The Role of Computer Modelling and Simulation in Medicine. The Paradigm of In Silico Oncology.

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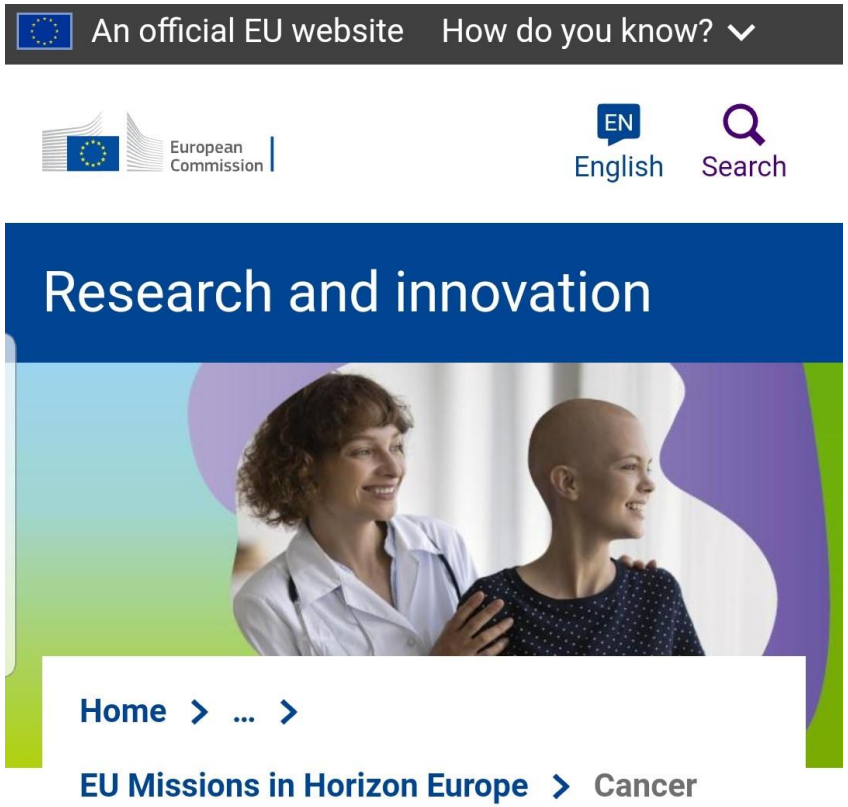
Avicenna Alliance
Association for Predictive Medicine

Overview

- Cancer treatment: a critical research mission
- The paradigm of in silico oncology
- Landmarks in the development of in silico oncology
- Exemplary achievements
- Future visions and requirements

Cancer research: one of the research missions of the European Commission



Each year in Europe (EU), cancers:

- Cost more than €100 BN
- Kill ~1.2 million people
- Scare ~ 2.6 million people diagnosed with cancer

We need a technology jump

https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe/eu-missions-horizon-europe/eu-mission-cancer_en

What is in silico oncology ?

In silico medicine (or computational medicine) uses computer modelling and simulation **to support**

- Medical research;
- Disease prevention;
- Diagnosis, prognosis and patient-specific treatment.

In silico oncology exploits in silico medicine to prevent and cure cancers

In silico oncology uses reliable and scientific computer models

In silico models and digital twins refer to:

- (Parts of) the human body (incl. pathologies)
- Any interacting drugs or medical devices
- Surrounding environment
- Patient activities

Models are made of:

- Knowledge driven: mechanistic modelling & simulation
- Data driven: AI / ML
- Advanced statistical modeling
- Combinations of the above

All models should be:

- Technically and **clinically** validated
- Certified before any regulatory or clinical use
- Fully complying with **Legal** AND **Ethical** rules

In silico oncology: a 20+ years journey, some landmarks

2002 — **Birth of in silico oncology**

2006 — A concrete outline of in silico oncology: a cluster of in silico medical specialties

2007 — 1st digital twin of in oncology, developed in EU and presented at Massachusetts General Hospital and Harvard Medical School

2008 — 1st transatlantic Workshop on Multiscale Cancer Modeling, Brussels

2010 — An early effort to mimic clinical studies on cancer (precursor of in silico clinical trials)

2010 — ACGT project digital twin (ACGT Oncosimulator), a "world first" for EC

2017 — Completion of the 4 year EU-US research project CHIC on in silico oncology

Cancers are diverse;
so are in silico oncology models and digital twins

Cancer types addressed

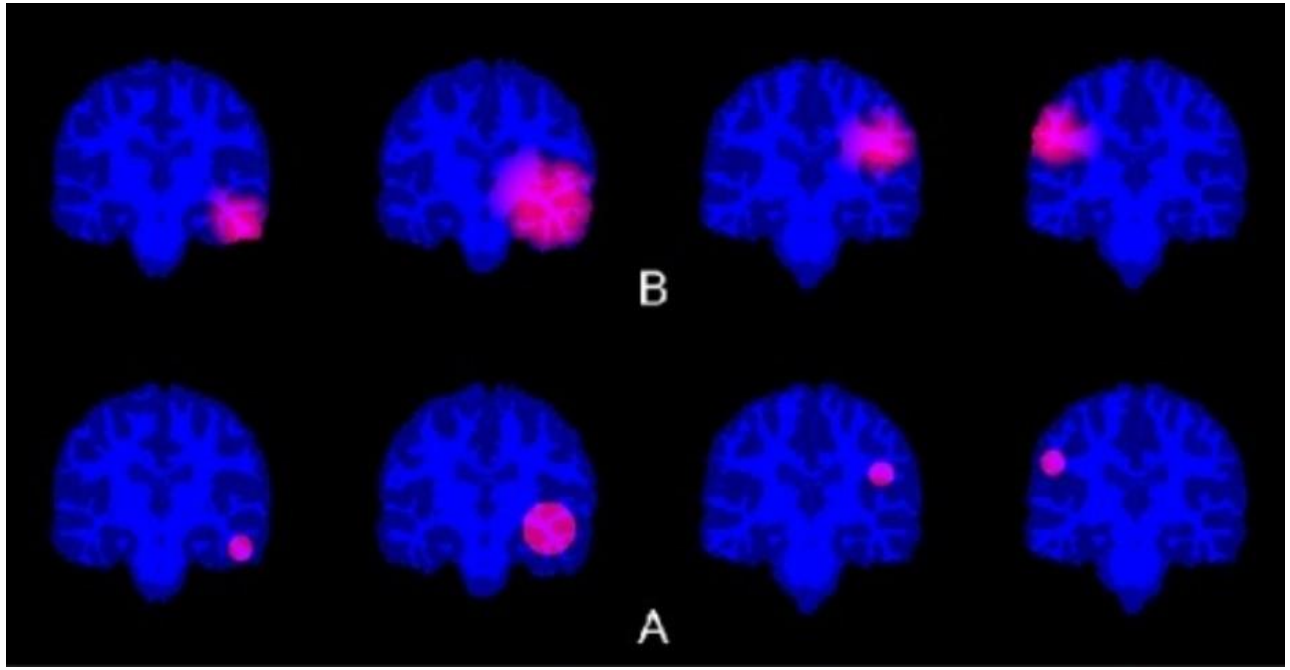
- Nephroblastoma (WT)
- Acute Lymphoblastic Leukemia (ALL)
- Breast Cancer
- Lung Cancer (NSCLC)
- Cervix Cancer
- Prostate Cancer
- Glioblastoma (GBM)
- Response of *normal* tissues to Radiotherapy
- Etc.

Cancer treatments addressed

- No Treatment (Free Tumour Growth)
- Chemotherapy
- Radiotherapy
- Hormonotherapy
- Immunotherapy
- Targeted Molecular Therapies (Anti-angiogenic Therapy)
- Combined Therapies
- Etc

In Silico Oncology and In Silico Medicine Group, National Technical University of Athens in collaboration with numerous research and clinical centres worldwide continuously create and improve advanced computer models to help fighting a wide range of cancer types.

Simulating glioblastoma tumour growth and invasion into the brain can help optimizing radiotherapy treatment



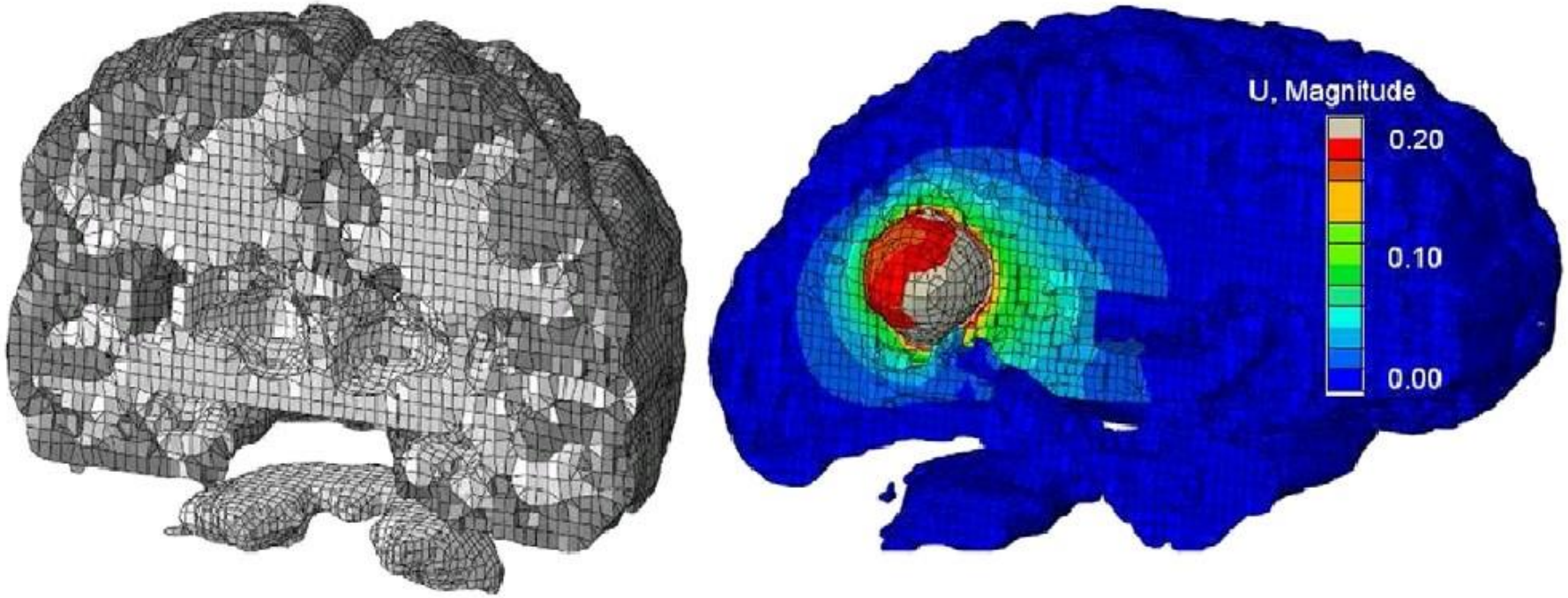
Depending on the initial **location** of the tumour within the brain (panel A), the **tumour will grow** and **invade** the surrounding normal brain tissue **in a different way** (panel B).

In silico oncology models predict spatiotemporal tumour evolution.

Glioblastomas can grow 1.4 percent in a single day!

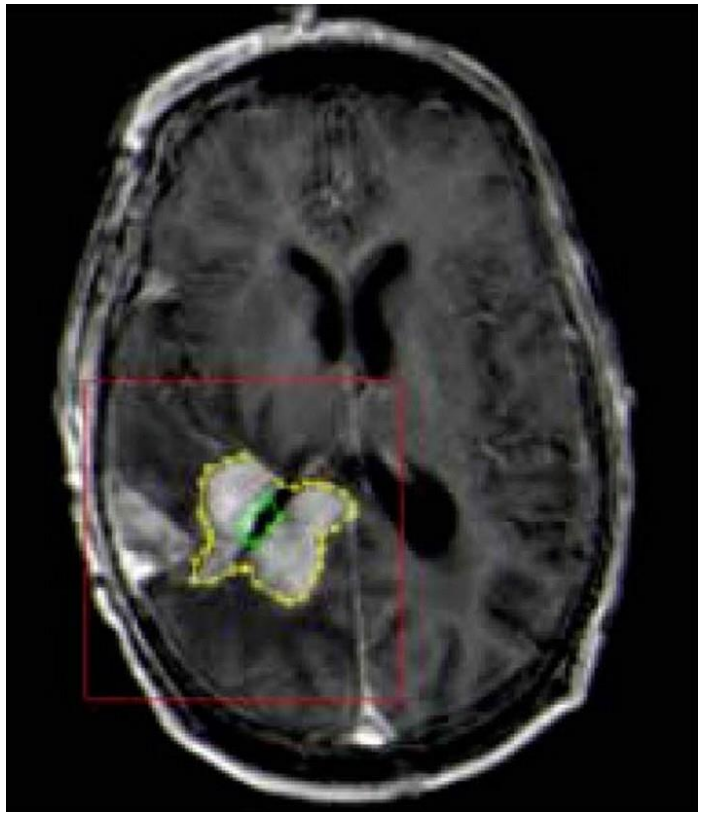
Cancer informatics 02/2017; 16(16):1-16.,
DOI:10.1177/1176935116684824

Coupling biological and mechanical simulation of a glioblastoma brain tumour growth and invasion can lead to more refined and reliable predictions



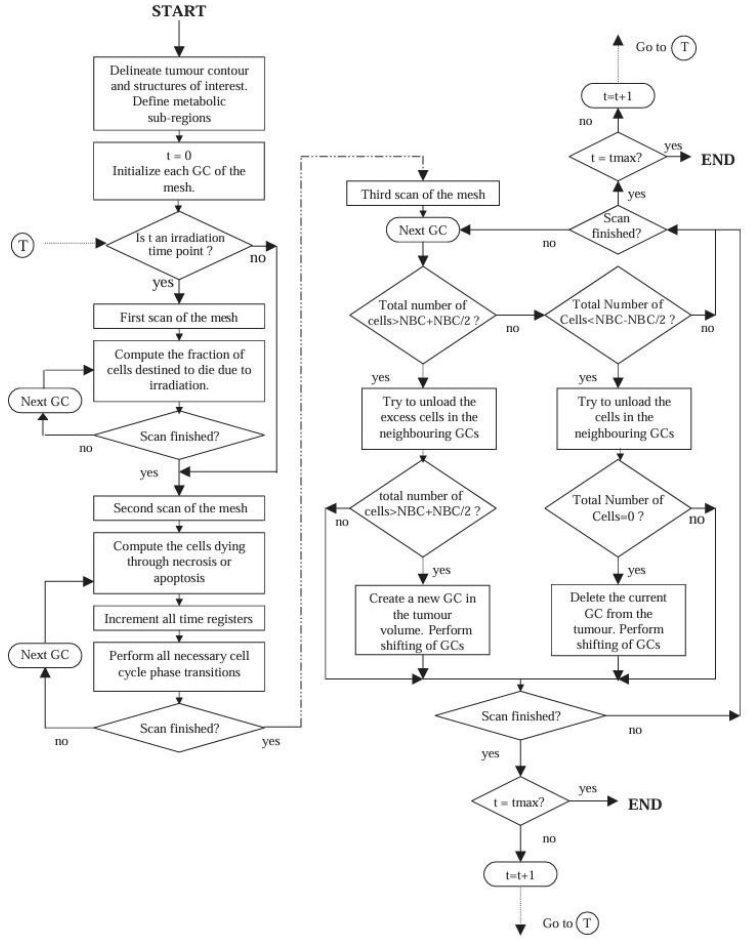
Progress in Biophysics and Molecular Biology 07/2011; 107(1):193-9., DOI:10.1016/j.pbiomolbio.2011.06.007

Beyond predicting tumour evolution, models can suggest personalized treatment



Simulating the response of a clinical brain tumour to various radiotherapy schemes

Selection of the most appropriate personalized schedule for a given patient



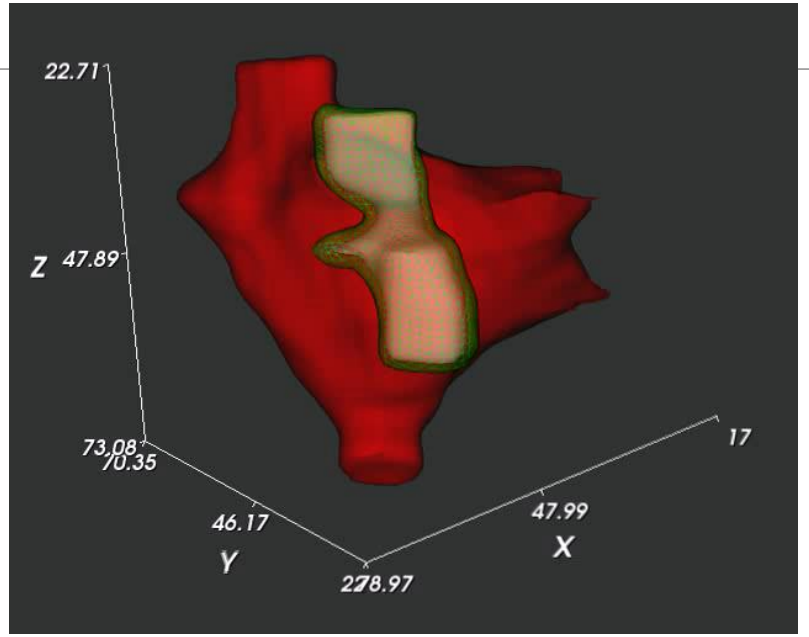
Numerical simulation protocol predicting the evolution of a brain tumour through in silico oncology.

Journal of Theoretical Biology 10/2004; 230(1):1-20.,
DOI:10.1016/j.jtbi.2004.03.024

In silico oncology provides assistance to the doctor and the patient

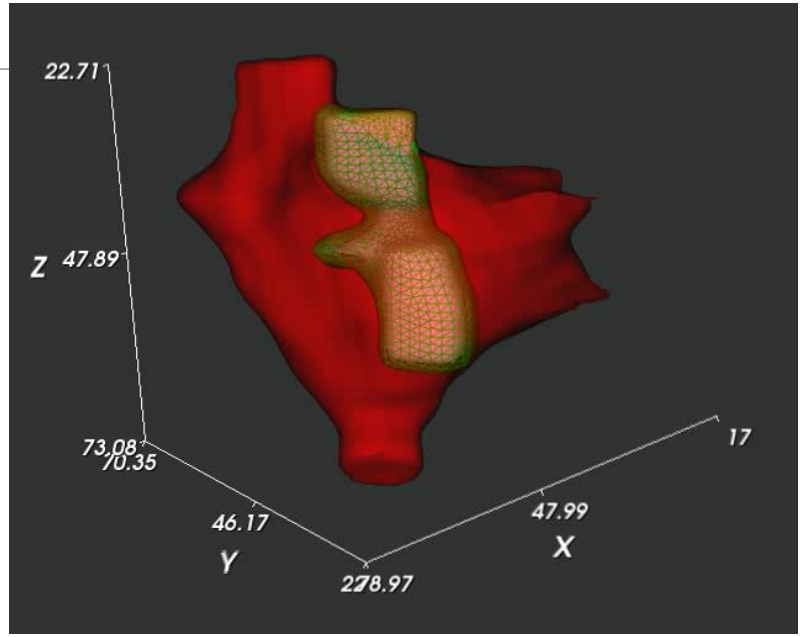
Reliably predicting the response of a clinical tumour to different radiotherapeutic schemes in space and time.

Helping the doctor and the patient to better understand existing treatment options and select the best one.



AHF_48

Accelereated Hyperfractionated scheme with total absorbed dose = 48 Gy



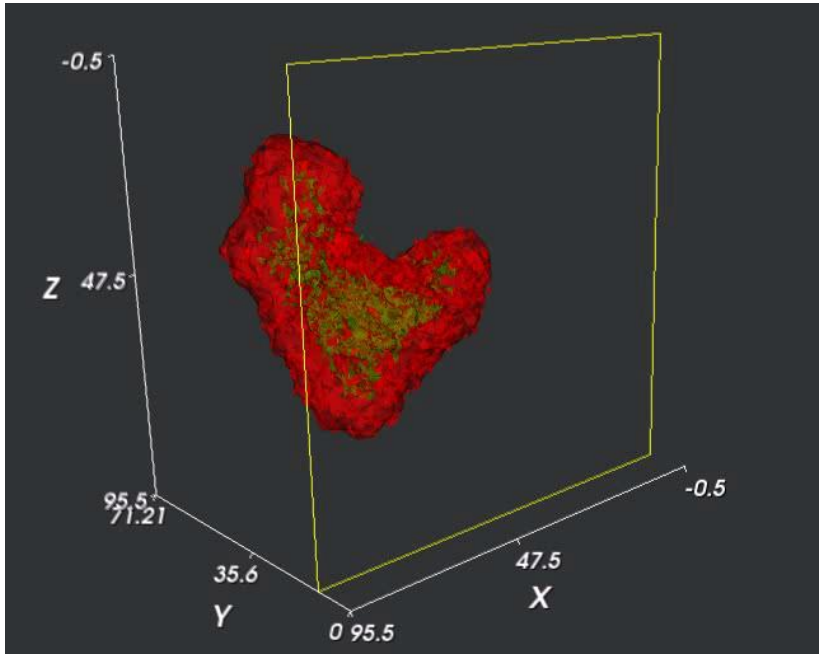
HF81_6

Hyperfractionated scheme with total absorbed dose = 81.6 Gy

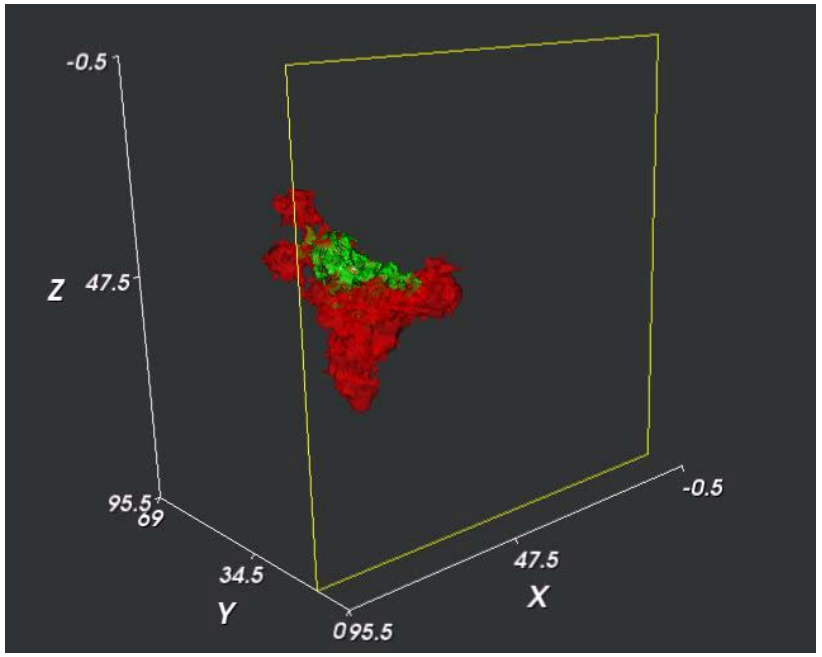
Video “ACGT project: The Oncosimulator,” YouTube, https://www.youtube.com/watch?v=fdKHl4ecfwg

G S Stamatakos et. al, The British Journal of Radiology 2006 79:941, pp.389-400, https://doi.org/10.1259/bjr/30604050

Predicting and understanding the tumour growth to better fight it



AHF_48_clipped



HF81_6_clipped

"Travelling" within a clinical tumour at a given time point for two different radiotherapeutic schemes

Provides an overview of the changing internal cellular structure of the tumour

Video "ACGT project: The Oncosimulator," YouTube, https://www.youtube.com/watch?v=fdKHl4ecfwg
G S Stamatakos et. al, The British Journal of Radiology 2006 79:941, pp.389-400, https://doi.org/10.1259/bjr/30604050

The in silico oncology paradigm of nephroblastoma pediatric tumour: a clinical perspective

Challenge

Nephroblastoma or Wilms tumour: a rare abdominal tumour occurring in young children.

The distinction **from other tumour entities** at diagnosis is essential to start the correct treatment.

Initial diagnosis primarily based on imaging: Wilms tumours **should not undergo an open biopsy before starting neoadjuvant chemotherapy**

Solution

In silico Oncology can improve the reliability of image assessment and **predict treatment response and outcome**.

Large datasets of **corresponding imaging, clinical and molecular data** → develop / evaluate tools for automated image analysis.

A **decentralized approach** ensures data protection and security as data will not leave their source hospitals.

Tool for radiologic assessment of tumours: **of great value for initial treatment decisions**.

Benefits

Prediction of the response to treatment from initial MRI imaging and eventually serum molecular data through in silico oncology → desperately needed better treatment stratifications.

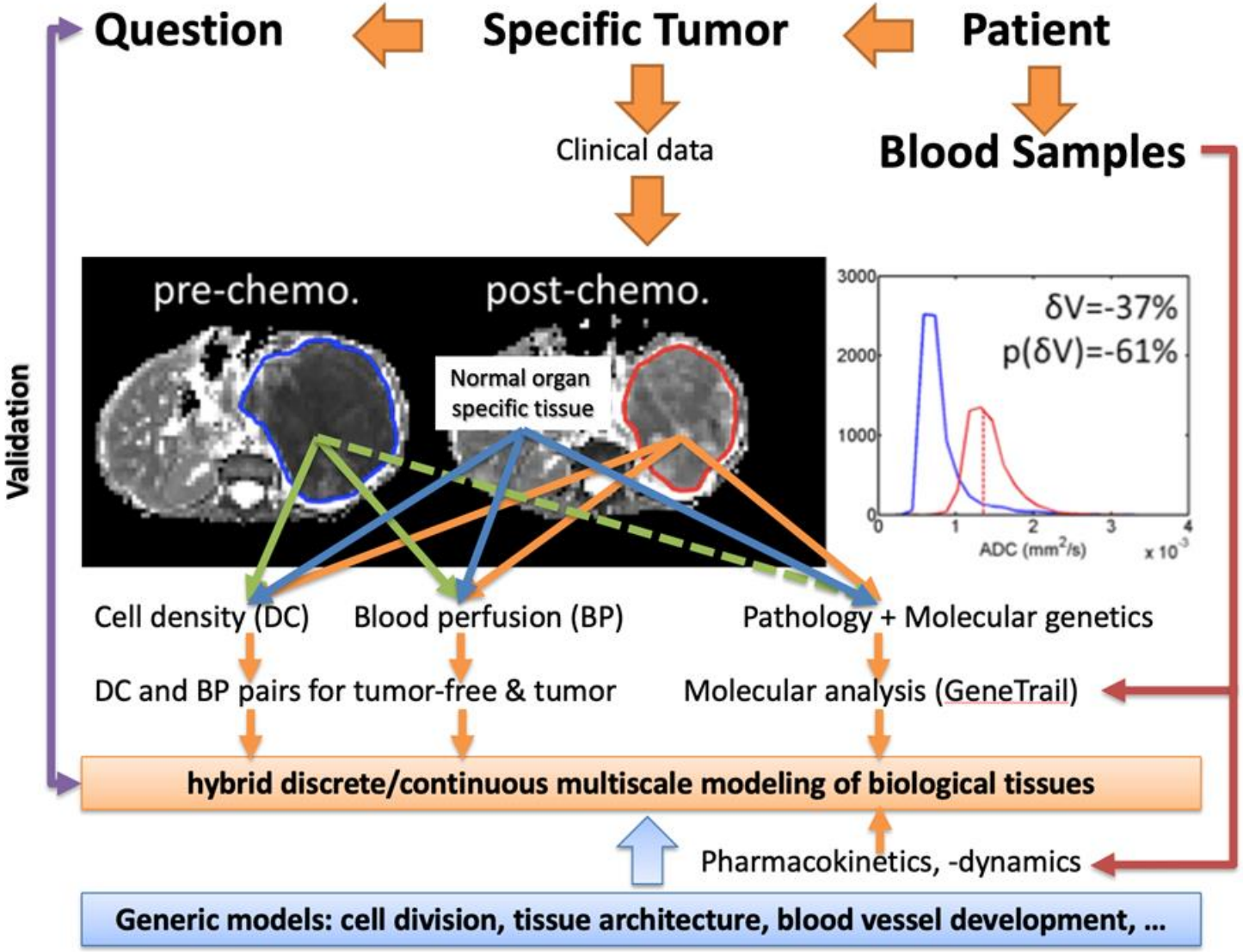
Despite a high survival rate (90% in patients with Wilms tumour), no improved outcome with conventional measures in past 10 to 20 years.

~ 10% of children with this tumour will die.

This approach = a **proof of principle** by expanding developed models **to other clinical centres / other tumour types**

Prof. Norbert Graf, MD, University of Saarland, Dept. for Pediatric Oncology and Hematology, Homburg, Germany

Data to be collected and used by a nephroblastoma digital twin

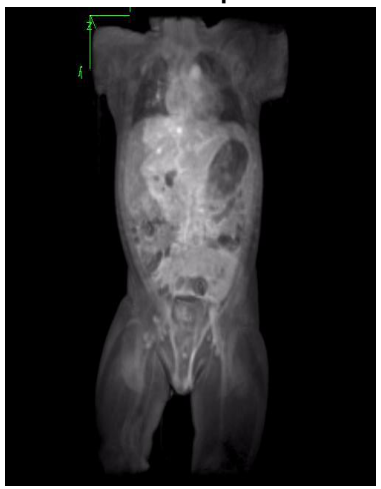


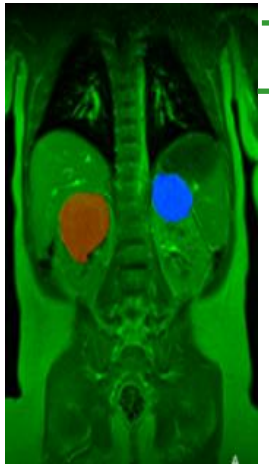
Actual response of a bilateral pediatric nephroblastoma tumour treated with chemotherapy (SIOP 2001/GPOH)

1st Time-point

2nd Time-point

3rd Time-point



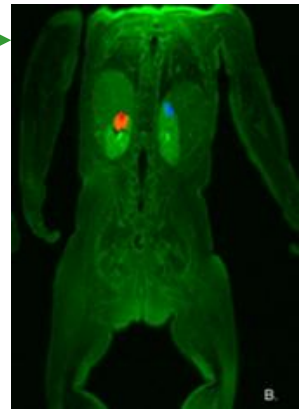


R

L

DV_R=90%

DV_L=89%

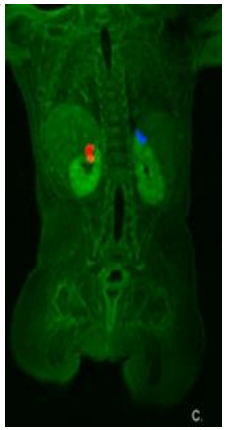


R

L

DV_R=94%

DV_L=95%



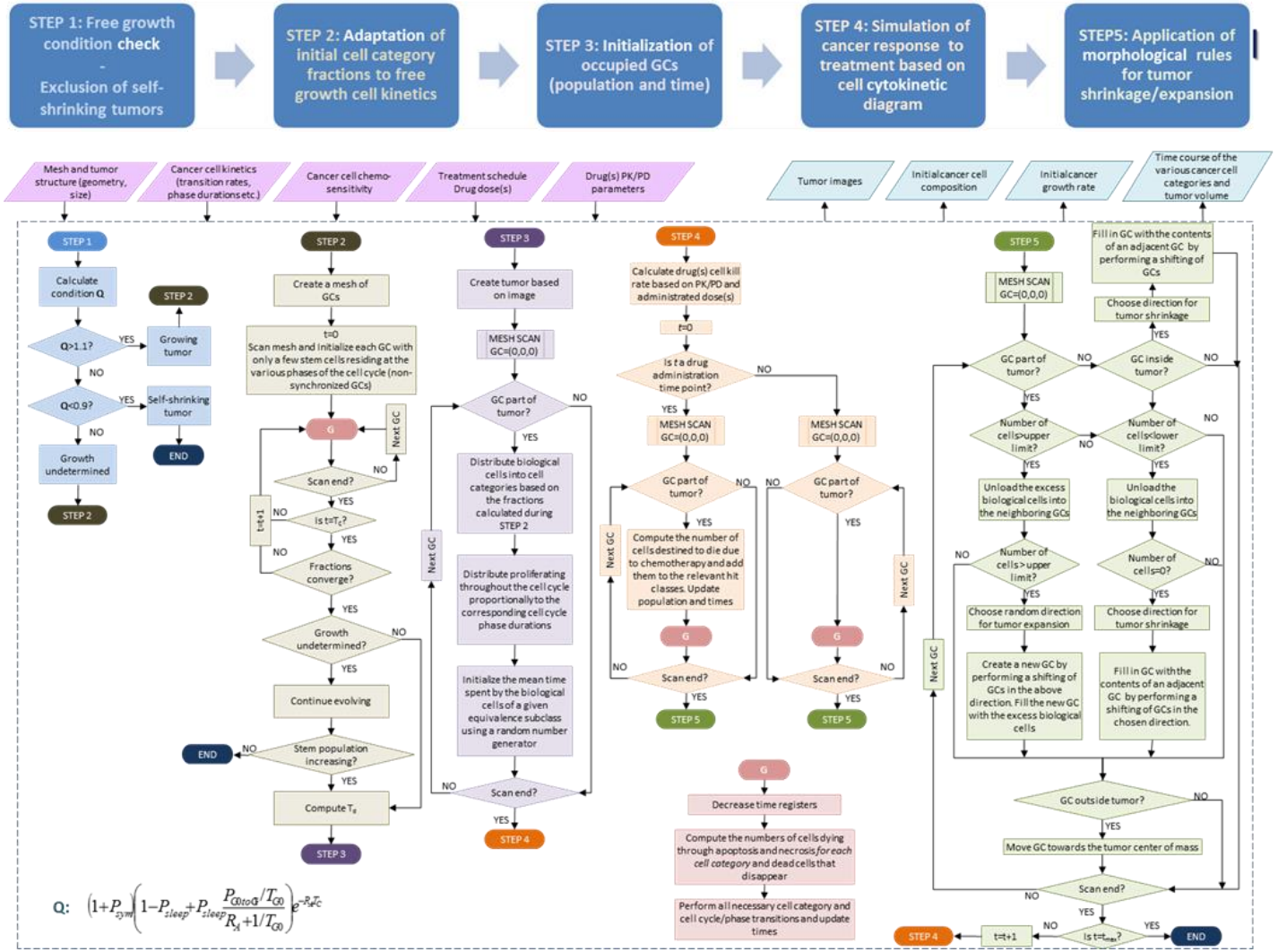
R

L

Images are not in scale

Data provided by Prof. Norbert Graf, MD, USAAR, Germany

A mechanistic multiscale model of the response of a solid tumour to chemotherapy

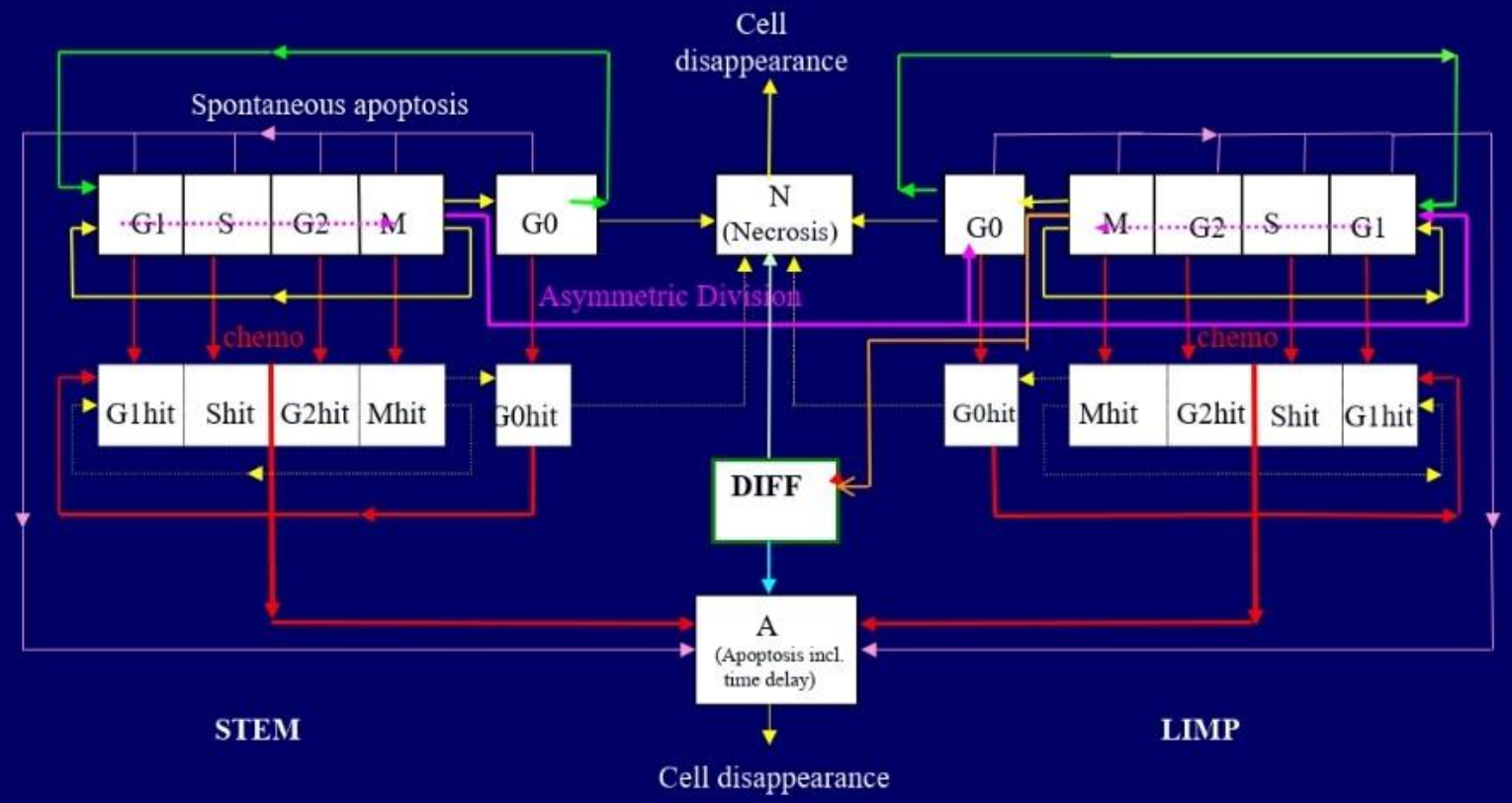


PLoS ONE 03/2011; 6(3):e17594., DOI:10.1371/journal.pone.0017594

Computers in Biology and Medicine 10/2012; 42(11):1064-78., DOI:10.1016/j.compbiomed.2012.08.008

Cytokinetic model
treatment response (the chemotherapy paradigm)

When cells are hit by chemo (treatment session) they enter a separate *cell cycle* at which they remain till they are led to apoptotic death from a point of the cell cycle specified by the mechanism of action of the drug (in the case of Epirubicin S phase is considered to be that point).

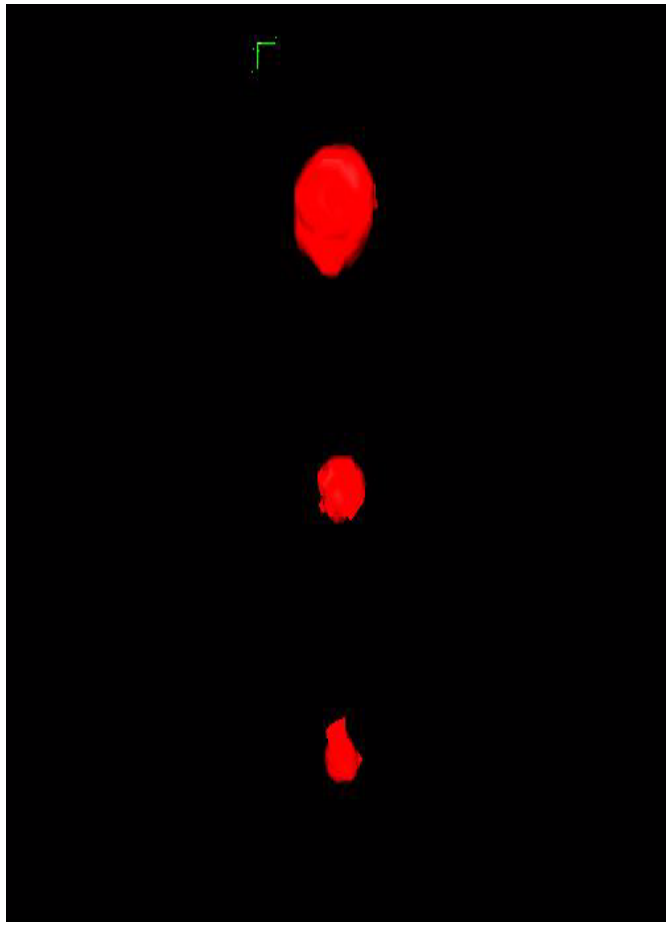


Prediction of the response of the previous clinical bilateral nephroblastoma tumour to the specific chemotherapeutic scheme administered

1st time-point

2nd time-point

3rd time-point

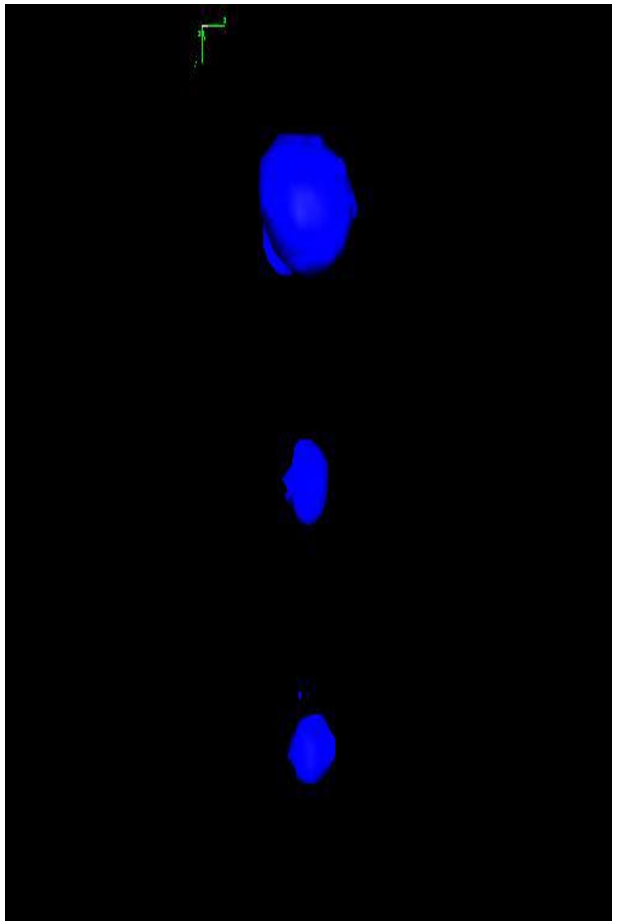


Tumour on the Right Kidney

1st time-point

2nd time-point

3rd time-point



Tumour on the Left KIdney

NTUA Nephroblastoma Oncosimulator

PLoS ONE 03/2011; 6(3):e17594., DOI:10.1371/journal.pone.0017594

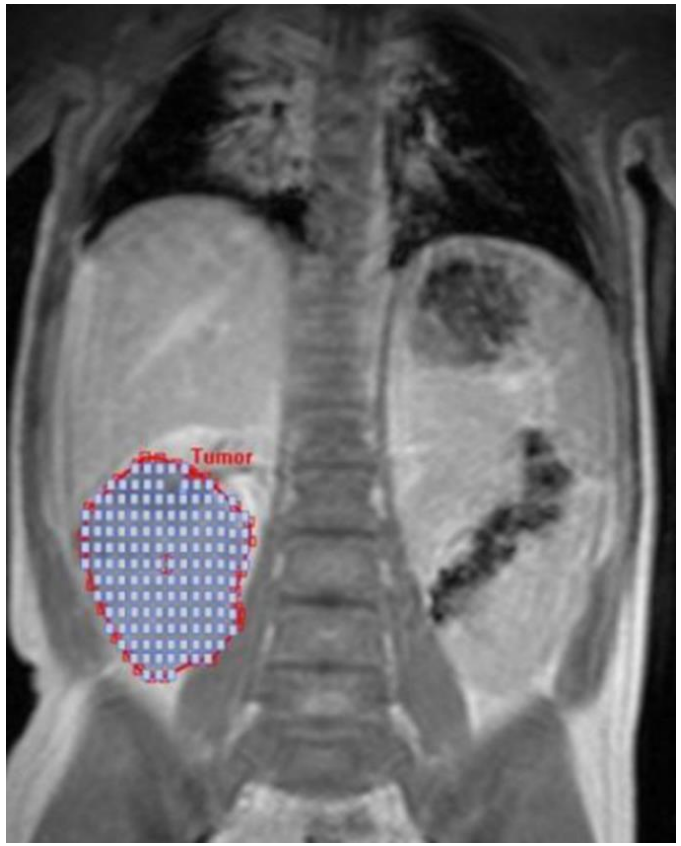
Computers in Biology and Medicine 10/2012; 42(11):1064-78., DOI:10.1016/j.compbiomed.2012.08.008

An advanced digital twin for the exemplary cases of nephroblastoma and breast cancer

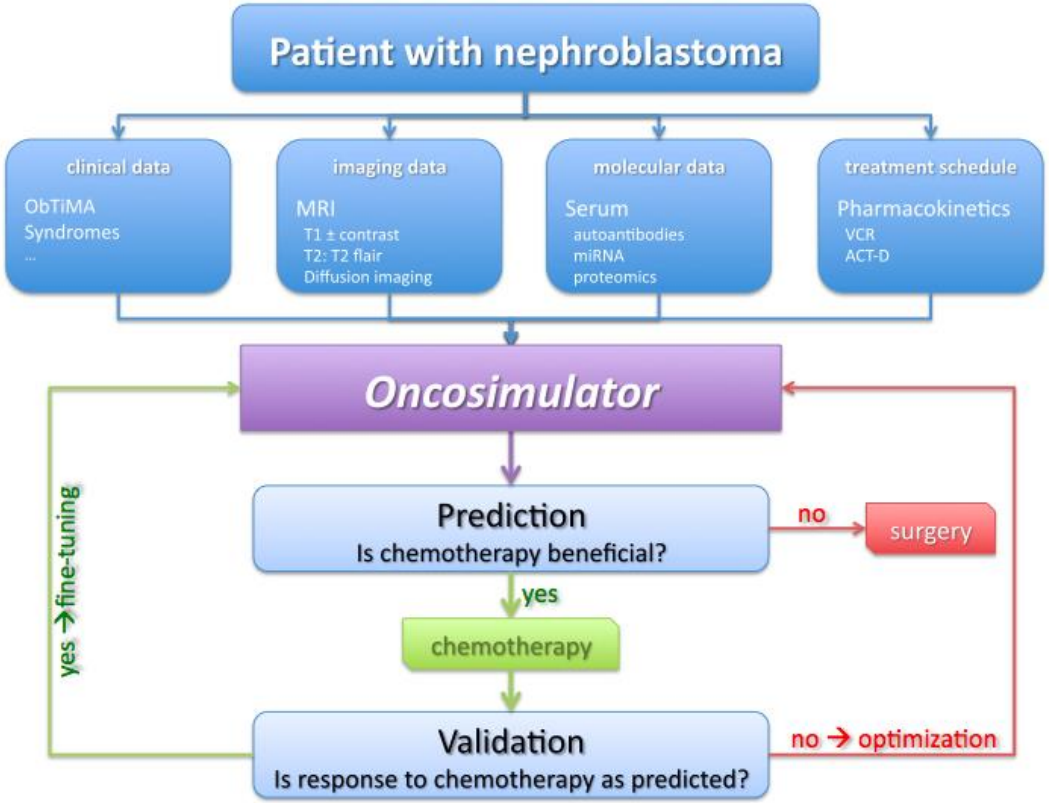
The Technologically Integrated Oncosimulator: Combining Multiscale Cancer Modeling With Information Technology in the *In Silico* Oncology Context

Georgios Stamatakos, *Member, IEEE*, Dimitra Dionysiou, Aran Lunzer, Robert Belleman, Eleni Kolokotroni, Eleni Georgiadi, Marius Erdt, Juliusz Pukacki, Stefan Rüeping, Stavroula Giatili, Alberto d' Onofrio, Stelios Sfakianakis, Kostas Marias, *Member, IEEE*, Christine Desmedt, Manolis Tsiknakis, *Member, IEEE*, and Norbert Graf, *Member, IEEE*

Semi-automatic data collection and processing can accelerate the efficiency of the Oncosimulator digital twin

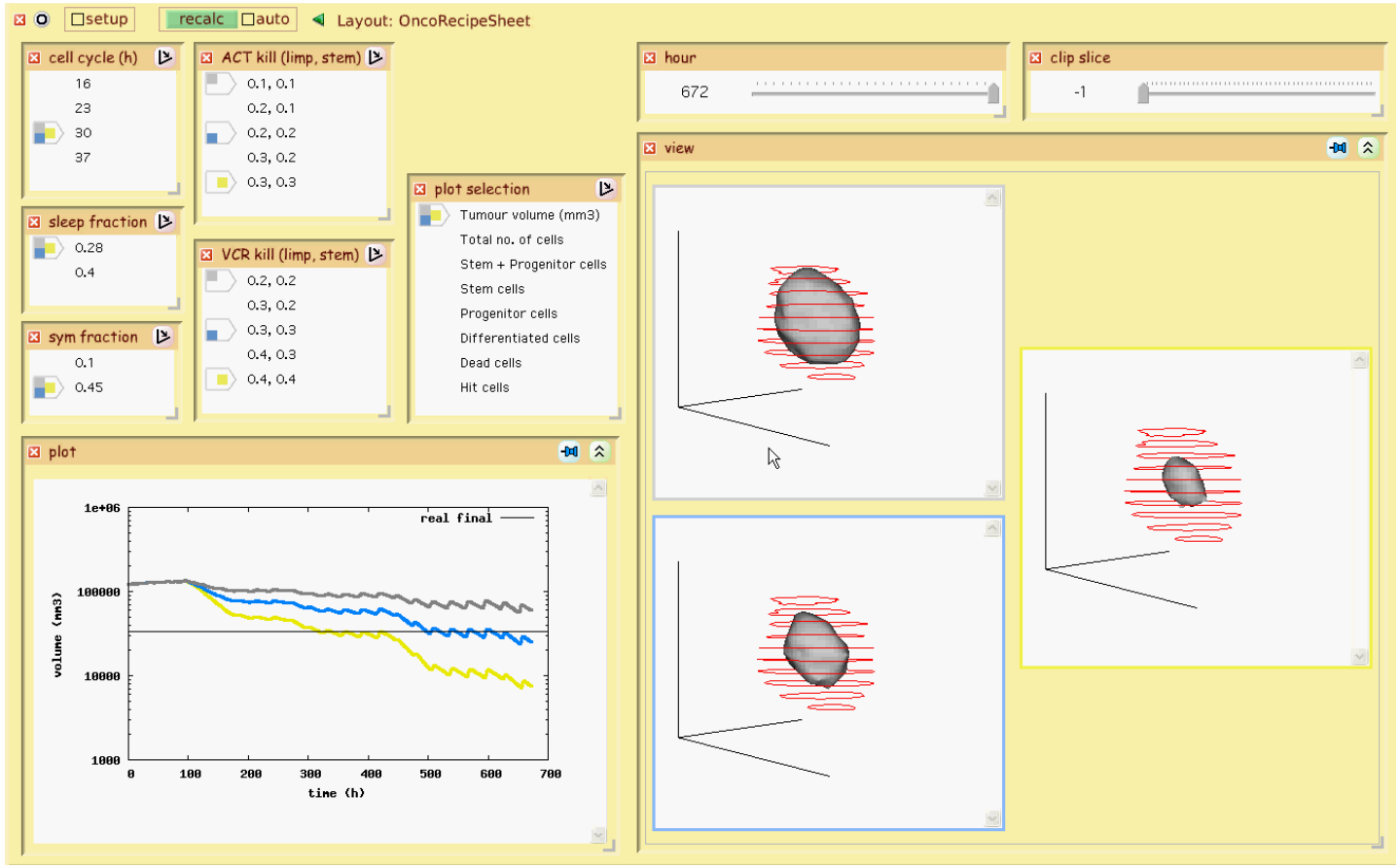


Segmentation and discretization of the nephroblastoma tumour using a cubic mesh.

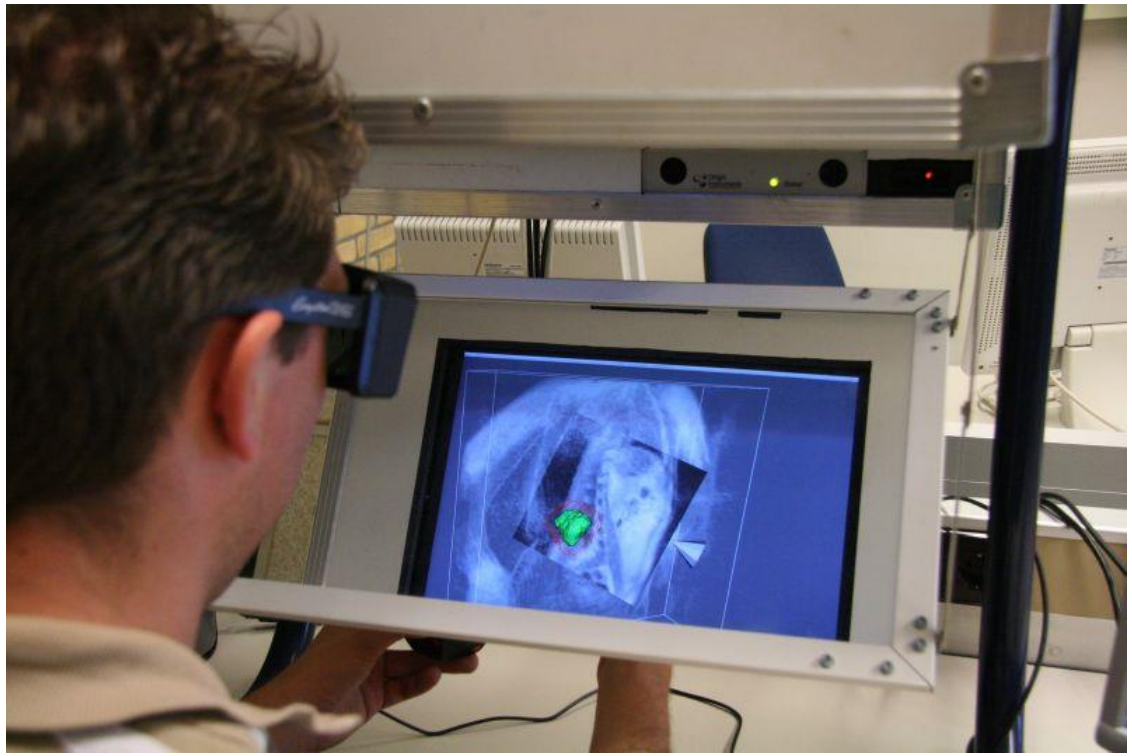


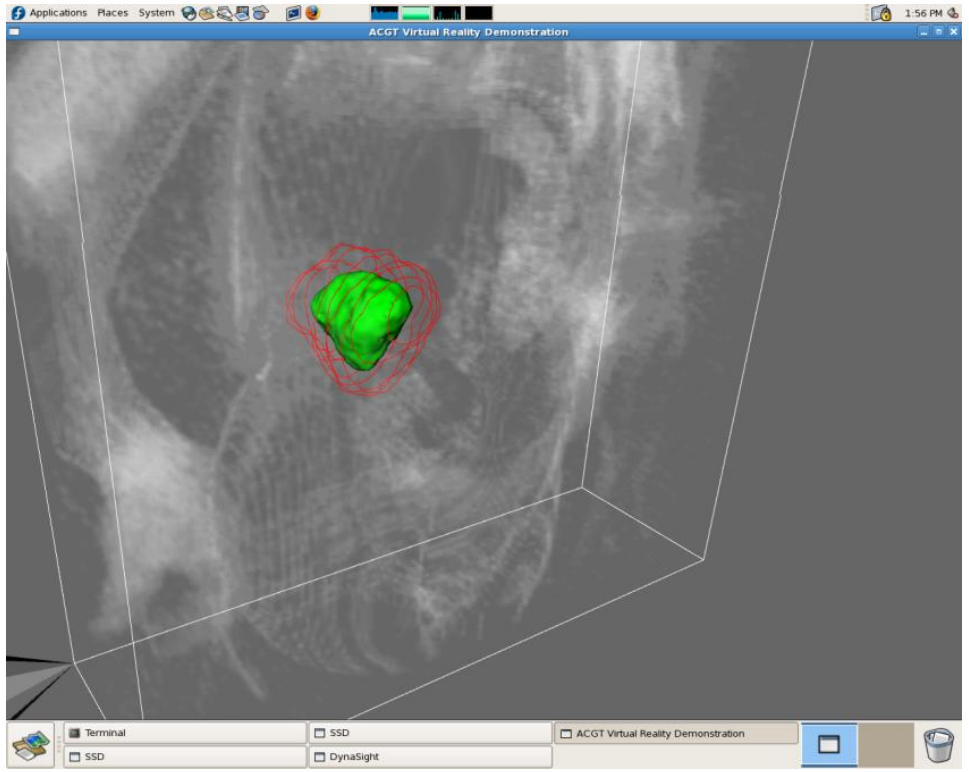
A simplified Onsosimulator functioning workflow from the clinical perspective

Advanced visualization features offer numerous possibilities for the optimal perception of the digital twin predictions



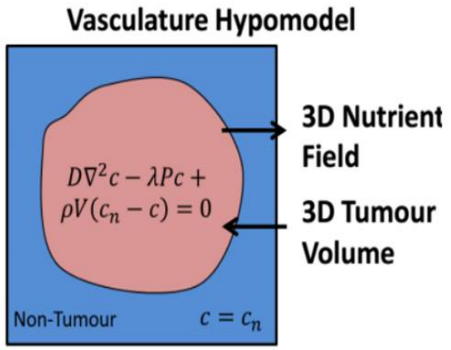
Virtual reality offers unparalleled possibilities for spatial visualization of the digital twin predictions



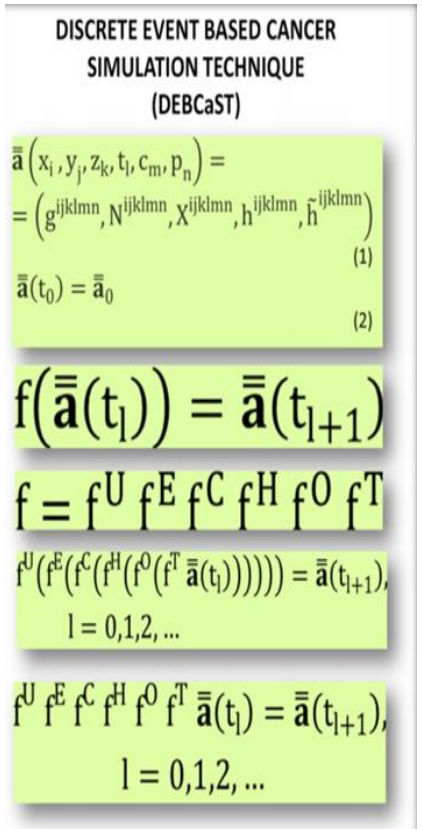


CLINICAL TUMOUR HYPERMODELLING: Tumour growth and treatment response hypermodel and mathematics hidden behind each constituent hypomodel

NEOANGIOGENESIS HYPOMODEL
Oxford University



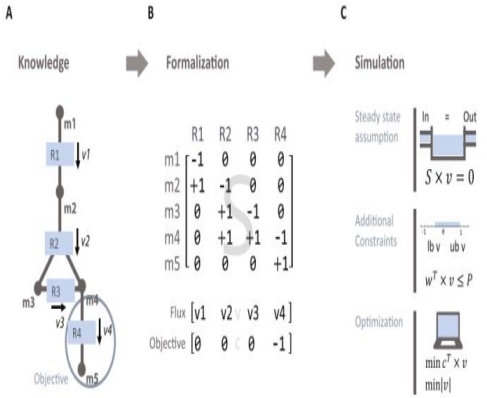
CORE TUMOUR GROWTH & TREATMENT RESPONSE HYPOMODEL
National Technical University of Athens (ICCS)



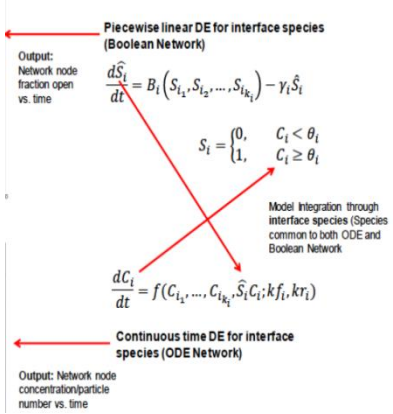
BIOMECHANICAL HYPOMODEL
University of Bern

$$\begin{pmatrix} S_{XX} \\ S_{YY} \\ S_{ZZ} \\ S_{XY} \\ S_{YZ} \\ S_{XZ} \end{pmatrix} = \frac{E}{(1+\nu)(1-2\nu)} \begin{pmatrix} 1-\nu & \nu & \nu & 0 & 0 & 0 \\ \nu & 1-\nu & \nu & 0 & 0 & 0 \\ \nu & \nu & 1-\nu & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{(1-2\nu)}{2} & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{(1-2\nu)}{2} & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{(1-2\nu)}{2} \end{pmatrix} \begin{pmatrix} E_{XX} \\ E_{YY} \\ E_{ZZ} \\ 2E_{XY} \\ 2E_{YZ} \\ 2E_{XZ} \end{pmatrix}$$

METABOLIC HYPOMODEL
Foundation for Research and Technology – Hellas



MOLECULAR HYPOMODEL
University of Pennsylvania



The CHIC EU-US Project http://www.chic-vph.eu/

Clinical Therapeutics 08/2017; 39(8):e107-e108., DOI:10.1016/j.clinthera.2017.05.333

Artificial intelligence as one of the pillars of in silico oncology

ERA PerMed

NEURO-ONCOLOGY

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1. General information

Project title	Implementation of mobile health tools and artificial intelligence for personalised radiation treatment planning and monitoring in prostate cancer
Project acronym	PersoRad
Project duration (months)	42
Starting date	June 1st 2020
Period covered by the report:	01/06/2020 – 30/11/2023
Periodic report:	Final

PersoRad has been coordinated by the University of Freiburg, Medical Centre, Department of Radiation Oncology, Germany

Neuro Oncol. 2017 Nov; 19(Suppl 6): vi32. PMCID: PMC5693096
Published online 2017 Nov 6. doi: 10.1093/neuonc/nox168.122

ATIM-28. IMMUNE PROFILES AT START OF TEMOZOLOMID-BASED STANDARD TREATMENT AND DC-BASED IMMUNOTHERAPY STRONGLY CORRELATE WITH OVERALL SURVIVAL OUTCOME IN GBM PATIENTS

Markos Antonopoulos,[1] Stefaan Van Gool,[2] Norbert Graf,[3] and Georgios Stamatakos[1]

▸ Author information ▸ Copyright and License information PMC Disclaimer

Clinical data and clinical guidance was provided by Prof. Stefaan Gool, Catholic University of Leuven, Belgium (at the time), currently Medical Director - Translational Oncology, IMMUN-ONKOLOGISCHES ZENTRUM KÖLN, Cologne, Germany

In Silico Psycho-Oncology

- Cancer patients face many types of **psychosocial problems** affecting their **quality of life** for many years.
- **Psychological symptoms**, **coping mechanisms, negative affect:** strong predictors for breast cancer patiens well-being (EC funded project BOUNCE).
- It is important to offer **supportive interventions** for patients who are at risk for psychological symptoms or decreased quality of life in the future.
- **Machine learning algorithms and AI** techniques can help professionals to find these patients at risk.
- **Psycho-oncology** is an important part of modern cancer care.

(P. Poikonen, Helsinki University Hospital)

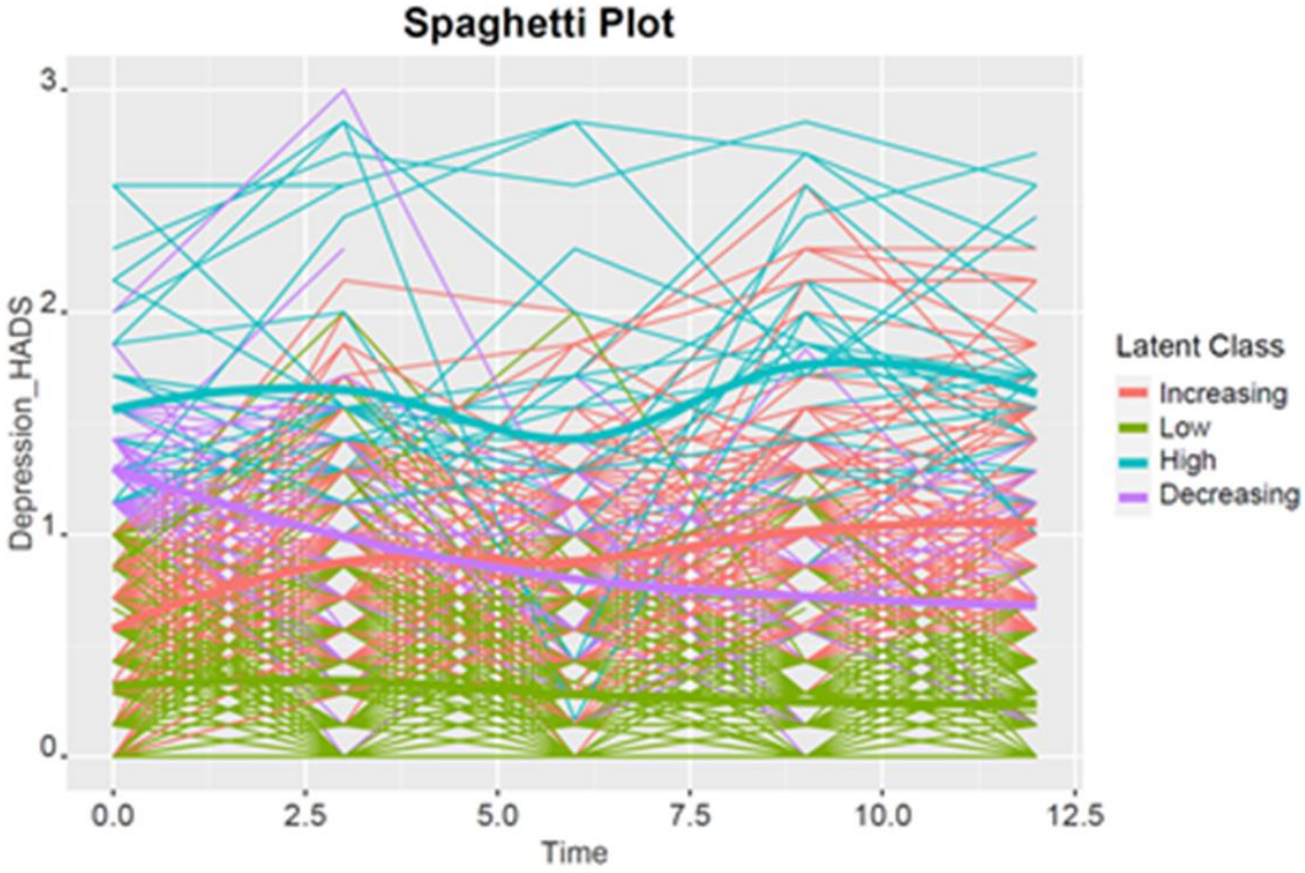

Figure 1. HADS (Hospital Anxiety and Depression Scale) depression trajectories. Each thin line connects the responses for the same patient over time. Thick lines are the mean HADS depression score at each time point (in months) for the four classes identified by the latent-class model.

(E. Kolokotroni et al., Abstract Book, Virtual Physiological Human Conference VPH2022, Porto, Portugal, 6-9 Sep. 2022, p. 112.

Future visions and requirements

BROADER GOALS

Accelerate, **optimize** and **personalize cancer treatment** through the development, clinical validation, certification and clinical translation of **in silico methods**

SPECIFIC TECHNICAL GOALS AND REQUIREMENTS

- Develop **clinically driven and overseen digital twins** of tumour growth and tumour and organism response to cancer treatment interventions.
- Ensure **trustworthiness**, **explainability**, **robustness, stability** and **good quality of component interconnection** for all underying mechanistic and/or AI and/or hybrid models.
- Technically and clinically **validate cancer digital twins** and **in silico clinical trials** through formal clinical studies.
- **Translate** cancer digital twins into **clinical practice** , following **regulatory certification**
- **Monitor** and **evaluate** the **clinical use** of certified cancer digital twins and **further exploit** the latter for in **silico clinical trials** and broader **clinical research**
- **Engage patients** and the **broader public** into the procedure of **acceptance of in silico methods**

ACKNOWLEDGMENTS

The contributions of all persons and organizations to the work presented or referred to in this lecture or to relevant supportive actions are duly acknowledged. An indicative list of collaborators, supporters and organizations is provided below. However, due to the very large number of collaborators and supporters (hundreds) across the globe as well as inevitable space limitations, in no way should this list be considered exhaustive.

RESEARCHERS FROM IN SILICO ONCOLOGY AND IN SILICO MEDICINE GROUP (PAST AND PRESENT) , NATIONAL TECHNICAL UNIVERSITY OF ATHENS (NTUA)

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