Optimal Control for Effective Radiotherapy

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1 System Dynamics

The two compartment kinetic model of cancer is chosen to formulate the cancer dynamics. The model is described as follows [?]:

$$\frac{dN_t}{dt} = z_t - \frac{1}{2} q A_t^2 N_t, \quad at \ \ t \neq t_k \tag{1}$$

$$\frac{dA_t}{dt} = -wA_t - 2qA_t^2, \quad at \ \ t \neq t_k \tag{2}$$

$$N(t_k^+) = N(t_k^-) exp(-\alpha(N(t_k^-))u(t_k)), \quad at \ \ t = t_k \tag{3}$$

$$A(t_k^+) = A(t_k^-) + \delta(N(t_k^-))u(t_k), \quad at \ \ t = t_k \tag{4}$$

$$N(0) = N_0$$

$$A(0) = 0$$

Here, $k = 1, 2, \ldots, n_q$. N_t is the number of tumor cells at time t. The repopulation rate of the tumor cells is given by z_t. A_t is the number of DNA double strand breaks at time t. The repair rate of the DNA double strand breaks is denoted by w. $N(t_k^+)$ and $N(t_k^-)$ are the number of tumor cells just before and after the impulse at time t_k. Similarly, $A(t_k^+)$ and $A(t_k^-)$ are the number of DNA double strand breaks just before and after an impulse is applied at t_k respectively. $N(0)$ and $A(0)$ are the number of tumor cells and the number of DNA double strand breaks at initial time.

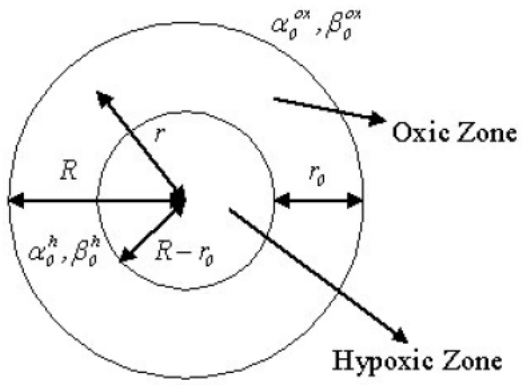


Figure 1: Spherical tumor with compartment model

A two compartmental linear model is shown in Fig. 1. Here, the oxygen diffuses from the outer layer to the inner layer. The outer layer is termed as the oxic region and the inner layer is called the hypoxic region due to the lower concentration of oxygen. r_0 is the oxygen diffusion distance which separates the oxic region from the hypoxic region. Let r be any point in oxic or hypoxic region, α_0^{ox} and α_0^h are values of α at radius R and R - r_0 respectively, similarly, β_0^{ox} and β_0^h are values of β at radius R and R - r_0 respectively. Due to this, there will be two cases for calculating the overall radiosensitivities:

- $R > r_0$: this contains both the oxic and hypoxic regions.Therefore,

$$
\begin{aligned}
N &= N_{ox} + N_h \\
\dot{N} &= \dot{N}_{ox} + \dot{N}_h \\
A &= A_{ox} + A_h \\
\dot{A} &= \dot{A}_{ox} + \dot{A}_h
\end{aligned}
$$

  Here, $N = (4/3)\pi\theta R^3$, $N_{ox} = (4/3)\pi\theta((R - r_0)^3 - r_0^3)$ and $N_h = (4/3)\pi\theta(R - r_0)^3$. Similarly, $A_{ox} = \frac{(R^3-(R-r_0)^3)}{R^3}A$ and $A_h = \frac{(R-r_0)^3}{R^3}A$. Using these in the previously mentioned equations, we get,

$$
\dot{R} = \frac{(z_b - (\frac{1}{2})qA_{ox}^2)(3R^2r_0 - 3Rr_0^2 + r_0^3)}{3R^2} + \frac{(R - r_0)^3((z_b - z_d) - \frac{1}{2}qA_h^2)}{3R^2} \tag{5}
$$

$$
\dot{A} = -wA - 2qA^2\left[2\left(\frac{(R - r_0)^3}{R^3}\right)^2 - 2\frac{(R - r_0)^3}{R^3} + 1\right] \tag{6}
$$

$$
R(t_k^+) = \left[[R(t_k^-)^3 - (R(t_k^-) - r_0)^3]e^{-\alpha_{eff}^{ox}u(t_k)} + (R(t_k^-) - r_0)^3e^{-\alpha_{eff}^h u_h(t_k)}\right]^{1/3} \tag{7}
$$

$$
A(t_k^+) = A(t_k^-) + \delta(\beta_{eff}^{ox}(t_k^-))u(t_k) + \delta(\beta_{eff}^h(t_k^-))u_h(t_k) \tag{8}
$$

- $R \leq r_0$: this contains only oxic region

$$
\dot{R} = \left(z_{ox} - (\frac{1}{2})qA^2\right)\frac{R}{3} \tag{9}
$$

$$
\dot{A} = -wA - 2qA^2 \tag{10}
$$

$$
R(t_k^+) = R(t_k^-)e^{-\alpha_{eff}^{ox}u(t_k)/3} \tag{11}
$$

$$
A(t_k^-) = A(t_k^-) + \delta(\beta_{eff}^{ox})u(t_k) \tag{12}
$$

2 Simulation Results

A linear model of adenocarcinoma is considered with the overall sensitivity values as shown in Fig. 2. As discerned from the table, the sensitivity parameters are a function of the overall tumor radius, R and the oxygen diffusion distance, r_0. The value of R is taken as $350\mu m$ and r_0 is taken to be $300\mu m$. The value of the model parameters for the equations described in § 1 are given in tables 1 and 2. The error criteria for convergence is $R_N < 8\mu m$, therefore the algorithm converges when the tumor radius at final time is less than $8\mu m$. The time duration for the radiotherapy treatment is taken to be 30 days or 30 $\times$ 24 hours. The interval at which the treatment is administered is $\Delta\tau = 1$ day = 24 hours. Thus, there are a total of 30 impulses. The integration time step is chosen to be 0.01.

The initial value of the tumor radius R can be altered based on the value obtained from the MRI scans. The value of the oxygen diffusion distance, r_0 is taken to be as a free parameter and can be altered as necessary. The initial number of DNA double strand breaks is taken to be 0 as the break is caused only due to radiation. The simulation results for IMPSP applied to the adenocarcinoma problem can be seen in Fig. 3. Here, the algorithm converges below the tolerance limit after about 700 hours. Thereby, it can be concluded that the IMPSP algorithm

case i) $R > r_0$: Oxic Zone ($R - r_0 \leq r \leq R$)	
Model	Linear
α^{ox}_{eff}	$\frac{\alpha_0^{ox}\left(12R^3 - 3r_0^3 + 12Rr_0^2 - 18R^2 r_0\right)}{12R^3 + 4Rr_0^2 - 12R^2 r_0} - \left(\alpha_0^{ox} - \alpha_0^h\right)\frac{(R - r_0)}{R}$
β^{ox}_{eff}	$\frac{\beta_0^{ox}\left(12R^3 - 3r_0^3 + 12Rr_0^2 - 18R^2 r_0\right)}{12R^3 + 4Rr_0^2 - 12R^2 r_0} - \left(\beta_0^{ox} - \beta_0^h\right)\frac{(R - r_0)}{R}$ $\frac{\left(\alpha_0^{ox}\right)^2\left(12R^3 - 3r_0^3 + 12Rr_0^2 - 18R^2 r_0\right)^2}{2\left(12R^3 + 4Rr_0^2 - 12R^2 r_0\right)^2} - \frac{\left(\alpha_0^{ox}\right)^2\left(15R^4 + 3r_0^4 - 15Rr_0^3\right)}{2} - \frac{\left(\alpha_0^{ox}\right)^2\left(-30R^3 r_0 + 30R^2 r_0^2\right)}{2}$
case i) $R > r_0$: Hypoxic Zone ($0 \leq r < R - r_0$)	
Model	Linear
α^{h}_{eff}	$\frac{3\alpha_0^h(R - r_0)}{4R}$
β^{h}_{eff}	$\frac{120\beta_0^h R(R - r_0) - 3\left(\alpha_0^h\right)^2 (R - r_0)^2}{160R^2}$
case ii) $R \leq r_0$: oxic zone	
Model	Constant
α^{ox}_{eff}	$\frac{3}{4}\alpha_0^{ox}$
β^{ox}_{eff}	$\frac{3}{4}\beta_0^{ox} - \frac{3}{160}\left(\alpha_0^{ox}\right)^2$

Figure 2: Overall sensitivity values

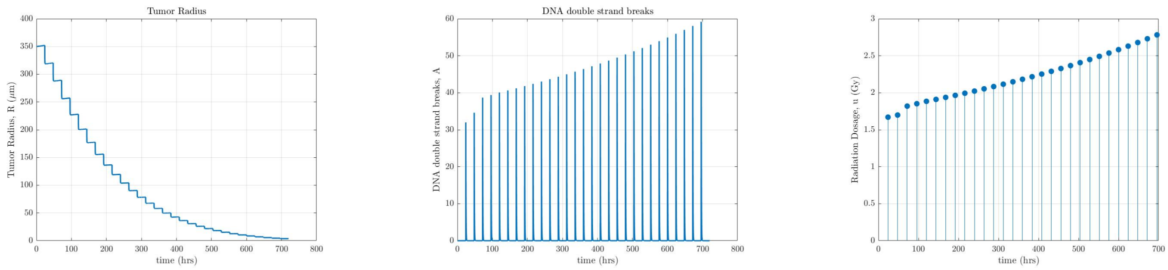
is successful in providing the optimal amount of radiation dosage for effective radiotherapy. The amount of radiation administered during each session is about 1.5 Gy - 3 Gy which is similar to the clinical values. The total amount of radiation dosages administered to the patient is 64.082 Gy.

Parameter	Description	Unit	Value
T_{pot}	potential doubling time	hr	39×24
$T_{1/2}$	half-life	hr	$5 \times 39 \times 24$
μ	repair rate	hr^{-1}	2
w	misrepair rate	hr^{-1}	$\mu \times 4 \times 10^{-4}$

Table 1: Sensitivities as of function of R

Model	α^0_{ox}	β^0_{ox}	α^0_h	β^0_h
Linear	0.164	0.061	0.143	0.002
Quadratic	0.204	0.078	0.179	0.004
Saturation	0.292	0.108	0.256	0.004

Table 2: Adenocarcinoma parameter values



(a) Tumor Radius, R (b) DNA DSBs, A (c) Radiation dosages, u

Figure 3: IMPSP applied to Radiotherapy Problem