# Identification and control of HIV drug therapy using fuzzy systems

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## Abstract

In this paper, a tool for decision support based on fuzzy logic is presented; it can provide an effective decision support in the HIV infection treatment. The approach presented, relies on modeling the changes of viral load and CD4+ T-cells counts during treatment in a fuzzy system. The obtained fuzzy system is used in treatment control. The therapy state can be presented by four parameters, (x) uninfected cells, (y) infected cells, (vi) infectious virus and (vni) noninfectious virus. Two drugs are used in the HIV infection therapy: Drug 1 is used to block new infection of CD4+ T-cells cells, and drug 2 is used to inhibit the viral production. If u1 and u2 are respectively the quantities used of drug 1 and drug 2, a question that summarizes the purpose and motivates the work presented in this paper is: How the parameters u1 and u2 can be adjusted tu reduce the viral load for a given state (x,y,vi,vni)?. A practicing doctor uses their expertise to answer that question. In this paper, design of fuzzy systems is surveyed and fuzzy identification of HIV infection therapy is introduced. A clustering method had been used to determine the basic parameters of the fuzzy system. The results of the simulation are presented.

## Introduction

In an antiviral drug treatment of HIV infection, CD4+ T-cells count and viral load can be used as an indicator of success or failure of treatment. With regular monitoring of viral load, doctors can detect resistance to treatment and adapt the treatment protocol.
The errors or the accuracy in screening tests plays a precious role in improving treatment protocols. Recently, automated screening tests have been created to monitor viral load in real time. Screening tests are able to detect a very low viral load in patients infected with AIDS, offer one of the highest degrees of sensitivity and allow doctors to think in terms of their experience and their expertise to make the right treatment decision. The current question is "how to make the exploitation of the massive information flow more effective?”.

One solution is to introduce a calculation tool that takes into account the data processing and the doctor's knowledge. Fuzzy logic has much to offer in the realm of uncertainty and imprecision [1].
The therapy can by identified using a fuzzy system, and the obtained fuzzy system can be used to control the therapy with the control parameters $u1$ and $u2$.

**Fuzzy system**

The HIV infection therapy can be presented by a MIMO system with 6 inputs: $X \in U \subset \mathbb{R}^6$, and 4 outputs: $Y \in V \subset \mathbb{R}^4$, where $X = (x, y, vi, vni, u1, u2)$ and $Y = (x, y, vi, vni)$. This MIMO system is described by a set of input/output measured data that have been collected during treatment. Fuzzy modelling and identification from measured data are effective tools for the approximation of uncertain non-linear systems. In [2] the multiple-input, multiple-output (MIMO) systems are identified by means of product-space fuzzy clustering with adaptive distance measure (the Gustafson-Kessel algorithm). The MIMO model is represented as a set of coupled input/output MISO models of the Takagi-Sugeno type.
Usually, a fuzzy system (S) is defined as:

$$(S): U \subset \mathbb{R}^n \longrightarrow \mathbb{R}^m \qquad (1)$$

Where $U$ is a compact in $\mathbb{R}^n$.

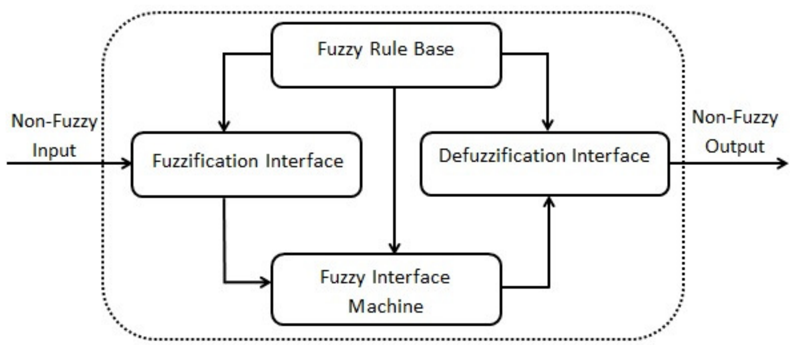

Figure1: Basic Configuration of Fuzzy System

Figure 1 presents a Basic configuration of fuzzy system. A fuzzy system typically consists of four elements: Fuzzification interface, Fuzzy rule base, Fuzzy interface machine and Defuzzification interface.
Fuzzification interface plant from an entries space $U \subset \mathbb{R}^n$ to a fuzzy subsets space defined on U. Note that a fuzzy set $A$ is defined on $U \subset \mathbb{R}^n$ by a membership function:

$$\mu_A: U \rightarrow [0,1] \qquad (2)$$

The fuzzy rule base is a set of fuzzy rules $R_j$ of type IF-THEN. The fuzzy IF-THEN rule is a conditional statement expressed as:

$$R_j: \text{IF } x_1 \text{ is } A_1^j \text{ and } x_2 \text{ is } A_2^j \text{ and } . . . \text{ and } x_n \text{ is } A_n^j \text{ then}$$

$$y_1 \text{ is } B_1^j \text{ and } y_2 \text{ is } B_2^j \text{ and} \ldots \text{ and } y_m \text{ is } B_m^j \tag{3}$$

Where:

$j = 1,2, \ldots, m$, and $x_i$ $(i = 1, 2, \ldots, n)$ is the ith component of the fuzzy system input vector. $y_i$ $(i = 1, 2, \ldots, m)$ is the ith component of the fuzzy system output vector.

$A_i^j$ and $B_i^j$ are a fuzzy subsets characterized respectively by the membership functions $\mu_{A_i^j}$ and $\mu_{B_i^j}$. Fuzzy interface machine is the core section of a fuzzy system, which combines the facts obtained from the fuzzification interface with the rule base and conducts the fuzzy reasoning process. In the defuzzification interface, the output of the fuzzy system (a numerical decision) is computed. The reader is invited to see more details on the fuzzy system in [3]. In the following section a design of the fuzzy system is made based on a clustering method.

## Design of fuzzy system using data

Construction of Fuzzy models involves selecting several parameters: the position, shape and distribution of the membership functions, building the rules basis, selection of logical operations, and the consequences of the rules. These may be estimated from data using different strategies, their goal is to minimize the approximation error between the output values and the computed values using the fuzzy model. Several strategies have been proposed in the literature for designing a fuzzy system using data: Table Lookup Scheme [4], Gradient Descent [4] and [5], Clustering method [6], and Evolutionary Strategies [7].

In this paper, clustering strategy is used to determine fuzzy system parameters.The most commonly used fuzzy clustering methods, include: Fuzzy C –Means method, Gustafson and Kessel algorithm[8], mountain clustering[9], and subtractive clustering[10].

The methods based on clustering are considered to be data-driven methods. The main idea of these methods is to identify structures (clusters) among the data according to their distribution in space and assimilate each cluster to a multidimensional fuzzy set representing a rule.

The subtractive clustering method is an extension of the mountain clustering method that was introduced by Yager and Filev in [9]. In subtractive clustering method, there is no need to determine the number of clusters at the beginning.

Note that the input data are defined on $U \subset \mathbb{R}^n$, and the output data are defined on $\mathbb{R}^m$, as in Equation 1. Two steps were designed to construct a fuzzy system in this paper:

- First step: the data are normalized, and grouped using the subtractive clustering method.
- Second step: the fuzzy system explicit expression for a data couple $(X, Y)$ is the weighted mean:

$$y_i = f(X) = \frac{\sum_{j=0}^{l} y_i^j \, \mu_{B_i^j}(X)}{\sum_{j=0}^{l} \mu_{B_i^j}(X)} \qquad i = 1,2, \ldots, m \tag{4}$$

Where:
$y_i^j$ is the center of the group $B_i^j$ related to the values of variable $Y_i$, these groups were generated in the first step. The integer $l$ is the number of rules .
The membership function $\mu_{B_i^j}$ of $B_i^j$ is defined by the following expression:

$$\mu_{B_i^j}(X) = \max_{i=1\dots n}\left(\mu_{A_i^j}(X)\right) \tag{5}$$

And

$$\mu_{A_i^j}(X) = \sum_{i=0}^{i=n} e^{-\alpha\|X-X^i\|^2} \tag{6}$$

$X^j = [x_1^j, x_2^j, \dots, x_n^j]$ where $x_i^j$ is the centre of the group $A_i^j$ $(i = 1,2,\dots,n)$ related to the values of $X$, these groups were generated in the first step using the subtractive clustering method. The integer $l$ is the number of groups $A^j$. The constant $\alpha$ is defined in the subtractive clustering method, you can find more about this parameter in [10].
According to [11] the Fuzzy systems Eq. 4 can approximate any function in a compact domain. The accuracy of the approximation depends on the maximum slope of the function and the distance between the centres of the fuzzy sets. Lee demonstrated that the fuzzy system presented in step 2 is a universal control tool [12,13], this system is used in the following section to identify the HIV infection therapy.

**Fuzzy Identification of HIV infection therapy**

The HIV infection drug therapy can be described by iterative MIMO system, the entries of this system at time $k$ are the variables cited previously $(x_k, y_k, vi_k, vni_k, u1_k, u2_k)$ and the output are $(x_{k+1}, y_{k+1}, vi_{k+1}, vni_{k+1})$. A mathematical model using the same variables has been presented in [14], in this model, a semi-implicit finite difference method is used to reach the solutions.
A fuzzy system describing this therapy can be defined as follow:

$$F : X_i \in \mathbb{R}^6 \longmapsto Y_i \in \mathbb{R}^4 \tag{6}$$

Where $X_i = (x_i, y_i, vi_i, vni_i, u1_i, u2_i)$ and

$$Y_i = F(X_i) = X_{i+1} \tag{7}$$

Because of the unavailability of real data, the input-output data or the couples $(X_i, Y_i)$ needed to determine the fuzzy system parameters are generated using a semi-implicit finite difference method introduced in [14].
The constructed fuzzy system can be used as an inverse fuzzy controller (figure 2). It takes the next desired state $(x_{i+1}, y_{i+1}, vi_{i+1}, vni_{i+1})$ as an input and calculates the decision $(u1_i, u2_i)$ which allows for this state. In other words, given the current state of the infection $(x_i, y_i, vi_i, vni_i)$, the doctor's concern is to determine the values of $u1_i$ and $u2_i$ that lead to the next desired state $(x_{i+1}, y_{i+1}, vi_{i+1}, vni_{i+1})$. The simulation results presented in the

next section give more information about the construction of the fuzzy system and illustrate its applications.

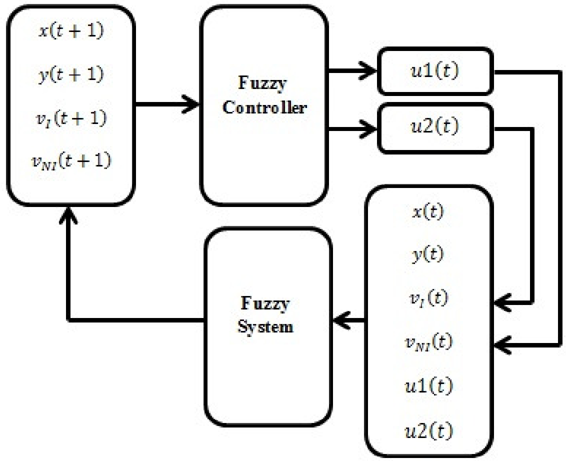

Figure2. Fuzzy Inverse Controller

**Simulation**

In the first step, the semi-implicit finite difference method SIFDM introduced in [14] was implemented to generate a set of hundred couple $(X_i, Y_i)$ of data. The data represent the behaviour of the therapy is presented by these data. The data were normalized using the following formula as introduced in [15]:

$$x \longleftarrow ((x - min)/(max - min)) * (HI - LO) + LO \tag{8}$$

This formula allows values between HI(= 0.9) and LO (= 0.1).
In the second step, the normalized data were grouped using the subtractive clustering method. The clustering method resulted in the generation of 18 groups. Finally, the fuzzy system described in Eq. 4 was built according to the centers of these groups.
Figures 3 to 11 represent a comparison between the results of the semi-implicit finite difference method and those of the obtained fuzzy system. It is clear from these figures that the fuzzy system built reproduces the same behavior as that of SIFDM.
Introducing a control parameter and using the least squares method to remove the acceptable error that appears in these results will help increase the accuracy of results.

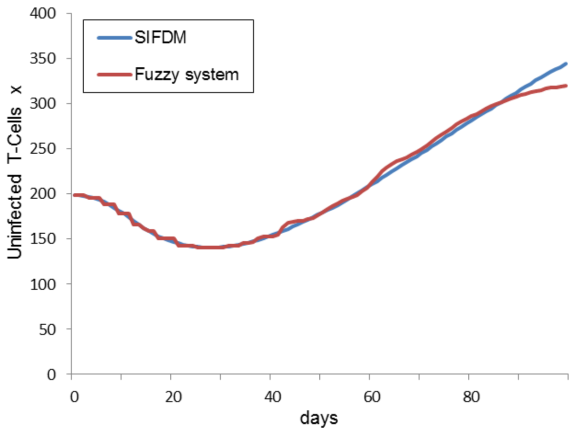


Figure 3: changes in the number of non- infected cells during therapy

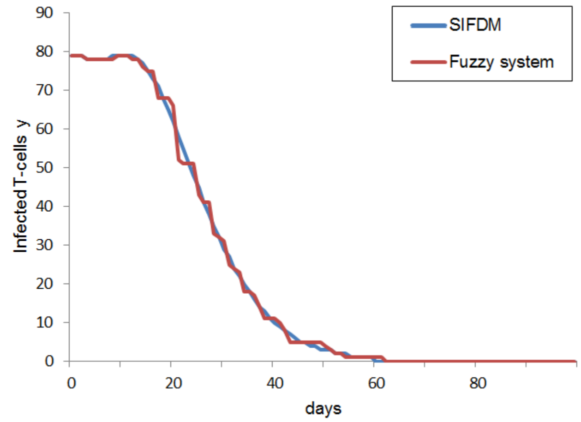


Figure 4: changes in the number of infected cells during therapy.

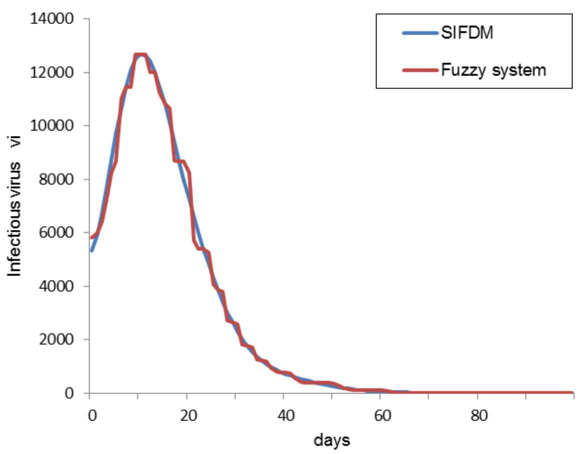


Figure 5: changes in the infectious viral load during therapy

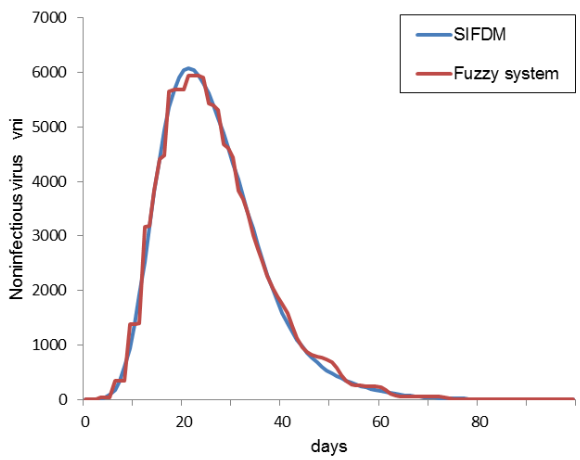


Figure 6: changes in the non-infectious viral load during therapy

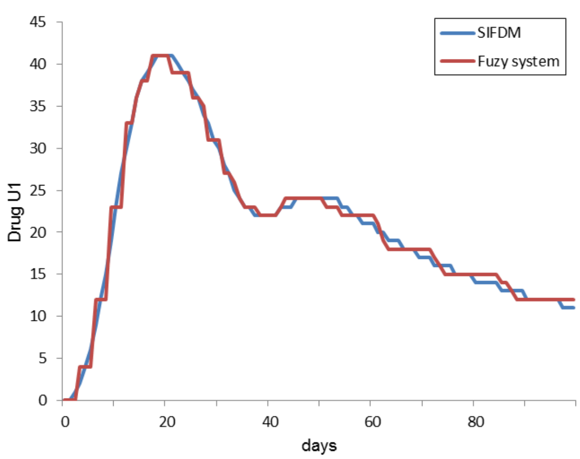


Figure 7: changes in the drug quantity of $u1$ during therapy

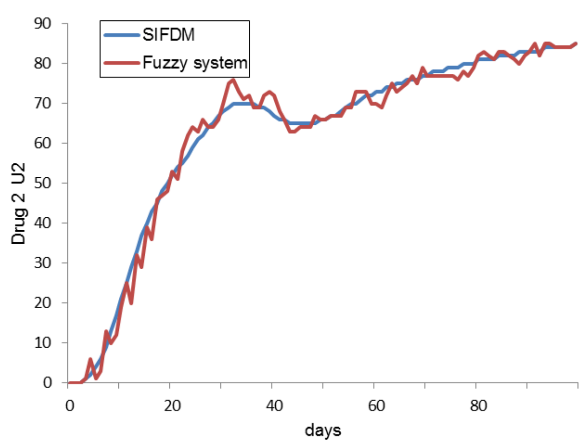


Figure 8: changes in the the drug quantity $u2$ during therapy.


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Figure 9 shows a comparison between the controlled behaviour of $v_i$ and the one given by the SIFDM. The obtained control parameters are presented in figure 10 and figure 11.

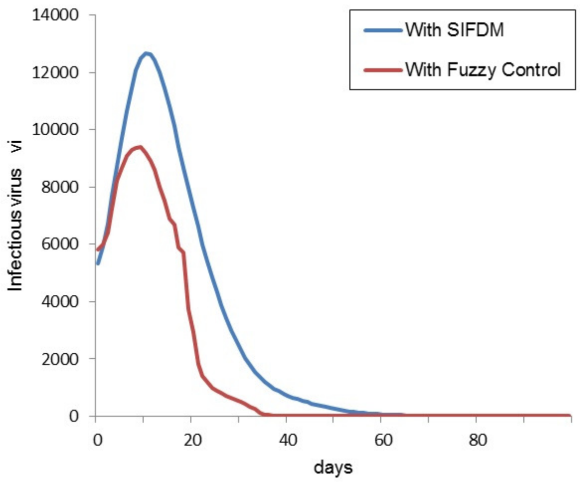


Figure 9: changes in infectious viral load during therapy

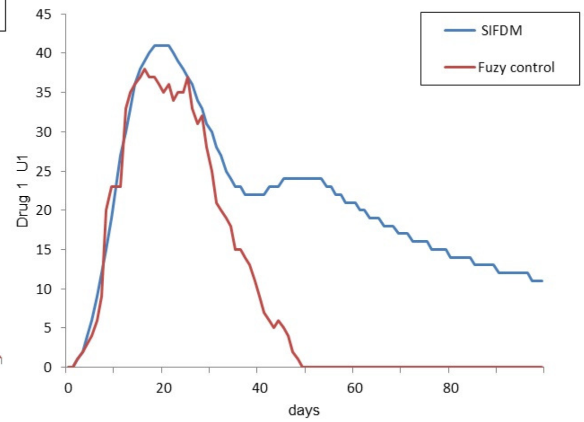


Figure 10: changes in the the drug quantity $u1$ during therapy

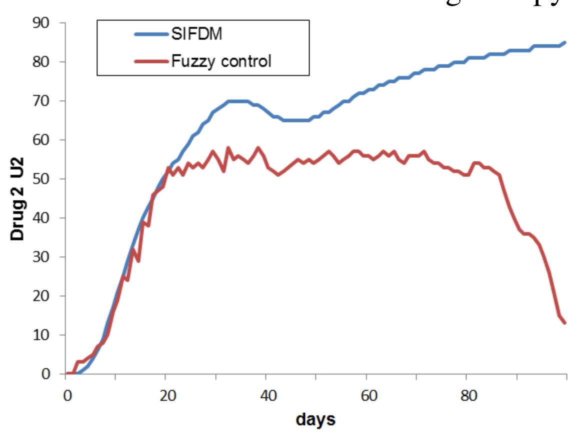


Figure 11: changes in the the drug quantity $u2$ during therapy.

## Conclusion

The introduction of new Clinical Decision Support in the area of drug treatment of viral infections is currently is a requested feature. Fuzzy logic offers an outstanding method to manage intuitively complex systems. The input-output data collected during the treatment of this type of infection, encapsulate the expertise of the doctor and the virus behaviour. The doctor's expertise is the set of decisions that were taken during treatment in different situations. From these data, a fuzzy system can identify the behaviour of the virus infection against the drug treatment, and at the same time can identify the infection behavior in relationship to the doctor's expertise. The simulation results motivate to test this tool on real data processing different viral infections, and verify its applicability in real life .

## References

[1] Celikyilmaz, A., & Turksen, I. B. (2009). Modeling uncertainty with fuzzy logic.*Studies in fuzziness and soft computing*, *240*.

[2] Babuska, R., Roubos, J. A., & Verbruggen, H. B. (1998, May). Identification of MIMO systems by input-output TS fuzzy models. In Fuzzy Systems Proceedings, 1998. IEEE World Congress on Computational Intelligence., The 1998 IEEE International Conference on (Vol. 1, pp. 657-662). IEEE.

[3] Cox, E., O'Hagan, M., Taber, R., & O'Hagen, M. (1998). *The Fuzzy Systems Handkbook with Cdrom*. Academic Press, Inc.

[4] Wang, L. X. (1994). *Adaptive fuzzy systems and control: design and stability analysis*. Prentice-Hall, Inc.

[5] Jang, J. S. (1992). *Neuro-fuzzy modeling: architectures, analyses, and applications*. University of California, Berkeley.

[6] Gomez-Skarmeta, A. F., Delgado, M., & Vila, M. A. (1999). *About the use of fuzzy clustering techniques for fuzzy model identification*. Fuzzy sets and systems, 106(2), 179-188.

[7] Bodenhofer, U. (1996). *Tuning of fuzzy systems using genetic algorithms*. na.

[8] Krishnapuram, R., & Kim, J. (1999). A note on the Gustafson-Kessel and adaptive fuzzy clustering algorithms. *IEEE Transactions on Fuzzy systems*,*7*(4), 453-461.

[9] Yager, R. R., & Filev, D. P. (1994). *Generation of fuzzy rules by mountain clustering*. Journal of Intelligent & Fuzzy Systems, *2*(3), 209-219.

[10] Chiu, S. (1997). Extracting fuzzy rules from data for function approximation and pattern classification. *Fuzzy Information Engineering: A Guided Tour of Applications. John Wiley&Sons*.

[11] Oviedo, J. J. E., Vandewalle, J. P., & Wertz, V. (2006). *Fuzzy logic, identification and predictive control*. Springer Science & Business Media.

[12] Lee, C. C. (1990). Fuzzy logic in control systems: fuzzy logic controller. II.*IEEE Transactions on systems, man, and cybernetics*, *20*(2), 419-435.

[13] Lee, C. C. (1990). Fuzzy logic in control systems: fuzzy logic controller. II.*IEEE Transactions on systems, man, and cybernetics*, *20*(2), 419-435.

[14] Hattaf, K., & Yousfi, N. (2012). Two optimal treatments of HIV infection model.*World Journal of Modelling and Simulation*, *8*(1), 27-35.

[15] Talssi, S., & Yousfi, N. (2014). Optimality Identification in Epidemiology Using Neural Networks. In *Proceedings of the 2014 IAJC-ISAM International Conference*.

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