Computer Simulations of Cancer Growth Using Cellular Automata

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ABSTRACT

One-dimensional and two-dimensional cellular automata-based models are used to generate computer simulations of cancer growth dynamics. Results of computer simulations using Java show close agreement with the Gompertz's model of tumor growth and the CA model of *in vitro* carcinogenesis developed by Serra and Villani [4].

Keywords: computer simulations, cancer growth, cellular automata, carcinogenesis, Java.

1. INTRODUCTION

A dreaded disease, cancer is the second most common cause of death after cardiovascular disease. It affects humans of all ages and inflicts a wide variety of organs. Apart from individual suffering, the economic burden to society is immense.

Cancers are characterized by the presence of tumors. Tumors are identified based on their tissue of origin:, e.g., sarcoma is derived from muscle tissue, glioma from brain tissue [1].

Previous cellular automata-based modeling studies of cancer growth dynamics are considered in [1] [2] [3] [4] and [5].

In the present study, we used one-dimensional and two-dimensional cellular automata-based models to generate computer simulations of cancer growth dynamics. The study is divided into two parts.

Part II deals with he simulation of tumor growth and comparing the results with the Gompertz model. Part II presents a modification of the study of Serra and Villani [4]

2. GOMPERTZ EQUATION AND TUMOR GROWTH

The Gompertz equation has been shown to provide a good fit for the growth data of numerous tumors [6] . Kaplan and

Glass [6] summarizes the Gompertz growth function as follows: The growth rate is proportional to the current value, but the proportionality factor decreases exponentially in time so that

$$\frac{dx}{dt} = ke^{-\alpha t}x \qquad (1)$$

where k and α are positive constants. The Gompertz equation can be solved [4] to yield

$$x(t) = x(0)e^{[\frac{k}{\alpha}(1-e^{\alpha t})]} \qquad (2)$$

For Gompertz growth, x approaches $x(0)e^{\frac{k}{\alpha}}$ as $t \to$ infinity. Thus, the asymptotic value depends on, and is always greater than, the initial value [6].

3. COMPUTER SIMULATIONS

In this section we present the method used in simulating tumor growth using one-dimensional and two-dimensional cellular automata.

3.1. ONE – DIMENSIONAL CA

Using a one – dimensional array, we counted the affected or cancerous cells using rule 30 on cellular automata (CA) [6]. We obtained the subsequent states of the cells by analyzing their neighbors simultaneously.

To do this, we must first declare a one- dimensional (1D) array of cells with their initial states. The values in this array constitute either 1 or 0, which we correspond to cancerous and non-cancerous cells, respectively.

Here, we used closed boundary condition for the cellular automata lattice. Below is the algorithm used for the 1D CA model:

For every generation
{

    if the observed cell is the front (first) cell

        left neighbor is the rear (last) cell

        right neighbor is the cell next to its position

    else if the observed cell is the rear (last) cell

        left neighbor is the cell previous to its position

        right neighbor is the front (first) cell

    else if the observed cell is in the "middle"

        left neighbor is the cell previous to its position

        right neighbor is the cell next to its position

}

We now construct the method implementing our rule that describes the new state of the cell given its neighbors. The method returns the new state of each cell in this rule, which is rule 30: $(111) \to 0$, $(110) \to 0$, $(101) \to 0$, $(100) \to 1$, $(011) \to 1$, $(010) \to 1$, $(001) \to 1$, $(000) \to 0$. The middle cell in every triple changes in state in $2^3 = 8$ possible arrangements.

The algorithm for this procedure is as follows:
For an observed cell
{
If observed cell is 1

    If left neighbor is 1

        If right neighbor is 1

            State of Observed Cell is 0

        Else if right neighbor is 0

            State of Observed Cell is 0

    Else if left neighbor is 0

        If right neighbor is 1

            State of Observed Cell is 0

        Else if right neighbor is 0

            State of Observed Cell is 1

Else if observed cell is 0

    If left neighbor is 1

        If right neighbor is 1

            State of Observed Cell is 1

        Else if right neighbor is 0

            State of Observed Cell is 1

    Else if left neighbor is 0

        If right neighbor is 1

            State of Observed Cell is 1

        Else if right neighbor is 0

            State of Observed Cell is 0

Return new state of observed cell

}

We now deal with the simulation of the growth of cancerous cells using a graph since we have the states of the cells in a given time frame (or number of generations). We obtained the graph by plotting the percentages versus the generation of cancerous cells.

The graph that we obtained using the CA model is in close agreement with the Gompertz model.

To further illustrate the one-dimensional approach, considered 50 cells initially arranged accordingly: 1000101010 0000110001 0000000010 0010100010 1100000010. Using rule 30, we obtain the following data in Table 3.1 after 60 generations.

Table 3.1 (Number of Cancerous Cells and Percentage in 60 Generations)

GENERATION	CANCEROUS CELLS USING CA	PERCENT USING CA
0	1	0.033333333
1	3	0.1
2	3	0.1
3	6	0.2
4	4	0.133333333
5	9	0.3
6	5	0.166666667
7	12	0.4
8	7	0.233333333
9	12	0.4
10	11	0.366666667
11	14	0.466666667
12	12	0.4

13	19	0.633333333
14	13	0.433333333
15	22	0.733333333
16	15	0.5
17	19	0.633333333
18	20	0.666666667
19	24	0.8
20	21	0.7
21	23	0.766666667
22	23	0.766666667
23	28	0.933333333
24	26	0.866666667
25	25	0.833333333
26	24	0.8
27	28	0.933333333
28	27	0.9
29	26	0.866666667
30	27	0.9
31	29	0.966666667
32	18	0.6
33	28	0.933333333
34	20	0.666666667
35	33	1.1
36	17	0.566666667
37	32	1.066666667
38	21	0.7
39	26	0.866666667
40	26	0.866666667
41	25	0.833333333
42	28	0.933333333
43	24	0.8
44	22	0.733333333
45	28	0.933333333
46	23	0.766666667
47	28	0.933333333
48	21	0.7
49	30	1
50	21	0.7
51	25	0.833333333
52	26	0.866666667
53	21	0.7
54	29	0.966666667
55	20	0.666666667
56	31	1.033333333
57	23	0.766666667
58	28	0.933333333
59	26	0.866666667

Note that we have a graph similar to the Gompertz graph, where it is increasing but asymptotic to 1 The data in Figure 3.1 were used to count the number of cancerous cells using the Gompertz equation.

The covariance between the results using 1D CA and the Gompertz equation is 0.075995.

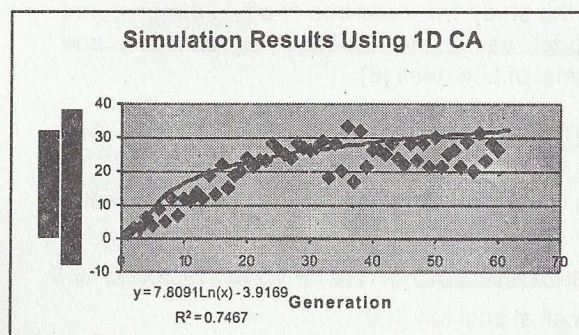Figure 3.1 (Simulation Results using 1D CA)

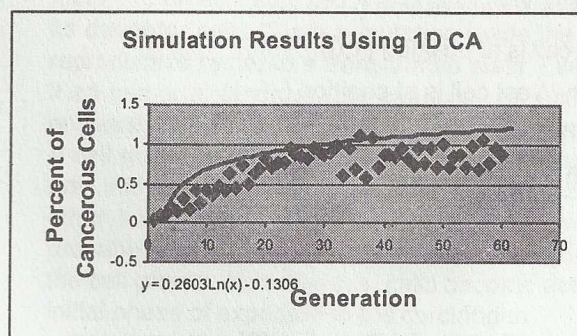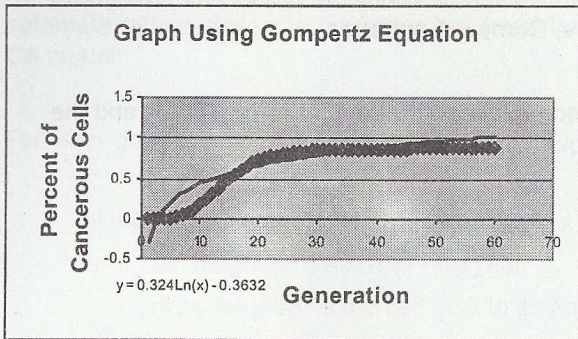Figure 3.2 (Simulation Results using 1D CA – Percentages)

Figure 3.3 (Graph of Gompertz Equation using Percentages)

Graph Using Gompertz Equation

y = 0.324Ln(x) - 0.3632
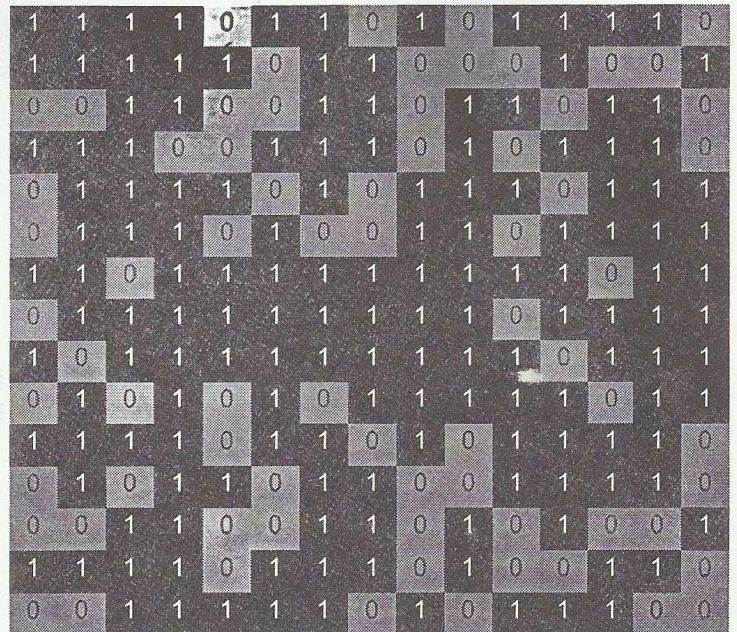
3.2. TWO – DIMENSIONAL CA

In this part of the study we made use of a two-dimensional (2D) CA model using the Moore neighborhood and Conway's Gamel of Life rules [6].

The following is the algorithm used to identify a given cell's neighbors.

For a certain cell at position (0,0)
{

    North-West cell is at position (-1,1)

    North cell is at position (0,1)

    North-East cell is at position (1,1)

    West cell is at position (-1,0)

    East cell is at position (1,0)

    South-West cell is at position (-1,-1)

    South cell is at position (0,-1)

    South-East cell is at position (1,-1)

}

Using Conway's Game of Life rules [6], we can now update the cell's state by counting the cells that are alive, that is, noncancerous, from its neighbors. The transition rule is as follows:

For the neighbors of the observed cell
{

    if(alive = 2)

        cell's state stays the same

    else if((alive = 3)

        cells' state will be the opposite

    else

        state will be dead

}

Let us now take an example to illustrate the method described previously. We take 225 cells arranged in a 15x15 matrix with values as in Table 3.2, where the black cells are the dead or cancerous cells and the gray alive or non-cancerous cells.

We now analyze these cells in 20 generations following the process we have discussed using Conway's Game of Life rule. The number of cancerous cells is summarized in Table 3.2.

Table 3.2 (Number of Cancerous Cells and Percentage in 20 Generations)

GENERATION	CANCEROUS CELLS USING CA	PERCENT USING CA
0	0	0
1	154	0.77
2	160	0.8
3	191	0.955
4	172	0.86
5	176	0.88
6	158	0.79
7	173	0.865
8	160	0.8
9	178	0.89
10	152	0.76
11	171	0.855
12	177	0.885
13	172	0.86
14	157	0.785
15	170	0.85
16	170	0.85
17	178	0.89
18	168	0.84
19	173	0.865
20	178	0.89

Figure 3.4 (Simulation Results Using 2D CA)

Simulation Results Using 2D CA

$y = 29.288\text{Ln}(x) + 98.042$
$R^2 = 0.3932$

Figure 3.5 (Simulation Results Using 2D CA - Percentages)

Simulation Results Using 2D CA

$y = 0.1464\text{Ln}(x) + 0.4902$
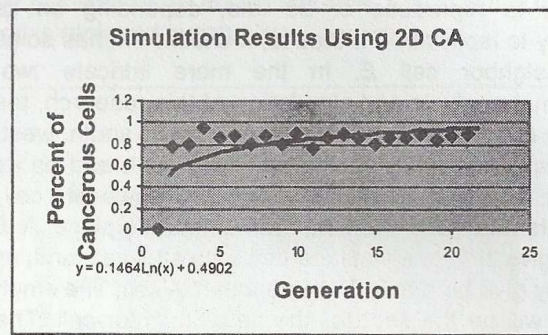
Figure 3.6 (Graph of Gompertz Equation using Percentages)

Graph Using Gompertz Equation

$y = 0.5134\text{Ln}(x) - 0.5525$
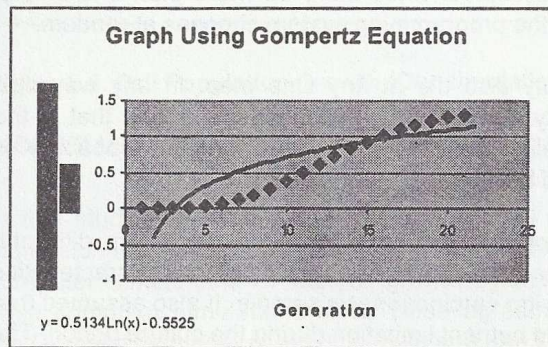
Figs. 3.5 and 3.6 show 2D CA model as compared with is the Gompertz model. The covariance obtained is 0.025932254.
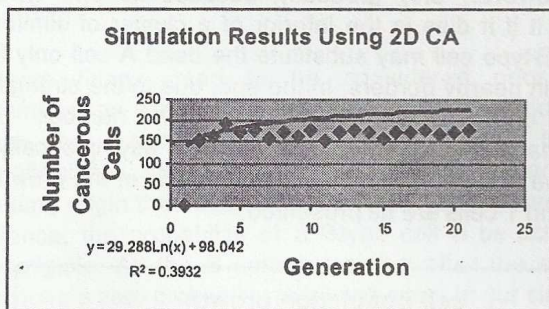
3.3. SIMULATION OF *IN VITRO* CARCINOGENESIS

Next, we used a modified version of Serra and Villani's study [4] of *in vitro* carcinogenesis.

An *in vitro* test uses cells which can mutate a number of times. A normal cell B in the test may undergo a series of mutations until it acquires a malignant phenotype. It may mutate to an activated cell A and pass this characteristic to its daughter cells. Such a mutation leads the A cell, in its reproductive cycle, to a transformed state T which renders it an immortalization or, the capability to replicate almost endlessly. However, if a transformation does not occur, the B cell grows to a full monolayer. T cells pile up, overgrow and infiltrate the monolayer. The B and A cells, on the other hand, inhibit their contact. It is assumed that the probability of spontaneous activation is negligible during the cell growth. Nonetheless, cells become activated in the initial phase of exposure to the carcinogen.

A cell may, as well, do nothing, duplicate, give birth to a different cell, or die. If the cell-doubling time is one time step, at each time step, a biological cell of type A or B may

either try to reproduce or be idle, depending on its probability to replicate. If it tries to, it checks if it has some empty neighbor cell E. In the more intricate two-dimensional analysis and simulation of this research, the B, A, T or E cell has eight neighbors— on its south, west, north, east, southeast, southwest, northwest, and on its northeast. And if it has at least one empty adjacent cell, some state change in the neighborhood takes place. A B cell may give birth to a similar B cell or to an A cell, and, an A cell may give birth to a T or to another A cell. The empty neighbor will be the spot for the new daughter cell. The algorithm for updating state cells, thus, proceeds in two steps: first, the CA cells occupied by B's or A's are considered, and each reproducing cell identifies the empty CA cell; then, all the empty CA's are considered, and those which have been selected by a neighbor for reproduction become occupied. Shall there be more than one empty location, the programming system chooses at random.

A cell may also die at any time step. In any way, the probability that a normal cell dies is less than that of the active cell. In the CA, a T cell's death probability is neglected because of its complexity.

In each of these cases, the model considers different probability alternatives— depending on the characteristics of the in vitro carcinogenesis sample. It also assumed that there is no nutrient limitation during the culture period. The growth of the population is bounded only by the crowding of the cells.

The pseudo-code for the transition rules of the CA-based carcinogesis dynamics is as follows:

For every time t
{
    For every non-empty cell
    {
        Determine, by a probabilistic method, whether the cells die off.

        If not
        {
            Determine whether reproduction will be attempted. [Let these cells be in G1]

            For every cell in G1, verify whether there is at least an empty cell in the neighborhood. [Let these be in G2]

            For every cell in G2, determine the direction of reproduction.

            If there are more available sites, choose at random.
        }
    }

}

For every empty cell
    {
        Determine whether at least one of the neighbors has a direction of reproduction pointing to it. [Let these be in G1]

        If all the cells in G1 have a common state, then let the next state of the current cell be similar.
        Otherwise, choose at random among the states

        If the new state is A, then change it to T according to a fixed probability
    }
}

Serra and Villani [4] performed computer experiments using a grid of 400*400=160,000 CA cells to visualize and study the properties discussed. A(t), B(t) and T(t) are denoted for the number of cells of A, B and T type at time t. M(t) = A(t) + B(t) is the total number of non transformed cells. Typically, there is first a phase where each initial cell, be it either A or E, generates a cluster of daughter T cells. The clusters are separated in space. AType clusters, therefore, grow undisturbed in this phase without the competition from the B cells. Nevertheless, their growth rate is slower than that of B-Type clusters because of their higher death rate. At a certain point, clusters begin to collide. Hence, A cells are contended. The whole space is eventually filled with cells. While the B cells invade and T cells increase, the A's eventually disappear. An AType fades, however, only gradually, because its own type replaces it if it dies in the interior of a cluster of similar cells. A B-type cell may substitute the dead A cell only if they are in nearby borders. In the end, due to the strength of the carcinogens applied, a high number of transformations makes T cells expand, asymptotically, across the system. The quantitative aspects of the growth of A, B and T cells are as presented.
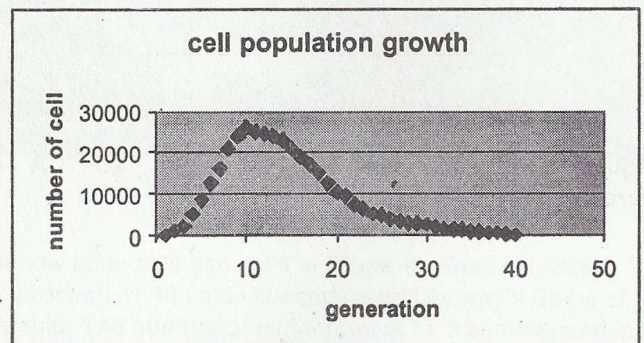

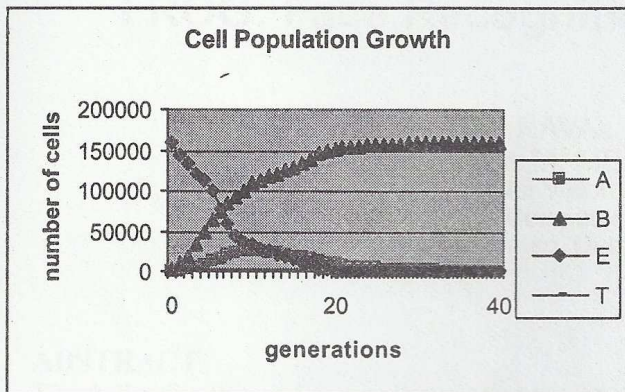Figure 3.6. Cell population growth of A-type

Figure 3.7 Cell population growth of A, B, E, T-type

In our own simulations, we used 50*50=2500 random cell types. We used Java Math.random(). Function. We assigned the various probabilities for each respective cell type:

    (i) the changeable probabilities of birth and death of A,B,T

```
double[] d = {0.001, 0.3, 0.0};
double[] b = {0.01, 0.49, 0.50};
```

    (ii) the probabilities of reproduction and transformation of A,B,E,T

```
double[][] r = { { 0.5, 0.5, 0.0},
                 { 0.5, 0.5, 0.0},
                 { 0.0, 0.0, 1.0} };
double[][] t = { { 0.5, 0.5, 0.0 },
                 {0.0, 0.5, 0.8 },
                 { 0.0, 0.0, 1.0 } };
```

We assigned each type a color in the visualization using applets.

Some things need to be considered prior to the comparison with Serra and Villani's [4] simulations. First are the parameters (or values) of the biological probabilities. Serra and Villani's simulations start off with a time origin that is set at the end of the exposure period. Hence, the probability of a B-type cell to be activated is negligible. All the B cells remaining after the exposure acquire a zero probability to be activated. In our simulation, since we are not dealing with in vitro test, we are considering the probability of an exposure to carcinogen during cell growth. Hence, there is a probability of a B-type turning into an A-type. This resulted to an increase of B at the start but a decline towards the end.

Also, our simulations used a bigger probability for A-type cells. That is, activation is more likely to transform with a constant exposure to carcinogen during cell growth. This will be evident in the resulting number of T cells compared to the results of Serra's simulations.

We followed Serra and Villani's [4] rule in which a cell dies and is replaced eventually.
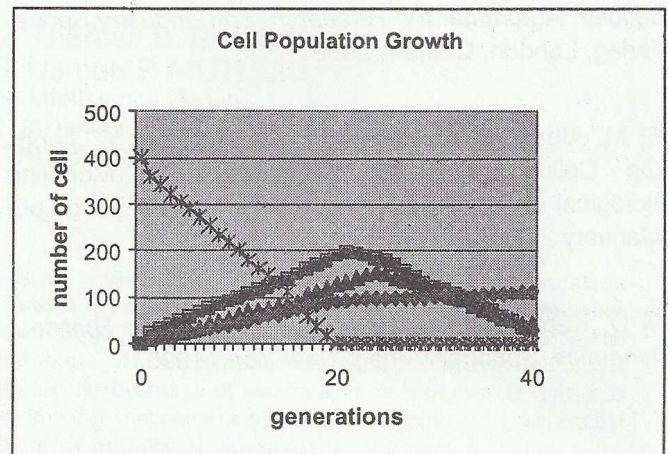

Figure 3.8. Cell Population Growth (Our simulations)

4. CONCLUSION

In this study, we have used one-dimensional and two-dimensional cellular automata-based models to generate computer simulations of cancer growth dynamics. Our Java computer simulations show close agreement with the Gompertz's model of tumor growth and the CA model of *in vitro* carcinogenesis developed by Serra and Villani [4].

ACKNOWLEDGMENTS

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