On the application of optimal control to infectious diseases

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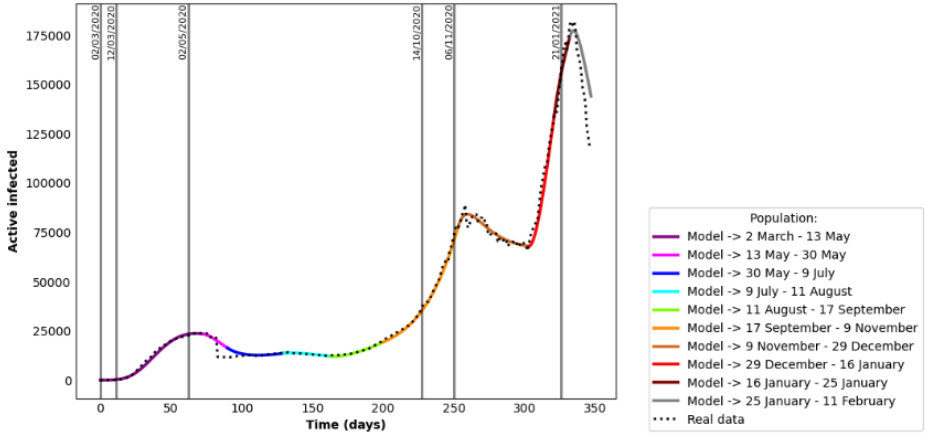
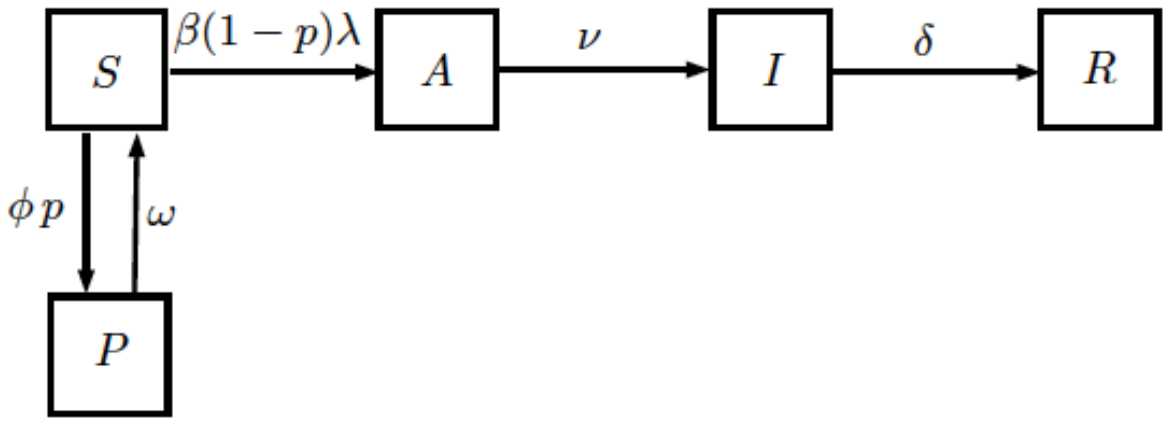
COVID-19 mathematical model



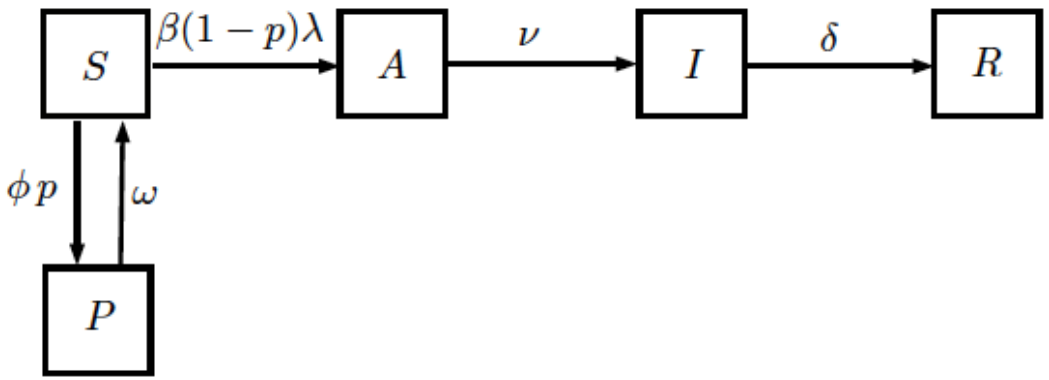
Deterministic *SAIRP* mathematical model for the transmission dynamics of SARS-CoV-2

Assume a homogeneous population subdivided into five compartments:

- S, susceptible (uninfected and not immune);
- A, infected but asymptomatic (undetected);
- I, active infected (symptomatic and detected/confirmed);
- R, removed (recovered and deaths by COVID-19);
- P, *protected/prevented* (not infected, not immune, but that are under protective measures).



SAIRP model: parameters



Parameter/	Description
β	Infection transmission rate
θ	Modification parameter
p	Fraction of susceptible S transferred to protected class P
ϕ	Transition rate of susceptible S to protected class P
$\omega = wm$	
w	Transition rate of protected P to susceptible S
m	Fraction of protected P transferred to susceptible S
$\nu = vq$	
v	Transition rate of asymptomatic A to active infected I
q	Fraction of asymptomatic A infected individuals
δ	Transition rate from active infected I to removed R

SAIRP model with vital dynamics and constant parameters

Model:

$$\begin{cases} \dot{S}(t) = \Lambda - \beta(1-p)\frac{(\theta A(t)+I(t))}{N(t)}S(t) - \phi p S(t) + \omega P(t) - \mu S(t), \\ \dot{A}(t) = \beta(1-p)\frac{(\theta A(t)+I(t))}{N(t)}S(t) - \nu A(t) - \mu A(t), \\ \dot{I}(t) = \nu A(t) - \delta I(t) - \mu I(t), \\ \dot{R}(t) = \delta I(t) - \mu R(t), \\ \dot{P}(t) = \phi p S(t) - \omega P(t) - \mu P(t). \end{cases}$$

Total population, $N(t) = S(t) + A(t) + I(t) + R(t) + P(t)$, with $t \in [0, T]$ representing the time (in days) and $T > 0$.

Λ - recruitment rate.

μ - natural death rate.

SAIRP model with vital dynamics and constant parameters

The equations of the SAIRP model with vital dynamics can be rewritten as

$$\dot{x}(t) = f\left(x(t),\, \alpha\right), \quad t > 0, \tag{1}$$

with $x = (S,\, A,\, I,\, R,\, P)^T \in \mathbb{R}^5$ and
$\alpha = (\Lambda,\, \mu,\, \beta,\, p,\, \theta,\, \phi,\, \omega,\, \nu,\, \delta)^T \in \mathbb{R}^9$, where the non-linear operator f is defined in $\mathbb{R}^5 \times \mathbb{R}^9$ by

$$f(x,\, \alpha) = \begin{pmatrix} \Lambda - \beta(1-p)\frac{(\theta A + I)}{N} - \phi p S + \omega P - \mu S \\ \beta(1-p)\frac{(\theta A + I)}{N} S - \nu A - \mu A \\ \nu A - \delta I - \mu I \\ \delta I - \mu R \\ \phi p S - \omega P - \mu P \end{pmatrix}. \tag{2}$$

Existence, positivity and boundedness of solutions

Introduce the compact region $\Omega \subset \mathbb{R}^5$ defined by

$$\Omega = \left\{ x = (S,\, A,\, I,\, R,\, P)^T \in \left(\mathbb{R}^+\right)^5 \,;\; 0 < S + A + I + R + P \leq \frac{\Lambda}{\mu} \right\}. \tag{3}$$

Theorem

For any $x_0 = (S_0,\, A_0,\, I_0,\, R_0,\, P_0)^T \in \Omega$, the Cauchy problem given by (1) and $x(0) = x_0$ admits a unique solution, denoted by $x(t,\, x_0)$, defined on $[0,\, \infty)$, whose components are non-negative. Furthermore, the region Ω defined by (3) is positively invariant.

Equilibrium points and basic reproduction number

The model (1) has two equilibrium points:

- disease-free equilibrium, denoted by Σ_0, given by

$$\Sigma_0 = (S_0, A_0, I_0, R_0, P_0) = \left(\frac{\Lambda\,(\omega+\mu)}{\mu\,(p\phi+\mu+\omega)}, 0, 0, 0, \frac{\phi\,p\Lambda}{\mu\,(p\phi+\mu+\omega)} \right);$$

- endemic equilibrium, Σ_+, whenever $R_0 > 1$, given by $\Sigma_+ = (S_+, A_+, I_+, R_+, P_+)$ with

$$S_+ = \frac{\Lambda(\omega+\mu)}{(p\phi+\mu+\omega)\mu} R_0^{-1}, \quad A_+ = \frac{\Lambda}{\nu+\mu} R_0^{-1}(R_0-1),$$

$$I_+ = \frac{\Lambda\nu}{(\nu+\mu)(\delta+\mu)} R_0^{-1}(R_0-1), \quad R_+ = \frac{\delta\Lambda\nu}{(\nu+\mu)(\delta+\mu)\mu} R_0^{-1}(R_0-1),$$

$$P_+ = \frac{\Lambda\phi p}{(p\phi+\mu+\omega)\mu} R_0^{-1},$$

where the basic reproduction number, R_0, is given by

$$R_0 = \frac{\beta\,(1-p)\,(\delta\,\theta+\mu\,\theta+\nu)\,(\omega+\mu)}{(\delta+\mu)\,(\nu+\mu)\,(p\phi+\mu+\omega)} = \frac{\mathcal{N}}{\mathcal{D}}.$$

Local asymptotic stability of the disease-free equilibrium (DFE)

Theorem

The disease-free equilibrium, Σ_0, is locally asymptotically stable whenever $R_0 < 1$.

Sketch of the proof:

Jacobian matrix of system (1) evaluated at the DFE:

$$M(\Sigma_0) = \begin{bmatrix} -(\phi\, p + \mu) & -\frac{\theta\, \beta\, (\mu+\omega)(1-p)}{\phi\, p+\mu+\omega} & -\frac{\beta\, (\mu+\omega)(1-p)}{\phi\, p+\mu+\omega} & 0 & \omega \\ 0 & -\frac{\beta\theta(1-p)(\mu+\omega)+(\mu+\nu)(p\phi+\mu+\omega)}{\phi\, p+\mu+\omega} & \frac{\beta\, (\mu+\omega)(1-p)}{\phi\, p+\mu+\omega} & 0 & 0 \\ 0 & \nu & -\delta - \mu & 0 & 0 \\ 0 & 0 & \delta & -\mu & 0 \\ \phi\, p & 0 & 0 & 0 & -(\mu+\omega) \end{bmatrix}.$$

Local asymptotic stability of the DFE - continuation of the proof

The eigenvalues of the matrix $M(\Sigma_0)$: $\lambda_1 = \lambda_2 = -\mu$, $\lambda_3 = -(\phi p + \mu + \omega)$ and λ_4, λ_5 that are the roots of the polynomial

$$p(\lambda) = \lambda^2 + B\lambda + C,$$

where $B = \frac{-\beta\theta(1-p)(\omega+\mu)}{(p\phi+\mu+\omega)} + \delta + 2\mu + \nu$ and $C = \frac{\mathcal{D}-\mathcal{N}}{p\phi+\mu+\omega}$.

Applying the Routh–Hurwitz criterion, we conclude that model (1) is locally stable if, and only if, $B > 0$ and $C > 0$. It is easy to show that $C > 0$ whenever $R_0 < 1$. The coefficient B is positive when

$$\beta\theta(1-p)(\omega+\mu) < (\delta + 2\mu + \nu)(p\phi + \mu + \omega)\,,$$

after some computations, we prove that $B > 0$ whenever $R_0 < 1$.

Global stability of the disease-free equilibrium (DFE)

Theorem

If $R_0 < 1$, then the disease-free equilibrium, Σ_0, is globally asymptotically stable in Ω.

Sketch of the proof:

Consider the following functional given by

$$L = S - S_0 - S_0 \ln \frac{S}{S_0} + A + \zeta I + \xi \left(P - P_0 - P_0 \ln \frac{P}{P_0} \right) + \chi \left(N - N_0 - N_0 \ln \frac{N}{N_0} \right),$$

where ζ and ξ are defined by

$$\zeta = \frac{k(1-\eta)(\nu+\mu) - \beta(1-p)\theta}{k\nu(1-\eta)}, \quad \xi = \frac{\omega P_0}{\phi p S_0}, \tag{4}$$

and χ is a positive constant which will be determined below.
As constructed, L is a non-negative functional and we have

$$L = 0 \iff (S, A, I, R, P) = \Sigma_0.$$

Now we compute the derivative of L along the solutions of the SAIRP model (1) starting in Ω.

Global stability of the DFE - continuation of the proof

Now we compute the derivative of L along the solutions of the SAIRP model (1) starting in Ω.
We have

$$\begin{aligned}
\dot{L} &= \left(1 - \frac{S_0}{S}\right)\dot{S} + \dot{A} + \zeta\dot{I} + \xi\left(1 - \frac{P_0}{P}\right)\dot{P} + \chi\left(1 - \frac{N_0}{N}\right)\dot{N} \\
&= \left(1 - \frac{S_0}{S}\right)\left[\Lambda - \beta(1-p)\frac{\theta A + I}{N}S - (p\phi + \mu)S + \omega P\right] \\
&+ \left[\beta(1-p)\frac{\theta A + I}{N}S - (\nu + \mu)A\right] + \zeta\left[\nu A - (\delta + \mu)I\right] \\
&+ \xi\left(1 - \frac{P_0}{P}\right)\left[\phi p S - (\omega + \mu)P\right] + \chi\left(1 - \frac{N_0}{N}\right)(\Lambda - \mu N).
\end{aligned}$$

Now we use the relations

$$\Lambda = (p\phi + \mu)S_0 - \omega P_0, \quad p\phi S_0 = (\omega + \mu)P_0$$

to obtain

$$\begin{aligned}
\dot{L} &= \left(1 - \frac{S_0}{S}\right)\left[-\beta(1-p)\frac{\theta A + I}{N}S - (p\phi + \mu)(S - S_0) + \omega(P - P_0)\right] \\
&+ \left[\beta(1-p)\frac{\theta A + I}{N}S - (\nu + \mu)A\right] + \zeta\left[\nu A - (\delta + \mu)I\right] \\
&+ \xi\left(1 - \frac{P_0}{P}\right)\left[\phi p(S - S_0) - (\omega + \mu)(P - P_0)\right] + \chi\left(1 - \frac{N_0}{N}\right)(\Lambda - \mu N).
\end{aligned}$$

...

Global asymptotic stability of the DFE - end of the proof

After several simplifications, we obtain

$$\begin{aligned}\dot{L} &\leq \left[\frac{\beta(1-p)\theta S_0}{2N_0\varepsilon} - \frac{\chi}{2}\mu\right]\frac{(N-N_0)^2}{N} + \left[\frac{\beta(1-p)S_0}{2N_0\varepsilon} - \frac{\chi}{2}\mu\right]\frac{(N-N_0)^2}{N} \\ &\leq \left[\frac{\beta(1-p)S_0}{N_0\varepsilon} - \chi\mu\right]\frac{(N-N_0)^2}{N},\end{aligned}$$

since $\theta \leq 1$. Finally, we choose $\chi > 0$ sufficiently large so that

$$\frac{\beta(1-p)S_0}{N_0\varepsilon} - \chi\mu < 0,$$

which guarantees that $\dot{L} \leq 0$. In other words, the functional L is a Lyapunov function for the flow induced by the SAIRP model (1). The conclusion follows from LaSalle's invariance principle [1].

Joseph LaSalle, *Some extensions of Liapunov's second method*, IRE Transactions on circuit theory 7 (4), 520–527 (1960).

Global asymptotic stability of the EE

Theorem

The compact region Γ defined by

$$\Gamma = \left\{ x = (S,\, A,\, I,\, R,\, P)^T \in \left(\mathbb{R}^+\right)^5 \,;\, S + A + I + R + P = \frac{\Lambda}{\mu} \right\}$$

is positively invariant under the flow induced by system (11). It contains the disease-free equilibrium, Σ_0, and the endemic equilibrium, Σ_+, if $R_0 > 1$. Furthermore, if $R_0 > 1$, then the endemic equilibrium Σ_+ is globally asymptotically stable in Γ.

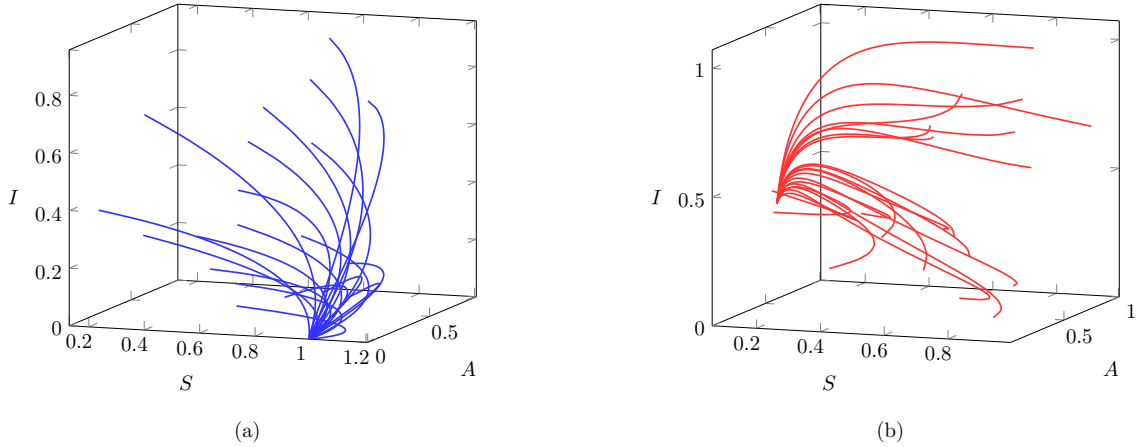


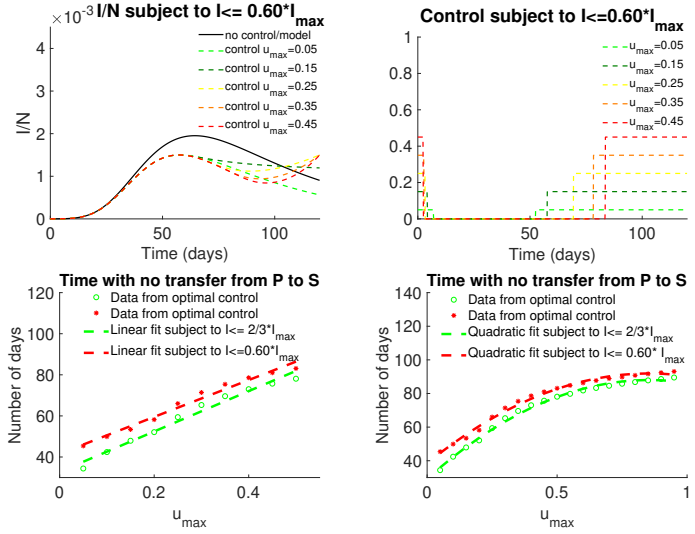
Figure: Phase portraits in the $(S,\, A,\, I)$ space.(a) Global stability of the DFE ($R_0 < 1$). (b) Global stability of the EE ($R_0 > 1$).

Remains to prove:

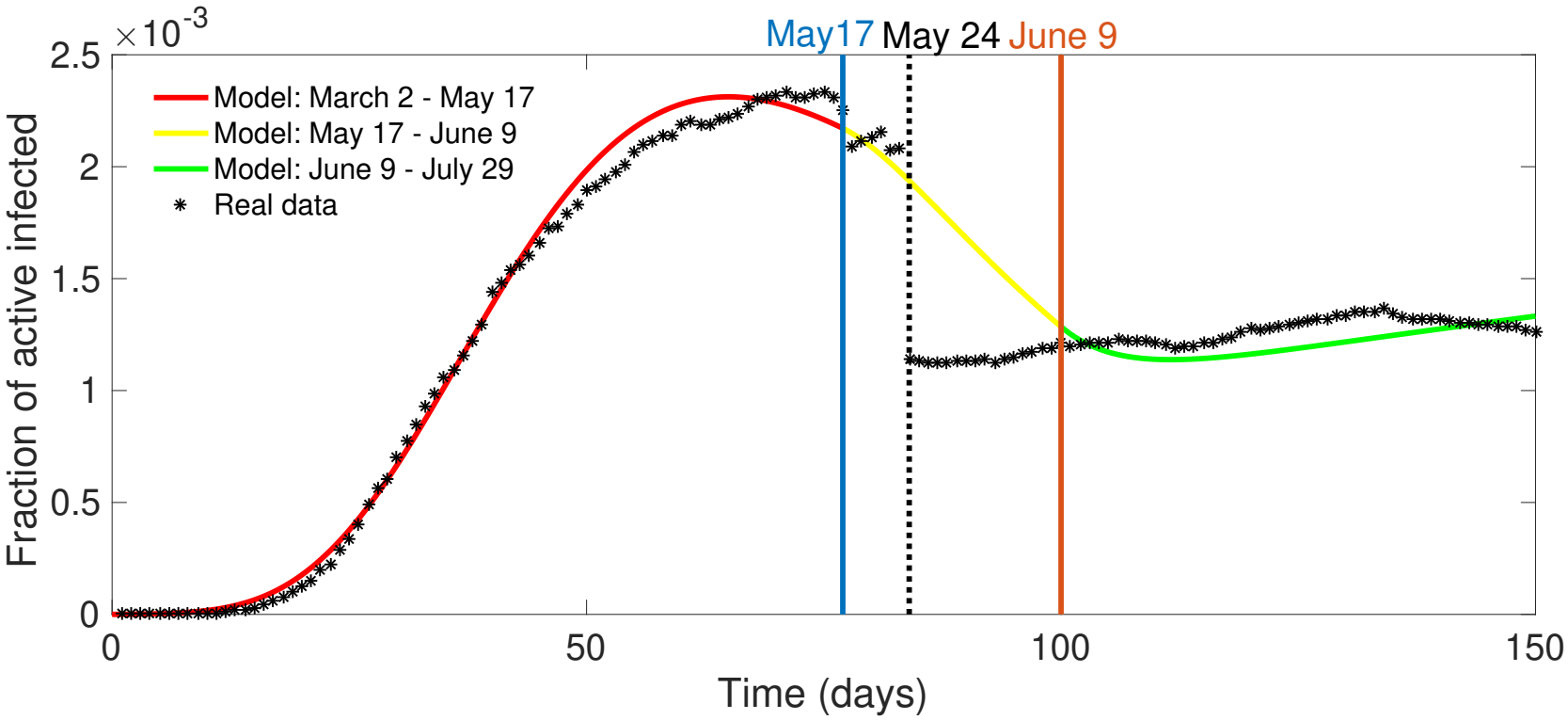
determine if the endemic equilibrium is globally asymptotically stable in the whole region Ω:

$$\Omega = \left\{ x = (S,\, A,\, I,\, R,\, P)^T \in \left(\mathbb{R}^+\right)^5 \,;\; 0 < S + A + I + R + P \leq \frac{\Lambda}{\mu} \right\}.$$

Optimal control

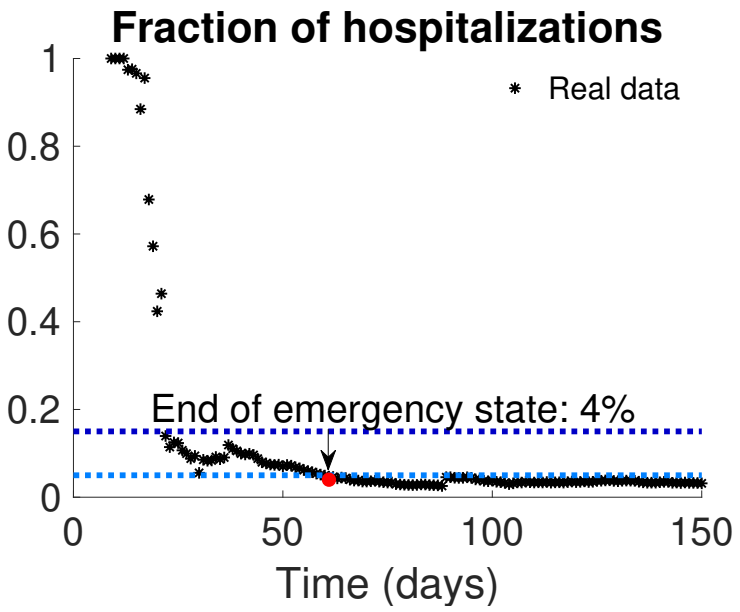


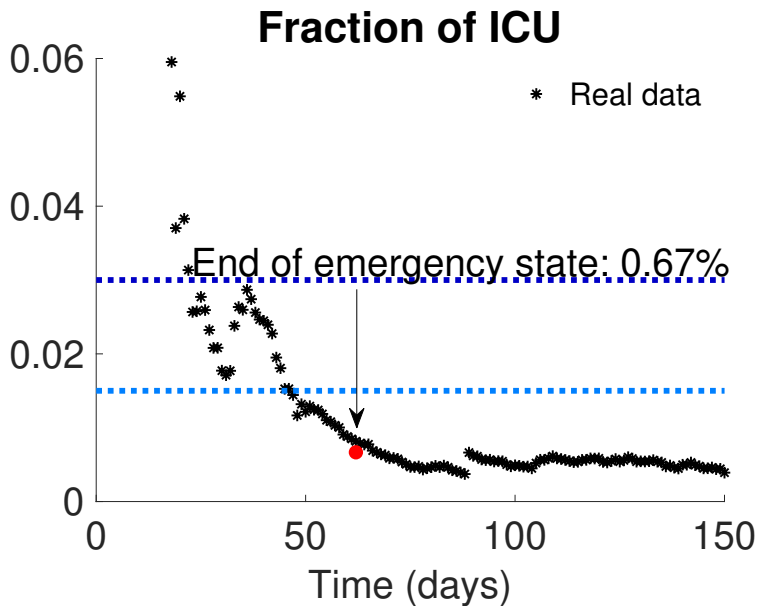
SAIRP model - fit the confirmed active infected cases in Portugal



- March 2, 2020 – first confirmed 2 infected cases were reported, in Portugal;
- March 12, 2020 – declared State of Emergency;
- March 18, 2020 – teaching as well as non-teaching and classroom training activities were suspended;
- May 2, 2020 – emergency status was canceled (duration of 45 days).

Hospitals and intensive care units occupancy beds by COVID-19 (until July 29, 2020)





Official real data, from March 02 to July 29, for the fraction of hospitalized individuals and in ICU due to COVID-19, with respect to the confirmed/active infected individuals.

Challenges:

- reopening of the economy while preserving the health of the population without collapsing the public health system;
- keep the schools open (children under 10 years old are not obliged to use a mask in Portugal) and prevent the economy to sink;
- there is a minimum number of people that need to be susceptible to infection;
- need to account that the population do not always follow the rules imposed by governments;

Goals:

- Develop tools to quantify this effect and include it into the equations.
- Investigate the use of optimal control theory to design strategies for this phase of the disease.

Optimal control problem: main goal

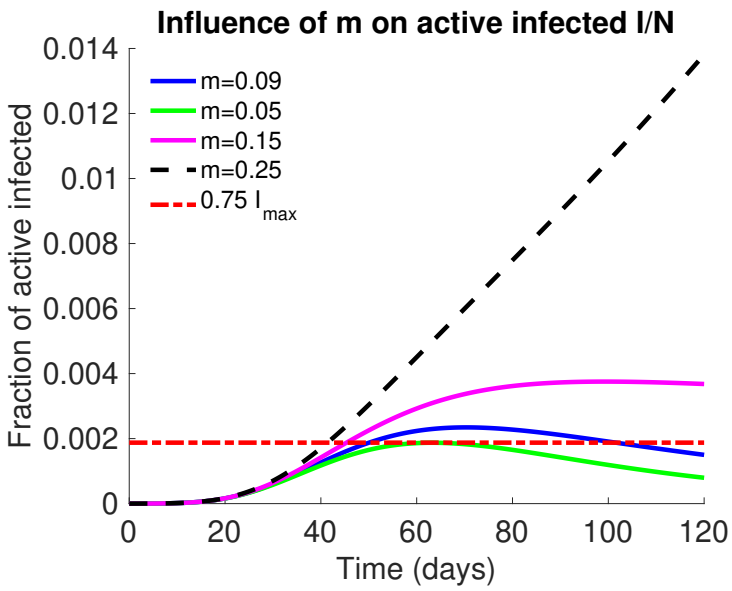
Goal:

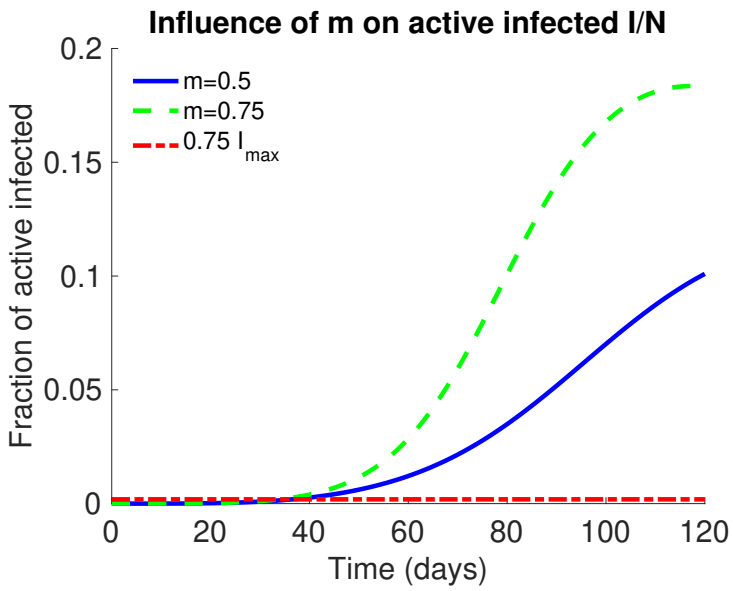
- maximize the number of people transferred from class P to the class S (that helps keeping the economy alive) and, simultaneously, minimize the number of active infected individuals and, consequently, the number of hospitalized and people needing ICU (in other words, ensuring that the health system is never overloaded);

- impose that the number of active infected cases is always below 2/3 or 60% of the maximum value observed up to July 29, 2020 ($I_{\max}$). This condition warrants that the health system does not collapse.

Sensitivity of class I with respect to parameter m

- Parameter m in model SAIRP: represents the fraction of protected individuals P that is transferred to susceptible S;
- the class of active infected individuals I is very sensitive to the change of the parameter m.





The dotted red line marks the level $0.75 \times I_{\max}$ that represents approximately 75% of the maximum fraction of active infected cases observed in Portugal (up to July 29, 2020).

Consider the fixed parameters $(\beta, p) = (1.464, 0.675)$ and all the other parameters from previous table.

Optimal control problem: control system

The parameter m in the $SAIRP$ model, is replaced by a control function $u(\cdot)$.
The control $u(\cdot)$ represents the fraction of individuals in class P of *protected* that is transferred to the class S.

Control system:

$$\begin{cases} \dot{S}(t) = -\beta(1-p)\left(\theta A(t) + I(t)\right) S(t) - \phi p S(t) + w u(t) P(t), \\ \dot{A}(t) = \beta(1-p)\left(\theta A(t) + I(t)\right) S(t) - \nu A(t), \\ \dot{I}(t) = \nu A(t) - \delta I(t), \\ \dot{P}(t) = \phi p S(t) - w u(t) P(t). \end{cases} \tag{5}$$

Control constraints: $0 \leq u(t) \leq u_{\max}$ with $u_{\max} \leq 1$. In other words, the solutions of the problem must belong to the following set of admissible control functions:

$$\Theta = \left\{ u,\ u \in L^1\left([0, t_f], \mathbb{R}\right) \mid 0 \leq u(t) \leq u_{\max} \quad \forall\ t \in [0, t_f] \right\}. \tag{6}$$

Optimal control problem: cost functional and state constraint

Mathematically, the main goal consists to **minimize the cost functional**

$$J(u) = \int_0^{t_f} k_1 I(t) - k_2\, u(t)\, dt\,, \tag{7}$$

representing the fact that we want to minimize the fraction of infected individuals I and, simultaneously, maximize the intensity of letting people from class P go back to class S. The constants k_i, $i = 1, 2$, represent the weights associated to the class I and control u.

State constraint: Moreover, the solutions of the optimal control problem must satisfy:
$I(t) \leq \zeta$ **with** $\zeta = 0.6 \times I_{\max}$ **and** $\zeta = 2/3 \times I_{\max}$.

Optimal control problem: numerical simulations

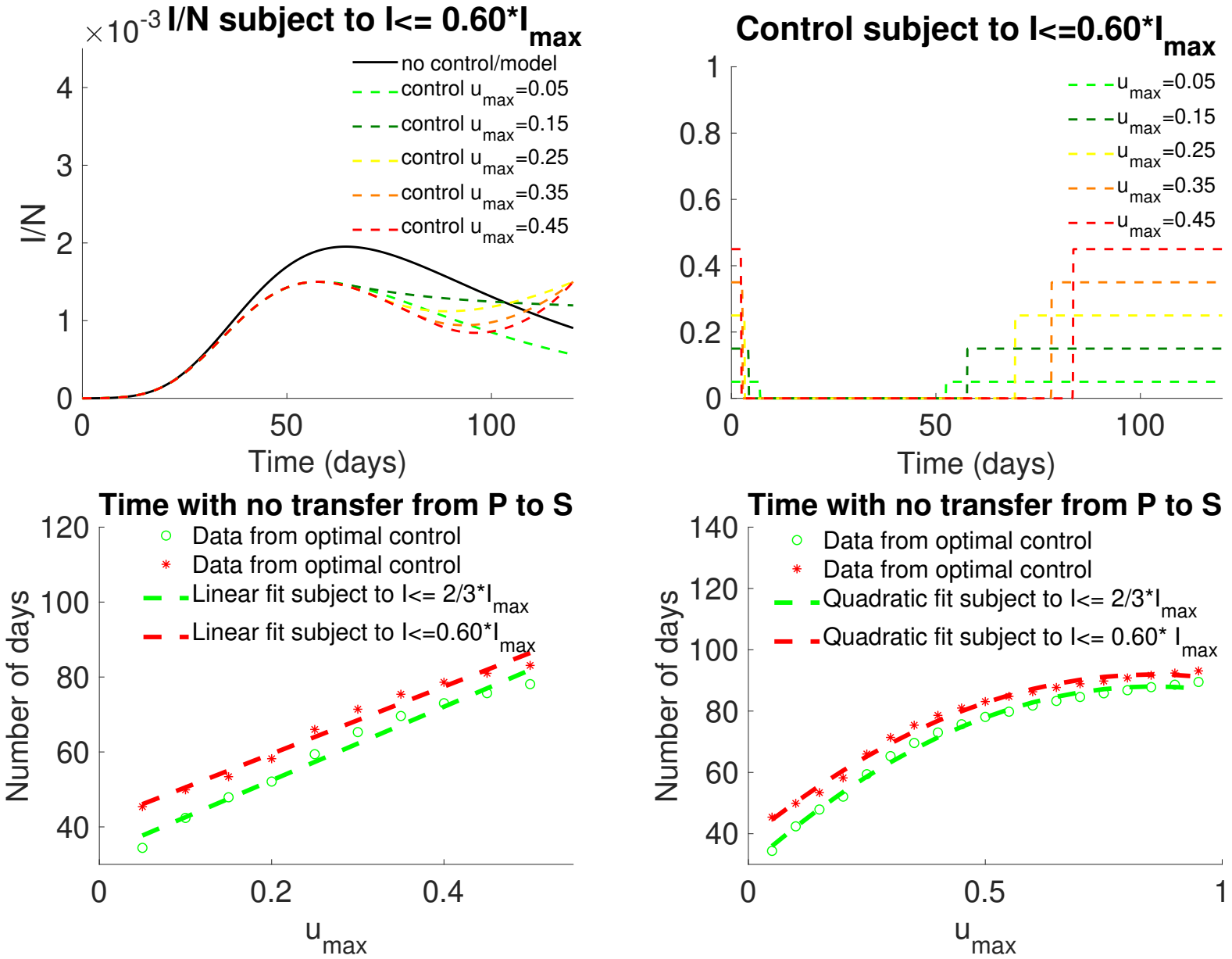
For the numerical simulations, we considered:

- $k_1 = 100$, $k_2 = 1$;
- $t_f = 120$ days;
- $(\beta, \delta) = (1.464, 1/30)$, $m = 0.09$, $p = 0.675$;
- all the other parameters from previous table.

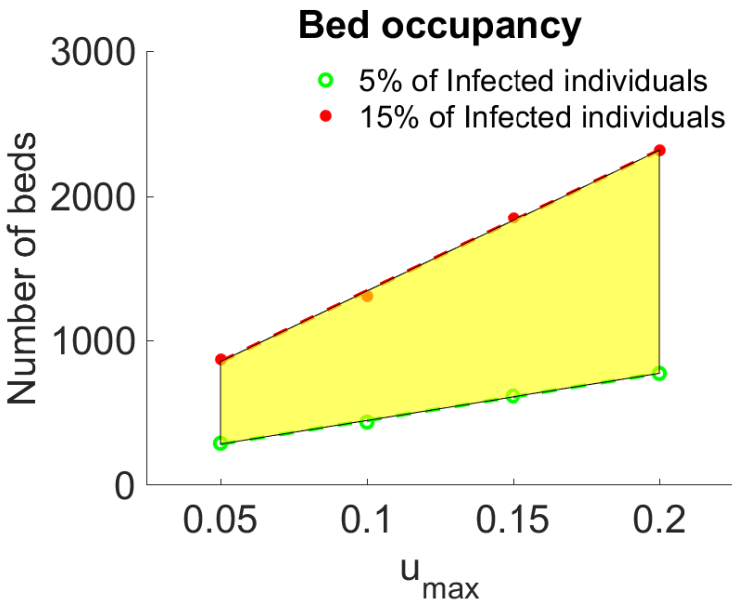
Numerically, we:

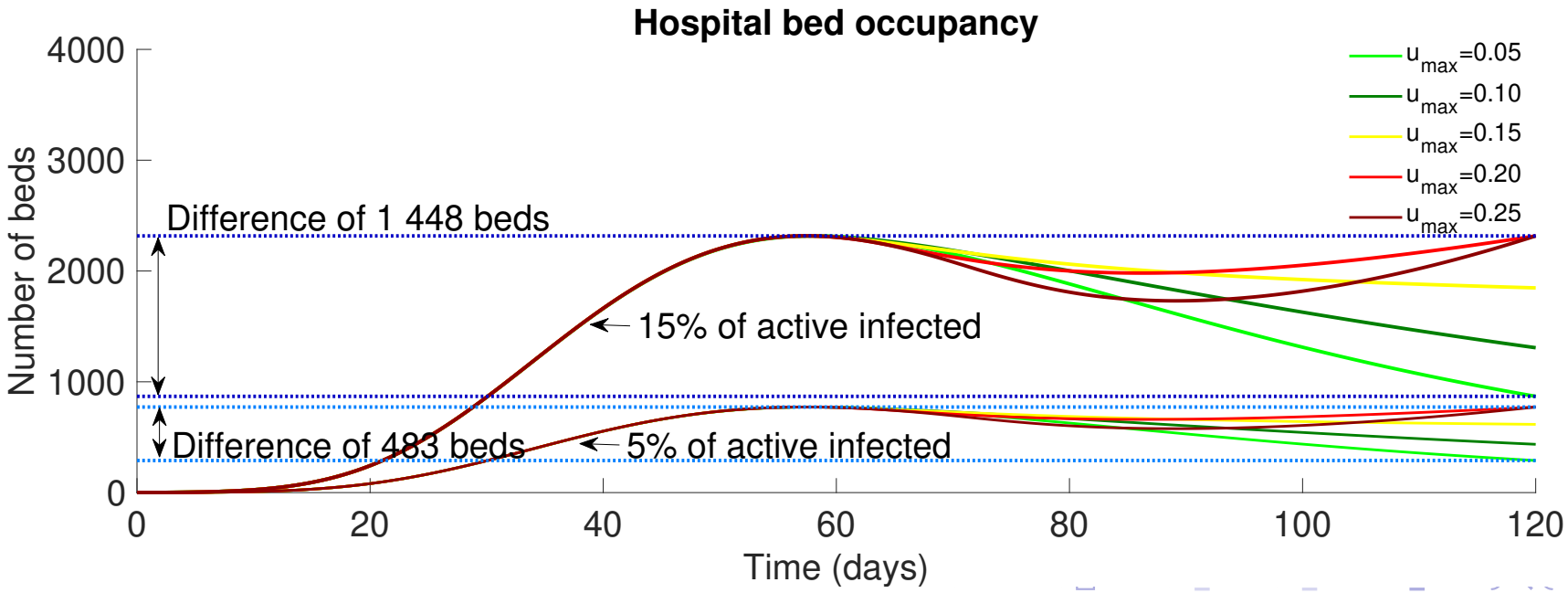
- discretized the optimal control problem to a nonlinear programming problem, using the Applied Modeling Programming Language (AMPL);
- after, the AMPL problem was linked to the optimization solver IPOPT;
- the discretization was performed with $n = 1500$ grid points using the trapezoidal rule as the integration method.

Active infected individuals: comparison of the solution of the SAIRP model with the optimal control problem



Number of hospital beds occupation for the optimal control solutions





ICU hospital bed occupancy for $u_{\max} \in \{0.05, 0.10, 0.15, 0.20, 0.25\}$ s.t. $I(t) \leq 0.60 \times I_{\max}$

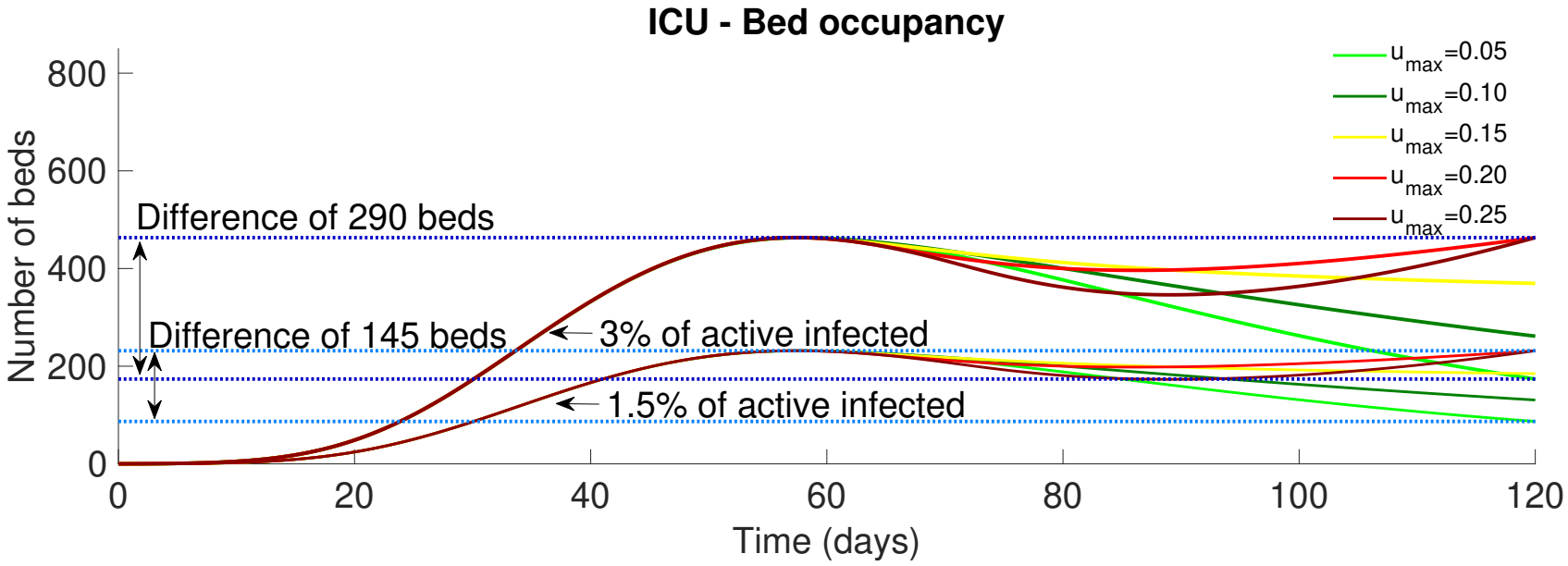


Figure: The ICU beds occupation represents between 1.5% and 3% of the number of active infected individuals.

Difference between protected individuals obtained via the SAIRP model wit and without control

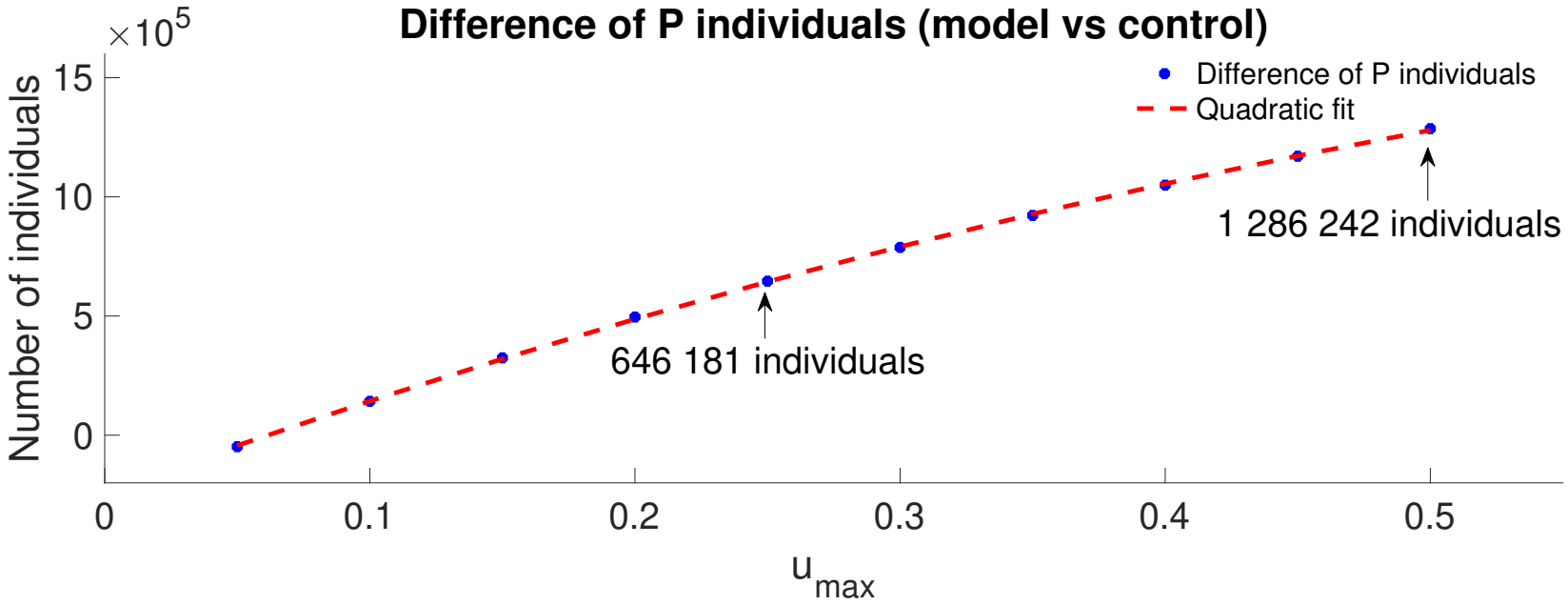
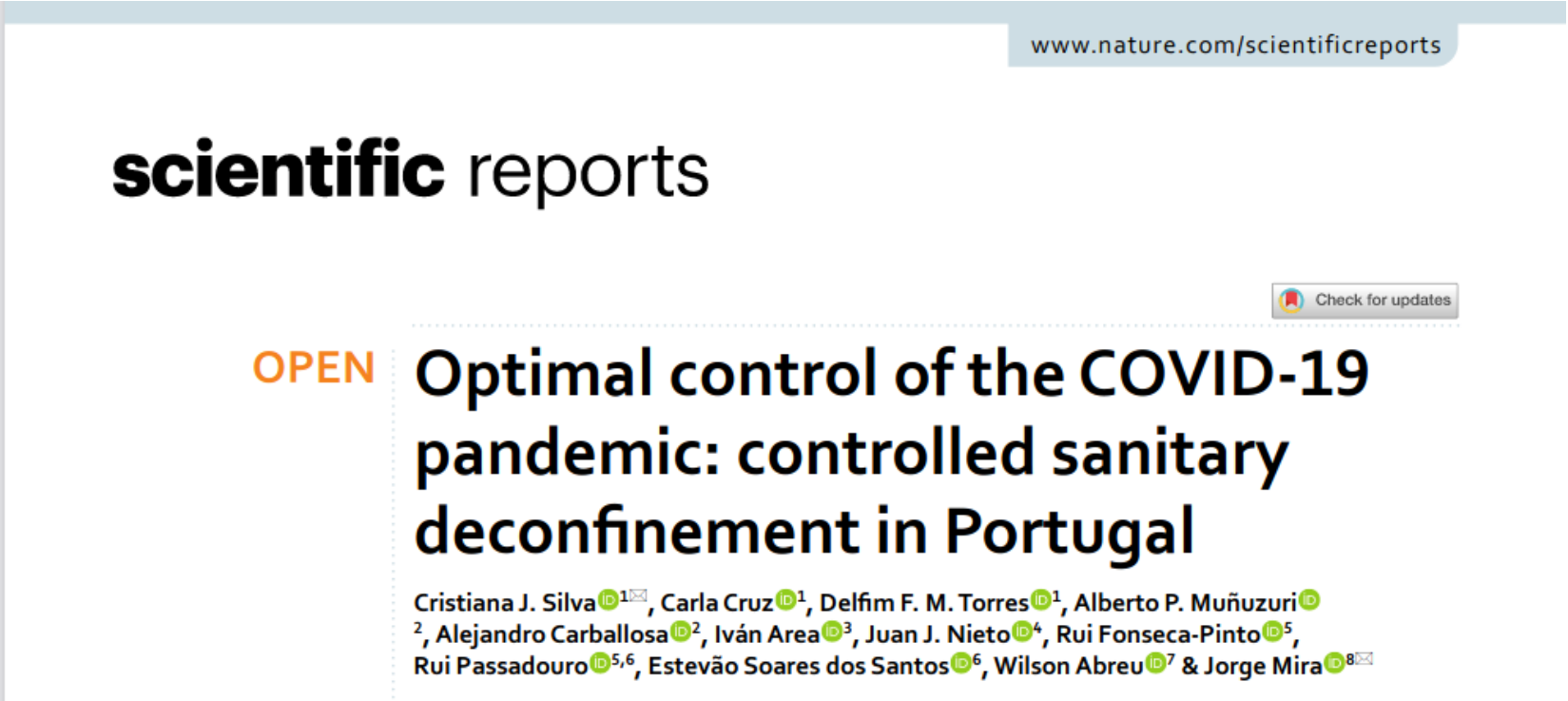


Figure: Consider the maximal value of the control $u_{\max} \in \{0.05, 0.10, \ldots, 0.45, 0.50\}$ and the constraint $I(t) \leq 0.60 \times I_{\max}$. The quadratic equation for fitting the difference between the number of individuals in class P obtained via de $SAIRP$ model without and with control $u_{\max} \in \{0.05, 0.10, \ldots, 0.45, 0.50\}$ (that is the number of released people from the protected class to the susceptible), respectively, is given by $y = -1984603.049\, x^2 + 4030952.677\, x - 239897.361$.

Reference



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Optimal control of the COVID-19 pandemic: controlled sanitary deconfinement in Portugal

Cristiana J. Silva[1], Carla Cruz[1], Delfim F. M. Torres[1], Alberto P. Muñuzuri[2], Alejandro Carballosa[2], Iván Area[3], Juan J. Nieto[4], Rui Fonseca-Pinto[5], Rui Passadouro[5,6], Estevão Soares dos Santos[6], Wilson Abreu[7] & Jorge Mira[8]

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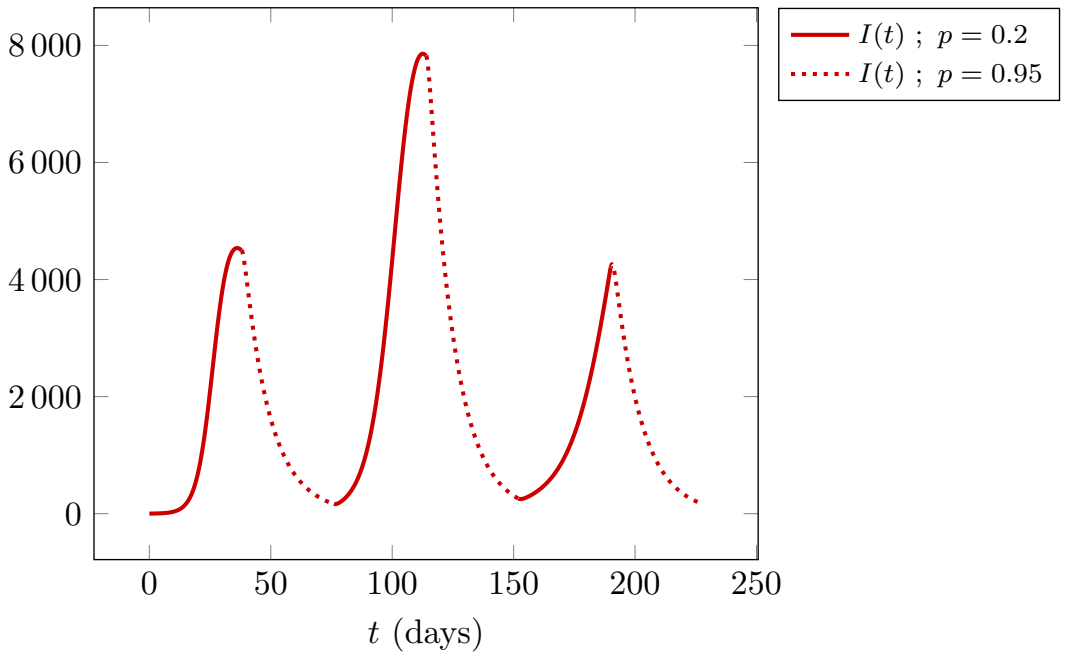
SAIRP model with piecewise constant functions: pseudo-periodic solutions and multiple epidemic waves



SAIRP model with piecewise constant functions

Generalize the previous SAIRP model to a non constant population model with piecewise constant parameters

$\Downarrow$

allows to model the governmental and public health decisions of political actors, which have a large influence on the behaviors of individuals, which in turn can change the dynamics of the epidemic

$\Downarrow$

also allows to mathematical model the human behavior in the application of non-pharmaceutical interventions (NPI), such as, physical distancing, limited size of indoor and outdoor gatherings, teleworking, regular cleaning of frequently-touched surfaces and appropriate ventilation of indoor spaces, mask use, avoiding close contact and hand washing.

Model with piecewise constant parameters

The human behavior and the governmental public health decision makers can change the dynamics of the SAIRP model.

Consider parameters determined by piecewise constant functions.

Subdivide the time line $[0, +\infty)$ into a finite number of n intervals

$$[T_0,\ T_1) \cup [T_1,\ T_2) \cup \cdots \cup [T_n,\ +\infty),$$

with disjoint unions, and introduce a piecewise constant function α defined on each time interval as

$$\alpha(t) = \alpha_i, \quad t \in [T_i,\ T_{i+1}), \quad 0 \leq i \leq n,$$

with $T_0 = 0$, $T_{n+1} = +\infty$ and $\alpha_i \in \mathbb{R}^9$.

Model with piecewise constant parameters: existence and uniqueness of global solutions

Next, consider the sequence of Cauchy problems defined for each initial condition $x_0 \in \Omega$ by

$$\begin{cases} x(0) = x_0, & \dot{x}(t) = f\big(x(t), \alpha_0\big), \quad T_0 < t < T_1, \\ x(T_i) = \lim\limits_{\substack{t \to T_i \\ t \in (T_{i-1}, T_i)}} x(t), & \dot{x}(t) = f\big(x(t), \alpha_i\big), \quad T_i < t < T_{i+1}, 1 \leq i \leq n \end{cases} \tag{8}$$

We are now in a position to derive the existence and uniqueness result.

Proposition

For any initial condition $x_0 \in \Omega$, the sequence of Cauchy problems given by (8) admits a unique global solution, denoted again by $x(t, x_0)$, whose components are non-negative. Furthermore, the region Ω is positively invariant.

Existence of pseudo-periodic solutions

- **Piecewise constant parameters can lead to pseudo-periodic solutions.**

Theorem

Assume that the disease-free equilibrium, Σ_0, admits a non-trivial basin of attraction $\Omega_0 \subset \Omega$ if $R_0 < 1$, and that the endemic equilibrium Σ^+ admits a non-trivial basin of attraction $\Omega^+ \subset \Omega$ if $R_0 > 1$. Let α_0 and α^+ denote two sets of parameters of system (11) such that $R_0(\alpha_0) < 1$ and $R_0(\alpha^+) > 1$. Let $x_0 \in \Omega_0$ and consider the sequence of Cauchy problems

$$\begin{cases} x(T_0) = x_0, & \dot{x}(t) = f\big(x(t), \alpha_0\big), \quad T_0 < t < T_1, \\ x(T_i) = \lim\limits_{\substack{t \to T_i \\ t \in (T_{i-1},\, T_i)}} x(t), & \dot{x}(t) = f\big(x(t), \alpha^+\big), \quad T_i < t < T_{i+1}, \quad \text{for } i \text{ odd}, \\ x(T_i) = \lim\limits_{\substack{t \to T_i \\ t \in (T_{i-1},\, T_i)}} x(t), & \dot{x}(t) = f\big(x(t), \alpha_0\big), \quad T_i < t < T_{i+1}, \quad \text{for } i \text{ even}, \end{cases} \tag{9}$$

for $1 \leq i \leq n$, where T_i is such that $x(T_i) \in \Omega^+$, for i odd, and $x(T_i) \in \Omega_0$, for i even. Then the solution $x(t, x_0)$, of the latter sequence of Cauchy problems, exhibits pseudo-oscillations between a neighborhood $\mathscr{N}_0$ of Σ_0 and a neighborhood $\mathscr{N}^+$ of Σ^+ in Ω.

Existence of pseudo-periodic solutions: example

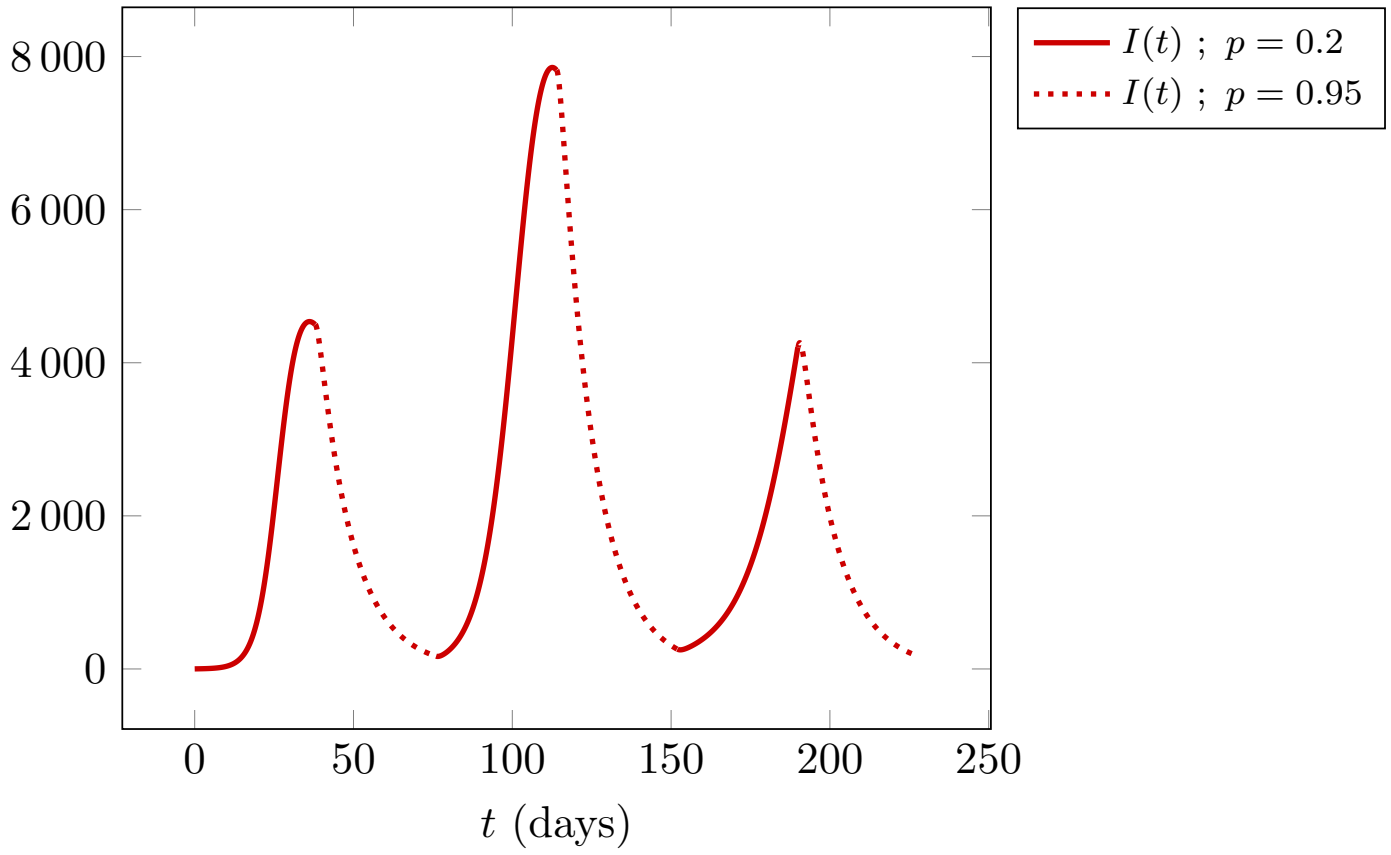


Figure: Solution of the sequence of Cauchy problems (9) exhibiting pseudo-oscillations between a neighborhood $\mathscr{N}_0$ of Σ_0 and a neighborhood $\mathscr{N}^+$ of Σ^+ in Ω. Here I denotes the number of active infected individuals and p the fraction, $0 < p < 1$, of susceptible individuals S that is transferred to the protected class P.

Model fitting - Portuguese COVID-19 data

Constant parameters

Parameter	Description	Value
Λ	Recruitment rate	$\frac{0.19\% \times N_0}{365}$
μ	Natural death rate	$\frac{1}{81 \times 365}$
θ	Modification parameter	1
v	Transfer rate from A to I	1
q	Fraction of asymptomatic A infected ind.	0.15
ϕ	Transfer rate from S to P	$1/12\, day^{-1}$
δ	Transfer rate from I to R	$1/27\, day^{-1}$
w	Transfer rate from P to S	$1/45\, day^{-1}$

Piecewise constant parameters from 2 March, 2020 until 15 April, 2021

Divide the time interval $[0, 410]$ days into 9 subintervals:

- 2 March – 13 May 2020
- 13 May – 30 May 2020
- 30 May – 9 July 2020
- 9 July – 11 August 2020
- 11 August – 17 September 2020
- 17 September – 9 November 2020
- 9 November – 30 December 2020
- 30 December 2020 - 24 January 2021
- 24 January – 15 April 2021

Some important dates:

- 2 March, 2020 - first confirmed cases in Portugal
- 12 March, 2020 - first emergency state (schools and borders closed)
- 2 May, 2020 - cancel emergency state
- 14 October, 2020 - Calamity state
- 6 November, 2020 - emergency state
- 21 January, 2021 - schools were closed and borders closed
- 27 April, 2021 - end of emergency state

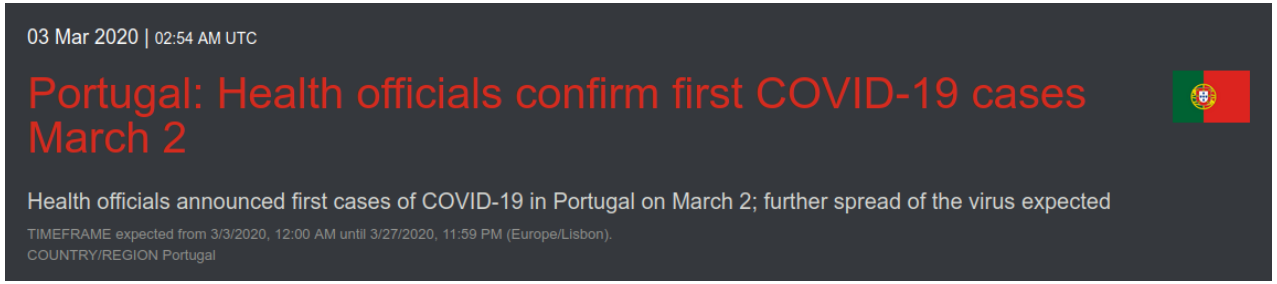
Piecewise constant parameters from 2 March, 2020 until 15 April, 2021

Time sub-interval	β_i (transmission rate)	p_i (transfer from S to P)	m_i (transfer from P to S)
$[0, 73]$	$\beta_1 = 1.502$	$p_1 = 0.675$	$m_1 = 0.066$
$[73, 90]$	$\beta_2 = 0.600$	$p_2 = 0.650$	$m_2 = 0.090$
$[90, 130]$	$\beta_3 = 1.240$	$p_3 = 0.580$	$m_3 = 0.180$
$[130, 163]$	$\beta_4 = 0.936$	$p_4 = 0.610$	$m_4 = 0.160$
$[163, 200]$	$\beta_5 = 1.531$	$p_5 = 0.580$	$m_5 = 0.170$
$[200, 253]$	$\beta_6 = 0.886$	$p_6 = 0.290$	$m_6 = 0.140$
$[253, 304]$	$\beta_7 = 0.250$	$p_7 = 0.370$	$m_7 = 0.379$
$[304, 329]$	$\beta_8 = 0.793$	$p_8 = 0.370$	$m_8 = 0.090$
$[329, 410]$	$\beta_9 = 0.100$	$p_9 = 0.550$	$m_9 = 0.090$

Estimated by Method of Least Squares.

Initial conditions - Portuguese COVID-19 data

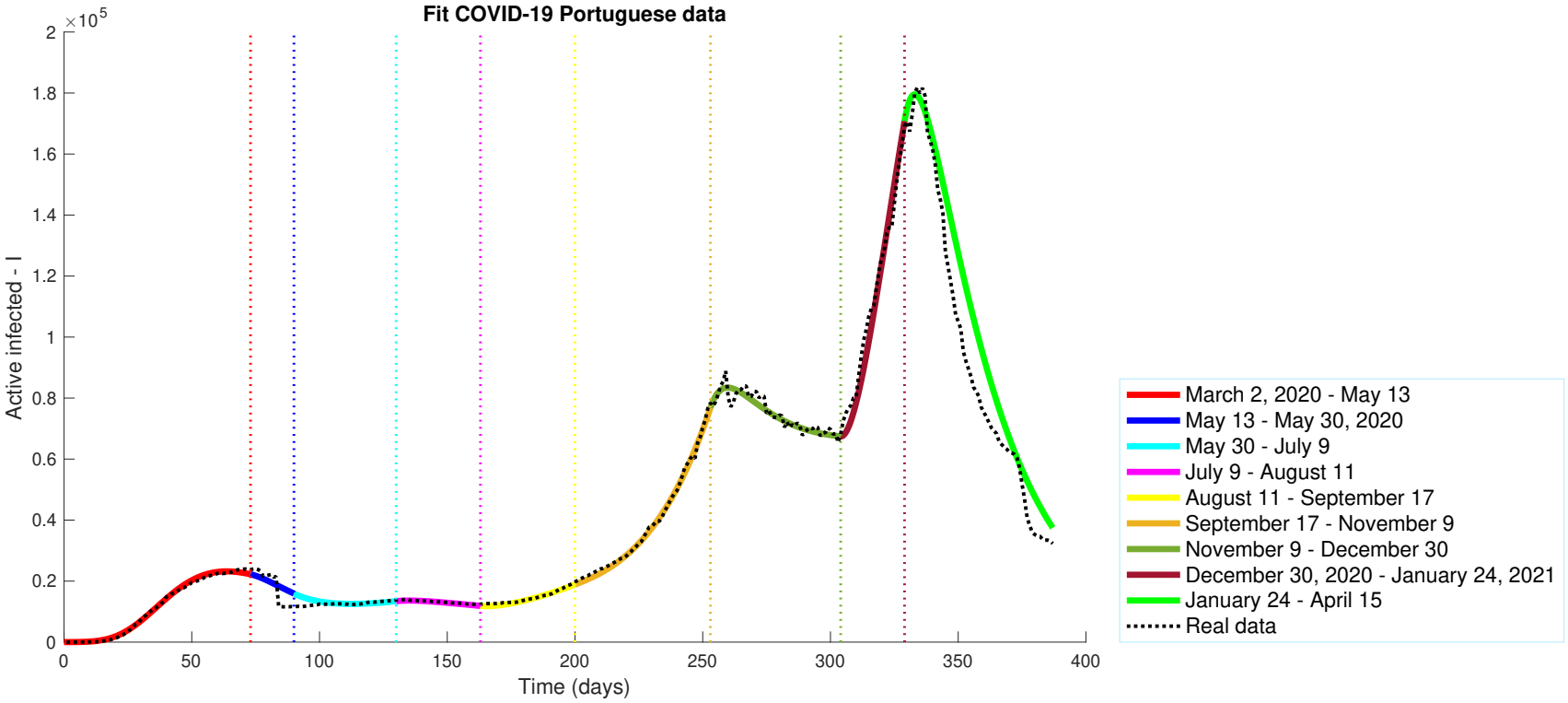
Initial condition	Value	Reference
$N = S_0 + A_0 + I_0 + R_0 + P_0$	10295907	INE
S_0	10295894	DGS
I_0	2	DGS
A_0	2/0.15	DGS
R_0	0	DGS
P_0	0	DGS



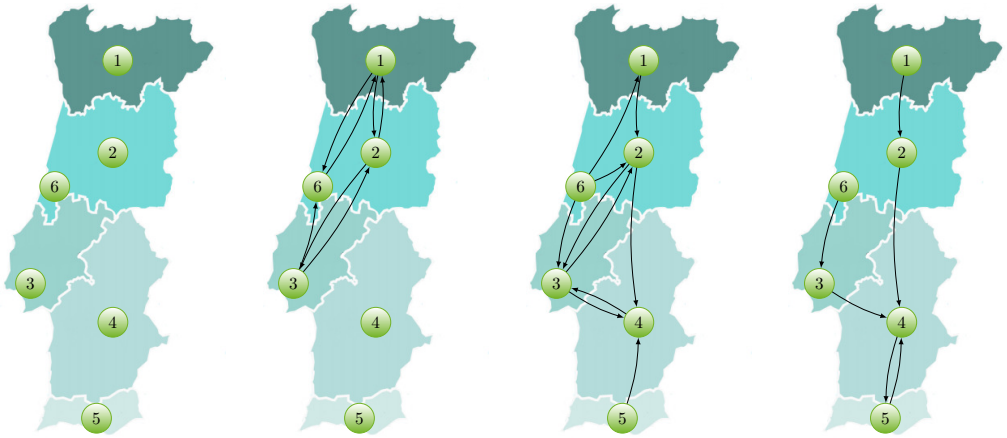
Source: `https://www.garda.com/crisis24/news-alerts/319326/`

`portugal-health-officials-confirm-first-covid-19-cases-march-2`

SAIRP model - fitting active infected cases in Portugal - 02 March, 2020 - 15 April, 2021



Complex network



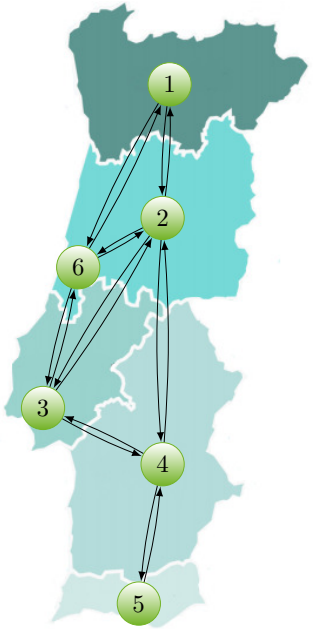
(a) (b) (c) (d)

Dynamics of a complex network of non-identical SAIRP models

- **Mobilities play an important role on the dynamics of epidemics.**

Goal:

- **study the propagation of the COVID-19 outbreak in Portugal by modeling this country by a complex network in which the six regions studied previously for the calibration of the SAIRP model with piecewise constant parameters.**



Construction of the complex network

- Consider the six regions of Portugal: *Norte* (1), *Centro* (2), *Lisboa e Vale do Tejo* (3), *Alentejo* (4), *Algarve* (5), *Pinhal Litoral* (6).
- Those six regions are connected by a finite number of links that define a graph $\mathscr{G} = (\mathscr{V}, \mathscr{E})$ made of a set $\mathscr{V}$ of 6 vertices, which correspond to the six regions, and of a set $\mathscr{E}$ of edges, which model the main connections between those 6 regions.
- Couple each vertex of the graph with one instance of the model (8).
- Since each region has its own specificity, we consider that the multiple instances of the model are non-identical, which means that the values of the parameters can differ from one region to another.

Construction of the complex network

Notations:

$$
\begin{aligned}
x_i &= (S_i\, A_i,\, I_i,\, R_i,\, P_i)^T \in \mathbb{R}^5, \quad 1 \le i \le 6, \\
X &= (x_1,\, \ldots,\, x_6)^T \in \left(\mathbb{R}^5\right)^6, \\
HX &= (Hx_1,\, \ldots,\, Hx_6)^T \in \left(\mathbb{R}^5\right)^6, \\
\alpha(t) &= \left(\alpha_1(t),\, \ldots,\, \alpha_6(t)\right) \in \left(\mathbb{R}^9\right)^6,
\end{aligned}
$$

where H is the matrix of coupling strengths defined by

$$
H = \begin{bmatrix} \sigma_S & 0 & 0 & 0 & 0 \\ 0 & \sigma_A & 0 & 0 & 0 \\ 0 & 0 & \sigma_I & 0 & 0 \\ 0 & 0 & 0 & \sigma_R & 0 \\ 0 & 0 & 0 & 0 & \sigma_P \end{bmatrix},
$$

with non negative coefficients σ_S, σ_A, σ_I, σ_R and σ_P.

Construction of the complex network - matrix of connectivity L

Define a matrix L of connectivity: for each edge $(k, j) \in \mathscr{E}$, $k \neq j$, we set $L_{j,k} = \varepsilon_{j,k} > 0$. If $(k, j) \notin \mathscr{E}$, $k \neq j$, we set $L_{j,k} = 0$. The diagonal coefficients satisfy

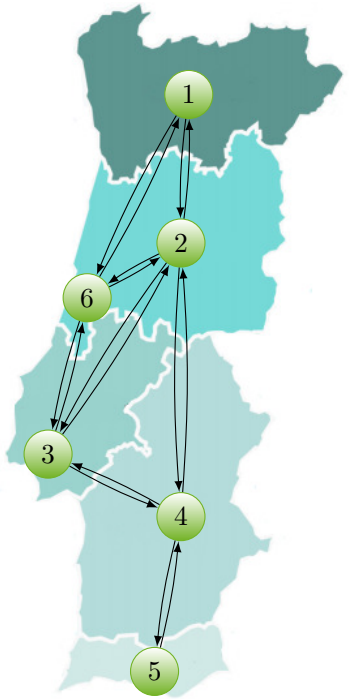
$$L_{j,j} = -\sum_{\substack{k=1 \\ k \neq j}}^{n} \varepsilon_{k,j},$$

thus L is a matrix whose sum of coefficients in each column is null.

Example, the connectivity matrix of the graph corresponding to Figure 7 is given by

$$L = \begin{bmatrix} L_{11} & \varepsilon_{12} & 0 & 0 & 0 & \varepsilon_{16} \\ \varepsilon_{21} & L_{22} & \varepsilon_{23} & \varepsilon_{24} & 0 & \varepsilon_{26} \\ 0 & \varepsilon_{32} & L_{33} & \varepsilon_{34} & 0 & \varepsilon_{36} \\ 0 & \varepsilon_{42} & \varepsilon_{43} & L_{44} & \varepsilon_{45} & 0 \\ 0 & 0 & 0 & \varepsilon_{54} & L_{55} & 0 \\ \varepsilon_{61} & \varepsilon_{62} & \varepsilon_{63} & 0 & 0 & L_{66} \end{bmatrix}, \text{ with}$$

$$\begin{aligned} L_{11} &= -(\varepsilon_{21} + \varepsilon_{61}), \\ L_{22} &= -(\varepsilon_{12} + \varepsilon_{32} + \varepsilon_{42} + \varepsilon_{62}), \\ L_{33} &= -(\varepsilon_{23} + \varepsilon_{43} + \varepsilon_{63}), \\ L_{44} &= -(\varepsilon_{24} + \varepsilon_{34} + \varepsilon_{54}), \\ L_{55} &= -\varepsilon_{45}, \quad L_{66} = -(\varepsilon_{16} + \varepsilon_{26} + \varepsilon_{36}). \end{aligned}$$



Construction of the complex network - continuation

- an edge $(k, j) \in \mathscr{E}$, $k \neq j$, models a connection between two regions k and j, which corresponds to human displacements from region k towards region j;
- the parameter σ_S models the rate of susceptible individuals in region k which migrate towards vertex j. The parameters σ_A, σ_I, σ_R and σ_P are defined analogously.
- our model can take into account the situation where a part of the population is not concerned with the migrations. For instance, it is relevant to consider $\sigma_I = \sigma_P = 0$, while $\sigma_S > 0$ and $\sigma_A > 0$.
- The set of edges $\mathscr{E}$ and the coupling strengths stored in the matrix H define what is usually called the *topology* of the complex network.

System of equations for each region

Equations that describe the state of region $j \in \{1, \ldots, 6\}$:

$$\begin{cases} \dot{S}_j = \Lambda_j - \beta_j(1-p_j)\frac{(\theta_j A_j + I_j)}{N_j} S_j - \phi_j p_j S_j + \omega_j P_j - \mu_j S_j + \sigma_S \sum_{k=1}^{5} L_{j,k} S_k, \\ \dot{A}_j = \beta_j(1-p_j)\frac{(\theta_j A_j + I_j)}{N_j} S_j - \nu_j A_j - \mu_j A_j + \sigma_A \sum_{k=1}^{5} L_{j,k} A_k, \\ \dot{I}_j = \nu_j A_j - \delta_j I_j - \mu_j I_j + \sigma_I \sum_{k=1}^{5} L_{j,k} I_k, \\ \dot{R}_j = \delta_j I_j - \mu_j R_j + \sigma_R \sum_{k=1}^{5} L_{j,k} R_k, \\ \dot{P}_j = \phi_j p_j S_j - \omega_j P_j - \mu_j P_j + \sigma_P \sum_{k=1}^{5} L_{j,k} P_k, \end{cases} \tag{10}$$

(time dependence is omitted, to lighten the notations).

Existence and uniqueness of global solutions to the complex network problem

Introduce the minimum mortality rate μ_0 defined by

$$\mu_0 = \min_{1 \leq j \leq 6} \mu_j,$$

the positive coefficient Λ_0 defined by

$$\Lambda_0 = \sum_{j=1}^{6} \Lambda_j,$$

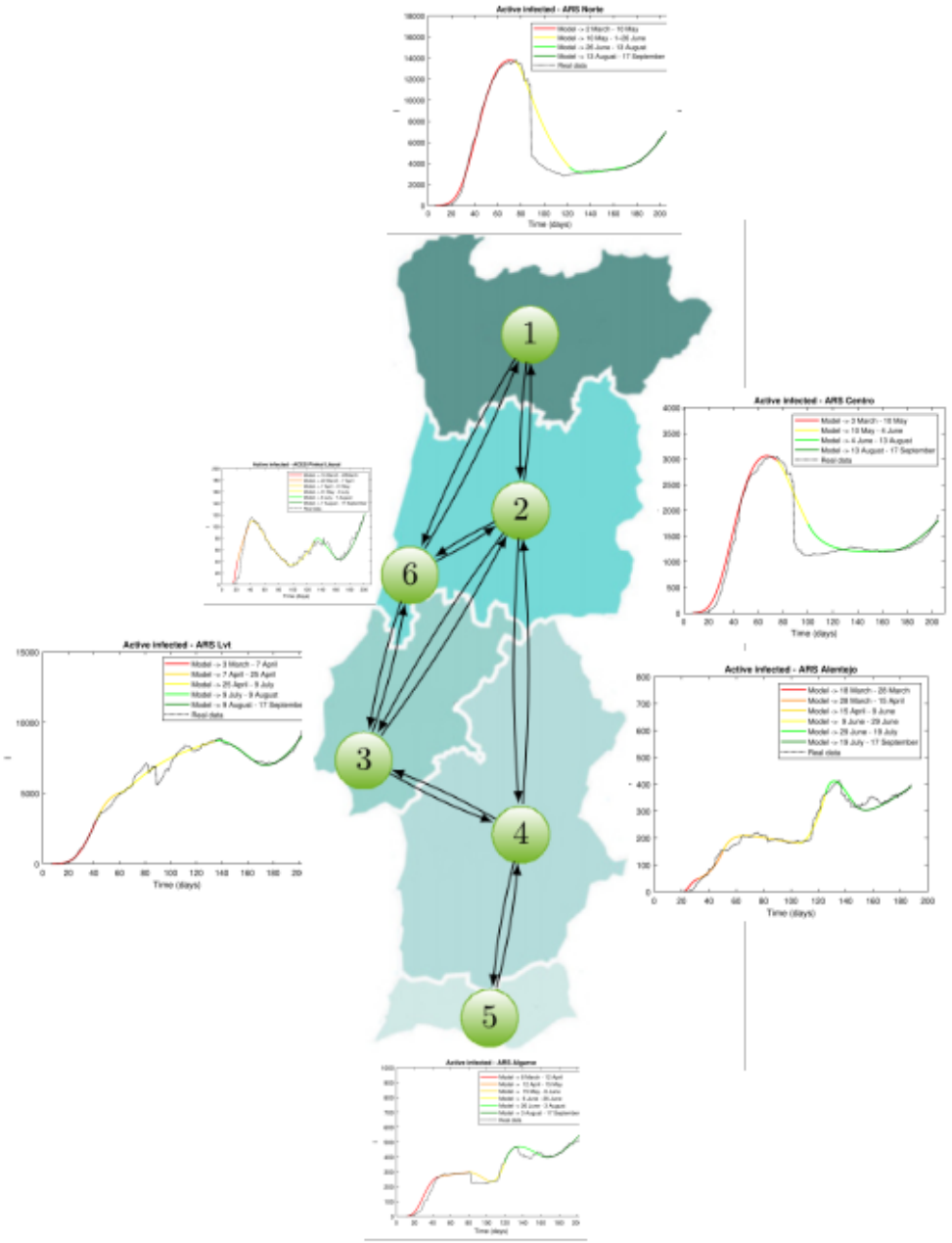
and the compact region

$$\Theta = \left\{ (x_j)_{1 \leq j \leq 30} \in (\mathbb{R}^+)^{30} \; ; \; \sum_{j=1}^{30} x_j \leq \frac{\Lambda_0}{\mu_0} \right\}.$$

Theorem

For any $X_0 \in \Theta$, the Cauchy problem given by (10) and $X(0) = X_0$ admits a unique solution denoted by $X(t, X_0)$, defined on $[0, \infty)$, whose components are non-negative. Furthermore, the region Θ is positively invariant.

Model with piecewise constant parameters: fit COVID-19 data in 6 Portuguese regions



Complex network model: numerical simulations for COVID-19 in Portugal

Goal:

- investigate the effect of the topology on the dynamics of the epidemics;
- analyze the existence of a topology which minimizes the average number of active infected individuals, during a fixed time interval;
- analyze if other topologies are likely to worsen the level of infection.

Set:

- $\sigma_S = \sigma_A > 0$, to model the mobilities of susceptible and asymptomatic individuals;
- fix $\sigma_I = \sigma_R = \sigma_P = 0$;
- test a sample of 1000 randomly generated topologies among 2^{16} topologies (*id est* sets of edges), for $\sigma_S = \sigma_A \in [0.01, 0.1]$;
- for each randomly generated topology, we perform a numerical integration of the complex network problem (10), with the same parameters $\alpha_1, \alpha_2, \ldots, \alpha_6$.

Numerical simulations: active infected individuals

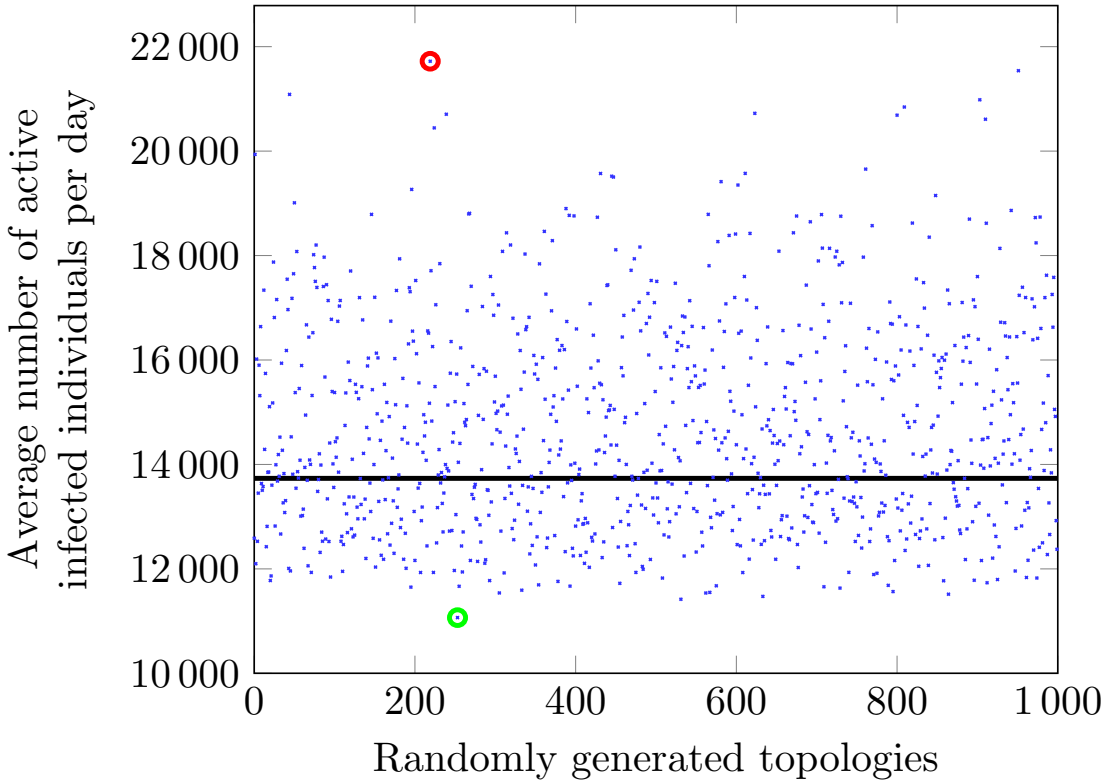


Figure: **Average number of active infected individuals, per day, f or a sample of** 1000 **randomly generated topologies, for** $\sigma_S = \sigma_A = 0.01$**.** The black line shows the level of infection for the empty topology. The green circle shows the optimum topology which minimizes the level of infection, whereas the red circle shows the topology which leads to the highest level of infection.

Numerical simulations: effect of coupling strengths

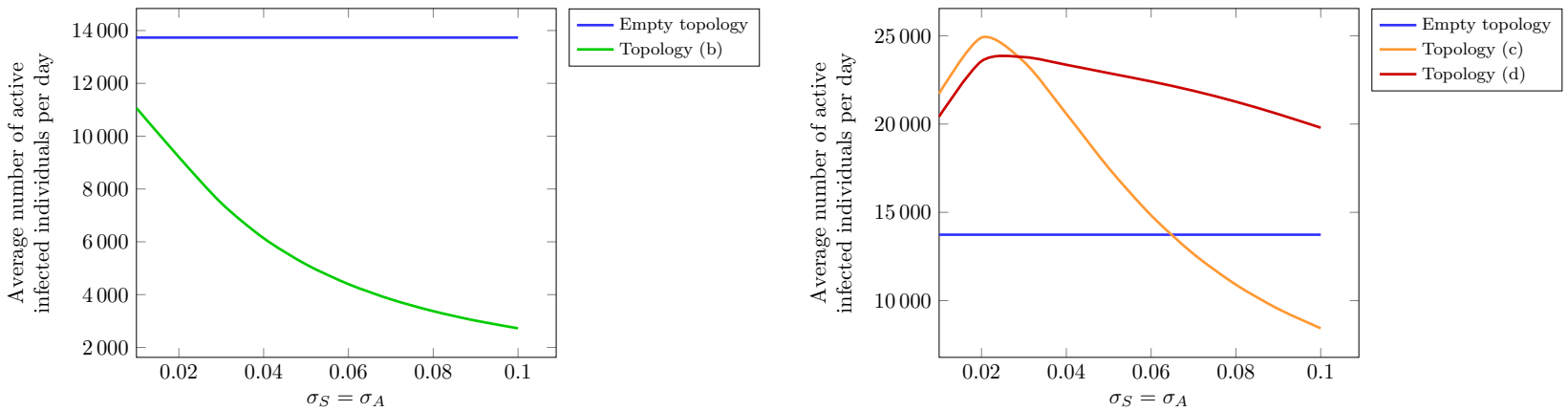


Figure: **Average number of active infected individuals, for each topology, with respect to the coupling strengths $\sigma_S = \sigma_A$.** Left: optimum topology which minimizes the level of infection of the epidemics. Right: two examples of topologies that can increase the level of infection, compared to the empty topology, which corresponds to the situation where individuals do not migrate from one region to another. Topology (c) leads to a level of infection that overcomes the level of the empty topology for only a weak coupling strength, whereas topology (d) seems to permanently overcome the level of the empty topology.

Numerical simulations: effect of coupling strengths

- **Existence of a certain number of topologies that decrease the level of infection, compared to the empty topology, which corresponds to the situation where individuals do not migrate from one region to another.**

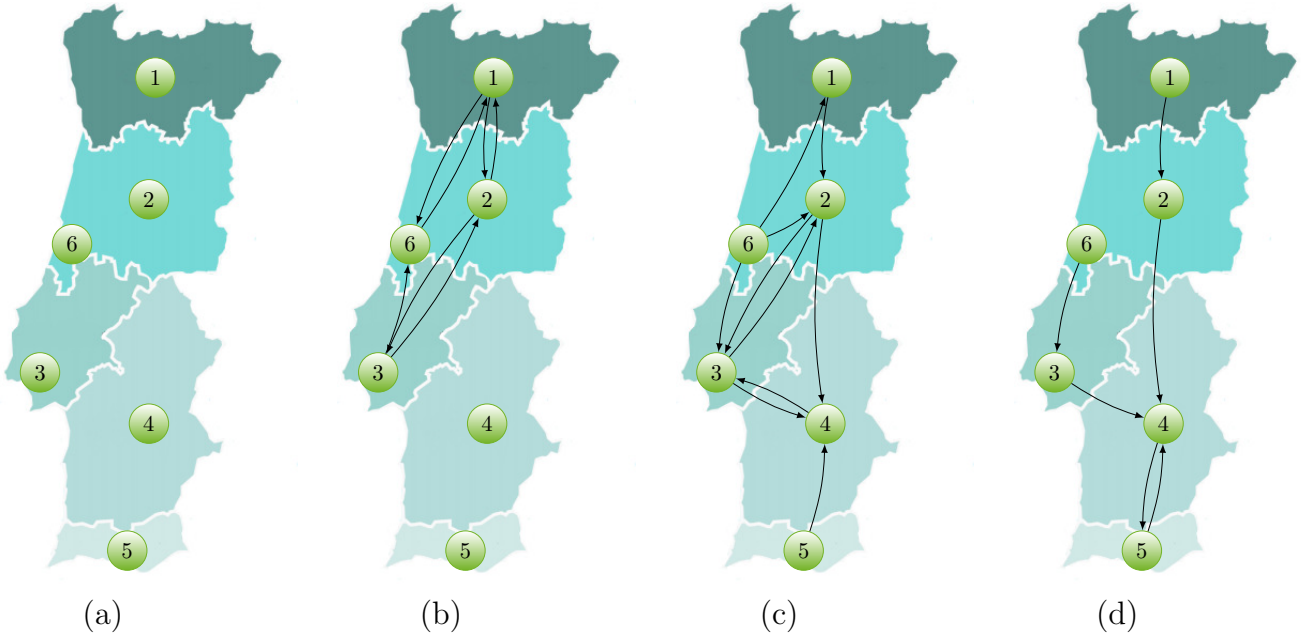
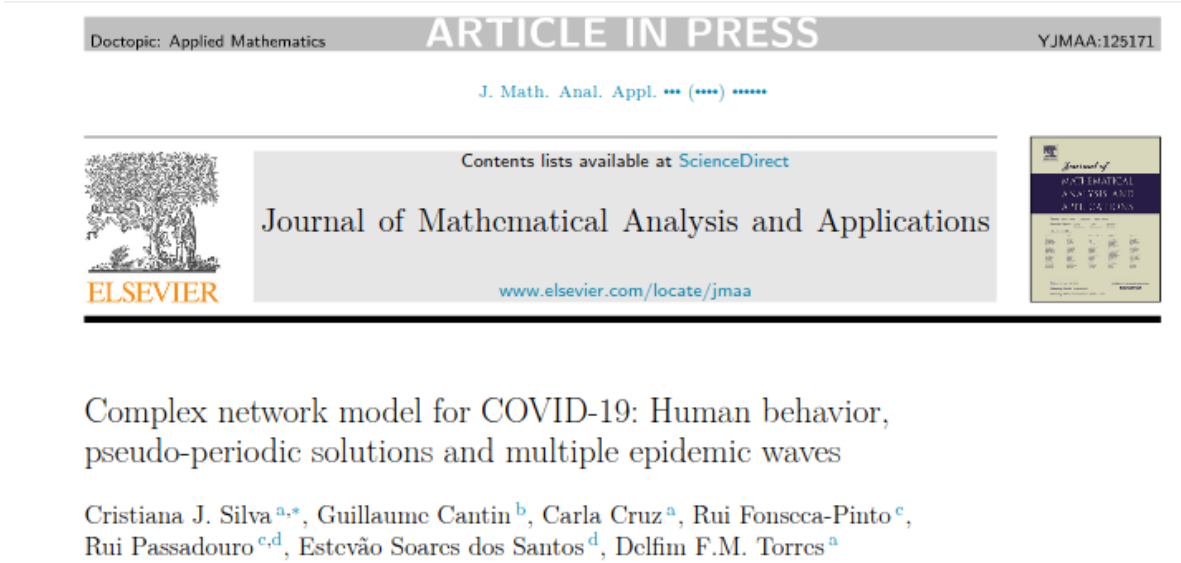


Figure: **Four remarkable topologies.** (a) Empty topology, which corresponds to the situation where individuals do not migrate from one region to another. (b) Topology that minimizes the level of infection. (c) Topology that leads to a level of infection greater than the level of the empty topology for only a weak coupling strength. (d) Topology that permanently overcomes the level of the empty topology.

Reference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Complex network model for COVID-19: Human behavior, pseudo-periodic solutions and multiple epidemic waves

Cristiana J. Silva [a,*], Guillaume Cantin [b], Carla Cruz [a], Rui Fonseca-Pinto [c], Rui Passadouro [c,d], Estevão Soares dos Santos [d], Delfim F.M. Torres [a]

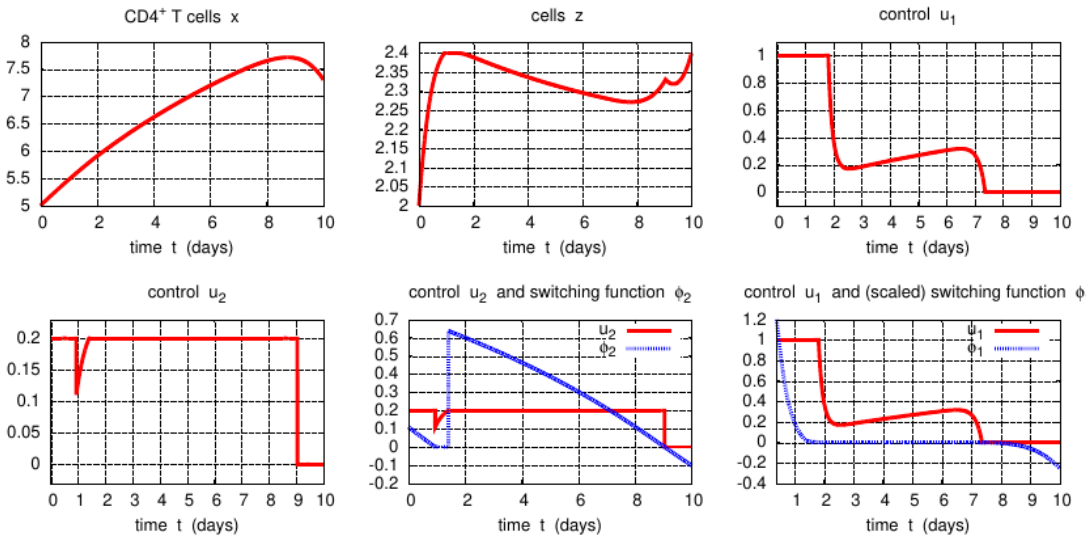
Cristiana J. Silva, Guillaume Cantin, Carla Cruz, Rui Fonseca-Pinto, Rui Passadouro da Fonseca, Estevao Soares dos Santos, Delfim F. M. Torres

Complex network model for COVID-19: human behavior, pseudo-periodic solutions and multiple epidemic waves, JMAA, in press.

Available at:

- **https://sites.google.com/view/comomatcovid19**
- **arXiv: https://arxiv.org/abs/2010.02368**

Optimal control of a delayed HIV model with state constraints



Motivation - antiretroviral (ART) drugs for HIV infection

- The most significant advance in medical management of HIV infection has been the treatment of patients with antiretroviral (ART) drugs, which can suppress HIV replication to undetectable levels.
- HIV treatment with ART requires to take medicine every day!

When to Start Antiretroviral Therapy

Last Reviewed: January 16, 2019

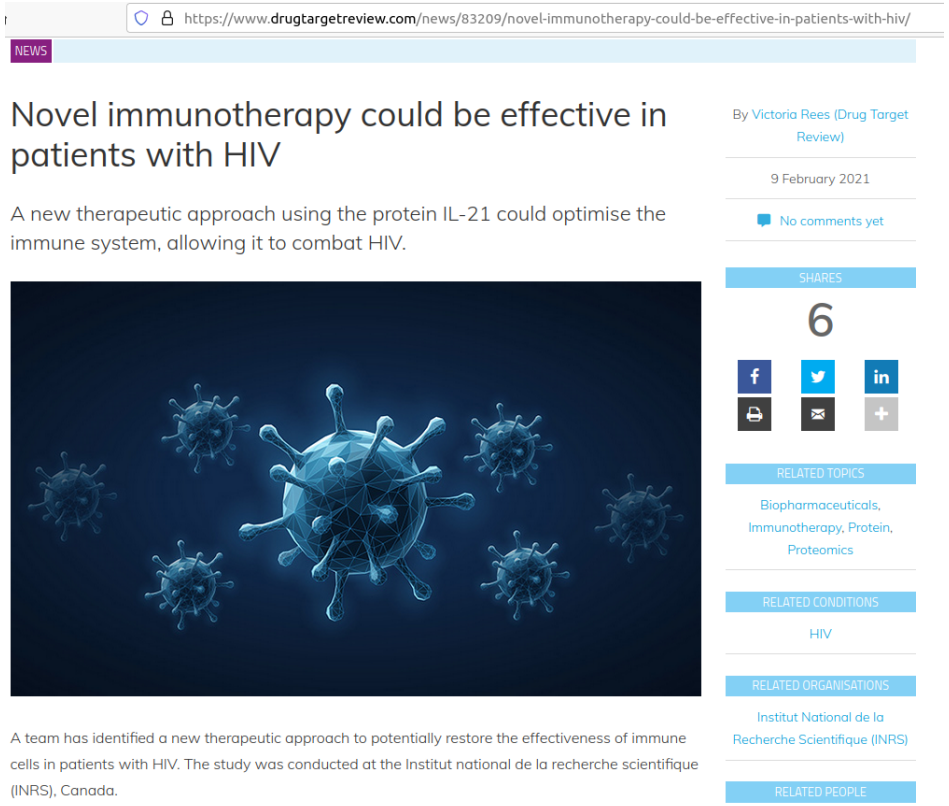
Key Points

- Antiretroviral therapy (ART) is the use of HIV medicines to treat HIV infection. ART is recommended for everyone who has HIV. ART helps people with HIV live longer, healthier lives and reduces the risk of HIV transmission.
- People with HIV should start ART as soon as possible. In people with HIV who have the following conditions, it's especially important to start ART right away: pregnancy, AIDS, certain HIV-related illnesses and coinfections, and early HIV infection. (Early HIV infection is the period up to 6 months after infection with HIV.)
- Before starting ART, people with HIV should discuss the importance of medication adherence —taking HIV medicines every day and exactly as prescribed—with their health care provider.

Source: `https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/21/52/when-to-start-antiretroviral-therapy`

Motivation - immunotherapy for HIV infection

- Immunotherapy of HIV infection, aimed at reducing inflammation, preventing immune activation by HIV, or promoting effective immune responses, is currently being investigated.
- The goal of immunotherapy is to eliminate the need of taking medicine every day while simultaneously chipping away at the latent reservoir of virus-infected cells.



https://www.drugtargetreview.com/news/83209/novel-immunotherapy-could-be-effective-in-patients-with-hiv/

NEWS

Novel immunotherapy could be effective in patients with HIV

A new therapeutic approach using the protein IL-21 could optimise the immune system, allowing it to combat HIV.

A team has identified a new therapeutic approach to potentially restore the effectiveness of immune cells in patients with HIV. The study was conducted at the Institut national de la recherche scientifique (INRS), Canada.

By Victoria Rees (Drug Target Review)

9 February 2021

No comments yet

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HIV

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Institut National de la Recherche Scientifique (INRS)

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HIV treatment and immunotherapy combination - challenge!

- The optimal treatment scheme for HIV-positive patients remains the subject of intense debate.

Goal

Propose effective optimal control solutions for the combination of HIV treatment and immunotherapy, ensuring a functional behavior of the immune system.

Hence there is considerable interest in searching for therapy regimes that may reduce virus load and restimulate immune responses*, thereby turning the* balance between HIV and the immune system in favor of the immune system*.*

D. Wodarz, M. Nowak, *Specific therapies could lead to long-term immunological control of HIV*, Proc. Natl. Acad. Sci. 96, 464–469 (1999)

The role of the immune response - HIV model by Culshaw et al. (2004)

Cytotoxic T lymphocytes (CTLs) play a critical role in antiviral defense by attacking virus-infected cells.
When HIV invades the body, it targets the CD4+ T cells.
The CTLs are cells that set out to eliminate infection by killing infected cells.

- x: uninfected $CD4^+$ T cells;
- y: infected $CD4^+$ T cells;
- z: CTL effectors (immune response cells).

$$\begin{cases} \dot{x} = \mu - dx - \beta xy, \\ \dot{y} = \beta xy - ay - pyz, \\ \dot{z} = cxyz - hz. \end{cases} \tag{11}$$

Assume: viral load is proportional to levels of infected cells.

R. V. Culshaw, S. Ruan, R. J. Spiteri,
Optimal HIV treatment by maximizing immune response, J. Math. Biol. 48, 545–562 (2004).

Delayed HIV model with incubation period

Introduce a discrete time-delay, $\tau > 0$, into the model (11), which represents the **incubation period** - the time between the new infection of a $CD4^+$ T cell and the time it becomes infectious.

$$\begin{cases} \dot{x}(t) = \mu - dx(t) - \beta x(t)y(t), \\ \dot{y}(t) = \beta x(t-\tau)y(t-\tau) - ay(t) - py(t)z(t), \\ \dot{z}(t) = cx(t)y(t)z(t) - hz(t). \end{cases} \tag{12}$$

Initial conditions:

$$x(\theta) = \varphi_1(\theta), \quad y(\theta) = \varphi_2(\theta), \quad z(\theta) = \varphi_3(\theta), \tag{13}$$

$-\tau \leq \theta \leq 0$, where $\varphi = (\varphi_1, \varphi_2, \varphi_3)^T \in C$ with C the Banach space $C\left([-\tau, 0], \mathbb{R}^3\right)$ of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}^3$.

Introduce control u_1: HIV treatment (ART) + pharmacological delay (ξ_1)

- introduce **drug therapy** by assuming that treatment reduces the rate of viral replication: $(1 - u_1)\beta xy$, $0 \leq u_1 \leq 1$;
- consider **pharmacological delay** in HIV treatment, represented by a discrete time delay in the **control variable** u_1, denoted by ξ_1, that is, $u_1(t - \xi_1)$, which represents the delay that occurs between the administration of drug and its appearance within cells, due to the time required for drug absorption, distribution, and penetration into the target cells. see e.g.

A. S. Perelson, A. U. Neumann, M. Markowitz, J. M. Leonard and D. D. Ho, *HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time*, Science, **271** (1996), 1582–1586.

Introduce control u_2: immunotherapy + absorption delay (ξ_2)

- introduce **immunotherapy**, represented by u_2, with $0 \leq u_2 \leq u_{max}$;
- include delay in u_2, denoted by ξ_2, since the human immune system takes some time to respond to the immune therapy, see e.g.

L. Göllmann and H. Maurer, *Optimal control problems with time delays: two cases studies in biomedicine*, Mathematical Biosciences and Engineering **15** (2018), no. 5, 1137–1154.

Delayed HIV model with combination of treatment and immunotherapy:

$$\begin{cases} \dot{x}(t) = \mu - dx(t) - (1 - u_1(t - \xi_1))\beta x(t)y(t), \\ \dot{y}(t) = (1 - u_1(t - \xi_1))\beta x(t - \tau)y(t - \tau) - ay(t) - py(t)z(t), \\ \dot{z}(t) = cx(t)y(t)z(t) - hz(t) + u_2(t - \xi_2). \end{cases} \tag{14}$$

Optimal control problem with state and control delays

Consider the delayed control system

$$\begin{cases} \dot{x}(t) = \mu - dx(t) - (1 - u_1(t - \xi_1))\beta x(t)y(t), \\ \dot{y}(t) = (1 - u_1(t - \xi_1))\beta x(t - \tau)y(t - \tau) - ay(t) - py(t)z(t), \\ \dot{z}(t) = cx(t)y(t)z(t) - hz(t) + u_2(t - \xi_2). \end{cases} \tag{15}$$

Determine an admissible control function $u = (u_1, u_2)$ that **maximizes** the objective functional

$$J(u_1(\cdot), u_2(\cdot)) = \int_0^{t_f} [x(t) + z(t) - u_1(t) - u_2(t)]\, dt\,.$$

subject to the delayed dynamic system (15), initial conditions/functions

$$\begin{aligned} &x(t) = x_0 = 5, \quad y(t) = y_0 = 1, \qquad \forall -\tau \le t \le 0, \\ &z(0) = z_0 = 2, \\ &u_1(t) = 0 \quad \forall -\xi_1 \le t < 0, \quad u_2(t) = 0 \quad \forall -\xi_2 \le t < 0, \end{aligned}$$

and control constraints

$$0 \le u_i(t) \le u_{i,\max} \quad \forall\, t \in [0, t_f] \quad (i = 1, 2).$$

Maximum Principle for Multiple Delayed Optimal Control Problems

First order optimality condition: Maximum Principle for Multiple Delayed Optimal Control Problems.

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THEORY AND APPLICATIONS OF OPTIMAL CONTROL PROBLEMS WITH MULTIPLE TIME-DELAYS

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ABSTRACT. In this paper we study optimal control problems with multiple time delays in control and state and mixed type control-state constraints. We derive necessary optimality conditions in the form of a Pontryagin type Minimum Principle. A discretization method is presented by which the delayed control problem is transformed into a nonlinear programming problem. It is shown that the associated Lagrange multipliers provide a consistent numerical approximation for the adjoint variables of the delayed optimal control problem. We illustrate the theory and numerical approach on an analytical example and an optimal control model from immunology.

Maximum Principle for Multiple Delayed Optimal Control Problems

Delayed state variables: $X(t) = x(t-\tau)$, $Y(t) = y(t-\tau)$.
Delayed control variables: $v_1(t) = u_1(t-\xi_1)$ and $v_2(t) = u_2(t-\xi_2)$.
Adjoint variables: $\lambda = (\lambda_x, \lambda_y, \lambda_z) \in \mathbb{R}^3$.
Hamiltonian:

$$\begin{aligned} H = {} & x + z - u_1 - u_2 + \lambda_x \left(\mu - dx - (1-v_1)\beta xy\right) \\ & + \lambda_y \left((1-v_1)\beta XY - ay - pyz\right) + \lambda_z \left(cxyz - hz + v_2\right). \end{aligned}$$

Adjoint equations:

$$\begin{cases} \dot{\lambda}_x(t) = -H_x[t] - \chi_{[0,t_f-\tau]} H_X[t+\tau], \\ \dot{\lambda}_y(t) = -H_y[t] - \chi_{[0,t_f-\tau]} H_Y[t+\tau], \\ \dot{\lambda}_z(t) = -H_z[t], \end{cases}$$

(the subscripts denote partial derivatives and $\chi_{[0,t_f-\tau]}$ is the characteristic function on the interval $[0, t_f - \tau]$.)
Transversality conditions:

$$\lambda(t_f) = (0,0,0)$$

(since the terminal state is free $(x(t_f), y(t_f), z(t_f)) \in \mathbb{R}^3$).

Maximum Principle for Multiple Delayed Optimal Control Problems

The maximizing controls are determined by the *switching functions*

$$\begin{aligned} \phi_1(t) &= H_{u_1}[t] + \chi_{[0,t_f-\xi_1]} H_{v_1}[t+\xi_1] \\ \phi_2(t) &= H_{u_2}[t] + \chi_{[0,t_f-\xi_2]} H_{v_2}[t+\xi_2] \end{aligned} \tag{16}$$

according to the *control law*

$$u_i(t) = \begin{cases} 0 & \text{if} \quad \phi_i(t) < 0, \\ u_{i,\max} & \text{if} \quad \phi_i(t) > 0, \\ \text{singular} & \text{if} \quad \phi_i(t) = 0 \ \text{ on } I_s \subset [0, t_f], \end{cases} \tag{17}$$

for $i = 1, 2$.

Numerical simulations - parameter values

Parameter	Description	Value
λ	source rate of $CD4+T$ cells	$1\ cells/day$
d	decay rate of $CD4+T$ cells	$0.1\ cells/day$
β	rate $CD4+T$ cells become infected	$[0.00025, 0.5]\ cells/day$
a	death rate infected, not by CTL killing	$0.2\ cells/day$
p	rate at which infected cells are killed by CTLs	$1/day$
c	immune response activation rate	$0.1/day$
h	death rate of CTLs	$0.1/day$

Table: Parameter values (Culshaw et. al, 2004).

Control constraints:

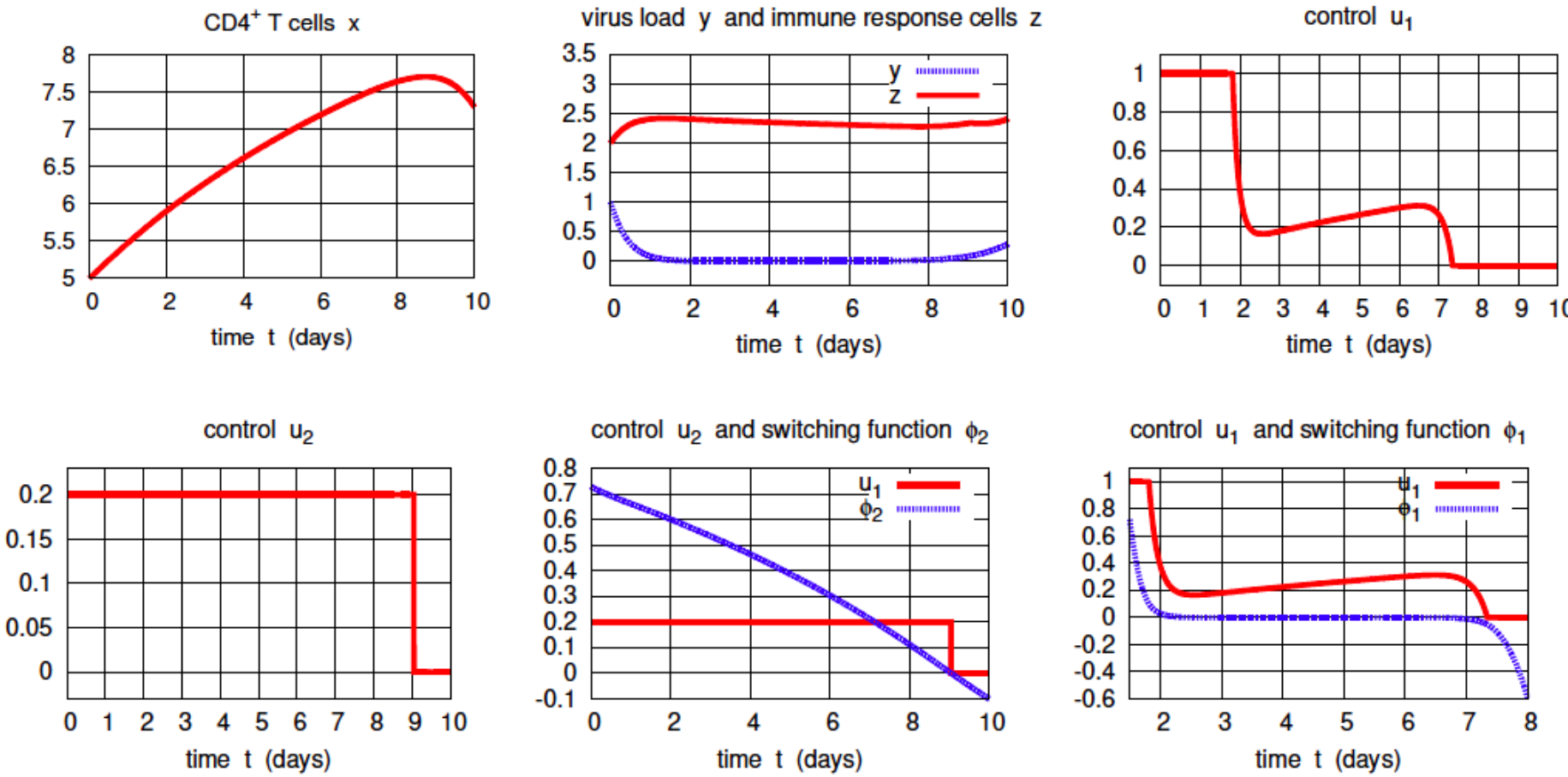
$$0 \leq u_1(t) \leq 1\,,$$
$$0 \leq u_2(t) \leq 0.2 \quad \forall\, t \in [0, t_f].$$

Delays	Description	Value
τ	incubation period	$0.5\ day$
ξ_1	pharmacological delay	$0.1\ day$
ξ_2	immunotherapy delay	$0.2\ day$

Numerical simulations: non-delayed OCP ($\tau = \xi_1 = \xi_2 = 0$)

The computations are done with $N = 5000$ grid points and the Implicit Euler Scheme.

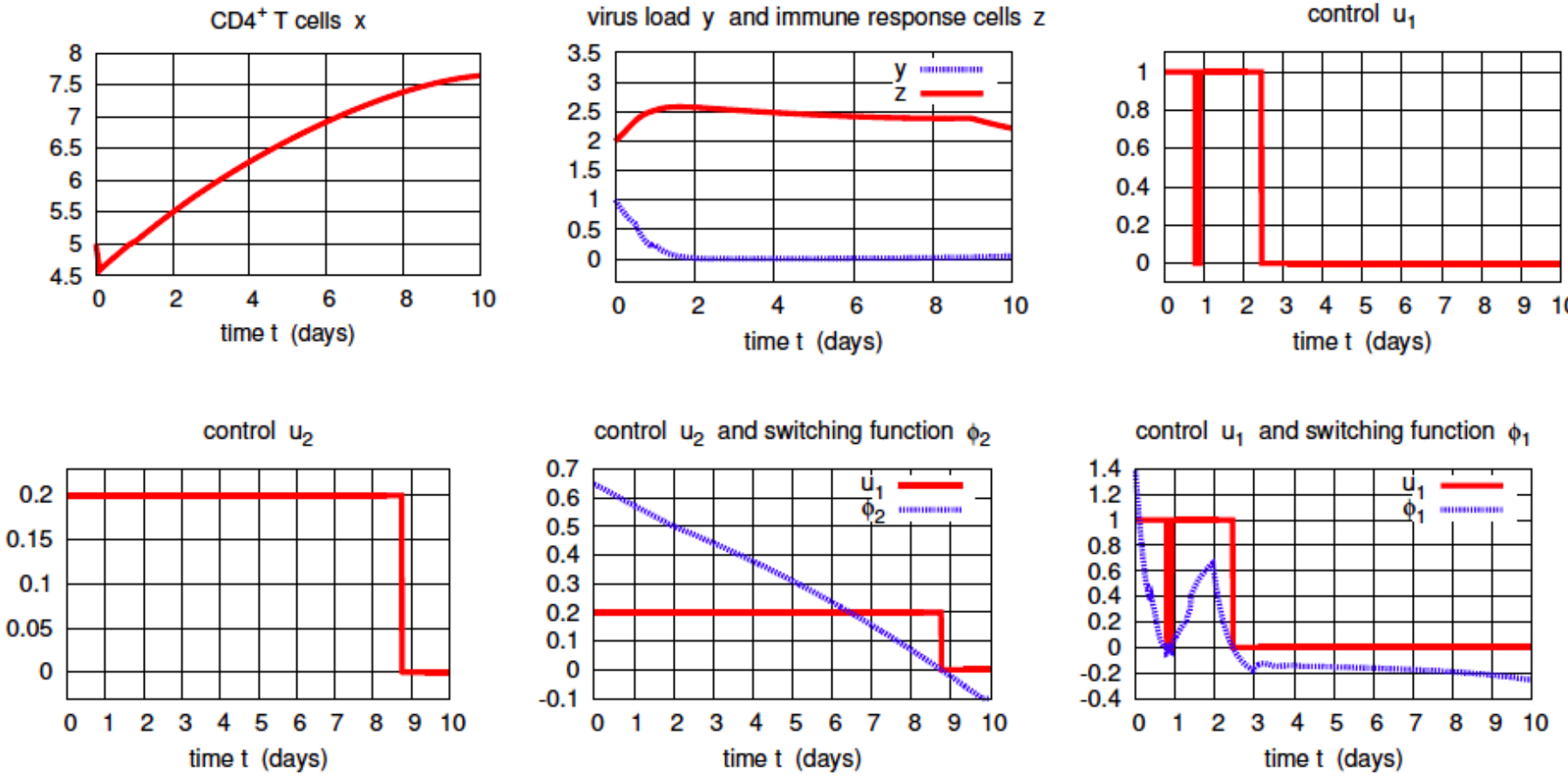
The simple Euler method would not detect bang-singular-bang control $u_1(t)$.



Numerical simulations: delayed OCP

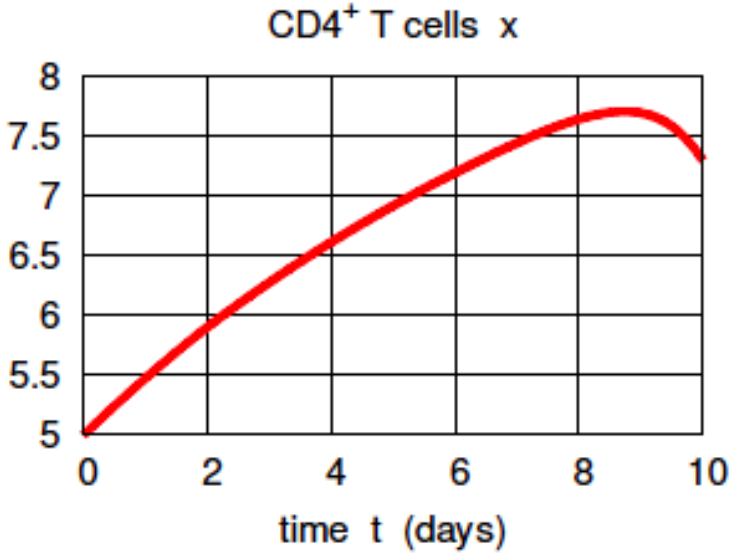
Consider the delays $\tau = 0.5, \xi_1 = 0.2, \xi_2 = 0.2$.

Now u_1 and u_2 and bang-bang controls with 3 and 1 switching times, respectively.

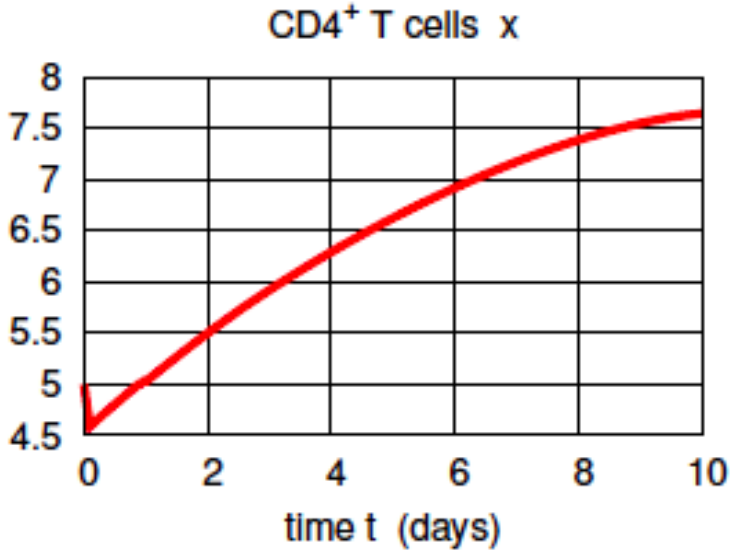


Numerical simulations: non-delayed vs delayed OCP - uninfected CD4$^+$T cells

- x: uninfected $CD4^+$ T cells;



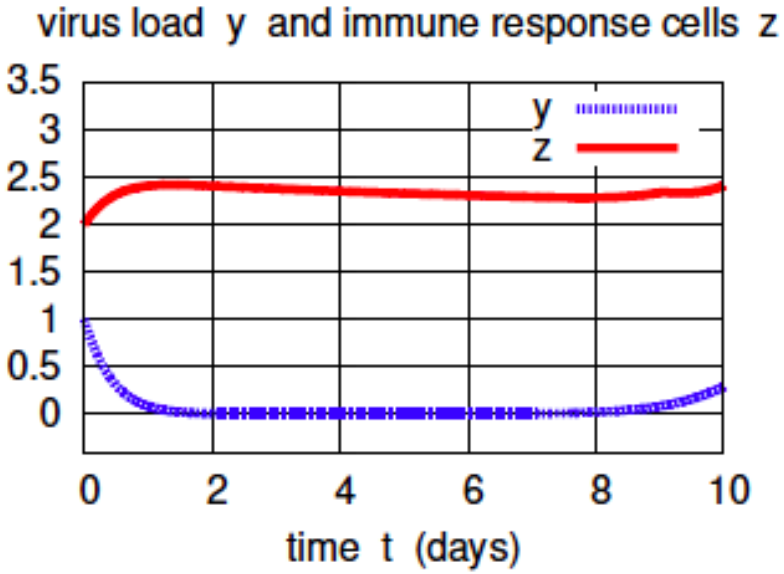
Non-delayed ($\tau = \xi_1 = \xi_2 = 0$)



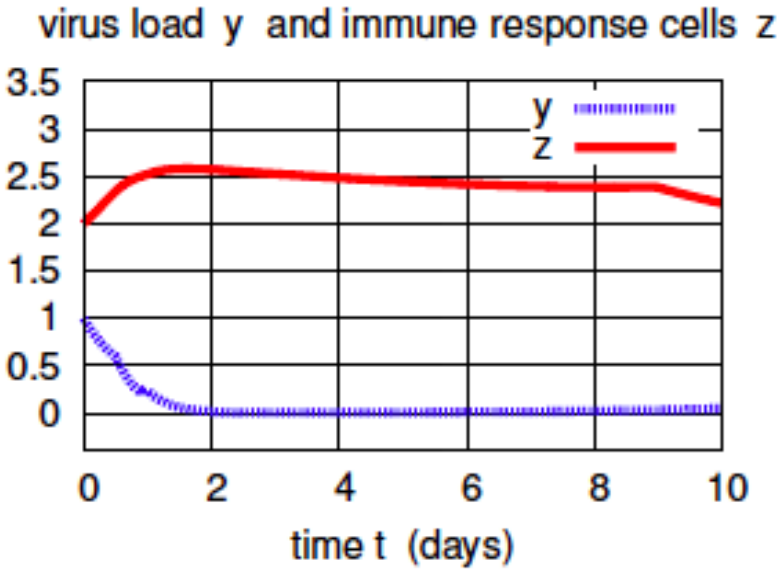
Delayed
($\tau = 0.5, \xi_1 = 0.2, \xi_2 = 0.2$)

Numerical simulations: non-delayed vs delayed OCP - infected CD4$^+$T cells and CTL's

- y: infected $CD4^+$ T cells;
- z: CTL effectors (immune response cells).



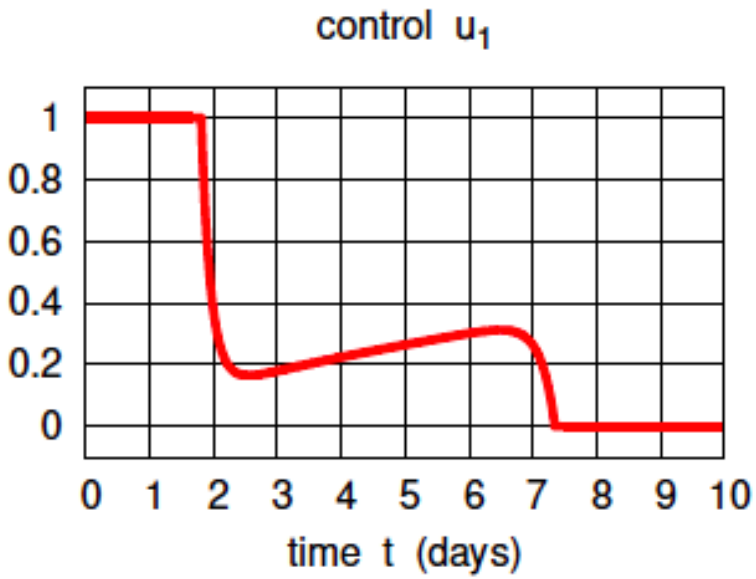
Non-delayed ($\tau = \xi_1 = \xi_2 = 0$)



Delayed
($\tau = 0.5, \xi_1 = 0.2, \xi_2 = 0.2$)

Numerical simulations: non-delayed vs delayed OCP - control u_1

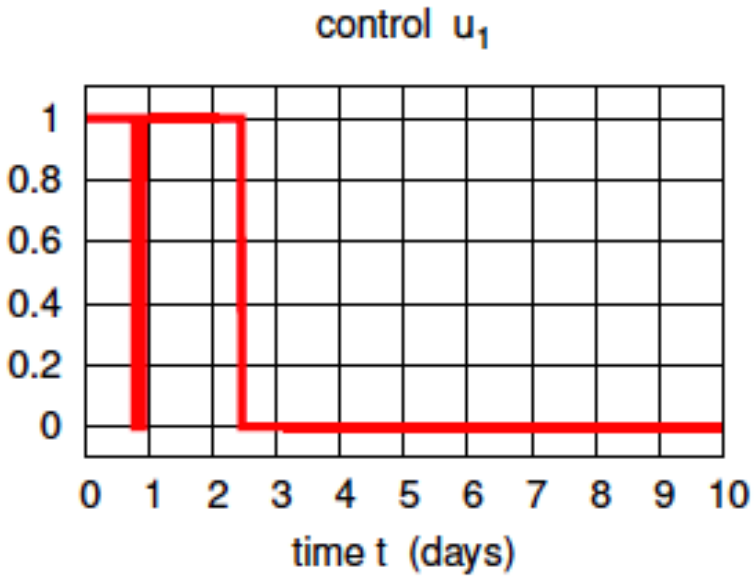
- u_1: ART drug therapy



Non-delayed $(\tau = \xi_1 = \xi_2 = 0)$

bang-singular-bang

singular arc for $1.81 \leq t \leq 7.34$



Delayed

$(\tau = 0.5, \xi_1 = 0.2, \xi_2 = 0.2)$

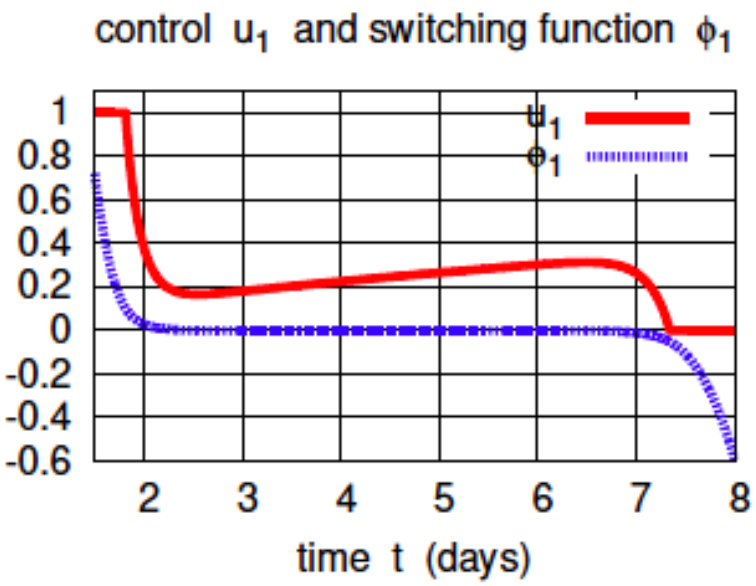
bang-bang, with 3 switching times

tiny bang arc $u_1(t) = 0$,

$0.875 \leq t \leq 0.905$

Numerical simulations: non-delayed vs delayed OCP - control u_1

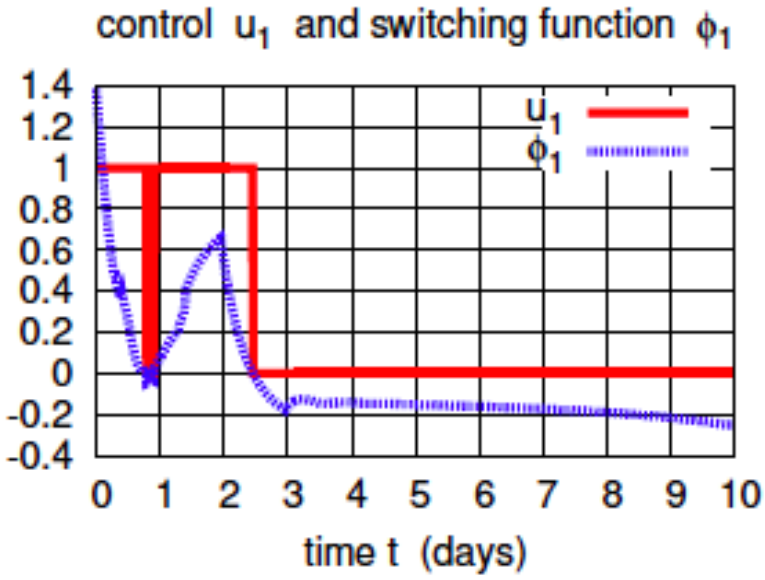
- u_1: ART drug therapy



Non-delayed ($\tau = \xi_1 = \xi_2 = 0$)

bang-singular-bang

singular arc for $1.81 \leq t \leq 7.34$



Delayed

($\tau = 0.5, \xi_1 = 0.2, \xi_2 = 0.2$)

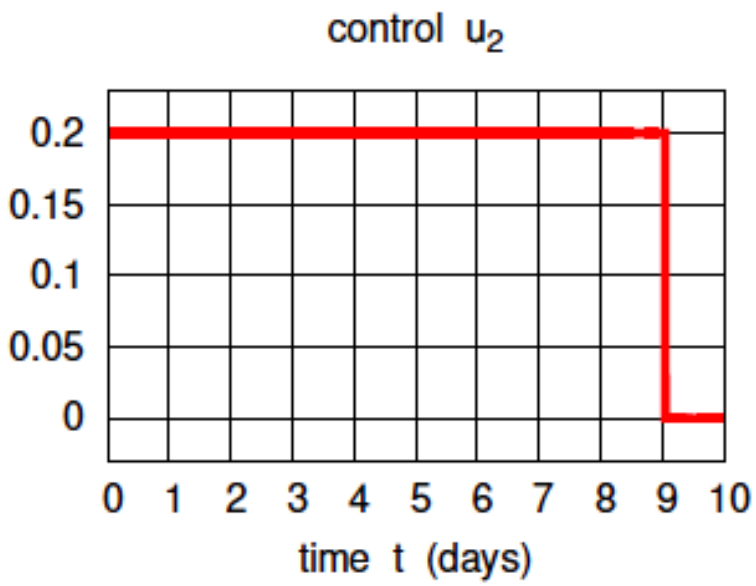
bang-bang, with 3 switching times

tiny bang arc $u_1(t) = 0$,

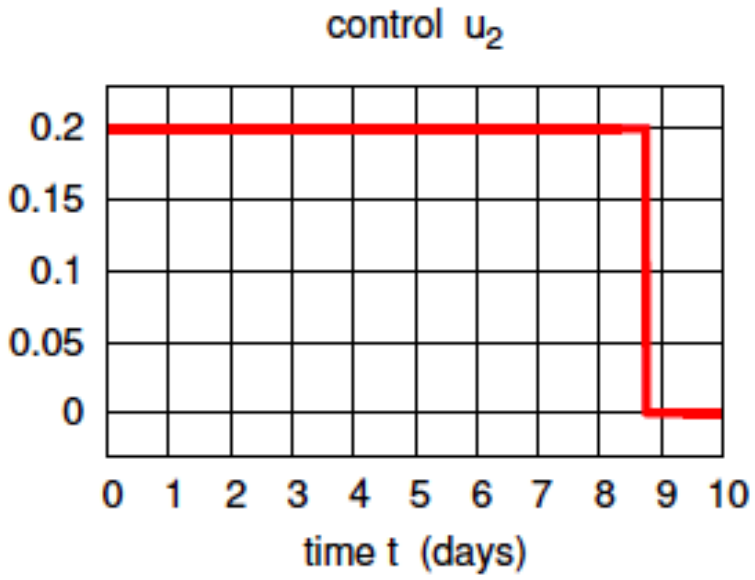
$0.875 \leq t \leq 0.905$

Numerical simulations: non-delayed vs delayed OCP - control u_2

- u_2: immunotherapy



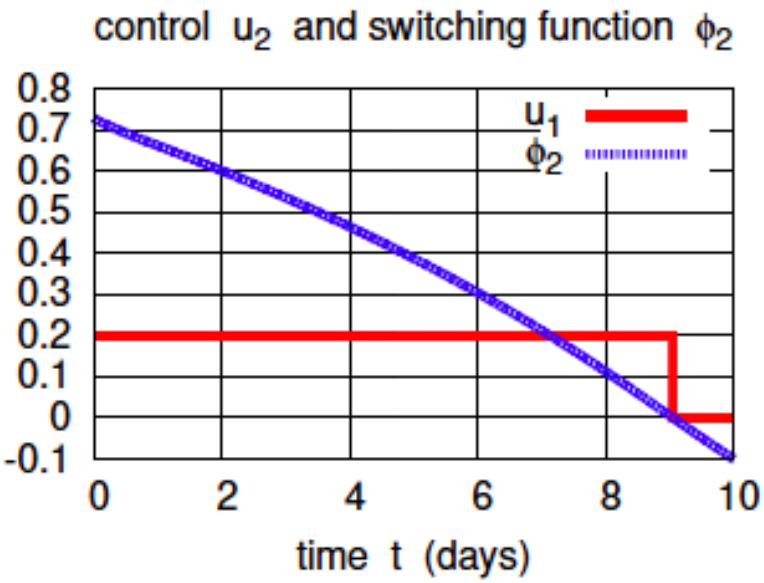
Non-delayed ($\tau = \xi_1 = \xi_2 = 0$)
bang-bang
one switch at $t = 9.05$



Delayed
($\tau = 0.5, \xi_1 = 0.2, \xi_2 = 0.2$)
bang-bang, with 1 switching time
at $t = 8.765$

Numerical simulations: non-delayed vs delayed OCP - control u_2

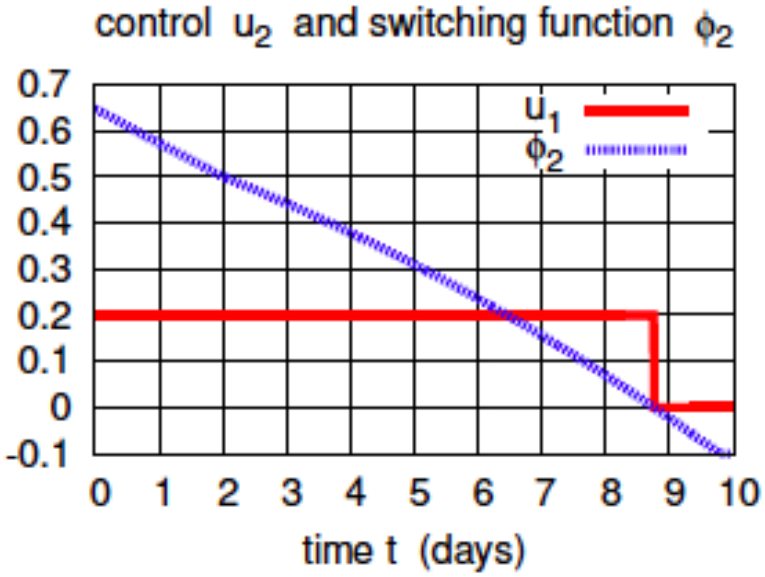
- u_2: immunotherapy



Non-delayed $(\tau = \xi_1 = \xi_2 = 0)$

bang-bang

one switch at $t = 9.05$



Delayed

$(\tau = 0.5, \xi_1 = 0.2, \xi_2 = 0.2)$

bang-bang, with 1 switching time

at $t = 8.765$

Time-delayed optimal control problem with state constraints

Consider the pure state inequality constraint:

$$z(t) \leq z_{\max} \quad \forall\, t \in [0, t_f]\,.$$

with an appropriate value $z_{\max}$ that ensures a functional behavior of the immune system.

Using the transformation technique in [Guinn, 1976], we can transform the time-delayed problem to an augmented non-delayed optimal control problem to which one may apply the necessary conditions in [Hartl et al., 1995] and [Maurer, 1979].

T. Guinn, *Reduction of delayed optimal control problems to nondelayed problems*, J. of Optimization Theory and Applications 18 (1976), pp. 371–377.

R.F. Hartl, S.P. Sethi, and R.G. Vickson, *A survey of the maximum principles for optimal control problems with state constraints*, SIAM Review 37 (1995), pp. 181–218.

H. Maurer, *On the minimum principle for optimal control problems with state constraints*, Rechenzentrum der Universität Münster, Report **41**, Münster, 1979.

Write the state constraint in the form

$$s(z(t)) = z_{max} - z(t) \geq 0 \quad \forall\, t \in [0, t_f].$$

The state constraint has *order one*, since the first total time derivative

$$s^{(1)}(x, y, z, v_2) = \frac{d}{dt} s(z) = cx(t)y(t)z(t) - hz(t) + u_2(t - \xi_2)$$

contains the control v_2 explicitly and satisfies the *regularity condition* $\partial s^{(1)}/\partial v_2 = 1 \neq 0$.

$$\Downarrow$$

The measure associated with the state constraint has a density $\eta(t)$ on a *boundary arc* with $z(t) = z_{max}$ for $t \in [t_1, t_2] \subset [0, t_f]$.

$$\Downarrow$$

Augmented Hamiltonian: adjoin the state constraint to the Hamiltonian H by a multiplier η:

$$\mathcal{H}(x, X, y, Y, z, \lambda, \eta, u_1, v_1, u_2, v_2) = H(x, X, y, Y, z, \lambda, u_1, v_1, u_2, v_2) + \eta(z_{max} - z).$$

The adjoint equations are modified by replacing the standard Hamiltonian H by the augmented $\mathcal{H}$.
Only the adjoint equation for λ_z changes to

$$\dot{\lambda}_z(t) = -H_z[t] + \eta(t) = \lambda_y(t)py(t) - \lambda_z(t)(cx(t)y(t) - h) + \eta(t)\,.$$

We consider again the switching functions

$$\begin{aligned}\phi_1(t) &= H_{u_1}[t] + \chi_{[0,t_f-\xi_1]} H_{v_1}[t+\xi_1]\\ \phi_2(t) &= H_{u_2}[t] + \chi_{[0,t_f-\xi_2]} H_{v_2}[t+\xi_2]\end{aligned}$$

On *interior arcs* with $z(t) < z_{max}$ the *usual* control law is valid:

$$u_i(t) = \begin{cases} 0 & \text{if} \quad \phi_i(t) < 0, \\ u_{i,max} & \text{if} \quad \phi_i(t) > 0, \\ \text{singular} & \text{if} \quad \phi_i(t) = 0 \ \text{ on } I_s \subset [0, t_f], \end{cases} \qquad i = 1, 2.$$

On a boundary arc $z(t) = z_{max}, t \in [t_1, t_2]$, the *boundary control* is determined by the equation $\dot{z}(t) = 0$ which yields

$$v_2(t) = u_2(t - \xi_2) = -cx(t)y(t)z_{max} + hz_{max}.$$

We observe that *boundary control behaves like a singular control*:
$0 < u_2(t - \xi_2) < u_{2,max}$ holds for $t_1+ < t < t_2-$.

$$\Downarrow$$

$$0 = \phi_2(t) = -1 + \lambda_z(t + \xi_2) \quad \forall\, t_1 < t < t_2.$$

$$\Downarrow$$

We are able to compute the multiplier η:

$$0 = \dot{\lambda}_z(t+\xi_2) = \lambda_y(t+\xi_2)py(t+\xi_2) - \lambda_z(t+\xi_2)(cx(t+\xi_2)y(t+\xi_2) - h) + \eta(t+\xi_2),$$

which yields

$$\eta(t + \xi_2) = (-\lambda_z py + cxy - h)(t + \xi_2)\,, \quad \forall\, t_1^+ \leq t \leq t_2^-\,.$$

The numerical computations will show that the multiplier satisfies the *complementarity* condition $\eta(t+\xi_2) \geq 0$ on $[t_1, t_2]$ and $\eta(t) = 0$ elsewhere.

Moreover, the adjoint variable $\lambda_z(t+\xi_2)$ may have jumps according to

$$\lambda_z((t_k+\xi_2)^+) = \lambda_z((t_k+\xi_2)^-) - \nu_k s_z(t_k+\xi_2) = \lambda_z((t_k+\xi_2)^-) + \nu_k\,, \quad \nu_k \geq 0,$$

$k = 1, 2$, provided that the control $v_2(t) = u(t-\xi_2)$ is *discontinuous* at t_k.

Note: The result on junctions between interior nonsingular arcs and boundary arcs proved in Theorem 5.1 in [Maurer, 1997] imply that the adjoint variable $\lambda_z(t+\xi_2)$ is *continuous* at t_k if the control $v_2(t) = u_2(t-\xi_2)$ is *discontinuous* at t_k, $k = 1, 2$.

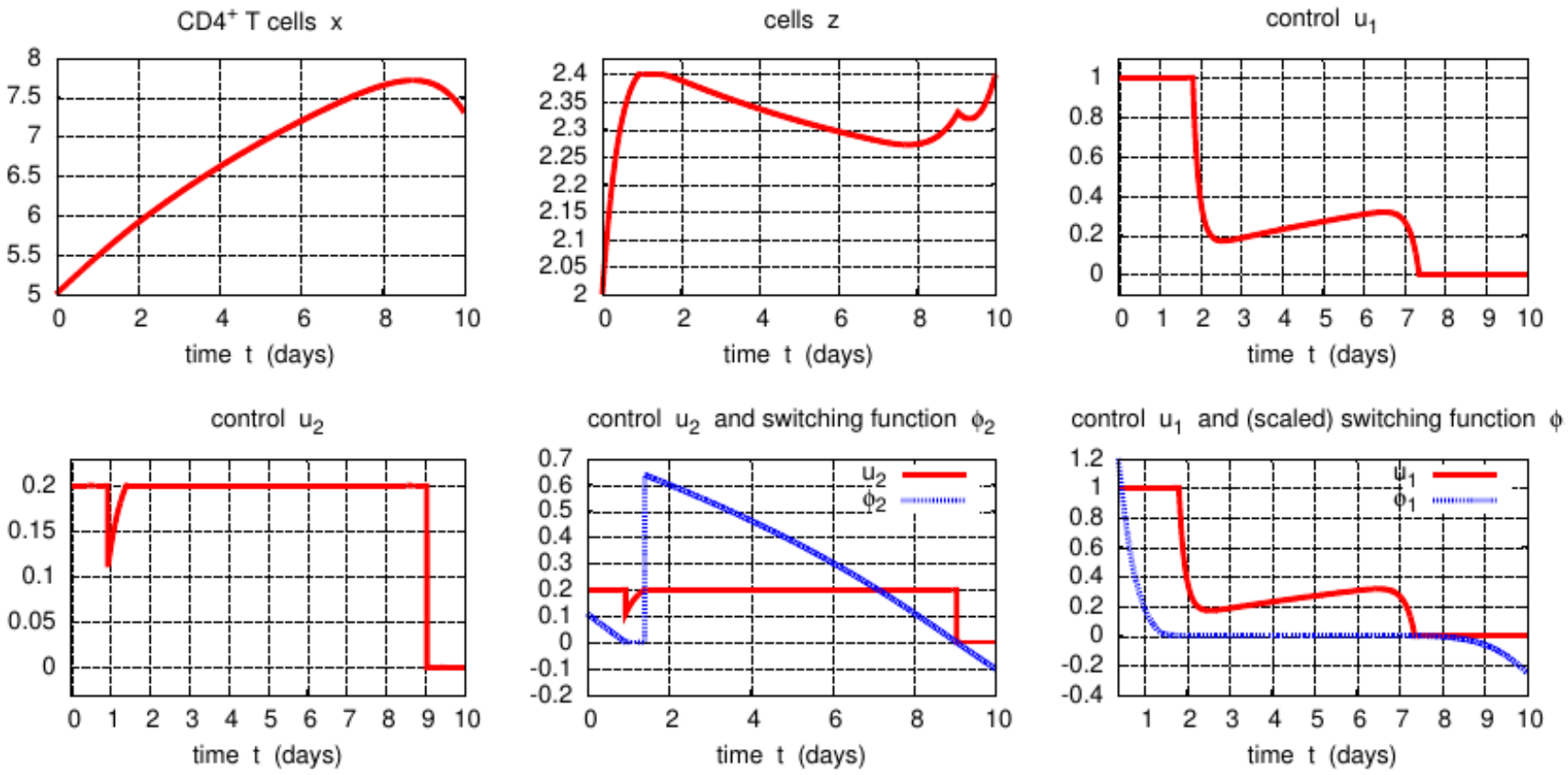
H. Maurer, *On optimal control problems with bounded state variables and control appearing linearly*, SIAM J. Control and Optimization, **15** (1997), 345–362.

Numerical simulations: non-delayed solution with state constraint

We consider the control problem without delays, but with the state constraint

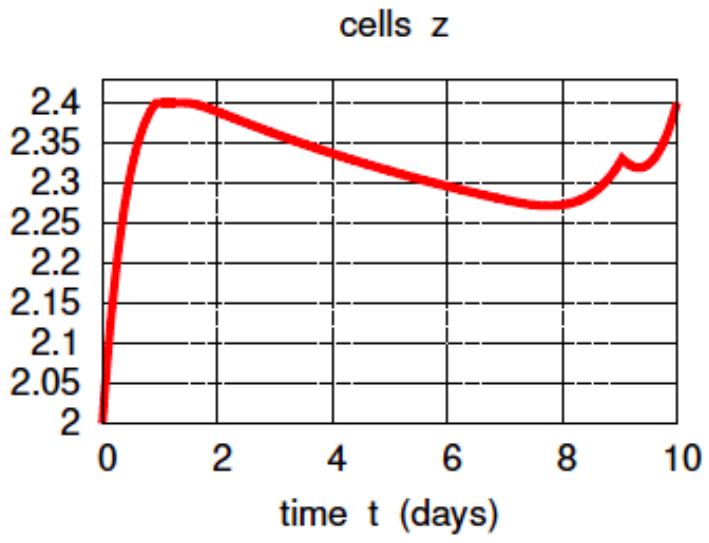
$$z(t) \leq 2.4 \quad \forall\, t \in [0, t_f].$$

Solution: boundary arc $z(t) = 2.4$ for $0.92 \leq t \leq 1.40$.

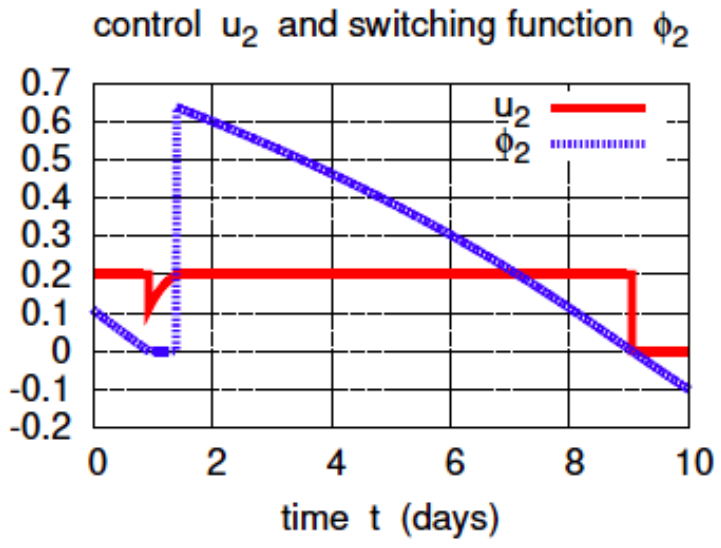


Numerical simulations: non-delayed solution with state constraint

Boundary arc:
$z(t) = 2.4,\ t_1 = 0.932 \leq t \leq 1.402 = t_2.$

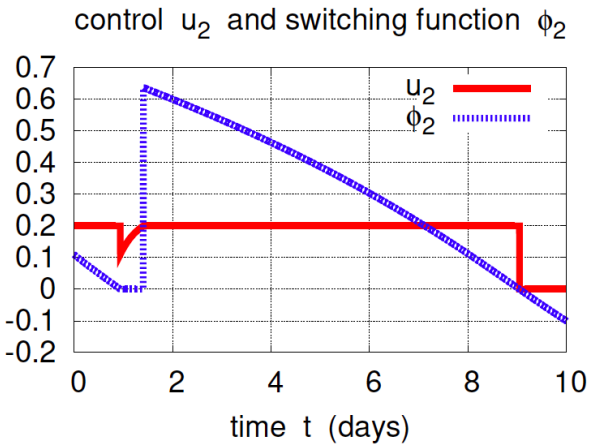


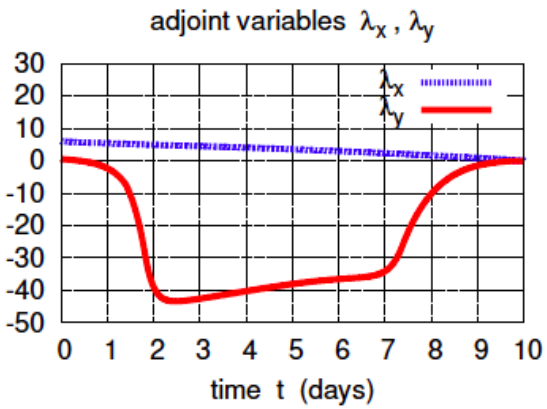
Boundary control:
$u_2(t) = -cx(t)y(t)z_{max} + h\, z_{max},$
satisfies (behaves like a singular control)
$0 < u_2(t) < 0.2$ for $t_1 < t < t_2$
which yields
$\phi_2(t) = -1 + \lambda_z(t) = 0$ for $t_1 < t < t_2.$

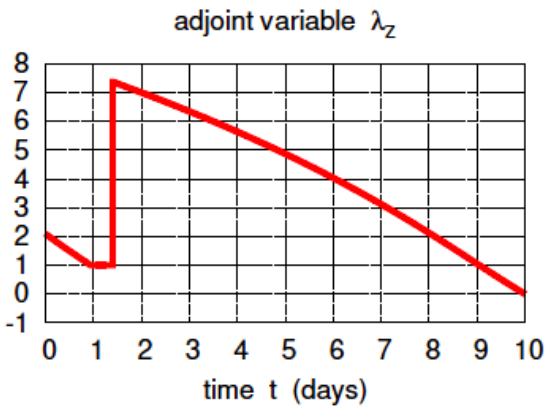


Numerical simulations: non-delayed solution with state constraint

The boundary control is *discontinuous* at the entry time $t_1 = 0.932$ of the boundary arc but is *continuous* at the exit time $t_2 = 1.40$.







From Theorem 5.1 in [Maurer, 1997], the adjoint variable $\lambda_z(t)$ and hence the switching function $\phi_2(t)$ is *continuous* at t_1, while $\lambda_z(t)$ and $\phi_2(t)$ may have a jump at t_2. Our computations yield

$$\lambda_z(t_2-) = 1, \quad \lambda_z(t_2+) = 7.3675.$$

H. Maurer, *On optimal control problems with bounded state variables and control appearing linearly*, SIAM J. Control and Optimization, **15** (1997), 345–362.

Numerical simulations: non-delayed solution with state constraint

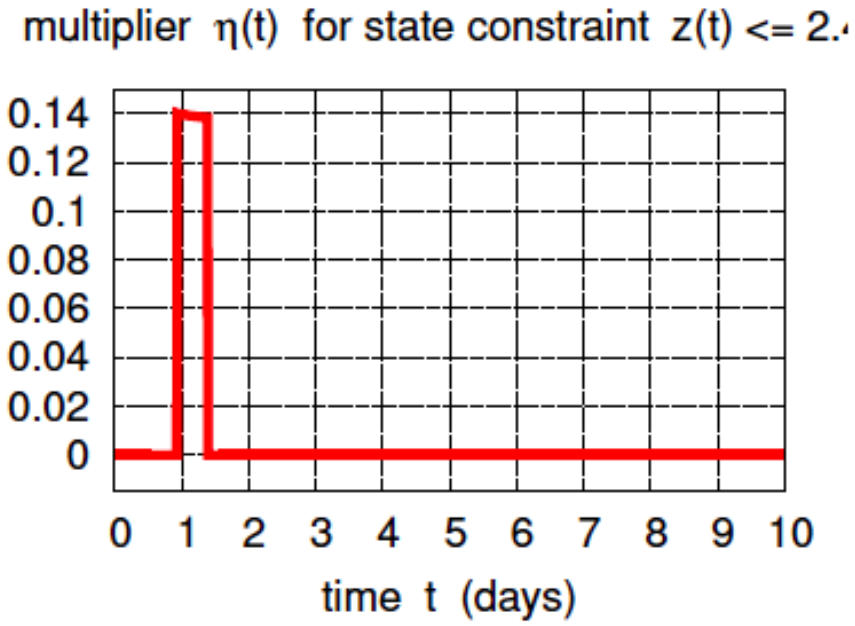
The multiplier for the state constraint is given by

$$\eta(t) = -\lambda_z(t)py(t) + cx(t)y(t) - h,$$

for the state constraint.

The multiplier $\eta(t)$ satisfies the *complementarity* condition:

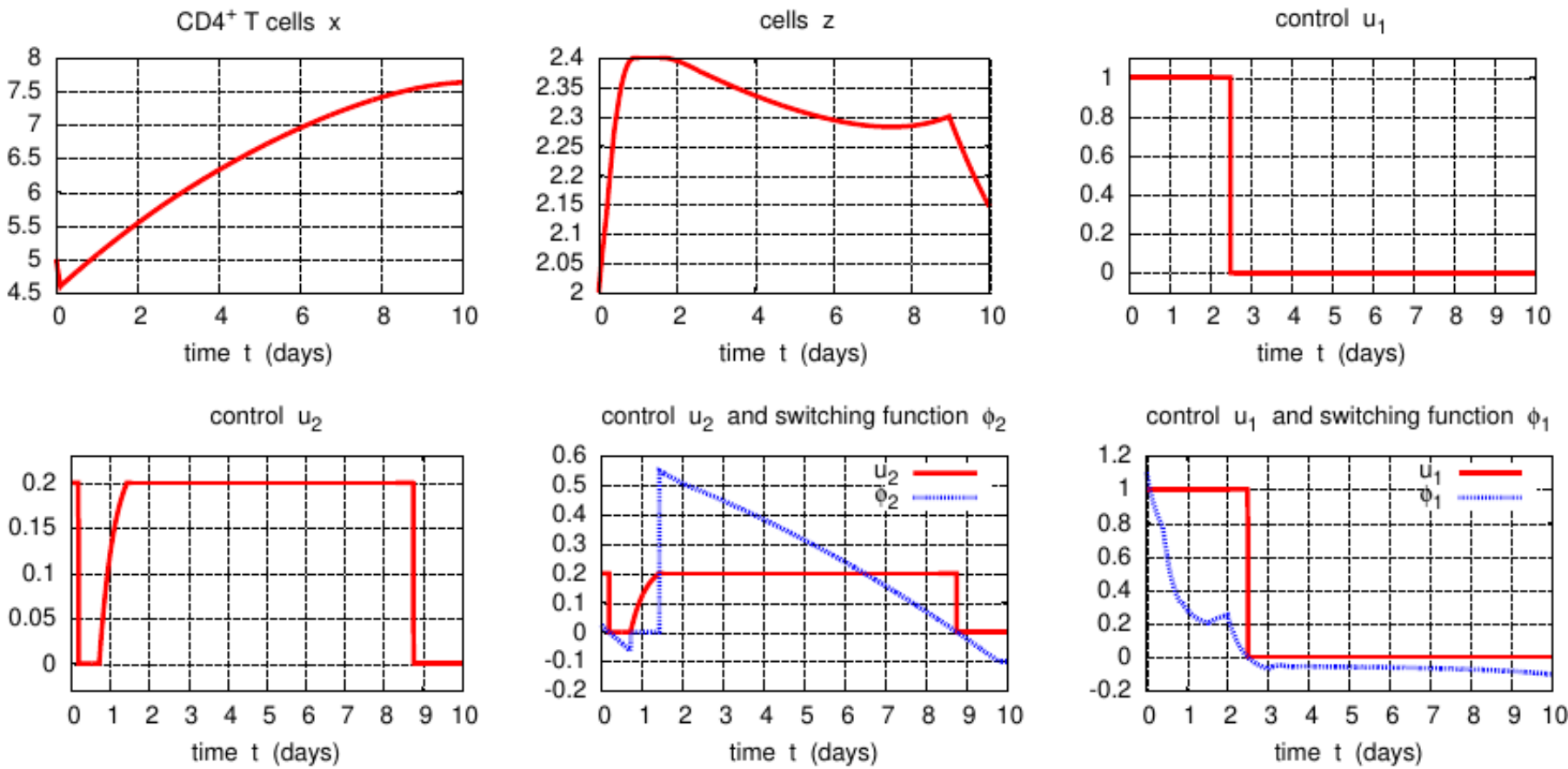
$$\eta(t + \xi_2) \geq 0 \quad \text{on} \quad [t_1, t_2] \quad \text{and} \quad \eta(t) = 0 \quad \text{elsewhere.}$$



Numerical simulations: delayed solution with state constraint

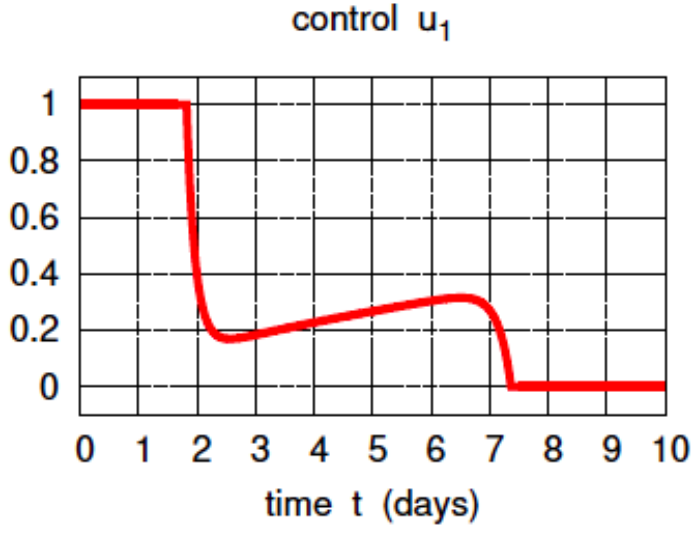
Study the solution with delays $\tau = 0.5, \xi_1 = 0.1, \xi_2$ and the state constraint

$$z(t) \leq z_{max} = 2.4, \; t \in [0, t_f].$$



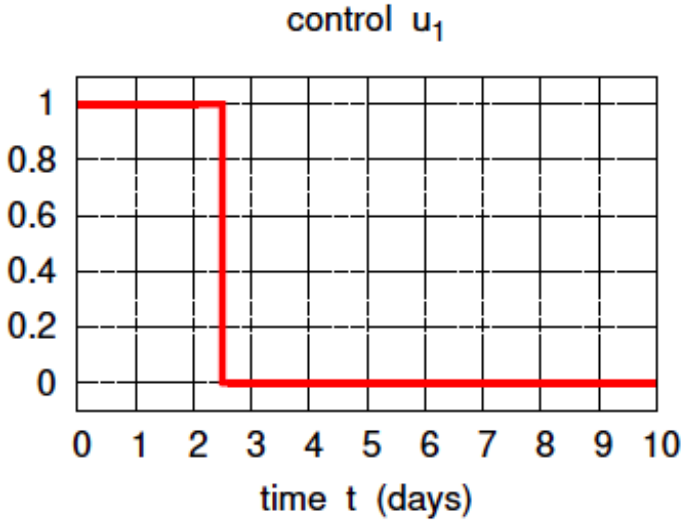
Numerical simulations: non-delayed vs delayed solution with state constraint - control u_1

No delays and with state constraint $z(t) \leq 2.4$.



The control $u_1(t)$ is bang-singular-bang with a singular arc for $1,81 \leq t \leq 7,34$.

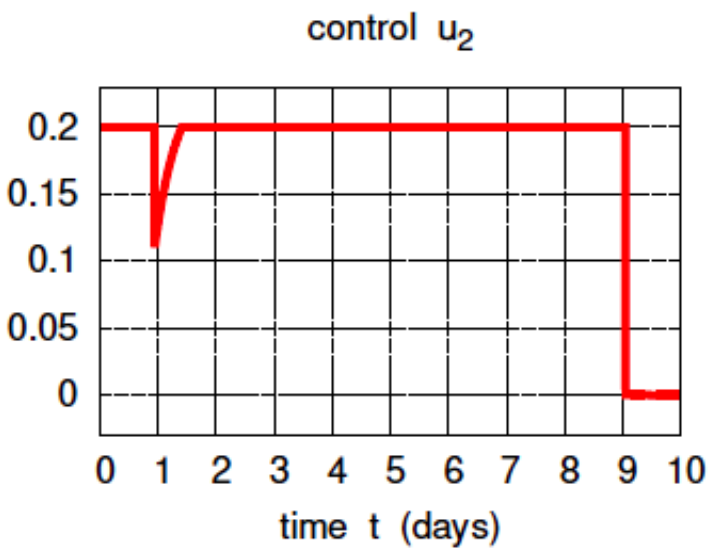
With delays and state constraint $z(t) \leq 2.4$.



The control $u_1(t)$ is bang-bang with only one switch from $u_1 = 1$ to $u_1 = 0$ at $t = 2.505$.

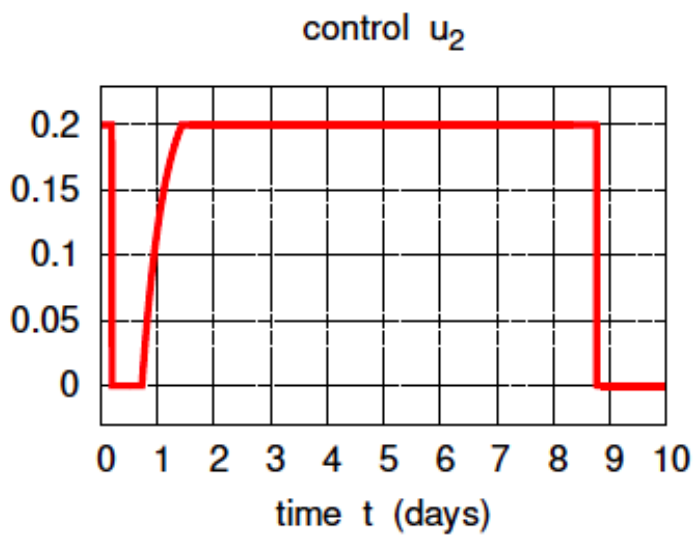
Numerical simulations: non-delayed vs delayed solution with state constraint - control u_2

No delays and with state constraint $z(t) \leq 2.4$.



u_2 is of the type
$u_2(t) = 1 \,|\, boundary \,|\, 1 \,|\, 0.$

With delays and state constraint $z(t) \leq 2.4$.

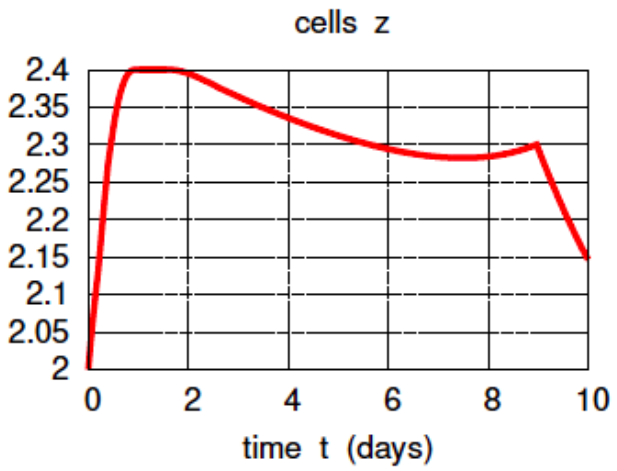


u_2 is of the type
$u_2(t) = 1 \,|\, 0 \,|\, boundary \,|\, 1 \,|\, 0.$

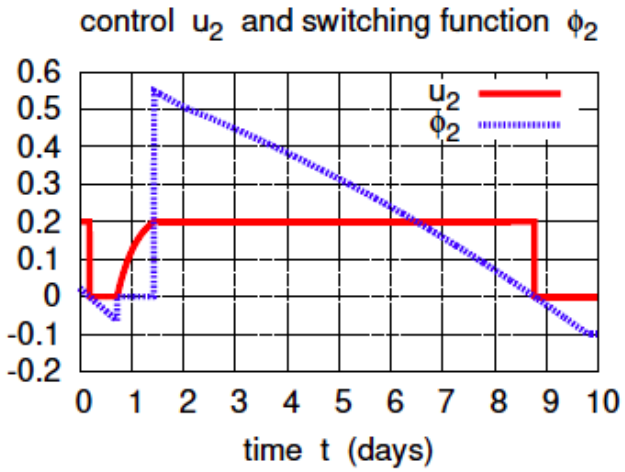
Numerical simulations: delayed solution with state constraint

The boundary arc is given by

$$z(t) = 2.4 \quad \text{for} \quad t_1 = 0.925 \leq t \leq 1.635 = t_2.$$

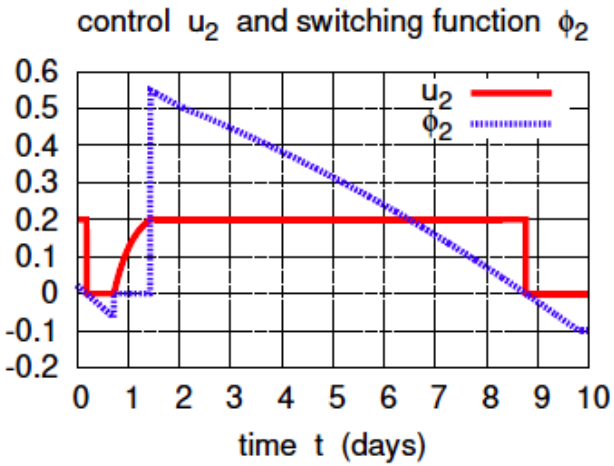


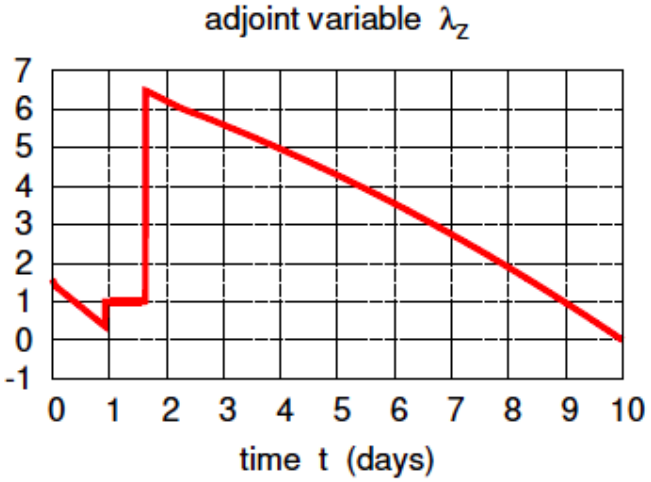
The boundary control
$v_2(t) = u_2(t - \xi_2) = -cx(t)y(t)z_{max} + h\, z_{max}$
behaves like a singular control
$0 < v_2(t) < 1$ for $t_1 < t < t_2$
which yields
$\phi_2(t) = -1 + \lambda_z(t + \xi_2) = 0$ for
$t_1 - \xi_2 = 0.725 < t < 1.435 = t_2 - \xi_2.$



Numerical simulations: delayed solution with state constraint

The boundary control $v_2(t)$ is *continuous* both at the entry time t_1 and exit time t_2 of the boundary arc. Then it follows from [Theorem 5.1, Maurer'1977] that the adjoint variable $\lambda_z(t)$ *may have jumps* both at $t_1 = 0.925$ and $t_2 = 1.625$:



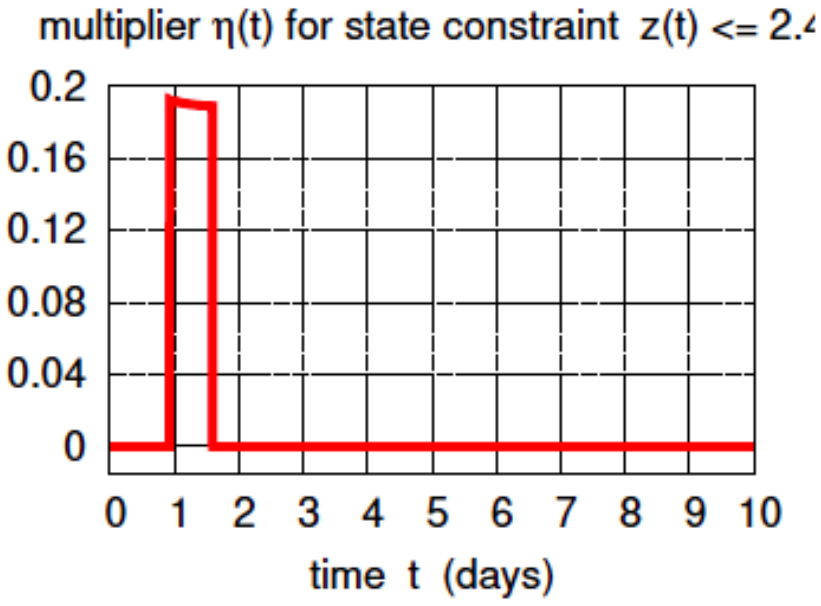


$$\lambda_z(0.925-) = 0.3600,\ \lambda_z(0.925+) = 1.0$$
$$\lambda_z(1.625-) = 1.0,\ \lambda_z(1.625+) = 6.483$$

Numerical simulations: delayed solution with state constraint

The multiplier $\eta(t)$ satisfies the *complementarity* condition:

$$\eta(t+\xi_2) \geq 0 \quad \text{on} \quad [t_1, t_2] \quad \text{and} \quad \eta(t) = 0 \quad \text{elsewhere.}$$



Reference

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Optim Control Appl Meth. 2020; 41:537–554.
https://doi.org/10.1002/oca.2558

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