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Optimal Control Problems for Mathematical Models of Cancer Treatments

Heinz Schaettler, Urszula Ledzewicz

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Optimal Control Problems for Mathematical Models of Cancer Treatments

NetCO 2014

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



**Heinz Schättler
Washington University
St. Louis, Mo, USA**

**Urszula Ledzewicz
Southern Illinois University
Edwardsville, Il, USA**

Collaborators and Support



Urszula Ledzewicz

**Southern Illinois University
Edwardsville, IL USA**



Helmut Maurer

**Rheinisch Westfälische
Wilhelms-Universität Münster,
Münster, Germany**



Andrzej Swierniak

**Silesian University of Technology,
Gliwice, Poland**

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Medical Advice



Alberto d'Onofrio

**European Institute for Oncology, Milano, Italy
& International Prevention Research Institute,
Eculy, France**



Nicolas André

**Childrens Hospital La Timone,
Marseille France**

Eddy Pasquier

**Children Cancer Institute Australia,
University of New South Wales, Sydney**



Mathematical Models For Cancer Treatments



What Kind of Models?

trend in **biological research** is to make models as complete and accurate as possible



“large” mathematical model that generally make an analysis impossible, but use numerical methods and techniques

advantage • realism and accuracy

disadvantage

- size and number of parameters
- limited validity of numerical results and conclusions

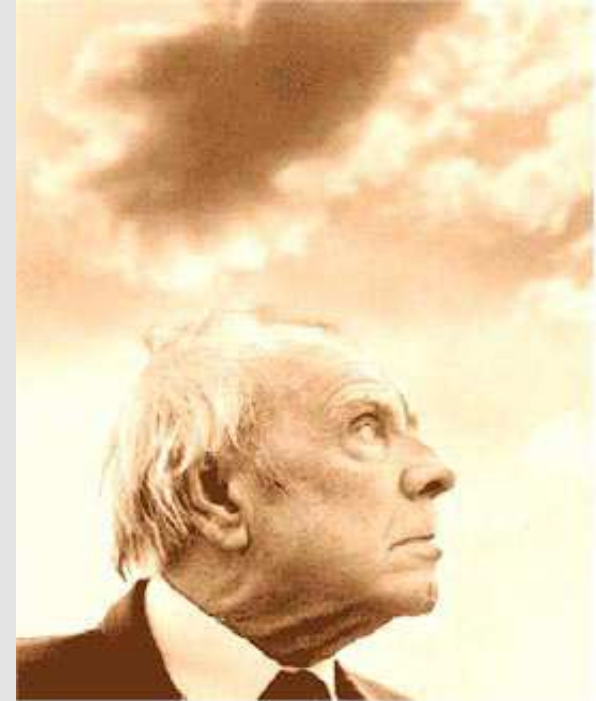
On Exactitude in Science

Jorge Luis Borges, *Collected Fictions*,

translated by Andrew Hurley

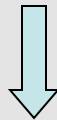
...In that Empire, the Art of Cartography attained such Perfection that the map of a single Province occupied the entirety of a City, and the map of the Empire, the entirety of a Province. In time, those Unconscionable Maps no longer satisfied, and the Cartographers Guilds struck a Map of the Empire whose size was that of the Empire, and which coincided point for point with it. The following Generations, who were not so fond of the Study of Cartography as their Forebears had been, saw that that vast Map was Useless, and not without some Pitilessness was it, that they delivered it up to the Inclemencies of Sun and Winters. In the Deserts of the West, still today, there are Tattered Ruins of that Map, inhabited by Animals and Beggars; in all the Land there is no other Relic of the Disciplines of Geography.

—Suarez Miranda, *Viajes devarones prudentes*, Libro IV,
Cap. XLV, Lerida, 1658



What Kind of Models?

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- size and number of parameters
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in medical research there also is an increasing interest in **minimally parameterized models**



disadvantage

- only a qualitative (if you want “crude”) approximation of reality

advantage

- just a few parameters
- enables use of analytical methods
- robust conclusions and interpretations

Main Questions

HOW MUCH?

(dosage)

HOW OFTEN?

(timing)

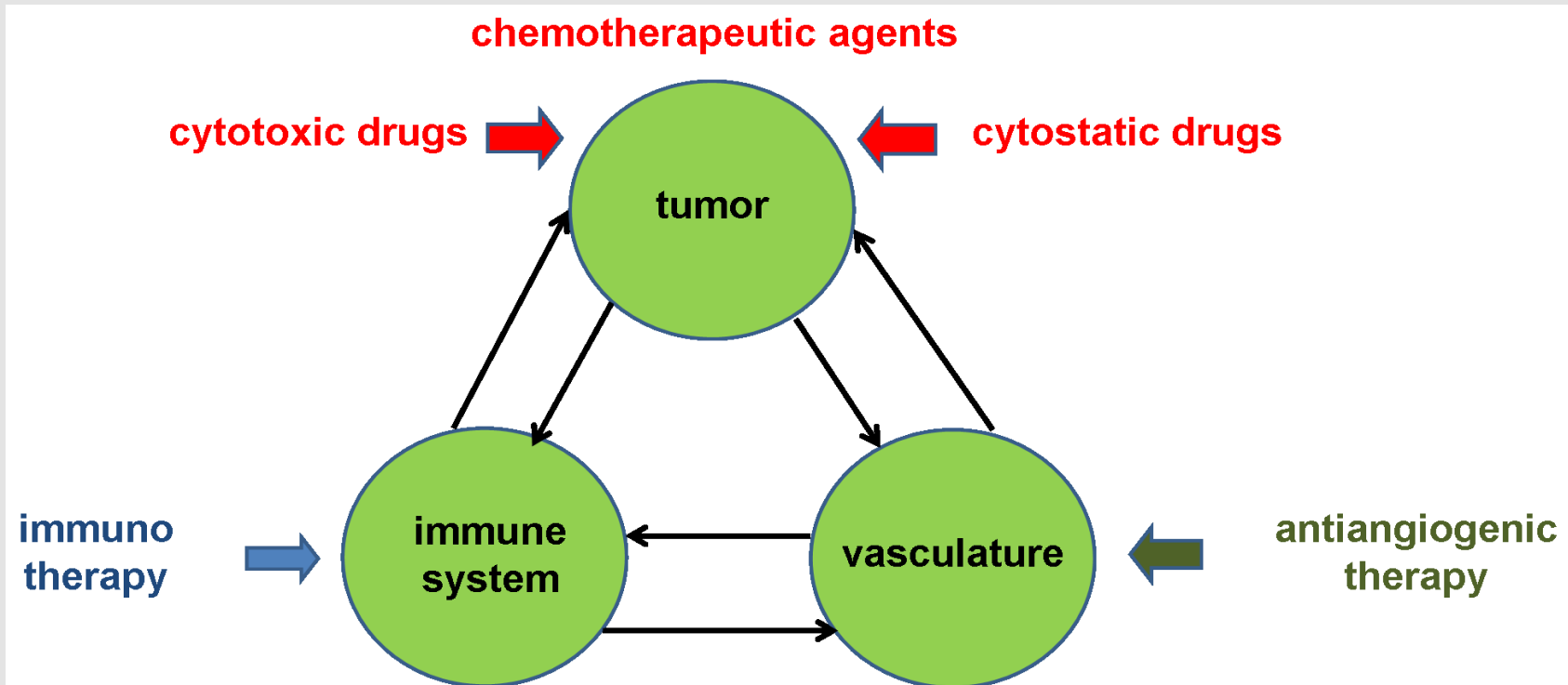
IN WHAT ORDER?

(sequencing)

→ are really “optimal control” type questions

What can **mathematical analysis** contribute?

Tumor Microenvironment



How to optimize the anti-tumor, anti-angiogenic and pro-immune effects of chemotherapy by modulating dose and administration schedule?



Tumor Metronomics: Timing and Dose Level Dynamics

July 17-20, 2012

Tufts University
Medford Campus
Boston, Massachusetts, USA

www.oanocer-systems-biology.org/workshop.html

Instructors

Philip Hahnfeldt, PhD - Tufts University School of Medicine, USA (Co-chair)

Giannoula Klement, MD - Tufts University School of Medicine, USA (Co-chair)

Nicolas André, MD, PhD - Hôpital pour Enfants de la Timone, FR

Sébastien Benzekry, PhD - Tufts University School of Medicine, USA

Barton Kamen, MD, PhD - UMDNJ, Robert Wood Johnson Medical School, USA

Urszula Ledzewicz, PhD - Southern Illinois University, USA

Carl Panetta, PhD - St. Jude Children's Research Hospital, USA

Eddy Pasquier, PhD - CCIA, University of New South Wales, AUS

Heinz Schaettler, PhD - Washington University in St. Louis, USA

David Waxman, PhD - Boston University School of Medicine, USA

Guest Speaker

Larry Norton, MD - Memorial Sloan-Kettering Cancer Center, USA



**More is Not
Necessarily Better**
Metronomic
Chemotherapy,

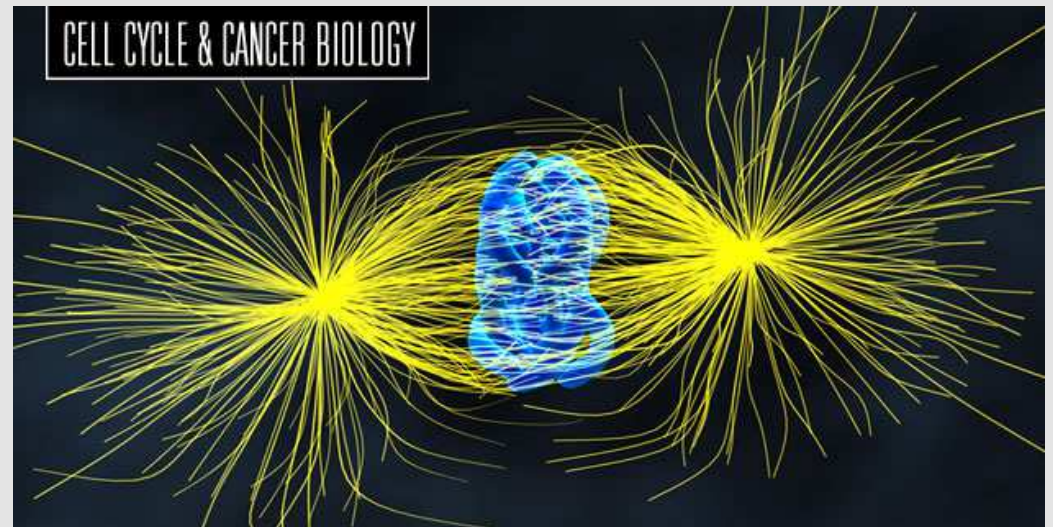
Eddy Pasquier and
Urszula Ledzewicz,

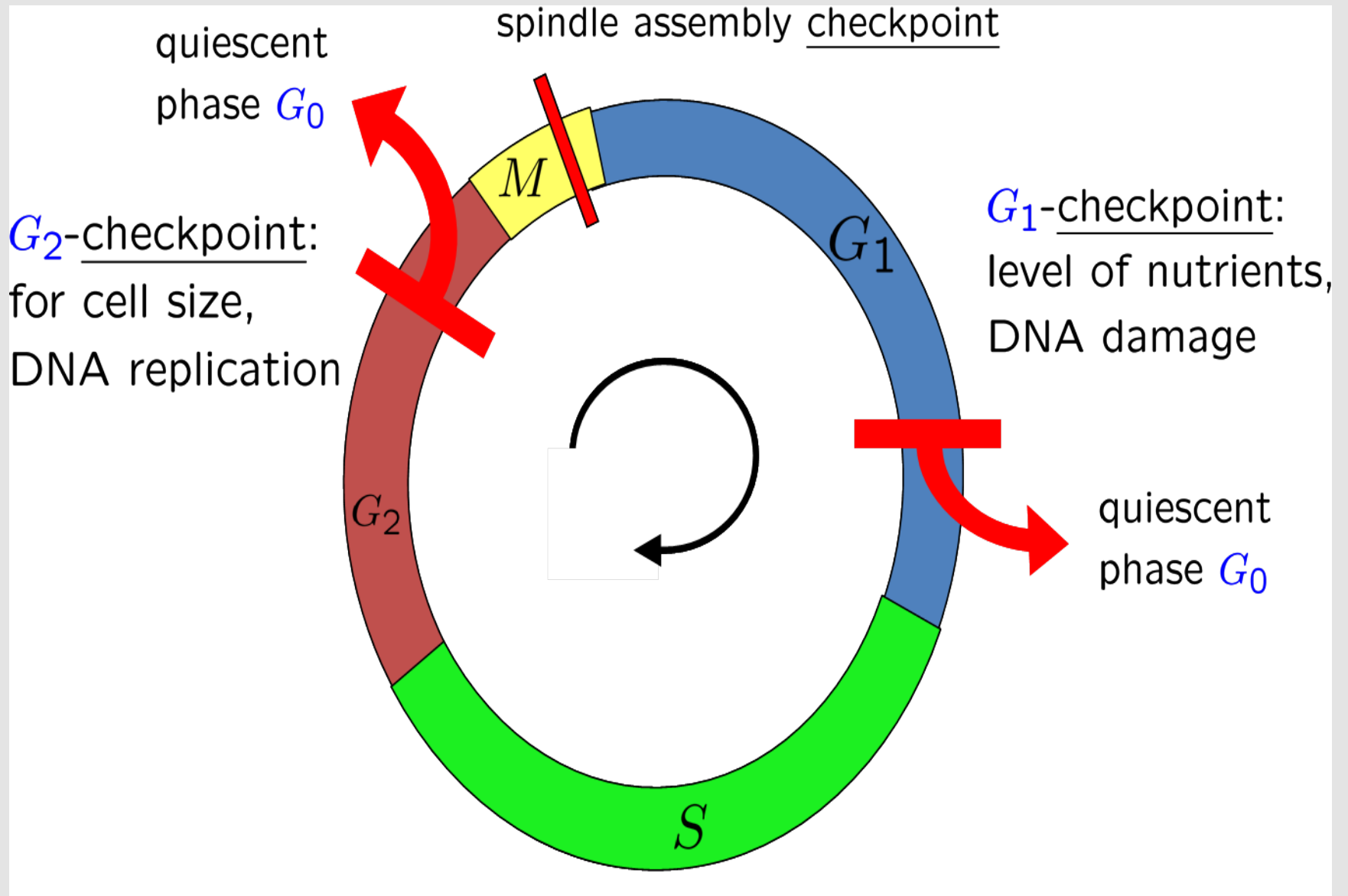
Newsletter of the Society
for Mathematical Biology,
Vol. 26, No.2, 2013

Sponsored by

The Integrative Cancer Biology Program of the National Cancer Institute, NIH
Center of Cancer Systems Biology, Steward St. Elizabeth's Medical Center
Tufts University School of Medicine

Cell-Cycle Specific Models for Multi-Drug Chemotherapy





Compartmental models: Dynamics

- **COMPARTMENTS :**
clusters of phases of cell-cycle or different types of chemotherapeutically sensitive cells
- **STATES :** $\mathbf{N} = (N_1 , \dots , N_n)$
represent the average numbers of (cancer) cells in the corresponding compartments
- **CONTROLS :** $\mathbf{u} = (u_1 , \dots , u_r)$
represent the drug dose rates/ concentrations/ effects of various drugs

values in compact intervals

- **DYNAMICS:** *describes the changes in the average number of cancer cells in the compartments*

$$\dot{N} = \left(A + \sum_{i=1}^r u_i B_i \right) N$$

$$A, B_i \in \mathbb{R}^{n \times n} \quad i = 1, \dots, r$$

$$a_i \leq u_i \leq b_i$$

(Swierniak, Ledzewicz, Schättler 2003)

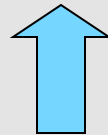
Mathematical Model: L_1 -type Objective

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

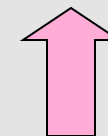
$$J(u) = \underbrace{rN(T)} + \underbrace{\int_0^T qN(t)dt} + \underbrace{\int_0^T \ell u(t)dt}$$



**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)**

Maximum Principle: Necessary Conditions for Optimality

define the Hamiltonian H as

$$H = qN + \lambda AN + \sum_{j=1}^m (\ell_j + \lambda B_j N) u_j$$

→ there exists a solution λ to the adjoint equation

$$\dot{\lambda} = -\frac{\partial H}{\partial N} = -q - \lambda(A + \sum_{j=1}^m u_j B_j), \quad \lambda(T) = r,$$

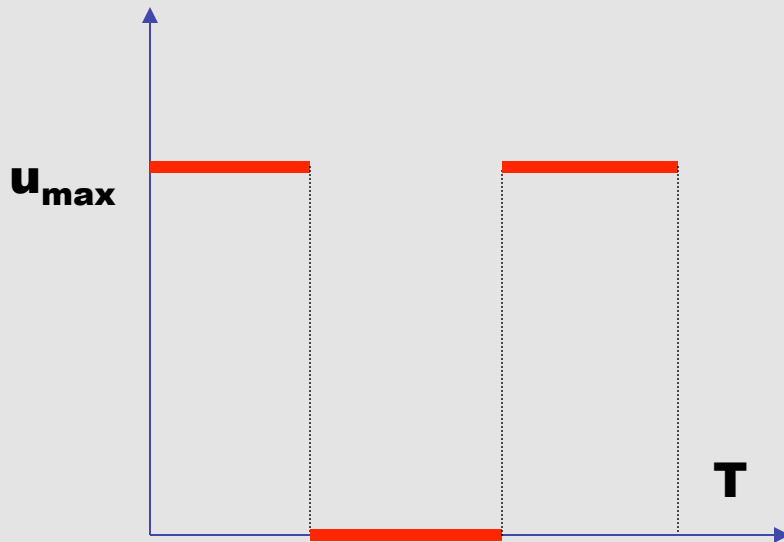
such that the optimal controls minimize the Hamiltonian H along (N_*, λ)

switching functions: $\Phi_j(t) = \ell_j + \lambda(t)B_j N(t)$

→
$$u_j^*(t) = \begin{cases} 0 & \text{if } \Phi_j(t) > 0 \\ ? & \text{if } \Phi_j(t) = 0 \\ u_{\max} & \text{if } \Phi_j(t) < 0 \end{cases}$$

Candidates for Optimal Protocols

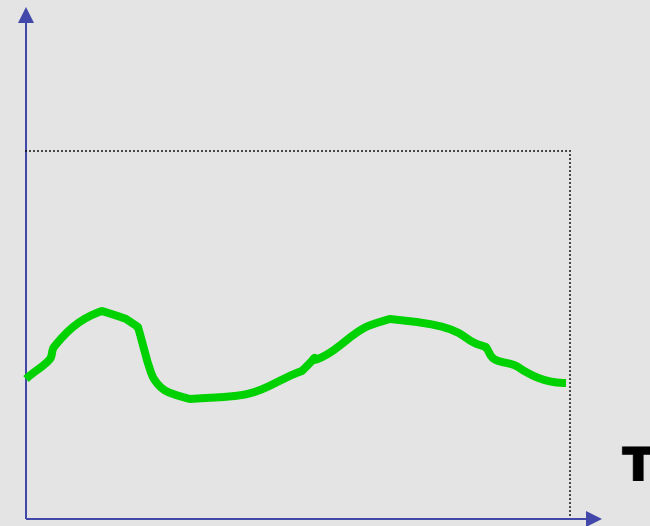
- bang-bang controls



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

MTD

- singular controls



continuous infusions of varying lower doses

BOD

Singular Controls and High-Order Necessary Conditions for Optimality

- u_j^* is singular on an open interval $I \iff \Phi_j(t) \equiv 0$
- all time derivatives must vanish as well
- “allows” to compute the singular control
- “order” k : the control appears for the first time in the $2k^{\text{th}}$ derivative
- **Generalized Legendre-Clebsch condition** for a single-input minimization problem

$$(-1)^k \frac{\partial}{\partial u} \frac{d^{2k}}{dt^{2k}} \frac{\partial H}{\partial u} \geq 0$$

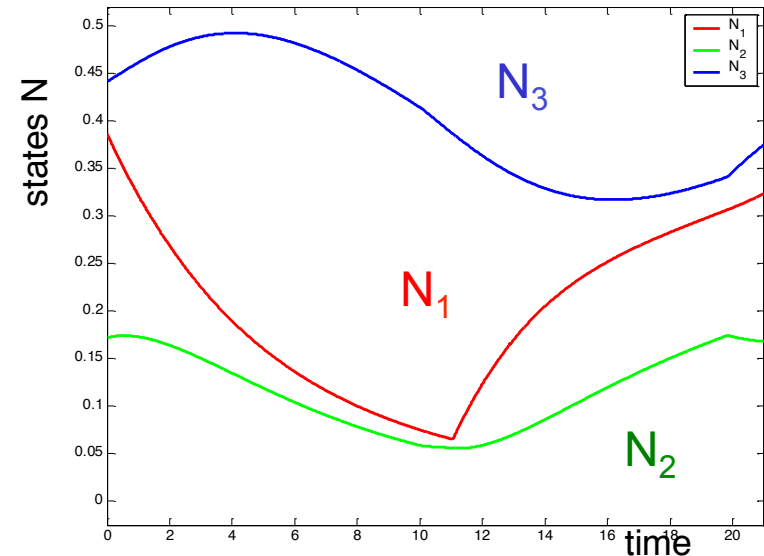
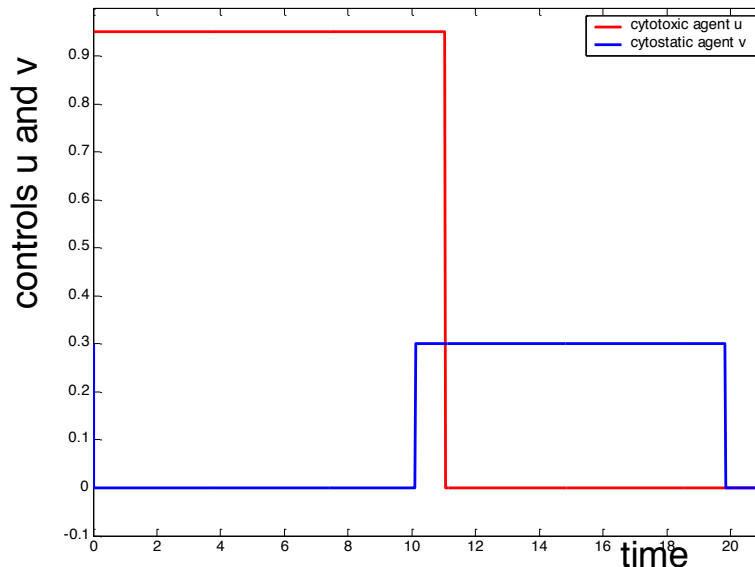
- **Goh condition** for a multi-input problems: if the controls u_i^* and u_j^* are simultaneously singular, then

$$\frac{\partial}{\partial u_i} \frac{d}{dt} \frac{\partial H}{\partial u_j} \equiv 0$$

Analysis of Mathematical Models for Tumor Only

- for **homogeneous** tumor populations consisting of **chemotherapeutically sensitive** cells, bang-bang controls (full dose chemotherapy with rest periods) are optimal and drugs are given up-front

“MTD (maximum tolerated dose)”



Analysis of Mathematical Models for Tumor Only

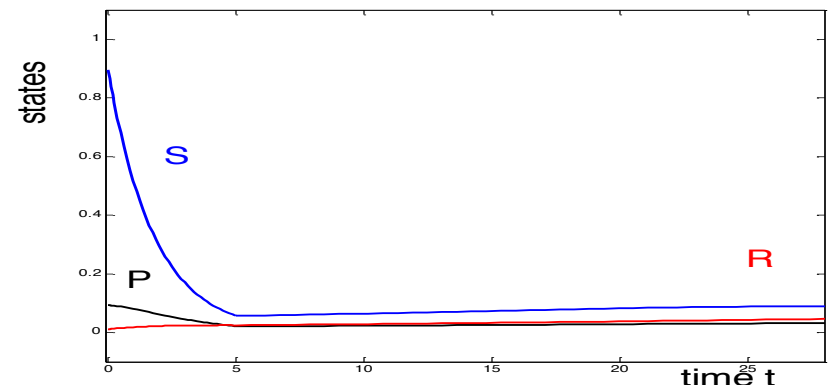
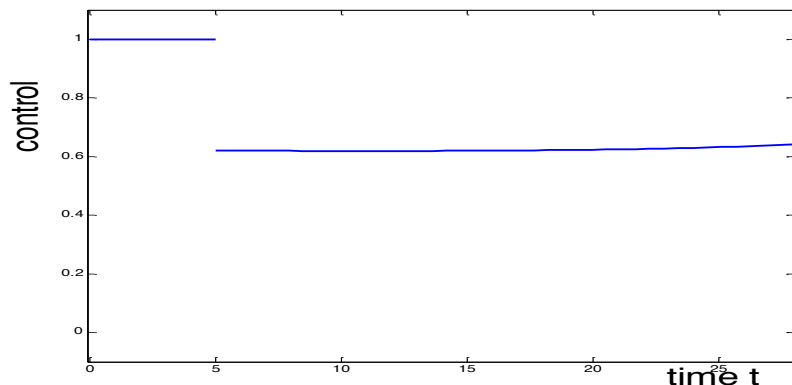
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“MTD (maximum tolerated dose)”

- for **heterogeneous** populations (differing drug sensitivities, drug resistance are taken into account), as the amount of resistant cells increases, singular controls (lower dose administrations) become viable candidates

lower dose protocols to balance benefit and harm

“chemo-switch” protocols



Analysis of Mathematical Models for Tumor Only

- for **homogeneous** tumor populations consisting of **chemotherapeutically sensitive** cells, bang-bang controls (full dose chemotherapy with rest periods) are optimal and drugs are given up-front

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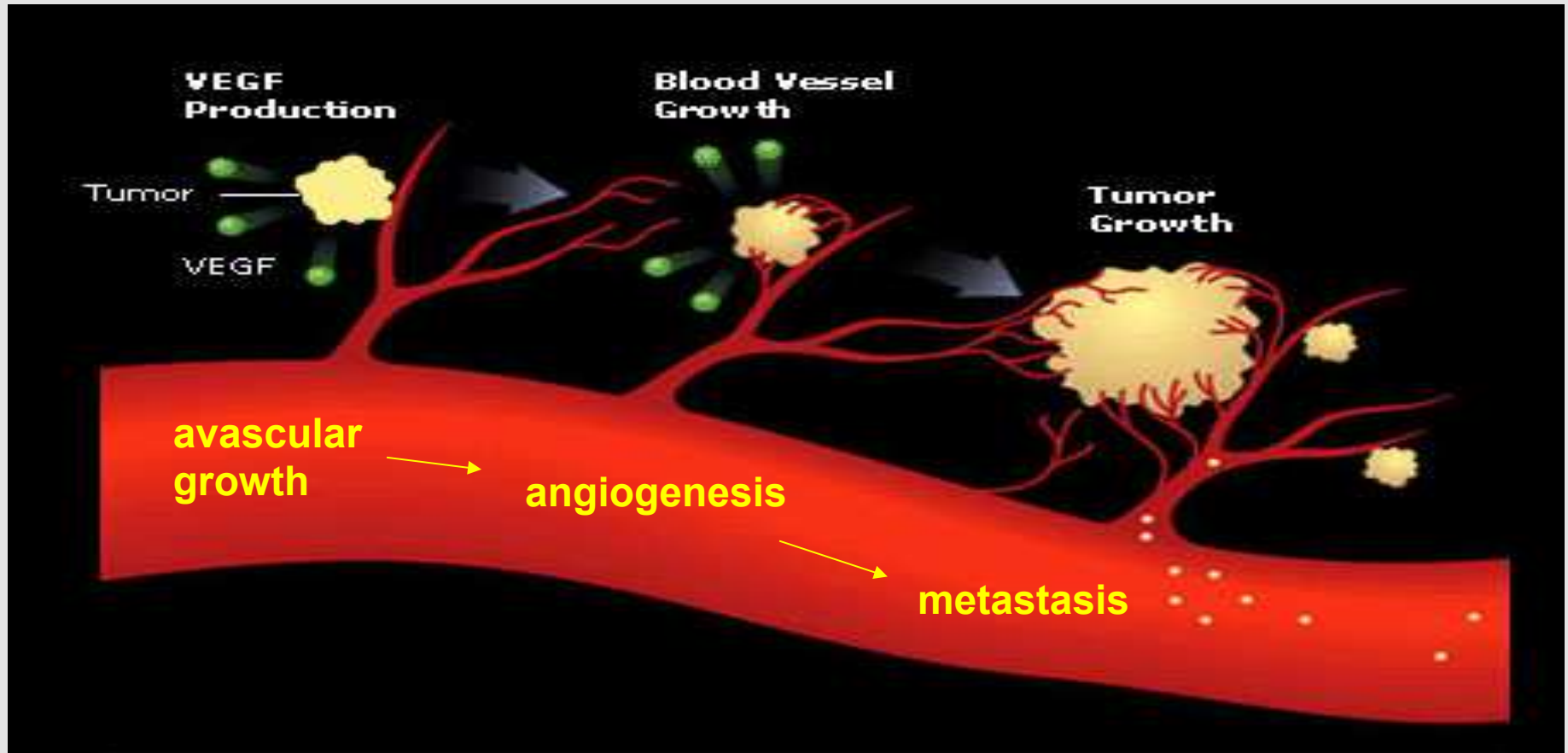
lower dose protocols to balance benefit and harm

“chemo-switch protocols”

- as drug resistance becomes too strong (dominant), chemotherapy can only delay the inevitable

other options (?)

Tumor Angiogenesis



[Hahnfeldt, Panigrahy, Folkman, Hlatky], *Cancer Research*, 1999

$$\dot{p} = -\xi p \ln \left(\frac{p}{q} \right),$$

$$\dot{q} = bp - (\mu + dp^{\frac{2}{3}})q - \gamma uq,$$

p – tumor volume

q – carrying capacity

u – anti-angiogenic
dose rate

p, q – volumes in mm^3

ξ - tumor growth parameter

b - endogenous stimulation (birth)

d - endogenous inhibition (death)

γ - anti-angiogenic inhibition parameter

μ - natural death

biological data for
Lewis lung carcinoma
implanted in mice

Optimal Control Problem [Ergun, Camphausen, Wein] *Bull. Math. Biol.*, 2003

For a free terminal time T **minimize** $p(T)$

over all functions $u : [0, T] \rightarrow [0, u_{\max}]$ that satisfy

$$\int_0^T u(t) dt \leq A$$

subject to the dynamics

$$\dot{p} = -\xi p \ln \left(\frac{p}{q} \right), \quad p(0) = p_0,$$

$$\dot{q} = bp - \left(\mu + dp^{\frac{2}{3}} \right) q - \gamma u q, \quad q(0) = q_0,$$

Dynamics in Vector Form

$$x = (p, q, y)^T$$

$$\dot{x} = f(x) + u g(x)$$

drift

control vector field

$$f(x) = \begin{pmatrix} -\xi p \ln\left(\frac{p}{q}\right) \\ bp - (\mu + dp^{\frac{2}{3}})q \\ 0 \end{pmatrix} \quad g(x) = \begin{pmatrix} 0 \\ -\gamma q \\ 1 \end{pmatrix}$$

Switching function $\Phi(t) = \langle \lambda(t), g(z(t)) \rangle$

Lie bracket: $[f, g](x) = Dg(x)f(x) - Df(x)g(x)$

Singular control

If u_* is singular on an open interval I , then

$$\Phi(t) = \langle \lambda(t), g(z(t)) \rangle \equiv 0 \longrightarrow \lambda_2(t) > 0$$

$$\dot{\Phi}(t) = \langle \lambda(t), [f, g]z(t) \rangle \equiv 0$$

$$\ddot{\Phi}(t) = \langle \lambda(t), [f + u_*g, [f, g]]z(t) \rangle \equiv 0.$$

$$-\frac{\partial}{\partial u} \frac{d^2}{dt^2} \frac{\partial H}{\partial u} = -\langle \lambda(t), [g, [f, g]]z(t) \rangle \equiv \lambda_2(t)b\gamma^2p(t) > 0.$$

order 1 singular control

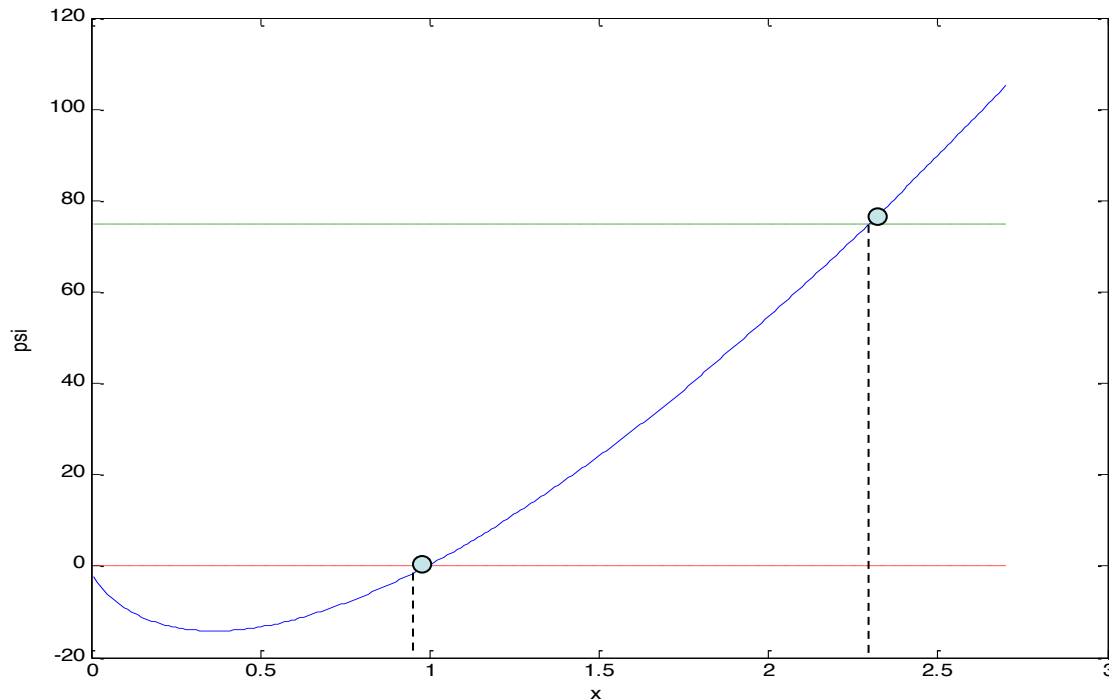
strengthened Legendre-Clebsch
condition is satisfied

$$u_{\text{sing}}(t) = -\frac{\langle \lambda(t), [f, [f, g]]z(t) \rangle}{\langle \lambda(t), [g, [f, g]]z(t) \rangle}$$

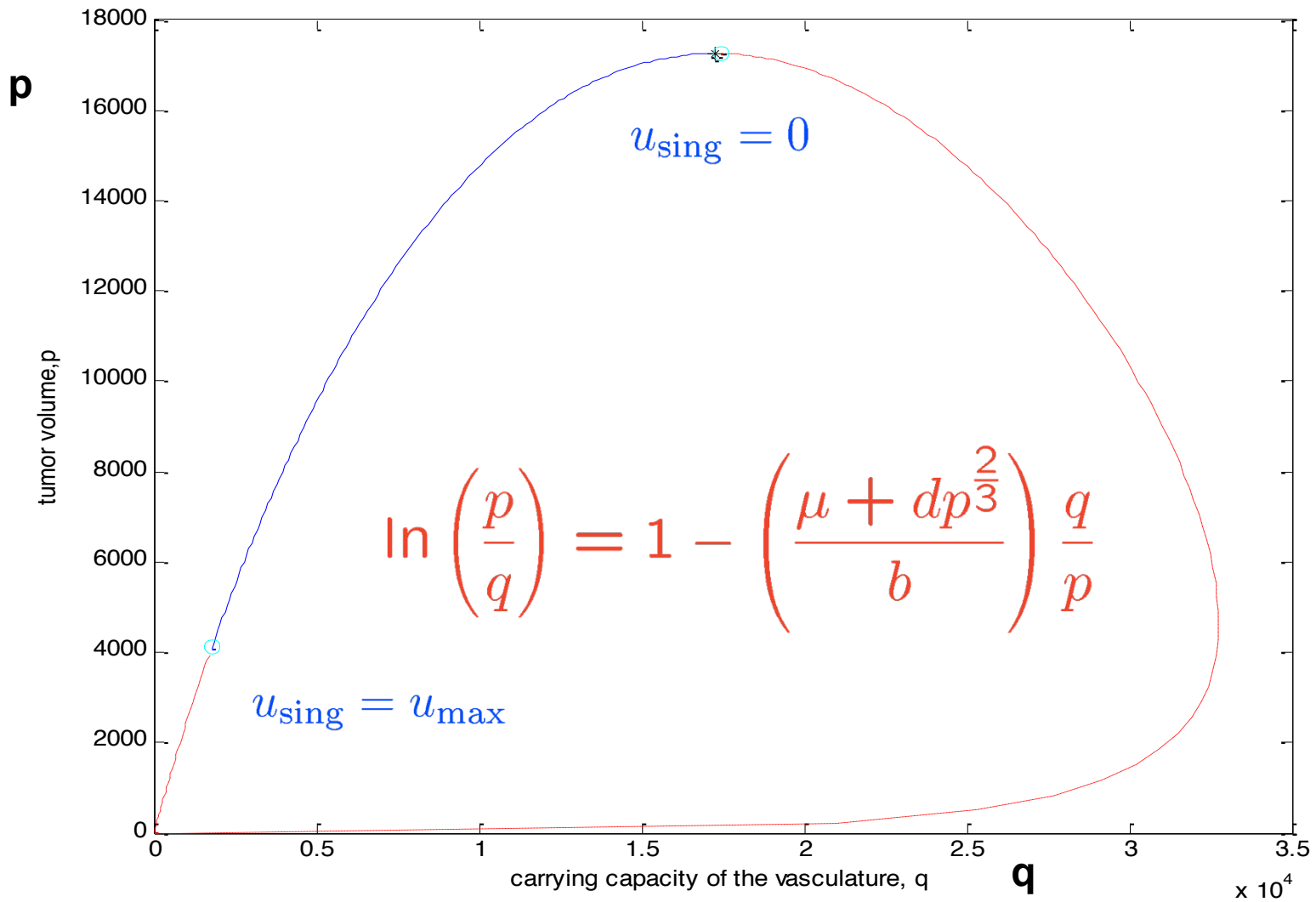
Singular Control

$$u_{\text{sing}}(x) = \frac{1}{\gamma} \left[\left(\frac{1}{3}\xi + bx \right) \ln x + \frac{2}{3}\xi \left(1 - \frac{\mu}{bx} \right) \right], \quad x = \frac{p}{q}$$

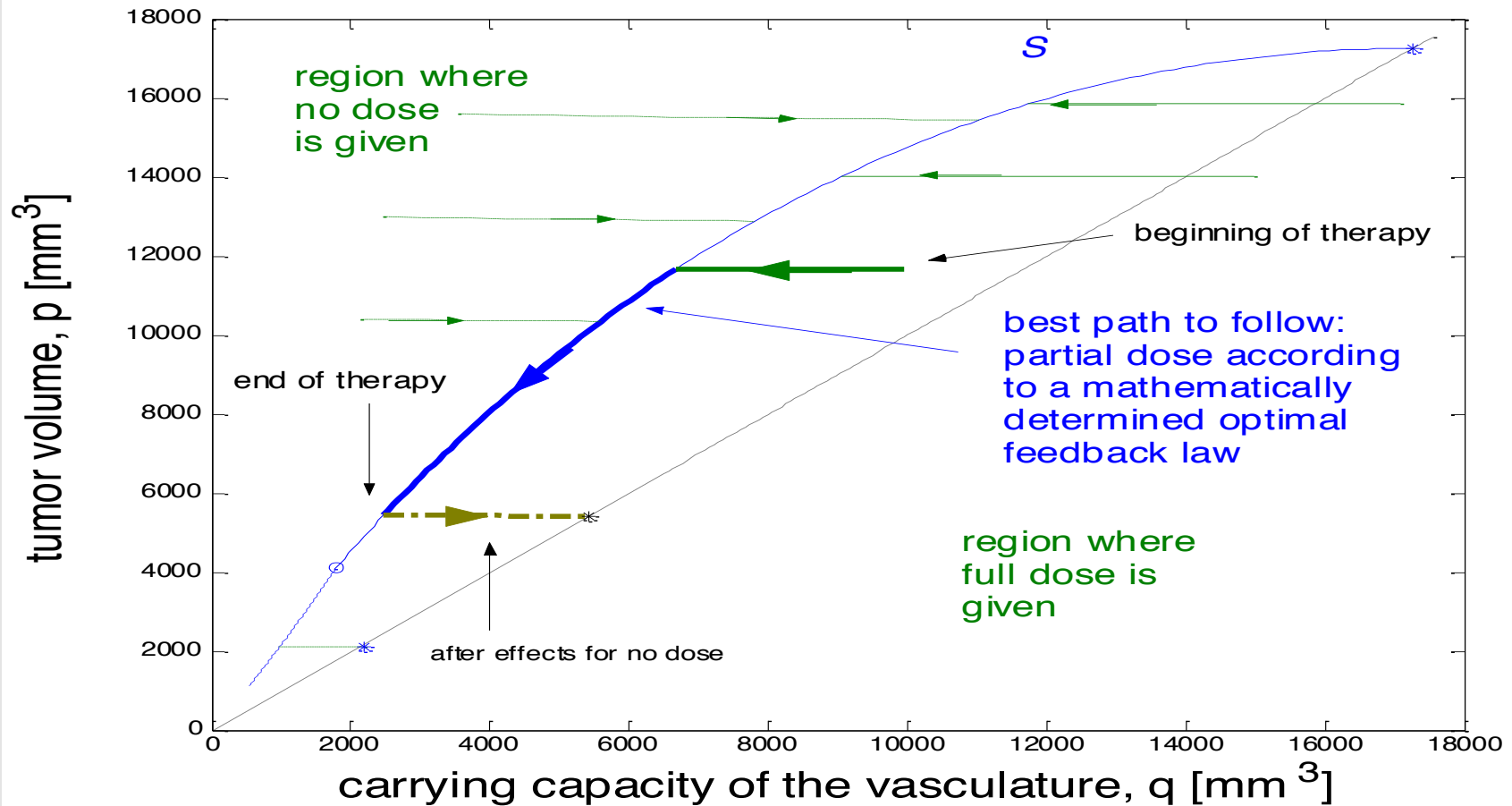
feedback control



Admissible Singular Arc



Synthesis of Optimal Controls



typical synthesis: $u_{\max} \rightarrow s \rightarrow 0$

What does it all mean?



- structure of optimal solutions is fully robust with respect to parameters

What does it all mean?



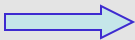
- structure of optimal solutions is fully robust with respect to parameters

- practical?

What does it all mean?



- structure of optimal solutions is fully robust with respect to parameters

- practical?  simple and again robust suboptimal approximations

What does it all mean?



- structure of optimal solutions is fully robust with respect to parameters

- practical? → simple and again robust suboptimal approximations
- practical? → robust with respect to the carrying capacity

What does it all mean?



- structure of optimal solutions is fully robust with respect to parameters

- practical? → simple and again robust suboptimal approximations
- practical? → robust with respect to the carrying capacity
- **for large tumor volume lower dose rates do better**: administer the given amount of inhibitors over a prolonged time interval rather than follow an MTD style attack

“dose intensification”

What does it all mean?



- structure of optimal solutions is fully robust with respect to parameters

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- practical? → robust with respect to the carrying capacity
- **for large tumor volume lower dose rates do better**: administer the given amount of inhibitors over a prolonged time interval rather than follow an MTD style attack

“dose intensification”

- there exists an **optimal relation between tumor volume and carrying capacity** along which the maximum tumor reductions are realized

“normalization of the vasculature”

What does it all mean?



- structure of optimal solutions is fully robust with respect to parameters

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“dose intensification”

- there exists an **optimal relation between tumor volume and carrying capacity** along which the maximum tumor reductions are realized

“normalization of the vasculature”

- **preserved under combinations with chemo- and radiotherapy**

Combination with Chemotherapy

[Mathematical Biosciences, 2009, MBE 2011]

Minimize $p(T)$ subject to

with d'Onofrio and H. Maurer

$$\dot{p} = -\xi p \ln \left(\frac{p}{q} \right) - \varphi p v, \quad p(0) = p_0,$$

$$\dot{q} = bp - (\mu + dp^{\frac{2}{3}})q - \gamma qu - \eta qv, \quad q(0) = q_0,$$

angiogenic inhibitors

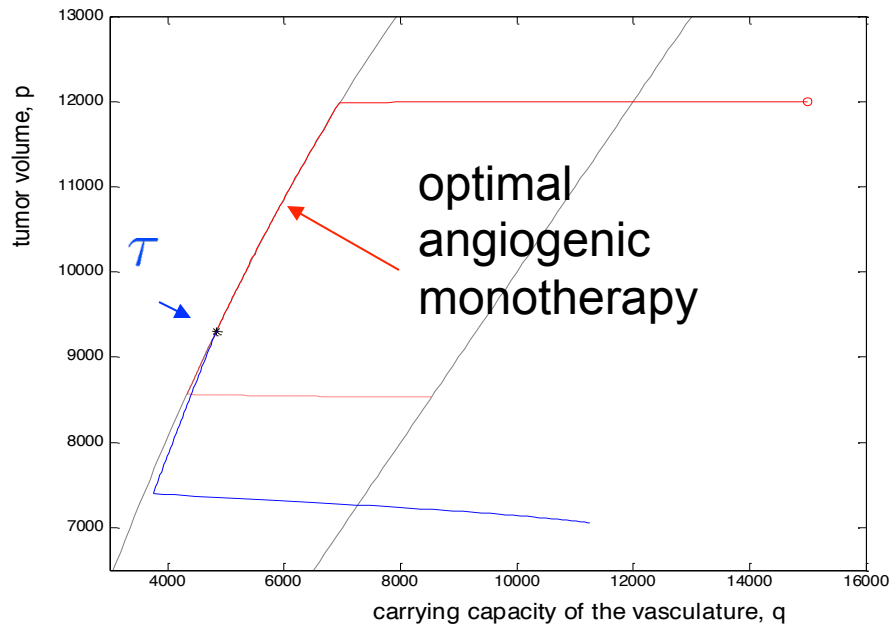
$$0 \leq u \leq u_{\max}, \quad \int_0^T u(t) dt \leq y_{\max}$$

cytotoxic agent or other killing term

$$0 \leq v \leq v_{\max}, \quad \int_0^T v(t) dt \leq z_{\max}$$

Optimal Protocols

- initially give no chemotherapy, $v = 0$, and follow the optimal angiogenic monotherapy: full dose \rightarrow singular
- at a specific time τ along the singular arc initiate chemotherapy,
 $v = v_{\max}$, and give all drugs in one session



1-dimensional
minimization problem
over the parameter τ

“therapeutic window”
Jain et al., 2006

A General Mathematical Model

$$\begin{aligned}\dot{p} &= pF\left(\frac{p}{q}\right) - (\alpha_p + 2\beta_p r_p)pw, & p(0) &= p_0, \\ \dot{q} &= S(p, q) - I(p, q) - \gamma qu - (\alpha_q + 2\beta_q r_q)qw, & q(0) &= q_0, \\ \dot{r}_i &= -\rho_i r_i + w, & r_i(0) &= 0, \\ \dot{y} &= u, & y(0) &= 0, \\ \dot{z} &= (1 + 2\theta_z r_z)w, & z(0) &= 0,\end{aligned}$$

healthy (late) tissue

$$i = p, q, z$$

singular anti-angiogenic dose rate - control u

$$\gamma u_{\sin}(t) + [(\alpha_q + 2\beta_q r) - (\alpha_p + 2\beta_p r)]w = \Psi(p(t), q(t))$$

optimal singular control for angiogenic monotherapy

the system really wants to maintain certain relations
between p and q

Sufficient Conditions for Optimality

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 where 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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IAM
38
Schättler · Ledzewicz

Interdisciplinary Applied Mathematics 38

Heinz Schättler
Urszula Ledzewicz



Geometric Optimal Control

**Geometric
Optimal Control**

Theory, Methods and Examples

Springer

How do we know solutions are optimal ?

synthesis of extremal controlled trajectories

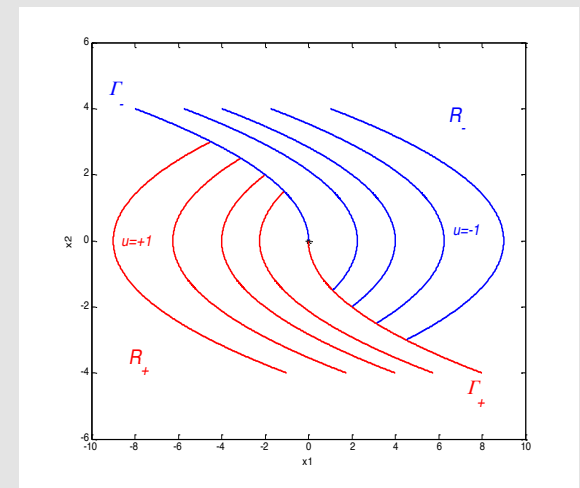
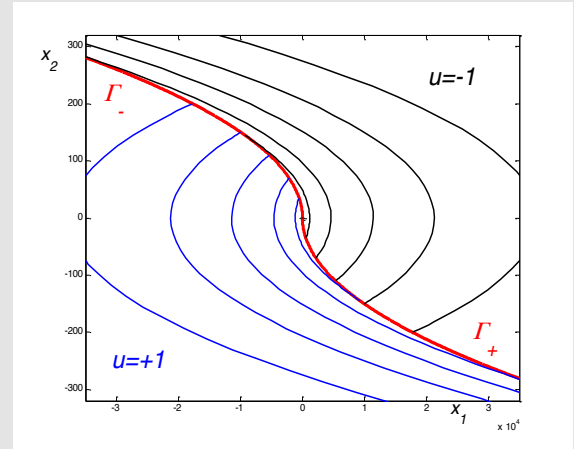


method of characteristics

the corresponding value function (cost-to-go function) is a **solution of the Hamilton-Jacobi-Bellman equation** with sufficient smoothness properties

e.g., continuous and continuously differentiable except for a locally finite collection of embedded submanifolds of positive codimension

approach and results in principle are local, but lead to **global optimality** results if construction can be done globally



Optimal Control Problem

Minimize the functional

$$\mathcal{J}(u) = \int_{t_0}^T L(s, x(s), u(s)) ds + \varphi(T, x(T))$$

over all locally bounded, Lebesgue measurable functions $u : [0, T] \rightarrow U \subset \mathbb{R}^m$, the admissible controls, for which the corresponding trajectory x ,

$$\dot{x}(t) = f(t, x(t), u(t)), \quad x(t_0) = x_0,$$

satisfies the terminal constraint $\Psi(T, x(T)) = 0$.

It is assumed that the matrix $D\Psi(T, x(T))$ is of maximal rank on the set $N = \{x \in \mathbb{R}^n : \Psi(T, x) = 0\}$.

Hamilton - Jacobi - Bellman equation

if the **value function** is differentiable at a point (t, x) , then it satisfies the first order “PDE”

$$\frac{\partial V}{\partial t}(t, x) + \min_{u \in U} \left(\frac{\partial V}{\partial x}(t, x) f(t, x, u) + L(t, x, u) \right) \equiv 0$$

and on the terminal manifold we have

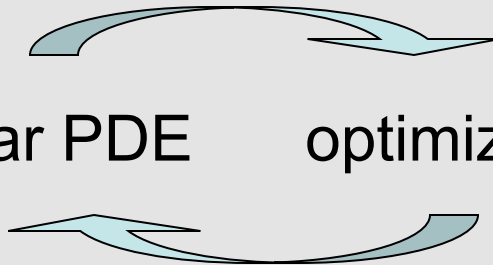
$$V(T, x) = \varphi(T, x) \quad \text{for all } (T, x) \text{ so that } \Psi(T, x) = 0$$

“**solution**” of (HJB) : a pair (V, u) consisting of a (differentiable) function V and a control u that solves the associated minimum problem

Method of Characteristics

- Classical procedure for constructing solutions to first-order PDEs by reducing them to a set of ordinary differential equations
 - the so-called **characteristic equations**
- the **Hamilton-Jacobi-Bellman equation** is a first order PDE, but **coupled with** the solution of an **optimization problem**

1st order linear PDE optimization



Parameterized Families of Extremals

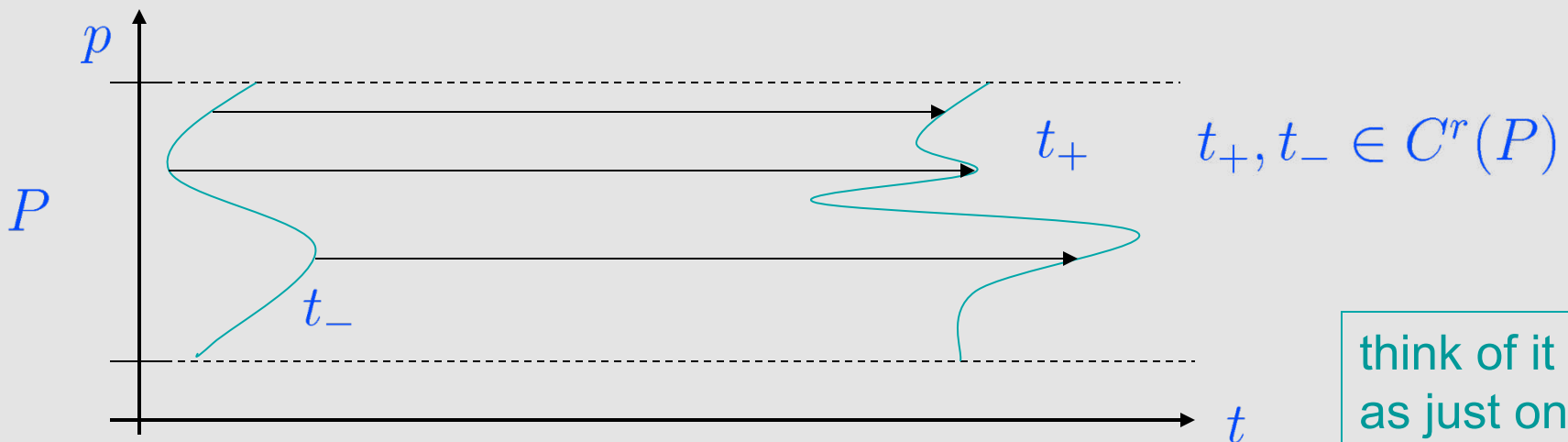
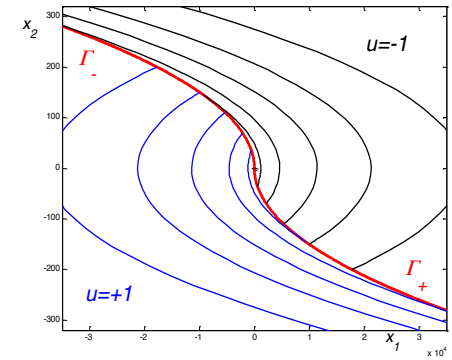
C^r -parameterized family of extremals:

a family of controlled trajectories $(x(t, p), u(t, p))$

that satisfy the conditions of the maximum principle

with corresponding multipliers $\lambda_0(p), \lambda(t, p)$ over some

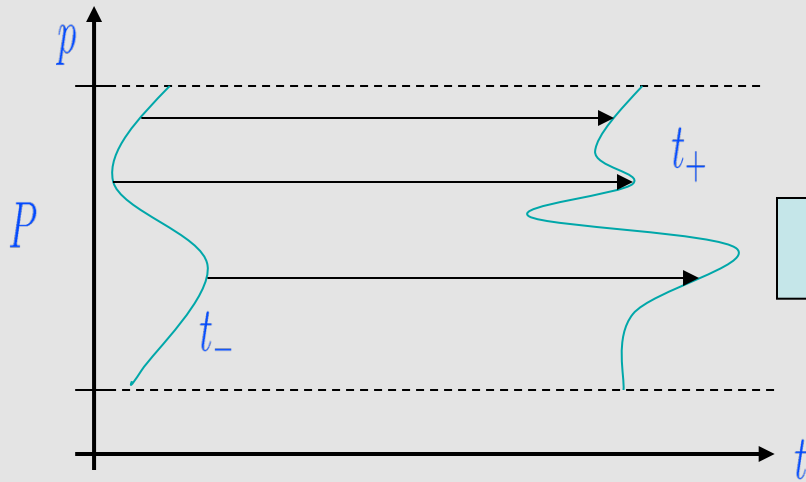
domain $D = \{(t, p) : t_-(p) \leq t \leq t_+(p), p \in P\}$



think of it
as just one
patch

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

Flow of extremals



$$(t, p) \mapsto F(t, p)$$

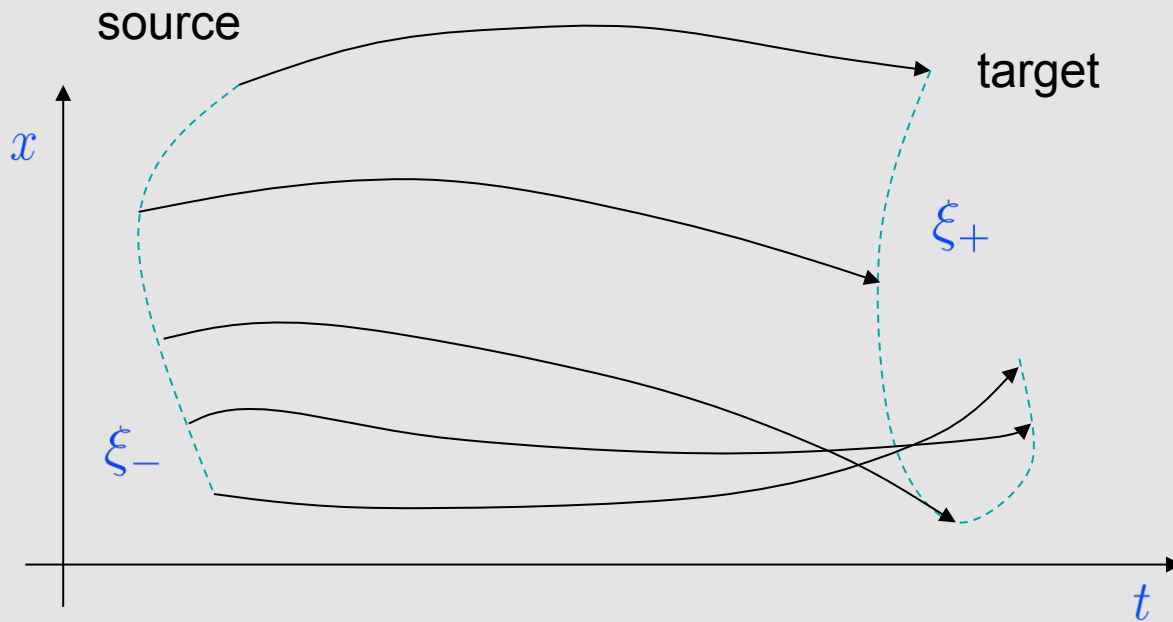
time-dependent:

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

[graphs of trajectories]

time-independent:

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



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

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

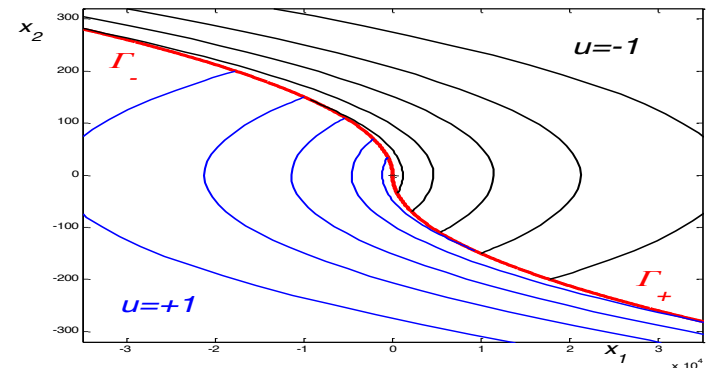
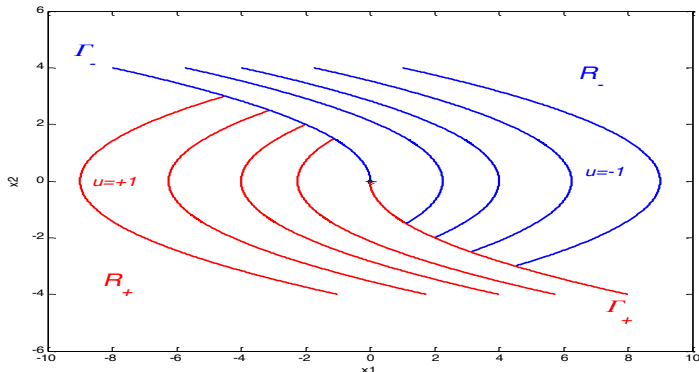
Parameterized Families with Cost

Given C^r functions γ_- and γ_+ that satisfy the **transversality condition**

$$\lambda(t_{\pm}(p), p) \frac{\partial \xi_{\pm}}{\partial p}(p) = \lambda_0(p) \frac{\partial \gamma_{\pm}}{\partial p}(p) + h(t_{\pm}(p), p) \frac{\partial t_{\pm}}{\partial p}(p)$$

define the parameterized cost (cost-to-go function) as

$$\begin{aligned} C(t, p) &= \gamma_-(p) - \int_{t_-(p)}^t L(s, x(s, p), u(s, p)) ds \\ &= \int_t^{t_+(p)} L(s, x(s, p), u(s, p)) ds + \gamma_+(p) \end{aligned}$$



Shadow Price Lemma

$$\lambda_0(p) \frac{\partial C}{\partial p}(t, p) = \lambda(t, p) \frac{\partial x}{\partial p}(t, p)$$

pf. fix the parameter p

(1) the adjoint equation and minimum condition of the **maximum principle** imply that both sides have the same time derivative

(2) the **transversality conditions** imply that both sides are equal for the time $t_-(p)$ respectively $t_+(p)$

COROLLARY:

If the flow $(t, p) \mapsto F(t, p)$ is a C^r -diffeomorphism onto some open set R in (t, x) space, then

$$V : R \rightarrow \mathbb{R}, \quad V = C \circ F^{-1},$$

is continuously differentiable and together with the admissible feedback control

$$u_* : R \rightarrow U, \quad u_* = u \circ F^{-1},$$

is a solution to the Hamilton-Jacobi-Bellman equation.

(entirely local !)

Pf. By definition we have $C(t, p) = V(t, x(t, p))$ (*)

Hence $\frac{\partial C}{\partial p}(t, p) = \frac{\partial V}{\partial x}(t, x(t, p)) \frac{\partial x}{\partial p}(t, p)$ ← non-singular

But also $\frac{\partial C}{\partial p}(t, p) = \lambda(t, p) \frac{\partial x}{\partial p}(t, p)$ ←

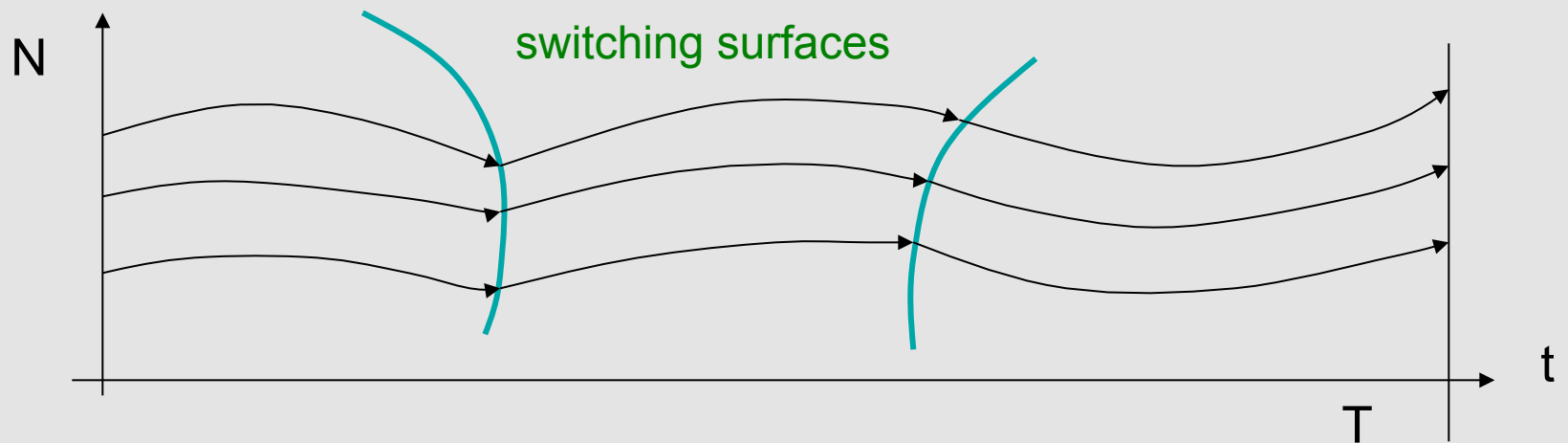
Given $(t, x) = (t, x(t, p)) \in R$ and any control $v \in U$

$$\begin{aligned} & V_t(t, x) + V_x(t, x)f(t, x, v) + L(t, x, v) \\ &= V_t(t, x(t, p)) + V_x(t, x(t, p))f(t, x(t, p), v) + L(t, x(t, p), v) \\ &= V_t(t, x(t, p)) + \lambda(t, p)f(t, x(t, p), v) + L(t, x(t, p), v) \\ &\geq V_t(t, x(t, p)) + \lambda(t, p)f(t, x(t, p), u(t, p)) + L(t, x(t, p), u(t, p)) \\ &= V_t(t, x(t, p)) + H(t, \lambda(t, p), x(t, p), u(t, p)) = 0 \end{aligned}$$

↑
differentiate (*) with respect to t

back to the problems considered above

concatenations of parameterized families of extremals



optimality properties of the reference controlled extremal depend on the mapping properties of the flow of controlled trajectories **between** and **at** the switching surfaces

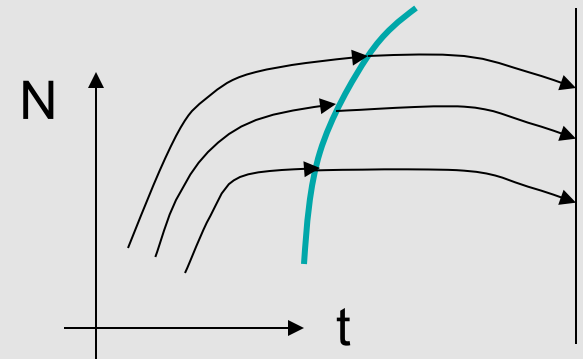
Bang-Bang Flows

the flow corresponding to bang-bang controls trivially is a diffeomorphism between switchings, but overlaps are possible at the switchings

- transversal crossings:

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

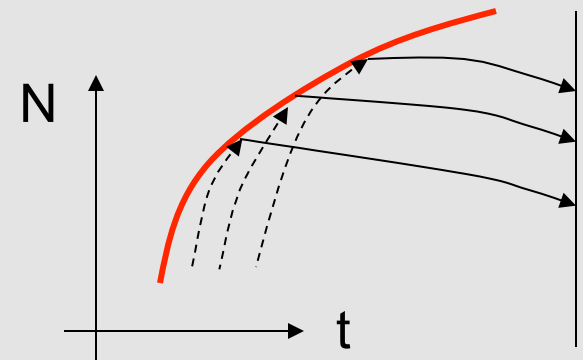
⇒ optimality is preserved



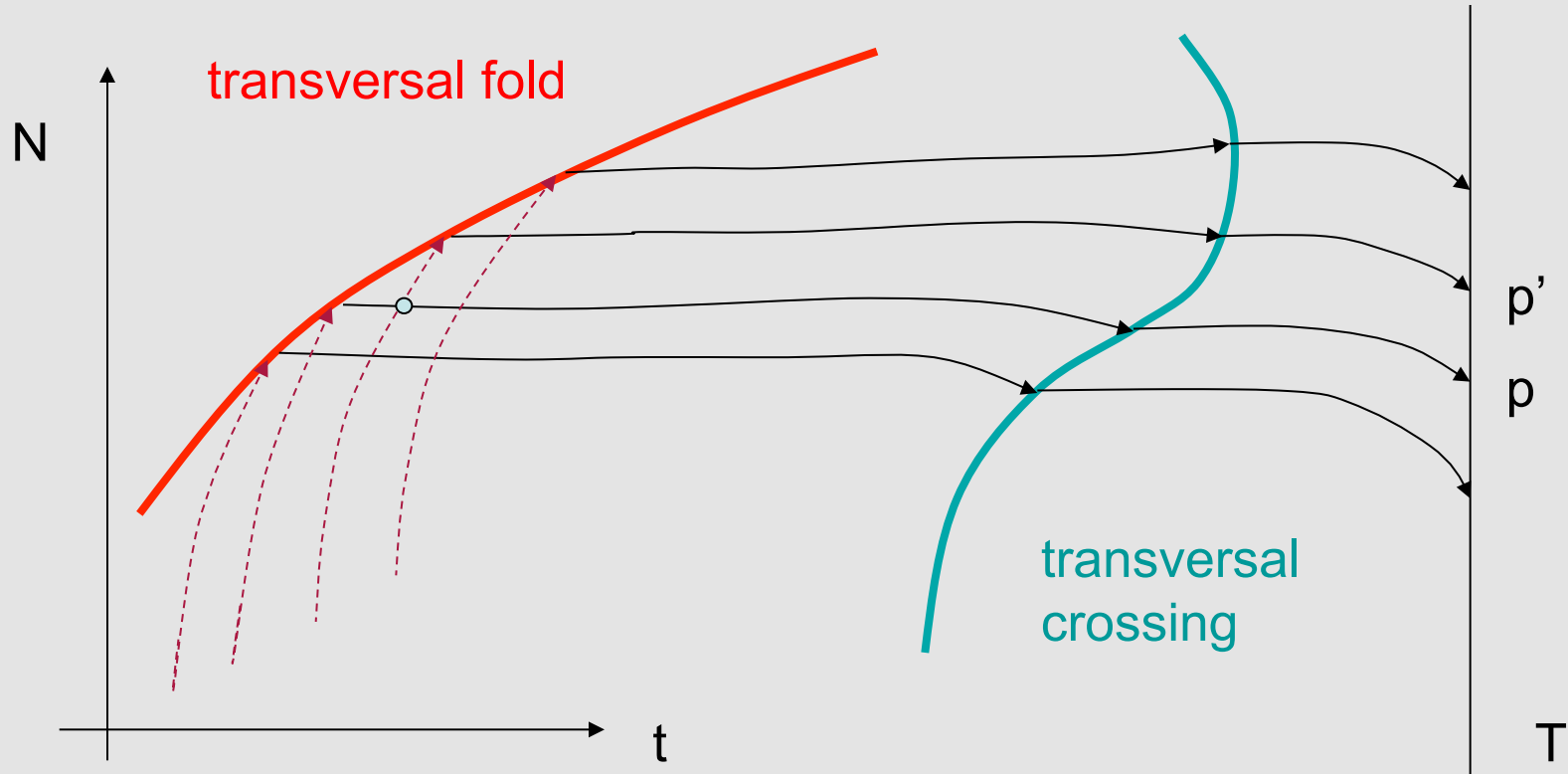
- or transversal folds:

conjugate points—envelope

⇒ optimality ceases



Flows of Extremal Bang-Bang Trajectories

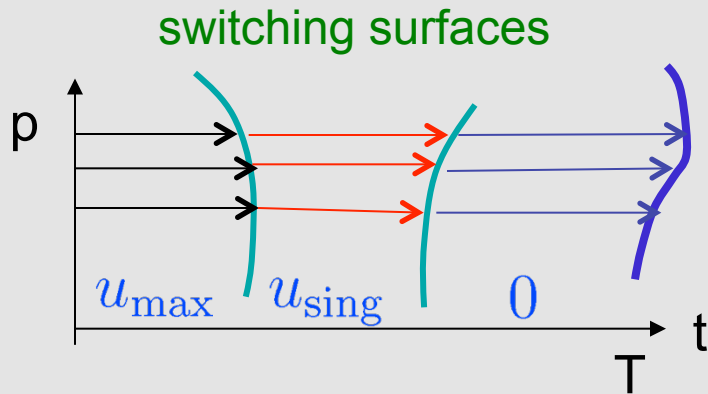


sensitivity calculations:

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

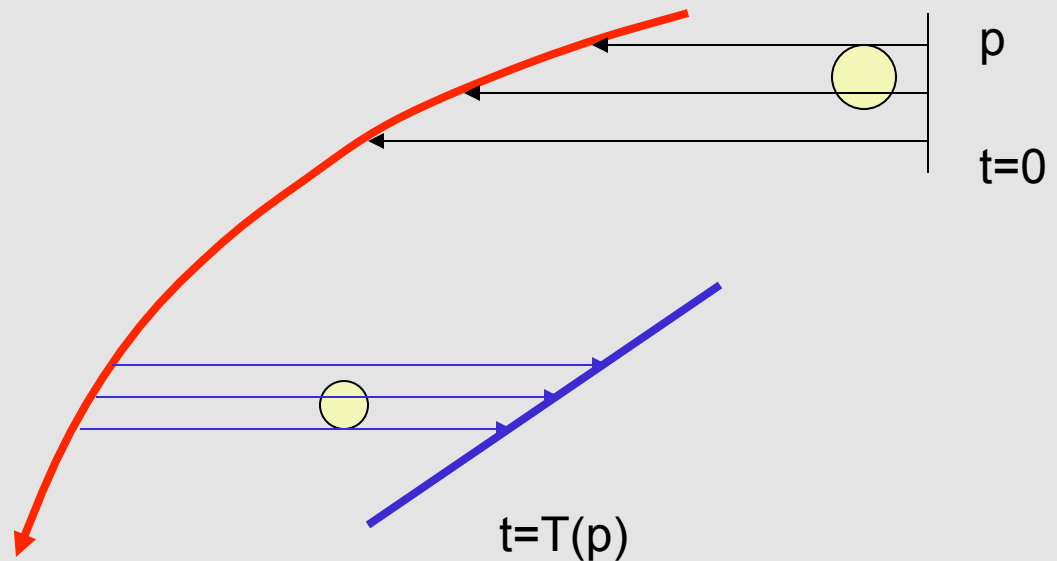
determines geometric situations

Bang-Singular-Bang Concatenations

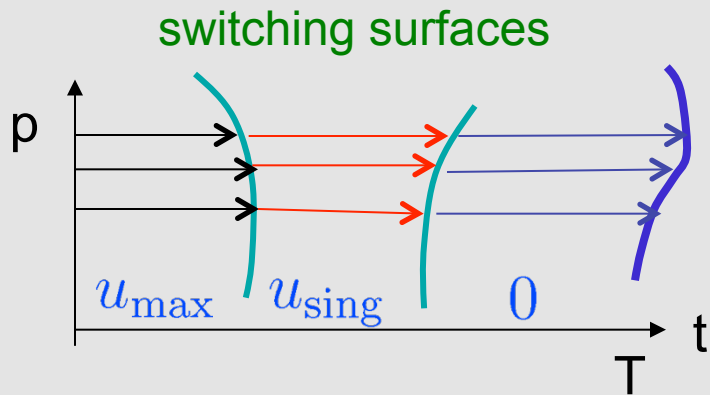


$$F : (t, p) \mapsto x(t, p)$$

as long as the flow covers a region in the state-space one-to-one, the cost-to-go functions gives rise to a solution of the Hamilton-Jacobi-Bellman equation

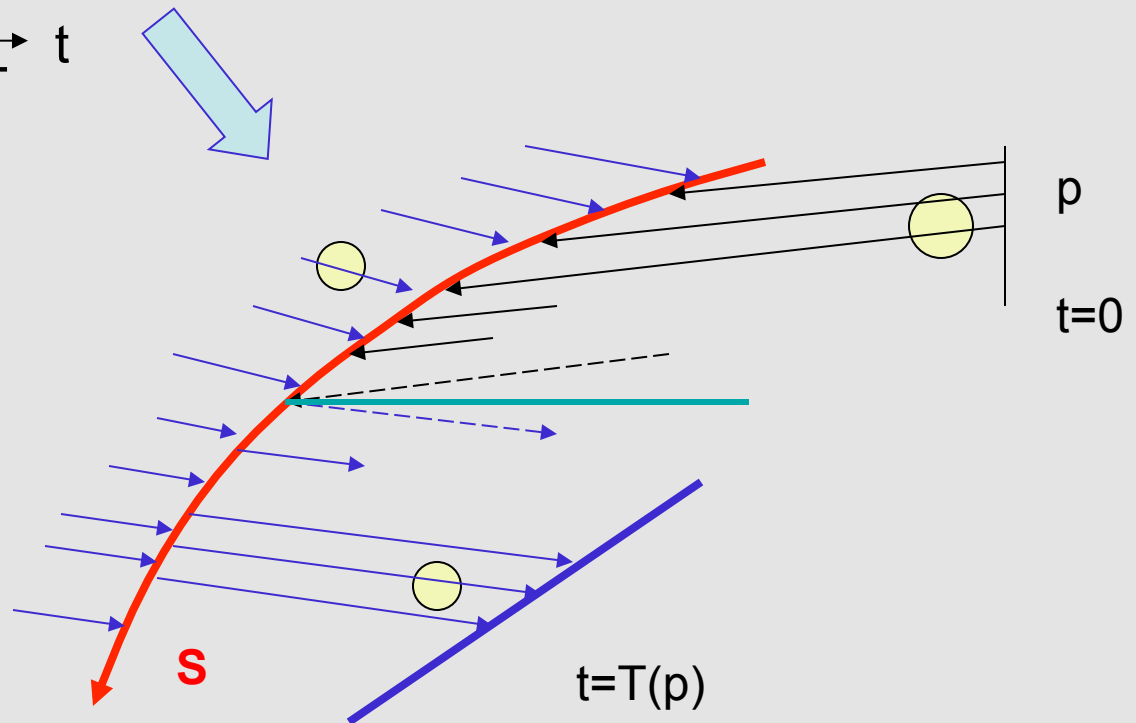


Bang-Singular-Bang Concatenations

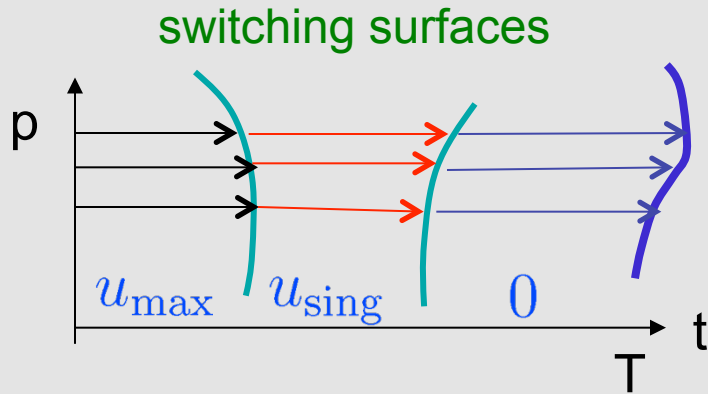


$$F : (t, p) \mapsto x(t, p)$$

can extend family to cover a neighborhood of reference trajectory



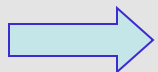
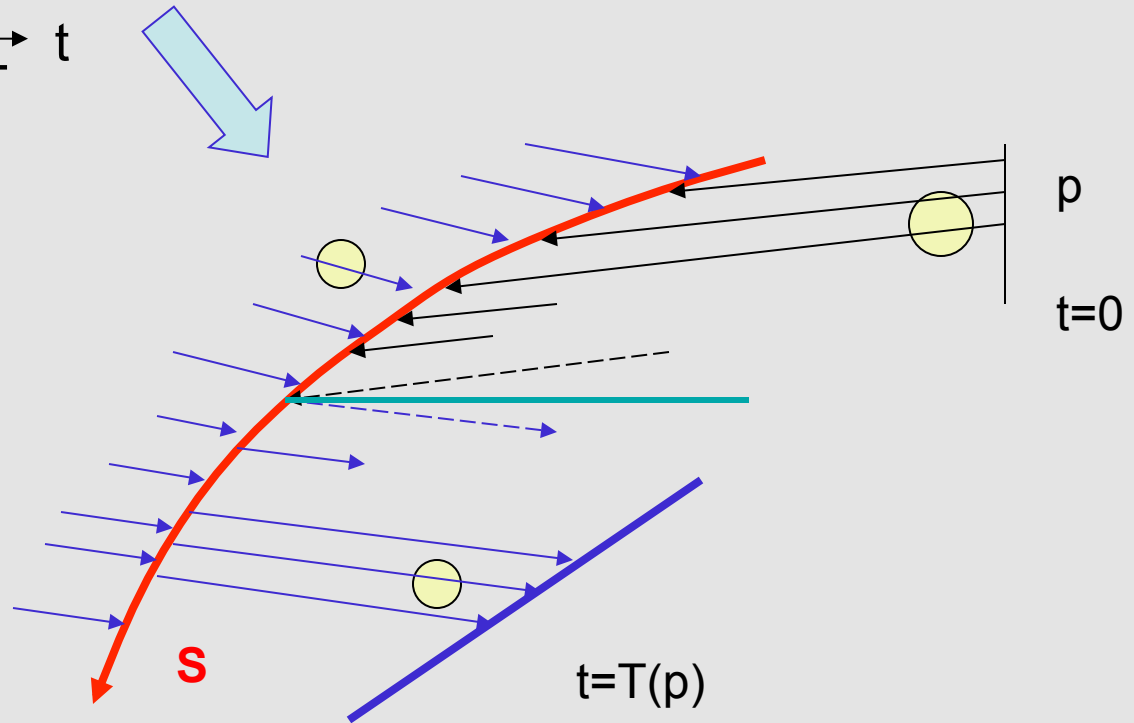
Bang-Singular-Bang Concatenations



$$F : (t, p) \mapsto x(t, p)$$

can extend family to cover a neighborhood of reference trajectory

value is continuous, but not differentiable along singular arc – no problem



strong local optimality results

‘regular’ synthesis type constructions [Piccoli-Sussmann]

mathematical models for cancer treatment

- for low-dimensional, minimally parameterized models it is possible to give complete optimal solutions (not necessarily easy, but can be done and it is worthwhile for a good model)
- knowledge of optimal solutions gives medical insights
- give rise to interesting mathematical questions in connections with proofs of optimality and challenging local synthesis

method of characteristics

a classical, effective geometric method to prove local optimality

also for broken extremals (when adapted to the optimal control formulation)

- * local synthesis near an optimal order 1 singular arc
(in dimension 3, Gardner-Moyer, 1973)
- * local synthesis near saturation points
(Sch & Jankovic, Bonnard & de Morant, 1990s)
- * local synthesis near an optimal order 2 singular arcs with chattering arcs (???, Zelikin 1991)
arises when pharmacokinetic equations are added to the model for antiangiogenic therapy