_0^T c(t)dt \le y_{max}\},$$

for $i = 3.$

Optimal control problems - EDOs with NORTON-SIMON -II

$$(OP_i)\left\{\begin{array}{l} \min J(u) = V(T) + \alpha \int_0^T u(t)dt \\ u \in U_{ad} \end{array}\right. , \quad \text{for} \quad i = 1, 2$$

$$(OP_3)\left\{\begin{array}{l} \min J(u) = V(T) + \alpha \int_0^T c(t)dt \\ u \in U_{ad} \end{array}\right.$$

$$V'(t) = \psi(V(t)) - L(u(t))\psi(V(t)), \quad t \in [0, T],$$

$$V(0) = V_0, \qquad \psi(V(t)) = \xi \log\left(\frac{\theta}{V(t)}\right) V(t)$$

Admissible controls

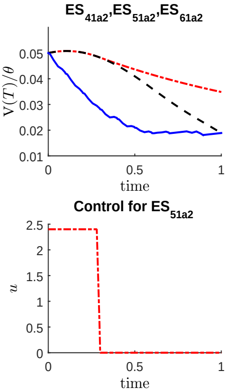
$$U_{ad} = \{u \in L^\infty(0, T) : 0 \le u(t) \le u_{max}, a.e.\ t \in (0, T)\}$$

Optimal controls for NORTON-SIMON

PD model: *Skipper* (L_1)

$\downarrow$

$$V'(t) = \psi(V(t)) - \psi(V(t))L_1(u(t))$$
$$0 \leq u(t) \leq u_{max}$$



	$L_1(u)$		Penalty term
(OP_1):	$k_1 u$		$\alpha \int_0^T u(t)dt$
(OP_2):	$k_1 c$		$\alpha \int_0^T u(t)dt$
(OP_3):	$k_1 c$		$\alpha \int_0^T c(t)\, dt$

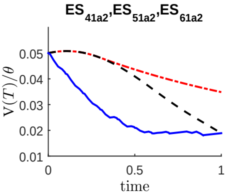
Problem	Non-trivial optimal controls (L_1)	
(OP_1)	Infinite optimal controls	
(OP_2)	$u_{max}/0$	
(OP_3)	Infinite optimal controls	

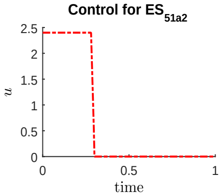
Optimal controls for NORTON-SIMON

PD model: *Skipper* (L_1)

$\downarrow$

$$V'(t) = \psi(V(t)) - \psi(V(t))L_1(u(t))$$
$$0 \le u(t) \le u_{max}$$





	$L_1(u)$		Penalty term
(OP_1):	$k_1 u$		$\alpha \int_0^T u(t)dt$
(OP_2):	$k_1 c$		$\alpha \int_0^T u(t)dt$
(OP_3):	$k_1 c$		$\alpha \int_0^T c(t)dt$

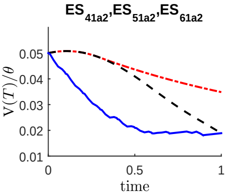
Problem	Non-trivial optimal controls (L_1)	log-kill
(OP_1)	Infinite optimal controls	
(OP_2)	$u_{max}/0$	$u_{max}/0$ $0/u_{max}/0$
(OP_3)	Infinite optimal controls	

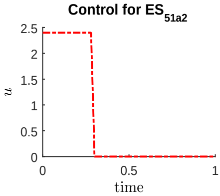
Optimal controls for NORTON-SIMON

PD model: *Skipper* (L_1)

$\downarrow$

$$V'(t) = \psi(V(t)) - \psi(V(t))L_1(u(t))$$
$$0 \le u(t) \le u_{max}$$





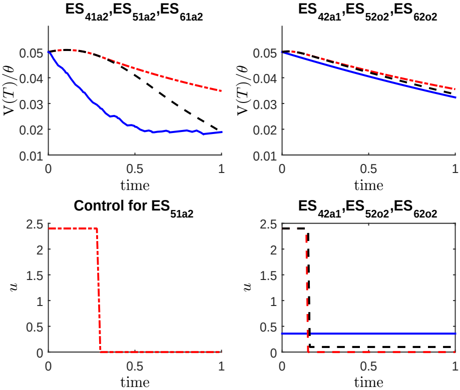
	$L_1(u)$		Penalty term
(OP_1):	$k_1 u$		$\alpha \int_0^T u(t)dt$
(OP_2):	$k_1 c$		$\alpha \int_0^T u(t)dt$
(OP_3):	$k_1 c$		$\alpha \int_0^T c(t)\, dt$

Problem	Non-trivial optimal controls (L_1)	log-kill
(OP_1)	Infinite optimal controls	$0/u_{max}$
(OP_2)	$u_{max}/0$	$u_{max}/0$ $\quad$ $0/u_{max}/0$
(OP_3)	Infinite optimal controls	$0/u_{max}$

Optimal controls for NORTON-SIMON

PD model: *Skipper* (L_1) $\quad E_{max}$ (L_2)

$$V'(t) = \psi(V(t)) - \psi(V(t))L(u(t))$$
$$0 \le u(t) \le u_{max}$$



	$L_1(u)$	$L_2(u)$	Penalty term
(OP_1):	$k_1 u$	$\frac{k_1 u}{k_2 + u}$	$\alpha \int_0^T u(t)dt$
(OP_2):	$k_1 c$	$\frac{k_1 c}{k_2 + c}$	$\alpha \int_0^T u(t)dt$
(OP_3):	$k_1 c$	$\frac{k_1 c}{k_2 + c}$	$\alpha \int_0^T c(t)dt$

Problem	Non-trivial optimal controls (L_1)	Non-trivial optimal controls (L_2)
(OP_1)	Infinite optimal controls	u_{sin}
(OP_2)	$u_{max}/0$	$u_{max}/0 \quad u_{max}/u_{sin}/0$
(OP_3)	Infinite optimal controls	u_{max}/u_{sin}

Conclusions

Comparison objectives

- The log-kill hypothesis and the Norton-Simon hypothesis.
- Several formulations for the level of therapy.
- Integral constraints and penalty terms to control the side effects.

Conclusions

- We've done a detailed study, filling a gap between the medical field and the mathematical one.
- We've charaterized the optimal controls in terms of the problem data in all our cases.
- We've given explicit optimal controls in the case of uniqueness.
- There are fewer and simpler cases under Norton-Simon hypothesis.
- "Late-intensification" proposed by Norton and Simon (1977) does not seem to be justified in this framework.

The most realistic optimal control problem - NORTON-SIMON hypothesis, E_{max} PD, PK ODE and penalty term

$V(t)$ tumor volume (or tumor size), $L(t)$ Level of therapy,
u the infusion rate of the drug, c drug concentration

(OP_3)

$$\begin{cases} \min J(u) = V(T) + \alpha \int_0^T c(t)dt \\ u \in U_{ad} \end{cases}$$

where V is the solution of the Cauchy problem.

$$\begin{cases} V'(t) = \psi(V(t))(1 - L(u(t))), & V(0) = V_0, \quad t \in [0, T], \\ \quad \text{where} \quad \psi(V(t)) = \xi \log\left(\frac{\theta}{V(t)}\right) V(t), & L(u) = \dfrac{k_1 c}{k_2 + c} \\ c'(t) = -\lambda c(t) + u(t), & c(0) = 0, \end{cases}$$

$$U_{ad} = \{u \in L^\infty(0, T) : 0 \leq u(t) \leq u_{max}, a.e.\ t \in (0, T)\}$$

where u_{max} and y_{max} are given positive real numbers.

Let us assume $L_0 \in (0, \theta)$ and that $\bar{u}$ is an optimal control for (OP_3) for some value $\alpha \geq 0$. Then, there exists $t_\alpha \in [0, T]$ such that

$$\bar{u}(t) = \begin{cases} u_{max}, & \text{if} \quad t \in [0, t_\alpha), \\ u_{max}(1 - e^{-\lambda t_\alpha}), & \text{if} \quad t \in (t_\alpha, T]. \end{cases}$$

The value $t_\alpha \in [0, T]$ can be determined as the solution of the problem:

$$\begin{cases} \min F_\alpha(t) = F(t) + \alpha G(t), \\ \\ t \in [0, T], \end{cases}$$

where $$F(t) = \theta \exp\left(\log\left(\frac{V_0}{\theta}\right) \exp\left(\xi(k_1 \tilde{H}(t) - T)\right)\right),$$

$$\tilde{H}(t) = t - \frac{k_2}{\lambda k_2 + u_{max}} \log\left(\frac{(\lambda k_2 + u_{max})e^{\lambda t} - u_{max}}{\lambda k_2}\right) + \\ + \frac{(T - t)u_{max}(1 - e^{-\lambda t})}{k_2 \lambda + u_{max}(1 - e^{-\lambda t})},$$

and

$$G(t) = \frac{u_{max}}{\lambda^2}\left(e^{-\lambda t}(1 + \lambda(t - T)) + \lambda T - 1\right),$$

that depend only on the parameters defining the control problem.

THANK YOU FOR YOUR ATTENTION!!

Ingredients of the proofs

- Existence of optimal solutions is standard
- Sometimes, there is a unique solution; in other, there are infinite.
- Pontryagin Maximum Principle,
- Explicit solution of generalized Gompertz ODE including L^∞ coefficients,
- First order optimality conditions and “ad hoc" argumentations.

Optimal control for (OP_3) under log-kill and Skipper model

Let us assume that $\bar{u}$ is a non-trivial optimal control for (OP_3). Then,

$$\bar{u}(t) = \begin{cases} 0, & \text{if} \quad t \in [0, t_1), \\ u_{max}, & \text{if} \quad t \in (t_1, T], \end{cases}$$

where t_1 is the unique solution in $(0, T)$ of the nonlinear equation

$$\lambda t_1 - \exp\left(\lambda(t_1 - T)\right) = \lambda T - 1 - \frac{\lambda^2 y_{max}}{u_{max}}.$$

Optimal control for (OP_3) under log-kill and E_{max} model

Let us assume that $\bar{u}$ is a non-trivial optimal control for (OP_3).Then, it has the following general structure

$$\bar{u}(t) = \begin{cases} 0, & \text{if} \quad t \in (0, t_1), \\ u_{max}, & \text{if} \quad t \in (t_1, t_2), \\ k_3(\lambda + \xi/2) \exp(\xi t/2) - \lambda k_2, & \text{if} \quad t \in (t_2, t_3), \\ u_{max}, & \text{if} \quad t \in (t_4, T], \end{cases}$$

for some unknowns t_1, t_2, t_3, t_4 and $k_3 > 0$ with $t_1(t_2 - t_1) = 0$. Moreover, $\bar{u}$ verifies

$$\int_0^T \bar{u}(t)\,(1 - \exp(\lambda(t - T)))\,dt = \lambda y_{max}.$$