# Robust Control of Biological Models

*Application to the combined therapy of cancer*

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University of Grenoble, France


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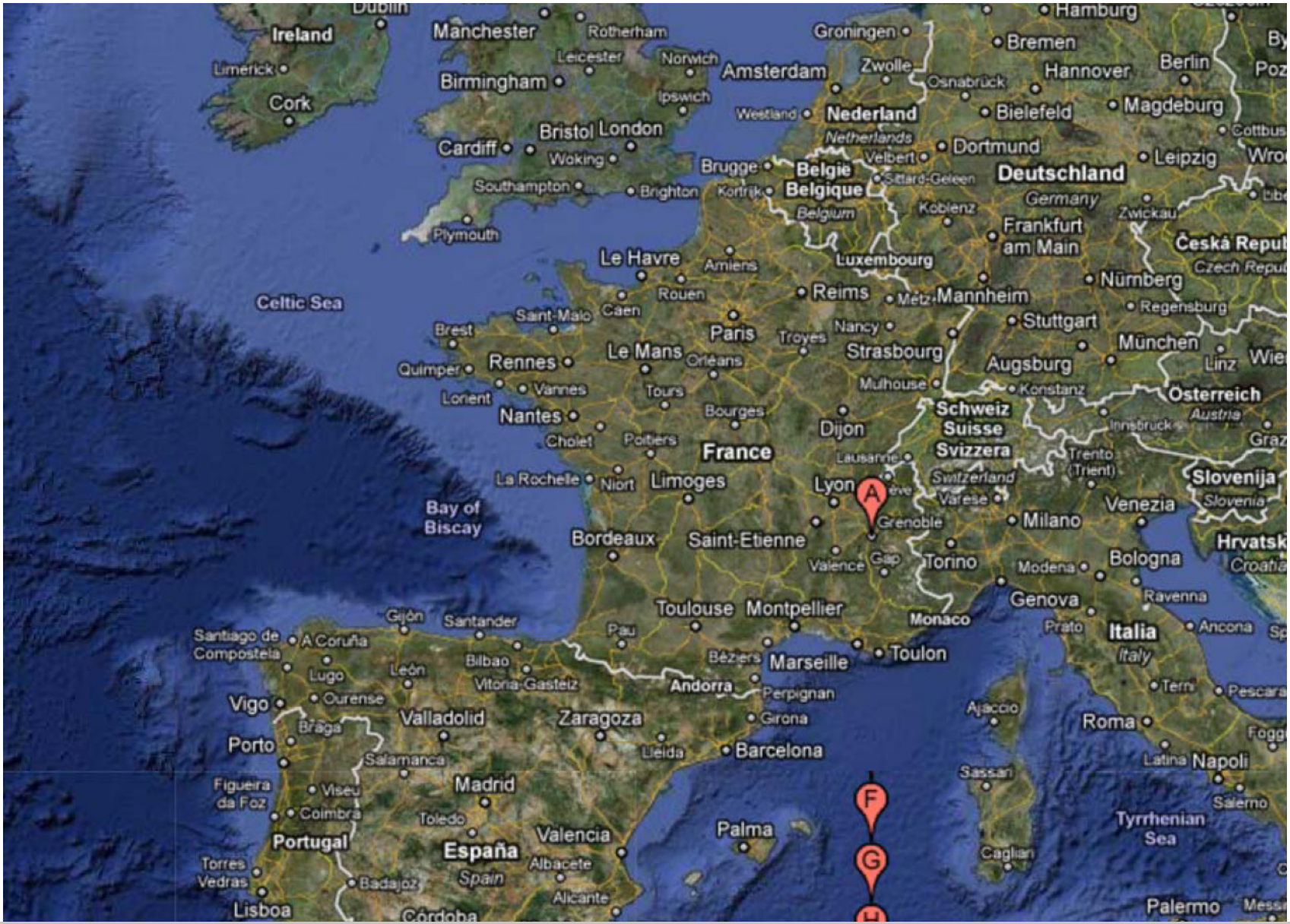

# Did you say, Grenoble ?

But also,

- Second French Scientific Pole (after Paris)
- First in Information Science
- Administered by Joseph Fourier
- 1 Nobel Price (Louis Néel)
- 1 Turing Price (Joseph Sifakis)
- Worldwide center in NanoTechnologies
- Winter Olympic Games (1968)
- Starting point for the French Revolution
- European Hub for Green Energy (KIC)
- Elected preferred French city to study in by students (2010)
- 70,000 students

# Outline

Biological Models & The Uncertainty Issue

Control-Related Paradigms in Systems Biology

New Control Paradigms in Cancer Therapy

The Hamilton-Jacobi-Isaacs PDE

Robust Combined Therapy Under Drug Limitation

Conclusion & Future Work

# Biological Models & The Uncertainty issue

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  - understand,
  - predict or to
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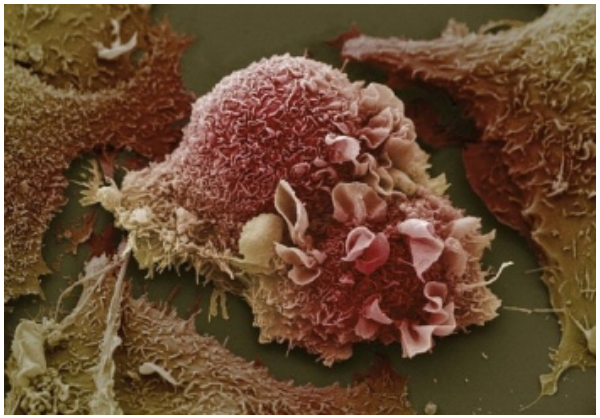
  on a given biological system.



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**Journal of Theoretical Biology**, *(61), 2005.*

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$$\mathscr{P}_1 : \min_{v_M(\cdot), v_L(\cdot), v_I(\cdot)} T(t_f)$$
$$\text{under } C(t) \geqslant C_{min}, \quad \forall t \in [0, t_f].$$

*S. Chareyron & M. Alamir*

**Journal of Theoretical Biology**, *(258), 2009.*

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$$\mathscr{P}_2 : \max_{v_M(\cdot),v_L(\cdot),v_I(\cdot)} \min_{t\in[0,t_f]} C(t)$$
$$\text{under } T(t_f) \leqslant \gamma T(0) \quad \text{with } \gamma \in ]0,1[.$$

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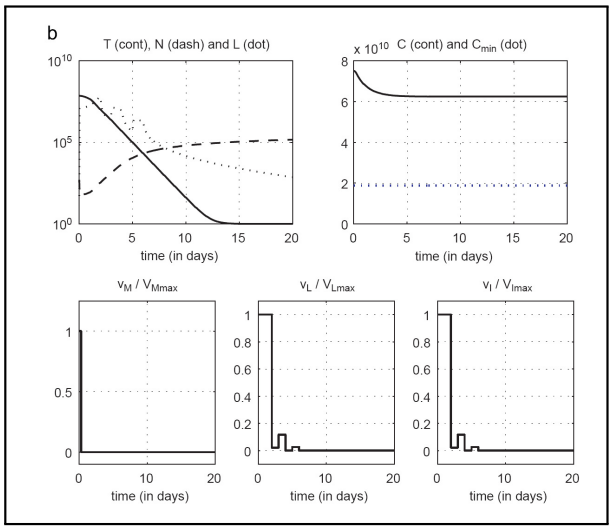


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- These model discrepancies can strongly question the nominal assertions.
- This robustness issue is rarely addressed in the systems biology related literature

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# Control-Related Paradigms in Systems Biology

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*Hahnfeldt et al.* Tumor development under angiogenic signaling: ...

**Cancer Research**, *(59), 1999.*

- $p$ tumor cells population level
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- $w \in \mathbb{R}^6$ model parameters

# Control-Related Paradigms in Systems Biology

Consider a biological model:

$$\dot{x} = f(x, u, w)$$

- $x \in \mathbb{R}^n$ (state)
- $u \in \mathbb{U} \subset \mathbb{R}^{n_u}$ (Control input)
- $w \in \mathbb{W} \subset \mathbb{R}^{n_w}$ (Disturbance)

typically

$$\mathbb{W} := \left\{ w \mid w_i = w^{nom}(1 + \eta_i) \right\}$$

Example of control formulation

$$\min_{u(\cdot)} \left[ p(T) \right] \quad \text{under } y_i(T) \leq y_i^{max}$$

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## Optimal Control Paradigm

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$\min_{u(\cdot)} \left[p(T)\right]$ under $y_i(T) \leq y_i^{max}$

- Existence of optimal solutions
- Pontryagin Maximum Principle
- Investigate the structure of optimal control profiles $u^{opt}(\cdot)$

△ *Ledzewics*, **IEEE CDC**, *2008.*

△ *Swan*, **IMA J. of Math. Appl. in Medicine and Biology**, *1988.*

△ *DePillis and Radunskaya*, **J. Theoretical Medicine**, *(3), 2005.*

△ *Alamir and Chareyron*, **Optimal Control Applications and Methods**, *2007*

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- hard to determine
- High sensitivity may arise

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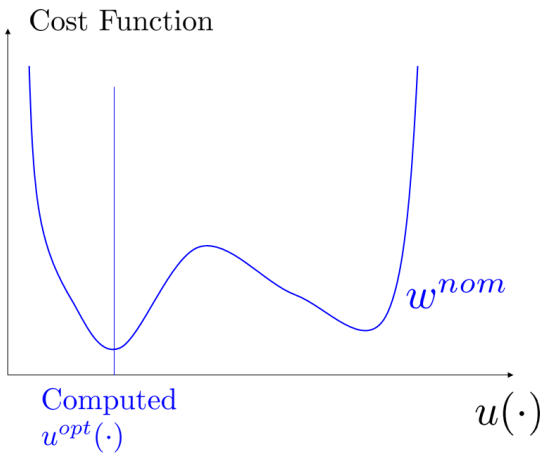


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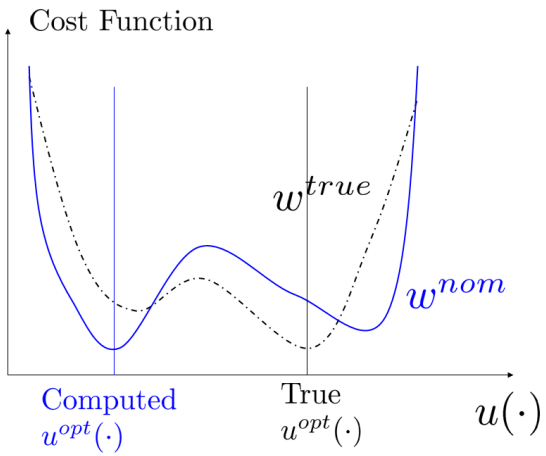


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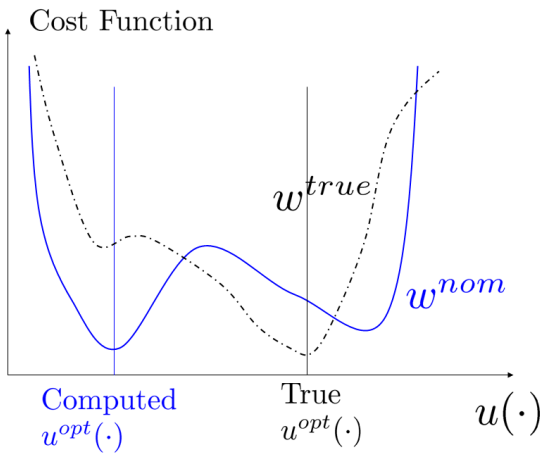


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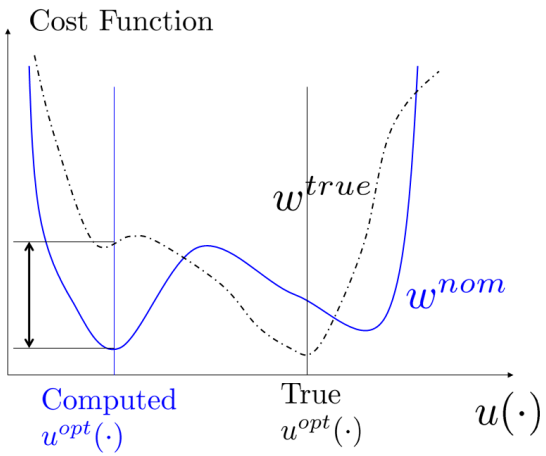


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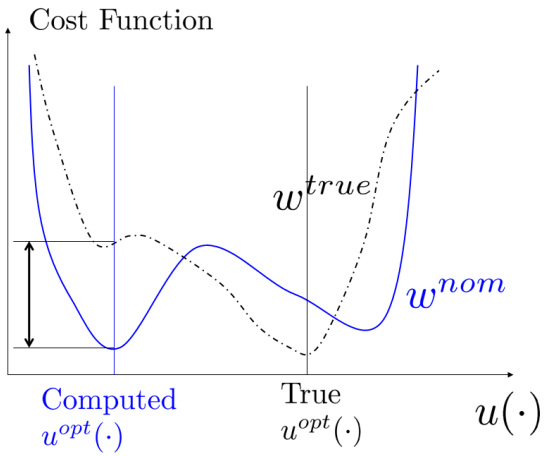


## Sensitivity Analysis Paradigm

Evaluate the sensitivity indicator of the nominally optimal solution:

$$\frac{\partial p^{opt}(T)}{\partial w}(x_0, w^{nom})$$

- For a specific initial state $x_0$
- Involved computation for a non constant $w(\cdot)$
- Local results

*K. L. Kiran & S. Lakshminarayanan, Global Sensitivity Analysis and Model-Based Reactive Scheduling of Targeted Cancer Immunotherapy.* **BioSystems**, *(101), 2010.*

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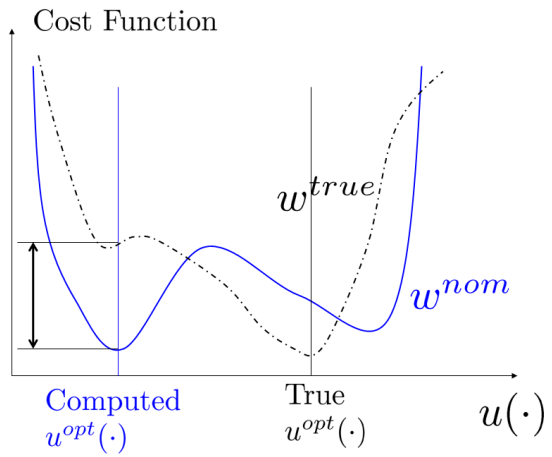


## Feedback Control Paradigm

1. At decision instant $t_k$, solve the optimal control problem to obtain $u^{opt}(\cdot, x(t_k))$ defined on $[t_k, T]$.
2. Apply $u^{opt}(t, x(t_k))$ for $t \in [t_k, t_{k+1}]$
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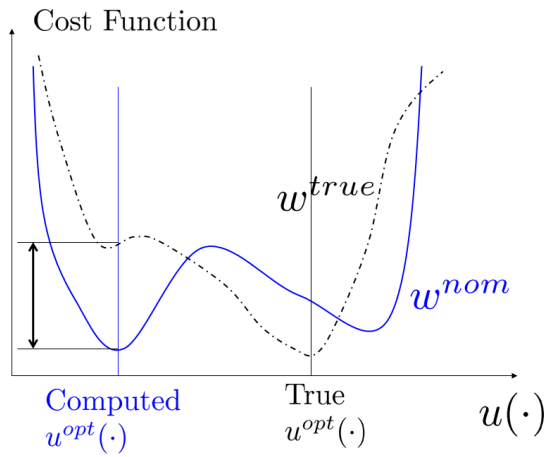


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This partially corrects the disturbance induced discrepancy over the duration of the therapy

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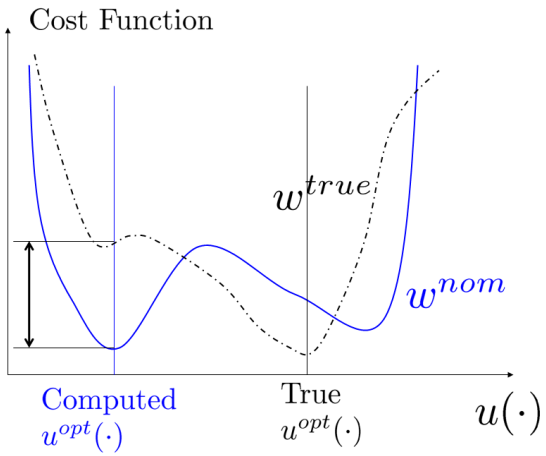
## Optimal Control Paradigm

$\dot{x} = f(x, u, w^{nom})$ under $u \in \mathbb{U}$

$\min_{u(\cdot)} \left[p(T)\right]$ under $y_i(T) \leq y_i^{max}$

**Unfortunately**,

- $w^{nom}$ is not constant
- hard to determine
- High sensitivity may arise




## Feedback Control Paradigm

1. At decision instant $t_k$, solve the optimal control problem to obtain $u^{opt}(\cdot, x(t_k))$ defined on $[t_k, T]$.
2. Apply $u^{opt}(t, x(t_k))$ for $t \in [t_k, t_{k+1}]$
3. measure the state at $t_{k+1}$,
4. $k \leftarrow k + 1$. Goto step 1

This is Model Predictive Control

*Florian et al.* **J. Computers in Biology and Medicine**, *(38), 2008.*

*S. Chareyron & M. Alamir*
**Journal of Theoretical Biology**, *(258), 2009.*

# Control-Related Paradigms in Systems Biology

## On-line Parameter Estimation

**Irrelevant** because of the lack of excitation needed to identify the high number of parameters.

## Feedback Control Paradigm

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# New Control Paradigms in Cancer Therapy

## Guaranteed Contraction Map

### Given

- A subset of initial state $\mathbb{X}$
- A subset of admissible parameter set $\mathbb{W}$
- A therapy duration $T$
- Allowable drug quantities $y_i^{max}$

### Compute

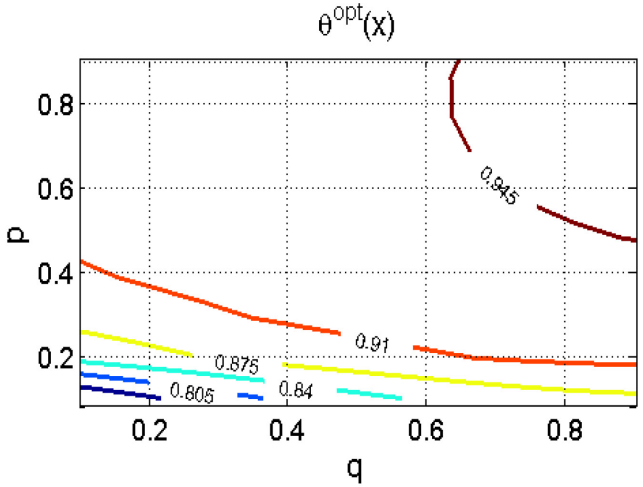
the Guaranteed Contraction Map (GCM) and the associated feedback control

$$u = K(t, x) \quad ; \quad t \in [0, T]$$

$$\dot{p} = -w_1 p \ln(\frac{p}{q}) - w_2 p v_2$$
$$\dot{q} = w_3 p - (w_4 + w_5 p^{\frac{2}{3}})q - w_6 v_1 q$$
$$\dot{y}_1 = v_1$$
$$\dot{y}_2 = v_2$$

*Hahnfeldt et al.* Tumor development under angiogenic signaling: ...

**Cancer Research**, *(59), 1999.*



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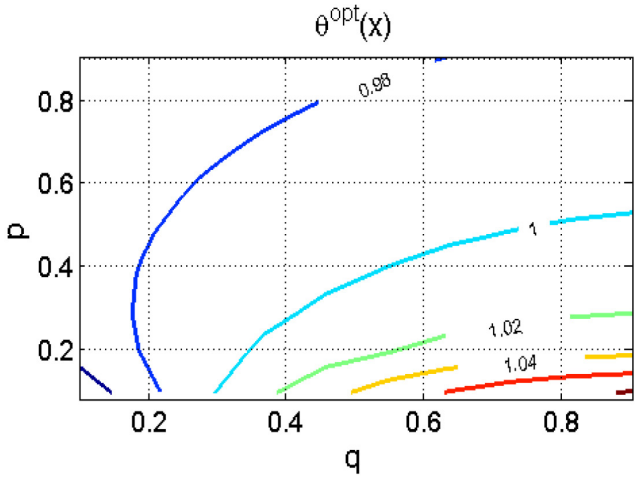

# New Control Paradigms in Cancer Therapy

## Necessary Drug Quantity

### Given

- An initial state $x_0 \in \mathbb{X}$
- A subset of admissible parameter set $\mathbb{W}$
- A targeted contraction ratio

$$\gamma := \frac{p(T)}{p(0)} < 1$$

### Compute

- The Feasibility
- The therapy duration $T$
- The quantity of drugs $y_i^{max}$ needed
- The feedback $K(t, x)$

$$\begin{aligned}
\dot{p} &= -w_1 p \ln(\frac{p}{q}) - w_2 p v_2 \\
\dot{q} &= w_3 p - (w_4 + w_5 p^{\frac{2}{3}}) q - w_6 v_1 q \\
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- $p$ tumor cells population level
- $q$ vasculature level
- $u_1$ Anti-angiogenic drug
- $v_1$ Chemotherapy drug
- $v_2$, $y_2$ Already injected drug
- $w \in \mathbb{R}^6$ model parameters

# Menu

- Robust Control Design:

  The **Hamilton-Jacobi-Isaacs** (HJI) PDE's

- Computational Framework
- Application to the combined Therapy
  (Chemotherapy/Anti-angiogenic)
- Preliminary Results
- Future Work (Research Proposal)

# The Hamilton-Jacobi-Isaacs PDE's

## System Model

$$\dot{x} = f(x, u, w)$$

## Cost Function

$$J := \Psi(x(T)) + \int_t^T L(x(\tau), u(\tau), w(\tau))d\tau$$

$$\frac{\partial V}{\partial t}(t, x) + \hat{H}\left(x, \frac{\partial V}{\partial x}(t, x)\right) = 0 \quad ; \quad V(T, x) = \Psi(x)$$

- $H(x, \lambda, u, w) = L(x, u, w) + \lambda^T f(x, u, w)$
- $\hat{H}(x, \lambda) := \min_{u \in \mathbb{U}(x)} \left[ \max_{w \in \mathbb{W}(x)} H(x, \lambda, u, w) \right]$

# The Hamilton-Jacobi-Isaacs PDE's

**Theorem 1** (Isaacs verification theorem). If $V(t,x)$ *is a function of class* $C^1$ *in* $t$ *and* $x$ *that satisfies the following Hamilton Jacobi Equation with boundary condition*:

$$V_t + \hat{H}(x, V_x, t) = 0, \quad V(T,x) = \Psi(x), \tag{7}$$

*where* $\hat{H}$ *is given by* (6), then *the control strategy*

$$u(\tau, x(\tau)) = \hat{u}(x(\tau), V_x(\tau, x(\tau)), \tau) \quad \tau \in [t, T] \tag{8}$$

*is an optimal solution for problem* (3). *Furthermore, the corresponding optimal value is exactly* $V(t, x(t))$.

*Isaacs, R.*
Differential Games
**RAND Corporation Research Memorandum**, *(1954)*

*Başar T. and Olsder G. J.*
Dynamic Non Cooperative Game Theory. **NY, Academic Press**, *(1982)*

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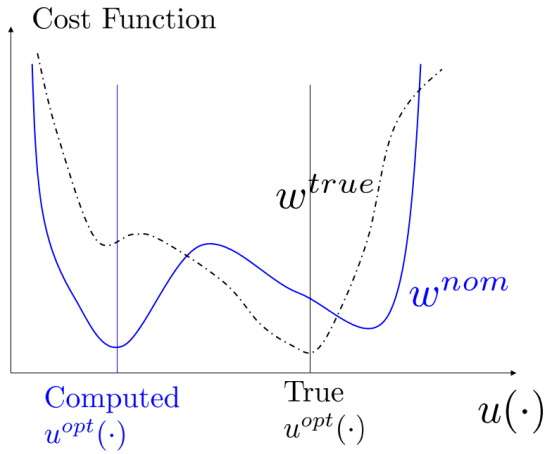


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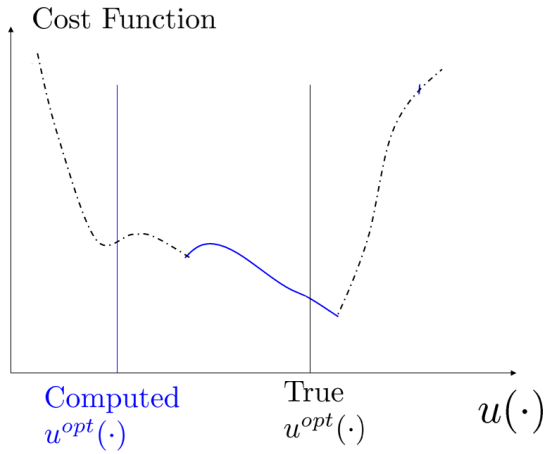


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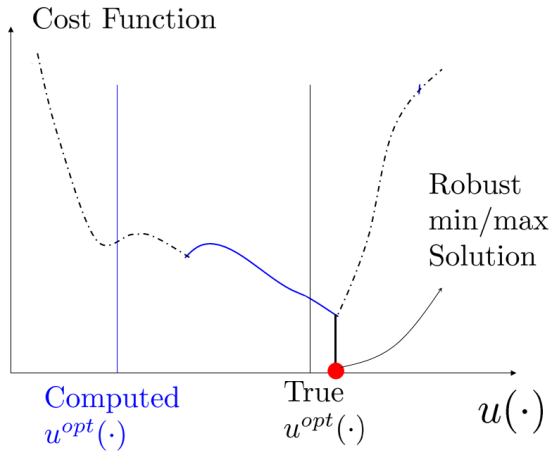


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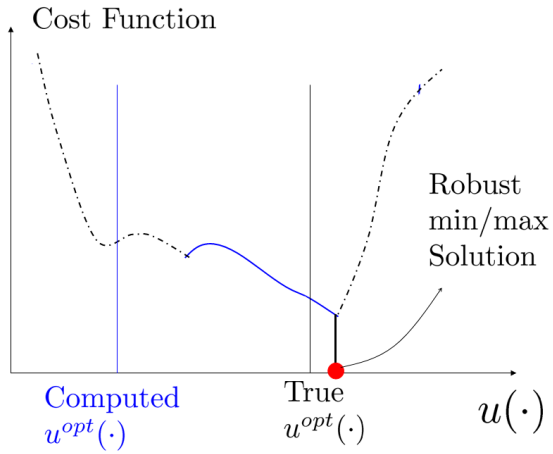


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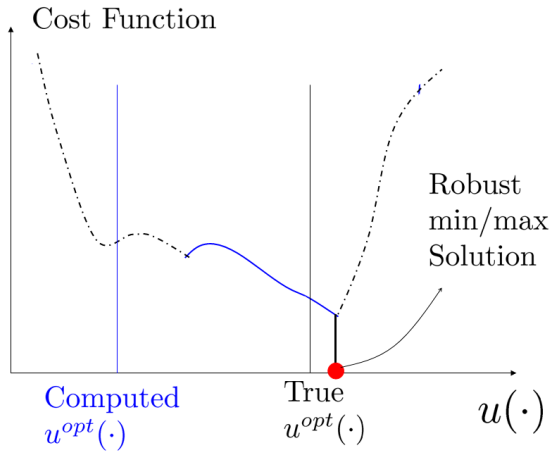


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For all $w(\cdot)$, one has:

$$\Psi(x(T)) + \int_t^T L(x(\tau), \hat{u}(\tau, x(\tau)), w(\tau)) d\tau \leq V(t,x(t))$$

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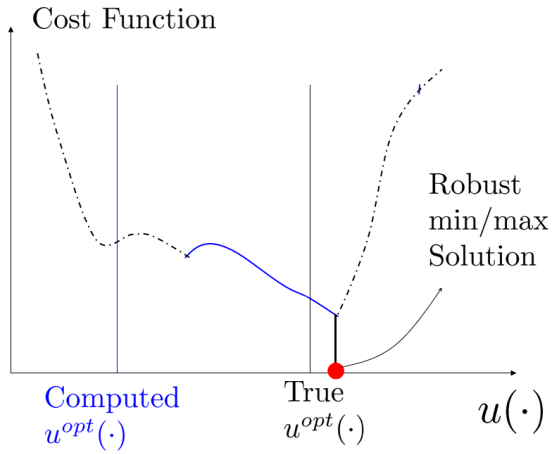


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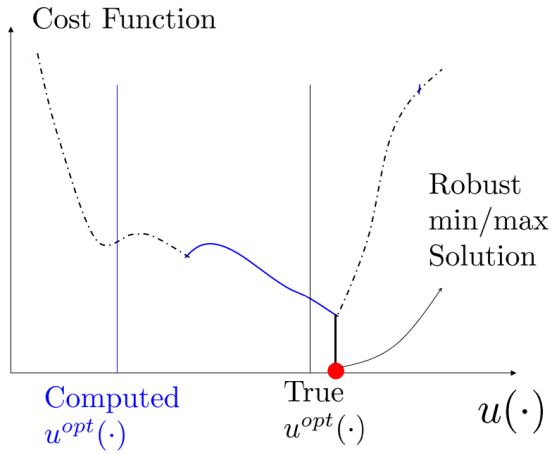


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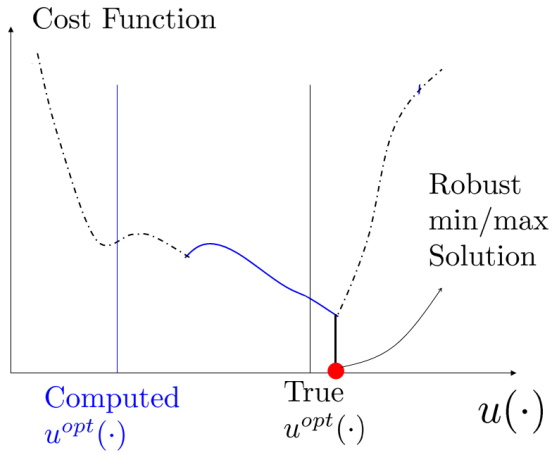


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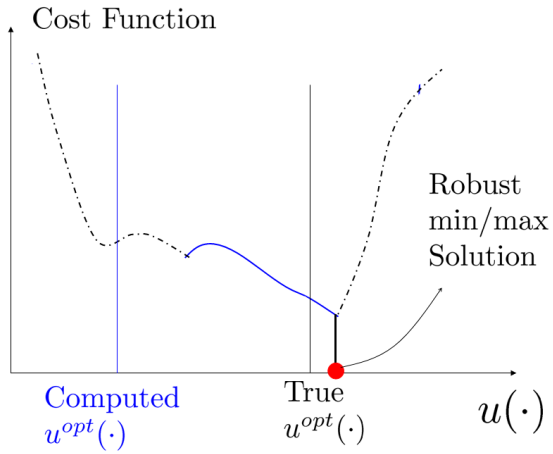


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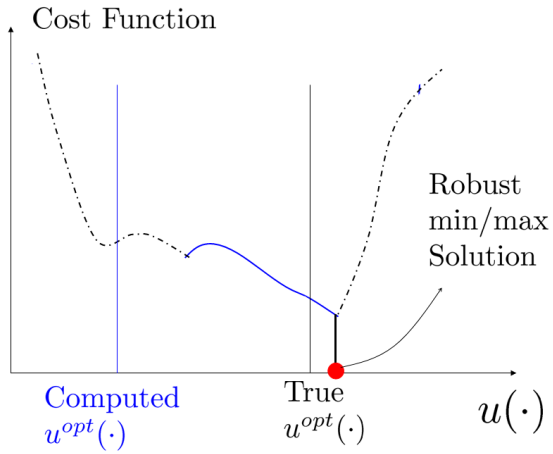


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Defining $\theta^{opt}(x(t)) := p(T)/p(t)$,

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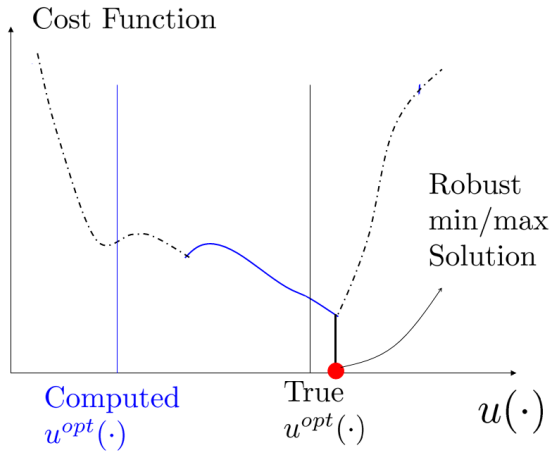


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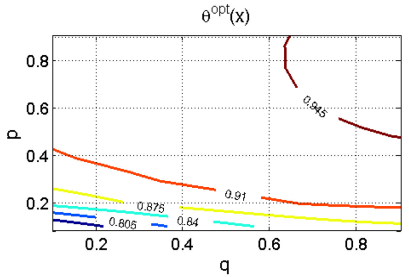


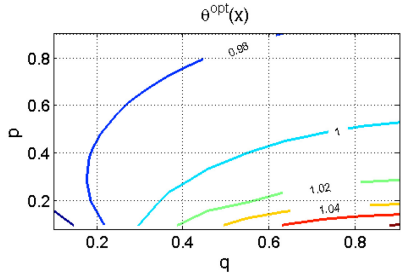


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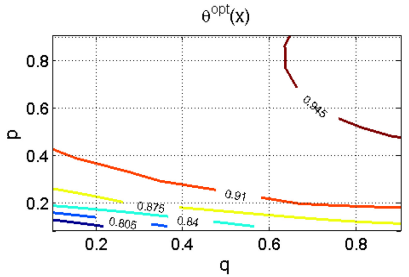
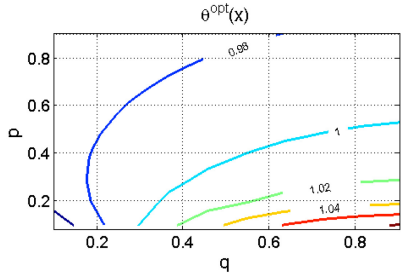
→ Guaranteed Tumor Contraction

# The Hamilton-Jacobi-Isaacs PDE's




$$\theta^{opt}(x(t)) := \frac{p(T)}{p(t)} \leq \frac{\gamma \cdot T \cdot \|\eta\|^2 + V(t, x(t))}{p(t)}$$

Initial tumor size

→ Guaranteed Tumor Contraction

# The Hamilton-Jacobi-Isaacs PDE's

Solution of the HJI PDE's

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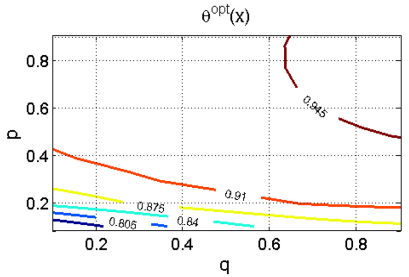


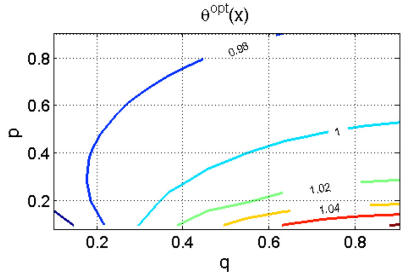

# The Hamilton-Jacobi-Isaacs PDE's

Therapy duration

Solution of the HJI PDE's

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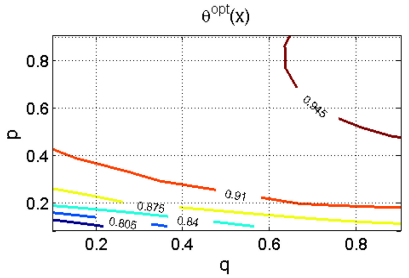
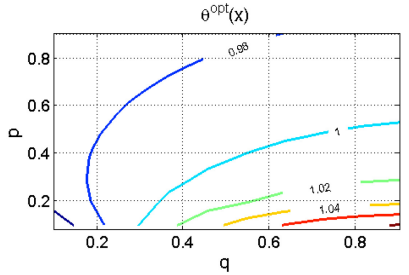


# The Hamilton-Jacobi-Isaacs PDE's

Therapy duration

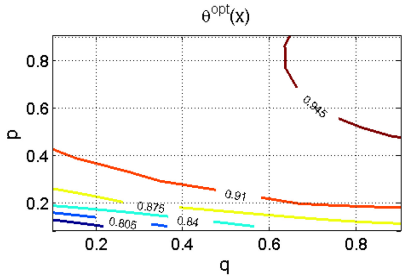
Relative uncertainty level

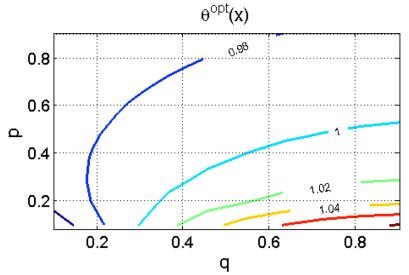
Solution of the HJI PDE's

$$\theta^{opt}(x(t)) := \frac{p(T)}{p(t)} \leq \frac{\gamma \cdot T \cdot \|\eta\|^2 + V(t, x(t))}{p(t)}$$

Initial tumor size

→ Guaranteed Tumor Contraction



# Solving the HJI Equations

$$\frac{\partial V}{\partial t}(t,x) + \hat{H}\left(x, \frac{\partial V}{\partial x}(t,x)\right) = 0 \quad ; \quad V(T,x) = \Psi(x)$$

- Nonlinear PDE's
- Exponential Complexity in the state dimension
- Only approximate solutions over bounded regions can be obtained
- Equivalent to the Differential Riccati Equation (DRE) for
  1. Unconstrained,
  2. Linear Models
  3. with Quadratic Cost

*Beard, R. W. and McLain, G. N.* Successive Galerkin approximation ....
**Int. J. of Control**, *(71), 5, (1997)*

*Alamir, M.* Solutions of Nonlinear Optimal and Robust Control ....
**Automatica**, *(37) (2001)*

# Solving the HJI Equations

Some features of the algorithm:

- PDE's $\longrightarrow$ ODE's
- Backward Integration
- Stabilization & Post Stabilization
- Relevance Indicator $K\tilde{\bar{V}}_{n+1}$

**Algorithm**

(1) Choose a complete set of $C^1$ basis functions $(\phi_i(x))_{i=1}^{\infty}$.
(2) Choose a sufficiently high $N \in \mathbb{N}$.
(3) Choose a fixed set of collocation points $(x^i)_{i=1}^{n_p}$ that contains a regular set w.r.t $(\phi_i(x))_{i=1}^{N}$.
(4) Compute
  (a) $M$ according to (11),
  (b) $\Sigma := M(M^{\mathrm{T}}M)^{-1}M^{\mathrm{T}}$,
  (c) $L = I - \Sigma$ [see (25)],
  (d) $K = L^{\mathrm{T}}Q$ where $Q$ is a solution of the linear system $(LL^{\mathrm{T}})Q = L$ (see Proposition 1).
(5) Choose sufficiently high $\alpha > 0$, a sampling period $k > 0$, a small parameter $\varepsilon > 0$ and $T \in \mathbb{R}_+ \cup \{\infty\}$.
(6) $n = 0$; $\bar{V}_n = \bar{\Psi}$.
(7) Compute $\tilde{\bar{V}}_{n+1}$ solution at $k$ of [see (18a)]

$$\dot{\bar{V}}(\tau) = -\bar{\Gamma}(T-\tau, \bar{V}) - \alpha K \bar{V}(\tau); \quad \bar{V}(0) = \bar{V}_n.$$

(8) $\bar{V}_{n+1} = (I - K)\tilde{\bar{V}}_{n+1}$ [see (18b)].
(9) *If* $(nk \geqslant T)$ OR $(\|\dot{\bar{V}}_n\|_{\infty} \leqslant \epsilon)$ *Then* STOP *Else* $n = n + 1$, GOTO Step 7.
(10) The approximate solution is given by

$$V(t,x) \approx [\Phi_N^{\mathrm{T}}(x)[M^{\mathrm{T}}M]^{-1}M^{\mathrm{T}}]\bar{V}_{n+1}(t). \qquad (26)$$

*4.2. Some convergence results*

*Alamir, M.* Solutions of Nonlinear Optimal and Robust Control ....

**Automatica**, *(37) (2001)*

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$$V(x) = 1.9123x_1^2 - 0.8284x_1x_2 + 1.3522x_2^2$$
$$- 0.8284x_1^4 + 2.7044x_1^3x_2 + 1.3522x_1^6$$

**Algorithm**

(1) Choose a complete set of $C^1$ basis functions $(\phi_i(x))_{i=1}^{\infty}$.
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*Alamir, M.* Solutions of Nonlinear Optimal and Robust Control ....

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Some features of the algorithm:

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- Backward Integration
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$$V_{28}(x) = 1.9067x_1^2 - 0.8223x_1x_2 + 1.3480x_2^2$$
$$- 0.8223x_1^4 + 2.6961x_1^3x_2 + 1.3480x_1^6$$

**Algorithm**

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Table 1
Convergence result for Example 5.1 (execution time $\approx 5$ s)

| $t = nk$ | $\|\|\bar{V}\|\|_\infty$ | $\|\|\dot{\bar{V}}\|\|_\infty$ | $\|\|K\tilde{\bar{V}}\|\|_\infty$ |
|---|---|---|---|
| 0.25 | 0.46 | 1.79 | 8.61E-07 |
| 1.00 | 1.49 | 0.88 | 7.70E-06 |
| 2.00 | 1.94 | 0.37 | 5.65E-06 |
| 3.00 | 2.08 | 0.10 | 2.45E-06 |
| 4.00 | 2.12 | 2.18E-02 | 8.40E-07 |
| 4.75 | 2.13 | 1.06E-02 | 5.29E-07 |

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*4.2. Some convergence results*

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**Automatica**, *(37) (2001)*

# Constrained Robust Combined Therapy

## Cost Function

$$\min_{v\in[0,v^{max}]^{[0,T]}} \quad \max_{w\in[\mathbb{R}^{n_w}]^{[0,T]}} \quad J(x_0, v(\cdot), w(\cdot)) :=$$
$$p(T) + \int_0^T \left[ \|v(\tau)\|_R^2 - \|w(\tau) - w^{nom}\|_W^2 \right] d\tau$$

$$W^{\frac{1}{2}} := \gamma^{\frac{1}{2}} \cdot \mathrm{diag}\left(\frac{1}{w_1^{nom}}, \ldots, \frac{1}{w_{n_w}^{nom}}\right)$$

## Constraints

- $v_i \in [0, v_i^{max}]$, $i \in \{1, 2\}$
- For $i \in \{1, 2\}$,

$$\int_0^T v_i(\tau) d\tau = y_i(T) \leq y_i^{max}$$

## Disturbance set

$$\mathbb{W} := \left\{ w \mid w_i = w^{nom}(1 + \eta_i) \right\}$$

$$\dot{p} = -w_1 p \ln\left(\frac{p}{q}\right) - w_2 p v_2$$
$$\dot{q} = w_3 p - (w_4 + w_5 p^{\frac{2}{3}}) q - w_6 v_1 q$$
$$\dot{y}_1 = v_1$$
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*Hahnfeldt et al.* Tumor development under angiogenic signaling: ...

**Cancer Research**, *(59), 1999.*

- $p$ tumor cells population level
- $q$ vasculature level
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- $v_2$, $y_2$ Already injected drug
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# Constrained Robust Combined Therapy

Normalized State Variable:

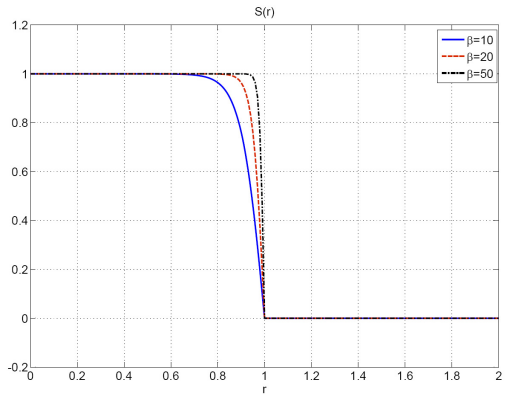
$$x = \left( \frac{p}{p^{max}} \quad \frac{q}{q^{max}} \quad \frac{y_1}{y_1^{max}} \quad \frac{y_2}{y_2^{max}} \right)^T \in \mathbb{R}^4$$

Change in the control variable:

$$v_i(t) = S(y_i(t)/y_i^{max}) \cdot u_i(t)$$

where $S(r) \in [0, 1[$ is given by:

$$S(r) = \max\{-\tanh(\beta_s(r-1)), 0\}$$




$$\begin{aligned}
\dot{p} &= -w_1 p \ln(\frac{p}{q}) - w_2 p v_2 \\
\dot{q} &= w_3 p - (w_4 + w_5 p^{\frac{2}{3}}) q - w_6 v_1 q \\
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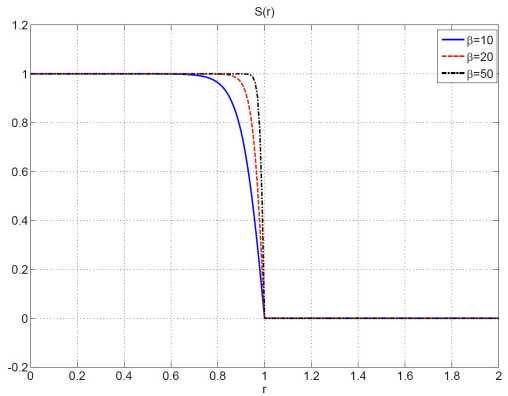


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$$f(x,u,w) := \begin{pmatrix} -w_1 x_1 \ln(\alpha x_1/x_2) - w_2 x_1 S(x_4) u_2 \\ \alpha w_3 x_1 - (w_4 + \beta w_5 x_1^{2/3}) x_2 - w_6 x_2 S(x_3) u_1 \\ \varrho_1 \cdot S(x_3) u_1 \\ \varrho_2 \cdot S(x_4) u_2 \end{pmatrix}$$

where $\alpha$, $\beta$, $\sigma$ and $\varrho_i$ are positive constant given by:

$$\alpha := \frac{p^{max}}{q^{max}} \; ; \; \beta := (p^{max})^{\frac{2}{3}} \; ; \; \sigma := \frac{1}{q^{max}} \; ; \; \varrho_i := \frac{1}{y_i^{max}}$$

# Constrained Robust Combined Therapy

## System Model

$$f(x,u,w) := \begin{pmatrix} -w_1 x_1 \ln(\alpha x_1/x_2) - w_2 x_1 S(x_4) u_2 \\ \alpha w_3 x_1 - (w_4 + \beta w_5 x_1^{2/3}) x_2 - w_6 x_2 S(x_3) u_1 \\ \varrho_1 \cdot S(x_3) u_1 \\ \varrho_2 \cdot S(x_4) u_2 \end{pmatrix}$$

## Cost Function

$$\Psi(x) = x_1$$
$$L(x,u,w) := u^T R u - \|w - w^{nom}\|_W^2$$

## The Hamiltonian

$$H(x,u,w) = u^T R u - \|w - w^{nom}\|_W^2 +$$
$$+\lambda^T (F_0(x) + F_1(x)u_1 + F_2(x)u_2)^T w + \lambda^T F_3(x) u$$

# Constrained Robust Combined Therapy

## System Model

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$$F_0(x) := \begin{pmatrix} -x_1 \ln(\alpha x_1/x_2) & 0 & 0\ 0 \\ 0 & 0 & 0\ 0 \\ 0 & \alpha x_1 & 0\ 0 \\ 0 & -x_2 & 0\ 0 \\ 0 & -\beta x_1^{2/3} x_2 & 0\ 0 \\ 0 & 0 & 0\ 0 \end{pmatrix}$$

## Cost Function

$$\Psi(x) = x_1$$
$$L(x,u,w) := u^T R u - \|w - w^{nom}\|_W^2$$

$$F_1(x), F_2(x) := \begin{pmatrix} 0 & 0 & 0\ 0 \\ 0 & 0 & 0\ 0 \\ 0 & 0 & 0\ 0 \\ 0 & 0 & 0\ 0 \\ 0 & 0 & 0\ 0 \\ 0 & -x_2 S(x_3) & 0\ 0 \end{pmatrix}, \begin{pmatrix} 0 & 0\ 0\ 0 \\ -x_1 S(x_4) & 0\ 0\ 0 \\ 0 & 0\ 0\ 0 \\ 0 & 0\ 0\ 0 \\ 0 & 0\ 0\ 0 \\ 0 & 0\ 0\ 0 \end{pmatrix}$$

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$$F_3(x) := \begin{pmatrix} 0 & 0 \\ 0 & 0 \\ \varrho_1 S(x_3) & 0 \\ 0 & \varrho_2 S(x_4) \end{pmatrix}$$

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$$f(x,u,w) := \begin{pmatrix} -w_1 x_1 \ln(\alpha x_1/x_2) - w_2 x_1 S(x_4) u_2 \\ \alpha w_3 x_1 - (w_4 + \beta w_5 x_1^{2/3}) x_2 - w_6 x_2 S(x_3) u_1 \\ \varrho_1 \cdot S(x_3) u_1 \\ \varrho_2 \cdot S(x_4) u_2 \end{pmatrix}$$

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## Optimal Game Feedback Strategies:

$$\hat{u}(x,\lambda) := \min_{u \in [0, v^{max}]} \frac{1}{2} u^T [\mathcal{R}(x,\lambda)] u + [f(x,\lambda)] u \quad (29)$$

$$\hat{w}(x,\lambda) := w^{nom} + \frac{1}{2} W^{-1} [\Theta_0(x,\lambda) + \Theta_1(x,\lambda)\hat{u}(x,\lambda)] \quad (30)$$

where

$$\mathcal{R}(x,\lambda) := 2R + \frac{1}{2}\Theta_1^T(x,\lambda) W^{-1} \Theta_1(x,\lambda) \quad (31)$$

$$f(x,\lambda) := \frac{1}{2}\Theta_0^T(x,\lambda) W^{-1} \Theta_1(x,\lambda) + \\ + \frac{1}{2}(w^{nom})^T \Theta_1(x,\lambda) + \lambda^T F_3(x) \quad (32)$$

$$\Theta_0(x,\lambda) := F_0(x)\lambda \quad (33)$$

$$\Theta_1(x,\lambda) := [F_1(x)\lambda, F_2(x)\lambda] \quad (34)$$

# Constrained Robust Combined Therapy

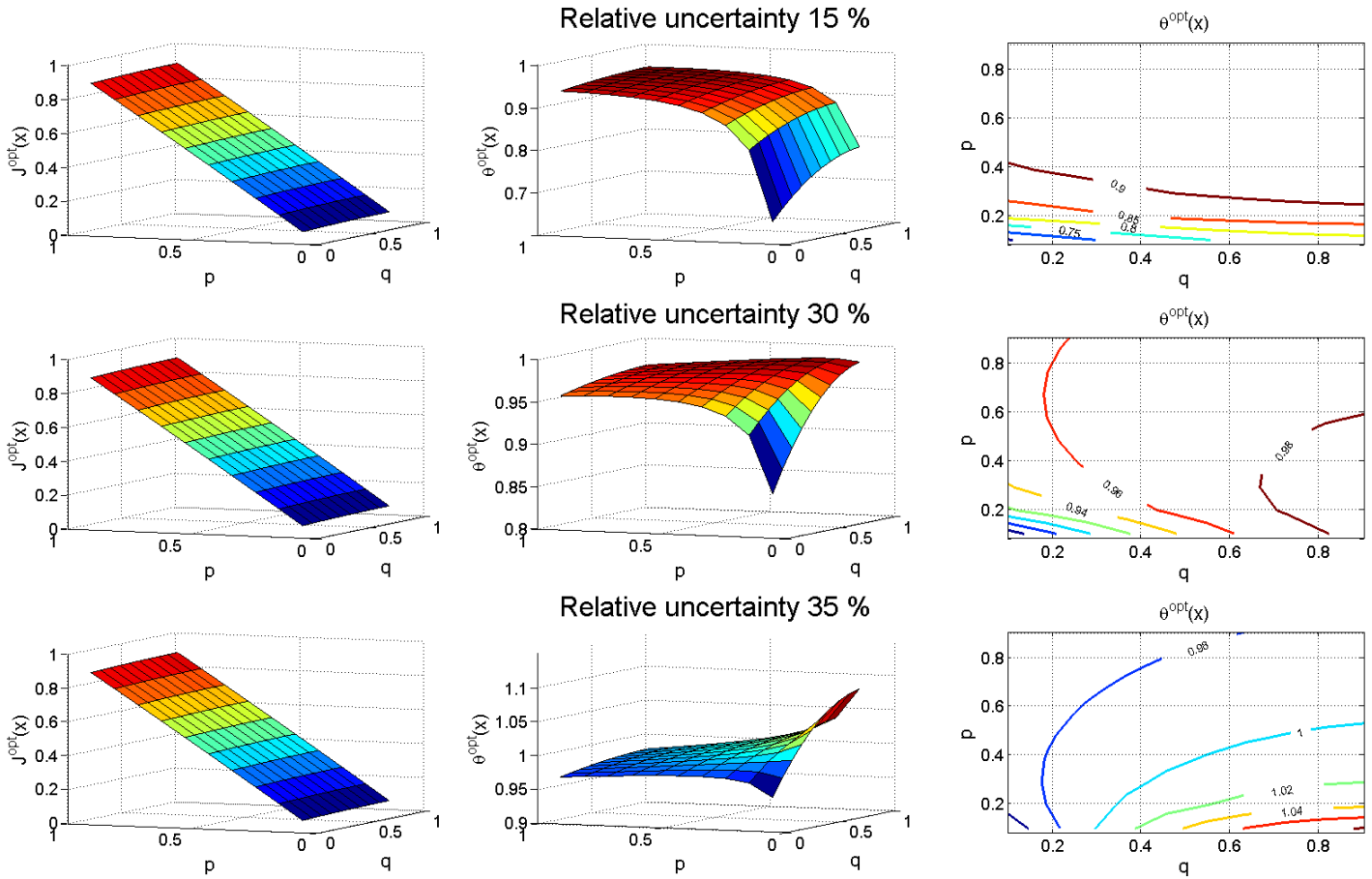
## Numerical Solution parameters:

- $T \in [0, 1]$
- $\gamma = 0.05$
- $N = 15$ (quadratic approximation)
- $n_p = 5^4 = 625$
- $y_i^{max} \in \{0.5, 1\}$
- $\eta_i \in \{15\%, 30\%, 35\%\}$
- $p^{max} = q^{max} = 2 \times 10^4$

## Simulations aim at investigating the impact of:

- The drug available quantities
- The treatment duration
- The initial condition $(p, q)$

# Constrained Robust Combined Therapy




achievable performance as a function of the normalized initial state $(p, q, 0, 0)$ with the integral constraints defined by $\mathbf{y_1^{max}} = \mathbf{y_2^{max}} = \mathbf{1}$ and a treatment duration $T = 1$. Left: optimal cost $J^{opt}$, Center: guaranteed contraction factor $\theta^{opt}$, Right: contour lines for $\theta^{opt}$.

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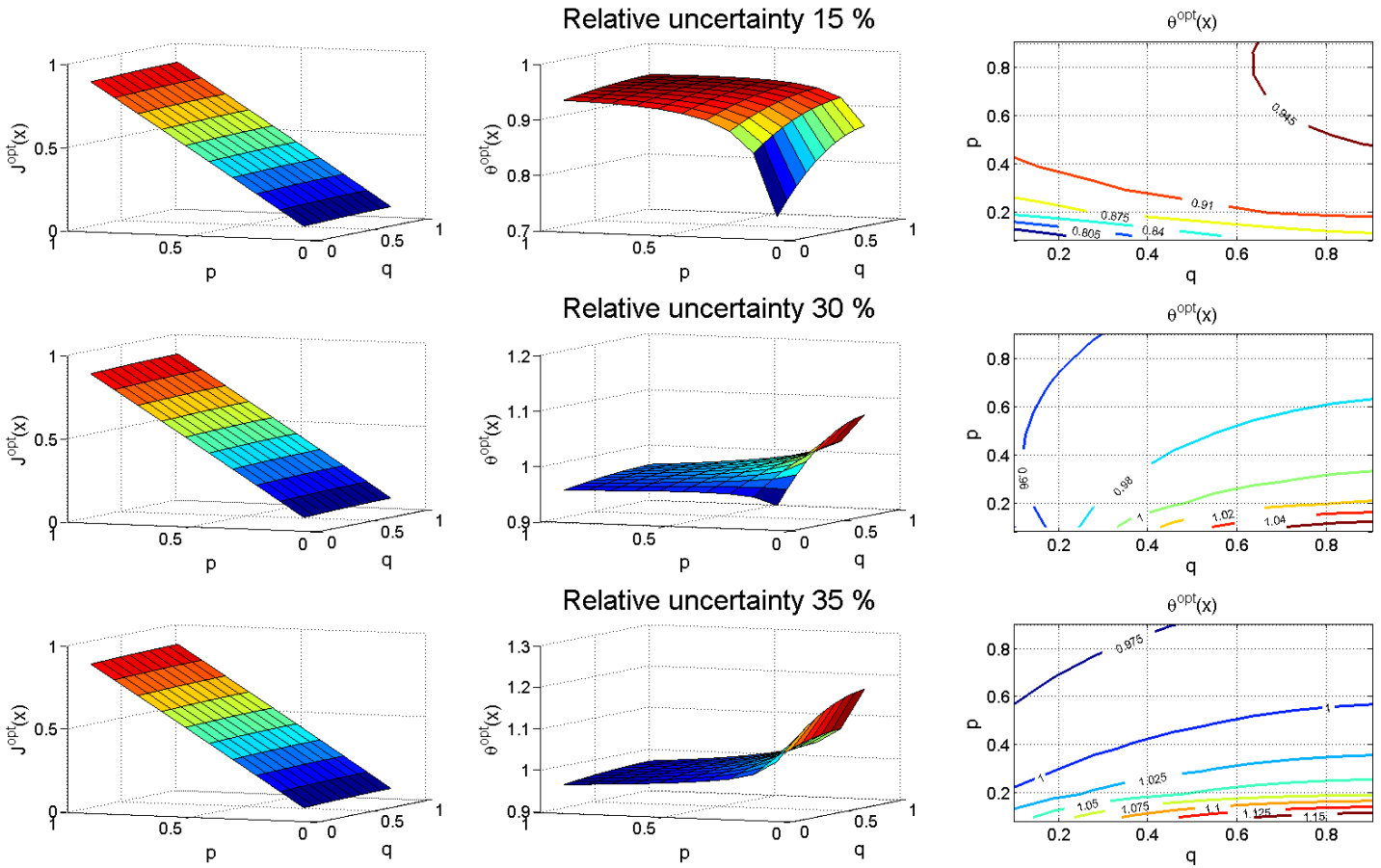


achievable performance as a function of the normalized initial state $(p, q, 0, 0)$ with the integral constraints defined by $\mathbf{y_1^{max} = y_2^{max} = 0.5}$ and a treatment duration $T = 1$. Left: optimal cost $J^{opt}$, Center: guaranteed contraction factor $\theta^{opt}$, Right: contour lines for $\theta^{opt}$.

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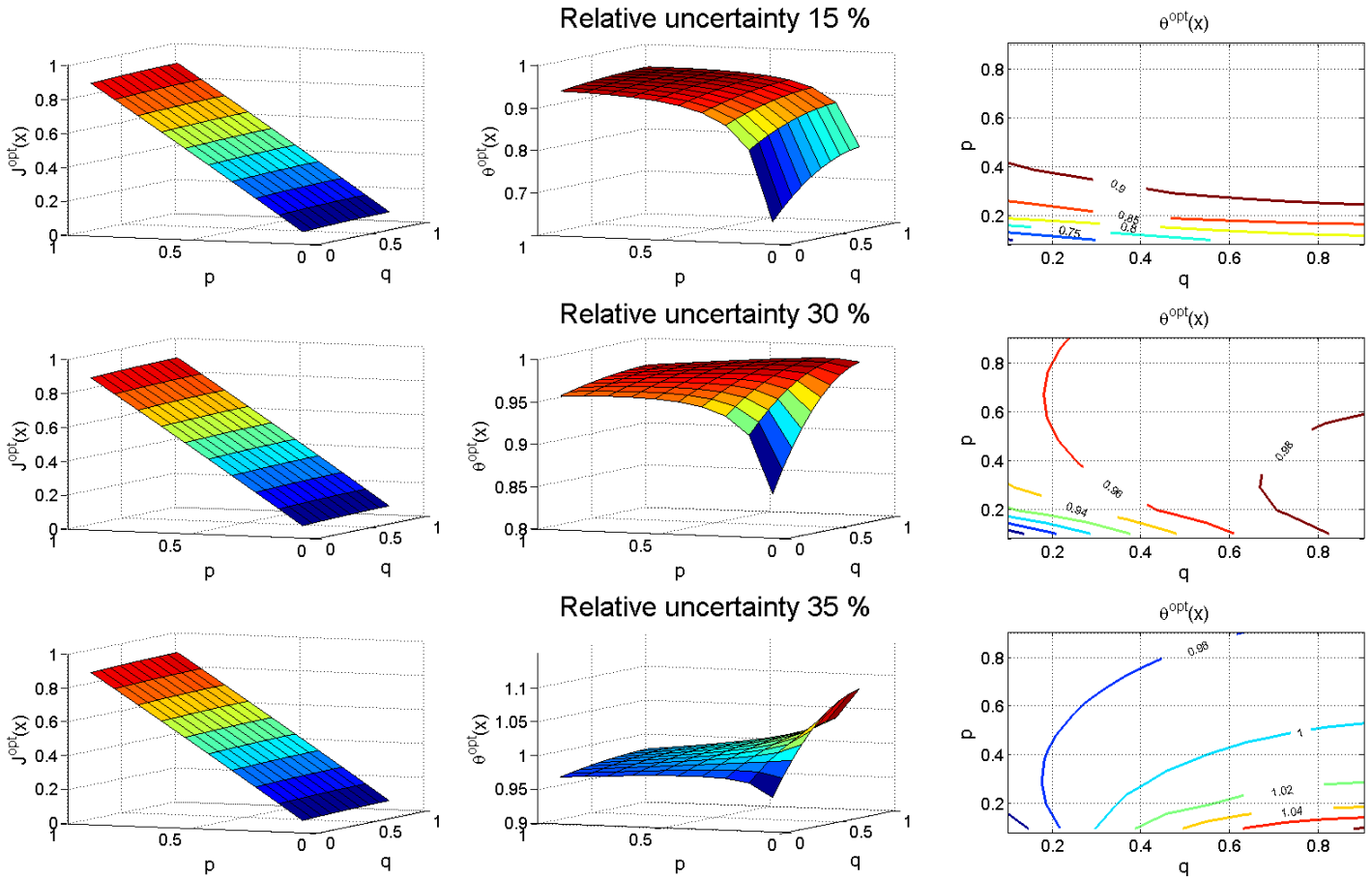


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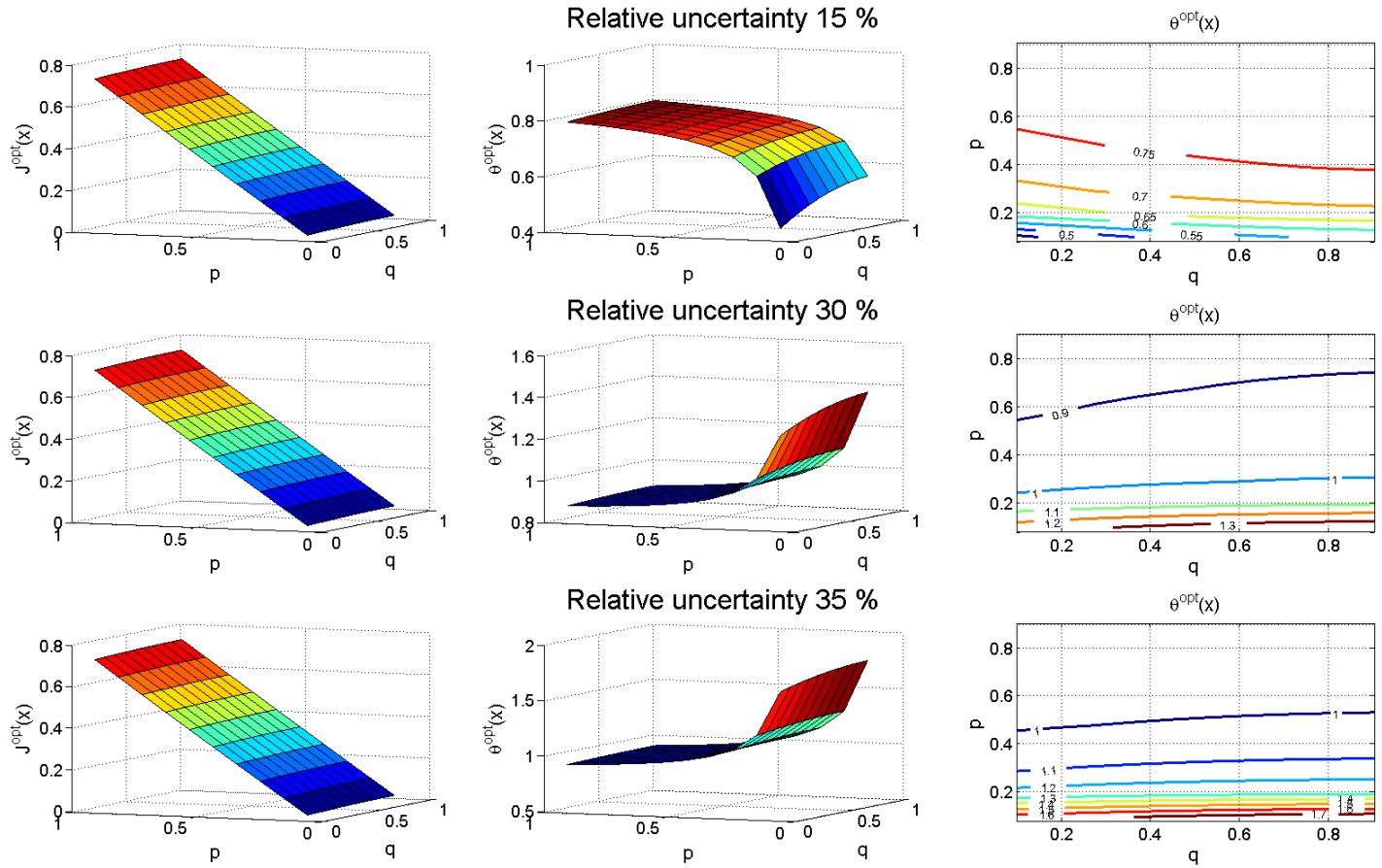


achievable performance as a function of the normalized initial state $(p, q, 0, 0)$ with the integral constraints defined by $y_1^{max} = y_2^{max} = 1$ and a treatment duration $\mathbf{T = 2}$. Left: optimal cost $J^{opt}$, Center: guaranteed contraction factor $\theta^{opt}$, Right: contour lines for $\theta^{opt}$.

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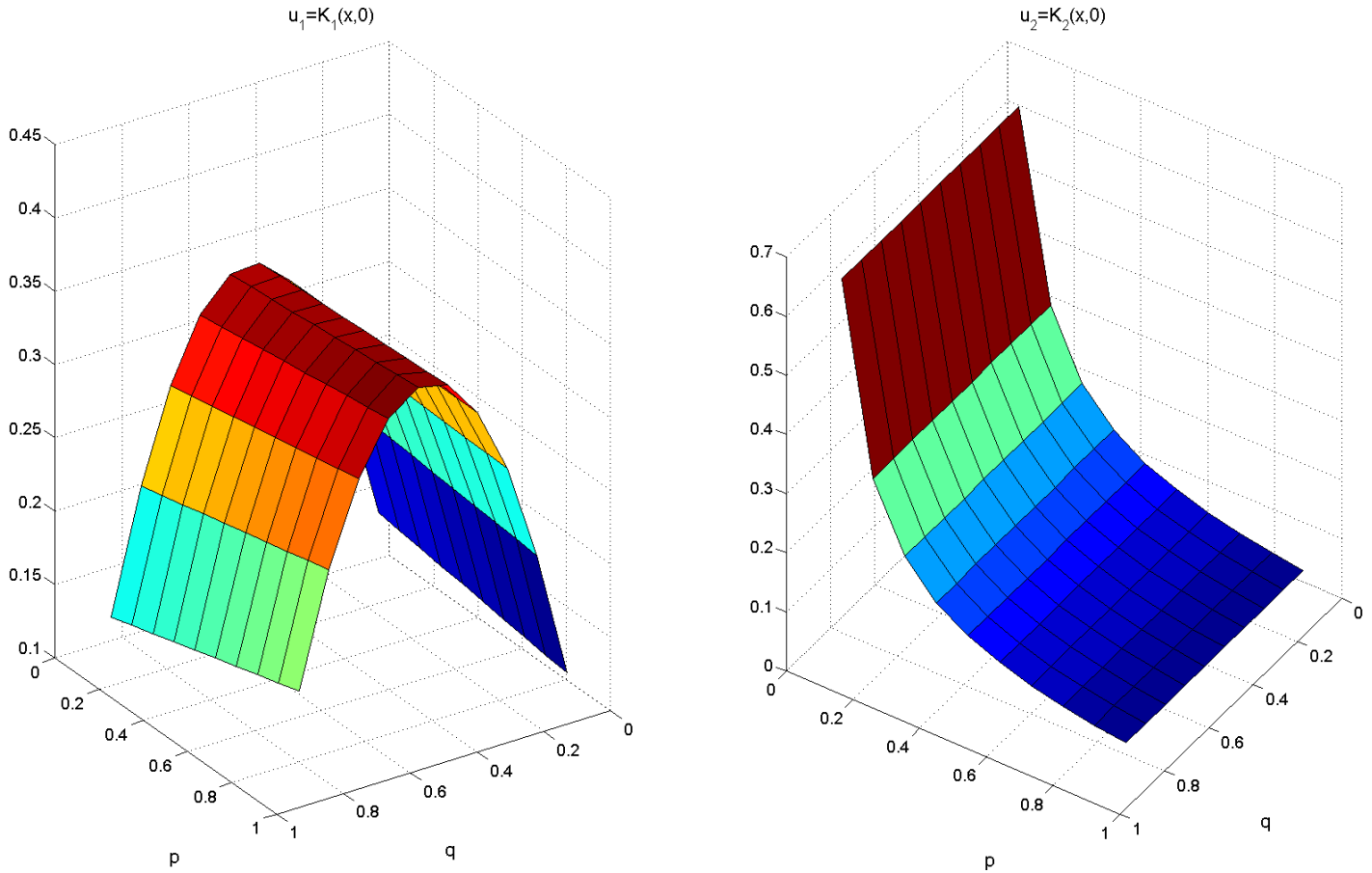


The state feedback map $u = K(0, x)$ for $x = (p, q, 0, 0)^T$ obtained when the integral saturations $y_1^{max} = y_2^{max} = 1$ is used together with the treatment duration $\mathbf{T = 1}$

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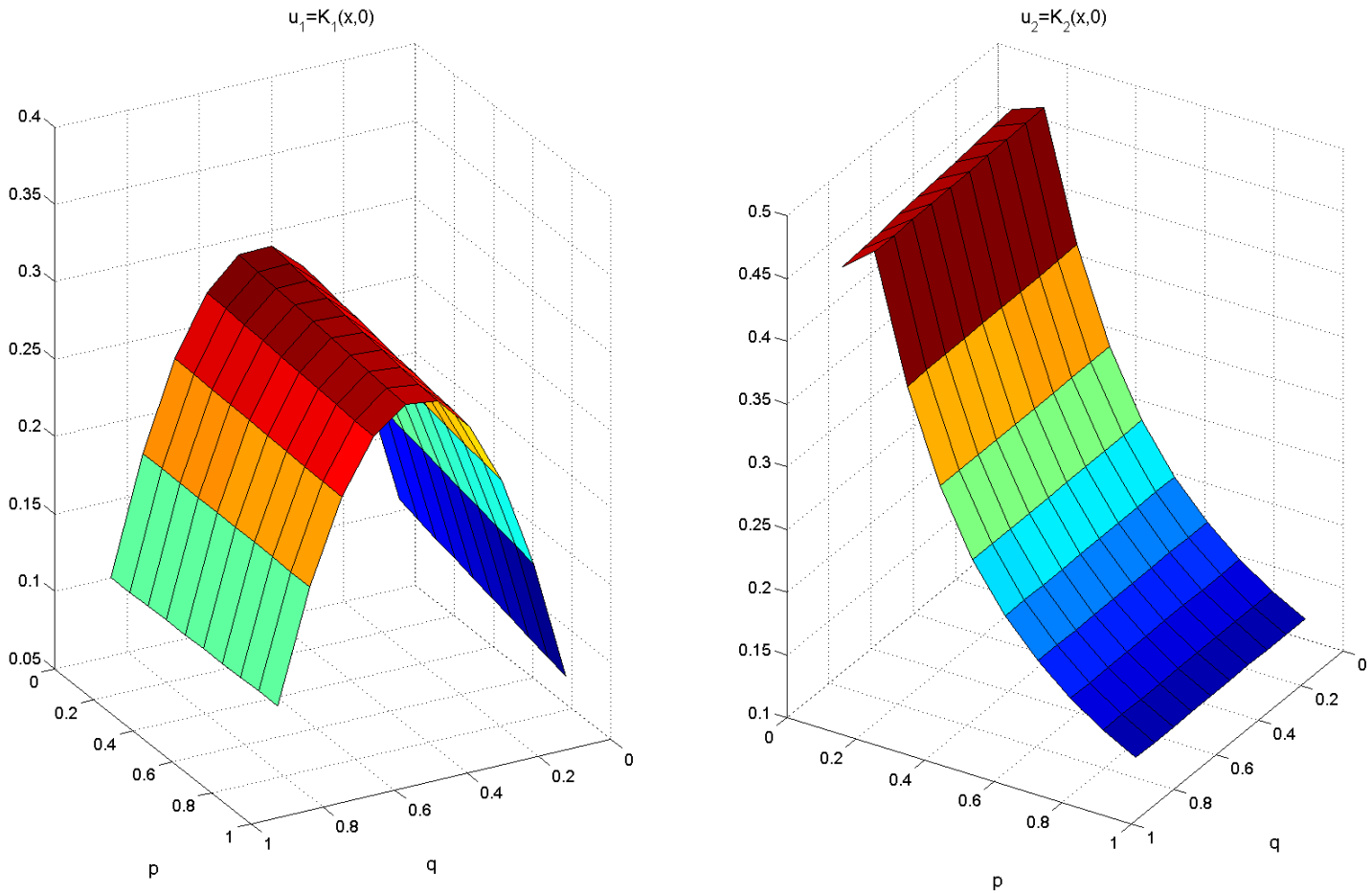


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For further details

M. Alamir, *Robust Feedback Design For Combined Therapy of Cancer*. **Optimal Control, Applications and Methods. (To Appear 2013)**.

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- **Unstructured Model Identification**

  $\dot{x} = f(t, x, p)$ with $p = K_M(x)$ and $y = h(x)$
  HJB $\rightarrow p = K(t, x(t))$ gives insight on $K_M(x)$

# Biological Models & The Uncertainty issue

of the treatment and neglected the issue of patient variability during the treatment course. Without such a strategy, any change in patient parameters may lead to sub-optimal treatment and poor patient outcomes. Very few works (Chareyron and Alamir, 2009; Florian et al., 2008) have examined this issue. These works cast the

*K. L. Kiran & S. Lakshminarayanan,*
*Global Sensitivity Analysis and Model-Based Reactive Scheduling of Targeted Cancer Immunotherapy.* **BioSystems**, *(101), 2010.*