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Mathematical modelling of the dynamics of prostate cancer with a curative vaccine☆

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ABSTRACT

A mathematical model for prostate cancer treatment using a curative vaccine is developed to determine the efficacy of constant drug infusion into the body tissues. It describes the interaction of prostate tumour cells, immune response, and treatment using the curative vaccine, commonly known as the Sipuleucel-T vaccine. Stability analysis of the model shows that, without treatment, prostate tumour cells would grow to the maximum carrying capacity. It is also demonstrated that the vaccine could clear prostate tumour cells from the body tissues if the curative vaccine efficacy is less than the ratio of the product of death of dendritic cells and its decay rate to the activation rate of the therapy. Global sensitivity analysis is investigated to establish critical factors that promote prostate cancer recurrence during treatment. Further analysis suggests that the recruitment rate of effector cells by dendritic cells, which leads to an increase in lysis of prostate tumour cells determines the curative vaccine's success. Numerical simulations show that when the curative vaccine is administered at minimum doses, androgen-independent cancer cells take a long time to be eliminated from the body tissue. At the same time, they can be cleared in a short period when a standard or higher dose is administered. The use of a standard dose is preferable as it lowers the side effects, although the treatment period would be relatively long.

1. Introduction

Cancer refers to a disease caused by uncontrolled, abnormal growth or changes of cells in any part of a body. Some of these changes are inherited, but most of them have their roots in the environment and lifestyle of an individual such as carcinogens contained in the food we eat or in the air we breathe, radiations among others [1]. According to Globocan 2018 data, cancer is a disease that kills more people on a global scale than AIDS, malaria and TB combined. The new cancer data

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have shown an estimated 18.1 millions of new cases and 9.6 million deaths worldwide. In particular, the data have shown that there is an estimated 1.3 million new cases of prostate tumour cells and 359,000 associated deaths worldwide in 2018.

Prostate cancer originate from prostate gland and is rated as the most dangerous disease for men and it is the second leading cause of death in men (the leading being lung cancer), particularly in Sub-Saharan Africa and the Caribbean countries [2,3], yet much is still not known about its interaction dynamics with immune cells [4]. Studies indicate that some patients treated for prostate cancer may relapse into the condition after a few years [5,6]. Various studies investigated the effects of single and combined therapies [7–12] for PCa treatment. For example, Peng et al. [12] developed a model that explores the interaction of prostate tumour cells and tumour microenvironment. Mouse data were used to guide the construction, parameters' selection, and model validation. The results showed that Treg depletion and Interleukin-2 (IL-2) neutralisation could effectively improve the treatment efficacy of PCa with combined therapies of Androgen Deprivation Therapy (ADT) and vaccination. However, results showed that Treg depletion had a higher energetic effect for prostate tumour clearance than IL-2. A study by Kronik et al. [10] pointed out that the therapeutic vaccine used against disseminated prostate cancer is partially effective in some prostate cancer patients, and individual vaccination regimens would enhance the efficacy of the treatment. The model constructed in [10] was validated using the results of clinical measured changes in Prostate-Specific Antigen (PSA) levels correlated with tumour burden. Doersch et al. [13] conducted a study on synergistic immunological targets for the treatment of PCa, where two immunologic factors, namely, IL-2 and transforming factor (β), were used as attractive therapeutic targets for PCa. The results affirmed that an increase in IL-2 and a decrease in β signalling might improve immunologic recognition and target prostate tumour cells.

Despite noticeable clinical and experimental studies, success in investigating and characterising prostate tumour cells' treatment with immunotherapy, much is still not understood on the curative vaccine. The main challenges include designing an appropriate dose, the best effective therapeutic drug or vaccine infusion strategy, and the crucial treatment characteristics [14]. Mathematical modelling plays a crucial role in answering such kinds of challenges, which would otherwise cost much experimentally.

Several mathematical studies, including [7–9,15–17] addressed the dynamics of prostate tumour and its treatments. Yang et al. [11] studied prostate tumour growth under intermittent androgen suppression, pointing out that the stronger the competitive ability of Androgen Dependent (AD) cells, the higher is the likelihood of achieving successful intermittent androgen suppression control. Further results affirmed that the competition and the restraint of a finite environment could enhance the possibility of a relapse Androgen Independent (AI) prevention. A recent study by Badziul et al. [18] showed that using vaccine therapy in the treatment of PCa is promising as more than half of patients investigated showed tumour responsiveness. They further argued that immune responses against PCa cells are highly heterogeneous, not only between the level of cancer advancement but also between different patients with the same type of cancer.

In this work, we accommodate the assumption by Kronik et al. [10], which is based on the fact that the Bacillus Calmette-Guérin vaccine injected in body tissues has prostate cancer antigen that stimulates cancer-specific immunity, but the normal regulatory mechanisms and the tumour suppress this immunity. In contrast, Sipuleucel-T used in this study resolves this draw-back by introducing more immune cells grown outside the body. Therefore when this vaccine is infused in the patient's body, it does not suffer the immune suppression that the tumour induces. The study employs curative vaccine therapy for the treatment of advanced prostate cancer based on the immune status of the patient. Other similar mathematical models on PCa with treatment can be found in [19–21].

This research paper is aimed at constructing and analysing a mathematical model of immunotherapy of the curative vaccine. The model consists of AD tumour cells, AI tumour cells, Dendritic Cells (DC), and Effector Cells (EC). The rest of the paper is organised as follows. "The model" introduces the mathematical model, defines the initial conditions of the model and the underlying model assumptions. "Model analysis" presents the model analysis while "Numerical simulations" presents numerical simulations. A global sensitivity analysis of the model parameters is presented in "Sensitivity analysis", and conclusive remarks are given in "Conclusion".

2. The model

The model consists of five dependent variables, namely; androgen-dependent cancer cells (A_d), androgen-independent cancer cells (A_i), curative vaccine (V_c), dendritic cells (D), and activated effector cells (E). The five state variables were chosen such that the model appears as simple as possible but sheds light on and sufficiently captures the dynamics of prostate tumour cells. The units of all state variables are given in number of cells, and time is measured in days. The interaction of various cells and the curative vaccine is shown in Fig. 1. Androgen dependent grows faster and eventually mutates to A_i.

2.1. Model assumptions

The following assumptions are made in setting up the model:

(i) Prostate tumour cells and health cells compete for space and nutrients within the body [22].
(ii) Tumour cell are taken as a single compartment; divided into AD and AI cancer cells [11,12].
(iii) Effector cells kill tumour cells (AD and AI) more effectively as the concentration of a curative vaccine is increased [23].
(iv) Some AD cancer cells escape immune response and hence undergo mutation leading to an increase in the amount of AI cancer cells [24].

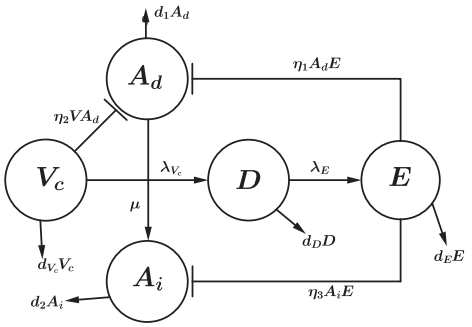

Fig. 1. The flow diagram that depicts the interaction of tumour cells with a curative vaccine and immune response. A_d represents androgen-dependent cancer cells, A_i represents androgen-independent cancer cells, V_c represents curative vaccine, D represents dendritic cells, and E represents effector cells. Sharp arrows($\longrightarrow$): Indicate activation, blocked arrows ($\dashv$): Indicate killing/blocking.

2.2. Model equations

Based on Fig. 1, model descriptions and assumptions, the following differential equations are obtained:

(i) **The equation for and rogen-dependent prostate cancer cells (A_d)**
Androgen dependent cancer cells grow faster than AI cancer cells in a patient with PCa and are killed by E and suppressed by the curative vaccine V_c at the rates η_1 and η_2 respectively. The mutation term for AD is represented by μA_d. A_d cells are assumed to propagate logistically with a carrying capacity (A_1) to account for competition for space among cancer cells. Therefore, the rate of change of AD cancer cells A_d takes the form

$$\frac{dA_d}{dt} = \lambda_1 A_d\left(1 - \frac{A_d}{A_1}\right) - \eta_1 A_d E - \eta_2 V_c A_d - \mu A_d - d_1 A_d, \tag{1}$$

where d_1 is the natural death rate of the AD cancer cells.

(ii) **Equations for androgen-independent prostate cancer cells** (A_i)
The growth of PCa depends on the secretion of testosterone by the testes. Surgical castration suggested by Hirata et al. [8] as a treatment for metastatic PCa can bring about regression of prostatic tumour cells and eventually progress as AI cancer cells. The equation for A_i is given by

$$\frac{dA_i}{dt} = \lambda_2 A_i\left(1 - \frac{A_i}{A_2}\right) - \eta_3 A_i E + \mu A_d - d_2 A_i, \tag{2}$$

where η_3 is the rate at which effector cells kill A_i cells, d_2 is the natural death for AI cancer cells, A_2 is the carrying capacity of AI cancer cells, and μ is the mutation rate of AD cancer cells.

(iii) **Equation for dendritic cells (D)**
Dendritic cells are activated by V_c at the rate λ_{V_c} also activated by other sources represented by S. Therefore the equation for DC is given by

$$\frac{dD}{dt} = S + \lambda_{V_c} D V_c - d_D D, \tag{3}$$

where d_D is the death rate of dendritic cells.

(iv) **Equation for curative vaccine (V_c)**
When AD and AI are killed by E that consist of macrophages, T cells and natural killer cells the tumour cells are cleared. Hence the equation for the V_c is

$$\frac{dV_c}{dt} = C_{V_c} - d_{V_c} V_c, \tag{4}$$

where C_{V_c} is the concentration of the V_c injected in the body of an individual, and d_{V_c} is the decay rate of the V_c.

(v) **Equation for effector cells**
Effector cells are activated by DC and cytokines, which in turn kill tumour cells (A_d and A_i) at different rates, i.e., η_1 and η_3 respectively so that the governing equation is

$$\frac{dE}{dt} = \lambda_E D - d_E E, \tag{5}$$

where λ_E is the rate of effective cell recruitment by mature DCs and d_E is the natural death of effector cells.
Thus, the full model system is composed of equations (1–5) as shown below

$$\frac{dA_d}{dt} = \lambda_1 A_d\left(1 - \frac{A_d}{A_1}\right) - \eta_1 A_d E - \mu A_d - \eta_2 V_c A_d - d_1 A_d,$$

$$\begin{aligned}
\frac{dA_i}{dt} &= \lambda_2 A_i\left(1-\frac{A_i}{A_2}\right) - \eta_3 A_i E + \mu A_d - d_2 A_i,\\
\frac{dV_c}{dt} &= C_{V_c} - d_{V_c} V_c,\\
\frac{dD}{dt} &= S + \lambda_{V_c} V_c D - d_D D,\\
\frac{dE}{dt} &= \lambda_E D - d_E E,
\end{aligned} \tag{6}$$

subject to the following initial conditions

$$A_d(0) = A_{do} \geq 0, A_i(0) = A_{io} \geq 0, D(0) = D_o > 0,\ V_c(0) = V_{co} \geq 0,\ E(0) = E_o > 0.$$

In Eqs. (1) and (2) the terms $\lambda_1 A_d\left(1-\frac{A_d}{A_1}\right)$, $\lambda_2 A_i\left(1-\frac{A_i}{A_2}\right)$ represent prostate tumour growth for AD and AI respectively. The terms $-\eta_1 A_d E$ and $-\eta_3 A_i E$ describe the loss of AD and AI by effector cells where η_1 and η_3 are killing rates for AD and AI respectively. Mutation from AD to AI is represented by the term $-\mu A_d$ where μ is the mutation rate. Suppression of the curative vaccine to AD is shown by the term $-\eta_2 V_c A_d$ where η_2 is the suppression rate; $-d_1 A_d$ and $-d_2 A_i$ represent the loss of tumour cells for AD and AI respectively. In Eq. (3), the time dependent function $C_{V_c}(t)$ represents curative vaccine infusion. It is prepared by using ones immune cells which activate DC and thereafter activate EC for prostate tumour killing, and $-d_{V_c} V_c$ describes decay of the curative vaccine where d_{V_c} is the rate of decay. In Eq. (4), S describes the source term for DC, the second term $\lambda_{V_c} V_c D$ models the activation of dendritic cells by the curative vaccine where λ_{V_c} is the activation rate; the death for dendritic cells is represented by $-d_D D$. In Eq. (5), $\lambda_E D$ models the effector cell recruitment by mature dendritic cells where λ_E is the recruitment rate and the last term $-d_E E$ is death of effector cells.

3. Model analysis

First we show that the model is well-posed in a biologically plausible domain, and then proceed with stability analysis of the model with constant curative vaccine infusion. Since the model describes cell populations, the cell densities should remain non-negative and bounded. The theorem for model well-posedness is stated as follows

Theorem 3.1.

(i) *There exists a unique solution to the system of Eq. (6) in the domain* $\Omega = (A_d,\ A_i, D, V_c, E) \in \mathbb{R}^5_+$.
(ii) *If* $A_d(0) \geq 0, A_i(0) \geq 0, D(0) > 0, V_c(0) \geq 0$ and $E(0) > 0$, *then* $A_d(t) \geq 0, A_i(t) \geq 0, D(t) > 0, V_c(t) \geq 0$ and $E(t) > 0, \forall t \geq 0$.
(iii) *The domain* Ω *is positively invariant for the model system (6) and hence biologically meaningful.*

Proof. (i) The existence and uniqueness of model solutions.

Theorem A.4 in [28] states as follows:

Let $\mathbb{R}^n = [0, \infty)$ be the cone of non-negative vectors in $F : \mathbb{R}^{n+1}_+ \to \mathbb{R}^n$ be locally Lipschitz,

$$F(t,x) = (F_1(t,x), F_2(t,x), \ldots, F_n(t,x)), \qquad x = (x_1, x_2, \ldots, x_n), \tag{7}$$

and satisfy

$$F_j(t,x) \geq 0 \quad \text{whenever} \quad t \geq 0, \qquad x \in \mathbb{R}^n_+, \qquad x_j = 0. \tag{8}$$

Then for every $x^0 \in \mathbb{R}^n_+$, there exists unique solution of $x' = F(t,x), \qquad x(0) = x^0$ with value in $\mathbb{R}^n_+$, defined on the some interval $[0, b), b > 0$. The functions $A_d,\ A_i,\ V_c,\ D,\ E$ on the left of model Eq. (6) are continuous on $\mathbb{R}^5_+$ and the conditions in (8) are satisfied.

(ii) Non-negativity of the solution

Using Eq. (1) we have

$$\frac{dA_d}{dt} = \lambda_1 A_d\left(1-\frac{A_d}{A_1}\right) - \eta_1 A_d E - \eta_3 V_c A_d - \mu A_d - d_1 A_d.$$

Using A.2 in [28] the solution of Eq. (1) becomes

$$A_d(t) = A_d(0) \exp\left[\int_0^t \left\{\lambda_1\left(1-\frac{A_d(s)}{A_1}\right) - \eta_1 E(s) - \eta_3 V_c(s)\right\} ds - (\mu + d_1)t\right] \geq 0, \tag{9}$$

as $A_d > 0$.

Let the model Eqs. (2), (3) and (5) be written in the form $x' = F(t,x)$. The function $F(x,t)$ on the right hand side of Eqs. (2), (3) and (5) have the property of $F(A_i, D, E, t) \geq 0$ whenever $x \in [0,\infty)^n, x_j = 0, t \geq 0$ and $x(t_0) \geq 0$ where $x = (A_i, D, E)$.

Thus, it follows from Proposition A.1 in [28] that $x(t) \in [0, \infty)^n$, for all $t \geq t_0 \geq 0$ whenever $x(t_0) \geq 0$ and thus the model solutions $x = (A_i, D, E)$ are positive for non-negative initial values x^0.

Integrating Eq. (4), we have

$$V_c(t) = \frac{C_{V_c}}{d_{V_c}} + \left[V_c(0) - \frac{C_{V_c}}{d_{V_c}}\right] e^{-d_{V_c} t} \geq 0. \tag{10}$$

Since all the equations in the system (6) are positive for all $t \geq 0$, this completes the proof.

The biological meaning of Eq. (10) is that, with constant drug infusion the drug is not completely cleared from the body tissue during treatment.

(iii) Boundedness of the model

We start with boundedness of A_d. By using a comparison argument

$$\frac{dA_d}{dt} = \lambda_1 A_d \left(1 - \frac{A_d}{A_1}\right) - \eta_1 A_d E - \eta_2 V_c A_d - \mu A_d - d_1 A_d \leq \lambda_1 A_d \left(1 - \frac{A_d}{A_1}\right), \tag{11}$$

which implies that

$$A_d(t) \leq \max\{A_d(0), A_1\}, \text{ that is } \lim_{t \to \infty} \sup A_d(t) \leq A_1.$$

Therefore A_d is eventually bounded.

Now we prove that A_i is bounded.

$$\frac{dA_i}{dt} = \lambda_2 A_i \left(1 - \frac{A_i}{A_2}\right) - \eta_3 A_i E + \mu A_d - d_2 A_i \leq \lambda_2 A_i \left(1 - \frac{A_i}{A_2}\right) + \mu A_d,$$

so,

$$\lim_{t \to \infty} \sup A_i(t) \leq \alpha + \frac{A_2}{2}, \text{ where } \alpha = \sqrt{\frac{\lambda_2 A_2^2 + 4\mu A_1 A_2}{4\lambda_2}}.$$

Therefore $A_i \leq \max\left\{A_i(0), \alpha + \frac{A_2}{2}\right\}$ and A_i is bounded.

From Eq. (4)

$$\frac{dV_c}{dt} = C_{V_c} - d_{V_c} V_c,$$

Integrating, we get,

$$V_c(t) = \frac{C_{V_c}}{d_{V_c}} + \left[V_c(0) - \frac{C_{V_c}}{d_{V_c}}\right] e^{-d_{V_c} t}. \tag{12}$$

and therefore,

$$\lim_{t \to \infty} \sup V_c(t) \leq \frac{C_{V_c}}{d_{V_c}},$$

hence $V_c(t) \leq \max\left\{V_c(0), \frac{C_{V_c}}{d_{V_c}}\right\}$.

The solution to the Eq. (3) is

$$D(t) = \frac{S d_{V_c}}{\beta} + \left[D(0) - \frac{S d_{V_c}}{\beta}\right] e^{-\frac{\beta}{d_{V_c}} t}, \tag{13}$$

where

$$\lim_{t \to \infty} \sup D(t) \leq \frac{S d_{V_c}}{\beta},$$

and hence $D(t) \leq \max\left\{D(0), \frac{S d_{V_c}}{\beta}\right\}$, if $\beta = d_D d_{V_c} \geq \lambda_D C_{V_c}$.

Similarly, for Eq. (5) $E(t) \leq \max\left\{E(0), \frac{\lambda_E S d_{V_c}}{\beta d_E}\right\}$, where

$$\lim_{t \to \infty} \sup E(t) \leq \frac{\lambda_E S d_{V_c}}{d_E \beta}.$$

□

By Theorem 3.1 the model solutions are positive and bounded, therefore, they are biologically meaningful.

3.1. Model without a curative vaccine

To investigate the efficacy of a curative vaccine and immune response to AD and AI cancer cells, we first study the model without treatment. When the variable on the curative vaccine is removed, the model system (6) becomes

$$\begin{aligned}
\frac{dA_d}{dt} &= \lambda_1 A_d\left(1-\frac{A_d}{A_1}\right) - \eta_1 A_d E - \mu A_d - d_1 A_d,\\
\frac{dA_i}{dt} &= \lambda_2 A_i\left(1-\frac{A_i}{A_2}\right) - \eta_3 A_i E + \mu A_d - d_2 A_i,\\
\frac{dD}{dt} &= S - d_D D,\\
\frac{dE}{dt} &= \lambda_E D - d_E E.
\end{aligned} \tag{14}$$

Proposition 1. *From the model system (14) we have three biologically meaningful steady states denoted by Y_1, Y_2, & Y_3 :*

A tumour-free steady state, $Y_1 = \left(0, 0, \frac{S}{d_D}, \frac{S\lambda_E}{d_E d_D}\right)$, which is stable if the growth rates of tumour cells are such that

$$\lambda_1 < \frac{\sigma_1}{d_E d_D}, \quad \lambda_2 < \frac{\sigma_2}{d_E d_D};$$

where

$$\sigma_1 = \mu d_D d_E + d_1 d_D d_E + S\eta_1\lambda_E, \text{ and } \sigma_2 = d_2 d_D d_E + S\eta_3\lambda_E,$$

otherwise it is unstable. This implies that when the death rate of immune cells in a body tissue is high, the growth of prostate tumour cells increases, and they will be few in numbers if the immune cell death rate is low.

A tumour endemic steady state is

$$Y_2 = (A_d^*, A_i^*, D^*, E^*),$$

where

$$A_d^* = \frac{A_1(d_E\lambda_1 d_D - \mu d_D d_E - d_1 d_E d_D - S\eta_1\lambda_E)}{d_E\lambda_1 d_D},$$

$$A_i^* = \frac{\sqrt{A_2\lambda_1\left(A_2\lambda_1 {p_1}^2 - 4A_1 d_E\lambda_2\mu d_D p_2\right)} - A_2\lambda_1(d_E d_D(d_2-\lambda_2) + S\eta_3\lambda_E)}{2d_E\lambda_1\lambda_2 d_D},$$

$$D^* = \frac{S}{d_D}, \quad E^* = \frac{S\lambda_E}{d_E d_D}.$$

The values of p_1 and p_2 are

$${p_1}^2 = (d_E d_D(d_2-\lambda_2) + s\eta_3\lambda_E), \text{ and } p_2 = (d_E d_D(d_1-\lambda_1+\mu) + s\eta_1\lambda_E).$$

The boundary equilibrium point is

$$Y_3 = (0, A_i^*, \frac{S}{d_D}, \frac{S\lambda_E}{d_E d_D}) \text{ where } A_i^* = \frac{A_2(d_E\lambda_2 d_D - d_2 d_E d_D - S\eta_3\lambda_E)}{d_E\lambda_2 d_D}.$$

Proof. The Jacobian matrix evaluated at Y_1 is

$$J_{Y_1} = \begin{pmatrix} -\mu - d_1 + \lambda_1 - \frac{S\eta_1\lambda_E}{d_D d_E} & 0 & 0 & 0\\ \mu & -d_2 + \lambda_2 - \frac{S\eta_3\lambda_E}{d_D d_E} & 0 & 0\\ 0 & 0 & -d_D & 0\\ 0 & 0 & \lambda_E & -d_E \end{pmatrix},$$

with eigenvalues

$$-d_D, -d_E, -\mu - d_1 + \lambda_1 - \frac{\eta_1\lambda_E S}{d_E d_D} \text{ and } -d_2 + \lambda_2 - \frac{\eta_3\lambda_E S}{d_E d_D}.$$

□

Biological interpretation:

Proposition 1 suggests that the tumour free equilibrium point Y_1 does not contain AD and AI cancer cells while the dendritic cells and effector cells remain in their steady states. This implies that the tumour cells would be eliminated by considering the conditions of Proposition 1 as stated.

The eigenvalues for the Jacobian matrix at endemic equilibrium point evaluated at Y_2 are $-d_D, -d_E, \alpha_1$ and α_2; where $\alpha_1 = \frac{\eta_1\lambda_E S}{d_E d_D} + d_1 - \lambda_1 + \mu$ and $\alpha_2 = \sqrt{\beta_1} - \beta_2$;

$\beta_1 = A_2\lambda_1\big(A_2\lambda_1(d_E d_D(d_2 - \lambda_2) + \eta_2\lambda_E S)^2 - 4A_1 d_E\lambda_2\mu d_D(d_E d_D(d_1 - \lambda_1 + \mu) + \eta_1\lambda_E S)\big)$ and $\beta_2 = 2A_2\lambda_1(d_E d_D(d_2 - \lambda_2) + \eta_2\lambda_E S)$.

The first two eigenvalues are negative, α_1 and α_2 would be negative if

$$\sqrt{\beta_1} < \beta_2 \text{ and } \frac{\eta_1\lambda_E S}{d_E d_D} + d_1 + \mu < \lambda_1,$$

hence globally stable, implying that the presence of the disease would necessitate medical treatment.

3.2. Global stability of disease free steady state

The global stability of the disease-free steady state is obtained by applying the Lyapunov principle [29]. This method involves finding a Lyapunov function which is positive definite; and its derivative along the trajectory, which is negative.

Theorem 3.2. *If the equilibrium point Y_1 is locally asymptotically stable in the interior of positive A_d, A_i, D, E, then it will be globally asymptotically stable.*

Proof. Suppose $x' = f(x)$ and $f(x^*) = 0$. We show that there exists a C^1 function $V : \mathbb{R}^4 \to \mathbb{R}$ such that:

(a) $V(x^*) = 0$
(b) $V(x) > 0$, for all $x \neq x^*$
(c) $V'(x) < 0$, for all $x \neq x^*$
(d) $\lim_{\|x\|\to\infty} V(x) = \infty V(x) \to \infty$, as $||x|| \to \infty$

then x^* is a globally asymptotically stable.

Now, consider the following Lyapunov function

$$V(D, E) = \gamma_1\left(D - D^* - D^* \ln\frac{D}{D^*}\right) + \gamma_2\left(E - E^* - E^* \ln\frac{E}{E^*}\right), \tag{15}$$

where V is C^1 in the interior of Ω, x^* is globally minimum of V on Ω and $V(x^*) = 0$. The derivative of V with respect to t is given as

$$\frac{dV}{dt} = \gamma_1\left(\frac{D - D^*}{D}\right)\frac{dD}{dt} + \gamma_2\left(\frac{E - E^*}{E}\right)\frac{dE}{dt}. \tag{16}$$

Substituting the last two equations of (6) into the Eq. (16) we have

$$\frac{dV}{dt} = P - Q, \tag{17}$$

where

$$P = \gamma_1(S + d_D D^*) + \gamma_2(\lambda_E D + E^* d_E) \text{ and } Q = \gamma_1\left(\frac{SD^*}{D} + d_D D\right) + \gamma_2\left(\frac{\lambda_E E^* D}{E} + d_E E\right).$$

If $P < Q$, then $V' < 0$ for all $A_d, A_i, D, E > 0$ and $V' = 0$ if and only if $D = D^*$ and $E = E^*$ is the singleton Y_1 where Y_1 is the disease free steady state of the model (13). Therefore, the largest compact invariant set in $D, E \in \Omega : V = 0$. By La Salles' [4] invariant principle it implies that Y_1 is globally asymptotically stable in Ω if $P < Q$. This implies that the disease could be wiped from the body tissue. □

3.3. The model with a curative vaccine

Model (6) is studied with a curative vaccine to investigate its effect on the androgen-dependent and androgen-independent cancer cells. By considering the treatment, the model system has three meaningful steady-state.

Proposition 2. *The three biologically meaningful steady states are: a tumour-free steady state*

$$V_1 = \left(0, 0, \frac{C_{V_c}}{d_{V_c}}, \frac{Sd_{V_c}}{d_D d_{V_c} - C_{V_c}\lambda_{V_c}}, \frac{\lambda_E S d_{V_c}}{d_E(d_D d_{V_c} - C_{V_c}\lambda_{V_c})}\right),$$

which is stable if the infusion rate of the vaccine is less than $d_D d_{V_c}/\lambda_{V_c}$, that is

$$d_D d_{V_c} - C_{V_c}\lambda_{V_c} > 0.$$

The boundary steady state is

$$V_2 = \left(0, A_i^*, \frac{C_{V_c}}{d_{V_c}}, D^*, E^*\right),$$

where

$$A_i^* = A_2\left(1 - \frac{\frac{\eta_3\lambda_E S d_{V_c}}{d_E\left(d_D d_{V_c} - C_{V_c}\lambda_{V_c}\right)} + d_2}{\lambda_2}\right), \quad D^* = \frac{S d_{V_c}}{d_D d_{V_c} - C_{V_c}\lambda_{V_c}}, E^* = \frac{\lambda_E S d_{V_c}}{d_E\left(d_D d_{V_c} - C_{V_c}\lambda_{V_c}\right)}.$$

The tumour endemic steady state is

$$V_3 = \left(A_d^*, A_i^*, V_c^*, D^*, E^*\right),$$

where

$$A_d^* = A_1\left(1 - \frac{\frac{\eta_1\lambda_E S d_{V_c}}{d_E\left(d_D d_{V_c} - C_{V_c}\lambda_{V_c}\right)} + \frac{\eta_2 C_{V_c}}{d_{V_c}} + d_1 + \mu}{\lambda_1}\right),$$

$$A_i^* = \frac{A_2\lambda_1 d_{V_c}\left(d_E(\lambda_2 - d_2)(d_D d_{V_c} - C_{V_c}\lambda_D) - \eta_3\lambda_E S d_{V_c}\right)}{2 d_E\lambda_1\lambda_2 d_{V_c}\left(d_D d_{V_c} - C_{V_c}\lambda_{V_c}\right)}, V_c^* = \frac{C_{V_c}}{d_{V_c}},$$

$$D^* = \frac{S d_{V_c}}{d_D d_{V_c} - C_{V_c}\lambda_{V_c}}, E^* = \frac{\lambda_E S d_{V_c}}{d_E\left(d_D d_{V_c} - C_{V_c}\lambda_{V_c}\right)}$$

The Jacobian matrix of the system (6) evaluated at V_1 is given by

$$J_{V_1} = \begin{pmatrix} q_1 & 0 & 0 & 0 & 0 \\ \mu & -d_2 + \lambda_2 - \frac{S d_{V_c}\eta_3\lambda_{V_c}}{d_E\left(d_D d_{V_c} - C_{V_c}\lambda_{V_c}\right)} & 0 & 0 & 0 \\ 0 & 0 & -d_V & 0 & 0 \\ 0 & 0 & \frac{S d_{V_c}\lambda_{V_c}}{d_D d_{V_c} - C_V\lambda_{V_c}} & \frac{\lambda_{V_c} C_{V_c}}{d_{V_c}} - d_D & 0 \\ 0 & 0 & 0 & \lambda_E & -d_E \end{pmatrix} \tag{18}$$

where

$$q_1 = -\mu - d_1 + \lambda_1 - \frac{C_{V_c}\eta_2}{d_{V_c}} - \frac{S d_{V_c}\eta_1\lambda_E}{d_E\left(d_D d_{V_c} - C_{V_c}\lambda_{V_c}\right)}.$$

and their corresponding eigenvalues are:

$$\begin{aligned} &-d_E, -d_{V_c}, \frac{C_{V_c}\lambda_{V_c} - d_D d_{V_c}}{d_{V_c}}, \frac{\eta_1\lambda_E S d_{V_c} + \lambda_1 d_E\left(C_{V_c}\lambda_{V_c} - d_D d_{V_c}\right)}{d_E\left(C_{V_c}\lambda_{V_c} - d_D d_{V_c}\right)} - \frac{\eta_2 C_{V_c}}{d_{V_c}} - d_1 - \mu, \\ &\frac{\eta_3\lambda_E S d_V + \lambda_2 d_E\left(C_{V_c}\lambda_{V_c} - d_D d_{V_c}\right)}{d_E\left(C_{V_c}\lambda_{V_c} - d_D d_{V_c}\right)} - d_2. \end{aligned} \tag{19}$$

The disease-free steady state is locally asymptotically stable if $C_{V_c}\lambda_{V_c} < d_D d_{V_c}$ since $\sigma_3 + \sigma_4 \geq 0$, where $\sigma_3 = \eta_i\lambda_E S d_{V_c}$ and $\sigma_4 = \lambda_i d_E\left(C_{V_c}\lambda_{V_c} - d_D d_{V_c}\right), i = 1, 2$. This implies that the disease can be eradicated by the vaccine from the body tissue if the ratio of combination rate of vaccine decay and DCs to activation rate of the vaccine to DCs be less than the infusion rate of the curative vaccine.

The eigenvalues of the Jacobian matrix evaluated at endemic equilibrium point, V_3 are

$$-d_E, -d_{V_c}, \frac{C_{V_c}\lambda_{V_c} - d_D d_{V_c}}{d_{V_c}}, \frac{B_1 - d_E\eta_2 C_{V_c}^2\lambda_{V_c} - d_E C_{V_c} d_{V_c}\lambda_{V_c}(d_1 - \lambda_1 + \mu)}{d_E d_{V_c}\left(d_D d_{V_c} - C_{V_c}\lambda_{V_c}\right)} \text{ and } -B_2,$$

which is locally asymptotically stable if

$$d_D d_{V_c} > C_{V_c}\lambda_{V_c}, \; B_1 < d_E\eta_2 C_{V_c}^2\lambda_{V_c} + d_E C_{V_c} d_{V_c}\lambda_{V_c}(d_1 + \lambda_1 - \mu)$$

and B_2 is real number, where

$$B_1 = d_E d_D d_{V_c}(\eta_2 C_{V_c} + d_{V_c}(d_1 - \lambda_1 + \mu)) + \eta_1\lambda_E S d_{V_c}^2,$$

$$B_2 = \frac{\sqrt{A_2\lambda_1 d_{V_c}(A_2\lambda_1 d_{V_c}(d_E\lambda_2 C_{V_c}\lambda_D + d_2 d_E(d_D d_{V_c} - C_{V_c}\lambda_D) - d_E\lambda_2 + d_D d_{V_c} + \eta_3\lambda_E S d_{V_c})^2 - B_3)}}{A_2 d_E\lambda_1 d_{V_c}\left(d_D d_{V_c} - C_{V_c}\lambda_{V_c}\right)},$$

and

$$\begin{aligned} B_3 =& 4A_1 d_E\lambda_2\mu\left(d_D d_{V_c} - C_{V_c}\lambda_{V_c}\right)\left(d_E d_D d_{V_c}(\eta_3 C_{V_c} + d_{V_c}(d_1 - \lambda_1 + \mu)) - d_E\eta_3 C_{V_c}^2\lambda_{V_c}\right. \\ &\left. - d_E C_{V_c} d_{V_c}\lambda_{V_c}(d_1 - \lambda_1 + \mu) + \eta_1\lambda_E S d_{V_c}^2\right). \end{aligned}$$

3.4. Global stability of the disease-free equilibrium in the presence of curative vaccine

Global stability of the disease-free steady state in the presence of curative vaccine is obtained as described in "Global stability of disease free steady state" Theorem 3.2.

Consider Lyapunov function

$$V(V_c, D, E) = \zeta_1\left(V_c - V_c^* - V_c^* \ln\frac{V_c}{V_c^*}\right) + \zeta_2\left(D - D^* - D^* \ln\frac{D}{D^*}\right) + \zeta_3\left(E - E^* - E^* \ln\frac{E}{E^*}\right), \tag{20}$$

where V is $\mathbb{C}^1$ in the interior of Ω, V_1^* is the global minimum of V on Ω, $V(V_1^*) = 0$.

The derivative of V with respect to t is given by

$$\frac{dV}{dt} = \zeta_1\left(\frac{V_c - V_c^*}{V_c}\right)\frac{dV_c}{dt} + \zeta_2\left(\frac{D - D^*}{D}\right)\frac{dD}{dt} + \zeta_3\left(\frac{E - E^*}{E}\right)\frac{dE}{dt}. \tag{21}$$

Substituting the derivative of equations $V_c,\ D, E$ in the model system (6) and simplifying give the following results: where

$$P_1 = \zeta_1\left(\frac{C_{V_c}V_c^*}{V_c} + V_c d_{V_c} D\right) + \zeta_2\frac{SD^*}{D} + \zeta_2(\lambda_{V_c}V_c D^* + d_D D) + \zeta_3\left(d_E E + \frac{\lambda_E D E^*}{E}\right). \tag{22}$$

$$Q_1 = \zeta_2\lambda_{V_c}V_c D + \zeta_3\lambda_E D + \zeta_1 C_{V_c} + \zeta_1 V_c^* d_{V_c} + \zeta_2 d_D D^* + d_E E^* + \zeta_2 S. \tag{23}$$

If $P_1 < Q_1$, then $V' \le 0$ for all $V_c, D, E > 0$ and $V' = 0$ if and only if $V_c = V_c^*, D = D^*, E = E^*$ is the singleton, V_1 where V_1^* is the equilibrium point of the dynamic model (6).

Therefore, the largest compact invariant set in $V_c = V_c^*, D = D^*, E = E^* \in \Omega : V = 0$. By using La Salle [4], the invariant principle V_1 is globally asymptotically stable in the interior of the region Ω.

Biologically, the global stability of disease-free steady state asserts that using curative vaccine the prostate tumour cells will eventually die out.

3.5. Global stability of endemic steady state

Using the same procedures as the proofs of Theorem 3.2 we have the following Lyapunov function,

$$\begin{aligned} V(V_c, D, E) =& \kappa_1\left(V_c - V_c^* - V_c^* \ln\frac{V_c}{V_c^*}\right) + \kappa_2\left(D - D^* - D^* \ln\frac{D}{D^*}\right) \\ &+ \kappa_3\left(E - E^* - E^* \ln\frac{E}{E^*}\right). \end{aligned} \tag{24}$$

The constants $\kappa_i > 0$ for $i = 1, 2, 3$. Lyapunov function V together with its constants $\kappa_1, \kappa_2, \kappa_3$ were chosen in such away that V is continuous and differentiable. With the time derivatives of equations $V_c,\ D,\ E$ defined in the model Eq. (6) and by using $C_{V_c} = d_{V_c}V_c^*$, $S = d_D D^* - \lambda_{V_c}V_c^*$ and $\lambda_E = \frac{d_E E^*}{D^*}$.

Substituting the last three equations of (6) into the time derivative similar to (21) we have

$$\begin{aligned} \frac{dV}{dt} =& -\frac{\kappa_1 d_{V_c}}{V_c}(V_c - V_c^*)^2 - \frac{\kappa_2 d_D}{D}(D - D^*)^2 \\ &+ \left[\frac{\kappa_2 d_E (D - D^*)(V_c - V_c^*)}{E} + \frac{\kappa_3\lambda_{V_c} d_E (E - E^*)(ED^* - ED^*)}{ED^*}\right]. \end{aligned} \tag{25}$$

Following the procedures by McCluskey [30] the function $F(V_c,\ D,\ E)$ is non-positive, hence $V' \le 0$. It can be observed that $V' = 0$ is the singleton V_3^* where V_3^* is the endemic steady state of the model (6). Therefore, the largest compact invariant set in $V_C,\ D,\ E \in \Omega : V = 0$. Thus, V_3^* is globally asymptotically stable in Ω Vargas-De-León [29].

4. Numerical simulations

In this section, numerical solutions are carried out to predict tumour response changes to a curative vaccine. Firstly, the tumour is assumed to have grown to its maximum size to necessitate treatment. The concentration are therefore taken to be $A_{do} = 10,000,000,\ A_{io} = 9,000,000,\ D_o = 100,000,\ V_{co} = 0$ and $E_o = 100,000$. We simulated the model with and without treatment, as shown in Fig. 2. The presence of mutation from AD to AI cancer cells leads to AD's disappearance even without treatment, as shown in Fig. 2 (a). In contrast, AI cancer cells are gradually cleared when the curative vaccine is administered. In the absence of treatment, the AI decreases to a certain steady amount; this is because the healthy immune cells fight against the invaders. Furthermore, at a moderate dose, the tumour cells are cleared to undetectable cell counts in about 7 months of specified regular dosage. On the other hand, the curative vaccine boosts the immune cells, as shown in Fig. 3.

Furthermore, after being activated by the curative vaccine, effector and dendritic cells clear the prostate tumour cells from the body, with the immune cells still remaining in their steady-state condition as depicted in Fig. 3 (a) and (b).

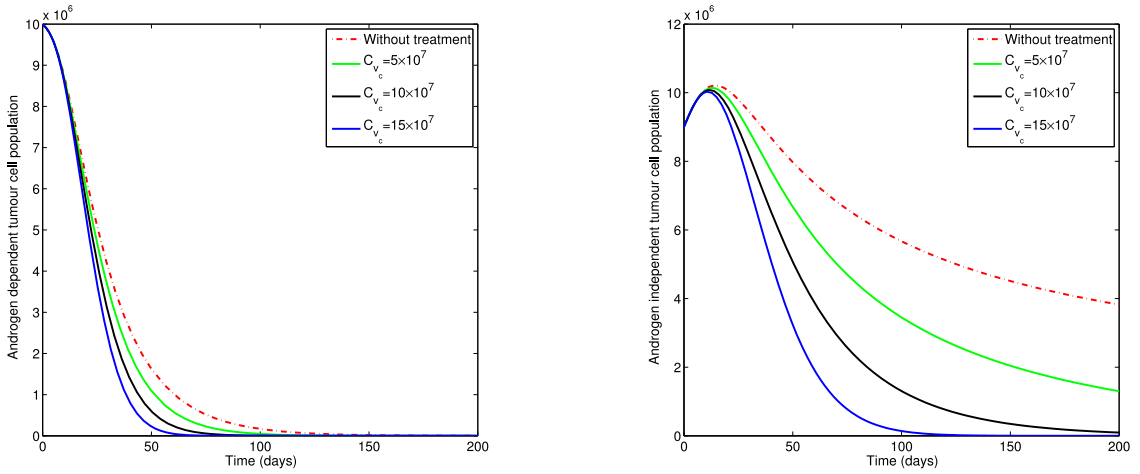

Fig. 2. Plots showing the effect of the curative vaccine on AD and AI tumour cells. As we increase the amount of drug, the number of days is reduced in wiping out the androgen-dependent and androgen-independent cancer cells.

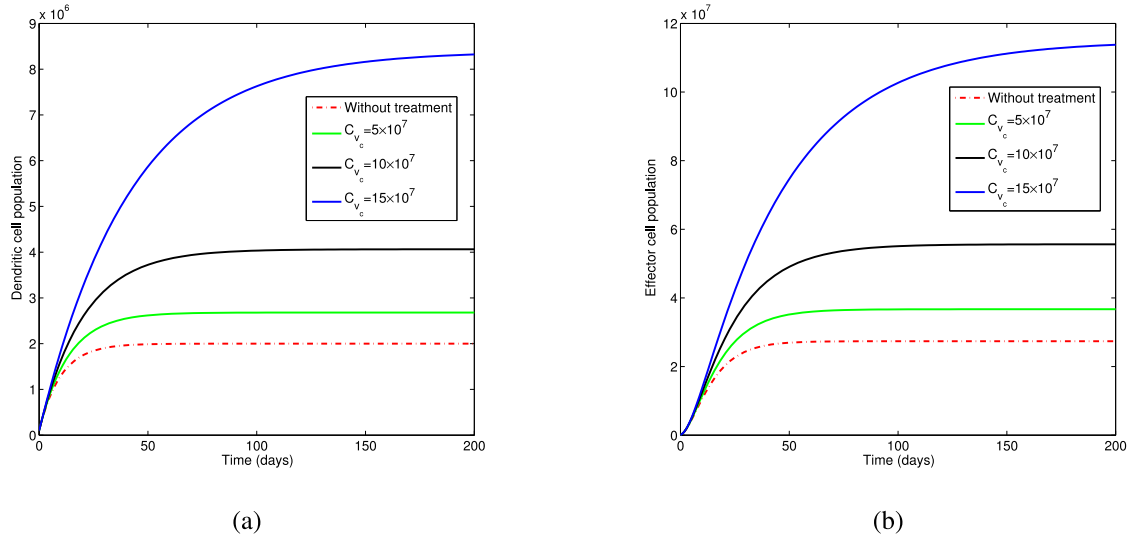

Fig. 3. Plots showing the effect of activated effector cells on AD and AI tumour cells after intervention.The figure also indicated that without any form of treatment the immune cells, that is, dendritic and effector cells are low, as the amount of curative vaccine increases more immune cells are recruited and consequently fighting against prostate tumour cells.

5. Sensitivity analysis

Following the approach by Marino et al. [31] and Malinzi et al. [23], we calculated the Partial Rank Correlation Coefficient (PRCCs) in order to determine which parameters are most sensitive to the model outcomes and hence determine the ones that could be more effectively controlled, in order to avoid PCa re-emission. It should be noted that parameters with a large PRCC value $|PRCC| \geq 0.5$, as well as corresponding small p-values (less than 0.05), are the most sensitive [32]. The closer the PRCC value to +1 or 1, the bigger the parameter influence. Therefore, we performed Latin hypercube sampling and generated 100 samples for calculating the PRCC and p-values to prostate tumour cells. The reason behind this choice is that PRCC produces accurate results for a smaller sample size compared to other techniques like Fourier Amplitude Sensitivity Test (eFAST) [31]. The parameter baseline values in Table 1 were varied in the range of 25% and the same initial values of cell densities as in the model simulations were used. The indices were calculated at $t = 60$, around the equilibrium point of prostate tumour cells, and immune cells. Fig. 4 displays a bar graph of PRCCs of the parameters. The parameters that are significantly positively correlated with the prostate tumour cells density, at $p < 0.01$ level of significance are the growth rate of androgen-independent cancer cells, the decay rate of curative vaccine, and death rate of dendritic and effector cells; those

Table 1
List of parameters used in model (6).

Symbol	Description	Value	Source
λ_1	Growth rate of AD	0.18–0.67 day^{-1}	[25]
λ_2	Growth rate of AI	0.2 day^{-1}	[26]
λ_E	Effector cell recruitment rate by mature DC	2.3 day^{-1}	Assumed
λ_{V_c}	Activation rate of DC by vaccine	0.0065 day^{-1}	Assumed
d_E	Natural death of EC	0.168 day^{-1}	[18]
C_{V_c}	Curative vaccine dose	5×10^7 cells	[10]
S	Source of DC	2.0 cells day^{-1}	Assumed
A_1	Carrying capacity of AD	1.2 $\times10^7$ Cells	[24]
A_2	Carrying capacity of AI	1.4 $\times10^7$ Cells	[24]
μ	Mutation rate of AD to AI	0.00005 day^{-1}	[9]
η_1	Killing rate of AD by EC	0.002 day^{-1}	Assumed
η_2	Suppression rate of the V_c to AD	1.0 $\times10^{-8}$ day^{-1}	Assumed
η_3	Killing rate of AI by EC	0.0001 day^{-1}	Assumed
d_1	Natural death of AD	0.17 day^{-1}	[27]
d_2	Natural death of AI	0.17 day^{-1}	[27]
d_D	Natural death of DC	0.1 day^{-1}	[22]
d_{V_c}	Decay rate of the curative vaccine	1.28–4.17 day^{-1}	[23]

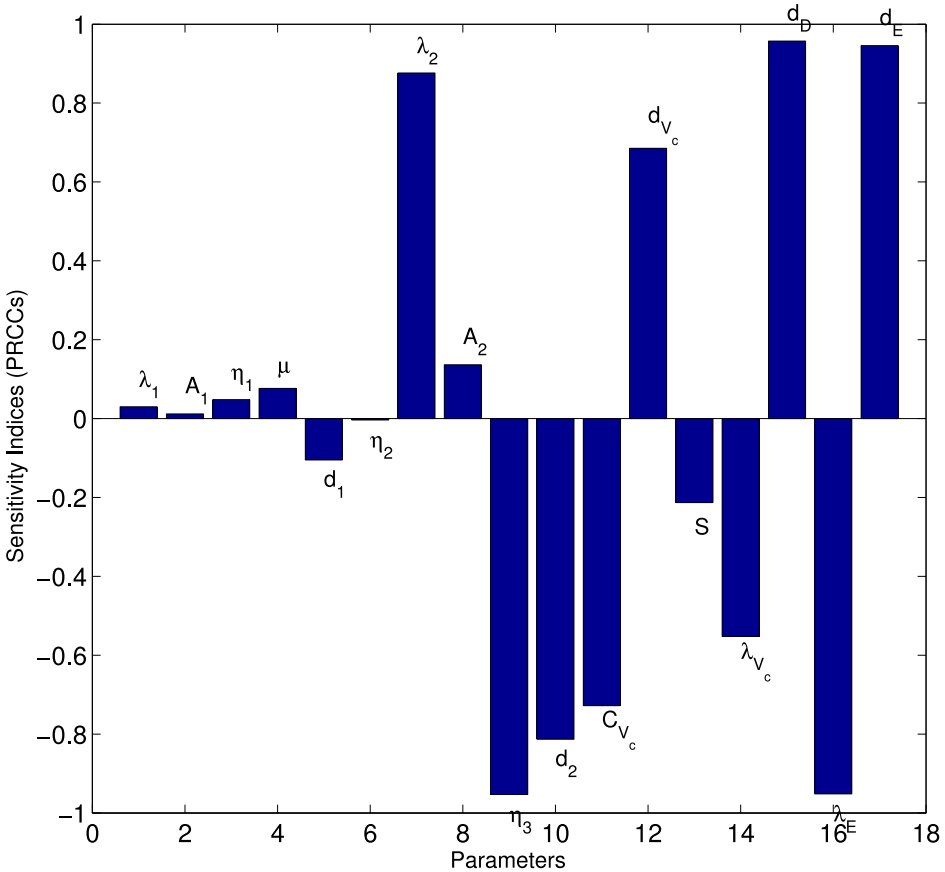

Fig. 4. PRCCs of model parameters with the prostate tumour cells density as baseline variable at the 60th day. The most sensitive parameters are $\lambda_2, \eta_3, d_{V_c}, d_D, d_E, d_2, \lambda_E, \lambda_{V_c}$ and C_{V_c} which are positively and negatively correlated.

that are negatively correlated are $\eta_3, \lambda_E, \lambda_{V_c}, C_{V_c}$ and d_2. When production level of androgen-independent cancer cells λ_2 rise leads to a high number of androgen independent cells. Similarly, an increase of d_D and d_E, which are death rates of immune cells, leads to a significant drop in body defense; thus, cancer will grow uncontrollably. An increase of therapy decay leads to less DC activation and hence less recruitment of EC by DC, consequently reducing the effector cells in killing prostate tumour cells. The higher the effector cell recruitment rate by DC, activation therapy rate to DC, and the natural death of AI, the lower the number of androgen-independent cells. This leads to a decrease in the number of prostate tumour cells since

many prostate tumour cells are killed by effector cells. Additionally, when a vaccine with a high decay rate is used, then the number of prostate tumour cells increases. If the vaccine does not decay rapidly, a number of PCa cells from the body tissue would be killed by the effector cells. This is due to the fact that the curative vaccine undergoes natural decay before DC activation. This further suggests that if the number of PCa cells increases, then the vaccine infusion should be increased. However, the increase of drug infusion should be within toxicity constraints. These results emphasis that curative vaccine decay and the infusion are a vital aspect to consider for curative vaccine modelling.

6. Conclusion

The immune response's primary role is to defend and protect the body from foreign invading pathogens [33]. The mechanism of tumour-immune interactions is still not clearly understood [34,35]. A full understanding of how prostate tumour cells and the immune system interact with them could lead to more efficient treatments of cancer [6]. In this article, we developed a mathematical model in the form of ODEs, which describes dynamical dependencies between the cellular curative vaccine and PCa cells by using the immune system, that is, dendritic and effector cells. This study aimed to investigate the curative vaccine's outcome in treating prostate cancer cells by using vaccine infusion. First, we validated the model equations by proving the solutions' existence, positivity, and boundedness. Both models with and without curative vaccine were investigated. The results revealed that a prostate tumour free state might be achieved if the prostate tumour growth rate is inversely proportional to the immune cells'. This condition points out that PCa treatment would be attained if we reduce the prostate tumour growth rate and increase induced death by immune cells. Furthermore, analysis of the coexistence equilibrium point has shown that the prostate tumour cells would be eradicated if the vaccine's decay rate is proportional to its infusion rate. Also, the numerical results revealed that androgen-independent prostate tumour cells would be cleared when a minimum dose of the curative vaccine is administered. However, the dosage period would last longer. Therefore, a moderate dose which is relatively less toxic and takes fewer days to administer is preferable. The finding obtained from this study will help the health policy makers to predict the future trends of PCa. Also, it will help health experts to select an appropriate treatment method. Future studies may include more aspects such as non-constant parameters, saturation and variable infusion strategies. Other aspects to be considered include combination therapies such as the curative vaccine and oncolytic virotherapy or checkpoint inhibitors. Furthermore, the model may be modified to incorporate AB-Caputo fractional operator, which utilise the nonsingular Mittag-Leffler function as in [36,37]. Nevertheless, the results of this study suggest using a dose of the curative vaccine during prostate tumour treatment and shed some light on the interaction dynamics of tumour cells, immune cells, and the vaccine.

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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