Optimal Control Applied In Mathematical Cancer Treatment Model

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ABSTRACT

Cancer is lethal disease, growing rapidly in most parts of the world. Treatments for cancer includes chemotherapy, radiotherapy, immunotherapy etc. The side effects of these treatments impact negatively on patient's health. Side effects can be reduced if proper control of the treatments is employed while keeping the tumor cells at low level. In this work, optimum solution to the cancer treatment is determined while side effects are minimised. Existing simple mathematical model is used to describe a hypothetical cancer patient. The selected model in this work is based on a combination of immunotherapy and anti-angiogenic treatment to a general cancer model. Two optimal control solutions based on Pontryagin's Maximum Principle are determined using different objective functions. The optimal control strategy applied is bang-bang control. Multi-objective Evolutionary Algorithms such as MODE, MOEAD, and MOPSO, are combined with the optimal control to adjust the weights in the objective functions in order to balance the cancer cells and drugs dosage minimization. The results showed that the use of anti-angiogenic is unnecessary as it was not useful in reducing the level of cancer cells. Inspired of that, the optimization lead to cancer cells minimization by using lesser amount of immunotherapy drug. Based on the results, it can be concluded that continuous administration of immunotherapy can reduce the cancer cells level.

Keywords—Cancer; Optimal Control; Immunotheraphy; Pontryagin's Maximum Principle; Multi-objective Evolutionary Algorithms

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1.0 INTRODUCTION

Cancer is a lethal disease if left untreated. At cellular level, abnormal cell divisions known as cell mutation is how cancer begins. These abnormal cells are usually called tumor or cancer cells. Tumor cells can spread to other parts of the body from where it originated. At this stage, patient survival rate is lower. There are many ways to treat cancer. Sometimes, different ways of treatment are combined together to treat cancer patients. Chemotherapy, radiotherapy, immunotherapy etc., are examples of cancer

treatment.

According to a summary of GLOBOCAN cancer statistics of the year 2020(Sung, et al., 2021), the estimated new cases of cancer were about 19.3 million and death from cancer cases were approximately 10.0 million. Female breast cancer was ranked at top in most commonly diagnosed cancer worldwide with 2.26 million of cases; lung cancer caused most death with a staggering number of 1.79 million (Ferlay, et al., 2021).

Cancer treatments can become complicated when taking in many considerations such as treatment side effects and patient overall health. Treatments that use drug to kill or fight cancer face the problem of drug resistance in which tumor cells become resistant to the drugs over time. When drug become ineffective, stronger drugs or higher dosage have to be administered to make the treatment effective again. This would impair patient's overall health and consequently leads to more serious side effects.As such, there is a need to find an optimum solution that can balance the treatment. Optimal control applied to mathematical model of cancer is one of the ways that can predict optimal drug regimen.

In this work, a simple mathematical model is used to describe a hypothetical cancer patient.The selected model in this research is using a combination of immunotherapy and anti-angiogenic treatment to a general cancer (Shi, He, & Ou, 2015). The model is simple and uses five ordinary different equations to describe the dynamic system. This model was later adopted by Bukkuri (2019) where optimal control using quadratic control in objective function was investigated. However, in the present work, linear control is analysed. Linear control with bang bangPontryagin's Maximum Principle (PMP) is more practical in cancer treatment. The problem can be solved in MATLABR2022a. The focus in this research is to balance the cancer cells and drugs dosage of the hypothetical cancer patient described by the selected mathematical model.

Immune system is the defending wall of infections and other diseases. The immune system consists of white blood cells, organs, and tissues of the lymph system. Cancer is a medical term for diseases in which the cell division is abnormal and continue without control and subsequently spreading it to other parts of the body by invading neighboring tissues(NCI Dictionaries, n.d.). Of course, cancer can lead to death if left untreated. The immunes system shall react to cancer cells as they are abnormal but in real, it does not. The immune system has to recognize the cancer cells in order to eliminate them kill the cancer cells. Cancer cells are mutated with patient's own DNA which the immune system would recognize as normal(Kelly, 2017). Furthermore, cancer cells can turn off immune cells by the protein on their surface and also modify the normal cells around to disrupt the immune system responds to cancer cells (Immunotherapy to Treat Cancer, 2019). Thismakes immune system impotent in the fight against cancer.

Cancer immunotherapy can be used as one of the cancer treatments today. Cancer immunotherapy helps immune system to fight cancer cells by making the immune system to recognize the cancer cells and kill them and restore body's response of normal anti-tumor immune (Tang, Li, Hou, & Zhu, 2020).Immunotherapy may not be widely used compared to other cancer treatments such as chemotherapy, radiotherapy, or surgery. However, there are experiments and clinical studies that have proven that immunotherapy is more advantageous than conventional cancer treatments, which can prolong progression-free survival and overall survival (Tan, Li, & Zhu, 2020). According to Cleveland

Clinic's website information on immunotherapy reviewed by a medical professional,the common types of cancer treated with immunotherapy are bladder cancers, brain cancer, breast cancer, cervical and ovarian cancer, colon cancer, head and neck cancer, kidney cancer, liver cancer, lung cancer, leukemia, skin cancer, and lymphoma (Immunotherapy, 2020).

Immunotherapy has different types. The major types are adoptive cell transfer, cancer vaccines, cytokine therapies, immune checkpoint inhibitor, and oncolytic virus therapies.Cancer vaccines trigger immune responses by utilizing tumor-specific antigens (Zhang & Zhang, 2020). In other words, this treatment works like any other vaccines, it uses patient's immune system to fight against cancer. The sources of cancer vaccines come from dead cancer cells, cancer cells protein, or immune system cells.

Immune and non-immune cells release cytokines in response to infection, inflammation, or tumorigenesis (Waldmann, 2018). Cytokines are the messengers of immune system to coordinate cellular interactions and communications. Cytokines therapies stimulate more cytokines to be released. The secreted cytokines generate potent and coordinated immune response to kill tumor cells by efficient immune signaling (Zhang & Zhang, 2020).

Immune tolerance is maintained by immune checkpoints which are molecules of coinhibitory signaling pathways(Pardoll, 2012). Cancer cells can exploit immune checkpoints to evade immunosurveillance by turning the checkpoints on or off. Immune checkpoint inhibitor are drugs that will release these checkpoints that will stop the cancer cells from harming healthy cells.

Oncolytic virus is a special type of infect that leverages genetically modified viruses to kill tumor cells. It works by augmenting systemic antitumor immunity by proinflammatory environment stimulation(Orange, Reuter, & Hobohm, 2016).

Dermatological side effects are common in using immunotherapy for cancer. A study in(Çelik, et al., 2020)haveaddressedthe dermatological side effects of oncology patients undergoing immunotherapy with immune checkpoint inhibitor and targeted therapy. This study had sixty-three oncology patients in which lung carcinoma, melanoma and colon carcinoma were the common diagnoses among the patients. Fifty patients were using targeted therapies and the rest of the thirteen patients were using immune checkpoint inhibitor. It was found that xerosis was the most common side effects among the patients, followed by acneiform rash, paronychia, eczema and pruritus. The side effects were grade 2 and 3 for most of the cases among the sixty-three patients. Furthermore, the study has also founded that psoriasis was a common side effect of immune checkpoint inhibitor.

Apart from dermatological side effects, a study in (LB Kennedy, 2020; Chhabra & Kennedy, 2021)have shown other common side effects of immune checkpoint inhibitor could also cause other common side effects such as diarrhea or colitis, hepatitis, endocrinopathies, hypothyroidism, hypophysitis, and pneumonitis. The study also includes some rare immune-related adverse effect from using immune checkpoint inhibitor. The adverse effects include neurologic toxicity, renal toxicity, ocular toxicity, cardio toxicity, and hematologic toxicity.

Optimization is to either to maximize or minimize the outcome (can be more than one objective). Optimal control can be applied on the system to find the best controls in order to get the desired maximized or minimized outcome. In mathematics, the outcome to be maximized or minimized can be

quantified by an objective functional (Moore, 2018). Optimal control can be viewed as a method to solve the mathematical model that describes a system behavior. It is not always necessary to find the optimal control from a mathematical model, it depends on what the goal is.

The goal of optimal control regimenis to find the best possible drug schedule to treat certain disease such as cancer, Human Immunodeficiency Virus (HIV) etc. In general, the mathematical model is dynamic. State variables are usually the key population cells and rate of growing or dying of the cells. The controls are generally the drugs feed to the patient, it can be chemo drug, immune booster etc. The control can be other factors that actually helps to control or cure the disease.

In(Moore, 2018), the patient is hypothetical and is treated with two different drugs. There are two different drug regimens given to this patient. The first one is feeding drugs to the patient at constant level dosage for 250 days. The other one is a predicted optimal-controlled drug regimen where the drug dosage is maximum at the beginning and gradually decreased to zero after some time. Both regimens successfully controlled the infected cells down to almost zero. However, the predicted regimen shows a better result on the recovery of "healthy cells" which is about 70% higher than the other regimen. The "healthy cell" here is referring to the CD4+ T cell which must be maintained above certain level else the patient will be considered to have the HIV transform into a more critical stage known as Acquired Immunodeficiency Syndrome (AIDS).

There are two different approaches in applying mathematics in cancer chemotherapy optimization problem. According to (Carrère, 2017; Moore, 2018), for complex system, numerical optimization is used; for simple system, theoretical optimal control is applied.

A complex system is specifically named quantitative systems pharmacology (QSP) in (Moore, 2018). A QSP model has several disadvantages over optimal control model. QSP model usually includes many interactions and currently-known mechanism in a certain setting. (Carrère, 2017) pointed out that cytotoxicity, anti-angiogenesis, toxicity for the rest of the organism, action on the immune system are usually considered in the model. Such complex model could have many parameters that are impossible to be estimated from data. Besides that, it may be very time-consuming on developing the model, and the size and scale of the system may be too large to perform optimization Best outcomes are less likely to be produced if there are too many therapies and dose level options Furthermore, complex models may be impractical for tumorbehavior prediction, and the real system's driving phenomena can be concealed. Due to these issues, (Moore, 2018) stated that QSP models are normally used to address problems such as mechanisms of action for efficacy and safety, translation of preclinical results to the clinic, and identification of new biomarkers.

Theoretical optimal approach is generally simpler with a few differential equations that describe the system behavior, and is also smaller than QSP models. This approach is used to address very specific problems that includes only the key cell populations. As such, the system describes a specific behavior that is built on a simpler model. In the later sections, there are examples of theoretical optimal models and they usually have around 2 to 4 differential equations.

In this project, optimal control based on Pontryagin's Maximum Principle was applied to a cancer treatment mathematical model extracted from (Shi, He, & Ou, 2015) and two optimal controls

with different objective functions were tested. All combination of multi-objective algorithm mixed with optimal control have shown that the use of anti-angiogenic to treat the cancer in the mathematical model was costly and inefficient as it could not give significant acceleration in bringing down the cancer cells to low level. In this work , Swarm Intelligence and Evolutionary Algorithms are hybridized with Optimal Control to further minimize the tumor and drugs. The results can be used to determine the minimum drugs required for optimum tumor reduction.

2.0 Methodology

Common Optimization Strategies in Optimal Control Problem Related to Cancer Mathematical Model

(Sweilam, et al, 2019)have done a review on strategies that are commonly applied in optimal control of cancer chemotherapy. In other words, it means different methods of solving optimal control problem in cancer chemotherapy. They have classified three general methods which are dynamic programming methods, indirect methods, and direct methods. The authors focused on comparing the direct and indirect methods.

Indirect methods are considered an easy approach. In these methods, the first step is to formulate the necessary conditions for optimality based on Pontryagin's Maximum Principle. Then, discretize it and solve it numerically. In most of the cases, the optimal control problems are usually two value boundary value problem. There are many numerical methods that can be used to applied in indirect methods to solve the optimal control problem. One of the methods is known as the forward-backward sweep methods. Such method required initial guesses of the controls and initial conditions of the states. In the first iteration, state equations can be solved by the initial guesses of the controls. Then, the adjoint/costate variables can be found from the substituting the states and controls. Finally, with all the states and adjoint/costate found, the controls can be updated accordingly. Examples of optimal control problem in cancer chemotherapy solved by forward-backward sweep method can be found in (Lenhart & Workman, 2007; Oke, et al, 2018).

Multi-Objective Optimization

Conflicting objectives is a common issue in optimization problem. As such, Vilfredo Pareto introduced multi-objective optimization to tackle this issue. The goal of multi-objective optimization is to find optimal solution from multiple objectives which allows the conflicting objectives to be compromised.

Pareto method is one of the two solutions of multi-objective problem. Pareto method applied in multi-objective problem can be written mathematically as

$$f_{1,opt} = min\, f_1(x) \quad (1)$$

$$f_{2,opt} = \min f_2(x) \quad (2)$$

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$$f_{n,opt} = \max f_n(x) \, (3)$$

Pareto method separates the elements of the solution vector during optimization. Figure 2.6 shows the mapping of the solution vector to the objective function vector.

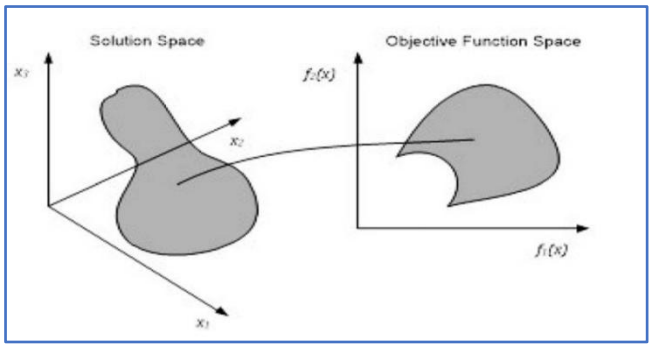

Figure 2.6: Mapping solution space and objective function space

Solutions in the objective function space will go through dominance filter to differentiate the dominated and non-dominated solutions. Generally, when one objective function cannot increase without reducing the other objective function, it becomes a dominance solution. This condition is known as Pareto optimality. Pareto optimal solution refers to the set of optimal solutions in multi-objective optimization. When one objective can be improved without reducing the other objective function, it becomes the non-dominated solution. The non-dominated solutions are referred to Pareto efficient or Pareto optimal. The collection of non-dominated solution is known as Pareto front. Figure 2.7 shows a common graph Pareto front. The optimal solution can be found from the Pareto front by choosing the closest point to the origin.

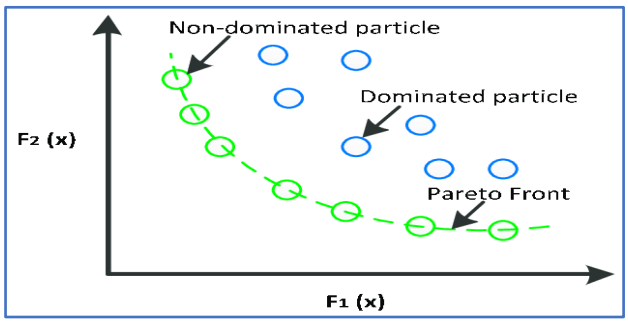

Figure 2.7: Typical example of Pareto front

Particle Swarm Optimization (PSO)

Particle Swam Optimization (PSO) is a swarm-like group of particles that move together in a certain search space looking for the optimal solution, with each particle representing a solution. The collection of all particles or the swarm, is called population. Every particle has position and velocity which are share among the entire population. The particles are guided by two sources of information: the history of the best location for each particle, denoted by p^{best}, and the history of the best position for the

entire population, denoted by g^{best}. Velocity of the particles are adjusted to change their corresponding the speed and direction. Guides are updated every time the particles reach a new position. Until this stage, one iteration is completed. The iteration will start over until a termination condition is reached (Kennedy & R., 1995).

MOPSO algorithms is based on the PSO algorithm. The particle flight path in MOPSO is determined by Pareto Dominance, and the previously best solutions are saved as non-denominated vectors that other particles use to steer their own flight to the best non-denominated solution.

Evolutionary Algorithms (EA)

EA is another population-based algorithm like PSO. All members in the population are evaluated to find the fitness that can be used to rank each solution among the population. The population's best individuals are identified, and the information from this population is used to create a new generation of people. At this stage, one iteration is completed. The iteration will start over until a termination condition is reached.

MODE and MOEAD algorithms are based on EA. The difference in between these two algorithms is that MODE uses differential evolution whereas MOEAD uses EA based on decomposition.

Swarm Intelligence and Evolutionary Algorithms with Optimal Control

Multi-objective optimization based on EA and SI was hybridized with optimal control theory based on Pontryagin's Maximum Principle to optimize cancer treatment mathematical model in which chemotherapy is used. Since, the objectives to minimize the chemotherapy drug and cancer cells are conflicting with each other, thus, multi-objective approach is adopted. The SI and EA such as MODE, MOEAD, and MOPSO was used to optimize the cancer cells and the drug. The results have shown that such methodology is superior toPSI (Particle Swarm Intelligence)and EA methodologies and consume significantly less computational time.

Objective Function (1)

In this section, the optimal control problem is reformulated by applying linear control with maximizing objective functional. By modifying the objective functional in (Bukkuri, 2019), the reformulated objective functional $J_{opt\,1}$ is as shown below. The approach of solving this optimal control problem is to apply Pontryagin's Maximum Principle.

$$MAX\, J_{opt\,1}(u_{imm}, v_{ang}) = \int_0^{T_f} \left(A_1 v(t) + A_2 x(t) - A_3 u_{imm}(t) - A_4 v_{ang}(t) - A_5 y(t)\right) dt \quad (4)$$

$$subjected\ to\ system\ (3)$$

$$where x(0) = 0.8; y(0) = 0.0006; z(0) = v(0) = 0 \quad (5)$$

The Hamiltonian of the optimal control problem is

$$H = \begin{cases} A_1 v(t) + A_2 x(t) - 0.5A_3 u_{imm}(t) - 0.5A_4 v_{ang}(t) - A_5 y(t) + \\ \lambda_x(\alpha_1 x(1-x) - q_1 xy) + \\ \lambda_y\left(\alpha_2 y\left(1 - \frac{y}{1+\gamma z}\right) - q_2 xy - q_3 yv + p_2 yz\right) + \\ \lambda_z\left(\beta y + \alpha_3 z(1-z) - \frac{p_5 zw}{a_3 + z}\right) + \\ \lambda_v(u_{imm} S_1 + ry - d_4 v) + \\ \lambda_w\left(v_{ang} S_2 - \frac{p_5 zw}{a_3 + z} d_5 w\right) \end{cases} \quad (6)$$

The costate equations are

$$\frac{\partial H}{\partial x} = \frac{d\lambda_x}{dt} = \left(A_2 + \lambda_x(\alpha_1(1-2x) - q_1 y) - \lambda_y q_2 y\right) \quad (7)$$

$$\frac{\partial H}{\partial y} = \frac{d\lambda_y}{dt} = \left(-A_5 - \lambda_x q_1 x - \lambda_y\left(\alpha_2\left(1 - \frac{2y}{1+\gamma z}\right) - q_2 x - q_3 v + p_2 z\right) - \lambda_z \beta - \lambda_v r\right) \quad (8)$$

$$\frac{\partial H}{\partial z} = \frac{d\lambda_z}{dt} = \left(\lambda_y\left(\frac{\alpha_2 y^2 \gamma}{(\gamma z+1)^2} + y p_2\right) - \lambda_z\left(\alpha_3(1-2z) - \frac{a_3 p_3 w}{(a_3+z)^2}\right) - \lambda_w\left(-\frac{a_3 p_5 w}{(a_3+z)^2}\right)\right) \quad (9)$$

$$\frac{\partial H}{\partial v} = \frac{d\lambda_v}{dt} = \left(A_1 - \lambda_y q_3 y - \lambda_v d_4\right) \quad (10)$$

$$\frac{\partial H}{\partial w} = \frac{d\lambda_w}{dt} = \left(\lambda_z\left(\frac{p_3 z}{a_3+z}\right) - \lambda_w\left(\frac{p_5 z}{a_3+z} + d_5\right)\right) \quad (11)$$

The optimality condition yields

$$\frac{\partial H}{\partial u_{imm}} = \lambda_v S_1 - A_3 \quad (12)$$

$$\frac{\partial H}{\partial v_{ang}} = \lambda_w S_2 - A_4 \quad (13)$$

The transversality condition yields

$$\lambda_x(T_f) = \lambda_y(T_f) = \lambda_z(T_f) = \lambda_v(T_f) = \lambda_w(T_f) = 0 \quad (14)$$

Objective Function (2)

In this section, the optimal control problem is reformulated by applying linear control with minimizing objective functional. The reformulated objective functional $J_{opt\,2}$ is as shown below. The approach of solving this optimal control problem is to apply Pontryagin's Maximum Principle.

$$MIN\ J_{opt\,2}(u_{imm}, v_{ang}) =$$

$$\int_0^{T_f}\left(A_1 y(t) + A_2 u_{imm}(t) + A_3 v_{ang}(t)\right) dt \quad (15)$$

$$subjected\ to\ system\ (3)$$

$$where\ x(0) = 0.8; y(0) = 0.0006; z(0) = v(0) = 0 \quad (16)$$

The Hamiltonian of the optimal control problem is

$$H = \begin{cases} A_1 y(t) + A_2 u_{imm}(t) + A_3 v_{ang}(t) + \\ \lambda_x(\alpha_1 x(1-x) - q_1 xy) + \\ \lambda_y\left(\alpha_2 y\left(1 - \frac{y}{1+\gamma z}\right) - q_2 xy - q_3 yv + p_2 yz\right) + \\ \lambda_z\left(\beta y + \alpha_3 z(1-z) - \frac{p_5 zw}{a_3 + z}\right) + \\ \lambda_v(u_{imm} S_1 + ry - d_4 v) + \\ \lambda_w\left(v_{ang} S_2 - \frac{p_5 zw}{a_3 + z} d_5 w\right) \end{cases} \quad (17)$$

The costate equations are

$$-\frac{\partial H}{\partial x} = \frac{d\lambda_x}{dt} = -\left(\lambda_x(\alpha_1(1-2x) - q_1 y) - \lambda_y q_2 y\right) \quad (18)$$

$$-\frac{\partial H}{\partial y} = \frac{d\lambda_y}{dt} = -\left(-A_1 - \lambda_x q_1 x - \lambda_y\left(\alpha_2\left(1 - \frac{2y}{1+\gamma z}\right) - q_2 x - q_3 v + p_2 z\right) + \lambda_z \beta + \lambda_v r\right) \quad (19)$$

$$-\frac{\partial H}{\partial z} = \frac{d\lambda_z}{dt} = -\left(\lambda_y\left(\frac{\alpha_2 y^2 \gamma}{(\gamma z+1)^2} + y p_2\right) + \lambda_z\left(\alpha_3(1-2z) - \frac{a_3 p_3 w}{(a_3+z)^2}\right) + \lambda_w\left(-\frac{a_3 p_5 w}{(a_3+z)^2}\right)\right) \quad (20)$$

$$-\frac{\partial H}{\partial v} = \frac{d\lambda_v}{dt} = -\left(-\lambda_y q_3 y - \lambda_v d_4\right) \quad (21)$$

$$-\frac{\partial H}{\partial w} = \frac{d\lambda_w}{dt} = -\left(\lambda_z\left(\frac{p_3 z}{a_3+z}\right) - \lambda_w\left(\frac{p_5 z}{a_3+z} + d_5\right)\right) \quad (22)$$

The optimality condition yields

$$0 = \frac{\partial H}{\partial u_{imm}} = \lambda_v S_1 + A_2 \quad (23)$$

$$0 = \frac{\partial H}{\partial v_{ang}} = \lambda_w S_2 + A_3 \quad (24)$$

The transversality condition yields

$$\lambda_x(T_f) = \lambda_y(T_f) = \lambda_z(T_f) = \lambda_v(T_f) = \lambda_w(T_f) = 0 \quad (25)$$

Multi-Objective Problem

Different set of weight in the objective function can yield different results for the controls and states. For certain sets of weight, cancer cells can be significantly reducedbut at the high cost of using too much of drugs. For such reason, multi-objective problem can be established to find out the best weights in the objective functions that can give a reasonable compromise between the drugs and cancer/normal cells.

The multi-objective problem for both the objective function 1 and 2 have three objectives which

are

a. minimize cancer cells
b. minimize amount of immune drug
c. minimize amount of anti-angiogenic drug

Three different multi-objective algorithms were used to solve the multi-objective problem which are MODE, MOEAD, and MOPSO. Then, the best results generated among these three algorithms were chosen.

Algorithm of the Optimal Control Problem 1 and 2

The flow chart in Figure 1 shows the steps of using forward-backward scheme to solve the optimal control problem 1 and 2 by applying Pontryagin's Maximum Principle. The time span for both optimal control 1 and optimal control 2 are 1700 days.

Since that optimal control 1 and optimal control 2 are formulated using Pontryagin's Maximum Principle, forward-backward scheme was applied to solve the problems. Note thatsingular arc is not an issue. To apply forward-backward scheme, initial guesses of the controls must be made and initial condition for the state variables have to be determined. The final conditions of the costate variables are determined by transversality condition. With these, the control initial guesses can be substitute into the system of ordinary differential equation of state variables and solve for the state variables forward in time. Then, the state variables found can be substitute into the system of ordinary differential equation of costate variables and solve for the costate variables backward in time. The solved costate variables can be substituted into switching functions to update the controls. At this stage, one iteration is completed, and the algorithm shall check for the termination condition to decide whether it should proceed to next iteration or end the process. The updated controls are carried forward to the next iteration.

The termination condition was supposed to be the error of the difference in between the current iteration objective function cost and the previous iteration objective function cost lies within the error tolerance. However, for some reasons, the cost of the objective functions may not converge or takes too many iterations to converge, thus, a maximum iteration may be set as a second termination conditions. As such, the termination condition of this algorithm was set to 3 iterations. The reason of selecting 3 iterations as the termination condition was to reduce the computational time of the multi-objective algorithms.

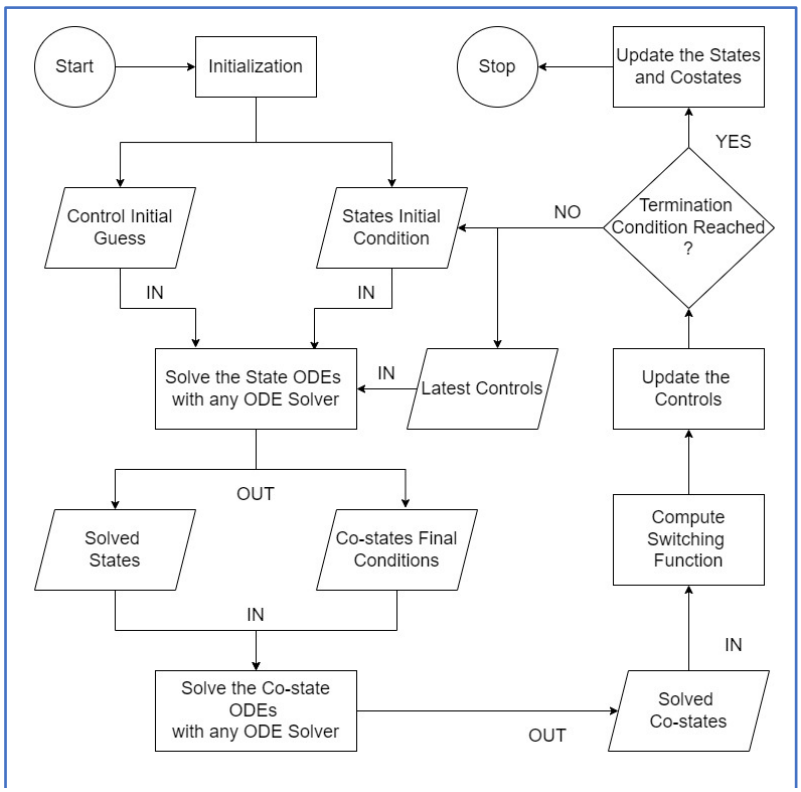

Figure 1: Simplified flow chart of solving the optimal control problem 1 and 2

Multi-Objectives Algorithms

The multi-objective algorithms were used for finding the best possible weight constants of optimal control 1 and optimal control 2 so that the three objectives are balanced. In all the algorithms, weight constants are the variables (it is known as population in the algorithm) and the outputs are total amount of immune drug, total amount of anti-angiogenic drug, and total amount of cancer cells. Such approach is the combination of multi-objective optimization and optimal control.

The termination condition is the maximum number of iterations, it has been set to 50 for all algorithms so that fair comparisons can be made among the algorithms. 50 iterations may be less or not enough, but it can shorten the computational time.

Figure 2 shows the flow chart of MODE algorithm. After the initialization process, DE algorithm will generate a number sets of weight constant. Then, the sets of weight constant generated from DE are inserted into the optimal control 1 or optimal control 2 to solve for the total amount of immune drug, anti-angiogenic drug, and cancer cells, these three values are the output of the optimal control function. Population selection will select the proper sets of weight constants based on the outputs from the optimal control function. After that, necessary data in the current iteration will be recorded. At this stage, an iteration is completed. If the termination condition is not reached, the next iteration will begin. If the termination condition has reached, a dominance filter will be applied to the sets of weight constants generated from the DE algorithm in the last iteration to get the pareto front and pareto set. Lastly, all the data recorded in all iterations, pareto front, and pareto set will be save as a *.mat* file.

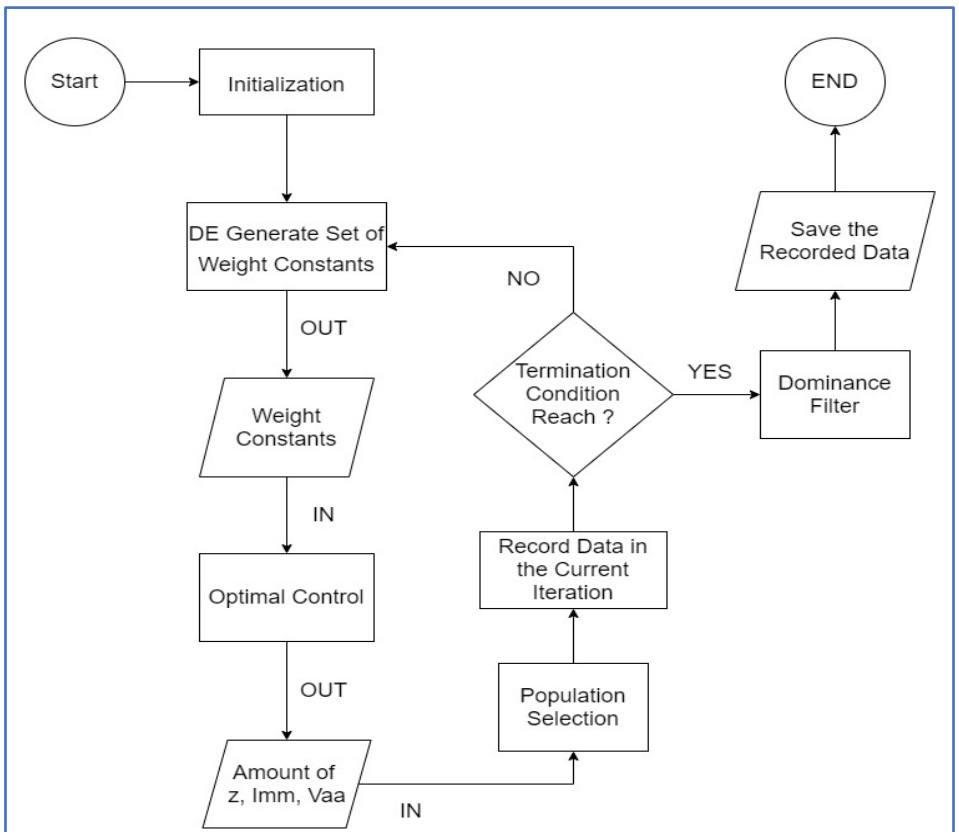

Figure2: Simplified flow chart of MODE algorithm

Figure 3 shows the flow chart of MOEAD algorithm. After the initialization process, EA algorithm will generate a number sets of weight constant. Then, the sets of weight constant generated from EA are inserted into the optimal control 1 or optimal control 2 to solve for the total amount of immune drug, anti-angiogenic drug, and cancer cells, these three values are the output of the optimal control function. Population decomposition will decompose the sets of weight constants based on the outputs from the optimal control function. Dominance filter is then applied to the decomposed sets of weight constants and update the pareto front and pareto set in the repository. Then, all necessary data in the current iteration will be recorded. At this stage, an iteration is completed. If the termination condition is not reached, the next iteration will begin. If the termination condition has reached, all the data recorded in all iterations, pareto front, and pareto set will be save as a *.mat* file.

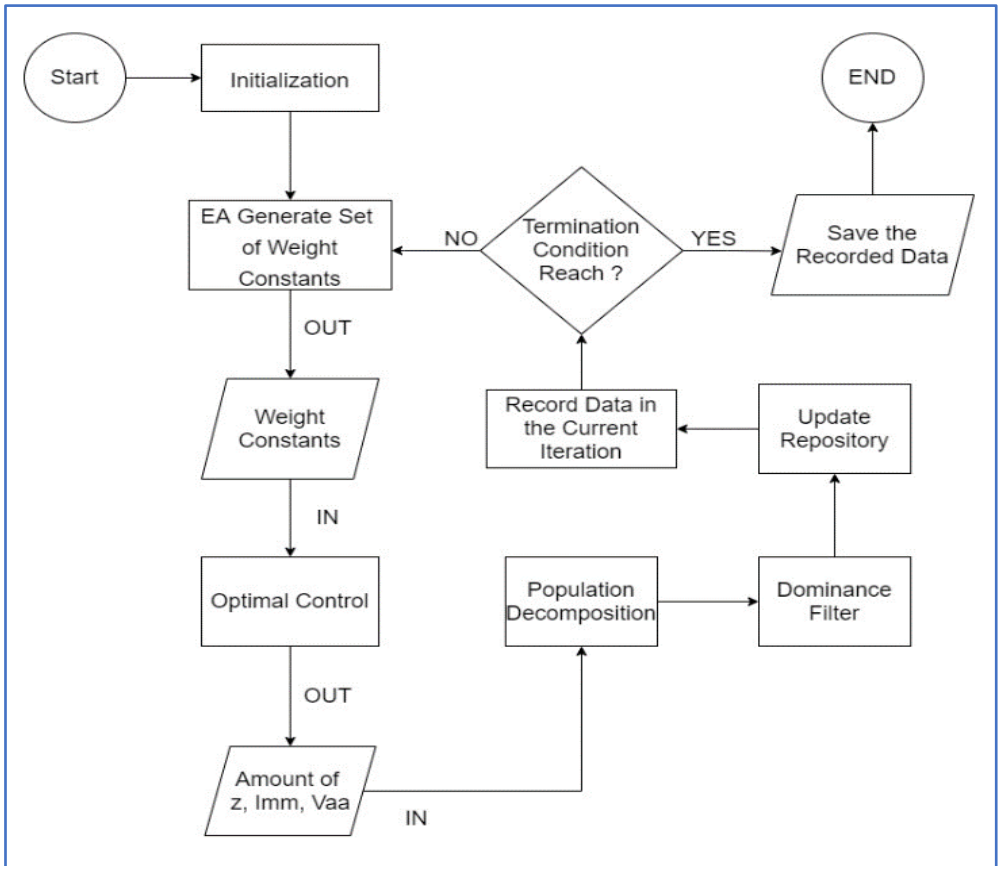

Figure3: Simplified flow chart of MOEAD algorithm

Figure 4 shows the flow chart of MOPSO algorithm. After the initialization process, EA algorithm will generate a number sets of weight constant. Then, the sets of weight constant generated from PSI are inserted into the optimal control 1 or optimal control 2 to solve for the total amount of immune drug, anti-angiogenic drug, and cancer cells, these three values are the output of the optimal control function. Population mutation will mutate the sets of weight constants based on the outputs from the optimal control function. Dominance filter is then applied to the decomposed sets of weight constants and update the pareto front and pareto set in the repository. Then, all necessary data in the current iteration will be recorded. At this stage, an iteration is completed. If the termination condition is not reached, the next iteration will begin. If the termination condition has reached, all the data recorded in all iterations, pareto front, and pareto set will be save as a *.mat* file.

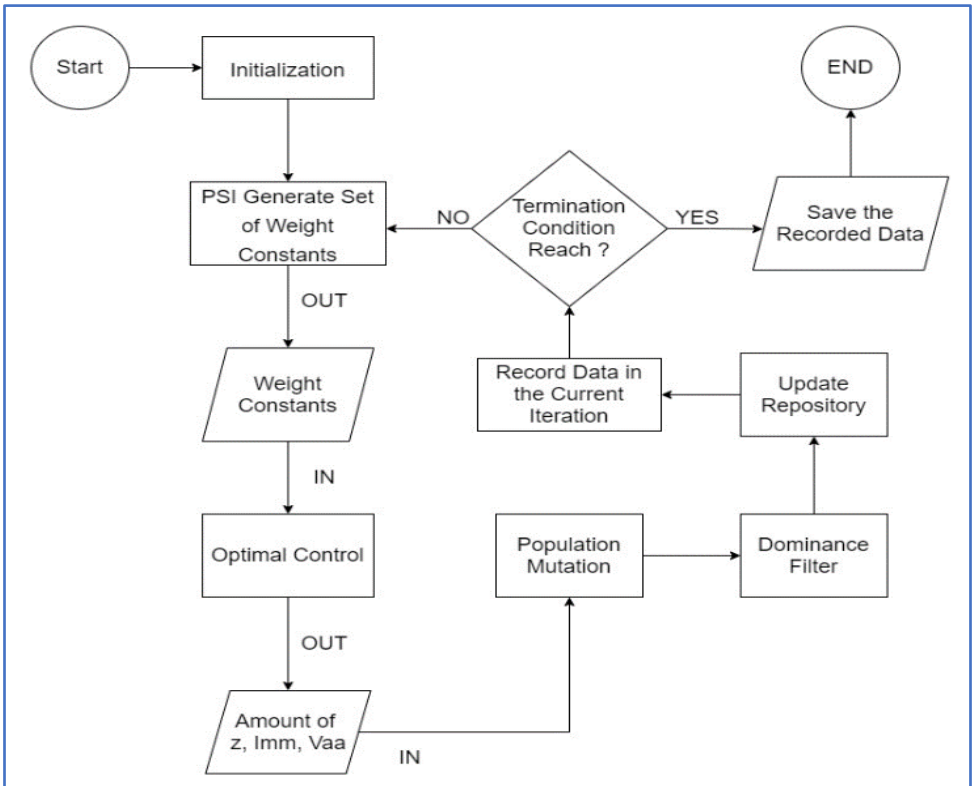

Figure4: Simplified flow chart of MOPSO algorithm

Repository for storing pareto front and pareto set were used in the MOEAD and MOPSO algorithm. The benefit of using the repository is that it can store deleted points for the pareto front and pareto set up to a certain number defined by the programmer. Besides that, increasing the number of points in the repository may have wider range for the pareto front and pareto set. MODE algorithm did not make use of the repository because it was coded from different author whereas MOEAD and MOPSO algorithm were coded by the same author.

Changes to the MODE algorithm can be made to fit in the feature of repository but it involves complicated coding. Insufficient knowledge in DE algorithm and the lack of skills in writing MATLAB codes may altered how the DE algorithm should work. Hence, the MODE algorithm is not modified to fit the repository feature.

Parameters of the Multi-Objective Algorithms

Table 1, Table 2, and Table 3shows the parameters used in MODE, MOEAD, and MOPSO respectively. Optimal control 1 and optimal control 2 shared the same parameters for all the multi-objective algorithms. Certain parameters are equal in all multi-objective algorithms for fair comparison among the algorithms.

Table 1: MODE Parameters

Parameter	Value
Maximum number of iterations	50
Population Size	50
Crossover Probability	0.2
Scaling Factor	0.5
Function Evaluations Bound	2500
Minimum Decision Variable	$1x10^{-6}$
Maximum Decision Variable	1

Table 2: MOEAD Parameters

Parameter	Value
Maximum number of iterations	50
Population Size	50
Archive Size	250
Crossover Probability	0.5
Minimum Decision Variable	$1x10^{-6}$
Maximum Decision Variable	1

Table 3: MOPSO Parameters

Parameter	Value
Maximum number of iterations	50
Population Size	50
Repository Size	250
Inertia Weight	0.5
Inertia Damping Weight	0.99
Personal Learning Coefficient	1
Global Learning Coefficient	2
Number of Grids per Dimension	7
Inflation Rate	0.1
Leader Selection Pressure	2
Deletion Selection Pressure	2
Mutation Rate	0.1
Minimum Decision Variable	$1x10^{-6}$
Maximum Decision Variable	1

Executing the Multi-Objective Algorithms Mixed with Optimal Controls

Everything was simulated and solved in MATLAB. The source codes of all the multi-objective algorithms are open source and they were obtained from the internet. The source code references are shown in Table 4.The codes are all written in MATLAB scripts. Slight modifications were made on each code, but original algorithmswere not altered.

Table 4: Multi-Objective Algorithm Source Code References

Algorithm	Reference
MODE	(Reynoso-Meza, 2012)
MOEAD	(Heris, Yarpiz, 2015)
MOPSO	(Heris, Yarpiz, 2015)

3.0 Results and Discussion

Plots of Optimal Control 1 with Different Multi-Objective Algorithm

Figure 5 shows the point with closest distance to the origin of three different multi-objective algorithms mixed with optimal control 1 in each iteration. MOEAD algorithm is the fastest to converge, followed by MODE, then MOPSO.Note that the meaning of shortest Euclidean distance and closest distance to the origin are the same.

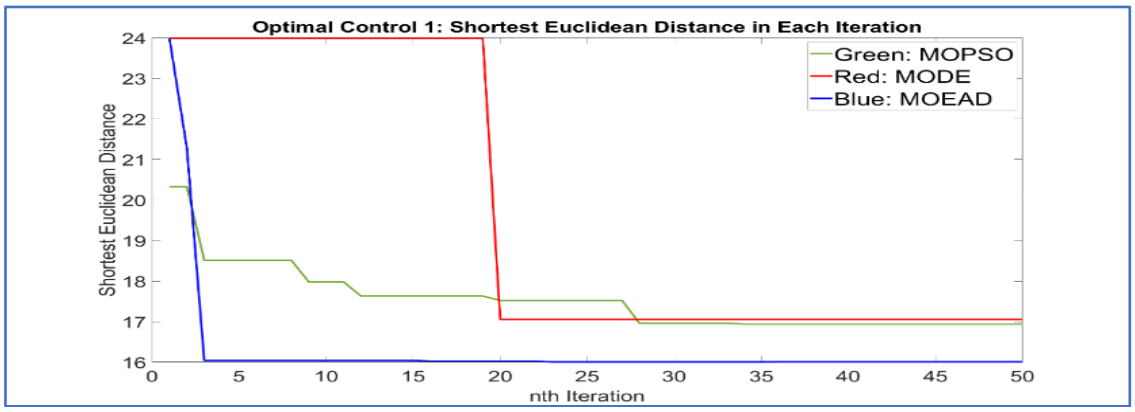

Figure 5: Closest distance to the origin of three different multi-objective algorithms mixed with optimal control 1

Figure 6 shows the 3-dimensional pareto front of three different multi-objective algorithms mixed with optimal control 1. MOPSO algorithm has the largest coverage of pareto front. MOEAD'spareto front has a saturated curve along the cancer cell axis and immune drug axis. MODE's pareto front is showing similar results with MOEAD's but some of the points lie at the inner conner of the plotting space as shown in Figure 6. The lines in three different colours show the points closest to the origin of the three different algorithms. All points closest to origin from the three algorithms suggest that the use of anti-angiogenic is unnecessary.

Figure 7 shows the 2-dimensional pareto front of three different multi-objective algorithms mixed with optimal control 1. The graph of anti-angiogenic versus immune drug does not show any relationship in between these two drugs. However, in the graph of anti-angiogenic versus immune drug, all solutions of MODE suggest the use of anti-angiogenic is unnecessary, and almost of solutions of MOEAD suggest the use of anti-angiogenic is unnecessary. The graph of cancer cells versus anti-angiogenic drug could not tell any useful information. The graph of cancer cells versus immune drug has shown that MOPSO algorithm is able to produce typical pareto front curve; MODE algorithm is also

able to produce a similar curve to that of MOPSO, but the coverage is not that wide as MOPSO; MOEAD algorithm solutions are almost all suggesting high dosage of immune drug to suppress the cancer cells. Based on the graph of cancer cells versus immune drug, it can be concluded that during the time span of 1700 days, 15 to 16 amount immunotherapy drug is effective in bringing the cancer cells down to low level.

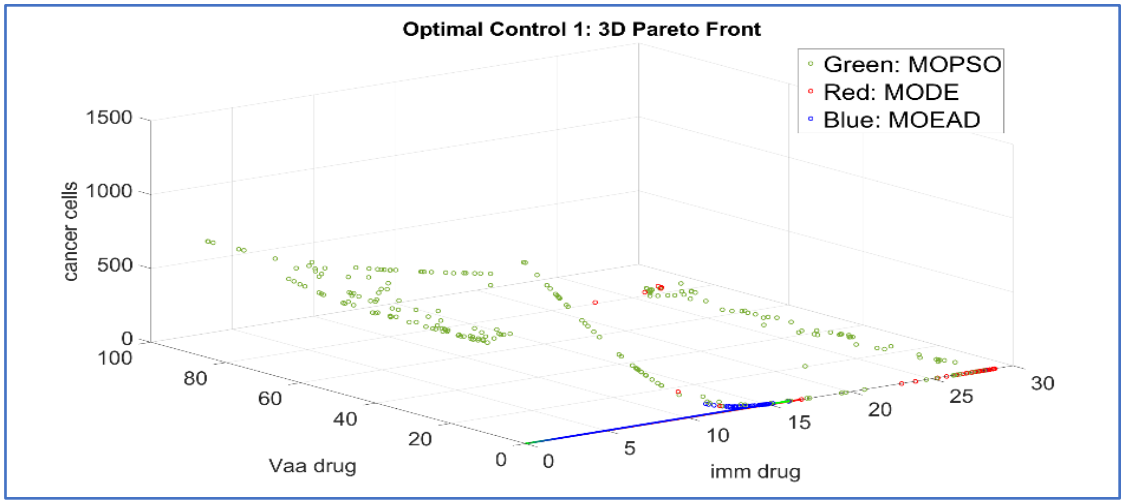

Figure 6: 3-dimensional pareto front of three different multi-objective algorithms mixed with optimal control 1

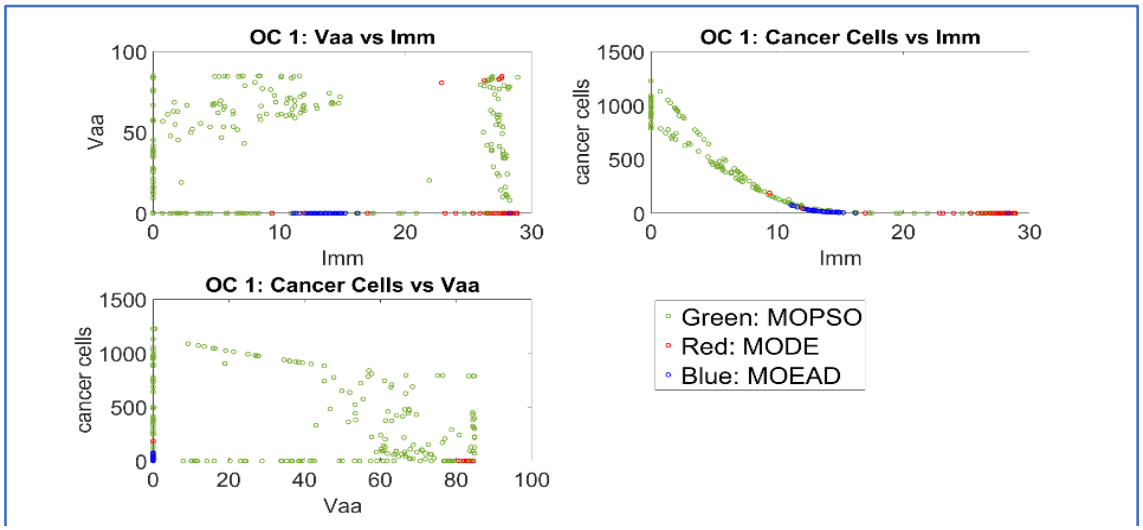

Figure 7: 2-dimensional pareto of three different multi-objective algorithms mixed with optimal control 1 (OC: Optimal; Vaa: Anti-Angiogenic Drug; Imm: Immune Drug)

Plots of Optimal Control 2 with Different Multi-Objective Algorithm

Figure 8 shows the point with closest distance to the origin of three different multi-objective algorithms mixed with optimal control 2 in each iteration. MOEAD algorithm is the fastest to converge, followed by MOPSO, then MODE. Note that the meaning of shortest Euclidean distance and closest distance to the origin are the same.

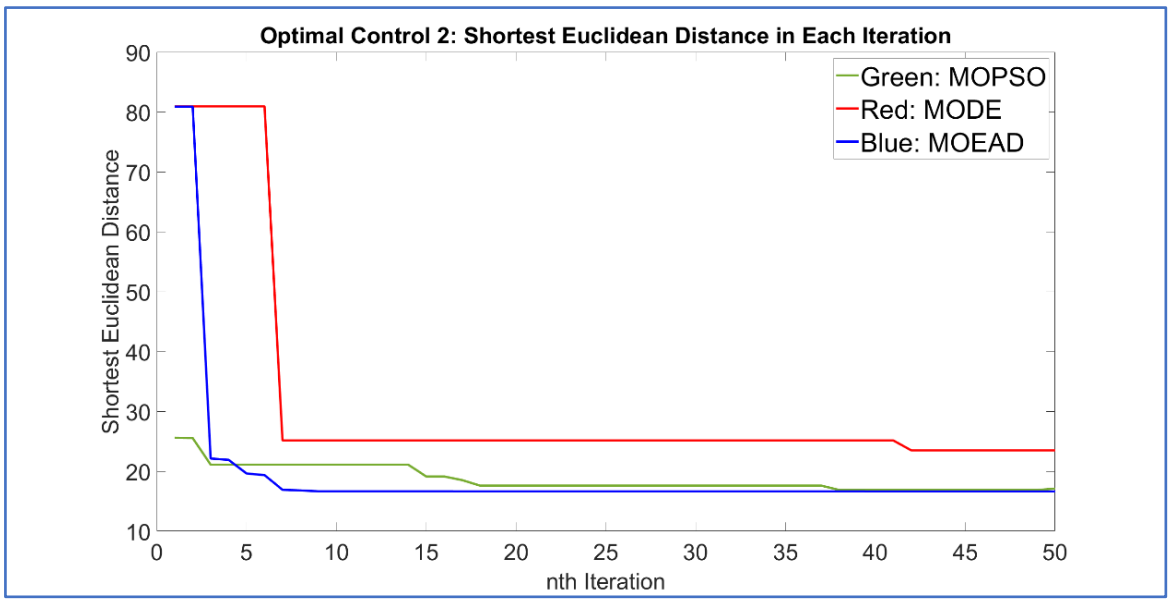

Figure 8: Closest distance to the origin of three different multi-objective algorithms mixed with optimal control 2

Figure 9 shows the 3-dimensional pareto front of three different multi-objective algorithms mixed with optimal control 2. MOPSO algorithm has the largest coverage of pareto front. Part of MOEAD's pareto front has a saturated curve along the cancer cell axis and immune drug axis whereas other part is scattered near the center of the three-dimensional space as in Figure 9. Major part of MODE's pareto front lie at the inner conner of the plotting space as shown in Figure 6. The lines in three different colours show the points closest to the origin of the three different algorithms. All points closest to origin from the three algorithms suggest that the use of anti-angiogenic is unnecessary.

Figure 10 shows the 2-dimensional pareto front of three different multi-objective algorithms mixed with optimal control 1. The graph of anti-angiogenic versus immune drug does not show any relationship in between these two drugs. However, in the graph of anti-angiogenic versus immune drug, most of the solutions from MODE suggest the combination of immune drug and anti-angiogenic drug is necessary, and almost of solutions of MOEAD suggest the use of anti-angiogenic is unnecessary. The graph of cancer cells versus anti-angiogenic drug could not tell any useful information. The graph of cancer cells versus immune drug has shown that MOPSO algorithm is able to produce typical pareto front curve; MODE algorithm is also able to produce a similar curve to that of MOPSO, but the coverage is not that wide as MOPSO; MOEAD algorithm solutions are almost all suggesting high dosage of immune drug to suppress the cancer cells. Based on the graph of cancer cells versus immune drug, it can be concluded that during the timespan of 1700 days, 15 to 16 amount immunotherapy drug is effective in bringing the cancer cells down to low level.

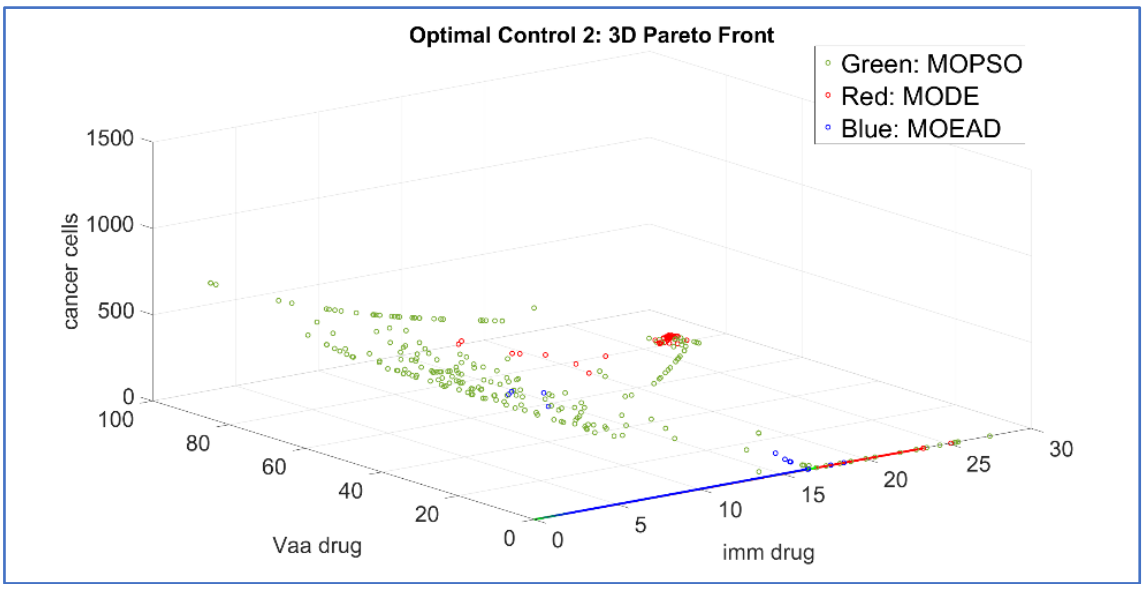

Figure 9: 3-dimensional pareto front of three different multi-objective algorithms mixed with optimal control 2

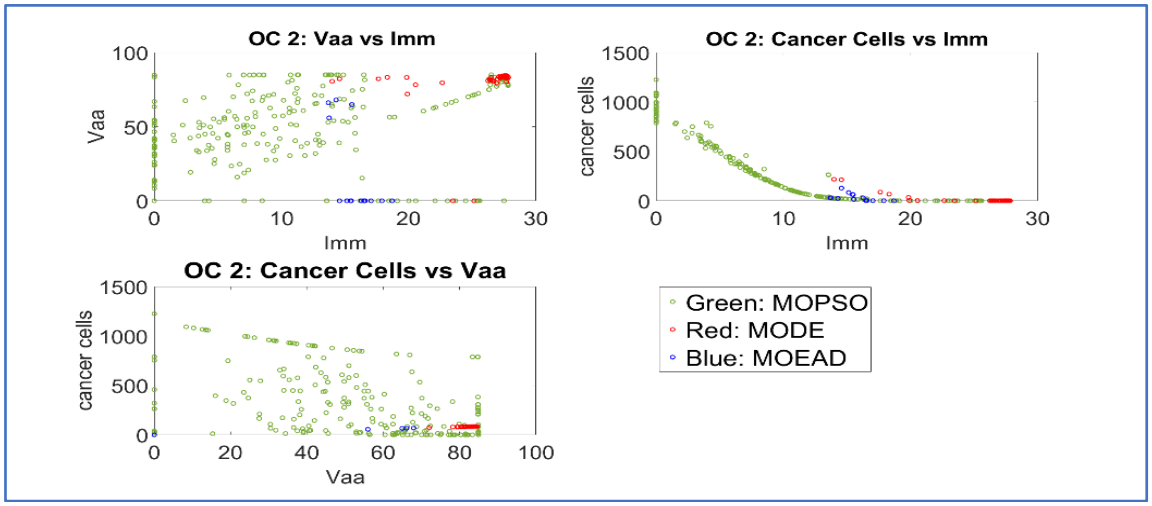

Figure 10: 2-dimensional pareto front of three different multi-objective algorithms mixed with optimal control 2 (OC: Optimal Control; Vaa: Anti-Angiogenic Drug; Imm: Immune Dru

Results Summary of Multi-Objective Algorithms Mixed with Optimal Controls

Table 5 shows all the necessary information (for comparison) obtained from three different multi-objective algorithms mixed with optimal control 1 and optimal control 2. All the values in Table 5are extracted in the last iteration of all the simulations of multi-objective mixed with optimal control.

Table5: Results obtained from all simulations of multi-objective mixed with optimal control

	MODE		MOEAD		MOPSO	
	Optimal Control 1	Optimal Control 2	Optimal Control 1	Optimal Control 2	Optimal Control 1	Optimal Control 2

Distanceof Closest Point to Origin	17.0538	23.4844	16.0065	16.6254	16.9378	17.1003
Convergence of Distance of Closest Point to Origin in 50 Iteration	20 (1.1755 hours)	42 (3.0715 hours)	36 (2.0782 hours)	40 (2.0039 hours)	34 (1.9606 hours)	Did not converge
Total Amount Immunotherapy Drug	16.9787	23.4813	15.2277	16.4857	16.2987	17.0297
Total Amount Anti-Angiogenic Drug	0	0	0	0	0	0
Total Amount of Cancer Cells	1.5985	0.3824	4.9319	2.1507	4.6088	1.5522
Total Time Consumed for Simulation (hour)	2.9387	3.6566	2.8864	2.5049	2.8833	2.5505
3D Hypervolume (normalized)	0.9923	0.9886	0.9918	0.9898	0.9969	0.9967

MODE algorithm mixed with optimal control 2 performed the worst in finding the closest distance to the origin.Distance of closest point to the origin from the rest of the multi-objective algorithms mixed with optimal controls have shown similar results which range from 16.0065 to 17.1003. Multi-objective algorithm wise, optimal control 1 has shorter distance than optimal control 2.

The convergence of closest distance point to the origin of all combination multi-objective algorithms and optimal controls is only considered in 50 iterations. If the simulations were allowed to run larger than 50 iterations, the values of the distance of closest point to the origin could be changing again. MOPSO algorithm mixed with optimal control 2 is the only combination that did not converge in the distance of closest point to the origin. Such combination has converged to 16.8639 from the 38^{th} iteration to 49^{th} iteration. However, the value changed to 17.1003 in the last iteration.

Solutions from MODE algorithm mixed with optimal control 1, MOEADalgorithm mixed with optimal control 2, and MOPSO algorithm mixed with optimal control 1 and optimal control 2, suggest using similar amount of immune drug. However, MOPSO algorithm mixed with optimal control 1 performed the worst among these solution sets as it suggests using similar amount of immune drug, but the amount of cancer cells is considerably high compared with other solution sets.

All combination of multi-objective algorithms and optimal controls suggested that the use of anti-angiogenic drug is unnecessary which indirectly reduced the multi-objective problem from three objectives problem to two objectives problem. MODE algorithm mixed with optimal control 2 has the worst balance of the three objectives in which it suggests using the highest amount of immune drug among all solutions to suppress the cancer cells.

Based on observation, the combinations of MODE algorithm mixed with optimal control 1, MOEAD algorithm mixed with optimal control 2, and MOPSO algorithm mixed with optimal control 2 have shown the best balance of three objectives overall.Among these three solutions, MODE algorithm mixed with optimal control 1 is positioned in the middle in terms of the amount of drugs and cancer cells. This combination has been chosen based on observation rather than closest distance to the origin or hypervolume.

The reasons of not using closest distance or hypervolume to determine the best solutions are given as the following:

a. MOEAD algorithm mixed with optimal control 1, being the solution that has closest distance to the origin, suggests using the least amount of immune drugs but it could not keep the amount of cancer cells as low as the other solutions.
b. The hypervolume indicator shows that MOPSO algorithm has the most diverse solutions compared with MOEAD and MODE algorithm. However, the hypervolume indicator may not be accurate as the MOPSO's hypervolume should be a lot larger than MOEAD and MODE based on the observation on Figure 6 and Figure 9.

Table 6 shows the optimized weight constants and their respective states in the objective functions. Recall that optimal control 1 objective function is maximization, negative weight constants in optimal control 1 correspond to minimization of the associated state. Column highlighted in green is the chosen set of weight constants. Based on the optimized weight constants, all multi-objective algorithms mixed with optimal control 1 have put the priority to minimize the amount of anti-angiogenic drug, less emphasize on minimizing cancer cells, and almost zero importance on minimizing the amount of immune drug. MODE and MOEAD algorithms mixed with optimal control 1 have more balance on the optimized weight constants in which none of the weight constants are too much higher or lower than the others. MOPSO algorithm mixed with optimal control 1 has only considered three weights as the weights on minimizing amount of anti-angiogenic drug and cancer cells are almost zero.

Table 6: Optimized weight constants and their respective states in the objective functions.

States in the Objective Functions	MODE		MOEAD		MOPSO	
	Optimal Control 1	Optimal Control 2	Optimal Control 1	Optimal Control 2	Optimal Control 1	Optimal Control 2
Immunotherapy Drug	A_3: -0.3188	A_1: $1x10^{-6}$	A_3: -0.7317	A_1: $1x10^{-6}$	A_3: -0.9203	A_1: $1x10^{-6}$
Anti-Angiogenic Drug	A_4: -0.8331	A_2: 0.9502	A_4: -0.4437	A_2: 0.7598	A_4: $-1x10^{-6}$	A_2: 0.2395
Cancer Cells	A_5: -0.5079	A_3: 0.0400	A_5: -0.4453	A_3: 0.0035	A_5: $-1x10^{-6}$	A_3: 0.0042
Normal Cells	A_1: 0.2967		A_1: 0.5572		A_1: 1.0000	
Effector Cells	A_2: 0.2474		A_2: 0.5679		A_2: 0.9773	

Plots of States and Controls Based on the Optimized Solution

By observation on the results in Table 5, MODE algorithm mixed with optimal control 1 shows the most balanced results in optimizing the drugs and cancer cells. Hence, this is the chosen optimal solution and the respective optimized weight constants are as shown in the green column in Table 6.

Figure 11 shows the plots of the states in 1700 days where the red point in graph *x* is the maximum point(1222, 0.9999), and the red point in graph *y* is the minimum point(1023, 4.2999×10^{-5}).Figure 12 shows the plots of the control in 1700 days based on the MODE algorithm mixed with optimal control 1.

The optimal control has shown that the cancer cells is able to be brought down to a level of 4.2999×10^{-5}in 1023 days by continuously administrating maximum amount of immunotherapy drug from 0^{th} day to 1000^{th} day. Normal cells rise to a level of 0.99 on the 958^{th} day and maintain above this level throughout. Cancer cells are rebounding exponentially after the immunotherapy drug is turned off. The immunotherapy drug could be turned on again if the simulation has allowed to run for a longer time span. Endothelial cells are growing exponentially as no anti-angiogenic drug is introduced during the treatment. Effector cells saturated quickly when the immunotherapy drugs are continuously taken but it drops exponentially right after the immunotherapy drugs is stopped being taken. The optimal solution has successfully reduced the side effects of immunotherapy by reducing the amount of immunotherapy drug in the 1700 days of treatment period and keeping the cancer cells at low level at the same time.

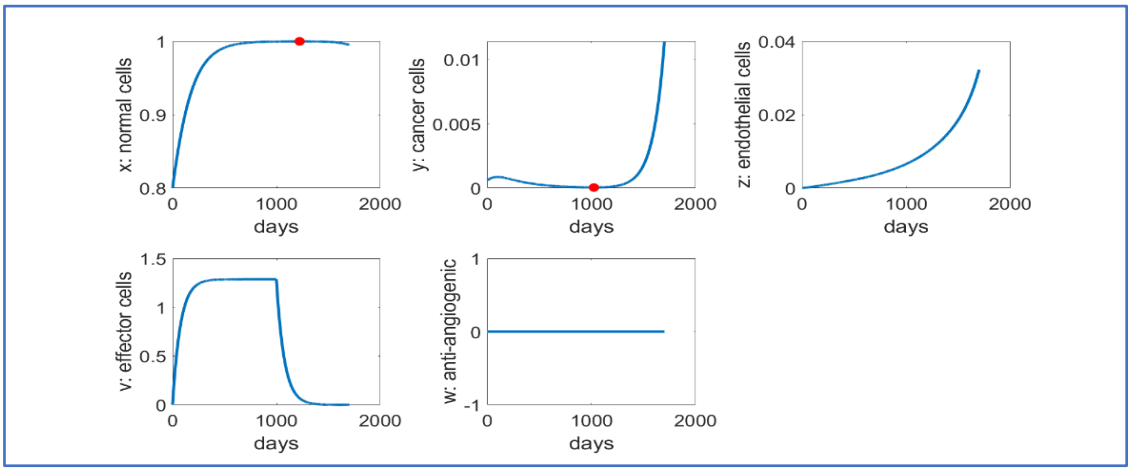

Figure 11: Plots of the state equations in 1700 days based on the MODE algorithm mixed with optimal control 1

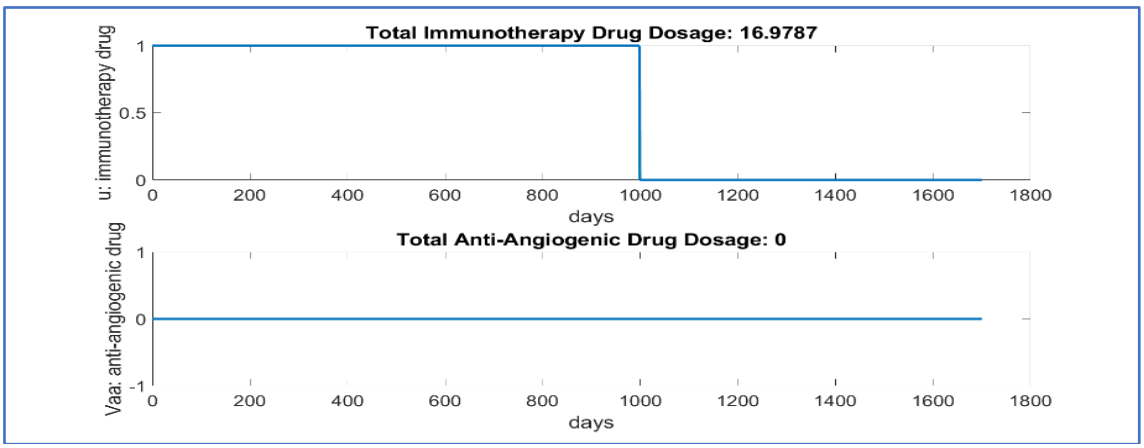

Figure 12: Plots of the control equations in 1700 days based on the MODE algorithm mixed with optimal control 1

(Bukkuri, 2019)'s concluded that the use of anti-angiogenic drug cannot be justified as his optimal results have suggested not to use anti-angiogenic drug. This results in this paper agrees to the conclusion from (Bukkuri, 2019) as the results of multi-objective mixed with optimal control in this paper have shown the same. The results in this paper have also suggested that the use of anti-angiogenic is a waste as immunotherapy alone is more than enough to bring the cancer cells down to a very low level. Direct comparison of the results in this project with (Bukkuri, 2019)'s is not feasible as both have different time span and (Bukkuri, 2019) has one wrong value for one of the parameters. Anti-angiogenic treatment alone does not have the ability to bring the cancer cells down. Despite that (Shi, et al, 2015) has shown the combination of immunotherapy and anti-angiogenic treatment can accelerate the speed in bringing the cancer cells down rather than immunotherapy alone, but this is considered to be ineffective because such combination could not accelerate much in bringing the cancer cells down yet uses too much of anti-angiogenic drug.

The problem of the mathematical model in (Shi, et al, 2015) is that the authors did not mention what is the cure conditions for the normal and cancer cells. The authors did mention that "cancer can be cured" when normal cells level is close to 1 and cancer cells level close to 0. However, due to the nature of the mathematical model, the cancer cells level is never zero, it can only be very close to zero which becomes a problem because when the immunotherapy drug is off, the cancer cells can grow back quickly. The nature of the mathematical model has also limited the effectiveness of anti-angiogenic treatment. As such, based on the results from this project, (Shi, et al, 2015), and (Bukkuri, 2019), it can be concluded that the best solution to bring the cancer cells down to low level is to full blast the immunotherapy drug for as long as needed. The bang-bangcontrol strategy presented in this paper is suitable for long-term control of the cancer provided that the cancer could never be cured.

In this project, optimal control based on Pontryagin's Maximum Principle was applied to a cancer treatment mathematical model extracted from (Shi, He, & Ou, 2015). Two optimal controls with different objective functions were tested. Three different multi-objective algorithms were applied to find the optimal weight constants that can balance the cancer cells and the amount of drugs used. The three objectives in the multi-objective optimization are minimizing cancer cells, immune drugs, and anti-

angiogenic drugs.

All combination of multi-objective algorithm mixed with optimal control have shown that the use of anti-angiogenic to treat the cancer in the mathematical model was costly and inefficient as it could not give significant acceleration in bringing down the cancer cells to low level. Based on observation on the results of the simulations, it was found that optimal control 1 mixed with MODE algorithm performed the best in balancing the three objectives.

The optimal solution presented in this project has minimized the cancer cells and reduce the side effect of immunotherapy in 1700 days of treatment in which the objectives were met. The immunotherapy is on for the first 1000 days instead of 1700 days which oppose to the strategy used in (Shi, He, & Ou, 2015). Besides that, the optimal solution can recover the normal cell to almost maximum level and keeping the cancer cells at low level in 1700 days. However, the cancer cells are on the rise exponentially due to the immunotherapy is off after 1000 days.

4.0 CONCLUSION

This project concludes that the best strategy to bring down the cancer cells of is to administer maximum amount of immunotherapy drug continuously until it drops to a desired low level. Unfortunately,(Shi, He, & Ou, 2015) did not mention the cure state conditions, thus, such strategy is applicable when a cure state for cancer cells and normal cells are defined. Bang-bang control strategy proposed in this project is only suitable for controlling the cancer cells for long-term in case of the cancer could never be cured.

By assuming that the cancer could never be cured, in the future, constraints could be applied to the system to keep the tumor cancer cells to keep it at a low level so that the hypothetical cancer patientis maintained at a healthy level.Furthermore, more multi-objective algorithm can be explored, and different optimal control strategy may be applied.Besides that, proper hypervolume indicator algorithm for 3-dimensional Pareto Front shall be investigated further.Lastly, the problem of unstable cost of the objective function should be investigated and solved.

ACKNOWLEDGEMENT

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REFERENCES

1. Bukkuri, A. (2019, November 30). Optimal control analysis of combined anti-angiogenic and tumor immunotherapy. *Open Journal of Mathematical Sicences*, 349-357. doi:10.30538/oms2019.0078
2. Carrère, C. (2017). Optimization of an in vitro chemotherapy to avoid resistant tumours. *Journal of Theoretical Biology, 413*, 24-33. doi:10.1016/j.jtbi.2016.11.009
3. Çelik, U., Aydemir, E. H., Engin, B., Oba, M. Ç., Yılmaz, M., & Meşe, Ş. G. (2020, November 2). Dermatological side effects of immunotherapy drugs and targeted cancer therapies: Importance of dermatology and oncology collaboration. *Journal of Oncology Pharmacy Practice*.

doi:10.1177/1078155220970621
4. Chhabra, N., & Kennedy, J. (2021, April 7). A Review of Cancer Immunotherapy Toxicity: Immune Checkpoint Inhibitors. *Journal of Medical Toxicology*. doi:2021
5. Ferlay, J., Colombet, M., Soerjomataram, I., Parkin, D. M., Piñeros, M., Znaor, A., & Bray, F. (2021). Cancer statistics for the year 2020: An overview. *International Journal of Cancer*.
6. *Immunotherapy*. (2020, January 10). Retrieved from Cleveland CLinic: https://my.clevelandclinic.org/health/treatments/11582-immunotherapy
7. *Immunotherapy to Treat Cancer*. (2019). Retrieved from National Cancer Institute: https://www.cancer.gov/about-cancer/treatment/types/immunotherapy
8. Kelly, C. (2017, July 24). *Forcing the Immune System to Attack Cancer*. Retrieved from Alliance of Advanced BioMedical Engineering: https://aabme.asme.org/posts/scientists-develop-virus-that-forces-the-immune-system-to-attack-cancer
9. LB Kennedy, A. S. (2020, January 16). A review of cancer immunotherapy toxicity. *American Cancer Society, 70*, 86-104. doi:doi.org/10.3322/caac.21596
10. Lenhart, S., & Workman, J. T. (2007). *Optimal Control Applied to Biological Model.* (A. M. Etheridge, L. J. Gross, S. Lenhart, P. K. Maini, S. Ranganathan, H. M. Safar, & E. O. Voitt, Eds.) Boca Raton London New York: Chapman & Hall/CRC.
11. Moore, H. (2018). How to mathematically optimize drug regimens using optimal control. *Journal of Pharmacokinetics and Pharmacodynamics*, 127-137.
12. *NCI Dictionaries*. (n.d.). Retrieved from National Cancer Institute: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/cancer
13. Oke, S. I., Matadi, M. B., & Xulu, S. S. (2018, April 24). Optimal Control Analysis of a Mathematical Model. *Mathematical and Computational Application*. doi:doi:10.3390/mca23020021
14. Orange, M., Reuter, U., & Hobohm, U. (2016). Coley's lessons remembered: augmenting mistletoe therapy. *Integrative Cancer Therapies, 15*(4), 502-511. doi:10.1177/1534735416649916
15. Pardoll, D. (2012). The blockade of immune checkpoints in cancer immunotherapy. *Nature Reviews Cancer, 12*, 252–264 .
16. Shi, X., He, X., & Ou, X. (2015). A Mathematical Model and Analysis of the Antiangiogenic. *International Conference on Computer Science and Network Technology.4*. Harbin, China: IEEE. doi:10.1109/ICCSNT.2015.7491025
17. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *A Cancer Journal for Clinicians*.
18. Sweilam, N., Tharwat, A., & Moniem, N. A. (2019, December 10). Different Opptimization Strategies for the Optimal Control of Tumor Growth. *Cancer Science and Therapy*, 52-62. doi:10.29328/journal.acst.1001010
19. Tang, Z., Li, D., Hou, S., & Zhu, X. (2020). The cancer exosomes: Clinical implications, applications and challenges. *International Journal of Cancer, 146*, 2946–2959. doi:10.1002/ijc.32762
20. Waldmann, T. A. (2018, December 3). Cytokines in Cancer Immunotherapy. *Cold Spring Harbor Perspective Biology, 12*. doi:10.1101/cshperspect.a028472
21. Zhang, Y., & Zhang, Z. (2020, July 1). implications, The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic. *Cellular and Molecular Immunology, 17*, 807-821. doi:10.1038/s41423-020-0488-6