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Fuzzy rules in asymptomatic HIV virus infected individuals model

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Abstract

The purpose of this paper is to study of the evolution of positive HIV population for manifestation of AIDS (Acquired Immunideficiency Syndrome). Our main interest is to model the transference rate in this stage. For this purpose, we use expert information on transference rate because it strongly depends of the viral load and of the level $CD4+$ of the infected individuals. More specifically, the transference rate is modeled as a fuzzy set that depends of the knowledge on viral load and $CD4+$, respectively. The main difference between this model and the classic one relies on the biological meaning of the transference rate λ. Medical science uses linguistic notions to characterize disease stages and to specify anti-retroviral therapy. Fuzzy set theory provides the formal framework to model linguistic descriptions such as the transference rate λ using expert knowledge.

1. INTRODUCTION

In the last decade, the mathematical literature on imprecision and uncertainty has grown considerably, especially in system modeling, control theory, and engineering areas. More recently, several authors have used the fuzzy set theory in epidemiology problems [6] and population dynamics [2].

Since the advent of the HIV infection, several mathematical models have been developed to describe its dynamics [3] and [5]. In this paper fuzzy set theory, introduced in the sixties by Lotfi Zadeh [9], is used to deal with imprecision on the time instant or moment in which AIDS begins its manifestation. Our study considers the transference rate λ, as used in the classical Anderson's model [3], as a fuzzy set.

Fuzzy set theory is a genuine generalization of classical set theory [1], [7] and [9] useful to model unsharp classes. In this paper, the parameter λ is viewed as a linguistic variable whose values are fuzzy sets that depends on the viral load v and on the $CD4+$ level. $CD4+$ is the main T lymphocyte attacked by the HIV retrovirus when it reaches the bloodstream. The notion of λ rate as a linguistic variable with fuzzy values captures its biological meaning more faithfully [6] and [7] to classify the disease stages, and to decide on when the antiretroviral therapy should be used. We assume that, initially, the fraction of infected asymptomatic individuals x is maximum and equal to 1, and that the fraction of AIDS symptomatic individuals y is null. The next section introduces the main definitions needed in this paper.

2. PRELIMINARY DEFINITIONS

A *fuzzy subset* F of the universe set U is defined by a *membership* function u that assigns to each element x of U a number $u(x)$ between *zero* and one to mean the degree of membership from x to F. Therefore, the fuzzy subset (or *set*, for short) F is its membership function $u: U \rightarrow [0,1]$. In this paper we will use the membership function u to denote the fuzzy set F. It is interesting to observe that a classic subset A of U is a particular fuzzy set for which the membership function is the characteristic function of A, this is, $\chi_A : U \rightarrow \{0,1\}$. The main tool that we will rely on in this paper concerns fuzzy rule-based systems [7], whose architecture is shown in figure 1. The method of fuzzy inference chosen is referred to as the Mamdani method.

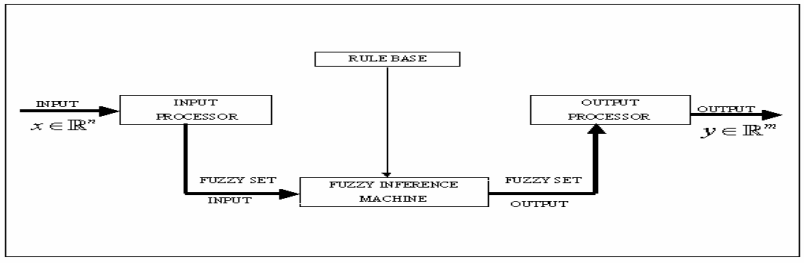

Figure 1: Architecture of fuzzy rule-based systems.

3. CLASSIC MODEL

The classical Anderson's model (1986) for AIDS is given by:

$$\frac{dx}{dt} = -\lambda(t)x \qquad x(0) = 1$$
$$\frac{dy}{dt} = \lambda(t)x = \lambda(t)(1-y) \qquad y(0) = 0 \qquad (1)$$

where $\lambda(t)$ is the transference rate between infected individuals and infected individuals that develop AIDS, x is the proportion of infected population that does not have AIDS symptoms yet, and y is the proportion of the population that has developed AIDS symptoms. Anderson assumes $\lambda(t) = at$, $a > 0$. Thus the solution of (1) is

$$x(t) = e^{-\frac{at^2}{2}} \qquad y(t) = 1 - e^{-\frac{at^2}{2}} \qquad (2)$$

4. FUZZY MODEL

When the HIV reaches the bloodstream, it attacks mainly the lymphocyte T of the $CD4+$ type. The amount of cells $CD4+$ in periferic blood has prognostics implication in infection evolution by HIV. Nowadays, the amount of immunecompetence cells is the most clinically useful and acceptable measure to treat of infected individuals by HIV, although it is not the only one. We can classify the amount of $CD4+$ cells/ml in the peripheral blood in four ranges (see: www.aids.gov.br):

1. **CD4+ > 0.5 cells/ml**: Stage of infection by HIV with low risk of to develop disease.
2. **CD4+ between 0.2 and 0.5 cells/ml**: Stage characterized for appearance of signs and shorter symptoms or constitutional alterations. Moderate risk to develop opportunist diseases.
3. **CD4+ between 0.05 e 0.2 cells/ml**: Stage with high possibility to develop opportunist diseases.
4. **CD4+ < 0.05 cells/ml**: High risk of get opportunist diseases such as Kaposi's sarcoma. High life risk and low survival chances.

On the other hand, a low HIV viral load not enough to destroy all the lymphocyte $CD4+$ of the organism. Thus, antibodies have chances to act against opportunist diseases. High viral load destroys large quantities of lymphocyte $CD4+$ and the immunologic system may lose its function.

In the beginning (or when change of anti-retroviral therapy occurs), the literature recommend viral load exams within one to two months period to evaluate the treatment. The results should be interpreted of the following way:

1. **Viral load below of 10.000 copies of RNA by ml**: low risk of disease progression.
2. **Viral load between 10.000 and 100.000 copies of RNA by ml**: moderate risk of disease progression.
3. **Viral load above of 100.000 copies of RNA by ml**: high risk of disease progression.

The identification of the disease stages and its respective treatment is based on the relation between viral load and $CD4+$ cells level. Control of the viral load and $CD4+$ cells level may interfere in the transference rate λ control.

Thus, the conversion from an asymptomatic individual to a symptomatic individual depends on the individual characteristics, as measured by the viral load v and $CD4+$. Therefore, we suggest the following modification of (1):

$$\begin{aligned} \frac{dx}{dt} &= -\lambda(v, CD4+)x & x(0) &= 1 \\ \frac{dy}{dt} &= \lambda(v, CD4+)x = \lambda(v, CD4+)(1-y) & y(0) &= 0 \end{aligned} \qquad (3)$$

The difference between this and the first model (1) is that now the parameter $\lambda = \lambda(v, CD4+)$ has a clear biological meaning and thus is a more faithful characterization of λ. From the mathematical point of view we can think of (3) as a parametric family of systems. In this case, λ is the parameter dependent of v and $CD4+$. It seems reasonable that λ, and consequently of the population y, can be controlled via v and $CD4+$. From (3) we have

$$x(t) = e^{-\lambda(v, CD4+)t} \quad y(t) = 1 - e^{-\lambda(v, CD4+)t}, \; t > 0 \qquad (4)$$

5. LINGUISTIC VARIABLES AND RULES BASE

Estimation of the transference rate $\lambda = \lambda(v, CD4+)$ is based on expert medical information. We adopt a fuzzy rule-based modeling approach assuming that the viral load (v), the $CD4+$ level, and the transference rate (λ) are linguistic variables [7]. According to section 4, the viral load is classified as low, medium and high whereas the $CD4+$ level is classified as very low, low, medium, high medium and high. The transference rate λ is classified as weak, medium weak, medium and strong. The $CD4+$ level between 0.2 and 0.5 cells/ml is divided in two ranges because it relates with an important phase of the transference of asymptomatic to symptomatic.

The fuzzy rule-based model uses the Mamdani inference method to derive the values of λ assuming the membership functions shown in figures 2, 3 and 4 and the following rule- base:

1. If v is low and $CD4+$ is very low then λ is strong.
2. If v is low and $CD4+$ is low then λ is medium.
3. If v is low and $CD4+$ is medium then λ is medium.
4. If v is low and $CD4+$ is high medium then λ is weak medium.
5. If v is low and $CD4+$ is high then λ is weak.
6. If v is medium and $CD4+$ is very low then λ is strong.
7. If v is medium and $CD4+$ is low then λ is strong.
8. If v is medium and $CD4+$ is medium then λ is medium.
9. If v is medium and $CD4+$ is high medium then λ is weak medium.
10. If v is medium and $CD4+$ is high then λ is weak.
11. If v is high and $CD4+$ is very low then λ is strong.
12. If v is high and $CD4+$ is low then λ is strong.
13. If v is high and $CD4+$ is medium then λ is medium.
14. If v is high and $CD4+$ is high medium then λ is medium.
15. If v is high and $CD4+$ is high then λ is medium.

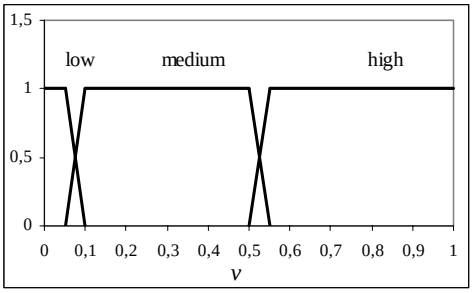

Figure 2: Membership functions viral load (v).

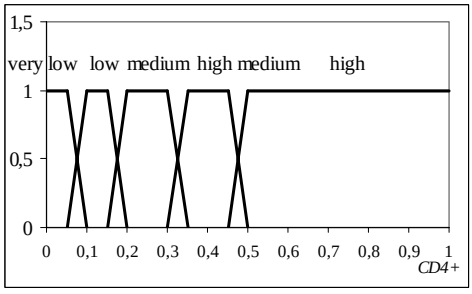

Figure 3: Membership functions CD4+ level.

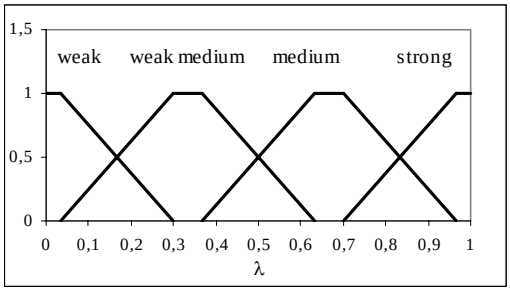

Figure 4: Membership functions lambda (λ).

6. THE TRANSFERENCE RATE λ

From of the rules base introduced in the previous section and from the inference method adopted, we simulate the viral load v and the $CD4+$ level to a HIV-positive individual during sixty months and to obtain the output $\lambda = \lambda(v, CD4+)$ as depicted in figure 5. A cross-section of the λ surface along a parallel plan to the $CD4+$ level axis is shown in figure 6.

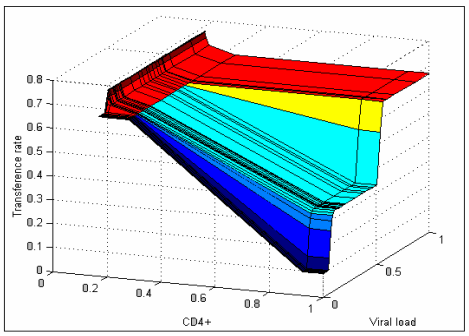

Figure 5: Function $\lambda = \lambda(v, CD4+)$.

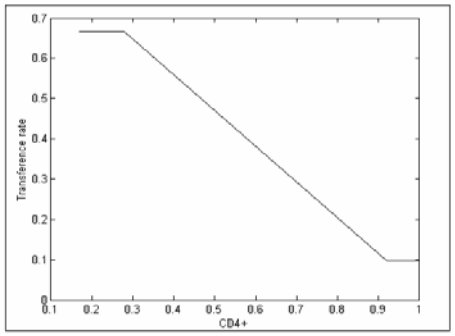

Figure 6: λ as a function of $CD4+$ (v = 0.036).

According with the section 4, $CD4+$ is the most useful parameter to control and to diagnose HIV. A more detailed study can be done assuming that the transference rate is $\lambda = \lambda(c)$, where $c = CD4+$ in the model (4). We assume λ given by the function of figure 6, that is, we assume $\lambda(c)$ as follows:

$$\lambda(c)=\begin{cases} 0 \quad if \quad c<c_{\min} \\ \dfrac{c_M-c}{c_M-c_{\min}} \quad if \quad c_{\min}\le c\le c_M \\ 1 \quad if \quad c_M<c<c_{\max} \end{cases} \tag{5}$$

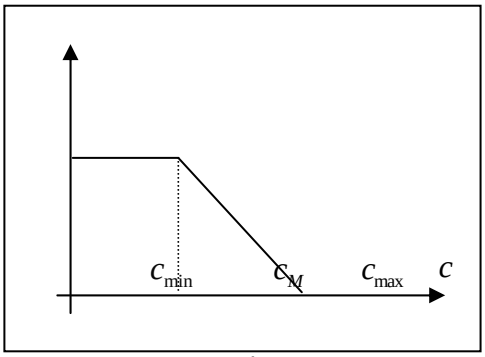

Figure 7: Transference rate λ in function of the $CD4+$.

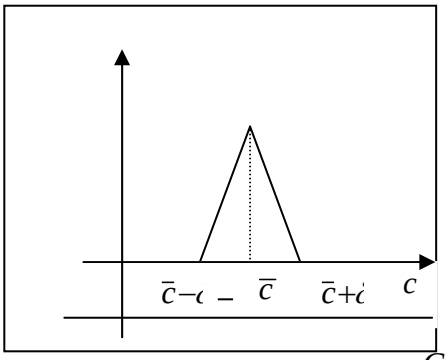

Figure 8: Membership function ρ adopted for C.

In the figure 7, $c_{\min}$ represents the minimum $CD4+$ level for which the individual becomes symptomatic, c_M represents the $CD4+$ level for which the chance to become symptomatic is minimum, and $c_{\max}$ is the largest quantity of $CD4+$ possible. In figure 6, we can observe the approximate values of $c_{\min}$ and c_M, this is, $c_{\min}$ is approximately 0.3 cells/ml and c_M is approximately 0.9 cells/ml. These values are compatible with the reality if $CD4+$ is less than 0.3 cells/ml the tendency is of the individual becomes symptomatic and when $CD4+$ is bigger than 0.9 cells/ml the tendency is of the individual to be asymptomatic. Thus, the number of asymptomatic and symptomatic individuals at the time instant *t* is:

$$x(t,c)=e^{-\lambda(v,CD4+)t} \qquad y(t,c)=1-e^{-\lambda(v,CD4+)t}$$

7. FUZZY EXPECTANCY OF THE ASYMPTOMATIC INDIVIDUALS

The fuzzy expectancy is introduced here as a deffuzification method to provide an average value of $x(t) = e^{-\lambda(v,CD4+)t}$, the number of asymptomatic individuals at the time instant *t*. To define fuzzy expectancy we need first to define a fuzzy measure. Let Ω an unempty set and $P(\Omega)$ the subsets of Ω. The function $\mu : P(\Omega) \to [0,1]$ is a fuzzy measure [4] if:

1. $\mu(\varnothing) = 0$ and $\mu(\Omega) = 1$.

2. $\mu(A) \le \mu(B) \quad if \quad A \subseteq B$.

The value of the fuzzy expectancy of the asymptomatic individuals of the fuzzy set $x = x(t,c)$ is given by [8]

$$FEV[x] = \sup_{0 \le \alpha \le 1} \inf[\alpha, \mu\{x \ge \alpha\}]$$

where $\{x \ge \alpha\} = \{c : x(c) \ge \alpha\}$ for each t and μ is a fuzzy measure. Let $H(\alpha) = \mu\{c : x(c) \ge \alpha\}$, for each $t > 0$. Here we suggest the following fuzzy measure: $\mu(A) = \begin{cases} \sup_{c \in A} \rho(c) & if \quad A \neq \varnothing \\ 0 & if \quad A = \varnothing \end{cases}$.

Let $A = [a, c_{\max}]$, where $a = c_M - (c_M - c_{\min})\left(\frac{-\ln \alpha}{t}\right)$. Observe that $c_{\min} < a \le c_M$. Note that μ is an optimist measure, in the way that the $CD4+$ level in a group is evaluated for individual with $CD4+$ best level.

Beyond of $c \in [0, c_{\max}]$, we assume that the $CD4+$ level of the group HIV-positive studied (C) has different possibility to occur. We assume c as a triangular fuzzy set (see figure 8) given by:

$$\rho(c) = \begin{cases} 0 & if \quad c \le \overline{c} - \delta \\ \frac{1}{\delta}(c - \overline{c} + \delta) & if \quad \overline{c} - \delta < c \le \overline{c} \\ \frac{-1}{\delta}(c - \overline{c} - \delta) & if \quad \overline{c} < c \le \overline{c} + \delta \\ 0 & if \quad c > \overline{c} + \delta \end{cases} \qquad (6)$$

The parameter $\overline{c}$ is the modal value and δ is the dispersion of each one the set fuzzy that defines the linguistic variable values. These fuzzy sets are defined from of the

values $c_{\min}$, c_M and $c_{\max}$ of the definition of λ. Thus, we the fuzzy expectancy by looking at three cases:

1. **Case:** $CD4+$ low (C_-). We assume $c_{\min} > \overline{c} + \delta$. Thus, $FEV[x] = e^{-t}$.
2. **Case:** $CD4+$ high (C^+). We assume $c_M \le \overline{c} - \delta$ and $\overline{c} + \delta \le c_{\max}$. Thus, $FEV[x] = 1$.
3. **Case:** $CD4+$ medium (C_-^+). We assume $\overline{c} - \delta > c_{\min}$ and $\overline{c} + \delta < c_M$. The third case is the most interesting for our purposes because most part of the individuals is within this range. After a number of manipulations, we obtain:

$$H(\alpha) = \begin{cases} 1 \quad if \quad 0 \le \alpha \le e^{-\lambda(\overline{c})t} \\ \rho(a) \quad if \quad e^{-\lambda(\overline{c})t} < \alpha < e^{-\lambda(\overline{c}+\delta)t} \\ 0 \quad if \quad e^{-\lambda(\overline{c}+\delta)t} \le \alpha \le 1 \end{cases} \tag{7}$$

where $\rho(a) = \frac{1}{\delta}\left[-c_M - (c_M - c_{\min})\left(\frac{\ln \alpha}{t}\right) + \overline{c} + \delta\right]$. As $H(\alpha)$ is continnuos and decreasing, it has a unique fixed point that coincides with $FEV[x]$. Thus we obtain the following inequality:

$$e^{-\lambda(\overline{c})t} < FEV[x] < e^{-\lambda(\overline{c}+\delta)t}. \tag{8}$$

The inequality above shows that in the best hypothesis (μ optimist) is possible the $FEV[x]$ is less than 1, since it is inferior a possible solution $e^{-\lambda(\overline{c}+\delta)t}$.

This way, for each $t > 0$ there exists a unique $c(t) \in (\overline{c}, \overline{c} + \delta)$, where $c(t) = c_M + (c_M - c_{\min})\left(\frac{\ln \alpha(t)}{t}\right)$. Thus, $FEV[x] = e^{-\lambda(c(t))t}$ is an exponential curve and, because the $CD4+$ level increases with *t*, $FEV[x]$ is decreasing. Consequently, the fuzzy expectancy is not solution of (3). Actually, at each instant t, the $FEV[x]$ coincides with the unique solution of (3). It is easy to verify that $FEV[x]$ is differentiable and that it satisfies the following differential equation with the time dependent parameter λ:

$$\frac{dx}{dt} = -\left[\lambda(c(t)) + t\frac{d\lambda}{dt}(c(t))\frac{dc}{dt}(t)\right]x \tag{9}$$

Note that for the three cases studied here, we obtain the following inequality:

$$e^{-FEV[\lambda]t} \leq e^{-\lambda(\bar{c})t} \leq FEV[x] \qquad (10)$$

8. CONCLUSION

The main difference between the deterministic and the fuzzy model is that the fuzzy model allows imprecise parameters and deffuzification at any time. In deterministic modeling, deffuzification is done in the beginning of the mathematical modeling. We may state that the deterministic models are particular instances of fuzzy models. In our case, the deterministic model (3) results the solution $x(t) = e^{-\lambda(\bar{c})t}$. The fuzzy model also provides a unique curve $FEV[x]$ when decisions are necessary. Fuzzy expectancy of *asymptomatic* individuals is bounded below by $e^{-\lambda(\bar{c})t}$. Therefore, the fuzzy model over evaluates the number of a*symptomatic* individuals. We emphasize that, despite of using an optimist fuzzy measure to evaluate the $CD4+$ level in the population, the $FEV[x]$ is less than $e^{-\lambda(\bar{c}+\delta)t}$ and thus depends of the populational dispersion δ of the $CD4+$ level of the group studied. From (8), we see that when $\delta \to 0$, $FEV[x] \to e^{-\lambda(\bar{c})t}$ that is, it depends only of $CD4+$, indicating a policy for treatment. Clearly, the fuzzy model provides a clearer and meaningful characterization of parameter λ that is compatible with medical knowledge and perception.

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