Modeling and Optimization of Metronomic Chemotherapy: More Questions than Answers

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Będlewo, Poland June 8-12, 2015

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Interdisciplinary Applied Mathematics

Heinz Schättler · Urszula Ledzewicz

Optimal Control for Mathematical Models of Cancer Therapies

An Application of Geometric Methods

This book presents applications of geometric optimal control to real life biomedical problems with an emphasis on cancer treatments. A number of mathematical models for both classical and novel cancer treatments are presented as optimal control problems with the goal of constructing optimal protocols. The power of geometric methods is illustrated with fully worked out complete global solutions to these mathematically challenging problems. Elaborate constructions of optimal controls and corresponding system responses provide great examples of applications of the tools of geometric optimal control and the outcomes aid the design of simpler, practically realizable suboptimal protocols. The book blends mathematical rigor with practically important topics in an easily readable tutorial style. Graduate students and researchers in science and engineering, particularly biomathematics and more mathematical aspects of biomedical engineering, would find this book particularly useful.

Mathematics

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springer.com

IAM 42 Schättler · Ledzewicz

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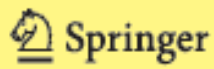
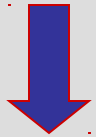


Metronomic Chemotherapy

concept that goes back to the work of J. Folkman and R. Kerbel

"The frequent adminstration of chemotherapy at relatively low, non-toxic doses without prolonged drug-free breaks"

(Hanahan et al., JCI 2000)



METRONOMICS

=

Metronomic Chemotherapy
+ Drug Repositioning

More is Not Necessarily Better: Metronomic Chemotherapy,

Eddy Pasquier and Urszula Ledzewicz,

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

Metronomics Global Health Initiative

Milan Metronomic and anti-angiogenic therapy Meeting 2014

June 24th - 25th 2014

ABSTRACT DEADLINE APRIL 25, 2014
You may submit your abstract by e-mail to francesco.bertolini@ieo.it

INSTRUCTIONS FOR ABSTRACT SUBMISSION
Participants with new data relevant to the subjects of the conference may submit one abstract to be considered for e-poster presentation. Only papers whose abstracts have been reviewed and approved by the Scientific Committee will be presented as e-posters or oral presentations. Abstracts must be written in English and the text should not exceed 2000 characters (title included). The title should appear in capital letters. For each author, type surname first followed by given name and initials (presenting author in capital letters). List affiliations after the authors' list. The full address with telephone, fax number, and e-mail of the corresponding author must be provided. This author will receive all the subsequent communications concerning this abstract.
Please include the following sections: Background, Material methods, Results, Conclusions. All the slides must be sent to the Abstract selection committee (francesco.bertolini@ieo.it) Please indicate your approval for publication in case the abstracts will be issued in a journal.

PLEASE NOTE
Only abstracts submitted by registered participants will be accepted. It is the responsibility of the presenting author to ascertain whether all authors are aware of the content of the abstract before submission.

Campus IFOM–IEO

IEO
Istituto Europeo di Oncologia

SEMM
European School of Molecular Medicine

36th EORTC-PAMM Winter Meeting

Wednesday 21 - Saturday 24 January, 2015
Marseille Provence Métropole, France

WELCOME LETTER

The 36th PAMM-EORTC Winter Meeting will focus on ground-breaking innovations in experimental and clinical oncology.

The PAMM (Pharmacology And Molecular Mechanism) Meeting is organized under the umbrella of European Organization for Treatment of Cancer (EORTC), to provide a unique opportunity for interdisciplinary and international exchange of ideas on implementing knowledge on optimizing cancer treatment. The conference will feature presentations from internationally recognized leaders in the field of experimental, translational and clinical oncology.

Scientists, researchers, and experts in the field of experimental therapeutics will offer new insights and innovative approaches to treat cancer, along with keynote lectures, oral and poster presentations.

Looking forward to meeting you all in Marseille in January 2015.

Local Organising Committee
Dr J. Ciccolini, *Marseille, France*
PAMM Scientific Committee
Pr G.J. Peters, *Amsterdam, The Netherlands*

MEETING SCHEDULE

Wednesday, January 21 (p.m.): PAMM Investigational Drugs & GPCO-Unicancer Business groups meetings (invitation only), welcome reception

Thursday, January 22: Plenary Sessions, Poster Session & Football Match

Friday, January 23: Plenary Sessions, Poster Session & Social Event

Saturday, January 24 (a.m.): Young Researcher Session

CALL FOR ABSTRACTS

Details and submission on www.pamm2015.com
Deadline: November 15, 2014

You are much welcome to submit materials for consideration by the PAMM-2015 Program Committee. Both PAMM and non-PAMM members are allowed to submit abstracts. PhD students and Post-Doc fellows can submit materials for the Young Researcher session.

Abstracts should be prepared as following:

- *An English language abstract must be in the terminology familiar to specialists.*
- *The text should be succinct and substantive. Results presented, full names and affiliations, the abstract must include: Purpose, Methods, Results, Conclusion, and Significance.*
- *Submit a Microsoft Word document no longer than 250 words or one page in length. (If you would like to include an image, be sure to embed the image in the Word document.*

Please specify whether you want your abstract to be considered for:

- **Plenary session** *(oral presentation - 22-23 January 2015)*
- **Poster session** *(22-24 January 2015)*
- **Young Researchers Session** *(oral presentation - 24 January 2015)*

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PRELIMINARY PROGRAM

36th EORTC-PAMM Winter Meeting

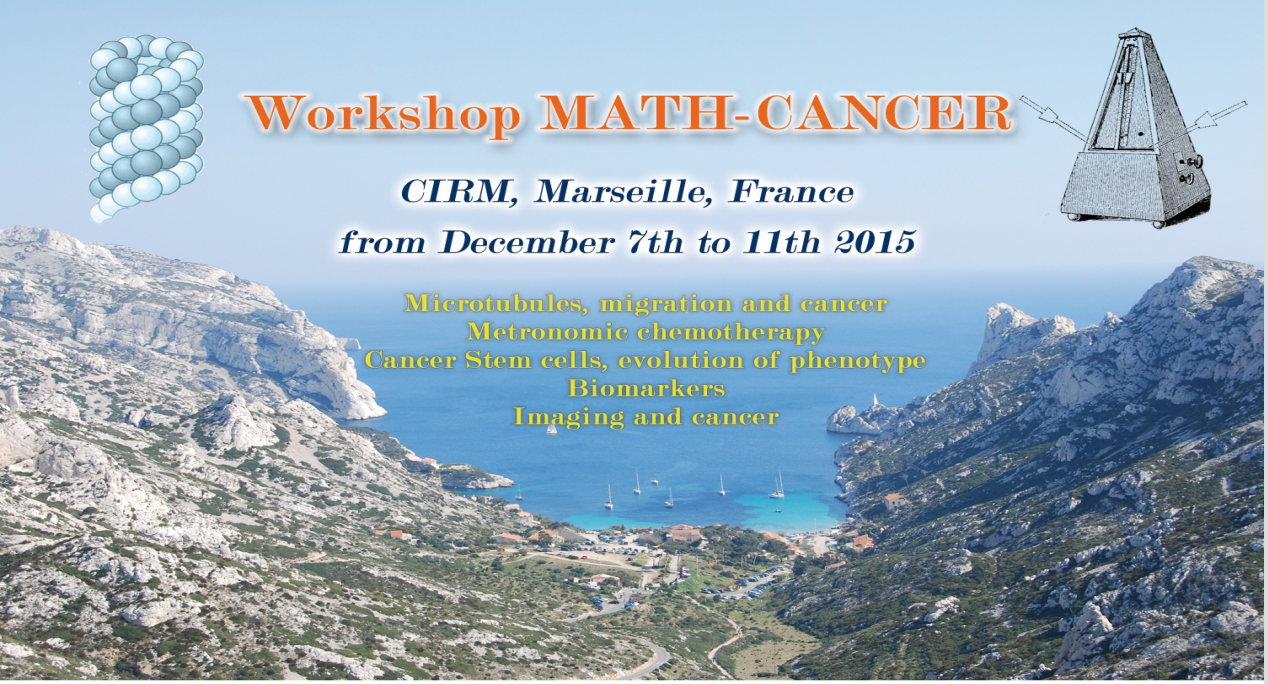
Wednesday 21 - Saturday 24 January, 2015
Marseille Provence Métropole, France

Time for paradigm shifts in oncology?

Local Organising Committee
Dr J. Ciccolini, *Marseille, France*
PAMM Scientific Committee
Pr G.J. Peters, *Amsterdam, The Netherlands*

Main topics
- Modelling & Simulation in Oncology
- Metronomic Chemotherapy
- Biology-guided Oncology
- Omics & Imaging in Oncology
- Nanotechnology & Drug Delivery
- Biotechnologies & Immunotherapy
- What's in the Pipe?

www.pamm2015.com



Workshop MATH-CANCER

CIRM, Marseille, France

from December 7th to 11th 2015

Microtubules, migration and cancer
Metronomic chemotherapy
Cancer Stem cells, evolution of phenotype
Biomarkers
Imaging and cancer

INVITED SPEAKERS

Sébastien Benzekry (INRIA Bordeaux, France), Catherine Bonnet (INRIA Saclay, France), Thierry Colin (INRIA Bordeaux, France), Phillip Hahnfeldt (Tufts University Medical School, Boston, USA), Jinzhi Lei (Tsingua University, Beijing, China), Anna Marciniak-Czochra (Heidelberg University, Germany), Nicolas Meunier (University Paris 5, France), Xavier Muracciole (AP-HM, Marseille, France), Roberto Natalini (University of Roma, Italy), Laeticia Padovani (AP-HM, Marseille, France), Eddy Pasquier (CRO2, Marseille, France), Victor M. Pérez García (University of Castilla-La Mancha, Spain), Benoit Perthame (University Paris 6, France), Angélique Stéphanou (CNRS, TIMC-IMAG, Grenoble, France), David Tayeb (AP-HM, Marseille, France), Alain Thierry (INSERM, Montpellier, France), Jack Tuszynski (University of Alberta, Canada).

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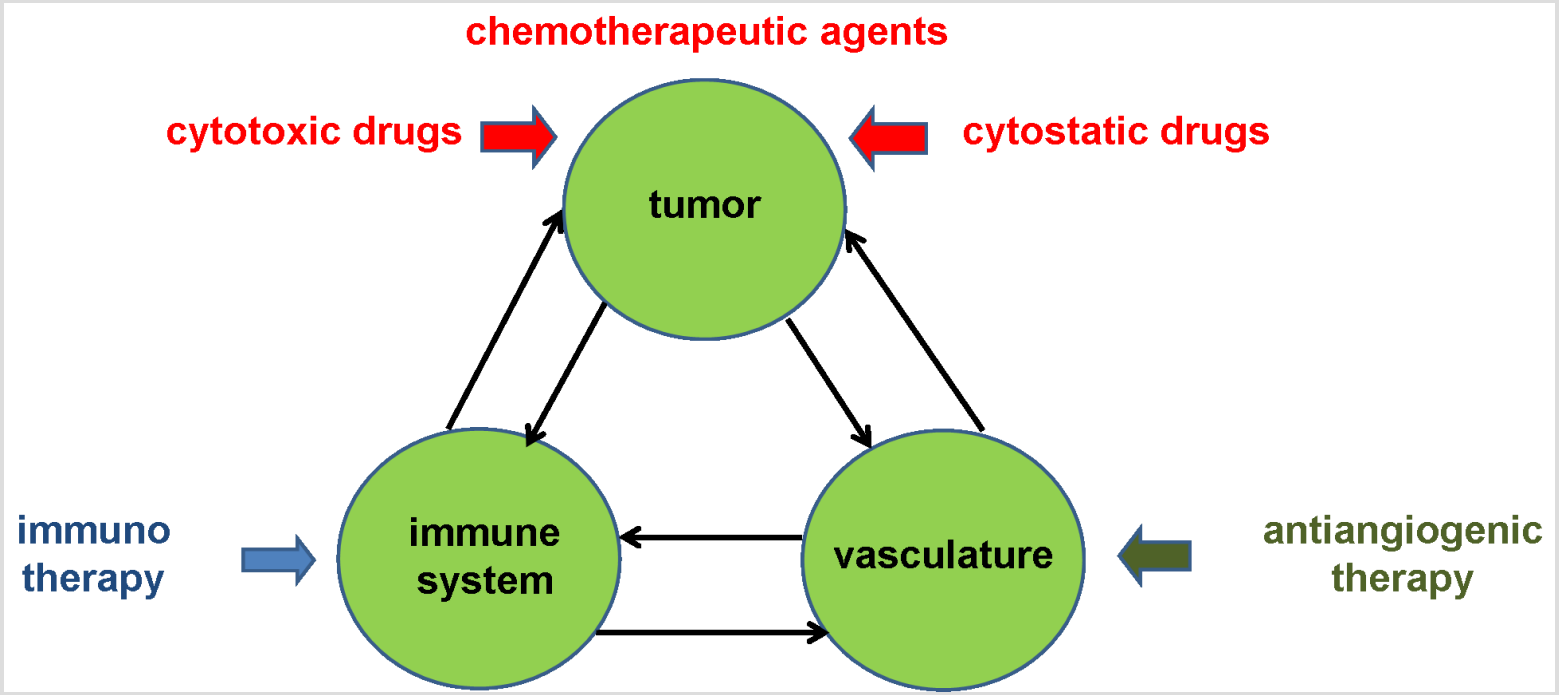
Information: http://math-cancer-cirm2015.math.cnrs.fr

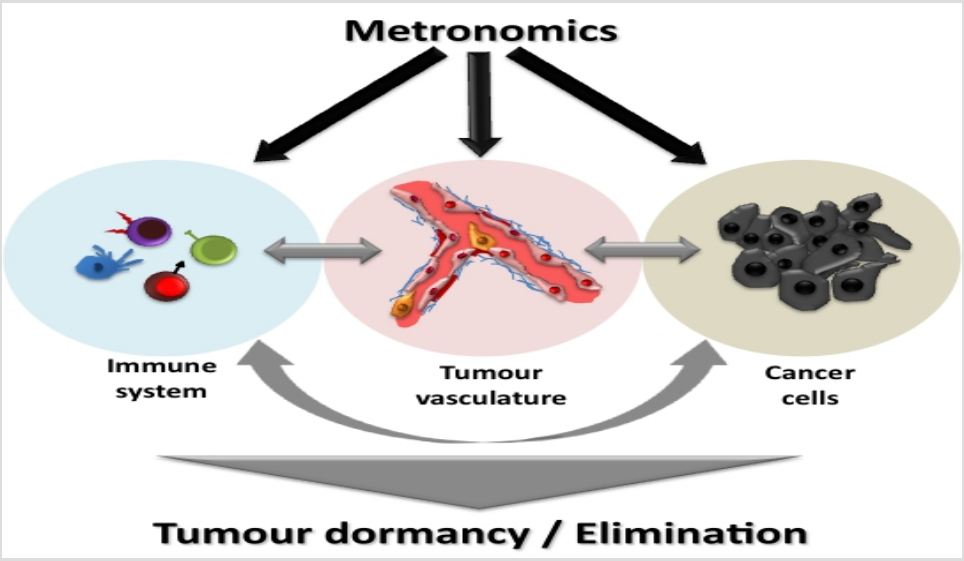
Cancer Treatment Protocols



How to optimize the antitumor, antiangiogenic and pro-immune effects of therapy by modulating dose and administration schedule?

Eddy Pasquier, Nicholas André

Metronomic Chemotherapy



1. lower 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

Medical Practice and Research

- **MTD** - maximum tolerated dose strategies

- **metronomic chemotherapy**

  – continuous, low-dose

- **chemo-switch** protocols (Hanahan)

- **adaptive therapy** (Gatenby)

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

Different therapeutic approaches:

- MTD/Metronomic: Chemo-Switch strategies (D. Hanahan)

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

Different therapeutic approaches:

- “Pure” metronomic / Metronomics (R. Kerbel, D. Hanahan)

- 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

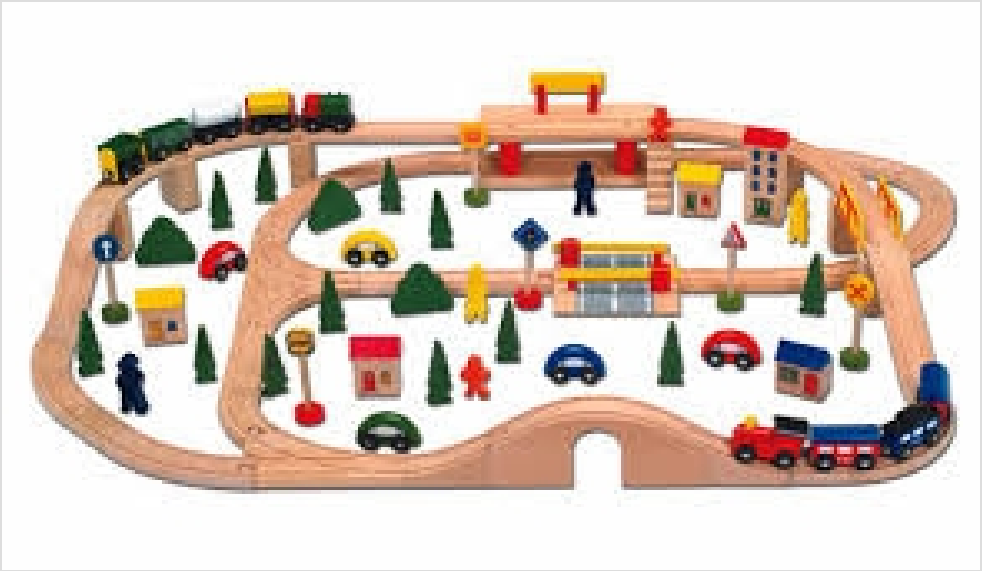
[6] Children’s Cancer Institute Australia, Lowy Cancer Research Centre, University of New South Wales, Randwick, NSW, Australia

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

Metronomic Chemotherapy: Modeling Challenges



Towards Modeling Metronomic Chemotherapy

How is it administered?

- treatment at lower doses

  (between 10% and 50% of MTD)

- **constant ?** **varying in time ?** **short rest periods ?**

What should be modeled ?

Minimally parameterized model

- cancer cells (heterogeneous, varying sensitivities)
- vasculature (angiogenic signaling)
- tumor immune interactions

- **Single-input control**:

  metronomic dosing of chemotherapy

A Combined Model for Low Dose Chemotherapy

Ledzewicz, Schättler, Amini, MBE, JMB to appear

p(t) – primary tumor volume

q(t) – carrying capacity of the tumor vasculature

r(t) – immunocompetent cell density

u(t) – concentration of a chemotherapeutic agent

$$
\begin{aligned}
\dot{p} &= -\xi p \ln\left(\frac{p}{q}\right) - \theta p r - \varphi_1 p u, \\
\dot{q} &= b p - (\mu + d p^{\frac{2}{3}}) q - \varphi_2 q u, \\
\dot{r} &= \alpha p (1 - \beta p) r - \delta r + \gamma + \varphi_3 r u,
\end{aligned}
$$

effectiveness of drug, φ_i *i=1,2,3*

Parameter values

mostly based on the papers by [Kuznetsov et al., 1994] and [Hahnfeldt et al., 1999] effectiveness (PD)

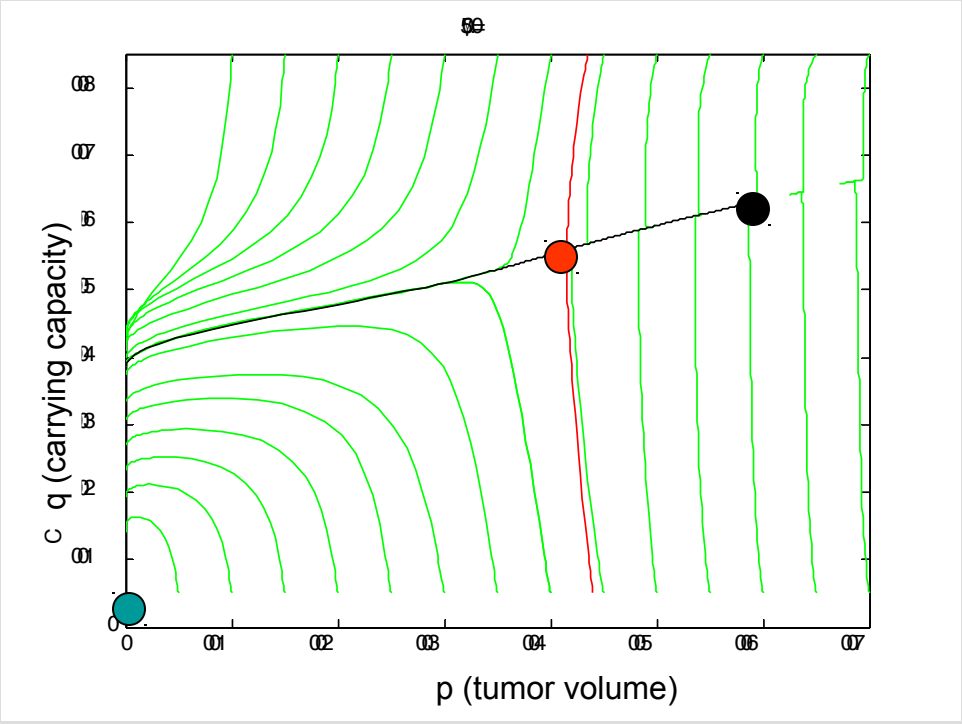
$$
\begin{aligned}
\alpha &= 0.0529, \\
\beta &= 0.00291, \\
\gamma &= 0,\ 0.01,\ 0.05\ \ldots \\
\delta &= 0.3743, \\
\theta &= 1, \\
\mu &= 0, \\
\zeta &= \frac{21}{32}\alpha = 0.0347, \\
b &= 5, \\
d &= \frac{1}{15}
\end{aligned}
$$

will vary γ

effectiveness (PD)

$$
\begin{aligned}
\varphi_1 &= 0.005, \\
\varphi_2 &= 0.06, \\
\varphi_3 &= 0.02,
\end{aligned}
$$

Bi-stability of Uncontrolled Model

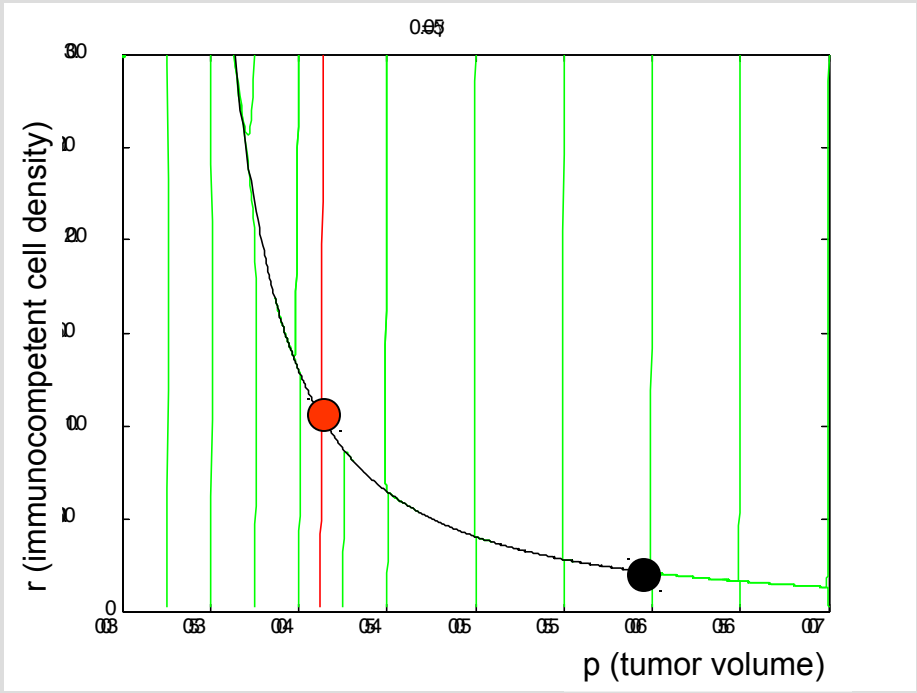


projections into (p,q)- and (p,r)-space

- asymptotically stable – "good", benign equilibrium

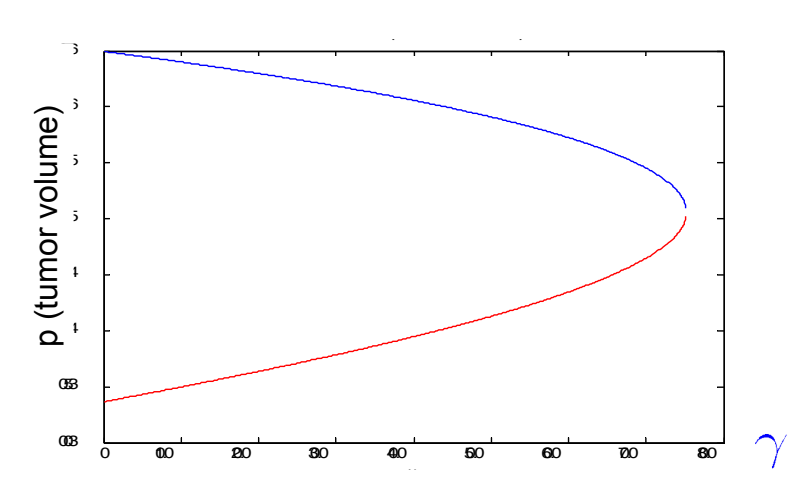
- saddle point and stability boundary

- asymptotically stable – "bad", malignant equilibrium



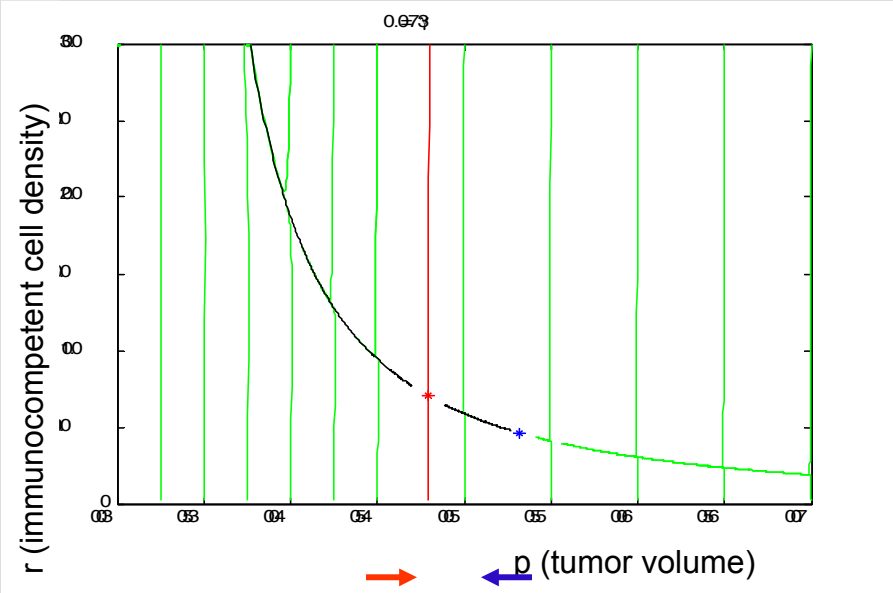
Bifurcations in Immune Influx

As the parameter γ increases, the unstable and malignant equilibrium disappear in a **saddle-node bifurcation**



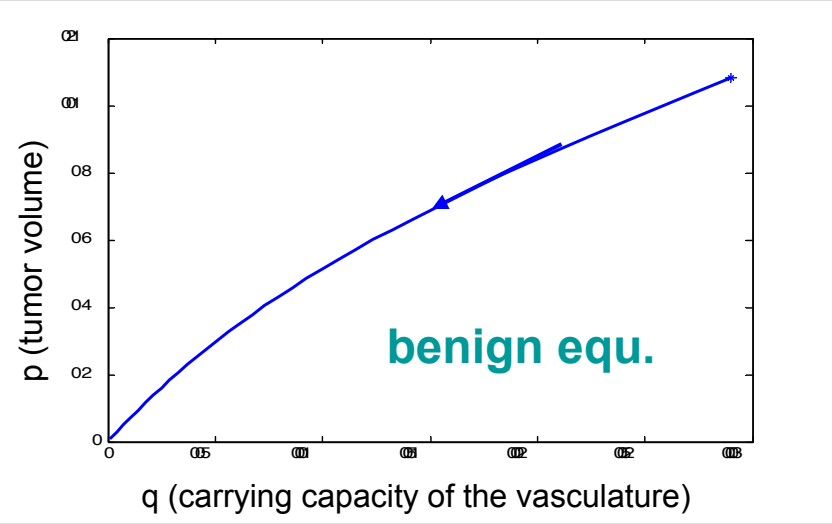
for large enough γ, the positive effects of the immune system are able to control the tumor

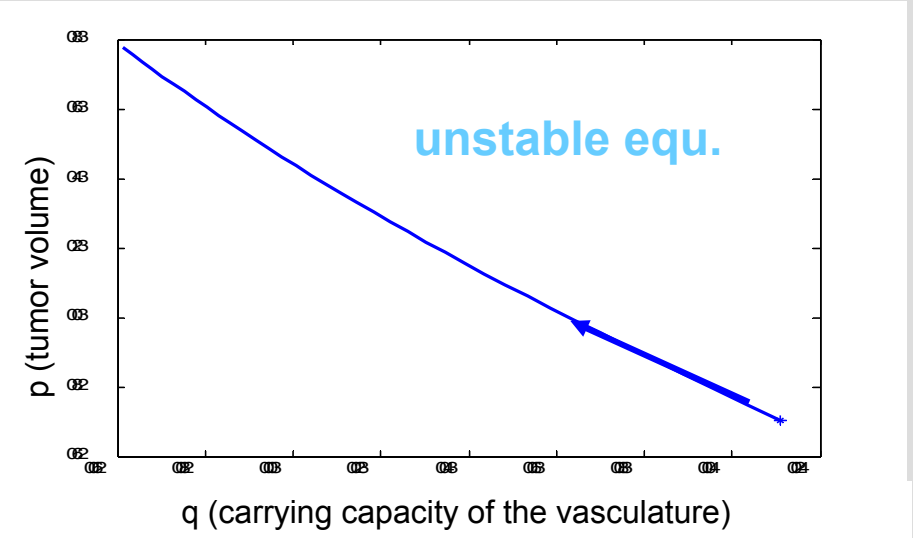
immune surveillance

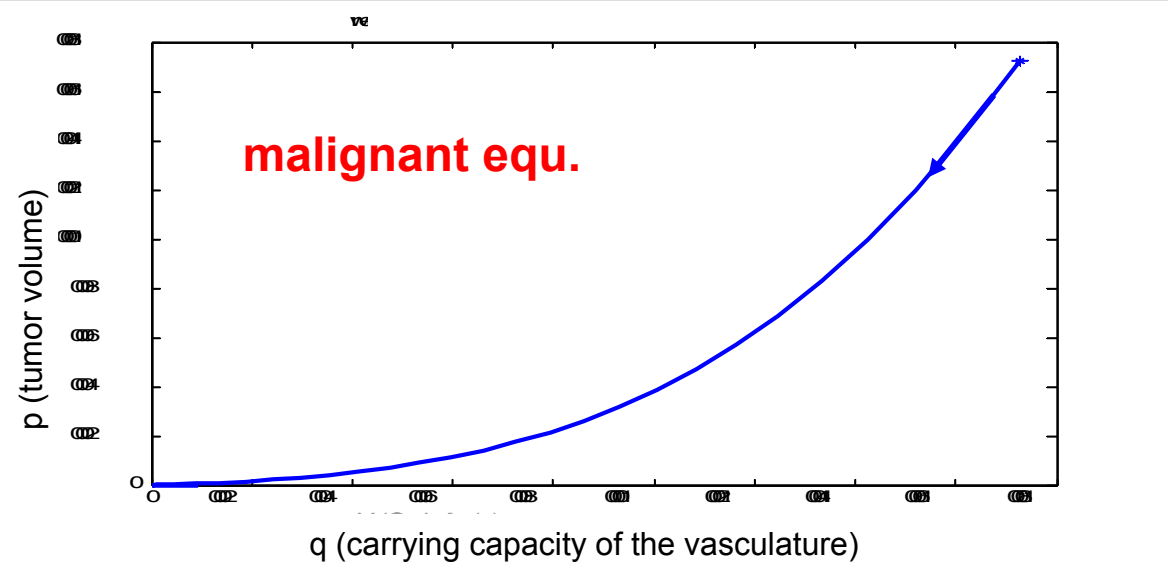


Equilibrium Properties under Low-dose Chemotherapy

for low dose, constant chemotherapy *u* the three equilibria persist, but all move closer to the disease free state at the origin as *u* increases







Equilibria for constant, low dose chemotherapy

$$\dot{p} = 0 \quad \Leftrightarrow \quad r = -\frac{1}{\theta}\left(\xi \ln\left(\frac{p}{q}\right) + \varphi_1 u\right),$$

$$\dot{q} = 0 \quad \Leftrightarrow \quad b\frac{p}{q} = \mu + \varphi_2 u + dp^{\frac{2}{3}},$$

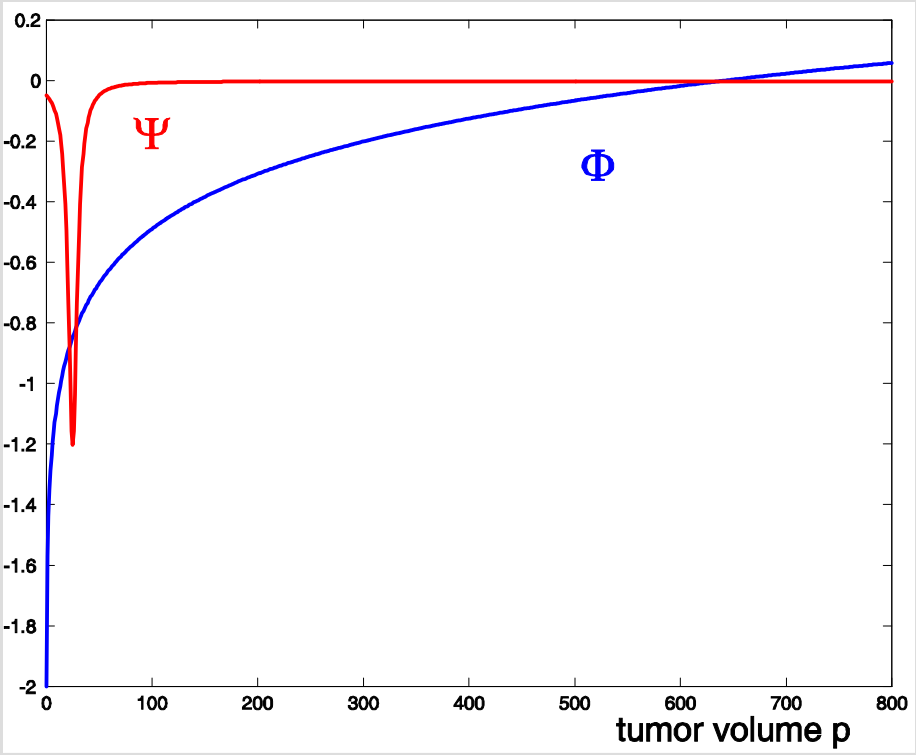
$$\dot{r} = 0$$

$$\xi \ln\left(\frac{\mu + \varphi_2 u + dp^{\frac{2}{3}}}{b}\right) + \varphi_1 u = -\frac{\theta\gamma}{\alpha\beta p^2 - \alpha p + \delta - \varphi_3 u}$$

Φ angiogenic signaling

Ψ tumor immune system interactions

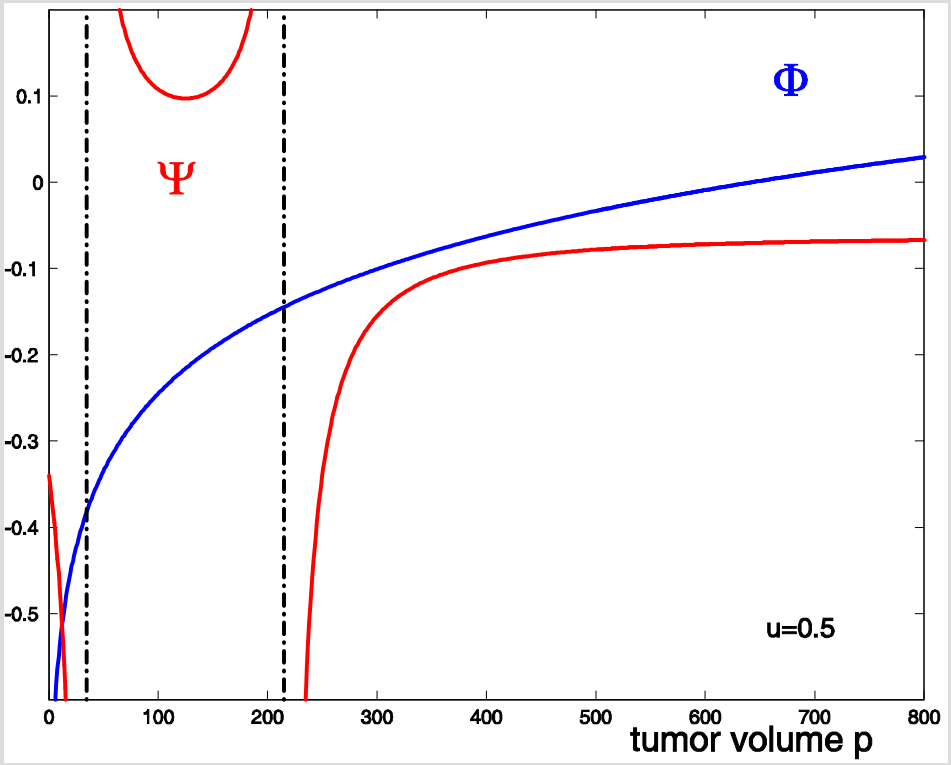
At most 3 Positive Equilibrium Points



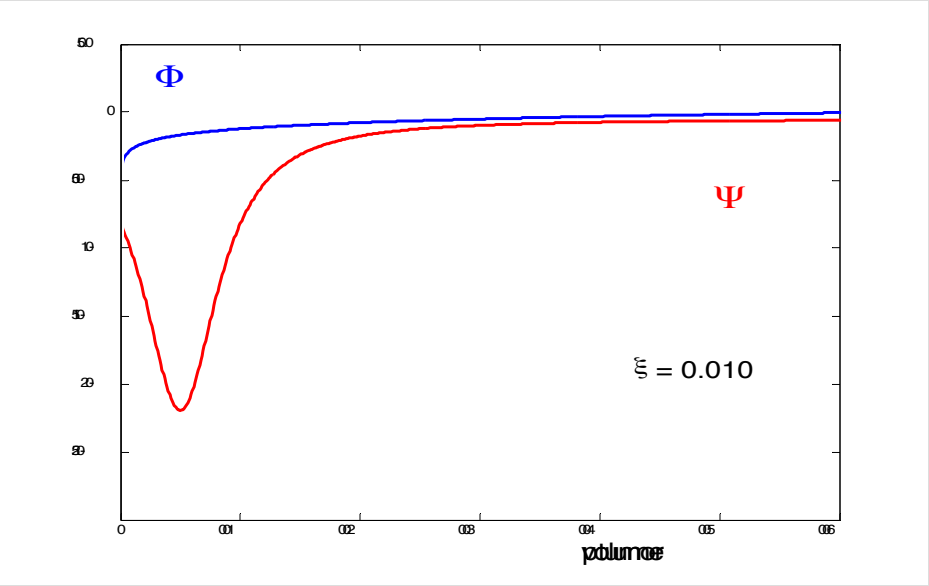
complex roots

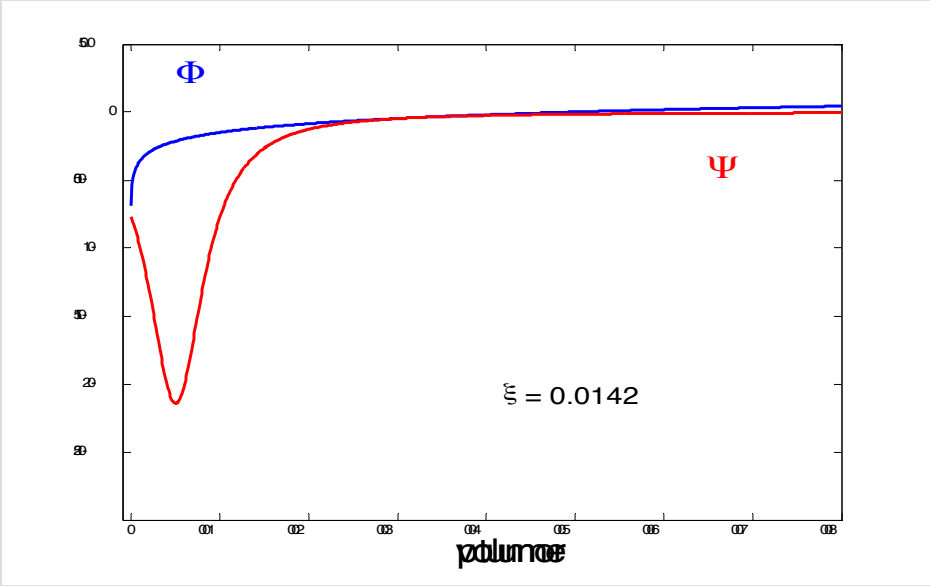
$$Q(p) = \alpha\beta p^2 - \alpha p + \delta - \varphi_3 u$$

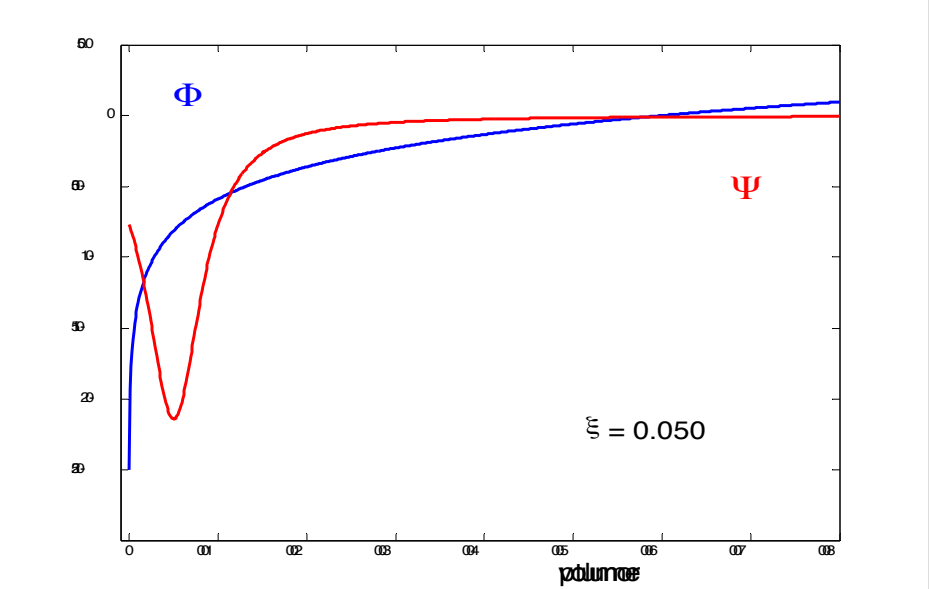
real roots

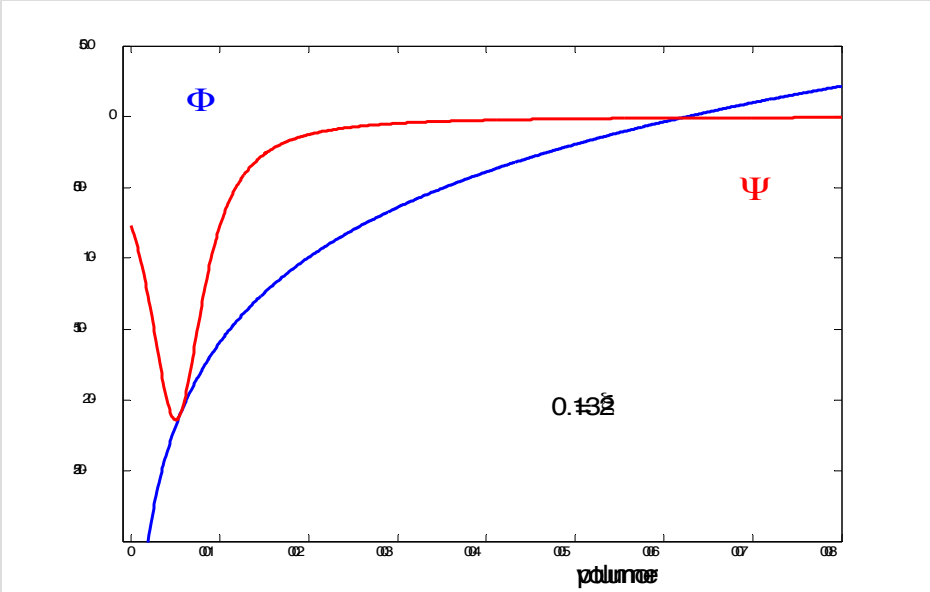


Bifurcations with Tumor Growth Rate

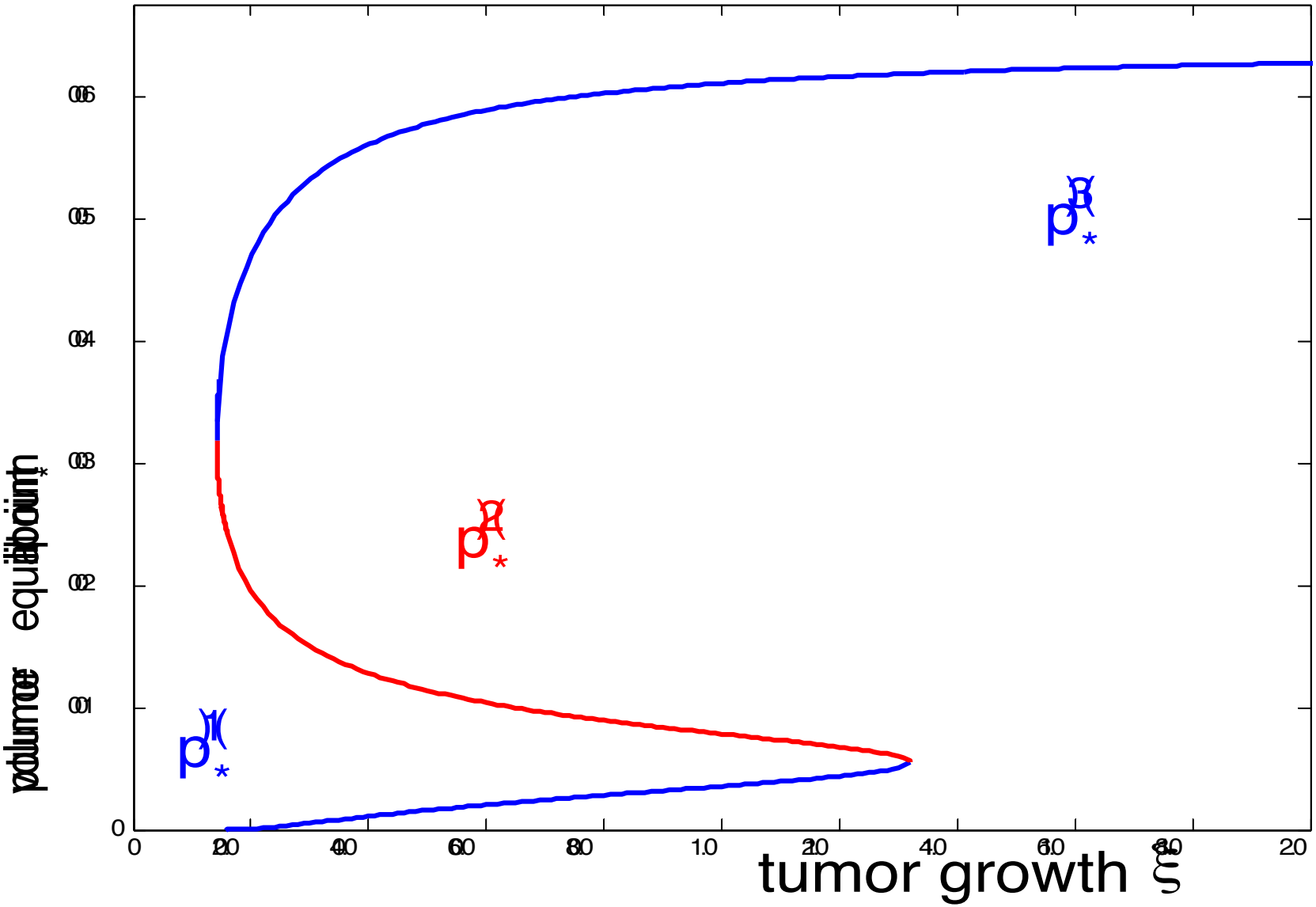








Bifurcation diagram in Tumor Growth Rate



Current and Future Work: Optimal Control Problem

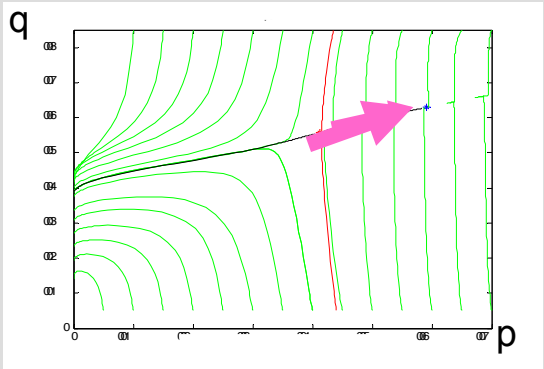
"move an initial condition that lies in the malignant region through chemotherapy into the benign region"

minimize $J(u) = Ap(T) + Bq(T) - Cr(T) + \int_0^T Mu(t)dt + ST$

over all Lebesgue measurable functions u: [0,T] → [0,u_{max}] subject to the dynamics

$$\begin{aligned}
\dot{p} &= -\xi p \ln\left(\frac{p}{q}\right) - \theta pr - \varphi_1 pu, \\
\dot{q} &= bp - (\mu + dp^{\frac{2}{3}})q - \varphi_2 qu, \\
\dot{r} &= \alpha p(1-\beta p)r - \delta z + \gamma + \varphi_3 ru,
\end{aligned}$$

where (A,B,-C) (A,B and C are positive) is the tangent vector to the unstable manifold of the saddle point, oriented to point from the benign into the malignant region.



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

Dynamics in Vector Form

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

drift

control vector field

$$f(x) = \begin{pmatrix} -\xi p \ln\left(\frac{p}{q}\right) - \theta pr \\ bp - (\mu + dp^{\frac{2}{3}})q \\ \alpha p(1 - \beta p)r - \delta z + \gamma \end{pmatrix} \quad g(x) = \begin{pmatrix} -\varphi_1 p \\ -\varphi_2 q \\ \varphi_3 r \end{pmatrix}$$

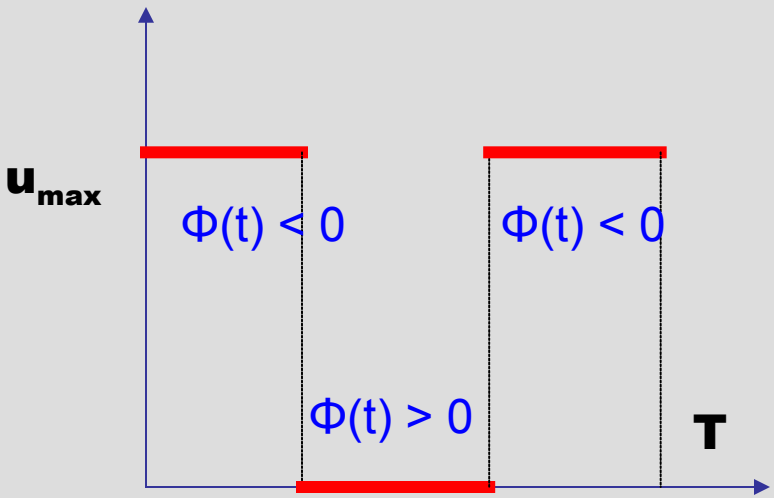
Lie bracket:

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

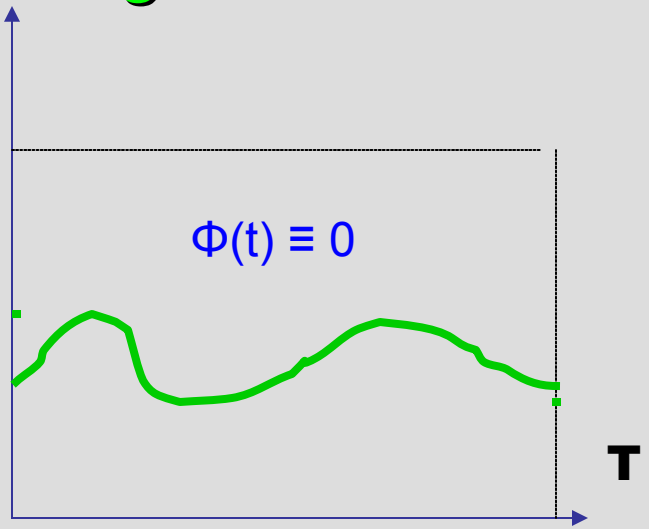
Candidates for Optimal Protocols

switching function $\Phi(t) = M + \langle \lambda, g(z) \rangle$

- 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

dimension = 3

at every point x the multiplier $\lambda = \lambda(x)$ along a singular control is uniquely determined by the conditions

$$\left.\begin{array}{lll} \text{from MP}: & \langle \lambda, f(x) \rangle & = -S \\ \Phi = 0: & \langle \lambda, g(x) \rangle & = -M \\ \dot{\Phi} = 0: & \langle \lambda, [f,g](x) \rangle & = 0 \end{array}\right\} \quad \Longrightarrow \quad \lambda = \lambda(x)$$

Legendre-Clebsch condition: $\langle \lambda(x), [g,[f,g]](x) \rangle < 0$

Singular control: $u_{sing}(x) = -\dfrac{\langle \lambda(x), [f,[f,g]](x) \rangle}{\langle \lambda(x), [g,[f,g]](x) \rangle}$

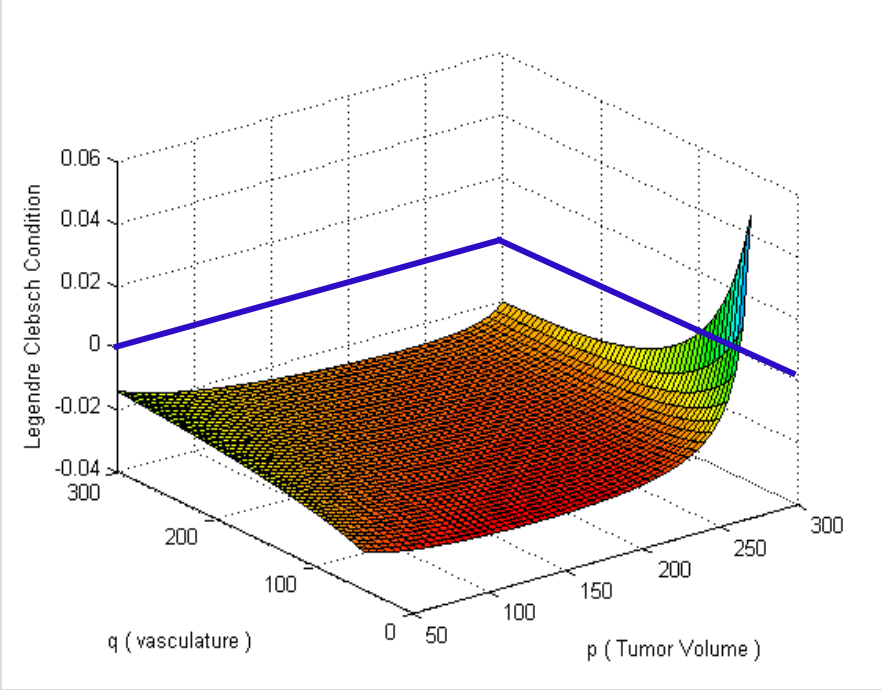
can compute the singular control as a **feedback control** for the full state-space

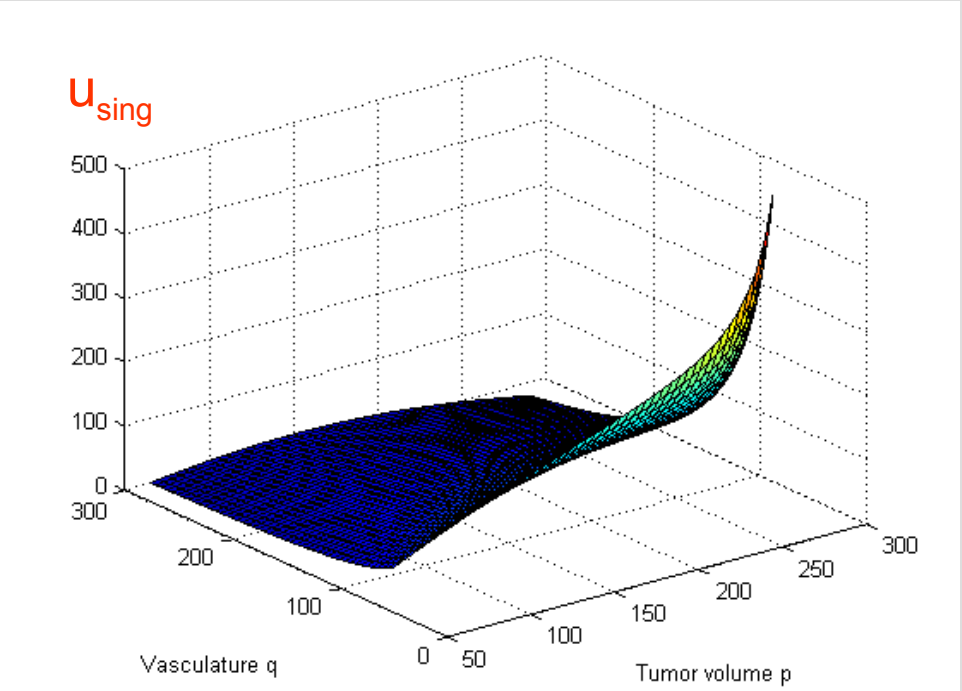
Legendre-Clebsch Condition and Singular Controls

slices for constant value of *r*

Legendre-Clebsch condition

$$\langle \lambda(x), [g,[f,g]](x) \rangle < 0$$





singular control

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

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

High Tumor Volumes

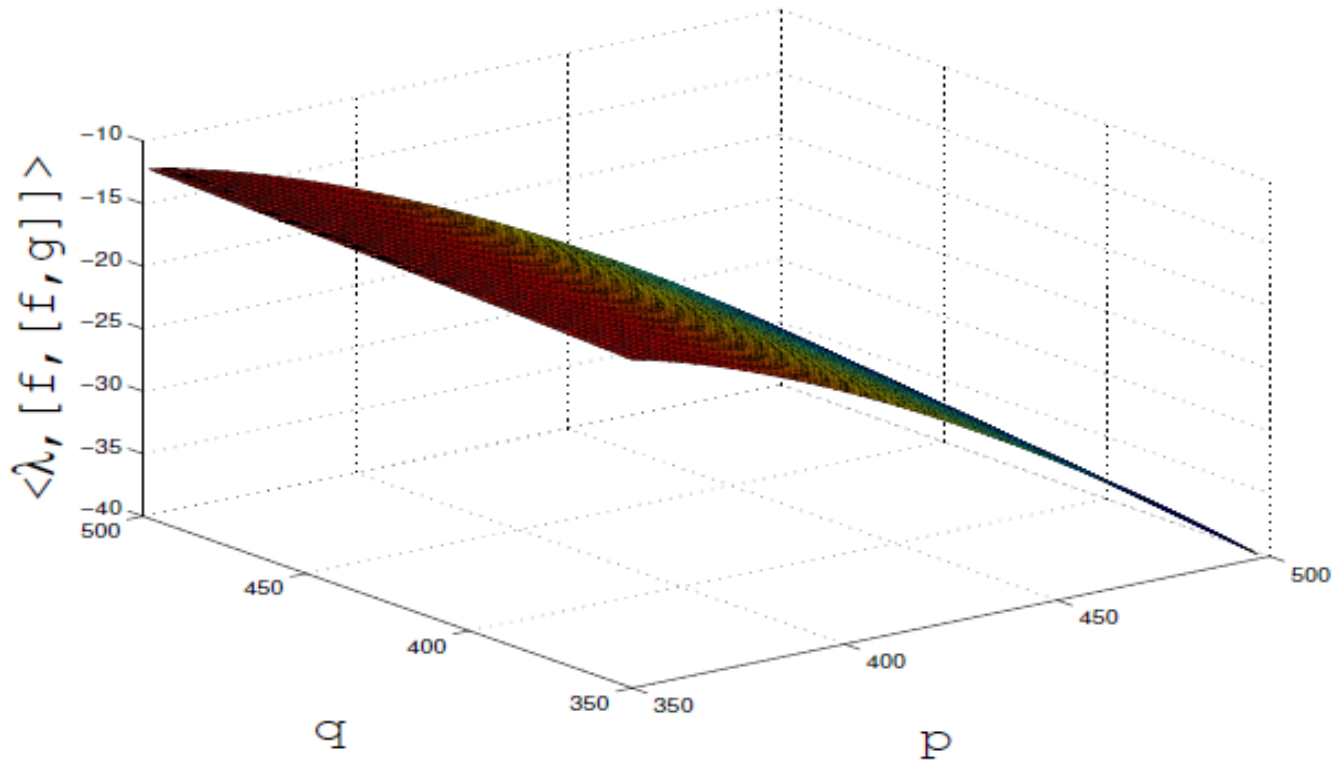


FIGURE : Slice of the graphs of the feedback functions $\langle \lambda_{\text{sing}}(z), [f,[f,g]](z) \rangle$ for $(p,q) \in [350,500] \times [350,500]$).

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

High Tumor Volumes

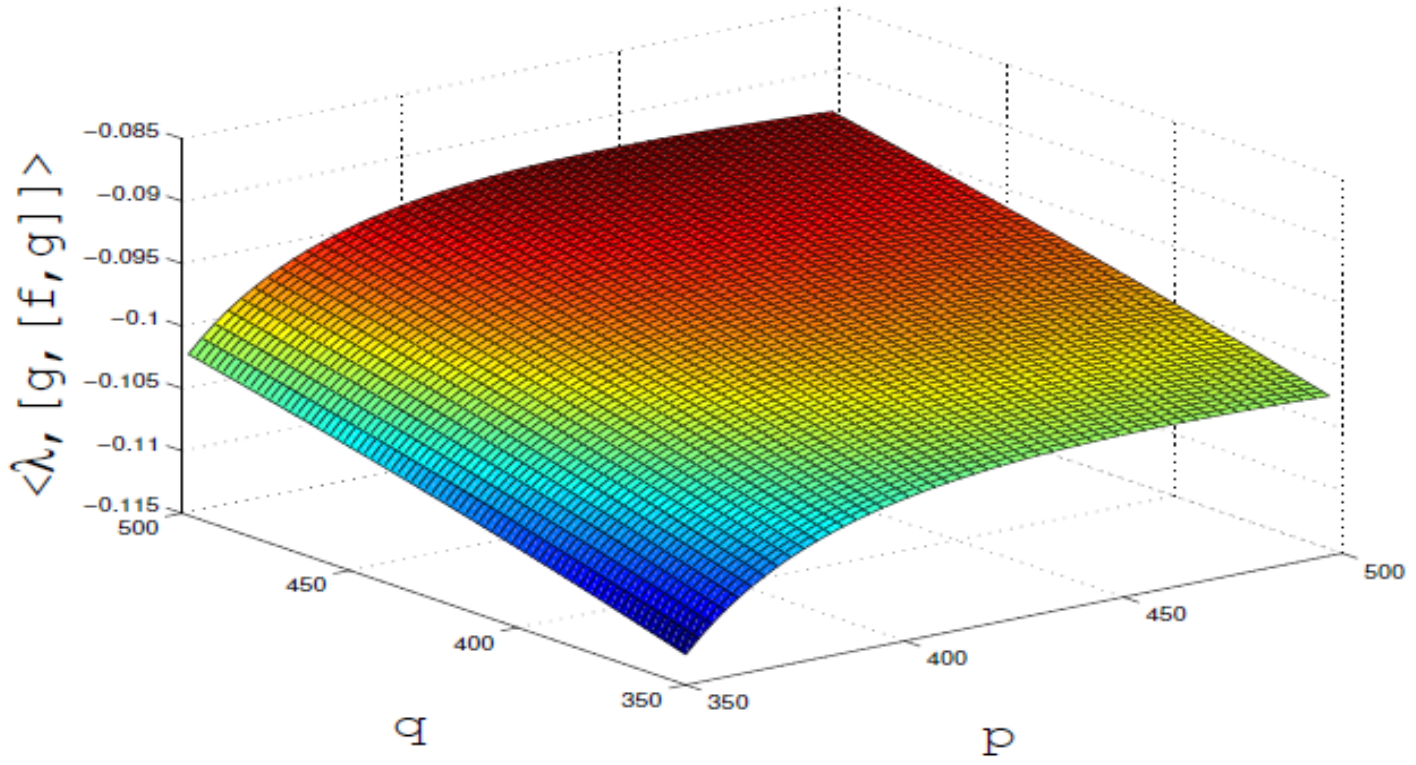


FIGURE : Slice of the graph of the feedback functions $\langle \lambda_{\text{sing}}(z), [g,[f,g]](z) \rangle$ for $(p,q) \in [350,500] \times [350,500]$ and $r = 0.5$.

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

High Tumor Volumes

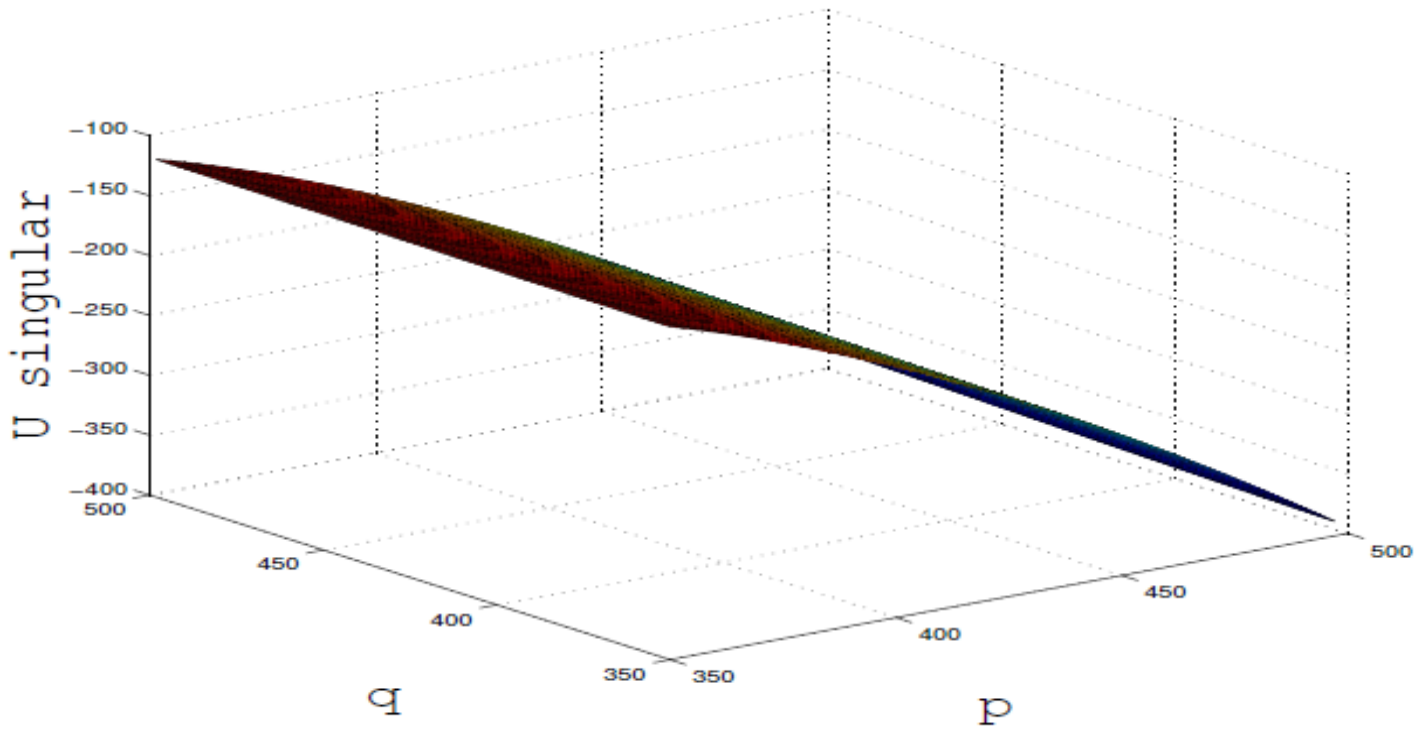


FIGURE : For $(p, q) \in [350, 500] \times [350, 500]$ and $r = 0.5$.

- **singular control is negative - inadmissible**
- **full dose is optimal in this region**

Chemo-Switch Protocols

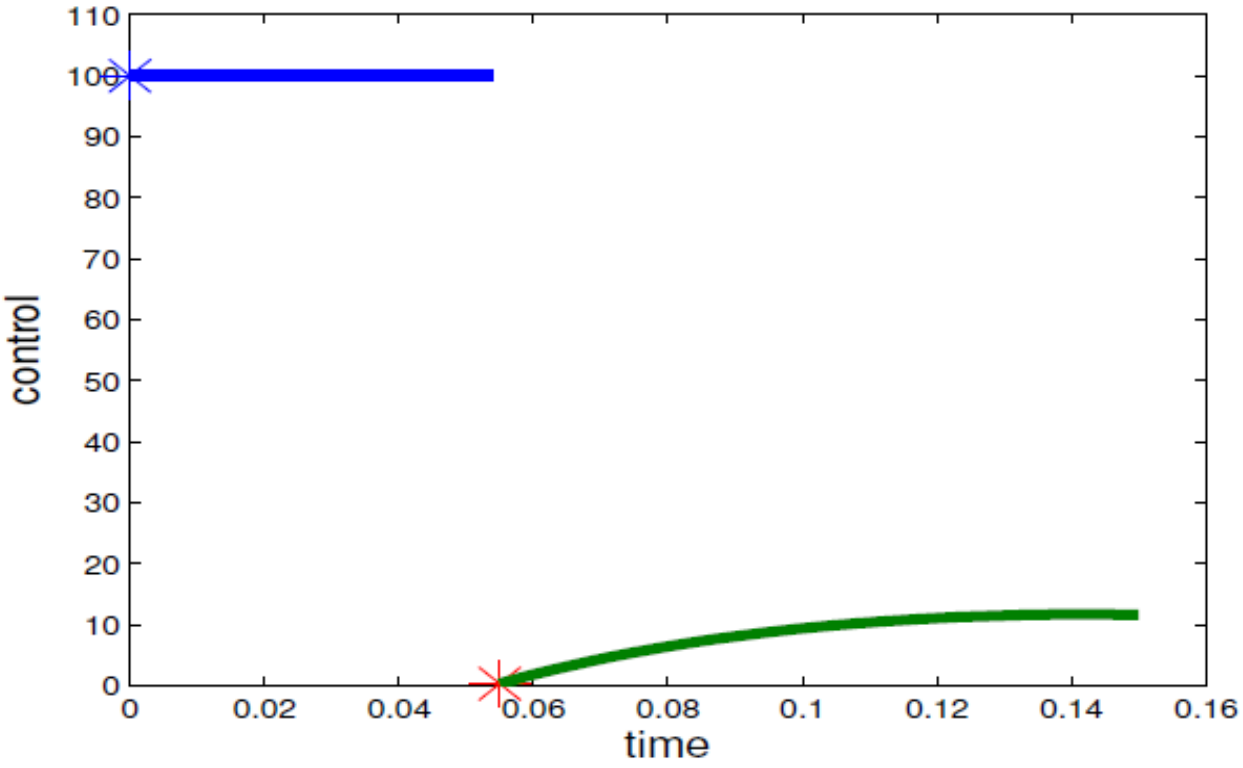


FIGURE : Time evolution of the control is full-dose at the first stage starting from initial value $(p_0, q_0, r_0) = (600, 750, 0.1)$ and then turns into singular contol.

Chemo-Switch Protocols

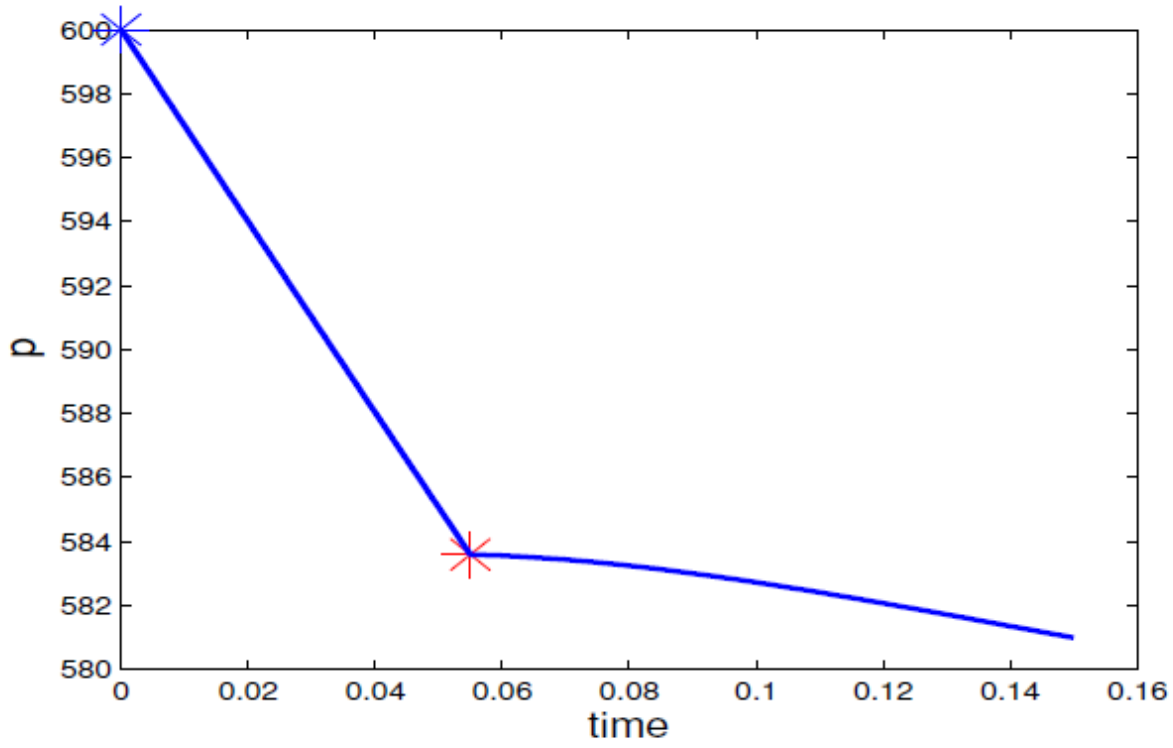


FIGURE : Time evolution of the tumor volume, starting from initial value $(p_0, q_0, r_0) = (600, 750, 0.1)$.

Chemo-Switch Protocols

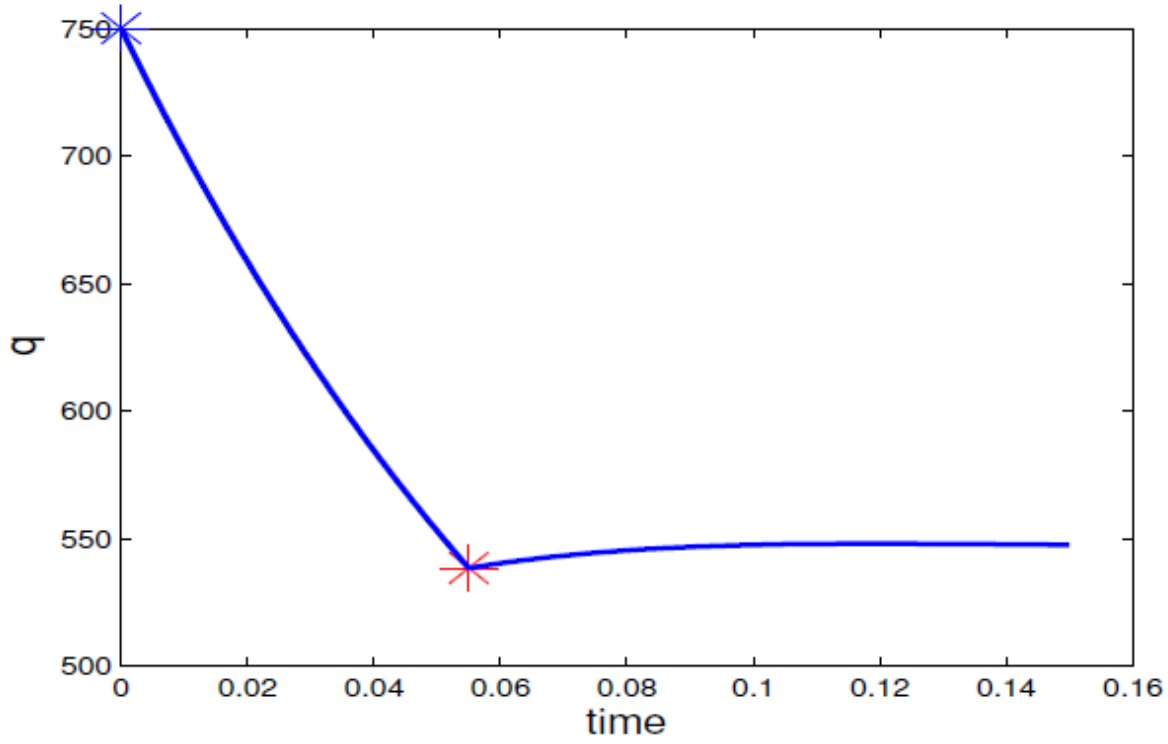


FIGURE : Time evolution of carrying vasculature, starting from initial value $(p_0, q_0, r_0) = (600, 750, 0.1)$.

Chemo-Switch Protocols

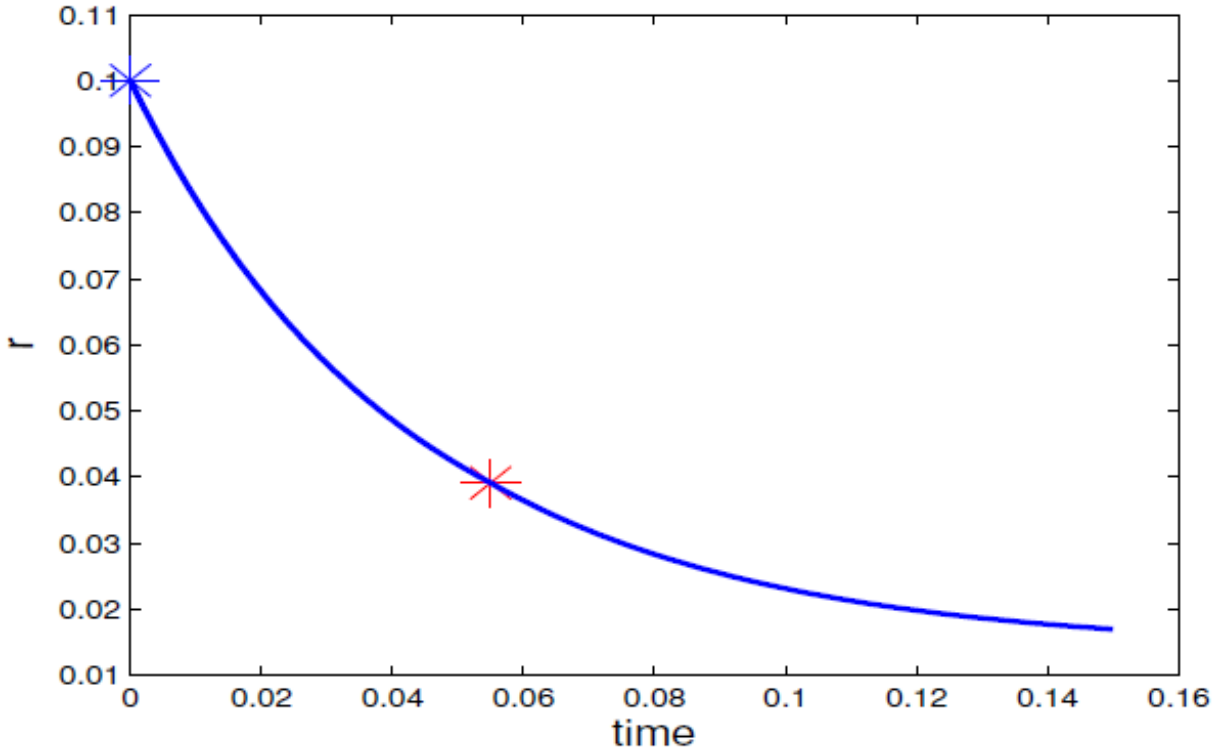


FIGURE : Time evolution of immune system starting from initial value $(p_0, q_0, r_0) = (600, 750, 0.1)$.

Instead of Conclusions

- although some mathematical insights are available that would indicate the optimality of low dose chemotherapy in some cases, overall

  there still are more questions than answers

- from the medical point of view …
- from the mathematical modeling and optimization point of view
  - will more complex models support the optimality of singular controls (low dose chemotherapy) ?
  - model different effects of MTD and metronomic chemotherapy on tumor and immune system ?
  - tumor promoting aspect of tumor immune interactions ?
  - …

Dziękuję