ON THE CONTROL OF TUMOR GROWTH VIA TYPE-1 AND INTERVAL TYPE-2 FUZZY LOGIC

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Abstract

This paper deals with growth control of cancer cells population using type-1 and interval type-2 fuzzy logic. A type-1 fuzzy controller is designed in order to reduce the population of cancer cells, adjust the drug dosage in a manner that allows normal cells re-grow in treatment period and maintain the maximum drug delivery rate and plasma concentration of drug in an appropriate range. Two different approaches are studied. One deals with reducing the number of cancer cells without any concern about the rate of decreasing, and the other takes the rate of malignant cells damage into consideration. Due to the fact that uncertainty is an inherent part of real systems and affects controller efficacy, employing new methods of design such as interval type-2 fuzzy logic systems for handling uncertainties may be efficacious. Influence of noise on the system is investigated and the effect of altering free parameters of design is studied. Using an interval type-2 controller can diminish the effects of incomplete and uncertain information about the system, environmental noises, instrumentation errors, and etc. Simulation results confirm the effectiveness of the proposed methods on tumor growth control.

Keywords: Interval type-2 fuzzy control, type-1 fuzzy controller, cancer cells, drug schedule, Gompertzian model.

1. Introduction

Cancer is one of the leading causes of death in the world accounting for 7.6 million deaths (around 13% of all deaths) in 2008. Deaths from cancer worldwide are projected to continue rising, with an estimated 13.1 million deaths in 2030 according to WHO [1]. Surgery, radiotherapy and chemotherapy are the three major types of cancer treatment. Mathematical models and control theories can be employed to improve the quality of treatment and obtain systematic strategies of drug delivery.

Although, cancer is the third cause of death in Iran, its mortality is on the rise during recent decades. In Iran, breast cancer ranks first among cancers diagnosed in women, comprising 24.4% of all malignancies with a crude incidence rate and age-standardized incidence rate (ASR) of 17.4 and 23.1[2].

Findings by Mousavi et al. in 2007 showed that the incidence rate of breast cancer in women in Iran was 22 per 100,000 and the prevalence in this same population was 120 per 100,000. Stage I was diagnosed in 18%, stage II in 57% and stage III in 25% of the cases. About 72% of the patients were diagnosed with a tumor over 2 cm[3].

Stage II is divided into two subcategories which are known as IIA and IIB. If tumor size is less than 2 cm and/or lymph nodes are involved or tumor size is greater than 2 cm and no lymph nodes are involved, the stage is called IIA but if tumor size is between 2 and 5 cm and lymph nodes are involved by the disease or if tumor size is greater than 5 cm but no lymph nodes are involved, the stage is called stage IIB. Chemotherapy after surgery is one of the common treatments for patients suffering from this stage of breast cancer.

Chemotherapy is usually a combination of anti-cancer drugs. The majority of chemotherapeutic drugs can be divided into alkylating agents, anti-metabolites, plant alkaloids and other anti-tumor agents[4].

In this paper as a first step a type-1 fuzzy controller is designed based on a Gompertzian model suggested by Khaloozadeh et al. [4] for patients suffering breast cancer at stage IIB. In order to reduce the population of cancer cells, the fuzzy controller adjusts the drug dosage in a manner that allows normal cells re-grow in treatment period and maintain the maximum drug delivery rate in appropriate. In addition to the importance of reducing the population of cells, tracking a reference trajectory is useful to prevent drug resistance. Concurrently, normal cells are damaged after injection of drug, this stimulates the body to repair the normal cells, and so at the end of the chemotherapy period, it is expected to reach at a desired level of population for both normal cells and cancer cells. In order to prevent continuous infusion of drug doses, a semi-continuous protocol is suggested. Uncertainties in measuring or calculating the number of cells via instrumentation or observers in feedback control systems, justify applying new methods for compensating the imperfections of information. Upon this fact an interval type-2 controller is introduced to reduce the effect of uncertainties on the system.

Great efforts have been devoted to this area of research. One of the first researches devoted to optimizing cancer chemotherapy was conducted by Swan[5]. A logistic growth model was used to describe macroscopic tumor growth, and chemotherapeutic effects of anticancer agents were considered to be proportional to multiplication of drug concentration and tumor size and also saturable with respect to plasma concentration of drug. The objective was to
achieve homeostasis by continuously administering an intravenous drug. While this continuous type of treatment is not impossible, it may lead to toxicity and become preventively expensive[6].

In 1992 Martin developed an optimal control model of cancer chemotherapy to construct drug schedules that reduce effectively the size of a tumor after a fixed period of treatment. By imposing constraints to the assumed model, tumor size has been inevitably decreased at or faster than a specific rate[7]. In 2001 Pillis et al. introduced a competition model of cancer tumor growth that includes both the immune system response and drug therapy. It was a four-population model that includes tumor cells, host cells, immune cells, and drug interaction. One of their goals was to identify treatment protocols using optimal control theory that could improve standard pulsed chemotherapy regimens[8]. In 2003 Floares et al. presented an optimal control chemotherapy scheduling in cancer, using neural networks. Their proposed neural network methodology, feedback linearization, is capable of automatically finding the optimal solutions for complex cancer chemotherapy problems[9]. A study was done by Burden et al. in 2004 that dealt with a mathematical model for the dynamics between tumor cells, immune-effectors cells, and the cytokine interleukin-2 (IL-2). In order to better determine under what circumstances the tumor can be eliminated, they implemented optimal control theory to design the control functional to maximize the effectors cells and interleukin-2 concentration and to minimize the tumor cells[10]. Augilar et al. provided the description on the identification process for a particular cancer mathematical model under the immunotherapy treatment by differential neural networks (DNN) and sliding mode type observer techniques in their document in 2006[11]. In 2009 Ghaffari et al. published a document demonstrating benefits of the theorem of Lyapunov stability to design treatment strategies for drug protocols that ensure a desired rate of tumor cell kill and push the system to the area with smaller tumor cells[12]. Also some experimental studies have been conducted in this area. An investigation was reported by Harrold et al. in 2009 in which a new methodology via mixed integer programming was proposed. In this research clinical relevance of their new methodology was considered on a preclinical mouse model[13]. Also Simeoni et al. presented a minimal pharmacokinetic-pharmacodynamic model that links the dosing regimen of a compound to the tumor growth in animal models[14].

Most of the available studies in this area propose a continuous profile for drug concentration as in [7, 15, 16]. Although these control schemes are sophisticated, but they are based on an assumption which is not consistent with the real clinical constraints. However in 2008 Khaloozadeh et al. designed an optimal dosage programming using type-1 fuzzy controller for patients suffering from breast cancer in stage IIB[17]. In this study a profile with four discrete levels for drug dosage was suggested for different stages of treatment. Also, in another study published by them in 2008, they employed optimal control to find a single level of dosage for each cycle of chemotherapy[4].

Furthermore there are some other applications of Fuzzy techniques in the cancer detection process. For instance in a study by EtehadTavakol et al. [18] two color segmentation techniques of K-means and Fuzzy c-means are studied in the detection of the tumor region using infrared thermal images. These techniques are based on the fact that the temperature pattern for cancerous tissue is different than healthy one. Also in another study by Tan et al. [19] proposed a tool based on Fuzzy Neural Network method that provides intuitive fuzzy rules and human-like reasoning for thermogram analysis. Thermogram is a strong screening tool that can be used for detection of breast cancer in women 10 years in advance; however, the interpretation of the thermogram depends on the analysts and so it is error-prone.

This paper proposes an interval type-2 fuzzy logic to discuss cancer treatment problem and is organized as following. The first section provided an overview to the framework and importance of area under consideration. Mathematical modeling of the system is introduced in the next section. Synthesis of type-1 controller, type-2 controller and introducing performance criteria are presented in section three. Simulation results are demonstrated in the fourth section and finally conclusions are discussed in the last section.

2. Mathematical Model

Growth of cancer cells population for patients suffering from breast cancer stage IIB can be modeled by Gompertzian Eq. (1)[4].

\[
\frac{dN(t)}{dt} = \lambda N(t) \ln\left(\frac{\theta}{N(t)}\right)
\]  

(1)

Where \(N(t)\) represents the cancer cell population at time \(t\), \(\lambda\) is the tumor growth coefficient that is a positive coefficient and \(\theta\) is the maximum number of cancerous cell that can be achieved.

The effect of chemotherapy is added to the Gompertzian Eq. (1) by a killing term as presented in Eq. (2).

\[
\frac{dN(t)}{dt} = N(t)(\lambda \ln\left(\frac{\theta}{N(t)}\right) - k(c - \beta)H(c - \beta))
\]  

(2)

Where \(k\) is the constant of proportionality, \(c(t)\) is the concentration of drug (CAF) at time \(t\) in mg/ml, \(\beta\) is the threshold of drug concentration level at which cancer cells start to be killed and \(H\) is the Heaviside unit function that have the form of Eq. (3).

\[
H(c - \beta) = \begin{cases} 
1 & c(t) \geq \beta \\
0 & c(t) < \beta 
\end{cases}
\]  

(3)
Also in order to present a comparative analysis between two proposed controllers, the uncertainty was simulated introducing random number with normal distribution (dashed square in Fig. 1) before entering the feedback to the controller box. Output data is corrupted by using Eq. (4)[20].

\[ N = N (1 + 0.001 \text{randn}) \]  

where \( \text{randn} \) is a random real number with standard Gaussian distribution.

\[ \frac{\text{d}c}{\text{d}t} = u - \gamma c(t) \]  

Fig. 1. Block diagram of the system

Drug delivery rate of \( u \) in mg/ml ×Day\(^{-1} \) is correlated to the concentration of drug in mg/ml in circulatory system via dynamics given by Eq. (5).\( \gamma \) is a constant in Day\(^{-1} \).

Acute toxicity is reached when the concentration of drug in plasma exceeds a maximum allowable value. Also an upper bound shall be considered for drug administered to demonstrate that it can be effective in a particular range. Due to these facts, constraints on the system which prevent patient suffering side effects of drugs are introduced in the form of Eq. s(6)[4].

\[ 0 \leq u(t) \leq 50 \]
\[ 0 \leq c(t) \leq 50 \]  

A desired profile for cancer cell population during chemotherapy is presented by Eq. (7). Fig 2 shows the reference trajectory.

\[ y_r(t) = \frac{1}{2} \left\{ y(t_f) - y(t_z) \right\} \tanh \left( \frac{t}{T} - K \right) + y(t_f) + y(t_z) \]  

where

\[ y_r(t) = -\ln \left( \frac{N(t)}{\theta} \right) \]  
\[ y(t_f) = -\ln \left( \frac{N(t_f)}{\theta} \right) \]  
\[ y(t_z) = -\ln \left( \frac{N(t_z)}{\theta} \right) \]  

where \( t_z \) and \( t_f \) are initial and final time of chemotherapy, respectively. In order to avoid toxicity effects, a desired profile with 126 days of treatment is considered here.
On the other hand, normal cells are also attacked by the delivered drug. The Gompertzian model in the form of Eq. (11) is used to predict the normal cells growth.

\[ x(t) = x_\infty - (x_\infty - x_s) e^{-kt} \]  

where \( x(t) \) is the scaled normal cell population at time \( t \), \( x_\infty \) is the scaled asymptotic desired normal cell population and \( x_s \) is the initial scaled normal cell population, \( k \) is a growth parameter. A nonlinear transformation as demonstrated in Eq. (12) has been applied to normal cell numbers, \( n(t) \), which has rescaled the desired population of normal cells, \( n_{desired} \), to level zero.

\[ x(t) = \ln(n(t)/n_{desired}) \]  

It is assumed that a stimulator such as drug can destroy normal cells population and consequently re-growth process will be activated according to Eq. (12). In order to ensure remaining above the critical value of normal cells during chemotherapy, the effect of drug should be investigated during simulation. Drug perturbation model can be described by Eq. (13) where \( \rho_x \) is a sensitivity parameter indicating the effect of drug on normal cell population after administration of drug [21].

\[ \Delta x(t) = -\rho_x u \]
\[ x_s = x_\infty - \Delta x(t) \]  

The values of the parameters for a patient with breast cancer in stage IIB are displayed in Table 1.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
<th>Explanation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \lambda )</td>
<td>( 9.9 \times 10^{-4} \text{ (Day}^{-1}) )</td>
<td>Eq (1)</td>
<td>[4]</td>
</tr>
<tr>
<td>( k )</td>
<td>( 8.4 \times 10^{-2} \text{ (Day}^{-1}) )</td>
<td>Eq (2)</td>
<td>[4]</td>
</tr>
<tr>
<td>( \beta )</td>
<td>10</td>
<td>Eq (2)</td>
<td>[4]</td>
</tr>
<tr>
<td>( \gamma )</td>
<td>0.27</td>
<td>Eq (5)</td>
<td>[4]</td>
</tr>
<tr>
<td>( \theta )</td>
<td>( 10^{22} \text{ (Day}^{-3}) )</td>
<td>Eq (1)</td>
<td>[4]</td>
</tr>
<tr>
<td>( c(0) )</td>
<td>0 (mg/ml \times \text{Day}^{-1})</td>
<td>Eq (5)</td>
<td>[4]</td>
</tr>
<tr>
<td>( \rho_x )</td>
<td>0.78</td>
<td>Eq (12)</td>
<td>[4]</td>
</tr>
<tr>
<td>( k_1 )</td>
<td>-ln(1-log(2)/2)/2</td>
<td>Eq (11)</td>
<td>[4]</td>
</tr>
<tr>
<td>( x_\infty \text{(or } n_{desired}) )</td>
<td>0 (or ( 10^{10} ))</td>
<td>Eq (13)</td>
<td>[4]</td>
</tr>
<tr>
<td>( K )</td>
<td>1.5</td>
<td>Eq (7)</td>
<td>-</td>
</tr>
<tr>
<td>( T )</td>
<td>40 (Day)</td>
<td>Eq (7)</td>
<td>-</td>
</tr>
<tr>
<td>( N(t_0) )</td>
<td>( 10^{10} )</td>
<td>Eq (10)</td>
<td>[4]</td>
</tr>
<tr>
<td>( N(t_f) )</td>
<td>( 1.2641 \times 10^9 )</td>
<td>Eq (10)</td>
<td>[4]</td>
</tr>
</tbody>
</table>

3. Control Synthesis

The design procedure for two types of fuzzy controllers is discussed in this section. Firstly, a type-1 fuzzy controller is discussed and then an interval type-2 fuzzy logic is used to reduce the effect of uncertainties in tumor measurement. Finally, performance criteria for comparing two different types of controllers are discussed.

3.1. Type-1 fuzzy controller

The aim of using the fuzzy controller is to decide a value for the rate of drug delivery based on the population of cancer cells in the tumor burden. Initial number of cells is assumed to be \( 10^{10} \) which is the initial cancer cell population for...
patients in $T_3N_0M_0$ state (tumor $> 5$ cm, no tumor is in regional lymph nodes and no distant metastasis[22]) and the desired level for cancerous cells is $10^4$. The effect of immune response is not considered in this article but it is supposed that after decreasing the number of cells to the reference level, the immune system would be prepared to defense body against malignant cells. Simulation results for this approach are discussed in the next section.

Table 2 suggests some values of drug delivery rate according to population of cells. Regarding to the allowed range of drug delivery, thirty rules are generated with thirty Gaussian membership functions defined on the interval of cancer cell population. Centers of Gaussian membership functions for control input are defined based on the values given in Table 2. Fig. 3 illustrates some of the membership functions used for fuzzy type-1 approach.

![Type-1 membership functions](image)

**Table 2.** Drug delivery rate(mg/ml/Day) vs. cancer cells number

<table>
<thead>
<tr>
<th>$\pi$</th>
<th>$10^0$</th>
<th>$10^0$</th>
<th>$10^0$</th>
<th>$10^1$</th>
<th>$10^1$</th>
<th>$10^2$</th>
<th>$10^2$</th>
<th>$10^3$</th>
<th>$10^3$</th>
<th>$10^3$</th>
<th>$10^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\pi$</td>
<td>12</td>
<td>10.7</td>
<td>9.5</td>
<td>8.2</td>
<td>7.0</td>
<td>5.7</td>
<td>4.5</td>
<td>3.3</td>
<td>2.0</td>
<td>0.8</td>
<td></td>
</tr>
</tbody>
</table>

The following equation is used to determine the control signal based on the above membership functions.

$$ u = \frac{\sum_{i=1}^{10} \exp \left( \frac{(N - \bar{N}_i)^2}{2\sigma_i^2} \right)}{\sum_{i=1}^{10} \exp \left( \frac{(N - \bar{N}_i)^2}{2\sigma_i^2} \right)} $$

(14)

Although the above controller is able to reduce the size of tumor burden, there is no control on the decreasing rate for cancerous cells. So in order to control the decreasing rate, a reference trajectory for reducing the population of cells is applied in this study. In order to implement a fuzzy controller to track a reference trajectory, a modification term correlated to the distance of the path line from the reference curve is added to the control signal calculated by the aforementioned fuzzy control system.

### 3.2. Type-2 Fuzzy Controller

As described before, uncertainty is an intrinsic part of the real systems. Recently type-2 fuzzy sets, characterized by membership functions that are themselves fuzzy, have been attracting attentions. Interval type-2 (IT2) fuzzy sets as a special case of type-2 fuzzy sets are currently the most widely used for their reduced computational cost. Unlike fuzzy sets of type-1, membership of an IT2 fuzzy set has an interval. IT2 is especially useful when the membership functions cannot be exactly determined[23]. Extensive procedure of the typical computations in an IT2 fuzzy logic system is described in[23]. A summary of the method is presented here.

Consider the rule-base of an IT2 fuzzy logic system consisting of $N$ rules has the following form:

$$ R^n: \text{IF } x_1^r \text{ is } X_1^n \text{ and } ... \text{ and } x_j^r \text{ is } X_j^n \text{ THEN } y \text{ is } Y^n $$

$$ n = 1, 2, ..., N $$

$$ X_i^n (i = 1, ..., f) $$

$$ Y^n = \left[ \sum_{n}^{N^n}, \bar{r}^n \right] $$

(15)

Assume that $y$ is the output and the input vector is $x' = (x_1', x_2', ..., x_j')$:

1) Membership of $x_j'$ on each $X_j^n$ is computed as:
\( X^n_i = \left\{ \mu_{x^n_i}(x^n_i), \mu_{x^n_i}(x^n_i) \right\}, \)
\[ i = 1, 2, \ldots, I, \]
\[ n = 1, 2, \ldots, N \]

2) Firing interval, \( F^n(x') \), of the \( n^{th} \) rule is computed as:

\[
F^n(x') = \left[ L^n, \bar{L}^n \right], n = 1, 2, \ldots, N
\]

\[
L^n = \mu_{x^n,i}(x^n_i) \times \cdots \times \mu_{x^n,i}(x^n_i)
\]

\[
\bar{L}^n = \mu_{x^n,i}(x^n_i) \times \cdots \times \mu_{x^n,i}(x^n_i)
\]

3) Type reduction is performed as following:

\[
y_l = \min_{k \in \{1, N-1\}} \frac{\sum_{k=0}^{N-1} L^n_k y_k^N + \sum_{k=0}^{N-1} L^n_{k+1} \bar{y}_k^N}{\sum_{k=0}^{N-1} L^n_k + \sum_{k=0}^{N-1} L^n_{k+1}}
\]

\[
y_r = \max_{k \in \{1, N-1\}} \frac{\sum_{k=0}^{N-1} L^n_k y_k^N + \sum_{k=0}^{N-1} L^n_{k+1} \bar{y}_k^N}{\sum_{k=0}^{N-1} L^n_k + \sum_{k=0}^{N-1} L^n_{k+1}}
\]

One of the earliest type reduction algorithms, and also the most popular one, is the Karnik-Mendel algorithm, which is an iterative method. A comparison of type reduction algorithms is presented in [24]. The main idea of the KM algorithm is to find the switch points for \( y_l \) and \( y_r \).

4) Defuzzified output is computed as:

\[
y = \frac{y_l + y_r}{2}
\]

Fig. 4 illustrate some of the membership functions of interval type-2 used for simulations. Generally both mean values and variances of the Gaussian membership functions may be uncertain but in this study uncertainty is put on the variances of the membership functions. The width of uncertainty is assumed to be a design degree of freedom.

Fig. 4. Interval Type-2 membership functions

For the case in this study, as it was mentioned previously, thirty rules are defined for this study based on the values shown in Table2 and Gaussian membership functions are used. Assume that the input is cancerous cells population, \( N \), and the output is the control signal which is the drug delivery rate, \( u \). So the rule-base of an IT2 fuzzy logic system can be reformulated as below:

\[
R^n: IF N is N^n THEN u is U^n, \quad n = 1, 2, \ldots, 30
\]

\[
U^n = [U^n^-, U^n^+]
\]

So if a bandwidth of \( \alpha \) is considered, a fuzzy type-2 membership function can be developed as below for \( n=1 \):

The optimum value for the bandwidth will be calculated in the next section.
Firing interval, $F^n(N)$, of the $n$th rule is computed as:

$$F^n(N) = [\mathcal{L}^n, \mathcal{F}^n], \ n = 1, 2, ..., 30$$

$$\mathcal{L}_n = \mu^{-1}_{\mathcal{L}}(N)$$

$$\mathcal{F}^n = \mu^{-1}_{\mathcal{F}}(N)$$

Type reduction is performed as following:

$$u_i = \min_{k \in \{1, 30\}} \frac{\sum_{k=1}^{n} \mathcal{L}^n \sigma^+ \sum_{k=1}^{30} \mathcal{L}^n \sigma_- u^k}{\sum_{k=1}^{n} \mathcal{F}^n + \sum_{k=1}^{30} \mathcal{F}^n}$$

$$u_r = \max_{k \in \{1, 30\}} \frac{\sum_{k=1}^{n} \mathcal{F}^n \sigma^+ + \sum_{k=1}^{30} \mathcal{F}^n \sigma_-}{\sum_{k=1}^{n} \mathcal{L}^n + \sum_{k=1}^{30} \mathcal{L}^n}$$

Defuzzified output is:

$$u = \frac{u_i + u_r}{2}$$

The simulation results based on the above formulation is shown in the next section.

### 3.3. Performance Criteria

For evaluating the control system response, three widely used performance criteria as given by Eq. (25)-(27) are utilized.

1. ITAE (Integral of the Time multiplied by the Absolute value of the Error)

$$ITAE = \int_t^\infty t |e(t)| \, dt$$  \hspace{1cm} (25)

2. IAE (Integral of the Absolute value of the Error)

$$IAE = \int_t^\infty |e(t)| \, dt$$ \hspace{1cm} (26)

3. ISE (Integral of Square Error)

$$ISE = \int_t^\infty [e(t)]^2 \, dt$$ \hspace{1cm} (27)

Error participates differently in each criterion. For instance larger values of error affect ISE more than IAE. Also in ITAE, time appears as a factor, and therefore, ITAE will penalize heavily errors that occur late in time but virtually ignore errors that occur early in time[25]. These criteria are broadly used for PID controller tuning but in this article these are utilized as an indication to compare controllers’ performance.

### 4. Results and Discussion

Simulation results for a system with parameters, presented in Table 1 are illustrated and discussed in this section. Firstly, an optimum parameter is found for the width of uncertainty in the variance of type-2 membership functions. Performance of type-1 and type-2 controllers for the disturbed system is demonstrated in the second subsection. Furthermore, a tracking trajectory problem also is solved and a comparison between type-1 and type-2 controller is
given in the third subsection. All the results are in the continuous form but continuous approach is difficult and expensive from clinical point of view. As a result a semi-continuous approach is introduced in the last subsection.

4.1. Optimum parameter of type-2 membership functions
To find a suitable width of uncertainty in membership functions, performance of IT2 controller is examined via changing width of uncertainty. Mean value, variance, mean squared error (MSE) and sum squared error (SSE) are evaluated during an interval of time for a noise induced system. Fig. 5 displays that an optimum point can be found for the width of uncertainty.
In the figures, width of uncertainty represents a fractional part of variance which is subtracted and added to it to produce an interval for uncertain variance.
The optimum point of performance which equals 0.75, found in this section is utilized for the type-2 controller in the following subsections.

![Fig. 5. Left column shows Mean and Variance of error for type-2 controller with different width of uncertainty (u_{sig}) and Right column shows MSE and SSE of error.]

4.2. Type-1 and Type-2 fuzzy controllers
Results of the type-1 and type-2 controllers on the disturbed system are presented in Fig. 6 to Fig. 9. At the end of the treatment (84 days), the cancer and the normal cell population reaches desired level. Rate of drug delivery is in the allowed range and maximum plasma concentration of drug is below the permitted limit according to constraints given in Eq. (6) which restricts toxicity effects. In spite of acceptable results, there is no control on the rate of cell number reduction. Tracking a trajectory for the reduction of cell population is preferred.
4.3. Trajectory tracking

A desired profile for reducing cancer cell number was introduced in second section, mathematical model. Regarding toxicity effects mathematical approaches suggest a total period of 126 days for the tracking problem. Simulation results in Fig. 10 to Fig. 13 show that cancer cells population track the trajectory and normal cells reach the desired level for both controllers. Rate of drug delivery is in the allowed range and maximum plasma concentration of drug is below the acceptable limit according to constraints given in Eq. (6) which restricts toxicity effects. In comparison with the previous simulation, tracking a trajectory reduces maximum level of drug concentration about 5 mg/ml. A total period of 126 days is recommended in this section.

In order to clarify comparison between two controllers, plots of error, ITAE, ISE and IAE, are displayed in Fig. 14 to Fig. 17. Also Table3 shows a summary of the final values for ITAE, ISE and IAE. In all cases type-2 shows a better performance although the difference is not significant. It is worthwhile to note that magnitude of order for error values is changing broadly through the simulation. Also, higher order values of error which have greater effects on the value of integration over the time, occur at a short period of time and at the beginning of simulation. Subsequently ITAE, ISE and IAE values do not change significantly as it is expected.

As discussed previously a single input fuzzy controller is used in this work. Another alternative to solve the trajectory tracking problem is using a fuzzy system with two inputs including error and its derivative. Note that designing a single input controller with a modification term simplifies the fuzzy rule base and reduces computational costs relative to multi input approaches.

<table>
<thead>
<tr>
<th>Approach</th>
<th>ITAE</th>
<th>ISE</th>
<th>IAE</th>
</tr>
</thead>
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<tr>
<td>Fuzzy Type 1</td>
<td>2.42 x 10^{10}</td>
<td>3.38 x 10^9</td>
<td>10.4 x 10^{17}</td>
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<tr>
<td>Fuzzy Type 2</td>
<td>2.2 x 10^{10}</td>
<td>3.25 x 10^9</td>
<td>10.2 x 10^{17}</td>
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</table>
Fig. 10. Cancer cell population vs. time for type-1 and type-2 controller (tracking trajectory)

Fig. 11. Normal cell population vs. time for type-1 and type-2 controller (tracking trajectory)

Fig. 12. Control signal (mg/ml × Day⁻¹) vs. time for type-1 and type-2 controller (tracking trajectory)

Fig. 13. Plasma concentration (mg/ml) vs. time for type-1 and type-2 controller (tracking trajectory)

Fig. 14. Error vs. time for type-1 and type-2 controller (tracking trajectory)

Fig. 15. ITAE criterion vs. time for type-1 and type-2 controller (tracking trajectory)
4.4. Suggesting a clinical treatment profile (Intravenously administration of drug)

Simulation results in the previous subsections demonstrate a continuous decreasing profile of drug delivery rate which is not practical for clinical applications. As indicated before, achieving a practical and systematic drug delivery schedule considering necessary constraints is highly appreciated. Oncologists administer chemotherapeutic drugs follow standard regimens; often these are cycles of 21 or 28 days in length. To obtain more accurate performance, the whole period of treatment is divided into six subsections in this article. The proposed drug doses are constant values at each period to avoid complexity of infusion process. Finally the suggested protocol is implemented in simulations and the results are analyzed. According to Fig. 18 to Fig. 21 normal cell and cancer cell population have a suitable condition. Moreover plasma concentration and drug dosage are in the allowable range.

5. Conclusions
The objective of this work was to solve model-based cancer treatment problem. It was shown that a fuzzy controller using expert knowledge can be applicable to control the population of cells thus this method can be a basis for preparation of a package that assists the clinicians to choose an efficient and methodical dosage program. Strong effect of expert knowledge on the dose selection is one of the most important benefits of fuzzy methods.

Significance of this method was tested on a model suggested by Khaloozadeh [4] for breast cancer. Cancer and normal cell population were considered in this model. Drug toxicity was checked at the end of the simulation.

Utilizing a type-2 fuzzy controller can reduce the effect of uncertain information about the system which is an important issue in model-based controller designs. Application of this control theory was shown on the mentioned cancer model in this study.

Simulation results illustrated that transformation of a continuous drug delivery profile into a semi-continuous curve not only made the presented protocol more clinical but also generated no significant change on the reduction of cancer cells population and normal cell re-growth dynamics.

References