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Derivation of Repair and Mis-Repair DNA Double-Strand Breaks (DSBs) Model: A Case with Two Simultaneously DSBs Repair Condition

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Abstract: "A double-edged sword-like of ionizing radiation", a common phrase used to describe the effect of irradiation to human cells. Our aim in this article is to study the dynamics of double-strand breaks (DSBs) damage on deoxyribonucleic acids (DNA) following irradiation. In particular, we derived a structured cell population model of DNA with respect to DSBs count and mis-repair DSBs, specifically in the present of two simultaneously DSBs repair. We also derived the characteristic of exact solution, which follows a Homologous-Cauchy condition of initial value problem. These results may give insights on modelling strategies of DNA response to irradiation.

Keywords: DNA DSBs, structured ODEs, DNA repair, irradiation

1. Introduction

It is known that DNA damage formation induces the damage repair pathways, and signaling that lead to cell-cycle arrest and apoptosis [1]. Exposure of human cells on irradiation may usually create DSBs in the arm of chromosomes. In general, a defect on a chromosome may cause chromosomal rearrangements that can lead to cancer [2]. Several mechanistic models attempted to study the cell's response of irradiation [3, 4]. The term "mechanistic" means these are models based on physical and chemical laws, which include parameters with physical, chemical, and biological meaning. The first model developed after the target model used the theory of dual radiation action [5]. The theory assumes that the number of irradiation-induced sublesions (DSBs) in eukaryotes is proportional to the dose of radiation. Two DSBs in a sensitive site will then interact and produce a lesion which can be thought of as a lethal chromosome aberration. The theory of dual radiation action is based on concepts of microdosimetry for energy deposition by irradiation.

Many factors can cause damage to the DNA, for instance by direct and indirect irradiation [6]. In direct irradiation, charged-particles radiation such as alpha- and beta-particles have sufficient energy to disrupt directly the atomic structure and produce chemical and biological changes. Whereas, indirect action occurs due to the formation of highly reactive free radicals. The interaction of DNA and free radicals create oxidative damage in DNA which causes

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structural DNA alterations. Thus, in this work, we are concern about the development of DNA DSBs damage model, which accounts for the survival of mammalian cells after irradiation exposure.

We first recall the model developed by Siam [7] on the evolution of cells after the DNA damage effect. Siam et al. [7] initiated the model by assuming the cells grouped according to their number of DSBs. On the onset of repair mechanism, cell "jumps" to another group based on their DSBs count and mis-repair DSBs. Few assumptions are made to tackle some complexity in the model formulation. The model considers a type of damage on DNA that is DSBs, not only one but many DSBs can be formed. The model does not incorporate any of the cell cycle phase progress and the repopulation of the cells is not considered. The model also did not allow the cell arrest phase, where under certain biological conditions, the cell can enter the quiescent state.

According to [7], the survival cells can be measured by the initial distribution of the DSBs count produced immediately after irradiation. Just before the time $t = 0$, irradiation of dose (D) is given. At time $t = 0$, the irradiation process is completed and all the initial number of DBSs are produced in each cell. The irradiation dose (D) is incorporated into the model through the initial distribution of an initial number of DSBs in each cell. A variable $N_{k,m}$ is used to represent a cohort of affected cells that have k number of DSBs and m number of mis-repair DSBs, with a pairing condition of $k + m \le k_{max}$ and k_{max} is the maximum number DSBs exist in a population of cells. Once the DSBs are mis-repaired, they cannot be repaired again. The quantity of $N_{k,m}$ is evolving as follows:

$$\begin{aligned} N_{k,m}(t+\Delta t) = N_{k,m}(t) - \Delta t d(k,m) N_{k,m}(t) + \Delta t \sum_{l=1}^{k} r(k,m,l) N_{k,m} \\ + \Delta t \sum_{j=0}^{m} \sum_{i=0}^{k_{\max}-k-m} \left[p(k+i+j, m-j, i, j)\, r(k+i+j, m-j, i+j) N_{k+i+j,m-j}(t) \right], \end{aligned} \tag{1}$$

where $d(k, m)$ is a function of the death rate of cells with k DSBs and m mis-repair DSBs and $r(k, m, l)$ is a function of repair rate of cells with k DSBs and m mis-repair DSBs to simultaneously repair l DSBs at a time. Parameter $p(k + i + j, m - j, i, j)$ is the probability of repair i DSBs correctly and j DSBs incorrectly in group of cells having $k + i + j$ DSBs and $m - j$ DSBs with a summation condition of $0 < i + j \le k_{max} - k$ and $i + j = l$. The unit for parameter d and r is $time^{-1}$. An example of the formulation of Model (1) is given in Appendix A.

Up to date, previous studies only consider the derivation of the model with $l = 1$, for instances [8, 9, 10, 11, 12, 13, 14]. In this paper, we aimed to fill in the gap by initiating a derivation of the model with the condition of $l = 2$. Before proceed, we first review the derivation of $l = 1$ in the following section. Please be noted that the initial condition and the respective functions will be discussed in Section 4.

2. Derivation of a model with 1 DSB repair at a time

In the biological repair mechanism of DSBs, DSBs can be repaired more than one at a time but Siam [7] limits the case where only 1 DSB repairs occur at a time. From here, the model has $l = 1$ and $i + j = 1$. Therefore, $i + j = 1$ means the model (1) attempts to repair 1 DSB only and has two situations, either

(i) successful repair of 1 DSB ($i = 1, j = 0$), or
(ii) unsuccessful repair of 1 DSB ($i = 0, j = 1$).

Hence,

$$\begin{aligned} N_{k,m}(t+\Delta t) = N_{k,m}(t) - \Delta t d(k,m) N_{k,m}(t) - \Delta t r(k,m,1) N_{k,m}(t) \\ + \Delta t p(k+1,m,1,0) r(k+1,m,1) N_{k+1,m}(t) \\ + \Delta t p(k+1,m-1,0,1) r(k+1,m,1) N_{k+1,m-1}(t), \end{aligned} \tag{2}$$

where $p(k + 1, m, 1, 0)$ is the probability of a group of cells with $k + 1$ DSBs and m mis-repair DSBs to successfully repair 1 DSB, while $p(k + 1, m - 1, 0, 1)$ is the probability of a group of cells with $k + 1$ DSBs and $m - 1$ mis-repair DSBs to unsuccessfully repair 1 DSB. Regardless of the DSBs count and mis-repair DSBs, each group of cells assumed to have the same probability of successfully repair 1 DSB and it expressed as ρ. The unsuccessful repair of 1 DSB is denoted as $1 - \rho$ for all groups. The repair mechanism is assumed to repair DSBs damage only, then the repair rate function depends on the DSBs count, therefore $r(k, m, 1)$ is denoted as $r(k)$. Hence,

$$\begin{aligned} N_{k,m}(t+\Delta t) = N_{k,m}(t) - \Delta t d(k,m) N_{k,m}(t) - \Delta t r(k) N_{k,m}(t) \\ + \Delta t \rho r(k+1) N_{k+1,m}(t) + \Delta t (1-\rho) r(k+1) N_{k+1,m-1}(t). \end{aligned} \tag{3}$$

By using the definition of first-order derivative such that:

$$\lim_{\Delta t \to 0} \frac{N_{k,m}(\Delta t)}{\Delta t} = \frac{dN_{k,m}(t)}{dt}. \tag{4}$$

The form of a linear structured ordinary differential equation (ODE) is written as:

$$\frac{dN_{k,m}}{dt} = -d(k,m)N_{k,m} - r(k)N_{k,m} + \rho r(k+1)N_{k+1,m} + (1-\rho)r(k+1)N_{k+1,m-1}, \tag{5}$$

where $k = 0, 1, 2, \ldots, k_{max}$, $m = 0, 1, 2, \ldots, k_{max}$ with $k + m \leq k_{max}$. The derivation concluded here. Next, by allowing less restrictive repair mechanisms such that 2 DSBs can be repaired in parallel will be discussed in the following section.

3. Derivation of a model with 2 DSB repair simultaneously

As to continue the derivation work by [7], we consider a condition of model (1) such that $l = 1$ and $l = 2$. From here, the model (1) attempts to repair 1 DSB as well as 2 DSBs at a time. Therefore, there will be five conditions of i and j, which is two conditions from $i + j = 1$ and three condition from $i + j = 2$. The conditions are:

(i) successfully repair 1 DSB ($i = 1, j = 0$),
(ii) unsuccessfully repair 1 DSB ($i = 0, j = 1$),
(iii) successfully repair 2 DSBs ($i = 2, j = 0$),
(iv) successfully repair 1 DSB and unsuccessfully repair 1 DSB ($i = 1, j = 1$),
(v) unsuccessfully repair 2 DSBs ($i = 0, j = 2$).

Hence,

$$\begin{aligned} N_{k,m}(t+\Delta t) = {} & N_{k,m}(t) - \Delta t d(k,m)N_{k,m}(t) - \Delta t r(k,m,1)N_{k,m}(t) - \Delta t r(k,m,2)N_{k,m}(t) \\ & + \Delta t p(k+1,m,1,0)r(k+1,m,1)N_{k+1,m}(t) + \Delta t p(k+1,m-1,0,1)r(k+1,m-1,1)N_{k+1,m-1}(t) \\ & + \Delta t p(k+2,m,2,0)r(k+2,m,2)N_{k+2,m}(t) + \Delta t p(k+2,m-1,1,1)r(k+2,m-1,2)N_{k+2,m-1}(t) \\ & + \Delta t p(k+2,m-2,0,2)r(k+2,m-2,2)N_{k+2,m-2}(t), \end{aligned} \tag{6}$$

where $p(k + 1, m, 1, 0)$ is the probability of successfully repair 1 DSB, $p(k + 1, m - 1, 0, 1)$ is the probability of unsuccessfully repair 1 DSB, $p(k + 2, m, 2, 0)$ is the probability of successfully repair 2 DSBs, $p(k + 2, m - 1, 1, 1)$ is the probability of successfully repair 1 DSB and unsuccessfully repair 1 DSB, and $p(k + 2, m - 2, 0, 2)$ is the probability of unsuccessfully 2 DSBs. Regardless the number of k and m in a group of cells, each of the probability is assumed the same, and $p(k + 1, m, 1, 0)$, $p(k + 1, m - 1, 0, 1)$, $p(k + 2, m, 2, 0)$, $p(k + 2, m - 1, 1, 1)$ and $p(k + 2, m - 2, 0, 2)$ will be denoted as ρ_1, $(1 - \rho_1)$, ρ_2, ρ_3 and $(1 - \rho_2)$, respectively. Next, since the repair function depends on DSBs count, the notation for $r(k, m, 1)$ and $r(k, m, 2)$ is denoted as $r_1(k)$ and $r_2(k)$, respectively. Hence,

$$\begin{aligned} N_{k,m}(t+\Delta t) = {} & N_{k,m}(t) - \Delta t d(k,m)N_{k,m}(t) - \Delta t r_1(k)N_{k,m}(t) \\ & - \Delta t r_2(k)N_{k,m}(t) + \Delta t \rho_1 r_1(k+1)N_{k+1,m}(t) + \Delta t(1-\rho_1)r_1(k+1)N_{k+1,m-1}(t) \\ & + \Delta t \rho_2 r_2(k+2)N_{k+2,m}(t) + \Delta t \rho_3 r_2(k+2)N_{k+2,m-1}(t) + \Delta t(1-\rho_2)r_2(k+2)N_{k+2,m-2}(t). \end{aligned} \tag{7}$$

By taking limit $\Delta t \to 0$, the form of linear ODE is written as follows:

$$\begin{aligned} \frac{dN_{k,m}}{dt} = {} & -d(k,m)N_{k,m} - r_1(k)N_{k,m} - r_2(k)N_{k,m} + \rho_1 r_1(k+1)N_{k+1,m} + (1-\rho_1)r_1(k+1)N_{k+1,m-1} \\ & + \rho_2 r_2(k+2)N_{k+2,m} + \rho_3 r_2(k+2)N_{k+2,m-1} + (1-\rho_2)r_2(k+2)N_{k+2,m-2}. \end{aligned} \tag{8}$$

where $k = 0, 1, 2, \ldots, k_{max}$, $m = 0, 1, 2, \ldots, k_{max}$ with $k + m \leq k_{max}$. In the next section, some parameters that appear in model equation (5) and (8) will be discussed.

4. Settings for parameter function and initial condition

The function of cells death is with respect to DSBs count and mis-repair DSBs, $d(k, m)$. When the number of DSBs is high, there is more chance of mis-repair the DSBs and lethal chromosomal aberrations. The death rate is expressed as follows:

$$d(k,m) = \alpha m + \beta k^2, \tag{9}$$

where α is the cell death factor due to mis-repair DSBs count and β is the cell death factor due to DSBs count. For the repair rate, the parameter in r is treated according to the model. In model Equation (5), the repair rate is expressed as:

$$r(k) = \frac{\sigma k}{\eta + k}, \tag{10}$$

where σ is the maximum rate DSBs repair and η is the steepness of the curve. Meanwhile, in model Equation (8), the repair function is treated in the same way but with a different parameter such that:

$$r_1(k) = \frac{\sigma_1 k}{\eta_1 + k} \quad \text{and} \quad r_2(k) = \frac{\sigma_2 k}{\eta_2 + k}, \tag{11}$$

where σ_1 is the maximum repair rate attempts for 1 DSB, σ_2 is the maximum repair rate attempts for 2 DSBs, and η_1 and η_2 are the steepness of repair rate curve.

Special emphasis is given to the initial condition as it indicates the size of a group of cells and k_{max} value. The number of DSBs is generated by the Poisson distribution function. The mean of the Poisson distribution is expressed by the average number of DSBs that possibly form after traversed by irradiation:

$$\mu = \delta \mathrm{D}, \tag{12}$$

where δ is the radio-sensitivity of the cells, given in unit DSBs Gy^{-1}. By analyzing the pattern of the models, the general form of the system with any maximum number of k_{max} can be written into a matrix form:

$$\frac{d\mathbf{N}}{dt} = \mathbf{A}\mathbf{N}, \qquad \mathbf{N}(0) = \mathbf{N}_0, \tag{13}$$

with the initial condition $\mathbf{N}_0$. According to [15, 16], the exact solution for the above initial value problem is:

$$\mathbf{N}(t) = \exp\{\mathbf{A}t\}\mathbf{N}_0. \tag{14}$$

$\mathbf{N}$(t) can be measured at any time t. However, $\mathbf{N}$(t) is not the final solution sought. The total survival cells at time t are computed as follows:

$$\text{Survival cells} = \sum_{k=0}^{k_{\max}} \sum_{m=0}^{k_{\max}-k} N_{k,m}(t). \tag{15}$$

For the reader enlightenment, an example on Equation (15) towards Model (8) is given in Appendix B.

5. Concluding remarks

To understand irradiation damage to mammalian cells, we have derived the cells' dynamical process involved in radiation response. In particular, a derivation on a simultaneously repair of two DSBs is presented. Previous studies have shown that the model derivation of 1 DSBs repair is consistent with the experimental measurement [8, 13]. Hence, it would be interesting to construct and study the qualitative and quantitative behaviour of the corresponding model of 2 simultaneously DSBs repair.

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Appendix A: An Example of formulation Equation (1)

Suppose $k_{max} = 4$, the evolution of cells group $N_{2,1}$ is:

$$N_{2,1}(t+\Delta t) = N_{2,1}(t) - \Delta t d(2,1) N_{2,1}(t) - \Delta t \sum_{l=1}^{2} r(2,1,l) N_{2,1}(t)$$
$$+\Delta t \sum_{j=0}^{1}\sum_{i=0}^{1}\Big[\, p(2+i+j, 1-j, i, j)\, r(2+i+j, 1-j, i+j) N_{2+i+j,1-j}(t)\Big].$$

Then,

$$N_{2,1}(t+\Delta t) = N_{2,1}(t) - \Delta t d(2,1) N_{2,1}(t) - \Delta t r(2,1,1) N_{2,1}(t)$$
$$-\Delta t r(2,1,2) N_{2,1}(t) + \Delta t p(3,1,1,0) r(3,1,1) N_{3,1}(t)$$
$$+\Delta t p(3,0,0,1) r(3,0,1) N_{3,0}(t) + \Delta t p(4,0,1,1) r(4,0,2) N_{4,0}(t).$$

Appendix B: An Example on formulation matrix N and A in Equation (13) using model Equation (8)

To obtain the pattern of the model, Equation (8) is simplified as follows:

$$\frac{dN_{k,m}}{dt} = G_{k,m} N_{k,m} + B_{k+1} N_{k+1,m} + C_{k+1} N_{k+1,m-1}$$
$$+ D_{k+2} N_{k+2,m} + E_{k+2} N_{k+2,m-1} + F_{k+2} N_{k+2,m-2},$$

where $G_{k,m} = -d(k,m) - r_1(k) - r_2(k)$, $B_{k+1} = \rho_1 r_1(k+1)$, $C_{k+1} = (1-\rho_1) r_1(k+1)$, $D_{k+2} = \rho_2 r_2(k+2)$, $E_{k+2} = \rho_3 r_2(k+2)$ and $F_{k+2} = (1-\rho_2) r_2(k+2)$.

(i) Suppose a cell population containing a maximum number of DSBs, k_{max} = 1. Hence, the population can be structured into 3 groups of cells, which are $N_{0,0}$, $N_{1,0,}$ and $N_{0,1}$. The system is given as follows:

$$\frac{dN_{0,0}}{dt} = G_{0,0}N_{0,0} + B_1N_{1,0},$$

$$\frac{dN_{1,0}}{dt} = G_{1,0}N_{1,0},$$

$$\frac{dN_{0,1}}{dt} = G_{0,1}N_{0,1} + C_1N_{1,0}.$$

Then, in matrix notation:

$$\frac{d}{dt}\begin{bmatrix} N_{0,0} \\ N_{1,0} \\ N_{0,1} \end{bmatrix} = \begin{bmatrix} G_{0,0} & B_1 & 0 \\ 0 & G_{1,0} & 0 \\ 0 & C_1 & G_{0,1} \end{bmatrix}\begin{bmatrix} N_{0,0} \\ N_{1,0} \\ N_{0,1} \end{bmatrix},$$

(ii) Suppose a cell population containing a maximum number of DSBs, k_{max} = 2. Hence, the population can be structured into 6 groups of cells, which are $N_{0,0}$, $N_{1,0}$, $N_{2,0}$, $N_{0,1}$, $N_{1,1,}$ and $N_{0,2}$. The system is given as follows:

$$\frac{dN_{0,0}}{dt} = G_{0,0}N_{0,0} + B_1N_{1,0} + D_2N_{2,0},$$

$$\frac{dN_{1,0}}{dt} = G_{1,0}N_{1,0} + B_2N_{2,0},$$

$$\frac{dN_{2,0}}{dt} = G_{2,0}N_{2,0},$$

$$\frac{dN_{0,1}}{dt} = G_{0,1}N_{0,1} + B_1N_{1,1} + C_1N_{1,0} + E_2N_{2,0},$$

$$\frac{dN_{1,1}}{dt} = G_{1,1}N_{1,1} + C_2N_{2,0},$$

$$\frac{dN_{0,2}}{dt} = G_{0,2}N_{0,2} + C_1N_{1,1} + F_2N_{2,0}.$$

Then, in matrix notation such that $\frac{d\mathbf{N}}{dt} = \mathbf{AN}$ where:

$$\mathbf{A} = \begin{bmatrix} G_{0,0} & B_1 & D_2 & 0 & 0 & 0 \\ 0 & G_{1,0} & B_2 & 0 & 0 & 0 \\ 0 & 0 & G_{2,0} & 0 & 0 & 0 \\ 0 & C_1 & E_2 & G_{0,1} & B_1 & 0 \\ 0 & 0 & C_2 & 0 & G_{1,1} & 0 \\ 0 & 0 & F_2 & 0 & C_1 & G_{0,2} \end{bmatrix}, \quad \text{and} \quad \mathbf{N} = \begin{bmatrix} N_{0,0} \\ N_{1,0} \\ N_{2,0} \\ N_{0,1} \\ N_{1,1} \\ N_{0,2} \end{bmatrix}.$$

The matrix **N** and the size of matrix **A** are derived based on the value of k_{max}. Therefore, the size of matrix **N** is $M \times 1$, and the size of matrix **A** is $M \times M$ such that:

$$M = \frac{(k_{\max}+1)(k_{\max}+2)}{2}.$$

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