A Fuzzy Delay Differential Equation Model for HIV Dynamics

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Abstract— *This paper presents a process to obtain the solution (or flux) of a fuzzy delay system and to determine the fuzzy expected curve for the HIV (human immunodeficiency virus) when HIV-positive individuals receive antiretroviral therapy. This delay is defined as the time between the infection of a CD4+ type T-lymphocyte cell by the virus and the production of new virus particles. The intracellular delay is represented by an uncertainty parameter that depends on the individual characteristics of HIV-positive patients. A fuzzy rule-based system is used to model this parameter. The solution of the system of delay differential equations, which is a fuzzy process, is obtained from Zadeh's Extension Principle. Lastly, for each instant t, we calculate the fuzzy expected value obtained by the Center of Gravity.*

Keywords— Delay Differential Equation; Epidemiological Modeling; Fuzzy Expected Value; Fuzzy Set; HIV Dynamics; Mamdani Controller.

1 Introduction

HIV is an uncommon type of virus called a retrovirus and drugs developed to disrupt the action of HIV are known as antiretrovirals, or ARVs. The AIDS (Acquired Immunodeficiency Syndrome) virus mutates rapidly, which makes it extremely skillful at developing resistance to drugs. To minimize this risk, people with HIV are generally treated with a combination of ARVs that attack the virus on several fronts at once. The advent of ARVs in 1996 transformed the treatment of HIV and AIDS, improving the quality and greatly prolonging the lives of many infected people in places where the drugs are available. Of the estimated 6.5 million people in need of antiretroviral treatment in June 2006, 1.65 million people were reported to have had access to ARV treatment in low- and middle-income countries (World Health Organization, Jun 2006) [1]. In HIV-1 infection, treatment with reverse transcriptase or protease inhibitors results in a decline of free virus in several distinct phases. Fig. 1 summarizes the results of clinical studies, representing the different phases of viral decline after *in vivo* [2] treatment. Initially, the plasma viral load remains at approximately pretreatment levels, which, in the asymptomatic stage of the infection, are almost stationary on a time scale of weeks. This phase, which lasts from 0 to 1 day, is called the quasi-stationary initial stage. This initial phase is followed by a transition phase of 1 or 2 days, which is explained by the combination of pharmacological and intracellular delay effects that cause the disappearance of the free particles of the virus and the decline of infected cells. Another phase observed is the rapid decline of the plasma virus, which lasts from 2 to 7 days. Finally, the decline flattens out and virus levels may even rise again [2].

In this paper, we propose a process to determine the fuzzy flux of HIV decline as a function of time and, for each t, we determine the fuzzy expected value when the HIV-positive individual is receives antiretroviral therapy, considering the intracellular delay of the viral life cycle. Intracellular delay is defined as the time between the infection of a T lymphocyte cell of the $CD4+$ type by the virus and the production of new virus particles. The main lymphocyte that HIV attaches to when it reaches the bloodstream is the $CD4+$ type T lymphocyte. Based on the solution of a delay differential equation system [2], considering that the antiretroviral therapy is 100% effective, we introduced the delay τ as a fuzzy triangular number, where the degree of pertinence 1 is assumed to be $\tau = 12$h. Starting from a fuzzy rule-based system (FRBS), we determined the mortality rate of the virus as a function of delay. The fuzzy rule base was obtained from information given in [2]. With this fuzzy parameter [3], and by means of Zadeh's extension principle, we obtained a solution for the system. With this methodology applied to each instant t, the solution was a fuzzy set. Hence, we found the degree of pertinence for each solution of the deterministic system as a function of time. We then calculated the fuzzy expected value for the solutions of the system at each instant t, using the center of gravity. The curve of the expected value shows a profile similar to the curves of the clinical data when antiretroviral therapy is applied, as illustrated in Fig. 1.

2 Classic Models

In [2] was introduced two microscopic models for HIV infection dynamics in the individual organism undergoing antiretroviral therapy. These models are used in this paper.

The first is a model for viral dynamics with three variables: the population of uninfected cells, $x(t)$; the population of infected cells that produce the virus, $y(t)$, and the plasma virus population, $v(t)$. In a first approximation of the dynamics, we assumed that the influx λ and death rate d of uninfected cells are constant. Uninfected cells and free virus produce infected cells at a rate of $\beta(t)x(t)v(t)$. Infected cells produce free virus particles at a rate of $k(t)$ and die at a rate of a. Free virus

ISBN: 978-989-95079-6-8

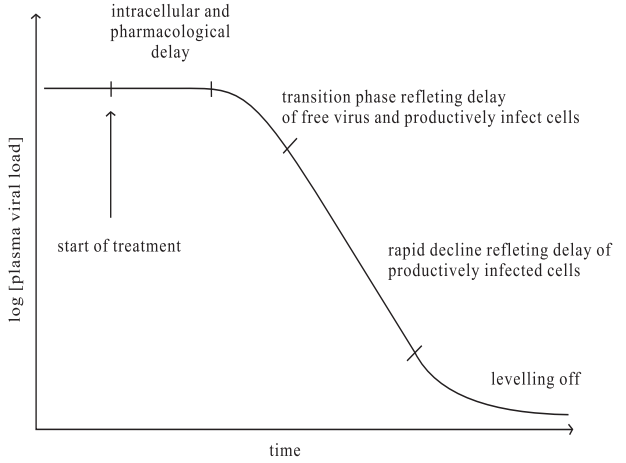

Figure 1: Schematic illustration of the different phases of plasma virus decline following antiretroviral therapy [2].

particles are cleared at a rate of u. To describe the effects of various drug therapies, the parameters $\beta(t)$ and $k(t)$ are time-dependent. Based on these assumptions, the differential equation system is given by:

$$\frac{dx(t)}{dt} = \lambda - dx(t) - \beta(t)x(t)v(t) \quad (1)$$

$$\frac{dy(t)}{dt} = \beta(t)x(t)v(t) - ay(t) \quad (2)$$

$$\frac{dv(t)}{dt} = k(t)y(t) - uv(t) \quad (3)$$

The model does not contain an intracellular time delay between infection of a cell and production of new virus particles. The model (4)-(6) incorporates the intracellular phase of the virus life cycle. In [2], it was assumed that virus production lags by a delay τ behind the infection of a cell. This implies that the recruitment of virus-producing cells, at time t, is given by the density of cells that were newly infected at time $t-\tau$ and are still alive at time t. Moreover, we assumed a constant death rate $\tilde{a}$ for infected but not yet virus-producing cells. The probability of survival from $t-\tau$ to time t is only $e^{-\tilde{a}\tau}$. More generally, the probability of survival is given by a nonincreasing function $f(\tau)$ with $0 \le f(\tau) \le 1$. Thus, (1), (2) and (3) can be written as:

$$\frac{dx(t)}{dt} = \lambda - dx(t) - \beta(t)x(t)v(t) \quad (4)$$

$$\frac{dy(t)}{dt} = \beta(t-\tau)x(t-\tau)v(t-\tau)e^{-\tilde{a}\tau} - ay(t) \quad (5)$$

$$\frac{dv(t)}{dt} = k(t)y(t) - uv(t) \quad (6)$$

The equation (5) has become a 'delay-differential equation τ'. Analytical solutions of this type of equation are generally difficult to find. However, for the problem in question, the populations of uninfected cells, infected virus-producing cells and free virus are at a steady-state level before treatment sets in [2]. This situation facilitates the mathematical analysis and enables us to derive simple analytical solutions. The nontrivial steady state of the system is given by:

$$x_0 = \frac{au}{\beta k}e^{\tilde{a}\tau}$$

$$y_0 = \frac{\lambda}{a}e^{\tilde{a}\tau} - \frac{du}{\beta k}$$

$$v_0 = \frac{ky_0}{u} \quad (7)$$

where β and k are constant pretreatment rates.

2.1 Protease Inhibitor Therapy

Reference [2] includes treatment with HIV protease inhibitors that block the production of new infectious virus v_I from already infected cells, allowing only noninfectious virus to be generated. As previously reported, the infectious virus declines but continues to infect cells [4] and [5].

According to [2], within the present framework, equation (6) also describes the dynamics of the total free virus. Infectious virus v_I, however, is not produced in $t > 0$ and declines according to $\frac{dv_I(t)}{dt} = -uv_I(t)$. Also, equations (4) and (5) remain valid if one replaces v with v_I.

In [2], it is assumed that the uninfected cell population remains constant, $x(t) = x_0$ within the time scale under consideration. For $x(t) = x_0$ and exponentially declining $v_I(t)$, equation (5) is solved by:

$$y(t) = \frac{y_0}{a-u}[ae^{-u(t-\tau)} - ue^{-a(t-\tau)}] \quad for \quad t > \tau. \quad (8)$$

From (6), the time evolution of free virus is then given by $v(t) = v_0$ for $0 < t \le \tau$ and

$$v(t) = v_0 e^{-u(t-\tau)} + \frac{uv_0}{a-u}\left\{\frac{u}{a-u}\left[e^{-a(t-\tau)} - e^{-u(t-\tau)}\right]\right\}$$

$$+\frac{uv_0}{a-u}\left\{a(t-\tau)e^{-u(t-\tau)}\right\} \quad for \quad t > \tau. \quad (9)$$

Combined reverse transcriptase inhibitor and protease inhibitor therapy may, in the long term, delay the evolution of drug-resistant virus strains [2].

After application of any antiviral drug, there is a short delay in the pharmacological effect due to the time required for drug absorption, distribution, and penetration into target cells. In the initial phase, the plasma virus load remains constant. The duration of this phase is the sum of the pharmacological delay [2], defined as the time span the drug requires to reach an effective concentration, and the intracellular delay, defined as the time between infection of a cell and production of new virus particles.

Thus, differences in plasma virus decline for a fixed half-life of infected cells ($a = 0.5$/day), with a delay of about 0.9 days, are shown in Fig. 2 for protease inhibitors. Intracellular delays were chosen to ensure that the long-term decline is identical in all cases. The curves differ mostly at the end of the shoulder phase, but even for strongly varying parameters, the differences are minor, see Fig. 3.

It is important to note that for different values of intracellular delay (τ) and rate of decline in the plasma virus concentration (u), the behavior of the plasma viral load (Fig. 3) is similar to that of the initial phases of antiretroviral treatment,

ISBN: 978-989-95079-6-8

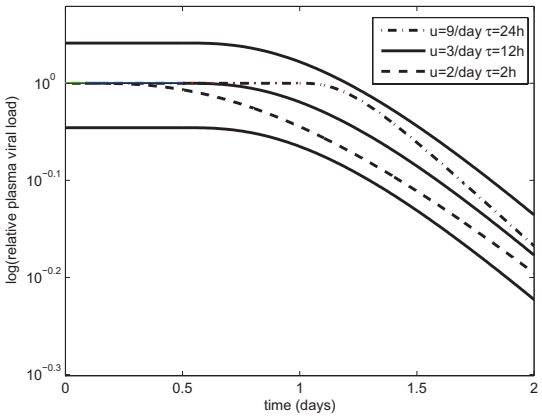

Figure 2: Sensitivity parameter of the protease inhibitor equation (9). Parameter a is fixed ($a = 0.5/day$), whereas u and τ vary. The two thin lines represent 10% deviations from the mean solution to illustrate expected measurement errors under ideal experimental conditions [2].

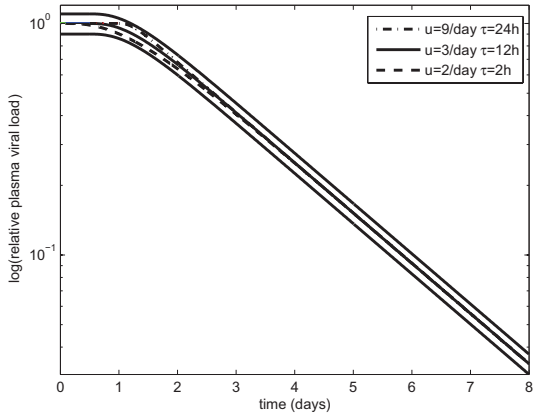

Figure 3: Range of HIV decline in response to protease inhibitor therapy [2].

as illustrated in Fig. 1, which summarizes the clinical studies, rendering the model credible (4)-(6). Reference [6] states that the length of delays is not directly measurable in vivo. Thus, additional in vitro data would prove valuable in expanding our knowledge of the characteristics of delay. Although these in vitro data are fraught with uncertainties, they clearly indicate that there is a delay between the initial infection and the production of new virus [7].

Reference [6] also states the need to explore the effects of different types of delay, such as distributed delays. Reference [7] assumes that the delay is given by a probability distribution. We propose a process to study the decline of the viral load after the beginning of protease inhibitor therapy. To this end, we consider that the intracellular and pharmacological delay is modeled by a fuzzy number, which takes into account a possibility distribution that can be given by a specialist.

The next section introduces the fuzzy model, which is the main object of this paper.

3 Fuzzy Model

Mathematical models for biological phenomena are normally fraught with uncertainties, in both the state variables and the parameters of the model's equations [8]. In our specific case, for reasons set forth in the introduction of this paper, we will consider that the delay time (τ) is uncertain and is modeled by the fuzzy set theory. Therefore, to study HIV decline over time, we developed a model which is a combination of classic delay differential equations and fuzzy logic.

A mathematical model in [4] was developed for protease inhibitor therapy, which fitted theoretically predicted curves of plasma virus decline to empirical data. The authors determined an average of about 0.9 days for the intracellular phase.

The next subsection presents a summary of the fuzzy set theory that was adopted in this work.

3.1 Fuzzy Sets

A *fuzzy subset* F of the universe set $\mathcal{U}$ is defined in terms of a function of *pertinence* u , which, at each element x of $\mathcal{U}$, associates a number $u(x)$ from *zero* and *one* called degree of pertinence of x to F. Thus, the fuzzy set F is symbolically indicated by its pertinence function

$$u_F : \mathcal{U} \rightarrow [0,1].$$

The values $u_F(x) = 1$ and $u_F(x) = 0$ indicate, respectively, the complete pertinence and the nonpertinence of element x to F.

A concept that will play a key role in this paper is fuzzy rule-based systems (FRBS) that have four components: an input processor, a collection of fuzzy rules called rule base, a fuzzy inference machine, and an output processor [9]. As the fuzzy inference machine we adopted the Mamdani Inference Method, while the output processor we used was the Center of Gravity.

Another concept used in this paper is Zadeh's Extension Principle.

Let X and Y be sets and f na application of X in Y. Let Abe a fuzzy set in X. The extension principle states that the image of A by the function f is a fuzzy set $B = f(A)$ in Y, whose pertinence function is given by

$$u_B(y) = \sup_x u_A(x) \tag{10}$$

for each $y \in Y$ with $x \in X$ and $y = f(x)$.

3.2 Methodology

Using an FBRS with the Mamdani Inference Method and center of gravity defuzzification, we obtained the defuzzified values of u as a function of τ. The least-square regression yielded $u(\tau)$. To represent the distributed delay, we adopted τ as a fuzzy triangular number. We then applied Zadeh's extension principle in two stages: first, to obtain the fuzzy u, and then to fuzzify the vital load. Finally, for each instant t, we calculated the fuzzy expected value by means of the Center of Gravity.

3.3 Fuzzy Rules

To determine the relationship between u and τ ($u = u(\tau)$), we adopted a FBRS, taking advantage of the fact that these variables are positively correlated [2].

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The intracellular delay (τ) and rate of decline in plasma virus concentration (u) are linguistic variables: the values of intracellular delay are expressed as $\{$*low*, *medium*, *high medium*, *high*, and *very high*$\}$, while the rate of decline in plasma virus concentration is expressed in the term set $\{$*low*, *medium*, *high medium*, *high*, *very high* $\}$.

Based on the values

- $u = 9/\text{day}$ and τ=0.08 day (approximately 2h);
- $u = 3/\text{day}$ and τ=0.5 day (12h);
- $u = 2/\text{day}$ and τ=1 day (24 h).

employed in the studies of [2], we adopted the domains of the pertinence functions of the intracellular delay (τ) and of the rate of decline in plasma virus concentration (u) as intervals that contain these values.

Following the positive correlation, the rule base that encodes the correlation between τ and u is given by:

- If τ is *low* then u is *low*.
- If τ is *medium* then u is *medium*.
- If τ is *high medium* then u is *high medium*.
- If τ is *high* then u is *high*.
- If τ is *very high* then u is *very high*.

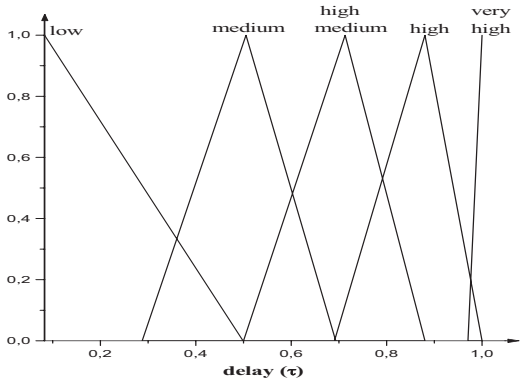

Figure 4: Membership functions for delay (τ).

The membership functions for each fuzzy set that specify the meaning of the linguistic variables for intracellular delay (τ) and rate of decline in plasma virus concentration (u) are shown in Fig. 4 and 5, respectively.

The data on virus mortality rate as a function of delay presented in Fig. 6 were obtained from the defuzzified values in the $[0.08, 1]$ interval of the FRBS. Using least-squares regression, we obtained the curve of the mortality rate of the virus as a function of delay, which is given by

$$u(\tau) = 1.67e^{1.63\tau} \tag{11}$$

with a determination coefficient (R^2) of 0.9873, as indicated in Fig. 6.

For biologic reasons, Mittler et al. [7] used a probabi-

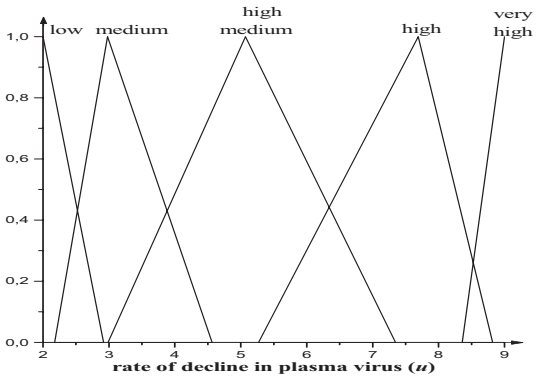

Figure 5: Membership functions for rate of decline in plasma virus concentration (u).

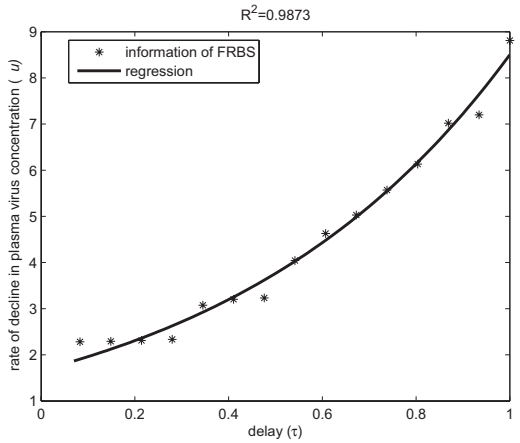

Figure 6: Regression of the rate of decline in plasma virus concentration

lity distribution function for τ. Here, in this paper, we will consider a possibility distribution instead a probability distribution function for τ. The rate of decline (u) will be obtained from a fuzzy rule-based system combined with the extension principle. Another method could be used for obtaining u. For example, the fuzzy systems given by gradual rules [10]. However, in this last case, we are not sure if these systems, in fact, approximate real functions.

3.4 Fuzzy Delay Distribution

We considered τ as a fuzzy parameter given by the fuzzy triangular number, whose support is [0.08,1] and maximum pertinence in 0.5, Fig.7.

The extension principle was used to obtain the image u of the fuzzy set τ, through function $u(\tau) = 1.67e^{1.63\tau}$. More specifically, from the formula:

$$\mu_{u(\tau)}(y) = \sup_{\{s:u(s)=y\}} \mu_{\tau}(s) \tag{12}$$

where τ is the fuzzy set whose membership function is u_τ, and $u(\tau)$ is the corresponding fuzzy set with membership function $\mu_{u(\tau)}$. Fig. 8 shows the extension principle for $u(\tau)$, assuming

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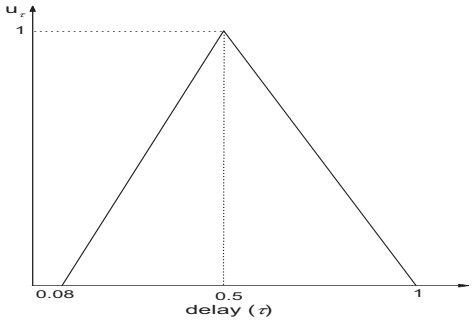

Figure 7: Fuzzy parameter (τ).

μ_τ, as in Fig. 7.

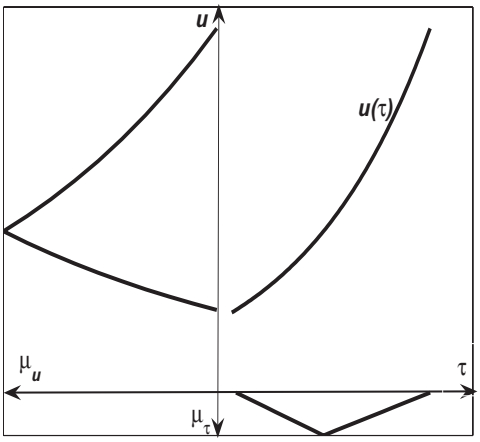

Figure 8: Computation μ_u.

3.5 *Fuzzy Solution*

The fuzzy solution for the viral load was obtained by fuzzification of the deterministic solution given by:
$v(t;\tau) = v_0$ for $0 < t \leq \tau$ and

$$v(t;\tau) = v_0 e^{-u(\tau)(t-\tau)} + \frac{u(\tau)v_0}{a-u(\tau)}\left\{\frac{u(\tau)}{a-u(\tau)}\left[e^{-a(t-\tau)} - e^{-u(\tau)(t-\tau)}\right]\right\}$$

$$+\frac{u(\tau)v_0}{a-u(\tau)}\left\{a(t-\tau)e^{-u(\tau)(t-\tau)}\right\} \quad for \quad t > \tau \qquad (13)$$

since we are admitting τ, and hence, u, as a fuzzy number.

At each instant t, Zadeh's Extension Principle is adopted for the function $v(t;\tau)$ applied in τ.

Fig. 9 presents the graphic solution of the fuzzy model. The light region shows the curves with the highest possibility of representing the phenomenon.

3.6 *Defuzzification of the Fuzzy Solution*

A common defuzzification scheme is the center of gravity method. For a fixed t, denote $v(t;\tau)$ by $v_t(\tau)$ to simplify the notation. Let $\mu_{v_t(\tau)}$ be the membership function of $v_t(\tau)$. Thus,

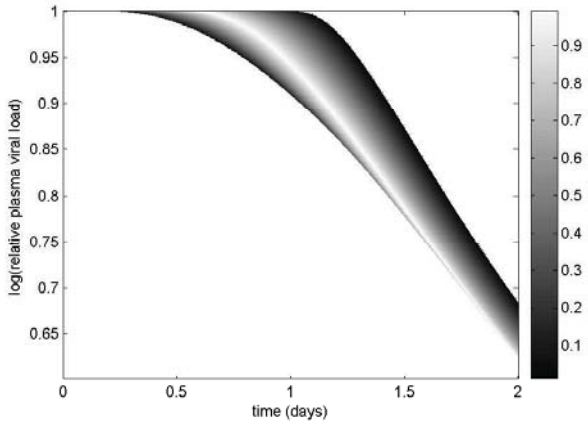

Figure 9: Solution of the fuzzy viral load for t varying from 0 to 2 days

a real-valued output $\bar{v}(t)$ is obtained at each time instant t, according to the formula:

$$\bar{v}(t) = \frac{\int\limits_{supp(v_t(\tau))} v_t(\tau)\mu_{v_t(\tau)}(v_t(\tau))dv_t(\tau)}{\int\limits_{supp(v_t(\tau))} \mu_{v_t(\tau)}(v_t(\tau))dv_t(\tau)} \qquad (14)$$

Given the fuzzy solution shown in Fig.9 and using the center of gravity, we obtained the defuzzified solution depicted in Fig.10.

The method generates a fuzzy expected curve which we have called a (defuzzified) solution $\bar{v}(t)$.

Reference [11] showed that this curve is the solution of the nonautonomous differential equation and may be viewed as the expected value of $v_t(\tau)$.

The solution $v(t;\tau)$ is obtained from a family of classic differential equations (Fig.11). However, it does not coincide with any solution for a fixed τ. For each t, $v(t;\tau)$ (14) is a value that belongs to the solution of the family of equations parameterized by $u(\tau)$. What differs here from the derived curve (14) suggested by the deterministic solutions is that, in deterministic solutions, all the uncertainties are excluded at the beginning (defuzzified at $t = 0$ and solved), whereas here the uncertainties evolve and defuzzification occurs at the time instant of interest (defuzzified when necessary) [11] and [12]. Hullermeier [13] suggests that the solution of a fuzzy differential equation is a fuzzy function obtained from a family of differential inclusions. Mizukoshi et al [14] have shown that when parameters (coefficients and/or initial conditions) are fuzzy, the Hullermeier solution is the same as that obtained from the extension principle. Therefore, we first obtained the solution of the classical differential equation and then used the extension principle to obtain fuzzy solutions. To obtain a real-valued trajectory, we adopted the center of gravity to defuzzify the fuzzy solution.

By means of equation (14), we obtained the fuzzy expected value $\bar{v}(t)$ at each instant t, which at first intercepts curves that present greater delays and, over time, intercepts curves with smaller delays, Fig. 11.

ISBN: 978-989-95079-6-8

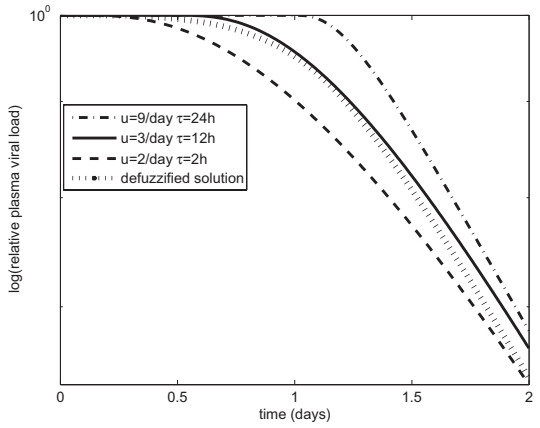

Figure 10: Defuzzified solution at each time instant t

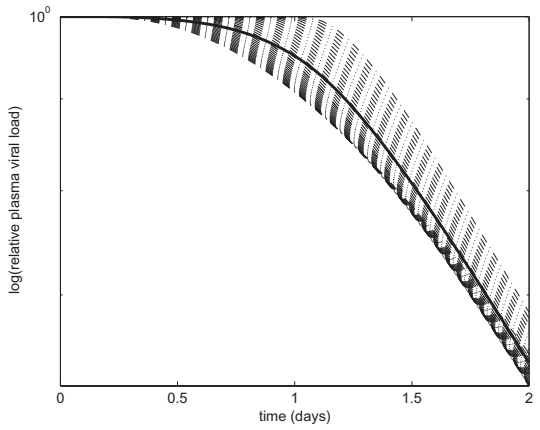

Figure 11: In the graph, the solid line represents the fuzzy expected value $\overline{v}(t)$.

4 Conclusions

In this work, emphasis was given to the study of the initial phase of treatment, since the plasma concentration of HIV declined by approximately 90% in the first two weeks of therapy due to the rapid elimination of free virus and the decline in infected cell productivity [15], see Fig. 10.

The work of [2] shows that intracellular delay may affect the magnitude of the range observed in Fig. 3, which represents variability or uncertainty. The adoption of distributed delay has yielded good results in the study of the dynamics of HIV under treatment [7]. In this paper, we adopted a fuzzy number to represent the distributed delay, which enabled us to obtain curves with different degrees of possibility to represent the phenomenon, Fig. 9. The degrees of pertinence of the curves come close to 1, as the curves approach the light region. This region is the one that best represents the phenomenon from the standpoint of credibility.

The defuzzified curve $\overline{v}(t)$ represents the amount of virus at each instant t. This curve is an average of the deterministic solutions given in (13), weighted by their respective degrees of possibility, which renders the curve more representative than each of the solutions of (13), adopting a value for τ.

Acknowledgements

The first author gratefully acknowledges CNPq, the Brazilian National Research Council, for granting a postdoctoral fellowship (152068/2007-4). The second author thanks FAPESP, the Research Foundation of the State of São Paulo, for grant no. 06/05920-7, and CNPq for grant no. 307890/2006-6.

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ISBN: 978-989-95079-6-8