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Computational Model of Population Dynamics Based on the Cell Cycle and Local Interactions
A New ODE Tumor Growth Modeling Based on Tumor Population Dynamics

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\textbf{Abstract.} In this paper a new mathematical model for the population of tumor growth treated by radiation is proposed. The cell dynamics population in each state and the dynamics of whole tumor population are studied. Furthermore, a new definition of tumor lifespan is presented. Finally, the effects of two main parameters, treatment parameter ($q$), and repair mechanism parameter ($r$) on tumor lifespan are probed, and it is showed that the change in treatment parameter ($q$) highly affects the tumor lifespan.

\textbf{Keywords:} Tumor Growth Modeling; Population Dynamics; Radiotherapy.

PACS: 45.30.+s,02.70.Ns.

\textbf{INTRODUCTION}

One of the typical methods for cancer treatment is the External Beam Radiation (EBR). It is verified that the ionization process initiated through radiation particles leads to lesions in cells and changes in DNA structure \cite{1}, which cause harmful side effects of the radiotherapy \cite{2}, \cite{3}. Examples and further detail of this can be found in the utilization of the Tumor Control Probability (TCP) \cite{4}, \cite{5}, \cite{6} as well as the Normal Tissue Complication Probability (NTCP) \cite{7}, \cite{8} in the classification and evaluation of the radiation treatment planning. Different stochastic models are developed to predict the tumor response in this process (see linear quadratic models in \cite{4}, \cite{9}, cell population dynamic models in \cite{10}, mixed-effects behavioral models in \cite{11}, and cell cycle models in \cite{12}). The clinical significance of the intra tumor heterogeneity of cell phenotypes or the cell damage is discussed in \cite{13}, \cite{14}, \cite{15}. Prior models have usually assumed that the cell sensitivity is constant during radiation \cite{16}. The same assumption is also taken into account for the cell population, which indicates that a surviving cell is expected to be viable regarded as irradiated cell. Therefore, all cells are believed to have a similar survival probability. Yet, there are strong evidences that a damaged cell would be unable to resist \cite{16}, \cite{17}. Providing a definition an effective treatment duration is a challenge, especially when variability of the therapeutic response is incorporated. In this regard Kienj et al.’s model uses Target Theory, which is based on the assumption that the cell is exposed to a
number of radio-sensitive targets [17]. Radiation particles lead to the death of a cell through deactivation of specific targets. This model can incorporate the post-treatment heterogeneity of the cell damage. This paper introduces a new approach to the tumor lifespan based on the dynamics of tumor cells, the effect of treatment on cells, and different reaction of each cell to radiation particles. i.e. the radiation (treatment) and immune system (repair mechanism) case that each cell moves between nodes. Therefore cells reaction to the treatment is different in the current model.

**GENERAL THEORY**

The main part of theory is based on the model developed by Keinjet. al. [16], where a discrete-time Markov chain multinominal model for the tumor growth based on the target and hit theory is proposed. The assumptions are as follows:

1. The number of targets in each cell is $m$.
2. $q$ be the probability that a target becomes inactive by a radiation particle after the application of a dose fraction.
3. Between two consecutive dose fraction, each target may activate again after the repair mechanism with the probability $r$.
4. The cell death happens after a dose fraction if the $m$ targets become deactivate.
5. There is no delay effect between the radiation dose applied to the mother cell and the damage consequences on daughter cells.
6. $u_0 = 2GY$ denotes the constant dose fraction of radiation applied every day.

Also, it is assumed that the tumor cells behave independently, i.e., the effect of radiation particles and repair mechanism on each cell is independent and they have the same phenotype. In other words the probability that a target becomes inactive after the treatment ($q$) and the probability that a target becomes active again after the repair mechanism ($r$) are equal for all cells. So it is sufficient to investigate the behavior of one cell in treatment process. In addition we don’t take into account the cell cycle positions. The main notations used in this paper are presented in table 1.

<table>
<thead>
<tr>
<th>Notation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k$</td>
<td>Time</td>
</tr>
<tr>
<td>$Z_k$</td>
<td>Number of deactivated targets in a cell</td>
</tr>
<tr>
<td>$P$</td>
<td>Transition matrix corresponding to $(Z_k)$</td>
</tr>
<tr>
<td>$R$</td>
<td>Matrix corresponding to treatment effects</td>
</tr>
<tr>
<td>$m$</td>
<td>Matrix corresponding to cell repair mechanism</td>
</tr>
<tr>
<td>$q$</td>
<td>Number of targets in a cancer cell</td>
</tr>
<tr>
<td>$r$</td>
<td>Probability to deactivate a target in a cancer cell</td>
</tr>
<tr>
<td>$n_0$</td>
<td>Probability for an inactive target to be reactivated in a cancer cell</td>
</tr>
<tr>
<td>$L$</td>
<td>Initial number of cancer cells composed the tumor</td>
</tr>
<tr>
<td>$T$</td>
<td>Tumor Lifespan</td>
</tr>
</tbody>
</table>

Consider a specific cell in the tumor. Let $Z_k$ be the number of inactivated targets in this cell after the application of $k^{th}$ dose fraction. For instance $Z_2 = 0$ implies that all targets of this cell are active, where second dose fraction has been applied. In this case, $k = 0$ related to the beginning of the treatment.

Also we suppose that $Z_k$ is a discrete-time Markov chain, i.e., the number of inactivated targets at time $(k + 1)$ is only depended on the number of inactivated targets at time $k$. 

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Let $\Pi$ be the transition matrix associated with $Z_k$. So, the dynamics of $Z_k$ is dependent on the effects of radiation damages on cells after each dose fractions. The repair mechanism happened between two consecutive dose fractions:

$$\Pi = PR(1)$$

Where $P$ describes the treatment effects and $R$ represents repair mechanism. $P$ and $R$ are described as follows

$$P(i,j) = \begin{cases} \binom{m-i}{j-i} q^{j-i}(1-q)^{m-j} & i \leq j \\ 0 & i > j \end{cases}$$

Here $P(i,j)$ denotes the probability that a cell move from state $i$ to state $j$ at time $k$.

$$R(i,j) = \begin{cases} \binom{j}{i} r^{i-j}(1-r)^{j-i} & j \leq i \leq m \\ 0 & i < j \end{cases}$$

In addition, if $i=m$, we have

$$R(m,m) = 1$$

And

$$R(m,j) = 0$$

For $0 \leq j < m$.

Therefore, $R(i,j)$ is the probability that a cell move back from state $i$ to state $j$ after the repair mechanism.

We suppose that a cell may be reproduced only if it is in state zero and still in this state after the application of a dose fraction, which occurs with a probability $P(0,0) = (1-q)^m$. Moreover, this kind of cells can divide and give birth into two daughter cells with probability ($\mu$). The new cells are in state zero.

Assume that the tumor initially contains $n_0$ cells. If $x_i(k)$ denotes the number of cells in state $i$, where $i = 0, \ldots, m$, and $n_k$ be the number of new added cells after the application of $k^{th}$ dose fraction then:

$$x_0(1) = n_0 \Pi(0,0) + n_1$$

And

$$x_i(1) = n_0 \Pi(0, i)$$

In this case:

$$n_1 = n_0 \mu (1-q)^m$$

And therefore:

$$x_0(1) = n_0 \Pi(0,0) + \mu (1-q)^m$$

This means that the number of added cells depends on the number of cells in state zero, and the probability that a cell can divide into two daughter cells. So we can formulate the number of added cells after the application of $k^{th}$ dose fraction based on the number of cells in state zero just before the application of $k^{th}$ dose fraction as below:

$$n_k = \mu (1-q)^m x_0(k-1)$$
Additionally,
\[ x_0(k) = n_k + \sum_{l=0}^{m-1} x_l(k-1) \Pi(l, 0) \]
\[ = x_0(k-1)(\Pi(0,0) + \mu(1 - q)^m) + \sum_{l=1}^{m-1} x_l(k-1) \Pi(l, 0) \] (9)

And for \( i = 1, ..., (m-1) \) we have:
\[ x_i(k) = \sum_{l=0}^{m-1} x_l(k-1) \Pi(l, i) \] (10)

It is clear that the population of cells in the tumor after the application of \( k^{th} \) dose fraction equals to
\[ N(k) = n_k + \sum_{l=0}^{m-1} x_l(k) \] (11)

Therefore the tumor lifespan based on tumor population dynamics is defined as
\[ L = \min \{ t : [N(t)] = 0 \} \] (12)

**THE MATHEMATICAL MODEL**

We use a continuous ODE system to model tumor growth:
\[ \dot{x} = f(x(t), t) \] (13)

Where \( x(t) \) is the value of the \( n \)-dimensional state vector at time \( t \), where \( n \) is the order of the system.

\[ x(t) = (x_1(t), ..., x_n(t))^T \] (14)
Suppose that $x_i$ be the subpopulation of cells with $i$ deactivated targets. Therefore, the conservation law for each subpopulation is written as:

$$\frac{dx_i(t)}{dt} = ln(t) - \text{Out}(t) \quad (15)$$

For $i = 0$

$$ln(t) = n_e + \sum_{l=1}^{m-1} x_i(t) \Pi(l, 0)$$

$$= \mu(1 - q)^m x_0(t) + \sum_{i=1}^{m-1} x_i(t) \Pi(l, 0) \quad (16)$$

Similarly for $i = 1, \ldots, (m - 1)$

$$ln(t) = \sum_{i=0}^{m-1} x_i(t) \Pi(l, i) \quad (17)$$

Now, we count the number of exiting cells.

After the application of $k^{th}$ dose fraction the number $x_0(k - 1) \Pi(j, i)$ move from subpopulation $x_j$ to subpopulation $x_i$.

Here, $\Pi$ is the transition matrix, therefore

$$\sum_{k=0}^{m} x_k(t) \Pi(j, k) = 1 \quad (18)$$

This leads us to:

$$\text{Out}(t) = x_0(t) \sum_{i=1}^{m} \Pi(j, k) \quad (19)$$

$$= x_0(t) [1 - \Pi(j, j)] \quad (20)$$

Combining these equations, the tumor growth model is described as follows:

$$\frac{d \ 0(t)}{dt} = [\Pi(0, 0) - \mu(1 - q)^m - 1] x_0(t) + \sum_{i=1}^{m-1} x_i(t) \Pi(l, 0) \quad (21)$$

$$\frac{d \ i(t)}{dt} = [\Pi(0, i) - 1] x_0(t) + \sum_{j=1}^{m} x_j(t) \Pi(l, j) \quad (22)$$

**NUMERICAL RESULTS**

For simplicity, the present model is studied when there are just three targets in the cancer cell ($m = 3$). Numerical results obtained for parameters $m = 3$ and $\mu = 1$ and different values of $r$, $q$, $n_0$. So we have the following systems of equations:

$$\frac{d \ 0(t)}{dt} = [\Pi(0, 0) - \mu(1 - q)^m - 1] x_0(t) + \Pi(1, 0) x_1(t) + \Pi(2, 0) x_2(t)$$

$$\frac{d \ 1(t)}{dt} = \Pi(0, 1) x_0(t) + [\Pi(1, 1) - 1] x_1(t) + \Pi(2, 1) x_2(t)$$
\[
\frac{d N(t)}{dt} = \Pi(0, 2)x_0(t) + \Pi(1, 2)x_1(t) + [\Pi(2, 2) - 1]x_2(t)
\]  

(23)

The influence of the number of dose fractions \( t \) on the cells population, \( N \), where \( m = 3 \) and \( n_0 = 100 \) are shown in Figure. (2), (3).

The tumor lifespan as function of the probability that a target becomes active again after the repair mechanism \( (r) \), has been shown in Figure. (4), where \( m = 3, q = 0.7 \), and \( n_0 = 100 \). Additionally, the tumor lifespan increases when the repair mechanism probability \( (r) \) increases. According to this graph the tumor lifespan is 16 and 23 for \( r = 0.3 \), and \( r = 0.5 \), respectively (see Table (2)).

Figure (5) shows the influence of the probability that a target becomes inactive after a dose fraction \( (q) \) on tumor lifespan \( (L) \), when \( m = 3, r = 0.1 \), and \( n_0 = 100 \). This graph shows that the tumor lifespan decreases, when the treatment mechanism \( (q) \) increases. For example, the tumor lifespan for \( q = 0.4 \) and \( q = 0.6 \) is 19 and 9, respectively (see Table (2)).

The variations of tumor lifespan \( (L) \) according to the changes in the initial numbers of tumor \( (n_0) \), where \( m = 3, r = 0.1 \) and \( q = 0.5 \) is presented in Figure. (6).

According to this graph the tumor lifespan for \( n = 10^2, 10^3, 10^4, 10^5 \) is 11, 16, 22, 27, respectively. The obtained results from this graph are in very good agreement with the results presented in [17] in Fig. 5(a).

Table (2) presents the numerical results associated with the above figures. For the fixed values \( m = 0.7 \), and \( n_0 = 100 \), Figure (4) shows the tumor lifespan \( (L) \) when \( r = 0.3 \) and \( r = 0.5 \). In this case, tumor lifespan \( (L) \) increases when the repair mechanism parameter \( (r) \) increases. Additionally, Figure (5) presents the tumor lifespan \( (L) \) when \( q = 0.4 \) and \( q = 0.6 \) for fixed parameters \( r = 0.1 \) and \( n_0 = 100 \). Here \( (L) \) decreases when \( (q) \) increases. Finally, Figure (6) shows the influence of \( (n_0) \) on \( (L) \) for fixed parameters value \( r = 0.1 \) and \( q = 0.5 \).

**FIGURE 2.** The Population Size Dynamics for \( m=3, q=0.6, n_0=100, \) and \( r=0.2 \). This system is stable at point \((0,0,0)\).
FIGURE 3. The Population Size Dynamics for $m=3$, $q=0.2$, $n_0=100$, and $r=0.4$. Here the system is unstable at origin.

FIGURE 4. Influence of the probability that a target becomes active again after the repair mechanism ($r$) on the tumor lifespan ($L$). The tumor lifespan for $r=0.3$ and $r=0.5$, where $m=3$ and $q=0.7$ are shown.
FIGURE 5. Influence of the probability that a target becomes inactive after a dose fraction ($q$) on the tumor lifespan ($L$). The tumor lifespan for $q=0.4$ and $q=0.6$, where $m=3$ and $r=0.1$ are shown.

FIGURE 6. Variations of Tumor lifespan ($L$) according to the changes in initial numbers of tumor ($n_0$), where $m=3$, $r=0.1$ and $q=0.5$. 
### TABLE 2: Influence of the multinomial parameters $q$, $r$ and $n_0$ on the Tumor Lifespan $L$

<table>
<thead>
<tr>
<th>Fixed parameters</th>
<th>Variable parameters</th>
<th>Tumor Lifespan ($L$)</th>
<th>Figure</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n_0=100$</td>
<td>$r=0.3$</td>
<td>16</td>
<td>Fig. (4)</td>
</tr>
<tr>
<td>$q=0.7$</td>
<td>$r=0.5$</td>
<td>23</td>
<td>Fig. (4)</td>
</tr>
<tr>
<td>$n_0=100$</td>
<td>$q=0.4$</td>
<td>19</td>
<td>Fig. (5)</td>
</tr>
<tr>
<td>$r=0.1$</td>
<td>$q=0.6$</td>
<td>9</td>
<td>Fig. (5)</td>
</tr>
<tr>
<td>$r=0.1$</td>
<td>$n_0=100$</td>
<td>11</td>
<td>Fig. (6)</td>
</tr>
<tr>
<td>$q=0.5$</td>
<td>$n_0=1000$</td>
<td>16</td>
<td>Fig. (6)</td>
</tr>
</tbody>
</table>

### CONCLUSION

In this paper, the population dynamics of a tumor has been studied through an ordinary differential equations system, which includes the heterogeneity of cells damages, and the repair mechanism between two consecutive dose fractions. Developing the probabilistic model [16], the effects of the probability that a target inactive after a dose fraction ($q$), and the probability that a target reactive again after the repair mechanism ($r$) have been studied numerically. Finally, we have shown that the results of our study are in good agreement with the results presented in [17].

### REFERENCES