Modeling of Solid Tumor Progression Thresholds using a Complex Adaptive System Approach

Didier Dréau¹; Ted Carmichael², Mirsad Hadzikadic²

¹Department of Biology and ²College of Computing and Informatics, University of North Carolina - Charlotte, NC.
{ddreau@uncc.edu, tedsaid@gmail.com, mirsad@uncc.edu}

Abstract
Simulation techniques used to generate complex biological models are becoming promising research tools in oncology. Using a general Complex Adaptive Systems model that can be tailored to map various phenomena, here, we describe how this model applies to tumor growth. The multi-agent modeling environment is generated using Netlogo. The stochastic model consists of active objects including normal immune and cancer cells. The simulations conducted mimicked the tumor progression success and failure and the status of the tumor mass despite constant variations remained stable for an extended time. Furthermore, increasing the efficiency of the immune cells led to decreases in tumor cell numbers variable in both occurrence time and duration.

Keywords: computer models; tumor progression; agents; self-organization; self-migration; cell simulation, threshold, Complex Adaptive Systems, non-linear behavior, feedback.

1 Introduction
During the past decade, progress in theoretical modeling of tumor growth, immune responses or angiogenesis has made computer modeling of tumor progression an attractive approach to evaluate both the likelihood of tumor recurrence as well as the aggressiveness of an individual tumor. Tumor cell growth has been defined using mathematical equations mostly using avascular spheroid tumor models [1-3]. Since tumor growth depend on vasculature remodeling, a two-dimensional hybrid cellular automaton model of early brain tumor growth that couples the remodeling of the microvasculature with the evolution of the tumor mass was developed [4-6]. These mathematical models heavily rely on random process [7].

The tumor mass can also be recognized as a self-organized and self-regulated system. In addition, to the tumor system, both the immune and the vascular system can be modeled as complex system [8-10]. The immune system through its immune cells’ capability to produce signaling molecules in response to environmental encounters and their constant feedback is a self-organized system [11, 12]. So are the development of vasculature within the tumor mass [13]. Furthermore, tumor, immune and vascular cells communicate through both cell-cell and chemical interactions [6]. The sum of those interactions defines both the success and the rate of tumor progression. The outcome of the sum of complex system interactions associated with tumor growth remains difficult to assess.

Complex Adaptive System (CAS) approaches take into account the different agents within the tumor mass, their status and through computation of feedback, self-organization and non-linear dynamic behavior may be a powerful framework for exploring tumor progression. Originally, the growth of cancer cells is slow partly because of the growth limitations imposed by the immune system, and the lack of vasculature. However, when the threshold is reached, the growth rate of cancer cells is greater and the limitations associated with the immune system and the lack of sufficient vascularization is overcome.

Therefore, here we present a new agent-based modeling of tumor progression evaluating the threshold effect associated with cancer progression.
2. Specifications of the CAS Model

2.1. The Agents
The general CAS model that we have developed utilizes two types of tissue cells (A-agents) and cytotoxic immune (B-agents) cells, with the following rules. A-agents can have a stepwise progression between two polar states (1-state = healthy, 0-state = cancerous). A tumor reaching the 0-state can affect the state of other tumor cells within its neighborhood towards the 0-state. Tumor cells have a chance of random movement toward either the 0-state or the 1-state. Finally, tumor cells have no velocity and lifetime set on infinity. Those characteristics are generally associated with tumor cells especially tumor stem cells. B-agents are mobile, moving randomly if the adjacent A-agent is not in the 0-state. They affect adjacent A-agents, moving their state towards the 1-state. They have a limited lifetime, can stimulate the recruitment of new B-agents as a positive function of the number of A-agents affected.

Many attributes of both tumor and immune cells can be adjusted in the model to produce various effects. These include the degree of random movement towards either the 0-state or the 1-state, the distance between the 0-state and 1-state for tumor cells. For immune cells, their efficiency (number of turns per simulation time-step), distance traveled per turn, and their lifetime for example can be adjusted. Currently, immune cells (B-agents) can only detect tumor cells (A-agents) that are within the same simulation grid point.

2.2. Implementation
We implemented our general CAS model – as well as the specific domain models – using the NetLogo programmable modeling environment [14]. NetLogo has a user-defined number of “patches” and “turtles.” The patches form a grid and the turtles can move across this grid. In our model, the patches are the A-agents (tumor cells immobile), and the turtles are the B-agents (immune cells, random movement adjacent to the patches).

2.3. Current Cancer Model
The tissue cells (A-agents) have a velocity of 0, and are aligned on a grid, such that there are 125 grid cells on a side, for a total of 15,625. We also define the progression between the 0-state and the 1-state in steps. The immune cells (B-agents) move about the simulation randomly, although if one happens upon a patch in the 0-state it will remain there, moving the patch in steps until the 1-state is reached. The neighborhood of the tissue cells (A-agents) is defined here as the eight grid cells that surround each tissue cell (A-agent).

To provide more stable complex behavior, we refined the immune cells (B-agents) with a limited lifetime, and a method of recruitment of similar cells. The lifetime is controlled by the operator as a function of the number of model time-steps, while the ability to recruit immune cells is a function of the number of “successes,” also defined by the operator. A success is defined as moving a 0-state tissue cell (A-agent) one step towards the 1-state. A “susceptibility” with a range [0, 1] as a normal distribution (0.5 ± 0.25) was attributed to the tumor cells (A-agents), such that the 0-state A-agents now have only a probability of moving an adjacent A-agent one step towards the 0-state.

In this model, both the efficiency of the tissue cells (A-agents) and that of the immune cells (B-agents) can be adjusted upward. This give tissue cells (A-agents) multiple opportunities to affect a neighboring tissue cells (A-agent) and immune cells (B-agents) multiple occasions to kill tumor cells during a single time-step. Finally, we also changed the general model to allow for a small random chance of change in an tissue cells (A-agent) each time-step, moving it one step towards either the 0-state or the 1-state.

3 Results
3.1 CAS Model of Tumor Growth Mimicking Failure and Success
The model of CAS tumor growth was validated using a previously published theoretic data set [12]. As in the original model, the growth and reduction over time in the number of tumor cells associated with a combination of either a strong immune response and a weak tumor type lead to suboptimal (below threshold) tumor growth (Figure 1A) and decrease in the number of tumor cells (tumor mass).

Figure 1. CAS Modeling of tumor growth failure (Left) and success (Right). The evolution of the number of cytotoxic immune cells (in red) and of tumor cells (in black) over time is represented. Note the difference in the Y axis scale between A and B.
In contrast, when the parameters are adjusted to allows the tumor to reach and exceed the threshold level of growth, the tumor mass is successfully maintained (Figure 1B). In Figure 1B, the number of tumor cells oscillates with limited volatility. The simulation was run for an extended period of time (approximately 700,000 time steps) without seeing a reversal back to the lower stable number of cancer cells.

The failure to growth is associated with low cells numbers, whereas tumor growth success was associated with an exponential increase in tumor cells after an extended period of no growth (Figure 1B). Furthermore, in those simulated conditions, once the growth plateau reached, the tumor cell number continued to oscillate.

With the following settings used to produce these outputs were as follows: immune-cells have 10 turns per time step; they can move 0.12 the distance of one grid cell each time they move; they can attract a new immune cell after moving a cancerous cell towards the healthy state 15 times; and their lifetime is 65 turns. Furthermore, a minimum number (n=270) of immune cells were added, to mimic the body’s natural status.

In those conditions, over the course of 500 simulation runs, the smallest number of time steps to produce the tipping point was 1456 simulation time steps; the largest number was 98,380. Approximately 79% of the time, however, the critical threshold was reached in less than 20,000 time steps, and the relationship of number of time steps to reach this threshold is such that it becomes increasingly unlikely to have simulation runs with an extended number of time steps.

3.2. CAS Model of Tumor Growth Low and High Steady States

Changes to only few of the simulation parameters led to drastic changes in the number of cells. These changes were associated an increased variability in the cell number throughout the stimulation (Figure 2). Furthermore, when the distance an immune cell can travel was increased from 0.12 to 0.18, immune cell lifetime was increased from 65 to 75 turns, and the minimum number of existent immune cells was reduced to 170 from 270, low and high steady state of tumor cell numbers were observed (Figure 2.). Those periods (3 in Figure 2) appeared to be random in their time of occurrence and duration. The conditions of the simulation were associated with an extreme oscillatory number of tumor cells as indicated by the thickness of the black line. In addition, the number of immune cells also oscillated, but to a much lesser extent.

4 Discussion

Computer simulations allows insight into the behavior of complex systems, and to make mechanistic predictions about their behavior. Solid tumor progression in particular has been modeled extensively, but the models have had limited success in predicting tumor growth rate, recurrence or therapy outcome [2, 3, 5, 6, 11, 15]. The CAS model presented here allows the study of inputs associated with tumor intrinsic properties, and the immune responsiveness in solid tumor progression using time-dependent interactions.

Although computer-based models are not yet reliable enough to substitute for randomized clinical trials in decision-making [16], CAS appears to be a more realistic model of tumor growth. Indeed, the CAS model may allow for a more complete understanding of a biological system because it integrate multiple features that interact in complex ways, including tumor intrinsic features, the net tumor cell growth, and the influence of the immune system [17]. Fractal geometry and mathematical models [18, 19] have had better success, but currently they provide only partial representations of the events associated with solid tumor growth and development [20]. Consequently, they are of limited use in determining tumor aggressiveness thresholds.

The CAS tumor model presented here does not directly induce a strong tumor growth as in [12]; rather, the development of an aggressive tumor is allowed to stochastically appear based on the small chance of random movement for the tissue cells, towards either the 0-state or the 1-state. Due to this, the simulation can run quite a long time before the threshold change between the two steady

**Figure 2 – Simulation of tumor cell random behavior.** Number of cancer (black) and immune (red) cells over 1,790,000 time steps in a simulation increasing the random cell behavior. The black bars mark periods of low cell numbers.
states: that of a relatively low number of cancer cells and a high number of cancer cells. The CAS model used here not only illustrates the tumor, the immune system but also may provide new sets of principles on the quantitative and dynamic relationships among those systems. The CAS model used here is particularly robust because it account for the adaptive nature of cancer progression. Although the simulations presented appear to mimic the development of a generic solid tumor, the model is based on assumptions that overall simplify the biology inherent to tumor progression. Nevertheless, the use of tumor cell intrinsic needs and immune cells still lead to realistic simulations.

Furthermore, in the CAS modeling presented here due to its stochastic nature, multiple runs using the same initial parameters lead to variations in the tumor burden compatible with biological variability. However, these variations were not a fundamentally different answer for each execution even when the system is adapting to environment and behavior of individual elements. These observations indicate that within the present model, the results are reproducible. Therefore, the timing to tumor growth and the speed of the tumor burden increase may have a specific pattern that can be defined.

The model also allowed simulations of alterations in number of immune cells and led to a much slower increase in the tumor burden mimicking variations in the immune responses over time and between patients which are the basis for cancer treatments aimed at boosting the patient immune responses [21, 22]. These simulations mimic both clinical and animal studies and support the key role of the initial immune responsiveness in the development of valid immunotherapy treatments [21, 22].

Both the variability due to the stochastic nature of the properties of the tissue, immune and tumor cells and the ability to modulate the immune response together suggest that CAS models may allow the description of individual tumors. The simulation presented here underline both the temporal and spatial variability associated with tumor progression. Furthermore, the model points to oscillatory variations that may be more difficult to demonstrate in patients. Finally, whether the oscillatory nature of the tumor growth could be informative to tailor the patient therapy in preventing cancer progression is an interesting prospect.

5. Conclusions and Future Work

Continued refinement of the CAS tumor model presented, and its applications to individual tumors may allow the determination the minimum of necessary components needed to model threshold effects in reliable prognosis of tumor progression. An improved CAS model would be tremendously useful to: 1) define the parameters associated with the aggressive tumor growth threshold; 2) suggest and generate models suitable for individual tumor modeling; and 3) better understand relationships between the different agents in tumor development that suggest new targets for diagnosis and treatment. Additional experiments are ongoing to more fully mimic the tumor microenvironment taking into account more fully the interactions between the different cell types present within the tumor microenvironment.

6 Acknowledgments

The authors would like to thank the entire CAS group at (UNC Charlotte) for helpful discussions and critical reading of the manuscript.
7 References


