Preface [Special issue on Modeling and Simulation of Tumor Development, Treatment and Control]

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Preface

Mathematical modeling and simulation of tumor growth in competition with the immune system is certainly one of the challenging frontiers of applied mathematics. The modeling generally includes also the description of therapeutical actions as well as of experiments related to understanding the complex phenomena related to the above physical systems.

Motivations are undoubtedly strong due to the fact that cancer is still one of the greatest killer in the world. It is true that mathematics cannot solve problems of immunology and medicine. However, it seems that a useful support to experiments and quantitative analysis of external actions to control the neoplastic growth can be developed by applied mathematics. Specifically, models and simulations of particular behaviors of the immune competition can reduce the amount of experiments which are necessary for therapy developments. A final target, an immune-mathematical theory can be developed in order to provide a detailed description of the evolution of the system hopefully focusing phenomena which may be difficult to observe experimentally.

Due to the above motivations, various scientific editions have been proposed over the last ten years. For instance, scientific journals have devoted special issues to publish scientific papers on tumor modeling. Among others, we mention the special issues edited by Bellomo [1], and Chaplain [2,3], as well as the collection of survey papers [4].

It is worth mentioning that modeling, qualitative analysis, and simulations of the physical system we are dealing with often involves quite sophisticated mathematical methods. Eventually, new mathematical structures may be necessary toward a sufficiently detailed description. Therefore, applied mathematicians can find additional motivations by dealing with the above topics.

This special issue reports a number of research papers which deal with different aspects of the mathematical problems which have been outlined above. These papers have been developed within the scientific activities of the European Union research and training network "Using Mathematical Modeling and Computer Simulations to Improve Cancer Therapy". Nevertheless, the interest in the activities is not limited to Europe as it is documented by the institutions of the authors who have contributed to this issue.

The contents of this issue covers three general topics:

(i) modeling cellular phenomena with special attention to the immune competition;
(ii) modeling macroscopic phenomena related to condensed tumors;
(iii) modeling control therapies.

In detail, on the first class of models and problems, the paper by Canetta, Leyrat, and Verdier deals with experiments and modeling the dynamics of cells with special attention to microadhesion phenomena. Particular attention is focused on the adhesion between a functionalised spherical microsphere. Interest in this type of analysis to modeling condensation of tumor cells into solid forms is evident.

The paper by De Angelis, Delitala, Marasco, and Romano deals with a bifurcation analysis

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for a class of integro-differential equations simulating the competition between tumor cells and immune cells in the medium of environmental cells [5]. The analysis is referred to a well-defined therapeutical action: namely the possibility of modifying the ability of neoplastic cells to inhibit the immune cells. The same framework is used by Kolev for a model of immune competition with special attention to the role of antibodies. Also this model is developed by statistical methods analogous to those of the kinetic theory and is expressed in terms of a system of integro-differential equations. The mathematical framework is the one analyzed in [6]. The background framework is the one of immune competition [7].

Particularly interesting is the analysis proposed by Gobron, Saada, and Triolo which deals with the analysis of the links between the microscopic and macroscopic description. The paper analyzes a competition-diffusion system, where populations of healthy and ill cells compete and move on a neutral matrix. Then a coupled system of nonlinear parabolic equations is derived through a scaling procedure from the microscopic, Markovian dynamics. The space dependent solutions show a behavior markedly different from the associated ODE system: for a large class of initial conditions, the asymptotic behavior of the system can be described through the analysis of associated traveling waves.

Referring to modeling macroscopic phenomena, the paper by Drasdo and Höhme proposes a mathematical and computer-based model on avascular tumor spheroids *in-vitro*. The great merit of this paper consists in the direct derivation of the model from experiments. This procedure allows us to link the model parameters to experimental accessible biomechanical and kinetic parameters and provides a potential, at least partly quantitative, description of growing avascular tumors in stages which are not primarily determined by nutrient or oxygen supply. Interesting computer simulations are reported to visualize the formation of morphological patterns which are characteristic for the growth regime of the unperturbated cell assembly before the death process starts. The impact of this type of analysis on medical action is definitively relevant. A similar aim is in the background of the paper by Swanson, Alvord, Jr., and Murray which deals with the analysis of a mathematical model to describe the growth and infiltration of glioma cells throughout an anatomically accurate virtual human brain. The model is based on a proliferation-migration mechanism including the effects of the complex spatial structure and intrinsic heterogeneity of the brain tissue. The model is related to development of therapies, and in particular, on treatment by resection. Macroscopic phenomena are analyzed by Scalerandi, Peggion, Capogrosso, Sansone, and Benati, who analyze cancer growth phenomena related to tumor cords, neoplasms forming cylindrical structures around blood vessels.

Two papers by Foryś and Bodnar analyze the qualitative behaviour of two simple models of solid avascular tumors based on the reaction-diffusion dynamics and mass conservation law which reduce to ordinary differential equations. Both papers analyze the effect of time delay on the qualitative behaviour of solutions. The first paper refers specifically to stability properties of equilibrium solutions, while the second one focuses, in addition to stability analysis, also to existence of periodic solutions. The analysis is related to therapeutical actions.

The last two papers are concerned with control problems for models described by ordinary differential equations. The general framework for modeling is the papers by Perelson and Weisbuch [8], and Hethcote [9]; while the mathematical control theory was initiated by Swan [10]. In detail the paper by de Pillis and Radunskaya refers to a mathematical model of tumor growth with an immune response and chemotherapy. The qualitative analysis of the orbits generates the desired control action. The long-term behavior of an orbit is classified according to the basin of attraction in which it starts. The addition of a drug term to the system can move the solution trajectory into a desirable basin of attraction. It is shown that the solutions of the model with a time-varying drug term approach the solutions of the system without the drug once treatment has stopped. Numerical experiments show that an optimal control therapy is able to drive the system into a desirable basin of attraction, whereas traditional pulsed chemotherapy is not.

The paper by Swierniak, Polanski, Smieja, and Kimmel deals with the analysis of the dynamical properties of models of emergence of resistance of cancer cells to chemotherapy. The model of the process has a form of an infinite system of linear and bilinear state equations. The paper shows that it can be decomposed into two parts: the first one is finite-dimensional bilinear, and the second one is infinite-dimensional linear, coupled by the positive feedback. Then classical results of the theory of feedback systems are used to study the asymptotic properties of the process.

The editors of this special issue hope that the contents of the above articles may be useful to applied mathematicians active in the above research field. Definitively and interesting aspects of the contents is that most papers show an active collaboration with clinicians and molecular biologists. Some of the problems generated by the articles are of great interest also on the level of analytic mathematical problems. So far, the interaction between mathematics and medicine can contribute also to the cultural development of medicine.

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