A novel method for response adaptive design for cancer clinical trials

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Introduction

Clinical trials serve as a standard way for assessing the chemotherapy plans (World Health Organization, 2016). They have significantly been applied to study drug effects as well as new treatment methods (Chow & Liu, 2005).

In real cases, for a given cancer, the oncologist uses a standard chemotherapy treatment regimen according to the results of many clinical trials, medical guidelines, current scientific publications and experiences acquired in former cases; hence, designing clinical trials is a time-consuming and costly process so that determining drug combinations and their dosages have always been a challenging work in the clinical trial design process. On the other hand, it is a difficult task to perform clinical trial for several chemotherapy plans. Those limitations and challenges necessitate the development of cost-effective techniques for designing clinical trials. To design a clinical trial with a high chance of success, it is necessary to identify new and effective drug combinations. Those drug combinations and their dosages are generally obtained by trial-and-error based on the experience of clinical researchers and oncologists. Alternatively, the type and dosage of drug combinations might be determined in such a manner that they can provide the patient with the highest treatment value while maintaining toxicity at a manageable level.

literature review

Many researches have performed in the field of chemotherapy treatment planning problem. Most of the studies examining chemotherapy treatment optimization propose various ways to model the interactions among the key factors such as cancerous cells, toxicity, survival and etc. Bertsimas et al. (2013) proposed a data-driven approach for the analysis and design of clinical trials with the goal of discovering most promising drug combinations for cancerous patients. However, the treatment costs were ignored in their model. Chemotherapy costs are divided into two main parts: costs associated to the selection of a better chemotherapy plan, and treatment costs. Though mathematical models prevent unreliable clinical trials and reduce the first type of costs by identifying effective drug combinations, they do not cover patients' treatment costs related to drugs. Bazrafshan & Lotfi (2016) extended the model presented by Bertsimas et al. (2013) aiming at simultaneously the maximization of patient's survival time and the minimization of current treatment costs in a treatment cycle. Results showed that the proposed multi-objective model yields a wide range of solutions establishing a reasonable tradeoff between patient's survival and treatment costs. However, they did not consider the adjustment of model parameters according to the patient's response along the treatment.

Sequential or dynamic treatment regimens are another new challenging topic in the literature. A dynamic treatment regimen is a sequential intervention in which the severity and/or type of treatment varies according to the patient needs (Collins et al., 2014). As powerful analytical tools for sequential decision making, we suggest the use of a finite-horizon Markov decision process (MDP) for modeling cancer chemotherapy treatment optimization problem aiming at developing novel dynamic treatment regimens for sequential treatment decision making in clinical trials. The applications of MDP in medical decision making (MDM) were best summarized by Schaefer et al. (2004).

Aims

We consider a finite-horizon MDP with finite state as well as action space to develop a model for finding the most effective chemotherapy treatment policies. The particular characteristic of our approach is that it uses the results of optimization model proposed by Bazrafshan & Lotfi (2016) in order to develop an MDP model. We benefit from the advantages of their approach, proposing most-promising and cost-effective new chemotherapy combinations, in our model. Hence, our main contribution is to develop an approach which can take the impact of the patient's response on the treatment regimen into account and propose the most promising dynamic treatment regimens also costing reasonable. In fact, our model provides the possibility of designing cost-effective most-promising clinical trials for sequential treatments.

Methods

This study employs the results of optimization model proposed by Bazrafshan & Lotfi (2016) in order to develop the MDP model for cancer chemotherapy treatment planning. The multi-objective mixed-integer optimization model, aimed at maximizing the patient's survival time and minimizing the chemotherapy costs during one treatment period, presents the cost-effective most-promising new drug combinations for designing clinical trials. The main constraints are limitations on the treatment side effects which force the treatment's toxicity to not exceed an acceptable threshold. In addition, some constraints ensure the feasibility of treatment regimens. Fig. 1 shows a schematic view of the relationship between the optimization model and the proposed MDP model.

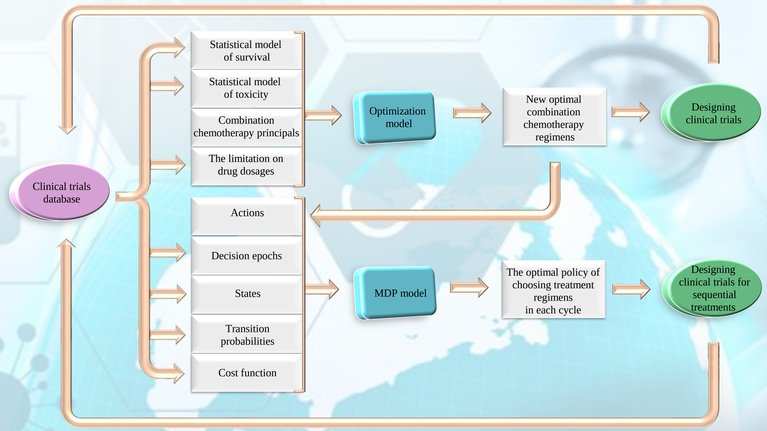

Fig. 1. Schematic illustration of the relationship between the optimization model and Markov model.

Table 1 lists the components of desired MDP model for cancer chemotherapy treatment planning. The MDP model is developed for N treatment cycles and stages. Fig. 2 shows a schematic view of the relevant stages and decision epochs. The decision t is made at the beginning of stage t and for the time interval between t and t+1. At each stage, the system is either transited from the current state to the next state or remains at the current state. The decision maker selects one of the actions based on the system's state in stage t, which incurs cost $c_t(s,a)$. At the end of stage N, the treatment period is completed.

Table 1. MDP components for cancer chemotherapy treatment planning problem.

Component	Notation	Definition
Stage	T=1,…,N	Treatment cycle
State	s∈S	Patient toxicity level
Action	A_s	Treatment Regimens proposed by optimization model
Transition probability	$p_t(s'\|s,a)$	Probability of transiting patient toxicity level from s at current treatment cycle t to s' though selecting treatment regimen a
Cost function	$C_t(s,a)$	Cost of applying treatment regimen a in treatment cycle t when patient toxicity level is s

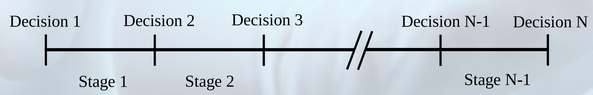

Fig. 2. Schematic illustration of stages and decision epochs.

We use the value iteration algorithm to find optimal policies for the developed finite-horizon MDP model. In this method, the Bellman equations (Bellman, 1957) are solved backward in time and acquired the optimal policies (Winston, 1997).

Results

The proposed MDP model for cancer chemotherapy treatment planning was implemented in GAMS 24.0.1 using the value iteration technique and solved with the Cplex solver. Noteworthily, our case study, in this paper, refers to the clinical trials database and computational results presented by Bazrafshan & Lotfi (2016). Table 3 shows the solution results.

Table 3. Results of MDP model for cancer chemotherapy treatment planning.

s	$d^*_1(s)$	$d^*_2(s)$	$d^*_3(s)$	$d^*_4(s)$	$d^*_5(s)$	$d^*_6(s)$	$d^*_7(s)$	$d^*_8(s)$
1	a_1	a_1	a_1	a_1	a_1	a_1	a_1	a_1
2	a_1	a_1	a_1	a_1	a_1	a_5	a_5	a_5
3	a_1	a_1	a_4	a_4	a_4	a_4	a_4	a_4

As observed, drug regimen 1 is prescribed for patients from the beginning of treatment period to the beginning of cycle 2, regardless of their toxicity level. From the beginning of cycle 3 to 5, the previous treatment is continued provided that the toxicity level is not too high; otherwise, the treatment regimen is changed to action 4. From cycle 6 to the end, at the beginning of each cycle, treatment regimens 1, 5 and 4 will be prescribed to patients with toxicity levels of low, moderate and high, respectively.

Noteworthily, the optimal policy, proposed by the MDP model in Table 3, is expectable with respect to the patient's toxicity level and cost function values. Treatment regimen 1 is completely acceptable if the patient's toxicity level remains low, because this regimen imposes the least possible costs. This regimen is always considered as the best choice provided that the toxicity level does not show a considerable rise. For patients with a moderate toxicity level at the beginning of treatment period, treatment regimen 1 would be the best prescription at the initial cycles. But, at the beginning of 6th cycle, treatment regimen 5 must be applied. The reason is that, during the initial cycles, although toxicity is medium, the cumulative toxicity level is not high enough to call for a change from treatment regimen 1. In final cycles, however, if toxicity level rises, making a change in treatment is necessary.

Conclusions

The research work presented herein features a novel concept for sequential treatment decision making in clinical trials which addresses the problems observed in designing clinical trials. In this paper, a finite-horizon MDP model for cancer chemotherapy treatment planning was developed. The proposed model aimed at minimizing the cost function in order to find the optimal sequence of chemotherapy treatment regiments for a period of treatment. Results showed that the proposed MDP model is capable of advising the most effective chemotherapy drug combination according to the patient's response to chemotherapy at each treatment cycle. Since the treatment regimens proposed by this model are as new ones, it also makes possible to design clinical trials for sequential treatment regimens. Directions for further research include finding the best treatment policies for combined treatment such as surgery, radiotherapy, chemotherapy and etc.

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