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Intuitionistic Fuzzy Control of Different Stratgies for Cancer Treatment

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Abstract: **Chemotherapy is one of the most effective treatment methods for cancer patients. An intuitionistic fuzzy logic control (IFLC) of chemotherapy drug delivery system is presented in this paper. An Ant Colony Optimization (ACO) algorithm is utilized to optimize the intuitionistic fuzzy input-output scaling factors of the drug infusion system. The controller is designed and tested for tracking two clinically relevant chemotherapy dose scheduling protocols. Moreover, the patient safety is implied in the design of our controller by considering maximum allowed level constraints on both drug infusion dose and drug-dose toxicity. The obtained results from the optimized control system are compared with the previous studies. The application of the developed controller resulted in lowering the number of remaining cancer cells to 0.1856. with the highest performance index of 29.31.**

Key words: Cancer Treatment; Chemotherapy; Drug Delivery System; Adaptive intuitionistic Fuzzy; Ant Colony Optimization.

1. INTRODUCTION

Cancer is a fetal disease, where number of abnormal cells start to be out of control and unfold into encompassing vital tissues. Cancer is one of the world's leading causes of mortality rates and death, with approximately 1,762,450 new cancer cases and 606,880 cancer deaths are estimated to happen in the United States [1] in 2019 . There are many techniques current used to tackle cancer, like surgery, radiation and chemotherapy.

Chemotherapy is an effective treatment type for fast spreading cancer. On the other hand, both surgery and radiation therapy remove, kill, or damage cancer cells in a specific area [2]. Use of chemotherapy drugs interrupts the cancer cell growth. Nevertheless, chemotherapy has two remarkable drawbacks that are drug resistance and the toxicity of drug [3]. All chemotherapy not only kill the cancerous cells, but they also have a bad effect on normal cells and destroy them. In contrast, inappropriate chemotherapeutic drugs can cause mutation of tumor cells.

The injection of chemotherapeutic agents into vein of the patient is referred to the intravenous chemotherapy clinical treatment. While drug dose scheduling plays a significant role to achieve an equilibrium between sparing the normal cells and killing the cancer cells with minimum level of toxicity and drug resistance impact [4]. The traditional intravenous infusion systems consist of a fluid container, administrator set, and a clamp to control the flow rate from the set to the patient. The major difficulty with this infusion system is that the flow cannot be accurately controlled and are always prone for human errors. To overcome this inaccuracy problems, electronic drug delivery systems are often used to regulate infused drug dose during chemotherapy sessions [5].

Mathematical modelling and control methods can be used to identify appropriate drug dose schedules for cancer treatment. Swierniak et al [6] and Araujo et al [7] provide reviews of how mathematical models were used to develop chemotherapeutic treatment schedules.

Drug resistance and toxicity, as already mentioned, are two significant issues that limit chemotherapy treatments. However, some earlier studies only took one of them into account. Batmani and Khaloozadeh [8] found certain optimal treatment regimens for cancer patients. But in their study, they did not consider the issue of drug resistance. Khaloozadeh et al. [9] achieved the best drug regimens taking into account two target functions to minimize the number of tumor cells and to protect normal cells. However, the drug resistance was also ignored in their models.

Martin [10] introduced an optimal chemotherapy drug scheduling model and solved it by applying nonlinear programming techniques. But he found difficulty while using these nonlinear techniques and hard to get a simplistic optimal control solution for all cancer chemotherapy drug scheduling problems. Tan et al [11] proposed a distributed evolutionary software that obtains automated solutions to the complex problem for the scheduling of chemotherapies. Liang et al. [12] updated the response model for chemotherapy in [10], because the drug toxicity modelling did not conform to relevant clinical work. This research team has been successful in achieving better outcomes by optimizing the schedule of chemotherapeutic agents using developed evolutionary algorithm; namely adaptive elitist-population-based genetic algorithms (AEGA) under specific toxicity tolerance [13]. Batmani et al. [14] extended the model proposed by Westman et al [15] to forecast the dynamics of tumor growth in the presence of chemo treatment and

then used Non-dominated genetic sorting to fix the problem of bi-objective optimization. Other methods have also been used for the treatment of cancer chemotherapy, such as improved immune algorithms [16] and the Multi-Objective Evolutionary Approach (MOEA) [17].

But these open-loop systems for medication delivery can't cope with patient variability. Moreover, they can't handle any unforeseen health circumstance, such as a rise in drug toxicity in the human body. In contrast, closed loop systems [18-20] contain a feedback mechanism, more accurate, robust in the existence of non-linearity and external noise sources. According to these features, closed loop control systems present a good alternative to safely achieve cancer chemotherapy treatment goals. Algoul et al. [21] applied PID and IPD controllers with a multi-objective genetic algorithm in the closed loop chemotherapy system to adjust controller parameters. The optimized PID controller was applied successfully to Martin's chemotherapy response model. However, one suitable solution for PID parameters must be carefully chosen from several optimal Pareto solution sets. Khadraoui et al [22] applied two PID controllers on a modified Martin's chemotherapy model to control both toxicity and drug concentration in patient body. But the authors in [21, 22] used conventional controller that usually does not obtain satisfactory performance under parameter variations [23].

Fuzzy logic controllers can work with imprecise inputs, handles non-linearities and is more robust than conventional controllers[24]. Fuzzy PID controllers have self-tuning ability and on-line adaptation to nonlinear, time varying, and uncertain systems [25]. However, fuzzy sets suffer from the restriction of the uncertain element because the lack of information. Uncertainty is an inseparable aspect of medical problems [26]. Among extensions of fuzzy sets, Atanassov's intuitionistic fuzzy sets [27] provide an intuitive structure for dealing with ambiguity from imprecise knowledge by taking non-membership into account as well as membership values.

In this study, a PID-like IFLC controller is utilized to control chemotherapy drug delivery system in a closed loop. An ACO optimization is used to tune the controller's parameters to achieve the best results from drug infusion process. Also, the control system is designed to achieve both clinical and cancer therapy needs.

The following is the organization of this paper. Section 2 explains the cancer chemotherapy drug scheduling model and the controller design in the closed loop infusion system. Section 3 presents the results of the developed control system and compares them with the results of previous works. Discussion is given in Section 4. Section 5 presents conclusion and comments on future work.

2. MATERIALS AND METHODS

2.1 patient model

The effect of cancer chemotherapy on the human body was represented by Martin [10] as a set of mathematical differential equations but he didn't take into account the ability of human body to recover from drug's effect. Liang et al [13, 28] modified Martin's model to solve its inconsistency problem with clinical results. The modified model can be described as follows :-

Let

$$\frac{dx_1}{dt} = -\lambda x_1 + k(x_2 - \beta)H(x_2 - \beta) \tag{1}$$

$$\frac{dx_2}{dt} = u - \gamma x_2 \tag{2}$$

$$\frac{dx_3}{dt} = x_2 - \eta x_2 \tag{3}$$

with the initial state $\boldsymbol{x^T(0) = [\ln(100).0.0]}$ and

$$H(x_2 - \beta) = \begin{cases} 1 & \text{if } x_2 \geq \beta \\ 0 & \text{if } x_2 < \beta \end{cases} \tag{4}$$

Where the transformed variable $\boldsymbol{x_1}$ is inversely related to the tumor mass. The mass of tumor is calculated by $\boldsymbol{N = 10^{12}\exp(-x_1)}$ cells,and treatment procedure with the initial population of cancer cells begins from $\boldsymbol{10^{10}}$cancer cells [10]. $\boldsymbol{x_2}$ represents the drug concentration at tumor site in drug units (D), and $\boldsymbol{x_3}$ is the toxicityof drug in the patient's body. The net change in number of cancerous cells per unit time is described in (1). In the right side of (1), the first term represents the normal increase in cancer cell because of cell proliferation, and the second term represents the decay in tumor cells due to cancer treatment. The positive constants λ and k are associated with the growing factor of cancer cells and the amount of lump cells that killed per unit time per unit drug concentration respectively. Equation (4) describes a threshold level β of the drug concentration. Below this value, the drug is not efficient as the amount of killed cancerous cells is very small compared to the reproduced level of cancerous cells. Equation (2) presents the change in the concentration of chemotherapy drug at the cancerous tissues. The variable u describes the drug doses that be infused into patient body, and the drug's half-time represents by ln (2)/γ, where γ describes the drug's biochemical parameter.

It is supposed that electronic drug delivery systems are used to regulate infused drug dose during treatment period. . The net change of the drug toxicity $\boldsymbol{x_3}$ per unit

time is described in equation (3). The first term on the right side of (3) represents the increase of the toxicity $\boldsymbol{x_3}$because of the drug concentration $\boldsymbol{x_2}$, The second term represents the decay in toxicity due to the body metabolism. this decay rate constant is represented in parameter ($\boldsymbol{\eta}$). The values of model's parameters are listed in Table 1.

TABLE 1. Parameters of Chemotherapy Model.

Parameter	Value
Λ	$9.9 * \mathbf{10^{-4}} \boldsymbol{days^{-1}}$
$\boldsymbol{k}$	$8.4 * \mathbf{10^{-3}} \boldsymbol{days^{-1}} [\boldsymbol{D}]^{-1}$
β	10 $[\boldsymbol{D}]$
$\boldsymbol{\gamma}$	0.27 $\boldsymbol{days^{-1}}$
$\boldsymbol{\eta}$	0.4 $\boldsymbol{days^{-1}}$

The performance index [10] is a tumor size indicator and is defined as:

$$I = x_1(t_f) \tag{6}$$

where the actual experiment time is ($\boldsymbol{t_f}$). As suggested in many previous studies [28-30], four cycles (84 days) are required to complete the experiment. Both of the duration of exposure of the body to the drug and the concentration of drug in blood govern the amount of toxicity in both cancerous lamp and normal cells [31]. Therefore, three constraints on the drug delivery, drug concentration and toxicity level in body ensure patient safety from harmful chemotherapy toxic effects as follows

$$u \geq 0 \tag{7}$$

$$0 \leq x_2 \leq 50 \tag{8}$$

$$x_3 \leq 100 \tag{9}$$

Drug resistance is an important issue in failure of chemotherapy treatment because the drug resistant cells increase when the cancerous lump increases [32]. In order to reduce the behavior of the resistant cells of drug, the cancerous lump is forced to decay by at least fifty percent every three weeks, so that

$$\mathrm{N}(21) \leq 5 * \mathbf{10^9} \tag{10}$$

$$\mathrm{N}(42) \leq 2.5 * \mathbf{10^9} \tag{11}$$

$$\mathrm{N}(63) \leq 1.25 * \mathbf{10^9} \tag{12}$$

2.2 Closed Loop Control Scheme

A closed loop control technique is established to determine the drug dose scheduling during the entire treatment period. Block diagram of the closed loop optimized PID-like IFLC control system (PID-IFLC) for chemotherapy is shown in Fig. 1. The drug concentration in the blood is returned as a feedback signal and compared to the desired rate of the drug concentration. Error and change of error signals are fed to the controller. The controller parameters are optimized using ACO .

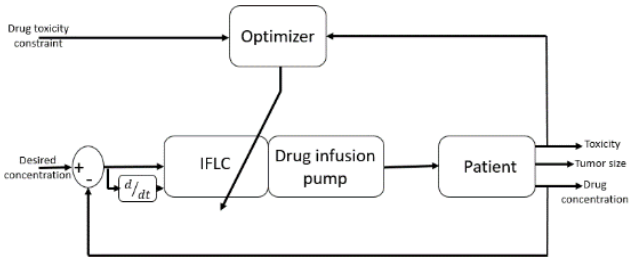

Fig. 1 Model with PID-IFLC controller with adaptive parameters**.**

For the purpose of clarifying the developed IFLC controller the following paragraph presents some essential definitions of intuitionistic fuzzy sets [33-35].

Definition 1. Let $A^* \subset E$ be a crisp and fixed set. An IFS *A* in *E* defines an object of the form as follows.

$$A = \{\langle x, \mu_A(x), \nu_A(x)\rangle \mid x \in E\} \tag{13}$$

where $\mu_A : E \to [0,1]$ and $\nu_A : E \to [0,1]$ are the degrees of membership and non-membership functions of the element $x \in E$, respectively, such that $0 \leq \mu_A(x) + \nu_A(x) \leq 1$ for every $x \in E$ in the set *A*.

Definition 2. The membership degree of non-determinacy or hesitancy of the element $x \in E$ to the IFS *A* is given by

$$\pi_A = 1 - \mu_A(x) - \nu_A(x) \tag{14}$$

where the value of $\pi_A(x)$ equals zero in case of ordinary fuzzy sets.

Definition 3. Let $\tilde{A}^I = \{(x, \mu_{\tilde{A}^I}(x), \nu_{\tilde{A}^I}(x)) : x \in \mathbb{R}\}$ is an intuitionistic fuzzy number (IFN). If the membership function $\mu_{\tilde{A}^I}(x)$ and non-membership function $\nu_{\tilde{A}^I}(x)$ are piecewise continuous from the set of real numbers $\mathbb{R}$ to the closed interval [0, 1], for every $x \in \mathbb{R}$, holding the following two conditions:

- IFN $\tilde{A}^I$ is normal, where the mean value of $\tilde{A}^I$ is $x_0 \in \mathbb{R}$ such that $\mu_{\tilde{A}^I}(x_0) = 1$ and $\nu_{\tilde{A}^I}(x_0) = 0$.
- IFN $\tilde{A}^I$ is convex IFS over $\mathbb{R}$.

Definition 4. A triangular intuitionistic fuzzy number(TIFN) $\tilde{A}^I = (a^l, a^m, a^u; a^l - \alpha, a^m, a^u + \beta)$ is graphically represented in Fig. 2, where $a^l, a^m, a^u, \alpha, \beta \in \mathbb{R}$ and α ,β are called left and right spreads of the non- membership function $v_{\tilde{A}^I}(x)$,(α, β≥ 0). The corresponding membership function $\mu_{\tilde{A}^I}(x)$ and non-membership function $v_{\tilde{A}^I}(x)$ are given in (15) and (16), respectively.

$$\mu_{\tilde{A}^I}(x) = \begin{cases} 0 & , x \le a^l \\ \dfrac{x - a^l}{a^m - a^l} & , a^l < x \le a^m \\ \dfrac{a^u - x}{a^u - a^m} & , a^m \le x < a^u \\ 0 & , x \ge a^u \end{cases} \quad (15)$$

And

$$v_{\tilde{A}^I}(x) = \begin{cases} 1 & , x \le (a^l - \alpha) \\ \dfrac{x - a^m}{b^l - a^m} & , (a^l - \alpha) < x \le a^m \\ \dfrac{a^m - x}{a^m - b^u} & , a^m \le x < (a^u + \beta) \\ 1 & , x \ge (a^u + \beta) \end{cases} \quad (16)$$

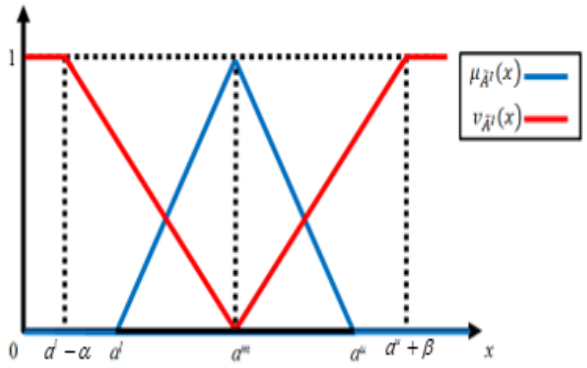

Fig. 2 A triangular intuitionistic fuzzy number (TIFN) $\tilde{A}^I$ with the membership function $\mu_{\tilde{A}^I}$ and non-membership function $v_{\tilde{A}^I}$.

Definition 5. The arithmetic operations on TIFNs $\tilde{A}^I = (a^l, a^m, a^u; a'^l, a^m, a'^u)$ and $\tilde{B}^I = (b^l, b^m, b^u; b'^l, b^m, b'^u)$ are expressed as:

- **Addition:**
  $\tilde{A}^I \oplus \tilde{B}^I = (a^l + b^l, a^m + b^m, a^u + b^u; a'^l + b'^l, a^m + b^m, a'^u + b'^u)$.
- **Multiplication:**
  $\tilde{A}^I \otimes \tilde{B}^I = (a^l b^l, a^m b^m, a^u b^u; a'^l b'^l, a^m b^m, a'^u b'^u)$
  such that $\tilde{A}^I, \tilde{B}^I > 0$.
- **Scalar multiplication:** Let λ be a real number, then
  $$\lambda \tilde{A}^I \begin{cases} (\lambda a^l, \lambda a^m, \lambda a^u; \lambda a'^l, \lambda a^m, \lambda a'^u), \text{for} \lambda \ge 0 \\ (\lambda a^u, \lambda a^m, \lambda a^l; \lambda a'^u, \lambda a^m, \lambda a'^l), \text{for} \lambda < 0 \end{cases}$$

Definition 6. In intuitionistic fuzzy logic, the truth value of each proposition is a real number and has two values; namely the "truth degree" and "falsity degree" in the interval [0, 1]. Let $p = (\mu_p, v_p)$ and $q = (\mu_q, v_q)$ be two intuitionistic fuzzy propositions and $\mu_p, v_p, \mu_q, v_q \in \mathbb{R}$, holding the constraints: $\mu_p + v_p \le 1$ and $\mu_q + v_q \le 1$. Then, the propositions *p* and *q* operations "conjunction" ($\wedge$), "disjunction" ($\vee$), "implication" ($\rightarrow$), and "(standard) negation" ($\neg$) are defined as follow:

- $p \wedge q = (\min(\mu_p, \mu_q), \max(v_p, v_q))$,
- $p \vee q = (\max(\mu_p, \mu_q), \min(v_p, v_q))$,
- $p \rightarrow q = (\max(v_p, \mu_q), \min(\mu_p, v_q))$,
- $\neg p = (v_p, \mu_p)$.

The basic structure of the developed intuitionistic fuzzy logic controller (IFLC) is depicted in Fig. 3. Similar to ordinary fuzzy controllers [36], the closed-loop IFLC receives the error signal(s) between the desired trajectory and the actual controlled output(s) as a crisp value, and produces the required crisp value of control action(s). The main components of IFLC include intuitionistic fuzzification, intuitionistic fuzzy inference system (FIS) with if-then rule base, and intuitionistic defuzzification [37]. In intuitionistic fuzzification process, the input data or the errors signal as real numbers are scaled by the gain K_E, and assigned to each intuitionistic fuzzy set with a membership function μ and non-membership function *v* of the interval [0, 1] in a certain input universe of discourse, as shown in Fig. 2. A collection of k^{th} intuitionistic fuzzy if-then rules forms the knowledge rule-base of inference engine as follows:

R_k^{μ} : if x_1 is $A_{1,k}^{\mu}$ AND x_2 is $A_{2,k}^{\mu}$ AND ... AND x_n is $A_{n,k}^{\mu}$
THEN y_1^{μ} is $B_{1,k}^{\mu}$ AND ... y_m^{μ} is $B_{m,k}^{\mu}$,

R_k^{v} : if x_1 is $A_{1,k}^{v}$ AND x_2 is $A_{2,k}^{v}$ AND ... AND x_n is $A_{n,k}^{v}$
THEN y_1^{v} is $B_{1,k}^{v}$ AND ... y_m^{v} is $B_{m,k}^{v}$

Based on the Center-of-Gravity (COG) defuzzification process [36, 38], FIS^{μ} and FIS^{v} produce the corresponding outputs y^{μ} and y^{v} using the membership function μ and non-membership function v , respectively, for all *M* if-then rules R_k , *k* = 1, 2, … , *M*. Finally, the overall crisp output of IFLC, i.e. the control signal *u*, is represented in (17) as a linear combination of y^{μ} and y^{v} with the hesitancy value π_c , such that $0 \le \pi_c \le 1$. The gain K_u is mainly required for tuning the controlled system response. Hence, the role of bio-inspired optimizer in this study is

to find the best values of IFLC parameters such as the gains K_e, $K_{\Delta e}$and K_u, as described in the following section.

$$u_c = K_u((1-\pi_c)y^{\mu} + \pi_c y^{v}) \quad (17)$$

Universe on the input of fuzzy controller is changed by the gain K_e,$K_{\Delta e}$, while universe on the output is changed by the gain K_u. The choice of the scale factors must achieve toxicity limitation.

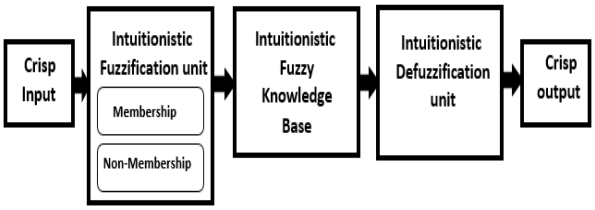

Fig. 3 Basic Structure of IFLC.

2.3 The Optimization Strategy.

The algorithm of ant colonies [39] relies on collective deposition and trailing behavior determined in ant colonies. the plan could be a transfer of all solutions identified in an iteration to a consequent iteration. And so, measurement of the pheromone quantity is needed for the next iteration as shown in fig.4.

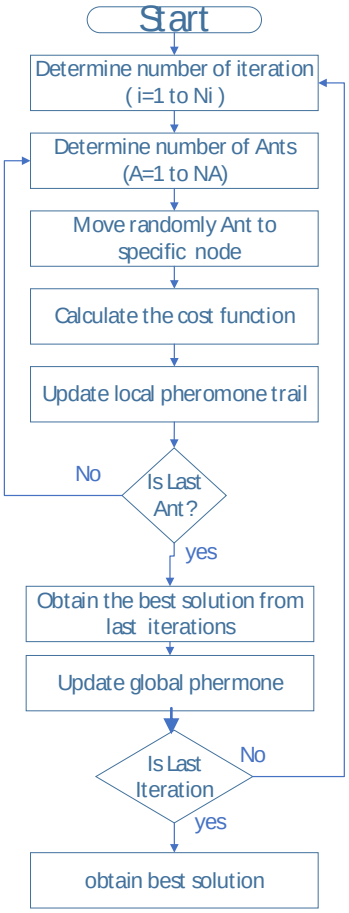

Fig. 4 ACO Algorithm Steps.

In [40], the authors suggested a modification to how the pheromone varies, thus offering a longer trace of the best solutions. Then specifically eliminate its pheromone matrix impact. The previous methods are modified in [41], introducing an moralist notion: The most successful ants are the only ones that can modify the pheromone at every iterationand the best previous solutions do not seem to be ignored, however changed to the most effective, so they'll become new reasonable solutions and it provides us the most effective case. Uthayakumar et al studied the dynamics of ACO in [42] and proposed a model, supported by the associated average of the expected behavior of the ants according to the following equation:

$$P_{ij} = \frac{[\tau_{ij}]^{\alpha}[\eta_{ij}]^{\beta}}{\sum_{h\in s}[\tau_{ij}]^{\alpha}[\eta_{ij}]^{\beta}} \quad (18)$$

where the pheromone is represented by τ , the distance between ants is η and j is elements of the solution iterations .

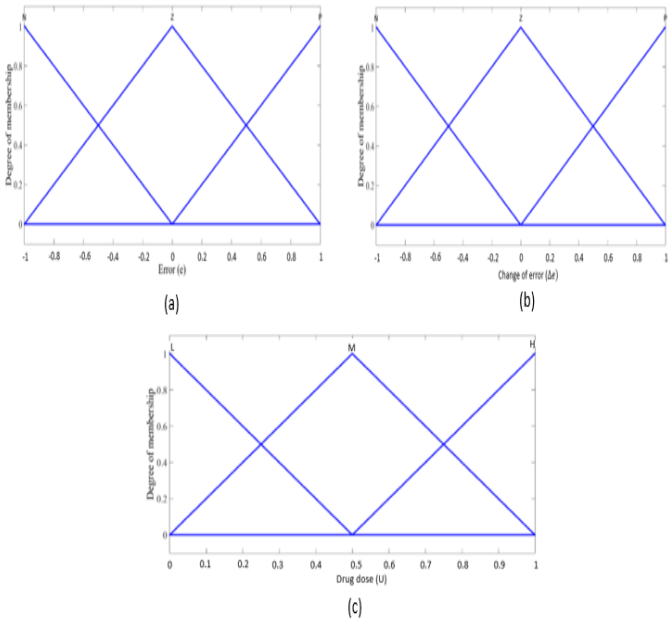

Fig. 5 Membership function for
(a) error (b) change of error (c) drug dose.

The PID-IFLC is developed in this work. Mamdani type fuzzy logic represented by three triangle membership function: Positive (P), Negative (N), Zero (Z) for two inputs and High (H), Medium (M), Low (L) for output as shown in fig.5 (a,b,c), Also, three triangle non membership function : NPositive (P'), NNegative (N'), NZero (Z') for input and NHigh (H'), NMeduim (M') and NLow (L') for output as shown in fig.6 (a,b,c) which lead to 9 rules as shown in table 2:

TABLE 2. Rule Base .

Erorr e	Change of error Δe		
	N	Z	P
N	L	L	M
Z	L	M	H
P	M	H	H

The universe of discourse value for the inputs and output are in range [0, 1]. The goal of fitness function of ACO is to reduce the toxicity level in blood such that its value doesn't exceed 100, using cost function as in (19) where G=0.99

$$\textit{Cost function} = G(\textit{toxicity} - 100) \qquad (19)$$

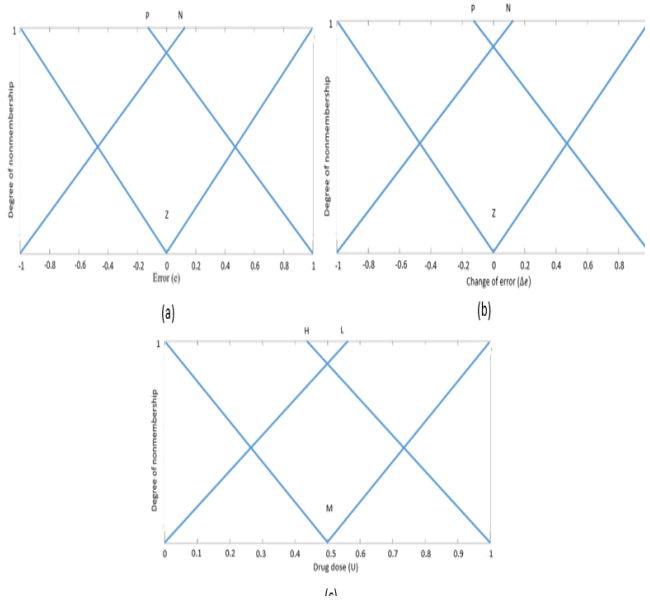

Fig. 6 Nonmembership function for (a) error (b) change of error (c) drug dose .

2.4 Cancer Treatment Protocols

The reference input is the drug concentration trajectory at cancer tumor as chemotherapy is infused into the body of the patient. Throughout this work, two separate treatment protocols for the 84-day treatment period were explored on the basis of medical knowledge and previous studies., as depicted in Fig. 7[13, 16, 21]. In Fig. 7(a), The first protocol for treatment begins with a high two-day drug dose as patients have strong metabolism capacities and at the beginning of treatment drug resistance in tumour cells is very low. So that, the optimum concentration of the drug is therefore at first set at 50.0 mg / ml. The concentration of the drug is decrease to 45.0 mg / ml for the next two days and further decreases in concentration to approximately 5.0 mg / ml in the next two days to prevent any toxic side-effects from chemotherapy. Then the reference value is 40.0 mg / ml for the remaining treatment period of 84 days [21].

Fig. 7(b) indicates the second protocol of treatment as specified in [16]. The optimal concentration of the drug is set for the first 4 days to the maximum value of 50 mg / ml. Then, a minimum drug concentration dose of 40 mg / ml for 80 days followed to ensure toxicity does not surpass the permissible medical range.

3. RESULTS

The ACO optimization algorithm was used in line to tune the PID-IFLC parameters to reduce and limit the patient body's toxicity effect. Population of 6 searching points for 100 iterations are used for the two treatment protocols. As shown in Fig.8, the minimum system cost function is 0.7656. Table 3 shows the optimized parameters of the PID-IFLC controller.

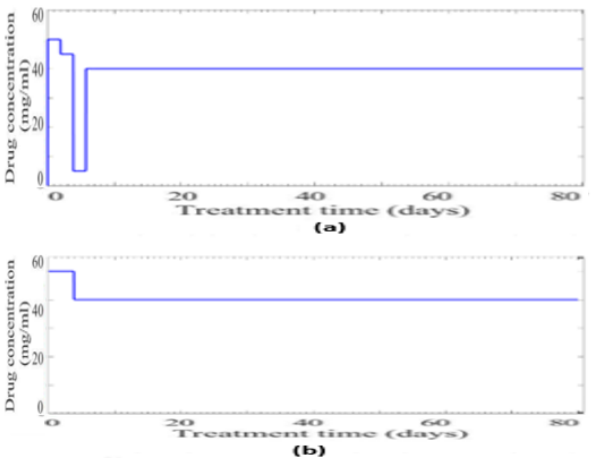

Fig. 7 Two different drug concentrations protocol for 84 days of treatment.

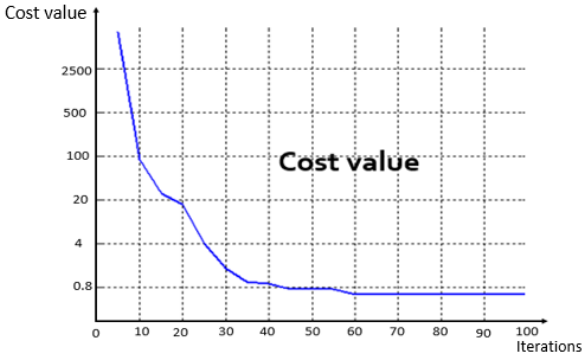

Fig. 8 Cost function minimization.

Table 3 Optimized parameters of PID like intuitionistic fuzzy controller.

The number of cancer cells is initialized before the drug infusion begins with 10^{10} cells for the two cancer treatment protocols [13, 21]. Figures 9 and 10 display simulation results for PID-IFLC with selected optimization parameters for the scheduling of the chemotherapy drug dose. In Fig.9a ,drug infusion doses are increased to 13.5 mg during the first two days, with the following days a minor drop to 12.45 mg. Therefore, the dose is sharply declined to give a minimum value of 1.35 mg. The doses are raised to a constant value of 10.8 mg until the end of the procedure. The drug concentration in the tumor tissues follow the reference input successfully (Fig.9b), resulting in a small root mean squared error (RMSE) of 0.0674. Fig. 8c-d shows the level of toxicity and the resulting remaining tumor cells of 99.98 (mg / ml / day) and 0.2482 cell, respectively.

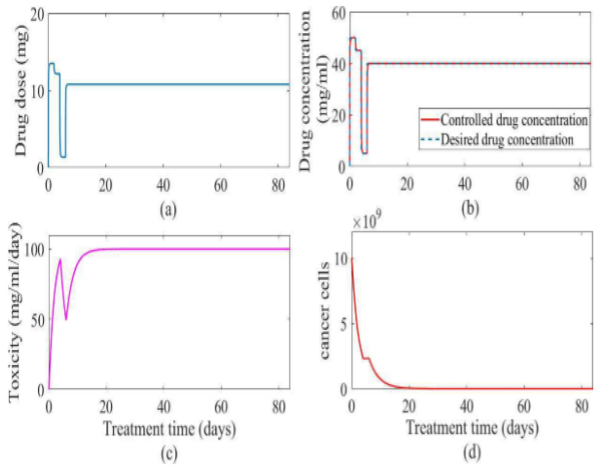

Fig. 9 Patient chemotherapy response results in the first treatment protocol using the PID-IFLC controller: (a) drug dose (b) drug concentration, (c) toxicity, and (d) cancer cells reduction.

The second treatment protocol, as shown in Figure 10a, offers 13.49 mg of drug doses in the first four days of treatment. Then the dose of drug infusion is maintained at 12.41 mg from the fifth day to the last day of treatment. The RMSE of the concentration of drugs in the blood relative to the target concentration is 0.0174, keeping the toxicity level under the maximum allowed level of 100 (mg/ml/day), as depicted in Fig. 10c. Fig. 10d.Moreover, this result indicates the efficacy in reducing the final numbers of cancer cells to substantially 0.1856 in this treatment protocol.

Table 4 offers a comparison of developed PID-IFLC and previous intravenous cancer chemotherapy control methods with regard to the performance index (5) and number of remaining cancer cells. The same model of drug response was used in previous studies [10, 12] in order to test their proposed methods of drug scheduling for a treatment period of 84 days. The optimized PID-IFLC with the second therapy protocol, achieves the best performance index of 29.3152 and smallest tumor cells of 0.1856.

Parameter	α	B	K_e	$K_{\Delta e}$	K_u
Value	0.5836	0.6247	3.94	5.7809	9.56

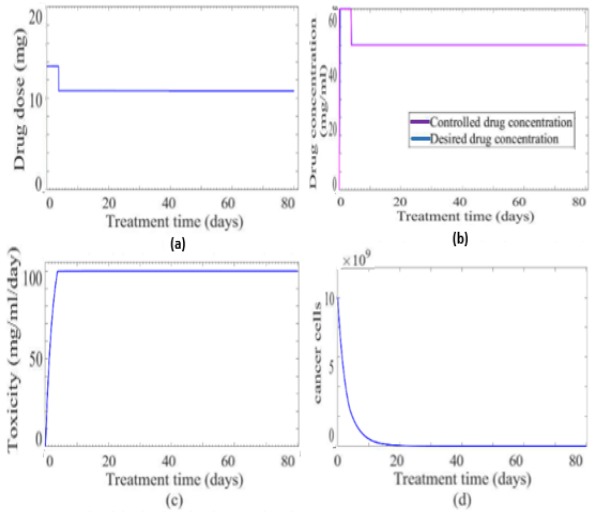

Fig. 10 Patient chemotherapy response results in the second treatment protocol using the PID-IFLC controller: (a) drug dose (b) drug concentration, (c) toxicity, and (d) cancer cells reduction.

Table 4 Comparative performance between developed controller and previous studies.

Method	Performance index	Final number of cancer cells
Martin [10]	16.836	$4.878*10^4$
Tan et al.[11]	17.993	$1.53*10^4$
Liang et al. [13]	20.158	$1.760*10^3$
Tsai et al. [16]	24.7406	18.0
Al-goul et al.[21]	24.9229	15.0
S. Khadraoui et al [22]	27.5559	1.078
Developed PID-IFLC (Treatment protocol-1)	29.0245	0.2482
Developed PID-IFLC (Treatment protocol-2)	29.3152	0.1856

4. DISCUSSION

This study showed that the optimized PID-IFLC controller is able to attain good performance in the delivery of automatic closed-loop cancer chemotherapy drugs under various treatment protocols, as shown in Fig. 9 & 10**.** Compared to previous investigations, clinical goals and limitations are inferred in the design of the PID-IFLC structure to replicate the decision-making process of specialist oncologists during the cycle of intravenous cancer chemotherapy drugs. As a result, the best

performance treatment index was 29.3152 using the defined PID-IFLC.

PID-IFLC parameters have been modified by using the ACO optimization algorithm to minimize the average error between the reference and the real drug concentration trajectories. The results of the controller didn't exceed the dangerous toxic level and achieved a minimum value of remaining cancer cells as shown in table 4 . As indicated by the results, the PID-IFLC achieved the best results in terms of toxicity in the body and the number of cancer cells remaining in the body, especially when applied to the second treatment protocol. However, theintravenous chemotherapy PID-IFLC controller cannot completely destroy all of the tumor cancer cellswith a probable implication that one remaining cell will replicate cancer during certain periods [3]. Therefore, the oncologists in clinical practice suggest mixed treatment methods, such as the form of radiotherapy, together with chemotherapy. Nonetheless, in Table 4, the performance assessment of evolved PID-IFLC outperforms the other controllers in achieving the best minimum quantity of remaining cancer cells.

5. CONCLUSION

An intuitionistic fuzzy controller has been utilized to improve the drug infusion control system using. cancer patient model. The objective of controller to kill maximum number of remain cell and minimizing the side-effects of the drug. This has been achieved by adding an optimizer (ACO) to tune the PID-IFLC controller parameters. In this way, the ACO optimization is built to boost the search area and avoid local optima points. Drug dose, toxicity and concentration of drugs were always below the human's allowable limits. The future study will include the use of the established controller in animal studies using a commercial chemotherapy drugs infusion system.

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