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Control of HIV/AIDS Infection System with Reverse Transcriptase Inhibitors Dosages Design via Robust Feedback Controller

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Abstract

Acquired Immune Deficiency Syndrome (AIDS) is a disease or continuum condition which is due to Human Immunodeficiency Virus (HIV) infection. One in five people are infected with HIV are not aware of the infection. Early detection of the infection helps the infected people to take medications to avoid future consequences and reduce the risk of transmitting the disease. Reverse transcriptase inhibitors (RTIs) were the first available drug and were considered a principal kind of medication available to treat HIV patients. These drugs are still successful, effective, and are considered to have imperative solutions for treating HIV when joined with different medications. Investigating effect of this branch of the drugs on HIV and model this interaction has a great of importance to control AIDS.

This need can be addressed by the control system engineering which uses control theory to estimate and design a system. Since Stability is the most significant requirement of the system, and a system of instability cannot be expected for a particular transient reaction or steady state error specification then objective which is needed to be achieved by working on this research is to design a stabilized model of a patient having AIDS. In this research feedback controllers, Root locus technique and Routh Hurwitz method have been adopted to design such an advanced transformative controller which robustly regulates RTIs infusion dosages considering the amount of HIV viruses in infected human body.

Introduction

AIDS stands for Acquired Immune Deficiency Syndrome [1-4]. Letter "A" stands for "Acquired" which means that it is a condition obtained, implying that a man gets to be contaminated with it [5,6]. Letter I stands for "Immune" which means HIV influences a man's resistant framework, the part of the body that battles off germs, for example, microbes or infections [7,8]. Letter D stands for "Deficiency" which means that the resistant framework gets to be lacking and does not work legitimately [9,10]. Letter S stands for "Syndrome" which means a person with AIDS might encounter different sicknesses and diseases in light of a debilitated insusceptible framework [4,11] Feinberb and Moore proposed an AIDS model to know the influence of medicine or vaccines on the HIV virus [12]. The vast majority of these medications come as tablets or capsules [13]. The lab makes a figuring in light of aggregate white blood cells and the extent of cells that are CD4 [14]. On the other hand, if the CD4 count is lesser then 200 cells/mm^3 this implies that the individual has diagnosed a stage 3 infection of AIDS [15].

Initially the discussion was regarding what can be done in order to control AIDS and what are techniques present today which can help an infected person to keep the level of the virus to a lower level [16,17]. The perspectives from the point of view of control theory which control systems are present to design the feedback system to control these viruses in an infected individual [18,19]. Next section of the research explains how the CD4 cells work and how they were developed and what can be done in order to control the infection and what factors determines the HIV life cycles and what is meant by the viral load count, how the lab tests are conducted on the bases of the CD4 count [20,21]. How can be a linear system and a non-linear framework distinguished [22]. Similarly, one of the important points covered in this section of the research enlightens on how the linearization works and how to determine the equilibrium points in a given framework [23].

Methodology

The state space representation of system can be expressed in state equation. The state variable is linearly self-determining and the choice affects the matrices. Transfer function is expressed as state space [24]. After the virus has be found out in the body and when the retroviral drug has been injected the system is altered. The system is modelled by linearizing resulting to the virus free system.

Next is analysing the technique to discover a state response of multivariable time changing systems. Systems are normally presented by an arrangement of differential equations via a state space model [25]. Usually, it is a thorough and difficult task to solve the time varying state space representation [24]. Representation of a time response requires the solving of the space dynamic by initial conditions. This requires the computing of the state transition matrix first. Laplace transforms equations to obtain efficiency and effectiveness of the drug that is used to fight against the virus.

Stability is the most vital requirement of the system, in this section; stability is discussed by applying Routh-Hurwitz method [26]. Routh-Hurwitz criterion is used to obtain a constant that will determine the stability of the system, which will give us an idea to use a suitable amount of drug to keep the spread of infection stable.

At the last root locus is used to design and analysis of the system.

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It helps in getting in knowing the details regarding the stability and the response system. We also discussed the different methods of sketching the root locus. In this chapter we focused on the gain adjustment. The gain modification is only done after the transient response is found out. The section is concluded by understanding positive feedback system and sketching the root locus of the mentioned system [27].

Feedback system

Control system engineering is a part of engineering which uses control theory to estimate and design a system [28]. There are four functions in the control theory i.e., measure, compare, compute and correct [29]. The open-loop control system framework uses an actuating device to control the procedure specifically without utilizing device [30]. The main reasons of using the block diagram rather than using other methods that block diagram analyse a simple control system in a way which cannot be analysed by the other methods because this method helps us in understanding the operation of the problem statement and how the control theory plays an important role in understanding the procedure of the given problem. Block diagram is a method which gives us the symbolic representation of complex signals making the problem easier so that it can be understood clearly it is a method which also helps to establish a relationship in between the subsystems. As by this method complicated equations which are representing the schematics can be avoided in other words this method helps an individual to understand the problem in the easiest way by avoiding all the complications. Block diagrams are normally utilized for larger amount, less point by point portrayals that are expected to clear up general ideas without the apprehension for the details of implementation [31].

The two drugs reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs) will be used as input variables for the feedback of the system. A "controller" which helps to decide that in which quantity these drugs must be injected in the body of an infected person because the combination of these drugs plays an important role in maintaining the level of the HIV viruses referred as the output for the feedback of the system. The block diagram of such a system has been shown in Figure 1.

Linearization

Problem can be solved by using the method of linearization. In a control system framework if any non-linear systems are present at that point it becomes necessary that the system must be linearize before the transfer function of a system have to be determined.

The final type of non-linearity which is important to discuss is "backlash nonlinearity" which means when the input course is altered at that point the output becomes steady till the input surpasses a firm assessment (the backfire is dispensed with nonlinear control systems analysis [32].

The first step in this method is to perceive the non-linear part and compose the non-linear differential mathematical statement. In the next step we linearize the non-linear differential mathematical statement, and after that we take the Laplace transformation of the linearized differential mathematical statement, accepting zero as the starting condition. Lastly, we isolate input and as well the output variables which perform an important role in the forming of a transfer function [27].

The transfer function is expressed in terms of state space. The general way of expressing the linear state equation of state space is [33]:

$$\dot{x}(t) = A(t)x(t) + B(t)u(t) \tag{1}$$

$$y(t) = C(t)x(t) + D(t)u(t) \tag{2}$$

Where the variables have been defined as shown in Table 1.

The result is obtained by two steps firstly by the state variable response is obtained and then by substituting it to obtain the y (t). The method used mostly is matrix method where the vector values are reduced into scalar values and are assigned to the respective matrices. For selecting a state vector the minimum number of state variable should be chosen as the factor of the state vector, the number of state variable explains the state of the system and factors should be linearly independent.

Laplace transforms system

As elucidated in previous section that systems were demonstrated in state space, where the state-space representation comprised of a state comparison and an output mathematical statement. In this segment, we utilize the Laplace change to tackle the state mathematical statements for the state and yield vectors. The Laplace transform is a reliable method for resolving ordinary and partial differential equations.

As mentioned earlier, RTIs drug is used to fight against the infection. Our main objective here in this section is to find the efficiency of the drug, which is to find $\frac{Y(s)}{U_1(s)}$. At the end, we will approximate a time the drug could take to show its highest possible effectiveness.

Variables	Abbreviation
X	state vector
$\dot{x}$	derivative of the state vector with respect to time
Y	output vector
U	input or control vector
A	system matrix
B	input matrix
C	output matrix
D	feed forward matrix

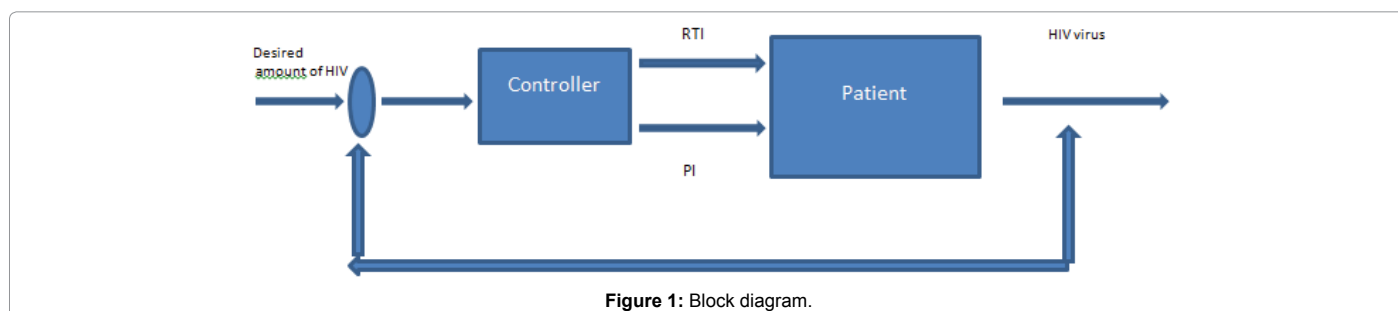**Table 1:** Variables defined for the Equations 1 and 2.

Figure 1: Block diagram.

Laplace transforms solution of state equations as follows [27]:

Laplace transform of the input equation:

$$X(s) = (sI - A)^{-1} x(0) + (sI - A)^{-1} BU(s) \tag{3}$$

Laplace transform of the output equation:

$$Y(s) = CX(s) + DU(s) \tag{4}$$

State space representation

We have seen in previous section that systems were demonstrated in state space, where the state-space representation comprised of a state comparison and an output mathematical statement. In this segment, we utilize the Laplace change to tackle the state mathematical statements for the state and yield vectors.

For the performance of the system, settling time formula of the first order system is used [27]. State space representation is a mathematical illustration of a system where the input and output of the transfer function including the state variable is represented by the first order differential equation [34]. The system could be formulated by utilization of Kronecker vector matrix structures [35,36]. The state variables are a subset and can depict the system state in a given time [27]. The order of the system is equivalent to the reduced denominator [29]. The general method of expressing the linear representation of state space is representing them as time invariant. As the system is dynamic the time invariant could be discrete or continuous [37,38]. In the course of the most recent decade, numerous effective hypotheses were created for first-order system definition of Stokes and Navier-Stokes equations. The first-order system presented in for Stokes comparisons included velocity, velocity flux, and pressure [39]. Equation of the Laplace is the most significant of all partial differential equations [40].

Routh-Hurwitz method

The objective of this section is to design a stable controller of the system. Stability is an important specification of the system. Routh-Hurwitz criterion is the method used to generate the information of stability by determining the number of poles [27]. The Routh-Hurwitz method involves two stages; producing Routh table and determining the Routh table to find out the number of poles in the planes and axis [27]. According to Routh- Hurwitz method, if all the poles are in the left-half plane then the system is stable. The system is unstable if any poles are in the right-half plane. The reason of being marginally stable is due to having undamped sinusoidal mode [41]. The graph gives us the idea regarding the zero as well as the poles of a transfer function of a dynamic system in a complex plane [42].

The characteristic equation illustrate the value of the gain, it estimates the behaviour of the system with changing values of the controller gain [29]. Controllability of a system is used to stabilize system by feedback or optimal control. Observability is a measure in which the present state can be decided on the fixed time interval using the output function [43].

Root locus

Root locus is a graphical technique which helps in inspecting the variety which happened in the roots of control system [27]. In the continuous transfer domain (CT) zeroes are the root of the polynomial of numerator and poles are for the denominator. The region of convergence (ROC) of a transfer function is a half-plane or vertical strip, either of which contains no poles [44]. In discrete time system the region of convergence contains no poles. The system has right sided impulse if the ROC moves away from the pole with progressive value other than infinite and then no poles are at infinity [45].

The steps for drawing a root locus are drawing the forward-loop poles and zeros and part of the locus that lies on the real axis then locating the centroid and sketching the asymptotes. Then by locating break point and estimating angles of arrival and departure. Calculating the imaginary axis crossing and then drawing the rest of the locus. By plotting the root locus it provides a detailed view of the stability of the closed loop controller. When two or more root loci converge initially and then diverges, that point is considered as break points. They occur in real as well as complex plane, but mostly real axis. The gain 'K' is calculated by dividing the product of the length between each pole to the point by the product of the length between each zero to the point.

Results and Discussion

The problem states that we have to design a block diagram which plays an important role in controlling the HIV viruses which are entering in the body of an infected individual. While constructing this block diagram we have to keep in mind the parameters for instance what will be the inputs and outputs. In this case we know that the two drugs reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs) will be used as input variables for our design of the block diagram as how much of these drugs are dispensed in the body of the infected person. As we need to consider the feedback of the system while designing the system so it is becoming clear that for this case we will be using a closed-loop system framework.

By the problem statement it is becoming clear that we have to apply linearization approach in order to find out the transfer function. We also know that the model present in the problem statement resembles the non-linear system framework which signifies the equations. Now the important thing which needs to be determined in the (a) part of the problem is to find out which equations are having the linear and non-linear characteristics. The first two equations are non-linear because of the Tv products on the right side [27]:

$$\frac{dT}{dt} = s - dT - \beta Tv \tag{5}$$

$$\frac{dT^*}{dt} = \beta Tv - \mu T^* \tag{6}$$

Now in the (b) part of this problem we have to determine the two equilibrium points present in the system in order to simplify the situation [27]:

To find the equilibrium let

$$\frac{dT}{dt} = \frac{dT^*}{dt} = \frac{dv}{dt} = 0 \tag{7}$$

Leading to:

$$T^* = \frac{\beta Tv}{\mu} T^* = \frac{cv}{k} T = \frac{c\mu}{\beta k} \tag{8}$$

Substituting the latter into the first equation after some algebraic manipulations we get that

$$T^* = \frac{cv}{k} = \frac{s}{\mu} - \frac{cd}{k\beta} \tag{9}$$

In this section we need to achieve the state space representation by linearizing the equation with equilibrium condition limiting to zero.

$$f_2 = (1-u_1)\beta Tv - \mu T^* \tag{10}$$

$$f_2 = (1-u_1)\beta Tv - \mu T^* \tag{11}$$

$$f_3 = (1-u_2)kT^* - cv \tag{12}$$

$$A = \begin{bmatrix} \dfrac{\partial f_1}{\partial T} & \dfrac{\partial f_1}{\partial T^*} & \dfrac{\partial f_1}{\partial v} \\ \dfrac{\partial f_2}{\partial T} & \dfrac{\partial f_2}{\partial T^*} & \dfrac{\partial f_2}{\partial v} \\ \dfrac{\partial f_3}{\partial T} & \dfrac{\partial f_3}{\partial T^*} & \dfrac{\partial f_3}{\partial v} \end{bmatrix} B = \begin{bmatrix} \dfrac{\partial f_1}{\partial u_1} & \dfrac{\partial f_1}{\partial u_2} \\ \dfrac{\partial f_2}{\partial u_1} & \dfrac{\partial f_2}{\partial u_2} \\ \dfrac{\partial f_3}{\partial u_1} & \dfrac{\partial f_3}{\partial u_2} \end{bmatrix} \tag{13}$$

Then just by direct substitution:

$$\begin{bmatrix} \dot{T} \\ \overset{y}{T^*} \\ \dot{v} \end{bmatrix} = \begin{bmatrix} -(d+\beta v_0) & 0 & -\beta T_0 \\ \beta v_0 & -\mu & \beta T_0 \\ 0 & k & -c \end{bmatrix} \begin{bmatrix} T \\ T^* \\ v \end{bmatrix} + \begin{bmatrix} \beta T_0 v_0 & 0 \\ -\beta T_0 v_0 & 0 \\ 0 & -kT^*_0 \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \end{bmatrix} \tag{14}$$

$$y = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} T \\ T^* \\ v \end{bmatrix} \tag{15}$$

$$\begin{bmatrix} \dot{T} \\ \overset{y}{T^*} \\ \dot{v} \end{bmatrix} = \begin{bmatrix} -(d+\beta v_0) & 0 & -\beta T_0 \\ \beta v_0 & -\mu & \beta T_0 \\ 0 & k & -c \end{bmatrix} \begin{bmatrix} T \\ T^* \\ v \end{bmatrix} + \begin{bmatrix} \beta T_0 v_0 \\ -\beta T_0 v_0 \\ 0 \end{bmatrix} u_1 \tag{16}$$

$$y = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} T \\ T^* \\ v \end{bmatrix} \tag{17}$$

Where the variables have been defined as shown in Table 2

After the substitution of parameter values,

$$\begin{bmatrix} \dot{T} \\ \overset{y}{T^*} \\ \dot{v} \end{bmatrix} = \begin{bmatrix} -0.04167 & 0 & -0.0058 \\ 0.0217 & -0.24 & 0.0058 \\ 0 & 100 & -2.4 \end{bmatrix} \begin{bmatrix} T \\ T^* \\ v \end{bmatrix} + \begin{bmatrix} 5.2 \\ -5.2 \\ 0 \end{bmatrix} u_1 \tag{18}$$

$$y = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} T \\ T^* \\ v \end{bmatrix} \tag{19}$$

Thus,

$$\frac{Y(s)}{U_1(s)} = -520 \frac{s+0.02}{(s+2.6419)(s^2+0.0398s+0.0048)}$$

By making an assumption that RTIs are 100% effective, we will approximate the time RTIs would take to show maximum effectiveness.

$$T_s(\text{Settling time}) = \frac{4}{0.0199} = 210\,days$$

The transfers function of the human immunodeficiency virus infection calculated in the previous chapter:

$$P(s) = \frac{Y(s)}{U_1(s)} = \frac{-520s - 10.3844}{s^3 + 2.6817s^2 + 0.11s + 0.0126} \tag{20}$$

Symbol/Abbreviation	Units
t (Time)	days
d (Death of uninfected T cells)	0.02 day
k (Rate of free viruses produced per Infected T cell)	100 counts/cells
s (Source term for uninfected T cells	10 mm³/day
β (Infectivity rate of free virus particles)	2.4 × 10⁻⁵ mm³/day
c (Death rate of viruses)	2.4 day
μ (Death rate of infected T cells)	0.24 day

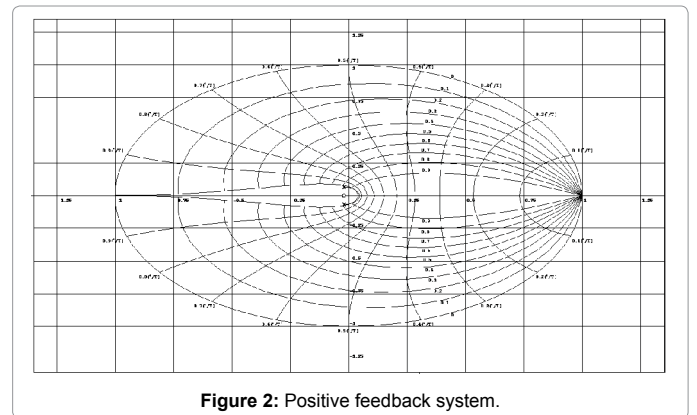**Table 2:** Typical parameter values for HIV/AIDs model (27).

Figure 2: Positive feedback system.

Considering K as a constant and the objective is to find a range of K by using Routh-Hurwitz method to determine that the system is closed loop stable.

$$1 + K \frac{-520s - 10.3844}{s^3 + 2.6817s^2 + 0.11s + 0.0126} = 0 \tag{21}$$

Therefore for system's stability:

$$0.0126 - 10.3844K > 0 \rightarrow K < 1.21 \times 10^{-3} \tag{22}$$

And

$$0.0126 - 10.3844K > 0 \rightarrow K < 1.21 \times 10^{-3} \tag{23}$$

The transfer function is linearized where the virus levels are controlled by the RTIs. Then to plot the root locus for all value of the gain greater than zero, initially for the open loop transfer function where the transfer function is greater equal to the gain; we need to show that which system is stable for the open loop transfer function for value of gain above zero.

(a) The open loop transfer function is

$$KG(s)P(s) = -\frac{K(520s + 10.3844)}{s^3 + 2.6817s^2 + 0.11s + 0.0126} \tag{24}$$

To obtain the breakaway points let

$$K = -\frac{1}{G(\sigma)H(\sigma)} = \frac{\sigma^3 + 2.6817\sigma^2 + 0.11\sigma + 0.0126}{520\sigma + 10.3844} \tag{25}$$

$$\frac{dK}{d\sigma} = \frac{(520\sigma + 10.3844)(3\sigma^2 + 5.3634 + 0.11) - 520(\sigma^3 + 2.6817\sigma^2 + 0.11\sigma + 0.012)}{(520\sigma + 10.3844)^2} \tag{26}$$

The value of K at σ=0.0446 is 6.82×10^{-4}. We have already found this result in the previous problem. That the system is closed loop stable for k<2.04×10^{-4}. The root locus sketch has been illustrated in Figure 2.

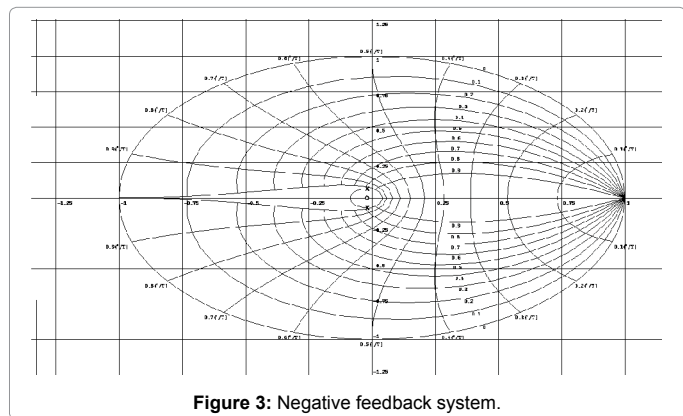| Symbols	Equations	
S^3	1	0.11+520K
S^2	2.6817	0.0126+10.3844K
S	$\dfrac{0.2824+1384.1K}{2.6817}$	--
S^0	0.0126+10.3844K	--

Table 3: Routh Table (27).

Figure 3: Negative feedback system.

Now for negative feedback system,

The value of K at σ=-1.33 is 0.0033 and value of K at σ=- 0.0879 is 6.5×10^{-4}

We use Routh-Hurwitz to show that the system is closed loop stable for all >0. The characteristic equation is:

$$1 + K\frac{520s+10.3844}{s^3+2.6817s^2+0.11s+0.0126} = 0 \qquad (27)$$

The Routh Array has been calculated as shown in Table 3.

The denominator of the transfer function is considered since we are keen in the poles of the system. At first, the columns are filled with powers of s from the most elevated power of the denominator of the closed-loop transfer function to s°. The remaining entries are filled according to the Routh- Hurwitz method as follows. Every section is a negative determinant of entries in the past two lines and determinant is divided by the entry which is present in the primary column specifically over the computed line. The left-hand segment of the determinant is dependably the main section of the past two lines, and the right-hand segment is the components of the segment above and to right side. The table is said to be complete when all the rows are calculated down to s°. It can easily be verified that all the entries in the first column are positive for all k>0 The root locus sketch has been shown in Figure 3.

In the negative feedback system, we could estimate that the number of branches is equal to the number of the poles which is obtained from the graph. The poles are symmetrical about the real axis. From the graph we could find out that for the root locus begins at poles and ends at the zeroes. The angle of the complex pole is used to obtain the damping ratio. The distance from the pole to the origin is referred as the natural frequency. As we have found out the damping ratio, the lines in the graph represent the damping lines; it helps to estimate the settling time, damped oscillation frequency and the overshoot. As the settling time decrease the damping ratio increase, likewise the rise time and peak time also decreases with the increase in the damping ratio. Taking overshoot percentage into criteria, the value reduces when the damping ratio increases. The compensator design is a modification of the root locus when the present situation where it is not possible to obtain the desired transient distinctiveness, so we alter it by adding zeroes or poles. Increasing in damping ratio is approximately referred as dropping of angle of the asymptotes.

Conclusion and Future work

Every year, millions of people die due to AIDs worldwide. It is estimated that 1.2 million people died due to AIDs related illness in the year of 2014 [46]. The death rate clearly makes the AIDs one of the most dangerous life taking disease of mankind. Since there is no cure for AIDs, controlling and monitor of AIDs can be a useful tool for the reduction of the spread of the virus.

In this paper, how the spread of the infection can be controlled is discussed, analysed and elaborated by the implementation of mathematical equations. Medication by means of drugs is used throughout our research as an input of the system. In section one; we obtained a clear feedback block diagram of the system after drugs used as input. Transfer function of the disease in found in the second section. Since the infection is non-linear, linearization of the system to obtain the space representation is done in section three. The effectiveness and the time to show maximum effectiveness are the core requirement of a successful drug. Based on assumptions, efficiency and time are calculated in section four. Stabilizing of the virus depending on the amount of the drugs required are analysed and discussed in section five. In the final section, graphical generation of the feedback systems are shown and explained. This research paper was only constrained to computer simulation. Future researchers can emphasis on development and employment of the testing apparatus for the simulations accomplished in this paper.

There is significant amount of probability regarding more work which can be done in the light of this research. In this research parametric study was constructed mainly but for the future many possibilities are present which can be done.

Artificial intelligence techniques such as Artificial Neural Networks (ANN) [47-49], Ring Probabilistic Logic Neuron [50,51], Fuzzy logic [52] and Genetic algorithm [53] are important algorithms which can be taken in account in order to perform the modelling of AIDS as future work.

Acknowledgment

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