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# Sufficient Conditions for Strong Local Optimality with Applications to Biomedical Problems

Urszula Ledzewicz

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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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# Collaborators and Support



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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

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38  
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Heinz Schättler  
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**

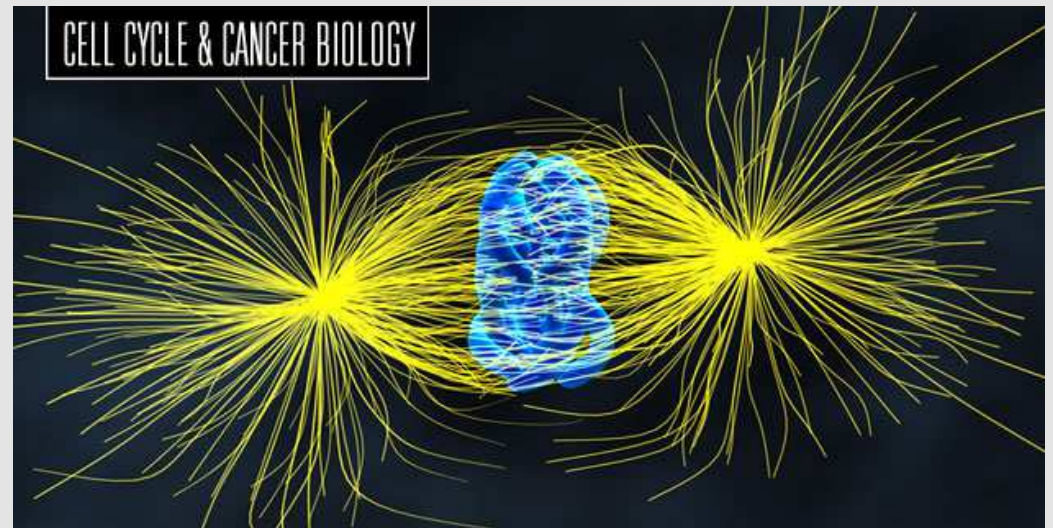
- **Urszula Ledzewicz and Heinz Schättler,**

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

**An Application of Geometric Methods**

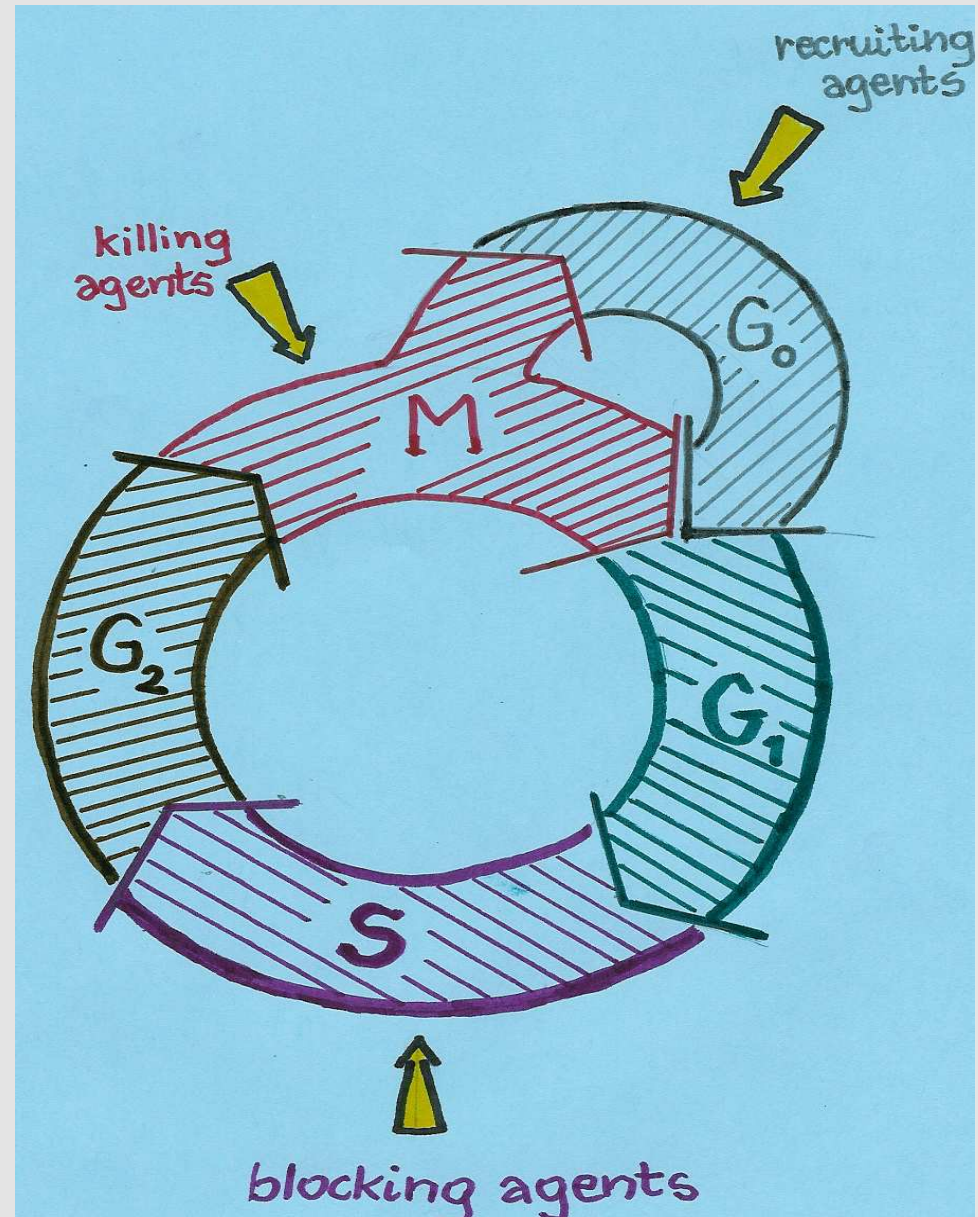
**Springer Verlag, 2015**

# 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 :

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

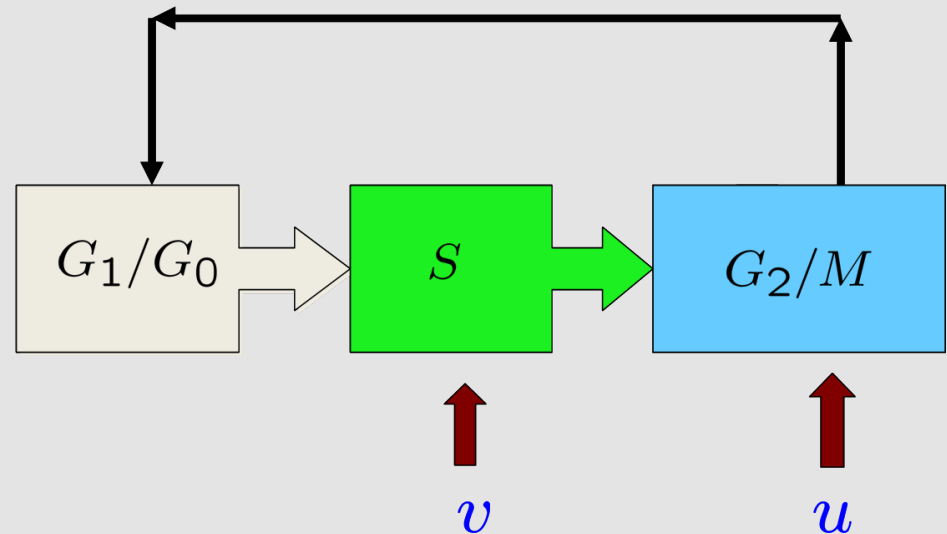
average number of cancer cells  
in respective compartments

- CONTROLS:  $u$  ,  $v$

*represent the dose rates of:*

$u$  - *cytotoxic (killing) agent*

$v$  - *cytostatic (blocking) agent*





# Dynamics

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

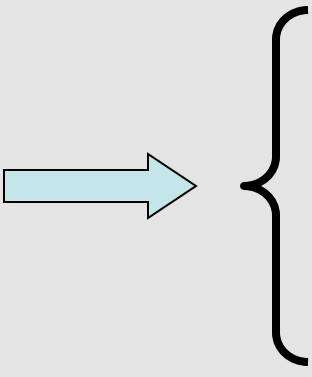
$$0 \leq u \leq 1, \quad 0 \leq v \leq v_{\max} < 1$$

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

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

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

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


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

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

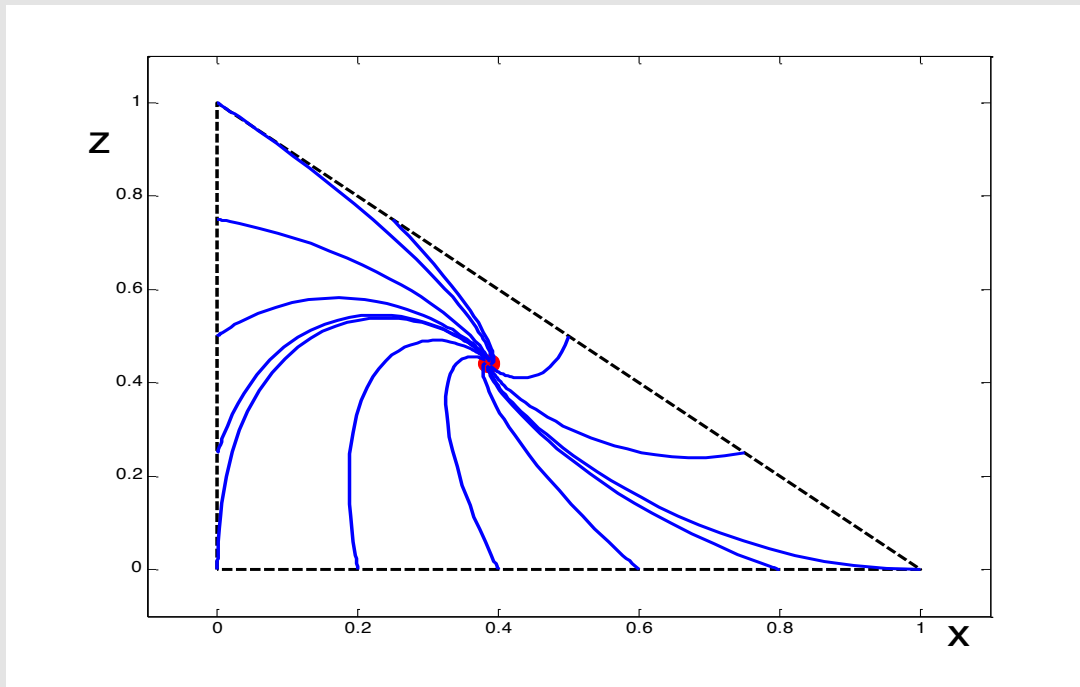
Riccati equations

# Steady State Proportions

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

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

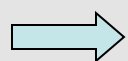
in its region of attraction (independent of cell-cycle coefficients)



**(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

$$J(u) = \underbrace{rN(T)}_{\text{Weighted average of number of cancer cells at end of therapy}} + \underbrace{\int_0^T qN(t)dt}_{\text{Weighted average of cancer cells during therapy}} + \underbrace{\int_0^T \theta_1 u(t) + \theta_2 v(t)dt}_{\text{Total doses given as measure for the toxicity of the drug (side effects on healthy cells)}}$$

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

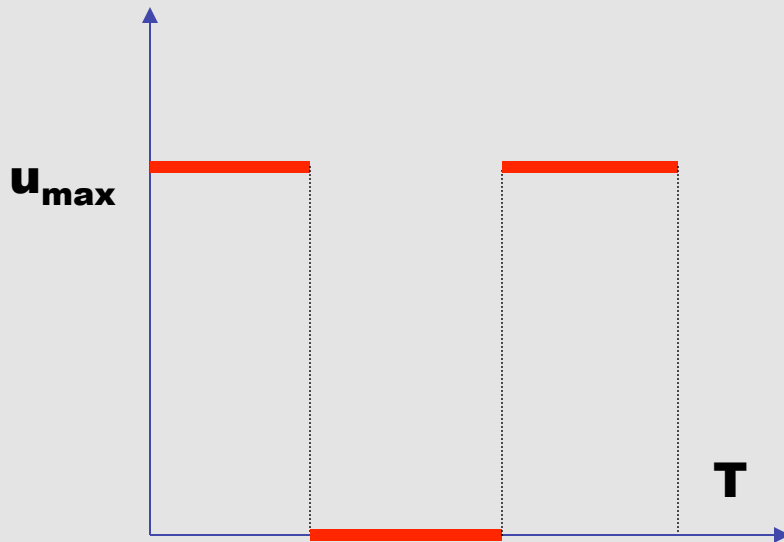
**Weighted average  
of cancer cells  
during therapy**

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

**(side effects on  
healthy cells)**

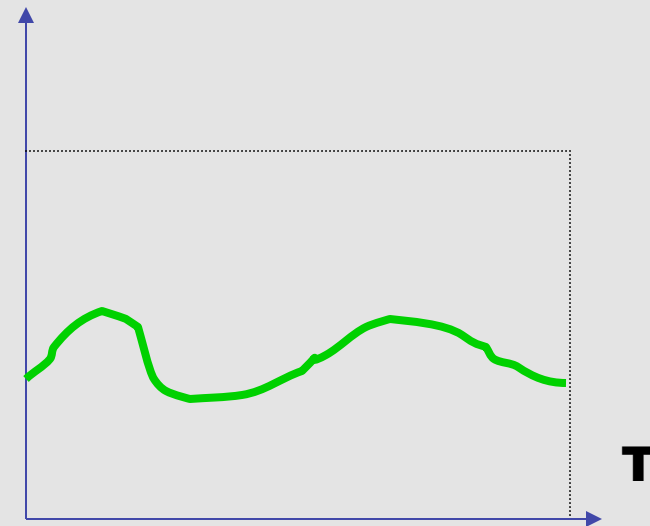
# Candidates for Optimal Protocols

- bang-bang controls



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

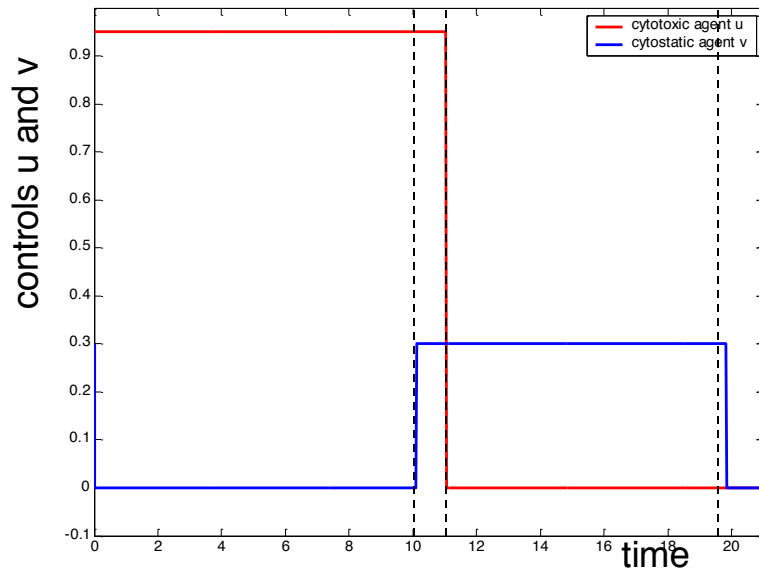
- singular controls



**continuous infusions of varying lower doses**

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

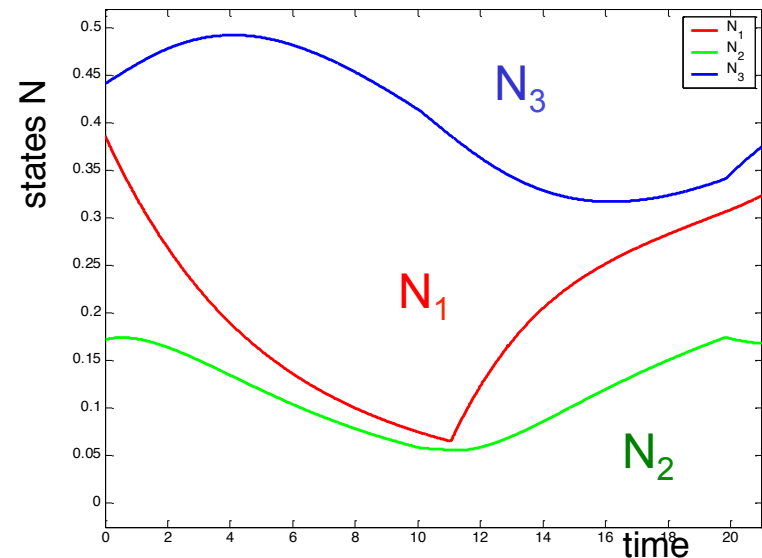
# Example of an $L_1$ -(optimal) Control [SchLMaurer,DCDSB, to appear]



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

corresponding trajectories

**OPTIMALITY?**



# Mathematical Model: L<sub>2</sub>-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**

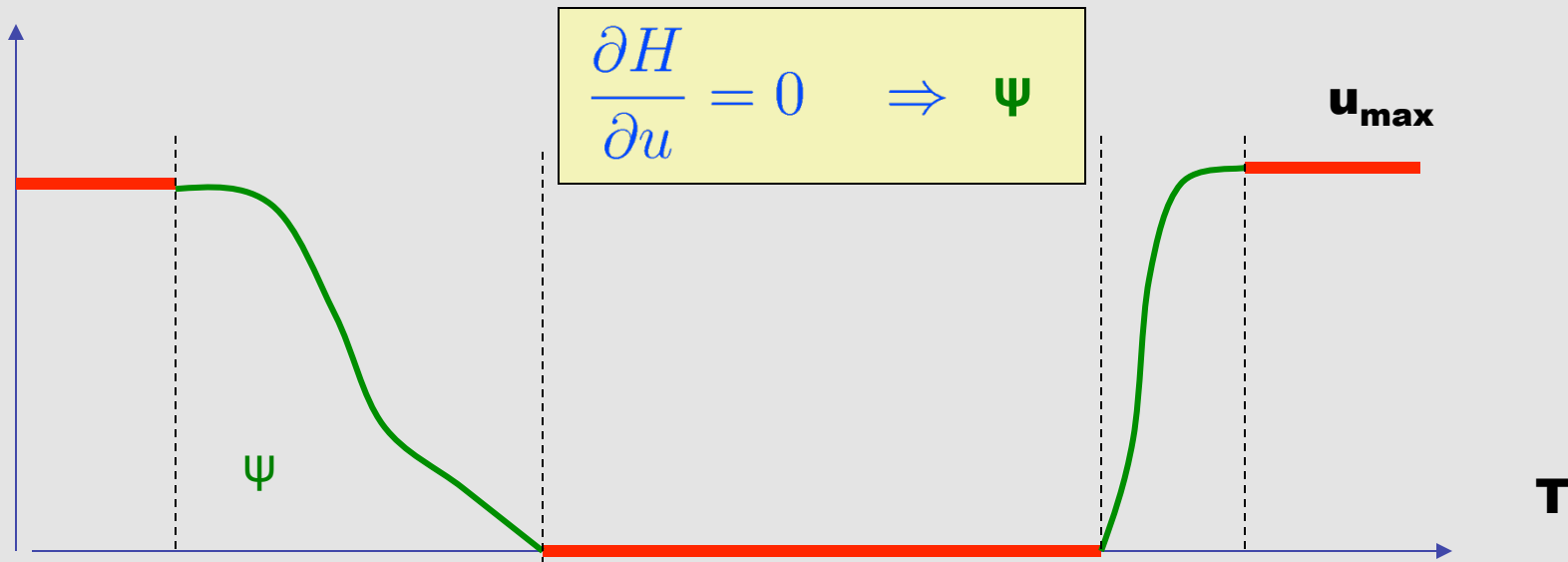
**Distorted measure for  
side effects on healthy  
cells**



induces a strictly convex structure in the Hamiltonian

# Candidates for Optimal Protocols

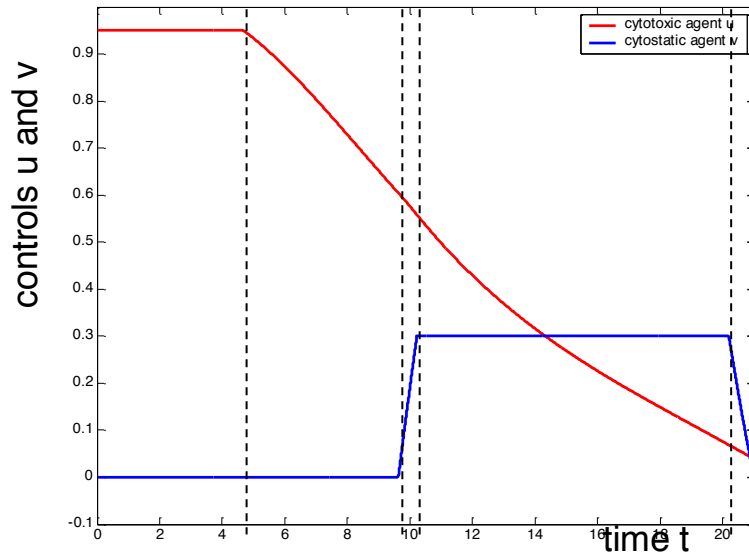
- Concatenations of **constant** controls with controls that take values in the **interior** of the control set and connect continuously with the constant segments



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

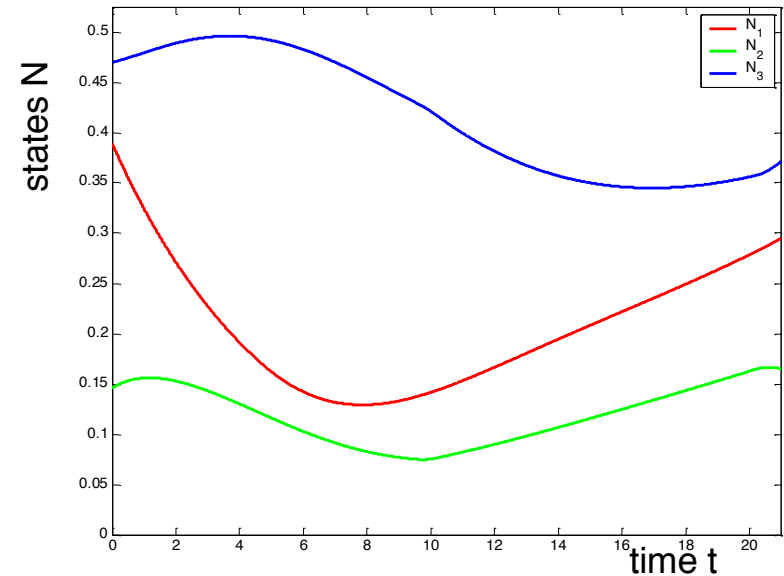


# Example of an $L_2$ -(optimal) Control [SchLMaurer,DCDSB, to appear]



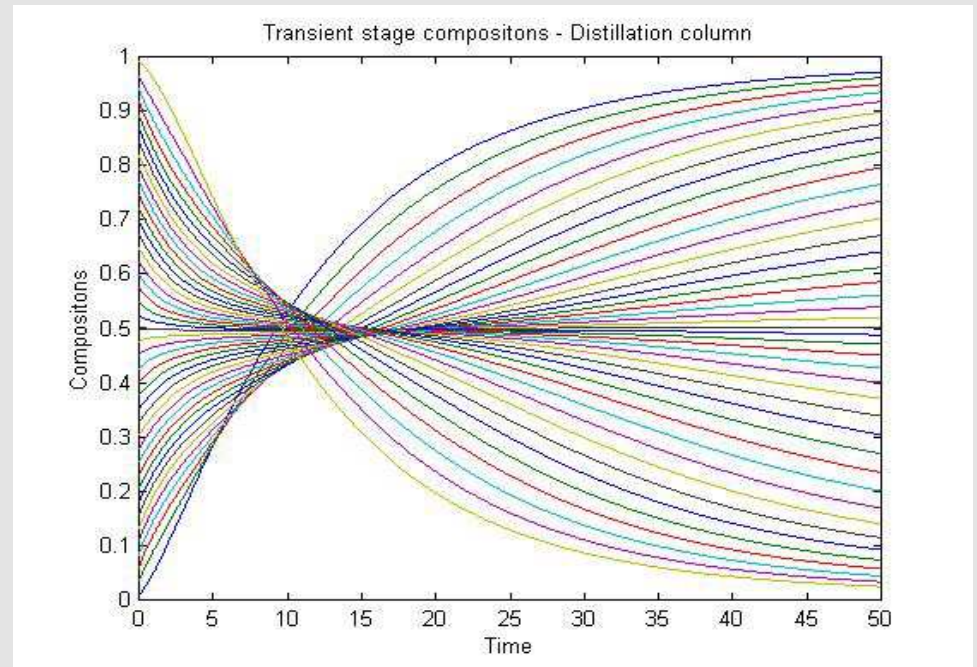
optimal protocols for **cytotoxic**  
and **cytostatic** agents

corresponding trajectories



**OPTIMALITY ?**

# Strong Local Optimality for $L_1$ - and $L_2$ -type Objectives



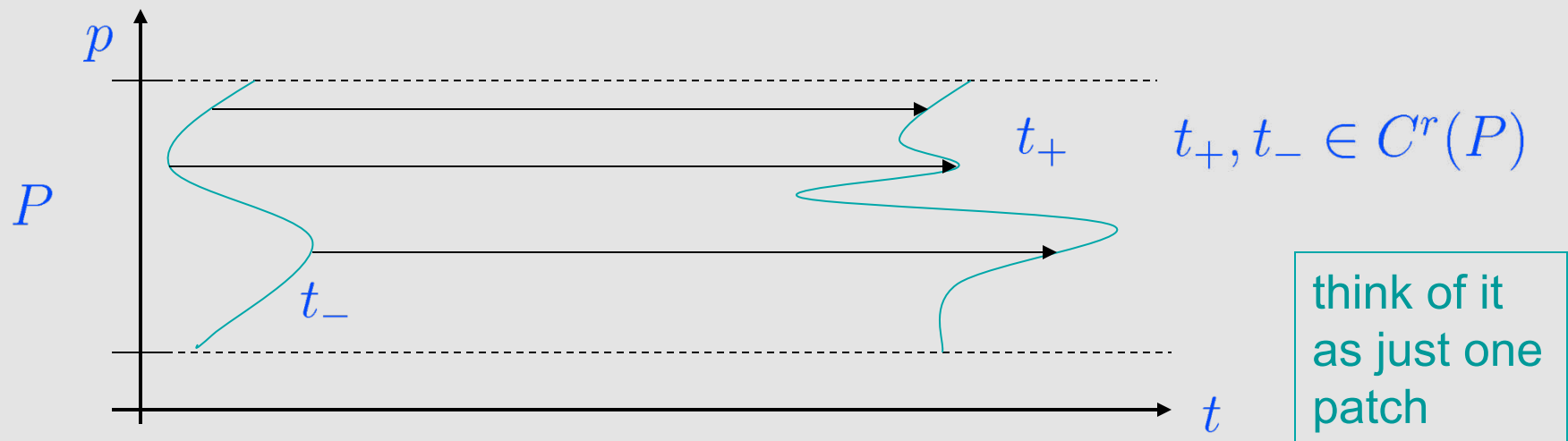
# Parameterized Families of Extremals

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

that satisfy the conditions of the maximum principle with

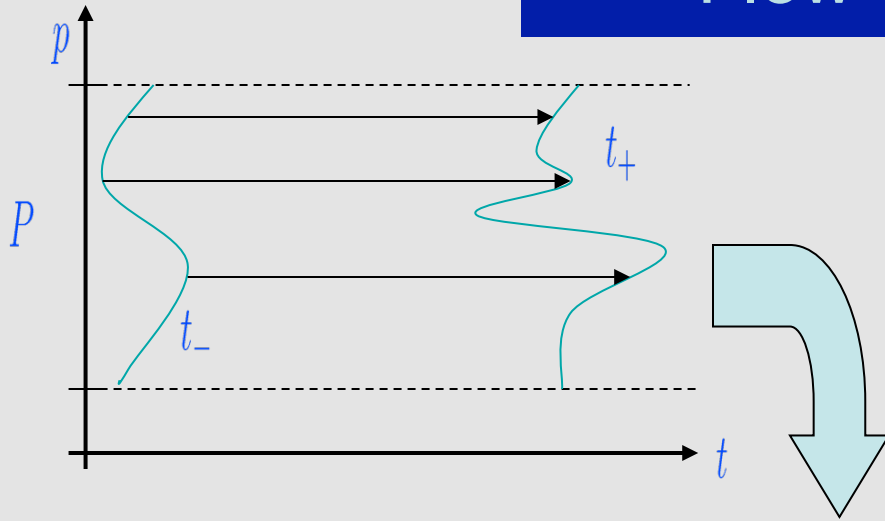
corresponding **multiplier**  $\lambda(t, p)$  over some domain

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



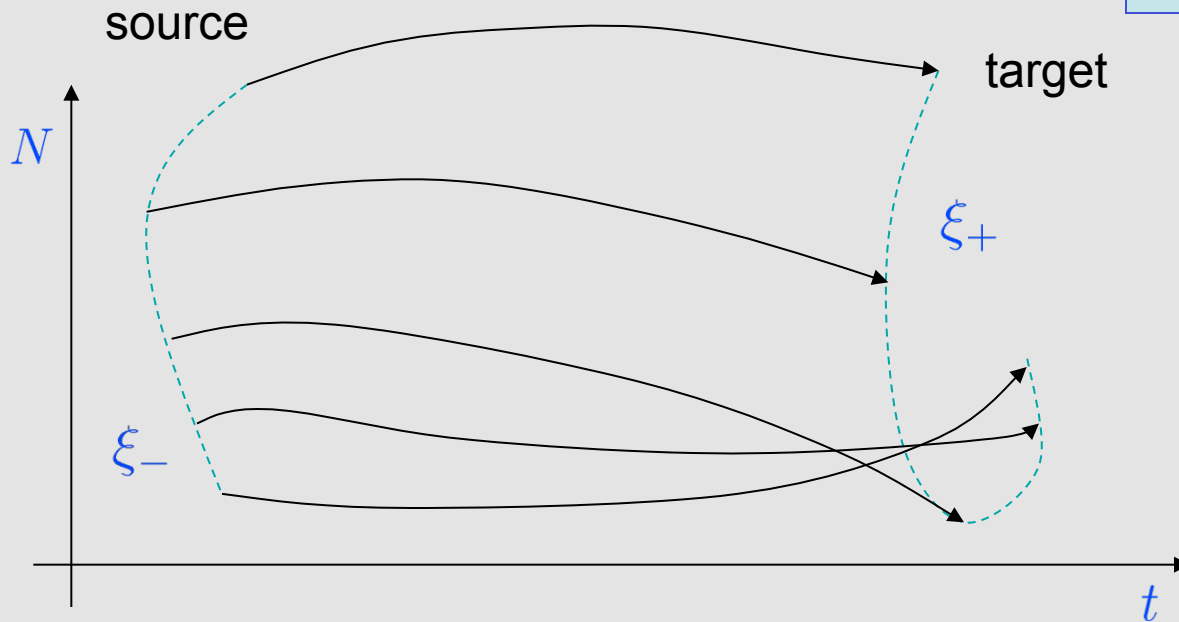
**assume:**  $u(t, p)$  is continuous and  $C^r$  in  $p$

# 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**

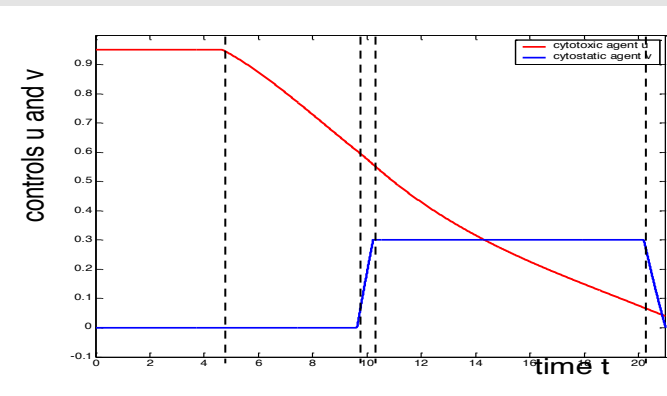
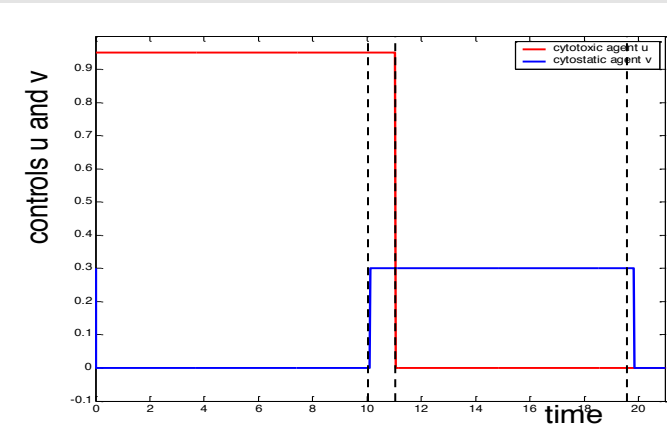
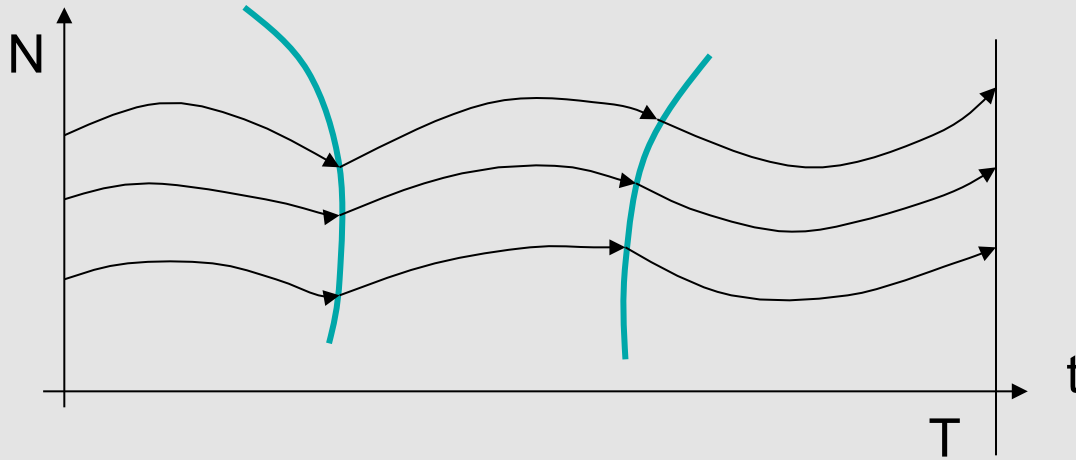
$$\xi_-(p) = N(t_-(p), p)$$

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

# 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

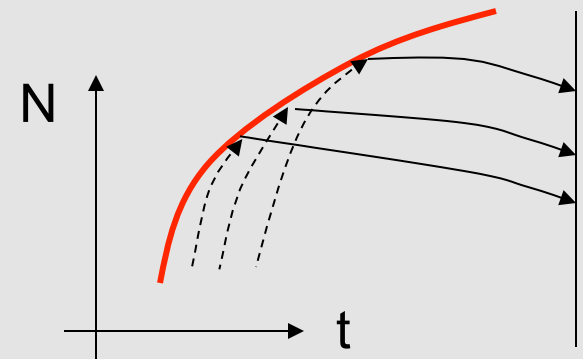
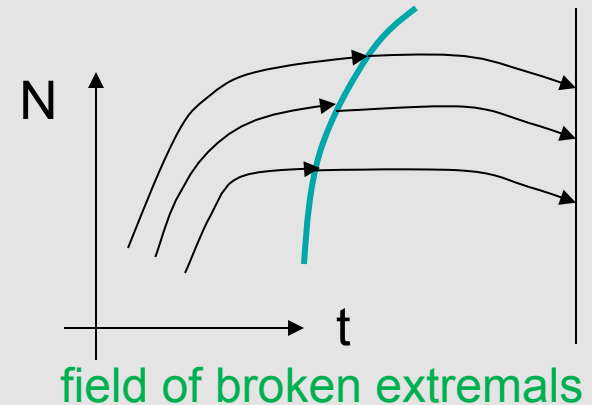
allows to construct a local solution of the Hamilton-Jacobi-Bellman equation

⇒ optimality is preserved

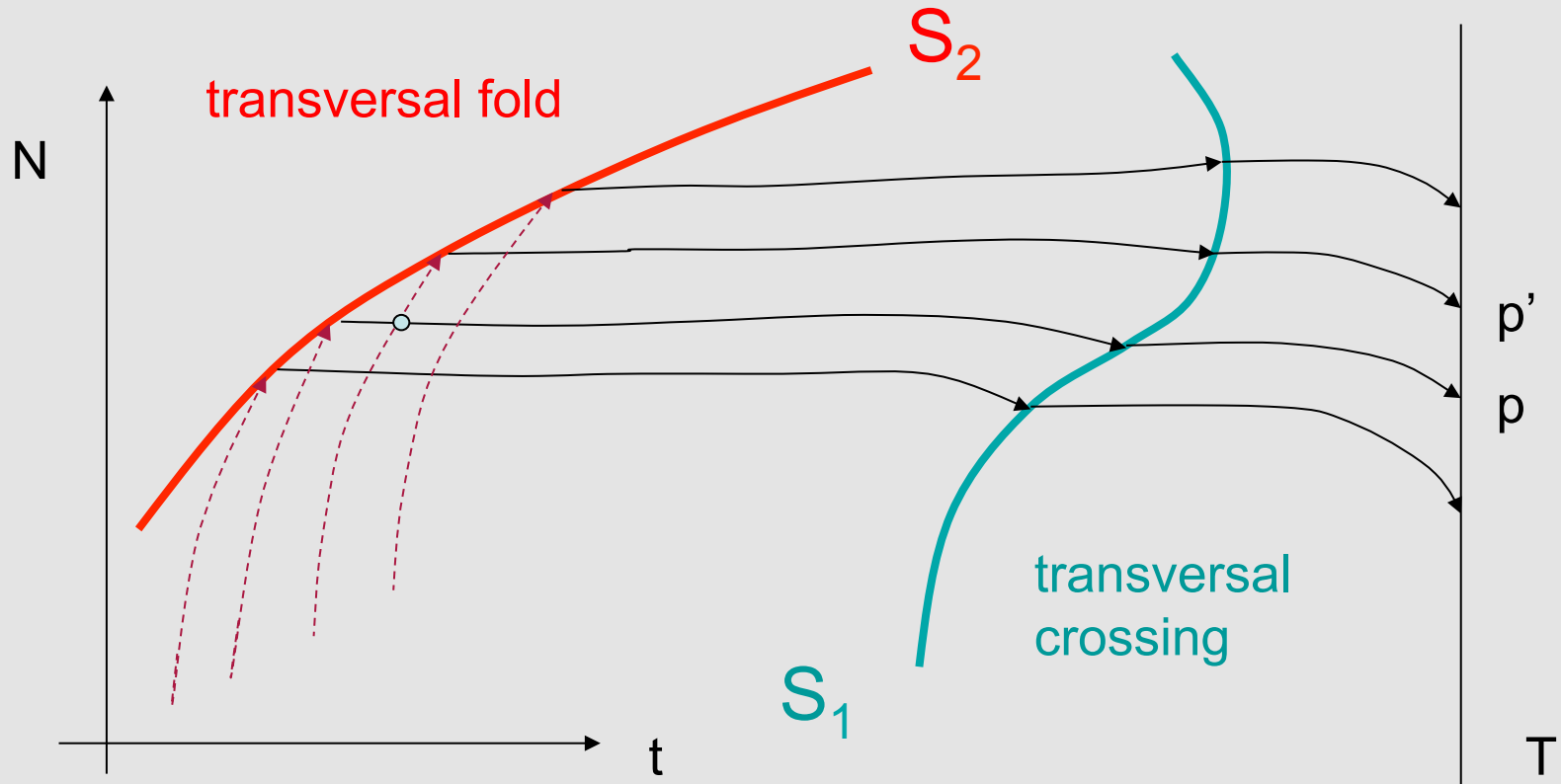
transversal fold

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

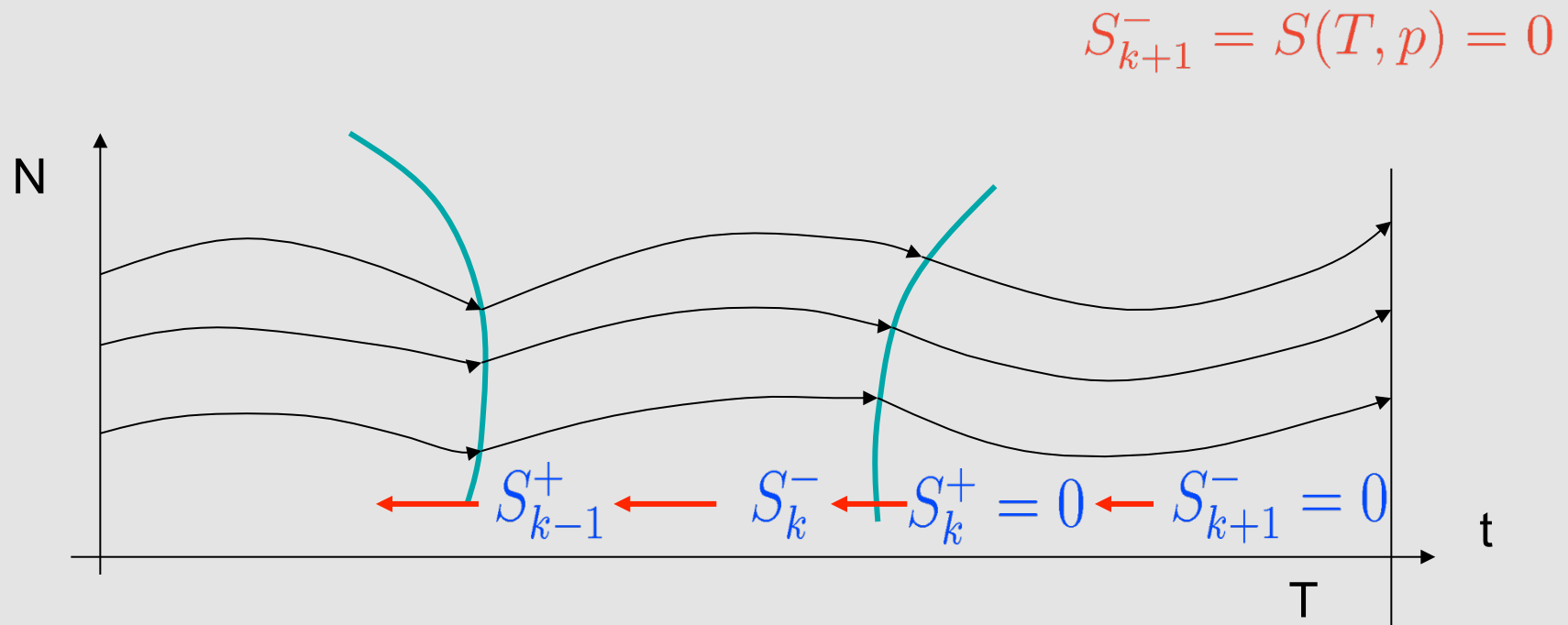
$$\lambda(T, p) \equiv r \quad \text{and} \quad N(T, p) = p$$

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**

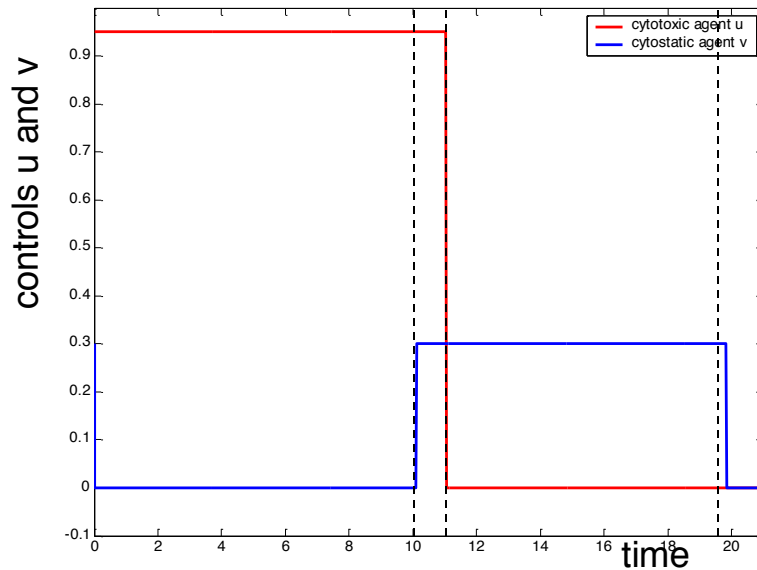
If, for  $i = k, k-1, \dots, 1$ , we have that

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

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

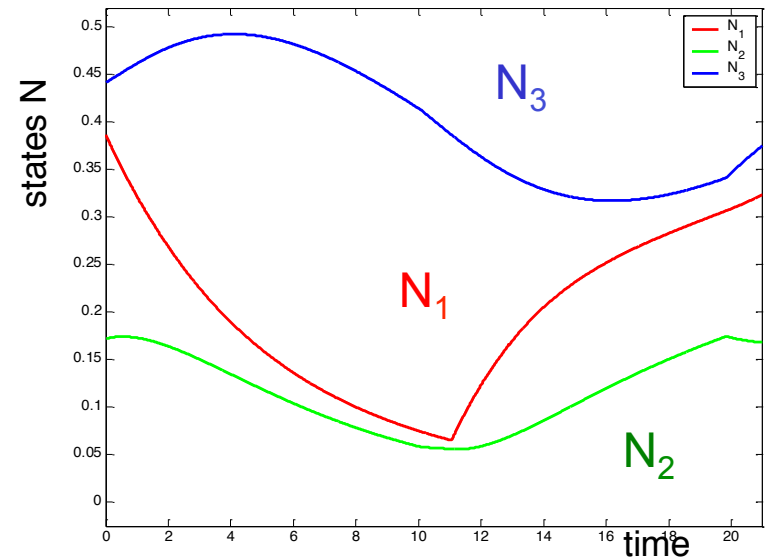
**Jacobi condition**

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



all switchings are  
transversal crossings

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

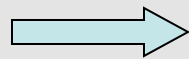


solutions are strong local minima

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

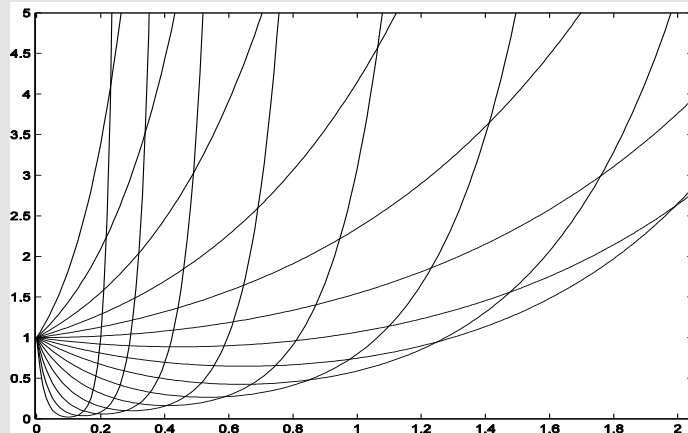
For optimal control problems with  $L_2$ -type objectives,

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

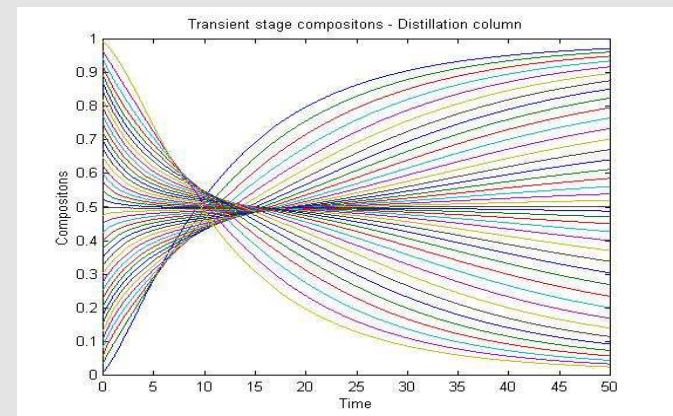


**singularities in the flow**

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**

# Algorithmic Determination

## THEOREM

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

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

(all partial derivatives are evaluated along the reference extremal  $\Gamma_*$  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  $S(T) \equiv 0$

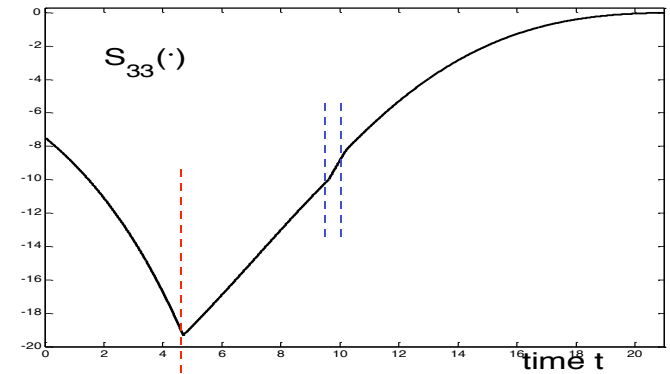
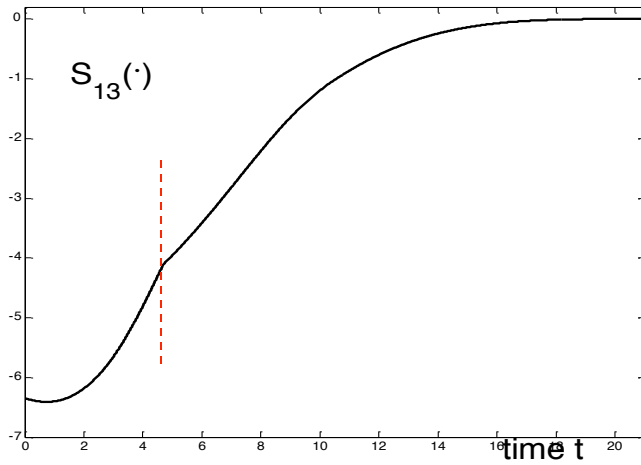
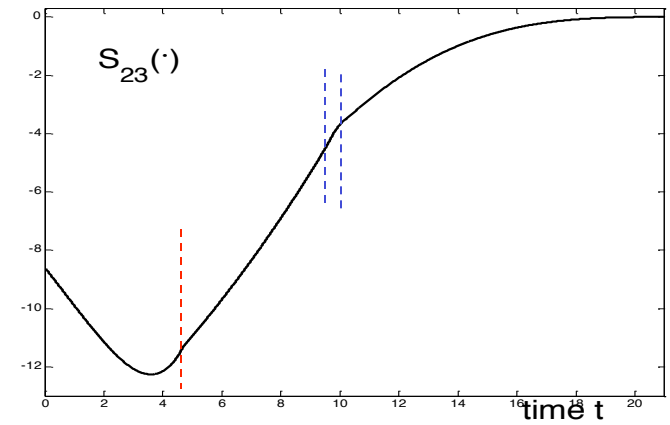
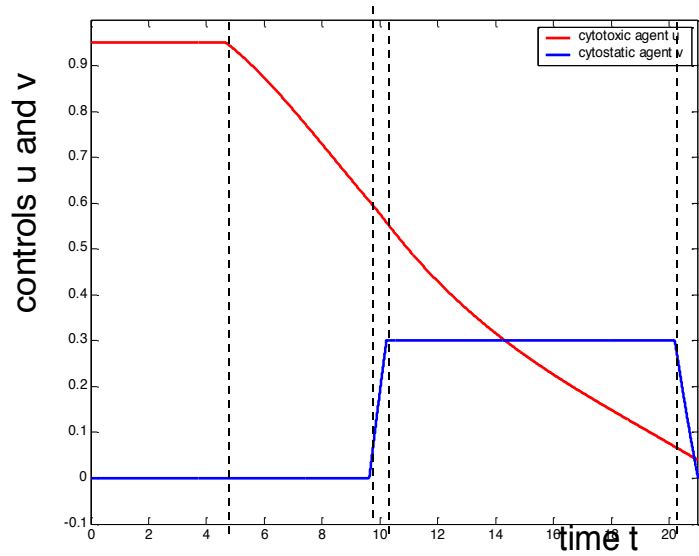
over the full interval  $[0, T]$ ,

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