Modeling Tumor Growth and Irradiation Response *in vitro*—A Combination of High-Performance Computing and Web-Based Technologies Including VRML Visualization

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***Abstract*—A simplified three-dimensional Monte Carlo simulation model of *in vitro* tumor growth and response to fractionated radiotherapeutic schemes is presented in this paper. The paper aims at both the optimization of radiotherapy and the provision of insight into the biological mechanisms involved in tumor development. The basics of the modeling philosophy of Duechting have been adopted and substantially extended. The main processes taken into account by the model are the transitions between the cell cycle phases, the diffusion of oxygen and glucose, and the cell survival probabilities following irradiation. Specific algorithms satisfactorily describing tumor expansion and shrinkage have been applied, whereas a novel approach to the modeling of the tumor response to irradiation has been proposed and implemented. High-performance computing systems in conjunction with Web technologies have coped with the particularly high computer memory and processing demands. A visualization system based on the MATLAB software package and the virtual-reality modeling language has been employed. Its utilization has led to a spectacular representation of both the external surface and the internal structure of the developing tumor. The simulation model has been applied to the special case of small cell lung carcinoma *in vitro* irradiated according to both the standard and accelerated fractionation schemes. A good qualitative agreement with laboratory experience has been observed in all cases. Accordingly, the hypothesis that *advanced simulation models for the in silico testing of tumor irradiation schemes could substantially enhance the radiotherapy optimization process* is further strengthened. Currently, our group is investigating extensions of the presented algorithms so that efficient descriptions of the corresponding clinical (*in vivo*) cases are achieved.**

***Index Terms*—Fractionation, high-performance computing, modeling, radiation therapy, simulation, tumor growth, visualization, World Wide Web.**

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I. Introduction

THE aim of this paper is to demonstrate how high-performance computing, Word Wide Web (WWW)-based technologies and advanced visualization tools can be combined in order to efficiently simulate the growth of three-dimensional multicellular tumor spheroids. Special emphasis is put on the response of this type of tumor models to various fractionated radiotherapeutic schemes. Multicellular tumor spheroids are being extensively used in various aspects of tumor biology such as tumor development [1], [2] and radiobiology [3, pp. 47–48, 52–57, 123–131, 153, 161], [4]. Due to their particular structural characteristics, they have proven to be of paramount importance in testing radiotherapeutic protocols. It has been experimentally shown that they can constitute a satisfactory *in vitro* model of solid tumors [5]. Therefore, a substantial volume of experimental work on tumor spheroids has been performed during the last years [6]–[8]. In parallel, a comparatively limited number of computer modeling approaches has appeared in the literature. The main purpose of such models is to perform virtual *in silico* experiments aiming at optimizing the various cancer treatment modalities. Examples of the modeling efforts include the following. Williams and Bjerknes [9] developed a stochastic model of the basal layer and of tumor development based on the contact birth process. In this process, individuals (cells) have fixed locations in some space. These individuals give birth to others according to what is called a *simple birth process*, and each of the newly born individuals is assigned a location relative to its parent at birth by drawing at random from a specified probability distribution, called a contact distribution, which can be of any form. The centers of the cells are assumed to be situated on a regular hexagonal grid. Cells tend to pack into a honeycomb mesh in layers, and when a cell divides in the basal layer, it and its daughter remain in the basal layer, displacing an adjacent cell to a higher layer. It is obvious that this model has a high degree of spatial anisotropy. Although it is adequate for plane-layered structures, it does not seem suitable for spheroidal tumor development. Adam and Maggelakis [10] developed an analytical treatment for an exactly spherical multilayer tumor based on diffusion theory. Although such an approach leads to a mathematically closed

form of the tumor growth process, it would be of limited usefulness to the majority of clinical cases where arbitrary geometries are present. Ginsberg [11] described the growth of an exactly spherical multilayer tumor *in vitro* by applying general control theory methods and appropriate commercial software. Again, the perfectly spherical geometry restricts the applicability of the model. Nahum [12] developed a radiotherapy model in which the main parameter of interest is the tumor control probability (TCP). Despite the simplicity of the treatment, neither the expansion nor the reoxygenation effects are accounted for.

The biophysical part of this paper is based on Duechting's approach [13]–[17], which has been substantially extended. A discrete time cell cycle model is applied to each one of the cells constituting the tumor. The discrete time and space character of such a model allows the imposition of arbitrary boundary conditions such as the spatial profile of the oxygen and glucose supply. Therefore, this kind of model can be easily extended to the *in vivo* case, where the presence of different tissues producing variable elastic and nutrient supply profiles in the vicinity of a tumor can greatly affect the growth pattern. Furthermore, simulation of the growth of a multifocal tumor or a tumor of arbitrary geometry can be readily performed.

This paper begins with a brief description of the most crucial assumptions concerning cell division and interaction. Subsequently, assumptions pertaining to the response of each tumor cell to the absorbed dose, as proposed by our group, are introduced. Algorithms describing the eventual expansion and shrinkage of the entire tumor system are formulated and the time quantization policy is clarified. The more technological portion of this paper includes an outline of the high-performance computing resources utilized, the WWW-based communication system developed, and the visualization techniques employed. As an application example, the case of small-cell lung cancer (SCLC) tumor spheroid *in vitro* is studied *in silico*. This paper concludes with a qualitative evaluation of the model, whereas an extension of our approach to the *in vivo* case is briefly outlined.

II. Assumptions on Cell Division and Interaction

The following fundamental assumptions have been made.

1) The cytokinetic model shown in Fig. 1 is adopted [16]. According to this model, a tumor cell when cycling passes through the phases G_1 (gap 1), S (DNA synthesis), G_2 (gap 2), and M (mitosis). After mitosis is completed, each one of the resultant cells reenters G_1 if the oxygen and nutrient supply in its current position is adequate. Otherwise, it enters the resting G_0 phase. It can stay there for a limited time T_{G0} if oxygen and nutrient supply are inadequate. Subsequently, it enters the necrotic phase leading to cell death unless the local environment of the cell becomes adequate before the expiration of T_{G0}. In the latter case, the cell reenters G_1. In addition to the previously described pathway (solid line), there is always a probability that the cell dies due to aging and apoptosis (dashed line).
2) Angiogenesis is not taken into account. This is a plausible hypothesis for both tumor growth in cell culture (where there is no possibility for blood-vessel formation) and the avascular early stages of tumor growth *in vivo*.
3) Side effects, immunologic reactions, heterogeneity, drug resistance, and the formation of metastases are neglected.
4) The following heuristic rules governing cell reproduction and interaction are applied: "If the minimum distance between a proliferating (cycling) tumor cell and the nutrient medium becomes greater than three cell layers, the tumor cell enters the G_0 phase and subsequently undergoes necrosis and lysis." Inversely, "If the minimum distance between a tumor cell residing at the G_0 phase and the nutrient medium becomes less than three cell layers, the tumor cell reenters the cell cycle." These rules constitute a rough description of the oxygen and glucose-diffusion-dependent phenomena.
5) Each cell residing in any phase other than necrosis dies with a probability of 1% per hour due to both aging and spontaneous apoptosis (overall cell loss not due to irradiation).

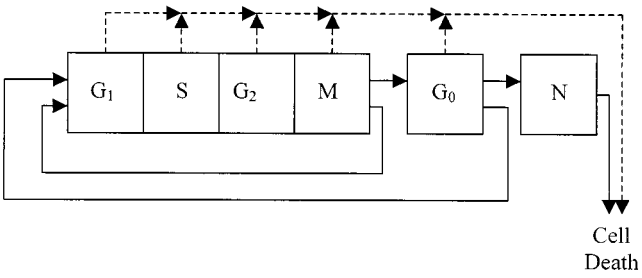


Fig. 1. Simplified cytokinetic model of a tumor cell. G_1: G_1 phase. S: DNA synthesis phase. G_2: G_2 phase. G_0: G_0 phase. N: cell necrosis. The dashed lines represent spontaneous or induced interface cell death (apoptosis).

III. Assumptions on Tumor Cell Response to Irradiation

1) Cells in any cell cycle phase are more radiosensitive than hypoxic cells residing in G_0. Cells in the S phase are more radioresistant than cells in any other cycle phase (G_1, G_2, and M). Three different sets of values for the α- and β—parameters of the linear quadratic (LQ) model are assumed: one set for the proliferating cell cycle phases, except the S phase, a second one for the S phase, and a third one for the resting G_0 phase. The reason for this is the experimentally established different values of radiosensitivity in the previously mentioned phases. The radiobiological parameters of the tumor cells (α- and β-parameters of the LQ model) are obtained by fitting the LQ model to an experimental survival curve. However, these values are often not very accurate as "tradeoff" between a and β allows a range of combinations of the two parameters to fit the data almost equally well. A useful alternative for the calculation of the linear component of cell killing is to use low-dose rate irradiation. The cell survival curve at a low-dose rate seems to extrapolate the initial slope of the high-dose rate curve [3, pp. 47–48, 52–57, 123–131, 153, 161].

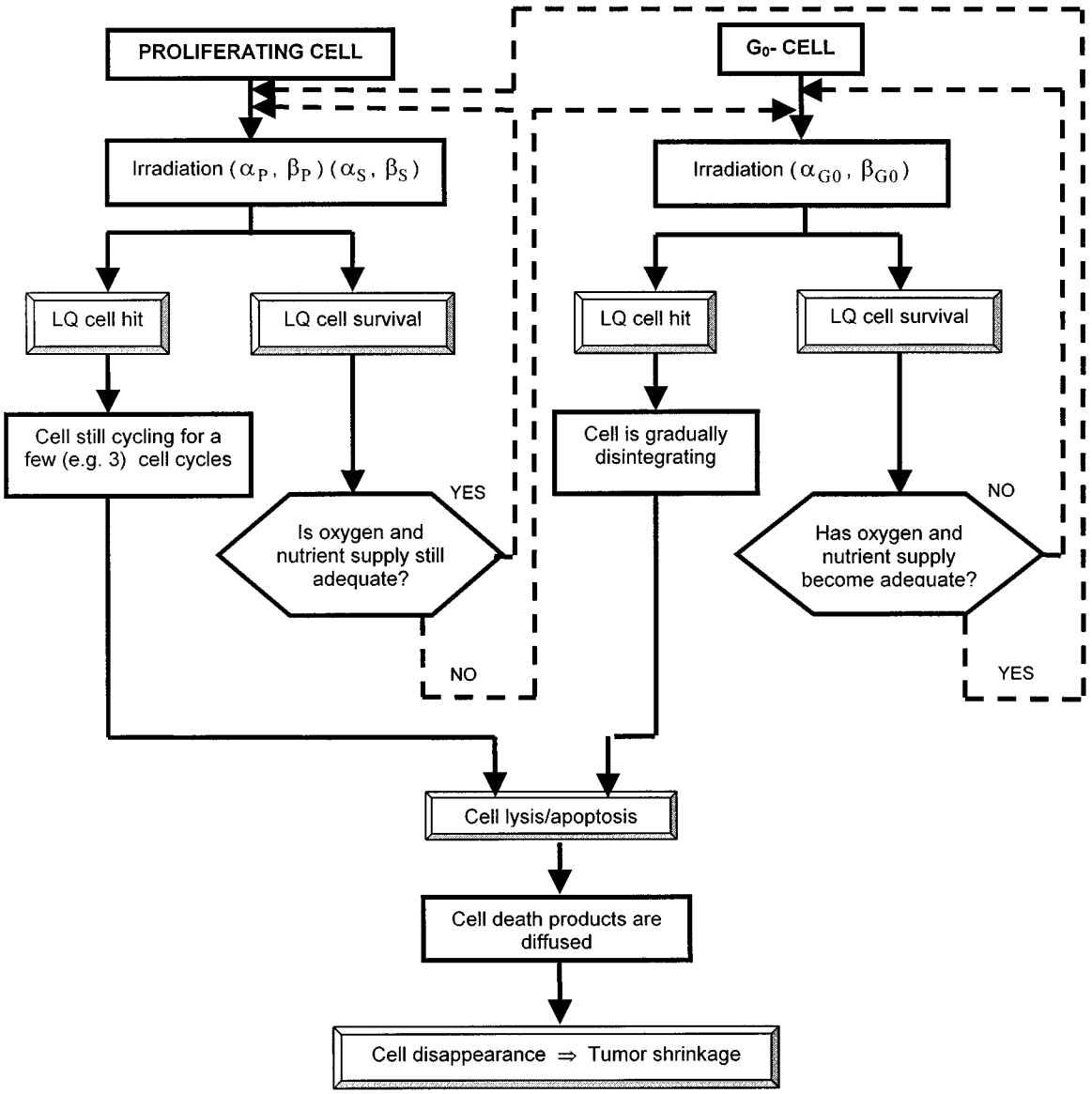


Fig. 2. Simplified flowchart for the response of a single tumor cell to irradiation. Symbol explanation: α_P and β_P stand for the α- and β-parameters of the LQ model for the tumor proliferating cells excluding those in phase S. The subscript S denotes cells in the DNA synthesis phase, whereas the subscript G_0 denotes cells in the resting (dormant) phase G_0.

2) The response of each cell to irradiation leading to absorbed dose D is described by the linear-quadratic model. According to this model, the survival probability S of the cell is given by the following:

$$S = \exp\left[-(\alpha D + \beta D^2)\right] \tag{1}$$

where α and β are the above-mentioned parameters [3, pp. 47–48, 52–57, 123–131, 153, 161], [4]. It is noted that (1) is effective after the expiration of a time interval sufficient for the sublethal damage to be repaired.
3) The flowchart for the response of a single tumor cell to irradiation shown in Fig. 2 is employed.

IV. Assumptions on Tumor Expansion and Shrinkage

1) A three-dimensional mesh quantizing the volume occupied by the cell culture is used. This volume includes the tumor, as well as part of the enclosing nutrient medium. Each geometrical cell of the mesh can be occupied by a single tumor cell, nutrient medium, or products of cell death.
2) The total space occupied by the simulated cell culture has been currently confined by our group to $100 \times 100 \times 100$ mesh cells. This limit depends on the available computer memory and power, as well as on the maximum tolerable runtime.
3) Only horizontal and vertical communication between cells is possible.
4) The tumor spheroid formation starts with the placement of a single tumor cell at the stage of mitosis at the center of the mesh. A tumor cell can divide even if there is no free space for the daughter cell to be accommodated.
5) The cell lysis/apoptosis products are gradually diffused toward the outer environment of the tumor. In case of *in vivo* tumor growth, such substances are expected to be

partly ingested by phagocytes. The macroscopic result of this mechanism is tumor shrinkage due to the exertion of external pressures.

6) Tumor expansion is computationally achieved by shifting a cell chain from the newly occupied mesh cell toward the external environment of the tumor. The shifting direction is selected according to the following rule proposed by our group: "The position of the "newborn" tumor cell is chosen in such a way that the number of tumor cells that shall have to shift (in a straight line) in order to give space to the newborn tumor cell is the least possible. In a case that tumor cell shifting in more than one direction is permissible, the selection of the shifting direction is made using a uniform distribution of random numbers." In this way, the generally different mechanical resistance to movement expressed by the various areas of the tumor is simulated. The opposite rule has been introduced for tumor shrinkage [21].

V. Assumptions on Time Quantization and the Statistical Behavior of the Phase Durations

1) Time is quantized and measured in appropriate units. In all applications of this paper, 1 h has been adopted as the unit of time.
2) The durations of the cell cycle phases follow normal (Gaussian) distribution.
3) The simulation can be considered a row-to-row computation of the cell algorithm for each individual cell. At each time step, the remaining time in the current phase of the cell under examination is reduced by one time unit. The configuration obtained in this way serves as the initial step of the subsequent calculation step.

VI. Visualization

An equatorial section of the spheroid at different instants is visualized in two dimensions using the standard software package MATLAB. The three-dimensional visualization of the growing and shrinking tumor is performed as follows. The simulation system developed by our group stores the results of the tumor growth simulation procedure as a series of raw data, each one consisting of a three-dimensional matrix that represents the physical space that the tumor can expand to. Each element of these arrays, called a *voxel*, is labeled by an integer number indicating the state that the cell occupying the voxel is in. First, the cell state that will be visualized is selected and the labeled generated volumes are segmented using the corresponding integer value. The enclosing surface of the segmented volume is then triangulated using a recently proposed implementation of the well documented marching cubes (MCs) algorithm [24]. According to this implementation, a generic rule able to triangulate all 15 standard cube configurations used in the classical MC algorithm, as well as additional cases presented in the literature, is introduced. Furthermore, the type-A "hole problem," which occurs when at least one cube face has an intersection point in each of its four edges, is handled [25], [26]. An optimized number of polygons, small enough to allow high-end PC-compatible computers to perform real-time surface rendering [27] is produced. The visualization system stores the triangulated surface in virtual-reality modeling language (VRML) 2.0 format. The procedure can be repeated if another snapshot is to be visualized and a new triangulation is produced. An arbitrary number of surfaces can be included in a single VRML file since the use of color, transparency, and surface rendering assists the visualization of complex cell structures.

VII. High-Performance Computing and Web-Based Computer Communication

The tumor growth simulation procedure becomes more realistic as the number of tumor cells considered increases. The CPU time required for the execution of the simulation code is roughly proportional to the number of the discretizing mesh cells. The Onyx Reality Engine 2 machine (four processors, 200 MHz, 256 MB) was initially used to explore the possible benefits from parallelization. As a first step, the Silicon Graphics Inc. (SGI) power FORTRAN analyzer (PFA) option was applied. The use of the PFA led to fine-grain parallelization of the code. As this simplistic method of parallelization did not provide any spectacular acceleration of the execution, use of a single processor was normally made (typical execution time: about 2 h). Advanced parallelization methods are currently under investigation. For the specific small-size application presented ($100 \times 100 \times 100$ mesh cells), a Pentium III (1 GHz, 512 MB) seems to be adequate for near-real time computation.

However, in the case of large tumors, it may not be feasible to predict the development of a tumor or its response to therapeutic schemes with the computing power installed in a hospital. In such a case, the calculation of tumor growth could be provided to hospitals or to research laboratories as an external service. An architecture implementing this approach is summarized as follows.

1) The tumor simulation/prediction program executes on a fast remote server, possibly dedicated to this purpose, e.g., the Onyx Reality Engine 2 machine with four processors located at the Institute of Communication and Computer Science (ICCS), National Technical University of Athens (NTUA), Athens, Greece. The client submits a request for the prediction program through a WWW page, which invokes the execution of a common gateway interface (CGI) script on the server.
2) The generated volumes are triangulated, as described in the previous section, and the corresponding VRML files are produced. At present, the results are in two formats, i.e., ASCI–numeric and VRML, the envisaged third format is a stereographic image that can be viewed by a virtual-reality headset.
3) The client receives the generated VRMLs through an e-mail message, or can access them through a password-protected WWW page. The use of a WWW-compatible format, such as VRML, allows great flexibility in exchanging data between the client and server.

It becomes evident that while the actual prediction can take place in a remote powerful server, the visualization may be performed on the client's computer, which may be as inexpensive as a high-end PC. The small size of the generated VRMLs permits the use of inexpensive hardware running just a shareware WWW Browser.

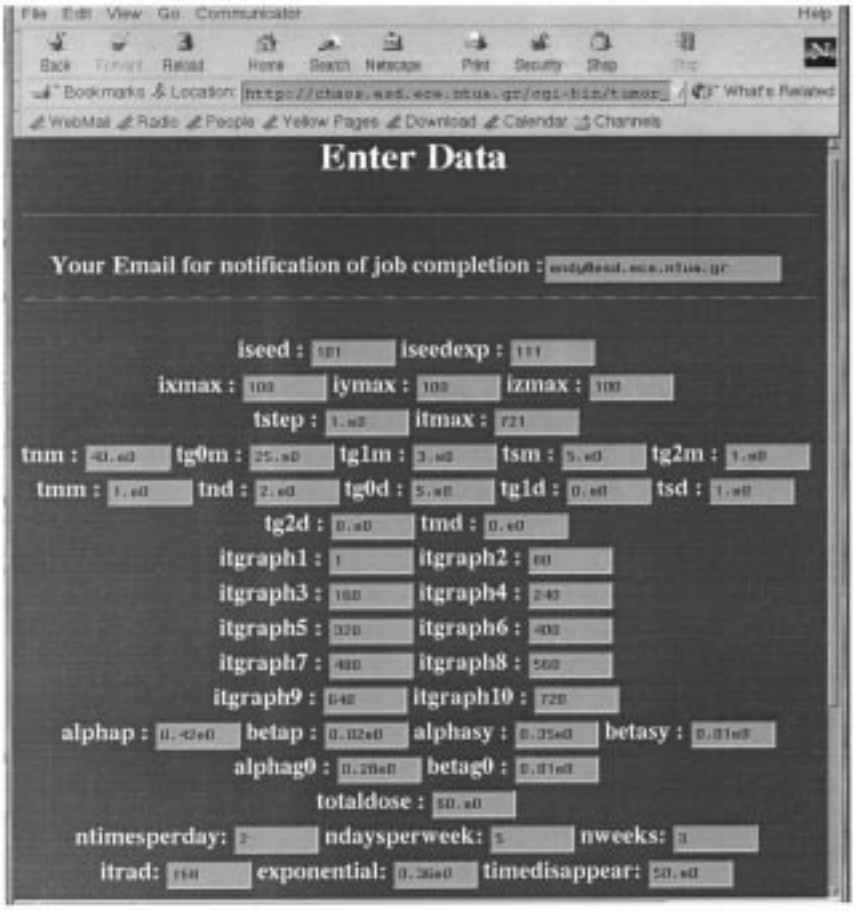


Fig. 3. Example of the data-entry form from the tumor growth WWW site.

TABLE I
MEAN VALUES AND STANDARD DEVIATIONS OF THE CELL CYCLE PHASE DURATIONS FOR SCLC TUMOR CELLS

Cell phase	Necrosis (N)	G_0	G_1	DNA Synthesis (S)	G2	Mitosis (M)
Mean duration	T_{NM}=40h	T_{G0M}=25h	T_{G1M}=3h	T_{SM}=5h	T_{G2M}=1h	T_{MM}=1h
Standard Deviation	T_{ND}=2h	T_{G0D}=5h	T_{G1D}=0h	T_{SD}=1h	T_{G2D}=0h	T_{MD}=0h

To run the software, the reader is directed to a web site.[1] After entering a password, the user is presented with the data entry form (Fig. 3). The form has already been preset with demonstration values for the variables, but these, if desired, can be altered. When the "post form" button is pressed, the tumor prediction growth software is activated. Upon completion, the user will be informed, via an HTML page, of the FTP location where the results are located. By following the FTP hyperlinks, the user can observe the predicted results.

The programming languages used to develop the application are as follows:

1) FORTRAN 77 and FORTRAN 90 for the implementation of the biophysical part of the model;
2) MATLAB for the production of the two-dimensional sections of the growing tumor;
3) C for the surface triangulations;
4) VRML 2.0 for the final three-dimensional presentation of the predictions;
5) CGI for the implementation of the WWW based client-server architecture.

The biophysical part of the *in vivo* extension of the model is being developed in C and Visual Basic.

VIII. CASE OF SCLC TUMOR SPHEROID *in vitro*

A. Input Parameters

As an example of tumor growth and response to radiotherapeutic schemes, the case of an SCLC tumor spheroid *in vitro* has been considered. SCLC tumors are fast-growing neoplasms. Typical mean values and standard deviations of the various phases of the constituting cells are shown in Table I [15]. Table II shows the mean values of the α- and β-parameters of the LQ model for the following three cell cycle phase groups: the proliferating phases, except the DNA synthesis, i.e., the

[1][Online]. Available: http://chaos.esd.ece.ntua.gr~tumor

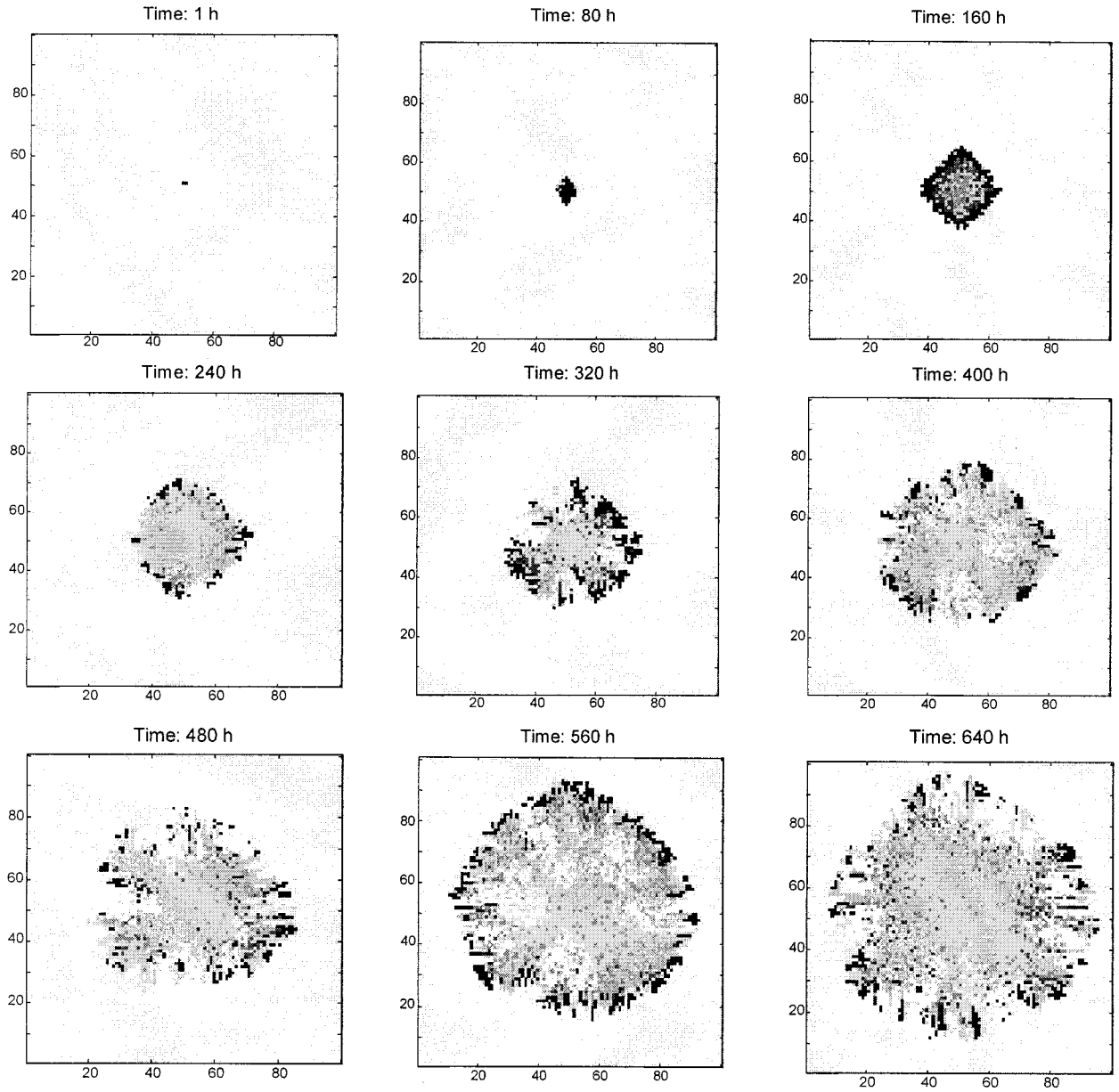


Fig. 4. Simulated evolution of an SCLC tumor spheroid *in vitro* (equatorial cross section) and response to the standard fractionation scheme (2 Gy once a day, five days per week, 60 Gy in total). Irradiation begins at $t = 168$ h from the placement of a single tumor cell in the phase of mitosis at the center of the discretizing mesh. Only the first three simulated weeks of the standard scheme are shown. Grey scale code: from light gray to black: nutrient medium (light gray), cell lysis products, necrosed cells, cells in G_0, cells in proliferating phases (black).

TABLE II
MEAN VALUES OF THE LQ MODEL PARAMETERS FOR SCLC CELLS

$\alpha_P = 0.42$ Gy^{-1}	$\alpha_S = 0.35$ Gy^{-1}	$\alpha_{G0} = 0.28$ Gy^{-1}
$\beta_P = 0.02$ Gy^{-2}	$\beta s = 0.016$ Gy^{-2}	$\beta_{G0} = 0.013$ Gy^{-2}

G_1, G_2, and M phases, (α_P, β_P) [15], [28], the DNA synthesis phase or S phase (α, β_S), and the resting G_0 phase (α_{G0}, β_{G0}). These values are related to the application of γ rays and fast electrons. The α and β values for the last two groups have been assumed as perturbations of the first group values according to the findings of experimental radiobiology. More precisely, the SCLC mean values of the α- and β-parameters for the proliferating phases originate from [15], [28]. According to [3, pp. 47–48, 52–57, 123–131, 153, 161], cells in the S-phase tend to be the most radioresistant. Classical experiments that have greatly supported this finding are those performed by Sinclair and Morton [29]. The survival curves showed that it was mainly the *shoulder* of the curve that changed in the various cell cycle phases. The shoulder was greatest for cells in S. Therefore, the initial slope (which equals the value of the α parameter of the LQ model) is minimum for the S phase compared with the rest of the cell cycle phases. This is the reason why a value for α_S smaller than the average value for α_P has been assumed. Furthermore, as hypoxic cells in G_0 are even more radioresistant, an even smaller value for α_{G0} has been chosen [3, pp. 47–48, 52–57, 123–131, 153, 161]. As the β behavior has not been equally well established, smaller values for β_S

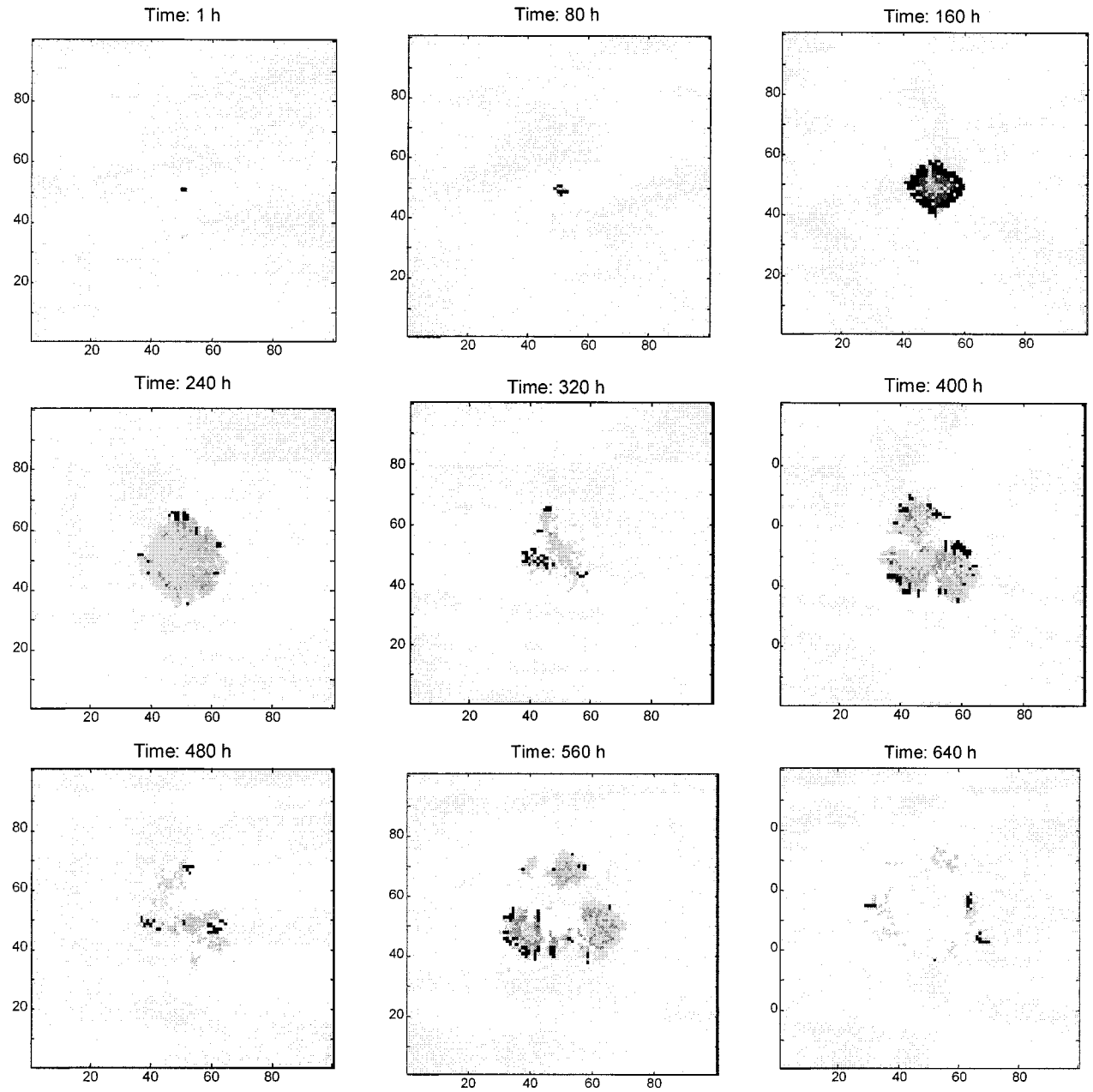


Fig. 5. Simulated evolution of an SCLC tumor spheroid *in vitro* (equatorial cross section) and response to the accelerated fractionation scheme (2 Gy twice a day, five days per week, 60 Gy in total). Irradiation begins at $t = 168$ h from the placement of a single tumor cell in the phase of mitosis at the center of the discretizing mesh. The gray-scale code of Fig. 4 is used.

and β_{G0} have also been chosen (thus, further contributing to an increase in the surviving fraction).

The mean time required for the disappearance of the cell death products from the tumor spheroid has been assumed to be 50 h.

B. Simulation of Fractionated Radiotherapeutic Schemes

The standard and accelerated fractionation schemes (2 Gy once a day, five days a week, 60 days in total, and 2 Gy twice a day, five days a week, 60 Gy in total, respectively) have been simulated. Figs. 4 and 5 show an equatorial section of the initially developing and subsequently responding to irradiation tumor. The various classes of cell phases (proliferating phases, G_0, necrosis, and lysis/apoptosis) can be readily distinguished. It is evident that repopulation during radiotherapy is kept substantially lower by accelerated than by standard fractionation. This is in accordance with extensive experimental findings [3, pp. 47–48, 52–57, 123–131, 153, 161]. Fig. 6 depicts the eventual regrowth of the tumor from its foci, which survived accelerated fractionation radiotherapy. Fig. 7 shows the number of proliferating tumor cells, Fig. 8 shows the number of cells resting in the G_0 phase, whereas Fig. 9 shows the total volume of the tumor spheroid, all as a function of time. Good qualitative agreement with the experimentally expected behavior has been noticed in all cases. In the three graphs, the repopulation effect of the weekend pause can be easily distinguished. Fig. 10 has been produced using VRML 2.0. and shows two equatorial sections of the tumor spheroid under consideration. Both snapshots correspond to the instant $t = 240$ h after the placement of

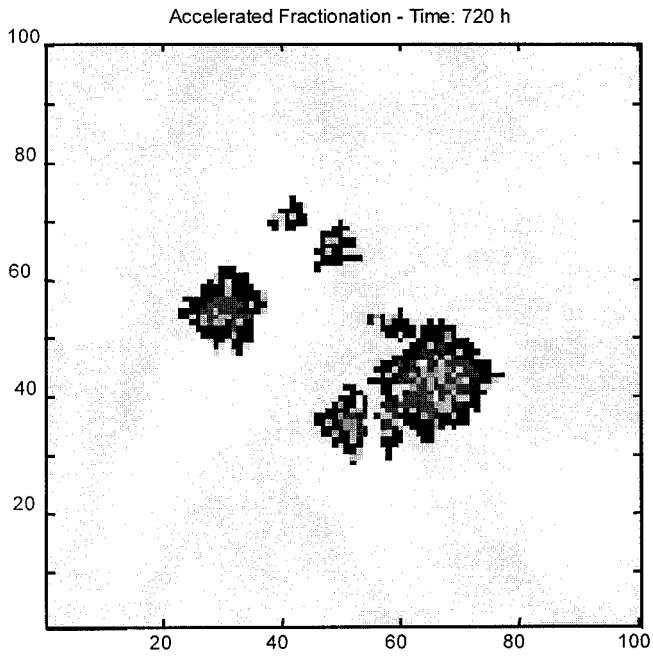


Fig. 6. Regrowth of the SCLC tumor after completion of the accelerated fractionation scheme.

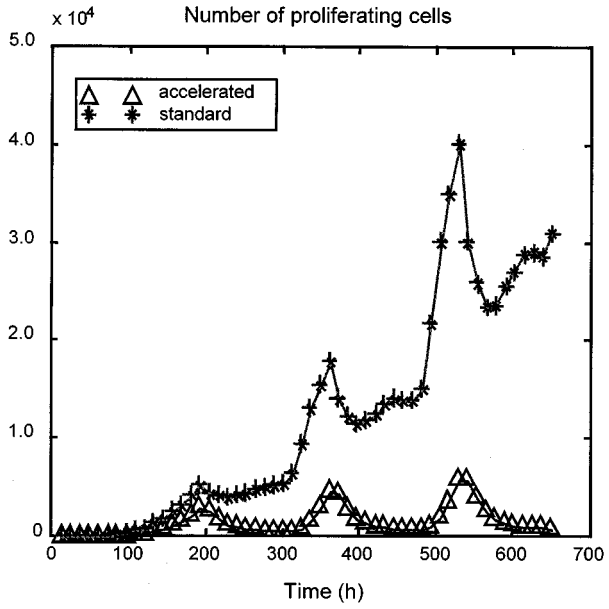


Fig. 7. Number of proliferating cells of an SCLC tumor spheroid as a function of time for accelerated and standard fractionated irradiation. Irradiation begins at $t = 168$ h from the placement of a single tumor cell in the phase of mitosis at the center of the discretizing mesh.

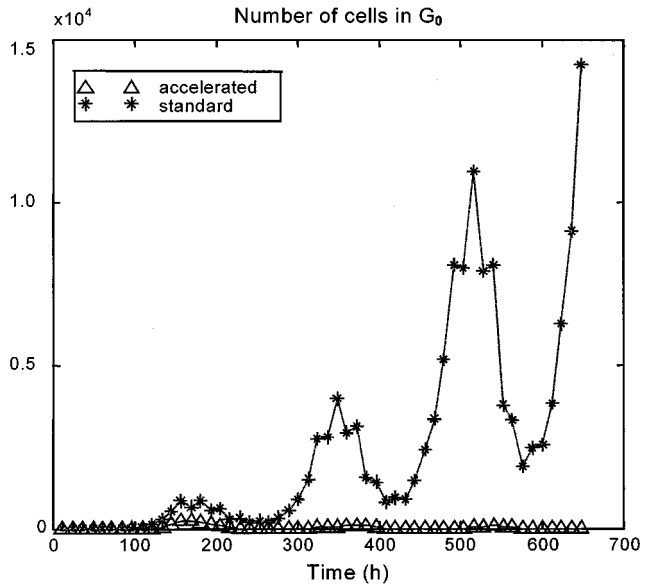


Fig. 8. Number of "dormant" cells in G_0 in an SCLC tumor spheroid as a function of time for accelerated and standard fractionated irradiation. Irradiation begins at $t = 168$ h from the placement of a single tumor cell in the phase of mitosis at the center of the discretizing mesh.

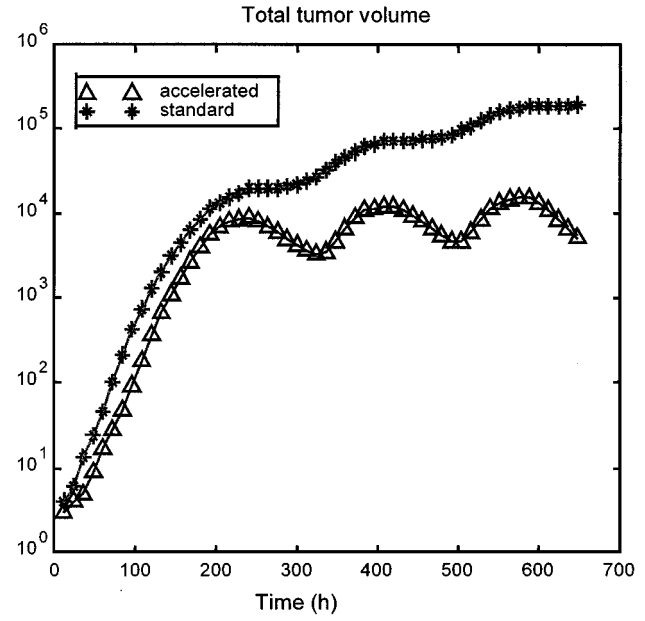
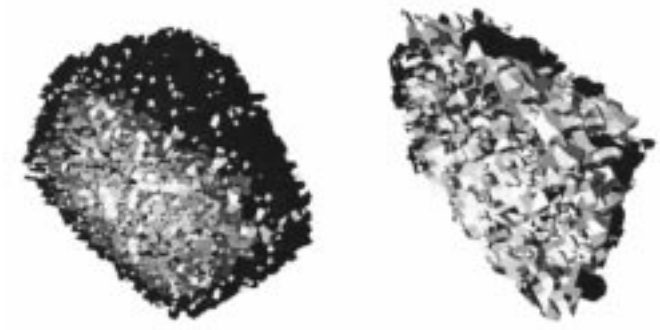


Fig. 9. Total volume of an SCLC tumor spheroid as a function of time for accelerated and standard fractionated irradiation. Irradiation begins at $t = 168$ h from the placement of a single tumor cell in the phase of mitosis at the center of the discretizing mesh.

a single tumor cell in the phase of mitosis at the center of the discretizing mesh. The section on the left corresponds to the case when no external interventions are applied. The section on the right corresponds to the case when the accelerated fractionation scheme (2 Gy twice a day, five days per week, 60 Gy total) is applied starting at $t = 168$ h. Cell death is apparently much more pronounced on the right section, as expected.

IX. Conclusion and Further Research

The simulation model presented (consisting of a biophysical, visualization, and computer network part) provides a novel platform for both gaining insight into the biological mechanisms involved in tumor growth and optimizing radiotherapy fractionation by performing "in silico" experiments. Therefore, the performance of expensive (in terms of both time and money) *in vitro* experiments might be substantially reduced. Although, at



(a) (b)

Fig. 10. A three-dimensional representation of the internal structure of an SCLC tumor spheroid using VRML 2.0. The snapshot corresponds to the instant $t = 240$ h after the placement of a single tumor cell in the phase of mitosis at the center of the discretizing mesh. (a) No external interventions are applied. (b) Accelerated fractionation scheme (2 Gy twice a day, five days per week, 60 Gy total) is applied starting at $t = 168$ h. Grey-scale code: from white to black: nutrient medium (white), cell lysis/apoptosis products (light gray), necrosed cells (medium gray), cells in G_0 (dark gray), cells in proliferating phases (black).

this stage, only a qualitative agreement of the system predictions with the experimental observations has been confirmed, it is expected that a more detailed description of the various biophysical mechanisms involved (e.g., cell loss, radiation induced apoptosis etc.) can add a more clinically significant dimension to the simulation output. The combination of high-performance computing with advanced visualization and WWW-based client–server computer architecture has been proven particularly fruitful.

As the simulation model is quite general, the cytokinetic and radiobiological properties of any particular type of tumor cells (capable of forming tumor spheroids in culture) can be the input to the computer program implementing the analysis presented. Therefore, apart from the provision of the cytokinetic and radiobiological data (α and β values of the LQ model) for the specific tumor cells, no modifications to the code are, in principle, necessary. Obviously, experimental feedback should always be used in order to improve the model reliability.

An imperative extension of the above-described simulation system is the temporal modeling of both untreated and treated *in vivo* tumors and normal tissues. Our group is currently developing an *in vivo* extension of the tumor growth model presented [31]. Brain astrocytoma treated with external beam radiation and breast cancer treated with brachytherapy are the first two clinical cases under consideration. It is evident that the complexity of such problems is considerably higher than the complexity of their *in vitro* counterparts. Phenomena such as angiogenesis, blood circulation, irradiation tolerance of the normal tissues, mechanical interaction of the tumor with the surrounding tissues, and parameters such as molecular predictive factors (e.g., p53, bcl-2), etc. should be taken into account. In order to be able to describe tumor growth and response to therapeutic interventions *in vivo*, the following modifications of the described model have already been performed by our group. Each cube of the discretizing mesh, instead of containing a single biological cell, contains a large number of cells (e.g., 10^6). Within each cube (otherwise called a "geometrical cell"), a number of equivalence classes of biological cells are defined according to the phase in which the cells are found at each given instant. Sufficient registers are used in order to characterize the state of each geometrical cell and each phase class within it (e.g., the number of biological cells in phase G_1, the time spent in phase G_1, the number of sublethally hit biological cells, etc.).

Phenomena such as angiogenesis, blood circulation, metabolic activity, etc. are described in a rather macroscopic way based on imaging data [e.g., positron emission tomography (PET) and functional magnetic resonance imaging (MRI)] of the anatomic region of interest. As an example, a tumor subvolume emitting a strong PET signal is expected to be able to support significant proliferation. The reason is that PET (or SPECT) provides information on the intensity of metabolism occurring in a tissue. As tumor cells divide faster than their normal counterparts, the volume layer mainly occupied by proliferating tumor cells (cells in the G_1, S, G_2, and M phases) is expected to emit a stronger PET signal [30, pp. 784–785, 1185–1186, 1280]. On the contrary, a necrotic tumor layer is expected to appear rather "dark." The layer of the tumor mainly occupied by resting G_0 cells will emit an intermediate intensity signal. It is stressed that there will be a statistical distribution of these three "phases" (proliferating, resting, and necrotic) in any tumor layer, although, in each layer, only one "phase" will generally predominate. This stems from the fact that a clinical tumor is a highly inhomogeneous structure due to, for example, its complex capillary system. Such inhomogeneities lead to an uneven oxygen and nutrient supply to the individual tumor cells. Therefore, a coexistence of different cell "phases" in the same tumor layer is to be expected. Concerning the distribution of the cells in the various cell cycle phases (G_1, S, G_2, and M) within the proliferating "phase" of the tumor, the following rule is applied: "the percentage of the cells in a specific cell cycle phase is equal to the specific cell cycle phase duration over the duration of the entire cell cycle, unless blocking in cell cycle checkpoints occurs." Appropriate pseudorandom number generators are used in order to simulate the statistical character of the phenomena under consideration. Algorithms simulating tumor shrinkage and expansion similar to the ones described in this paper have been developed. The radiobiological data of the normal tissues adjacent to the tumor are used in each mesh cube occupied by these kinds of tissue.

The aim of the approach is to predict both the early and late effects of radiotherapy on normal tissues. Besides, large clinical follow-up databases have been planned to be employed in order to both test and optimize the corresponding simulation models. Finally, the vision of our research group is to develop an integrated decision and individualized treatment planning support system based on both physical and biological optimization of radiotherapy.

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