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A Stochastic Optimal Control Model for BCG Immunotherapy in Superficial Bladder Cancer

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Abstract. Urologic studies have reported in several papers that the optimal dose of Bacillus Calmette-Guérin (BCG) immunotherapy in superficial bladder cancer, is still a subject of research. Our main goal from this paper, is to find treatment regimens that minimize the total number of tumors in the presence of a diffusion process. For this, we devise a stochastic model in the form of a nonlinear system of four stochastic differential equations (SDEs) that describe tumor-immune dynamics after BCG instillations. Therefore, we study the existence and the stability results. Then, we introduce a control function in the mathematical model, to represent the dose of BCG intravesical therapy, and we seek its optimal values through the application of a stochastic version of Pontryagin's maximum principle. Finally, we present some numerical simulations using iterative stochastic Runge-Kutta progressive-regressive schemes which we propose for solving the optimality system of the obtained stochastic two-point boundary value problem.

Keywords and phrases: BCG immunotherapy, Stochastic Stability, Stochastic maximum principle, Bladder cancer, Optimal control.

Mathematics Subject Classification: 92C50, 49K45, 60H10, 93E15, 93E20

1. Introduction

1.1. Overview on Bacillus Calmette-Guérin (BCG)

Edmond Nocard, a french veterinarian and microbiologist, isolated Mycobacterium bovis in 1904, from a cow affected by mammary tuberculosis, and sent it to doctor Calmette [11]. In 1908, Calmette and Guérin cultivated this bacteria on a beef bile at the Pasteur Institute of Lille to obtain homogeneous cultures with a better dispersion of bacilli [11]. During 13 years and after 231 experiences, Calmette and Guérin, observed in 1918 that this mycobacterium had lost its large virulence to become an attenuated mycobacterium, and Bacille Calmette-Guérin (BCG) was developed [12]. It was not until 1921 and for the first time that a child was vaccinated against tuberculosis using the attenuated mycobacterium [12]. At that time, this bacteria strain was used only from fresh cultures of mycobacteria and hence, different

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strains were developed from the French strain and distributed worldwide.

In the midst of many years ago, between 1929 and 1977, researchers suggested the use of BCG in the treatment of tuberculosis and in cancer therapies [29]. Nowadays, BCG intravesical therapy is the treatment of reference for bladder tumors that do not infiltrate the bladder muscle with a high risk of recurrence and progression (high-grade carcinoma in situ) [8]. According to recent studies, and based on many trials of patients, Michael A. O'Donnel reported efficacy of BCG in preventing cancer growth, explaining the connection between tumor grades and the effect of BCG [28]. The classical experimental induction treatment of BCG immunotherapy comprises an intravesical instillation per week for 6 weeks, and can be followed by switch maintenance treatment which consists of an instillation per week for 1 to 3 weeks, administered for 6, 12, 18, 24, 30 and 36 months [28]. Despite of several results that have recently been conducted on BCG, researchers still struggle to provide an accurate explanation of its mechanism of action [11],[28]. Physicians have currently developed drugs in fight against cancer. However, toxic side-effects of these clinical products are not yet limited and their treatment efficacy is not assumed to be really optimized due to management problems. In fact, the choice of an optimal therapeutic strategy is mainly conditioned by a good knowledge of the disease evolution, especially by a precise classification of its stage, and a control of the inter-individual variability (the action of the drug may vary from one patient to another, even if they belong to the same population) in order to design adapted treatments in function of each case. The inter-individual variability may cause a problem when the therapeutic goal is very accurate, and can be counted as the main reason to use chemotherapy after measuring biological variables, using blood sampling of each patient. However, depending on the type of chemotherapeutic drugs and the quantity administered, chemotherapy cause unpleasant side-effects such as damaging normal cells because it targets rapidly dividing cancer cells and then also healthy cells.

Compared to other anti-tumor drugs, BCG immunotherapy is the most effective clinical procedure for intermediate and high-risk patients [33]. In particular, BCG efficacy is limited by its potential adverse reaction profile showing a cause of side-effects for approximately 90% of patients affected with bladder cancer [12],[29]. Recently, Roxana Agurid$\check{a}$ et al. [3] reported many kind of BCG side-effects including arthritis for a 50 years-old female patient affected with bladder cancer, operated in January 2014. On the other hand, research on urology reported in several papers that the optimal dose of BCG, its maintenance schedule and duration of its treatment, are yet unknown [1].

In this context, BCG optimization based on mathematical modeling could be a very effective tool to resolve such dosage problems, seeking an optimal dosage amount of BCG for lesser side-effects and for stimulating the immune-system cells that could destroy the tumors.

1.2. BCG immunotherapy and mathematical modeling

Generally, among the objectives of mathematical modeling in cancer therapies, is to provide a posology to ensure drug effect over time while minimizing its possible toxic action. Several research papers on oncology have published works on mathematical models that describe in an approximate way, cancers existing until now for which researchers have not found remedies and definitive therapeutic procedures for cure [6],[14],[20],[21]. Mathematical models of bladder cancer were established for the first time by Bunimovich et al. [7],[8], describing dynamical behavior of tumoral cells with immune-system cells after the injection of BCG in human bladder.

In the following, we will present briefly the deterministic version of the mathematical modeling of BCG immunotherapy in superficial bladder cancer.

Parameter	Physical interpretation (units)	Estimated value	Reference
μ_1	BCG mortality rate (days^{-1})	0.1	[4]
μ_2	E mortality rate (days^{-1})	0.041	[22]
p_1	BCG mortality rate killed by APC (cells^{-1}days^{-1})	1.25×10^{-7}	[34]
p_2	Tumor cells infection rate by BCG ...	0.285×10^{-7}	[7]
p_3	T_b destruction rate by effector cells ...	1.1×10^{-7}	[22]
p_4	Immune response activation rate ...	0.2×10^{-7}	[7]
p_5	E deactivation rate after binding with T_i ...	3.45×10^{10}	[22]
α	E stimulation rate by T_b ($t^{-1} = days^{-1}$)	0.052	[34]
β	$1/\beta$ =tumor carrying capacity (cells^{-1})	0.11×10^{-7}	[24]
r	Tumor growth rate ($t^{-1} = days^{-1}$)	0.0032	[32]

TABLE 1. List of all parameters of the system (1.2):

1.2.1. Deterministic model

Let us first present the mathematical form of the deterministic optimal control problem studied with different approaches in [12] and [13] based on the mathematical model devised by Bunimovich et al. in [7].
In fact, the control system has been considered as follows

$$\begin{cases} X'(t) = f(t, X(t), u(t)); \quad 0 \leq t \leq t_f \\ X(t_0) = X_0 \quad given. \end{cases} \tag{1.1}$$

with the state vector $X(t) = \begin{pmatrix} B(t) \\ E(t) \\ T_i(t) \\ T_u(t) \end{pmatrix} \in \mathbb{R}^4$, the control function $u(t) \in \mathbb{R}$ is assumed to be bounded between two numerical values $\lambda_1 = p \times 3.14 \times 10^7 c.f.u.$ (colony forming unit) and $\lambda_2 = p \times 9.14 \times 10^7 c.f.u.$ [10],[12] where p=0.01 meaning that only 1% of BCG that remains functional when it is administered in the bladder [7].
Explicitly, the differential system (1) has been expressed using the following ordinary differential equations

$$\begin{cases} \dfrac{dB}{dt}(t) = -\mu_1 B(t) - p_1 E(t) B(t) - p_2 B(t) T_u(t) + u(t) \\ \dfrac{dE}{dt}(t) = -\mu_2 E(t) + \alpha T_i(t) + p_4 E(t) B(t) - p_5 E(t) T_i(t) \\ \dfrac{dT_i}{dt}(t) = -p_3 E(t) T_i(t) + p_2 B(t) T_u(t) \\ \dfrac{dT_u}{dt}(t) = -p_2 B(t) T_u(t) + r(1 - \beta T_u(t)) T_u(t) \end{cases} \tag{1.2}$$

where B, E, T_i and T_u denote the concentrations of BCG in the bladder, activated immune-system cells, uninfected and infected tumor cells with BCG respectively. We present in Table 1 the verified values of all experimental parameters of the mathematical model above mentioning their references.

In [12] and [13], the authors have considered the mathematical model (2) which describes the tumor-immune interactions, and we have suggested two different optimal control problems which aimed to minimize the optimal dose of BCG sufficient for the eradication of cancer cells and the activation of the immune system with lesser side-effects. In the first study [12], the authors formulated an isoperimetric optimal control problem which considers a constraint on the total amount of BCG, while in the second work [13], they discussed the therapeutic problem when there is either a quadratic treatment cost, or a linear one.

In this work, we take into account some random biological factors. In fact, real biological systems, are often unprotected from natural perturbations that could not always be understood for

reason they produce in a microscopic level, difficult to observe, and that complicates the detection and analysis of cellular or molecular reactions that often create a noise or a stochasticity [6]. To highlight this phenomenon in the case of our study, we suppose in the next section, that the differential system (2) follows a diffusion process. In other words, we suppose that the behavior of the dynamics of the tumor population with the immune-system during the instillations of BCG in the bladder, is not deterministic. Seeking an optimal dose of BCG with taking into account all those considerations, lead us to propose and study a stochastic version of the previous optimal control problem.

In the following, we are interested to provide a mathematical study of the stochastic model we will suggest, including the characterization, the existence and the stability results. As regards to the final section, we will present some numerical simulations of the stochastic case, in an attempt to provide a comparison with the deterministic case results obtained in [12] and [13].

1.2.2. Stochastic model

The main goal of this paper is to seek an optimal dose of BCG taking in considerations natural perturbations that can affect the biological components of the bladder immune-system, and also BCG when it is injected. It leads to resolve a stochastic optimal control problem, that we choose to resolve based on a stochastic version of Pontryagin's maximum principle [5],[30],[36].

For this, let $(\Omega; \mathcal{F}; \mathcal{P}; \{\mathcal{F}_t\}_{t\geq 0})$ be a filtered probability space satisfying the usual conditions. Assume that a standard 4-dimensional Brownian motion $\{W_t\}_{t\geq 0}$ is defined on this space, and consider the following stochastic differential system.

$$\begin{cases} dX(t) = f(t, X(t), u(t))dt + \sigma(t, X(t))dW_t \\ X(t_0) = X(0) \quad given. \end{cases} \tag{1.3}$$

where $\sigma(t, X(t))$ is a diffusion coefficient function, and

$$f(t, X(t), u(t)) = \begin{pmatrix} -\mu_1 B(t) - p_1 E(t)B(t) - p_2 B(t)T_u(t) + u(t) \\ -\mu_2 E(t) + \alpha T_i(t) + p_4 E(t)B(t) - p_5 E(t)T_i(t) \\ -p_3 E(t)T_i(t) + p_2 B(t)T_u(t) \\ -p_2 B(t)T_u(t) + r(1 - \beta T_u(t))T_u(t) \end{pmatrix}.$$

The study of existence for solutions of (3) will be provided in the section 3.

2. Statement of stochastic maximum principle

Either in the deterministic optimal control problem or in the stochastic case, we often need an optimal control, solution of a cost functional which defines our optimization objective.
Let

$$J(u) = \mathbb{E}(\varphi(t_0, t_f, X(t_0), X(t_f)) + \int_{t_0}^{t_f} g(t, X(t), u(t))dt)$$

be the objective functional of our problem and where g and φ represent respectively the current and terminal gain functions, subject to (1.3).

Motivated by the desire to keep the BCG dose low while minimizing the total number of tumor cells we define by $T = T_i + T_u$ in a minimal period, we choose
$\varphi(t_0, t_f, X(t_0), X(t_f)) = 0$ and $g(t, X(t), u(t))dt) = T(t) + \frac{b}{2}.u^2(t)$.

Thus, the objective functional J becomes
$J(u) = \mathbb{E}(\int_0^{t_f}[T(t) + \frac{b}{2}.u^2(t)]dt)$ over the control space U defined by
$U([0, t_f]) = \{u(t)\ \mathcal{F}_t\text{-}progressively\ mesurable | \lambda_1 \leqslant u(t) \leqslant \lambda_2, t \in [0, t_f]\}$
with b a constant severity weight for the control u.

We can formulate the hamiltonian of SDE in general form by
$H(t, X(t), \mu(t), \nu(t), u(t)) = T(t) + \frac{b}{2}.u^2(t) + \mu^T f(t, X(t), u(t)) + tr[\nu^T \sigma(t, X(t))]$,
where $(\mu(t), \nu(t)))$ is a pair of adjoint variables satisfying the following adjoint BSDE (Backward stochastic differential equation)

$$\begin{cases} d\mu(t) = -[f_X^T(t, X(t), u(t))\mu(t) + \sum_{j=1}^{k} {\sigma_X^j}^T(t, X(t), u(t))\nu_j(t) \\ \qquad\quad +g_X(t, X(t), u(t))]dt + \nu(t)dW_t, \\ \mu(t_f) = \varphi_X(t_0, t_f, X(t_0), X(t_f)). \end{cases} \tag{2.1}$$

Here $.^T$ means the transposition. Using a stochastic version of Pontryagin's maximum principle [36], we characterize the optimal control u in the following theorem to find its analytical formulation.

Theorem 2.1. *(Stochastic maximum principle and characterization of u)*
If there exists an optimal pair (X^*, u^*) and a pair of processes $(\mu(t), \nu(t))$ satisfying (4), then we have

$$H(t, X^*(t), \mu(t), \nu(t), u^*(t)) = \min_{u \in U} H(t, X(t), \mu(t), \nu(t), u(t)).$$

Moreover, we obtain the bounded stochastic control

$$u^* = min(max(\lambda_1, -\frac{\mu_1(t)}{b}), \lambda_2),$$

solution of the FBSDEs (Forward-backward stochastic differential equations)

$$\begin{cases} dX(t) = f(t, X(t), u(t))dt + \sigma(t, X(t))dW_t, \\ d\mu(t) \ = -[f_X^T(t, X(t), u(t))\mu(t) \\ \qquad\quad + \sum_{j=1}^{k} {\sigma_X^j}^T(t, X(t))\nu_j(t) + g_X(t, X(t), u(t))]dt \\ \qquad\quad +\nu(t)dW_t, \\ X(0) \ = X_0, \\ \mu(t_f) \ = 0. \end{cases} \tag{2.2}$$

Proof: Since our control u is bounded, we then prove the previous theorem by using the following lagrangian

$$L = T(t) + \frac{b}{2}.u^2(t) + \mu^T f(t, X(t), u(t)) + tr[\nu^T \sigma(t, X(t))] + \omega_1(\lambda_2 - u) + \omega_2(u - \lambda_1),$$

where $\omega_1, \omega_2 \geqslant 0$ verifying at $u = u^*$, the two conditions

$$\omega_1(\lambda_2 - u^*) = 0 \text{ and } \omega_2(u^* - \lambda_1) = 0.$$

Owing to the condition of minimization we define by

$$L(t, X^*(t), \mu(t), \nu(t), u^*(t), \omega_1(t), \omega_2(t)) = \min_{u \in U} L(t, X(t), \mu(t), \nu(t), u(t), \omega_1(t), \omega_2(t)).$$

We differentiate the lagrangian with respect to u on the set $\{t | \lambda_1 \leqslant u(t) \leqslant \lambda_2\}$ to obtain the optimality equation

$$\frac{dL}{du}(t, X(t), \mu(t), \nu(t), u(t), \omega_1(t), \omega_2(t))|_{u=u^*} = bu(t) + \mu_1(t) - \omega_1(t) + \omega_2(t) = 0.$$

Furthermore, we find $u^*(t) = -\frac{\mu_1(t) - \omega_1 + \omega_2}{b}$.

- ***if*** $\lambda_1 < u^*(t) < \lambda_2$***, then*** $w_1(t) = w_2(t) = 0$ *, therefore* $u^*(t) = -\frac{\mu_1(t)}{b}$.

- ***if*** $u^*(t) = \lambda_1$ ***then*** $w_1(t) = 0$, *therefore* $\lambda_1 = -(\frac{\mu_1(t) + w_2(t)}{b})$ *implying that* $w_2(t) = -(\mu_1(t) + b\lambda_1)$.
Due to $w_2(t) \geq 0$ *and* $b > 0$, *we obtain* $u^*(t) \leq -\frac{\mu_1(t)}{b}$
- ***if*** $u^*(t) = \lambda_2$ ***then*** $w_2(t) = 0$ *thus* $\lambda_2 = -\frac{\mu_1(t) - w_1(t)}{b}$ *implying that* $w_1(t) = \mu_1(t) + b\lambda_2$.
In view of $w_1(t) \geq 0$ *and* $b > 0$, *we get* $u^*(t) \geq -\frac{\mu_1(t)}{b}$.

Using these standard optimality arguments, we characterize the control $u^*(t)$ by

$$u^*(t) = \begin{cases} -\frac{\mu_1(t)}{b} \ if \ \ \lambda_1 < -\frac{\mu_1(t)}{b} < \lambda_2 \\ \lambda_1 \qquad if \ \ -\frac{\mu_1(t)}{b} \leqslant \lambda_1 \\ \lambda_2 \qquad if \ \ -\frac{\mu_1(t)}{b} \geqslant \lambda_2 \end{cases}$$

or by a more reduced form, we can rewrite $u^*(t) = min(max(\lambda_1, -\frac{\mu_1(t)}{b}), \lambda_2))$.
In the deterministic case, we can verify the existence of the control by its compactness, state spaces and the convexity in the problem; see such results in Theorem 4.1 in [17] and its uniqueness is due to the uniqueness of the solutions of the optimality system following the Lipschitz properties that are valid if the final time is sufficiently small [15].

3. Existence of the stochastic optimal control

The state system (1.3) is rewritten as follows

$$\begin{array}{l} dX(t) = (\hat{f}(t, X(t)) + f_1(X(t))u(t))dt + \sigma(t, X(t))dW(t), \\ X(0) = X_0 \quad given. \end{array} \tag{3.1}$$

where

$$\hat{f}(t, X(t)) = \begin{pmatrix} -\mu_1 B(t) - p_1 E(t)B(t) - p_2 B(t)T_u(t) \\ -\mu_2 E(t) + \alpha T_i(t) + p_4 E(t)B(t) - p_5 E(t)T_i(t) \\ -p_3 E(t)T_i(t) + p_2 B(t)T_u(t) \\ -p_2 B(t)T_u(t) + r(1 - \beta T_u(t))T_u(t) \end{pmatrix},$$

with $f_1(X(t)) = (1, 0, 0, 0)$.

Note that $f : [0, t_f] \times \mathbb{R}^4 \times U \to \mathbb{R}^4$, $\sigma : [0, t_f] \times \mathbb{R}^4 \to \mathbb{R}^4 \bigotimes \mathbb{R}^4$
and $g : [0, t_f] \times \mathbb{R}^4 \times U \to \mathbb{R}$ are measurable such that
$f(t, x, .) : U \to \mathbb{R}^4$, and $g(t, x, .) : U \to \mathbb{R}^4$ are continuous,
f, σ and g are bounded, and there exists a constant $K > 0$ such that for all $t \in [0, t_f]$ and for all $X, X^{'} \in \mathbb{R}^4$, the following properties are checked [5],[30]

$$|f(t, X(t), u(t)) - f(t, X^{'}(t), u(t))| + ||\sigma(t, X(t)) - \sigma(t, X^{'}(t))|| \leq K|X - X^{'}| \tag{3.2}$$

In fact, if we suppose $X = (B, E, T_i, T_u)$, $X^{'} = (B', E', T_i', T_u') \in \Omega \subset \mathbb{R}^4$ with $\Omega =]a_1, a_2[\times]b_1, b_2[\times]c_1, c_2[\times]d_1, d_2[$ ($a_{i=1,2}, b_{i=1,2}, c_{i=1,2}$ and $d_{i=1,2}$ are positive constants), and noting that in this paper, we will consider thereafter that $\sigma(t, X(t)) = (\sigma_1(X_1 - X_1^*), \sigma_2(X_2 - X_2^*), \sigma_3(X_3 - X_3^*), \sigma_4(X_4 - X_4^*))^T$ a definite positive matrix with X^*; the stability cancer equilibrium point, and $\sigma_{i=1,..,4}$ positive constants, then, in order to prove (3.2), we can take a constant $K_1 = \max(\sigma_1, \sigma_2, \sigma_3, \sigma_4)$ to obtain $||\sigma(t, X(t)) - \sigma(t, X^{'}(t))|| \leq K_1|X - X^{'}|$,
while taking also
$K_2 = \max(\mu_1, \mu_1 + p_1 b_2 + p_2 d_2)$,
$K_3 = \max(\mu_2, \mu_2 + p_4 a_2 + p_5 c_2)$,

$K_4 = \max(p_3 b_2 + p_2 a_2 d_2)$
and $K_5 = \max(p_2 a_2, p_2 a_2 + 2\beta d_2)$,
Thus, using the maximum norm, we have
$|f_1(t, X(t), u(t)) - f_1(t, X^{'}(t), u(t))| \leq K_2 |X - X^{'}|$,
$|f_2(t, X(t), u(t)) - f_2(t, X^{'}(t), u(t))| \leq K_3 |X - X^{'}|$,
$|f_3(t, X(t), u(t)) - f_3(t, X^{'}(t), u(t))| \leq K_4 |X - X^{'}|$
and $|f_4(t, X(t), u(t)) - f_4(t, X^{'}(t), u(t))| \leq K_5 |X - X^{'}|$

with f_1, f_2, f_3, and f_4 the right-hand sides of differential equations in (1.2). Thus, by setting $f = (f_1, f_2, f_3, f_4)$, the property (3.2) is checked by considering $K = \max(K_1, K_2, K_3, K_4, K_5)$.

and we should also have

$$|g(t, X(t), u(t)) - g(t, X^{'}(t), u(t))| \leq K |X - X^{'}|. \tag{3.3}$$

which can easily be checked for the particular integrand supposed here.

Proposition 3.1. *The optimal control problem identified by the objective functional J and linked to the state system (1.3) which satisfies the properties (3.2) and (3.3) admits an optimal control pair.*

Proof: At first, a backward stochastic differential equation (BSDE) with a terminal condition is introduced

$$\begin{array}{l} dY(t) = -g(t, X(t), u(t))dt + Z(t)dW(t),\ t \in [0, t_f] \\ Y(t_f) = 0 \quad given. \end{array} \tag{3.4}$$

where

$$g(t, X(t), u) = T(t) + \frac{b}{2}.u^2(t))$$

Note that under the previous observations, (3.2) and (3.3), for $(X_0, u) \in \mathbb{R}^3 \times U \times U$, the backward stochastic differential equation (3.4) becomes linear. Therefore, the state system admits a unique strong solution [36] that is written in the following form $X(.) \equiv X(.; X_0, u)$.
Moreover, for a given $(X(.), u)$, the backward stochastic differential equation (3.4) admits a unique adapted solution $(Y(.), Z(.)) \equiv (Y(.; X_0, u), Z(.; X_0, u))$ which depends on (X_0, u) through $(X(.), u)$.
Notice that for $t \in [0, T]$, the process $Y(t)$, solution of (3.4) has the general form

$$Y(t) = Y(t_f) + \int_t^{t_f} g(t, X(t), u(t))dt - \int_t^{t_f} Z(t)dW(t), \tag{3.5}$$

Denote that $\mathcal{F}_t$ is the natural filtration of the Brownian motion $W(t)$. Here, $Y(t)$ is $(\mathcal{F}_t)_{t \geq 0}$-adapted [36] implying that

$$Y(t) = \mathbb{E}[Y(t)|\mathcal{F}_t], \quad t \in [0, t_f]. \tag{3.6}$$

Thus,

$$Y(0) = J(u) = \mathbb{E}[\int_0^{t_f} (T(t) + \frac{b}{2} u^2(t))dt] \tag{3.7}$$

Now, the objective functional J can be rewritten as

$$J(u) = Y(0; X_0, u) \tag{3.8}$$

Considering the new formulation of the objective function (3.8), a forward backward stochastic differential equations (FBSDE) system is introduced

$$\begin{array}{l} dX(t) = (\hat{f}(t, X(t)) + f_1(X(t))u(t))dt + \sigma(t, X(t), u(t))dW(t), \\ dY(t) = -(T(t) + \frac{b}{2} u^2(t))dt + Z(t)dW(t), \\ X(0) = X_0, \quad Y(t_f) = 0 \quad \text{given}. \end{array} \tag{3.9}$$

In the following, we will use an appropriate approach in order to use a parabolic formulation and to establish the existence result.

In fact, if (X, Y, Z) is an adapted solution of (3.9). Then, there exists an appropriate function θ such that the following relationship is verified [27]

$$Y(t) = \theta(t, X(t), u(t)),\ t \in [0, t_f]\ \ a.s.\mathcal{P}, \tag{3.10}$$

where the undetermined function θ is assumed to be of $\mathcal{C}^{1,2,0}([0, t_f] \times R^4 \times U)$.

The control u is sought to minimize the cost functional $Y(0) = J(u)$. From (3.9), we have

$$dY(t) = -(T(t) + \frac{b}{2}u^2(t))dt + Z(t)dW(t).$$

For applying Ito's formula to $\theta(t, X(t), u(t))$, start by using Taylor's polynomial

$$d\theta(t, X(t), u(t)) = \theta_t(t, X(t), u(t))dt + \theta_X(t, X(t), u(t))dX + \frac{1}{2}\theta_{XX}(t, X(t), u(t))(dX)^2,$$

recall that

$$dX(t) = (\hat{f}(t, X(t)) + f_1(X(t))u(t))dt + \sigma(t, X(t))dW(t).$$

Replacing the formulation of $dX(t)$ in $d\theta(t)$

$$\begin{aligned} d\theta(t, X(t), u(t)) &= \theta_t(t, X(t), u(t))dt + \theta_X(t, X(t), u(t))[\hat{f}(t, X(t)) + f_1(X(t))u(t)]dt \\ &+ \theta_X(t, X(t), u(t))\sigma(t, X(t))dW(t) \\ &+ \frac{1}{2}\theta_{XX}(t, X(t), u(t))[((\hat{f}(t, X(t)) + f_1(X(t))u(t))dt)^2 \\ &+ (\sigma(t, X(t))dW(t))^2 + 2\sigma(t, X(t))(\hat{f}(t, X(t)) + f_1(X(t))u(t))dtdW(t)]. \end{aligned}$$

and using Ito's multiplication, to obtain the final formulation of $d\theta(t)$

$$\begin{aligned} d\theta(t, X(t), u(t)) &= [\theta_t(t, X(t), u(t)) + \frac{1}{2}\theta_{XX}(t, X(t), u(t))\sigma^2(t, X(t)) \\ &+ \theta_X(t, X(t), u(t))(\hat{f}(t, X(t)) + f_1(X(t))u(t))]dt \\ &+ \theta_X(t, X(t), u(t))\sigma(t, X(t))dW(t)., \end{aligned}$$

According to (3.9), by equating corresponding drift terms $dY(t)$ and $d\theta(t)$, the following parabolic PDE is obtained

$$\begin{aligned} d\theta(t, X(t), u(t)) &= [\theta_t(t, X(t), u(t)) + \frac{1}{2}\theta_{XX}(t, X(t), u(t))\sigma^2(t, X(t)) \\ &+ \theta_X(t, X(t), u(t))(\hat{f}(t, X(t)) + f_1(X(t))u(t)]dt \\ &+ \theta_X(t, X(t), u(t))\sigma(t, X(t))dW(t). \\ &= -(T(t) + \frac{b}{2}u^2(t))dt + Z(t)dW(t). \end{aligned}$$

Substitute $Z(t) = \theta_X(t, X(t), u(t))\sigma(t, X(t))$ into the above parabolic PDE to obtain

$$\begin{aligned}
0 &= \theta_t + \frac{1}{2}\theta_{XX}\sigma^2 + \theta_X(\hat{f} + f_1 u) + T + \frac{b}{2}u^2 \\
&= \theta_t + \frac{1}{2}\theta_{XX}\sigma^2 + \theta_X\hat{f} + T + f_1\theta_X u + \frac{b}{2}u^2 \\
&= \theta_t + \frac{1}{2}\theta_{XX}\sigma^2 + \theta_X\hat{f} + T \\
&+ f_1\theta_X u + \frac{b}{2}u^2 + \frac{1}{2b}|f_1\theta_X|^2 - \frac{1}{2b}|f_1\theta_X|^2 \\
&= \theta_t + \frac{1}{2}\theta_{XX}\sigma^2 + \theta_X\hat{f} + T \\
&- \frac{1}{2b}|f_1\theta_X|^2 + \frac{b}{2}[u^2 + \frac{|f_1\theta_X|^2}{b^2} + \frac{2f_1\theta_X u}{b}] \\
&= \theta_t + \frac{1}{2}\theta_{XX}\sigma^2 + \theta_X\hat{f} + T + \frac{b}{2}[u + \frac{f_1\theta_X}{b}]^2 - \frac{1}{2b}|f_1\theta_X|^2.
\end{aligned}$$

By rearranging terms, the above equation can be written in the form of a backward parabolic PDE with a terminal condition on θ

$$\begin{aligned}
&\theta_t + \tfrac{1}{2}\theta_{XX}\sigma^2 + \theta_X\hat{f} + T - \tfrac{1}{2b}|f_1^T\theta_X|^2 + \tfrac{b}{2}[u + \tfrac{f_1^T\theta_X}{b}]^2 = 0 \\
&\theta(t_f, X(t_f)) = 0, \quad X \in \mathbb{R}^3.
\end{aligned} \tag{3.11}$$

Using Maximum principle for parabolic partial differential equations (PPDE) [23], the biggest θ solution should be the one of the following PPDE problem

$$\begin{aligned}
&\theta_t + \tfrac{1}{2}\theta_{XX}\sigma^2 + \theta_X\hat{f} + T - \tfrac{1}{2b}|f_1^T\theta_X|^2 = 0 \\
&\theta(t_f, X(t_f)) = 0, \quad X \in \mathbb{R}^3.
\end{aligned} \tag{3.12}$$

For the resolution of (3.12), results from Ladyzenskaja et al. [23] show that there exists a unique classical solution for comparable types of parabolic partial differential equations. In this case, the control u is sought in order to minimize the objective function J such that

$$\min_{u\in U} J(u) = J(u^*),$$

Thus

$$\min_{u\in U} \theta(0; X(0), u) = \theta(0; X(0), u^*),$$

Then, using (3.5),(3.10) and (3.11) to obtain

$$\begin{aligned}
\int_0^{t_f} g(t, X(t), u(t))dt = \theta(0, X(0)) - \theta(t_f, X(t_f)) + \int_0^{t_f} Z(t)dW(t) \\
+ \theta_t + \frac{1}{2}\theta_{XX}\sigma^2 + \theta_X\hat{f} + T \\
- \frac{1}{2b}|f_1^T\theta_X|^2 + \frac{b}{2}[u + \frac{f_1^T\theta_X}{b}]^2.
\end{aligned}$$

Values of d for the **forward** scheme	Mean square error adapted to the algorithm
0.25	0.0020735
0.5	0.002089
0.75	0.0022725
Values of d for the **backward** scheme	Mean square error adapted to the algorithm
0.25	0.0019467
0.5	0.003119
0.75	0.006266

TABLE 2. Values of the constant d, with equivalent errors to each case

Therefore,

$$\begin{aligned} J(u) &= \mathbb{E}[\theta(0,X(0)) - \theta(t_f,X(t_f)) + \int_0^{t_f} Z(t)dW(t) \\ &+ \theta_t + \frac{1}{2}\theta_{XX}\sigma^2 + \theta_X\hat{f} + T \\ &- \frac{1}{2b}|f_1^T\theta_X|^2 + \frac{b}{2}[u + \frac{f_1^T\theta_X}{b}]^2 \\ &= \theta(0,X(0)) + \frac{b}{2}\mathbb{E}[u + \frac{f_1^T\theta_X}{b}]^2 \\ &\geq \theta(0,X(0)) = J(u^*). \end{aligned}$$

Consequently, it is finally concluded that $u^* = -\frac{f_1\theta_X}{b}$ is an optimal control. In the next section, we will study the stability of the considered problem.

4. Stochastic stability of the positive equilibrium

For simulations tests, we choose the diffusion coefficients functions σ and ν by $\sigma(t,X(t)) = d.(X(t) - X^*)$ and $\nu(t) = d\mu(t)$ with $d = 0.25$ a constant for the natural biological system disturbances and X^* the stability cancer equilibrium point. Table (2) exhibits the importance of choosing a specific value for d in 0.25, rather than other constants.

We recall that in the deterministic case [7], the differential system (2) admitted two points of cancer equilibrium when the first ordinary differential equation is expressed by $\frac{dB}{dt}(t) = -\kappa_1 B(t) - p_1 E(t)B(t) - p_2 B(t)T_u(t) + u(t)$ when $u(t) = c > 0$; an experimental optimal constant rate of BCG vaccine dosage and which is defined in a specific interval as reported in [10].
In other words, the deterministic mathematical model (2) is Lyapunov stable in the absence of therapy and locally stable in two different cases in the presence of therapy [7]. The following results were proved in [7] and are here just recalled because they are very relevant to the stochastic stability part.

Proposition 4.1. *In the absence of therapy, the equilibrium of system (1.2) is* $E_2 = (0,0,0,1/\beta)^T$.
In the presence of therapy; the equilibria of system (1.2) are E_1^c *and* E_2^c *such that:*

- *if* $\frac{r}{p_2} < c < \frac{\mu_2}{p_4}$, *we have* $E_1^c = (c,0,0,0)^T$ *which represents the tumor equilibrium point;*
- *if* $\frac{r}{p_2} < \frac{\mu_2}{p_4} < c$, *we have* $E_2^c = \left(\frac{\mu_2}{p_4}, \frac{cp_4}{\mu_2 p_1} - \frac{1}{p_1}, 0, 0\right)^T$ *which represents the side-effects equilibrium point.*
- *if* $r > r_{crit} = \frac{\mu_2 p_2}{p_4}$, *the positive equilibrium of system (1.2) is*

$$E_+ = \left(B^* = \frac{(1-\beta T_u^*)r}{p_2}, E^* = \frac{p_2 B^* T_u^*}{p_3 T_i^*}, T_i^* = \frac{p_1(1-\beta T_u^*)^2 r^2 T_u^*}{p_3(cp_2 + r(1-\beta T_u^*)(1-p_2 T_u^*))}, T_u^*\right)^T,$$

which represents the logistic tumor equilibrium.

To affect the cancer equilibrium X^* point, we define by

$$\sigma(t,X(t),u(t)) = d.(X(t)-X^*) = \begin{pmatrix} d.(B(t)-B^*) \\ d.(E(t)-E^*) \\ d.(T_i(t)-T_i^*) \\ d.(T_u(t)-T_u^*) \end{pmatrix}$$

the diffusion coefficient function in states and control with

$$B^* = \begin{cases} c & if \ \ \frac{r}{p_2} < c < \frac{\mu_2}{p_4} \\ \frac{\mu_2}{p_4} & if \ \ \frac{r}{p_2} < \frac{\mu_2}{p_4} < c \end{cases}, \ E^* = \begin{cases} 0 & if \ \ \frac{r}{p_2} < c < \frac{\mu_2}{p_4} \\ \frac{cp_4}{\mu_2 p_1} - \frac{1}{p_1} & if \ \ \frac{r}{p_2} < \frac{\mu_2}{p_4} < c \end{cases},$$

$T_i^* = 0$ and $T_u^* = 0$. For more details see [7,9].

In the stochastic case, system (2), we assume that the stochastic perturbations of the variables around their values at E^+ are of white noise type, which are proportional to the distances of $B,\ E,\ T_i, T_u$ from values $B^*,\ E^*,\ T_i^*, T_u^*$ [9]. So system (2) can be rewritten as

$$\begin{aligned} dB &= [-\mu_1 B - p_1 EB - p_2 BT_u + c]dt + \sigma_1(B-B^*)d\xi_t^1 \\ dE &= [-\mu_2 E + \alpha T_i + p_4 EB - p_5 ET_i]dt + \sigma_2(E-E^*)d\xi_t^2 \\ dT_i &= [-p_3 ET_i + p_2 BT_u]dt + \sigma_3(T_i - T_i^*)d\xi_t^3 \\ dT_u &= [-p_2 BT_u + G(T_u)]dt + \sigma_4(T_u - T_u^*)d\xi_t^4 \end{aligned} \tag{4.1}$$

where $\sigma_i,\ i = 1,\ldots,\ 4$, are real constants, $\xi_t^i = \xi_i(t),\ i = 1,\ldots,\ 4$, are independent from each other standard Wiener processes [19] and $c^* < c < c_0$. We inquire whether the dynamical behavior of model (1.1) is robust with respect to such a kind of stochasticity by investigating the asymptotic stochastic stability behaviour of equilibrium E^+ for (4.1) and comparing the results with those obtained for (1.1). In the following we will consider (4.1) as an Itô stochastic differential system of the type

$$\begin{aligned} dX_t &= f(t,X_t)dt + g(t,X_t)d\xi_t, \\ X_{t_0} &= X_0,\ t \in [t_0,t_f], \end{aligned} \tag{4.2}$$

where the solution $\{X_t, t \in [t_0,\ t_f]\}$ is an Itô process, f is the slowly varying continuous component or *drift coefficient* and g is the rapidly varying continuous random component or *diffusion coefficient* [18]. f is a d-vector-valued function, g is a $d \times m$ matrix-valued function and ξ_t is an m-dimensional stochastic process having scalar Wiener process components which increments $\Delta\xi_t^j = \xi_{t+\Delta t}^j - \xi_t^j = \xi_j(t+\Delta t) - \xi_j(t),\ j = 1,\ldots,m$ are independent Gaussian random variables $N(0,\Delta t)$.
Owing to system (4.1) it is $m = d = 4$ and $X = (B,E,T_i,T_u)^T$, $\xi_t = (\xi_t^1,\xi_t^2,\xi_t^3,\xi_t^4)^T$,

$$f = \begin{pmatrix} -\mu_1 B - p_1 EB - p_2 BT_u + c \\ -\mu_2 E + \alpha T_i + p_4 EB - p_5 ET_i \\ -p_3 ET_i + p_2 BT_u \\ -p_2 BT_u + G(T_u) \end{pmatrix} \tag{4.3}$$

$$g = \begin{pmatrix} \sigma_1(B-B^*) & 0 & 0 & 0 \\ 0 & \sigma_2(E-E^*) & 0 & 0 \\ 0 & 0 & \sigma_3(T_i-T_i^*) & 0 \\ 0 & 0 & 0 & \sigma_4(T_u-T_u^*) \end{pmatrix} \tag{4.4}$$

As the diffusion matrix (4.4) depends on the solution $X = (B,E,T_i,T_u)^T$, system (4.1) is said to have multiplicative noise. In addition, from the diagonal form of the diffusion matrix (4.4), system (4.1) is said to have (multiplicative) diagonal noise.
The stochastic differential system (4.1) can be centered at its positive equilibrium

$$E_+ = \left(B^* = \frac{(1-\beta T_u^*)r}{p_2}, E^* = \frac{p_2 B^* T_u^*}{p_3 T_i^*}, T_i^* = \frac{p_1(1-\beta T_u^*)^2 r^2 T_u^*}{p_3(cp_2 + r(1-\beta T_u^*)(1-p_2 T_u^*))}, T_u^* \right)^T \tag{4.5}$$

and T_u^* is a real positive root of a fifth-order polynomial. The Jacobian matrix at E_+ is

$$J = \begin{pmatrix} -1 - p_1E^* - p_2T_u^* & -p_1B^* & 0 & -p_2B^* \\ p_4E^* & -\mu + p_4B^* - p_5T_i^* & \alpha - p_5E^* & 0 \\ p_2T_u^* & -p_3T_i^* & -p_3E^* & p_2B^* \\ -p_2T_u^* & 0 & 0 & -p_2B^* + r - 2r\beta T_u^* \end{pmatrix} \tag{4.6}$$

It is easier to work on the SDEs obtained by linearizing the vector function f in (4.3) around the positive equilibrium E_+. In the next, we use the change of variables $\psi_1 = B - B^*,\ \psi_2 = E - E^*,\ \psi_3 = T_i - T_i^*,\ \psi_4 = T_u - T_u^*$. From the Jacobian matrix (4.6) the linearized SDEs around E_+ have the form

$$d\psi(t) = f(\psi(t))dt + g(\psi(t))d\xi(t), \tag{4.7}$$

where $\psi(t) = (\psi_1(t), \psi_2(t), \psi_3(t), \psi_4(t))^T$ and

$$f(\psi(t)) = \begin{pmatrix} (-1 - p_1E^* - p_2T_u^*)\psi_1 - p_1B^*\psi_2 - p_2B^*\psi_4 \\ p_4E^*\psi_1 + (p_4B^* - \mu - p_5T_i^*)\psi_2 + (\alpha - p_5E^*)\psi_3 \\ p_2T_u^*\psi_1 - p_3T_i^*\psi_2 - p_3E^*\psi_3 + p_2B^*\psi_4 \\ -p_2T_u^*\psi_1 + (r - p_2B^* - 2r\beta T_u^*)\psi_4 \end{pmatrix} \tag{4.8}$$

$$g(\psi(t)) = \begin{pmatrix} \sigma_1\psi_1 & 0 & 0 & 0 \\ 0 & \sigma_2\psi_2 & 0 & 0 \\ 0 & 0 & \sigma_3\psi_3 & 0 \\ 0 & 0 & 0 & \sigma_4\psi_4 \end{pmatrix} \tag{4.9}$$

Indeed in (4.7) the positive equilibrium E_+ corresponds to the trivial solution $\psi(t) = 0$. We have the following theorem.

Theorem 4.2. *Let $\mathcal{U}$ be the set $\mathcal{U} = \{(t \geq t_0) \times \mathbb{R}^n,\ t_0 \in \mathbb{R}^+\}$. Suppose there exists a function $V(t, \psi) \in C_2^0(\mathcal{U})$ satisfying the inequalities*

$$K_1|\psi|^p \leq V(t, \psi) \leq K_2|\psi|^p, \tag{4.10}$$

$$LV(t, \psi) \leq -K_3|\psi|^p,\ K_i > 0,\ p > 0. \tag{4.11}$$

Then the trivial solution of (4.7) is exponentially p-stable for $t \geq 0$.

Proof. For the proof, see the book by Alfanas'ev et al. [2]. □

It is worthy note that, if in (4.10) and (4.11) $p = 2$, then the trivial solution of (4.7) is *exponentially mean square stable*. Moreover, the trivial solution of (4.7) is *globally asymptotically stable in probability*. For more details on definitions of stability, see [2].
Remark that, with reference to (4.7),

$$LV(t, \psi) = \frac{\partial V(t, \psi(t))}{\partial t} + f^T(\psi(t))\frac{\partial V(t, \psi)}{\partial \psi} + \frac{1}{2}Tr\left[g^T(\psi(t))\frac{\partial^2 V(t, \psi)}{\partial \psi^2}g(\psi(t))\right] \tag{4.12}$$

with $g = g^T$ and where

$$\frac{\partial V}{\partial \psi} = col\left(\frac{\partial V}{\partial \psi_1}, \frac{\partial V}{\partial \psi_2}, \frac{\partial V}{\partial \psi_3}, \frac{\partial V}{\partial \psi_4}\right), \quad \frac{\partial^2 V(t, \psi)}{\partial \psi^2} = \left(\frac{\partial^2 V}{\partial \psi_j \partial \psi_i}\right)_{i,j=1,\ldots,4}.$$

We have the following theorem.

Theorem 4.3. *Let be*

$$E^+ = \left(B^* = \frac{(1-\beta T_u^*)r}{p_2}, E^* = \frac{p_2 B^* T_u^*}{p_3 T_i^*}, T_i^* = \frac{p_1(1-\beta T_u^*)^2 r^2 T_u^*}{p_3(cp_2 + r(1-\beta T_u^*)(1-p_2 T_u^*))}, T_u^* \right) \tag{4.13}$$

with

$$0 < B^* < \frac{\mu}{p_4}, \quad E^* > \frac{\alpha}{p_5} \quad \text{and} \quad T_u^* > \frac{1}{2\beta}. \tag{4.14}$$

Assume that for some positive real value ω_4 the following inequality holds true

$$\omega_4 < \frac{B^*(p_1 - p_2)}{p_2 T_u^*}, \tag{4.15}$$

with $p_1 > p_2$.
Then if

$$\sigma_1^2 < 2(1 + p_1 E^* + p_2 T_u^*), \quad \sigma_2^2 < \frac{2[(\mu - p_4 B^* + p_5 T_i^*)\omega_2^* + (\mu - p_4 B^* + p_5 T_i^* + p_3 T_i^*)\omega_5^*]}{\omega_2^* + \omega_5^*} \tag{4.16}$$

$$\sigma_3^2 < \frac{2[(-\alpha + p_5 E^* + p_3 E^*)\omega_5^* + p_3 E^* \omega_3^*]}{\omega_3^* + \omega_5^*}, \quad \sigma_4^2 < \frac{2[(p_2 B^* - r + 2r\beta T_u^*)\omega_4^* + (-r + 2r\beta T_u^*)\omega_5^*]}{\omega_4^* + \omega_5^*}, \tag{4.17}$$

where $\omega_2^* = \frac{p_1 B^* - p_4 E^* \omega_5}{p_4 E^*}$, $\omega_3^* = \frac{[(p_3+p_5)E^* - \alpha + r(2\beta T_u^* - 1)]\omega_5^*}{p_2 B^*}$, $\omega_5^* = \frac{p_2 B^* + p_2 T_u^* \omega_4}{p_4 E^*}$, the zero solution of system (4.7) is asymptotically mean square stable.

Proof. Let us consider the Lyapunov function

$$L(\psi(t)) = \frac{1}{2}\left[\psi_1^2 + \omega_2\psi_2^2 + \omega_3\psi_3^2 + \omega_4\psi_4^2 + \omega_5(\psi_2 + \psi_3 + \psi_4)^2\right]^{\frac{1}{2}}, \tag{4.18}$$

where ω_i, $2 = 1, \ldots, 5$, are real nonnegative constants to be chosen in the following.
It is clear to check that inequalities (4.10) hold true with $p = 2$.
Furthermore,

$$\begin{aligned}
LV(\psi(t)) &= [(-1 - p_1 E^* - p_2 T_u^*)\psi_1 - p_1 B^* \psi_2 - p_2 B^* \psi_4]\psi_1 \\
&+ [p_4 E^* \psi_1 + (-\mu + p_4 B^* - p_5 T_i^*)\psi_2 + (\alpha - p_5 E^*)\psi_3]\omega_2 \psi_2 \\
&+ [p_2 T_u^* \psi_1 - p_3 T_i^* \psi_2 - p_3 E^* \psi_3 + p_2 B^* \psi_4]\omega_3 \psi_3 \\
&+ [-p_2 T_u^* \psi_1 + (-p_2 B^* + r - 2r\beta T_u^*)\psi_4]\omega_4 \psi_4 \\
&+ [p_4 E^* \psi_1 + (-\mu + p_4 B^* - p_5 T_i^* - p_3 T_i^*)\psi_2 + (\alpha - p_5 E^* - p_3 E^*)\psi_3 + (r - 2r\beta T_u^*)\psi_4]\omega_5 \psi_{234} \\
&+ \frac{1}{2} Tr\left[g(\psi(t)) \frac{\partial^2 V(t,\psi)}{\partial \psi^2} g(\psi(t)) \right]
\end{aligned}$$

with $\psi_{234} = \psi_2 + \psi_3 + \psi_4$, i.e.,

$$\begin{aligned}
LV(\psi(t)) &= -(1 + p_1 E^* + p_2 T_u^*)\psi_1^2 + (p_4 E^* \omega_2 - p_1 B^*)\psi_1 \psi_2 + p_2 T_u^* \omega_3 \psi_1 \psi_3 \\
&+ (-p_2 B^* - p_2 T_u^* \omega_4)\psi_1 \psi_4 + (-\mu + p_4 B^* - p_5 T_i^*)\omega_2 \psi_2^2 \\
&+ [(\alpha - p_5 E^*)\omega_2 - p_3 T_i^* \omega_3]\psi_2 \psi_3 \\
&- p_3 E^* \omega_3 \psi_3^2 + p_2 B^* \omega_3 \psi_3 \psi_4 \\
&+ (-p_2 B^* + r - 2r\beta T_u^*)\omega_4 \psi_4^2 \\
&+ [p_4 E^* \psi_1 + (-\mu + p_4 B^* - p_5 T_i^* - p_3 T_i^*)\psi_2 + (\alpha - p_5 E^* - p_3 E^*)\psi_3 + (r - 2r\beta T_u^*)\psi_4]\omega_5 \psi_{234} \\
&+ \frac{1}{2} Tr\left[g(\psi(t)) \frac{\partial^2 V(t,\psi)}{\partial \psi^2} g(\psi(t)) \right].
\end{aligned}$$

Then,

$$\begin{aligned}
LV(\psi(t)) &= -(1+p_1E^*+p_2T_u^*)\psi_1^2+(p_4E^*\omega_2-p_1B^*+p_4E^*\omega_5)\psi_1\psi_2\\
&+(p_2T_u^*\omega_3+p_4E^*\omega_5)\psi_1\psi_3+(-p_2B^*-p_2T_u^*\omega_4+p_4E^*\omega_5)\psi_1\psi_4\\
&+[(-\mu+p_4B^*-p_5T_i^*)\omega_2+(-\mu+p_4B^*-p_5T_i^*-p_3T_i^*)\omega_5]\psi_2^2\\
&+[(\alpha-p_5E^*)\omega_2-p_3T_i^*\omega_3+(\alpha-p_5E^*-p_3E^*)\omega_5+(-\mu+p_4B^*-p_5T_i^*-p_3T_i^*)\omega_5]\psi_2\psi_3\\
&+[(-\mu+p_4B^*-p_5T_i^*-p_3T_i^*)\omega_5+(r-2r\beta T_u^*)\omega_5]\psi_2\psi_4\\
&+[(\alpha-p_5E^*-p_3E^*)\omega_5-p_3E^*\omega_3]\psi_3^2\\
&+[p_2B^*\omega_3+(\alpha-p_5E^*-p_3E^*)\omega_5+(r-2r\beta T_u^*)\omega_5]\psi_3\psi_4\\
&+[(-p_2B^*+r-2r\beta T_u^*)\omega_4+(r-2r\beta T_u^*)\omega_5]\psi_4^2\\
&+\frac{1}{2}Tr\left[g(\psi(t))\frac{\partial^2V(t,\psi)}{\partial\psi^2}g(\psi(t))\right]
\end{aligned}\tag{4.19}$$

Now remark that,

$$\frac{\partial^2V}{\partial\psi^2}=\begin{pmatrix}1&0&0&0\\0&\omega_2+\omega_5&\omega_5&\omega_5\\0&\omega_5&\omega_3+\omega_5&\omega_5\\0&\omega_5&\omega_5&\omega_4+\omega_5\end{pmatrix}\tag{4.20}$$

Then,

$$g(\psi(t))\frac{\partial^2V}{\partial\psi^2}g(\psi(t))=\begin{pmatrix}\sigma_1^2\psi_1^2&0&0&0\\0&(\omega_2+\omega_5)\sigma_2^2\psi_2^2&\omega_5\sigma_2\psi_2\sigma_3\psi_3&\omega_5\sigma_2\psi_2\sigma_4\psi_4\\0&\omega_5\sigma_2\psi_2\sigma_3\psi_3&(\omega_3+\omega_5)\sigma_3^2\psi_3^2&\omega_5\sigma_3\psi_3\sigma_4\psi_4\\0&\omega_5\sigma_2\psi_2\sigma_4\psi_4&\omega_5\sigma_3\psi_3\sigma_4\psi_4&(\omega_4+\omega_5)\sigma_4^2\psi_4^2\end{pmatrix}\tag{4.21}$$

Hence,

$$\frac{1}{2}Tr\left[g(\psi(t))\frac{\partial^2V}{\partial\psi^2}g(\psi(t))\right]=\frac{1}{2}\left[\sigma_1^2\psi_1^2+(\omega_2+\omega_5)\sigma_2^2\psi_2^2+(\omega_3+\omega_5)\sigma_3^2\psi_3^2+(\omega_4+\omega_5)\sigma_4^2\psi_4^2\right]\tag{4.22}$$

If in (4.19) we choose,

$$\begin{aligned}
p_4E^*\omega_2-p_1B^*+p_4E^*\omega_5&=0\\
-p_2B^*-p_2T_u^*\omega_4+p_4E^*\omega_5&=0\\
p_2B^*\omega_3+(\alpha-p_5E^*-p_3E^*)\omega_5+(r-2r\beta T_u^*)\omega_5&=0
\end{aligned}$$

so,

$$\begin{aligned}
\omega_2^*&=\frac{p_1B^*-p_4E^*\omega_5}{p_4E^*},\\
\omega_5^*&=\frac{p_2B^*+p_2T_u^*\omega_4}{p_4E^*},\\
\omega_3^*&=\frac{(\alpha-p_5E^*-p_3E^*)\omega_5+(r-2r\beta T_u^*)\omega_5}{p_2B^*}.
\end{aligned}$$

By virtue of (4.19) and (4.22) we get

$$\begin{aligned}
LV(\psi(t)) &= -(1+p_1E^*+p_2T_u^*)\psi_1^2 \\
&+ (p_2T_u^*\omega_3+p_4E^*\omega_5)\psi_1\psi_3 \\
&+ [(-\mu+p_4B^*-p_5T_i^*)\omega_2+(-\mu+p_4B^*-p_5T_i^*-p_3T_i^*)\omega_5]\psi_2^2 \\
&+ [(\alpha-p_5E^*)\omega_2-p_3T_i^*\omega_3+(\alpha-p_5E^*-p_3E^*)\omega_5+(-\mu+p_4B^*-p_5T_i^*-p_3T_i^*)\omega_5]\psi_2\psi_3 \\
&+ [(-\mu+p_4B^*-p_5T_i^*-p_3T_i^*)\omega_5+(r-2r\beta T_u^*)\omega_5]\psi_2\psi_4 \\
&+ [(\alpha-p_5E^*-p_3E^*)\omega_5-p_3E^*\omega_3]\psi_3^2 \\
&+ [(-p_2B^*+r-2r\beta T_u^*)\omega_4+(r-2r\beta T_u^*)\omega_5]\psi_4^2 \\
&+ \frac{1}{2}\left[\sigma_1^2\psi_1^2+(\omega_2+\omega_5)\sigma_2^2\psi_2^2+(\omega_3+\omega_5)\sigma_3^2\psi_3^2+(\omega_4+\omega_5)\sigma_4^2\psi_4^2\right] \qquad (4.23)
\end{aligned}$$

It is easy to check that

$$LV(\psi(t)) = -\psi^T Q\psi + q\psi_1\psi_3, \qquad (4.24)$$

where

$$Q = \begin{pmatrix} q_{11} & 0 & 0 & 0 \\ 0 & q_{22} & \frac{q_{23}}{2} & \frac{q_{24}}{2} \\ 0 & \frac{q_{23}}{2} & q_{33} & 0 \\ 0 & \frac{q_{24}}{2} & 0 & q_{44} \end{pmatrix} \qquad (4.25)$$

with

$$\begin{aligned}
q_{11} &= 1+p_1E^*+p_2T_u^*-\frac{1}{2}\sigma_1^2 \\
q_{22} &= (\mu-p_4B^*+p_5T_i^*)\omega_2+(\mu-p_4B^*+p_5T_i^*+p_3T_i^*)\omega_5-\frac{1}{2}(\omega_2+\omega_5)\sigma_2^2 \\
q_{23} &= (-\alpha+p_5E^*)\omega_2+p_3T_i^*\omega_3+(-\alpha+p_5E^*+p_3E^*)\omega_5+(\mu-p_4B^*+p_5T_i^*+p_3T_i^*)\omega_5 \\
q_{24} &= (\mu-p_4B^*+p_5T_i^*+p_3T_i^*)\omega_5+(-r+2r\beta T_u^*)\omega_5 \\
q_{33} &= (-\alpha+p_5E^*+p_3E^*)\omega_5+p_3E^*\omega_3-\frac{1}{2}(\omega_3+\omega_5)\sigma_3^2 \\
q_{44} &= (p_2B^*-r+2r\beta T_u^*)\omega_4+(-r+2r\beta T_u^*)\omega_5-\frac{1}{2}(\omega_4+\omega_5)\sigma_4^2 \\
q &= p_2T_u^*\omega_3+p_4E^*\omega_5
\end{aligned}$$

Then,

$$LV(\psi(t)) \le -\psi^T Q\psi + \frac{q}{2}|\psi(t)|^2. \qquad (4.26)$$

On the other hand, (4.16) and (4.17) imply that Q is a real symmetric positive definite matrix and therefore all its eigenvalues $\lambda_i(Q),\ i=1,\dots,4$, are positive real numbers.
Let $\lambda_m = \min\{\lambda_i(Q),\ i=1,\dots,4\}$, $\lambda_m > 0$. From (4.26) we get

$$LV(\psi(t)) \le -(\lambda_m - \frac{q}{2})|\psi(t)|^2. \qquad (4.27)$$

It suffices to take $\lambda_m > \frac{q}{2}$, then according to Theorem 4.2 the proof is completed. □

Remark 4.4. Alternative conditions for asymptotic mean square stability of trivial solutions of (4.7) can be obtained by the same Lyapunov function (4.18). Hence, from (4.23) it is

$$LV(\psi(t)) \le -q_{11}\psi_1^2+\frac{q}{2}\psi_1^2+\frac{q}{2}\psi_3^2-q_{22}\psi_2^2+\frac{q_{23}}{2}\psi_2^2+\frac{q_{23}}{2}\psi_3^2+\frac{q_{24}}{2}\psi_2^2+\frac{q_{24}}{2}\psi_4^2-q_{33}\psi_3^2-q_{44}\psi_4^2, \quad (4.28)$$

then,

$$LV(\psi(t)) \leq -(q_{11} - \frac{q}{2})\psi_1^2 - (q_{22} - \frac{q_{23}}{2} - \frac{q_{24}}{2})\psi_2^2 - (q_{33} - \frac{q}{2} - \frac{q_{23}}{2})\psi_3^2 - (q_{44} - \frac{q_{24}}{2})\psi_4^2. \tag{4.29}$$

Now assume that there exists $\{\omega_i, i = 2, \ldots, 5\}$ such that

$$q_{11} - \frac{q}{2} > 0 \tag{4.30}$$

$$q_{22} - \frac{q_{23}}{2} - \frac{q_{24}}{2} > 0 \tag{4.31}$$

$$q_{33} - \frac{q}{2} - \frac{q_{23}}{2} > 0 \tag{4.32}$$

$$q_{44} - \frac{q_{24}}{2} > 0 \tag{4.33}$$

Otherwise, if we rewrite (4.26) as

$$LV(\psi(t)) \leq -\psi^T Q'\psi. \tag{4.34}$$

It is equivalent to choose $\{\omega_i, i = 2, \ldots, 5\}$ such that the real symmetric matrix Q' is to be strict diagonally dominant matrix.
Where

$$Q' = \begin{pmatrix} q_{11} & 0 & \frac{q}{2} & 0 \\ 0 & q_{22} & \frac{q_{23}}{2} & \frac{q_{24}}{2} \\ \frac{q}{2} & \frac{q_{23}}{2} & q_{33} & 0 \\ 0 & \frac{q_{24}}{2} & 0 & q_{44} \end{pmatrix} \tag{4.35}$$

Then, the zero solution of (4.7) is asymptotically mean square stable.

5. Numerical Results

The resolution of the optimality system is made numerically based on an iterative stochastic Runge-Kutta scheme combined with the Forward-Backward Sweep Method (FBSM) that are used to solve the stochastic two-point boundary value problem in our case. Using an explicit Runge-Kutta iterative scheme of a general order m developed by Rümlin [31] for stochastic differential equations with nonconstant diffusion functions.

Moreover, benefiting from numerical approximations suggested by Lenhart [25] which are adapted for the resolution of a deterministic optimality system. We can define the stochastic two-point boundary value problem (5) expressed in terms of f, u and σ by the following algorithm

Initial conditions:
$for \;\; i = 0 \;\; X_0$ *and* u_0 *are given,*
$\forall i \; t_{i+1} = t_i + h, \;\; \Delta W_i \sim \sqrt{h}N(0, 1).$
Numerical process for the resolution of the forward stoschastic differential control system using a general order m stochastic Runge-Kutta iterative scheme:
$for \;\; i = 0, ..., N$ (N *is the number of optimization steps*)
$k_1 = f(t_i, X_i, u_i),$
$g_1 = \sigma(t_i, X_i).$
$k_2 = f(t_i + \frac{h}{2}, X_i + \frac{h}{2}k_1, \frac{u_i+u_{i+1}}{2}),$
$g_2 = \sigma(t_i + \frac{h}{2}, X_i + \frac{h}{2}g_1).$
$k_3 = f(t_i + \frac{h}{2}, X_i + \frac{h}{2}k_2, \frac{u_i+u_{i+1}}{2}),$
$g_3 = \sigma(t_i + \frac{h}{2}, X_i + \frac{h}{2}g_2).$
$k_4 = f(t_{i+1}, X_i + hk_3, u_{i+1}),$
$g_4 = \sigma(t_{i+1}, X_i + hg_3).$

$\vdots$
$k_m = f(t_i + h\gamma_m, X_i + h\gamma_m k_{m-1}, u_i + h\gamma_m),$
$g_m = \sigma(t_i + h\gamma_m, X_i + h\gamma_m g_{m-1}).$
$X_{i+1} = X_i + \sum_{i=1}^{m} p_i k_i h + \sum_{i=1}^{m} q_i g_i \Delta w_i,$
where $\sum_{i=1}^{m} p_i = \sum_{i=1}^{m} q_i = 1$ *and* γ_m *a constant*

Final condition:
for $j = N$ μ_N *is given* (N *is the number of optimization steps*)

Numerical process for the resolution of the adjoint backward stochastic differential control system using a general order m stochastic Runge-Kutta iterative scheme:
for $j = N, N-1, ..., 0$ (N *is the number of optimization steps*)
$k_1 = M(t_j, \mu_j, X_j, u_j),$
$g_1 = \nu(t_j, \mu_j).$
$k_2 = M(t_j - \frac{h}{2}, \mu_j - \frac{h}{2}k_1, \frac{X_j + X_{j-1}}{2}, \frac{u_j + u_{j-1}}{2}),$
$g_2 = \nu(t_j - \frac{h}{2}, \mu_j + \frac{h}{2}g_1).$
$k_3 = M(t_j - \frac{h}{2}, \mu_j - \frac{h}{2}k_2, \frac{X_j + X_{j-1}}{2}, \frac{u_j + u_{j-1}}{2}),$
$g_3 = \nu(t_j - \frac{h}{2}, \mu j + \frac{h}{2}g_2).$
$k_4 = M(t_{j-1}, \mu_j - hk_3, X_{j-1}, u_{j-1}),$
$g_4 = \nu(t_{j-1}, \mu_j - hg_3).$
$\vdots$
$k_m = M(t_i - h\gamma_m, \mu_j - h\gamma_m k_{m-1}, u_j - h\gamma_m),$
$g_m = \nu(t_i - h\gamma_m, \mu_j - h\gamma_m g_{m-1}).$
$\mu_{j-1} = \mu_j - \sum_{i=1}^{m} p_i k_i h - \sum_{i=1}^{m} q_i g_i \Delta w_i,$
where $\sum_{i=1}^{m} p_i = \sum_{i=1}^{m} q_i = 1$ *and* γ_m *a constant*

and $M(t_j, \mu_j, X_j, u_j) = -[f_{X_j}^T(t_j, X_j, u_j)\mu_j + \sum_{j=1}^{k} {\sigma_X^j}^T(t_j, X_j, u_j)\nu_j(t) + g_{X_j}(t_j, X_j, u_j)]$

Convergence test:
We choose a Stopping criterion when the condition test $= min(t_X, t_u, t_\mu) < \delta$ *with* $t_X = E(\|\Delta X\|^2), t_u = E(|\Delta u|^2), t_\mu = E(\|\Delta\mu\|^2)$, *and* δ *is a small positive constant.*

In the following illustrations, we consider that the order m is equal to 4, and we present the different behaviors of BCG concentration, effector cells and tumor cells functions in the absence and in the presence of the control u. In doing so, we choose the numerical values of the control bounds by $\lambda_1 = 3.14 \times 10^5 c.f.u.$ and $\lambda_2 = 9.14 \times 10^5 c.f.u.$, the severities weight by $a = 1$ and $b = 10^{-6}$ [13]. Furthermore, we consider $c = 4.92 \times 10^5 c.f.u.$ for the tumor equilibrium point and the average value of an optimal experimental dose by an amount of $27mg$. We propose equivalent to an average amount $c = 6.14 \times 10^5 c.f.u.$ ($c = \frac{\lambda_1 + \lambda_2}{2}$) for the side-effects equilibrium point [7].

In the absence of therapy, Figure 1 shows that the immune response represented by effector cells is activated during 50 days only because of cancer while uninfected tumor cells reach the equilibrium point X^*.

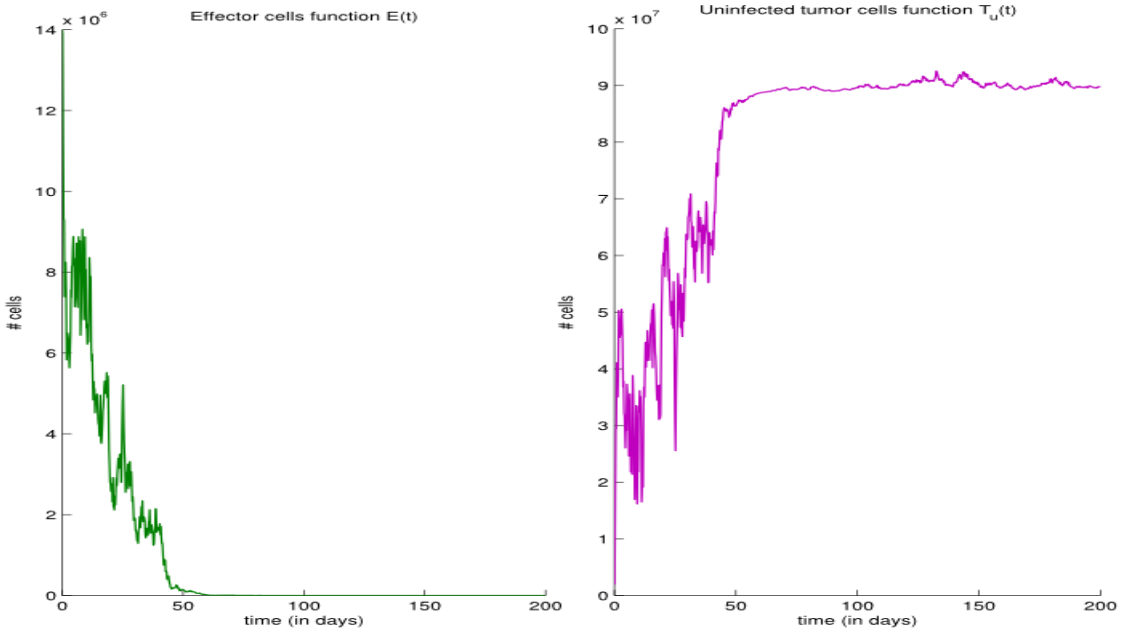

FIGURE 1. Estimation of the stochastic effector and uninfected tumor cells functions E and T_u in the absence of control u during 200 days.

In the case when $\frac{r}{p_2} < c < \frac{\mu_2}{p_4}$ (tumor equilibrium E_1^c), we can observe from Figure 2 that when there is an injection of BCG into the bladder, there is not a significant change in the shape of effector cells (stimulation just for 15 days of more compared to 1) but we arrive to eradicate uninfected tumor cells on a minimum time interval of 105 days while an important amount of infected tumor cells appears during 65 days, exactly during the same period of maximal value of treatment $\lambda_2 = 9.14 \times 10^5 c.f.u.$ and remains stable on zero in the final phase of BCG instillations. More explicitly, we can understand from the $u^*(t)$ shape that it is recommended to maintain the initial dose of BCG for a period of 65 days and we deduce from Figure 2 that the optimal should not exceed a value of $9.14 \times 10^5 c.f.u.$ and it should be reduced after, to a dosage value of $\lambda_1 = 3.14 \times 10^5 c.f.u.$

In the case when $\frac{r}{p_2} < \frac{\mu_2}{p_4} < c$ (side-effects equilibrium E_2^c), we show in Figure 3 the efficacy of BCG in the stimulation of effector cells for a longer period of 80 days. It is also clearly showed that we can achieve to a faster eradication of tumors with a dosage of $9.14 \times 10^5 c.f.u.$ during 70 days of treatment.

For both formulations of the equilibrium point X^* in Figures 2 and 3, we can also deduce that we get a decrease of infected and uninfected tumor cells counts faster than the deterministic results obtained in [13] and [12] and where it was shown that the infected and the uninfected cancer cells could be stabilized to minimal values closer to zero after more than 150 days with a period of BCG administration of 200 days which represents a longer period than the one suggested here, and that means even in the presence of some factors of stochasticity, we can obtain better results than the deterministic case.

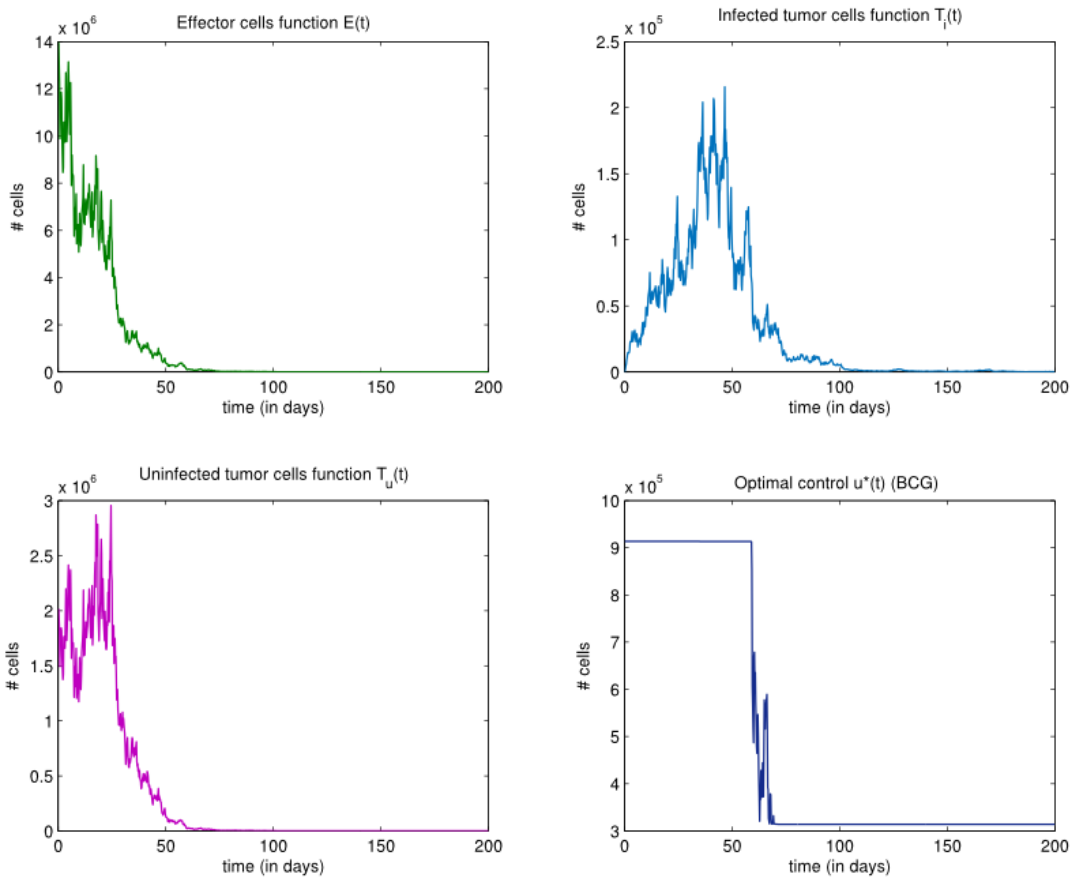

FIGURE 2. Estimations associated to the tumor equilibrium X^* for the simulation of the stochastic effector, infected and uninfected tumor cells functions E, T_i and T_u in the presence of BCG control dose u during 350 days. "**d=0.25**".

6. Conclusion

In this work, we proposed a stochastic optimal control model in order to simulate a BCG bacterium as an immunotherapeutic agent in the case of superficial bladder cancer.
Due to the characteristics of the cell population of the bladder, we remarked the efficiency of the stochastic approach.
In fact, the stochastic optimal control model has provided us satisfactory results closer to the natural dynamics between the immune active cells and tumors.
Compared to the deterministic case studied in [12] and [13], we can conclude that using the proposed stochastic optimal control approach, we obtain the fastest eradication of tumor cells, and prove a promising potential for the success of BCG bacterium as an effective immunotherapeutic agent even in the presence of biological stochasticity.

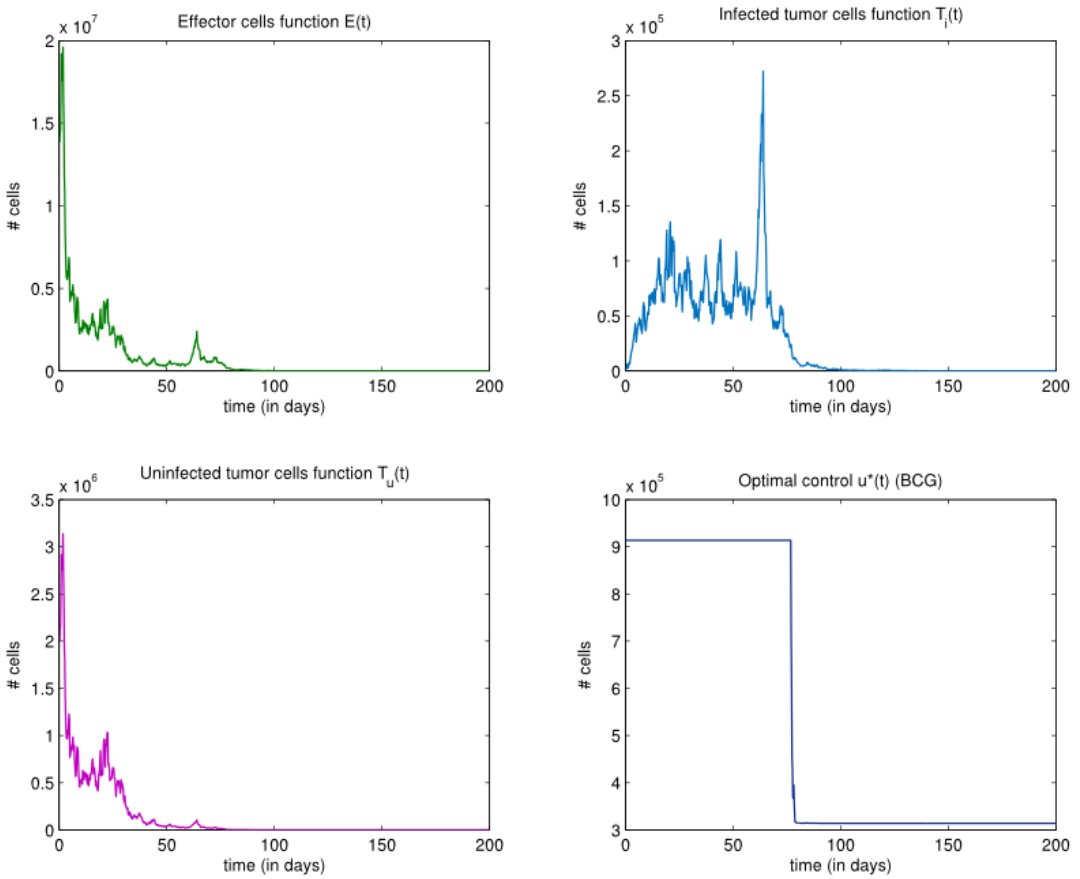

FIGURE 3. Estimations associated to the side-effects equilibrium X^* for the simulation of the stochastic effector, infected and uninfected tumor cells functions E, T_i and T_u in the presence of BCG control dose u during 350 days. "**d=0.25**".

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