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New Method for Tumor Growth Modeling: Software Environment and Mathematical

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Abstract: Understanding tumor development crossing multiple spatial-temporal scales is of great practical importance to better fighting against cancers. It is hard to attack this problem with pure biological means. In recent decades, computer-based modeling and simulation techniques have been playing an increasingly important role in addressing it. After reviewing the literature, however, we notice that existing tumor models are either highly simplified or too complicated to be scaled to large tumor systems. In light of these problems, we have developed a software environment TUGME to facilitate the multi-scale modeling and simulation of tumor development based on the agent-based method. The most important feature of this software environment is its flexibility which enables straight-forward model reuse and extension. Tumor models of TUGME are hybrid as discrete and continuous approaches are coupled to model the discrete and continuous nature of the tumor system. TUGME is highly modularized, thus changing one module only requires few or no modifications to the others.

Keywords: Cancer, Hybrid models, micro-environmental

1. Introduction

Basic cancer research by biologists is mainly carrying out experiments in the laboratory (the so-called wet-lab experiments [15]). In general, the experimental materials are various types of cancer cells, which are either injected into living animals like mice to induce tumors within them (In vivo tumors) or cultivated in culture medium with properly supplied nutrients like glucose (in vitro tumors). Research directly based on in situ and metastasis tumors within the body of persons with a cancer can seldom done as a set of very strict regulations have to be passed. In vivo environment (the body of animals) is obviously mostly similar to human bodies. Hence, experimental results drawn based on the in vivo

tumors are usually believed more reliable. However, many aspects of the in vivo environment are hardly controllable to researchers, especially the individual-tumor dependent factors as well as the intrinsic randomness. Compared with in vivo environment, the environment of in vitro tumors can be better controlled, but it is relatively less real for the absence of normal tissue cells that surround in vivo tumor tissues. In general, easy to control and limited effects of secondary factors of in vitro environment allow a more direct investigation of individual factors (univariate analysis), which makes the in vitro tumors popular among experimental oncologists. Tumor monolayer is prevalent in vitro, where tumor cells grow on a Petri dish with necessary nutrients for sustaining cell growth and proliferation. One important characteristic of tumor monolayers is that all cultured cells have basically the even accessibility to nutrients, hence, distinct tumor cell dynamics are considered as the result of all other factors except nutrients. It is an important experimental means for investigating and analyzing the growth and invasion mechanisms of tumors [16, 17]. Besides, tumor monolayers have been widely used as test systems to investigate the curative effects of anti-cancer drugs, radiotherapy, and chemotherapy etc [1]. Unfortunately, tumor monolayers cannot represent many aspects of actual tumor cell aggregates, for example, the 3D structure and the biological and biophysical properties of closely related to the 3D structure as it has been discussed in [2]. Multicellular tumor spheroids (MTSs) first used to investigate the effects of radiotherapy on tumor cells by Sutherland et al. in 1971 [3] are now prominently applied to cancer research. MTSs are thought to be more real and suitable in vitro tumor models for preserving the 3D structure of real tumor cell aggregates. Furthermore, significant differences or even contradictory phenomena have been indeed observed by conducting comparative experiments using tumor monolayers and MTSs [4]. MTSs provide an alternative with intermediate complexity between tumor monolayers and in vivo tumors, and more importantly, they can be used to model the avascular growth of real tumors that are too small to detect clinically. In addition, quantitative measurements of MTSs are very important references for validating the in silico cancer models.

2. Tumor Models and Cell Representation

Generally there are three classes of approaches for cancer modeling: namely the continuum, the discrete and the hybrid [4]. Each type of approach has its own characteristics which make

it proper for investigating certain features of tumors and tumor cells. Continuum models are generally realized by Ordinary differential Equations (OREs) or Partial Differential Equations (PDEs). They are usually applied to study the large scale properties, such as the population and the volume of tumor tissues [6] or the density of tumor cells [5]. Reaction-Diffusion Equations (RDEs) are commonly adopted to model the transport and metabolism of nutrients [6], where the diffusion term and the reaction term correspondingly model the molecular diffusion and consumption by cells.

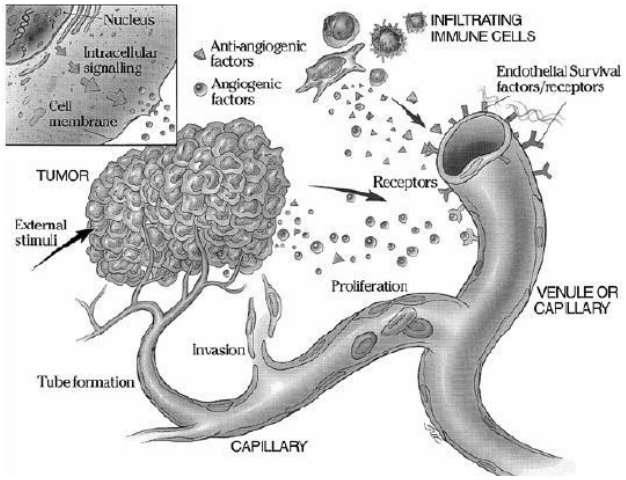

***Figure 1**. Growth Tumor[2]*

Continuum models have many valuable advantages. First of all, they can be scaled to very large tumors without substantially increasing the computational cost of modeling solving. Secondly, they can be solved e-ciently on computers, since there are many classical methods particularly for solving complex PDEs numerically. The disadvantage of continuum models is that the discreteness of individual tumor cells is di-cult to explicitly model. As the basic building units of a tumor tissue, cells are discrete by nature. Cellular membranes separate the inner cell world from the surroundings. Behaviors of cells, such as growth, proliferation, movement and death, are individual-cell- based. Furthermore, tumor cells are heterogeneous [8]. To take into account the discrete nature, the discrete approach has been proposed naturally. The discrete approach enables much higher flexibility in representing individual tumor cells compared with the continuum approach. Its basic idea is to treat each tumor cell as an individual object, where cell growth, proliferation, motion, death, interactions can be explicitly modeled as the behaviors of the individual cell objects. ABM is naturally adopted. However, the discrete approach isn't versatile in representing all the aspects of tumors or tumor cells. For example, the transport and metabolism of biochemical molecules are too nescient to realize with the discrete approach. The hybrid approach, which naturally integrates the continuum and discrete approaches, gradually becomes the favor of tumor modelers in recent years [9].

3. The Mathematical Method and Software Tools

ABM is a powerful technique for model design in computer-based simulations. On the one hand, simulation is often utilized to investigate agent systems, for example multi-agent systems (MAS) [8]. On the other hand, ABM has been widely used as a standard model design method for a wide range of applications in computer-based simulations [9]. An agent is a computer system capable of autonomous action in its environment. Agents can be thought as objects with strong notion of autonomy. Normal objects of systems encapsulate states and corresponding state-updating operation methods. In contrast, an agent has the ability to actively sense the changes in its environment, to deal with the perceived information and to make decision for its further actions (see figure 1). In a word, an agent is not only passively affected by environment, but also actively change the environment for its own preference.

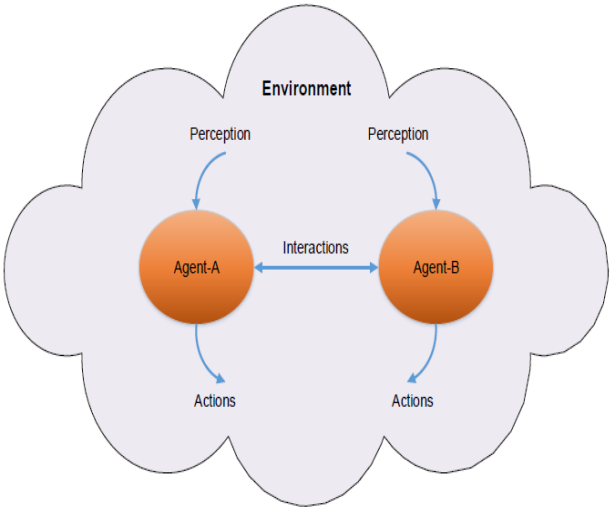

Figure 2*.Diagram illustrating agent-agent and agent-environment interactions[5].*

Mathematical based applications basically consist of a common environment and a set of agents within it. In an agent-based system, an agent interacts with other agents (its neighbors) as well as its environment. Like a society, an agent-based system allows agents to achieve collective goals via cooperation's and coordination's, and to achieve individual aims through competitions. ABM is very powerful for model description. Agents of an agent-based system may share some properties and also can vary significantly in some properties and behaviors. Besides, a complex agent can be further decomposed into sub-agents too. With such high flexibility and strong description capability, ABM has a wide range of applications, which has stimulated the emergence of software environments or toolkits

to facilitate construction of agent-based models. Here, some of them are briefly reviewed from the perspective of the possible application in agent-based cancer modeling. The software tools are representative with respect to the way of constructing an agent-based model. One may fund more software tools for general applications of agent-based modeling and simulation like FLAME or SWARM.

4. Role of Mathematical and Software Method's in cancer therapy

Mathematical modeling and simulation is a versatile tool in comprehending the system behavior and has been used for di errant applications in natural science and engineering disciplines. A mathematical model is an abstraction of a process system. It is composed of model equations and parameters. Usually, available experimental data is used for estimating the model parameters and for validating its prognostic ability. Then, parametric analysis (sensitivity analysis with respect to parameters) of the model is performed to understand the domain and variations of the system behavior with the variation in the parameters. With understanding of the system and a valid model, one can pursue model based process control and optimization. In a similar fashion, the applications of the tumor growth modeling are many. Firstly, cancer growth can be predicted and the main parameters responsible for it can be better understood. Secondly, these models can be combined with pharmacokinetic and pharmacodynamics models of the therapeutic agents to study their impact on cancer growth. Thus, the combination model can serve as a decision-making tool for planning and scheduling of the different therapies. In addition, inter-patient and intra-patient variability scenarios can be imitated by perturbing the parameters and optimization techniques can be used to schedule a therapy accordingly. Modeling and in silico experiments can provide new insights and over different possibilities to understand and treat cancer. Experimentalists and clinicians are becoming increasingly aware of the role of mathematical modeling and its value-addition along with medical techniques and experimental approaches in order to accelerate our understanding in distinguishing various possible mechanisms responsible for the tumor growth.

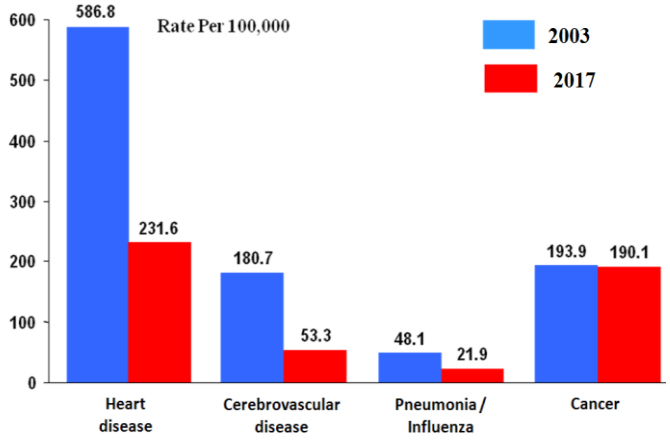

***Figure 3**. Change in death rates of different diseases in US from 2003 to 2017[6].*

5. Conclusion

Cancer is a global issue and an important multidisciplinary field of research with a lot of open ended and challenging problems. The main thrust of this thesis is to highlight that application of process systems engineering techniques can play an important role in addressing the problems related to cancer dynamics and its treatment. The main focus of this thesis is to study the initial stages of cancer progression avascular tumor growth and its interaction with the therapeutic agents. In the first two chapters, the role of modeling in cancer, broader review of works which were done hitherto, challenges and contributions of this thesis were introduced. The second objective was to propose a therapeutic protocol for a given patient while considering practical multiple objectives associated with cancer therapies. Chemotherapy is the common adjuvant therapy given to the patient at stage or another during the course of cancer treatment and, nowadays, they are combined with the targeted therapies to reduce the side effects. Thus, the multiple objectives can be broadly related to tumor reduction and reduction of side effects. This scenario is dealt in chapter 4 by formulating a multi-objective optimization problem using a tumor immune-chemo model (patient representation) adapted from the literature. NSGA -II was used to find the solution set known as Pareto set and the decision variables represented the timing and dosage of the interventions. Then, post-Pareto-optimality analysis was done to choose a solution from Pareto set. The results for the considered patient have shown that the performance of the proposed chemotherapy protocol was better than the standard protocol employed in medical practice. However, at the end of the treatment course the number of tumor cells were in the range of 105 cells. Alternatively, the combination of chemotherapy and immunotherapy resulted in almost complete elimination of tumor cells. Also, post-treatment analysis based on tumor relapse time has indicated that combination therapy is better than chemotherapy. As a whole, this work suggests that the immunogenicity factor (intensity of tumor-immune interactions)

must be taken into account prior to every therapeutic intervention.

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