Optimizing a multi-objective master surgical scheduling under probabilistic length of stay and demand uncertainty

Mohammad Ebrahimi[1], Arezoo Atighehchian[2] , Majid Esmaelian [3]

[1]Department of Management, Faculty of Administrative Sciences and Economics, University of Isfahan, Isfahan, Iran. Email: mohammadebrahimi@ase.ui.ac.ir. Tel/Fax: +989156268099.

[2]Department of Industrial Engineering and Futures Studies, Faculty of Engineering, University of Isfahan, Isfahan, 81746-73441, Iran. Email: a.atighehchian@ase.ui.ac.ir. Tel/Fax: +98 (31) 37935615, +989133191719.

[3]Department of Management, Faculty of Administrative Sciences and Economics, University of Isfahan, Isfahan, Iran. Email: m.esmaelian@ase.ui.ac.ir. Tel/Fax: +989131286484.

Abstract

The Master surgical scheduling (MSS) program is used at the tactical level of operating room scheduling, and its optimal creation can reduce the waiting queue of patients, as well as hospital costs. The patients' length of stay (LOS) has a great impact on the downstream resources management. The uncertain nature of LOS and surgeries demand increases the challenges of MSS creation. The aim of the article is to determine the MSS program integrated with combination of surgical operations of each block of the operating rooms. For this purpose, a novel mathematical model was proposed for multi-objective MSS problems with a probabilistic LOS. Then, the chance-constrained programming (CCP) method was employed to cope with the uncertain demands. The ε-constraint method was used for small-scale problems. Moreover, two metaheuristic algorithms including the multi-objective grey wolf optimizer (MOGWO) and the non-dominated sorting genetic algorithm-II (NSGAII) were designed to deal with large-scale problems. Based on the results, the MOGWO outperforms the NSGAII in terms of both the mean ideal distance (MID) measure and the run time. The sensitivity analysis on the capacity of the wards parameter at different levels of demand uncertainty was performed to help managers to decide about the appropriate capacity of the wards.

Keywords: master surgical scheduling, chance-constrained programming, NSGAII, MOGWO

1. Introduction

The proper management of hospitals is very important to use the resources appropriately, to provide satisfactory services to patients, and to increase hospital revenue [1]. The operating room (OR) is among the costliest facilities in hospitals. The optimal and effective use of these rooms with an efficient scheduling has become an important priority for hospitals [2]. In surgery scheduling, several related factors including operating rooms, surgeons, ward and ICU beds, surgical duration, patient stay duration, and the conflicting priorities of different stakeholders are involved, making it a complex task [3].

There are different stages in scheduling ORs. A conceptual model was presented by Blake and Carter [4] to schedule ORs. In this model, there are three levels of decision making including strategic level planning, tactical level decisions, and operational level planning. The strategic level which is usually annual involves long-term planning. In this level, the capacity of the OR is allocated to each surgical group [5].

The case mix planning (CMP) problem refers to the decisions concerning the capacity assignment of the OR to each group of patients. The tactical level is associated with a medium-term period (usually six months) during which the master surgical scheduling (MSS) problem is used. In a weekly planning horizon, the MSS problem assigns surgeons to a particular OR time block, day, and room [6]. In operational planning, the decisions are made for daily and weekly periods [7]. The scheduling procedure for the surgical department in nearly all hospitals has two principal steps. These two steps include allocating the patients to the OR and sequencing of the allocated patients in each room. [8].

The MSS problem is considered at the tactical level and the medium-term interval. The block scheduling strategy in which a specific time block is reserved for each surgeon or surgical team is adopted for elective patients. Because the resources available for surgery and after it (such as ward beds) are limited, designing an optimal MSS problem could contribute to an efficient management of hospital resources [9]. The patients' length of stay (LOS) has a great impact on the available downstream resources in each cycle of the planning horizon. Leveling the workload of nurses should also be investigated to enhance their job satisfaction.

In real world situations, the parameters of patients' LOS and demand that are used in forming the MSS program are uncertain. So far, no research has been carried out that considers the combination of surgeries and surgeon's timetables in an integrated manner and also the two parameters of LOS and demand of surgeries are considered non-deterministic at the same time. Besides, in this article, the leveling of nurses' workload is considered as an objective function. Non-deterministic considering of the two mentioned parameters at the same time can be a challenging issue. Classical methods have not been able to solve problems in large dimensions, so providing algorithms that can solve problems in large dimensions and consider parameters as non-deterministic is one of the other challenges we are facing.

The main research question in this study is how to solve the multi objective MSS problem considering the uncertainty in the related parameters. The sub questions are as follows: How can a mathematical model be presented for the MSS problem with probabilistic LOS and uncertain demand of surgeries? What is the appropriate solution method for solving the problem in large dimensions? What is the appropriate capacity of wards at different levels of demand uncertainty?

Assigning the time blocks of the ORs to each surgeon or surgical group and determining the combination of surgical operations in each block, with the objective of minimizing the costs of ORs and leveling the workload of nurses are assessed in this study. In this article, both the mathematical model and the meta-heuristic algorithms are used to create the MSS program, and also the two mentioned parameters are considered non-deterministic at the same time.

The LoS parameter is considered to have a discrete probability distribution. Furthermore, using a stochastic programming method, the problem in the current study is developed by considering the uncertain demands of surgery. In the present study, chance-constrained programming (CCP) which is one of the main methods for considering uncertain parameters in optimization problems is used. The MSS problem is considered to be multi-objective and a mathematical model is developed for it. In small-scale problems, the CPLEX solver and the ε-constraint method are utilized. Two metaheuristic algorithms are used to solve large-scale problems and the results are evaluated using a specific measure. Also a sensitivity analysis of capacity of wards leads to managerial recommendations to decide about capacity of wards considering the associated costs.

The present paper is structured in the following way. In Section 2, the literature review is presented. In Section 3, the problem is described. The mathematical model is introduced in Section 4. The problem solving methodology is described in Section 5. The numerical experiments and sensitivity analysis are presented in Section 6. Section 7 concludes the paper.

2. Literature review

To create an MSS, some factors such as the compatibility between the ORs and the specialties, the presence of sufficient downstream resources including the ICU and ward beds, and the availability of surgeons should be considered [10]. In this section, a number of articles on MSS are reviewed. The research on MSS can be classified into deterministic and nondeterministic categories.

To create an MSS, Beliën et al. [11] presented a decision support system. In their paper, they had three goals: leveling the beds occupied in the wards, sharing the ORs as much as possible, and making the MSS as simple and repeatable as possible. Tànfani and Testi [12] presented a zero-one integer programming model to create an MSS that could be solved using a heuristic algorithm. Using a mathematical model, they attempted to minimize the patients' waiting time in the first step. Next, they used a heuristic algorithm to solve this model. Gunawan and Lau [13] proposed a mathematical model in which the different constraints of the problem were considered. To run the large-scale model, they used a heuristic algorithm. Yahia et al. [9] presented a new MIP model for the MSS problem. Their objective function had two parts (summed in a weighted manner) including the minimization of the daily workload of nurses and the daily bed occupancy. Aringhieri et al. [14] presented a two-stage hierarchical model to assign surgical blocks to surgeons. The objective function in this model reduced the waiting time and the hospital costs. The model was solved by using a two-level metaheuristic method. Cappanera et al. [15] proposed a mixed integer goal-programming model for the MSS. The mathematical model presented in their article was deterministic. Penn et al. [16] proposed a multi-criteria MILP model to generate a new MSS. This model considered the availability of surgeons and minimized the maximum number of the required beds.

Ghandehari and Kianfar [17] planned the OR using a block strategy. Two mixed-integer linear programming models have been developed for the problem, the first of which models and solves the whole problem in one step, and the second model deals with opening the OR and assigning surgeons to the operating room. Deklerck et al. [18] presented a deterministic optimization model that is based on the concept of service level to define more than expected values for patient demand. Patrão et al. [19] presented a deterministic integer linear programming model in which CMP and MSS levels are integrated. The objective function includes maximizing the allocation of operating rooms to surgeons and avoiding the misplacing of patients in the wrong wards.

Some nondeterministic studies on the MSS are mentioned below. In nondeterministic studies, such parameters as the LOS, the duration of surgery, and the demand for surgery can be nondeterministic.

A mathematical model for MSS where LOS was assumed to be uncertain was proposed by van Oostrum et al. [20]. To maximize the utilization of ORs and hospital bed leveling, they used the column generation method. Mannino et al. [21] proposed an MSS program with two MIP mathematical models. The first model aimed to balance the surgery demands for various specialties. The next model which had a light robustness and in which the demand for surgery was uncertain minimized the OR overtime. Banditori et al. [5] used an optimization-simulation method to generate an MSS. In the first stage of their study, they presented a deterministic MIP model. In the second stage, the robustness of the model was examined with respect to the duration of surgery and the patients' LOS (the latter was uncertain). These stages resulted in a combined optimization-simulation approach with high robustness and efficiency. Hulshof et al. [22] presented an MILP model for generating an MSS. In their proposed model, several resources, time periods, and groups of patients with uncertain treatment paths were considered. Fügener et al. [23] presented an MSS program. They initially proposed a stochastic analytical approach which calculated the exact distribution of demand for the downstream resources in a given MSS. Then, they proposed a heuristic algorithm to reduce the use of downstream resources. Cappanera et al. [24] utilized an optimization-simulation method to create an MSS. They developed an MIP model for this problem with three different objective functions and compared them with each other. They utilized the simulation method to evaluate the robustness of their model in which the surgical duration and the patients' LOS were assumed to be uncertain. Li et al. [25] presented an MSS with a goal programming approach. Four objective functions were considered in their problem. Kumar et al. [26] presented a stochastic MIP model for the MSS program. This model considered the limitations of downstream resources. In their model, the patients' LOS was considered uncertain. The simulation method was adopted to obtain the best scenario. Shafaei and Mozdgir [27] proposed a goal programming (GP) model. In their proposed probabilistic model, they employed a binomial distribution for surgical duration as the uncertain parameter. They used the robust estimator method to appraise this uncertain parameter. Marques et al. [6] presented an MIP model for MSS. In this model, four optimization criteria associated with four scopes were considered. In their model, the duration of surgery was assumed to be uncertain. Heider et al. [28] proposed a mixed-integer quadratic model which optimized the surgery schedule at the tactical stage to level the expected daily occupancy of the planned patients in the ICU. The uncertainty of LOS was included in their model. Van den Broek d'Obrenan et al. [29] proposed an integer linear programming (ILP) to generate an MSS. Afterward, they used local search and simulation methods to improve the ILP solution. Bovim et al. [30] used the optimization-simulation method to solve the MSS model. In the optimization phase, they used a two-stage stochastic optimization model, while in the simulation phase, they employed a discrete-event simulation model.

Shehadeh and Padman et al. [31] allocated elective patients to OR blocks. In their article, the duration of surgery and the LOS of patients are considered non-deterministic. Mazloumian et al. [32] presented a multi objective integer linear programming in which tactical and operational levels are integrated in their model. The model presented by them has become a robust model and in addition, a two stage stochastic integer linear programming model has been developed for the problem. Santos and Marques [33] presented a two-stage stochastic model for the MSS problem, in which the demand is non-deterministic and the objective function includes the overuse penalty of the beds. Beritt et al. [34] developed a stochastic hierarchical mathematical programming model for an MSS problem. The duration of surgery and the LOS of patients are considered uncertain.

In this article, a new generation meta-heuristic algorithm (multi-objective grey wolf optimizer (MOGWO)) and a classical algorithm (non-dominated sorting genetic algorithm-II (NSGAII)) have been used to solve problem.

Das et al. [35] presented a modified genetic algorithm in which the crossover and mutation operators are considered different from the general mode. Negi et al. [36] investigated various meta-heuristic algorithms. Their paper uses a hybrid PSO-GWO algorithm. Sadhu et al. [37] investigated the applicability and performance comparison of 4 classical algorithms (i.e. SA, GA, PSO and differential evolution (DE)) and new generation algorithms (i.e. Firefly algorithm (FFA), Krill herd (Kh), GWO and symbiotic organism search (SOS)). SOS and Kh algorithms reached the optimal solution in the minimum time in most of the problems.

Some of the most relevant articles in the field of MSS have been compared with the current study regarding the state of the model, the model variables, the uncertain parameters (operations' durations, LOS, demand, emergency patients), the solution method, and the objective functions. A summary of the results can be seen in Table 1.

[Insert Table 1]

Reviewing the existing literature showed that a few articles determined the surgeons' time table integrated with combination of surgeries in each block (shown in table 1) but none of the studies simultaneously considered the two parameters LOS and demand as uncertain. The uncertain nature of these two parameters has a great impact in designing a proper MSS considering downstream resources. In addition, in previous studies, the CCP approach was not used to address the uncertainty.

The contributions of this study were as follows: designing a new mathematical model for a multi-objective MSS problem with a probabilistic LOS and an uncertain demand; presenting a CCP model to deal with an uncertain demand parameter; generating Pareto solutions by considering both the cost of ORs and leveling the workload of nurses; proposing the NSGAII and MOGWO metaheuristic algorithms and analyzing their results through solving different instances.

3. Problem description

The problem addressed in the present paper determines which surgeon is assigned to which surgical block on which day of the week. It also demonstrates the volume and combination of surgical operations in each block. Minimizing the cost of idle time and overtime of the ORs and minimizing and leveling the nurses' maximal daily workload are the objective functions of the present study. In the present study, two types of nurses are considered: those who work in ORs and those who provide services to patients after surgery and during hospitalization in the downstream units such as the wards. Each OR on each day consists of two blocks to which the surgical procedures of the surgeons are assigned. The demands of different types of surgical procedures for each surgeon are based on his/her specialty estimated according to the demand data in the past. Each surgeon is associated with one of the surgical wards (u) according to his/her specialty. For each surgical procedure, the patients' LOS is defined as a discrete probability function. Each surgeon prefers specific days of the week for performing the surgeries. These days are defined as a matrix. The surgical block in one day preferred by a surgeon is given the value of one. Otherwise, it is given the value of zero. This problem involves the development of an MSS during the planning horizon

(T). Symbol t indicates the days of the week on which the surgeries are performed in a hospital. Here, the MSS is a plan for 7-day cycles and is iterated during the medium-term period. If a patient's surgery is performed in the current cycle, depending on his/her LOS in the ward, he/she may still stay in a ward in the next cycle. This will affect both the available downstream resources and the planning of surgeries in the next week. These conditions may continue for two or three subsequent cycles. Thus, it is necessary to consider the constraints of ward beds in a cyclic manner. The model assumptions in this study are as follows:

1) The OR schedule is only considered for the elective patients since it is assumed that there are emergency ORs for emergency patients.

2) Surgery is not performed at the end of the week. Therefore, the ORs will be closed in these days.

3) Hospitalized patients are those who have stayed in a hospital for at least one day.

4) The patients' LOS in the ward has a discrete probability distribution which could be appraised from the archival data of the hospital.

5) The patients can be discharged from the hospital on any week day.

6) The OR setup time is considered to be sequence independent.

7) The duration of surgery includes the OR setup time and both of them are considered deterministic.

8) In the first model, the demand for each surgeon's different types of surgery is considered to be deterministic and is estimated based on the average demand of the past. In the second model, the demand is considered nondeterministic.

In Table 2, the parameters, indices, and variables of the problem are tabulated:

[Insert Table 2]

4. Mathematical model

First, an MIP model with the probabilistic constraint of LOS is presented in sub-section 4-1. Then, in sub-section 4-2, a stochastic model is presented and the demand parameter is considered to be uncertain.

4.1. The first MIP model with a probabilistic LOS (Model I)

In this sub-section, a mathematical model of the problem is proposed in which the patients' LOS is assumed to be probabilistic and a discrete probability distribution function is considered for it. The demand parameter is considered to be deterministic and the average of historical data is used for it. The developed MIP model for generating an MSS is as follows:

$$MinObj_1 = \sum_j \sum_t \sum_b (Co * \alpha_{jtb} + Cu * \beta_{jtb}) \qquad (1)$$

$$MinObj_2 = MDNRM + MDNRA + \sum_u MDN_u \qquad (2)$$

$$\sum_k X_{bjtk} \leq 1 \quad \forall b \in B, j \in J, t \qquad (3)$$

$$\sum_j \sum_t \sum_b Y_{pkbjt} \geq d_{kp} \quad \forall k \in K, p \in P \qquad (4)$$

$$\sum_p dur_p * Y_{pkbjt} \leq M_b * X_{bjtk} \quad \forall k \in K, b \in B, j \in J, t \qquad (5)$$

$$\sum_k \left[(\sum_p dur_p * Y_{pkbjt}) - (dur_b * X_{bjtk}) \right] \leq \alpha_{jtb} \quad \forall j \in J, t, b \in B \qquad (6)$$

$$\sum_{k}\left[(dur_b * X_{bjtk}) - (\sum_{p} dur_p * Y_{pkbjt})\right] \le \beta_{jtb} \quad \forall j \in J, t, b \in B \tag{7}$$

$$\sum_{j} X_{bjtk} \le AV_{kbt} \quad \forall k \in K, b \in B, t \tag{8}$$

$$I_{ut} = \sum_{uk_u}\sum_{j}\sum_{kp_k}\sum_{b}\sum_{\tau=0}^{\left\lceil \frac{h_p}{T} \right\rceil}\sum_{l=1}^{t}\sum_{l'=t-l+1+(\tau * T)}^{h_p} C_{p,l'} * Y_{pkbjl} + \sum_{uk_u}\sum_{j}\sum_{kp_k}\sum_{b}\sum_{\tau=0}^{\left\lceil \frac{h_p}{T} \right\rceil}\sum_{l=t+1}^{T}\sum_{l'=t-l+1+(\tau+1)*T}^{h_p} C_{p,l'} * Y_{pkbjl} \tag{9}$$

$$I_{u,t} \le bed_u \quad \forall u \in U, t \tag{10}$$

$$\sum_{p}\sum_{k}\sum_{j} Y_{pkbjt} * SNNP = N_{b_1,t} \quad \forall t \in T, b = b_1 \tag{11}$$

$$N_{b_1,t} \le MDNRM \quad \forall t \in T \tag{12}$$

$$\sum_{p}\sum_{k}\sum_{j} Y_{pkbjt} * SNNP = N_{b_2,t} \quad \forall t \in T, b = b_2 \tag{13}$$

$$N_{b_2,t} \le MDNRA \quad \forall t \in T \tag{14}$$

$$I_{u,t} * SNNU \le NW_{u,t} \quad \forall u \in U, t \tag{15}$$

$$NW_{u,t} \le MDN_u \quad \forall t \in T \tag{16}$$

$$\alpha_{jtb} \ge 0 \quad \forall j \in J, t, b \in B \tag{17}$$

$$\beta_{jtb} \ge 0 \quad \forall j \in J, t, b \in B \tag{18}$$

$$I_{u,t} \ge 0 \quad \forall u \in U, t \tag{19}$$

$$Y_{pkbjt} \geq 0 \text{ and integer } \forall p \in P, k \in K, b \in B, j \in J, t \qquad (20)$$

$$X_{bjtk} \in \{0,1\} \ \forall b \in B, j \in J, t, k \in K \qquad (21)$$

$$NW_{u,t} \text{ Positive integer } \forall u \in U, t \qquad (22)$$

$$N_{b,t} \text{ Positive integer } \forall t, i = 1,2 \qquad (23)$$

The first objective function (Eq. 1) minimizes the overtime and idle time costs of the ORs in a week. The second objective function (Eq. 2) minimizes the maximal daily workload of nurses. Constraint 3 ensures that only one surgical group is assigned to each OR block. Eq. 4 limits the number of scheduled surgery type p for each surgeon according to the demand for that type of surgery. Constraint 5 states that if a block from the OR is assigned to a surgeon, the surgeon's surgeries with different lengths of time can be assigned to that block. Therefore, the total time of operations performed in each block is controlled by the M_b parameter. In other words, this parameter limits the maximum overtime of each block. Constraint (6) calculates the overtime of the OR. Constraint (7) calculates the idle time of the OR. Constraint (8) indicates the surgeon's preferences in the assigned blocks to him/her. Eq. (9) calculates the number of beds of ward u occupied on day t considering both the number of patients who had surgery on the days $(t+1)^{th}$ of the previous cycles $(l = t+1,...,T)$ and their stay continued until day t of the current cycle and the sum of patients who had surgery on the days $(l = 1,...,t)$ of the current cycle and the previous cycles and their stay still continued. For the bed constraint, the probability parameter $C_{p,l'}$ was used to consider the probability of the patients' LOS.

Constraint 10 ensures that the number of used beds does not surpass the capacity of each ward. Constraints 11-14 are used to calculate the maximal daily workload of nurses in ORs. Constraints 11 and 13 calculate the workload of nurses on day t over blocks $b = 1$ and $b = 2$, respectively. Constraints 12 and 14 determine the workload peak of the nurses in each block. Constraints 15 and 16 are used to calculate the maximal daily workload of nurses in the wards. Constraint 15 computes the workload of nurses on day t in ward u. Constraint 16 limits the maximum workload of nurses in each ward. The variables have been defined through constraints 17-23.

4.2. The stochastic model with an uncertain demand (Model II)

The chance-constrained method is widely used to solve optimization problems with different uncertainties. In this sub-section, a stochastic MSS model is proposed in which the surgery demand is considered to be uncertain. The CCP approach is used to handle the uncertainty of this parameter. Charnes et al. [38] proposed this approach to determine the level of confidence for constraints with a stochastic parameter.

In the current research, the CCP method is employed to convert the MSS problem into a stochastic MIP. The CCP model proposed for MSS is presented below:

$$MinObj_1 = \sum_j \sum_t \sum_b (Co * \alpha_{jtb} + Cu * \beta_{jtb})$$

$$MinObj_2 = MDNRM + MDNRA + \sum_u MDN_u$$

s.t.

- Eqs. (3), - Eqs. (5) – (23),

$$\sum_j \sum_t \sum_b Y_{pkbjt} \geq \tilde{d}_{kp} \quad \forall k \in K, p \in P \tag{24}$$

As can be seen in the above model, the demand for surgeon k for surgery type p ($\tilde{d}_{kp}$) is considered as an uncertain parameter. The probability distribution of the demand parameter is derived from historical data. To solve the uncertain model, it should first be converted into a deterministic one using the CCP approach. To obtain the feasible area, the constraint with an uncertain parameter must undergo some changes. The least probability to meet the rewritten constraint is $(1-\alpha)$. Therefore, considering the general probability distribution for parameter $\tilde{d}_{kp}$, the CCP model for constraint 24 is as follows:

$$\Pr(\sum_j \sum_t \sum_b Y_{pkbjt} \geq \tilde{d}_{kp}) \geq 1-\alpha \quad \forall k \in K, p \in P \quad (25)$$

The point $(\tilde{d}_{kp})_\alpha$ with $\Pr(\tilde{d}_{kp} \leq (\tilde{d}_{kp})_\alpha) = 1-\alpha$ could be calculated using $\int_{-\infty}^{(\tilde{d}_{kp})_\alpha} f(\tilde{d}_{kp}) d(\tilde{d}_{kp}) = 1-\alpha$. In this equation, $f(\tilde{d}_{kp})$ is the probability density function. Hence, the following equation is obtained:

$$\sum_j \sum_t \sum_b Y_{pkbjt} \geq (\tilde{d}_{kp})_\alpha \quad \forall k \in K, p \in P \qquad (26)$$

In the present research, the uniform distribution in (Ld_{kp}, Ud_{kp}) is regarded for the uncertain demand. Consequently, constraint 30 is converted into constraint 27.

$$\sum_j \sum_t \sum_b Y_{pkbjt} \geq \alpha * Ld_{kp} + (1-\alpha) Ud_{kp} \quad \forall k \in K, p \in P \qquad (27)$$

5. Problem solving methodology

The proposed MIP models were solved in small-scale problems using the ε-constraint method and the CPLEX solver. The ε-constraint method was employed for solving the mathematical model in small dimensions. The ε-constraint approach is widely used for solving multi-objective problems. It solves these types of problems by converting all their objective functions (except for one) into constraints at each stage [39]. Given the fact that the MSS problem is NP-hard [40], the metaheuristic algorithms NSGAII and MOGWO are utilized to solve it. In addition, these metaheuristic algorithms are also used to solve large-scale problems.

5.1. The proposed metaheuristic algorithms

The genetic family usually has a good performance in all optimization problems [41]. The second version of the genetic algorithm (GA) (i.e. the NSGAII) was proposed by Deb et al. [42]. The NSGAII is a multi-objective optimization algorithm. The aim of the NSGAII is to increase the adaptive fit of a set of candidate solutions to a Pareto front for the objective functions. This algorithm uses evolutionary operators such as selection, mutation, and crossover. The population is ordered into an array of sub-populations according to the Pareto dominance order. In general, the N-sized population is considered and the solutions are ordered into a hierarchy of non-dominated Pareto fronts. Among the algorithms presented in recent years, the GWO has a higher computational ability and a relative superiority [43]. The GWO, which is newer and more efficient than the other meta-heuristic algorithms, was used in the present study [44]. The GWO algorithm was introduced by Mirjalili et al. [45]. Mirjalili et al. [46] also presented the multi-objective version of this algorithm. In the GWO algorithm, four types of gray wolves (alpha, beta, delta, and omega) are employed for the simulation of the leadership hierarchy. In this algorithm, the three main stages of hunting are the search for prey, encircling the prey, and attacking the prey. The best solution is called alpha (α) and the second and third solutions are called beta (β) and delta (δ), respectively. The other solutions are considered omega (ω) wolves. The GWO algorithm uses the three solutions α, β, and δ to guide the hunt (optimization) and the ω solution follows these three solutions. In this paper, two meta-heuristic algorithms were utilized to solve the investigated problem.

In this article, a new generation meta-heuristic algorithm (MOGWO) and a classical algorithm (NSGAII) have been used to solve problems in large dimensions. As stated in the literature review and also in the article of Sadhu et al. [37], new generation algorithms perform better than classical algorithms. Meanwhile, Mirjalili et al. [45] compared the GWO algorithm with other meta-heuristic algorithms, including Gravitational search algorithm (GSA), Evolutionary programming (EP) and Evolution strategy (ES). The results showed that the GWO algorithm has provided very competitive results compared to known meta-heuristic algorithms. This good performance of GWO algorithm is due to the high ability of this algorithm in searching unknown spaces as well as exploration and exploitation phases.

5.2. The solution structure

A key factor in devising metaheuristic algorithms is the appropriate solution structure to set feasible values for all decision variables with minimum calculations. In this paper, the solution structure has two parts. In the first part, the block and the OR are assigned to the surgeon. In Fig. 1, the given values in the matrix cells (genes) are real numbers ranging from 0 to 1. The matrix cells are set as follows: B, T, and J indicate block, day, and OR, respectively. The value of each cell determines the ID number of the assigned surgeon.

[Insert Fig. 1]

As observed, with a value of 0.91, the first gene determines the surgeon assigned to block 1, on day 1, in OR 1. If there are four surgeons, Eq. 28 is used to determine the ID number of the surgeon.

$$k = \lfloor gene * K \rfloor + 1 = \lfloor 0.91 * 4 \rfloor + 1 = 4 \qquad (28)$$

In the second part, first, the value of the variable Y_{pkbjt} is set. Next, the values of the other decision variables are determined accordingly. For this purpose, similar to the first part, a 4-dimensional chromosome is converted into a 1-dimensional chromosome. At first, a row is added to the matrix of the second part of the chromosome below the columns of the surgery types. The values of this row show the difference between the number of assigned surgery demands and the number of demands for that type of surgery and the related surgeon. The non-covered demands of each surgery type are stored in the added row and should be minimized. The Y_{pkbjt} decision variable can be calculated using Eq. 29:

$$Y_{pkbjt} = \frac{cell_{bjtp}}{\sum_{p \in kp_k} cell_{bjtp}} * D_{kp} \quad \forall k \qquad (29)$$

where, $cell_{bjtp}$ belongs to the second part of the solution. The value of *Y* is used to determine the value of *X*. If *Y* is greater than 0, the value of *X* in the corresponding index will be 1. In the proposed algorithm, first, the value of *Y* is calculated. Afterward, the value of *X* is determined based on the value of *Y*. The other variables of the model are determined based on the value of *Y* and the conditions of the model. The pseudocodes and details of the MOGWO and the NSGAII are found in the studies of Mirjalili et al. [46] and Deb et al. [42], respectively.

5.3. Tuning the parameters of the proposed algorithms

To enhance the performance of the developed algorithms in solving various numerical problems, it is required to obtain the optimal levels of their parameters. In this study, the parameters of the MOGWO (i.e. the number of iterations and agents) and the NSGAII (i.e. the number of population, the number of iterations, the crossover rate, and the mutation rate) are tuned based on the experimental design. The experimental design is performed according to the response surface methodology (RSM). The parameter ranges of the algorithms are shown in Table 3.

[Insert Table 3]

After running the necessary tests using the RSM method in the Design-Expert software (version 12), the optimal values for the parameters of the proposed algorithms were obtained as tabulated in Table 4.

[Insert Table 4]

6. Numerical results and discussion

In the present paper, the planning horizon was supposed to consist of 7 days (T=7). At first, several random instances were generated to evaluate the model and the proposed algorithms and to tune their parameters. To generate random instances, the duration of surgery was considered as a random value in the interval of [0.5, 5] hours and the LOS was randomly generated in {1, 5} days. The surgical demands of the surgeons for each type of surgery were randomly set in {1, 5}. Given that there must be a correlation between the number of surgeons and the number of ORs, two intervals were considered for producing the instances. In other words, for {7-10} ORs, {14-30} surgeons would be considered and for {11-15} ORs, {31-45} surgeons would be assumed. The probability of the LOS was estimated using a discrete probability function in the sense that the probability of the patients' LOS in a ward was in [0, 1] and the total probability of LOS was one. Because multi-objective algorithms have a set of Pareto solutions called the Pareto front, it is necessary to define the criterion which illustrates the quality of the Pareto members for comparison. The present study used a well-known performance evaluation metric for quantitative comparisons between the algorithms:

- The mean ideal distance (MID) computes the mean distance between the ideal point $(\vec{f}_{ideal})$ and the non-dominated set. The MID is calculated as follows:

$$MID = \sum_{i=1}^{n} \frac{c_i}{n} \quad (30)$$

where $c_i = \left\| \vec{f}_i - \vec{f}_{ideal} \right\|, \vec{f}_{ideal} = \{\min(f_1), \min(f_2), ..., \min(f_k)\}$, and *n* represents the number of non-dominated solutions. The lower the value of the MID, the better the performance of the algorithm.

6.1. Comparing the proposed algorithms with the mathematical models with respect to small-scale instances

Five small numerical instances were randomly generated to compare the results of the proposed algorithms with those of the mathematical models. Using the MID measure, their efficiencies were compared. The number of iterations and population sizes were identical in the NSGAII and MOGWO. The features of the instances are shown in Table 5.

[Insert Table 5]

In this section, five instances with specified sizes (Table 5) are considered. As can be seen in Table 6, the models (I and II) and the metaheuristic algorithms (NSGAII and MOGWO) are compared in terms of the MID measure and the run time. Because a different Pareto front is generated for each run in meta-heuristic algorithms, the algorithms are run five times for each problem with different alphas. The averages of these five runs for each problem are compared in terms of the MID measure. Furthermore, the average run time for these five runs is shown. To consider the uncertainty in the demand parameter, three scenarios were designed in which alpha had three different values $(\alpha = 0.05, 0.1, 0.15)$.

[Insert Table 6]

Table 6 illustrates the values of the MID measure for Model I, Model II, and the two metaheuristic models. This table demonstrates that in comparing the results of Model II, NSGAII, and MOGWO in an uncertain environment, the MID measure has the best value for Model II followed by the MOGWO and the NSGAII. The results show that the MID measure has the lowest value for $\alpha = 0.15$ and the highest value for $\alpha = 0.05$. By comparing the results, it becomes clear that the MOGWO outperforms the NSGAII. As can be seen, the solving time of the mathematical model increases sharply as the dimensions of the problem increase. The shortest run time belongs to the MOGWO. Therefore, the MOGWO outperforms the NSGAII in terms of both the MID measure for different alphas and the run time.

The Pareto fronts obtained from the metaheuristic algorithms and Model II ($\alpha = 0.15$) in the fifth small instance are shown in Fig. 2. The Pareto front generated by the NSGAII and the MOGWO is similar to that of the efficient frontier. In the bound at the end of the frontier, the solutions of these algorithms are fitted to the efficient frontier. This indicates the efficiency of these algorithms in solving small-scale problems. Since these meta-heuristic algorithms can solve the instances in a short time and their Pareto fronts are close to the efficient frontier, they can be used to solve large-scale problems.

[Insert Fig. 2]

In general, in solving small-scale problems, the algorithms have a close performance and do not differ much from one another. To examine the performance of the proposed algorithms in solving large-scale problems more accurately, some numerical instances are presented.

6.2. Evaluating the efficiency of the proposed algorithms in solving large-scale instances

Thirty large-scale instances were randomly produced for three different alphas (Table 7) to evaluate the efficiency of the proposed algorithms. In Table 7, 30 large-scale instances with the sizes of K×R×P×W (surgeon×operating room×type of surgery×wards) for the NSGAII and the MOGWO are run five times. In addition, the averages of these five runs are compared in terms of the MID measure for three different scenarios.

[Insert Table 7]

As observed in Table 7, The MOGWO outperforms the NSGAII in solving all the instances with different alphas in terms of the MID measure.

To better show the results, Figure 3 compares the MOGWO and NSGAII based on $\alpha = 0.1$. According to Fig 3, it can be seen that MOGWO algorithm performed better than NSGAII algorithm. In addition, with the increase in the dimensions of the problem, the MID measure decreased, which shows the good performance of the algorithms in the exploration and exploitation phases in large scale problems.

[Insert Fig. 3]

According to Table 7, in both algorithms, the MID has the highest value for $\alpha = 0.05$ and the lowest value for $\alpha = 0.15$. The MID measure decreased with the increase of α for both algorithms. In other words, by increasing the flexibility of the model, a better value has been obtained for this measure.

In what follows, the sensitivity analysis of the number of beds is performed for a large-scale instance with 20 operating rooms, 47 surgeons, 7 wards, and 120 different types of surgery. For this purpose, the number of beds is changed in 4 scenarios (+15%, -15%, +30%, and -30%) and the results are analyzed. Figure 4 shows that as the number of beds increases, the workload of nurses and the costs increase, and when it decreases, these two values decrease. These changes are more pronounced in the figure for ±30%. In order to better analyze the results of each scenario, the uncovered demand is also calculated. With a 30% increase in the number of beds, the covered demand is increased by 27% (from 346 to 440), while the workload of nurses and the costs are respectively increased by 29% and 21%. Reducing the number of beds by 30% decreases the covered demand, the costs, and the workload of nurses by 22%, 11%, and 46%, respectively. As the number of beds increases, the number of surgeries in the hospital and the uncovered demand decrease. However, the workload of nurses and the costs increase.

[Insert Fig. 4]

According to Figure 4, with the increase in the number of beds, the costs and the workload of nurses also increase. The increase in the costs could be due to the greater demand coverage. With the increase in the number of beds, the probability of allocating more surgeries to the ORs increases. As a result, the overtime cost may increase. As the number of beds and the number of surgeries allocated to the ORs increase, the workload of nurses also increases. The increase in demand coverage can be investigated through a sensitivity analysis on the alpha parameter in the CCP model. The covered demand can be obtained from the results of the model. By changing the alpha parameter, the feasibility of the model is checked. By implementing the model, it is observed that the model is infeasible for $\alpha = 0$ up to $\alpha = 0.13$. Put differently, by considering the number of beds, the maximum probability of covering the demand is 87%. Five Pareto points for $\alpha = 0.13$ are selected. The objective functions and the covered demands of these points are shown in Table 8.

[Insert Table 8]

It is noted that with an increase in idle time costs, the workload of nurses decreases, leading to less demand coverage. When the number of beds is increased by 30%, the amount of covered demand can increase. By changing the alpha parameter in the CCP model, it is observed that the model becomes infeasible for $\alpha = 0$ up to $\alpha = 0.07$. Therefore, in this scenario, the probability of demand coverage can increase by 6% compared to the previous scenario. The changes for the five Pareto points are shown in Table 9.

[Insert Table 9]

According to the above results, it is clear that as the number of beds increases, more surgeries are performed. This leads to an increase in overtime costs, a decrease in idle time costs, and an increase in the workload of nurses. In other words, the hospital managers can cover 93% of the demand with a 30% increase in the number of beds. When the number of beds is increased by 34%, the maximum number of covered demand reaches 98%. In other words, the value of $\propto$ is 0.02. In Table 10, the results are illustrated. An increase of more than 34% in the number of beds does not affect the covered demand. Put differently, the upper limit of the increase in the number of beds is 34% and $\alpha = 2\%$.

[Insert Table 10]

7. **Concluding remarks**

Designing an optimal MSS could contribute to an efficient management of hospital resources due to limitation in available resources for surgery and after it (such as ward beds).

In response to research questions in this paper, a multi-objective MIP model has been developed considering the LOS in a probabilistic manner (Model I). In the proposed model, the objective functions include minimizing the costs of idle-time and overtime of the operating rooms and minimizing the maximal daily workload of nurses. The model determines the surgeon and combination of surgical operations of a specific block of the OR considering the preferences of surgeons. This new mathematical model was proposed for a situation in which the constraints of the downstream resources are considered in a cyclical manner and the uncertain nature of the patients' LOS is considered in a probabilistic manner. Then, a stochastic model was developed in which the demand parameter was considered to be uncertain using the CCP approach (Model II). By considering these two parameters as uncertain, the model got closer to the real state. This model can be used as an auxiliary tool in hospital management to make final decisions about assigning the OR blocks to different surgeons and surgery types by optimizing the costs of ORs and leveling the workload of nurses. Since the MSS was NP-hard, two metaheuristic algorithms including NSGAII and MOGWO were used to solve it in large dimensions. An appropriate comparison measure was utilized to evaluate the efficiency of these algorithms in solving different numerical instances with different dimensions. According to the results, the MOGWO outperformed the NSGAII. The proposed model considered the bed constraint for an unlimited time horizon in order to reduce significantly the concerns of hospital managers about bed shortages. The sensitivity analysis of the number of beds is performed that can be used as a tool to help hospital managers to decide about proper wards capacity.

Designing a new mathematical model for a multi-objective MSS problem with a probabilistic LOS and an uncertain demand; presenting a CCP model to deal with an uncertain demand parameter; generating Pareto solutions by considering both the cost of ORs and leveling the workload of nurses; proposing the NSGAII and MOGWO metaheuristic algorithms and analyzing their results through solving different instances, are the main contributions of this paper. The limitations of the research include lack of access to real hospital information, not considering emergency patients, and not considering the ICU bed constraint.

Some suggestions for future studies in this field are using the robust approach, considering other sources of uncertainty and proposing appropriate methods for solving them, and developing other efficient methods for solving large-scale problems.

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Figure and table captions:

Table 1. Comparing the features of the current study with those of relevant studies

Table 2. The parameters, indices, and variables of the problem

Table 3. The bounds of the parameters of the proposed algorithms

Table 4. The optimal values for the parameters of the proposed algorithms

Table 5. The features of the small-scale instances

Table 6. Comparing the mathematical models with the meta-heuristic algorithms for different values of alpha

Table 7. The results of the proposed algorithms in solving different instances

Table 8. Five Pareto points for ∝=0.13

Table 9. Five Pareto points for ∝=0.07 with a 30% increase in the number of beds

Table 10. Five Pareto points for ∝=0.02 with a 34% increase in the number of beds

Figure. 1. The solution structure

Figure. 2. The comparison of the Pareto fronts obtained from Model II and the metaheuristic algorithms

Figure. 3. Comparison of multi-objective grey wolf optimizer (MOGWO) and the non-dominated sorting genetic algorithm-II (NSGAII) based on α=0.1

Figure. 4. The Pareto front changes in different scenarios for the parameter of the number of beds

Table 1

Authors	Model		Variable		Uncertain parameter				Solution method	Objective function
	Deterministic	Nondeterministic	Composition of surgeries	Surgeons' schedule table	Duration	Length of Stay(LOS)	Demand	Emergency patients		
Santibáñez et al. [10]	•		•	•				•	Mixed Integer Programming(MIP) model	Minimizing the bed utilization and maximizing the total throughput
Banditori et al. [5]		•	•	•	•	•			Simulation-optimization (MIP model)	Maximizing the total throughput, minimizing the penalties due to missing due dates, and minimizing bed mismatching
Cappanera et al. [24]		•	•	•	•	•			Simulation-optimization (MIP model)	Minimizing the maximum daily utilization of Operating rooms(ORs), minimizing the difference between the maximum and minimum daily use of resources, and minimizing the deviation between the actual and target use of resources

Yahia et al. [9]	•		•	•					MIP model	Minimizing the bed occupancy and the workload of nurses
Cappanera et al. [15]	•		•						Goal programing	Minimizing the penalties due to missing due dates, leveling the OR usage, leveling the use of post-surgical wards, and maximizing the number of planned surgeries
Penn et al. [16]	•			•					MIP model	Minimizing the gap between the number of accessible beds and the number of needed beds, maximizing the surgeons' preferences, and maximizing the number of times the same surgeon is allocated to successive time blocks in the same OR and on the same day
M'Hallah, and Visintin [3]		•		•	•	•			MIP and sample average approximation	Maximizing the throughput
Marques et al. [6]		•		•	•				MIP model	Minimizing the workload of wards, assigning the surgeons with the same surgical specialty to the same room to the extent possible, minimizing the deviation between the shift dedicated to each surgeon and the shift which the surgeon would like to have, and minimizing the deviations of the OR time allocated to each surgeon from the median value of the time utilized by the surgeon
Heider et al. [28]		•	•	•		•		•	Quadratic programming	Minimizing the difference between the actual and target bed usage
Van den Broek d'Obrenan et al. [29]		•		•		•			Integer Linear Programming (ILP) model, Tabu search, Monte Carlo simulation	Minimizing the variability of the required bed capacity, maximizing the number of operations, minimizing the waiting time
Bovim et al. [30]		•	•	•	•	•		•	Simulation-optimization (two-stage stochastic optimization model)	Minimizing the number of planned surgeries, minimizing the number of cancellations, and minimizing the number of patients hospitalized in wards not allocated for this purpose
The current research		•	•	•		•	•		**MIP model, Chance Constraint Programming (CCP) model, two metaheuristic algorithms**	**Minimizing the overtime and idle time costs of the ORs and leveling the workload of nurses**

Table 2

Indices	
p: Types of surgical procedures $p=1,...,P$	T: The number of planning horizon days
K: The number of surgeons $k=1,...,K$	t: The days of the week on which the surgeries are performed $t=1,...,5$
J: The number of available Operating Rooms (ORs) $j=1,...,J$	U: The number of surgical wards $u=1,...,U$
b: The OR blocks	l: The set of stay days in the hospital $l=1,...,h_p$
Parameters	

h_p	The maximum LOS of the patient with surgery type p
$C_{p,l'}$	The probability of staying l' days in the ward for a patient with surgery type p
AV_{kbt}	Binary parameter: 1 if the k^{th} surgeon is available in block b on day t; otherwise 0

	Lower bound (-1)	Medium bound (0)	Higher bound (1)
Number of iterations	50	125	200
Population	30	65	100
Crossover rate	0.5	0.7	0.9
Mutation rate	0.1	0.25	0.4

Co	OR overtime cost/unit of time
Cu	OR idle time cost/unit of time
dur_p	The duration of the surgical procedure type p
dur_b	The duration of block b of the OR
bed_u	The number of beds available in ward u
d_{kp}	Weekly demand for surgeon k for surgery type p
kp_k	The set of surgeon k's surgical operations
uk_u	The set of surgeons related to the u^{th} ward
T	The number of cycles a patient has stayed in the ward
SNNR	The standard number of nurses needed to provide services to one patient in the ORs.
SNNU	The standard number of nurses needed to provide services to one patient in the downstream units (wards).
M_b	The parameter controlling the allocated hours and the maximum OR overtime
Variables	
Y_{pkbjt}	The number of surgeon k's surgery type p allocated to block b of the OR j on day t
X_{bjtk}	$\begin{cases} 1 & \text{If block } b \text{ from } OR\ j \text{ is assigned to surgeon } k \text{ on day } t \\ 0 & \text{Otherwise} \end{cases}$
α_{jtb}	The overtime of block b of OR j on day t
β_{jtb}	The idle time of block b of OR j on day t
$I_{u,t}$	The number of beds in ward u occupied on day t
$N_{b,t}$	The workload of nurses during time block b on day t for all ORs
MDNRM	The maximum daily workload of nurses for all ORs in the first block
MDNRA	The maximum daily workload of nurses for all ORs in the second block
MDN_u	The maximum daily workload of nurses for ward u
$NW_{u,t}$	The workload of nurses on day t for ward u

Table 3

Table 4

The instance size		Number of iterations	Population	Crossover rate	Mutation rate
Small	NSGAII	100	50	0.7	0.2
	MOGWO	80	30	-	-
Medium	NSGAII	100	50	0.7	0.2
	MOGWO	100	30	-	-
Large	NSGAII	150	100	0.7	0.3
	MOGWO	100	40	-	-

Table 5

Numerical instances	Number of Surgeons	Number of ORs	Number of surgery types	Number of wards
SM1	5	3	5	3
SM2	6	4	8	3
SM3	9	6	10	4
SM4	12	8	12	4
SM5	15	9	15	5

Table 6

Instance Number	Model I		Model II				NSGAII				MOWO			
	MID	Run time(sec)	MID			Average run time(sec)	MID			Average run time(sec)	MID			Average run time(sec)
			∝= 0.05	∝= 0.1	∝= 0.15		∝= 0.05	∝= 0.1	∝= 0.15		∝= 0.05	∝= 0.1	∝= 0.15	
1	3.85	371	4.24	4.11	3.97	376	4.96	4.88	4.75	193	4.68	4.54	4.39	182
2	3.08	683	3.77	3.62	3.31	689	4.89	4.69	4.28	311	4.04	3.86	3.62	274
3	2.73	2455	3.01	2.95	2.84	2510	3.83	3.56	3.54	792	3.58	3.44	3.2	683
4	2.39	6829	2.65	2.61	2.49	6836	3.46	3.37	3.15	937	3.09	2.78	2.6	820
5	1.88	16593	2.23	2.12	1.95	16621	2.88	2.83	2.73	1140	2.59	2.34	2.28	972

Table 7

Instance	Size	MID					
	(K×R×P×W)	NSGAII			MOGWO		
		MID			MID		
		∝= 0.05	∝= 0.1	∝= 0.15	∝= 0.05	∝= 0.1	∝= 0.15
1	(8×3×15×3)	4.97	4.8	4.7	4.79	4.64	4.59
2	(10×4×15×3)	4.91	4.71	4.27	4.36	4.13	4.1
3	(10×4×18×3)	4.84	4.64	4.18	4.27	4.08	4.09
4	(11×3×18×3)	4.56	4.49	4.16	4.25	3.96	3.94
5	(11×4×15×3)	4.43	4.42	4.37	4.46	3.95	3.92

6	(12×4×15×4)	4.24	4.19	4.09	4.18	3.91	3.84
7	(12×4×20×4)	4.06	3.97	3.8	3.89	3.62	3.6
8	(14×4×25×4)	3.74	3.63	3.6	3.69	3.58	3.56
9	(14×4×30×4)	3.7	3.56	3.48	3.57	3.47	3.48
10	(15×5×45×4)	3.52	3.47	3.43	3.52	3.41	3.41
11	(15×5×60×4)	3.4	3.35	3.3	3.39	3.3	3.3
12	(18×4×60×5)	3.38	3.34	3.3	3.39	3.27	3.23
13	(18×4×70×5)	3.28	3.2	3.17	3.26	3.13	3.14
14	(20×5×70×5)	3.1	3.05	2.99	3.08	3.02	2.99
15	(22×7×90×5)	2.99	2.92	2.81	2.9	2.84	2.85
16	(22×7×105×5)	2.95	2.9	2.81	2.9	2.81	2.77
17	(24×6×110×5)	2.91	2.77	2.71	2.8	2.65	2.64
18	(24×6×110×6)	2.9	2.85	2.8	2.89	2.64	2.61
19	(26×4×110×6)	2.84	2.72	2.68	2.77	2.62	2.57
20	(26×4×115×6)	2.7	2.61	2.49	2.58	2.52	2.53
21	(28×5×115×6)	2.64	2.52	2.43	2.52	2.39	2.38
22	(28×5×120×6)	2.49	2.52	2.43	2.52	2.38	2.38
23	(30×6×120×6)	2.43	2.35	2.31	2.4	2.32	2.33
24	(30×6×120×7)	2.37	2.32	2.24	2.33	2.16	2.15
25	(34×7×120×7)	2.3	2.22	2.2	2.29	2.14	2.11
26	(34×7×120×7)	2.24	2.19	2.14	2.23	2.11	2.11
27	(40×8×120×7)	2.16	2.1	2.04	2.13	2.03	1.97
28	(40×8×115×7)	2.1	1.93	1.91	2	1.89	1.89
29	(42×10×110×7)	2.03	1.98	1.88	1.97	1.85	1.88
30	(42×10×120×7)	1.96	1.82	1.77	1.86	1.75	1.74

Table 8

$\propto = 0.13$	$Objective_1$(Overtime, Idle time)	$Objective_2$	Covered demand
1	(11270, 2310)	222	301
2	(11150, 2640)	220	299
3	(11000, 2970)	219	295
4	(10910, 3300)	218	293
5	(10800, 3520)	216	292

Table 9

$\propto = 0.07$	$Objective_1$(Overtime, Idle time)	$Objective_2$	Covered demand
1	(15270, 1690)	248	322
2	(15240, 1760)	245	319
3	(15040, 2040)	241	318

4	(14610, 2300)	240	317
5	(14310, 2710)	237	315

Table 10

$\propto= 0.02$	$Objective_1$(Overtime, Idle time)	$Objective_2$	Covered demand
1	(18320, 1400)	258	339
2	(18200, 1530)	255	338
3	(17900, 1900)	251	336
4	(17740, 2180)	249	334
5	(17570, 2500)	247	330

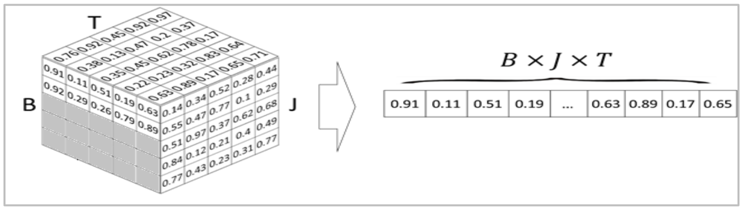

Fig. 1

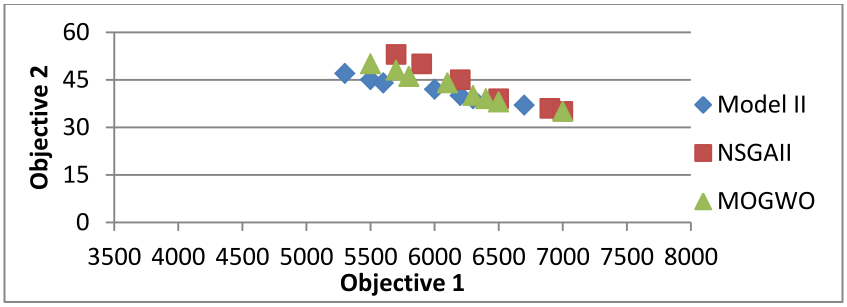

Fig. 2

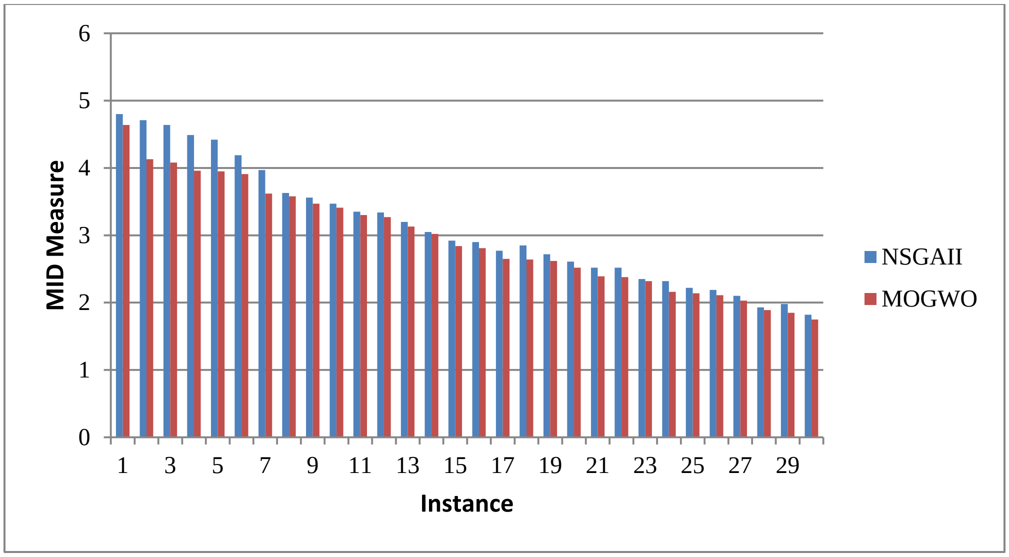

Fig. 3

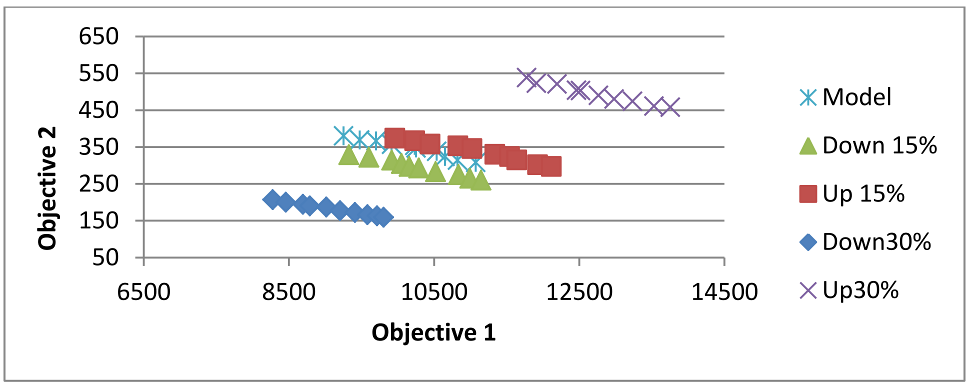

Fig. 4

Biographical notes:

Mohammad Ebrahimi got his BSc in Industrial Engineering from the Shahid Bahonar University of Kerman, Iran in 2013 and MSc in Industrial Engineering from the Mazandaran University of Science and Technology, Babol, Iran in 2015. He received his PhD of Industrial Management (Operations Research) at the University of Isfahan, Iran. His research interest is theory and application of operations research in health system optimization.

Arezoo Atighehchian received her Bachelor of Science and MS in Industrial Engineering from the Isfahan University of Technology, Isfahan, Iran in 2003 and 2006. She received her PhD in Industrial

Engineering at the Tarbiat Modares University, Tehran, Iran in 2012. Her PhD thesis is about stochastic operating room scheduling. She is a faculty member of the Department of Industrial Engineering and Futures Studies, Faculty of Engineering, University of Isfahan, Isfahan, Iran. Her main area of interest is health system optimization, Production Planning and Scheduling.

Majid Esmaelian graduated in 2002 and 2005 with BS and MS degrees in Operations Research. He achieved his Ph.D. in Operations Research in 2010 from University of Tehran, Tehran, Iran. Currently, he is the faculty member of the Department of Management at University of Isfahan, Isfahan, Iran. He is the author of two books and several published papers at national and international levels in refereed journals and conferences since 2005. His research interests are Production Planning, Scheduling, Artificial Intelligence, Optimization and Multi Attribute Decision Making.