Computer Methods and Programs in Biomedicine 189 (2020) 105327

Contents lists available at ScienceDirect

Computer Methods and Programs in Biomedicine

journal homepage: www.elsevier.com/locate/cmpb

The combined effect of optimal control and swarm intelligence on optimization of cancer chemotherapy

Omar Shindi[a], Jeevan Kanesan[a,*], Graham Kendall[b], Anand Ramanathan[c]

[a] Department of Electrical Engineering, Faculty of Engineering, University of Malaya, 50603, Kuala Lumpur, Malaysia
[b] School of Computer Science, University of Nottingham, Malaysia Campus, 43500 Semenyih, Malaysia
[c] Department of Oral & Maxillofacial Clinical Sciences, Oral Cancer Research – Coordinating Centre, Faculty of Dentistry, University of Malaya, 50603, Kuala Lumpur, Malaysia

ARTICLE INFO

Article history:
Received 28 June 2019
Revised 16 December 2019
Accepted 8 January 2020

Keywords:
Hybrid optimal control
Multi objective optimization
Constrained multi-objective optimization
Cancer chemotherapy
Particle swarm optimization
Evolutionary algorithms

ABSTRACT

Background and Objectives: In cancer therapy optimization, an optimal amount of drug is determined to not only reduce the tumor size but also to maintain the level of chemo toxicity in the patient's body. The increase in the number of objectives and constraints further burdens the optimization problem. The objective of the present work is to solve a Constrained Multi- Objective Optimization Problem (CMOOP) of the Cancer-Chemotherapy. This optimization results in optimal drug schedule through the minimization of the tumor size and the drug concentration by ensuring the patient's health level during dosing within an acceptable level.

Methods: This paper presents two hybrid methodologies that combines optimal control theory with multi-objective swarm and evolutionary algorithms and compares the performance of these methodologies with multi-objective swarm intelligence algorithms such as MOEAD, MODE, MOPSO and M-MOPSO. The hybrid and conventional methodologies are compared by addressing CMOOP.

Results: The minimized tumor and drug concentration results obtained by the hybrid methodologies demonstrate that they are not only superior to pure swarm intelligence or evolutionary algorithm methodologies but also consumes far less computational time. Further, Second Order Sufficient Condition (SSC) is also used to verify and validate the optimality condition of the constrained multi-objective problem.

Conclusion: The proposed methodologies reduce chemo-medicine administration while maintaining effective tumor killing. This will be helpful for oncologist to discover and find the optimum dose schedule of the chemotherapy that reduces the tumor cells while maintaining the patients' health at a safe level.

1. Literature review

Cancer remains as one of the major worldwide health problems causing 8.8 million deaths in 2015 according to the World Health Organization (WHO) [1]. In the United States, cancer is the second highest cause of mortality, with an estimated 1735,350 new cancer patients and 609,640 deaths in 2018 [2]. This disease is caused by abnormal cells that spread and grow unbounded which destroys the patient's body and may cause death if no treatment is given at an early stage.

Cancer is a serious threat to a human's health. This disease can be treated by immunotherapy, surgery, chemotherapy and radiation therapy. Selection of the treatment relies on some criteria such as location, the stage of the tumor and the patient's health at that time. Chemotherapy occupies a crucial place in the current arsenal of treatments where it has proven to be very effective in treating cancer [3]. Chemotherapy stops the growth of the cancer cells and eventually kills them. However, it also affects the normal cells and for that reason, chemotherapy must be administered to the tumor cells in doses that balance its anticancer activity with minimum damage to normal cells [3–8]. This poses a problem for clinicians as the tumor resists the treatment at low drug concentrations but then increases in the drug concentration will destroy normal cells. Furthermore, cancer treatments have a huge economic impact. In 2015, the direct costs in the United States

* Corresponding author.
E-mail addresses: jievan@um.edu.my (J. Kanesan), graham.kendall@nottingham.edu.my (G. Kendall), drranand@um.edu.my (A. Ramanathan).

https://doi.org/10.1016/j.cmpb.2020.105327
0169-2607/

reached $80.2 billion [9] according to the Agency for Healthcare Research and Quality (AHRQ).

There is an urgent need to deliver the optimal amount of chemotherapy that maximizes the efficiency whilst reducing the toxic effects and at the same time reducing the financial cost of cancer treatment. Alleviating this problem involves engineers and mathematicians cooperating with clinicians and research oncologists to investigate and build mathematical models of tumor growth, aiming to better understand how the various aspects of growth and treatment interact with one another so as to deliver optimum chemotherapy treatments. In literature, there are many mathematical models that represent the effects of chemotherapy on the growth of tumor. Most of the mathematical models were built to emulate the pharmacodynamic and pharmacokinetic processes [10]. The pharmacodynamic processes describe the effects of the treatment dose on normal and malignant cells while pharmacokinetic processes characterize the distribution and metabolism of the treatment dose.

In optimal chemotherapy treatment analysis, traditional mathematical models have neglected the inter-influence of normal and cancerous cells as they focused on decreasing the tumor size by increasing the dose and reducing the treatment period in order, to decrease the drug resistance that develops at a low therapy intensity, thus eliminating the small tumor mass [11]. Later models embedded the negative effects of cancer cells on the normal cells in the optimal chemotherapy analysis [12], and the drug was applied constantly at maximum rate under the constraint of the normal cell population size to be maintained above a certain level along with constrained drug concentration. Unlike the previous models, the treatment period is determined based on the drug and toxicity constraints.

One of the important factors for tumor response to treatment is the strength of the patient's own immune response to the drug. Pillis and Radunskaya [13] developed a mathematical model of the immune response augmented to normal and tumor cells response towards chemotherapy in order to improve the optimal analysis of the chemotherapy treatment. Another mathematical model takes obesity into account where they found that diet and losing weight enhances the efficiency of the chemotherapy treatment [6]. The improvement in the cancer therapy models inevitably increases the number of constraints and objectives with the evolution from single objective optimization that focuses to minimize the tumor size to the multi-objective optimization that aims to reduce tumor size and the drug concentration. It appears there is a need for a robust optimization method that yields optimum outcome.

Optimal Control (OC) is applied to most of the existing cancer therapy mathematical models to obtain the optimum tumor and drug concentration. This can be carried out by two approaches, firstly the stochastic or the direct approach where the OC problem is converted into the Non-Linear Program (NLP). The second approach is more deterministic. Taking advantage of Pontryagin Maximum/Minimum Principle (PMP), the OC problem is converted into a boundary value problem. Some works used unconventional techniques. For example, one of them used the two PID controllers (proportional – integral – derivative) to maintain an acceptable treatment dose, toxicity and body drug concentration [14]. A linear time varying approximation technique was also used to solve the multi objective optimization problem of chemotherapy in cancer treatment to eliminate the cancer cells and to minimize the amount of drug concentration in the simulated model [5]. Sharifi et al. [15]used the Multiple Model Predictive Control (MMPC) to find the effective treatment program for the mixed chemotherapy and immunotherapy as a new cancer treatment strategy aimed to minimize the required treatment and reduce the tumor size.

Recently, with the increase in the number of objectives, variables and state constraints, most researchers tend to utilize Swarm Intelligence (SI) and Evolutionary Algorithms (EA) to address the constrained multi-objective optimization problem (CMOOP). Dhiman and Kumar [16] proposed a Multi-objective Spotted Hyena Optimizer (MOSHO) to address a constrained multi-objective engineering design problem. The ability of this algorithm to address the CMOOP was demonstrated by applying it to real-life optimization problems such as speed reducer design where the results showed good performance. Lobato et al. [17] used multi-objective optimization differential evolution algorithm (MODE) and Non-dominated Sorting Genetic Algorithm (NSGA II) to solve a multi-objective optimization problem that aims to find the optimal control strategy for drug cancer treatment. Fan et al. [18] proposed Push and Pull Search (PPS) combined with evolutionary algorithms to solve a multi objective optimization problem. The PPSO-MOEA/D showed the best results in comparison to five other algorithms; C-MOEA/D, MOEA/D-CDP, MOEA/D-IEpsilon, MOEA/D-SR and MOEA/D-Epsilon.

Zhang et al. [19–23] proposed new MOPSO algorithms to handle multi-objective optimization problems based on different features, such as Bare-Bones Multi-objective Particle Swarm Optimization algorithm (BB-MOPSO) to solve the environment/economic dispatch problems (EED) [21]. They introduced Cooperative Evolvement Multi-Objective Particle Swarm Optimization (CEMOPSO) based on cooperative sub swarm to deal with complex multi-objective optimization problems [22]. Another MOPSO algorithm based on adaptive jump operator called JMOPSO is proposed to solve the feature selection problem with unreliable data [23]. Also, a Multi- Objective Particle Swarm based on Feature Selection with Hybrid Mutation HMPSOFS proposed as a first study to solve the cost-based feature selection problems [20]. A new multi objective Feature Selection approach based on Two-Archive Multi-Objective Artificial Bee Colony algorithm (TMABC-FS) proposed to handle with a cost-sensitive feature selection problem to reduce the feature cost and increase the classification performance [19]. The simulation results showed the ability and the performance of the proposed algorithms for solving the specified problems compared with other knowns multi-objective optimizers. Zihin et al. [24] proposed a modified multi-objective particle swarm optimization algorithm (M-MOPSO) for solving CMOOP problems and explained how it avoided the weakness of the MOPSO algorithm especially for problems with high dimensions.

However, it's not a trivial task to find the optimum dose of chemotherapy that prevents unwanted effects while maximizing the efficiency for killing cancer cells. Despite the existence of many methodologies to solve the mathematical model and obtain the desired result, there is potential for improvement with the possibility of hybridization of these methodologies. This work introduces hybrid algorithms that combines the indirect approach of OC theory with Evolutionary Algorithm (EA) and the Swarm Intelligence (SI) to address CMOOP for the mathematical model of Pillis and Radunskaya [13]. The performance of the hybrid methodologies is evaluated against standard EA's and SI's algorithms for three different cases.

The main contribution of this paper is improvement of CMOOP results while reducing the computational cost by hybridizing the optimal control theory based on Pontryagin Max/Min with multi-objective optimizers based on EA and SI. This work takes advantage of the strength of OC theory as local minimizer while ensuring near global optimum is reached using SI and EA metaheuristics.

This paper is structured as follows. Section 2 presents the mathematical model of tumor growth. Section 3 presents the multi-objective optimization problem and the state constraint. Then, in Section 4, the proposed methodologies to solve the CMOOP is described. Section 5 shows the optimal control design. Section 6 presents the constraint handling methods. The second order sufficient conditions are explained in Section 7. In Section 8, a

general description for PSO and EA algorithms is given. Section 9 presents the experiment results and discussion. Finally, the conclusion is presented in Section 10.

2. The tumor model

By utilizing mathematical tools such as partial differential equations (PDEs) and ordinary differential equations (ODEs), many mathematical models have been developed to simulate tumor growth, with each one such as having advantages and disadvantages. This article utilizes the non-linear cancer mathematical model that was developed by Pillis and Radunskaya [13]. This model was adopted as the growth of the tumor is considered as a population dynamic problem that doesn't focus on a specific type of cancer disease. Moreover, the spatial property of the tumor growth along with the surrounding of the tissue is not included in this mathematical model. This model is very important in developing an effective drug schedule for cancer treatment [5]. The tumor mathematical model consists of three ordinary differential equations that simulate the dynamic interactions of the tumor between the drug effect and cells including the death and growth of the cells. These equations represent the tumor cells, normal cells and immune cells with respect to time t.

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

$$\dot{T} = r_1 T(1 - b_1 T) - c_2 IT - c_3 TN - a_2 u \qquad T(0) = T_0 \tag{2}$$

$$\dot{I} = s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I - a_1 u \qquad I(0) = I_0 \tag{3}$$

N represents the number of normal cells, T denote the number of tumor cells and I represents the number of immune cells at time t. All of them are positive values. u represents the amount of drug at time t in the cancer site.

All parameters in this model are positive and every group of parameters represent a different property. The growth law used this model is based on logistic growth represented by r_1 and r_2. Because the immune cell source is assumed to be outside of the system, the influx rate s is assumed to be constant with this limitation ($0 < s < 0.5$). c_1,c_2,c_3,c_4 are the competition terms. Tumor cells and normal cells vie for space and resources. a_1,a_2,a_3 are the cell death response coefficients ($a_2 \geq a_1 \geq a_3$,*while* $0 < a_i < 0.5$). b_1,b_2 are the carrying capacities per capita. Mortality rate is represented by d_1. ρ represents the rate of immune response per capita ($0 \leq \rho \leq 1$) and α represents the threshold rate ($0 \leq \alpha \leq 0.5$).

3. Multi-objective optimization problem

A lot of optimization problems have several conflicting objectives to be optimized while satisfying a set of constraints. These kinds of problems are referred to constrained multi-objective optimization problems (CMOOP). They are represented as follow:

$$\min \qquad F(x) = (f_1(x), f_2(x), \ldots\ldots f_n(x)) \tag{4}$$

$F(x)$ is the objective vector, with n is the number of objectives subject to j equality constraint/s and i is the inequality constraint/s.

$$\begin{aligned} &subject\ to \quad g_i^o(x) \geq 0, i = 1, 2, \ldots\ldots, q \\ &\qquad\qquad\ h_j^p(x) = 0, j = 1, 2, \ldots\ldots, e \end{aligned} \tag{5}$$

$$\begin{aligned} &x_m \in \left[R_m^u, R_m^l\right]; \\ &functions\ orders \qquad o, p \in [1\,2\,\ldots[; \end{aligned} \tag{6}$$

With m being the number of variables, the values of these variables are between upper and lower boundaries, $[R_m^u, R_m^l]$. The optimization searches over the vector $x = [x_1,x_2,\ldots, x_m]$ that complies with the equality and inequality constraints and optimizes the vector function $F(x)$. For these kinds of problems, there is no optimal unique solution but there are a set of non-dominant solutions called the pareto optimal set. This concept was proposed by the Italian engineer Vilfredo Pareto where he used it in economic studies for calculating economical efficacy. For example, suppose x_1,x_2 are two solutions belonging to the vector S or the feasible solution set, that all have feasible solutions that satisfy the constraints. x_1 dominates x_2 if and only if $f_e(x_1) \leq f_e(x_2)$,$\forall e \in \{1, \ldots, n\}$, the value of the objective function of x_1 is less than or equal to the value of the objective function of x_2 for all objectives functions in minimization problem. The pareto optimal solutions are within the Pareto optimal set when all feasible solutions in the vector S aren't dominated by other solutions. The pareto front is the mapping of pareto optimal set [18,25].

This work has two objective functions given in Eqs. (7) and 8. The aim is to minimize the size of the tumor and the drug concentration respectively with a state's constraints shown in Eq. (9) to ensure the normal cells are kept above a specific level to protect the health of the patient during the treatment period.

$$\min \int T dt \tag{7}$$

$$\min \int u dt \tag{8}$$

States constraint:

$$N \geq 0.75 \tag{9}$$

4. Optimization methodologies for solving CMOOP

To maintain a good balance between minimizing the objectives and satisfying the constraints, Optimal Control (OC) theory is combined with an Evolutionary Algorithms (EA) and a Particle Swarm (PS) algorithms to address the CMOOP. This work addresses the optimization problem by using three methodologies:

1. PURE SI & EA: addresses the constrained multi objective optimization problem (CMOOP) by using only swarm intelligence (SI) such as M-MOPSO and MOPSO or only evolutionary algorithms (EA) such as MODE and MOEAD to find the pareto optimal set with penalty strategy to satisfy the state constraint.
2. Hybrid 1: The indirect method of OC theory optimizes its single composite objective function decomposed into the multi-objectives of Particles Swarm and Evolutionary Algorithms (PS and EA) to find the pareto optimal set with penalty strategy in PS and EA to satisfy the state constraint.

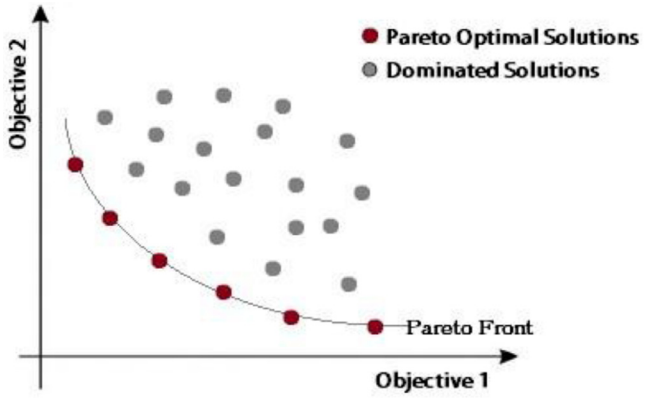

Fig. 1. Pareto Optimal Solutions and Pareto Optimal Front.

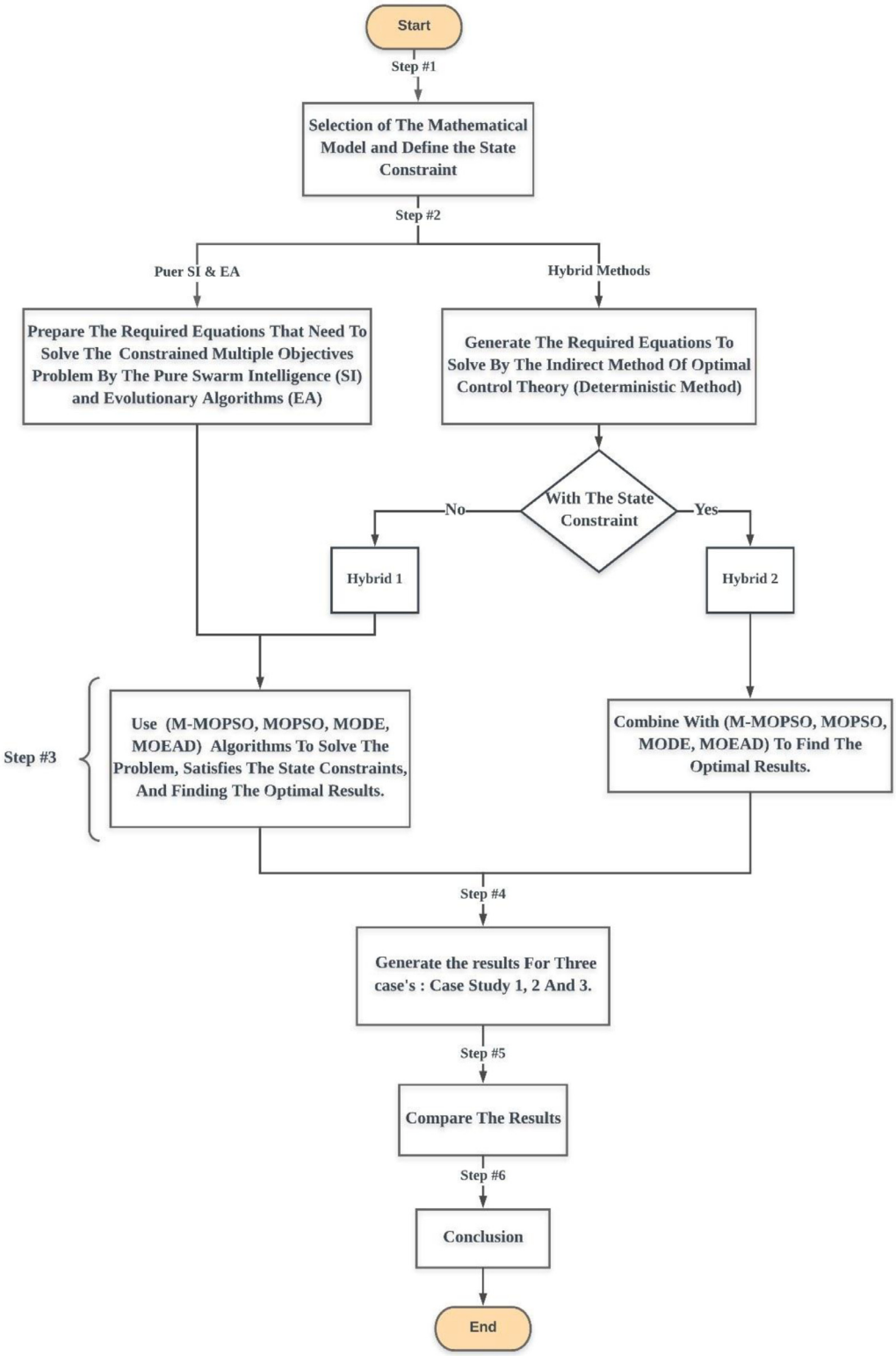

Fig. 2. Flow Chart of the Methodology.

3. Hybrid 2: Indirect method of OC theory with Augmented Lagrangian (AL) to satisfy constraints that optimizes its single composite objective function decomposed into the multi-objectives of particles swarm and evolutionary algorithms to find the pareto optimal set.

The flowchart of the three methodologies are given in Fig. 2. First methodology (PURE SI & EA) employs PS and EA only, whereas the second and third methodologies (Hybrid 1 and 2) are hybrids of OC with PS and EA. The difference between the latter two is mainly due to how each of them handle the constraints. In Hybrid 1, the constraints are imposed by using penalty strategy in multi-objectives of PS and EA. If the penalty is avoided during the optimization process, the constraints are considered satisfied. Hybrid 2 imposes constraint via augmented Langrage of OC. This means the OC handles the constraint itself without constraining

the multi-objective function of PS and EA. The simulations were carried out by these three methodologies on three different cases, to test the performance of the hybrids algorithms, Hybrid 1 and 2 against the first methodology where the results for the different methodologies are compared and analyzed.

5. Optimal controller design and necessary conditions

The solution of optimal control theory has two approaches; direct and indirect. The direct method employs stochastic non-linear programming (NLP) to search for optimal solutions whereas indirect methods are often cumbersome to model especially for many constraints OC problems but due to the deterministic nature consumes less computational time than the direct method. In our hybrid approach, we adopted the indirect method to be hybridized with PS and EA as the Radunska and Phillis model has only one constraint. The bang-bang control using indirect method is adopted in Hybrid 1 and 2. In Hybrid 1, state constraint is not included in the OC theory. However, it is satisfied by using penalty scheme in the multi-objective function of SI and EA algorithms. In Hybrid 2, the state constraint is embedded in the OC theory via AL, with the SI and EA algorithms only being utilized to find the Pareto optimal set. To construct the objective function for optimal control theory, a weighting scheme is used to treat the multi-objective problem as a single objective problem where Eqs. (7) and (8) are combined to form Eq. (10):

$$\min K = w_1 \int T dt + w_2 \int u dt \tag{10}$$

As Eq. (10) is in Bolza form, it is converted to Mayer fo7890rm to get a new differential Eq. (11):

$$\dot{K} = w_1 T + w_2 u \tag{11}$$

where:

$$w_1 + w_2 = 1 \tag{12}$$

In Hybrid 1 and 2, only one variable of PS and EA is required to represent the weight w_1,w_2 as shown in Eqs. (10) and (12). The PS and EA will generate weight that enhances the optimization using OC. The search space for weight w_1,w_2 are limited between 0 and 1. The results of OC for tumor and drug concentration are then evaluated by objective functions of PS and EA given in Eqs. (7) and 8. Hence, we realize the hybridization of OC with PS and EA.

The inequality constraint Eq. (9) becomes:

$$C = 0.75 - N \leq 0 \tag{13}$$

Hence, we construct the Hamiltonian equation for Hybrid 1:

$$H_{H1} = w_1 T + w_2 u + \lambda_1 \dot{N} + \lambda_2 \dot{T} + \lambda_3 \dot{I} + \lambda_4 \dot{K} \tag{14}$$

For Hybrid 2, the Hamiltonian equation will be:

$$H_{H2} = H_{H1} + \eta(0.75 - N) \tag{15}$$

From the Hamiltonian, we obtain the co-states functions:

$$\dot{\lambda}_1 = -\frac{\partial H}{\partial N} \tag{16}$$

$$\dot{\lambda}_2 = -\frac{\partial H}{\partial T} \tag{17}$$

$$\dot{\lambda}_3 = -\frac{\partial H}{\partial I} \tag{18}$$

$$\dot{\lambda}_4 = -\frac{\partial H}{\partial K} \tag{19}$$

Control or switching function:

$$switching\_function = w_2(1 + \lambda_4) - a_3\lambda_1 - a_2\lambda_2 - a_1\lambda_3 \tag{20}$$

The constraint multiplier η is found through the derivation of the switching function with time:

$$\eta_1 = \frac{1}{a_3}\left[-a2\left(-w_1 + \lambda_1 c_4 N - \lambda_2 r_1 + 2\lambda_2 r_1 b_1 T + \lambda_2 c_2 I + \lambda_2 c_3 N - \lambda_3\left(\frac{\alpha\rho I}{(\alpha+T)^2}\right) + \lambda_3 c_1 I - w_1\lambda_4\right)\right.$$
$$\left. -a1\left(\lambda_2 c_2 T - \lambda_3\left(\frac{\rho T}{\alpha+T}\right) + \lambda_3 c_1 T + \lambda_3 d_1\right)\right] - (-r_2\lambda_1 + 2r_2 b_2 \lambda_1 N + \lambda_1 c_4 T + \lambda_2 c_3 T) \tag{21}$$

where:

$$\eta = \begin{cases} \eta_1, & 0.75 - N \geq 0 \\ 0, & otherwise \end{cases} \tag{22}$$

Bang-bang input control to minimize the objectives function:

$$u = \begin{cases} u_{\min}, & switching\_function > 0 \\ u_{boundary}, & C \geq 0 \\ u_{\max}, & switching\_function < 0 \end{cases} \tag{23}$$

The condition of the state constraint is first order, hence the control value is at the boundary arc when it reaches the state constraint, can be obtained by deriving the state constraints Eq. (13) with the time and equal it to zero.

$$C^1 = -\dot{N} = 0 \tag{24}$$

From Eq. (24) the control value inside the boundary arc when $C > 0$, equal:

$$u_{boundary} = \frac{1}{a_3}[r_2 N(1 - b_2 N) - c_4 T N] \tag{25}$$

6. Constraint handling

As mentioned in Section 4, the constraint in Hybrid 2 will be embedded in the optimal control theory and that is shown in Section 5. For the first (pure SI&EA) and second methodology (Hybrid 1), the SI and EA algorithm handles the constraints via a penalty scheme. Though there are a few techniques that can be incorporated with the SI and EA in order to handle the constraint, the penalty method still remains as the commonly used method for solving Constrained Optimization Problems (COP) as it is widely accepted due to theoretical reliability and its simplicity [26]. The present work adopted this technique where the penalty method converted the CMOOP to an unconstrained multi-objective optimization problem. The penalty method has two approaches, the first is the interior method which penalizes the feasible solutions. And the second is the exterior method that penalizes infeasible solutions. Most researchers including the authors of this work prefer using the latter as there is no requirement for an initial feasible solution [26]. In general, the main concept of the penalty method is to convert the COP to an equivalent unconstrained optimization problem based on adding a specific value to the objective function that depends on the magnitude of the constraint violation that appears in a specific solution.

The objectives and constraint functions that are given in Eqs. (7)–(9) become:

$$\min(\phi_1(t)) = f_1(t) + \mu p(C(t)) \tag{26}$$

$$\min(\phi_2(t)) = f_2(t) + \mu p(C(t)) \tag{27}$$

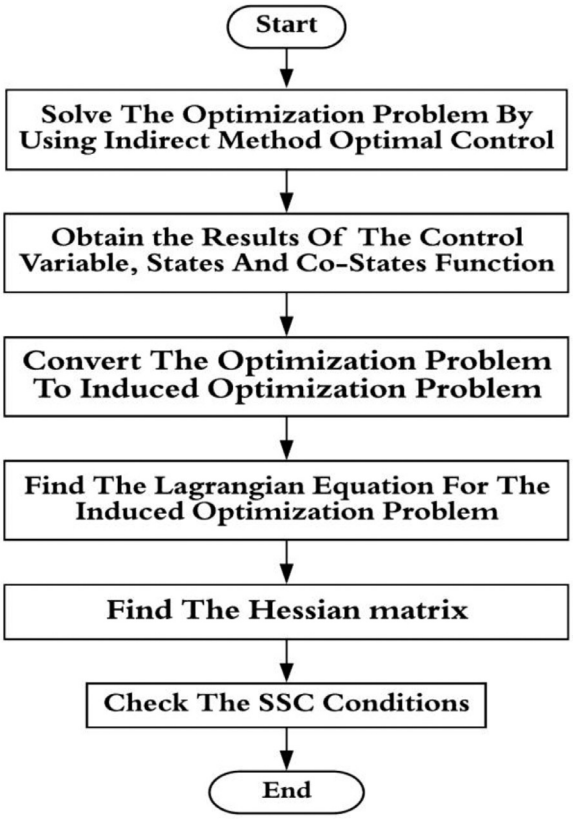

Fig. 3. The SSC Flowchart.

whereas f_1 *and* f_2, are the objectives functions given in Eqs. (7) and (8) earlier, μ is the penalty parameter and p is the penalty value that depend on C the constraint function that is presented in Eq. (13):

$$p(x) = \begin{cases} 0, & C_i > 0 \\ C_i, & else \end{cases} \tag{28}$$

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

7. Second order sufficient condition

In OC, singular trajectories may not guarantee optimality [27–31] and therefore the outcome of bang-singular in this work will need careful analysis to verify and validate the optimality. The Generalized Legendre Clebsh Condition are used to verify the optimality of bang-bang control. However, it may not be adequate for problems involving bang-singular control [32]. Bang singular is the outcome of constrained OC using AL. For these kinds of problems, first order and second order optimality conditions are developed using induced optimization. For second order optimality verification, Second Order Sufficient Condition (SSC) is applied for problem where control variable enters the system in non-linear fashion [33–35] as in the present case of state constrained OC with AL. Though computational comparison is made to verify and validate the constrained OC, exploiting SSC to prove positive definite will further justify our findings achieving optimality.

The SSC model developed was based on Vossen [36] and the SSC flowchart in Fig. 3 is used as reference. Once the state and co-state values are obtained, the problem is converted to induced optimization where optimized problem is converted to a new finite optimization problem that includes the optimization variable, switching time, initial and final time, with respect to the optimization variable $z = (t_1,\ldots..,\ t_s,t_{s+1})^T, t_{s+1} = t_f, z \in R^{s+1}$, where s is the amount of switching times.

8. Algorithm description

This work utilizes four algorithms; M-MOPSO (Modified Multi-Objective Particle Swarm Optimizer), MOPSO (Multi-Objective Particle Swarm Optimizer) which are based on swarm intelligence (SI), MODE (Multi-Objective Differential Evolution) and MOEAD (Multi-Objective Evolutionary Algorithm based on Decomposition) which are based on Evolutionary Algorithms (EA). The highlight of this work is the development of SI and EA hybrid with OC theory to find the optimal solution for the CMOOP. The results are shown as a pareto optimal set.

8.1. Particle swarm optimization (PSO)

Particle Swam Optimization (PSO) is a group of particles that behave and communicate like a swarm moving together in a specified search space looking for the best solution where every particle represents a solution. Each one of them has two properties; position and velocity. The swarm population share this information with each other. The particles use two guides, the history of the best position for each particle symbolized by p^{best} and the history of the best position from the entire population called best global symbolized by g^{best}. The particles change their respective position by adjusting their velocity. After the particles reach a new position, the guides are updated. This process is repeated until the stopping criterion is met [37,38].

Both MOPSO and M-MOPSO algorithms are based on the PSO algorithm. They are quite similar but have some differences in their use of mutation, repository update, population evolution and repository member deletion [24,39]. In MOPSO the particle flight direction is based on Pareto Dominance and the previously best solutions are stored into non-denominated vectors used by other particles to guide their own flight to reach the best non-denominated solutions [39]. M-MOPSO uses the same procedure with some modifications on the archiving procedure that reduces archiving computational cost and maintain the pareto front diversity to overcome the weakness of MOPSO with the premature convergence problem that appears with the increasing complexity in multi objective optimization problem. MMOPSO uses a new mechanism of dynamic search boundary to escape local optimal by leveraging balance between exploration and exploitation [24].

8.2. Evolutionary algorithms

Evolutionary Algorithms (EA) starts by random initialization of a population, every individual represents a solution. Then all the individuals of the population are evaluated to find the fitness that may be used to rank each solution within the population. The best individuals in the population are found and the information for the best population is used to generate the new generation of the population. These steps will be repeated until a stopping creation is satisfied [40,41].

The MODE and MOEAD are based on EA where the MODE used differential evolution and the MOEAD used evolutionary algorithms based on decomposition. Souza et al. [42] discussed the robustness of MODE for solving the multi-objective optimization problem. The optimization procedure and main differences between MODE and MOEAD algorithms are discussed in detail in [17, 43].

PSO and EA algorithms are initiated by randomly initializing the population's matrix as given in Eq. (29).

$$X_{i,v} = \begin{bmatrix} X_{1,1} & \cdot & \cdot & X_{1,v} \\ \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot \\ X_{i,1} & \cdot & \cdot & X_{i,v} \end{bmatrix} \tag{29}$$

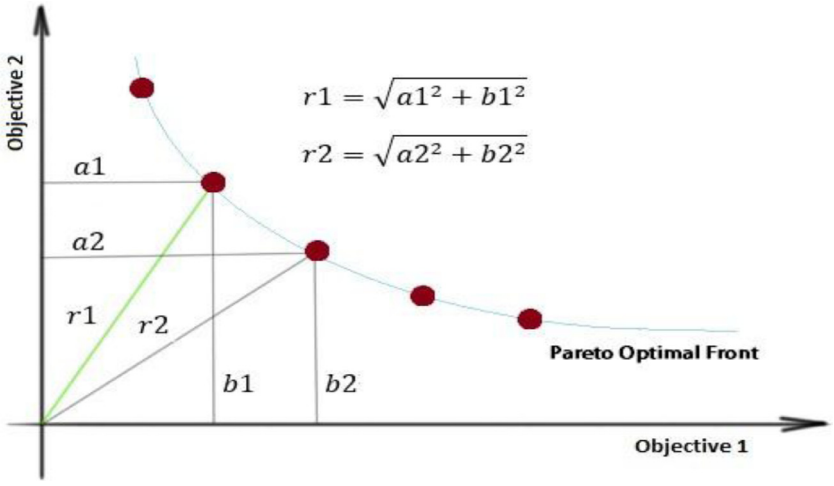

Fig. 4. Finding the Closest Point to the Origin in the Pareto Optimal Front.

where the i is the number of populations, and v is the number of variables that is used to find the optimal solution. The number of variables is determined by the amount of chemotherapy $u_i \in [\ u_{\min}\ \ u_{\max}\ ]$ at specific time where the simulation time is discretized into N of time intervals from the first day t_0 until the final day t_f of the treatment period such that:

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

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

The amount of the drug $u_i \in [\ u_{\min}\ \ u_{\max}\ ]$ during each interval time $t_i \in [\ t_i\ \ t_{i+1}\ ]$ is called bang-bang arcs. The time $t_i \in [\ t_i\ \ t_{i+1}\ ]$ is represented as decision variables which amount to N. Pure SI&EA based on pure PS or EA whereas the number of decision variables used is 16. This value is selected arbitrarily to ensure possibility of multiple bang-bang arcs optimization solution are not neglected. The arbitrary selection of N may be overestimated or perhaps underestimated. To avoid this uncertainty, PS and EA are hybridized with OC theory to develop Hybrid 1 and Hybrid 2. Hybrid 1 and 2 employ only one variable to represent the weight w as shown in Eq. (10). By this way, the number of variables is easily pre-determined based on the number of objectives used. This also leads to significant reduction of variables used for Hybrid 1 and 2 compared to Pure SI&EA. Consequently, the convergence speed of the optimization increases.

9. Results and discussion

As discussed earlier, the cancer chemotherapy model by Pillis and Radunskaya [13] is analyzed and the performance of the hybrid methodologies (Hybrid 1 and 2) proposed in this work are compared to SI and EA method's (Pure SI&EA). Three different cases of cancer chemotherapy model [13] are addressed using three methodologies (pure SI&EA, Hybrid 1 and Hybrid 2). Since the cancer chemotherapy model has a constraint that has to be respected, the optimization is called Constrained Multi-Objective Optimization Problem (CMOOP) and by applying the necessary and sufficient optimality conditions explained in Section 5 and 7, the problem becomes two points Boundary Value Problem (BVP) where the initial values of the states and the final values of the co-states are known. The Runge-Kutta 4-5th order method is used to integrate the equations. Hypervolume (HV) metric indicator have used also in the comparison of the results. HV indicator measures the volume of the region between the pareto front and a dominated reference point in n-dimensional objective space whereas higher HV means better set of nondominated solutions with respect to diversity and convergence viewpoints, where$n$ is the number of objectives [44].

Table 1
Parameter values of the swarm and evolutionary algorithms used.

Algorithms	Parameter	Value
M-MOPSO& MOPSO	Inflation Rate	0.1
	Number of Grids per Dimension	10
	Number of populations	50
	Repository Size	50
	Leader Selection Pressure	4
	Deletion Selection Pressure	2
	Mutation Rate	0.5
MODE	Population size	50
	Scaling factor	0.5
	Crossover Probability	0.2
	Function evaluations bound	20,000
MOEAD	Population size	50
	size of the weight's neighborhood	10
	crossover parameter	0.5

States initial values:

$$I(0) = 0.25 \tag{30}$$

$$N(0) = 0.9 \tag{31}$$

$$T(0) = 0.25 \tag{32}$$

Co-states final values:

$$\lambda_1(t_f) = \lambda_2(t_f) = \lambda_3(t_f) = \lambda_4(t_f) = 0 \tag{33}$$

The closest point to the origin in the Pareto Optimal Front, is the point with the distance to the origin point as shown in Fig. 4 along with the number of iterations required to find it. These criterions are used to evaluate the methodologies developed in this work. The time simulation runs from 0 to 149 days.

The parameters that were used in SI and EAs algorithms are given in Table 1.

The results of this work were carried out by using a computer, core i7 with 8 G RAM with MATLAB R2016a software used for simulation. The simulation was carried out 20 times and the average outcome of each case study are shown in the tables.

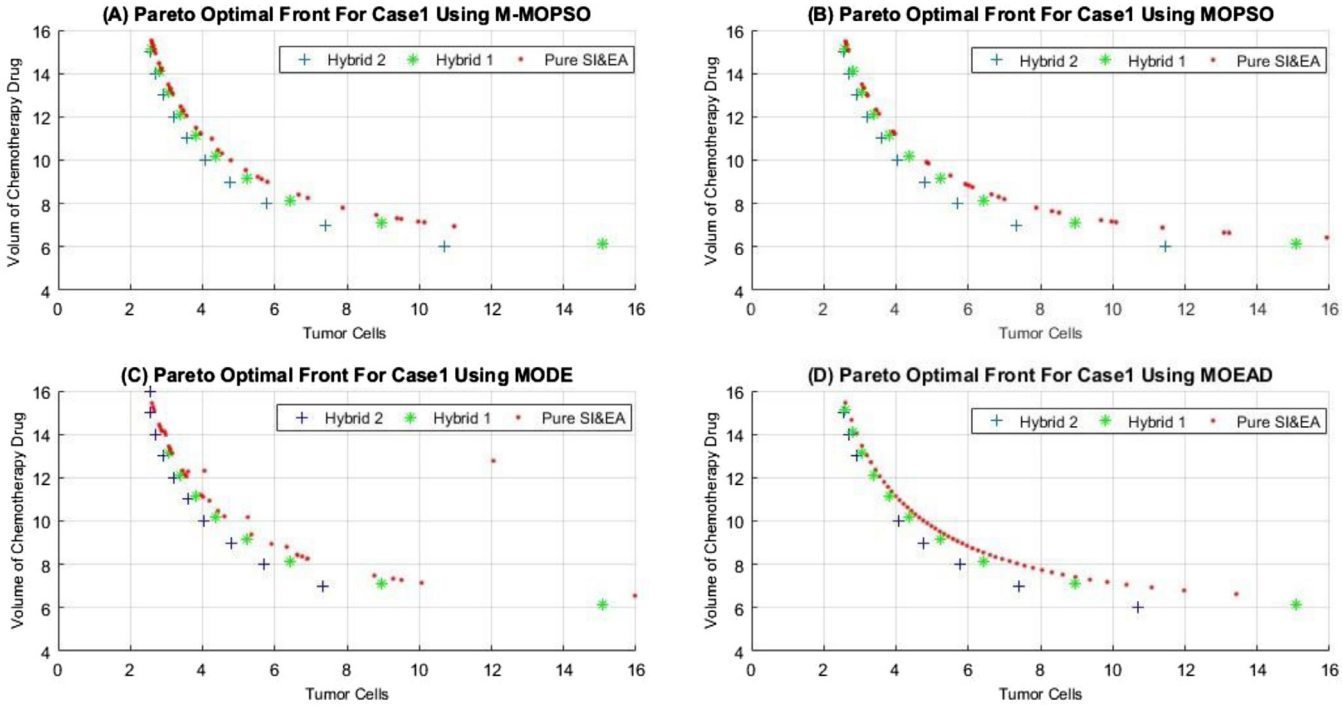

Fig. 5. Pareto Optimal Front for Case Study 1 by Using: (A) M-MOPSO, (B) MOPSO, (C) MODE and (D) MOEAD.

9.1. Case study 1

As explained in Section 2, the mathematical model that was used in this work has 14 parameters and the meaning of each parameter is given in the same section. The following values are considered for the first case study:

$a_1 = 0.2$, $a_2 = 0.3$, $a_3 = 0.1$, $c_1 = 1$, $c_2 = 0.5$, $c_3 = 1$, $c_4 = 1$, $b_1 = 1$, $b_2 = 1$, $d_1 = 0.2$, $r_1 = 1.5$, $r_2 = 1$, $s = 0.33$, $\rho = 0.01$, $\alpha = 0.3$.

Fig. 5 shows the results of the Pareto Optimal Front for the three methodologies explained in Fig. 2 with the SI and EA. The Pareto Optimal Front for the three methodologies are shown in Fig. 5(A)–(D) using M-MOPSO, MOPSO, MODE and MOEAD respectively. The results of Pure SI & EA methodology are represented by red points, the green points represent the results of Hybrid 1 and Hybrid 2 results are shown by the blue points. As it appears, Hybrid 2 Pareto Front curve is closer to the origin in comparison with Pure SI & EA and Hybrid 1 whereas Hybrid 1 is better than Pure SI&EA as it shows improved Pareto Front. The results reveal that Hybrid 2 that employs AL approach removes the SI's and EA's burden to handle constraint which in return aids the optimization. Hybrid 1 comes short of Hybrid 2 but performs better than Pure SI&EA. In Hybrid 1, SI and EA handle the constraint via Penalty Method in their objective function. This makes the search space larger, consequently Hybrid 1 performs less satisfactorily compared to Hybrid 2. However, in general, the results show that the OC theory is a very efficient optimizer if combined with SI or EA.

Fig. 6 shows the results of the distance for the closest point to the origin in the Pareto Optimal Front with the number of iterations for the three methodologies that are explained in Fig. 2 combined with the SI and EA algorithms. The distance of the Pareto Optimal Front for the three methodologies are shown in Fig. 6(A)–(D) using M-MOPSO, MOPSO, MODE and MOEAD respectively. The results of Pure SI&EA are represented by the red line, the results of Hybrid 1 by the green line and the results of Hybrid 2 by the blue line.

From Fig. 6(A), Pure SI&EA using M-MOPSO takes more than 140 iterations to find the closest point to the origin; Pure SI&EA using MOPSO needed more than 100 iterations to saturate at its closest point to the origin as shown in Fig. 6(B). Pure SI&EA based on MODE required more than 160 iterations to converge to its closest point to the origin whereas Pure SI&EA based on MOEAD took more than 350 iterations to discover the closest point to the origin. In contrast, Hybrid 1 and 2 for SI's and EA's used only two iterations to achieve its closest point to the origin. The OC theory in Hybrid 1 and 2 directs the optimization toward global optimum saving the considerable effort used to discover the closest point to the origin by Pure SI&EA. Hybrid 2 achieves the best results among the three methodologies.

The simulation was carried out 20 times and the outcome of average tumor size, average drug volume, average number of iterations and average consumed time for the closest point to the origin, as well as the average HV indicator for case study 1, are given in Table 2. The closest point to the origin is shown in the form of distance from origin. The Hybrid methodologies obtained improved minimum outcome in terms of tumor cell concentration and drug volume compared with Pure SI&EA. Hybrid 2 obtained the best results among the three methodologies. The average distance of the four algorithms with origin point for Hybrid 2 is 9.847 and for Hybrid 1 is 10.39, while for Pure SI&EA the average distance is 10.685. Based on the results of the closest point to the origin, SI's and EA's have differences in the performance within Pure SI&EA. However, such differences did not appear for Hybrid 1 and 2 as each methodology performed equally for different type of SI and EA used. Based on Table 2, the computational time consumed by Hybrid 2 is the least among the three methodologies, while computational time consumed by the Hybrid 1 is similar or higher than Pure SI&EA. The combined approach of Penalty method and the OC theory in Hybrid 1 makes the search procedure consume more computational time. However, this problem ceases if the penalty method is replaced by AL approach in OC theory as developed for Hybrid 2. The outcome shows Hybrid 2 is not only robust but computationally faster than Pure SI&EA

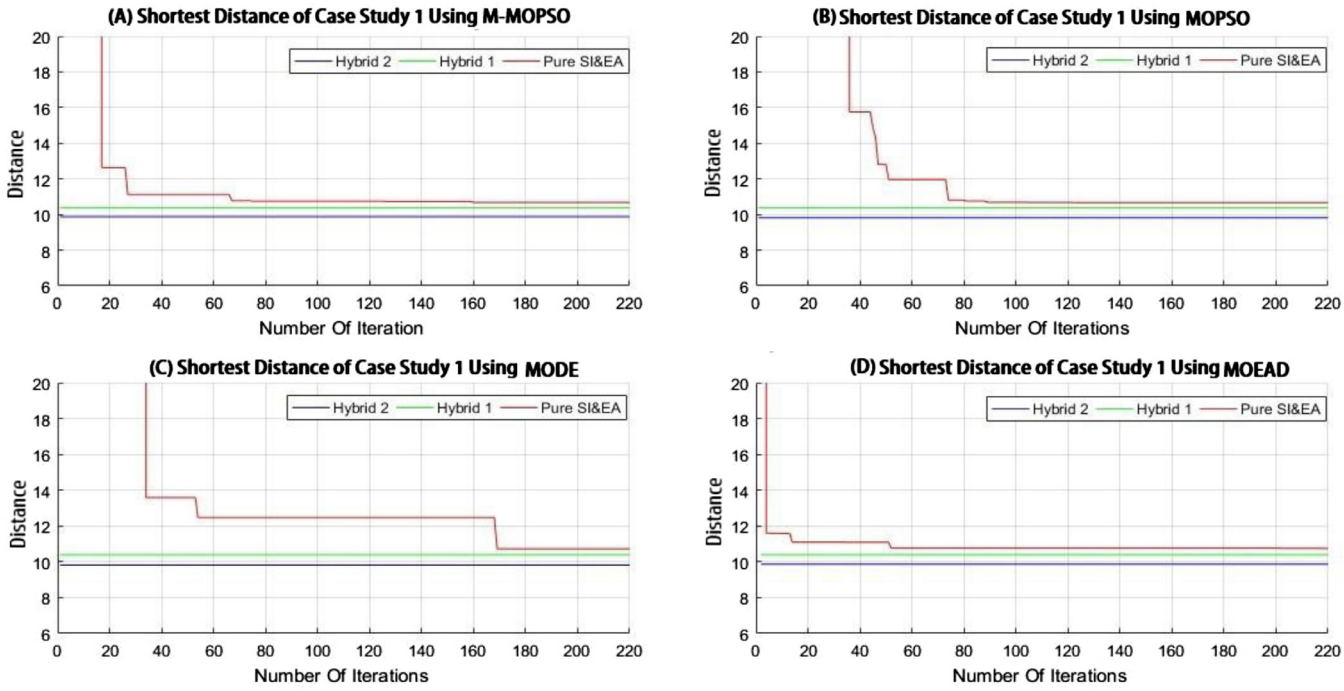

Fig. 6. Distance for the Closest Point to Origin in the Pareto Optimal Front for Case Study 1 vs Number of Iterations by Using: M-MOPSO, (B) MOPSO, (C) MODE, (D) MOEAD.

Table 2
The results summary for case study 1.

	Pure SI&EA				Hybrid 1				Hybrid 2			
Algorithms	M-MOPSO	MOPSO	MODE	MOEAD	M-MOPSO	MOPSO	MODE	MOEAD	M-MOPSO	MOPSO	MODE	MOEAD
Distance of Closest Point to Origin	10.68	10.67	10.71	10.68	10.39	10.39	10.39	10.39	9.875	9.82	9.82	9.875
Number of Iterations	160	123	165	317	2	2	2	2	2	2	2	2
Tumor cells concentration	6.303	6.127	5.911	5.891	6.44	6.44	6.44	6.44	5.68	5.69	5.69	5.789
Drug volume	8.222	8.375	8.941	8.848	8.159	8.159	8.159	8.159	8	8	8	8
Consumed Time (sec)	543	702	410	982	578	820	470	792	282	245	309	213
HV (Hypervolume)	126.5	124.3	123.3	125.9	127.1	127.1	123.2	127.1	138.7	136.2	129.3	131.2

and that relies purely on SI's and EA's. HV is calculated for the three methods with respect to a dominated reference point (17,17). As appears, Hybrid 2 has obtained the largest values followed by Hybrid 1 whereas the Pure SI&EA obtained the lowest HV results, consequently, Hybrid 2 Pareto results are better with respect to the convergence and diversity viewpoints than Pareto results of Hybrid 1 and Pure SI&EA. Overall, the results show Hybrid 2 achieved reduction both in tumor cell concentration and chemotherapy using far less computation effort. The AL used in OC of Hybrid 2 relieved the SI's and EA's from handling constraint via penalty strategy as it was previously used in objective function of Hybrid 1. The outcome enabled Hybrid 2 to improve the closest point to the origin and hence reduce tumor cell concentration and drug volume in comparison to Hybrid 1.

9.2. Case study 2

As mentioned in Section 2, the source of immune cells supposed to be outside the system, and it is represented by the value of parameter *s*. The value of immune cells steady source rate *s* is reduced to become equal to 0.3 [17] in case study 2 compared with that in case study 1 while the values of other parameters are retained the same as used in case study 1.

The results of Pareto Optimal Front for case study 2 are presented in Fig. 7 for the three methodologies are explained in Fig. 2 with the SI and EA algorithms. Fig. 7(A)–(D) shows Pareto Optimal Front for the three methodologies that were obtained by using M-MOPSO, MOPSO, MODE, MOEAD respectively. The red points represent the results of Pure SI&EA, green points represent the results of Hybrid 1 and the blue points represent the results of Hybrid 2.

As indicated, Hybrid 2′s Pareto Front curve is nearest to the origin compared to Pure SI&EA and Hybrid 1. Hybrid 1′s Pareto Front curve shows improved outcome compared to the Pareto Front of Pure SI&EA. The improved performance of Hybrid 2 compared to the other two methodologies is dedicated to AL Approach that handled the state constraint, enabling reduction of search space for SI's and EA's optimization. Pure SI&EA and Hybrid 1 used the Penalty Approach in the objective function of SI and EA algorithms to handle the state constraint and that causes increase in search space which leads to performance drop. The search space for Pure SI&EA and Hybrid 1 are larger than Hybrid 2 as many infeasible solutions are generated. The infeasible solutions are subsequently penalized by penalty scheme in objective function of Pure SI&EA and Hybrid 1. This process inevitably prolongs the optimization as more time is needed to increase chances of feasible solutions to be found and optimized. Hybrid 2 produces only feasible solutions as AL ensures infeasible solutions are eluded thus ensuring objective function of Hybrid 2 devoid of penalty scheme. Though the performance of Hybrid 1 is not as good as Hybrid 2, it is still better than Pure SI&EA. Hybrid 2 performed better than Hybrid 1 and

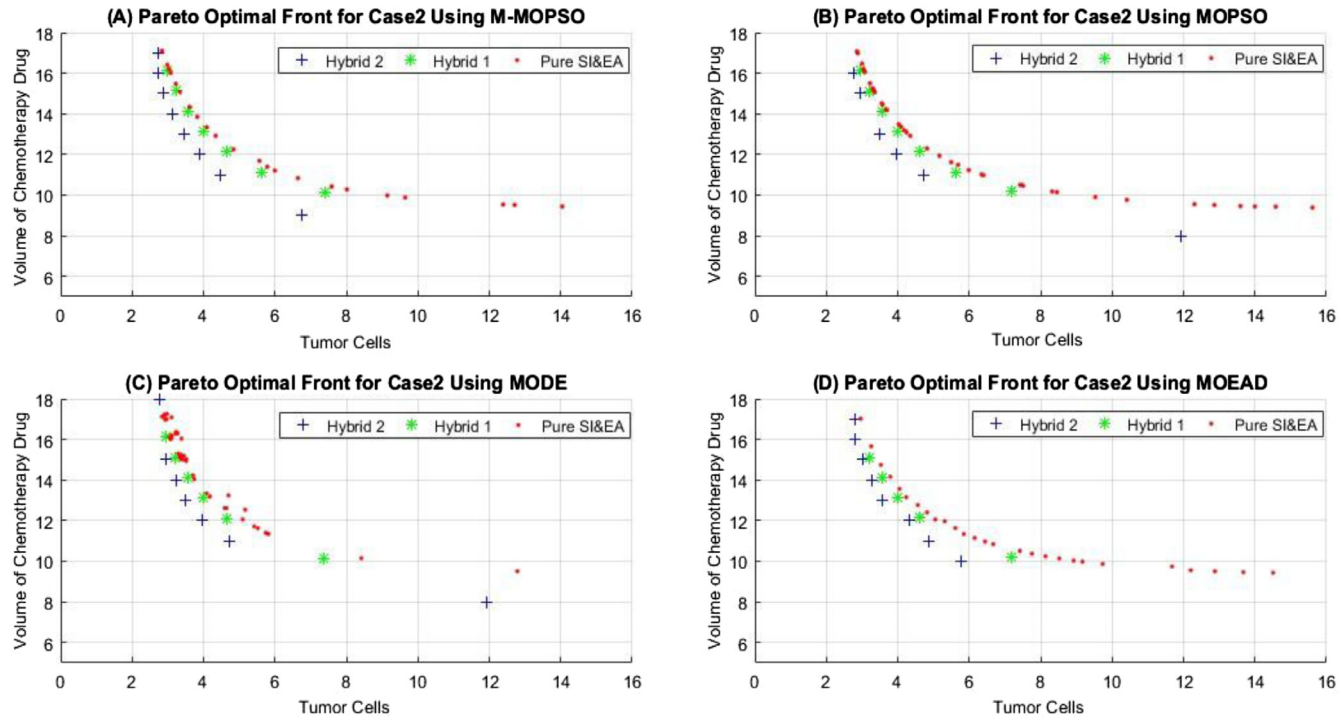

Fig. 7. Pareto Optimal Front for Case Study 2 By Using: (A) M-MOPSO, (B) MOPSO, (C) MODE and (D) MOEAD.

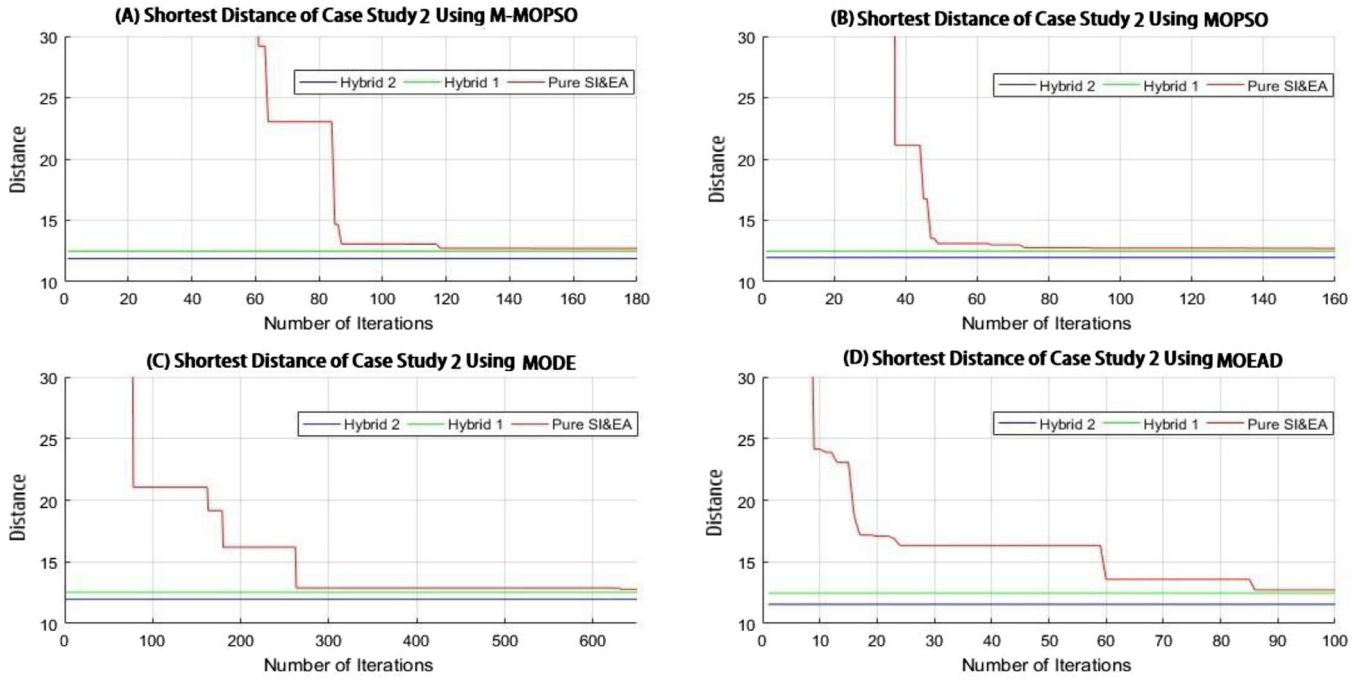

Fig. 8. Distance for the Closest Point to Origin in the Pareto Optimal Front for Case Study 2 vs Number of Iterations by Using: (A) M-MOPSO, (B) MOPSO, (C) MODE and (D) MOEAD.

pure SI&EA in terms of reduced tumor cell and drug volume as well as shorter computational time.

Fig. 8 shows the results of the closest point to the origin in the Pareto Optimal Front with the number of iterations for the three methodologies that was explained in Fig. 2. The closest point to the origin in the Pareto Optimal Fronts for the three methodologies are shown in Fig. 8(A)–(D), using M-MOPSO, MOPSO, MODE and MOEAD respectively. The results of Pure SI&EA are represented by the red line, the results of Hybrid 1 by the green line and the results of Hybrid 2 by the blue line.

As shown in Fig. 8(A), Pure SI&EA using M-MOPSO takes more than 110 iterations to find its closest point to the origin, Pure SI&EA based on MOPSO needed more than 140 iterations to saturate at its closest point to the origin as shown in Fig. 8(B). Pure SI&EA using MODE took more than 600 iterations to converge to its closest point to the origin whereas Pure SI&EA based on MOEAD took around 85 iterations to discover closest point to the origin. In

Table 3
The results summary for case study 2.

	Pure SI&EA				Hybrid 1				Hybrid 2			
Algorithms	M-MOPSO	MOPSO	MODE	MOEAD	M-MOPSO	MOPSO	MODE	MOEAD	M-MOPSO	MOPSO	MODE	MOEAD
Distance of Closest Point to Origin	12.71	12.70	12.76	12.71	12.47	12.47	12.52	12.48	11.87	11.96	11.96	11.65
Number of Iterations	118	146	640	87	2	2	2	2	2	2	2	2
Tumor Cells Concentration	6.235	6.234	5.838	6.304	5.63	5.641	7.364	7.198	4.479	4.7	4.71	5.88
Drug Volume	11.08	11.06	11.34	11.05	11.12	11.12	10.13	10.19	11	11	11	10
Consumed Time (sec)	498	782	1576	537	549	1052	574	889	253	537	267	251
HV	136.3	136.9	133.5	136.8	136.2	130.9	129.8	128.7	150.4	146.3	146.2	137.7

contrast, Hybrid 1 and 2 for SI's and EA's used only two iterations to achieve its closest point to the origin.

The simulation was carried out 20 times and the outcome of case study 2 for the closest point to the origin as well as the average HV results are shown in Table 3. The results are shown as average tumor size, average drug volume, average consumed time for the three methodologies used in this work. As shown, the results of Hybrid 1 and 2 achieved the minimum results in terms of tumor cell concentration and drug volume compared with Pure SI&EA. The average distance of the four algorithms with origin point for Hybrid 2 is 11.68 and for Hybrid 1 is 12.49, while for Pure SI&EA the average distance is 12.72. It is clear that Hybrid 2 achieved the best results by using less time among the three methodologies. Hybrid 1 and 2 needed only 2 iterations which is far less compared to Pure SI&EA. Hybrid 2 achieved reduction both in tumor cell concentration and drug concentration using far less computation effort compared with the first methodology that used purely SI and EA and Hybrid 1 as shown in Table 3. Hybrid 1 may not necessarily be computationally faster than pure SI&EA methodology as shown in Table 3 as it depends on the type of SI or EA used in the hybridization. This results from the OC theory with penalty scheme in the objective function cost high computational time. Hybrid 1 becomes computationally expensive to control the outcome from OC theory using weighting scheme and via penalty strategy in the multi-objectives of SI or EA. However, Hybrid 2 is developed to be computationally faster than Hybrid 1 and Pure SI&EA. The AL approach in Hybrid 2 relieved the SI's and EA's from handling constraint in comparison to penalty strategy used in the objective function of Hybrid 1, thus enabling Hybrid 2 to reduce the distance of closest point to the origin with reduced tumor cell concentration and drug volume in comparison to Hybrid 1. In this case, HV is calculated for the three methods with respect to a dominated reference point (19,19). Again, as similar to Case 1, Hybrid 2 has obtained the largest values, followed by Pure SI&EA while Hybrid 1 has obtained the lowest results in Case 2. In general, optimization based on OC theory hybridized with SI and EA is more efficient than optimization based on purely SI and EA despite the drawback in terms of computational time for Hybrid 1.

After reducing the immune source rate in case study 2 compared with case study 1, the results of case study 2 shows an increase in the amount of chemotherapy needed compared with the chemotherapy in case study 1. The chemotherapy will assist in killing the tumor cells until the immune system is able to deal with the tumor cells, hence reducing immune cells source rate of the patient translates the patient into needing more assistance from chemotherapy.

9.3. Case study 3

In case study 3, the value of immune response rate ρ increased to become equal to 0.02 [17] while the values of the other parameters were maintained as in case study 1.

Fig. 9 shows the results of the Pareto optimal front for the three methodologies that were explained in Fig. 2 with SI and EA algorithms. Fig. 9(A)–(D) presents the curves of Pareto optimal front for the three methodologies by using M-MOPSO, MOPSO, MODE and MOEAD respectively. The red points represent the results for Pure SI&EA, green points show the results of Hybrid 1 and the results of Hybrid 2 is represented by the blue points. As indicated in Fig. 9, the results of Pareto Optimal Front of Hybrid 2 are closest to the origin point compared to the results of Pure SI&EA and Hybrid 1 with the results of Hybrid 1 showing better performance compared with the results of Pure SI&EA. The state constraint in Hybrid 2 as discussed earlier is handled by the AL approach of OC theory. By this way, the difficulties facing SI and EA for handling the constraint, such as increased search space is reduced. Pure SI&EA and Hybrid 1 employ penalty schemes within the SI and EA's objective function to deal with state constraint. Penalty scheme penalizes infeasible solutions and optimization is forced to generate feasible solutions. This increases the search space of SI and EA optimization. Despite this, the results of the Hybrid 1 show a better performance compared with the first methodology that purely depends on SI and EA. It is clear by using OC theory combined with SI and EA, we can obtain improved optimization results.

Fig. 10 shows the results of the closest point to the origin in the Pareto Optimal Front with the number of iterations for the three methodologies that are explained in Fig. 2 combined with the SI and EA algorithms. The closest point to the origin in the Pareto Optimal Fronts for the three methodologies are shown in Fig. 10(A)–(D) using M-MOPSO, MOPSO, MODE and MOEAD respectively. The results of Pure SI&EA are represented by the red line, the results of Hybrid 1 by the green line and the results of Hybrid 2 by the blue line.

As shown in Fig. 10(A), Pure SI&EA using M-MOPSO takes more than 100 iterations to find its closest point to the origin while Pure SI&EA using MOPSO needed more than 120 iterations to saturate at its closest point to the origin as shown in Fig. 10(B). Pure SI&EA based on MODE needed more than 85 iterations to converge to its closest point to the origin whereas Pure SI&EA based on MOEAD just required around 80 iterations to discover the closest point to the origin. In contrast, Hybrid 1 and 2 for SI's and EA's used only two iterations to achieve its closest point to the origin. The OC theory in Hybrid 1 and 2 directs the optimization toward global optimum saving the considerable effort used to discover closest point to the origin by Pure SI&EA. Hybrid 2 achieves the best results among the three methodologies.

The simulation was carried out 20 times and the outcome of case study 3 such as average tumor size, average drug volume, average consumed time and average number of iterations for the closest point as well as the average distance from origin for case study 3 and the average HV results for the three methodologies are shown in Table 4. As shown, Hybrid 2 obtained the best minimum results using the least time among the three methodologies followed by the results obtained by Hybrid 1 found to be superior than the results of the Pure SI&EA. The average distance with origin point of the four algorithms of Hybrid 2 is 9.5455 and for Hybrid 1 is 9.994, while for Pure SI&EA the average distance is 10.275.

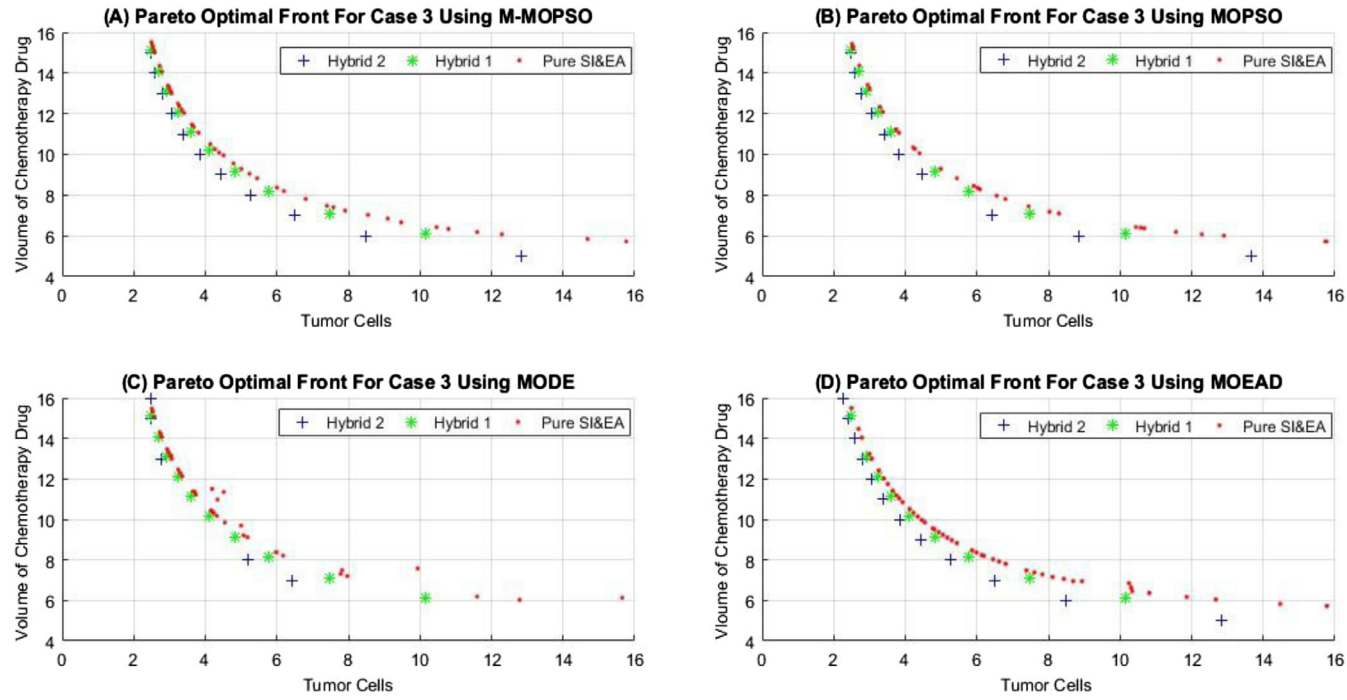

Fig. 9. Pareto Optimal Front for Case Study 3 By Using: (A) M-MOPSO, (B) MOPSO, (C) MODE and (D) MOEAD.

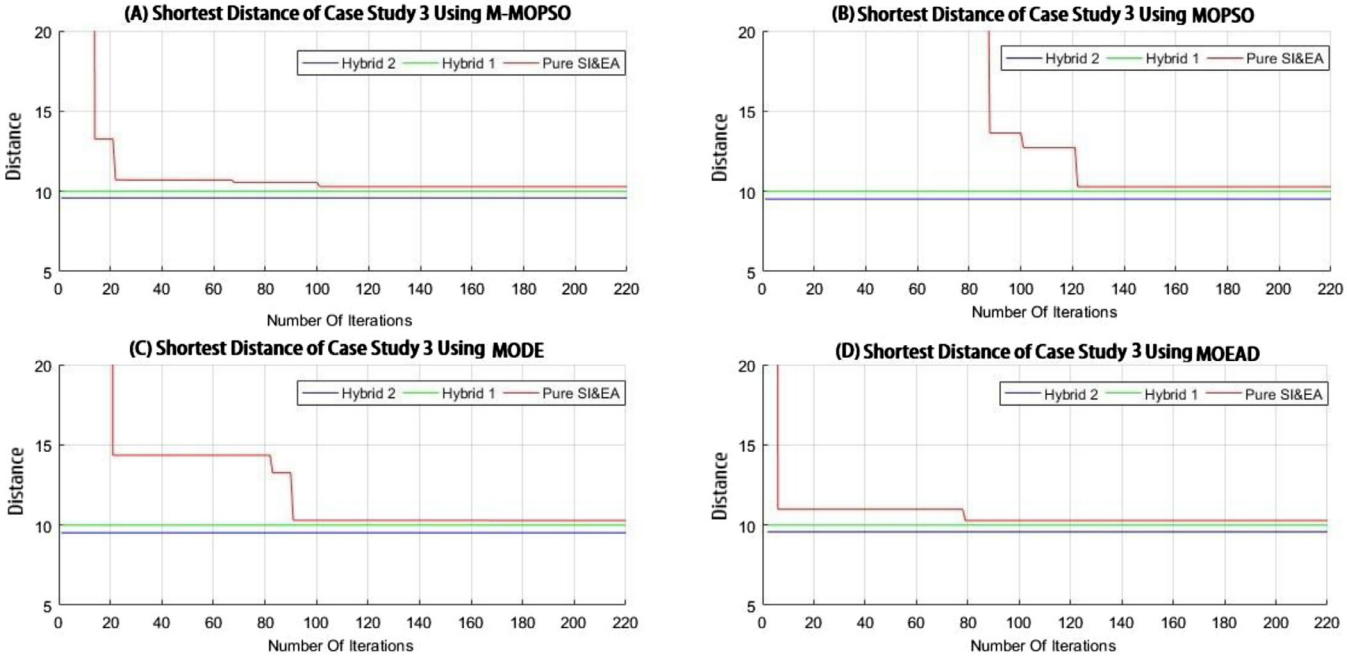

Fig. 10. Distance for the Closest Point to Origin in the Pareto Optimal Front for Case Study 3 vs Number of Iterations by Using: (A) M-MOPSO, (B) MOPSO, (C) MODE and (D) MOEAD.

Table 4
The results summary for case study 3.

	Pure SI&EA				Hybrid 1				Hybrid 2			
Algorithms	M-MOPSO	MOPSO	MODE	MOEAD	M-MOPSO	MOPSO	MODE	MOEAD	M-MOPSO	MOPSO	MODE	MOEAD
Distance of Closest Point to Origin	10.28	10.27	10.28	10.27	9.994	9.994	9.994	9.994	9.578	9.513	9.513	9.578
Number of Iterations	101	122	88	81	2	2	2	2	2	2	2	2
Tumor cells concentration	6.209	6.193	6.126	6.191	5.772	5.772	5.772	5.772	5.267	6.441	6.441	5.267
Drug volume	8.199	8.199	8.265	8.199	8.159	8.159	8.159	8.159	8	7	7	8
Consumed Time (sec)	689	429	682	441	1312	712	558	667	273	363	245	226
HV	135.2	136.1	132.7	136.6	135.4	134.7	134.4	135.5	143.8	143.4	138.1	143.4

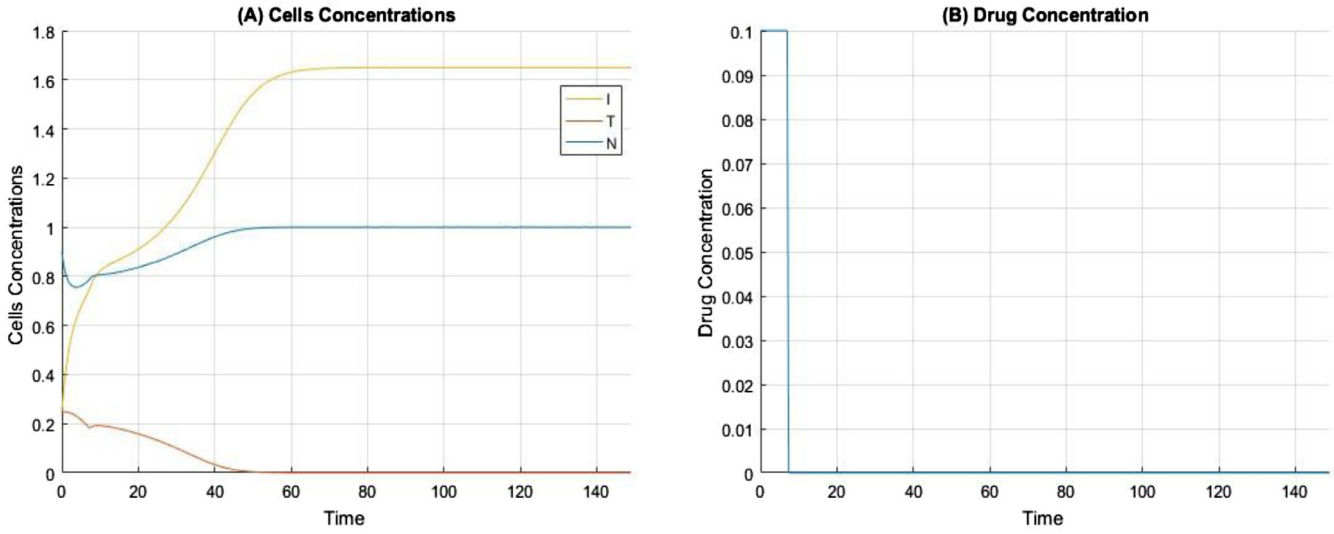

Fig. 11. Drug Concentration (B) and Cells Concentrations (A) for Case Study 3 Using Pure SI&EA and MOEAD.

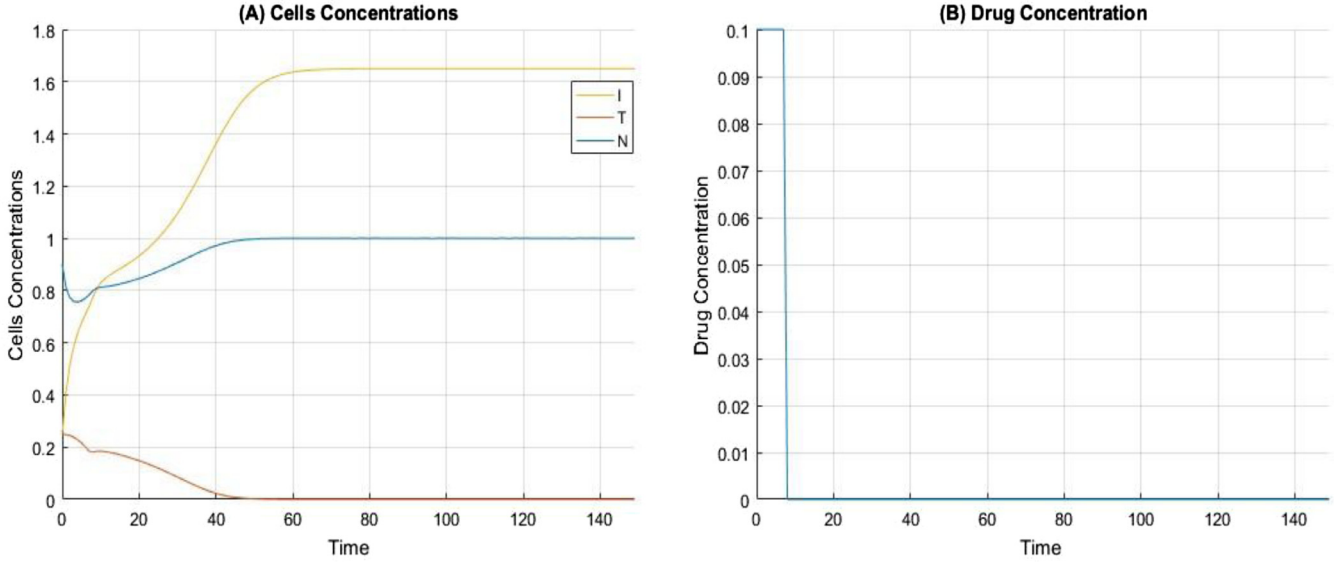

Fig. 12. Cells Concentrations (A) and Drug Concentration (B) for Case Study 3, Using Hybrid 1 and MOEAD.

HV calculated for the three methods with respect to a dominated reference point (17,17). As shown in Table 4, Hybrid 2 has obtained the largest values, while the Pure SI&EA and Hybrid 1 HV results was close to each other, establishing Hybrid 2 as method that provides improved set of solutions from both convergence and diversity viewpoints. As the hybridization between the SI and EA with the OC in Hybrid 1 and 2 shows an increase in the quality of results, it also used less iterations compared with that used by the Pure SI&EA that depended purely on SI and EA algorithms for solving CMOOP. In Hybrid 2, embedding the state constraint in OC via AL, the SI and EA deals with only feasible solutions in its objective function thus improving the results compared to Pure SI&EA and Hybrid 1 that used penalty scheme in its objective function to satisfy the state constraint. The standard deviation of the hybrid methods (Hybrid 1 and Hybrid 2) are zero, in all SI and EA algorithms tested.

Figs. 11–13 show the chemotherapy and cell concentrations against time for the closest point to the origin of the three methodologies using MOEAD of case study 3. As shown in Table 4, the MOEAD algorithm used the least number of iterations compared with other algorithms in Pure SI&EA to converge at the closest point to the origin.

Fig. 11(A) shows the results of the drug and the cell concentrations against time using Pure SI&EA based on MOEAD. The cell concentration includes normal cells marked by the blue line, the tumor cells concentration marked by the red line and the immune cells concentration marked by the yellow line. The chemo medicine input control obtained for Pure SI&EA using MOEAD is shown in Fig. 11(B). The profile of the control variable and the cells concentrations for Hybrid 1 is shown in Fig. 12. The results of the drug concentration and cells concentrations for Hybrid 2 are shown in Fig. 13. Part (B) of the Figs. 11–13 show the drug concentration profile with the time and the results of this drug profile on the cells concentration are shown in part (A). By killing the tumor cells and reducing the toxicity to save the normal cells concentrations above certain level, the main goals for this optimization problem

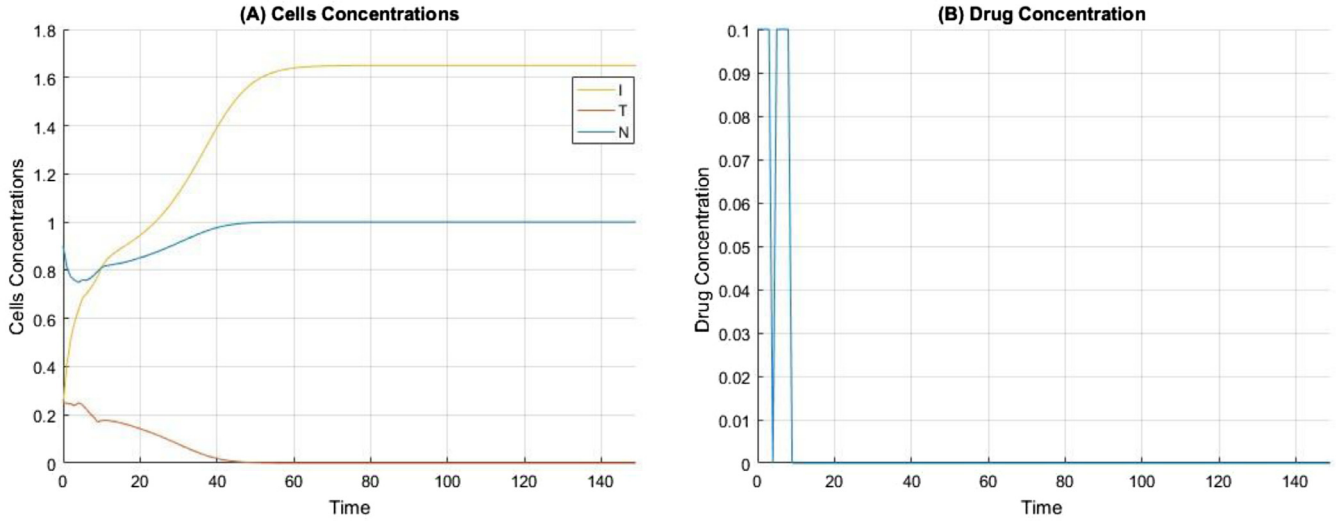

Fig. 13. Drug Concentration (A) and Cells Concentrations (B) for Case Study 3, Using Hybrid 2 and MOEAD.

achieved by all the methodologies are shown in part (A) and (B) in Figs. 11–13.

As shown in Fig. 12(B) by Hybrid 1, the chemotherapy was applied continuously at the maximum level during the treatment period similar to Fig. 11(B) found by Pure SI&EA. Meanwhile, as for the results obtained by Hybrid 2 as shown in Fig. 13, the concentration of the normal cells dropped to the boundary of 0.75 and the state constraint Eq. (13) became active. The drug concentration at that time is reduced to boundary level in order to decrease the toxicity and subsequently when the concentration of the normal cells increased above the state constraint, the condition of Eq. (13) becomes inactive where the drug concentration is banged to the maximum level to resume killing of the tumor cells. From this result, the drug concentrations obtained by Hybrid 2 shown in Fig. 13(B) depicts the schedule of the chemotherapy protocol Maximum Tolerated Dose (MTD) that is used in real life as it is clinically accepted to treat the cancer. The chemotherapy applied is the maximum allowable level and there is a break or drug off period between after each round of the treatment, to give time for the normal cells to recuperate and reduce the toxicity [45], Hybrid 2 is found to produce the best and most suited for clinical application among the three methodologies developed in this work.

To complement the validation through comparison with Pure SI&EA methodology, SSC is obtained to proof optimality. The Hessian of Lagrangian, $L_{zz}(\bar{z})$ is computed using Vossen [36] given in the SSC flowchart of Fig. 3:

$$L_{zz}(\bar{z}) = \begin{bmatrix} 0.7511 & 2.6984 & 0.0716 \\ 2.6984 & 9.6939 & 0.2573 \\ 0.0716 & 0.2573 & 0.0068 \end{bmatrix} 10^{53}$$

And the Jacobian of the terminal conditions 30–32 is obtained as:

$$\Phi_z(\bar{z}) = \begin{bmatrix} -0.0554 & -0.010 & 0.0127 \\ 0.0186 & 0.0325 & 0.0368 \\ 0.2013 & 0.1998 & 0.2276 \end{bmatrix}$$

While the Jacobian of the in-equality state constraint is given by:

$$S_z(\bar{z}) = \begin{bmatrix} 0.0554 & 0.010 & -0.0127 \end{bmatrix}$$

The Rank $(\Phi z(\bar{z})) = 3$, full rank and the Rank $(Sz(\bar{z})) = 1$, which means it's verified the first order sufficient condition, Rank$(\Phi z(\bar{z}))$ + Rank$(Sz(\bar{z}))$ = s+1. For the Hessian of Lagrangian it's a positive definite. With the switching time vector $[\bar{z}_1 \quad \bar{z}_2 \quad \bar{z}_3]$ corresponding to switching time [1 3 7] obtained from Fig. 13(B), the SSC obtained from SSC flowchart is positive definite implying the switching time is optimal. This results further validates the optimal outcome of constrained OC with AL.

Results comparison with previous work

In previous work, Lobato et al. [17] combined MODE and NSGA II with OC theory respectively for solving the chemotherapy problem. Lobato et al. minimized tumor and chemotherapy of Pillis and Radunskaya [13] model using OC with MODE and NSGA II to satisfy the Differential Algebraic Equation (DAE) as constraint. The constraints are satisfied with tumor and chemotherapy minimized using control input permutation generated by MODE and NSGA II. Hybrid 1 and 2 which embeds indirect method of OC theory with SI and EA are compared with Lobato et al. in Table 5. The results of

Table 5
Comparison with present work.

		Hybrid 1				Hybrid 2				Lobato et al. [17].	
	Algorithms	M-MOPSO	MOPSO	MODE	MOEAD	M-MOPSO	MOPSO	MODE	MOEAD	MODE	NSGA II
Case Study 1	Distance of Closest Point to Origin	10.39	10.39	10.39	10.39	9.875	9.82	9.82	9.875	14.43	15.31
	Tumor cells concentration	6.44	6.44	6.44	6.44	5.68	5.69	5.69	5.789	4.67	4.60
	Drug volume	8.159	8.159	8.159	8.159	8	8	8	8	13.66	14.61
Case Study 2	Distance of Closest Point to Origin	12.47	12.47	12.52	12.48	11.87	11.96	11.96	11.65	25.33	25.59
	Tumor cells concentration	5.63	5.641	7.364	7.198	4.479	4.7	4.71	5.88	12.79	12.94
	Drug volume	11.12	11.12	10.13	10.19	11	11	11	10	21.87	22.08
Case Study 3	Distance of Closest Point to Origin	9.994	9.994	9.994	9.994	9.578	9.513	9.513	9.578	11.96	10.90
	Tumor cells concentration	5.772	5.772	5.772	5.772	5.267	6.441	6.441	5.267	6.21	8.58
	Drug volume	8.159	8.159	8.159	8.159	8	7	7	8	10.23	6.73

average drug concentration, average tumor volume and the average distance for nearest point to the origin of the present work for Hybrid 1 and 2 are given in Table 5 for the three cases study against the results of Lobato et al. As shown in Table 5, Hybrid 1 and Hybrid 2 give improved results compared to Lobato et al. [17] of all the three cases study. Furthermore, the difference in the results between Hybrid 1 and 2 with Lobato in Table 5 is clear especially for more challenging optimization problem such as case study 2. The present work provides effective hybridization between the SI and EA with the OC in Hybrid 1 and 2 to avoid trapping in the local optimal solutions to obtain the improved non-dominant results and to overcome the problems of exploration and exploitation.

10. Conclusion

This paper proposed a hybrid optimal control swarm intelligence optimization technique to address Constrained Multi Objectives Optimization Problem using cancer chemotherapy mathematical model introduced by Pillis and Radunskaya [13] that aimed to minimize the drug and tumor cells concentrations while keeping the concentration of the normal cells above safe level. In this work, three methodologies were developed namely Pure SI&EA, Hybrid 1 and Hybrid 2 which used M-MOPSO, MOPSO, MODE and MOEAD. The results show that:

1. The hybrid methodologies such as Hybrid 1 and 2 used much fewer iterations compared with the Purely SI and EA.
2. Hybrid 2 that included the constraints in optimal control theory obtained the best results in comparison to Pure SI&EA and Hybrid 1 in terms of cancer cell and drug concentration reduction as well as computational cost.
3. Hybrid 2 chemotherapy results show close proximity to chemotherapy protocol maximum tolerated dose (MTD) compared to Pure SI&EA and Hybrid 1.
4. Hybrid 1 results are improved compared to Pure SI&EA in all the case studies but it came short against Hybrid 2 in terms of cancer cell and drug concentration reduction.

Overall, the performance of hybrid techniques based on optimal control theory and the swarm and evolutionary algorithms are robust and better than the performance of the methodology that is based purely on swarm and evolutionary algorithms. The present study selected the cancer chemotherapy model that is independent of cancer type as this work hopes to show the advantage of hybrid optimization techniques on general cancer treatment problem in comparison to optimization technique that is purely based on SI or EA. These results will be helpful for oncologists and mathematicians to further analyze the hybridization of optimal control with other optimization techniques to enhance the optimization. The outcome would relieve the patient's pain and reduce the cost of chemotherapy treatment. In future work Hybrid Bare-Bones PSO algorithm [46] will used to handle the constraints. The authors would provide the Matlab codes of the work if requested via email of the corresponding author.

Declaration of Competing Interest

The authors of this paper entitled "The Combined Effect of Optimal Control and Swarm Intelligence on Optimization of Cancer Chemotherapy" would like state there is no conflict of interest in submitting this work to the journal of Computer Methods and Programs in Biomedicine.

Acknowledgement

This work is supported by Faculty Research Grant, GPF010A-2018, Faculty of Engineering, University Malaya, Malaysia

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cmpb.2020.105327.

References

[1] W. H. Organization, Cancer - Key Facts, 2018 Available: http://www.who.int/news-room/fact-sheets/detail/cancer.
[2] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2018, CA Cancer J. Clin. 68 (2018) 7–30.
[3] D. Galmarini, C.M. Galmarini, F.C. Galmarini, Cancer chemotherapy: A critical analysis of its 60 years of history, Crit. Rev. Oncol. Hematol. 84 (2012) 181–199.
[4] J.M. Harrold, R.S. Parker, Clinically relevant cancer chemotherapy dose scheduling via mixed-integer optimization, Comput. Chem. Eng. 33 (Dec 2009) 2042–2054.
[5] M. Itik, M.U. Salamci, S.P. Banks, Optimal control of drug therapy in cancer treatment, Nonlinear Anal. Theory Methods Appl. 71 (2009) e1473–e1486.
[6] R.A. Ku-Carrillo, S.E. Delgadillo-Aleman, B.M. Chen-Charpentier, Effects of the obesity on optimal control schedules of chemotherapy on a cancerous tumor, J. Comput. Appl. Math. 309 (2017) 603–610.
[7] X. Wu, Q.D. Liu, K.J. Zhang, M. Cheng, X. Xin, Optimal switching control for drug therapy process in cancer chemotherapy, Eur. J. Control 42 (Jul 2018) 49–58.
[8] J.H. Shi, O. Alagoz, F.S. Erenay, Q. Su, A survey of optimization models on cancer chemotherapy treatment planning, Ann. Oper.Res. 221 (Oct 2014) 331–356.
[9] A. C. Society, Economic Impact of Cancer, 2018 Available: https://www.cancer.org/cancer/cancer-basics/economic-impact-of-cancer.html.
[10] J.C. Panetta, K.R. Fister, Optimal control applied to competing chemotherapeutic cell-kill strategies, SIAM J. Appl. Math. 63 (2003) 1954–1971.
[11] R.B. Martin, Optimal control drug scheduling of cancer chemotherapy, Automatica 28 (1992) 1113–1123.
[12] A.S. Matveev, A.V. Savkin, Optimal control applied to drug administration in cancer chemotherapy: the case of several toxicity constraints, in: Proceedings of the IEEE Conference on Decision and Control, 2000, pp. 4851–4856.
[13] L.G. De Pillis, A. Radunskaya, The dynamics of an optimally controlled tumor model: a case study, Math. Comput. Modell. 37 (2003) 1221–1244.
[14] S. Khadraoui, F. Harrou, H.N. Nounou, M.N. Nounou, A. Datta, S.P. Bhattacharyya, A measurement-based control design approach for efficient cancer chemotherapy, Inf. Sci. 333 (2016) 108–125.
[15] N. Sharifi, S. Ozgoli, A. Ramezani, Multiple model predictive control for optimal drug administration of mixed immunotherapy and chemotherapy of tumours, Comput. Methods Progr. Biomed. 144 (2017) 13–19.
[16] G. Dhiman, V. Kumar, Multi-objective spotted hyena optimizer: A multi-objective optimization algorithm for engineering problems, Knowl. Based Syst. 150 (2018) 175–197.
[17] F.S. Lobato, V.S. Machado, V. Steffen, Determination of an optimal control strategy for drug administration in tumor treatment using multi-objective optimization differential evolution, Comput. Methods Progr. Biomed. 131 (Jul 2016) 51–61.
[18] Z. Fan, W. Li, X. Cai, H. Li, C. Wei, Q. Zhang, et al., Push and pull search for solving constrained multi-objective optimization problems, Swarm Evolut. Comput. 44 (2018) 665–679.
[19] Y. Zhang, S. Cheng, Y. Shi, D.-w. Gong, X. Zhao, Cost-sensitive feature selection using two-archive multi-objective artificial bee colony algorithm, Expert Syst. Appl. 137 (2019) 46–58.
[20] Y. Zhang, D. Gong, J. Cheng, Multi-Objective particle swarm optimization approach for cost-based feature selection in classification, IEEE/ACM Trans. Comput. Biol. Bioinf. 14 (2017) 64–75.
[21] Y. Zhang, D.-W. Gong, Z. Ding, A bare-bones multi-objective particle swarm optimization algorithm for environmental/economic dispatch, Inf. Sci. 192 (2012) 213–227.
[22] Y. Zhang, D.-W. Gong, N. Geng, Multi-Objective optimization problems using cooperative evolvement particle swarm optimizer, J. Comput. Theor. Nanosci. 10 (3) (2013) 655–663.
[23] Y. Zhang, C. Xia, D. Gong, X. Sun, Multi-Objective PSO Algorithm for Feature Selection Problems with Unreliable Data, 2014.
[24] M.Z.b Mohd Zain, J. Kanesan, J.H. Chuah, S. Dhanapal, G. Kendall, A multi-objective particle swarm optimization algorithm based on dynamic boundary search for constrained optimization, Appl. Soft Comput. 70 (2018) 680–700.
[25] K. Deb, A. Pratap, S. Agarwal, T. Meyarivan, A fast and elitist multiobjective genetic algorithm: NSGA-II, IEEE Trans. Evol. Comput. 6 (2002) 182–197.
[26] C.A. Coello Coello, Theoretical and numerical constraint-handling techniques used with evolutionary algorithms: a survey of the state of the art, Comput. Methods Appl. Mech. Eng. 191 (2002) 1245–1287.
[27] L.G. de Pillis, W. Gu, K.R. Fister, T. Head, K. Maples, A. Murugan, et al., Chemotherapy for tumors: an analysis of the dynamics and a study of quadratic and linear optimal controls, Math. Biosci. 209 (2007) 292–315.
[28] U. Ledzewicz, H. Schättler, Optimal bang-bang controls for a two-compartment model in cancer chemotherapy, J. Optim. Theory Appl. 114 (September 01 2002) 609–637.
[29] U. Ledzewicz, H. Schattler, Optimal control for a bilinear model with recruiting agent in cancer chemotherapy, in: Proceedings of the Forty-Second IEEE International Conference on Decision and Control (IEEE Cat. No.03CH37475), 3, 2003, pp. 2762–2767.

[30] U. Ledzewicz, H. Schättler, Optimal controls for a model with pharmacokinetics maximizing bone marrow in cancer chemotherapy, Math. Biosci. 206 (2007) 320–342.
[31] U. Ledzewicz, H. Schattler, A synthesis of optimal controls for a model of tumor growth under angiogenic inhibitors, in: Proceedings of the Forty-Fourth IEEE Conference on Decision and Control, 2005, pp. 934–939.
[32] H. Maurer, G. Vossen, Sufficient conditions and sensitivity analysis for optimal bang-bang control problems with state constraints, in: System Modeling and Optimization, 2009, pp. 82–99.
[33] H. Maurer, First and second order sufficient optimality conditions in mathematical programming and optimal control, in: H. König, B. Korte, K. Ritter (Eds.), Mathematical Programming at Oberwolfach, Springer Berlin Heidelberg, Berlin, Heidelberg, 1981, pp. 163–177.
[34] V. Zeidan, The riccati equation for optimal control problems with mixed state–control constraints: necessity and sufficiency, SIAM J. Control Optim. 32 (1994) 1297–1321.
[35] H. Maurer, S. Pickenhain, Second-order sufficient conditions for control problems with mixed control-state constraints, J. Optim. Theory Appl. 86 (1995) 649–667.
[36] G. Vossen, Switching time optimization for bang-bang and singular controls, J. Optim. Theory Appl. 144 (2010) 409–429.
[37] J. Kennedy, R. Eberhart, Particle swarm optimization, in: Proceedings of the ICNN'95 - International Conference on Neural Networks, 4, 1995, pp. 1942–1948.
[38] Y. d. Valle, G.K. Venayagamoorthy, S. Mohagheghi, J. Hernandez, R.G. Harley, Particle swarm optimization: basic concepts, variants and applications in power systems, IEEE Trans. Evol. Comput. 12 (2008) 171–195.
[39] C.A.C. Coello, M.S. Lechuga, MOPSO: a proposal for multiple objective particle swarm optimization, in: Proceedings of the 2002 Congress on Evolutionary Computation. CEC'02 (Cat. No.02TH8600), 2, 2002, pp. 1051–1056.
[40] B.T. ck, H. Schwefel, An overview of evolutionary algorithms for parameter optimization, Evol. Comput. 1 (1993) 1–23.
[41] C.M. Fonseca, P.J. Fleming, An overview of evolutionary algorithms in multiobjective optimization, Evol. Comput. 3 (1995) 1–16.
[42] D. Souza, F. Lobato, R. Gedraite, Robust multiobjective optimization applied to optimal control problems using differential evolution, Chem. Eng. Technol. 38 (2015).
[43] F. Xue, A.C. Sanderson, R.J. Graves, Pareto-based multi-objective differential evolution, in: Proceedings of the Congress on Evolutionary Computation, 2003. CEC '03., 2, 2003, pp. 862–869.
[44] E. Zitzler, D. Brockhoff, L. Thiele, The hypervolume indicator revisited: on the design of pareto-compliant indicators via weighted integration, in: Evolutionary Multi-Criterion Optimization, 2007, pp. 862–876. Berlin, Heidelberg.
[45] U. Ledzewicz, H. Schattler, M.R. Gahrooi, S.M. Dehkordi, On the mtd paradigm and optimal control for multi-drug cancer chemotherapy, Math. Biosci. Eng. 10 (Jun 2013) 803–819.
[46] Y. Zhang, D.-w. Gong, N. Geng, X.-y. Sun, Hybrid bare-bones pso for dynamic economic dispatch with valve-point effects, Appl. Soft Comput. 18 (2014) 248–260.