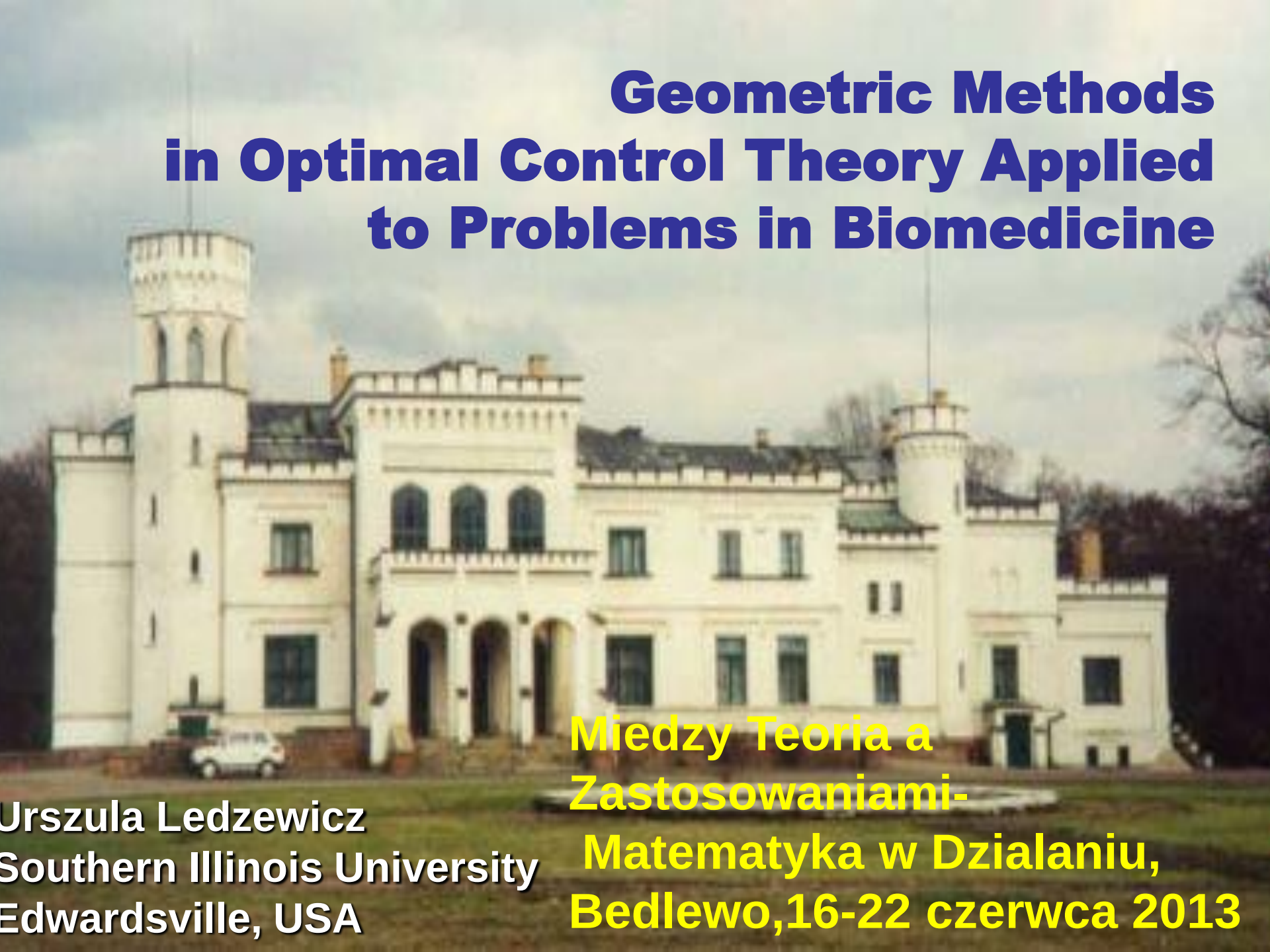
Geometric Methods in Optimal Control Theory Applied to Problems in Biomedicine



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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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Geometric Optimal Control

Interdisciplinary Applied Mathematics 38

Heinz Schättler
Urszula Ledzewicz

Geometric Optimal Control

Theory, Methods and Examples

Springer

Books

- **Heinz Schättler and Urszula Ledzewicz,**

  Geometric Optimal Control – Theory, Methods, Examples

  Springer Verlag, July 2012

- **Urszula Ledzewicz and Heinz Schättler,**

  Geometric Optimal Control Applied to Biomedical Models

  Springer Verlag, 2014

- **Mathematical Methods and Models in Biomedicine**

  Urszula Ledzewicz, Heinz Schättler, Avner Friedman and Eugene Kashdan, Eds.

  Springer Verlag, October 2012

Lecture Notes on Mathematical Modelling in the Life Sciences

Urszula Ledzewicz · Heinz Schättler · Avner Friedman · Eugene Kashdan *Editors*

Mathematical Methods and Models in Biomedicine

Mathematical biomedicine is a rapidly developing interdisciplinary field of research that connects the natural and exact sciences in an attempt to respond to the modeling and simulation challenges raised by biology and medicine.

There exist a large number of mathematical methods and procedures that can be brought in to meet these challenges and this book presents a palette of such tools ranging from discrete cellular automata to cell population based models described by ordinary differential equations to nonlinear partial differential equations representing complex time- and space-dependent continuous processes. Both stochastic and deterministic methods are employed to analyze biological phenomena in various temporal and spatial settings.

This book illustrates the breadth and depth of research opportunities that exist in the general field of mathematical biomedicine by highlighting some of the fascinating interactions that continue to develop between the mathematical and biomedical sciences. It consists of five parts that can be read independently, but are arranged to give the reader a broader picture of specific research topics and the mathematical tools that are being applied in its modeling and analysis. The main areas covered include immune system modeling, blood vessel dynamics, cancer modeling and treatment, and epidemiology. The chapters address topics that are at the forefront of current biomedical research such as cancer stem cells, immunodominance and viral epitopes, aggressive forms of brain cancer, or gene therapy. The presentations highlight how mathematical modeling can enhance biomedical understanding and will be of interest to both the mathematical and the biomedical communities including researchers already working in the field as well as those who might consider entering it. Much of the material is presented in a way that gives graduate students and young researchers a starting point for their own work.

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Mathematical Methods and Models in Biomedicine

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Urszula Ledzewicz · Heinz Schättler
Avner Friedman · Eugene Kashdan
Editors

Mathematical Methods and Models in Biomedicine

Springer

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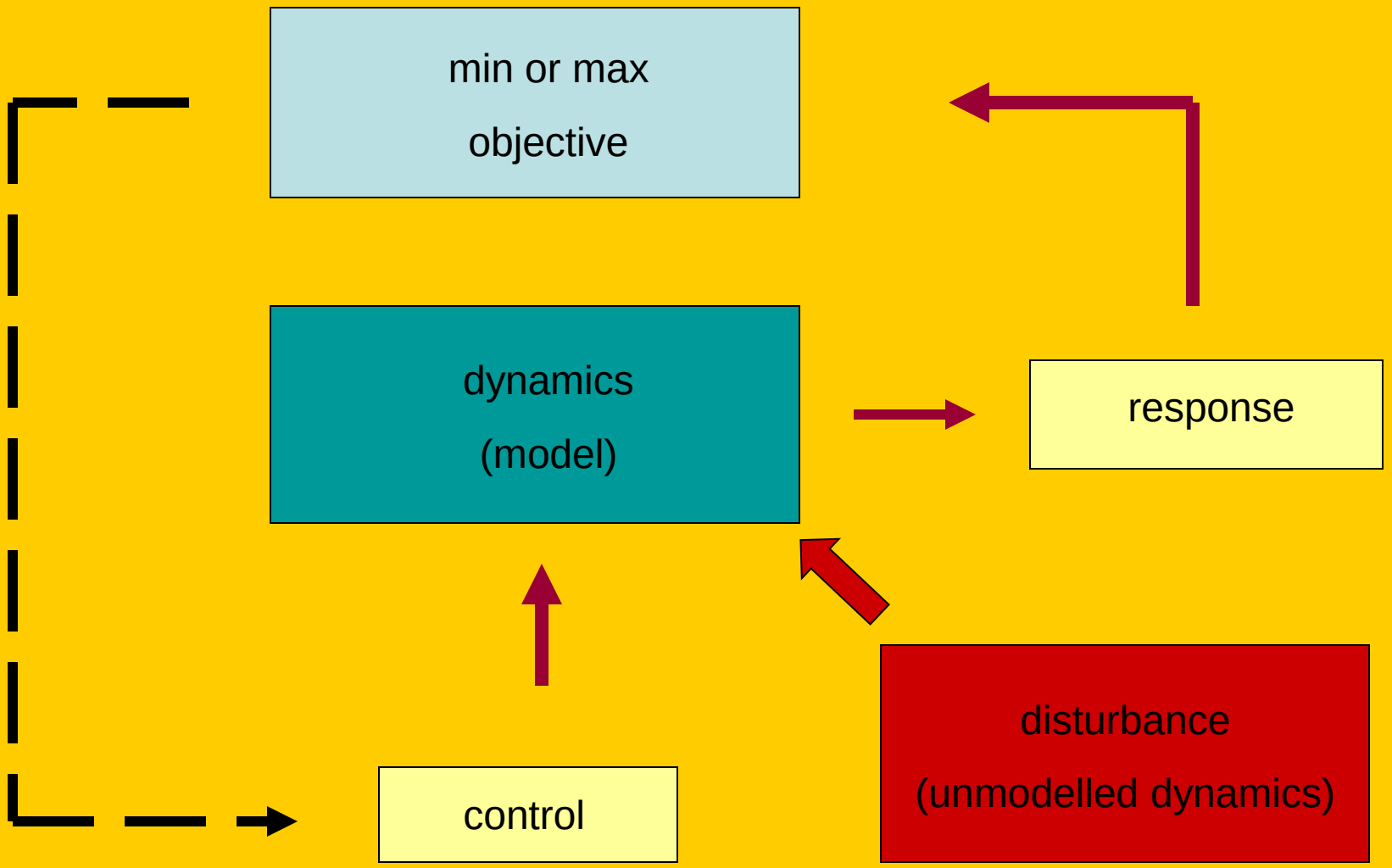
Optimal Control Problems



Outline – An Optimal Control Approach to …

- **a model for growth and invasion in glioblastoma**
- **a model for chemotherapy for heterogeneous tumors**
- **a model for antiangiogenic therapy**
  (alone and in combination with chemotherapy)
- **a model for chemotherapy and immune boost**
- **future directions metronomic chemotherapy**

Optimal Drug Treatment Protocols

Main Questions

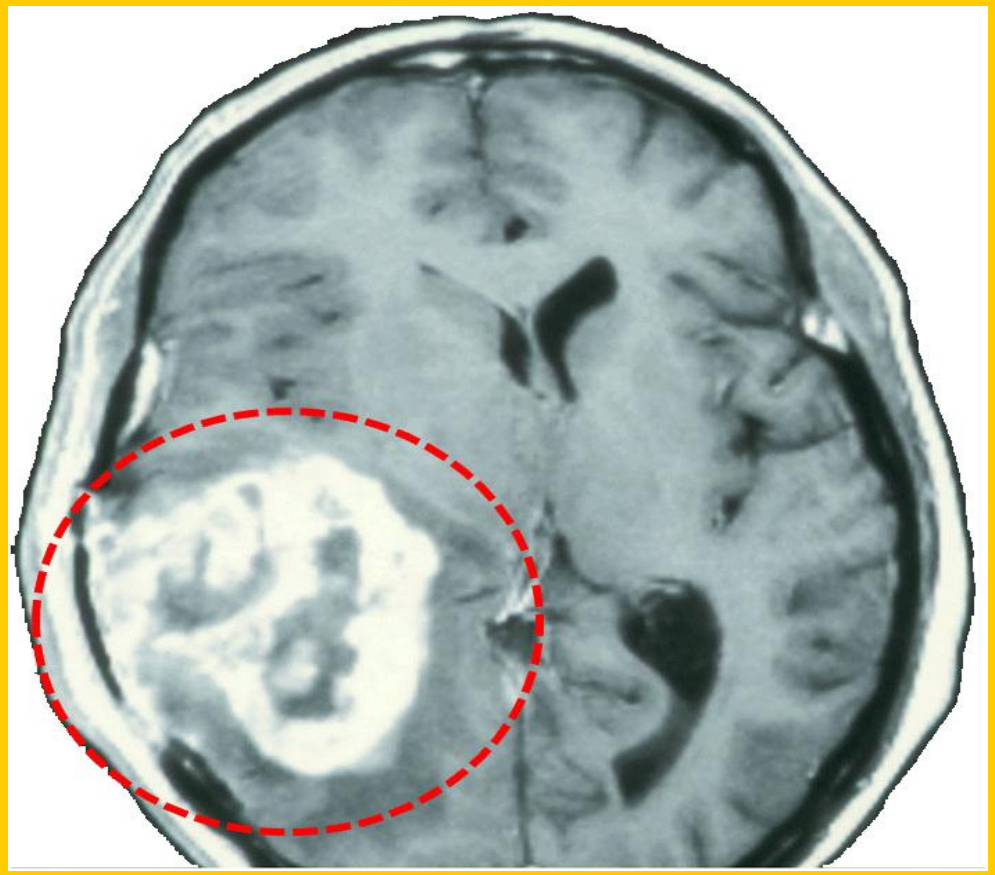
HOW MUCH? **(dosage)**

HOW OFTEN? **(timing)**

IN WHAT ORDER? **(sequencing)**

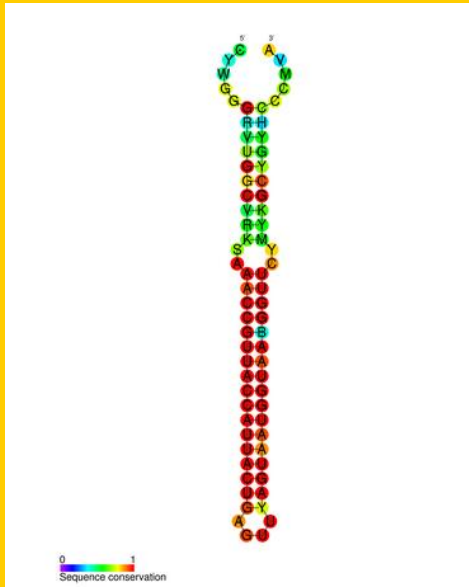
A Model for Growth and Invasion in Glioblastoma

Glioblastoma



- a particularly aggressive form of brain cancer characterized by alternating phases of rapid growth and tissue invasion with a mean survival time of just about one year
- treatment: surgery
- problem: distant tumor satellites

- **normal glucose levels** up-regulate the **microRNA miR-451** level leading to **cell proliferation** and decreased cell migration
- **low glucose levels** induce a down-regulation of miR-451, which, in turn, promotes **cell motility and invasion**, but inhibits proliferation.



Dynamics of the miR-451 AMPK Complex [Kim, Roh, Lawler and Friedman, PLoS One, (2011)

miR 451 - micro RNA's regulate the expression levels of genes

AMPK – adenosine monophosphate-activated protein kinase

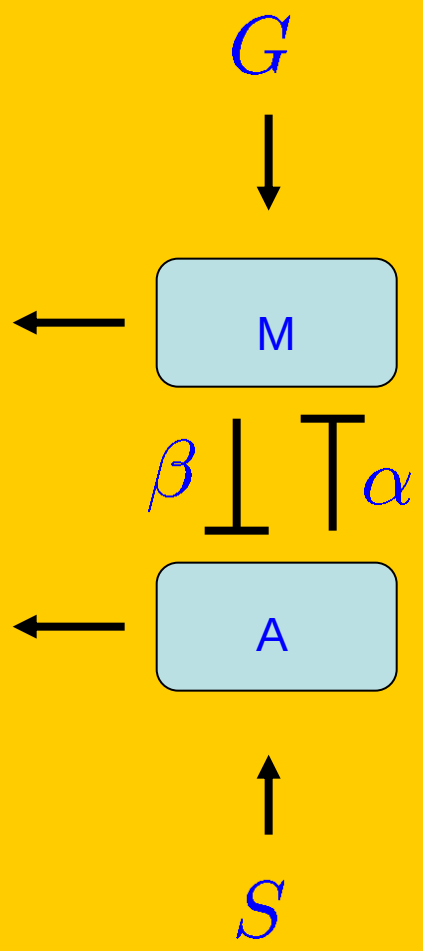
an enzyme that plays a role in cellular energy homeostasis including glucose uptake

M – concentration of miR-451

A – concentration of AMPK complex

G – glucose level

S – source of AMPK complex



Dynamics of the miR-451 AMPK Complex [Kim and Roh, Discr. and Cont. Dyn. Syst., (2013)

$$\dot{M} = G + \frac{\kappa_1}{1+\alpha A^2} - M,$$
$$\varepsilon \dot{A} = S + \frac{\kappa_3}{1+\beta M^2} - A,$$

non-dimensionalized, minimally parameterized version of the model

$\varepsilon \ll 1$ *A* degrades much faster than *M* (half-life of miR 451 is in the range of 100-200 hours, for AMPK about 6 hours)

α – inhibition of miR-451 by AMPK (Hill-type, scaled)

β - inhibition of AMPK by miR-451 (Hill-type, scaled)

κ_1 - autocatalytic strength of miR-451 (scaled)

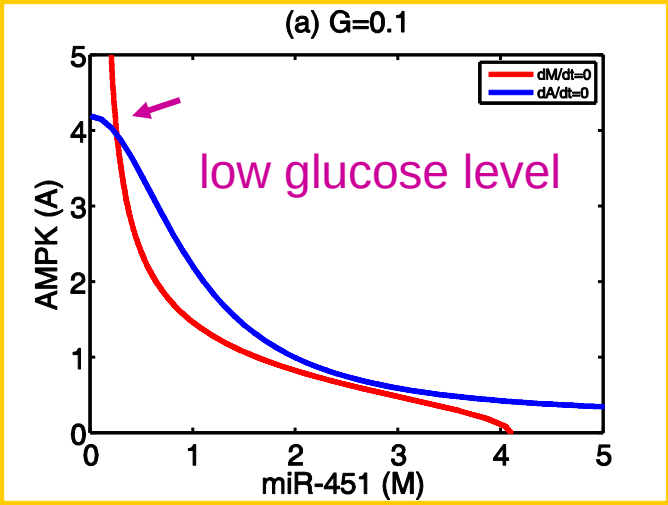
κ_3 - autocatalytic strength of AMPK (scaled)

ε - scaling factor related to the degradation rates of miR-451 and AMPK,

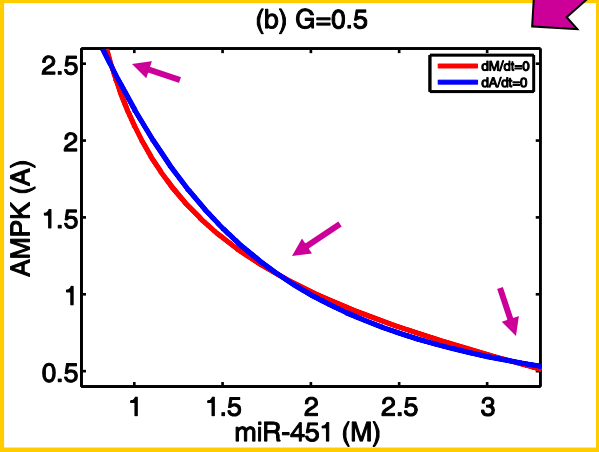
G constant

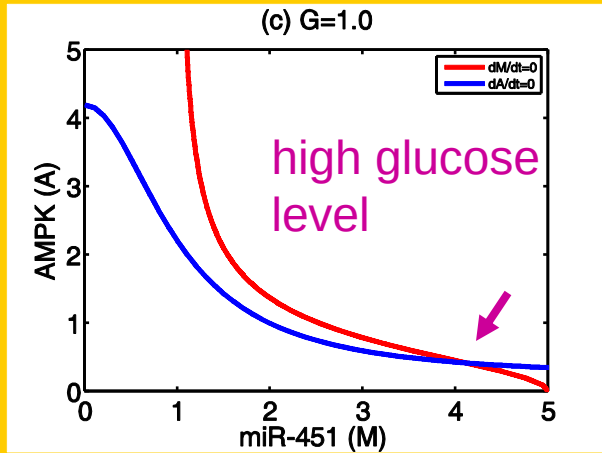
Differential-Algebraic Model

$$\left.\begin{aligned} \dot{M} &= G + \frac{\kappa_1}{1+\alpha A^2} - M, \\ 0 &= S + \frac{\kappa_3}{1+\beta M^2} - A, \end{aligned}\right\} \Rightarrow \dot{M} + \cdots$$



multi-stability for intermediate glucose level



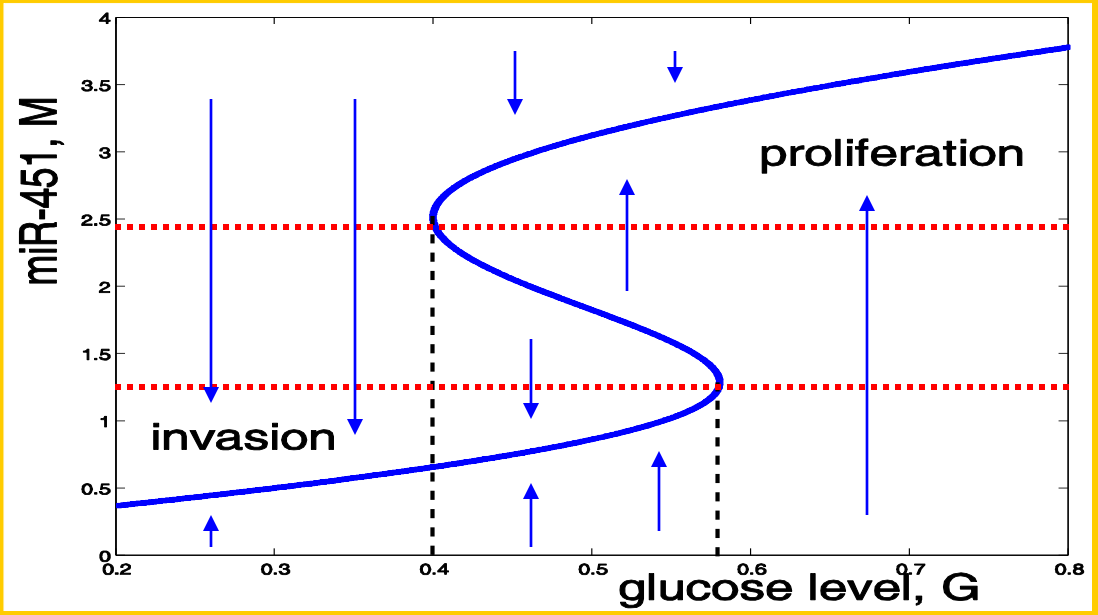


blue curve = slow manifold

red curve = equilibrium manifold

Hysteresis

for a constant glucose level, *G=const*, the following hysteresis picture for the equilibria and their stability arises

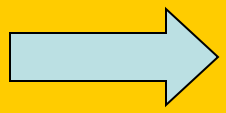


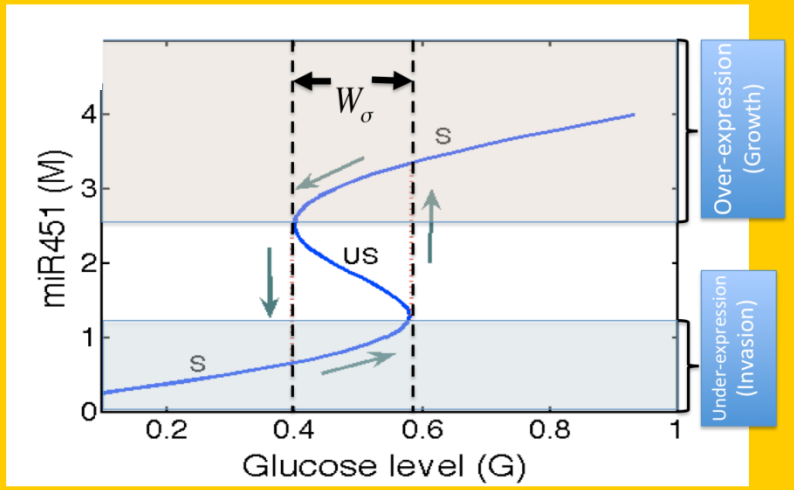
growth

(over-expression)

invasion

(under-expression)





cycle for differential algebraic model

Goal

- maintain the miR-451 level M above a threshold M_{th} so that glioma cells remain in the proliferation phase and do not switch into their invasive migratory phase

- effective control: the level of glucose

$$\dot{G} = -\lambda G + u, \qquad G(0) = G_0$$

we allow for both bolus injections or continuous infusions and do not limit the control variable in its size

- use as little glucose as possible in order to limit the cancer growth

→ **minimize the overall amount of glucose given**

Optimal Control Problem

[M] for a fixed terminal time T, minimize the objective

$$J = \sum_{i=1}^{k} G_i + \int_0^T u(t)dt$$

over all times $t_i \in [0, T]$, bolus dosages G_i , $k \in \mathbb{N}$ and all Lebesgue measurable functions $u : [0, T] \to [0, \infty)$

subject to the dynamics

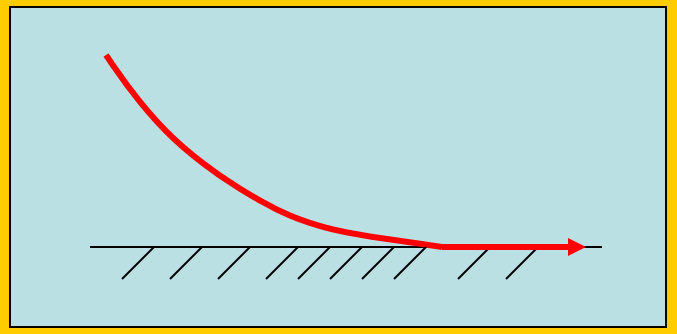
$$\begin{aligned} \dot{M} &= G + \frac{\kappa_1}{1 + \alpha A^2} - M, \\ \varepsilon \dot{A} &= S + \frac{\kappa_3}{1 + \beta M^2} - A, \\ \dot{G} &= -\lambda G + u \end{aligned}$$

and state-space constraint $M(t) \geq M_{th}$ for all $t \in [0, T]$

State-Space Constraint

- the state-space constraint $M(t) \geq M_{th}$ is of order 2:

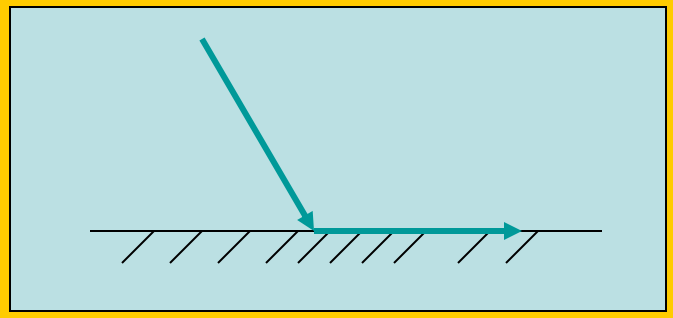
$$\begin{aligned} \dot{M} &= G + \frac{\kappa_1}{1+\alpha A^2} - M = 0, \\ \ddot{M} &= -\lambda G + u + \cdots + = 0 \end{aligned}$$



- this makes transitions with the constraint difficult

  (possibly chattering, …)

- consider a modified problem with an order 1 state-space constraint



Optimal Control Problem II

[G] for a fixed terminal time T, minimize the objective

$$J = \sum_{i=1}^{k} G_i + \int_0^T u(t)dt$$

over all times $t_i \in [0, T]$, bolus dosages G_i, $k \in \mathbb{N}$ and all Lebesgue measurable functions $u : [0, T] \to [0, \infty)$

subject to the dynamics

$$\begin{aligned} \dot{M} &= G + \frac{\kappa_1}{1 + \alpha A^2} - M, \\ \varepsilon \dot{A} &= S + \frac{\kappa_3}{1 + \beta M^2} - A, \\ \dot{G} &= -\lambda G + u \end{aligned}$$

and state-space constraint $G(t) \geq G_{th} = G(M_{th})$ for all $t \in [0, T]$

Solution for [G]

- for problem [M] to be well-posed, we assume that

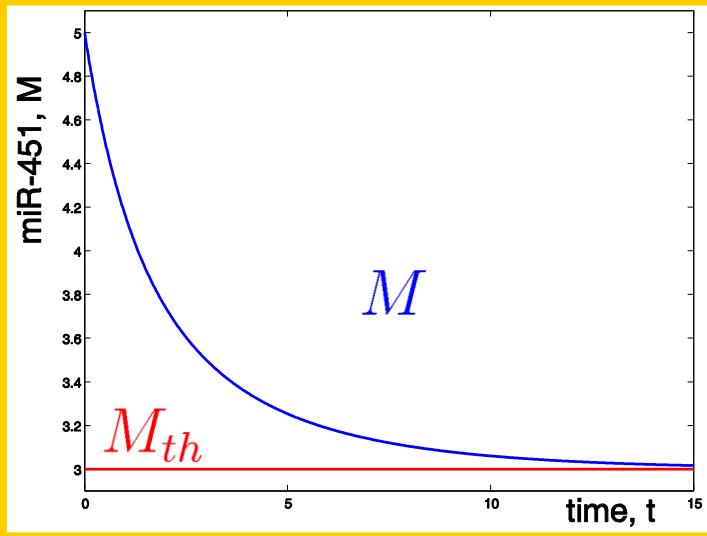
$$M_0 = M(0) \geq M_{th}$$

- according to the fast dynamics for *A* we also assume that

$$A_0 = A(0) = S + \frac{k_3}{1+\beta M_0^2}$$

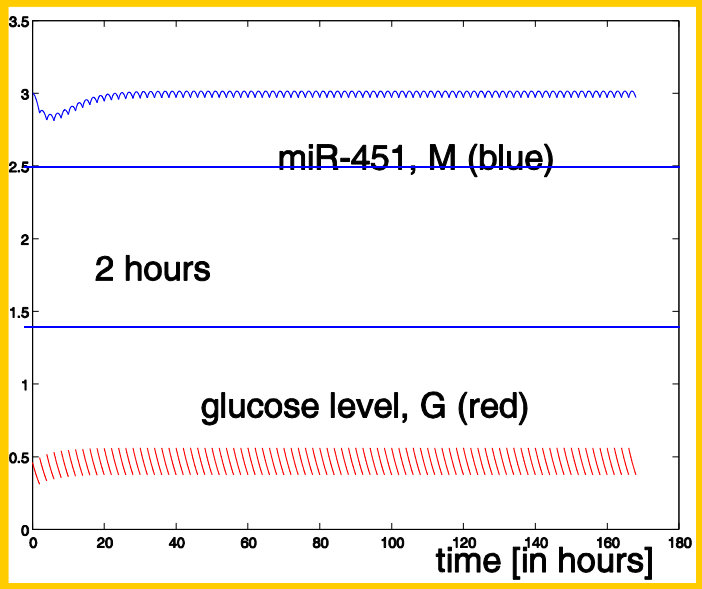
Theorem [SchKimLed, 52nd, CDC 2013]

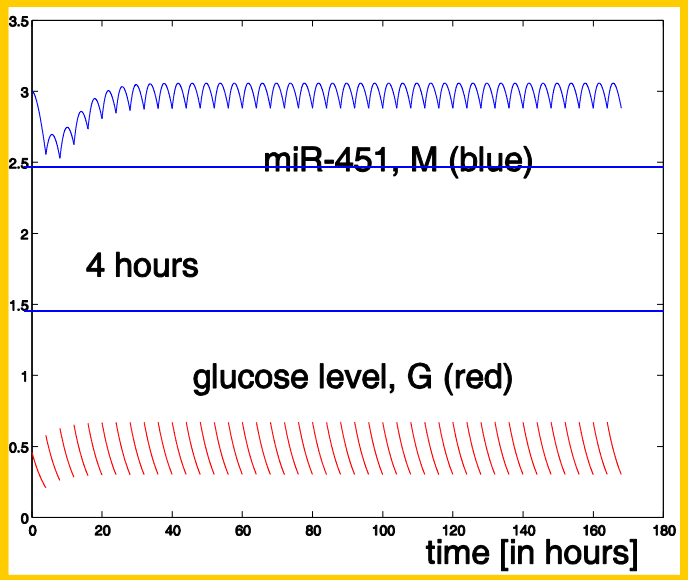
For these initial conditions the solution to the optimal control problem *[G]* is given by administering an initial bolus dose G_1 of glucose that brings the system to the threshold level G_{th} at time *0* (if it lies below) followed by constant infusion at rate $u_* \equiv \lambda G_{th}$. This control maintains the level of *M* above its lower threshold M_{th}.

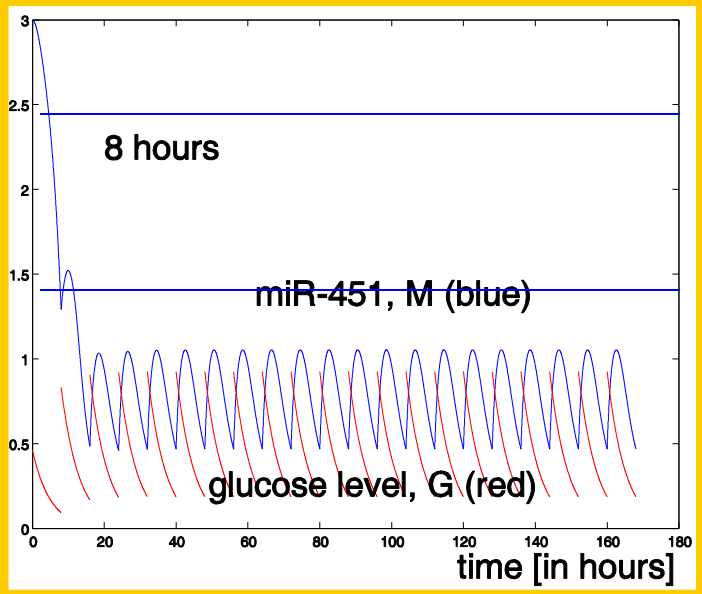


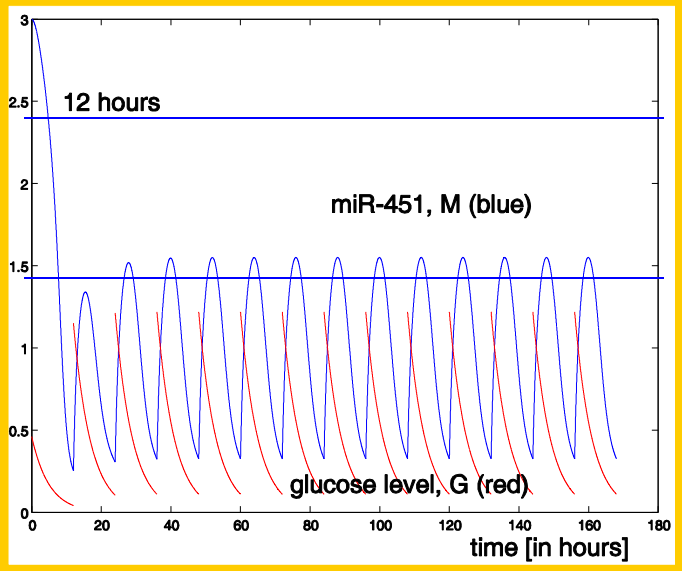
continuous administration does better than spaced boli

Periodic Bolus Injections

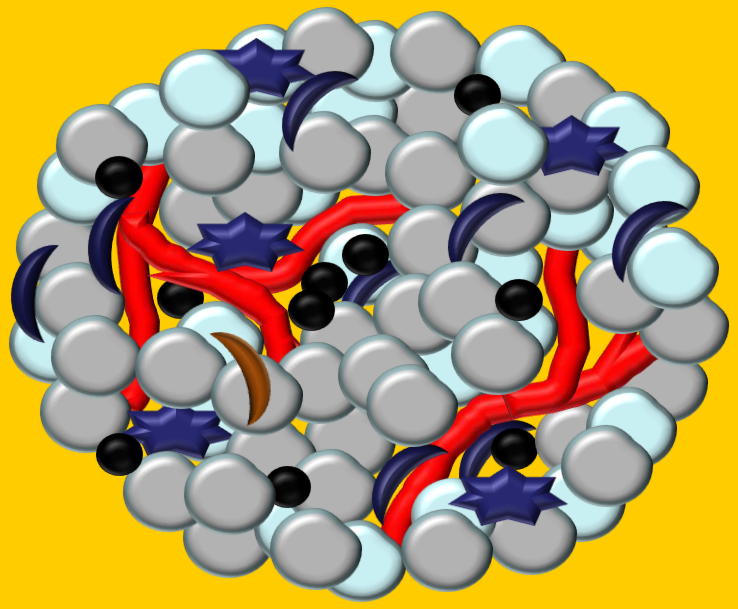








Heterogeneous Tumor Cell Populations

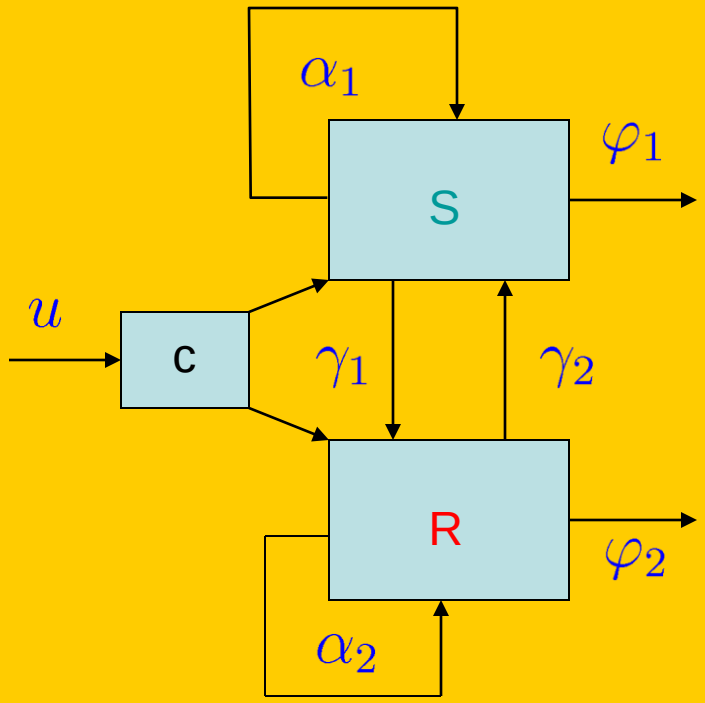


Mathematical Model
[Hahnfeldt, Folkman and Hlatky, JTB, 2003]

for simplicity, just consider two populations of different chemotherapeutic sensitivity and call them ‘sensitive’ and ‘resistant’

$$
\begin{aligned}
\dot{S} &= (\alpha_1 - \gamma_1 - \varphi_1 c)S + \gamma_2 R \\
\dot{R} &= \gamma_1 S + (\alpha_2 - \gamma_2 - \varphi_2 c)R \\
\dot{c} &= -\beta c + u
\end{aligned}
$$

N=(S,R)



S – sensitive cell population

R – resistant cell population

α_1 – growth rate of sensitive population

α_2 – growth rate of resistant population

γ_1 – transfer rate from sensitive to resistant population

γ_2 – transfer rate from resistant to sensitive population

φ_1 – linear log-kill parameter for sensitive population

φ_2 – linear log-kill parameter for resistant population

β – pharmacokinetic parameter related to half-life of chemotherapeutic agent

Mathematical Model: Objective

minimize the number of cancer cells ***N = (S,R)***

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

Toxicity of the drug

(side effects on healthy cells)

As Optimal Control Problem (LSch, JBS, 2013, submitted)

For a fixed therapy horizon $[0, T]$ **minimize**

$$J = r_1 S(T) + r_2 R(T) + \int_0^T q_1 S(t) + q_2 R(t) + u(t) dt$$

over all functions $u : [0, T] \to [0, u_{\max}]$ subject to the dynamics

$$\begin{aligned} \dot{z} &= (A + cB)z, & z(0) &= z_0 \\ \dot{c} &= -\beta c + u, & c(0) &= 0 \end{aligned}$$

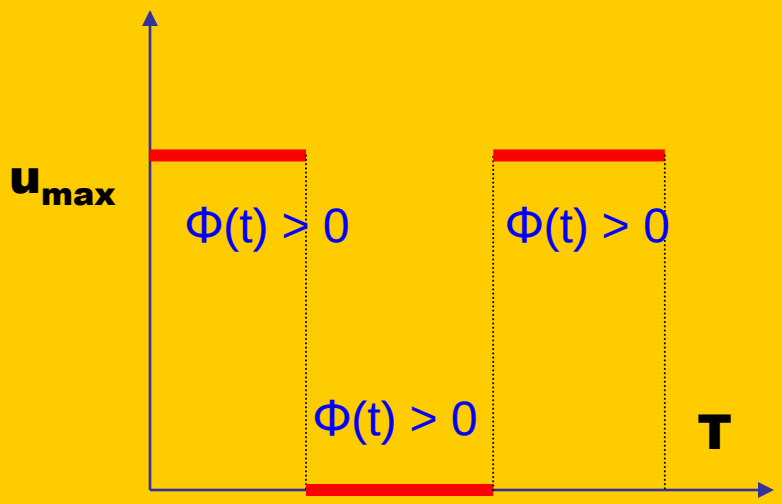
where

$$A = \begin{pmatrix} \alpha_1 - \gamma_1 & \gamma_2 \\ \gamma_1 & \alpha_2 - \gamma_2 \end{pmatrix} \qquad B = \begin{pmatrix} -\varphi_1 & 0 \\ 0 & -\varphi_2 \end{pmatrix}$$

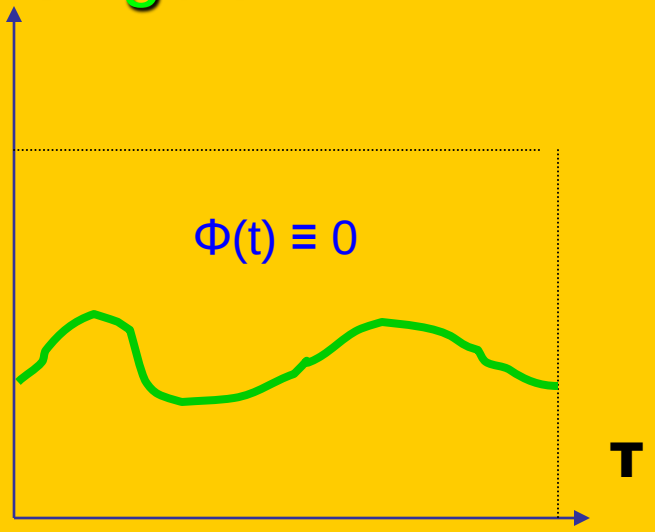
Candidates for Optimal Protocols

switching function $\Phi(t)$

- bang-bang controls



- singular controls



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

MTD

continuous infusions of varying lower doses

BOD

Singular Controls

- u_* is singular on an open interval I

  $\Longleftrightarrow$ switching function $\Phi(t) \equiv 0$ on I
- 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
- **Legendre-Clebsch condition** (minimize)

$$(-1)^k \frac{\partial}{\partial u} \Phi^{(2k)}(t) \geq 0$$

Bang-bang vs. Singular Solutions

- in the region BB,

$$BB = \{(S,R) : [(\varphi_1 - \varphi_2)\beta\gamma_2 - q_2\varphi_1\varphi_2 S(t)]R(t) \leq q_1\varphi_1^2 S(t)^2\}$$

the Legendre-Clebsch condition is violated and optimal controls are **bang-bang**; in particular, this holds if

$$S \geq \beta \frac{\varphi_1 - \varphi_2}{\varphi_1\varphi_2}\frac{\gamma_2}{q_2}$$

•outside the region *BB,*

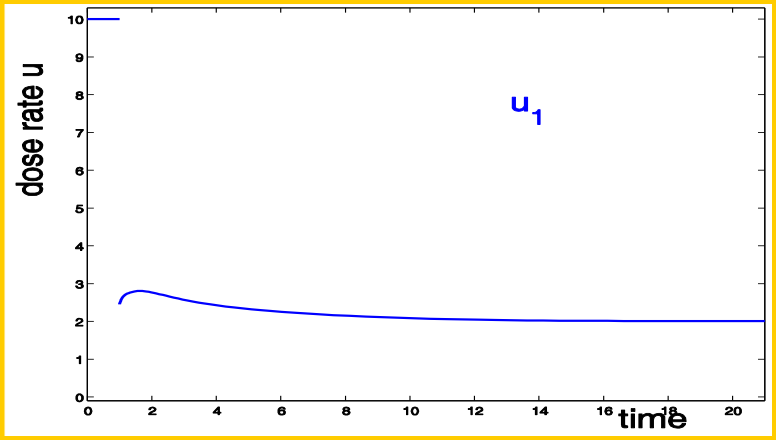
the Legendre-Clebsch condition is satisfied, but singular controls are of order 2 and concatenations with bang controls are through chattering arcs

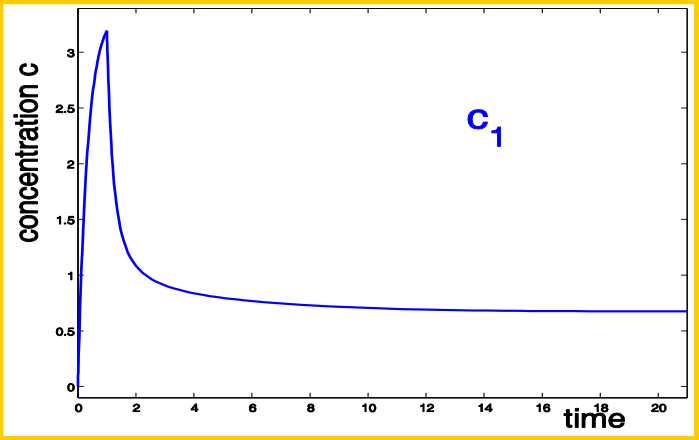
singular controls become a viable option as the sensitive cells get depleted through chemotherapy and the resistant population becomes dominant

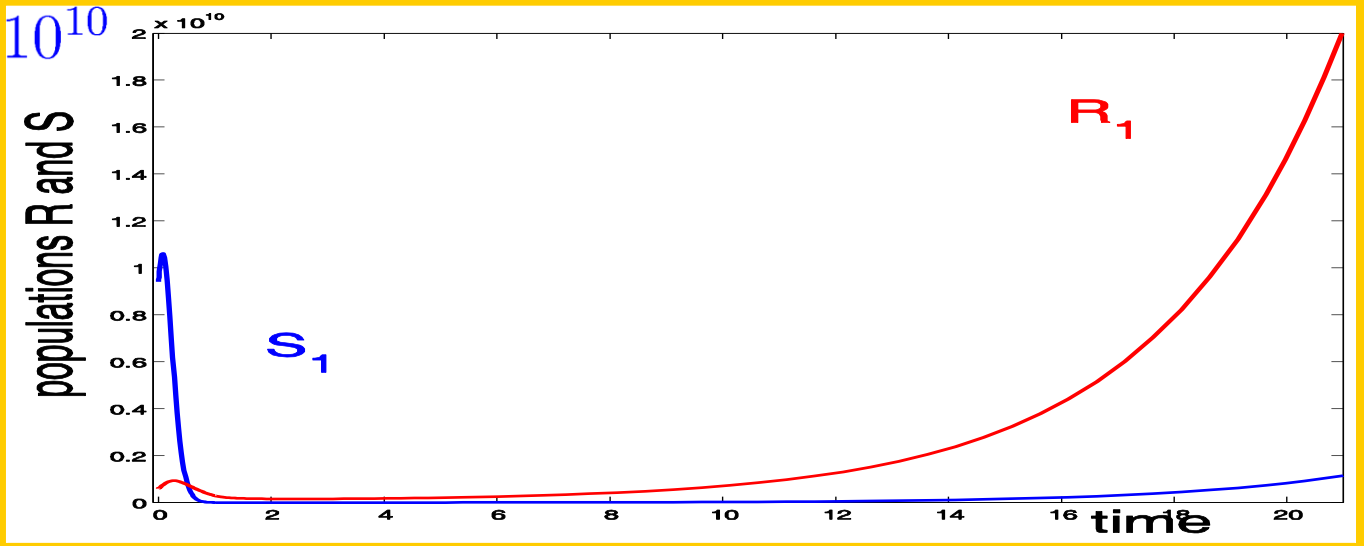
Numerical Simulations

$$u_\tau(t) = \begin{cases} u_{\max} & \text{for } 0 \le t \le \tau, \\ u_{\text{sing}} & \text{for } \tau < t \le T. \end{cases}$$

$\tau = 1$





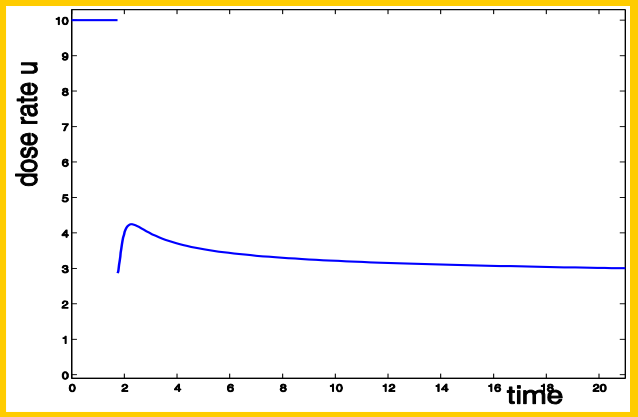


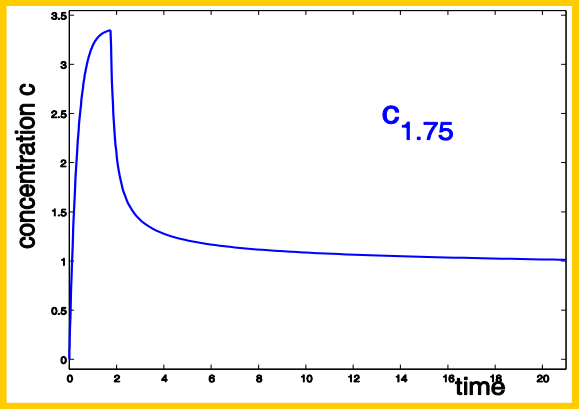
$T = 21$

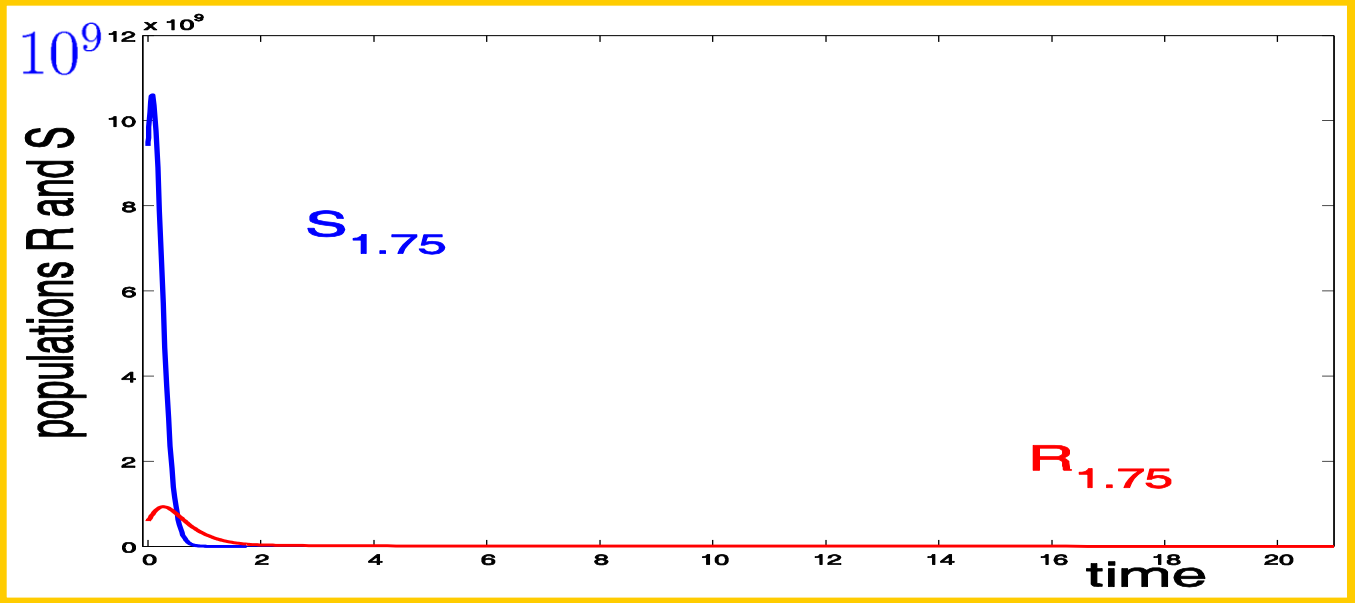
Numerical Simulations

$$u_\tau(t) = \begin{cases} u_{\max} & \text{for } 0 \le t \le \tau, \\ u_{\text{sing}} & \text{for } \tau < t \le T. \end{cases}$$

$\tau = 1.75$





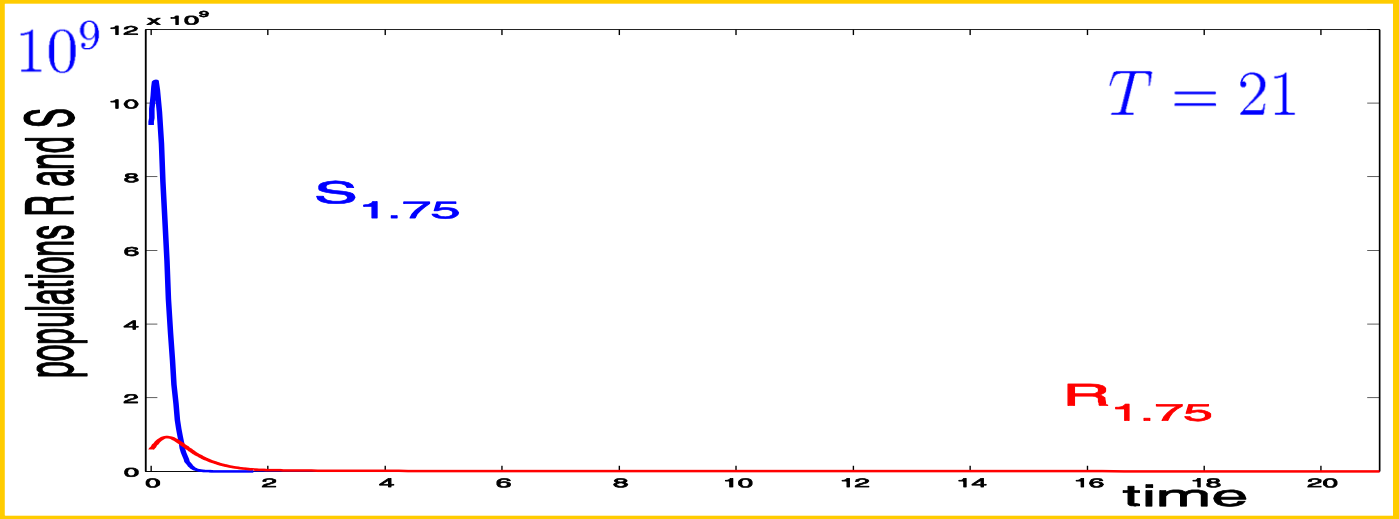


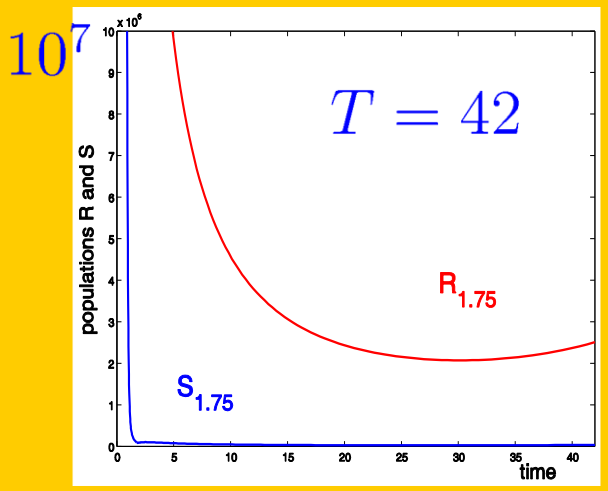
$T = 21$

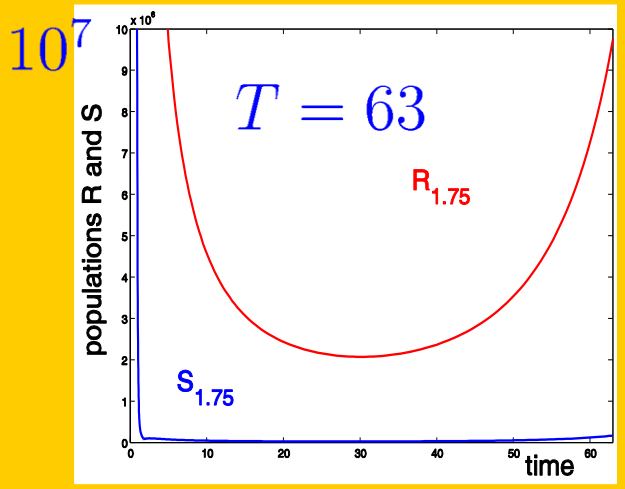
Numerical Simulations

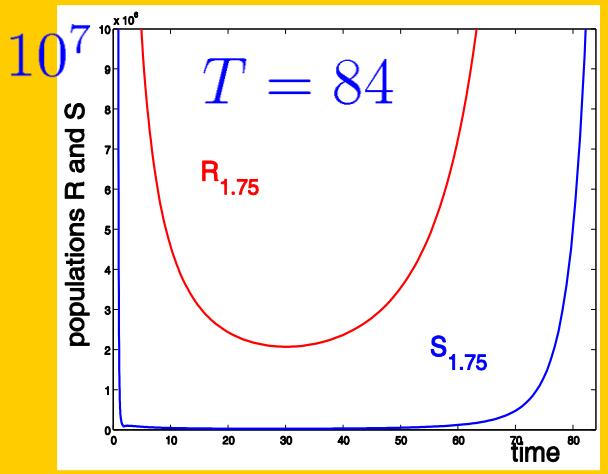
$$u_\tau(t) = \begin{cases} u_{\max} & \text{for } 0 \le t \le \tau, \\ u_{\sing} & \text{for } \tau < t \le T. \end{cases}$$

$\tau = 1.75$





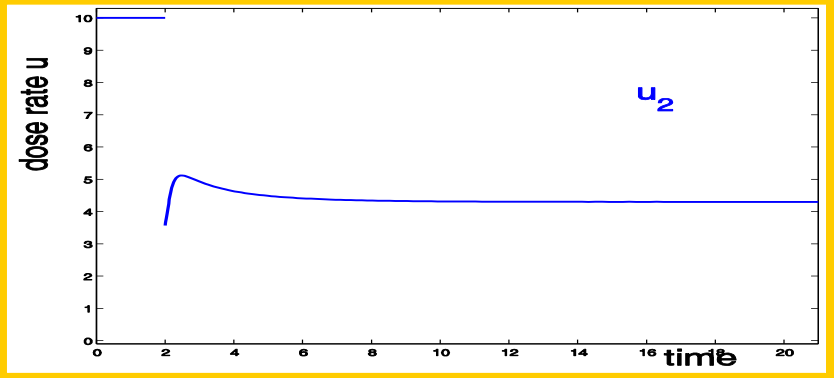


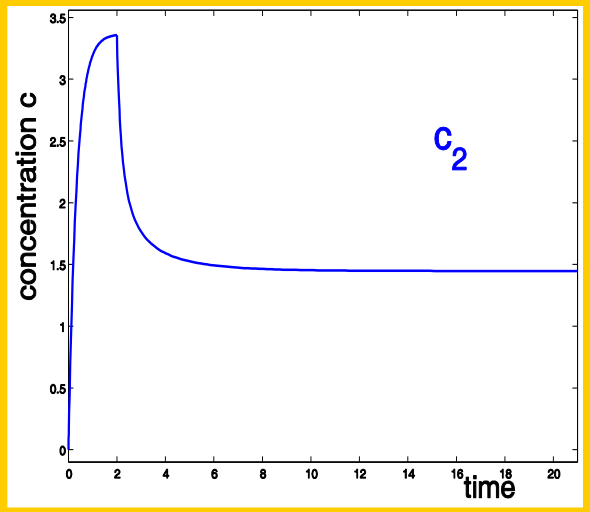


Numerical Simulations

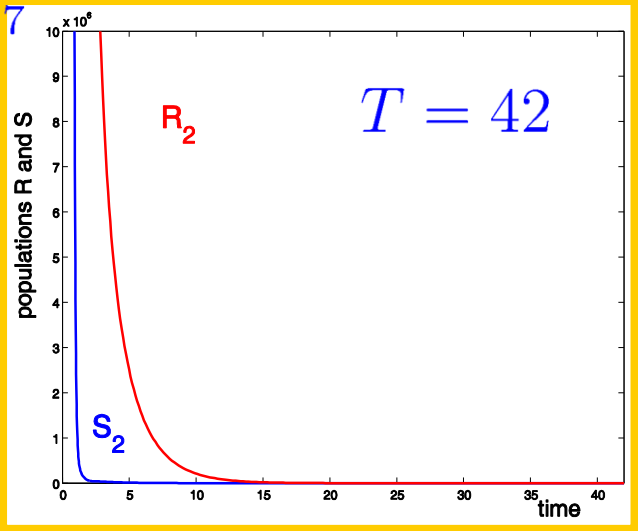
$$u_\tau(t) = \begin{cases} u_{\max} & \text{for } 0 \le t \le \tau, \\ u_{\text{sing}} & \text{for } \tau < t \le T. \end{cases}$$

$\tau = 2$



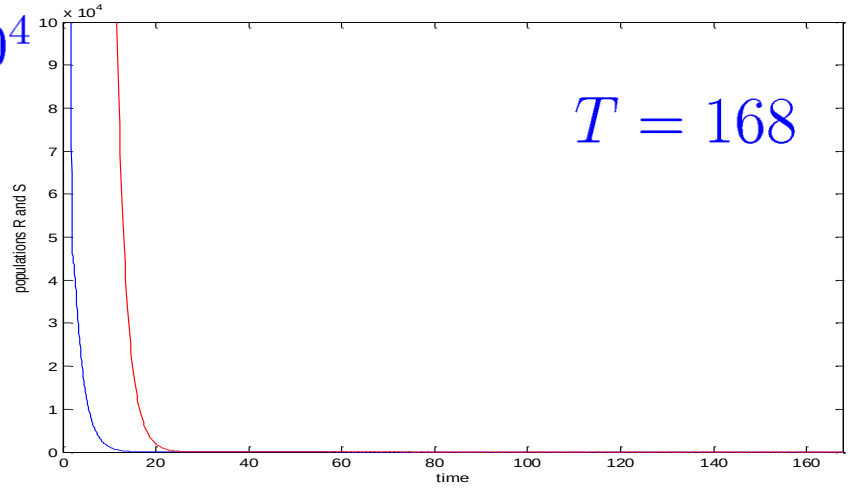


10^7



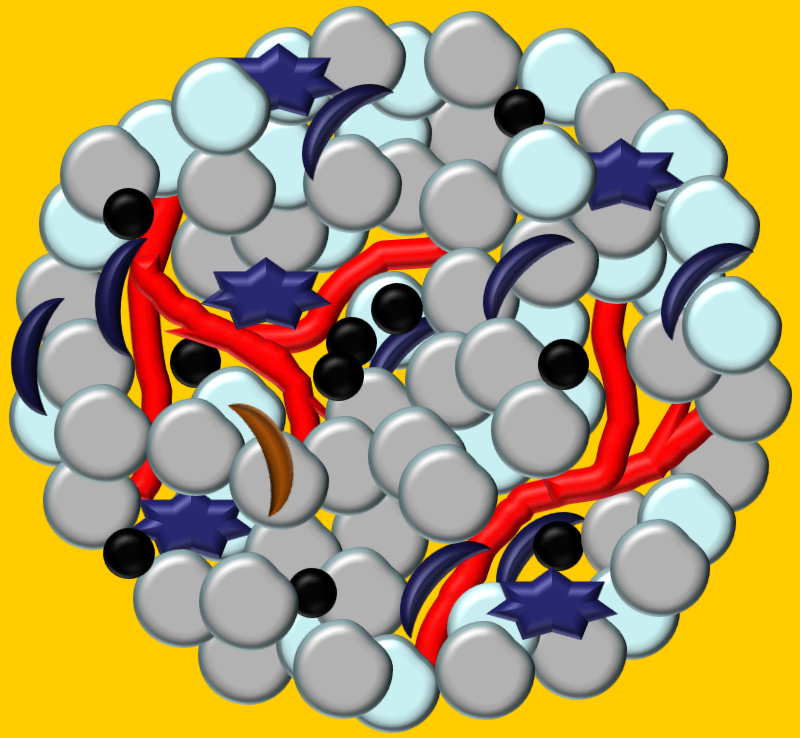
$T = 42$

10^4



$T = 168$

Tumor Microenvironment – Other Treatments



Chemo-sensitive tumor cell

Chemo-resistant tumor cell

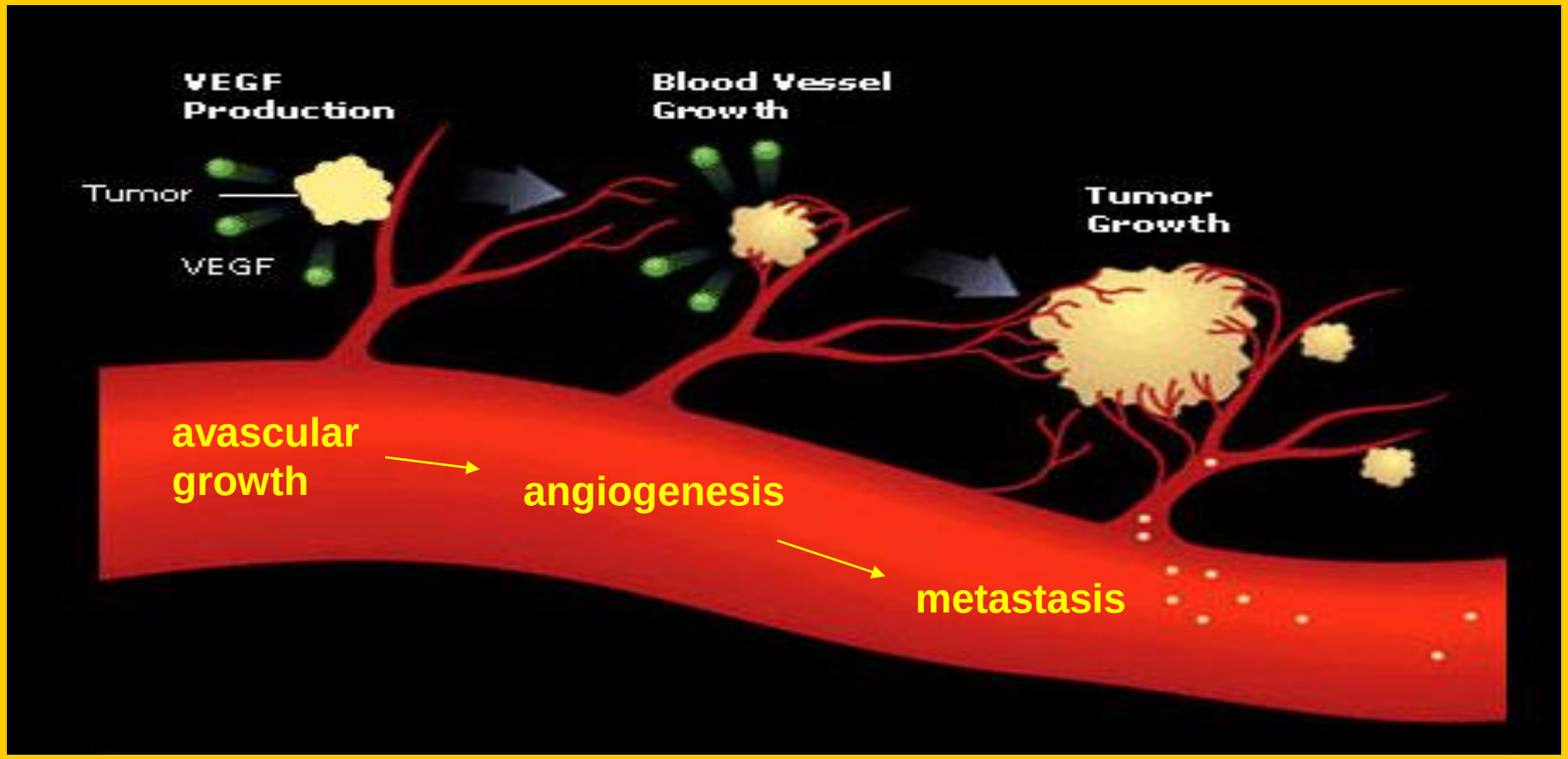
Fibroblast

Endothelia

Tumor stimulating myeloid cell

Surveillance T-cell

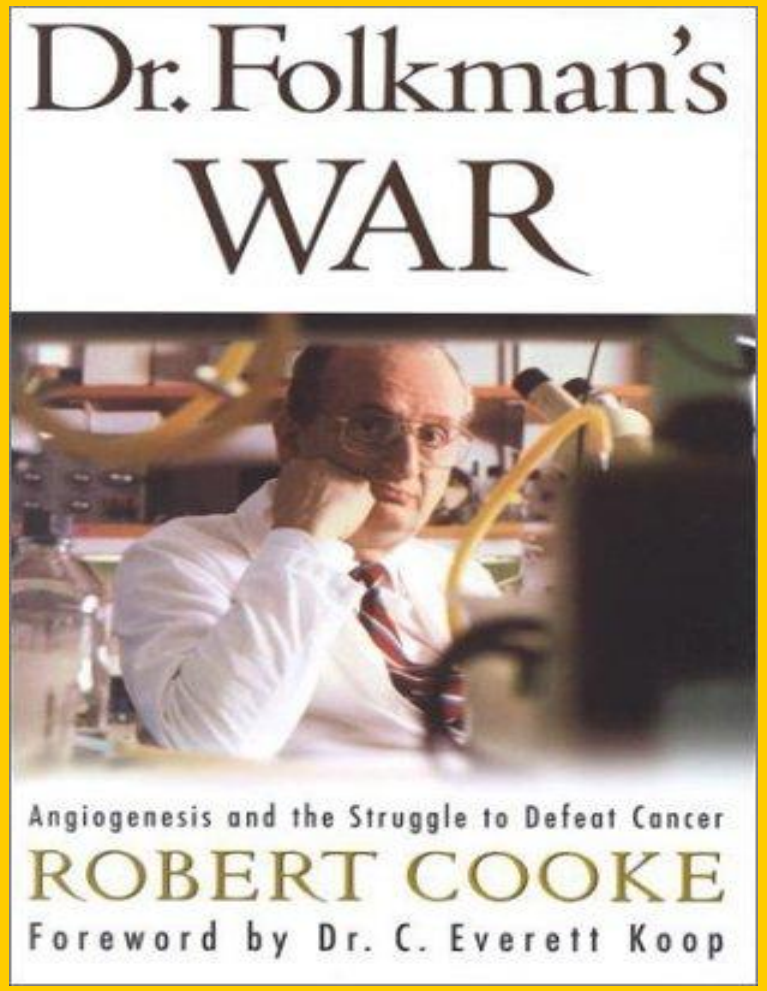
Tumor Antiangiogenesis



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

Tumor Anti-Angiogenesis

Judah Folkman, 1972



- suppress tumor growth by preventing the recruitment of new blood vessels that supply the tumor with nutrients

  indirect approach

- done by inhibiting the growth of the endothelial cells that form the lining of the new blood vessels therapy **"resistant to resistance"**

- anti-angiogenic agents are biological drugs (enzyme inhibitors like **endostatin**) – **very expensive** and with **side effects**

Model [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** $\xi = 0.084$

b **- endogenous stimulation (birth)** $b = 5.85$

d **- endogenous inhibition (death)** $d = 0.00873$

γ **- anti-angiogenic inhibition parameter** $\gamma = 0.15$

μ **- natural death** $(\mu = 0)$ $\mu = 0.02$

Lewis lung carcinoma implanted in mice

Optimal Control Problem

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

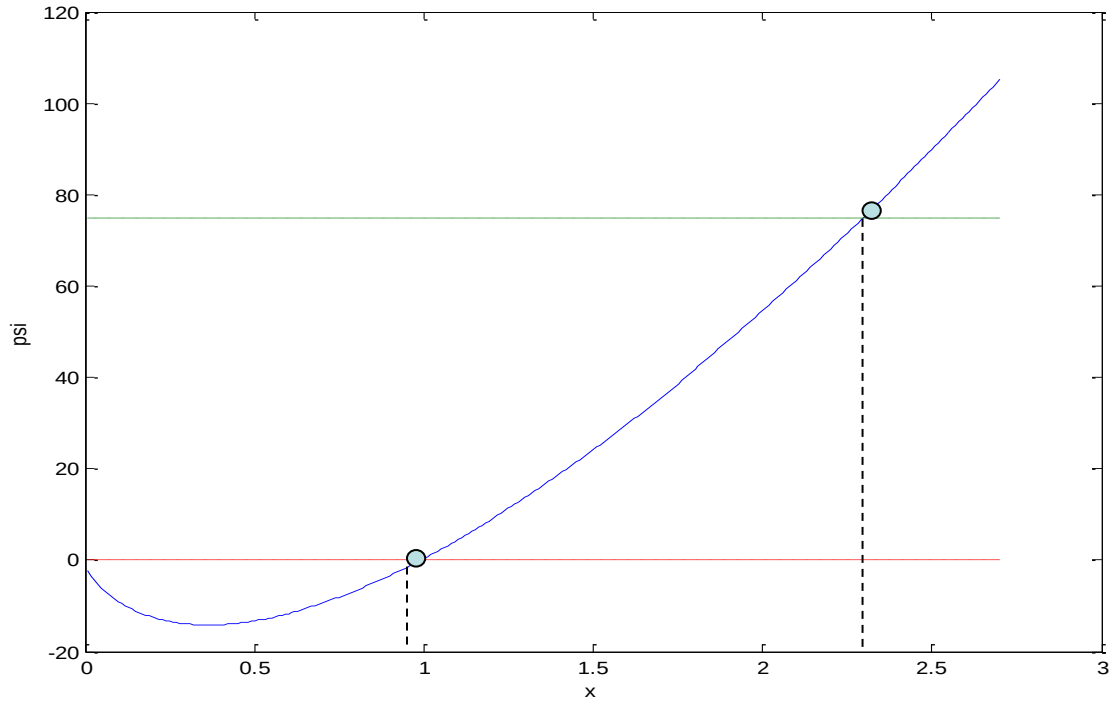
$$\dot{p} = -\xi p \ln\left(\frac{p}{q}\right), \qquad p(0) = p_0,$$

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

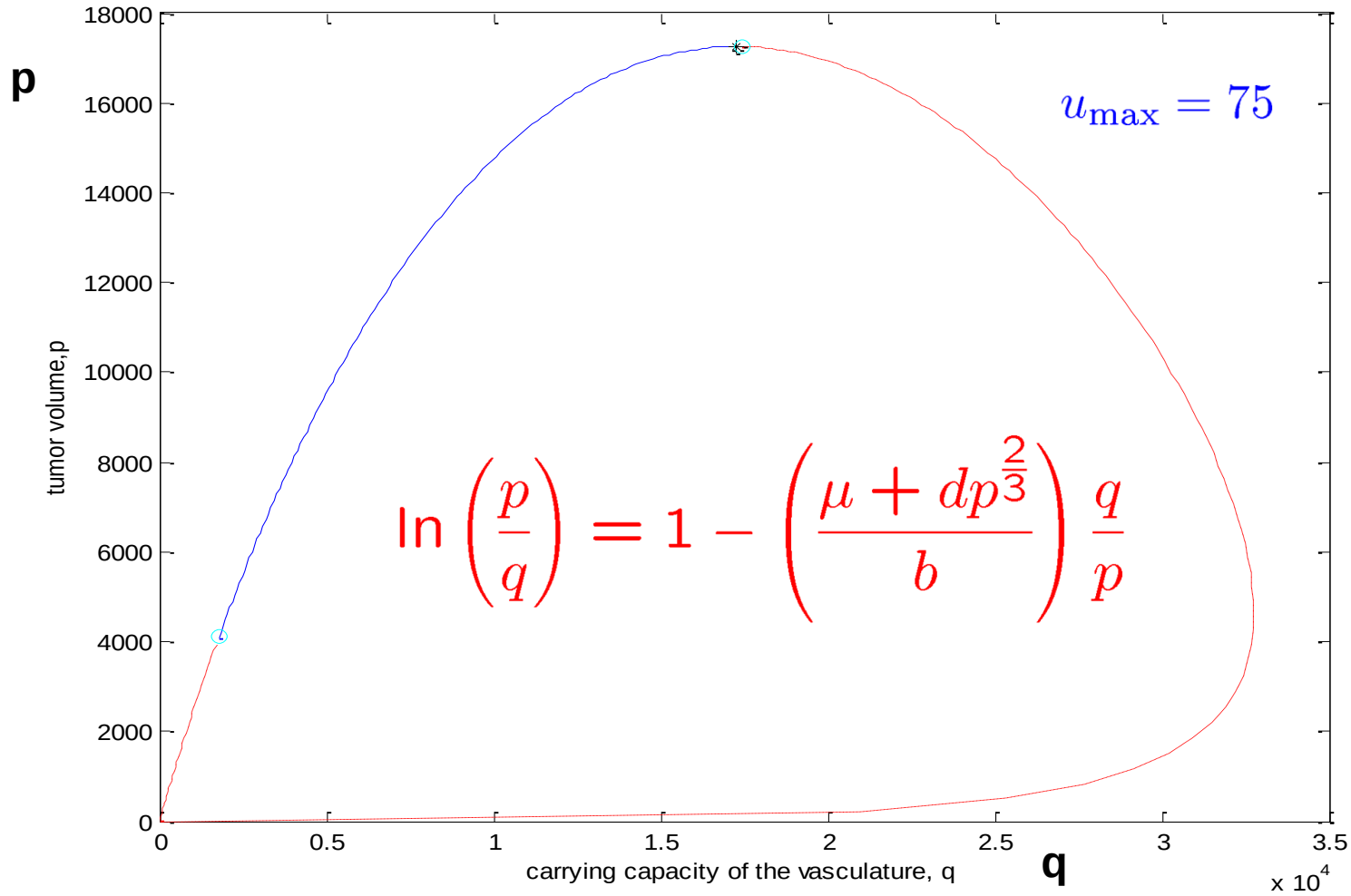
Singular Control

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

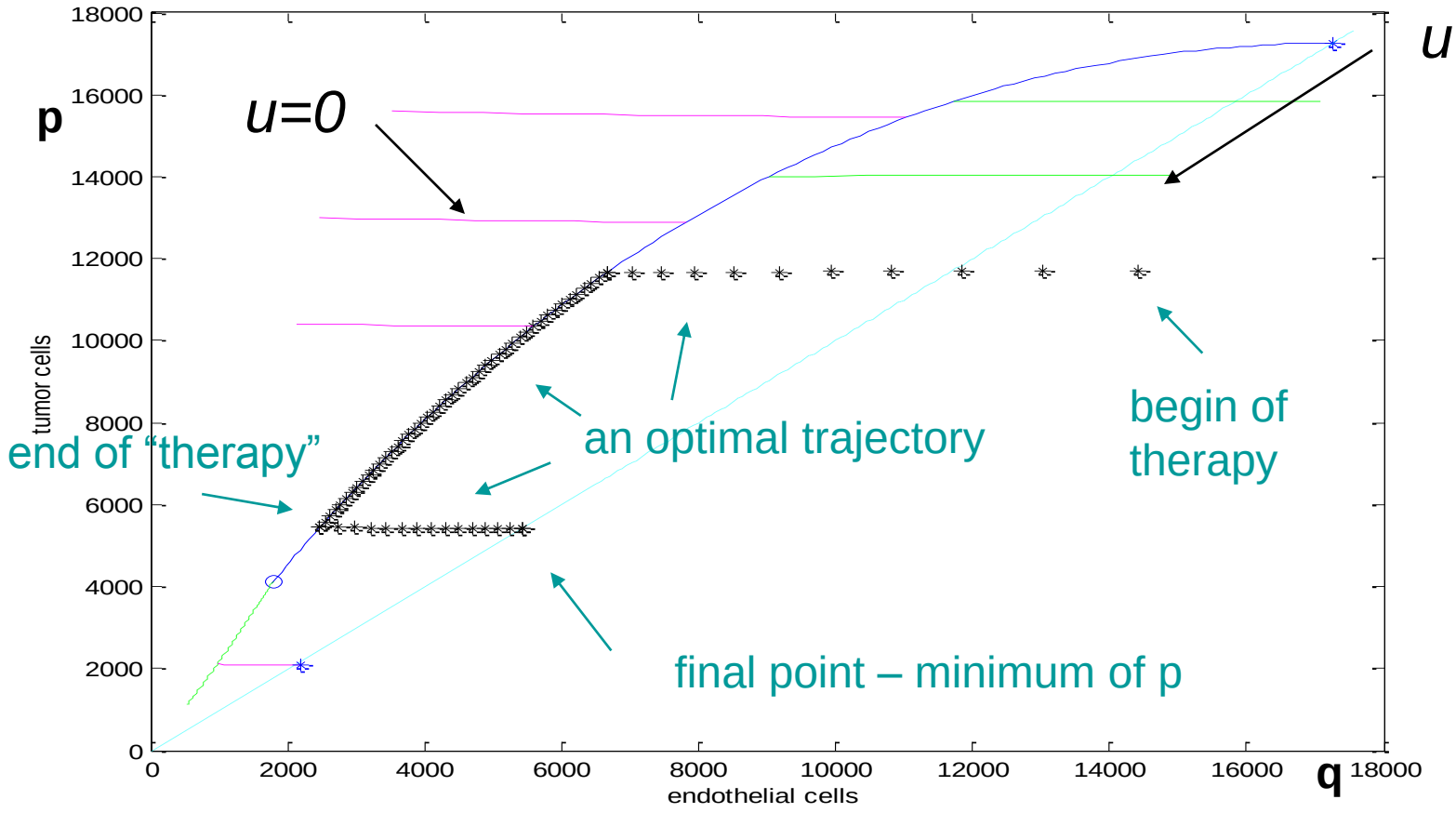
feedback control



Admissible Singular Arc



Synthesis of Optimal Controls [LSch, SICON, 2007]

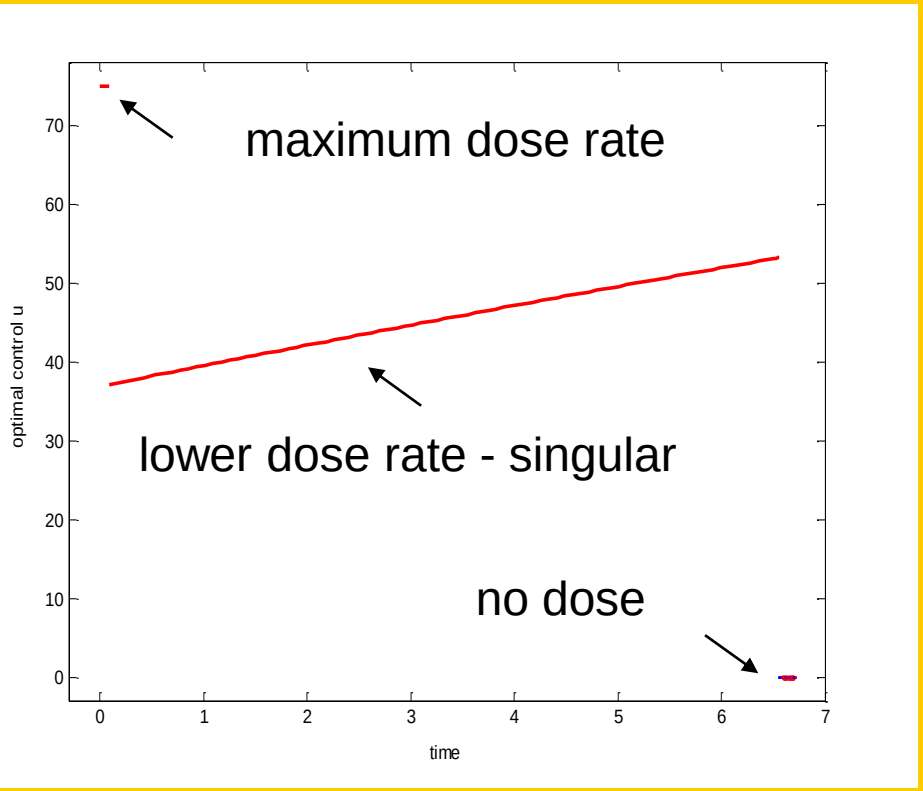


typical synthesis: $u_{max} \rightarrow s \rightarrow 0$

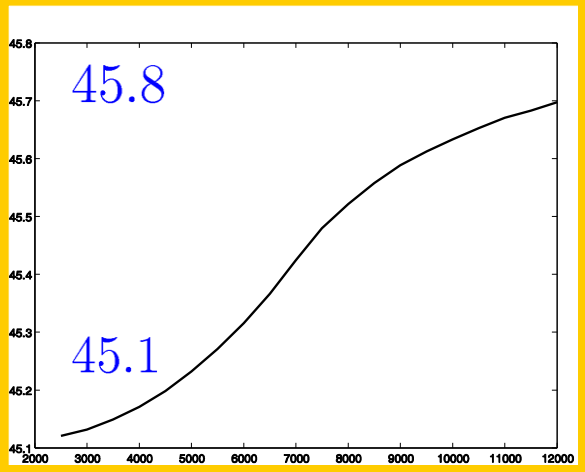
Some Practical Aspects

An Optimal Controlled Trajectory for [Hahnfeldt et al.]

Initial condition: p_0 = 12,000 q_0 = 15,000, u_{max}=75



u



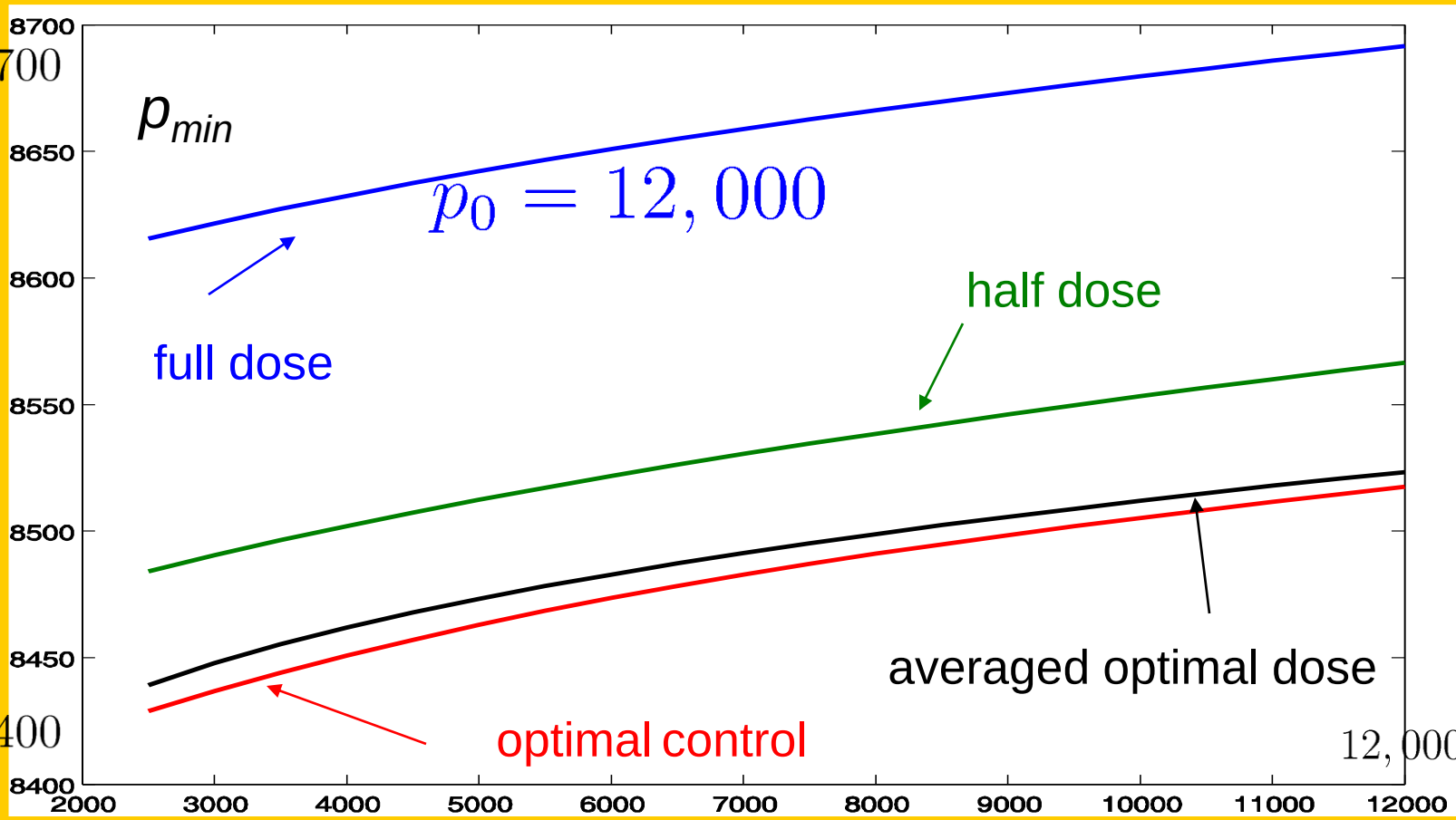
q_0

averaged optimal dose

$$\bar{u} = \frac{1}{\bar{T}} \int_0^{\bar{T}} u_{opt}(t)dt = \frac{A}{\bar{T}}$$

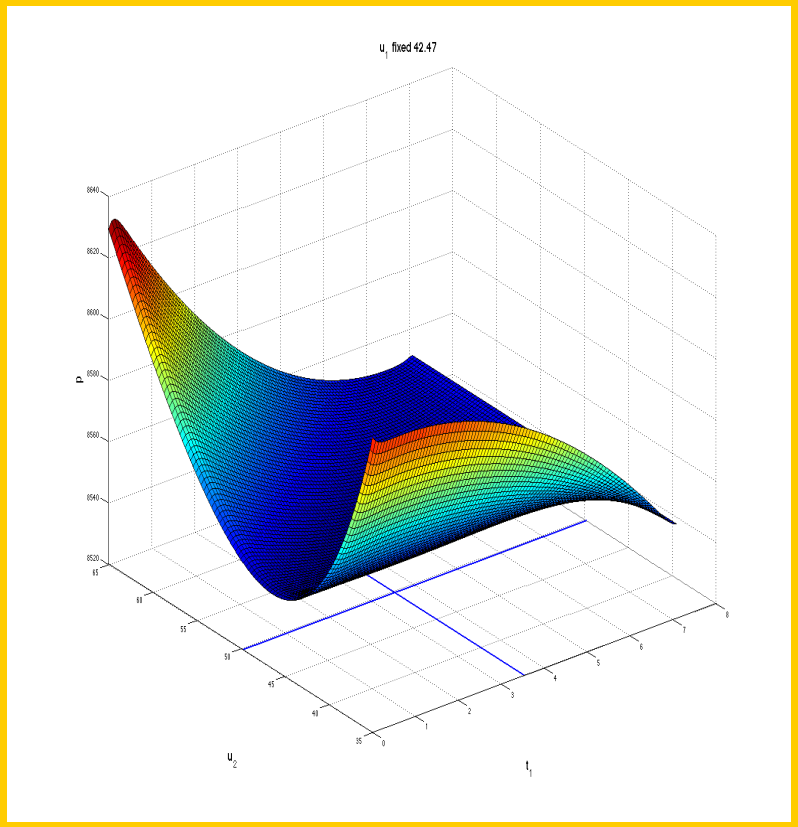
robust with respect to q_0

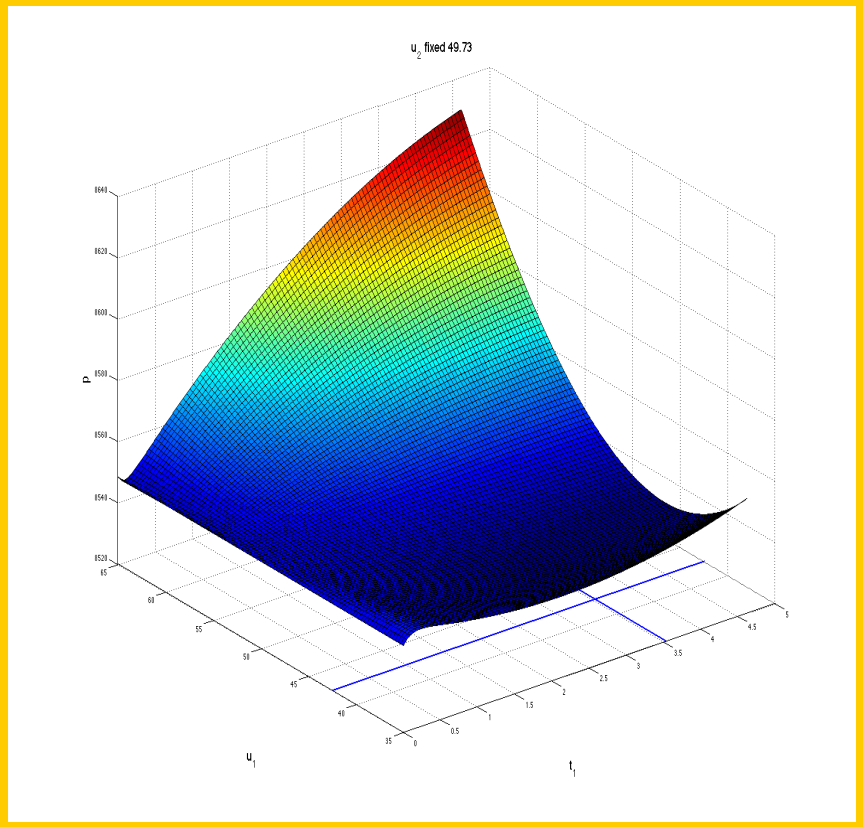
Minimum Tumor Volumes under Suboptimal Constant Dose Protocols [LSch, JTB, 2008]



Values of the minimum tumor volume for a fixed initial tumor p_0 volume as functions of the initial endothelial support q_0

Response to Two Dose Protocols, [LMMSch, Math. Med. &Biology, 2010]





$u_1 = 42.48$ fixed

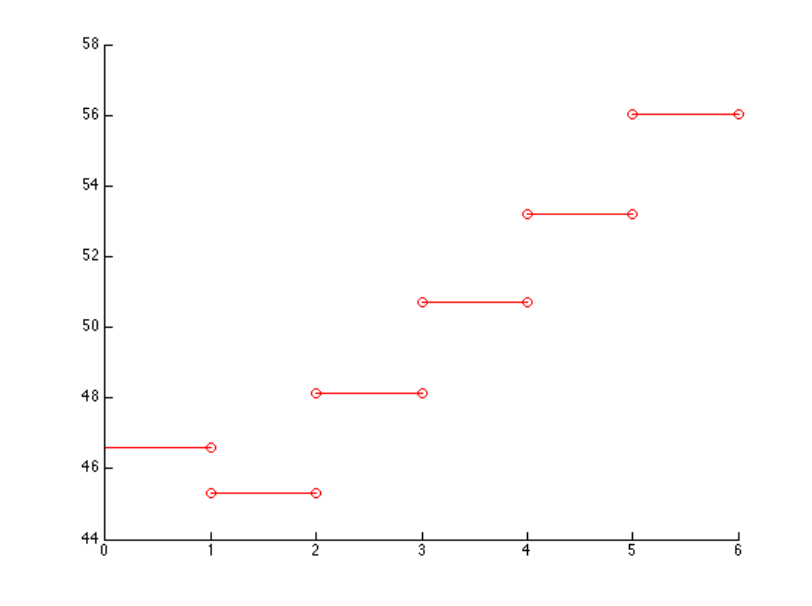
$u_2 = 49.73$ fixed

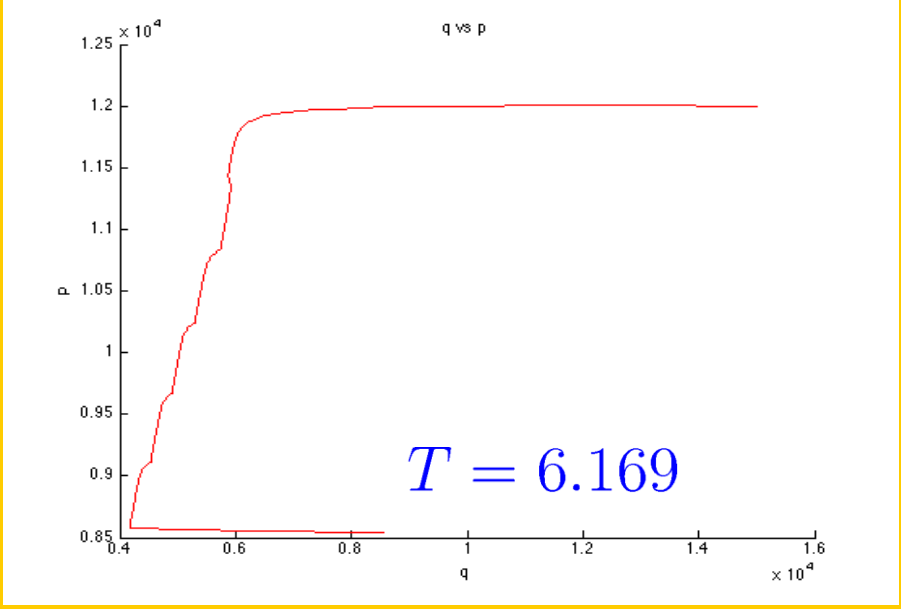
Optimal Daily Dosages

Give all inhibitors in 6 daily doses and then follow the trajectory for $u = 0$ until the minimal value is realized on the diagonal

$$u_1 = 46.61, \quad u_2 = 45.31, \quad u_3 = 48.15,$$
$$u_4 = 50.71, \quad u_5 = 53.20, \quad u_6 = 56.02,$$

$$p_d = 8544.40$$





Combination Therapy: Antiangiogenic Treatment with Chemotherapy

A Model for a Combination Therapy [d'OLMSch, Mathematical Biosciences, 2009]

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

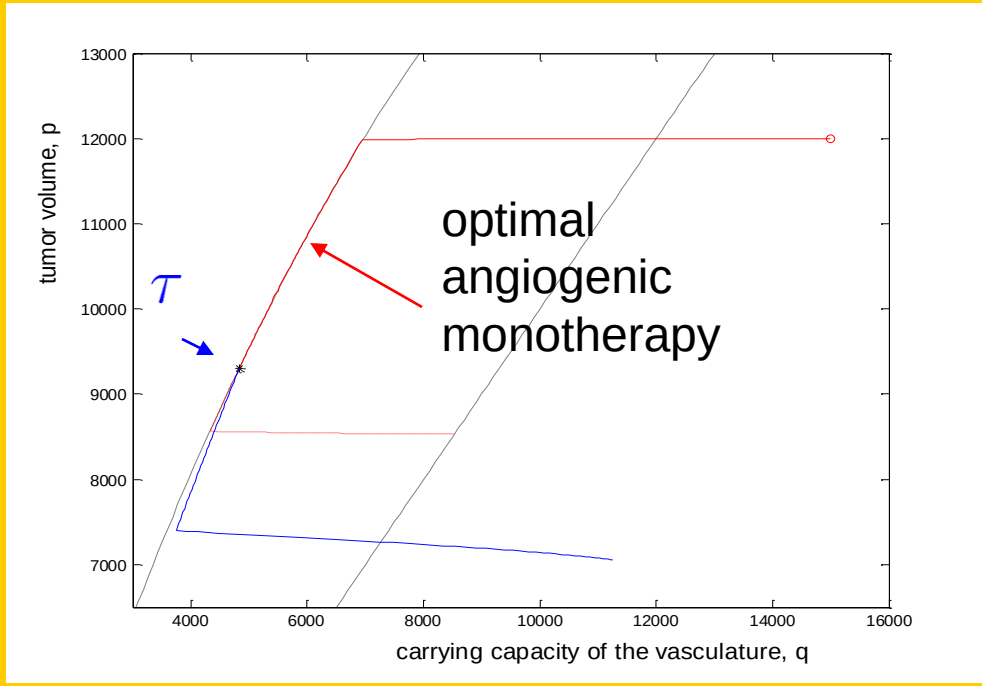
$$0 \le u \le u_{\max}, \qquad \int_0^T u(t)dt \le y_{\max}$$

cytotoxic agent or other killing term

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

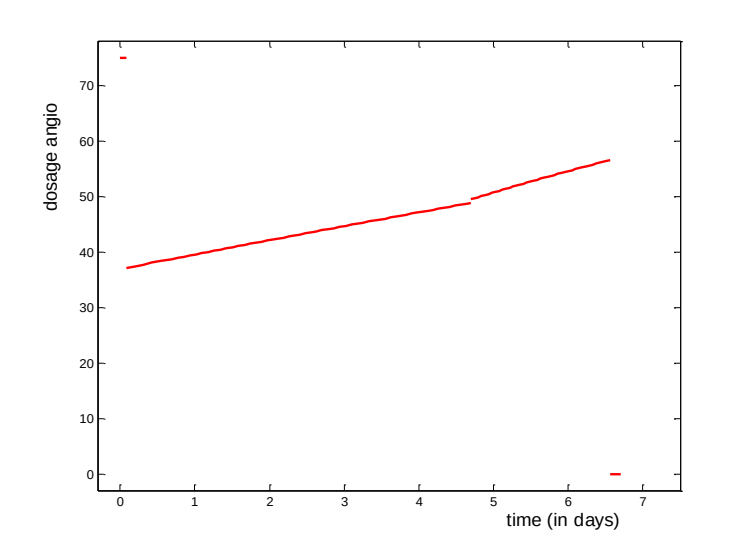
Optimal Protocols: what comes first?

- 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

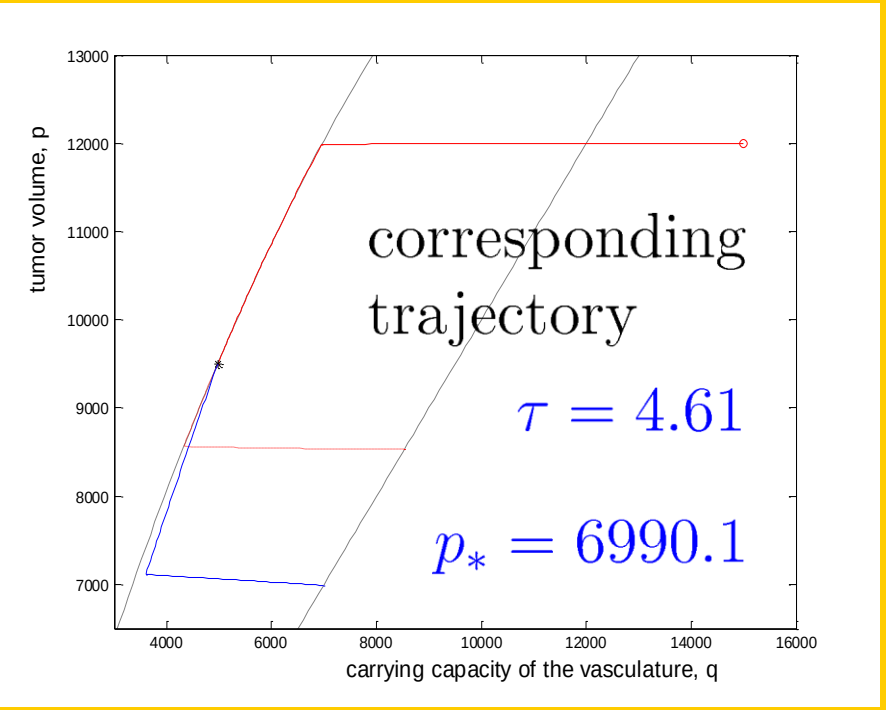


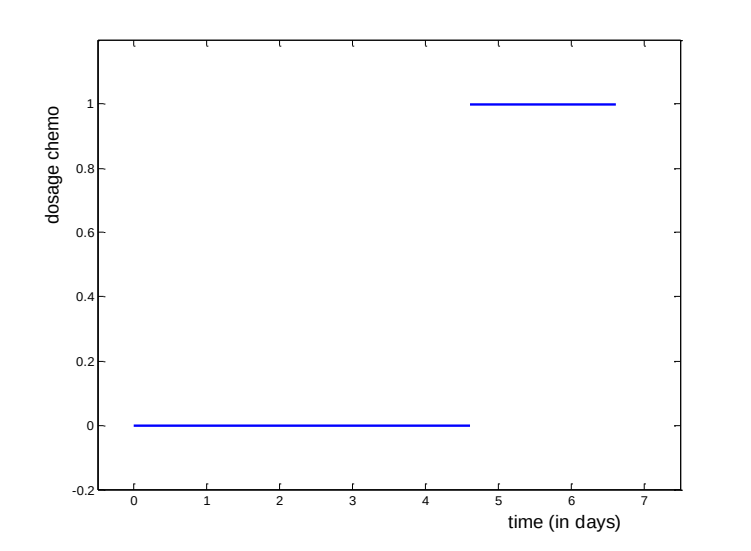
1-dimensional minimization problem over the parameter τ

Controls and Trajectory [for dynamics from Hahnfeldt et al.]



$\longleftarrow u$ - angiogenic inhibitors





$\longleftarrow$ v - chemotherapy

Medical Aspect

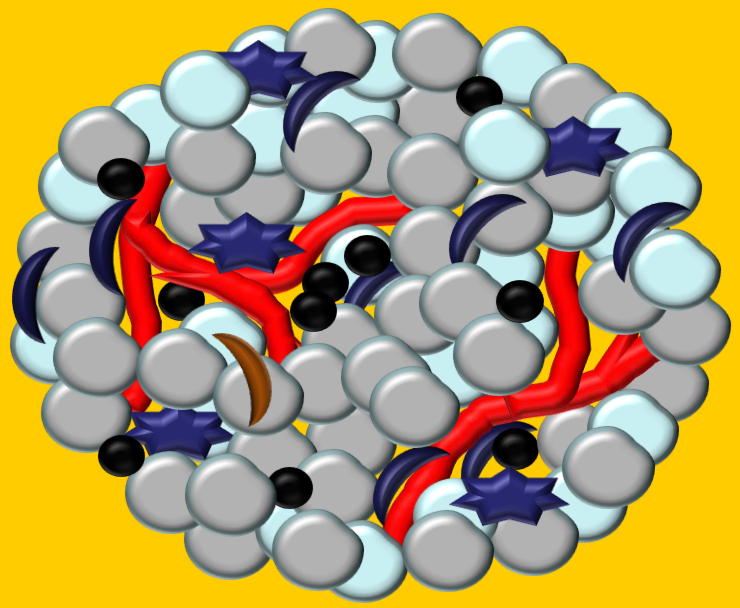
Rakesh Jain,

Steele Lab, Harvard Medical School,

→ *"there exists a* ***therapeutic window*** *when changes in the tumor in response to anti-angiogenic treatment may allow chemotherapy to be particularly effective"*

Connection between mathematical results and experimental data ??

Tumor Immune Interactions



A Model for Tumor-Immune Interactions

- **Stepanova, *Biophysics,* 1980**

  Kuznetsov, Makalkin, Taylor and Perelson, *Bull. Math. Biology,* 1994

  de Vladar and Gonzalez, *J. Theo. Biology,* 2004,

  d'Onofrio, *Physica D,* 2005

→ **renewed interest in the topic also in connection with immune-dynamics and immuno-therapy**

Stepanova-Type Mathematical Models for Tumor-Immune Dynamics

- **STATE:**

$x(t)$ - **primary tumor volume**

$y(t)$ - **immunocompetent cell-density**
(related to various types of T-cells)

Dynamical Model

$$\begin{aligned} \dot{x} &= \mu_C x F(x) - \gamma x y, \\ \dot{y} &= \mu_I \left(x - \beta x^2\right) y - \delta y + \alpha, \end{aligned}$$

[Stepanova]

μ_C - **tumor growth parameter**

F - **growth function**

γ - **rate at which cancer cells are eliminated through the activity of T-cells**

α - **constant rate of influx of T-cells generated by primary organs**

δ - **natural death of T-cells**

μ_I, β - **calibrate the interactions between immune system and tumor**

$\frac{1}{\beta}$ - **threshold beyond which immune reaction becomes suppressed by the tumor**

Growth Models on the Tumor Volume *x*

$$\dot{x} = \mu_C x F(x),$$

F is positive, twice continuously differentiable

$$\dot{x} = \mu_C x,$$

exponential growth

Stepanova, 1980

Kuznetsov et al., 1994

$$\dot{x} = -\mu_C x \ln\left(\frac{x}{x_\infty}\right),$$

Gompertzian

de Vladar and Gonzalez, 2004

$$\dot{x} = \mu_C x \left(1 - \left(\frac{x}{x_\infty}\right)^\theta\right), \quad \theta > 1, \ \theta = 1, \ \theta < 1$$

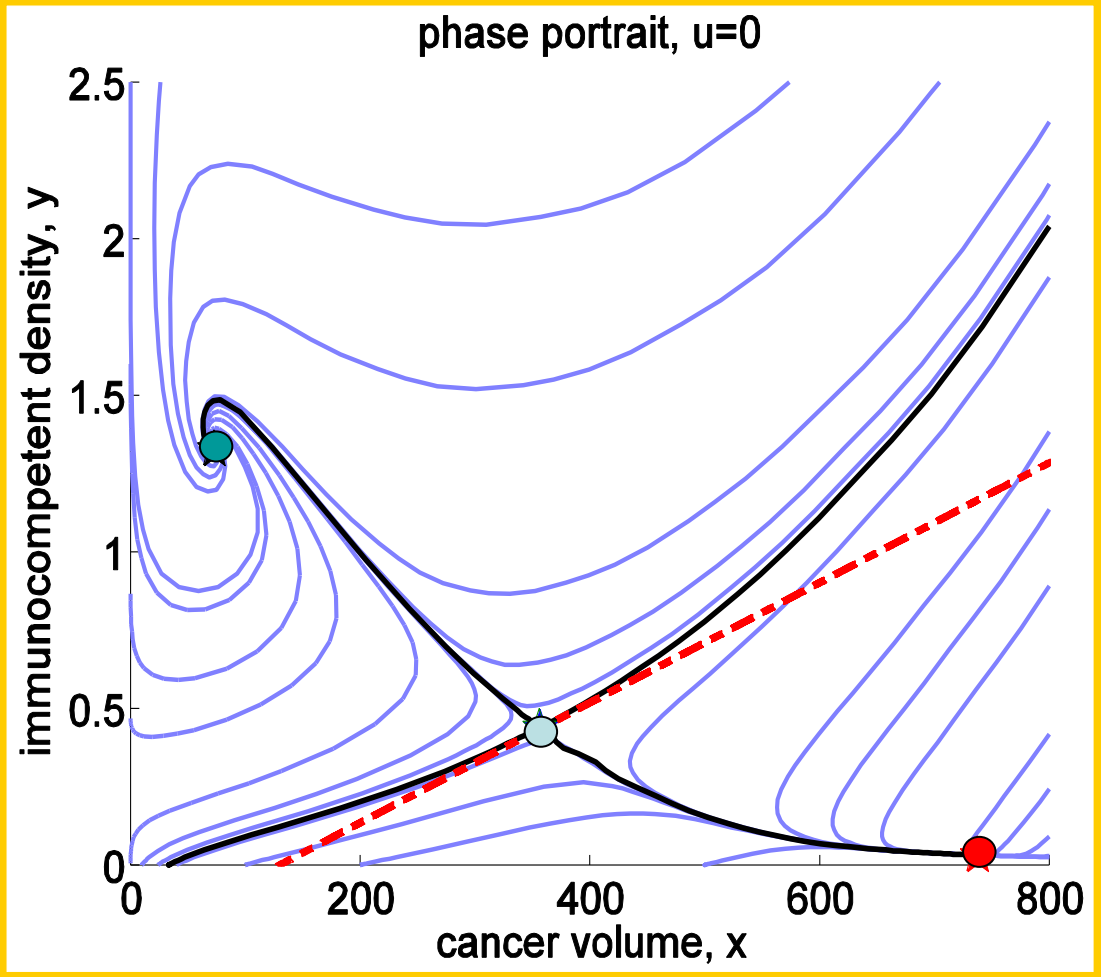
logistic growth

d'Onofrio, 2005

L Sch Olumoye, 2013

Phaseportrait for Gompertzian Model

multiple stable equilibrium points



- asymptotically stable focus – “good”, benign equilibrium
- saddle point
- asymptotically stable node – “bad”, malignant equilibrium

$$\mu_I = 0.00484 \quad \mu_C = 0.5618$$

$$\alpha = 0.1181 \quad \beta = 0.00264$$

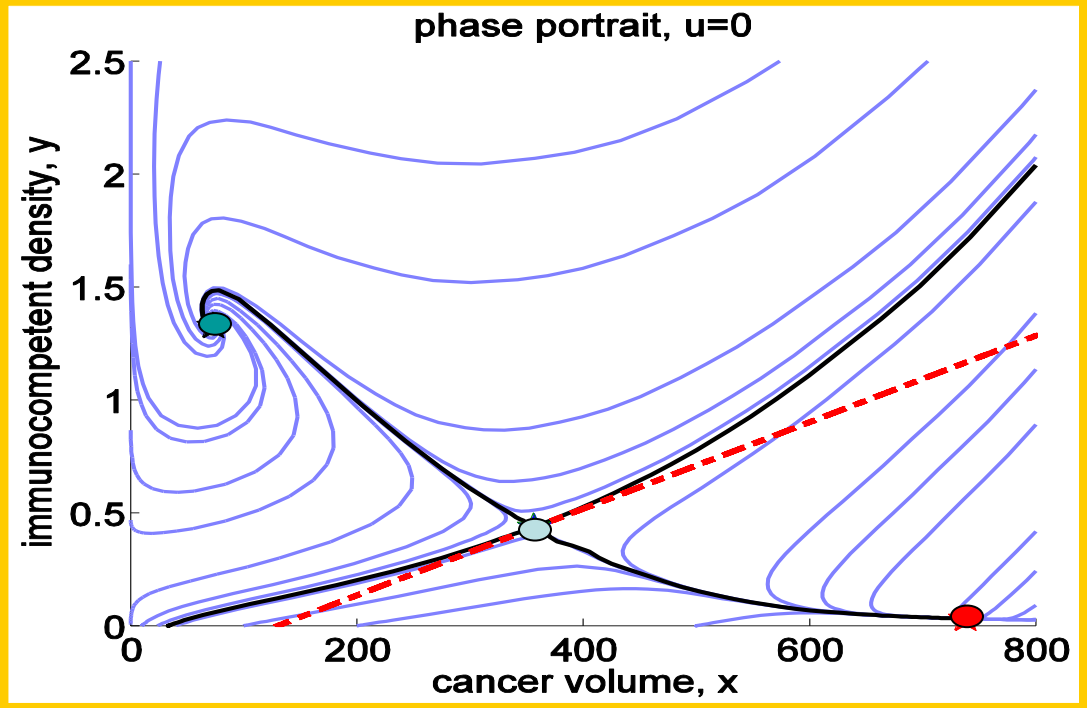
$$\gamma = 1 \qquad \delta = 0.3745$$

$$x_\infty = 780$$

[Kuznetsov et al., 1994

de Vladar et al., 2004]

Phaseportrait of uncontrolled dynamics



saddle point

$$(\bar{x}, \bar{y}) = (356.174, 0.439)$$

stable eigenvector

$$\begin{pmatrix} b \\ a \end{pmatrix} = \begin{pmatrix} 1 \\ 0.00192 \end{pmatrix}$$

- **we want to move the state of the system into the region of attraction of the benign equilibrium**

→ minimize $ax(T) - by(T)$

Optimal Control Problem (LSch, CDC 2012)

For a free terminal time **T** **minimize**

$$J(u) = ax(T) - by(T) + \int_0^T (cu(t) + dv(t))dt + sT$$

over all measurable functions $u : [0, T] \to [0, 1]$ and $v : [0, T] \to [0, 1]$ subject to the dynamics

Chemotherapy – log-kill hypothesis

$$\dot{x} = \mu_C x F(x) - \gamma xy - \kappa_X xu, \qquad x(0) = x_0,$$

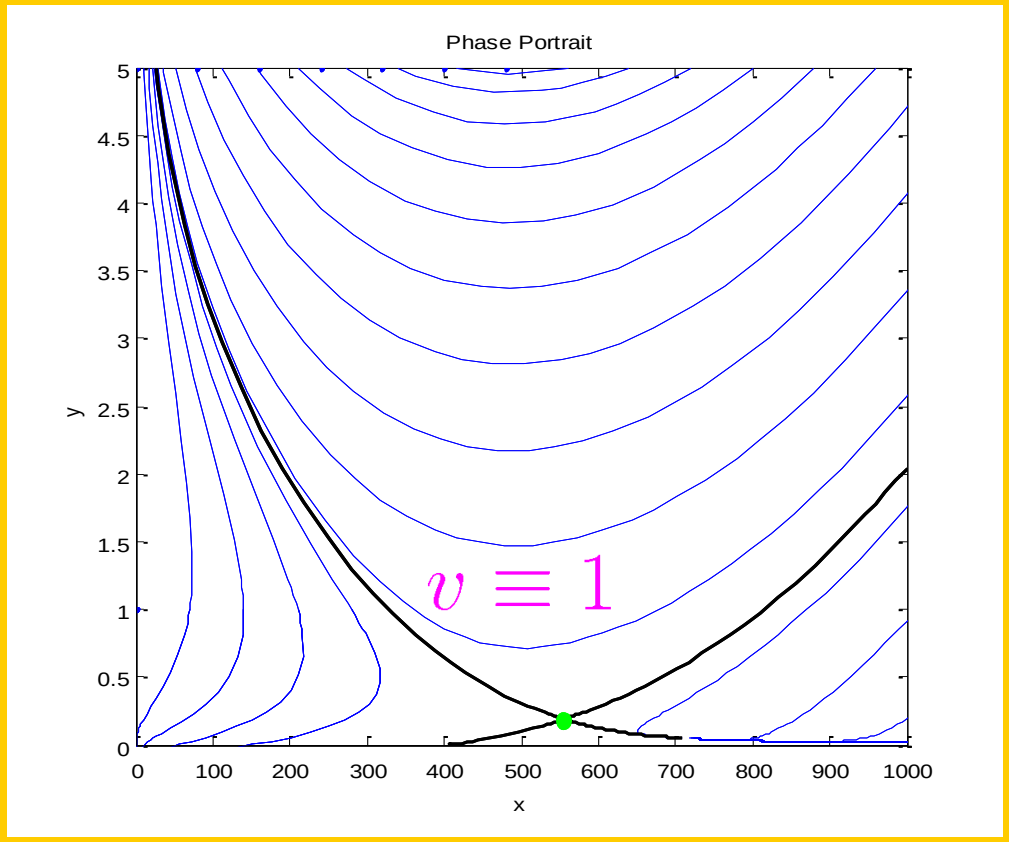
$$\dot{y} = \mu_I \left(x - \beta x^2\right) y - \delta y + \alpha + \kappa_Y yv, \qquad y(0) = y_0,$$

Immune boost

Immunotherapy only

$$\dot{x} = -\mu_C x \ln\left(\frac{x}{x_\infty}\right) - \gamma x y, \qquad x(0) = x_0,$$

$$\dot{y} = \mu_I \left(x - \beta x^2\right) y - \delta y + \alpha + \kappa_Y y v, \qquad y(0) = y_0,$$



malignant region persists

↓

Immunotherapy alone is not successful in this region

↓

Chemotherapy is needed

Dynamics revisited

Write the system as

$$\dot{z} = f(z) + u g_1(z) + v g_2(z) \qquad \text{with} \quad z = (x, y)^T$$

drift vector field

$$f(z) = \begin{pmatrix} -\mu_C x \ln\left(\frac{x}{x_\infty}\right) - \gamma x y \\ \\ \mu_I \left(x - \beta x^2\right) y - \delta y + \alpha \end{pmatrix},$$

control vector fields

$$g_1(z) = \begin{pmatrix} -\kappa_X x \\ \\ 0 \end{pmatrix}, \qquad g_2(z) = \begin{pmatrix} 0 \\ \\ \kappa_Y y \end{pmatrix}$$

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

g_1 and g_2 commute: $[g_1, g_2](z) \equiv 0$

$$\langle \lambda(t), [g_1, [f, g_1]](z_*(t)) \rangle \leq 0$$

Legendre-Clebsch Condition for *u* (Chemotherapy)

$$[g_1, [f, g_1]](z) = \theta_1(z) g_1(z) + \theta_2(z)[f, g_1](z)$$

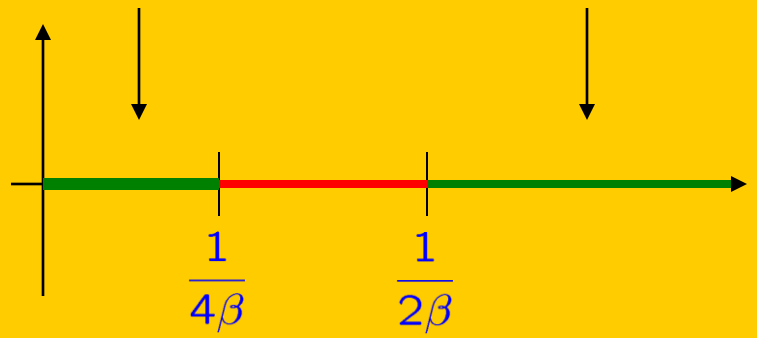
$$\longrightarrow \quad \langle \lambda(t), [g_1, [f, g_1]](z_*(t)) \rangle = -c\theta_1(z_*(t))$$

The **Legendre-Clebsch condition** is satisfied if and only if

$$\theta_1(z_*(t)) \geq 0$$

singular controls are locally optimal

$$\theta_1(z) = \kappa\mu_C \frac{1 - 4\beta x}{1 - 2\beta x}$$



Legendre-Clebsch Condition for Control *v* (Immunotherapy)

Suppose the control *v* is singular on an interval *I* . For optimality we need that

$$\langle \lambda(t), [g_2, [f, g_2]](z_*(t)) \rangle \leq 0$$

But in this case

$$\langle \lambda(t), [g_2, [f, g_2]](z_*(t)) \rangle = \frac{2\kappa_Y \alpha}{y} > 0$$

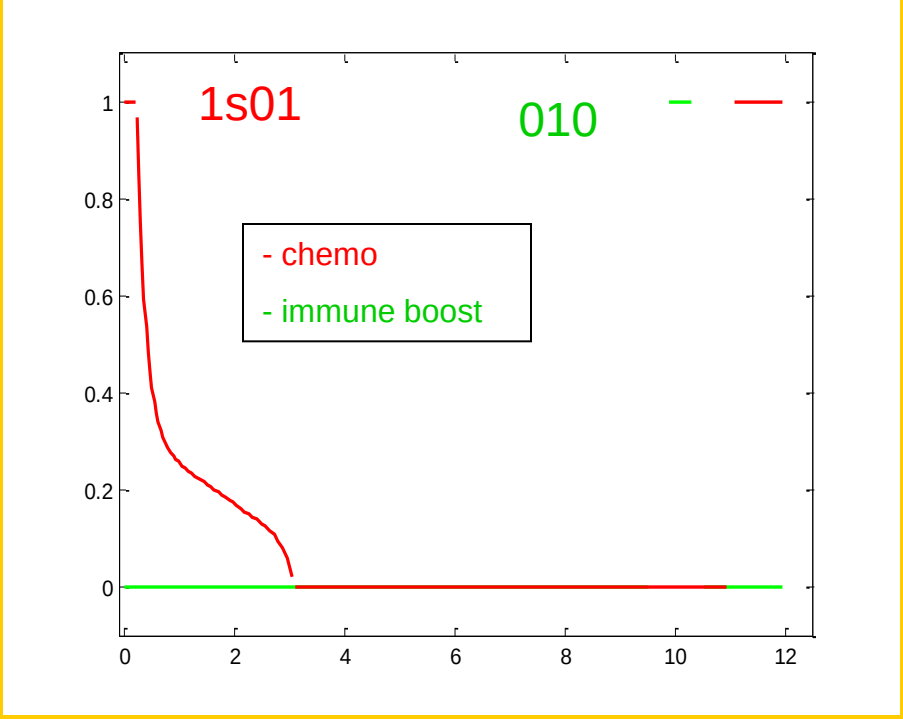
→ **singular controls are maximizing, so not optimal**

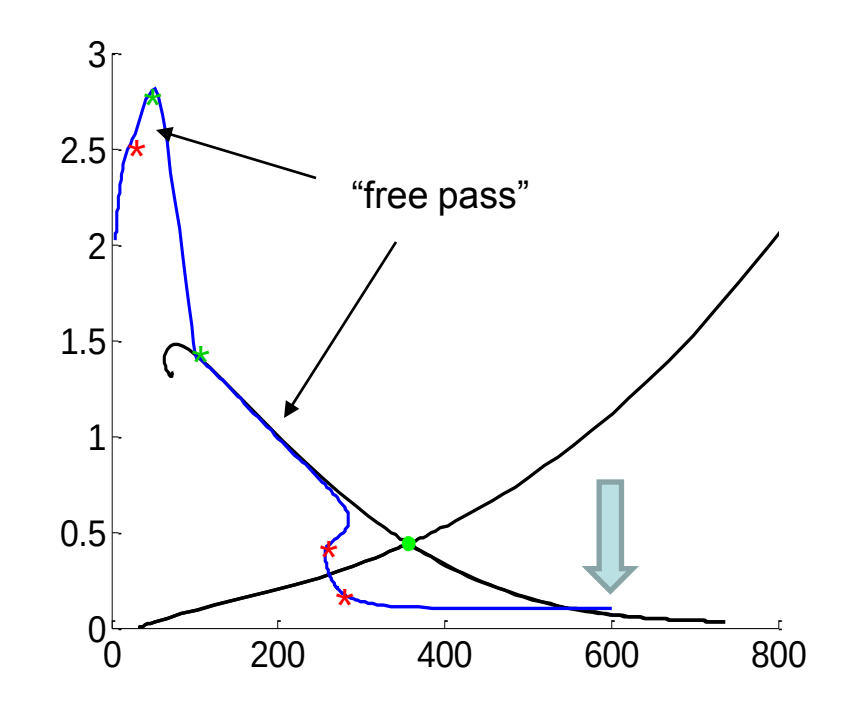
→ **the control *v*, i.e., immune boost, should be bang-bang**

Chemotherapy with Immune Boost [DCDSB, 2013]

- **"cost" of immune boost is high** and effects are low compared to chemo

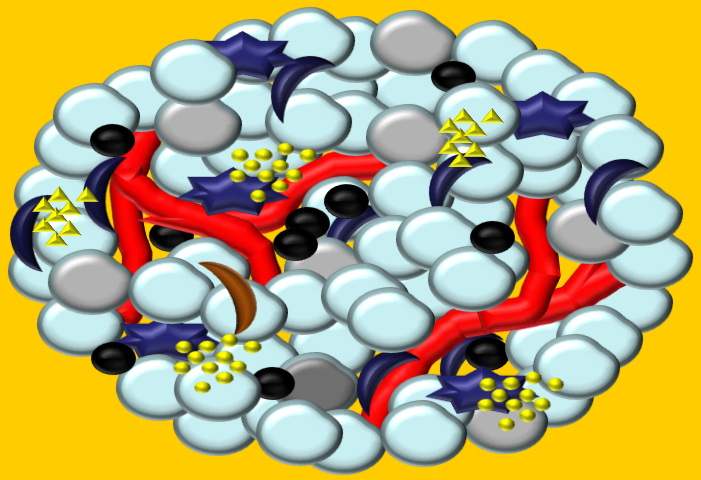
- trajectory follows the optimal chemo monotherapy and provides final boosts to the immune system and chemo at the end





$\kappa_X = 2,\ \kappa_Y = 1,\ A = 0.00192,\ B = 1,\ C = 0.01,\ D = 0.205,\ S = 0.001,$

Metronomics and Other Alternatives to MTD



with Eddy Pasquier, CCIA, University of New South Wales

2nd Annual Workshop on Cancer Systems Biology

Tumor Metronomics:
Timing and Dose Level Dynamics

July 17-20, 2012

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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

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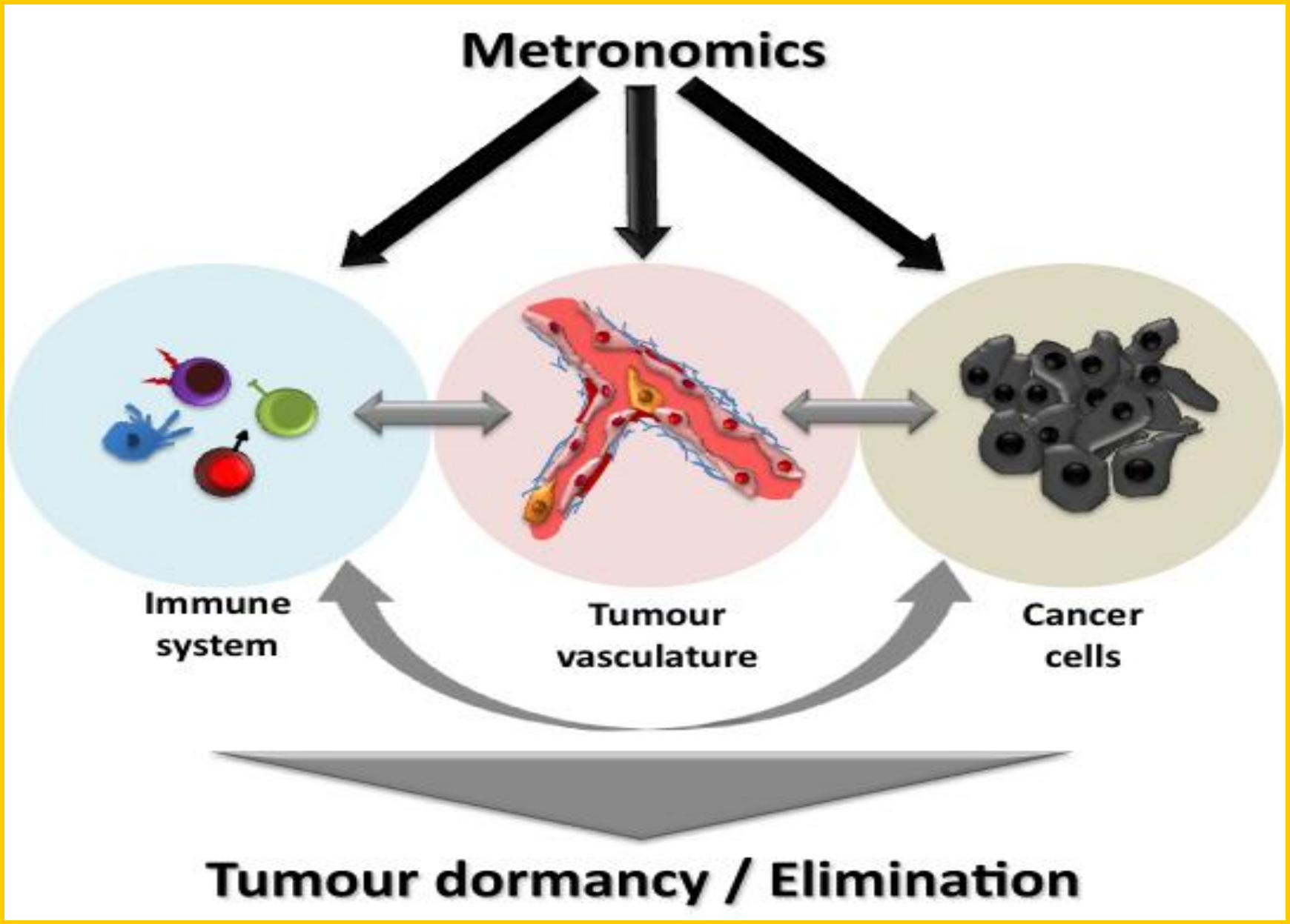
Center of Cancer Systems Biology, Steward St. Elizabeth's Medical Center
Tufts University School of Medicine

Metronomic Chemotherapy

The frequent administration of chemotherapy drugs at relatively low, non-toxic doses, without prolonged drug-free breaks (Hanahan et al., *JCI* 2000)

METRONOMICS
=
Metronomic Chemotherapy + Drug Repositioning



Adapted from Pasquier *et al.*, *Nature Reviews Clinical Oncology*, 2010

Metronomic Chemotherapy: modeling challenge

2nd Annual Workshop on Cancer Systems Biology

Tumor Metronomics:
Timing and Dose Level Dynamics

How is it administered?

- treatment at lower doses

  (between 10% and 80% of the MTD)

- constant or not?

Advantages (to be modelled):

1. **lower, but continuous cytotoxic effects on tumor cells**
   - **lower toxicity (in many cases, none)**
   - **lower drug resistance and even resensitization effect**
2. **antiangiogenic effects**
3. **boost to the immune system**

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

Different therapeutic approaches:

- "Pure" metronomic / Metronomics

-Weekly VLB
-Daily CPA
-2x weekly MTX
-Daily CLX

www.impactjournals.com/oncotarget/ Oncotarget, December, Vol.2, No 12

Pilot study of a pediatric metronomic 4-drug regimen

Nicolas André[1,2], Sylvie Abed[1], Daniel Orbach[3], Corinne Armari Alla[4], Laetitia Padovani[5], Eddy Pasquier[2,6], Jean Claude Gentet[1], Arnauld Verschuur[1,2]

[1] Service d'Hématologie et Oncologie Pédiatrique, Hôpital pour Enfants de La Timone, Marseille, France
[2] Metronomics Global Health Initiative, Marseille, France
[3] Service d'Oncologie Pédiatrique, Institut Curie, Paris, France
[4] Service d'Oncologie Pédiatrique, Grenoble, France
[5] Service de Radiothérapie, Hôpital de La Timone, Marseille, France
[6] Children's Cancer Institute Australia, Lowy Cancer Research Centre, University of New South Wales, Randwick, NSW, Australia

Phase I/II Trial of Metronomic Chemotherapy With Daily Dalteparin and Cyclophosphamide, Twice-Weekly Methotrexate, and Daily Prednisone As Therapy for Metastatic Breast Cancer Using Vascular Endothelial Growth Factor and Soluble Vascular Endothelial Growth Factor Receptor Levels As Markers of Response

Nan Soon Wong, Robert A. Buckman, Mark Clemons, Shailendra Verma, Susan Dent, Maureen E. Trudeau, Kathie Roche, John Ebos, Robert Kerbel, Gerrit E. DeBoer, Donald J.A. Sutherland, Urban Emmenegger, Joyce Slingerland, Sandra Gardner, and Kathleen I. Pritchard

J Clin Oncol 2010

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

Different therapeutic approaches:

- **"Pure" metronomic / Metronomics**
- **MTD / Metronomic sequencing**

(Bang-Bang-Metro, Metro-Bang-Bang…)

A Multitargeted, Metronomic, and Maximum-Tolerated Dose "Chemo-Switch" Regimen is Antiangiogenic, Producing Objective Responses and Survival Benefit in a Mouse Model of Cancer

Kristian Pietras and Douglas Hanahan

J Clin Oncol 2005

Activity of a multitargeted chemo-switch regimen (sorafenib, gemcitabine, and metronomic capecitabine) in metastatic renal-cell carcinoma: a phase 2 study (SOGUG-02-06)

Joaquim Bellmunt, José Manuel Trigo, Emiliano Calvo, Joan Carles, José L Pérez-Gracia, Jordi Rubió, Juan Antonio Virizuela, Rafael López, Martín Lázaro, Joan Albanell

Lancet Oncol 2010

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

Different therapeutic approaches:

- "Pure" metronomic / Metronomics

- MTD / Metronomic sequencing (Bang-Bang-Metro, Metro-Bang-Bang…)

- Adaptive therapy

Mathematical Oncology

Adaptive Therapy

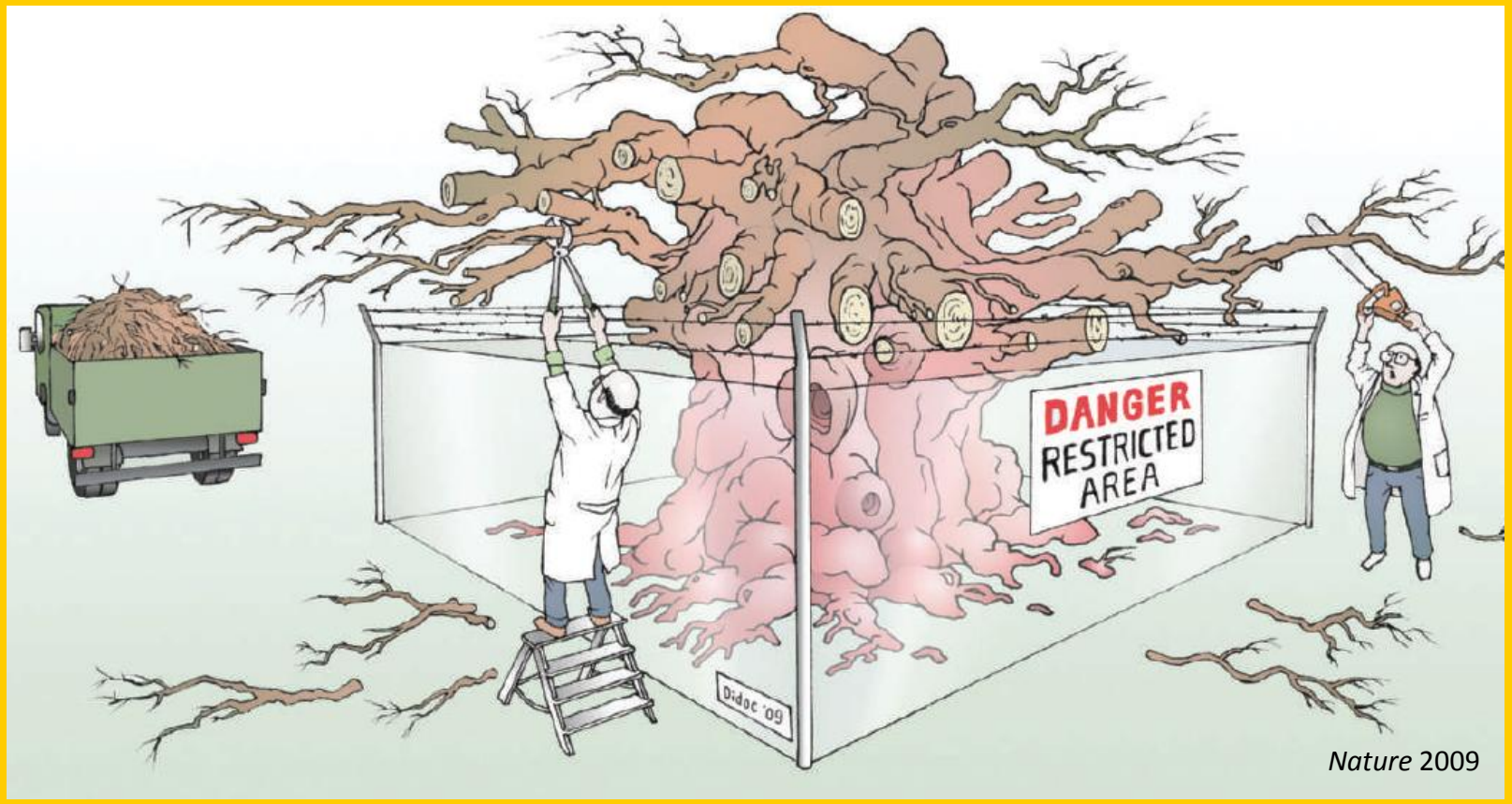
Cancer Research 2009

Robert A. Gatenby,[1] Ariosto S. Silva,[1] Robert J. Gillies,[1] and B. Roy Frieden[2]

[1]Department of Integrative Mathematical Oncology, Moffitt Cancer Center, Tampa, Florida and [2]School of Optical Sciences, University of Arizona, Tucson, Arizona

A change of strategy in the war on cancer

Patients and politicians anxiously await and increasingly demand a 'cure' for cancer. But trying to control the disease may prove a better plan than striving to cure it, says **Robert A. Gatenby**.



Nature 2009

For cancer, seek and destroy or live and let live?

Nature 2009

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

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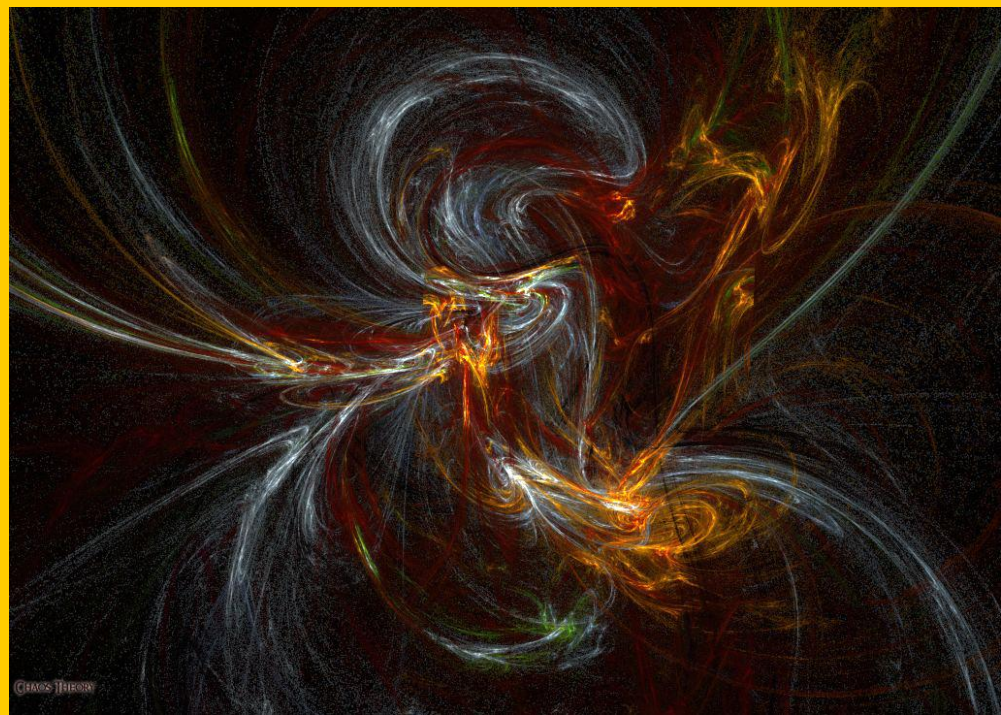
- Adaptive therapy

- Chaos therapy



Metronomics Global Health Initiative (MGHI)

http://metronomics.newethicalbusiness.org/

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Dziękuję za uwagę