

Optimal Control Problems for Mathematical Models of Cancer Treatments

Heinz Schaettler, Urszula Ledzewicz

▶ **To cite this version:**

Heinz Schaettler, Urszula Ledzewicz. Optimal Control Problems for Mathematical Models of Cancer Treatments. NETCO 2014, 2014, Tours, France. hal-01024610

HAL Id: hal-01024610
https://inria.hal.science/hal-01024610

Submitted on 17 Jul 2014

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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





Andrzej Swierniak

Silesian University of Technology,
Gliwice, Poland

Helmut Maurer

Rheinisch Westfälische
Wilhelms-Universität Münster,
Münster, Germany

Research supported by collaborative research NSF grants

DMS 1008209/100822 , DMS 1311729/1311733

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

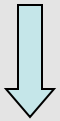
Mathematical Models

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

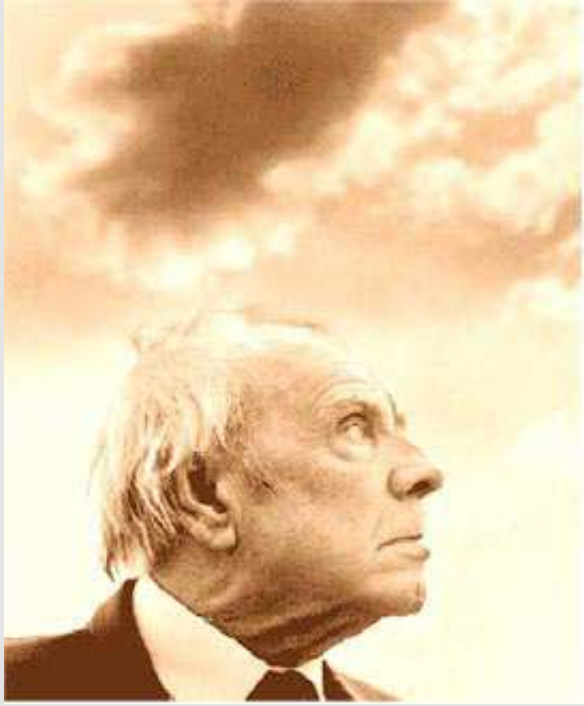
advantage • realism and accuracy

disadvantage

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

On Exactitude in Science

Jorge Luis Borges, Collected Fictions,



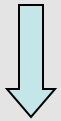
translated by Andrew Hurley

…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?

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

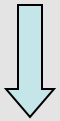


"large" mathematical model that generally make an analysis impossible, but use numerical methods and techniques

advantage
- realism and accuracy

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

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

Optimal Treatment Protocols

Main Questions

HOW MUCH? **(dosage)**

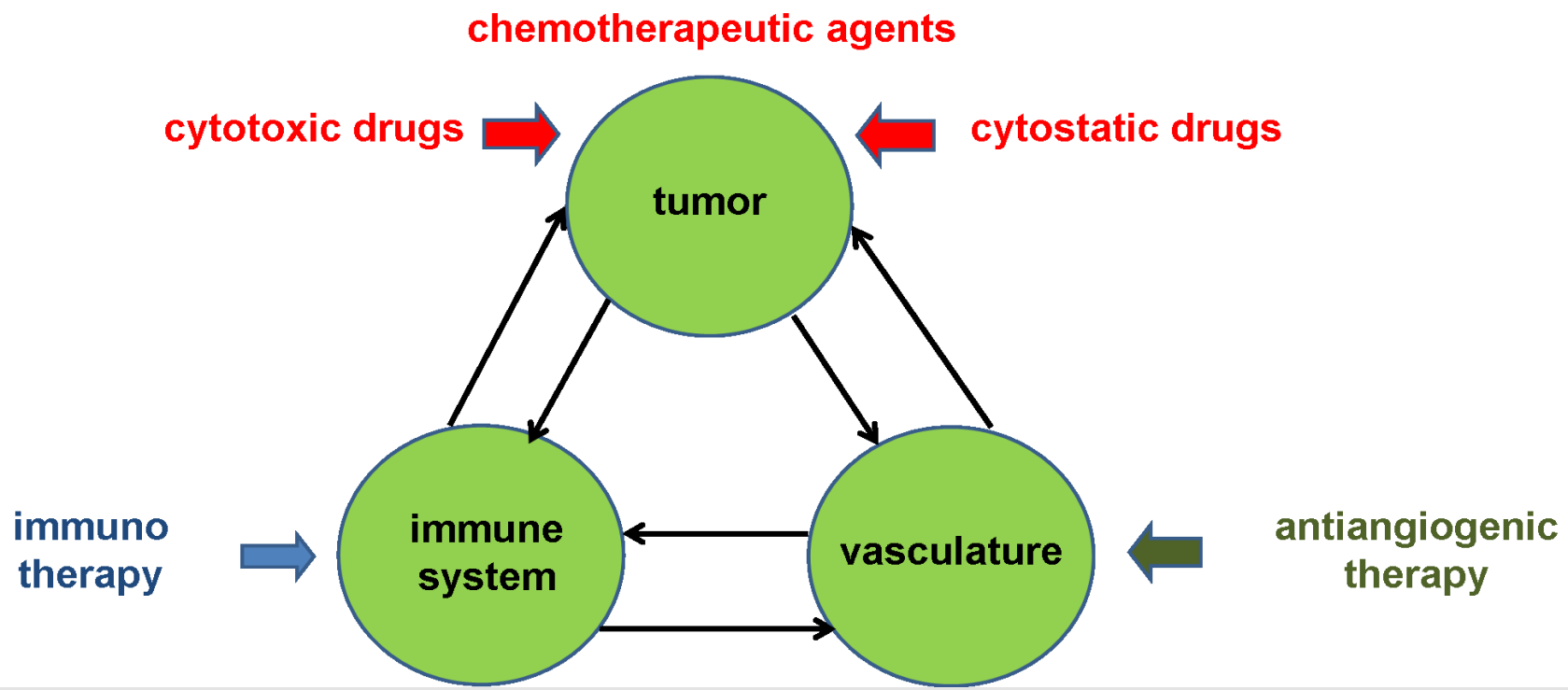
HOW OFTEN? **(timing)**

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?



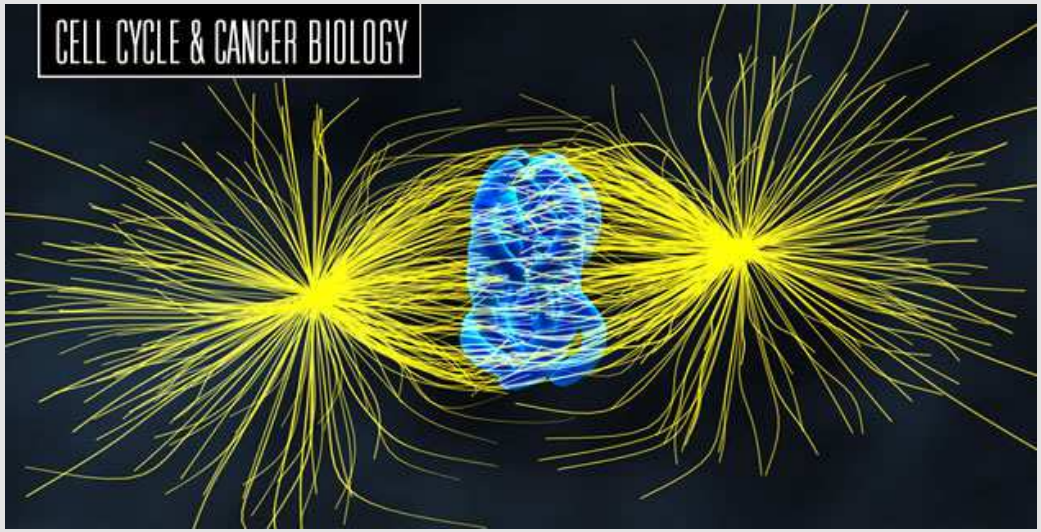
More is Not Necessarily Better

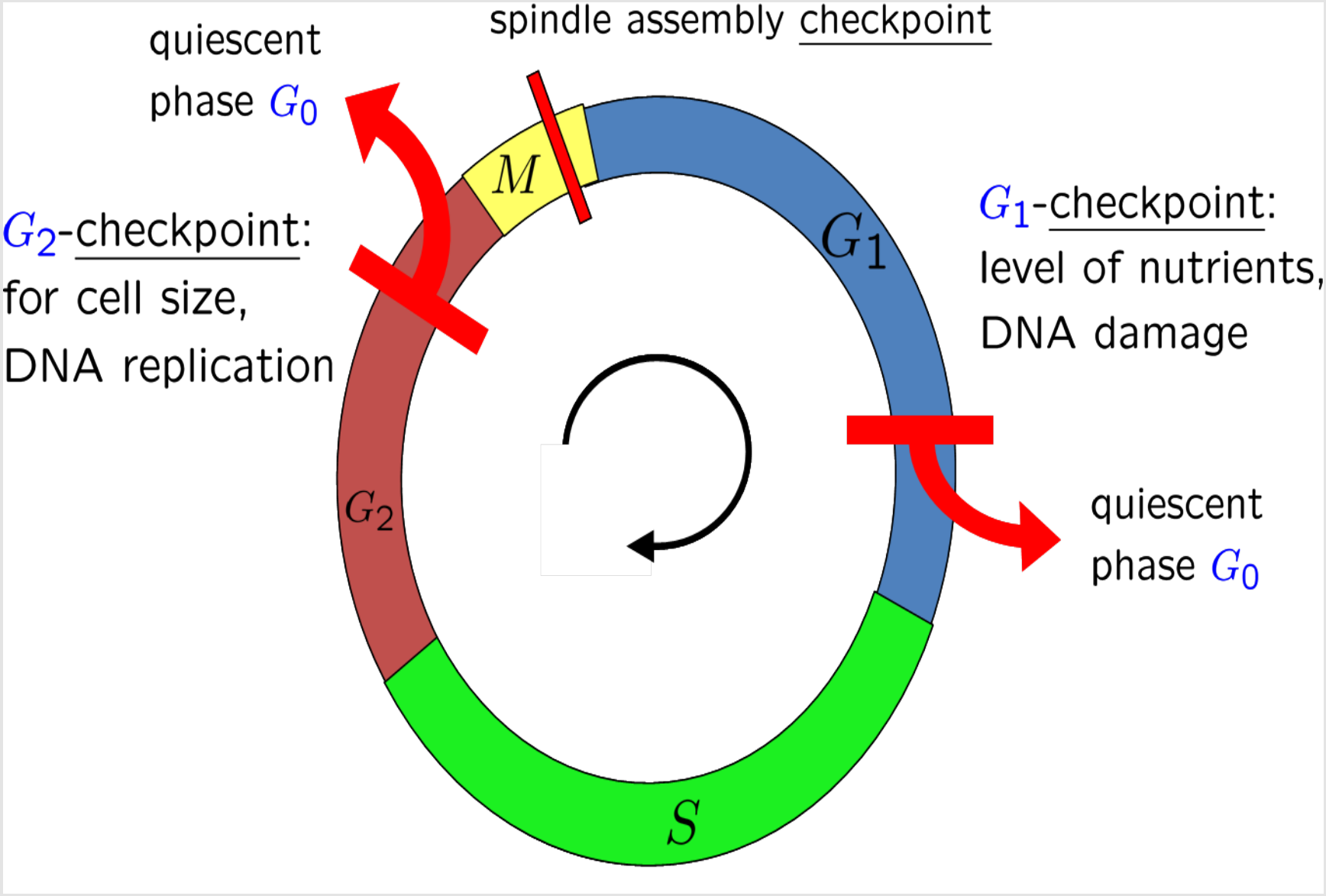
Metronomic Chemotherapy,

Eddy Pasquier and Urszula Ledzewicz,

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

Cell-Cycle Specific Models for Multi-Drug Chemotherapy




quiescent
phase G_0
spindle assembly checkpoint
G_2-checkpoint:
for cell size,
DNA replication
M
G_1
G_1-checkpoint:
level of nutrients,
DNA damage
G_2
quiescent
phase G_0
S

Compartmental models: Dynamics

- **COMPARTMENTS :**
  clusters of phases of cell-cycle or different types of chemotherapeutically sensitive cells

- **STATES : N = (N_1 , … , N_n)**
  represent the average numbers of (cancer) cells in the corresponding compartments

- **CONTROLS : u = (u_1 , … , 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*

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

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

$$a_i \leq u_i \leq b_i$$

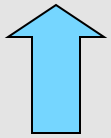
(Swierniak, Ledzewicz, Schättler 2003)

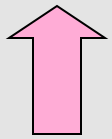
Mathematical Model: L_1-type Objective

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

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







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

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

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

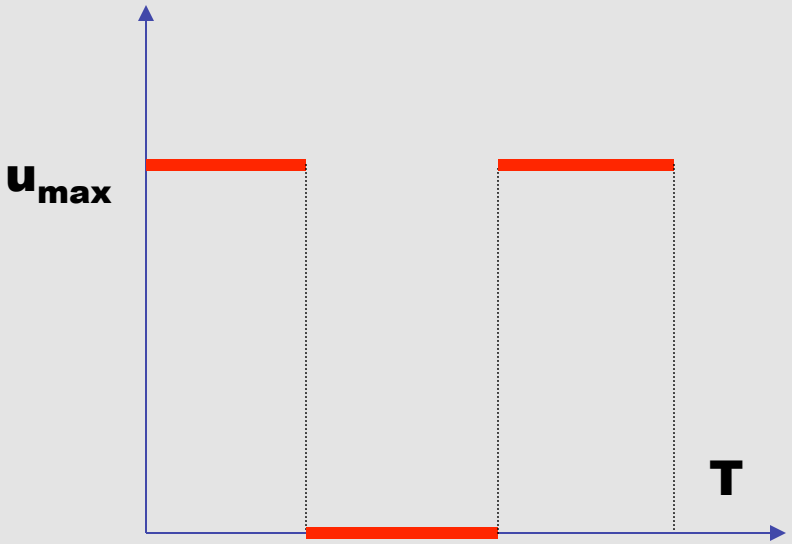
switching functions: $\Phi_j(t) = \ell_j + \lambda(t) B_j N(t)$

⟹

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

Candidates for Optimal Protocols

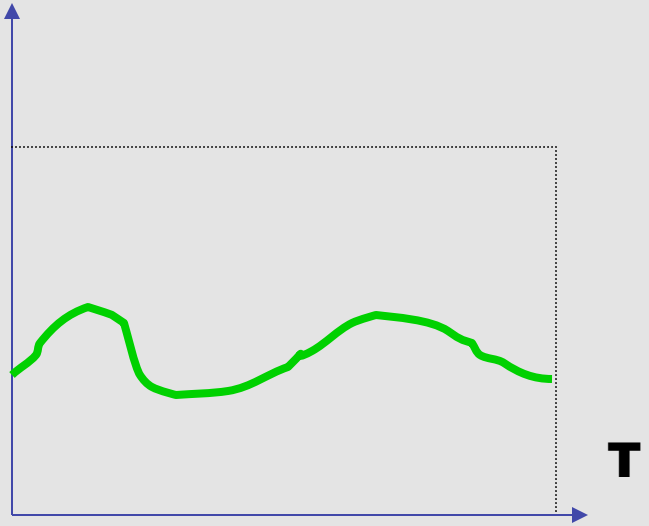
- bang-bang controls



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 $2k^{th}$ derivative
- **Generalized Legendre-Clebsch condition** for a single-input minimization problem

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

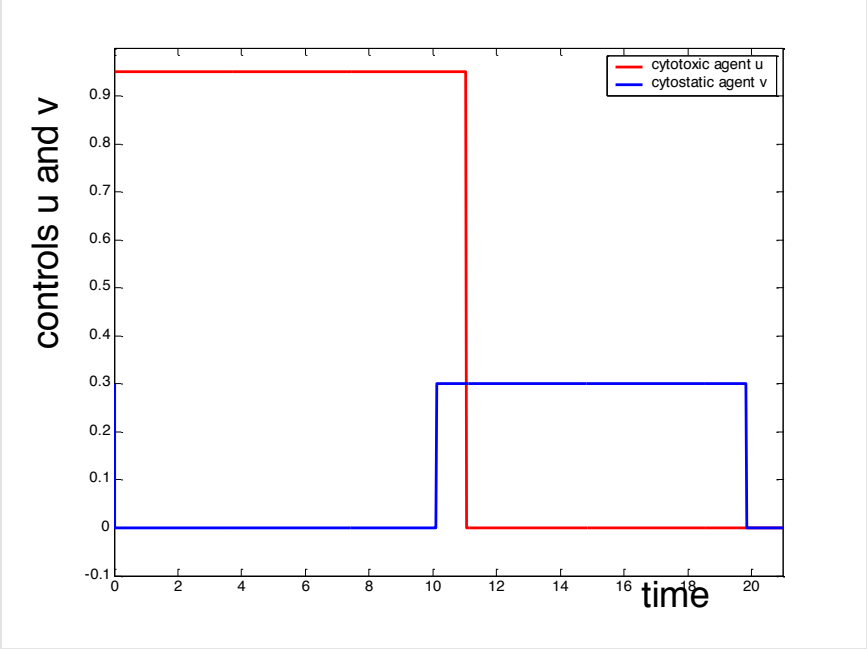
- **Goh condition** for a multi-input problems: if the controls u_i^* and u_j^* are simultaneously singular, then

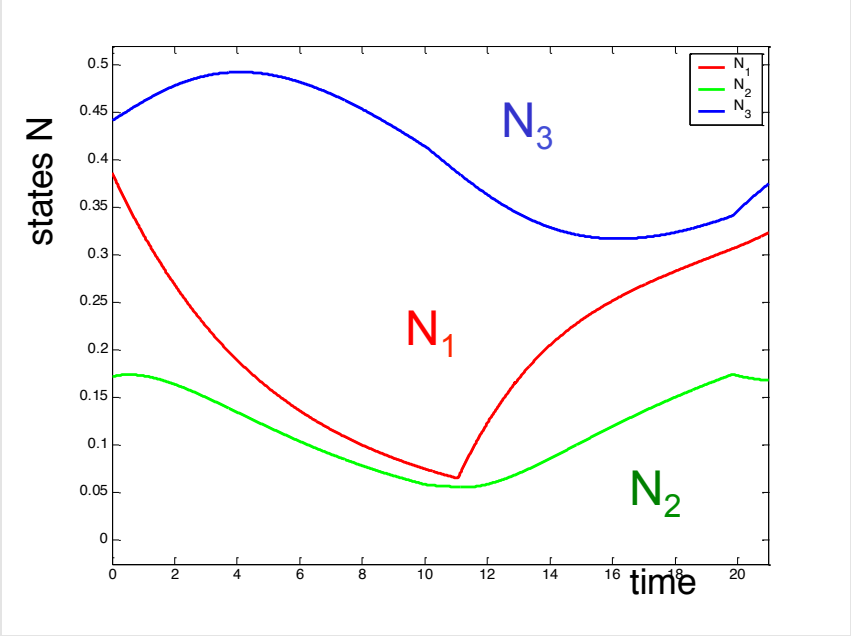
$$\frac{\partial}{\partial u_i} \frac{d}{dt} \frac{\partial H}{\partial u_j} \equiv 0$$

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

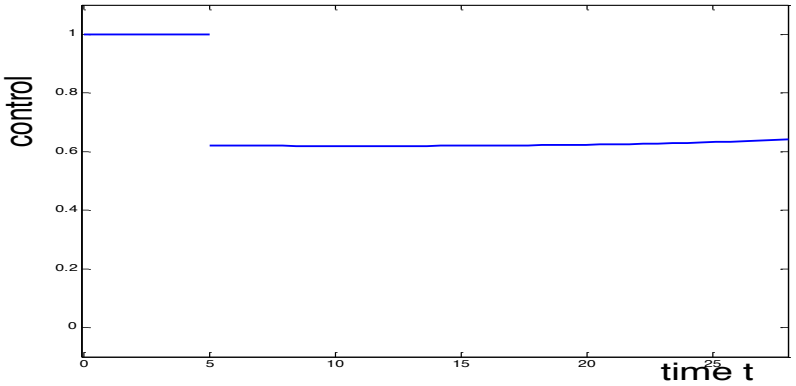
- for homogeneous tumor populations consisting of chemotherapeutically sensitive cells, bang-bang controls (full dose chemotherapy with rest periods) are optimal and drugs are given up-front

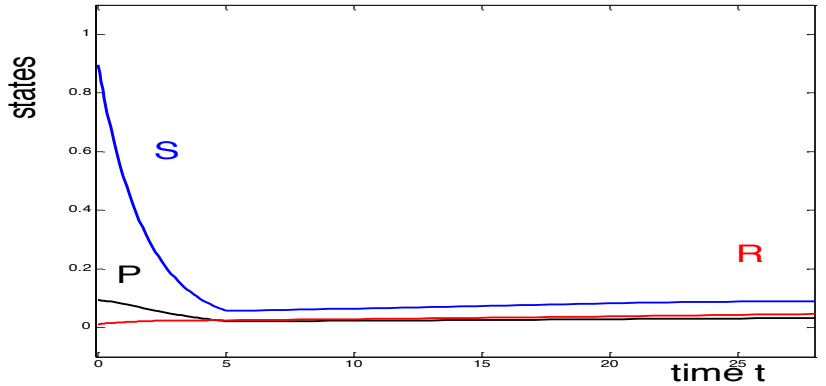
  "MTD (maximum tolerated dose)"

- 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

  "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

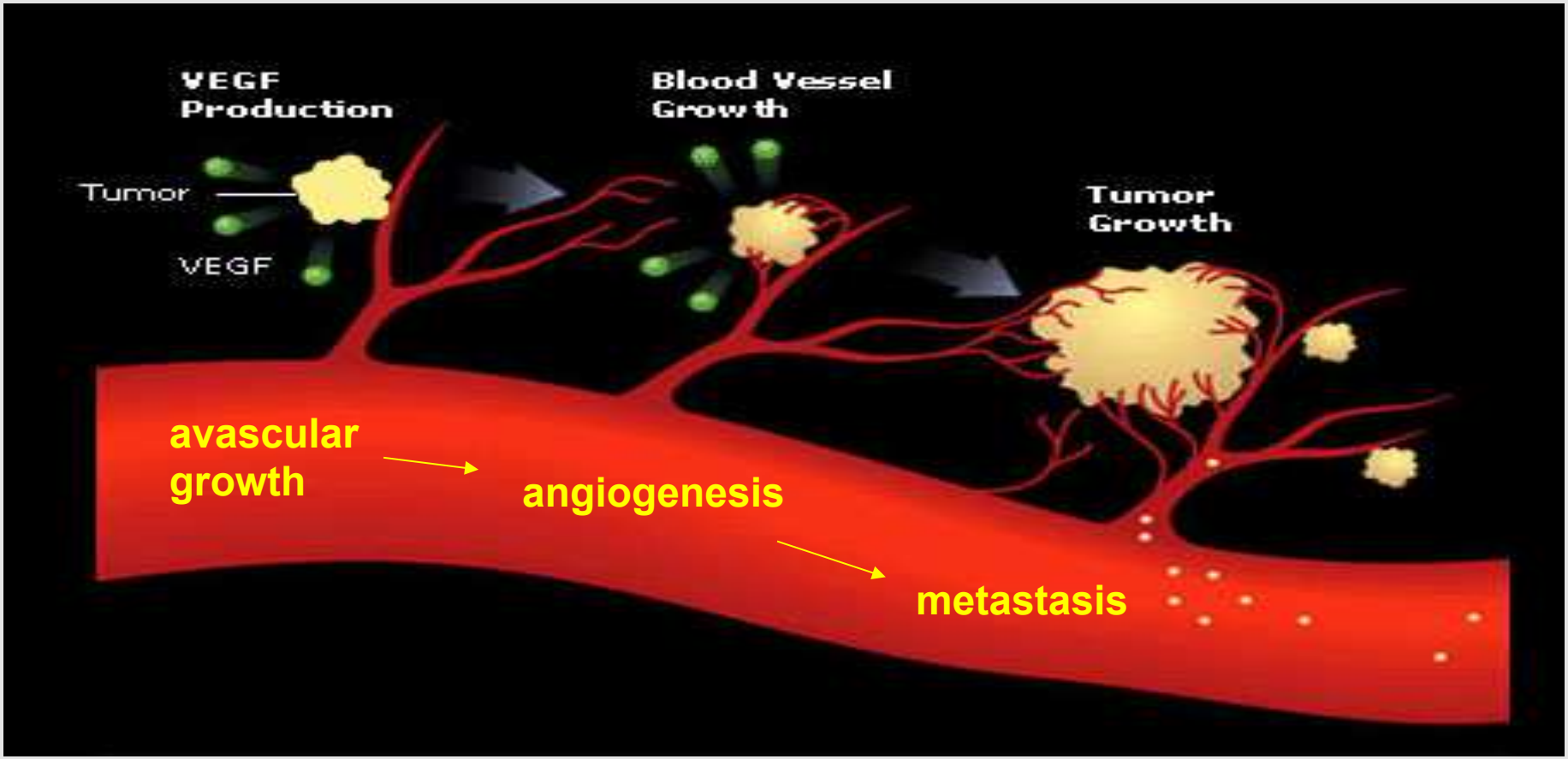
  lower dose protocols to balance benefit and harm

  "chemo-switch protocols"

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

  other options (?)

Tumor Angiogenesis



http://www.gene.com/gene/research/focusareas/oncology/angiogenesis.html

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

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

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

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 $u : [0, T] \to [0, u_{\max}]$ that satisfy

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

subject to the dynamics

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

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

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

Dynamics in Vector Form

$$\dot{x} = f(x) + ug(x)$$

drift

control vector field

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

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

$$\begin{aligned}
\Phi(t) &= \langle \lambda(t), g(z(t)) \rangle \equiv 0 \quad \longrightarrow \quad \lambda_2(t) > 0 \\
\dot{\Phi}(t) &= \langle \lambda(t), [f,g] z(t) \rangle \equiv 0 \\
\ddot{\Phi}(t) &= \langle \lambda(t), [f + ug, [f,g]] z(t) \rangle \equiv 0.
\end{aligned}$$

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

order 1 singular control

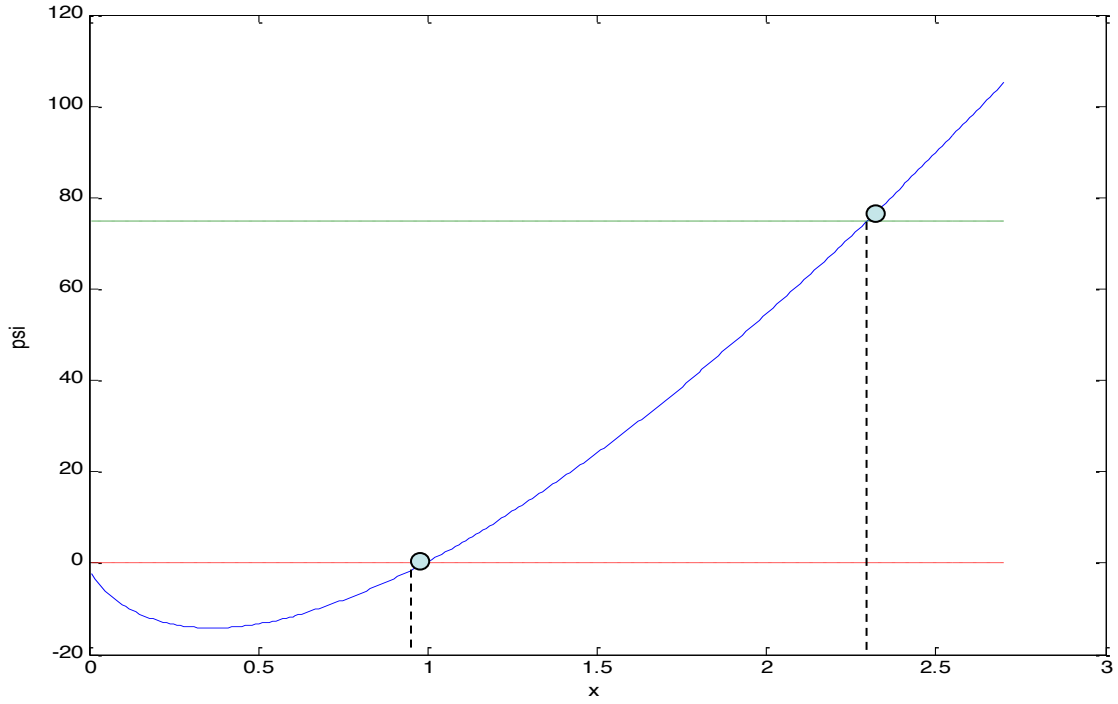
strengthened Legendre-Clebsch condition is satisfied

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

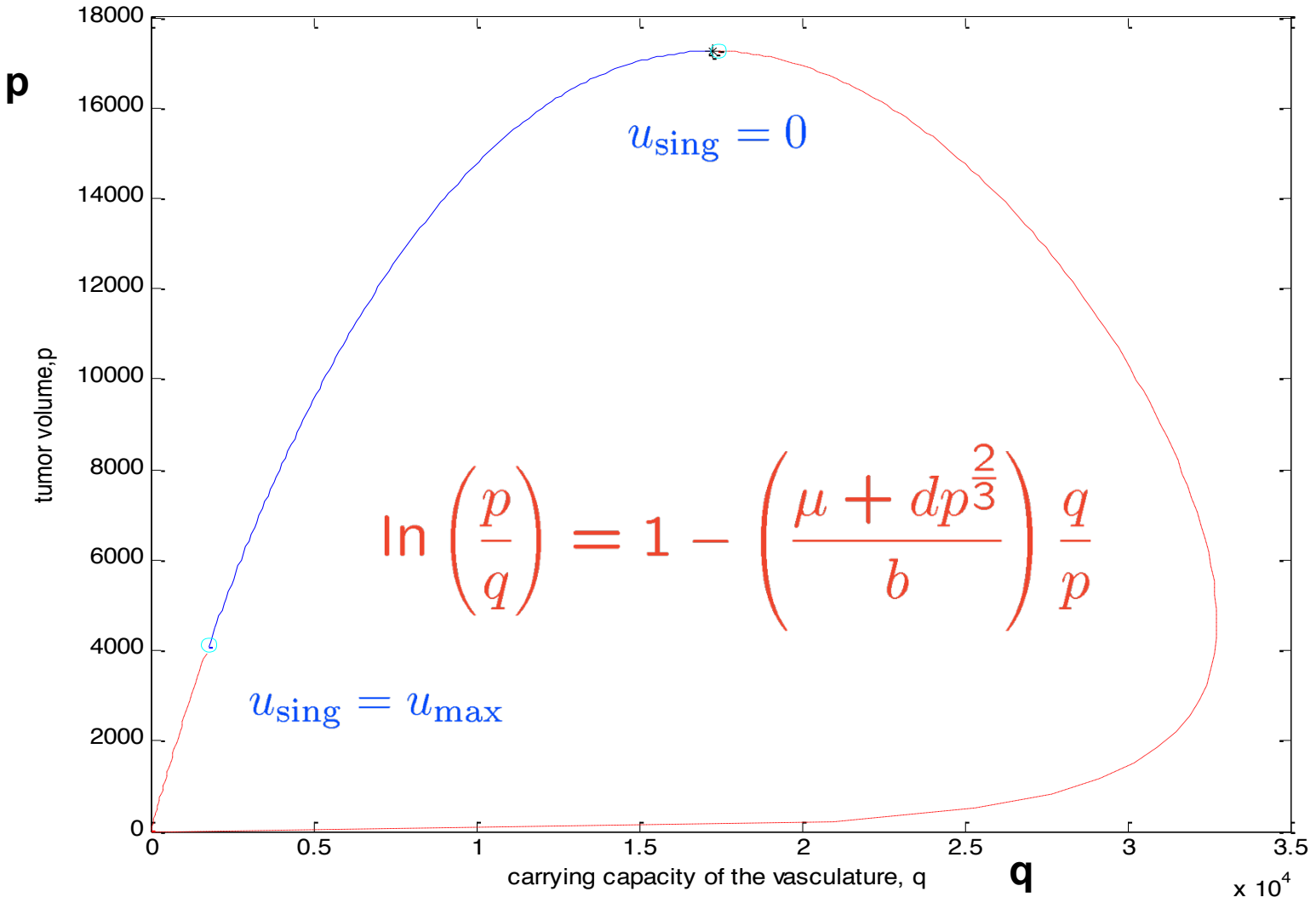
Singular Control

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

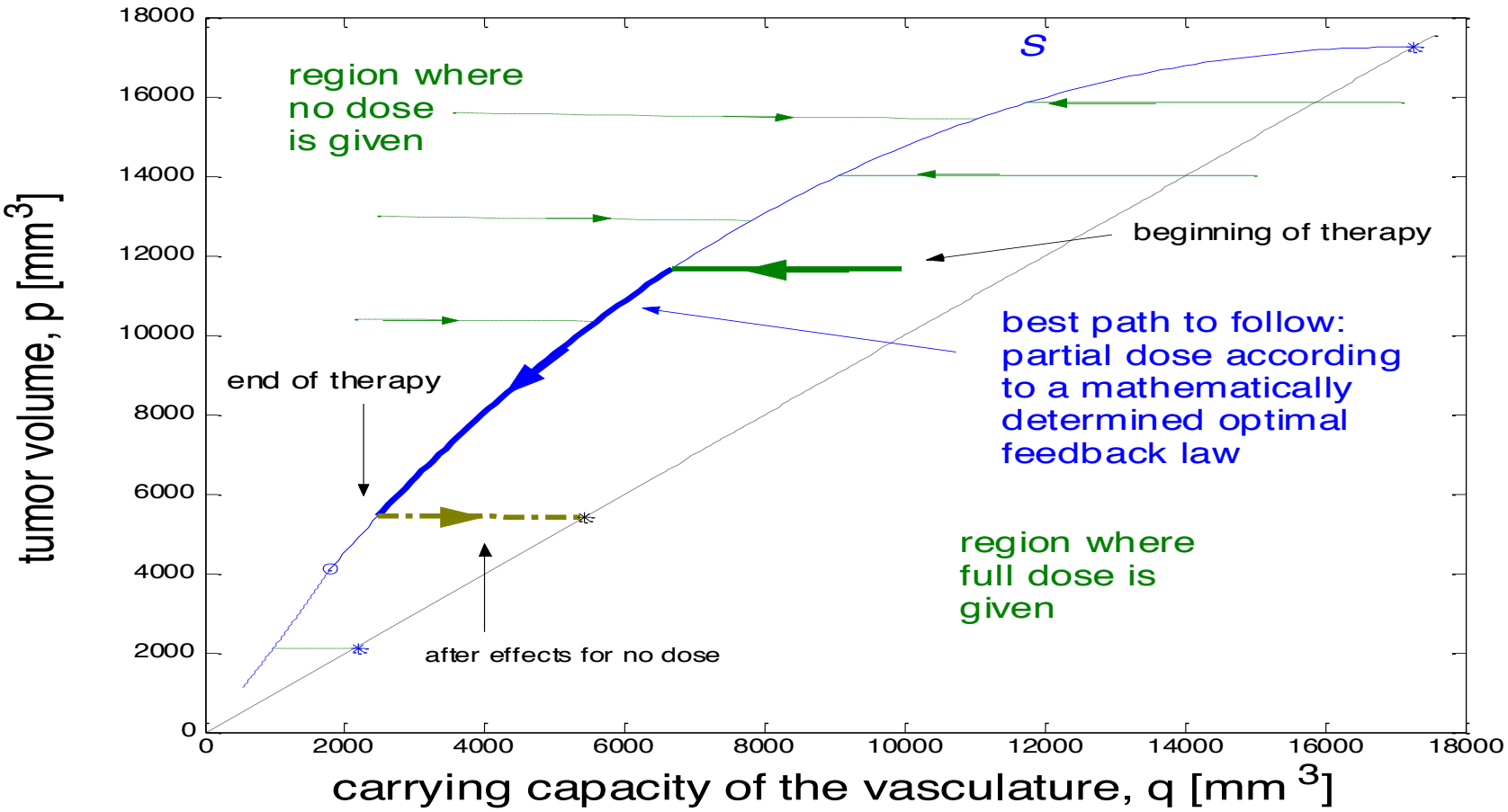
feedback control



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

• 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"

• 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

• 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"

• 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]

with d'Onofrio and H. Maurer

Minimize $p(T)$ subject to

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

$$\dot{q} = bp - (\mu + dp^{\frac{2}{3}})q - \gamma q u - \eta q v, \qquad q(0) = q_0,$$

angiogenic inhibitors

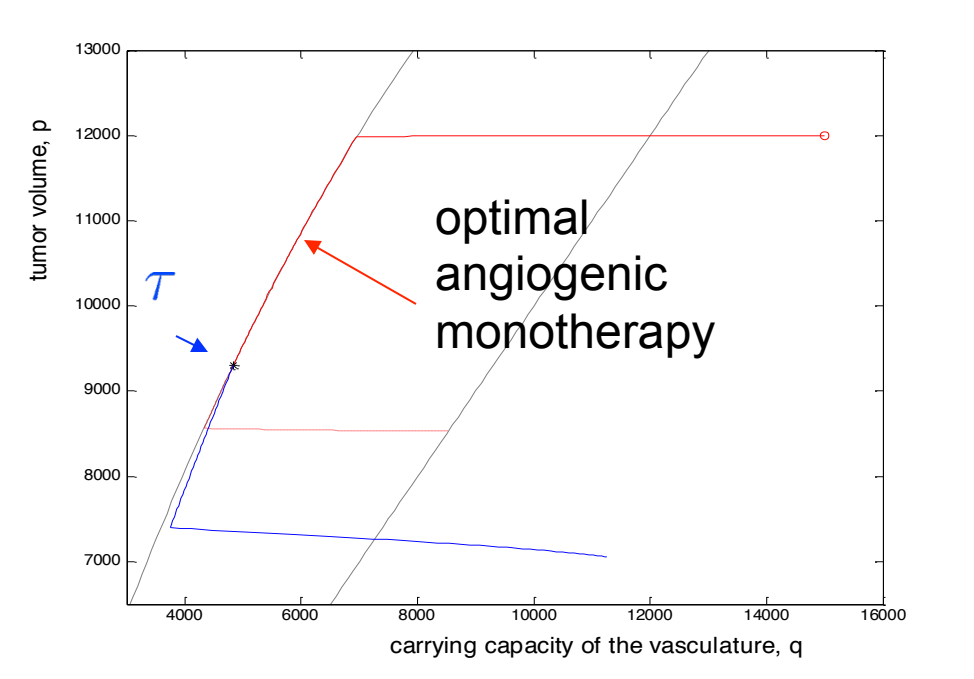
$$0 \le u \le u_{\max}, \qquad \int_0^T u(t)dt \le y_{\max}$$

cytotoxic agent or other killing term

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

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

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

healthy (late) tissue

$i = p, q, z$

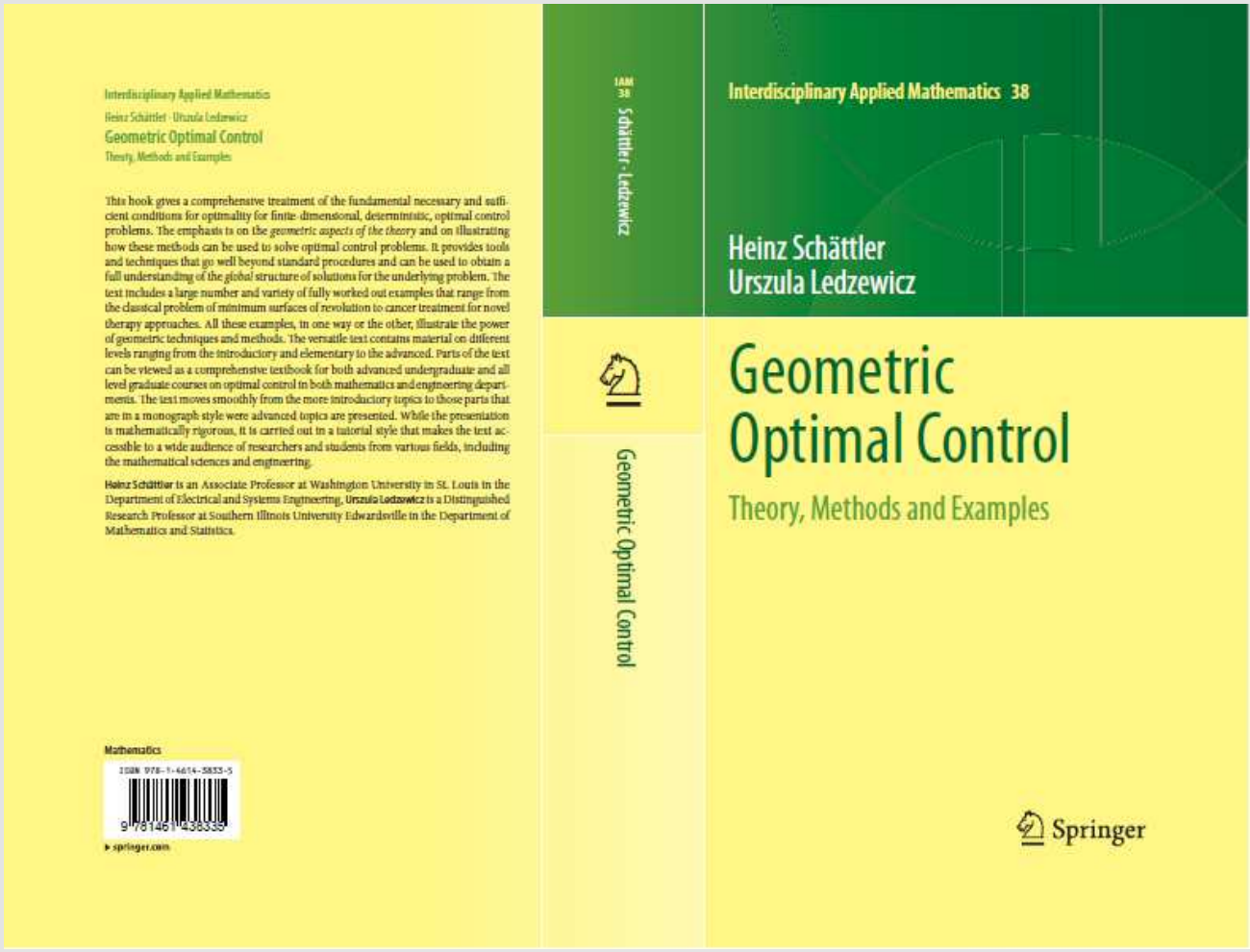
singular anti-angiogenic dose rate - control u

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

optimal singular control for angiogenic monotherapy

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

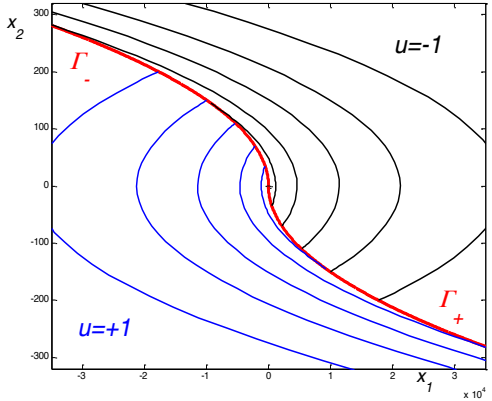
Sufficient Conditions for Optimality



How do we know solutions are optimal ?

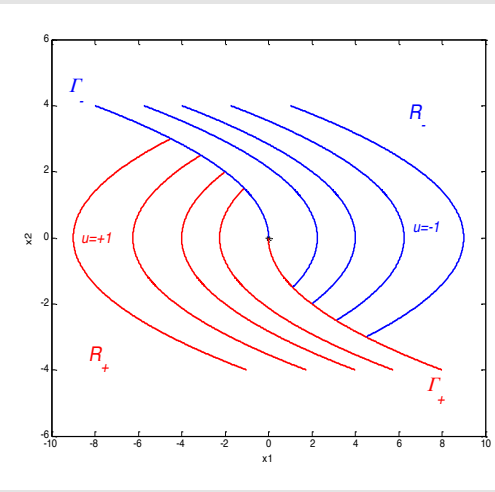
synthesis of extremal controlled trajectories

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 $u : [0, T] \to U \subset \mathbb{R}^m$, the admissible controls, for which the corresponding trajectory x,

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

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

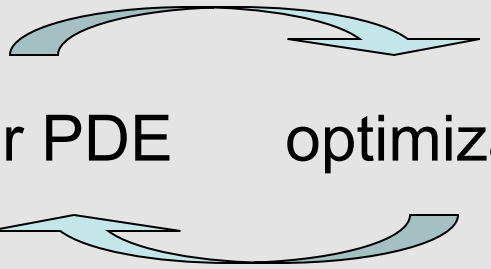
$V(T,x) = \varphi(T,x)$ for all (T,x) so that $\Psi(T,x) = 0$

“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

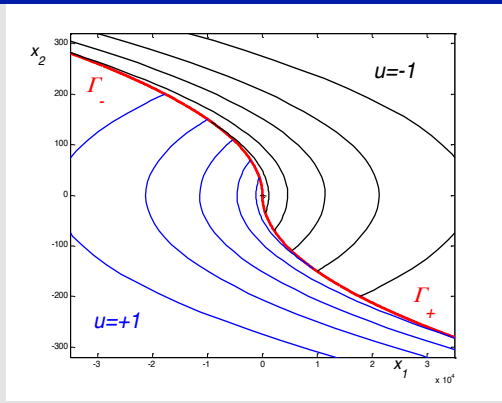
- the Hamilton-Jacobi-Bellman equation is a first order PDE, but coupled with the solution of an optimization problem



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

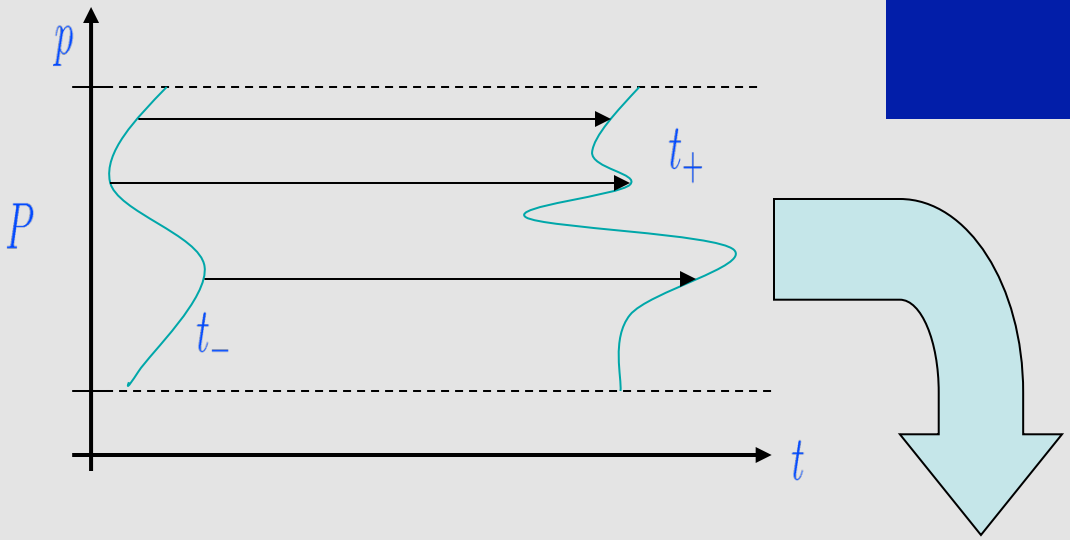


$t_+, t_- \in C^r(P)$

think of it as just one patch

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

Flow of extremals



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

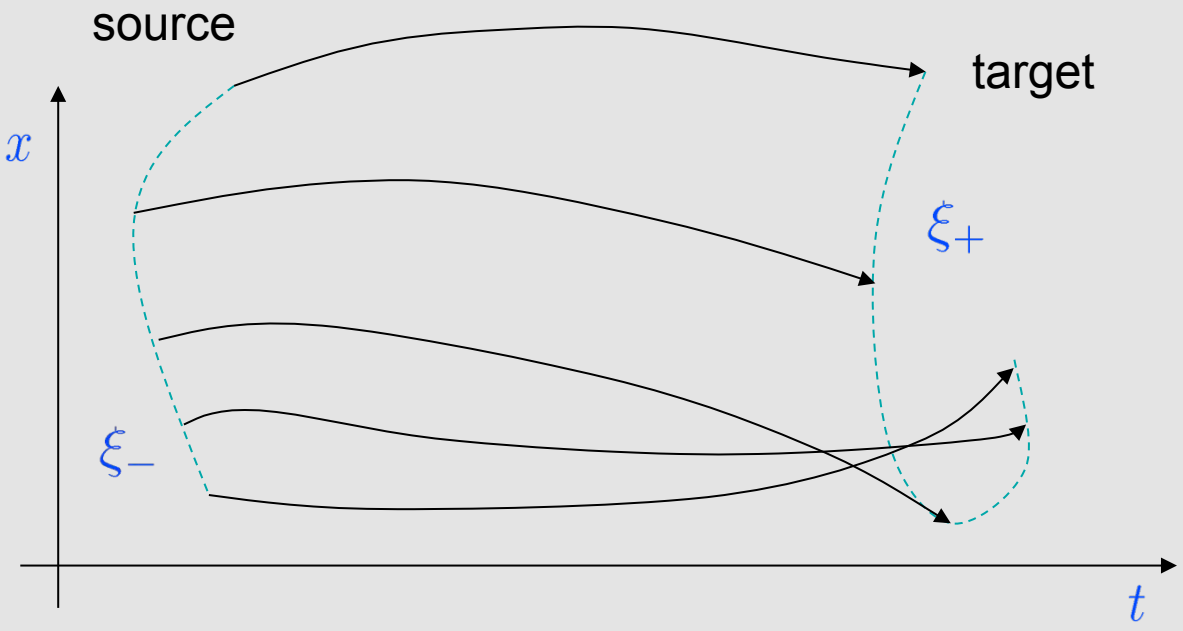
time-dependent:

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

[graphs of trajectories]

time-independent:

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



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

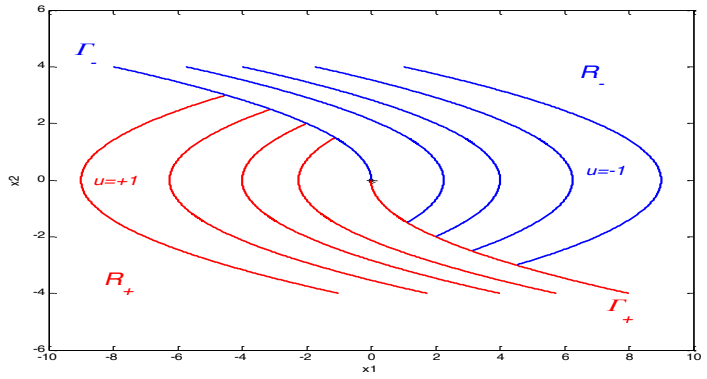
Parameterized Families with Cost

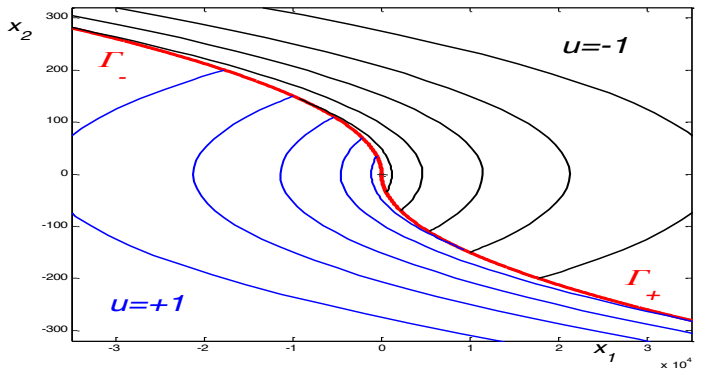
Given C^r functions γ_- and γ_+ that satisfy the transversality condition

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

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 minimumcondition 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

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

is continuously differentiable and together with the admissible feedback control

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

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

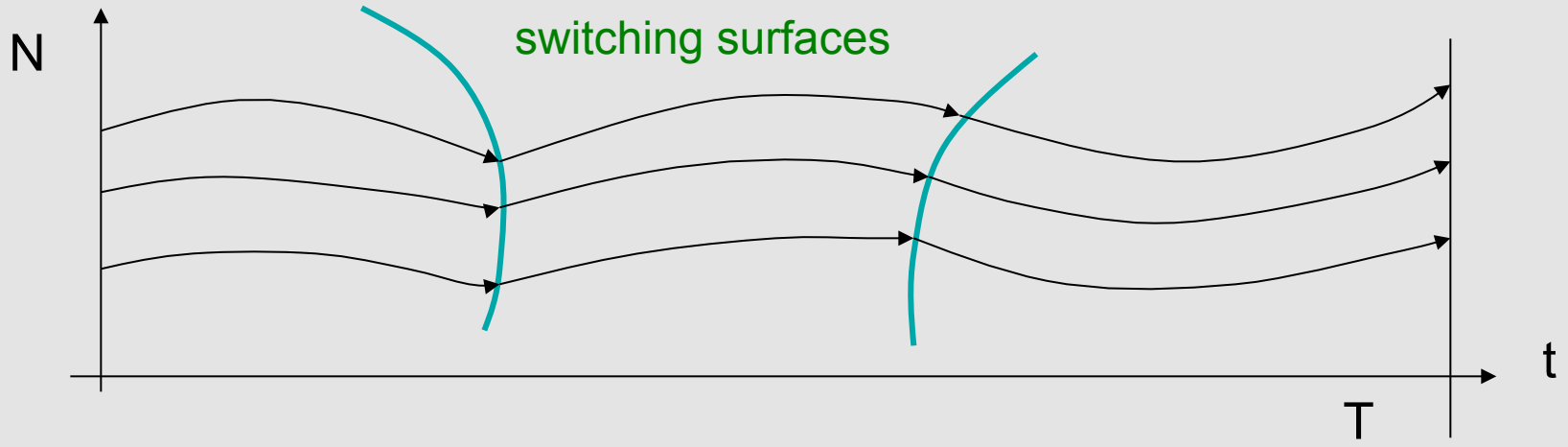
Given $(t,x) = (t, x(t,p)) \in R$ and any control $v \in U$

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

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

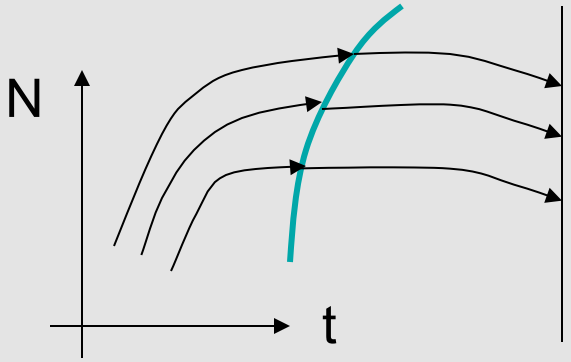
Bang-Bang Flows

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

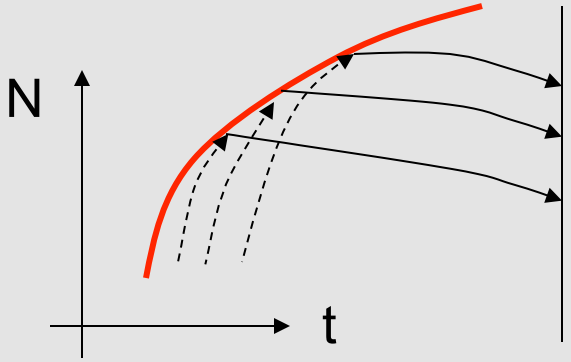
  $\Rightarrow$ optimality is preserved



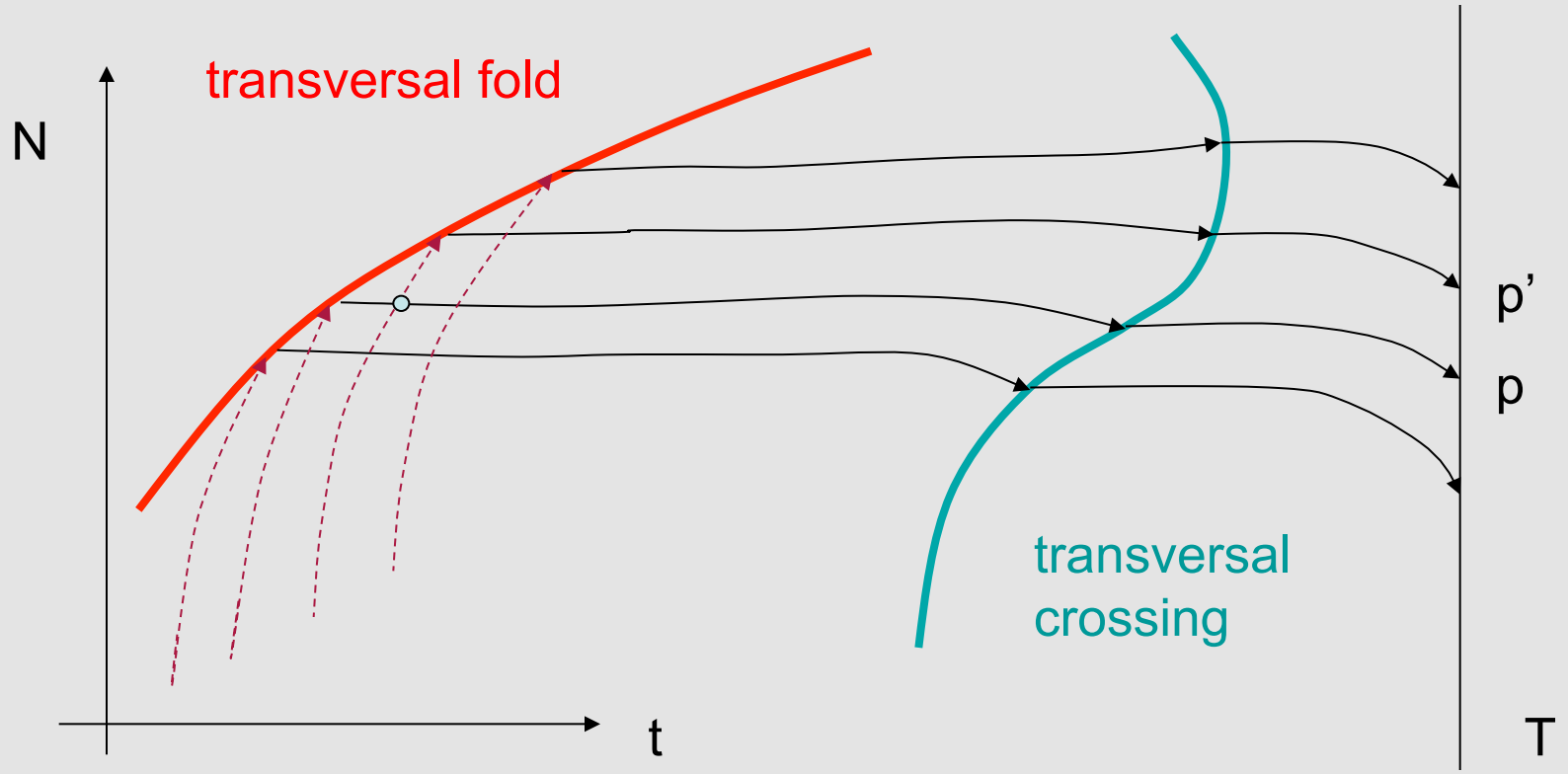
- or transversal folds:

  conjugate points—envelope

  $\Rightarrow$ optimality ceases



Flows of Extremal Bang-Bang Trajectories

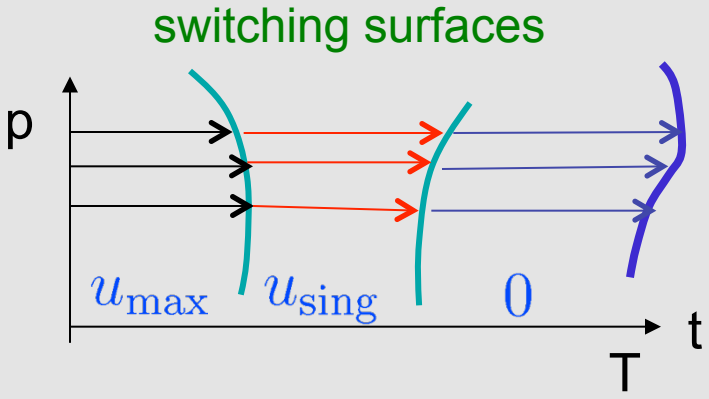


sensitivity calculations:

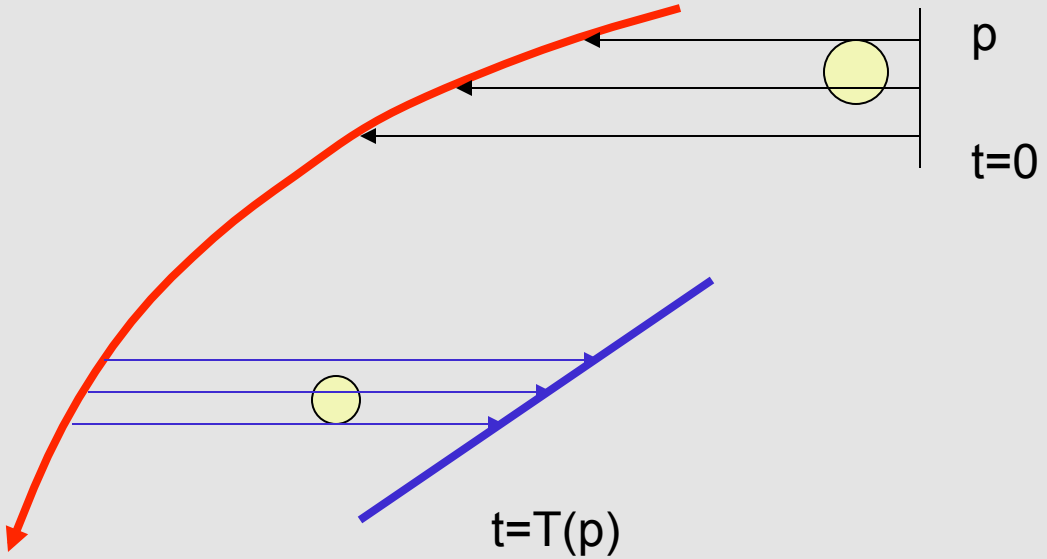
$$S(t,p) = \frac{\partial \lambda^T}{\partial p}(t,p) \left(\frac{\partial N}{\partial p}(t,p) \right)^{-1}$$

determines geometric situations

Bang-Singular-Bang Concatenations

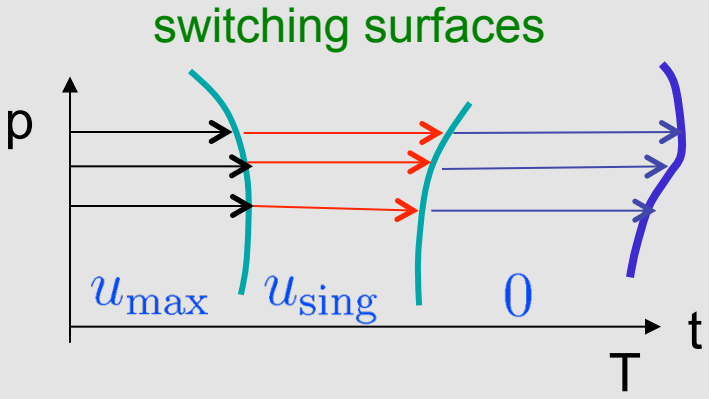


$$F: \ (t,p) \mapsto x(t,p)$$



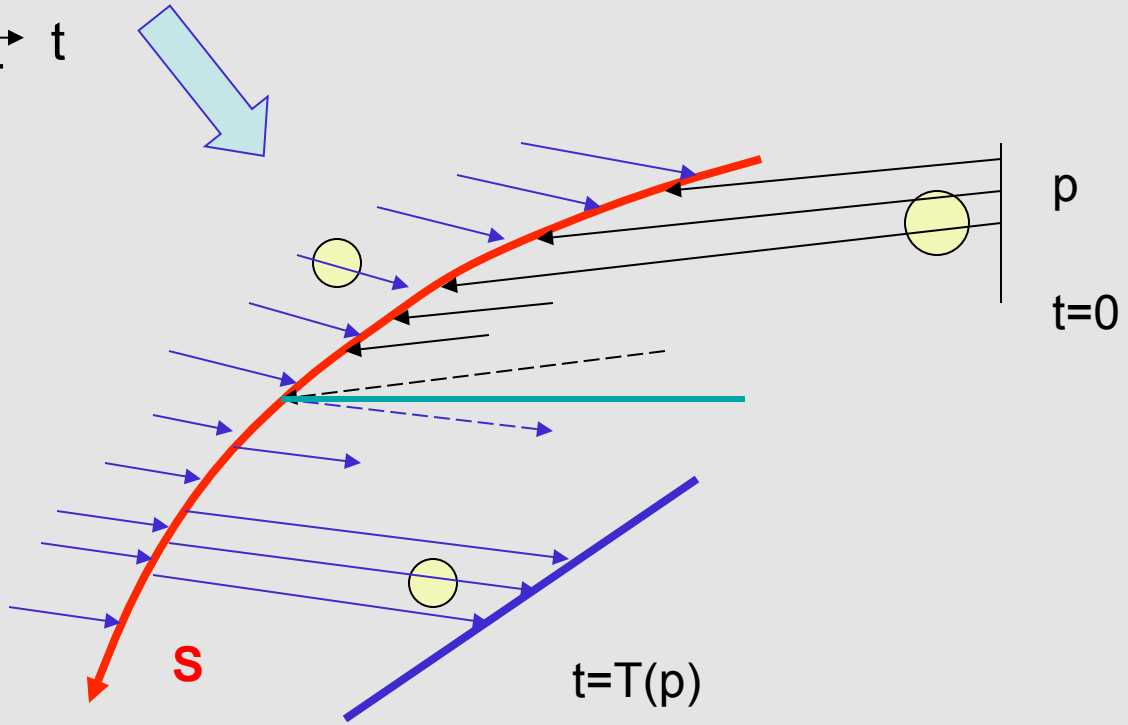
as long as the flow covers a region in the state-space one-to-one, the cost-to-go functions gives rise to a solution of the Hamilton-Jacobi-Bellman equation

Bang-Singular-Bang Concatenations

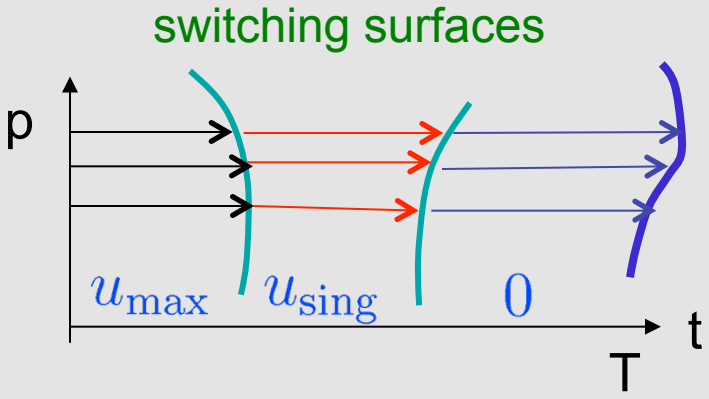


$$F: \ (t,p) \mapsto x(t,p)$$

can extend family to cover a neighborhood of reference trajectory



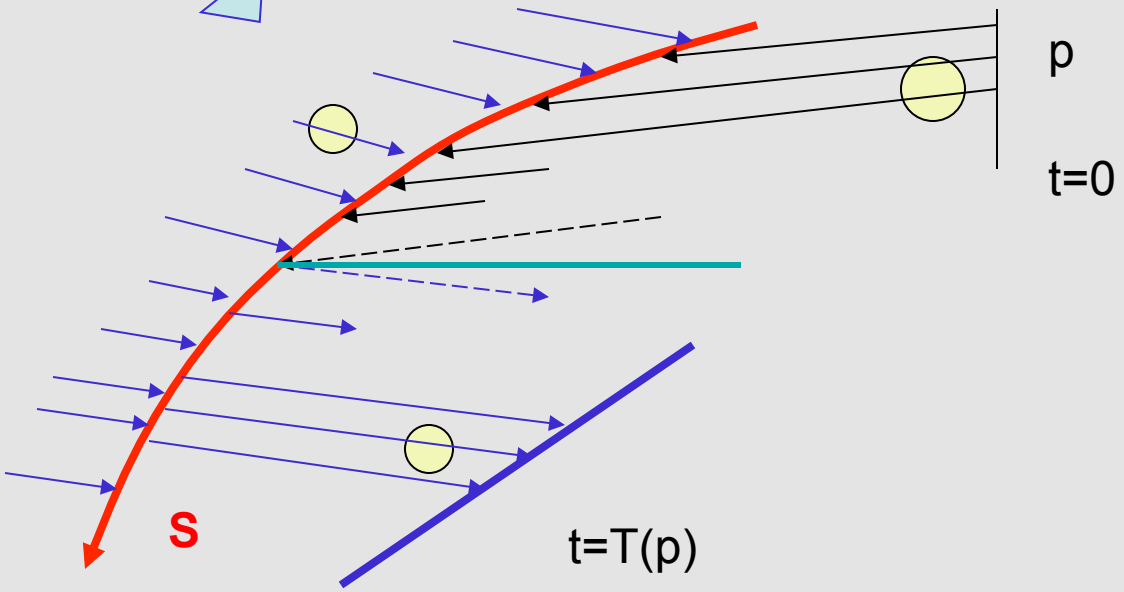
Bang-Singular-Bang Concatenations



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

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]

Conclusion

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