HYBRID OPTIMAL CONTROL-SWARM INTELLIGENCE FOR OPTIMIZATION OF SELECTED CANCER CHEMOTHERAPY MODEL

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ABSTRACT

Cancer chemotherapy optimization problem one of the critical cases until now, the researchers still working on it, to find the optimal amount of the drug, that reduce the toxicity and the tumor size. That caused increasing in the number of objectives and constraints, so increasing in the complexity of the optimization problem. This research project proposes two hybrid techniques that's combined between the optimal control theory (OCT) with the swarm intelligence (SI) and evolutionary algorithms (EA), and check the performance of this techniques, with the popular method that used purely SI and EA algorithms, such M-MOPSO, MOPOS, MOEAD, MODE. The comparison between these methods, is done by solved a constraints multi-objectives optimization problem CMOOP, for the optimization problem of cancer chemotherapy treatment. The results of the hybrid techniques appear more efficient than that discovered by the purely SI and EA method. That's improve the ability of the hybrid methods for solving the CMOOP with a high performance more than used a purely swarm intelligence. This will be very helpful for the clinicians and oncologist to discover and find the optimum dose schedule of the chemotherapy that's reduce the tumor cells and save the patients' health at a safe level.

ABSTRAK

Masalah pengoptimuman kemoterapi kanser salah satu daripada kes kritikal sehingga sekarang, para penyelidik masih mengusahakannya, untuk mencari jumlah ubat yang optimum, yang mengurangkan ketoksikan dan saiz tumor. Ini menyebabkan peningkatan dalam bilangan objektif dan kekangan, begitu meningkat dalam kerumitan masalah pengoptimuman. Projek penyelidikan ini mencadangkan dua teknik hibrid yang digabungkan antara teori kawalan optimum (OCT) dengan kecerdasan pintar (SI) dan algoritma evolusi (EA), dan menyemak prestasi teknik ini, dengan kaedah popular yang menggunakan algoritma SI dan EA semata , seperti M-MOPSO, MOPOS, MOEAD, MODE. Perbandingan antara kaedah ini dilakukan dengan menyelesaikan masalah pengoptimuman multi-objektif CMOOP, untuk masalah pengoptimalan rawatan kemoterapi kanser. Hasil teknik hibrida nampak lebih efisien daripada yang ditemui oleh metode SI dan EA murni. Ini meningkatkan keupayaan kaedah hibrida untuk menyelesaikan CMOOP dengan prestasi tinggi daripada menggunakan kecerdasan semata-mata. Ini akan sangat membantu para doktor dan ahli onkologi untuk mengetahui dan mencari jadual dos optimum kemoterapi yang mengurangkan sel-sel tumor dan menyelamatkan kesihatan pesakit di tahap yang selamat.

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I must express my very profound gratitude to my parents and to my brothers and sisters for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this research report to finish my master's degree. This accomplishment would not have been possible without them.

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LIST OF SYMBOLS AND ABBREVIATIONS

WHO	:	World Health Organization
AHRQ	:	Agency of Healthcare and Research Quality
NLP	:	Non-Linear Programming
SI	:	Swarm Intelligence
EA	:	Evolutionary Algorithm
MTD	:	Maximum Tolerated Dose
OCT	:	Optimal Control Theory
POF	:	Pareto Optimal Front
ALA	:	Augmented Lagrangian Approach
PMP	:	Pontryagin Maximum/Minimum Principle
M-MOPSO	:	Modify Multi Objective Particle Swarm Optimization
MOPSO	:	Multi Objective Particle Swarm Optimization
MOEAD	:	Multi Objective Evolutionary Algorithm Based on Decomposition
MODE	:	Multi Objective Differential evolution Algorithm
PSO	:	Particle Swarm Optimizer
MOOP	:	Multi Objective Optimization problem
CMOOP	:	Constrained Multi Objective Optimization Problem
BVP	:	Boundary Value Problem
MOSHO	:	Multi Objective Spotted Hyena Optimizer
PID	:	Proportional Integral Derivative Controller
LTV	:	Linear Time varying Approximation Method

CHAPTER 1: INTRODUCTION AND LITREATURE REVIEW

1.1 Introduction

This chapter provide a general introduction under the Background, explanation of the problem statement and shown the objectives of this work, with the scope explanation, finally the organization of this work shown in the end of this chapter.

1.2 Background

Cancer is considered one of the most diseases that causes death around the world. According to the World Health Organization (WHO) (Organization, 2018), in 2015 the cancer causing 8.8 million deaths. With estimated 1,735,350 new cancer patients and 609,640 deaths during 2018 in the united states (Siegel, Miller, & Jemal, 2018), whereas the cancer is considered the second caused of mortality there. Simply, the cancer is unbonded grow and spread for abnormal cells, that harm the patient body and almost causing the death if it doesn't treat early.

Chemotherapy, immunotherapy, radiation therapy and surgery, are the main treatments for the cancer disease. There are some criteria's used for selecting the proper treatment, like patient health situation at the time of treatment, stage and the location of the tumor. Chemotherapy is the most commonly used treatment, that showed a high efficiency for treating the cancer (Galmarini, Galmarini, & Galmarini, 2012).

Chemotherapy causing death for the cancer cells, but it's also causing death for the normal cells that may be caused patients death in some cases. so the chemotherapy must be delivered to the patient's body in ideal does that reduce the normal cells damage.(Galmarini et al., 2012; Harrold & Parker, 2009; Itik, Salamci, & Banks, 2009;

Ku-Carrillo, Delgadillo-Aleman, & Chen-Charpentier, 2017; Shi, Alagoz, Erenay, & Su, 2014; Wu, Liu, Zhang, Cheng, & Xin, 2018).

This negative side of chemotherapy caused another problem for the clinicians, where they need to know the best dose of treatment that should gave to the patient. Furthermore, there a big economic impact from this treatment, according to the Agency for Healthcare Research and Quality (AHRQ) in united states during 2015 the main costs of chemotherapy treatment reached $80.2 billion (Society, 2018).

So, there is a need for finding the optimal dose of chemotherapy, that keep the treatment efficiency high, at the same time reduce the negative effects, that's will also decrease the amount of financial expenses on the treatment.

Solving of this problem needed a cooperation with the engineers, mathematicians, oncologist, and clinicians, to build a mathematical model that simulate that dynamics of the tumor cells and how it's affected with the chemotherapy, also shows the behaviors of normal cells with the treatment, then solving this model to discover the optimal dose of chemotherapy that kills the cancerous cells and reduce the toxicity level. And because they're a many of factors effect on the growth of the tumor cells, there are many of mathematical models depended on different factors. However, all of them simulate the pharmacokinetic that characterized the distribution and metabolism of the treatment dose, also the pharmacodynamic processes that describe the effects of the treatment dose on normal and malignant cells (Panetta & Fister, 2003).

Previously, the mathematical model neglected the negative effects of the chemotherapy on the normal cells, whereas the optimal treatment analysis was focusing on reducing the tumor size by increasing the amount of chemotherapy, to avoid any drug resistance from the cancerous cells (Martin, 1992).

Later, the chemotherapy negative effects on the normal cells added inside the mathematical models, so it's became a part of the optimal analysis of the chemotherapy that aimed to reduce the tumor size at the same time reduce the drug toxicity (Matveev & Savkin, 2000).

The strength of the immune system, it's an important factor in the cancer treatment that effects on the response of cancerous cells with the treatment. The mathematical model that proposed in 2003 by Pillis and Radunskaya (De Pillis & Radunskaya, 2003), considered the dynamics of the immune cells with the drug, normal cells and the tumor cells, besides, the response of the tumor cells and normal cells with the chemotherapy, this is to increase the efficiency of the drug optimal analysis. Other researchers considering another factors, besides, the response of immune, tumor and normal cells, like the mathematical model proposed in this article (Ku-Carrillo et al., 2017), taken into account the obesity to check the effects of the diet on the efficiency of chemotherapy treatment, the result was, losing weight leads to improving the efficiency of chemotherapy.

With this improvement on the mathematical models, the optimization problem also shifted from a single objectives optimization problem to the multi-objective optimization problem, addition to a constraints to be constrained multi-objective optimization problem (CMOOP), that aimed to maximize or minimize two or more of objectives at the same time achieve the constraints, from here the needs for robust optimization method appears, to solve this kind of optimization problem and find the optimum results.

The two main conventional approaches for solving the optimal control optimization problem, first one called direct or stochastic approach, whereas the optimal control problem converted into Non-linear programming (NLP). The second one called in-direct or deterministic approach, that based on the Maximum/Minimum Pontryagin Principle,

whereas the optimal control problem converts into boundaries values problem, both use some numerical methods like single and multiple shooting methods, for solving the problem. Some of researchers used un-conventional methods, like method proposed in this article (Khadraoui et al., 2016), whereas it's used two PID (Proportional - Integral – Derivative) controllers, to keep the dose of chemotherapy in acceptable level, that's to reduce the drug concentration as possible. Another one used the linear time varying approximation (LTV) method to solve the multi objective optimization problem for chemotherapy treatment that aimed to minimize the tumor size and the drug concentration (Itik et al., 2009).

Nowadays, most of engineering and the real life optimization problems are CMOOP, and because the Increasing in the number of objectives, constraints, states and variables in the mathematical model of the optimization problem, the researchers move toward using the SI's and EA's algorithms, to solve the CMOOP, replacement for the conventional approaches, for example, Dhiman and Kumar (Dhiman & Kumar, 2018) solving a CMOOP by using a multi-objective spotted hyena optimizer (MOSHO), to check the validity of this optimizer for real life optimization problem. Lobato, Machado and Steffen (Lobato, Machado, & Steffen, 2016) used the multi objective optimization differential evolution algorithm (MODE) for solving CMOOP for cancer chemotherapy treatment. A modified multi-objectives particle swarm optimization algorithm (M-MOPSO) proposed by Zihin et. al. (Mohd Zain, Kanesan, Chuah, Dhanapal, & Kendall, 2018), to solve the CMOOP, and explained how it's avoid the weakness of MOPSO algorithm especially for optimization problem with high dimension. That's because the increasing in the complexity of optimization problem put many of challenges for using conventional approaches.

1.3 Problem Statement

For an effective chemotherapy treatment, the dose must reach the site of the cancer in an optimal amount that caused the death of cancerous cells and reducing the tumor size, at the same time avoiding the drug resistance that happens at low concentration but increasing in the drug concentration will caused the death for the normal cells, that influence negatively on the patient's health.

1.4 Objectives of Research

The main objectives of this work:

1. Minimize the drug concentration and the tumor cells.
2. Validate the hybrid method (optimal control theory combined with swarm and evolutionary algorithm) improve the quality of the result.

1.5 Scope of Study

The scope of this work is solving a selected mathematical model for cancer chemotherapy optimization problem, by three optimization methods, that aimed to reduce the tumor size and the drug concentration, to check the validate of the hybrid proposed methods, comparing with the current methods that used purely SI and EA algorithms to solve CMOOP.

1.6 Thesis Organization

After given an introduction and explained the research project objectives in chapter one, the rest of this work organized as follows, chapter two has the literature review, chapter three contains the methodology and explain the mathematical calculations that used in this work, chapter four have the results and that discussion, finally the conclusion and the recommendations for future work explained in chapter five.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

This chapter explain the different approaches of the optimal control, some of numerical methods, and the multi objectives optimization problem, also show the pseudocode for the SI and EA algorithms that used in this work.

2.2 Optimal Control

Optimal control, it's an extension from the calculus of variations, whereas the optimal control dealing with maximization or minimization problem to find the optimum result. Mainly the optimal control problem consisting of two kind of functions:

a- Cost Function or objective function.

$$J = \varphi(x_f, t_f) + \int_{t_0}^{t_f} L(x(t), u(t), t)dt \tag{2.1}$$

b- Dynamical system or states Functions: that's describe the behaviors of the states with the time.

$$\dot{x} = f(x(t), u(t), t) \tag{2.2}$$

Whereas the $x = [x_1, x_2, ..., x_n]^T$ is a states vector with n of states functions, and $u = [u_1, u_2, ..., u_m]$ is the control vector with m control functions, x_f is the final values for the state vector, t_0 and t_f are the initial and final time.

Subject to kind of functions add to the previous functions called path constraints functions:

$$h(x(t), u(t)) \geq 0, \qquad t \in [t_0 \quad t_f] \tag{2.3}$$

Simply, the optimal control is finding the optimum result of the control function that maximize/minimize the cost function, at the same time achieving the path and states constraints as shown in Figure 2.1.

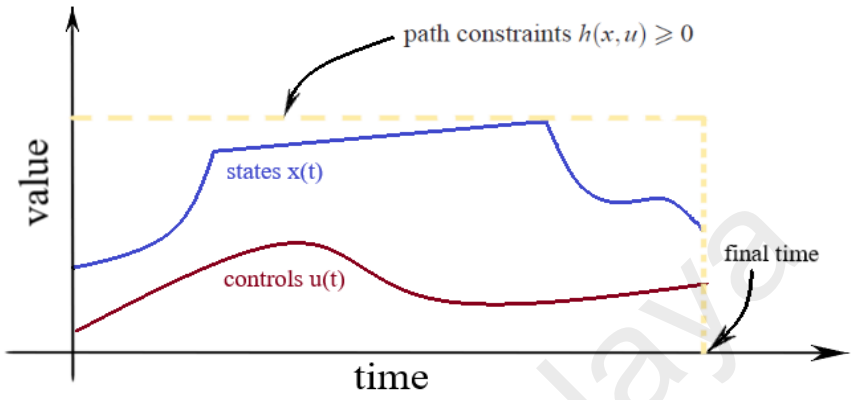

Figure 2.1: Explained Optimal Control Problem

The optimal control methods basically classified into two approaches, direct and indirect methods, the following Figure 2.2 shows these approaches and the popular numerical methods that are using in each approach.

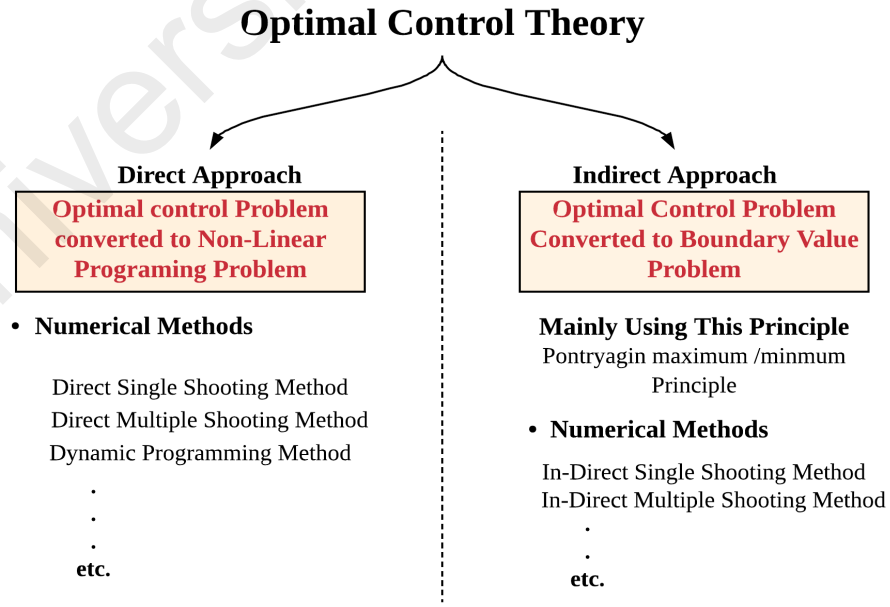

Figure 2.2: Flow Chart for the Different Approaches of The Optimal Control

The direct method process starts by discretizing the control problem, after that using the NLP techniques to solve the problem and find the results, for that it's called stochastic approach. But in the indirect approach, the optimal control problem converted to a boundary value problem by building the Hamiltonian equation:

$$H(x,u,\lambda,t) = L(x(t),u(t),t) + \lambda(t)^T f(x(t),u(t),t) + \eta(t)^T h(x(t),u(t),t) \tag{2.4}$$

Then derive it with respect to states variables to find the co-states functions Eq 2.5, and the control functions Eq 2.6, now the problem became a boundary value problem (BVP), whereas it's consists of ODEs equations combined from the states and co-states functions, after that, the indirect numerical methods use to solve the BVP and find the optimal results for the control variables, for that it's called a deterministic method.

$$\lambda n = \frac{\partial H}{\partial x_n} \tag{2.5}$$

$$Hu_m = \frac{\partial H}{\partial u_m} \tag{2.6}$$

2.3 Multi Objectives Optimization Problem (MOOP)

Nowadays the complexity of the optimal control problem increases for different applications, whereas the optimal control problems shifted from a single objective optimization problem that aimed to minimized or maximized only one objective, to CMOOP that aimed to minimized or maximized two or more of objectives and achieve the constraints.

$$\max/\min \qquad J(x) = [j_1(x) \quad j_2(x) \quad \ldots \quad j_n(x)] \tag{2.7}$$

subject to inequality and equality constraints:

$$h_i \geq 0, i = 1,2,\ldots\ldots\ldots,r \tag{2.8}$$

$$g_i = 0, i = 1, 2, \ldots\ldots\ldots, e \tag{2.9}$$

Whereas $J(x)$ is the objectives vector, n is the number of the objectives function.

Nowadays, most of engineering and real-life optimal control problem are CMOOP, this kind of problems have a group of solutions called pareto optimal set, as shown in Figure 2.3 the pareto front or the set of pareto optimal solutions appeared in red points, are a combination form the non-dominated solutions by any other feasible solutions.

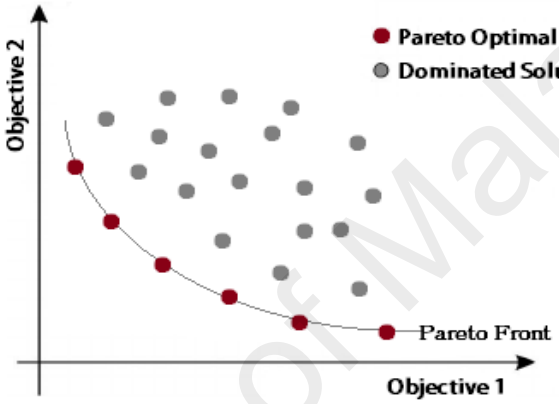

Figure 2.3: Pareto Optimal Front

Solving the CMOOP not easy by the traditional ways, so with the development and the ability increasing for the computers, the researchers start using unconventional methods that based on swarm and evolutionary algorithms, that based on the stochastic method to solve CMOOP and finding the Pareto optimal front.

2.4 PSO Algorithms

Particle Swarm Optimizer (PSO) proposed first time in 1995 by Kennedy and Eberhart, PSO algorithm uses the swarm intelligence (SI) that inspired from the swarm bird's movement during searching on the food, mathematically it simulates this social behavior to find the best results that achieves the objectives within the path constraints. Figure 2.4 shown the flow chart of the basic PSO algorithm.

PSO can be applied for verity range of applications like neural network training, structural optimization, and nowadays it's uses to solve CMOOP for the optimal control applications.

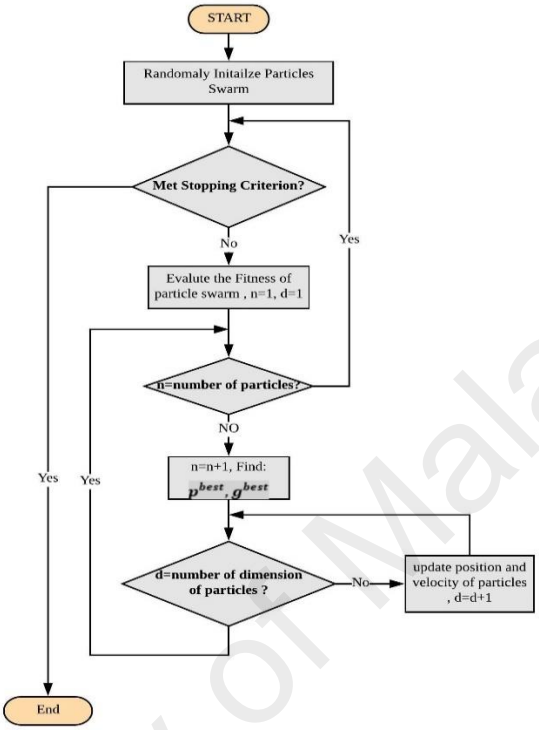

Figure 2.4: Particle Swarm Optimizer PSO

MOPSO and M-MOPSO algorithms, that have been used in this research project and explained later in this section are basing on some of PSO algorithm, that build to solve the MOOP.

2.4.1 MOPSO Algorithm

Multi-Objectives Particle Swarm Optimization (MOPSO) a mathematical algorithm based on PSO, with some of modifications on the basic PSO algorithm, the MOPSO algorithm formed to be able for handling with MOOP and finding the pareto optimal set. Following are the main modifications that have been applied on PSO to build the MOSPO algorithm happened on: External archive Maintenance, Select Global Leaders, Update personal best, Mutation operator (perturbation).

MOPSO proposed first time in 2002 by Coello and Lechuga, and for more information you can check this reference (Coello & Lechuga, 2002), Following is the pseudocode of the MOPSO algorithm:

BEGIN

For i=1 to n (Amount of particles)
Initialize Position (i)
Initialize Velocity (i)
End For
Initialize External Archive
Penalty = 0

Do While (stopping criterions not be satisfied**)**

For i=1 to n (Amount of particles)
Select Members for External Archive
Calculate New Position (i) and new Velocity (i)
Update Best Position
End For

End While

As shown, MOPSO start initialization for the position and the velocity of each particle and initialize the external archive extra on the normal procedure of PSO, then start the searching procedure until reached stopping criteria's, like maximum number of iterations.

2.4.2 M-MOPSO Algorithm

Modify Multi-Objectives Particle Swarm Optimization (M-MOPSO), almost have the same procedure of MOPSO algorithm, but with some enhancements and modifications on the searching and archiving system, to increase the efficiency and avoid the weak points of MOPSO like constraints handling capability and convergence especially for dealing with the high dimensional problems. For more information, Zihin et. al.(Mohd Zain et al., 2018) explained in details the procedure of M-MOPSO and discussed the differences points with the MOPSO.

2.5 EA Algorithms

Evolutionary Algorithms (EA), one of the important algorithms in the optimization world, and it's can be using to solve a wide range of problems for different life applications. EA algorithms it’s a mathematical simulation for the mechanism of natural selection to solve a hard problem that almost can't be solved by a conventional method (Yu & Gen, 2012). The following Figure 2.5, shown the flowchart of basic EA algorithm.

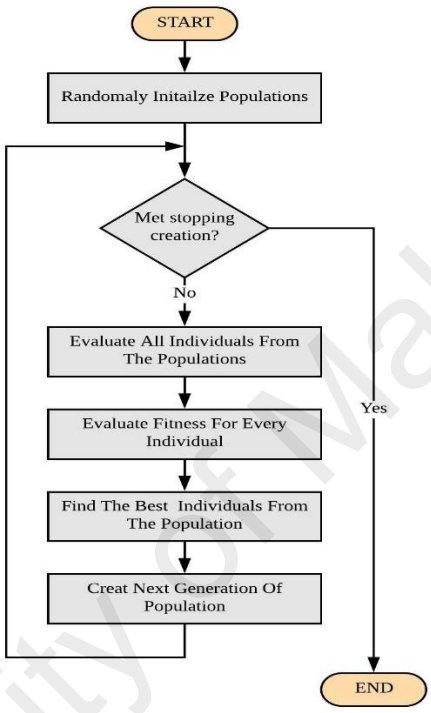

Figure 2.5: Evolutionary Algorithm EA

As it’s appeared, EA mainly has four steps:

1- Initialization: Randomly population initialization.
2- Selection: Evaluate members of the population according to fitness function and find the best members.
3- Genetic operators: The Crossover and Mutation processes are using in this step to build the new next generation.
4- Termination: Stopping creations, like maximum number of iterations.

MODE and MOEAD algorithms, that have been used in this research project and explained later in this section are basing on some of EA algorithms that build to solve and find the pareto optimal front for MOOP.

2.5.1 MODE Algorithm

Multi-Objective Differential evolution (MODE), one of the algorithms that employed the EA's to solve MOOP. This algorithm based on Differential evolution algorithm (DE) that proposed first time by Storn and Price (Storn & Price, 1997), and it's one of EA's algorithms. Basically, DE is a structure for generating the trial parameters vectors, that by adding the weighted difference between two vectors of the population, to a third vector.

Figure 2.6 shows the flowchart of MODE algorithm. Simply, it begins with random initialization for the populations, then DE procedure starts for selection and the generating for the next generation, then through the non-dominated step, all the dominated solutions are removed from the populations, and this procedure repeated until meet one of stopping creation.

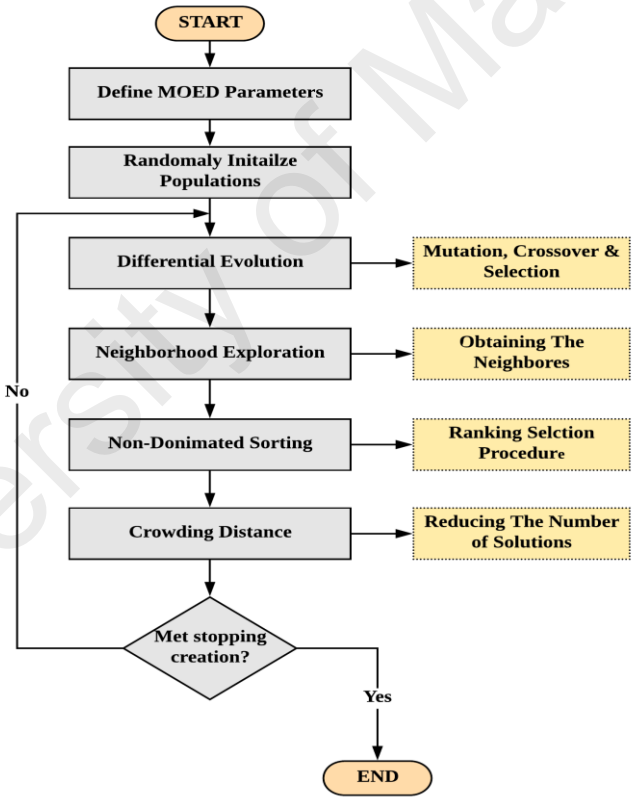

Figure 2.6: Flowchart of the MODE Algorithm

2.5.2 MOEAD Algorithm

Multi-Objective Evolutionary Algorithm based on decomposition (MOEAD), proposed first time by Zhang and Lie (Zhang & Li, 2007). Simply, MOEAD decomposes the multi-objective optimization problem into of many single-objective problems and solve them at the same time.

MOEAD algorithm has less computational cost compared with non-dominated sorting genetic algorithm, whereas It uses the information of solutions of neighborhood subproblems. Has many of successful applications in many fields, like smart phone, and social network problems, flowshop and scheduling problems…etc.

MOEAD basically has this procedure:

1- Decomposed the MOOP into several scalar subproblems, and the weighting sum approach is the most commonly method that can be used.
2- Then, all scalar subproblems are optimizing at the same time.
3- The information's are taking from its neighboring subproblems, the optimization of those decomposed subproblems results in a low computational cost.
4- This procedure repeated until reached one of stopping creations.

For more information about MOEAD, Taghian el. Al. (Taghian, 2015) explained in details the work principle of MOEAD with addition of the flowchart, and described the different methods that can be used for decomposition process.

2.6 Penalty Approach to Handling Inequality State Constraint

Handling with the inequality constraints, it's one of the big challenges faced SI's and EA's algorithms for solving CMOOP, to deal with this there is a need to convert the CMOOP to un-constrained optimization problem. Penalty approach is the most popular method for solving the constrained optimization problem until now, because of its simplicity and theoretical reliability (Luenberger, 2003).

The main idea for penalty approach is converting the constrained optimization problem to un-constrained optimization problem, based on the amount of constraint violation that present in a certain solution, there is a certain value will add or subtract from the objective function.

Mathematically, Eq 2.7 subject to inequality constraint Eq 2.8, by applying the penalty approach it becomes:

$$\max/\min, \Phi_z = J_z + \mu.p(x) \tag{2.10}$$

Where, J_z it's the objective function, z it's the number of objectives functions, μ multiplier factor, and $p(x)$ the amount of penalty subject to:

$$p(x) = \begin{cases} 0, & \text{if constraint is satisfied} \\ d, & \text{if constraint is violated} \end{cases} \tag{2.11}$$

Whereas, d is the amount of constraint violation at a certain point.

However, the penalty has two approaches, first one is interior method that penalize infeasible solutions, whereas, the value of penalty term is chosen to be small at points away from the constraint boundaries and it's will goes to infinity when approached the constraint boundaries, second one is the exterior approach, which penalize feasible

solutions, it's start with an infeasible solution and then move towards the feasible region. Most of researchers prefer using the exterior approach, because there is no need for initial feasible solution (Coello Coello, 2002).

CHAPTER 3: METHODOLOGY

3.1 Introduction

This chapter explain the Methodology of this work, shows the solution procedure, and presents the Mathematical model, also describe the controller design steps, and shows the value of main parameters for the PSO and EA algorithms that have been used in this work.

3.2 Mathematical Model

This work used the mathematical model that proposed by (De Pillis & Radunskaya, 2003), the reasons for selecting this model being in the main characteristic of this model whereas this mathematical model doesn't simulate a behavior of a specific type of cancer, also there many of research used this mathematical model with or without addition. This mathematical model is very important and according to this research (Itik et al., 2009) for developing an effective schedule of the chemotherapy treatment.

$$\dot{T} = r_1 T(1 - b_1 T) - c_2 IT - c_3 TN - a_2 u \qquad T(0) = T_0 \qquad (3.1)$$

$$\dot{N} = r_2 N(1 - b_2 N) - c_4 TN - a_3 u \qquad N(0) = N_0 \qquad (3.2)$$

$$\dot{I} = s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I - a_1 u \qquad I(0) = I_0 \qquad (3.3)$$

The situation of tumor cells is simulating by T, whereas as the behavior of the normal cells represented by symbol N, and the amount of immune cells is representing by I, with the time t. While u denote to the drug concentration with the time.

The different properties in this model represented by a different group of parameters, whereas, a_i represented the cells death rate caused by the chemotherapy, carrying capacity represented by group parameters b_i, group parameters c_i represented

the cells competition rates, cells growing rate appeared by group parameters r_i, immune influx, threshold rates and response are represented by s, α, ρ respectively.

The following Table 3.1 explain and shows the rang of the different parameters that used in the mathematical model, whereas the values of all parameters are positive.

Table 3.1: Range of The Different Parameters of The Mathematical Model

Parameters	Description	Range
$\boldsymbol{a_1, a_2, a_3}$	Cells Death Coefficients Response by the chemotherapy.	$a_2 \geq a_1 \geq a_3$ $0 < a_i < 0.5$
$\boldsymbol{b_1, b_2}$	Carrying Capacities per Capita	$b_1 \leq b_2$
$\boldsymbol{c_1, c_2, c_3, c_4}$	Cells Competition Rates	$c_i \geq 0$
$\boldsymbol{d_1}$	Cells Death Rate	$d_i \geq 0$
$\boldsymbol{r_1, r_2}$	Cells Growth Rate	$r_2 < r_1 < \frac{c_2 s}{d_1} + c_3$
$\boldsymbol{s}$	Influx Rate of Immune cells	$0 \leq s \leq 0.5$
$\boldsymbol{\alpha}$	Immune Threshold Rate	$0 \leq \alpha \leq 0.5$
$\boldsymbol{\rho}$	Immune response per capita	$0 \leq \rho \leq 1$

3.3 Objectives Functions

As mentioned before this work aimed to minimize the tumor size and the drug concentration:

$$min \int T \, dt \tag{3.4}$$

$$min \int u \, dt \tag{3.5}$$

At the same time keep the concentration of the normal cells in a safe level by adding a state constraint:

$$N \geq 0.75 \tag{3.6}$$

3.4 Optimization Methods Description

Solving CMOOP it's not an easy job especially by using the classical methods for that many of researchers used un-conventional methods that based on Particle Swarm Optimization (PSO) and Evolutionary Algorithms (EA) to solve this kind of multi objectives optimization problem as a replacement for the conventual method optimal control theory.

As mentioned before this work aimed to solve the CMOOP by a hybrid methods that combined between swarm intelligence (SI) algorithms and the optimal control theory (OCT). There three methods used in this work:

1- Method 1: The CMOOP solved by untraditional methods that used purely SI and EA algorithms, (M-MOPSO, MOPSO, MOEAD, MODE).
2- Method 2: The CMOOP solve by using a hybrid algorithm, that combined between OCT with SI and EA algorithms, but the state constraint will be achieve by the SI and EA.
3- Method 3: The CMOOP will solve by using the hybrid algorithm, but this time the state constraint included in the optimal control theory, whereas the only job for the SI and EA algorithms is finding the Pareto Optimal set.

In the first method the objectives function and the state constraint will achieve by the SI and EA algorithms, but in the second and third method the hybrid algorithm will be use, in method 3 the objectives or performance index and state constraint will achieve by the indirect method, while in method 2, indirect method will be achieve the performance index, while the state constraint achieved by the SI's and EA's algorithms.

The following Figure 3.1 have the methodology flow chart for this research project:

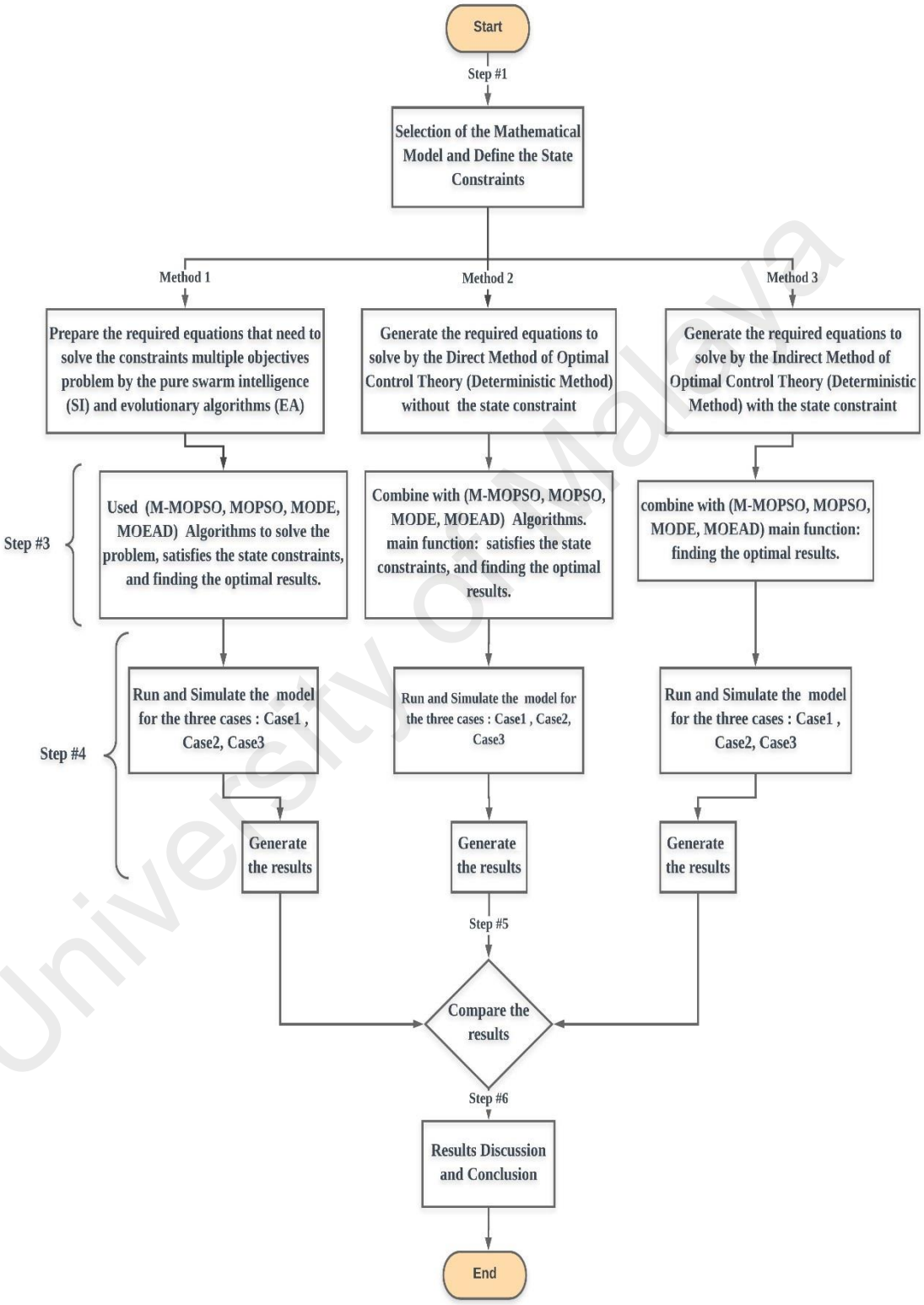

Figure 3.1: Methodology Flow Chart

3.5 Optimal Controller Design and Necessary Conditions

The optimal control theory as explained before in section 2.3 has two approaches, this work used Bang-Bang controller that classified under the indirect approach (Deterministic Method) that's take the benefit from Pontryagin maximum / minimum principle (PMP).

The following steps are explaining the Calculations of the optimal control theory:

- The two objectives functions Eq 3.4 and Eq 3.5 combined together in a single equation by using the weighting method.

$$\min K = w_1 \int T dt + w_2 \int u dt \tag{3.7}$$

Whereas; $w_1 = 1 - w_2$ (3.8)

- Converted the Eq 3.7 from Bolza form to Mayer form, by supposed another state:

$$\dot{K} = w_1 T + w_2 u \tag{3.9}$$

- The inequality Eq 3.6 state constraint became:

$$C = 0.75 - N \leq 0 \tag{3.10}$$

- The Hamiltonian equation for method 2:

$$H_{M2} = w_1 T + w_2 u + \lambda_1 \dot{T} + \lambda_2 \dot{N} + \lambda_3 \dot{I} + \lambda_4 \dot{K} \tag{3.11}$$

- Hamiltonian equation for Method 3:

$$H_{M3} = H_{M2} + \eta C \tag{3.12}$$

- Co-states functions for Method 2:

$$\dot{\lambda}_1 = -\frac{\partial H}{\partial N} = -r_2\lambda_1 + 2r_2 b_2 \lambda_1 N + \lambda_1 c_4 T + \lambda_2 c_3 T \tag{3.13}$$

$$\dot{\lambda}_2 = -\frac{\partial H}{\partial T} = -w_1 + \lambda_1 c_4 N - \lambda_2 r_1 + 2\lambda_2 r_1 b_1 T + \lambda_2 c_2 I + \lambda_2 c_3 N - \lambda_3 \left(\frac{\alpha \rho I}{(\alpha + T)^2} \right) + \lambda_3 c_1 I - w_1 \lambda_4 \tag{3.14}$$

$$\dot{\lambda}_3 = -\frac{\partial H}{\partial I} = \lambda_2 c_2 T - \lambda_3 \left(\frac{\rho T}{\alpha + T} \right) + \lambda_3 c_1 T + \lambda_3 d_1 \tag{3.15}$$

$$\dot{\lambda}_4 = -\frac{\partial H}{\partial K} = 0 \tag{3.16}$$

- The co-states of method 3 are the same of method 2, only the first co-state function has the constraint multiplier:

$$\dot{\lambda}_1 = -\frac{\partial H}{\partial N} = -r_2\lambda_1 + 2r_2 b_2 \lambda_1 N + \lambda_1 c_4 T + \lambda_2 c_3 T + \eta \tag{3.17}$$

- Control or switching function, that found by deriving the Hamiltonian equation with respect to control variable u :

$$switching\_function = \frac{\partial H}{\partial u} = w_2(1 + \lambda_4) - a_3\lambda_1 - a_2\lambda_2 - a_1\lambda_3 \tag{3.18}$$

- The value of the constraint multiplier η , that found by deriving the switching function once with the time.

$$\eta_1 = \frac{1}{a_3}\left[-a2\left(-w_1 + \lambda_1 c_4 N - \lambda_2 r_1 + 2\lambda_2 r_1 b_1 T + \lambda_2 c_2 I + \lambda_2 c_3 N - \lambda_3 \left(\frac{\alpha \rho I}{(\alpha + T)^2} \right) + \lambda_3 c_1 I - w_1 \lambda_4 \right) \right.$$
$$\left. -a1\left(\lambda_2 c_2 T - \lambda_3 \left(\frac{\rho T}{\alpha + T} \right) + \lambda_3 c_1 T + \lambda_3 d_1 \right) \right] - \left(-r_2\lambda_1 + 2r_2 b_2 \lambda_1 N + \lambda_1 c_4 T + \lambda_2 c_3 T \right) \tag{3.19}$$

- Whereas:

$$\eta = \begin{cases} \eta_1, & 0.75 - N \geq 0 \\ 0, & otherwise \end{cases} \tag{3.20}$$

- Bang-bang control to minimize the objectives function:

$$u = \begin{cases} u_{\min}, & switching\_function > 0 \\ u_b, & C \equiv 0 \\ u_{\max}, & switching\_function < 0 \end{cases} \tag{3.21}$$

- The control value inside the boundary arc period, when the state value reached the state constraint, $C \equiv 0$ equal:

$$u_b = \frac{1}{a_3}\left[r_2 N(1 - b_2 N) - c_4 TN\right] \tag{3.22}$$

- The value of control variable $u_i \in \left[u_{\min} \quad u_{\max}\right]$ between or equal the minimum u_{min}= 0, and the maximum limit u_{max}=0.1, inside time periods of the simulation time $t_i \in [t_i \quad t_{i+1}]$ that discretized into N of intervals from the first day t_0 until the final day t_f of the treatment period such that:

$$t_0 = t_0 < t_1 < ..... < t_i < .. < t_N = t_f$$

$$i = 1, 2, ..., N$$

3.6 Constraint Handling Technique for Method 1 and Method 2

As mentioned in the beginning of this chapter, the state constraint in method 1 and method 2 achieved by SI's and EA's algorithm, by using the penalty method that explained before in section 2.6, whereas the CMOOP, converted to un-concentrated MOOP. After applied the penalty method on the Eq 3.4 and Eq 3.5 with the state constraint Eq 3.6 became:

$$\min(\Psi_1(t)) = J_1(t) + \mu p(C(t)) \tag{3.23}$$

$$\min(\Psi_2(t)) = J_2(t) + \mu p(C(t)) \tag{3.24}$$

Whereas, J_1 is the first objective function Eq 3.4, J_2 is the second objective function Eq 3.5, and μ is the penalty factor. $p(C(t))$ it's the penalty value such that:

$$p(t) = \begin{cases} 0, & C_i > 0 \\ C_i, & else \end{cases} \tag{3.25}$$

Whereas, $i \in [1 \quad N]$, N is the number of time discretization.

CHAPTER 4: RESULTS AND DISCUSSION

4.1 Introduction

This chapter explain the equipment's that have been used in this work, also present and discuss the results of the three Cases Study, the pareto optimal front and the results of the best point combining with the number of iterations that used to discover out.

4.2 Equipment's:

The results of this work carried out by using a desktop computer, core i7 with 8G RAM, and MATLAB R2016a is the software that had been used.

4.3 Case Study 1:

The mathematical model that used in this work has 14 parameters there are shown and explained in section 3.2, the values of some these parameters are the main differences with the three cases. The following Table 4.1 show the values that have been used in case study 1:

Table 4.1: Parameter Values for Case Study 1

Parameter	a_1	a_2	a_3	b_1	b_2	c_1	c_2	c_3	c_4	r_1	r_2	d_1	α	ρ	s
Value	0.2	0.3	0.1	1	1	1	0.5	1	1	1.5	1	0.2	0.3	0.01	0.33

The following Figure 4.1 shows the Pareto Optimal Front (POF) of case study 1 for the three methods that mentioned before in section 3.4 by using M-MOPSO algorithm, Figure 4.2 presents the results of POF using MOPSO algorithm, figure 4.3 display the

POF results for the three methods using MOEAD algorithm, and the POF results that generated by using MODE algorithm shown in figure 4.4. The red points represent the results of POF for method 1, the green points represent the results of POF for method 2 and POF of method 3 represented by blue points.

The POF curves for each method of the three almost the same with the all used algorithms. In general, the results of POF for method 3 are the closest to the origin point comparing with the POF results of other two methods, followed by the results of method 2 that's apparently better than the POF curve of method 1 that used purely SI and EA algorithms to solve the CMOOP. This result appeared in the all figures (4.1- 4.4) of POF for the first case study.

This result shows increasing in the results efficiency by the hybridization between the Augmented Lagrangian Approach (ALA) and the SI and EA algorithm, especially in method 3 whereas the state constraint achieved by the optimal control theory, this thing removed all the challenges that face the SI and EA for dealing with the sate constraint, and that's make the search space smaller than in method 1. Despite of this, the hybridization in Method 2 also shows results improvement comparing with purely algorithms in method 1.

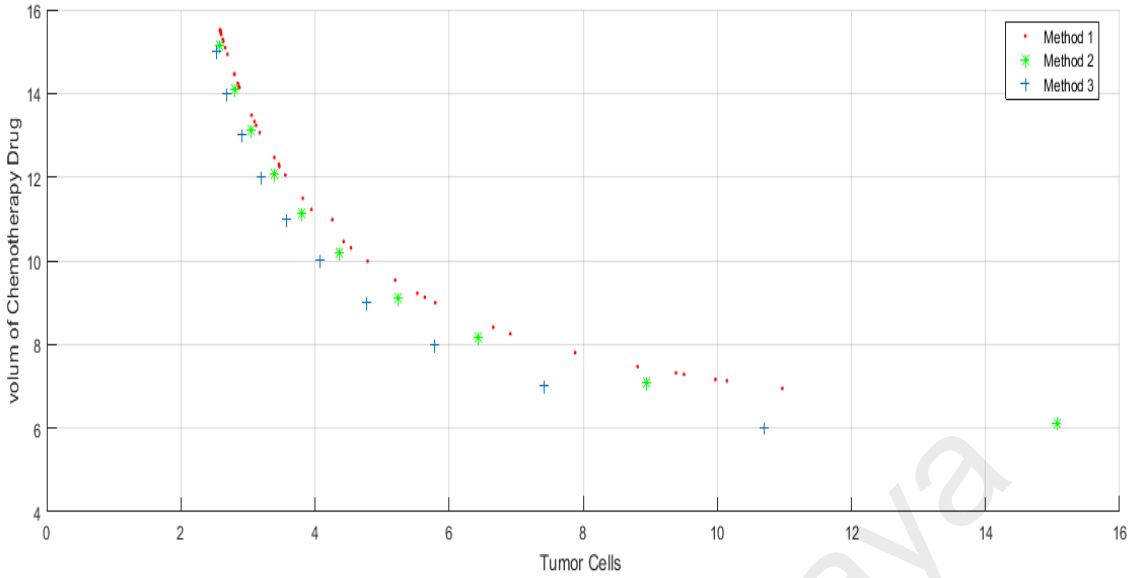

Figure 4.1: Pareto Optimal Set for Case1 By Using M-MOPSO

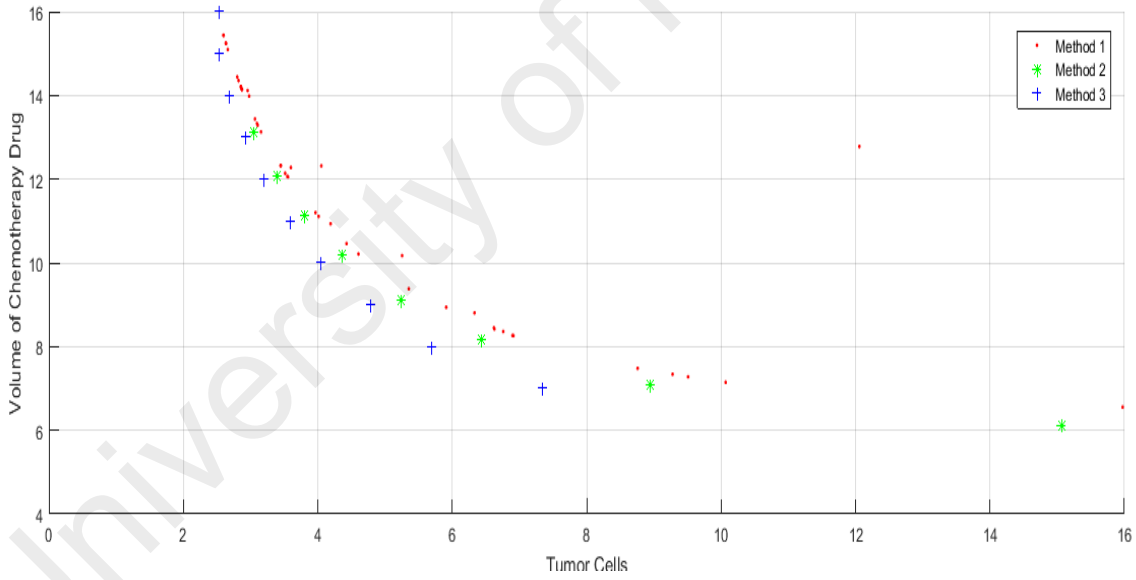

Figure 4.2: Pareto Optimal Set for Case1 By Using MOPSO

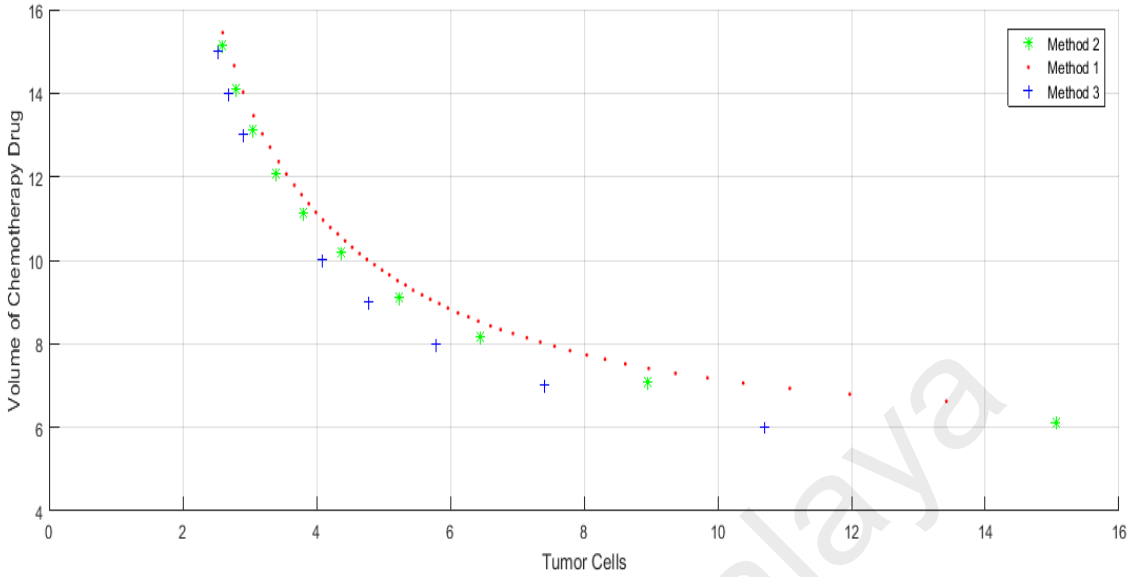

Figure 4.3: Pareto Optimal Set for Case1 By Using MOEAD

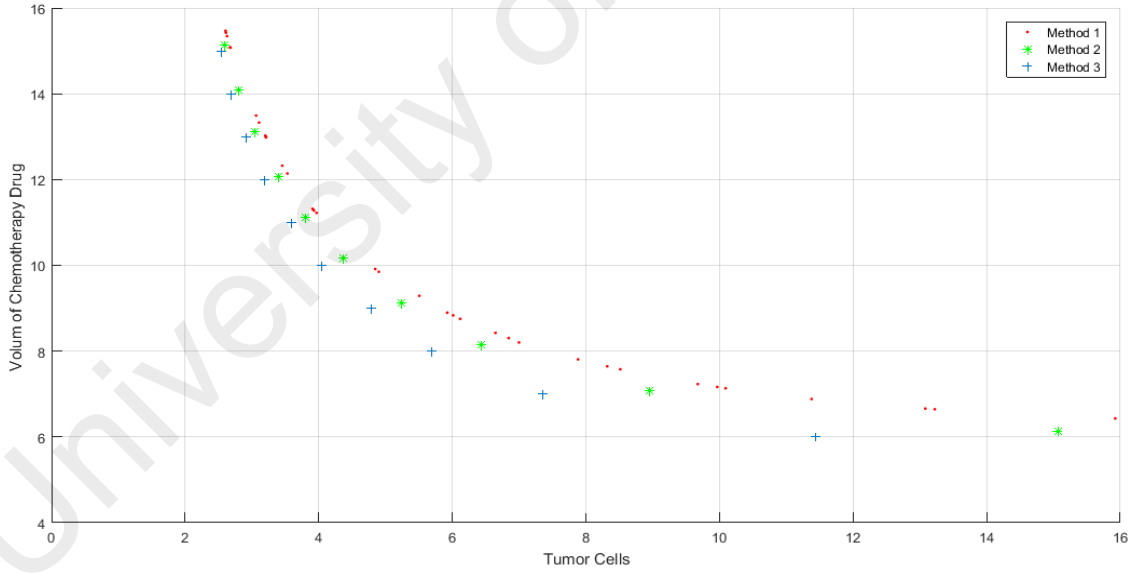

Figure 4.4: Pareto Optimal Set for Case 1 By Using MODE

Figures (4.5 - 4.8), shows the curves of the best point with the number of iterations for the three methods that explained before in section 3.4 using M-MOPSO, MOPSO, MOEAD, and MODE sequentially. Whereas the results of method 1 appears by the red line, the results of method 2 represent by the green line, and the blue line shows the results of method 3.

Method 1 by using M-MOPSO have taken more than 120 iterations until discovered the best point as appears in Figure 4.5, as shown in Figure 4.6 method 1 needed 150 iterations using MOPSO to find the best point, and more than 50 iterations have been used for method 1 by using MOEAD as display in Figure 4.7, finally, around 30 iterations needed for MODE in method 1 to figured out the best point of its own, while the hybridizations methods 2 and 3 they used just two iterations within all algorithms until discovered the best point.

As shown, Method 2 and 3 have used a number of iterations much less than used by Method one. This result shows how the hybridizations methods reached the best point faster than that used a purely SI and EA algorithms.

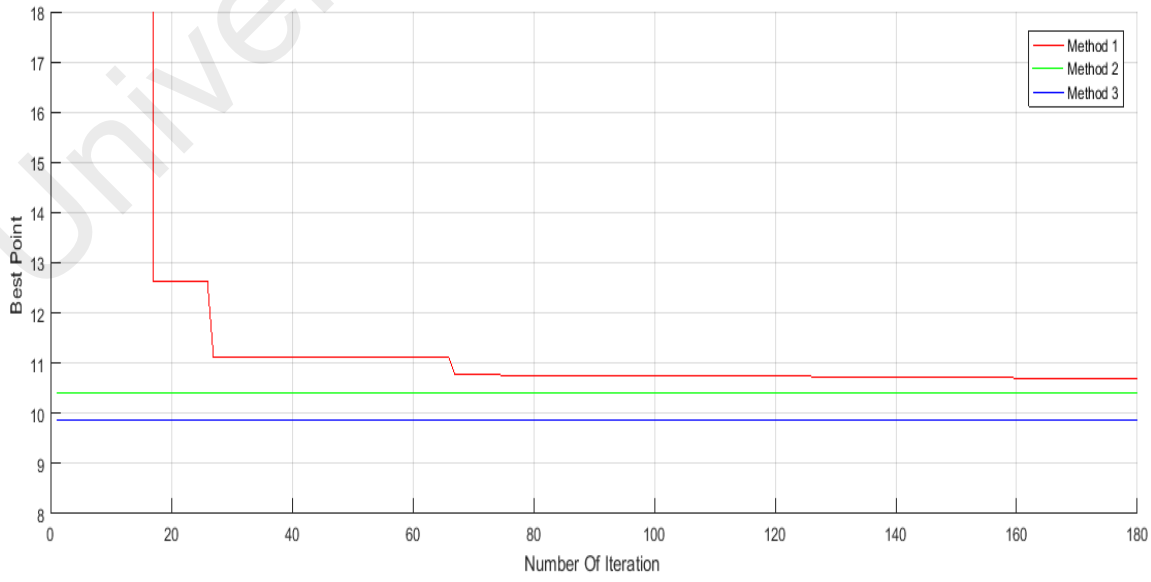

Figure 4.5: Best Point vs Iterations Case 1 By Using M-MOPSO

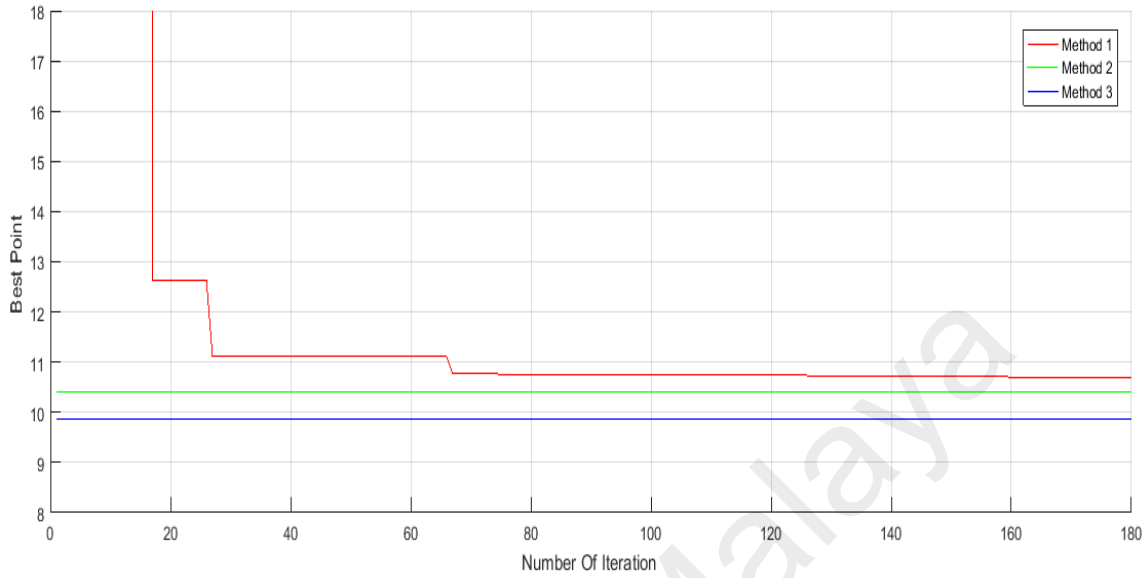

Figure 4.6: Best Point vs Iterations Case 1 By Using MOPSO

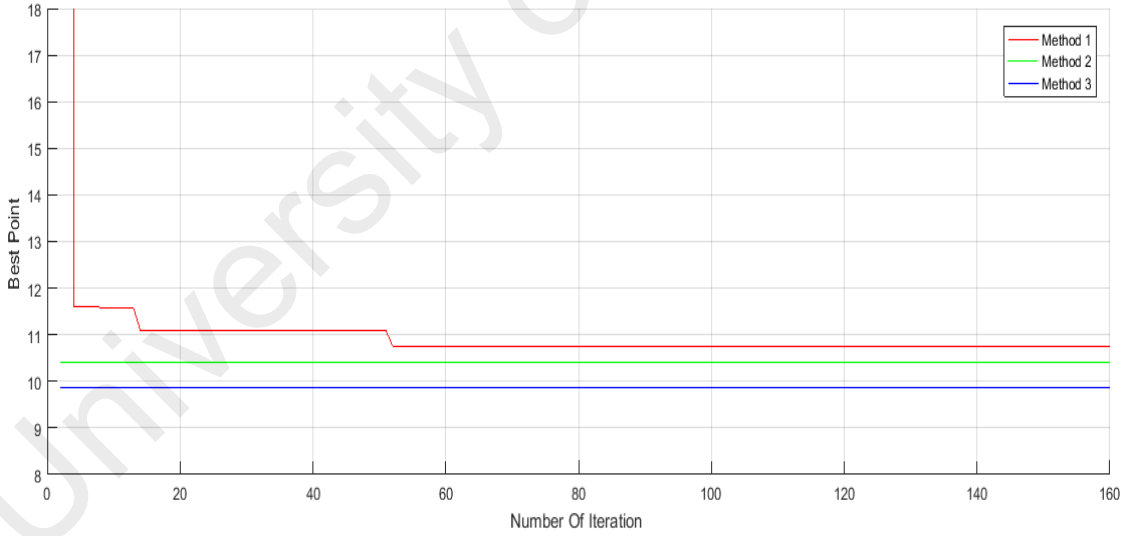

Figure 4.7: Best Point vs Iterations Case 1 By Using MOEAD

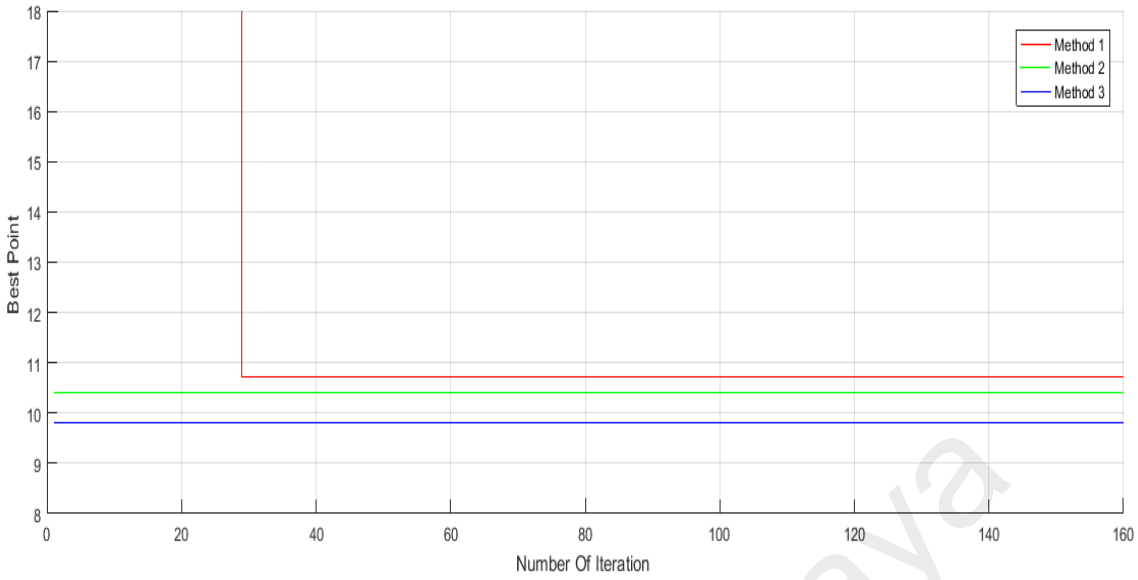

Figure 4.8: Best Point vs Iterations Case 1 By Using MODE

The following Table 4.2, summarized the best point results of case study 1, for the three methods, and it's shows the best points for each method, and the distance between the origin point and the best point, the number of iterations that used, also the tumor size and chemotherapy concentration for that point.

As appears, method 3 have the lowest point between the three methods, followed by the best point of method 2 that's shown better than of method 1. Also, the results difference between SI's and EA's algorithms, for the chemotherapy and tumor concentrations in method 1 is clearly appeared, while in method 2 and 3 the results almost the same regardless the algorithm that have been used. This improved how the hybridizations methods became robust more than the purely method.

Table 4.2: Final Results for Case Study 1

Method	Algorithm	Best Distance	No. Iterations	Tumour Concentration	Drug Concentration
1st Method	M-MOPSO	10.68	160	6.303	8.622
	MOPSO	10.67	123	6.127	8.375
	MOEAD	10.68	376	5.891	8.848
	MODE	10.71	165	5.911	8.911
2nd Method	M-MOPSO	10.39	2	6.44	8.159
	MOPSO	10.39	2	6.44	8.159
	MOEAD	10.39	2	6.44	8.159
	MODE	10.39	2	6.44	8.159
3ed Method	M-MOPSO	9.875	2	5.68	8
	MOPSO	9.82	2	5.69	8
	MOEAD	9.875	2	5.789	8
	MODE	9.82	2	5.69	8

4.4 Case Study 2:

In Case Study 2, the values of the parameters are the same that have been used in case study 1, only with a change in the value of the influx rate s to became equal 0.31. The main difference between case study 1 and 2 is the value of source rate of immune cells.

The following figures shows the results of the POF for case study 2, that generated for all Methods, but every time assisted with different algorithm, Figure 4.9 have the POF by Using M-MOPSO, the results in Figure 4.10 by using MOPSO, Figure 4.11 present the results of the pareto optimal front by using MOEAD, Finally the results in Figure 4.12 by using MODE.

As appears, the hybrid methods have a better POF results comparing with that's in purely method, whereas, the curve of POF for method 3 has the shortest distance with the origin point, followed by the POF of method 2, while the results of POF for method 1 has the longest distance with the origin point.

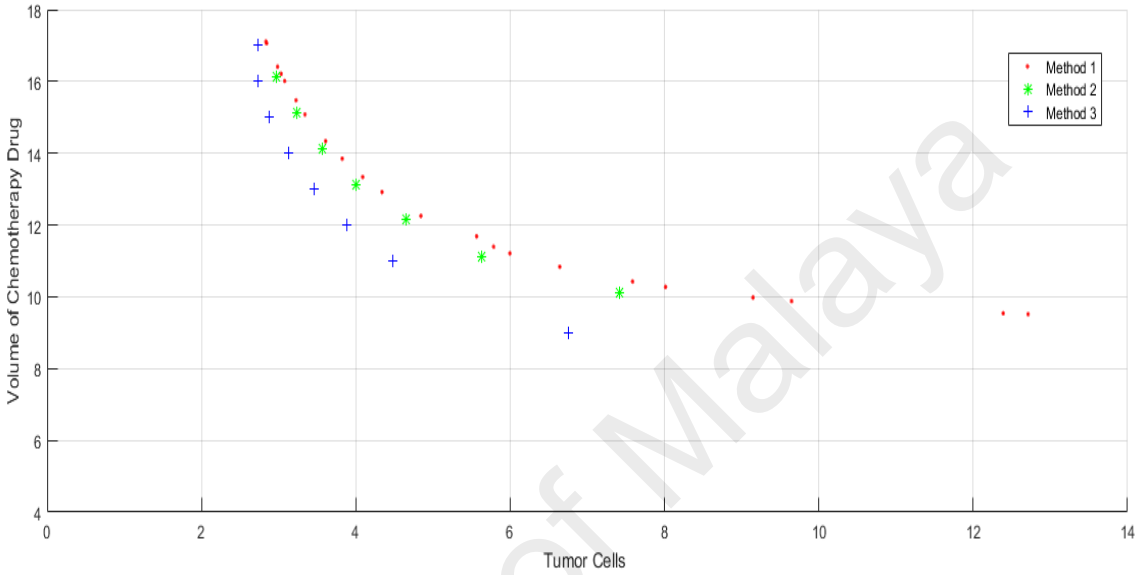

Figure 4.9 Pareto Optimal Set for Case 2 By Using M-MOPSO

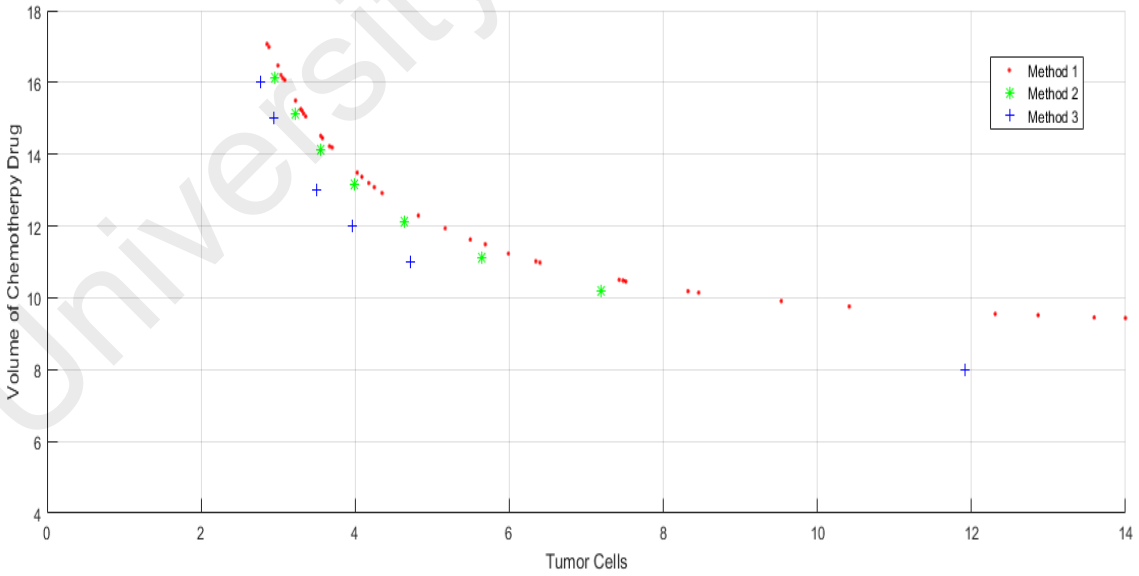

Figure 4.10: Pareto Optimal Set for Case 2 By Using MOPSO

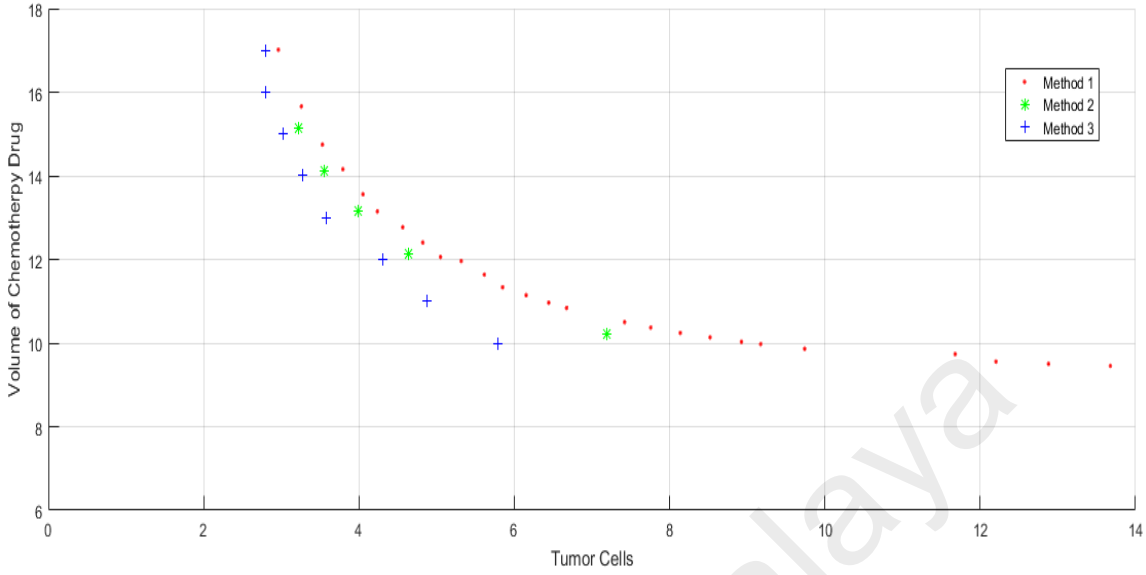

Figure 4.11: Pareto Optimal Set for Case 2 By Using MOEAD

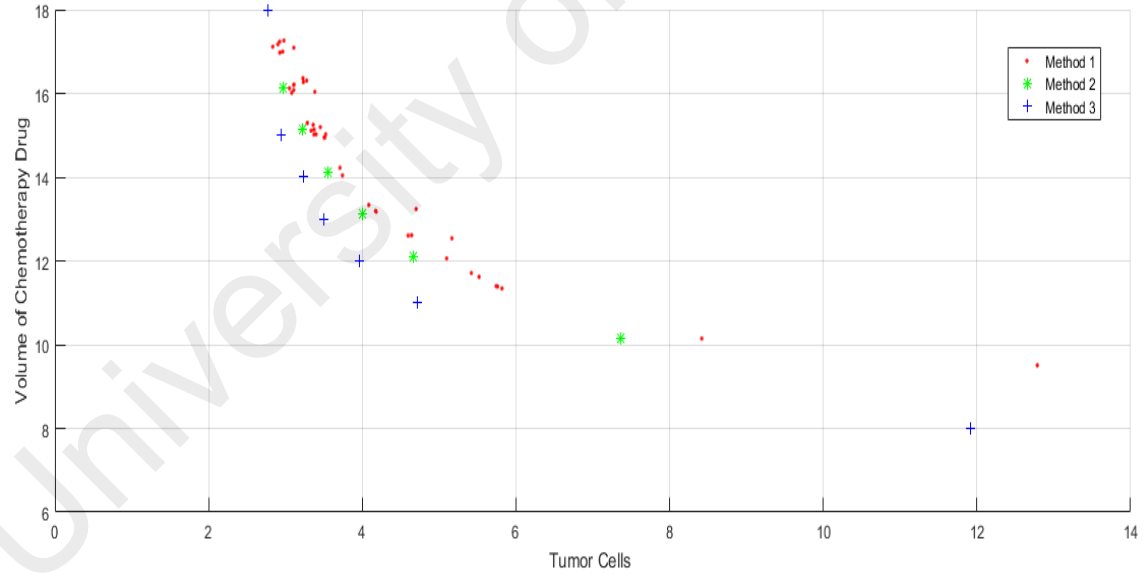

Figure 4.12: Pareto Optimal Set for Case 2 By Using MODE

Figures (4.13 – 4.16), shows the curves of the best point with the number of iterations of case study 2 for the three methods that explained before in section 3.4 using M-MOPSO, MOPSO, MOEAD, and MODE sequentially. Whereas the results of method

1 appears in the red line, the results of method 2 represent by the green line, and the blue line shows the results of method 3.

As appears in Figure 4.13, M-MOPSO have taken more than 120 iterations in method 1 until discovered the best point, as shown in Figure 4.14 method 1 needed 90 iterations using MOPSO to find the best point, and around 35 iterations have been used for method 1 by using MOEAD algorithm as display in Figure 4.15. Finally, more than 600 iterations needed for MODE in method 1 to figured out the best point of its own as appear in Figure 4.16, while the hybrid methods 2 and 3 used just two iterations within all algorithms until discovered the best point. As shown, Method 2 and 3 have used a number of iterations much less than used by Method one. This result shows how the hybridizations methods reached the best point faster than that used a purely SI and EA algorithms.

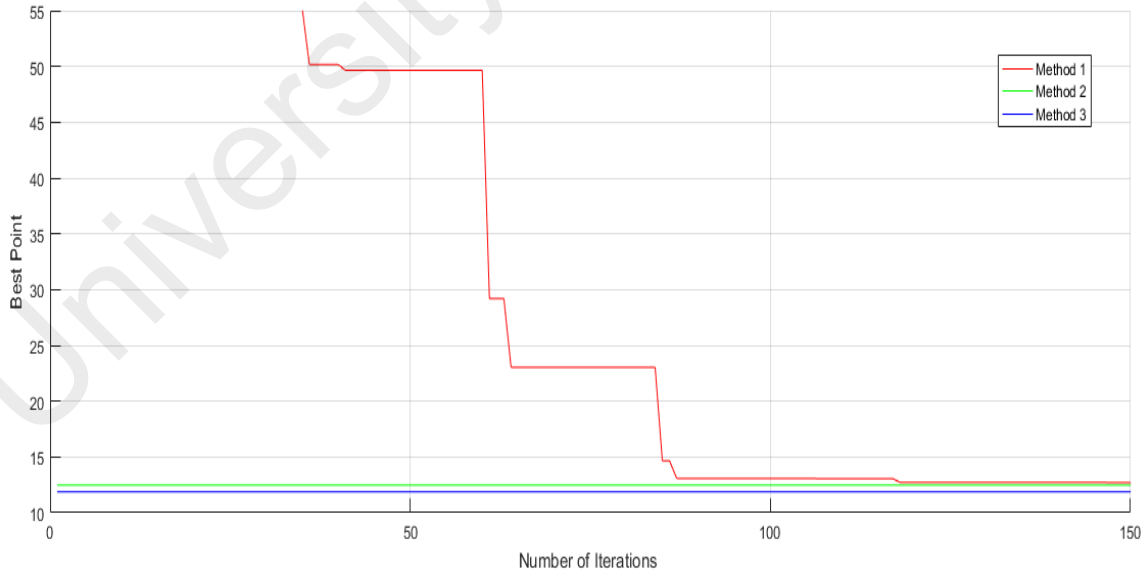

Figure 4.13: Best Point vs Iterations Case 2 By Using M-MOPSO

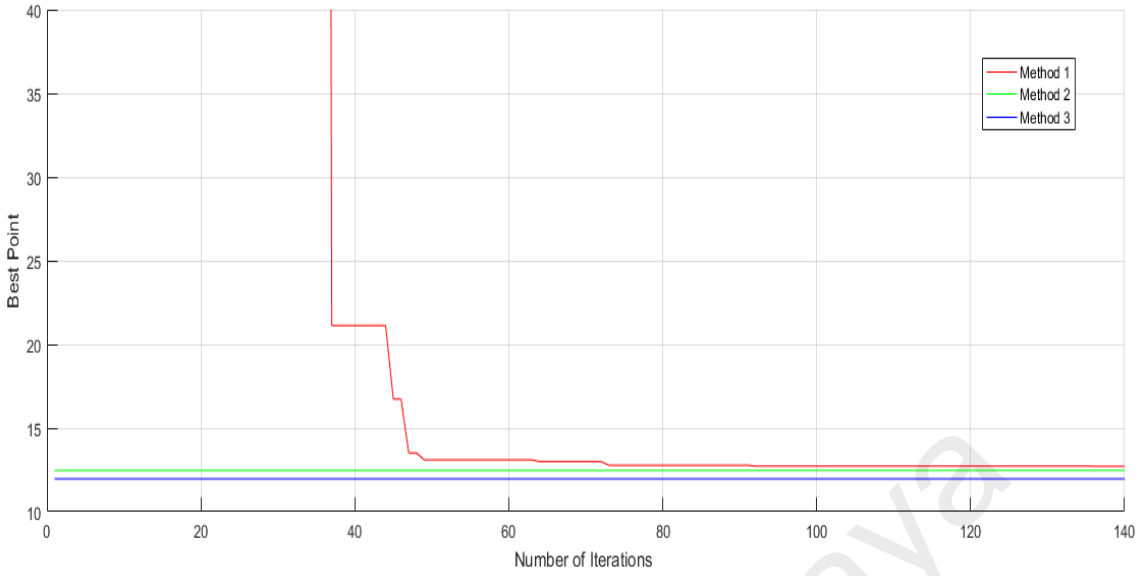

Figure 4.14: Best Point vs Iterations Case 2 By Using MOPSO

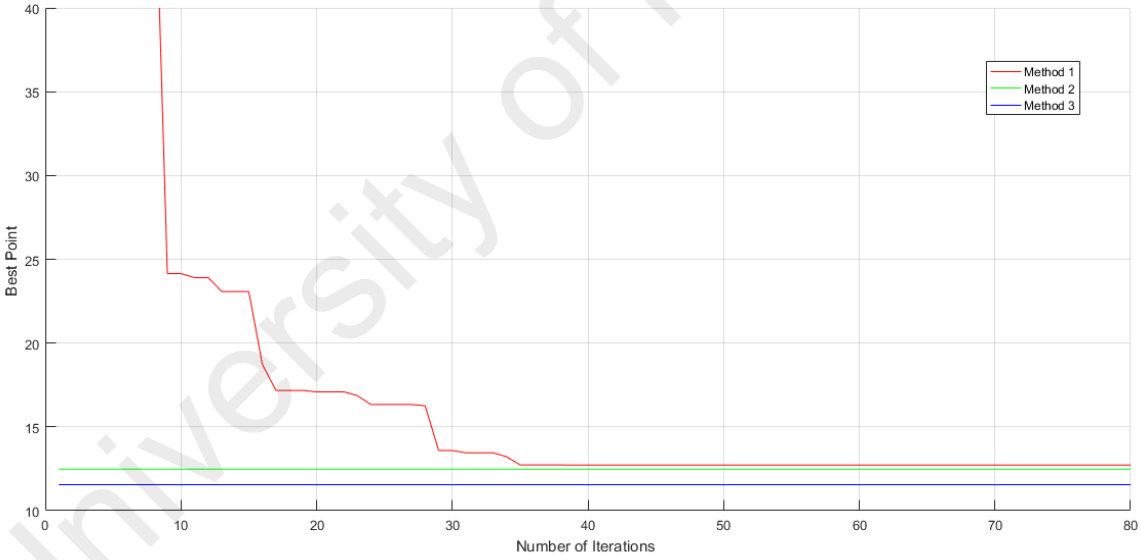

Figure 4.15: Best Point vs Iterations Case 2 By Using MOEAD

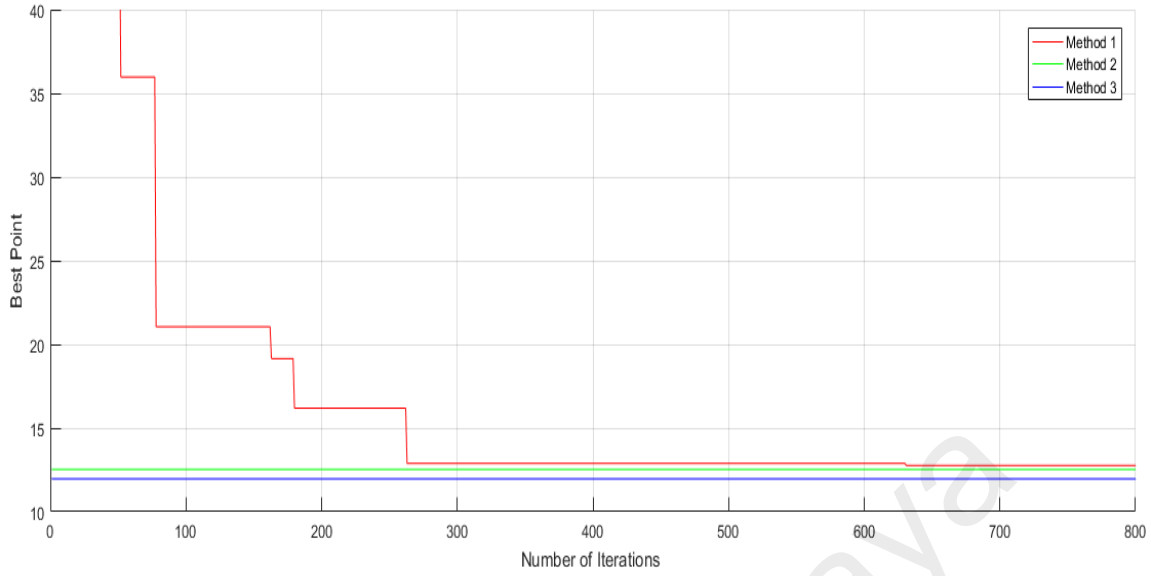

Figure 4.16: Best Point vs Iterations Case 2 By Using MODE

The following Table 4.3, summarized the best point results of case study 2, for the three methods that explained before in section 3.4, and it's shows the best points for each method, and the distance between the origin point and the best point, the number of iterations that used, also the tumor size and chemotherapy concentration at that point.

As appears, the best point of method 3 has the lowest distance with the origin point, between the results of best points for the three methods, followed by the best points of method 2, while the best points of method 1 have the longest distance with the origin. This result shows how the efficiency of the results increased by hybridization between optimal control theory and un-conventional methods (SI and EA algorithms).

Another result, as appears from Table 4.3, The reduction in the immune source rate in case study 2, caused increases in the volume of chemotherapy compared with that have been found in case study 1, that shown in Table 4.2, whereas the job of chemotherapy is assisting the immune system. The chemotherapy will be deliver to the tumor site until the immune system becomes strong enough to kill and fight against the tumor alone.

Table 4.3: Final Results for Case Study 2

Method	Algorithm	Best Distance	No. Iterations	Tumour Concentration	Drug Concentration
1st Method	M-MOPSO	12.714	118	6.235	11.08
	MOPSO	12.70	155	6.234	11.06
	MOEAD	12.71	39	6.309	11.047
	MODE	12.756	640	5.838	11.341
2nd Method	M-MOPSO	12.47	2	5.63	11.124
	MOPSO	12.47	2	5.641	11.12
	MOEAD	12.48	2	7.198	10.198
	MODE	12.52	2	7.634	10.13
3ed Method	M-MOPSO	11.87	2	4.479	11
	MOPSO	11.96	2	4.7	11
	MOEAD	11.65	2	5.88	10
	MODE	11.96	2	4.71	11

4.5 Case Study 3

The parameters values in case study 3 are the same in case study 1, just with changing in the value of immune response rate ρ reduced to became equal to 0.02.

The following figures (4.17 – 4.20) shows the results of the POF's for case study 3, that generated for all three methods, but every time assisted with different algorithm, M-MOPSO, MOPSO, MOEAD and MODE sequentially. The results of POF for method 1 represented by red points, the green pointes represent the results of POF for method 2, and the blue points represent the results of POF for method 3.

The results of the hybrids methods 2 and 3 shown more efficient than un-hybrid method Whereas the results of POF for method 1 are the worst between the POF's results of the three methods, where it has the longest distance with the origin point, and the POF

of method 3 has the lowest distance with the origin point, followed by the POF results of method 2. This proved how the hybridization between un-conventional method's (SI, EA) and the conventional method (OCT) increase the results quality.

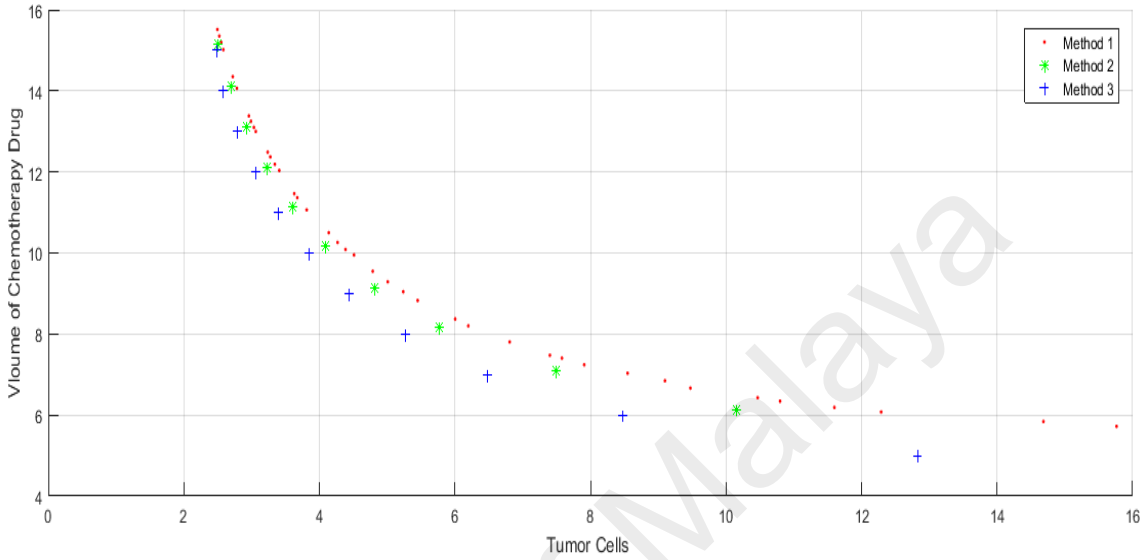

Figure 4.17: Pareto Optimal Set for Case 3 By Using M-MOPSO

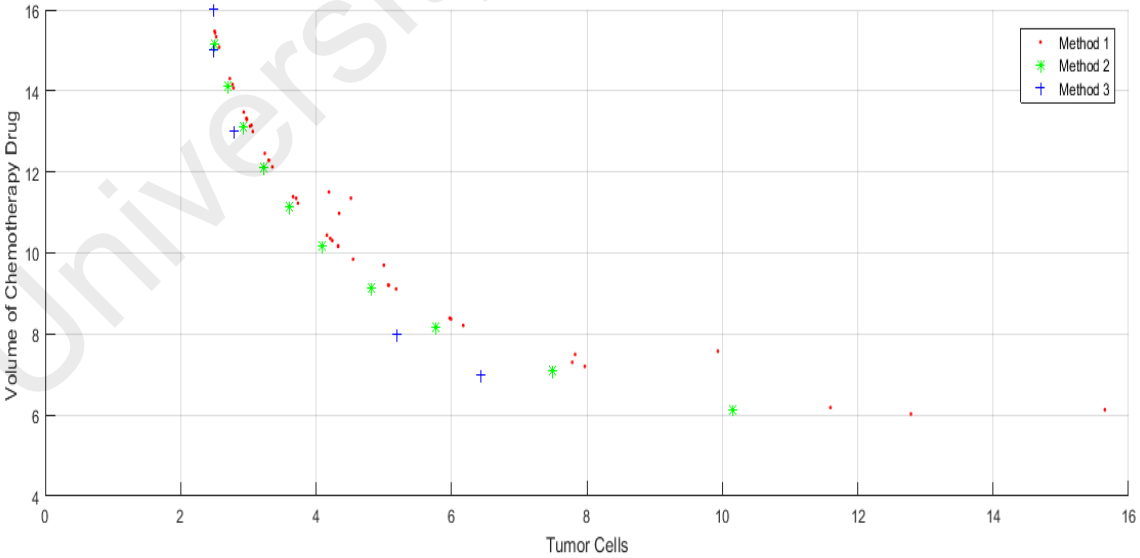

Figure 4.18: Pareto Optimal Set for Case 3 By Using MOPSO

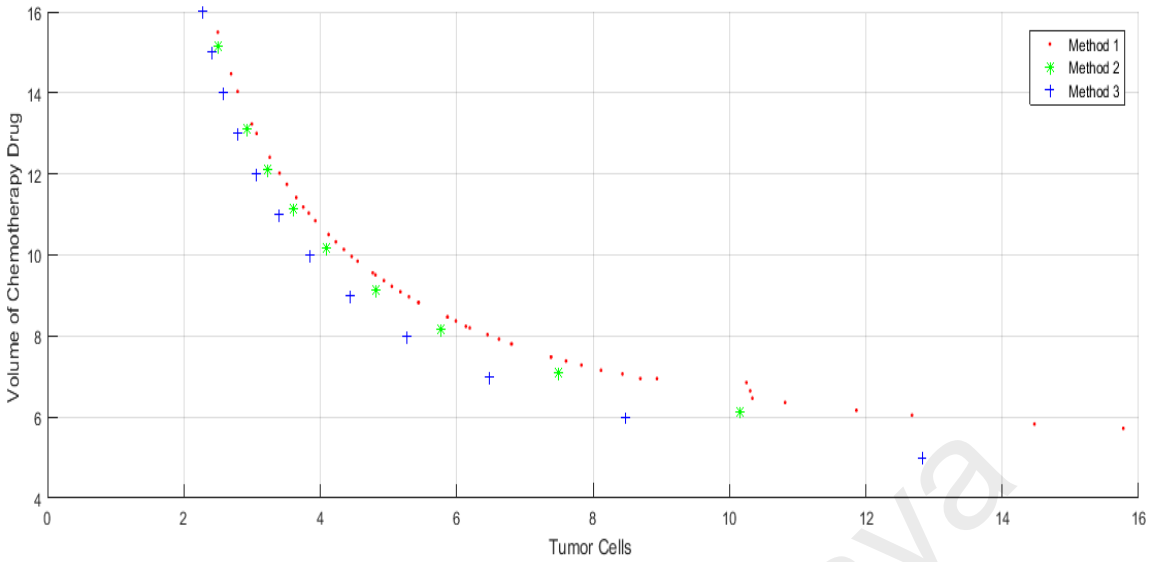

Figure 4.19: Pareto Optimal Set for Case 3 By Using MOEAD

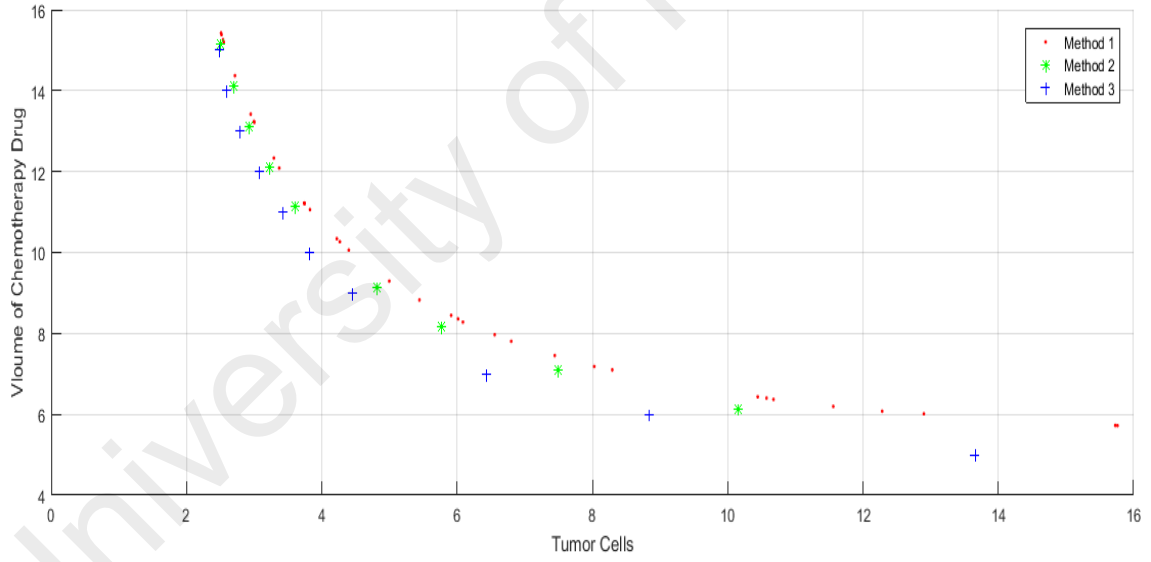

Figure 4.20: Pareto Optimal Set for Case 3 By Using MODE

The curves of the best point with the number of iterations for case study 3 shown in Figures (4.21 – 4.24), using M-MOPSO, MOPSO, MOEAD, and MODE sequentially, for the three methods. Whereas the results of method 1 appear in the red line, the results of method 2 represent by the green line, and the blue line shows the results of method 3.

As shown, method 1 by using M-MOPSO have taken more than 100 iterations until discovered the best point as appears in Figure 4.21, method 1 needed 80 iterations using MOPSO to find the best point as shown in Figure 4.22, and around 75 iterations have been used for method 1 by using MOEAD as display in Figure 4.23. Finally, more than 120 iterations needed by MODE in method 1 to figured out the best point of its own, as shown in Figure 4.24, while the hybridizations methods 2 an 3 they just used two iterations within all algorithms until discovered the best point. This results as like the previous, shows and proves how the hybridizations methods became faster than the pure method, and the quality of the best point points became higher.

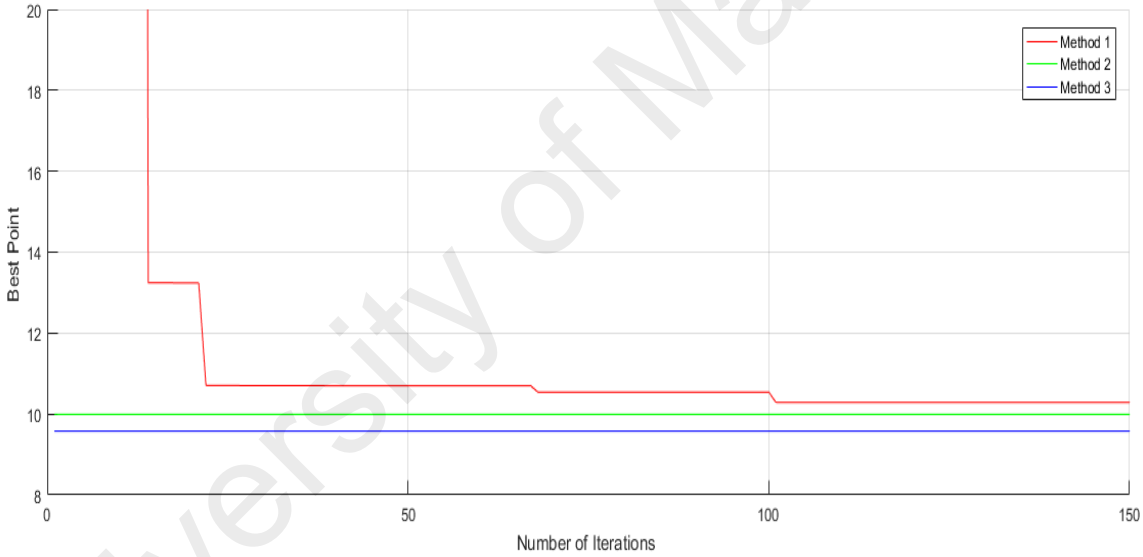

Figure 4.21: Best Point vs Iterations Case 3 By Using M-MOPSO

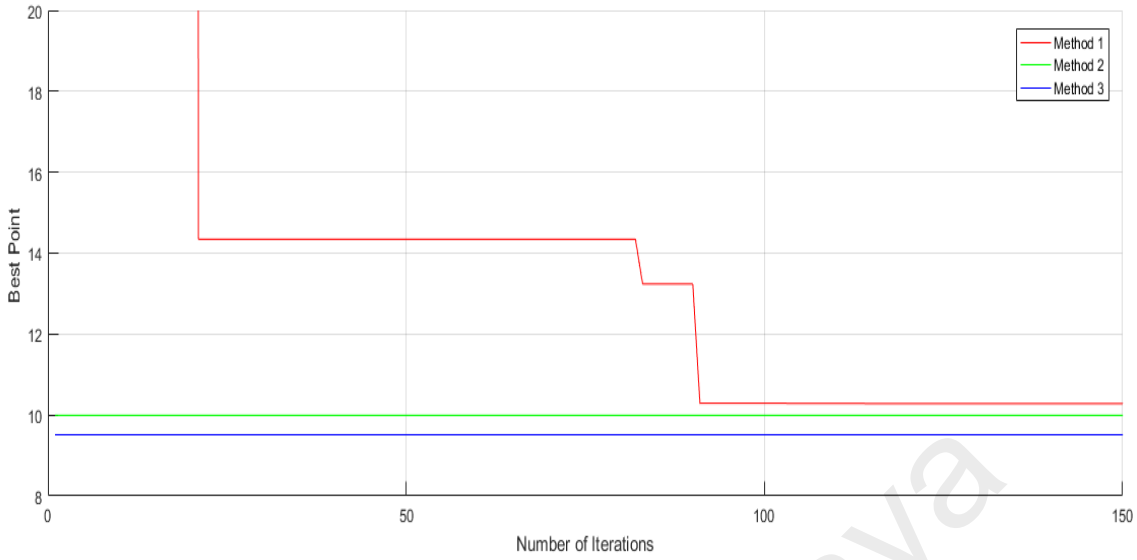

Figure 4.22: Best Point vs Iterations Case 3 By Using MOPSO

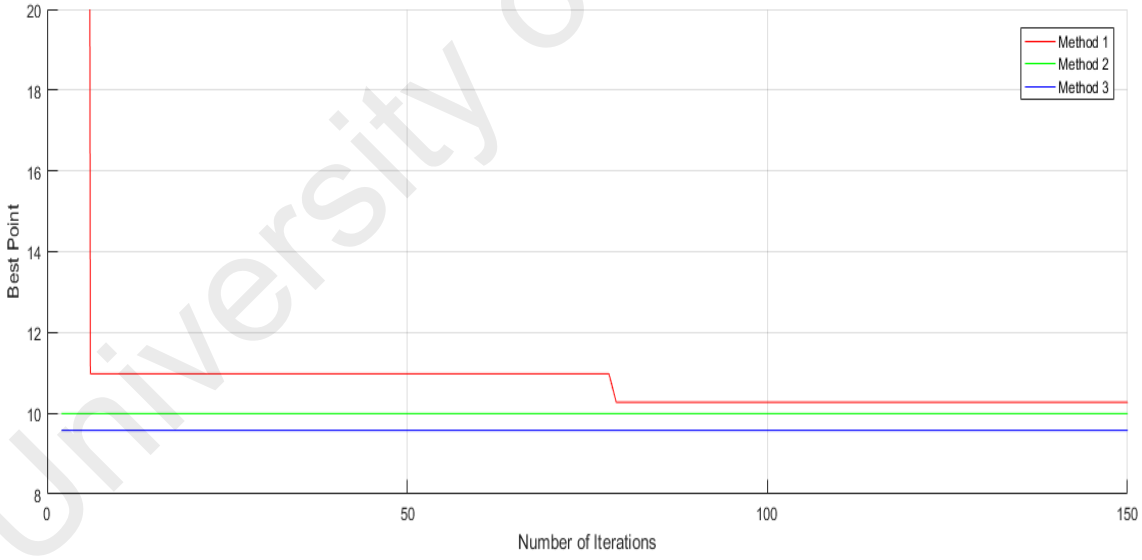

Figure 4.23: Best Point vs Iterations Case 3 By Using MOEAD

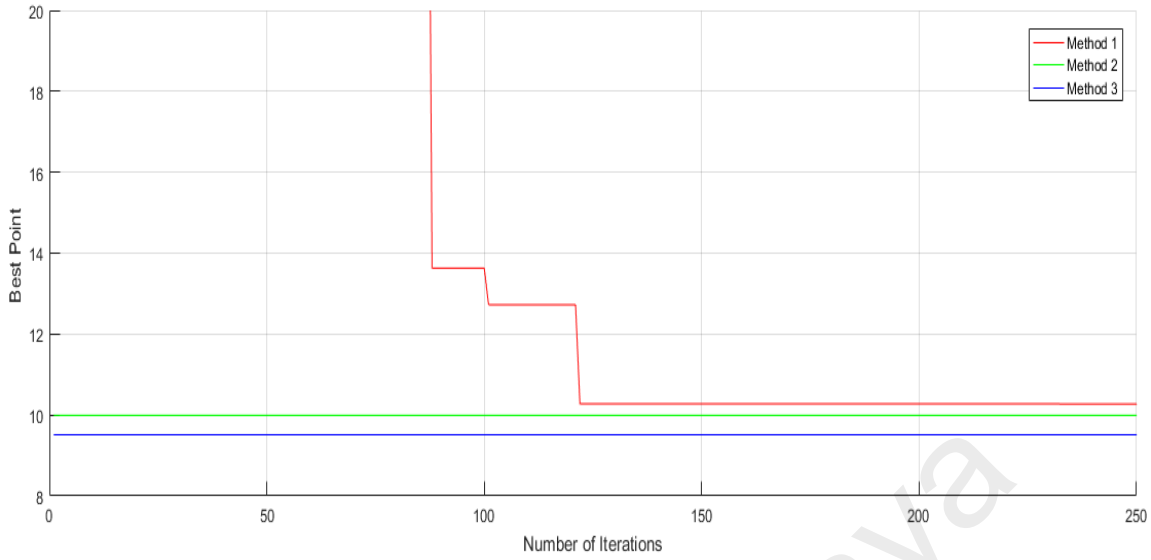

Figure 4.24: Best Point vs Iterations Case 3 By Using MODE

The results summary of the best point for case study 3, shown in the following Table 4.4, it shows the best points for each method, and the distance between the origin point and the best point, the number of iterations that used, also the tumor size and chemotherapy concentration at that point.

As shown in Table 4.4, the best points of method 1 are the farthest from the origin point, while the best points of method 3 are the lowest to the origin point, followed by the results of method 2. The best point's result for the hybridization methods has the lowest amount of chemotherapy and tumor size, these results show and proved how the integration between the augmented Lagrangian in OCT with the SI's and EA's algorithms reducing the searching efforts and increase the results efficiency.

Table 4.4: Final Results for Case Study 3

Method	Algorithm	Best Distance	No. Iterations	Tumour Concentration	Drug Concentration
1st Method	M-MOPSO	10.28	101	6.209	8.199
	MOPSO	10.27	122	6.193	8.199
	MOEAD	10.27	95	6.191	8.199
	MODE	10.28	91	6.126	8.265
2nd Method	M-MOPSO	9.994	2	5.772	8.159
	MOPSO	9.994	2	5.772	8.159
	MOEAD	9.994	2	5.772	8.159
	MODE	9.994	2	5.772	8.159
3ed Method	M-MOPSO	9.578	2	5.267	8
	MOPSO	9.513	2	6.441	7
	MOEAD	9.578	2	5.267	8
	MODE	9.513	2	6.441	7

The following Figures (4.25 – 4.27) show the best point for method 1, method 2 and method 3, sequential, of case study 3, by using MODE algorithm that used the lowest number of iterations compared with other algorithms in method 1, part A presented the cells concentrations, red line presented the tumor cells, blue line represent the concentration of normal cells, and yellow line represents the immune cells concentration. Part B shows the time schedule for the chemotherapy.

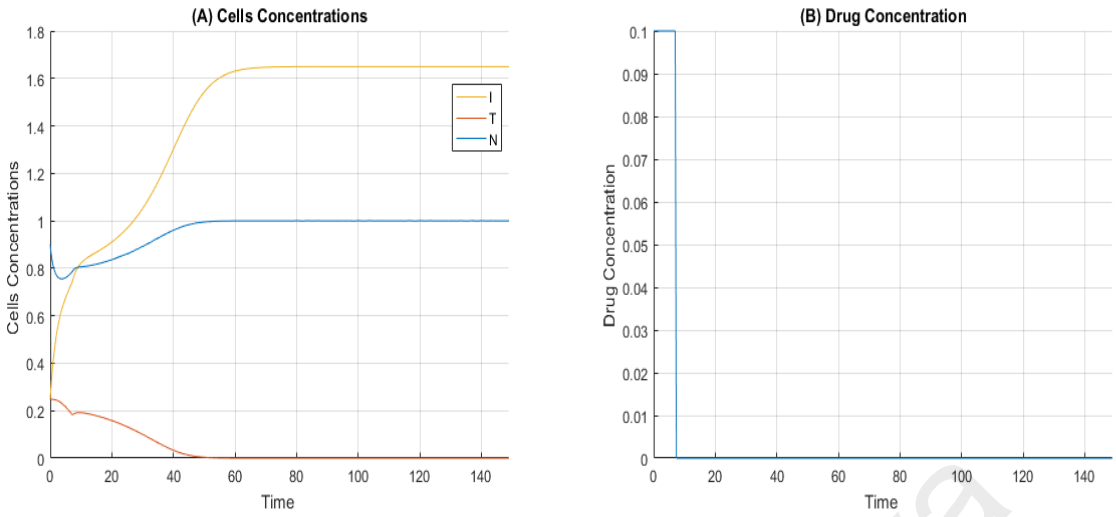

Figure 4.25: Best Point of Case 3, Cells Concentrations (A) and Drug Concentration (B) for Method 1 Using MOEAD

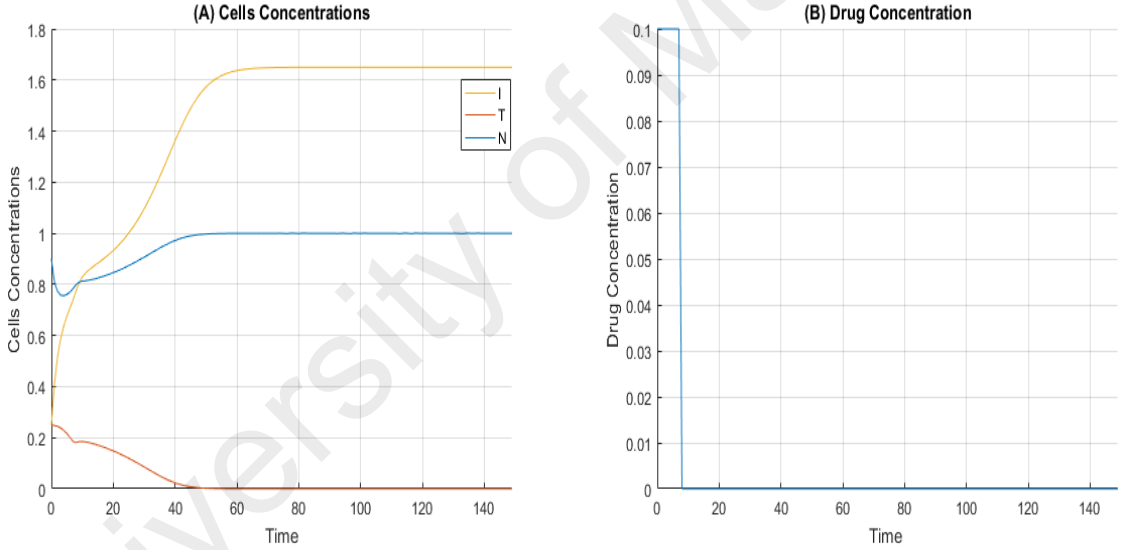

Figure 4.26: Best Point of Case 3, Cells Concentrations (A) and Drug Concentration (B) for Method 2 Using MOEAD

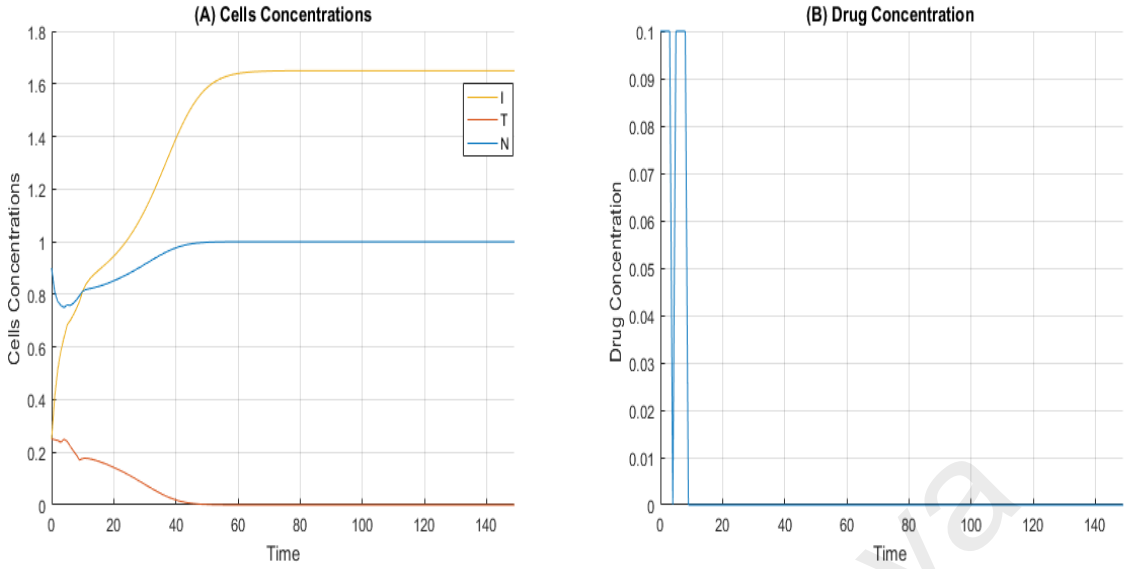

Figure 4.27: Best Point of Case 3, Cells Concentrations (A) and Drug Concentration (B) for Method 3 Using MOEAD

As shown, the chemotherapy applied and that caused death of the tumor cells, until the immune system become strong enough to fight alone against the tumor cells. As appears in Figure 4.25 (B) and Figure 4.26 (B) dose schedule of method 1 and 2, the chemotherapy applied continuously without any break. While, as appears in Figure 4.27 for method 3, when the normal cells concentration reached the safe limit and the state constraint Eq 3.6 became true, chemotherapy treatment stopped to give a chance for the normal cells to grow and the concentration of normal cells become beyond the safe level, for reducing the toxicity, then the chemotherapy applied again until the end of the treatment period.

Method 3 chemotherapy profile Figure 4.27 (B) is more real than in method 1 and 2, it's similar to the real life chemotherapy schedule that called chemotherapy protocol maximum tolerated dose (MTD) , whereas, drug dose is apply in a maximum allowable level followed by break after each round of the treatment, to reduce the toxicity and give time for the normal cells for growing (Ledzewicz, Schattler, Gahrooi, & Dehkordi, 2013).

CHAPTER 5: CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

This research project proposed a hybrid optimal control swarm intelligence to solve a CMOOP, two hybrid methods proposed, and the performance of these methods compared to the usual method (purely SI's and EA's algorithms), by solved a cancer chemotherapy mathematical model that proposed by Pillis and Radunskaya (De Pillis & Radunskaya, 2003), to minimize the drug and tumor cells concentrations with a state constraint to keep the concentration of the normal cells above some safe level. M-MOPSO, MOPSO, MODE, MOEAD are the four algorithms that have been used in this research project, the main results show as follow:

1- The hybrid methods (Method 2 & 3) used a much smaller number of iterations compared with that used by the purely SI and EA algorithms (Method 1).
2- Method 3, whereas the constrains including in calculations of the optimal control theory, got the best results comparing with that found by Method 1 and 2.
3- The results of method 2 are best than in Method 1.

This is leading to say the performance of hybrid techniques that combined between the optimal control theory and SI and EA algorithms is better than the performance of the usual methods that used purely SI and EA algorithms, for solving CMOOP. Hope these results will be helpful for clinicians or other people who are doing research on the chemotherapy treatment, that's finally aimed to reduce the suffering of the patients during the treatment period and save they lives.

5.2 Future Work

Using these hybrid methods to build an effective schedule for the chemotherapy treatment. And compare the result with treatment schedule that used in real life.

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