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In Silico Oncology: Exploiting Clinical Studies to Clinically Adapt and Validate Multiscale Oncosimulators*

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***Abstract*—This paper presents a brief outline of the notion and the system of oncosimulator in conjunction with a high level description of the basics of its core multiscale model simulating clinical tumor response to treatment. The exemplary case of lung cancer preoperatively treated with a combination of chemotherapeutic agents is considered. The core oncosimulator model is based on a primarily top-down, discrete entity - discrete event multiscale simulation approach. The critical process of clinical adaptation of the model by exploiting sets of multiscale data originating from clinical studies/trials is also outlined. Concrete clinical adaptation results are presented. The adaptation process also conveys important aspects of the planned clinical validation procedure since the same type of multiscale data – although not the same data itself- is to be used for clinical validation. By having exploited actual clinical data in conjunction with plausible literature-based values of certain model parameters, a realistic tumor dynamics behavior has been demonstrated. The latter supports the potential of the specific oncosimulator to serve as a personalized treatment optimizer following an eventually successful completion of the clinical adaptation and validation process.**

I. Introduction

In silico medicine appears to be the latest trend regarding the translation of mathematical and computational biological science into clinical practice through a massive exploitation of information technology. The core idea is to view disease as a hyper-complex and multiscale *natural phenomenon* amenable to modeling and simulation [1-4]. *In silico* (i.e. on the computer) experimentation for each individual patient using their own multiscale clinical data is expected to significantly improve the effectiveness of treatment, since reliable computer predictions could suggest the optimal treatment scheme(s) and schedules(s) for each separate case. In order to address this vision, a number of combined multiscale modeling [5] and information technology approaches [4] have appeared in the last years.

In this paper, an outline of the clinically driven and clinically oriented notion and system of oncosimulator is presented in conjunction with a brief description of a specific core simulation model addressing tumor response to chemotherapy in the case of lung cancer. The adopted clinical adaptation method making use of actual multiscale clinical data is delineated. Indicative results supporting the validity of the approach are also presented. It is noted that the clinical adaptation process is expected to convey important aspects of the clinical validation procedure [6] since the same type of multiscale data – although not the same data itself- will be used for the latter.

II. The Notion and the System of the Oncosiimulator

The *oncosimulator* is at the same time a concept of multilevel integrative cancer biology, a complex algorithmic construct, a biomedical engineering system and eventually in the future a clinical tool which primarily aims at supporting the clinician in the process of optimizing cancer treatment in the patient individualized context through *in silico* experimentation. Additionally, the oncosimulator is a platform for simulating, investigating, better understanding and exploring the natural phenomenon of cancer, supporting the design and interpretation of clinicogenomic trials and finally training doctors, researchers and interested patients alike [1],[4]. An outline of the clinical utilization of the oncosimulator, as envisaged to take place following an eventually successful completion of its clinical adaptation, optimization and validation process is provided in the flow diagram of Fig.1.

In the rest of this section a brief description of the basics of the generic core multiscale model of the oncosimulator is provided. The anatomic region of interest is discretized by a virtual mesh of which the elementary cube is termed *geometrical cell* [1-4]. A hypermatrix i.e. a mathematical matrix of (matrices of (matrices…of (matrices or vectors or scalars))) corresponding to the region of interest is subsequently defined [1]. The latter describes explicitly or

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implicitly the local biological, physical and chemical dynamics of the region [1].

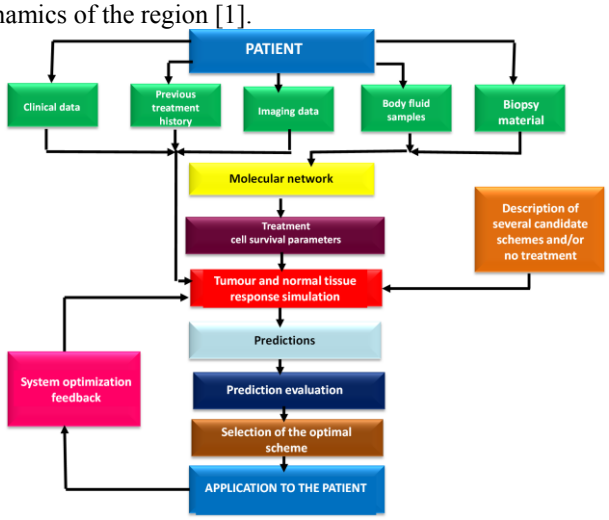

Fig.1 A synoptic diagram of the Onscosimulator

The following (sets of) parameters are used to identify a cluster of biological cells belonging to a given equivalence class within a geometrical cell of the mesh at a given time point: **I.** The spatial coordinates of the discrete points of the discretization mesh with spatial indices i, j, k respectively. It is noted that each discrete spatial point lies at the center of a geometrical cell of the discretization mesh. **II.** The temporal coordinate of the discrete time point with temporal index l. **III.** The mitotic potential category [i.e. stem or progenitor (=limited mitotic potential bearing or LIMP) or terminally differentiated] of the biological cells with mitotic potential category index m. **IV.** The cell phase (within or out of the cell cycle) of the biological cells with cell phase index n. The following phases are considered: {G1, S, G2, M, G0, A, N, D}, where G1 denotes the G1 cell cycle phase; S denotes the DNA synthesis phase; G2 denotes the G2 cell cycle phase; M denotes mitosis; G0 denotes the quiescent (dormant) G0 phase; A denotes the apoptotic phase; N denotes the necrotic phase and D denotes the remnants of dead cells.

For the biological cells belonging to a given mitotic potential category AND residing in a given cell phase AND being accommodated within the geometrical cell of which the center lies at a given spatial point AND being considered at a given time point; in other words for the biological cells clustered in the same equivalence class denoted by the index combination ijklmn, the following state parameters are provided**: i.** local oxygen and nutrient provision level**, ii.** number of biological cells, **iii**. average time spent by the biological cells in the given phase, **iv.** number of biological cells hit by treatment, **v.** number of biological cells not hit by treatment.

The initial constitution of the tumor i.e. its biological, physical and chemical state has to be estimated based on the available medical data through the application of pertinent algorithms. This state corresponds to the instant just before the start of the treatment course to be simulated. The entire simulation can be viewed as the periodic and sequential application of a number of algorithms (operators) on the hypermatrix of the anatomic region of interest which takes place in the following order: **a)** time updating i.e. increasing time by a time unit (e.g. 1h). **b)** estimation of the local oxygen and nutrient provision level. **c)** estimation of the effect of treatment referring mainly to cell hit by the treatment, cell killing and cell survival. Available molecular and/or histological information is integrated primarily at this point. **d)** application of cell cycling, possibly perturbed by treatment. Transition between mitotic potential cell categories, such as transition of the offspring of a terminally divided progenitor cell into the terminally differentiated cell category, is also tackled by this algorithm set. **e)** handling of differential tumor expansion/ shrinkage or more generally spatial geometry and tumor mechanical dynamics. **f)** updating the local oxygen and nutrient provision level at each time step. It is worth noting that stochastic perturbations about the mean values of several model parameters are considered (hybridization with the Monte Carlo technique). Further details are available in [1-4],[7-9]. An in depth description of the basics of the specific simulation model considered can be found in the previous publications of the *In Silico Oncology* group [7-8].

III. Cytokinetic Models of Free Growth and Treatment Response

A. Free growth

The adopted cytokinetic model (Fig.2) [7, 8] includes critical model parameters that have been studied in the present work. It incorporates the progression through the active cell cycle, exiting to the quiescent state, differentiation and cell loss. Tumor progression is sustained by a small cell population that exhibits stem cell like properties. These so called cancer stem cells have the ability to self-renew, as well as to give rise to cells of limited mitotic potential (LIMP cells) that follow the developmental hierarchy towards terminal differentiation (DIFF cells). A proliferating cancer stem or LIMP cell passes through the successive cell cycle phases (G1, S, G2, M). Upon completion of mitotic division, a fraction of daughter cells will become dormant. On top of internal molecular pathway interactions, the local oxygen and nutrient supply conditions regulate transition to the dormant G0 phase and "awakening" of dormant cells. All living cell categories may die through spontaneous apoptosis. However, the loss of dormant and differentiated cells is primarily attributed to inadequate nutrient and oxygen supply that triggers the necrotic loss.

B. Treatment response

At the time instances when chemotherapeutic treatment is administered, a fraction of stem and LIMP cells are assumed to undergo lethal damage by the drug. These cells follow a rudimentary cell cycle before apoptotic death through a cell cycle phase dictated each time by the

mechanism of action of the specific chemotherapeutic agent. The effect of the drug is assumed instantaneous at the time of its administration.

IV. A Paradigm of Exploiting Clinical Data for the Clinical Adaptation of the Core Model: The Lung Cancer Case

A. Clinical Data

Lung cancer is the most common cause of cancer death wordwide [10]. Within the framework of the ContraCancrum project, the core discrete simulation model of the ICCS-NTUA *In Silico* Oncology Group (ISOG) [Fig.2] has been applied to the case of neoadjuvant preoperative chemotherapeutic treatment of primary non small cell lung cancer with various combinations of the agents cisplatin, gemcitabine, vinorelbin and docetaxel. The model has been applied to sets of multiscale data originating form 13 patients. This anonymized data has been provided by the Institute of Pathology, University Hospital of Saarland, Germany. The proof of concept analysis presented in this paper, focuses on a subset of three patients with squamous cell carcinoma, treated with a combination of cisplatin and gemcitabine (2 three-week cycles. On the first day of the treatment cycle the patient is given both gemcitabine and cisplatin. On the same day of the following week (day eight) only gemcitabine is administered.

B. Modeling of the action mechanisms of the drugs considered

Cisplatin is a cell cycle - non specific drug [11]. It binds covalently to DNA to form intra- and interstrand DNA cross-links, leading to DNA breakage during replication. This inhibits DNA transcription, synthesis and function [12]. In our modeling approach, tumor cells are assumed to absorb cisplatin at cycling and dormant phases, as well as at G0 phase, whereas apoptotic death of hit cells takes place in the S phase.

Gemcitabine is a nucleoside analogue that is cell cycle-specific with activity in the S phase [11]. The active metabolite has several functions: (a) it is incorporated into DNA, resulting in chain termination and inhibition of DNA synthesis and function, (b) it is incorporated into RNA, resulting in altered RNA processing and translation, (c) it inhibits several DNA polymerases which disrupt DNA chain elongation, DNA synthesis, and DNA repair [13]. In our modeling approach, tumor cells are assumed to absorb the drug at cycling phases only, whereas apoptotic death of hit cells takes place in the S phase.

V. Clinical Adaptation

The patient specific data that has been exploited by the model includes the applied chemotherapeutic scheme (drugs and administration instants) and the 3D reconstructed images of the tumor derived from CT scans. The sets of imaging data were provided for two time instants before and after the completion of the treatment. Due to the non availability of information in the reconstructed CT imaging data related to any distinct internal metabolic regions, the virtual tumor implemented has been assumed homogeneous with a shape compliant to the reconstructed tumor image. A two - step adaptation process is followed. The first step refers to the adaptation of the model parameters that regulate tumor free growth kinetics (Table I). Due to the non-availability of proliferation indices, such as Ki-67,and data that could allow the precise estimation of the tumor growth (e.g. at least two imaging scans before and/or after therapy), a literature review has provided biologically reasonable values for critical tumor kinetics features. The latter has focused on studies aiming at determining the volume doubling time based on volumetric methods and attempting to assess the prognostic value of the cellular proliferation index Ki-67.

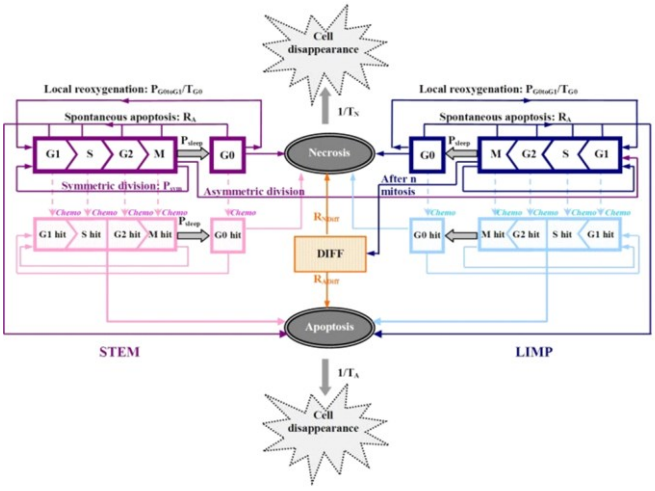

Fig. 2. General cytokinetic model for tumor response to chemotherapy. STEM: stem cells. LIMP: Limited proliferative potential cells. DIFF: terminally differentiated cells. G1: Gap 1 phase. S: DNA synthesis phase. G2: Gap 2 phase. M: Mitosis phase. G0: Dormant, resting phase. Chemo: Chemotherapeutic treatment. Hit: Cells lethally hit by the drug. For model parameters symbols and definition see Table I.

In the adaptation paradigm presented here the following assumptions/constraints have been imposed, based on literature:

i. Volume doubling time (T_d): 200 days [14].
ii. Growth fraction: 60% [15].

At the second step, the cell kill rate (CKR) of the drugs is adapted to the observed tumor size reduction. Since the regimen given consists of two chemotherapeutic agents, it is not possible to accurately determine the cell kill rate of each drug from the data provided, even in the ideal case of the availability of all required proliferation indices and tumor free growth kinetics features that would enable an excellent fitting of the model parameters to the clinical case examined. In the paradigm presented here an 'apparent' combination of the CKR of the drugs involved, for the virtual tumor implementation considered, is determined (Table II). An excellent fitting between the simulation results and the patient volumetric data has been achieved in all three clinical cases (deviation less than 0.5%).

The results indicate a realistic value range of the apparent CKR of the drugs. However, due to the small size of the

sample examined and the consideration of only one possible virtual tumor implementation, no definite conclusion can be drawn as yet. Fig.3 shows the simulated time course of tumor volume for all clinical cases. The time instances of drug administration are evident. The onset (time 0) and the end time point of the simulation correspond to the time instances of the initial and the final tumor CT image acquisition. A tumor dynamics behavior in accordance with clinical experience is noticeable. The simulation results successfully demonstrate tumor shrinkage and the resulting tumor repopulation after each chemotherapeutic session .

This process will be repeated for numerous sets of real multiscale data in order to optimize the clinical adaptation of the specific oncosimulator model and subsequently achieve its clinical validation.

TABLE I. ADAPTATION OF THE PARAMETER VALUES USED FOR THE SIMULATION OF THE CLINICAL CASES CONSIDERED AND RESULTING TUMOR CHARACTERISTICS

Parameter	Description	Value
T_c	Cell cycle duration	90 h
T_{G0}	Duration of dormant phase	96 h
T_N	Time needed for necrosis' products to disappear from the tumor	100 h
T_A	Time needed for apoptosis products to be removed from the tumor	6 h
N_{LIMP}	Number of mitoses performed by LIMP cells before they become terminally differentiated	7
R_A	Apoptosis rate of stem/LIMP cells	0.001 h^{-1}
R_{ADiff}	Apoptosis rate of differentiated cells	0.001 h^{-1}
R_{NDiff}	Necrosis rate of differentiated cells	0.022 h^{-1}
P_{G0toG1}	Fraction of dormant cells that re-enter the cell cycle	0.01
P_{sleep}	Fraction of cells that enter the G0 phase following mitosis	0.31
P_{sym}	Fraction of stem cells that perform symmetric division	0.6
Tumor Characteristic		**Value**
Doubling Time		200 d
Fraction of tumor stem cells		0.12
Fraction of tumor LIMP cells		0.46
Fraction of tumor proliferating cells		0.40
Fraction of tumor dormant cells		0.18
Fraction of terminally differentiated tumor cells		0.07
Fraction of dead cells		0.35
Growth fraction		0.61

TABLE II. CELL KILL RATE ADAPTATION

	Case Study		
	A	B	C
Cisplatin cell kill rate	**0.15**	**0.2**	**0.22**
Gemcitabine cell kill rate	**0.13**	**0.19**	**0.2**
Sum of cell kill rates	**0.28**	**0.39**	**0.42**
Initial tumor volume (mm^3)	100264	568264	101216
Final tumor volume based on DICOM (mm^3)	46824	168048	26336
Simulated final tumor volume (mm^3)	46890	168894	25976
Relative reduction of the tumor volume based on the DICOM data (% of the original volume)	53.30	70.43	73.98
Relative reduction of the tumor volume based on the simulation predictions (% of the original volume)	53.23	70.28	74.34
Relative deviation between predicted and real tumor shrinkage (% of the real shrinkage)	**0.12**	**0.21**	**-0.48**

VI. CONCLUSIONS

The presented indicative results support the potential of the specific oncosimulator to be translated into the clinic following completion of an eventually successful clinical validation procedure. The exploitation of proliferation indices, when available, is expected to considerably enhance the adaptation and the clinical validation processes. The potential use of the oncosimulator for the *a priori* assessment of neoadjuvant therapeutic strategies (strategies that primarily aim at reducing tumor size before surgery) justify the use of tumor volume as a metric to judge the validity of our simulation results. A clinically adapted and validated oncosimulator is expected to serve as a platform for conducting *in silico* experiments based on the individual multiscale data of the patient. This fundamental science based system is expected to considerably advance personalized optimization of cancer treatment.

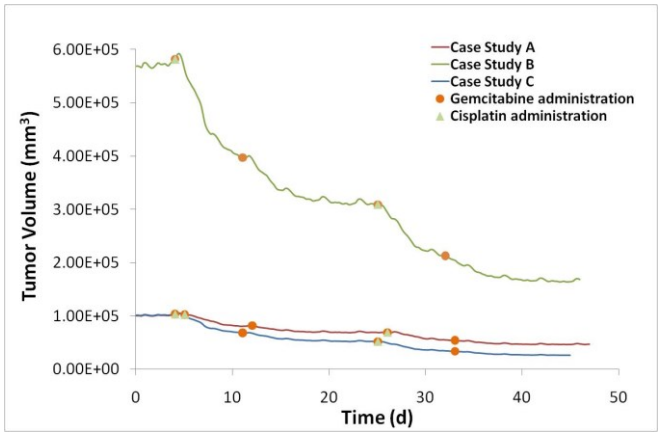

Fig. 3. Simulated time course of the tumor volume for the case studies A, B and C. The time points of each drug administration (gemcitabin, cisplatin) is indicated for each clinical case.

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