10-year jubilee of the European Research Council's ERC Starting and Advanced Grant program

2017.03.03.

Engineering methods for cancer treatment

Dr. Johanna Sájevicsné Sápi

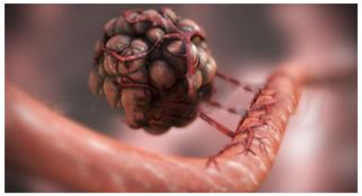
Óbuda University
Research and Innovation Center of Óbuda University
Physiological Controls Research Center

Physiological Controls Research Center

European Research Council

Contents

Concept of the research



Physiological and pathophysiological knowledge

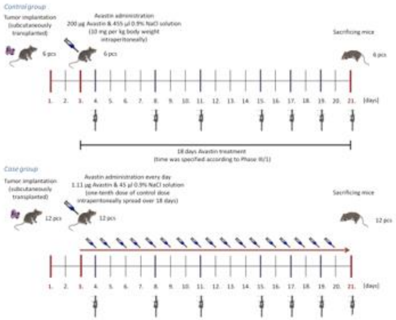
Hahnfeldt model

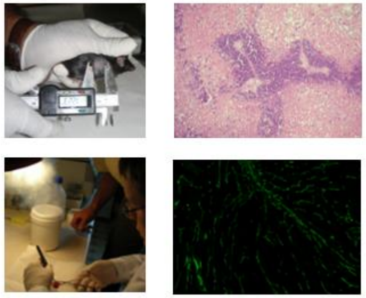
$$V' = -\lambda_1 V \cdot ln\left(\frac{V}{K}\right)$$

$$K' = -\lambda_2 K + bV - dKV^{2/3} - eKg(t)$$

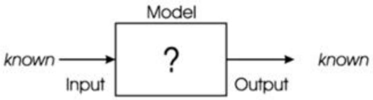
$$g(t) = \int_0^t c(t')\exp(-clr(t-t'))\,dt'$$

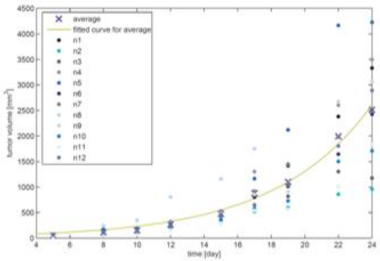
Animal experiments





Tumor growth model identification

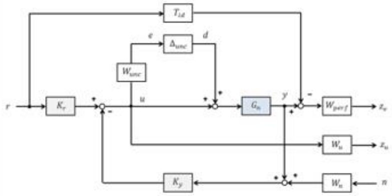


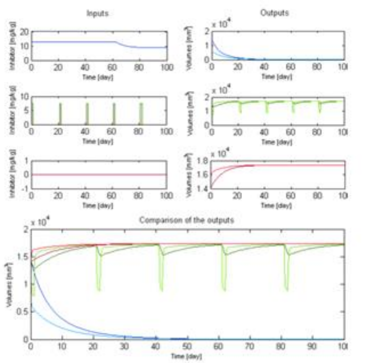


$$W_{pIII/2case}(t) = \frac{-61.79s + 14.33}{s^2 - 0.1409s + 0.004963}$$

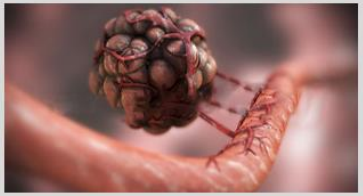
$$W_{pIII/2control}(t) = \frac{-12.34s + 3.764}{s^2 - 0.2292s + 0.01313}$$

Controller design and simulations





Concept of the research



Physiological and pathophysiological knowledge

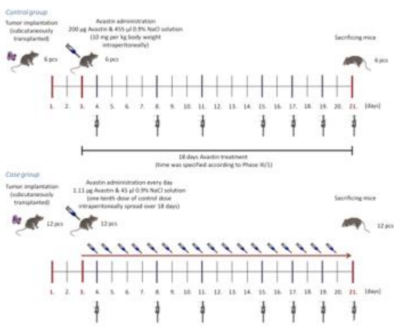
Hahnfeldt model

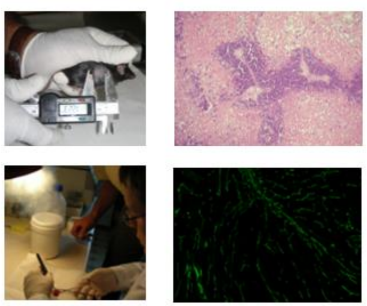
$$V' = -\lambda_1 V \cdot \ln\left(\frac{V}{K}\right)$$

$$K' = -\lambda_2 K + bV - dKV^{2/3} - eKg(t)$$

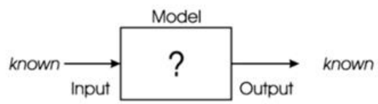
$$g(t) = \int_0^t c(t')\exp(-clr(t-t'))\,dt'$$

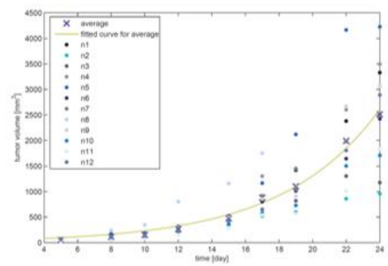
Animal experiments





Tumor growth model identification

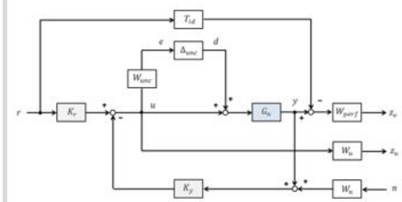


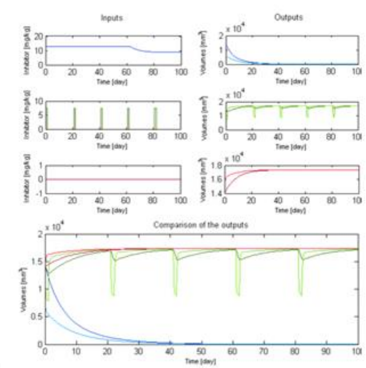


$$W_{pIII/2case}(t) = \frac{-61.79s + 14.33}{s^2 - 0.1409s + 0.004963}$$

$$W_{pIII/2control}(t) = \frac{-12.34s + 3.764}{s^2 - 0.2292s + 0.01313}$$

Controller design and simulations

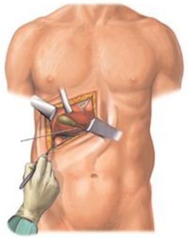




1. Physiological and pathophysiological knowledge
2. Previously investigated tumor growth model (Hahnfeldt model)
3. Controller design and simulations for Hahnfeldt model
4. Animal experiments
5. Tumor growth model identification
6. Controller design and simulations for the new tumor growth model

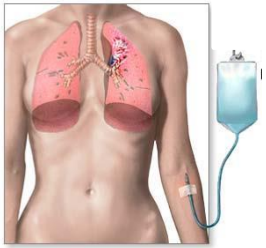
Cancer treatments

Surgical oncology



- the tumor cells can be totally removed (zero-order kinetics)
- tumor can be recurrent in many cases

Chemotherapy

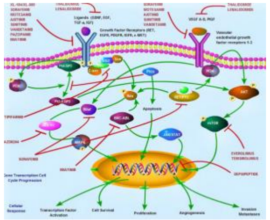


- uses drugs to destroy cancer cells
- acts in general ways (by killing rapidly dividing cells)
- have many side effects
- tumor cells can become resistant to chemotherapy drugs

Radiotherapy

- destroy cancer cells with radiation
- acts in general ways (by killing rapidly dividing cells)
- have many side effects

Targeted molecular therapies (TMTs)

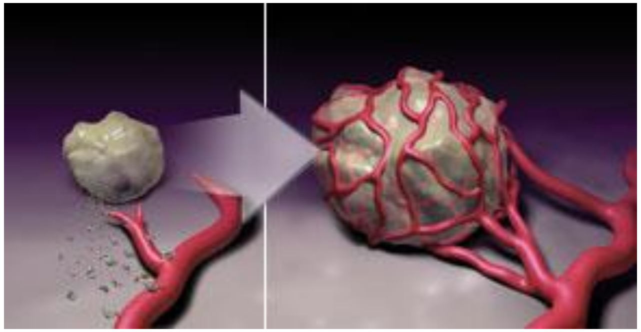


- fight specifically against different cancer mechanisms
- can be more effective and have limited side effects

Antiangiogenic therapy

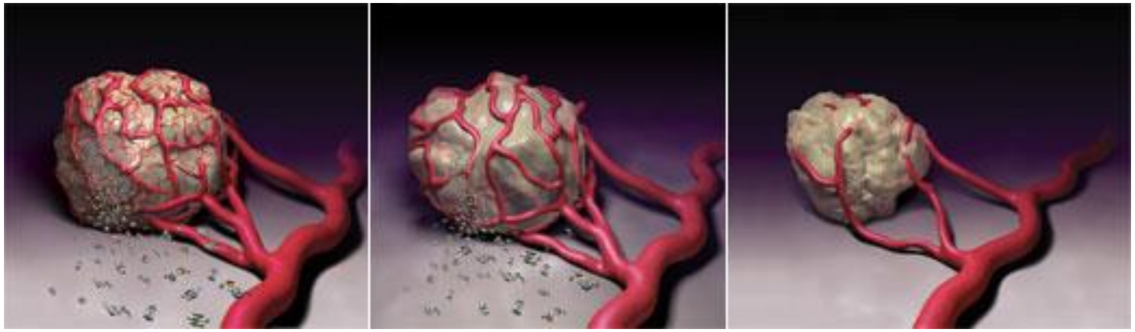
Tumor vasculogenesis

- start of the proliferation → avascular nodule (dormant)
- limitation of oxygen and nutrients → tumor development stops
- angiogenic switch → exponential tumor growth



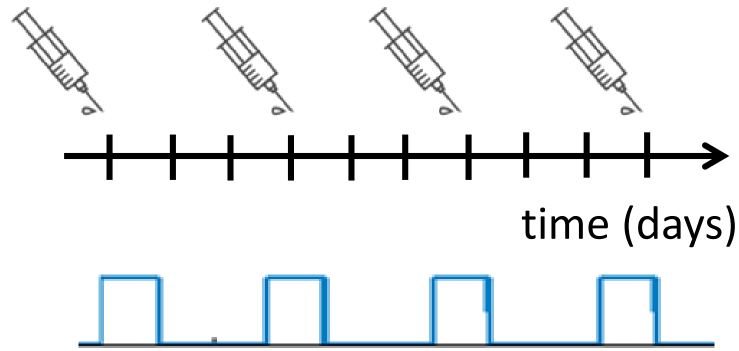
Antiangiogenic therapy

- prevent tumors from forming new blood vessels
- without angiogenesis tumor growth is inhibited



Cancer protocols in the light of the dosage problem

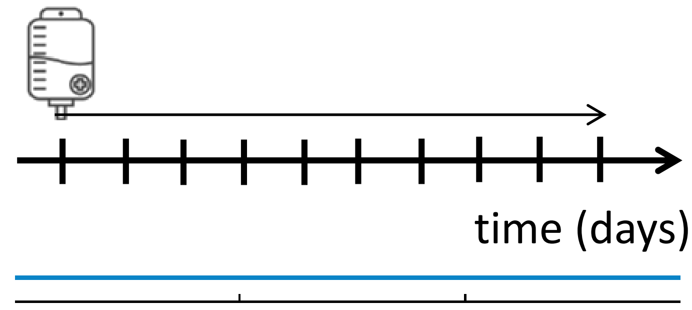
1. intermittent bolus doses administration



- ✓ patient receives drug on given days
- ✓ therapy has rest periods
- ✓ injected amount of boluses can be
  - a) maximum tolerated dose (MTD)
    - ✓ length of the rest periods depends on the amount of boluses
    - ✓ disadvantage:
      - a) it involves re-growth of tumor cells
      - b) resistant to the therapy
  - b) low-dose metronomic (LDM) regimen
    - ✓ low doses over prolonged periods without extended rest periods
    - ✓ advantages: antitumor efficacy, reduced acute toxicities
    - ✓ disadvantage: empiricism associated with determining the *optimal biologic dose (OBD)*

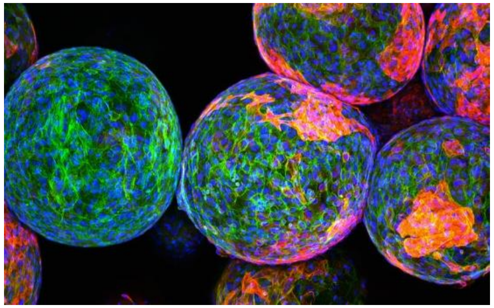
2. continuous infusion therapy

- ✓ applicable within clinical environment
- ✓ not yet as a portable device
- ✓ prolonged delivery



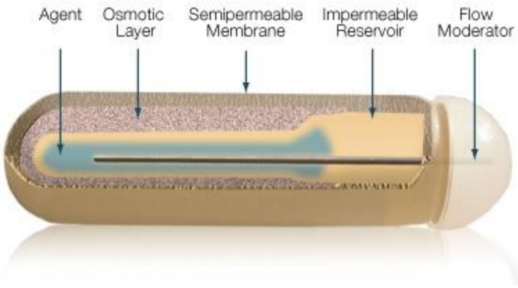
a) cell encapsulation systems

- microencapsulated in vivo releasing endostatin was biologically active and significantly inhibited the migration of endothelial cells



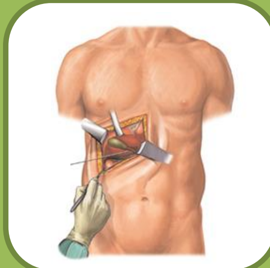
b) mini-osmotic pumps

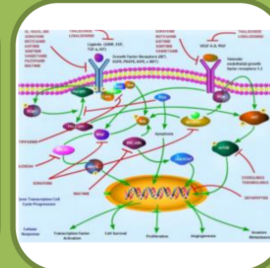
- continuous administration was more effective (97% inhibition of tumor growth) than daily bolus doses (66%), using the same dosage



Interdisciplinary design

Medical knowledge





cancer treatments

general protocols

Healing of the patient

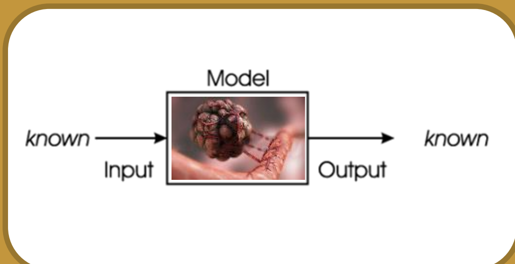
find more effective solutions in healing

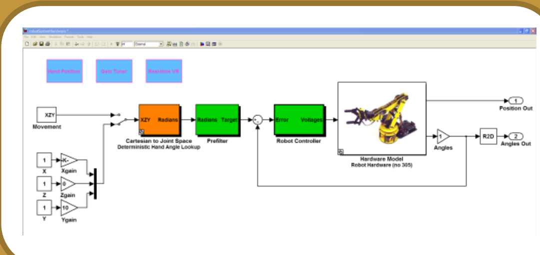
individual treatment for the patient

model identification

model-based protocols

Engineering knowledge



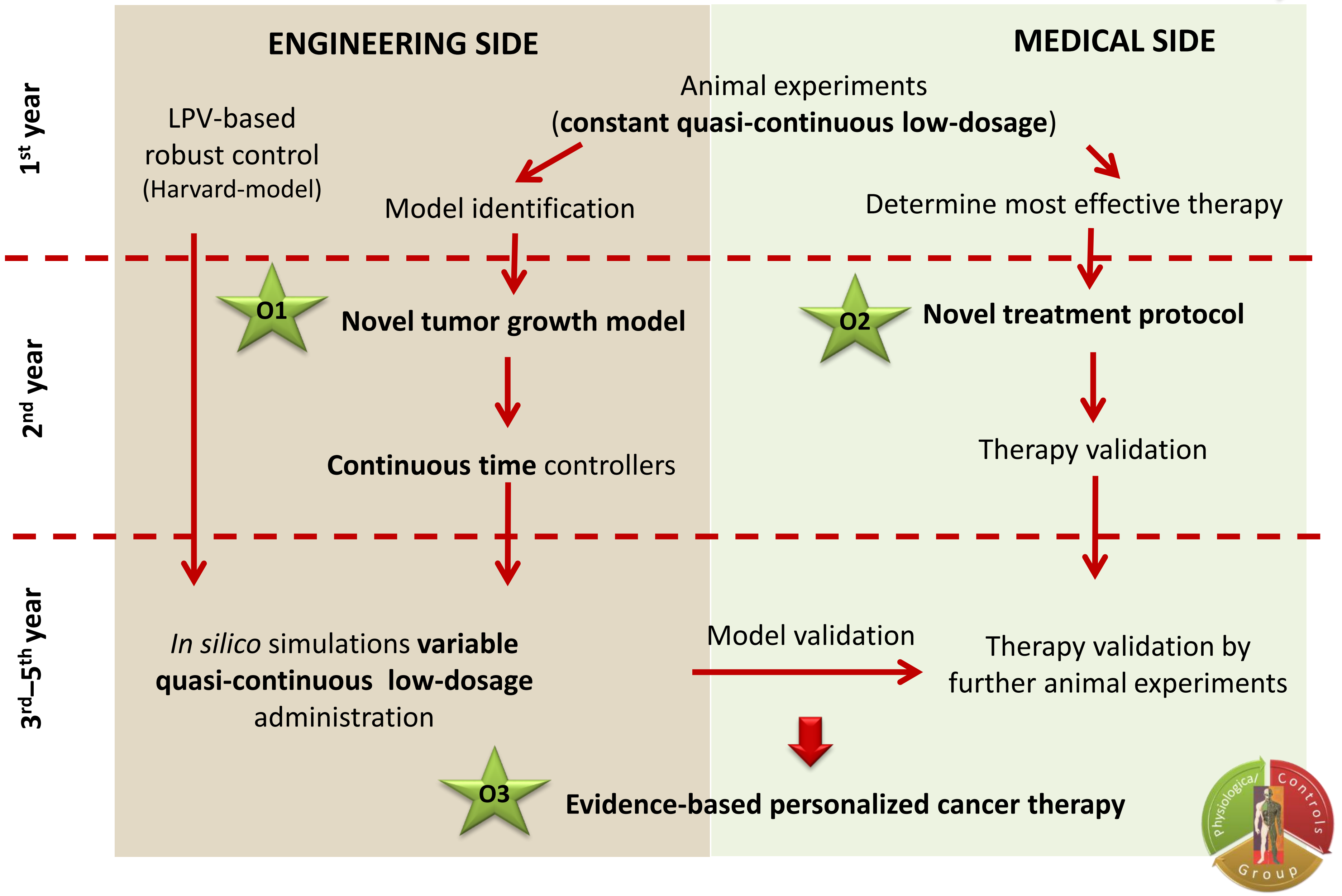


1. Physiological and pathophysiological knowledge
2. Previously investigated tumor growth model (Hahnfeldt model)
3. Controller design and simulations for Hahnfeldt model
4. Animal experiments
5. Tumor growth model identification
6. Controller design and simulations for the new tumor growth model

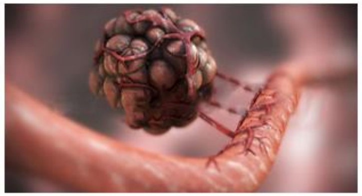
The (control) problem

Antiangiogenic therapy		
Protocols for medical treatment		**Therapy with a controller**
often unknown efficacy	**aim: low tumor volume**	controller design for appropriately-low tumor volume
constant drug dosage	**dosage**	minimizes the input signal as far as possible → less side effects greater cost-effectiveness
individual therapy is not possible	**difficulties**	model uncertainties and measurement noise
?	**solution for difficulties**	modern robust control

Methodology



Concept of the research



Physiological and pathophysiological knowledge

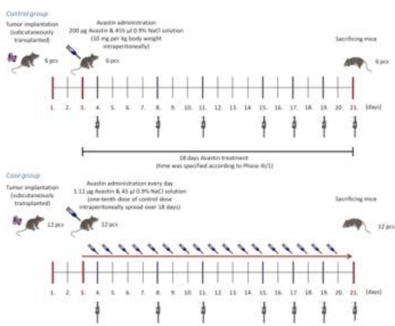
Hahnfeldt model

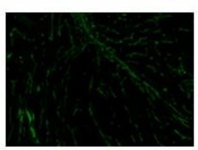
$$V' = -\lambda_1 V \cdot ln\left(\frac{V}{K}\right)$$

$$K' = -\lambda_2 K + bV - dKV^{2/3} - eKg(t)$$

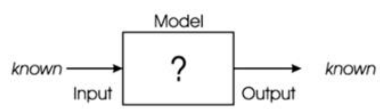
$$g(t) = \int_0^t c(t')\exp(-clr(t-t'))\,dt'$$

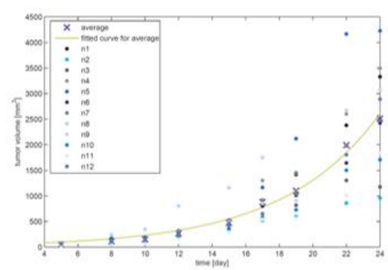
Animal experiments





Tumor growth model identification

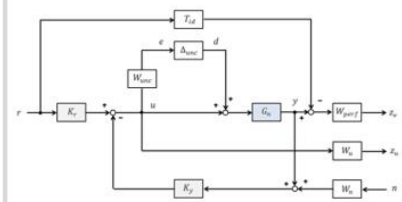


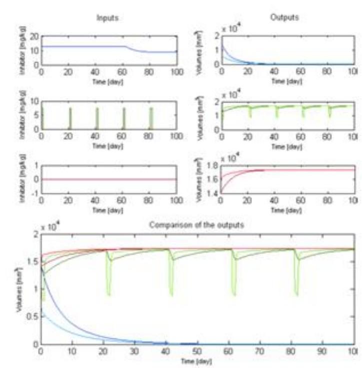


$$W_{pIII/2case}(t) = \frac{-61.79s + 14.33}{s^2 - 0.1409s + 0.004963}$$

$$W_{pIII/2control}(t) = \frac{-12.34s + 3.764}{s^2 - 0.2292s + 0.01313}$$

Controller design and simulations





Previously investigated tumor growth model

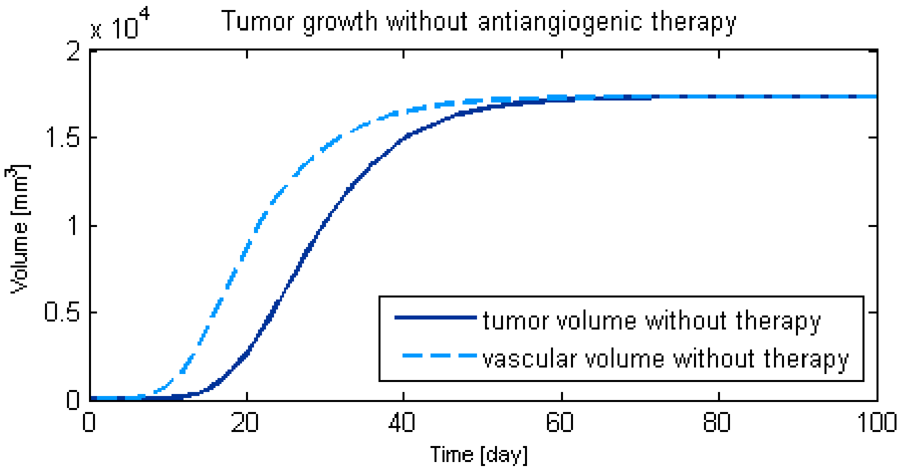
- P. Hahnfeldt et al. (1999)

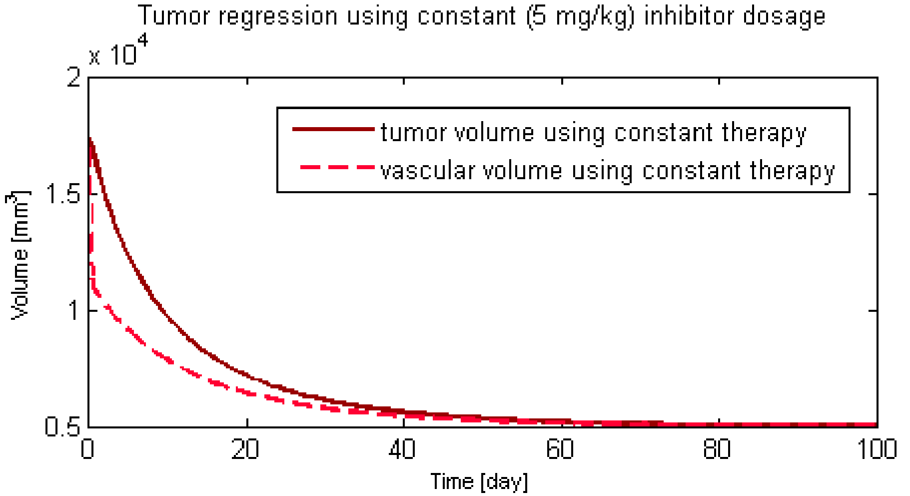
$$\dot{x}_1 = -\lambda_1 x_1 \cdot ln\left(\frac{x_1}{x_2}\right)$$

$$\dot{x}_2 = bx_1 - d \cdot x_1^{2/3} \cdot x_2 - ex_2 g$$

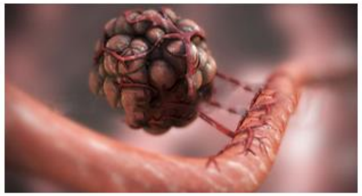
$$y = x_1$$

x_1 : tumor volume (*mm³*)
x_2 : endothelial volume (*mm³*)
g : concentration of the administered inhibitor (*mg/kg*).





Concept of the research



Physiological and pathophysiological knowledge

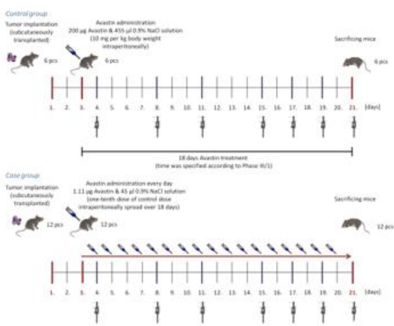
Hahnfeldt model

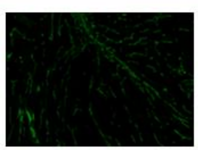
$$V' = -\lambda_1 V \cdot \ln\left(\frac{V}{K}\right)$$

$$K' = -\lambda_2 K + bV - dKV^{2/3} - eKg(t)$$

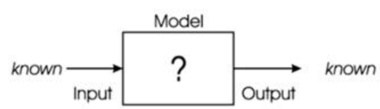
$$g(t) = \int_0^t c(t')\exp(-clr(t-t'))\,dt'$$

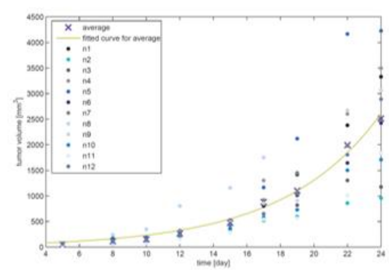
Animal experiments





Tumor growth model identification

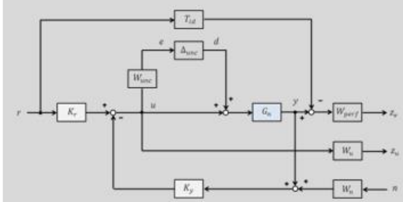


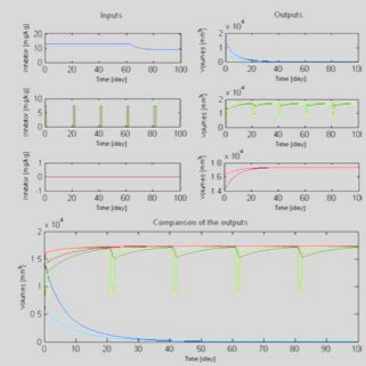


$$W_{pIII/2case}(t) = \frac{-61.79s + 14.33}{s^2 - 0.1409s + 0.004963}$$

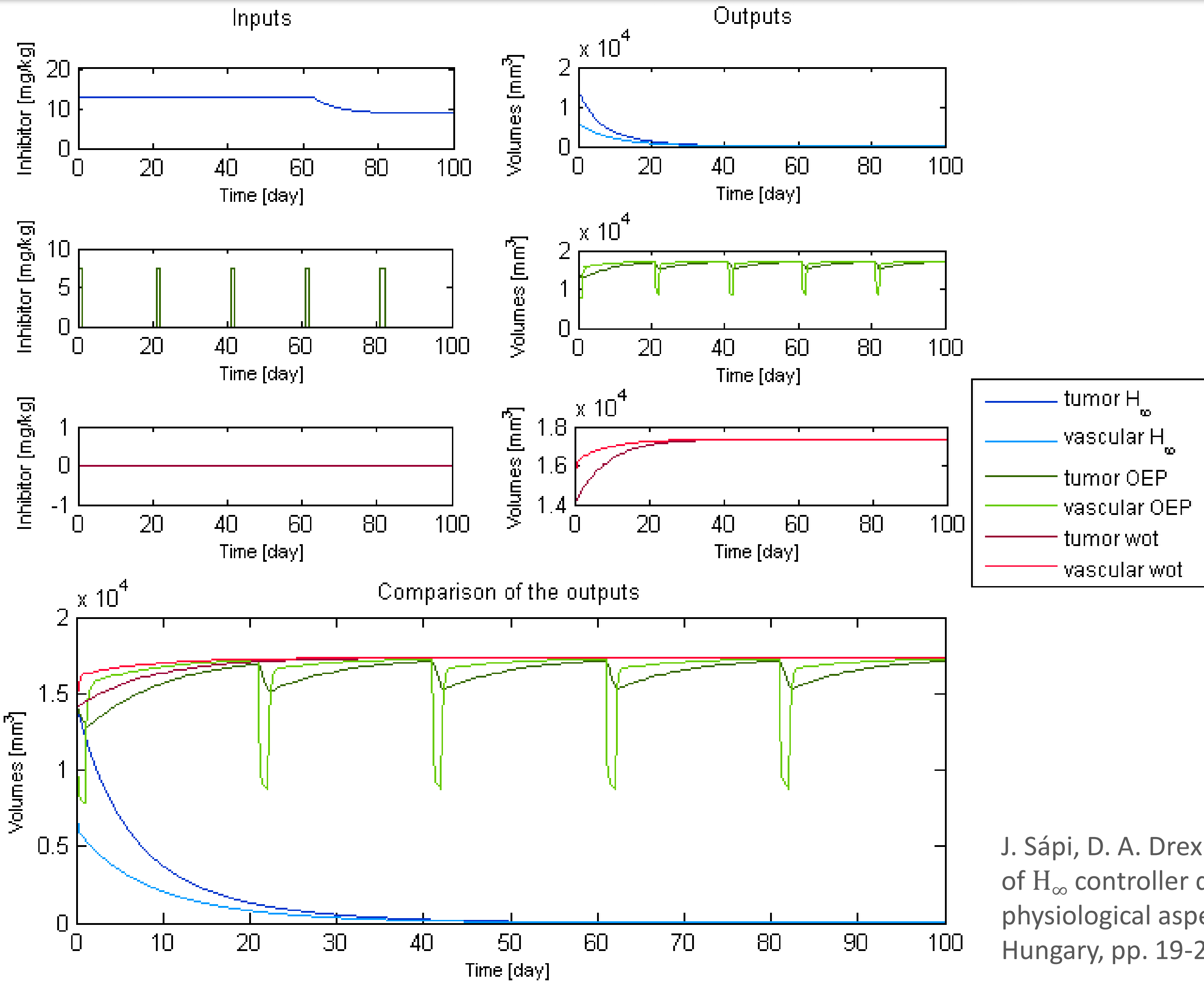
$$W_{pIII/2control}(t) = \frac{-12.34s + 3.764}{s^2 - 0.2292s + 0.01313}$$

Controller design and simulations





Simulation results of robust control



Comparison of changes in tumor volume using different therapies

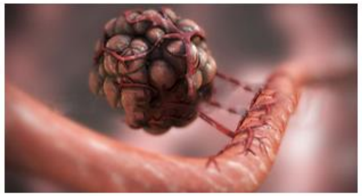
a) therapy using the controller which was designed using the Robust Control method

b) therapy based on the Hungarian OEP protocol for antiangiogenic monotherapy

c) without therapy

J. Sápi, D. A. Drexler, L. Kovács, “Parameter optimization of H_∞ controller designed for tumor growth in the light of physiological aspects”, in *Proc. CINTI 2013* Budapest, Hungary, pp. 19-24.

Concept of the research



Physiological and pathophysiological knowledge

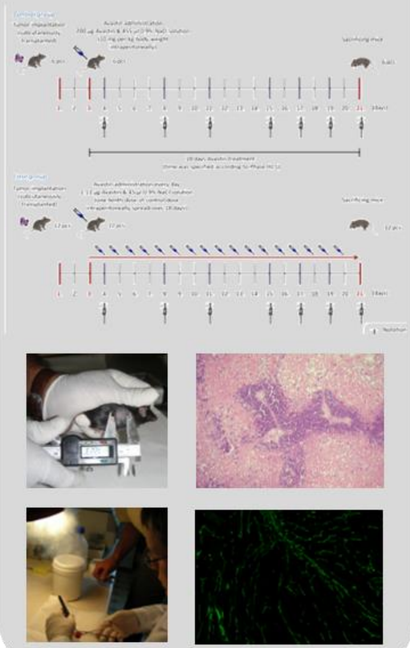
Hahnfeldt model

$$V' = -\lambda_1 V \cdot ln\left(\frac{V}{K}\right)$$

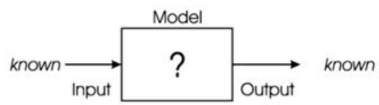
$$K' = -\lambda_2 K + bV - dKV^{2/3} - eKg(t)$$

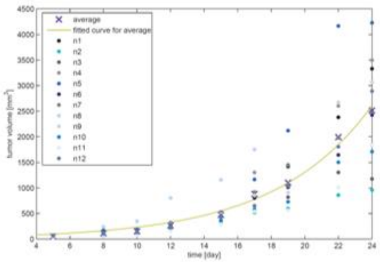
$$g(t) = \int_0^t c(t')\exp(-clr(t-t'))\,dt'$$

Animal experiments



Tumor growth model identification

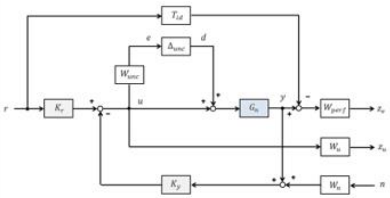


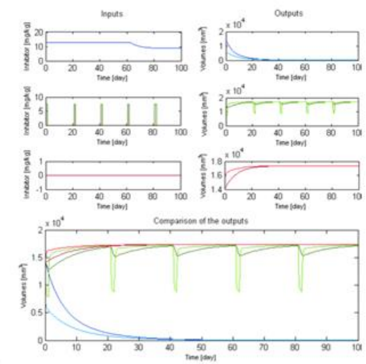


$$W_{pIII/2case}(t) = \frac{-61.79s + 14.33}{s^2 - 0.1409s + 0.004963}$$

$$W_{pIII/2control}(t) = \frac{-12.34s + 3.764}{s^2 - 0.2292s + 0.01313}$$

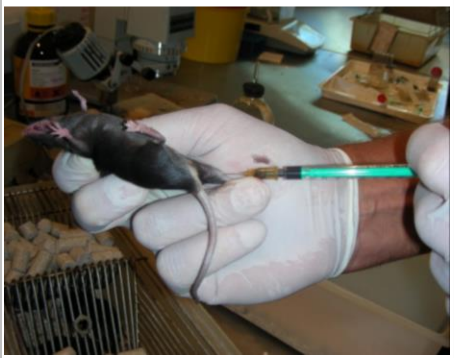
Controller design and simulations



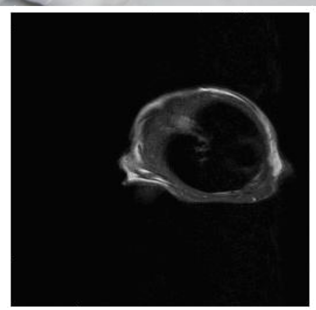


Animal experiments

Tumor implantation/ Bevacizumab administration



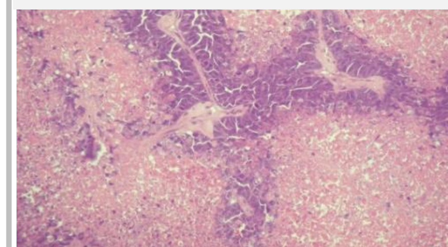
Tumor volume measurement

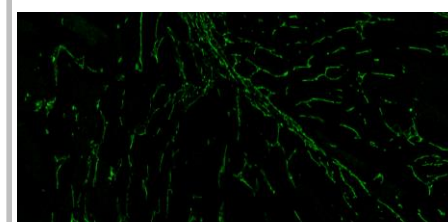


Sacrificing mice, remove tumor

Tumor sample processing

H&E staining





Immunohistochemistry staining

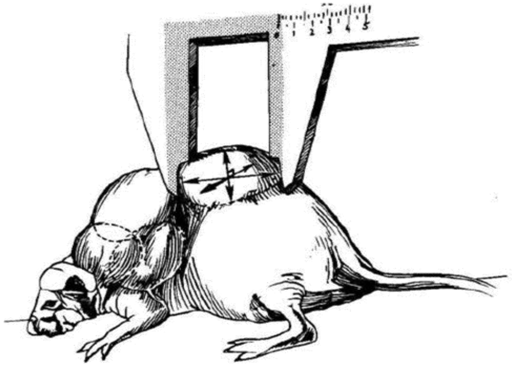
J. Sápi, D. A. Drexler, I. Harmati, A. Szeles, B. Kiss, Z. Sápi, and L. Kovács, "Tumor growth model identification and analysis in case of C38 colon adenocarcinoma and B16 melanoma", in *Proc. SACI 2013* Timisoara, Romania, pp. 303-308

The importance of accurate tumor volume estimation

- measurement of volume is necessary to monitor
  - ✓ the progression of the disease
  - ✓ the efficiency of the given therapy

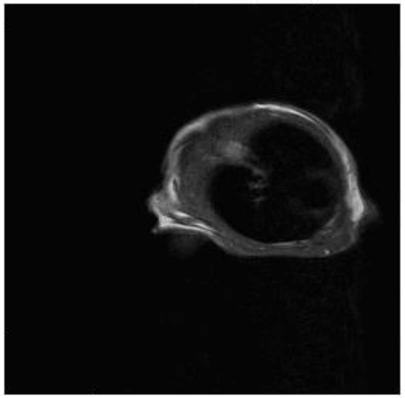
Caliper

- ✓ width and length can be measured, but the third dimension is estimated
- ✓ tumor volume is approximated assuming a shape (e.g. ellipsoid)
- ✓ in the case of irregular tumor structure, it may result in significant error in tumor volume



Magnetic Resonance Imaging (MRI)

- ✓ non-invasive, does not use ionizing radiation
- ✓ computes the precise location, shape and orientation of the tumor mass
- ✓ expensive



The importance of accurate tumor volume estimation

Models estimating tumor volume based on caliper measurements

- three dimensions:

length (l), width (w), height (h)

Xenograft tumor model protocol

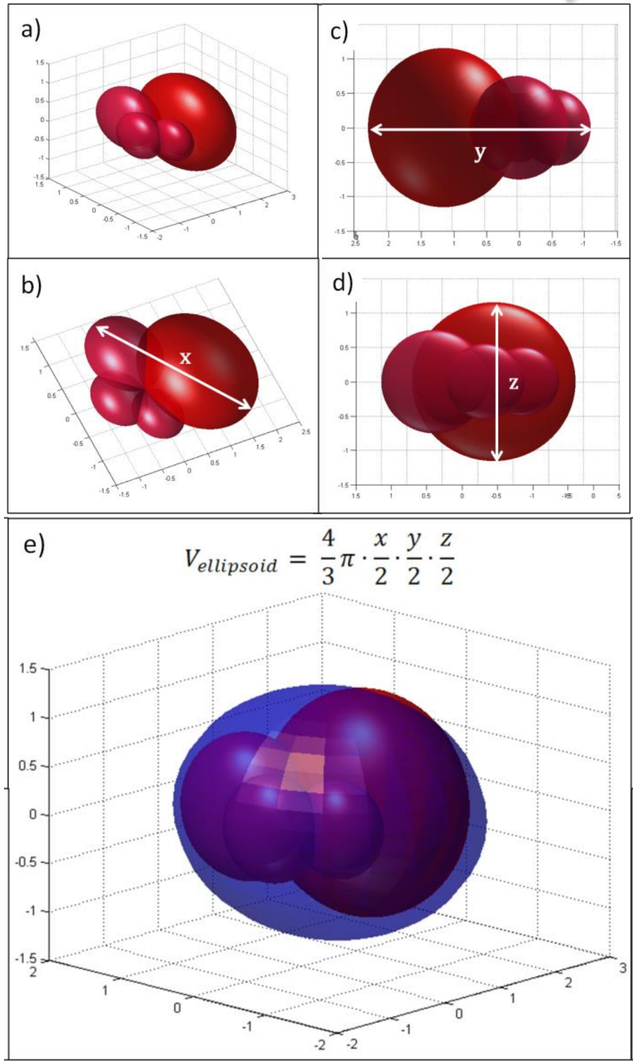
$$V = w^2 \cdot \frac{l}{2}$$

Ellipsoid shape

$$V = \frac{4}{3} \cdot \pi \cdot \frac{l}{2} \cdot \frac{w}{2} \cdot \frac{h}{2}$$

Two-dimensional model

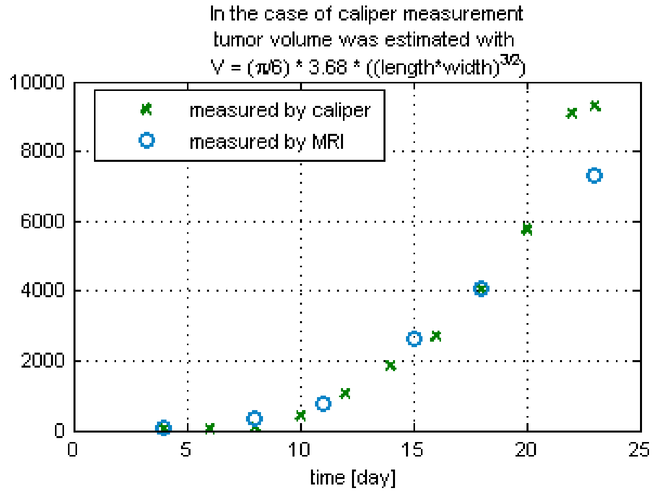
$$V = \frac{\pi}{6} \cdot f \cdot (l \cdot w)^{3/2}$$

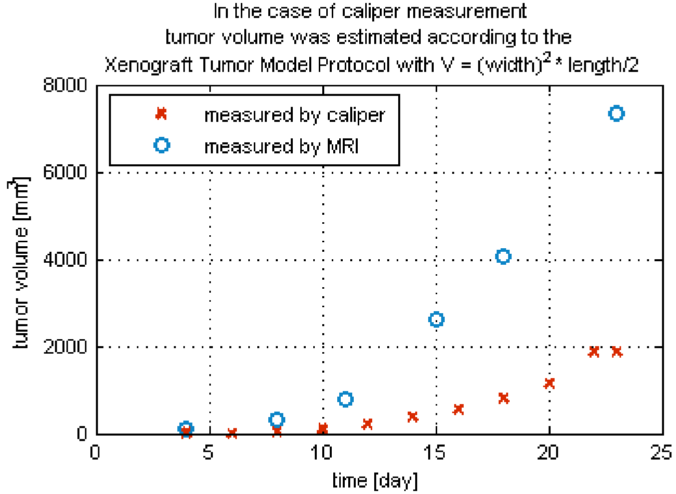


J Sápi, L Kovács, D A Drexler, P Kocsis, D. Gajári, and Z Sápi (2015). “Tumor Volume Estimation and Quasi-Continuous Administration for Most Effective Bevacizumab Therapy” *PLoS ONE 10:(11) PAPER E0142190. 20 P. (2015)*

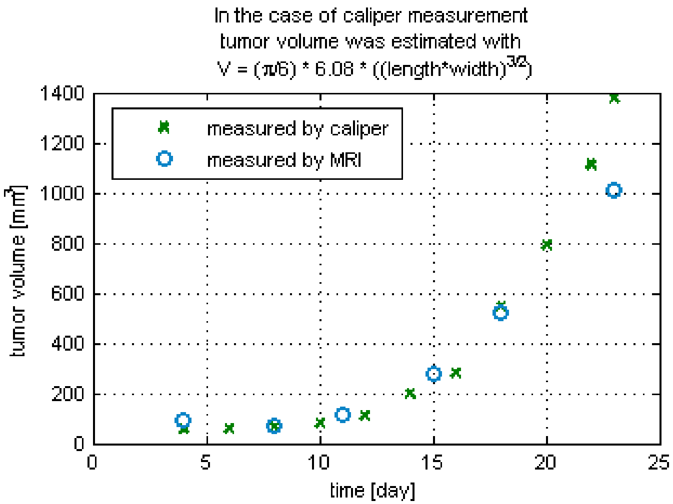
The importance of accurate tumor volume estimation

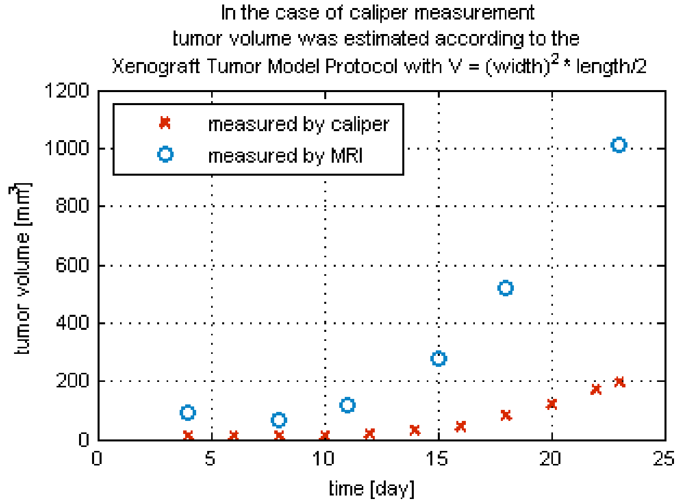
Control group (C4)





Case group (E9)

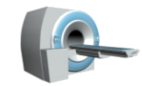




our new model estimates tumor volume similarly accurate as MRI, using only caliper measurement

Finding the effective dosage for optimal therapy

MRI



Phase I

without therapy

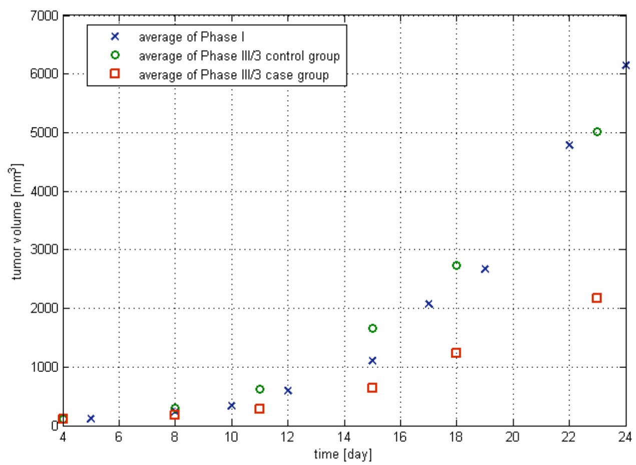
$p = 0.572$

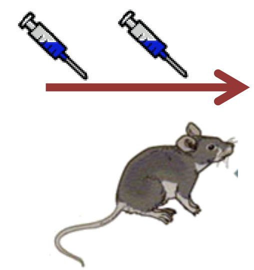
$p = 0.002$

daily 1/180 dosage
is more effective
than one large dose

Phase III/3 control group

therapy based on
the protocol
(200 µg)

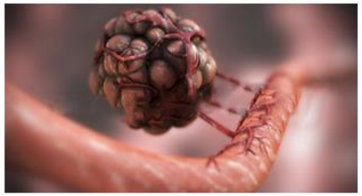




Phase III/3 case group

therapy with daily
administration
(1.11 µg)

Concept of the research



Physiological and pathophysiological knowledge

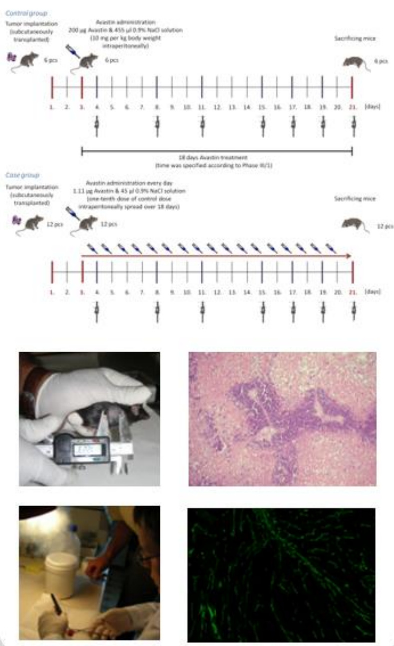
Hahnfeldt model

$$V' = -\lambda_1 V \cdot \ln\left(\frac{V}{K}\right)$$

$$K' = -\lambda_2 K + bV - dKV^{2/3} - eKg(t)$$

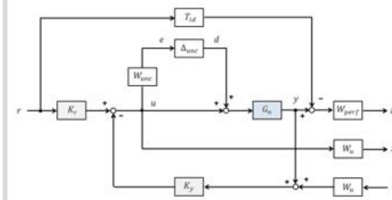
$$g(t) = \int_0^t c(t') \exp(-clr(t-t'))\, dt'$$

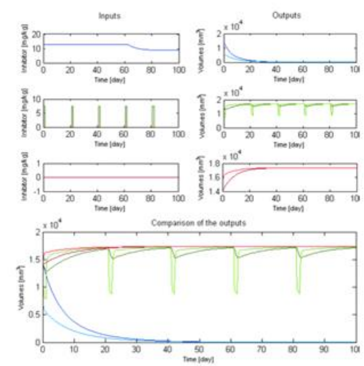
Animal experiments



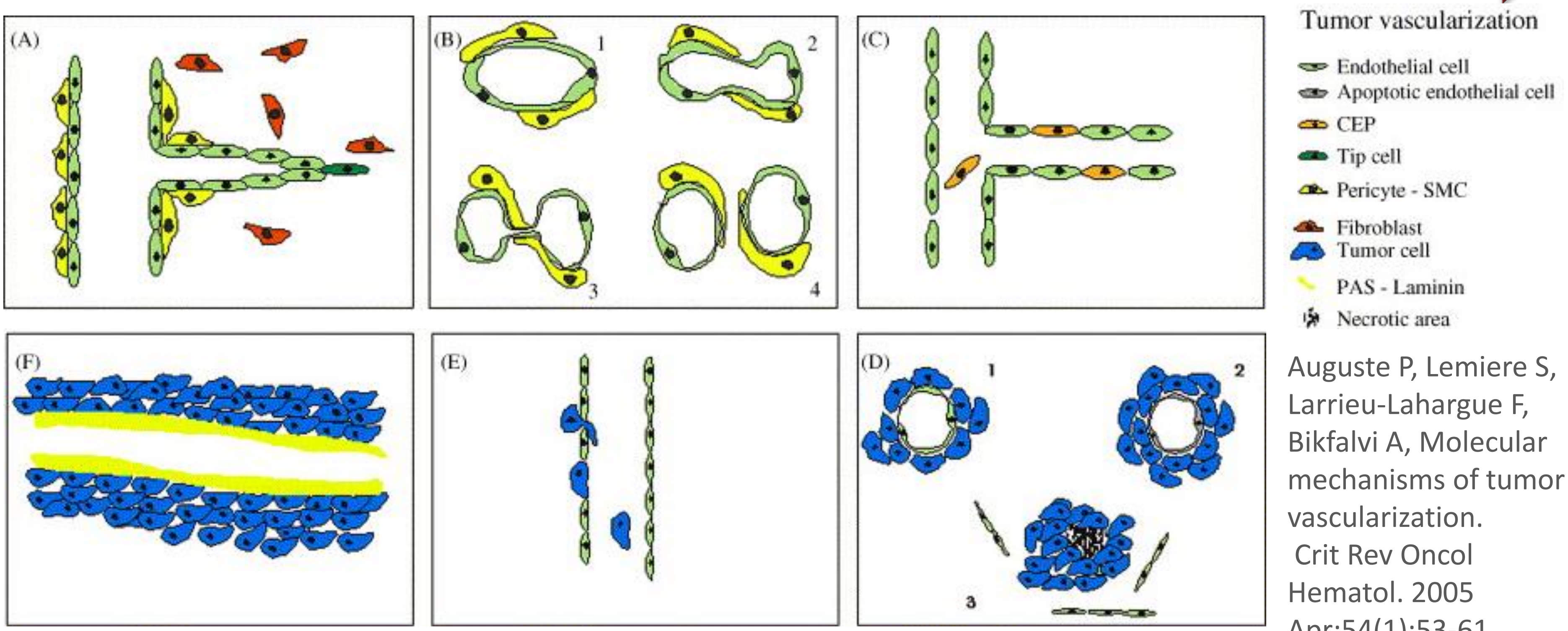
More details in Dr. Dávid Csercsik's presentation

Controller design and simulations





Motivation of new tumor growth model identification

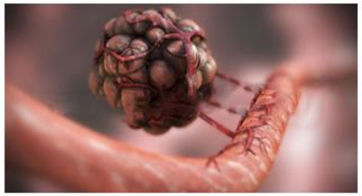


Auguste P, Lemiere S, Larrieu-Lahargue F, Bikfalvi A, Molecular mechanisms of tumor vascularization. Crit Rev Oncol Hematol. 2005 Apr;54(1):53-61.

(A) Endothelial Sprouting; (B) Intussusceptive Microvascular Growth (IMG); (C) Postnatal Vasculogenesis; (D) Vessel Co-Option; (E) Mosaic vessels; (F) Vasculogenic Mimicry.

New, non-sprouting vascularization methods which are not taken into account in Hahnfeldt model → outdated model

Concept of the research



Physiological and pathophysiological knowledge

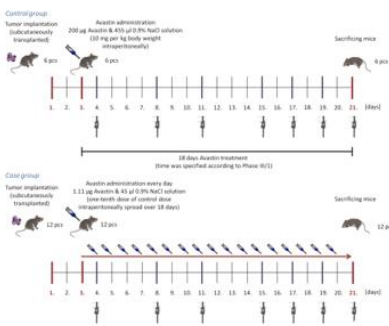
Hahnfeldt model

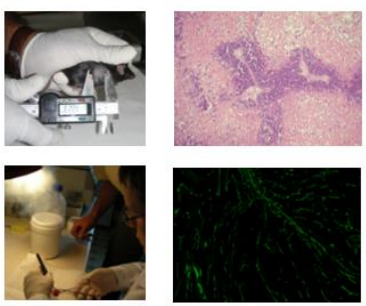
$$V' = -\lambda_1 V \cdot ln\left(\frac{V}{K}\right)$$

$$K' = -\lambda_2 K + bV - dKV^{2/3} - eKg(t)$$

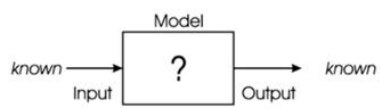
$$g(t) = \int_0^t c(t') \exp(-clr(t-t'))\, dt'$$

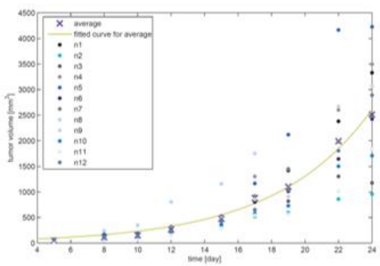
Animal experiments





Tumor growth model identification





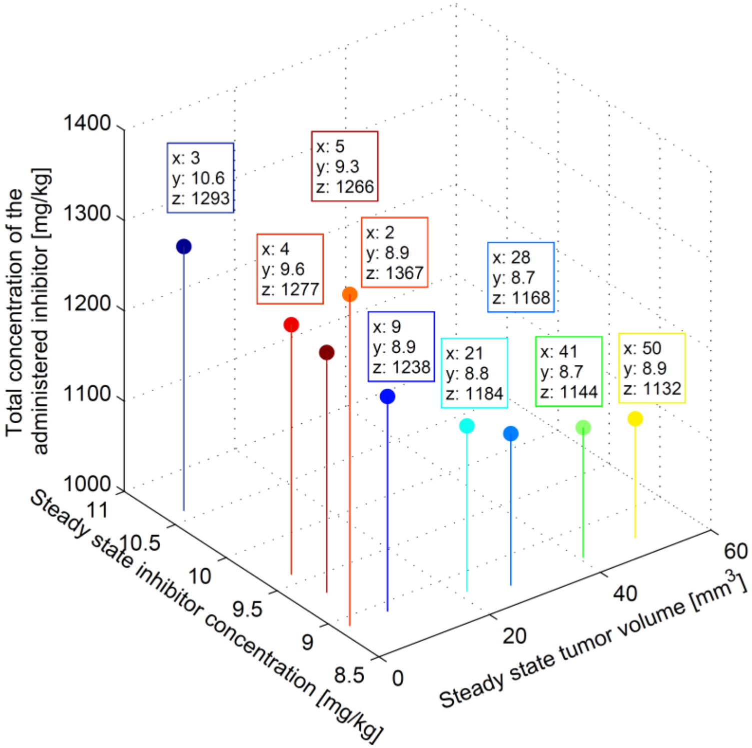
$$W_{pIII/2case}(t) = \frac{-61.79s + 14.33}{s^2 - 0.1409s + 0.004963}$$

$$W_{pIII/2control}(t) = \frac{-12.34s + 3.764}{s^2 - 0.2292s + 0.01313}$$

More details in Dr. Drexler Dániel András' presentation

What can we offer for medical doctors?

- alternatives for optimal, personalized protocols based on multi-criteria



Evaluated criterion: total concentration of the administered inhibitor during the treatment (mg/kg)		R = 0.1	R = 1	R = 10	R = 100	R = 1000
operating point: 10 mm^3	saturation: 25 mg/kg	1556	1500	1486	1483	1483
	saturation: 15 mg/kg	1367	1329	1318	1316	1316
	saturation: 13 mg/kg	1300	1277	1268	1266	1266
operating point: 100 mm^3	saturation: 25 mg/kg	1369	1430	1365	1308	1292
	saturation: 15 mg/kg	1353	1288	1227	1184	1169
	saturation: 13 mg/kg	1293	1243	1184	1144	1132
operating point: 5000 mm^3	saturation: 25 mg/kg	1380	1439	1345	1245	1131
	saturation: 15 mg/kg	1351	1283	1210	1131	1044
	saturation: 13 mg/kg	1293	1238	1168	1096	1017
operating point: 10000 mm^3	saturation: 25 mg/kg	1405	1439	1345	1244	1129
	saturation: 15 mg/kg	1351	1283	1209	1130	1042
	saturation: 13 mg/kg	1293	1238	1168	1096	1016

Evaluated criterion: steady state inhibitor concentration at the end of the treatment (mg/kg)		R = 0.1	R = 1	R = 10	R = 100	R = 1000
operating point: 10 mm^3	saturation: 25 mg/kg	8.8	8.8	8.8	8.8	8.8
	saturation: 15 mg/kg	8.9	8.8	8.8	8.8	8.8
	saturation: 13 mg/kg	12.3	9.6	9.3	9.3	9.3
operating point: 100 mm^3	saturation: 25 mg/kg	8.8	8.7	8.7	8.7	8.7
	saturation: 15 mg/kg	8.8	8.8	8.7	8.7	8.7
	saturation: 13 mg/kg	10.7	8.9	8.7	8.7	8.7
operating point: 5000 mm^3	saturation: 25 mg/kg	8.7	8.8	8.7	8.6	8.3
	saturation: 15 mg/kg	8.9	8.8	8.7	8.6	8.3
	saturation: 13 mg/kg	10.6	8.9	8.7	8.6	8.3
operating point: 10000 mm^3	saturation: 25 mg/kg	8.8	8.8	8.7	8.6	8.3
	saturation: 15 mg/kg	8.9	8.8	8.7	8.6	8.3
	saturation: 13 mg/kg	10.6	8.9	8.7	8.6	8.3

Evaluated criterion: steady state tumor volume at the end of the treatment (mm^3)		R = 0.1	R = 1	R = 10	R = 100	R = 1000
operating point: 10 mm^3	saturation: 25 mg/kg	2	4	5	5	5
	saturation: 15 mg/kg	2	4	5	5	5
	saturation: 13 mg/kg	3	4	5	5	5
operating point: 100 mm^3	saturation: 25 mg/kg	3	8	21	41	50
	saturation: 15 mg/kg	3	8	21	41	50
	saturation: 13 mg/kg	3	8	21	41	50
operating point: 5000 mm^3	saturation: 25 mg/kg	3	9	28	86	259
	saturation: 15 mg/kg	3	9	28	86	259
	saturation: 13 mg/kg	3	9	28	86	259
operating point: 10000 mm^3	saturation: 25 mg/kg	3	9	28	86	264
	saturation: 15 mg/kg	3	9	28	86	264
	saturation: 13 mg/kg	3	9	28	86	264

J Sápi, D A Drexler, I Harmati, Z Sápi, and L Kovács (2015). "Qualitative analysis of tumor growth model under antiangiogenic therapy – choosing the effective operating point and design parameters for controller design". *OPTIMAL CONTROL APPLICATIONS AND METHODS* 37:(5) pp. 848-866. (2016)

10-year jubilee of the European Research Council's ERC Starting and Advanced Grant program

2017.03.03.

Thank you for your attention!

Contacts:

Dr. Johanna Sájevicsné Sápi sapi.johanna@nik.uni-obuda.hu
Óbuda University,
Research and Innovation Center of Óbuda University,
Physiological Controls Group

Prof. Dr. Levente Kovács kovacs.levente@nik.uni-obuda.hu
Óbuda University,
Research and Innovation Center of Óbuda University,
Physiological Controls Group