Applications of Bang-Bang and Singular Control Problems in Biology and Biomedicine

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Overview

- Optimal Control of the Chemotherapy of HIV :
  L^2 versus L^1 Functional
- Optimal Control Problems with Control Appearing Linearly:
  A Bit of Theory of Bang-Bang and Singular Controls:
- Numerical Methods:
  - Discretization and NLP Methods
  - Induced Optimization Problem: Optimize Switching Times
- Optimal Control of the SEIR model in Epidemiology
  with L^1 Objectives and Control-State Constraints
  (joint work with Maria do Rosario de Pinho)
- Phase Tracking of the Circadian Rhythm by Optimal Control
  (joint work with Dirk Lebiedz)

Optimal Control Problem

$x(t) \in \mathbf{R}^n$	:	state variable, $0 \le t \le t_f$,
$u(t) \in \mathbf{R}^m$	:	control variable,
$t_f > 0$	:	final time, fixed or free,
$p \in \mathbf{R}^q$	:	perturbation parameter.

Optimal Control Problem $OCP(p)$ for parameter $p \in P_0 \subset \mathbf{R}^q$:
Determine a measurable (piecewise continuous) control function $u : [0, t_f] \to \mathbf{R}^m$ that

$$
\begin{aligned}
\text{minimizes} \quad & h(x(t_f), p) + \int_0^{t_f} f_0(x(t), u(t), p)\, dt \\
\text{subject to} \quad & \dot{x}(t) = f(x(t), u(t), p) \qquad a.a.\ t \in [0, t_f]\,, \\
& x(0) = x_0, \quad \varphi(x(t_f), p) = 0\,, \\
& u_{\min} \le u(t) \le u_{\max} \qquad a.a.\ t \in [0, t_f]\,, \\
& c(x(t), u(t), p) \le 0 \qquad a.a.\ t \in [0, t_f]\,.
\end{aligned}
$$

Optimal Control of the Chemotherapy of HIV

D. Kirschner, S. Lenhart, S. Serbin, *Optimal control of the chemotherapy of HIV*, J. Mathem. Biology **35**, 775–792 (1996).

State and control variables:

$T(t)$	:	concentration of uninfected $CD4^+$ T cells,
$T^*(t)$	:	concentration of latently infected $CD4^+$ T cells,
$T^{**}(t)$	:	concentration of actively infected $CD4^+$ T cells,
$V(t)$	:	concentration of free infectious virus particles,
$u(t)$	:	control, rate of chemotherapy, $0 \leq u(t) \leq 1$,
		$u(t) = 1$: maximal chemo, $u(t) = 0$: no chemo.

Optimal Control Problem

Dynamical model for $0 \le t \le t_f$

$$\frac{dT}{dt} = \frac{s}{1+V} - \mu_T T + rT\left(1 - \frac{T + T^* + T^{**}}{T_{\max}}\right) - k_1 VT\,,$$

$$\frac{dT^*}{dt} = k_1 VT - \mu_T T^* - k_2 T^*\,,$$

$$\frac{dT^{**}}{dt} = k_2 T^* - \mu_b T^{**},$$

$$\frac{dV}{dt} = (1 - u(t))\, N\mu_b T^{**} - k_1 VT - \mu_V V\,,$$

$$0 \le u(t) \le 1 \quad \forall \; t \in [0, t_f].$$

L^2 Functional versus L^1 Functional

Minimize $\quad J(x,u) = \int_0^{t_f} (-T(t) + Bu(t)^2)\, dt \quad (B = 50).$

Minimize $\quad J(x,u) = \int_0^{t_f} (-T(t) + Bu(t))\, dt \quad (B = 50).$

Chemotherapy of HIV: Parameters

Dynamic modeling and parameter fitting by Perelson et al.

		Parameters and constants	Value
μ_T	:	death rate of uninfected CD4$^+$ T cells	$0.02\ \mathrm{d}^{-1}$
μ_{T^*}	:	death rate of latently infected CD4$^+$ T cells	$0.02\ \mathrm{d}^{-1}$
μ_b	:	death rate of actively infected CD4$^+$ T cells	$0.24\ \mathrm{d}^{-1}$
μ_V	:	death rate of free virus	$2.4\ \mathrm{d}^{-1}$
k_1	:	rate of CD4$^+$ T cells infected by free virus	$2.4 \times 10^{-5}\ \mathrm{mm}^3\ \mathrm{d}^{-1}$
k_2	:	rate T* cells convert to actively infected	$3 \times 10^{-3}\ \mathrm{mm}^3\ \mathrm{d}^{-1}$
r	:	rate of growth for the CD4$^+$ T cells	$0.03\ \mathrm{d}^{-1}$
N	:	number of free virus produced by T^{**} cells	1200
$T_{\max}$	:	maximum CD4$^+$ T cell level	$1.5 \times 10^3\ \mathrm{mm}^{-3}$
s	:	source term for uninfected CD4$^+$ T cells, where s is the parameter in the source term	$10\ \mathrm{d}^{-1}\ \mathrm{mm}^{-3}$ $s/(1+V)$

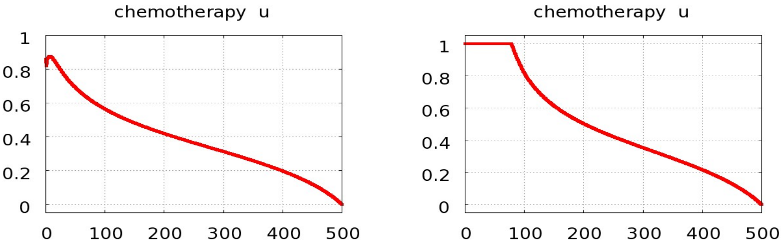
Chemotherapy of HIV: Solution for L^2 Functional

Begin of treatment after 800 days : initial conditions

$$T(0) = 982.8,\ T^*(0) = 0.05155,\ T^{**}(0) = 6.175 \cdot 10^{-4},\ V(0) = 0.07306.$$

Begin of treatment after 1000 days : initial conditions

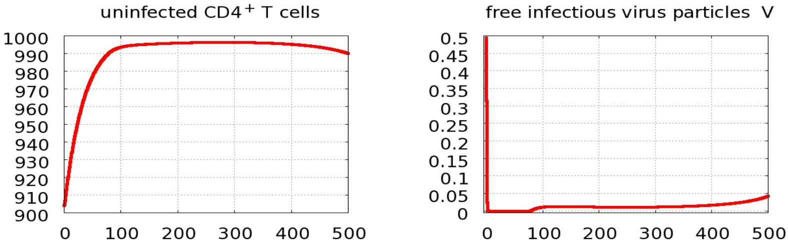
$$T(0) = 904.1,\ T^*(0) = 0.3447,\ T^{**}(0) = 41.67 \cdot 10^{-4},\ V(0) = 0.4939.$$



optimal control : after 800 days, after 1000 days

Chemotherapy of HIV: Solution for L^2 Functional

Begin of treatment after 1000 days :



Second-order sufficient conditions (SSC) are satisfied, since the strict Legendre condition holds and the associated matrix Riccati equation has a bounded solution.

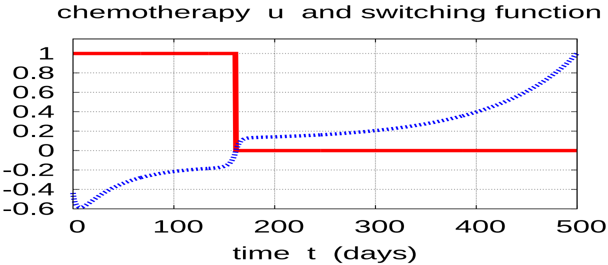
(Malanowski, Maurer, Osmolovskii, Pickenhain, Zeidan)

Computations: R. Hannemann

Chemotherapy of HIV: Solution for L^1 Functional

$$\text{Minimize} \quad J(x,u) = \int_0^{t_f} (-T(t) + B\,u(t))\,dt \quad (B = 50)\,.$$

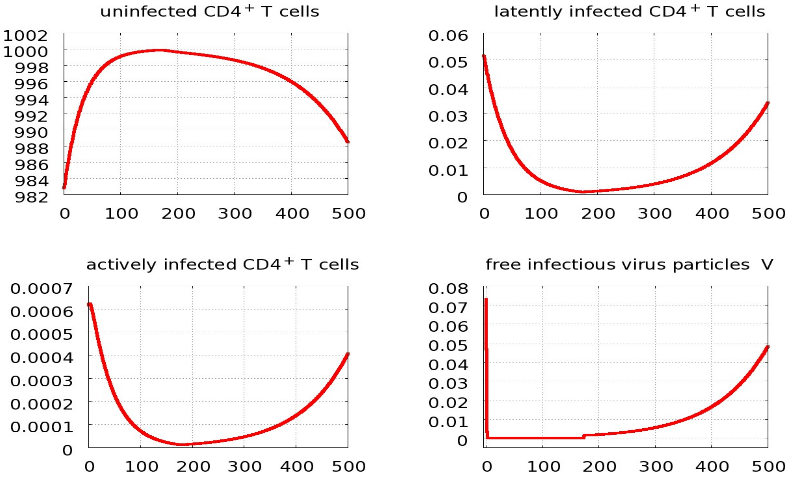
Treatment after 800 days:



Optimal control is bang–bang and satisfies SSC :

$$u(t) = \left\{ \begin{array}{lll} 1 & \text{for} & 0 \le t < t_1 = 161.69 \\ 0 & \text{for} & t_1 \le t < t_f = 500 \end{array} \right\}, \quad \frac{d^2 J}{dt_1^2} = 1.5469 > 0\,.$$

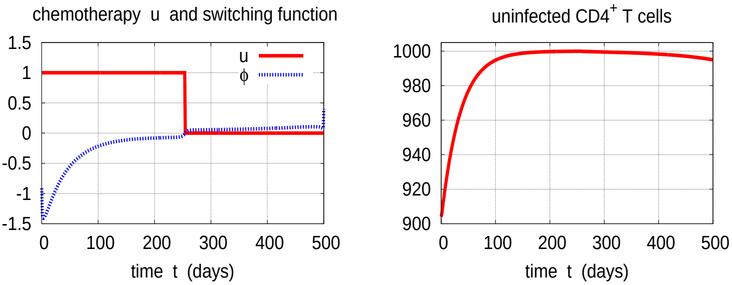
Chemotherapy of HIV: State Variables for L^1 Functional



State variables $T, \; T^*, \; T^{**}, \; V$

Chemotherapy of HIV: L^1 Functional, Terminal Constraint

Treatment after 1000 days and terminal constraint $T(t_f) = 995$



Optimal control is bang–bang. First-Order Sufficient Conditions :

$$u(t) = \left\{ \begin{array}{lll} 1 & \text{for} & 0 \le t < t_1 = 254.54 \\ 0 & \text{for} & t_1 \le t < t_f = 500 \end{array} \right\}, \quad \frac{d^2 J}{dt_1^2} = 1.6764 > 0 \,.$$

Optimal Control Problems with Control Appearing Linearly

$x(t) \in \mathbf{R}^n$	:	state variable, $0 \le t \le t_f$,
$u(t) \in \mathbf{R}^m$	:	control variable,
$t_f > 0$	:	final time, fixed or free,
$p \in \mathbf{R}^q$	:	perturbation parameter.

Optimal Control Problem $OCP(p)$ for parameter $p \in P_0 \subset \mathbf{R}^q$:
Determine a measurable (piecewise continuous) control function $u : [0, t_f] \to \mathbf{R}^m$ that

$$\text{minimizes} \quad h(x(t_f), p) + \int_0^{t_f} (f_0(x(t), p) + g_0(x(t), p)u(t))\, dt$$

$$\text{subject to} \quad \dot{x}(t) = f(x(t), p) + g(x(t), p)u(t), \qquad a.a.\ t \in [0, t_f]\,,$$

$$x(0) = x_0, \quad \varphi(x(t_f), p) = 0\,,$$

$$u_{\min} \le u(t) \le u_{\max} \qquad a.a.\ t \in [0, t_f]\,.$$

It suffices to consider a Mayer Problem with $f_0 = g_0 = 0$.

Minimum Principle: Necessary Optimality Conditions

Hamiltonian function: adjoint variable $\lambda \in \mathbf{R}^n$ (row vector)

$$H(x, \lambda, u, p) := \lambda f(x, p) + \lambda g(x, p) u \,.$$

Adjoint equations:

$$\begin{aligned} \dot{\lambda}(t) &= -H_x(x(t), \lambda(t), u(t), p)\,, \\ \lambda(t_f) &= (h + \rho\varphi)_x(x(t_f), p)\,, \quad \rho \in \mathbf{R}^r. \end{aligned}$$

Switching function:

$$\phi(x, \lambda, p) := H_u = \lambda g(x, p), \quad \phi(t, p) = \phi(t, x(t), \lambda(t), p)\,.$$

Optimal control minimizes the Hamiltonian: for $i = 1, \ldots, m$

$$u_i(t, p) = \begin{cases} u_{\text{min, i}} \,, & \text{if} \quad \phi_i(t, p) > 0\,, \\ u_{\text{max,i}} \,, & \text{if} \quad \phi_i(t, p) < 0\,, \\ \text{singular} \,, & \text{if} \quad \phi_i(t, p) \equiv 0 \quad \text{in } I_s \subset [0, t_f]\,. \end{cases}$$

The control component $u_i(t, p)$ is bang-bang in an interval $I_b \subset [0, t_f]$, if the switching function $\phi_i(t, p)$ has only finitely many zeros at which the control switches between $u_{\text{min,i}}$ and $u_{\text{max,i}}$.

Bang–Bang Control : Induced Optimization Problem

ASSUMPTIONS:

1. The optimal control $u(t, p_0)$ for the nominal parameter p_0 has finitely many bang–bang arcs with switching times

$$0 = t_0 < t_1^* < t_2^* < ... < t_s^* < t_{s+1}^* = t_f \ .$$

2. Control components $u_i(t)$, $i = 1, \ldots, m$, do not switch simultaneously.

Hence, there exists vectors $u_k^* \in U \subset \mathbf{R}^m$ such that the nominal control for the parameter $p = p_0$ is given by

$$u(t, p_0) = u_k^* \quad \text{for} \quad t \in [t_{k-1}^*, t_k^*) \qquad (k = 1, ..., s+1),$$

$$u_{k,i}^* \in \{ u_{min,i}, u_{max,i} \} \qquad (i = 1, \ldots, m).$$

Put $z := (t_1, \ldots, t_s, t_{s+1})$ for $0 = t_0 < t_1 < \ldots < t_s < t_{s+1} = t_f$.

Let $x(t; z, p)$ denote the continuous solution with $x(0; z, p) = x_0$ such that for $k = 1, \ldots, s+1$:

$$\dot{x}(t) = f(x(t), p) + g(x(t), p)u_k^* \quad \text{for} \quad t_{k-1}^+ \le t \le t_k^- \, .$$

Induced Parametric Optimization Problem:

$$IOP(p) \begin{cases} \text{Minimize} & h_0(z, p) := h(x(t_f; z, p), p), \ z \in \mathbf{R}^{s+1}, \\ \text{subject to} & \varphi_0(z, p) := \varphi(x(t_f; , p), p) = 0 \, . \end{cases}$$

Lagrange function in normal form:

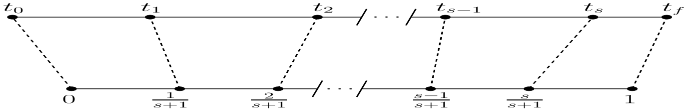
$$\mathcal{L}(z, \rho, p) := h_0(z, p) + \rho^* \varphi_0(z, p), \quad \rho \in \mathbf{R}^{n_\varphi} \, .$$

Nominal solution for $p = p_0$: $(z_0, \rho_0) \in \mathbf{R}^{s+1} \times \mathbf{R}^{n_\varphi}$

Numerical Solution : Arc-Parameterization Method

Arc lengths $\xi_k = t_k - t_{k-1}$ $(k = 1, .., s, s+1)$, $t_0 = 0$, $t_{s+1} = t_f$.

Linear time scaling: $t \in [t_{k-1}, t_k] \Leftrightarrow \tau \in [\frac{k-1}{s+1}, \frac{k}{s+1}]$.



Transformed ODE : control $u(\tau, p) = u_k^*$ for $\tau \in \left[\frac{k-1}{s+1}, \frac{k}{s+1} \right]$

$$\frac{dx}{d\tau} = (s+1)\,\xi_k\,(\,f(x(\tau), p) + g(x(\tau), p)u_k^*\,)\,.$$

H. Maurer, C. Büskens, J.-H.R. Kim, Y. Kaya: *Optimization methods for the verification of second-order sufficient conditions for bang-bang controls*, OCAM **26**, 129–156 (2005).

cf. scaling technique of Kaya, Loxton, Teo et al.

SSC for Bang-Bang Control

Theorem: Suppose that the following conditions are satisfied:

- SSC hold for the nominal optimization problem IOP(p_0) :

  (1) rank $\left(\frac{\partial \varphi_0}{\partial z}(z_0, p_0) \right) = n_\varphi$,

  (2) $\mathcal{L}_z(z_0, \rho_0, p_0) = 0$,

  (3) $v^T \mathcal{L}_{zz}(z_0, \rho_0, p_0) v > 0 \quad \forall\, v \neq 0,\ \frac{\partial \varphi_0}{\partial z}(z_0, p_0) v = 0$.

- Strict bang–bang property holds:

  (a) $\phi_i(t, p_0) \neq 0 \quad \forall\, t \neq t_{i,k} \quad (t_{i,k}$ is switching time of $u_i)$,

  (b) $\dot{\phi}(t_k, p_0)\,(u(t_k-) - u(t_k+)) > 0, \quad k = 1, ..., s$.

Then the bang–bang control with s switching times $t_1, ..., t_s$ provides a strict strong minimum for the nominal optimal control problem $OCP(p_0)$. $\diamond$

Proof: Agrachev, Stefani, Zezza (2002), Osmolovskii, M. (2003–)

Book on SSC for Bang-Bang and Regular Control

SSC and Sensitivity Analysis for Bang-Bang Control

Sensitivity analysis for optimization problems: Fiacco (1976) et al.

Sensitivity Theorem for Bang-Bang Control Problems :

Assume that SSC are satisfied for the solution (z_0, ρ_0) to the nominal optimal control problem $OCP(p_0)$. Then the perturbed control problem $OCP(p)$ has an optimal solution $(z(p), \rho(p))$ with switching times $t_k(p)$, $k = 1, .., s$, for all parameters p in a neighborhood of p_0 such that

(a) $(z(p_0), \rho(p_0)) = (z_0, \rho_0)$,

(b) $(z(p), \rho(p))$ is of class C^1 w.r.t. to p .

The sensitivity derivatives are given by

$$\begin{pmatrix} dz/dp \\ d\rho/dp \end{pmatrix} = - \begin{pmatrix} \mathcal{L}_{zz}(z(p), \rho(p), p) & (\varphi_0)_z(z(p), p)^* \\ (\varphi_0)_z(z(p), p) & \mathbf{0} \end{pmatrix}^{-1} \cdot \begin{pmatrix} \mathcal{L}_{zp}(z(p), \rho(p), p) \\ (\varphi_0)_p(z(p), p) \end{pmatrix} .$$

SEIR Model for the Control of Infectious Diseases

M.H.A. Biswas, L.T. Paiva and M.R. de Pinho, *A SEIR model for control of infectious diseases with constraints*, Mathematical Biosciences and Engineering, **11**, No. 4, (2014), 761–784.

H. Maurer, M.R. de Pinho, *Optimal Control of Epidemiological SEIR Models with L^1–Objectives and Control–State Constraints*, submitted to Pacific J. of Optimization.

The following is joint work with Maria Rosario de Pinho.

Consider 4 Compartments:

S	:	**Susceptible** individuals
E	:	**Exposed** individuals
I	:	**Infectious** individuals
R	:	**Recovered** individuals
N	:	**Total population** $N = S + E + I + R$
$u(t)$	:	control, fraction of **vaccinated susceptibles**, $0 \leq u(t) \leq 1$,

Control Problem for the SEIR Model: $x = (S, E, I, N)$

Dynamical model for $0 \le t \le T$

$$
\begin{aligned}
\dot S(t) &= b\,N(t) - d\,S(t) - c\,S(t)\,I(t) - u(t)\,S(t), & S(0) &= S_0,\\
\dot E(t) &= c\,S(t)\,I(t) - (e+d)\,E(t), & E(0) &= E_0,\\
\dot I(t) &= e\,E(t) - (g+a+d)\,I(t), & I(0) &= I_0,\\
\dot N(t) &= (b-d)\,N(t) - a\,I(t), & N(0) &= N_0,\\
0 &\le u(t) \le 1. & &
\end{aligned}
$$

L^1 objective

Minimize $\quad J = \int_0^T (I(t) + B\,u(t))\,dt \quad (B > 0)$

ODE for total number of vaccines W:

$$\dot W(t) = u(t) S(t), \quad W(0) = 0.$$

Parameters in the SEIR Model

Parameter	Description	Value
b	natural birth rate	0.525
d	natural death rate	0.5
c	incidence coefficient	0.001
e	exposed to infectious rate	0.5
g	recovery rate	0.1
a	disease induced death rate	0.2
B	weight parameter	$\in [2, 10]$
T	number of years	20
S_0	initial susceptible population	1000
E_0	initial exposed population	100
I_0	initial infected population	50
R_0	initial recovered population	15
N_0	initial population	1165

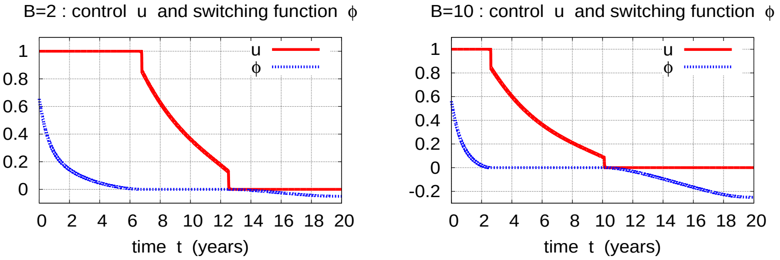
Unlimited Vaccines: Control for $B = 2$ and $B = 10$

Adjoint variable $\quad \lambda = (\lambda_S, p\lambda_E, \lambda_I, \lambda_N)$

Switching function $\quad \phi(x,p) = H_u = -B - \lambda_S\, S$

Optimal control law for Maximum Principle:

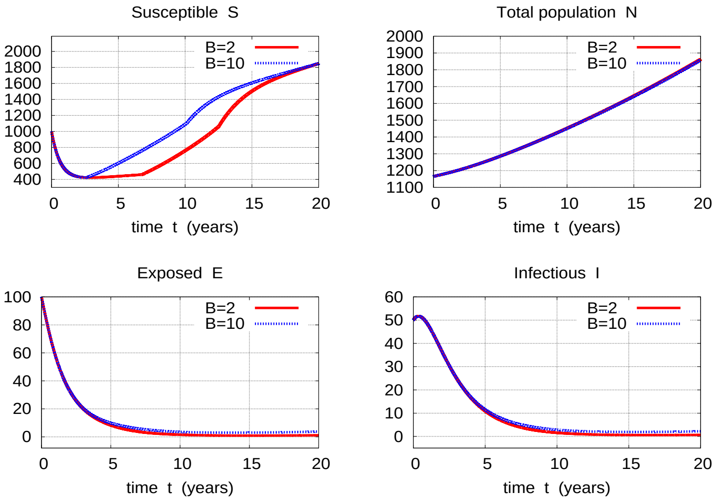
$$u(t) = \left\{ \begin{array}{cccl} 1 & , & \text{if} & \phi(t) > 0 \\ 0 & , & \text{if} & \phi(t) < 0 \\ u_{sing} & , & \text{if} & \phi(t) = 0 \;\; \forall\, t \in [t_1, t_2] \subset [0, T] \end{array} \right\}.$$



Optimal control for $B = 2$ and $B = 10$ is bang-singular-bang.

Unlimited Vaccines: State Variables

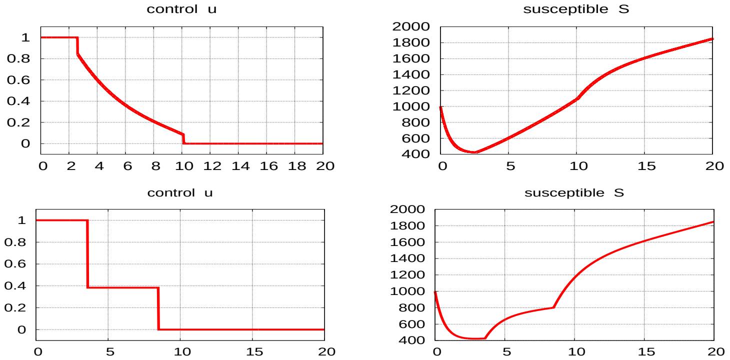
Comparison of state variables for $B = 2$ and $B = 10$:



Unlimited Vaccines: Approximation of Optimal Control

Approximation of bang-singular bang control:

$$u(t) = \begin{cases} 1 & \text{for} \quad 0 \le t < t_1 \\ u_c & \text{for} \quad t_1 \le t \le t_2 \\ 0 & \text{for} \quad t_2 < t \le T \end{cases}, \quad \begin{aligned} t_1 &= 3.58927, \\ u_c &= 0.383110 \\ t_2 &= 8.50110 \end{aligned}$$



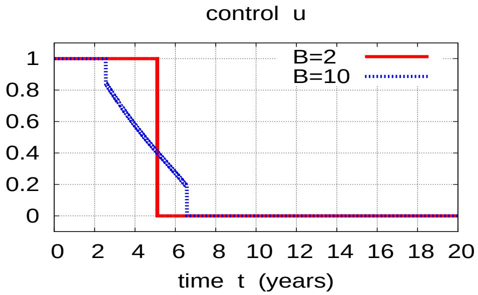
Functional value $J = 262.981$ versus optimal $J = 262.605$.

Limited Vaccines: Optimal Control for $B = 2$ and $B = 10$

Unlimited case: Total amount of vaccines $W = 4880$.

Limited case: terminal constraint $W(T) = 2500$ for ODE

$$\dot{W}(t) = u(t)\, S(t), \quad W(0) = 0\,, \; W(T) = 2500\,.$$



Optimal control for $B = 2$ is bang-bang : SSC hold !

Optimal control for $B = 10$ is bang-singular-bang.

Mixed Constraint $u(t)S(t) \leq 125$

Instead of restricting the total amount of vaccines $W(T) = 2500$, the vaccines $u(t)S(t)$ are restricted at each time t .

Mixed control-state constraint

$$u(t)\, S(t) \leq 125 = W(T)/T \quad \forall\, t \in [0, T]\,.$$

Switching function $\phi(t) = -B - \lambda_S(t)\, S(t)$.

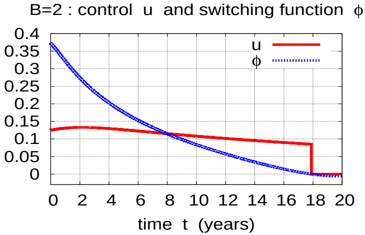
Control law of the Maximum Principle :

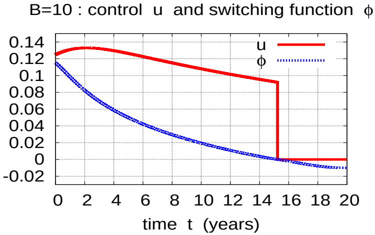
$$u(t) = \left\{ \begin{array}{ccc} 125/S(t) & , & \text{if} \quad \phi(t) > 0 \\ 0 & , & \text{if} \quad \phi(t) < 0 \end{array} \right\}.$$

The multiplier for the mixed constraint is given by

$$q(t) = \phi(t)/S(t)\,.$$

$$u(t) = \begin{cases} 125/S(t) & \text{for} \quad 0 \le t < t_1 \\ 0 & \text{for} \quad t_1 \le t \le T \end{cases}, \qquad \begin{matrix} B = 2 & : & t_1 = 17.887 \\ B = 10 & : & t_1 = 15.234 \end{matrix}$$





The new control v defined by $v = u \cdot S$ is bang-bang with one switching at t_1. The SSC are satisfied !

In particular, the strict bang-bang property holds:

$$\phi(t) > 0 \quad \text{for} \quad 0 \le t < t_1\,, \qquad \dot{\phi}(t_1) < 0, \qquad \phi(t) < 0 \quad \text{for} \quad t_1 < t < T\,.$$

Further Work on SEIR and Tuberculosis Models

- State constraint : $S(t) \leq S_{max}$
- Epidemiological models with state delays
- Apply similar methods to optimal control strategies for tuberculosis treatment.

L^2 Functional in:

Cristiana J. Silva and Delfim F. M. Torres, *Optimal control strategies for tuberculosis treatment: a case study in Angola*, Numerical Algebra, Control and Optimization **2**, 601–617 (2012).

Control of the Circadian Rhythms

A. Goldbeter, *Computational approaches to cellular rhythms*, Nature 420, pp. 238-245 (2002).

J.C. Leloup and A. Goldbeter, *A model for circadian rhythms in Drosophila incorporating the formation of a complex between PER and TIM proteins*, J. Biological Rhythms **13**, pp. 70–87 (1998).

O.S. Shaik, S. Sager, O. Slaby, and D. Lebiedz, *Phase tracking and restoration of circadian rhythms by model-based optimal control*, IET Systems Biology, Vol. 2, pp. 16-23 (2008).

O. Slaby, S. Sager, O.S. Shaik, and D. Lebiedz, *Optimal control of self-organized dynamics in cellular signal transduction*, Mathematical and Computer Modelling of Dynamical Systems , Vol. 13, pp. 487-502 (2007).

The following is joint work with Dirk Lebiedz (Ulm).

Circadian Clock of Drosophila

- Self-organized rhythmic processes are encountered at all levels in cell biology.
- The role of circadian rhythms with a period of nearly 24 h is of particular importance, because many physiological and behavioural functions of living creatures appear to be governed by this so-called "master clock".
- Rhythmic alterations may cause illnesses like cancer.
- The dynamical model for Drosophila consists of 10 ODEs and 38 parameters (Lelouch, Goldbeter). Light entrainment necessitates modelling the transriptional regulation of both key proteins PER and TIM.
- Targeted manipulations of circadian rhythms by optimal control: bring back a disturbed rhythm to a desired target state.

Drosophila Model Equations

State vector $x = (M_p, P_0, P_1, P_2, M_T, T_0, T_1, T_2, C, C_N) \in \mathbf{R}^{10}$

$$
\begin{aligned}
\frac{dM_p}{dt} &= v_{sP}\frac{K_{IP}{}^n}{K_{IP}{}^n + C_N{}^n} - v_{mP}\frac{M_P}{K_{mP}+M_P} - k_d M_P\\
\frac{dP_0}{dt} &= k_{sP} M_P - \nu_{1P}\frac{P_0}{K_{1P}+P_0} + \nu_{2P}\frac{P_1}{K_{2P}+P_1} - k_d P_0\\
\frac{dP_1}{dt} &= \nu_{1P}\frac{P_0}{K_{1P}+P_0} - \nu_{2P}\frac{P_1}{K_{2P}+P_1} - \nu_{3P}\frac{P_1}{K_{3P}+P_1} + \nu_{4P}\frac{P_2}{K_{4P}+P_2} - k_d P_1\\
\frac{dP_2}{dt} &= \nu_{3P}\frac{P_1}{K_{3P}+P_1} - \nu_{4P}\frac{P_2}{K_{4P}+P_2} - k_3 P_2 T_2 + k_4 C - v_{dP}\frac{P_2}{K_{dP}+P_2} - k_d P_2\\
\frac{dM_T}{dt} &= v_{sT}\frac{K_{IT}{}^n}{K_{IT}{}^n + C_N{}^n} - v_{mT}\frac{M_T}{K_{mT}+M_T} - k_d M_T\\
\frac{dT_0}{dt} &= k_{sT} M_T - \nu_{1T}\frac{T_0}{K_{1T}+T_0} + \nu_{2T}\frac{T_1}{K_{2T}+T_1} - k_d T_0\\
\frac{dT_1}{dt} &= \nu_{1T}\frac{T_0}{K_{1T}+T_0} - \nu_{2T}\frac{T_1}{K_{2T}+T_1} - \nu_{3T}\frac{T_1}{K_{3T}+T_1} + \nu_{4T}\frac{T_2}{K_{4T}+T_2} - k_d T_1\\
\frac{dT_2}{dt} &= \nu_{3T}\frac{T_1}{K_{3T}+T_1} - \nu_{4T}\frac{T_2}{K_{4T}+T_2} - k_3 P_2 T_2 + k_4 C - u\cdot\nu_{dT}\frac{T_2}{K_{dT}+T_2} - k_d T_2\\
\frac{dC}{dt} &= k_3 P_2 T_2 - k_4 C - K_1 C + k_2 C_N - k_{dC} C\\
\frac{dC_N}{dt} &= k_1 C - k_2 C_N - k_{dN} C_N
\end{aligned}
$$

Control u is the light stimulus: $1 \le u(t) \le 3$. **Darkness** : $u(t) = 1$

Kinetic parameter	Parameter value	Kinetic parameter	Parameter value
ν_{sP}	1.1 nMh^{-1}	k_d	0.01 h^{-1}
ν_{sT}	1 nMh^{-1}	k_{dC}	0.01 h^{-1}
ν_{mP}	0.7 nMh^{-1}	k_{dN}	0.01 h^{-1}
ν_{mT}	0.7 nMh^{-1}	$\nu_{1\mathrm{P}}$	8 nMh^{-1}
K_{mP}	0.2 nM	$\nu_{1\mathrm{T}}$	8 nMh^{-1}
K_{mT}	0.2 nM	$\nu_{2\mathrm{P}}$	1 nMh^{-1}
k_{sP}	0.9 h^{-1}	$\nu_{2\mathrm{T}}$	1 nMh^{-1}
k_{sT}	0.9 h^{-1}	$\nu_{3\mathrm{P}}$	8 nMh^{-1}
ν_{dP}	2.0 nMh^{-1}	$\nu_{3\mathrm{T}}$	8 nMh^{-1}
ν_{dT}	1.8532 nMh^{-1}	$\nu_{4\mathrm{P}}$	1 nMh^{-1}
k_1	0.6 h^{-1}	$\nu_{4\mathrm{T}}$	1 nMh^{-1}
k_2	0.2 h^{-1}	$K_{4\mathrm{T}}$	2.0 nM
k_3	1.2 $\mathrm{nM}^{-1}\mathrm{h}^{-1}$	$K_{4\mathrm{P}}$	2.0 nM
k_4	0.6 h^{-1}	$K_{3\mathrm{T}}$	2.0 nM
K_{IP}	1.0 nM	$K_{3\mathrm{P}}$	2.0 nM
K_{IT}	1.0 nM	$K_{2\mathrm{T}}$	2.0 nM
K_{dP}	0.2 nM	$K_{2\mathrm{P}}$	2.0 nM
K_{dT}	0.2 nM	$K_{1\mathrm{T}}$	2.0 nM
n	4	$K_{1\mathrm{P}}$	2.0 nM

Computation of Periodic Solution

State variable $x = (M_p, P_0, P_1, P_2, M_T, T_0, T_1, T_2, C, C_N) \in \mathbf{R}^{10}$
Control variable u (light modulation)

Dynamics with affine control : $\dot{x} = f(x, u) = f_1(x) + f_2(x)\,u\,.$

Periodic Boundary Conditions with period t_f

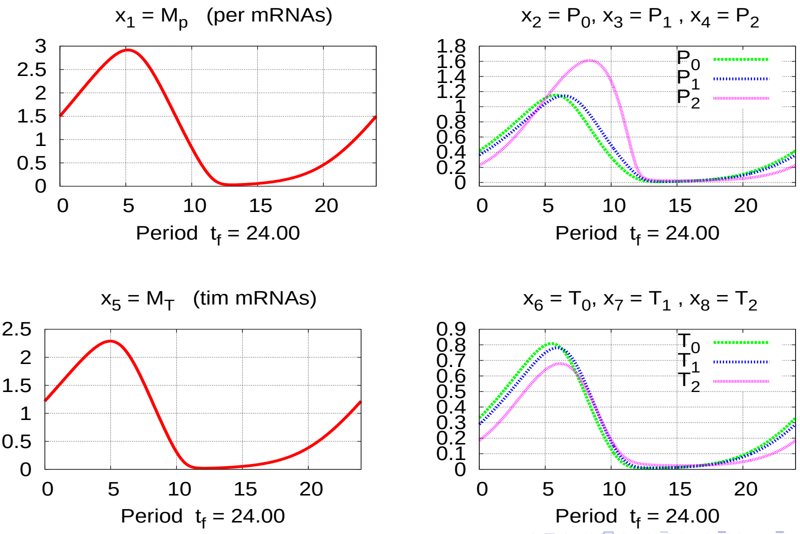
$$\begin{aligned} x_1(0) &= 1.5, \quad \text{(we can prescribe one initial condition)} \\ x_k(t_f) &= x_k(0), \quad k = 1, ..., 10. \end{aligned}$$

Optimization problem for computing the period t_f

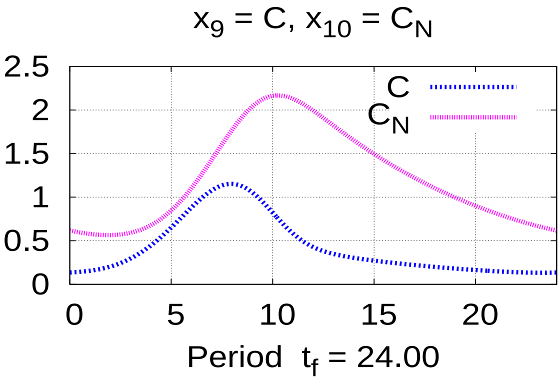
Minimize t_f subject to $\dot{x}(t) = f(x(t), u_1(t)), \quad u_1(t) \equiv 1,$
and periodic boundary conditions.

Optimal control package NUDOCCCS (C. Büskens, Bremen).
By "optimizing" the parameter ν_{dT} in the ODE dT_2/dt we obtain the exact period $t_f = 24.0000\ [hrs]$ for $\nu_{dT} = 1.8532$!

Periodic solution $x_1, \dots, x_8$ with period $t_f = 24.00$



Periodic solution x_9, x_{10} with period $t_f = 24.00$



Stability of periodic solution via eigenvalues of Monodromy Matrix.

Optimal Control Problem for Phase Restoration

State	$x \in \mathbf{R}^{10}$	
Shifted State	$y \in \mathbf{R}^{10}$	(time shift of variable x)
Control variable	u	(light stimulus)

ODE system for reference state x and controlled state y

$$\begin{aligned} \dot{x} &= f(x, u_1), & x(0) &= x_0, & (u_1 &\equiv 1) \\ \dot{y} &= f(y, u), & y(0) &= x(12), & &\text{(half a period)} \\ 1 &\le u(t) \le 3, & t &\in [0, t_f]. \end{aligned}$$

Optimal Control Problem: Minimize quadratic deviations

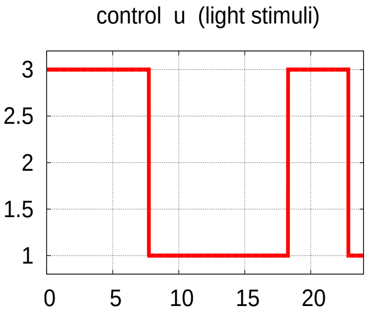
$$\begin{aligned} J(x, y, u) \;=\; & w \cdot (\, ||y(t_f) - x(t_f)||_2^2 + ||\dot{y}(t_f) - \dot{x}(t_f)||_2^2 \,) \\ & + \int_0^t ||y(t_f) - x(t)||_2^2 \, dt \quad (\, w \ge 100 \,) \end{aligned}$$

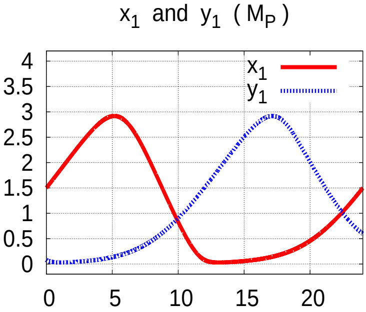
Optimal control package NUDOCCCS (C. Büskens, Bremen).

Formulation with AMPL and interior-pont solver IPOPT.

Restoration of Circadian Rhythm : $t_f = 24$

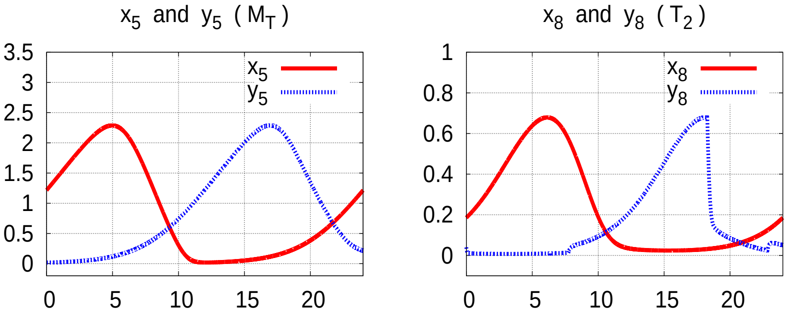
Optimal control is bang-bang: SSC hold.





$t_f = 24$: phase restoration is not yet successful.

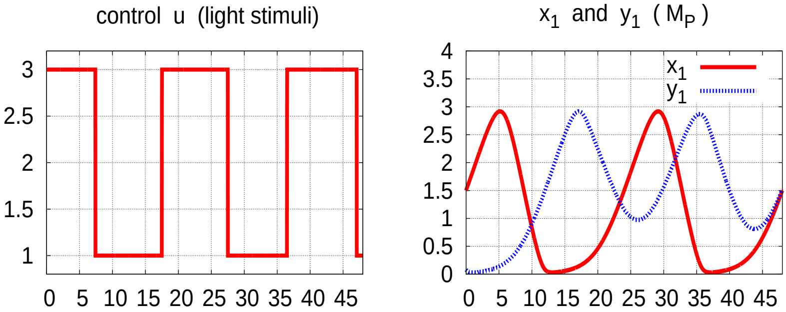
Restoration of Circadian Rhythm : $t_f = 24$



$t_f = 24$: phase restoration is not yet successful.

Restoration of Circadian Rhythm : $t_f = 48$

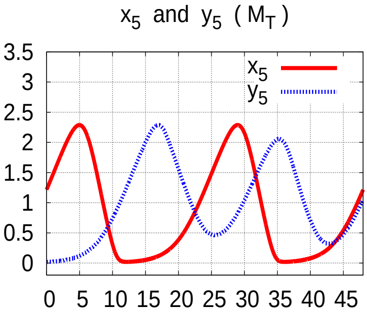
Optimal control is bang-bang : SSC hold.

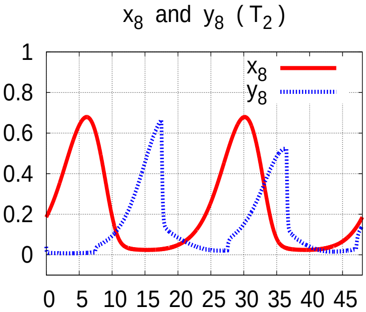


$t_f = 48$: phase restoration is "nearly" successful !

Restoration of Circadian Rhythm : $t_f = 48$

Optimal control is bang-bang : SSC hold.

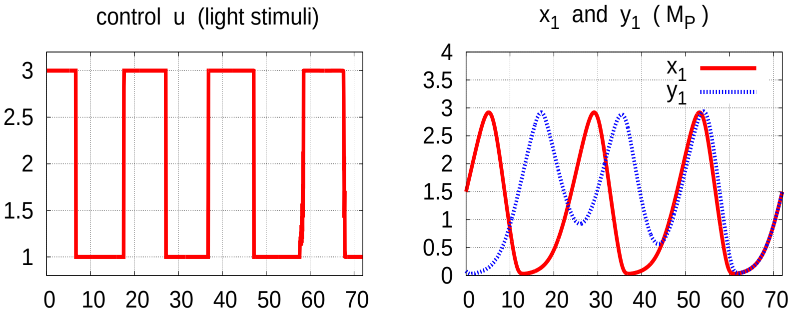




$t_f = 48$: phase restoration is "nearly" successful.

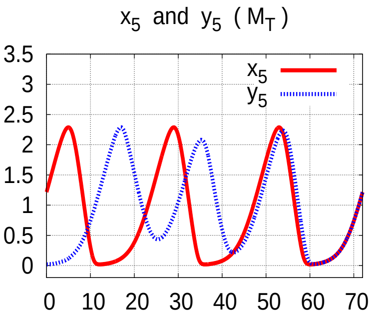
Restoration of Circadian Rhythm : $t_f = 72$

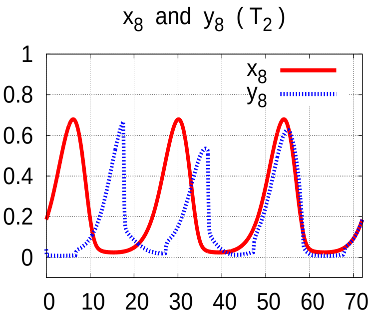
Optimal control is bang-singular



$t_f = 72$: phase restoration is successful after $\approx 50\ hrs$.

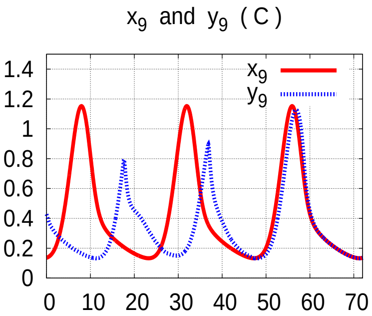
Restoration of Circadian Rhythm : $t_f = 72$

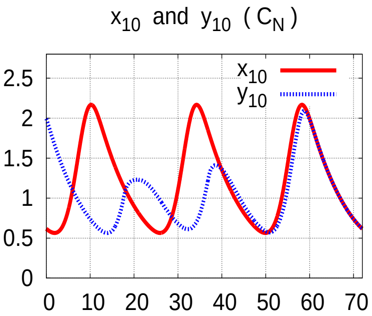




$t_f = 72$: phase restoration is successful after ≈ 50 *hrs* .

Restoration of Circadian Rhythm : $t_f = 72$





$t_f = 72$: phase restoration is successful after ≈ 50 *hrs* .

Conclusion

There are many more optimal control applications in biology and biomedicine. But not for now:

Thank you for your attention !