A Comparative Study between Gompertz Equation and Cellular Automaton in Modelling Tumor Growth

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I. Introduction

Tumor growth modelling has always been considered a puzzling phenomenon for many scientists and mathematicians. This is because of the stochastic tendencies of its growth and the retardation factor of each tumor type.

Researchers have used different mathematical models, such as cube root growth and logistic growth curve, to describe tumor growth. However, these models tend to veer away from the clinical and empirical data regarding tumor growth. Thus, during 2017, Paek, Jayeong and Choi used a stochastic Gompertz equation (GE) to lessen the discrepancies between the models and real-life experiments. [2]

Cellular Automaton (CA) is also widely used computational model to simulate the spatial and temporal change of tumor growth. Poleszczuk and Enderling (2014) proposed a CA model for tumor growth which considered the proliferation, migration and death of the cells under stochastic rules. [1]

Since the two models (i.e. GE and CA) are some of the commonly used models for cancerous cells, there must be some bridge between the two models. The aim of this study is to make a proper transition of the GE into a stochastic CA and compare both models' capabilities to describe tumor growth. [3]

II. Related Studies

In the paper of Laird, GE was used to model the behavior of tumor growth. This type of function was chosen to model the tumor growth because GE models the behavior that exhibits slow growth at the beginning, exponential growth in a certain period of time and slows down until the growth is negligible. [2] Laird used the GE of this form:

Equation 1: Gompertz Equation

$$\frac{W}{W_o} = e^{\frac{A}{\alpha}(1-e^{-\alpha t})}$$

This equation is going to be useful for the creation of CA. Informally, a CA is a lattice of cells with finite, predetermined, discrete states. There exists many variations of CAs. They can be of any dimensions but are typically one-dimensional and two-dimensional. They can also be either finite or infinite. Transition rules can be applied synchronously or asynchronously. Transitions can be deterministic or stochastic. Other variations exist but these are the typical ones [4].

Differential equations (DE) and CA are tools often used by researchers to characterize different systems. Despite the latter's promising approach in modelling complex spatial system, differential equations are the standard tool for this endeavor. This is because users of CAs are limited by the difficult task of coming up with suitable rules needed to model real events. [3]

Equation 2: DE

$$\frac{dx}{dt} = f(x, y)$$

In the paper of Ruanxiaogang, he devised a method to convert DEs to an equivalent cellular automata. This was done by simplifying DEs of the form similar to Equation 1 to an equivalent finite difference equation (FDE) and limiting its variables to work in a discrete space. [3]

Equation 3: Equivalent FDE of Equation 2

$$x(t+1) = x(t) + f(x(t), y(t))$$

By limiting the scope of the variables of FDE, the value of *f+1* is similar as the next state of a cellular automaton, since both of them are working in the same space. Thus, the behavior of the cellular

automaton can be represented using the FDE and rules that will be set depending on the system created. [3]

III. Methodology

In this paper, the GE used in the paper of Laird will be converted to an equivalent CA using the method done in the paper of Ruanxiaogang. As described in the paper, the final form of the DE derived through implicit differentiation and substitution will be

Equation 4: W_{CA}, the final form of the FDE that will be used to create the CA

$$\Delta W_{CA} = AT_o W_o e^{\frac{A}{\alpha}(1-e^{-\alpha t})} e^{-\alpha t}$$

Equation 4 is the equivalent DE that was converted from GE with discrete time steps. For one-dimensional cellular automaton, the maximum possible growth of the tumor at discrete time *t* at each discrete interval is represented by W_{max}.

Equation 5: W_{max}

$$\Delta W_{max}(t) = 2 \times V_c = \frac{8\Pi}{3} {r_c}^3$$

We can now start building the equivalent CA. Since the CA for the GE has an element of randomness, we use $p^i(t)$ to describe the stochastic property of cell *i*. $p^i(t)$ is defined as follows:

Equation 6: $p^i(t)$

$$p^i(t) = \begin{cases} 0 & s_{i-1}(t) = 0 \text{ and } s_{i+1}(t) = 0 \\ 1 & s_{i-1}(t) = 1 \text{ and } s_{i+1}(t) = 1 \\ \frac{\Delta W_{CA}(t)}{\Delta W_{max}(t)} & otherwise \end{cases}$$

where $s_i(t)$ is the state of cell *i* at a given discrete time t. We assume that the state of any cell in the CA to be irreversible meaning it can not go from one to zero but it can go zero to one. As for the rules, we use

Equation 7: $s_i(t)$

$$s_i(t + T_o) = \begin{cases} s_i(t) & p^{(i)}(t) \le P_T \\ s_i(t) + 1 & otherwise \end{cases}$$

where P_T is the probable threshold ranging from 0 to 1 and T_0 is the amount of time between each state transition. P_T is generated using a uniform probability density function. There will be cases where $p^{(i)}(t)$ is greater than 1 meaning the chosen cell will surely be converted to a tumor cell. To account for this excess in $p^{(i)}(t)$, the same process will be applied to the adjacent cells of the chosen cell. To apply this CA model, we need to simply code using these conditions and follow these rules. The CA shall prompt the user for the number of cells in the one-dimensional CA, the initial cells with a tumor cell, and the constants *A* and *α* as described in Equation 4. The CA constructed using this method should yield similar results to the DE.

IV. Results and Conclusions

For this study, we model the tumor Walker W26B1, and follow the constants used by Laird in her study. Thus, the value of A that will be used is 0.220 and the value of that will be used is 0.0218. It should also be noted that the cell volume is solved by fixing the cell radius as 1 unit. After building the CA and simulating it with GE in a program written in Java up to t = 1000, the 2 results are recorded for every time interval and are analyzed afterwards.

Figure 1: Difference of Cellular Automaton Values and Gompertz Equation Values

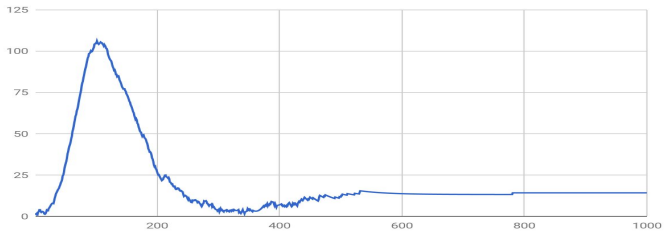

Figure 1 describes the difference graph of the CA's average results to GE's results. For the majority of the simulation, the CA produced higher growth with respect to GE's growth since volume incrementation happens at multiples of cell volume in the CA while the GE happens in fractions depending on the variables given. It is either all or nothing for the CA while the GE precisely and accurately produce continuous growth.

The oscillation proves CA's stochasticity, a nature of an actual tumor growth. The first half of the graph

shows the automata's random discrete growth with respect to GE's consistent continuous growth. Meanwhile, the second half shows the conformity of both models to the behavior of tumor growth by having almost constant differences after a long period of time. This tells us that both models have both reached its asymptotic limit of growth after some time.

Table 1: Mean Absolute Error of each Test compared to GE

Test no.	Mean Absolute Difference
Test 1	18.51426937
Test 2	20.13813407
Test 3	20.79268662
Test 4	30.45496448
Test 5	24.20424447

In table 1, the MAE with respect to the GE is computed for each CA simulation. Considering that these differences are on a minute level of measurement i.e. mm and cm, the results are all low relative to the actual volume and its growth despite the random behavior. This is because CA still simulated tumor growth by having GE for its probabilistic rules. This tells us that despite the randomness of the CA, every test would still be yielding results close to the preferred behavior.

Figure 2: Tumor Growth as Modelled using a CA and GE

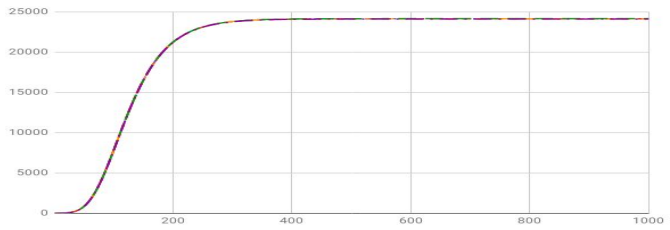

Figure 2 shows the performance of the GE (blue line) and the CA in average (red dashed lines) throughout the simulation. It can be seen that Gompertz curve were both produced by the models. It can be also observed that under persistent simulation, the models have yielded very similar results with negligible differences. This tells us that the CA is really able to perform tumor growth and is reliable as much as the GE.

The two models have their own advantages. GE's volume change occurs in a continuous system so it is more accurate and more precise as compared to the discrete system of CA. Meanwhile, since CA is stochastic and dynamic, it is also fit for modeling real life tumor growth system which is also both stochastic, being subject to irregular growth, and dynamic, being composed of further smaller systems.

Incorporating both models' performances may result to new interesting simulations. The DE produces ideal and consistent values while the CA originally proposes ideal behavior. The conversion of DE to CA made the simulation more realistic while still functioning as the targeted phenomenon.

We do not conclude, however, which model is better. Instead, this study proves that both models are able to simulate tumor growth but also holds different advantages. Depending on the conditions and behaviors needed, one of the two models may be fitter to be used than the other.

We hope future researchers fully understand these advantages and utilize them in real-life phenomenon modelling such as coming up ways to integrate and improve concepts like this paper.

References

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