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Forecasting the stochastic vicious cycle of cancer progression and immune response

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ABSTRACT

It is accepted that cancer progression is a stochastic process, and there is a bifurcation in cancer cell count, which gets chaotic if not treated at preliminary stages. Therefore, strategies for fighting cancer at early stages are highly desired. However, the interaction of the immune system with cancer cells is not a straightforward process. The stochastic cell interactions lead to uncontrollable dynamics and sometimes to the death of the patient. A stochastic computational framework developed based on principles of the cancer-immune cell interaction is proposed in this article. The results obtained using the framework for breast cancer are close to the experimental findings, confirming that it can be a useful tool for identifying possible control measures. This study concludes that a control strategy based on stochastic modeling is promising and that a deep understanding of the interaction cell rates is essential for timely cancer control measures.

Introduction

The human immune system has a sort of army of immune cells comprised of T and B cells. These cells fight against foreign invaders such as viruses and bacteria. They also fight against malignant cancerous cells. T cells release toxins against foreign cells, and B cells make the antibodies to neutralize them. The human organs are made up of millions of cells. The proteins in each cell are responsible for its functioning. Peptides from these proteins appear on the cells' surface as molecules and are called MHC/HLA. During T cell surveillance, the cells scan each foreign cell through the T-cell receptor (TCR) mechanism. Suppose T cells identify a foreign cell as usual. In that case, they leave that cell, whereas if peptides came from the invader proteins, then T cells recognize it and release cytokines and factors to eliminate the abnormal cell [2].

Sometimes, the cancer cells are masked, or the immune system is weak, and the immune response fails to fight against the cancer cells. Tumors usually build a defense system against immune cells. For example, the checkpoints PD1 and CTLA-4 are released by cancer cells and bound to T cells and inhibit their activity by deactivating them. Tumor cells also release proteins such as cytokine (IL-10, TGF-β, IDO), which stop T cells from functioning and reverse their role by transforming them into tumor-friendly cells. These trader T cells are called regulatory T cells and are an enemy of the immune system.

The field of immunotherapy has developed during the last century (since the 1890's when the first vaccine was developed (Coley) [19]) and has shown significant signs of progress. There are two main approaches towards immunotherapy: Enhancing the immune response, making it more robust, and using drugs to inhibit the tumors' suppressive immune environment.

Enhancing the immune response

One enhancement method for the immune system is to create vaccines. Foreign antigens can be recognized by identifying mutated proteins of the tumor (Neoantigens). These mutated proteins can be given to the immune system to activate the patient's T cells, and thus the tumor vaccine fights against the tumor cells. Another method is the adoptive T cells transfer, where T cells are taken out of the patient's body, grown in the laboratory, and educated to recognize cancer or even modified to become much more robust. These fiber cells are then transferred back into the patient. A third approach is by cytokines, also termed as stimulating factors. Cytokines are proteins like the interleukins 2, 7, 12, and 15 that cause T cells to multiply and become stronger. A fourth

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enhancement approach is the "Agonist Antibodies", such as Anti-OX40, Anti-GITR, Anti-41BB, and others, to cause T cells to be grown and strengthen.

Using drugs to inhibit the suppressive immune environment of the tumors

Strategies have been developed to knock down the cancer defense mechanism. Some antibodies or drugs neutralize inhibitory and anti-inflammatory factors, such as anti-IL-10 and anti-tgfβ and IDO inhibitors. Food and Drug Administration (FDA) approved some of these approaches like Anti-PD1-PDL1 and Anti-CTLA-4.

On March 8, 2019, FDA approved "atezolizumab" in combination with "paclitaxel (protein-bound)" for the treatment of adult patients with metastatic triple-negative breast cancer (TNBC) or locally advanced unresectable whose tumors express programmed death-ligand 1 (PD-L1). FDA also approved the Ventana PD-L1 (SP263) Assay device for qualitative detection and immunohistochemical assessment of PD-L1 for TNBC patients. Although not very common, these treatments have side effects and are life-threatening if not treated. These include thyroid dysfunction or diabetes, some endocrine diseases that lead to weakness.

Cancer is the most deadly disease globally, with the lowest clinical success rate compared to other conditions. It is a very heterogeneous disease characterized by the accumulation of mutations that leads to tumor growth, immune escape, clinical progression, and drug resistance. CTLs destroy tumor cells, and the overwhelming amount of T cells circulate in the blood and lymph. The majority are non-cytotoxic and are referred to as naive T cells. The lymph nodes located throughout the body have a large number of naive T lymphocytes, which can become cytotoxic after activation. Millions of variant T cells are produced by the human body, each with its ability to distinguish distinct invaders. Mathematical modeling of cancer cells has been used to synthesize and review clinical trials' key findings to predict their limitations and future consequences. For two decades, mathematical models based on ordinary differential equations (ODEs) have been used to study the dynamics of oncolytic viruses propagating through tumors. In deterministic mathematical modeling, the output is entirely based on initial conditions and the values of parameters. On the other hand, stochastic mathematical modeling is considerably more complicated and has inherent randomness that leads to an ensemble of different output against the set of parametric values and initial conditions. A comprehensive review of deterministic and stochastic models for tumor-immune dynamics can be found in [1,18].

The real world is mainly driven by stochasticity, and hence stochastic models are more qualitative than quantitative. Therefore, stochastic modeling has become an efficient and practical approach to random model outputs of human body systems. In the case of malignancy caused by cancer, the stochastic effects dominate the involved dynamic. Hence, this study is designed to develop a stochastic mathematical model, which incorporates biological data of the breast cancer dynamics [15], to provide a cancer control strategy by varying the model's parametric values.

Stochastic modeling of cytotoxic T and tumor cells

Deterministic modeling

We designed a deterministic model under the following assumptions: tumor cells grow logistically in the absence of immune response [6]; cytotoxic T lymphocytes can kill tumor cells [17]; tumor cells can activate naive and noncytotoxic cells [10]; after the activation of cytotoxic T cells, they grow logistically; cytotoxic T cells became inactive after some number of interactions with tumor cells [1]. The model describing the kinetics of tumor cell and cytotoxic T cell was modeled by a system of ordinary differential equations as:

$$\frac{dx_1}{dt} = f(x_1, x_2) = \alpha_1 x_1\left(1 - \frac{x_1}{\alpha_2}\right) - \alpha_3 x_1\left(\frac{x_2}{\alpha_4 + x_2}\right), \tag{1}$$

$$\frac{dx_2}{dt} = g(x_1, x_2) = \alpha_5 x_2\left(1 - \frac{x_2}{\alpha_6}\right)\left(\frac{x_1}{\alpha_7 + x_1}\right) - \alpha_8 x_1 x_2 - \alpha_9 x_2, \tag{2}$$

where $\alpha_i,\ i = 1, 2, \ldots, 9$, are dimensionless parameters [15].

Stochastic modeling

A stochastic process, in broad terms, is a mathematical process that evolves probabilistically. It represents the family of random variables $\{X(t) : t \in \tau\}$ defined on probability space (Ω, Λ, P), where both index (t) and random variable $(X(t))$ can be discrete and continuous [7]. The stochastic model equations can be divided into two main groups: the first group deals with the modeling trajectories of the process, provided by the random variable $X(t)$. A system of differential equations that describes these trajectories with stochastic terms is generally called a system of stochastic differential equations (SDEs), and hence its solution is a stochastic process. The second group is concerned with the use of deterministic differential equations to evaluate probability $p(x, t) = \text{Prob}[X(t) = x]$.

In most cases, mathematical models make simplifying assumptions about the characteristics of the phenomenon being studied. These modeling assumptions typically affect model accuracy and tractability. When applying stochastic processes to modeling, the common assumption is the Markov property; thus, we limit our attention to Markov processes in the following. If the state of a process at any time $t_n \in \tau$ determines the future state of the process, then it is called a Markov process. Specifically, a stochastic process is a Markov process if for $t_1 < t_2 < t_3 < \ldots < t_n < t_{n+1}$, $P(X(t_{n+1}) \leqslant x_{n+1} | X(t_n) = x_n) = P(X(t_{n+1}) \leqslant x_{n+1} | X(t_1) = x_1, X(t_2) = x_2, \ldots, X(t_n) = x_n)$. Wiener process (also known as Brownian motion) is a typical example of a continuous process of Morkove type [5]. One-dimensional Wiener process is stochastic process $W(t)$ for $t \geqslant 0$ and such that the increment $W_{t+s} - W_s$ has the Normal $(0, t)$ distribution while increments for non-overlapping time intervals are independent. An r-dimensional Wiener process is a vector-valued stochastic process $W(t) = \left(W^{(1)}(t), W^{(2)}(t), W^{(3)}(t), \ldots, W^{(r)}(t)\right)$ whose components $W^{(i)}(t)$ are independent one-dimensional Wiener processes.

To derive a stochastic model for the interaction between tumor and cytotoxic T cells (see Fig. 1), we used a standard modeling procedure proposed by [3]. Here, we also use the same notations used in [3] to facilitate the understanding of our results. We also followed the steps given in [9] for the derivation of SDE models. First, all possible changes δ of the system and corresponding transition probabilities p in a small interval of time Δt were determined to design a discrete stochastic model. Then, the SDE model was formulated by calculating the expectation value and covariance matrix to change the discrete process. The drift coefficient was obtained by changing the expected value divided by Δt. Similarly, the diffusion coefficient was obtained by the covariance matrix's square root divided by Δt.

Let's consider $X(t) = (X_1(t), X_2(t))^T$, where $X_1(t)$ is representing the population of tumor cells and $X_2(t)$ the population of cytotoxic T lymphocyts (CTLs) at $t \geqslant 0$. Now, let's assume that $\Delta X(t)$ is a change in a small interval of time Δt in which a state $X_1(t)$ and $X_2(t)$ can be changed by $-\lambda_1, 0$, or λ_1 and $-\lambda_2, 0$, or λ_2, respectively, where $\lambda_1, \lambda_2 \geqslant 0$ [3]. According to the deterministic model of tumor and cytotoxic T cells given by Eqs. 1,2, there are four possible changes for states $X_1(t)$ and $X_2(t)$ in time interval Δt. The possible changes and their corresponding probabilities up to $O((\Delta t)^2)$ are given in Table 1. Also, the probability of no change $(\Delta X(t) = [0, 0]^T)$ is $1 - \sum_{i=1}^{4} p_i$.

The expected change and co-variance matrix are calculated as:

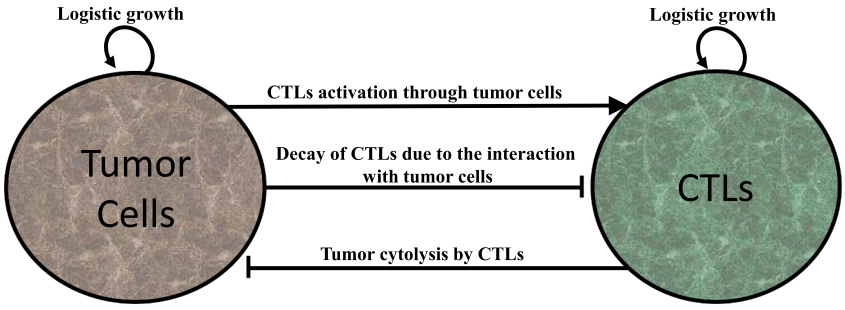


Fig. 1. Schematic diagram depicting the interaction of tumor cells with CTLs.

Table 1
Possible changes in tumor-CTLs interaction model corresponding to their probabilities.

Change	Probability
$\Delta X^{(1)} = [1,0]^T$	$p_1 = P_1(t,X_1,X_2)\Delta t$
$\Delta X^{(2)} = [0,1]^T$	$p_2 = P_2(t,X_1,X_2)\Delta t$
$\Delta X^{(3)} = [-1,0]^T$	$p_3 = P_3(t,X_1,X_2)\Delta t$
$\Delta X^{(4)} = [0,-1]^T$	$p_4 = P_4(t,X_1,X_2)\Delta t$

$$E(\Delta X) = \sum_{i=1}^{4} p_i \Delta X^{(i)}(t) = \begin{pmatrix} P_1(t,X_1,X_2) - P_3(t,X_1,X_2) \\ P_2(t,X_1,X_2) - P_4(t,X_1,X_2) \end{pmatrix} \Delta t, \tag{3}$$

and

$$E(\Delta X(\Delta X)^T) = \sum_{i=1}^{4} p_i (\Delta X^{(i)}(t))(\Delta X^{(i)}(t))^T = \begin{pmatrix} P_1(t,X_1,X_2)+P_3(t,X_1,X_2) & 0 \\ 0 & P_2(t,X_1,X_2)+P_4(t,X_1,X_2) \end{pmatrix} \Delta t. \tag{4}$$

We define:

$$\mu = \frac{E(\Delta X)}{\Delta t} = \begin{pmatrix} P_1(t,X_1,X_2) - P_3(t,X_1,X_2) \\ P_2(t,X_1,X_2) - P_4(t,X_1,X_2) \end{pmatrix}, = \begin{pmatrix} \alpha_1 x_1 \left(1 - \frac{x_1}{\alpha_2}\right) - \alpha_3 x_1 \left(\frac{x_2}{\alpha_4 + x_2}\right) \\ \alpha_5 x_2 \left(1 - \frac{x_2}{\alpha_6}\right)\left(\frac{x_1}{\alpha_7 + x_1}\right) - (\alpha_8 x_1 + \alpha_9) x_2 \end{pmatrix} \tag{5}$$

$$V = \frac{E(\Delta X(\Delta X)^T)}{\Delta t} = \begin{pmatrix} P_1(t,X_1,X_2)+P_3(t,X_1,X_2) & 0 \\ 0 & P_2(t,X_1,X_2)+P_4(t,X_1,X_2) \end{pmatrix}, = \begin{pmatrix} \alpha_1 x_1 \left(1 - \frac{x_1}{\alpha_2}\right) + \alpha_3 x_1 \left(\frac{x_2}{\alpha_4 + x_2}\right) & 0 \\ 0 & \alpha_5 x_2 \left(1 - \frac{x_2}{\alpha_6}\right)\left(\frac{x_1}{\alpha_7 + x_1}\right) + (\alpha_8 x_1 + \alpha_9) x_2 \end{pmatrix} \tag{6}$$

and the square root of co-variance matrix V as:

$$B(t,X_1,X_2) = \sqrt{V(t,X_1,X_2)}. \tag{7}$$

Finally, the SDE model of tumor-CTLs interaction is given by:

$$dX(t) = \mu(t,X_1,X_2)dt + B(t,X_1,X_2)dW(t), \tag{8}$$

$$X(0) = X_0, \tag{9}$$

where $W(t) = (W_1(t), W_2(2))^T$ is a vector of two independent Wiener processes corresponding to differential $dW(t)$.

Non-negativity criteria

First, we recall main theorems that were formulated for system of SDEs and yield the necessary and sufficient condition for the invariance of rectangular subsets [20,8]. Let's consider the general form of Ito SDEs:

$$d\mathbf{X}(t) = F(t,\mathbf{X}(t))dt + G(t,\mathbf{X}(t))dW(t), \tag{10}$$

$$\mathbf{X}(0) = \mathbf{X}_0, \tag{11}$$

where $F : [0,\infty) \times R^n \to R^n$ and $G : [0,\infty) \times R^n \to R^{n\times r}$ are Borel-measurable function and Borel-measurable mapping, respectively. Also, that $W(t)$ is a Wiener process and $dW(t)$ is corresponding Ito differential.

Definition 1. A subset $K \subset R^n$ is said to be invariant for stochastic system (F,G) if for any $t_0 \geqslant 0$ and $\mathbf{X}_0 \in K$, the solution $\mathbf{X}(t)$ for $t \geqslant t_0$ also attains values within set K.

Theorem 1. *A set* $K := \{x \in R^n : a_j \leqslant x_j \leqslant b_j, j = 1,2,3,\ldots,n\}$, *where* a_j, $b_j \in R$ *with* $b_j > a_j$, *is invariant for stochastic system* (F,G) *iff:*

$F_j(t,x) \geqslant 0$ for $x \in K$ such that $x_j = a_j$,

$F_j(t,x) \leqslant 0$ for $x \in K$ such that $x_j = b_j$,

$G_{j,k}(t,x) \geqslant 0$ for $x \in K$ such that $x_j \in \{a_j, b_j\}$,

for all $t \geqslant 0$ *and* $k = 1,2,3,\ldots,r$. The invariance of the positive cone is an important case for the application of non-negativity of solutions.

Theorem 2. *A set* $K^+ := \{x \in R^n : x_j \geqslant 0, j = 1,2,3,\ldots,n\}$ *is invariant for stochastic system* (F,G) *iff:*

$F_j(t,x) \geqslant 0$ for $x \in K^+$ such that $x_j = 0$,

$G_{j,k}(t,x) \geqslant 0$ for $x \in K^+$ such that $x_j = 0$,

for all $t \geqslant 0$ *and* $k = 1,2,3,\ldots,r$.

Proposition 1. *The stochastic model for tumor-CTLs interaction given by Eqs. 8,9 has the following properties:*

(i) *The solution of underlying deterministic system remains non-negative.*
(ii) *The stochastic model preserves non-negativity, independently of Ito or Stratonovich's interpretation of SDEs.*

Proof. The stochastic model for tumor-CTLs interaction is:

$$dX(t) = \begin{pmatrix} \alpha_1 x_1\left(1-\frac{x_1}{\alpha_2}\right) - \alpha_3 x_1\left(\frac{x_2}{\alpha_4+x_2}\right) \\ \alpha_5 x_2\left(1-\frac{x_2}{\alpha_6}\right)\left(\frac{x_1}{\alpha_7+x_1}\right) - (\alpha_8 x_1+\alpha_9)x_2 \end{pmatrix} dt + \begin{pmatrix} \sqrt{\alpha_1 x_1\left(1-\frac{x_1}{\alpha_2}\right) + \alpha_3 x_1\left(\frac{x_2}{\alpha_4+x_2}\right)} & 0 \\ 0 & \sqrt{\alpha_5 x_2\left(1-\frac{x_2}{\alpha_6}\right)\left(\frac{x_1}{\alpha_7+x_1}\right) + (\alpha_8 x_1+\alpha_9)x_2} \end{pmatrix} dW(t). \tag{12}$$

By taking into account the functions:

$$F_1(x_1,x_2) = \alpha_1 x_1\left(1-\frac{x_1}{\alpha_2}\right) - \alpha_3 x_1\left(\frac{x_2}{\alpha_4+x_2}\right),$$

$$F_2(x_1,x_2) = \alpha_5 x_2\left(1-\frac{x_2}{\alpha_6}\right)\left(\frac{x_1}{\alpha_7+x_1}\right) - (\alpha_8 x_1+\alpha_9)x_2,$$

$$G_1(x_1,x_2) = \sqrt{\alpha_1 x_1\left(1-\frac{x_1}{\alpha_2}\right) + \alpha_3 x_1\left(\frac{x_2}{\alpha_4+x_2}\right)},$$

$$G_2(x_1,x_2) = \sqrt{\alpha_5 x_2\left(1-\frac{x_2}{\alpha_6}\right)\left(\frac{x_1}{\alpha_7+x_1}\right) + (\alpha_8 x_1+\alpha_9)x_2}.$$

One can verify that:

$$F_1(0,x_2) \geqslant 0, \qquad F_2(x_1,0) \geqslant 0,$$

and

$$G_1(0,x_2) = 0, \qquad G_2(x_1,0) = 0.$$

This satisfies the conditions of Theorem 1. Hence, the deterministic and stochastic solutions of tumor-CTLs model preserves non-negativity. □

Numerical simulations and discussion

There are different numerical schemes to solve stochastic differential equations where Euler-Maruyama and Milstein methods are most common [4]. Euler-Maruyama uses truncation of stochastic Taylor series after the first-order terms, while Milstein's method uses truncation of stochastic Taylor series after the second-order terms. We have tried both techniques to solve the proposed SDE model of tumor-CTLs interaction, but both failed to solve the model numerically due to its strong nonlinearity. We then used Runge-Kutta (RK) numerical schemes to solve the proposed SDE model. The nth-order RK algorithm for the numerical integration of SDEs is given by:

$$x_{k+1} = x_k + \sum_{j=1}^{n} b_j k_j, \tag{13}$$

$$k_j = hF\left(t_k + c_j h, x_k + \sum_{i=1}^{j-1} a_{ji} k_i\right) + hG\left(t_k + c_j h, x_k + \sum_{i=1}^{j-1} a_{ji} k_i\right) w_j, \tag{14}$$

where w_j is an independent and identically distributed vector of random processes [16]. We used the RK method of order four to solve the proposed SDE model with the coefficients and parameters indicated in Tables 2 and 3.

The results of numerical simulations are shown in Fig. 2 that show decay oscillations in the population of CTLs. This cyclic fluctuation has a close agreement with experimental studies of breast cancer. Fig. 2a represents the state profiles of tumor cells and CTLs, while Fig. 2b depicts phase portrait analysis of tumor-immune dynamics. A noisy behavior can be seen in SDE dynamics which looks realistic and matched with experimental studies. In the literature, it has been reported that immune cells can eliminate tumors at early stages, and most of the tumor cells are destroyed within two days [21,12]. From the numerical simulations, we can see that the proposed model shows a large oscillation in the population of the CTLs and that the tumor cells decrease at earlier stages. It can also be seen that the tumor is not obliterated. If a tumor has a size less than 2 mm in diameter and a population level less than 6×10^5, then the tumor remains small and stable [22]. This phenomenon is termed "cancer without disease", and many studies have suggested that microscopic tumor never progresses to an invasive one [13,11,14].

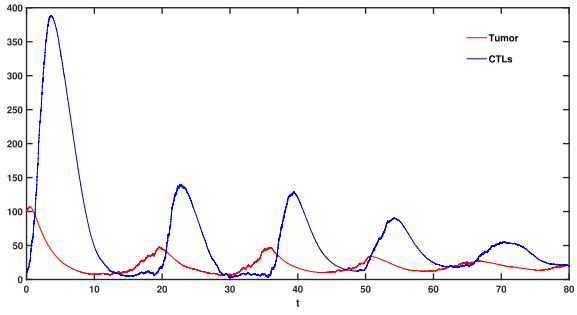
Fig. 3, one can understand the change in the population of CTLs after

Table 2
Coefficients of RK-4 method and corresponding values [16].

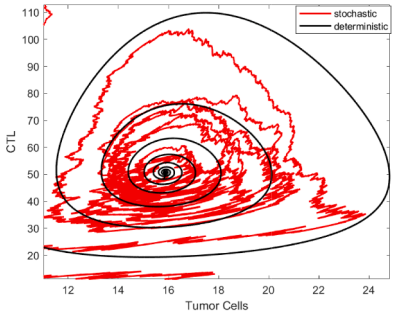
Coefficients	Values
a_{21}	2.71644396264860
a_{31}	−6.95653259006152
a_{32}	0.78313689457981
a_{41}	0.0
a_{42}	0.48257353309214
a_{43}	0.26171080165848
b_1	0.47012396888046
b_2	0.36597075368373
b_3	0.08906615686702
b_4	0.07483912056879

Table 3
Parameters of the proposed SDE model and corresponding values [15].

Parameters	Values
α_1	0.6387
α_2	10^3
α_3	1
α_4	20
α_5	5.7484
α_6	8×10^2
α_7	10^2
α_8	7.812×10^{-4}
α_9	0.8729

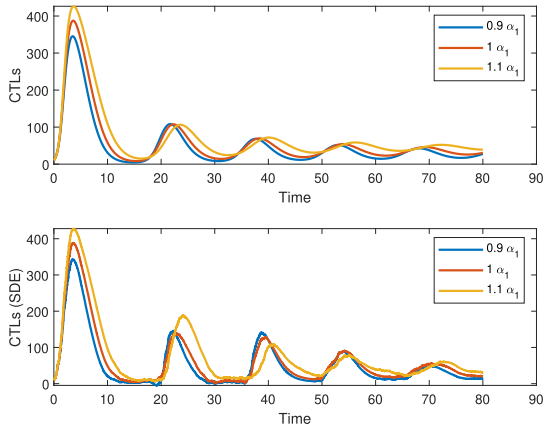


(a) Stochastic view of state profiles of CTLs and tumor cells.

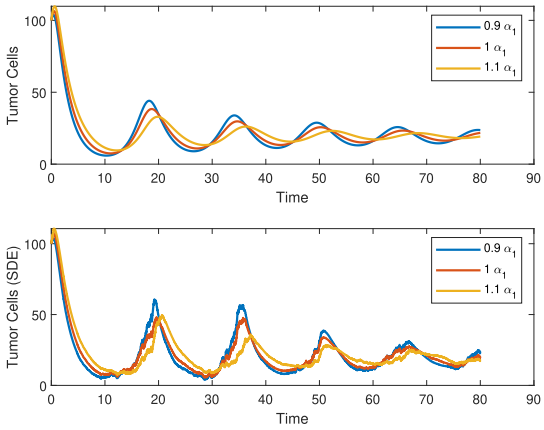


(b) Stochastic view of phase portraits of CTLs vs tumour cells.

Fig. 2. Illustration of numerical simulations of proposed stochastic model.

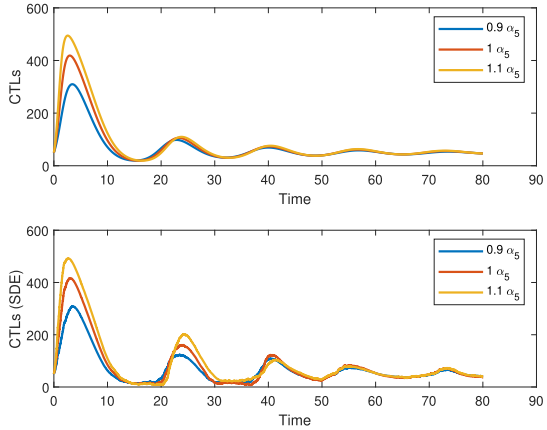


(a) CTLs density profile for different values of "α_1".

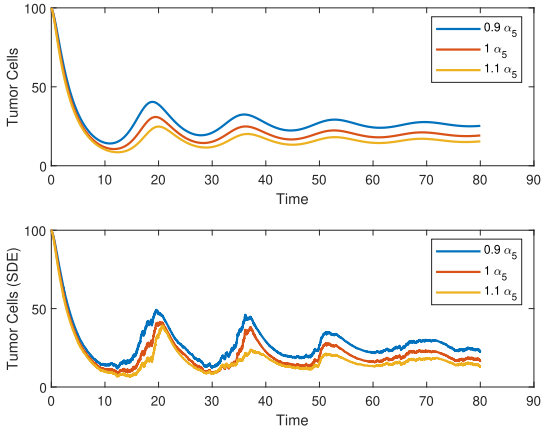


(b) Tumor cells density profile for different values of "α_1".

Fig. 3. Tumor-CTLs density profiles for different values of "α_1".



(a) CTLs density profile for different values of "α_5".



(b) Tumor cells density profile for different values of "α_5".

Fig. 4. Tumor-CTLs density profiles for different values of "α_5".

the interaction with tumor cells. During the first cycle, they are over-expressed as a result of their surveillance characteristic. Then, as cancer cells develop resistance against the immune system, the CTLs population's size decreases periodically. The period is significant while developing cancer drugs. We studied the variation imposed by parameter α_1, which controls cancer cells' growth rate. For increasing values of α_1, CTLs grow in number. Fig. 3a presents the CTLs dynamics when deterministic and stochastic approaches are used, while Fig. 3b illustrates tumor dynamics. One can see the flattening in the graph for increased values of α_1; this is not the case in reality. On the contrary, this flattening effect is not presented when stochastic dynamics are used. Hence stochastic dynamics are more realistic as compared to deterministic.

From [15], sensitivity analysis results reveal that α_5 is a crucial

parameter in order to control tumor population. This parameter is negatively correlated with the population of tumor cells. Fig. 4 shows the change in the dynamics of tumor cells and immune cells relative to CTLs growth rate. Tumor cells and their noisy behavior is decreasing with a more significant value of α_5. Thus, this parameter is also affecting the randomness of the SDE model.

Conclusion

Stochastic modeling of biological processes has emerged as a powerful tool that has provided substantial insight into intra-cellular processes. It advances computing technology and enables real-time imaging of expression at the single-cell level, which was previously unattainable. In this article, we present a stochastic model of breast tumor interaction with CTLs. The designed model adheres to the standard modeling processes of Ito stochastic models. We have effectively demonstrated the non-negativity criteria for the solution of the proposed SDE model. The computational model developed during this study is novel. Based on parametric values extracted from experimental data and the obtained numerical results, one can conclude that the cancer onset and its interaction with the immune system can be better interpreted with the aid of a stochastic modeling approach. Due to strong non-linearities, both the first-order numerical technique Euler-Maruyama and the second-order Milstein approach failed to solve the designed SDE model. Therefore, we discuss the nth-order RK algorithm for the numerical integration of the SDE model and propose fourth-order RK to solve the designed model numerically. The stochastic modeling and simulation approaches proposed in this study are promising and simple for future control studies. We highlight important parameters and discuss tumor control strategies by varying values of these parameters. From numerical simulations, it can be concluded that CTLs can remove the small tumor but fail to remove the larger tumor. However, in the future, we are interested in extending our model by adding the effects of chemotherapy and immunotherapy.

CRediT authorship contribution statement

Muhammad Idrees: Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing - original draft, Writing - review & editing. **Ayesha Sohail:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **João Manuel R.S. Tavares:** Formal analysis, Funding acquisition, Methodology, Software, Visualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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