Available online at www.sciencedirect.com
ScienceDirect
C. R. Biologies 331 (2008) 823–836
COMPTES RENDUS BIOLOGIES
http://france.elsevier.com/direct/CRASS3/

Biological modelling / Biomodélisation

A fully continuous individual-based model of tumor cell evolution

Pablo Gómez-Mourelo [a,*,1], Eva Sánchez [a,1], Luis Casasús [a], Glenn F. Webb [b,2]

[a] *Dpto. Matemática Aplicada. ETSI Industriales (Universidad Politécnica de Madrid), c/ José Gutiérrez Abascal, 2, 28006 Madrid, Spain*
[b] *Department of Mathematics, Vanderbilt University, Nashville, TN 37240, USA*

Received 22 April 2008; accepted after revision 12 August 2008

Available online 27 September 2008

Presented by Pierre Auger

Abstract

The aim of this work is to develop and study a *fully continuous* individual-based model (IBM) for cancer tumor invasion into a spatial environment of surrounding tissue. The IBM *improves* previous spatially discrete models, because it is continuous in all variables (including spatial variables), and thus not constrained to lattice frameworks. The IBM includes four types of individual elements: tumor cells, extracellular macromolecules (MM), a matrix degradative enzyme (MDE), and oxygen. The algorithm underlying the IBM is based on the dynamic interaction of these four elements in the spatial environment, with special consideration of mutation phenotypes. A set of stochastic differential equations is formulated to describe the evolution of the IBM in an equivalent way. The IBM is scaled up to a system of partial differential equations (PDE) representing the limiting behavior of the IBM as the number of cells and molecules approaches infinity. Both models (IBM and PDE) are numerically simulated with two kinds of initial conditions: homogeneous MM distribution and heterogeneous MM distribution. With both kinds of initial MM distributions spatial fingering patterns appear in the tumor growth. The output of both simulations is quite similar. ***To cite this article: P. Gómez-Mourelo et al., C. R. Biologies 331 (2008).***

Keywords: Individual-based models; Computational mathematics

1. Introduction

In this paper we construct and analyze a *fully continuous* individual-based model (IBM) for cancer invasion.

There have been many recent studies of tumor growth in spatial settings, including [1–11]. In our model of spatial tumor growth our aim is two-fold: first we construct an IBM founded on stochastic events, which yields readily interpreted graphical visualizations of tumor growth. Second, we transform the IBM to a system of partial differential equations (PDE) for the continuum densities of the IBM elements (in the limit of large numbers of particles). Then we obtain the numerical solution of the PDE, and this solution is qualitatively compared to the IBM output, in order to validate the IBM approach.

Individual-based models in mathematical biology have been used extensively recently, because increased

* Corresponding author.
E-mail addresses: pablo.gomez.mourelo@upm.es (P. Gómez-Mourelo), evamaria.sanchez@upm.es (E. Sánchez), luis.casasus@upm.es (L. Casasús), glenn.f.webb@vanderbilt.edu (G.F. Webb).

[1] Sánchez and Gómez-Mourelo are supported by Ministerio de Educación y Ciencia (Spain), proyecto MTM2005-00423, and FEDER.
[2] Webb is supported by the NCI Integrative Cancer Biology Program (PHS-NIH grant 1P50CA113007-01).

1631-0691/$ – see front matter
doi:10.1016/j.crvi.2008.08.010

computational capability allows the possibility of emulating in virtual worlds the huge variability of individual behavior. The consideration of different kinds of individuals is natural in IBM technology, with heterogeneity of individuals embedded in object-oriented programming. A frequent assumption in differential equations models of population dynamics is the so-called *mean-field* description, which assumes that individuals are homogeneous in a spatial context. In such models the influence of environment and the interactions between individuals are averaged throughout space, and spatial dependence is simplified or omitted. For many biological processes, however, spatial heterogeneity of individuals is an essential feature in understanding population behavior, and IBM approaches are advantageous for inclusion of spatial heterogeneity (a basic reference for IBM is [12]).

Although the visual aspect of IBM simulations are appealing to non-experts, IBMs still lack a general theoretical framework to interpret their output, which are different every run. In order to bridge the gap between computer simulation and mathematical description of our tumor invasion IBM, we use a set of *scaling techniques* to derive large-scale descriptions from the individual behavior. General references for this approach are [13] and [14], and the seminal paper [15].

The biological aims of our study are to develop a mathematical description of tumor growth with emphasis on spatial invasion into surrounding extracellular matrix. The biological complexity of this process invokes multi-scale levels – sub-cellular, cellular, and tissue. Mathematical frameworks provide a medium for the biological understanding of tumor growth through integration of these levels. The larger biological aim of our study is to develop a reliable predictor of tumor growth amenable to computer simulations specific to individual patients.

In this paper we focus on a hybrid discrete-continuous model recently presented by A. Anderson in [16], which we use as starting point. Related developments and numerical treatments can be found in [17]. We refer the reader to these references for the biological considerations and features of the model. We build and study an improved model for the same phenomenon. The improvements to Anderson's model are:

(1) Our model does not have a rigid discrete lattice spatial structure, but instead provides a more biologically realistic continuum spatial setting for cell growth and proliferation;
(2) Our model includes a cell age structure connected to a PDE formulation to describe individual cell behavior, and in particular allows inclusion of the phases of the cell cycle correspondent to cell age;
(3) Our model is convertible to a completely PDE formulation (the model in [16] was only partially convertible) and is advantageous for computational simulations;
(4) Our model can be analyzed theoretically and the significance of the parameters can be quantified.

As in [16], we analyze conditions under which tumor growth exhibits *fingering*, and in order to study this phenomena, design simulations with different initial MM distributions: homogeneous and heterogeneous.

With the aim of validating the individual-based approach, we scale-up the IBM (Lagrangian framework) to obtain a density-based Eulerian procedure. We construct a set of PDEs equivalent to a large number of runs of the computer simulations. We obtain numerically the solutions to these PDEs and qualitatively compare the results of both approaches with special interest on fingering patterns. We have made extensive numerical simulations, which strongly indicate that both approaches show very similar results. A formal validation of the equivalence of the two approaches will be explored in future work.

The organization of the paper is as follows: Section 2 contains a brief description of the biological features which are taken into account for the construction of the model; in Sections 3 and 4 we describe the tumor invasion IBM and its equivalent formulation in terms of PDEs. Section 5 focuses on the numerical analysis of the PDE model. Section 6 concludes with a discussion of results and conclusions.

2. Biological background

Tumors develop as mutations occurring in key regulatory genes of cell proliferation. According to [16,18], one of the most important mutations involves the *p53 gene*, the so-called *Guardian of Genome*, which is found in mutated form in over half of all cancers. The p53 protein controls three cellular functions: proliferation, death and DNA repair, so that a loss of p53 function due to mutation allows for the propagation of damaged DNA to other cells.

The aim of this paper is to develop a model for the growth of a generic solid tumor for which we will assume a blood supply has been established. We are especially interested in the influence of cell adhesion (i.e., cell–cell and cell–matrix adhesion) in the tumor shape, as this is a key question in the invasive process. Molecules in charge of cell adhesion not only regulate