A rák megszelítítése irányításelméleti módszerekkel
Taming cancer using control engineering methods

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Matematikai modellalkotás szeminárium, BME

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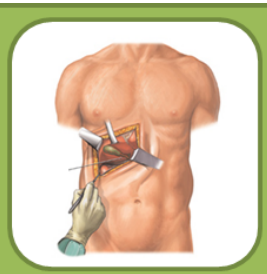
Main concept of the research

Medical knowledge




cancer treatments — general protocols

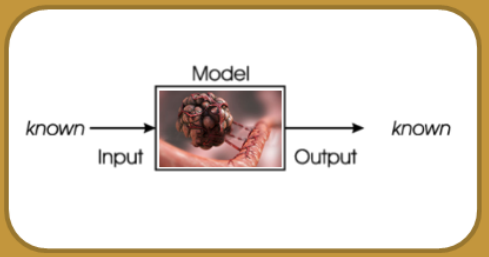
Healing of the patient

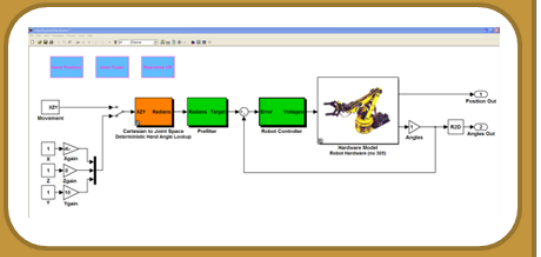
find more effective solutions in healing

individual treatment for the patient

model identification — model-based protocols

Engineering knowledge





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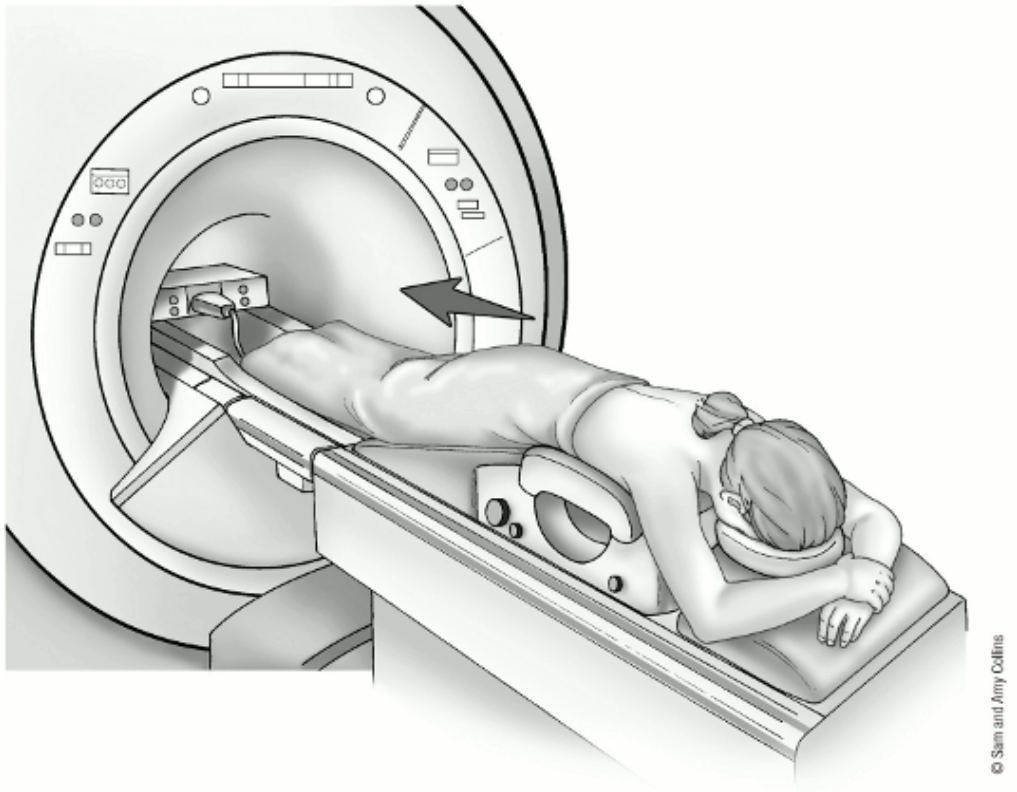
The treatment scenario

The patient visits the doctor in fixed intervals. We will call this interval the sampling time, denote it by T_s and measure it in days.

The treatment scenario

At each visit, the doctor examines the patient, and we suppose that as a result all internal states (tumor volume, endothelial volume, inhibitor serum level) become available.



The treatment scenario

The doctor defines the desired tumor volume for the next investigation. The minimal amount of drug injection that is required to reach the desired tumor volume is calculated using the tumor growth model and the information acquired from the measurements in the previous step using an optimization algorithm.

The optimization problem

- At the kth investigation (kth step) we know the internal states of the system $x_1[k] := x_1(kT_s)$, $x_2[k] := x_2(kT_s)$, and $g[k] := g(kT_s)$.
- The desired tumor volume for the next step is denoted by $x_{1,d}[k+1]$.
- We are looking for the minimal amount of injection $u[k]$ such that the tumor volume in the next step is less than or equal to the desired tumor volume, i.e. $x_1[k+1] \leq x_{1,d}[k+1]$.

The optimization algorithm

Input: The initial values $x_1[k]$, $x_2[k]$ and $g[k]$. The TOL accuracy of the solution. The desired tumor volume $x_{1,d}[k+1]$. The maximal drug injection $UMAX$.
Result: The minimal drug dosage $u[k]$ that is required to reach the desired tumor volume in the next step.

The optimization algorithm

Let $u_{\max} = UMAX$ and $u_{\min} = 0$
while $u_{\max} - u_{\min} > TOL$ **do**
  $u = (u_{\max} - u_{\min})/2$ Calculate the tumor volume in the next time instant $(k+1)T_s$ by solving the initial value problem on time interval $[kT_s, (k+1)T_s]$ defined by the model with initial values $x_1[k]$, $x_2[k]$, $g[k] + u$; denote it by $x_1[k+1]$
  if $x_1[k+1] > x_{1,d}[k+1]$ **then**
    $u_{\min} := u$
  else
    $u_{\max} := u$
  end
end

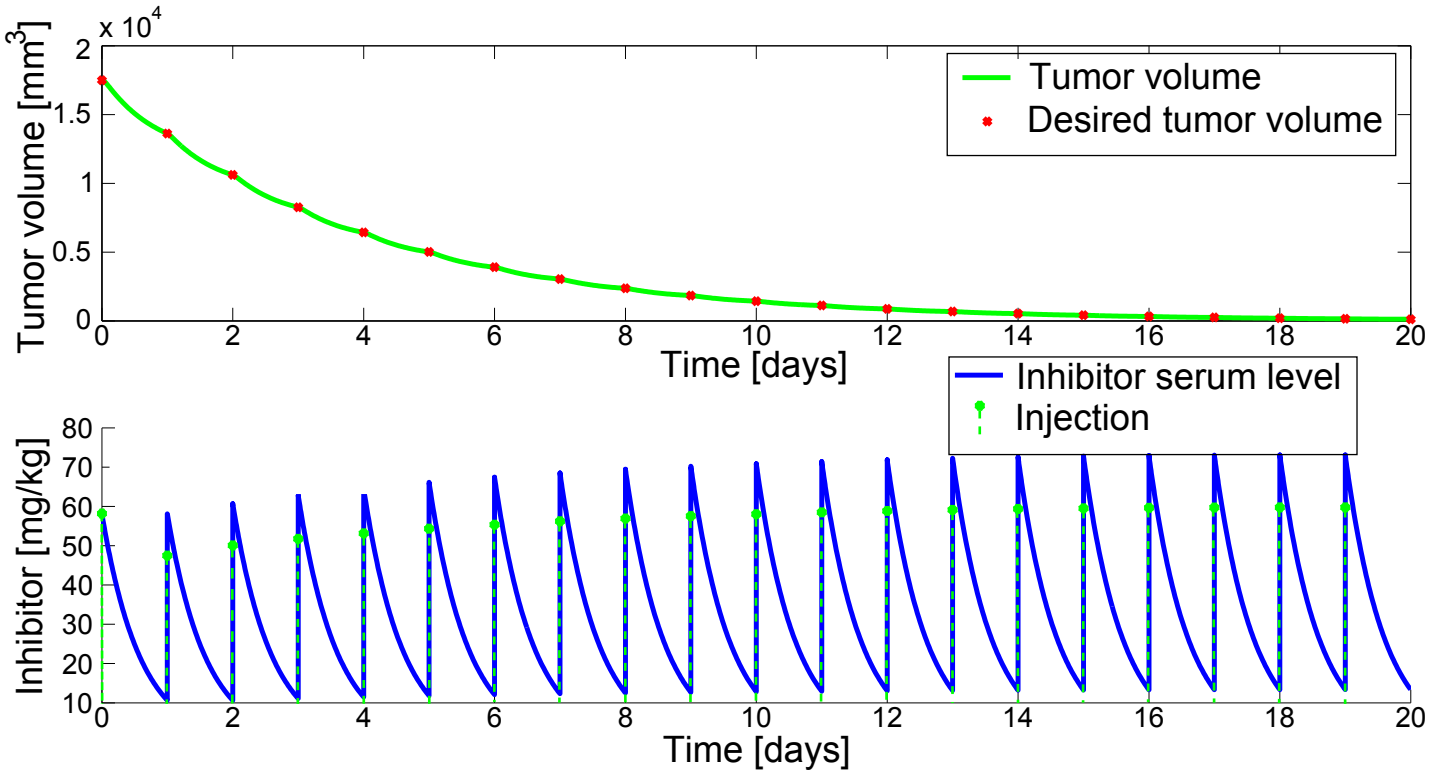
Optimal solution

The previous algorithm is a binary search algorithm, thus it only works if the model output is monotonous in the input.

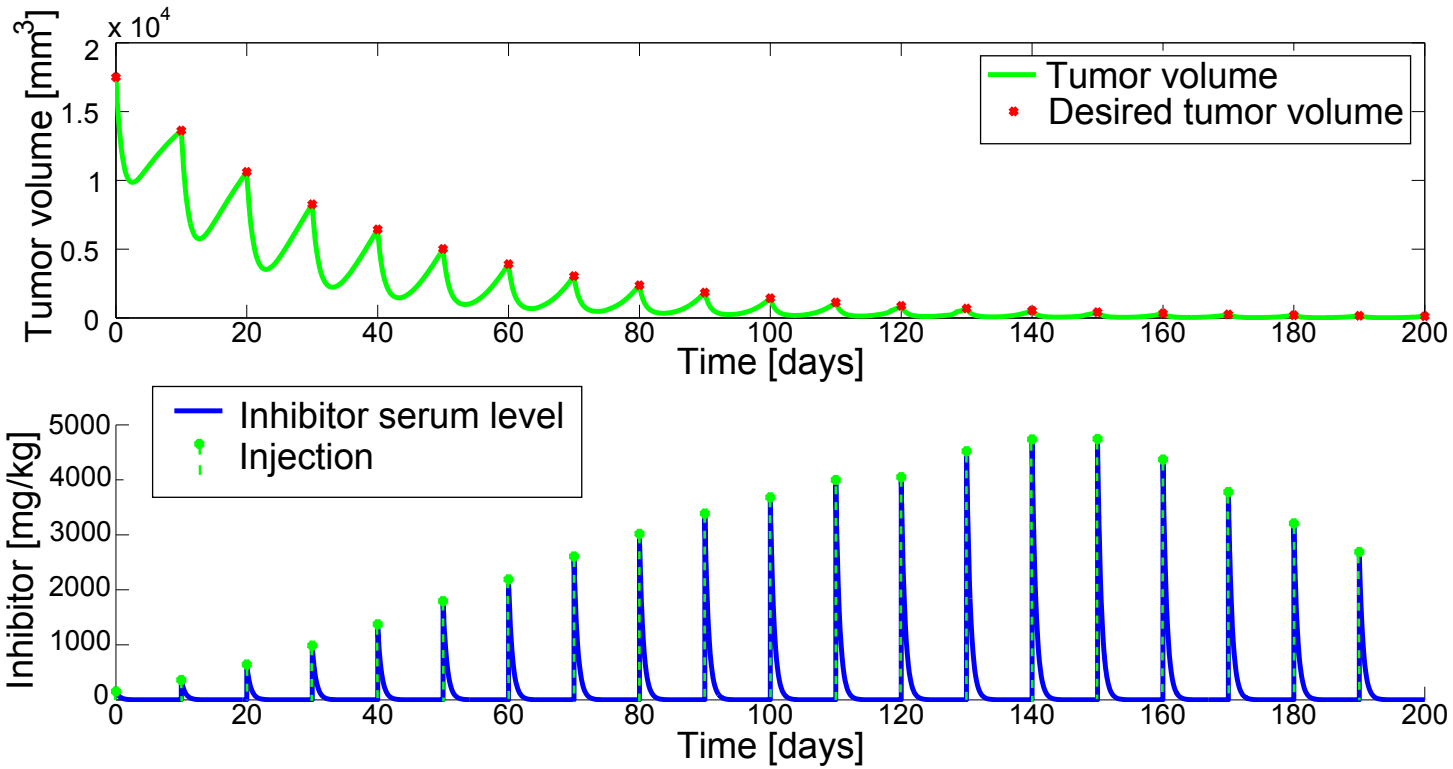
Theorem

The output of the Hahnfeldt-model with linear pharmakokinetics is monotonous in the input.

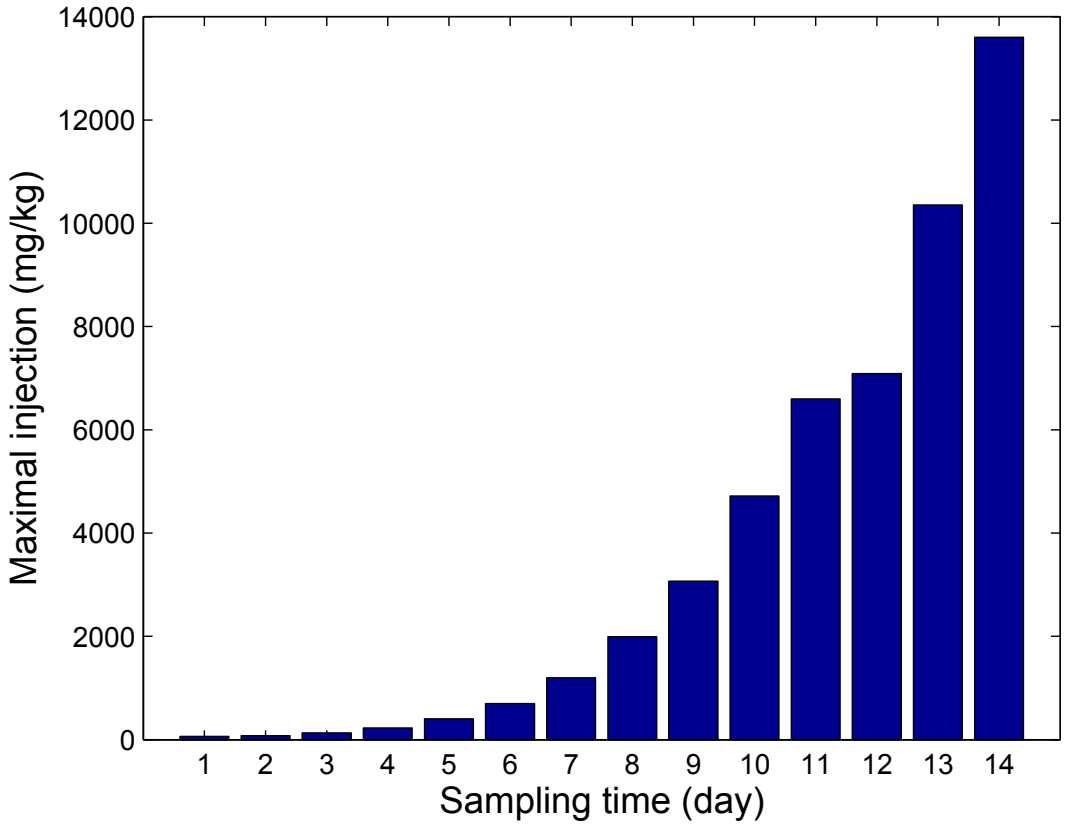
$T_s = 1$ day, $x_{1,d}[k] = x_1(0)\exp(-4k)$



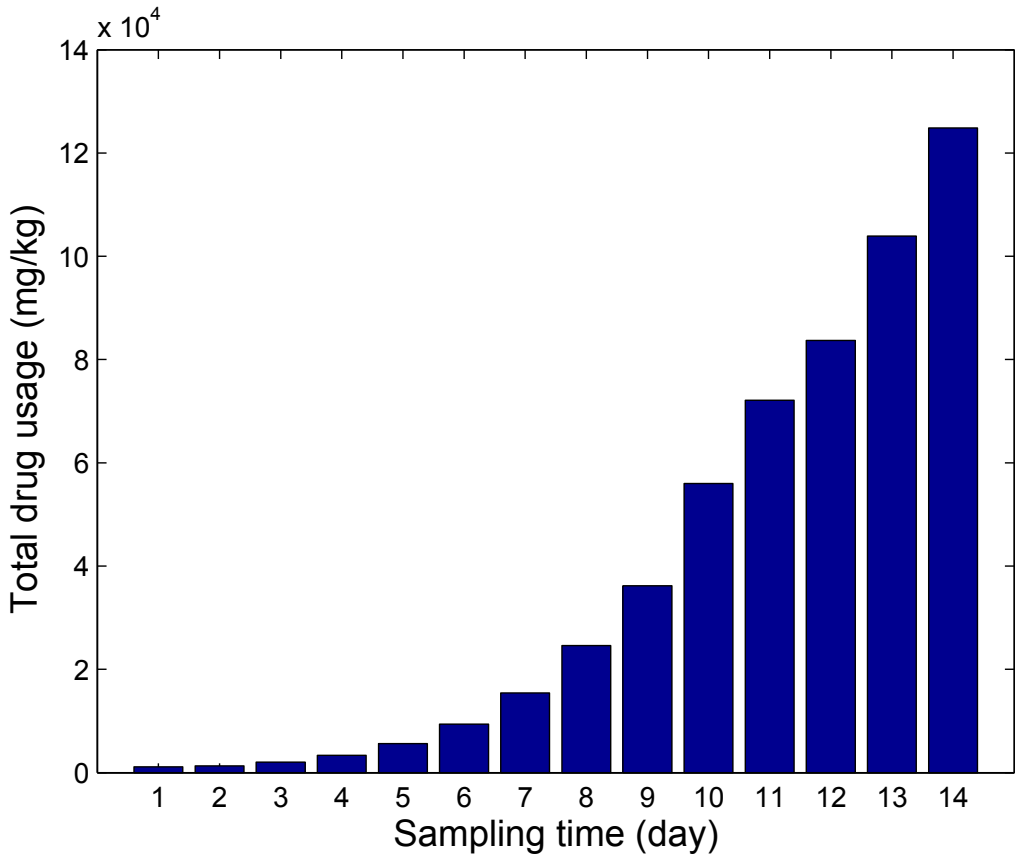
$T_s = 10$ day, $x_{1,d}[k] = x_1(0)\exp(-4k)$



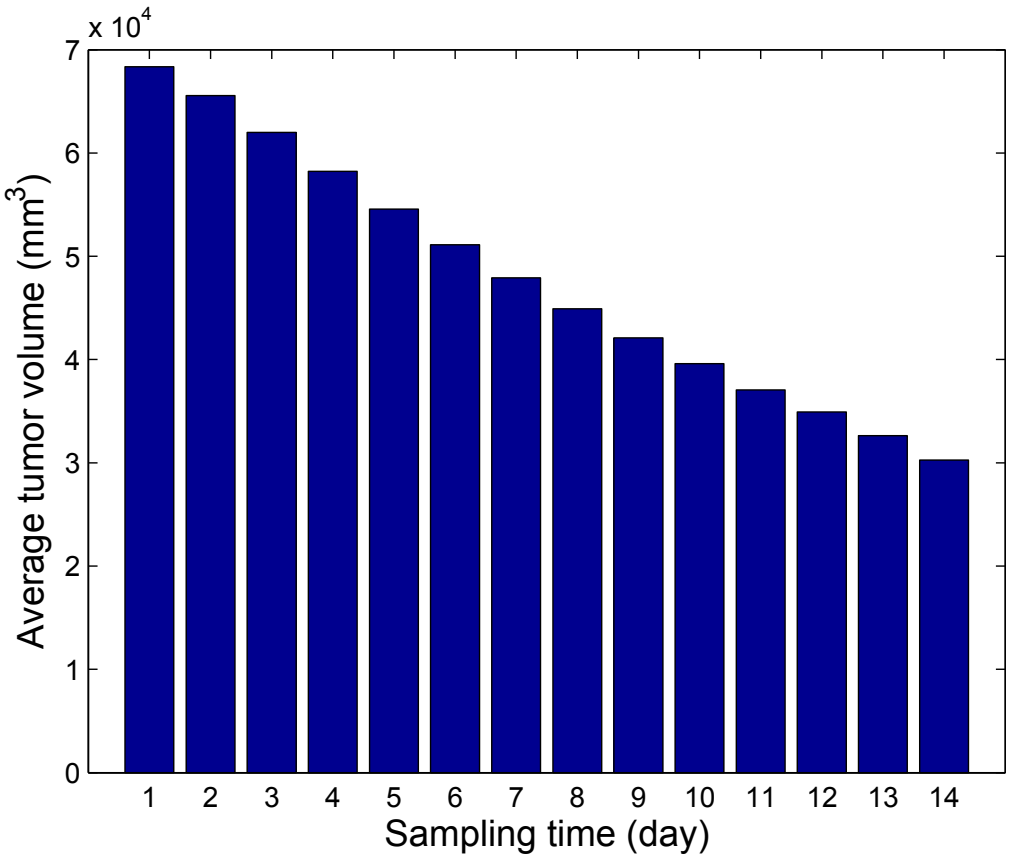
Maximal injection vs. Sampling Time



Total inhibitor vs. Sampling Time



Average tumor volume vs. Sampling Time



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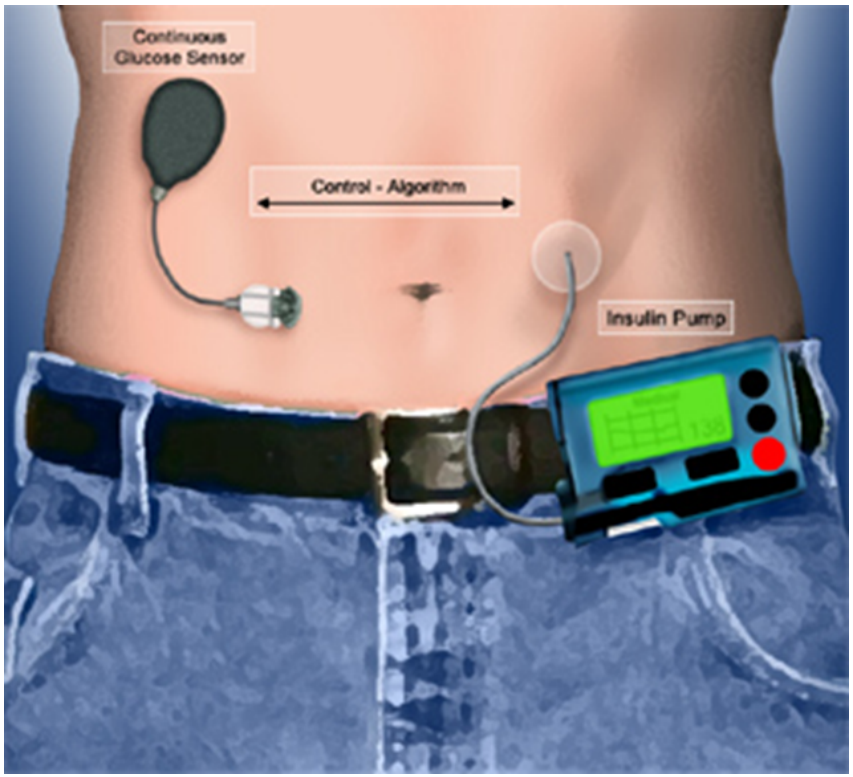
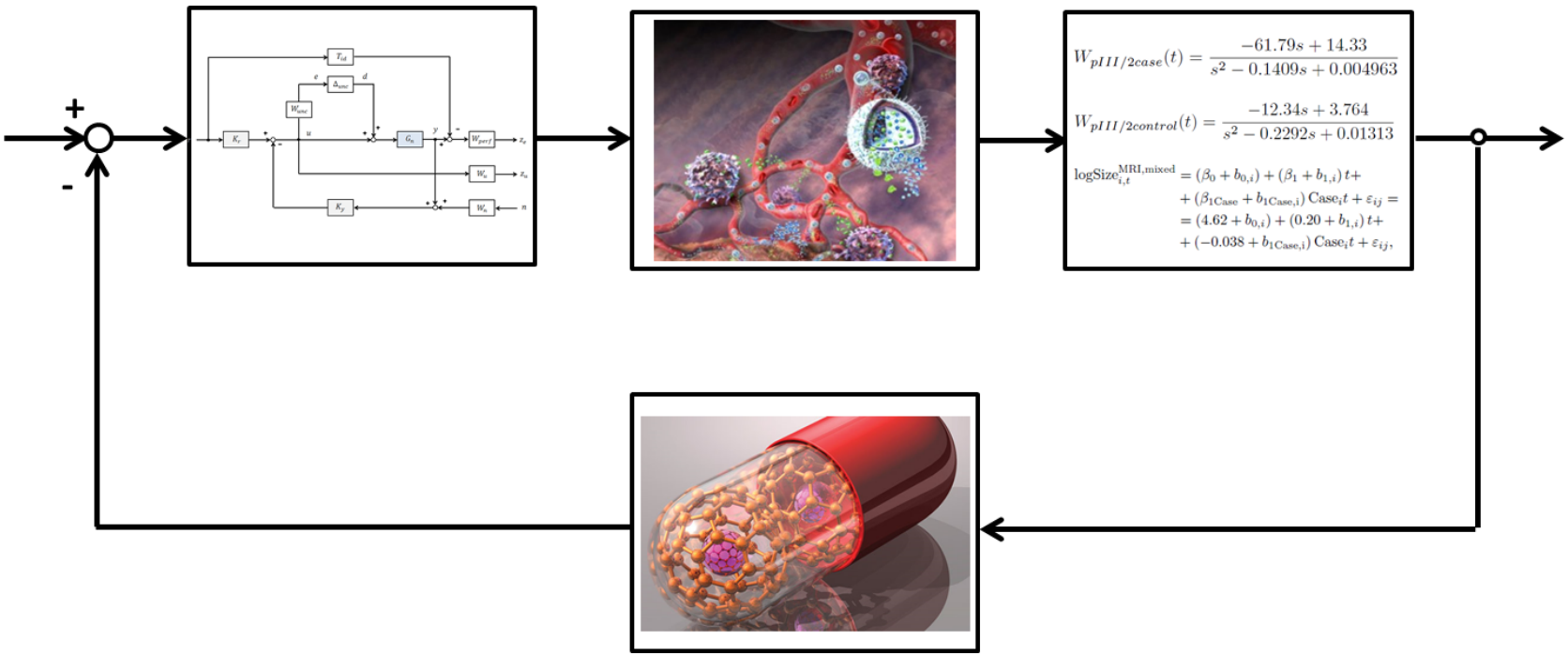
Artificial pancreas



Future concept



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Modeling the effect of bevacizumab

$$
\begin{aligned}
\dot{x}_1 &= a x_1 - n x_1 - b \frac{x_1 x_3}{ED_{50} + x_3} \\
\dot{x}_2 &= n x_1 + b \frac{x_1 x_3}{ED_{50} + x_3} \\
\dot{x}_3 &= -c \frac{x_3}{K_B + x_3} - b_\kappa \frac{x_1 x_3}{ED_{50} + x_3} + u,
\end{aligned}
$$

- x_1 volume of the proliferating tumor cells [mm^3];
- x_2 volume of the necrotic tumor cells [mm^3];
- x_3 serum level of the drug [mg/ml];
- $y = x_1 + x_2$ measured tumor volume [mm^3];
- u drug injection rate [mg/ml/day].

Modeling the effect of bevacizumab: tumor proliferation

Tumor proliferation (mass-action kinetics)

$$X_1 \xrightarrow{a} 2X_1$$

$$\begin{aligned}
\dot{x}_1 &= ax_1 - nx_1 - b\frac{x_1 x_3}{ED_{50} + x_3} \\
\dot{x}_2 &= nx_1 + b\frac{x_1 x_3}{ED_{50} + x_3} \\
\dot{x}_3 &= -c\frac{x_3}{K_B + x_3} - b_\kappa \frac{x_1 x_3}{ED_{50} + x_3} + u,
\end{aligned}$$

Modeling the effect of bevacizumab: tumor necrosis

Tumor necrosis (mass-action kinetics)

$$X_1 \xrightarrow{n} X_2$$

$$\begin{aligned}
\dot{x}_1 &= ax_1 - nx_1 - b\frac{x_1 x_3}{ED_{50} + x_3} \\
\dot{x}_2 &= nx_1 + b\frac{x_1 x_3}{ED_{50} + x_3} \\
\dot{x}_3 &= -c\frac{x_3}{K_B + x_3} - b_\kappa \frac{x_1 x_3}{ED_{50} + x_3} + u,
\end{aligned}$$

Modeling the effect of bevacizumab: effect of the drug

Effect of the drug (Michaelis-Menten kinetics), pharmacodynamics

$$X_1 + X_3 \xrightarrow{b} X_2$$

$$\begin{aligned}
\dot{x}_1 &= a x_1 - n x_1 - b \frac{x_1 x_3}{ED_{50} + x_3} \\
\dot{x}_2 &= n x_1 + b \frac{x_1 x_3}{ED_{50} + x_3} \\
\dot{x}_3 &= -c \frac{x_3}{K_B + x_3} - b_\kappa \frac{x_1 x_3}{ED_{50} + x_3} + u,
\end{aligned}$$

Modeling the effect of bevacizumab: depletion of the drug

Depletion of the drug (Michaelis-Menten kinetics), mixed-order pharmacokinetics

$$X_3 \xrightarrow{c} 0$$

$$\begin{aligned}
\dot{x}_1 &= a x_1 - n x_1 - b \frac{x_1 x_3}{ED_{50} + x_3} \\
\dot{x}_2 &= n x_1 + b \frac{x_1 x_3}{ED_{50} + x_3} \\
\dot{x}_3 &= -c \frac{x_3}{K_B + x_3} - b_\kappa \frac{x_1 x_3}{ED_{50} + x_3} + u,
\end{aligned}$$

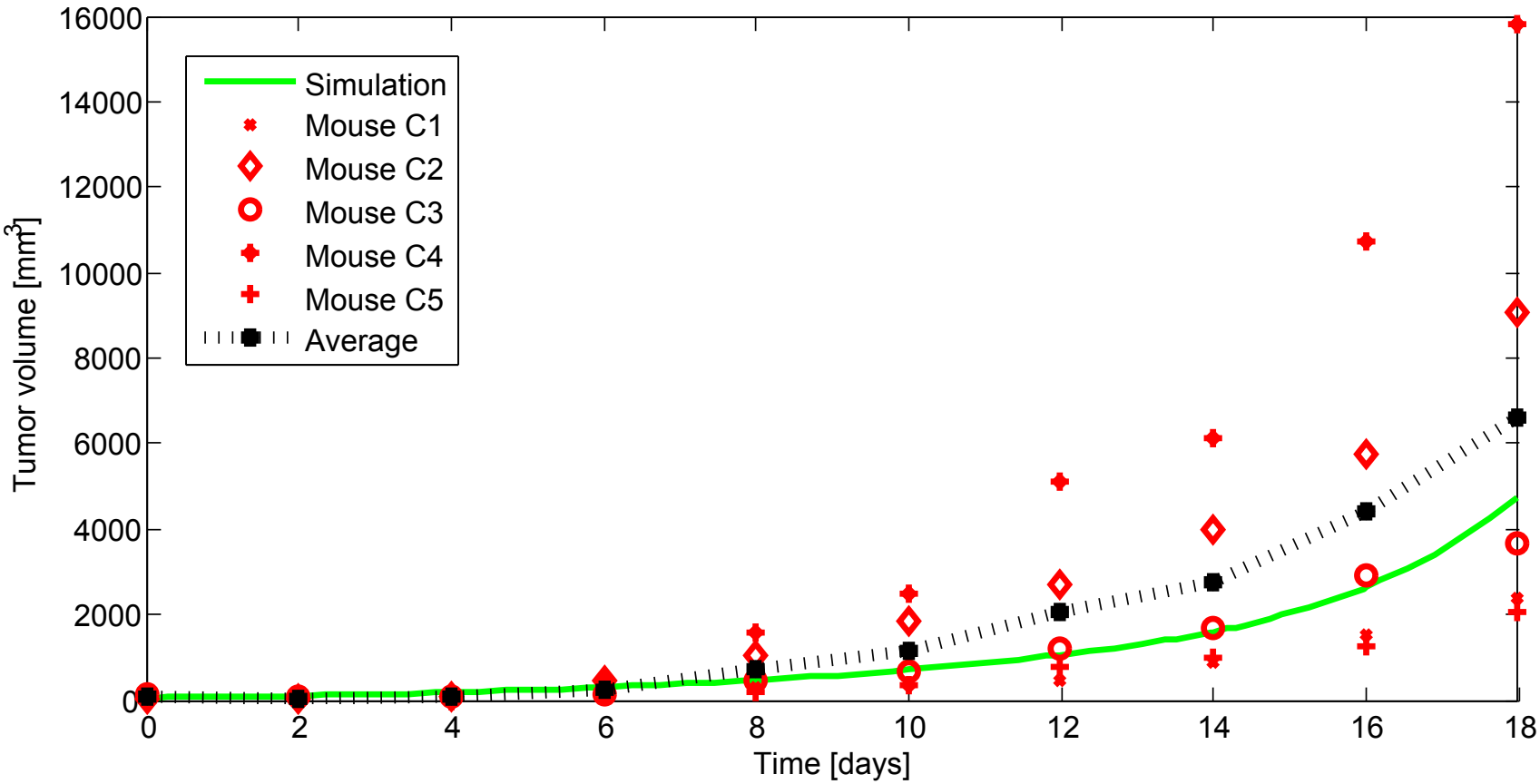
Modeling the effect of bevacizumab: the input

The input of the model increases the drug serum level

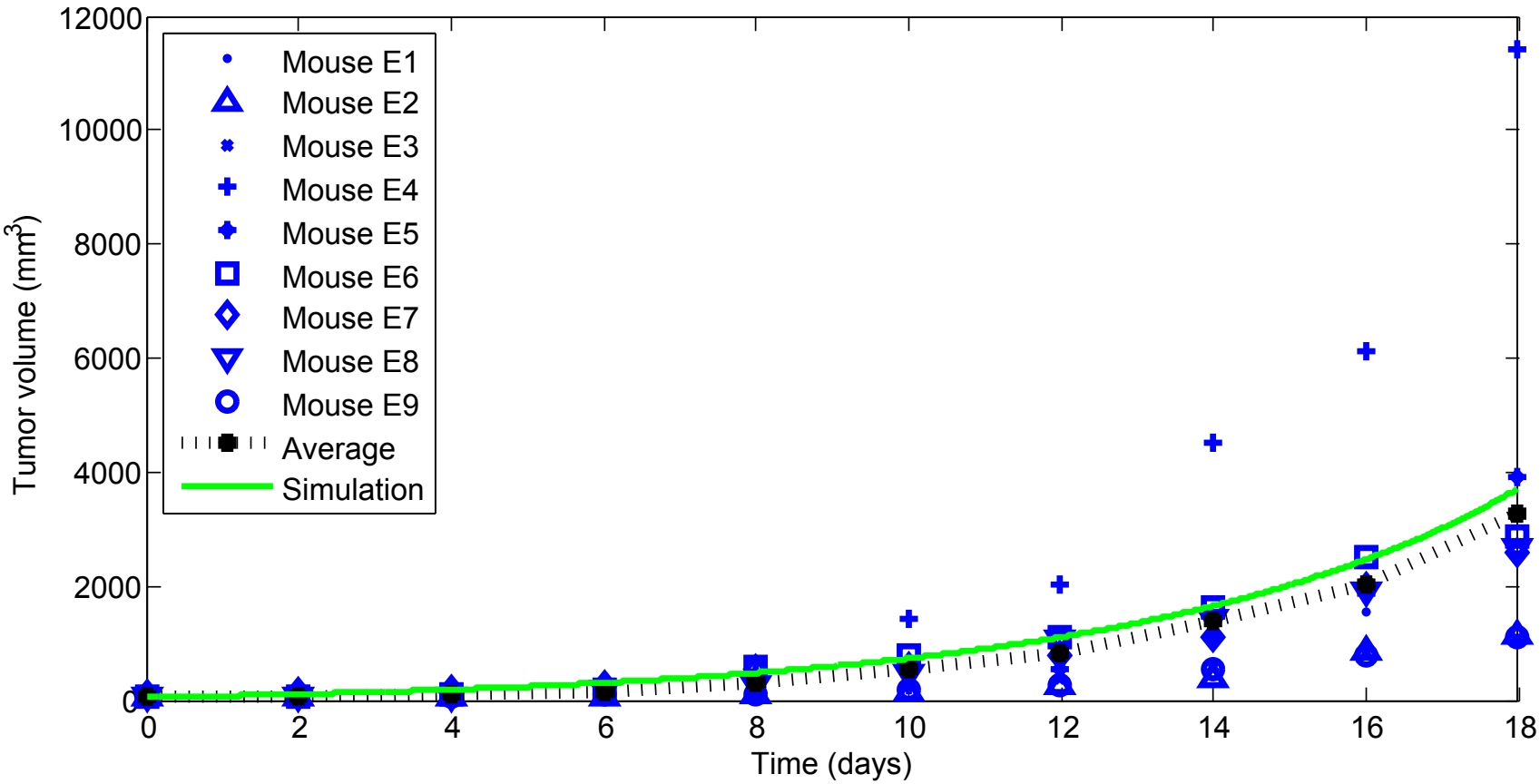
$$u \geq 0$$

$$\begin{aligned}
\dot{x}_1 &= a x_1 - n x_1 - b \frac{x_1 x_3}{ED_{50} + x_3} \\
\dot{x}_2 &= n x_1 + b \frac{x_1 x_3}{ED_{50} + x_3} \\
\dot{x}_3 &= -c \frac{x_3}{K_B + x_3} - b_\kappa \frac{x_1 x_3}{ED_{50} + x_3} + u,
\end{aligned}$$

Model validation and measurements (one injection)



Model validation and measurements (daily injections)



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Model equations

Model reduction

$$\begin{aligned}
\dot{x}_1 &= a x_1 - n x_1 - b \frac{x_1 x_3}{ED_{50} + x_3} \\
\dot{x}_2 &= n x_1 + b \frac{x_1 x_3}{ED_{50} + x_3} \\
\dot{x}_3 &= -c \frac{x_3}{K_B + x_3} - b_\kappa \frac{x_1 x_3}{ED_{50} + x_3} + u,
\end{aligned}$$

The second equation can be omitted since the other equations do not depend on x_2.

Model equations, closed-loop system

Planar system

$$\begin{aligned}\dot{x}_1 &= ax_1 - nx_1 - b\frac{x_1 x_3}{ED_{50} + x_3} \\ \dot{x}_3 &= -c\frac{x_3}{K_B + x_3} - b_\kappa \frac{x_1 x_3}{ED_{50} + x_3} + u,\end{aligned}$$

Closed-loop system

The applied control law is state feedback, i.e. $u = k_1 x_1 - k_3 x_3$.
Thus, the model of the closed-loop system is

$$\begin{aligned}\dot{x}_1 &= ax_1 - nx_1 - b\frac{x_1 x_3}{ED_{50} + x_3} \\ \dot{x}_3 &= -c\frac{x_3}{K_B + x_3} - b_\kappa \frac{x_1 x_3}{ED_{50} + x_3} + k_1 x_1 - k_3 x_3.\end{aligned}$$

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Equilibria of the closed-loop system

First equilibrium

$$x_1^* = 0, x_3^* = 0.$$

The eigenvalues of the linearized system are

$$\begin{aligned} \lambda_1 &= -ED_{50}\frac{c + k_3 K_B}{K_B} < 0 \\ \lambda_2 &= ED_{50}(a - n). \end{aligned}$$

If $a - n > 0$, then the tumor grows (the growth rate is larger than the necrotic rate), in this case this point is a saddle (the tumor grows, the drug depletes).
If $a - n < 0$, then the tumor shrinks (the growth rate is smaller than the necrotic rate), in this case this point is a stable node.

Equilibria of the closed-loop system

Second equilibrium

$$x_1^* = 0, x_3^* = -\frac{c + k_3 K_B}{k_3} < 0.$$

This equilibrium is physiologically unfeasible, since the inhibitor serum level can not be negative.

Equilibria of the closed-loop system

Third equilibrium

$$x_3^* = -\frac{ED50(a-n)}{a-b-n}.$$

The physiologically interesting case is when $a - n > 0$, i.e. the tumor does not heal spontaneously. The equilibrium point for x_3^* is positive if and only if

$$a - b - n < 0.$$

It has been shown earlier that this is the condition for the drug to be effective against tumor.

Equilibria of the closed-loop system

Third equilibrium

$$x_1^* = \frac{x_{1,n}}{x_{1,d}}$$

with

$$\begin{aligned} x_{1,n} &= bED_{50}(a-n)\left(b(c+k_3K_B)\right. \\ &\quad -a(c+k_3(-ED_{50}+K_B)) \\ &\quad \left.+(c-ED_{50}k_3+k_3K_B)n\right) \\ x_{1,d} &= (a-b-n)(ab_\kappa - bk_1 - b_\kappa n)\cdot \\ &\quad \cdot(a(ED_{50}-K_B)+bK_B \\ &\quad +(-ED_{50}+K_B)n). \end{aligned}$$

Equilibria of the closed-loop system

Third equilibrium

Taking into account the previous conditions, this equilibrium is positive if either

$$\begin{aligned} k_1 &> b_\kappa \frac{a-n}{b} \\ k_3 &> c \frac{a-b-n}{aED_{50} - aK_B + bK_B - ED_{50}n + K_B n} \end{aligned}$$

or

$$\begin{aligned} k_1 &< b_\kappa \frac{a-n}{b} \\ k_3 &< c \frac{a-b-n}{aED_{50} - aK_B + bK_B - ED_{50}n + K_B n}. \end{aligned}$$

Equilibria of the closed-loop system

Third equilibrium

If the Jacobian J is a 2×2 matrix, then the eigenvalues of the Jacobian are

$$\lambda_{1,2} = \frac{\mathrm{Tr}(J) \pm \sqrt{\mathrm{Tr}(J)^2 - 4\,\mathrm{Det}(J)}}{2}.$$

In order to have eigenvalues with negative real parts (i.e., to guarantee that the equilibrium point is stable) the parameters should be chosen such that

$$\begin{aligned} \mathrm{Tr}(J) &< 0 \\ \mathrm{Det}(J) &> 0. \end{aligned}$$

Equilibria of the closed-loop system

Third equilibrium

The equilibrium is stable iff

$$\begin{aligned} k_1 &> b_\kappa \frac{a-n}{b} \\ k_3 &> \frac{\varphi}{\omega} \end{aligned}$$

$$\begin{aligned} \varphi &= c(-a+b+n)^2(a^2 b_\kappa(ED_{50}-K_B) \\ &\quad -b^2 k_1 K_B + 2ab_\kappa(-ED_{50}+K_B)n \\ &\quad +b_\kappa(ED_{50}-K_B)n^2) \\ \omega &= (a(ED_{50}-K_B)+bK_B \\ &\quad +(-ED_{50}+K_B)n)^2(a^2 b_\kappa \\ &\quad +b^2 k_1 - 2ab_\kappa n + b_\kappa n^2). \end{aligned}$$

Equilibria of the closed-loop system

Decreasing the third equibrium tumor volume

$$x_1^* = \frac{x_{1,n}}{x_{1,d}}$$

$$\begin{aligned} \partial_{k_3} x_{1,n} &= bED_{50}(a-n)(bK_B - a(-ED_{50}+K_B) \\ &\quad +(-ED_{50}+K_B)n) > 0 \end{aligned}$$

Decreasing k_3 decreases equilibrium tumor volume, however, the closed-loop system may become unstable.

Control input

$$u = k_1 x_1 - k_3 x_3.$$

Decreasing k_3 results in increasing control input.

Equilibria of the closed-loop system

Decreasing the third equibrium tumor volume

$$x_1^* = \frac{x_{1,n}}{x_{1,d}}$$

$$\begin{aligned} \partial_{k_1} x_{1,d} &= b(-a+b+n)(a(ED_{50}-K_B)+bK_B \\ &\quad +(-ED_{50}+K_B)n) > 0 \end{aligned}$$

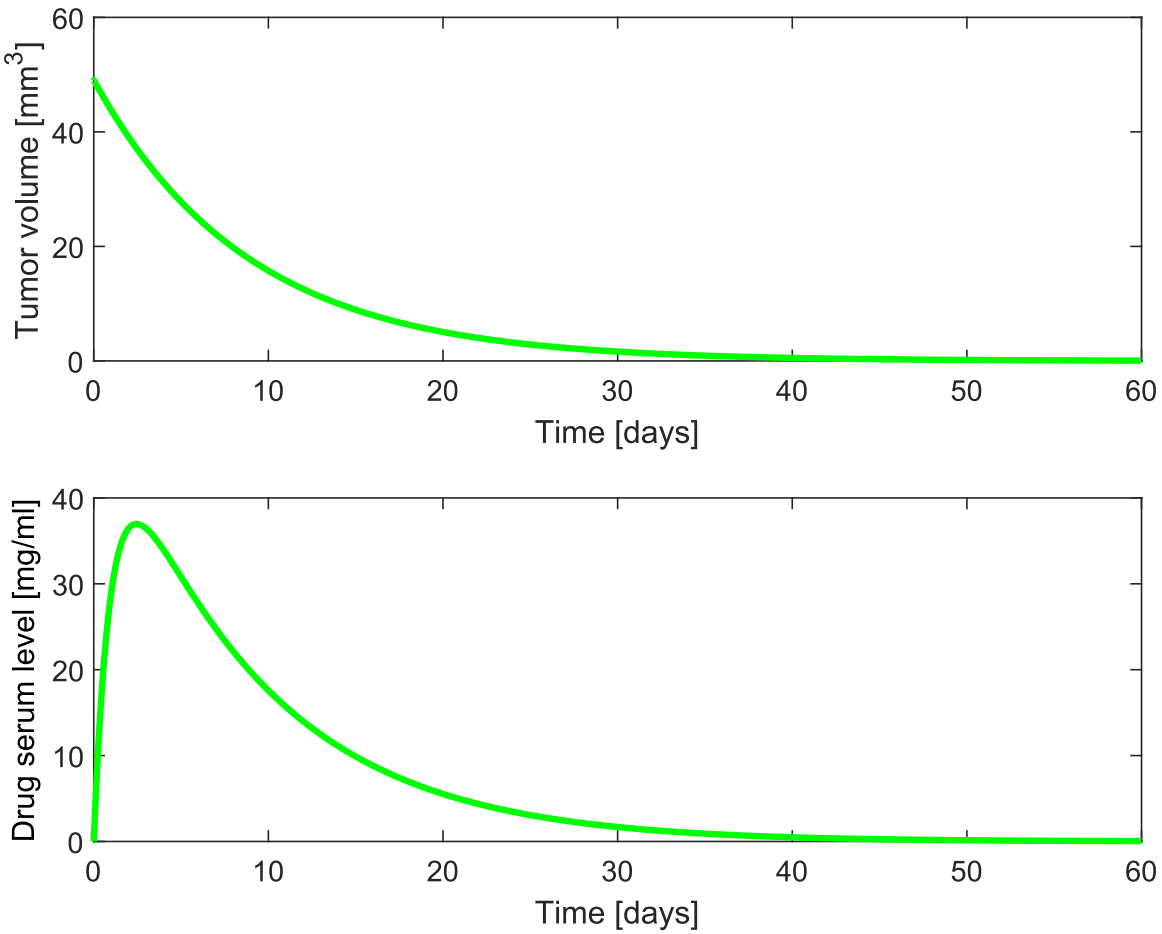
Increasing k_1 means decreasing equilibrium tumor volume, no conflict with stability.

Control input

$$u = k_1 x_1 - k_3 x_3.$$

Increasing k_1 means increasing control input.

Equilibria of the closed-loop system



Thank you for your attention!

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