An Itô stochastic differential equations model for the dynamics of the MCF-7 breast cancer cell line treated by radiotherapy

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**HIGHLIGHTS**

- Tumor cells population dynamics is modeled via a three-dimensional stochastic differential equation.
- A new definition for tumor lifespan is introduced based on the cells population dynamics.
- The transition rates are estimated by using the data from MCF-7 breast cancer cell line.
- The stability results of the proposed system are examined.
- The proposed model is richly appropriate for finding the tumor lifespan and comparing the effect of different treatments on it.

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**ABSTRACT**

In this paper, a new mathematical model is proposed for studying the population dynamics of breast cancer cells treated by radiotherapy by using a system of stochastic differential equations. The novelty of the model is essentially in capturing the concept of the cell cycle in the modeling to be able to evaluate the tumor lifespan. According to the cell cycle, each cell belongs to one of three subpopulations \(G, S,\) or \(M,\) representing gap, synthesis and mitosis subpopulations. Cells in the \(M\) subpopulation are highly radiosensitive, whereas cells in the \(S\) subpopulation are highly radio-resistant. Therefore, in the process of radiotherapy, cell death rates of different subpopulations are not equal. In addition, since flow cytometry is unable to detect apoptotic cells accurately, the small changes in cell death rate in each subpopulation during treatment are considered. Subsequently, the proposed model is calibrated using experimental data from previous experiments involving the MCF-7 breast cancer cell line. Consequently, the proposed model is able to predict tumor lifespan based on the number of initial carcinoma cells. The results show the effectiveness of the radiation under the condition of stability, which describes the decreasing trend of the tumor cells population.

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1. Introduction

Cancer is a term referring to a group of diseases that trigger cells in the body to grow out of control. Most types of cancer cells eventually produce tumors which are named based on the tumor’s location in the body. Breast cancer is globally among the most common forms of cancer. This cancer begins in the breast tissue. Surgery, chemotherapy and radiotherapy (RT) are the most well-known treatments for this type of cancer, however radiotherapy is effective only in the early stages.

Ionizing of the DNA molecules can cause single- and double-strand damages (Curtis, 1986; Wyman and Kanaar, 2006). Among the mathematical models, stochastic models serve the best in explaining these types of damages. Among these models, we refer the reader to Tumor Control Probability (TCP) in Zaider and Minerbo (2000), Dawson and Hillen (2006) and Normal Tissue Complication Probability (NTCP) in Gay (2007) for further details. The goal of most of these stochastic models is to predict the tumor’s response to radiation (e.g. cell population dynamics (Sachs and Hlatky, 2001; Lo, 2007), linear quadratic models (Belkic and Belkic, 2013), and cell cycle models (Tyson et al., 2002; Sible and Tyson, 2007)). One of the main drawbacks of these models is that cell sensitivity is considered to be constant during the treatment period (Keinj et al., 2012). Also, these models unrealistically assumed that the cell death rate caused by treatment is constant during the treatment.

Investigating the effects of treatments on breast cancer cell
lines involves determining how they influence cell proliferation rate. As cells proliferate, they progress through a series of distinct phases. In the first phase, the G_1 (gap phase), cells are only receptive to environmental signals. This phase is named so as it appears as a gap between the previous cell division stage and subsequent DNA synthesis phase (Alberts et al., 2014). If a cell decides to divide, it makes an irreversible decision to progress into the S phase, or the synthesis phase, during which DNA synthesis occurs. Upon DNA synthesis completion, the cell moves into the G_2 phase (the second gap phase), when accumulated errors in the replicated DNA are reviewed and corrected. The cell then moves into the M phase (mitosis phase), where the duplicated chromosomes are separated into two sets of nuclei. At the end of the M phase, the cell splits into two identical cells via a process called cytokinesis. Both daughter cells begin their cycle again in the G_1 phase (Alberts et al., 2014; Weinberg, 2013).

Several mathematical models for cell cycle progression have been developed (Sible and Tyson, 2007; Bertuzzi et al., 1981). For instance, Piantadosi et al.’s cell cycle model which contains five compartments: G_0, G_1, S, G_2, and M (Piantadosi et al., 1985). It uses a system of six nonlinear ODEs in order to model the tumor growth. Similar approaches have been presented in Piantadosi (1985) and Sachs and Hlatky (2001), by considering two compartments. According to Piantadosi (1985), cells are divided into quiescent and active compartments. Sachs and Hlatky (2001) considers hypoxic and normoxic tumor cells in the subpopulation. Basse et al. studied tumor growth populations in human cell lines through a multi-compartment model of cell cycles (Basse et al., 2004). Using an age structure model, Albano and Giorno developed a mathematical model of cell population dynamics for colorectal cancer (Albano and Giorno, 2006). Simms et al. (2012), applied a three-compartment cell cycle model to the MCF-breast cancer cell line. It introduced a cell population dynamic based on three main subpopulations, namely G, S and M, each of which is divided into three, two, and two subpopulations, respectively. This approach resulted in a system of seven nonlinear delay ODEs describing cell population dynamics.

One common drawback among above mentioned mathematical models is that they all suffer from lack of considering the inherent error in the death rate caused by the flow cytometry method. This error is rooted in recognizing apoptotic cells as live cells (Daukšite, 2012). The current work succeeds in considering random changes in cell death rate measurement through flow cytometry in addition to cells population dynamics and cell cycles. 

One of the most important problems in treatment planning is to answer the following question that how many dose fractions are necessary to remove the whole tumor cells? We define this number as the tumor lifespan in definition 2.1. Therefore, the proposed model is able to calculate the tumor lifespan as well.

The rest of this paper is organized as follows. The model is illustrated in Section 2. The general theory is presented in Subsection 2.1. The cell population dynamics are modeled via a system of Stochastic Differential Equations, which is presented in Section 2.2. Section 3 is dedicated to evaluating the model’s main parameters based on the experimental results. The existence and uniqueness of the solution and system explicit solution are presented in Sections 4 and 5. Thereafter, system stability analysis is probed in Section 6. The numerical results are presented in Section 7. First, the Euler-Maruyama (E-M) method is applied to solve the SDE system, and then the best values for the parameters are estimated by applying the parametric and nonparametric Simulated Likelihood Estimation methods in (Subsections 7.1 and 7.2). Subsequently, the tumor lifespan for 200 times of simulated data is evaluated in Subsection 7.3. Finally, Sections 8 and 9 are for discussion and conclusion, respectively.

2. The model

The loss of intrinsic reproductive capacity is almost unanimously accepted for the cell death in radiotherapy, which can be applied to the tumor cells in the process of irradiation. Quantification of the cells death rate is difficult due to the fact that cells die at various times after irradiation, often taking one or two cycles. (Van der Kogel and Joiner, 2009). According to experimental results, cells’ radio-sensitivity change based on the cell cycle stage (Valenzuela et al., 2000). The experiments has verified that a cell is more radio-sensitive during the G2/M-phase (Quitet et al., 1991; Tell et al., 1998) and more radio-resistant in the S-phase (Howard and Pelc, 1986; Nagasawa et al., 1994).

In the proposed model, the tumor cell population is divided into three subpopulations according to radio-sensitivity (Simms et al., 2012; Wake and Byrne, 2013; Falchetta et al., 2013; Weber et al., 2014; Gurkan-Cavusoglu et al., 2011), i.e., gap (G), synthesis (S), and mitosis (M), with the possibility of cell death in each subpopulation. These represent a concise formulation of the cell cycle.

2.1. Assumptions

- **A1**: The magnitude of radiation is constant (2Gy) during treatment.
- **A2**: Cells population consists of three time-dependent subpopulations G(t), S(t) and M(t), which in turn representing Gap, Synthesis and Mitosis.
- **A3**: The transition rate of cells moving from subpopulation G into subpopulation S is the time-dependent rate at(t); the transition from subpopulation S into subpopulation M is the constant rate β and subpopulation M to subpopulation G is the constant rate γ, which can be considered the birth rate.
- **A4**: All cells are at risk of dying, but at different rates. The death rate of cells in subpopulation G is a constant rate q_1, whereas cells in subpopulations S and M have q_2 and q_3 rates respectively.
- **A5**: Due to environmental effects such as accuracy of the cytometry method in counting cells in the apoptosis stage, a noise in the death rate is deemed to capture these effects. Therefore, cell death rates are given by:

\[
\begin{align*}
\nu(t) &= q_1 + r_1(t) \\
\gamma(t) &= q_2 + r_2(t) \\
\delta(t) &= q_3 + r_3(t)
\end{align*}
\]

(2.1)

where \( r_1(t), r_2(t), \) and \( r_3(t) \) are stochastic noise terms, and \( q_2 < q_1 < q_3 \).

2.2. Stochastic differential equation model

When cells are proliferating, they move from one subpopulation into another (Bernard and Herzl, 2006; Johnston et al., 2007). During the radiotherapy with gamma rays (2–4 Gy), the transition rates of cell movement change at checkpoints G_1 and G_2. As illustrated in Fig. 1, using transition rates between subpopulations, the population dynamic is described by:
By applying (2.1), (2.2) can be written as:

\[
\begin{align*}
\frac{dG(t)}{dt} &= -\left[\alpha(t) + (q_1 + r_1(t))\right]G(t) + \gamma M(t) \\
\frac{dS(t)}{dt} &= \alpha(t)G(t) - \left[\gamma + \left(q_2 + r_2(t)\right)\right]S(t) \\
\frac{dM(t)}{dt} &= \beta S(t) - (\gamma + h(t))M(t)
\end{align*}
\]

(2.2)

Assuming that \( r_i(t)dt = \sigma_i dW^i \) for \( i = 1, 2, 3 \) (Evans, 2014), the stochastic differential equation system describing the population dynamics of cells is written as:

\[
\begin{align*}
\frac{dG(t)}{dt} &= -\left[\alpha(t) + (q_1 + r_1(t))\right]G(t) + \gamma M(t) \\
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\frac{dM(t)}{dt} &= \beta S(t) - (\gamma + \left(q_3 + r_3(t)\right)M(t)
\end{align*}
\]

(2.4)
Fig. 3. Cell population dynamics for the different subpopulations over 100 trajectories by solving (2.4). Here, the black circles are the trajectories corresponding to the observed numbers of cells (parametric method). The blue lines represent the first and third quartiles of the simulated trajectories and the red lines illustrate 95% confidence interval areas obtained by taking, at each time, the 2.5th and 97.5th percentiles of the simulated trajectories. The green line is the empirical mean of the process. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
\[ d\mathbf{X} = A\mathbf{X}dt - \sigma \mathbf{X}dW \]  

where \( A \) and \( \sigma \) are the following matrices:

\[
A = \begin{bmatrix}
-(\alpha + q_1) & 0 & 2\gamma \\
\alpha & - (\beta + q_2) & 0 \\
0 & \beta & - (\gamma + q_3)
\end{bmatrix}, \quad \sigma = \begin{bmatrix}
\sigma_1 & 0 & 0 \\
0 & \sigma_2 & 0 \\
0 & 0 & \sigma_3
\end{bmatrix}
\]

By using (2.5), the tumor’s lifespan can be defined as follows:

**Definition 2.1.** The tumor lifespan is defined as the minimum necessary dose fractions needed for the tumor removal. As such, the tumor lifespan is defined as:

\[ L = \min\{t : N_t(t) = 0\} \]  

where \( N_t(t) \) is the total number of tumor cells, which is written as:

\[ N_t(t) = G_t(t) + S_t(t) + M_t(t) \]  

### 3. Model calibration

#### 3.1. Steady-State solutions

To evaluate the main model parameters \( \alpha, \beta, \gamma \), and \( \chi \), it is first assumed that \( q_1 = q_2 = q_3 = 0 \) and \( r_1 = r_2 = r_3 = 0 \). If \( \alpha \) is constant (which is here by called unchanging environmental conditions), then our system will eventually reach a certain steady-state behavior that we call steady-state phase.

System (2.5) is in a steady state phase, when the proportion of cells across the model phases is constant over time. Note that, as it is experimentally observed, the actual cell populations do not reach a steady-state and instead grow exponentially. Other mathematical models such as Begg et al. (2010) take these steady-state conditions into account by incorporating the terms balancing exponential growth. Throughout this paper, we refer to this condition as a steady-state phase, or an unchanging environmental conditions. As it is seen below, parameter \( \alpha \) as well as constants of proportions of the model phase could be expressed in terms of experimentally determined parameters.

3. The cell cycle can be modeled as:

\[
\begin{align*}
\frac{dG_t(t)}{dt} &= - \alpha G_t(t) + 2\gamma M_t(t) \\
\frac{dS_t(t)}{dt} &= \alpha G_t(t) - \beta S_t(t) - \gamma M_t(t) \\
\frac{dM_t(t)}{dt} &= \beta S_t(t) - \gamma M_t(t)
\end{align*}
\]  

Now, suppose that

\[
\begin{align*}
\hat{G}_t(t) &= \frac{G_t(t)}{N_t(t)} \\
\hat{S}_t(t) &= \frac{S_t(t)}{N_t(t)} \\
\hat{M}_t(t) &= \frac{M_t(t)}{N_t(t)}
\end{align*}
\]  

are the ratios of cells in each subpopulation. Then by using (2.8), (3.1) and (3.2) we have:

\[
\frac{dN_t(t)}{dt} = \gamma M_t(t) = \gamma \hat{M}_t(t) N_t(t)
\]  

The proliferation rate is defined as:

\[
\rho = \gamma \hat{M}_t
\]  

### Table 4

<table>
<thead>
<tr>
<th>( G_{40} )</th>
<th>( S_{40} )</th>
<th>( M_{40} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process Mean</td>
<td>23.53</td>
<td>25.60</td>
</tr>
<tr>
<td>Process Variance</td>
<td>6.84</td>
<td>4.14</td>
</tr>
<tr>
<td>Process Median</td>
<td>23.37</td>
<td>25.52</td>
</tr>
<tr>
<td>95% confidence interval for the trajectories</td>
<td>[21.92, 29.75]</td>
<td>[21.94, 29.73]</td>
</tr>
<tr>
<td>Process Kurtosis</td>
<td>0.37</td>
<td>0.16</td>
</tr>
<tr>
<td>Process Skewness</td>
<td>3.42</td>
<td>2.42</td>
</tr>
</tbody>
</table>

### Table 5

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimated Value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \gamma )</td>
<td>0.2088</td>
<td>[0.1967, 0.2219]</td>
</tr>
<tr>
<td>( \alpha )</td>
<td>0.0771</td>
<td>[0.0528, 0.1014]</td>
</tr>
<tr>
<td>( \beta )</td>
<td>0.0890</td>
<td>[0.0768, 0.1012]</td>
</tr>
</tbody>
</table>

Fig. 4. Histogram of the observed number of cells in each subpopulation at time \( T = 40 \) over 100 trajectories with Euler-Maruyama approximation.
Fig. 5. Cell population dynamics for different subpopulations. The black circles show the trajectories corresponding to the observed data (nonparametric method). The blue lines represent the first and third quartiles of the simulated trajectories and the red lines illustrate the 95% confidence interval areas obtained by taking, at each time, the 2.5th and 97.5th percentiles of the simulated trajectories. The green line is the empirical mean of the process. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
\[ \frac{d\hat{G}(t)}{dt} = \frac{d\hat{G}(t)}{N(t)} = \frac{1}{N(t)} \frac{dG(t)}{dt} - \frac{G(t)}{N(t)} \frac{dN(t)}{dt} \]
\[ = \frac{1}{N(t)} (-\alpha G(t) + 2\gamma M(t)) - \rho \hat{G}(t) \]
\[ = - (\alpha + \rho) \frac{\hat{G}(t)}{G(t)} + 2\gamma \hat{M}(t) \]
\[ \text{(3.5)} \]

Therefore the system (3.1) is converted to:

\[ \begin{aligned}
\frac{d\hat{G}(t)}{dt} &= - (\alpha + \rho) \hat{G}(t) + 2\gamma \hat{M}(t) \\
\frac{d\hat{S}(t)}{dt} &= \alpha \hat{G}(t) - (\beta + \rho) \hat{S}(t) \\
\frac{d\hat{M}(t)}{dt} &= \beta \hat{S}(t) - (\gamma + \rho) \hat{M}(t)
\end{aligned} \]
\[ \text{(3.6)} \]

In the steady-state,

\[ \begin{aligned}
\frac{d\hat{G}(t)}{dt} &= 0 \\
\frac{d\hat{S}(t)}{dt} &= 0 \\
\frac{d\hat{M}(t)}{dt} &= 0
\end{aligned} \]
\[ \text{(3.7)} \]

Therefore,

\[ \begin{aligned}
- (\alpha + \rho) \hat{G} + 2\gamma \hat{M} &= 0 \\
\alpha \hat{G} - (\beta + \rho) \hat{S} &= 0 \\
\beta \hat{S} - (\gamma + \rho) \hat{M} &= 0
\end{aligned} \]
\[ \text{(3.8)} \]

In the steady-state, this problem is equivalent to the following eigenvalue and eigenvector problem.

\[ \begin{pmatrix}
-\alpha & 2\gamma & \\
\alpha & -\beta & 0 \\
0 & \beta & -\gamma
\end{pmatrix} \begin{pmatrix}
\hat{G} \\
\hat{S} \\
\hat{M}
\end{pmatrix} = \rho \begin{pmatrix}
\hat{G} \\
\hat{S} \\
\hat{M}
\end{pmatrix} \]
\[ \text{(3.9)} \]

Now, according to the Perron–Frobenius theorem (Richard, 2013), \( \hat{G}, \hat{M}, \hat{S} \) and \( \rho \) can be explicitly stated as the solution to (3.9) in terms of \( \alpha, \beta, \gamma \). There are three different solutions for \( \hat{G}, \hat{M}, \hat{S} \) and \( \rho \) possible but positivity of the matrix selects the Perron solution.

\[ \begin{aligned}
\alpha &= \gamma + \rho \hat{M} \\
\beta &= \gamma + \rho \hat{M} \\
\gamma &= \rho \hat{M}
\end{aligned} \]
\[ \text{(3.10)} \]

### 3.2. Evaluation of the parameters

In this section experimental data is engaged to numerically evaluate the main model parameters. Here by combining Eqs. (3.3) and (3.4) we get:

\[ \frac{dN(t)}{dt} = \rho N(t) \]
\[ \text{(3.11)} \]

Therefore

\[ N(t) = N(0)e^{\rho t} \]
\[ \text{(3.12)} \]

Assuming that \( K \) is the doubling time, we will have

\[ \rho = \frac{\ln(2)}{K} \]
\[ \text{(3.13)} \]

In Sutherland et al. (1983), multiple experiments were performed to determine the average steady-state values of \( G, S \) and \( M \) under the same growth conditions. The results are reported as 48.9 ± 0.6%, 39.4 ± 0.6% and 11.6 ± 0.3%, for \( G, S \) and \( M \) respectively. The doubling time is reported to be 24 hours and thus \( \rho = 0.0289 \). The data does not provide any particular margin of error for the observed doubling time. Yet, the large enough number of repetition of the experiment warrants a reasonably accurate value for the doubling time. Replacing \( \rho \) by its numerical value in (3.10), yields to the values of main model parameters listed in Table 1.

### 4. Existence and uniqueness of the solutions

Since the coefficient functions are linear they are globally Lipschitz, so standard theorems on global existence and uniqueness of the solution hold (Kloeden and Platen, 1992; Øksendal, 2010).

### 5. Explicit solution

As vector linear stochastic differential equations, using the multidimensional Itô formula, the explicit solution to the system (2.5) is written as Kloeden and Platen (1992):

\[ X(t) = e^{A-\frac{1}{2}A^2}e^{\int_{0}^{t}WdW}X(0) \]
\[ \text{(5.1)} \]

Where \( X(0) \) is constant. The expected value of \( X(t) \) solves the deterministic equation:

\[ dE[X(t)] = AE[X(t)]dt \]
\[ \text{(5.2)} \]

which results in solution:

\[ E[X(t)] = e^{At}E[X(0)] \]
\[ \text{(5.3)} \]

### 6. Linear moment stability analysis

In this section, stability of stochastic differential equations is introduced. There are several kinds of stability questions and several ways to define stability for stochastic differential equations (Wei-Chua, 2006).

**Theorem 6.1.** Suppose that \( A \) is the matrix in (2.6). System

\[ d\mathbb{E}[X(t)] = A\mathbb{E}[X(t)]dt \]
\[ \text{(6.1)} \]

is stable if and only if

\[ 1 + \frac{q_1}{\alpha} + \frac{q_2}{\beta} + \frac{q_3}{\gamma} > 0 \]
\[ \text{(6.2)} \]

**Proof.** Suppose that \( \lambda_1, \lambda_2, \lambda_3 \) are the eigenvalues of matrix \( A \). Therefore

\[ \text{tr}(A) = -[(\alpha + q_1) + (\beta + q_2) + (\gamma + q_3)] = \lambda_1 + \lambda_2 + \lambda_3 \]
\[ \text{(6.3)} \]

\[ \text{det}(A) = 2\alpha \beta \gamma - [(\alpha + q_1)\beta + q_2(\gamma + q_3)] = \lambda_1 \lambda_2 \lambda_3 \]
\[ \text{(6.4)} \]

In addition
The system (6.1) is stable if and only if

\[ \text{det}(A) < 0 \]

From Eqs. (6.3) and (6.5), it is clear that

\[ \text{tr}(A) < 0 \]

Therefore the system is stable if and only if

\[ 2\alpha\rho - [(\alpha + q_1)(\beta + q_3)(\gamma + q_3)] < 0 \]

which proves the result. □

**Remark 6.1.** Fig. 2a and b demonstrate the stability region and the system phase diagram which are corresponding to parameters \( q_i \), \( q_{i+1} \), and \( q_{i+2} \) respectively. The initial values (30,40,30), (50,30,20) and (49,39,12) are depicted in the phase diagram with red, blue and green lines.

### 7. Simulation results

The Euler-Maruyama and Milstein algorithms are two common numerical methods for solving stochastic differential equations (Kloeden and Platen, 1992). Both parametric and nonparametric methods could be applied to estimate the model parameters. Note that we have estimated parameters \( \alpha, \beta, \) and \( \gamma \) based on the experimental data provided for these parameters in (Sutherland et al., 1983). The other parameters such as \( q_i, s_i, \ldots \) and the initial conditions are considered as constant parameters.

The nonparametric method is applicable to both Euler-Maruyama and Milstein algorithms, and the parametric method is only applicable to the Euler-Maruyama algorithm. We have utilized the modified version of the SDE Toolbox 1.4.1 of MATLAB for the simulation (Picchini, 2007).

The estimated values corresponding to the transition rates are reported in Table 1. Moreover, the values given in Table 2 were selected for the death rates. As mentioned before, the initial values reported by Sutherland et al. (1983) are used for subpopulations \( G, S \) and \( M \). These values are:

\[ \hat{G}(0) = 49\% \]
\[ \hat{S}(0) = 39\% \]
\[ \hat{M}(0) = 12\% \]

### 7.1. The Euler-Maruyama algorithm–parametric method

In this case, the model is run 100 times and the data is generated. The parameters are estimated by parametric method. In addition, the Euler-Maruyama algorithm with step size \( h=0.01 \) is used to solve (2.4) with parameter values in (7.1). By using the parametric method, the main parameters \( \alpha, \beta, \) and \( \gamma \) are estimated and provided in Table 3.

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**Table 6**
Monte Carlo Statistics for the G, S and M subpopulations at time \( T=40 \) h.

<table>
<thead>
<tr>
<th></th>
<th>( G_{40} )</th>
<th>( S_{40} )</th>
<th>( M_{40} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>26.54</td>
<td>27.01</td>
<td>6.60</td>
</tr>
<tr>
<td>Var</td>
<td>9.66</td>
<td>5.24</td>
<td>0.33</td>
</tr>
<tr>
<td>95% CI</td>
<td>[21.88, 22.90]</td>
<td>[31.58, 32.20]</td>
<td>[5.64, 6.76]</td>
</tr>
</tbody>
</table>

**Table 7**
Statistical features of the tumor lifespan (L).

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Lifespan (L)</td>
<td>175.465</td>
<td>9.0758</td>
<td>175</td>
</tr>
</tbody>
</table>

---

**Fig. 6.** (a) Cell population dynamics in the whole tumor over 20 trajectories, where the system of SDEs (2.4) is solved by Euler-Maruyama algorithm and the parameters are estimated by parametric method; (b) Cell population dynamics in the whole tumor over 20 trajectories, where the system of SDEs (2.4) is solved by Euler-Maruyama or Milstein algorithm and the parameters are estimated by nonparametric method.
and compare the effect of two different treatments or drugs on cancer therapy. As an innovation, it was considered that the cell death rates in the subpopulations differ to their radio-sensitivity to radiotherapy. As an innovation, it was proposed using a system of stochastic differential equations. The proposed SDE system was solved numerical with the Euler-Maruyama and Milstein algorithms and the parameters were estimated by applying parametric and nonparametric methods. In this section the model is run 100 times. The parameters are estimated by nonparametric method and the Euler-Maruyama method with step size \( h = 0.01 \) is used to solve (2.4) numerically with the initial parameter values

\[
G(0) = 49, \quad S(0) = 39, \quad M(0) = 12
\]

The main parameters \( \alpha, \beta, \) and \( \gamma \) are estimated and the results are presented in Table 5.

Fig. 5a, c and e represent the simulation of 100 trajectories of the cell population dynamics in subpopulations \( G, S \) and \( M \) corresponding to 100 simulation rounds. Applying the Monte-Carlo simulation yields the process, statistical analyses (i.e., mean value, variance, median, 95%-percent confidence interval for the trajectories, first and third quartiles, process skewness and kurtosis). The results are given in the Table 4. Finally, the number of cells in each subpopulation after applying the last dose fraction are shown in Fig. 4a–c.

7.2. The Euler-Maruyama algorithm–nonparametric method

In this section the model is run 100 times. The parameters are estimated by nonparametric method and the Euler-Maruyama method with step size \( h = 0.01 \) is used to solve (2.4) numerically with the initial parameter values

\[
G(0) = 49, \quad S(0) = 39, \quad M(0) = 12
\]

The main parameters \( \alpha, \beta, \) and \( \gamma \) are estimated and the results are presented in Table 5.

Fig. 5a, c and e represent the simulation of 100 trajectories of the cell population dynamics in subpopulations \( G, S \) and \( M \) corresponding to 100 simulation rounds. Applying the Monte-Carlo simulation yields the process, statistical analyses (i.e., mean value, variance, median, 95%-percent confidence interval for the trajectories, first and third quartiles, process skewness and kurtosis). The results are given in the Table 4. Finally, the number of cells in each subpopulation after applying the last dose fraction are shown in Fig. 4a–c.

7.3. Evaluation of the tumor lifespan

One of the most important problems in treatment planning is to answer the question of how many dose fractions are needed to remove the whole tumor cells. We have defined this number as the tumor in the Definition 2.1. The proposed model is able to calculate the tumor the lifespan. In this regard, the simulation is run 200 times and for each time the tumor lifespan is evaluated. Fig. 7-a shows the tumor lifespan corresponding to each sample and Fig. 7-b represents histogram of the tumor lifespan. The statistical features of the tumor lifespan in represented in Table 7.

8. Discussion

Based on the results, it is evident that there is no significant difference in cell population dynamics between the two parametric (Fig. 6a) and nonparametric (Fig. 6b) methods. The tumor lifespan is estimated and presented in Fig. 7. Figs. 3 and 5 show the difference in cell population dynamics between the two parametric and nonparametric methods. The tumor population has a decreasing trend when \( q_1 = 0.06, q_2 = 0.02 \) and \( q_3 = 0.01 \).

9. Conclusion

A mathematical model of tumor cell population dynamics was proposed using a system of stochastic differential equations. The tumor cells were categorized into three subpopulations according to their radio-sensitivity to radiotherapy. As an innovation, it was considered that the cell death rates in the subpopulations differ and change during treatment. Then the main model parameters, \( \alpha, \beta, \) and \( \gamma \) were estimated using experimental data provided by Sutherland et al. (1983). The existence and uniqueness of the system solution was discussed and a criterion for stability was provided. The proposed SDE system was solved numerically with the Euler-Maruyama and Milstein algorithms and the parameters were estimated by applying parametric and nonparametric methods. In each case, \( G_{\text{eff}}(t), S_{\text{eff}}(t) \) and \( M_{\text{eff}}(t) \) were analyzed. Finally, the population dynamics of all tumor cells \( (N_t) \) were shown based on the population dynamics of cells in subpopulations \( G, S \) and \( M \). In summary, the proposed model can:

- Evaluate the entire tumor lifespan.
- Be applied to other treatments such as chemotherapy, and anticancer drugs.
- Test the effect of other treatments on cancer therapy.
- and compare the effect of two different treatments or drugs on a cancer.

References

