Numerical Solution for a Model on Cancer Growth Reduction Using both Chemotherapy and Radiotherapy

Purity Kioro Gikunda, Dr. Mark Kimathi and Dr. Mary Wainaina

The Catholic University of Eastern Africa, P.O BOX 62157-00200, Nairobi, Kenya.

Abstract

Using mathematical models to simulate dynamic biological processes has a long history. In this study, we have employed mathematical modeling to understand the behavior of cancer and its interaction with both chemotherapy and radiotherapy. We have studied a drug delivery and drug-cell interaction model along with cell proliferation. Simulation is done with different values of the parameters with a continuous delivery of the drug and assuming that the growth rate is not a constant. The numerical result shows that cancer dies after short apoptotic cycles if the cancer is highly vascularized. This suggests promoting perfusion of the drug. The obtained result is similar to the situation where proliferation is not considered since the constant release of drug overcomes the growth of the cells and thus the effect of proliferation can be neglected.

Nomenclature

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$</td>
<td>Rate at which cancer cells grow</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Fraction of dying cells each time difference</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Fraction of dividing cells each time difference</td>
</tr>
<tr>
<td>$k$</td>
<td>Carrying capacity</td>
</tr>
<tr>
<td>$\eta_\mu$</td>
<td>Cellular uptake rate of the drug per volume</td>
</tr>
<tr>
<td>$\eta_k$</td>
<td>Death rate of tumor cells per unit cumulative drug concentration</td>
</tr>
<tr>
<td>$D$</td>
<td>Drug diffusitivity</td>
</tr>
<tr>
<td>$\nabla^2$</td>
<td>Laplacian operator</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Drug concentration</td>
</tr>
<tr>
<td>$\varphi$</td>
<td>Density of cancer cells</td>
</tr>
<tr>
<td>$r$</td>
<td>Radial distance</td>
</tr>
<tr>
<td>$r_b$</td>
<td>Radius of the blood vessel</td>
</tr>
<tr>
<td>$t$</td>
<td>Time</td>
</tr>
<tr>
<td>BVF</td>
<td>Blood Volume Fraction</td>
</tr>
</tbody>
</table>
INTRODUCTION
Cancer has become a main problem since it is a major killer disease today. Cancer treatment developed over the years includes chemotherapy, radiotherapy and surgery. Further research is needed to determine an effective combination of the treatments and subsequently improve patient’s response to the treatment.

Recently Simbawa, 2017 developed a model for cancer growth and response to only chemotherapy. The model assumes that the growth rate is constant, which is not realistic since growth rate is a function of time. The model only considers treatment by chemotherapy only, but empirical studies indicate that a combination of treatment strategies is more effective.

In this study, we extend the model of Simbawa to study the effectiveness of combining both chemotherapy and radiotherapy in treating cancer whose growth rate is non-constant.

Objectives of the study
- Develop a model combining both chemotherapy and radiotherapy.
- Non-dimensionalise the model equations.
- Numerically solve the non-dimensional model equations to determine the effectiveness of combining chemotherapy and radiotherapy in cancer treatment.

Significance of the study
Mathematical modeling is a powerful tool to test hypotheses, confirm experiments, and simulate the dynamics of complex systems.

Our model provides an insightful tool to explore and predict the growth of cancer as well as the response to therapy by using biological and physical properties. The results will help oncologists customize therapy for each patient by understanding the physical and biological barriers that make some cancer patients not respond to therapy.

The model considers the spatial influences on the dynamics between cancer and therapy with continuous drug delivery. The model thus can be used to compare drug uptake rate for continuous infusion and bolus drug delivery.

Numerous dynamic growth rate functions with applicability to tumor growth are discussed. The Gompertz growth is shown to reproduce biological growth that decelerates with population size, and is therefore applicable to observed tumor growth slowdown with tumor size.

The models results provide the opportunity to understand the interaction between cancer, chemotherapy and radiotherapy. They can be used as a basis to model more complicated situations.
RESEARCH QUESTIONS

1. Does the combination of chemotherapy and radiotherapy really eliminate the cancer cells more effectively?
2. How can radiotherapy be incorporated into the Simbawa model?
3. What are the key biological parameters in the model?

LITERATURE REVIEW

Modeling of cancer growth and treatment has been developed over years by different researchers in an attempt to find the most appropriate solution.

A model of tumor growth and response to radiation in which each tumor cell was taken into account individually was introduced (Borkenstein et al., 2004). It was found out that short cell cycle time, high growth fraction and tumor angiogenesis all increased tumor. Proliferation rates accelerated time dose patterns results to lower total doses needed for tumor control but the extent of dose reduction depends on the kinetics and radio sensitivity of tumor cell. Tumor angiogenesis affected the radiation response.

It has been hypothesized that continually releasing drug molecules into a tumor over an extended period of time may significantly improve the chemotherapeutic efficacy by overcoming physical transport limitations of conventional drug treatment (Wang et al., 2016).

Much emphasis were also done to predict treatment response for combined chemotherapeutic and radiation therapy for non-Small cell lung cancer patients using a bio-mathematical model (Geng et al., 2017). They predicted Kaplan–Meier survival curves and found out that there was an improvement in overall survival for 3 and 5 years for stage III patients.

Lately the behavior of cancer and its interaction with chemotherapy was modeled (Simbawa, 2017). The model incorporated drug delivery and drug-cell interaction along with cell proliferation. The model assumed that the growth rate was a constant. The numerical results showed that cancer dies after short apoptotic cycles if the cancer was highly vascularized or if the penetration of the drug was high.

In this project we propose to model cancer growth and treatment using both chemotherapy and radiotherapy. Drug delivery and drug cell interaction will be incorporated along with cell proliferation. We propose to model growth rate as a function of time and not a constant. We will numerically simulate the model for different biological parameters with continuous drug delivery to obtain the most effective solution.
MODEL FORMULATION

Assumptions

The following assumptions are made during this study:

- Cancer cells are not resistant to drugs.
- Drug administration is continuous.
- Growth rate is a function of time and not a constant.

GOVERNING EQUATIONS

1. Diffusion equation

One of the most important equations is the drug diffusion equation. It represents diffusion of the drug into the cancer cells after it is delivered through the blood vessel and the binding rate to cancer cells. (Simbawa, 2017)

\[
\frac{\partial \sigma}{\partial t} = D \nabla^2 \sigma - \eta_u \varphi \sigma 
\]

(1)

Where \(D\) is the drug diffusivity and \(\eta_u\) is the cellular uptake rate of drug per-volume.

2. Death rate equation

Another useful equation is the death rate caused by the drug and the growth rate of cancer cells. (Simbawa, 2017)

\[
\frac{\partial \varphi}{\partial t} = -\eta_k \eta_u \varphi(\tilde{\sigma}, \tau) \int_{0}^{\tau} \sigma(\tilde{\sigma}, \tau') \varphi(\tilde{\sigma}, \tau') d\tau' + \alpha \varphi
\]

(2)

where \(\sigma(\tilde{\sigma}, \tau)\) is the drug concentration, \(\varphi(\tilde{\sigma}, \tau)\) is the density of cancer cells, \(\eta_k\) is the death rate of tumor cells per unit cumulative drug concentration, \(\eta_u\) is the cellular uptake rate of drug per-volume and \(\alpha\) is the growth rate of cancer cells. Note that \(\tilde{\sigma}\) is a vector i.e. \(\tilde{\sigma} = (r, \theta, z) = x, \hat{r} + x, \hat{\theta} + x, \hat{z}\).

The model equations (1) and (2) are preferred over others because it has a proliferation term which is one of the key features and also it has a detailed equation for diffusion of drugs and uptake by the cancer cells. However, the model assumed that the growth rate is constant which is not realistic.
Specific Model Equations.

We assume that diffusion rate of the drug is faster than the cell cycle, then the time derivative in equation (1) is replaced by zero.

Thus

\[ 0 = D \nabla^2 \sigma - \eta_u \varphi \sigma \] ..............................(3)

In this study, we model growth rate \( \alpha \) as a function of time and not a constant by using Gompertz growth model

\[ \frac{d\varphi(t)}{dt} = \gamma \varphi(t) \log \frac{k}{\varphi(t)} \] ..............................(4)

Where, \( \varphi \) is the evolution of the tumor cell number (i.e. volume times cell density), \( t \) is the tumor volume and \( k \) is the carrying capacity. \( \gamma \) and \( k \) are the specific parameters determining the growth curve of the tumor.

Moreover, we extend the model by introducing radiotherapy effect (Geng et al., 2017) as a means of achieving a more effective cancer treatment strategy;

\[ \frac{d\varphi(t)}{dt} = -\rho \left[ t + \beta t^2 \right] \varphi(t) \] ..............................(5)

Where, \( \rho \) is fraction of dividing cells in each time interval and \( \beta \) is fraction of dying cell in each time interval.

Using Gompertz model (4) on equation (2) we obtain;

\[ \frac{\partial \phi}{\partial t} = -\eta_u \eta_v \phi(\bar{x}, \bar{t}) \int_0^1 \sigma(\bar{x}, \bar{r}) \phi(\bar{x}, \bar{r}) d\tau + \left[ \gamma \log \frac{k}{\varphi(t)} \right] \phi(t) \] ..............................(6)

On introducing radiotherapy effect (5) we obtain

\[ \frac{\partial \phi}{\partial t} = -\eta_u \eta_v \phi(\bar{x}, \bar{t}) \int_0^1 \sigma(\bar{x}, \bar{r}) \phi(\bar{x}, \bar{r}) d\tau + \left[ \gamma \log \frac{k}{\varphi(t)} \right] \phi(t) - \left[ \rho t + \beta t^2 \right] \phi(t) \] ..............................(7)

The specific model equations are therefore equations (3) and (7)
Specification of the initial and boundary conditions

We assume that the domain surrounding the blood vessel is cylindrical. Thus we let the system depend on two parameters: time $t$ and radial distance $r$. Initially, we suppose that $\varphi$ is homogenous. At the blood vessel, there is a constant rate of drug release $\sigma_0$ for example through nanocarriers. If $r \to \infty$ there is no flux (the tumor is infinitely sized). Accordingly, we have the following initial and boundary conditions:

$$\varphi(x,0) = \varphi_0$$

$$\sigma(r_b,t) = \sigma_0$$

$$n \cdot \nabla \sigma \bigg|_{x \to \infty} = 0$$

Where $r_b$ is the radius of the blood vessel.

Non-dimensionalization of the model

Before we numerically solve the model, we non-dimensionalize the system to obtain the key biological parameters. Let $\sigma = \sigma_0 \sigma', \varphi = \varphi_0 \varphi', \tilde{x} = \tilde{x}' L, r_b = \frac{r_b'}{L}$ and $t = t'T$ where $\sigma', \varphi', \tilde{x}'$ and $r_b'$ are dimensionless. $L$ is the diffusion length of the drug.

For $L = \sqrt{\frac{D}{\varphi_0 \eta}}$, then equation (3) becomes,

$$0 = \nabla' \varphi' - \varphi' \sigma'$$

For equation (7), we also consider $t = T', \tau = T \tau'$

Taking $T = (\eta \eta_0 \sigma_0 \varphi_0)^{-\frac{1}{2}}$, we obtain:

$$\frac{\partial \phi'}{\partial \tau'} = -\phi' \int_0^1 \sigma' \phi' d\tau' + \left[ \gamma_0 \log \left( \frac{K_0}{\phi'} \right) \right] \phi' - \left[ \rho \phi' + \beta_0 (\tau')^3 \right] \phi'$$

Where $K_0 = \frac{K}{\varphi_0}, \gamma_0 = \gamma T, \rho_0 = \rho T^2, \beta_0 = \beta T^3$
The initial and boundary conditions (8) becomes;
\[ \varphi'(\tilde{x}',0) = 1 \] ...........................(11)
\[ \sigma'(r_b',t') = 1 \] ....................................................(12)
In one dimension, \( \tilde{x}' = r' \tilde{r} \) and thus the second boundary condition becomes,
\[ \frac{d\sigma'}{dr'} \bigg|_{r'\to\infty} = 0 \] .................................(13)

We assume that cancer cells depend on the closest blood vessel, which has the dimensionless radius \( \frac{r_b}{L} \). Therefore, we estimate the dimensionless radius of the cylindrical region supported by the blood vessel by \( \frac{r_b}{(L\sqrt{\text{BVF}})} \). BVF is the blood volume fraction (the ratio of blood to the volume of the tumor), which is less than 1. A higher BVF represents a highly vascularized tumor, this means that there are more blood vessels and therefore more treatment will be delivered to the tumor. Therefore (13) can be written as
\[ \frac{d\sigma'}{dr'} \bigg|_{r'\to r_b/(L\sqrt{\text{BVF}})} = 0 \] ....................................................(14)

In the chapters below we drop the prime for simplicity.

**Calculating the ratio of viable cancer mass to the initial mass**

First, we integrate the density of the viable cancer cells at each time step over the cylindrically symmetric domain around the blood vessel (after drug diffusion). This is done during the numerical simulation. Then, we calculate the ratio of the viable cancer mass \( M \) to the initial mass \( M_0 \) as follows:
\[ f(t) = \frac{M}{M_0} = \frac{2\pi}{V_0} \int_{r_b/L}^{\eta/(L\sqrt{\text{BVF}})} \varphi r dr \] ....................................................(15)

The initial mass is equal to the volume of the tumor, since \( \varphi = 1 \) at \( t = 0 \), which is given by
\[ V_0 = \pi \left(\frac{V_b}{L\sqrt{\text{BVF}}} \right)^{\frac{3}{2}} - \left(\frac{r_b}{L} \right)^{\frac{3}{2}} \]
Discretization of the specific equations

1. The diffusion equation

In cylindrical coordinates for a 2 dimensional case and considering the problem in one dimension, equation (9) reduces to:

$$0 = \frac{1}{r} \frac{\partial \sigma}{\partial r} + \frac{\partial^2 \sigma}{\partial r^2} - \varphi \sigma$$

Note that the primes are dropped for simplicity.

To discretize \( \sigma \), we first subdivide the intervals of \( r \) and \( t \) i.e.

\[ r_i = i\Delta r, i = 0,1,2,3, \ldots, N \]
\[ t_k = k\Delta t, k = 0,1,2,3, \ldots, K \]

Therefore \( \sigma(r,t) \approx \sigma(r_i,t_k) = \sigma(i,k) \)

Using Taylor expansion we evaluate the central difference approximation for first and second derivative as follows:

$$\sigma'(i,k) = \frac{\sigma(i+1,k) - \sigma(i-1,k)}{2\Delta r} + O(\Delta r)^3$$

$$\sigma''(i,k) = \frac{\sigma(i+1,k) - 2\sigma(i,k) + \sigma(i-1,k)}{(\Delta r)^2} + O(\Delta r)^2$$

Where;

$$\Delta r = \frac{L}{N-1}.$$  

N is the total number of spatial nodes including those on the boundary.

Substituting equations (17) and (18) into equation (16) gives:

$$0 = \frac{\sigma(i+1,k) - \sigma(i-1,k)}{r(i)2\Delta r} + \frac{\sigma(i+1,k) - 2\sigma(i,k) + \sigma(i-1,k)}{(\Delta r)^2} - \varphi(i,k)\sigma(i,k)$$

Rearranging,

$$\sigma(i,k) = \frac{\Delta r}{r(i)[4 + 2(\Delta r)^2 \varphi(i,k)]} \left[ \sigma(i+1,k) - \sigma(i-1,k) + r(i)[\sigma(i+1,k) + 2\sigma(i,k) - \sigma(i-1,k)] \right]$$

Subject to the discretized boundary conditions below;

$$\sigma(r_b,t_k) = \sigma(r_b,k) = 1$$
\[ \sigma(i + 1, k) - \sigma(i - 1, k) = 0 \quad \text{........}(21) \]

2. The death rate equation

To solve equation (10), we first approximate the integral part of the equation using Simpson’s \( \frac{1}{3} \) formulae.

Let;

\[ \int_0^t \sigma'(r, \tau) \phi'(r, \tau) d\tau = I \quad \text{..................}(22) \]

Putting equation (22) into equation (10), we obtain,

\[ \frac{\partial \phi}{\partial t} = -\phi I + \left[ r_0 \log\left( \frac{k_0}{\phi'} \right) \right] \phi' - \left[ \rho_0 t' + \beta_0 (t')^2 \right] \phi' \quad \text{...............}(23) \]

Letting:

\[ f(t, \phi, \sigma) = -\phi + \left[ r_0 \log\left( \frac{k_0}{\phi'} \right) \right] \phi' - \left[ \rho_0 t' + \beta_0 (t')^2 \right] \phi' \]

We can solve (23) using the 4th order Runge Kutta method as outlined below.

\[ \phi(i, k + 1) = \phi(i, k) + \frac{1}{6} (k_1 + 2k_2 + 2k_3 + k_4) \]

Where, \( k_1 = hf\left[ (t_k, \phi(i, t_k), \sigma(i, t_k) ) \right] \)

\[ k_2 = hf\left[ t_k + \frac{h}{2}, \phi(i, t_k) + \frac{k_1}{2}, \sigma(i, t_k) \right] \]

\[ k_3 = hf\left[ t_k + \frac{h}{2}, \phi(i, t_k) + \frac{k_2}{2}, \sigma(i, t_k) \right] \]

\[ k_4 = hf\left[ t_k + h, \phi(i, t_k) + k_3, \sigma(i, t_k) \right] \]

Subject to the initial condition \( \phi(i, 0) = \phi_0 = 1 \)
After obtaining the discrete values of \( \phi \), we then approximate the integral part of equation (23) using Simpsons \( \frac{1}{3} \) rule.

\[
I \approx 2\pi \frac{h}{V_0} \left[ \phi(r_0, k) r_b + 2\left[ \phi(2, k) r(2) + \phi(4, k) r(4) \right] + \ldots + 4\left[ \phi(3, k) r(3) + \phi(5, k) r(5) \right] + \ldots + \phi\left( (r_N, k) r_N \right) \right] \text{.................(24)}
\]

For \( r_N = r_b / L \sqrt{BV F} \)

RESULTS AND DISCUSSION

To the model equations representing the interaction between cancer density and drug concentration, we added radiotherapy effect at a non constant growth rate. We now perform numerical simulations for different values of parameters such as the ratio of radius of the blood vessel to the diffusion length of the drug and blood volume fraction. In the simulations we considered two cases i.e. without and with radiotherapy effect.

We numerically solve equations 9-12 and 14 using, \( r_b / L = 0.25, BV F = 0.05, r_0 = 1, k_0 = 1, \rho_0 = 0.05, \beta_0 = 0.05, \phi_0 = 1 \) (initial condition), \( r_b = 0.1 \) (initial), \( r_N = 1 \) for \( N=100 \) subdivisions, \( T_0 = 0, T_N = 10 \) for \( N=100 \) subdivisions

![Graph](image)

**Fig 1(a):** Variation of cancer density with time without radiotherapy

From this result, it can be realized that cancer density decreases with time. This is due to increased drug concentration with time as well as nutrients competition. It is also noticeable that far away from the blood vessel, the cells proliferate. This is because there is lowered local drug concentration. In addition, these cells may also experience other micro-environmental conditions such as low nutrient competition.
Fig 1(b): Variation of cancer density with time with radiotherapy.

With the introduction of radiotherapy, cancer density decreases even further with time though at the beginning of the simulation, cancer cells near the blood vessel wall die (due to drug penetration) and further away cells proliferate. Cancer density is much lower here compared to fig 1(a). This means that adding radiotherapy to the treatment leads to more effective treatment.

Fig 2: Variation of drug concentration with time

This result indicates an increase in drug concentration with time. The drug concentration increases with time since there is continuous drug administration. This drug concentration though decreases with increased distance from the point of administration. Continuous drug administration is preferred over bolus. This is because cancer cells might proliferate between doses in the case of bolus treatment.
Continuous drug delivery will overcome proliferation.

![Figure 3(a)](image1.png)

**Figure 3(a):** Ratio of viable cancer mass to the initial mass with varying $r_b/L$ without radiotherapy.

The results of the ratio of viable cancer mass to the initial mass with variations in $r_b/L$ (fixing BVF) without radiotherapy shows that high ratio is achieved at low values of $r_b/L$. From the results we found out that at low value of $r_b/L$, there is more blood diffusion and thus more effective treatment. Increase in $r_b/L$ means there is less drug diffusion and cancer progress more and drug needs to be given more period of time.

![Figure 3(b)](image2.png)

**Figure 3(b):** Ratio of viable cancer mass to the initial mass with varying $r_b/L$ with radiotherapy.
On varying $r_b/L$, fixing BVF and with radiotherapy cells die after a short period of time i.e. ten cycles. This is a clear indicator that radiotherapy brings about a more successive treatment.

Figure 4(a): Ratio of viable cancer mass to the initial mass with varying BVF without radiotherapy.

The above result is obtained on varying BVF (fixing $r_b/L$). Increased BVF represents highly vascularized cancer cells thus high drug penetration. High BVF thus leads to more treatment. Without radiotherapy cells need to be given more period of time.

Figure 4(b): Ratio of viable cancer mass to the initial mass with varying BVF with radiotherapy.
On varying BVF (fixing $r_b/L$) and introducing radiotherapy, cells die after ten cycles. Increased BVF represents highly vascularized tumors. We also found out that a continuously administered drug is more effective if the tumor is highly vascularized (which means more exposure to the treatment) or if the drug penetration is high.

On considering the ratio of the viable cancer mass to the initial mass, it is noticeable that with radiotherapy the drug overcomes proliferation and cancer is killed in a short time. From the results it seems that at low value of $r_b/L$, high BVF and with radiotherapy effect, treatment is more successful.

![Figure 5: Ratio of viable cancer mass to the initial mass with and without radiotherapy.](image)

Comparing the ratio of viable cancer mass to the initial with and without radiotherapy, it is noticeable that with radiotherapy, treatment is achieved after ten cycles but without radiotherapy more time is needed.

**CONCLUSION AND RECOMMENDATIONS**

From the results, it can be concluded that combining chemotherapy and radiotherapy eliminates cancer cells more effectively. This is achieved with low value of the ratio of radius of the blood vessel to the diffusion length of the blood and high values of blood volume fraction. However, we need to know the extent that these values can be decreased and increased for better results. This will guide the oncologists to choose the optimal therapy with minimal suffering to the patient. Our model was studied with continuous delivery of the drug from the blood vessel. Future work can also include investigating the situation where the drug is given as a bolus dose in repeated cycles and then compare the two results. One can also investigate on the cancer stage $\theta$ in which this treatment can work better.
REFERENCES


