International Journal of Combinatorial Optimization Problems and Informatics, 11(3), Sep-Dec 2020, 61-75. ISSN: 2007-1558.

www.editada.org

Solving multi-objective functions for cancer treatment by using Metaheuristic Algorithms

Farid Heydarpoor [1], Seyed Mehdi Karbassi [1,], Narges Bidabadi [1], Mohammad Javad Ebadi [2]*
[1]Department of Applied Mathematics, Yazd University, Yazd, Iran
[2]Faculty of Marine Science, Chabahar Maritime University, Chabahar, Iran
[*]Corresponding Author: *smkarbassi@yazd.ac.ir*

Abstract. In this context, we introduce a multi-objective optimization problem (MOOP) to simultaneously minimize the objectives of cancerous cells density as well as the approved drug amount in order to optimize the medical remedy of a tumor. The main aim is gaining a proper pattern for medical supervision to sick people with malignant cancer. To this end, a comparison is made between the two important and useful methods of non-dominated sorting genetic algorithm II (NSGA-II) and multi-objective particle swarm optimization (MOPSO). The gained Pareto's Curve here yields a series of optimal protocols. A desired optimal technique is then selected from these optimal protocols for drug supervision, relating to an under consideration criterion. The results show that in both criterions, the convergence and expansion of Pareto optimal fronts of the performance of the NSGA-II method is better compared to MOPSO.
Keywords: Optimal Control, Cancer Drug Therapy, Particle Swarm Optimization, Genetic Algorithm, Multimodal Functions

Article Info
Received Mar 6, 2019
Accepted Dec 24, 2019

1 Introduction

Cancer is a group of diseases that are created by irregularities of the natural function of the body cells, and it is one of the most important causes of death in Iran, where its growth rate is higher than world rate. Liver cancer, lung cancer, stomach cancer, breast cancer, and colorectal cancer are considered as the main kinds of cancer. The principle treatment of cancer consists of surgical procedure, chemotherapy, radiotherapy, bisphosphonates, hormone therapy, stem cell and bone marrow transplants, and organic remedies. Among these treatment strategies, chemotherapy has an important and widespread application for most cancers.

Displaying of tumor cells movement is an agile investigation subject for biologists, mathematicians, and engineers. Distinctive methodologies are utilized as a part of the scientific demonstration of cancer and its control. Many mathematical models have been improved for predicting tumor growth after the chemotherapy implementation as well as controlling cancer during the treatment course by minimizing the number of cancer cells [1-8]. The influence of the drug and the interactions among tumor and normal cells, a consequence of the chemotherapy treatment are considered in these models. These are very helpful to acquire the optimum cancer chemotherapy protocols able to minimize the amount of the tumor cells during the treatment. These protocols can also minimize the drug doses to the minimum level with fewer side effects under a series of constraints utilizing optimization methods.

In recent years, many methods have been presented for treatment and optimal control of cancerous tumor [9-15]. Calzada et al. [12] and De Pillis and Radunskaya [9] introduced a performance index based on the number of tumor cells and optimal measured dose of a drug in order to minimize tumor density. El-Gohary [10] studied optimal control of tumor and irregularities behavior of its model before and after drug injection and have investigated system stability in balance points. Shuo Wang and Heinz Schattler [14] introduced an optimal treatment of cancer to minimize the density of tumor and its malicious effects during a certain period

of time. Urszula Ledzewicz, et al. [15] discussed the bout effects of irregularities of growth of tumor and drug resistance on the treatment process and optimal control of a mathematical model.

Evolutionary computation gives exact sensible solutions for hard optimization problems. Evolutionary Algorithms (EAs) own many exclusive advantages: generality, reliability and robustness performance, and just low data required for the problem to be resolved by a simple implementation. Hence, these algorithms have a widespread and successful application for solving COPs [16]. Tes et al. [17], proposed an ideal treatment of cancer to minimize the drug density in chemotherapy treatment by utilizing a genetic algorithm (GA). Liang et al. [18] applied GA for designing the Pharmaceutical planning of the non-specific cancer chemotherapy treatment. In another study conducted by McCall and Co-worker [19], MOOPs were utilized for designing chemotherapy treatment scheduling with constraints of toxic side effect and drug doses. Alam et al. [20] offered a way of phase-specific drug scheduling by applying MOPSO and designed a closed-loop control method, which gives other options to exchanging off between the toxic side effects and cell killing.

In this study, because minimizing number of cancerous cells with the lowest prescribed drug is considered as a type of Np-hard problem, we utilize efficient meta-heuristic algorithms of MOPSO and NSGA-II which have high convergence for solving large scale problems. Several Pareto analyzing criteria are considered to make a comparison between these two meta-heuristic algorithms [21, 22].

The organization of the remaining paper is as follows. The mathematical model of tumor growth is presented in part 2. MOPSO and NSGA-II are recalled briefly in part 3. The presented methodology is discussed in detail in part 4. The results graphically are shown in part 5, and finally, in part 6, a conclusion is made.

2 Mathematical modeling of tumor growth

As treating malignancy tumor is vital, this kind of expanding technology has absorbed the interest of specialized medical experts, mathematicians, and technicians. Many models for tumor expansion are improvement by applying numerical tools. The model that we study to build up an optimal medication methodology for malignancy tumor remedy is deduced from [23, 24]. In such a model, tumor expansion is recognized as a society dynamics problem, which will not reach the goal to focus on a particular type of tumors [23, 24].

The model targets the tissue nearby the tumor location and consists of three dissimilar cell crowds and the normal cells, tumor cells and immune cells at time t are specified by $N(t)$, $T(t)$ and $I(t)$, respectively. The next model provides the dynamics of tumors interplays keeping between cells and drug result [24].

$$\dot{N}(t) = r_2 N(t)\big(1 - b_2 N(t)\big) - c_4 T(t)N(t) - F_1\big(u(t)\big)N(t); \quad (1)$$

$$\dot{T}(t) = r_1 T(t)\big(1 - b_1 T(t)\big) - c_2 I(t)T(t) - c_3 T(t)N(t) - F_2\big(u(t)\big)T(t); \quad (2)$$

$$\dot{I}(\mathrm{t}) = \mathrm{s} + \frac{\rho I(t)T(t)}{\alpha + T(t)} - c_1 I(t)T(t) - d_1 I(t) - F_3\big(u(t)\big)I(t), \quad (3)$$

The result of the drug is distributed by $F_i\big(u(t)\big)$, where $i = 1,2,3$. It is added up to all equations since chemotherapy eliminates different types of cells with a dissimilar exterminate proportion. The chemotherapy influencing the system is in fact as follow [24]:

$$F_i\big(u(t)\big) = a_i\big(1 - e^{-u(t)}\big) = a_i\Big(1 - \big(1 - u(t)\big)\Big) = a_i u(t) \quad (4)$$

The variables $a_1, a_2\ and\ a_3$, are the several answer coefficients of normal, tumor and immune system cells to the used medication, all at once. In the formula, $i = 1$ is associated with tumor cells and $i = 2$ with normal cells. These cells compete with each other for available resources growing logistically with parameters r_i and b_i. This parameters indicates per capita growth rates and reciprocal carrying capacity, respectively. The parameters $c_1, c_2, c_3$and c_4 are competition terms. Also ρ and α are positive

constants. Actually, u denotes the drug focus in the tissues or blood. However, the value of medication dose prescribed for the sick by oral, injections or in the future technology by some type of lightweight pumps or straps that could proffer drug consistently to blood flow could be determined as described below[24]:

$$\dot{u}(\mathrm{t}) = v(t) - d_2 u \tag{5}$$

Where $v(t)$ is the used drug amount by oral or injections before influencing the bloodstream and d_2 is the per capita death count of the drug [24].

3 Solution Strategies

The optimality strategy of the MOOP [30] differs from one-goal optimization. In the MOOP, finding a single-purpose solution serving all other purposes is not possible. However, a set of optimal solutions are required that are named pareto optimal front [31].

A general formula for MOOP that simultaneously reduces several target functions is expressed as the following mathematical model [30]:

$$\text{Minimize } f(x) = \{f_1(x), f_2(x), \dots, f_m(x)\}, \quad x \epsilon D \tag{6}$$

where $f(x)$ denotes the objectives vector and The decision variable x is mapped by $f_i = R^n \to R, i = 1,2,\dots,m,$ into the target space. The feasible region D is constrained by $J + k$ equality and inequality constraints, and the decision variable x is restricted in this region. i.e.

$$D = \{x: g_j(x) \le 0, h_k(x) = 0, \qquad k = 1,2,\dots,k;\ j = 1,2,\dots,J\} \tag{7}$$

The decision variable x could be expressed more properly as $x = [x_1, x_2, x_3, \dots, x_n\ ]^T$, that x_i are limited to lower $x_i^{(\min)}$ and upper $x_i^{(\max)}$ bounds. These bounds are called the decision space [30]. In Tumor treatment problem $m = 2$. So, (6) is expressed as described below:

$$\text{Minimize } f(x) = \{f_1(x), f_2(x)\}, \qquad x \epsilon D \tag{8}$$

The function $f_1(x)$ represents the minimization of the concentration of cancer cells, and the function $f_2(x)$ represents the minimization of the drug volume given to the patient. In the following provides a summary description of the history and explanations of the two compared methods for solving the defined mathematical model.

3.1. MOPSO Algorithm

The PSO was initially composed and presented by Eberhart and Kennedy [25-26]. This novel algorithm was used in many engineering, medical and science usages [27, 38-44]. In this algorithm, every particle refreshes its velocity based on its current velocity and its best location ($pbest_{i,j}^t$), also the best all particle location ($gbest_{i,j}^t$). At the t- th iteration, according to the $i - th$ particle, the location vector and the vector of speed are $X_i^t = (x_{i,1}^t, \dots, x_{i,n}^t)$ and $V_i^t = (v_{i,1}^t, \dots, v_{i,n}^t)$. The speed and location updating rules are given by

$$v_{i,j}^{t+1} = \omega v_{i,j}^t + \alpha_1 R_1 (pbest_{i,j}^t - x_{i,j}^t) + \alpha_2 R_2 (gbest_{i,j}^t - x_{i,j}^t), \tag{9}$$

$$x_{i,j}^{t+1} = x_{i,j}^t + v_{i,j}^{t+1} \tag{10}$$

$$j \in \{1,2,\dots,n\},$$

,

where α_1 and α_2 are positive constants, $R_1$and $R_2$are two monotonously distributed random numbers in the domain [0,1] and $\omega \in$ [0,1] is the inertia factor.

$$\omega = \frac{\omega_{max} - [(\omega_{max} - \omega_{min}) \times iter]}{\max iter} \tag{11}$$

$$\omega_{max} = initial\ weight,$$
$$\omega_{min} = final\ weight,$$
$$max\ iter = Maximum\ iteration\ number,$$
$$iter = Current\ iteration\ number.$$

The variable V_i^t is limited to the range$\pm V_{max}$ in this version. As a particle finds a situation that is superior to its previous positions, the new position is considered as pbest. The velocity regulation is presented by Clerc and Kennedy [28] as follows:

$$v_{i,j}^{t+1} = \chi\left(v_{i,j}^t + \alpha_1 R_1 (pbest_{i,j}^t - x_{i,j}^t) + \alpha_2 R_2 (gbest_{i,j}^t - x_{i,j}^t)\right), \tag{12}$$
$$\text{where } \chi = \frac{2\kappa}{\left|2-\varphi-\sqrt{\varphi^2-4\varphi}\right|} \text{ with } \varphi = \alpha_1 + \alpha_2 > 4.$$

Because of the constriction coefficient χ, the algorithm needs no clear restriction V_{max}. An analysis was conducted on Eq. (9) By Krohling and dos Santos Coelho [29] and they concluded that the interval [0.72, 0.86] could be a possibly proper select for χ. Therefore, rather than χ, the absolute value of the Gaussian likelihood giving out with zero average and unit variance $abs(N(0,1))$ is brought into the velocity equation.

$$v_{i,j}^{t+1} = \beta_1 (pbest_{i,j}^t - x_{i,j}^t) + \beta_2 (gbest_{i,j}^t - x_{i,j}^t)), \tag{13}$$

Where β_1 and $\beta_2$are generated by using $abs(N(0,1))$. Due to the statistical knowledge, the median of $abs(N(0,1))$ is 0.789, and the variance is 0.34.

Moore and Chapman [32], introduced the initial improvement of the PSO methodology to solve MOOPs, which is diagnosed as the main MOPSO. In MOPSO, a series of unbeatable solutions have to supplant the single overall best solution in the PSO case. Furthermore, it might be no single local best particular for every swarm particle, also the choice of the international best and regional best to direct the swarm particles turns into a non-trivial duty in the multi-objective space. In the displayed methodology, elitism is additionally regarded by duplicating any non-dominated solution got to an outside put for holding the latest unbeatable solutions acquired during generations and the outside set is refreshed normally to retain just the unbeatable solutions. The steps of the MOPSO algorithm are displayed in Figure 1 [22, 33 and 34].

3.2. NSGA-II Algorithm

Genetic algorithms were enlightened by Holland [35] in the 1960s and further represented by Goldberg [36]. GA is defined as a stochastic global search method which solves problems during natural evolution by imitating processes observed. According to the survival and reproduction of the fitness, GA continuously employs new and more appropriate solutions without any pre-assumptions, including continuity and unimodality.

The NSGA-II introduced by Deb et al. (2002) [34] is an indicator algorithm that is widely applied in multi-objective optimization Since it applies the rapid non dominated sorting style to ordering and choice the population ahead. Then the algorithm employs the standard crossover and mutation to compound the current crowd and its offspring generated as the next output. The NSGA-II will preserve diversity and improve the solutions without adding new parameters to NSGA. The process of selection by applying the crowding distance operator, uniformly spread out to Pareto optimal front.Eventually, the best group in terms of non-dominance and variety are elected as the solutions. A summary of the NSGA-II process is shown in Figures 2 [22, 34].

4 Methodology

In this study, the values that control variable u of (the amount of consumed medicine) adopts over specific time intervals (u_{max} or u_{min}). Suppose the period $t \in [t_0, t_f]$ be divided into Nt subintervals, such that $t_0 = t_0 < t_1 < \cdots < t_{Nt} = t_f$, which for each $t \in [t_i, t_{i+1}], i = 1,2, \dots, Nt$, let the control variable be estimated as follows [21]:

$$u = u_i(u_{min}\ or\ u_{max}) \text{ for } \quad t_i \le t \le t_{i+1} \tag{14}$$

Therefore, we show that the values of the control variable for each $t \in [t_0, t_f]$with the unknown $u_1, u_2, \dots, u_{Nt}$ follow the bang-bang control, and each of them represents the amount of prescription medicine to the patient's body in the related time interval. Therefore, there are a total of $2Nt - 1$ variables that are optimized by random algorithms, where Nt is 15. In this study, minimizing the tumor cells concentration and the amount of drug consumed by the sick are considered as a two objective optimization problem which is represented as follows:

$$\min \int T dt \quad \text{and} \quad \min \int u dt$$

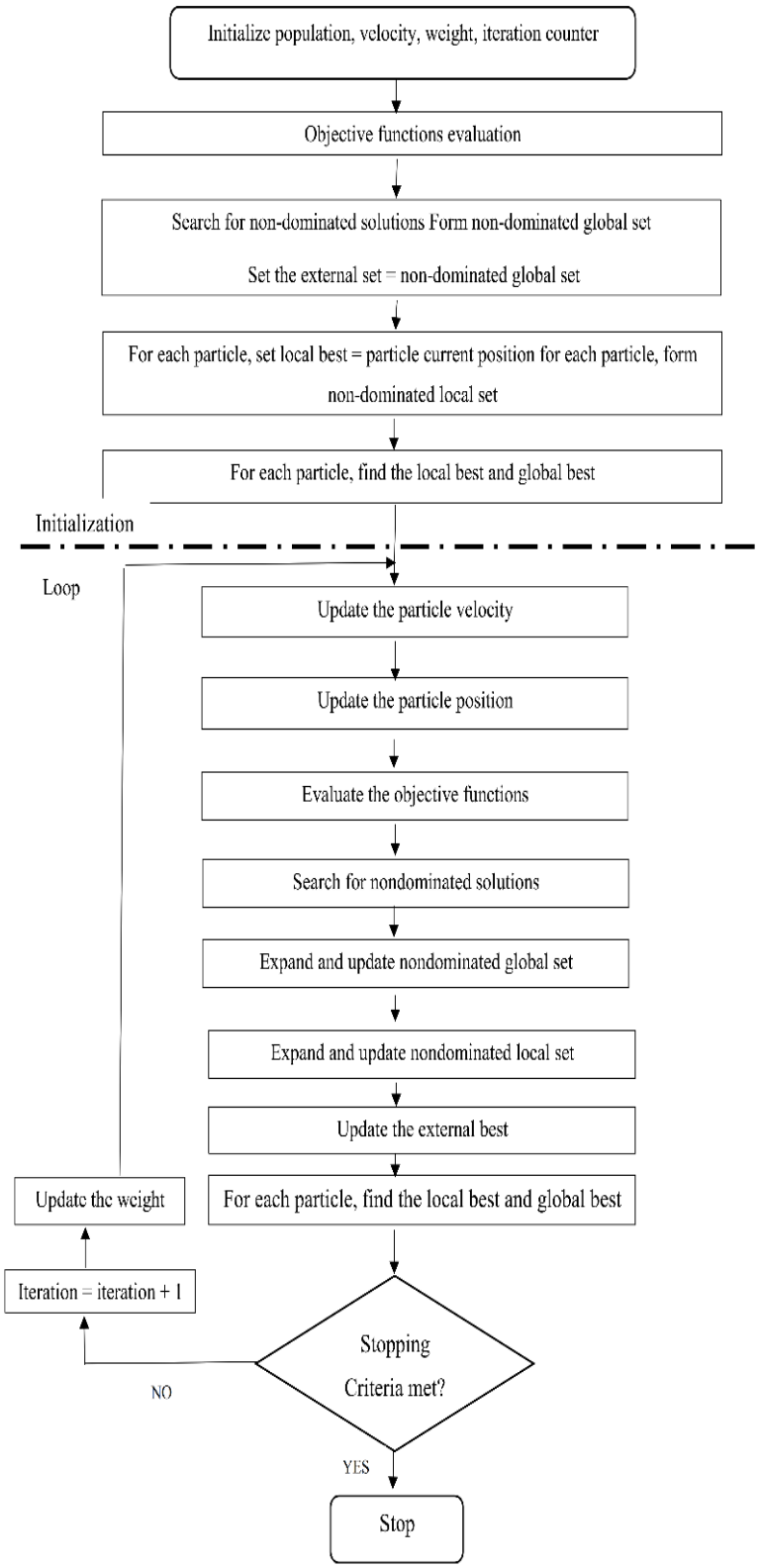


Fig. 1 *The MOPSO Flow chart*

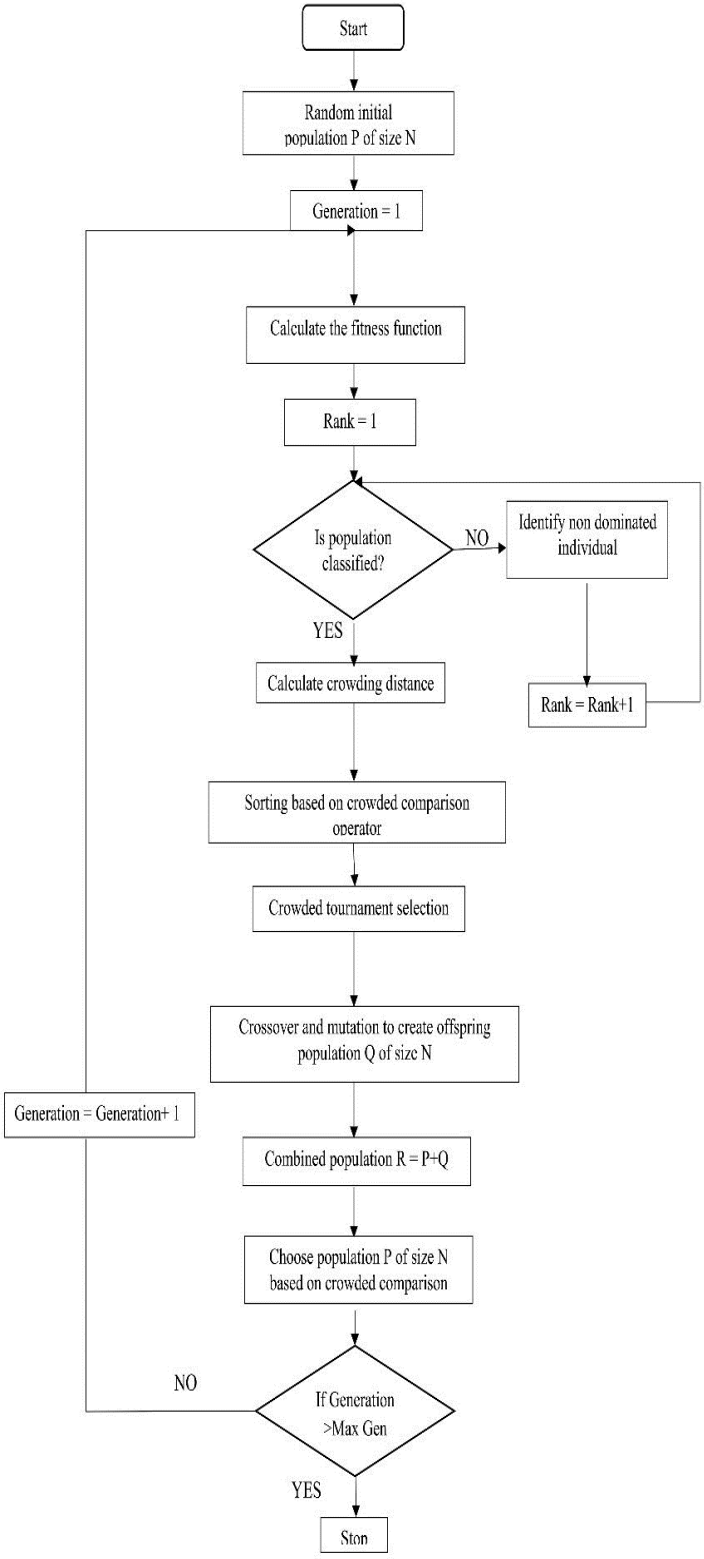


Fig. 2 The NSGA-II Flow chart

5 Experiments and Results Analysis

This part consists of two segments. Firstly, original parameters applied in the mathematical model, MOPSO and NSGA-II are presented. Secondly, the results of the mathematical model are displayed. Also, a comparison is made between the ability of these two metaheuristics.

5.1. Input parameters

We utilize the same model parameters in [23, 37].They are given as:

$$a_1 = 0.1 \quad a_2 = 0.3 \quad a_3 = 0.2 \quad b_1 = b_2 = 1 \quad \alpha = 0.3 \quad c_1 = c_3 = c_4 = 1$$

$$c_2 = 1 \quad d_1 = 0.2 \quad d_2 = 1 \quad r_1 = 1.5 \quad r_2 = 1 \quad \mathrm{s} = 0.33 \quad \rho = 0.01$$

Also, the main parameters of NSGA-II and MOPSO and parameters related to the stop criterion are shown in Table 1.

Table 1 MOPSO (a) and NSGA-II (b) Parameters

Explanation	**Symbol**	**Value**
Number of population	N_P	50
Cognitive acceleration constant	R_1	1
Social acceleration constant	R_2	2
Inertia weight	ω	0.5
Maximum iteration		200
Maximum velocity of the particle		$V_{max} = u_b$
(a)		

Explanation	**Symbol**	**Value**
Number of particles	N_P	50
Crossover rate		0.8
Mutation rate		0.02
Maximum iteration		200
(b)		

5.2. Final solutions

The results acquired after the processing of the NSGA-II and MOPSO algorithms are indicated in this part. MATLAB 7.0 software is applied to run the algorithms using a computer with Intel(R) Core(TM) i7-2330M CPU 2.67 GHz 4 GB RAM. The proposed approaches are applied for minimizing both cancerous cells attentiveness and the approved drug amount. The initial positions are considered as: $N(0) = 0.9, T(0) = O.25, and\ I(0) = 0.25$. The size of the population and the number of generations is 50. The values of other parameters are determined in Table 1.

In this research, three case studies are taken into account for the desired issue which in the first of these, applied the parameters given in Table 1. The parameters for case studies II and III are the same with those in case study I. Except for s = 0.3 as well as ρ

= 0.02 for case studies II and III, respectively. For each of the three case studies of I, II and III, the proposed algorithms are performed, and the results are presented by figures and table, and they are compared together.

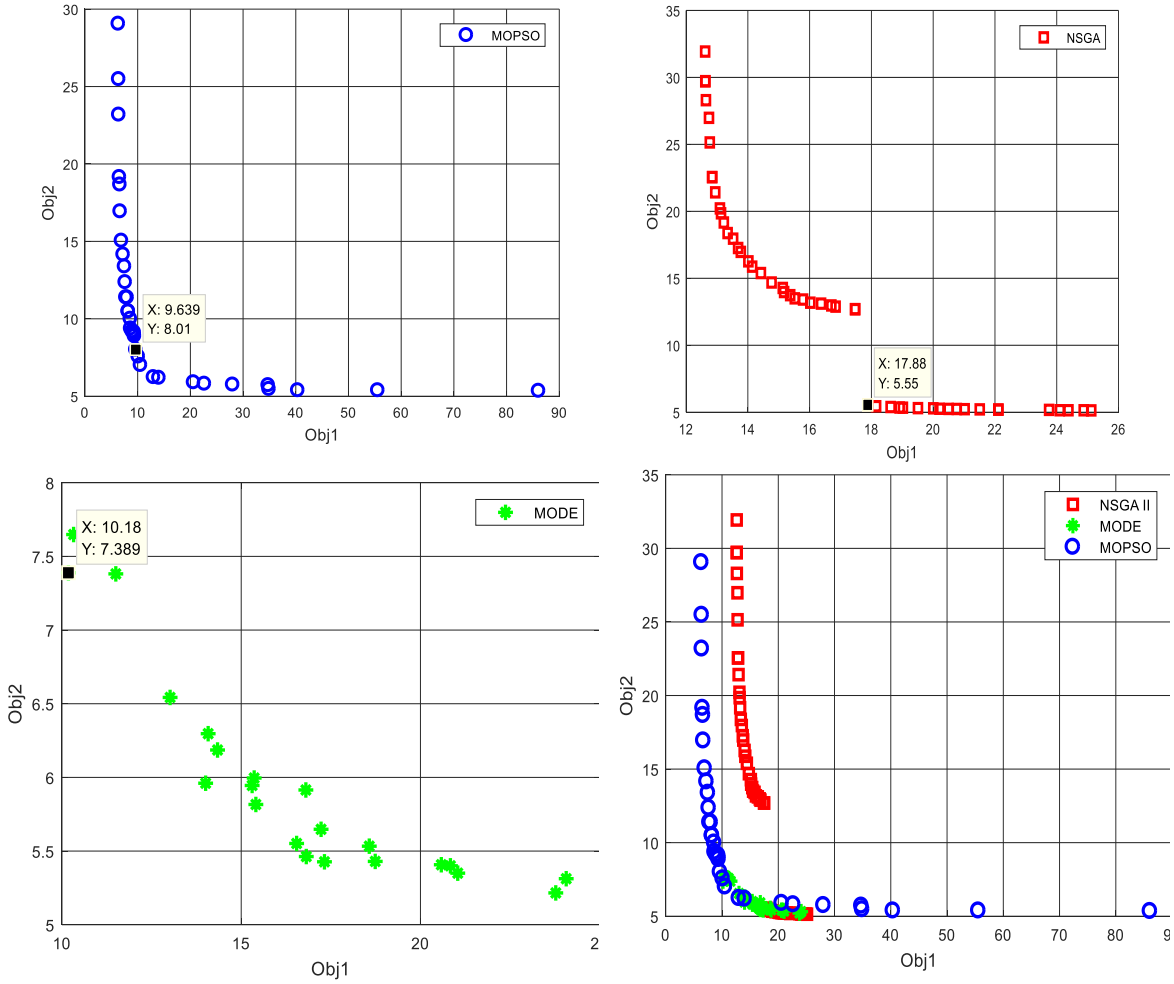
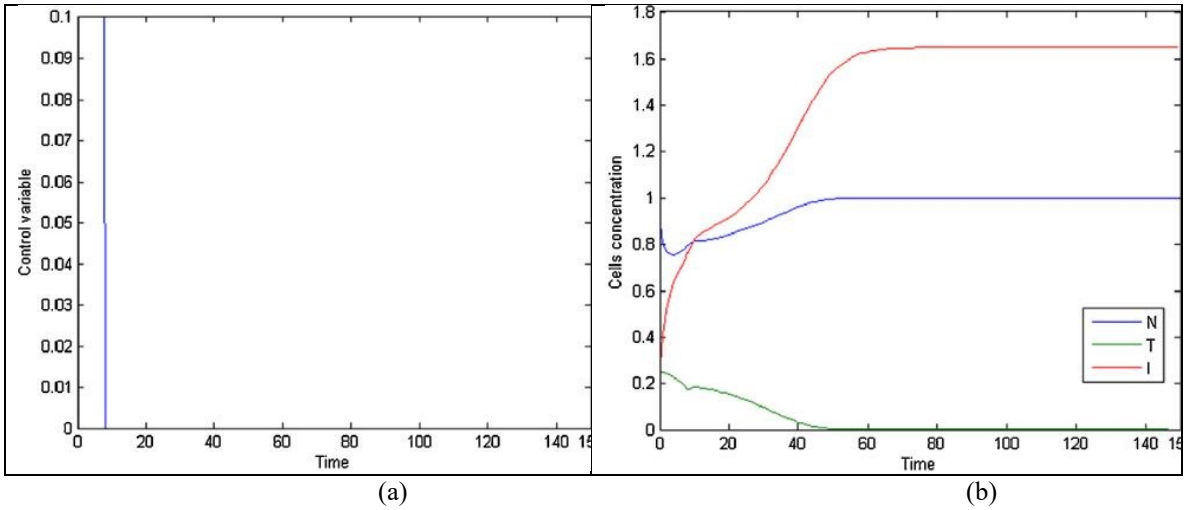


Fig. 3. Pareto optimal front for a case study I.



(a) (b)

Fig. 4. Control variable (a) and cells concentration (b) for case study I.

Figures 3, 5 and 7 indicate the Pareto fronts obtained for each of the algorithms for cases I, II, and III, respectively, which the superiority of the MOPSO algorithm to NSGA-II and MODE is obviously observed in terms of the convergence of responses.

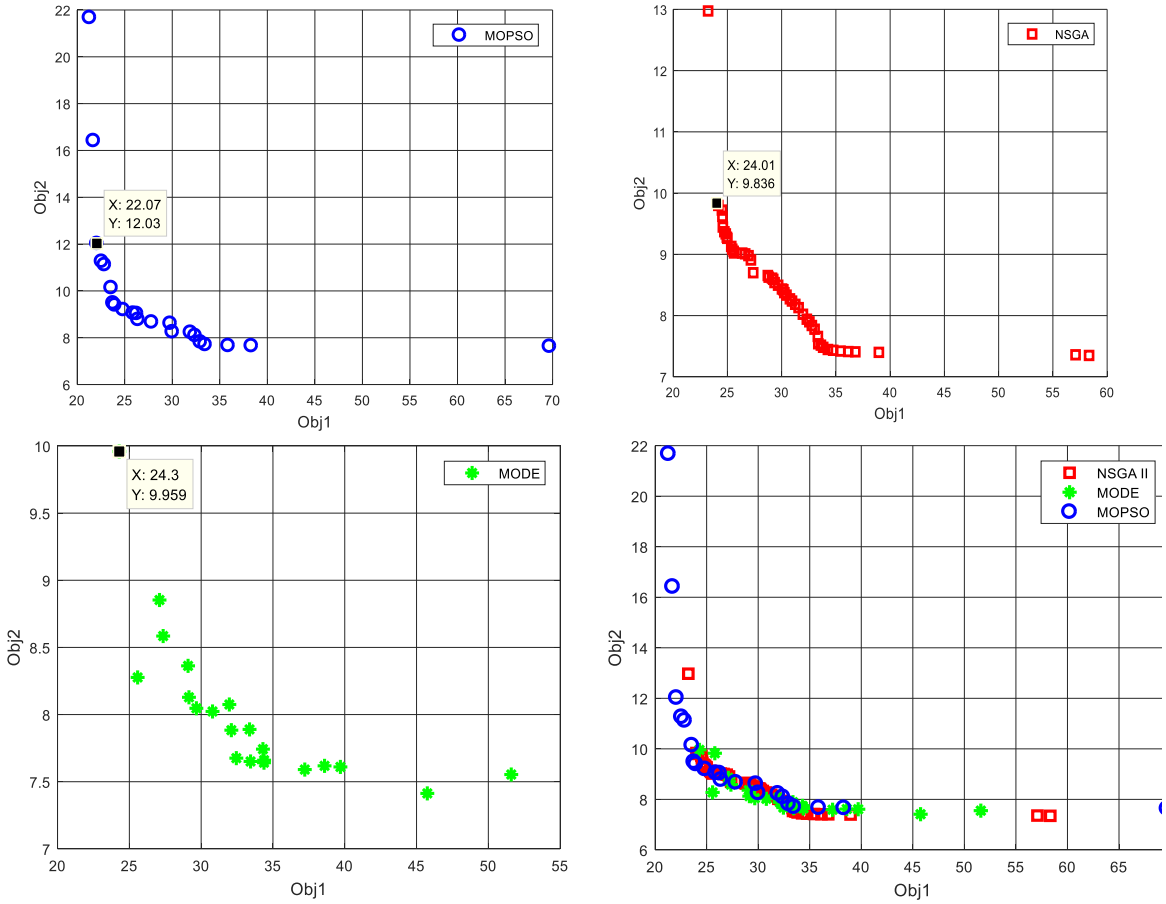
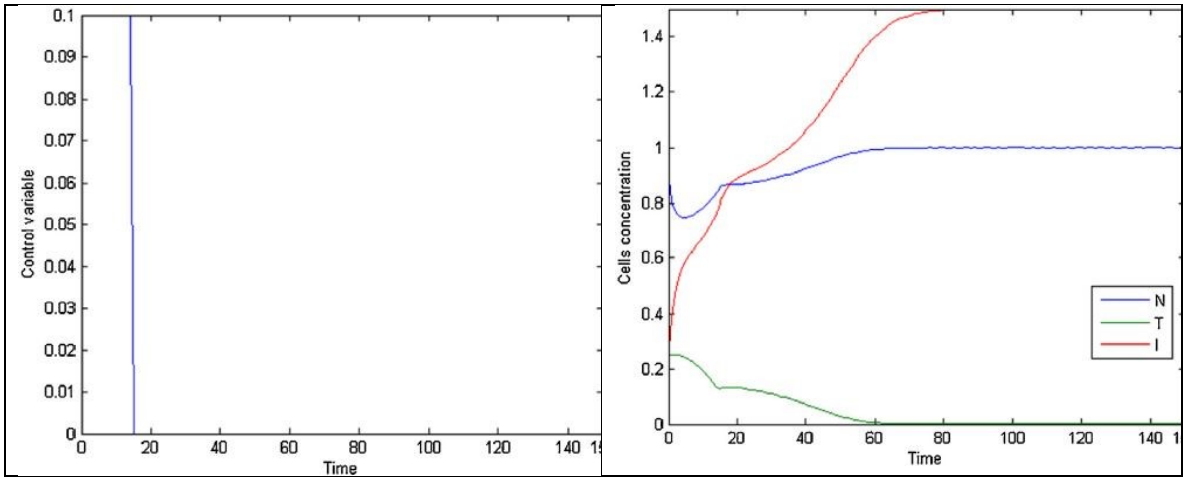


Fig. 5. Pareto optimal front for case study II.



(a) (b)

Fig. 6. Control variable (a) and cells concentration (b) for case study II.

Table 2 Results for a case study I

Algorithm	Distance	Tumor cell concentration	Drug volume
MOPSO	12.5327	9.639	8.01
NSGA-II	18.7215	17.88	5.55
MODE	12.5789	10.18	7.389

Table 3 Results for case study II

Algorithm	Distance	Tumor cell concentration	Drug volume
MOPSO	25.1357	22.07	12.03
NSGA-II	25.9466	24.01	9.836
MODE	26.2616	24.3	9.959

Figures 14 (a), 16 (a) and 18 (a) show the amount of medicine consumed for different time intervals during treatment and Figures 14 (b), 16 (b) and 18 (b) show the effect of the medicine on tumor , normal and immune cells for cases I, II, and, III, respectively. From Figure 14 (a), it can be seen that the medicine is consumed in the first eight days of treatment, but it is discontinued. Hence, it is obviously observed in Figure 14 (b), that normal and tumors cells are simultaneously reduced due to the medicine usage in the first eight days of treatment. However, after that, only the number of tumor cells decreases due to the presence of immune cells. Figures 16 and 18 related to II and III also has the same pattern in Figure 14, but, the duration of medicine usage increases because of the low number of immune cells in case study II. Also, regarding case study III, the duration of medicine usage decreases due to the increased immune cells.

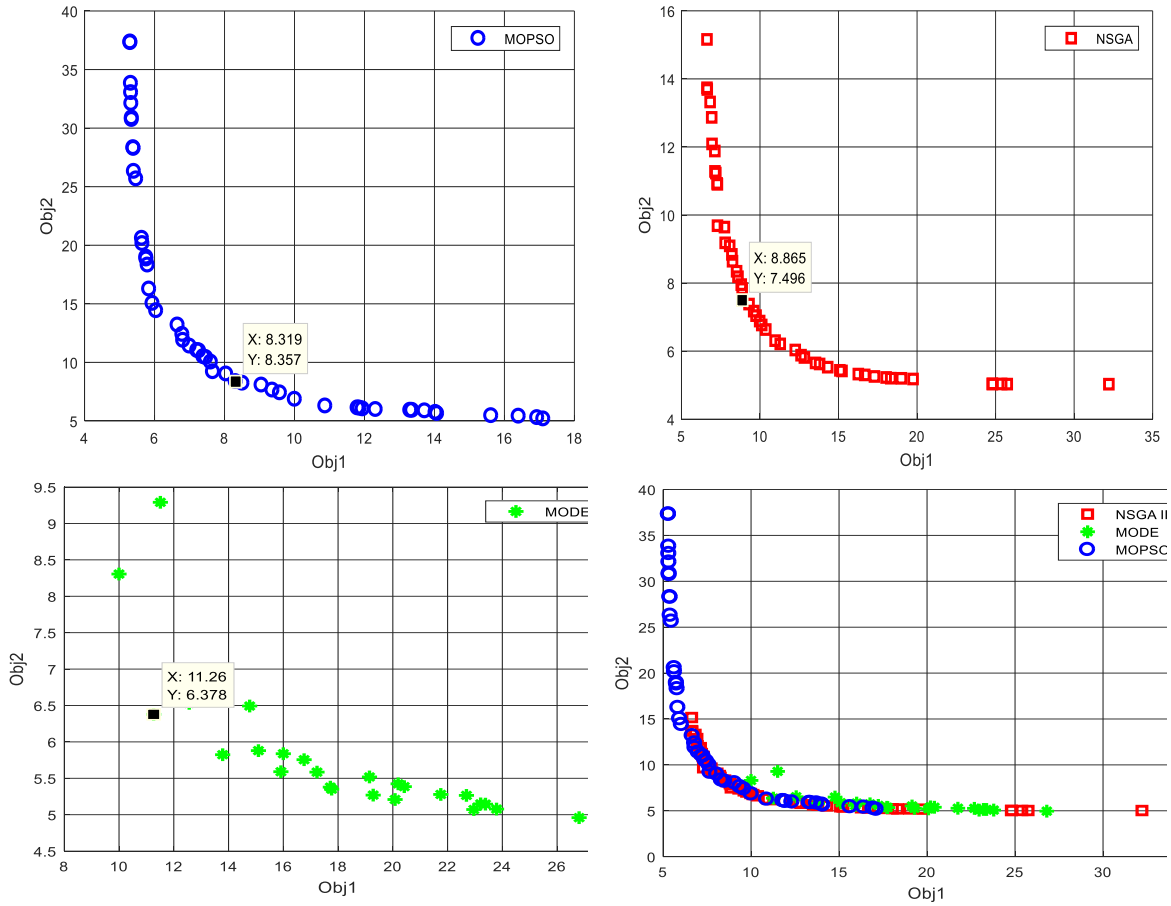
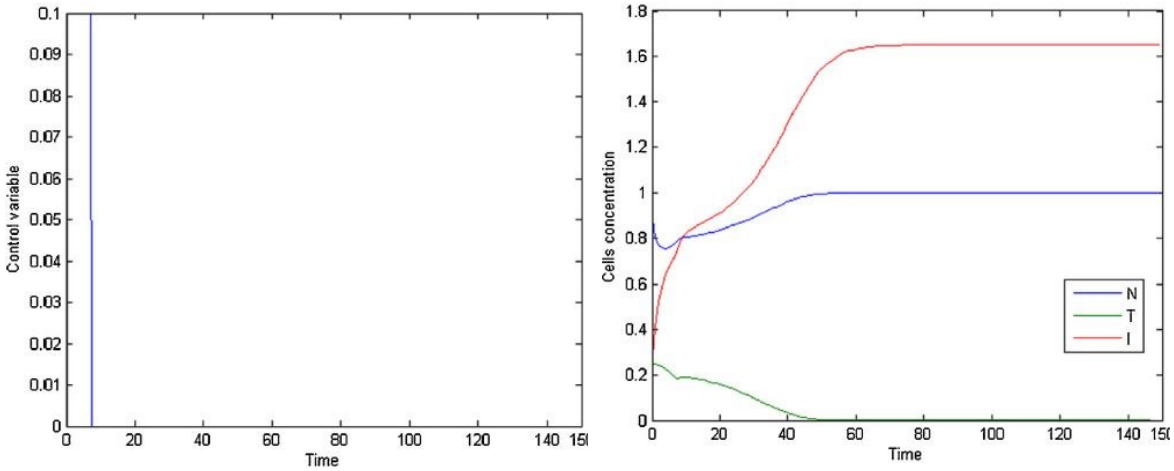


Fig. 7. Pareto optimal front for case study III.



(a) (b)

Fig. 8. Control variable (a) and cells concentration (b) for case study III.

In tables 2, 3 and 4, we compare the proposed algorithms with the assistance of the amount of medicine usage criteria, the number of tumor cells and the smallest Euclidean distance of Pareto front obtained by the algorithms and the point of (0, 0). Except for case III, in the two cases of I and II, the MOPSO algorithm has a smaller Euclidean distance compared to two other algorithms. Also, the MOPSO algorithm has the lowest amount of cancer cells than two other algorithms in all three cases. The NSGA-II algorithm has the lowest amount of drug cells than two other algorithms in the two cases of I and II.

Table 4 Results for case study V

Algorithm	Distance	Tumor cell concentration	Drug volume
MOPSO	11.7917	8.319	8.357
NSGA-II	11.6094	8.865	7.496
MODE	12.9408	11.26	6.378

6 Conclusion

In this context, we introduce (MOOP) to synchronically minimize the targets of cancerous cells density as well as the approved medicine amount in order to medically remedy the tumor. The main aim of this study is gaining a proper pattern for medical supervision to sick people with malignant cancer. Since this problem is considered as a type of Np-hard problem, we utilize efficient meta-heuristic algorithms of MOPSO, MODE and NSGA-II which have high convergence for solving large-scale problems. A set of optimal protocols is gained that is called Pareto's Curve. A desired optimal technique is then selected from these optimal protocols for drug supervision, relating to an under consideration criterion. Several Pareto analyzing criteria are considered to make a comparison between these three meta-heuristic algorithms. The results gained for the three case studies show that in both criteria of the convergence as well as the expansion of Pareto optimal fronts the performance of the MOPSO method is better compared to the other two algorithms, especially the NSGA algorithm.

Utilizing a mathematical model related to optimization tools may help to develop optimal protocols for using in real patients in the future. These protocols do not guarantee the optimal optimization, and other protocols may be found to have the same effectiveness but utilize less total drug administration.

References

[1] Ledzewicz, U., Schatteler, U., and Marriott, J.: 'Piecewise Constant Suboptimal Controls for a System Describing Tumor Growth under Angiogenic Treatment', IEEE International Conference on Control Applications, 2009, 2, (3), pp. 77-82

[2] Ribba, B., You, B., and Tod, M., et al.: 'Chemotherapy may be delivered based on an integrated view of tumor dynamics', IET Syst. Biol., 2009, 3, (3), pp. 180-190

[3] Neilan and Lenhart, 'An Introduction to Optimal Control with an Application in Disease Modelling', DIMACS Series in Discrete Mathematics and Theoretical Computer Science, 2010, 75, (6), pp. 67-81

[4] Michor, F., Beal, K.: 'Improving Cancer Treatment via Mathematical Modeling: Surmounting the Challenges Is Worth the Effort', Cell 163, November 19, 2015, 3, (5), pp. 1059–1063

[5] Lestari, D., Lestari, R.D.: 'A Local Stability of Mathematical Models for Cancer Treatment by Using Gene Therapy', International Journal of Modeling and Optimization, 2015, 5, (3), pp. 202–206

[6] Serre, R., Benzekry, S., and Padovani, L., et al.: 'Mathematical modeling of cancer immunotherapy and its synergy with radiotherapy', American Association for Cancer Research, to be printed.

[7] Ashyani, A., Mohammadinejad, H., and RabieiMotlagh, O., 'Stability Analysis of Mathematical Model of Virus Therapy for Cancer', Iranian Journal of Mathematical Sciences and Informatics, 2016, 11, (2), pp. 97–110

[8] Shakeri, E., Latif-Shabgahi, G., and Abharian, A. E.: 'Adaptive non-linear control for cancer therapy through a Fokker–Planck observer', IET Syst. Biol., 2018, 12, (2), pp. 73-82

[9] De Pillis, L.G., Radunskaya, A.: 'A mathematical tumor model with immune resistance and drug therapy', an optimal control approach, 2001, 3, (5), pp. 79–100
[10] El-Gohary, A.: 'Chaos and optimal control of equilibrium states of tumor system with drug', Chaos Solitons Fract, 2009, 41, (2), pp. 425–435
[11] Engelhart, M., Lebiedz, S., and Sager, S.:'Optimal control for selected cancer chemotherapy ODE models: a view on the potential of optimal schedules and choice of objective function', Mathematical Biosciences, 2011, 229, (1), pp. 123–134
[12] Calzada, M.C., Fernández-Cara, E., and Marín, M.: 'Optimal control oriented to therapy for a free-boundary tumor growth model', J Theor Biol, 2013, 325, (7), pp. 1–11
[13] Agrawal, T., Saleem, M., and Sahu, S.K. : 'Optimal control of the dynamics of a tumor growth model with Hollings' type-II functional response', Compute Appl Math, 2014, 33, (6), pp. 591–606
[14] Wang, S., Schattler, H.: 'Optimal control of a mathematical model for cancer chemotherapy under tumor heterogeneity', Mathematical Biosciences and engineering, 2016, 13, pp. 1223-1240
[15] Ledzewicz, U., Wang, S., and Schattler, H., et al.: 'on drug resistance and metronomic chemotherapy: A mathematical modeling and optimal control approach', Mathematical Biosciences and engineering, 2017, 14, pp. 217-235
[16] Coello, C.A.C.: 'Theoretical and numerical constraint-handling techniques used with evolutionary algorithms', a survey of the state of the art, Computer Methods in Applied Mechanics and Engineering, 2002, 191, 1245–1287
[17] Tes, S., Liang, Y., Leung, K., et al.: 'A Memetic Algorithm for Multiple-Drug Cancer Chemotherapy Scheduling Optimization', IEEE Trans on Systems, Man, and Cybernetics-part B, 2007, 37, pp. 84-91
[18] Liang, Y., Leung, K., and Mok, T.: 'Evolutionary drug scheduling models with Different toxicity metabolism in cancer chemotherapy', Applied soft computing, 2008, 8, pp. 140-149
[19] McCall, J., Petrovski, A., and Shakya, A.: 'Evolutionary Algorithms for Cancer Chemotherapy Optimization," Computational Intelligence in Bioinformatics, 2008, pp. 265-296
[20] Alam, S., Algol, S., Hossain, A., et al.: 'Multi-objective Particle Swarm Optimization for Phase Specific Cancer Drug Scheduling', First Int. Conf. CSBio, 2010, pp. 180-192
[21] Lobato, F. S., Machado, V. S., and Steffen, V.: 'Determination of an optimal control strategy for drug administration in tumor treatment using multi-objective optimization differential evolution', computer methods and programs in biomedicine, 2 0 1 6, 131, (11), pp. 51–61
[22] Ghodratnama, A., Jolai, F., and Tavakkoli-Moghaddam, R., "Solving a new multi-objective multi-route flexible flow line problem by multi-objective particle swarm optimization and NSGA-II", Journal of Manufacturing Systems, 2015, (14), pp. 1-14
[23] Pillis, L.G., Radunskaya, A.: 'The dynamics of an optimally controlled tumor model', a case study, Math. Compute. Model, 2003, 37, pp. 1221-1244.
[24] Itik, M., Salamci, M.U., and Banks, S.P., "Optimal control of drug therapy in cancer treatment", Nonlinear Analysis, 2009, 71, pp. 1473-1486
[25] Eberhart, R., Kennedy, J.: 'A New Optimizer Using Particles Swarm Theory, Proc. Sixth International Symposium on Micro Machine and Human Science (Nagoya, Japan)', IEEE Service Center, Piscataway, 1995, pp. 39-43
[26] Kennedy, J., and Eberhart, R.: 'Swarm Intelligence' (Morgan Kaufmann Publishers, Inc., San Francisco, CA, 2001)
[27] Marandi, A., Afshinmanesh, F., Shahabadi, M., et al.: 'Boolean Particle Swarm Optimization and Its Application to the Design of a Dual-Band Dual-Polarized Planar Antenna', CEC, 2006, pp. 3212-3218
[28] Kennedy, J.: 'Eberhart Particle swarm optimization', In: IEEE International Conference on Neural Networks, IV. 1995, pp. 1942–1948
[29] Krohling R.A, Coelho, D, S.: ' Coevolutionary particle swarm optimization using Gaussian distribution for solving constrained optimization problems', IEEE Transactions on Systems, Man, Cybernetics Part B:Cybernetics, 2006, 36, pp. 1407–1416
[30] Deb, K.: 'Multi-objective Optimization using Evolutionary Algorithms', (John Wiley & Sons, Chi Chester, UK, 2001, ISBN 0-471-87339-X).
[31] Pareto, V. and Rouge, F.: "Cours D'Economie Politique', vol. I and II, Lausanne, 1896
[32] Moore, J., Chapman, R.: 'Application of particle swarm to multi-objective optimization', Department of Computer Science and Software Engineering. AuburnUniversity, 1999
[33] Salmasnia, A., Hasannejad, S., and Mokhtari, H.: 'A multi-objective optimization for brush monofilament tufting process design', Journal of Computational Design and Engineering, 2018, 5, pp. 120–136

[34] Deb, K., Pratap, A., Agarwal, S., et al.: 'A fast and elitist multi-objective genetic algorithm', IEEE Trans. Evol. Compute, 2002, 6, pp. 182–197
[35] J.H. Holland, Adaptation in Natural and Artificial Systems, University of Michigan Press, Michigan, US, 1975.
[36] E. David. Goldberg, Genetic Algorithms in Search, Optimization & Machine Learning. Addison-Wesley, 1998.
[37] de Pillis, L.G., Radunskaya, A.E.: 'The dynamics of an optimally controlled tumor model', A case study, Mathematical and Computer Modelling, 2003, 24, pp. 1221-1244.
[38] Zhang J, Wang L, Xing L. Large-scale medical examination scheduling technology based on intelligent optimization. Journal of Combinatorial Optimization. 2018:1-20.
[39] Chen C, Wei Y. Robust multiobjective portfolio optimization: a set order relations approach. Journal of Combinatorial Optimization. 2018:1-29.
[40] Du G, Zheng L, Ouyang X. Real-time scheduling optimization considering the unexpected events in home health care. Journal of Combinatorial Optimization. 2019 Jan 15;37(1):196-220.
[41] Chang J, Zhang L. Case Mix Index weighted multi-objective optimization of inpatient bed allocation in general hospital. Journal of Combinatorial Optimization. 2017:1-9.
[42] Lu X, Yin B, Zhang H. A reinforcement-learning approach for admission control in distributed network service systems. Journal of Combinatorial Optimization. 2016 Apr 1;31(3):1241-68.
[43] Rahimi-Vahed AR, Mirghorbani SM. A multi-objective particle swarm for a flow shop scheduling problem. Journal of combinatorial optimization. 2007 Jan 1;13(1):79-102.
[44] Dehghani MO, Montazeri Z, Ehsanifar A, Seifi AR, Ebadi MJ, Grechko OM. Planning of energy carriers based on final energy consumption using dynamic programming and particle swarm optimization. Электротехника и электромеханика. 2018(5 (eng)).