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A multinomial model of tumor growth treated by radiotherapy

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Abstract: A main challenge in radiotherapy is to personalize the treatment by adapting the dose fractionation scheme to the patient. One way is to model the treatment effect on the tumor growth. In this study, we propose a new multinomial model based on a discrete-time Markov chain, able to take into account both of cell repair and cell damage heterogeneity. The proposed model relies on the 'Hit' theory in Radiobiology and assumes that a cancer cell contains m targets which must be all deactivated to produce cell death. The malignant cell population is then split up into m categories to incorporate the variation of cancer cell radio-sensitivity according to their states. This work gives also a new formulation of the tumor control probability (TCP) suited to the perspective of dynamic fractionation schedules in radiotherapy.

Keywords: Markov chain, multinomial model, tumor growth, radiotherapy

1. INTRODUCTION

Table 1. Notations

In radiotherapy, the pattern of fractionation of radiation treatment has an important consequence on both tumor cell kill and the damage in the surrounding healthy normal tissue [Withers (1992)]. Since radiation delivery at a precise point of cells is generally described as a stochastic process, the effects of the radioactive treatments on cancer and healthy cells are characterized by two probabilities: (i) the tumor control probability (TCP) and (ii) the normal tissue complication probability (NTCP) [Dawson and Hillen (2006); Gay and Niemierko (2007)] respectively. Both are based on mathematical models like the survival curves [Fowler (1989)], population-dynamic models [Sachs et al. (2001)] or the cell-cycle models [Kirby et al. (2002)]. These models are also used to express the dynamic fractionation scheme as a control problem [Tervo et al. (2007)]. Unfortunately two main aspects of tumor growth are often missing in these modelling studies: (i) the cell reparation between two consecutive dose fractions and more particularly (ii) the heterogeneity of damages induced by radiations in the cancer cell population after each dose fraction. The objective of this work is to propose:

- a modelling solution to take into account both cell reparation and treatment effect heterogeneity;
- a new expression of TCP.

This paper is structured as follows: hit models and target theory are firstly introduced in Section 2. We develop a multinomial model of tumor growth in Section 3, and a new expression of tumor control probability in Section 4. Finally, numerical results are presented in Section 5.

Not.	Definition
f	number of dose fractions during the radiotherapy
k	discrete time
m	number of targets in the cancer cells
n_0	initial number of cancer cells in the tumor
p	survival probability of a target after treatment
p_c	survival probability of a cell after treatment
q	probability that a radiation particle inactivates a target
r	probability for an inactive target to be reactivated
\mathbf{P}	transition matrix associated to treatment effects
\mathbf{R}	transition matrix associated to cell repair process
Π	transition matrix associated to both of treatment effects and repair process, $\Pi = \mathbf{PR}$
S_j	binary state of the j^{th} cell
t	time variable
u	radiation dose (Gy)
$X_k(i)$	number of cancer cells with i deactivated targets
Z_k	damage state of a cell (nb of deactivated targets)

2. HIT MODELS AND TARGET THEORY

The *target theory* and *hit-modeling paradigm* were introduced in the 1920s when biologists were beginning to develop quantum approaches to inactivation phenomena in irradiated biological tissue [Dessauer (1922); Blau and Altenburger (1922); Crowther (1924)]. The modeling of radiation effects on living cells were continued both theoretically and experimentally by K. C. Atwood and A. Norman [Atwood and Norman (1949)], D. E. Lea [Lea (1955)], E. C. Pollard and coworkers [Pollard et al. (1955); Pollard (1959)]. Since these seminal works, a lot of mathematical models expressing the interaction of radiation particles with biological cells have been proposed [Fowler (1964); Sy

and Han (1982); Ditlov (2001); Satow and Kawai (2006); Chapman (2007); Ditlov (2009)]. Most of existing mathematical models used in radiotherapy dosimetry, *e.g.* cell survival curves, derive from the *Target Theory*. In this theoretical setting, a target is a necessary and indispensable place of a cell to exist. It is an idea that the cell death happens when a radiation particle hits the target. The underlying assumptions of the hit models are:

- a cell has one critical target;
- the probability q that a radiation particle will hit a critical target is constant;
- the hit events are independently distributed in a cell;

Thereafter, we define $n_q = u\rho$ the total number of radiation particles with u the amount of dose and ρ the number of radiation particles per unit dose. n_q is assumed to be an integer for the simplification. Let Y be the random variable denoting the number of radiation particles that hit the critical target. Then, $Y \sim \mathcal{B}(n_q, q)$ (binomial distribution) and the probability that exactly j radiation particles hit the critical target is given by [Satow and Kawai (2006)]:

$$Pr(Y = j) = \binom{n_q}{j} q^j (1-q)^{n_q-j}, \quad j = 0, 1, 2, \dots, n_q. \quad (1)$$

If n_q is large enough and q is low, and fixing $n_q q = \lambda$, eq. (1) can be approximated by a Poisson distribution,

$$Pr(Y = j) = \frac{\lambda^j}{j!} e^{-\lambda}, \quad j = 0, 1, 2, \dots \quad (2)$$

λ is the expected number of primary lesions; the parameter $\alpha = \frac{\lambda}{u}$ can be interpreted as a basic characteristic of the damage process itself, *i.e.*, as radiosensitivity in its literal sense [Hanin et al. (1996)]. There are several classes of hit models classified by the number of targets and the number of hits.

2.1 Single target – single-hit model

In this model structure, it is implicitly assumed that a cell has one lethal target and that the cell dies when it is hit by one or more radiation particles. The probability that the cell dies is then given by

$$q_c = \sum_{j=1}^{\infty} \frac{\lambda^j}{j!} e^{-\lambda} = 1 - e^{-\lambda}. \quad (3)$$

2.2 Single target – multi-hit model

In the multi-hit model structure, it is assumed that the cell dies when it is hit by at least h radiation particles. In other words, h is a threshold number of cell inactivation. The parameter h is the critical number of radiation-induced primary lesions a cell can bear without being killed. h is also called *extrapolation number*. The probability that the cell dies is then given by

$$q_c = \sum_{j=h}^{\infty} \frac{\lambda^j}{j!} e^{-\lambda}. \quad (4)$$

The multi-hit model of cancer is a way to outline the progression of cancer as the accumulation of mutations in the genome of cells. Much data has supported the multi-hit model of cancer. In essence, each mutation to a cell

generation's genome is a hit and the accumulation of hits is what creates the tumor potential of the dividing progeny.

2.3 Multi-target – single-hit model

In this model, cell death results from the lethal damage to the subcellular targets, the intracellular sensitive sites. In other terms, it is assumed that there exist different targets within a nucleus which must be inactivated to kill the cell. For instance, it is accepted that the chromosomes are sensitive targets [Dertinger and Jung (1970)] but there is additional evidence that the nuclear membrane, or things close to the nuclear membrane are targets [Datta et al. (1976)]. This model structure is used thereafter by considering m distinct targets within a nucleus. Underlying assumptions of this model are also specify further along in this paper.

3. MULTINOMIAL MODEL OF A TUMOR

Hit models could be used to express the fractionated radiation therapy as a control problem [Tervo et al. (2007)]. Unfortunately two main aspects of tumor growth are generally missing in these models: (i) the cell reparation between two consecutive dose fractions and (ii) the heterogeneity of damages induced by radiations in the cancer cell population after each dose fraction. Thereafter, we thus propose to take these two issues into account in a multinomial model relying on the multi-target – single-hit modeling paradigm. In this paragraph, the first row and first column of a matrix will be noted by the index value 0.

3.1 Radiation static signal

We restrict our study to fractionated radiation schedules that have 5 dose fractions per week. More specifically, the first fraction is given on Monday morning, and there is no treatment on the weekends. The treatment is based on a static (*i.e.*, fraction sizes do not vary over time) scheme illustrated in Fig. 1, which is characterized by the magnitude u_0 of each dose fraction and the total number of fractions f , ($f u_0$) then corresponds to the total delivered dose. k is the discrete time based on a daily sampling rate.

3.2 Heterogeneity of cell states after radiations

We consider that a cell contains m targets. Each target can be made inactive by a single hit. In this case, the cell death occurs when m targets are deactivated, it is the hypothesis of the *multi-target* model. We suppose that the targets can reactivate between two consecutive dose fractions when the cell is still alive (repair of sublethal damages). Most of modelling studies also assume the homogeneity of cell states after the delivery of each dose fraction which is rarely the case in practice. The target reactivation and cell state heterogeneity, are addressed hereafter. After the first fraction of treatment, different states of living cells can appear. Therefore, we have $m + 1$ possible states for a cell:

- state i , the cell has i inactive targets, $i \in \{0, 1, \dots, m-1\}$, these are the m states of a surviving cell.

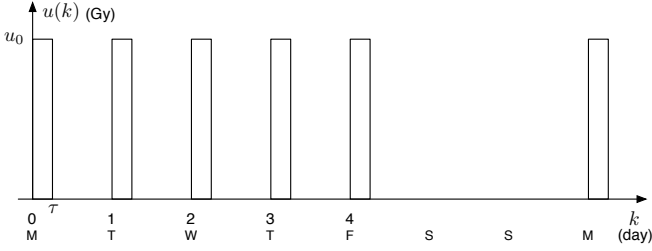


Fig. 1. Radiation static scheme

- state m , the cell has m inactive targets, it is a dead cell.

Fig. 2 shows the case of a 3-targets cell.

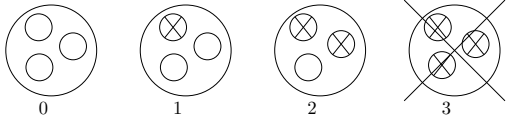


Fig. 2. Heterogeneous states of a cell ($m = 3$) after radiation exposure

3.3 Discrete-time Markov chain model of a cancer cell

A discrete-time Markov chain model is proposed to describe the heterogeneity of cellular damages during the fractionated treatment.

Let us first consider a single cell composed of m targets. Let Z_k be the random variable describing the state of the cell at time k , $Z_k = i \in \{0, 1, \dots, m\}$ means that the cell has i deactivated targets at time k . We suppose that (Z_k) is a discrete-time Markov chain, *i.e.* the cell state at time $k+1$ only depends on the current state at time k . We firstly formulate the transition matrix of $(Z_k)_{k \in \mathbb{N}}$ by considering only the effects of dose fractions, and we secondly integrate repair mechanisms into this matrix in such a way that the dynamics of the Markov chain takes both treatment effects and repair mechanisms into account.

Treatment effect modelling. Let \mathbf{P} be the transition matrix of $(Z_k)_{k \in \mathbb{N}}$. We firstly consider the effects of dose fractions. $\mathbf{P}(i, j)$ is the transition probability to deactivate by the treatment j targets at time $k+1$ when i targets are disabled at time k . Let q be the probability to inactivate a target after a fraction dose u_0 , therefore $1 - q$ is the probability that an active target remains active. Moreover, we suppose that the disabling of targets in the cell are independent events. Thus after applying a fraction dose, various scenarios are possible:

- a cell in state 0 at time k , has $m+1$ possible outcomes. It may switch at time $k+1$ to the state l by the deactivation of l target(s) among the m active ones with $0 \leq l \leq m$ and a transition probability

$$\mathbf{P}(0, l) = \binom{m}{l} q^l (1 - q)^{m-l}; \quad (5)$$

- a cell in state 1 at time k has m possible outcomes. It may switch at time $k+1$ to the state l by the deactivation of $l-1$ target(s) among the $m-1$ active ones, with $1 \leq l \leq m$ and a transition probability

$$\mathbf{P}(1, l) = \binom{m-1}{l-1} q^{l-1} (1 - q)^{m-l}; \quad (6)$$

- ...

- a cell in state $m-1$ at time k has 2 possible outcomes at time $k+1$: either it remains in the state $m-1$ with a probability $\mathbf{P}(m-1, m-1) = 1 - q$, or it dies after the deactivation of the last active target with a probability $\mathbf{P}(m-1, m) = q$.
- Finally, a dead cell remains in state m with probability $\mathbf{P}(m, m) = 1$.

Then, we obtain the general expression of the transition matrix (upper triangular matrix)

$$\mathbf{P}(i, j) = \begin{cases} \binom{m-i}{j-i} q^{j-i} (1 - q)^{m-j} & i \leq j \\ 0 & j < i. \end{cases} \quad (7)$$

and the explicit expression is given by

$$\mathbf{P} = \begin{pmatrix} (1 - q)^m & \binom{m}{1} q (1 - q)^{m-1} & \dots & q^m \\ 0 & (1 - q)^{m-1} & \dots & q^{m-1} \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & q \\ 0 & 0 & \dots & 1 \end{pmatrix},$$

Fig. 3 shows the transition graph corresponding to the Markov chain (Z_k) before taking into account the repair of inactive targets, for the case of a 3-targets cell ($m = 3$).

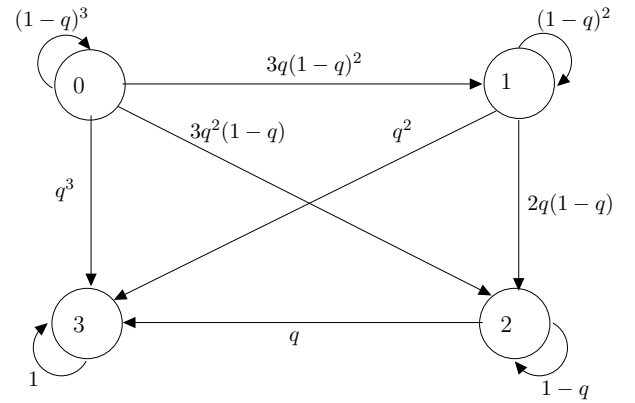


Fig. 3. Transition graph of the Markov chain $(Z_k)_{k \in \mathbb{N}}$.

Cellular reparation modelling. We introduce now repair mechanisms of deactivated targets which occur between two consecutive fractions. We assume that the repair process of a deactivated target is constant and independent of the number of active targets in the cell. Let r be the probability of an inactive target in a living cell to revive during the period that separates two consecutive dose fractions. Then we have:

- a cell in state 0 at $t = k$, remains in this state at $t = k+1$ with probability 1, because it has no target to repair;
- a cell in state 1 at $t = k$, has 2 opportunities at $t = k+1$:
 - either it returns to 0 with probability r ;
 - or it remains in state 1 with probability $1 - r$;
- ...
- a cell in state $m-1$ at $t = k$, has m opportunities at $t = k+1$. It can return to state l with probability $\binom{m-1}{m-1-l} r^{m-1-l} (1 - r)^l$, $0 \leq l \leq m-1$;
- finally, a dead cell remains in state m with probability 1.

The transition matrix \mathbf{R} (lower triangular matrix) corresponding to the repair mechanisms is then given by

$$\mathbf{R}(i, j) = \begin{cases} \binom{i}{j} r^{i-j} (1-r)^j & j \leq i < m \\ 0 & i < j, \end{cases} \quad (8)$$

for $i = m$, $\mathbf{R}(m, m) = 1$ and $\mathbf{R}(m, j) = 0$ for all $j \neq m$. The explicit expression is given by

$$\mathbf{R} = \begin{pmatrix} 1 & 0 & 0 & \dots & 0 \\ r & 1-r & 0 & \dots & 0 \\ r^2 & \binom{2}{1} r(1-r) & (1-r)^2 & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ r^{m-1} & \binom{m-1}{1} r^{m-2} (1-r) & \dots & \dots & 0 \\ 0 & 0 & 0 & \dots & 1 \end{pmatrix}, \quad (9)$$

When we introduce the reparation mechanisms, the transition matrix of the Markov chain $(Z_k)_{k \in \mathbf{N}}$ previously defined, is then given by $\mathbf{\Pi} = (\pi_{i,j})_{i,j \in \{0,1,\dots,m\}}$,

$$\mathbf{\Pi} = \mathbf{P}\mathbf{R}, \quad (10)$$

where $\pi_{i,j} = Pr(Z_{k+1} = j \mid Z_k = i)$. For the case of a 3-targets cell, let $q' = 1 - q$ and $r' = 1 - r$, then

$$\mathbf{\Pi} = \begin{pmatrix} (rq + q')^3 - (rq)^3 & 3r'qq'^2 + 6rr'q^2q' & 3q^2q'r'^2 & q^3 \\ rq'^2 + 2r^2qq' & r'q'^2 + 4rr'qq' & 2r'^2qq' & q^2 \\ r^2q' & 2rr'q' & r'^2q' & q \\ 0 & 0 & 0 & 1 \end{pmatrix} \quad (11)$$

Fig. 4 shows the transition graph corresponding to the Markov chain (Z_k) after taking the repair of inactive targets into account.

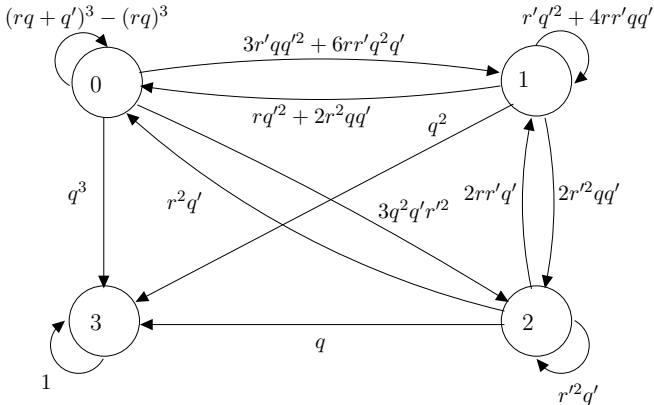


Fig. 4. Transition graph corresponding to $(Z_k)_{k \in \mathbf{N}}$.

Probability distribution of Z_k . In order to determine the probability distribution of Z_k , we introduce the vector $\nu_k = (\nu_k^0, \dots, \nu_k^m)$, $\nu_k^i = Pr(Z_k = i)$. From the transition matrix $\mathbf{\Pi}$ and the initial probability distribution ν_0 of Z_0 , we can determine ν_k , for all $k \in \mathbf{N}^*$, using the Markov chain property,

$$\nu_k = \nu_0 \mathbf{\Pi}^k. \quad (12)$$

If we assume that the cell is initially in state 0, in this case we have $Pr(Z_0 = 0) = 1$, then $\nu_0 = (1, 0, \dots, 0)$. Therefore, we obtain

$$\nu_k^i = \Pi^k(0, i) \quad i \in \{0, \dots, m\}. \quad (13)$$

3.4 Multinomial model of the tumor

Consider a group of n_0 cells $\{\delta_j\}_{j \in \{0,1,\dots,n_0\}}$ that compose the tumor. For each cell δ_j , we associate a discrete-time

Markov chain $(Z_k^{(j)})$, where $Z_k^{(j)}$ is the random variable denoting the state of the cell δ_j at time k . We assume that all the cells behave independently, and with the same dynamics, which implies that the Markov chains $\{(Z_k^{(j)})\}_{j \in \{0,1,\dots,n_0\}}$, are independent and have the same transition matrix $\mathbf{\Pi}$.

Our aim is to determine the probability distribution of the number of cells in each state. Let $X_k(i)$ be the random number of cells in state $i \in \{0, \dots, m\}$, at time k , among the n_0 initial cells. Since $Z_k^{(1)}, \dots, Z_k^{(n_0)}$ are *i.i.d.*, and follow a categorical distribution, then the state vector of the tumor $\mathbf{X}_k = (X_k(0), \dots, X_k(i), \dots, X_k(m))$ follows a multinomial distribution with parameters n_0 and $\nu_k = (\nu_k^0, \dots, \nu_k^m)$, where ν_k^i are the event probabilities defined by (13). The probability mass function of the multinomial distribution, $g(h_0, \dots, h_m, n_0, \nu_k^0, \dots, \nu_k^m) = Pr(X_k(0) = h_0, \dots, X_k(m) = h_m)$, is given by

$$g = \begin{cases} \frac{n_0!}{h_0! \dots h_m!} (\nu_k^0)^{h_0} \dots (\nu_k^m)^{h_m} & \text{if } \sum_{i=0}^m h_i = n_0 \\ 0 & \text{otherwise} \end{cases} \quad (14)$$

where h_i , $i \in \{0, \dots, m\}$, are non-negative integers. The average number of cells in state i at time k is

$$E(X_k(i)) = n_0 \nu_k^i = n_0 \Pi^k(0, i). \quad (15)$$

3.5 Number of surviving cells

In the *multinomial* model, the number of surviving cells after the k^{th} dose fraction is given by

$$N_k = X_k(0) + \dots + X_k(m-1) = n_0 - X_k(m). \quad (16)$$

Since $X_k(m) \sim \mathcal{B}(n_0, \Pi^k(0, m))$, then

$$N_k \sim \mathcal{B}(n_0, 1 - \Pi^k(0, m)). \quad (17)$$

This implies that :

$$E(N_k) = n_0 (1 - \Pi^k(0, m)) \quad (18)$$

and

$$\text{Var}(N_k) = n_0 (1 - \Pi^k(0, m)) \Pi^k(0, m). \quad (19)$$

4. TUMOR CONTROL PROBABILITY

The probability that no cancer cell remains in a tumor after radiation is known as the tumor control probability (TCP). This probability may be useful to evaluate either the quality of a treatment planning or for the optimization process.

4.1 Classical expressions of TCP

Two formulations of TCP are generally used in radiotherapy planning:

- if the number of surviving cancer cells follows a binomial distribution, then

$$TCP = (1 - p_c)^{n_0}; \quad (20)$$

- and if it follows a Poisson distribution, then

$$TCP = e^{-n_0 p_c}, \quad (21)$$

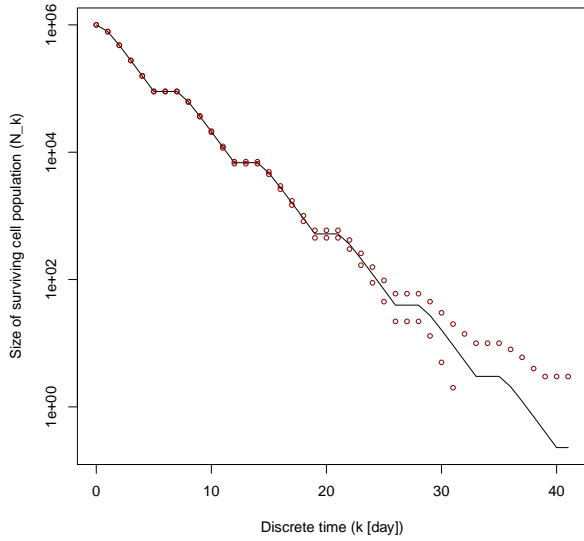


Fig. 5. Discrete-time response of the surviving cancer cells (mean response in solid line, 99.9%-confidence interval in dotted line, both computed in R with the function `qbinom`)

where p_c denotes the survival probability of a cancer cell after the radiation exposure and n_0 is the initial number of cancer cells in the tumor. Other TCP expressions are given in the setting of birth and death processes, and some of them depend explicitly on time [Zaider and Minerbo (2000); Dawson and Hillen (2006)]. The main drawback of these TCP expressions is to ignore the repair mechanism and the heterogeneous distribution of the cellular damages over the tumor and over time.

4.2 Multinomial model-based TCP

By considering the *multinomial* model defined in eq. (14), TCP_k is the probability that there is no living cell of type: $0, 1, \dots, m-1$, after delivery of the k^{th} dose fraction, *i.e.* the probability that all the cells are in state m at time k . Since

- each cell (supposed to be initially in state 0), among the n_0 cells, is in state m at time k with probability $\Pi^k(0, m)$;
- all the n_0 cells behave independently,

then

$$TCP_k = (\Pi^k(0, m))^{n_0}. \quad (22)$$

5. NUMERICAL ANALYSIS

We have implemented the *multinomial* model in the R¹ environment for statistical computing to determine the temporal response of surviving cancer cells to a classical radiation treatment and to analyze effects of three model parameters: q, r and m on the tumor control probability. In all these cases, the treatment scheduling is based on a static scheme composed of 5 dose fractions per week during six weeks.

¹ www.r-project.org/

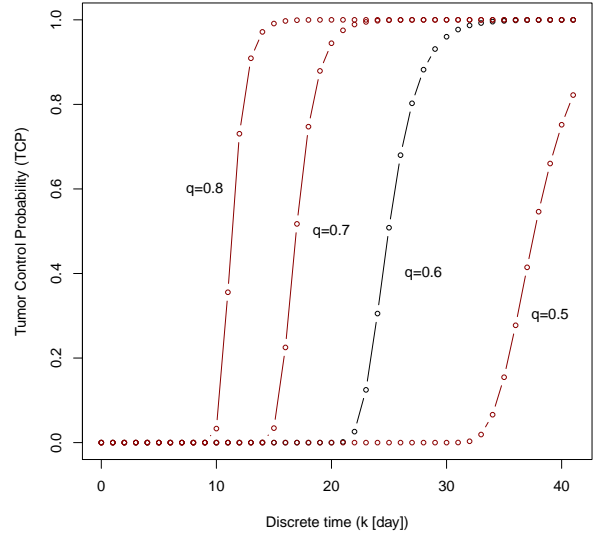


Fig. 6. Effects of the target deactivation parameter q on the TCP

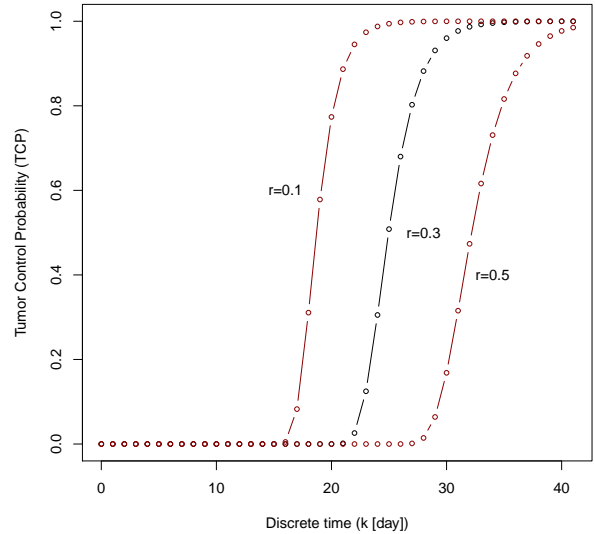


Fig. 7. Effects of the repair parameter r on the TCP

Fig. 5 describes on a semi-logarithmic plot the temporal response of the surviving cell population to the treatment. We clearly observe decrease periods of the number of surviving cells during the five days of treatment and stable periods during the week-ends.

Fig. 6, 7 and 8 display the effects of the model parameters q, r and m respectively on the TCP. When the probability q that a radiation particle inactivates a target is increasing, TCP is increasing. Inversely, the smaller r and m are, the larger TCP is. These three parameters also influence the slope of the transition period of TCP between the two extreme values 0 and 1.

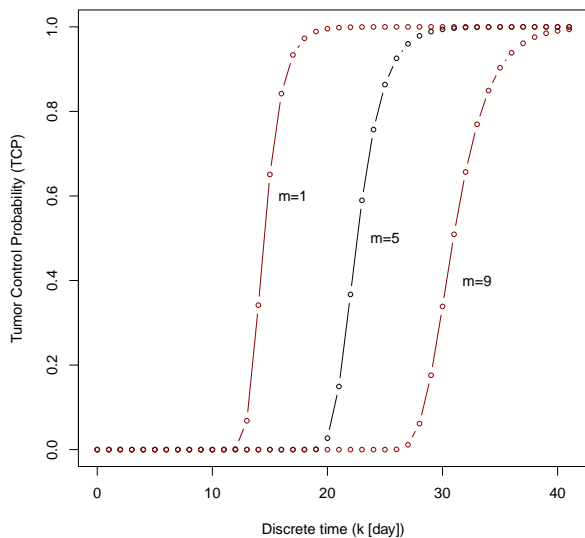


Fig. 8. Effects of the target parameter m on the TCP

6. CONCLUSIONS AND PERSPECTIVES

In this paper, we proposed a *multinomial* model for the radiation treatment of cancer cell, which takes into account (i) the variety of cell responses to treatment according to their biological states and (ii) the repair mechanisms that occur between dose fractions. Therefore, we can obtain a better estimation of the tumor growth during and after radiotherapy.

For future works, we plan to pursue several directions. The first one consists in comparing it with classical models used in Target theory in order to better emphasize its advantages and limits. Another direction is to study how this model can be used to control values of dose fractions and their number with the aim of achieving an efficient treatment.

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