Mathematical and Computer Modelling 54 (2011) 1989–2006

Contents lists available at ScienceDirect

Mathematical and Computer Modelling

journal homepage: www.elsevier.com/locate/mcm

Studying the growth kinetics of untreated clinical tumors by using an advanced discrete simulation model

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ARTICLE INFO

Article history:
Received 27 November 2010
Received in revised form 3 May 2011
Accepted 3 May 2011

Keywords:
Cancer modeling
Tumor free growth
Tumor kinetics
Exponential tumor growth
In silico oncology

ABSTRACT

Prior to an eventual clinical adaptation and validation of any clinically oriented model, a thorough study of its dynamic behavior is a sine qua non. Such a study can also elucidate aspects of the interplay of the involved biological mechanisms. Toward this goal, the paper focuses on an in-depth investigation of the free growth behavior of a macroscopically homogeneous malignant tumor system, using a discrete model of tumor growth. We demonstrate that when a clinical tumor grows exponentially, the following preconditions must be fulfilled: (a) time- and space-independent tumor dynamics, in terms of the transition rates among the considered cell categories and the duration of the cell cycle phases, and (b) a tumor system in a state of population equilibrium. Moreover, constant tumor dynamics during the simulation are assumed. In order to create a growing tumor, a condition that the model parameters must fulfill has been derived based on an analytical treatment of the model's assumptions. A detailed parametric analysis of the model has been performed, in order to determine the impact and the interdependences of its parameters with focus on the free growth rate and the composition of cell population. Constraining tumor cell kinetics, toward limiting the number of possible solutions (i.e., sets of parameters) to the problem of adaptation to the real macroscopic features of a tumor, is also discussed. After completing all parametric studies and after adapting and validating the model on clinical data, it is envisaged to end up with a reliable tool for supporting clinicians in selecting the most appropriate pattern, extracted from several candidate therapeutic schemes, by exploiting tumor- and patient-specific imaging, molecular and histological data.

1. Introduction

Over the past decades, a considerable effort has been made by the research community to reveal and elucidate the fundamental mechanisms that govern cancer initiation and progression. Despite considerable progress, many biological aspects still remain obscure. The mathematical modeling of tumor growth and response to treatment could serve as a powerful tool for studying cancer in a more systematic way. Models can help to better comprehend the underlying biological processes, verify or discard assumptions about the natural mechanisms involved and guide the next research steps.

The great diversity that characterizes tumors, even those of the same type, creates the need for sophisticated models that encompass biological phenomena on a multiscale basis. A number of models have been proposed in the literature trying to incorporate findings, derived from cumulative experimental or clinical observations and knowledge, regarding mechanisms such as cell cycling, quiescence, differentiation, loss, as well as avascular and vascular phases of growth, angiogenesis, tumor

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doi:10.1016/j.mcm.2011.05.007

interaction with the surrounding tissue(s), invasion and metastasis. Simulation models can be categorized into two main groups: predominantly continuous and predominantly discrete.

The simplest and earliest predominantly continuous models introduced to describe tumor growth are based on the laws of exponential or Gompertzian growth [1,2]. Corrective factors have been proposed to account for the presence of cell heterogeneity within the tumor, in respect to proliferation rate, cell loss, quiescence and differentiation [3–5]. More sophisticated modeling approaches are based on a closed system of partial differential equations. The principle upon which these models are built is that the growth of a tumor is regulated by the diffusion of growth factors [6] and various nutrients [7–10] within the tumor region. Transport/mass conservation equations are utilized, in order to describe the interaction mechanisms between the tumor and the nutrient molecules, with glucose and oxygen being the most representative ones. Variations of the diffusion–reaction equation have also been proposed by taking into account the surrounding tissue heterogeneity and anisotropy [11]. Moreover, partial differential equations have been applied to describe the invasion of tumor cells into the surrounding tissue(s) [9,12–15], as well as tumor-induced angiogenesis [16]. The system is typically solved numerically, for example using finite difference methods, such as the Crank–Nicholson method, unless some approximations or simplifications enable the derivation of analytical solutions. Traveling-wave solutions have also been recruited [17,18].

Models based on predominantly discrete mathematics rely primarily on the use of cellular automata, which may correspond to an individual cell or a cluster of cells, evolving in discrete space and time [19–29]. Cellular automata facilitate incorporation of heterogeneous populations of cells and modeling of intracellular dynamics by means of several discrete states in which cells may be found (e.g. cell cycle phases, stem cell state, etc.). Rules based on several possible "decision calculators", such as cytokinetic diagrams, agent-based techniques, etc., govern transitions between these states (e.g. cell necrosis following a prolonged residence of a tumor cell in the $G0$ phase, etc.). Apart from cellular automata, other discrete approaches can also be found in the literature, such as lattice Boltzmann methods [30,31] and techniques based on stochastic mathematics [32,33].

Prior to an eventual use in the clinical context, any clinically oriented simulation model must undergo a thorough adaptation, validation and optimization procedure. The first step would be an exhaustive examination of model behavior with respect to the variation of its input parameters. Such a study is essential for model parameters' adaptation and plausible value range identification, in order to guarantee a biologically relevant virtual tumor behavior. Furthermore, aspects of the interplay and possible interdependences of the biological mechanisms modeled, which often cannot be grasped intuitively, can be enlightened and biological experimental observations can be deciphered.

In the present paper, a clinically oriented, multiscale, spatiotemporal simulation model of solid tumor free growth has been investigated. Even though the full model [34,35] includes the simulation of the spatiotemporal evolution of a cancerous system under chemotherapeutic treatment, an analysis focusing only on free growth behavior is essential since free growth takes place prior to treatment initiation, as well as between drug administration instances. Compared to previous publications [34,35], a thorough, systematic and in-depth parametric analysis, covering all model parameters that affect tumor free growth kinetics, is presented. The model core stems from previous work of the *In Silico* Oncology Group, ICCS, National Technical University of Athens [21–27] and its advancements are substantiated by (a) the explicit distinction of proliferating cells into stem cells and cells of limited mitotic potential, and (b) the adaptation of the initial cell composition of the tumor to the cell category/phase transition rates and the duration of the various cell phases (the rationale is discussed in subsequent paragraphs). The model addresses tumors well beyond their initiation phase and aims at simulating their spatiotemporal evolution. It has been designed to incorporate patient-specific data such as imaging-based, histopathological, molecular and treatment data.

The structure of the paper is as follows. In Section 2, a brief outline of the model is given, emphasizing on the developed cytokinetic diagram for free growth. Continuing, in Section 3, the behavior of a macroscopically homogeneous tumor under free growth is discussed. Based on an analytical study, a condition which the model parameters must fulfill for monotonic free growth is derived and examined. Sections 4 and 5 are dedicated to the parametric analysis of the model and the study of input parameter interdependences with respect to the tumor's dynamics. The paper concludes with the Discussion and Conclusions sections.

2. Brief outline of the simulation model

A detailed description of the simulation model can be found in previous publications [34,35]. The model is based on the consideration of a discrete time and space stochastic cellular automaton, representing the tumor region. More specifically, the tumor region can be considered as a grid (or "mesh") of "Geometrical Cells" (GCs, the elementary volume of the grid). Each GC corresponds to a cluster of heterogeneous cells found in various states. Specific rules regulate the transitions between these states, as well as the cell movement throughout the tumor volume. More specifically, the following five categories (or "equivalence classes") of cancer cells are considered in the model: stem cells (cells of unlimited mitotic potential), LIMP cells (LImited Mitotic Potential or committed progenitor cells, which can perform a limited number of mitoses before terminal differentiation), terminally differentiated cells, apoptotic and necrotic cells. The various cell cycle phases ($G1$, S, $G2$, M) and the dormant ($G0$) phase constitute subclasses in which stem or LIMP cells may reside.

The adopted cytokinetic model (Fig. 1(a)) incorporates the biological mechanisms of cell cycling, quiescence, recruitment, differentiation and death. Tumor sustenance is attributed to the presence of the cancer stem cells, which have the ability