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PRELIMINARY MATHEMATICAL MODEL FOR CANCER TREATMENT USING BORON NEUTRON CANCER THERAPY (BNCT)

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ABSTRACT

This article outlines a revolutionary approach to immunotherapy and stem-cell cancer treatments that leverages Boron Neutron Cancer Therapy (BNCT). We formulated two models, one being the immunotherapy-BNCT model and the other featuring a stem-cell model and BNCT therapy. The former simulates the dynamics of the concentration of BNCT with anticancer properties present at the cancer site, the number of cancer cells, and the blood drug concentration, while considering periodicity. Similarly, using boronophenylalanine in the simulation, our stem-cell BNCT model evaluates the drug's impact on the dynamics of cancer cells, stem cells, effector cells, and BNCT involvement. Using the eigenvalues of the Jacobian matrix calculated from those solutions, each model is examined for the stability of equilibrium solutions. Next, the equilibrium solution is generated and found to be unstable using the simulation parameters given in the literature. Furthermore, one of the equilibrium solutions has a zero-value variable, rendering it practically meaningless. The models have impacted the new approach to utilizing BNCT in immunotherapy and stem-cell therapy, underscoring the need for follow-up in developing stable and balanced model parameters. Such efforts will improve the existing model while also yielding positive results from the BNCT approach.

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1. INTRODUCTION

In the last five years, there have been advancements in the field of cancer treatment, specifically in addressing the variations within tumors and cancer cells. We know that chemotherapy still causes side effects on healthy tissue for combating cancer [1]. Research is still being done on how to optimize the dose used to minimize healthy tissue around the cancer area. One of the latest studies using optimal control is based on Pontryagin's maximum principle, where free end-time is formulated and solved numerically with the Runge-Kutta method [2]. Similarly, immunotherapy techniques are also one of the superior techniques for overcoming cancer and are used together with anti-cancer drugs [3], [4]. Stem-cell therapy also helps to recreate tissue damaged by cancer or by other therapeutic processes carried out that damage tissue [5]. This approach is also popular as an alternative to being free from cancer [6]. Similarly, an anti-angiogenic process can be carried out where this process inhibits the growth of blood vessels that grow in cancer whose blood supply is from healthy tissue [7].

Among the emerging techniques, Boron Neutron Capture Therapy (BNCT) stands out due to its ability to target tumor cells while sparing cells. This makes it one of the therapies available. BNCT involves administering a compound containing boron to the patient and exposing them to low-energy neutrons [8]. These captured neutrons release high-energy particles that specifically damage tumor cells, which makes BNCT ideal for treating cancers located in critical areas where conventional radiation therapy may harm healthy tissues nearby. It is worth mentioning that glioblastoma, melanoma, and head and neck cancers are some of the types of malignancies being studied for BNCT [4], [6].

The primary benefit of BNCT is its precise targeting, which is made possible by the tumor cells' preferential uptake of the boron molecule. This strategy seeks to lessen adverse effects while improving therapeutic results. It's crucial to note that BNCT has its drawbacks and is still viewed as an experimental therapy. The lack of nuclear reactors in hospitals limits access to neutron sources, and the present boron-10 isotope's efficacy is constrained. As a result, more study is required to improve BNCT's effectiveness through mathematical modeling, enabling the use of novel treatment procedures.

The literature lacks precise mathematical models for therapeutic approaches incorporating BNCT, even though numerous mathematical models have been put forth for other cancer therapies. The mathematical model presented in this article combines the BNCT principles with current therapeutic modalities, including chemotherapy[9], [10]. The mathematical model takes into account the immunotherapy's periodicity, which calls for repeated treatments. Additionally, two alternative strategies are examined in this study: using BNCT in conjunction with immunotherapy to maintain the patient's immunity during treatment, and using BNCT in conjunction with stem cell therapy to maintain the rate of stem cell proliferation around cancer cells that have been treated with BNCT medications [3]. These methods are anticipated to increase the overall effectiveness of therapeutic methods, and the mathematical model put out here is an essential instrument in their evaluation and implementation.

2. RESEARCH METHODS

In this paper, we will present our study by considering that the developed model is based on the treatment used to combat cancer. A mathematical model is necessary to have efficiency in a therapeutic strategy. We refer to two approaches, i.e., combining immunotherapy and BNCT and doing BNCT with stem cell therapy [3]. The first approach proposes to stabilize the patient's immunity during the BNCT treatment. The second approach is maintaining the growth rate of stem cells around cancer cells, which are BNCT drugs. Due to its function, immunotherapy should have a periodic treatment, leading to a mathematical model with periodicity.

Fig. 1 illustrates the process of BNCT, providing readers with a simplified understanding of how the technique is employed to treat a patient [8]. The patient is irradiated with a low-energy neutron beam that triggers fission of the boron-10 (^{10}B) isotope on tumor cells, releasing high-energy α particles, and Lithium(Li) particles that destroy cancer cells. This method is known as boron neutron capture therapy (BNCT), in which boron-10 is taken up by tumor cells and reacts when exposed to low-energy neutrons, producing high-energy particles that selectively damage cancer cells. Another procedure to combat cancer is using stem cell therapy. To develop an optimized therapeutic strategy, mathematical modeling is applied to investigate the heterogeneous population of cancer cells, their interactions with the microenvironment,

immune system cells, reactions to therapy, and the emergence of resistance, along with the intricate processes involved in stem cells. This process is depicted in Fig. 2.

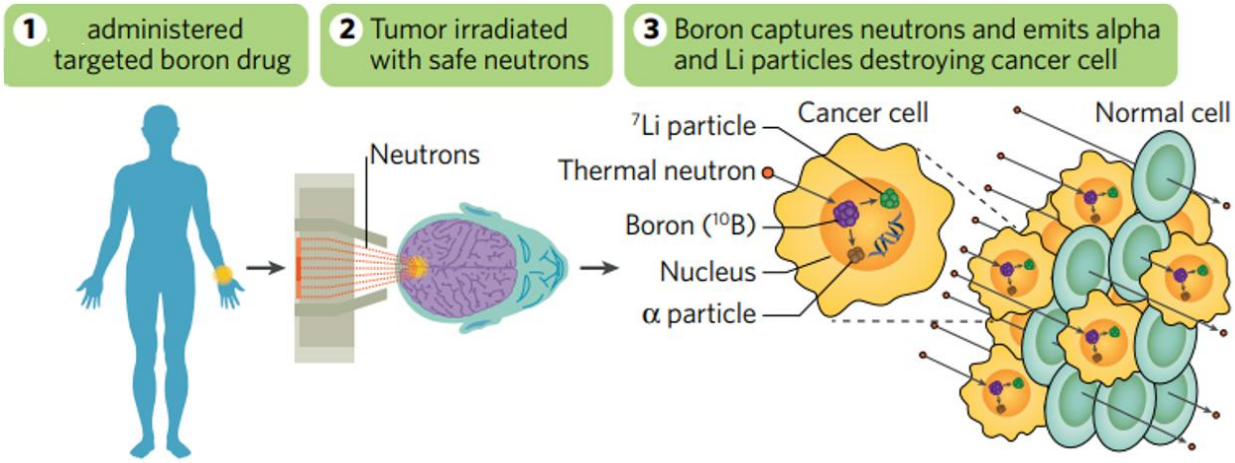

Figure 1. A Low-Energy Neutron Beam that Triggers Fission of the ^{10}B Isotope in Tumor Cells is Irradiating and Causing a Release of High-Energy α-Particle and Lithium (Li) Particles that Destroy Cancer Cells [11]

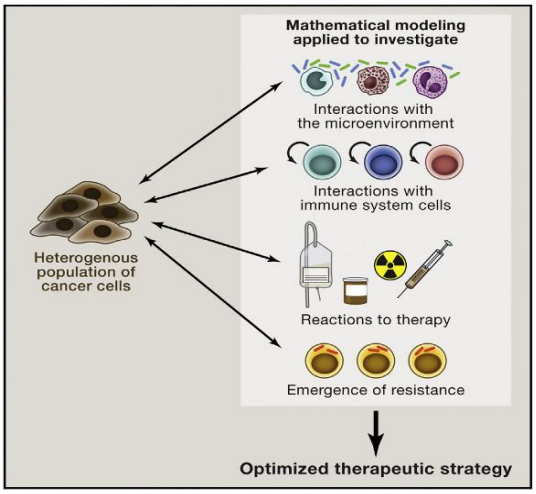

Figure 2. Some Treat Cancer Cells
(*Source:* [11])

However, further research and mathematical modeling are needed to optimize its efficiency and combine it with other therapies to maximize its therapeutic potential which are shown in this article. Therefore, the main novelty of this article is that by referring to the existing mathematical models of the treatment of cancer therapy using chemotherapy with its immunotherapy and stem cell therapy, those models are updated here by implementing BNCT's drug, such as boronophenylalanine (BPA) as a boron delivery agent [12].

2.1 Mathematical Model for Cancer Treatment using Immunotherapy-BNCT

When proposing BNCT to a patient, the immune system in the body must be maintained since the immune system responds to cancer by mediating cytotoxic T lymphocytes (CTL) cells and natural killer (NK) cells [13]. Though BNCT is considerably the safest treatment for many various tumors and cancer cells, immunotherapy is powerful enough to improve the effectiveness of BNCT. Additionally, BNCT is using drugs such as boronophenylalanine (BPA) as a boron delivery agent [12]. The two treatments are studied through a mathematical model here. Based on this, in the end, we explore the therapeutic effects of the drug BNCT, as well as mixed immunotherapy with combination BNCT. The model refers to the combination of immunotherapy and BNCT, which is distinguished later on by the used parameters [9]. For writing the model, variables and parameters are introduced here, i.e.,

x : the concentration of BNCT with anticancer activity in the cancer site;

y : the number of cancer cells;
z : the blood drug concentration;
τ : the therapeutic period;
μ_1 : the infusion dose of BNCT with anticancer activity every time;
μ_2 : an increment of the blood drug concentration due to delivering the drug at time $t = n\tau$ and $x(t^+)$, $y(t^+)$ and $z(t^+)$ denote the right limits of $x(t)$, $y(t)$, and $z(t)$ at time t, respectively.

Additionally, several parameters are also used in the model, namely:

p : the constant rate of BNCT concentration (growth rate);
R : Cancer cell growth rate;
B : Carrying capacity;
δ : the natural rate of death of immune cells;
ε : the fraction of immune cells that die due to BNCT;
α : the fraction of cancer cells that die due to immune cells;
β : the fraction of cancer cells that die due to BNCT;
γ : the rate of decay of BNCT drugs in the blood.

Blood drug concentration is the level of therapeutic drugs that are distributed in the patient's bloodstream after administration. This amount is important for modeling the effects of drugs on cancer cells and the immune system because it determines how much drug is available to work at the target site.

The model is made by referring to a predator-prey model [14], [15], and here, a step-by-step modeling process is shown.

1. The growth of the concentration of BNCT can be constant, and it should also be reduced. Therefore, it is suggested to have:

$$\frac{dx}{dt} = a - d_1 x \, .$$

However, due to its interaction with cancer cells, its concentration is also smaller, which is written as $c_1 xy$. Additionally, its concentration is also reduced due to the blood drug concentration. Therefore, the complete model for a growth rate of x is proposed as follows:

$$\frac{dx}{dt} = a - d_1 x - c_1 xy - \alpha_1 (1 - e^{-z}) x, \quad t \neq n\tau. \tag{1}$$

The rate at which the number of cancer cells increases initially may reach its maximum. This means that it grows as $\frac{dy}{dt} = ry(1 - by)$. Similarly, in the case of x, its interaction with x leads to slower growth. By the presence of the blood drug concentration, it is simultaneously decreasing exponentially. Finally, the model for the rate of y yields

$$\frac{dy}{dt} = ry(1 - by) - c_2 xy - \alpha_2 (1 - e^{-z}) y, \quad t \neq n\tau. \tag{2}$$

2. The blood drug concentration is independent of the other variables. The equation of $z(t)$ blood concentration is compiled based on the assumption of pharmacokinetics order 1. This means that the blood is eliminated from the blood flow that is proportional to the concentration at that time. Mathematically, it means written

$$\frac{dz}{dt} = -d_2 z \, , \quad t \neq n\tau. \tag{3}$$

where $d_2 > 0$ is the natural decay (elimination) rate of the drug. The solution is an exponential decay, which is the standard form for many chemotherapeutic and BNCT-related agents. Since the treatment is given periodically at times $t = n\tau$, we include a jump condition that models the discrete infusion: $z(t^+) = z(t) + \mu_2, \; t = n\tau$, where μ_2 denotes the increment of the drug concentration in the blood after each administration and τ is the therapeutic period. Equivalently, this can be expressed in compact form using a Dirac delta representation, i.e,:

$$x(t^+) = x(t) + \mu_1, \qquad t = n\tau, \tag{4}$$

$$y(t^+) = y(t), \qquad t = n\tau, \tag{5}$$

$$z(t^+) = z(t) + \mu_2, \qquad t = n\tau. \tag{6}$$

To represent the rapid and periodic administration of BNCT therapy, this model uses an impulsive differential equations approach: the continuous dynamics between administration times are governed by the ODE system, while at the time of therapy ($t = n\tau$) discrete changes occur. To ensure reproducibility of the simulations, we explicitly describe how Eqs. (1)-(3) are combined and integrated. The combination of radiation therapy and immune screening inhibitors has also been studied in the context of the optimization of the administration schedule, which can be a reference to extend the analysis of our simulation results [16].

Eqs. (4)-(6) establish the jump condition, i.e., the increase in the concentration of BNCT in the tumor (x) by μ_1, the increase in the concentration of drugs in the blood z by μ_2 and the number of y cancer cells that remain continuous because of their biological effects appear gradually. This approach is physiologically realistic, simpler for numerical analysis, and allows dose parameters (μ_1,μ_2) to be determined from clinical data or the literature.

The solutions of the resulting models from Eqs. (1)-(6) have been shown analytically, with some limitations for chemotherapy and immunotherapy simultaneously [17]. This article prefers solving the system using the Runge Kutta method as one of the powerful numerical tools in the Python language.

2.2 Stem Cells Therapy -BNCT Model

Stem cell therapy is the other well-known therapy for combating cancers with chemotherapy [18], [19]. Stem cells contribute about 220 different cells to the whole body. The BNCT treatment kills the infected cells, where stem cells are expected to grow the normal cells inside and support the effector cells to improve the immune system. The mathematical model is necessary to research the effectiveness of stem cell therapy and BNCT simultaneously. Therefore, new variables and parameters are introduced here to propose the model. These are: $C(t)$: cancer cells; $S(t)$: stem cells; $E(t)$: effector cells.

Additionally, during the BNCT treatment, the BNCT's drug, such as boronophenylalanine (BPA) [12] is employed plays an important role here, and its concentration is denoted as $B(t)$. $B(t)$: concentration of BNCT drugs (e.g., BPA); K: rate of cell division; p_1 : symmetric self-renewal probability; p_2 : probability of symmetric differentiation (commitment differentiation); δ_s: the rate of death of the stem cell during division; η: the decay rate of the concentration of stem cells; σ: the rate of production of effector cells; dE: the rate of death of effector cells; rC: the rate of growth of cancer cells; b: the capacity to support cancer cells; φ: the fraction of cancer cells killed by BNCT; λ: the interaction rate of effector–cancer cells; δ_B: the decay rate of BNCT drugs; A: amplification factor; $V(t)$: external influx of BNCT drug, time-dependent. Finally, the modeling process is described here as follows:

1. Stem cells are expected to grow exponentially, but are bound by their integration with the BNCT drug. The model yields to

$$\frac{dS}{dt} = \gamma_1 S - k_S BS, \tag{7}$$

where γ_1 is the parameter indicating the decay rate of the concentration of stem cells S, and it may consist of the probability for symmetric self-renewal of a stem cell to become stem cells (denoted by α_S) and the probability for the asymmetric one (denoted by α_A) and stem cells S divide at a rate k and die out at a rate δ_S. We refer to the literature that $\gamma_1 = k(\alpha_S - \alpha_D \delta_S)$ [18]. The parameter k_S is the fractional stem cell killed by the presence of the BNCT's drug, such as boronophenylalanine.

2. Furthermore, the rate of affected cells can be constant (denoted by α) should be slower due to its interaction with stem cells, indicated by parameter μ, cancer cells and the presence of BNCT's drug. The proposed model is as follows, i.e.,

$$\frac{dE}{dt} = \alpha - \mu E + \frac{p_1 ES}{(S+f_1)} - p_2(C+B)E, \tag{8}$$

where p_1: the maximum proliferation rate of effector cells; p_2: the decay rate of the effector cells killed cancer cells and BNCT's treatment.

3. Cancer cells alone will grow rapidly, or one writes as $\frac{dC}{dt} = rC$. However, there is competition in cancer cells, and hence, the maximum may be achieved, leading to a logistic model, i.e.,

$$\frac{dC}{dt} = r(1 - bC)C. \quad (9)$$

These cancer cells are combated by BNCT's drug and affected cells, leading to a slower dynamic of cancer cells. This statement provides the dynamics of cancer cells into

$$\frac{dC}{dt} = r(1 - bC)C - (p_3E + k_CB)C. \quad (10)$$

The component p_3EC shows the interaction of the effector cells with cancer cells.

4. Finally, the dynamic of BNCT's drug must decrease and converge to the time-dependent external influx of BNCT's drug. One yields:

$$\frac{dB}{dt} = -\gamma_2 B + V(t), \text{ where } B(0) = 0, \text{if } V(0) = 0. \quad (11)$$

Similar to the case of $\frac{dS}{dt}$, the rate of change of B is given by $\gamma_2 = kA(2\alpha_D + \alpha_A)$ where A is an amplification factor [18].

2.3 Methods for Solutions

There are several methods to solve a system of ordinary differential equations. This method is created according to the type of system of differential equations. The system of differential equations for the mathematical model of Rubella was using the fractal-fractional exponential decay kernel [20] or the moved Vieta–Lucas polynomial type (SVLPT) [21]. As for the dynamic system of Lassa hemorrhagic fever (LHF), the fractional calculus method and solving with the Laplace transform were applied [22]. In the glioblastoma multiforme (GBM) model, the Caputo-Fabrizio fractional derivation procedure is used [23]. Similarly, numerical methods were also implemented in systems of fractional differential equations (SFDEs) with Chebyshev approximations and Grünwald–Letnikov's approach [24]. The Reduced Differential Transform Method (RDTM) was implemented for fractional-order biological systems [25]. The nonlinear Emden-Fowler systems have been generated with numerical methods in Newtonian astrophysics [26]. Adams-Bashforth-Moulton (GABMP) to achieve NFFMA's goals that reflect global economic growth [27]. The nonlinear *Anopheles* mosquito was modeled, and the homotopy disruption strategy (HPM) was employed to examine the logically surmised answer for the nonlinear control issue [28]. While the system of differential equations that we study here is simulated with a standard numerical method, namely the Runge-Kutta method, this method is one of the numerical methods with the finite difference method for solving systems of ordinary differential equations. We use Python code to do the numerical solutions and simulations.

3. RESULTS AND DISCUSSION

In this section, we will show some simulations, using the Runge-Kutta method, which is available in the Python library via Collaboratory. Therefore, the method is not specifically discussed since the method it is a standard numerical method; one may refer to the related literature for the details [29]. The simulation results are obtained from the solutions of Eqs. (1)-(3) in the case of a mathematical model for cancer treatment using Immunotherapy- BNCT in Eqs. (7)-(11) to the case of stem cell therapy -BNCT Model.

3.1 Result and Discussion of Immunotherapy – BNCT Model

We will write here the parameters to present the simulations, some of which are adopted from the literature using existing parameters [9].

Table 1. Parameter Description and Values in the Model of Immunotherapy-BNCT Model

Parameter	Description	Value (Unit/day)
$x(0)$	The initial concentration of BNCT with anticancer activity at the cancer site	0.8
$y(0)$	The initial concentration of cancer cells	0.5
$z(0)$	The initial blood drug concentration	2
a	The constant rate of the BNCT concentration	0.01
d_1	Nature's death rate of the immune cells	0.15

Parameter	Description	Value (Unit/day)
c_1	Immune cell death rate due to interaction with cancer cells	0.15
α_1	Fractional immune cells are killed by BNCT	0.2
α_2	Fractional cancer cells are killed by immune cells	0.11
r	Cancer cells growth rate	2
b	Cancer cells' carrying capacity	0.07
c_2	Fractional cancer cells are killed by BNCT	0.07
d_2	Rate of BCCT drug decay	0.1
μ_1	The dosage of immunotherapy	3
μ_2	An increment in the blood drug concentration caused by BNCT	1
τ	Therapeutic period	10

The result shows that the number of cancer cells periodically increases for the given blood drug concentration and the concentration of BNCT cells with anticancer activity. This is not properly correct. Therefore, the simulation is tried for different values of parameters. Two results of the simulation of the model Eqs. (1)-(6) are depicted in Fig. 3 and Fig. 4. Fig. 3 shows that $y(t)$ changes with the highest value of time, where the value increases, and periodicity occurs in the same period as the other variables. The variables $x(t)$ and $z(t)$ advance down periodically, which eventually converges towards about 0, while $y(t)$ increases with its periodicity. This situation changes when there is a change in the value of b, where $b = 0.07$ in Fig. 3 and $b = 0.5$ in Fig. 4.

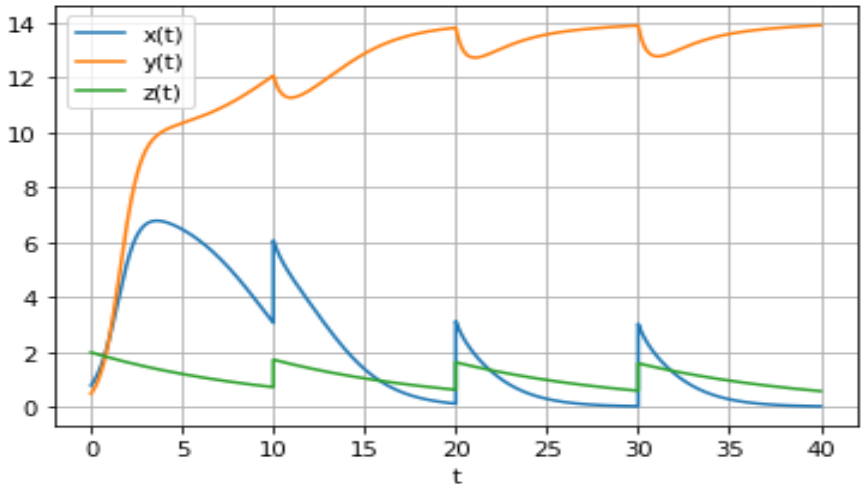

Figure 3. The Used Parameters for the Immunotherapy-BNCT model:
$\boldsymbol{a = 0.01;\ p = 1.8;\ d_1 = 0.15;\ c_1 0.15; \alpha_1 = 0.2;\ \alpha_2 = 0.11;\ r = 2; b = 0.07; c_2 = 0.07;}$
$\boldsymbol{\alpha_2 = 0.11; d_2 = 0.1; \mu_1 = 3;\ \mu_2 = 1\ ; \tau\ = 10; x(0) = 0.8; y(0) = 0.5; z(0) = 2}$

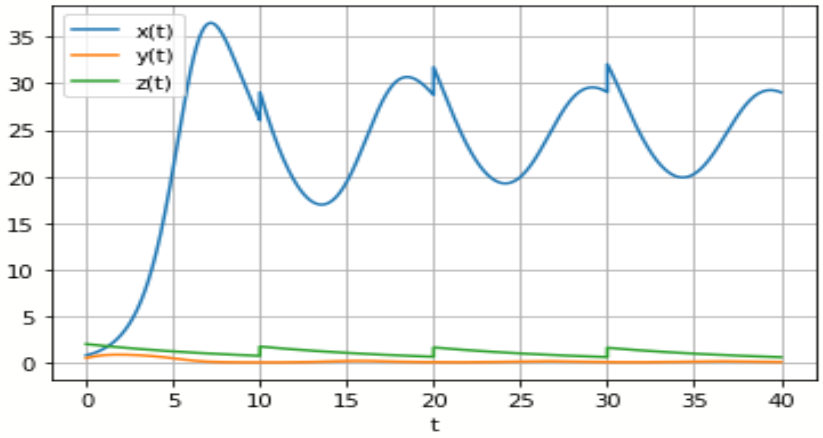

Figure 4. Simulation Results from the Immunotherapy-BNCT Module Model with Several Parameters in Figure 3, except $b = 0.5$

The simulation in Fig. 3 shows that the given parameters make the number of cancer cells $(y(t))$ increase. Fig. 4 shows that the number of cancer cells goes to 0, as expected. Similarly, if we look at Fig. 5 and Fig. 6, the desired phenomenon has been shown. Fig. 5 and Fig. 6 show that the concentration of the drug in the blood $(z(t))$, which originally increased periodically and slowed down, decreased even more slowly than the concentration of many cancer cells, so this is acceptable.

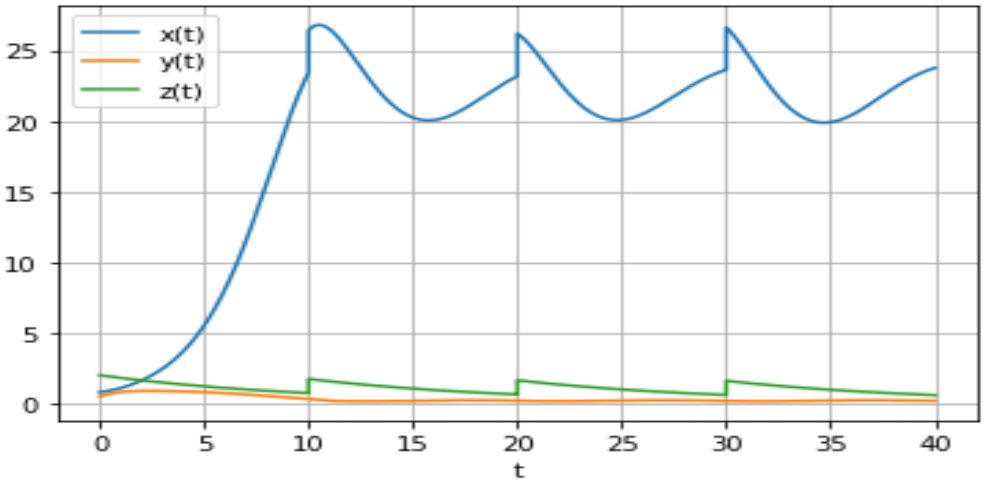

Figure 5. Simulation Results from the Immunotherapy-BNCT Module Model with Several Parameters in Figure 3, except $b = 1$

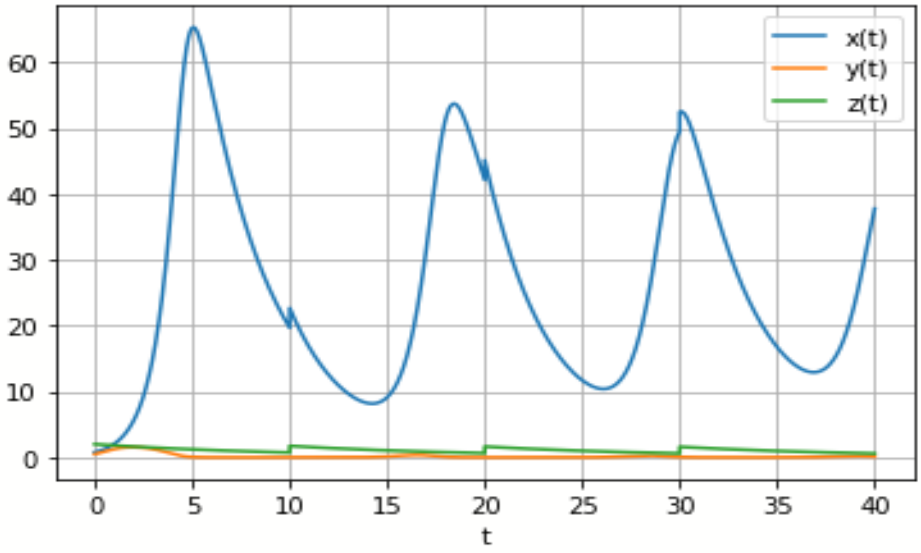

Figure 6. Simulation Results from the Immunotherapy-BNCT Module Model with Several Parameters in Figure 3, except $b = 0.25$

In Fig. 5 to Fig. 6, we see that the cancer cells tend to zero while the concentration of BNCT is still periodically existing. We conclude that the effect of the magnitude of the value of b is very significant in the success of the model in describing the results of Immunotherapy-BNCT.

3.2 Result and Discussion of Stem Cells Therapy- BNCT model

In this section, we will simulate the stem cell therapy-BNCT model based on the models in Eqs. (7)-(10). At the beginning of the simulation, we use the parameters present in the literature [18]. Here, we list the adjustment in Table 2. Simulation of 4 variables following models in Eqs. (7), (8), (9), and (10) are represented in Fig. 7.

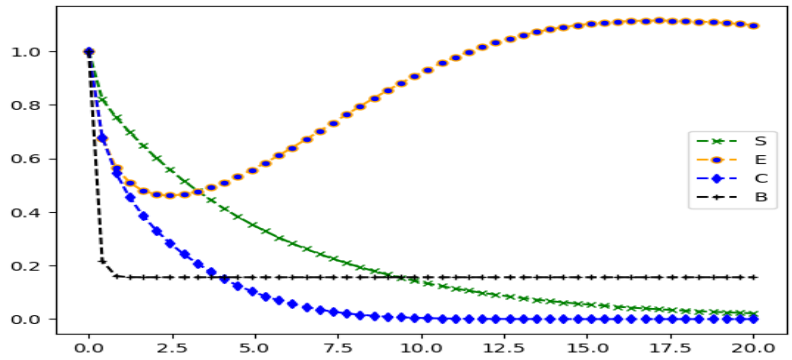

Figure 7. The used Parameters for Stem Cells Therapy- BNCT model:
$\boldsymbol{\alpha = 0.17; \mu = 0.03; f_1 = 1;\ \alpha_S = 0.17; \alpha_D = 0.17;\ \delta_S = 0.1;\ \alpha_A = 0.1; k = 1; A = 1;}$
$\boldsymbol{p_1 = 0.1245; r = 0.18; b = 10e-9; p_2 = 1;\ p_3 = 0.9; \gamma_1 = -0.085; \gamma_2 = 6.4; V = 0.1}$

The dynamic of the interaction is observed through the increasing effector cells and tending to a constant concentration, denoted by E. Effector cells serve as a link between therapy (BNCT) and the body's immune response, as well as being a key indicator to assess the success of treatment in our model. We have added this explanation to the method section so that readers can more easily understand the contribution of effector cells in system dynamics. It is observed that the cancer cells decay in the presence of BNCT's drug, where finally BNCT's drug is also decaying very quickly compared to others, to a constant positive value. Various observations are conducted with different parameter values. It is important to note that the effector cells are not initially defined and have an initial value of $E(0) = 0$. Though the cancer cells are decaying and tending to zero as we expected, we observe in Fig. 7 that the effector cells should also reduce.

Table 2. Parameter Description and Values for the Stem Cells-BNCT Model

Parameter	Description	Value (Unit/day)
S_0	Stem cells initial concentration	1
E_0	Effector cells initial concentration	0.0
C_0	The density of free cancer	1
B_0	BNCT initial concentration	0.5
k	The rate when the stem cells S are divided	1
α_S	Probability of symmetric self-renewal with probability to become two stem cells.	0.17
α_D	Probability of symmetric commitment differentiation with probability	0.17
δ_S	The rate of die out the stem cells when the stem cells are divided at rate *k*.	0.1
γ_1	The decay rate of concentration of stem cells	$k(\alpha_S - \alpha_D\delta_S)$ or -0.085[16]
α	The rate of produced the effector cells	0.17
μ	The natural death of cancer cells	0.03
b	Carrying capacity of cancer celss	10e-9
p_1	Maximum proliferation rate of effector	0.1245
f_1	Additive stem cells factor due to interaction with effector cells	1
r	Cancer growth rate	0.18
p_2	Decay rate of the effector cells killed cancer cells and BNCT concentration	1
p_3	Decay rate of interaction of effector cells and cancer cells	1
k_C	Fractional cancer cells killed by BNCT	0.9
A	Amplification factor A to describe the interaction between the effector cells, cancer cells, and the stem cells	1-10
γ_2	Decay rate of BNCT drug	$kA(2\alpha_D + \alpha_A)$ or 6.4 [16]
$V(t)$	The time dependent external influx of BNCT drug	0.1

Value $\gamma_2 = kA(2\alpha_D + \alpha_A)$ = 6.4 Units/day obtained based on literature [19]. Each stem cell divides at the rate k. With a probability of α_D, a symmetrical division occurs that produces two stem cells, while with a certain probability, there is an asymmetric division that produces a single stem cell. Thus, the expected number of stem cells resulting from each division can be calculated. This result is then multiplied by the rate of division k and the multiplier factor A which represents the influence of BNCT, so that the net growth rate is obtained.

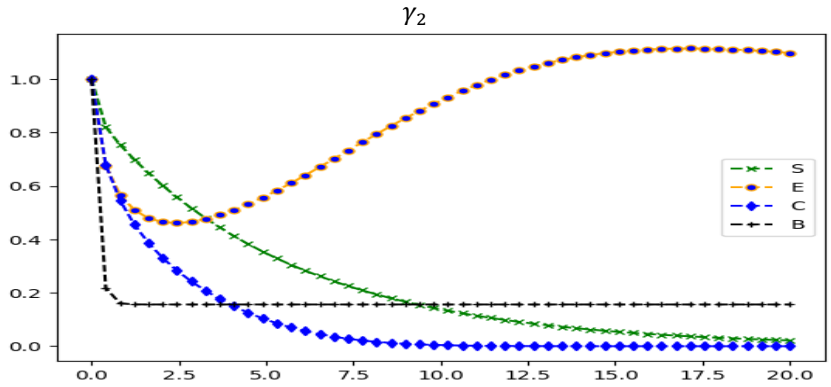

Figure 8. The Parameter Value is the Same as in Figure 7, with a Different Starting Value of $B(0) = 1$

We get an increasing concentration of BNCT over time, as depicted in Fig. 8, then a constant that simultaneously decreases cancer cells and goes towards 0. This gives the expected result in the BNCT treatment that the reaction of BNCT use causes cancer cells to go extinct even faster, where the declining effector cells do not go extinct to zero but are constant positive. In this condition, we see that there is a stable situation for each of the dynamic variables involved in a system of differential equations, where stem cells S and BNCT (symbolized B) are at the same concentration. The initial value is very influential on the results given. Using the same parameter where effector cells concentrate 0 while the others are the same, we can better see the rate of change for the 4 variables shown in Fig. 9. The influence of BNCT can also be shown in this parameter, i.e., $\gamma_2 = kA(2\alpha_D + \alpha_A)$. Therefore, parameter A is varied, as the amplification factor. By making the value $A = 10$, we can show in Fig. 10 that BNCT drops are increasing most rapidly, so that it is constant, and cancer cells also decrease to zero as expected. While the concentration of effector cells increases and stem cells decrease, which is also towards zero, like cancer cells.

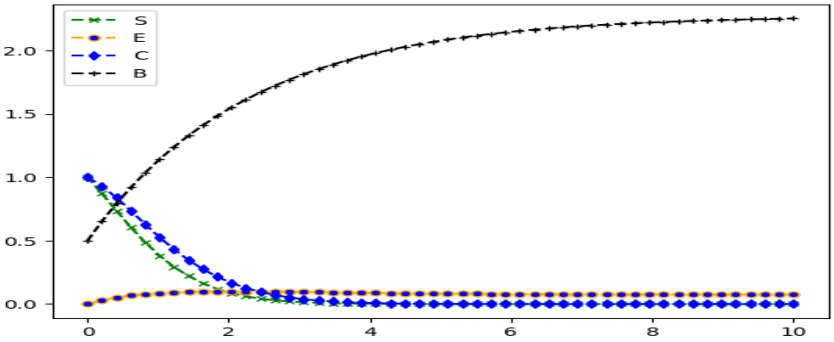

Figure 9. The Used Parameters for Stem Cells Therapy- BNCT model:
$\alpha = 0.17; \mu = 0.03; f_1 = 1;\ \alpha_S = 0.17; \alpha_D = 0.17;\ \delta_S = 0.1;\ \alpha_A = 0.1; k = 1; A = 1;$
$p_1 = 0.1245; r = 0.18; b = 10e-9; p_2 = 1; \gamma_1 = k(\alpha_S - \alpha_D\delta_S); \gamma_2 = kA(2\alpha_D + \alpha_A);$
$V = 0.1; S(0) = 1; E(0) = 0; C(0) = 1; B(0) = 0.5$

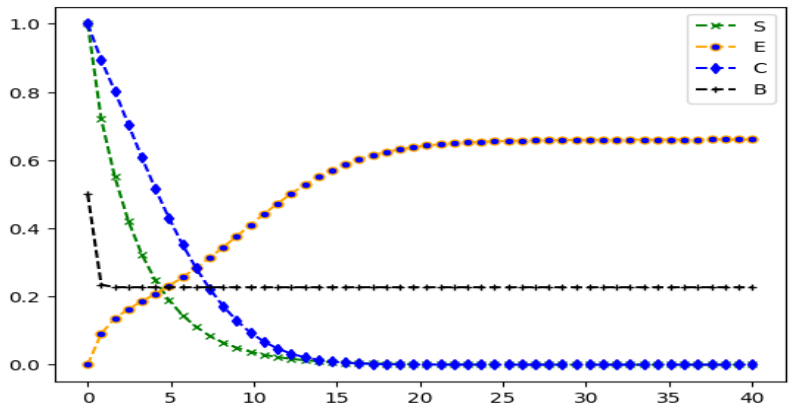

Figure 10. Simulation of the Stem Cells Therapy–BNCT Model with the Same Parameters as Figure 9, but Antigen Capacity A=10. The Initial Conditions Remain the Same

From Fig. 7 to Fig. 10, we have seen how BNCT affects therapy with stem cells. In general, the concentration of BNCT given decreases rapidly, which also affects the decline in concentration of cancer cells to extinction, which is followed by a decrease in stem cells. While effector cells increase to a constant level, this is seen significantly when the influence of BNCT is large enough. It should be noted that during computation, we have not done dimensional analysis, where all computations are done using parameters from the literature with some adjustments because of different approaches, namely the BNCT treatment in immunotherapy and in stem cell therapy. With the results obtained, it was concluded that BNCT treatment in both therapies has succeeded in supporting the killing of cancer cells. Of course, we can develop further approaches where these two therapies can complement each other so that the mathematical model obtained can be further developed.

3.3 Derivation of Equilibrium Solutions

In studying ordinary differential equation models, it is important to think about the stability of equilibrium solutions. These equilibrium solutions occur when the system equals zero. Moving forward, let's label x^*, y^*, and z^* as equilibrium solutions for the immunotherapy-BNCT model and S^*, E^*, C^*, and B^* as equilibrium solutions for the stem cells-BNCT model. Therefore, we are searching for solutions that will either remain balanced or stay constant over time.

3.2.1 Equilibrium for Immunotherapy- BNCT Model

Finding the right balance between the immune system's response and the therapeutic effects of BNCT is crucial for maximizing the treatment's effectiveness and reducing potential side effects or immunosuppression. In this context, the concept of equilibrium comes into play. A zero value must be assigned to each right segment to achieve the necessary equilibrium solutions, i.e.,

$$\frac{dx}{dt} = a - d_1 x - c_1 xy - \alpha_1 (1 - e^{-z})x = 0, \tag{12}$$

$$\frac{dy}{dt} = ry(1 - by) - c_2 xy - \alpha_2 (1 - e^{-z})y = 0, \tag{13}$$

$$\frac{dz}{dt} = -d_2 z \ = 0. \tag{14}$$

We gain $z^* = 0$ as the equilibrium of z from Eq. (14). By inserting $z^* = 0$ into Eqs. (12)-(13) we get

$$a - d_1 x - c_1 xy = 0 \text{ or } a - x(d_1 - c_1 y) = 0, \tag{15}$$

$$ry(1 - by) - c_2 xy = 0. \tag{16}$$

Eq. (16) can be rewritten as:

$$y(r(1 - by) - c_2 x) = 0.$$

It leads to $y^* = 0$ or $r(1 - by) - c_2 x = 0, with\ y \neq 0$. Substituting $y^* = 0$ and $z^* = 0$ in Eq. (12), we get $a - d_1 x \ = 0$. As a result, $a = d_1 x$, or $x^* = \frac{a}{d_1}$. Thus, the first equilibrium is $\left(\frac{a}{d_1}, 0, 0\right)$. The equilibrium

practically is meaningless since two variables are zero solutions. Therefore, we need to find a non-zero equilibrium solution. In Eq. (14), it is clear that the solution of the equilibrium z is always $z^* = 0$. One yields $r(1-by) = c_2 x$ from Eq. (16).

Eq. (15) becomes

$$a = x(d_1 - c_1 y) \text{ or } x = \frac{a}{d_1 - c_1 y}. \tag{17}$$

Inserting $x = \frac{a}{d_1 - c_1 y}$, one yields

$$ry(1-by) - c_2 \frac{ay}{(d_1 - c_1 y)} = 0,$$

or

$$\frac{ry(d_1 - c_1 y)(1-by)}{(d_1 - c_1 y)} - \frac{ayc_2}{(d_1 - c_1 y)} = 0. \tag{18}$$

One yields $(d_1 - c_1 y)(1-by) - \frac{ac_2}{r} = 0$.

This equation is simply quadratic equation in y. We rewrite as

$$bc_1 y^2 - (d_1 b + c_1)y + d_1 - \frac{ac_2}{r} = 0.$$

Therefore using quadratic formula we gain

$$y^* = \frac{(d_1 b + c_1) \pm \sqrt{(d_1 b + c_1)^2 - 4bc_1(d_1 - \frac{ac_2}{r})}}{2bc_1}. \tag{19}$$

Thus, the second equilibrium solution is: $z^* = 0$; $x^* = \frac{a}{d_1 - c_1 y^*}$, ; $y^* \neq \frac{d_1}{c_1}$ and y^* is given by Eq. (19).

Additionally, there are six free parameters whose values can be selected in the simulation process, in choosing the value of parameters in y^*. Later on the equilibrium solutions must be checked for the related stabilities. The stabilities are observed by constructing the Jacobian matrix from a system of Eqs. (1)-(3), i.e.,

$$J(x,y,z) = \begin{bmatrix} \frac{\partial f_1}{\partial x} & \frac{\partial f_1}{\partial y} & \frac{\partial f_1}{\partial z} \\ \frac{\partial f_2}{\partial x} & \frac{\partial f_2}{\partial y} & \frac{\partial f_2}{\partial z} \\ \frac{\partial f_3}{\partial x} & \frac{\partial f_3}{\partial y} & \frac{\partial f_3}{\partial z} \end{bmatrix}.$$

Write Eqs. (12)-(14) as

$$\frac{dX}{dt} = F = \left(f_1(x,y,z), f_2(x,y,z), f_3(x,y,z)\right)^T,$$

with

$$\begin{aligned} \frac{dx}{dt} &= f_1(x,y,z) = a - d_1 x - c_1 xy - \alpha_1(1 - e^{-z})x, \\ \frac{dy}{dt} &= f_2(x,y,z) = ry(1-by) - c_2 xy - \alpha_2(1 - e^{-z})y, \\ \frac{dz}{dt} &= f_3(x,y,z) = -d_2 z. \end{aligned}$$

The Jacobian matrix can be derived, i.e.,

$$\nabla F = \begin{pmatrix} \frac{\partial f_1}{\partial x} & \frac{\partial f_1}{\partial y} & \frac{\partial f_1}{\partial z} \\ \frac{\partial f_2}{\partial x} & \frac{\partial f_2}{\partial y} & \frac{\partial f_2}{\partial z} \\ \frac{\partial f_3}{\partial x} & \frac{\partial f_3}{\partial y} & \frac{\partial f_3}{\partial z} \end{pmatrix}, \tag{20}$$

where

$$\frac{\partial f_1}{\partial x} = d_1 - c_1 y - \alpha_1(1 - e^{-z}); \frac{\partial f_1}{\partial y} = -c_1 x; \frac{\partial f_1}{\partial z} = -\alpha_1 x e^{-z};$$
$$\frac{\partial f_2}{\partial x} = -c_2 y; \frac{\partial f_2}{\partial y} = r(1 - 2by) - c_2 x - \alpha_2(1 - e^{-z}); \frac{\partial f_2}{\partial z} = -\alpha_2 y e^{-z};$$
$$\frac{\partial f_3}{\partial x} = 0; \frac{\partial f_3}{\partial y} = 0; \frac{\partial f_3}{\partial z} = -d_2.$$

By inserting $z^* = 0$, one yields

$$\frac{\partial f_1}{\partial x} = d_1 - c_1 y; \frac{\partial f_1}{\partial y} - c_1 x ; \frac{\partial f_1}{\partial z} = -\alpha_1 x;$$
$$\frac{\partial f_2}{\partial x} = -c_2 y; \frac{\partial f_2}{\partial y} = r(1 - 2by) - c_2 x; \frac{\partial f_2}{\partial z} = -\alpha_2 y;$$
$$\frac{\partial f_3}{\partial x} = 0; \frac{\partial f_3}{\partial y} = 0; \frac{\partial f_3}{\partial z} = -d_2.$$

Write into the matrix, i.e.:

$$\nabla F_{z^*=0} = \begin{pmatrix} d_1 - c_1 y & -c_1 x & -\alpha_1 x \\ -c_2 y & r(1 - 2by) - c_2 x & -\alpha_2 y \\ 0 & 0 & -d_2 \end{pmatrix}.$$

The first equilibrium solution $\left(\frac{a}{d_1}, 0,0\right)$ leads to

$$\nabla F_{\left(\frac{a}{d_1},0,0\right)} = \begin{pmatrix} d_1 & -\frac{ac_1}{d_1} & -\alpha_1 \frac{a}{d_1} \\ 0 & r - c_2 \frac{a}{d_1} & 0 \\ 0 & 0 & -d_2 \end{pmatrix}. \tag{21}$$

Finally, by substituting all parameters in ∇F, we get a constant matrix to obtain its eigenvalues. Similarly, the second equilibrium solution can be substituted in Eq. (21) to achieve the stability of the second equilibrium solution. In the first case, for instance, we have the parameters in Fig. 3, i.e., $a = 0.01; d_1 = 0.15; d_2 = 0.1;\ c_1 = 0.15; \alpha_1 = 0.2;\ \alpha_2 = 0.11;\ r = 2; b = 0.07; c_2 = 0.07; \alpha_2 = 0.11.$ By inserting these values in ∇F we obtain negative, positive, and zero eigenvalues, i.e., $\lambda_1 = -1.1168$, $\lambda_2 = 16.1168, \lambda_2 = 0.0$. These values indicate unstable solution equilibriums [28]. We also observed that the ∇F is independent of the b-value, which was concluded in Fig. 3 - Fig. 5, that the b-value determines the profile of the solution. However, the stability of the first equilibrium solution is independent of b. One needs to do more studies in this case. In the context of an immunotherapy-BNCT (Boron Neutron Capture Therapy) model, an "equilibrium solution" refers to a stable state or condition that the system reaches over time. This concept is used in mathematical modeling to analyze the long-term behavior of the biological system under the influence of both immunotherapy and BNCT. A condition in which the immune system and cancer cells achieve a dynamic balance could be represented by the equilibrium solution. This balance may involve the ongoing interplay between the immune system's capacity to identify and eradicate cancer cells and the cells' possible development of resistance or evasion strategies. The equilibrium solution may point to the ideal situation in which BNCT and immunotherapy work together to effectively and sustainably suppress cancer cells. This equilibrium might represent a situation in which the immune system, strengthened by immunotherapy, combines with the targeted actions of BNCT to eradicate or manage malignant cells. The equilibrium in the model represents a dynamic equilibrium in which adaptive changes in the cancer cell population, the effects of BNCT, and the immune system's reactions interact continuously. The regulatory procedures and feedback mechanisms that stabilize the system may be part of this dynamic equilibrium. The equilibrium solution points to circumstances when the combination therapy strategy keeps cancer cells from

growing out of control for a long time, keeping them in a stable state that is better for the host. It is essential to comprehend the equilibrium solutions in an immunotherapy-BNCT model to forecast the treatment strategy's long-term efficacy. It helps scientists and medical professionals identify possible resistance mechanisms, optimize treatment settings, and create plans that improve the synergy between BNCT and immunotherapy for improved long-term outcomes in cancer patients.

3.2.2 Equilibrium Solution for Stem Cells-BNCT Model

An equilibrium solution could stand in for a situation in which the interactions between cancer cells, stem cells, and the therapeutic intervention (BNCT) have stabilized in the setting of a Stem Cells-BNCT model. This stability indicates a balance between the production and removal of cells in the system, accounting for things like stem cell proliferation, therapeutic response, and the dynamics of malignant cell populations. We know that the equilibrium solution will be obtained if the following equations are satisfied simultaneously, i.e.,

$$\gamma_1 S - k_S BS = 0; \text{ where we choose } \gamma_1 = 1, \tag{22}$$

$$\alpha - \mu E + \frac{p_1 ES}{(S + f_1)} - p_2 (C + B)E = 0, \tag{23}$$

$$r(1 - bC)C - (p_3 E + k_C B)C = 0, \tag{24}$$

$$-\gamma_2 B + V(t) = 0. \tag{25}$$

From Eq. (22), we get $S(1 - k_S B) = 0$, since S will not be zero, we take $(1 - k_S B) = 0$. We get $B^* = 1/k_S$. However, Eq. (25) gives us $B^* = \frac{V(t)}{\gamma_2}$. Substituting it into Eq. (22), one yields $S(1 - k_S \frac{V(t)}{\gamma_2}) = 0$ leading to $1 - k_S \frac{V(t)}{\gamma_2} = 0$ or $1 = k_S \frac{V(t)}{\gamma_2}$. Hence $V(t) = \frac{\gamma_2}{k_S}$. If $B^* = 1/k_S$, then substituting it into Eq. (25), $-\gamma_2 1/k_S + V(t) = 0$ and we get $V(t) = \gamma_2/k_S$. Substitute this result into Eq. (23), where $f_1 = 1$, we have

$$\alpha - \mu E + \frac{p_1 ES}{(S + 1)} - p_2 (C + 1/k_S)E = 0,$$

or

$$\alpha - \left(\mu - \frac{p_1 S}{(S + 1)} + p_2 \left(C + \frac{1}{k_S} \right) \right) E = 0. \tag{26}$$

Let us see Eq. (25) by inserting $B^* = \frac{1}{k_S}$, we get $\left(r(1 - bC) - \left(p_3 E + k_C \frac{1}{k_S} \right) \right) C = 0$. It is obvious that C is practically meaningful, if $C^* \neq 0$. As a result, we solve

$$r(1 - bC) - \left(p_3 E + k_C \frac{1}{k_S} \right) = 0 \text{ or } r - \left(p_3 E + k_C \frac{1}{k_S} \right) = rbC^*.$$

Thus,

$$C^* = \frac{1}{b} - \frac{1}{br} \left(p_3 E^* + k_C \frac{1}{k_S} \right). \tag{27}$$

where E^* has not been determined. Note that the C^* is a linear function of E^*. Since $\frac{p_3}{br} > 0$, then the linear function has a negative gradient, which indicates monotone nonincreasing. Inserting Eq. (27) into Eq. (26), one yields

$$\alpha - \left(\mu - \frac{p_1 S}{(S + 1)} + p_2 \left(\frac{1}{b} - \frac{1}{br} \left(p_3 E^* + k_C \frac{1}{k_S} \right) + \frac{1}{k_S} \right) \right) E^* = 0,$$

or

$$\left(\mu - \frac{p_1 S^*}{(S^* + 1)} + p_2 \left(\frac{1}{b} - \frac{1}{br} \left(p_3 E^* + k_C \frac{1}{k_S} \right) + \frac{1}{k_S} \right) \right) E^* = \alpha. \tag{28}$$

Eq. (28) still contains unknowns $E^*$and S^* which leads to the solution of equilibria, and these cannot be obtained explicitly. The process above suggests that one needs numerical methods, such as solving the nonlinear system of Eqs. (22)-(25) to get the roots as the equilibrium solutions [30], [31]. Swarm optimization can be a useful method to get optimal solutions [32]. Later on, these solutions are inserted into the Jacobian matrix as the first derivatives of the right-hand side of the model in Eq. (7)-(11) to obtain the equilibrium solutions.

The model implies that cancer cells and stem cells can coexist steadily in the presence of BNCT under specific circumstances. This equilibrium represents a situation in which the therapy effectively suppresses cancer cells without going below a certain point in the population of stem cells. The equilibrium solution reflects the ideal condition in which a therapeutic intervention, BNCT, successfully and sustainably suppresses malignant cells while permitting the preservation or proliferation of healthy cells, including stem cells. The equilibrium solution suggests a dynamic balance between the factors in the system that encourage and obstruct cell division and expansion.

4. CONCLUSION

The research presented here addresses the mathematical models for describing approaches incorporating Boron Neutron Capture Therapy (BNCT). The initial models were referred to from the literature, where the dynamics of using immunotherapy and stem cell therapy for combating cancers were modeled by two different models of system differential equations. The authors developed the immunotherapy-BNCT model as a dynamic model of the concentration of BNCT with anticancer activity in the cancer site, the number of cancer cells, and the blood drug concentration as nonlinear ordinary differential equations. The second system of differential equations model was the stem cells BNCT model, evaluating the drug's impact on the dynamics of cancer cells, stem cells, and effector cells. We compute the equilibrium solutions manually for each model by using parameters taken from the literature, which are adjusted for the need to update models due to the use of BNCT in the two models. When discussing that the number of cancer cells can be suppressed to zero through BNCT therapy, we refer directly to Fig. 7 and Fig. 8. When explaining that stem cells and effector cells tend to reach a stable state, we add references to Fig. 9 and Fig. 10. We observed that the stability of equilibrium solutions is unstable which are analyzed from the different signs of the eigenvalues into Jacobian matrices derived from inserting the equilibrium solutions to the Jacobian matrices. Additionally, the components of equilibrium solutions are zero, which is meaningless practically. With these results, this research needs to be improved so that equilibrium solutions can be obtained that are meaningful.

Author Contributions

Suryasatriya Trihandaru: Conceptualization, Funding Acquisition, Software. Hanna Arini Parhusip: Data Curation, Methodology, Project Administration, Visualization, Writing - Original Draft. Yohannes Sardjono: Resources, Supervision, Validation. Isman Mulyadi Triatmoko: Formal Analysis, Investigation. Gede Sutresna Wijaya: Development or Design of Methodology, Creation of models. Jane Labadin: Writing - Review and Editing. All authors discussed the results and contributed to the final manuscript.

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Declarations

The authors declare no conflicts of interest to report study.

Declaration of Generative AI and AI-assisted Technologies

Generative AI tools (e.g., ChatGPT) were used solely for language refinement, including grammar, spelling, and clarity. The scientific content, analysis, interpretation, and conclusions were developed entirely by the authors. All final text was reviewed and approved by the authors.

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