Mathematical oncology: my personal perspective

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Colloquium MIM

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UNIVERSITY OF WARSAW

BIOMATΣMATYKA TEORIA GIER

Beginnings

25 years ago

In Oberwolfach Research Institute for Mathematics

Beginnings

EU programmes

- “Using Mathematical Modelling and Computer Simulation to Improve Cancer Therapy”, No. HPRN-CT-2000-00105, in the framework of the 5th EU Programme, 2000–2003;
- “Modelling, Mathematical Methods and Computer Simulation of Tumour Growth and Therapy”, No. MRTN-CT-2004-503661, in the framework of 6th EU Programme, 2004–2008.

People

Nicola Bellomo

Professor of Mathematical Physics and Applied Mathematics

Recent Open Source Papers

What is life? A perspective of the mathematical kinetic theory of active particles

A multiscale model of virus pandemic: Heterogeneous interactive entities in a globally connected world

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- International Research Projects
- Journals and Book Series
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- Books
- Videos
- Papers: refer to my Research ID Publication List

Distinguished Professor at the University of Granada
Profile - E-mail: nicola.bellomo@ugr.es

Professor emeritus at the Polytechnic University of Torino
Profile - E-mail: nicola.bellomo@polito.it

Research ID: B-3431-2010

Highly Cited: search Web of Science index

University of St Andrews | FOUNDED 1413

School of Mathematics and Statistics

Prof Mark Chaplain

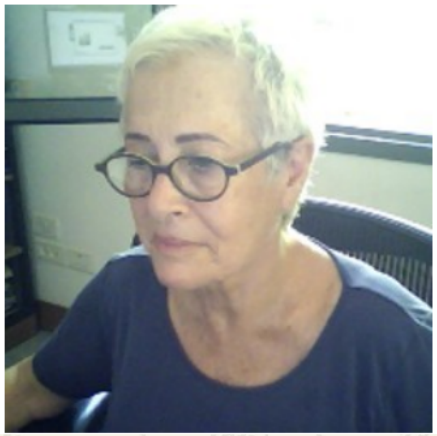
Gregory Chair of Applied Mathematics

Researcher profile

Research areas

Cancer is one of the major causes of death in the world, particularly the developed world, with around 11 million people diagnosed and around 9 million people dying each year. The World Health Organisation (WHO) predicts that current trends show the number rising to 11.5 million in 2030. There are few individuals who have not been touched either directly or indirectly by cancer. While treatment for cancer is continually improving, alternative approaches can offer even greater insight into the complexity of the disease and its treatment. Biomedical scientists and clinicians are recognising the need to integrate data across a range of spatial and temporal scales (from genes through cells to tissues) in order to fully understand cancer.

My main area of research is in what may be called "mathematical oncology" i.e. formulating and analysing mathematical models of cancer growth and treatment. I have been involved in developing a variety of novel mathematical models for all the main phases of solid tumour growth, namely: avascular solid tumour growth, the immune response to cancer, tumour-induced angiogenesis, vascular tumour growth, invasion and metastasis.



Prof. Zvia Agur – President

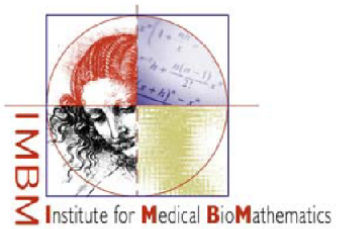
Professor Zvia Agur is Founder and President of the scientific research Institute for Medical BioMathematics (IMBM). As the senior scientist in IMBM, ZA is responsible for the innovative aspects and the soundness of the scientific concepts and methodologies developed in IMBM. ZA has more than four decades of scientific research in mathematical biomedicine and over twenty years of experience in leading technology development in the Healthcare domain. During these years she has made major contributions to the theory of disease dynamics, chemotherapy optimization and vaccination policies. She has led innovative development and was initiator and co-author of 15 granted USA, European and international patents. She has been Co-Founder & President of the Israeli Society of Theoretical and Mathematical Biology and Co-Founder & Member of the Board of Directors of the European Society of Mathematical and Theoretical Biology (ESMTB). Agur was a 2016 finalist for the EU Prize for Women Innovators and was elected to the rank of 2022 Fellow of the American Association for the Advancement of Science for “developing computational models of diseases and incorporating these into medical software devices to facilitate drug development and personalized patient treatment.”

Mathematical oncology: idea

Mathematical oncology

This is a term that began to gain popularity
with the establishment of centers around the world
in which scientists of various specialities,
including **mathematicians**
working on mathematical modeling
of the studied processes and therapies,
started to comprehensively deal with the problem of cancer.

Mathematical oncology: Institute for Medical Biomathematics, Israel



IMBM for Drug Development

IMBM develops sophisticated scientific methods for optimizing cancer clinical treatments. At present, we focus on optimization programs for various chemotherapeutic protocols with or without different combinations of hemopoietic growth factors. The methods are based on the analysis of mathematical models describing the complex cancer and hemopoietic dynamics, and on elaborate optimization algorithms. These developments enable a significant reduction of time and expenses in the drug-development process.

Analyzing Drug Efficacy

Analyzing drug efficacy is based on the mathematical models and technologies existing at IMBM. It contains detailed mathematical models for the dynamics of cancer growth and the hemopoietic process under drug administration. These single-purpose models are tightly based on an up-to-date biological, pharmaco-dynamic and pharmaco-kinetic information and adjusted according to the specifications of the drug developer. We use these models for constructing a single-purpose software tool to be used for evaluating specific administration protocols.

Optimizing Treatment Protocols

IMBM implements its mathematical models in a further development for determining the optimal treatment protocol for a specific drug. Thus, sophisticated optimization algorithms are adapted to the specific characteristic of the drug to operate on the cancer models. Protocol's "optimality" is determined by using pre-specified constraints on its applicability (e.g., the maximum tolerable toxicity), and a mathematical function of many different criteria is used for testing its efficacy.

IMBM for Cancer Clinics

A long-term objective of IMBM is to develop sophisticated scientific methods for optimizing cancer treatments. Notably, we focus on the development of optimization programs for various chemotherapeutic protocols with or without different combinations of hemopoietic growth factors (some of these factors are still in clinical trials). The methods are based on the analysis of mathematical models describing the complex cancer and hemopoietic dynamics, and on elaborate optimization algorithms. These developments are expected to guarantee optimization of the treatment program for each individual patient, so as to ensure the best results according to physicians' definitions.

Mathematical oncology: Moffitt Cancer Center, USA

Home / Research Science / Divisions and Departments / Quantitative Science / Integrated Mathematical Oncology

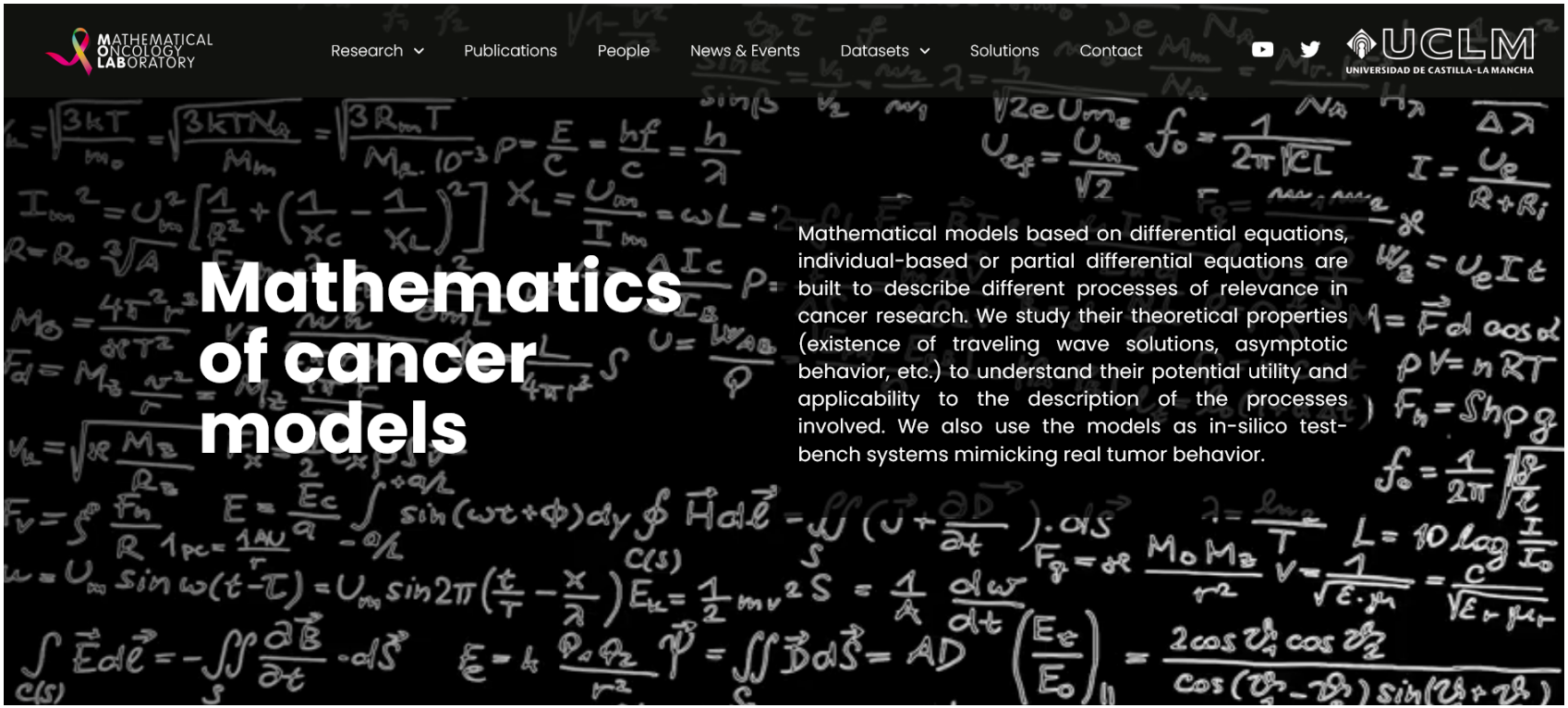
Integrated Mathematical Oncology

Integrate: to combine one thing with another so that they become a whole

Cancer is a dynamic complex multiscale system that can only truly be understood via the integration of theory and experiments. The mission of the **Integrated Mathematical Oncology (IMO) Department** is to use such an integrated approach to better understand cancer initiation, progression and treatment and to aid in the clinical utilization of integrated models in precision medicine. The multiscale nature of cancer, in which genetic mutations occurring at a subcellular level manifest themselves as functional changes at the cellular and tissue scale, requires modeling approaches of a similar nature. Within the IMO, we have been developing a suite of mathematical and computational models that allow us to consider each of these scales in detail as well as bridge them. Theoretical models are ideal for studying the complex dialogue between the tumor and its environment, and has brought a new foci to Moffitt developing around the themes of tumor evolution and the microenvironment.

Just because cancer is a complex dynamic process does not mean that we cannot fully understand it. In fact, many complex systems are driven by relatively simple laws. By using a range of mathematical modeling approaches targeted at specific types of cancer IMO is aiding in the development and testing of new treatment strategies as well as facilitating a deeper understanding of why they fail. This multi-model, multi-scale approach has led to a diverse and rich interdisciplinary environment within IMO, one that is creating many novel approaches for the treatment and understanding cancer.

Mathematical oncology: MOLAB, Spain



Underlying tumor growth law

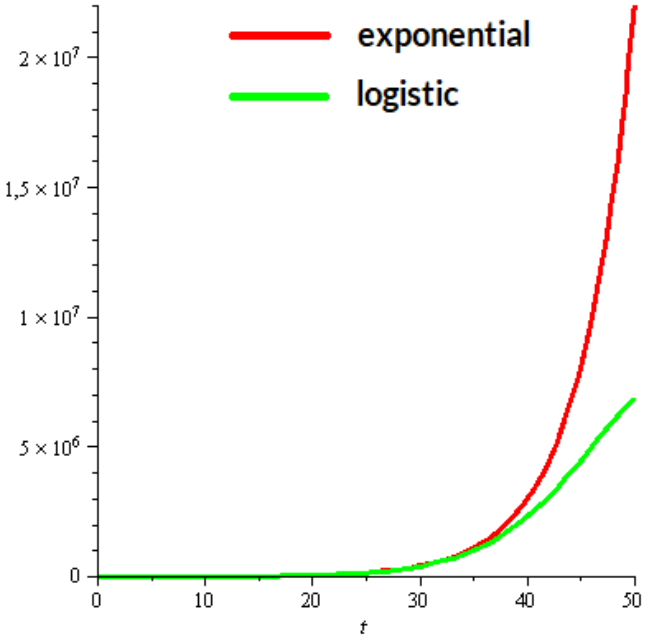
PROBLEM:

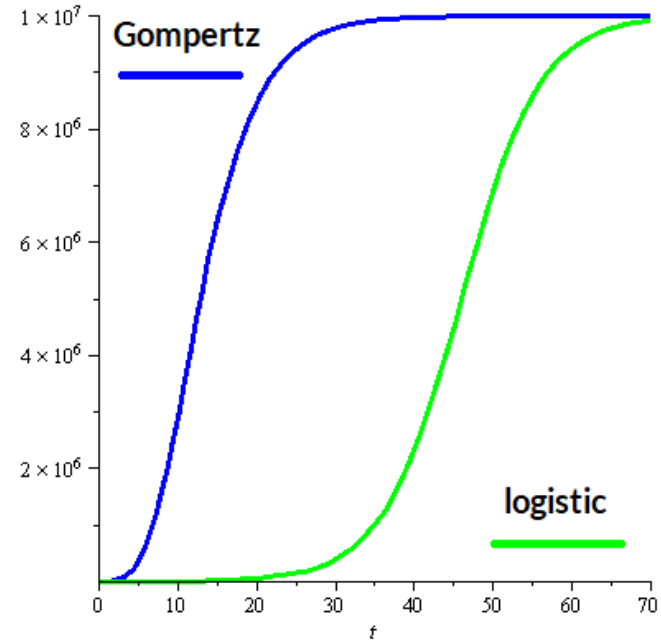
there is no universal law...

Basic laws:

- exponential growth
  $\dot{T} = rT;$
- Gompertz growth
  $\dot{T} = -rT \ln \frac{T}{K};$
- logistic growth
  $\dot{T} = rT\left(1 - \frac{T}{K}\right).$

and many others...





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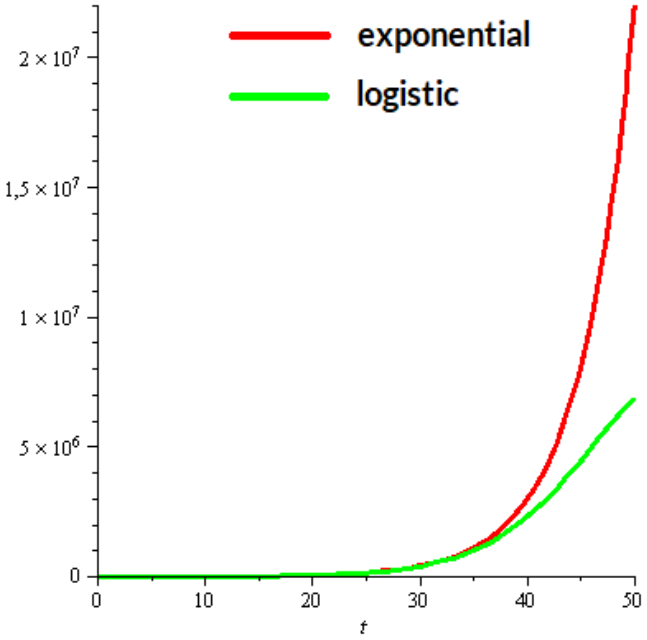

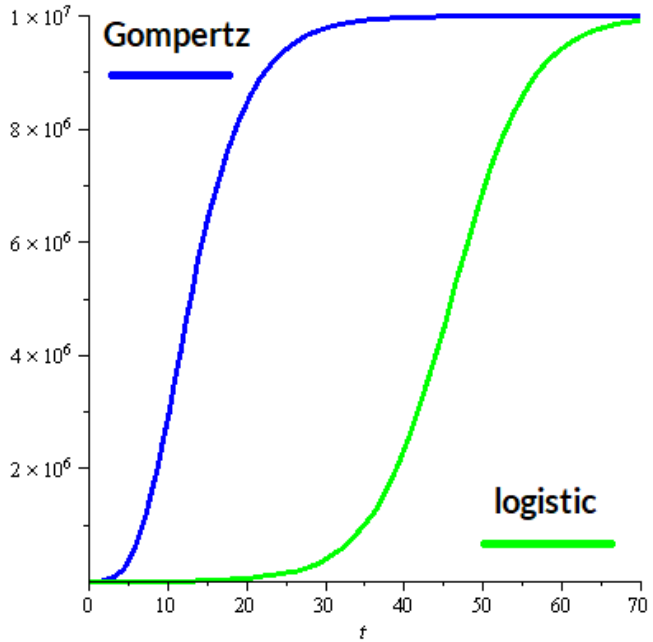

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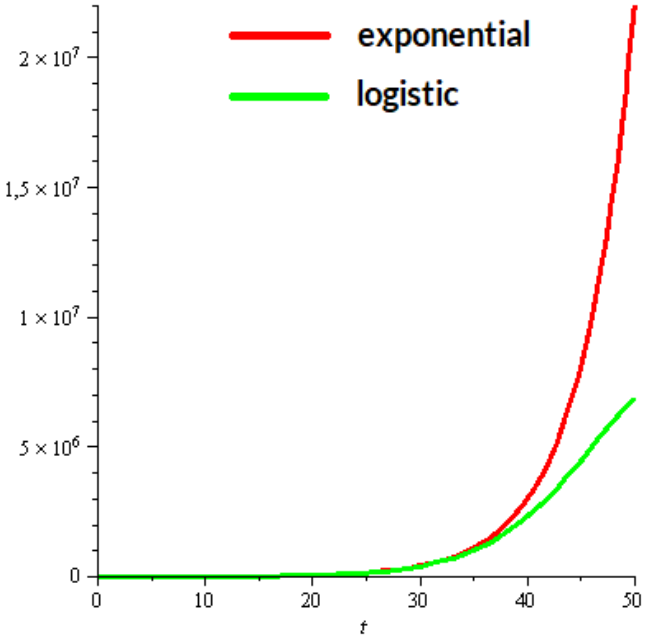

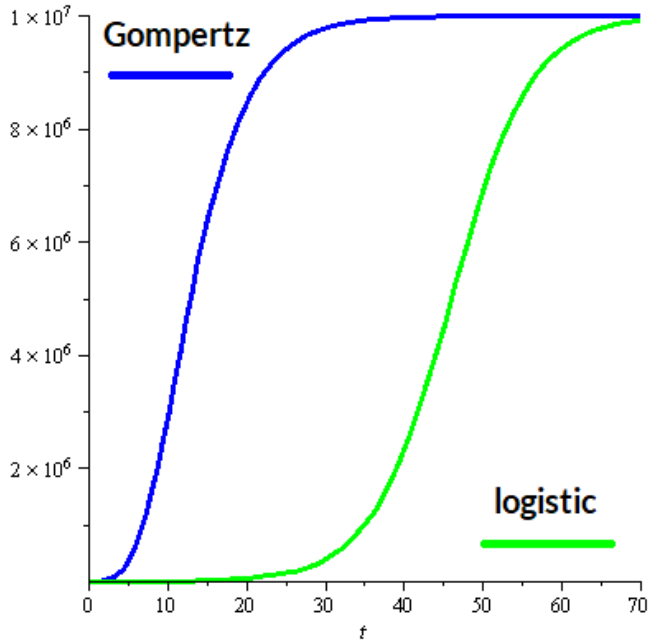

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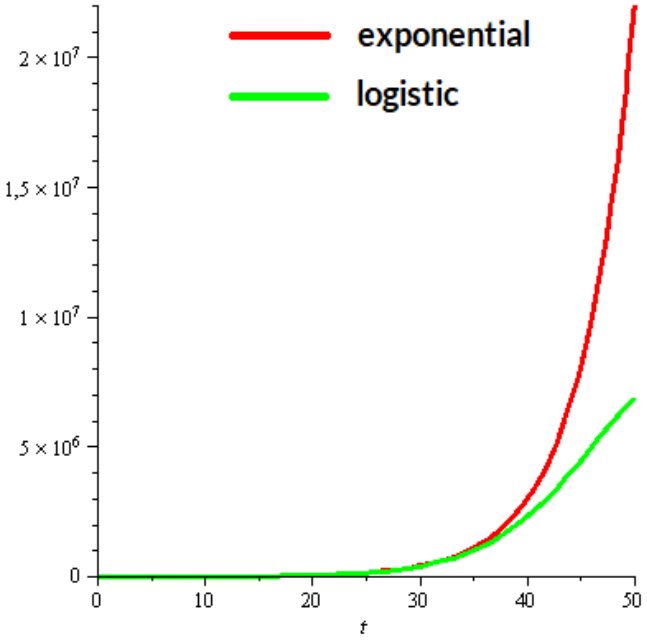

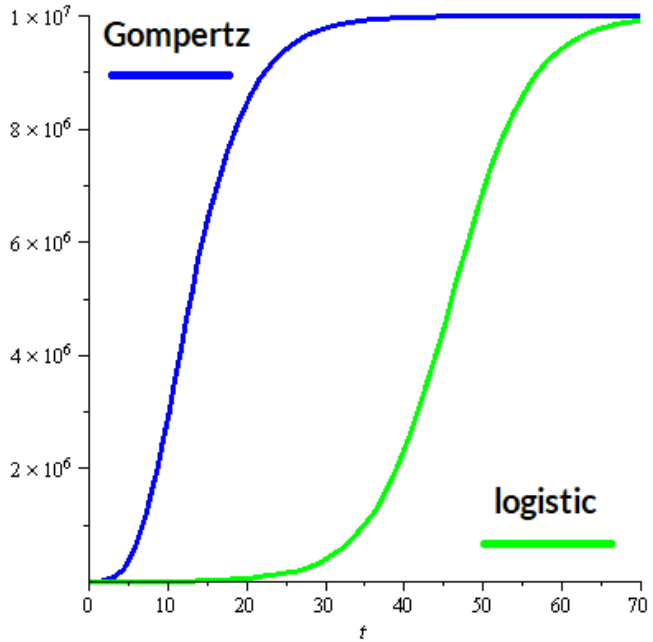

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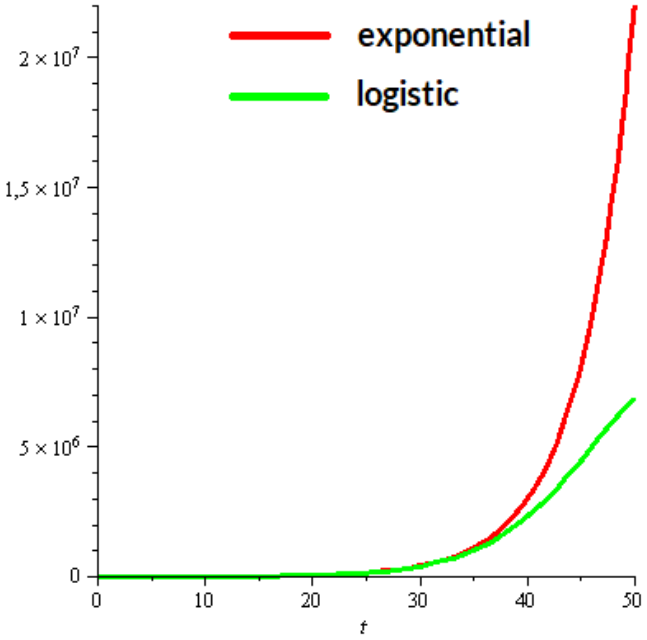
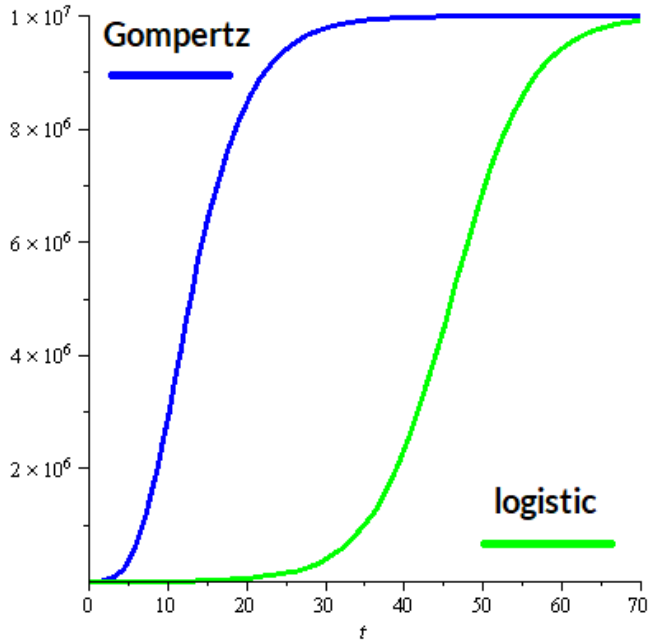




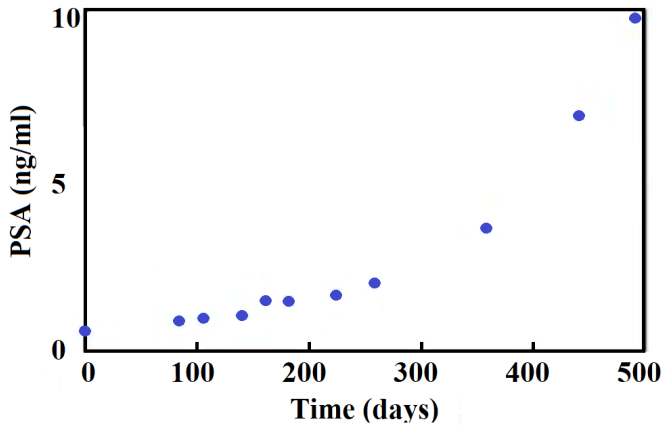
Underlying tumor growth law: case of the prostate cancer (PC)

$$\dot{P} = Pf(P),$$

$$f(P) = \begin{cases} a, & \text{for } P \in [0, P_R], \\ a\left(1 + b \ln \frac{P}{P_R}\right)^{\gamma}, & \text{for } P > P_R, \end{cases}$$

$P(t)$ – amount of the PSA (tumor marker) at time t.

- U.F., A. Nahshony, M. Elishmereni, Mathematical model of hormone sensitive prostate cancer treatment using leuprolide: A small step towards personalization, *Plos one* **17**(2), 2022, e0263648.



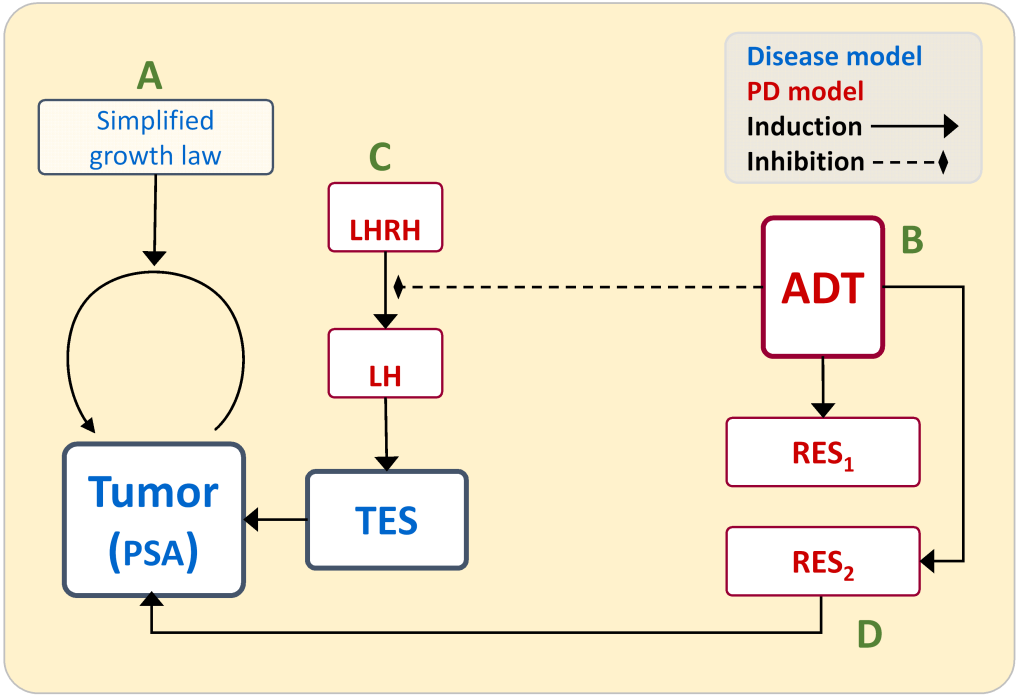
Example of the clinical data from Mayo clinic

Modeling: PART II (specific treatment)

Androgen deprivation therapy for hormone sensitive PC patients

Drugs used during ADT eventually lead to acquired drug resistance, HSPC evolves to castrate-resistant prostate cancer (CRPC).

Our interest lies mainly in the prediction of time to biochemical failure of ADT.



- **A** underlying growth law of the tumor;
- **B** PK-PD model for leuprolide;
- **C** testosteron secretion;
- **D** influence of resistance.

B PK model for leuprolide

The mechanism of the drug release (PK) is based on polymer micro-spheres.
We consider diffusion of the drug out of the spheres,

$$\frac{\partial \rho}{\partial t} = D\nabla^2 \rho,$$

where ρ is the drug concentration and D is the diffusion coefficient. Under some symplifying assumptions, we solve this equation and then the concentration can be integrated to obtain the amount M_{in} of the drug within the sphere

$$M_{\text{in}}(t) = 4\pi \int_0^R \rho(r,t)\, r^2 dr = \sum_{n=1}^{\infty} \frac{8\rho_0 R^3}{n^2\pi} \mathrm{e}^{-\frac{n^2\pi^2 D}{R^2}t}.$$

B PK model for leuprolide

Once the drug leaves the micro-sphere, it is cleared from the body at a rate d_L, therefore

$$\dot{M}_{\text{out}} = -\dot{M}_{\text{in}} - d_L M_{\text{out}},$$

where M_{out} is the amount of the drug outside the sphere.

The final equation for leuprolide within the patients body

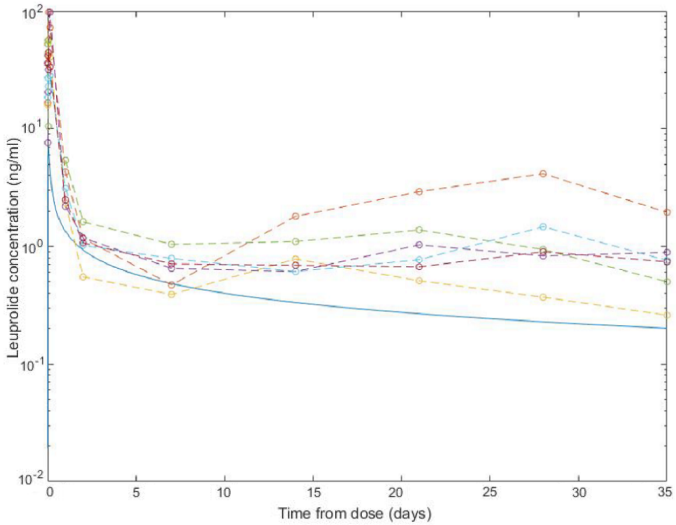
$$\dot{L} = k\psi\left(\frac{\alpha t}{M_0}\right) - d_L L,$$

$\psi(x) = \sum_{n=1}^{\infty} e^{-\pi^2 n^2 x}$ and $M_0 = \frac{4}{3}\pi R^3 \rho_0$ is the initial mass of the drug within the sphere.

Modeling: ADT for HSPC

B PK model for leuprolide

The function L was fitted to FDA data on leuprolide.



B PD model for leuprolide

We take into account a kind of the competition between one of the hormons in the testosteron secretion path (LHRH) and the drug.

Modeling: ADT for HSPC

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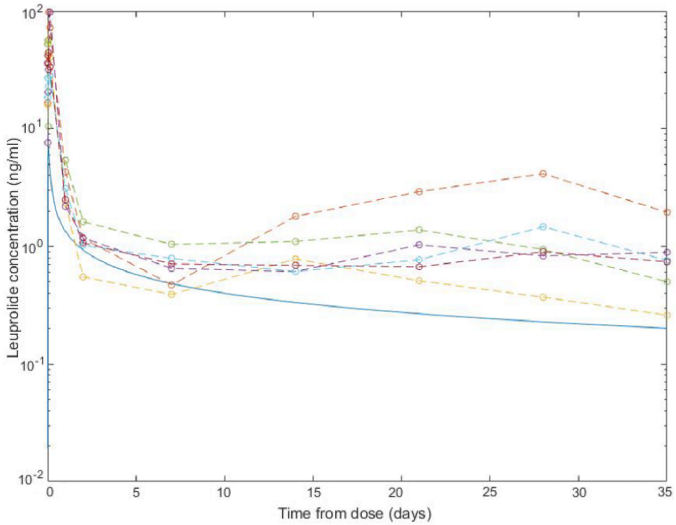

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Modeling: ADT for HSPC

C Modeling of testosterone secretion

Testosteron secretion is regulated by a three-component feedback network consisting with three hormones:

- luteinizing hormone releasing hormone LHRH;
- luteinizing hormone LH;
- testosterone TES.

However, we found that the intermediate hormone LH can be omitted in the model.

C Modeling of testosterone secretion

$$\dot{x} = h_1(z) - d_1 x,$$
$$\dot{z} = p_3 x - d_3 z,$$

where

- $x(t)$, $z(t)$ are concentrations of LHRH and TES at time t,
- h_1 is a smooth positive decreasing function.

Influence of leuprolide on testosterone secretion

Instead of linear production term $p_3 x$ we take

$$h_3(x, L) = \frac{p_3 x}{1 + b_3(x + L)}.$$

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Influence of leuprolide on testosterone secretion

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$$h_3(x, L) = \frac{p_3 x}{1 + b_3(x + L)}.$$

The model without resistance

$$\dot{P} = Pf(P) + d_P(z - \bar{z}_0)P,$$
$$\dot{x} = h_1(z) - d_1 x,$$
$$\dot{z} = h_3(x, L) - d_3 z,$$

where $\bar{z}_0$ is the testosteron steady state without the treatment, and general functions f, h_1, h_3 satisfy:

1. f is of class $\mathbf{C}^1$ and has positive values on some interval $(0, K)$, where either $K < \infty$ and then it reflects maximal tumor size or $K = \infty$ and then tumor growth is unbounded;
2. h_1 and h_3 are positive bounded functions of class $\mathbf{C}^1$;
3. $\frac{dh_1}{dz} < 0$, $\frac{\partial h_3}{\partial x} > 0$, $\frac{\partial h_3}{\partial (x+L)} < 0$.

D Influence of resistance

The last step in the model development is to include resistance. We distinguish two different mechanisms:

- resistance to the drug, that causes testosterone to rise in the presence of ADT,
- emerging independence from testosterone, which causes PSA to rise even though the testosterone is low.

Including resistance we introduce two additional variables r_i, $i = 1, 2$, reflecting the strength of resistance, described by

$$\dot{r}_i = \beta_i L \left(1 - \frac{r_i}{l_i}\right).$$

The model with resistance

- The first variable r_1 influences the level of PSA and therefore is included into the first equation.
- The second variable r_2 influences the level of TES due to the presence of the drug, so we include it into the third equation.

$$\dot{P} = Pf(P) + d_P(z - \bar{z}_0 + g_1(r_1))P,$$
$$\dot{x} = h_1(z) - d_1 x,$$
$$\dot{z} = h_3\left(x, g_2(r_2)\right) - d_3 z,$$
$$\dot{r}_1 = \beta_1 L\left(1 - \frac{r_1}{l_1}\right),$$
$$\dot{r}_2 = \beta_2 L\left(1 - \frac{r_2}{l_2}\right),$$

- $g_1(0) = 0$ and g_1 is increasing;
- $g_2(0) = L$ and g_2 is decreasing.

Modeling: immunotherapy of glioma

Articles

- N. Kronik *et al.*, Improving alloreactive CTL immunotherapy for malignant gliomas using a simulation model of their interactive dynamics, *Cancer Immunol Immunother*, 2008 **57**: 425–439.
- Y. Kogan, U.F. *et al.*, Cellular immunotherapy for high grade gliomas: mathematical analysis deriving infusion rates based on patients requirements, *SIAM J. APPL. MATH.*, 2010 **70**(6): 1953–1976.

Modeling: immunotherapy of glioma

Model of immunotherapy of MG/GBM

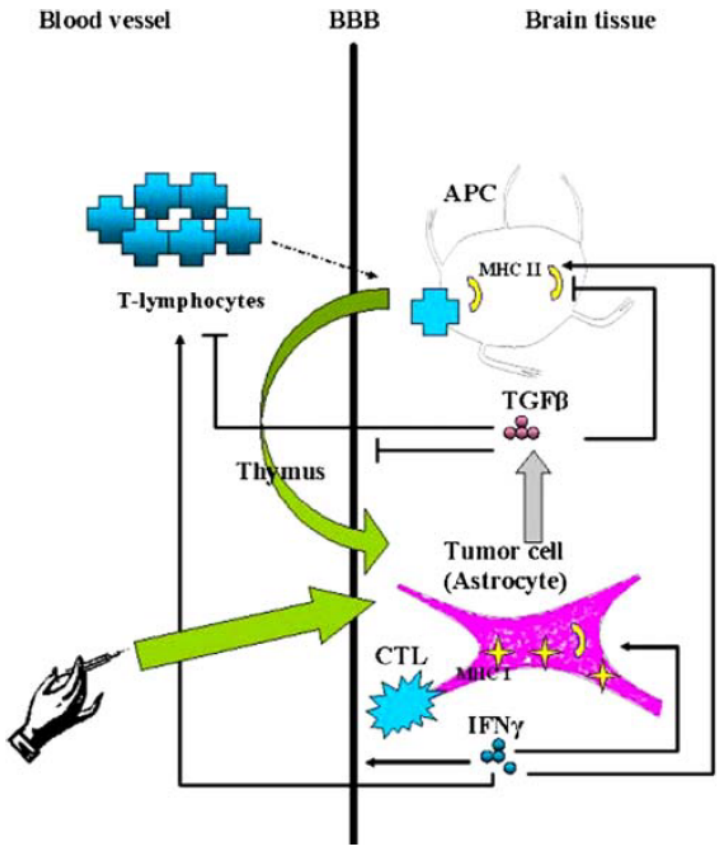
We model interactions between immune system and tumour cells.

Immune system is stimulated by external influx of ex vivo activated alloreactive cytotoxic-T-lymphocytes (aCTL).

There are 6 variables taken into account:

- tumor cells (T),
- CTLs (C),
- cytokines: TGF-β (F_β), INF-γ (F_γ),
- major histocompatibility complex: class I (M_I) and class II (M_{II}).

Scheme of the model:



Model of immunotherapy of MG/GBM

$$
\begin{aligned}
\dot{T} &= r(T)T - f_T(F_\beta)g_T(M_I)h(T)CT,\\
\dot{C} &= f_C(TM_{II})g_C(F_\beta) - \mu_C C + S(t),\\
\dot{F}_\beta &= f_\beta(T) - \mu_\beta F_\beta,\\
\dot{F}_\gamma &= f_\gamma(C) - \mu_\gamma F_\gamma,\\
\dot{M}_I &= f_I(F_\gamma) - \mu_I M_I,\\
\dot{M}_{II} &= f_{II}(F_\beta)g_{II}(F_\gamma) - \mu_{II} M_{II},
\end{aligned}
$$

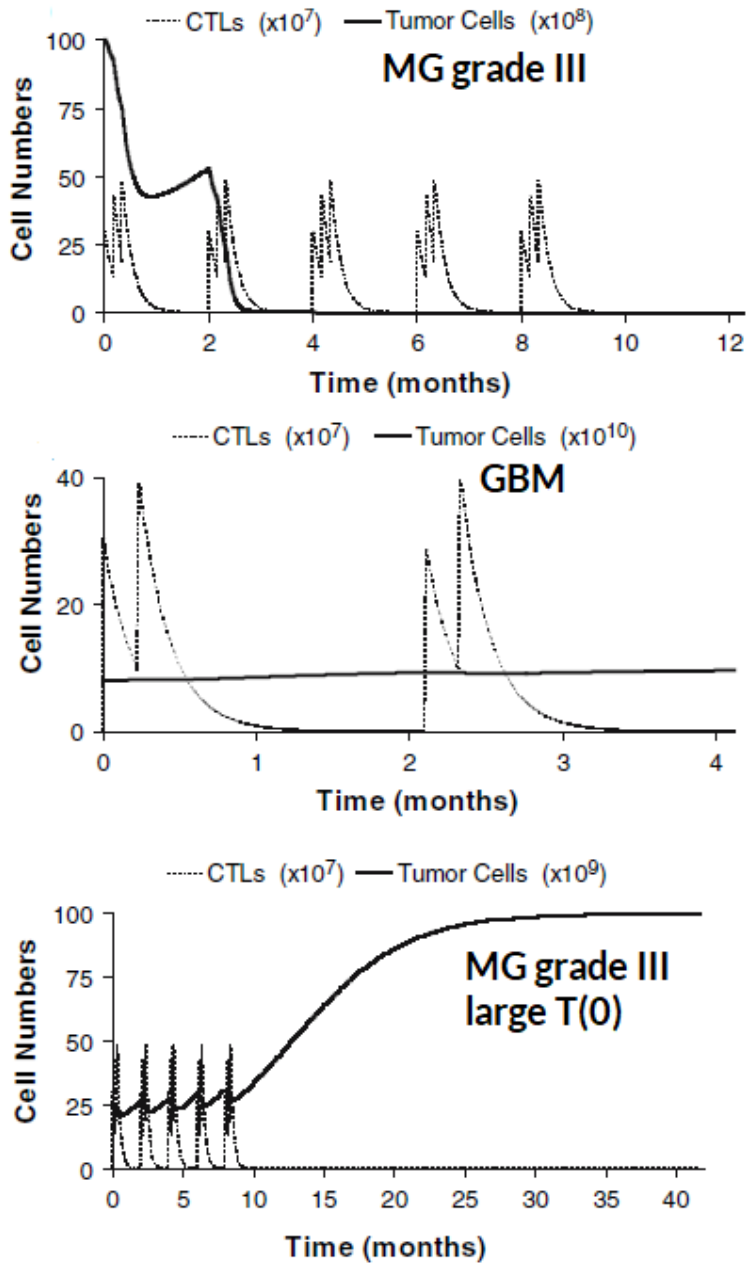
with non-negative functions $r, f_T, g_T, h, f_C, g_C, S, f_\beta, f_\gamma, f_I, f_{II}$,
having appropriate properties,
and positive coefficients $\mu_C, \mu_\beta, \mu_\gamma, \mu_I, \mu_{II}$.

Modeling: immunotherapy of glioma

Results of modeling

Using the model we are able to retrive the results of clinical trials conducted by Prof. Carol Kruse (Sidney Kimmel Cancer Center) on MG grade III (successful) and GBM (unsuccessful).

The clinically administered total aCTL dosage to GBM patients, ca. 12×10^8 aCTL, was about 20-fold smaller than that predicted by the model to be effective (27×10^9).



Modeling: immunotherapy of glioma

Results of modeling

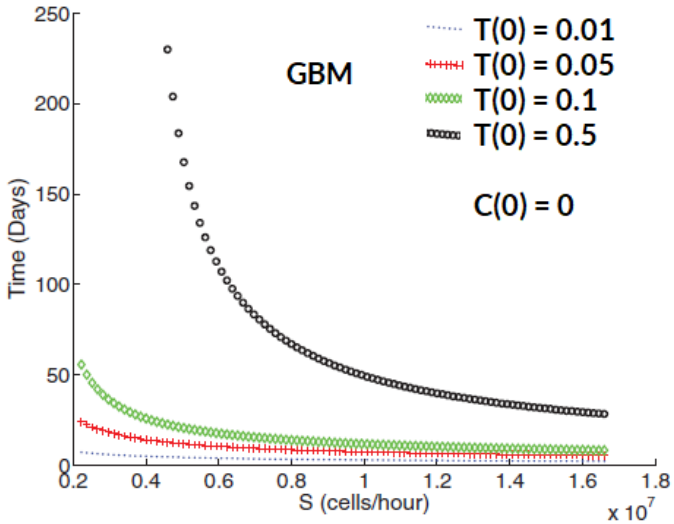
We are able to find a condition for cure analytically:

$$\frac{S}{\mu_C} g_T\left(\frac{f_I\left(\frac{f_\gamma(S/\mu_C)}{\mu_\gamma}\right)}{\mu_I}\right) > \frac{r_0}{f_T\left(\frac{f_\beta(0)}{\mu_\beta}\right)},$$

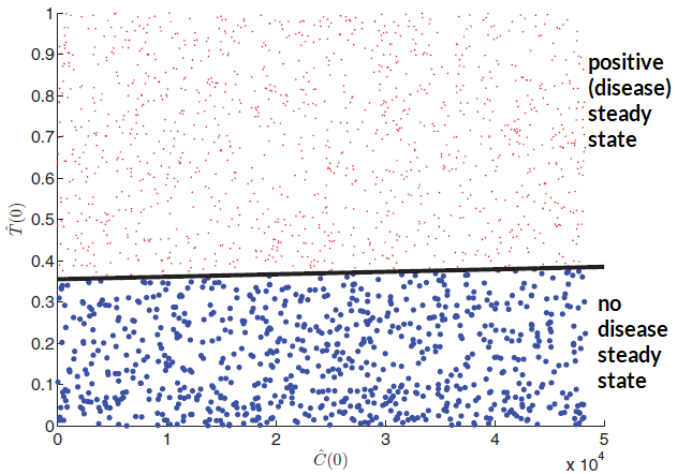
and for the estimated parameters and specific functions used in the original article by Kronik *et al.* we have

- $S \approx 30.4\, cells/h$ for MG grade III,
- $S \approx 84.7\, cells/h$ for GBM.

Estimation of time to cure



Basins of attraction for two steady states



Modeling: control theory

The role of control theory

Using control theory we are able to propose optimal treatment schedule assuming some constraints.

In general, the goal of optimal control applied to cancer models is to minimize the size of cancer (at the end and during the treatment duration) and the amount of drug (cost of therapy and side effects) used in this treatment.

It occurs that for homogeneous populations of cancer cells the structure of optimal control is typically bang-bang, meaning:

- either maximal tolerated dose (MTD) is applied,
- or no dose is applied.

Control theory for heterogeneous cancers

Malignant cancer are not homogeneous.

Is it optimal to use standard treatment schemes based on MTD?

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Control theory for heterogeneous cancers

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Modeling: control theory

Control theory for heterogeneous cancers

Common research with:

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  Piotr Bajger – my former PhD student,

- 

  Mariusz Bodzioch (University of Warmia and Mazury in Olsztyn)

Control theory: simple model of heterogeneous cancer

We consider a population of cancer cells divided into two subpopulations:
sensitive and resistant to the drug which is applied.

$$\dot{n}_1 = \gamma_1 n_1 (1 - n_1 - n_2) - \tau_1 n_1 + \tau_2 n_2 - n_1 u(t),$$
$$\dot{n}_2 = \gamma_2 n_2 (1 - n_2 - n_1) + \tau_1 n_1 - \tau_2 n_2,$$

where:

- n_1, n_2 are the non-dimensional volumes of cells respectively sensitive and resistant to chemotherapy,
- $u : [0, T] \to [0, 1]$ is the non-dimensional chemotherapy dose (or control).

Control theory: objective functional for heterogeneous cancer

We aim, aside from penalising tumour size, to penalise drug-resistant phenotype.

$$\begin{aligned} J(u(\cdot)) &= M\left(n_1(T)+n_2(T)\right) + \int_0^T L\left(n_1(t), n_2(t), u(t)\right) dt \\ &= \omega_1 n_1(T) + \omega_2 n_2(T) \\ &+ \int_0^T \left(\eta_1 n_1(t) + \eta_2 n_2(t) + \xi G\left(\tfrac{n_2-n_1}{\epsilon}\right) + \theta u(t)\right) dt \end{aligned}$$

and the problem becomes
to minimise J over all measurable functions $u : [0,T] \to [0,1]$.
Here $\omega_1 < \omega_2$, η_1, η_2, ξ and θ are non-negative weights.

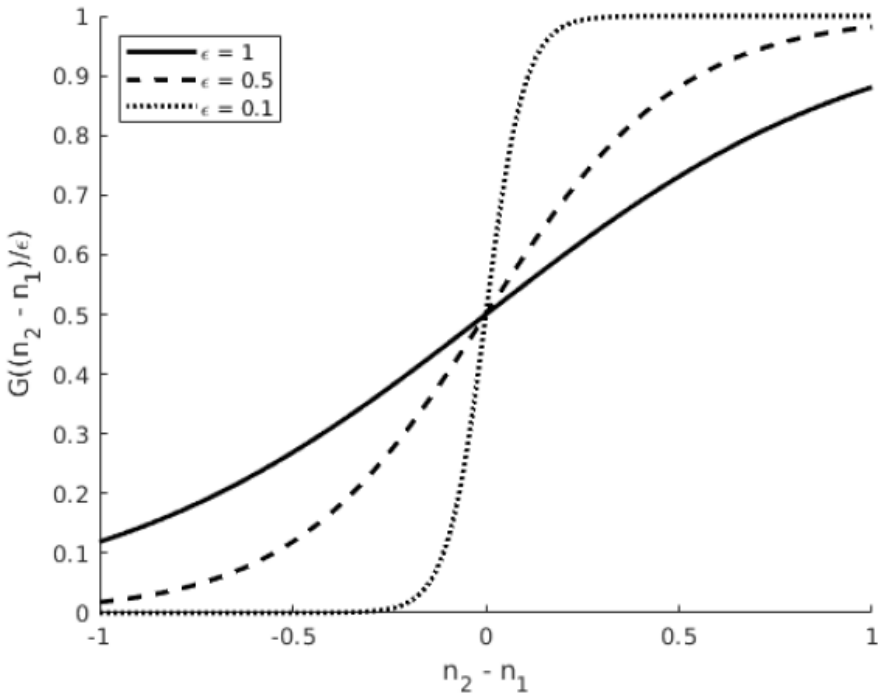
Modeling: control theory for heterogeneous cancers

Control theory: objective functional for heterogeneous cancer

The only non-standard part of the functional J is related to the function G.

Formally, we require G to have the following properties:

- $G(x) \to 0$ as $x \to -\infty$,
- $G(x) \to 1$ as $x \to +\infty$,
- $G'(x) > 0$ for all x,
- $xG''(x) < 0$ for $x \neq 0$,
- $G(0) = 0.5$ and $G'(0) = 0.5$.

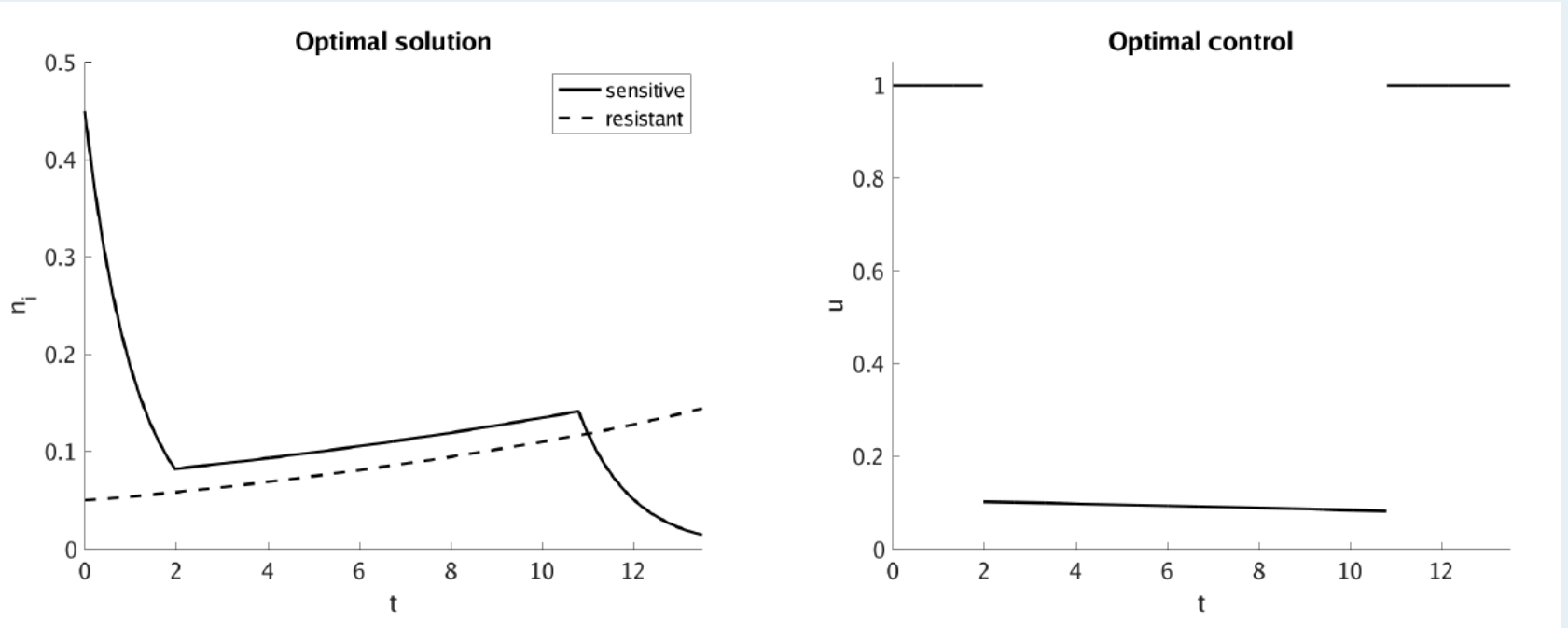


Typical choice for a resistance penalty: $G(z) = \frac{1}{2}\left(1 + \tanh(z)\right)$.

Control theory: results for heterogeneous cancer

We found that the scheme of optimal control is the following:

MTD singular control MTD



The singular interval in the middle – during which the control is applied at about 10% of the MTD dose – is crucial in preserving the sensitive phenotype.

Modeling: control theory for heterogeneous cancers

Metronomic for heterogeneous cancer

Optimality of metronomic treatment (low-dose long-term) for malignant cancers is a hypothesis discussed intensively last years.

The results of our analysis support the hypothesis that inclusion of explicit resistance penalty in the objective functional leads to the low-dose metronomic-type protocols being optimal.

Personalized treatment

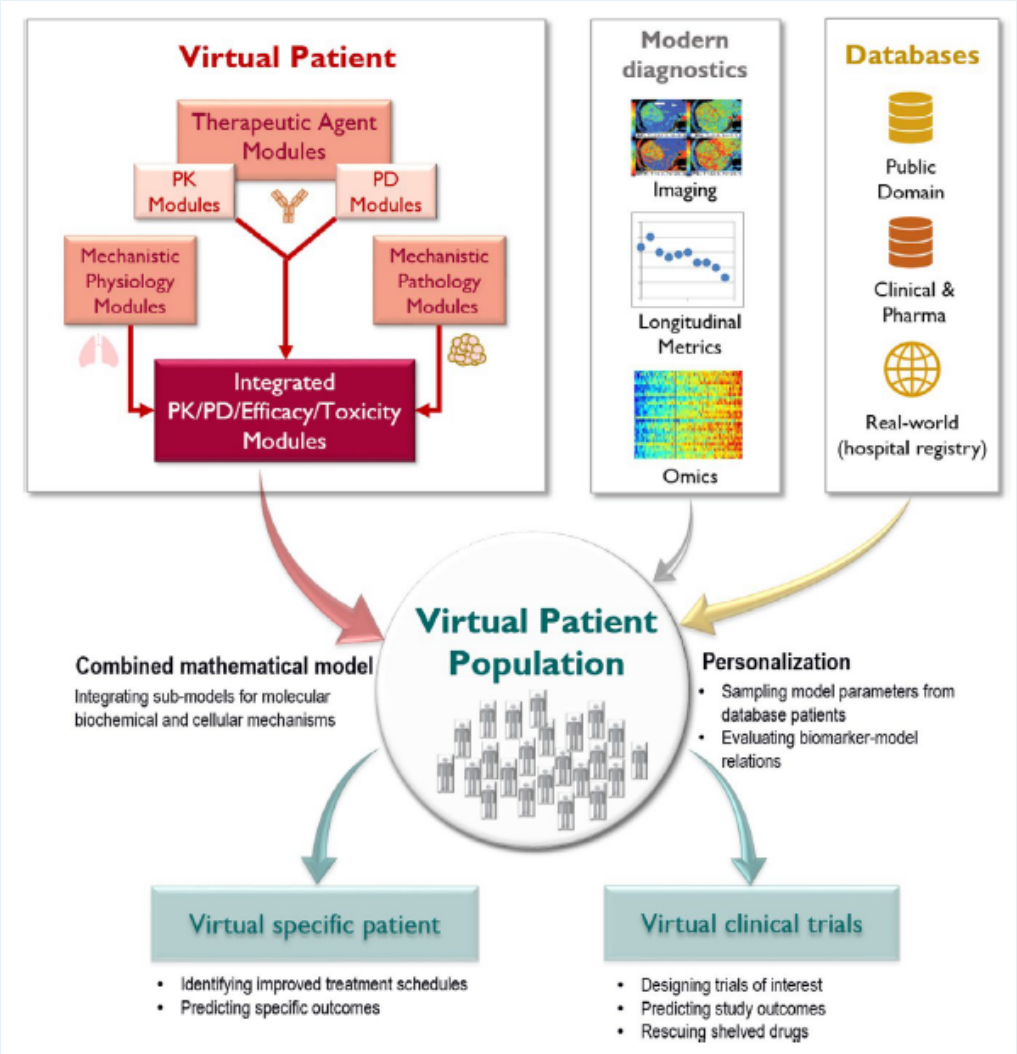
"In the last decade, we have witnessed a paradigm shift in medicine, from the one-size-fits-all concept to precision medicine."

- Z. Agur, M. Elishmereni, U.F., Y. Kogan, Accelerating the development of personalized cancer immunotherapy by integrating molecular patients' profiles with dynamic mathematical models, *Clinical Pharmacology & Therapeutics* 2020 **108**(3): 515–527.

To achieve the goal of fighting cancer we need to join two approaches:

- statistical methods evaluating the relationships between static patient profiling (e.g., genomic and proteomic) and a simple clinically motivated output (e.g., yes/no responder),
- dynamic interactions in the patient-disease-drug system described by appropriate model.

Idea of virtual patient



Personalized treatment

Hoping we will benefit from such methods in the nearest future, not only in cancer diseases...

Thank you for your attention!