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Sufficient Conditions for Strong Local Optimality with Applications to Biomedical Problems

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► **To cite this version:**

Urszula Ledzewicz. Sufficient Conditions for Strong Local Optimality with Applications to Biomedical Problems. NETCO 2014 - New Trends in Optimal Control, Jun 2014, Tours, France. hal-01024597

HAL Id: hal-01024597

<https://inria.hal.science/hal-01024597>

Submitted on 16 Jul 2014

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Sufficient Conditions for Strong Local Optimality with Applications to Biomedical Problems

**NetCO 2014
Conference on New Trends in Optimal Control,
Tours, France July 23-27, 2014**



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Research supported by collaborative research

NSF grants **DMS 1008209/100822, DMS 1311729/1311733**

Interdisciplinary Applied Mathematics

Heinz Schättler · Urszula Ledzewicz

Geometric Optimal Control

Theory, Methods and Examples

This book gives a comprehensive treatment of the fundamental necessary and sufficient conditions for optimality for finite-dimensional, deterministic, optimal control problems. The emphasis is on the *geometric aspects of the theory* and on illustrating how these methods can be used to solve optimal control problems. It provides tools and techniques that go well beyond standard procedures and can be used to obtain a full understanding of the global structure of solutions for the underlying problem. The text includes a large number and variety of fully worked out examples that range from the classical problem of minimum surfaces of revolution to cancer treatment for novel therapy approaches. All these examples, in one way or the other, illustrate the power of geometric techniques and methods. The versatile text contains material on different levels ranging from the introductory and elementary to the advanced. Parts of the text can be viewed as a comprehensive textbook for both advanced undergraduate and all level graduate courses on optimal control in both mathematics and engineering departments. The text moves smoothly from the more introductory topics to those parts that are in a monograph style were advanced topics are presented. While the presentation is mathematically rigorous, it is carried out in a tutorial style that makes the text accessible to a wide audience of researchers and students from various fields, including the mathematical sciences and engineering.

Heinz Schättler is an Associate Professor at Washington University in St. Louis in the Department of Electrical and Systems Engineering, Urszula Ledzewicz is a Distinguished Research Professor at Southern Illinois University Edwardsville in the Department of Mathematics and Statistics.

Mathematics

ISBN 978-1-4414-3833-5



springer.com

IAM
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Interdisciplinary Applied Mathematics 38

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Urszula Ledzewicz



Geometric Optimal Control

Geometric Optimal Control

Theory, Methods and Examples

 Springer

- **Heinz Schättler and Urszula Ledzewicz,**

**Geometric Optimal Control
Theory, Methods, Examples**

Springer Verlag, 2012

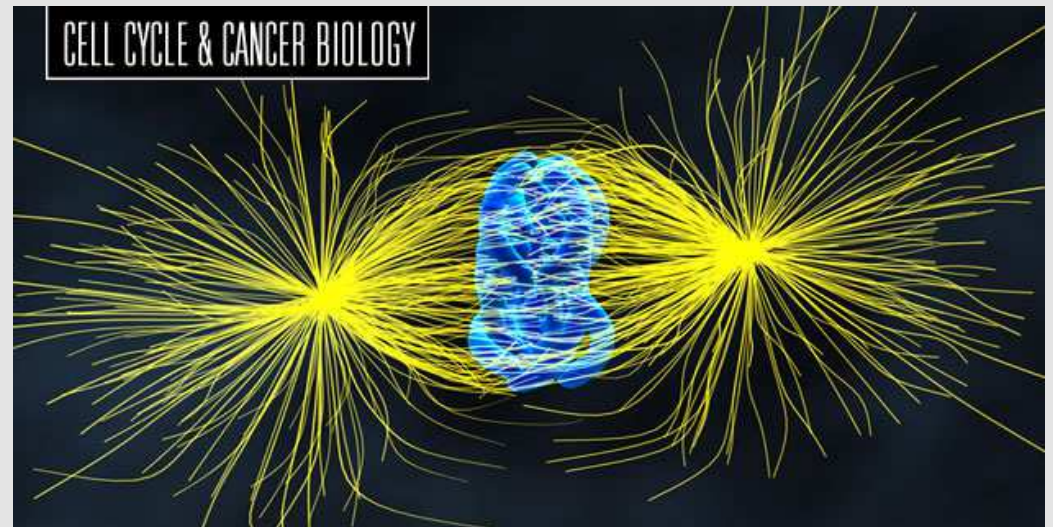
- **Urszula Ledzewicz and Heinz Schättler,**

**Optimal Control of Mathematical Models for Cancer
Therapies**

An Application of Geometric Methods

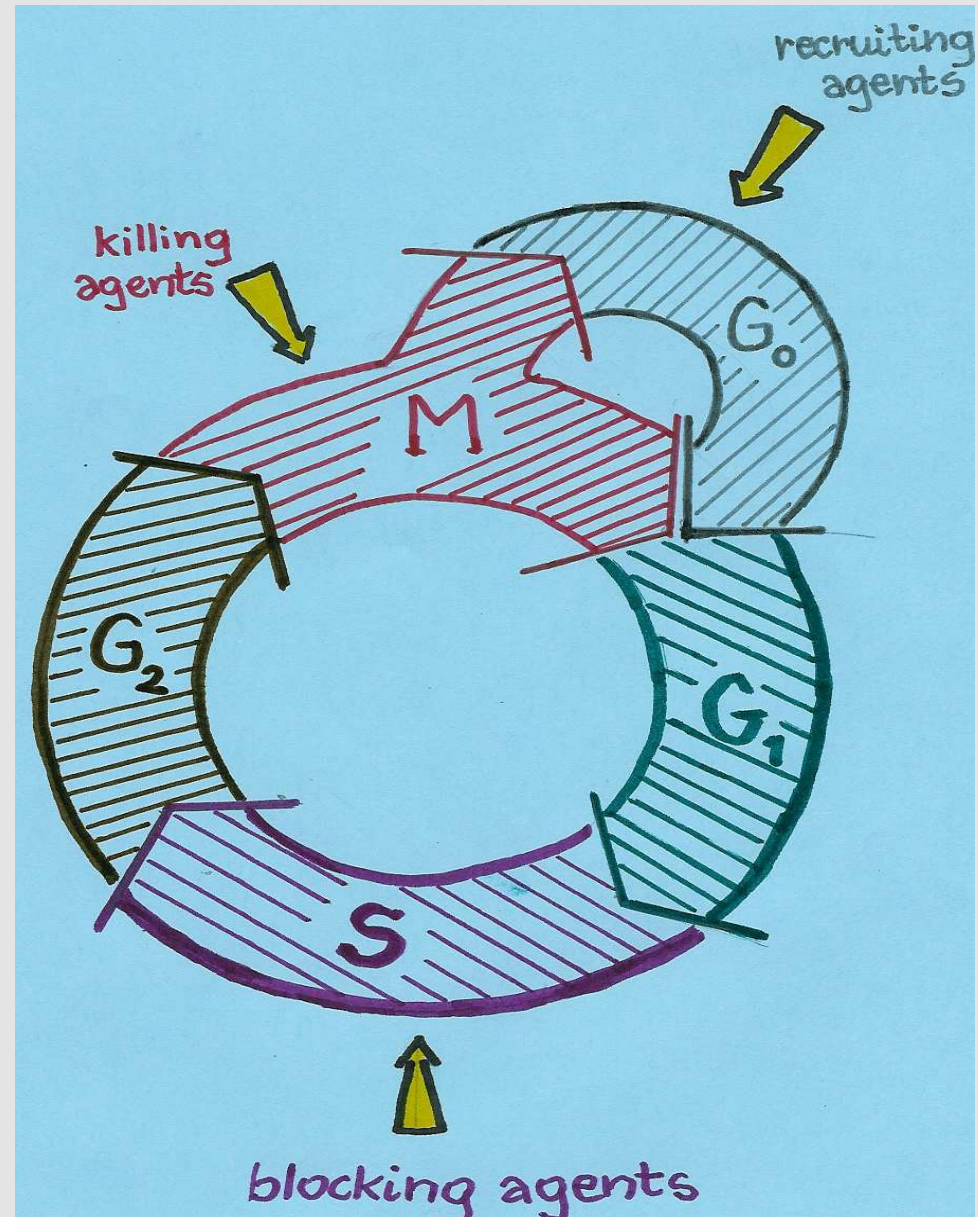
Springer Verlag, 2015

Cell-Cycle Specific Models for Multi-Drug Chemotherapy



Cell-cycle specific models for cancer chemotherapy

- **CELL CYCLE SPECIFICITY**
drugs act at various stages of the cell cycle
- * **Killing agents** in G_2/M
(Taxol, Spindle poisons,...)
- * **Blocking agent** in S
(hydroxyurea,...)
(gastro-intestine cancers)
- * **Recruiting agent** in G_0
(interleukin-3, granulate colony stimulation factors, ..)
(leukemia)



A 3-Compartment Model with Cytostatic and Cytotoxic Agents

[Swierniak, 1995, LSch, JBS 2002, LSch et al CDC 2012, MBE, 2013]]

- STATES :

$$\mathbf{N} = (N_1 , N_2 , N_3)$$

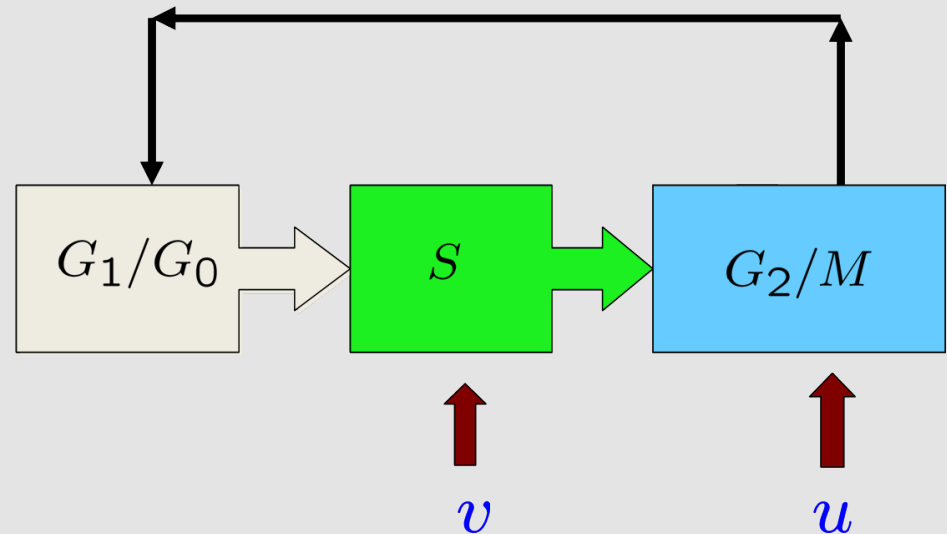
average number of cancer cells
in respective compartments

- CONTROLS: u , v

represent the dose rates of:

u - *cytotoxic (killing) agent*

v - *cytostatic (blocking) agent*



Dynamics

$$\dot{N} = (A + uB_1 + vB_2)N,$$

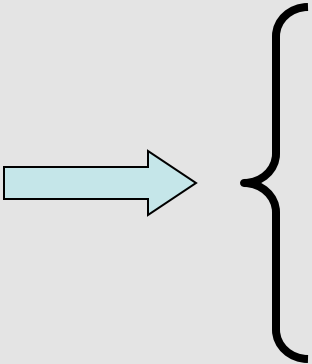
$$0 \leq u \leq 1, \quad 0 \leq v \leq v_{\max} < 1$$

$$\dot{N} = \left\{ \underbrace{\begin{pmatrix} -a_1 & 0 & 2a_3 \\ a_1 & -a_2 & 0 \\ 0 & a_2 & -a_3 \end{pmatrix}}_A + u \underbrace{\begin{pmatrix} 0 & 0 & -2a_3 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}}_{B_1} + v \underbrace{\begin{pmatrix} 0 & 0 & 0 \\ 0 & a_2 & 0 \\ 0 & -a_2 & 0 \end{pmatrix}}_{B_2} \right\} N$$

Steady State Proportions [LSch et al., MBE, 2013]

$$x(t) = \frac{N_1(t)}{C(t)}, \quad y(t) = \frac{N_2(t)}{C(t)}, \quad z(t) = \frac{N_3(t)}{C(t)},$$

$$C(t) = N_1(t) + N_2(t) + N_3(t)$$


$$\begin{cases} \dot{x} = -a_1x + 2a_3z - a_3xz, \\ \dot{y} = a_1x - a_2y - a_3yz, \\ \dot{z} = a_2y - a_3z - a_3z^2 \end{cases}$$

$$x(t) + y(t) + z(t) \equiv 1$$

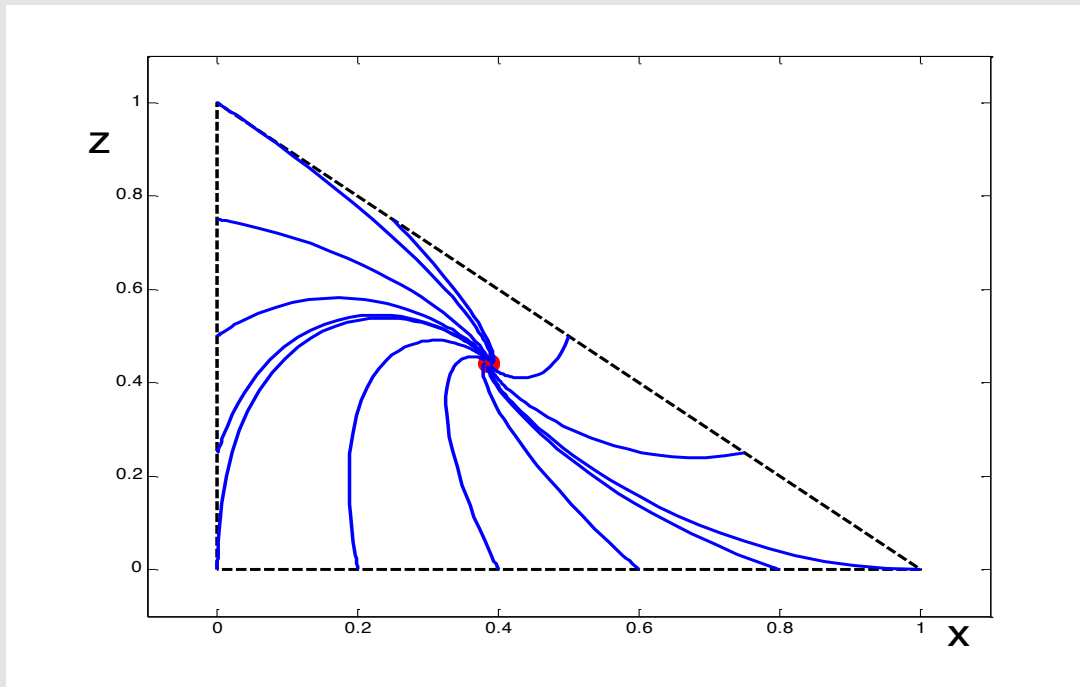
Riccati equations

Steady State Proportions

There exists a **unique, locally asymptotically stable equilibrium point** (x^*, y^*, z^*) that contains the unit simplex

$$\Sigma = \{(x, y, z) : x \geq 0, y \geq 0, z \geq 0, x + y + z = 1\}$$

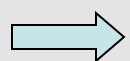
in its region of attraction (independent of cell-cycle coefficients)



(Poincaré-Bendixson theory)

$$a_1 = \frac{\ln 2}{T} \left(\frac{2}{x_*} - 1 \right)$$
$$a_2 = \frac{\ln 2}{T} \frac{1 + z_*}{y_*}$$
$$a_3 = \frac{\ln 2}{T} \frac{1}{z_*}$$

T – tumor doubling time



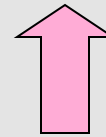
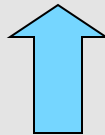
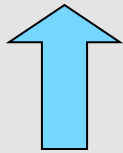
initial conditions $N(0) = C(0)(x_*, y_*, z_*)$

flow cytometry

Mathematical Model: L_1 -type Objective

minimize the number of cancer cells left without causing too much harm to the healthy cells

$$J(u) = \underbrace{rN(T)} + \underbrace{\int_0^T qN(t)dt} + \underbrace{\int_0^T \theta_1 u(t) + \theta_2 v(t)dt}$$



**Weighted average
of number of
cancer cells at
end of therapy**

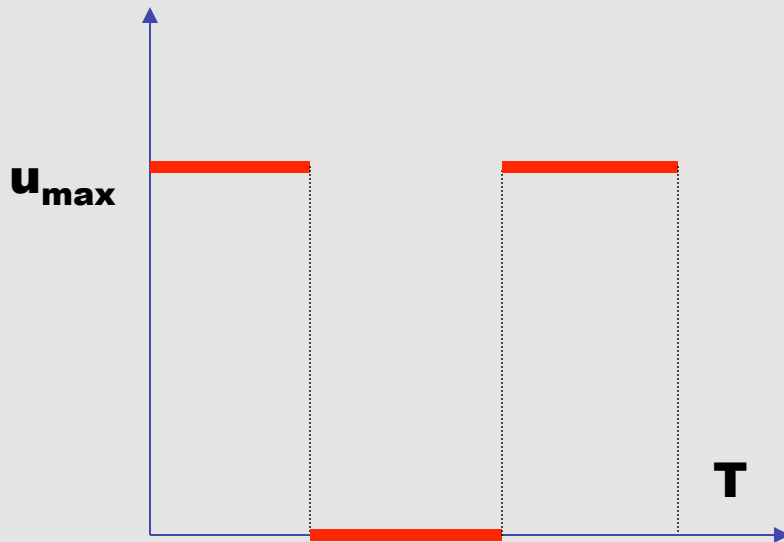
**Weighted average
of cancer cells
during therapy**

**Total doses given
as measure for
the toxicity of
the drug**

**(side effects on
healthy cells)**

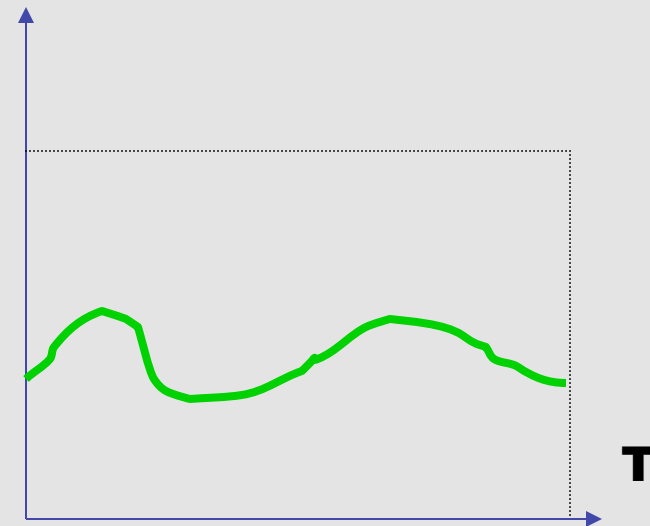
Candidates for Optimal Protocols

- bang-bang controls



treatment protocols of maximum dose therapy periods with rest periods in between

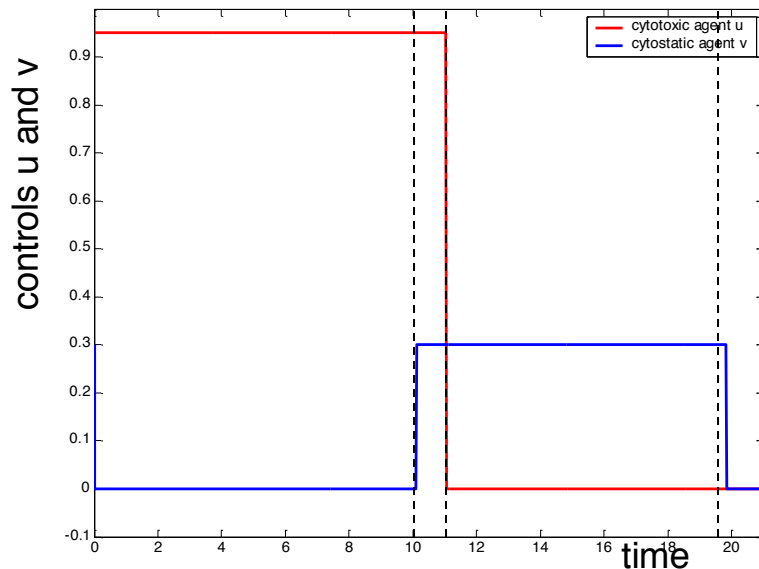
- singular controls



continuous infusions of varying lower doses

- singular controls are not optimal
(Legendre-Clebsch and Goh conditions)

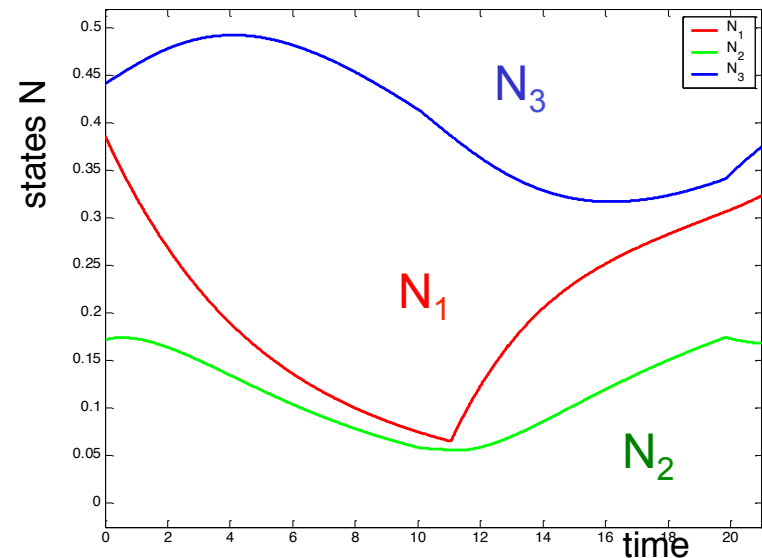
Example of an L_1 -(optimal) Control [SchLMaurer,DCDSB, to appear]



corresponding trajectories

OPTIMALITY?

optimal protocols for **cytotoxic**
and **cytostatic** agents



Mathematical Model: L₂-type Objective

minimize the number of cancer cells left without causing too much harm to the healthy cells

$$J(u) = \underbrace{rN(T)}_{\text{blue arrow}} + \underbrace{\int_0^T qN(t)dt}_{\text{blue arrow}} + \underbrace{\int_0^T \frac{1}{2}\theta_1 u(t)^2 + \frac{1}{2}\theta_2 v(t)^2 dt}_{\text{pink arrow}}$$

**Weighted average
of number of
cancer cells at
end of therapy**

**Weighted average
of cancer cells
during therapy**

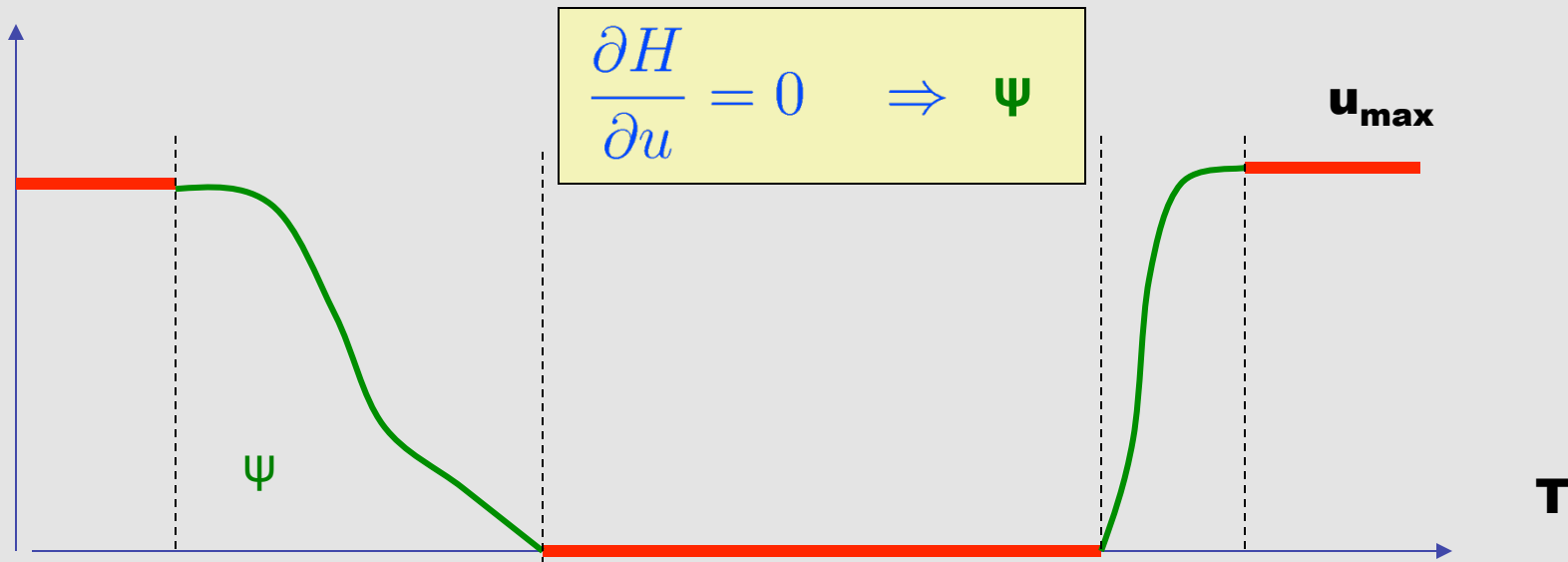
**Distorted measure for
side effects on healthy
cells**



induces a strictly convex structure in the Hamiltonian

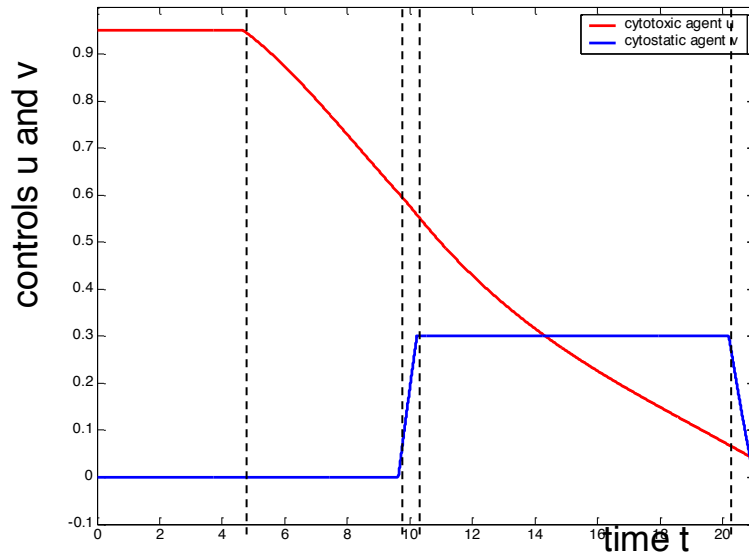
Candidates for Optimal Protocols

- Concatenations of **constant** controls with controls that take values in the **interior** of the control set and connect continuously with the constant segments



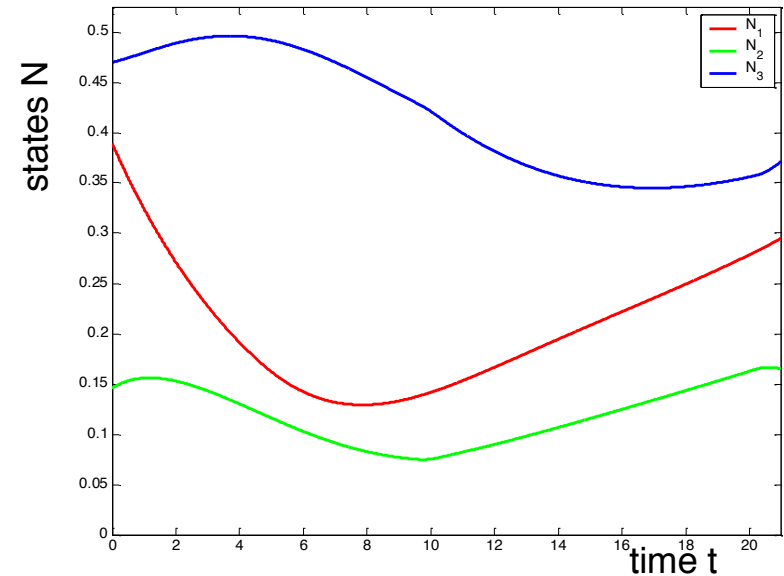
$$u^* = \max\{0, \min\{u_{\max}, \psi\}\}$$

Example of an L_2 -(optimal) Control [SchLMaurer,DCDSB, to appear]



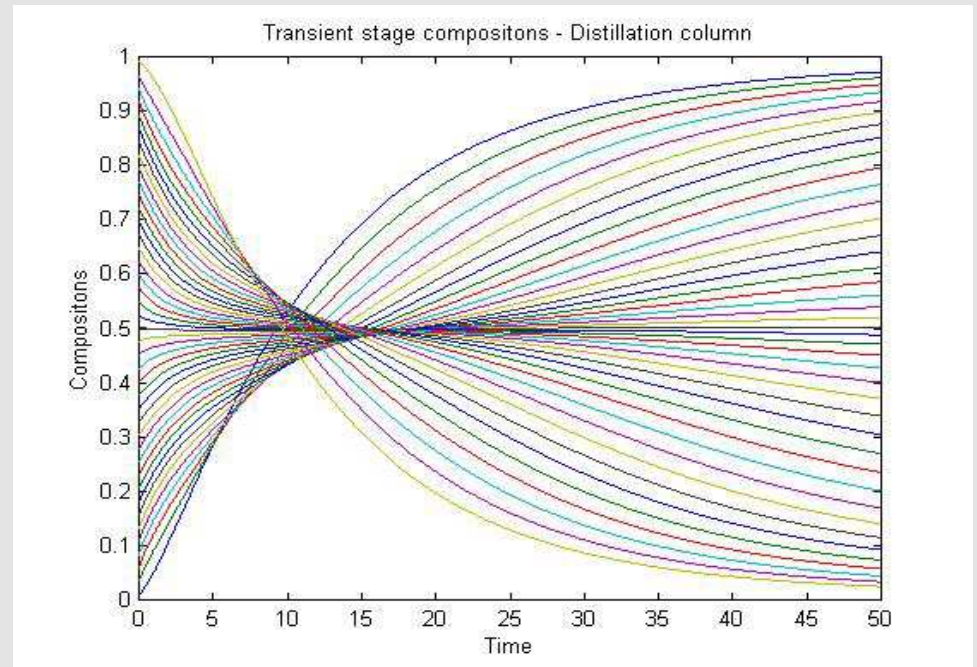
optimal protocols for **cytotoxic**
and **cytostatic** agents

corresponding trajectories



OPTIMALITY ?

Strong Local Optimality for L_1 - and L_2 -type Objectives



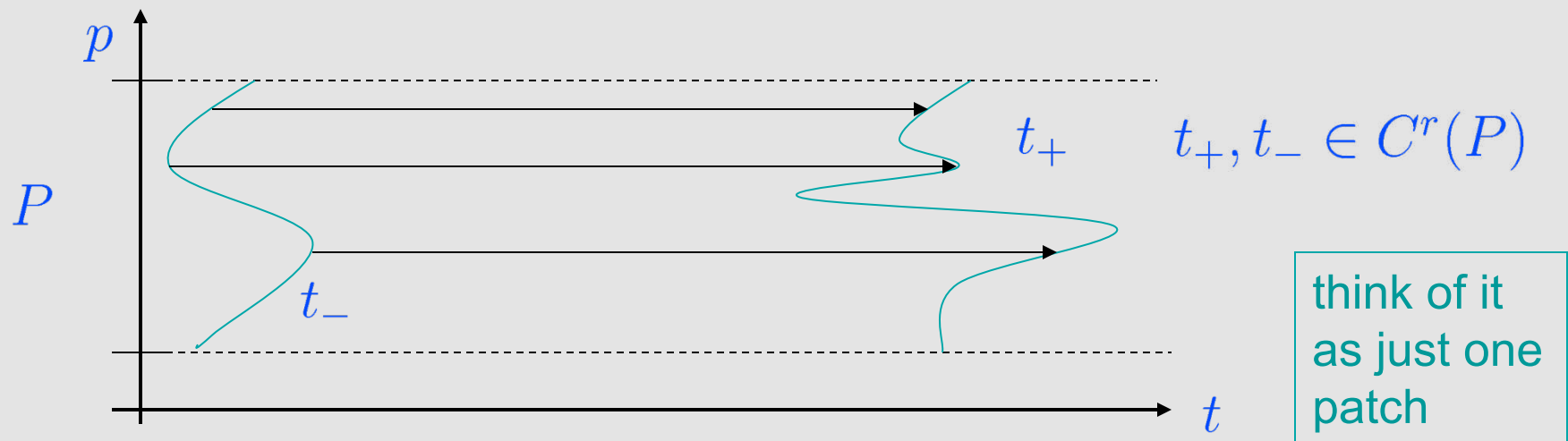
Parameterized Families of Extremals

a family of **controlled trajectories** $(N(t, p), u(t, p), v(t, p))$

that satisfy the conditions of the maximum principle with

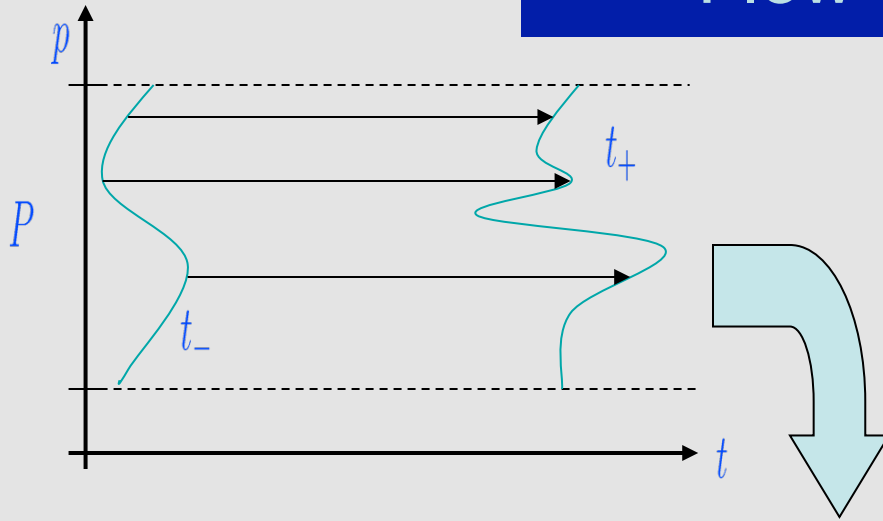
corresponding **multiplier** $\lambda(t, p)$ over some domain

$$D = \{(t, p) : t_-(p) \leq t \leq t_+(p), p \in P\}$$



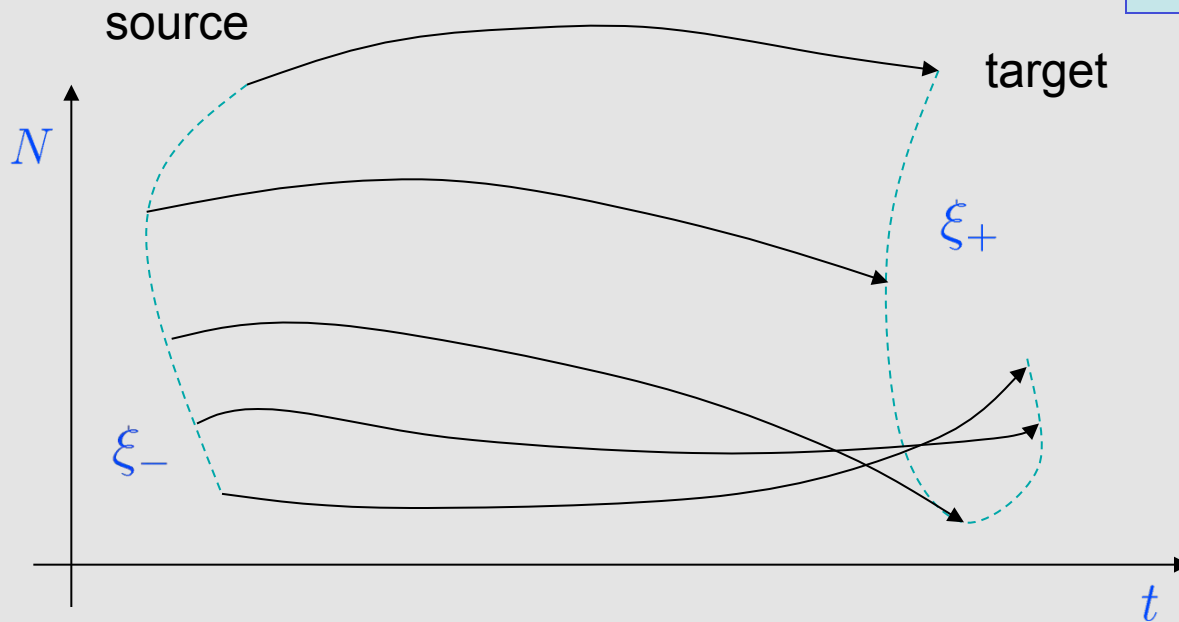
assume: $u(t, p)$ is continuous and C^r in p

Flow of Controlled Trajectories



The corresponding flow of trajectories is defined in terms of the **graphs** of trajectories as

$$F(t, p) = (t, N(t, p))$$



**time-dependent
optimal control
problem**

**just one
patch**

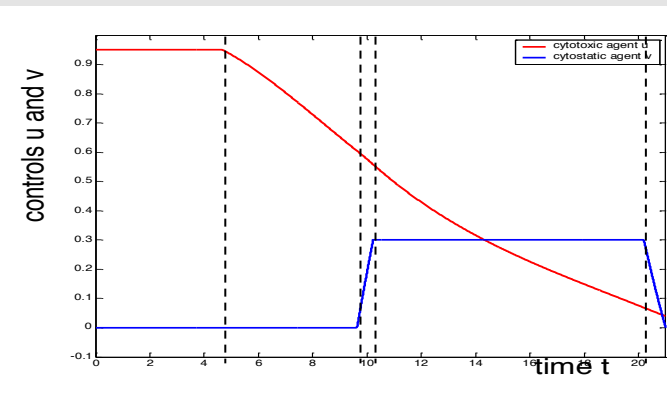
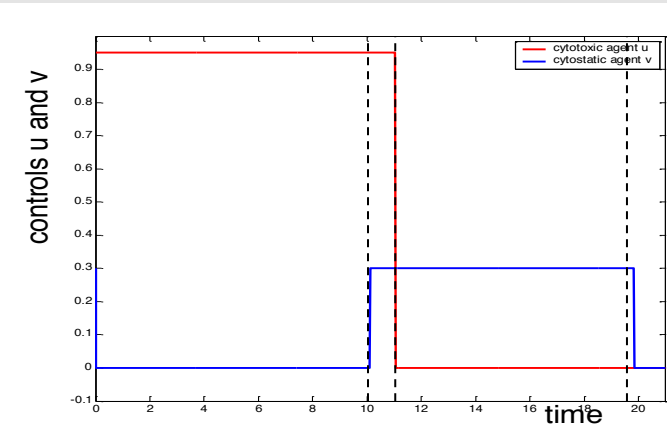
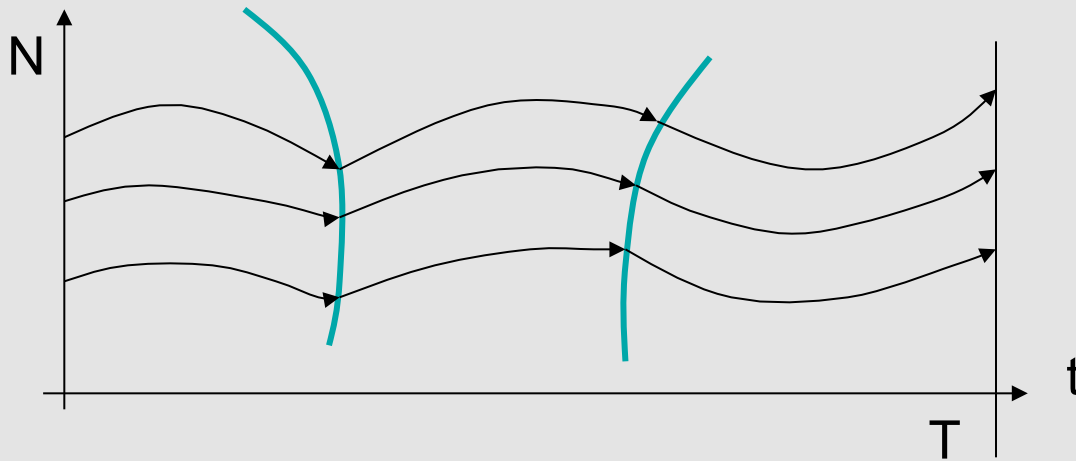
$$\xi_-(p) = N(t_-(p), p)$$

$$\xi_+(p) = N(t_+(p), p)$$

Parameterized Families of Broken Extremals

concatenations of parameterized families of extremals

switching / junction surfaces



the **strong local optimality** of the reference controlled extremal is determined by the mapping properties of the **flow of controlled trajectories** **between** and **at** the switching surfaces

Case of L1:Bang-Bang Flows

For bang-bang controls,

- the flows of the trajectories are diffeomorphisms between the switching surfaces
- overlaps can occur at the switchings.

transversal crossings

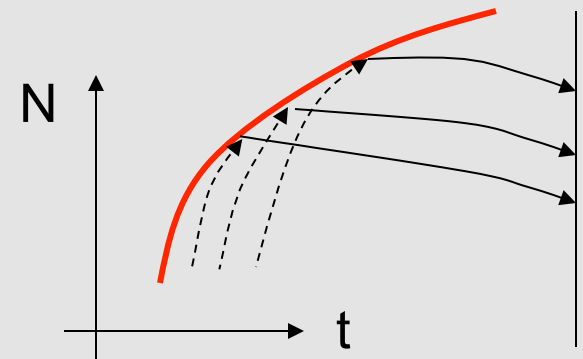
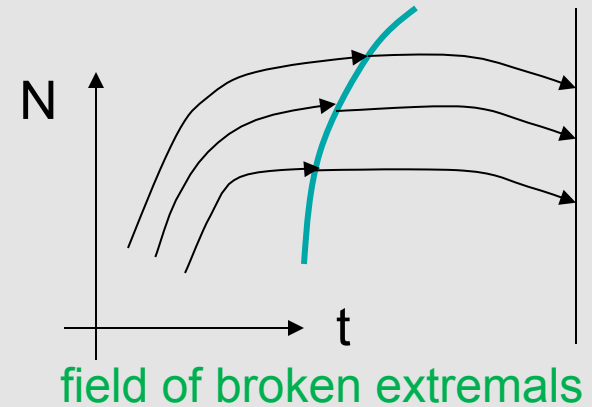
allows to construct a local solution of the Hamilton-Jacobi-Bellman equation

⇒ optimality is preserved

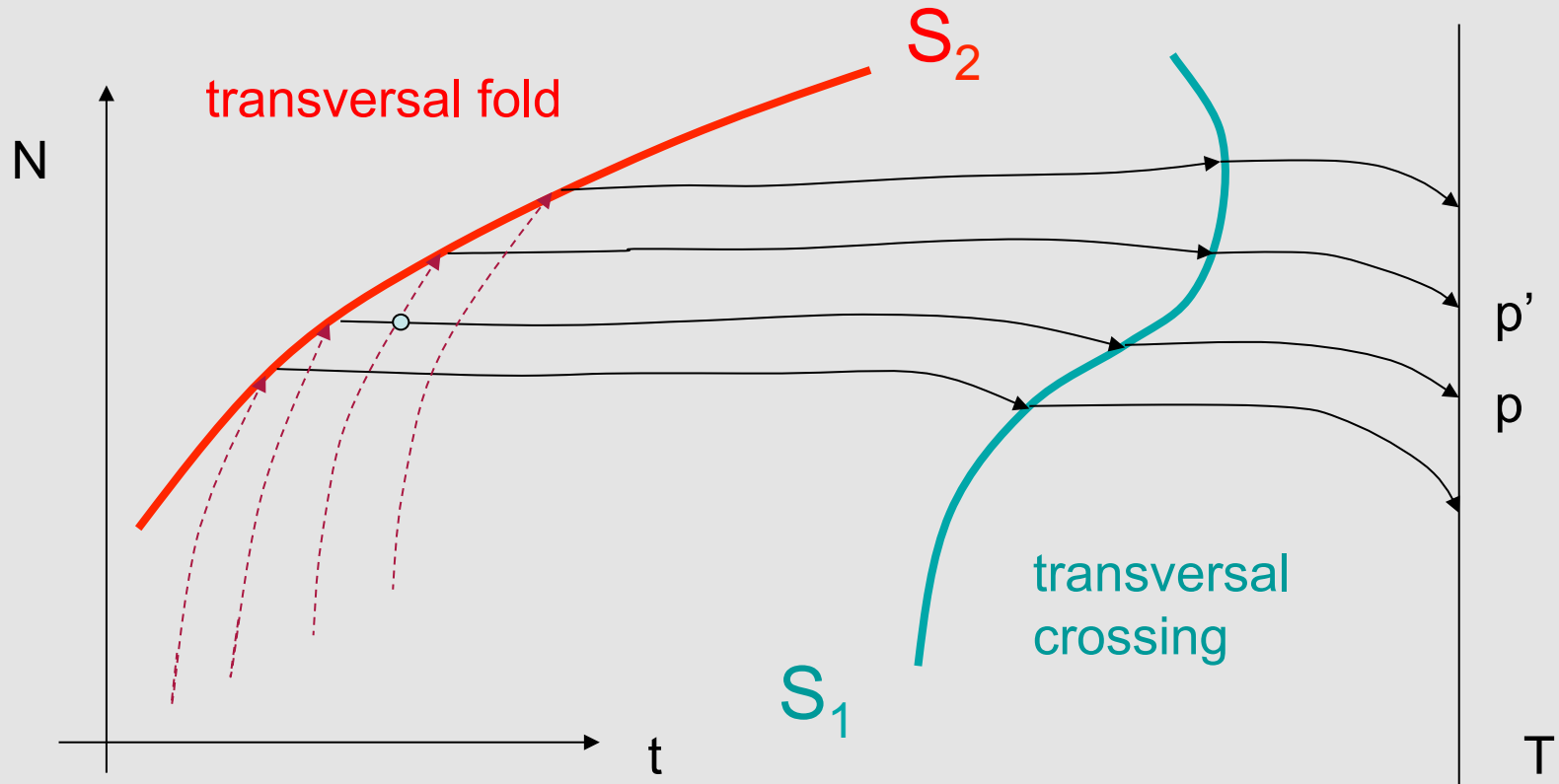
transversal fold

conjugate points—envelope

⇒ optimality ceases



Parameterized Family of Bang-Bang Extremals



Algorithmic Determination

The algorithmic determination of whether switchings are transversal crossings or folds can efficiently be done based on the following quantity

$$S(t, p) = \frac{\partial \lambda^T}{\partial p}(t, p) \left(\frac{\partial N}{\partial p}(t, p) \right)^{-1}$$

Note that



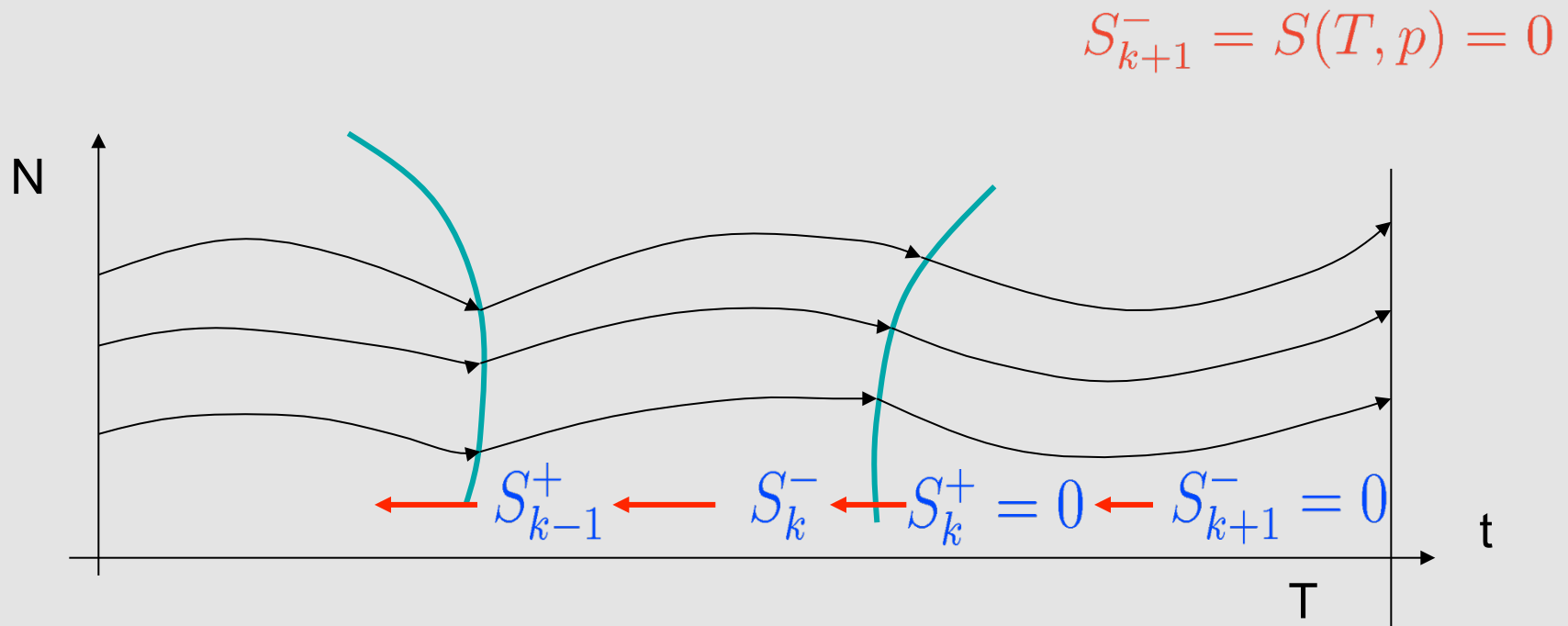
sensitivity equations

$$\lambda(T, p) \equiv r \quad \text{and} \quad N(T, p) = p$$

and thus

$$S(T, p) \equiv 0$$

Case of L1: Algorithmic Determination



efficient finite numerical procedure to determine the **strong local optimality** for L_1 type objectives

Case of L1: Algorithmic Determination

Set $S_{k+1}^- \equiv 0$ and for $i = k, k-1, \dots, 1$, inductively define

$$S_i^+ = \exp \left(\left(A + \sum_{j=1}^m u_j^i B_j \right)^T (t_{i+1} - t_i) \right) S_{i+1}^- \exp \left(\left(A + \sum_{j=1}^m u_j^i B_j \right) (t_{i+1} - t_i) \right)$$

$$G_i = -\frac{\theta_J}{|\dot{\Phi}_J^*(t_i)|} \left(\lambda_*(t_i) B_J + N_*^T(t_i) B_J^T S_i^+ \right)$$

$$S_i^- = \left(B_J^T \lambda_*^T(t_i) G_i + S_i^+ \right) \left(Id + \frac{B_J N_*(t_i) G_i}{1 - G_i B_J N_*(t_i)} \right)$$

**partial derivatives
are discontinuous
at switchings**

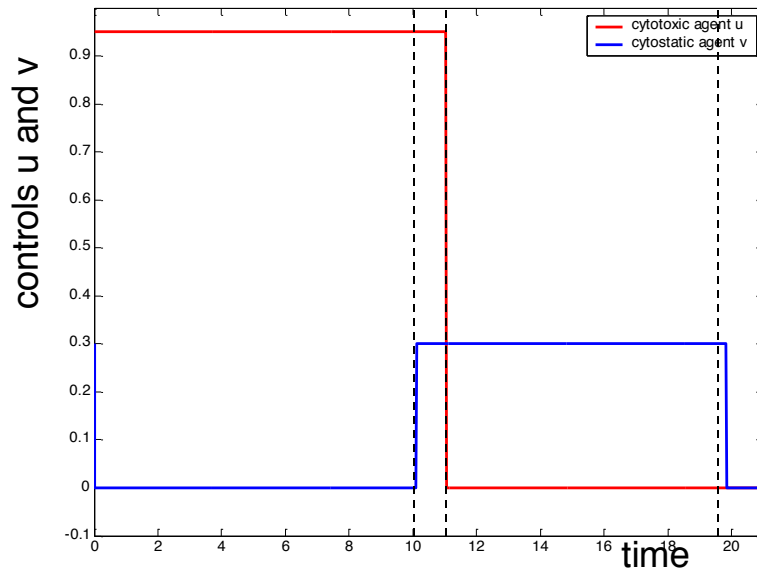
If, for $i = k, k-1, \dots, 1$, we have that

$$|\dot{\Phi}_J^*(t_i)| + \theta_J \left\{ \lambda_*(t_i) B_J + N_*^T(t_i) B_J^T S_i^+ \right\} B_J N_*(t_i) > 0,$$

then this algorithm is well-defined, every switching is a **transversal crossing**, and u_* is a strong local minimum.

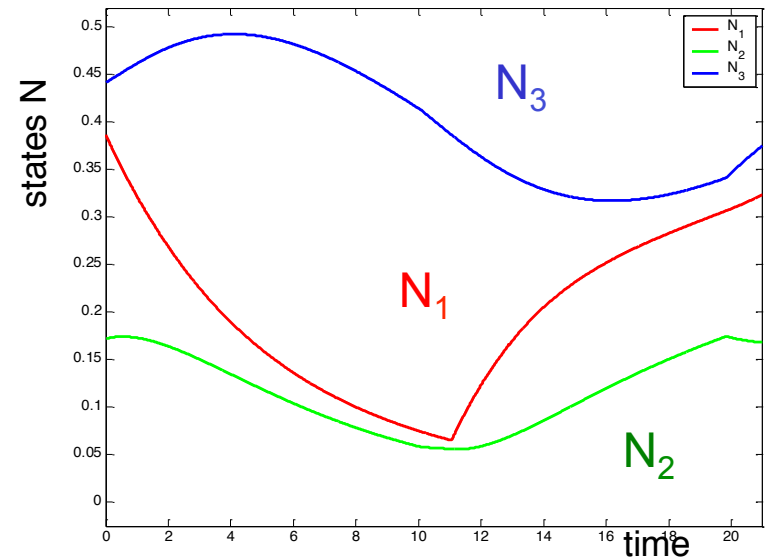
Jacobi condition

Example of an L_1 -optimal Control [SchLMaurer,DCDSB, to appear]



all switchings are
transversal crossings

optimal protocols for **cytotoxic**
and **cytostatic** agents

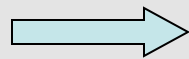


solutions are strong local minima

Extremals for L_2 -type Objective [SchLM, DCDSB, to appear]

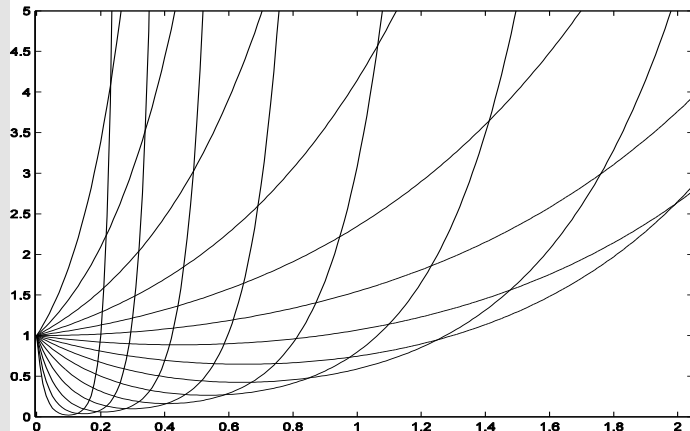
For optimal control problems with L_2 -type objectives,

- controls remain continuous at junctions and **all junctions are transversal crossings**,
- but **conjugate points** are possible along the flow between junctions

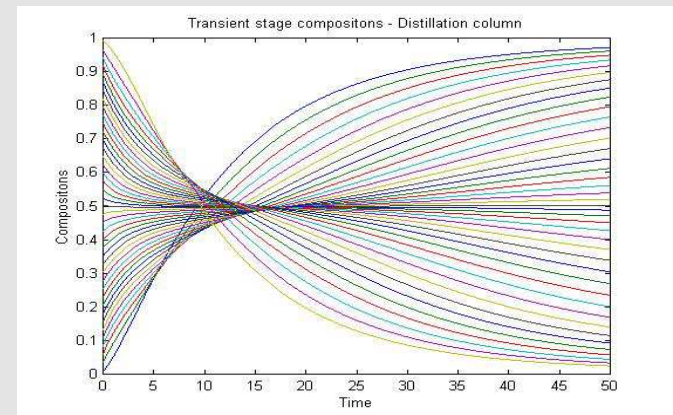


singularities in the flow

fold



simple cusp



Algorithmic Determination

the flow $F(t, p) = (t, N(t, p))$ is local injective



the matrix $\frac{\partial N}{\partial p}(t, p)$ is nonsingular.

equivalently

$$S(t, p) = \frac{\partial \lambda^T}{\partial p}(t, p) \left(\frac{\partial N}{\partial p}(t, p) \right)^{-1}$$

satisfies a **Riccati** differential equation over the full interval without explosion (**conjugate points**)

Jacobi condition

THEOREM

Algorithmic Determination

If there exists a solution S_* to the matrix Riccati differential equation

$$\begin{aligned} \dot{S} + SH_{\lambda^T N} + H_{N\lambda^T} S + H_{NN} \\ - \sum_{j \in J(t)} \frac{1}{\theta_j} (SH_{\lambda^T u_j} + H_{Nu_j}) (SH_{\lambda^T u_j} + H_{Nu_j})^T \equiv 0, \end{aligned}$$

(all partial derivatives are evaluated along the reference extremal Γ_* and $j \in J(t)$ if and only if the j th control u_j takes values in the interior of the control set) with terminal condition $S(T) \equiv 0$

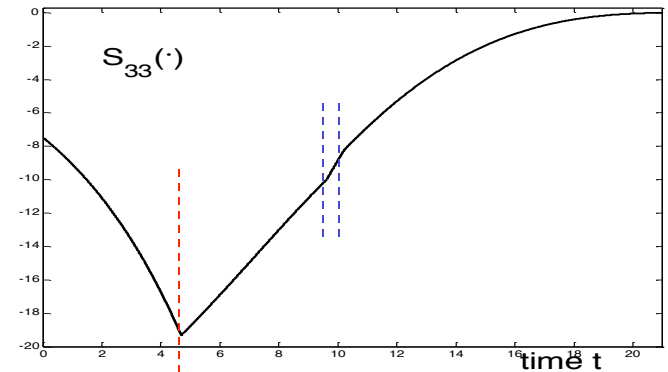
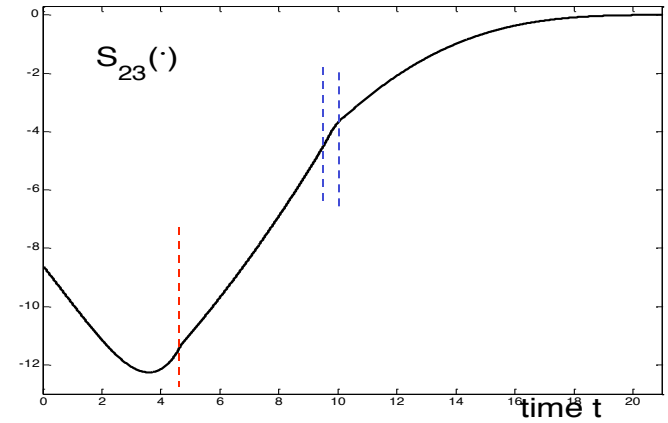
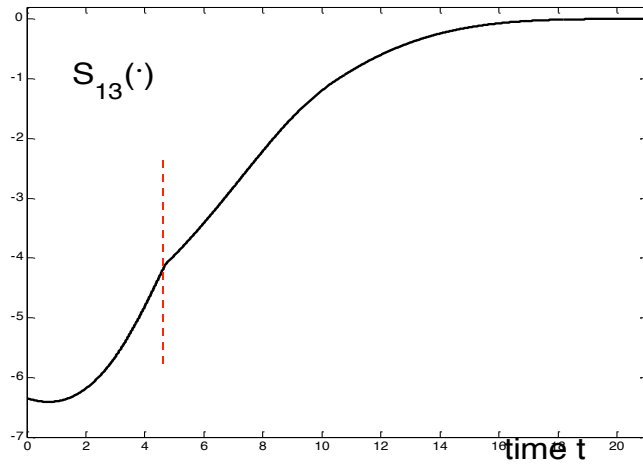
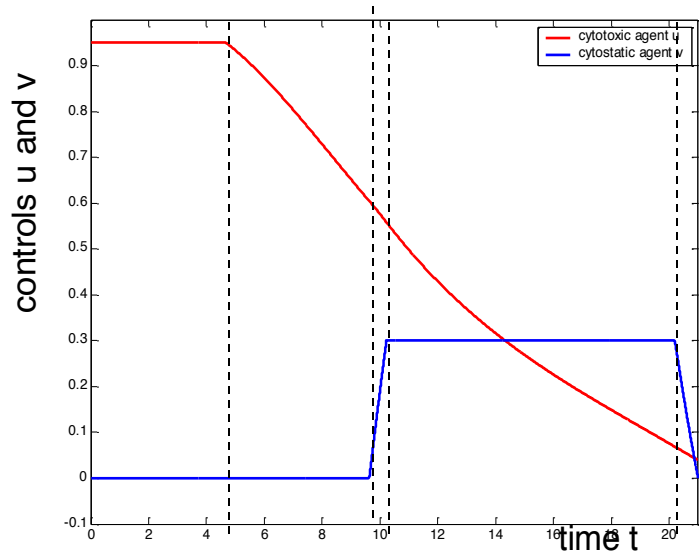
over the full interval $[0, T]$,

then there exists a neighborhood P of $N_*(T)$ such that the flow

$$F(t, p) = (t, N(t, p))$$

restricted to $[0, T] \times P$ is a diffeomorphism and the reference control u_* is a strong local minimum.

Examples for L_2 -optimal Control [SchLM, DCDSB, to appear]



efficient algorithmic procedures to determine the strong local optimality of a reference controlled extremal based on the **method of characteristics** and **mapping properties of the underlying flow**

- **L_1 -problems** : we developed an algorithm that determines whether optimality persists at switching surfaces (**transversal crossing**) or whether optimality ceases (**transversal fold**)
- **L_2 -problems**: following ideas from classical LQ optimal control with no control constraint and following the procedure that was developed for L_1 -problems, we **generalized the Riccati differential equation approach to systems with control constraints**
- applies in greater generality (**terminal constraints, free terminal time**), but becomes more technical to describe

THANK YOU



MERCI