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Fuzzy logic controller for the chemotherapy of brain tumor

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***Abstract*—An advanced Fuzzy Logic Controller (FLC) that considers all the states of the brain tumor system is designed for the chemotherapy treatment. A Mamdani-type FLC is proposed for dynamically controlling the chemotherapy drug for the tumor system; the chemotherapy treatment of brain tumors requires advanced strategies which mainly depend upon the severity of the tumor. In this work, the advanced FLC designed aims both at determining the amount of chemotherapy to eliminate tumor cells, and at preserving the minimum amount of healthy and immune cells. The controller's performance is verified using MATLAB software based on different control parameters, showing its effectiveness in reducing the tumor cells. It has shown favorable results in terms of steady-state error, rate of convergence, and amount of drug consumed.**

***Index Terms*—brain tumor, fuzzy control, controller design, malignant tumor.**

I. Introduction

Over the years, the brain tumor has spread rapidly among humans of different ages, involving both males and females as victims of the abnormality of cells inside the brain. Although tumors appear outside the skull as well, the most lethal tumors appear inside, and are classified as benign and malignant tumors. In fig.1, a comparison between the two types of tumors is showed; it is observed that a benign tumor is smaller in size with certain boundaries, while the malignant one is larger in size and has irregular edges.

Many people across the world suffer from brain tumors every year. Based on the analysis of cancer registries in 70 countries, the age-standardized incidence of malignant brain tumors varies by region, from 6.76 cases per 100,000 person-years in Europe to 2.81 in Africa. Further, in Asian developing countries, the total volume of benign and malignant brain and spinal tumors is over 940,000 cases per year. In the USA alone, some 24530 cases of malignant brain tumors and 59040 cases of non-malignant brain tumors has been registered in 2021, and above 18600 people lost their lives [2]. In recent years, some visible research has been done to tackle this problem. The first mathematical tumor model has been proposed in [3], whereas the improvements in this model have been made by applying optimal nonlinear control to kill the tumor cells in [4], [5]. Recently, the nonlinear sliding mode and back-stepping controllers have been introduced for the nonlinear control of tumors and used Lyapunov stability theory to prove the asymptotic stability of the system [6].

The process for treating a brain tumor depends on a number of factors, including the tumor's size, location and kind, the patient's age, the medical condition, the time when the tumor first began to grow, its rate of spread, the likelihood of relapse, and the patient's tolerance level. Surgery, radiation therapy, and chemotherapy are all effective treatments for low-grade malignant tumors [1], [2], whereas chemotherapy or a clinical study is preferable for high-grade malignant tumors.

When the patient is uncertain about the initial diagnosis or recurrence, chemotherapy is suggested. In this research, the treatment of severe brain tumors through chemotherapy using the FLC has been analyzed. Fuzzy logic plays a vital role in the field of drug designing, bio-informatics, management of diseases, and clinical trials [17]–[22]. For the treatment of brain tumors, it is the first time that an advanced FLC is being designed, considering all the states. Previously, an attempt has been made to formulate basic fuzzy rules for a general tumor model in [10].

The FLC design for brain tumor would be a significant improvement in understanding the complex tumor system. The logic-based rules of FLC would help reduce the model's uncertainties; also, it ensures convergence and utilizes fuzzy rules to overcome changes with time in the system values. The fuzzy method is preferred with respect to classic methods because of its simple technique, low computational cost, practical success, and desired uniformity. From past decades, the problem of controlling the rate of the drug at the tumor site during the chemotherapy has been considered a rigorous task [7]–[9]. Previously, the optimal and nonlinear controllers have been designed to regulate the drug in the brain tumor system with fixed values of the parameters [4], [5], [11], [12]. One

of the main reasons to design a FLC is that if the rules of the parameters in the tumor system change with time, the overall dynamics of the tumor system would react differently, and the conventional controllers would be unable to act appropriately.

In this research, the state space form of the brain tumor model has been used to design the FLC. The study of the system is analyzed using the fuzzy logic theory which uses fuzzy rules considering the behavior of the states. This FLC would facilitate analyzing the response of the brain tumor system in a better way by using fuzzy rules. Due to the ability of a FLC to overcome the complexity of the system, the FLC of brain tumors would be practicable, effective and efficient.

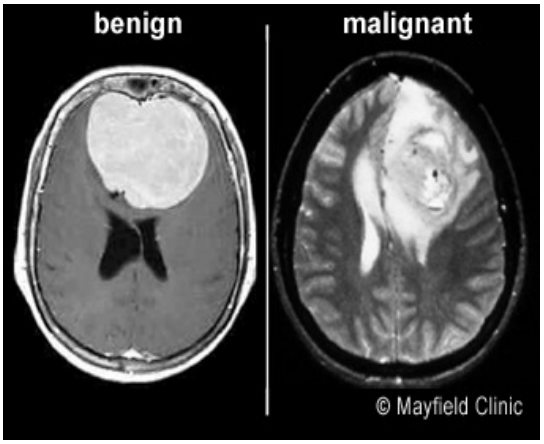

Fig. 1. MRI scan of benign and malignant brain tumors

In this work, the aim is to minimize the number of tumor cells and preserve a suitable number of immune and healthy cells by controlling the drug at the tumor site. A Mamdani-type FLC is proposed for dynamically controlling the chemotherapy drug for the tumor system. The working procedure followed the sequence of observing the behavior of states for rule formulation, use of fuzzy rules for making membership functions, connecting membership functions with the brain tumor system in MATLAB, and performing the simulations in MATLAB.

The paper is organized as follows: the nonlinear model of brain tumors is described in section II. The procedure for designing the FLC and PID are described in section III-A and section III-B respectively. Simulation results are shown and discussed in section IV, while the conclusion and future work are outlined in section V.

II. Nonlinear Brain Tumor Model

The mathematical model [4] adopted in this paper is described as follows:

$$\frac{dT(t)}{dt} = T(t)[r_1(1-b_1T(t))-c_2I(t)-c_3H(t)-a_1(1-e^{-D(t)})] \quad (1a)$$

$$\frac{dH(t)}{dt} = H(t)[r_2(1-b_2H(t)) - c_4T(t) - a_2(1-e^{-D(t)})] \quad (1b)$$

$$\frac{dI(t)}{dt} = s+I(t)\left[\frac{r_3T(t)}{\alpha+T(t)} - c_1T(t) - d_1 - a_3(1-e^{-D(t)})\right] \quad (1c)$$

$$\frac{dD(t)}{dt} = v(t) - d_2D(t) \quad (1d)$$

where:

- T: Number of tumor cells
- H: Number of healthy cells
- I: Number of immune cells
- D: Amount of drug
- s: Immune cells influx rate (per day)
- d_1: Cells natural death rate (per day)
- d_2: Consumption rate of the drug (per day)
- r_1: Tumor cells growth rate (per day)
- r_2: Healthy cells growth rate (per day)
- b_1: Tumor cells replication rate (per day)
- b_2: Healthy cells replication rate (per day)
- $a_1, a_2, a_3, c_1, c_2, c_3, c_4$: Control coefficients
- $v(t)$: Input (drug dose)

In this model, tumor, healthy and immune cells are modeled by a logistic growth law. The immune cells target the tumor cells through a kinetic process [11]–[13]. It can be noted that the immune response is not sufficient on its own to entirely combat the rapid growth of the tumor population; the drug therapies are proposed from the conditions that minimize the final population of tumor cells. It is reasonable to assume that chemotherapy increases capability of immune cells to protect healthy cells [14]; these immune cells have a constant influx rate s and in the absence of any tumor will die off at a per capita rate of d_1.

El Gohary, [4], reduced the original model of twelve parameters to eight, defining x_1= b_1T, x_2= b_2H, x_3= d_2I/s and x_4= D.

The model (1a)-(1d) could be rewritten as follows:

$$\dot{x}_1 = x_1\{k_1(1-x_1) - n_2x_3 - n_3x_2 - m_1(1-e^{-x_4})\} \quad (2a)$$

$$\dot{x}_2 = x_2\{k_2(1-x_2) - n_4x_1 - m_2(1-e^{-x_4})\} \quad (2b)$$

$$\dot{x}_3 = 1 + x_3\left\{\frac{k_3x_1}{v_1+x_1} - n_1x_1 - v_2 - m_3(1-e^{-x_4})\right\} \quad (2c)$$

$$\dot{x}_4 = u - x_4 \quad (2d)$$

where:

- n_1, n_2, n_3, n_4 are positive real constants;
- m_1, m_2, m_3 are the system response coefficients of tumor, healthy and immune cells respectively;
- k_1, k_2, k_3 represent replication rates for tumor, healthy and immune cells respectively
- The term 1-e^{-x_4} relates to injected amount of drug, while u represents the control input.

III. Controller Design Methodology

In this section, we have proposed a fuzzy logic-based controller by making use of the system (2). The main purpose of designing FLC is to achieve the goal of killing tumor cells and preserving safe number of healthy and immune cells.

A. Fuzzy Logic Controller

The working procedure of FLC can be arranged in the following manner:

1. Selection of Membership Function and Fuzzification: In the context of fuzzy sets, the selection of the membership function is a fundamental challenge. For this purpose, a technique of exploratory evaluation followed by the combining of specific decision rules into fuzzy groups is proposed in [15], which offers the best classification quality. Since, treatment of brain tumor is a user-centric application so the interpretability of fuzzy rule base systems (FRBSs) is essential. On the similar lines, in the case of brain tumors, simple membership functions like singletons and triangular shape membership functions are not recommended. The fuzzy knowledge-based techniques are widely used in the design of computer-based medical diagnostic systems to model the complex strategies and decision-making rules involved in the solution of diagnostic problems [16]. For brain tumors, the selection of Gaussian and trapezoid membership functions is favorable because in such cases the learning procedures require gradient and also the changes of parametric values. Further, in the next step taking the crisp input values and converting them into a fuzzy set is done, which is termed as fuzzification.

2. Rule Base: This is a set of if-then rules that define the behavior of the system. In Table-I, the fuzzy rules on the basis of desired results for the brain tumor system are made. It can be seen that for the derisory values of tumor cells, the number of healthy and immune cells should increase. On the other hand for perilous values of tumor cells, the number of healthy and immune cells would stand at low. The fuzzy rules for managing chemotherapeutic medicine are developed using the fuzzy inference method. They use if-then statements which are used in the fuzzy rules. To maintain a high amount of immune and healthy cells, a medium range of the amount of drug is required. Similarly, for the Perilous range of tumor cells, the control effort required would be very high as can be seen in Table I. Previously, some basic rules which are only for a general system tumor are described in [10]. Here, it is an extension of the rules in which we considered all the states of a brain tumor system.

3. Inference Engine: It is comprised of fuzzification, evaluation of control rules and de-fuzzification. This is the part of the system that interprets the fuzzy input, applies the rules, and produces a fuzzy output.

4. De-fuzzification: In this step, the fuzzy output is taken and converted back into a crisp output. The de-fuzzification method used for fuzzy controllers is the centroid. It is used to transform a fuzzy set into a crisp set by determining the center of gravity of the fuzzy set. This is done by taking the weighted average of the fuzzy set's membership values. In the FLC for brain tumors, the input values are converted to linguistic data in the form of fuzzy sets using input membership functions. The fuzzy rules for managing chemotherapeutic medicine are developed using the fuzzy inference method [10]. These if-then statements are used in the inference unit to determine the rules. A de-fuzzifier uses an output membership function to transform the output fuzzy sets into a non-fuzzy control signal output. In short, the working of the designed controller is based on: assessing the knowledge base, defining the input and output variables, fixing the process by which the input parameters are transformed into fuzzy sets, developing the computational block which assesses the fuzzy rules, and decides how to transform proposed fuzzy actions into the crisp control actions.

TABLE I
Rules of Fuzzy logic control

Tumor Cells	Healthy Cells	Immune Cells	Drug Amount	Control Input
Derisory	Very High	Very High	Derisory	Very Low
Very Low	Very High	Very High	Very Low	Very Low
Low	High	High	Low	Low
Low	Very High	Very High	Low	Low
Low	Very High	Very High	Low	Medium
Medium	High	Very High	Low	Medium
Medium	High	High	Medium	Medium
Medium	High	High	Medium	High
Medium	High	Medium	Medium	High
Dangerous	Medium	Medium	High	High
Dangerous	Low	Medium	High	High
Dangerous	Low	Low	High	High
Perilous	Medium	Medium	High	Very High
Perilous	Low	Medium	High	Very High
Perilous	Low	Low	Very High	Very High

Figure 2 depicts a layout of a fuzzy control system for a regulating control operation. This employs fuzzy control in two dimensions: the error e and difference of error Δe from the crisp output are first transformed into fuzzy variables; where error e is for a specific value of cells, while Δe is for change in the value of cells. The errors for the controller are defined as follows:

$$\Delta e_1 = x_1 - x_{1ref} \tag{3}$$

$$\Delta e_2 = x_2 - x_{2ref} \tag{4}$$

$$\Delta e_3 = x_3 - x_{3ref} \tag{5}$$

$$\Delta e_4 = x_4 - x_{4ref} \tag{6}$$

where e_1, e_2 and e_3 represent the errors defined for tumor, healthy, and immune cells respectively, while e_4 is the error for the amount of drug at the tumor site. The terms x_{1ref}, x_{2ref}, x_{3ref}, and x_{4ref} are the reference values for tumor cells, healthy cells, immune cells and the amount of drug respectively. In the architecture given in Figure 2, it can be seen that after the calculation of each Δe the fuzzy inference

unit is placed evaluating the control rules by utilizing the knowledge base. The suitably estimated control action is then transformed into the crisp value necessary for the control operation.

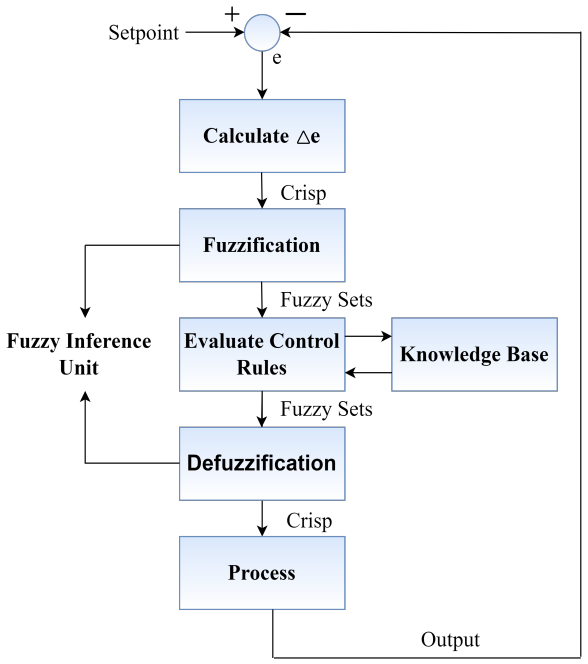

Fig. 2. Architecture of Fuzzy Logic Controller

For the fuzzy logic control design, the membership function for each system state has been considered in Fig. (3) - Fig.(6) whereas the membership functions for the control input $u(t)$ are defined in Fig. (7). There are six membership functions taken for tumor cells: derisory, very low, low, medium, dangerous, and perilous as can be seen in fig.(3). For healthy and immune cells these are taken as low, medium, high, and very high given in fig.(4) and fig.(5) respectively. For the amount of drug, they are named as derisory, very low, low, medium and high drawn in fig.(6). For the control input they are taken as very low, low, medium, high and very high drawn in fig.(7).

B. PID Controller

The PID controller is a classic control action used in different fields, for its effectiveness and its simplicity; for the brain tumor it is designed a PID controller for comparison with the fuzzy logic one, even if the structural differences among these two controllers are evident. For this purpose, the error of the state of tumor cells i.e. x_1 is utilized as mentioned in eq.(8), while the control function is designed using the following equation:

$$u(t) = k_p e(t) + k_i \left[\int_0^t e(t)\, dt \right] + k_d de(t)/dt \qquad (7)$$

where x_{1ref} is the reference for the tumor cells and $e(t) = x_1 - x_{1ref}$ is the error. The best method for tuning the gains of a PID controller depends on the specific system that the controller is being used for. The PID gains of the given tumor system are set by using the Ziegler-Nichols approach. This method involves step-testing the system and using the resulting response curve to determine the ultimate gain and period of the system. These values are used to calculate the proportional, integral, and derivative gains of the PID controller. By combining these three components, a PID controller can accurately control a wide range of physical systems.

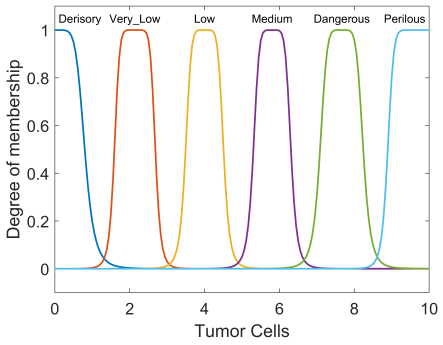

Fig. 3. Membership function of tumor cells

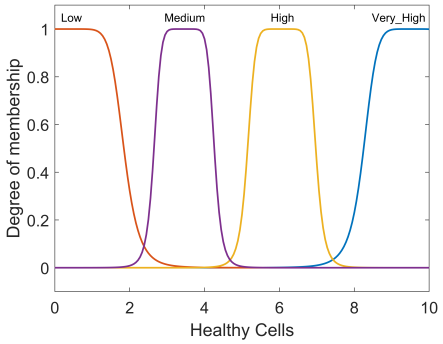

Fig. 4. Membership function of Healthy cells

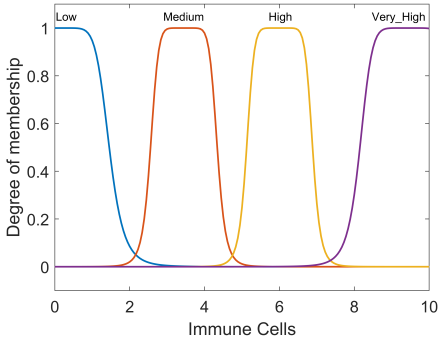

Fig. 5. Membership function of Immune cells

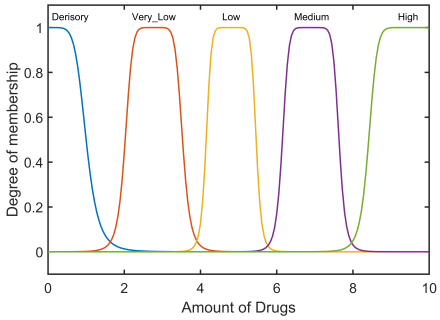

Fig. 6. Membership function of amount of drugs

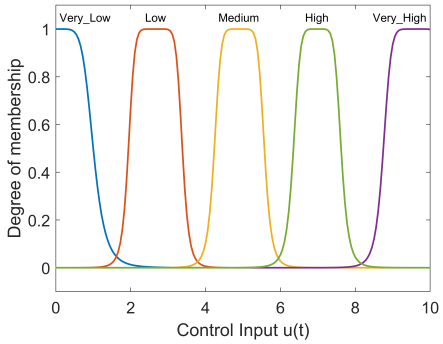

Fig. 7. Membership function of Control Input (u)

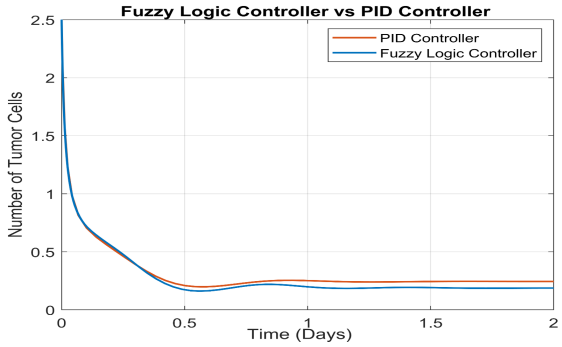

Fig. 8. Comparison of Fuzzy Logic Controller with PID

IV. Simulation Results

In this section, the simulation results of FLC for the brain tumor system are presented. Also, the comparison of the behavior of tumor cells for FLC and PID is given in this section. These simulations are performed by Matlab software using the model parameters given in table II, gain values k_p, k_i and k_d used in eq.(7) of PID given in Table III, and by inculcating the fuzzy rules made in the table I. The values of the parameters given in table II are selected from the range of the values of parameters defined in [4]. The range of values for k_1, k_2, k_3 are 25-35, 8-30 and 9-29, while for n_1, n_2, n_3, n_4 they are 2-2.5, 1.20-2.45, 0.45-5.25 and 8-8.15, and for m_1, m_2, m_3 they are 8-10, 14-16 and 3-5 respectively. The behaviour of tumor cells using a FLC can be observed in fig.8. It depicts that FLC as compared to PID tracks the tumor cells faster and also for FLC the chattering is negligible. Therefore, FLC controller outsmarts PID controller.

Further, the healthy cells fall in the safe limit [6] for the proposed controller this can be seen in fig.9, and that they are being tracked efficiently. The healthy cells grow faster initially and then attain steady state value. Further, these cells take less time to reach steady state value. The number of immune cells under the influence of the FLC controller is shown in fig.10. As can be shown, the FLC takes 1.92 days (sample is small) to get immune cells to the reference with no steady state error, and shows satisfactory rate of convergence. The amount of medication utilised in the case of FLC is 39.8, which has increased gradually, as shown in fig.11. Note that it is calculated by evaluating the area under the curve. Further, the chattering and convergence rates make it very evident that the FLC is a suitable controller for the tumor system. Also, the comparison of the behaviour of tumor cells can be made with results in [10].

Parameter	Value of Parameter
$x_1(0)$	$2.5mgL^{-1}s^{-1}$
$x_2(0)$	$0.25mgL^{-1}s^{-1}$
$x_3(0)$	$1.55mgL^{-1}s^{-1}$
$x_4(0)$	$0mgL^{-1}s^{-1}$
n_l	2
n_2	1.3
n_3	0.47
n_4	8
k_1	$30d^{-1}$
k_2	$48d^{-1}$
k_3	$29d^{-1}$
m_1	$9d^{-1}$
m_2	$15d^{-1}$
m_3	$4d^{-1}$
v_1	0.25
v_2	10
u_{max}	10

TABLE II
VALUES OF PARAMETERS

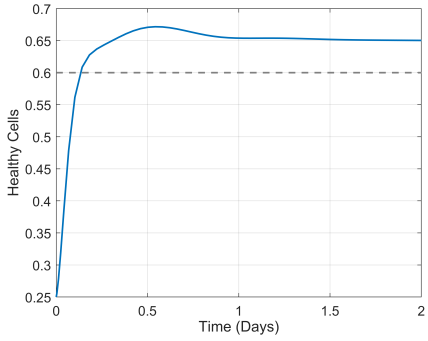

Fig. 9. Number of Healthy Cells using Fuzzy Logic Controller. The dotted line is the reference value.

Parameter	Value of Parameter
k_p	1
k_i	0.9
k_d	0.2

TABLE III
VALUES OF PARAMETERS

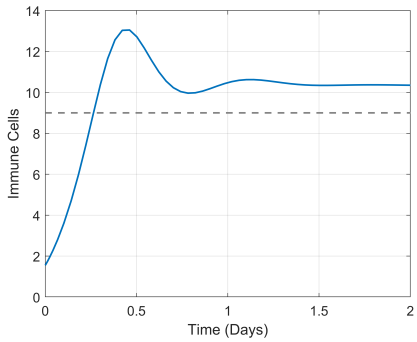

Fig. 10. Number of Immune Cells using Fuzzy Logic Controller. The dotted line is the reference value.

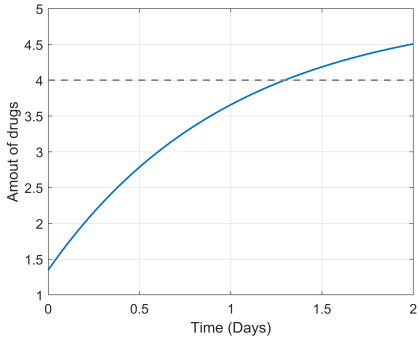

Fig. 11. Amount of drug using Fuzzy Logic Controller. The dotted line is the reference value.

V. CONCLUSION

In this work an updated model of brain tumor has been considered, and for first time an advance FLC has been designed to set the fuzzy rules for all the states of a brain tumor system, and to monitor drug dose in the brain tumor system. State of the art FLC is proposed to eliminate tumor cells, and to retain safe number of healthy as well as immune cells. A complete systematic analysis has been given to illustrate the working of the proposed controller using fuzzy theory. Results of the controller has been verified by performing MATLAB simulations where it is noticed that FLC for tumor system works satisfactory in terms of the rate of convergence and chattering of tumor cells. Further, it also ensures that the healthy and immune cells do not decrease during the chemotherapy process.

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