8th IFAC Symposium on Biological and Medical Systems
The International Federation of Automatic Control
August 29-31, 2012. Budapest, Hungary

Model of cell damage in single session radiation treatments based on continuous-time Markov chains

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Abstract: A new continuous-time statistical model for modeling the effect of radiotherapy treatment is proposed. In contrast with classical models, it takes in account heterogeneity of cell damage and repair. In this paper, a bi-scale continuous-time model is derived to describe tumor and normal tissue lifespans. We show that the cell and the tumor lifespans can be determined. The tumor control probabilities and normal tissue complication probabilities are expressed. The model has been implemented into Matlab and numerical simulations have emphasized the effects of the model parameters on the model output.

Keywords: cancer, radiotherapy, continuous-time Markov chain, cell damage heterogeneity, lifespan, optimization treatment.

1. INTRODUCTION

One of the common therapies used to treat cancer consists in using ionizing (X-ray) or non-ionizing (light) radiations to cause a variety of possible lesions in cells (Curtis, 1986). Mathematical modeling may help to quantify the effects of radiation-based treatments on cell populations. It can be used to predict tumor growth and cancer spread, but also allows to determine the effectiveness of a specific treatment.

In a previous paper (Keinj et al., 2011), the authors studied the cell response to treatment and the tumor growth by considering Markov chains. The discrete times correspond to the successive times of application of radiation dose fractions. In this paper, we consider continuous-time processes to model the tumor response during the continuous application of radiation dose in treatments such as permanent brachytherapy in which the duration of the total dose may vary from a few weeks to a month, or photodynamic therapy, where the duration of the light dose may vary from seconds to tens of minutes. The proposed bi-scale model reproduces both damages in cell and tumor scales. At the cell scale, the damage level is described by a discrete-state variable. We show that the probability to be in a given state follows a system of linear differential equations. We also establish the lifespan model of a cancer cell and the one of a tumor.

Two probabilities are generally involved in the design of a treatment plan in radiotherapy : (i) the tumor control probability (TCP) and (ii) the normal tissue complication probability (NTCP). The TCP is the probability that all cancer cells are dead in the irradiated region, see (Zaider and Minerbo, 2000; Dawson and Hillen, 2006). The NTCP is another probability that measures the sensitivity of normal tissue to radiations. These two probabilities are strongly related to the cell and tumor lifespans. In this paper, we use this relationship to give new expressions of TCP and NTCP suited to single session treatments.

This paper is organized as follows. In Section 2, we develop a continuous-time Markov chain model of a cancer cell response to radiation treatment. In Section 3, we express the lifespans of tumors and normal tissues and we give a detailed calculation of their properties. In section 4, we formulate the new expressions of TCP and NTCP.

2. MARKOV MODEL OF THE CELL STATE

In this section, the behavior of a single cell during the treatment is considered.

2.1 Reminders related to the multinomial model

Let us briefly recall the main features of the model which has been developed in (Keinj et al., 2011, 2012) in the context of fractioned radiotherapy treatment:

978-3-902823-10-6/12/$20.00 © 2012 IFAC

10.3182/20120829-3-HU-2029.00081

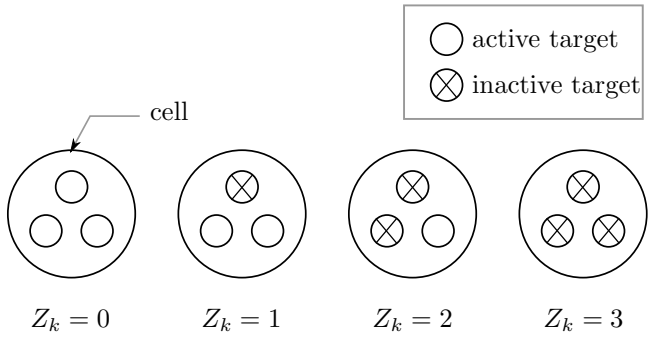

Fig. 1. Damage state Z_k of a cell with $m = 3$ targets

- each cell has m targets,
- each target can be deactivated by a single hit with a radiation particle with probability q,
- death occurs when the m targets are inactive,
- between two consecutive doses a target can be reactivated (repair process) with probability r, while the cell is still alive.

Figure 1 shows the case of a 3-target cell and the corresponding cell states.

Let Z_k be the random number of deactivated targets in the cell at time k, *i.e.* after the k^{th} dose fraction. It is supposed that $(Z_k)_{k\geqslant 0}$ is a Markov chain which takes its values in $\{0, 1, \ldots, m\}$. Denote $\mathbf{\Pi}$ the associated transition matrix. The effect of the treatment and the repair process are taken into account by supposing that $\mathbf{\Pi} = \mathbf{PR}$ where:

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

$$\mathbf{R}(i,j) = \begin{cases} \binom{i}{i-j} r^{i-j}(1-r)^{j} & j \leqslant i < m \\ 0 & i < j, \end{cases} \quad (2)$$

where by convention the first row and column are labeled 0.

Note that q and hence α, depends on the applied radiation dose u. Polynomial models, like the Linear Quadratic model (Fowler, 1989), can be used to describe this relationship between α and u.

2.2 Toward the model of continuous-time Markov chain

Suppose that $h = \Delta t$ is a small interval of time. For a given cell, let Z_{kh} be the number of deactivated targets at time $t = kh$. It is assumed that $(Z_{kh})_{k\geqslant 0}$ is a Markov chain with transition $\mathbf{\Pi}_h$ depending on the three parameters m, q_h and r_h. The parameter q_h is the probability that an active target is deactivated in any small interval $[kh, (k+1)h]$. Similarly, r_h is the probability that an inactive target in a living cell is repaired during the interval $[kh, (k+1)h]$. Since h is small, it seems natural to assume that both q_h and r_h are small: between two consecutive times t and $t + \Delta t$, the cell stays mainly in the same state: changes are possible but with a low probability. More precisely, we suppose:

$$q_h = \alpha h + o(h) \quad (3)$$

$$r_h = \rho h + o(h) \quad (4)$$

with $\alpha, \rho > 0$ and $\lim_{h\to 0} \frac{o(h)}{h} = 0$.

From equations (1) and (3), it is easy to show that:

$$\begin{cases} \mathbf{P}_h(i,i) = 1 - \alpha(m-i)h + o(h) & \\ \mathbf{P}_h(i,i+1) = \alpha(m-i)h + o(h) & i < m \\ \mathbf{P}_h(i,j) = o(h^2) & j > i+1 \\ \mathbf{P}_h(i,j) = 0 & j < i \end{cases} \quad (5)$$

and from (2) and (4), we obtain:

$$\begin{cases} \mathbf{R}_h(i,i) = 1 - i\rho h + o(h) & \\ \mathbf{R}_h(i,i-1) = i\rho h + o(h) & i > 0 \\ \mathbf{R}_h(i,j) = o(h^2) & j < i-1 \\ \mathbf{R}_h(i,j) = 0 & j > i \end{cases} \quad (6)$$

So, using classical analysis, we can deduce that the transition probabilities $\mathbf{\Pi}_h(i,j) = \mathbf{P}_h\mathbf{R}_h$ of $(Z_{kh})_{k\geqslant 0}$ is given by the following identities:

$$\mathbf{\Pi}_h(i,j) = Pr(Z_{kh+h} = j | Z_{kh} = i) =$$
$$\begin{cases} \alpha(m-i)h + o(h) & j = i+1, \ 0 \leqslant i \leqslant m-1 \\ 1 - [\alpha(m-i) + i\rho]\, h + o(h) & j = i, \quad 0 \leqslant i \leqslant m-1 \\ i\rho h + o(h) & j = i-1, \ 1 \leqslant i \leqslant m-1 \\ 1 & j = i = m \\ 0 & \text{else.} \end{cases}$$

2.3 Definition of the continuous-time Markov chain (Z_t)

Let Z_t be the number of deactivated targets in a cell at time t. We suppose that $(Z_t)_{t\geqslant 0}$ is a continuous-time Markov chain. Previous analysis suggests to set:

$$Pr(Z_{t+h} = j | Z_t = i) = \boldsymbol{\pi}_h(i,j) \quad (7)$$

if $t \geqslant 0$, $h > 0$, $0 \leqslant i, j \leqslant m$ and

$$\boldsymbol{\pi}_h(i,j) = \begin{cases} 1 + \mathbf{Q}(i,j)h + o(h) & \text{if } j = i \\ \mathbf{Q}(i,j)h + o(h) & \text{if } j \neq i \end{cases} \quad (8)$$

where $\mathbf{Q}(i,j)$ is defined by:

$$\mathbf{Q}(i,j) =$$
$$\begin{cases} \alpha(m-i) & j = i+1, \ 0 \leqslant i \leqslant m-1 \\ -[\alpha(m-i) + i\rho] & j = i, \quad 0 \leqslant i \leqslant m-1 \\ i\rho & j = i-1, \ 1 \leqslant i \leqslant m-1 \\ 0 & \text{else.} \end{cases} \quad (9)$$

We deduce easily from (9):

$$\begin{cases} \mathbf{Q}(i,j) \leqslant 0 & \text{if } i = j \\ \mathbf{Q}(i,j) \geqslant 0 & \text{if } i \neq j \\ \sum_{j=0}^{m} \mathbf{Q}(i,j) = 0 & 0 \leqslant i \leqslant m \end{cases} \quad (10)$$

As a consequence, Theorem 2.8.2 in (Norris, 1997) and (10) imply existence of a Markov chain $(Z_t)_{t\geqslant 0}$ with generator matrix $\mathbf{Q}$ and $\{0, 1, \ldots, m\}$-valued.

2.4 Probability distribution of Z_t

Given the generator matrix $\mathbf{Q}$, we can determine the transition probability matrix $\mathbf{\Pi}(t)$ with entries $\mathbf{\Pi}_t(i,j)$. Each entries is the probability for the cell to being in the state j at time $t \geqslant 0$ when its initial state is $Z_0 = i$:

$$\boldsymbol{\pi}_{i,j}(t) \triangleq Pr(Z_t = j | Z_0 = i) \quad 0 \leqslant i, j \leqslant m. \quad (11)$$