



3D MODELING OF TUMOR GROWTH

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Abstract — This paper briefly describes a numerical model of avascular solid tumors that has recently been developed in Trieste and Verona. The model includes a mathematical description of the cell metabolism and of the cell cycle and includes the cells' biomechanics. The model has been successfully validated with experimental data. The resulting software may be used to perform in-silico tests, and can be further upgraded in a modular way.

Index Terms — tumor growth model, C++, physicochemical modeling, numerical simulation

1 BACKGROUND

In the last decades different mathematical models of tumor growth have been developed. These models manage the biological complexity by picking different simplifying hypothesis and structural assumptions. Here we illustrate a numerical model of tumor spheroids where cells are represented as soft spheres that interact with one another and with the environment by exchanging nutrients, exerting cell-cell forces and moving freely in a 3-dimensional space (see Fig 1.)

2 OBJECTIVES

The model has been developed to study tumors in the pre-diagnostic stage, where the diameter is

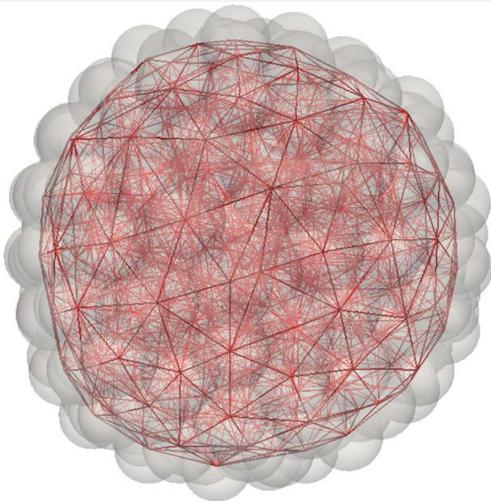


Figure 1: Simulated cell aggregate with the underlying disordered network of nearest-neighbor links.

Parameter	Value	Reference
tumor cell diameter	~ 16 μm	J.P.Freyer and R.M.Sutherland, <i>Cancer Res.</i> 40 , 3956 (1980)
tumor diameter at the end of the a-vascular phase	~ 2 mm	D.Ribatti, A.Vacca and F.Dammacco, <i>Neoplasia</i> 1 , 293 (1999)
tumor diameter at diagnosis (breast carcinoma)	~ 2 cm	U.Güth et al. <i>Cancer Epidemiol.</i> 32 , 224 (2008)
tumor diameter at death (90% patients with breast carcinoma)	~ 10 cm	J.S.Michaelson et al. <i>Cancer Res.</i> 115 , 5095 (2009)
tumor doubling time (human carcinomas)	~ 100 days	E.Mehrara et al. <i>Cancer Res.</i> 67 , 3970 (2007)

Figure 2: Tumor progression phases. Our mathematical model is related to the pre-diagnosis tumor, in particular before angiogenesis has occurred.

typically smaller than 2 mm and the tumor is avascular (Fig. 2). Interestingly, almost all of a tumor's lifetime is spent in this pre-diagnostic stage. Therefore a deeper understanding of tumor evolution at this early stage can provide important insights in our fight against cancer.

3 APPROACH & METHODS

General approach

There are different modeling strategies to simulate a tumor growth: we use a “bottom-up” approach that starts at the single-cell level. Individual cells exchange nutrients with the environment and utilize them according to specific pathways modeled by reaction-diffusion equations. Inside each cell nutrients can either be stored into ATP and other molecules, or directly participate to metabolic and other pathways. A small but effective set of molecular pathways were studied independently and included in the model. The absorption of nutrients drives cell growth and proliferation. The biomechanics of cells includes volume growth, mitosis and realistic cell-cell forces. Cell aggregates can be simulated as they grow and their shape evolves as a result of volume growth, and of the continuous cell proliferation. Simulations have been carried out up to a total of 1.5 million cells.

Methods

The model includes both deterministic and stochastic steps. The reaction-diffusion part is described – in the present version of the program – by 25 nonlinear differential equations/cell. The resulting differential system is stiff, and it spans at least 3 orders of magnitude in space and over 12 orders of magnitude in time. The differential equation solver is robust and was implemented as a part of simulation program. The program is written in C++, and utilizes several high level libraries like Boost and CGAL, and it also includes OpenMP preprocessor directives to parallelize the code and reduce execution time.

4 RESULTS

The results of the simulations performed with the present version of the simulation program have shown that the model is robust and provides data and information that match experiments, i.e. reproducibility of the experimental growth curve, distribution of live cells, oxygen and glucose concentration, see the figures below.

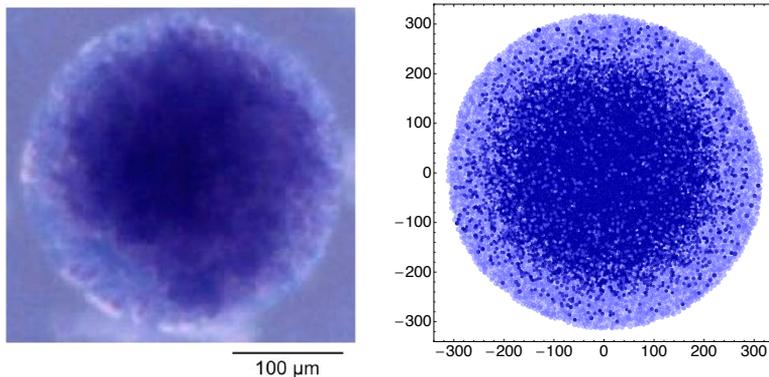


Figure 3: A spheroid grown in vitro from HeLa cell (left) is compared with a simulated spheroid at 450 h of simulated time (right). The darker color marks dead cells, and it is easy to identify the necrotic core. A similar structure is visible in the simulation.

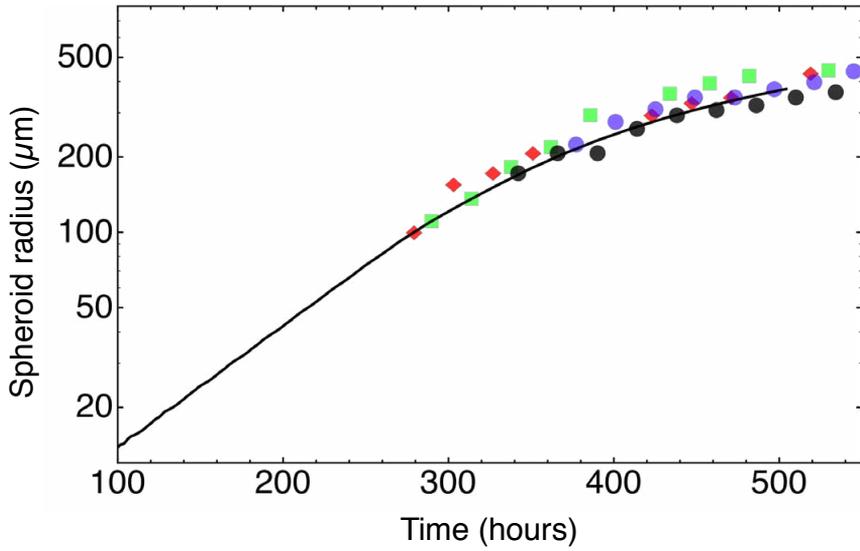


Figure 4: Tumor growth curve: here simulation (solid line) is compared with experiment (colored circles)[1]

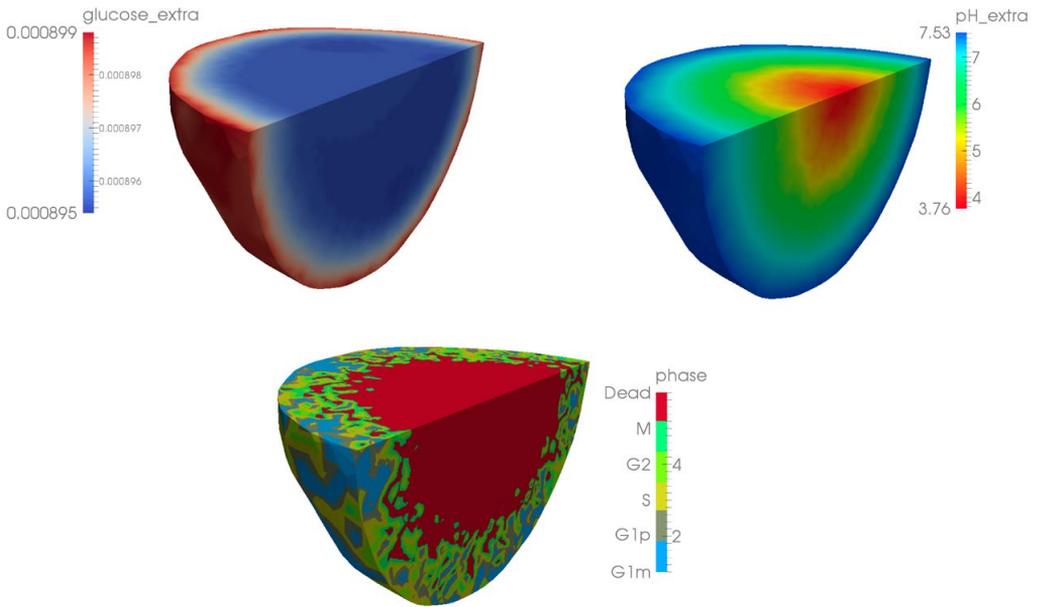


Figure 5: Simulated tumor spheroid sections displaying different dynamical variables. This simulated spheroid has a 300 μm radius, and the different snapshots show: the oxygen concentration (pg/μm³) (left), the cell cycle's phase (center) and the PH value (right).

5 POTENTIAL USEFULNESS OF THE MODEL

The good match between simulation and experiment make our numerical model the basic scaffolding for a virtual biological laboratory, a tool for in-silico experiments. Indeed the model has an incremental structure that allows for the inclusion of additional molecular pathways and processes, to suite to a particular set of biological investigations.

The existing model of the simulation program is already a powerful working prototype, however, at present we are also considering the introduction cytokine mediated cell-cell signaling, in particular by including the tumor necrosis factor (TNF-alpha) cytokine pathways.

REFERENCES

- [1] E. Milotti and R. Chignola. Emergent properties of tumor microenvironment in a real-life model of multicell tumor spheroids. PLoS ONE 5 (2010) e13942
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