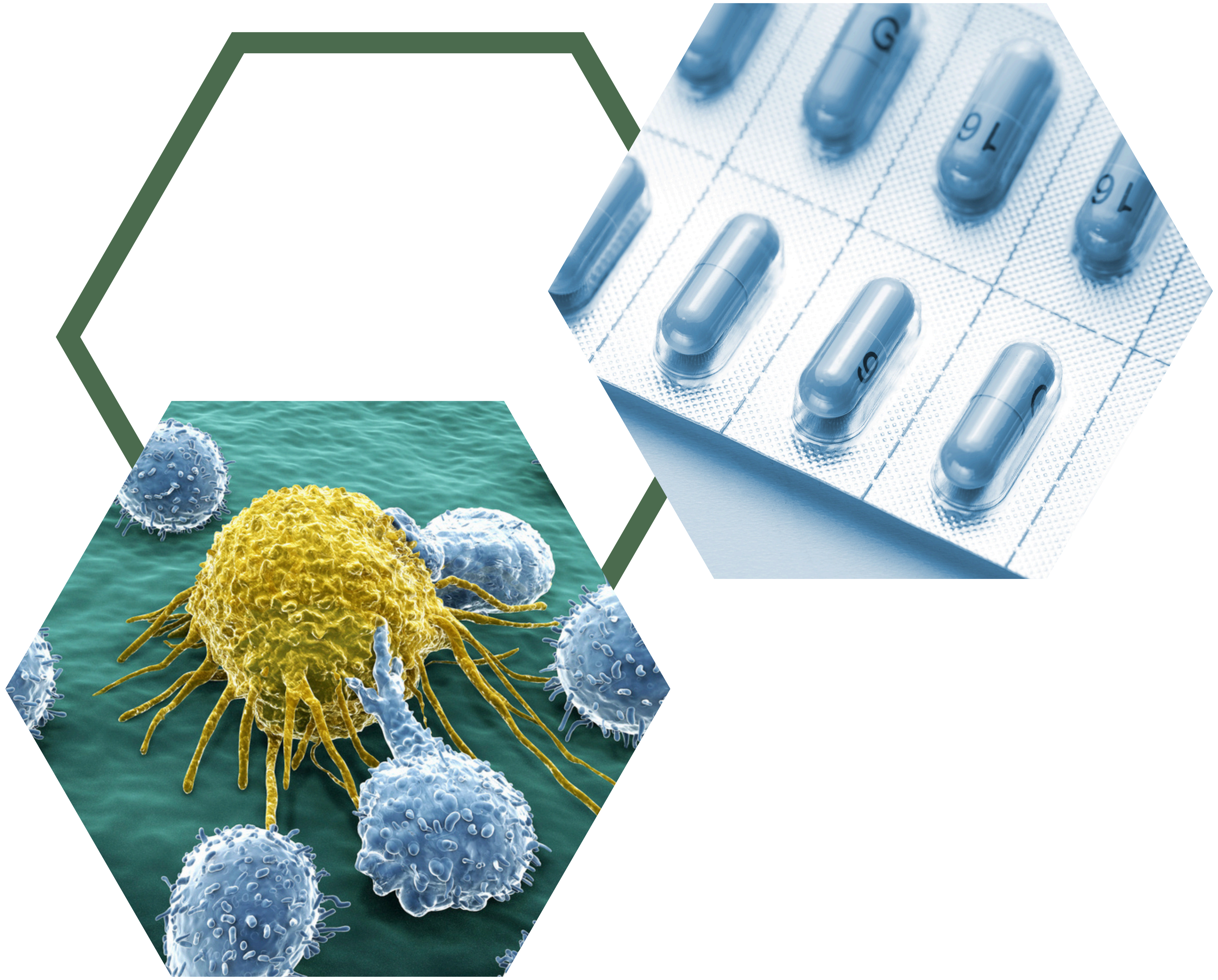
Stability analysis of the singular points and Hopf bifurcations of a tumor growth control model

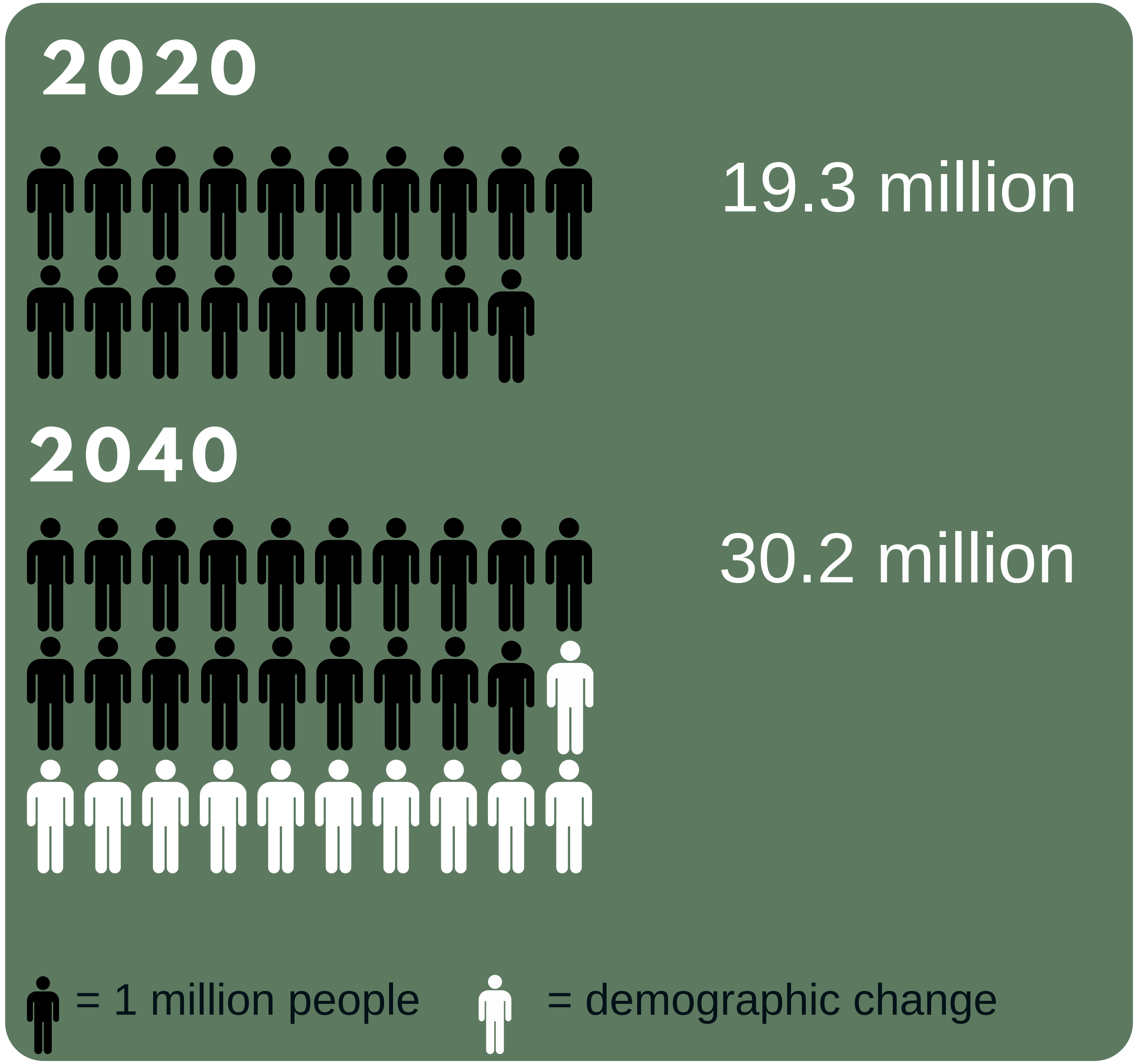
Dániel András Drexler
Obuda University, Physiological Controls Research Center

Farkas Miklós Seminar on Applied Analysis, Budapest University of Technology and Economics
March 27, 2025

TAMED CANCER
ERC Stg Grant
Physiological Controls Research Center
Obuda University
European Commission
Horizon 2020
European Union funding
for Research & Innovation
erc
European Research Council
Nemzeti Kutatási, Fejlesztési és Innovációs Hivatal
AZ NKFI ALAPBÓL MEGVALÓSULÓ PROJEKT

Number of people with cancer





smaller doses

mathematical model

unique parameters

PERSONALIZED AND OPTIMIZED THERAPY

- → Fewer side effects.
- → Smaller risk of drug resistance.

Mathematical model

- **Dynamics of the living tumor**
- **Dynamics of the dead tumor**
- **Dynamics of the drug in the blood**
- **Dynamics of the drug in the tissues**

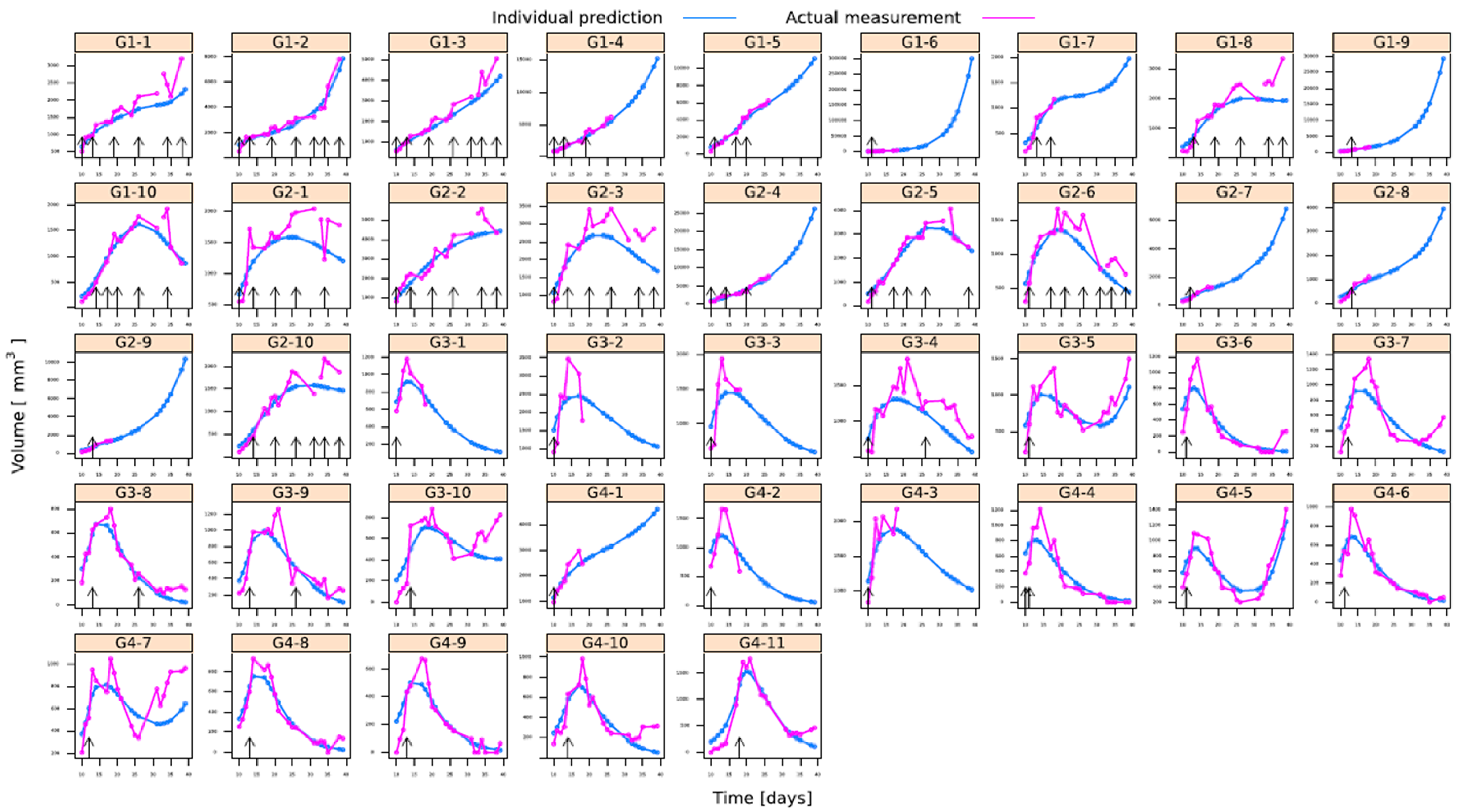
$$\dot{x}_1 = (a - n)x_1 - b\frac{x_1 x_3}{ED_{50} + x_3}$$

$$\dot{x}_2 = nx_1 - b\frac{x_1 x_3}{ED_{50} + x_3} - wx_2$$

$$\dot{x}_3 = -(c + k_1)x_3 + k_2 x_4$$

$$\dot{x}_4 = k_1 x_3 - k_2 x_4$$

Personalization

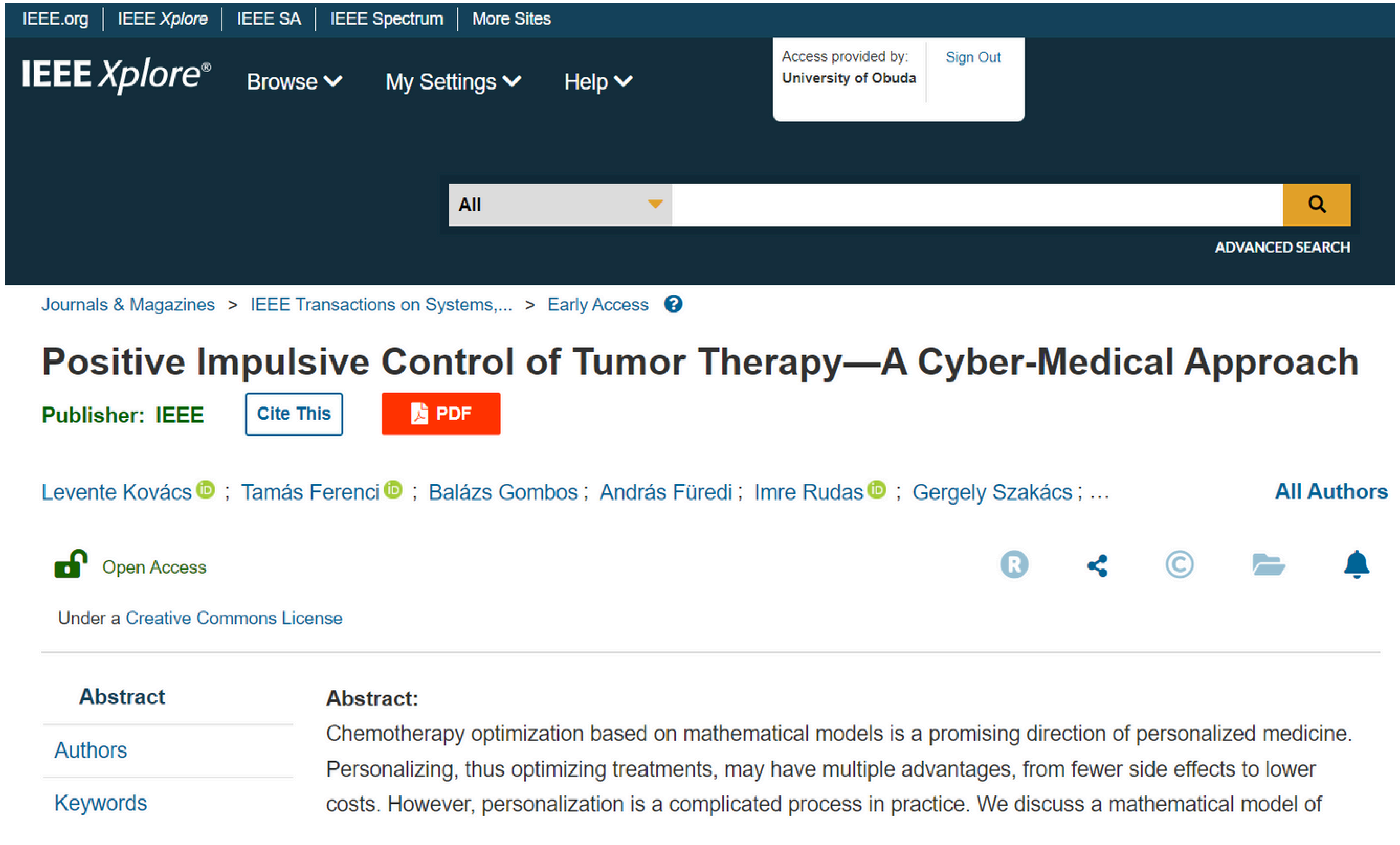


Model

vs

Measurement

L. Kovács, T. Ferenci, B. Gombos, A. Füredi, I. Rudas, G. Szakács, D. A. Drexler,
Transactions on Systems, Man, and Cybernetics: Systems, 54(1), pp. 597 - 608, 2024



This article has been accepted for inclusion in a future issue of this journal. Content is final as presented, with the exception of pagination.

Positive Impulsive Control of Tumor Therapy—A Cyber-Medical Approach

Levente Kovács, *Senior Member, IEEE*, Tamás Ferenci, *Member, IEEE*, Balázs Gombos, András Füredi, Imre Rudas, *Life Fellow, IEEE*, Gergely Szakács, and Dániel András Drexler, *Member, IEEE*

***Abstract*—Chemotherapy optimization based on mathematical models is a promising direction of personalized medicine. Personalizing, thus optimizing treatments, may have multiple advantages, from fewer side effects to lower costs. However, personalization is a complicated process in practice. We discuss a mathematical model of tumor growth and therapy optimization algorithms that can be used to personalize therapies. The therapy generation is based on the concept of keeping the drug level over a specified value. A mixed-effect model is used for parametric identification, and the doses are calculated using a two-compartment model for drug pharmacokinetics, and a nonlinear pharmacodynamics and tumor dynamics model. We propose personalized therapy generation algorithms for having a maximal effect and minimal effective doses. We handle inter- and intra-patient variability for the minimal effective dose therapy. Results from mouse experiments for the personalized therapy are discussed and the algorithms are compared to a generic protocol based on overall survival. The experimental results show that the introduced algorithms significantly increased the overall survival of the mice, demonstrating that by control engineering methods an efficient modality of cancer therapy may be possible.**

***Index Terms*—Impulsive system, min–max therapy, optimal treatment, positive system, therapy generation, tumor model.**

Manuscript received 10 May 2023; accepted 8 September 2023. This work was supported in part by the European Research Council (ERC) through the European Union's Horizon 2020 Research and Innovation Programme under Grant 679681; in part by the National Research, Development and Innovation Fund of Hungary, financed under the 2019-1.3.1- Funding Scheme under Project 2019-1.3.1-KK-2019-00007; in part by the Hungarian National Research, Development and Innovation Fund of Hungary, financed under the TKP2021-NKTA-36 Funding Scheme and under Grant Horizon2020-2017-RISE-777911; and in part by the Collaboration Between the Research Centre for Natural Sciences of the Eötvös Lóránd Research Network and the Szentágothai Research Centre of the University of Pécs on Internationally Recognized Medical Research Projects. The work of Dániel András Drexler was supported by the Starting Excellence Researcher Program of Óbuda University, Budapest, Hungary. The work of András Füredi was supported by the HORIZON.1.2—Marie Skłodowska-Curie Actions (MSCA) Postdoctoral Fellowship (POC-TDM) under Grant 101065044. This article was recommended by Associate Editor C. Platania. *(Corresponding author: Dániel András Drexler.)*

Levente Kovács, Imre Rudas, and Dániel András Drexler are with the Physiological Controls Research Center, University Research and Innovation Center, Óbuda University, 1034 Budapest, Hungary (e-mail: drexler.daniel@uni-obuda.hu).

Tamás Ferenci is with the Physiological Controls Research Center, University Research and Innovation Center, Óbuda University, 1034 Budapest, Hungary, and also with the Department of Statistics, Corvinus University of Budapest, 1093 Budapest, Hungary.

Balázs Gombos is with the Drug Resistance Research Group, HUN-REN Research Centre for Natural Sciences, 1117 Budapest, Hungary, and also with the Molecular Medicine PhD School, Semmelweis University, 1085 Budapest, Hungary.

András Füredi is with the Drug Resistance Research Group, HUN-REN Research Centre for Natural Sciences, 1117 Budapest, Hungary, and also with the Microsystems Laboratory, HUN-REN Centre for Energy Research, 1121 Budapest, Hungary.

Gergely Szakács is with the Center for Cancer Research, Medical University of Vienna, 1090 Vienna, Austria, and also with the Drug Resistance Research Group, HUN-REN Research Centre for Natural Sciences, 1117 Budapest, Hungary.

Color versions of one or more figures in this article are available at https://doi.org/10.1109/TSMC.2023.3315637.

Digital Object Identifier 10.1109/TSMC.2023.3315637

I. Introduction

CYBER-MEDICAL systems play an important role in modern medicine, and their importance is growing. The application of STEM in medicine offers prosperous results in medical practice. For example, engineering methods can be used for brain fatigue detection [1], [2], [3], prediction of in-hospital death of trauma [4], skeleton maturity assessment [5], [6], or Parkinson's disease diagnosis [7]. System-theoretic methods are used in several drug dosing problems, like control of anesthesia [8], or control of blood glucose level with artificial pancreas [9].

System-theoretic methods can also be utilized to optimize drug dosing in cancer therapies. The therapies used in conventional chemotherapy usually have a large resting time, i.e., a long time between the injections and large injected doses [10]. They use the maximum tolerable dose (MTD) in order to achieve a maximal effect without killing the patient. Another approach is the low-dose metronomic (LDM) therapy, which applies lower doses with larger frequency. In some cases, this approach was proven more effective against cancer cells, which often become resistant to the treatment [11], [12]. LDM therapy can also be cheaper with fewer side effects. We aim to provide algorithms for the mathematical model-based generation of LDM therapies.

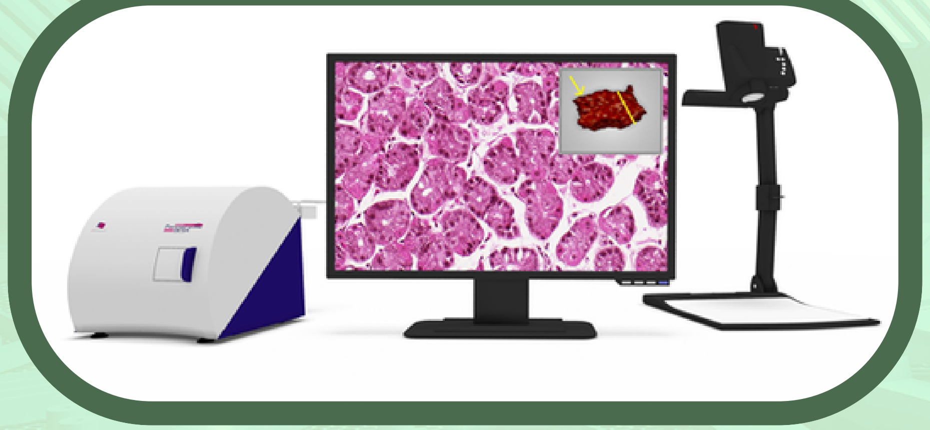
Scheduling LDM therapy and providing the required doses is a challenging task. A promising engineering approach is to use a mathematical model describing the effect of the drug on tumor growth and use this model to generate an optimal therapy. There are numerous models in the literature (see [10], [13], [14], [15] and several therapy generation algorithms [10], [16], [17], [18]). A specific characteristic of this physiological problem is that the input is the injection, which is positive, and the system is impulsive. Such systems are rare in engineering practice, and thus handling them requires unconventional solutions [19], [20], [21]. Besides therapy generation, the usage of nanorobots in cancer treatments is also exploited by Shi et al. [22], [23], [24], while robotic capsules are used for site-specific drug delivery in [25].

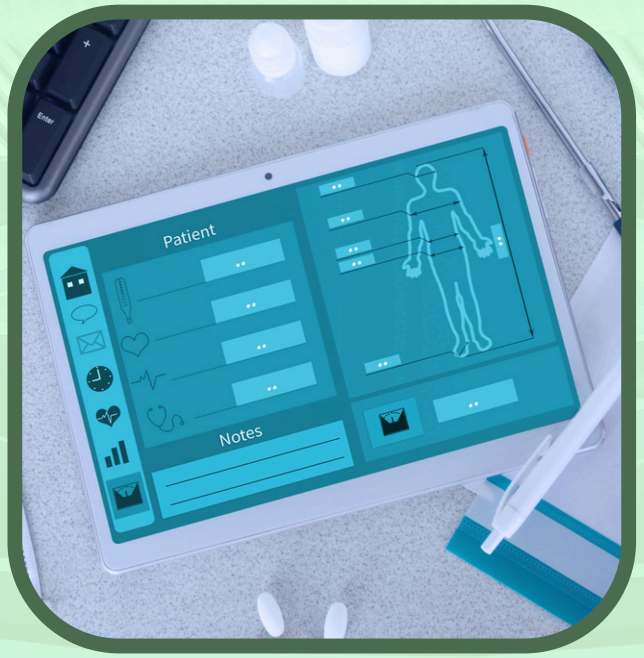
Cyber-Medical Competence Center (KiKoK)

3DHISTECH

ÓBUDAI EGYETEM
ÓBUDA UNIVERSITY

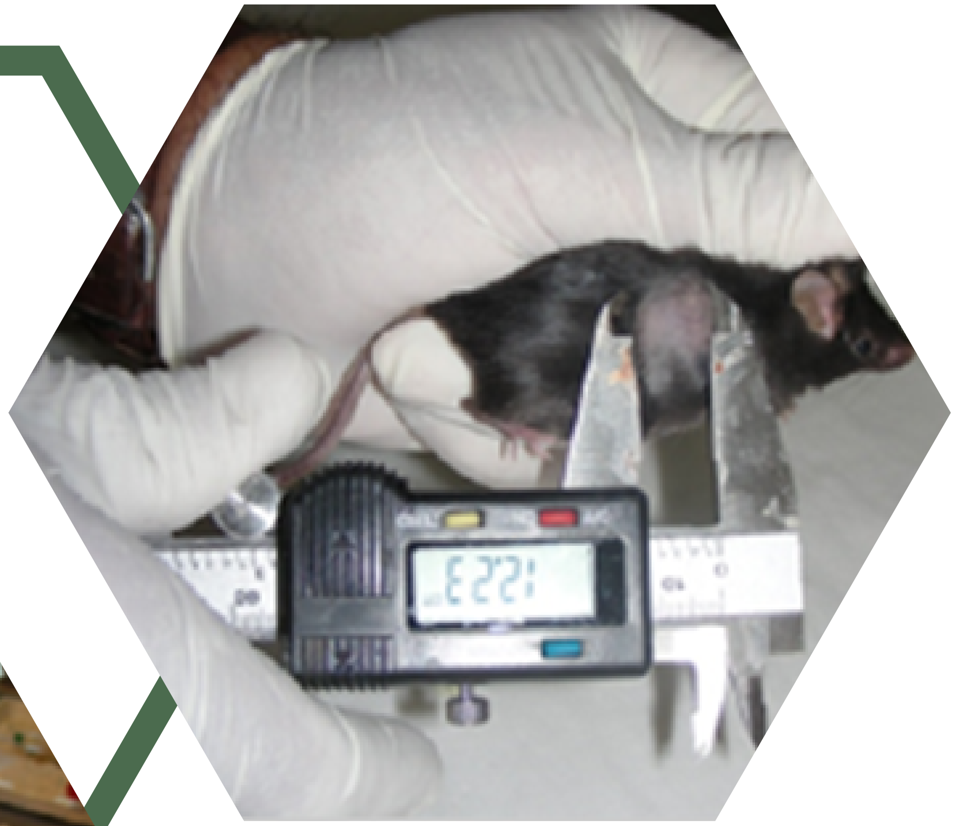
ttk

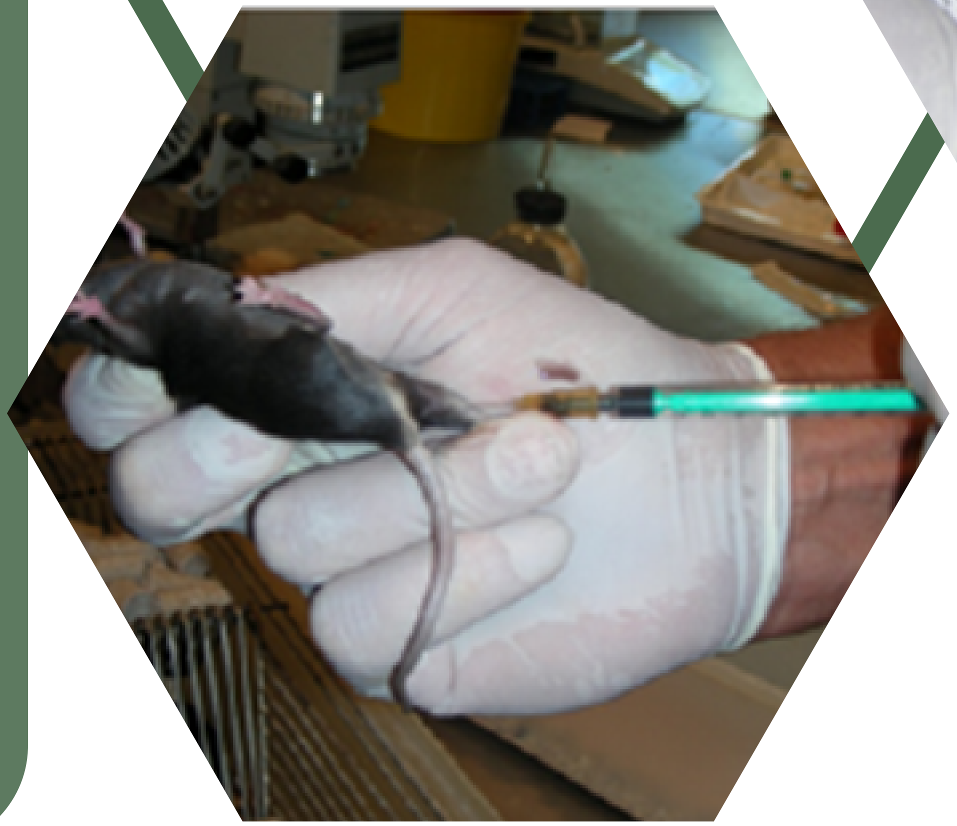




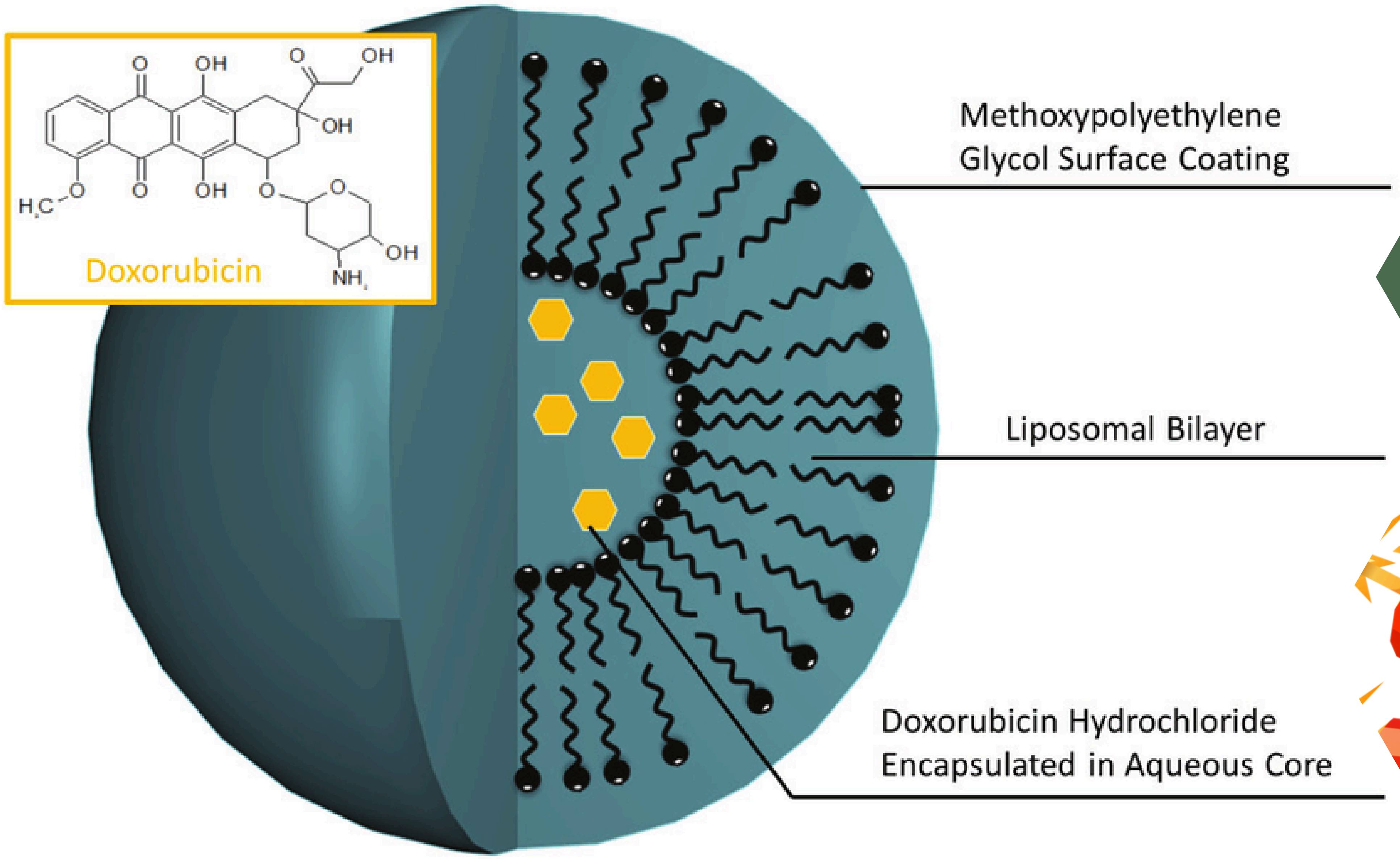
Animal experiments

- Genetically engineered mouse model of breast cancer.
- Brca1, a DNA repair gene knocked out breast epithelial cells
- p53, a regulator of cell cycle and genome stability knocked out breast epithelial cells breast epithelial cells.
- The resulting mammary tumors highly resemble the Brca1-linked, triple-negative, hereditary breast cancer in humans





Chemotherapy: Doxil



Chemotherapy Optimization: results

CONTROL GROUP

- 12 mice
- Longest survival: 290 days
- Cummulated dose: 100% (ground truth)

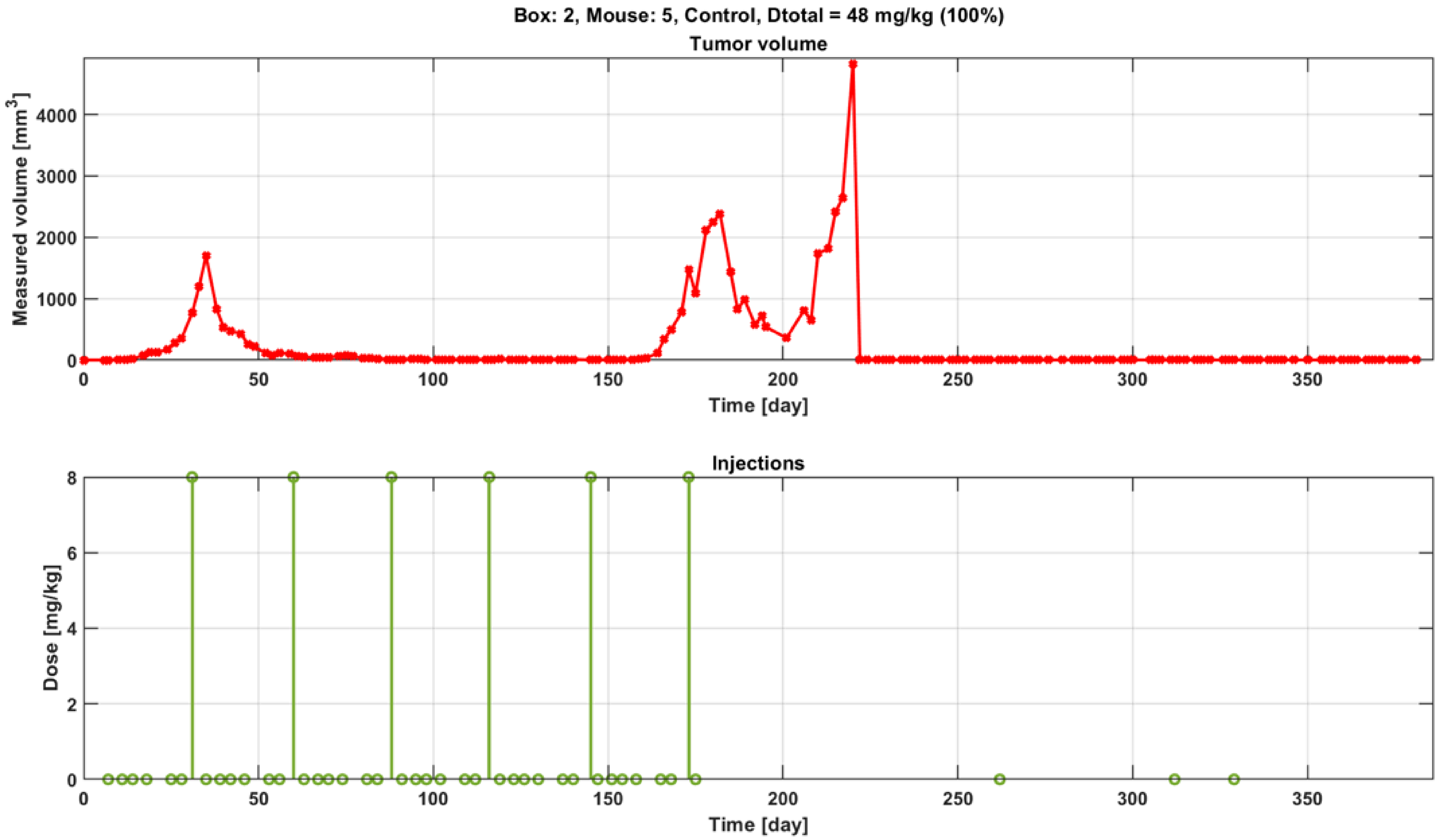
MPC GROUP

- 21 mice
- Longest survival: 513 days
- Cummulated dose: 89.14%

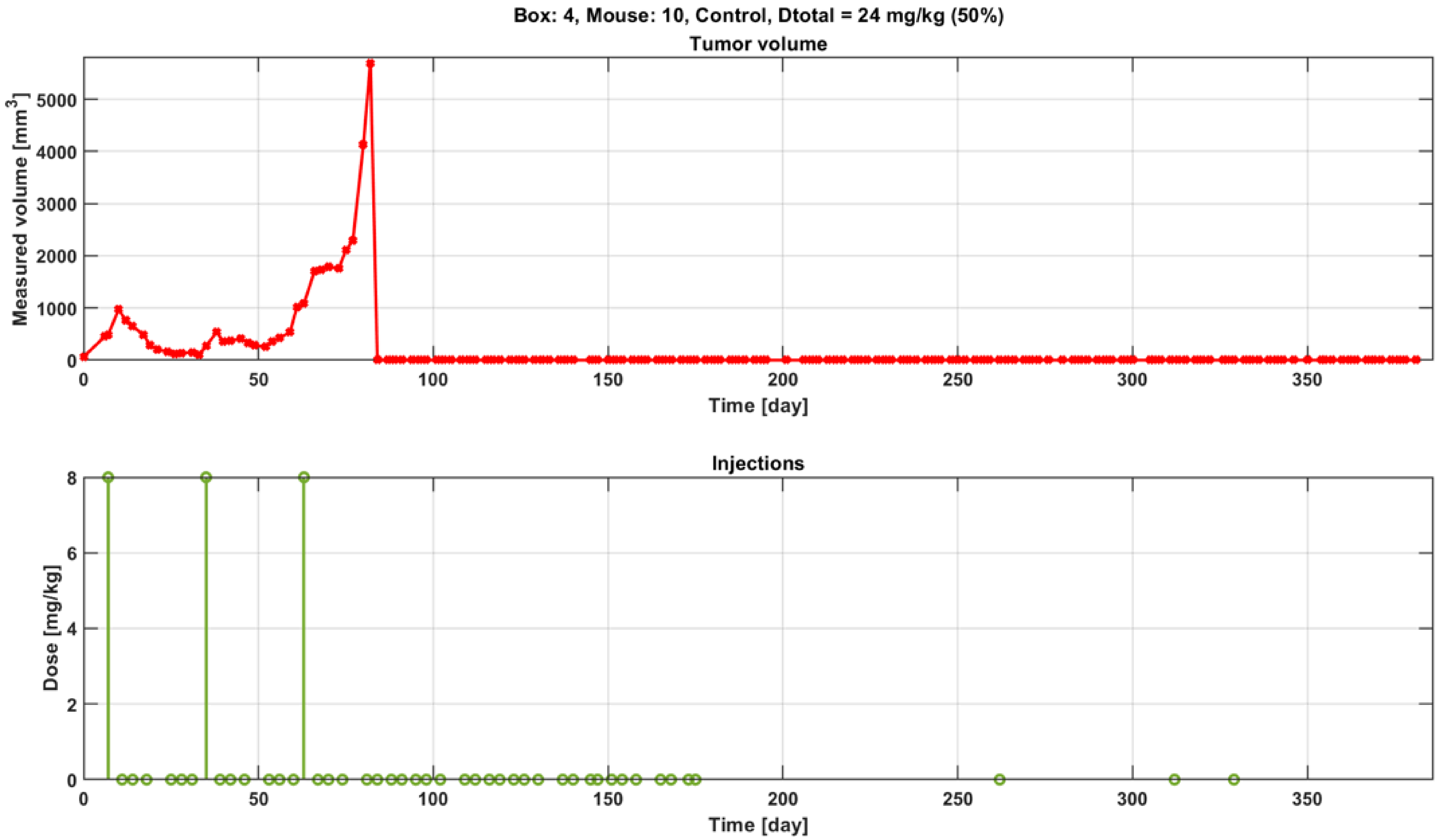
PDPK GROUP

- 21 mice
- 1 mouse healed
- Cummulated dose: 68.79%

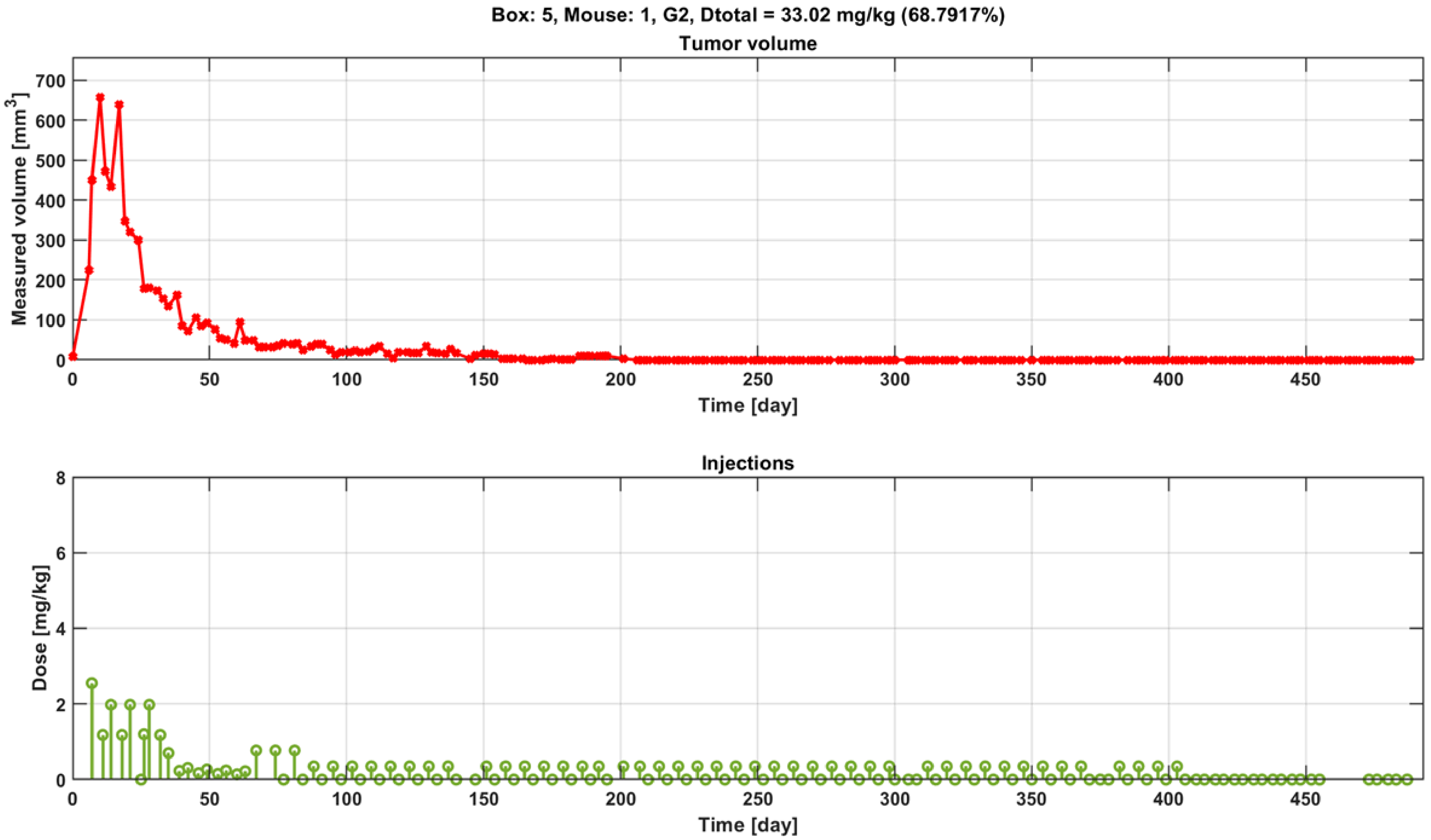
Chemotherapy Optimization: control group



Chemotherapy Optimization: control group



Chemotherapy Optimization: PDPK



D. A. Drexler, I. Nagy, V. G. Romanovski, **Stability analysis of the singular points and Hopf bifurcations of a tumor growth model**, Mathematical Methods in the Applied Sciences, 2024

Mathematical Methods in the Applied Sciences

RESEARCH ARTICLE | Open Access

Stability analysis of the singular points and Hopf bifurcations of a tumor growth control model

Dániel András Drexler, Ilona Nagy, Valery G. Romanovski

First published: 17 January 2024 | https://doi.org/10.1002/mma.9885

SECTIONS PDF TOOLS SHARE

Abstract

We carry out qualitative analysis of a fourth-order tumor growth control model using ordinary differential equations. We show that the system has one positive equilibrium point, and its stability is independent of the feedback gain. Using a Lyapunov function method, we prove that there exist realistic parameter values for which the systems admit limit cycle oscillations due to a supercritical Hopf bifurcation. The time evolution of the state variables is also represented.

Received: 1 July 2022 | Revised: 14 October 2023 | Accepted: 14 December 2023

DOI: 10.1002/mma.9885

RESEARCH ARTICLE WILEY

Stability analysis of the singular points and Hopf bifurcations of a tumor growth control model

Dániel András Drexler[1] | Ilona Nagy[2] | Valery G. Romanovski[3,4,5]

[1]Physiological Controls Research Center, Obuda University, Budapest, Hungary
[2]Department of Analysis and Operations Research, Institute of Mathematics, Budapest University of Technology and Economics, Budapest, Hungary
[3]Faculty of Electrical Engineering and Computer Science, University of Maribor, Maribor, Slovenia
[4]Center for Applied Mathematics and Theoretical Physics, University of Maribor, Maribor, Slovenia
[5]Faculty of Natural Science and Mathematics, University of Maribor, Maribor, Slovenia

Correspondence
Ilona Nagy, Department of Analysis and Operations Research, Institute of Mathematics, Budapest University of Technology and Economics, Műegyetem rkp. 3., H-1111 Budapest, Hungary.
Email: nagyi@math.bme.hu

Communicated by: Y. S. Xu

Funding information
National Research, Development and Innovation Fund of Hungary, Grant/Award Number: 2019-1.3.1-KK; Hungarian National Research, Development and Innovation Fund of Hungary, Grant/Award Number: TKP2021-NKTA-36; Horizon 2020-2017-RISE-777911; Starting Excellence Researcher Program of Óbuda University, Budapest, Hungary; Slovenian Research Agency, Grant/Award Number: P1-0306 and BI-HU/19-20-002; Al-Farabi Kazakh National University, Grant/Award Number: AP09260317

We carry out qualitative analysis of a fourth-order tumor growth control model using ordinary differential equations. We show that the system has one positive equilibrium point, and its stability is independent of the feedback gain. Using a Lyapunov function method, we prove that there exist realistic parameter values for which the systems admit limit cycle oscillations due to a supercritical Hopf bifurcation. The time evolution of the state variables is also represented.

KEYWORDS
bifurcation, cancer therapy, limit cycle, singular point, tumor control, tumor therapy

MSC CLASSIFICATION
34C07, 34C25, 34D20, 37G15

Mathematical model

$$\dot{x}_1 = ax_1 - nx_1 - bx_1 \frac{x_3}{ED_{50} + x_3}$$

$$\dot{x}_2 = nx_1 - wx_2 + bx_1 \frac{x_3}{ED_{50} + x_3}$$

$$\dot{x}_3 = -cx_3 - k_1 x_3 + k_2 x_4 + u$$

$$\dot{x}_4 = k_1 x_3 - k_2 x_4.$$

Wearable injection device control law

$$u(x_1, x_2) = ky = k\left(x_1 + x_2\right)$$

Nontrivial singular point

$$x_1^* = -\frac{cED_{50}(a-n)w}{k(a-b-n)(a+w)}$$

$$x_2^* = -\frac{acED_{50}(a-n)}{k(a-b-n)(a+w)}$$

$$x_3^* = -\frac{ED_{50}(a-n)}{a-b-n}$$

$$x_4^* = -\frac{ED_{50}k_1(a-n)}{k_2(a-b-n)}$$

$a - n > 0$

The immune system can not handle the tumor

$a - b - n < 0$

The drug is effective against the tumor

The singular points are all positive

The Jacobian at the singular point and its characteristic polynomial

$$J = \begin{pmatrix} 0 & 0 & J_{1,3} & 0 \\ a & -w & J_{2,3} & 0 \\ k & k & -c-k_1 & k_2 \\ 0 & 0 & k_1 & -k_2 \end{pmatrix}$$

$$J_{1,3} = -\frac{c(a-n)(-a+b+n)w}{bk(a+w)}$$

$$J_{2,3} = \frac{c(a-n)(-a+b+n)w}{bk(a+w)}$$

$$\begin{aligned} p(s) = \frac{1}{b}\big(&-a^2ck_2w + abck_2w + 2ack_2nw - bck_2nw - ck_2n^2w \\ &- a^2cws + abcws + bck_2ws + 2acnws - bcnws - cn^2ws \\ &+ bck_2s^2 + bcws^2 + bk_1ws^2 + bk_2ws^2 \\ &+ bcs^3 + bk_1s^3 + bk_2s^3 + bws^3 + bs^4\big) \end{aligned}$$

The characteristic polynomial

$$p(s) = \frac{1}{b}\left(-a^2ck_2w + abck_2w + 2ack_2nw - bck_2nw - ck_2n^2w \right.$$
$$- a^2cws + abcws + bck_2ws + 2acnws - bcnws - cn^2ws$$
$$+ bck_2s^2 + bcws^2 + bk_1ws^2 + bk_2ws^2$$
$$\left. + bcs^3 + bk_1s^3 + bk_2s^3 + bws^3 + bs^4\right)$$

Does not depend on *k*!

Looking for pure imaginary eigenvalues

We look for model parameter values such that the characteristic polynomial can be writen in the form

$$p(s) = \left(b_0 + b_1 s + b_2 s^2\right)\left(s^2 + W\right)$$

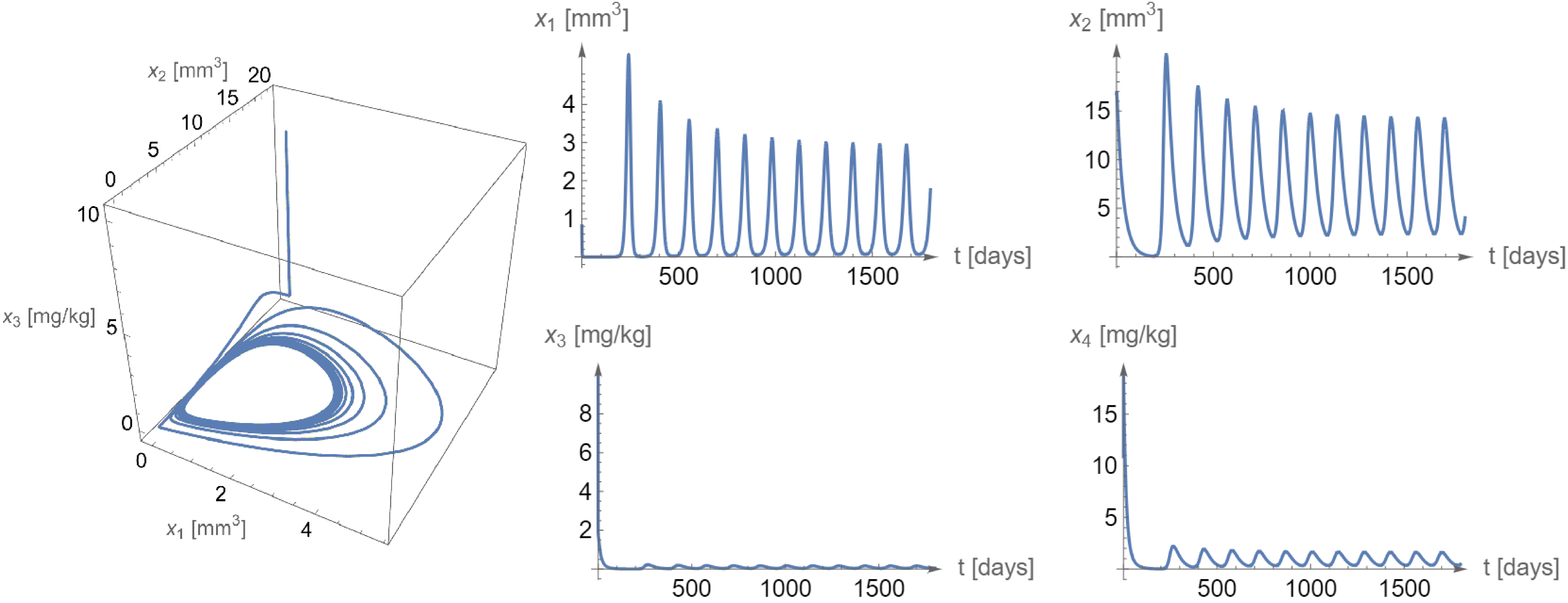
with W>0.

Using realistic parameter values, we get a two dimensional center manifold

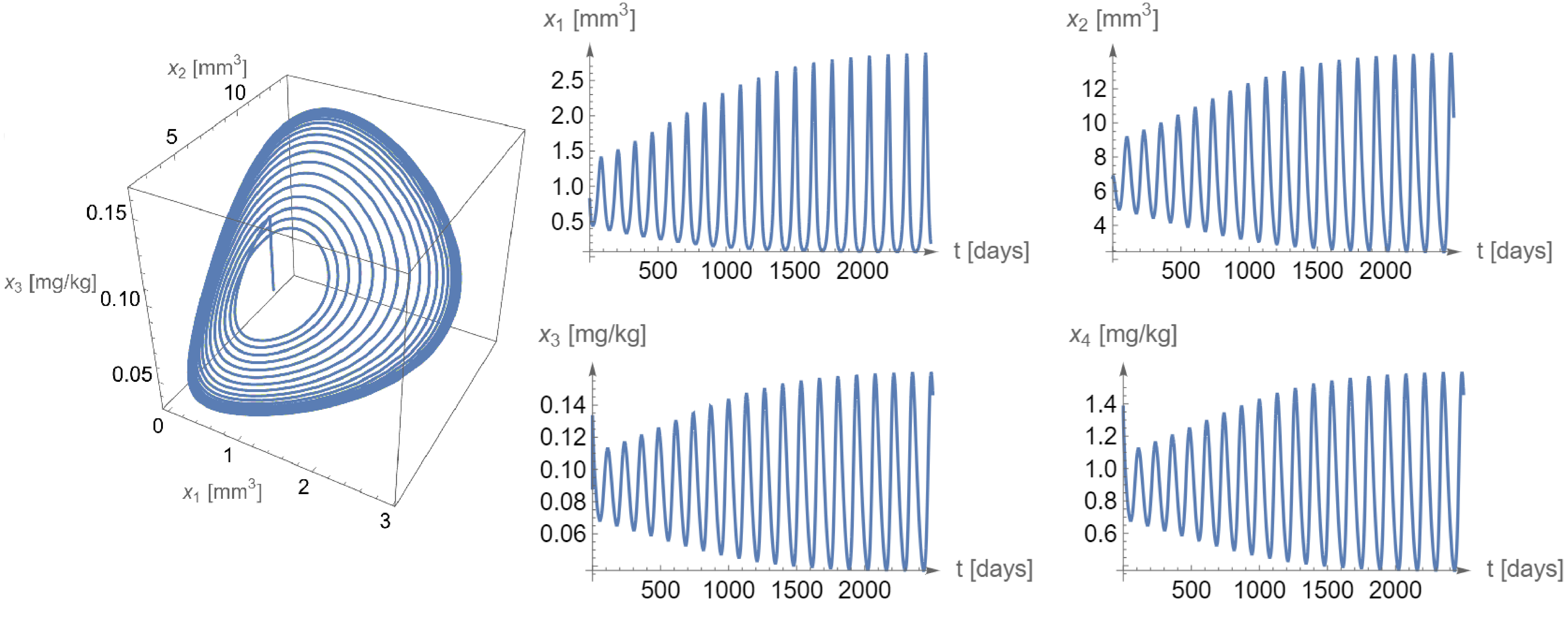
$$s_1 = -183.979$$
$$s_2 = -0.108065$$
$$s_3 = +0.0485016i$$
$$s_4 = -0.0485016i$$

Lyapunov method showed it is a stable focus: The system admits a supercritical Hopf bifurcation

Starting from the outer part of the cycle



Starting from the inner part of the cycle



Conclusion

Qualitative theory can be applied to understand several phenomena in chemotherapy.

Can the same theory be applied for impulsive systems?

What is the class of functions used in the feedback such that the qualitative properties do not depend on the function parameters?

Thank you for your attention!

Contact: **Dániel András Drexler**
Obuda University, Hungary
Research, Innovation and Service Center of Obuda University
Physiological Controls Research Center *(physcon.uni-obuda.hu)*
drexler.daniel@uni-obuda.hu

Farkas Miklós Seminar on Applied Analysis, Budapest University of Technology and Economics
March 27, 2025

TAMED CANCER ERC Stg Grant
Physiological Controls Research Center Obuda University
European Commission
Horizon 2020 European Union funding for Research & Innovation
erc European Research Council
Nemzeti Kutatási, Fejlesztési és Innovációs Hivatal
AZ NKFI ALAPBÓL MEGVALÓSULÓ PROJEKT