

Pareto Front for Chemotherapy Schedules

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Abstract

In this paper we consider a multi-objective approach to chemotherapy optimization. We assume that the dynamics of the tumor are modeling for the stochastic Gompertz growth model with a linear cell-loss effect . We consider fuzzy constraints for the problem. The primary objective is to eradicate the tumor (curative treatment) , the second objective of cancer chemotherapy is to prolong the patient survival . time maintaining a reasonable quality of life during the palliation period. Numerical results are presented for a particular case (bladder cancer).

Mathematics Subject Classification: 92C50, 90C29

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1 Introduction

Systemic administration of cytotoxic drugs is the primary treatment strategy for patients with disseminated cancer. Whereas a wide range of treatment regimens are used in clinical practice, their fundamental goal is typically to induce lethal toxicity in the largest possible number of tumor cells. Thus, most research efforts in chemotherapy are focused on discovery of agents and combinations of agents, doses, and dose schedules that maximally kill tumor cells while minimizing the toxicity to the host. In most clinical therapies, patient tolerance is the primary factor that limits the dose of cytotoxic agents.

That is, cancer patients are usually treated at or near the maximum tolerated dose with implicit intent to eradicate (cure) the tumor even when such an outcome, based on extensive clinical experience, is highly improbable. Mathematical modeling of tumor growth and treatment has been approached by a number of researchers using a variety of models over the past decades . In the treatment of most common cancers multi-drug combinations are usually used. Combination treatments are developed through empirical trials of different combinations, dosing, schedules and sequencing . Traditionally, treatments are optimized with only one objective in mind. As a result of this, a particular patient may be treated in the wrong way if the decision about the most appropriate treatment objective was inadequate. In this paper we consider a multiobjective computational model to predict drug combinations, doses, and schedules likely to be effective in reducing tumor size and prolonging patient life.

Section 2 briefly we present the chemotherapy problem. Section 3 we introduce the optimization multi-objective problem. In Section 4 we present a variant of mini-max method. Finally, numerical results and conclusions are provided.

2 The Chemotherapy Problem

Chemotherapy is a cancer treatment based on the administration of drugs. Generally these drugs are supplied to the patient following a schedule in which there are n doses given at times t_1, t_2, \dots, t_n .

In the case of multi-drug treatments, each dose is a cocktail of d drugs with concentrations levels C_{ij} , $i \in \{1, 2, \dots, n\}, j \in \{1, 2, \dots, d\}$. Restrictions for chemotherapy treatment vary from drug to drug as well as with cancer type. But they have the following general form:

1. *Maximum instantaneous dose*

$$g_1(\mathbf{C}) = \{C_{maxj} - C_{ij} \geq 0, \forall i \in \{1, 2, \dots, n\}, \forall j \in \{1, 2, \dots, d\}\} \quad (1)$$

2. *Maximum cumulative dose*

$$g_2(\mathbf{C}) = \{C_{cumj} - \sum_{i=1}^n C_{ij} \geq 0, \forall j \in \{1, 2, \dots, d\}\} \quad (2)$$

3. *Maximum size of tumor*

$$g_3(\mathbf{C}) = \{N_{max} - N(b_i) \geq 0, i \in \{1, 2, \dots, n\}\} \quad (3)$$

4. Side Toxic Effects

$$g_4(\mathbf{C}) = \{C_{sc_k} - \sum_{j=1}^d \eta_{kj} C_{ij} \geq 0, \forall i \in \{1, 2, \dots, n\}, \forall j \in \{1, 2, \dots, d\}\} \quad (4)$$

We denote the constraints (1), (2), (3) and (4) as (Q). The factors η_{kj} that appear in the constraints indicate the risk of damage on the organ or tissue k by the drug j .

There are several models to describe the tumor response to treatment, but one of the most used is the Gompertz growth model with a linear cell-loss effect[4], whose stochastic equation respect of the Brownian movement of state is:

$$dN_t = N_t \left[\lambda \log \left(\frac{\theta}{N_t} \right) - \alpha(t, C) \right] dt + \sigma N_t dB_t \quad (5)$$

where $\alpha(t, C) = \sum_{j=1}^d \kappa_j \sum_{i=1}^n C_{ij} \{H(t - t_i) - H(t - t_{i+1})\}$, N_t represents the number of cells of tumor in time t , λ , θ are the growth parameters, $H(t)$ is the function of Heaviside and κ_j measures the effectiveness of the drug. The equation express that the fluctuation is proportional at N_t . In [5] uniqueness and existence of the equation (5) is proved.

The objectives are:

$$f_1(C) = \int_0^T E(N_\tau) d\tau \quad (6)$$

$$f_2(C) = \sum_{j=1}^d \sum_{i=1}^n C_{ij}, \quad (7)$$

where $E(N_t)$ is the expectation of N_t .

The first objective is minimize the average size of tumor and the second objective is minimize the total of drugs administered.

3 Formulation of multiobjctive optimization problem

The general formulation of a multiobjective optimization problem is:

$$\begin{aligned} \min_{\mathbf{x} \in \Omega} F(\mathbf{x}) &= [f_1(\mathbf{x}), f_2(\mathbf{x}), \dots, f_m(\mathbf{x})] \\ g_j(\mathbf{x}) &\leq 0, \quad j = 1, 2, \dots, J, \\ h_i(\mathbf{x}) &= 0, \quad i = 1, 2, \dots, I, \\ x_k^l &\leq x_k \leq x_k^u, \quad k = 1, 2, \dots, K, \end{aligned} \quad (8)$$

where x_k^u and x_k^l are the lower and upper bounds of x_k , respectively; $f_1(\mathbf{x})$, $f_2(\mathbf{x}), \dots, f_m(\mathbf{x})$ are the individual objective functions and h_i and g_j are equality and inequality constraint functions, respectively. We denote this constraints as (R).

The Pareto optimal solution is defined as follows:

Definition 1 A vector $\mathbf{x}^* \in \Omega$ is a Pareto optimum if and only if for any $\mathbf{x} \in \Omega$, $f_j(\mathbf{x}^*) \leq f_j(\mathbf{x})$, $\forall j \in \{1, 2, \dots, m\}$ and $\exists i \in \{1, 2, \dots, m\} : f_i(\mathbf{x}^*) < f_i(\mathbf{x})$. Denoting P the Pareto optimum set, and we call $F(P)$ to the Pareto Front.

Remark If $\mathbf{w}, \mathbf{v} \in \Omega$ and $f_j(\mathbf{w}) \leq f_j(\mathbf{v})$, $\forall j \in \{1, 2, \dots, m\}$ and $\exists i \in \{1, 2, \dots, m\} : f_i(\mathbf{w}) < f_i(\mathbf{v})$. Then we denoted $\mathbf{w} \preceq \mathbf{v}$. This is a partial order relation of Ω . We say that a subset $A \subset \Omega$ is totally ordered if for any pair $\mathbf{x}, \mathbf{y} \in A$ $\mathbf{x} \preceq \mathbf{y}$ or $\mathbf{y} \preceq \mathbf{x}$. And we say that $\mathbf{c} \in \Omega$ is an lower bound for A if $\mathbf{c} \preceq \mathbf{x}$ for every $\mathbf{x} \in A$. We say that $\mathbf{m} \in \Omega$ is a minimal element of Ω if there is no element $\mathbf{z} \in \Omega$ such that $\mathbf{z} \preceq \mathbf{m}$ except for $\mathbf{m} = \mathbf{z}$. We say that Ω is inductive if every totally ordered subset A in Ω has an lower bound.

Lemma 1 (Zorn) Every nonempty ordered set that is inductive has a lower element.

Definition 2 A set $Y \subset \mathbb{R}^m$ is \mathfrak{R}_+^m -semicompact if for every open cover of Y whith the form $\{(\mathbf{y}^i - \mathfrak{R}_+^m)^c | \mathbf{y}^i \in Y, i \in I\}$, I a set index, admit a finite subcover.

Theorem 1 If $F(\Omega) \subset \mathfrak{R}^m$, $F(\Omega) \neq \emptyset$ and is \mathfrak{R}_+^m -semicompact, then $F(P) \neq \emptyset$.

Proof Any element of $F(P)$ is an minimal element with partial order relation of Pareto. We prove that $F(\Omega)$ is inductive order and we apply the Zorn lemma in order to obtain an element of $F(P)$. We suppose that $F(\Omega)$ is not inductive order. The last sentence implies that there is a sequence $F(\Omega)^I = \{\mathbf{y}^i\}_{i \in I} \subset F(\Omega)$ has not a lower bound. Then we obtain

$$\bigcap_{i \in I} \{F(\Omega) \cap (\mathbf{y}^i - \mathfrak{R}_+^m)\} = \emptyset,$$

because if exists an element $\tilde{\mathbf{y}}$ in the intersection then $\tilde{\mathbf{y}} \preceq \mathbf{y}^i$, $\forall i \in I$. This involve that $\tilde{\mathbf{y}}$ is lower bound of $F(\Omega)^I$. Then $\forall \mathbf{y} \in F(\Omega) \exists \mathbf{y}^i \in F(\Omega)^I$ such that \mathbf{y} is not an element of $\mathbf{y}^i - \mathfrak{R}_+^m$. Then $\{(\mathbf{y}^i - \mathfrak{R}_+^m)^c\}_{i \in I}$ is a open cover of $F(\Omega)$. Since $\mathbf{y}^i - \mathfrak{R}_+^m \subset \mathbf{y}^j - \mathfrak{R}_+^m$ if and only if $\mathbf{y}^i \preceq \mathbf{y}^j$ this set are totally ordered by the include. By hypothesis $F(\Omega)$ is \mathfrak{R}_+^m -semicompact, then this open cover

admit a finite subcover and as this is a totally ordered exists $\mathbf{y}^{i_0} \in F(\Omega)^I$ such that

$$F(\Omega) \subset (\mathbf{y}^{i_0} - \mathfrak{R}_+^m)^c$$

but this contradicts that $\mathbf{y}^{i_0} \in F(\Omega)$. The $F(\Omega)$ is total order and by the lemma of Zorn exist an element \mathbf{y} minimal of $F(\Omega)$, in other word, $\mathbf{y} \in F(P)$. ■

Definition 3 A set $Y \subset \mathfrak{R}^m$ is \mathfrak{R}_+^m -compact if $\forall \mathbf{y} \in Y$ the set $Y \cap (\mathbf{y} - \mathfrak{R}_+^m)$ is compact.

Proposition 1 If $F(\Omega) \subset \mathfrak{R}^m$ is \mathfrak{R}_+^m -compact, then is \mathfrak{R}_+^m -semicompact.

Proof Let $\{(\mathbf{y}^i - \mathfrak{R}_+^m)^c | \mathbf{y}^i \in F(\Omega), i \in I\}$ be an open cover of $F(\Omega)$. Let $i_0 \in I$ be arbitrary, we have that $\{(\mathbf{y}^i - \mathfrak{R}_+^m)^c | \mathbf{y}^i \in F(\Omega), i \in I, \mathbf{y}^i \neq \mathbf{y}^{i_0}\}$ is a open cover of $F(\Omega) \cap (\mathbf{y}^{i_0} - \mathfrak{R}_+^m)$. This set is compact because $F(\Omega)$ is \mathfrak{R}_+^m -compact. Then, it admit a finite subcover, this subcover together with $(\mathbf{y}^{i_0} - \mathfrak{R}_+^m)^c$ is a finite subcover of $F(\Omega)$. Then $F(\Omega)$ is \mathfrak{R}_+^m -semicompact. ■

Theorem 1 and Proposition 1 involve the following result

Proposition 2 If $F(\Omega)$ is \mathfrak{R}_+^k -compact, then $F(P) \neq \emptyset$.

Proposition 3 The following problem

$$\begin{aligned} & \min_{\mathbf{x} \in \Omega} [f_1(\mathbf{x}), f_2(\mathbf{x})] \\ & \text{subject to } (Q), \end{aligned}$$

were $f_1(\mathbf{x})$ and $f_2(\mathbf{x})$ are given by (6) and (7), have solution.

Proof We have that $\mathbf{C} \in \{\Omega = \mathbf{x} \in \mathfrak{R}^2 : g_j(\mathbf{x}) \leq 0\}$ implies $\sum_{j=1}^d \sum_{i=1}^n \mathbf{C}_{ij} < \sum_j \mathbf{C}_{maxj} = \mathbf{C}_{max}$. This involve that $0 \leq f_2(\mathbf{C}) \leq C_{max}$.

Moreover,

$$E(N_t) = \exp \left\{ \mu + e^{-\lambda t} (\ln(N_0) - \mu) + \frac{1}{2} \left[\frac{\sigma^2}{2\lambda} (1 - e^{-2\lambda t}) \right] \right\},$$

were $\mu = \frac{\sigma^2/2 + \alpha(t, \mathbf{C})}{\lambda}$ [8]. This involve that $f_1(\mathbf{x})$ is bounded. Then $F(\Omega)$ is bounded, namely $\delta(F(\Omega)) < \infty$. Since $F(\Omega) \cap (\mathbf{y} - \mathfrak{R}_+^k) \subset F(\Omega)$, for $\mathbf{y} \in F(\Omega)$, we have that $\delta(F(\Omega) \cap (\mathbf{y} - \mathfrak{R}_+^k)) \subset \delta(F(\Omega)) < \infty$, then $F(\Omega) \cap (\mathbf{y} - \mathfrak{R}_+^k)$ is bounded. Now, if $(\mathbf{y}_n) \subset F(\Omega) \cap (\mathbf{y} - \mathfrak{R}_+^k)$ whit $\mathbf{y}_n \rightarrow \mathbf{w}$, we have that $\mathbf{y}_n = \mathbf{y} + \mathbf{w}_n$, where $\mathbf{w}_n \in \mathfrak{R}_+^k$. Since $\mathbf{y}_n \rightarrow \mathbf{w}$ we have that $\mathbf{w}_n \rightarrow \tilde{\mathbf{w}} = \mathbf{y} - \mathbf{w}$. Since \mathfrak{R}_+^k is closed, $\tilde{\mathbf{w}} \in \mathfrak{R}_+^k$. Then $\mathbf{y}_n \rightarrow \mathbf{y} - \tilde{\mathbf{w}} \in F(\Omega) \cap (\mathbf{y} - \mathfrak{R}_+^k)$. This involve that $F(\Omega) \cap (\mathbf{y} - \mathfrak{R}_+^k)$ is closed. Then $F(\Omega) \cap (\mathbf{y} - \mathfrak{R}_+^k)$ is a closed and bounded

subset of \mathfrak{R}^k , then is compact and by Proposition 2 $F(P) \neq \emptyset$. This implies that there is a solution of our problem. ■

The optimization model in order to find the ideal value of each objective is given by:

$$\min_{\mathbf{x}} f_t(\mathbf{x}), \quad t = 1, \dots, m \quad (9)$$

$$g_j(\mathbf{x}) \leq 0, \quad j = 1, 2, \dots, J, \quad (10)$$

$$h_l(\mathbf{x}) = 0, \quad l = 1, 2, \dots, I, \quad (11)$$

$$x_k^l \leq x_k \leq x_k^u, \quad k = 1, 2, \dots, K. \quad (12)$$

The solution of the above model is the ideal solution of each objective function, \mathbf{x}'_i , and the objective function at the ideal solution is then given by:

$$f_t^u = f_t(\mathbf{x}'_t) \quad t = 1, \dots, m.$$

where f_i^u is the ideal value of i th objective function. The vector (f_1^u, \dots, f_m^u) is call the ideal objective vector.

We can boarding the problem (8) minimizing some distance measure at the ideal objective vector. We can use the following metric:

$$d_{\alpha, w}(\mathbf{x}) = \sqrt[\alpha]{\sum_{i=1}^m w_i \left| \frac{f_i(\mathbf{x}) - f_i^{id}}{f_i^{id}} \right|^\alpha},$$

where $\alpha \in [1, +\infty]$ (usually $\alpha = 2$ is used).

Minimizing this metric function results in a commonly encountered mini-max method, since for this metric the optimum $\tilde{\mathbf{x}}$ can be defined as:

$$\min_{\mathbf{x} \in \Omega} \max_i \left(w_i \left| \frac{f_i(\mathbf{x}) - f_i^{id}}{f_i^{id}} \right| \right), \quad (13)$$

where $\mathbf{w} = (w_1, w_2, \dots, w_m)$ with $\sum_{j=1}^m w_j = 1$, $w_i \geq 0$, $i \in \{1, 2, \dots, m\}$ represents the degree of importance of the i th objective criterion.

3.1 The fuzzy multi-objective optimization model

Formulating a fuzzy optimization problem [15] entails developing membership functions for each constraint and each objective. A relatively high value for a membership function of a constraint set indicates a near or definite membership in the set, i.e., a high likelihood of the constraint satisfaction. Therefore, the goal of a fuzzy optimization problem is to maximize all membership functions simultaneously. The proposed procedure is summarized as follows.

(1) Finding the minimal feasible value and maximum feasible value of each objective function:

$$m_i = \min f_i \tag{14}$$

$$M_i = \max f_i \tag{15}$$

where m_i and M_i are the minimum feasible value and maximum feasible value of i th objective function.

(2) Establishing the membership function of each fuzzy objective function: Most applications that involve fuzzy set theory tend to be independent of the specific shape of the membership functions. Various types of membership functions are used, such as a linear membership function, a tangent type of a membership function, an interval linear membership function, an exponential membership function, inverse tangent membership function, logistic type of membership function, and concave piecewise linear membership function. Example problems have suggested that varying the nature of the membership function does affect the final solution, but the differences between the various outcomes are not substantial. The fuzzy objective stated by a designer can be quantified by eliciting a corresponding membership function using the following trapezoidal representation:

$$\mu_{\tilde{f}_i}(\mathbf{x}) = \begin{cases} 1 & \text{si } f_i(\mathbf{x}) \leq m_i \\ 1 - 2 \left(\frac{f_i(\mathbf{x}) - m_i}{M_i - m_i} \right)^2 & \text{si } m_i \leq f_i(\mathbf{x}) \leq \frac{m_i + M_i}{2} \\ 2 \left(\frac{f_i(\mathbf{x}) - M_i}{M_i - m_i} \right)^2 & \text{si } \frac{m_i + M_i}{2} \leq f_i(\mathbf{x}) \leq M_i \\ 0 & \text{si } f_i(\mathbf{x}) \geq M_i \end{cases} \tag{16}$$

(3) Establishing the membership function of each fuzzy constraint function: In the traditional optimization, the design feasibility is considered as either satisfied or violated. For many engineering applications, the transition from infeasibility to feasibility is not obvious, because of not only the vague information in the design constraints, but also the factors that can affect the design scenario, such as designer’s knowledge, manufacture precision, and material properties. For this reason, the constraints are modeled in such a way that the transition from infeasible state to feasible state is smooth and gradual with subjectivity. For simplicity, a linear membership function is used to reflect the smooth transition. Other types of the membership function can also be used depending on the problems under consideration. The linear membership function is given by

$$\mu_{\tilde{g}_j}(\mathbf{x}) = \begin{cases} 1 & \text{si } g_j(\mathbf{x}) \leq b_j \\ 1 - 2 \left(\frac{g_j(\mathbf{x}) - b_j}{d_j} \right)^2 & \text{si } b_j \leq g_j(\mathbf{x}) \leq \frac{b_j + 2d_j}{2} \\ 2 \left(\frac{g_j(\mathbf{x}) - (b_j + d_j)}{d_j} \right)^2 & \text{si } \frac{b_j + 2d_j}{2} \leq g_j(\mathbf{x}) \leq b_j + d_j \\ 0 & \text{si } g_j(\mathbf{x}) \geq b_j + d_j \end{cases} \quad (17)$$

where b_j and $b_j + d_j$ form an allowable fuzzy transition interval for the j th inequality constraint.

(4) Additional constraints: The ideal value of the degree of objective deviation in additional constraints is 0. Considering the collaborative relationship among objectives and their membership functions, the additional constraints are introduced by the following equality constraints:

$$w_i \left| \frac{f_i(\mathbf{x}) - f_i^{id}}{f_i^{id}} \right| = w_j \left| \frac{f_j(\mathbf{x}) - f_j^{id}}{f_j^{id}} \right|, \quad i \neq j \quad (18)$$

and

$$\sum_{i=1}^m w_i = 1. \quad (19)$$

The goal of adding additional constraints into the multiobjective optimization model is to make collaboration among the objectives. By doing so, not only the degree of importance deviation between each objective and its ideal value can be minimized.

(5) Establishing fuzzy multi-objective optimization model: The fuzzy multi-objective optimization model can be developed as follows:

$$\max \lambda$$

subject to

$$\lambda \leq \mu_{\tilde{f}_i}(\mathbf{x}), \quad i = 1, 2, \dots, m,$$

$$\lambda \leq \mu_{\tilde{h}_i}(\mathbf{x}), \quad i = 1, 2, \dots, I,$$

$$\lambda \leq \mu_{\tilde{g}_i}(\mathbf{x}), \quad i = 1, 2, \dots, J,$$

$$w_i \left| \frac{f_i(\mathbf{x}) - f_i^{id}}{f_i^{id}} \right| = w_j \left| \frac{f_j(\mathbf{x}) - f_j^{id}}{f_j^{id}} \right|, \quad i \neq j, \quad (20)$$

$$\sum_{i=1}^m w_i = 1,$$

$$0 \leq \lambda \leq 1,$$

$$x_k^l \leq x_k \leq x_k^u, \quad k = 1, 2, \dots, K.$$

Problem (20) and problem (8) converge to the same optimum solution with the specific objective weighting rank [5].

4 Numerical results

In this section we presented a numerical example for a standard schedule of bladder cancer. Table 1 shows the doses for this standard schedule \mathbf{C}_0 . It consists of four drugs that are delivered at days $t_1 = 0$, $t_2 = 1$, $t_3 = 14$ and $t_4 = 21$. According to this program, we obtain the following values for the objectives $f_1(\mathbf{C}_0) = 2.8990 \times 10^9$ cell·day and $f_2(\mathbf{C}_0) = 199$ mg. Considering a fluctuation equal to $\sigma = 0.03$, the following values $\kappa_1 = 0.0060$, $\kappa_2 = 0.0050$, $\kappa_3 = 0.0060$, $\kappa_4 = 0.0050$ and one of the weights varying between 0 and 1, we compute the Pareto front shown in the Figure 1. The schedule, \mathbf{C} , is obtained when $w_1 = 0.7$ and $w_2 = 0.3$, the objective functions in this case are: $f_1(\mathbf{C}) = 6.1240 \times 10^9$ cell·day and $f_2(\mathbf{C}) = 105,8433$ mg.

Figure 1 shows a numerical Pareto Front obtained varying a weight w_1 ($w_2 = 1 - w_1$) between 0 and 1 with $h = 1/30$. We resolve the problem 20 for each pair of weights.

If $p = (p_1, p_2) \in F(P)$ and $\left| \frac{df_2}{df_1}(p_1) \right| \gg 1$ or $\left| \frac{df_2}{df_1}(p_1) \right| \ll 1$ we have that considerable change in the objective 1 generates a small change in the objective 2 and viceversa. In these situations we can say that a objective can be significantly improved without the other worse. If $\frac{df_2}{df_1}(p_1) = m$ we have got that $\Delta f_2 \approx m \Delta f_1$. In the case where $m = -1$ an improvement in a objective implies that the other is worse in equal magnitude.

Table 1. Standard Schedule.

	Methotrexate	Vinblastine	Doxorubibin	Cisplatin
$t = 0$	30	0	0	0
$t = 1$	0	3	30	70
$t = 14$	30	3	0	0
$t = 21$	30	3	0	0

Table 2. Numerical Schedule.

	Methotrexate	Vinblastine	Doxorubibin	Cisplatin
$t = 0$	12.1277	0.9604	0.9382	0.9604
$t = 1$	0	0	7.6359	48.8883
$t = 14$	14.4183	0.9681	0.4673	0.5680
$t = 21$	14.8915	1.2856	0.8482	0.8854

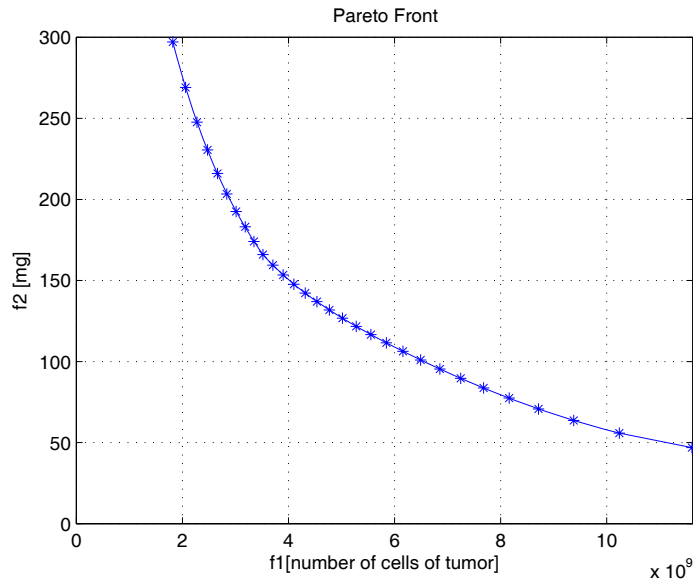


Figure 1

5 Conclusions

We generated a Pareto front whose elements are equivalent solution of optimization problem for chemotherapy schedules. Pareto front provides a set of possible schedules applicable to the cancer in question, in this case we consider a cancer of the bladder. Depending on the patient it is possible that we can choose the most convenient schedule varying the weights in the algorithms. As we can see the average tumor size, in numerical results, is of the same order as that achieved by the standard schedule, but the quantity supplied is lower.

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