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

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***Abstract*—This paper outlines the major components and function of the technologically integrated oncosimulator developed primarily within the Advancing Clinico Genomic Trials on Cancer (ACGT) project. The Oncosimulator is defined as an information technology system simulating *in vivo* tumor response to therapeutic modalities within the clinical trial context. Chemotherapy in the neoadjuvant setting, according to two real clinical trials concerning nephroblastoma and breast cancer, has been considered. The spatiotemporal simulation module embedded in the Oncosimulator is based on the multiscale, predominantly top-down, discrete entity—discrete event cancer simulation technique developed by the *In Silico* Oncology Group, National Technical University of Athens. The technology modules include multiscale data handling, image processing, invocation of code execution via a spreadsheet-inspired environment portal, execution of the code on the grid, and the visualization of the predictions. A refining scenario for the eventual coupling of the oncosimulator with immunological models is also presented. Parameter values have been adapted to multiscale clinical trial data in a consistent way, thus supporting the predictive potential of the oncosimulator. Indicative results demonstrating various aspects of the clinical adaptation and validation process are presented. Completion of these processes is expected to pave the way for the clinical translation of the system.**

***Index Terms*—Advancing Clinico Genomic Trials on Cancer (ACGT) project, breast cancer, *in silico* medicine, *in silico* oncology, multiscale cancer modeling, nephroblastoma, oncosimulator, Virtual Physiological Human (VPH).**

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I. Introduction

In silico medicine, an emergent scientific and technological domain based on clinically driven and oriented multiscale biomodeling, appears to be the latest trend regarding the translation of mathematical and computational biological science to clinical practice through massive exploitation of information technology. The term *multiscale* refers to several scales or levels of the manifestation of life such as the molecular, the cellular, the tissue, the organ, and the body system scales addressed concurrently. The idea is to view disease as a hypercomplex and multiscale *natural phenomenon* amenable to modeling and simulation [1]–[10]. *In silico* (i.e., on the computer) experimentation for each individual patient using their own multiscale biomedical data is expected to significantly improve the effectiveness of treatment in the future, since reliable computer predictions could suggest the optimal treatment scheme(s) and schedules(s) for each separate case.

It is noted that generic treatment schemes and schedules are based on the average response of a population of patients. Despite the fact that those patients share certain characteristics

of the disease, other critical disease characteristics may differ tremendously across the population. This may lead to remarkably differing actual responses to the same treatment among patients.Therefore, a thorough exploitation of all the critical disease characteristics of a given patient and their dynamic interdependences at several spatiotemporal scales is expected to lead to an optimal treatment tailored to the patient's biological constitution. Such an approach may dictate the prescription of more effective drugs and dosages for any given patient and the minimization of side effects. This may obviously have considerable clinical, societal, and financial implications.

In order to address this vision, a number of combined multiscale modeling and information technology approaches have appeared over the last few years [1]. In the area of *in silico oncology* the technologically integrated oncosimulator (IOS) developed primarily within the framework of the European Commission (EC) funded integrated project ACGT (Advancing ClinicoGenomic Trials on Cancer, FP6–2005-IST-026996) appears to be the first worldwide effort of its kind. [11].

The ACGT project proposed the design and implementation of a dedicated cancer information technology (IT) environment able to seamlessly integrate clinico-genomic data and support the development of complex models. Within this context, simulating disease evolution and/or disease outcome was a milestone for the technological advancement of predictive medicine-based decision support. The major expected outcome is twofold: first, we hope to alleviate the patient from unnecessary treatment. Excess treatment may be administered in cases where lack of knowledge regarding critical aspects of the molecular constitution and the multiscale dynamics of the tumor prevents the prediction of an eventually good and fast response to a given therapeutic scheme from being formulated. *In silico* oncology is expected to substantially alleviate the potentially serious side effects of excess treatment in such cases. Second, we hope to eventually optimize treatment via *in silico* simulation of candidate therapeutic schemes.

The IOS embedded within the ACGT architecture is a software system simulating *in vivo* tumor response to therapeutic modalities within the clinical trial context. The four dimensional (4-D) (spatiotemporal) simulation module that has been embedded in the oncosimulator is primarily based on the multiscale, predominantly top-down, discrete entity—discrete event cancer simulation technique developed by the *In Silico* Oncology Group (ISOG) of the Institute of Communication and Computer Systems, National Technical University of Athens (www.in-silico-oncology.iccs.ntua.gr) [2]–[10]. The top-down method starts from the macroscopic imaging data and proceeds toward lower biocomplexity levels. When there is a need for an upward movement in the biocomplexity scales, a summary of the available information pertaining to the previous lower level is used.

Within the ACGT project, we have addressed two preoperative chemotherapy scenarios using real clinical trial data: nephroblastoma and breast cancer. The technology modules include multiscale data handling, image processing, invocation of code execution via a spreadsheet-inspired environment portal (RecipeSheet), execution of the computer code on the grid, and visualization of the predictions of the simulations. Adaptation of parameter values to multiscale clinical trial data has been achieved in a consistent way as described in Section IX. The latter endorses the predictive potential of the oncosimulator. Both clinical adaptation and validation procedures are in progress. In addition to already published predictive results [8], [10] demonstrating various aspects of the clinical adaptation and validation procedures, new illustrative simulation examples are presented in this paper. Clinical adaptation and validation, when completed, are expected to pave the way for the clinical translation of the system. A scenario for the eventual coupling of the oncosimulator with immunological models so as to refine the original simulation tumor dynamics models is also presented.

A. Nephroblastoma Case

Nephroblastoma is the most common malignant renal tumor in children. Treatments are based on prospective multicenter trials and studies conducted by the International Society of Pediatric Oncology (SIOP) in Europe and the Children's Oncology Group, North America (COG) in North America [12]. Information from these nephroblastoma studies on both sides of the Atlantic have allowed the identification of prognostic indicators independent of whether patients are treated by immediate surgery (COG) or surgery after preoperative chemotherapy (SIOP).

The identification of histological subtypes of Wilms' tumor in addition to stage classification and response to treatment is of prognostic value. In this way, the SIOP trials and studies largely focus on the issue of preoperative therapy [13], [14]. Response to treatment can be measured individually by tumor volume reduction and percentage of therapy-induced necrosis or remaining vital blastema at the time of surgery in the histological specimen. In nephroblastoma, the blastemal subtype after preoperative chemotherapy is recognized as an unfavorable entity. This gives an early individual prognostic parameter and is used for further stratification and more individualization of the postoperative treatment [12], [13].

The nephroblastoma case is ideal for the development and validation of *in silico* models since the highly successful treatment rate in SIOP provides an excellent, reliable reference for both developing and validating such models. The main goal in this context is to quantitatively predict the response to preoperative chemotherapy in every case. The model aims at avoiding unnecessary treatment in nonresponding tumors and applying chemotherapy only to those patients that would benefit most. At the same time, the provision of a clinical decision support tool for the less experienced clinicians treating this disease is of particular importance.

B. Breast Cancer Case

The breast cancer branch of the oncosimulator addresses breast cancer treatment with epirubicin, an anthracycline drug used for chemotherapy. Although anthracycline drugs are among the most effective chemotherapies in breast cancer, their efficacy is restricted to a subset of the breast cancer patient population, and a small proportion of women suffer severe side

effects, including congestive heart failure. By identifying those women who are most likely to benefit from treatment, it might be possible to reduce the unnecessary exposure of some women to such a risk and to take an important step toward the individualization of breast cancer treatment. The traditional approach to tackle this problem has been the identification of novel predictive biomarkers. Topoisomerase IIA (TOP2 A) is arguably the most promising marker for predicting the efficacy of anthracycline-based chemotherapy for breast cancer patients. However, several groups have reported conflicting results with regard to its predictive value. The primary aim of the TOP trial [15] was to prospectively evaluate the predictive value of TOP2 A and the secondary aim to identify biomarkers of response/resistance to anthracyclines.

This trial has demonstrated a significant correlation of TOP2 A amplification—but not protein overexpression—with the response to anthracyclines [15]. Additionally, an anthracycline-based score (A-Score) using gene expression data has been proposed. By including the A-Score into the IOS, a multiscale model has been developed to simulate treatment outcome based on the characteristics of individual patients for optimizing breast cancer treatment.

II. Brief Outline of the Multiscale Model of Cancer Dynamics and Response to Treatment Units

In this section, a brief description of the basics of the IOS multiscale models is provided. The models start from the macroscopic high biocomplexity level (imaging data) and proceeds toward lower biocomplexity levels. The macroscopic anatomic region of interest is either manually or semi-automatically annotated by the clinicians on MRI imaging sets acquired at time of diagnosis (see Section III.) A virtual cubic mesh is used for the discretization of the area of interest (tumor) of which the elementary cube is termed geometrical cell [2]–[9]. A hypermatrix, i.e., a mathematical matrix of [matrices of (matrices. . .of (matrices or vectors or scalars))] corresponding to the anatomic region of interest is subsequently defined [9]. The latter describes explicitly or implicitly the local biological, physical, and chemical dynamics of the region [2]–[10]. 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.

1) 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.
2) The temporal coordinate of the discrete time point with temporal index l.
3) The mitotic potential category (i.e., stem or progenitor or terminally differentiated) of the biological cells with mitotic potential category index m.
4) 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 whose 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:

1) local oxygen and nutrient provision level;
2) number of biological cells;
3) average time spent by the biological cells in the given phase;
4) number of biological cells hit by treatment;
5) number of biological cells not hit by treatment.

The *initial* constitution of the tumor has to be estimated based on the available medical data through the application of pertinent algorithms [8]. 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. 1) time updating, i.e., increasing time by a time unit (e.g., 1 h); 2) estimation of the local oxygen and nutrient provision level; 3) 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. 4) 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. 5) Handling of differential tumor expansion/ shrinkage or more generally spatial geometry and tumor mechanical dynamics. 6) 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). A generic tumor cell cytokinetic model is depicted in Fig. 1. For further details see [8] and [10].

III. Image Processing of the Medical Data

For patients with nephroblastoma, imaging studies (MRI $T1$, $T1$ with contrast enhancement, $T2$ and $T2$ flair) are available at the time of diagnosis and after 4 weeks of preoperative chemotherapy. The imaging studies at the time of diagnosis are used for the prediction of tumor shrinkage during and after 4 weeks of vincristine and actinomycin-D chemotherapy.

One of the main inputs into the IOS is the volumetric data of nephroblastoma. This data consists of isotropic voxel dimensions in order to facilitate the computation of tumor dynamics simulation. Since MRI slices are usually reconstructed containing highly nonisotropic voxels, interpolation of the binary segmentation volumes is performed [16].

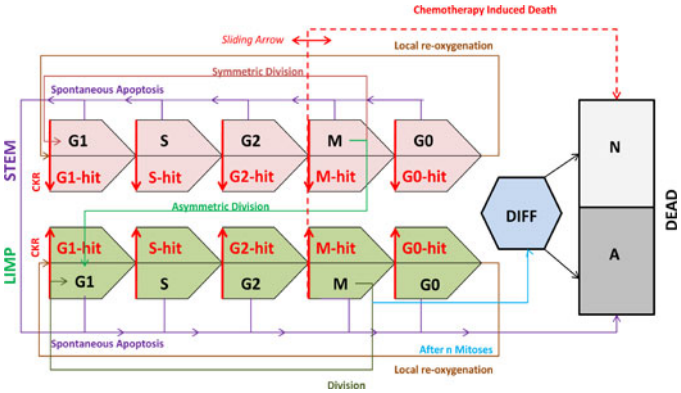

Fig. 1. Generic cytokinetic model used. LIMP: Limited Mitotic Potential cells. DIFF: terminally differentiated cells. G1: Gap 1 phase. S: DNA synthesis phase. G2: Gap 2 phase. M: Mitosis. G0: dormant phase. N: necrosis. A: apoptosis. Hit: cells lethally hit by chemotherapy. CKR: Cell Kill Rate. The arrow indicating chemotherapy-induced death is a sliding arrow, with position dependent on drug pharmacodynamics.

Segmentation of the tumor is important in order to provide information on the shape and location of the tumor. This process is also important for model validation since it allows quantitative comparison of the simulation predictions with the actual development of the tumor *in vivo*. Within the ACGT project, a novel semiautomatic snake-based method for cancer segmentation was developed, where a spatially adaptive behavior of the snake is accomplished with minimal user interaction. The method achieved has improved results over traditional snakes, due to local snake bending. This spatially adaptive active contour technique introduced a local snake bending to improve traditional snake's performance for segmenting tumors. The key point is the use of adaptable parameters, instead of constant ones, in order to adjust the bending of the curve locally according to image characteristics such as gradient magnitude and corner strength. The result is a more flexible/accurate delineation of tumor regions reported in more than 150 real MRI cases. Validation has been performed using the clinical expert's annotations as ground truth [17]. Fig. 2, shows an example where this improved method better delineates the tumor without getting stuck in local maxima.

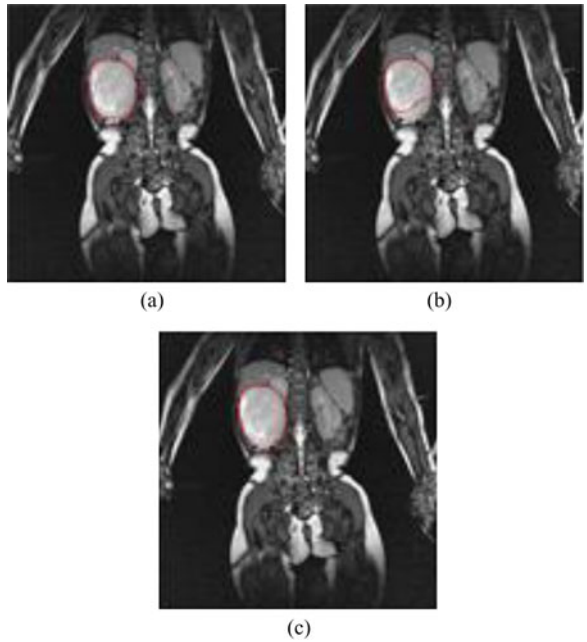

Fig. 2. Renal tumor segmentation on MR abdominal images: (a) clinician's annotation, (b) result using traditional snakes due to tumor inhomogeneity, and (c) result using spatially adaptive active contours.

IV. Subjunctive Interface System for the Exploration of the Oncosimulator

In this section, the front-end facilities that were created to support the IOS developers in its technical validation are briefly described. Validation, in the sense used here, means confirming that the simulator delivers credible results when applied to tumors of differing sizes and shapes, and that adjustment to each of its parameters, singly or in combination, has the expected impact on the results.

The validation is therefore a form of exploration within the space of possible simulation results, with the following characteristics. 1) The exploration must be overseen by a human user. For each simulation, the developers must confirm not just that the final predicted outcome (percentage growth or shrinkage of the tumor) is reasonable, but that the simulation followed a legitimate and credible course to that outcome. 2) The parameter space is very large. The versions of the simulator being validated have between 35 and 40 independently variable parameters. An interface offering simultaneous access to all these parameters would be unwieldy, so the users must be able to choose which parameters to vary. They must also be assisted in keeping track of which parameter–value combinations have been explored so far. 3) Validation calls heavily on comparison. The developers must initially confirm that for each step in the value of a single parameter, the results change by a reasonable increment in the predicted direction. They must also check the effects of changing settings on multiple parameters. 4) Some result visualizations require interaction. The results from the oncosimulator include representations of the tumor shape in three dimensions; these can be rendered in 2-D for on-screen display, but in order to understand the entire solid shape a user typically needs to interact with the view, for example by rotating it or taking slices.

Data presentations and visualizations for the validation are obtained through RESTful web services. These provide both alphanumeric ("raw") representations of IOS results as well as graphical, such as graph plots, 2-D views (isocontours, scatterplots, cutting planes), 3-D views (isosurfaces, volume rendering), and animated views that show the evolution of a tumor over time. Multimodal visualizations are also supported that simultaneously represent IOS results with medical images (e.g., CT, MRI) and manual annotations of pre/post-therapy tumor regions. Given the importance of comparison between alternative cases, as noted above, linked views are supported to provide a consistent view on multiple cases at the same time.

The validation interface is based on the RecipeSheet [18], an end-user programming environment that explicitly includes

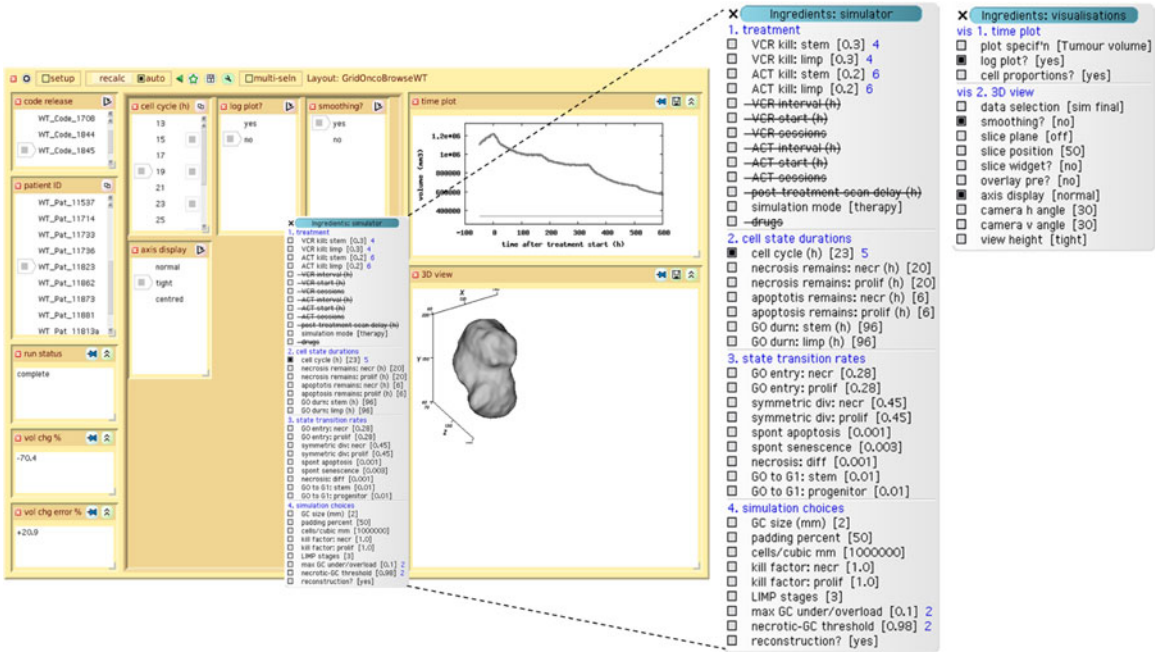

Fig. 3. Main OncoRecipeSheet (ORS) showing the menus for selecting simulation and visualization parameters.

subjunctive interface facilities [19], [20] to help users request, compare, and interact with multiple alternative results simultaneously. On the "OncoRecipeSheet" (ORS) created for this project, a user can specify up to 12 independent scenarios at a time, each scenario defining a combination of simulation–parameter values. If a simulation has already been run for a specified parameter combination, visualizations of its results are retrieved from an online server and displayed on the sheet; if the simulation has not yet been run, the ORS includes a simple tool for submitting it immediately as a grid job.

Fig. 3 presents the main ORS interface with a single scenario showing the results. The patient identifier and the version of simulator code are chosen using the sheet cells at top left. The large pop-up menu (shown expanded on the right) offers the 38 parameters that can be varied in the chosen code version; here, the user has requested a control to vary the "cell cycle" parameter, which the menu shows would otherwise default to 23 h. The displayed result is from a simulation run with default values for all other parameters. On the far right is an expanded version of a second menu that offers parameters for tailoring the result display. Here, the user has asked to control three of those parameters, so they too appear as cells on the sheet. Fig. 4 shows three examples of how a sheet can be set up with multiple scenarios, defined by choosing alternative values for simulation or visualization parameters, and how the scenarios' results are displayed to assist comparison.

By the end of the ACGT project some 7000 simulations had been run using the ORS; early results of this work were published in [21] and [22], [23]. In general, the simulator was shown to be robust and predictable across a broad range of parameter settings, but the ability to make comparisons did help to discover various unexpected behaviors that the simulator developers were then able to resolve.

V. Executing the Oncosimulator on the Grid Via the OncoRecipeSheet (ORS) and Via the Workflow Environment

The oncosimulator application can take an advantage of the Grid environment designed within the ACGT project [24]. The most important components of the grid [25] infrastructure that take part in the grid execution of the IOS are the following: grid resource management service (GRMS), responsible for resource management, and data management system (DMS), a grid storage system (see Fig. 5). GRMS is an open source metascheduling system which allows developers to build and deploy resource management systems for large scale distributed computing infrastructures. GRMS is based on dynamic resource selection, mapping and an advanced scheduling methodology, and deals with dynamic grid environment and resource management challenges, e.g., load-balancing among clusters, remote job control, or file staging support.

Therefore, the main goal of the GRMS is to manage the whole process of remote job submission to various batch queuing systems, clusters, or resources. It has been designed as an independent core component for resource management processes, which can take advantage of various low-level core services and existing technologies. The main features of GRMS are job submission, job control (suspending, resuming, canceling), the ability to choose "the best" resource for the job execution using multicriteria matching algorithms, support for job checkpointing and migration, support for file staging, storing information about the job execution, user notifications support, workflow jobs support, etc.

The data management system (DMS) is composed of several specialized components and allows building a distributed system of services capable of delivering mechanisms for seamless management of large amounts of data. It is based on the pattern

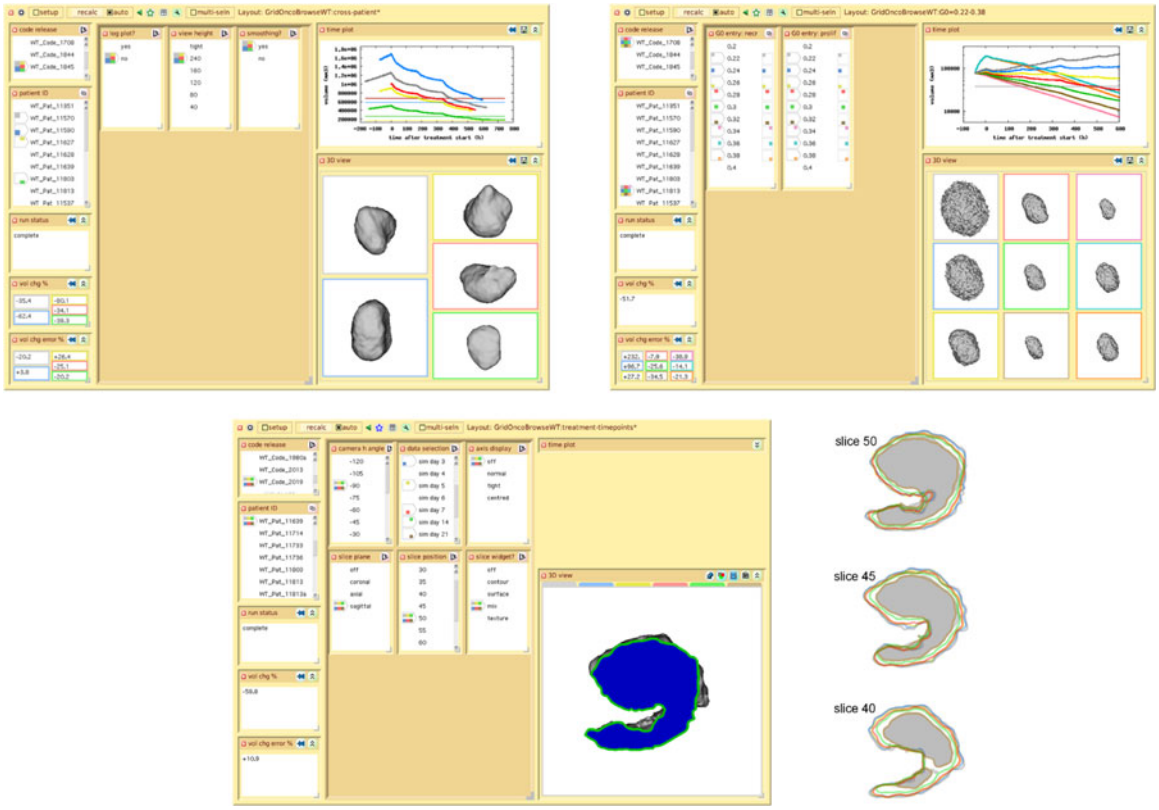

Fig. 4. Three multiscenario setups of the OncoRecipeSheet. At top left, the user has requested to view the equivalent simulation results for five patients; at top right, the results for a single patient using nine alternative values for probability of cells entering the G0 state. The sheet at bottom has results from six stages of a single simulation, showing a slice plane through the tumor at one of the stages. Next to it are three examples of how the tumor view would appear when overlay mode is enabled: the outer contours of the slices from all six time points are shown together, to aid comparison.

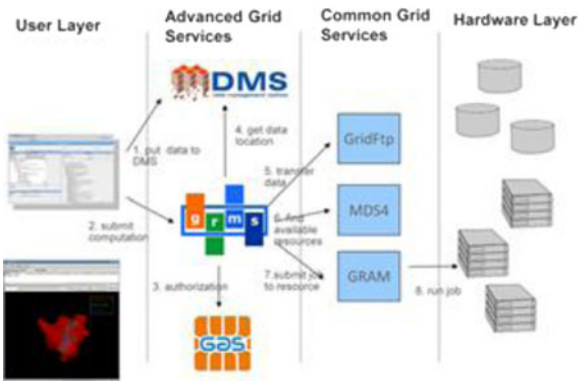

Fig. 5. Components of the grid environment: DMS: data management system, GRMS: grid resource management system, GAS: Grid authorization service, GridFTP—grid fie tyransfer service, GRAM: globus resource allocation manager, MDS4: monitoring and discovery system ver. 4.

of autonomic agents using the accessible network infrastructure for mutual communication. From the external applications point of view DMS is a virtual file system keeping the data organized in a tree-like structure. The main units of this structure are metadirectories, that enable the creation of hierarchies which encompass other data objects and metafiles. Metafiles represent a logical view of data regardless of their physical storage location. The DMS consists of three logical layers: the data broker, which serves as the access interface to the DMS system and implements the brokering of storage resources, the metadata repository that keeps the information about the data managed by the system, and the data container, which is responsible for the physical storage of data. In addition, DMS contains modules which extend its functionality to fulfill the enterprise requirements. These include the fully functional web-based administrator interface and a proxy to external scientific databases. The proxy provides a simple object access protocol, interface to the external databases, such as those provided by sequence retrieval system.

The scenario for running the oncosimulator in the grid environment is mostly based on the aforementioned services. The first step is devoted to the preparation of input data for the computation. The clinician needs to prepare, e.g., MRI sets of slices of a nephroblastoma tumor corresponding to the tumor before chemotherapeutic treatment with vincristine and dactinomycin. Using specialized tools they also need to delineate the tumor boundaries on the provided slices as well as to prepare the rest of the multiscale input data. The user uploads all required files from their machine to the DMS using a web client. The files are then managed by DMS and can be accessed by the user or the other services acting on behalf of the user.

To execute the IOS in the grid, an appropriate job description XML (Extensible Markup Language) document is produced. It defines the job as a set of tasks with dependences among them. Each task is described as resource requirements and description

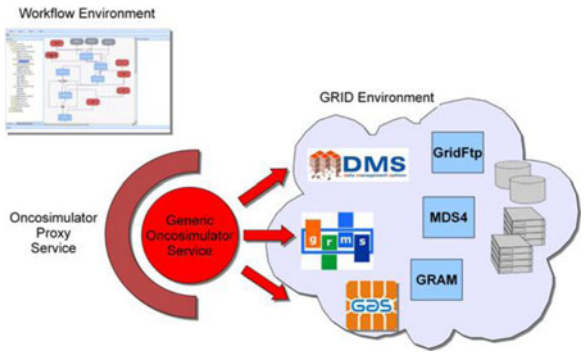

Fig. 6. Oncosimulator service.

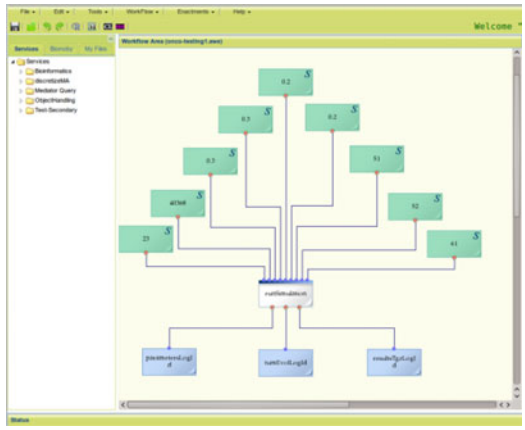

Fig. 7. Example of workflow created in the ACGT workflow environment.

of the executable: environment variables, parameters of the execution, input and output files (or directories), executable file etc.

Users are supported in the production of the Job Description XML document through the use of the OncoRecipeSheet (ORS) [18]–[23], [26], which is responsible for creating a proper XML document based on the forms that are presented to the user, showing parameters of the application in a convenient way for the user. Subsequently ORS submits the description to the GRMS and monitors job execution. Based on the provided information GRMS finds available resources on the grid, transfers the input data from DMS to the grid node, and starts the computation. On successful completion of the job it moves the output data to DMS thus making it available for ORS for downloading. Using the ORS interface users can browse the results, compare the values, and submit new simulations if necessary. An overview of the scenario and the infrastructure components that are taking part in it is depicted in Fig. 5.

An alternative way of integrating the IOS into the ACGT architectural framework is a service implementation. In this approach, grid execution of the application is wrapped with the web service implementation such that the IOS can be used within the workflow environment of ACGT. The workflow infrastructure is a set of services and tools that allows the users to create scientific experiments by joining different service invocations into a single flow of actions. There are many services that are incorporated into the environment, some of them are focused on accessing different databases while others are able to process the data using statistical packages (e.g., R).

The workflow environment lies on the top of the grid infrastructure of ACGT. The oncosimulator service has been designed and developed in order to take advantage of the workflow environment of ACGT and to provide a means to integrate it with the rest of ACGT software (see Fig. 6).

VI. Executing the Oncosimulator Through Workflows

The ACGT Workflow Editor [27], [28] is the end user application for designing and executing high-level scientific workflows (see Fig. 7). In this web-based application, the user is encouraged to graphically combine the data retrieval and discover services and the knowledge extraction and data analysis tools. The definition of the syntactic representation of the data and most importantly the annotation of the services with semantic metadata descriptions gives great flexibility in the workflow editor for supporting user friendliness and intelligence. If properly annotated, incompatible services cannot be directly connected because the data types of their inputs and outputs do not conform to each other, either in the syntactic or the semantic level, while service recommendation and intelligent workflow composition can also be supported.

Furthermore, the ACGT Workflow Editor features the following functionality: 1) provides a graphical environment for the end users to build their scientific experiments by combining the ACGT tools and facilitate their execution on the Grid; 2) supports access to all the ACGT tools and services, including the gridified version of the R package; 3) supports separate storage area per user, gives access to grid file system, and supports publication of a workflow to the ACGT community, execution monitoring and logging of a workflow; 4) supports user provided metadata (tagging) for custom search and retrieval of workflows; and 5) supports the storage and management of the provenance information gathered during the execution of the user workflows.

The oncosimulator when wrapped as another Grid Service, as described in Section V, can be integrated into more complex scientific workflows. This integration is achieved in a transparent way. The user creates their own workflow by creating a distinct functional entity which accepts its own parameter set and delivers its output. This seamless integration is further enhanced by the ability to include multiple instances of the onsosimulator in the same workflow but with different input parameters. Under the hood, all the different executions of the oncosimulator can be performed in parallel enabled by the scheduling and the run time support of the grid infrastructure. In this way, scientific experimentation and discovery becomes less time consuming, more efficient, and more productive.

VII. Clinical Adaptation and Validation Aspects

In order to adapt and validate the oncosimulator, clinical data including preoperative and postoperative imaging studies is being used and compared with the *in silico* predictions. The

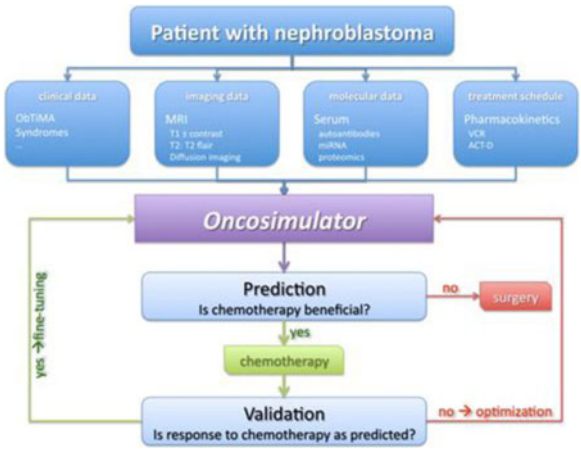

Fig. 8. Workflow of the Oncosimulator for nephroblastoma.

learning loop included in the biomedical usage workflow of the oncosimulator and shown in Fig. 8 for the special case of nephroblastoma is utilized to finely tune the models.

Up to now 16 cases of nephroblastoma and 20 cases of breast cancer have been collected and their multiscale data are under exploitation. Initial clinical adaptation results using this data have already been published [8], [10], whereas a number of new relevant articles are currently in the publication process. Additional results demonstrating aspects of the clinical adaptation and validation process are presented in Section IX (A and B.)

VIII. Coupling the Oncosimulator With Immunological Models in the Future: A Plausible Scenario

Tumor cells (TCs) are characterized by a vast number of genetic and epigenetic events leading to the appearance of specific antigens triggering reactions by the immune system (IS) [29]. Thus, the competition between TCs and the IS is complex and also involves many spatial phenomena [30]. Currently a number of immunotherapies are being developed, although the results of their clinical trials are often puzzling. Theoretical immunology [31] suggests that the latter mirror the dynamic complexity of this interplay. This demands an approach that is based on detailed multiscale models that are amenable to clinical validation.

Thus, the Oncosimulator might be an ideal frame for the patient-specific simulation of immunotherapies. Moreover, the integration of an "Immune System Module" (ISM) might also allow the oncosimulator to perform finer predictions of the postchemotherapeutic time course of immunogenic tumors. In such tumors, the role of the IS in the elimination of the residual disease could be highly important.

An ISM has been designed at the information flow level by adopting a hybrid, i.e., partly stochastic and partly deterministic modeling approaches. A stochastic detailed model (the Oncosimulator) describing the dynamics of tumor growth and treatment response is coupled to a stochastic mean-field model for the description of the IS effectors. In this case, this approach has some advantageous features. There is no need to modify the core component of the oncosimulator, whereas only simple changes in accessory components accounting for the exchange of information between the main component and the ISM are required.

Due to the polymorphic interplay of TCs-IS, ISM does not implement a single specific model, but it is rather a tool for the definition and validation of models. Users may choose a specific model from a database of models, or they may choose from some more general families of models. Here, "parameters" are user-defined functions, whose "adherence" to the chosen family is checked by the system.

The implementation of ISM adopts the following design challenges: 1) the user is in charge: support of human guided exploration; 2) the "plug-and-play" principle: no essential changes in the Oncosimulator are required; 3) a large model space: ISM must support the implementation of large families of models; 4) model comparison is key: validation requires that the user is able to compare results between multiple possible models; 5) supporting "multi-mathematics": models of TCs-IS interplay are symbolically challenging and heterogeneous.

IX. Results

In the following two sections, we demonstrate how the oncosimulator can be adapted to various scenarios. This is achieved through the processing of multiscale data and the adjustment of simulation codes.

The paradigms of breast cancer treated with epirubicin and nephroblastoma (Wilms tumor) treated according to the SIOP 2001/GPOH clinical trial protocol are addressed. For both the clinical adaptation and the clinical validation of each one of the models the same kind of data—although not the same data itself—and the same simulation code are to be used. Therefore, the following examples also convey important aspects of the clinical validation process. The presented proof of concept adaptation studies focus on one breast cancer and two nephroblastoma clinical cases. Simulation results involving the full set of clinical cases provided within ACGT project and related clinical adaptation/validation methods will be the subject of dedicated journal papers under preparation.

A. Breast Cancer

In this section, a clinical adaptation paradigm of the breast cancer branch of the *oncosimulator* is provided. A plausible value range of the apparent *cell kill rate* (CKR) of epirubicin is suggested following the exploitation of the actual clinical data originating from one real clinical breast cancer case and the simulation itself. CKR can be thought of as summarizing important genetic determinants influencing the tumor response to epirubicin monotherapy.

The available patient specific data utilized by the model are the following (see Fig. 9): 1) the maximum dimension of the tumor before and after completion of treatment as measured by ultrasound; 2) the dates of the corresponding examinations; 3) the detailed chemotherapeutic scheme including the dates and the dose of each epirubicin administration session; 4) the histological grade of the tumor determining the degree of differentiation; and 5) the available proliferation markers and more

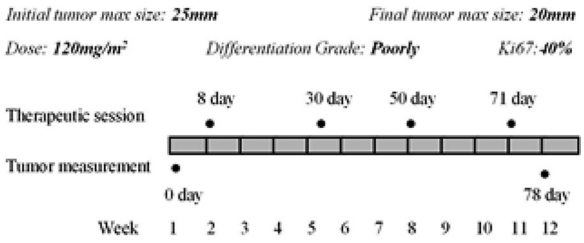

Fig. 9. Treatment schedule and tumor measurement time points for the set of multiscale data considered.

specifically the Ki67 index serving as a quantitative measure of the tumor growth fraction.

A macroscopically spatially homogeneous tumor of spherical shape has been assumed, with a diameter equal to the given maximum size. This approximation is dictated by 1) the provision of only a single tumor dimension at each measurement time point and 2) the nonavailability of MRI or CT data that could enable both the 3-D reconstruction of the tumor shape and the consideration of internal regions of variable metabolic activity (proliferating, quiescent, necrotic).

A two-step adaptation process is followed. The first step refers to the adaptation of the model parameters regulating tumor-free growth kinetics. In general a large number of virtual tumor implementations (virtual instances) corresponding to certain given or known parameter values exist. Narrowing this large window of possible solutions, ideally to one solution for a specific clinical case, is a critical first step in the adaptation procedure. In the present paradigm, the following assumptions/constrains were imposed, based on the literature and patient specific kinetics data.

1) *Cell cycle duration:* Breast cancer cell cycle duration estimated based on cell line studies or *in vivo* methods (such as percent labeled mitosis curves) may vary from approximately 20 to 96 h [32]–[34]. A mean value of 60 h is considered here [32]–[34].
2) *Growth fraction:* $\pm 10\%$ of patient Ki67 index ($=40\%$).
3) *Volume doubling time (T_d):* Studies aiming at determining breast cancer growth rate based on volumetric methods have revealed a great interindividual variability with volume doubling times ranging from a few weeks to years [35], [36]. In the present analysis, we assume a lower limit of Td $>$ 30 days.
4) *Fraction of stem cells:* Based on [37], breast tumor stem cells are a minority population with a frequency of 5% at best. Here, we assume that the frequency of cancer stem cells among living tumor cell population does not exceed the above value ($< 5\%$).

The free growth adaptation outcome is presented in Table I.

In the second step, CKR is adapted to the observed tumor size reduction yielding the apparent CKR of the specific virtual tumor implementation. Since no data on the tumor growth rate of the patient are available, the procedure is repeated for other virtual tumor implementations with growth rates that cover the value range reported in the literature. This is achieved by varying a model parameter that primarily influences growth rate while ensuring consistency with the aforementioned imposed constraints. The chosen parameter is the fraction of stem cells that perform symmetric divisions (P_{sym}). According to Figs. 10 and 11 even though the variation of P_{sym} for the range of values considered has a negligible effect on the tumor cell composition, it does nevertheless induce a dramatic change in the volume

TABLE I
MODEL (CODE) INPUT PARAMETERS RELATED TO BREST CANCER FREE TUMOR GROWTH AND THEIR VALUES FOLLOWING CLINICAL ADAPTATION

Description	Value
Cell cycle duration	60 h
Duration of the dormant phase	170 h
Time interval needed for the necrosis products to disappear	120 h
Time interval needed for the apoptosis products to disappear	6 h
Number of mitoses performed by progenitor cells before they become differentiated	10
Apoptosis rate of stem and progenitor cells	0.001 h^{-1}
Apoptosis rate of differentiated cells	0.005 h^{-1}
Necrosis rate of differentiated cells	0.01 h^{-1}
Fraction of dormant cells that have just left the dormant compartment and re-enter the cell cycle	0.01
Fraction of cells that enter G0 phase following mitosis	0.27
Fraction of stem cells that perform symmetric division	0.451-0.51

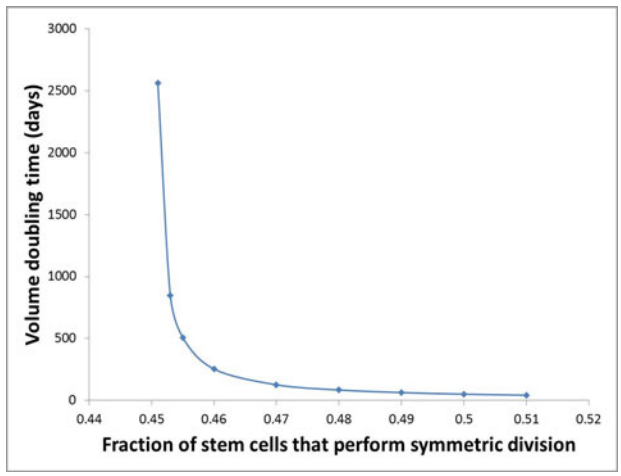

Fig. 10. Predicted volume doubling time as a function of the fraction of stem cells that perform symmetric division.

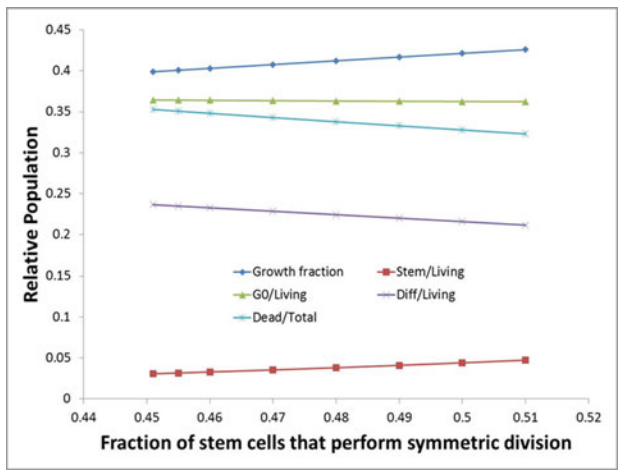

Fig. 11. Predicted relative population of various tumor cell categories as a function of the fraction of stem cells that perform symmetric division.

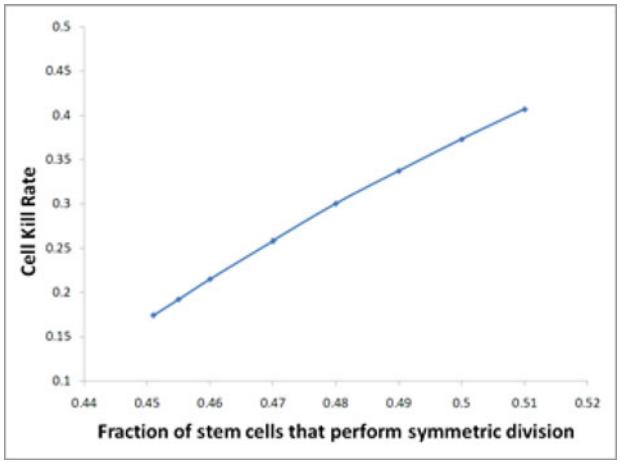

Fig. 12. Predicted cell kill rate as a function of the fraction of tumor stem cells that perform symmetric division.

doubling time. In the present paradigm, T_d varies from 43 days up to 2562 days ($\sim$ 7 years). In Fig. 12, we observe that virtual tumor implementations with shorter T_d (higher P_{sym}) require a higher CKR in order to achieve the same tumor shrinkage. Based on those results, the apparent CKR for the clinical case considered lies approximately in the range 0.17–0.41.

Concluding, the realism of the model behavior has been demonstrated in previous publications [8]. More specifically tumor shrinkage after each chemotherapeutic session and the consequent tumor repopulation has been successfully demonstrated in accordance to clinical experience. In the present analysis, the model has been applied for the *in vivo* estimation of the apparent CKR, a measure of drug toxicity on tumor cells, taking into consideration the repopulation of tumor cells after each therapeutic session. The validity of our results is ensured by 1) the compliance of the virtual tumors kinetic characteristics with the ones reported in the literature and 2) the negligible deviation between the simulation results and the patient volumetric data (less than 0.2%) for all virtual tumor implementations with different P_{sym} (data not shown).

B. Nephroblastoma

Several nephroblastoma tumor cases of which sets of multiscale data were collected in the context of SIOP 2001/GPOH trial have been modeled with IOS so far. As an indicative example, the *in silico* response of two nephroblastoma cases (cases I and II) of stromal type to preoperative combined chemotherapy with actinomycin-D and vincristine in the context of SIOP 2001/GPOH trial is presented in this section.

Anonymized imaging and clinical data have been provided. The initial and final virtual tumors have been spatiotemporally initialized based on the MRI tomograms of their real clinical counterparts collected at two time instants before the start of chemotherapy (2 days for case I and 6 days for case II) and after the completion (4 days for case I and 0 days for case II). The chemotherapeutic scheme administered is according to the SIOP 2001/GPOH clinical trial protocol for unilateral stages I–III nephroblastoma tumors (see Fig. 13). In [38]–[54] the authors

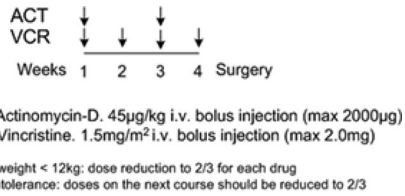

Fig. 13. Simulated Wilms tumor preoperative chemotherapy treatment protocol of the SIOP/GPOH clinical trial.

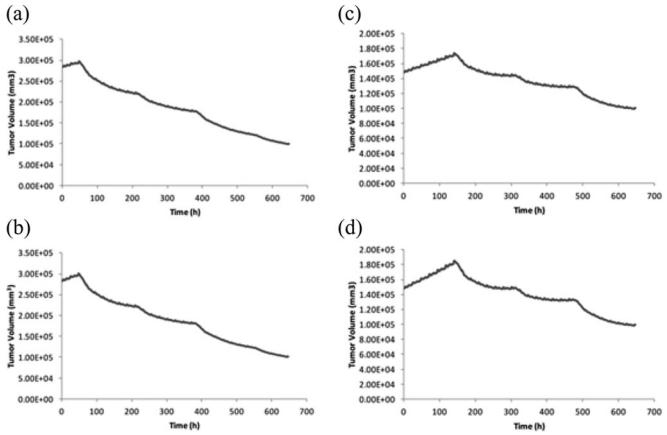

Fig. 14. Time evolution of tumor volume for the four virtual scenarios of Table II: (a). T1 (Case I-Scenario A), (b). T2 (Case I-Scenario B), (c). T3 (Case II-Scenario A), and (d). T4 (Case II-Scenario B).

provide pertinent literature that has been utilized throughout the following analysis.

Two adaptation scenarios are considered. The following assumptions have been made based on both literature and imaging clinical information.

1) Doubling time in the range of 11–40 days [49]–[53].
2) Growth fraction 1.5–20% for stromal type nephroblastomas [54].
3) The imaging data-specified volume reduction of case I is 65% and of case II is 32%.

According to the first adaptation scenario (A), both nephroblastoma tumors are considered to have common growth kinetics as they are of the same histological type (stromal). The CKR of the chemotherapeutic drugs is adapted in order to simulate the volume reduction induced by chemotherapy.

According to the second adaptation scenario (B), the effect of the chemotherapeutic drugs is considered common in both cases and the growth rate of the tumors is adapted within the range defined by the reported literature. This is achieved by perturbing the values of important growth kinetic parameters according to model sensitivity analyses [10].

The aforementioned assumptions, in conjunction with accumulated basic science and clinical experience based plausible values, lead to the selection of the entries for the run-time parameters of the tumor model (see Table II) for cases I, II, and under scenarios A and B. The time course of the four virtual tumors is presented in Fig. 14.The resultant virtual tumor characteristics and volume reduction are given in Table III. All four virtual scenarios are in good agreement with the clinical data in terms of

TABLE II
DEFINITION OF THE TUMOR MODEL PARAMETERS. REFERENCE VALUES AND CORRESPONDING LITERATURE REFERENCES. VALUES ASSIGNED TO THE MODEL PARAMETERS FOR THE IMPLEMENTATION OF FOUR VIRTUAL TUMORS.

Symbol (Unit)	Definition	Reference Value	References	T1 (Case I-Scenario A)	T2 (Case I-Scenario B)	T3 (Case II-Scenario A)	T4 (Case II-Scenario B)
Model Parameters Studied in the Sensitivity Analyses							
Tc (h)	Cell cycle duration	23.0	[44]	23.0	40	23.0	55
T_{G0} (h)	G0 (dormant phase) duration, i.e. time interval before a dormant cell dies through necrosis	96	[45]	96	96	96	40
T_N (h)	Time needed for necrosis to be completed and its lysis products to be eliminated from the tumor	20	[38,39, 46]	20	20	20	120
T_A (h)	Time needed for apoptosis to be completed and its products to be eliminated from the tumor	6	[47,48]	6	6	6	6
R_A (h^{-1})	Apoptosis rate of living stem and LIMP tumor cells (fraction of non-differentiated cells dying through apoptosis per hour)	0.001	Derived from T_A, based on [47,48]	0.001	0.0008	0.001	0.001
R_{ADiff} (h^{-1})	Apoptosis rate of differentiated tumor cells per hour	0.003		0.003	0.003	0.003	0.05
R_{NDiff} (h^{-1})	Necrosis rate of differentiated tumor cells per hour	0.001	Derived from T_N, based on [38,46]	0.001	0.001	0.001	0.05
P_{G0toG1}	The fraction of stem or LIMP cells having just left the G0 compartment that re-enter the cell cycle	0.01		0.01	0.01	0.01	0.01
N_{LIMP}	The maximum number of mitoses that a LIMP cell can perform before becoming terminally differentiated	3		3	3	3	3
P_{sym}	Fraction of stem cells that perform symmetric division.	0.45		0.71	**0.44**	0.45	**0.465**
P_{sleep}	Fraction of cells that enter G0 phase following mitosis	0.28		0.40	0.28	0.28	0.36
CKR_{VCR}	Cell kill rate for the specific vincristine dose	0.3	Derived based on [40,41]	**0.32**	0.3	**0.252**	0.33
CKR_{ACT}	Cell kill rate for the specific actinomycin-D dose	0.2	Derived based on [42,43]	**0.213**	0.2	**0.168**	0.22
CKR_{TOTAL}*	Combined cell kill rate of the two drugs (dependent parameter)	0.5	Additive drug effect considered	**0.533**	0.5	**0.42**	0.55

Values assigned to the model parameters for the implementation of four virtual tumors.
CKR_{Total} is not an independent parameter of the model.

TABLE III
TUMOR CHARACTERISTICS AND VOLUME REDUCTION PERCENTAGES FOR THE FOUR VIRTUAL TUMOR SCENARIOS DEFINED BY THE PARAMETER VALUES GIVEN IN TABLE II

RESULTANT INITIAL TUMOR CHARACTERISTICS	T1 (Case A-Scenario A)	T2 (Case A-Scenario B)	T3 (Case B-Scenario A)	T4 (Case B-Scenario B)
Volume Doubling Time, $T_d = \ln 2/k$ (days)	28.5	40.37	28.5	19.8
Initial percentage of proliferating cells (Growth Fraction) (%)	13.38	12.62	13.38	14.52
Tumor volume reduction percentage (%)	64.24	65.02	32.17	32.58

volume reduction (see Table III). In addition, a good agreement is also accomplished in terms of the tumor growth characteristics presented in Table III when compared with values reported in the literature.

X. DISCUSSION AND CONCLUSION

A synoptic delineation of the IOS, primarily developed *within the framework* of the EC funded ACGT project but also extended within the framework of other EC funded projects, has been presented. Both the modeling principles and the technological components of the system have been briefly, yet comprehensively addressed. Successful demonstrations of the system during the implementation of the ACGT project have ensured its technological reliability as well as its potential to be translated into the clinic following completion of the ongoing lengthy and demanding clinical validation process.

Clinical adaptation and validation of the multiscale modeling component of the system continues among other environments within the framework of the currently running EC funded projects p-medicine (FP7-ICT-2009–6–270089) and CHIC (FP7-ICT-2011–9–600841.) A number of clinical adaptation scenarios addressed in this paper have demonstrated the basics of several aspects of the clinical adaptation and validation process. Following the completion of the latter, the IOS is expected to be translated into clinical practice and serve as a platform for optimizing both patient individualized treatment and the design of new clinical trials.

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