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MATHEMATICAL MODEL OF CELLULAR AUTOMATA IN SIMULATION OF CANCEROUS GROWTH USING PERCOLATION THEORY

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Abstract : Recent years have seen increasing understanding of the way in which simple system of Difference Equations can exhibit an astonishing array of dynamic behavior. Phenomenological techniques have been developed for analyzing apparently complicated, irregular behavior of discrete dynamical system. This paper has been designed to be a descriptive version non-linear dynamical system, making it speculative and thought provoking. A brief of application of non-linear dynamics is explained. There are various tools to gain the comprehensive over view of non-linear like cellular automata, Hurst component, and percolation theory etc. We shift the center of focus from general systems to specific medial analysis within the Mathematical framework. Using Cellular automata (CA) and Percolation theory we have modeled the tumor growth. We propose the models for studying cancerous disorders. These CA and Percolation models are used to support the current Biological thinking.

IndexTerms **–** Cellular automata, percolation, cancerous growth, discrete dynamical system

1. INTRODUCTION

The world of Mathematics has been confined to the linear world. This is to say, Mathematicians have overlooked dynamical systems as random and un predictable. . The only system that could be understood in the past was those that we believed to be linear, that is to say, systems that follow predictable patterns and arrangements. However the problem arises that we human do not live in an even remotely linear world; in fact our world should be categorized as non-linear [1].

Using the tools cellular automata (CA) and percolation theory, non-linear systems can be overviewed in a comprehensive manner. These mathematical tools serve as a novel computational approach with which we demonstrate using simulated data that the approach has good power for identifying high-order, non-linear interactions in dynamical systems regarding Biomedical Science used to capture some essential characteristics of cancer cell kinetics.

The identification and characterization of common complex mathematical multifactorial human diseases remain a statistical and computational challenge. On the biomedical front, reasonable levels of progress have been made and are being made in the fight against cancer [2]. Despite the advances however, challenges remain in the detection, treatment and management of these diseases that engender multidisciplinary approaches in many circumstances.

Against this background, we propose and consider mathematical models of the cancer using CA and Percolation theory. These models are used to capture some essential characteristics of cancer cell kinetics.

1.1. CELLULAR AUTOMATA

The increasing prominence of computers has led to a new way of viewing nature as a form of computation. That is, we treat objects as simple Robots, each obeying its own set of laws.

What is cellular automata?

- Cellular automata is a branch of Automata which is a branch of Computer science.
- A cellular automaton is an array of identically programmed automata or " cells" which interact according to the set of rules which have a greater proximity to their neighboring cells [3].
- It is a dynamical system in which cells are generated according to some law
- This generation is based on initial conditions. So starting with initial condition applying certain law cells are generated.
- The transition of cells takes place over a period of time.
- The array usually form a one dimensional string of cells, a two dimensional grid or a three dimensional solid.

CA is a perfect feedback machines. More precisely, they are mathematical finite state machines, which change the state of their cells step by step. Each cell has one of 'k' possible states. Sometimes of a k-state Cellular Automaton.

Dynamics of CA is entirely discrete in time, space and state. It is a Robot which gives specific responses to specific inputs. The space of the system, which consists of cell of one, two or three dimensions, may be finite or infinite. In each cell, the system can assume a discrete number of state values say k values. The configuration of the entire system at any time is defined by the set of state values $\{s_i\}$ in all the cells $\{i\}$

To run a cellular automaton we need two entities of information:

1) An initial state of its cells (i.e. an initial layer)
2) A set of rules or laws [4].

These rules describe how the state of a cell in a new layer (in the next step) is determined from the states of a group of cells from the preceding layer. Here the state of each cell "i" interacts with only its nearest neighbors "i-1" and "i+1" by the following equation

$$\mathbf{a_i^{(t+1)} = \varphi[a_{i-1}^{(t)}, a_i^{(t)}, a_{i+1}^{(t)}]} \qquad \ldots\ldots\ldots\ldots\ldots (1)$$

The rules should not depend on the position of the group within the layer.

1.2 AUTOMATION RULES

There are several ways a rule may determine the state of a cell in the succeeding layers.
In fig (a), the state of a new cell is determined by the states of 2 cells.
In fig (b), by the state of 3 cells.
In fig (c) and (d) the states of 5 cells determine the states of a new cell,
But note that the position of the new cell with respect to the group is different in (c)) and (d).

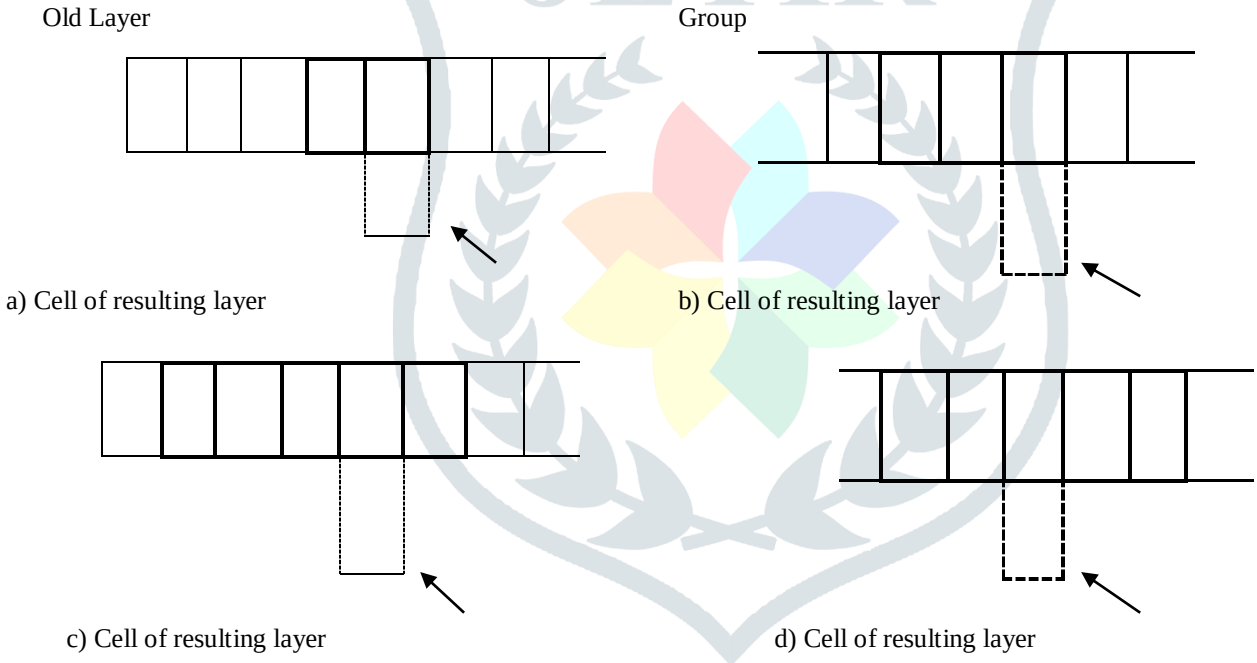

Fig-1. Automation Rules

The cellular automata approach has many advantages.

For example,
1. CA approach is non-parametric
2. It is model free

That is no mode of inheritance needs to be specified. In its current form this approach can be directly applied to simulate any multifactorial human diseases. In particular we use cellular automata to simulate the growth of Brain tumor.

1.2 PERCOLATION

Percolation is originated from the Latin words "per" which means "through" and "colare" which means "to flow". In everyday language percolation is associated with the movement of water through the random fissures in soil or coffee rounds.

When a structure changes from a collection of many disconnected parts into basically one big conglomerate, we say that Percolation occurs. In a more technical sense, invasion percolation is an algorithm that models the expansion of a network throughout a medium with randomly distributed heterogeneities in strength. The resulting networks always expand into the weakest available sides, yielding structures with voids on a wide range of length scales and pathways that are tortuous over many scales as well.

For example, assume that the whole 2-dimensional plan is partitioned into regular array of pores which are either open (with probability 'p') or closed (with probability 1-p)

- Let us pick one of the open pores at random and try to inject a fluid at that point. As a consequence, if the formation is below the percolation threshold "i.e if the probability p is less than p_c"
- We expect that the pore is a part of a relatively small cluster of open pores. By a cluster we mean a collection of connected open pores, which is completely surrounded by closed none.

In other words, below the threshold we will be able to inject only some finite amount of the fluid until the cluster is filled but more. If the probability is above the threshold value then the chances are good that the corresponding cluster is infinitely large. We can inject as much as fluid as we like. Right at the percolation threshold p_c the maximal cluster is a fractal. In a practical example, the water percolates through the coffee grains.

2. SIMULATION OF CANCEROUS GROWTH USING CELLULAR AUTOMATA AND PERCOLATION

The last few years have seen a new wave of mathematical models for cancer biology. Mathematical modelling of cancer growth dates back at least as far as the 1950s. The establishment during the 1900s of detailed molecular mechanisms underlying tumor growth and progression are enabling a new generation of specific and data-oriented models [2].

Cellular automata are models of distributed dynamical systems whose structure is particularly well-suited to ultra-fast, exact numerical simulation [5]. We use cellular automata to simulate the growth of Brain tumor. The term **Cancer** applies only to malignant tumors [6].

At any particular instant of the cancer patient, cancer cells and other cell positions can be monitored. 1-D and 2-D cellular automata modes are designed and implanted in order to simulate brain tumor growth [5]. Specifically a 2-Dimensional M rows, N columns (MxN) grid is implemented. Each cell of the grid represents the location of a living cell. At each time instant, each one of the cells obtains any one of the following values

N - Normal Cell
C - Cancer cell in reproduction phase
C - Cancer cell
D - Dead cell
Each cell is provided with a lifetime and dissolution time.
With the help of medical knowledge the dynamics of CA can be described by the following rules

1. N → c (i.e. the normal cell turns into a cancer cell)
2. c → C (i.e. the cancer cell turns into the reproduction cell)
3. C → 2c (i.e. the reproduction cell becomes twice cancer cells)
4. c → D (i.e. cancer cell dies)
5. N → D (i.e. the normal cell dies)
6. D → N (i.e. the dead cell location is occupied by a normal cell)
7. D → c (i.e. the dead cell location is occupied by a cancer cell)

The above rules of the cellular automata are used to evolve it. The process 1,2 and 3 are continuous whereas 4,5,6 and 7 takes place after a long period. Initially we set up an arbitrary grid of cells like

N	**c**	**C**	**C**	**D**

Using a programming in C language to simulate the brain tumor growth we have used the rules 1, 2 and 3 and carried out the iterations for 60 times steps.

The output of the iterations for simulation of the CA model is as follows

t=0	N	c	C	C	D
t=1	C	C	C	2c	D
t=2	C	2c	2c	2C	D
t=3	2c	2C	2C	4c	D
t=4	2C	4c	4c	4C	D
t=5	4c	4C	4C	8c	D
t=6	4C	8c	8c	8C	D
t=7	8c	8C	8C	16c	D
t=8	8C	16c	16c	16C	D
t=9	16c	16C	16C	32c	D
t=10	16C	32c	32c	32C	D
t=11	32c	32C	32C	64c	D
t=12	32C	64c	64c	64C	D
t=13	64c	64C	64C	128c	D

t=14	64C	128c	128c	128C	D
t=15	128c	128C	128C	256c	D
t=16	128C	256c	256c	256C	D
t=17	256c	256C	256C	512c	D
t=18	256C	512c	512c	512C	D
t=19	512c	512C	512C	1024c	D
t=20	512C	1024c	1024c	1024C	D
t=21	1024c	1024C	1024C	2048c	D
t=22	1024C	2048c	2048c	2048C	D
t=23	2048c	2048C	2048C	4096c	D
t=24	2048C	4096c	4096c	4096C	D
t=25	4096c	4096C	4096C	8192c	D
t=26	4096C	8192c	8192c	8192C	D
t=27	8192c	8192C	8192C	16384c	D
t=28	8192C	16384c	16384c	16384C	D
t=29	16384c	16384C	16384C	32768c	D
t=30	16384C	32768c	32768c	32768C	D
t=31	32768c	32768C	32768C	65536c	D
t=32	32768C	65536c	65536c	65536C	D
t=33	65536c	65536C	65536C	131072c	D
t=34	65536C	131072c	131072c	131072C	D
t=35	131072c	131072C	131072C	262144c	D
t=36	131072C	262144c	262144c	262144C	D
t=37	262144c	262144C	262144C	524288c	D
t=38	262144C	524288c	524288c	524288C	D
t=39	524288c	524288C	524288C	1048576c	D
t=40	524288C	1048576c	1048576c	1048576C	D
t=41	1048576c	1048576C	1048576C	2097152c	D
t=42	1048576C	2097152c	2097152c	2097152C	D
t=43	2097152c	2097152C	2097152C	4194304c	D
t=44	2097152C	4194304c	4194304c	4194304C	D
t=45	4194304c	4194304C	4194304C	8388608c	D
t=46	4194304C	8388608c	8388608c	8388608C	D
t=47	8388608c	8388608C	8388608C	16777216c	D
t=48	8388608C	16777216c	16777216c	16777216C	D
t=49	16777216c	16777216C	16777216C	33554432c	D
t=50	16777216C	33554432c	33554432c	33554432C	D
t=51	33554432c	33554432C	33554432C	67108864c	D
t=52	33554432C	67108864c	67108864c	67108864C	D
t=53	67108864c	67108864C	67108864C	134217728c	D
t=54	67108864C	134217728c	134217728c	134217728C	D
t=55	134217728c	134217728C	134217728C	268435456c	D
t=56	134217728C	268435456c	268435456c	268435456C	D
t=57	268435456c	268435456C	268435456C	536870912c	D
t=58	268435456C	536870912c	536870912c	536870912C	D
t=59	536870912c	536870912C	536870912C	1073741824c	D
t=60	536870912C	1073741824c	1073741824c	1073741824C	D

Incorporating the rules 4, 5, 6 and 7 are carried out further iterations and we observe an enormous growth of cancer cells.

The output at the end of 100 iterations is as follows

t=0	N	c	C	C	D
t=60	536870912C	1073741824c	1073741824c	1073741824C	D
t=61	1073741824c	1073741824C	1073741824C	2147483648c	D
t=62	1073741824C	2147483648c	2147483648c	2147483648C	D
t=63	2147483648c	2147483648C	2147483648C	4294967296c	D
t=64	2147483648C	4294967296c	4294967296c	4294967296C	D
t=65	4294967296c	4294967296D	4294967296D	8589934592c	D
x→D					
t=66	4294967296C	4294967296D	4294967296D	8589934592C	D
t=67	8589934592c	4294967296D	4294967296D	$1.7179869184 \times 10^{10}$c	D
t=68	8589934592C	4294967296D	4294967296D	$1.7179869184 \times 10^{10}$C	D
t=69	$1.7179869184 \times 10^{10}$c	4294967296D	4294967296D	$3.4359738368 \times 10^{10}$c	D
t=70	$1.7179869184 \times 10^{10}$C	4294967296N	4294967296N	$3.4359738368 \times 10^{10}$C	D
D→N					
t=71	$3.4359738368 \times 10^{10}$c	4294967296D	4294967296D	$6.8719476736 \times 10^{10}$c	D
N→D					

t=72	3.4359738368 x 10^{10}C	4294967296D	4294967296D	6.8719476736 x 10^{10}C	D
t=73	6.8719476736 x 10^{10}c	4294967296D	4294967296D	1.37438953472 x 10^{11}c	D
t=74	6.8719476736 x 10^{10}C	4294967296D	4294967296D	1.37438953472 x 10^{11}C	D
t=75	1.37438953472 x 10^{11}c	4294967296D	4294967296D	2.74877906944 x 10^{11}c	D
t=76	1.37438953472 x 10^{11}C	4294967296D	4294967296D	2.74877906944 x 10^{11}C	D
t=77	2.74877906944 x 10^{11}c	4294967296D	4294967296D	5.49755813888 x 10^{11}c	D
t=78	2.74877906944 x 10^{11}C	4294967296c	4294967296c	5.49755813888 x 10^{11}C	C
D→c					
t=79	5.49755813888 x 10^{11}c	4294967296C	4294967296C	1.099511627776 x 10^{12}c	C
t=80	5.49755813888 x 10^{11}C	8589934592c	8589934592c	1.099511627776 x 10^{12}C	2c
t=81	1.099511627776 x 10^{12}c	8589934592C	8589934592C	2.199023255552 x 10^{12}c	2C
t=82	1.099511627776 x 10^{12}C	1.7179869184 x 10^{10}c	1.7179869184 x 10^{10}c	2.199023255552 x 10^{12}C	4c
t=83	2.199023255552 x 10^{12}c	1.7179869184 x 10^{10}C	1.7179869184 x 10^{10}C	4.398046511104 x 10^{12}c	4C
t=84	2.199023255552 x 10^{12}C	3.4359738368 x 10^{10}c	3.4359738368 x 10^{10}c	4.398046511104 x 10^{12}C	8c
t=85	4.398046511104 x 10^{12}c	3.4359738368 x 10^{10}D	3.4359738368 x 10^{10}D	8.796093022208 x 10^{12}c	8D
c→D					
t=86	4.398046511104 x 10^{12}C	3.4359738368 x 10^{10}D	3.4359738368 x 10^{10}D	8.796093022208 x 10^{12}C	8D
t=87	8.796093022208 x 10^{12}c	3.4359738368 x 10^{10}D	3.4359738368 x 10^{10}D	1.7592186044416 x 10^{13}c	8D
t=88	8.796093022208 x 10^{12}C	3.4359738368 x 10^{10}D	3.4359738368 x 10^{10}D	1.7592186044416 x 10^{13}C	8D
t=89	1.7592186044416 x 10^{13}c	3.4359738368 x 10^{10}D	3.4359738368 x 10^{10}D	3.5184372088832 x 10^{13}c	8D
t=90	1.7592186044416 x 10^{13}C	3.4359738368 x 10^{10}N	3.4359738368 x 10^{10}N	3.5184372088832 x 10^{13}C	8N
D→N					
t=91	3.5184372088832 x 10^{13}c	3.4359738368 x 10^{10}D	3.4359738368 x 10^{10}D	7.0368744177664 x 10^{13}c	8D
N→D					
t=92	3.5184372088832 x 10^{13}C	3.4359738368 x 10^{10}D	3.4359738368 x 10^{10}D	7.0368744177664 x 10^{13}C	8D
t=93	7.0368744177664 x 10^{13}c	3.4359738368 x 10^{10}D	3.4359738368 x 10^{10}D	1.40737488355328 x 10^{14}c	8D
t=94	7.0368744177664 x 10^{13}C	3.4359738368 x 10^{10}D	3.4359738368 x 10^{10}D	1.40737488355328 x 10^{14}C	8D
t=95	1.40737488355328 x 10^{14}c	3.4359738368 x 10^{10}D	3.4359738368 x 10^{10}D	2.81474976710656 x 10^{14}c	8D
t=96	1.40737488355328 x 10^{14}C	3.4359738368 x 10^{10}D	3.4359738368 x 10^{10}D	2.81474976710656 x 10^{14}C	8D
t=97	2.81474976710656 x 10^{14}c	3.4359738368 x 10^{10}D	3.4359738368 x 10^{10}D	5.62949953421312 x 10^{14}c	8D
t=98	2.81474976710656 x 10^{14}C	3.4359738368 x 10^{10}c	3.4359738368 x 10^{10}c	5.62949953421312 x 10^{14}C	8c
D→c					
t=99	5.62949953421312 x 10^{14}c	3.4359738368 x 10^{10}C	3.4359738368 x 10^{10}C	1.125899906842624 x 10^{15}c	8C
t=100	5.62949953421312 x 10^{14}C	6.8719476736 x 10^{10}c	6.8719476736 x 10^{10}c	1.125899906842624 x 10^{15}C	16c

After 1000 iterations the growth of the cancer cells becomes uncontrollable. The obtained simulated dynamics are compared to theoretical mathematical models of cancer growth, as well as the date of cell culture experiments.

Hopefully these mathematical models will lead to improved strategies and better treatment of cancer. The growth of cancer cells is considered as one of the chaotic patterns in natural science. The growth of cancer cells can be better explained by using fractals, in particular, percolation theory. The cancer cells seem to follow a specific power law in the growth pattern. By studying the relation of the cancer cells and the percolation theory it is possible to obtain the time period for the growth of the cells and also a pattern to identify the infectious and non-infectious cells and the path minimum gaps between them.

Given a square lattice of tissue with L^2 sites, we describe the cells according to the chosen probability. We assume that all those cells which are located along the left side of the square are infected or cancerous. We take this to be our initial condition. In this simple model we can simulate the cancerous growth. We proceed in discrete time step. In each step, the cancer cells turn all its neighboring normal cells to cancerous one.

If the normal cells are very sparse, due to a low probability 'p' then the cancer cells have not much normal cells to infect and it leaves most of the cells in the lattice unharmed quickly. If the normal cells are very dense, then they do not have much chance for survival. That is the cancerous growth will be rapid.

So there must be an intermediate probability which leads to a maximal duration of infection of cancer cells which is termed as the "percolation threshold". The maximal cluster size is closely related to the duration of infection or the tumor growth. At the percolation threshold p_c the normal cluster is a fractal. The fractal percolation cluster at the threshold is called the "incipient percolation cluster".

As a numerical/algorithmic check, the algorithms for computing fractal dimensions are tested on computer generated percolation clusters at the percolation threshold [7]. On observation, fractal behavior was noticed on length scales, dependent in the actual cluster size and the fractal characteristics are determined for each cluster.

In sights provided by the fractal image analysis and percolation model provide a unifying framework yielding mechanistic explanations for a combination of observations within the tumor [8]. Using invasion percolation we are able to simulate the cancer or the tumor growth [9].

Implementations of these mathematical tools have made a remarkable contribution in the field of Medical Biology in minimizing cancerous growth through mathematical treatments.

FUTURE ASPECTS

The remarkable inference made from the mathematical treatments is that the concept discussed in CA and in percolation theory during simulation, paves a way for the better strategies and improved treatment of cancer.

As discussed earlier, for the growth rate of the cancer cell to be small, the normal cells in the lattice considered should be very sparse. So we suggest the pharmacologists, to invent medicinal drugs which would keep the cells in sparse (i.e.) increase the distance between the cells, so that the growth of cancer cells would be minimized leaving the patient safe.

Hence by implementing percolation theory in drug therapy we opt to a mathematical treatment of cancer, by reducing the infection caused by cancer cells. This will be an improved strategy in mathematical treatment of cancer. Cellular automata constitute a radical departure from the traditional Partial Differential Equations (PDE) approach to distributed dynamics.

Linkages and agreements between the data and our models show how well the models perform in capturing biomedical reality. Within this framework we propose models for studying cancerous and pre-cancerous disorders. These models are used to support the current biomedical thinking.

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