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Paper

From Breast Cancer to Computational Science

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Computational science focuses on the development of predictive computer models of the world around us. Scientific computing methods have become more accurate in the discovering of tumor treatment possibilities, than laboratory experiments have ever proven. This thesis will provide the mathematical modeling of breast tumor growth, including different aspects of how the immune system together with cycle-phase-specific chemotherapy can defeat the disease. The delay differential equations representing the tumor environment are solved using the Runge Kutta fourth method, taking in consideration different phases of the cell-cycle.

Submitted as full paper.

From Breast Cancer to Computational Science

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Abstract

Computational science focuses on the development of predictive computer models of the world around us. Scientific computing methods have become more accurate in the discovering of tumor treatment possibilities, than laboratory experiments have ever proven. This thesis will provide the mathematical modeling of breast tumor growth, including different aspects of how the immune system together with cycle-phase-specific chemotherapy can defeat the disease. The delay differential equations representing the tumor environment are solved using the Runge Kutta fourth method, taking in consideration different phases of the cell-cycle.

Keywords : Computational science, Delay differential equation, Breast cancer, Immune system, Cell cycle, Cycle-specific chemotherapy, Quiescent cells, Proliferating cells, Paclitaxel(Taxol)

This thesis is dedicated to my grandmother, who lost the battle against cancer.

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Contents

1 Introduction

Cancer is one of the leading causes of morbidity and mortality worldwide. The number of cancer patients has been alarming for the past years. In 2012 there were about 14 million new cases, and it is expected that a rise of about 70% will take place over the next 2 decades. In 2015 the number of deaths caused by cancer was around 8.8 million. The disease is taken seriously in various aspects of science, for the reason that it is categorized as the second leading cause of death in the world [1].
The most abundant cancer form among women is breast cancer. Because of the large interest in the aspect of breast cancer, the thesis will focus on this form of cancer [2]. Roughly one out of three Danes will experience some type of cancer in their lifetimes. About 60 percent of cancer patients will survive for more than five years after they have been diagnosed. The Danish reviews based on cancer patients do not look promising. Danish women got the Nordic record in all forms of cancer for the past 20 years, where breast cancer is one of the leading condition as mentioned above. Looking at the survival rates, about 61 percent of women are alive five years after their cancer diagnoses and this is unsatisfactory compared to the other Nordic countries. According to the World Cancer Research Fond from 2012, Denmark has 329 women cancer patients for every 100,000 residents. In 2015 there have been 64.405 breast cancer cases [3] [4] [5].

This thesis will focus on the numerical and mathematical analysis of data within cancer. It aims to gain understanding of the process in which cancer develops and to design and improve better treatment strategies to eliminate the disease or to improve the life of the patient. Numerical analysis implements the study of algorithm, which deals with numerical approximations for the problems of mathematical analysis[6].

The leading interest is to model the effects and interactions between tumor cells and immune cells, when cycle-phase-specific drugs, such as chemotherapy, are given to the patient. The systems will be subdivided into different cycle phases of tumor cells to control and model a more explicit method of how chemotherapy works.

To understand the complexity of biological systems, different mathematical models have been applied and manipulated throughout the years. Each new model and method contribute in its own way to a better understanding of cancer development and gives new insight on how a disease can be defeated. Some specific models will be discussed and taken into consideration throughout the thesis.
To understand the design of a system in which delay differential equations are solved, a simulation of real life is established and supported within the bounds of fundamental knowledge [7] [8] [9] [10].

The main topic of research in this thesis is how a tumor behaves at a cellular level. A rudimentary introduction about the disorder will give a better understanding of the mathematical model in a biological context. The biological systems are described and established into mathematical delay differential equations and solved by the iterative Runge Kutta fourth order method [6].

2 Theory

2.1 Breast Cancer, Immunological Response and Previous Studies

Cancer is a common term for a lot of types of diseases that can affect any part of the human body. It arises from the transformation of normal cells into tumor cells. The developing step has multiple phases in which a pre-cancerous lesion can evolve into a malignant tumor and can therefore be life-threatening. One way to define a tumor is the rapid formation of abnormal cells that grow beyond their usual boundaries [11].

Cancer cells only become apparent when the immune system weakens and the body's normal cells stop their usual cycle and take an abnormal path instead. When a cell changes its path, the immune system no longer recognizes and defeats it. Another consequence caused by the spontaneous change of path cycle is the fast reproduction of these new organisms, which have no boundaries. The phenomenon described is often called a malignant growth, in which cancer cells during their

division mutate even more so that the immune cells no longer recognize their genetic material and the cancer cells invade the whole body. Cancerous cells do not necessarily divide faster than the other cells in the body, but they lose the ability to regulate the cell cycle. A consequence of this is that proliferation of these cells cannot be controlled [11] [12].

During the last years a considerable number of drugs, therapies, researches and other analysis have been studied, among which chemotherapy has been the most efficient. Chemotherapy is a way of treating specific cancer types by injecting it in the veins of the patient. Chemotherapy may be a curative goal treatment, it may aim to prolong the life of the patient or to reduce the wide variety of symptoms which are caused by cancer. As any other medication chemotherapy has its undesirable side-effects. Chemotherapy not only attacks the cancer cells, but in time it also attacks the body's own inborn cells, which are necessary in recognizing and defeating cancer [13] [14] .

The system discussed in this thesis is very complex, including the body's own concentration of immune cells and cancer cells regard to the dose of chemotherapy a patient receives. The system has four individual paths of a cells cycle, the 'pre-synthethic phase' – G1 phase, the 'synthetic phase' – S phase, the 'post-synthetic phase' – G2 phase and mitosis. To make the model more manageable the G1, G2 and S phase are categorized as the interphase stage in which the division of a cell is prepared. Interphase is the phase in which a cell lives most of its life. It is the stage in which the cell copies its DNA and prepares for mitosis. In this phase the cell develops, obtains nutrients and metabolizes them so it can control other cell functions. Once mitosis is completed each daughter cell can enter the cycle again or shift into a quiescent phase [8] [15] [16].

Malignant cells as well as benign cells can become quiescent. Quiescence is an important phase in the development of cancer cells, also called G0 phase. The quiescent phase describes a cellular state outside of the replicative cell cycle. The definition of quiescent cells could be a reversible absence of proliferation. This means a cell is not dividing, but it can start dividing if the appropriate cell conditions are going to be present. Quiescent cells must be stimulated to reenter the cell cycle. Some of the cells never enter this phase, while others never leave this phase. Cells in quiescent phase are resistant to cytotoxic agents such as chemotherapy, and this is an important attribute because chemotherapy is cytotoxic to both immune cells and tumor cells [15].

Quiescent tumor cells have shown to complicate the diagnosis and treatment of cancer patients, because of their resistance to chemotherapy. Even after a patient receives chemotherapy, quiescent cells persist in developing and rapidly resume their cell cycle. It has been discovered that non-proliferating cells, such as quiescent tumor cells, need another medication than chemotherapy to be defeated [17].

Another significant part of the cell cycle system are the cytokines. Cytokines are very important hormones in cell signaling. They are secreted by cells and can change the properties of the cell which secretes them or of other cells around. Cytokines are known for their substantial functions in the immune system, where they are used by B-lymphocytes to activate T-lymphocytes. Lymphocytes originate from the bone marrow and migrate later in different parts of the lymphatic system. There are different type of T-lymphocytes, but the ones which directly have an effect on cancer cells and are supposed to eliminate them, are the cytotoxic T-cells [18].
Tumor cells have however the competence to deactivate lymphocytes, such as cytotoxic T-cells, so in the end, the absence of cytotoxic T-cells can be fatal, because the immune system cannot combat the tumor cells anymore. These cytotoxic T-cells mentioned are taken into consideration throughout the thesis, because of their significant importance in defending the human body from foreign organisms. However one should be aware that the immune system is much more complex than the role of cytotoxic T-cells. A simpler approach often gives a better understanding of the whole assembly [19] [20] [21].

2.2 Numerical Solutions of Delay Differential Equations

Differential equations provide a mathematical language for describing continuous change. Most of the fundamental laws of science are expressed as differential equations. Even models of systems that do not change over time are often best understood as being in an equilibrium state of a rele-

vant differential equation. The state of a system at any given time t, is described by some vector function $y(t)$, where y: $\Re \to \Re^n$. The components of $y(t)$ represent the concentrations or amount of chemical substances or number of cells. Differential equations therefore describe a relationship between this unknown state function $y(t)$ and one or more of its derivatives with respect to t that must hold at any given time [6].

In order to solve a differential equation the objective is to determine a differentiable function $y(t)$ that satisfies the prescribed relationship. Finding a solution of a specific differential equation can predict the future evolution of a system in time. However it is not necessary to determine the differentiable function. In this thesis the values of the different populations were calculated by differential equations to represent the graphic of biological systems.

There are two main models which have been studied during the years and will also be discussed and analyzed in this report. Both models only have one independent variable, and that is time, t. The two models mentioned are described entirely in the following papers: Heuristic Design of Cancer Chemotherapies by M. Villasana and G. Ochoa and Dynamics Analysis and Limit Cycle in a Delayed Model for Tumor Growth with Quiescence by R. Yafia [8] [9]. Beside the two models mentioned above a third model is established, where these models are combined to improve the complexity of the system [7] [8] [9] .

The models which have been studied in the past few years describe either how tumor cells will behave in different stages of their life or how the application of the chemotherapy drug Paclitaxel helps in threating cancer patients [16] [22] [23].
To have an outcome of the problem, a mathematical interpretation is required to simulate reality. The mathematical design behind the formation of a computational implementation will be established with the help of delay differential equations.

A delay differential equation, also called DDE is a differential equation in which the derivative of the unknown function at a certain time is given in terms of the values of the function at previous times. Delay differential equations are applied for time-delay systems, in which the system is composed of some type of aftereffect. [7] [6]
Simple Delay differential equations have the form:

$$y'(t) = f(t, y(t), y(t-\tau_1), y(t-\tau_2), ..., y(t-\tau_k)) \tag{1}$$

where the time delays τ_k are positive constants.

A fundamental technique to solve delay differential equations is to reduce them to a sequence of ordinary differential equations. It is clear that time delays equations have made a huge impact in the biological science, such as the dynamics of a population, because of their predictive information. When considering time delay systems, the best example to pick, is the predator-prey model, which is the building block for biological-systems. The classical predator-prey model was suggested by Lotka and Volterra in 1926 for an ordinary differential equation [24] and has the form:

$$\frac{dx(t)}{dt} = a1 \cdot x(t) - b1 \cdot x(t) \cdot y(t) \tag{2}$$

$$\frac{dy(t)}{dt} = -a2 \cdot x(t) + b2 \cdot x(t) \cdot y(t) \tag{3}$$

The predator-prey model is composed of two populations, $x(t)$ which represents the population of prey and $y(t)$ which represents the population of predators. The sizes of $x(t)$ and $y(t)$ depend on the time t and have the following initial conditions:

$$x(0) = x_0 \; and \; y(0) = y_0. \tag{4}$$

In the two equations (2) and (3) there are some positive constants: a1, a2, b1, b2 which represent different attributes of a system. These parameters can describe different significant parts of a system, such as natural birth rates, death rates or division of cells. If there is more than one

population $y(t)$ in the system, some of the parameters can indicate the interactions between the populations.
These systems are taken into considerations when the birth rate of predators is affected by prior levels of predators or prey, rather than by only the current levels in a predator-prey model. [24] Additional information is required to specify a system of delay differential equation. If the value of $x(t)$ does not immediately affects the value of $y(t)$ throughout the change in time and the other way around, then a delay differential equation must be taken into consideration.

$$\frac{dy(t)}{dt} = a1 \cdot x(t) - b1 \cdot x(t) \cdot y(t - \tau_1) \tag{5}$$

$$\frac{dy(t)}{dt} = -a2 \cdot x(t) + b2 \cdot x(t - \tau_2) \cdot y(t) \tag{6}$$

For DDE's, instead of simple initial conditions, initial history functions must be taken into consideration. The derivative in eq. (1) depends on the solution at a previous time $t - \tau_j$ and therefore it is necessary to provide an initial history function to specify the value of the solution before time $t = 0$.

$$x(0) = x_0, \quad x(s) = \phi(t), \quad y(0) = y_0, \quad y(s) = \varphi(t), \quad -\tau < t < 0 \tag{7}$$

where $\tau_1 > 0$ and $\tau_2 > 0$ and the functions $\varphi(s)$ and $\phi(s)$ are the initial past history functions. In this thesis an initial value of the functions is given in such a way that the program takes the first values in time and provides an initial history function to specify the value of the solution before time $t = 0$. The initial conditions are properly described in the three mathematical models [7] [6].

2.3 Mathematical Model - Runge Kutta Fourth Order

The mathematical method applied to solve the differential equations is Runge Kutta of fourth order [6]. Runge Kutta methods are single step methods which replace higher derivatives by finite difference approximations based on values of f at points between t_n and t_{n+1}. Runge Kutta method of 4'th order is derived by applying numerical integration to the following interval:

$$y_{n+1} - y_n = \int_{t_n}^{t_{n+1}} (f(t, y(t))dt) \tag{8}$$

Derivation of the Runge Kutta method happens with the help of the Taylor Series Methods [6], where the second derivative of $y^{'}$ is given by:

$$y^{''} = f_t + f_y \cdot f, \tag{9}$$

and every function will now be evaluated at (t, y), where f_t is the derivative of time, t, and f_y is the derivative of y.

Runge Kutta of 4'th order uses four estimates of the slope to give an approximation of greater accuracy than using a single slope at the beginning of an interval. The more estimates of a slope are taken into considerations, the more accurate the result are expected to be .
Therefore Runge Kutta of fourth order is a good approximation method for the complex system evaluated in this thesis. Runge-Kutta methods are easy to program, (for the reason that they do not provide any error estimate based on the step size chosen for the mathematical system) and to develop in time they do not need any history, and are therefore self-starting, so the value of step-size can be changed during the integration. Even if Runge-Kutta methods do not need history functions, the system can have another approach for which it is develops dependent of a time delay [6]. The method approximates the solution to a first order differential equation given by,

$$\frac{dy(t)}{dt} = y'(t) = f(y(t), t) \tag{10}$$

with initial condition

$$y(t_0) = y_0. \tag{11}$$

An initial value of the function must be specified to start the algorithm. To estimate the slope at time t_0, the following four slope approximations will be evaluated. The approximation to $y(t_0)$ will be defined as $y^*(t_n)$, for $n = 0, 1, 2...$.

$$k1_{rk4} = f(y^*(t_n), t_n) \tag{12}$$

$$k2_{rk4} = f(y^*(t_n) + k1_{rk4} \cdot \frac{h}{2}, t_n + \frac{h}{2}) \tag{13}$$

$$k3_{rk4} = f(y^*(t_n) + k2_{rk4} \cdot \frac{h}{2}, t_n + \frac{h}{2}) \tag{14}$$

$$k2_{rk4} = f(y^*(t_n) + k3_{rk4} \cdot \frac{h}{2}, t_n + h), \tag{15}$$

here h is the time step used for the development of $y(t_0)$ in time. Each one of the four slopes to the function, describes something specific [6].

The first approximation k1, is the slope at the beginning of the time step. The slope $k1_{rk4}$ will be further used to step halfway through the time step, and $k2_{rk4}$ will be the new estimate of the slope at the midpoint. Then if $k2_{rk4}$ is used to step halfway through the time step, $k3_{rk4}$ is then another estimate of the slope at the midpoint. The last slope used is $k3_{rk4}$ to step all the way across the time step, $k4_{rk4}$ will then be another estimate of the slope. To get the final estimate of the approximations, following equation is applied:

$$y^*(t_n + h) = y^*(t_n) + \frac{(k1_{rk4} + 2 \cdot k2_{rk4} + 2 \cdot k3_{rk4} + k4_{rk4})}{6} h = (y^*(t_n) + m \cdot h), \tag{16}$$

where m is a weighted average slope approximation [6].

3 Mathematical and Biological Methods

3.1 Cancer Method 1 - Tumor Cells Behavior during Mitosis & Interphase

The first model is presented by M. Villasana, G. Ochoa and A. Radunskaya in multiple papers and does not include quiescent tumor cells [7] [8].

For the mathematical models to work, the best method is to have a specific amount of data for each cancer patient and analyze the system of each patient individually. The set of parameters mentioned throughout the thesis belong to a cancer patient with uncontrollable tumor. The parameters are non-dimensionalized and are taken into consideration in all the simulations (*Appendices B-E*) . These parameters will be explained throughout the thesis [7] [8].

When considering a large populations of cells, ordinary differential equation can be applied to build a mathematical model of a certain cell cycle in the system. This model is a system of ODE's that describes the lymphocytes division.

$$\frac{N_0(t)}{dt} = -(\alpha_0 + \beta_0) \cdot N_0(t) \tag{17}$$

$$\frac{N_j(t)}{dt} = -2 \cdot \alpha_{j-i} \cdot N_{j-i} - (\alpha_j + \beta_j) \cdot N_j(t), \tag{18}$$

where $j = 1, 2...J$.
Where for j=1,2.., J, let $N_j(t)$ be the population of the lymphocytes at time t, after j divisions. J is the amount of cell divisions that are going to take place. α_j indicates the rate of cell proliferation and β_j indicates the rate of cell death. The first term in the previous equation: $2 \cdot \alpha_{j-i}$ indicates the fact that a cell during mitosis splits into two new daughter cells. Cell division is a discrete system and therefore very complex, in account of that there is involved a discrete time delay starting at the time the cell is born until it divides [10].

One of the drugs which has been used for treating cancer is Paclitaxel, also named Taxol. Paclitaxel interferes with mitosis, disabling the cell from continuing in the cell cycle. This happens by blocking the cell from entering the normal cell cycle and just stops the cell from proliferating and permits the immune system to eliminate cancerous cells in a natural way.

Chemotherapeutic medication not only defeats cancer cells, but also kills the body's own immune cells. Paclitaxel is relevant in this model because it is involved in the cell cycle which targets the S-phase, and is a part of the interphase. Paclitaxel has been shown to attack the tumor cells while they are in the interphase, but they only die at the time where they are in the mitoses phase, some days later. The resident time of cells in interphase is described by τ [22].

The time delay τ is only taken into consideration when talking about interphase. Mitosis is a very short period of the cell cycle, in which the time delay will be insignificant and that is the reason why it is not studied in this chase.

The system created separates the tumor cells into interphase cells $T_I(t)$ and mitosis cells $T_M(t)$. Beside these another term, $I(t)$ is introduced. $I(t)$ represents the population of the body's own immune cells, the cytotoxic T-lymphocytes. Because cancer cells do not die immediately, but only after several divisions, chemotherapy is given in repeated doses in different forms [23].

At first we have the three equations the systems is built upon [8]:

$$\frac{dT_1(t)}{dt} = 2 \cdot a_4 \cdot T_M(t) - c_1 \cdot T_I(t) \cdot I(t) - d_2 \cdot T_I - a_1 \cdot T_I(t-\tau) \tag{19}$$

$$\frac{dT_M(t)}{dt} = a_1 \cdot T_I(t-\tau) - d_3 \cdot T_M(t) - a_4 \cdot T_M(t) - c_3 \cdot T_M(t) \cdot I(t) - k_1(1 - e^{-k_2 \cdot w(t)}) \cdot T_M(t) \tag{20}$$

$$\frac{dI(t)}{dt} = k + \frac{\rho \cdot I(t) \cdot (T_I(t) + T_M(t))^n}{\alpha + (T_I(t) + T_M(t))^n} - c_2 \cdot I(t) \cdot T_I(t) - c_4 \cdot T_M(t) \cdot I(t) - d_1 \cdot I(t) - k_3((1 - e^{-k_4 \cdot w(t)}) \cdot I(t)) \tag{21}$$

With the two states $w_1(t)$ and $w_2(t)$ which are given by:

$$\frac{dw_1(t)}{dt} = -\lambda_1 \cdot w_1(t) + c(t) \tag{22}$$

$$\frac{dw_2(t)}{dt} = -\lambda_2 \cdot w_2(t) + c(t) \tag{23}$$

Which together collaborate to the second and third function, respectively $T_M(t)$ and $I(t)$:

$$w(t) = r_1 \cdot w_1(t) + r_2 \cdot w_2(t) \tag{24}$$

$w(t)$ is a linear combination of the two terms $w_1(t)$ and $w_2(t)$, and $c(t)$ is the term which describes the concentration of the chemotherapeutic drug, Paclitaxel, which is administered by the patient at time t. The drug decay is assumed to be exponential and λ is a coefficient that includes both the elimination and absorption impacts of the drug. The terms $d_2 \cdot T_I$, $d_3 \cdot T_M$ and $d_1 \cdot I$ represent proportions of natural cell death(apoptosis), while a_1 and a_4 represent the different rates at which cells reproduce. c_i terms represent the losses from conflict of immune cells with tumor cells [25] [26].

If high concentrations of chemotherapy are given, the drug hinders the tumor cells in mitosis phase, so the tumor cell is taken out of the cycle and cannot proliferate.
This system can be modeled by following terms: $k1(1 - e^{-k_2 \cdot w(t)})$ constitutes the impact of the drug on mitosis and $k3(1 - e^{-k_4 \cdot w(t)})$ constitutes the impact of the drug on the cytotoxic T cells. This means that high concentrations of chemotherapy will destroy the immune cells. Once the drug encounters the tumor cell, the tumor cell is taken out of the cycle and can no longer proliferate. If the drug dosage is too high the value of these terms will have another significance, because the drug will also eliminate the body's own immune cells [27].

Given the initial conditions, the previous functions can be calculated with help of delay differential equations:

$$T_I(t) = \phi_1(t), for\ t \in [-\tau, 0] \tag{25}$$

$$T_M(t) = \phi_2(t), for\ t \in [-\tau, 0] \tag{26}$$

$$I(t) = \phi_3(t), for\ t \in [-\tau, 0] \tag{27}$$

$$w_1(0) = 0 \tag{28}$$

$$w_2(0) = 0 \tag{29}$$

$T_M \cdot I$ and $T_I \cdot I$ are standard competition terms that represent losses due to encounters among the different cell types. The time decay taken into consideration is based on the drug Paclitaxel. There will be one decay rate in the bloodstream and one decay rate in the peripheral tissues when Paclitaxel is given [8] [22].
Following term:

$$\frac{\rho \cdot I(t) \cdot (T_I(t) + T_M(t))^n}{\alpha + (T_I(t) + T_M(t))^n}, \tag{30}$$

is the nonlinear growth of immune cells population due to the presence of a tumor [8]. The form in which this term is established is by a Michaelis-Menten model [28]. The reason for which this model is applied, is because proliferation of tumor-specific effector cells, such as immune cells, are stimulated by the presence of tumor cells. Immune cells will at a certain time reach a saturation level at tumor populations.

Another important term is the constant k which represents the birth rate of the immune cells in the absence of cancer. Tumor cells reside in interphase for a certain period of time τ before entering the mitosis phase. The term $T_I(t - \tau)$ accounts for the stage in which tumor cells leave the interphase. Assuming that cells reside in interphase τ units of time, then cells that enter the mitosis stage at time t are those cells that entered interphase at time τ.

The parameters ρ, α and μ depend on which type of tumor the system consists of and at which state the cancer exists. The growth of tumor cell population is obtained through the mitosis term and is given by the constants a_1, a_4 and τ which regulate the rate of cell division present in T_M. ϕ describes the increase of immune cells suitable to a stimulant. α represents the half value of the immune response. The two parameters are dependent on each other in such a way, that when the tumor level is equal to α the immune response is half way to its maximum value π.

The parameter n determines the shape of the response term and was examined in different *invitro* studies. Based on these studies the best value of the exponent was found to be $n = 3$ [8]. The same value of n is applied for all three models in this thesis. Large values of n means that the immune system has difficulties recognizing the tumor and it takes the immune system longer then expected. τ describes the time delay of the number of days in which the tumor cells reside in the interphase stage [7] [7] [9].

3.2 Cancer Method 2 - Quiescent Tumor Cells Behavior

The second model is based on the article *Dynamics Analysis and Limit Cycle in a Delayed Model for Tumor Growth with Quiescence* which generates a delay differential equation model for the interactions of proliferating and quiescent tumor cells, without including the immunological or medicational components [9].

Drugs that have been used for threating cancer have also affected the other cells in the organism and prevented their development and functions. As mentioned earlier quiescence is the state of a cell, in which the cell does not divide. It is not guaranteed that it will improve the understanding of cancer treatment, but some organ have a higher amount of quiescent cells than proliferating cells, therefore it is important to understand the development of different types of cancers situated in different sections of the human body [27] [29].

All existing drugs mainly affect the proliferating cells but also, to a certain extent, the quiescent cells.

The idea of not including the drug terms in this model is to compute some fixed points of the cancerous environment in which the chemotherapeutic drugs are not present. This contributes to the understanding and further analysis of the drug-free system. Beside the absence of drugs, the model will not take account of the immune response either [9].

The mathematical model used for this approach is the following:

$$\frac{dP(t)}{dt} = b \cdot P(t-\tau) - r_P \cdot (N(T)) \cdot P(t) + r_Q \cdot (N(t)) \cdot Q(t) \tag{31}$$

$$\frac{dQ(t)}{dt} = r_p \cdot (N(t)) \cdot P(t) - \mu_Q \cdot Q(t) - r_Q \cdot (N(t)) \cdot Q(t) \tag{32}$$

$$P(t) \equiv P_0,\ Q(t) \equiv Q_0,\ -\tau < t < 0 \tag{33}$$

Where $P(t)$ indicates the number of proliferating tumor cells and $Q(t)$ indicates the number of quiescent tumor cells. $N(t)$ indicates the total number of tumor cells, which is build up by $N(t) = P(t) + Q(t)$. Some other parameters are taken into consideration, where if $\beta > 0$ is the division rate of the proliferating tumor cells, while $\mu_p > 0$ is the death rate of the proliferating cells, then $b = \beta - \mu_p > 0$ is the intrinsic growth rate of the proliferating cells.

As mentioned quiescent cells do not divide, so there is no need to have a division parameter for them. $u_Q \leq 0$ represents the mortality rate of these cells, $r_P(N)$ incorporates the transition of proliferating cells to quiescent cells and $r_Q(N)$ incorporates the transition of quiescent cells to proliferating cells. The time delay describes here the time it takes proliferating cells to divide and there is of course no time delay for the quiescent cells because they are in a state with no division. The term $\mu_Q \cdot Q(t)$ is the term which describes the natural death of quiescent cells. The system has been tested by Yafia [9] both with and without time delay. If there is no time delay the system will become an ordinary differential equation model, where the time delay is $\tau = 0$ [9].

3.3 Cancer Method 3 - Combination of Method 1 & 2 and the Impact of Paclitaxel

The last model is a combination of the two models used in the two papers written by Villasana together with Ochoa and Yafia. Some additional terms are taken into consideration to ascertain the impact of the chemotherapy drug, Paclitaxel, on the quiescent cells [22] [23].

This system is based on the data from the same patient but with perspective on the body's own defense, immune cells, quiescent cells together with the chemotherapeutic drug treatment. Another important detail included is the combination of cytotoxic T-cells with quiescent tumor cells. Quiescent tumor cells are resistant to cytotoxic agents, so a specific parameter representing the resistance of these tumor cells must be established.

The term $T_Q(t)$ describes the population of tumor cells in the quiescent stage of their cell cycle. The term $N(t)$ describes the total cancer cell population. In the equations from model 2 there are few terms which are kept under control in this model, among other the transition states $r_P(N) = a5$ and $r_Q(N) = a6$ which in this chase are constants. $d4$ is another constant which represents the natural death rate of the quiescent tumor cells, while $c5$ represents the kill rate of quiescent cells by the cytotoxic T-cells.
As in the first model a chemotherapeutic drug treatment has to be represented in the mathematical model of the delay differential equations. Paclitaxel is a cycle specific chemotherapeutic drug, which works by stopping cancer cells from separating into two new cells. This blocks the growth of the cancer, because it targets the tumor cells in their interphase stage. Like any other medicine, Paclitaxel can have side effects, and one of the most dangerous side effects is drug overdoses. This will lead to damaging and killing of the healthy inborn and immune cells [21] [29].

The final mathematical model simulates the following:

$$\frac{dT_Q(t)}{dt} = a_5 \cdot T_I(t-\tau) - a_6 \cdot T_Q(t) - d_4 \cdot T_Q(t) - c_5 \cdot I(t) \cdot T_Q(t) - u_1(t) \cdot T_Q(t) \tag{34}$$

$$\frac{dT_I(t)}{dt} = 2 \cdot a_4 \cdot T_M(t) - a_5 \cdot T_1(t-\tau) + a_6 \cdot T_Q(t) - c_1 \cdot T_I(t) \cdot I(t) - d_2 \cdot T_I(t) - a_1 \cdot T_I(t-\tau) \tag{35}$$

$$\frac{dT_M(t)}{dt} = a_1 \cdot T_I(t-\tau) - d_3 \cdot T_M(t) - a_4 \cdot T_M(t) - c_3 \cdot T_M(t) \cdot I(t) - u_2 \cdot T_M(t) \tag{36}$$

$$\frac{dI(t)}{dt} = k + \frac{\rho \cdot I(t) \cdot (T_Q(t) + T_I(t) + T_M(t))^n}{\alpha + (T_Q(t) + T_I(t) + T_M(t))^n} - c_2 \cdot I(t) \cdot T_I(t) - c_4 \cdot T_M(t) \cdot I(t) - c_6 \cdot T_Q(t) \cdot I(t) - d_1 \cdot I_(t) - u_3(t) \cdot I(t) \tag{37}$$

Same as in model 1, $w(t)$ (eq.24) is a linear combination of the states $w_1(t)$ (eq.22) and $w_2(t)$ (eq.23). For a better understanding of model 3, the individual parameters are elaborated earlier in *Cancer method* 1.
Parameters a_1 and a_4 represent the fraction of cells which cycle from interphase to mitosis and from mitosis to interphase. Both constants need to have a value between 0.2 and 1.0 per day (usually between 0.7 and 1.0).
Constants d_1, d_2 and d_3 represent fractions of natural death, also called apoptosis, and should be between the value of 0.1 and 0.3. Constants c_i model the losses of the cells due on the encounter with another cell (usually between 0.1 and 0.3).

The function must be evaluated together with some initial conditions,

$$T_Q(t) \equiv 0.8, for\ t \in [-\tau, 0] \tag{38}$$

$$T_I(t) \equiv 1.3, for\ t \in [-\tau, 0] \tag{39}$$

$$T_M(t) \equiv 1.2, for\ t \in [-\tau, 0] \tag{40}$$

$$I(t) \equiv 0.9, for\ t \in [-\tau, 0] \tag{41}$$

The function describing the importance of cytotoxic T-cells, $I(t)$, has a similar term as in model 1, but here the quiescence is taken into account. Here the term is a nonlinear growth of immune population, when cancer is present in the patient:

$$\frac{\rho \cdot I(t) \cdot (T_Q(t) + T_I(t) + T_M(t))^n}{\alpha + (T_Q(t) + T_I(t) + T_M(t))^n} \tag{42}$$

To make sure the last model can be applied for further studies, some controls from already existing literature [8] are taken into consideration, where the following applies:

$$u_1(t) = k_5 \cdot (1 - e^{k_6} \cdot w(t)) \tag{43}$$

$$u_2(t) = k_1 \cdot (1 - e^{k_2} \cdot w(t)) \tag{44}$$

$$u_3(t) = k_3 \cdot (1 - e^{k_4} \cdot w(t)) \tag{45}$$

$u_1(t)$ is a term used in eq.(34) and describes the tumor cells in quiescent stage. $u_2(t)$ is a term used in eq.(36) and describes the change of tumor cells in interphase stage. While $u_3(t)$ is the term used in eq.(37) to describe the population of the immune cells, which means the cytotoxic T-cells. All the following constants are positive and under the value 1: a_1, a_4, a_5, a_6, d_1, d_2, d_3, d_4, c_1, c_2, c_3, $c4$, c_5 and c_6. Some of the parameter values are the same as in some of the previous studies. There is no unique set of parameters values for any given model, because every parameter varies between tumor types and from patient to patient [7]. Some of the constants listed here under are used for the numerical values, but there are some other parameters that have been chosen without benefit of data, this is the reason why I allowed myself to vary some of the values for purpose of analysis, leading to a deeper understanding of the behavior of the model [8] [9].

Like discussed in previous studies, it has been discovered that quiescent tumor cells are resistant to drugs, but up till a particular moment, where they exit the quiescent stage and reenter the cell-cycle [29] [32].
$u_1(t)T_Q(t)$ is the term which takes into account the loss of quiescent cells. If $k_5 = 0$ it means that the quiescent cells present in the system are not affected by the medicine, because they are cancerous. Even if the human body is attacked by the tumor, the immune system still works in some way, so the immune cells will still destroy some of the quiescent tumor cells.
$c_5T_I(t)T_Q(t)$ is the term which describes the loss of quiescent tumor cells caused by the immune system. $c_5I(t)T_Q(t)$ describes the deactivation of immune cells caused by the quiescent tumor cells. If $c_6 = 0$ it is possible to see how the systems develops if the quiescent cells do not deactivate the immune cells. Looking back at Yafia's model [9] it includes another term $bP(t-\tau)$, where the term b is the intrinsic rate of proliferation, this means $b = birth - death$.

The time delay corresponds to the time it takes the cells to proliferate. The birth rate and death rate are getting separated, because death has logically no time delay. $a_6T_I(t-\tau)$ is the term which describes the rate of change of tumor cells during mitosis. This models the proliferation of cells, together with the delay corresponding to the time the cells spend in the interphase stage before they replicate. $d_3T_M(t)$ is the term which represents the instantaneous death of the mitotic tumor cells, that is when the tumor cells are in the mitosis stage of the cell cycle [7] [8] [9].

4 Computational methods

4.1 Script and Considerations

One of the challenges for this thesis was to acquire a knowledge of programming in python 2.7 [30] [31].
I managed to create a script that calculates the detailed mathematical methods mentioned in the theory section (*Appendix B-D*) and the new method based on the latest discoveries (*Appendix E*).
Four different codes were implemented, one for each model. All the four scripts have the same course of action and make use of the mathematical method Runge Kutta of fourth order.

The way in which the code has been designed, is by creating user-defined functions for the differential equations of the different populations. Such a function describes a block of organized, reusable code that is used to perform a single, related action. Depending on which mathematical method is used, diverse functions were analyzed.

Every function depends on some specific parameters within the area of interest. One of the functions created, states the computation of how Runge Kutta of fourth order operates on the different cell population functions. Every iteration starts from a specific initial value of the cell populations. The program specifies that the first values of the iterations, n_{steps}, remain untouched for a short period of time, so a history function of the delay can be created as it is requested in the differential equations for the term $(t-\tau)$.

Every population has an initial condition from which a specific differential equation is evaluated. The script returns values that are determined by the number of iterations the program runs. The number of iterations describe the number of days in which the populations develop in time. Another specification used by the program, is the time-step 0.01 chosen for the program. The time-step is extremely important for the design of a program, because it says something about the time interval for which a simulation will progress during next "step".

The initial values applied for the systems have either been calculated mathematically or chosen arbitrary to see how sensitive the script is.
The parameters on which the script operates depend on the patient, but the initial values are chosen in order to understand the influence of tumor cells, immune system and chemotherapy in relevance to each other.
The parameters used in the scripts are non-dimensional, for this reason the y axis varies from one

graph to another, especially in Fig. 1.a and 1.b. For a better understanding of the population values, the individual parameters could be multiplied with a whole number, to receive higher values. In this way the population could be compared with a concentration of the number of cells.

5 Numerical Results & Discussion

5.1 Results for Cancer Method 1 - *Appendix B*

This section aims to focus on model 1, which has been studied among the years by various scientists. To make sure model 1 functions as instructed, the values of the three populations, interphase tumor cells $T_I(t)$, mitosis tumor cells $T_M(t)$ and cytotoxic T-cells $I(t)$ are the same as for the results from past research. The reason for which I chose to use same values as in the earlier studies is to check if the mathematical methods I apply have same output [8]. With the initial function values $[T_I(0), T_M(0), I(0)] = [0, 0, 0.9]$, where if $t \leq 0$ the cancer cells are not present, therefore interphase cancer cells or mitosis cancer cells should remain zero, while the immune cells approach a steady state. For the first analysis the script will run through 100 days.

The first analysis, (fig. 1.a), gives an overview of the system when neither cancer cells nor medication are present. Only the cytotoxic T cells develop during the first analyses approaching a steady state value of roughly 0.12 after 10 days, while the tumor cells in interphase and mitosis remain at zero. The cytotoxic T-cells depend on the constant k, which is the birth rate constant of the body's immune cells when the tumor is absent. I can hereby conclude that a low value of tumor cells will let the cytotoxic T cells develop. Because if $T_I(0)$ and $T_M(0)$ equal zero, then these terms will simplify $I(0)$ eq. (21) and only take into account the number of the immune cells. The reason for which the cytotoxic T-cells decrease is because of the operational sign, because for the initial values in fig 1.a, $dI(t)/dt = k - (d_1 * I(t))$.

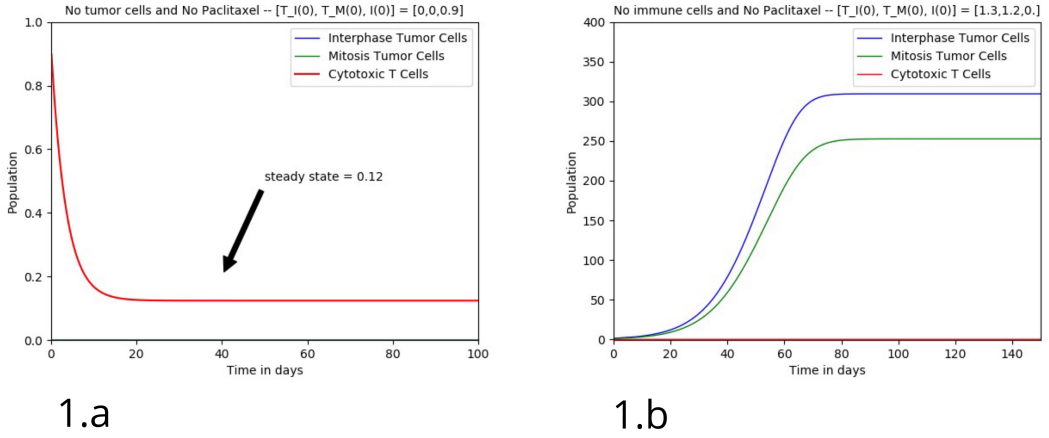


Figure 1: 1.a No tumor cells & no drug, 1.b No immune cells & no drug.

To understand the development of the tumor alone, another script (fig. 1.b) was established in which the immune cells are absent and the patient does not receive any medication.
As expected the cytotoxic T-cells do not develop throughout the analysis, while the interphase and mitosis tumor cells develop relatively fast in the beginning and then after 60 days both populations approach a steady state. Even if it is not conventional to have such a weak immune system, it gives a great understanding of the importance the immune system has in defeating a disease.

The next analysis (fig. 2.a) is based on the primary models studied by Villasanna & Ochoa, in which all three populations decrease rapidly the first 10 days, for after to approach a steady state between 0.1 and 0.2 depending on the population.

In this analysis no medication is administered to the patient [8].

In the simulations where no drug is administered the following terms are taken out of the calculations: $(-k_1(1-e^{-k_2 \cdot w(t)})) \cdot T_M(t)$ and $(-k_3((1-e^{-k_4 \cdot w(t)}) \cdot I(t)))$ because they represent the kill terms of the drug on mitosis tumor cells and the cytotoxic T-cells, respectively. So by removing these terms the states $w_1(t)$ and $w_2(t)$ will not be taken into consideration either.

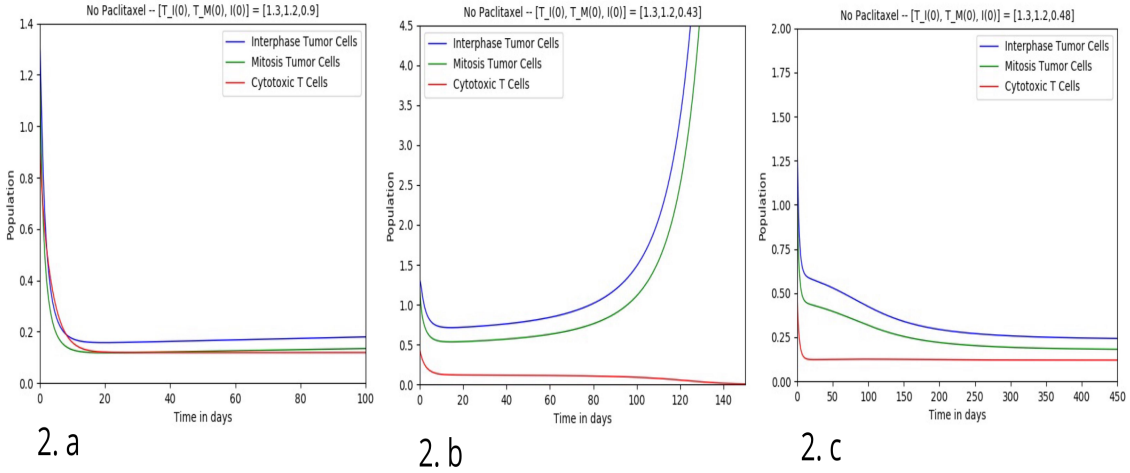


Figure 2: 2.a No drug - I(0) = 0.9, 2.b No drug - I(0) = 0.43, 2.c No drug - I(0) = 0.48

To understand the function of the immune system, the start values for both tumor cells populations is kept the same, but the start value of cytotoxic T-cells will be changed to 0.43 and 0.48 (fig 2.b and fig 2.c). With a start value of 0.9 for the cytotoxic T-cells population (fig. 2.a), the tumor is reduced for a shorter period of time, but a lower initial value of the immune system (fig 2.b & 2.c) may influence the patient's capability to defeat the tumor.
The start value of the cytotoxic T-cells population for the first analysis is 0.43 (fig. 2.b) and for the other analysis 0.48 (fig. 2.c). The reason for which fig. 2.c spans over 450 days is to see the development for a longer period, cause for shorter periods the steady states of the three functions were not visible. For figure 2.b it was not necessary to show the development over a longer period of time, because the tumor cells kept increasing. The importance of the days is not significant here as much as it is for the simulations in which chemotherapy is given.

It is expected that with low start concentrations of cytotoxic T-cells, the tumor cells develop much faster, because the immune system is not capable to defeat the tumor cells. Fig. 2.b is a simulation of the system over 150 days, in which the tumor cells increase in population quite fast, while the immune cells decrease more and more.

Comparing the three simulations (fig. 2.a - 2.c) I can observe that patients with a weak immune system are more likely to die from cancer, while patients with a stronger immune system are able to battle the disease for some amount of time. A patient with a cytotoxic T-cell start population of 0.9 is categorized to be in a balanced condition, while a patient with an initial value of 0.48 or under is classified as a person with a weakened immune system.

To understand the function of chemotherapy on tumor cells, a new system is established(fig. 3.a - 3.c), in which Paclitaxel is given to the patient for certain days. The time in which the patient receives medication is given by, $c(t) = 1$ if $0 \leq t \leq 10, 20 \leq t \leq 30$ *and* $50 \leq t \leq 60$ and c(t) = 0 in the other chases. Around time $t = 0, 20, 50$ the influence of Paclitaxel is apparent(fig. 3.a & 3.c), where the population of both interphase and mitosis tumor cells decrease for some time, while the cytotoxic T-cells approach a steady state.

The reason for which the mathematical methods simulate short periods of time in which chemother-

apy is given, has to do with the damaging characteristics of chemotherapy on long term.

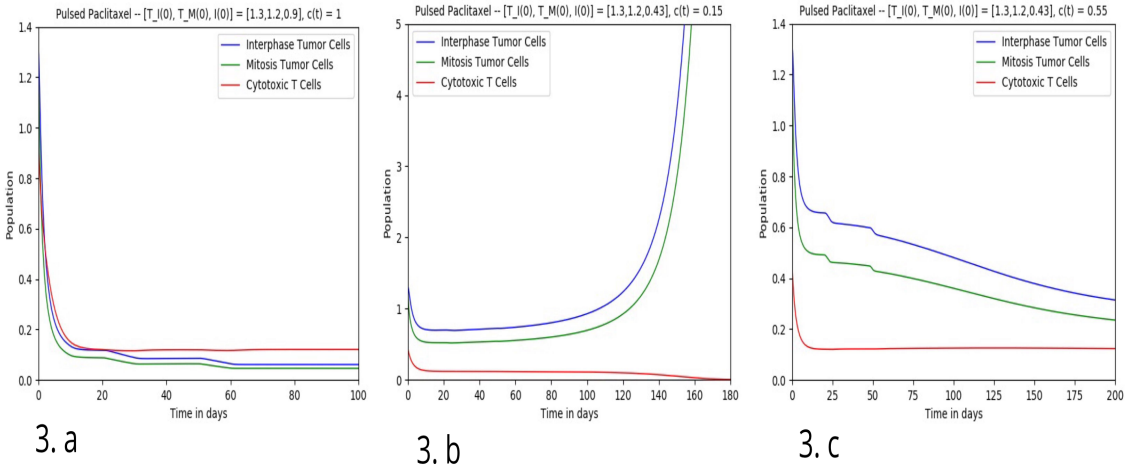


Figure 3: 3.a Pulsed drug - c(t) = 1, 3.b Pulsed drug - c(t) = 0.15, 3.c Pulsed drug - c(t) = 0.55

To have in mind, chemotherapy not only defeats the tumor cells, but also kills the healthy inborn cells [16]. Fig. 3.b represents the case in which the immune system is extremely low in comparison to the population of the tumor cells, and the amount of drug received is only $c(t) = 0.15$. In fig. 3.c the initial value of cytotoxic cells is 0.43, with the following inputs: $c(t) = 0.55$ for $0 \leq t \leq 3, 20 \leq t \leq 23, 48 \leq t \leq 50$ and $c(t) = 0$ in the other chases (eq. 22-23). It is clear in fig. 3.b that even when the patient's immune system is very weak, the low dosage of chemotherapy will still make a difference and defeat the tumor cells for a time.

Another thing to consider is the importance of the chemotherapeutic concentration that the patient receives. Will chemotherapy still work if the dosage is smaller, because we know that if the dosage gets too high it only damages the body more. What if the dosage gets smaller then $c(t) = 0.55$, will it still work?

The time in which the patient receives chemotherapy should be considered as well. Chemotherapy is damaging for the body and spreading the treatment for a longer evenly distributed period could have an impact [16]. Like any other disease the sooner you discover it, the easier and more approachable it is to cure. So the importance of receiving medication right after the disease is discovered, is essential. To prove this statement another analysis is established (fig. 4.a - 4.c), in which additional low level pulses are added. For this analyses the drug concentration is either $c(t) = 0.15$ or $c(t) = 0.30$, and beside the earlier three pulses an additional pulse is taken into consideration. First, a early additional pulse $7 \leq t \leq 9$ is considered for which the drug concentration equals $c(t) = 0.15$.

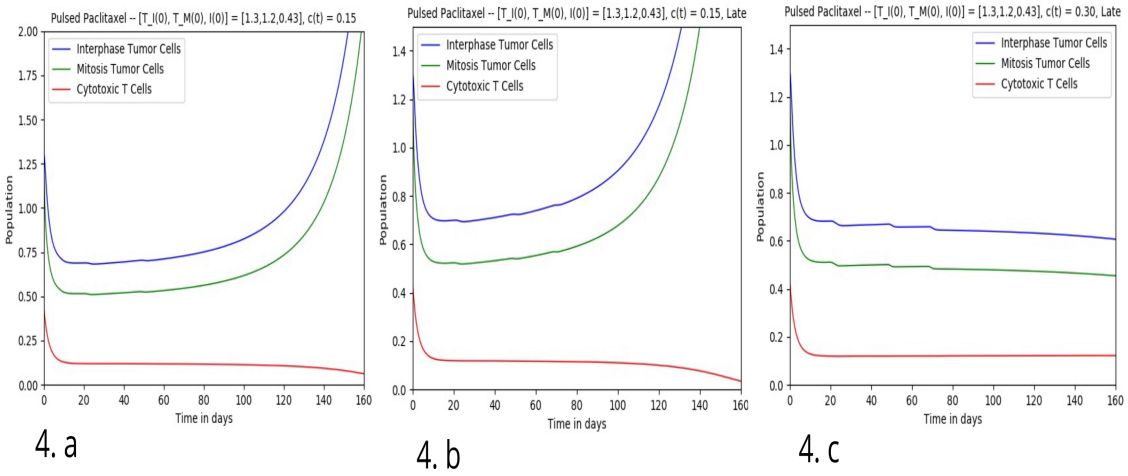


Figure 4: 4.a Early pulsed Paclitaxel & c(t) = 0.15, 4.b late pulsed Paclitaxel & c(t) = 0.15, 4.c late pulsed Paclitaxel & c(t) = 0.30

Tumor cells react to the chemotherapy received, but only for a short period of time of about 10 days. To prove that it is significant to threat the disease as soon as possible, the low level pulse added before is replaced with a later low level pulse at time $68 \leq t \leq 70$ with a dosage of $c(t) = 0.15$ (fig 4.b) and $c(t) = 0.30$ (fig 4.c). Like expected additional chemotherapy pulses will reduce the population of tumor cells, but even if only a small additional dosage is prescribed to the patient, it can be damaging for the patient's healthy cells, which are sensitive to chemotherapy.
Fig. 4.c shows clearly that a higher, more frequent dosage of chemotherapy kills the tumor cells, but may kill some other cells too.

Chemotherapy dosage is as important as the amount of times the drug is administered to the patient. A frequent low dosage of chemotherapy may be more efficient then a high rare dosage of chemotherapy.

5.2 Results for Cancer Method 3 - *Appendix D*

I chose to present the results for *model* 3 and only mention *model* 2 in *Appendix A and C*, because of the outcome from the numerical results. *Model* 2 displays unphysical results, because of the insufficiency and lack of precision that the method provides.

As for model 1 (fig 1.a), a simulation only including the cytotoxic T-cells was implemented (fig. 5.a) and the results appeared to be the same. The way the immune cells developed and the steady state value showed to be the same.
The simulations for model 3 which I am going to discuss have nearly same onset as model 1, but to compare the two models I need to have same pattern of the immune cells and cancer cells alone when neither the drug nor the immune cells are present.

To make sure the code works as it should, to be compared to real life, there are some initial values that have to be tested. For the first run(fig 5.a) all three populations have same initial values as for model 1 in which $[T_Q(0), T_I(O), T_M(0), I(0)] = [0, 0, 0, 0.9]$ when chemotherapy is absent.

For further analysis I consider what influence the quiescent tumor cells have on the simulation by either given it the initial value 0 (fig. 5.b) or 1.8 (fig. 5.c). The quiescence component of the differential equations is present in the interpretation of the other tumor cells, as well as the immune systems cytotoxic T-cells, therefore it is important to see how the population of quiescent tumor cells develops in time.
This simulation takes into account chemotherapy with a dosage of $c(t) = 0.55$ at times $0 \leq t \leq 10, 20 \leq t \leq 30, 60 \leq 70$ and $c(t) = 0$ in the other cases, first where quiescence is absent

$[T_Q(0), T_I(O), T_M(0), I(0)] = [0, 1.3, 1.2, 0.4]$ and second where quiescence is present $[T_Q(0), T_I(O), T_M(0), I(0)] = [1.8, 1.3, 1.2, 0.4]$.

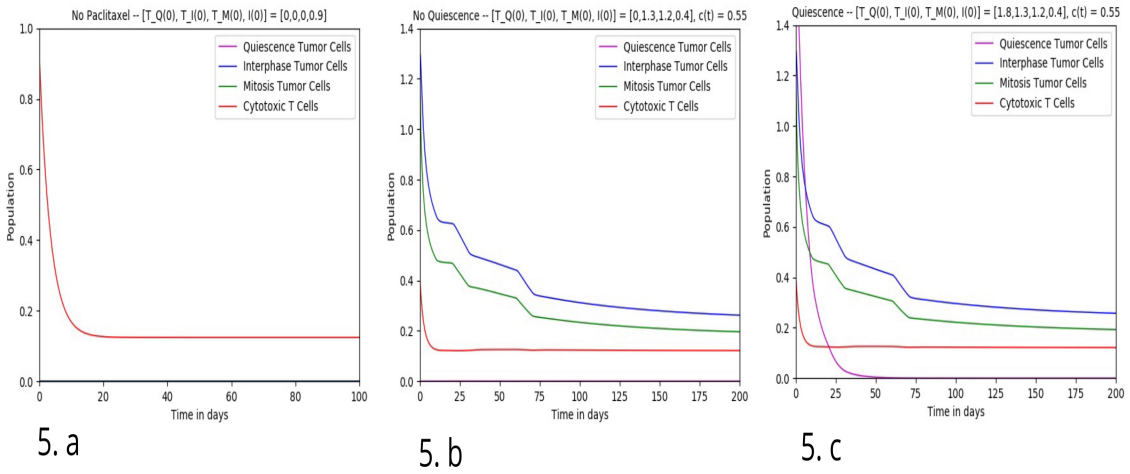


Figure 5: 5.a No Paclitaxel - only Cytotoxic T-cells, 5.b No quiescence cells - c(t) = 0.55, 5.c Quiescence present - c(t) = 0.55

In model 1 the initial value for the cytotoxic T-cells population was 0.9, but it did not show any significant change, because the value represented a patient with an extremely strong immune system. For this reason the initial value 0.4 is based on a patient with a weak immune system like in fig. 3.a - 3.c. From fig. 5.b and 5.c there is no significant change to be observed, beside the value of quiescent cells. This is because of the way the differential equations are build. The quiescent term in the equations is not of big importance, so only looking at the graphs will not give a wide perspective of the importance of the quiescent tumor cells, but for further research the small change in the values may be significant. A more detailed system based on quiescent tumor cells could be a step forward in discovering the importance of the quiescent stage.

To understand the meaning of how high or low the initial values of the different population concentrations should be, three simulations with same initial function values are tested (fig. 6.a - 6.c). Where $[T_Q(0), T_I(O), T_M(0), I(0)] = [1, 1, 1, 1]$, $[T_Q(0), T_I(O), T_M(0), I(0)] = [0.1, 0.1, 0.1, 0.1]$ and $[T_Q(0), T_I(O), T_M(0), I(0)] = [0.01, 0.01, 0.01, 0.01]$. As shown in the previous examples and model 1, the value of the cytotoxic T-cells $I(0)$ is quite important. A high starting value of tumor cells population and a low starting value of cytotoxic T-cells population will only make the tumor cells develop more. While high initial values of cytotoxic T-cells population will decrease the tumor for some time and then find a steady state for the system. In the first case where all the initial values are 1 (fig. 6.a), all three populations go towards zero. This means that even if the starting population of the tumor cells is high, the high initial value of cytotoxic T cells is able to defeat the tumor for some time and stabilize it afterwards.

By lowering the initial values to 0.1 (fig. 6.b), the quiescent cells will go towards zero, the tumor cell populations in mitosis are defeated for a very short period of time from day 0 to day 3, but then start growing again, while the interphase tumor cells will increase in population for most of the time. The cytotoxic T-cells population increase and eventually find a steady state, because they are still able to develop and divide when the population of tumor cells is so low. In the last case where all the initial values equal 0.01 (fig. 6.c), even if the starting value of cytotoxic T-cells is low, the immune system value is still able to develop in time and increase, while the tumor cells population will increase a little and find a steady state or decrease towards zero.

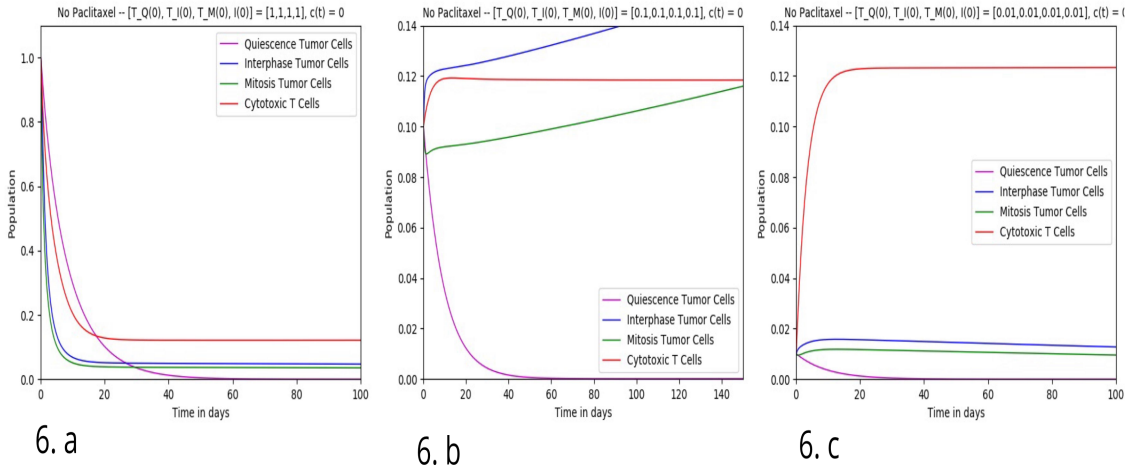


Figure 6: 6.a No Paclitaxel - all initial values 1, 6.b No Paclitaxel - all initial values 0.1, 6.c No Paclitaxel - all initial values 0.01.

From these three analyses (fig. 6.a, 6.b and 6.c) I can observe that the steady state of the cytotoxic T-cells is about 0.12. Hereby I can conclude that a normal healthy person will have an initial value of cytotoxic T-cells population around 0.12. For this I can now test how Paclitaxel will help the patient, depending on the patient's immune system.
If 0.12 is the initial value of cytotoxic T-cells for a normal healthy person, I would like to investigate how a person with an extreme immune system and a weakened immune system will react to the chemotherapy, since chemotherapy and the immune system depend on each other.

At first if the patient has an outstanding immune system the initial value of the cytotoxic T-cells population is set to 0.1488 (fig. 7.a & 7.b), while for the patient with a fragile immune system the initial value is set to 0.0912 (fig. 8.a 8.b). Fig. 7.a and 7.b show the development of the system for a healthy patient in the presence and absence of chemotherapy, respectively. In both chases the tumor cells decrease for some time. In the first case where Paclitaxel is absent the immune system defeats the tumor for a very short time and then develops by some means slowly, but when chemotherapy is present the tumor cells are defeated much faster and go towards zero.

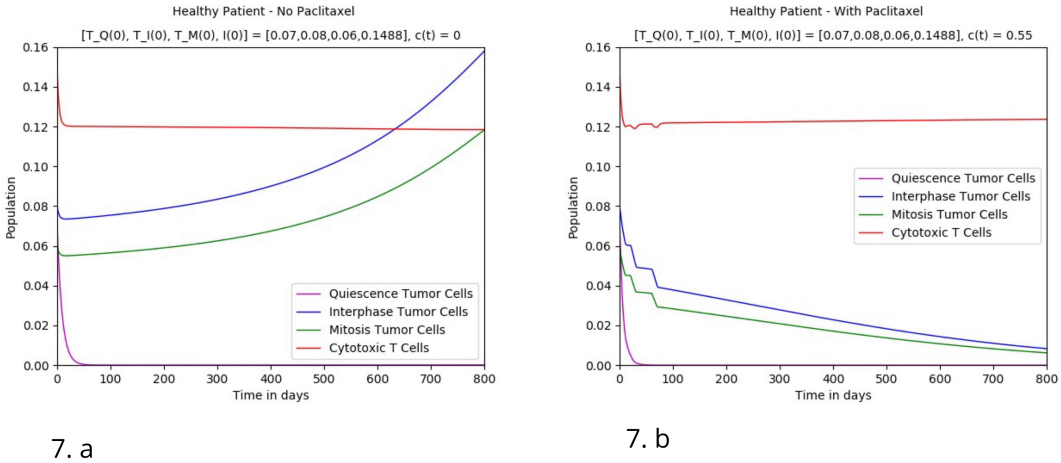
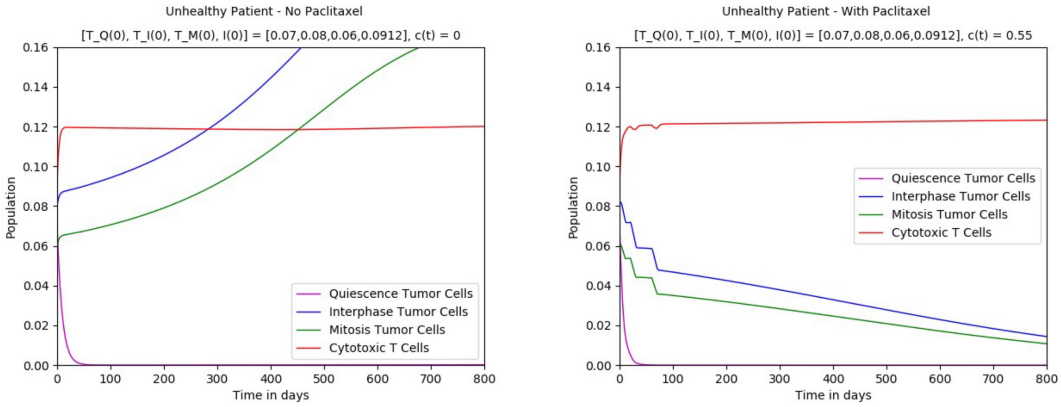


Figure 7: 7.a Patient with an extreme high immune system - No Paclitaxel, 7.b Patient with an extreme high immune system - With 3 pulses of Paclitaxel.

In fig 8.a and 8.b it is visible that the unhealthy patient cannot defeat the tumor without the presence of chemotherapy. Again, it proves how important a patient's immune system is, before any medication is taken into consideration.

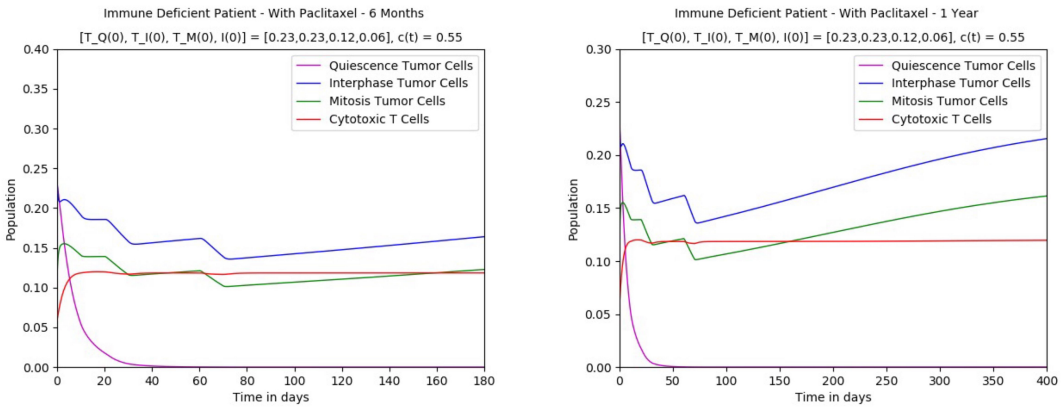


8. a

8. b

Figure 8: 8.a Patient with a weak immune system - No Paclitaxel, 8.b Patient with a weak immune system - With 3 pulses of Paclitaxel

To further understand the importance of immune system and immune deficiency the initial value of cytotoxic T-cells population is set to 0.06 (fig. 9.a & 9.b). Such a low cytotoxic T-cells population value represents an immune deficient patient, whose immune response no longer functions properly. The initial function values for the tumor cells are raised for this analysis to represent a cancerous patient in a critical stage, where $[T_Q(0), T_I(O), T_M(0), I(0)] = [0.23, 0.23, 0.12, 0.6]$ Fig 9.a and 9.b give a survey on how immune deficient patients struggle in defeating cancer with chemotherapy treatment.



9. a

9. b

Figure 9: 9.a Immune deficient patient - 6 months of Paclitaxel, 9.b Immune deficient patient - 1 year of Paclitaxel.

As we see in both analysis Paclitaxel helps for a short period of time, but because of the extremely low value of cytotoxic T-cells, the patient is not able to cooperate with the chemotherapy, because in this case the chemotherapy starts influencing the body's own cells.

5.3 Discussion based on New Studies

The models involved in this thesis have been tested for the last years and have provided numerous answers concerning tumor cells. Recently some strange characteristics of the quiescent state of tumor cells have been noticed. In almost all analysis I acquire similar response from my simulations as the previous studies mentioned throughout the thesis [7] [8] [9]. Referring to the new discoveries, none of the graphs in which quiescent tumor cells decrease consist with recent observations in patients.
It has been shown that quiescent cells should not be dependent of chemotherapeutic drugs, since they are resistant to them and no change will occur.

Studies from 2015 up to 2018 have shown that human solid tumor growth depends not only on proliferating cancer cells but also on the continuous production of slow proliferations, such as quiescent cancer cells. The second mathematical method, "Cancer Method 2", mentioned in this thesis was only based on proliferating and quiescent cells. Based on the new discoveries, method 3 is misleading. The reason for which I conclude this among other things, is because of eq. (34) that should not depend on the kill-term $u_1(t) = k_5 \cdot (1 - e^{k_6} \cdot w(t))$ caused by chemotherapeutic medication, because quiescent tumor cells are not controlled by chemotherapy. Based on the new studies, eq. (35) should not be dependent of quiescence population T_Q, but eq. (36) should. The reason for this is because quiescence cells are produced after the mitosis-phase of the proliferating tumor cells is over. Most of cancer cells proliferate very slowly or not at all within human tumors. Quiescent tumor cells should not decrease in population immediately, but remain stable for some amount of time and eventually start to increase if they escape the quiescent state and resume their cell cycle.

The quiescent tumor population in model 3 is influenced by chemotherapy due to the way the differential equation is designed. The presence of quiescent cell populations in tumors represents a major challenge in treating the disease. Quiescent tumor cells show limited sensitivity to chemotherapeutical drugs, and tend to resume proliferation, resulting in tumor reseeding and growth. It is very important to develop therapies that target these quiescent cell populations, to achieve long-lasting remission. Most human tumors are thought to depend on AKT kinase signaling, which promotes tumor growth, survival and progression. It has been discovered that proliferating cancer cells, divide into $AKT1^{low}$ daughter cells, which are slowly proliferating, tumor-initiating and chemotherapy resistant. These daughter cells are considered to be in the quiescent state of a cell-cycle. Selective depletion of $AKT1^{low}$ slow-proliferator-cells have proved to reduce the tumor growth and further studies containing AKT mutations and AKT inhibitors are expanding [32] [17] [33]. Not only that these slow-proliferator-cells are resistant to cytotoxic agents, they also promote cytotoxic stress resistance of proliferating neighbors, through non-cell autonomous communication. Quiescent tumor cells have shown survival over 4 to 6 months of chemotherapeutic drugs. When considering this, quiescent cells may be the reason why metastasis occurs [34] [35] [36]. Based on the new information, I managed to assemble another cancer method, for which I take into account the new theories mentioned above.

$$\frac{T_{QS}(t)}{dt} = a_5 \cdot T_I(t-\tau) - a_6 \cdot T_{QS}(t) - d_4 \cdot T_{QS}(t) - c_5 \cdot I(t) \cdot T_{QS}(t) \tag{46}$$

$$\frac{T_{QR}(t)}{dt} = a_5 \cdot T_I(t-\tau) - a_6 \cdot T_{QR}(t) - d_4 \cdot T_{QR}(t) - c_5 \cdot I(t) \cdot T_{QR}(t) \tag{47}$$

$$\frac{T_I(t)}{dt} = 2 \cdot a_4 \cdot T_M(t) - a_5 \cdot T_1(t-\tau) - c_1 \cdot T_I(t) \cdot I(t) - d_2 \cdot T_I(t) - a_1 \cdot T_I(t-\tau) \tag{48}$$

$$\frac{T_M(t)}{dt} = a_1 \cdot T_I(t-\tau) - d_3 \cdot T_M(t) - a_4 \cdot T_M(t) - c_3 \cdot T_M(t) \cdot I(t) + a_6 \cdot T_{QS}(t) + a_6 \cdot T_{QR}(t) - k_1 \cdot (1 - e^{k_2} \cdot w(t)) \cdot T_M(t) \tag{49}$$

$$\frac{I(t)}{dt} = k + \frac{\rho \cdot I(t) \cdot (T_{QS}(t) + T_{QR}(t) + T_I(t) + T_M(t))^n}{\alpha + (T_{QS}(t) + T_{QR}(t) + T_I(t) + T_M(t))^n} - c_2 \cdot I(t) \cdot T_I(t) - c_4 \cdot T_M(t) \cdot I(t)$$

$$- c_6 \cdot T_{QS}(t) \cdot I(t) - c_6 \cdot T_{QR}(t) \cdot I(t) - d_1 \cdot I(t) - k_3 \cdot (1 - e^{k_4} \cdot w(t)) \cdot I(t) \tag{50}$$

$$\frac{C_M(t)}{dt} = (r_m \cdot C_M(t) \cdot (1 - \frac{C_M(t)}{M_{max}})) + (q_m \cdot C_k \cdot (1 - ds) \cdot T_{QS}(t) \cdot N_t) + (q_m \cdot C_k \cdot T_{QR}(t) \cdot N_t) + (q'_m \cdot C_k \cdot C_M(t) \cdot N_t) \tag{51}$$

$w(t)$ is calculated as mentioned in model 1 (eq. 24).

The new method has substantial changes in the differential equations. Instead of one differential equation based on quiescence cells, I have now formed two equations, one containing sensitive quiescent cells (eq. 48)and the other containing resistant quiescent cells (eq. 49). The whole system includes now both the sensitive and the resistant quiescent cells.

Relative to *model* 3, three new differential functions are taken into consideration. T_{QS} describes the sensitive quiescent tumor cells, T_{QR} describes the resistant quiescent tumor cells and C_M is the metastasis tumor cells population. The drug term: $-k_5 \cdot (1 - e^{k_6} \cdot w(t))$ is not present in eq. (48) and (49), because the quiescent cells do not respond to chemotherapy or other cytotoxic agents. Even if in method 3, the patient receives chemotherapy, the mathematical model can be changed in such a way that the patient received some other medication for the quiescent tumor cells. Another thing I changed is the term $a_6 \cdot T_{QS}(t)$ and $a_6 \cdot T_{QR}(t)$, which are taken into considerations in the differential equation for mitosis(eq. 51) and not in the differential equation for interphase tumor cells(eq. 52) as in model 3(eq. 35). The reason for this is because quiescent cells have shown to go in this non-proliferating stage after mitosis and should not be dependent of the interphase, even if interphase is the longest stage. The cytotoxic T-cell differential equation (eq. 52) has been changed with two additional terms $T_{QS}(t)$ and $T_{QR}(t)$.

The last differential equation (eq.53) is a part of a study from 2016, for which I take into consideration the development of quiescent cells combined with chemotherapy and the issue that resistant quiescent cells provide. Eq. 53 has some new parameters which I obtained from the studies mentioned above, while other parameters have been determined and approximated from method 3.
C_M is the number of new metastatic cells after therapy. r_m is the metastatic growth rate. M_{max} is the maximal carrying capacity of the new metastatic cells. qm is the dissemination rate of the drug for the sensitive cancer cells, while q'_m is the dissemination rate of the drug for the resistant cancer cells. The rates depend on the existing sensitive and resistant quiescent tumor sizes. C_k is the angiogenic cell number, which describes the formation of new blood vessels, but is set to be a constant in this case. The term $(1 - ds) \cdot T_{QS}(t)$ describes the drug effect on sensitive metastatic cells. ds was also set to be a constant [37].

I only considered the last two cases analyzed for method 3 (fig 7.b and 8.b), in which we have a patient with a very strong immune system and a patient with a very weak immune system. From previous studies I achieved information for the initial values of quiescent sensitive and resistant tumor cells populations [37]. The new system established has not been examined in detail, but some of the developments of the different populations look promising. There is a slightly difference in the development of the different populations from the two patients (fig 11.a and 11.b).

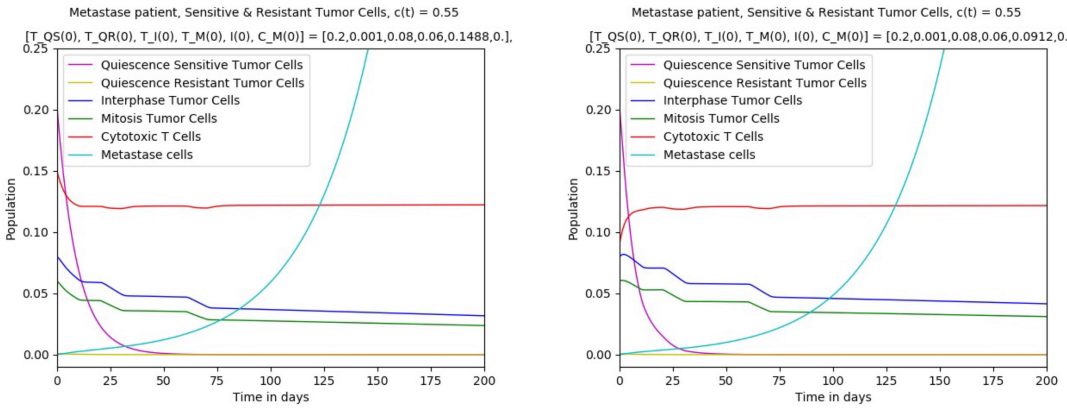


Figure 10: 11.a Patient with strong immune system & 11.b Patient with weak immune system

It is clear that the method can be considered for further research. A lot of biological perspective can be discussed based on the two figures, one of the most significant developments is the one of the quiescent sensitive tumor cells. The population of sensitive quiescent cells decreases in time, this may have a significance according to the fact that quiescent tumor cells escape the quiescent phase after some time. In association with this, the metastases cells population increases about the same time as the quiescent sensitive tumor cells reach steady state. So when the quiescent sensitive tumor cells escape the quiescent phase, a patient will experience metastasis. The reason why the metastasis cell population keeps increasing (fig 11.a and 11.b), is because the development process of the system has not stopped. Here another medicational interpretation should be applied, because metastasis T-cells have to be defeated as well. The development of interphase and mitosis tumor cells look similar, but there is already a little difference in the beginning of the graph, where the tumor cells decrease immediately for the patient with a stronger immune system. The cytotoxic T-cells find a steady state, as shown in previous models. Quiescent resistant tumor cells remain unchanged and this proves that they do not respond to chemotherapeutical drugs.

6 Conclusion & Suggestions for Future Research

There are many choices for how a cancer system should be modeled since there are numerous elements to be investigated for this topic. I observed that the early detection of cancer and a high immune system mean a lot when receiving chemotherapy. The simulations I established proved that even if chemotherapy is given, the human body cannot defeat the disease without a strong immune system. To have a deeper understanding of the way cancer cells develop, quiescent tumor cells were included in the system. The development of quiescent cells suggested in *method* 3, does not agree with the new discoveries of quiescent tumor cells growth. For this reason I experimented with a combination of *method* 3 and a new mathematical modeling of therapy-induced cancer drug resistance from 2016 [37]. The differential equation system behind the biological understanding is acceptable, but the complexity of the oncological structure is not accurate in earlier studies. This was the reason for why I attempted to describe a different system(fig 11.a and 11.b). Experimental data is necessary for a precise and complete outcome of the new model. Further research for this topic is needed in order to understand the implications of the model that I have developed. Quiescent tumor cells complicate the diagnosis and treatment of cancer patients in real life. Based on the differential equation I observed the same obstacle. A model of two different systems could be considered in further research. One of the systems containing quiescent, proliferating and Cytotoxic T cells while chemotherapy is given and the other system includes the metastases conditions mentioned above, which only start processing the data achieved from the first system after some time. The model including the tumor populations should depend both on chemotherapy, but also on terms that affect the quiescent cells, such as inhibitors.

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Appendices

A Results for Cancer Method 2

Model 2 was mentioned and taken into consideration to show the development of proliferating tumor cells in combination with quiescent tumor cells. Neither immune cells nor chemotherapy is present in this model. This means no parameters will prevent the development of cancer cells.

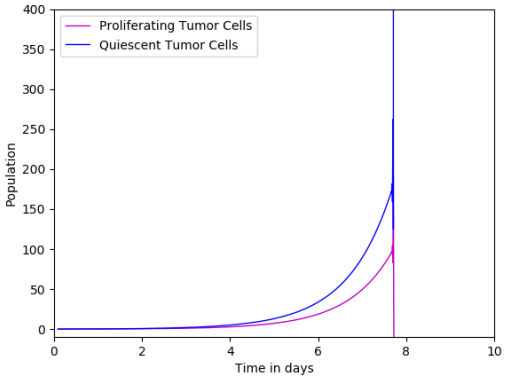

Figure 11: Model of Quiescent & Proliferating Tumor Cells

It is not clear that including quiescence cells in the model improves the understanding impact of a particular chemotherapy treatment that attacks only proliferating cells. In model 1 & model 3 chemotherapy specific parameters related to the proliferating tumor cells were present. Figure 10 does not show considerable information, beside that the combination of proliferating and quiescent cells in the absence of both the immune system and chemotherapy, only makes the two populations develop aberrant after 7 days. In biological interpretation it tells us the patient will collapse, because the tumor cells develop too fast. The figure as it looks reports an unphysical system from day 7 and forward, because the development of the quiescent tumor cells gives no biological understanding.

B Cancer Method 1 - Script

```
import numpy as np
import matplotlib.pyplot as plt
import math

# MODEL 1

# Definitions for the different population of cells

def dT_interphase_dt(list1):
# Constants dependent of the development of Interphase tumor cells
a4 = 0.8
c1 = 0.9
d2 = 0.11
a1 = 0.98

# Placement of the new calculated values
T_mitosis = list1[0]
T_interphase = list1[1]
I_cytotoxic = list1[2]
T_delay = list1[3]
```

```
# Differential equation
dT_interphase_dt = 2 * a4 *T_mitosis - c1 * T_interphase * I_cytotoxic - d2 * T_interphase - a1 *

return dT_interphase_dt

def dT_mitosis_dt(list2):

a1 = 0.98
d3 = 0.4
a4 = 0.8
c3 = 0.9
k1 = 0.47
k2 = 0.57

T_interphase = list2[0]
T_mitosis = list2[1]
I_cytotoxic = list2[2]
w_t = list2[3]
T_delay = list2[4]


dT_mitosis_dt = a1*T_delay - d3*T_mitosis - a4*T_mitosis - c3*T_mitosis * I_cytotoxic - k1*(1 - ma
return dT_mitosis_dt



def dI_cytotoxic_dt(list3):

k = 0.036  #constant birth rate of immune cells without presence of tumor cells
rho = 0.1
alfa = 0.2
c2 = 0.085
c4 = 0.085
d1 = 0.29
k3 = 0.49
k4 = 0.061
n = 3

I_cytotoxic = list3[0]
T_interphase = list3[1]
T_mitosis = list3[2]
w_t = list3[3]

#dI_cytotoxic_dt = 0

dI_cytotoxic_dt = k + ((rho*I_cytotoxic * (T_interphase + T_mitosis)**n)/(alfa+(T_interphase + T_m
return dI_cytotoxic_dt

def dw1_dt(w1):

global c

lambda1 = 126.12

dw1_dt = - lambda1 * w1 + c
return dw1_dt
```

```
def dw2_dt(w2):

global c
lambda2 = 0.85

dw2_dt = - lambda2 * w2 + c
return dw2_dt

def w_t(w1,w2):
r1 = 0.73
r2 = 0.27


w_t = r1*w1 + r2*w2
return w_t

# Runge Kutta fourth method with which we solve all the other equations

def rk4(T, T_list, y, h):

# T is the function to be propagated, feks: dT_Interphase_dt, dT_mitosis_dt etc.
# T_list is the list of results created as time passes by
# y is the value on which the T function works on
# h is the time-step

y = np.array(y)

k1_rk4 = h * T (y)
k2_rk4 = h * T (y + 0.5 * k1_rk4)
k3_rk4 = h * T (y + 0.5 * k2_rk4)
  k4_rk4 = h * T (y + k3_rk4)


  runge_kutta = (k1_rk4 + k2_rk4 + k2_rk4 + k3_rk4 + k3_rk4 + k4_rk4) / 6

return runge_kutta

# Iteration times and delay constant
time_list = []
n_steps = 16000
delay = 1


#Specify start values of the population, and taking the delay values in consideration, so for the
T_interphase_list = [1.3 for i in range(10)]  #interphase cells #y(0)
T_mitosis_list = [1.2 for i in range(10)]  #mitosis cells
I_cytotoxic_list = [0.43 for i in range(10)]  #cytotoxic cells
w1_list = [0. for i in range(10)]   #linear combination of states
w2_list = [0. for i in range(10)]   #linear combination of states
w_t_list = [0. for i in range(10)]


# Iteration in time, for which the functions are only solved after the ninth place in the list
for i in range(9,n_steps):


if 0 <= i * 0.01 <= 3 or 20 <= i * 0.01 <= 23 or 48 <= i * 0.01 <= 50 or 68 <= i * 0.01 <= 70:
c = 0.30
```

```
else:
c = 0

#c(t) = 0 if no drug
#c(t) = 1 if drug present
# h = 0.1, and represents the time step

T_interphase_rk = rk4(dT_interphase_dt, T_interphase_list,[T_mitosis_list[i], T_interphase_list[i]
T_interphase_list.append(T_interphase_list[i]+T_interphase_rk)

T_mitosis_rk = rk4(dT_mitosis_dt,T_mitosis_list,[T_interphase_list[i], T_mitosis_list[i], I_cytoto
T_mitosis_list.append(T_mitosis_list[i]+T_mitosis_rk)

I_cytotoxic_rk = rk4(dI_cytotoxic_dt, I_cytotoxic_list, [I_cytotoxic_list[i], T_interphase_list[i]
I_cytotoxic_list.append(I_cytotoxic_list[i]+I_cytotoxic_rk)

w1_rk = rk4(dw1_dt, w1_list,w1_list[i],0.01)
w1_list.append(w1_list[i]+w1_rk)

w2_rk = rk4(dw2_dt,w2_list,w2_list[i],0.01)
w2_list.append(w2_list[i]+w2_rk)

w_t_list.append(w_t(w1_list[i],w2_list[i]))

time_list.append(0.01*i)



Interphase = plt.plot(time_list,T_interphase_list[10:], 'b-', label = 'Interphase Tumor Cells', li
Mitosis = plt.plot(time_list,T_mitosis_list[10:], 'g-', label = 'Mitosis Tumor Cells', linewidth=1
Cytotoxic = plt.plot(time_list,I_cytotoxic_list[10:], 'r-', label = 'Cytotoxic T Cells', linewidth
plt.legend()
plt.title('Pulsed Paclitaxel -- [T_I(0), T_M(0), I(0)] = [1.3,1.2,0.43], c(t) = 0.30, Late', fonts
plt.xlabel('Time in days', fontsize = 10)
plt.xlim((0,160))
plt.ylabel('Population', fontsize = 10)
plt.ylim((0,1.5))
plt.savefig('model1_x4LatePulsedDrug043c030.png')
plt.show()
```

C Cancer Method 2 - Script

```
import numpy as np
import matplotlib.pyplot as plt
import math

# MODEL 2

# Definitions for the different population of cells

def dT_proliferating_dt(list1):
# The tumor becomes a malignant tumor for b > 0 and becomes benign for b < 0.
# Constants dependent of the development of Interphase tumor cells
beta = 2
u_p = 1
```

```
b = beta - u_p
r_p = 0.9
r_q = 0.5

# Placement of the new calculated values
T_proliferating_delay = list1[0]
T_proliferating = list1[1]
T_quiescence = list1[2]

# Differential equation
dT_proliferating_dt = (b * T_proliferating_delay) - (r_p * (T_proliferating + T_quiescence) * T_pr
return dT_proliferating_dt


def dT_quiescence_dt(list2):

r_p = 0.9
u_q = - 0.9
r_q = 0.5


T_proliferating = list2[0]
T_quiescence = list2[1]


dT_quiescence_dt = (r_p *(T_proliferating + T_quiescence) * T_proliferating) - (u_q * T_quiescence
return dT_quiescence_dt

# Runge Kutta fourth method with which we solve all the other equations

def rk4(T, T_list, y, h):

# T is the function to be propagated, feks: dT_Interphase_dt, dT_mitosis_dt etc.
# T_list is the list of results created as time passes by
# y is the value on which the T function works on
# h is the time-step
y = np.array(y)


k1_rk4 = h * T (y)
k2_rk4 = h * T (y + 0.5 * k1_rk4)
k3_rk4 = h * T (y + 0.5 * k2_rk4)
  k4_rk4 = h * T (y + k3_rk4)


  runge_kutta = (k1_rk4 + k2_rk4 + k2_rk4 + k3_rk4 + k3_rk4 + k4_rk4) / 6

return runge_kutta


# Iteration times and delay constant
time_list = []
n_steps = 1000
delay = 1

# Specify start values of the population, and taking the delay values in consideration, so for the
T_proliferating_list = [0.1 for i in range(10)]
T_quiescence_list = [0.1 for i in range(10)]
```

```
# Iteration in time, for which the functions are only solved after the ninth place in the list
for i in range(9,n_steps):

# h = 0.1, and represents the time step

T_proliferating_rk = rk4(dT_proliferating_dt, T_proliferating_list,[T_proliferating_list[i-delay],
T_proliferating_list.append(T_proliferating_list[i] + T_proliferating_rk)

T_quiescence_rk = rk4(dT_quiescence_dt, T_quiescence_list, [T_proliferating_list[i], T_quiescence_
T_quiescence_list.append(T_quiescence_list[i] + T_quiescence_rk)


time_list.append(0.01*i) # h steps


plt.plot(time_list,T_proliferating_list[10:], 'm-', label = 'Proliferating Tumor Cells', linewidth
plt.plot(time_list,T_quiescence_list[10:], 'b-', label = 'Quiescent Tumor Cells', linewidth=1.0)
plt.legend()
plt.xlabel('Time in days', fontsize = 10)
plt.xlim((0,10))
plt.ylabel('Population', fontsize = 10)
plt.ylim((-10,400))
plt.savefig('model2_delay.png')


plt.show()
```

D Cancer Method 3 - Script

```
import numpy as np
import matplotlib.pyplot as plt
import math

# MODEL 3

# Definitions for the different population of cells

def dT_quiescence_dt(list1):
# Constants dependent of the development of Interphase tumor cells
a5 = 0.0001
a6 = 0.00015
d4 = 0.1
c5 = 50 * 10**(-3)
k5 = 0.47
k6 = 0.57

# Placement of the new calculated values
T_delay = list1[0]
T_quiescence = list1[1]
I_cytotoxic = list1[2]
w_t = list1[3]

# Differential equation
dT_quiescence_dt = (a5 * T_delay) - (a6 * T_quiescence) - (d4 * T_quiescence) - (c5 * I_cytotoxic
```

```
return dT_quiescence_dt


def dT_interphase_dt(list2):

a4 = 0.8
c1 = 0.9
d2 = 0.11
a1 = 0.98
a5 = 0.0001
a6 = 0.00015


T_mitosis = list2[0]
T_interphase = list2[1]
I_cytotoxic = list2[2]
T_delay = list2[3]
T_quiescence = list2[4]

dT_interphase_dt = (2 * a4 *T_mitosis) - (a5 *T_delay) + (a6 * T_quiescence) - (c1 * T_interphase
return dT_interphase_dt


def dT_mitosis_dt(list3):

a1 = 0.98
d3 = 0.4
a4 = 0.8
c3 = 0.9
k1 = 0.47
k2 = 0.57


T_interphase = list3[0]
T_mitosis = list3[1]
I_cytotoxic = list3[2]
w_t = list3[3]
T_delay = list3[4]

dT_mitosis_dt = (a1*T_delay) - (d3*T_mitosis) - (a4*T_mitosis) - (c3*T_mitosis * I_cytotoxic) - (k
return dT_mitosis_dt



def dI_cytotoxic_dt(list4):

k = 0.036 #constant birth rate of immune cells without presence of tumor cells
rho = 0.1
alfa = 0.2
c2 = 0.085
c4 = 0.085
c6 = 85 * 10**(-5)
d1 = 0.29
k3 = 0.49
k4 = 0.061
n = 3 # 1 or 2

I_cytotoxic = list4[0]
```

```
T_interphase = list4[1]
T_mitosis = list4[2]
w_t = list4[3]
T_quiescence = list4[4]


dI_cytotoxic_dt = k + ((rho*I_cytotoxic * (T_quiescence + T_interphase + T_mitosis)**n)/(alfa+(T_q
return dI_cytotoxic_dt

def dw1_dt(w1):

global c
lambda1 = 126.12

dw1_dt = - lambda1 * w1 + c
return dw1_dt

def dw2_dt(w2):

global c
lambda2 = 0.85

dw2_dt = - lambda2 * w2 + c
return dw2_dt

def w_t(w1,w2):
r1 = 0.73
r2 = 0.27

w_t = r1*w1 + r2*w2
return w_t

#Runge Kutta fourth method with which we solve all the other equations

def rk4(T, T_list, y, h):

# T is the function to be propagated, feks: dT_Interphase_dt, dT_mitosis_dt etc.
# T_list is the list of results created as time passes by
# y is the value on which the T function works on
# h is the time-step
y = np.array(y)


k1_rk4 = h * T (y)
k2_rk4 = h * T (y + 0.5 * k1_rk4)
k3_rk4 = h * T (y + 0.5 * k2_rk4)
  k4_rk4 = h * T (y + k3_rk4)


  runge_kutta = (k1_rk4 + k2_rk4 + k2_rk4 + k3_rk4 + k3_rk4 + k4_rk4) / 6

return runge_kutta

# Iteration times and delay constant
time_list = []
n_steps = 18000
delay = 1
```

```
#Specify start values of the population, and taking the delay values in consideration, so for the
T_quiescence_list = [0.23 for i in range(10)]
T_interphase_list = [0.23 for i in range(10)]  #interphase cells #y(0)
T_mitosis_list = [0.12 for i in range(10)]  #mitosis cells
I_cytotoxic_list = [0.06 for i in range(10)]  #cytotoxic cells
w1_list = [0. for i in range(10)]   #linear combination of states
w2_list = [0. for i in range(10)]   #linear combination of states
w_t_list = [0. for i in range(10)]


# Iteration in time, for which the functions are only solved after the ninth place in the list
for i in range(9,n_steps):


if 0 <= i * 0.01 <= 10 or 20 <= i * 0.01 <= 30 or 60 <= i * 0.01 <= 70:
c = 0.55


else:
c = 0

#c(t) = 0 if no drug
#c(t) = 1 if drug present
#h = 0.1, and represents the time step

T_quiescence_rk = rk4(dT_quiescence_dt, T_quiescence_list, [T_interphase_list[i-delay], T_quiescen
T_quiescence_list.append(T_quiescence_list[i]+T_quiescence_rk)

T_interphase_rk = rk4(dT_interphase_dt, T_interphase_list,[T_mitosis_list[i], T_interphase_list[i]
T_interphase_list.append(T_interphase_list[i]+T_interphase_rk)

T_mitosis_rk = rk4(dT_mitosis_dt,T_mitosis_list,[T_interphase_list[i], T_mitosis_list[i], I_cytotc
T_mitosis_list.append(T_mitosis_list[i]+T_mitosis_rk)

I_cytotoxic_rk = rk4(dI_cytotoxic_dt, I_cytotoxic_list, [I_cytotoxic_list[i], T_interphase_list[i]
I_cytotoxic_list.append(I_cytotoxic_list[i]+I_cytotoxic_rk)

w1_rk = rk4(dw1_dt, w1_list,w1_list[i],0.01)
w1_list.append(w1_list[i]+w1_rk)

w2_rk = rk4(dw2_dt,w2_list,w2_list[i],0.01)
w2_list.append(w2_list[i]+w2_rk)

w_t_list.append(w_t(w1_list[i],w2_list[i]))

time_list.append(0.01*i) # h steps

Quiescence = plt.plot(time_list,T_quiescence_list[10:], 'm-', label = 'Quiescence Tumor Cells', li
Interphase = plt.plot(time_list,T_interphase_list[10:], 'b-', label = 'Interphase Tumor Cells', li
Mitosis = plt.plot(time_list,T_mitosis_list[10:], 'g-', label = 'Mitosis Tumor Cells', linewidth=1
Cytotoxic = plt.plot(time_list,I_cytotoxic_list[10:], 'r-', label = 'Cytotoxic T Cells', linewidth
plt.legend()
plt.title('[T_Q(0), T_I(0), T_M(0), I(0)] = [0.23,0.23,0.12,0.06], c(t) = 0.55', fontsize = 10)
plt.suptitle('Immune Deficient Patient - With Paclitaxel - 6 Months', fontsize = 10)
plt.xlabel('Time in days', fontsize = 10)
plt.xlim((0,180))
plt.ylabel('Population', fontsize = 10)
plt.ylim((0,0.4))
```

```
plt.savefig('model3_ImmuneDeficient6Months.png')
plt.show()
```

E New Cancer Method - Script

```
import numpy as np
import matplotlib.pyplot as plt
import math

# NEW MODEL

# Definitions for the different population of cells

def dT_quiescenceS_dt(list1):

# Constants dependent of the development of Interphase tumor cells
a5 = 0.0001
a6 = 0.00015
d4 = 0.1
c5 = 50 * 10**(-3)
k5 = 0.47
k6 = 0.57


# Placement of the new calculated values
T_delay = list1[0]
T_quiescenceS = list1[1]
I_cytotoxic = list1[2]
# w_t = list1[3]
# dT_quiescence_dt = 0

# Differential equation
dT_quiescenceS_dt = (a5 * T_delay) - (a6 * T_quiescenceS) - (d4 * T_quiescenceS) - (c5 * I_cytotox
return dT_quiescenceS_dt


def dT_quiescenceR_dt(list2):

a5 = 0.0001
a6 = 0.00015
d4 = 0.1
c5 = 50 * 10**(-3)
k5 = 0.47
k6 = 0.57

T_delay = list2[0]
T_quiescenceR = list2[1]
I_cytotoxic = list2[2]
#w_t = list2[3]


#dT_quiescence_dt = 0
dT_quiescenceR_dt = (a5 * T_delay) - (a6 * T_quiescenceR) - (d4 * T_quiescenceR) - (c5 * I_cytotox
return dT_quiescenceR_dt
```

```
def dT_interphase_dt(list3):

a4 = 0.8
c1 = 0.9
d2 = 0.11
a1 = 0.98
a5 = 0.0001
a6 = 0.00015


T_mitosis = list3[0]
T_interphase = list3[1]
I_cytotoxic = list3[2]
T_delay = list3[3]

#T_quiescence = list2[4]

dT_interphase_dt = (2 * a4 *T_mitosis) - (a5 *T_delay)- (c1 * T_interphase * I_cytotoxic) - (d2 *
return dT_interphase_dt


def dT_mitosis_dt(list4):

a1 = 0.98
d3 = 0.4
a4 = 0.8
c3 = 0.9
k1 = 0.47
k2 = 0.57
a6 = 0.00015

T_interphase = list4[0]
T_mitosis = list4[1]
I_cytotoxic = list4[2]
w_t = list4[3]
T_delay = list4[4]
T_quiescenceS = list4[5]
T_quiescenceR = list4[6]

dT_mitosis_dt = (a1*T_delay) - (d3*T_mitosis) - (a4*T_mitosis) - (c3*T_mitosis * I_cytotoxic) + (a
return dT_mitosis_dt



def dI_cytotoxic_dt(list5):

k = 0.036 #constant birth rate of immune cells without presence of tumor cells
rho = 0.1
alfa = 0.2
c2 = 0.085
c4 = 0.085
c6 = 85 * 10**(-5)
d1 = 0.29
k3 = 0.49
k4 = 0.061
n = 3 # 1 or 2
```

```
I_cytotoxic = list5[0]
T_interphase = list5[1]
T_mitosis = list5[2]
w_t = list5[3]
T_quiescenceS = list5[4]
T_quiescenceR = list5[5]


dI_cytotoxic_dt = k + ((rho*I_cytotoxic * (T_quiescenceS + T_quiescenceR + T_interphase + T_mitosi
return dI_cytotoxic_dt


def C_metastase_dt(list6):

rm = 0.03
qm = 0.035
q_m = 0.015
N_t = 1
M_max = 100
C_k = 0.1
k6 = 0.57
k5 = 0.47
d_s = 0.5

C_metastase = list6[0]
T_quiescenceS = list6[1]
T_quiescenceR = list6[2]
# w_t = list6[3]


C_metastase_dt = (rm * C_metastase * (1-(C_metastase/M_max))) + (qm * C_k * (1-d_s) * T_quiescence

# (- k5*(1 - math.exp(-k6*w_t)))
return C_metastase_dt

def dw1_dt(w1):
global c
lambda1 = 126.12

dw1_dt = - lambda1 * w1 + c
return dw1_dt

def dw2_dt(w2):

global c
lambda2 = 0.85

dw2_dt = - lambda2 * w2 + c
return dw2_dt

def w_t(w1,w2):
r1 = 0.73
r2 = 0.27

w_t = r1*w1 + r2*w2
return w_t
```

```
# Runge Kutta fourth method with which we solve all the other equations
def rk4(T, T_list, y, h):

# T is the function to be propagated, feks: dT_Interphase_dt, dT_mitosis_dt etc.
# T_list is the list of results created as time passes by
# y is the value on which the T function works on
# h is the time-step
y = np.array(y)


k1_rk4 = h * T (y)
k2_rk4 = h * T (y + 0.5 * k1_rk4)
k3_rk4 = h * T (y + 0.5 * k2_rk4)
  k4_rk4 = h * T (y + k3_rk4)


  runge_kutta = (k1_rk4 + k2_rk4 + k2_rk4 + k3_rk4 + k3_rk4 + k4_rk4) / 6

return runge_kutta

# Iteration times and delay constant
time_list = []
n_steps = 20000
delay = 1

#Specify start values of the population, and taking the delay values in consideration, so for the
T_quiescenceS_list = [0.2 for i in range(10)]
T_quiescenceR_list = [0.001 for i in range(10)]
T_interphase_list = [0.08 for i in range(10)]  #interphase cells #y(0)
T_mitosis_list = [0.06 for i in range(10)]  #mitosis cells
I_cytotoxic_list = [0.1488 for i in range(10)]  #cytotoxic cells
w1_list = [0. for i in range(10)]   #linear combination of states
w2_list = [0. for i in range(10)]   #linear combination of states
w_t_list = [0. for i in range(10)]
C_metastase_list = [0. for i in range(10)] # Metastase cells

# Iteration in time, for which the functions are only solved after the ninth place in the list
for i in range(9,n_steps):

if 0 <= i * 0.01 <= 10 or 20 <= i * 0.01 <= 30 or 60 <= i * 0.01 <= 70:
c = 0.55


else:
c = 0

#c(t) = 0 if no drug
#c(t) = 1 if drug present
# h = 0.1, and represents the time step

T_quiescenceS_rk = rk4(dT_quiescenceS_dt, T_quiescenceS_list, [T_interphase_list[i-delay], T_quies
T_quiescenceS_list.append(T_quiescenceS_list[i]+T_quiescenceS_rk)

T_quiescenceR_rk = rk4(dT_quiescenceR_dt, T_quiescenceR_list, [T_interphase_list[i-delay], T_quies
T_quiescenceR_list.append(T_quiescenceR_list[i]+T_quiescenceR_rk)

T_interphase_rk = rk4(dT_interphase_dt, T_interphase_list,[T_mitosis_list[i], T_interphase_list[i]
T_interphase_list.append(T_interphase_list[i]+T_interphase_rk)
```

```
T_mitosis_rk = rk4(dT_mitosis_dt,T_mitosis_list,[T_interphase_list[i], T_mitosis_list[i], I_cytotoc
T_mitosis_list.append(T_mitosis_list[i]+T_mitosis_rk)

I_cytotoxic_rk = rk4(dI_cytotoxic_dt, I_cytotoxic_list, [I_cytotoxic_list[i], T_interphase_list[i]
I_cytotoxic_list.append(I_cytotoxic_list[i]+I_cytotoxic_rk)

w1_rk = rk4(dw1_dt, w1_list,w1_list[i],0.01)
w1_list.append(w1_list[i]+w1_rk)

w2_rk = rk4(dw2_dt,w2_list,w2_list[i],0.01)
w2_list.append(w2_list[i]+w2_rk)

w_t_list.append(w_t(w1_list[i],w2_list[i]))

C_metastase_rk = rk4(C_metastase_dt, C_metastase_list, [C_metastase_list[i], T_quiescenceS_list[i]
C_metastase_list.append(C_metastase_list[i]+C_metastase_rk)

time_list.append(0.01*i) # h steps


QuiescenceS = plt.plot(time_list,T_quiescenceS_list[10:], 'm-', label = 'Quiescence Sensitive Tumo
QuiescenceR = plt.plot(time_list,T_quiescenceR_list[10:], 'y-', label = 'Quiescence Resistant Tumo
Interphase = plt.plot(time_list,T_interphase_list[10:], 'b-', label = 'Interphase Tumor Cells', li
Mitosis = plt.plot(time_list,T_mitosis_list[10:], 'g-', label = 'Mitosis Tumor Cells', linewidth=1
Cytotoxic = plt.plot(time_list,I_cytotoxic_list[10:], 'r-', label = 'Cytotoxic T Cells', linewidth
MetastaseSR = plt.plot(time_list,C_metastase_list[10:],'c-', label = 'Metastase cells', linewidth=
plt.legend()
plt.title('[T_QS(0), T_QR(0), T_I(0), T_M(0), I(0), C_M(0)] = [0.2,0.001,0.08,0.06,0.1488,0.], ',
plt.suptitle('Metastase patient, Sensitive & Resistant Tumor Cells, c(t) = 0.55', fontsize = 10)
plt.xlabel('Time in days', fontsize = 10)
plt.xlim((0,200))
plt.ylabel('Population', fontsize = 10)
plt.ylim((-0.01,0.25))
plt.savefig('metastase_healthypatient.png')
plt.show()
```