POSTGRADUATE SUBJECT TITLE

Multiscale Cancer Modelling and *In Silico* Medicine (MSCM & *IS*M)

PROPOSED BY

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APPROVED TO BE TAUGHT BY THE PROPOSER IN

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BASIC TEXTBOOK

Multiscale Cancer Modeling, T. Deisboeck and G. Stamatakos Eds, CRC Press, Boca Raton, FL , USA, 2011. http://www.crcnetbase.com/isbn/9781439814420 - to be denoted as "TEXTBOOK"

ADDITIONAL MATERIAL

VPH2012 – Integrative Approaches to Computational Biomedicine
(Proceedings of the Virtual Physiological Human Conference, London 2012) – to be denoted as "PROCEEDINGS"

CONTENTS

CHAPTER NUMBER	CHAPTER TITLE	CONTENTS	REFERENCES TO THE TEXBOOK AND OTHER INDICATIVE SOURCES
1.	Introduction to Multi-scale Disease Modelling (MSDM) and In *Silico* Medicine (*IS*M) The paradigm of Multi-scale Cancer Modelling (MSCM) and *In Silico* Oncology (*IS*O)	Definitions. Clinical, scientific and technological framework. Necessity and prospects of MSDM / MSCM and *IS*M/*IS*O. Historical aspects. Importance of the subject for the electrical and computer engineer. Contents outline.	PROCEEDINGS TEXTBOOK - Preface PAPER_A [G. Stamatakos, D. Dionysiou, A. Lunzer, R. Belleman, E. Kolokotroni, E. Georgiadi, M. Erdt, J. Pukacki, S. Rueping, S.Giatili, A. d' Onofrio, S. Sfakianakis, K. Marias, Ch. Desmedt, M. Tsiknakis and N. Graf, "The Technologically Integrated Oncosimulator: Combining multiscale cancer modeling with information technology in the *in silico* oncology context," IEEE J. Biomedical and Health Informatics (retitled from the

			IEEE Transactions on Information Technology in Biomedicine) Vol. 18, No. 3, May 2014, pp. 840-854. DOI: 10.1109/JBHI.2013.2284276
2.	*I*SM/*I*SO: Fundamental science aspects	Fundamentals of MSDM. The paradigm of cancer. Examples from the cardiovascular, the musculoskeletal, the immune and other body systems. The "*summarize and jump*" principle. Basic categories of normal physiology and disease models. Classes of mathematical methods (discrete/continuous, deterministic/stochastic, mechanistic/machine learning etc.) Examples of tumour classes and types to be addressed (non small cell lung cancer, breast cancer, glioblastoma multiforme, nephroblastoma, cervix cancer, acute lymphoblastic leukemia.) Patient individualized treatment optimization through experimentation *in silico* (i.e. on the computer.) The Oncosimulator. Multidimensional spaces. The hypermatrix of the anatomic region of interest. Operators of basic biological mechanisms. Use of discrete mathematics concepts and tools (finite state machines, cellular automata, Monte Carlo technique, cell clustering into equivalence classes, dedicated algorithms etc.) Discrete Entity – Discrete Event Simulation.	TEXTBOOK - Chapter 18 PAPER_B [G. Stamatakos, E. Kolokotroni, D. Dionysiou, E. Georgiadi, C. Desmedt, "An advanced discrete state–discrete event multiscale simulation model of the response of a solid tumor to chemotherapy: Mimicking a clinical study," Journal of Theoretical Biology 266 (2010) 124–13] PROCEEDINGS

		Use of continuous mathematics concepts and tools (ordinary differential equations, partial differential equations, integral equations etc.) Four dimensional multiscale simulation of tumour growth *in vivo.* Four dimensional multiscale simulation of the response of solid malignant tumours to classical therapeutic modalities (chemotherapy, external radiation therapy, brachytherapy) *in vivo*. Computer simulation of the development of leukemias and their response to therapeutic modalities. Computer simulation of the response of malignant tumours to new/targeted therapeutic methods (immunotherapy, antiangiogenetic treatment etc.) Computer simulation of normal tissuesto treatment modalities. Development of semantic metamodels and hypermodels in the cancer and *in silico* oncology domains. **Analogies with and extensions to other diseases in the generic *IS*M context**.	
3.	*IS*M/*IS*O: Technological aspects	Architecture of the technologically integrated Oncosimulator. Workflow design systems. High performance computer systems and platforms. Automated scenarios for biosimulation execution. Preprocessing of multiscale	TEXTBOOK - Chapter 18 PAPER_A (see above) PROCEEDINGS

		data (imaging, histological, molecular, clinical, treatment schedule data etc.) Anonymization and pseudonymization of clinical data. Ethical and legal aspects and related technologies. Repositories of multiscale clinical data, models and model predictions. Visualization of the multiscale predictions of the Oncosimulator. Systems for the analysis of the predictions and the behaviour of the Oncosimulator. Oncosimulator integrative technologies. Portals. **Analogies with and extensions to other diseases in the generic *IS*M context**.	
4.	*IS*I/*IS*O: Clinical requirements and clinical application aspects	Clinical questions as drivers for the Oncosimulator development. Principles and processes for the clinical adaptation and validation of Oncosimulators. Clinical trials as sources of multiscale data for the clinical adaptation and validation of Oncosimulators. Biobanks and related technologies. Clinical prerequisites for the translation of multiscale models and Oncosimulators into clinical practice. **Analogies with and extensions to other diseases in the generic *IS*M context.**	TEXTBOOK - Chapter 19 PROCEEDINGS
5.	Mathematical model formulation of clinical tumour invasion using the non linear partial differential	The case of glioma (including glioblastoma multiforme.) Non invasive estimation of the kinetic parameters of glioma *in vivo*. Mathematical	TEXTBOOK - Chapter 16 TEXTBOOK - Chapter 17 PROCEEDINGS

	equation of diffusion-reaction with pertinent boundary conditions. **Related mathematical and computational problems in the generic *IS*M.**	description of parameter estimation. Anisotropic tumour cell movement within inhomogeneous brain tissue. Estimation of tumour necrosis and regrowth using pertinent mathematical parameters. Estimation of the effect of the microenvironment on glioma growth by comparing MRI and PET tomographic images. **Analogies with and extensions to other diseases in the generic *IS*M context.**	
6.	Numerical methods for the solution of the spatiotemporal problem of tumour invasion into normal tissues including an explicit consideration of the boundary conditions. **Related mathematical and computational problems in the generic *IS*M.**	Finite Difference – Time Domain (FDTD) techniques. Application of the Crank-Nicolson technique in conjunction with the conjugate gradient method for the numerical solution of the partial differential equation (PDE) of reaction-diffusion during glioma growth and infiltration into normal brain tissue. Numerical application of the boundary Neumann conditions between skull and intracranial tissues. Exploitation of the results for the patient individualized radiation treatment planning. Glioma biomechanics using numerical methods such as the Finite Element Method (FEM.) **Analogies with and extensions to other diseases in the generic ISM context.**	PAPER_C [S. Giatili and G. Stamatakos, “A detailed numerical treatment of the boundary conditions imposed by the skull on a diffusion–reaction model of glioma tumor growth. Clinical validation aspects,” Applied Mathematics and Computation 218(2012) pp. 8779-8799] PROCEEDINGS

7.	Modelling and simulation of angiogenesis during tumour growth. **Related mathematical and computational problems in the generic *IS*M.**	Tumour- microenvironment interaction. Partial differential equation for the description of angiogenesis. Blood flow and capillary blood vessel network formation. Adaptation and restructuring of the capillary vessel network. Numerical solution methods. Computational exploration of the angiogenesis phenomenon and the basic factors they affect its course. **Analogies with and extensions to other diseases in the generic *IS*M context.**	TEXTBOOK - Chapter 13 PROCEEDINGS
8.	Modelling and simulation of molecular interactions, molecular pathways, molecular signal transmission and the resulting behaviour of the cancer cell. **Related mathematical and computational problems in the generic *IS*M.**	Molecular simulations at the atomistic level based on the Newton's and Coulomb's laws and quantum mechanics principles. Molecular binding models. Drug molecule – protein interaction simulations in oncology. Molecular dynamics methods for the characterization of the structural properties of mutated gene products. Use of ordinary differential equations for the description of oncogenetic and general networks and pathways of molecular signalling and interaction. Resulting behaviour of the tumour cell. **Analogies with and extensions to other diseases in the generic ISM context.**	TEXTBOOK - Chapter 2 PROCEEDINGS