The ContraCancrum *Oncosimulator*: Integrating Biomechanisms Across Scales in the Clinical Context

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***Abstract*— This short communication briefly outlines the major components and the integration steps of the *Oncosimulator* that is being developed within the framework of the European Commission funded ContraCancrum project. The *Oncosimulator* is a technologically advanced multiscale tumor growth and treatment response system aiming at supporting patient individualized treatment decisions. An indicative example of the adopted mathematical approaches as well as a simple example of numerical code validation are provided. The document concludes with a short discussion on the characteristics of the major modeling approaches that refer to the cellular and higher biocomplexity levels since the latter constitute the basis for the entire *Oncosimulator* integration.**

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I. Introduction

THE accelerated accumulation of important experimental and clinical data as well as biological and medical knowledge pertaining to the *natural phenomenon* of cancer renders quantitative integration over many scales of biocomplexity a pressing necessity. Specially designed mathematical and computational models and systems appear to constitute the only rational way to respond to this need. The long term goal of model and related system development is to optimize treatment in the patient individualized context by exploiting quantitative understanding of cancer in conjunction with the exploitation of available multiscale biodata. Obviously, a strict and lengthy clinical adaptation and validation process is an inelastic prerequisite for the eventual clinical translation of such models and systems. Within this framework the European Commission funded project ContraCancrum (contracancrum.eu) includes the development of an integrated multiscale malignant tumor simulator (*Oncosimulator*) able to simulate tumor growth and response to treatment across biocomplexity scales. Glioblastoma multiforme and lung cancer are addressed as two tumor paradigms.

Regarding the mathematical approaches adopted on the cellular and higher biocomplexity levels the following decisions have been taken. Diffusive tumor growth is addressed primarily via a diffusion equation based

continuous description which is transformed into an algebraically solvable finite difference or finite element formulation. On the other hand tumor response to treatment is addressed primarily via a discrete entity – discrete event formulation.

This document provides a brief outline of the *Oncosimulator* components and the integration policy adopted. It also briefly outlines an elementary problem addressed which is nevertheless indicative of the many stages of model development. The short communication concludes with a brief discussion on the characteristics of the major modeling approaches that refer to the cellular and higher biocomplexity levels since the latter constitute the basis for the entire Oncosimulator integration.

II. A Brief Outline of the Oncosimulator Component Integration Strategy

The following indicative biomodels are currently under integration yet at a varying level of mutual linkage:

i. Patient specific chemotherapy drug targeting (e.g. interactions between ligand/inhibitor and receptor tyrosine kinases in gliomas and lung cancer). Molecular dynamics simulations.
ii. Molecular interdependence networks for cell survival probabilities
iii. Non imageable tumor growth
iv. Angiogenesis
v. Invasion via cell diffusion
vi. Imageable tumor growth
vii. Tumor response to chemotherapy, radiotherapy and radio-chemotherapy
viii. Tumor and normal tissue biomechanics
ix. Macroscopic image analysis of the anatomic region of interest
x. Consideration of treatment limitations imposed by normal tissue toxicities induced by candidate treatment schemes and / or schedules.

Elementary model integration is heavily based on the *top-down*, discrete entity – discrete event multiscale cancer modeling approach [1-10] since it provides great flexibility which is crucial to achieve that goal .

The adopted sequence of the major integration steps is the following:

a. Fusion of the **T**umor growth and treatment response models with the respective **B**iomechanical models to produce the *TB integrator*
b. Fusion of the *TB integrator* with the **I**mage analysis module to produce the *TBI integrator*
c. Fusion of the affected **N**ormal tissue module with the *TBI integrator* to produce the *TBIN integrator*
d. Fusion of the **M**olecular simulations and networks module with the *TN integrator* to produce the *TBINM integrator*
e. Logical and technical testing and optimization of the integrated simulation system before undergoing clinical adaptation and validation.

In order to integrate biological mechanisms acting on different biocomplexity scales (levels) the *summarize and jump* strategy delineated in [9] has been adopted.

III. Introduction to One of the Mathematical Approaches Adopted

As an example of the mathematical approaches adopted the diffusion equation based treatment is briefly outlined. In the continuum context tumor growth can be approximately expressed by the following differential equation [11,12] formulated in words as:

Rate of change of tumor cell population= diffusion (motility) of tumor cells + net proliferation of tumor cells - loss of tumor cells due to treatment

and the appropriate boundary conditions.

Using standard mathematical symbols the previous statement takes the following form:

$$\left\{\begin{array}{l} \dfrac{\partial c}{\partial t} = \nabla (D \nabla c) + \rho c - G(t)c \quad in\ R \\ c(\mathbf{x},0) = f(\mathbf{x}), \quad initial\ condition \\ \mathbf{n} \cdot D \nabla c = 0 \quad on \quad \partial R, \quad boundary\ condition \end{array}\right\} \tag{1}$$

The variable c denotes the cell concentration at any spatial point and time t. The parameter D denotes the diffusion coefficient and represents the active motility of tumor cells. The term ρ denotes the net rate of tumor growth including proliferation, loss and death. $G(t)$ accounts for the temporal profile of treatment such as radiotherapy and/or chemotherapy. $\mathbf{n}$ is the unit normal to the boundary ∂R of the domain R and f is a known function. In the mathematical model implemented as a first approximation $G(t)=k$ is constant. To solve the above equation and boundary condition system several methods such as the Crank Nicholson technique in conjunction with the conjugate gradient solver have been applied.

IV. Indicative Intermediate Investigational Results

The following simple problem can be viewed as a typical example of the many developmental and exploratory stages of the *Oncosimulator* construction. In order to check an implementation of the Crank-Nicholson numerical scheme used in conjunction with the conjugate gradient method for the solution of the diffusion equation for glioma growth [11,12], a simple *artificial* problem has been defined and solved. Equation (1) has been solved for the cubic region (7 cm x 7 cm x 7 cm, x = 7 cm) with diffusion coefficient D = 0.0065 cm^2/day, time step dt = 1 sec, dx = 0.1 cm,

growth rate = 0.012 units/day and loss rate = 0.0013 units/day. The initial shape of the tumor has been a sphere of radius=0.2 cm and cell density 35000 tumor cells per mm^3. Cell density falls abruptly to zero outside the sphere (which is a biologically unrealistic scenario). Skull bone has been assumed to lie on the boundaries of the cubic mesh (boundary conditions). Skull bone does not practically allow glioma cells to be diffused through it. Execution of the simulation code for a time interval equal to 90 days has been performed. The tumor cell concentration as a function of time is presented on day 45 and day 90 (Fig.1). The predictions are in agreement with the diffusion aspects of the problem provided that the rate values are taken into account. It should be stressed, however, that the artificial problem outlined so far has been designed only to facilitate mathematical validation of the corresponding code and by no means as a representation of the complete glioblastoma invasion problem.

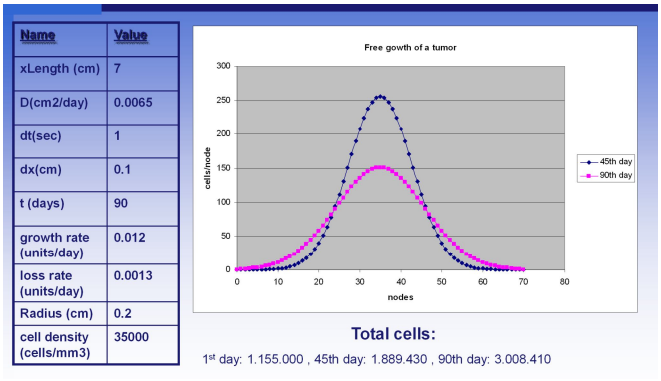

Fig.1 Tumor cell concentration (initial spherical tumor cell density = 35000 cells/ mm^3)

V. DISCUSSION

Due to the wide scope of the ContraCancrum *Oncosimulator* system, several modeling approaches have been adopted. Referring to the cellular and higher biocomplexity levels which provide the matrix for the overall *Oncosimulator* integration, two major *cancer modeling schools* can be identified. The *continuous entity based formulation school* (having the diffusion equation at its core (in practice in a *finitized* form)) and the *discrete entity - discrete event formulation school* (dealing with purely discrete notions such as proliferative potential cell categories, cell cycle phases, cycling or non cycling cell states etc.). Both intuition and research experience suggest that none of the formulations can perform equally efficiently when dealing with (a) markedly diffusive tumor growth and (b) tumor response to treatment. The continuous entity based formulation has shown to be better positioned in answering questions of the type "*what is the real spatial extent and the actual concentration profile of a glioblastoma tumor within the brain (including both imageable and non imageable components) ?*" On the other hand the discrete entity – discrete event formulation has shown to be better positioned in answering questions of the type "*what will spatiotemporally be the biological constitution of a tomograhically, histopathologically and molecularly characterized tumor following administration of a chemotherapeutic cycle of a given drug?*". Therefore, care should be taken in formulating the questions to be addressed by mathematical and computer modeling before proceeding to the formulation of the modeling approach.

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