# Stochastic models for tumors submitted to a radiotherapy treatment

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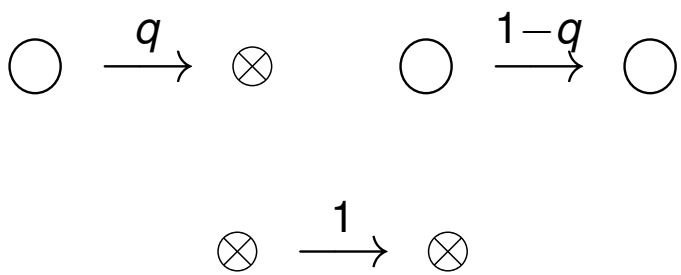
# 1. INTRODUCTION

1. Associated collaborators S. Pinel, M. Barberi-Heyob and T. Bastogne (CRAN).
2. The aim : a simple stochastic model.
3. The ionizations induced by radiation (radiotherapy) cause a variety of possible lesions in the cells and more specifically to DNA.
4. A bi-scale model which is a generalization of the target theory.

# Assumptions

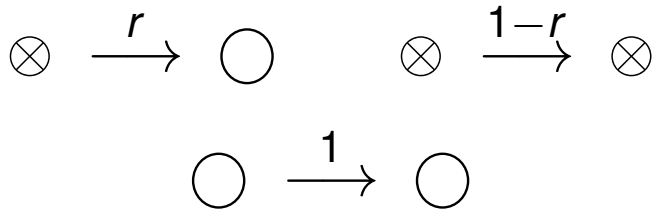
1. Time is discrete, one period = one day.
2. Each cell has $m$ targets. Death occurs when all the targets are inactive.
3. Each target may be made inactive after the application of a fraction dose $u_0$ of radiation, with probability $q$.



Moreover we have the LQ relation

$$q = \left(1 - \exp\{-\alpha u_0 - \beta u_0^2\}\right)^{1/m}.$$

4 Between two consecutive dose fractions if the cell is still alive then an inactive target can be repaired with probability $r$.




5 Behaviors of targets are independent.

# Definitions

1. Let $Z_k$ be the (random) number of deactivated targets in the cell at time $k$.
2. $k = 0$ corresponds to the beginning of treatment.
3. $(Z_k)$ is a Markov chain with transition probability matrix:

$$\Pi = \mathbf{PR}.$$

4. $(Z_k)$ is valued in $\{0, 1, \cdots, m\}$ and $m$ is an absorbing state.
5. A **tumor** is a collection of $n_0$ independent and non-interacting cells.

# Properties of the above model

1. The parameters are $m$, $q$ and $r$.
2. We can measure efficiency of the treatment with:
   1. lifetime of cells and lifetime of the tumor ([KBV], JTB 2012)
   2. The **Tumor Control Probability (TCP)** :

$$TCP_k := \Big(P(Z_k = m | Z_0 = i_0)\Big)^{n_0}$$

   where $n_0$ is the initial number of cells.
3. Easy numerical calculations of the above quantities.
4. An "optimization" of the treatment via a balance between efficiency and the significant damages on the adjacent normal tissues is possible

# Limitations

1. A slightly more general model can take into consideration proliferation of cells but with an unsatisfactory way.
2. It clear that :

$$TCP_k := \Big(P(Z_k = m | Z_0 = i_0)\Big)^{n_0} \to 0, \quad as\ n_0 \to \infty.$$

Note that

$$TCP_k = \Big[\Pi^k(i_0, m)\Big]^{n_0}.$$

## 2. ONE WAY TO RECOVER EFFICIENCY

(joint work with T. Bastogne)

The main idea is to choose $q$ as an increasing function of $n_0$ so that:

$$\lim_{n_0 \to \infty} q(n_0) = 1, \lim_{n_0 \to \infty} TCP_k = 1.$$

**Theorem 1**

*Let* $0 \leq i_0 < m$ *and* $\varepsilon := 1 - q$. *Then*

$$1 - \Pi^k(i_0, m) \sim (m - i_0)\big(1 + (m-1)r\big)^{k-1} \varepsilon^k, \quad \varepsilon \to 0.$$

**Remark** *Since the coefficient in front of* $\varepsilon^k$ *is explicitly given in terms of* $i_0, m, r$ *and* $k$. *This permits interpretations.*

# Few words about the proof

Using definition of the matrix **P**, it can be proved easily that **P** admits the following asymptotic expansion :

$$\mathbf{P} = \mathbf{P}_0 + \varepsilon \mathbf{P}_1 + \varepsilon^2 \mathbf{P}_2(\varepsilon).$$

Since $\Pi = \mathbf{PR}$ we have :

$$\Pi = A_0 + \varepsilon A_1 + \varepsilon^2 A_2(\varepsilon)$$

and

$$\begin{aligned} \Pi^k &= \Big(A_0 + \varepsilon A_1 + \varepsilon^2 A_2(\varepsilon)\Big)^k \\ &= B_0 + \varepsilon B_1 + \varepsilon^2 B_2(\varepsilon). \end{aligned}$$

Therefore

$$\Pi^k(i_0, m) = 1 + a\varepsilon + \varepsilon o(1).$$

The above Theorem says there are non-trivial cancelations.

## Proposition 2

*Let* $\theta_0 \in ]0,1[$. *Let* $q$ *such that*

$$\varepsilon = 1 - q := \frac{\psi_1}{n_0^{1/k}}$$

*where*

$$\psi_1 = \psi_1(i_0, m, r, k, \theta_0) := \left( \frac{-\ln(\theta_0)}{(m - i_0)(1 + (m-1)r)^{k-1}} \right)^{1/k}$$

*Then*

$$\lim_{n_0 \to \infty} TCP_k = \theta_0.$$

## Application

Recall that $q = \left(1 - \exp\{-\alpha u_0 - \beta u_0^2\}\right)^{1/m}$. Suppose that $\beta = 0$. Since $u_0$ is large, then:

$$q = \left(1 - e^{-\alpha u_0}\right)^{1/m} = 1 - \frac{e^{-\alpha u_0}}{m} + \cdots .$$

and $1 - q = \dfrac{\psi_1}{n_0^{1/k}}$ as soon

$$u_0 \sim \frac{\ln(n_0)}{\alpha k} \quad \left(\Rightarrow TCP_k \sim \theta_0\right).$$

Let us introduce a new parameter to measure efficiency of the treatment:

$$\widehat{TCP}_k(\alpha) := \mathbb{P}\left(\frac{N_k}{n_0} \leq \alpha\right)$$

where $\alpha \in [0, 1[$ and $N_k$ is the number of cells still alive at time $k$.

- The goal is to have
$$\widehat{TCP}_k(\alpha) \approx 1.$$
- Note that:
$$TCP_k \leq \widehat{TCP}_k(\alpha)$$
and
$$TCP_k = \widehat{TCP}_k(0).$$

## Theorem 3

*Let $\theta_0 \in ]0,1[$. Suppose that $\alpha \approx 0$ and $n_0$ is large.*
*If we take:*

$$1 - q = \psi_2 \times \left(1 - \psi_3 \sqrt{1-\alpha}\, \frac{1}{\sqrt{\alpha n_0}}\right)^{1/k} \alpha^{1/k}$$

*then:*

$$\widehat{TCP}_k(\alpha) \approx \theta_0$$

*where*

$$\psi_2 := \left(\frac{1}{(m-i_0)\left(1+(m-1)r\right)^{k-1}}\right)^{1/k}, \quad \psi_3 := -2\ln(1-\theta_0).$$

In particular if moreover $n_0\alpha \gg 1$ then:

$$1 - q \approx \psi_2 \alpha^{1/k} \quad \Rightarrow \quad \widehat{TCP}_k(\alpha) \approx \theta_0.$$

**Remark** *Recall that* $1 - q = \dfrac{\psi_1}{n_0^{1/k}} \quad \Rightarrow \quad TCP_k \approx \theta_0.$

# 3. A BRANCHING MODEL

(a joint work in progress with T. Bastogne and J.-L. Marchand)

We consider a new model where the cells are labeled $abc$ where:

1. $a \in \{0, 1, 2\}$. The cycle of a $2bc$ cell is 24 hours, the one of $1bc$ cell is 36 hours. A cell $0bc$ is quiescent.
2. $b = 1$ means that the cell has a restoration capacity, and $b = 0$ otherwise.
3. A stable cell $ab0$ always ends its cycle.
4. A total of 10 possible states.

**Examples**

- The cell 100 has a faithful proliferation 36H later and $100 \rightarrow 101 + 101$.
- The cell 201 can have either a faithful proliferation 24H later $201 \rightarrow 201 + 201$, or a degradation 1H later $201 \rightarrow 100$, or dies.

Let

- $Z_e(t)$ be the number of cells in state $e$ at time $t$.
- $Z^*(t)$ be the number of cells which are alive at time $t$.

**Few features of the model**

- $\big(Z_e(t)\big)$ is a multitype branching process which is non-homogeneous in time.
- 14 parameters are necessary to describe the offspring distributions.
- This model is related to a phototherapy treatment, one shot.
- In practice, possibility to measure $Z^*(t)$ and therefore to have the empirical distribution of $\big(Z^*(t_1), \cdots, Z^*(t_k)\big)$.

# Two main results

1. We have recursive equations with allow to calculate numerically the Laplace transform of $Z^*(t)$ and its first moment, for $t$ less than one month.
2. The model is identifiable, i.e. if for any $t$,

$$Z^*(\theta, t) \overset{(d)}{=} Z^*(\theta', t).$$

then

$$\theta = \theta'.$$