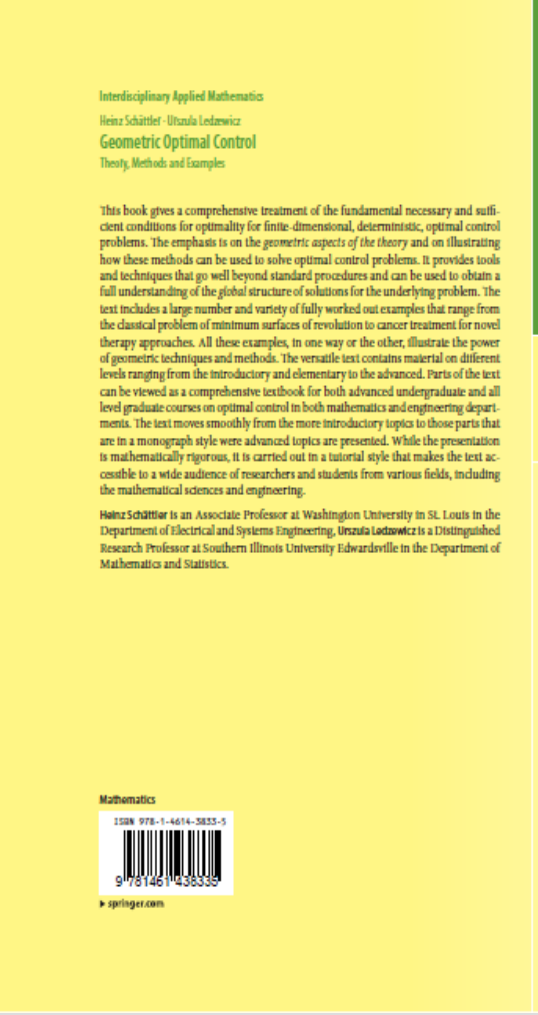
Minimally Parameterized Mathematical Models for the Tumor Microenvironment: Challenges in Modeling and Analysis

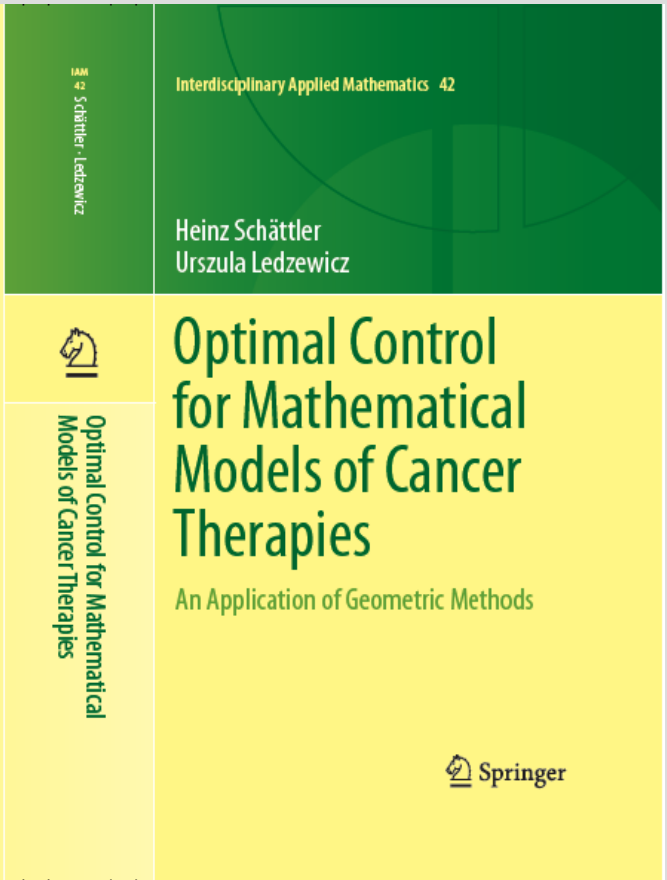
Workshop Math-Cancer CIRM,

December 7-11 2015 **Marseille, France**

Urszula Ledzewicz
Southern Illinois University Edwardsville, IL, USA
and Lodz University of Technology, Lodz, Poland

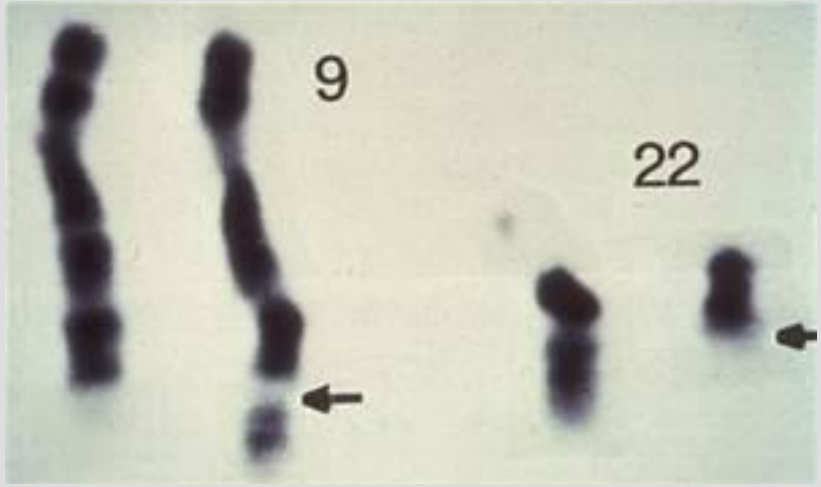


Springer
2012



Springer
September 2015

Part I:
Mathematical Model for CML



Research grant from Bristol-Myers Squibb

Co-author and Support

Helen Moore
Bristol-Myers-Squibb
Princeton, NJ USA

Research grant from

Bristol-Myers Squibb

Chronic Myeloid Leukemia

- Chronic myeloid leukemia (CML) is a hematologic neoplasm characterized by translocation between chromosomes 9 and 22, producing a “Philadelphia chromosome”. Fusion of the breakpoint cluster region with the Abl kinase gene produces continuous Abl activation leading to excessive proliferation of hematopoietic progenitor cells.
- BMS is studying the combination of *dasatinib*, a potent ABL tyrosine kinase inhibitor, with *nivolumab*, an immune checkpoint inhibitor. Dasatinib has the additional unique feature of immune modulation which may be supra-additive with nivolumab and other immunotherapies.

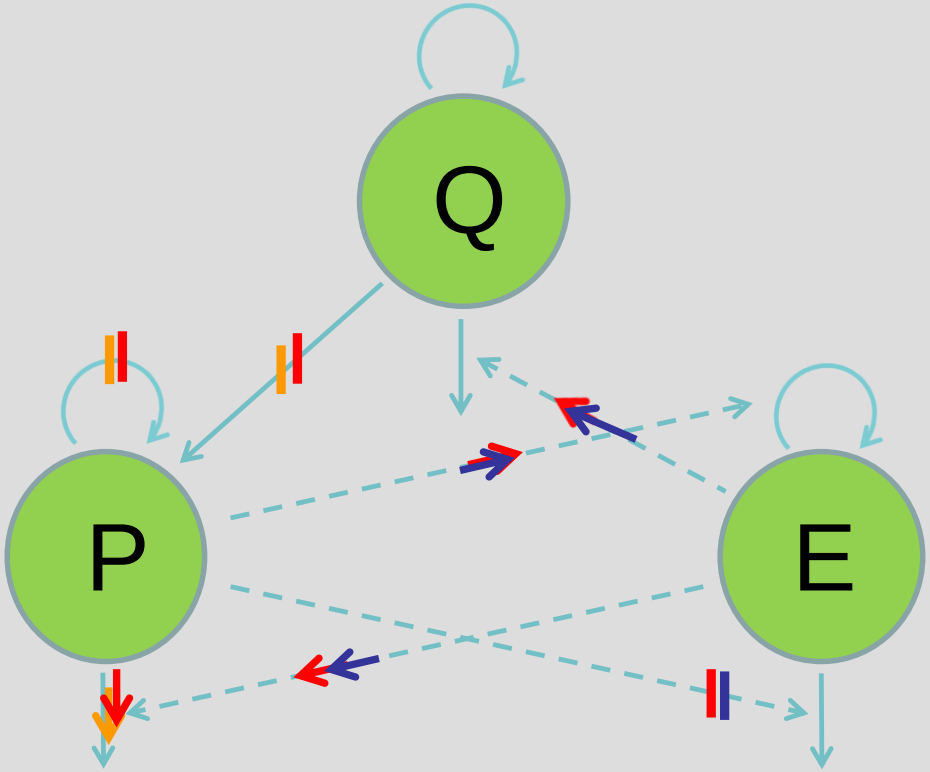
Bristol-Myers Squibb

Bristol-Myers Squibb

CML Model

Q = quiescent leukemic stem cells
P = proliferating leukemic cells
E = effector T cells

u_1 = general ABL inhibitor (e.g., imatinib)
u_2 = dasatinib
u_3 = nivolumab/other immunotherapy



Bristol-Myers Squibb

Mathematical Model

$$(1)\quad \frac{dQ}{dt} = \left(r_Q - \delta_Q \left[1 + \left(1 + \frac{U2_{\max,1} u_2}{U2C_{50} + u_2} \right) \left(1 + \frac{U3_{\max,1} u_3}{U3C_{50} + u_3} \right) \frac{E_{\max,1} E}{EC_{50} + E} \right] \right) \cdot Q$$

$$(2)\quad \frac{dP}{dt} = \left(1 - \frac{U1_{\max,1} u_1}{U1C_{50} + u_1} \right) \left(1 - \frac{U2_{\max,2} u_2}{U2C_{50} + u_2} \right) \cdot \left[k_P Q + r_P P \ln\left(\frac{P_{ss}}{P} \right) \right]$$

$$- \delta_P \left(1 + \frac{U1_{\max,2} u_1}{U1C_{50} + u_1} \right) \left(1 + \frac{U2_{\max,3} u_2}{U2C_{50} + u_2} \right) \cdot P$$

$$- \delta_P \left(1 + \frac{U2_{\max,1} u_2}{U2C_{50} + u_2} \right) \left(1 + \frac{U3_{\max,1} u_3}{U3C_{50} + u_3} \right) \frac{E_{\max,2} E}{EC_{50} + E} \cdot P$$

$$(3)\quad \frac{dE}{dt} = s_E \left[1 + \left(1 + \frac{U2_{\max,4} u_2}{U2C_{50} + u_2} \right) \left(1 + \frac{U3_{\max,2} u_3}{U3C_{50} + u_3} \right) \frac{P_{\max,1} P}{PC_{50} + P} \right] \cdot E \ln\left(\frac{E_{ss}}{E} \right)$$

$$- \delta_E \left[1 + \left(1 - \frac{U2_{\max,5} u_2}{U2C_{50} + u_2} \right) \left(1 - \frac{U3_{\max,3} u_3}{U3C_{50} + u_3} \right) \frac{P_{\max,2} P}{PC_{50} + P} \right] \cdot E$$

Variables and Parameters

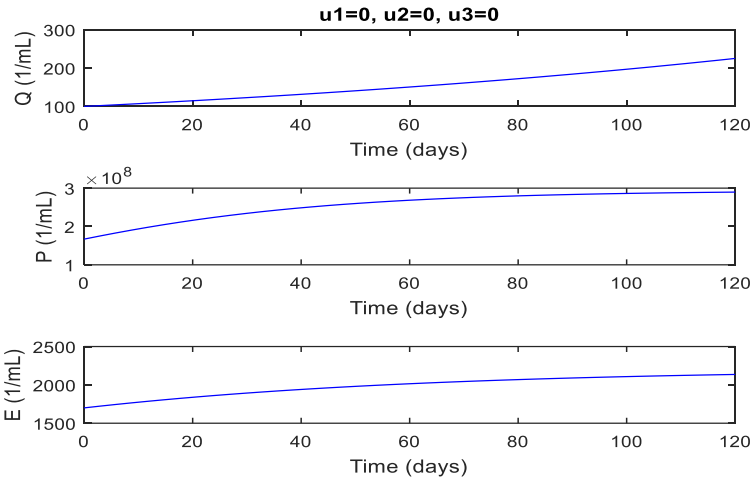
Values used in this talk are from the literature or are hypothetical

symbol	interpretation	dimension
Q	cancer stem cells	10^3 cells/mL
P	proliferating cancer cells	10^7 cells/mL
P_{ss}	carrying capacity of proliferating cancer cells	10^7 cells/mL
E	effector T cells	$2 \cdot 10^3$ cells/mL
E_{ss}	carrying capacity of effector T cells	$2 \cdot 10^3$ cells/mL
r_Q	replication rate of cancer stem cells	1/day
δ_Q	natural death rate of cancer stem cells	1/day
k_P	rate at which stem cells Q differentiate into proliferating cancer cells P	1/day
r_P	replication rate of proliferating cancer cells	1/day
δ_P	natural death rate of proliferating cancer cells	1/day
s_E	growth rate of effector T-cells	1/day
δ_E	natural death rate of effector T-cells	1/day
$E_{\max,1}$	maximum effect of effector T-cells E onto quiescent cancer cells Q	
$E_{\max,2}$	maximum effect of effector T-cells E onto proliferating cancer cells P	
EC_{50}	size of E with half the maximum effect	1/mL
$P_{\max,1}$	maximum growth effect of proliferating cancer cells P on effector T-cells E	
$P_{\max,2}$	maximum death effect of proliferating cancer cells P on effector T-cells E	
PC_{50}	size of P with half the maximum effects	1/mL

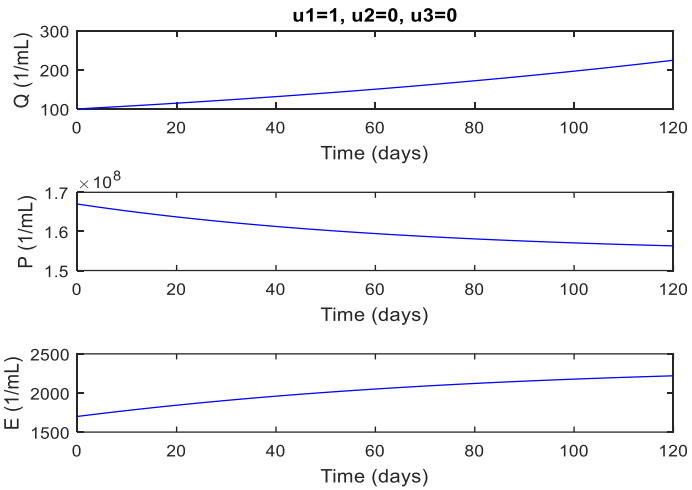
symbol	interpretation
u_1	concentration of a general ABL (e.g., Imatinib)
$U1_{\max,1}$	maximum possible effect of u_1 on retarding transfer of quiescent cells Q into P inhibiting growth of proliferating cells P
$U1_{\max,2}$	maximum possible effect of u_1 on death of proliferating cells P
$U1C_{50}$	concentration of u_1 that gives half the maximum effects
u_2	concentration of dasatinib cytotoxic and immune stimulatory agent
$U2_{\max,1}$	maximum possible effect of u_2 on death of cancer cells (the same for P and Q)
$U2_{\max,2}$	maximum possible effect of u_2 on retarding transfer of quiescent cells Q into P inhibiting growth of proliferating cells P
$U2_{\max,3}$	maximum possible effect of u_2 on death of proliferating cells P
$U2_{\max,4}$	maximum possible effect of u_2 on stimulation ('birth') of effector T cells
$U2_{\max,5}$	maximum possible effect of u_2 on prevention of the death of effector T cells
$U2C_{50}$	concentration of u_2 that gives half the maximum effects
u_3	concentration of nivolumab (or a similar immune stimulatory agent)
$U3_{\max,1}$	maximum possible effect of u_3 on death of cancer cells (the same for P and Q)
$U3_{\max,2}$	maximum possible effect of u_3 on stimulation ('birth') of effector T cells
$U3_{\max,3}$	maximum possible effect of u_3 on prevention of the death of effector T cells
$U3C_{50}$	concentration of u_3 that gives half the maximum effects

System Behavior for One Drug

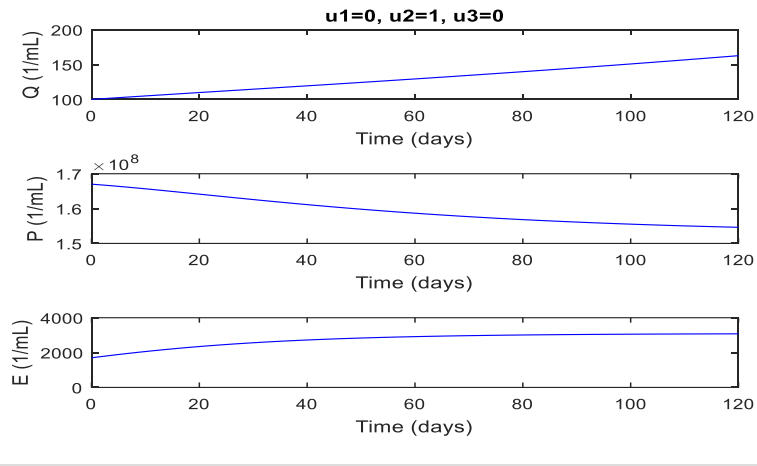
uncontrolled



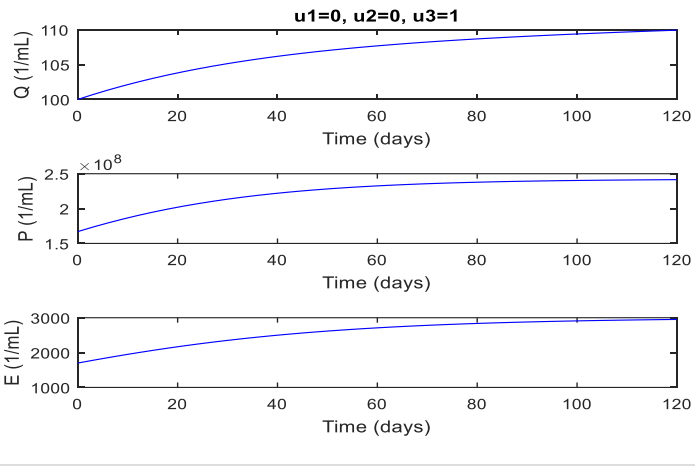
u_1 – (e.g., imatinib)



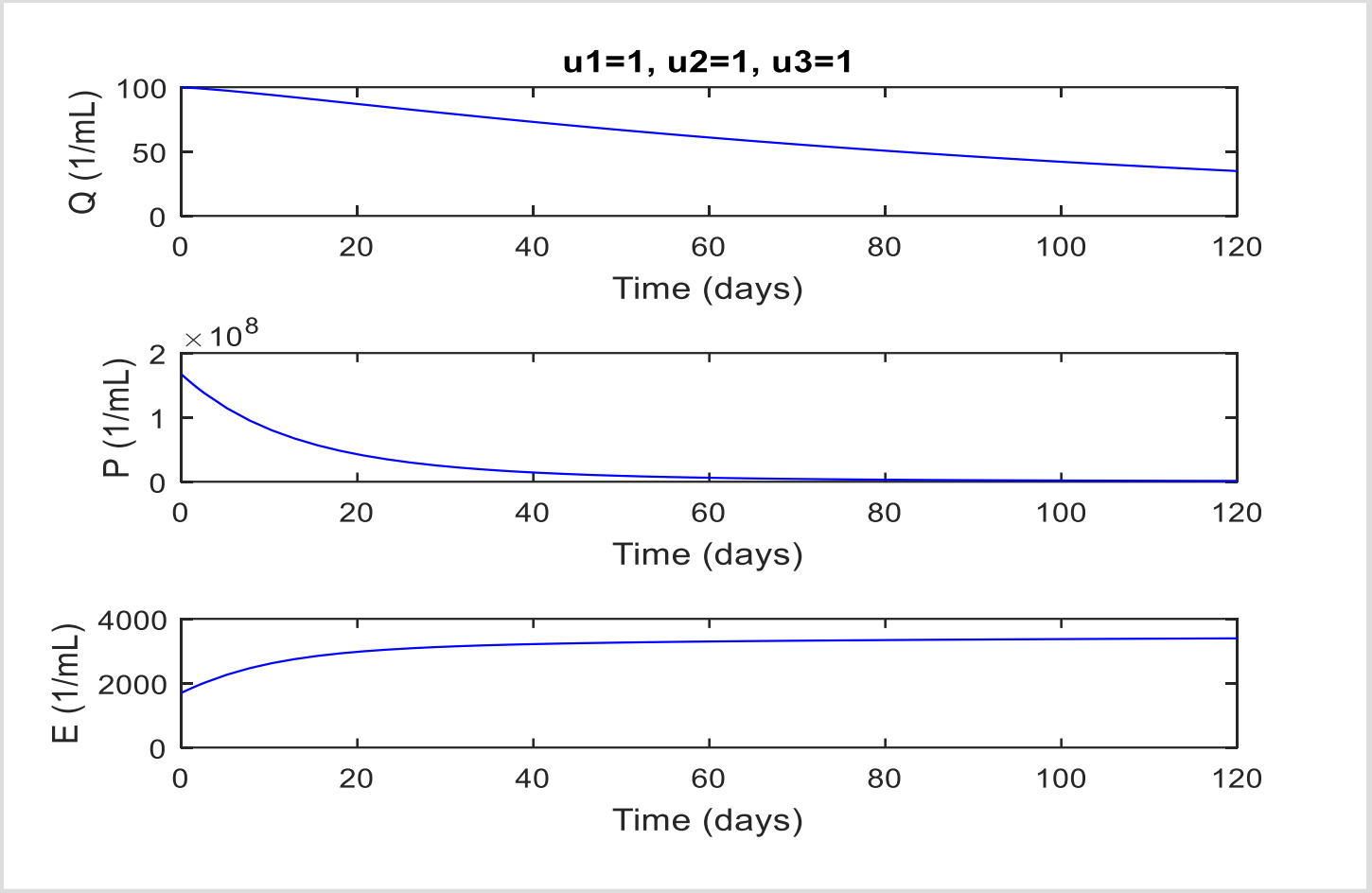
u_2 – (e.g., dasatinib)



u_3– (e.g., nivolumab)



System Behavior for Combination of all Drugs



Back to the Model

$$(1)\quad \frac{dQ}{dt} = \left(r_Q - \delta_Q \left[1 + \left(1 + \frac{U2_{\max,1} u_2}{U2C_{50} + u_2} \right) \left(1 + \frac{U3_{\max,1} u_3}{U3C_{50} + u_3} \right) \frac{E_{\max,1} E}{EC_{50} + E} \right] \right) \cdot Q$$

$$(2)\quad \frac{dP}{dt} = \left(1 - \frac{U1_{\max,1} u_1}{U1C_{50} + u_1} \right) \left(1 - \frac{U2_{\max,2} u_2}{U2C_{50} + u_2} \right) \cdot \left[k_P Q + r_P P \ln\left(\frac{P_{ss}}{P} \right) \right]$$

$$- \delta_P \left(1 + \frac{U1_{\max,2} u_1}{U1C_{50} + u_1} \right) \left(1 + \frac{U2_{\max,3} u_2}{U2C_{50} + u_2} \right) \cdot P$$

$$- \delta_P \left(1 + \frac{U2_{\max,1} u_2}{U2C_{50} + u_2} \right) \left(1 + \frac{U3_{\max,1} u_3}{U3C_{50} + u_3} \right) \frac{E_{\max,2} E}{EC_{50} + E} \cdot P$$

$$(3)\quad \frac{dE}{dt} = s_E \left[1 + \left(1 + \frac{U2_{\max,4} u_2}{U2C_{50} + u_2} \right) \left(1 + \frac{U3_{\max,2} u_3}{U3C_{50} + u_3} \right) \frac{P_{\max,1} P}{PC_{50} + P} \right] \cdot E \ln\left(\frac{E_{ss}}{E} \right)$$

$$- \delta_E \left[1 + \left(1 - \frac{U2_{\max,5} u_2}{U2C_{50} + u_2} \right) \left(1 - \frac{U3_{\max,3} u_3}{U3C_{50} + u_3} \right) \frac{P_{\max,2} P}{PC_{50} + P} \right] \cdot E$$

Adjustment of Parameters for Constant Concentrations

$$\hat{k}_P = \left(1 - \frac{U1_{\max,1} u_1}{U1C_{50} + u_1}\right)\left(1 - \frac{U2_{\max,2} u_2}{U2C_{50} + u_2}\right) k_P,$$

$$\hat{r}_P = \left(1 - \frac{U1_{\max,1} u_1}{U1C_{50} + u_1}\right)\left(1 - \frac{U2_{\max,2} u_2}{U2C_{50} + u_2}\right) r_P,$$

$$\hat{\delta}_P = \left(1 + \frac{U1_{\max,2} u_1}{U1C_{50} + u_1}\right)\left(1 + \frac{U2_{\max,3} u_2}{U2C_{50} + u_2}\right) \delta_P,$$

$$\hat{E}_{\max,1} = \left(1 + \frac{U2_{\max,1} u_2}{U2C_{50} + u_2}\right)\left(1 + \frac{U3_{\max,1} u_3}{U3C_{50} + u_3}\right) E_{\max,1},$$

$$\hat{E}_{\max,2} = \frac{\left(1 + \frac{U2_{\max,1} u_2}{U2C_{50} + u_2}\right)\left(1 + \frac{U3_{\max,1} u_3}{U3C_{50} + u_3}\right)}{\left(1 + \frac{U1_{\max,2} u_1}{U1C_{50} + u_1}\right)\left(1 + \frac{U2_{\max,3} u_2}{U2C_{50} + u_2}\right)} E_{\max,2},$$

$$\hat{P}_{\max,1} = \left(1 + \frac{U2_{\max,4} u_2}{U2C_{50} + u_2}\right)\left(1 + \frac{U3_{\max,2} u_3}{U3C_{50} + u_3}\right) P_{\max,1},$$

$$\hat{P}_{\max,2} = \left(1 - \frac{U2_{\max,5} u_2}{U2C_{50} + u_2}\right)\left(1 - \frac{U3_{\max,3} u_3}{U3C_{50} + u_3}\right) P_{\max,2}.$$

Theoretical Analysis of Dynamics

- The equilibrium solutions E=0 and P=0 are repelling; Q=0 can be repelling and/or attractive.

- There exists at most one positive equilibrium point (Q_*, P_*, E_*)

  - unstable if $\hat{P}_{max,2} > \hat{P}_{max,1}$

  - locally asymptotically stable if

$\hat{P}_{max,1} > \hat{P}_{max,2}$ and $\delta_P E_{max,2} > \delta_Q E_{max,1}$

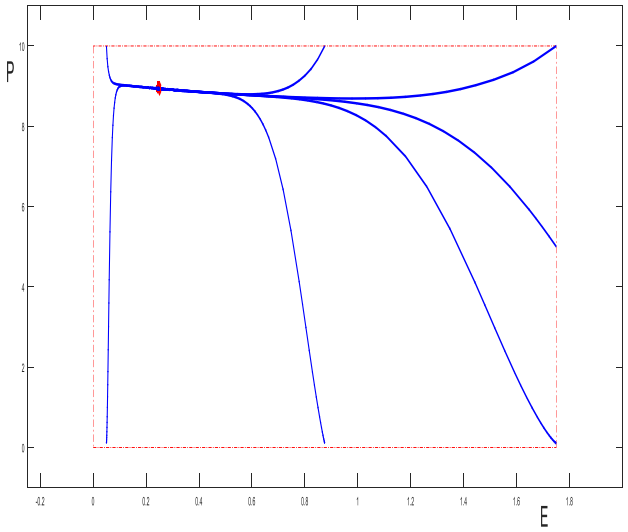
natural condition

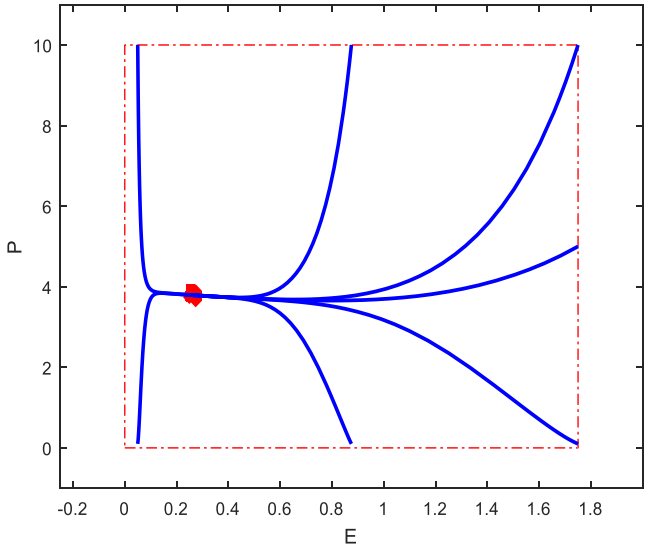
Phaseportrait for Q=0

$u_1=0$

$u_2=0$

$u_3=0$





$u_1=1$

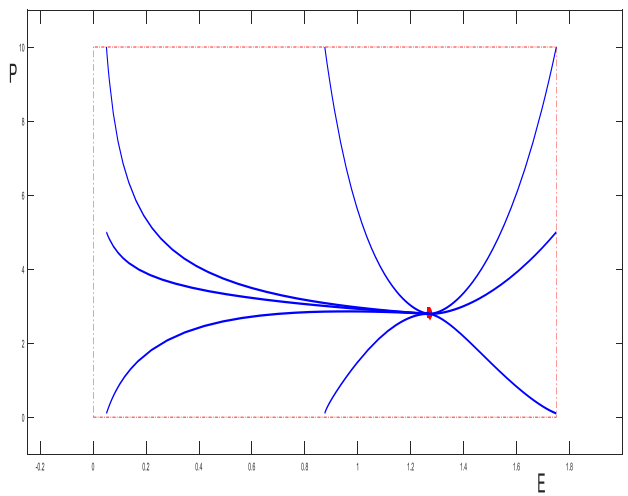
$u_2=0$

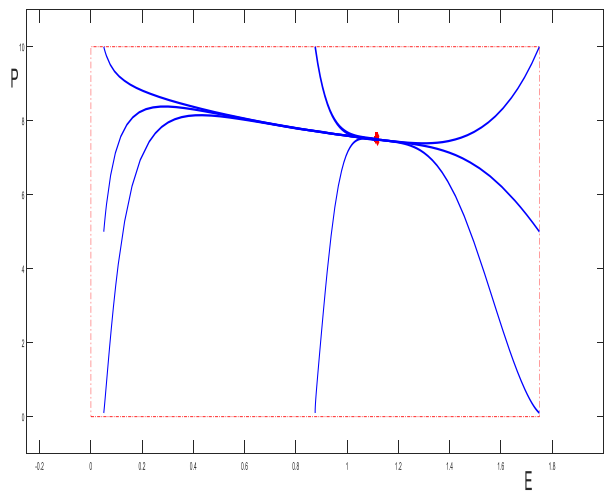
$u_3=0$

$u_1=0$

$u_2=1$

$u_3=0$





$u_1=0$

$u_2=0$

$u_3=1$

Optimal Control Formulation

minimize

$$J(u) = \alpha_1 Q(T) + \alpha_2 P(T) + \int_0^T \beta_1 Q(t) + \beta_2 P(t) dt$$

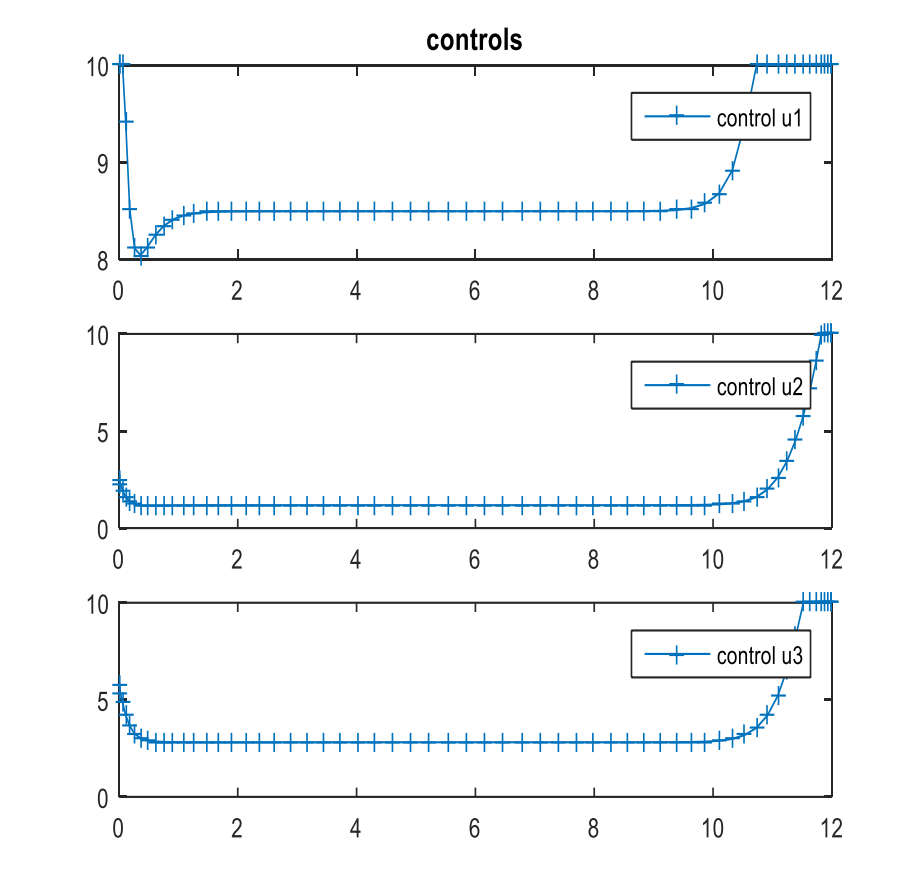
$$+ \int_0^T \gamma_1 u_1(t) + \gamma_2 u_2(t) + \gamma_3 u_3(t) dt$$

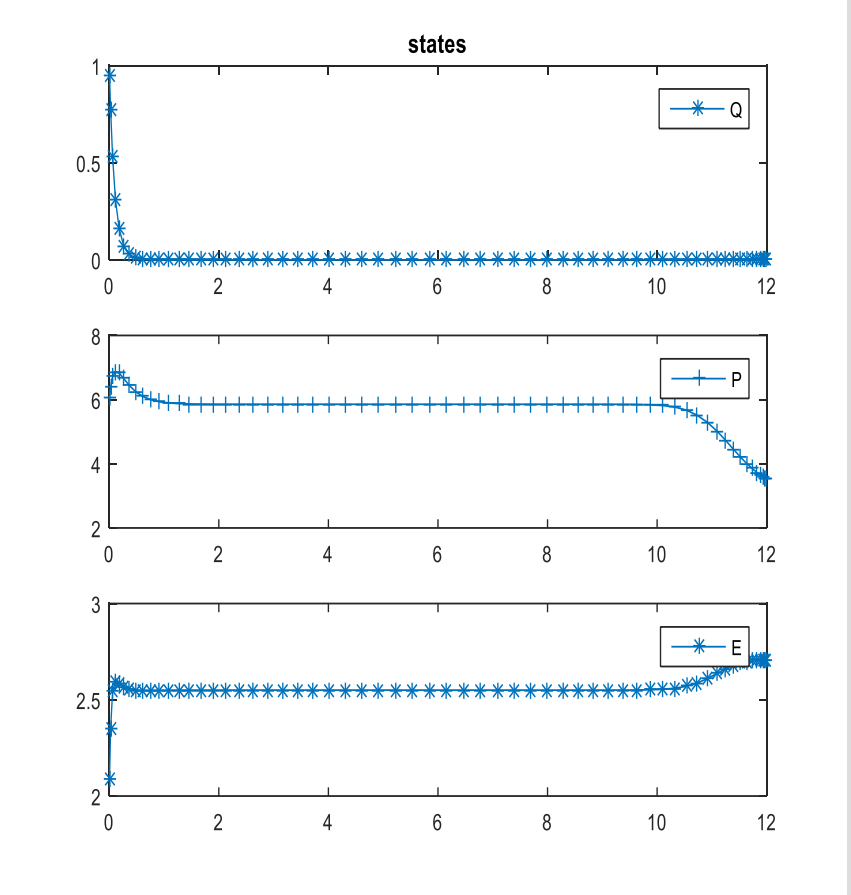
Weighted average of

- cells at end of therapy,
- during therapy,
- and side effects (proportional to AUC)

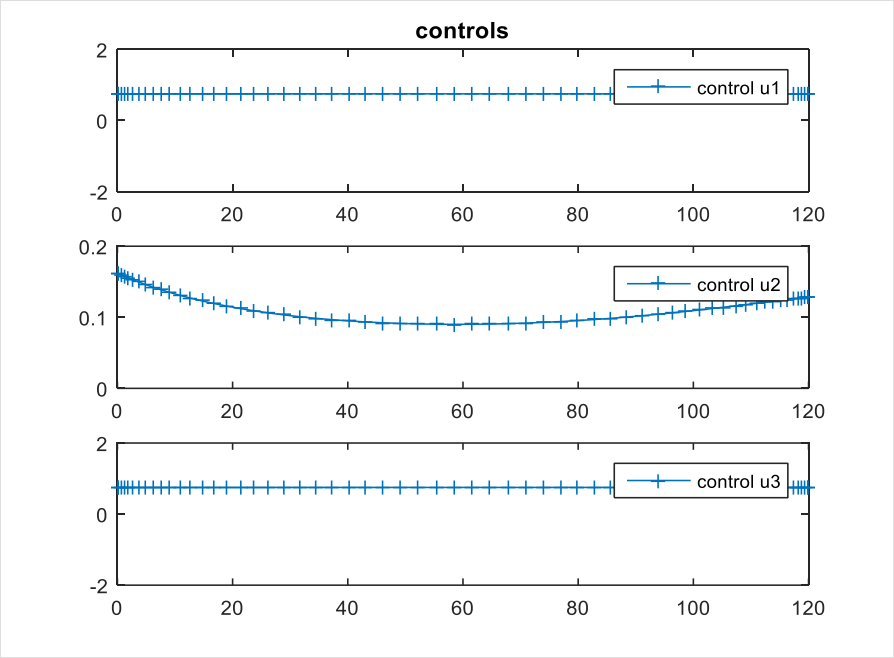
Numerical Calculations of Optimal Controls

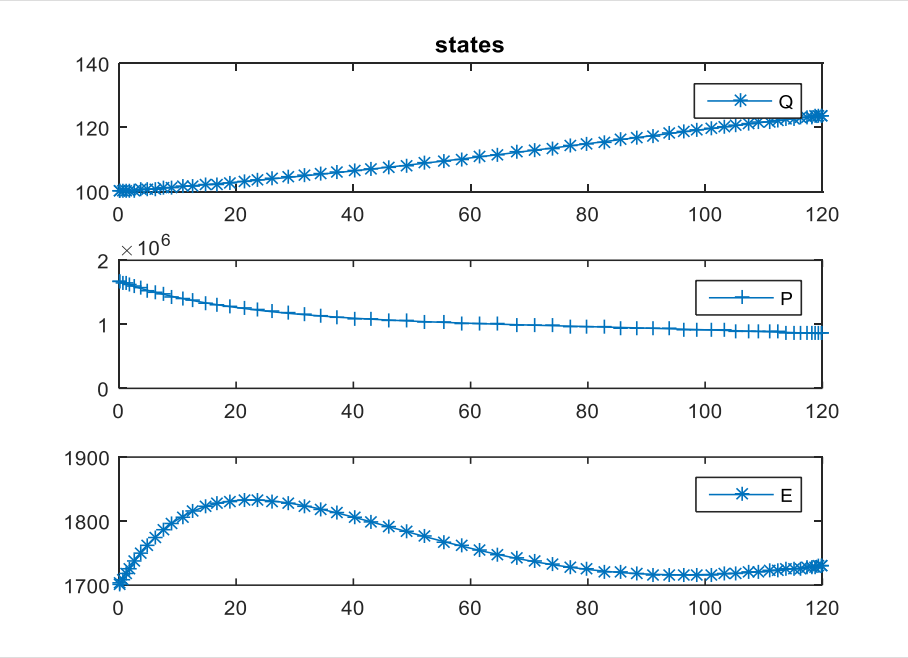
The objective functional was minimized using TOMLAB packages (BASE 8.0, SNOPT 8.0, and PROPT, Tomlab Optimization) with MATLAB (R2015a, Mathworks).



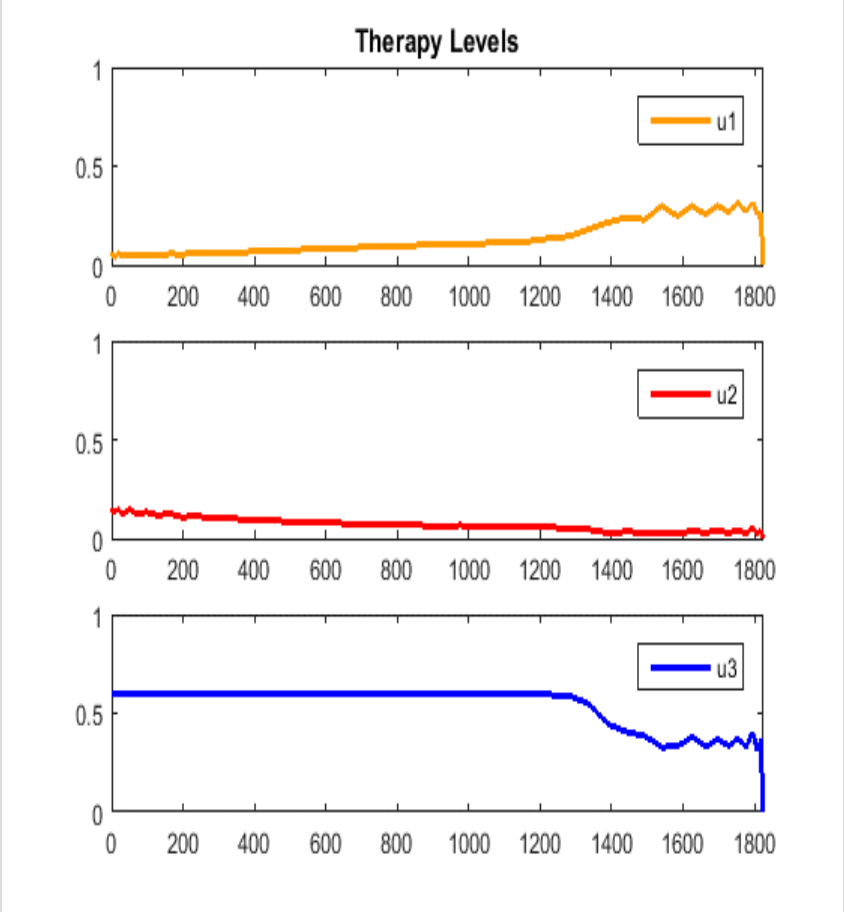


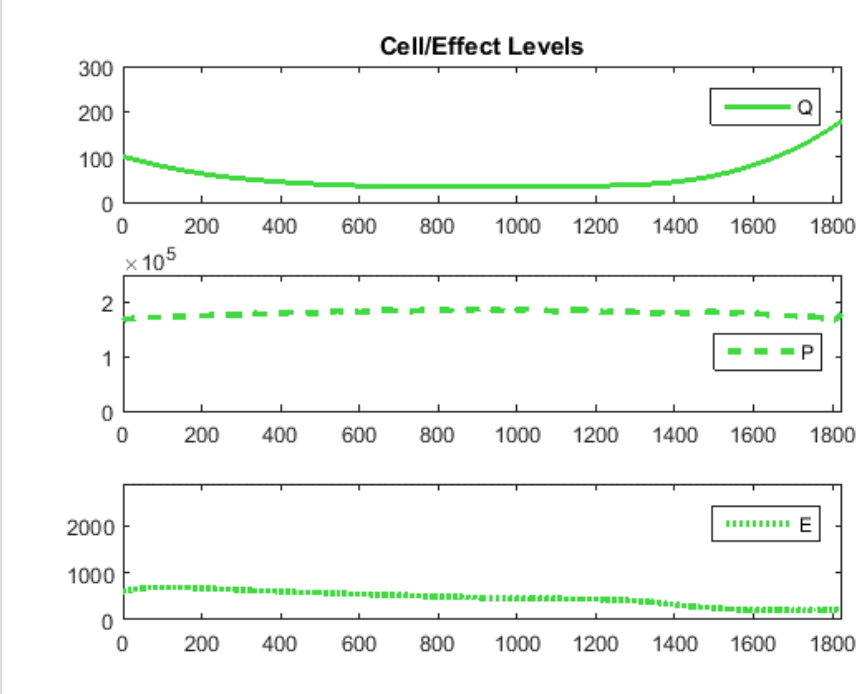
Numerical Calculations of Optimal Controls





Numerical Calculations for Long Term Controls





Back to the Model!

$$(1)\quad \frac{dQ}{dt} = \left(r_Q - \delta_Q \left[1 + \left(1 + \frac{U2_{\max,1} u_2}{U2C_{50} + u_2} \right) \left(1 + \frac{U3_{\max,1} u_3}{U3C_{50} + u_3} \right) \frac{E_{\max,1} E}{EC_{50} + E} \right] \right) \cdot Q$$

$$(2)\quad \frac{dP}{dt} = \left(1 - \frac{U1_{\max,1} u_1}{U1C_{50} + u_1} \right) \left(1 - \frac{U2_{\max,2} u_2}{U2C_{50} + u_2} \right) \cdot \left[k_P Q + r_P P \ln\left(\frac{P_{ss}}{P} \right) \right]$$

$$- \delta_P \left(1 + \frac{U1_{\max,2} u_1}{U1C_{50} + u_1} \right) \left(1 + \frac{U2_{\max,3} u_2}{U2C_{50} + u_2} \right) \cdot P$$

$$- \delta_P \left(1 + \frac{U2_{\max,1} u_2}{U2C_{50} + u_2} \right) \left(1 + \frac{U3_{\max,1} u_3}{U3C_{50} + u_3} \right) \frac{E_{\max,2} E}{EC_{50} + E} \cdot P$$

$$(3)\quad \frac{dE}{dt} = s_E \left[1 + \left(1 + \frac{U2_{\max,4} u_2}{U2C_{50} + u_2} \right) \left(1 + \frac{U3_{\max,2} u_3}{U3C_{50} + u_3} \right) \frac{P_{\max,1} P}{PC_{50} + P} \right] \cdot E \ln\left(\frac{E_{ss}}{E} \right)$$

$$- \delta_E \left[1 + \left(1 - \frac{U2_{\max,5} u_2}{U2C_{50} + u_2} \right) \left(1 - \frac{U3_{\max,3} u_3}{U3C_{50} + u_3} \right) \frac{P_{\max,2} P}{PC_{50} + P} \right] \cdot E$$

Back to theory! Extended Model

STATES

Q = quiescent leukemic cells
P = proliferating leukemic cells
E = immune effect

The nonlinear Michaelis-Menten terms on the controls in the original dynamics are represented as the steady-state of a simple dynamical system

y_1 = normalized effect of ABL inhibitors (e.g., imatinib)
y_2 = normalized effect of dasatinib
y_3 = normalized effect of immuno agent (e.g., nivomulab)

in steady-state $$y_i = \frac{u_i}{UiC_{50} + u_i}$$

CONTROLS

u_1 = concentration of ABL inhibitors (e.g., imatinib)
u_2 = concentration of dasatinib
u_3 = concentration of immuno agent (e.g., nivomulab)

Extended Model

$$\frac{dQ}{dt} = \left(r_Q - \delta_Q \left[1 + (1 + U2_{\max,1} y_2)\left(1 + U3_{\max,1} y_3\right) \frac{E_{\max,1} E}{EC_{50} + E} \right] \right) Q,$$

$$\frac{dP}{dt} = \left(1 - U1_{\max,1} y_1\right)\left(1 - U2_{\max,1} y_2\right)\left(k_P Q + r_P P \ln\left(\frac{P_{ss}}{P} \right) \right)$$

$$- \delta_P \left(1 + U1_{\max,1} y_1\right)(1 + U2_{\max,3} y_2) P$$

$$- \delta_P (1 + U2_{\max,1} y_2)\left(1 + U3_{\max,1} y_3\right) \frac{E_{\max,2} E}{EC_{50} + E} P,$$

$$\frac{dE}{dt} = s_E \left[1 + \left(1 + U2_{\max,4} y_2\right)\left(1 + U3_{\max,2} y_3\right) \frac{P_{\max,1} P}{PC_{50} + P} \right] E \ln\left(\frac{E_{ss}}{E} \right)$$

$$- \delta_E \left[1 + \left(1 - U2_{\max,5} y_2\right)\left(1 - U3_{\max,3} y_3\right) \frac{P_{\max,2} P}{PC_{50} + P} \right] E,$$

$$\frac{dy_1}{dt} = -U1C_{50} y_1 + (1 - y_1) u_1,$$

$$\frac{dy_2}{dt} = -U2C_{50} y_2 + (1 - y_2) u_2,$$

$$\frac{dy_3}{dt} = -U3C_{50} y_3 + (1 - y_3) u_3,$$

$$y_i = \frac{u_i}{UiC_{50} + u_i}$$

Control Affine System

STATE $z=(Q, P, E; y_1, y_2 , y_3)^T$

$x=(Q, P, E)^T$ $y=(y_1, y_2, y_3)^T$

CONTROLS $u=(u_1, u_2, u_3)^T$

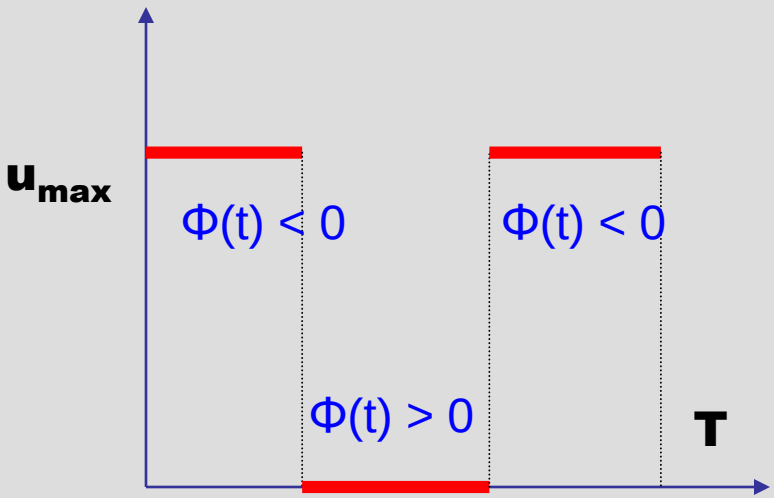
$$\frac{dz}{dt} = F(z) + u_1 G_1(z) + u_2 G_2(z) + u_3 G_3(z)$$

where F is the drift vector fields and the G_i's are the control vector fields, i=1,2,3.

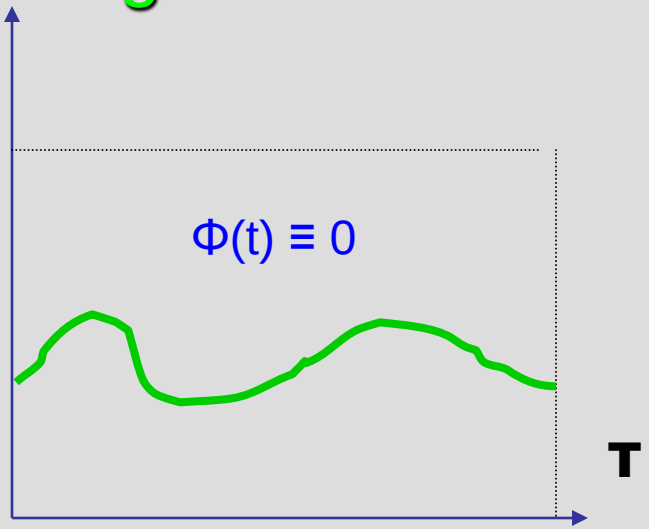
Candidates for Optimal Protocols

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

Formula for Singular Control

Legendre-Clebsch condition is satisfied:

$$\left\langle (\lambda,\mu),[G_1,[F,G_1]](z)\right\rangle = -c_1\left\langle (\lambda,\mu),[F,G_1](z)\right\rangle + \left\langle (\lambda,\mu),\begin{pmatrix}0\\0\\0\\2a_1b_1c_1\\0\\0\end{pmatrix}\right\rangle = 0 + 2a_1b_1c_1\mu_1 < 0$$

all three optimal controls can be singular and can be computed from

$$u_i^*(t) = -\frac{\left\langle (\lambda(t),\mu(t)),\left[F+\sum_{i\neq j}u_jG_j,[F,G_i](z_*(t))\right]\right\rangle - \left\langle (q,0),[F,G_i](z_*(t))\right\rangle}{\left\langle (\lambda(t),\mu(t)),\left[G_i,[F,G_i]\right](z_*(t))\right\rangle}$$

Conclusion and Future Work

✓ **Advantage:** control-affine structure allows theoretical analysis

⟹ a priori information about structure of optimal controls

singular controls which represent therapies at less than the maximum level considered, possibly time-varying, achieve better outcomes indicating that "**more is not necessarily better**"

✓ **Explicit analytical formulas** for these controls allows us to integrate them into numerical computations

Future work

- calculate mathematically optimal dosing protocols
- sensitivity analysis and additional calibration of significant parameters using preclinical and clinical data
- Towards reality: optimize among regimens: daily 5 times a week and two rest periods

Part II:

Model for Metronomic Chemotherapy

"**more is not necessarily better**"

Co-author and Support

Heinz Schättler

Washington University
St. Louis, MO USA

NSF grant

DMS 1311729/1311733

Biomedical Collaborators

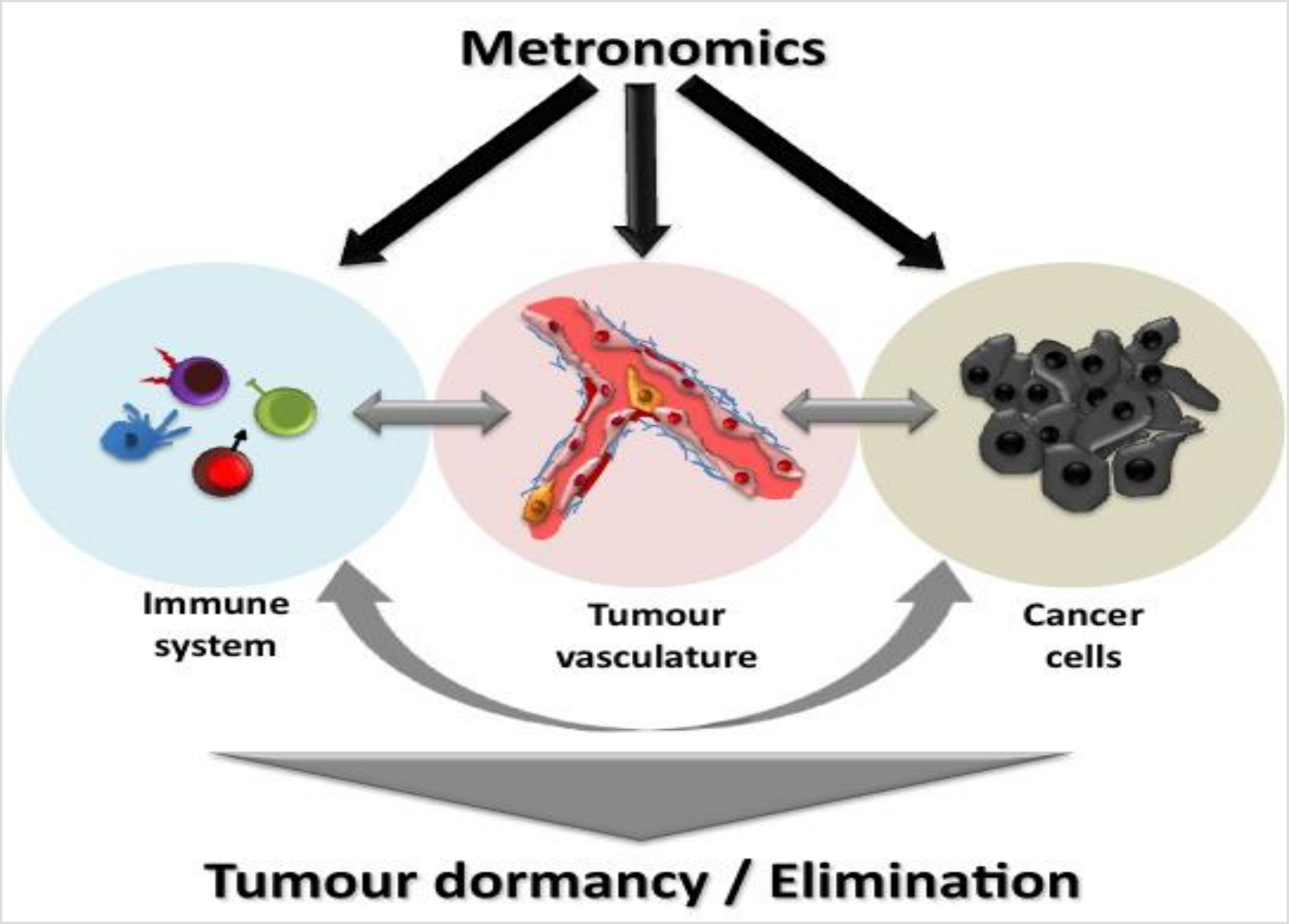
Metronomics Global Health Initiative

Nicolas André

Childrens Hospital La Timone, Marseille France

Eddy Pasquier

UMR S 911 CRO2 Aix Marseille Université, Marseille France



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

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

Metronomic Chemotherapy: Modeling Challenges

A Combined Model for Low Dose Chemotherapy

Ledzewicz, Schättler, Amini,

JMB 2015, MBE 2015

p(t) – primary tumor volume

q(t) – carrying capacity of the tumor vasculature

r(t) – immunocompetent cell density

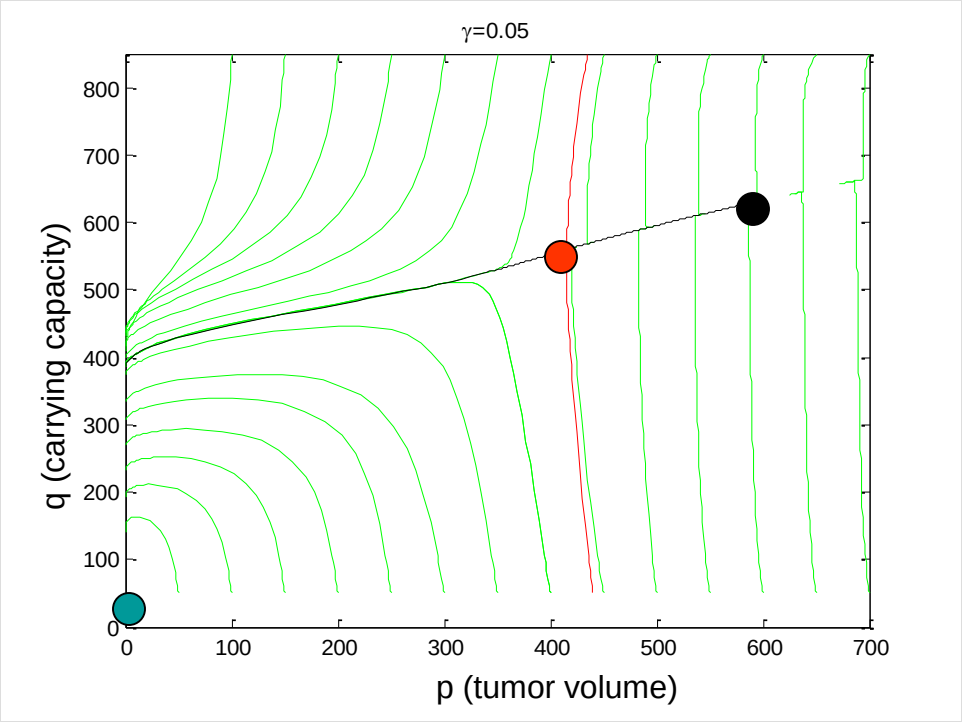
u(t) – concentration of a chemotherapeutic agent

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

effectiveness (PD)

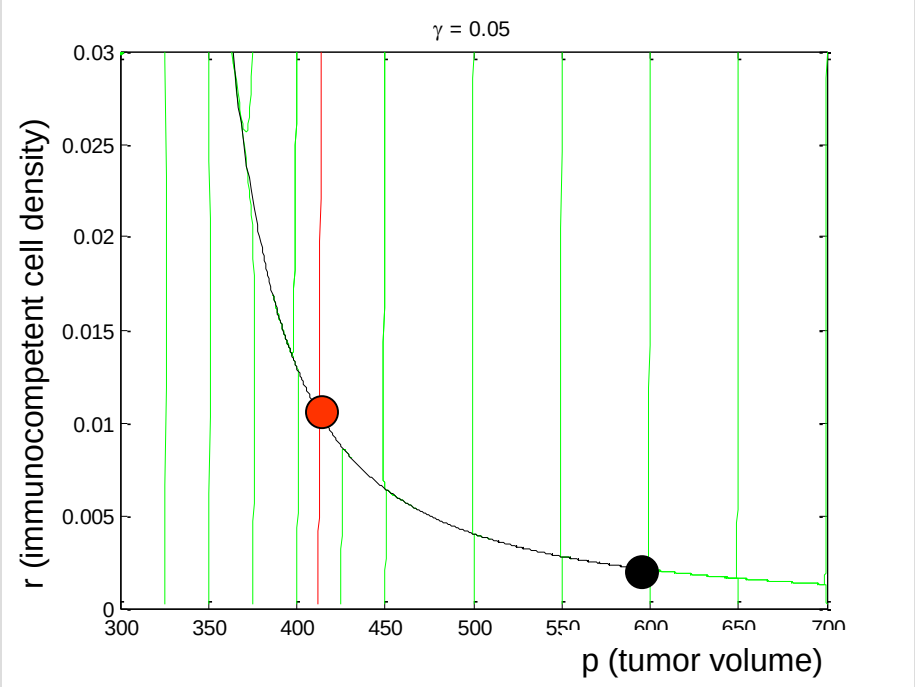
$$
\begin{aligned}
\varphi_1 &= 0.005, \\
\varphi_2 &= 0.06, \\
\varphi_3 &= 0.02,
\end{aligned}
$$

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

Current and Future Work: Optimal Control Problem

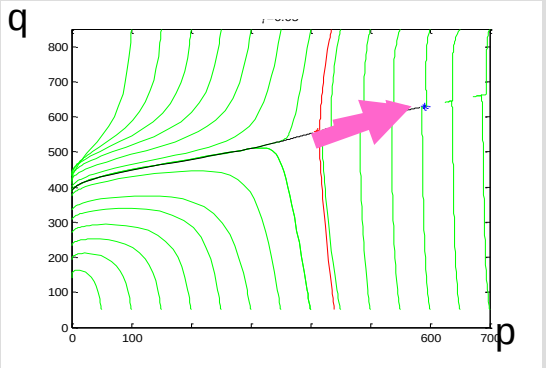
"move an initial condition that lies in the malignant region through chemotherapy into the benign region"

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.

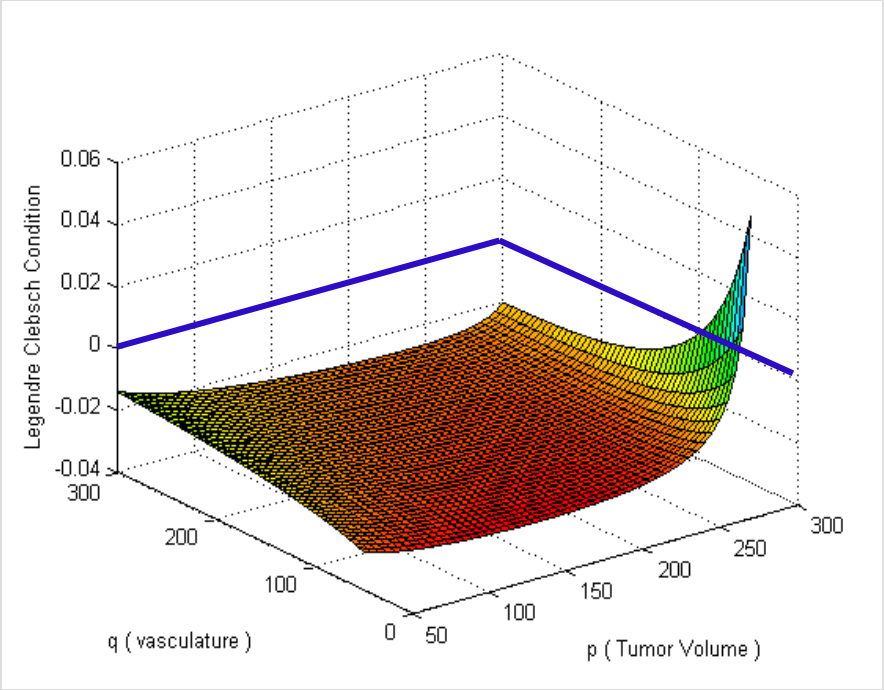


Legendre-Clebsch Condition and Singular Controls

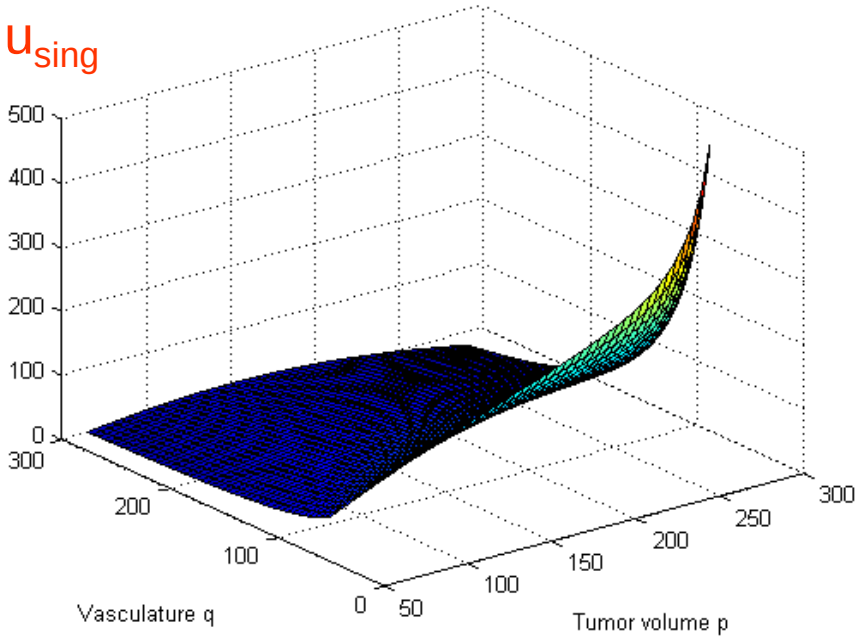
slices for constant value of *r*

Legendre-Clebsch condition

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



u_{sing}



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

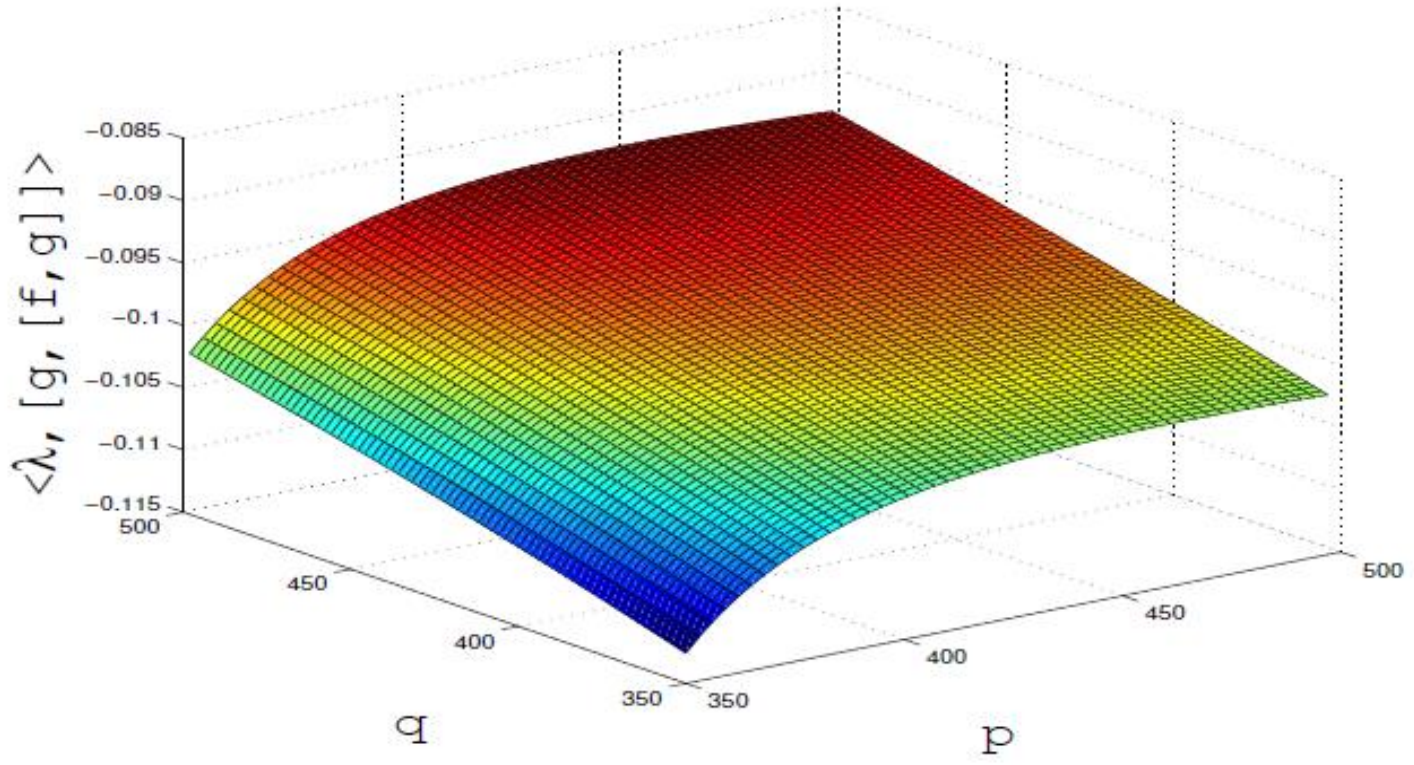


FIGURE : Slice of the graph of the feedback functions $\langle \lambda_{\text{sing}}(z), [g,[f,g]](z) \rangle$ for $(p,q) \in [350,500] \times [350,500]$ and $r = 0.5$.

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

High Tumor Volumes

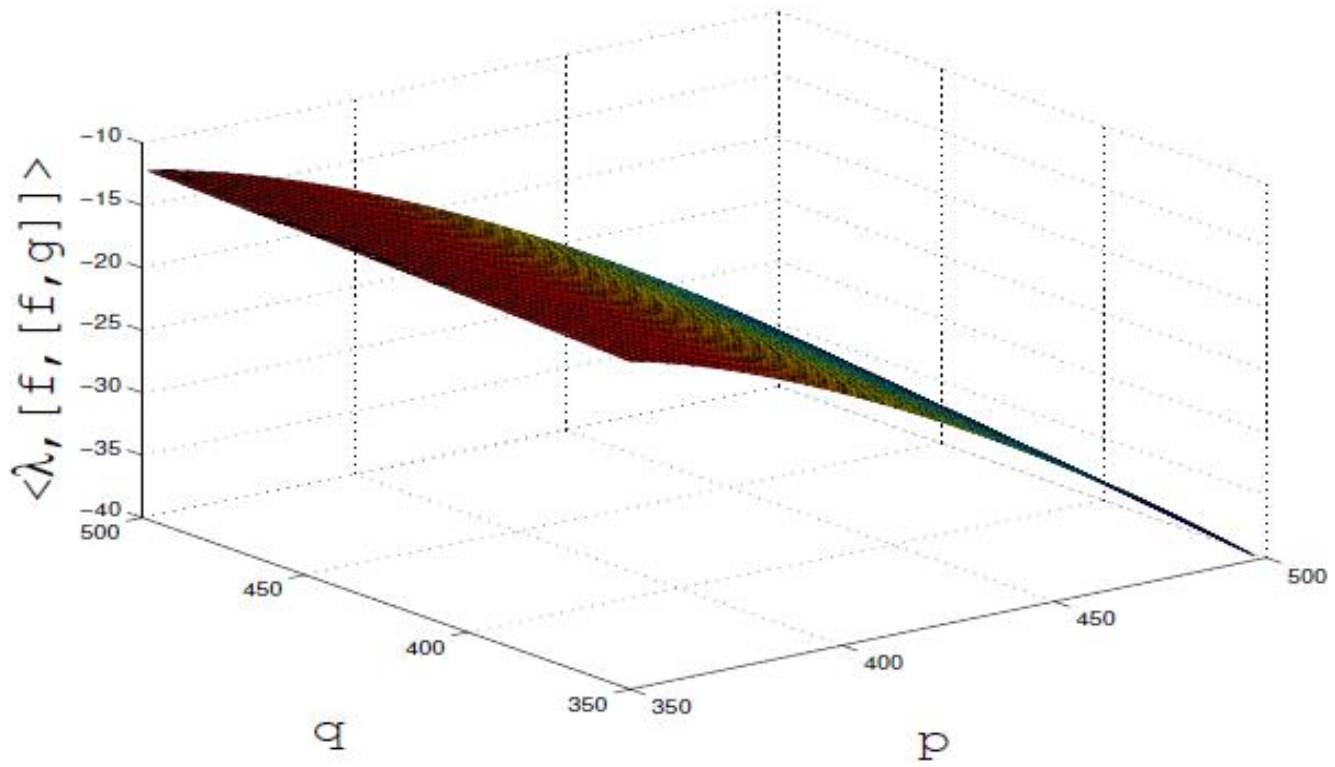


FIGURE : Slice of the graphs of the feedback functions $\langle \lambda_{\text{sing}}(z), [f,[f,g]](z) \rangle$ for $(p,q) \in [350,500] \times [350,500]$).

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

High Tumor Volumes

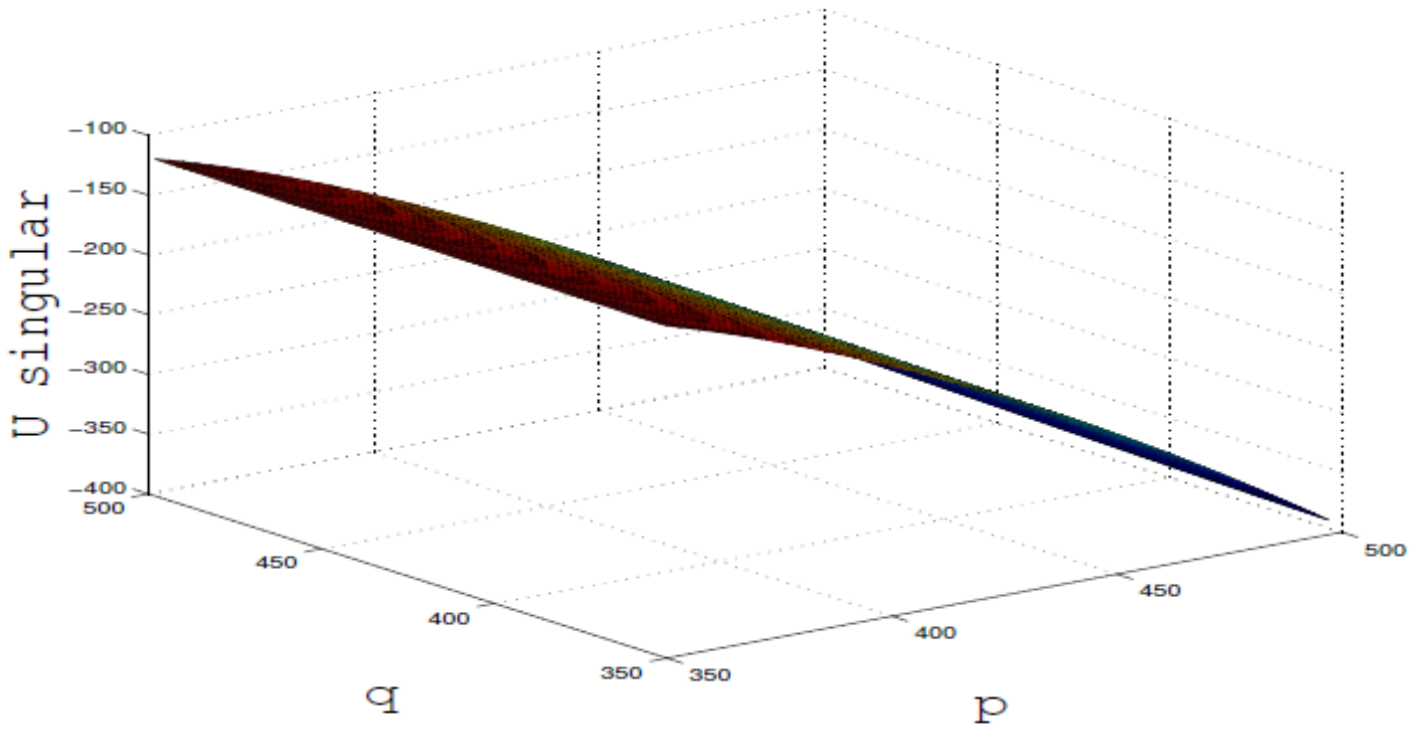


FIGURE : For $(p, q) \in [350, 500] \times [350, 500]$ and $r = 0.5$.

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

Chemo-Switch Protocols

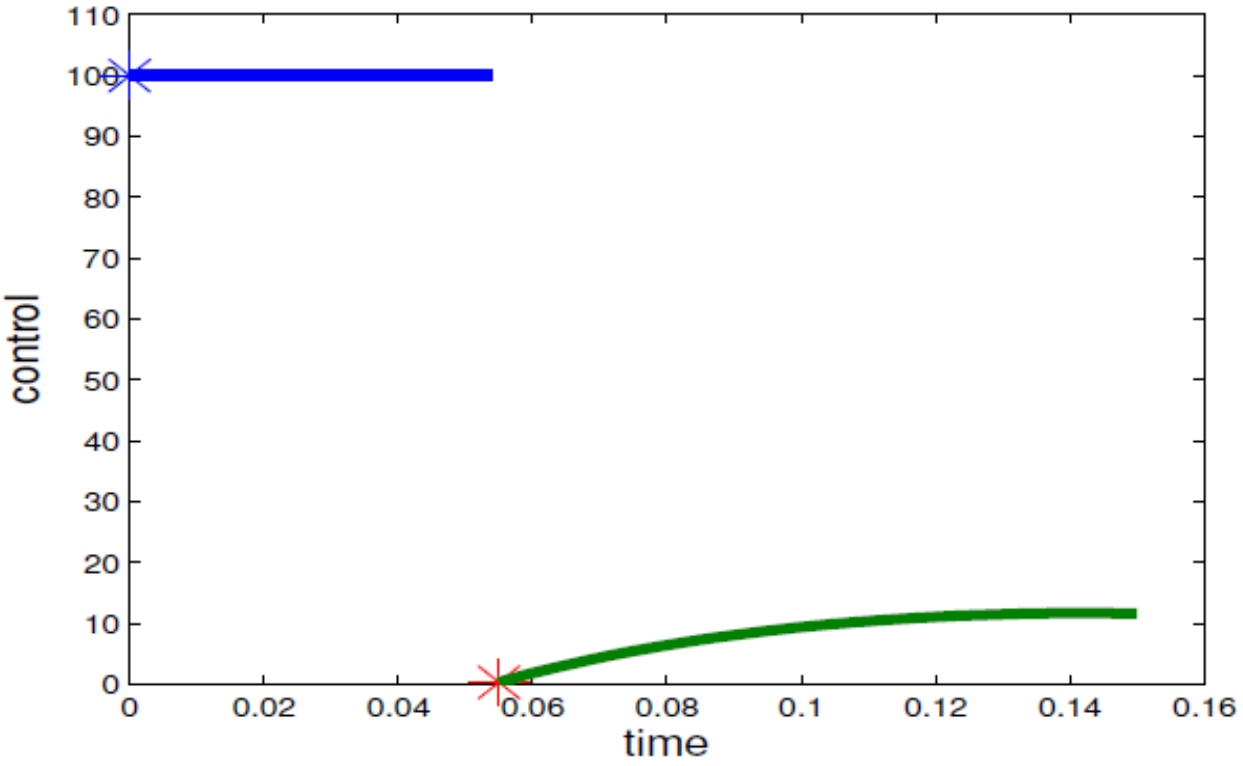


FIGURE : Time evolution of the control is full-dose at the first stage starting from initial value $(p_0, q_0, r_0) = (600, 750, 0.1)$ and then turns into singular contol.

Food for thoughts

- 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 ?
  - …

Instead of conclusion: **More is not necessary better**: the role of **BOD (biologically optimal dose)**

Merci!