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ESTIMATION OF HIV/AIDS PARAMETERS

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Abstract: This paper shows how well-established control system techniques can be introduced to formulate guidelines for clinical testing and measurement of the HIV/AIDS disease for the estimation of HIV/AIDS parameters. It is assumed that the viral load and CD4+ T cell count in plasma blood are measured. The objective is to estimate all parameters in the basic three dimensional HIV/AIDS model. For this purpose, through an observability analysis, the minimal number of measurement samples for the CD4+ T cell and the viral load counts is first obtained. The paper determines then the HIV progression stages when an estimation of all parameters is impossible. Outside these stages, the paper proposes two on-line estimation algorithms for all HIV parameters based on the well-known techniques of adaptive identifers and adaptive observers. Conditions for parameter convergence are discussed. Simulation results are demonstrated for the parameter estimation using adaptive observers. ©*2002 IFAC*

Keywords: adaptive identifier, adaptive observer, biomedical, HIV/AIDS, nonlinear systems, observability

1. INTRODUCTION

Over the last two decades tremendouseffort has been applied to the mathematical modeling of the epidemiology and immunology dynamics of HIV (Perelson and Nelson, 1999; Nowak and May, 2000; Covert and Kirschner, 2000). There are several approaches to the modeling of the infectious diseases at the cellular level to describe the immune system and the host-pathogen interaction. These modeling approaches give profound insights to the dynamics of the disease (Ho, *et al*, 1995; Wei, *et al*, 1995).

While many of the models have tended to focus on explaining the dynamics of CD4+ T cells and viral load in blood, model parameters were only estimated for the virus clearance rate and the death rate of infected CD4+ T cells for a post-treatment period of very strong chemotherapy of reverse transcriptor inhibitors and protease inhibitors in (Ho, *et al*, 1995; Wei, *et al*, 1995), and later re-calibrated in (Perelson, *et al*, 1996). These early estimations are very rough, because the key assumption that inhibition is 100% effective has not been verified and is hardly practical. As for other parameters, very little attention has been given to the estimation except for an analysis based on the quasi-steady state of the asymptomatic period before it is disturbed by chemotherapy (Wein, *et al*, 1997).

This paper shows how well-established control system techniques can be introduced to formulate guidelines for clinical testing and measurement of the HIV/AIDS disease for the estimation of HIV/AIDS parameters. It is assumed that the viral load and CD4+ T cell count in plasma blood are measured. The objective is to estimate all parameters in the basic three dimensional HIV/AIDS model. For this purpose, through an observability analysis in §2, the minimal number

of measurement samples for the CD4+ T cell and the viral load counts is first obtained. The paper determines then the HIV progression stages when an estimation of all parameters is impossible. Outside these stages, the paper proposes in §3 and §4 two on-line estimation algorithms for all HIV parameters based on the well-known techniques of adaptive identifiers and adaptive observers. Conditions for parameter convergence are discussed. Simulation results are demonstrated in §5 for adaptive observers. In §6, some conclusions are drawn.

2. MODEL OF HIV/AIDS AND ITS OBSERVABILITY

Consider the following three dimensional model of HIV/AIDS

$$\begin{cases} \dot{x}_1 = s - dx_1 - \beta x_1 x_3 \\ \dot{x}_2 = \beta x_1 x_3 - \mu_1 x_2 \\ \dot{x}_3 = k x_2 - \mu_2 x_3 \end{cases} \tag{1}$$

A description of the model follows:

The first equation is the population dynamics of the uninfected CD4+ T cells. Since it is a one-compartment model, x_1 is identified with the CD4+ T cell counts in blood per cubic millimeter. s represents the rate at which new CD4+ T cells are created from sources within the body, such as the thymus. T cells can also be created by proliferation of existing T cells. A proliferation term can be added to the right hand side (Perelson, *et al*, 1993; Kirschner, *et al*, 1997; Perelson and Nelson, 1999; Alvarez-Ramirez, *et al*, 2000). Some authors assume, however, that the source term s is constant, and the proliferation effect may be lumped into the constant d (see (Nowak and May, 2000) and references therein). In this paper, the proliferation term is not considered separately for simplicity reasons. In the presence of HIV, T cells become infected. This infection is represented by a "mass-action" term in which the rate of infection is given by $\beta x_1 x_3$, with β being the infection rate constant. x_3 is explained below.

The second equation is the population dynamics of the infected cells. Infected cells are produced at a rate of $\beta x_1 x_3$ from the infection of healthy cells by HIV. μ_1 is the death rate of infected cells.

The last equation represents the dynamics of the concentration of free virions. The free virions are produced by the infected CD4+ T cells at a rate constant k, and μ_2 is the death rate of free virions. In this equation, the loss of virus due to infection of a cell is ignored.

This basic model has been considered in (Nowak and Bangham, 1996; Nowak and May, 2000; Perelson and Nelson, 1999). To reveal more detailed progression of the disease, the model has also been extended to higher dimensions in (Perelson, *et al*, 1993; Kirschner, *et al*, 1997; Perelson and Nelson, 1999; Alvarez-Ramirez, *et al*, 2000; Nowak and May, 2000). The identifiability properties of some higher dimensional models will be discussed elsewhere.

In this paper, it is assumed that the measurement of the viral load and the CD4+ T cell counts in plasma is available. This assumption is in accordance with the current prevailing medical practice. Also since the number of infected CD4+ T cells (x_2) is found to be too small compared to the number of healthy CD4+ T cells (x_1) (Embretson, *et al*, 1993; Janeway and Travers, 1997; Chun, *et al*, 1997), one can safely assume that the CD4+ T test gives the healthy CD4+ cell counts. That is, the measured outputs are $y_1 = x_1$ and $y_2 = x_3$.

Observability is a basic system property of whether all state variables can be calculated from the measured output, even though many other definitions of observability of nonlinear systems exist (Conte, *et al*, 1999). In this basic sense, the system (1) is observable, since one calculates that $x_1 = y_1$, $x_2 = (\dot{y}_2 + \mu_2 y_2)/k$, $x_3 = y_2$, for $k \neq 0$. Note that $k = 0$ corresponds to the case that no HIV virus matures despite the CD4+ T cells being infected, which is not the case for most HIV patients.

Then higher order differential equations of the output can be obtained as,

$$\dot{y}_1 = \theta_1 + \theta_2 y_1 + \theta_3 y_1 y_2, \tag{2}$$

$$\ddot{y}_2 = \theta_4 \dot{y}_2 + \theta_5 y_2 + \theta_6 y_1 y_2, \tag{3}$$

where $\Theta = (\theta_1, \ldots, \theta_6)^T = (s, -d, -\beta, -\mu_1 - \mu_2, -\mu_1\mu_2, k\beta)^T$. Θ is invertible for $\beta \neq 0$ and $\mu_1 \neq \mu_2$. It is known that for most HIV patients, $\beta \neq 0$ and $\mu_2 > \mu_1$ (Nowak and May, 2000). In this case, it has the following inversion,

$$\begin{bmatrix} s \\ d \\ \beta \\ \mu_1 \\ \mu_2 \\ k \end{bmatrix} = \begin{bmatrix} \theta_1 \\ -\theta_2 \\ -\theta_3 \\ \dfrac{-\theta_4 - \sqrt{\theta_4^2 + 4\theta_5}}{2} \\ \dfrac{-\theta_4 + \sqrt{\theta_4^2 + 4\theta_5}}{2} \\ -\dfrac{\theta_6}{\theta_3} \end{bmatrix}. \tag{4}$$

From equation (4), the identifiability of the original parameters of (1) is equivalent to that of Θ. Thus, all the original parameters are identifiable from the measurement of the viral load and the CD4+ T cell counts in the blood of an HIV patient.

Identifiability means that all parameters can be determined from measuring the output. To actu-

ally determine these parameters, it is necessary to generate a minimum of six equations based on (2) and (3), three from each equation. One concludes that at least four measurements of the CD4+ T cell count y_1 and five measurements of the viral load are needed for a complete determination of all the HIV/AIDS parameters in the 3-dimensional model (1).

For simplicity, assume that the following measurements are available,

$$
\begin{aligned}
&y_1^0 = y_1(t_0), y_1^1 = y_1(t_0 + d_1)\\
&y_1^2 = y_1(t_0 + d_1 + d_2), y_1^3 = y_1(t_0 + d_1 + d_2 + d_3);\\
&y_2^0 = y_2(t_0), y_2^1 = y_2(t_0 + d_1),\\
&y_2^2 = y_2(t_0 + d_1 + d_2), y_2^3 = y_2(t_0 + d_1 + d_2 + d_3),\\
&y_2^4 = y_2(t_0 + d_1 + d_2 + d_3 + d_4).
\end{aligned}
$$

The CD4+ T cell counts and the viral load may be measured at different time intervals, in this case, interpolation and/or expolation can be used.

From these measurements, the following three equations can be generated based on (2), in which the derivative of y_1 is approximated by $\Delta y_1/\Delta t$,

$$
A \begin{bmatrix} \theta_1 \\ \theta_2 \\ \theta_3 \end{bmatrix} = \begin{bmatrix} 1 & y_1^0 & y_1^0 y_2^0 \\ 1 & y_1^1 & y_1^1 y_2^1 \\ 1 & y_1^2 & y_1^2 y_2^2 \end{bmatrix} \begin{bmatrix} \theta_1 \\ \theta_2 \\ \theta_3 \end{bmatrix} = \begin{bmatrix} \dfrac{y_1^1 - y_1^0}{d_1} \\ \dfrac{y_1^2 - y_1^1}{d_2} \\ \dfrac{y_1^3 - y_1^2}{d_3} \end{bmatrix}
$$

If the matrix A is nonsingular, then there is a unique solution for θ_1, θ_2 and θ_3, and hence estimates for s, d and β.

On the other hand, when either y_1 or y_2 is constant, then A can never be nonsingular for any choice of measurement interval. In the long asymptomatic stage, the viral load y_2 remains constant, and in the short period after chemotherapy treatment, the CD4+ T cell count does not change much (see the assumption made in (Ho, *et al*, 1995; Wei, *et al*, 1995)). Therefore during these two time periods, a complete determination of s, d and β is impossible.

Similar conclusions can be drawn from working with (3).

3. ESTIMATION USING ADAPTIVE IDENTIFIERS

The estimation described in the previous section requires the approximation of the derivatives of y_1 and y_2, as is sensitive to noise. It is a standard practice in adaptive estimation to design a suitable filter for the available signals (Sastry and Bodson, 1989).

Let $\lambda_1(s) = s + \lambda_{11}$, $\lambda_2(s) = s^2 + \lambda_{22}s + \lambda_{21}$ be two Hurwitz polynomials, *i.e.*, $\lambda_{11}, \lambda_{21}$ and λ_{22} are all positive. Denote the Laplace transforms of $y_1(t), y_2(t)$ and $y_1(t)y_2(t)$ as $y_1(s), y_2(s)$ and $\overline{y_1 y_2}(s)$, respectively. Then from (2) and (3),

$$
\begin{aligned}
y_1(s) &= \frac{1}{\lambda_1(s)}\phi_{11} + \frac{y_1(s)}{\lambda_1(s)}\phi_{21} + \frac{\overline{y_1 y_2}(s)}{\lambda_1(s)}\phi_{31},\\
y_2(s) &= \frac{s y_2(s)}{\lambda_2(s)}\phi_{12} + \frac{y_2(s)}{\lambda_2(s)}\phi_{22} + \frac{\overline{y_1 y_2}(s)}{\lambda_2(s)}\phi_{32},
\end{aligned}
$$

where the new parameterization is,

$$
\Phi = \begin{bmatrix} \phi_{11} & \phi_{12} \\ \phi_{21} & \phi_{22} \\ \phi_{31} & \phi_{32} \end{bmatrix} = \begin{bmatrix} \theta_1 & \lambda_{22} + \theta_4 \\ \lambda_{11} + \theta_2 & \lambda_{21} + \theta_5 \\ \theta_3 & \theta_6 \end{bmatrix}.
$$

Define the following time-domain realizations

$$
\begin{cases} \dot{\xi}_1 = -\lambda_{11}\xi_1 + 1, \\ \dot{\xi}_2 = -\lambda_{11}\xi_2 + y_1, \\ \dot{\xi}_3 = -\lambda_{11}\xi_3 + y_1 y_2, \end{cases}
$$

$$
\begin{cases} \dot{\xi}_{21} = \xi_{22}, \\ \dot{\xi}_{22} = -\lambda_{21}\xi_{21} - \lambda_{22}\xi_{22} + y_2, \end{cases}
$$

$$
\begin{cases} \dot{\xi}_{31} = \xi_{32}, \\ \dot{\xi}_{32} = -\lambda_{21}\xi_{31} - \lambda_{22}\xi_{32} + y_1 y_2, \end{cases}
$$

and denote

$$
W = \begin{bmatrix} w_{11} & w_{12} \\ w_{21} & w_{22} \\ w_{31} & w_{32} \end{bmatrix} = \begin{bmatrix} \xi_1 & \xi_{22} \\ \xi_2 & \xi_{21} \\ \xi_3 & \xi_{31} \end{bmatrix},
$$

and one can define the following identifier output

$$
Y_i(t) = \begin{bmatrix} y_{i1}(t) \\ y_{i2}(t) \end{bmatrix} = \Phi^T W(t), \tag{5}
$$

and the identifier error

$$
E(t) = \begin{bmatrix} e_1(t) \\ e_2(t) \end{bmatrix} = Y_i(t) - Y(t), \tag{6}
$$

in which

$$
Y(t) = \begin{bmatrix} y_1(t) \\ y_2(t) \end{bmatrix}.
$$

Then the parameter updating law is given by the following standard gradient algorithm

$$
\dot{\Phi} = -\begin{bmatrix} g_1 e_1(t) W_1(t) & g_2 e_2(t) W_2(t) \end{bmatrix}, \tag{7}
$$

in which $g_1 > 0$ and $g_2 > 0$.

An alternative is the normalized gradient algorithm

$$
\dot{\Phi} = -\begin{bmatrix} \dfrac{g_1 e_1(t) W_1(t)}{1 + \gamma_1 W_1^T W_1} & \dfrac{g_2 e_2(t) W_2(t)}{1 + \gamma_2 W_2^T W_2} \end{bmatrix}, \tag{8}
$$

in which $W_1(t), W_2(t)$ are the columns of $W(t)$, and $\gamma_1 > 0$ and $\gamma_2 > 0$.

In any case, $Y_i(t)$ approaches $Y(t)$. In order for the parameters to converge (Sastry and Bodson, 1989), it is necessary for the vector $\bar{W}(t) = (w_{11}(t), w_{21}(t), w_{31}(t), w_{12}(t), w_{22}(t), w_{32}(t))^T$ to be *persistently exciting (PE)*. Note that the transfer function from $\bar{u} = (1, y_1(t), y_2(t), y_1(t)y_2(t))^T$ to $\bar{W}(t)$ is

$$H(s) = \begin{bmatrix} \frac{1}{\lambda_1(s)} & 0 & 0 & 0 \\ 0 & \frac{1}{\lambda_1(s)} & 0 & 0 \\ 0 & 0 & 0 & \frac{1}{\lambda_1(s)} \\ 0 & 0 & \frac{s}{\lambda_2(s)} & 0 \\ 0 & 0 & \frac{1}{\lambda_2(s)} & 0 \\ 0 & 0 & 0 & \frac{1}{\lambda_2(s)} \end{bmatrix}. \quad (9)$$

Decomposing $\bar{W}(t)$ into $\bar{W}^1(t) + \bar{W}^2(t)$ such that

$$\begin{aligned} \bar{W}(s) &\stackrel{\text{def}}{=} \bar{W}^1(s) + \bar{W}^2(s) \\ &\stackrel{\text{def}}{=} H^1(s)\bar{u}(s) + (0,0,0,y_2(s),0,0)^T \end{aligned}$$

The following two assumptions are made:

Assumption 1: $\bar{u}(t) = (1, y_1(t), y_2(t), y_1(t)y_2(t))^T$ satisfy the persistent excitation condition, *i.e.*,

$$\int_t^{t+T} \bar{u}(\tau)\bar{u}(\tau)^T d\tau \geq k > 0$$

is satisfied for some $T > 0$, and every $t \geq 0$.

Assumption 2: $y_2(t) \in L_2$, that is, the viral load is a square integrable function of time.

Since $H^1(s)$ is stable, minimum phase and rational, by Assumption 1 and Lemma 2.6.7 of (Sastry and Bodson, 1989), $\bar{W}^1(t)$ is PE. By Assumption 2 and Lemma 2.6.6 of (Sastry and Bodson, 1989), $\bar{W}(t)$ is PE.

The technical Assumption 1 and 2 may not look easy to understand. But an intuitive interpretation of the above analysis is that when the curve of y_1 and y_2 are bent enough and "the cumulated strength of the virus" (y_2) is bounded, then all six parameters can be accurately estimated. Two typical such phases in HIV/AIDS progression are the primary infection stage and the period after chemotherapy treatment when both the viral load and CD4+ T cell counts are changing.

Coincidentally, one notices that all previous estimations of the virus clearance rate (μ_2) and the death rate of infected cell (μ_1) were made for a post-treatment period of very strong chemotherapy using reverse transcriptor inhibitors and protease inhibitors (Ho, *et al*, 1995; Wei, *et al*, 1995; Perelson, *et al*, 1996). This choice becomes obvious from the above analysis of parameter convergence.

4. ESTIMATION USING ADAPTIVE OBSERVERS

It will be shown in this section that adaptive observers of the Marino-Tomei type provide another globally convergent parameter estimator. Refer to (Marino and Tomei, 1995; Marino and Tomei, 2000; Xia, 2000) for details of the design and some recent applications of adaptive observers.

The procedures for designing adaptive observer estimators is described as follows.

For the system (1), let $z_1 = x_1, z_2 = kx_2 + \mu_1 x_3, z_3 = x_3$, when $k \neq 0$, this transformation is invertible, and the system (1) can be transformed into the following *observer form*:

$$\begin{cases} \dot{z}_1 &= \theta_1 + \theta_2 y_1 + \theta_3 y_1 y_2, \\ \dot{z}_2 &= \theta_6 y_1 y_2 + \theta_5 y_2, \\ \dot{z}_3 &= z_2 + \theta_4 y_2, \\ y_1 &= z_1, \\ y_2 &= z_3. \end{cases} \quad (10)$$

Define the filtered transformation,

$$\eta_1 = z_1, \eta_2 = z_2 - \theta_6\xi_1 - \theta_5\xi_2 - \theta_4\xi_3, \eta_3 = z_3,$$

in which

$$\begin{aligned} \dot{\xi}_1 &= -b\xi_1 + y_1 y_2, \\ \dot{\xi}_2 &= -b\xi_2 + y_2, \\ \xi_3 &= -b\xi_2, \end{aligned}$$

with $b > 0$, then the system can be transformed into *an adaptive observer form*:

$$\begin{cases} \dot{\eta}_1 &= \theta_1 + \theta_2 y_1 + \theta_3 y_1 y_2, \\ \dot{\eta}_2 &= b[\theta_6\xi_1 + \theta_5\xi_2 + \theta_4(\xi_3 + y_2)], \\ \dot{\eta}_3 &= \eta_2 + [\theta_6\xi_1 + \theta_5\xi_2 + \theta_4(\xi_3 + y_2)], \\ y_1 &= \eta_1, \\ y_2 &= \eta_3. \end{cases} \quad (11)$$

An adaptive observer can then be designed as the following

$$\begin{aligned} \dot{\hat{\eta}}_1 &= k_1\hat{\eta}_1 + \hat{\theta}_1 + \hat{\theta}_2 y_1 + \hat{\theta}_3 y_1 y_2 - k_1 y_1, \\ \dot{\hat{\eta}}_2 &= k_2\hat{\eta}_3 + b[\hat{\theta}_6\xi_1 + \hat{\theta}_5\xi_2 + \hat{\theta}_4(\xi_3 + y_2)] - k_2 y_2, \\ \dot{\hat{\eta}}_3 &= k_3\hat{\eta}_3 + \hat{\eta}_2 + [\hat{\theta}_6\xi_1 + \hat{\theta}_5\xi_2 + \hat{\theta}_4(\xi_3 - y_2)] - k_3 y_2, \end{aligned} \quad (12)$$

$$\begin{bmatrix} \dot{\hat{\theta}}_1 \\ \dot{\hat{\theta}}_2 \\ \dot{\hat{\theta}}_3 \end{bmatrix} = \Gamma_1 \begin{bmatrix} 1 \\ y_1 \\ y_1 y_2 \end{bmatrix} (y_1 - \hat{\eta}_1), \quad (13)$$

$$\begin{bmatrix} \dot{\hat{\theta}}_4 \\ \dot{\hat{\theta}}_5 \\ \dot{\hat{\theta}}_6 \end{bmatrix} = \Gamma_2 \begin{bmatrix} y_2 + \xi_3 \\ \xi_2 \\ \xi_1 \end{bmatrix} (y_2 - \hat{\eta}_3), \qquad (14)$$

where Γ_1, Γ_2 are symmetric positive definite matrices, k_1 is any negative number, $k_2 = -b$ and $k_3 = -b - \lambda$ for $\lambda > 0$.

The estimation of the original parameters can be determined by the estimation of θ through (4).

The convergence of parameters using adaptive observers can be discussed along similar lines as for adaptive identifiers, and it is omitted due to space limitation. It can be noted that the parameter convergence conditions for adaptive observers are the same as for adaptive identifiers.

5. SIMULATION

The simulation is carried out in the Matlab/Simulink environment. Results are shown only for parameter estimation using adaptive observers.

Assume that the model has the following parameters: $s = 7$, $d = 0.007$, $\beta = 0.00000042163$, $\mu_1 = 0.0999$, $\mu_2 = 0.2$, $k = 90.67$.

Using these parameters, the HIV progression is depicted in Figure 1. It can be noted that this set of parameter corresponds to a typical HIV infection and progression over a four year period. After the initial infection, the healthy CD4+ T cell drops from the usual 1000 per milli cubic meter to less than four hundred in about four months' time. The viral load increases dramatically in the acute infection stage and peaks at about three months after infection. A quasi-steady state is reached after about five hundred days.

Since the numerical values of the CD4+ T count and the virus load are not in the same order of magnitude, the variables are first normalized in the simulation. The adaptive observer is chosen to start from day 225 after infection. This choice is arbitrary subject to the condition that the signals are sufficiently excited. The results are demonstrated in Figure 2. It can be found from these results that very good estimations can be obtained using about 3 months' data. It can also be found that the estimates of s, d, β and k are relatively smooth, while the estimations of μ_1 and μ_2 undergo some small fluctuations. This phenomenon is in accordance with the fact that virus and infected cells have a very rapid turnover (Ho, *et al*, 1995; Wei, *et al*, 1995).

6. CONCLUSION

In this paper, the problem of estimating all parameters in the basic HIV/AIDS model is studied by making use of well-established control system techniques. Through an observability analysis, the minimal number of sample measurement for the CD4+ T cell and the viral load was obtained for a complete model parameter estimation. The HIV progression stages when an estimation of all parameters is impossible were then determined. Outside these stages, on-line estimations of all parameters were given based on two well-known techniques in control theory: adaptive identifiers and adaptive observers. Conditions for parameter convergence were discussed. Simulation results were shown for the adaptive observers.

This study enables one to formulate the following guidelines for the clinical testing and measurement, as far as the estimation of all six HIV/AIDS parameters in the basic model is concerned.

(1) At least four measurements of CD4+ T cell count and five measurements of viral load are needed for a complete determination of all the HIV/AIDS parameters;
(2) In the asymptomatic stage of HIV, a complete determination of all parameters is impossible;
(3) In the short period after chemotherapy treatment when the CD4+ T cell count does not change much, a complete determination of all parameters is impossible;
(4) It is most probable to determine all parameters in the primary infection stage;
(5) All parameters can be estimated by sufficiently disturbing the quasi-steady state in the asymptomatic stage of HIV using effective anti-retrovirus drug.

Remaining issues to be investigated include clinical data verification. For this purpose, the assumption that daily blood samples are available is of course not very practical. Interpolation must be implemented. In practice, samples are sometimes taken more frequently, e.g., hourly (Perelson and Nelson, 1999), especially after treatment. This will certainly improve the efficiency of the estimation.

Estimation algorithms will be useful in a study of drug resistance, since resistance can be represented by the fact that the parameters β and/or k become smaller. A quantitative study about resistance can be given by detecting the change of the estimates of β and k.

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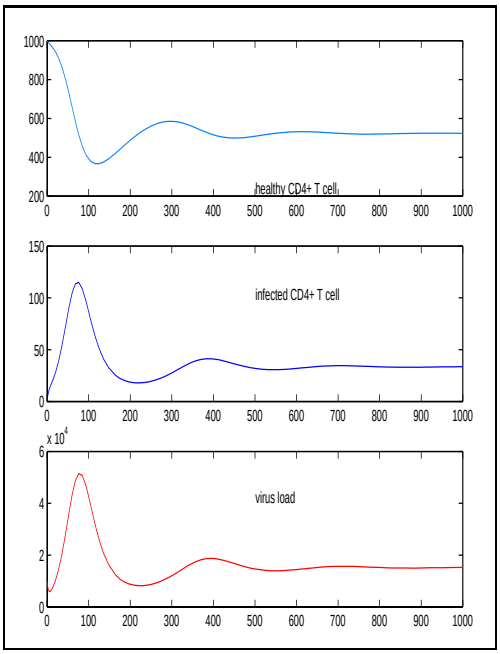

Fig. 1. Typical HIV infection and progression

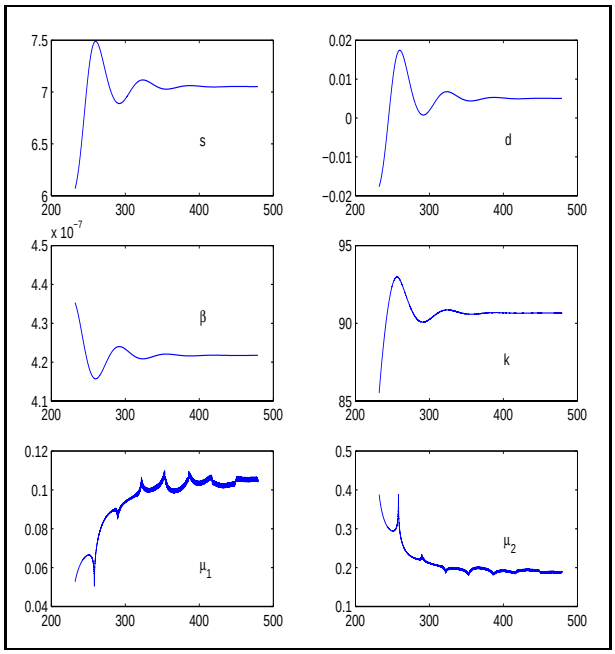

Fig. 2. Estimation HIV/AIDS parameters

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