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Stochastic Modeling of Dormant Cancer Tumors

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ABSTRACT

During tumor progression, many interactions are established between cancer cells and their micro-environment. These interactions promote the survival of cancer cells and resistance to therapy. This ability of the tumor to develop resistance to therapy resides in the mechanism of dissemination of cancer cells from the primary tumor. Disseminated cancer cells may remain dormant for a certain period of time. These dormant cells reactivate under the influence of an environment and cause therapeutic failure. In this paper, we propose a stochastic computational model of tumor dormancy and resistance. This mathematical model is based on the description of the tumor cell colony as a branching process. With this model, we identify the patient's status at diagnosis, and optimized treatment strategies by investigating the therapeutic efficiency, resistance and tumor relapse.

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1 Introduction

Cancer represents one of the major menaces to human health. This disease refers to an uncontrolled growth of cells invading and asphyxiating neighbouring organs. Cancer therapy has long had as its sole objective the direct elimination of tumor cells (Fridman and Sautès-Fridman, 2014). Targeted therapy, surgery, radiotherapy, chemotherapy, hormone therapy and immunotherapy want to remove, block proliferation or destroy cancer cells. Many cancers can be cured by treating them. But in some cases resistance happens (Baar et al., 2016; Werner-Klein, 2019; Goss and Chambers, 2010). Tumor resistance has received a much of attention in the medical and biological domain (Birbrair, 2020; Marx, 2018; Frangioni, 2008; Goss and Chambers, 2010; Werner-Klein, 2019; Gelao et al., 2013; Dagogo-Jack and Shaw, 2017; Klffel and Schatton, 2012; Almog, 2010; Aguirre-Ghiso, 2011; Sosa et al., 2013; Robert, 2013; Borriello and DeClerck, 2014; Quesnel, 2008; Albrengues et al., 2014; Azzi and Gavard, 2014; Hubert and Abastado, 2014; Bidard and Poupon, 2012; Fridman and Sautès-Fridman, 2014; Boisgerault and Richard, 2014; Bensimon, 2012), as well as in mathematical modeling communities over the last decades (de Pillis and Radunskaya, 2003; Eftimie et al., 2011; d'Onofrioa et al., 2010; Baar et al., 2016; Haeno et al., 2012; Sun et al., 2016; Zapperi et al., 2012; Iwasa et al., 2006; David, 2006; Goldstein, 1989).

The significant progress in the research of the cause of tumor therapeutic resistance was carried out. Evidence suggests that cancer cells disseminated from the primary tumor may remain dormant (Almog, 2010; Aguirre-Ghiso, 2011; Sosa et al., 2013; Goss and Chambers, 2010; Klffel and Schatton, 2012; Robert, 2013). Dormant cells define themselves as malignant tumor cells that have escaped treatment of the primary tumor, remain at the tumor site in an asymptomatic, dormant stage for substantial periods of time (Aguirre-Ghiso, 2011; Klffel and Schatton, 2012) without proliferation (Bensimon, 2012; Quesnel, 2008). Then, in response to signals which have not been completely elucidated (Hubert and Abastado, 2014; Boisgerault and Richard, 2014), some of these cells resume proliferation and develop into micro-metastases and then macro-metastases (Sosa et al., 2013; Bidard and Poupon, 2012; Marx, 2018). This phenomenon may exist after a treatment in the form of a prolonged asymptomatic residual disease (Almog, 2010; Goss and Chambers, 2010) and is objectified through relapses or recurrences sometimes occurring several decades after the initial diagnosis (Robert, 2013; Quesnel, 2008). As science begins to learn more about cancer cell biology, it therefore seems reasonable and desirable to model resistance to therapy taking into account asymptomatic residual disease.

Mathematical modeling is very useful in the study and understanding of resistance to cancer therapy. Extensive literature has been devoted to the mathematical modeling of cancer tumors (de Pillis and Radunskaya, 2003; Eftimie et al., 2011; d'Onofrioa et al., 2010; Baar et al., 2016; Haeno et al., 2012; Sun et al., 2016; Zapperi et al., 2012; Iwasa et al., 2006; Wodarz and Komarova,

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2014; Foo and Leder, 2013) and the references therein. Most of these models are constructed according to different types of criteria such as the scale of the study (macroscopic or microscopic), the data used, or possible applications. Based on the results of the Diefenbach experiments, de Pillis and Radunskaya (2003) have developed a mathematical model of tumor growth using a system of differential equations to address some of the questions that arise regarding the mechanisms involved in the immune response to a tumor challenge. To model the metastatic invasion of pancreatic cancer, Haeno et al. (2012) developed a binary branching model. Sun et al. (2016) developed a diffusion model to describe tumor resistance during treatment. To study the evolution of cellular interactions during the immune response, Baar et al. (2016) used a logistic birth and death process model. Despite that Mathematical models have significantly advanced understanding of tumor initiation and progression, this area dormant tumors has, to date, been under-investigated.

In this paper, we design and analyze a stochastic mathematical model of tumor dormancy and resistance. This mathematical model is based on the description of the tumor cell colony as a branching process. The construction of this model is motivated by the experimental model of tumor dormancy proposed by Quesnel (2008) and the work of Hubert and Abastado (2014). In Quesnel's model, certain induced tumors remain dormant until the patient's adaptive immunity is altered, which promotes tumor development. However, dormant cells can come out of their dormancy at any moment and start proliferating again (Hubert and Abastado, 2014). We will answer the following questions by constructing a mathematical model that takes into account the awakening of dormant cells that takes place at any time during and after treatment: What is the patient's status at diagnosis? What treatment strategy permits to avoid tumor resistance during treatment? When does the reappearance of cancer after remission occur?

2 Tumor Growth Model

2.1 Biological Description

Consider the expansion of cancer cells starting from a single cell that has not developed the ability to resist a therapy. These cells are called type-0 cells. Type-0 cells divide and give rise to two types-0 cells. Type-0 cells die under the effect of treatment or natural death, depending on environmental conditions. Type-0 cells can also enter dormancy and give rive to type-1 cells. Type-1 cells remain at the latent tumor site, without tumor growth. Some of these cells resume proliferation and give rise to type-0 cells or to cells that resist the therapy previously used. Cells that resist this therapy are called type-2 cells. The type-2 cells divide and give rise to two types-2 cells. Type-2 cells die from natural death, depending on environmental conditions, or from a treatment other than that previously used against cells of type-0. We have illustrated all these phenomena in Figure 1.

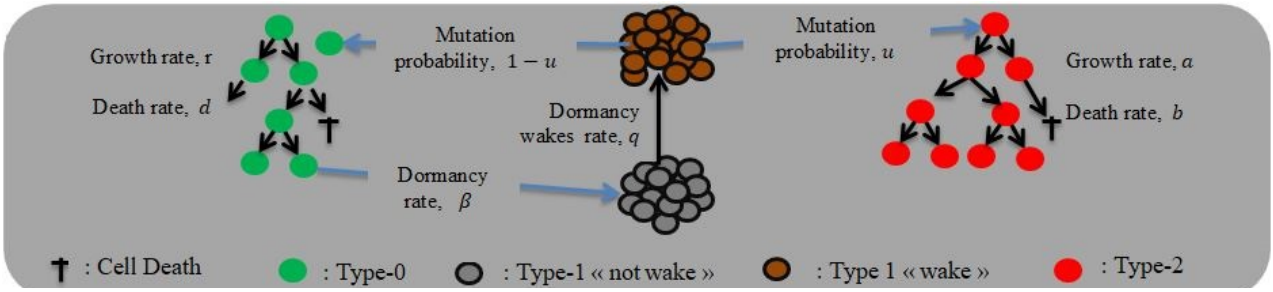

Figure 1: Mechanisms for proliferation of dormant tumors. Type-0 cells (green) divide at rate r and die at rate d per unit time. Type-0 cells give rise to type-1 (grey) at rate β. Type-1 cells remain at the tumor site in a non-proliferate state and with probability q, one of these cells (orange) enters tumor proliferation and give rise to type-0 cells with a probability $1-\mu$ or to type-2 cells (red) with a probability μ. Type-2 cells divide at rate a and die at rate b per unit time.

2.2 Stochastic Description

We now provide a more detailed mathematical description of the model we propose. We look at a random process that describes the population size dynamics. Every time of birth, the process increases by 1 and every time of death it decreases by 1. The times at which births and deaths occur are random. These processes are continuous-time Markov chains. There is a extensive literature on these processes and we will not be exhaustive on biography. For example, we will refer to the books of Norris (1997), Anderson (1991), Allen (2003), Durrett (1999), Karlin and Taylor (1995), Pardoux (2009) or Bhattacharya and Waymire (1990).

We adopt the following notations, which will be used in all of this manuscript

- $K \in \mathbb{R}_+$ the tumor load capacity. That is, the largest number of tumor cells that the body can support.

- $\Lambda_K = \left\{n = (n_0, n_1, n_2) \in \mathbb{N}^3 \;\middle|\; n_0 + n_1 + n_2 \in \{0, \ldots, K\}\right\}$ state space;
- $t_\iota, t \in \mathbb{R}_+$ the times and ι time index;
- $i = 0, 1, 2$ cell type index;
- $X_K^i(t)$ number of individuals of type i at time t;
- $X_K(t) = \left\{X_K^i(t)\right\}_{i=0,1,2}$ the population size at time $t \geq 0$;
- $\triangle t$ sufficiently small period of time;
- $o(\triangle t)$ ("little oh" $\triangle t$) the Landau order symbol.

Let $\{X_K(t), t \geq 0\}$ a process defined on a probability space $(\Omega, \mathcal{F}, \mathbb{P})$, with values in a set Λ_K, such that, for all finite set $0 \leq t_1 < t_2 < \cdots < t_\iota < t_{\iota+1}$ of "times," and corresponding set $i_1, i_2, \ldots, i_{\iota-1}, n, k$ of states in Λ_K with

$$\mathbb{P}\left[X_K(t_\iota) = n, X_K(t_{\iota-1}) = t_{\iota-1}, \ldots, X_K(t_1) = t_1\right] > 0,$$

we have

$$\mathbb{P}\left[X_K(t_{\iota+1}) = k \;\middle|\; X_K(t_\iota) = n, X_K(t_{\iota-1}) = i_{\iota-1}, \ldots, X_K(t_1) = i_1\right] = \mathbb{P}\left[X_K(t_{\iota+1}) = k \;\middle|\; X_K(t_\iota) = n\right].$$

We assume each of the following:

(i) For $t = 0, X_K(0) = (1, 0, 0)$.

(ii) For all $i = 0, 1, 2$ and all $t \geq 0, X_K^i(t) = \sum_{j=1}^K \delta_i\left(\text{type}_j(t)\right)$ where δ_i denotes the Dirac measure at i and $\text{type}_j(t)$ denotes the type of j^{th}-individual in the tumor population at the time t. The process $\left\{X_K^i(t), t \geq 0\right\}$ $(i = 0, 1, 2)$ takes values in $\{0, \ldots, K\}$ and, indicates the number of individuals of type i at time t.

(iii) $\{X_K(t), t \geq 0\}$ is a continuous-time Markov chain, homogeneous, with values in a set Λ_K. So, for all $s, t \geq 0$ such that $0 \leq s \leq t$ and all $n, k \in \Lambda_K, \mathbb{P}\left[X_K(t) = k \;\middle|\; X_K(s) = n\right] = \mathbb{P}\left[X_K(t-s) = k \;\middle|\; X_K(0) = n\right]$ and the function $p_{n,k}(t) \overset{def}{=} \mathbb{P}\left[X_K(t) = k \;\middle|\; X_K(0) = n\right]$ is called the transition function of the process (Anderson, 1991, Chapter 1, Section 1.1).

(iv) In a sufficiently small period of time $\triangle t$ between t and $t + \triangle t$, the evolution of this population is described by eight events. If at time $t \geq 0$, the size of the population is $n = (n_0, n_1, n_2) \in \Lambda_K$, then, between the times t and $t + \triangle t$,

1. the probability that a type-0 cell gives birth to a type-0 cell is $rn_0 \triangle t + o(\triangle t)$;
2. the probability that a type-0 cell gives birth to a type-1 cell is $\beta n_0 \triangle t + o(\triangle t)$;
3. the probability that a type-1 cell gives birth to a type-0 cell is $(1-\mu) qn_1 \triangle t + o(\triangle t)$;
4. the probability that a type-1 cell gives birth to a type-2 cell is $\mu q n_1 \triangle t + o(\triangle t)$;
5. the probability that a type-2 cell gives birth to a type-0 cell is $an_2 \triangle t + \circ(\triangle t)$;
6. the probability that type-0 cells decrease by one is $dn_0 \triangle t + o(\triangle t)$;
7. the probability that type-2 cells decrease by one is $bn_2 \triangle t + o(\triangle t)$;
8. the probability that tumor population continues to live without a change of state est

$$1 - \left[(r + d + \beta) n_0 + qn_1 + (a + b) n_2\right] \triangle t + o(\triangle t).$$

(v) The probability of more than one birth in time $\triangle t$ in negligible. The assumption that the probability is negligible means it is of order $\triangle t$ or $o(\triangle t)$. That is $\lim_{\triangle t \to 0} \triangle t / o(\triangle t) = 0$ or $o(\triangle t)$ approaches zero faster than $\triangle t$.

Definition 2.1. *The process $\{X_K(t), t \geq 0\}$ is called a birth and death process with mutation, with values in Λ_K. For $\triangle t$ sufficiently small, the transition probabilities satisfy*

$$p_{n,k}(\triangle t) = \begin{cases} rn_0 \triangle t + o(\triangle t) & \text{if} \quad k = (n_0 + 1, n_1, n_2), \\ dn_0 \triangle t + o(\triangle t) & \text{if} \quad k = (n_0 - 1, n_1, n_2), \\ \beta n_0 \triangle t + o(\triangle t) & \text{if} \quad k = (n_0 - 1, n_1 + 1, n_2), \\ (1-\mu) qn_1 \triangle t + o(\triangle t) & \text{if} \quad k = (n_0 + 1, n_1 - 1, n_2), \\ \mu q n_1 \triangle t + o(\triangle t) & \text{if} \quad k = (n_0, n_1 - 1, n_2 + 1), \\ an_2 \triangle t + o(\triangle t) & \text{if} \quad k = (n_0, n_1, n_2 + 1), \\ bn_2 \triangle t + o(\triangle t) & \text{if} \quad k = (n_0, n_1, n_2 - 1), \\ 1 - \Lambda(n) \triangle t + o(\triangle t) & \text{if} \quad k = (n_0, n_1, n_2), \\ o(\triangle t) & \text{otherwise}, \end{cases} \tag{1}$$

for all $n = (n_0, n_1, n_2) \in \Lambda_K$ where $\Lambda(n) = (r + d + \beta) n_0 + qn_1 + (a + b) n_2, \forall n = (n_0, n_1, n_2) \in \Lambda_K$.

3 Model Properties

Let's present some results on the continuous-time Markov chain, useful for the rest of this work. We consider the instant $t_0 \geq 0$ and the notations introduced in Section 2 with the process $\{X_K(t), t \geq t_0\}$ having state space Λ_K.

3.1 Q-matrix

The process $\{X_K(t), t \geq t_0\}$ is a continuous-time Markov chain. It is known that continuous-times Markov chain is characterized by its infinitesimal generator, that is its Q-matrix (Norris, 1997; Allen, 2003; Anderson, 1991). Let $Q = \left\{q_{n,k}\right\}_{n,k\in\Lambda_K}$ the Q-matrix of the process $\{X_K(t), t \geq t_0\}$. The $q_{n,k}$ are called transition rates. The transition probabilities $p_{n,k}$ are used to derive transition rates $q_{n,k}$ (Allen, 2003, page 175 and page 180). By Allen (2003), we have the following:

Definition 3.1. *The elements $q_{n,k}$ of the matrix Q are defined by*

$$q_{n,k} = \begin{cases} rn_0 & \text{if} \quad k = (n_0+1, n_1, n_2), \\ dn_0 & \text{if} \quad k = (n_0-1, n_1, n_2), \\ \beta n_0 & \text{if} \quad k = (n_0-1, n_1+1, n_2), \\ (1-\mu)\, qn_1 & \text{if} \quad k = (n_0+1, n_1-1, n_2), \\ \mu q n_1 & \text{if} \quad k = (n_0, n_1-1, n_2+1), \\ an_2 & \text{if} \quad k = (n_0, n_1, n_2+1), \\ bn_2 & \text{if} \quad k = (n_0, n_1, n_2-1), \\ -\Lambda(n) & \text{if} \quad k = (n_0, n_1, n_2), \\ 0 & \text{otherwise}, \end{cases} \tag{2}$$

for all $k, n \in \Lambda_K$.

Let $P(t) = \left\{p_{n,k}(t)\right\}_{n,k\in\Lambda_K}$, for all $t \geq t_0$. Matrix $P(t)$ is called the transition function of the random variable $X_K(t)$. This matrix satisfies the following result, which can be found in, for example, Norris (1997, Theorem 2.1.1, page 62).

Theorem 3.2. *The transition function satisfies the following properties:*

1. *$\{P(t), t \geq t_0\}$ is the unique solution to the backward equation*

$$\frac{dP(t)}{dt} = QP(t) \text{ with } P(t_0) = I, \text{ that is } \frac{dp_{n,k}(t)}{dt} = \sum_{l\in\Lambda_K} q_{n,l}p_{l,k}(t), \ \forall n,k \in \Lambda_K. \tag{3}$$

2. *$\{P(t), t \geq t_0\}$ is the unique solution to the forward equation*

$$\frac{dP(t)}{dt} = P(t)Q \text{ with } P(t_0) = I, \text{ that is } \frac{dp_{n,k}(t)}{dt} = \sum_{l\in\Lambda_K} p_{n,l}(t)q_{l,k} \ \forall n,k \in \Lambda_K. \tag{4}$$

3.2 Long-Time Behavior

An important feature of stochastic models opposed to deterministic models is that populations can become extinct (Baar et al., 2016). Since extinction appears to be assured, let's look- at the stationary probability distribution and the explosion of the continuous time Markov $\{X_K(t), t \geq t_0\}$. For precise mathematical description of these results, see, for example, Reuter (1961), Iglehart (1964) and Anderson (1991).

Proposition 3.3. *The continuous-time Markov chain $\{X_K(t), t \geq t_0\}$ satisfying (1) is non-explosive, and admits a unique positive stationary probability distribution if* $\min\{d, b\} < \max\left\{r+\beta, q, a\right\}$.

Proof. Matrix Q is irreducible and regular. So we show that Q is positive recurrent. We use Proposition 3.2 from Anderson (1991, page 310) to show that Q is positive recurrent. For all $k = 0, 1, \ldots$ we pose the following:

$$\mathcal{E}_k = \left\{n = (n_0, n_1, n_2) \in \Lambda_K \setminus \{(0,0,0)\} \,\middle|\, n_0 + n_1 + n_2 = k\right\}.$$

We define $\mu_k = \min_{n\in\mathcal{E}_k}\{dn_0 + bn_2\}$ and $\lambda_k = \max_{n\in\mathcal{E}_k}\left\{(r+\beta)n_0 + qn_1 + an_2\right\}$, and we pose $\pi_k = \frac{\lambda_0\lambda_1\cdots\lambda_{k-1}}{\mu_1\mu_2\cdots\mu_k}$. Then, Q is positive recurrent if $\sum_{k=0}^{\infty}\pi_k < +\infty$. It can be verified easily that the Markov chain $\{X_K(t), t \geq t_0\}$ satisfies the preceding

condition. There exists constants $\mu = \min\{d, b\}$ and $\lambda = \max\{r+\beta, q, a\}$ such that $\lambda_k \leq \lambda k$ and $\mu_k \geq \mu k$. Using these inequalities, the preceding summation becomes

$$\sum_{k=1}^{+\infty} \frac{\mu_k \dots \mu_1}{\lambda_k \dots \lambda_1} \leq \sum_{k=1}^{+\infty} \left(\frac{\mu}{\lambda}\right)^k = \begin{cases} +\infty, & \text{if } \lambda < \mu, \\ < \infty, & \text{if } \lambda > \mu. \end{cases}$$

Thus Q is positive recurrent iff $\lambda > \mu$. From where, the continuous-time Markov chain $\{X_K(t), t \geq t_0\}$ satisfying (1) is non-explosive, and admits a unique positive stationary probability distribution if $\mu = \min\{d, b\} < \lambda = \max\{r+\beta, q, a\}$. □

Note: Later, we assume that condition $\min\{d, b\} < \max\{r+\beta, q, a\}$ is verified.

3.3 Expected Number of Each Type

We study the expected number of each cell type. The direct Kolmogorov equation gives a calculation method from the probability generating function. For all $t \geq t_0$, the probability generating function of $X_K(t)$ given $X_K(t_0) = n^* \in \Lambda_K$, denoted as $G_t(. \mid n^*)$, is defined as

$$G_t(s \mid n^*) = \mathbb{E}\left[s_0^{X_K^0(t)} s_1^{X_K^1(t)} s_2^{X_K^2(t)} \mid X_K(t_0) = n^*\right], \ \forall s = (s_0, s_1, s_2) \in [0;1]^3, t \geq t_0. \tag{5}$$

By using Kolmogorov forward equation (4), we have:

Proposition 3.4. *For all $s = (s_0, s_1, s_2) \in [0;1]^3$, all $n^* \in \Lambda_K$ and all $t \geq t_0$*

$$\begin{aligned} \frac{\partial G_t(s \mid n^*)}{\partial t} &= \left\{r s_0^2 - (r+d+\beta)s_0 + d + \beta s_1\right\} \frac{\partial G_t(s \mid n^*)}{\partial s_0} \\ &\quad + q\left\{(1-\mu)s_0 + \mu s_2 - s_1\right\} \frac{\partial G_t(s \mid n^*)}{\partial s_1} + \left\{a s_2^2 - (a+b)s_2 + b\right\} \frac{\partial G_t(s \mid n^*)}{\partial s_2} \end{aligned} \tag{6}$$

with $G_{t_0}(s \mid n^*) = s_0^{n_0^*} s_1^{n_1^*} s_2^{n_2^*}$ when $n^* = (n_0^*, n_1^*, n_2^*) \in \Lambda_K$.

Proof. Let $s = (s_0, s_1, s_2) \in [0;,1]^3$ and $n^* \in \Lambda_K$. Equation (5) leads to

$$G_t(s \mid n^*) = \sum_{n_0+n_1+n_2=0}^{K} s_0^{n_0} s_1^{n_1} s_2^{n_2} P_{n^*,n}(t), \text{ for all } t \geq t_0.$$

By equation (4), the function $t \mapsto G_t(s \mid n^*)$ is derived on $[t_0; +\infty[$ and its derivative is given by:

$$\frac{\partial G_t(s \mid n^*)}{\partial t} = \sum_{n_0+n_1+n_2=0}^{K} s_0^{n_0} s_1^{n_1} s_2^{n_2} \sum_{k \in \Lambda_K} P_{n^*,k}(t) Q_{k,n}. \tag{7}$$

By equation (2), we obtain: for all $t \geq t_0$ and all $n^*, n \in \Lambda_K$

$$\begin{aligned} \sum_{k \in \Lambda_K} P_{n^*,k}(t) Q_{k,n} &= (n_0+1)\beta P_{n^*,(n_0+1,n_1-1,n_2)}(t) + (n_1+1)(1-\mu) q P_{n^*,(n_0-1,n_1+1,n_2)}(t) \\ &\quad + (n_0-1) r P_{n^*,(n_0-1,n_1,n_2)}(t) + d(n_0+1) P_{n^*,(n_0+1,n_1,n_2)}(t) \\ &\quad + (n_1+1)\mu q P_{n^*,(n_0,n_1+1,n_2-1)}(t) \\ &\quad + (n_2-1) a P_{n^*,(n_0,n_1,n_2-1)}(t) + (n_2+1) d P_{n^*,(n_0,n_1,n_2+1)}(t) \\ &\quad - \left\{(r+d+\beta)n_0 + \beta n_1 + (a+b)n_2\right\} P_{n^*,(n_0,n_1,n_2)}(t). \end{aligned}$$

Substituting this last equation into the equation (7) and we obtain (6). □

Let

$$m_i(t) = \mathbb{E}\left[X_K^i(t) \mid X_K(t_0) = n^*\right], \text{for all } t \geq t_0, \text{all } n^* \in \Lambda_K \text{ and or all } i = 0, 1, 2. \tag{8}$$

The equation (6) is used to obtain the following lemma:

Lemma 3.5. *The function $t \mapsto (m_0(t), m_0(t), m_0(t))$ is the solution of the system of equations:*

$$\begin{cases} \dot{m}_0(t) = (r-d-\beta)m_0(t) + (1-\mu)\, qm_1(t), \\ \dot{m}_1(t) = \beta m_0(t) - qm_1(t), \\ \dot{m}_2(t) = (a-b)m_2(t) + \mu q m_1(t), \end{cases}$$

for all $t \geq t_0$ with initial conditions $m_i(t_0) = n_i^*$ for all $i = 0, 1, 2$ with fixed $\left(n_0^*, n_1^*, n_2^*\right) \in \Lambda_K$.

Proof. For all $t \geq t_0$ and all $s = (s_0, s_1, s_2) \in [0;1]^3$, the equation (8) leads to

$$m_i(t) = \mathbb{E}\left[X_K^i(t) \mid X_K(t_0) = n^*\right] = \frac{\partial G_t}{\partial s_i}(s \mid n^*)\Big|_{s_0=s_1=s_2=1}, \ \forall i = 0,1,2 \text{ et } \forall n^* \in \Lambda_K. \tag{9}$$

Since the function $(s,t) \mapsto G_t(s \mid n^*)$ is at least of class $\mathcal{C}^2$(Theorem 3.2), we obtain the system of differential equation which $(m_0(t), m_1(t), m_2(t))$ is solution, by deriving successively (6) by s_0, s_1, s_2: for all $t \geq t_0$, all $s = (s_0, s_1, s_2) \in [0;1]^3$ and all $n^* \in \Lambda_K$

$$\begin{cases} \frac{\partial}{\partial t}\left[\frac{\partial G_t(s|n^*)}{\partial s_0}\right] = \left\{2rs_0 - (r+d+\beta)\right\}\frac{\partial G_t(s|n^*)}{\partial s_0} + (1-\mu)\, q\frac{\partial G_t(s|n^*)}{\partial s_1} \\ \qquad + \left\{rs_0^2 - (r+d+\beta)s_0 + d + \beta s_1\right\}\frac{\partial^2 G_t(s|n^*)}{\partial s_0^2} \\ \qquad + q\left\{(1-\mu)s_0 + \mu s_2 - s_1\right\}\frac{\partial^2 G_t(s|n^*)}{\partial s_0 \partial s_1} + \left\{as_2^2 - (a+b)s_2 + b\right\}\frac{\partial^2 G_t(s|n^*)}{\partial s_0 \partial s_2}, \\ \frac{\partial}{\partial t}\left[\frac{\partial G_t(s|n^*)}{\partial s_1}\right] = \left\{rs_0^2 - (r+d+\beta)s_0 + d + \beta s_1\right\}\frac{\partial^2 G_t(s|n^*)}{\partial s_1 \partial s_0} - q\frac{\partial G_t(s|n^*)}{\partial s_1} + \beta\frac{\partial G_t(s|n^*)}{\partial s_0} \\ \qquad + q\left\{(1-\mu)s_0 + \mu s_2 - s_1\right\}\frac{\partial^2 G_t(s|n^*)}{\partial^2 s_1} + \left\{as_2^2 - (a+b)s_2 + b\right\}\frac{\partial^2 G_t(s|n^*)}{\partial s_1 \partial s_2}, \\ \frac{\partial}{\partial t}\left[\frac{\partial G_t(s|n^*)}{\partial s_2}\right] = \left\{rs_0^2 - (r+d+\beta)s_0 + d + \beta s_1\right\}\frac{\partial^2 G_t(s|n^*)}{\partial s_2 \partial s_0} \\ \qquad + \mu q\frac{\partial G_t(s|n^*)}{\partial s_1} + q\left\{(1-\mu)s_0 + \mu s_2 - s_1\right\}\frac{\partial^2 G_t(s|n^*)}{\partial s_2 \partial s_1} \\ \qquad + \left\{2as_2 - (a+b)\right\}\frac{\partial G_t(s|n^*)}{\partial s_2} + \left\{as_2^2 - (a+b)s_2 + b\right\}\frac{\partial^2 G_t(s|n^*)}{\partial^2 s_2}. \end{cases} \tag{10}$$

By passing to the limit when (s_0, s_1, s_2) tends to $(1,1,1)$ in(10) and using (9), we obtain the system of differential equations in Lemma 3.5. □

The system of equation's the Lemma 3.5 can be resolved analytically. We have

Theorem 3.6. *The expected number of each cell type is given by: for all $n^* = \left(n_0^*, n_1^*, n_2^*\right) \in \Lambda_K$*

$$\begin{cases} m_0(t) = \frac{n_0^* - n_1^*\{\lambda_2+q\}}{\beta\{\lambda_1-\lambda_2\}}\left\{\lambda_1+q\right\}e^{\lambda_1(t-t_0)} - \frac{n_0^* - n_1^*\{\lambda_1+q\}}{\beta\{\lambda_1-\lambda_2\}}\left\{\lambda_2+q\right\}e^{\lambda_2(t-t_0)} \\ m_1(t) = \frac{\beta n_0^* - n_1^*\{\lambda_2+q\}}{\lambda_1-\lambda_2}e^{\lambda_2(t-t_0)} - \frac{\beta n_0^* - n_1^*\{\lambda_1+q\}}{\lambda_1-\lambda_2}e^{\lambda_1(t-t_0)} \\ m_2(t) = n_2^* e^{\frac{a-b}{K}(t-t_0)} + \frac{\mu q\{\beta n_0^* - n_1^*[\lambda_1+q]\}}{(a-b-\lambda_2)\{\lambda_1-\lambda_2\}}\left\{e^{\lambda_2(t-t_0)} - e^{\lambda_2 t_0 + (a-b)(t-t_0)}\right\} \\ \qquad - \frac{\mu q\{\beta n_0^* - n_1^*(\lambda_2+q)\}}{\{a-b-\lambda_1\}\{\lambda_1-\lambda_2\}}\left\{e^{\lambda_1(t-t_0)} - e^{\lambda_1 t_0 + (a-b)(t-t_0)}\right\} \end{cases}$$

for all $t \geq t_0$ where $\lambda_1 = \frac{r-d-\beta-q-\sqrt{(q-r+d+\beta)^2-4q(\mu\beta+d-r)}}{2}$ and $\lambda_2 = \frac{r-d-\beta-q+\sqrt{(q-r+d+\beta)^2-4q(\mu\beta+d-r)}}{2}$.

Proof. Let $m(t) = (m_0(t), m_1(t), m_2(t)) \in \mathbb{R}^3$. The system of equation in Lemma 3.5 can be written in the form: for all $t \geq t_0$

$$\frac{dm(t)}{dt} = Am(t) \text{ where } A = \begin{pmatrix} r-d-\beta & (1-\mu)q & 0 \\ \beta & -q & 0 \\ 0 & \mu q & a-b \end{pmatrix}.$$

This equation has a unique solution given by $m(t) = e^{(t-t_0)A}\, m(t_0)$ for all $t \geq t_0$. The matrix A is, of eigenvalues $\lambda_2 = \frac{r-d-\beta-q+\sqrt{(q-r+d+\beta)^2-4q(\mu\beta+d-r)}}{2}$, $\lambda_1 = \frac{r-d-\beta-q-\sqrt{(q-r+d+\beta)^2-4q(\mu\beta+d-r)}}{2}$ and $\lambda_0 = a-b$, and of eigenvectors respective: $v_1 = (0,0,1)$, $v_2 = {}^t\left(\frac{-(\lambda_2+q)(a-b-\lambda_1)}{\mu q\beta}, -\frac{1}{\mu q}(a-b-\lambda_1), 1\right)$ and $v_3 = {}^t\left(\frac{-(\lambda_2+q)(a-b-\lambda_2)}{\mu q\beta}, \frac{-1}{\mu q}(a-b-\lambda_2), 1\right)$. Then this solution is given in the form of the system of the Theorem 3.6. □

3.4 Probability of Extinction in Time

We wish to calculate the following probabilities: for all $n^* \in \Lambda_K$ and all $t \geq t_0$,

$$\mathbb{P}\left[X_K(t) = 0 \,\middle|\, X_K(t_0) = n^*\right],$$
$$\mathbb{P}\left[X_K^1(t) = 0, X_K^2(t) = 0 \,\middle|\, X_K(t_0) = n^*\right],$$
$$\mathbb{P}\left[X_K^0(t) = 0, X_K^2(t) = 0 \,\middle|\, X_K(t_0) = n^*\right].$$

These probabilities can be obtained from the analytical resolution of (6) (first method) or by another method(second method) suggested, for example, by Goldstein (1989) and Athreya and Ney (1972, page 201). The resolution of the equation (6) is difficult, then we use the second method. This second method is based on the use of the Kolmogorov retrograde equation. By the second method, we have

Theorem 3.7. *For all $s = (s_0, s_1, s_2) \in [0;1]^3$ and all $n^* = (n_0^*, n_1^*, n_2^*) \in \Lambda_K$*

$$G_t(s \mid n^*) = \prod_{i=0}^{2} \left[G_t^{(i)}(s)\right]^{n_i^*}, \ \forall t \geq t_0 \tag{11}$$

where, with $G_{t_0}^{(i)}(s) = s_i$ for all $i = 0, 1, 2$, for all $t \geq t_0$

$$\begin{cases} \dfrac{\partial G_t^{(0)}(s)}{\partial t} = r\left[G_t^{(0)}(s)\right]^2 - (r + d + \beta)G_t^{(0)}(s) + \beta G_t^{(1)}(s) + d, \\ \dfrac{\partial G_t^{(1)}(s)}{\partial t} = (1-\mu)qG_t^{(0)}(s) - qG_t^{(1)}(s) + \mu q G_t^{(2)}(s), \\ \dfrac{\partial G_t^{(2)}(s)}{\partial t} = a\left[G_t^{(2)}(s)\right]^2 - (a+b)G_t^{(2)}(s) + b. \end{cases} \tag{12}$$

Proof. Let $X_K(t_0) = (n_0^*, n_1^*, n_2^*)$. Using the branching process definition, when the initial population consists n_i^*-individuals of type-i ($i = 0, 1, 2$), the sub-processes, resulting these n_i^*-ancestors are independent. For all $i = 0, 1, 2$, we can write $X_K^i(t)$ as

$$X_K^i(t) = \mathcal{X}^{i,1} + \mathcal{X}^{i,2} + \cdots + \mathcal{X}^{i,n_i^*}$$

where for any $i = 0, 1, 2$, $\left\{\mathcal{X}^{i,k}(t), t \geq t_0\right\}$, $k = 1, 2, \ldots, n_i$, are independent processes and the same law, that of a branching process from- a single individual (Harris, 1963, page 119). Then we can write:

$$X_K(t) = \mathcal{X}^{0,1} + \cdots + \mathcal{X}^{0,n_0^*} + \mathcal{X}^{1,1} + \cdots + \mathcal{X}^{1,n_1^*} + \mathcal{X}^{2,1} + \cdots + \mathcal{X}^{2,n_2^*}.$$

Since, the sub-processes from he n_i^* ancestors are also independent from each other, in particular, for all $t \geq t_0$, the generating function for he random variable $X_K(t)$ equals the product of generating functions the random variables $\mathcal{X}_K^{i,k}(t)$: for all $s = (s_0, s_1, s_2) \in [0;1]^3$ and all $t \geq t_0$

$$G_t(s \mid n^*) = \prod_{i=0}^{2} \mathbb{E}\left(s_0^{X_K^0(t)} s_1^{X_K^1(t)} s_2^{X_K^2(t)} \,\middle|\, X_K(t_0) = n_i^* e_{i+1}\right) = \prod_{i=0}^{2} \left[G_t^{(i}(s)\right]^{n_i^*}$$

where $e_1 = (1, 0, 0)$, $e_2 = (0, 1, 0)$, $e_1 = (0, 0, 2)$ and for all $i = 0, 1, 2$

$$G_t^{(i)}(s) = \mathbb{E}\left(s_0^{X_K^0(t)} s_1^{X_K^1(t)} s_2^{X_K^2(t)} \,\middle|\, X_K(t_0) = e_{i+1}\right) \text{ with } G_{t_0}^{(i)}(s) = s_i.$$

Using Kolmogorov backward equation (3): for all $s = (s_0, s_1, s_2) \in [0;1]^3$:

$$\frac{\partial G_t^{(i)}(s)}{\partial t} = \sum_{n_0+n_1+n_2=0}^{K} s_0^{n_0} s_1^{n_1} s_2^{n_2} \frac{\partial P_{e_i,n}}{\partial t}(t) = \sum_{n_0+n_1+n_2=0}^{K} s_0^{n_0} s_1^{n_1} s_2^{n_2} \sum_{k \in \Lambda_K} Q_{e_i,k} P_{k,n}(t)$$

where, $Q_{n,k}$ is defined in (2). We obtain (12), by writing

$$\begin{aligned} \frac{\partial G_t^{(i)}(s)}{\partial t} &= \sum_{k \in \Lambda_K} Q_{e_i,k} \sum_{n_0+n_1+n_2=0}^{K} s_0^{n_0} s_1^{n_1} s_2^{n_2} P_{k,n}(t) = \sum_{k \in \Lambda_K} Q_{e_i,k} G(s, t \mid k) \\ &= \sum_{k=(k_0,k_1,k_2) \in \Lambda_K} Q_{e_i,k} \left[G_t^{(0)}(s)\right]^{k_0} \left[G_t^{(1)}(s)\right]^{k_1} \left[G_t^{(2)}(s)\right]^{k_2}. \end{aligned}$$

□

Note: We can obtain these probabilities by using equation (11) by a numerical resolution of equation (12). In fact, all for $t \geq 0$,

$$\begin{aligned}
\mathbb{P}\left[X_K^1(t) = 0, X_K^2(t) = 0 \,\middle|\, X_K(t_0) = n^*\right] &= G_t\left((1,0,0) \mid n^*\right), \\
\mathbb{P}\left[X_K(t) = 0 \,\middle|\, X_K(t_0) = n^*\right] &= G_t\left((0,0,0) \mid n^*\right), \\
\mathbb{P}\left[X_K^0(t) = 0, X_K(t) = 0 \,\middle|\, X_K(t_0) = n^*\right] &= G_t\left((0,1,0) \mid n^*\right).
\end{aligned}$$

4 Cancer Treatment Applications

It is important to know the chances of a patient surviving after being diagnosed with cancer. The diagnosis refers to the initial detection of the tumor during the patient's first hospital visit. We present some analytical results that can help develop a better treatment plan. It is a direct application of the stochastic model developed in the Section 2 to the cancer treatment regime. This involves identifying the patient's condition at diagnosis and optimizing treatment strategies by examining the therapeutic effectiveness, resistance and tumor relapse.

4.1 Patient Status at Diagnosis

The effectiveness of the therapy is often limited by the phenomena of resistance existing at the start of treatment. Random mutations occurring in the pool of tumor cells during their progression make the tumor heterogeneous. This tumor heterogeneity consists of the various types of cells. Each type of cell has a variable sensitivity to chemical or physical agents. This explains some of the therapeutic failures. It is therefore necessary to know the patient's condition at the start of treatment. Here, tumor heterogeneity is made up of cells of the type-0, type-1 and type-2.

Let M the number of cells clinically observed during diagnosis. The number M consists of cells of type-0 and type-2 because type-1 cells are not clinically observable. Once the tumor is diagnosed, we look for the different types of tumor cells that exist at diagnosis. To do this, we determine the time the tumor reaches M. This time is random and difficult to obtain, but some approximations exist (Wodarz and Komarova, 2014; Haeno and Michor, 2011; Yamamoto and Haeno, 2015; Iwasa et al., 2006). We use an approximation that is the solution to the equation (14) below. We note this deterministic time τ_M and determine the probability that resistant and dormant cells do not exist at the time of diagnosis.

Theorem 4.1. *If the tumor population increases from a type-*0 *cell and a cancer diagnosed with M cells, then the probability that no type-*1 *and type-*2 *at diagnosis is given by*

$$\mathbb{P}\left[X_K^1(\tau_M) = 0, X_K^2(\tau_M) = 0 \,\middle|\, X_K(0) = (1,0,0)\right] = G_{\tau_M}^{(0)}(1)$$

where, with $G_0^{(0)}(1) = 1$, for all $t \in [0;\tau_M]$, $G_t^{(0)}(1)$ is the solution of the equation:

$$\begin{aligned}
\frac{\partial G_t^{(0)}(1)}{\partial t} &= r\left[G_t^{(0)}(1)\right]^2 - (r+d+\beta)G_t^{(0)}(1) + d \\
&\quad + \beta\, e^{-qt}\int_0^t (1-\mu)q\, e^{q\kappa}\, G_\kappa^{(0)}(1) + \mu q\, e^{q\kappa}\left\{e^{-(a-b)\kappa} - 1\right\}\left\{e^{-(a-b)\kappa} - \frac{a}{b}\right\}^{-1} d\kappa. \qquad (13)
\end{aligned}$$

with $\lambda_1 = \frac{r-d-\beta-q-\sqrt{(q-r+d+\beta)^2 - 4q(\mu\beta+d-r)}}{2}$, $\lambda_2 = \frac{r-d-\beta-q+\sqrt{(q-r+d+\beta)^2 - 4q(\mu\beta+d-r)}}{2}$ *and*

$$M = \frac{(\lambda_1+q)\, e^{\lambda_1\tau_M} - (\lambda_2+q)\, e^{\lambda_2\tau_M}}{\beta\{\lambda_1-\lambda_2\}} + \frac{\mu q\beta\left\{\frac{e^{\lambda_2\tau_M} - e^{(a-b)\tau_M}}{a-b-\lambda_2} - \frac{e^{\lambda_1\tau_M} - e^{(a-b)\tau_M}}{a-b-\lambda_1}\right\}}{\lambda_1-\lambda_2}. \qquad (14)$$

Proof. If cancer is diagnosed with a M size at time τ_M, we get: $X_K^0(\tau_M) + X_K^2(\tau_M) = M$. By the Theorem 3.7 with $n^* = (1,0,0)$, we obtain equation (14) where $\mathbb{E}\left[X_K^0(\tau_M) \,\middle|\, X_K(0) = (1,0,0)\right] + \mathbb{E}\left[X_K^2(\tau_M) \,\middle|\, X_K(0) = (1,0,0)\right] = M$. To derive equation (13), we use equation (11) to obtain $\mathbb{P}\left[X_K^1(\tau_M) = 0, X_K^2(\tau_M) = 0 \,\middle|\, X_K(0) = (1,0,0)\right] = G_{\tau_M}((1,0,0) \mid (1,0,0)) = G_{\tau_M}^{(0)}(1)$. However, using equation (12), we obtain

$$\begin{cases}
\dfrac{\partial G_t^{(0)}(1)}{\partial t} = r\left[G_t^{(0)}(1)\right]^2 - (r+d+\beta)G_1^{(0)}(1) + \beta G_t^{(1)}(0) + d, \\
\dfrac{\partial G_t^{(1)}(0)}{\partial t} = (1-\mu)qG_t^{(0)}(1) - qG_t^{(1)}(0) + \mu q G_t^{(2)}(0), \\
\dfrac{\partial G_t^{(2)}(0)}{\partial t} = a\left[G_t^{(2)}(0)\right]^2 - (a+b)G_t^{(2)}(0) + b,
\end{cases} \qquad (15)$$

for all $t \in [0;\tau_M]$ with $G_0^{(0)}(1) = 1$ and $G_0^{(1)}(0) = G_0^{(2)}(0) = 0$. So, we determine $G_t^{(0)}(1)$ by solving the system (15). We solve this system as follows:

- We begin by solving the third equation of the system (15). With $G_0^{(2)}(0) = 0$, its solution is given by

$$G_t^{(2)}(0) = \left\{e^{-(a-b)t} - 1\right\}\left\{e^{-(a-b)t} - \frac{a}{b}\right\}^{-1}, \text{ for all } t \in [0;\tau_M].$$

- Using this expression of $G_t^{(2)}(0)$, by using the method of variation of the constant and $G_0^{(1)}(0) = 0$, we obtain the solution of the second equation of the system (15) which is

$$G_t^{(1)}(0) = e^{-qt}\int_0^t (1-\mu)q\, e^{q\kappa}\, G_\kappa^{(0)}(1) + \mu q\, e^{q\kappa}\left\{e^{-(a-b)\kappa} - 1\right\}\left\{e^{-(a-b)\kappa} - \frac{a}{b}\right\}^{-1} ds$$

We introduce this new expression of $G_t^{(1)}(0)$ in the first equation of the system (15) and obtain (13). □

We derive analytical approximation for the previous result. Also, since many cells of type-1 and type-2 eventually disappear, but may not have disappeared by the time tumor is detected, we derive the deterministic approximation of the following amounts at diagnosis: (i) The probability that of type-1 cells exist at diagnosis and the expected number of type-1 cells at diagnosis; (ii) The probability that the type-2 cells exist at diagnosis and the number of such cells at diagnosis. In the following, we outline the derivations of these quantities.

Proposition 4.2. *If the tumor population increases from a cell of type-*0*, and the cancer diagnosed with a M size, then*

*i) the probability that at least one cell of type-*1 *exists at diagnosis is given by*

$$P_{cell1} = \left\{1 - e^{\frac{-q}{\lambda_1\lambda_2} + \frac{\{\lambda_2+q\}e^{\lambda_2\tau_M}}{\lambda_2\{\lambda_1-\lambda_2\}} - \frac{\{\lambda_1+q\}e^{\lambda_1\tau_M}}{\lambda_1\{\lambda_1-\lambda_2\}}}\right\}\left\{1 - e^{\frac{q\beta}{\lambda_1\lambda_2} - \frac{q\beta}{\lambda_1-\lambda_2}\left\{\frac{e^{\lambda_2\tau_M}}{\lambda_2} - \frac{e^{\lambda_1\tau_M}}{\lambda_1}\right\}}\right\}$$

*and the expected number of type-*1 *cells at diagnosis is given by*

$$m_1(\tau_M) = \frac{\beta}{\lambda_1-\lambda_2}\left\{e^{\lambda_1\tau_M} - e^{\lambda_2\tau_M}\right\},$$

*ii) the probability that at least one cell of type-*2 *exists at diagnosis is given by*

$$P_{cell2} = \left[1 - e^{\frac{-q}{\lambda_1\lambda_2} + \frac{\{\lambda_2+q\}e^{\lambda_2\tau_M}}{\lambda_2\{\lambda_1-\lambda_2\}} - \frac{\{\lambda_1+q\}e^{\lambda_1\tau_M}}{\lambda_1\{\lambda_1-\lambda_2\}}}\right]\left[1 - e^{\frac{uq\beta}{\lambda_1\lambda_2} - \frac{uq\beta}{\lambda_1-\lambda_2}\left\{\frac{e^{\lambda_2\tau_M}}{\lambda_2} - \frac{e^{\lambda_1\tau_M}}{\lambda_1}\right\}}\right]$$

*and the expected number of type-*2 *cells at diagnosis is given by*

$$m_2(\tau_M) = \left[1 - e^{\frac{-q}{\lambda_1\lambda_2} + \frac{\{\lambda_2+q\}e^{\lambda_2\tau_M}}{\lambda_2\{\lambda_1-\lambda_2\}} - \frac{\{\lambda_1+q\}e^{\lambda_1\tau_M}}{\lambda_1\{\lambda_1-\lambda_2\}}}\right] e^{(a-b)\tau_M + \frac{uq\beta}{\lambda_1\lambda_2}}$$
$$\times \int_0^{\tau_M}\left[1 - e^{-\frac{uq\beta}{\lambda_1-\lambda_2}\left\{e^{\lambda_2\sigma} - e^{\lambda_1\sigma}\right\}}\right] e^{\frac{-uq\beta\left\{\lambda_1 e^{\lambda_2\sigma} - \lambda_2 e^{\lambda_1\sigma}\right\}}{\lambda_1\lambda_2\{\lambda_1-\lambda_2\}} - (a-b)\sigma} d\sigma.$$

*iii) the probability that cells of type-*1 *and cells type-*2 *do not exist at the time of diagnosis is*

$$P_{nocell1\&cell2} = 1 - P_{cell2} - e^{\frac{uq\beta}{\lambda_1\lambda_2} - \frac{uq\beta}{\lambda_1-\lambda_2}\left\{\frac{e^{\lambda_2\tau_M}}{\lambda_2} - \frac{e^{\lambda_1\tau_M}}{\lambda_1}\right\}} P_{cell1}.$$

Proof. Let $t \in [0;\tau_M]$ and the expected numbers $m_0(t)$ of type-0 cells and $m_1(t)$ of type-1 cells obtained by the Theorem 3.6. With $n^* = (1,0,0)$, for all $t \in [0;\tau_M]$

$$m_0(t) = \frac{\{\lambda_1+q\}e^{\lambda_1 t} - \{\lambda_2+q\}e^{\lambda_2 t}}{\beta\{\lambda_1-\lambda_2\}} \text{ and } m_1(t) = \frac{\beta}{\lambda_1-\lambda_2}\left\{e^{\lambda_2 t} - e^{\lambda_1 t}\right\}.$$

For all $t \in [0;\tau_M]$, we assume that $\beta m_0(t)$ type-0 cells are dormant and $qm_1(t)$ type-1 cells get out of their dormancy, of which $\mu q m_1(t)$ will be of type-2 cells. Once a type-2 cells appears at time t, its lineage will increase exponentially. In interval $[t, t+\triangle t]$

its expected number is give by $e^{(a-b)\triangle t}$.

Proof of i: We assume that the number of type-1 cells created when there are x type-0 cells follows a Poisson distribution with mean $qm_1(t)$. So the probability that at least one type-1 cell exists at the time of diagnosis is given by

$$\begin{aligned} P_{cell1} &= \left\{1 - e^{-\int_0^{\tau_M} \beta m_0(t)dt}\right\}\left\{1 - e^{-\int_0^{\tau_M} qm_1(t)dt}\right\} \\ &= \left\{1 - e^{\frac{-q}{\lambda_1\lambda_2} + \frac{\{\lambda_2+q\}e^{\lambda_2\tau_M}}{\lambda_2\{\lambda_1-\lambda_2\}} - \frac{\{\lambda_1+q\}e^{\lambda_1\tau_M}}{\lambda_1\{\lambda_1-\lambda_2\}}}\right\}\left\{1 - e^{\frac{q\beta}{\lambda_1\lambda_2} - \frac{q\beta}{\lambda_1-\lambda_2}\left\{\frac{e^{\lambda_2\tau_M}}{\lambda_2} - \frac{e^{\lambda_1\tau_M}}{\lambda_1}\right\}}\right\}. \end{aligned}$$

where $e^{-\int_0^{\tau_M} \beta m_0(t)dt}$ is the probability that no type-0 have emerged until time τ_M, while the probability that the successful type-0 arises at time τ_M is given by $1 - e^{-\int_0^{\tau_M} qm_1(t)dt}$.

Proof of ii: The branching processes initiated by the various types-2 cells obtained by waking the type-1 cells are independent of each other. At $t \in [0;\tau_M]$, we assume that the number of type-2 cells created from type-0 cells follows a Poisson distribution with mean $\mu q m_1(t)$. Hence we have

$$\begin{aligned} P_{cell2} &= \left[1 - e^{-\int_0^{\tau_M} \beta m_0(t)dt}\right]\left[1 - e^{-\int_0^{\tau_M} \mu q m_1(t)dt}\right] \\ &= \left[1 - e^{\frac{-q}{\lambda_1\lambda_2} + \frac{\{\lambda_2+q\}e^{\lambda_2\tau_M}}{\lambda_2\{\lambda_1-\lambda_2\}} - \frac{\{\lambda_1+q\}e^{\lambda_1\tau_M}}{\lambda_1\{\lambda_1-\lambda_2\}}}\right]\left[1 - e^{\frac{uq\beta}{\lambda_1\lambda_2} - \frac{uq\beta}{\lambda_1-\lambda_2}\left\{\frac{e^{\lambda_2\tau_M}}{\lambda_2} - \frac{e^{\lambda_1\tau_M}}{\lambda_1}\right\}}\right] \end{aligned}$$

where $1 - e^{-\int_0^{\tau_M} \beta m_0(t)dt}$ is the probability that the successful type-2 arises at time τ_M. To determine the expected number of cells of type-2, we consider $\sigma \in [0;\tau_M]$ and note $L(\sigma)$ the probability of having at least one cell of type-2 at the time σ: $L(\sigma) = \left\{1 - e^{-\frac{uq\beta}{\lambda_1-\lambda_2}\{e^{\lambda_2\sigma} - e^{\lambda_1\sigma}\}}\right\} e^{\frac{uq\beta}{\lambda_1\lambda_2} - \frac{uq\beta}{\lambda_1-\lambda_2}\left\{\frac{e^{\lambda_2\sigma}}{\lambda_2} - \frac{e^{\lambda_1\sigma}}{\lambda_1}\right\}}$. However, the expected number of cells of type-2 at the instant τ_M is given by

$$\begin{aligned} m_2(\tau_M) &= \int_0^{\tau_M} \left[1 - e^{\frac{-q}{\lambda_1\lambda_2} + \frac{\{\lambda_2+q\}e^{\lambda_2\tau_M}}{\lambda_2\{\lambda_1-\lambda_2\}} - \frac{\{\lambda_1+q\}e^{\lambda_1\tau_M}}{\lambda_1\{\lambda_1-\lambda_2\}}}\right] L(\sigma)\, e^{(a-b)(\tau_M-\sigma)}\, d\sigma \\ &= \left[1 - e^{\frac{-q}{\lambda_1\lambda_2} + \frac{\{\lambda_2+q\}e^{\lambda_2\tau_M}}{\lambda_2\{\lambda_1-\lambda_2\}} - \frac{\{\lambda_1+q\}e^{\lambda_1\tau_M}}{\lambda_1\{\lambda_1-\lambda_2\}}}\right] e^{(a-b)\tau_M + \frac{uq\beta}{\lambda_1\lambda_2}} \\ &\quad \times \int_0^{\tau_M} \left[1 - e^{-\frac{uq\beta}{\lambda_1-\lambda_2}\{e^{\lambda_2\sigma} - e^{\lambda_1\sigma}\}}\right] e^{\frac{-uq\beta\{\lambda_1 e^{\lambda_2\sigma} - \lambda_2 e^{\lambda_1\sigma}\}}{\lambda_1\lambda_2\{\lambda_1-\lambda_2\}} - (a-b)\sigma}\, d\sigma. \end{aligned}$$

□

We graphically compare the results of the Proposition 4.2 and Theorem 4.1; Proposition 4.2 and Theorem 3.6. These comparisons are made in Figure 2.

Note: The probability that no cell of type-1 and type-2 exists at the diagnosis obtained by the Theorem 4.1 and its approximation obtained by Proposition 4.2 are plotted in Figure 2(a). A dependence of the curves obtained is observed. Next, we compare the expected number of types-2 cells obtained by Theorem 3.6 and its approximation obtained by Proposition 4.2 (Figure 2(b)). Also, we note the dependence of this results.

4.2 Therapeutic Strategy

We consider a tumor diagnosed with n_i-cells of type-i ($i = 1, 2$). A therapy can only be called successful if the whole tumor is eradicated or kept small for a long time. A natural idea is thus to use two treatment protocols as proposed by Landsberg et al. (2012). To model this scenario, we just need a drug A that will be sensitive to cells of type 0 and a drug B that will attack resistant cells A. Drug A will increase the mortality rate of type-0 cells by a factor η and reduce the birth rates of these cells and their dormant entry rate by a factor γ and ν respectively. During treatment, these rates become $(1+\eta)d$, $(1-\gamma)r$, and $(1-\nu)\beta$ respectively. Type-2 cells are sensitive to drug B which required for destroying the cancerous cells that escape drug A. Drug B will increase the death rate of type-2 cells by a factor η_1 and reduce their birth rate by a factor γ_1. During treatment, these rates become $(1+\eta_1)b$ and $(1-\gamma_1)a$. Type-1 cells exit dormancy according to rate q where one of these cells becomes to type-0 with a probability $1-\mu$ or to type-2 with a probability μ. In the simplest case, the treatment starts at τ_M and can continue until to any time $t \geq \tau_M$.

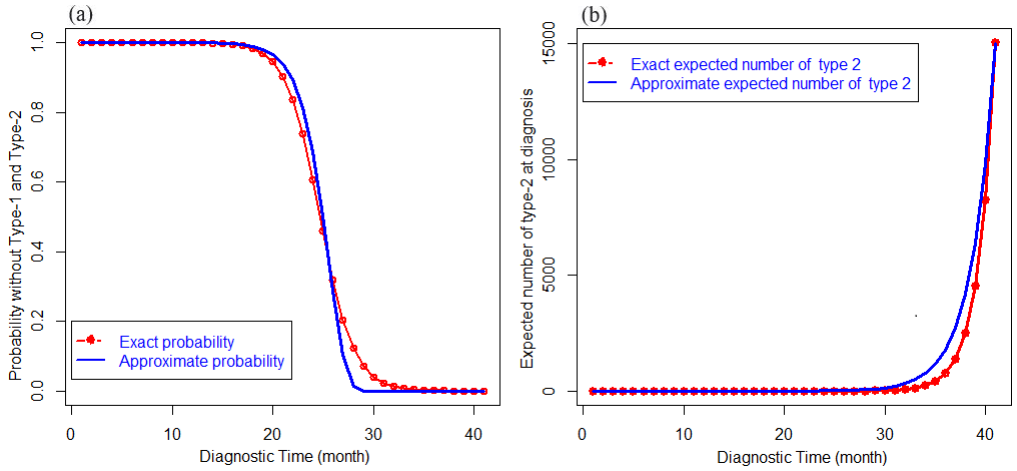

Figure 2: Comparison of the results of Theorem 4.1 and Proposition 4.2; Proposition 4.2 and Theorem 3.6. Blue curves indicate the predictions proposed by Proposition 4.2. Red curves indicate the results obtained by Theorem 4.1 and Theorem 3.6. Parameter values are chosen as in Haeno et al. (2012): $r = 0.9$, $d = 0.001 \times r$, $q = 6.311 \times 10^{-7}$, $\beta = 0.04$, $u = 6.31 \times 10^{-5}$, $a = 0.4$ and $b = 0.001 \times a$ and varied the detection size M from 0 to 2.10^{13} cells. This varies the detection time from 0 to 40 months (Figure 3 and Table 1).

4.2.1 Treatment Efficiency

Let's look at the lifetime of the tumor under treatment. During treatment, it is necessary to know whether the patient will be cured or not. For example, if all cancer cells are susceptible to treatment, tumor progression can stop immediately. For the same reason, tumor progression may stop at all time during treatment. The question is when and with probability tumor cells will be totally eradicated. We give a result of the probability of tumor extinction under treatment. Let T^{ex}_{cell} the tumor lifetime modeled by the process $\{X_K(t), t \geq \tau_M\}$. With the convention, if $\{t \geq \tau_M; X_K(t) = (0,0,0)\} = \emptyset$ then $T^{ex}_{cell} = +\infty$, we define

$$T^{ex}_{cell} = \inf\{t \geq \tau_M; X_K(t) = (0,0,0)\}.$$

Proposition 4.3. *If the tumor population increases from a type-0 cell and a cancer diagnosed with M cells, of which n_i-cells of type-i ($i = 0,1$). Then, for all $t \geq \tau_M$*

$$\mathbb{P}\left[T^{ex}_{cell} > t \,\middle|\, X_K(\tau_M) = (n_0, n_1, M - n_0)\right] = 1 - \left[G^{(2)}_t(0)\right]^{M-n^*_0} \prod_{i=0}^{1} \left[G^{(i)}_t(0)\right]^{n^*_i},$$

where, $G^{(0)}_{\tau_M}(0) = G^{(1)}_{\tau_M}(0) = G^{(2)}_{\tau_M}(0) = 0$ and for all $t \geq \tau_M$

$$\begin{cases} \dfrac{\partial G^{(0)}_t(0)}{\partial t} = \left\{(1-\gamma)\, r G^{(0)}_t(0) - (1+\eta)\, d\right\}\left\{G^{(0)}_t(0) - 1\right\} + (1-\nu)\,\beta G^{(1)}_t(0), \\ \dfrac{\partial G^{(1)}_t(0)}{\partial t} = (1-\mu) q G^{(0)}_t(0) - q G^{(1)}_t(0) + \mu q G^{(2)}_t(0), \\ \dfrac{\partial G^{(2)}_t(0)}{\partial t} = \left\{(1-\gamma_1)\, a G^{(2)}_t(0) - (1+\eta_1)\, b\right\}\left\{G^{(2)}_t(0) - 1\right\}. \end{cases} \tag{16}$$

Proof. Using (11), we can write

$$\begin{aligned} \mathbb{P}\left[T^{ex}_{cell} > t \,\middle|\, X_K(\tau_M) = (n_0, n_1, M - n_0)\right] &= 1 - \mathbb{P}\left[T^{ex}_{cell} \leq t \,\middle|\, X_K(\tau_M) = (n_0, n_1, M - n_0)\right] \\ &= 1 - \mathbb{P}\left[X_K(t) = 0 \,\middle|\, X_K(\tau_M) = (n_0, n_1, M - n_0)\right] \\ &= 1 - \left[G^{(2)}_t(0)\right]^{M-n^*_0} \prod_{i=0}^{1} \left[G^{(i)}_t(0)\right]^{n^*_i}. \end{aligned}$$

To conclude, we replace r, β, d, a and b by $(1-\gamma)\, r$, $(1-\nu)\,\beta$, $(1+\eta)\, d$, $(1-\gamma_1)\, a$ and $(1+\eta_1)\, b$ in (12) and we obtain (16). □

4.2.2 Therapeutic Resistance

Tumor escape may be characterized by the phenomenon of tumor resistance or the failure to treat. Many tumors escape treatment: this is the case for melanoma, colon cancer, kidney cancer, numerous sarcomas and brain tumors in particular. So we're going to look at the probability of the tumor escaping treatment. This probability is the same as the probability that the tumor colony will not die despite treatment. We calculate this probability using the methodology developed by Katouli and Komarova (2011). Let $P_{escape}(.,t)$ the probability that the cancer cells will escape treatment at $t \geq \tau_M$ knowing that the condition of the patient at diagnosis is known.

Theorem 4.4. *Let $i = 1, 2$. If the tumor population increases from a type-0 cell and a cancer diagnosed with M cells, of which n_i-cells of type-i, then, for all $t \geq \tau_M$*

$$P_{escape}(n_2, t) = \left\{1 - \left[G_t^{(2)}(0)\right]^{M-n_2} \prod_{i=0}^{1} \left[G_t^{(i)}(0)\right]^{n_i}\right\} \left\{1 - \left(\frac{d+\beta}{r}\right)^{M-n_2} \left(\frac{b}{a}\right)^{n_2}\right\}^{-1}$$

where the functions $t \mapsto G_t^{(i)}(0)$ $(i = 0, 1, 2)$ are solutions of (16).

Proof. Cancer cells that exist at time t are those that have escaped natural death with a probability of $1 - \left(\frac{d+\beta}{r}\right)^{M-n_2} \left(\frac{b}{a}\right)^{n_2}$ and death due to treatment with a probability of $P_{escape}(n_2, t)$. So, for all $t \geq \tau_M$

$$1 - G_t(0 \mid (M - n_2, n_1, n_2)) = \mathbb{P}\left[T_{cell}^{ex} > t \,\middle|\, X_K(\tau_M) = (M - n_2, n_1, n_2)\right] = \left\{1 - \left(\frac{d+\beta}{r}\right)^{M-n_2} \left(\frac{b}{a}\right)^{n_2}\right\} P_{escape}(n_2, t). \quad \square$$

4.2.3 Tumor Relapse

Relapses are a clinical-pathological reappearance of the cancer process after a loco-regional treatment resulting in a clinical eradication of the cancer disease. This is not a second cancer, but a resurgence of a cancer that has already been treated. This does not mean that the initial treatment was unnecessary but insufficient. These relapses may be local in the primitive tumor, regional with the appearance of metastatic. Relapses have meanings that difficult to specify. For example, for some authors, the phenomenon of relapse would result in the emergence of "dormant" metastatic cells (Almog, 2010). Here, Relapse is the reappearance of type-0 cells or type-2 cells. We give a result to quantify the relapse caused by the dormant cells. Let T_{cd}^{ex} the extinction time of the type-0 and type-2 cells. With the convention, if $\left\{t \geq \tau_M; X_K^0(t) + X_K^2(t) = 0\right\} = \emptyset$ then $T_{cd}^{ex} = +\infty$, we define

$$T_{cd}^{ex} = \inf\left\{t \geq \tau_M; X_K^0(t) + X_K^2(t) = 0\right\}.$$

Conditionally at the time T_{cd}^{ex}, we observe persistence of type-1 cells that are not clinically observable, with an expected number given by Theorem 3.6, that is

$$m_1\left(T_{cd}^{ex}\right) = \frac{(1-\nu)\beta(M-n_2) - n_1\left\{\lambda_2^* + q\right\}}{\lambda_1^* - \lambda_2^*} e^{\lambda_2^*\left(T_{cd}^{ex} - \tau_M\right)} - \frac{(1-\nu)\beta(M-n_2) - n_1\left\{\lambda_1^* + q\right\}}{\lambda_1^* - \lambda_2^*} e^{\lambda_1^*\left(T_{cd}^{ex} - \tau_M\right)} \tag{17}$$

where $\lambda_2^*, \lambda_1^* = \frac{(1-\gamma)r - (1+\eta)d - (1-\nu)\beta - q \pm \sqrt{\left(q - (1-\gamma)r + (1+\eta)d + (1-\nu)\beta\right)^2 - 4q(\mu(1-\nu)\beta + (1+\eta)d - (1-\gamma)r)}}{2}$. Tumor dormancy is an important cause of cancer recurrence (Sosa et al., 2013; Almog, 2010). During dormancy periods, cancer cells reshape their genetic makeup and prepare for the next stage of progression. Then, without dormancy, cancer cells would not be able to survive in a new environment or become resistant to attacks from the immune system and therapy. In this result below, we assume that the patient has had his cancer resolved and we give the probability of a recurrence at time t.

Theorem 4.5. *Let $i = 1, 2$. Assume the tumor population increases from a type-0 cell and a cancer diagnosed with M cells, of which n_i-cells of type-i $(i = 0, 1)$. If conditionally at $\left\{t > T_{cd}^{ex}\right\}$, the type-1 cells appear, followed a Poisson distribution with mean $qm_1\left(T_{cd}^{ex}\right)$, then*

$$\mathbb{P}\left[X_K^0(t) + X_K^2(t) > 0 \,\middle|\, t > T_{cd}^{ex}, X_K(\tau_M) = (M - n_2, n_1, n_2)\right] = \frac{1 - e^{-q\left(t - T_{cd}^{ex}\right)m_1\left(T_{cd}^{ex}\right)}}{\left[G_t^{(0)}(0)\right]^{M-n_2}\left[G_t^{(1)}(1)\right]^{n_1}\left[G_t^{(2)}(0)\right]^{n_2}}$$

where the functions $t \mapsto G_t^{(0)}(0)$, $t \mapsto G_t^{(1)}(1)$ and $t \mapsto G_t^{(2)}(0)$ are solutions of (16) with $G_{\tau_M}^{(0)}(0) = G_{\tau_M}^{(2)}(0) = 0$ and $G_{\tau_M}^{(1)}(1) = 1$, and $m_1\left(T_{cd}^{ex}\right)$ given by equation (17).

Proof. We have

$$\mathbb{P}\left[X_K^0(t)+X_K^2(t)>0 \,\middle|\, t>T_{cd}^{ex}, X_K(\tau_M)=(M-n_2,n_1,n_2)\right]=\frac{\mathbb{P}\left[X_K^0(t)+X_K^2(t)>0, t>T_{cd}^{ex} \,\middle|\, X_K(\tau_M)\right]}{\mathbb{P}\left[T_{cd}^{ex}<t \,\middle|\, X_K(\tau_M)=(M-n_2,n_1,n_2)\right]}.$$

If for all $t > T_{cd}^{ex}$, the appearance of the type-0 and type-2 cells, after type-1 cells wake up, follows a Poisson distribution with mean $qm_1\left(T_{cd}^{ex}\right)$, we obtain:

$$\begin{aligned}\mathbb{P}\left[X_K^0(t)+X_K^2(t)>0, t>T_{cd}^{ex} \,\middle|\, X_K(\tau_M)\right] &= 1-\mathbb{P}\left[X_K^0(t)+X_K^2(t)=0, t>T_{cd}^{ex} \,\middle|\, X_K(\tau_M)=(M-n_2,n_1,n_2)\right]\\ &= 1-\mathrm{e}^{-q\left(t-T_{cd}^{ex}\right)m_1\left(T_{cd}^{ex}\right)}.\end{aligned}$$

where $m_1\left(T_{cd}^{ex}\right)$ given by equation (17). Also, if cancer is diagnosed with n_i-cells of type-i, using by Theorem 3.7 we have

$$\begin{aligned}\mathbb{P}\left[t>T_{cd}^{ex} \,\middle|\, X_K(\tau_M)=(M-n_2,n_1,n_2)\right] &= \mathbb{P}\left[X_K^0(t)=0, X_K^2(t)=0 \,\middle|\, X_K(\tau_M)=(M-n_2,n_1,n_2)\right]\\ &= \left[G_t^{(0)}(0)\right]^{M-n_2}\left[G_t^{(1)}(1)\right]^{n_1}\left[G_t^{(2)}(0)\right]^{n_2}\end{aligned}$$

where the functions $t \mapsto G_t^{(0)}(0)$, $t \mapsto G_t^{(1)}(1)$ and $t \mapsto G_t^{(2)}(0)$ are solutions of (16) with $G_{\tau_M}^{(0)}(0) = G_{\tau_M}^{(2)}(0) = 0$ and $G_{\tau_M}^{(1)}(1) = 1$. Then, we obtain

$$\mathbb{P}\left[X_K^0(t)+X_K^2(t)>0 \,\middle|\, t>T_{cd}^{ex}, X_K(\tau_M)=(M-n_2,n_1,n_2)\right]=\frac{1-\mathrm{e}^{-q\left(t-T_{cd}^{ex}\right)m_1\left(T_{cd}^{ex}\right)}}{\left[G_t^{(0)}(0)\right]^{M-n_2}\left[G_t^{(1)}(1)\right]^{n_1}\left[G_t^{(2)}(0)\right]^{n_2}}.$$

□

5 Numerical Simulations and Discussions

Branching models are introduced to study population development, in which individuals reproduce independently from each other. These models are particularly used in many different biological contexts. In ecology, for example, branching processes have been developed to calculate the success of a species invasion into a new habitat, but without taking evolutionary changes into account. Branching models were also used to explain the temporal evolution of cancer. Here, we used a branching process with mutations to study the dynamics of a tumor population that is not completely exponential. Because part some of the tumor cells are continually lost from the tumor proliferates pool due to cell dormancy. The tumor population considered in this study is composed of three types of cells: cells that are sensitive to the treatment being administered, cells that escape treatment and enter a dormant phase, and cells that resist this treatment.

In the rest of this section, we produce the curves of the results of the previous section. For numerical simulation, we chose parameter values as suggested by Haeno et al. (2012), i.e., $r = 0.9$, $d = 0.001 \times r$, $q = 6.31 \times 10^{-7}$, $u = 6.31 \times 10^{-5}$, $a = 0.4$, $b = 0.001 \times a$ and, when β is not varied, $\beta = 0.04$. For the number of cancer cells at diagnosis, we used the work of Frangioni (2008). We chose the number of cells at diagnosis $M = 10^9$ when M is not varied. All this show that our model is capable of replicating patient survival if we have this experimental data. Experimental data of patients will be needed in the future to fit crucial model parameters. To better understand the importance of our results and what can reasonably be expected, it is important to note that cancer treatment is tailored to each situation. Each cancer patient is a special case and requires appropriate care. The choice of treatment depends on several factors: type of cancer, the extent of cancer, presence of other diseases, age of the patient, general condition of the patient, etc. However, with our mathematical model, we can better measure cancer evolution and study or predict some of these properties. We have proposed a stochastic mathematical model that allows to identify the patient's status at the time of diagnosis, and optimizing treatment strategies by studying therapeutic effectiveness, resistance and tumor relapse. Again, our mathematical approach could represent a valuable tool to support this research on tumor dormancy.

The goals of a cancer diagnosis and treatment program are to cure patients or significantly extend their lives and ensure the best possible quality of life for those who survive. These programs require knowledge of the patient's condition at diagnosis. Through the Theorem 4.1 and the Proposition 4.2, we gave analytical results to describe the different cells at diagnosis. The curves of these results are given by Figure 3 and some values are given by Table 1. For the realization of its various curves, we have varied the detection size M from 0 to 10^{14}-cells. This causes the detection time to vary from 0 to 50 per month (Figure 3(a)). The probability curve for the prediction of dormant cells and diagnostic-resistant cells is shown in Figure 3(b). From this figure we deduce Figure 3(b) that resistant cells may appear and disappear at any time before diagnosis. However, after their appearance, resistant cells and dormant cells may develop rapidly (Figure 3(c) and Figure 3(d)). This explains why the tumor contains cells that already have the ability to resist treatment, and that resistance depends on when the tumor is detected.

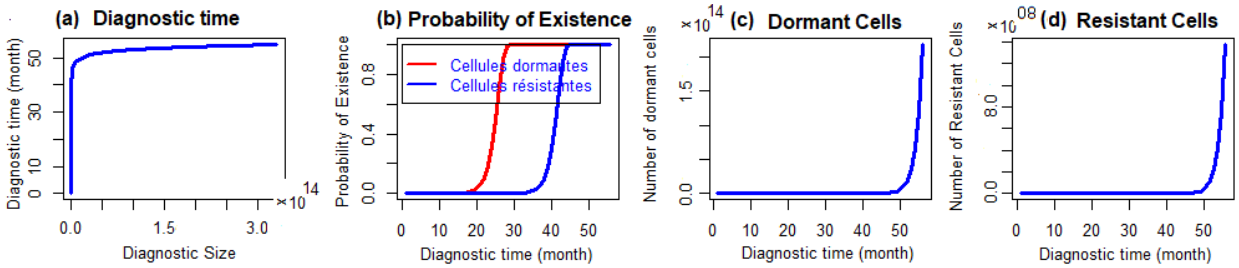

Figure 3: Patient status at diagnosis (Theorem 4.1 and the Proposition 4.2).

Table 1: Quantities obtained from Figure 3.

Tumor size	Times	Probability of existence		Number of Cells	
M	τ_M(Month)	dormant	resistant	dormant	resistant
0.74×10^{04}	5	1.28×10^{-4}	2.40×10^{-8}	2.13×10^{02}	4.19×10^{-4}
3.49×10^{08}	10	8.65×10^{-3}	5.46×10^{-7}	2.32×10^{03}	1.16×10^{-2}
1.40×10^{11}	20	3.37×10^{-2}	2.16×10^{-4}	9.30×10^{05}	5.71×10^{0}
5.61×10^{13}	30	9.99×10^{-1}	8.67×10^{-02}	3.73×10^{08}	2.35×10^{03}

We also looked at the effect of the dormancy rate on quantities that are available at diagnosis (Theorem 4.1). Our theoretical results have shown that the patients who are more likely not to have dormant cells or Cancer cells that exist at time t are those that have escaped natural death (Figure 4).

Thus, a better therapeutic strategy would be to prevent cancer cells from dormant during treatment. This therapeutic strategy may consist in using one or more treatments, depending on the nature of the cancer. In this case, it is wise to use a A protocol, where most cells will be sensitive, a C protocol to wake the dormant cells, and a B protocol that will attack the cells that will be resistant to the A protocols. The effectiveness probability curve of such a protocol is given by Figure 5(a) and the failure probability curve given by Figure 5(b).

The goal of cancer treatment is to achieve remission. Remission corresponds to an undetectable level of tumor cells by the different exploration methods used (imaging, blood samples, etc.), that is, between 0 and 109 malignant cells in the body of the patient (Frangioni, 2008). It's called residual disease. This disease, which is invisible and undetectable neither by the clinic nor by additional examinations (at a level of PET Scan), can constitute a population of active residual cells. This is, why healing is used when a remission is sufficiently longer, more than 10 years, depending on the type of cancer. However, the tumor may reappear or begin to develop after a few weeks, months or years of treatment. This is called tumor relapse or tumor recurrence. An analytical result of the probability of tumor relapse is given by the Theorem 4.5. This result is the detection probability of a tumor relapse. A curve from this result is shown in Figure 6.

We note that the appearance of the relapse curve (Figure 6) may change depending on the cancer and the patient. Nevertheless, it provides some information on the general course of cancer disease and helps us understand tumor relapse. The relapse curve (Figure 6) shows that the probability of relapse increases and then decreases over a period of time, which we can call it "peak relapse": this is the time during which the likelihood of relapse is greatest. After the peak, the risk of relapse gradually decreases and we can conclude that the patient is heading towards complete remission. "Peak relapse" is different from patients and cancer.

6 Conclusion

The clinically detected cancerous tumor is characterized by a degree of heterogeneity. We developed and studied a mathematical model rich enough to accurately represent population dynamics of interacting heterogeneous tumor cells. This model studies the evolution of solid tumors, taking into account sensitive cells, dormant cells and resistant cells for treatment. Our model is exceptional, We analyzed it analytically and numerically using the values we selected in cancer research. Using approximation methods, we estimated the amounts of tumor cells at diagnosis, during treatment and after treatment.

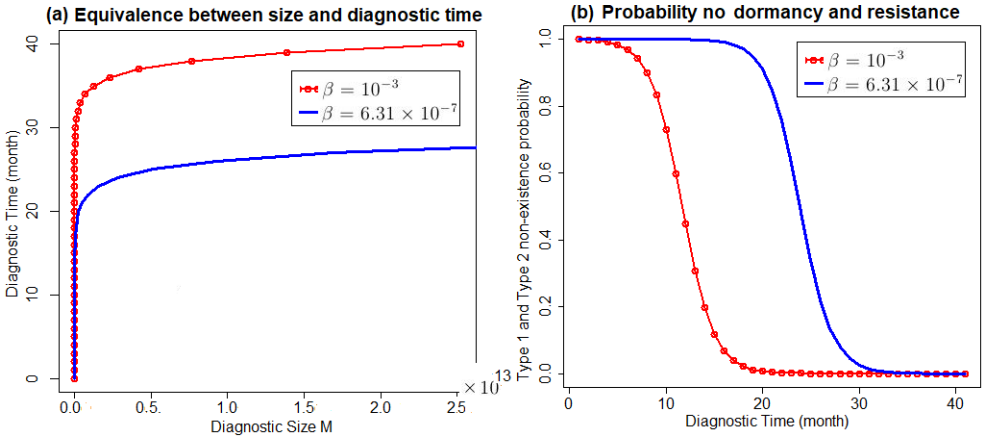

Figure 4: Influence of dormancy on existing quantities in diagnosis (Theorem 4.1). Figure (a) gives relationship between diagnostic time and diagnostic size. Figure (b) gives predictions of the non-existence of dormant cells and resistant cells at diagnostic. We took $\beta = 10^{-3}$ for the red curve and $\beta = 6.31 \times 10^{-7}$ for the blue curve.

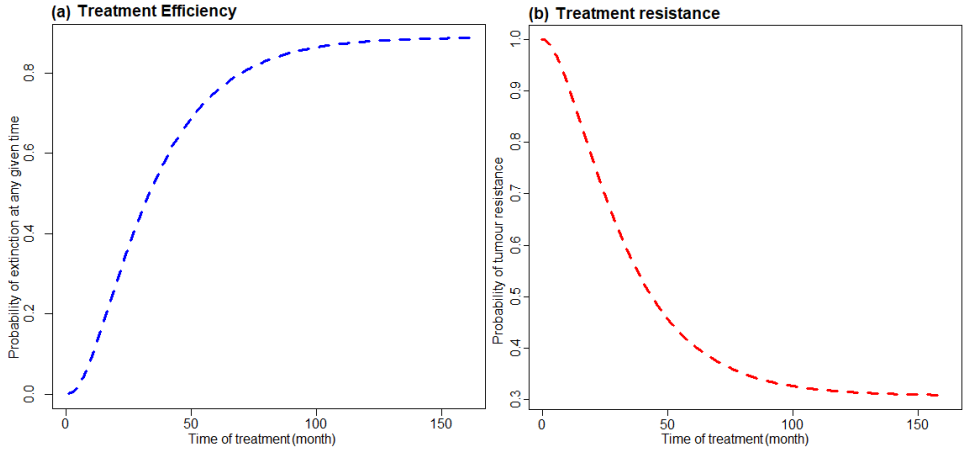

Figure 5: Survival Curves During Processing (Proposition 4.3 and Theorem 4.4).

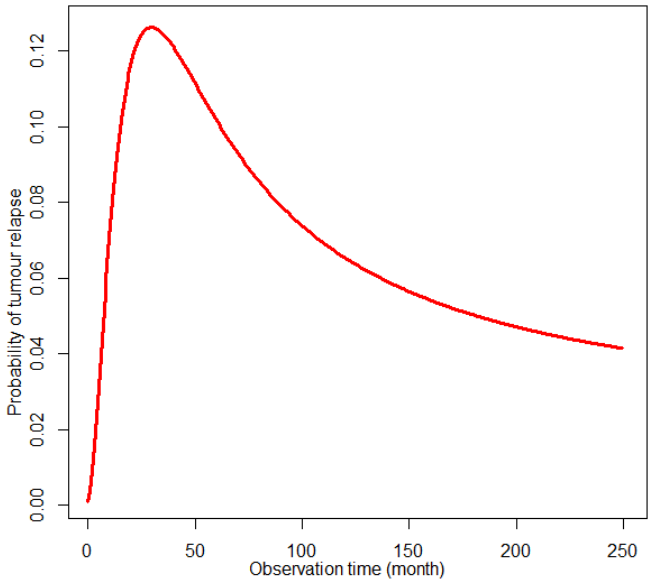

Figure 6: Probability of tumor relapse illustration (Theorem 4.5). Other parameters are: $\eta = 0.7, \gamma = 0.9, \eta_1 = 0.6, \gamma_1 = 0.9$, $n_1 = 3.73 \times 10^{07}$ and $n_2 = 2.3 \times 10^{10}$.

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