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Estimation of Dormant Cell Population in Cancer Patients: A New Approach

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Abstract

The branching processes form a configuration for modeling tumor cells. Faced with unobserved data on dormant cells, inference based on the branching process is not easy to achieve. In large populations, we construct a new framework for estimating dormant cells and tumor dormancy rates. This inference uses of control theory is based on deterministic process statistics approximating branching process in large populations. Precisely, we use an auxiliary system called an observer whose solutions tend exponentially towards those of the limit deterministic model. This observer uses only available measurable data on tumor cells and provides estimates of the number of dormant cells. In addition, the constructed observer does not use the parameter of the generally unknown tumor dormancy rate. We also derive a method to estimate it using the estimated states. We apply this estimation method using simulated data from the branching process.

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1 Introduction

In recent decades, the survival of cancer patients has been improved thanks to earlier detection and therapeutic advances. Cancer is one of the main threats to human health. It results from the appearance of dysfunctions in certain cells of the body. These cells contribute to the formation of a cell mass called a tumor. These are called tumor cells. Tumor cells can spread from the place where they were born (primary tumor) to other parts of the body, where they can form tumors. This process is called metastasis. The development of metastases can be described as follows: cancer cells are confined to the primary tumor where they spread to nearby tissues. They detach from the primary tumor and move to other parts of the body.

Cancers initially develop from normal cells that acquire the ability to proliferate in an aberrant way and eventually become malignant. First, they develop into clonal tumors, then they have the potential to metastasize and develop resistance to treatment. Cancer recurrence represents a critical clinical challenge in the effective treatment of malignancies and for the quality of life of patients. Indeed, this resistance considerably limits the effectiveness of the treatment. Tumor recurrence has received great attention in the medical and biological domain[46, 63, 15, 37], as well as in mathematical modeling communities in recent decades[38, 5, 29, 59]. Currently, the survival of cancer patients has been improved due to earlier detection and therapeutic advances. However, dormant cells that evolve favourably after initial treatment, often many years later, present aggressive tumor recurrence[1, 27, 53, 66]. Cancer recurrence is a crucial clinical challenge for the effective treatment of malignant tumors and for patients' quality of life.

Tumor dormancy is the fact that tumor cells will be able to persist for a longer or shorter time in an organism without declaring cancer. Tumor dormancy then describes a prolonged phase of cancer progression. During this phase, which tumor cells remain clinically hidden and show no signs of growth, thus preserving their capacity for malignant progression[1, 27]. This dormancy can occur after a first phase of treatment, although the patient has entered a period of remission. The possibility that cancers remain dormant in the body for long periods without giving rise to new growth has been recognized for several decades[30]. Many publications refer to a dormant period of more than 5 years. Indeed, it has been reported that 20% of breast cancer patients who did not have clinical disease after surgical removal of their primary tumor developed recurrences 5 to 25 years later[35, 56, 21]. Similarly, a meta-analysis showed that the mean disease-free interval in patients with primary cutaneous melanoma was 14.3 years after diagnosis and 22.3 years in patients with primary ocular melanoma[13]. In addition, epidemiological studies of tumor recurrence in patients with various types of cancer confirm the existence of dormant tumor cells[12].

The development of residual disease leading to tumor dormancy differs from patient to patient and from cancer to cancer. Considerable efforts have been made to understand the control mechanisms underlying tumor dormancy. These efforts reveal that tumor dormancy can be divided into three groups: (i) "cell dormancy" or "tumor cell dormancy"; (ii) "tumor mass dormancy" or "tumor population dormancy" [37] and (iii) "clinical dormancy" [58]. Cell dormancy can occur when tumor cells enter a pause state in the state G_0 of the cell cycle[1]. Unlike cell dormancy, tumor dormancy is not characterized by the absence of proliferation and apoptosis at the cell level[37]. On the contrary, it describes the balance between proliferation and apoptosis preventing the tumor from growing. Clinical dormancy reflects the time between initial treatment and cancer recurrence[58].

Dormant cells that develop favorably before or after the initial treatment, often several years later, present an aggressive tumor recurrence[1, 35, 56, 21]. The use of mathematical modeling could be useful as potential prognostic tools in clinical practice. A large literature has been devoted to mathematical modeling of cancerous tumors[38, 52, 19, 50]. Mathematical modeling has important implications for the biological and clinical theory of tumor growth. To model the metastatic invasion of pancreatic cancer, [29] developed a linear model of

birth-death processes. Although mathematical models have significantly advanced the understanding of tumor initiation and progression, the field of dormant tumors is still being studied. Recently, [38] have proposed a stochastic model of tumor dormancy and resistance. This mathematical model is based on the description of the tumor cell colony as a branching process. Using this model, they identified the patient's status at the time of diagnosis and optimized treatment strategies by studying therapeutic efficacy, resistance and tumor relapse.

In this work, we present a new approach for the estimation of dormant cells and tumor dormancy rate. More precisely, we use an auxiliary system called observer whose solutions tend exponentially towards those of the original model. This server uses only available measurable data on cancer cells and provides estimates of dormant cells that cannot be measured by clinical methods. This therefore makes it possible to estimate all the cancer cells of a cancer patient. Such a method is used to give an estimate of the total parasitic load of the patient and the infection rate in an intra-host model of malaria [7]. Estimation of the state for a dynamic model of schistosomiasis infection described by a continuous nonlinear system when only the infected human population is measured. The central idea is studied from two major angles [18].

We construct the original model using the branching model presented by [38] for modeling dormant cancerous tumors. For large populations, this model gives a deterministic approximation defined as a solution to an ordinary system of differential equations. Indeed, multidimensional branching processes are often used to model tumor cells. However, due to incomplete dormant cell data on dormant cells, inference based on branching process is not easy to perform. In large populations, we construct a new approach to estimate key parameters of the branching model. Namely, the estimation of the number of dormant cells and the rate at which cells enter dormancy using control theory. More precisely, we use an auxiliary system called an observer whose solutions tend exponentially towards those of the limit deterministic process of the branching process in large populations. This limit deterministic process that we designate as the original model.

2 Model Formulation

2.1 A mathematical framework to investigate growth and dissemination

The model considers three cell types. Consider the expansion of cancer cells starting from a single cell that has not developed the ability to resist a therapy as [38]. These cells are called type-0 cells. Type-0 cells divide and give rise to two type-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 rise 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 type-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. The Table 1 describes the parameters of the model.

Table 1. Model's parameters description

Parameters	Description
r	Birth rate of susceptible cells
d	Mortality rate of susceptible cells
a	Birth rate of of resistant cells
b	Mortality rate of resistant cells
β	Dormancy entry rate of sensitive cells
q	Dormancy exit rate of Tumor cells
μ	Resistance probability of a dormant cells

Let's consider the following assumptions:

- (H1): The number of type-0 cells increases when type-0 cells are produced, either during the division of type-0 cells at rate r , or during the exit from the dormancy of type-1 cells at rate $(1 - \mu)q$.
- (H2): The number of type-0 cells decreases by natural death or by death due to the treatment of type-0 cells at rate d .
- (H3): The number of type-1 cells increases when type-0 cells enter dormancy at rate β
- (H4): The number of type-1 cells decreases when type-1 cells emerge from dormancy at rate q
- (H5): The number of type-2 cells increases when type-2 cells are produced, either during the division of type-2 cells at rate a , or during the exit from the dormancy of type-1 cells at rate μq .
- (H6): The number of type-2 cells decreases by natural death or by death due to a different type of treatment than the one that destroys type-0 cells at rate b .

Schematically, the interaction between these three cell types is given by the following Fig. 1.

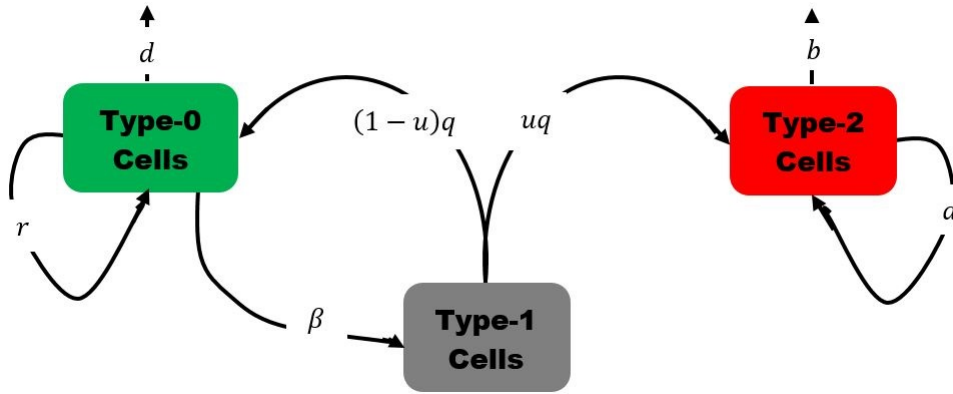


Fig. 1. Interaction schematics of dormant cancer tumor cells.

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

- $K \in \mathbb{R}_+$: Tumor carrying capacity. That is, the largest number of tumor cells that the body can support.
- $\Lambda_K = \left\{ n = (n_i)_{i=0,1,2} \in \mathbb{N}^3 \mid \sum_{i=0}^2 n_i \in \{0, \dots, K\} \right\}$: State space;
- $t \in \mathbb{R}_+$: times and $i = 0, 1, 2$: Index of tumor cell type;
- $X_K^i(t)$: Number of type- i individuals at time t ;
- $X_K(t) = \{X_K^i(t)\}_{i=0,1,2}$: Population size at time $t \geq 0$;
- Δt : Sufficiently small period of time and $o(\Delta t)$ ("little oh Δt ") the Landau order symbol.

Let $\{X_K(t) = \{X_K^i\}_{i=0,1,2}, t \geq 0\}$ a continuous-time Markov jump processes, with values in Λ_K , modeling the population of the tumor considered. At each instant of birth, the continuous-time Markov chain $\{X_K(t), t \geq 0\}$ increase by 1 and at each instant of death it decreases by 1. Specifically, in a sufficiently small period of time Δt between t and $t + \Delta t$, the jump events and transition rates of the Markov process $\{X_K(t), t \geq 0\}$ are 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 $t + \Delta t$,

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

$$1 - \Lambda(n) \Delta t + o(\Delta t).$$

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

Remark 2.1. The probability of more than one birth in time Δt is negligible. The assumption that the probability is negligible means it is of order Δt or $o(\Delta t)$. That is $\lim_{\Delta t \rightarrow 0} \Delta t / o(\Delta t) = 0$ or $o(\Delta t)$ approaches zero faster than Δt .

These three cells interact specifically with each other, and the general condition of the cancerous tumor depends on the proportions of these three types of cells in the body. For this, we consider the process $\{\mathcal{Y}_K(t) = \{\mathcal{Y}_K^i(t)\}_{i=0,1,2}, t \geq 0\}$ which is the the normalized continuous-time Markov process with values in $\frac{1}{K}\Lambda_K$ where

$$\mathcal{Y}_K^i(t) = \frac{X_K^i(t)}{K}, \quad \text{for all } t \geq 0 \text{ and all } i = 0, 1, 2.$$

For all $i = 0, 1, 2$, the random variable $\mathcal{Y}_K^i(t)$ represents the proportion of cells of types i at time $t \geq 0$ and the process $\{\mathcal{Y}_K(t), t \geq 0\}$ describes the density dynamics of the population under consideration. At each birth time, the process $\{\mathcal{Y}_K(t) = \{\mathcal{Y}_K^i(t)\}_{i=0,1,2}, t \geq 0\}$ increase by $\frac{1}{K}$ and at each time of death it decreases by $\frac{1}{K}$.

Formally, this framework leads to the definition of a continuous-time Markov jump processes, the dynamics of which can be expressed as follows [28, 11]:

$$\begin{aligned} \mathcal{Y}_K(t) = & \mathcal{Y}_K(0) + P_{v_r} \left(rK \int_0^t \mathcal{Y}_K^0(s) ds \right) v_r + P_{v_{(1-\mu)q}} \left((1 - \mu)qK \int_0^t \mathcal{Y}_K^1(s) ds \right) v_{(1-\mu)q} \\ & + P_{v_{\mu q}} \left(\mu qK \int_0^t \mathcal{Y}_K^1(s) ds \right) v_{\mu q} + P_{v_a} \left(aK \int_0^t \mathcal{Y}_K^2(s) ds \right) v_a + P_{v_b} \left(bK \int_0^t \mathcal{Y}_K^2(s) ds \right) v_b \\ & + P_{v_\beta} \left(\beta K \int_0^t \mathcal{Y}_K^0(s) ds \right) v_\beta + P_{v_d} \left(dK \int_0^t \mathcal{Y}_K^0(s) ds \right) v_d. \end{aligned} \quad (2.1)$$

where $\{P_l, l \in \Theta\}$ is a family of mutually independent Poisson processes of rate 1, independent of initial value $\mathcal{Y}_K^i(0)$ $\mathcal{Y}_K^i(0)$, defined for all $l \in \Theta = \{v_r, v_d, v_a, v_b, v_{(1-\mu)q}, v_{\mu q}, v_\beta\}$ where Θ is the set of transition vectors of the

process $\{\mathcal{Y}_K(t), t \geq 0\}$ with $v_{(1-\mu)q} = \frac{1}{K} \begin{bmatrix} 1 \\ -1 \\ 0 \end{bmatrix}$, $v_r = \frac{1}{K} \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}$, $v_d = \frac{1}{K} \begin{bmatrix} 0 \\ -1 \\ 0 \end{bmatrix}$, $v_a = \frac{1}{K} \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix}$, $v_b = \frac{1}{K} \begin{bmatrix} 0 \\ 0 \\ -1 \end{bmatrix}$, $v_{\mu q} = \frac{1}{K} \begin{bmatrix} 0 \\ -1 \\ 1 \end{bmatrix}$, $v_\beta = \frac{1}{K} \begin{bmatrix} -1 \\ 1 \\ 0 \end{bmatrix}$.

2.2 Approximation of large population

We can observe that the calculations quickly become very complicated for the birth and death process $\{\mathcal{Y}_K(t), t \geq 0\}$ that we have just introduced and it may be interesting to have more manageable approximations of it. When the population size K becomes very large, the jump rates become so large that the times between jumps are infinitesimal and tend to 0. It is therefore very difficult to observe all the jump events that occur and in the limit of very large populations, the population size dynamics will be close to a continuous process in time. In this paragraph, we introduce a deterministic approximation valid for large populations and thus find a classical model of population dynamics.

Under some regularity conditions detailed in [23, 28, 20, 11], the dynamic of the system (2.1) converges to a deterministic behaviour as the population size tends to infinity. Then the $\{\mathcal{Y}_K(t), t \geq 0\}$ process converges to a deterministic process when K tends to infinity. The more precise meaning that we can give to this limit is a convergence almost surely. Demonstrating that a stochastic epidemic model (for population proportions) converges to a particular deterministic process is also important for applications. This motivates the use of deterministic models, which are easier to analyze, for large populations.

We use [11], Part I, page 30 and we obtain:

Theorem 2.1. *Let $T \geq 0$ fixed. If $\lim_{K \rightarrow \infty} \mathcal{Y}_K(0) = x(0)$, then, almost surely*

$$\lim_{K \rightarrow \infty} \sup_{t \in [0; T]} |\mathcal{Y}_K(t) - x(t)| = 0$$

where the process $\{x(t) = (x_i(t))_{i=0,1,2}, t \in [0; T]\}$ is the unique solution of the ordinary differential equation

$$\begin{cases} \dot{x}_0(t) = (r - d - \beta)x_0(t) + (1 - \mu)qx_1(t) \\ \dot{x}_1(t) = \beta x_0(t) - qx_1(t) \\ \dot{x}_2(t) = (a - b)x_2(t) + \mu qx_1(t) \end{cases} . \quad (2.2)$$

with $x(0) = (x_i(0))_{i=0,1,2} \in \mathbb{R}_+^3$.

Remark 2.2. For every $t \in [0; T]$ and every $i = 0,1,2$, the $x_i(t)$ variable can be seen as the average number of cells of i types at the time t . By equations (2.2), the $x_i(t)$ verify:

$$\begin{cases} x_0(t) = \frac{x_0(0) - x_1(0) \{\lambda_2 + q\}}{\beta \{\lambda_1 - \lambda_2\}} \{\lambda_1 + q\} e^{\lambda_1 t} - \frac{x_0(0) - x_1(0) \{\lambda_1 + q\}}{\beta \{\lambda_1 - \lambda_2\}} \{\lambda_2 + q\} e^{\lambda_2 t} \\ x_1(t) = \frac{\beta x_0(0) - x_1(0) \{\lambda_2 + q\}}{\lambda_1 - \lambda_2} e^{\lambda_2 t} - \frac{\beta x_0(0) - x_1(0) \{\lambda_1 + q\}}{\lambda_1 - \lambda_2} e^{\lambda_1 t} \\ x_2(t) = \frac{\mu q \{\beta x_0(0) - x_1(0) [\lambda_1 + q]\}}{(a - b - \lambda_2) \{\lambda_1 - \lambda_2\}} \{e^{\lambda_2 t} - e^{(a-b)t}\} \\ \quad - \frac{\mu q \{\beta x_0(0) - x_1(0) (\lambda_2 + q)\}}{\{a - b - \lambda_1\} \{\lambda_1 - \lambda_2\}} \{e^{\lambda_1 t} - e^{(a-b)t}\} + x_2(0)e^{(a-b)t}. \end{cases}$$

Proof of Theorem 2.1 .

Proof of the Theorem 2.1 requires knowledge of a result that we will develop in the Lemme 2.3. For this result we take $T \geq 0$ and put

$$M_j(t) = P_j(t) - t, \quad \forall j \in \Theta \quad \text{and} \quad \forall t \in [0; T] . \quad (2.3)$$

First, We use the law of large numbers for Poisson processes to get the following result.

Lemma 2.2. *For all $j \in \Theta$ and all $u_0 > 0$,*

$$\lim_{K \rightarrow +\infty} \sup_{u \leq u_0} |M_j(uK)| = 0 \quad \text{almost surely.}$$

Proof of Lemma 2.2. For all $j \in \Theta$, P_j is a Poisson Process. So according to the law of large numbers of Poisson processes, for all $u_0 > 0$, we have, almost surely

$$\lim_{K \rightarrow +\infty} \sup_{u \leq u_0} |M_j(uK)| = \lim_{K \rightarrow +\infty} \sup_{u \leq u_0} \left| \frac{P_j(Ku)}{K} - u \right| = 0$$

□

Then we use (2.3) and rewrite (2.1) to obtain,

$$\mathcal{Y}_K(t) = \mathcal{Y}_K(0) + M \sum_{i=1}^3 \int_0^t \mathcal{Y}_K^{1-i}(s) ds e_i + \sum_{i=1}^3 \mathcal{M}_K^{1-i}(t) e_i \quad \text{for all } t \geq 0 \tag{2.4}$$

where $e_1 = (1, 0, 0)$, $e_2 = (0, 1, 0)$, $e_3 = (0, 0, 1)$ and

$$M = \begin{pmatrix} r - d - \beta & (1 - \mu)q & 0 \\ \beta & -q & 0 \\ 0 & \mu q & a - b \end{pmatrix}, \tag{2.5}$$

and for all $t \in [0; T]$

$$\begin{cases} \mathcal{M}_K^0(t) = -\frac{1}{K} M_{v_\beta} \left(\beta K \int_0^t \mathcal{Y}_K^0(s) ds \right) + \frac{1}{K} M_{v_{(1-\mu)q}} \left((1 - \mu)qK \int_0^t \mathcal{Y}_K^0(s) ds \right) \\ \quad + \frac{1}{K} M_{v_r} \left(rK \int_0^t \mathcal{Y}_K^0(s) ds \right) - \frac{1}{K} M_{v_d} \left(dK \int_0^t \mathcal{Y}_K^0(s) ds \right) \\ \mathcal{M}_K^1(t) = \frac{1}{K} M_{v_\beta} \left(\beta K \int_0^t \mathcal{Y}_K^0(s) ds \right) - \frac{1}{K} M_{v_{\mu q}} \left(\mu q K \int_0^t \mathcal{Y}_K^1(s) ds \right) \\ \quad - \frac{1}{K} M_{v_{(1-\mu)q}} \left((1 - \mu)qK \int_0^t \mathcal{Y}_K^1(s) ds \right) \\ \mathcal{M}_K^2(t) = \frac{1}{K} M_{v_a} \left(aK \int_0^t \mathcal{Y}_K^2(s) ds \right) - \frac{1}{K} M_{v_b} \left(bK \int_0^t \mathcal{Y}_K^2(s) ds \right) \\ \quad + \frac{1}{K} M_{v_{\mu q}} \left(\mu q K \int_0^t \mathcal{Y}_K^1(s) ds \right) \end{cases} \tag{2.6}$$

So, let's give a result on the processes $\{\mathcal{M}_K^i(t), 0 \leq t \leq T\}$ for all $i = 0, 1, 2$.

□

Lemma 2.3. Let $T \geq 0$, for all $i = 1, 2, 3$

$$\sup_{0 \leq t \leq T} |\mathcal{M}_K^i(t)| \rightarrow 0 \quad \text{almost surely when } K \rightarrow +\infty.$$

Proof of Lemma 2.3. For all $t \in [0; T]$, from equation (2.6) we obtain

$$\begin{cases} |\mathcal{M}_K^0(t)| \leq \frac{1}{K} \left[\left| M_{v_r} \left(rK \int_0^t \mathcal{Y}_K^0(s) ds \right) \right| + \left| M_{v_d} \left(dK \int_0^t \mathcal{Y}_K^0(s) ds \right) \right| \right. \\ \quad \left. + \left| M_{v_\beta} \left(\beta K \int_0^t \mathcal{Y}_K^0(s) ds \right) \right| + \left| M_{v_{(1-\mu)q}} \left((1 - \mu)qK \int_0^t \mathcal{Y}_K^0(s) ds \right) \right| \right] \\ |\mathcal{M}_K^1(t)| \leq \frac{1}{K} \left[\left| M_{v_\beta} \left(\beta K \int_0^t \mathcal{Y}_K^0(s) ds \right) \right| + \left| M_{v_{\mu q}} \left(\mu q K \int_0^t \mathcal{Y}_K^1(s) ds \right) \right| \right. \\ \quad \left. + \left| M_{v_{(1-\mu)q}} \left((1 - \mu)qK \int_0^t \mathcal{Y}_K^1(s) ds \right) \right| \right] \\ |\mathcal{M}_K^2(t)| \leq \frac{1}{K} \left[\left| M_{v_a} \left(aK \int_0^t \mathcal{Y}_K^2(s) ds \right) \right| + \left| M_{v_b} \left(bK \int_0^t \mathcal{Y}_K^2(s) ds \right) \right| + \left| M_{v_{\mu q}} \left(\mu q K \int_0^t \mathcal{Y}_K^1(s) ds \right) \right| \right] \end{cases}$$

This gives, for all $t \in [0; T]$,

$$\left\{ \begin{array}{l} \sup_{0 \leq t \leq T} |\mathcal{M}_K^0(t)| \leq \frac{1}{K} \left[\sup_{0 \leq t \leq T} \left| M_{v_r} \left(rK \int_0^t \mathcal{Y}_K^0(s) ds \right) \right| + \sup_{0 \leq t \leq T} \left| M_{v_d} \left(dK \int_0^t \mathcal{Y}_K^0(s) ds \right) \right| \right. \\ \left. + \sup_{0 \leq t \leq T} \left| M_{v_\beta} \left(\beta K \int_0^t \mathcal{Y}_K^0(s) ds \right) \right| + \sup_{0 \leq t \leq T} \left| M_{v_{(1-\mu)q}} \left((1-\mu)qK \int_0^t \mathcal{Y}_K^0(s) ds \right) \right| \right] \\ \sup_{0 \leq t \leq T} |\mathcal{M}_K^1(t)| \leq \sup_{0 \leq t \leq T} \left| M_{v_{\mu q}} \left(\mu q K \int_0^t \mathcal{Y}_K^1(s) ds \right) \right| + \sup_{0 \leq t \leq T} \left| M_{v_\beta} \left(\beta K \int_0^t \mathcal{Y}_K^0(s) ds \right) \right| \\ \left. + \frac{1}{K} \left[\sup_{0 \leq t \leq T} \left| M_{v_{(1-\mu)q}} \left((1-\mu)qK \int_0^t \mathcal{Y}_K^1(s) ds \right) \right| \right] \\ \sup_{0 \leq t \leq T} |\mathcal{M}_K^2(t)| \leq \frac{1}{K} \left[\sup_{0 \leq t \leq T} \left| M_{v_a} \left(aK \int_0^t \mathcal{Y}_K^2(s) ds \right) \right| + \sup_{0 \leq t \leq T} \left| M_{v_b} \left(bK \int_0^t \mathcal{Y}_K^2(s) ds \right) \right| \right. \\ \left. + \sup_{0 \leq t \leq T} \left| M_{v_{\mu q}} \left(\mu q K \int_0^t \mathcal{Y}_K^1(s) ds \right) \right| \right] \end{array} \right\}$$

We pose $\Xi = \{r, d, a, b, \beta, \mu q, (1-\mu)q\}$ and $\eta = j \int_0^t \mathcal{Y}_K^i(s) ds$ for all $i = 0, 1, 2$, all $j \in \Xi$ and all $t \in [0; T]$. Since for all $t \in [0; T]$ and all $i = 0, 1, 2$, $0 \leq \mathcal{Y}_K^i(s) \leq 1$, we can write, for all $j \in \Xi$

$$0 \leq \eta = j \int_0^t \mathcal{Y}_K^i(s) ds \leq j \int_0^T \mathcal{Y}_K^i(s) ds \leq jT.$$

From this relationship, by changing the variable in the previous system, we obtain:

$$\left\{ \begin{array}{l} \sup_{0 \leq t \leq T} |\mathcal{M}_K^0(t)| \leq \sup_{0 \leq \eta \leq rT} \left| \frac{M_{v_r}(\eta K)}{K} \right| + \sup_{0 \leq \eta \leq (1-\mu)qT} \left| \frac{M_{v_{(1-\mu)q}}(\eta K)}{K} \right| + \sup_{0 \leq \eta \leq dT} \left| \frac{M_{v_d}(\eta K)}{K} \right| \\ \left. + \sup_{0 \leq \eta \leq \beta T} \left| \frac{M_{v_\beta}(\eta K)}{K} \right| \right. \\ \sup_{0 \leq \eta \leq T} |\mathcal{M}_K^1(t)| \leq \sup_{0 \leq \eta \leq \beta T} \left| \frac{M_{v_\beta}(\eta K)}{K} \right| + \sup_{0 \leq \eta \leq \mu q T} \left| \frac{M_{v_{\mu q}}(\eta K)}{K} \right| + \sup_{0 \leq \eta \leq (1-\mu)qT} \left| \frac{M_{v_{(1-\mu)q}}(\eta K)}{K} \right| \\ \sup_{0 \leq \eta \leq T} |\mathcal{M}_K^2(t)| \leq \sup_{0 \leq \eta \leq aT} \left| \frac{M_{v_a}(\eta K)}{K} \right| + \sup_{0 \leq \eta \leq bT} \left| \frac{M_{v_b}(\eta K)}{K} \right| + \sup_{0 \leq \eta \leq \mu q T} \left| \frac{M_{v_{\mu q}}(\eta K)}{K} \right|. \end{array} \right\}$$

From Lemma 2.2 we deduce: for all $i = 0, 1, 2$,

$$\sup_{0 \leq t \leq T} |\mathcal{M}_K^i(t)| \rightarrow 0 \text{ p.s. when } K \rightarrow +\infty.$$

□

Finally, the proof of the Theorem 2.1 is:

Proof of Theorem 2.1. Let $T \geq 0$. We want to show uniform convergence on $[0; T]$. From (2.4) we can write: For all $t \in [0; T]$,

$$|\mathcal{Y}_K(t) - x(t)| \leq |\mathcal{Y}_K(0) - x(0)| + \sup_{0 \leq t \leq T} |\mathcal{M}_K(t)| + |M| \int_0^t |\mathcal{Y}_K(s) - x(s)| ds$$

By Grönwall's inequality [[34], page 288] we obtain

$$|\mathcal{Y}_K(t) - x(t)| \leq |\mathcal{G}_T^0| e^{|M|t}.$$

where $\mathcal{G}_T^0 = \mathcal{Y}_K(0) - x(0) + \sup_{0 \leq t \leq T} |\mathcal{M}_K(t)|$. Then

$$\sup_{0 \leq t \leq T} |\mathcal{Y}_K(t) - x(t)| \leq |\mathcal{G}_T^0| e^{M|t|}.$$

Thus, by Lemma 2.3, when $\mathcal{Y}_K(0) \rightarrow x(0)$ and when $K \rightarrow +\infty$, we can deduce that

$$\lim_{K \rightarrow +\infty} \sup_{0 \leq t \leq T} |\mathcal{Y}_K(t) - x(t)| = 0.$$

□

To specify the asymptotic behavior of the $\{\mathcal{Y}_K(t), t \in [0; T]\}$ process around its deterministic limit $\{x(t), t \in [0; T]\}$, we continue our approach by defining a "central limit theorem" for $\{\mathcal{Y}_K(t), t \in [0; T]\}$. This approach is developed in Chapter 2 of Part 1 page 34 of [11].

Theorem 2.4. When $\lim_{K \rightarrow +\infty} \sqrt{K} [\mathcal{Y}_K(0) - x(0)] = 0$, then, when $K \rightarrow +\infty$,

$$\left\{ \sqrt{K} [\mathcal{Y}_K(t) - x(t)]_{t \geq 0} \right\} \Rightarrow \left\{ U_t = (U_i(t))_{i=0,1,2} \right\}_{t \geq 0}$$

where

$$\begin{cases} U_0(t) = (r - d - \beta) \int_0^t U_0(s) ds + (1 - \mu)q \int_0^t U_1(s) ds + \frac{1}{K} \left[\int_0^t \sqrt{rx_0(s)} dB_r(s) \right. \\ \quad \left. - \int_0^t \sqrt{\beta x_0(s)} dB_\beta(s) - \int_0^t \sqrt{dx_0(s)} dB_d(s) \right] \\ U_1(t) = \beta \int_0^t U_0(s) ds - q \int_0^t U_1(s) ds + \frac{1}{K} \left[\int_0^t \sqrt{\beta x_0(s)} dB_\beta(s) - \int_0^t \sqrt{\mu q x_1(s)} dB_{\mu q}(s) \right. \\ \quad \left. - \int_0^t \sqrt{(1 - \mu)q x_1(s)} dB_{(1 - \mu)q}(s) \right] \\ U_2(t) = (a - b) \int_0^t U_2(s) ds + \mu q \int_0^t U_1(s) ds + \frac{1}{K} \left[\int_0^t \sqrt{ax_2(s)} dB_a(s) - \int_0^t \sqrt{bx_2(s)} dB_b(s) \right. \\ \quad \left. - \int_0^t \sqrt{\mu q x_1(s)} dB_{\mu q}(s) \right] \end{cases}$$

with B_j ($j \in \Xi$) mutually independent standard Brownian motions.

Proof. Just use the theorem 2.3.2, page 34 of [11] with function $\beta_{(\cdot)}(\cdot, \cdot)$ and function $b(\cdot)$ define by: for every $t \geq 0$: $\beta_{v_r}(t, x(t)) = rx_0(t)$; $\beta_{v_d}(t, x(t)) = dx_0(t)$; $\beta_{v_a}(t, x(t)) = ax_2(t)$; $\beta_{v_b}(t, x(t)) = bx_2(t)$; $\beta_{v_\beta}(t, x(t)) = \beta x_0(t)$; $\beta_{v_{\mu q}}(t, x(t)) = \mu q x_1(t)$; $\beta_{v_{(1-\mu)q}}(t, x(t)) = (1 - \mu)q x_1(t)$ and $b(t, x(t)) = Mx(t)$ to get the result of Theorem 2.4. □

3 Estimating Parameters and State Variables

We propose the deterministic process inference defined by (2.2). For more literature on the method used, refer to [10, 49, 31, 7, 16, 45, 8]. We recall that, in the deterministic model (2.2), cells of type- i ($i = 0,1,2$) are designated by $x_i(t)$ at the time $t \geq 0$.

3.1 Problem formulation

We construct an estimator, called an observer, for the dynamic system (2.2) by adopting the estimation method presented, for example, by [7]; [10] or [49]. Thus, the observer constructed will be used to estimate the state variables and the parameter β of this system. First, we define the known and unknown entries of the dynamic

system (2.2). In practice, the dormancy rate β is not known, so we consider the term $\beta x_1(t)$ that appears in the dynamic system (2.2) as an unknown entry and we pose: $v(t) = \beta x_1(t)$. We assume that the other parameters are known. We assume that susceptible and resistant cells are observed and dormant cells are not observed. That is, $x_0 + x_2$ is measured and x_1 is not measured. Now we will use some classical notations of control theory. We note \mathcal{X} the measurable output of the dynamic system (2.2). The measurable output corresponds to the number of susceptible and resistant cells, i.e.:

$$\mathcal{X}(t) = x_0(t) + x_2(t), \text{ for all } t \geq 0. \quad (3.1)$$

We rewrite the dynamic system (2.2) based on known inputs, measurable output \mathcal{X} , and unknown term v , so we have:

$$\begin{cases} \dot{x}(t) = Ax(t) + Ev(t) \\ \mathcal{X}(t) = Cx(t) \end{cases}, \text{ for all } t \geq 0. \quad (3.2)$$

where the matrices A , E and C are defined as follows:

$$E = \begin{pmatrix} -1 \\ 1 \\ 0 \end{pmatrix}; \quad C = (1, 0, 1) \quad \text{and} \quad A = \begin{pmatrix} r - d & (1 - \mu)q & 0 \\ 0 & -q & 0 \\ 0 & \mu q & a - b \end{pmatrix}.$$

The new dynamic system (3.2) consists of the initial dynamic system model (2.2) and the measurable output described by (3.1). The first equation of the dynamic system (3.2) describes system dynamics, while the second equation provides information about what is being measured. The construction of the observer requires knowledge of all model parameters. However, the dynamic system (3.2) consists of the unknown parameter β which makes the component $v(t)$ unknown. By the $v(t)$ component, the dynamic system (3.2) becomes an observer with unknown input (UIO: Unknown Input Observer). The key to building the UIO is to decouple the dynamic system (3.2) from the unknown component $v(t)$ [7]. For this reason, we consider the equation $\mathcal{X}(t) = Cx(t)$ and by derivation we obtain:

$$\dot{\mathcal{X}}(t) = C \dot{x}(t) = C [Ax(t) + v(t)E] = CAx(t) + CEv(t).$$

Since $CE = -1$, we can write

$$v(t) = -\dot{\mathcal{X}}(t) + CAx(t). \quad (3.3)$$

By substituting (3.3) in the first equation of the dynamic system (3.2), we obtain:

$$\begin{aligned} \dot{x}(t) &= Ax(t) + E [-\dot{\mathcal{X}}(t) + CAx(t)] \\ &= [I_3 + EC] Ax(t) - E \dot{\mathcal{X}}(t). \end{aligned}$$

In this case, the dynamic system (3.7) becomes:

$$\begin{cases} \dot{x}(t) = [I_3 + EC] Ax(t) - E \dot{\mathcal{X}}(t) \\ \mathcal{X}(t) = Cx(t) \end{cases}. \quad (3.4)$$

By taking $\mathcal{X}(t)$ and $\dot{\mathcal{X}}(t)$ as inputs, the dynamic system (3.4) contains only known terms and estimates can be made by an appropriate method. Therefore, our next concern is to use this dynamic system (3.4) to estimate both the unobserved state variables and the unknown parameter β . This requires the construction of an observer whose values converge exponentially to the original model (3.4). However, the system must satisfy either the observability property or the detectability property.

Remark 3.1. The dynamic system described by the (3.4) system requires an ensemble of initial conditions to complete its formulation. When the tumor population is growing from a cell of type-0, a initial conditions for the system (3.4) is $x_0(0) = 1$, $x_1(0) \geq 0$ and $x_2(0) = 0$.

3.2 Observer design: states estimation

The construction of an observer for the dynamic system (3.4) requires that the pair $([I_3 + EC] A, C)$ be observable or detectable[45, 8]. A dynamic system written as (3.4) is observable if $\tau > 0$ exists such that knowledge of $\mathcal{X}(t)$ for every $t, 0 \leq t \leq \tau$, is sufficient to determine $x(0)$ [49]. Equally, observability implies that knowledge of an output of a dynamic system makes it possible to reconstruct the entire state of the system[45]. Specifically, we have:

Definition 3.1. (*Kalman observability criterion*)

A general time-invariant dynamic system of size $n \times n$ that can be written as the dynamic system (3.4) is said to be observable if and only if the Kalman observability matrix, that is the matrix $\mathcal{O}([I_3 - EC] A, C)$ defined

$$\text{by: } \mathcal{O}([I_3 - EC], C) = \begin{pmatrix} C \\ C [I_3 - EC] A \\ \vdots \\ C ([I_3 - EC] A)^{n-1} \end{pmatrix} \text{ is full rank. That is, } \text{rank } \mathcal{O}([I_3 + EC], C) = n.$$

When the pair $([I_3 - EC] A, C)$ is not observable, we can study the detectability of the pair $([I_3 - EC] A, C)$.

Definition 3.2. [10] (Detectability)

The pair $([I_3 - EC] A, C)$ is detectable if all states of the dynamic system (3.4) that cannot be observed tend (exponentially) to zero when time t tends to infinity.

In the following, we will show that the system (3.4) is not observable but detectable, which allows us to construct an observer for this system[10].

Lemma 3.1. *The pair $([I_3 + EC] A, C)$ is not observable but detectable when $a < b$ and $r < d$.*

Proof. We have successively: $EC = \begin{pmatrix} -1 & 0 & -1 \\ 1 & 0 & 1 \\ 0 & 0 & 0 \end{pmatrix}$, $I_3 + EC = \begin{pmatrix} 0 & 0 & -1 \\ 1 & 1 & 1 \\ 0 & 0 & 1 \end{pmatrix}$ and

$$[I_3 + EC] A = \begin{pmatrix} 0 & -\mu q & -a + b \\ r - d & 0 & a - b \\ 0 & \mu q & a - b \end{pmatrix}. \tag{3.5}$$

The matrix of Kalman $\mathcal{O}([I_3 - EC] A, C)$ becomes $\mathcal{O}([I_3 + EC], C) = \begin{pmatrix} 1 & 0 & 1 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$.

Then $\text{rang} \mathcal{O}([I_3 + EC] A, C) = 1 < 3$. According to the Definition 3.1, the Kalman observability criterion is not satisfied. Then, the pair $([I_3 + EC] A, C)$ is not observable. In this case, we can make a coordinate change to isolate observable and non-observable states and see if the pair $([I_3 + EC] A, C)$ is detectable[10]. Therefore, it is sufficient to consider the canonical form of the linear part of the dynamic system (3.4): either the generic system

$$\begin{cases} \dot{x}(t) = [I_3 + EC] Ax(t) \\ \mathcal{X}(t) = Cx(t) \end{cases} \tag{3.6}$$

to separate observable and non-observable parts from the dynamic system. Since $\mathcal{O}([I_3 + EC] A, C) = 1$, we can find two matrices Q and T with $\text{rank} Q = 1$ and an invertible matrix of order such as

$$\mathcal{O}([I_3 + EC] A, C) = [Q, O_{23}] T \tag{3.7}$$

where O_{23} is the null matrix of type 2×3 .

However, for the system model (3.6), the matrices $Q = \begin{pmatrix} 1 \\ 0 \\ 0 \end{pmatrix}$ and $T = \begin{pmatrix} 1 & 0 & 1 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}$ satisfy the condition of the equation (3.7). If we now introduce a coordinate change as suggested by [10]:

$$z(t) = Tx(t). \quad (3.8)$$

Then, by the dynamic system (3.6), the equation (3.8) takes us to the following dynamic system:

$$\begin{cases} \dot{z}(t) = T[I_3 + EC]AT^{-1}z(t) \\ \mathcal{X}(t) = CT^{-1}z(t) \end{cases}. \quad (3.9)$$

Thus, since $CT^{-1} = \begin{pmatrix} 1 & 0 & 0 \end{pmatrix}$ and $T[I_3 + EC]AT^{-1} = \begin{pmatrix} 0 & 0 & 0 \\ r-d & 0 & a-b+d-r \\ 0 & \mu q & a-b \end{pmatrix}$, we can pose $\tilde{A}_{11} = 0$; $\tilde{C} = 1$; $O_{12} = \begin{pmatrix} 0 & 0 \end{pmatrix}$; $\tilde{A}_{21} = \begin{pmatrix} r-d \\ 0 \end{pmatrix}$, $\tilde{A}_{22} = \begin{pmatrix} 0 & a-b+d-r \\ \mu q & a-b \end{pmatrix}$ and we obtain $T[I_3 + EC]AT^{-1} = \begin{pmatrix} \tilde{A}_{11} & O_{12} \\ \tilde{A}_{21} & \tilde{A}_{22} \end{pmatrix}$ and $CT^{-1} = \begin{pmatrix} \tilde{C} & O_{12} \end{pmatrix}$.

In addition, if $z = (z_1, z_2)^T$ with z_1 of dimension 1, the model system (3.9) becomes

$$\begin{cases} \dot{z}_1(t) = \tilde{A}_{11} z_1(t) \\ \dot{z}_2(t) = \tilde{A}_{21} z_1(t) + \tilde{A}_{22} z_2(t) \\ \mathcal{X}(t) = \tilde{C} z_1(t) \end{cases} \quad (3.10)$$

z_1 is an observable state of the dynamic system (3.10) whereas z_2 is an unobservable state of this system. The pair $(\tilde{A}_{11}, \tilde{C})$ is clearly observable because the matrices \tilde{A}_{11} and \tilde{C} are one-dimensional. Thus, for the pair $([I_3 + EC]A, C)$ to be detectable, it is necessary and sufficient that the matrix \tilde{A}_{22} be Hurwitz, that is to say all the eigenvalues of \tilde{A}_{22} must be real negative parts. The matrix \tilde{A}_{22} eigenvalues are $a - b \pm \sqrt{(a - b)^2 + 4\mu q(a - b - r + d)}$. Obviously, these values are all negative on the assumption (vii). Therefore, according to the Definition 3.2 the pair $([I_3 + EC]A, C)$ is detectable. \square

Since the dynamic system (3.4) has satisfied the detectability condition, we can now construct its corresponding observer. For the dynamic system (3.4), we construct a Luenberger observer. That is, an observer of form[8]:

$$\begin{cases} \dot{w}(t) = Fw(t) + G\mathcal{X}(t) \\ \hat{x}(t) = w(t) + H\mathcal{X}(t) \end{cases}. \quad (3.11)$$

where F, G and H are matrices of appropriate dimensions, choose so that for all initial conditions $\hat{x}(0)$ and $x(0)$: for a positive real number λ ,

$$\| \hat{x}(t) - x(t) \| \leq \exp(-\lambda t) \| \hat{x}(0) - x(0) \|,$$

To determine the matrices F, G and H , we use the ideas introduced in [31, 7, 16, 68, 16]. In these works, the matrices F, G and H are determined so that the system (3.11) is an exponential observer of the system (3.4). Otherwise, we determine the matrices F, G and H such that the error $e(t) = x(t) - \hat{x}(t)$ tends exponentially to 0 independently of the initial condition.

Theorem 3.2. When the pair $([I_3 + EC]A, C)$ is detectable, the observer of the system dynamics (3.4) is:

$$\begin{cases} \dot{w}(t) = \{(I_3 + EC)A - LC\}w(t) + \{L + \{(I_3 + EC)A - LC\}E\}\mathcal{X}(t) \\ \hat{x}(t) = w(t) + E\mathcal{X}(t) \end{cases}$$

where $L = (l_1, l_2, l_3)^T$ with $(l_1, l_3) \in \mathbb{R}^+ \times \mathbb{R}^+ \setminus \{(0; 0)\}$ and $l_2 \in \mathbb{R}$.

Proof. Let's look at how to choose the matrices F , G and H in the dynamic system (3.11) and the matrix L in the Theorem 3.2 so that the dynamic system of the Theorem 3.2 becomes an exponential observer of the system (3.4). Otherwise, how to choose these matrices so that the error $e(t) = x(t) - \hat{x}(t)$ tends exponentially to zero for all initial condition. We use the derivative of the function $t \rightarrow e(t)$: $\dot{e}(t) = \dot{x}(t) - \dot{\hat{x}}(t)$. For the dynamic systems (3.4) and (3.9), this derivative can be written:

$$\begin{aligned} \dot{e}(t) &= [I_3 + EC]Ax(t) - E\dot{\mathcal{X}}(t) - \dot{w}(t) - H\dot{\mathcal{X}}(t) \\ &= [I_3 + EC]Ax(t) - E\dot{\mathcal{X}}(t) - Fw(t) - G\mathcal{X}(t) - H\dot{\mathcal{X}}(t) \\ &= [I_3 + EC]Ax(t) - F[\hat{x}(t) - H\mathcal{X}(t)] - (E + H)\dot{\mathcal{X}}(t) \\ &= F[x(t) - \hat{x}(t)] - (E + H)\dot{\mathcal{X}}(t) + \{[I_3 + EC]A - GC + FHC - F\}x(t) \\ &= Fe(t) + -(E + H)\dot{\mathcal{X}}(t) \{+[I_3 + EC]A - [G - FH]C - F\}x(t). \end{aligned} \tag{3.12}$$

Thus, for the dynamic of the error to be homogeneous, it is necessary that: $H = -E$ and $F = [I_3 + EC]A - [G - FH]C$. With these conditions, the error dynamics of the equation (3.12) is written $\dot{e}(t) = Fe(t)$. In this case, the matrix F must be chosen so as to ensure the asymptotic stability of $e(t)$ and the convergence (exponential) of $e(t)$ to 0. One way to choose F is to pose $L = G - FH$. Thus, we write F in the form: $F = [I_3 + EC]A - LC$. So, just choose the matrix L such as $\lim_{t \rightarrow +\infty} e(t) = 0$. In this case we use the detectability of the dynamic system (3.4) and we choose the matrix L such that the matrix $F = [I_3 + EC]A - LC$ is Hurwitz. When L is a column matrix defined by: $L = (l_1, l_2, l_3)^T$, by equation (3.5) we can write:

$$\begin{aligned} F &= \begin{pmatrix} 0 & -\mu q & -a + b \\ r - d & 0 & a - b \\ 0 & \mu q & a - b \end{pmatrix} - \begin{pmatrix} l_1 \\ l_2 \\ l_3 \end{pmatrix} \begin{pmatrix} 1 & 0 & 1 \end{pmatrix} \\ &= \begin{pmatrix} -l_1 & -\mu q & -l_1 - a + b \\ -l_2 + r - d & 0 & -l_2 + a - b \\ -l_3 & \mu q & -l_3 + a - b \end{pmatrix}. \end{aligned}$$

Since $-l_1 - l_3$ and $\pm \frac{1}{2} \left[-\sqrt{a^2 - 2ab + 4aq\mu + b^2 - 4bq\mu - 4qr\mu} + a - b \right]$ are the eigenvalues of the matrix F , thus, based on the assumption (vii), the matrix $F = [I_3 + EC]A - LC$ is Hurwitz if $(l_1, l_3) \in \mathbb{R}^+ \times \mathbb{R}^+ \setminus \{(0; 0)\}$ and $l_2 \in \mathbb{R}$. Therefore, in addition to the conditions i) and ii) above, an observer defined by the dynamic system (3.11) admits an error governed by $\dot{e}(t) = Fe(t)$ if and only if the following matrix equations are true:

- (a) $F = (I_3 + EC)A - LC$;
- (b) $G = L + \{(I_3 + EC)A - LC\}E$;
- (c) $H = -E$
- (d) $L = (l_1, l_2, l_3)^T$ with $l_2 \in \mathbb{R}$ and $(l_1, l_3) \in \mathbb{R}^+ \times \mathbb{R}^+ \setminus \{(0; 0)\}$.

Hence, the dynamic system (3.11) becomes:

$$\begin{cases} \dot{w}(t) = \{(I_3 + EC)A - LC\}w(t) + \{L + \{(I_3 + EC)A - LC\}E\}\mathcal{X}(t) \\ \hat{x}(t) = w(t) + E\mathcal{X}(t) \end{cases}$$

with $L = (l_1, l_2, l_3)^T$ where $(l_1, l_3) \in \mathbb{R}^+ \times \mathbb{R}^+ \setminus \{(0; 0)\}$ and $l_2 \in \mathbb{R}$. □

The observer obtained by the Theorem 3.2 depends only on the known inputs, outputs and parameters of the system (3.4) .

Corollary 3.3. For $([I_3 + EC] A, C)$ detectable, the estimator $\hat{x}(t) = \{\hat{x}_i(t)\}_{i=0,1,2}^T$ of $x(t) = \{x_i(t)\}_{i=0,1,2}^T$ such that the error $x(t) - \hat{x}(t)$ converge (exponentially) to zero when time t tends to infinity satisfied

$$\begin{cases} \dot{\hat{x}}_0(t) = -l_1\hat{x}_0(t) - \mu q\hat{x}_1(t) - [l_1 + a - b]\hat{x}_2(t) + l_1\mathcal{X}(t) - \dot{\mathcal{X}}(t) \\ \dot{\hat{x}}_1(t) = [r - d - l_2]\hat{x}_0(t) + [a - b - l_2]\hat{x}_2(t) + l_2\mathcal{X}(t) + \dot{\mathcal{X}}(t) \\ \dot{\hat{x}}_2(t) = -l_3\hat{x}_0(t) + \mu q\hat{x}_1(t) + [a - b - l_3]\hat{x}_2(t) + l_3\mathcal{X}(t) \end{cases} \quad (3.13)$$

with $(l_1, l_3) \in \mathbb{R}^+ \times \mathbb{R}^+ \setminus \{(0; 0)\}$ and $l_2 \in \mathbb{R}$.

Proof. We use the observer obtained by the Theorem 3.2. Since

$$(I_3 + EC) A - LC = \begin{pmatrix} -l_1 & -\mu q & -a + b - l_1 \\ r - d - l_2 & 0 & a - b - l_2 \\ -l_3 & \mu q & a - b - l_3 \end{pmatrix}$$

and

$$L + \{(I_3 + EC) A - LC\} E = \begin{pmatrix} 2l_1 - \mu q \\ 2l_2 - r + d \\ 2l_3 + \mu q \end{pmatrix},$$

this observer may write: with $w(t) = \{w_i(t)\}_{i=0,1,2}^T$

$$\begin{cases} \dot{w}_1(t) = -l_1w_1(t) - \mu qw_2(t) + (-a + b - l_1)w_3(t) + (2l_1 - \mu q)\mathcal{X}(t) \\ \dot{w}_2(t) = (r - d - l_2)w_1(t) + (a - b - l_2)w_3(t) + (2l_2 - r + d)\mathcal{X}(t) \\ \dot{w}_3(t) = -l_3w_1(t) + \mu qw_2(t) + (a - b - l_3)w_3(t) + (2l_3 + \mu q)\mathcal{X}(t) \\ \hat{x}_0(t) = w_1(t) - \mathcal{X}(t) \\ \hat{x}_1(t) = w_2(t) + \mathcal{X}(t) \\ \hat{x}_2(t) = w_3(t). \end{cases} \quad (3.14)$$

Using $w_3(t) = \hat{x}_2(t)$; $w_2(t) = \hat{x}_1(t) - \mathcal{X}(t)$ and $w_1(t) = \hat{x}_0(t) + \mathcal{X}(t)$, the system dynamic (3.14) is equivalent to the dynamic system:

$$\begin{cases} \dot{\hat{x}}_0(t) = -l_1\hat{x}_0(t) - \mu q\hat{x}_1(t) - [l_1 + a - b]\hat{x}_2(t) + l_1\mathcal{X}(t) - \dot{\mathcal{X}}(t) \\ \dot{\hat{x}}_1(t) = [r - d - l_2]\hat{x}_0(t) + [a - b - l_2]\hat{x}_2(t) + l_2\mathcal{X}(t) + \dot{\mathcal{X}}(t) \\ \dot{\hat{x}}_2(t) = -l_3\hat{x}_0(t) + \mu q\hat{x}_1(t) + [a - b - l_3]\hat{x}_2(t) + l_3\mathcal{X}(t). \end{cases}$$

□

3.3 Estimation of the dormancy rate

The tumor dormancy rate is a important parameter of tumor cell proliferation. However, the value of this parameter is very little known. We estimate this parameter using the results from the previous section.

Proposition 3.1. Let t_0 the initial observation time and t_f the final observation time. Let $\{t_0 < t_1 < \dots < t_n = t_f\}$ with $n \in \mathbb{N}$ a subdivision of $[t_0; t_f]$. The estimator $\hat{\beta}$ of the β obtained from the estimated states satisfied :

$$U_2 = \hat{\beta}U_1 \quad (3.15)$$

where U_2 and U_1 are appropriate dimension column vectors, whose respective components are $U_{2i} = \hat{x}_1(t_{i+1})e^{qt_{i+1}} - \hat{x}_1(t_i)e^{qt_i}$ and $U_{1i} = \int_{t_i}^{t_{i+1}} \hat{x}_0(s)e^{qs}$.

Proof of Proposition 3.1. Consider the dynamics of x_1 in the system (2.2): $\dot{x}_1(t) = \beta \dot{x}_0(t) - q \dot{x}_1(t)$. Let t_0 the initial observation time. By the constant variation method, we can write: $x_1(t) = x_1(t_0)e^{-q(t-t_0)} + \beta \int_{t_0}^t x_0(s)e^{-q(t-s)} ds$. Then $x_1(t)e^{qt} - x_1(t_0)e^{qt_0} = \beta \int_{t_0}^t x_0(s)e^{qs} ds$. By substituting $x_1(t)$ and $x_0(t)$ with their estimates provided by the Corollary 3.3, that is $\hat{x}_1(t)$ and $\hat{x}_0(t)$ respectively, and noting $\hat{\beta}$ an estimator of the parameter β , we can obtain from the estimated states

$$\hat{x}_1(t)e^{qt} - \hat{x}_1(t_0)e^{qt_0} = \hat{\beta} \int_{t_0}^t \hat{x}_0(s)e^{qs} ds. \tag{3.16}$$

The equation (3.16) is valid for all t . In particular, by noting t_f at the final instant, and considering $\{t_0 < t_1 < \dots < t_n = t_f\}$ with $n \in \mathbb{N}$ a subdivision of the interval $[t_0; t_f]$, we obtain:

$$\hat{x}_1(t_{i+1})e^{qt_{i+1}} - \hat{x}_1(t_i)e^{qt_i} = \hat{\beta} \int_{t_i}^{t_{i+1}} \hat{x}_0(s)e^{qs} ds. \tag{3.17}$$

For all $i = 0, 1, \dots, n$, the equation (3.17) can be written as: $U_{2i} = \hat{\beta}U_{1i}$. where $U_{2i} = \hat{x}_1(t_{i+1})e^{qt_{i+1}} - \hat{x}_1(t_i)e^{qt_i}$ and $U_{1i} = \int_{t_i}^{t_{i+1}} \hat{x}_0(s)e^{qs} ds$. We can therefore calculate, for each $i = 0, 1, \dots, n$, U_{2i} and U_{1i} . Therefore, considering U_2 and U_1 appropriate dimension column vectors, whose respective components are U_{2i} and U_{1i} , we have: $U_2 = \hat{\beta}U_1$. \square

4 Computational Simulation Results and Discussion

Let's show how our method of estimating all the tumor cells of the observed cells can be applied. In addition, we explain here how we choose known biological parameters. The parameters are chosen according to two references that refer to the experimental data. Thus, Table 2 is from [29] and Table 3 is from [44]. For the unknown parameter β , we took an arbitrary value:

$$\beta = 0.04. \tag{4.1}$$

Table 2. Biological parameters according to [29]

Parameters	Values per unit time
r	0,9
b	$0,001 \times a$
d	$0,001 \times r$
μ	$6,31 \times 10^{-5}$
a	0,4
q	$6,31 \times 10^{-7}$

Indeed, in [29], the authors have modeled the growth dynamics of pancreatic cancer and the development of metastases using a binary branching model. With the real data of the patients with pancreatic cancer, they were able to obtain the values of the parameters of their model that are in the Table 2.

With the values of the parameters of the Table 3, in [44], the authors demonstrate that the phenotypic plasticity of melanoma cells in an inflammatory microenvironment contributes to tumour relapse after initially successful T-cell immunotherapy.

With these values, we present numerical simulation results for the model (2.2), as well as the dynamics of the estimated states given in Section 3.2. We also give a result of the estimated value of the parameter β given in Section 3.3. The methodology is to establish in an objective way the growth curve of the cancer of an individual, modeled by the model (2.2) with the [24]'s algorithm, from a certain number of measurable cells which are in a

Table 3. Biological parameters according to [44]

Parameters	Values per unit time
r	0.12
b	0.02
d	0.02
μ	2×10^{-5}
a	0.12
q	0.0008

way only discrete witnesses of a process which is continuous in time. These simulations of Table 2 and Table 3 values show that the typical behavior of the model solutions is much better adjusted by a Gompertz model (Fig. 2). Thus, in this section, we will consider the cancer kinetics evolving according to these Gompertz models.

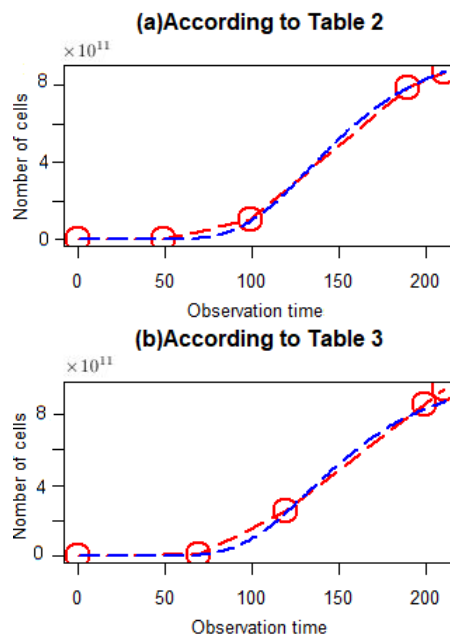


Fig. 2. Comparison of the tumor cell dynamics

The Fig. 2 above compares the tumor cell dynamics obtained from the Table 2 and Table 3, and the curve of the Gompertz model. In these figures, the cell dynamics obtained by the Table 2 and Table 3 are red and the curve of the Gompertz function is blue. Analysis of these curves shows that the data were well adjusted by the Gompertz model curve.

4.1 Gompertz model in growth analyzes

Most of the 20th century has seen attempts to understand the kinetics of tumor growth through efforts to decide which of the many proposed tumor growth models "best matches the growth data". The main impetus for these attempts was the need for a quantitative description of tumor growth [70, 33, 25], for understanding basic mechanisms regulating growth [2, 47] and for predicting tumor response [29, 59]. The most widely applied and successful deterministic model for adapting to experimental and clinical data is the well-known Gompertz model.

The most widely applied and successful deterministic model for adapting to experimental and clinical data is the well-known Gompertz model. This is probably the most popular non-linear model found in the literature related to tumor growth. Gompertz model introduced in 1825 by Benjamin Gompertz is well known and widely used in many aspects of biology.

The Gompertz model[26] has been used as a growth model even longer than its better known parent, the logistics model[61]. Soon, researchers began to adapt this model to their regression data, and over the years, the Gompertz model has become a preferred regression model for many types of organism growth. Researchers have adapted the Gompertz model to everything from plant growth, bird growth quotes[54], fish growth quotes[62], animal growth quotes[43], growth in the number or density of microbes quotes[14, 43], tumor growth quotes[39, 48] and cancer patient survival quotes[55] and bacterial growth quotes[64]. The literature is huge.

The Gompertz model is the most widely used to describe tumor progression[6]. Experiments with breast, lung and liver cancers show that tumor cells develop exponentially when the population is small, but growth slows when the population increases in size[36]. The Gompertz model was then an important theoretical and clinically important model of human breast cancer growth. Speer et al. citeSpe proposed that all individual tumors develop initially with identical gompertz parameters, but then develop kinetic heterogeneity by a time-dependent random process. Yang et al.[69] used the Gompertz model to accurately track growth trajectories of xenograft tumors in non-target control groups. In sum, several studies have reported that the Gompertz model generates very good adjustments to describe experimental data[67, 6, 60]. Thus, in the rest of this work, it should be considered that the observed tumor growth kinetics (sensitive cells and resistant cells) is a Gompert function. This allows the simultaneous modeling of tumor dynamics as a whole and in particular to the estimation of different types of cells.

Multiple expressions and parameterizations of Gompertz model coexist in the literature. But, the definition that the curve of observed data obtained by simulation of the model (2.2) proved much better, allows us to assume that $\mathcal{X}(t)$ has the special form of differential equation:

$$\frac{d\mathcal{X}(t)}{dt} = \alpha\mathcal{X}(t) \ln\left(\frac{K}{\mathcal{X}(t)}\right) \tag{4.2}$$

where $\alpha \in \mathbb{R}_+$ with $\mathcal{X}(0) \in \mathbb{R}_+$.

Gompertz model (4.2) adopted here is characterized by an exponential decrease in the specific growth rate with a rate noted here by α . The parameter α is an experimental coefficient determining the slope of the quote curve[40, 41, 42]. The value $\mathcal{X}(0)$ is the size of the tumor at the time of the initial observation.

4.2 Computational simulation of results

The first numerical results we get is the determination of the different types of cells that make up the tumor mass. Using the stochastic model (2.2), the Table 2 gives Figs 3-4 and the Table 3 gives Figs.6-7.

Tumor heterogeneity has just been determined through these figures. This leads to the second numerical results which concern the estimation of the states, on the one hand, and on the other hand, the estimation of the rate at which tumor cells enter dormancy. The estimated functions of the curves in Figs. 3-8 are given in Figs. 9-14 respectively.

Finally, using the values of the Tables 2 and 3, we give some values of the numerical simulation of the model in the Tables 4 and 5. We use these values to give the estimated value of the dormancy rate parameter using the equation (3.15). Indeed, during the growth of a solid tumor, over time, cancer cells become more and more malignant due to the increase in mutations. An important consequence of this is that dormant cancer cells increase. This is reflected in our model by the tumor dormancy rate β . In the tables 4 and 5, we give some values from the numerical simulation of our model (??) in order to give the estimated value of the parameter of the rate at which the cancer cells enter dormancy.

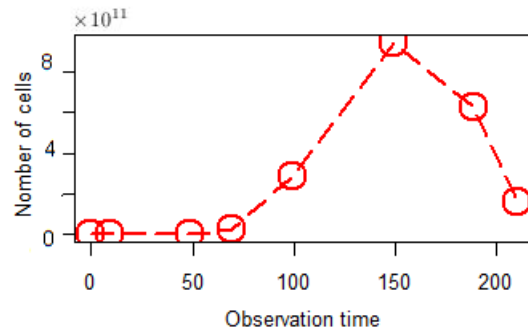


Fig. 3. Susceptible cells dynamics according to Table 2.

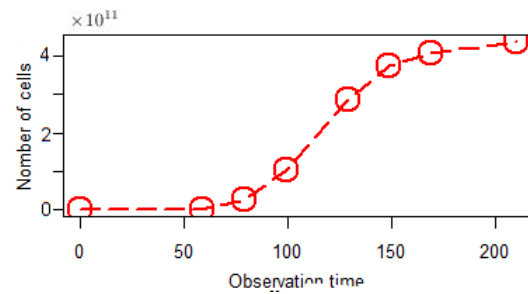


Fig. 4. Dormant cells dynamics according to Table 2.

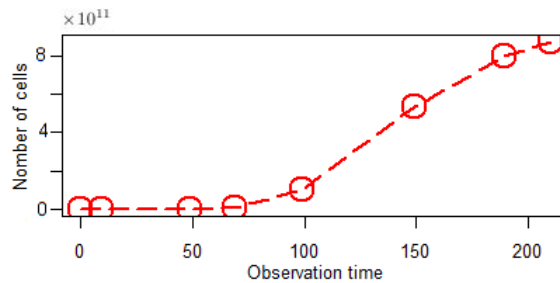


Fig. 5. Resistant cells dynamics according to Table 2.

The values of Table 4 are obtained using the values of Table 2. With the data from Table 4 and we can give the value of the estimator $\hat{\beta}$ of the tumor dormancy parameter β . We use the equation (3.15) we obtain $\hat{\beta} = 0.0421$. This value of $\hat{\beta} = 0.0421$ is approximately equal to the arbitrary value we gave to the unknown parameter $\beta = 0.04$.

The values of Table 5 are obtained using the values of Table 3. With the data from Table 5 we can give the value of the estimator $\hat{\beta}$ of the tumor dormancy parameter β . We use the equation (3.15) and we obtain $\hat{\beta} = 0.0385$. This value of $\hat{\beta} = 0.0385$ is approximately equal to the arbitrary value we gave to the unknown parameter $\beta = 0.04$.

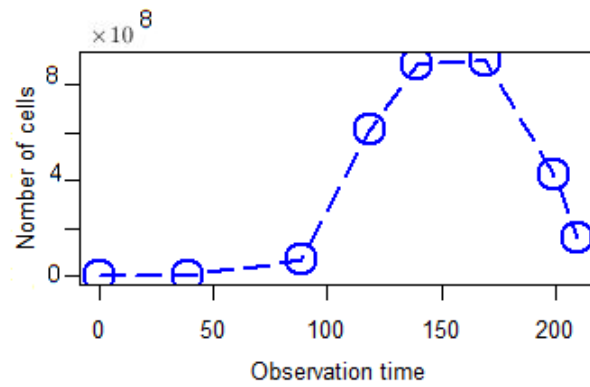


Fig. 6. Susceptible cells dynamics according to Table 3.

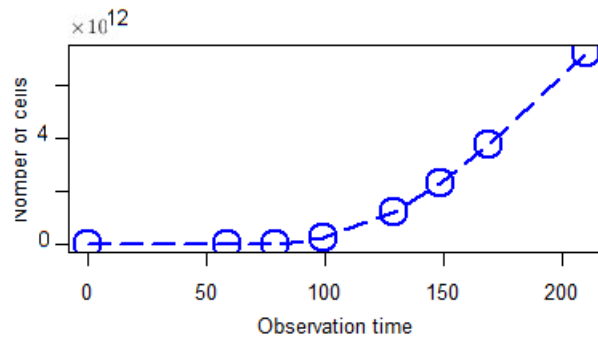


Fig. 7. Dormant cells dynamics according to Table 3.

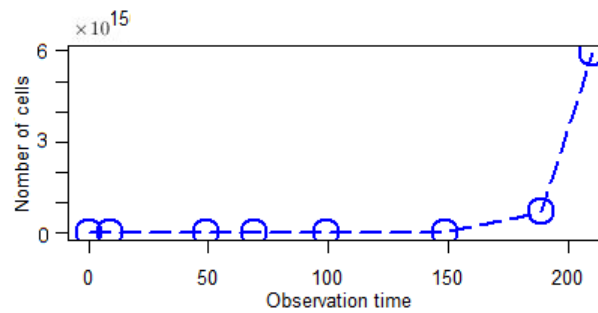


Fig. 8. Resistant cells dynamics according to Table 3.

Remark 4.1. The estimators $\hat{\beta}$ obtained by the values of Tables 4 and 5 are approximately equal to the arbitrary value that we have given to the unknown parameter $\beta = 0.04$.

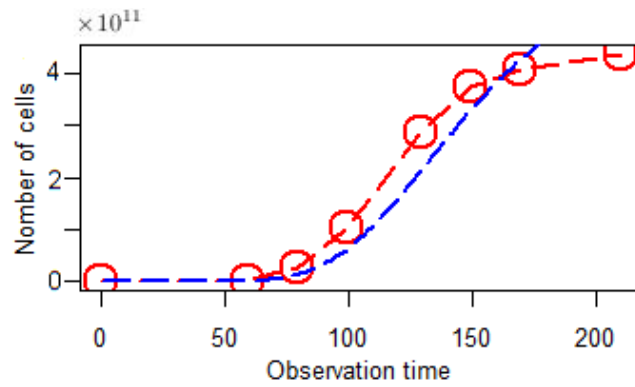


Fig. 9. Dormant cells dynamics (red) and its estimated (blue) according to Table 2.

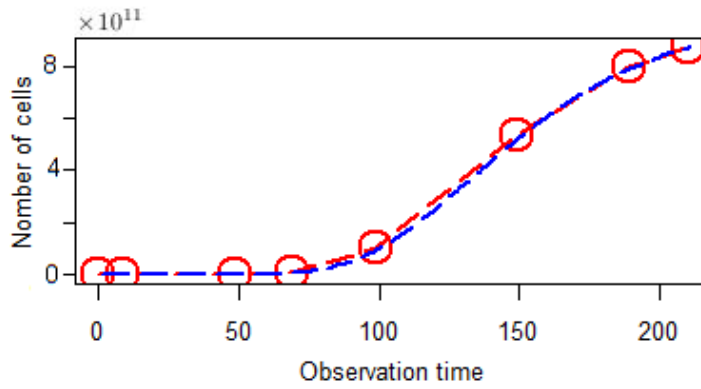


Fig. 10. Resistant cells dynamics (red) and its estimated (blue) according to Table 2.

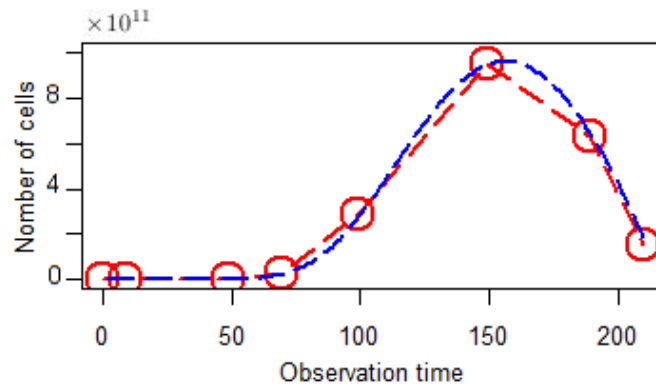


Fig. 11. Susceptible cells dynamics (red) and its estimated (blue) according to Table 2.

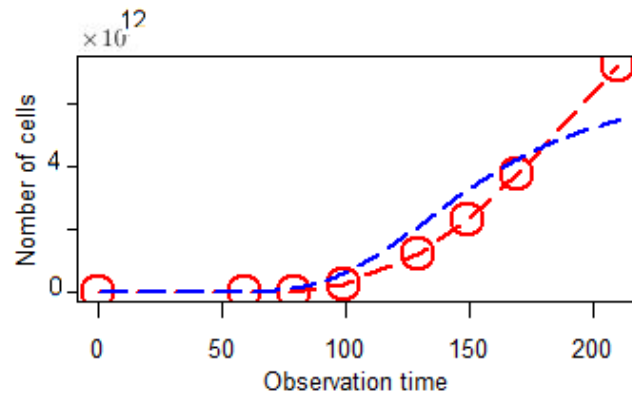


Fig. 12. Dormant cells dynamics (red) and its estimated (blue) according to Table 3.

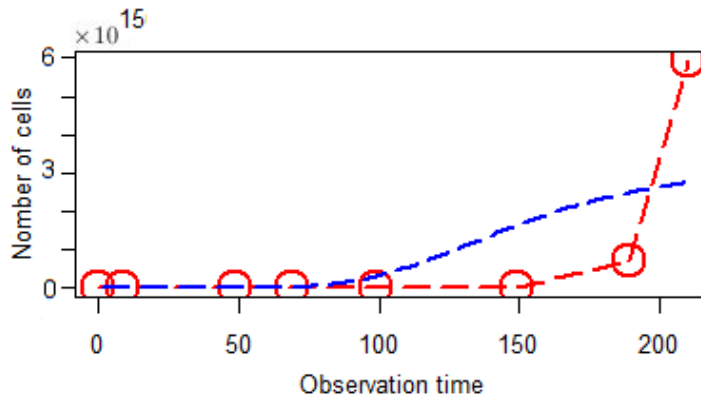


Fig. 13. Resistant cells dynamics (red) and its estimated (blue) according to Table 3.

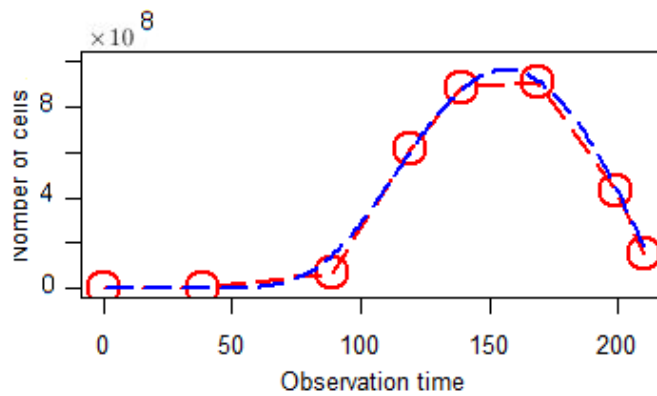


Fig. 14. Susceptible cells dynamics (red) and its estimated (blue) according to Table 3.

Table 4. Data estimates with observer(3.13) using Table 2

Times (months)	Simulated Cells		Estimated Cells		
	Observed	Dormant	Susceptible	Dormant	Resistant
1/30	1.00	1.00	0.00	1.00	1.00
10	2.89×10^2	3.40×10^2	1.65×10^1	3.43×10^2	2.7279×10^2
50	3.45×10^8	3.90×10^2	1.30×10^7	3.89×10^8	3.32×10^8
70	8.28×10^9	8.90×10^8	2.68×10^8	8.89×10^8	8.02×10^9
100	1.08×10^9	1.00×10^{11}	2.87×10^9	1.03×10^{11}	1.05×10^{11}
150	5.43×10^{11}	3.75×10^{11}	9.47×10^9	3.72×10^{11}	5.34×10^{11}
190	8.03×10^{11}	4.13×10^{11}	6.31×10^9	4.11×10^{11}	7.97×10^{11}
221	8.74×10^{11}	4.35×10^{11}	1.58×10^9	4.36×10^{11}	8.72×10^{11}

Table 5. Data estimates with observer(3.13) using Table 4

Times (months)	Simulated Cells		Estimated Cells		
	Observed	Dormant	Susceptible	Dormant	Resistant
1	0.00	1.00	0.00	0.00	1.00
10	1.85×10^2	0.00	3.43×10^2	1.00	2.73×10^2
50	5.87×10^5	3.30×10^8	3.89×10^8	3.27×10^8	5.74×10^5
70	6.31×10^7	1.00×10^5	5.81×10^5	7.86×10^{11}	2.06×10^7
100	4.93×10^8	1.00×10^{11}	6.29×10^7	1.03×10^5	8.22×10^8
150	1.12×10^{10}	5.08×10^5	9.845×10^9	5.23×10^5	1.33×10^9
190	2.71×10^{11}	7.49×10^5	1.99×10^{11}	7.51×10^5	7.27×10^{10}
221	1.19×10^{11}	8.73×10^5	5.99×10^{11}	8.71×10^5	5.93×10^{11}

4.3 Discussions

Resistance to therapies is a major issue in cancer treatment. This resistance is often caused by tumor dormancy. Tumor dormancy is defined as the long-term persistence of occult cancer cells. It has been reported for several cancers, including breast cancer, melanoma, kidney cancer, osteogenic sarcoma and gastric cancer. This phenomenon has also been observed clinically after treatment. It is thought to reflect the existence of residual tumor cells that do not respond to conventional treatments. We have proposed a mathematical method for estimating dormant cells and the rate at which cancer cells enter dormancy. This estimation method allows to simulate the different types of cancer cells, in order to predict the response of a tumor to a series of therapies, and thus find the therapeutic combination for which the patient will not develop resistance. Comparison with experimental data is promising at this time. This method is based on the statistical inference of a deterministic limit process of birth and death in a large population.

Tumor dormancy is a condition defined by the presence of fully transformed cells in a host that does not cause cancerous disease and thus differs from other pre-cancerous conditions. In preclinical models, dormant tumor cells exist either as solitary cells scattered throughout the organs or as non-angiogenic micrometastases. However, a small fraction (metastatic subclone) of dormant tumor cells appear late in tumor progression and have the capacity to disseminate to form metastases. Dissemination of tumor cells prior to surgical resection of tumors poses a serious risk to the disease-free survival of cancer patients.

Although most tumor cells die under hypoxic conditions, some can adapt and survive for days or months in a dormant state. Dormant tumor cells are characterized by cell cycle arrest in the G_0 phase and low metabolism,

and are refractory to current chemotherapy, causing metastasis. Dormant cells are then the source of metastasis. The development of metastasis is the leading cause of death in cancer patients. As science begins to learn more about the formation of the metastatic process of cancer, it therefore seems reasonable and necessary that we propose a method for estimating dormant cells and the rate at which cancer cells enter dormancy. In the Section 3 we presented a mathematical method to estimate the different types of cells that the tumor mass contains. In the Section 4.2, we have shown that our results from the Section 3 can reproduce the dynamics of a cancer, thus helping practitioners in their decision making. We hope that the results obtained from this estimation method will facilitate the design of dormant cancer clinical trials and accelerate the design of effective and robust tumor therapies.

5 Conclusion

In this work, we have developed an approach for estimating tumor cells and the rate at which these cells enter dormancy. Its originality is based on two main aspects. On the one hand, the modeling of tumor heterogeneity as a population consisting of three cell types: sensitive cells, resistant cells and dormant cells. Dormant tumor cells explore a process much studied, nowadays, by practitioners but rarely addressed in the mathematical modeling of the cancerous tumor. And on the other hand, the estimation of the different types of cancer cells and the rate of tumor dormancy using control theory through the construction of a linear observer with unknown inputs. The latter explores a process little known to biologists and rarely addressed in mathematical models of the dormant cancerous tumor.

An analytical resolution has been developed. And a set of numerical simulations of the results obtained has been set up to explore our problems and quantify our observations on the behavior of tumor cells. Not lacking real data on patients, we simulated the branching model of [38] and made a comparative study with the observer obtained. The results provided by the observer are encouraging. We note that the estimation is all the more effective than the data of a cancer patient. However, these results were obtained for fixed values of parameters of existing works. The biological parameters established by existing work have allowed us to compare the dynamics of simulated cancer cells and their estimates. However, the use of experimental data is encouraging.

Competing Interests

Authors have declared that no competing interests exist.

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