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Design a Cellular Environment Model to Predict Radiation Damage of Lung Cells Induced Radon Progeny Alpha Particles

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ABSTRACT

Alpha particle irradiation from radon progeny is one of the major natural source of effective dose for public population. Oncogenic transformation is a biological effectivness of radon progeny alpha particle hits.
Various biological models including cultured cells and animals have been found useful for studing the carcinogenesis effects of radon progeny alpha particles.
In this paper, sugarscape cellular automata has been presented for computational study of complex biological effect of radon progeny alpha particles in lung bronchial airways. The model included mechanism of DNA damage induced alpha particles hits and formation of transformation in the lung cells. The metabolism rate of infected cell induced alpha particles traversals in sugarscape cellular automata was followed to reach oncogenic transformation.
The model results were successfully validated by comparison with in vitro oncogenic transformation data for C3H 10T1/2 cells.
This model provides an opportunity to study the cellular and molecular changes at the various stages in radiation carcinogenesis involving human cells.
It has become well known that simulation can be used to investigate complex biomedical systems in situations where traditional methodologies are difficult or too costly to employ.

KEY WORDS: Sugarscape Cellular Automata; Oncogenic transformation; Lung cells; Radon Progeny; Alpha Particles.

INTRODUCTION

Epidemilogical studyies have shown a relation between exposure to radon and lung cancer [1, 2, 3].

The biological effects caused by exposure to ionizing radiation are the result of a complex series of physical, chemical, biological and physiological interactions. The cellular and molecular mechanisms for radon-induced carcinogenesis are not clear yet [4].

Several methods have been designed to explain the mechanism involved in the interactions between ionizing radiation and cell response, but all of them have some advantages and disadvantages [1].

The complexity of carcinogenesis process and lack of experimental data for surveying and studying has led the scientists to take advantage of computational and modeling methods to predict, recognize and treat of this dreaded disease [7, 8, 9].

Mathematical formalism, Artificial intelligent and Artificial Life are some of the computational tools of predictive radiation biology.

The cellular automata (CA) are one of the powerful tools of artificial life technique for optimization complex biological systems. This method by using simple functions and local convergence while taking neighboring effects into account could result accurate global solution [5].

Cellular automata enable by using cellular dynamics and including interaction between cells provide the suitable computational model for the study of complex system such as carcinogenesis process [5].

A cellular automaton is a collection of cells on a grid of specified shape that evolves through a number of discrete time steps according to a set of rules based on the states of neighboring cells. The rules are then applied iteratively for as many time steps as desired. Von Neumann was one of the first people to consider such a model,

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and incorporated a cellular model into his "universal constructor." Cellular automata were studied in the early 1950s as a possible model for biological systems. A CA model is represented as a lattice or array of cells. The size of this lattice is referred to as the dimension of the CA [5, 6]. The characteristics of cellular automata are given in references [5-6,7,8].

In the present work a methodology based on a combination of cellular automata and sugarscape is proposed to predict oncogenic transformation induced Radon progeny alpha particles.

Sugarscape was first introduced by Epstein and Axtell [10]. This environment is multi-agent system that used for modeling and organizing social, biological, political and economic process.

Main elements of model are Cellular Automata (environment), agents, sugar (source) and rules [7, 8, 9, 11].

Agents refer to the elements which live in the environment and have a set of properties that can change during time. Agents need to consume sugar for survival. Sugar is a generalized source which should be eaten by agents for survival. In this model agents refers to human lung cells and sugar refers to glucose that is needed for metabolism.

Biomarkers are invaluable tools for cancer detection, diagnosis, patient prognosis and treatment selection. Enhanced glucose utilization is a prominent and fundamental change in many tumors irrespective of their histological origin and the nature of mutations [12].

Metabolism as an important biomarker to diagnosis cancerous cells is used in this model to follow states of damaged cells induced alpha particles hits to be oncogenic transformation states.

The simulation results have been compared with available experimental data. To predict transformation probability induced alpha particles hits we have to define mathematical formulation for this stochastic and probabilistic event.

The objective of the present work is to evaluate oncogenic transformation by following changes in metabolism rate of infected cells which had traversal with radon progeny alpha particles.

MATERIALS AND METHODS

The cellular sugarscape model was performed in Matlab using the 2 dimensional lattices. A square lattice of size L×L grids was used to present configuration in order to explain the changes in all cell stages in a lung tissue.

Initial healthy cells are randomly distributed across the sugarscape environment (lung tissue). Every cell has the amount of sugar which is randomly from 0 to 1. Each site of lattice has the sugar level which is uniformly (Gaussian) distributed between 0 and 1. At each time step sugar level of the lattice regenerates randomly.

The direct biological effect of ^{214}Po and ^{218}Po alpha particles which passed lung cells nucleus can be the oncogenic transformation.

Epidemiologic studies on lung cancer show that the number of cells hit is an important quantity to evaluate radiation biological effect. For this purpose considering the number of hits is necessary. From experimental data cellular hits by alpha particles is described by the Poisson distribution [13, 14].

In this study, the average number of hits is calculated for different doses over 4 years exposure period, representing the average working exposure time for miners.

Alpha particle hits the normal cell, and this hits occurred with Poisson distribution as mentioned earlier. The state of each hit cell changes to infected cells. These infected cells collected the sugar from sites that they are located in and increment their sugar level. In the model, metabolism rate is used to determine cell state.

The meaning of each stage is defined as follows:

Infected stage 1 (Landscape1): a cell that has been recently infected when cellular hit with alpha particles is occurred with the Poisson distribution. In this stage by considering dose and time of exposure, the mean number of hit is calculated and based on this parameter the actual number of hits in nucleus of lung basal or secretory cells is selected from Poisson distribution.

Infected stage 2 (L2): The infected cell has been already recognized. When alpha particles pass through the cell nuclei DNA, damage is happened and cell is initiated. The metabolism rate of these damaged cells has been increased because of their cell cycle is became shorter and their mitosis is occurred rapidly. Thus they need to receive more nutrients to upgrade their level to survive. They have to compete with each other to receive threshold nutrient to continue life. If the sugar level of cells is less than threshold its stage does not change. If cell's stage didn't change within 2 time step, they become necroses and die.

Infected stage 3 (L3): The infected cell in this stage have received stage's sugar threshold. In this stage random Gaussian distribution of sugar is performed again. If the sugar wealth of cell is greater than stage's threshold, increment of stage is occurred. If the sugar level of cells is less than threshold its stage does not change. If cell's stage didn't change within 2 time step, they become necroses and die.

Transformants (T) (L4): the cells that reach this stage have the most metabolism rate and have maximum chance to be cancerous cells.

In the highest level of metabolism (Landscape 4), model is convergence. The numbers of cells in this level are oncogenic transfomant cells induced alpha particle hits which they have the maximum chance to make tumor.

The model outlined above have been implemented according to 2 dimensional CA model based on the classic sugarscape model, which describes the evolution of alpha particles infection under different condition such as dose and exposure time. The simulation flow chart of model is shown in figure 1.

We believe that cellular automata (CA) with carefully selected parameter values can obtain a clearer picture of the effects of Radon progeny alpha particles infection on the lung cells.

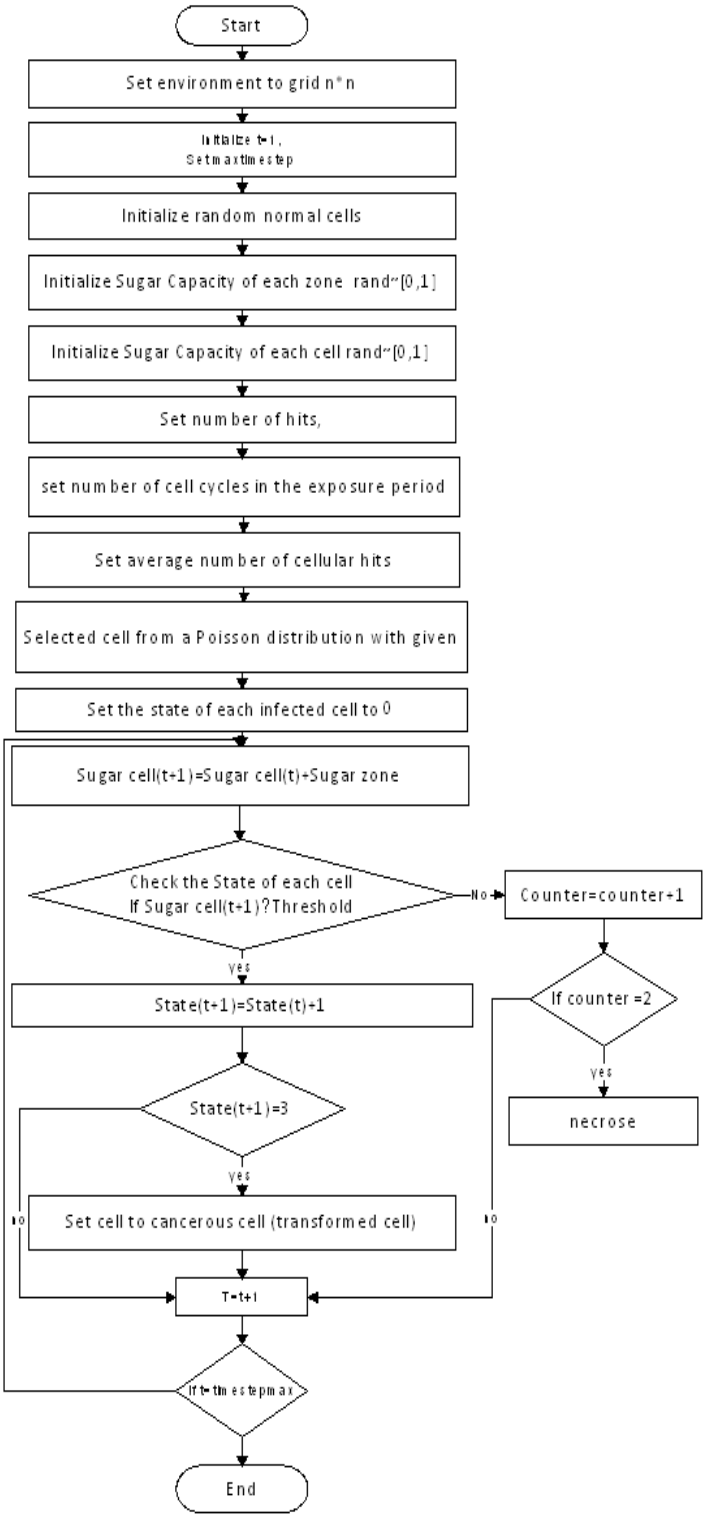

Figure 1- Flow chart describing transition between 4 infected cells stages.

RESULTS AND DISCUSSION

In this study, a stochastic CA model associated with the sugarscape environment is explored under various parameters and focused on the changes in metabolism rate due to DNA damage by Radon progeny alpha particles hits. The model determines the cellular hits with alpha particles by using Poisson distribution as above described.

Oncogenic transformation of cells, which is a necessary intermediate step in the sequence of events leading to carcinogenesis, may presently be the most relevant cellular effect for simulating carcinogenesis.
Experimental studies indicate that after alpha particles hits, some of DNA cells are broken and biological effect originate [15, 16]. If the cell is transformants, its cell cycle is changed shorter and mitosis rate is increased thus metabolism rate is increment and required more nutrient to continue life.

Oncogenic transformation predicted by CA model with comparison to experimental data of mouse C3H 10T1/2 Cells exposure to alpha particles are presented in table 1 [17, 18]. These data shows the number of transformant cells and oncogenic transformation are as a function of dose and has a liner relationship.

Data are well fitted with experimentally data that observed in vitro oncogenic transformation and survival data for C3H 10T1/2 mouse cell exposed to alpha particles by Bettega et al. and Miller et al. experimental data [17, 18].

Variation of oncogenic transformation with dose is plotted in fig 2 and compared with Miller et al. experimental data [17]. The points are the results of several independent run, performed in different time.

Table1 - Oncogenic transformation frequency predicted by CA model of lung cells exposure to alpha particles of Radon progeny in different doses comparison to experimental data of Mouse C3H 10T1/2 Cells exposure to alpha particles by Miller et al. 1995 [17].

Dose (Gy)	Number of viable cells	Number of transfomants (miller et al.1995)	Transformation frequency/ surviving cells $\times 10^{-4}$ (miller et al.1995)	Number of transformants (model prediction)	Transformation frequency/ surviving cells $\times 10^{-4}$ (model prediction)
0.1	70610	18	2.55	13	1.8
0.2	39872	18	4.51	14	3.5
0.3	47610	38	7.98	30	6.3
0.4	38739	34	8.87	28	7.2
0.5	19966	24	12	20	10
0.6	58410	67	11.5	58	9.9
0.7	24880	39	15.7	30	12.1
0.8	24120	50	20.7	41	17.1
0.9	19584	46	23.5	35	17.8
1	18750	57	30.4	45	24.2
1.2	22464	66	29.4	60	27

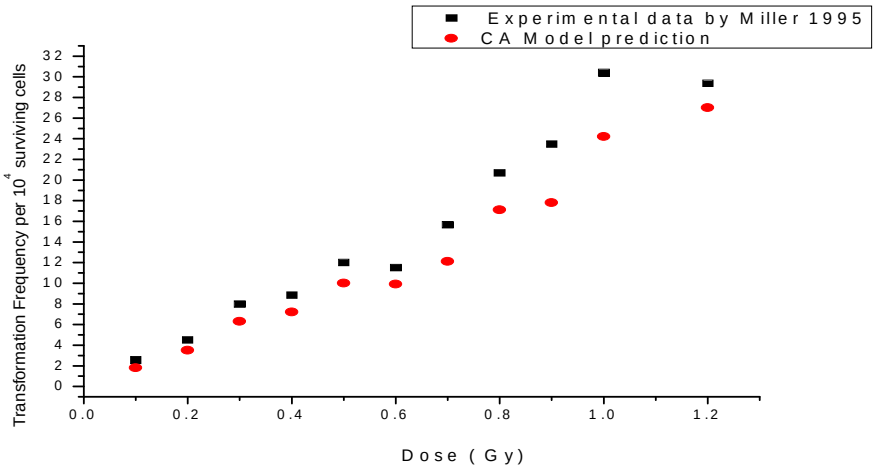

Figure2 - Trasformants per surviving cells for exposure Radon progeny alpha particles predicted by CA model and comparison with experimental data of C3H 10T1/2 cells exposure to alpha particles with Miller et al. 1995[17].

Figure 3 shows that how the number of initial infected cells change during different metabolism landscape in sugarscape cellular automata model for Dose= 4 Gy. We consider these states for changing cell from healthy to transformant based on cellular alpha particle hit and nutrient distribution.

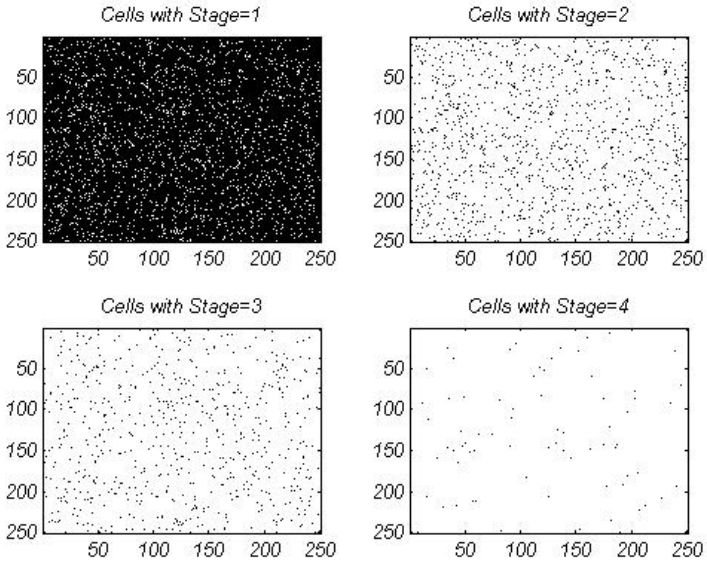

Figure 3- The number of lung cells in different stages of model based on Poisson distribution of alpha particle hit and Gaussian sugar distribution in each state. The number of cells are changed between these staged based on their metabolism rates. The cells in state 4 have the maximum metabolism rate and the most positional to become cancerous cell.

Sensitivity and specificity of this model is compared favorably with experimental approaches. This comparison shows that the Cellular Sugarscape model predicts oncogenic transformation with the highest precision, lowest error, simplest rule of the reality of the biological system, lowest time and the best fitness of complexity and stochastically of this phenomenon.

DISCUSSION

The present study was designed to investigate number of lung cell transformants in the different dose of radon progeny alpha particles by using CA model based on Sugarscape.

For the first time, a cellular sugarscape environment is used to calculate transformation frequency in lung bronchial airways induced Radon. Our major objective is an assessment of oncogenic transformation by following mechanism of cell action in different radiation doses**.**

Metabolism as an important biomarker used in this model to follow states of damaged cells induced alpha particles hits to be oncogenic transformation states.

The comparison with the experimental data indicates that metabolism rate and cellular hits are the suitable parameters to follow cancerous cells induced ionizing radiation.

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