An (SDARE) Based Treatment Scheduling For Enhancing Immune Response to (HIV)

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Abstract

   In this paper, the problem of designing dynamic multidrug therapies scheduling to medicate the **H**uman **I**mmunodeficiency **V**irus (HIV) type 1 infection is described. The control approach used for this purpose is the "**S**tate **D**ependent **A**lgebraic **R**iccati **E**quation", (SDARE), which is one of the highly promising and rapidly emerging methodologies for designing nonlinear feedback controllers. A nonlinear dynamical model which consists of six states, where the interaction of the (HIV) particles with the immune system of a human being, and the **H**ighly **A**ctive **A**ntiretrovirus **T**herapy (HAART) as Control Inputs are described, and employed to design the dynamical multidrug therapies.

   The (SDARE) approach is applied to the (HIV) mathematical model to design a suboptimal tracking controller to drive the states of the (HIV) model to a stationary state in which the immune system of the (HIV) patient can be bolstered enough against the virus in a way to lead to long-term control of the (HIV) by the immune System of (HIV) patient by itself after discontinuation of therapy.

Keywords: (HIV) Control, Nonlinear (SDARE) Control.

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جدولة العلاج بالاعتماد على طريقة "معادلة ريكاتي الجبرية المعتمدة على الحالة" لتحسين الاستجابة المناعية لفيروس نقص المناعة

الخلاصة

   تم في هذا البحث ، طرح مشكلة تصميم جدولة مُعالجات ديناميكية متعددة العقار لعلاج الإصابة بفيروس نقص المناعة (HIV) ، إن طريقة السيطرة المستخدمة لهذا الغرض هي طريقة (معادلة ريكاتي الجبرية المعتمدة على الحالة) أو (SDARE) ، وهي واحدة من الطرق الواعدة والصاعدة في مجال تصميم مسيطرات التغذية العكسية اللا خطية ، وقد تم توظيف موديل رياضي لا خطي والذي يتكون من (6) حالات حيث يصف الموديل التفاعل بين جزيئات الـ(HIV) مع نظام المناعة للإنسان وكذلك يصف علاج الـ(HAART) كمُدخلات للسيطرة ، وذلك بهدف تصميم جدولة مُعالجات ديناميكية متعددة العقار. إن طريقة الـ(SDARE) قد طبقت على موديل الـ(HIV) الرياضي لتصميم مسيطر متعقب قريب من الأفضل لقيادة الحالات للموديل الرياضي للـ(HIV) إلى حالة ثابتة يكون فيها نظام المناعة قد دُعم بشكل كاف ضد الفيروس بطريقة تقود إلى سيطرة بعيدة الأمد على الـ(HIV) من قبل نظام المناعة للمريض المصاب بالـ(HIV) بعد توقف العلاج.

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Nomenclature

$A(x)$, Plant Matrix in Nonlinear State Dependent Coefficient (SDC) Representation;

$a(x)$, Vector of Non-parameterizable Terms;

$B(x)$, Control Distribution Matrix in Nonlinear State Dependent Coefficient (SDC) Representation;

b_E, Maximum Birth Rate For Immune Effectors;

c, Virus Natural Death Rate.

d_1, Target Cell Type 1 Death Rate;

d_2, Target Cell Type 2 Death Rate;

d_E, Maximum Death Rate For Immune Effectors;

E, Concentration Of Immune Effectors;

EQ1, Equilibrium Point1;

EQ2, Equilibrium Point2;

EQ3, Equilibrium Point3;

f, Treatment Efficacy Reduction In Population 2;

J, Cost Function;

k_1, Population 1 Infection Rate;

k_2, Population 2 Infection Rate;

k_b, Saturation Constant For Immune Effector Birth;

k_d, Saturation Constant For Immune Effector Death;

$k(x)$, State Dependent Gain Matrix;

m_1, Immune-Induced Clearance Rate For Population 1;

m_2, Immune-Induced Clearance Rate For Population 2;

N_T, Virions Produced Per Infected Cell;

$P(x)$, Solution of State Dependent Algebraic Riccati Equation;

Q, State Weighting Matrix;

R, Control Weighting Matrix;

T_1, Concentration Of Non-Infected (CD4+) T-Cells;

T_2, Concentration Of Non-Infected Target Cells Of Second Kind.

T_1^*, Concentration Of Infected (CD4+) T-Cells;

T_2^*, Concentration Of Infected Target Cells Of Second Kind;

$\grave{u}$, Maximum Dose Efficacy;

$\grave{u}$, Minimum Dose Efficacy;

$\tilde{u}$, Unlimited Control Vector;

V, Concentration Of Free (HIV);

x, State Vector;

x_d, Desired Trajectory Vector;

Greek Symbols:

$\in_1$, Efficacy Of Reverse Transcriptase Inhibitor (RTI);

$\in_2$, Efficacy Of Protease Inhibitor (PI);

$\in_1^{max}$, Maximum Efficacy of (RTI);

$\in_2^{max}$, Maximum Efficacy of (PI);

$\in_1^{min}$, Minimum Efficacy of (RTI);

$\in_2^{min}$, Minimum Efficacy of (PI);

d, Infected Cell Death Rate;

d_E, Natural Death Rate For Immune Effectors;

l_1, Target Cell Type 1 Production (Source) Rate;

l_2, Target Cell Type 2 Production (Source) Rate;

l_E, Immune Effector Production (Source) Rate;

$\tilde{\prod}(x)$, State Dependent Tracking Function;

1.Inroduction

Human **I**mmunodeficiency **V**irus (HIV) is a retrovirus that causes the Acquire Immunodeficiency Syndrome (AIDS). It was first published on June,5th,1981 in five

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homosexual men in Los Angeles/USA [1]. (HIV) infects (CD4+) T-cells (a fundamental component of human immune response system), the (CD4+) T-cells are often referred to as "Helper" T-cells. These cells can be considered "messengers", or the command centers of the immune system, since they signal other immune cells that an invader is to be fought. The (CD8+) cells or Cytotoxic T Lymphocytes (CTL)s, are the cells that will respond to this message and set out to eliminate infections by killing infected cells [2]) and other target cells, hijacking their replication mechanisms [3] as (HIV) uses a host cell to replicate itself and thus proliferate. Inclusion of (HIV) particles in immune cells leads to massive production of new viral particles, death of the infected cells and, ultimately, devastation of the immune system [4].

In western countries, the life expectancy of patients infected by (HIV) has increased to tens of years due to improved medical treatments. Nowadays the most common medications for treating (HIV) is the Highly Active Anti-Retrovirus Therapy (HAART) which is a "Cocktail" consisting of three or more drugs. Currently the two most important categories of (HAART) anti-HIV drugs are Reverse Transcriptase Inhibiters (RTIs), and Protease Inhibiters (PIs). Usually the typical (HAART) cocktail consists of two or more (RTIs) and a (PI) [5]. The (RTI) prevents HIV's (RNA) from being converted into (DNA), thus blocking integration of the viral code into the target cell [6]. On the other hand, Protease Inhibitors (PIs) affect the viral assembly process in the final stage of the viral life cycle

[3] by interfering with the replication of viruses by infected cells. Typically virions may still be produced, but they are generally non infectious; that is, they are not capable of infecting new target cells. In practice, (RTIs) cannot completely block the virus integration of the (DNA) in target cells. Also, some infectious viruses are produced under (PI) medications [5].

For the (HIV) infected patients, you can see three phases or stages of the disease, or the way that (HIV) particles may deal with the immune system, the first phase named **"Acute phase"**, the "Acute phase" is defined as the period of initial infections following the acquisition of (HIV). During the "Acute phase": the (HIV) viral levels can rise from zero to millions of copies, the immune system has not begun to control the virus (no antibodies), and individuals are "biologically hyper-infectious" [7]. The second stage is the "**chronic phase"**, where the T-cells and (CTLs) cells are continuously declining and viral load increasing [8].The previous two stages if not treated will lead to the third Phase, the **"profound Immuno-suppression"**, where the immune system collapses, and the human body is exposed to opportunistic infections such as for example the "Kaposi's Sarcoma" [9].

To deal with the problem for designing dynamic multidrug scheduling , one of the highly promising and rapidly emerging methodologies for designing a nonlinear controller is the "State Dependent Algebraic Riccati Equation" or the "SDARE" approach is used. This method which was proposed in 1996 by Cloutier et al. [10], is a general design method

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which provides a systematic and effective means of designing nonlinear controller [11] to nonlinear system stabilization which relies on representing a nonlinear system's dynamics in a manner to resemble linear dynamics, but with State Dependent Coefficient "SDC" matrices that can be inserted into "SDARE" to generate a feedback law. In essence, the (SDARE) approach involves mimicking the "Linear Quadratic Regulation" or "LQR" formulation for linear systems [12], except that parameterization is state dependent.

2.Nonlinear (HIV) Model

This section explains a dynamical (HIV) model that describes the interaction of the immune system with the (HIV) and that permits drug "cocktail" therapies. The (HIV) model was developed in [3], and can be described in the following set of ordinary differential equations:

$$\dot{T}_1 = I_1 - d_1 T_1 - (1 - \in_1)k_1 V T_1$$

$$\dot{T}_2 = I_2 - d_2 T_2 - (1 - f \in_1)k_2 V T_2$$

$$\dot{T}_1^* = (1 - \in_1)k_1 V T_1 - dT_1^* - m_1 E T_1^*$$

$$\dot{T}_2^* = (1 - f \in_1)k_2 V T_2 - dT_2^* - m_2 E T_2^* \quad \dots (1)$$

$$\dot{V} = (1 - \in_2)N_T d(T_1^* + T_2^*) - [c + (1 - \in_1)r_1 k_1 T_1 + (1 - f \in_1)r_2 k_2 T_2]V$$

$$\dot{E} = I_E + b_E \frac{T_1^* + T_2^*}{T_1^* + T_2^* + k_b} E - d_E \frac{T_1^* + T_2^*}{T_1^* + T_2^* + k_d} E - d_E E$$

and the states used describe concentrations of: T_1, non-infected (CD4+) T-Cells, T_2, non-infected target cells of second kind, T_1^*, infected (CD4+) T-Cells, T_2^*, infected target cells of second kind, V, free (HIV) (infectious virus plus non infectious), E, Immune Effectors (number of (CD8+)

Cytotoxic T-Lymphocytes (CTLs)). The Variables $\in_1$, and $\in_2$ represents the control inputs for Reverse Transcriptase Inhibitor (RTI) efficacy and Protease Inhibitor (PI) efficacy, respectively. The nonlinear model (equations (1)) contains numerous parameters that must be assigned values before simulations can be carried. Table (1) contains the values of parameters, and the definitions of each one [3].

The nonlinear model (1) exhibits several equilibrium points, those equilibrium points were examined by using the "First Method of Lyapunov" to investigate the local stability properties, the equilibrium points and their stability properties are summarized in Table (2).

The EQ1 represents a healthy state, because it has a high (CD4+) T-Lymphocytes count, high (HIV)-specific Cytotoxic T-cells (CTLs) count, and small viral load. So, this Equilibrium point will be named as "Healthy State". The "Healthy State" can also be named "Immune Dominant State" wherein the immune system can deal with the (HIV) virus and can prevent proliferation. The EQ2 can be put in the Acute or Early Infection phase because despite that it has a good (CD4+) T-cells counts, but the counts of the immune effectors (CTLs) are very small, this will be called as "Acute State". The EQ3 can be put in chronic phase since it corresponds to dangerously high viral set point, depleted T-cells and minimal immune response (number of (CTLs) are small), EQ3 will be called as "Unhealthy State". It can be noticed that both EQ2 and EQ3 can be named "Viral Dominant State" because the immune system fails to reduce the count of viral load and the ability of

the (HIV) to proliferate are increasing more and more.

Finally, the treatment efficacy factors ($\in_1$ & $\in_2$) which represent the effective treatment impact, ($0 \leq \in_1, \in_2 \leq 1$) representing (HAART) drug level, where ($\in_i = 0$) are fully off and ($\in_i = 1$) are fully on. Since (HIV) treatment is nearly always administrated as combination or "cocktail" therapy [3].

3. Nonlinear (SDARE) Methodology

Consider the general autonomous infinite-horizon cost or performance index of the form [13]:

$$J = \frac{1}{2} \int_0^\infty \left[x^T Q x + u^T R u \right] dt \ldots (2)$$

where the minimization is done with respect to state vector (x) and control vector (u) subject to the nonlinear differential constraint:

$$\dot{x} = f(x) + g(x, u(x)) \ldots (3)$$

Where: $x \in R^n$ (n is the order of nonlinear system); $u \in R^m$ (m is the number of control inputs); $f(x) \in C^k$ is a nonlinear state dynamics (k is the degree of nonlinearity); $g(x, u(x)) \in C^k$ is a nonlinear control distribution function; $Q \in R^{n \times n}$ is state weighting which is symmetric positive semi definite (SPSD) matrix; $R \in R^{m \times m}$ is control weighting symmetric positive definite (SPD) matrix; C denotes the class of vector functions, which are continuously differentiable [14].

The nonlinear dynamics of equation (3) can be rewritten in a linear-like structure in the following way [14]:

$$\dot{x} = A(x)x + B(x)u \ldots (4)$$

where: A(x): is (n×n) plant matrix, and B(x) : is (n×m) control distribution matrix. This linear-like structure is called "State Dependent Coefficient" (SDC) parameterization. The (SDARE) approach finds the control (u) that minimizes the quadratic performance index (equation (2)), and the control (u) can be found by the following state feedback law:

$$u = -R^{-1} B^T(x) P(x) x \ldots (5)$$

where the $P(x)$ is the state dependent positive definite symmetric matrix and it is the solution of the following State Dependent Algebraic Riccati Equation (SDARE):

$$P(x)A(x) + A^T(x)P(x) -$$

$$P(x)B(x)R^{-1}B^T(x)P(x) + Q = 0 \ldots (6)$$

In order to apply (SDARE) approach, the system should satisfy the following two conditions [12]:

- Condition(1): *f(x)* is a continuously differentiable function of x.
- Condition(2): $f(0) = 0$.

It can be Noticed that the Nonlinear (HIV) model (Equations (1)) suffers from the existence of scalar terms (I_1, I_2, and I_E) which means that (HIV) model does not satisfy condition (2) mentioned above and thus can not be parameterized to the plant matrix $A(x)$ directly. Thus, the first modification is to change the structure of the (SDC) parameterization (equation (4)). The *f(x)* is composed of two parts: The first one is the parameterizable part which can be put in the form of ($A(x)x$), and the second is the non-parametrizable part, for a general description we call it ($a(x)$).

$a(x)$ is chosen in such away that ($f(0) - a(0) = 0$), so Equation (4) can be re-written as :

$$\dot{x} = A(x)x + a(x) + B(x)u \ldots (7)$$

That is , $f(x)$ is parameterized as:

$$f(x) = A(x)x + a(x) \dots(8)$$

And:

$$a(x) = f(x) - A(x)x \dots(9)$$

Rewriting performance index (equation (2)) in the following way:

$$J = \frac{1}{2}\int_0^\infty \left[(x - x_d)^T Q(x - x_d) + u^T Ru \right] dt \dots(10)$$

where x_d represents the tracking vector (here the tracking desired vector will be the stable Equilibrium point stated in Table (2) in the previous section which is referred to as Desired Healthy State).

It is seen in previous section that (HIV) treatment is limited between a minimum and maximum dose, in other words ($0 \le \in_1, \in_2 \le 1$) where (0) is the least quantity which can be assigned for minimum dose, and (1) is the uppermost quantity which can be assigned to the maximum dose.

Re-driving the (SDARE) approach with the Modified (SDC) form (equation (7)) as a <u>first modification</u> and applying the Pontryagin Minimum Principle to the (SDARE) approach to derive limited optimal control as a <u>second modification</u> (the derivation is explained in details in [14]) so the new modified method will be:

i. Bring the nonlinear (HIV) dynamics (equations (1)), to the form of equation (7).

ii. Solve the State Dependent Algebraic Riccati Equation (SDARE) (equation (6)) to find the matrix *P(x)*.

iii. Construct the Nonlinear State Tracking function $\widetilde{\prod}(x)$ which is stated as follows:

$$\widetilde{\prod}(x) = \left(A^T(x) - P(x)B(x)R^{-1}B^T(x) \right)^{-1} \left(Qx_d - P(x)a(x) \right) \dots(11)$$

iv. Construct the Nonlinear State Feedback Controller which produce an unlimited control action $\widetilde{u}$ by using the following equation:

$$\widetilde{u} = -R^{-1}B^T(x)[P(x)x + \widetilde{\prod}(x)] \dots(12)$$

v. This control action will be limited by sending the unlimited Control $\widetilde{u}$ through a saturation function represented by the following equation:

$$u = \max[\overset{\backslash}{u}, \min[\overset{\backprime}{u}, \widetilde{u}]] \dots(13)$$

where $\overset{\backprime}{u}$: maximum dose.

$\overset{\backslash}{u}$: minimum dose.

4.Simulation Results

The Jacobian of $f(x)$ is chosen to be the plant matrix $A(x)$. That is:

$$A(x) = \frac{\partial f(x)}{\partial x} \dots(14)$$

For the (HIV) model; (Equations (1)) the Jacobian is given by:

$$A(x) = \begin{bmatrix} -d_1 - k_1 V & 0 & 0 & 0 & -k_1 T_1 & 0 \\ 0 & -d_2 - k_2 V & 0 & 0 & -k_2 T_2 & 0 \\ k_1 V & 0 & -d - m_1 E & 0 & k_1 T_1 & -m_1 T_1^* \\ 0 & k_2 V & 0 & -d - m_2 E & k_2 T_2 & -m_2 T_2^* \\ -r_1 k_1 V & -r_2 k_2 V & N_T d & N_T d & A_{55} & 0 \\ 0 & 0 & A_{63} & A_{64} & 0 & A_{66} \end{bmatrix}$$

Where:

$$A_{55} = -c - r_1 k_1 T_1 - r_2 k_2 T_2,$$

$$A_{63} = A_{64} = \frac{b_E k_b E}{\left(T_1^* + T_2^* + k_b\right)^2} - \frac{d_E k_d E}{\left(T_1^* + T_2^* + k_d\right)^2},$$

$$A_{66} = \left[\frac{b_E}{T_1^* + T_2^* + k_b} - \frac{d_E}{T_1^* + T_2^* + k_d} \right](T_1^* + T_2^*) - d_E .$$

And the Control Distribution matrix in Equation (7) is given by:

$$B(x) = \begin{bmatrix} k_1 VT_1 & 0 \\ fk_2 VT_2 & 0 \\ -k_1 VT_1 & 0 \\ -fk_2 VT_2 & 0 \\ r_1 k_1 VT_1 + fr_2 k_2 VT_2 & -N_T d(T_1^* + T_2^*) \\ 0 & 0 \end{bmatrix} \dots(15)$$

At each time step, the State Dependent Algebraic Riccati Equation (SDARE) (equation(6)) is solved to generate a stabilizing solution $P(x)$, which will be inserted into the

following nonlinear state Tracking function $\tilde{\prod}(x)$ (equation(11)), which will be inserted with $P(x)$ into the (equation (12)) to generate the state feedback control law.

This control law will be limited by using the Saturation Function (equation (13)) to generate the feedback control law within limitations using the (SDARE) approach.

The nonlinear (SDARE) controller should track the (HIV) model states to the Desired Healthy State as, so the Desired State Vector x_d will be:

$$x_d = EQ1 \ldots(16)$$

where: $EQ1$ is the equilibrium point 1 in Table (2). The simulation is applied for 2000 day by using two initial conditions, as follows:

1. For the Acute or the early infection phase, the unstable Equilibrium point2 (EQ2) or the Acute state is used, so the initial condition will be:

$$x(0) = EQ2 \ldots(17)$$

where: $EQ2$ is the equilibrium point 2 in Table (2).

2. For the chronic phase, the stable Equilibrium point3 (EQ3) or the Unhealthy State is used, so the initial condition will be:

$$x(0) = EQ3 \ldots(18)$$

where: $EQ3$ is the equilibrium point 3 in Table (2).

It should be noted that:

1. Note that using the unstable Acute initial condition (Equation (17)) means that the medication starts immediately after the (HIV) infection which is unrealistic assumption from the practical point of view, but we are interested here in studying the behavior of

nonlinear (SDARE) controller within the Acute Phase in which the virus levels can rise from zero to millions of copies. So, if the controller can handle the epidemic and succeed in lowering the virus counts to the acceptable level of Desired Healthy State (Equation (16)), and boost the Immune Effectors (E) counts to high level of Desired Healthy State (Equation (16)), this will be a good sign of overall potential of the controller to deal with other cases.

2. The stable Unhealthy initial condition (Equation (18)) represents a patient who has not taken medication after (HIV) infection, this initial condition represent a realistic assumption, because most patients subject to medication commonly start their therapy regimen from this point.

The following weighting matrices are chosen by trial and error:

$$Q = diag([0 \quad 0 \quad 0 \quad 0 \quad 1 \quad 10]) \ldots(19)$$

$$R = (2 \times 10^7) diag([r_1 \quad r_2])$$

where: $r_1 = \dfrac{1}{\in_1^{max}}$, $r_2 = \dfrac{1}{\in_2^{max}}$,

It Should be noticed, in cost function Equation (10) the performance index is multiplied by (0.5), here this multiplication is ignored. In this simulation, the maximum efficacy of Reverse Transcriptase Inhibitor (RTI), $\in_1^{max}$, and the Protease Inhibitor (PI), $\in_2^{max}$, are chosen to be (0.7,0.3), respectively. The minimum efficacy of Reverse Transcriptase Inhibitor (RTI), $\in_1^{min}$, and the minimum Protease Inhibitor (PI), $\in_2^{min}$ are chosen to be (0,0), respectively. The reason for choosing to penalize state V and E to reduce the viral load

(V) state and to increase the number of Immune Effectors (E) state which have the ability to kill the Virus in blood plasma, and this will lead to increase the number of (T-cells), consequently this will help the immune system to take role and control the virus level by oneself.

4.1 Starting from Acute State

Figure (1) depicts the dynamics of the suboptimal Reverse Transcriptase Inhibitor (RTI) control ($\in_1$), while Figure (2) shows the dynamics of suboptimal Protease Inhibitor (PI) Control ($\in_2$). Figure (1) shows that the control ($\in_1$) starts with on-off cycles for the first (40) days giving the patient very brief drug Holidays, at approximately the (41st) day the control dose ($\in_1$) starts to increase gradually until it reaches the full dose ($\in_1^{max}$) in about (3.5) months.

The ($\in_1$) dose level reaches the full dose level and stay for less than (3) months, to start after that to decrease gradually until it reaches zero level in another (3) months at approximately the (318th) day. After (318) days of applying the Therapy Regimen, the feedback control based-treatment ($\in_1$) starts a series of on-off short cycles repeated every (15 or 16) days (giving the (HIV) patient a drug holidays of (15 or 16) day), and the dose level decreases gradually until the control ($\in_1$) stopped completely on the (754th) day. ($\in_2$) control has behavior similar to ($\in_1$) control as shown in Figure (2) that ($\in_2$) control is stopped completely on the (770th) day after starting the medication. The corresponding states progressions T_1, T_2, T_1^*, T_2^*, V,

and E are shown in Figures (3), (4), (5), (6), (7), and (8), respectively.

As it is clear in state variables history that the nonlinear (SDARE) controller succeeds in moving the Immune System of (HIV) patient from the Acute initial Condition (Equation (17)) to the neighborhood of the Desired Healthy State (Equation (16)) after (318) days from starting the therapy. It can be seen that T_2, T_1^*, T_2^*, V, and E states start to oscillate in the neighborhood of the "Healthy" equilibrium point (Equation (16)) until those states gradually converge to its desired values before the (700th) day. As shown in Figure (3), (T_1) state tapers off to its minimum value concentration which is ($39689\,Cells/mL$) on the (24th) day. While (T_2) state shown in Figure (4) tapers off to its minimum value concentration which is ($0.2289\,Cells/mL$) on the (21st) day (recall that the initial concentration was $T_1(0) = 1000000\,Cells/mL$ and $T_2(0) = 3198\,Cells/mL$). This significant drop in (for both type1, and 2 CD4+ T-cells) concentration is anticipated because as explained previously in section 2 that in the Acute Phase the viral load may increase to millions of copies and this may happen during Short periods. As shown in Figure (7) that the (V) state or the virus load reaches in the (21st) day to its maximum value concentration which is ($1397100\,Virions/mL$), this massive viral load results from infecting a large number of (CD4+ T-cells). As shown in Figure (5) and (6) that (T_1^*) and (T_2^*) concentrations increased to a large values during the

first (21) days of Therapy Regimen as compared with its initial values. We should consider that (E) state or the number of Immune Effectors is very small during this interval. The nonlinear (SDARE) controller, succeeds in fighting the (HIV) load well, and in (318) days it succeed to lower the viral load to the neighborhoods of the Desired Healthy State (Equation (16)). Moreover, increasing the number of Immune Effectors or (E) state counts to very high levels, as a consequence this will boost the Immune System to fight the (HIV) invasion by itself, so that there is no longer need for the drugs because the Immune System becomes strong enough and that's clear since the control is stopped for both ($\in_1$ and $\in_2$) after (700) day of Therapy.

4.2 Starting From Unhealthy State

Next, the simulation starting from Unhealthy Initial Condition (Equation (18)) is performed. Figure (9) depicts the dynamics of the Reverse Transcriptase Inhibitor (RTI) control ($\in_1$) and Figure (10) depicts the dynamics of Protease Inhibitor (PI) control ($\in_2$). As noticed in these figures, both ($\in_1$) and ($\in_2$) controls reach the maximum efficacies ($\in_1^{max} = 0.7$, and $\in_2^{max} = 0.3$) and stay fixed at that levels for the full interval of simulation (2000) day. Although the controls ($\in_1$ and $\in_2$) do not stop ever, unfortunately no one of the state Variables shown in Figures (11), (12), (13), (14), (15), and (16) for T_1, T_2, T_1^*, T_2^*, V, and E, respectively, could reach to the Desired Healthy State (Equation (16)), and the worst is that most of the states steady near the values of

the Unhealthy initial condition (Equation (18)) which means that Immune System could not leave the "Viral Dominant State".

Because Therapy Regimen failed to transfer the Immune System from the Unhealthy State (Equation (18) to the Desired Healthy State (Equation (16)), it is necessary to modify it. Trying different weighting matrices instead of the one of Equation (19), does not give better results so another modification is done by increasing the maximum efficacy ($\in_1^{max}$) of the Reverse Transcriptase Inhibitor (RTI) to be (0.75), and keeping the maximum efficacy ($\in_2^{max}$) of the Protease Inhibitor (PI) at (0.3), the simulation is repeated again using weighting matrices (Equation (19)). Figure (17) and (18), show the dynamics of suboptimal Reverse Transcriptase Inhibitor (RTI) control ($\in_1$), and the dynamics of suboptimal Protease Inhibitor (PI) control ($\in_2$), respectively. As noticed here that the ($\in_1$) control needs to overstep the (0.7) level during the first (300) days after starting the Modified Therapy Regimen. This slight increase in the maximum efficacy ($\in_1^{max}$) has significant effect in a way that revives the Immune System of the (HIV) patient to fight the (HIV) alone. It can be noticed that after (277) days after starting the Modified Therapy Regimen, both ($\in_1$ and $\in_2$) controls start a series of on-off cycles repeated every (15 or 16) days (giving the (HIV) patient drug holidays of 15 or 16 days), the dose level decreases gradually until the control ($\in_1$) stopped completely on (697th) day, while ($\in_2$) control

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stopped completely in the day (746th) day.

In general both ($\in_1$ and $\in_2$) controls resulting from Modified Therapy Regimen have Behavior similar to their analogue that result from the original Therapy Regimen. The corresponding state progression T_1, T_2, T_1^*, T_2^*, V, and E are shown in Figures (19), (20), (21), (22), (23), and (24), respectively. It is clear that all the states reached the "Desired Healthy State" (Equation (16)). After (277) days of Modified Therapy Regimen the states T_2, T_1^*, T_2^*, V, and E start to oscillate in the neighborhood of the stable "Healthy" Equilibrium point (Equation (16)) until these states gradually converge their desired values before the (700th) day. The nonlinear (SDARE) controller using Modified Therapy Regimen succeeds to downgrading the counts of T_1^*, T_2^*, and V state, and boosts the states T_1, T_2, and E state to the Desired Healthy State (Equation (16)). It succeeded to transfer the Immune System of the (HIV) patient from the "Viral Dominant State" to the "Immune Dominant State".

Conclusions

The (SDARE) approach is applied to a mathematical model for (HIV) progression includes compartments for target cells, infected cells, and Immune response that are subjected to multiple (RTI- and PI- type) drug treatments as controllers are used to design a realistic Therapy Regimen. This succeeded to transfer the Immune system of the (HIV) patient from "Viral Dominant State" to "Immune Dominant State".

The designed Therapy Regimen will lead to long-term control of (HIV) by using the Immune system of the (HIV) patient itself after the discontinuation of the therapy, as a result, this will lead to prolong time to onset of Acquired Immune Deficiency Syndrome (AIDS) for tens of years.

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Table (1): Parameters used in nonlinear model (1) and their definitions.

Par.	Value	Unit	Description
l_1	10000	$\dfrac{cells}{mL.day}$	Target cell type 1 production (source) rate
d_1	0.01	$\dfrac{1}{day}$	Target cell type 1 death rate
$\in_1$	$\in [0,1]$	_____	Efficacy of Reverse Transcriptase inhibitor (RTI)
$\in_2$	$\in [0,1]$	_____	Efficacy of Protease Inhibitor (PI)
k_1	8×10^{-7}	$\dfrac{mL}{virions.day}$	Population 1 infection rate
l_2	31.98	$\dfrac{cells}{mL.day}$	Target cell type 2 production (source) rate
d_2	0.01	$\dfrac{1}{day}$	Target cell type 2 death rate
f	0.34	_____	Treatment efficacy reduction in Population 2
k_2	1×10^{-4}	$\dfrac{mL}{virions.day}$	Population 2 infection rate
d	0.7	$\dfrac{1}{day}$	Infected cell death rate
m_1	1×10^{-5}	$\dfrac{mL}{cells.day}$	Immune-induced clearance rate for population 1
m_2	1×10^{-5}	$\dfrac{mL}{cells.day}$	Immune-induced clearance rate for population 2
N_T	100.0	$\dfrac{virions}{cell}$	Virions produced per infected cell
c	13.0	$\dfrac{1}{day}$	Virus natural death rate
r_1	1.0	$\dfrac{virions}{cell}$	Average number virions infecting a type 1 cell
r_2	1.0	$\dfrac{virions}{cell}$	Average number virions infecting a type 2 cell

l_E	1	$\dfrac{cells}{mL.day}$	Immune effector production (source) rate
b_E	0.3	$\dfrac{1}{day}$	Maximum birth rate for immune effectors
k_b	100	$\dfrac{cells}{mL}$	Saturation constant for immune effector birth
d_E	0.25	$\dfrac{1}{day}$	Maximum death rate for immune effectors
k_d	500	$\dfrac{cells}{mL}$	Saturation constant for immune effector death
d_E	0.1	$\dfrac{1}{day}$	Natural death rate for immune effectors

**Table (2): The Steady States or Equilibria Of Nonlinear (HIV)
Model (1) and their local stability status**

	EQ1	EQ2	EQ3	Unit
T_1	967839	1000000	163573	$\dfrac{cells}{mL}$
T_2	621	3198	5	$\dfrac{cells}{mL}$
T_1^*	76	10^{-4}	11945	$\dfrac{cells}{mL}$
T_2^*	6	10^{-4}	46	$\dfrac{cells}{mL}$
V	415	1	63919	$\dfrac{virions}{mL}$
E	353108	10	24	$\dfrac{cells}{mL}$
Local Stability status	Stable	Unstable	Stable	____

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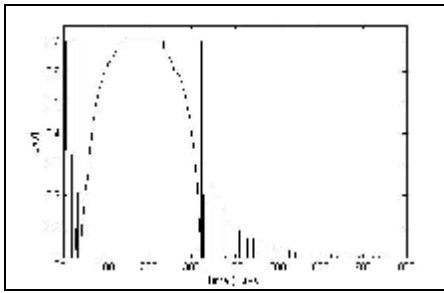
Figure (1): RTI ($\in_1$) Starting from Acute Initial Condition.
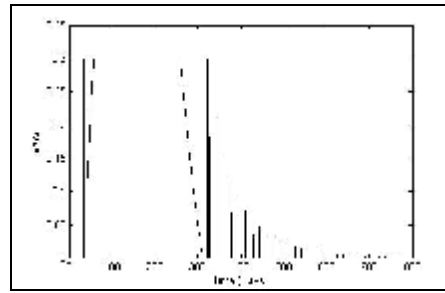
Figure (2): PI ($\in_2$) Starting from Acute Initial Condition.
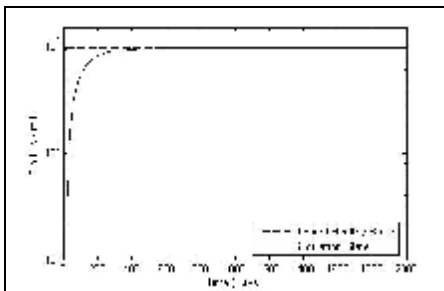
Figure (3): (T_1) State History Starting from Acute Initial Condition.
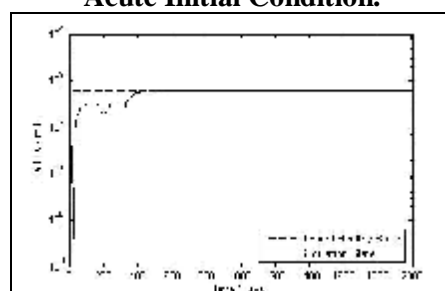
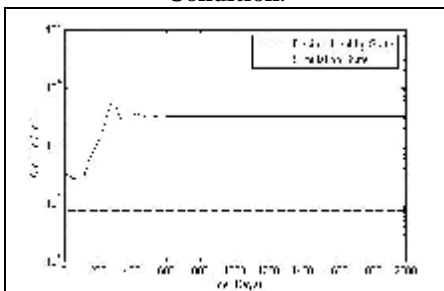**Figure (4): (T_2) State History Starting from Acute Initial Condition.**
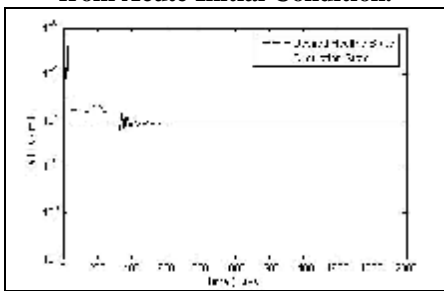
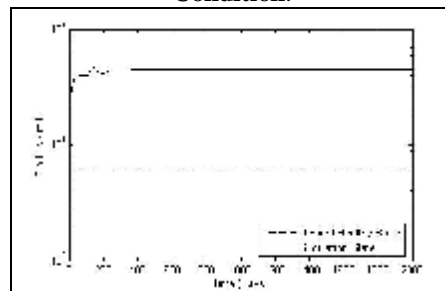Figure (5): (T_1^*) State History Starting from Acute Initial Condition.
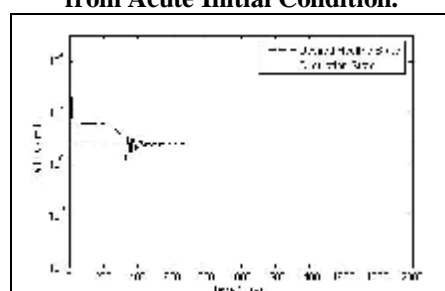
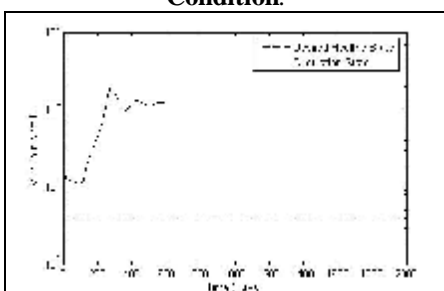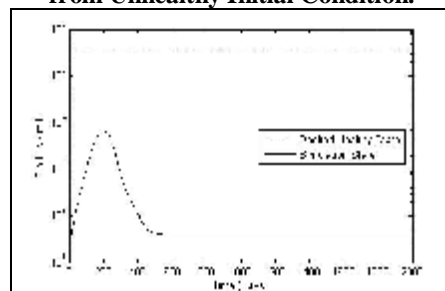Figure (6): (T_2^*) State History Starting from Acute Initial Condition.
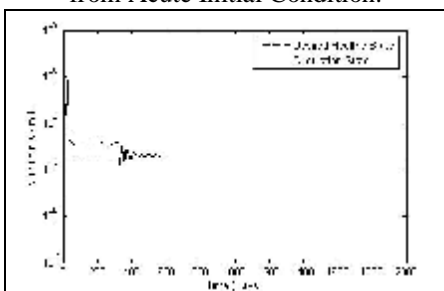
Figure (7): (V) State History Starting from Acute Initial Condition.
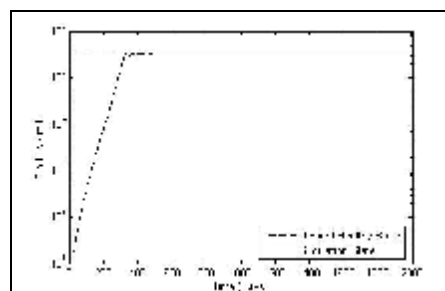
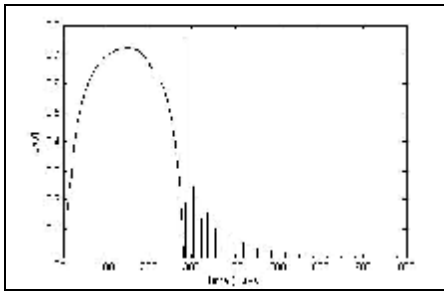**Figure (8): (E) State History Starting**

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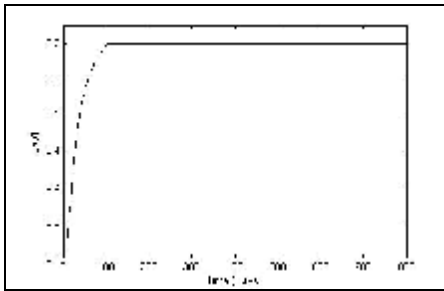
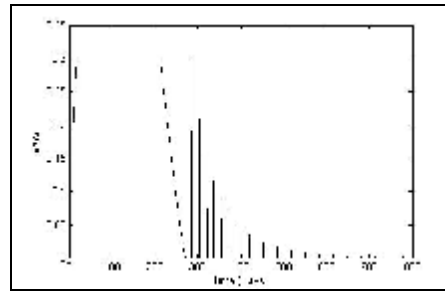**Figure (9): RTI ($\in_1$) Starting From Unhealthy Initial Condition.**
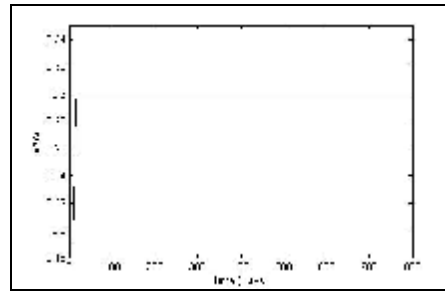
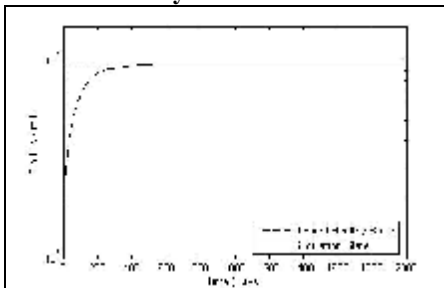**Figure (10): PI ($\in_2$) Starting From Unhealthy Initial Condition.**
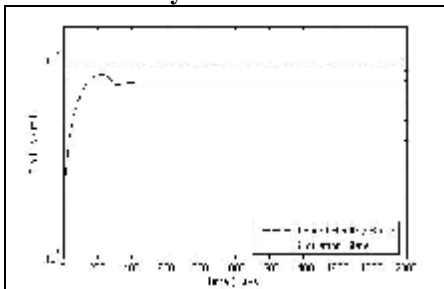
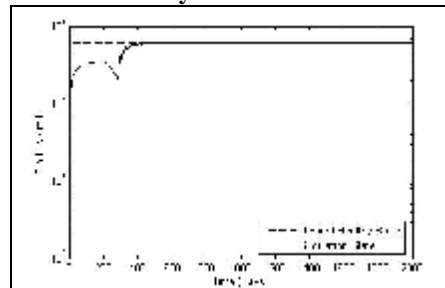**Figure (11): (T_1) State History Starting from Unhealthy Initial Condition.**
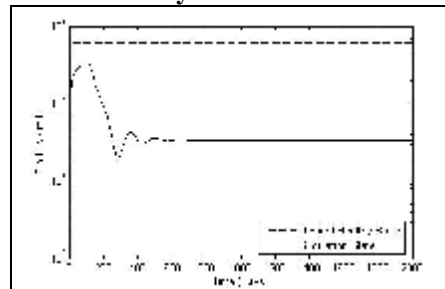
Figure (12): (T_2) State History Starting from Unhealthy Initial Condition.

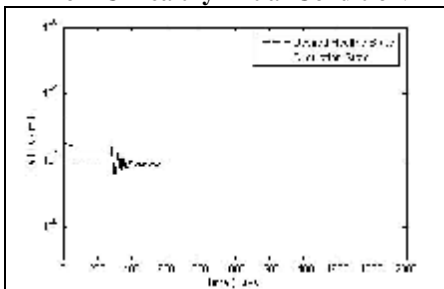
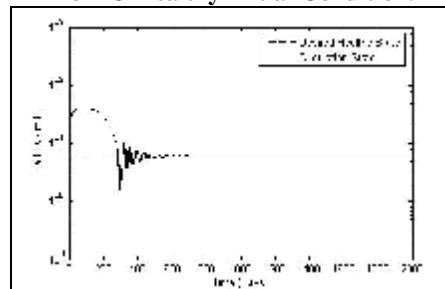**Figure (13): (T_1^*) State History Starting from Unhealthy Initial Condition.**

Figure (14): (T_2^*) State History Starting from Unhealthy Initial Condition.

Figure (15): (V) State History Starting from Unhealthy Initial Condition.

Figure (16): (E) State History Starting from Unhealthy Initial Condition.

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**Figure (17): RTI ($\in_1$) Starting From
Unhealthy Initial Condition.**

**Figure (18): PI ($\in_2$) Starting From
Unhealthy Initial Condition**.

**Figure (19): (T_1) State History Starting
from Unhealthy Initial Condition**.

**Figure (20): (T_2) State History Starting
from Unhealthy Initial Condition.**

**Figure (21): (T_1^*) State History Starting
from Unhealthy Initial Condition.**

**Figure (22): (T_2^*) State History Starting
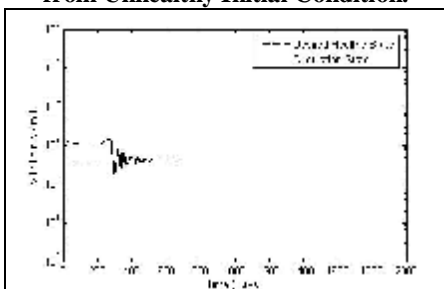from Unhealthy Initial Condition.**

**Figure (23): (V) State History Starting
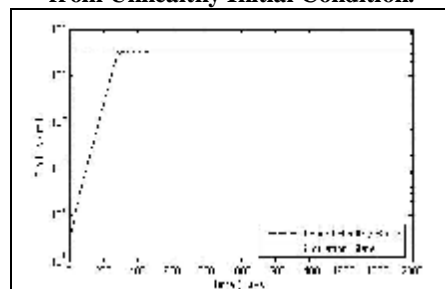from Unhealthy Initial Condition.**

**Figure (24): (E) State History Starting
from Unhealthy Initial Condition.**

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