Using Web Technologies and Meta-Computing to Visualise a Simplified Simulation Model of Tumor Growth in Vitro

Georgios S. Stamatakos, Evangelia I. Zacharaki, Nikolaos A.Mouravliansky,
Konstantinos K.Delibasis, Konstantina S. Nikita, Nikolaos K. Uzunoglu,
and Andy Marsh*
Department of Electrical and Computer Engineering, Division of Electroscience,
National Technical University of Athens,157 80 Zografou, Athens, Greece.
*Fax: +301772 3557, Tel: +3017722287, Email: euromed@naxos.esd.ece.ntua.gr

Abstract - The aim of this paper is to demonstrate the impact that Web technologies and meta computing can have on the simulation of biological processes such as tumor growth. A client-server architecture allowing real time surface and volume rendering using a standard Web browser is proposed. A simplified three-dimensional cytokinetic simulation model of tumor growth in vitro is developed and results are obtained concerning the development of a small cell lung cancer (SCLC) tumor spheroid in cell culture. A Gaussian distribution of the cell cycle phase durations is considered. The behavior of the model is compared with both published data and laboratory experience. The application of Web technologies and meta computing leads to a spectacular three-dimensional visualisation of both the external and the internal structure of a growing tumor spheroid.

1. Introduction

Tumor growth modeling has proved to be a particularly useful means of both gaining insight into the biological process of tumor development [16,23,26,30] and optimising therapeutic techniques in oncology [16,19,26]. The fact that cancer is characterised by uncontrolled cell proliferation has stimulated biomathematicians to construct cell proliferation models (continuous, discrete, deterministic, stochastic) usually based on differential equations describing growth and kinetics of abnormal cell multiplication [2,3,16]. Based on these findings, W.Duechting formulated the hypothesis that *'cancer can be interpreted as structurally unstable, negative feedback control loops'* [4-17]. By applying systems analysis, control and automata theory, heuristics and computer science, Duechting and his collaborators managed to produce elaborate, flexible and efficient simulation models, revolutionising tumor growth modeling [4-17, 20, 29]. Duechting's basic philosophy has been adopted in the development of the biophysical part of this paper. An improved algorithm for the simulation of the cell to cell communication (assumption 13 in Section 2) has also been introduced.

As the main purpose of the present work is to demonstrate the impact that modern visualisation techniques and the use of remote computing resources can have on tumor growth simulations rather than to improve the simulations themselves, a simplified three-dimensional cytokinetic model of tumour growth in vitro is developed. The model takes into account only the very basic characteristics of the process, sometimes even in a rather qualitative manner [28]. External actions, such as therapeutic schemes, or space limitations are not considered in this model. Simulation results concerning the development of small cell lung cancer (SCLC) tumor spheroids in cell culture are obtained. Initially, an equatorial section of the spheroid in different

moments is visualized using a standard mathematical software package e.g. MATLAB. The results are compared with both published simulation data and laboratory experience. A satisfactory agreement regarding at least the gross features of the process is observed.

For the three-dimensional (3D) visualization of the results, a standard Web browser is used allowing real time surface and volume rendering on inexpensive computer hardware. Its application to the model leads to a spectacular three-dimensional visualization of both the external surface and the internal structure of a growing tumor spheroid. In addition, a procedure to animate volumes or triagulated surfaces is suggested as an extension to the proposed visualization system. Finally, the issue of utilising remote computational resources for calculating the tumor growth prediction in a client-server architecture is addressed.

2. Assumptions of the model

The following simplifying assumptions have been used for the development of the simulation model.

1. A three-dimensional mesh discretizing the volume of the cell culture (including tumor and nutrient medium) is used. Each geometrical cell of the mesh can be occupied by a single biological cell of cubic shape, by nutrient medium or by the products of cell lysis.
2. The total space of the modeled cell culture is limited to $100 \times 100 \times 100$ geometrical cells. This type of limitation depends on the computer memory and power available as well as on the maximum tolerated simulation run time .
3. Time is discretized and measured in appropriate units such as hours (h).
4. Vascularization is not considered. This can refer to either tumor growth in vitro or to the early stages of avascular tumor growth in vivo.
5. Side effects, immunologic reactions, heterogeneity, drug resistance and the formation of metastases are neglected.
6. The development of a tumor spheroid starts immediately after the placement of a single tumour cell in the phase of mitosis at the centre of the mesh.
7. The simplified cytokinetic model of a tumor cell shown in Fig.1 is considered. A probability of 0.01 for each cell to undergo lysis every hour due to apoptosis is adopted.
8. The duration of each cell cycle phase follows a Gaussian distribution.
9. Only horizontal and vertical communication between neighboring cells is possible.
10. The simulation may be considered as a row-to-row computation of the cell algorithm for each individual cell. At each time step, the time remaining for the current phase of each cell is reduced by one unit. The configuration obtained in this way serves as the initial step of the subsequent calculation step.
11. The following heuristic cell production and interaction rule is employed in order to describe the cell-to-cell communication: 'If the distance between the dividing tumor cell and the nutrient medium is more than three cell layers, the tumor cell will transfer to the resting (dormant) phase G0 and later to the phase of necrosis and to lysis'.

12. A tumor cell can divide even if there is no empty space available for a daughter cell; this rule is restricted by the previous distance-dependent statement .
13. The position of a conventionally 'newborn cell' is chosen in such a way that the number of cells that will have to shift (in a straight line) in order to give space to the 'newborn cell' is the least possible. In case that cell shifting in more than one direction is permissible, the selection of the shifting direction is made using a random number generator (Monte Carlo technique).

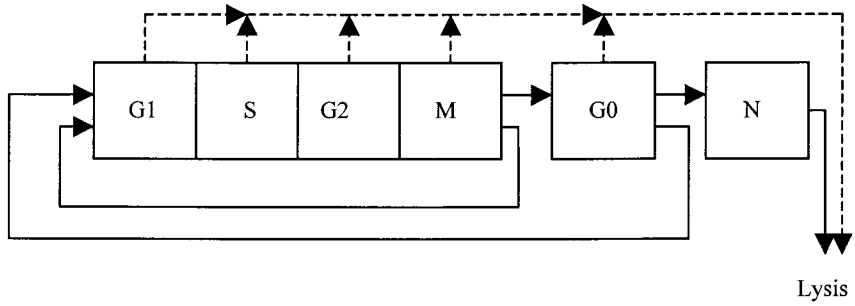

Fig.1 A simplified cytokinetic model of a tumor cell

As an example of tumor growth in vitro, the case of small cell lung cancer (SCLC) tumour growth in cell culture has been considered. SCLC is a rapidly growing neoplasm. The mean durations and deviations of its cell cycle phases are as follows [13, 14]: necrosis duration $T_N=40 \pm 2$ h, resting phase duration $T_{G0}=25 \pm 5$h, first gap phase duration $T_{G1}=3 \pm 0$ h, DNA synthesis duration $T_S=5 \pm 1$ h, second gap phase duration $T_{G2}=1 \pm 0$ h, mitosis duration $T_M=1 \pm 0$ h. The time unit has been taken equal to 1 h. Six mesh snapshots corresponding to the simulated instants 1 h, 40 h, 80 h, 120 h, 160 h, 200 h (after the placement of the initial SCLC cell at the centre of the nutrient medium) were stored for further visualization processing.

3. The visualization system

The visualization of 3D anatomical or biological structures is traditionally performed by displaying a series of 2D transverse intersections (slices) or contours from which the observer tries to conceive the 3D shape of the structure. The facts that:

a) there is a number of states that a cell can be in (e.g. G0, M etc.) and
b) what needs to be visualized is not just a 3D volume but a dynamically evolving structure, equivalent to a 4D modality

make the use of new visualization techniques imperative, if the expert is to comprehend the full width of the information produced by the tumor growth simulation. The requirements that the proposed visualization system satisfies can be summarized as follows:

a) The input of the system is raw data with voxels labeled by a code number corresponding to a specific cell state.

b) The output of the system is a set of triangulated surfaces that allow real time surface and volume rendering to be performed on hardware as inexpensive as a high end Pentium based PC compatible computer. The output files are WWW compatible (i.e. in VRML format).

4. Detailed description of the visualization system

The simulation system stores the results of the tumor growth simulation procedure as a series of raw data, each of which consists of a 3D matrix that represents the physical space that the tumor can expand to. The elements of these arrays will be called voxels, since they represent elementary volumes of the tumor physical space. The voxels are labeled by an integer number indicating the state that the cell that occupies 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 concept of surface generation from volumetric data (or an array of contours) is well established in many areas of science [1, 22] including many applications in biomedical physics and imaging [e.g. 27, 31]. The enclosing surface of the segmented volume is triangulated using a novel implementation of the well documented Marching Cubes (MC) algorithm [18, 24, 32]. The version of MC employed has been developed and implemented with a substantial difference from traditional implementations [25]. In the specific implementation, a generic rule is used to optimally triangulate the image voxels, instead of employing prespecified voxel configurations. This approach compares favourably to the existing, traditional ones, in terms of both the number of triangles/polygons and the execution time. The novel implementation of the MC algorithm produces an optimized number of polygons, small enough to allow high end PC compatible computers to perform real time volume rendering. The triangulated surfaces produced by the employed MC algorithm can be easily visualized for a number of 10^6 evolving cells. Therefore, it is evident that the limiting factor is the speed of the server performing the actual tumor growth simulation rather than the volume rendering process, assuming that the later takes place on a high end Pentium based PC.

The visualization system stores the triangulated surface in VRML (Virtual Reality Modelling Language) 2.0 format. The procedure can be repeated if another cell state is to be visualized and a new triangulated surface is produced. An arbitrary number of surfaces can be included in a single VRML file, since the use of color, transparency and volume rendering assists the visualization of complex cell structures.

The proposed visualization procedure is not only efficient in visualizing complex 3D structures, but can also be used as a tool to handle 4D images, such as the dynamically changing tumors that evolve from the growth simulation system. VRML 2.0 allows the creation of animations that demonstrate the volume evolution in a graphical and interactive way [21]. The procedure that has been developed to animate volumes or triangulated surfaces can be summarized as follows.

I) A series of cell volumes is produced in time steps sufficiently small so that the shape change between consecutive volumes can be tolerated by the algorithm.

II) Starting with the volume with the largest number of cells V_t ,

II.A) Volumes V_t and V_{t-1} are registered considering only the spatial translation of their centres of mass. A new surface V'_{t-1} is constructed.

II.B) For each vertex i of the triangulated surface of V_t

II.B.1) The vertex j from the triangulated surface of V_{t-1} for which the Euklidean distance from i is minimal is located.

II.B.2) The Euclidean coordinates of vertex i of V'_{t-1} are set equal to the Euclidean coordinates of vertex j of V_{t-1} i.e. $V'_{t-1}(i) = V_{t-1}(j)$

II.C) After the mapping is finished, the triangulated surface of V_{t-1} is replaced by V'_{t-1} .

II.D) If spatial registering took place, the inverse transform is applied to V'_{t-1} .

II.E) $t = t-1$

II.F) If $t > 0$, go to step II.A, else end.

The mapped series of the triangulated surfaces of $\{V_t, V'_{t-1}, ..., V'_0\}$ is now adequate to be introduced into the VRML 2.0 so that the animation may be performed.

5. The client - server architecture

The simulation of tumor growth becomes more realistic as the number of tumor cells increases. However, this results in a very fast increase in the computing time demands of the application. Therefore, in the case of in vivo tumor growth it may not be feasible to predict the development of a tumor or its response to specific 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 schematically, shown in Figure 2, implementing this approach can be summarised as follows:

a) The tumor simulation/prediction program executes on a fast, remote server, possibly dedicated to this purpose, for example the Onyx Infinite Reality[2] with 4 processors located at the ICCS/NTUA (Greece). The client submits a request for the prediction program through a Web page, which invokes the execution of a CGI (Common Gateway Interface) script on the server.

b) The generated volumes are triangulated, as it is described in the previous section and the corresponding VRML files are produced. At present the results are in two formats ASCI-Numeric and VRML, the envisaged 3rd format is a stereographic image that can be viewed by a Virtual Reality headset.

c) The client receives the generated VRMLs through an e-mail, or can access them through a password protected Web page. The use of a Web compatible format, like VRML, allows great flexibility in exchanging data between the client and the server.

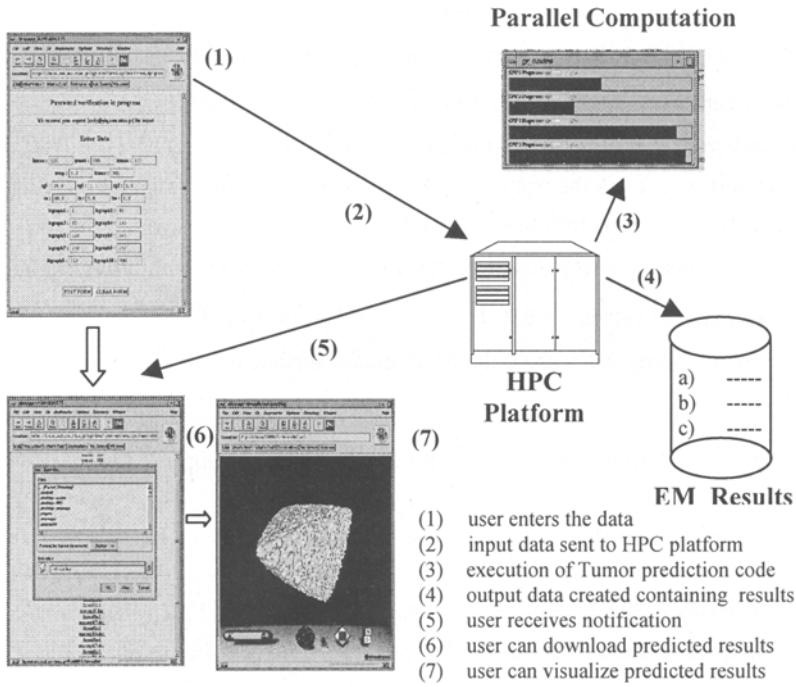

Figure 2 : A client-server architecture coupling meta-computing and web technologies

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 Web Browser. Figures 3 and 4 have been produced by applying the visualization procedure described in sections 3 and 4. The execution time for the presented examples takes about 20 mins on the four processor Onyx platform. Fig. 3 demonstrates the evolution of the external surface of the tumor. Fig. 4 gives a 3D view of the internal structure of the tumor. It consists of a series of 3D sections of the tumor. The simulation model predictions compare favorably with those of Duechting [13,14]. Agreement with laboratory experience, at least as far as the gross features of the simulated process are concerned, has also been observed.

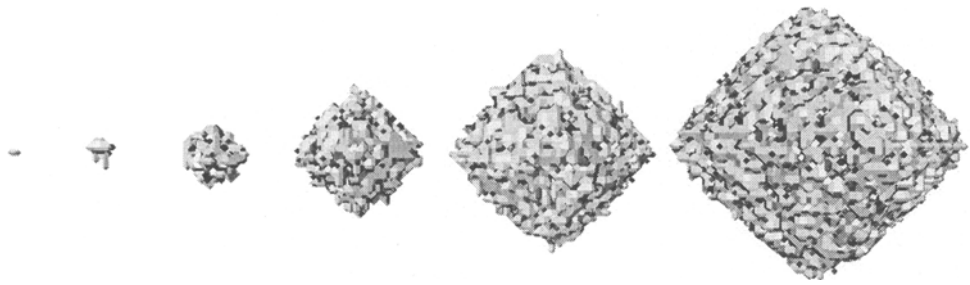

Fig. 3 Small cell lung carcinoma (external surface)
Sequence of visualization instants: 1h, 40h, 80h, 120h, 160h, 200h
[Color code: **yellow:** proliferating phases (G1, S, G2), **red**: mitosis ,**blue**: products of cell lysis.]
On the external surface of the spheroid most of the cells are in the proliferating phases (G1,S,G2) whereas cells in the process of mitosis or products of cell lysis can also be seen.

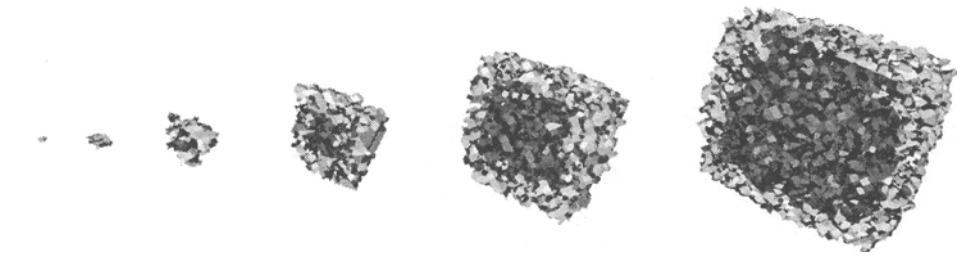

Fig.4 Small cell lung carcinoma (section)
Sequence of visualization instants: 1h, 40h, 80h, 120h, 160h, 200h
[Color code: **yellow:** proliferating phases (G1, S, G2), **red**: mitosis, **blue**: products of cell lysis, **pink**: G0, **green**: necrosis]
In the right snapshot the lysis products mainly lie in the central region of the tumor and are enclosed by the majority of necrotic cells. The next tumor shell basically contains resting cells (in the G0 phase), whereas the proliferating cells are to be found in the external layer of the tumor. Products of lysis can be found anywhere in the tumor as they can be produced either by the process of necrosis or by apoptosis.

6. Discussion

The simulation model presented seems to be a useful platform for the theoretical investigation of the biological process of tumor growth. It should be noted that graphs giving the temporal dependence of quantities such as the number of cells in a certain phase can be readily produced from the quantities calculated at each step of the model. Obvious improvements would include, the introduction of differential equations in order to describe the diffusion of oxygen and glucose in a quantitative manner [20], the consideration of non cubic shapes of the cells etc. It should be pointed out that the octahedral rather than spheroidal shape of the growing tumor that is apparent in Fig. 3 and Fig. 4 results from the restriction of the cell communication to horizontal and vertical directions.

The usefulness of the simulation model would be greatly enhanced if the effects of various therapeutic schemes such as chemotherapy and radiation therapy were taken into account. A simulation of tumor growth in vivo where the effects of angiogenesis would be considered in addition to its response to various therapeutic modalities would certainly be of much more practical interest. Such an advanced tool might substantially contribute to approaching the ultimate goal of cancer modeling which is the optimization of treatment prior to any therapeutic or paliative intervention. Our team is currently working on the extention of the present simulation model so that the above mentioned factors will be taken into account. In addition to the modeling itself, the proposed VRML visualization system proved capable of substantially contributing to an efficient 3D perception of the biological growth process. It is expected that its contribution to the visualization of tumor growth in vivo will be of even greater importance to clinicians. The use of VRML represents the first stage of utilising Virtual Reality techniques to visualize tumor growth [33]. Techniques based on Augmented Reality and Fully Emersive Virtual Reality are currently being explored. The ultimate goal of this work is to present the tumor growth as a holographic image. Furthermore, the proposed client-server architecture of the entire system will bring tumor growth modeling closer to the medical practice.

7. Conclusions

A simplified cytokinetic simulation model of tumor growth in vitro has been developed. The model has been used to simulate the growth of a SCLC tumor spheroid in cell culture. An equatorial section of the spheroid has been visualized at different instants using the software package MATLAB. For the three-dimensional visualization of the results, a special procedure allowing real time surface and volume rendering on inexpensive computer hardware has been proposed and applied. A spectacular 3D virtual reality visualization of both the external surface and the internal structure of a growing SCLC tumor spheroid has been achieved. Satisfactory agreement of the model predictions with both published simulation results and laboratory experience has been established. A procedure to animate volumes or triangulated surfaces has been suggested as an extension to the proposed visualization system. A client-server architecture of the entire simulation-visualization system has also been proposed and implemented. In conclusion, it has become clear that the application of advanced visualization techniques can significantly enhance the potentiality of tumor growth simulation models.

8. Acknowledgments

The authors would like to thank both the European Commission DGIII/B for supporting the EUROMED Project under the ISIS '95 Programme and the State Fellowship Foundation of Greece (IKY) for supporting G.S.Stamatakos' post doctoral research project. The authors would also like to thank Prof. Nikoloaos Zamboglou and Prof. Dimos Baltas of the Staedtische Kliniken Offenbach, Germany, for their contribution to the macroscopic evaluation of the model.

References

[1] J. D. Boissonat, Shape Reconstruction from Planar Cross Sections, Computer Vision, Graphics and Image Processing 44 (1988) 1-29.

[2] C. J. Clem, J.P. Rigaud, Computer simulation modelling and visualization of 3D architecture of biological tissues. Simulation of the evolution of normal, metaplastic and dysplastic states of the nasal epithelium, Acta Biotheor. 43(4) (1995) 425-442.

[3] R. Demicheli, R. Foroni, A. Ingrosso, G. Pratesi, C. Soranzo, M. Tortoreto, An exponential-Gompertzian description of LoVo cell tumor growth from in vivo and in vitro data, Cancer Res , 49(23) (1989) 6543-6.

[4] W. Duechting, Krebs, ein instabiler Regelkreis. Versuch einer Systemanalyse, Kybernetik 5(2) (1968) 70-77.

[5] W. Duechting, Modelling and simulation of normal and malignant tissue, in: M.H.Hamza and S.G. Tzafestas eds., Advances in Measurement and Control, Vol. 3 (ACTA Press, Anaheim, 1979) 909-918.

[6] W. Duechting and G. Dehl, Spatial growth of tumors. A simulation study, in: L.Fedina, B.Kanyar, B.Kocsis, M.Kollai eds., Adv. Physiol. Sci., Vol. 34 (Akademiai Kiado, Budapest, 1981) 123-131.

[7] W. Duechting and T. Vogelsaenger, Aspects of modelling and simulating tumor growth and treatment, J. Cancer Res. Clin. Oncol 105 (1983) 1-12.

[8] W. Duechting, Computer models applied to cancer research, in: M. Thoma and A. Wyner eds, Lecture Notes in Control and Information Sciences, 121 (Springer-Verlag, Berlin, 1988) 397-411.

[9] W. Duechting, Recent progress in 3-D computer simulation of tumor growth and treatment, Acta Applicandae Mathematicae 14 (1989), 155-166.

[10] W. Duechting, R. Lehring, G. Rademacher, W. Ulmer, Computer simulation of clinical irradiation schemes applied to in vitro tumor spheroids, Strahlenther. Onkol. 165 (1989) 873-878.

[11] W. Duechting, Computer simulation in cancer research, in:D.P.F. Moeller, ed., Advanced Simulation in Biomedicine (Springer-Verlag, NY, 1990) 117-139.

[12] W. Duechting, Tumor growth simulation, Comp. & Graph. 14(1990) 505-508.

[13] W. Duechting, W. Ulmer, R. Lehring, T. Ginsberg, E. Dedeleit, Computer simulation and modelling of tumor spheroid growth and their relevance for optimization of fractionated radiotherapy, Strahlenther. Onkol. 168 (1992), 354-360.

[14] W. Duechting, W. Ulmer and T. Ginsberg, Modelling of tumor growth and irradiation, in: A.R. Hounsel, J.M. Wilkinson and P.C. Williams, eds, Proceedings of the Xith International Conference on the Use of Computers in Radiation Therapy (North Western Medical Physics Department, Christie Hospital, Manchester, UK, 1994) 20-21.

[15] W.Duechting, T. Ginsberg, W. Ulmer, Modelling of radiogenic responses induced by fractionated irradiation in malignant and normal tissue, Srem Cells 13(suppl 1) (1995) 301-306.

[16] W. Duechting, W. Ulmer and T. Ginsberg, Cancer: A challenge for control theory and computer modelling, European J. of Cancer, 32A(1996) 1283-1292.

[17] W. Duechting, W. Ulmer and T. Ginsberg, Computer models for optimizing radiation therapy, in: H.U.Lemke, K.Inamura, M.W.Vannier, A.G.Farman, eds, CAR' 96, Computer Assisted Radiology (Elsevier, Amsterdam, 1996)

[18] M.J.Durst, Additional reference to "Marching Cubes", Computer Graphics 22(2) (1988) 72-73.

[19] J.F. Fowler, Review of radiobiological models for improving cancer treatment,in: K.Baier and D. Baltas, eds, Modelling in Clinical Radiobiology, Freiburg Oncology Series, Monograph No. 2 (Albert-Ludwigs-University Freiburg, Germany, 1997)

[20] T. Ginsberg, Modellierung und Simulation der Proliferationsregulation und Strahlentherapie normaler und maligner Gewebe (Fortschr.-Ber. VDI, Reihe 17, Nr 140, VDI Verlag, Duesseldorf,1996).

[21] Lemay L, Couch J and Murdock K, 3Dgraphics and VRML 2.0 (Sams.net Publishing, 1996)

[22] W.C. Lin, S.Y. Chen and C.T. Chen, A new surface interpolation technique for reconstructing 3D objects from serial cross sections, Computer Vision, Graphics and Image Processing 48 (1989) 124-143.

[23] H.Lodish, D.Baltimore, A. Berk, S. L.Zipursky, P.Matsudaira, J.Darnell, Molecular Cell Biology (Scientific American Books, NY, 1995) 1247-1294.

[24] W.E. Lorensen and H.E. Cline, Marching Cubes: High resolution 3D surface construction algorithm, Computer Graphics 21(3) (1987) 163-169.

[25] G.K.Matsopoulos, N.Mouravliansky, K.K.Delibasis and K.S. Nikita, A novel and efficient implementation of the Marching Cubes Algorithm, Computer & Graphics, accepted, October 1998.

[26] H.I. Pass, J.B.Mitchell, D.H. Johnson, A.T.Turrisi, Lung Cancer, Principles and Practice (Lippincott-Raven, Philadelphia, New York, 1996).

[27] B.A. Payne and A.W. Toga, Surface mapping brain function on 3D models, IEEE Computer Graphics and Applications 10(2) (1990) 33-41.

[28] G.S.Stamatakos, N.K.Uzunoglu, K.Delibasis, M.Makropoulou, N. Mouravliansky, A.Marsh, A simplified simulation model and virtual reality visualization of tumour growth in vitro, Future Generation Computer Systems 14(1998) 79-89.

[29] T. Vogelsaenger, Modellbildung und Simulation von Regelungsmechanismen wachsender Blutgefaessstrukturen in normalen Geweben und malignen Tumoren, Ph.D. Thesis, Department of Electrical Engineering, University of Siegen, Germany, 1986.

[30] J.D.Watson, N.H.Hopkins, J.W.Roberts, J.A.Steitz, A.M.Weiner, Molecular Biology of the Gene, 4th Edition (The Benjamin/Cummings Publishing Company, Inc., Menlo Park,California, 1987) 1058-1096.

[31] S.B. Xu and W.X. Lu, Surface Reconstruction of 3D Objects in computerized Tomography, Computer Vision, Graphics and Image Processing 44 (1988) 270-278.

[32] C. Zhou, R. Shu and M. S. Kankanhalli, Handling small features in isosurface generation using Marching Cubes, Comp. & Graphics 18(6) (1994) 845-848.

[33] B. Grant, "Virtual Reality gives medicine a powerful new tool", Biophotonics International, November/December 1997, p. 40-45.