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RESEARCH ARTICLE

Mathematical Model of the Generation of Radiation-induced DNA Double-strand Breaks and Misrepair Cells by Direct and Indirect Action

Hamizah Rashid[a,*], Fuaada Mohd Siam[a], Normah Maan[a], Wan Nordiana W. Abd Rahman[b], Mohamad Hanis Nasir[c]

[a] Department of Mathematical Sciences, Faculty of Science Universiti Teknologi Malaysia, 81310 Johor Bahru, Malaysia; [b] School of Health Sciences, Universiti Sains Malaysia, Kubang Kerian,16150, Kota Bharu, Kelantan; [c] Faculy of Ocean Engineering Technology and Informatics, Universiti Malaysia Terengganu, 21030, Kuala Nerus, Malaysia

Abstract Hydrated electron (e_{aq}^-), hydroxyl radical (•OH), hydrogen radical (•H), ionized water, hydroperoxyl radical and hydrogen peroxide are examples of free radical products. Among these three free radicals, DNA damage dominantly caused by hydroxyl radical (•OH) because it is found to be highly reactive compared to others. This paper aimed to develop a model by using structured population dynamics approach to study the effects of ionizing radiation by direct and indirect actions. The effects of ionizing radiation are mathematically described in the model using Ordinary Differential Equations (ODEs). The simulation results are fitted to the Linear Quadratic (LQ) formulation to give the ratio for α/β. Next, the parameter estimation of the model is carried out using experimental data of human colon carcinoma cell by the aid of the MATLAB programming. The estimated parameter values can explain the biological meaning, which can support the result of the experimental design. The result showed that the sum-squared error (SSE) between simulation data and experimental data obtained is 0.0019 which indicates an excellent fit to the experimental data. Thus, the model developed is in line with the experimental result. The model can explain the dynamics process of the direct and indirect effect of ionizing radiation on the cell population.

Keywords: Machine breakdown, minor breakdown, major breakdown, repair, model predictive control.

***For correspondence:**
hamizahrashid90@gmail.com

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Introduction to target hit model

Ionizing radiation such as gamma rays and x-rays hits cell directly and alters the deoxyribonucleic acid (DNA) structure. Such action is predominant by high-linear energy transfer (LET) which eventually leads cell death. Therefore, it is highly demanded in treating cell cancer. High-LET such as neutron and heavy charged particles, travel in a straight line and directly hit the cells.

The composition of water in the human body is about 70% by weight, approximately 46% is inside cells and 23% is present outside cells [1]. Cell cancer is the main target of ionizing radiation to stop the growth of cell cancer. Therefore, during cancer treatment, the radiation interacts easily with water molecule, ionizes the water molecule, and produced free radical. Free radicals carry an unpaired electron in the outer shell which make them very toxic to DNA. The interaction of radiation with water molecule is called indirect action of ionizing radiation. Indirect actions of radiation induce a high number of cell damage

than direct actions due to high composition of water molecule in cell [2]. Deoxyribonucleic acid (DNA) carries genetic instruction for cell growth, therefore, the primary target of cell killing is to cause DNA damage by breaking the DNA strand. The DNA structure is formed from two sugar-phosphate backbones that twist each other, resemble a ladder called double helix.

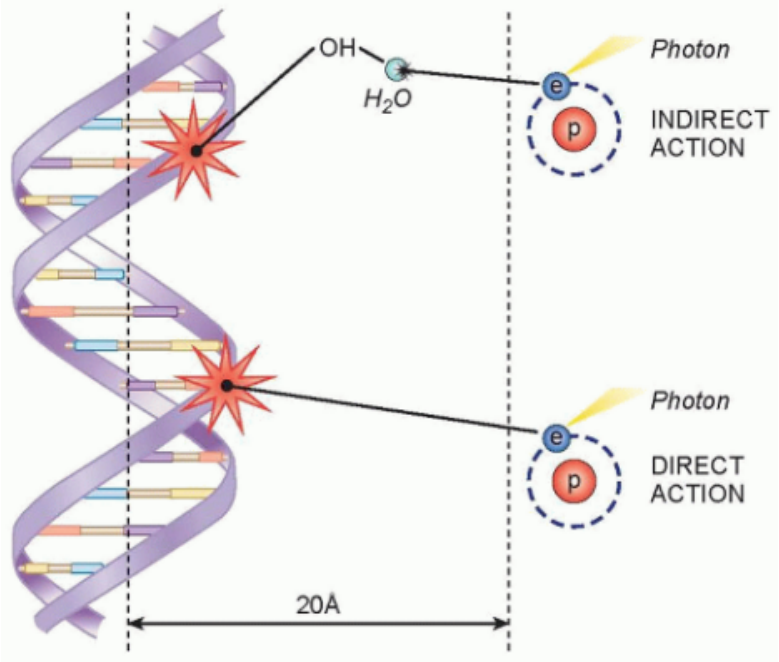

Figure 1: An illustration of direct and indirect action of radiation [3].

Figure 1 shows an illustration of the direct and indirect actions of ionizing radiation on DNA strand. Direct action of ionizing radiation hits directly DNA strand. Reactive oxygen species such as hydroxyl radical is a product of interaction between ionizing radiation and water molecule. This interaction is called as indirect action of ionizing radiation.

Indirect Action

The number of cell damage by direct and indirect action of ionizing radiation depends on the amount of radiation dose given. According to Alizadeh et al., direct effects of radiation are caused by direct action of radiation which occur in dry system, while indirect effects are damages caused by another agent such as reactive oxygen species (ROS) with the presence of water molecule [4]. Then, Desouky et al. [1] noticed that the ionizing radiation effects are not restricted to the targeted cell, the production of free radicals has caused the nearby cell to receive the same effect as targeted cell.

The interaction between ionising radiation and water molecule produced free radicals such as hydrated electron (e_{ag}^-), hydroxyl radical (•OH), hydrogen radical (•H), ionized water, hydroperoxyl radical and hydrogen peroxide. Some water radiolysis radicals such as hydroxyl radical (•OH) and hydroperoxyl radical contain oxygen also known as reactive oxygen species (ROS). Among these free radicals, DNA damage dominantly caused by hydroxyl radical (•OH) because it is found to be highly reactive compared to others [5, 6, 7].

Hydroxyl radical is formed form from the reaction between ion radical, H_2O^+, and water molecule, H_2O as shown below:

$$H_2O^+ + H_2O \rightarrow H_3O_+ + {}^{\bullet}OH$$

Hydroxyl radical can diffuse in a short distance to reach the target and attacking nearby cells, thus caused more DNA damage [8-10].

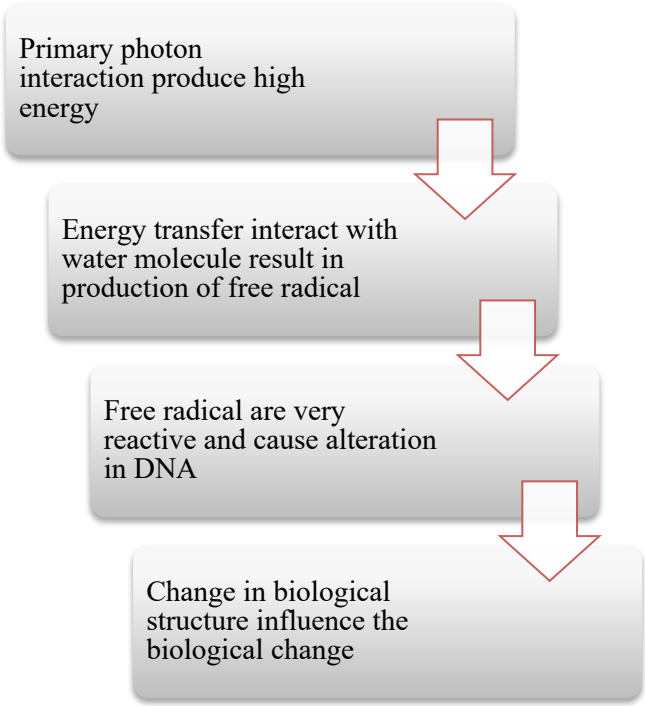

Figure 2. Process of biological damage by free radical.

Figure 2 explains the process of biological process caused by free radicals. High ionizing radiation is given to ionize atom by ejecting electrons. These electrons interact with water molecule and produce new product called free radicals which are very reactive. Free radicals caused biological change to the targeted and non-targeted cell while moving. The biological damage arises as ROS agents can move freely and continue to cause DNA damages for a few days because of the continuous generation of new ROS [8-10].

Literature review on mathematical model of radiation damage

Free radicals induced by ionizing radiation are mostly derived from oxygen with the presence of water molecules. Thus, water radiolysis is the decomposition of water molecules by radiation, results in the formation of reactive oxygen species, which contains one or more oxygen atoms [11].

It has been discovered that free radicals can cause cell damage. Liu et al. [12] conducted an experiment to study the effects of ROS on mice by observing the mitochondrial, a double-membrane-bound organelle found in most mammalian cells . From their result, ROS production contribute to mitochondrial damage, when the ROS is increased [12]. In another experiment, Lee at al. used ferrous chloride and hydrogen peroxide solution to generate hydroxyl radicals [13]. It was then tested on DNA for 5 minutes at various concentration. The findings revealed an increase in DNA damage caused by ROS, such as base oxidation and single-strand break. Both experiments shoed that, ROS were capable to cause biological change.

Therefore, several mathematical models have been developed to support the findings on the effects of ionizing radiation by ROS. In 2016, Satow and Kawai designed a new mathematical model to calculate the number of DNA damage caused by ROS agents [14]. The model considered three ROS agents generated by the interaction of ionizing radiation and the water molecule. However, they only focused on the formation of DNA damage by ROS without considering another aspect that can influence cell survival following the indirect effects of ionizing radiation. Later, Molavian et al. [15] proposed a mathematical model to improve the work done by Satow and Kawai. They assumed that the number of cell death depends on the amount of hydroxyl radical by presenting a linear relationship to calculate the number of cell death. However, the dynamic of cell damage such as death rate following the indirect

affects was not addressed.

Then in 2018, Siam et al. [16] developed a mechanistic realistic model of the effects of ionizing radiation on DNA in mammalian cells. They considered a population of cells structured by the number of double strand breaks (DSBs) and misrepair cells after a dose of low-LET radiation. The mechanistic model highlighted DSBs because it is the most lethal damage caused by ionizing radiation. The model consists of cell death, repair rate and the probability of correctly cell's repair following ionizing radiation. From the model, the survival fraction of cells is obtained. Then, this model is significantly modified by Siam and Nasir in modelling the radiation-induced bystander effects [17]. However, these models do not consider the indirect effects of ionizing radiation by another agents.

Therefore, in this study, a mathematical model for ionizing radiation effects is presented, which includes two compartments: direct and indirect effects of ionizing radiation. The model can simulate the overall effects of ionizing radiation by combining the two approaches of Siam et al. and Satow and Kawai [16,14]. The works start with the deviation of the dynamics of direct effects followed by indirect effects of ionizing radiation. Next, the cell survival curve will be plotted to represent survival fraction of direct and indirect effects of ionizing radiation.

Linear Quadratic (LQ) formulation

In radiobiology, linear quadratic (LQ) formulation is used to describe the relationship between cells survival and delivery dose. The α/β ratio from the LQ formulation can be used to analyze the cell sensitivity and predict the biological response of cell. The respond of cells toward ionizing radiation can be understood through the shape of a cell' survival curve. The survival curve describes the relationship of dose effect in cell culture. The surviving fraction is then fitted to the Linear Quadratic (LQ) formulation to obtain the value of α/β. The cells surviving fraction which can be represented by Linear-Quadratic formulation is given as

$$S(D) = e^{-(\alpha D+\beta D^2)} \tag{1}$$

the value of α/β ratio is important to measure the sensitivity of cell towards radiation. According to Williams et al, highly sensitive cells have α/β ratio between 6 - 14 Gy, while α/β ratio between 1.5-5 Gy represent late respond of cells to radiation [18]. This is supported by the mechanism involves in each type of action. Direct action hit cells in short order while indirect action is a reaction between radiation and water molecule occurs in few hours after the direct action [19, 20]. Since cells are composed of water, inorganic ions and carbon containing molecule, the indirect action by ROS will take hours and days to cause biological change, therefore, in this study we stop the reaction at t=24 for every dose in order to understand the indirect effects.

Mathematical model of Direct effects by Siam et al. [16]

Studies have shown that ionizing radiation can be harmful to human as it can damage cells which exposed to it. The biological effects following radiation include base damage, DNA single-strand breaks (SSBs) and double-strand breaks (DSBs). However, only two effects from ionizing radiation, double-strand-breaks (DSBs), k, and misrepair cells, m, are highlighted in [16]. Double strand breaks (DSBs) refer to broken of both DNA strand which can not simply rejoin using apposite template. Misrepair cells refer to the incorrectly joined of chromosome end during the repair process of DNA damage. The authors suggested a mechanism of ionizing radiation effects which is based on the structured population approach. This structured population model only considered direct action of radiation where the number of DSBs and misrepair cells are calculated. In their work, double-strand break becomes the main focus because it is more fatal than the single strand break. Besides that, the DSBs induced by ionizing radiation play a major role in cell population because it can lead to cell death. Double strand breaks (DSBs) are produced depend on the amount of radiation dose. The probability of cell acquiring DSB follows a Poisson distribution with mean

$$\lambda = \delta D, \tag{2}$$

where D is the radiation dose (in Gray), δ is a measure of the cells radiosensitivity. Thus, the probability of DSBs induced by ionizing radiation is given by

$$\mathrm{P(no.DSBs=k)}=\frac{\lambda^k e^{-\lambda}}{k!}. \tag{3}$$

The mechanistic model in [16] is a structured population model where λ is given by (1). The model gives the number of cell survival fraction at time, $t=24\mathrm{h}$, by considering the dynamics of DNA damage following ionizing radiation using ODEs such as repair rate, death rate and probability of correctly repair. The Ordinary Deferential Equation (ODE) system in [16] is given by

$$\frac{dN_{k,m}}{dt}=-\chi(k,m)N_{k,m}-\gamma(k)N_{k,m}+\ p(k+1)\gamma(k+1)N_{k,m}+\ (1-p(k+1))\gamma(k+1)N_{k+1,m-1} \tag{4}$$

The ODEs contain the repair rate, $\gamma(k)=\frac{\mathrm{V}_{\max}k}{K_M+k}$, where $\mathrm{V}_{\max}$ and K_M are maximum repair rate and repair rate of DSBs is half of $\mathrm{V}_{\max}$. Another function is death rate, $\chi(k,m)=\alpha_1 m+\alpha_2 k^2$, where α_1 is misrepair rate constant while α_2 is lethal binary misrepair rate at two DNA strands.

Probability of correctly repair, $p(k+1)\gamma(k+1)N_{k,m}$ and probability of incorrectly repair, $(1-p(k+1))\gamma(k+1)N_{k+1,m-1}$.The solution to the ODE system is given by:

$$\boldsymbol{N}(t)=N(0)e^{\mathbf{A}t} \tag{5}$$

where $\boldsymbol{N}(t)$ is a matrix which contains the number of cells survived, while $N(0)$ is initial condition define by Poisson distribution in Equation (2). **A** is matrix defined by ODEs in (4). In this work, time, t , is set to 24 hours to make sure that the repair process is completed [2].

Estimation number of DSBs lesions by Indirect Action follow Satow's model

Ionizing radiation directly hits DNA structure causing the sugar-phosphate backbone to break, followed by breaking the bases which are attached to the sugar-phosphate backbone. The radiation effects are then continued by ROS agent which is called as indirect effects of ionizing radiation. Therefore, in order to consider the direct and indirect effects of ionizing radiation, the work done by Satow and Kawai is highlighted in this study. In their work, they calculated the number of DNA damage by indirect action, *Indirect (D)*, with respect to dose, *D,* at time, *t*, as follows;

$$Indirect(D)=\frac{6.02\times10^{20}\chi_1(D)}{\vartheta} \tag{6}$$

where 6.02×10^{20} is a constant, and ϑ refer to concentration of cells with value$1.4\mathrm{x}10^6(cells/ml)\cdot\chi_1(D)$ is the concentration of base damage caused by ROS agent which is given by

$$\chi_1(D)=\eta M(D)\frac{1-\exp\{\chi_2(M(D)-\eta)t\}}{\eta-M(D)\exp\{\chi_2(M(D)-\eta)t\}}, \tag{7}$$

where $q=\frac{1}{\vartheta}\cdot\chi_2$ is rate constant for bases in DNA strand and η is concentration of bases in DNA strand, $M(D)=\frac{1}{6.02\times10^{23}}\frac{10^3}{q}R(D)$ refers to molarity of free radical with dose, *D*. The number of free radical with respect to dose, *D*, react with a cell is given by $R(D)=GD(6.24\times10^{13})m$ where $G=0.027$ represents the coefficients of hydroxyl radical generated when water absorbed 100eV.

In this work, we only consider hydroxyl radicals only, as it apparently dominates DNA damage [8]. According to Chargaff's rules, the total ratio of four component bases in DNA is 1. Therefore, we consider all the component of DNA bases as a constant and set the concentration of bases per cell , $\eta = 1$ [21]. Besides that, the mass of cell is set to $m = 4\times10^{-13}$ (g) [14] and time, $t = 1/3600$ for converting seconds to hour. Thus, Equation (7) can be rewritten as follows

$$\chi_1(D) = 1\times M(D)\frac{1-\exp\{\chi_2(M(D)-1)1/3600\}}{1-M(D)\exp\{\chi_2(M(D)-1)1/3600\}} \tag{8}$$

then, χ_2 is set between $5.1\times10^9 - 9.2\times10^9$, which is the rate constant for DNA bases [11]. The molarity of hydroxyl radical, $M(D)$, with respect to dose, D, is simplified as below

$$\begin{aligned} M(D) &= \frac{1}{6.02\times10^{23}}\frac{10^3}{q}R(D) \\ &= \frac{1}{6.02\times10^{23}}\frac{10^3}{7.142\times10^{-1}}R(D) \\ &= 1.661\times10^{-24}(1.4\times10^{10})R(D) \\ &= 2.3254\times10^{-14}R(D). \end{aligned} \tag{9}$$

R(D) has previously defined, therefore, Equation (9) is rewritten as follows

$$\begin{aligned} M(D) &= 2.3254\times10^{-14}(0.6739)D, \\ &= 1.5771\times10^{-14}D. \end{aligned} \tag{10}$$

Therefore, Equation (8) is written and simplified as follows

$$\chi_1(D) = 1\times1.5771\times10^{-14}D\frac{1-\exp\{\chi_2(1.5771\times10^{-14}D-1)(1/3600)\}}{1-1.5771\times10^{-14}D\exp\{\chi_2(1.5771\times10^{-14}D-1)(1/3600)\}} \tag{11}$$

Finally, number for DNA damage by indirect effect per cell is given by

$$\begin{aligned} Indirect(D) = (6.02\times10^{20})(\frac{1}{1.4\times10^{6}})(1.5771\times10^{-14}D)\times \\ \frac{1-\exp\{\chi_2(1.5771\times10^{-14}D-1)(1/3600)\}}{1-(1.5771\times10^{-14}D)\exp\{\chi_2(1.5771\times10^{-14}D-1)(1/3600)\}}. \end{aligned} \tag{12}$$

Simulation Model of Direct and Indirect action of ionizing radiation

It is known that radiation damage can occur directly and also indirectly. Thus, in this work, we modify the Equation (2). The expected number of DSBs created by direct and indirect actions is assumed as follows:

$$\text{No of DSB} = \delta D + Indirect(D) \tag{13}$$

where, Equation (13) is the mean of DSBs by direct effects and indirect effects from Equation (2) and Equation (12). The simulation is carried out using MATLAB R2018a based on the algorithm as follows:

1. Generate random initial number of cells with DSBs follow Poisson Distribution in Equation (3).
2. Solve the ODE system introduced by Siam et al. [16] up to time $t = T$ for T = 24 *h*. This time, *t*, is chosen in order to make sure the repair process is completed [2].
3. Compute the fraction of surviving cells, $S = \frac{\sum N_{k,m}(T)}{\sum N_{k,m}(0)}$
4. Plot the surviving cells in log scale, ln S , versus the dose, D

5. Repeat steps (1)-(4) for ten runs in order to get the averaged value of ln *S*
6. Fit the generated data to the LQ relation using optimization method, "*fminsearchbnd*".

Results

Simulation of direct and indirect effects

In the present thesis we generate simulation data for up to D = 5 *Gy* for the value of parameters, δ = 1.5 Gy^{-1} $cell^{-1}$, α_1 = 1.5 h^{-1}, α_2 = 0.0001 h^{-1}, p = 0.95, V_{max} = 1 h^{-1} and K_M = 3 in Equation (3) while parameter for indirect is $\chi_2 = 8 \times 10^9$ $mol^{-1}s^{-1}l$. These values are randomly chosen as an example. The simulation results are shown in Figure 3.

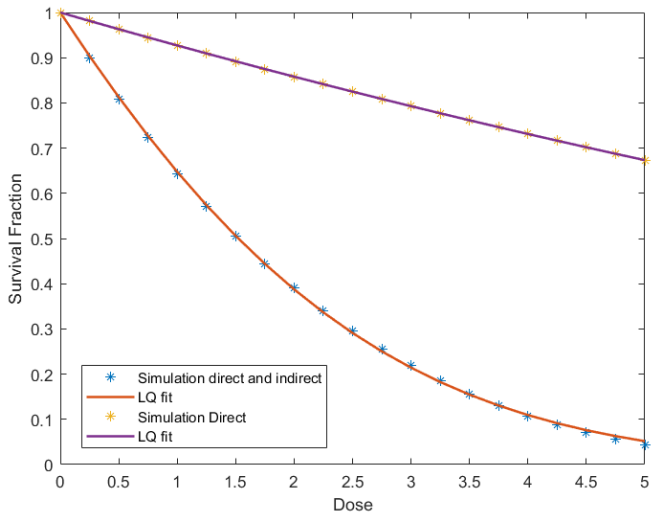

Figure 3: The simulation result for single dose at t = 24 hours The simulation is then fitted to LQ formulation.

Figure 3 shows that the survival fraction curve for direct effects and combination of direct and indirect effect following ionizing radiation. The combination of direct and indirect effects represented by the orange line, while the purple line represents the direct effects. It can be seen that the survival fraction for combination of direct and indirect effects is lower that the direct effects indicating that more cell dies due to the effects of direct and indirect action of ionizing radiation.

The shoulder of cell survival shape is well explained by the ratio α/β (Gy^{-1}). Table 1 shows the ratio α/β (Gy^{-1}) which obtained from cells survival curve using LQ fitting [22].

Table 1. The ratio of α/β in Gray (Gy^{-1}) for two types of action by direct and indirect.

Types of action	LQ relation	Ratio α/β in Gray (Gy^{-1})
Direct and Indirect	$\ln S = e^{-(0.3957D+0.0393D^2)}$	10.0567
Direct	$\ln S = e^{-(0.0750D+0.0008D^2)}$	91.7649

It can be seen that, the ratio of α/β for direct action is higher than the combination of direct and indirect effect. In cell culture, high proliferating cells are less sensitive to radiation. It is representing by high α/β ratio. In contrast to slow proliferating cells, they are very sensitive and have low α/β ratio [19].

Parameter estimation of the model

In this section, we perform parameter estimation to obtain parameter values that fit the experimental data. The parameter's value will be able to describe the characteristics of the cell population. The model formulation in this paper contains 7 parameters: $\mathbf{X}=[\delta, \chi_2, \alpha_1, \alpha_2, p, V_{max}, K_M]$. To estimate all the parameters value, we will incorporate experimental data by Rashid et al. [23] into the model. The experiment is conducted to study the effects of ROS agents produced by radiosensitizer on cell population. The human colon carcinoma cells (HCT 116) were irradiated with 150 MeV proton beams with a few types of nanoparticles. The generation of ROS and cell survival were measured. Their result shows that the generation of ROS in aqueous solution resulted in high number of cell death.

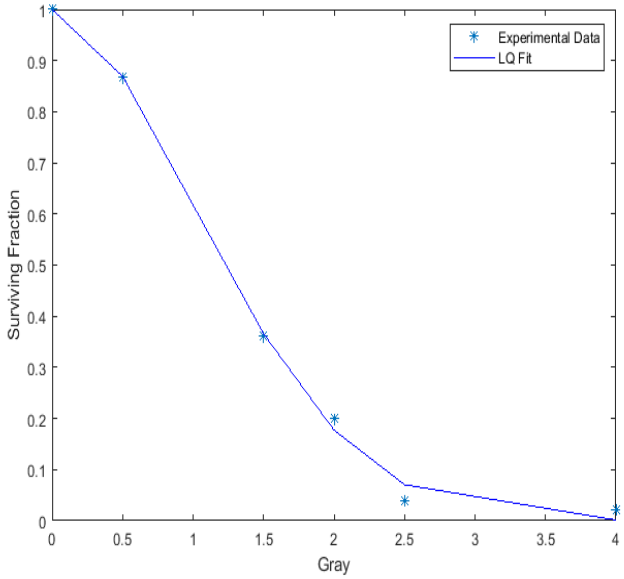

Figure 4: Cell survival on human colon carcinoma cell irradiated with 150 MeV generate reactive oxygen species (ROS).

Figure 4 shows the survival fraction of cells following ionizing radiation using nanoparticle called platinum nanodendrites (PtNDs) irradiated with 150 MeV proton beam. The dose ranged from 0 to 4 Gy was delivered to approximately 1000 cells in a single fraction. The survival fraction of human colon carcinoma cells (HCT 116) decreased due to the generation of ROS. From the experimental data obtained, it is showed that, the generation of ROS influences the survival fraction.

Table 2, shows list of parameter and boundary of each parameter value so that the parameter search will bounded in these regions. Then, the third column is the result of parameter estimation using "*fminsearchbnd*" MATLAB routine.

Table 2: Estimated parameter value using "*fminsearchbnd*" MATLAB routine.

Parameter	Boundary	Result of estimated parameter
δ	(0.0001,40) [12]	0.6264
χ_2	($5.1\text{x}10^9$, $9.2\text{x}10^9$) [14]	$7.7992\text{x}10^9$
α_1	(0.0277, 20.79) [12]	1.8635
α_2	(0.0001,0.005) [12]	0.005
p	(0, 1)	0.9782
V_{max}	(0.1, 3) [12]	2.8891
K_M	(0.0001,5) [12]	0.0015

We employ the estimated parameters as in Table 2 into the model and observe how fit the simulation against the experimental data (See Figure 5).

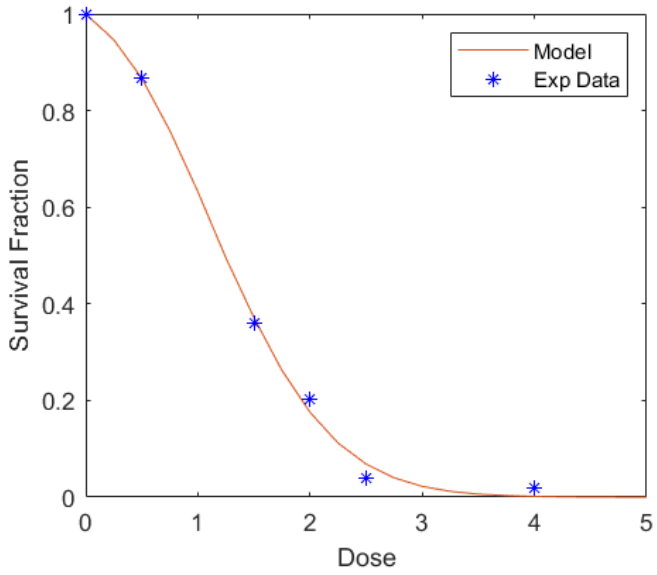

Figure 5. Simulation on human colon carcinoma using estimated parameter values estimated.

Figure 5 shows the survival fraction of human carcinoma cell using estimated parameter value and model simulation data. The sum-squared error (SSE) between experimental data and simulation data is obtained with value 0.0019 which is close to zero. The value of sum-squared error obtained indicate an excellent fit between model and experimental data.

Sensitivity analysis of the model parameters

Next, we analyze the sensitivity of parameter towards survival fraction, S, which are δ and V_{max}. We focus on these two parameters because δ represent the sensitivity of cells which will generate the number of DSB. Cells with high radiosensitivity will response to ionizing radiation quickly and reduce the deficiency of repair rate of lethal injury. Nonhomologous DNA end joining (NHEJ) and homologous recombination (HR) are the major DSB repair pathways in higher eukaryotes. The repair pathway will activate once DNA damages are detected in order to prevent the production of secondary cancer cell, hence $V_{\max}$ which represents the maximum repair rate for cells is considered. By using the same method analysis used by Nasir and Siam [24], the index of survival fraction with respect to δ and V_{max} are defined:

$$S_{\delta}^{scaled} \approx \frac{S(\delta+\Delta\delta)-S(\delta)}{\Delta\delta}\times\frac{\delta}{S(\delta)}, \tag{14}$$

$$S_{V_{\max}}^{scaled} \approx \frac{S(V_{\max}+\Delta V_{\max})-S(V_{\max})}{\Delta V_{\max}}\times\frac{V_{\max}}{S(V_{\max})}, \tag{15}$$

where S_{δ}^{scaled} and $S_{V_{\max}}^{scaled}$ each is the index change in survival fraction for parameter δ and $V_{\max}$, respectively. The rate of change of δ and $V_{\max}$ increasing the parameter value by 1% are represented by Δ which give $\Delta\delta = 0.01\times\delta, \Delta V_{\max} = 0.01\times V_{\max}$ respectively. We use the estimated parameter listed in Table 2 to perform the index calculations in Equation (14) and Equation (15).

Figure 6 shows sensitivity analysis for parameter δ and $V_{\max}$. As shown in Figure 6, by increasing 1% of model parameter δ, the survival fraction will decrease, which means that cells are sensitive to ionizing radiation. In the same time, by increasing 1% of model parameter V_{max}, the survival fraction will increase. Cells sensitivity can be increased by increasing the oxygen level where more free radical will be produce and reach targeted cells easily. In results, will increase the number of cell death. Therefore, the cell's sensitivity should be increase by increasing the radiation dose so that more interaction with water molecule will take place resulted in the formation of ROS.

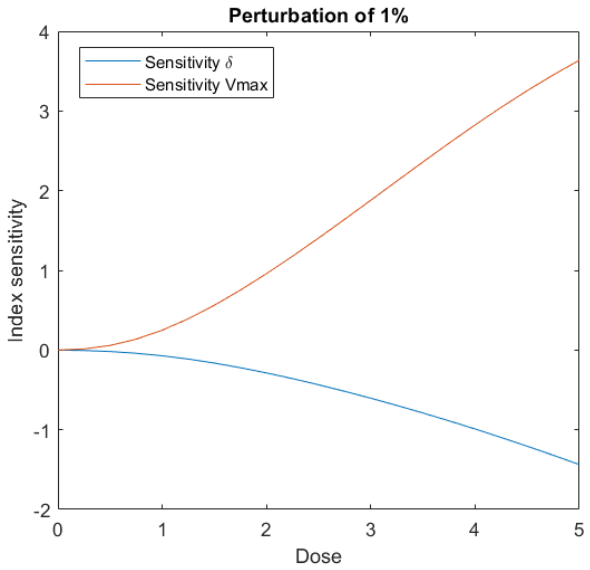

Figure 6: Sensitivity of the cell's survival fraction with respect to δ and.

Conclusion

This paper focused on the mathematical model and the simulation of ionizing radiation effects on cells population when direct and indirect action are taken into consideration. The results show that, the combination between direct and indirect action of ionizing radiation has shown adverse effects in radiotherapy treatment through the production of free radical. The simulation is in agreement with the literature, where ionizing radiation effects are also caused by the generation of free radical. By increasing the oxidative stress such as oxygen, this can be an alternative in cancer treatment. Besides that, in radiobiology, Linear-Quadratic formulation have been used widely in interpreting the shape of the estimated survival curve. The ratio α/β (Gy^{-1}) obtained equal to 10.0567 indicates that the cells are sensitive to the combination of direct and indirect action of ionizing radiation. Parameter estimation is also carried out in this work, to validate the proposed model. In addition, the estimated parameter's values will describe the biological meaning of cell population following ionizing radiation. Two parameters were chosen to analyze the sensitivity of the parameters on the cell population. The results showed that by increasing 1% value of maximum repair rate, V_{max}, the cell survival fraction decreased, whereas, the cell survival fraction was increased when the value of radiosensitivity of cell was increased. This model can explain the overall biological effects and process involved following ionizing radiation. In addition, this model can be preliminary plan before radiotherapy treatment by increasing oxidative stress using oxygen or apply radioprotector to reduce the side effects of ionizing radiation.

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