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Model Predictive Static Programming with Impulse Control for Effective Radiotherapy

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Abstract: In this paper, a relatively new computationally efficient technique, called model predictive static programming (MPSP), is extended further to incorporate a sequence of 'impulse' control inputs, which is subsequently used to propose an effective suboptimal automatic feedback radiotherapy strategy. A realistic two compartment kinetic model with oxygen effect is considered for computing the control sequence. Biologically effective dose constraints on early and late normal tissue are also considered. The proposed strategy essentially drives the radius of a tumor below the radius of a single cell, thereby driving the number of cancer cells to 'zero'. Time interval between impulses is taken as 8 hrs and it is found that the tumor is driven to zero with approximately 25 impulses. Note that the MPSP algorithm is computationally quite efficient and it takes only 3-4 min in a regular desktop and MATLAB environment.

Keywords: Model predictive static programming, Impulse control, Radiotherapy, Solid tumor

1. INTRODUCTION

Cancer is one of the main causes of deaths worldwide, almost 50% of cancer patients receive radiation therapy during the course of their treatment (Baskar et al. [2012]). In external radiotherapy, radiations are transferred from outside the patient's body. Cell has deoxyribonucleic acid (DNA), which carries genetic information. When cell is exposed to radiations, some of the radiations causes DNA double strand breaks. Cells have got inherent capacity for damage repair. However, if it fails then it results in cell death and that is how the radiation therapy works. In external radiotherapy, normal cells are also exposed to radiations. Aim of radiotherapy is to maximize damage on cancerous cells with minimum damage to normal cells. To achieve this, radiation dosages are given at different points of time (which is called as fractionated radiation therapy), so that in between the intervals damaged normal cells can repair. In radiotherapy, linear quadratic (LQ) model is widely accepted (O'Rourke et al. [2009]). LQ model quantifies the fraction of surviving cells, when a radiation dosage is given in single or multiple fractions. Basic single dose linear quadratic (LQ) model is given by, $S = e^{-\left(\alpha u + \beta u^2\right)}$. Here, S is the surviving fraction i.e., $S = (N_2/N_1)$, where N_1 and N_2 are number of tumor cells before and after radiation dosage u respectively at large times. If radiation dosage is delivered in n equal fractions at different times so that time interval between fractions are large, then LQ model is given by, $S = e^{-n\left(\alpha u + \beta u^2\right)}$. Effect, E of radiation dosage on cells is given by, $E = n\left(\alpha u + \beta u^2\right)$. Biologically effective dose (BED) is a concept which is often used to compare effect of dosage from different regimens, it not equal to physical dose and it is give by, $BED = (E/\alpha) = n\left(u + (\beta/\alpha)\, u^2\right)$. LQ model is empirical, algebraic and is applicable when time interval between the fractions is large (Sachs et al. [1997]). Therefore, different kinetic models were proposed, which gives the same survival fraction as LQ model when time is large. In Wein et al. [2000], Hlatky et al. [1994] model is modified to include reoxygenation effect (hypoxia) and optimal control problem is proposed to maximize tumor control probability with BED constraints on early and late normal tissue. Solution is obtained by using dynamic programming method. In Bertuzzi et al. [2013], optimal solutions are obtained. Here, LQ model with two R's (repair and repopulation) is used.

In this work, application of model predictive static programming (MPSP) is considered for computation of temporal distribution of radiation dosages to drive cancer cells to zero for external beam radiotherapy. Kinetic model with oxygen effect using two compartment model is used. BED constraints on early and late normal tissue are considered. MPSP with impulse control is extension of MPSP, which is for continuous system (Padhi and Kothari [2009]). Here, impulse instants (radiation dosage time) is fixed a priori and impulse control magnitude (radiation dosages) are computed. External beam radiotherapy can be regarded as impulse control problem as DNA damage is caused in 10^{-12} sec (Ling et al. [2010]). We used kinetic model suggested by Bertuzzi et al. [2008](Appendix). Motivated from the work of Wein et al. [2000], in which dynamical model is modified to include reoxygenation effect, we included reoxygenation effect in the model as suggested in Horas et al. [2005]. In Horas et al. [2005], three models of radiosensitivity parameters are suggested: linear, quadratic and saturation.These radiosentitivity parameters are function of tumor radius. Overall radiosensitivity of spherical tumor is calculated by dividing tumor into oxic and hypoxic (less oxygen) compartments. We used linear model for control design. Parameters are selected for head

and neck squamous cell carcinoma (HNSCC). Simulation results are shown.

2. SYSTEM DYNAMICS

Radiotherapy tumor dynamics model is adopted from Bertuzzi et al. [2008]. The Model is described as

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

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

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

where, $k = 1, 2, \ldots, n_k$

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

$$N\left(0^-\right) = N_0 \tag{5}$$

$$A\left(0^-\right) = 0 \tag{6}$$

From (1), N_t is the number of tumor cells at time t, z_t is repopulation rate of tumor cells at time t in *cells* hr^{-1}, it can be constant (exponential growth) or function of N_t (e.g. logistic or gompretz), also it can include both death and birth rate of tumor cells. q is constant parameter in hr^{-1} . From (2), A_t is the number of DNA double strand breaks at time t. w is the repair rate of DNA double strand breaks in hr^{-1} . From (3), n_k is total number of impulses, $N\left(t_k^-\right)$ and $N\left(t_k^+\right)$ are number of tumor cells just before and after impulse at t_k respectively. $\alpha\left(N\left(t_k^-\right)\right)$ is radiosensitivity parameter in Gy^{-1} ($1Gy = 1J/Kg$), it can be function of $N\left(t_k^-\right)$ or constant. $u\left(t_k\right)$ is the impulse control input (radiation dosage) at time t_k in Gy. From (4), $A\left(t_k^-\right)$ and $A\left(t_k^+\right)$ are number of DNA double strand breaks just before and after impulse at t_k respectively. δ is parmater in Gy^{-1}, it can be a function of $N\left(t_k^-\right)$ or constant. N_0 is the initial value of tumor cells. Note that α is due to the damage caused by single radiation track and δ is due to the damage caused by two different tracks $\left(\delta = \sqrt{(4\beta w)/q}\right)$. Both α and δ and are dependent on type of cell, type of radiation and oxygen status of cells (Hlatky et al. [1994]). From (2), $-wA_t$ represents repair involving one DNA double strand break and $-2qA_t^2$ represents misrepair involving two DNA double strand breaks . One fourth of this misrepaired DNA results in cell death, it is represented by $(1/2)\, qA_t^2 N_t$ in (1). More details about the model can be obtained from Hlatky et al. [1994].

In this work, for oxygen effect, two compartmental linear model from Horas et al. [2005] is considered. Consider a spherical tumor of radius R, as shown in Fig.1. Oxygen will diffuse from outer cells to inner cells, let r_0 be the oxygen diffusion distance. Outer region of width r_0 is called as oxic zone and inner region of width $R - r_0$ is called as hypoxic (less oxygen) zone. 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. Let $\alpha(r, R)$ and $\beta(r, R)$are values of α and β at any point r . Here, α_0^{ox}, α_0^h, β_0^{ox} and β_0^h are assumed to be known and $\alpha(r, R)$ and $\beta(r, R)$ are derived from these values. In linear model it is assumed that α and β will decrease linearly from outer to inner cells. $\alpha(r, R)$ and $\beta(r, R)$ are radiosensitivities at a particular radius, therefore for whole tumor radiosensitivities are calculated by using $\alpha(r, R)$ and $\beta(r, R)$ by taking volumetric average. Equations (1) - (6) is dynamical system where, tumor cells N will change continuously, therefore tumor radius R will also change continuously. Therefore, there will be two cases for calculating overall radiosensitivities: i) $R > r_0$: it will contain both oxic and hypoxic region. ii) $R \leq r_0$: it will contain only oxic region. Overall radiosensitivities are represented by α_{eff}^{ox} and β_{eff}^{ox} (Table 1).

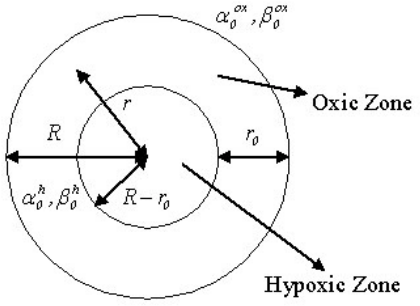

Fig. 1. Schematic diagram of spherical tumor with two (oxic and hypoxic) compartments.

Two compartment oxygen model is considered for control design. Growth rate z_t , α and β will be different in these compartments, hence, (1)-(4) will be different in these compartments. However, kinetic model is of differential equations which needs initial conditions and we do not have separate initial conditions for these compartments. Therefore kinetics of both the compartments are combined with the total kinetic of system as follows.

Case – 1: $R > r_0$ (presence of both oxic and hypoxic compartments) : Let N_{ox} is number of cells in oxic region and N_h is the number of cells in hypoxic region at any time instant. N_{ox} and N_h will add upto total number of cells N at that time instant. Hence, assuming total derivative of cells will be sum of derivatives of cells in oxic and hypoxic compartment, one can write

$$N = N_{ox} + N_h \tag{7}$$

$$\dot{N} = \dot{N}_{ox} + \dot{N}_h \tag{8}$$

Similarly , if A_{ox} and A_h are number of DNA double strand breaks in oxic and hypoxic region at any time instant respectively. Then, total number of DNA double strand breaks at that time instant, A is given by,

$$A = A_{ox} + A_h \tag{9}$$

therefore,

$$\dot{A} = \dot{A}_{ox} + \dot{A}_h \tag{10}$$

from (7) at impulse instants,

$$N\left(t_k^+\right) = N_{ox}\left(t_k^+\right) + N_h\left(t_k^+\right) \tag{11}$$

from (9) at impulse instants,

$$A\left(t_k^+\right) = A_{ox}\left(t_k^+\right) + A_h\left(t_k^+\right) \tag{12}$$

α and β are functions of R (Table 1), R is introduced as $N = (4/3)\pi\theta R^3$, $N_{ox} = (4/3)\pi\theta(R^3-(R-r_0)^3)$, $N_h = (4/3)\pi\theta(R-r_0)^3$, $A_{ox} = \frac{\left(R^3-(R-r_0)^3\right)}{R^3}A$ and $A_h = \frac{(R-r_0)^3}{R^3}A$. Here, θ is cell density in *cells* μm^{-3}. Therefore, after carrying out necessary algebra we get following set of equations in R ,

$$\dot{R} = \frac{\left(z_{ox} - \left(\frac{1}{2}\right)qA_{ox}^2\right)\left(3R^2r_0 - 3Rr_0^2 + r_0^3\right)}{3R^2} + \frac{(R-r_0)^3\left(z_h - \left(\frac{1}{2}\right)qA_h^2\right)}{3R^2} \quad (13)$$

$$\dot{A} = -wA - 2qA^2\left[\begin{array}{l} 2\left(\frac{(R-r_0)^3}{R^3}\right)^2 \\ -2\frac{(R-r_0)^3}{R^3} + 1\end{array}\right] \quad (14)$$

$$R\left(t_k^+\right) = \left\{\begin{array}{l}\left[R\left(t_k^-\right)^3 - \left(R\left(t_k^-\right) - r_0\right)^3\right] \\ \quad \times e^{-\alpha_{eff}^{ox}\left(R\left(t_k^-\right)\right)u(t_k)} \\ + \left(R\left(t_k^-\right) - r_0\right)^3 \\ \quad \times e^{-\alpha_{eff}^{h}\left(R\left(t_k^-\right)\right)u_h(t_k)}\end{array}\right\}^{1/3} \quad (15)$$

$$A\left(t_k^+\right) = A\left(t_k^-\right) + \delta\left(\beta_{eff}^{ox}\left(t_k^-\right)\right)u\left(t_k\right) + \delta\left(\beta_{eff}^{h}\left(t_k^-\right)\right)u_h\left(t_k\right) \quad (16)$$

In (15) and (16), u_h is used but u_{ox} is not used because, hypoxic region will receive part of radiation and oxic zone will receive all the radiations as hypoxic zone is inside of spherical tumor, $u_h(t_k) = \frac{\left(R\left(t_k^-\right)-r_0\right)^3}{R\left(t_k^-\right)^3}u(t_k)$. Here, $z_{ox} = z_b$ and $z_h = z_b - z_d$, where z_b is birth rate of cells and z_d is death rate of cells.

Case – 2: $R \le r_0$ (presence of only oxic compartment) : Necessary algebra is carried out by using $N = (4/3)\pi\theta R^3$ in (1)-(4), therefore we get,

$$\dot{R} = \left(z_{ox} - \left(\frac{1}{2}\right)qA^2\right)\frac{R}{3} \quad (17)$$

$$\dot{A} = -wA - 2qA^2 \quad (18)$$

$$R\left(t_k^+\right) = R\left(t_k^-\right)e^{-\alpha_{eff}^{ox}\left(R\left(t_k^-\right)\right)u(t_k)/3} \quad (19)$$

$$A\left(t_k^+\right) = A\left(t_k^-\right) + \delta\left(\beta_{eff}^{ox}\left(t_k^-\right)\right)u\left(t_k\right) \quad (20)$$

Thus, kinetic equations (13)-(16) is used in control design when $R > r_0$ and equations (17)-(20) is used in control design when $R \le r_0$. Parameters of model (13)-(20) is given in Table 2.

3. MODEL PREDICTIVE STATIC PROGRAMMING WITH IMPULSE CONTROL

The relatively recent model predictive static programming (MPSP) algorithm (Padhi and Kothari [2009]) is extended in this paper to cater for a distinctly separated sequence of impulsive control inputs. MPSP is suboptimal control design technique applicable to finite horizon nonlinear control problems with terminal constraints. MPSP is formulated as static optimization problem. MPSP is iterative algorithm which gives quick solution for control history update, MPSP is computationally efficient. Here the following impulsive system dynamics is considered

$$\dot{X} = f(X), \quad for\ t \neq t_k \quad (21)$$

$$X_k^+ = g\left(X_k^-, U_k\right), \quad for\ t = t_k \quad (22)$$

$$Y = h(X) \quad (23)$$

$$X(0) = X_0 \quad (24)$$

where, $k = 1, 2, 3, \ldots, n_k$, $X \in \Re^n$ are the states, $Y \in \Re^p$ are outputs which need to be controlled, $U_k \in \Re^m$ are control at time t_k , $f: \Re^n \to \Re^n$, $h: \Re^n \to \Re^P$ and $g: \Re^n \times \Re^m \to \Re^n$. X_k^- and X_k^+ are states just before and after impulse control at time t_k respectively. Let t_0 and t_f be initial and final time. System (21) and (23) is discretized in time steps from t_0 to t_f . For (21), Euler discretization is used, such that

$$X_{k+1} = X_k + \Delta t\, f(X_k) \quad (25)$$

Discretized system has following form,

$$X_{k+1} = F(X_k) \quad (26)$$

$$Y_k = h(X_k) \quad (27)$$

$$X_k^+ = g\left(X_k^-, U_k\right) \quad (28)$$

Total time t_0 to t_f is divided into N distinct time steps. Let t_k for $k = 1, 2, \ldots, n_k$, be the distinct time when impulse control is applied. Let n_k be the number of impulses for each control at time of impulses. If there are more than one controls, then all the control elements will operate simultaneously at time of impulse. Application of impulsive control will divide state trajectory into different segments, let n_{seg} be the number of segments, hence, $n_{seg} = n_k + 1$ (as all the controller will operate simultaneously). Each segment is divided into equal number of nodes, let n_d be the number of nodes per segment for each state. Let Y^d be the desired value of Y which needs to be achieved at t_f i.e., $Y_N \to Y^d$. Let $\Delta Y_N = Y^d - Y_N$, assuming ΔY_N is small so that, $\Delta Y_N \simeq dY_N$. Using (27) and Taylor series first order approximation, dY_N can be written as,

$$dY_N = \left[\frac{\partial Y_N}{\partial X_N}\right]dX_N \quad (29)$$

from (26), considering, first order Taylor series approximation,

$$dX_{k+1} = \left[\frac{\partial F(X_k)}{\partial X_k}\right]dX_k \quad (30)$$

From (30), dX_{k+1} is function of dX_k , similarly dX_N will be function of dX_{N-1} , dX_{N-1} will be function of dX_{N-2} and so on upto n_k^{th} impulse, i.e.,

$$dY_N = \left[\frac{\partial Y_N}{\partial X_N}\right]\left[\frac{\partial F}{\partial X_{N-1}}\right]\left[\frac{\partial F}{\partial X_{N-2}}\right]\cdots \cdots\left[\frac{\partial F}{\partial X^+_{N-(n_d-1)}}\right]dX^+_{N-(n_d-1)} \quad (31)$$

Note that, we have started from last node and moving towards first node, and n_k^{th} impulse is located at $N-(n_d-1)^{th}$ node. At the impulsive points, (28) will be followed, from (28),

$$dX_k^+ = \left[\frac{\partial g\left(X_k^-, U_k\right)}{\partial X_k^-}\right]dX_k^- + \left[\frac{\partial g\left(X_k^-, U_k\right)}{\partial U_k}\right]dU_k \quad (32)$$

Thus, using (30) at different non impulsive grid points and (32) at different impulsive grid points, finally (31) will be expressed as:

$$dY_N = B_1 dU_1 + B_2 dU_2 + \cdots + B_k dU_k \tag{33}$$

$$B_k = \left[\frac{\partial Y_N}{\partial X_N}\right]\left[\frac{\partial F}{\partial X_{N-1}}\right]\cdots\left[\frac{\partial F}{\partial X^{+}_{N-(n_d-1)}}\right]\times \left[\frac{\partial g}{\partial X^{-}_{N-(n_d-1)}}\right]\left[\frac{\partial F}{\partial X_{N-(n_d-1)-1}}\right]\cdots \cdots\left[\frac{\partial F}{\partial X^{+}_{N-[n_k-(k-1)](n_d-1)}}\right]\left[\frac{\partial g}{\partial U_k}\right] \tag{34}$$

for $k = 1, 2 \ldots, n_k$. $B_k's$ are called as sensitivity matrices (note that sensitivity matrices can be computed recursively, therefore MPSP algorithm becomes fast). If number of output variables are less than number of control, i.e., $p < mn_k$, then following optimization problem is proposed.

$$J = \left(\frac{1}{2}\right)\sum_{k=1}^{n_k}\left(U_k + dU_k\right)^T R_k \left(U_k + dU_k\right) \tag{35}$$

subject to constraint (33). Here, U_k is the guess value of control, $U_k + dU_k$ is updated value of control and R_k is positive definite matrix. Equations (35) and (33) contain an optimization problem, which can be solved using principle of Lagrange multiplier (Rao [1996]). Thus, we get

$$U_k + dU_k = R_k^{-1} B_k^T \left(\sum_{k=1}^{n_k} B_k R_k^{-1} B_k^T\right)^{-1} \times \left(dY_N + \sum_{k=1}^{n_k} B_k U_k\right) \tag{36}$$

Control objective is to minimize (35) subject to (33). This will ensure that tumor is driven to zero with minimum control (radiation), which in turn will ensure that minimum radiation is passed through normal cells. Note that, algorithm is iterative in nature, initially, control values are guesses at n_k values, then, dY_N is checked so that dY_N should be zero or close to zero, if dY_N does not satisfy the error criteria then optimization problem (35) and (33) is solved to get updated control. Then again if dY_N does not satisfy error criteria, optimization problem is solved with previous updated control value as the guess value. This process is repeated till the convergence. Also, if control is constrained then Matlab Fmincon toolbox is used to solve (35) and (33). Note that recursive computation of sensitivity matrices and more details of MPSP for impulse control is given in Sakode and Padhi [2014].

4. CONTROL DESIGN FOR EXTERNAL BEAM RADIOTHERAPY

Objective of control design is to drive tumor cells to zero at final time with BED constraints on early and late tissue. Control design is based on MPSP algorithm with impulse control ((35) and (33)). Tumor kinetics ((13)-(20)) with two compartment model for oxygen is used in algorithm. To start with, algorithm needs desired value of states which is to be achieved at final time t_f. There are two states, tumor radius R and number of DNA double strand breaks, A. $R \rightarrow 0$ will ensure tumor cells to go to zero $\left(N = (4/3)\pi\theta R^3\right)$ irrespective of value of A. Therefore, control design is carried out by using one output variable, i.e, R. Error criteria for convergence is $dR \approx 0$, note that dR is not set as exactly zero because $\delta = \sqrt{(4\beta w)/q}$ and β is function of R . As this is iterative algorithm, therefore, there is a chance of getting negative R in some iteration which will make δ as complex value. Control design is carried out with following constraints,

$$u_k \geq 0, \quad \text{for } k = 1, 2, \ldots, n_k \tag{37}$$

where, u_k are control values at time t_k, it can also be represented by $u(t_k)$. (37) will ensures control solution with positive value of radiation, as radiation will enter into the system, it can also be verified from control law ((15),(16) ,(19),(20)). As kinetics (13)-(20) will resemble LQ model at large time and LQ model is applicable only for low and intermediate radiation dosages (Sachs et al. [1997]), therefore, there is upper limit, H on u_k,

$$u_k \leq H, \quad \text{for } k = 1, 2, \ldots, n_k \tag{38}$$

Radiation limit is considered by using BED limit, BED is computed by using equation from Yang and Xing [2005], Wein et al. [2000], described below

$$\left(\frac{2}{m_E}\right)\sum_{i=1}^{n_k-1}\sum_{j=i+1}^{n_k} u_i u_j e^{-\omega_E(t_j - t_i)} + \sum_{k=1}^{n_k} u_k + \left(\frac{1}{m_E}\right)\sum_{k=1}^{n_k} u_k^2 - \frac{\gamma_E}{\alpha_E} t \leq BED_E \tag{39}$$

$$\left(\frac{2}{m_L}\right)\sum_{i=1}^{n_k-1}\sum_{j=i+1}^{n_k} u_i u_j e^{-\omega_L(t_j - t_i)} + \sum_{k=1}^{n_k} u_k + \left(\frac{1}{m_L}\right)\sum_{k=1}^{n_k} u_k^2 \leq BED_L \tag{40}$$

Here, u_k, u_i, u_j are control values at time t_k, t_i, t_j respectively, i.e., $u(t_k)$, $u(t_i)$, $u(t_j)$. $m_E = \alpha_E/\beta_E$, α_E and β_E are radiosensitivity parameters for early tissue, w_E is repair rate of early tissue, γ_E is death rate of early tissue. BED_E is maximum BED limit of early tissue. $m_L = \alpha_L/\beta_L$, α_L and β_L are radiosensitivity parameters for late tissue, w_L is repair rate of late tissue, BED_L is maximum BED limit of late tissue. α_E, β_E, α_L and β_L are taken as constant values. (39) is followed for each time step i.e., for u_1, $u_1 u_2$, $u_1 u_2 u_3, \cdots$ and so on. (40) is followed only once by considering all $u_k's$. Table 2 gives the values of different parameters.

5. SIMULATION RESULTS

Model ((13) - (20)) and parameters of head and neck squamous call carcinoma (HNSCC) is used (Table 2). Equations (13)-(16) is used when $R > r_0$ and equations (17) - (20) is used when $R \leq r_0$ in control design with MPSP with impulse control. Initial conditions are $R = 5000\,\mu m$, $r_0 = 250\,\mu m$ and $A = 0$. t_f is taken as 10 days, i.e., 240 hrs (Yang and Xing [2005]). Error criteria for algorithm is, desired value of R i.e., $R^d = 3\,\mu m$, $dR_N > 0.1\,\mu m$ and $R_N > 0\,\mu m$. Note that R^d is set as close to zero not exactly zero. Also R^d is less than radius of single

cell (radius of single cell is $6.2\,\mu m$ as cell density chosen $\left(\theta = 10^{-3}\, cells\ \mu m^{-3}\right)$, thus when $R < 6\,\mu m$, tumor is eliminated. Time interval between the control impulses (u) is taken as 8 hrs (Yang and Xing [2005]). Total number of impulses is calculated as $n_k = t_f(in\,hrs)/\Delta I$, ΔI is interval between impulses. Number of nodes per segment is calculates as, $n_d = (t_k - t_0)/dt + 1$ (by converting in nearest integer), dt is time step of integration.

Fig. 2 shows the variation of tumor radius R after application of impulse control, here $r_0 = 250\,\mu m$. Initially, $R > r_0$, therefore system will have both oxic and hypoxic region, at around $150\,hrs$, $R \approx r_0$ and after that $R < r_0$, here system will have only oxic region. Oxic region growth rate is given by birth rate of cells and in hypoxic region growth rate is given by combination birth and death rate of cells. Inbetween the impulses, tumor radius increases as overall tumor growth rate is positive ((13) and (17)). At the point of impulses there is sudden decrease in tumor radius ((15) and (19)). Fig. 2 also shows a subplot, it can be seen that radius decreases for small time after impulse, this change in nature of plot is represented by small rectangle. This seems to be contrary as tumor growth rate is positive. However, this is happening because impulses will decrease R at the same time it will increase A ((16) and (20)) and positive A will decrease R if it counters positive tumor growth rate. Two data points are shown, left shows time when tumor is eliminated i.e., $R < 6\,\mu$m and other data point shows the tumor radius at final time, t_f (240 hrs).

Fig. 3 shows the variation of A and u. At the time of impulses, A will show sudden rise ((16) and (20)). Inbetween the impulses, A will decrease because of repair of DNA double strand breaks ((14) and (18)). u is continuously increasing upto 150 hrs. This is because tumor has both oxic and hypoxic region upto 150 hrs. Hypoxic region will decrease and oxic zone will increase in proportion after control impulse, as oxic zone has positive growth rate more control will be required. Note that α is function of R, hypoxic region has lesser value of α and β than oxic region, and hypoxic region contains both death and birth terms whereas in oxic region only birth terms are present. After 150 hrs, only oxic region is present, also there is not much variation in value of u, generally, as tumor decreases u should also decrease. This is not happening because of control law, from (19), $R\left(t_k^+\right) = R\left(t_k^-\right) e^{-\alpha_{eff}^{ox}\left(R\left(t_k^-\right)\right)u(t_k)/3}$ in terms of N it will become $N\left(t_k^+\right) = N\left(t_k^-\right) e^{-\alpha_{eff}^{ox}u}$. It is nothing but the LQ model with only α term. α_{ox} is constant when only oxic zone is present Table 1. Total u $(u_1 + u_2 + \cdots + u_{n_k})$ is 47.83 Gy . In Jeong et al. [2013], it is seen that for tumor of 0.5 cm $(5000\,\mu m)$ radius, $54\,Gy$ is needed for 50% tumor control. All control values are between 1-2 Gy, in clinical practice standard value is 2 Gy per fraction (Yang and Xing [2005]). Thus, we claim that MPSP algorithm with impulse control gives clinically relevant results.

6. CONCLUSION

Generally, radiotherapy is given in open loop , hence not very effective. In this paper, a relatively new computationally efficient technique, called model predictive static programming (MPSP), is extended further to incorporate a sequence of 'impulse' control inputs, which is subsequently used to propose an effective suboptimal automatic feedback radiotherapy strategy. A realistic two compartment kinetic model with oxygen effect is considered for computing the control sequence. Biologically effective dose constraints on early and late normal tissue are also considered. The proposed strategy essentially drives the radius of a tumor below the radius of a single cell, thereby driving the number of cancer cells to 'zero'. As per the knowledge of the authors, this is the first algorithm for external beam radiotherapy (impulse control) with the kinetic model. Note that the proposed MPSP algorithm takes only 3-4 min in a regular desktop and MATLAB environment.

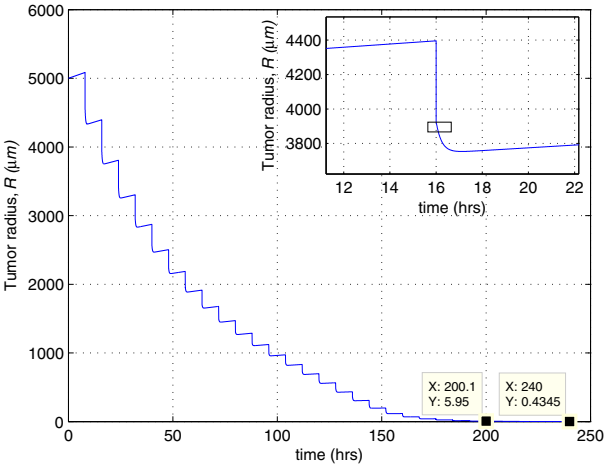

Fig. 2. Tumor radius R after application of impulse control for $r_0 = 250$ μm

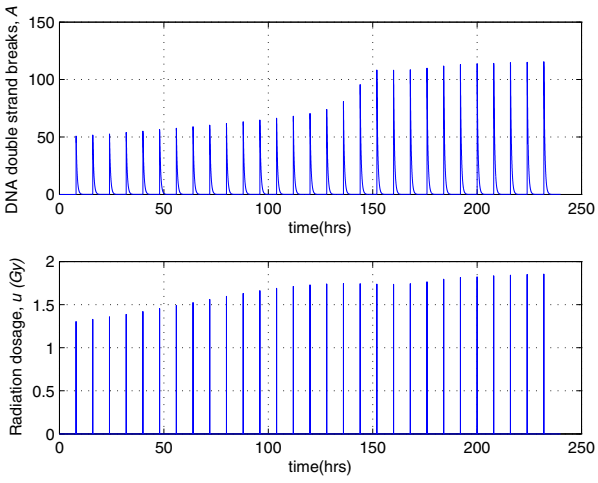

Fig. 3. Top: DNA double strand breaks after application of impulse control for $r_0 = 250$ μm . Bottom: Impulse control with interval of 8 hrs for $r_0 = 250$ μm

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Table 1. Overall radiosensitivity as a function of R, Horas et al. [2005]

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

Table 2. Parameter values

Para-meter	Value	Unit	Reference
α_0^{ox}	0.0421	Gy^{-1}	derived from Jeong et al. [2013]
β_0^{ox}	0.5208	Gy^{-2}	derived from Jeong et al. [2013]
α_0^h	0.3913	Gy^{-1}	derived from Jeong et al. [2013]
β_0^h	0.0467	Gy^{-2}	derived from Jeong et al. [2013]
z_b	$\left(\frac{0.5}{24}\right) \times \left(\frac{\ln(2)}{2}\right)$	hr^{-1}	Jeong et al. [2013]
z_d	$\left(\frac{\ln(2)}{28.2}\right) \times \left(\frac{1}{24}\right)$	hr^{-1}	Chvetsov et al. [2008]
θ	10^{-3}	cells μm^{-3}	Jeong et al. [2013]
w	2	hr^{-1}	Yang and Xing [2005]
q	$w \times 4 \times 10^{-4}$	hr^{-1}	Hlatky et al. [1994]
H	9	Gy	Sheu et al. [2013]
m_E	10	Gy	Yang and Xing [2005]
w_E	2	hr^{-1}	Yang and Xing [2005]
γ_E/α_E	0.08	$Gy\,hr^{-1}$	Wein et al. [2000]
BED_E	60	Gy	Fowler [2010]
m_L	3	Gy	Yang and Xing [2005]
w_L	0.25	hr^{-1}	Yang and Xing [2005]
BED_L	115	Gy	Fowler [2010]

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