The "Clinical Oncosimulator": a multilevel, "top-down", clinically oriented simulation system of tumor growth and organism response to therapeutic schemes.

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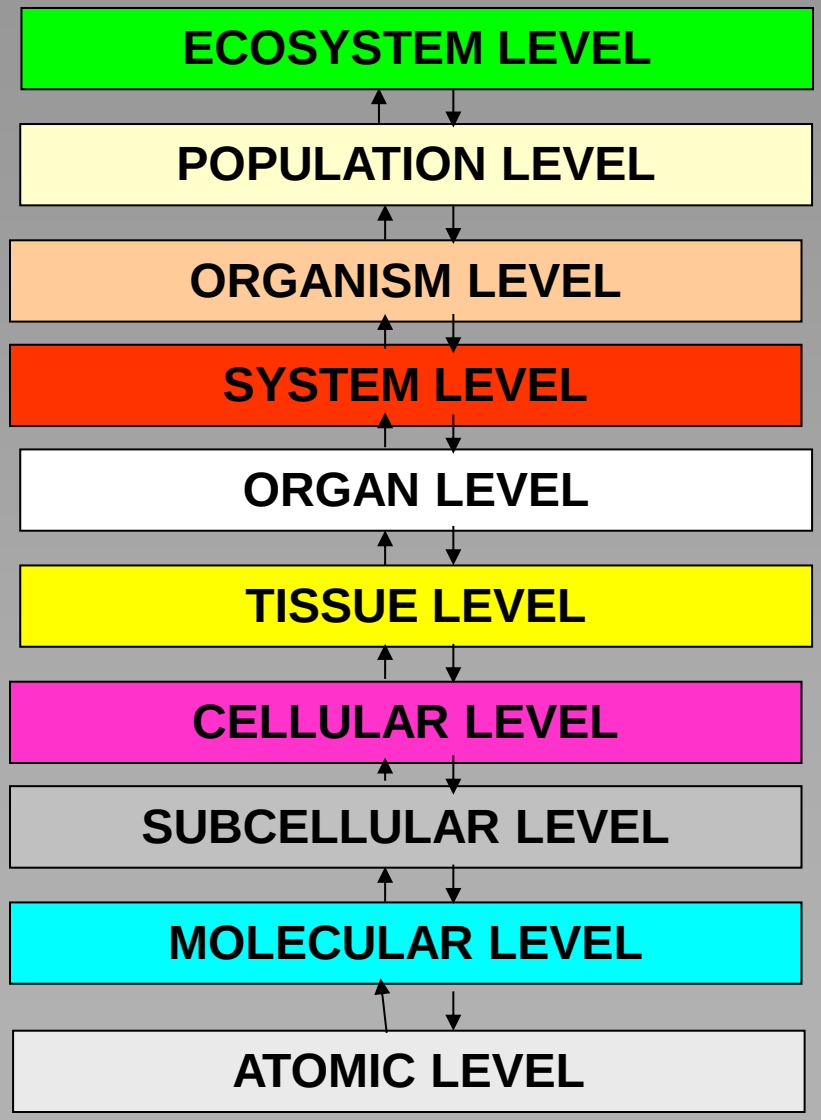
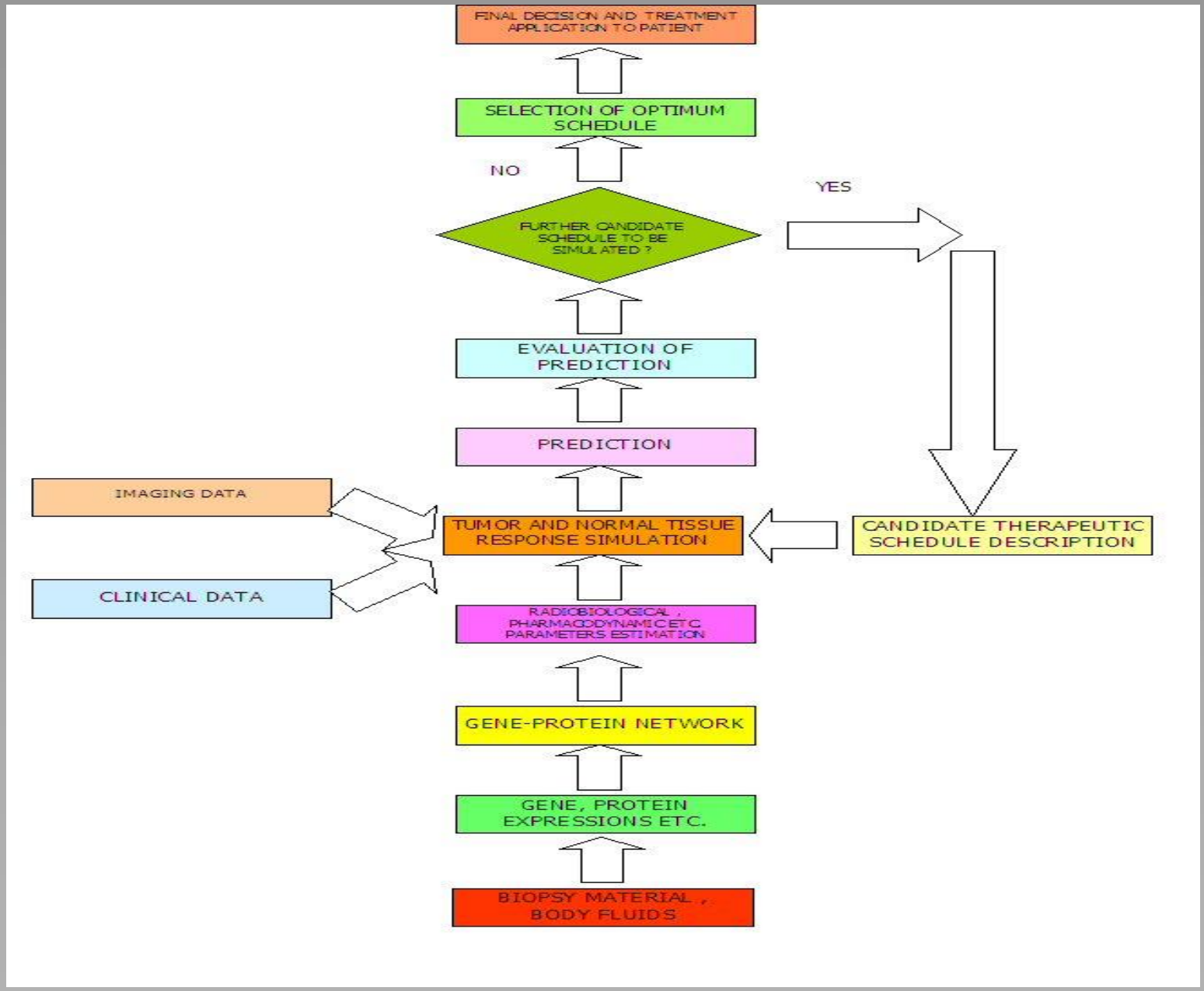
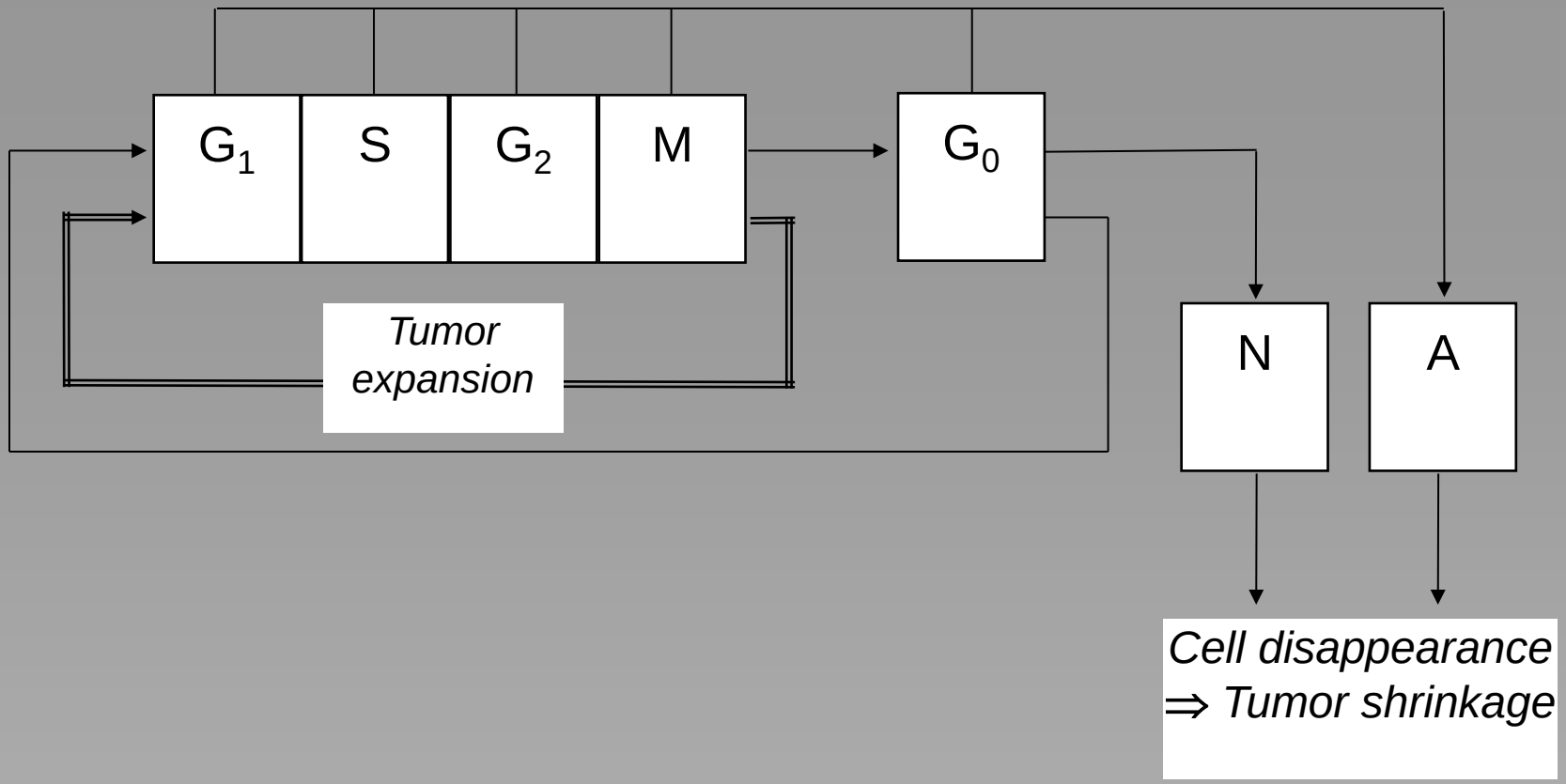
The ten levels of biocomplexity



The “Clinical Oncosimulator”

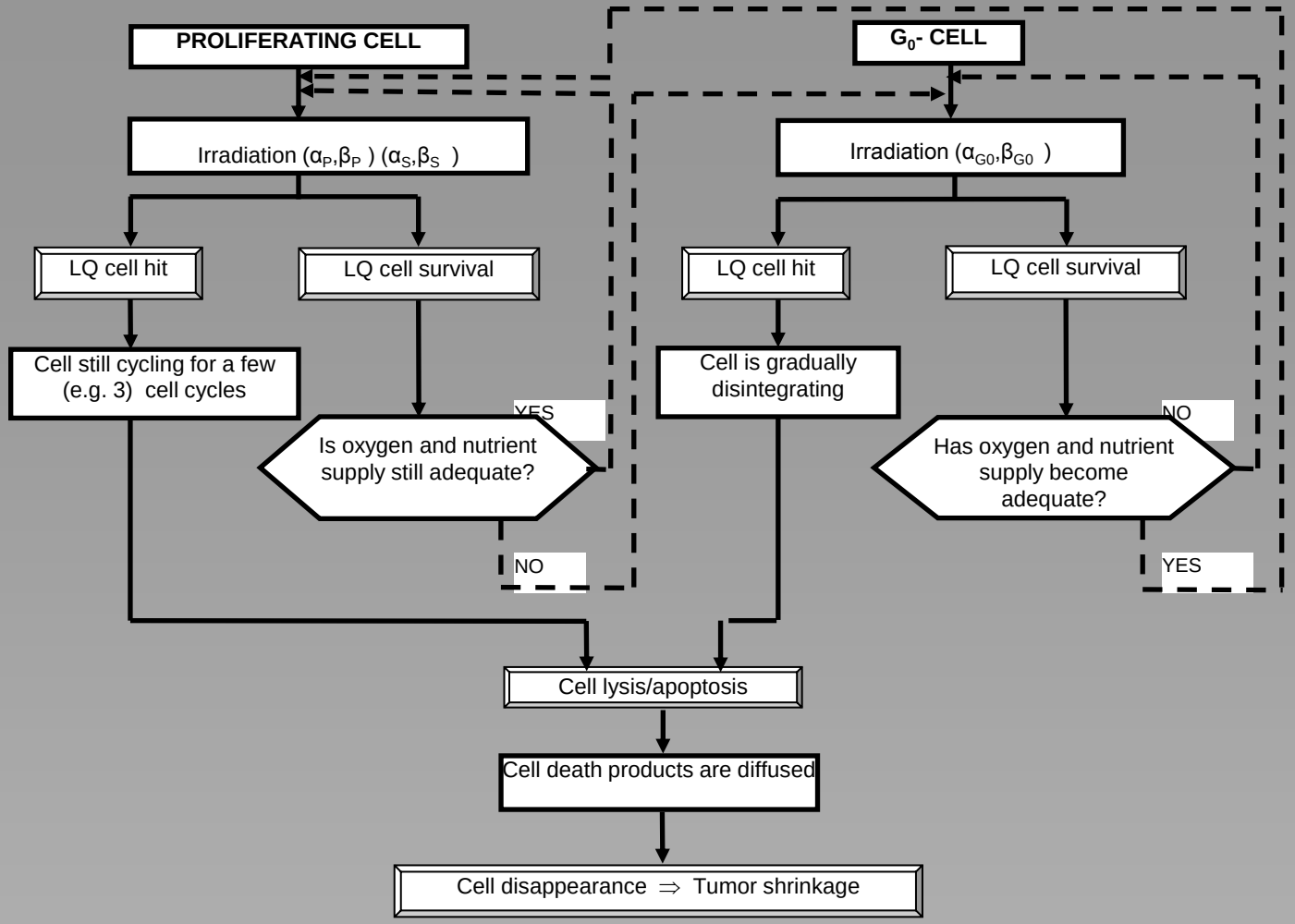




A simplified cytokinetic model of a tumor cell.

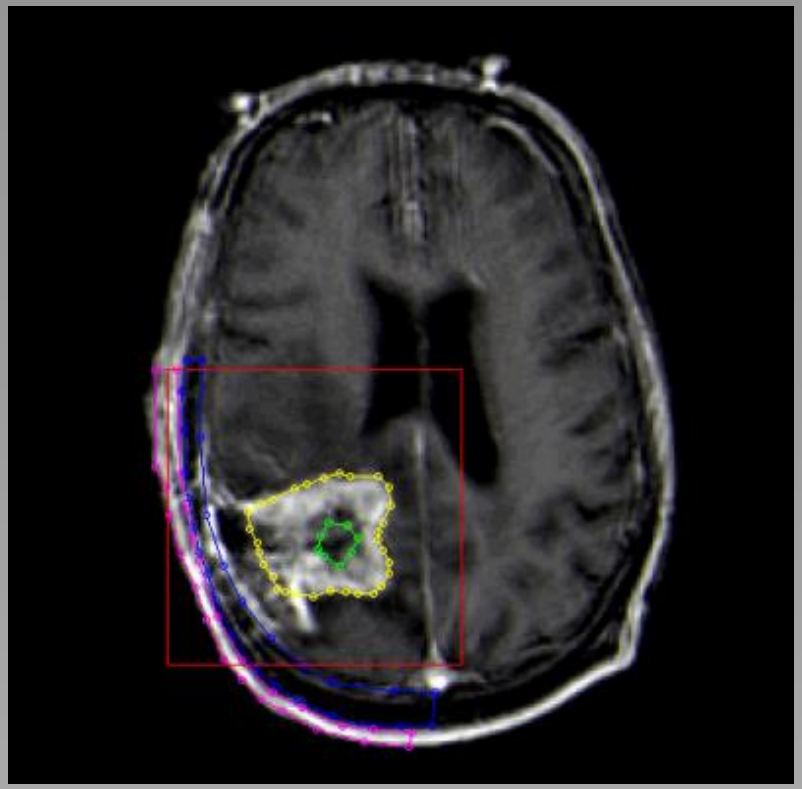
Symbol explanation: G1: G1 phase, S: DNA synthesis phase, G2: G2 phase, G0: G0 phase, N: necrosis, A: apoptosis.

[see G.Stamatakos, D.Dionysiou, E.Zacharaki, N.Mouravliansky, K.Nikita, and N.Uzunoglu, "*In Silico* Radiation Oncology: Combining Novel Simulation Algorithms with Current Visualization Techniques," Proc. IEEE, Special Issue on "Bioinformatics: Advances and Challenges" Vol.90, No.11, November 2002, pp.1764-1777]



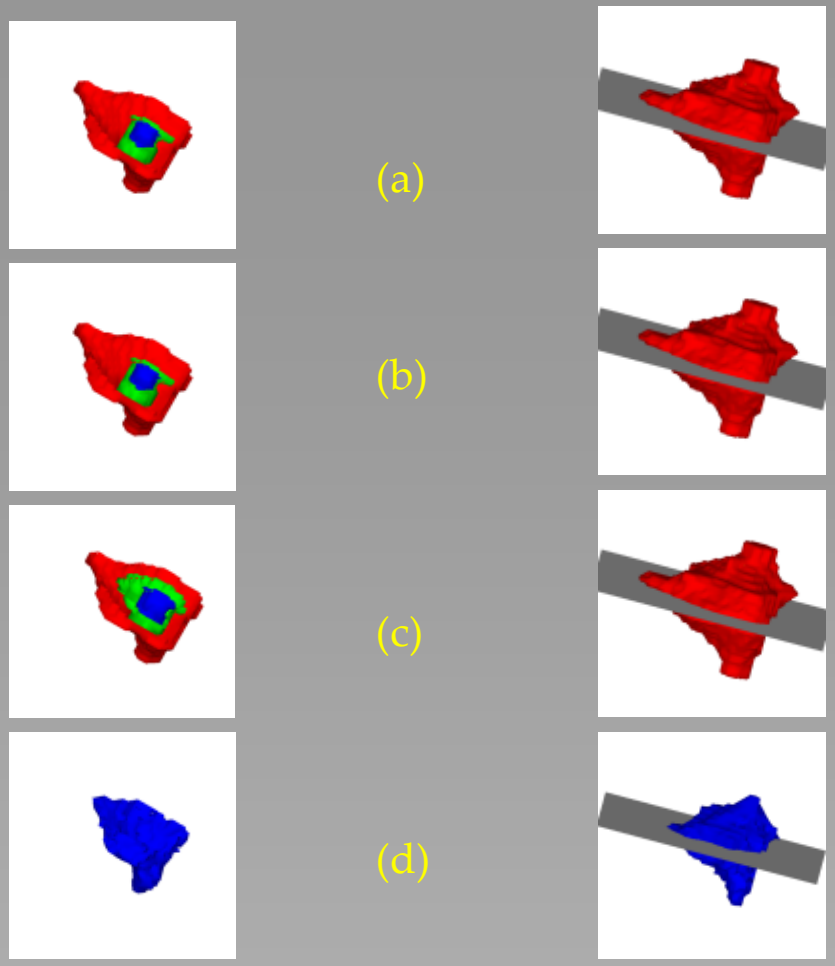
Simplified flow chart for the response of a single tumour cell to irradiation. Symbol explanation: α_P and β_P stand for the α and β parameters of the linear quadratic model for the tumour proliferating cells excluding those in phase S. The subscript S denotes cells in the DNA synthesis phase, whereas the subscript G0 denotes cells in the resting (dormant) phase G0.

[see G.Stamatakos, D.Dionysiou, E.Zacharaki, N.Mouravliansky, K.Nikita, and N.Uzunoglu, "*In Silico* Radiation Oncology: Combining Novel Simulation Algorithms with Current Visualization Techniques," Proc. IEEE, Special Issue on "Bioinformatics: Advances and Challenges" Vol.90, No.11, November 2002, pp.1764-1777]



An MRI slice depicting a glioblastoma mutiforme. Both the gross volume of the tumour and its central necrotic area have been delineated. The present case has been considered for the preliminary checks of the simulation model.

[see G.Stamatakos, D.Dionysiou, E.Zacharaki, N.Mouravliansky, K.Nikita, and N.Uzunoglu, "*In Silico* Radiation Oncology: Combining Novel Simulation Algorithms with Current Visualization Techniques," Proc. IEEE, Special Issue on "Bioinformatics: Advances and Challenges" Vol.90, No.11, November 2002, pp.1764-1777]

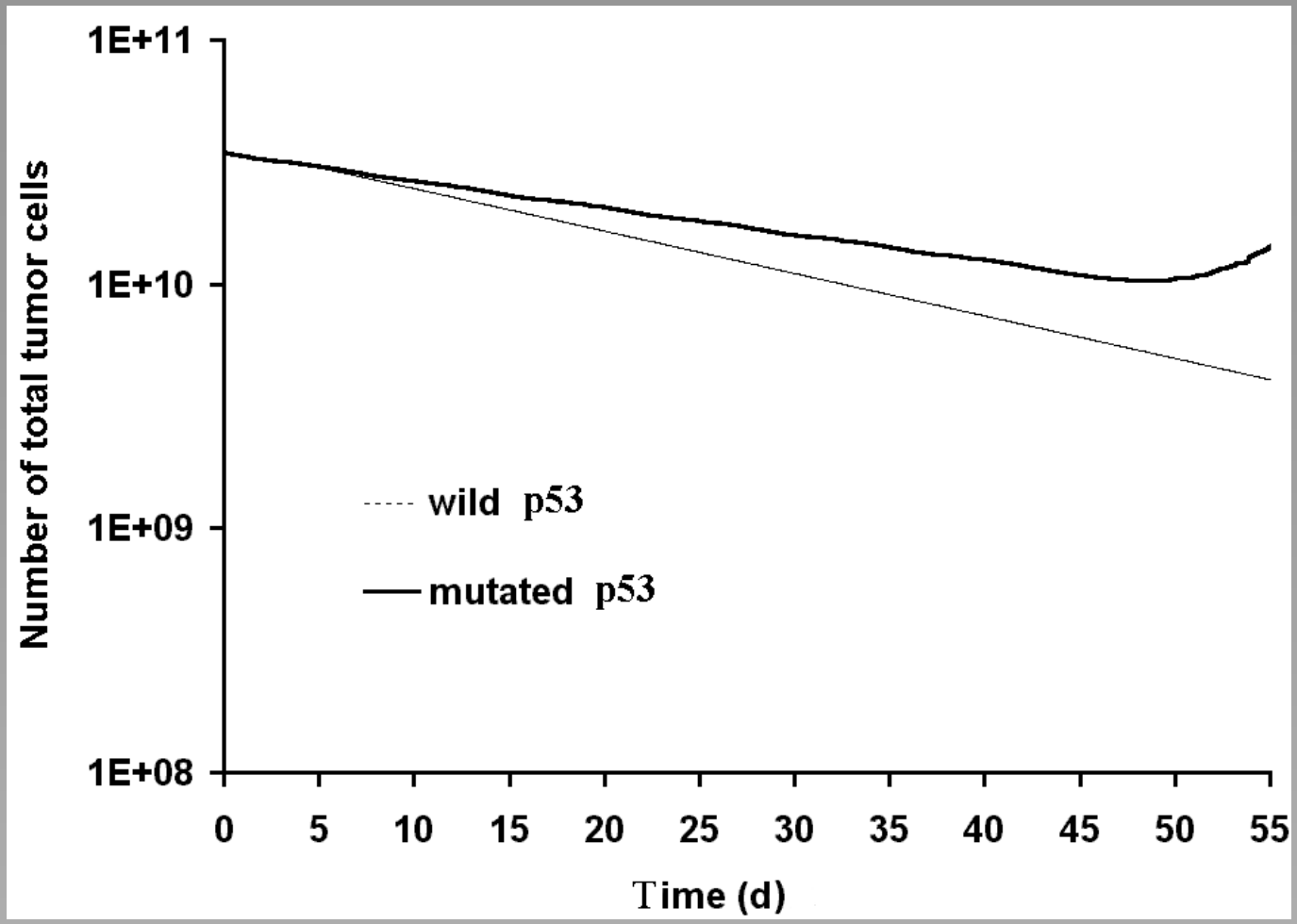


Irradiation according to the standard fractionation scheme

(2 Gy once a day, 5 days per week, 60 Gy in total). Left panel: three dimensional sections of the tumour shown in the right panel: (a) **before the beginning of irradiation**, (b) **1 *fictitious* day after the beginning of irradiation**, (c) **2 *fictitious* days** after the beginning of irradiation and (d) **3 *fictitious* days** after the beginning of irradiation. ***Colour code* red:** proliferating cell layer, **green**: dormant cell layer (G0), **blue**: dead cell layer. The **colouring criterion "99.8%"** used to visualize the predictions has been defined as follows.

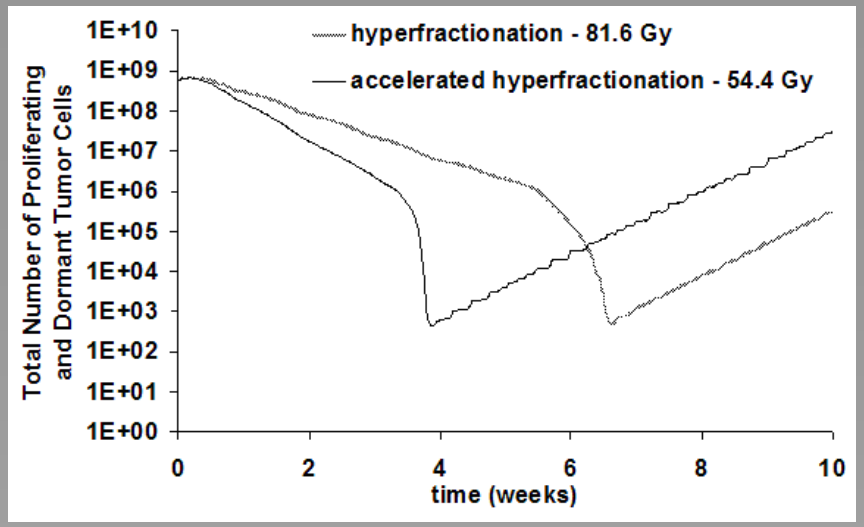
"For a geometrical cell of the discretizing mesh, if the percentage of dead cells is lower than 99.8% then
{ if percentage of proliferating cells > percentage of G0 cells, then paint the geometrical cell red (proliferating cell layer),
else paint the geometrical cell green (G0 cell layer) } else paint the geometrical cell blue (dead cell layer)"

The values of certain parameters (e.g. cell loss) have been **deliberately exaggerated** in order to facilitate the demonstration of the ability of the model to simulate the **shrinkage effect**. [see G.Stamatakos, D.Dionysiou, E.Zacharaki, N.Mouravliansky, K.Nikita, and N.Uzunoglu, "*In Silico* Radiation Oncology: Combining Novel Simulation Algorithms with Current Visualization Techniques," Proc. IEEE, Special Issue on "Bioinformatics: Advances and Challenges" Vol.90, No.11, November 2002, pp.1764-1777]

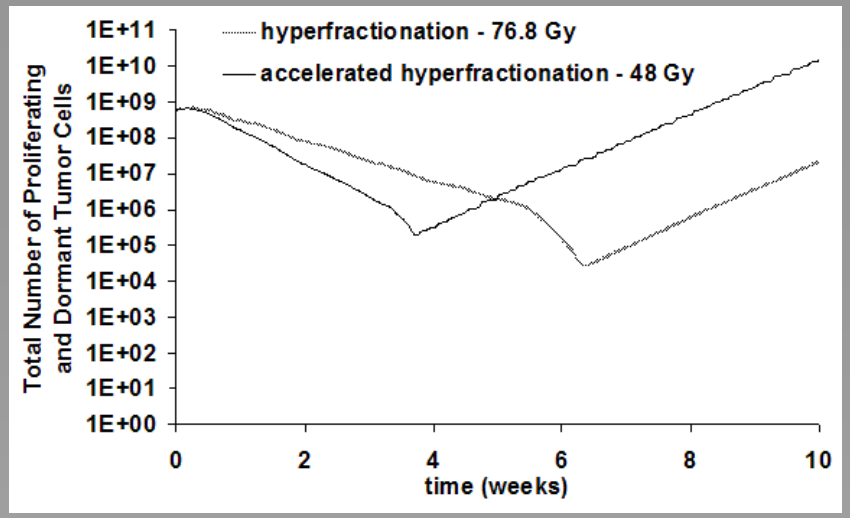


Simulation predictions of the number of total tumour cells (mt p53 and wild type p53) for the standard fractionation scheme. An OER=3.0 has been assumed.

[see V. P Antipas, G. S Stamatakos, N. K Uzunoglu, D. D Dionysiou, R. G Dale, " A spatio-temporal simulation model of the response of solid tumours to radiotherapy *in vivo*: parametric validation concerning oxygen enhancement ratio and cell cycle duration," *Phys. Med. Biol.* 49 (2004) 1485–1504 [Pubmed Link: http://www.ncbi.nlm.nih.gov/entrez /query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15152687&query_hl=14]]



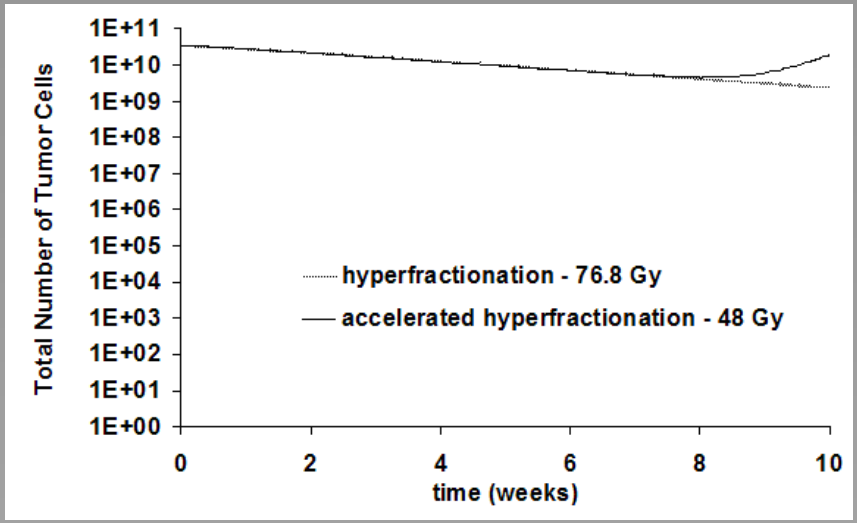
(a)



(b)

(a) **Total number of proliferating and dormant tumour cells as a function of time for the hyperfractionated** (1.2 Gy twice daily, 5 days per week to the dose of 81.6 Gy, "HF-81.6") and **accelerated hyperfractionated** (1.6 Gy twice daily, 5 days per week to the dose of 54.4 Gy, "AHF-54.4") **radiotherapy schedules.** HF-81.6 is completed on day 46 after initiation of treatment whereas AHF-54.4 is completed on day 23. In all fractionation schedules considered in this paper no radiation is administered on Saturdays and Sundays. **(b) Total number of proliferating and dormant tumour cells as a function of time for the hyperfractionated** (1.2 Gy twice daily, 5 days per week to the dose of 76.8 Gy, "HF-76.8") and **accelerated hyperfractionated** (1.6 Gy twice daily, 5 days per week to the dose of 48 Gy, "AHF-48") **radiotherapy schedules.** Both irradiation schedules start on the first day of the first week of treatment. HF-76.8 is completed on day 44 after initiation of treatment whereas AHF-48 is completed on day 19.

[see G. S. Stamatakos, V.P. Antipas, N. K. Uzunoglu, R. G. Dale, "A four dimensional computer simulation model of the *in vivo* response to radiotherapy of glioblastoma multiforme: studies on the effect of clonogenic cell density." *British Journal of Radiology*, 2006, vol. 79, 389-400 [http://bjr.birjournals.org/cgi/content/abstract/79/941/389].]

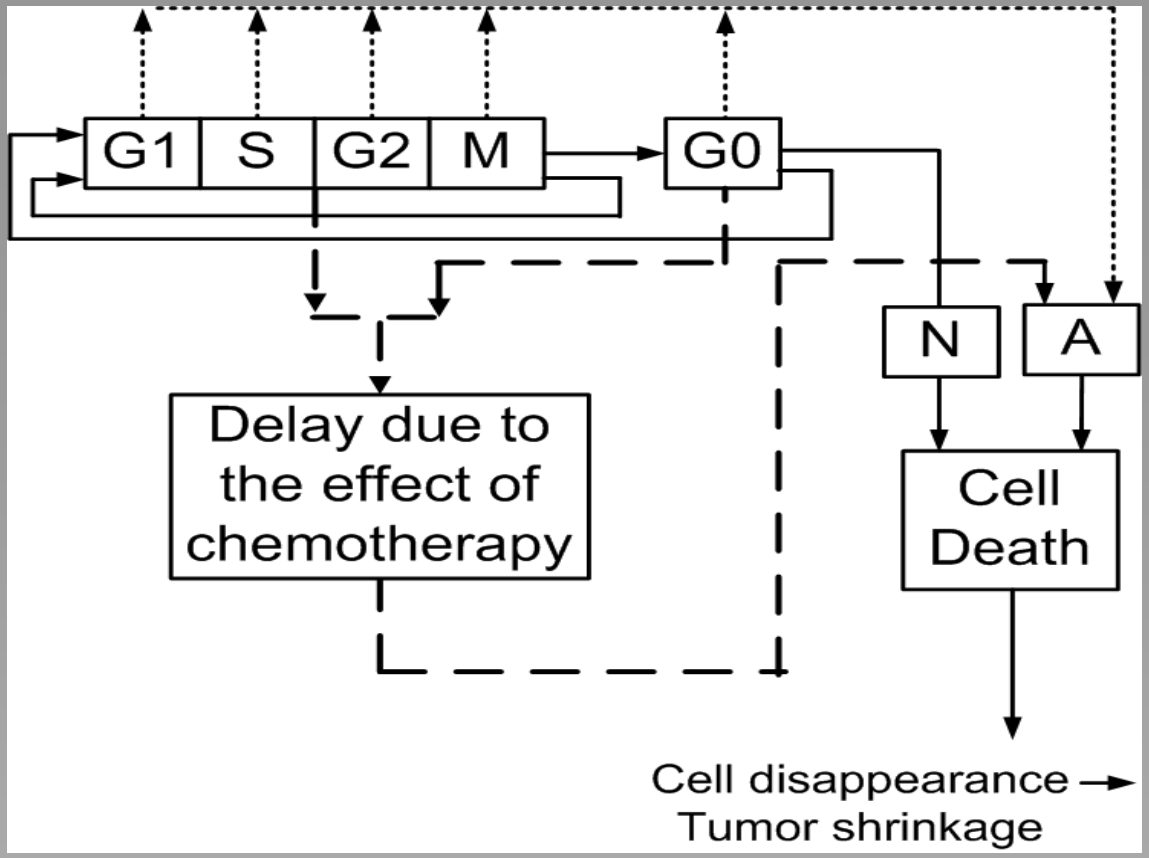


Total number of tumour cells (proliferating, dormant and dead cells) as a function of time for the hyperfractionated (1.2 Gy twice daily, 5 days per week to the dose of 76.8 Gy, "HF-76.8") and **accelerated hyperfractionated** (1.6 Gy twice daily, 5 days per week to the dose of 48 Gy, "AHF-48") **radiotherapy schedules.** Irradiation starts on the first day of the first week. HF-76.8 is completed on day 44 after initiation of treatment whereas AHF-48 is completed on day 19. Both irradiation schedules start on the first day of the first week of treatment.

[see G. S. Stamatakos, V.P. Antipas, N. K. Uzunoglu, R. G. Dale, "A four dimensional computer simulation model of the *in vivo* response to radiotherapy of glioblastoma multiforme: studies on the effect of clonogenic cell density." *British Journal of Radiology*, 2006, vol. 79, 389-400 [http://bjr.birjournals.org/cgi/content/abstract/79/941/389].]

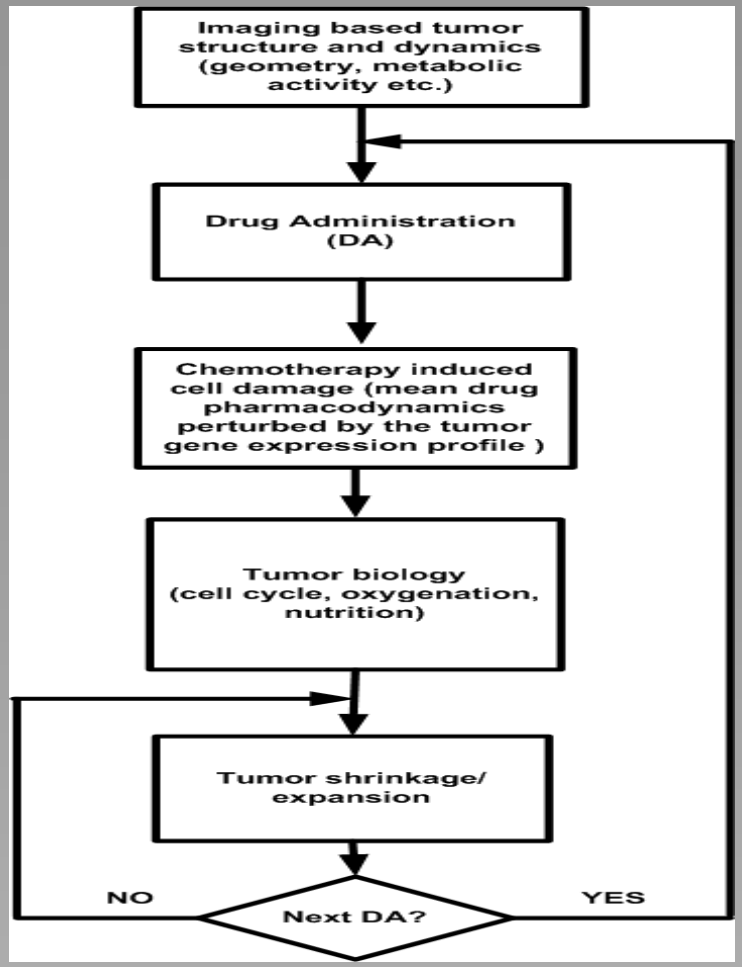
Simulation predictions **agree** with the outcome of the **Radiation Therapy Oncology Group (RTOG) Study 83-02**.

[see G. S. Stamatakos, V.P. Antipas, N. K. Uzunoglu, R. G. Dale, "A four dimensional computer simulation model of the *in vivo* response to radiotherapy of glioblastoma multiforme: studies on the effect of clonogenic cell density." *British Journal of Radiology*, 2006, vol. 79, 389-400 [http://bjr.birjournals.org/cgi/content/abstract/79/941/389].]



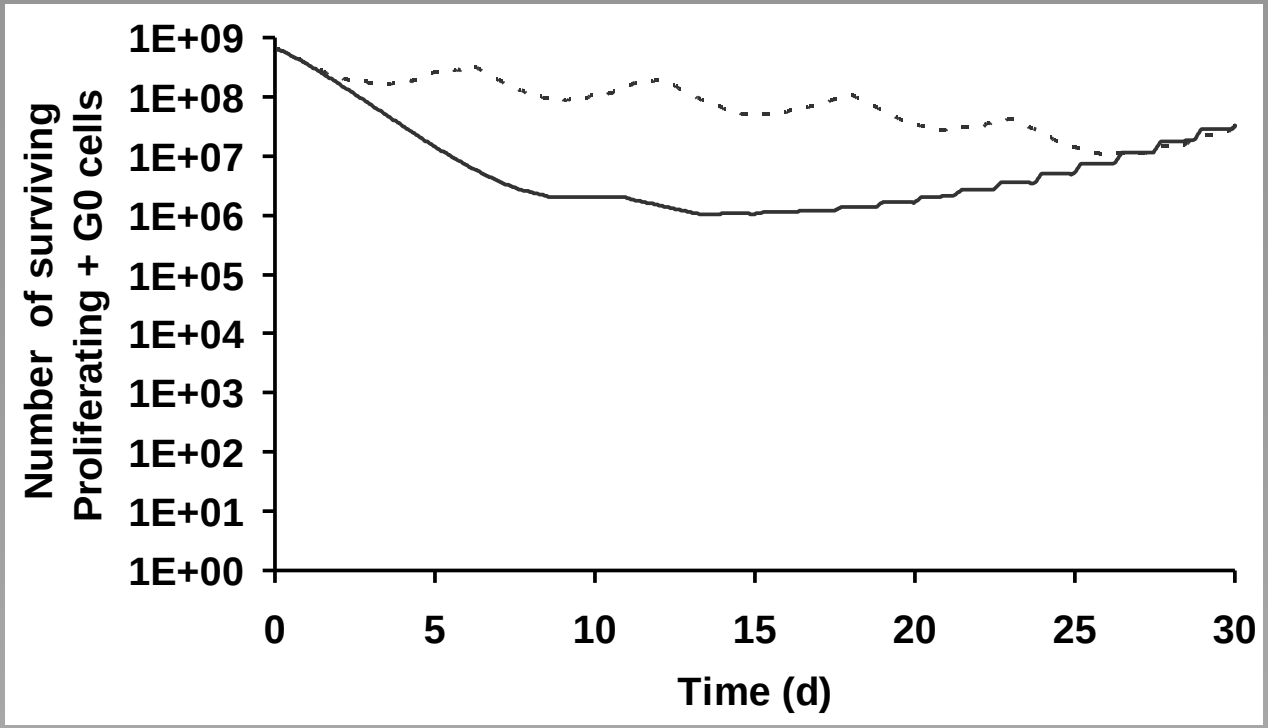
A simplified cytokinetic model of a tumour cell. *Symbol explanation*: G1: G1 phase; S: DNA synthesis phase; G2: G2 phase; G0: G0 phase; N: necrosis; A: apoptosis. The cytotoxicity produced by **TMZ** is primarily modeled by a delay in the S phase compartment (TDS) ("Delay due to the effect of chemotherapy" in the diagram) and subsequent apoptosis. The *delay box* simply represents the time corresponding to at most two cell divisions being required before the emergence of temozolomide cytotoxicity. It is not a time interval additional to the times represented by the cell cycle phase boxes.

[see G. S. Stamatakos, V. P.Antipas, and N. K. Uzunoglu, "A spatiotemporal, patient individualized simulation model of solid tumor response to chemotherapy *in vivo*: the paradigm of glioblastoma multiforme treated by temozolomide" *IEEE Transactions on Biomedical Engineering*, Vol. 53, No 8, pp.1467-1477, August 2006]



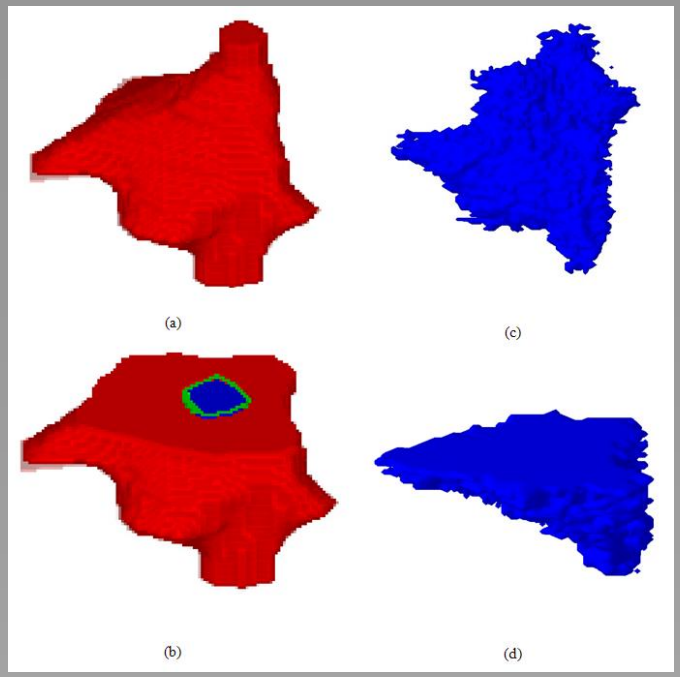
A simplified flowchart of the proposed chemotherapy simulation algorithm. Following introduction of the baseline **tumour structure** and **metabolic activity** data and the **drug administration schedule**, simulation of the various response stages takes place as shown in the flowchart.

[see G. S. Stamatakos, V. P.Antipas, and N. K. Uzunoglu, "A spatiotemporal, patient individualized simulation model of solid tumor response to chemotherapy *in vivo*: the paradigm of glioblastoma multiforme treated by temozolomide" *IEEE Transactions on Biomedical Engineering*, Vol. 53, No 8, pp. 1467-1477, August 2006]



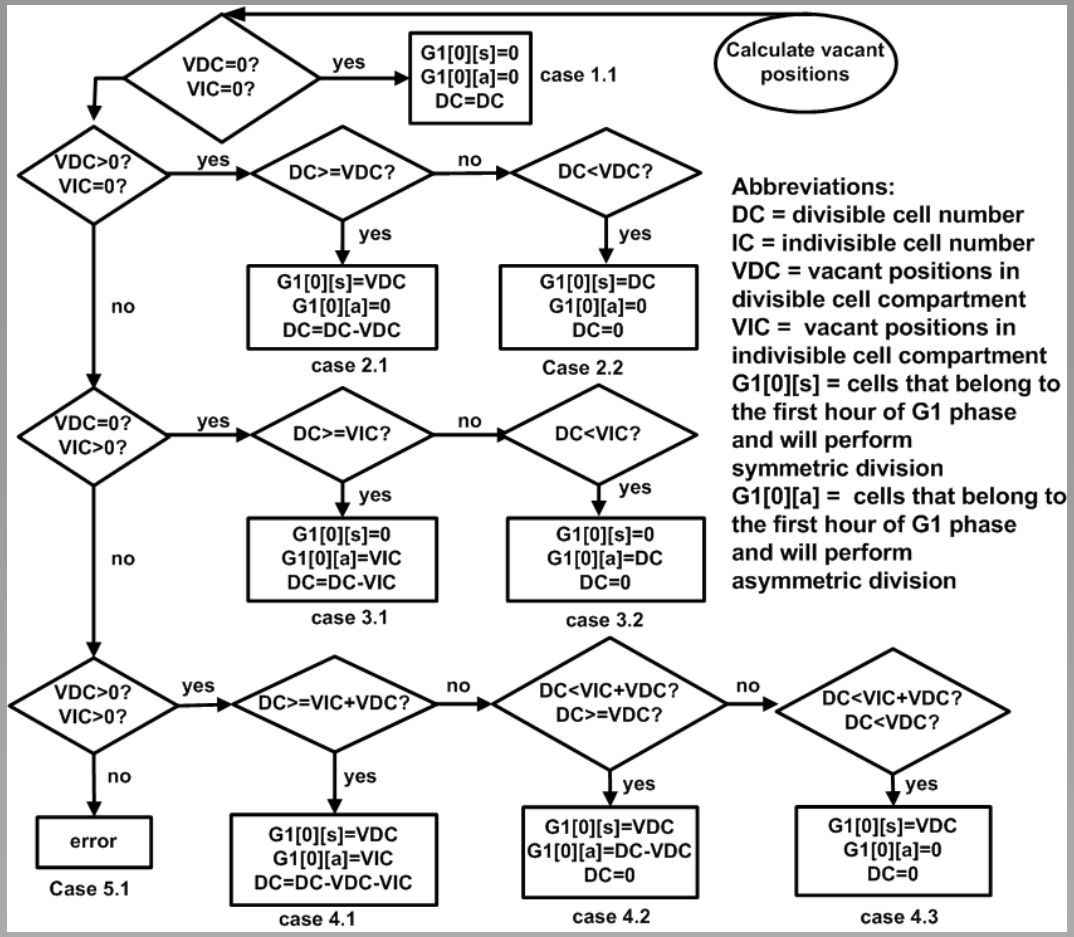
Number of surviving (metabolically living) proliferating and dormant (G0) tumour cells corresponding to the particular GBM tumour considered as a function of time. TMZ is administered according to fractionation **scheme A** (solid line) or **B** (dashed line) (see previous figure). Each chemotherapy fraction corresponds to **150mg/m²**. The cell cycle has been assumed equal to Tc=30h and the mean clonogenic cell density equal to CCD = 10^4 cells/mm^3 (clonogenic cell density in the *proliferating cell layer* = 2×10^4 cells/mm^3). Only one chemotherapy cycle per scheme has been simulated.

[see G. S. Stamatakos, V. P.Antipas, and N. K. Uzunoglu, "A spatiotemporal, patient individualized simulation model of solid tumor response to chemotherapy *in vivo*: the paradigm of glioblastoma multiforme treated by temozolomide", *IEEE Transactions on Biomedical Engineering*, Vol. 53, No 8, pp.1467-1477 , August 2006]



Three dimensional visualization of the simulated response of a clinical glioblastoma multiforme tumour to 1 cycle of chemotherapeutic scheme (**150 mg/m²** orally once daily for 5 consecutive days per 28-day treatment cycle, (fractionation scheme A)). (a) External surface of the tumour before the beginning of chemotherapy, (b) internal structure of the tumour before the beginning of chemotherapy, (c) external surface of the tumour 20 days after the beginning of chemotherapy (d) internal structure of the tumour 20 days after the beginning of chemotherapy. Pseudocolor Code: red: proliferating cell layer, green: dormant cell layer (G0), blue: dead cell layer. The following "99.8%"criterion has been devised and applied: "For a geometrical cell of the discretizing mesh, if the percentage of dead cells within it is lower than 99.8% then {if percentage of proliferating cells > percentage of G0 cells, then paint the geometrical cell red (proliferating cell layer), else paint the geometrical cell green (G0 cell layer) } else paint the geometrical cell blue (dead cell layer)"

[see G. S. Stamatakos, V. P.Antipas, and N. K. Uzunoglu, "A spatiotemporal, patient individualized simulation model of solid tumor response to chemotherapy *in vivo*: the paradigm of glioblastoma multiforme treated by temozolomide", *IEEE Transactions on Biomedical Engineering*, Vol. 53, No 8, pp.1467-1477 , August 2006]



An oversimplified flowchart of the possible decisions that can be made by the normal tissue response simulation system concerning the transitions among its various states. Every cell that dies creates a vacant position. When there is demand for functional cells caused by apoptosis or lysis the vacant position stimulates the divisible functional compartment to leave the resting phase G0 and to pass over to the cell cycle.

[see V.Antipas, G.Stamatakos, N.Uzunoglu, "A patient-specific *in vivo* tumor and **normal tissue** model for prediction of the response to radiotherapy," ***Methods Inf Med*** 6/2006, 45: (*in press*)

ACGT

Advancing Clinicogenomic Trials on Cancer:

Open Grid Services for Improving Medical Knowledge Discovery

a European Commission funded 4 year integrated project
(FP6-2005-IST-026996)
Start date: 1 February 2006

http://www.eu-acgt.org

WORKPACKAGE 8

Technologies and Tools for In Silico Oncology

WP Leader: Institute of Communication and Computer Systems,
In Silico Oncology Group, National Technical University of Athens
(Dr Georgios Stamatakos, gestam@central.ntua.gr)

Clinical adaptation, optimization and validation of the ACGT “Oncosimulator”

Pertinent clinical, imaging, histopathologic and molecular data in conjunction with the ACGT conventional clinical trials are exploited in order to validate the ACGT “Oncosimulator” constituent models both prospectively and retrospectively.

More specifically, the corresponding *in silico* oncology trial is based on the **nephroblastoma SIOP 2001/GPOH trial** for which the **University Hospital of Saarland,Paediatric Haematology and Oncology, Homburg, Germany** (Professor Norbert Graf, Norbert.Graf@uniklinikum-saarland.de) is responsible

and the **epirubicin breast cancer TOP trial**, for which the **Institut Jules Bordet, Centre des Tumeurs** (Dr Christine Desmedt, christine.desmedt@bordet.be), Brussels, **Belgium** is responsible.

Both these trials have been considerably enhanced in terms of data collection in order to meet the remarkably high demands of the *in silico* trial.

The whole effort is also scientifically supported by the **Center for the Development of a Virtual Tumor (CViT)** (External ACGT Advisor: T. Deisboeck DEISBOEC@HELIX.MGH.HARVARD.EDU, CViT Ask the Expert Forum)

WHAT COULD BE AVAILABLE TO CViT

As the ACGT end product will follow the *Open Access* policy, the *clinically validated* and *optimized* ACGT "Oncosimulator" software will be accessible from CViT as well as from a large number of other entities.

Thank you

Ευχαριστώ