Differential Evolution Multi-objective Optimisation for Chemotherapy Treatment Planning

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Abstract. Differential evolution is currently one of the most popular population based stochastic meta-heuristics. In the paper, we propose an extension of the Differential Evolution algorithm for multi-objective optimization problem with constraints of chemotherapy scheduling for a medical treatment. The differential evolution idea is used with some significant improvements concerning the DE strategies and parameters adaptation. The numerical results show that the proposed algorithm is stable and robust in handling medical applications especially for a chemotherapy planning process.

Keywords: Differential evolution meta-heuristics · Multi-objective approach · Optimisation algorithm · Chemotherapy dose schedules

1 Introduction

The Differential Evolution approach is nowadays in great interests. The simplicity and the effectiveness in solving many multi-dimensional and multi-objective constrained optimization problems gives the great popularity to this approach [1,2,11,16,17]. The main idea is to construct, at each generation of the algorithm, a mutant vector for each element of the population. The gradient information could be available in this moment. The new mutant vector is constructed adding differences between randomly selected individuals to another individual. The proposed mutation operator allows a gradual exploration on the search space.

The quick convergence and robustness of differential evolution (DE) approach has turned to be one of the best evolutionary algorithms in many areas [4,6,15, 20,21]. In many papers [5,11,12,20] it has been stated that fixed values of DE control parameters is a poor idea. The limitations on DE structure had inspired many researchers to propose modifications to the original DE approach. With Differential Evolution being so popular and efficient algorithm, self-adaptation of key parameters in crossover and mutation operations has been investigated to make it even better and easier to use on various single- and multi-objective optimization problems [2,11,18,20].

Wide surveys of the research in the field of differential evolution were recently published [1, 2, 11, 12, 22]. Often current knowledge on differential evolution and its parameters values is based on empirical observations, not on a theoretical analysis. So in the DE field for chemotherapy treatment planning it is necessary to extract from numerical experiments some empirical rules on the algorithm behavior. In the paper we propose an extension of the Differential Evolution algorithm for multi-objective optimization problem with constraints of chemotherapy scheduling for a medical treatment planning.

2   Multi-objective Nature of Chemotherapy Process

A chemotherapy is a treatment of cancer using set of cytotoxic drugs to control and eradicate a cancer. The application of very toxic drugs reduces a tumor meanwhile leading to damage to the immune system and giving unacceptable effects to the patient. The drugs are administered to the body using schedules of multi-drugs and drug doses in time intervals. The drugs create a certain concentration in the bloodstream, which will systematically kill both cancerous and normal healthy cells [3, 8, 13]. The toxic drugs have great influence on a Patient Survival Time (PST) and it is very important to define very precisely the feasible set of constraints.

The aim of a chemotherapy treatment depends on maintaining the effective damage to the tumor burden while managing the toxic effects on the human body. Looking for the best schedule for drugs and drug doses in time intervals to be given with minimization of tumor burden and minimization of toxic side-effects determines the balance between killing cancer cells and limiting the damage of human body.

Mathematical model of tumour growth and reduction is based on most popular approach, taking under consideration the Gompertz growth model with a linear cell-loss effect [10, 13]. The model takes the following form:

$$\frac{dn(x,t)}{dt} = \Lambda n(x,t) \, ln(\frac{\theta}{n(x,t)} - n_c(x,t), \tag{1}$$

where $n(x,t)$ represents the number of tumor cells in time t for a variables vector x. The vector $x = [x_{11}, x_{12}, ..., x_{ij}, ..., x_{ND}]$ is a template of drug doses for i defined as index of time interval, $i \in 1, ..., N$ and j is an index of j drug, for indexes $j \in 1, ..., D$. Each dose is a cocktail of D drugs characterized by a concentration level $c_1(x,t)$ of drug j at N switching periods of time in the bloodplasma. The variable x_{ij} determines a schedule of drug j at time interval t_i, the two coefficients define the tumor parameters, $n_c(x,t)$ describes a cell-kill effect of the multiple drugs on a cancer.

2.1   Constraints of an Chemotherapy Optimization Problem

The cancer chemotherapy treatment influences at a tumor site but also for the normal organs. We have to ensure that the human body tolerates anticancer

drugs toxic side-effects. The drugs cause damage to sensitive tissues elsewhere in the body. So the toxicity constraints play the very important role in the cancer chemotherapy treatment and the constraint concerning the tumor size must be maintained below a lethal level.

The constraints of chemotherapy treatment process will be as follows:

1. The rate of drug j accumulation in urine is directly proportional to $c_{1j}(x,t)$ and must not exceed the fixed value C_{maxj} for each drug:

$$c_{1j}(x,t) \leq C_{maxj} \; for \; i \in 1,...,N \tag{2}$$

2. The White Blood Cells (WBC) count must be not less then a fixed down level W_D:

$$w_j(x,t_i) \geq W_D \; for \; i \in 1,...,N \tag{3}$$

3. An additional constraint concerns the time $t_u(x,T_{max})$ over which the White Blood Cells count $w(x,t)$ remains below a fixed upper level W_u, to be less than time T_u:

$$t_u(x,T_{max}) \leq T_u \; for \; i \in 1,...,N \tag{4}$$

4. Maximum feasible size $n(x,t)$ of the tumor has not be greater then N_{max}:

$$n(x,t) \leq N_{max}. \tag{5}$$

The set X of constraints of chemotherapeutic treatment process is represented by the relations (2)–(5). The chemotherapy schedule determines the dosages and drug combinations at each time interval throughout the whole treatment period.

2.2 Treatment Objectives in a Chemotherapy Optimization Problem

The first objective function, concerning the curative treatments attempt to eradicate the cancer tumor burden. The eradication means a reduction of the tumor from an initial size of around 10^9 cells to below 10^3 cells. The tumor burden, equal 10^9 is the minimum detectable tumour size [13]. The first objective function is to minimize the number of tumor cells $n(x,t)$ at a fixed period of time:

$$min_{x \in X} \; n(x,t) \tag{6}$$

The cells loss is proportional to the number of tumor cells and to the concentration $c_1(x,t)$ of toxic drugs. One commonly used performance measure of controlling treatment is toxic side-effect of anti-cancer drugs on human body, which is equivalent to maximizing a Patient Survival Time, defined by minimization of a concentration of toxic drugs in plasma in the form:

$$min \sum_{i \in 1,..,N} \sum_{j \in 1,..,D} c_{1j}(x_{ij},t_i). \tag{7}$$

The two presented objectives on the set of constraints (2)–(5) character-
ize the cancer chemotherapy treatment as a complex treatment process. These
two objectives functions conflict with each other, due to the toxicity of used
anti-cancer drugs. The specific chemotherapy treatment with different objectives
defined on a complex set of constraints is an interesting and difficult domain for
a multi-objective optimization approach.

3   Multi-objective Optimization with Differential Evolution Approach

Multi-objective optimization problem is to find a set of optimal vectors $x*$ opti-
mizing a set of objective functions on the set X of all feasible solutions using
Differential Evolution approach [5,7,9,12]. The minimum is taken in the sense
of the standard Pareto order on an objective functions space. Thus, the idea of
Pareto-dominance is used. A solution is said to be dominated, if another solu-
tion exists in the search space with better performance on at least one objec-
tive. At each step of the optimization process in a multi-objective differential
evolution approach a set of solutions is constructed and we try to designate
non-dominated points among evaluated dominated solutions. Differential Evo-
lution (DE) for multi-objective (MO) optimization combines the MO algorithm
NSGA-II [5,17,18] with the strength and simplicity of the differential evolution
algorithm. DE is a new floating point encoded evolutionary algorithm for global
optimization, owing to the special kind of differential operator which create new
offspring from parents chromosomes instead of classical crossover and mutation.
The unique in the DE approach is a reproduction procedure. The Differential
Evolution algorithm aims evolving a population of NP $(N * D)$-dimensional
individual vectors in the population t as below:

$$x^i(t) = [x_{11}^k, \ x_{12}^k, ..., x_{ND}^k] \ \ for \ k \in 1, ..., NP \tag{8}$$

In the initial population the ijth variable of the kth individual takes the
following form:

$$x_{ij}^k(0) \ = \ L_{ij} \ + \ rand_{ij}(0,1) \, (U_{ij} - L_{ij}) \tag{9}$$

where L_{ij} and U_{ij} determine the lower and upper bounds of variable ij and
$rand_{ij}(0,1)$ is a uniformly distributed random variable from the range [0,1].

3.1   Differential Mutation and Crossover Operators

New candidate solutions are created by combining the parent individuals and
several other individuals of the same population. At each generation and for
each individual DE employs mutation and crossover operations to produce a
donor vector in the current population. There are many variants of offspring
creation procedures. These strategies diversify by the way how to choose three
vectors from the current population. The often applied mutation scheme uses

a randomly selected vector $x^p(t)$. Only one weighted difference vector with the coefficient F is used to perturb the received mutant vector $v^i(t)$ in the form:

$$v^i(t) \; = \; x^p + F \; (x^r(t) - x^s(t)) \tag{10}$$

where $p, \; r, \; s \in [1, ..., NP]$. The difference between two randomly chosen vector makes the mutation operation self-adaptive according to the decreasing mutation step. The parameter F also influence on the mutation step and typically takes the value from the range [0,1]. The mutation scheme is referred as $DE/base/num/cross$, where DE stands for Differential Evolution idea, $base$ represents a string denoting the vector to be perturbed (usually a random or the best individual), num is the number of difference vectors considered for perturbation of base and cross stands for the type of crossover being used. The parameter base can be randomly selected or it is the best vector in the population with respect to fitness value. DE can use two kinds of crossover scheme: exponential or binomial to increase the potential diversity of the population. After the mutation phase the crossover operation, namely binomial or exponential, is used. The mutant vector with an individual x^i_j create the new vector $u^i_j(t)$ in the following form:

$$u^i_j(t) \; = \; v^i_j(t) \tag{11}$$

in the case, when

$$rand_j(0, 1) \; \leq \; C_r \; or \; j = j_{rand} \tag{12}$$

where C_r defines the crossover probability. Otherwise the new vector: $u^i_j(t) = x^i_j(t)$. The crossover operator determines, which variable $x^i_j(t)$ or $v^i_j(t)$ will correspond to the trial vector $u^i_j(t)$.

We try to improve the strength Pareto differential evolution approach for multi-objective optimization algorithm for design and optimization of a chemotherapy treatment planning. The non-dominated optimal solutions are found using modified differential evolution algorithm for bi-criteria optimization problem with the help of standardization of constraints and constrained dominance operator. In discussed problem the range of values for modified parameters is very narrow for binomial crossover, but in the case of exponential crossover it is impossible to identify it.

In a cancer chemotherapy optimization problem given schedules of drugs doses can minimize a tumor size determining minimal toxic effects on human body. A schedule of medical treatment plan can be calculated based on a mathematical growth model described by a set of differential equations, when used in conjunction with an differential evolution approach. The drugs should be scheduled to ensure that the patients will tolerate its toxic side effects.

3.2 Chemotherapy Treatment Planning

The non-dominated optimal solutions are found with the help of proposed multi-objective differential evolution algorithm using differential mutation algorithm and differential crossover operator DE/rand/1/bin. The computer-based system,
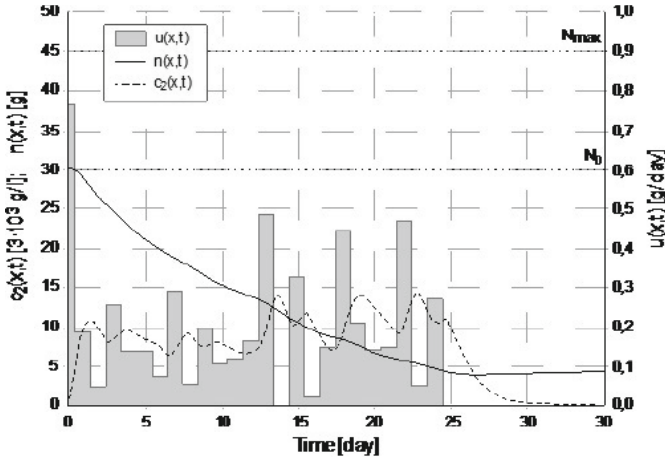
Fig. 1. The number of tumor cells n(x,t) and toxicity effects $c_2(x,t)$, based on optimal drug doses schedule u(x,t) on 25 days treatment period.
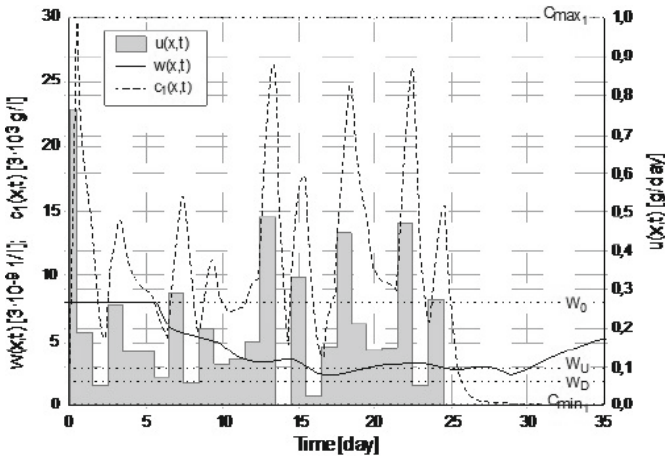

Fig. 2. The effective drug concentration $c_1(x,t)$ and the constraint White Blood Cells count $w(x,t)$ on optimal drug dose schedule during 25 days treatment interval.

which supports the physicians, allow an user to input treatment and patient parameters [19]. The system has to analyze very carefully a feasibility of constraints, because of the threat to life. For the problem of multi-objective chemotherapy optimization it is very difficult to determine the true Pareto front of non-dominated solutions. The system contains a database of chemotherapy treatment for simulation and optimization of drug doses and schedules. The difficulties in fulfilling the constraints are observed during numerical tests. Sometimes it is more important to receive the feasible point, not Pareto-optimal to give the

patient the quarantee of life. The parameters of the experimental treatment process concern the curative regime for 25 days of treatment with calculated drug doses. The Fig. 1 shows the first objective function $n(x,t)$ the reduction of the number of tumor cells during the time t_N described by optimal drug doses shown as $u(x,t)$. The second objective function $c_1(x,t)$, the constraint White Blood Cells count $w(x,t)$ and optimal dose schedule are shown on the Fig. 2 [14]. The drug concentration $c_1(x,t)$ is going to the minimal value on the end of treatment process, but in the time intervals with great drug doses the toxic drug concentration increases, but below the maximum allowed concentration value equal C_{min}. The WBC count remains controlled at level higher than a fixed down level W_D.

The most difficult constraint to be fulfilled concerns the time t_u, shown in the relation (4), which ensures the necessary protection from leukopenia. The time $t_u(x,T_{max})$ over which WBC count $w(x,t)$ remains below a fixed upper level W_u, has to be less than the time T_u. It is necessary to underline that the different simulation results we can obtain for different patients, according to their own properties. For some people the time T_u ought to be changed according the individual features of a patient and according to the upper level for time t_u.

4 Conclusion

The multi-objective optimization of chemotherapy treatment planning based on differential evolution approach demonstrates the high capabilities that can be effectively used especially for the complex set of constraints and objective functions, describing the cancer treatment procedure. In the process the user has the possibility to change input parameters in the search for a better optimization result. This search may be very time-consuming, depending on patient medical parameters, the experience of physicians and the complexity of the case. All numerical results show that the proposed algorithm is stable and robust in handling medical applications especially for a chemotherapy planning process.

References

1. Ali, M., Siarry, P., Pant, M.: An efficient differential evolution based algorithm for solving multi-objective optimization problems. Eur. J. Oper. Res. **217**(2), 404–416 (2012)
2. Amirian, H., Sahraeian, R.: Multi-objective evolution algorithm for the flow shop scheduling problem with a modified learning effect. IJE. Trans. C: Aspects **27**(9), 1395–1404 (2014)
3. Barbour, R., Corne, D., McCall, J.: Accelerated optimization of chemotherapy dose schedules using fitness inheritance. In: IEEE Congress on Evolutionary Computation (2010)
4. Beji, N., Jarboui, B., Siarry, P., Chabchoub, H.: A differential evolution algorithm to solve redundancy allocation problems. Int. Trans. Oper. Res. **19**, 809–824 (2012)

5. Cichon, A., Szlachcic, E.: Multi-objective differential evolution algorithm with self-adaptive learning process. In: Fodor, J., Klempous, R., Suárez Araujo, C.P. (eds.) Recent Advances in Intelligent Engineering Systems. SCI, pp. 131–150. Springer, Heidelberg (2010)
6. Das, S., Suganthan, P.N.: Differential evolution: a survey of the state-of-the-art. IEEE Trans. Evol. Comput. **15**(1), 4–31 (2009)
7. Ehrgott, M.: Multi-Criteria Optimization, 2nd edn. Springer Verlag, Berlin (2005)
8. Fdes-Olivares, J., Castillo, L., Czar, J.A., Prez, O.G.: Supporting clinical processes and decisions by hierarchical planning and scheduling. Comput. Intell. **27**(1) (2011)
9. Gong, W., Cai, Z.: A multi-objective differential evolution algorithm for constrained optimization. In: IEEE Congress on Evolutionary Computation, pp. 181–188. IEEE (2008)
10. Iliades, A., Barbalosi, D.: Optimizing drug regimes in cancer chemotherapy by an efficacy-toxicity mathematical model. Comput. Biomed. Res. **33**, 211–226 (2000). Academic Press, France
11. Wang, L., Qu, H., Chen, T.: An effective hybrid self-adapting differential evolution algorithm for the joint replenishment and location-inventory problem in a tree-level supply chain. Sci. World J. **2013**, 11 (2013). Article ID 270249
12. Neri, H., Tirronen, V.: Recent advances in differential evolution: a survey and experimental analysis. Artif. Intell. Rev. **33**(1–2), 61–106 (2010)
13. Petrovski, A., McCall, J., Sudha, B.: Multi-objective optmimization of cancer chemotherapy using swarm intelligence. School of Computing, The Robert Gordon University, AB25 3UE, UK
14. Porombka, P.: A meta-heuristic approach for the medical treatment planning, M.Sc. thesis, Wroclaw University of Technology, Wroclaw (2010)
15. Price, K.V., Storn, R.M., Lampinen, J.A.: Differential Evolution: A Practical Approach to Global Optimization. Springer, Heidelberg (2005)
16. Qian, W., Li, A.: Adaptive differential evolution algorithm for multi-objective optimization problems. Appl. Math. Comput. **201**(1–2), 431–440 (2008)
17. Robič, T., Filipič, B.: DEMO: differential evolution for multiobjective optimization. In: Coello Coello, C.A., Hernández Aguirre, A., Zitzler, E. (eds.) EMO 2005. LNCS, vol. 3410, pp. 520–533. Springer, Heidelberg (2005)
18. Santana-Quintero, L.V., Hernandez-Diaz, A.G., Molina, J., Coello-Coello, C.A., Caballero, R.: DEMORS: a hybrid multi-objective optimization algorithm using differential evolution and rough set theory for constrained problems. Comput. Oper. Res. **37**, 470–480 (2009). Elsevier
19. Szlachcic, E., Porombka, P.: Decision support system for cancer chemotherapy schedules. In: Moreno-Díaz, R., Pichler, F., Quesada-Arencibia, A. (eds.) EUROCAST. LNCS, vol. 8112, pp. 226–233. Springer, Heidelberg (2013)
20. Tang, L., Zhao, Y., Liu, J.: An improved differential evolution algorithm for practical dynamic scheduling in steelmaking-continuous casting production. IEEE Trans. Evol. Comput. **18**(2), 209–225 (2014)
21. Zaharie, D.: Influence of crossover on the behavior of differential evolution algorithms. Appl. Soft Comput. **9**(3), 1126–1138 (2009)
22. Zaharie, D.: Differential evolution: from theoretical analysis to practical insights (2012)