A Control Approach for ODE Cancer Models

Khalid Kassara

MACS://Systems & Control Group
University Hassan II, Casablanca

8^{th} ECMTB, **Krakow** (PL)

Outline

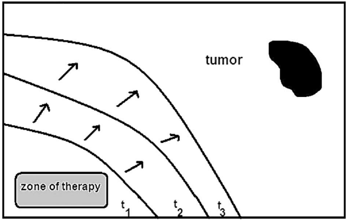
1. **Motivations of the work**
2. **A control approach**
   - Statement of the problem
   - The set-valued framework
   - Cancer control
3. **Simulation results**
   - Anti-angiogenic therapy
   - Tumor-immune interactions with chemotherapy
   - Immunotherapy

Outline

Mathematical modeling and cancer

- central role in cancer research, to understand how tumors develop
- control theory : for fighting cancer through mathematical models
  - **optimal control** : criterion minimized $\Longrightarrow$ cancer cells reduced
    Bellomo, de Pillis, D'Onofrio, Fister, Ledzewicz, Lenhart, Piccoli etc
  - **direct approach**
    - for **PDE**s,

by using spreading control
El Jai , Kassara, IJC (2006)

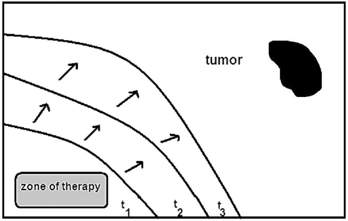


    - for **ODE**s,
      Kassara, Moustafid, in MCM, PAMM, SIAM J. Cont., MB (2006-2011)
  - other approaches : agent-based modeling, cellular automata, stochastic, etc

Mathematical modeling and cancer

- central role in cancer research, to understand how tumors develop
- control theory : for fighting cancer through mathematical models
  - **optimal control** : criterion minimized $\Longrightarrow$ cancer cells reduced
    Bellomo, de Pillis, D'Onofrio, Fister, Ledzewicz, Lenhart, Piccoli etc
  - **direct approach**
    - for **PDE**s,

      by using spreading control
      El Jai , Kassara, IJC (2006)

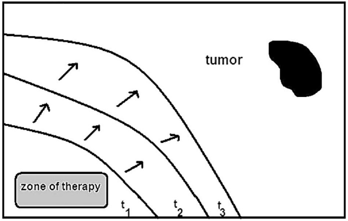


    - for **ODE**s,
      Kassara, Moustafid, in MCM, PAMM, SIAM J. Cont., MB (2006-2011)
  - other approaches : agent-based modeling, cellular automata, stochastic, etc

Mathematical modeling and cancer

- central role in cancer research, to understand how tumors develop
- control theory : for fighting cancer through mathematical models
  - **optimal control** : criterion minimized $\Longrightarrow$ cancer cells reduced
    Bellomo, de Pillis, D'Onofrio, Fister, Ledzewicz, Lenhart, Piccoli etc
  - **direct approach**
    - for **PDE**s,

by using spreading control
El Jai , Kassara, IJC (2006)

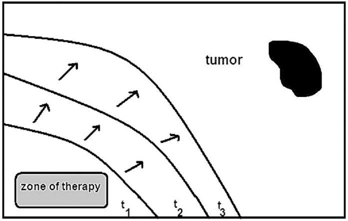


    - for **ODE**s,
      Kassara, Moustafid, in MCM, PAMM, SIAM J. Cont., MB (2006-2011)
  - other approaches : agent-based modeling, cellular automata, stochastic, etc

Mathematical modeling and cancer

- central role in cancer research, to understand how tumors develop
- control theory : for fighting cancer through mathematical models
  - **optimal control** : criterion minimized $\Longrightarrow$ cancer cells reduced
    Bellomo, de Pillis, D'Onofrio, Fister, Ledzewicz, Lenhart, Piccoli etc
  - **direct approach**
    - for **PDE**s,

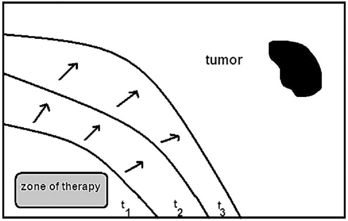
by using spreading control
El Jai , Kassara, IJC (2006)



- for **ODE**s,
  Kassara, Moustafid, in MCM, PAMM, SIAM J. Cont., MB (2006-2011)
- other approaches : agent-based modeling, cellular automata, stochastic, etc

Mathematical modeling and cancer

- central role in cancer research, to understand how tumors develop
- control theory : for fighting cancer through mathematical models
  - **optimal control** : criterion minimized $\Longrightarrow$ cancer cells reduced
    Bellomo, de Pillis, D'Onofrio, Fister, Ledzewicz, Lenhart, Piccoli etc
  - **direct approach**
    - for **PDE**s,



by using spreading control
El Jai , Kassara, IJC (2006)

    - for **ODE**s,
      Kassara, Moustafid, in MCM, PAMM, SIAM J. Cont., MB (2006-2011)
  - other approaches : agent-based modeling, cellular automata, stochastic, etc

Outline

Cancer as a control problem

$$\dot{x} = f(x,\tau) + G(x,\tau)u$$
$$\dot{\tau} = \tau\psi(x,\tau)$$

- $u \to K$ administered cells
- $K \doteq [0, u_1^{\max}] \times \cdots \times [0, u_p^{\max}]$
- τ tumor cells
- $x \to \mathbb{R}_+^n$ cells in competition with tumor cells
- f, G, ψ smooth functions

Definition

A protocol is a control $\bar{u}$:

1. $\bar{u} : [0\ \infty) \to K$
2. the system has a global solution $(\bar{x}, \bar{\tau})$
3. $\lim_{t\to\infty} \bar{\tau}(t) = 0$

The feedback map

For $\beta > 0$ let $D_\beta \doteq \{(x,\tau) \in \mathbb{R}^n_+ \times \mathbb{R}_+ \mid \psi(x,\tau) \leq -\beta\}$, and

$$\mathcal{F}_\beta(x,\tau) \doteq \left\{u \in K \mid (f(x,\tau) + G(x,\tau)u, \tau\psi(x,\tau)) \in T_{D_\beta}(x,\tau)\right\}$$

for each $(x,\tau) \in D_\beta$, where $T_D(\cdot)$ is the contingent cone. Assume the linear growth condition : there are $m_1(\cdot)$, $m_2(\cdot)$, continuous such that :

$$|f(x,\tau)| \leq m_1(\tau)|x| \text{ and } |G(x,\tau)| \leq m_2(\tau)|x| \text{ on } D_\beta$$

Then Aubin viability theory leads to

Theorem :

If σ is a selection of $\mathcal{F}_\beta$ and $(x_0, \tau_0) \in D_\beta$, then

- feedback $u \doteq \sigma(x,\tau)$ produces a solution $(\bar{x}, \bar{\tau})$ on $[0,\infty)$
- $\bar{u} \doteq \sigma(\bar{x}, \bar{\tau})$ is a protocol and $\bar{\tau}(\cdot) \searrow 0$, exponentially (such σ is called a protocol law)

The feedback map

For $\beta > 0$ let $D_\beta \doteq \{(x,\tau) \in \mathbb{R}^n_+ \times \mathbb{R}_+ \mid \psi(x,\tau) \leq -\beta\}$, and

$$\mathcal{F}_\beta(x,\tau) \doteq \Big\{u \in K \mid (f(x,\tau) + G(x,\tau)u, \tau\psi(x,\tau)) \in T_{D_\beta}(x,\tau)\Big\}$$

for each $(x,\tau) \in D_\beta$, where $T_D(\cdot)$ is the contingent cone. Assume the linear growth condition : there are $m_1(\cdot), m_2(\cdot)$, continuous such that :

$$|f(x,\tau)| \leq m_1(\tau)|x| \text{ and } |G(x,\tau)| \leq m_2(\tau)|x| \text{ on } D_\beta$$

Then Aubin viability theory leads to

Theorem :

If σ is a selection of $\mathcal{F}_\beta$ and $(x_0,\tau_0) \in D_\beta$, then

- feedback $u \doteq \sigma(x,\tau)$ produces a solution $(\bar{x},\bar{\tau})$ on $[0\ \infty)$
- $\bar{u} \doteq \sigma(\bar{x},\bar{\tau})$ is a protocol and $\bar{\tau}(\cdot) \searrow 0$, exponentially (such σ is called a protocol law)

The feedback map

For $\beta > 0$ let $D_\beta \doteq \left\{(x,\tau) \in \mathbb{R}^n_+ \times \mathbb{R}_+ \mid \psi(x,\tau) \leq -\beta\right\}$, and

$$\mathcal{F}_\beta(x,\tau) \doteq \left\{u \in K \mid (f(x,\tau) + G(x,\tau)u, \tau\psi(x,\tau)) \in T_{D_\beta}(x,\tau)\right\}$$

for each $(x,\tau) \in D_\beta$, where $T_D(\cdot)$ is the contingent cone. Assume the linear growth condition : there are $m_1(\cdot), m_2(\cdot)$, continuous such that :

$$|f(x,\tau)| \leq m_1(\tau)|x| \text{ and } |G(x,\tau)| \leq m_2(\tau)|x| \text{ on } D_\beta$$

Then Aubin viability theory leads to

Theorem :

If σ is a selection of $\mathcal{F}_\beta$ and $(x_0,\tau_0) \in D_\beta$, then

- feedback $u \doteq \sigma(x,\tau)$ produces a solution $(\bar{x},\bar{\tau})$ on $[0\ \infty)$
- $\bar{u} \doteq \sigma(\bar{x},\bar{\tau})$ is a protocol and $\bar{\tau}(\cdot) \searrow 0$, exponentially (such σ is called a protocol law)

Expression of the feedback map

For each $(x,\tau) \in D_\beta$ we have,

$$\mathcal{F}_\beta(x,\tau) = \left| \begin{array}{lll} K & \text{if} & \psi(x,\tau) < -\beta, \\ C(x,\tau) & \text{if} & \psi(x,\tau) = -\beta, \end{array} \right.$$

where,

$$C(x,\tau) \doteq \{u \in K \mid \langle h(x,\tau), u\rangle \geq \ell(x,\tau)\},$$

and h, ℓ are given by,

$$h \doteq -G' \nabla_x \psi,$$

$$\ell \doteq \langle \nabla_x \psi, f \rangle + \tau\psi \frac{\partial \psi}{\partial \tau}$$

Two sets of protocol laws

Further the linear growth condition, assume the qualification condition

$$\text{for all } (x,\tau) \in D_\beta, \text{ there is } u \in K : \langle h(x,\tau), u\rangle > \ell(x,\tau)$$

then :

- minimal protocol law

$$\zeta_{\min}(x,\tau) \doteq \begin{vmatrix} 0 & \text{if} \quad \psi(x,\tau) < -\beta \\ \pi_{C(x,\tau)}(0) & \text{if} \quad \psi(x,\tau) = -\beta \end{vmatrix}$$

π : the projector

- continuous protocol law

$$\zeta_\lambda(x,\tau) \doteq e^{\lambda(\psi(x,\tau)+\beta)}\pi_{C(x,\tau)}(0) \qquad (\lambda > 0)$$

for each $(x,\tau) \in D_\beta$

Two sets of protocol laws

Further the linear growth condition, assume the qualification condition

$$\text{for all } (x,\tau) \in D_\beta, \text{ there is } u \in K : \langle h(x,\tau), u\rangle > \ell(x,\tau)$$

then :

- minimal protocol law

$$\zeta_{\min}(x,\tau) \doteq \begin{vmatrix} 0 & \text{if} \quad \psi(x,\tau) < -\beta \\ \pi_{C(x,\tau)}(0) & \text{if} \quad \psi(x,\tau) = -\beta \end{vmatrix}$$

π : the projector

- continuous protocol law

$$\zeta_\lambda(x,\tau) \doteq e^{\lambda(\psi(x,\tau)+\beta)}\pi_{C(x,\tau)}(0) \qquad (\lambda > 0)$$

for each $(x,\tau) \in D_\beta$

Two sets of protocol laws

Further the linear growth condition, assume the qualification condition

$$\text{for all } (x,\tau) \in D_\beta, \text{ there is } u \in K : \langle h(x,\tau), u\rangle > \ell(x,\tau)$$

then :

- minimal protocol law

$$\zeta_{\min}(x,\tau) \doteq \left| \begin{array}{lll} 0 & \text{if} & \psi(x,\tau) < -\beta \\ \pi_{C(x,\tau)}(0) & \text{if} & \psi(x,\tau) = -\beta \end{array} \right.$$

π : the projector

- continuous protocol law

$$\zeta_\lambda(x,\tau) \doteq e^{\lambda(\psi(x,\tau)+\beta)}\pi_{C(x,\tau)}(0) \qquad (\lambda > 0)$$

for each $(x,\tau) \in D_\beta$

Two sets of protocol laws

Further the linear growth condition, assume the qualification condition

$$\text{for all } (x,\tau) \in D_\beta,\ \text{there is } u \in K : \langle h(x,\tau), u\rangle > \ell(x,\tau)$$

then :

- minimal protocol law

$$\zeta_{\min}(x,\tau) \doteq \left| \begin{array}{lll} 0 & \text{if} & \psi(x,\tau) < -\beta \\ \pi_{C(x,\tau)}(0) & \text{if} & \psi(x,\tau) = -\beta \end{array} \right.$$

  π : the projector

- continuous protocol law

$$\zeta_\lambda(x,\tau) \doteq e^{\lambda(\psi(x,\tau)+\beta)}\pi_{C(x,\tau)}(0) \qquad (\lambda > 0)$$

  for each $(x,\tau) \in D_\beta$

A strategy to eliminate cancer cells

(x,τ) is said to be at stage I if $\psi(x,\tau) < 0$, at stage II if $\psi(x,\tau) \geq 0$ and it is *amenable* to stage I. Otherwise it is said to be at stage III

(i) For (x_0, τ_0) at stage I, let $\beta = -\psi(x_0, \tau_0)$
- apply a protocol law on D_β
  - minimal if preference is to reduce amount of doses
  - continuous if smoothness is rather required
- $\bar{\tau}(\cdot)$ will decrease and $\bar{\tau}(t) \leq e^{-\beta t}\tau_0$ for all t

(ii) For (x_0, τ_0) at stage II, bring it to stage I and apply (i)
A method :
- let ξ be a continuous selection of the map

$$C_\lambda(x,\tau) \doteq \{u \in K \mid \langle h(x,\tau), u\rangle - \ell(x,\tau) \geq \lambda\} \qquad (\lambda > 0)$$

- apply feedback control $u = \xi(x,\tau)$, and assume that the system has a solution $(\bar{x},\bar{\tau})$ on horizon $[0, t_{\rm im}]$, where $t_{\rm im} > \psi(x_0,\tau_0)/\lambda$
- set $(x_1, \tau_1) \doteq (\bar{x}(t_{\rm im}), \bar{\tau}(t_{\rm im}))$, then (x_1, τ_1) is at stage I

(iii) For (x_0, τ_0) at stage III : not curable

A strategy to eliminate cancer cells

(x,τ) is said to be at stage I if $\psi(x,\tau) < 0$, at stage II if $\psi(x,\tau) \geq 0$ and it is *amenable* to stage I. Otherwise it is said to be at stage III

(i) For (x_0,τ_0) at stage I, let $\beta = -\psi(x_0,\tau_0)$

- apply a protocol law on D_β
  - minimal if preference is to reduce amount of doses
  - continuous if smoothness is rather required
- $\bar{\tau}(\cdot)$ will decrease and $\bar{\tau}(t) \leq e^{-\beta t}\tau_0$ for all t

(ii) For (x_0,τ_0) at stage II, bring it to stage I and apply (i)

A method :

- let ξ be a continuous selection of the map

$$C_\lambda(x,\tau) \doteq \{u \in K \mid \langle h(x,\tau), u\rangle - \ell(x,\tau) \geq \lambda\} \qquad (\lambda > 0)$$

- apply feedback control $u = \xi(x,\tau)$, and assume that the system has a solution $(\bar{x},\bar{\tau})$ on horizon $[0,t_{\text{im}}]$, where $t_{\text{im}} > \psi(x_0,\tau_0)/\lambda$
- set $(x_1,\tau_1) \doteq (\bar{x}(t_{\text{im}}),\bar{\tau}(t_{\text{im}}))$, then (x_1,τ_1) is at stage I

(iii) For (x_0,τ_0) at stage III : not curable

A strategy to eliminate cancer cells

(x, τ) is said to be at stage I if $\psi(x,\tau) < 0$, at stage II if $\psi(x,\tau) \geq 0$ and it is *amenable* to stage I. Otherwise it is said to be at stage III

(i) For (x_0, τ_0) at stage I, let $\beta = -\psi(x_0, \tau_0)$

- apply a protocol law on D_β
  - minimal if preference is to reduce amount of doses
  - continuous if smoothness is rather required
- $\bar{\tau}(\cdot)$ will decrease and $\bar{\tau}(t) \leq e^{-\beta t}\tau_0$ for all t

(ii) For (x_0, τ_0) at stage II, bring it to stage I and apply (i)

A method :

- let ξ be a continuous selection of the map

$$C_\lambda(x,\tau) \doteq \{u \in K \mid \langle h(x,\tau), u\rangle - \ell(x,\tau) \geq \lambda\} \qquad (\lambda > 0)$$

- apply feedback control $u = \xi(x,\tau)$, and assume that the system has a solution $(\bar{x}, \bar{\tau})$ on horizon $[0, t_{\text{im}}]$, where $t_{\text{im}} > \psi(x_0,\tau_0)/\lambda$
- set $(x_1, \tau_1) \doteq (\bar{x}(t_{\text{im}}), \bar{\tau}(t_{\text{im}}))$, then (x_1, τ_1) is at stage I

(iii) For (x_0, τ_0) at stage III : not curable

A strategy to eliminate cancer cells

(x, τ) is said to be at stage I if $\psi(x, \tau) < 0$, at stage II if $\psi(x, \tau) \geq 0$ and it is *amenable* to stage I. Otherwise it is said to be at stage III

(i) For (x_0, τ_0) at stage I, let $\beta = -\psi(x_0, \tau_0)$

- apply a protocol law on D_β
  - minimal if preference is to reduce amount of doses
  - continuous if smoothness is rather required
- $\bar{\tau}(\cdot)$ will decrease and $\bar{\tau}(t) \leq e^{-\beta t}\tau_0$ for all t

(ii) For (x_0, τ_0) at stage II, bring it to stage I and apply (i)

A method :

- let ξ be a continuous selection of the map

$$C_\lambda(x, \tau) \doteq \{u \in K \mid \langle h(x, \tau), u\rangle - \ell(x, \tau) \geq \lambda\} \qquad (\lambda > 0)$$

- apply feedback control $u = \xi(x, \tau)$, and assume that the system has a solution $(\bar{x}, \bar{\tau})$ on horizon $[0, t_{\text{im}}]$, where $t_{\text{im}} > \psi(x_0, \tau_0)/\lambda$
- set $(x_1, \tau_1) \doteq (\bar{x}(t_{\text{im}}), \bar{\tau}(t_{\text{im}}))$, then (x_1, τ_1) is at stage I

(iii) For (x_0, τ_0) at stage III : not curable

A strategy to eliminate cancer cells

(x,τ) is said to be at stage I if $\psi(x,\tau) < 0$, at stage II if $\psi(x,\tau) \geq 0$ and it is *amenable* to stage I. Otherwise it is said to be at stage III

(i) For (x_0,τ_0) at stage I, let $\beta = -\psi(x_0,\tau_0)$

- apply a protocol law on D_β
  - minimal if preference is to reduce amount of doses
  - continuous if smoothness is rather required
- $\bar{\tau}(\cdot)$ will decrease and $\bar{\tau}(t) \leq e^{-\beta t}\tau_0$ for all t

(ii) For (x_0,τ_0) at stage II, bring it to stage I and apply (i)
A method :

- let ξ be a continuous selection of the map

$$C_\lambda(x,\tau) \doteq \{u \in K \mid \langle h(x,\tau),u\rangle - \ell(x,\tau) \geq \lambda\} \qquad (\lambda > 0)$$

- apply feedback control $u = \xi(x,\tau)$, and assume that the system has a solution $(\bar{x},\bar{\tau})$ on horizon $[0,t_{\rm im}]$, where $t_{\rm im} > \psi(x_0,\tau_0)/\lambda$
- set $(x_1,\tau_1) \doteq (\bar{x}(t_{\rm im}),\bar{\tau}(t_{\rm im}))$, then (x_1,τ_1) is at stage I

(iii) For (x_0,τ_0) at stage III : not curable

A strategy to eliminate cancer cells

(x,τ) is said to be at stage I if $\psi(x,\tau) < 0$, at stage II if $\psi(x,\tau) \geq 0$ and it is *amenable* to stage I. Otherwise it is said to be at stage III

(i) For (x_0,τ_0) at stage I, let $\beta = -\psi(x_0,\tau_0)$
- apply a protocol law on D_β
  - minimal if preference is to reduce amount of doses
  - continuous if smoothness is rather required
- $\bar{\tau}(\cdot)$ will decrease and $\bar{\tau}(t) \leq e^{-\beta t}\tau_0$ for all t

(ii) For (x_0,τ_0) at stage II, bring it to stage I and apply (i)
A method :
- let ξ be a continuous selection of the map

$$C_\lambda(x,\tau) \doteq \{u \in K \mid \langle h(x,\tau), u\rangle - \ell(x,\tau) \geq \lambda\} \qquad (\lambda > 0)$$

- apply feedback control $u = \xi(x,\tau)$, and assume that the system has a solution $(\bar{x},\bar{\tau})$ on horizon $[0,t_{\rm im}]$, where $t_{\rm im} > \psi(x_0,\tau_0)/\lambda$
- set $(x_1,\tau_1) \doteq (\bar{x}(t_{\rm im}),\bar{\tau}(t_{\rm im}))$, then (x_1,τ_1) is at stage I

(iii) For (x_0,τ_0) at stage III : not curable

A more general class of models

$$\dot{x} = f(x,\tau) + G(x,\tau)u$$
$$\dot{\tau} = \tau(\psi(x,\tau) + H(x,\tau)v)$$

- $(u, v) \to K \subset \mathbb{R}^p \times \mathbb{R}^q$ administered cells
- τ tumor cells
- x cells in competition with tumor cells

Method : recover the previous setting as follows :

- let $z \doteq (x, v)'$
- define $\varphi(z,\tau) \doteq \psi(x,\tau) + H(x,\tau)v$
- consider the augmented system, controlled by (u, w),

$$\dot{z} = (f(x,\tau) + G(x,\tau)u, w)'$$
$$\dot{\tau} = \tau\varphi(z,\tau)$$

Outline

Hahnfeldt et al. model

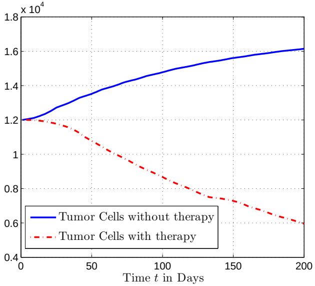
Cancer Res. 59 (1999)

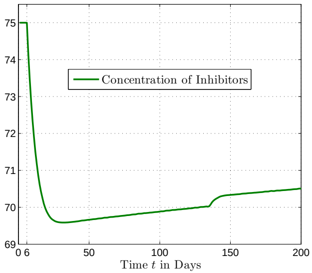
- x endothelial cells,
- u inhibitors dose

$$\begin{aligned}\dot{x} &= -\mu x + S(x,\tau) - I(x,\tau) - Gxu \\ \dot{\tau} &= \tau\psi_\alpha(x,\tau)\end{aligned}$$

with

$$S(x,\tau) \doteq b\tau^\gamma x^{1-\gamma},$$
$$I(x,\tau) \doteq d\tau^{\frac{2}{3}} x$$



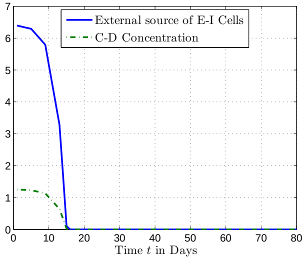


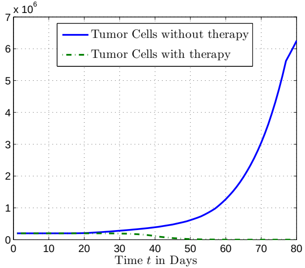
de Pillis et al. model

Math. Biosc. 209 (2007)

- x_1 effector-immune cells,
- x_2 lymphocytes,
- x_3 chemotherapy
- u_1 chemotherapy drugs,
- u_2 external effector-immune cells

$$
\begin{aligned}
\dot{x}_1 &= g\frac{\tau}{h+\tau}x_1 - rx_1 - px_1\tau \\
&\qquad -k_1 x_1 x_3 + s_1 u_1, \\
\dot{x}_2 &= -\delta x_2 - k_2 x_3 x_2 + s_2, \\
\dot{x}_3 &= -\gamma x_3 + u_2, \\
\dot{\tau} &= a\tau(1-b\tau) - c_1 x_1 \tau - k_3 x_3 \tau
\end{aligned}
$$

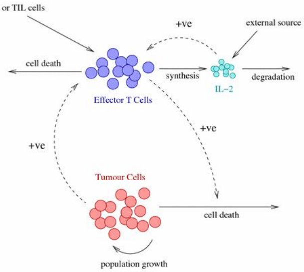




Panetta-Kirschner model

J. Math. Biol. 37(1998)

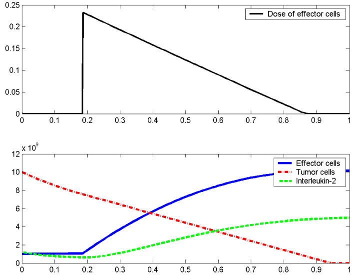
$$\dot{x}_1 = c\tau - \mu_2 x_1 + \frac{p_1 x_1 x_2}{g_1 + x_2} + s_1 u_1$$
$$\dot{x}_2 = \frac{p_2 x_1 \tau}{g_3 + \tau} - \mu_3 x_2 + s_2 u_2$$
$$\dot{\tau} = \tau(r_2(1 - b\tau) - \frac{a x_1}{g_2 + \tau})$$



- x_1 effector cells
- x_2 interleukin
- u_1 source of effector cells
- u_2 source of interleukin

Results

- $\mu_2 = 0.1667, p_1 = 0.6917$
- $g_1 = 0.02, g_2 = 10^{-4}, r_2 = 1$
- $a = 5.5556, b = 1$
- $\mu_3 = 55.5556, p_2 = 27.778, g_3 = 10^{-6}$
- $s_1 = 600$ and $c = 0.1388$
- initial data : $x_0^1 = 1,\ x_0^2 = 1.2, \tau_0 = 10$



Summary

Conclusion

- universal formulas for the protocols
- curability of a cancer depends on its initial stage
- minimality and smoothness of a protocol highlighted
- exponential estimates to control the session duration
- can be applied to other diseases

Open problems

- study more general classes of ODE models
- extend to PDE cancer models : similar results may hold for semilinear parabolic models

Summary

Conclusion

- universal formulas for the protocols
- curability of a cancer depends on its initial stage
- minimality and smoothness of a protocol highlighted
- exponential estimates to control the session duration
- can be applied to other diseases

Open problems

- study more general classes of ODE models
- extend to PDE cancer models : similar results may hold for semilinear parabolic models