Cellular Automaton Model Based On the G0 Cell Cycle

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***Abstract*—The epithelial-mesenchymal transition (EMT) of tumor cells is a crucial prerequisite for tumor metastasis, and quantitative research on the process of epithelial-mesenchymal transition is of great significance. This article mainly discusses the growth kinetics of tumor cells by designing a cellular automaton model based on the cell cycle mechanism to replicate the process of epithelial-mesenchymal transition.**

***Index Terms*—G0 cell cycle, Cellular automaton, cell division mechanism.**

I. Introduction

Cancer is a proliferative disease characterized by abnormal cell growth, initiated by malignant proliferation of cells, exhibiting invasiveness and metastasis, posing a serious threat to health and life. The metastasis of tumor cells is a significant factor leading to patient mortality. Tumor stem cells play a crucial role in cancer recurrence[1]. Conventional treatments often lead to drug resistance, allowing tumors to regenerate and reconstruct heterogeneity through division. One of the main manifestations of heterogeneity is the epithelial-mesenchymal transition process during tumor development. This process contributes to cancer recurrence after surgery and the tendency of cancer cells to invade distant sites.

The classical mathematical model describing the dynamics of stem cell regeneration was proposed by Burns and Tanock in the 1970s[2]. In this model, the cell cycle is uniformly divided into a resting phase (G0) and a proliferative phase (G1, S, G2 phases, and mitotic M phase). During each cell cycle, proliferating cells either undergo apoptosis or divide into two daughter cells. However, cells in the resting phase either irreversibly differentiate into terminally differentiated cells or re-enter the proliferative phase. This G0 phase cell cycle model describes the general process of stem cell proliferation.

Researchers typically construct deterministic models to explain biological phenomena, with mathematical models based on ordinary differential equation (ODE) systems being the most common approach. Deterministic models offer advantages such as high computational efficiency, selective description of complex systems, and ease of simple mathematical analysis. These models have been widely used to study reaction kinetics and various other physical phenomena[3].However, deterministic models fall short in fully capturing biological processes. At the cellular scale, the stochastic behavior exhibited by cell proliferation, differentiation, migration, and apoptosis, along with the resulting complex spatial dynamics and individual diversity, is inadequately represented. Therefore, in recent years, there has been an increasing use of frameworks such as cellular automata to model cellular-scale processes[4,5,6].

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II. Model Description

A. Biological Assumptions

In this model, we make the following assumptions:

1.The model employs a Moore neighborhood type, where each cell has eight neighbors.

2.Cells are categorized into three phenotypes: epithelial (E) cells, mesenchymal (M) cells, and E/M hybrid cells. Epithelial cells have a fixed migration rate of 0, M mesenchymal cells exhibit a higher migration rate, while E/M hybrid cells have a lower migration rate. Cell migration occurs within a range of 30→60 neighborhoods from the cell's original position. If there are no empty automaton cells at the destination, the cell remains stationary and does not attempt migration.

3.Positions in the cellular automaton are initially empty, with each grid capable of accommodating one cell.

4.Cell division results in two daughter cells occupying neighboring grids, following a default sequence of left down-left-left up-up-right up-right-right-right down-down. If there are fewer than two empty neighboring grids, the cell becomes quiescent.

5.Proliferation rates, death rates, and rates of apoptosis/differentiation are uniform across all cells and are solely dependent on cell density, irrespective of cell type, phenotype, or age.

6.Cell growth occurs within a bounded region, representing physical constraints within an organism, such as organ size. Cells at the boundary of the region do not participate in cell proliferation and division, and the physical limitations of the organism cannot be breached.

7.Cell migration in this model is relatively rapid compared to the simulation cycle, so the model directly displays cell migration paths upon migration events.

B. Algorithm Details

After setting up a Moore neighborhood to generate cellular automata, in the growth-permitted area, each automaton cell is initially blank, representing the cell's growth environment. Then, one or more automaton cells are randomly designated to be in a quiescent state, with static cell status, and their gene expression levels are randomly assigned. Time is discretized into units representing one day. At each time step:

1.Cellular Automaton Model: The model proposed by [8] is utilized to update parameters related to changes in cell

population size. This model is independent of cell type, phenotype, and age, and solely dependent on cell count. The model is updated by calculating the number of cells in the system.

2.Cell Type Check: Check the state of each automaton cell, which can be static, dividing, dead, apoptotic, or transitioning from quiescence to proliferation. Static cells are those alive in the system but relatively stationary at all stages. Dividing cells have grown during the proliferation phase to a certain point and are ready to divide into two daughter cells in the next moment. Dead cells naturally die during quiescence. Apoptotic cells undergo normal apoptosis during proliferation. Dead and apoptotic cells are marked as dead during system updates. Dividing cells mark their own automaton cell as dead during system updates, while the surviving status of the two daughter cells is marked as alive. The remaining cell states are set to alive.

3.Phenotype Check: Check the phenotype of each automaton cell. In this case, cell phenotypes are categorized as E epithelial cells, E/M epithelial-mesenchymal hybrid cells, and M mesenchymal cells. Epithelial cells have a migration rate of 0, indicating no migratory function, while E/M epithelial-mesenchymal hybrid cells have a small migration rate, representing both epithelial cell adhesiveness and mesenchymal cell motility. Mesenchymal cells have a larger migration rate, indicating a higher likelihood of detachment from primary tumors and invasion into other tissue organs in the system. The phenotype of each automaton cell is determined by the expression levels of two genes in the current cell.

4.Invasion: Based on the cell phenotype, determine its migration rate. If it meets the migration conditions, the cell migrates by setting the current cell as dead. In the 35-cell radius neighborhood, randomly select a blank cell and inherit the current cell's state to the blank cell.

5.Cell Division: When checking the survival type of each cell, cells in the dividing state undergo cell division. Check if the current cell's neighbors have more than two blank cells. If there are more than two blank cells, execute division by placing daughter cells in the blank cells according to the assumed order, and set the current cell as dead. During cell division, reset the cell state, including gene expression rates determined by a genetic probability function [7].

6.System Update: Check the survival type of each cell: alive or dead. Cells change the survival type of each automaton cell in the system to alive through proliferation and migration, and change the survival type of each automaton cell in the system to dead through death, apoptosis, and migration out.

III. Simulation Results

A. *Tumor Cell Proliferation*

First, using the CA model designed above, we simulated the invasive growth of multicellular tumor spheroids (MTS) observed in vitro and observed the occurrence of EMT within them. Tumors grow within the permissible growth area; beyond this area, they are considered to lack oxygen and nutrients. Initially, n non-migratory tumor epithelial cells were introduced into the permissible growth area, and the tumor began to grow. The values of the cellular kinetic model are as follows:

$$\kappa = 0.009\ ,\ \tau = T - T_1\ ,\ \mu = 0.007\ ,\ \beta = \beta_0 \frac{\theta}{\theta + c}.$$

where

$$\beta_0 = 0.2\ ,\ \theta = 100\ ,\ \rho_1 = 0.0001\ ,\ \rho_2 = 0.00001.$$

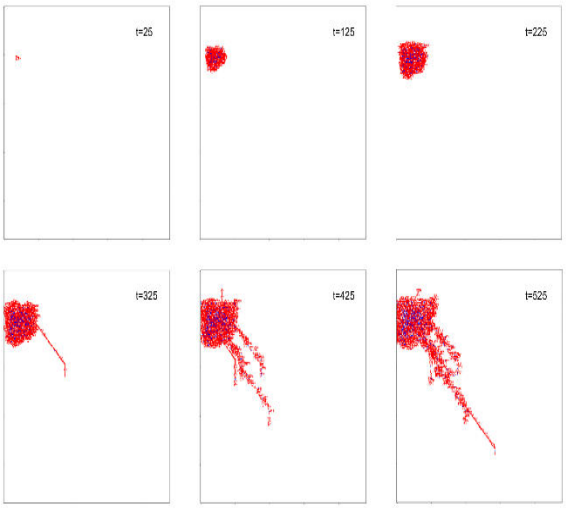

Fig.1 Tumor cell proliferation

In the following tumor visualization, we applied the following coloring rules: the growth-permitted area is white, proliferating tumor cells are red, and non-proliferating tumor cells are blue. Figure 1 illustrates the simulated EMT morphology. It's evident that in the early stages of tumor growth, there's an outward expansion trend in cell growth. Simultaneously, internal cells within the tumor pause their growth due to lack of nutrients and oxygen, losing their proliferative capacity. The tumor is visibly divided into two layers: an outer layer of proliferating tumor cells and an inner layer where tumor cell growth is halted. As the number of tumor cells increases, the tumor volume expands, accompanied by the appearance of phenotypic transitions corresponding to the biological phenomenon of distant invasion in tumors.

B. *The distant invasion of tumor cells*

During proliferation, tumors undergo distant invasion, as depicted in Figure 2, where migrating cells are exclusively in the E state. Following invasion, through cell proliferation, tumor cell clusters redevelop at the invasion site. In the early stages of tumor growth, the growth rate isn't rapid, but after invasion, the tumor rapidly expands, covering the entire cellular automaton in a short time. Additionally, in Figure 2, it's observed that after distant invasion in the primary tumor growth area, there isn't significant migration of the primary tumor itself. Instead, new cells along the tumor cell migration path undergo extensive migration, indicating that the primary cause of distant invasion in tumors is due to phenotypic changes in cells.

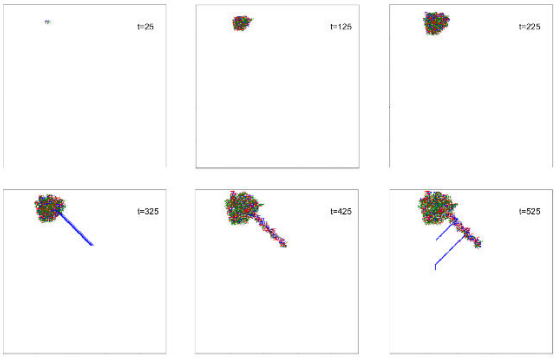

Fig.2 Distal invasion of tumor cells

C. *Phenotypic transformation of tumor cells*

Figure 2 shows that at the start of the simulation, there is only one cell with an epigenetic state of E (green). By t=25, there's a phenotypic transition in cell types, with two mobile cell types (blue and red) mutating from the initially set cell type. This transition is driven by the genetic probability function, and over time, the tumor tissue volume increases. By t=325, due to changes in the epigenetic state of mobile cells, tumor cells undergo distant invasion. After invasion, cells along the migration path rapidly undergo phenotypic transitions and proliferate at the invasion destination. By t=525, due to the high migration rate of cells that have undergone migration, coupled with the genetic probability function, their offspring also have a high migration rate, resulting in more frequent distant invasion events in the system.

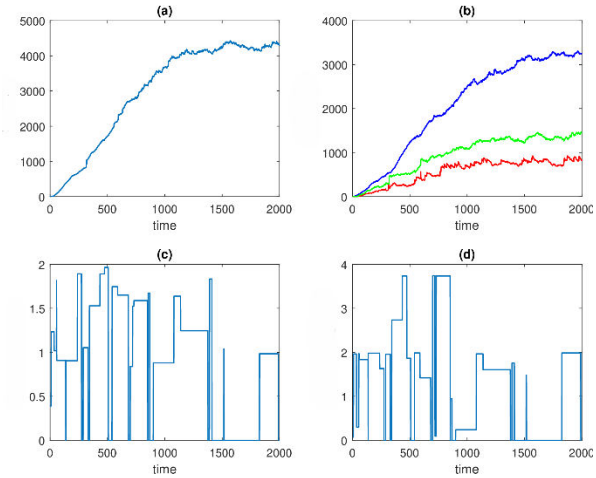

Fig.3 CA model simulates EMT phenomenon

During the simulation, Figure 3a depicts that the cell count aligns with the heterogeneous G0 cell cycle model, stabilizing after reaching a threshold, with the total number of cells remaining constant within a cycle. At the simulation's onset, only one E-type cell exists in the cell pool, lacking migration capability. With increasing cell numbers, E-type cells give rise to migratory M-type cells and E/M hybrid cells, initiating the EMT process, leading to malignant tumor migration. In Figure 3b, at t=0, only one cell exists, followed by the appearance of three phenotypic cells in the cell pool, stabilizing after a certain time. The proliferation rate of M-type cells surpasses the other two phenotypes, consistent with the CA model's assumptions, indicating that after EMT, phenotypic transitions become more frequent. Figures 3c-d illustrate the temporal gene expression levels of a cell in the cellular automaton, showing fluctuations over time, reflecting changes in cell phenotype, and biological properties. A gene expression value of 0 signifies cell death or apoptosis, removing it from the simulated cell pool.

IV. CONCLUSION

Using a CA model based on a genetic probability function mechanism, we visually demonstrated the EMT phenomenon during tumor tissue growth. The simulation concluded that genetic probability functions guide tumor cells to undergo EMT.

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