Computational Modelling

Combining cellular automata and lattice Boltzmann method to model multiscale avascular tumor growth coupled with nutrient diffusion and immune competition

Davide Alemani [a,1], Francesco Pappalardo [b,*,1], Marzio Pennisi [b], Santo Motta [b], Vladimir Brusic [c]

[a] EPFL, Lausanne, Switzerland
[b] University of Catania, Catania, Italy
[c] Cancer Vaccine Center Bioinformatics Core, Dana-Farber Cancer Institute, Boston, MA, USA

ARTICLE INFO

ABSTRACT

In the last decades the Lattice Boltzmann method (LB) has been successfully used to simulate a variety of processes. The LB model describes the microscopic processes occurring at the cellular level and the macroscopic processes occurring at the continuum level with a unique function, the probability distribution function. Recently, it has been tried to couple deterministic approaches with probabilistic cellular automata (probabilistic CA) methods with the aim to model temporal evolution of tumor growths and three dimensional spatial evolution, obtaining hybrid methodologies. Despite the good results attained by CA-PDE methods, there is one important issue which has not been completely solved: the intrinsic stochastic nature of the interactions at the interface between cellular (microscopic) and continuum (macroscopic) level. CA methods are able to cope with the stochastic phenomena because of their probabilistic nature, while PDE methods are fully deterministic. Even if the coupling is mathematically correct, there could be important statistical effects that could be missed by the PDE approach. For such a reason, to be able to develop and manage a model that takes into account all these three level of complexity (cellular, molecular and continuum), we believe that PDE should be replaced with a statistic and stochastic model based on the numerical discretization of the Boltzmann equation: The Lattice Boltzmann (LB) method. In this work we introduce a new hybrid method to simulate tumor growth and immune system, by applying Cellular Automata Lattice Boltzmann (CA-LB) approach.

1. Introduction

The most important works on computational and mathematical modeling of tumor growth started in the 1970s. These works were the first that highlight the strategic importance of the presence of nutrients in the micro-environment that surrounds a tumor. In such a framework, a theory was developed to study the movement of solid tumors in response of arbitrary distribution of nutrients (Greenspan, 1976). An important result established in this paper states that colonies of cells which share the same food supply repel each other and move apart. The importance of nutrient distribution in the micro-environment of a tumor was studied in McElwain and Ponzo (1977). In this work a model for tumor growth was established in conditions of non-uniform oxygen consumption.

After that, a huge amount of computational models that analyze the different stages in tumor growth has been developed. Recent and important papers model the avascular stage

(Dormann and Deutsch, 2002; Ferreira et al., 2002, 2003), the invasion and metastasis stages (Gatenby and Gawlinski, 1996, 2003; Anderson, 2005; Panetta, 1996; Clare et al., 2000) and the vascularization via tumor angiogenesis (Anderson and Chaplain, 1998; Panovska et al., 2008; Kubo and Suzuki, 2007; Erdem and Serdal, 2007; Harrington et al., 2007; Owen et al., 2008). However, many of them neglect the fact that tumor growth occurs in a heterogeneous environment (Baum et al., 1999). Only recently, the influence of this factor on many features of the tumor growth process has been considered (Alarcon et al., 2003). Detailed reviews of computational models of tumor growths and inherent problems and perspectives are shown in (Deutsch and Dormann, 2005; Roose et al., 2007).

There are also a considerable amount of models that couple together tumor growth and immune system dynamics. Most of the works are deterministic, i.e. they describe the behavior of the mass (not individual) of tumor cells, host cells and immune cells (mainly B and T lymphocytes) with a set of ordinary or partial differential equations (ODEs or PDEs) (Arciero et al., 2004). Recently, many authors have tried to couple such deterministic approaches with probabilistic cellular automata (CA) methods with the aim to model temporal evolution of tumor growths and three dimensional spatial evolution. Indeed, CA methods are very powerful in dealing with problems at the cellular–molecular level. These approaches that mix PDEs and CA methods are called hybrid methods.

Hybrid methods have been successful applied to simulate complex systems in fluid dynamics (Borghi and Cristofolini, 2001), molecular dynamics (Neri et al., 2005) and reaction–diffusion systems (Albuquerque et al., 2006; Bandman, 2001). In particular, CA and PDEs have been used to investigate tumor growth and the dynamics of the immune system (Pettet et al., 2001; Araujo and McElwain, 2004). Furthermore, the combination of CA and PDE has produced hybrid mathematical models, that have been successfully used to model tumor growth (Mallet and De Pillis, 2006; De Pillis et al., 2007), chemotherapeutic treatments (Ferreira et al., 2003) and the effect of vascularization on tumor growth. The results obtained show good agreement with both the experimental and theoretical literature.

Hybrid methods has been proven to be very successfully in reproducing realistic tumor growth and immune system responses because they are able to handle the different level of scales present at cellular, molecular and continuum levels (Dormann and Deutsch, 2002; Patel et al., 2001; Mallet and De Pillis, 2006; Anderson, 2005). Despite the good results attained by CA-PDE methods, there is one important issue which has not been completely solved: the intrinsic stochastic nature of the interactions at the interface between cellular (microscopic) and continuum (macroscopic) level. CA methods are able to cope with the stochastic phenomena because of their probabilistic nature, while PDE methods are fully deterministic. Even if the coupling is mathematically correct, there could be important statistical effects that could be missed by the PDE approach. For such a reason, to be able to develop and manage a model that takes into account all these three levels of complexity (cellular, molecular and continuum), we believe that PDE should be replaced with a statistic and stochastic model based on the numerical discretization of the Boltzmann equation: The Lattice Boltzmann (LB) method.

In the last decades the Lattice Boltzmann method (LB) has been successfully used to simulate a variety of processes (for a complete review see Wolf-Gladrow, 2000). The LB model describes the microscopic processes occurring at the cellular level and the macroscopic processes occurring at the continuum level with a unique function, the probability distribution function. The LB was used alone (Alemani, 2007) or coupled with other methods (Albuquerque et al., 2006) to simulate physical, biological and chemical processes. On the other hand, LB methods are able to address problem at a mesoscopic level, which is in between microscopical and macroscopical levels. For that reason a good compromise is to use together CA and LB methods in such a way that typical cellular–molecular interactions are treated with CA (like the immune system and the tumor growth) and typical molecular–macroscopic processes are treated with LB (like the nutrient diffusion). This is the main idea underlying the hybrid CA-LB approach.

In this work we introduce a new hybrid method to simulate tumor growth and immune system, by applying Cellular Automata Lattice Boltzmann (CA-LB) approach. The CA-LB approach consists in using a Cellular Automata method to keep track of the immune system and the tumor shape and a Lattice Boltzmann diffusion formulation to follow the variation of nutrient concentrations in the micro-environment of the tumor. The main aim is to use the CA-LB model to describe the interactions between a growing tumor next to a nutrient source and the immune system of the host organism.

The starting points are two models independently developed in Ferreira et al. (2002) and Pappalardo et al. (2005, 2008). The first model (Ferreira et al., 2002) is a reaction–diffusion model for tumor growth in presence of nutrients. It was improved by Mallet and De Pillis (2006) and De Pillis et al. (2007) with the addition of a probabilistic CA model able to keep track of the immune system response to tumor growths and cell to cell adhesion. However, the immune system is described only with natural killer (NK) cells and cytolytic T lymphocytes (CTL).

The second model (Pappalardo et al., 2005) is based on a detailed description of the immune system at the cellular level with a Lattice Gas Cellular Automata (LGCA) method. The model is successfully used for cancer immunoprevention vaccine applications in mice (Motta et al., 2005). However, tumor growth is not modeled in detail and diffusive nutrient effects are missing. This model and its further developments have been applied to several immunology related issues, giving good results (Pappalardo et al., 2011; Palladini et al., 2010; Halling-Brown et al., 2010; Pennisi et al., 2008, 2010; Pappalardo et al., 2006). Both models have shown good agreement in reproducing different morphologies of growing tumors (De Pillis et al., 2007) and experimental data in naive and vaccinated mice (Pappalardo et al., 2007). The main idea is to fill the gap of the above mentioned two models combining the capabilities of both of them to qualitatively and quantitatively describe the micro-environment of a tumor growth, the diffusion of nutrients and the response of the immune system together with possible immunoprevention vaccine applications.

In our hybrid model, the immune system response is modeled using SimTriplex while the reaction diffusion process of the nutrients is solved by using a mesoscopic approach, i.e. a lattice Boltzmann method. The LB method is