Decision Support System for Cancer Chemotherapy Schedules

Ewa Szlachcic and Pawel Porombka

Institute of Computer Engineering, Control and Robotics
Wrocław University of Technology
11/17 Janiszewskiego St., 50-372 Wrocław, PolandBirmingham
ewa.szlachcic@pwr.wroc.pl, pporombka@gmail.com

Abstract. In a chemotherapy scheduling process a chemotherapy is a treatment of cancer using a set of toxic drugs. In the paper we propose a Decision Support System for the anti-cancer medical treatment to improve physicians' decisions about drugs doses selection and scheduling. A hybrid meta-heuristic algorithm has been applied to the problem of bi-criteria optimization allowing to find effective chemotherapy drugs dose scheduling as the minimization of a tumor size at a fixed period of time and maximization of Patient Survival Time. The numerical tests of proposed algorithm gives the possibility of producing a set of alternative treatment scenarios according to the final decision.

1 Introduction

In a curative cancer chemotherapy treatment the main goal is to eradicate a tumor using a set of anti-cancer toxic drugs. A cell is cancerous when it has lost its ability to regulate cell growth and division [7,10,20]. The drug regimes tend to minimize a tumor size but the drugs are highly toxic and they strongly impact on Patient Survival Time (PST). There is very small difference among a treatment and survival process. It becomes very important to design treatment scenarios for specific tumors and drugs protocols without overdosing the patient in a chemotherapy scheduling. In the [1,2] different objective functions are described like the minimization of tumor burden or a prolongation of PST. At [10] the goal is to drive the dynamical system model inside the estimated basin of attraction of the tomor free fixed point, while maintaining the immune system population at an acceptable level. It leads to main objective, which is going to minimize the average and final tumor burden. The introduction of toxic drugs to a human body gives the damage of different vital organs and drug doses have to be limited according to the clinical trials [2,13,14,20].

In a treatment process the toxic drugs are used. They kill cancer cells but also damage patient healthy cells. A dose of drugs is given to a patient than after the period of time for the body to recover the next dose is prepared. Tumor development is delivered by toxic drugs and the influence of drugs on human body is also checked subject to a number of conflicting constraints. They have also a very negative influence on a patient quality of life and for the length of

R. Moreno-Díaz et al. (Eds.): EUROCAST 2013, Part II, LNCS 8112, pp. 226–233, 2013.

life [12,13,14]. In a cancer chemotherapy optimization problem given schedules of drugs doses that can minimize the tumor size calculating toxic effects on human body as a set of constraints [1,2,20]A schedule of medical treatment can be calculated based on a mathematical growth model described by a set of differential equations, when used in conjunction with an evolutionary approach [11,12,13,14,19]. The drug regimes tend to minimize a tumor size.

In the paper we propose a Desicion Support System for Chemotherapy Scheduling Problem in an anti-cancer medical treatment. Hybrid evolutionary algorithm with differential evolution approach for multi-objective problem is proposed to calculate a set of non-dominated solutions.

2 Problem Formulation

In a chemotherapy treatment the applications of very toxic drugs reduces the tumor meanwhile leading to damage the immune system and giving unacceptable effects to the patient. The anti-cancer drugs are best used together in a combination regime. Looking for the best schedule of multi-drugs and drug doses in time intervals to be given with minimization of tumor burden and minimization of toxic effects determines the balance between killing cancer cells and limiting the damage for human body. The cancer consists of the rapid uncontrolled growth of cells. It is necessary to use a suitable mathematical model, which essentially characterizes a growth of cancer tumor [7,20].

2.1 Treatment Objectives and Constraints

In the design process of an effective chemotherapy two objectives functions, describing the human body behavior in a curtive cancer chemotherapy treatment are proposed. The main idea concerns how to minimize the tumor burden. It is known that the chemotherapy process cannot eradicate the whole tumor. In the last period of the treatment if the tumor is small enough, other processes such as immune system behavior or programmed cell death will be held and have finished the treatment procedure. The second objective is to maintain a reasonable quality of life including highly toxic drug regimes by minimizing toxic side effects of a treatment.

The multi-drug chemotherapy process is realized in discrete n doses given at treatment intervals $t_1, t_2, ...t_N$. A dose schedule for j drug for whole treatment period takes the form:

$$u_j(x,t) = \sum_{i=1}^{N} \frac{x_{ij}}{t_i - t_{i-1}} \left[H(t-t_i) - H(t-t_{i-1})\right] \tag{1}$$

where $x = [x_{ij}]$ is a template of drug doses for i defined as index of time interval, $i = 1, 2, ..., N$ and j - index of j drug , for $j = 1, 2, ..., D$ and $H(t)$ is the Heaviside step function. Each dose is a cocktail of D drugs, characterized by a concentration level $c_{1j}(x,t)$ of drug j for at N switching times. The schedule for D drugs and their doses at N timeintervals has to be determined.

The first objective function is to minimize the number of cancer tumor cells $n(x,t)$at a fixed period of time:

$$\min_{x \in X} n(x,t). \tag{2}$$

The Gompertz growth model with linear cell-loss effect [7,10] is taken to simulate a response of a tumor to a chemotherapy process:

$$\frac{dn(x,t)}{dt} = f(n(x,t)) - L(x,t). \tag{3}$$

The function $f(n(x,t))$ determines a real valued function, which models the growth of a untreated tumor and $L(x,t)$characterizes cells loss due to the effects of anti-cancer drugs. The cells loss is proportional to the number of tumor cells and to the concentration $c_1(x,t)$ of anti-drugs at the tumor site.The second objective function determines the toxic side effects on human body, which is equivalent to maximizing a Patient Survival Time, as follows:

$$min \sum_{i=1}^{N} \sum_{j=1}^{D} c_{1j}(x_{ij}, t_i) \tag{4}$$

The drug dose schedule will be determined analyzing the concentration of drug j in plasma $c_{1j}(x,t)$. These two objectives functions conflict with each other on the set X of constraints, due to the toxicity of used drugs. There are fixed limits on doses to make the possibility to protect healthy cells. Drugs used in cancer chemotherapy all have narrow therapeutic indices. The most effective drugs dose levels are close to those levels at which unacceptable toxic side effects result. Toxicity $a_j(x, T_{max})$ of each drug j at experimental interval T_{max}must not exceed specified limit $A_{max,j}$:

$$a_j(x, T_{max}) \leq A_{max,j} \qquad for \quad j = [1, 2, ..., D] \tag{5}$$

and

$$\frac{da_j(x,t)}{dt} = c_{1j}(x,t). \tag{6}$$

Maximum concentration of drug j determines renal toxicity. The rate of drug j accumulation in urine is directly proportional to $c_{1j}(x,t)$ and must not exceed the fixed value $C_{max,j}$ for each drug $j = [1, 2, ..., D]$:

$$c_{1j}(x,t) \leq C_{max,j}. \tag{7}$$

The White Blood Cells count $w(x,t)$ is the very important parameter for patient's life, which has to remain under strict control. This constraint ensures necessary protection from leukopenia. The White Blood Cells (WBC) must remain controlled at levels higher than a fixed down level W_D :

$$w(x, t+\tau) \geq W_D \tag{8}$$

The WBC count as the number of WBC per unit of volume is calculated based on differential equation. An additional protection against leukopenia is to constrain the time $t_U(x, T_{max})$ over which $w(x,t)$ remains below a fixed upper level W_U to be less than T_U :

$$t_U(x, T_{max}) \leq T_U. \tag{9}$$

The constraints limit the different toxic parameters and restrain the toxic side effects of anti-cancer multi-drug chemotherapy.

2.2 Pareto Optimal Front Concept of Multi-objective Hybrid Differential Evolution Algorithm

The chemotherapy treatment optimization is carried out using meta-heuristic algorithm with bi-criteria evolutionary algorithms [3,8,9,16,17]. The Pareto optimal solutions are found using hybrid multi-objective optimization algorithm with differential evolution approach and a normalization of constraints [5,18]. Especially in the problem of curative anti-cancer treatment the whole set of constraints play a fundamental role. The constraints have to be fulfilled because of the threat to life. Taking under consideration the whole set of constraints X in the form:

$$X = [x : \; g_i(x) \leq \overline{g_i}(x) \quad for \; i = 1, 2, ..., (2dD + 2)] \,. \tag{10}$$

the normalized value $C_i(x)$ of constraint i for chromosome x is entered as:

$$C_i(x) = \frac{g_i(x) - L_i(x)}{U_i(x) - L_i(x)} \tag{11}$$

where $\mathrm{L}_i(x)$ and $\mathrm{U}_i(x)$ denote the minimal and maximal values of constraint i on each step of a calculation process.

The system contains a database of chemotherapy treatment information for simulation and optimization of drugs doses. It is necessary to solve the set of differential equations to evaluate a chromosome and to calculate a fitness function values. The Pareto optimal solutions are found by the Hybrid Differential Evolution algorithm with the help of modified mutation operator and differential crossover like DE/rand/1/bin. The spread of non-dominated solutions is a weakest point of known multi-objective meta-heuristic algorithms. In this case the well-spread Pareto set is very important in the chemotherapy treatment. The oncologist can choose one of the non-dominated solution, which will be suitable to an individual patient. Each human body responses differently for a set of toxic drugs, so the chemotherapy schedules ought to be personal. Taking under consideration the necessity of well–spread non-dominated solutions front the normalization of the set of constraints gives the very good results. It allows to construct the constrained dominance operator used in the selection process. In the procedure in the first part each individual is compared with all other chromosomes using Pareto dominance operator and the first Pareto front is constructed. In the second part the remaining fronts are determined. To accelerate

the procedure the fast sorting operator is used, based on a crowded distance operator (CD). This operator describes the distance among two chromosomes in the objective functions space and it allows to reject some individuals, which are too close. CD operator leads to receive the well-spread Pareto set of solutions, specifying different dose schedules.

3 Experimental Results

The functioning of the hybrid multi-objective differential algorithm on the problem of multi-drug cancer chemotherapy optimization is illustrated by considering four typical treatment periods. Test problems were performed for curative medical treatment for different experimental intervals (10, 20, 25,30 days) and different drug dose scenarios. In the cancer chemotherapy optimization an initial population of 150 chromosomes is randomly generated. For each instance with the same parameters 15 independent runs were performed. The results of HMODE algorithm are illustrated at Fig.1.

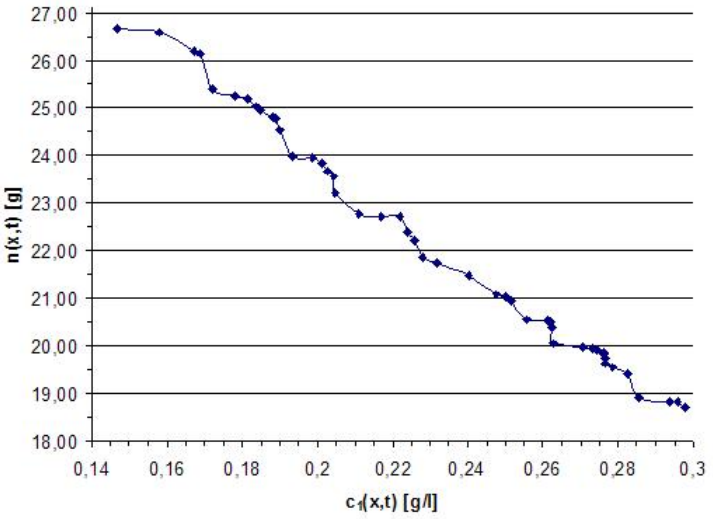

Fig. 1. Tumor response $n(x,t)$ and effective drug concentration $c_1(x,t)$ as the optimal front of Pareto solutions on the objective functions space

The presented curve shows the Pareto optimal front of non-dominating solutions on the objective functions space for one of the treatment period equal 25 days. For each bi-criteria optimal solution, defined by the best chromosome the Decision Suport System gives the possibility of observation the objective functions values with the set of feasible constraints for a chosen patient. The number of tumor cells $n(x,t)$,the effective drug concentrations $c_1(x,t)$ and optimal drug dose schedules $u(x,t)$ greatly depend on the desired treatment parameters and

modeling of patient dynamics. The constraint WBC count, which answers for absolute protection from leukopenia, remains among fixed down and up levels.

The proposed schedule preparing the great part of doses in the first part of treatment, next the small quantity of drugs in the middle of treatment period and at the end the great part of doses again results the feasible solution with significant reduction of tumor burden. Well-chosen value of Crowded Distance operator (CD) leads to receive the well-spread Pareto set of solutions. The usefulness of well-spread non-dominated solutions gives the possibility to the physicians to explore wide range of chemotherapy schedules. Finally, there exists a great diversity of initial parameters as concerns different drugs, cancer type and human body features. So it leads to varied parameters during constraints settings.

In many cases optimal solutions of mathematical models are not feasible or clinically acceptable. In the simulation 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.

4 Implementation of Decision Support System

The Decision Support System for ChSP is a computer-based system, that supports physicians in a decision making process. It allows an user to input treatment design parameter and analyzes the relations among two objective functions values and a set of constraints especially in the case of unfeasible solutions. Pareto non-dominated solutions values can be observed and compared with the previous doses, used in a treatment. The DSS allows to review proposed treatment scenarios according to Pareto set and review and evaluate simulated results according to the tumor growth rates, toxic effects and drug's effectiveness rates. The physicians make trade-off decisions between a set of prepared treatment schedules taking under considerations the feasibility of solutions. An evaluation of treatment outcome was prepared in a manner, which is comprehensible to the user.

There are some rules, which have to be undertaken in implementing a DSS [4,14,19]. It is necessary to assure, that the knowledge is taken from a rich knowledge source, as the end users always expect to be known about the rules. Physicians and other end users have to understand the strength and limitation of DSS system. The system allows physicians to capture, view and modify the patient information on each stage of scheduling for individual person and provide decision support system on dosing and scheduling the drugs.

The proposed DSS consists of four coopering modules. The first module concerns an I/O system parameters, where set of parameters are modified dynamically according to the medical treatment possibilities, next module manages numerical calculations such as objective functions - a tumor burden, a drug concentration and constraints functions for each time interval and Runge-Kutty method, used for each time interval. Module of simulation and optimization procedures realizes the Hybrid M Differential Evolution algorithm. Module of

Treatment Editor with GUI module answers for system parameters setting, drugs parameters setting and results viewer (statistics and figures presentation), accordingly to actual needs. This functionality allows to save results for many simulated configurations and gives a possibility to make an analysis, returning to the same settings.

5 Conclussions

The Decision Support System for Chemotherapy Scheduling Problem gives a tool to an oncologist, which can explore a wide range of treatment schedules before deciding upon suitable doses regimes for an anti-cancer chemotherapy treatment. Large number of initial parameters influences for the final chemotherapy dose distribution schedule. The chemotherapy scheduling problem is solved by the bi-criteria optimization problem, which minimizes the number of tumor cells at a fixed period of time and minimizes the toxicity of drug's regimes on the set of constraints. The Pareto set of non-dominated solutions with different dose schedules gives the wide range of solutions , which can be taken under consideration by oncologists. The DSS allows physicians to input treatment design parameters, to review proposed scenarios and simulated results and to make trade-off decisions between a set of Pareto optimal treatment schedules.

Additional application of DSS for ChPP is to use of a system for training medical students. They can use the computer-based system to simulate patient cases in a virtual way and to observe possible results. DSS would positively influence on their medical learning and help them to understand the impact of a chemotherapy dose scheduling for a treatment of cancer.

References

1. Barbour, R., Corne, D., McCall, J.: Accelarated optimisation of chemotherapy dose schedules using fitness inheritance. IEEE Congress on Evolutionary Computation (2010)
2. Chingola, T., Foroni, R.I.: Estimating the growth kinetics of experimental tumors from as few as two determinations of tumor size: Implications for clinical oncology. IEEE Trans. on Biomedical Engineering 5, 808–815 (2005)
3. Ehrgott, M.: Multi-criteria optimization, 2nd edn. Springer, Berlin (2005)
4. Fdes-Olivares, J., Castillo, L., Cózar, J.A., Pérez, O.G.: Supporting clinical processes and decisions by hierarchical planning and scheduling. Computational Intelligence 27(1) (2011)
5. Gong, W., Cai, Z.: A multiobjective differential evolution algorithm for contrained optimization. IEEE Congress on Evolutionary Computation, 181–188 (2008)
6. Henderson, D., McCall, J., Boyle, J.: Decision support system for designing chemotherapeutic regimes. In: Pappas, C., Maglavera, N., Scherrer, J.R. (eds.) Medical Informatics Europe 1997, pp. 353–357. IOS Press (1997) ISSN: 0926-9630
7. Iliadis, A., Barbolosi, D.: Optimizing drug regimens in cancer chemotherapy by an efficacy-toxicity mathematical model. Computers and Biomedical Research 33, 211–226 (2000)

8. Liu, J., Li, J.E., Wei, W.: Hybrid genetic and particle swarm algorithm for service composition, Piscatawy, NJ 08855-1331, United States, pp. 564–567 (2007)
9. Mallipeddi R., Sugganthan P.N.: Evaluation of novel adaptive evolutionary programming on four constraint handling techniques. In: IEEE Congress on Evolutionary Computation, Hong Kong, China, 4045-4052 (2008).
10. Ochoa, G., Villasana, M., Burke, E.K.: An evolutionary approach to cancer chemotherapy scheduling, School of Computer Science and IT, University of Nottingham, Nottingham, England (2004)
11. Peňa-Reyes, C.A., Sipper, N.: Evolutionary computation in medicine an overview. Artificial Intelligence Med. 19, 1–23 (2000)
12. Petrovski, A., McCall, J.: Multi-objective optimisation of cancer chemotherapy using evolutionary algorithms. In: First Intern. Conf. on Evolutionary Multi-Criterion. Optimization (2001)
13. Petrovski, A., Shakya, S., McCall, J.: Optimising cancer chemotherapy using an estimation of distribution algorithm and genetic algorithms, Medal Report No. 2008005 (January 2008)
14. Petrovski, A., Sudha, B., McCall, J.A.W.: Optimising cancer chemotherapy using particle swarm optimisation and genetic algorithms. In: Yao, X., et al. (eds.) PPSN 2004. LNCS, vol. 3242, pp. 633–641. Springer, Heidelberg (2004)
15. Porombka, P.: A Meta-heuristic approach for the medical treatment planning, M.Sc. Thesis (unpublished), Wroclaw University of Technology, Wroclaw (2010)
16. 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)
17. Qu, B.Y., Suganthan, P.N.: Multi-objective evolutionary programming without non-domination sorting is up to twenty times faster. In: Proceedings of the IEEE Congress on Evolutionary Computation (CEC 2009), pp. 2934–2939 (2009)
18. Santana-Quintero, L.V., Hernadez-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. Computers and Operations Research 37, 470–480 (2009)
19. Winz, I.: A decision support system for radiotherapy treatment planning, Master's thesis, Department of Engineering Science, School of Engineering, University of Auckland, New Zealand (2007)
20. Wheldon, T.: Mathematical models in cancer research, Adam Hilger, Bristol and Philadelphia (1988)