Check for updates

*CORRESPONDENCE
Ophir Nave
✉ naveof@gmail.com;
✉ ophirn@g.jct.ac.il

Asymptotic analysis of mathematical model describing a new treatment of breast cancer using AZD9496 and palbociclib

Ophir Nave[1,2]*

[1]Faculty of Computer Science, The College of Management Academic Studies, Rishon Lezion, Israel,
[2]Department of Mathematics, Faculty of Science, Jerusalem College of Technology, Jerusalem, Israel

Introduction: Cancer is a collective name for a group of diseases consisting of dozens of different types of malignant tumors, characterized by rapid and uncontrolled proliferation of cells in the body. Cancer can start almost anywhere in the human body such as the breast, prostate, colorectal, brain, bones, lungs, bladder etc. The main differences between the different types of cancer are related to the organ in which the tumor develops and the type of cells that compose the tumor.

Method: This paper focused on the breast cancer. Breast cancer is a malignant tumor that originates in the breast tissue. It is the most common malignant tumor in women. There are several types of breast cancer, but in all types early diagnosis and treatment is crucial. In this study, the treatment of breast cancer involving a combination of two drugs was investigated: the oral estrogen receptor inhibitor AZD9496 and the CDK4/6 protein inhibitor Palbociclib. The mathematical model that described the interaction between the cancer cells, the treatment, and the immune system cells includes a system of nonlinear ordinary differential equations of the firs order. In general, dynamic variables of a given system change each at a different rate. And it is not possible to know from the mathematical model which variable is fast and which is slow. Therefore, in order to reveal the hierarchy of the system of equations ,a numerical algorithm called the singularly perturbed vector field (SPVF) was applied. This algorithm transform the mathematical model to a new coordinate system in which the rate of change of each dynamic variable of the system can be known.

Results and Discussion: After writing the mathematical model in new coordinates, the equilibrium point was obtained analytically. The stability of the equilibrium points is investigated, which is essential from a practical perspective. Investigating the stability of the equilibrium points allows determination of when the tumor does not continue to develop and thereby allows adjustment of treatment continuation.

1 Introduction

Breast cancer accounts for approximately one-third of new cancer cases among women annually. It is the most common malignant disease among women worldwide (There were 2,296,840 new cases of breast cancer in 2022 among women (1)). Currently, at least one in eight women may experience breast cancer during their lifetime. The disease occurs mainly in women but is also found in men (the risk for men is 100 times lower than that for women). In cancer, uncontrolled cell proliferation occurs in an organ of the body. Breast cancer develops in the breast tissues, usually in the ducts that carry milk to the nipple and in the glands that produce milk. The disease is caused by a set of factors, some of which are congenital or depend on age and medical history, while others are related to lifestyle. Only approximately 10% of cases are due to heredity. Examination by a doctor (sometimes, self-examination is sufficient to determine the presence of a breast lump) is essential in cases where an unfamiliar breast lump is noticed. Breast cancer awareness is key to health because the earlier the disease is diagnosed, the higher are the chances of recovery. Approximately 80% of the lumps detected in the breast are benign, i.e., not malignant, and do not pose a risk. These include fibroadenomas (lumps of fibrous tissue), cysts (fluid sacs), and congestion. However, certain benign lumps may increase the risk of developing breast cancer (2–6).

Women diagnosed with breast tumors usually undergo surgery for tumor resection (lumpectomy or partial excision of the breast) (7, 8). A sample is also obtained from the lymph nodes in the armpit (sentinel gland biopsy). Sometimes, a more extensive operation is necessary (9, 10), such as removal of the entire breast (mastectomy or complete excision) or extensive excision of lymph nodes from the armpit. In most cases, when a complete mastectomy is necessary, breast reconstruction surgery can be performed immediately (11–14).

Radiation. After surgery, complementary radiation therapy is usually required, especially if a partial excision is performed. Radiation can be administered to the entire breast, and sometimes to the lymph nodes that drain the breast. In some cases, one dose of radiation administered during the resection surgery is sufficient (15–17).

Chemotherapy. Chemotherapy includes drugs that damage tumor cells. Chemotherapy sometimes has side effects such as nausea, vomiting, and hair loss. These side effects can be alleviated by medication. Notably, every patient with breast cancer patient may not require chemotherapy. Chemotherapy can be administered before or after surgery (18–27).

Biological treatments. Unlike chemotherapy, biological treatments are more specific to tumor cells and reduce damage to the remaining body, resulting in fewer side effects. The biological drugs used against breast cancer include Herceptin and Lapatinib (28–31).

Antihormonal treatments. After completion of chemotherapy and radiation treatment, some patients are recommended complementary antihormonal treatment as pills for 5 10 years. Such treatment is suitable for women whose tumors have hormone receptors, and it aims to reduce the risk of tumor recurrence. An example of an antihormonal drug is tamoxifen (32–37).

In recent years, researchers, such as mathematicians and physicists, have also been trying to find unconventional ways of treating this disease. This usually involves the development of a mathematical model; which on one hand includes models that take as many variables and parameters related to the patient as possible and on the other hand, models that can be studied, not necessarily in a numerical manner (38–42).

The advantages of a mathematical model are that it does not require a laboratory in the initial stage but only mathematical tools. This also does not require a high budget. Another advantage is that the parameters of the system can be easily changed and adapted to different patients to allow personalized treatment. The disadvantages are that a mathematical model does not reflect reality one-to-one but only provides an approximation; however, many studies indicate that the obtained approximation is sufficiently good (43–47).

In the present study, the investigation focused on a mathematical model that describes cancer treatment using a combination of two drugs: the oral estrogen receptor inhibitor AZD9496 and a CDK4/6 protein inhibitor Palbociclib using an asymptotic method called singular perturbed vector field (SPVFM), which allows us to determine the equilibrium points of the system, which is essential from a practical viewpoint of view.

The paper is organized as follows: In the next section the mathematical model of breast cancer and its treatment is presented. Subsequently, the algorithm of singularly perturbed vector fields and its application to the mathematical model were introduced. Finally, the results of the research and their analysis are presented.

2 Mathematical model definition

In this section, a mathematical model derived from the article (47) is presented for ER-positive breast cancer treatment using two different drugs: AZD9496 and palbociclib. In this study, a new personalized treatment based on analytical functions dependent on two parameters is proposed: the dosage of the medicine and the time interval between treatments. These two parameters enable us to control the treatments such that the dosage and time intervals can be modified depending on the tumor size. For this purpose, an ODE equation describing the treatment function in relation to tumor size wasted. The solution profiles of these equations show the dosage and time interval as a function of the tumor size at each given time. The dynamical variables of the model are as follows: C_C [cell] is the MCF-7 tumor cell population, N_K [$cellL^{-1}$], is the NK cell population, W_{BC} [$cellL^{-1}$] is the WBC population, C_{TL}[$cellL^{-1}$] is the CTL population, A_{ZD}^{nc} [mg] is the AZD9496 not in circulation, A_{ZD}^c [mg] is the AZD9496 in circulation, P_a^{nc} [mg] is the Palbociclib not in circulation, P_a^c [mg] Palbociclib in circulation, $\mathcal{F}$ [mg] and $\mathcal{H}$ [mg] are functions of AZD9496 and Palbociclib treatments, respectively, ($q_{A_{ZD}}$ is the amount of AZD9496, and q_{P_a} is the amount of Palbociclib). Based on the above assumptions, the mathematical model is a system of first-order nonlinear ordinary differential equations in the form:

$$\frac{dC_C}{dt} = C_C \left(a e^{-\alpha_9 P_a^c} + \frac{c e^{-\alpha_{10} A_{ZD}^c} E C_C}{1 + \alpha_1 E + \beta_1 C_C^2} \right) \left(1 - \frac{C_C}{K} \right)$$

$$- \frac{p_1 C_C N_K^2}{1 + \alpha_2 C_C + \beta_2 N_K^2} - \frac{p_6 C_C^2 C_{TL}}{1 + \alpha_6 C_C^2 + \beta_6 C_{TL}} \equiv F_1(\vec{W}), \qquad (1)$$

$$\frac{dN_K}{dt} = e W_{BC} - f N_K - p_2 N_K C_C + \frac{p_3 N_K C_C}{1 + \alpha_3 C_C + \beta_3 N_K} \equiv F_2(\vec{W}), \quad (2)$$

$$\frac{dW_{BC}}{dt} = \alpha - \beta W_{BC} \equiv F_3(\vec{W}), \qquad (3)$$

$$\frac{dC_{TL}}{dt} = \left(\frac{C_C K_L - C_{TL} C_C}{K_L(\alpha_5 + C_C)} \right) \left(p_4 L_N + \frac{p_5 I}{\alpha_4 + I} C_{TL} \right) - d C_{TL}$$

$$\equiv F_4(\vec{W}), \qquad (4)$$

$$\frac{dA_{ZD}^{nc}}{dt} = -\alpha_7 A_{ZD}^{nc} + \mathcal{F}(t) \equiv F_5(\vec{W}), \qquad (5)$$

$$\frac{dA_{ZD}^c}{dt} = \alpha_7 A_{ZD}^{nc} - \beta_4 A_{ZD}^c \equiv F_6(\vec{W}), \qquad (6)$$

$$\frac{dP_a^{nc}}{dt} = -\alpha_8 P_a^{nc} + \mathcal{H}(t) \equiv F_7(\vec{W}), \qquad (7)$$

$$\frac{dP_a^c}{dt} = \alpha_8 P_a^{nc} - \beta_5 P_a^c \equiv F_8(\vec{W}), \qquad (8)$$

$$\frac{d\mathcal{F}}{dt} = \mathcal{F}^{\varepsilon_1}(t) C_C - \mathcal{F}^{\varepsilon_2}(t) \equiv F_9(\vec{W}), \qquad (9)$$

$$\frac{d\mathcal{H}}{dt} = \mathcal{H}^{\varepsilon_3}(t) C_C - \mathcal{H}^{\varepsilon_4}(t) \equiv F_{10}(\vec{W}) \qquad (10)$$

The initial conditions of the model at $t = 0$ are:

$$C_C = 8.72 \cdot 10^7, N_K = 2.5 \cdot 10^8, W_{BC} = 4.3 \cdot 10^9, C_{TL} = 6.6 \cdot 10^8, A_{ZD}^{nc} = 0,$$

$$A_{ZD}^c = 0, P_a^{nc} = 0, P_a^c = 0, \mathcal{F}(0, q_{A_{ZD}}) = q_0^1, \mathcal{H}(0, q_{P_a}) = q_0^2.$$

$$(11)$$

The vector $\vec{W}$ will be define in section 4.1. The following parameters are used for numerical simulations of the application.

Parameters

$K = 10^9 [cell]$, Tumor cell carrying capacity,

$c = 0.00147 [LCell^1 Day^{-1} pmol^{-1}]$, Tumor growth rate induced by E2,

$\alpha_{10} = 0.2263 \ [mg^{-1}]$, Tumor growth inhibition by AZD9496,

$\alpha_1 = 0.507 \ [Lpmol^{-1}]$, Half saturation constant,

$\beta_1 = 7.08 \cdot 10^{-8} \ [Cell^{-2}]$, Half saturation constant,

$p_1 = 8.7 \cdot 10^{-4} \ [L^2 Cell^{-2} Day^{-1}]$, NK induced tumor death,

$\alpha_2 = 7 \cdot 10^6 \ [Cell^{-1}]$, Half saturation constant,

$\beta_2 = 5.4 \cdot 10^{-5} \ [L^2 Cell^{-2}]$, Half saturation constant,

$\beta = 6.3 \cdot 10^{-3} \ [Day^{-1}]$, WBC death rate,

$\alpha = 5 \cdot 10^7 \ [CellL^{-1} Day^{-1}]$, WBC production rate,

$e = 0.00486 \ [Day^{-1}]$, Fraction of WBCs becoming NK cells,

$f = 0.0693 \ [Day^{-1}]$, NK cell death rate,

$p_2 = 3.42 \cdot 10^{-6} \ [CellDay^{-1}]$, NK cell inactivation by tumor cells,

$p_3 = 1.87 \cdot 10^{-8} \ [Cell^{-1} Day^{-1}]$, NK cell recruitment rate

$\alpha_3 = 1.6 \cdot 10^{-5} \ [Cell^{-1}]$, Half saturation constant,

$\beta_3 = 3.27 \ [LCell^{-1}]$, Half saturation constant,

$p_6 = 2.04 \cdot 10^{-3} \ [LCell^{-2} Day^{-1}]$, CTL induced tumor death,

$\alpha_6 = 0.268 \ [Cell^2]$, Half saturation constant,

$\beta_6 = 4341 \ [LCell^{-1}]$, Half saturation constant,

$K_L = 8 \cdot 10^8 \ [CellL^{-1}]$, CTL carrying capacity,

$p_5 = 4.14 \ [LCell^{-2} Day^{-1}]$, CTL growth rate induced by IL-2,

$d0.41 \ [Day^{-1}]$, CTL death rate,

$\alpha_5 = 1000 \ [Cell]$, Half saturation constant,

$\alpha_7 = 24.3659 \ Day^{-1}]$, Absorption rate of AZD9496,

$\beta_4 = 4.7541 \ [Day^{-1}]$, Elimination rate of AZD9496,

$p_4 = 9 \cdot 10^{-5} \ [Day^{-1}]$, Fraction of naive CTL activated,

$\alpha_4 = 2.3 \cdot 10^{-11} \ [gL^{-1}]$, Half saturation constant,

$L_N = 2.3 \cdot 10^8 \ [CellL^{-1}]$, Naive CTL population,

$I = 2.3 \cdot 10^{-11} \ [gL^{-1}]$, IL-2 concentration,

$\beta_5 = 0.64 \ [Day^{-1}]$, Elimination rate of palbociclib,

$\alpha_8 = 14.1512 \ [Day^{-1}]$, Absorption rate of palbociclib,

$\alpha_9 = 0.01 \ [mg^{-1}]$, Tumor growth inhibition by palbociclib,

$\alpha_{10} = 0.2263 \ [mg^{-1}]$, Tumor growth inhibition by AZD9496,

$\varepsilon_i = 1.01$ dimensionless Free parameter.

3 Slow-fast subsystems, the singular perturbed vector fields method

The singular perturbed vector field method is presented in this section.

Generally, given a system of nonlinear differential equations, it is impossible to obtain an analytical solution in most cases. Various numerical methods can be applied to the system of nonlinear differential equations. However, the numerical solutions sometimes miss important and useless information especially when dealing with a mathematical model of cancer research. In addition, by applying numerical methods, graphs representing the solution can be generated, from which it is difficult to understand and draw conclusions from the solution profiles of the system and data on the system. Therefore, in most cases, applying asymptomatic methods or reduction methods that reduce the number of equations and investigating the "small" subsystems without losing important information about the entire system are preferred. However, to reduce the original system, the fast and slow variables of the system need to be determined; i.e., the exact hierarchy of the system of differential equations needs to be known and this is why standard asymptotic methods cannot be applied. Because in order to apply these methods, the mathematical model should be of the form of SPS system, i.e., the hierarchy of the system of equations should be exposed. Therefore, the primary objective of this section was to determine the hierarchy of the system. A transformation of the system to a new coordinate system will be applied. In the new coordinates, the hierarchy of the system will be revealed by calculating the eigenvalues and eigenvectors of the new system. This is the main aim of this section.

3.1 SPVFM

This section provides a detailed description of the SPVF method. The mathematical model has the dimension $n = 10$. The following steps are implemented

1: Select N vectors, $\Gamma = \{\vec{x}_1, ..., \vec{x}_N\}$, $\vec{x}_i \in R^n$, where $N \gg n$.

2: Compute the mean value of the vector filed over the point from step 1: $\bar{F} = \frac{1}{N} \sum_{i=1}^{N} \vec{F}(\vec{x}_i)$,

$$\bar{F} = \begin{pmatrix} \frac{1}{N} \sum_{I=1}^{N} F_1(\vec{x}_i) \\ \frac{1}{N} \sum_{I=1}^{N} F_2(\vec{x}_i) \\ \vdots \\ \frac{1}{N} \sum_{I=1}^{N} F_n(\vec{x}_i) \end{pmatrix} = \frac{1}{N} \sum_{i=1}^{N} \begin{pmatrix} F_1(\vec{x}_i) \\ F_2(\vec{x}_i) \\ \vdots \\ F_n(\vec{x}_i) \end{pmatrix}.$$

3: Define the following set: $\Gamma_{cs} = \{\vec{x}_i \in \Gamma : \|\vec{F}(x_i)\| > \|\bar{F}\|\}$ for simplicity let reindex $\Gamma_{cs} = \{\vec{x}_1, ..., \vec{x}_{N_{cs}}\}$.

4: Build the ordered basis sets:

$B_i = \{\vec{x}_{(i-1)n+1}, ..., \vec{x}_{in}\}$ with the corresponding matrix

$$A_i = \begin{pmatrix} x_{1,(i-1)n+1} & \cdots & x_{1,in} \\ x_{2,(i-1)n+1} & \cdots & x_{2,in} \\ \vdots & \cdots & \vdots \\ x_{n,(i-1)n+1} & \cdots & x_{n,in} \end{pmatrix}$$

and let $\mathbb{B} = \{B_1, B_2, ..., B_m\}$, $\mathbb{A} = \{A_1, A_2, ..., A_m\}$, where $m = \lfloor \frac{N_{cs}}{n} \rfloor$.

5: Select only the reference basis set from step 4 which have $|Det(A_i)|$ above the average level over all determinate basis i.e., let $\Omega = \frac{1}{m} \sum_{i=1}^{m} |Det(A_i)|$, then the reference basis is $B_{rb} = \{B_i : |Det(A_i)| \geq \Omega, i = 1, ..., m\}$. Again let us reindex, $B_{rb} = \{B_1, B_2, ..., B_k\}$ with the matching reindex of vectors $\vec{x}$.

6: For each $i = 1, 2, ..., k$ compute the eigenvalues of following matrix T_i that correspond to the matching basis B_i,

$$T_i = \begin{pmatrix} F_1(\vec{x}_{(i-1)n+1}) & \cdots & F_1(\vec{x}_{in}) \\ F_2(\vec{x}_{(i-1)n+1}) & \cdots & F_2(\vec{x}_{in}) \\ \vdots & \cdots & \vdots \\ F_n(\vec{x}_{(i-1)n+1}) & \cdots & F_n(\vec{x}_{in}) \end{pmatrix}.$$

i.e., compute the determinant of the following matrix $|T_i - \lambda I|$ where I is the unit matrix, and solve the equation:

$$|T_i - \lambda I| = 0$$

7: let $\{\lambda_1^i, \lambda_2^i, ..., \lambda_n^i\}$ be in ascending ordered eigenvalues of T_i. For each T_i the maximum gap is computed as:

$$gap_{max_i} = \max_n(|\lambda_{n+1}^i(T_i)|/|\lambda_n^i(T_i)|).$$

8: Denote by i_{max} the index for which gap_{max_i} is maximal. Compute the eigenvectors of $T_{i_{max}}$, i.e, solve the system of equations:

$$T_{i_{max}} - \vec{w} = 0$$

and obtain the eigenvectors: $\{\vec{w}_1^{i_{max}}, \vec{w}_2^{i_{max}}, ..., \vec{w}_n^{i_{max}}\}$, that correspond to $\{\lambda_1^{i_{max}}, \lambda_2^{i_{max}}, ..., \lambda_n^{i_{max}}\}$ consist of the desired coordinate system. Let n_s - be the index for which $(|\lambda_{n+1}^{i_{max}}(T_{i_{max}})|/$

$|\lambda_n^{i_{max}}(T_{i_{max}})|))$ is maximal. Then the vectors $\{\vec{w}_1^{i_{max}}, \vec{w}_2^{i_{max}}, ..., \vec{w}_{n_s}^{i_{max}}\}$ and, $\{\vec{w}_{n_s+1}^{i_{max}}, \vec{w}_{n_s+2}^{i_{max}}, ..., \vec{w}_n^{i_{max}}\}$ are the new slow and fast vectors of the slow and fast system correspondingly.

9: Rewrite the original system in the new coordinate using the eigenvectors $\{\vec{w}_1^{i_{max}}, \vec{w}_2^{i_{max}}, ..., \vec{w}_n^{i_{max}}\}$.

4 Analysis and results

In this section, the SPVF method was applied to a mathematical model for cancer treatment. The mathematical model was transferred to a new coordinate system, allowing the model to be split into fast and slow subsystems. These subsystems were studied, and equilibrium points were found and analyzed for stability.

4.1 Transformation the mathematical model to a new coordinates, eigenvalues, eigenvectors

In this section, the mathematical model is transformed to new coordinates using the eigenvectors of the vector field.

By applying the SPVF method to the system of Equations 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, The following eigenvalues and eigenvectors were obtained:

$$\lambda_1 = 2645971.569, \lambda_2 = 7477.865, \lambda_3 = 4635.569, \lambda_4 = 7876.957,$$

$$\lambda_5 = 9666.424, \lambda_6 = 872.764, \lambda_7 = 563.466, \lambda_8 = 366.763,$$

$$\lambda_9 = 35.534, \lambda_{10} = 2.077.$$

$$(12)$$

According to the algorithm of the *SPVF*, the maximum gap is $gap_{max_i} = \frac{\lambda_1}{\lambda_2} = 353.840$. The corresponding eigenvectors are as follows:

$\vec{w}_1 = (5.667, 1.536, 0.419, 2.644, 3.728, 1.012, 4.137, 4.123, 2.466, 3.532)^T$

$\vec{w}_2 = (2.667, 2.588, 1.688, 3.997, 3.476, 4.366, 4.477, 5.266, 4.373, 5.464)^T$

$\vec{w}_3 = (0.488, -1.346, -2.037, -3.156, -2.134, -3.544, -0.348, 4.478, 4.377, 0.743)^T$

$\vec{w}_4 = (2.334, -9.442, 3.204, -1.378, 4.326, 5.466, -6.378, 7.626, 6.773, 0.089)^T$

$\vec{w}_5 = (2.024, 3.244, -2.387, 2.377, -1.376, 2.525, 1.267, -3.987, 2.337, 0.377)^T$

$\vec{w}_6 = (0.876, 0.870, 0.875, 0.346, -4.565, 3.557, -3.765, -9.768, -2.975, -2.765)^T$

$\vec{w}_7 = (-1.121, 0.032, 0.578, 1.897, 2.543, 7.523, -1.876, 2.205, 2.880, -8.255,)^T$

$\vec{w}_8 = (-0.786, -5.879, 0.000, 0.000, 0.000, 0.876, 0.772, -0.012, 0.772, 0.766)^T$

$\vec{w}_9 = (0.877, -4.865, 0.000, 9.000, 7.000, 6.000, -1.099, -1.778, -9.765, -1.987)^T$

$\vec{w}_{10} = (-0.000, 4.765, 3.865, 3.544, -5.544, -5.346, -4.897, -0.463, -0.984, -1.987)^T,$

$$(13)$$

where T denote the transpose operator. This means that the original system of equations can be decomposed into fast and slow subsystems, where the fast direction of the system is in the direction of the eigenvector $\vec{w}_1$ corresponding to the eigenvalue λ_1, and the slow direction of the system is in the direction of the eigenvectors $\vec{w}_2 - \vec{w}_{10}$ corresponding to the eigenvalue $\lambda_2 - \lambda_{10}$.

The next step of the *SPVF* method is to transform model (1-10) using the above eigenvectors; hence, let $\vec{W}$ be a vector of the dynamical variables of the mathematical model:

$\vec{W} = (C_C, N_K, W_{BC}, C_{TL}, A_{ZD}^{nc}, A_{ZD}^{c}, P_a^{nc}, P_a^{c}, \mathcal{F}, \mathcal{H})$ and, $\vec{V} = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9, x_{10})$ be the variables of the model in the new coordinates. Hence, the system can be rewritten as

$$\vec{V} = \mathcal{A}\vec{W}, \qquad (14)$$

where the matrix $\mathcal{A}$ contains the eigenvectors obtained by applying the SPVF method.

The next step is to express the old system variables as functions of the new variables. To achieve this, multiply the set of Equations 14 by the inverse matrix of $\mathcal{A}$

$$\vec{W} = \mathcal{A}^{-1}\vec{V}. \qquad (15)$$

Take the derivative of the system (14) with respect to time:

$$\frac{d\vec{V}}{dt} = \mathcal{A}\frac{d\vec{W}}{dt}. \qquad (16)$$

Then substitute the expressions of the *RHS* (right-hand side) from the system (1) â (10) instead of $\frac{d\vec{W}}{dt}$ in (16); that is,

$$\frac{d\vec{V}}{dt} = \mathcal{A}\frac{d\vec{W}}{dt} = \mathcal{A}\vec{F}(\vec{W}), \qquad (17)$$

Where

$$\vec{F}(\vec{W}) = \left(F_1(\vec{W}), F_2(\vec{W}), F_3(\vec{W}), F_4(\vec{W}), F_5(\vec{W}), F_6(\vec{W}), F_7(\vec{W}), F_8(\vec{W}), F_9(\vec{W}), F_{10}(\vec{W})\right)^T \qquad (18)$$

Finally, substitute Equation 15 into Equation 17 to obtain the original mathematical model in the new coordinates with the initial conditions as follows:

$$\frac{d\vec{V}}{dt} = \mathcal{A} \cdot \vec{F}(\mathcal{A}^{-1}\vec{V}) \equiv \vec{B}(\vec{V}),$$
$$\vec{V}(0) = \mathcal{A}\vec{W}(0). \qquad (19)$$

The system of differential equations obtained (19) is a system of equations that only describes a mathematical model and has no biological or physical meaning because the new variables are a combination of the old variables without any expression meaning. However, the great advantage of this system is that in these new coordinates, the hierarchy of the system is precisely known; therefore, the fast and slow variables are exactly known. This procedure enables division of the new ODE system into fast and slow subsystems. The procedure for splitting into fast and slow subsystems is as follows:

$$\left(\frac{dx_1}{dt}, \frac{dx_2}{dt}, ..., \frac{dx_{10}}{dt}\right) = \left(\frac{1}{\varepsilon}B_{fast}(\vec{x}), \vec{B}_{slow}(\vec{x})\right), \qquad (20)$$

Where $\vec{x} = (x_1, ..., x_{10})$ is the vector of dynamical variables of the model in the new coordinates. As shown, variable x_1 is a fast variable of the new system that corresponds to the direction of the eigenvector corresponding to the largest eigenvalue λ_1 obtained by applying the SPVF algorithm. This procedure allows us to reduce the system (19) written in new coordinates to only one significant

subsystem (in this case, one equation). According to the theory of asymptotic analysis for a given system in the singular perturbed system (SPS) form, a fast subsystem can be studied while the slow system is frozen. When investigating a fast system, no important or relevant information regarding the entire system is lost. The main aim of this study was to determine the equilibrium points of the system and their stability. The advantage of the SPVF method is that the eigenvalues do not change in size under a linear transformation. Therefore, by determining the equilibrium points of the new system and analyzing their stability, an inverse transformation can be performed (using the inverse matrix of the eigenvectors) to find the equilibrium points of the original system and guarantee that these will be stable equilibrium points of the original mathematical model. The equilibrium point of the new system is determined by solving the following equation:

$$\varepsilon\frac{dx_1}{dt} = B_{fast}(\vec{x}), \qquad (21)$$

for $\frac{dx_1}{dt} = 0$, i.e.,

$$B_{fast}(\vec{x}) = 0. \qquad (22)$$

While the other variables of the system remain constant (frozen), they can be considered values of the initial conditions in the new system. As stated before, the mathematical model is transferred from the coordinates of the dynamical variables presented by the vector to new coordinates presented by the vector using the eigenvectors $\vec{w}_i$. The transformation process involved expressing the new dynamic variables of the system as functions of the original model's dynamical variables, i.e., the new variables are combinations of the old variables. The results are presented in Figures 1 and 2 for different parameter values. In these figures, the black line represents the solution profile of the combination of the original variables, which cause the cancer cells to achieve stability. The red line represents the solution profile of cancer cells that achieve stability at the equilibrium point.

The parameters data that used in this research are presented in the relevant Figure. Figure 1: This combination of variables and parameters behaves in a roughly cyclic manner, meaning that it rises and falls; however, the general trend is downward. The intervals are approximately constant; however, the values on the y-axis vary. For this combination, the cancer cells stabilize at a relatively fast rate, meaning that there is a very sharp decrease at the beginning, which then reaches an equilibrium state very quickly. The sharp decrease at the beginning of treatment is attributed to the high combination of variables and parameters at the beginning of treatment, which causes a sharp decrease in cancer cells.

Figure 3: For these combinations of parameters and variables, it can be observed that, initially, cancer cells increase relatively sharply and then gradually fall, but not as in the previous case, where they fell cyclically. In this case, cancer cells do not decrease quickly and stabilize, but rather take relatively more time to stabilize.

Figure 2: For this combination of parameters, the values constantly increase in the dynamic variables of the original system.
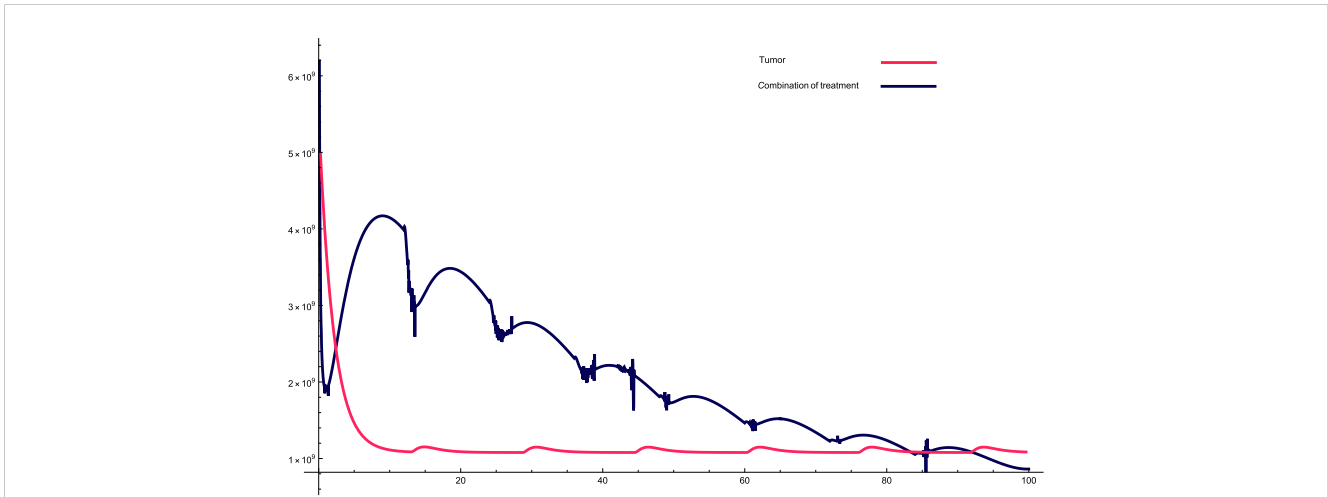
FIGURE 1

The solution profiles of the system of equations for a combination of parameters and the cancer cells stability. The parameters used for calculations are $K = 10^9$, $c = 0.00147$, $\alpha_{10} = 0.2263$, $\alpha_1 = 0.507$, $\beta_1 = 7.08 \cdot 10^{-8}$, $\alpha_2 = 7 \cdot 10^6$, $\beta_2 = 5.4 \cdot 10^{-5}$, $\beta = 6.3 \cdot 10^{-3}$, $\alpha = 5 \cdot 10^7$, $e = 0.00486$, $f = 0.0693$, $p_2 = 3.42 \cdot 10^{-6}$, $p_3 = 1.87 \cdot 10^{-8}$, $\beta_3 = 3.27$ $p_6 = 2.04 \cdot 10^{-3}$, $\alpha_6 = 0.268$, $\beta_6 = 4341$, $K_L = 8 \cdot 10^8$, $p_5 = 4.14$, $d = 0.41$, $\alpha_5 = 1000$, $\alpha_7 = 24.3659$, $\beta_4 = 4.7541$, $p_4 = 9 \cdot 10^{-5}$, $\alpha_4 = 2.3 \cdot 10^{-11}$, $L_N = 2.3 \cdot 10^8$, $l = 2.3 \cdot 10^{-11}$, $\beta_5 = 0.64$, $\alpha_8 = 14.1512$, $\varepsilon_i = 1.01$.

This indicates the aggressiveness of the treatment, that is, the variables increase over time with the treatment. With this combination, the cancer cells stabilized very quickly, indicating that they initially decreased very quickly and then stabilized in a straight step.

In all cases, a correlation is observed between the variables and parameters to the state where the equilibrium points stabilize.

4.2 Equilibrium points and stability analysis (46)

The equilibrium points of the mathematical model are examined in this section (written in the new coordinates) and

their stability. In general, given a mathematical model presented by nonlinear ODE system, where the hierarchy of the variables is hidden, it is very hard and even impossible to study the stability of the equilibrium points analytically. Therefore, the great advantage of transforming the mathematical model to new coordinates is first of all exposing the hierarchy of the dynamic variables of the system, that is, of the mathematical model, subsequently, the model is split into a fast subsystem and a slow subsystem. by orders of magnitude of the eigenvalues ˆaaˆof the matrix that represents the vector field of the mathematical model. After splitting the mathematical model into subsystems, the fast subsystem can be analyzed, the equilibrium points can be found analytically in most cases as a function of the system parameters, while the other variables remain constant, and
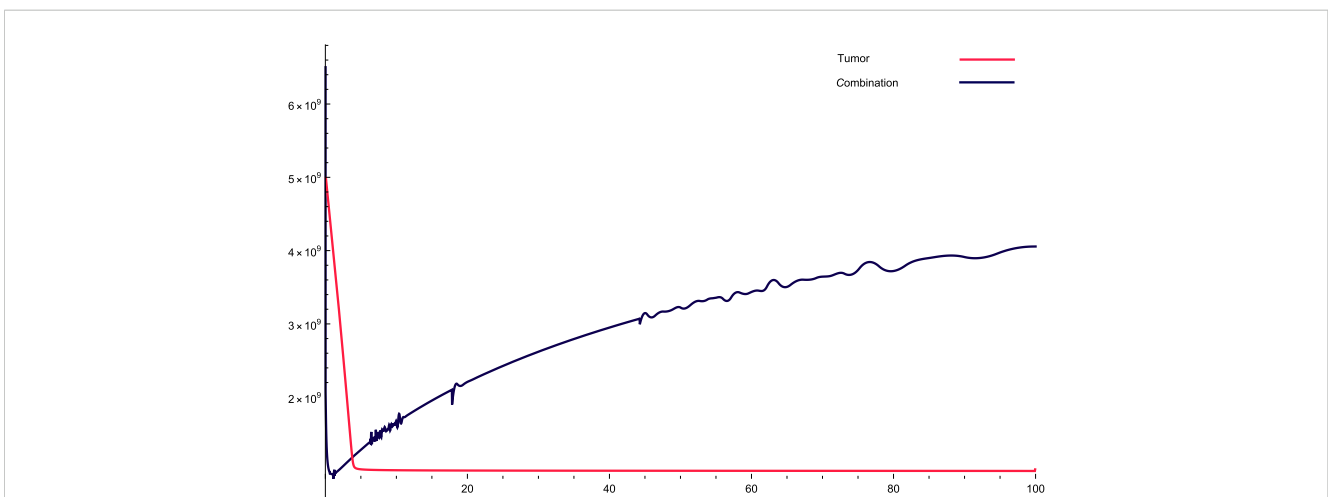

FIGURE 2

The solution profiles of the system of equations for a combination of parameters and the cancer cells stability. The parameters used for calculations are $K = 7^6$, $c = 0.0633$, $\alpha_{10} = 0.6467$, $\alpha_1 = 0.756$, $\beta_1 = 2.89 \cdot 10^{-7}$, $\alpha_2 = 6 \cdot 10^4$, $\beta_2 = 1.2 \cdot 10^{-5}$, $\beta = 7.3 \cdot 10^{-3}$, $\alpha = 3 \cdot 10^7$, $e = 0.646$, $f = 2.84739$, $p_2 = 3.455 \cdot 10^{-5}$, $p_3 = 2.45 \cdot 10^{-8}$, $\beta_3 = 2.66$ $p_6 = 2.76 \cdot 10^{-4}$, $\alpha_6 = 3.766$, $\beta_6 = 9875$, $K_L = 5 \cdot 10^5$, $p_5 = 2.45$, $d = 0.65$, $\alpha_5 = 1240$, $\alpha_7 = 59.8735$, $\beta_4 = 4.3$, $p_4 = 9 \cdot 10^{-4}$, $\alpha_4 = 5.5 \cdot 10^{-10}$, $L_N = 7.2 \cdot 10^9$, $l = 1.9 \cdot 10^{-10}$, $\beta_5 = 1.89$, $\alpha_8 = 29.83$, $\varepsilon_i = 0.1$.
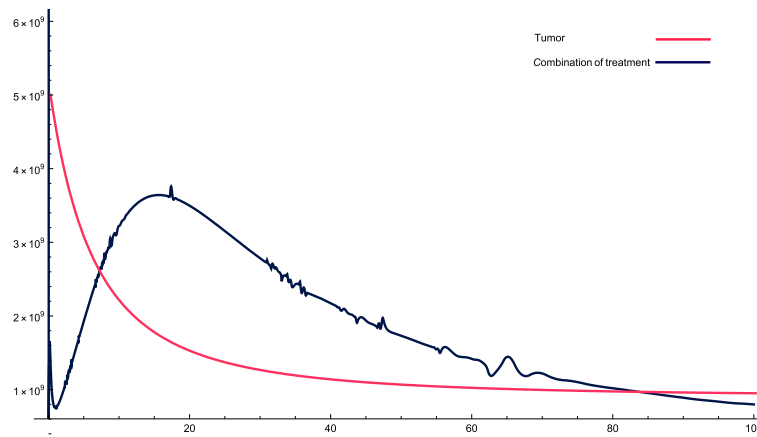
FIGURE 3
The solution profiles of the system of equations for a combination of parameters and the cancer cells stability. The parameters used for calculations are $K = 7^6$, $c = 0.0633$, $\alpha_{10} = 0.6467$, $\alpha_1 = 0.756$, $\beta_1 = 2.89 \cdot 10^{-7}$, $\alpha_2 = 6 \cdot 10^4$, $\beta_2 = 1.2 \cdot 10^{-5}$, $\beta = 7.3 \cdot 10^{-3}$, $\alpha = 3 \cdot 10^7$, $e = 0.00486$, $f = 0.766$, $p_2 = 6.42 \cdot 10^{-5}$, $p_3 = 1.87 \cdot 10^{-8}$, $\beta_3 = 5.43$ $p_6 = 2.76 \cdot 10^{-4}$, $\alpha_6 = 0.688$, $\beta_6 = 8765$, $K_L = 5 \cdot 10^6$, $p_5 = 4.14$, $d = 0.41$, $\alpha_5 = 1400$, $\alpha_7 = 49.6533$, $\beta_4 = 4.3522$, $p_4 = 9 \cdot 10^{-5}$, $\alpha_4 = 4.5 \cdot 10^{-11}$, $L_N = 1.2 \cdot 10^8$, $l = 2.3 \cdot 10^{-11}$, $\beta_5 = 0.64$, $\alpha_8 = 14.6544$, $\varepsilon_i = 0.09$.

can be taken as the values of the initial conditions of the model. After finding the equilibrium points, their stability was analyzed, followed by an inverse transformation to the equilibrium points, based on principles from linear algebra, the equilibrium points and their stability are preserved under the linear transformation.

According to the results of the eigenvalues presented above the fast subsystem contain only the first variable i.e., x_1 while $x_2, \ldots, x_{10}$ are the slow variables.

The following steps are implements for finding the equilibrium points of the mathematical model in the new coordinates and determining their stability.

1. Substitute the slow variables as a constant into the fast subsystem (one can take the initial condition of the slow variables as the constants).

2. Setting the fast variable derivative to zero i.e., solve the fast subsystem (with slow variables as constants) and find the equilibria points of the fast variables x_1^*

$$B_{fast}^1(x_1^*, x_2(0), x_3(0), \ldots, x_{10}(0)) = 0,$$

(where the star notation denoted the fast equilibrium points).

3. Substitute the equilibrium points from step $2(x_1^*)$ into the slow subsystem, solve the slow subsystem and find the equilibrium points of the slow variables $(x_2^*, \ldots, x_{10}^*)$

$$\vec{B}_{slow}^{2,\ldots,10}(x_1^*, x_2^*, x_3^*, \ldots, x_{10}^*) = 0 \qquad (23)$$

Here, the system consists of eight equations and eight unknown variables $(x_3^*, \ldots, x_{10}^*)$.

4. Substitute the equilibrium points from steps 2 and 3 at the Jacobian matrix of the full system (the model at the new coordinates).

5. Compute the eigenvalues of the Jacobian matrix of the system (the model at the new coordinates) for each set of equilibrium point (the stable points are those with a negative real part of the eigenvalues).

6. Transform only the equilibrium points that are stable from steps 2 and 3 to the original coordinates using the inverse matrix of the eigenvectors, i.e., compute

$$\vec{V}_{stable}^* = \mathcal{A}^{-1} \vec{W}_{stable}^{i*} \qquad (24)$$

where i indicates for different stable equilibrium points. In Figure 4 The solution profiles of the fast variable, depending on time t, are presented. As one can see from the plot graph the stability point reached after $t \approx 30$ days. It is very important to note at this stage that the mathematical model in the new coordinates has no biological meaning since the new variables are a linear combination of the old variables. The only variables that have biological significance are the old variables. The important parameter from the stability analysis that can be extracted from the graph shown in Figure 4 is time. An inverse linear transformation to the equilibrium points shows that after the same time parameter, both the cancer tumor and the whole system, as described by the mathematical model, stabilize.

Conclusions

This study improves upon the mathematical model presented by (47), and added a system of differential equations that describe the treatment method depending on the dose and time of drug
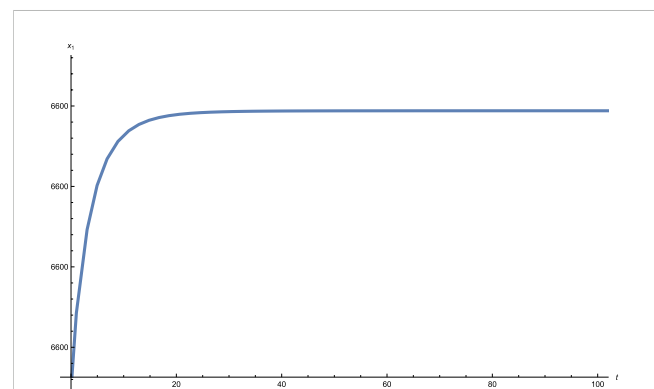

FIGURE 4
The solution profiles of the fast variable as a function of the time t.

administration. The application of the SPVFM algorithm allowed for the reduction of the system's dimensions. The model was then rewritten using the new coordinates to clearly expose its hierarchy. Representing the model in this manner allowed us to split the system into fast and slow subsystems. The fast subsystem was explored while the slow subsystem remained frozen in time. The equilibrium points of the fast subsystem were determined, and their stability was then studied. This information was transferred back to the original system of equations through an inverse transformation. A strong correlation was found between the combination of dynamic variables, system parameters, and cancer cells. The higher the values of the dynamic variables of the system, which also means that the more aggressive the treatment, the faster is the decrease in cancer cells, which tend to reach a state of equilibrium as quickly as possible.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

ON: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Funding

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. World Cancer Research Fund International. Available online at: https://www.wcrf.org/. (Accessed November 28, 2024)

2. National Breast Cancer Foundation. Available online at: https://www.nationalbreastcancer.org/dcis/. (Accessed November 28, 2024)

3. American Cancer Society. Available online at: https://www.cancer.org/cancer/types/breastcancer/about/how-common-is-breast-cancer.html. (Accessed November 28, 2024)

4. World Health Organization. Available online at: https://www.who.int/news-room/fact-sheets/detail/breastcancer. (Accessed November 28, 2024)

5. Centers for Disease Control and Prevention and Breast Cancer Statistics. Available online at: https://www.cdc.gov/cancer/breast/statistics/index.htm. (Accessed November 28, 2024)

6. Natinal Cancer Institute. Cancer Stat Facts: Female Breast Cancer. Available online at: https://seer.cancer.gov/statfacts/html/breast.html. (Accessed November 28, 2024)

7. Wen X, Guo X, Wang S, Lu Z, Zhang Y. Breast cancer diagnosis: A systematic review. In: *Biocybernetics and Biomedical Engineering*, vol. 44. Elsevier BV (2024). p. 119–48. doi: 10.1016/j.bbe.2024.01.002

8. He Z, Chen Z, Tan M, Elingarami S, Liu Y, Li T, et al. A review on methods for diagnosis of breast cancer cells and tissues. In: *Cell Proliferation*, vol. 53. Wiley (2020). doi: 10.1111/cpr.12822

9. Magnoni F, Alessandrini S, Alberti L, Polizzi A, Rotili A, Veronesi P, et al. Breast cancer surgery: new issues. *Curr Oncol*. (2021) 28:4053–66. doi: 10.3390/curroncol28050344

10. Riis M. Modern surgical treatment of breast cancer. In: *Annals of Medicine and Surgery*, vol. 56. Ovid Technologies (Wolters Kluwer Health (2020). p. 95–107. doi: 10.1016/j.amsu.2020.06.016

11. Bhushan A, Gonsalves A, Menon JU. Current state of breast cancer diagnosis, treatment, and theranostics. *Pharmaceutics*. (2021) 13:723. doi: 10.3390/pharmaceutics13050723

12. Nounou MI, ElAmrawy F, Ahmed N, Abdelraouf K, Goda S, Syed-Sha-Qhattal H. Breast Cancer: Conventional Diagnosis and Treatment Modalities and Recent Patents and Technologies. In: *Breast Cancer: Basic and Clinical Research*, vol. 9s2. SAGE Publications (2015). p. BCBCR.S29420. doi: 10.4137/bcbcr.s29420

13. Idowu MO, Shah PA, Hackney MH, Grimes MM, Geyer CE, Arthur DW, Bear HD eds. *Diagnosis and Management of Breast Tumors*. Springer International Publishing (2018). doi: 10.1007/978-3-319-57726-5

14. Riggio AI, Varley KE, Welm AL. The lingering mysteries of metastatic recurrence in breast cancer. *Br J Cancer*. (2020) 124:13–26. doi: 10.1038/s41416-020-01161-4

15. Purswani JM, Hardy-Abeloos C, Perez CA, Kwa MJ, Chadha M, Gerber NK. Radiation in early-stage breast cancer: moving beyond an all or nothing approach. *Curr Oncol*. (2022) 30:184–95. doi: 10.3390/curroncol30010015

16. Ruan H, Okamoto M, Ohno T, Li Y, Zhou Y. Particle radiotherapy for breast cancer. *Front Oncol*. (2023) 13:1107703. doi: 10.3389/fonc.2023.1107703

17. Poland S, Ebina W, Muggia F, Guth A. Breast radiation-associated secondary Malignancies: A review. *Clin Surg Oncol*. (2023) 2:100010. doi: 10.1016/j.cson.2023.100010

18. Wang J, Wu S-G. Breast Cancer: An Overview of Current Therapeutic Strategies, Challenge, and Perspectives. In: *Breast Cancer: Targets and Therapy*, vol. 15. Informa UK Limited (2023). p. 721–30. doi: 10.2147/bctt.s432526

19. Moo T-A, Sanford R, Dang C, Morrow M. Overview of breast cancer therapy. *PET Clinics*. (2018) 13:339–54. doi: 10.1016/j.cpet.2018.02.006

20. Claessens AKM, Ibragimova KIE, Geurts SME, Bos MEMM, Erdkamp FLG, Tjan-Heijnen VCG. The role of chemotherapy in treatment of advanced breast cancer: an overview for clinical practice. *Crit Rev Oncology/Hematol*. (2020) 153:102988. doi: 10.1016/j.critrevonc.2020.102988

21. Park YH, Lal S, Lee JE, Choi Y-L, Wen J, Ram S, et al. Chemotherapy induces dynamic immune responses in breast cancers that impact treatment outcome. In: *Nature Communications*, vol. 11. Springer Science and Business Media LLC (2020). doi: 10.1038/s41467-020-19933-0

22. Jacobo Jacobo M, Donnella HJ, Sobti S, Kaushik S, Goga A, Bandyopadhyay S. An inflamed tumor cell subpopulation promotes chemotherapy resistance in triple negative breast cancer. In: *Scientific Reports*, vol. 14. Springer Science and Business Media LLC (2024). doi: 10.1038/s41598-024-53999-w

23. Pavlov MV, Bavrina AP, Plekhanov VI, Golubyatnikov G, Orlova AG, Subochev PV, et al. Changes in the tumor oxygenation but not in the tumor volume and tumor vascularization reflect early response of breast cancer to neoadjuvant chemotherapy. *Breast Cancer Res*. (2023) 25. doi: 10.1186/s13058023-01607-6

24. Burstein HJ, Curigliano G, Loibl S, Dubsky P, Gnant M, Poortmans P, et al. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. *Ann Oncol.* (2019) 30:1541–57. doi: 10.1093/annonc/mdz235

25. Li X, Lewis MT, Huang J, Gutierrez C, Osborne CK, Wu M-F, et al. Intrinsic resistance of tumorigenic breast cancer cells to chemotherapy. *JNCI J Natl Cancer Instit.* (2008) 100:672–9. doi: 10.1093/jnci/djn123

26. Lazebnik T. Cell-level spatio-temporal model for a bacillus calmette-guerinBased immunotherapy treatment protocol of superficial bladder cancer. *Cells.* (2022) 11:2372. doi: 10.3390/cells11152372

27. Mutebi M, Anderson BO, Duggan C, Adebamowo C, Agarwal G, Ali Z, et al. Breast cancer treatment: A phased approach to implementation. *Cancer.* (2020) 126:2365–78. doi: 10.1002/cncr.32910

28. Lawson M, Cureton N, Ros S, Cheraghchi-Bashi A, Urosevic J, Darcy S, et al. The next-generation oral selective estrogen receptor degrader camizestrant (AZD9833) suppresses ER+ Breast cancer growth and overcomes endocrine and CDK4/6 inhibitor resistance. *Cancer Res.* (2023) 83:3989–4004. doi: 10.1158/0008-5472.can-23-0694

29. Hopcroft L, Wigmore EM, Williamson SC, Ros S, Eberlein C, Moss JI, et al. Combining the AKT inhibitor capivasertib and SERD fulvestrant is effective in palbociclib-resistant ER+ breast cancer preclinical models. *NPJ Breast Cancer.* (2023) 9. doi: 10.1038/s41523-02300571-w

30. Yaniv-Rosenfeld A, Savchenko E, Rosenfeld A, Lazebnik T. Scheduling BCG and IL-2 injections for bladder cancer immunotherapy treatment. *Mathematics.* (2023) 11:1192. doi: 10.3390/math11051192

31. Neupane N, Bawek S, Gurusinghe S, Ghaffary EM, Mirmosayyeb O, Thapa S, et al. Oral SERD, a novel endocrine therapy for estrogen receptor-positive breast cancer. *Cancers.* (2024) 16:619. doi: 10.3390/cancers16030619

32. Debela DT, Muzazu SG, Heraro KD, Ndalama MT, Mesele BW, Haile DC, et al. New approaches and procedures for cancer treatment: Current perspectives. In: *SAGE Open Medicine*, vol. 9. SAGE Publications (2021). p. 205031212110343. doi: 10.1177/20503121211034366

33. Pucci C, Martinelli C, Ciofani G. Innovative approaches for cancer treatment: current perspectives and new challenges. In: *Ecancer Medical Science*, vol. 13. Ecancer Global Foundation (2019). doi: 10.3332/ecancer.2019.961

34. Anand U, Dey A, Chandel AKS, Sanyal R, Mishra A, Pandey DK, et al. Cancer chemotherapy and beyond: Current status, drug candidates, associated risks and progress in targeted therapeutics. In: *Genes & Diseases*, vol. 10. Elsevier BV (2023). p. 1367–401. doi: 10.1016/j.gendis.2022.02.007

35. Advancing Cancer Therapy. *Nature Cancer* Vol. 2. Springer Science and Business Media LLC (2021) p. 245–6. doi: 10.1038/s43018-021-00192-x

36. Zhou Z, Li M. Targeted therapies for cancer. *BMC Med.* (2022) 20. doi: 10.1186/s12916-022-02287-3

37. Naser R, Dilabazian H, Bahr H, Barakat A, El-Sibai M. A guide through conventional and modern cancer treatment modalities: A specific focus on glioblastoma cancer therapy (Review). *Oncol Rep.* (2022) 48. doi: 10.3892/or.2022.8405

38. Vieira LC, Costa RS, Valerio D. An overview of mathematical modelling in cancer research: fractional calculus as modelling tool. *Fractal Fraction.* (2023) 7:595. doi: 10.3390/fractalfract7080595

39. Brady R, Enderling H. Mathematical Models of Cancer: When to Predict Novel Therapies, and When Not to. In: *Bulletin of Mathematical Biology*, vol. 81. Springer Science and Business Media LLC (2019). p. 3722–31. doi: 10.1007/s11538019-00640-x

40. Yin A, Moes DJAR, van Hasselt JGC, Swen JJ, Guchelaar H. A Review of Mathematical Models for Tumor Dynamics and Treatment Resistance Evolution of Solid Tumors. In: *CPT: Pharmacometrics & Systems Pharmacology*, vol. 8. Wiley (2019). p. 720–37. doi: 10.1002/psp4.12450

41. Savchenko E, Rosenfeld A, Bunimovich-Mendrazitsky S. Mathematical modeling of BCG-based bladder cancer treatment using socio-demographics. *Sci Rep.* (2023) 13. doi: 10.1038/s41598-023-45581-7

42. Adam JA. Mathematical Models of Tumor Growth: From Empirical Description to Biological Mechanism. In: *Advances in Experimental Medicine and Biology*. Springer US (2003). p. 287–300. doi: 10.1007/978-1-4419-9019-819

43. Bellomo N, Preziosi L. Modelling and mathematical problems related to tumor evolution and its interaction with the immune system. *Math Comput Model.* (2000) 32:413–52. doi: 10.1016/s08957177(00)00143-6

44. Adongo D, Fister KR. Delay Dynamics of Cancer and Immune Cell Model. In: *Mathematical Modelling of Natural Phenomena*, vol. 7. EDP Sciences (2012). p. 261–78. doi: 10.1051/mmnp/20127112

45. Lestari D, Sari ER, Arifah H. Dynamics of a mathematical model of cancer cells with chemotherapy. *J Phys: Conf Ser.* (2019) 1320:12026. doi: 10.1088/1742-6596/1320/1/012026

46. Khalil HK. Lyapunov Stability Theory. In: Baillieul J, Samad T, editors. *Encyclopedia of Systems and Control*. Springer, Cham (2021). doi: 10.1007/978-3-03044184-5-77

47. Wei H-C. Mathematical modeling of ER-positive breast cancer treatment with AZD9496 and palbociclib. In: *AIMS Mathematics*, vol. 5. American Institute of Mathematical Sciences (AIMS 2020). p. 3446–55. doi: 10.3934/math.2020223