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Adaptively adjusted footprint of uncertainty in interval type 2 fuzzy controller for cancer drug delivery

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Abstract

This paper presents chemotherapy scheduling of cancer patients using type 1 and type 2 fuzzy logic controllers which are optimized by genetic algorithm. To handle the uncertainties of the model, we introduce a method to adjust the foot print of uncertainty (FOU) in interval type 2 (IT2) fuzzy systems based on the amount of uncertainty. Based on previous researches, type two fuzzy logic is more effective than type 1 in handling uncertainties in a model. According to this fact, proposed method tries to change the FOU of fuzzy sets adaptively based on the amount of uncertainty in counting tumor cells which always exist in real world. In addition, we have introduced two new indices to evaluate the results. Simulation results show that the proposed method can control the drug regimens better than IT2 and type 1 (IT1) fuzzy controllers.

Keywords: Drug regimens; Footprint of Uncertainty; Interval Type 2 Fuzzy Controllers

1. Introduction

Cancer is one of the most dangerous diseases which causes many deaths every year. Although new medical methods such as gene therapy and immunotherapy have been developed by scientists in recent years, these methods are still in their infancy. Different ways such as surgery, chemotherapy, radiation, and hormone therapy have been used in treatment of cancer. Chemotherapy is still one of the most effective methods in this field although it has many side effects such as toxicity and drug resistance [1]. Therefore the dosage of the therapy must be carefully adjusted in order to cause the minimum damage to healthy tissue whilst killing a maximum number of tumor cells [2]. In this field, feedback control theory can be applied to optimize the dosage of the therapy. Different approaches are introduced in modelling of the growth of tumor and normal cells. Some of these models were based on cellular automata [3-4] and some of them are introduced based on PDE's and cellular automata [5-6].

Mathematical models and control theories can be employed to improve the quality of treatment and obtain

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systematic strategies of drug delivery. In one of the first efforts in this way, Swan used a logistic growth model to optimize the drug delivery of treatment procedure [7]. Later, Martin developed an optimal controller to schedules the drug delivery for a patients [8]. Competition model of cancer tumor based on immune system response and drug therapy which includes tumor cells, immune cells, host cells and drug interaction has been introduced by Pillis where optimal control theory was used to optimize chemotherapy regimens [9].Neural network was applied in a study for optimizing drug delivery based on feedback linearization by Floares [10]. Maximizing the effectors cells and interleukin-2 concentration has been considered in drug delivery optimization by Burden [11]. Lyapunov stability theorem has been applied in a closed loop control system proposed by Ghaffari to push the system to the area with smaller tumor cells [12]. Fuzzy logic was also applied in dosage optimization by Khaloozade [13]. Gompertzian model of tumor growth was used in optimization a cost function which considered the number of tumor and healthy cells simultaneously. Recently, a multi approach model introduced by Westman et al [1] has been used by Batmani and Khaloozade [15]. In this model a compartmental model was extended to appropriately describe drug resistance and two constraints were imposed on the value of the anticancer drug dynamics to avoid toxicity [14]. In this paper, we propose a simple method to adjust the footprint of uncertainty (FOU) of IT2 adaptively (called AIT2) based on the amount of uncertainty generated in counting the number of tumor cells.

This paper is organized as following. The second section provides an overview to the mathematical frameworks including patient's model and adjustable interval type 2 fuzzy controllers. Proposed model of the system is introduced in the third section. Simulation results are demonstrated in the fourth section and finally conclusions are discussed in the last section.

2. Mathematical Framework

2.1. Westman's Model

In Westman's model each cell has four phases (called G1, S, G2 and M) in its life cycle. In G1, protein and RNA synthesis are active and consequently DNA is produced in phase S. In G2 phase, duplicated chromosomes are condensed and finally nuclear and cytoplasmic divisions occur in phase M. Based on the cell cycle, tumor cells which might be sensitive or resistant to the drug are divided into the two groups P and C in Westman's model. Four compartments are defined which compartments Ps and Pr belong to the group P (sensitive and resistant cells respectively) and compartment Cs and Cr belong to the group C (sensitive and resistant cells respectively).Dynamic equations (1) describe the mathematical models of these compartments and their interactions.

$$\frac{dP_s(t)}{dt} = \Big(\big(1-\alpha_s-\mu_{P_sC_r}-\mu_{P_sP_r}\big)P_s(t)+\mu_{P_rP_s}P_r(t)\Big)F+\beta_sC_s(t)-\delta_{P_s}P_s(t)+\Big(-\mu_{P_sP_{r,d}}P_s(t)+\beta_{s,d}C_s(t)-K_{p,d}P_s(t)\Big)W(drug)$$

$$\frac{dP_r(t)}{dt} = \Big(\big(1-\alpha_r-\mu_{P_rC_s}-\mu_{P_rP_{sr}}\big)P_r(t)+\mu_{P_sP_r}P_s(t)\Big)F+\beta_rC_r(t)-\delta_{P_r}P_r(t)+\Big(-\mu_{P_sP_{r,d}}P_s(t)+\beta_{r,d}C_r(t)-K_{p,d}P_s(t)\Big)W(drug)$$

$$\frac{dC_s(t)}{dt} = \Big(\alpha_sP_s(t)+\mu_{P_rC_s}P_r(t)\Big)F-\beta_sC_s(t)-\delta_{C_s}C_s(t)-\big(\beta_{s,d}+K_{C,d}\big)C_s(t)W(drug)$$

$$\frac{dC_r(t)}{dt} = \Big(\alpha_rP_r(t)+\mu_{P_sC_r}P_s(t)\Big)F-\beta_rC_r(t)-\delta_{C_r}C_r(t)-\beta_{r,d}C_r(t)W(drug)$$

$$F=\lambda\log\left(\frac{K}{P_s(t)+P_r(t)+C_s(t)+C_r(t)}\right) \quad (1)$$

Parameters in the mathematical model are listed in table 1. Initial values of differential equations are $P_s(0)=1$, $P_r(0)=C_r(0)=C_s(0)=0$. (Note: if drug delivery time is considered as $t=0$, initial values will be changed. In this paper the initial values are considered 600 days after the cells are located in propagation phase which are about $P_s(0)=1.4\times10^{10}, P_r(0)=60, C_r(0)=15.5, C_s(0)=3.7\times10^9$). Drug delivery in (1) is determined by following equation [15]:

$$W(drug) = k(c(t) - \sigma)H(c(t) - \sigma) \quad , \quad H(x) = \begin{cases} 1; & x > 0 \\ 0; & x \leq 0 \end{cases} \tag{2}$$

where $c(t)$ is drug concentration which can be realized such as $\frac{dc(t)}{dt} = u(t) - \gamma c(t)$. In this equation $\gamma = 0.27$ is a constant related to the drug elimination rate and $u(t)$ is drug delivery rate which should be less than 2 $Day^{-1}\, ml/mg$ at each cycle of chemotherapy [14].Total number of tumor cells is calculated by $NT_1(t) = P_s(t) + P_r(t) + C_s(t) + C_r(t)$.

2.2. Healthy Cells

Gompertzian model is considered for the number of healthy cells. Proposed model is as follow [10]:

$$\frac{dx(t)}{dt} = \lambda_x \log\left(\frac{x_\infty}{x(t)}\right) x(t) - k_x c(t) x(t) \tag{3}$$

where $\lambda_x = 02128\ Day^{-1}$, $k_x = 0.78\ Day^{-1}\, ml/mg$, $x_\infty = 10^{12}$, $x(0) = 10^{12}$ and $x(t)$ is the number of normal cells at time $'t'$.

Table 1. Parameters of Westman's Model

Parameter		Parameter		Parameter		Parameter	
$\boldsymbol{\alpha_s = \alpha_r}$	0.2	$\mu_{P_s C_r}$	10^{-11}	β_s	$10^{-10}\ Day^{-1}$	$\beta_{s,d}$	$0.5 ml/mg$
$\boldsymbol{\mu_{P_r C_s}}$	10^{-11}	$\delta_{P_s} = \delta_{P_r}$	$0.0192\ Day^{-1}$	K	$5 \times 10^{14}\ Cells$	$\mu_{P_s P_{r,d}}$	$5 \times 10^{-9}\ ml/mg$
$\boldsymbol{\mu_{P_s P_r}}$	10^{-10}	$\delta_{C_s} = \delta_{C_r}$	$0.0173\ Day^{-1}$	λ	$0.00396\ Day^{-1}$	$K_{p,d}$	$0.98\ ml/mg$
$\boldsymbol{\mu_{P_r P_s}}$	10^{-10}	β_r	$10^{-10} Day^{-1}$	$\beta_{r,d}$	$0.5\ ml/mg$	$K_{c,d}$	$0\ ml/mg$

2.3. Fuzzy Controllers

Fuzzy systems and fuzzy controllers have been widely used in industrial and biological systems. Type-2 fuzzy logic was introduced by Zadeh [15] and has been applied in widespread applications in the recent years [16-19]. Type-2 fuzzy set $\tilde{A}$ is characterized by a type-2 membership function $\mu_{\tilde{A}}(x,u)$ such as:

$$\tilde{A} = \{\big((x,u), \mu_{\tilde{A}}(x,u)\big) \big| \forall x \in X, \forall u \in [0,1], \mu_{\tilde{A}}(x,u) \in [0,1]\} \tag{4}$$

To reduce the computational cost, interval type-2 fuzzy system (IT2-FS) which assumes interval membership grades for each type-2 fuzzy set, has been applied in this work [20]. Similar T2-FLS, the membership functions of IT2-FLS includes an uncertainty area, called footprint of uncertainty (FOU) (Fig. 1).

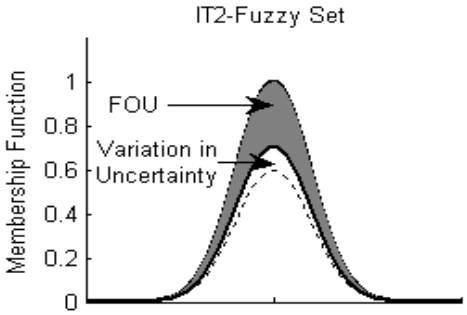

Fig. 1 Foot Print of Uncertainty

The i^{th} $(i = 1,2, \dots, R)$ rule of a typical IT2-TSK model is as follow:

$$If\ x_1\ is\ A_1^i\ and\ x_2\ is\ A_2^i\ and \dots x_n\ is\ A_n^i\ then\ y_i = a_0^i + a_1^i x_1 + \cdots + a_n^i x_n$$

where A_j^i and x_j are j^{th} $(j = 1,2, \dots, n)$ IT2 membership function and j^{th} input respectively, output coefficients $a_{\bar{k}}^i$ $(\bar{k} = 0,1, \dots n)$ are IT2 factors in range $[\underline{a}_{\bar{k}}^i, \bar{a}_{\bar{k}}^i]$ to handle the uncertainty in the outputs. Final output is equal to:

$$Y = \frac{Y_l + Y_r}{2} \text{ where } Y_l = \min_{\substack{\forall Y \\ \forall \mu}} \frac{\sum_{i=1}^{R} y_i \mu_i}{\sum_{i=1}^{R} \mu_i} \text{ and } Y_r = \max_{\substack{\forall Y \\ \forall \mu}} \frac{\sum_{i=1}^{R} y_i \mu_i}{\sum_{i=1}^{R} \mu_i} \tag{5}$$

Karnik-Mendel algorithm [16] should be applied to find Y_l and Y_r in (5). In above equation, we have $\mu_i \in [\underline{\mu}_i, \overline{\mu}_i]$,$Y_i \in [\underline{y}_i, \overline{y}_i]$ $(\underline{\mu}_i = \min(\underline{A}_1^i(x_1), \underline{A}_2^i(x_2), \dots, \underline{A}_n^i(x_n))$ and $\bar{\mu}_i = \min(\bar{A}_1^i(x_1), \bar{A}_2^i(x_2), \dots, \bar{A}_n^i(x_n))$) where $\underline{A}_j^i(x_j)$ and $\bar{A}_j^i(x_j)$ are minimum and maximum range in FOU of j^{th} membership function in i^{th} rule of IT2-TSK model. In this paper, FOU is adaptively adjusted by an uncertainty factor (U_f) as determined in (14) for antecedent parts and consequent parts of the rules:

$$\underline{A}_j^i(x_j) = (0.8 - U_f) \times \bar{A}_j^i(x_j) \text{ and } a_{\bar{k}}^i \in [\bar{a}_{\bar{k}}^i \times (0.8 - U_f), \bar{a}_{\bar{k}}^i], (\bar{k} = 1, \dots n) \tag{6}$$

where $U_f \epsilon [0,0.6]$ is a bounded factor. It is clear that larger U_f gives larger area in FOU.

3. Proposed Model

Fig. 2 shows the proposed model for drug delivery controller with adaptive FOU.

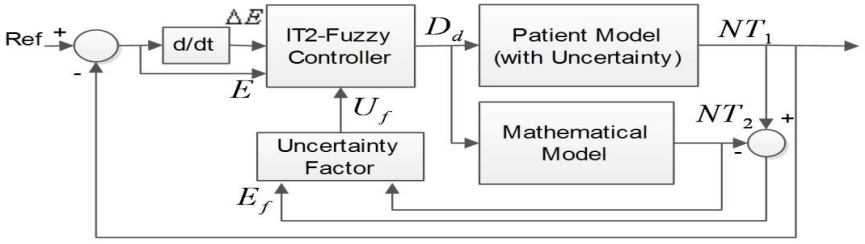

Fig. 2 Block Diagram of the Proposed Model

In this figure, fuzzy controller has two inputs: scaled error (E) between reference amount of tumor cells (10^4) and number of tumor cells estimated in the body of patient (NT_1) and change of error (ΔE) .Fuzzy rules are formed as (7):

$$if\ E\ is\ A_e^i\ and\ \Delta E\ is\ A_{\Delta e}^i\ then\ D_d^i = a_0^i + a_1^i\ E + a_2^i\ \Delta E \tag{7}$$

where D_d^i is drug delivery of i^{th} rule, A_e^i and $A_{\Delta e}^i$ are IT2 Gaussian membership functions of error and change of error respectively and a_j^is are output coefficients of consequent part of the rules. Error and change of error have been calculated every 14, 21 or 28 days after chemotherapy and scaled such that $-1 \le E \le 0$ and $-0.5 \le \Delta E \le 0.5$ where are fuzzified by five fuzzy sets VL, L, M, H and VH for each of them (Note: since the number of tumor cells is often more than reference value (10^4), error is a negative value). In this block diagram, it is supposed that the patient model is constructed by mathematical model plus a random uncertainty factor (α_u) such that $NT_1 = (1 + \alpha_u) \times NT_2,\ \alpha_u \in [-0.5\ , 0.5\ ]$ (this is because of some error in counting the tumor cells).

As it is shown in equation (6), the FOUs of membership functions of error (E), change of error (ΔE) and their coefficients in antecedent part are changed adaptively dependent to the uncertainty factor U_{f_E} and $U_{f\_\Delta E}$. The idea of adjusting the FOU is based on this fact: more uncertainty in the model, larger FOU. For this reason following equation has been used to adjust the FOUs by U_{f_E} and $U_{f\_\Delta E}$:

$$U_{f\_E} = \min(\frac{|NT_1 - NT_2|}{NT_2} = \frac{|E_f|}{NT_2},\ 0.6)\ ,\quad U_{f\_\Delta E} = \min(|\rho(t) - \rho(t-1)|,\ 0.6) \tag{8}$$

where NT_1 and NT_2 are the number of tumor cells of patient and mathematical model of patient (which is expected to be true) respectively (Fig. 2). More difference between NT_1 and NT_2 causes larger U_f which in turn expands FOU by equation (7). In (8), $\rho(t)$ is equal $\frac{|NT_1 - NT_2|}{NT_2}$ in time $'t'$ where $\rho(0) = 0$. Regardless of type 2 fuzzy model, genetic algorithm has been used to determine the parameters of fuzzy rules (Centers and standard deviations of Gaussian functions in antecedent parts and output coefficients (a_j^i) in consequent parts) by minimizing a cost function.

4. Results

GA has been used to set the unknown parameters of fuzzy model to optimize the following cost function:

$$J = \mathrm{w}_1 \log(J_1) + w_2 \log(J_2) \tag{9}$$

where $J_1 = \int (NT_1 - 10^4)^2 dt, J_2 = \int (x(t) - 10^{12})^2\ dt, x(t)$ is the number of healthy cells in time $'t'$ (equation 3), 10^4 and 10^{12} are desired amounts of number of tumor and healthy cells respectively (Note: we use logarithmic function in cost function to close J_1 and J_2 to each other). The weights w_1 and w_2 are coefficients that according to the patients are determined by physicians and $w_1 + w_2 = 1$. In this paper, we set $w_1 = 0.95$ and $w_2 = 0.05$. IT1 (interval type 1) and IT2 membership functions of variables have been shown in Fig. 3. Model performance has been evaluated in three different chemotherapy period (14, 21 and 28 days). Type 1 (IT1), interval type 2 (IT2) and adaptive interval type 2 (AIT2) fuzzy models have been compared with two criteria: S_D (sum of delivered dosage in 84 days) and R_{TN} (rate of tumor cells to normal cells) determined by (18).

$$R_{TN} = \frac{NT_1(t=84)}{x(t=84)} \tag{10}$$

where $NT_1(t = 84)$ and $x(t = 84)$ are number of tumor and normal cells at the final day.

Tumor and normal cells of three chemotherapy period by IT1 controller are shown in Fig. 4. With regard to some error in counting the number of tumor cells in real case, the difference between patient's model and mathematical model is shown in this figure. The model is evaluated with three types of controllers IT1, IT2 and AIT2. Since α_u is a uniform random value, all types of controllers are evaluated 30 times and the mean of S_D and R_{TN} are given in table 2. As it is given in table 2, in all cases of controllers, R_{TN} of AIT2 model is less than the others which shows that the adaptive change in FOU could increase the dosage and decrease the number of tumor cells. In addition, the results shown in table 2, illustrate the superiority of IT2 model compared with IT1.

Table 2. Simulation Results at the Last Day (t=84)

	Chemotherapy period=14			**Chemotherapy period=21**			**Chemotherapy period=28**			
	IT1	IT2	AIT2	IT1	IT2	AIT2	IT1	IT2	AIT2	
S_D	7.1634	7.5357	7.5716	5.6135	5.8045	5.8220	4.8302	4.9230	4.9275	$\times 1$
R_{TN}	1.887	1.0325	0.95877	20.676	13.532	13.013	72.787	58.463	57.585	$\times 10^{-7}$
NT_1	0.12956	0.067512	0.062451	1.8781	1.2140	1.1656	7.1042	5.6901	5.6036	$\times 10^{6}$
x	6.8644	6.5385	6.5134	9.0836	8.9713	8.9572	9.7610	9.7334	9.7321	$\times 10^{11}$

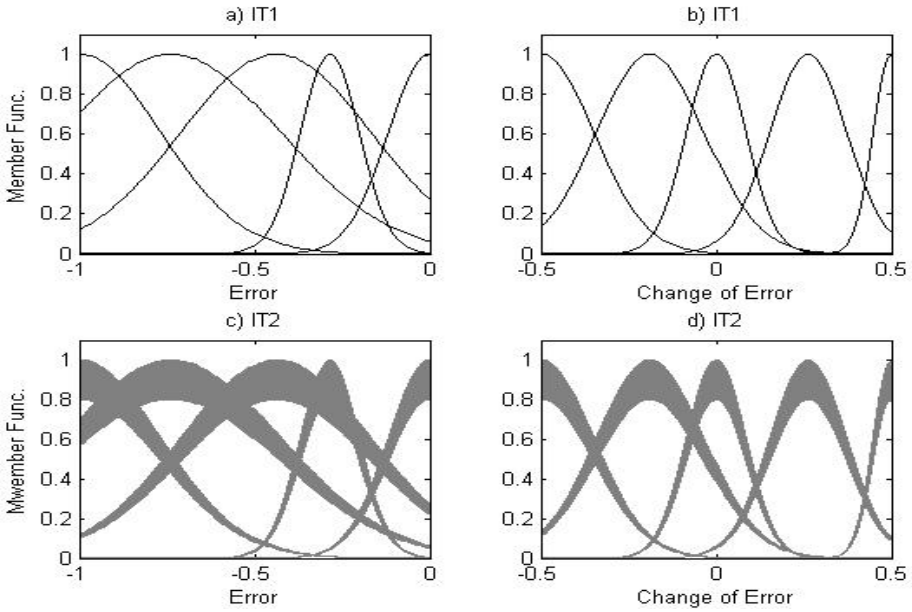

Fig 3. Membership Functions of Error (a and c) and Change of Error (b and d)

5. Conclusion

In this paper, adaptive FOU of type 2 fuzzy model (AIT2) has been considered. We proposed a method to adjust the FOU of membership functions regarded to the uncertainty in the model. Proposed method and new defined indices are evaluated by patient's model under chemotherapy. The performance of IT2 and IT1 models are also compared in this paper. Results show the superiority of AIT2 compared to IT2 and IT1 models. In fact, it is shown that in the selected model, the area of FOU can be adaptively changed regarded to the amount of uncertainty to improve the defined indices. In future, proposed method can be evaluated by other bio or industrial systems. More researches are needed to verify the relation between area of FOU and uncertainty in the industrial model.

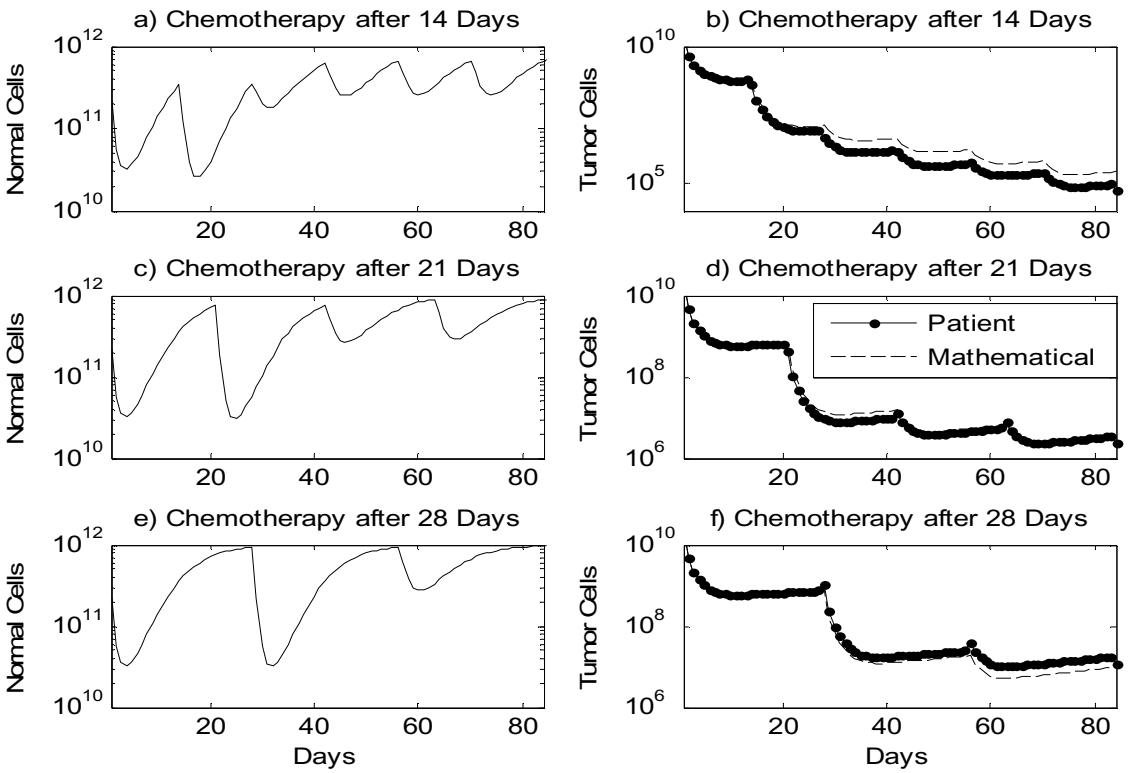

Fig.4 Number of normal cells (a, c, e) and tumor cells (b, d, f) for 14, 21 and 28 days of chemotherapy period. (b, d and f) show different between mathematical and patient model.

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