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

E.A. Kolokotroni *, D.D. Dionysiou, N.K. Uzunoglu, G.S. Stamatakos

In Silico Oncology Group, Laboratory of Microwaves and Fiber Optics, Institute of Communication and Computer Systems, School of Electrical and Computer Engineering, National Technical University of Athens, Iroon Polytechniou 9, Zografos GR 157 80, EU, Greece

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

* Corresponding author. Tel.: +30 210 7722287; fax: +30 210 7723557.
E-mail address: ekolok@mail.ntua.gr (E.A. Kolokotroni).

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doi:10.1016/j.mcm.2011.05.007