Mathematical Model for Combined Radiotherapy and Chemotherapy that Fits with Experimental Data

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Abstract. One of the most challenges to effective treatment of cancer is radiation resistance. Published data from a notably experiment performed to examine the ability of a compound therapy to overcome radiation resistance is utilized. The chemotherapeutic drug used was vinblastine. The experiment included control tumors and tumors which were treated with radiation, chemotherapy, or both. In this paper a mathematical model is developed. The model fits with the data reported from the mentioned experiment. Starting with a suggested model for the tumor growth, the model is expanded to include the effect of radiotherapy, chemotherapy, and combined chemotherapy and radiotherapy. By fitting the model with the experimental data, the parameters of the model are obtained in each stage. The final mathematical model acquired can be used with the case with no treatment, with radiotherapy treatment, with chemotherapy treatment, and with combined chemotherapy and radiotherapy treatment. Results capture the behavior of the tumor in all cases in a reasonable way.

1. Introduction
In recent decades, cancer is a major kill source all over the world for humans, as it is a leading cause of death worldwide. For example, nearly 10 million deaths in 2020 [1]. Universally, the cancer burden is expected to rise to approximately 21.4 million cases and 13.5 million deaths by 2030 [2]. Cancer treatments are intermittently diverse and successful, its types are surgery, radiotherapy [3], targeted therapy, hormone therapy [4], viral therapy [5], chemotherapy [6], and immunotherapy [7-9], among others, either separately or in combination of two or more.

Mathematical models have emerged where it is possible to simulate the effects of radiotherapy on tumor growth [3,10,11]. Also, there are many of mathematical models suggested to model the treatment with chemotherapy [6,12,13]. Furthermore, there are a lot of studies that provide mathematical models for treating cancer by radiotherapy and chemotherapy [14-18]. Radiation resistance is a challenge to effective treatment of cancer. A significant experiment was accomplished to test the ability of therapeutic compound to overcome radiation resistance [17,18]. Breast cancer cells were put in a 96-well plate and let grow in a hanging drop for three days. After these three days the resulting spheroid was put in a gravity plate where it stayed for another day. The time was set to zero and the area of the spheroid was measured for the first time. There were control tumors and tumors which were treated with radiation or chemotherapy or both. First the radiation was administered once and after that the chemotherapeutic drug, vinblastine, was administered. The drug stayed in the nutrient solution for six days before it was washed away. The area of the spheroid was measured again on the days 3, 6, 9 and 12. The drug used was vinblastine, a naturally produced from a plant called *Vinca rosea* grows in Madagascar, and it had proved to be effective inhibitors of mammary cancer cell growth. The tumor is assumed to be solid, homogeneous and in an avascular
state. In the current research work, it is intended to develop suitable mathematical model that fits with the data reported from the explained experiment. It is aimed to let the model covers reality and considers the influences of treatment. A mathematical model for the growth of the tumor is suggested first and then modified to include the radiotherapy, the chemotherapy, and combined therapy of both. In each step the parameters of the model are obtained by fitting the model with the experimental data. The model can provide an appropriate insight into the interaction between the cancer cells and the therapy. It can help in predicting the foremost effective therapy and strategy and in minimizing the whole drug administered. Hence, it can improve the existing treatment procedures.

2. The Mathematical Model

2.1. Tumor growth

2.1.1. Mathematical model. The proposed model for tumor growth is the logistic growth model given by

\[
\frac{dT}{dt} = aT(1 - bT)
\]

where \(T(t)\) represents the number of tumor cells, \(a\) is the tumor growth rate, and \(b\) is the reciprocal of the tumor carrying capacity. The two parameters \(a\) and \(b\) are going to be estimated from the experimental data.

2.1.2 Fitting the model to data. In the considered experiment, breast cancer cells were put in a 96-well plate and let grow in a hanging drop for three days, and the resulting spheroid was put in a gravity plate for another day. The time \(t\) was set to zero and the area of the spheroid was measured for the first time. For the tumor growth without therapy, the area of the spheroid was measured on days 3, 6, 9, and 12. The Table 1 gives the number of tumor cells over that period [17,18].

| Hours | 0   | 72  | 144 | 216 | 288 |
|-------|-----|-----|-----|-----|-----|
| Number of cells | 596.3 | 2424.5 | 6986.6 | 9581.6 | 10659 |

To estimate the required parameters, the *Mathematica* commercial program is used to generate a parametric solution for the model in terms of the parameters \(a\) and \(b\). This has been performed using the built-in function “ParametricNDSolveValue”. Using this parametric function, the method of Levenberg-Marquardt is applied using the built-in *Mathematica* function “FindFit”, to estimate these two parameters. The estimated values for the two parameters are \(a = 2.35332 \times 10^{-2}\) h\(^{-1}\) and \(b = 9.278756 \times 10^{-5}\) cell\(^{-1}\).

2.2. Radiotherapy

2.2.1. Mathematical model. To model the effect of radiation on the tumor, the following model is suggested:

\[
\begin{align*}
\frac{dT}{dt} &= aT(1 - bT) - \epsilon_r D T \\
\frac{d\epsilon_r}{dt} &= d_r \epsilon_r (1 - \epsilon_r)
\end{align*}
\]

where \(D\) is the amount of radiation administered in Gray, \(\epsilon_r(t)\) is the efficacy of the radiotherapy, and \(d_r\) is the growth rate of the efficacy. This form for the efficacy allows the variation of the efficacy during the medication period. Parameters \(a\) and \(b\) have the values estimated in section 2.1.2. The parameter \(d_r\) and the initial value for the efficacy \(\epsilon_r(0)\) are going to be estimated from the experimental data.

2.2.2. Fitting the model to data. The same procedure for the considered experiment had been performed, but the cells had been treated with radiotherapy this time. The tested cells had been divided
into four groups and in the beginning of day zero they were radiated with a dosage of 2, 4, 6 and 8 Gray respectively, where 1 Gray was administered in 2 minutes. The area of the spheroid was measured on days 3, 6, 9, and 12 and Table 2 gives the number of tumor cells over that period [17,18].

| Radiation ‘D’ in Gray | Number of cells | Hours |
|----------------------|----------------|-------|
| 2                    | 596.3          | 0     |
|                      | 2048.9         | 72    |
|                      | 4636.0         | 144   |
|                      | 5681.7         | 216   |
|                      | 7167.2         | 288   |
| 4                    | 596.3          | 0     |
|                      | 1801.4         | 72    |
|                      | 3063.3         | 144   |
|                      | 3950.6         | 216   |
|                      | 4194.8         | 288   |
| 6                    | 596.3          | 0     |
|                      | 2145.8         | 72    |
|                      | 3130.3         | 144   |
|                      | 2819.0         | 216   |
|                      | 4072.0         | 288   |
| 8                    | 596.3          | 0     |
|                      | 1968.3         | 72    |
|                      | 2319.7         | 144   |
|                      | 1939.2         | 216   |
|                      | 2944.5         | 288   |

Table 2. Number of cells treated with radiotherapy over a period of 12 days

Mathematica commercial program is used for the curve fitting via the order FindFit. Each group gives different values for \(d_r\) and \(\varepsilon_r(0)\). The values for \(d_r\) are closed to each other, hence, a fixed value for it has been specified, \(d_r = 1.8 \times 10^{-3}\) hr\(^{-1}\), and the Mathematica has been run again to estimate the corresponding value for \(\varepsilon_r(0)\) for each group. It has been found that the returned values for \(\varepsilon_r(0)\) can be approximated in the form

\[
\varepsilon_r(0) = \frac{e_r}{\sqrt{D}}
\]

where \(e_r\) is a constant which has been estimated to be \(e_r = 3.8 \times 10^{-3}\) hr\(^{-1}\).

2.3. Chemotherapy

2.3.1. Mathematical model. To model the effect of chemotherapy on the tumor, the following model is suggested:

\[
\frac{dT}{dt} = aT(1 - bT) - \varepsilon_c C T \tag{5}
\]

\[
\frac{d\varepsilon_c}{dt} = d_c \varepsilon_c (1 - \varepsilon_c) \tag{6}
\]

\[
\frac{dC}{dt} = -\gamma C \tag{7}
\]

where \(\varepsilon_c(t)\) is the efficacy of the chemotherapy, \(C(t)\) is the concentration of the chemotherapy, \(d_c\) is the growth rate of the efficacy, and \(\gamma\) is the decay rate of the concentration. Parameters \(a\) and \(b\) have the values estimated in section 2.1.2. The parameter \(d_c\) and the initial value for the efficacy \(\varepsilon_c(0)\) are going to be estimated from the experimental data. The model given in Eq. 6 for the efficacy allows the variation of it during the medication period. The model of the concentration given in Eq. 7 presents the decay in the concentration of the chemotherapy during the application period. An assumed value of \(\gamma = 0.01\) hr\(^{-1}\) is given to the decay rate of the concentration. The initial value for the concentration for each group \(C_0\) is specified according to the experimental data, which means that

\[
C(0) = C_0 \tag{8}
\]

2.3.2. Fitting the model to data. The considered experiment had been progressed with the same steps as in the case explained in section 2.2.2, however, in the time the cells had been treated with the vinblastine chemotherapeutic drug. The tested cells had been divided into five groups and in the beginning of day zero the drug was added with concentrations of 0.3, 1, 3, 10 and 30 μM respectively. Table 3 gives the number of tumor cells over the experimental period [17,18].
Table 3. Number of cells treated with vinblastine over a period of 12 days

| Hours | Number of cells |
|-------|----------------|
| 0     | 596.3          |
| 72    | 1479.5         |
| 144   | 2303.3         |
| 216   | 2134.1         |
| 288   | 3480.3         |

To estimate \( d_c \) and \( \epsilon_c(0) \), Mathematica commercial program is used for the curve fitting via the order FindFit. Each group gives different values for \( d_c \) and \( \epsilon_c(0) \). The values for \( d_c \) are closed to each other, hence, a fixed value for it has been specified, \( d_c = 1.46 \times 10^{-2} \) hr\(^{-1} \), and the Mathematica has been run again to estimate the corresponding value for \( \epsilon_c(0) \) for each group. It has been found that the returned values for \( \epsilon_c(0) \) can be approximated in the form

\[
\epsilon_c(0) = \frac{e_c}{C_0^{0.95}}
\]

where \( e_c \) is a constant which has been estimated to be \( e_c = 7.6 \times 10^{-3} \) hr\(^{-1} \).

2.4. Combined therapy

2.4.1. Mathematical model. It is observed that combining radiotherapy with chemotherapy does not simply mean to add the effect of each of them. Hence the combined therapy is not as good as the sum of the single therapies. A kind of efficacy for the combination has to be considered. Hence, the following model is suggested:

\[
\frac{dT}{dt} = aT(1 - bT) - \epsilon_1(\epsilon_r D T + \epsilon_c C T)
\]

\[
\frac{dC}{dt} = -\gamma C
\]

\[
\frac{d\epsilon_r}{dt} = d_r \epsilon_r (1 - \epsilon_r)
\]

\[
\frac{d\epsilon_c}{dt} = d_c \epsilon_c (1 - \epsilon_c)
\]

\[
\frac{d\epsilon_1}{dt} = d_1 \epsilon_1 (1 - \epsilon_1)
\]

where \( \epsilon_1(t) \) is the efficacy of the combined radiotherapy and chemotherapy, and \( d_1 \) is the growth rate of the efficacy. Parameters \( a, b, d_r, \epsilon_r, d_c, \gamma, \) and \( e_c \) have the values given in sections 2.1.2., 2.2.2., 2.3.1., and 2.3.2. The initial conditions are as follow:

\[
T(0) = 596.3, \quad C(0) = C_0, \quad \epsilon_r(0) = \frac{e_r}{V_D}, \quad \epsilon_c(0) = \frac{e_c}{C_0^{0.95}}
\]

It can be noticed that these initial conditions are the ones given in the previous sections. The parameter \( d_1 \) and the initial value for the efficacy \( \epsilon_1(0) \) are going to be estimated from the experimental data. The model given in Eq. 14 for the efficacy allows the variation of it during the medication period.
2.4.2. Fitting the model to data. In this part of the experiment, the cells had been treated with both radiation and vinblastine chemotherapeutic drug. The tested cells had been divided into five groups and in the beginning of day zero the drug was added to each group with concentrations of 0.3, 1, 3, 10, and 30 \( \mu M \) respectively. Each group is divided to four subgroups and each subgroup were radiated with a dosage of 2, 4, 6 and 8 Gray, respectively. The area of the spheroid was measured on days 3, 6, 9, and 12 and Tables 4-7 give the number of tumor cells over that period for each group except the group with 30 \( \mu M \) since the data is missing for that group [17,18].

Table 4. Number of cells treated with radiotherapy and chemotherapy, \( C_0 = 0.3 \mu M \)

| Hours | 0  | 72  | 144  | 216  | 288  |
|-------|----|-----|------|------|------|
|       |    |     |      |      |      |
| **Radiation ‘D’** |    |     |      |      |      |
| 2     | 596.3 | 1258.1 | 1695.7 | 1588.9 | 1283.0 |
| 4     | 596.3 | 1202.1 | 1992.4 | 2242.5 | 2191.6 |
| 6     | 596.3 | 1037.9 | 1842.7 | 1905.6 | 1442.5 |
| 8     | 596.3 | 1195.5 | 1606.8 | 1424.7 | 1416.8 |

Table 5. Number of cells treated with radiotherapy and chemotherapy, \( C_0 = 1 \mu M \)

| Hours | 0  | 72  | 144  | 216  | 288  |
|-------|----|-----|------|------|------|
|       |    |     |      |      |      |
| **Radiation ‘D’** |    |     |      |      |      |
| 2     | 596.3 | 1208.9 | 1507.9 | 1436.8 | 850.9 |
| 4     | 596.3 | 1005.3 | 1663.7 | 1537.5 | 1403.4 |
| 6     | 596.3 | 1156.8 | 1669.3 | 1742.6 | 1097.7 |
| 8     | 596.3 | 967.5  | 1485.0 | 1542.5 | 1136.1 |

Table 6. Number of cells treated with radiotherapy and chemotherapy, \( C_0 = 3 \mu M \)

| Hours | 0  | 72  | 144  | 216  | 288  |
|-------|----|-----|------|------|------|
|       |    |     |      |      |      |
| **Radiation ‘D’** |    |     |      |      |      |
| 2     | 596.3 | 1268.2 | 1708.5 | 1197.2 | 892.7 |
| 4     | 596.3 | 965.0  | 1667.3 | 1492.7 | 1531.6 |
| 6     | 596.3 | 925.6  | 1594.8 | 1359.8 | 764.6 |
| 8     | 596.3 | 982.9  | 1377.4 | 1371.2 | 1079.1 |

Table 7. Number of cells treated with radiotherapy and chemotherapy, \( C_0 = 10 \mu M \)

| Hours  | 0  | 72  | 144  | 216  | 288  |
|--------|----|-----|------|------|------|
|        |    |     |      |      |      |
| **Radiation ‘D’** |    |     |      |      |      |
| 2      | 596.3 | 1134.1 | 1274.6 | 1097.1 | 711.1 |
| 4      | 596.3 | 1079.4 | 1305.0 | 1383.0 | 1619.8 |
| 6      | 596.3 | 905.6  | 1566.5 | 1568.2 | 1023.8 |
| 8      | 596.3 | 1138.6 | 1443.0 | 1280.1 | 905.1 |

FindFit order for the curve fitting in Mathematica commercial program is used to estimate \( d_1 \) and \( \varepsilon_1(0) \). Each subgroup gives deferent values for \( d_1 \) and \( \varepsilon_1(0) \). The values for \( \varepsilon_1(0) \) are closed to each other, hence, a fixed value for it has been specified, \( \varepsilon_1(0) = 0.63 \text{ hr}^{-1} \), and the Mathematica has
been run again to estimate the corresponding value for $d_1$ for each subgroup. It has been found that the returned values for $d_1$ can be approximated in the form:

$$d_1 = \frac{e_1}{D^{2.6} C^{0.5}}$$

(16)

where $e_1$ is a constant which has been estimated to be $e_1 = 0.1 \text{ hr}^{-1}$. It can be noticed that $d_1$ is a function of time i.e., it changes with the alteration of time.

3. Results

Figure 1 represents the tumor variation for each subgroup with radiotherapy of 2 Gy, 4 Gy, 6 Gy, and 8 Gy with initial concentration of vinblastine chemotherapeutic drug $C_0 = 3 \mu M$. The corresponding points of the experimental data in Table 6 are also shown in the figure. Results capture the behavior of the tumor in all cases in a reasonable way. Similar results have been obtained for other values of $C_0$, however, they are not included because of the space limitation.

Figure 1. Tumor from mathematical model of combined radiotherapy and chemotherapy (solid lines) assessed with experimental data (big dots), $C_0 = 3, T(0) = 596.3, a = 2.35332 \times 10^{-2}, b = 9.278756 \times 10^{-5}, d_r = 1.8 \times 10^{-3}, e_r = 3.8 \times 10^{-3}, d_c = 1.46 \times 10^{-2}, e_c = 7.6 \times 10^{-3}, \text{ and } \gamma = 0.01, e_c(0) = 0.63, e_1 = 0.1$

4. Discussion and Conclusion

A mathematical model has been constructed to simulate the interaction between the tumor and the therapy. The therapy could be a radiotherapy, a chemotherapy, or a combined chemotherapy and radiotherapy. The model has been designed to simulate an experiment designed to test the ability of therapeutic compound to overcome radiation resistance. The aim has been to cover reality and to consider the influences of treatment.

The construction of the model has started with a simple model for the tumor growth, and the model has been extended to include the effect of radiotherapy, chemotherapy, and combined chemotherapy and radiotherapy. Parameters of the model have been obtained in each stage by fitting the model with the experimental data. Many groups and subgroups had been treated in the cited experiment; hence, some parameters have been assumed as variables which are functions of the radiation dosage, the
concentration of the drug, or both. Notably, same expressions for the parameters have been used for all groups. It has been observed that combining radiotherapy and chemotherapy would not result in adding the effect of both, as a result of radiation resistance. Hence, an efficacy for the combination has been included. Results capture the behavior of the tumor during the medication period in all cases in an adequate way.

The mathematical model constructed in this research work has given an insight to the cited experiment. It has highlighted some shadow sites of the experiment. It could be used in predicting the most effective treatment intervention strategies. It can minimize the drug administration, and in general it can enhance the current medication techniques.

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