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The "Oncosimulator": a multilevel, clinically oriented simulation system of tumor growth and organism response to therapeutic schemes. Towards the clinical evaluation of *in silico* oncology.

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***Abstract*—The "Oncosimulator" is at the same time a concept of multilevel integrative cancer and (treatment affected) normal tissue biology, an algorithmic construct and a software tool which aims at supporting the clinician in the process of optimizing cancer treatment on the patient individualized basis. Additionally it is a platform for better understanding and exploring the *natural phenomenon* of cancer as well as training doctors and interested patients alike. In order to achieve all of these goals it has to undergo a thorough clinical optimization and validation process. This is one of the goals of the European Commission funded integrated project "ACGT: Advancing Clinicogenomic Trials on Cancer". Nephroblastoma (Wilms' tumor) and breast cancer have been selected to serve as two paradigms to clinically specify and evaluate the "Oncosimulator" as well as the emerging domain of *in silico* oncology.**

I. Introduction

APART from a disease cancer is a spatiotemporal *natural phenomenon* and as such it must be amenable to some sort of mathematical and computational description in analogy with the phenomena addressed by classical or modern physics. Obviously the fact that cancer – as well as numerous other biological phenomena – is characterized by strong multiscale dynamics, hypercomplexity and *apparent* stochasticity implies that multiscale, complex and non purely deterministic mathematical and computational methods have to be developed in order to tackle it. The central reason for such an approach is to enhance the reliability and effectiveness of cancer treatment decisions by exploiting basic science in a scientifically strict, analytical, quantitative and dynamical way on the patient's individualized context. This could be achieved through performing *in silico* (=on the computer) experiments of the likely outcome of several candidate therapeutic schemes based on the particular clinical, imaging, histopathological and molecular data of the individual patient. Additional reasons for the *in silico* approach are deeper understanding of important biological phenomena as well as the training of clinicians and possibly interested patients.

A *sine qua non* prerequisite for the clinical applicability of the *in silico* approach is the implementation of strict, thorough and statistically meaningful clinical trials of the simulation models. This is one of the goals of the EU funded integrated project "ACGT: Advancing Clinicogenomic Trials on Cancer" [1]. Within the framework of ACGT the "Oncosimulator", a multilevel integrative cancer and (treatment affected) normal tissue computational biology construct and software tool is being developed and clinically tested. Nephroblastoma (Wilms' tumor) and breast cancer have been selected to serve as two paradigms for the clinical specialization and evaluation of the "Oncosimulator" as well as the emerging domain of *in silico* oncology.

II. The "Oncosimulator" Basics

The "Oncosimulator" is based on the "top-down" multiscale simulation strategy developed by the *In Silico* Oncology Group, National Technical University of Athens (www.in-silico-oncology.iccs.ntua.gr) [2-5]. Provided that the "Oncosimulator" has already been validated (retrospectively and prospectively) for a specific application, the imaging, histopathological, molecular and clinical data of any given patient following pertinent preprocessing are introduced into the *Tumor and Normal Tissue Response Simulation Module*. This module executes the simulation code for a defined candidate treatment scheme (Fig.1). The prediction is judged by the clinician and if a decision is made to test a further scheme *in silico* this is done in an analogous way. Finally the clinician decides on the optimal

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treatment scheme to be administered to the patient based on his or her formal medical education and knowledge and the predictions of the "Oncosimulator".

The most fundamental processes implemented by the "Oncosimulator" are the following. Processed molecular data is used in order to perturb the radiobiological or pharmacodynamic cell-kill parameters about their population-based mean values. At the heart of the simulation approach lies a prototype system of quantizing cell clusters included within each geometrical cell of a discretizing mesh, covering the anatomic area of interest. Cell-cycle phase durations and imaging-based metabolism distribution define the quantization equivalence classes considered. Several algorithms have been developed so as to simulate various macroscopic mechanisms such as tumour expansion or shrinkage and mechanical boundary conditions, as well as the effects of particular drugs (eg vincristine, epirubicin etc.) as well as radiation on the tumorous and normal tissue under consideration.

From the mathematical point of view the "Oncosimulator" constituent models make use of several notions and methods such as nondeterministic finite-state automata, the generic Monte Carlo technique, differential equations, general algorithm and complexity theory etc. From the technological point of view numerous current technologies are used in order to dynamically and multidimensionally visualize both medical data input and simulation predictions (e.g. through the use of virtual reality platforms), to process medical images [6], to accelerate executions (e.g. through the use of grid architectures), to securely and legally transfer and store biomedical data (e.g. through pseudonymization) etc. To this end most of the 26 European and Japanese ACGT partner institutions are involved either directly or indirectly in the development and validation of the integrated "Oncosimulator".

Regarding the clinical adaptation, optimization and validation of the "Oncosimulator" pertinent clinical, imaging, histopathologic and molecular data in conjunction with the ACGT conventional clinical trials are exploited in order to validate its constituent models both prospectively and retrospectively. More specifically, the corresponding *in silico* oncology trial is based on the nephroblastoma SIOP 2001/GPOH trial for which the University of Saarland, Germany [7-9] is responsible and the breast cancer TOP trial, for which the Institute Jules Bordet, Brussels, Belgium [10] is responsible. Both these trials have been considerably enhanced in terms of data collection in order to meet the remarkably high demands of the *in silico* trial. The whole effort is also scientifically supported by the Center for the Development of a Virtual Tumor (CViT) [11], an international community of computational cancer biology investigators based at the University of Harvard, USA.

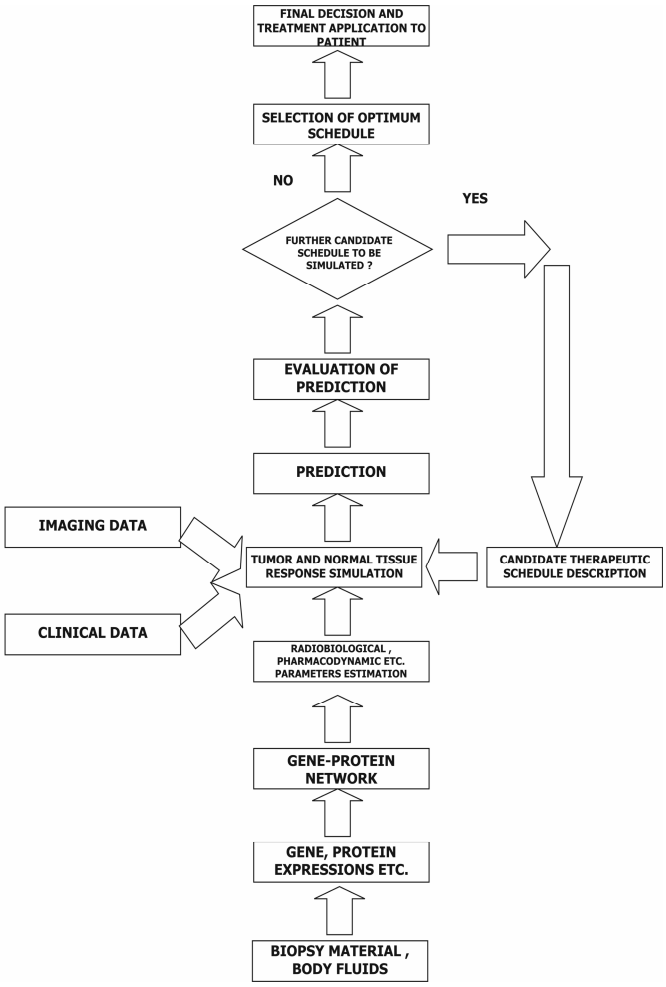

Fig. 1. A block diagram of the "Oncosimulator"'s function

III. The Paradigm of Nephroblastoma Treated by Vincristine

In the following a short outline of the simulation paradigm concerning a nephroblastoma tumor treated with vincristine is given. The nephroblastoma neoplasm (Wilms' tumour) is a common pediatric solid kidney tumor mainly affecting children younger than 5 years. Although the genetic causes that lead to this neoplasm have not yet been clarified, nephroblastoma has been associated with gene WT1 [12]. It is normally treated with chemotherapy and surgery. Vincristine is widely used in nephroblastoma treatment, mainly in combination with other drugs (dactinomycin and/or doxorubicin). The present simulation treatment is to be considered a first, yet quite representative, step towards the simulation of the combined chemotherapy schemes.

There are two different clinical treatment approaches, one requiring chemotherapy to take place prior to surgery and the other one dictating the use of chemotherapeutic agents after removal of the tumor. The model under discussion might contribute to the selection of the optimal treatment for any individual patient taking also into account specific

serum biochemical data.

The scheme simulated is the following: intra venous (i.v.) bolus injection of 1,5mg/m^2 every week for four successive weeks. This scheme is widely used in clinical practice. The model can however be readily adapted to simulate different dose administration schemes.

IV. Vincristine Pharmacokinetics and Pharmacodynamics

A. Vincristine Pharmacokinetics

Following an extensive bibliographical study of vincristine pharmacokinetics, reference [13] has been selected as the most suitable source of pharmacokinetic parameters of vincristine for the model developed. An algebraic analysis, using the corresponding parameters and appropriate pharmacology equations resulted in the following equation:

$$C = 0.117e^{-6.300t} + 3.868 \cdot 10^{-3.000} e^{-0.014t} mg/L, \qquad (1)$$

where C is the concentration of vincristine in plasma and t is the time elapsed after injection.

Equation 1 is used by the model to determine the concentration of vincristine in the plasma of the patient. This information is also exploited by the corresponding pharmacodynamics equation.

B. Vincristine Pharmacodynamics

Both a qualitative and a quantitive analysis of vincristine pharmacodynamics are vital for the proper simulation of the drug's cytotoxic effect.

Vincristine's antineoplastic effect is usually attributed to the drug's ability to destroy the cell's microtubules' functionality by binding to the protein tubulin [14]. The microtubules form the mitotic spindle. Failure of the mitotic spindle causes the cell cycle to stop during mitosis, inducing programmed cell death (apoptosis) [14]. This is the reason why vincristine is characterised as an M-phase specific drug. In order to quantitatively express the drug's antitumour effect the survival curve presented in [15] has been used.

V. Fundamental Algorithms

The concept of *nondeterministic finite state automata* has been adapted in order to model cell cycling and transitions to and from possible cell states (cytokinetic diagram). The cytokinetic diagram constructed to integrate vincristine's cytotoxic action is depicted in Fig.2. Vincristine can enter the cell and bind to tubulin at any point of the cell cycle, but its cytotoxic effect is observed only when the cell enters mitosis.

The tumour is computationally placed within a virtual discretizing mesh, each geometrical cell of which is considered to occupy a certain size of space and can therefore contain a specific number of biological cells. The growth or shrinkage of the tumour is modeled with the shift of the contents of the discretizing mesh cells, so that some geometrical cells can be added to the tumour or can no longer belong to it, depending on the local cell population at any given time [16].

VI. Technical Issues and Validation

Object oriented programming has been introduced into the computer implementation of the model.

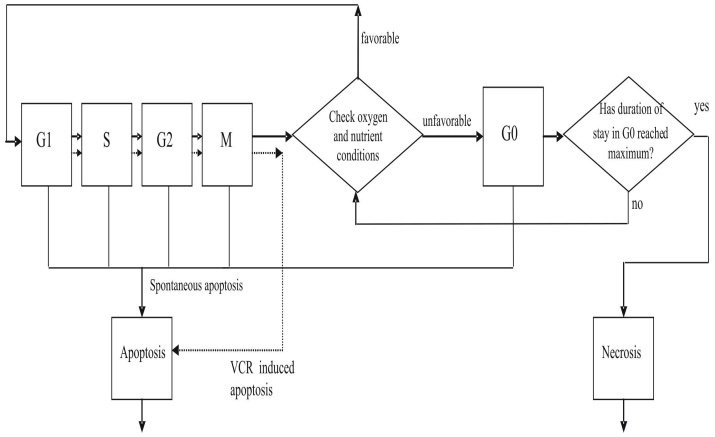

Fig.2 The cytokinetic diagram proposed and applied in the model

The code developed can be easily adapted and most of the classes implemented can be *reused* in the case of simulating different drugs for nephroblastoma or even different kinds of neoplasms.

A typical execution time is 2 min for the simulation of the response of a 600 mm^3 tumour to the above mentioned therapeutic scheme lasting 28 days on a Pentium 4, 3 GHz, 512 MB RAM.

As far as validation is concerned, various numerical, qualitative and quantitative tests have been devised and implemented so as to check the integrity and the stability of the code.

VII. Results

Typical simulation results for the above mentioned chemotherapeutic scheme applied to a spherical tumor (a three dimensional ellipsoid of three equal axes) of initial radius 0.5 cm are depicted in Fig. 3. The figure quantifies the effect of an eventual delay in the administration of the third chemotherapeutic session. Provided that the fourth dose is given as scheduled, the model suggests that there is no significant effect on the final outcome. Validation tests including comparison with clinical data can be found in [16].

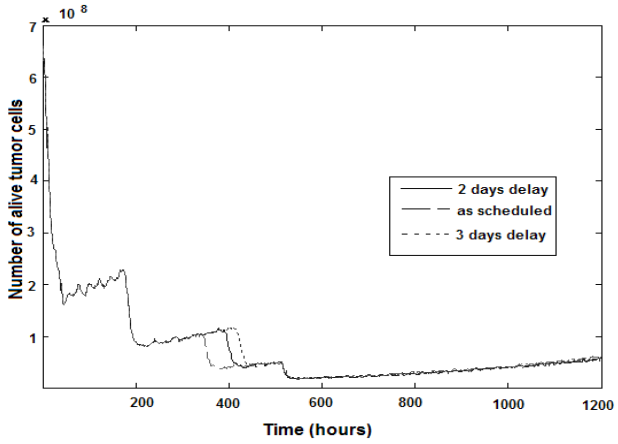

Fig. 3. The effect of an eventual delay in the administration of the third chemotherapeutic session, provided that the fourth dose is given as scheduled (see text for details)

VIII. Discussion

The specific paradigmal model presented, after having been extended, clinically tested, adapted, optimized and validated is expected to be able to support clinicians' decisions concerning various candidate cancer treatment schemes and thus facilitate patient individualized treatment optimization. Suggestion of new therapeutic strategies as well as contribution to the training of doctors, life scientists, researchers or interested patients by demonstrations of the likely tumour response to different therapeutic schemes are further expected uses of the model. A long term validation is taking place within the frame of the ACGT project.

Adaptation of the model to include co-administration of vincristine with dactinomycin is in progress. Further adaptations include the use of the actual shape and size of the tumour instead of the ellipsoidal tumor assumption and the integration of serum protein data which are expected to considerably enhance molecular individualization of the model.

IX. Conclusions

The development and subsequent clinical adaptation, optimization and validation of the "Oncosimulator", although a tremendous challenge, is seen as a necessary step towards the rational and quantitative individualization of cancer treatment. At the same time the whole endeavor is viewed as an excellent opportunity for the advancement of the *re-formulation* of both biology and medicine in spatiotemporal mathematical and computational terms. In this context an expression of the form "Philosopiae Naturalis Principia Mathematica, Pars II: Materia Vivens" (Mathematical Principles of Natural Philosophy, Second Part: Living Matter) might describe to some extent the strongly collaborative, multilevel, interdisciplinary and intercontinental effort to *quantitatively* understand perhaps the most intriguing *natural phenomena*: *life* and *disease*.

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