Control engineering challenges and results

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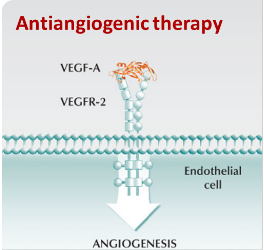
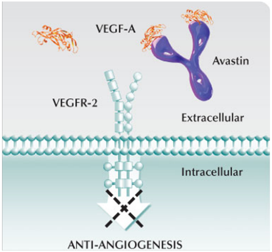
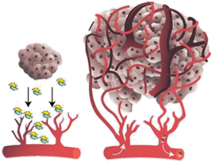
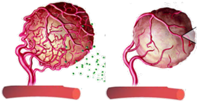
Antiangiogenic therapy









Hahnfeldt model (1999)[1]

$$\dot{x}_1 = -\lambda_1 x_1 \ln\left(\frac{x_1}{x_2}\right)$$
$$\dot{x}_2 = bx_1 - dx_1^{2/3}x_2 - ex_2 u$$

- x_1 is the function of tumor volume
- x_2 is the function of endothelial volume (blood vessels)
- u is the function of inhibitor level in the patient

[1] P. Hahnfeldt et al., Tumor Development under Angiogenic Signaling: A Dynamical Theory of Tumor Growth, Treatment Response, and Postvascular Dormancy, Cancer Researh 59, pp. 4770–4775, 1999

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The minimal model – Differential equation

Linear dynamics expanded with bilinear term:

$$\dot{x}(t) = ax(t) - bx(t)y(t) = (a - by(t))x(t)$$

- x is the function of tumor volume (mm^3)
- y is the inhibitor level in the patient (mg/kg)
- a is the tumor growth rate (1/day)
- b is the inhibition rate (kg/(mg · day)).

The pharmakokinetics of the inhibitor is linear, i.e.

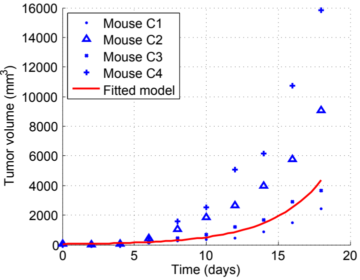
$$\dot{y}(t) = -cy(t) + I(t)$$

- u is the function of inhibitor injection rate (mg/(kg · day))
- c is the clearance of the inhibitor (1/day).

LS estimation

The values of the identified parameters are

- $x(0) = 45.46 \text{ mm}^3$;
- $a = 0.27 \text{ 1/day}$;
- $b = 0.0074 \text{ kg}/(\text{mg} \cdot \text{day})$.



$$x(t) = 45.46 \exp(0.27t - \dots)$$

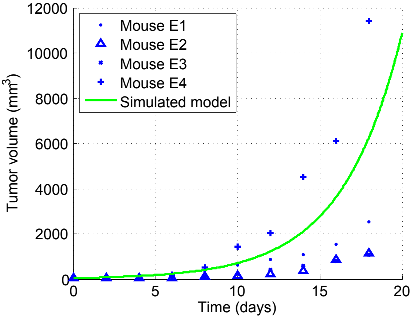
Results without therapy from 2014[c]

$$\begin{aligned} x(t) &= 29020 \exp(0.29788t) \\ &\quad -29010 \exp(0.29789t) \\ &\approx 10 \exp(0.29789t) \end{aligned}$$

[c] J. Sápi et al., CINTI 2014, pp. 443–448

Validation

Mice got injection each day, simulation is carried out with parameters acquired from identification.



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Motivation and control problem

- The control input in most physiological systems in nonnegative.
- Most controllers can not ensure that the input is positive without using saturation.
- Saturation distorts the model and may lead to unexpected behavior.
- Moreover, physiological models are usually nonlinear.

Ensuring positive input

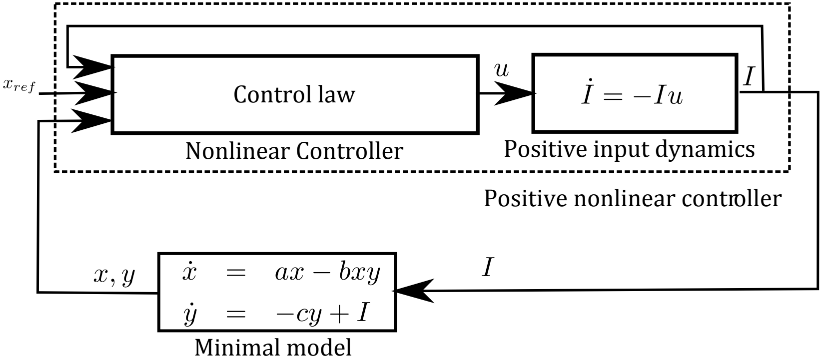
$$\begin{aligned}\dot{x}(t) &= ax(t) - bx(t)y(t) \\ \dot{y}(t) &= -cy(t) + I(t)\end{aligned}$$

Denote the rate of injection (input of the physiological system) by I, and introduce the fictive input dynamics

$$\dot{I}(t) = -I(t)u(t)$$

and let u be the new (fictive) input. The new differential equation ensures that $I(t)$ is positive for all $t > 0$ if $I(0) > 0$. The fictive input u can be negative.

Ensuring positive input



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Path tracking control

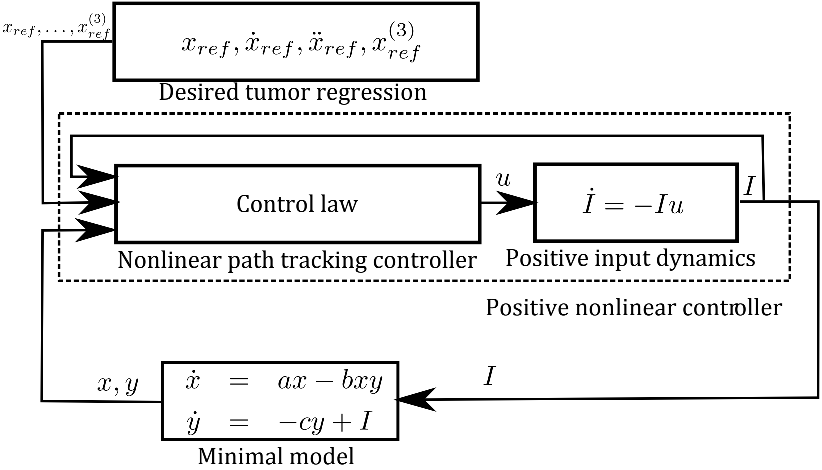
We apply the control law

$$u = \frac{k_0(x_{ref} - h) + k_1(\dot{x}_{ref} - L_f h) + k_2(\ddot{x}_{ref} - L_f^2 h) + x_{ref}^{(3)} - L_f^3 h}{bxI}.$$

with

$$\begin{aligned} h &= x \\ f &= \begin{pmatrix} ax - bxy \\ -cy + I \\ 0 \end{pmatrix} \\ L_f h &= h' f \\ L_f^2 h &= (L_f h)' f \\ L_f^3 h &= (L_f^2 h)' f \end{aligned}$$

Path tracking control



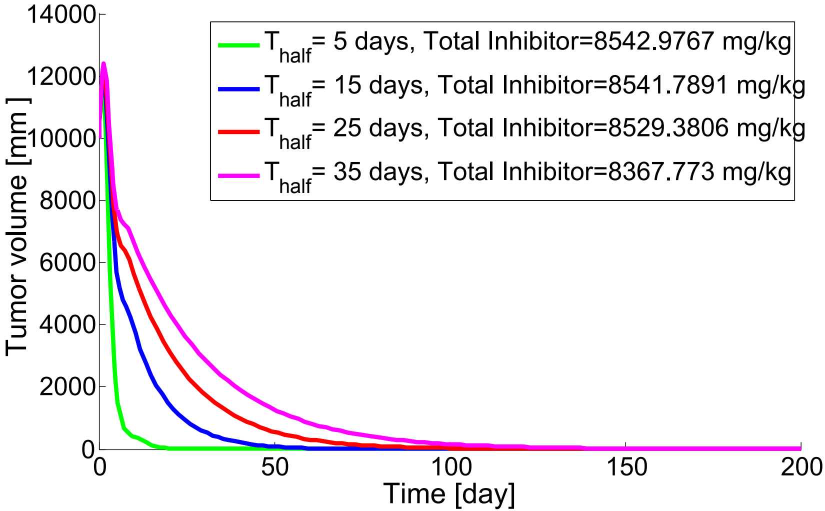
Results

The reference tumor volume in our simulations is

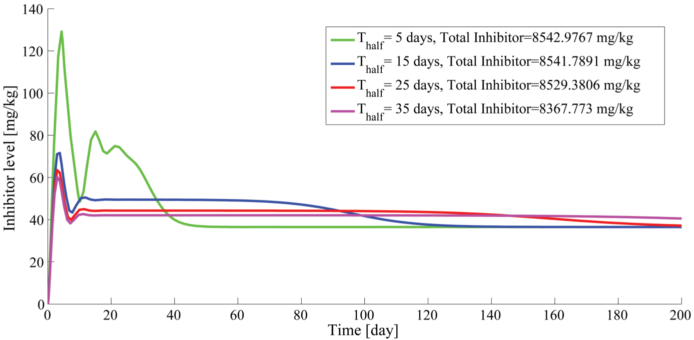
$$x_{ref} = (x(0) - 1)e^{-t/(\ln(2)T_{half})}$$

and its derivatives. We analyze the results acquired with different T_{half} half-times.

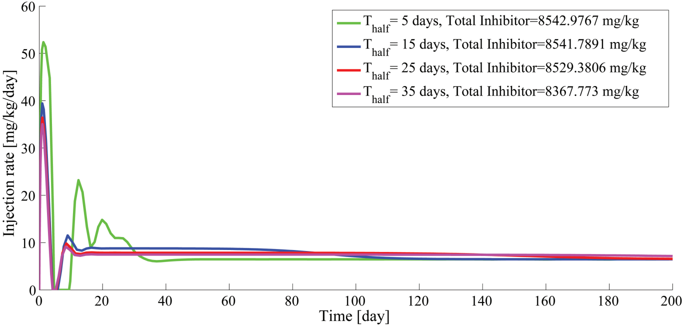
Tumor volume



Inhibitor level



Injection rates



Thank you for your attention!

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