

# Prediction of Lung Cells Oncogenic Transformation for Induced Radon Progeny Alpha Particles Using Sugarscape Cellular Automata

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## Abstract

**Background:** Alpha particle irradiation from radon progeny is one of the major natural sources of effective dose in the public population. Oncogenic transformation is a biological effectiveness of radon progeny alpha particle hits. The biological effects which has caused by exposure to radon, were the main result of a complex series of physical, chemical, biological and physiological interactions. The cellular and molecular mechanisms for radon-induced carcinogenesis have not been clear yet.

**Methods:** Various biological models, including cultured cells and animals, have been found useful for studying the carcinogenesis effects of radon progeny alpha particles. In this paper, sugars cape cellular automata have been presented for computational study of complex biological effect of radon progeny alpha particles in lung bronchial airways. The model has included mechanism of DNA damage, which has been induced alpha particles hits, and then formation of transformation in the lung cells. Biomarkers were an objective measure or evaluation of normal or abnormal biological processes. In the model, the metabolism rate of infected cell has been induced alpha particles traversals, as a biomarker, has been followed to reach oncogenic transformation.

**Results:** The model results have successfully validated in comparison with “in vitro oncogenic transformation data” for C3H 10T1/2 cells. This model has provided an opportunity to study the cellular and molecular changes, at the various stages in radiation carcinogenesis, involving human cells.

**Conclusion:** It has become well known that simulation could be used to investigate complex biomedical systems, in situations where traditional methodologies were difficult or too costly to employ.

**Keywords:** Sugars cape; Cellular Automata; Oncogenic transformation; Lung cells; Radon Progeny; Alpha Particles

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## Introduction

The human health risks that have posed by ionizing radiation have been well known. Radon gas was So far as the most important source of ionizing radiation among those that were natural origin.

Radon (<sup>222</sup>Rn) is a noble gas which has formed from radium (<sup>226</sup>Ra), then is a decay product of Uranium (<sup>238</sup>U). Uranium and radium have both occurred naturally in soils and rocks. Radon gas, which had a half-life of 3.8 days, emanated from rocks and soils and tended to concentrate in enclosed spaces like underground mines or houses.

It is a major contributor to the ionizing radiation dose which has received by the general population [1]. The average percentage contribution of various sources of ionizing radiation exposure of typical residents of the United States population in 2006 has illustrated in a pie-chart (Figure1) and prepared by the National Council for Radiation Protection and Measurement [2].

Health effects of radon, most notably lung cancer, have investigated for several decades. The proportion of all lung cancers have linked to radon, has estimated to lie between 3- 14%, depending on average radon concentration in the country, and on

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the method of calculation [2]. When radon gas has inhaled, densely ionizing alpha particles, has emitted by deposited short-lived decay products of radon (<sup>218</sup>Po and <sup>214</sup>Po) could interact with biological tissue in lungs and could lead to DNA damage and trigger cancer [1, 3].

Epidemiological studies have shown a relation between exposure to radon and lung cancer [4- 6]. Radon has caused between 3%-15% of lung cancer in the world [1]. Cancer has initiated by alterations in genes, such as oncogenes and tumour suppressors that regulate cell proliferation, survival, and other homeostatic functions.

Experimental studies have indicated that after alpha particles hits, some of DNA cells have broken, and then biological effects have originated [7, 8]. If the cell was transformants, its cell cycle has changed shorter and mitosis rate has increased thus metabolism rate was increment and has required more nutrient to continue life [4, 5, 9]. We have found p53 mutations in lung cancer associated with residential radon exposure. Unusual mutation patterns in lung tumors among underground miners have been indicated that radon had specific alterations in the genome, but the data were not sufficient [10].

**Mechanisms of Radiation Carcinogenesis**

Radiation has termed "ionizing" when it had the capacity to accelerate electrons in atomic orbitals in matter. When this matter has happened to be the double helical molecule of Deoxyribonucleic Acid (DNA) that constitutes the genetic material of our chromosomes, ionizing radiation becomes a mechanism for mutagenesis. Mutations in the genome of somatic body cells form a point of initiation of carcinogenesis. Mutations could be of three broad kinds, Point Mutations, Dimerization and Direct Physical Changes.

**Point mutations** are those changes that have affected single nucleotides, changing the nucleotide sequence and interfering with base pairing. The biochemical mechanisms are not well understood, but one such pathway is as follows [3]:

<b>Thymine (T)</b>	<i>mutation</i>	<b>5-Bromouracil (BU)</b>
<b>Base Pairs</b>	<b>A—T</b>	<i>mutation</i> <b>A—BU</b>
<b>BU</b>	<i>éolisation</i>	<b>BU*</b>

BU\* has behaved as Cytosine (C) instead of Thymine (T) in original nucleotide forming the base pair arrangement

BU—G if possible, or a localized area of unpaired bases as shown below:

<b>A C T G C T A C</b>	<b>A C BU G C T A C</b>
<b>T G A C G A T G</b>	<b>T G T G C G A</b>
	<b>A</b>

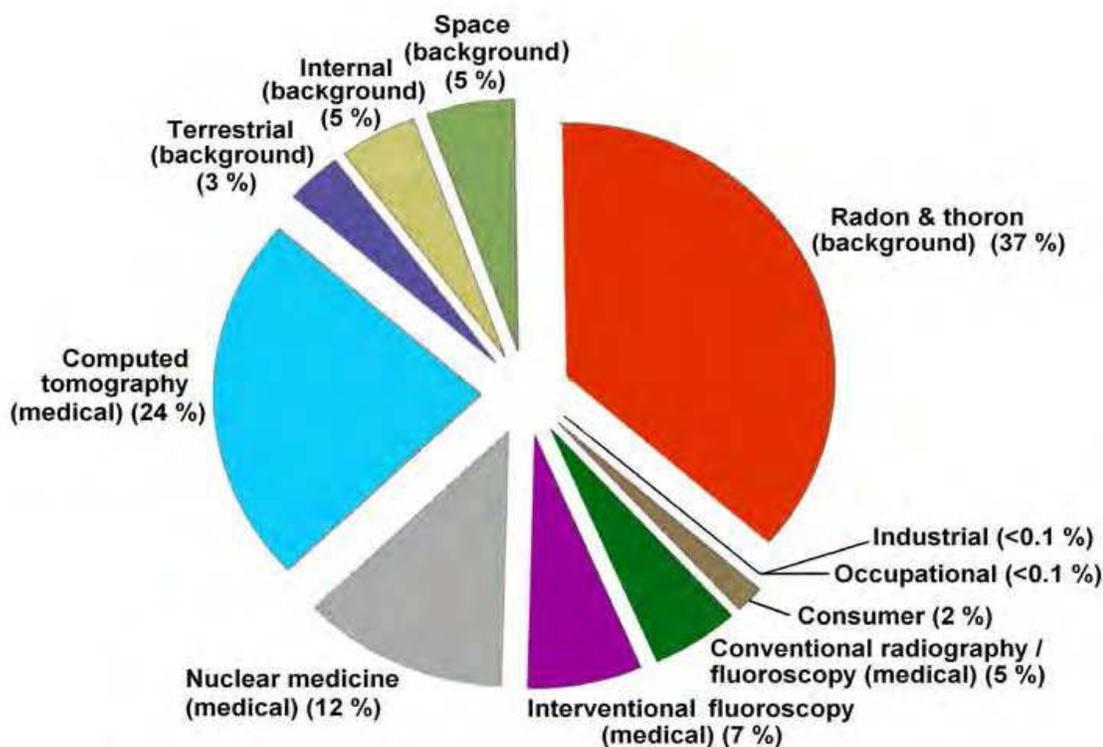
The above mechanism is substitution event; point mutations have also included insertions and deletions. Insertions have consisted of base or base pair additions to the nucleotide sequences, whilst deletions were removal of bases or base pairs. Point mutations have changed either the nucleotide sequence in the case of substitutions or the reading frame of the DNA sequence in the case of insertions and deletions, all of which has flown on to mRNA transcription and protein biosynthesis by translation [3].

**Dimerization** could occur between adjacent bases on a DNA strand preventing accurate copying.

<b>A C G G T A</b>	<b>A C G=G T A</b>
<b>T G C C A T</b>	<b>T G AT</b>
	<b>CC</b>

**Physical changes** have included the breakage or loss of part of a DNA strand or translocational rearrangement. These changes have tended to occur on a chromosomal level. When cellular DNA has irradiated and resulted in chromosomal breakage, a lot of things could continuously happen. In the majority of cases the strands would rejoin to the identical chromosome and returned to the original undamaged state. However, if there were many chromosomal breaks, then the broken ends of two different chromosomes might occur to form an abnormal chromosome, this process has an exchange type aberration. In some cases a broken fragment could be totally the lost leaving on incomplete fragment as known an acentric fragment or terminal deletion. Among the radiation induced chromosome aberrations the frequency of terminal deletions increases in a linear fashion with increasing radiation doses. In case of exchange type aberrations two breaks could cause by one ionizing particle (one hit event) and similarly their frequency increased linearly with increasing radiation dose. If however the breaks have caused by different particles (two hit event) then the frequency of aberrations increased proportional to the square of the radiation dose. The frequency of aberration varies with the type of ionizing radiation. Radiation that has induced by cancer was a complex, and then not completely understood process involving multiple events, but not limited to cellular DNA damage, up and down regulation of genes, intercellular communication, tissue and organ responses, clonal expansion of altered cell lines, and possibly eventual malignancy [3].

Many surveys have been designed to explain the mechanism involved in the interactions between ionizing radiation and cell response, but all of these researches had both advantages and disadvantages [5].



**Figure 1.** It shows percentage contribution of various exposure sources to ionizing radiation to the average annual effective dose (6.2 mSv) per person in the United States population (about 300 million people) in 2006 [2].

The complexity of carcinogenesis process, and lack of experimental data for surveying and studying, both has led the scientists to take advantage of computational and modeling methods to predict, diagnose and treat the dreaded disease.

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

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

Cellular automata have enabled by using cellular dynamics, and included interaction between cells provides the suitable computational model for the study of complex system such as carcinogenesis process [11, 12].

A cellular automaton was a collection of cells on a grid of specified shape that evolved through a number of discrete time steps, according to a set of

the rules based on the states of neighboring cells. The rules have then applied iteratively, as many times as desired. Von Neumann was one of the first people who considered such a model, and incorporated a cellular model into his "universal constructor." Cellular automata have studied in the early 1950s as a possible model for biological systems. A CA model has represented as a lattice or array of cells. The size of this lattice has referred to as the dimension of the CA. The characteristics of cellular automata have given in references [11-16].

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

Sugarscape has first introduced by Epstein and Axtell [16]. This environment was multi-agent system that used for modeling and organizing social, biological, political and economic process. Main elements of model were Cellular Automata (environment), agents, sugar (source) and rules [12-17].

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

Biomarkers were invaluable tools for cancer detection, diagnosis, patient prognosis and treatment selection. Enhanced glucose utilization was a prominent and fundamental change in many tumors irrespective of their histological origin and the nature of mutations [18].

Metabolism as an important biomarker to diagnosis cancerous cells has 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 that we had to define mathematical formulation for this stochastic and probabilistic event.

The objective of the present work was to evaluate oncogenic transformation of infected cells which had traversal with radon progeny alpha particles, using sugars cape cellular automata.

## Materials and Methods

The cellular sugars cape model has performed in Mat lab, using the 2 dimensional lattices. A square lattice of size  $L \times L$  grids has used to present configuration in order to explain the changes in all cell stages in a lung tissue.

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

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

Epidemiologic studies on lung cancer have shown that the number of cells hit is an important quantity to evaluate radiation biological effect. For this purpose we should consider the number of hits is necessary. From experimental data cellular hit by alpha particles, has described by the Poisson distribution [9, 19].

In this study, the average number of hits has calculated for different doses over 4 years exposure

period, representing the average working exposure time for miners.

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

The meaning of each stage has defined as follows:

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

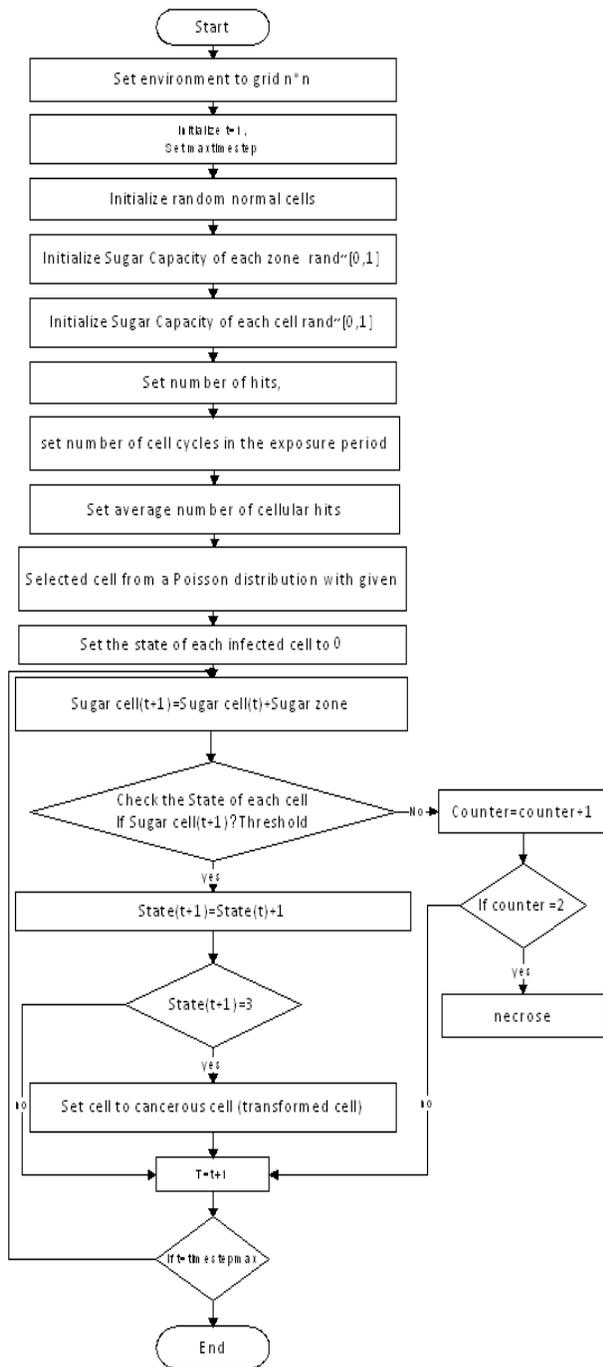
Infected stage 2 (L2): The infected cell has been already recognized. When alpha particles pass through the cell nuclei DNA, damage has happened and cell has initiated. The metabolism rate of these damaged cells has been increased because of their cell cycle has become shorter and their mitosis has occurred rapidly. Thus they needed to receive more nutrients to upgrade their level to survive. They had to compete with each other to receive threshold nutrient, to be able to continue life. If the sugar level of cells was less than threshold, then its stage has not changed. If cell's stage has not changed within 2 time steps, then they have become necrosis, 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 has performed again. If the sugar wealth of cell was greater than stage's threshold, then increase of stage has occurred. If the sugar level of cells was less than threshold, then its stage has not changed. If cell's stage hasn't changed within 2 times step, they have become necrosis, and then die.

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

In the highest level of metabolism (Landscape 4), model was convergence. The numbers of cells in this level were oncogenic transformant cells induced alpha particle hits which they had the maximum chance to make tumor.

The model outlined above have been implemented according to 2 dimensional CA model based on the classic sugars cape model, which has described the evolution of alpha particles infection under different condition such as dose and exposure

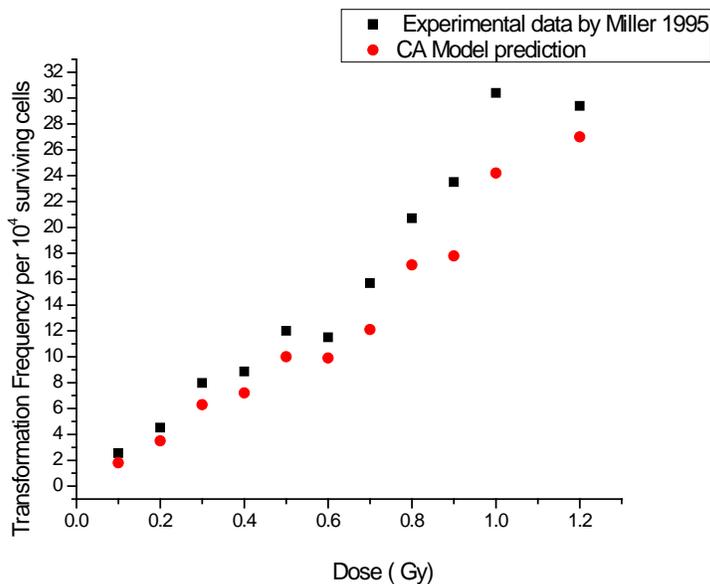


**Figure 2.** It shows flow chart shows the algorithm of the program and transition between 4 infected cells stages.

time. The simulation flow chart of model has shown in figure 2.

**Results**

In this study, a stochastic CA model has associated with the sugarscape environment has



**Figure 3.** It shows 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 [20].

explored under various parameters and focused on the changes in metabolism rate due to DNA damage by Radon progeny alpha particles hits. The model has determined the cellular hits with alpha particles by using Poisson distribution as above described.

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

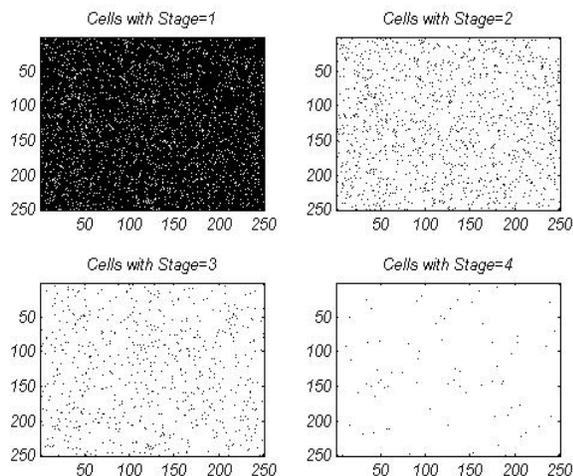
Oncogenic transformation of cells, which was a necessary intermediate step in the sequence of events leading to carcinogenesis, might presently be the most relevant cellular effect for simulating carcinogenesis.

Oncogenic transformation predicted by CA model, in comparison with experimental data of mouse C3H 10T1/2 Cells, exposure to alpha particles have presented in table 1 [20, 21] . These data have shown the number of transformant cells and oncogenic transformation, which were as dose functions, and had a liner relationship.

Oncogenic transformation that has obtained by CA model have well fitted with experimentally data that have observed in vitro oncogenic transformation, and survival data for C3H 10T1/2 mouse cell that

**Table 1 .** 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 [20].

Dose (Gy)	Number of viable cells	Number of transformants (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



**Figure 4.** It shows 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 have 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.

has exposed to alpha particles by Bettega et al. and Miller et al. experimental data [20, 21].

Oncogenic transformation has varied with dose has plotted in figure 3 and compared with Miller et al. experimental data [20]. The points were the

results of several independent run, performed in different time.

Figure 4 has shown that how the number of initial infected cells could be changed during different metabolism landscape in sugars cape cellular automata model for Dose= 4Gy. We have considered these states for changing cell from healthy to transformant, based on cellular alpha particle hit and nutrient distribution.

Sensitivity and specificity of this model has compared favorably with experimental approaches. This comparison has shown 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

Epidemiological evidence has consistently linked exposure to ionizing radiation with increased rates of carcinogenesis in any organ in which cancer could occur. Exposure to alpha particle emitting radiation and other high LET radiation sources, particularly Radon 222 and its radioactive breakdown products has especially damaged to living cells. Occupational exposure to Radon 222 has proved to directly cause lung cancer via inhalation of the gas, and its decay products. The epidemiological data has well supported by genetic studies which has demonstrated a clear correlation between radiation exposure and

mutations in the p53 tumor suppressor gene in bronchial epithelium. There was hence no safe level of radiation exposure, no safe way to mine, process or handle radiation or dispose of the associated wastes [1].

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

By comparing the proposed methods with results that have obtained previously using Epidemiological dosimetric and biological approaches, the reliability, speed and quality of the solution have verified, and the benefits of this method have been demonstrated.

## Conclusion

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

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

It had been demonstrated that, proposed method in this paper had some advantages such as increasing the ability of complicated problem solving, increasing the velocity and result qualification (time and cost) in optimization procedure.

In comparison with the experimental data that has indicated the metabolism rate and cellular hits could be the suitable parameters to follow cancerous cells induced ionizing radiation.

This model has provided an opportunity to study the cellular changes at the various stages in radon progeny alpha particles carcinogenesis in lung bronchial epithelial cells.

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## Conflict of Interest

The authors have no conflict of interest in this study.

## Authors' Contribution

Samaneh Baradaran has designed and written this article, Niaz Maleknasr wrote the computer programme, Saeed Setayeshi reviewed and revised the manuscript, Mohammad Esmail Akbari was consultant of the paper. All the authors read and approved the final manuscript.

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