Stabilization of An Unstable Interaction Between T Cells, HIV, and ARD in A Dynamic System

K.W. Bunonyo, L. Ebiwareme, J. D. Jephter

***Abstract* — This research involves mathematical formulation to investigate the stabilization of an unstable interaction between Tcells, HIV and ARD in a dynamic system. The models were solved analytically where the steady state solutions were obtained. After abtaining the various steady solutions, we did linearization analytically, and the steady solution was found to be unstable. Hence, we introduced a control on some of the pertinent parameters and obtained the new set of eigen values that contains some other parameters. Thereafter, numerical simulation was done using Matlab, by varying the constant supply of the drug to study the effect of the system as well as the HIV. The study showed that the control introduced was effective in stabilising the trivial steady state solution of the dynamic system.**

***Keywords* — ARD, Dynamic System, HIV, Modelling, Treatment ODE, T cell.**

I. Introduction

T lymphocytes (T cells) are a type of white blood cell that plays an important role in the immune system.T cells develop in the thymus after starting in the bone marrow. In the thymus, T cells grow and differentiate into helper, regulatory, or cytotoxic T cells, as well as memory T cells. They are subsequently transported to peripheral tissues or circulated in the bloodstream or lymphatic system. The body can respond to nearly any antigen since it includes millions of T cells, many of which have unique receptors [1].

$CD4^+$ T cells are referred to as "helper" cells since they do not kill pathogens but rather activate the immune system's response to them. CD8 T cells, so named because of the type of protein found on their surface, respond by creating chemicals (antibodies) that aid in the battle against viruses and other external invaders [2]. $CD4^+$ T cells are mature T cells that express the $CD4^+$ protein on their surface. Within the immune system, $CD4^+$ T cells are assumed to play a specified role as helper T cells [3].

A healthy immune system necessitates the selection of T cells with MHC-restricted receptors that are self-antigen tolerant but not MHC-restricted. This happens mostly in the thymus, where lymphocyte precursors first put together a surface receptor [4]. Maintaining self-tolerance while maintaining the ability to develop effective immune responses against invading pathogens is a complex process that requires regulating immune responses to self-antigens [5].

Regulates adaptive immunity to pathogens and cancer by activating other effector immune cells. Treg cells are $CD4^+$ T cells that are in charge of suppressing potentially harmful Th cell activities.

Reference [6]. $CD4^+$T cells are clearly a distinct branch of the adaptive immune system that is critical in achieving a regulated and effective immune response to pathogens, and their proper functioning is critical for survival [7].

For example, HIV, a virus that primarily infects CD4 T cells (but is capable of infecting other important immune system cells, such as macrophages that express $CD4^+$, exemplifies the importance of helper T cells collectively [8]. Loss of functional $CD4^+$ T cells in the advanced stages of HIV infection is referred to as the acquired immunodeficiency syndrome (AIDS). When HIV is detected early in blood or other bodily fluids, proper adherence to antiretroviral therapy will prevent the progression of HIV into AIDS and allow the body to naturally restore its own $CD4^+$ cell count. A small proportion of individuals, referred to as "elite controllers" or "long-term non-progressors," are able to achieve prolonged control of viral load without a significant decline in T cell levels over time without the aid of antiretroviral therapy [9].

Since the early 1980s, when the human immunodeficiency virus (HIV) was discovered, the disease has spread in waves to almost every region on the planet [10].

According to reports, HIV has infected more than 60 million people, with more than a third of them

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dying as a result [11]. When a foreign substance (antigen) is introduced into the body, the immune system responds by releasing a cellular immune response or a humoral immune response in an attempt to clear the object from the body [12].

II. Mathematical Formulation

We consider the following assumptions when developing a system of mathematical models to investigate the interaction between HIV, Tcells, and ARD in order to understand how well ARD can help in stabilizing the dynamic system: For example, there is a constant supply of ARD to maintain the immune system; after a while, the drug fades away. We also believe that HIV and ARD interact, resulting in cell death in both cell-dominated regions. Following the assumptions made by [13], [14], we present the models as follows:

A. Mathematical Models

$$\frac{dT}{dt} = \phi - r_1 T - \beta_2 TH - \alpha_1 DT \tag{1}$$

$$\frac{dH}{dt} = r_1(1 - p_2 H)H - \alpha_3 DH \tag{2}$$

$$\frac{dD}{dt} = \mu_0 - rD \tag{3}$$

where $T(t)$ represents the concentration of healthy CD4$^+$ T cells population at time t, $H(t)$ is the concentration of HIV infected CD4$^+$ T cells population and $D(t)$ is the concentration of anti-retroviral drugs(ARD) at time t.

where:

$$\beta_2 = 62\times10^{-8}, \quad \alpha_1 = 1.101\times10^{-6}, \quad \alpha_3 = 3.422\times10^{-6}, \quad r_1 = 0.44, \quad r = 0.0245, \quad \phi = 1000$$

B. Steady State Solution and Linearization

We let $T \to T_e, D \to D_e, H \to H_e$ so that

$$\frac{dT_e}{dt} = 0, \frac{dH_e}{dt} = 0, \frac{dD_e}{dt} = 0 \tag{4}$$

Applying (4) into (1)-(3), we have:

$$\phi - r_1 T_e - \beta_2 T_e H_e - \alpha_1 D_e T_e = 0 \tag{5}$$

$$r_1(1 - p_2 H_e)H_e - \alpha_3 D_e H_e = 0 \tag{6}$$

$$\mu_0 - rD_e = 0 \tag{7}$$

Solving the (5)-(7), we obtained the following steady state solutions:

$$E_1(T_e, H_e, D_e) = \left(\frac{\phi}{r_1}, 0, 0\right) \tag{8}$$

$$E_2(T_e, H_e, D_e) = \left(\frac{\phi}{\left(r_1 + \frac{\mu_0\alpha_1}{r}\right)}, 0, \frac{\mu_0}{r}\right) \tag{9}$$

$$E_3(T_e, H_e, D_e) = \left(0, \left(\frac{1}{p_2} - \frac{\mu_0\alpha_3}{p_2 r_1 r}\right), \frac{\mu_0}{r}\right) \tag{10}$$

$$E_4\left(T_e,H_e,D_e\right)=\left(\frac{\phi}{\left(r_1+\left(\beta_2\left(\frac{1}{p_2}-\frac{\alpha_3\mu_0}{r_1rp_2}\right)+\frac{\alpha_1\mu_0}{r}\right)\right)},\left(\frac{1}{p_2}-\frac{\alpha_3\mu_0}{r_1rp_2}\right),\frac{\mu_0}{r}\right) \tag{11}$$

where equations (8)–(11) denote the trivial steady state solution (TSSS), the Tcell dominated steady state solution (TDSSS), the HIV dominated steady state solution (HDSSS), and the coexistence steady state solution (CESSS), respectively.

C. Linearization and Characteristics Polynomials

We let (1)-(3) to be equal to F_1, F_2 and F_3 respectively, so that:

$$F_1\left(T,H,D\right)=\frac{dT}{dt}=\phi-r_1T-\beta_2TH-\alpha_1DT \tag{12}$$

$$F_2\left(T,H,D\right)=\frac{dH}{dt}=r_2\left(1-p_2H\right)H-\alpha_3DH \tag{13}$$

$$F_3\left(T,H,D\right)=\frac{dD}{dt}=\mu_0-rD \tag{14}$$

We differentiate (12)-(14) at the steady state solutions in (8)-(11) in order to form the Jacobian matrix, which is:

$$J\left(T_e,H_e,D_e\right)=\begin{pmatrix}\left.\frac{\partial F_1}{\partial T}\right|_{T=T_e} & \left.\frac{\partial F_1}{\partial H}\right|_{H=H_e} & \left.\frac{\partial F_1}{\partial D}\right|_{D=D_e}\\ \left.\frac{\partial F_2}{\partial T}\right|_{T=T_e} & \left.\frac{\partial F_2}{\partial H}\right|_{H=H_e} & \left.\frac{\partial F_2}{\partial D}\right|_{D=D_e}\\ \left.\frac{\partial F_3}{\partial T}\right|_{T=T_e} & \left.\frac{\partial F_3}{\partial H}\right|_{H=H_e} & \left.\frac{\partial F_3}{\partial D}\right|_{D=D_e}\end{pmatrix}=\begin{pmatrix}J_{11} & J_{12} & J_{13}\\ J_{21} & J_{22} & J_{23}\\ J_{31} & J_{32} & J_{33}\end{pmatrix} \tag{15}$$

Substitute (8)-(11) into the Jacobian matrices in (15), we have:

$$J\left(T_e,H_e,D_e\right)=\begin{pmatrix}-r_1-\beta_2H_e-\alpha_1D_e & -\beta_2T_e & -\alpha_1T_e\\ 0 & r_2\left(1-2p_2H_e\right)-\alpha_3D_e & -\alpha_3H_e\\ 0 & 0 & -r\end{pmatrix} \tag{16}$$

We can calculate the Jacobian at the various steady state solutions. The first is the one at the trivial steady state solution in (8), we have:

$$J_1\left(E_1\left(T_e,H_e,D_e\right)\right)=\begin{pmatrix}\left(-r_1-\frac{\alpha_1\mu_0}{r}\right) & 0 & 0\\ 0 & -\frac{\alpha_3\mu_0}{r} & 0\\ 0 & 0 & -r\end{pmatrix} \tag{17}$$

Secondly, T cell dominated steady state solution (TDSSS) in (9), we have:

$$J_2\left(E_2\left(T_e,H_e,D_e\right)\right)=\begin{pmatrix}-r_1-\frac{\alpha_1\mu_0}{r} & -\frac{\beta_2\phi}{\left(r_1+\frac{\mu_0\alpha_1}{r}\right)} & -\frac{\alpha_1\phi}{\left(r_1+\frac{\mu_0\alpha_1}{r}\right)}\\ 0 & r_2-\frac{\alpha_3\mu_0}{r} & 0\\ 0 & 0 & -r\end{pmatrix} \tag{18}$$

Thirdly, the HIV dominated steady state solution (HDSSS) in (10), we have:

$$J_3\left(E_3\left(T_e,H_e,D_e\right)\right)=\begin{pmatrix} -r_1-\beta_2\left(\frac{1}{p_2}-\frac{\mu_0\alpha_3}{p_2r_1r}\right)-\frac{\alpha_1\mu_0}{r} & 0 & 0 \\ 0 & r_2\left(1-\left(2-\frac{2\mu_0\alpha_3}{r_1r}\right)\right)-\frac{\alpha_3\mu_0}{r} & -\left(\frac{\alpha_3}{p_2}-\frac{\mu_0\alpha_3^2}{p_2r_1r}\right) \\ 0 & 0 & -r \end{pmatrix} \tag{19}$$

Finally, the coexistence steady state solution (CESSS) in equation (11), we have:

$$J_4\left(T_e,H_e,D_e\right)=\begin{pmatrix} -r_1-\left(\frac{\beta_2}{p_2}-\frac{\alpha_3\beta_2\mu_0}{r_1rp_2}\right)-\frac{\alpha_1\mu_0}{r} & -\beta_2T_e & -\alpha_1T_e \\ 0 & r_2\left(1-\left(2-\frac{2\alpha_3\mu_0}{r_1r}\right)\right)-\frac{\alpha_3\mu_0}{r} & -\left(\frac{\alpha_3}{p_2}-\frac{\alpha_3^2\mu_0}{r_1rp_2}\right) \\ 0 & 0 & -r \end{pmatrix} \tag{20}$$

where $T_e=\dfrac{\phi}{\left(r_1+\left(\beta_2\left(\frac{1}{p_2}-\frac{\alpha_3\mu_0}{r_1rp_2}\right)+\frac{\alpha_1\mu_0}{r}\right)\right)}$

The polynomial resulting from the trivial steady state solution (TSSS) in (8) is

$$P_1\left(\lambda\right)=\left(\phi_{01}-\lambda\right)\left(\phi_{02}-\lambda\right)\left(-r-\lambda\right)=0 \tag{21}$$

where $\phi_{01}=\left(-r_1-\dfrac{\alpha_1\mu_0}{r}\right),\phi_{02}=-\dfrac{\alpha_3\mu_0}{r}$

The polynomial resulting from the T cell dominated steady state solution (TDSSS) in (9) is:

$$P_2\left(\lambda\right)=\left(\phi_1-\lambda\right)\left(\phi_4-\lambda\right)\left(-r-\lambda\right)=0 \tag{22}$$

where $\phi_1=\left(-r_1-\dfrac{\alpha_1\mu_0}{r}\right),\phi_2=-\dfrac{\beta_2\phi}{\left(r_1+\frac{\mu_0\alpha_1}{r}\right)},\phi_3=-\dfrac{\alpha_1\phi}{\left(r_1+\frac{\mu_0\alpha_1}{r}\right)},\phi_4=\left(r_2-\dfrac{\alpha_3\mu_0}{r}\right)$

The polynomial resulting from HIV dominated steady state solution (HDSSS) in (10) is:

$$P_3\left(\lambda\right)=\left(\phi_5-\lambda\right)\left(\phi_6-\lambda\right)\left(-r-\lambda\right)=0 \tag{23}$$

where $\phi_5=\left(-r_1-\beta_2\left(\dfrac{1}{p_2}-\dfrac{\mu_0\alpha_3}{p_2r_1r}\right)-\dfrac{\alpha_1\mu_0}{r}\right),\phi_6=\left(r_2\left(1-\left(2-\dfrac{2\mu_0\alpha_3}{r_1r}\right)\right)-\dfrac{\alpha_3\mu_0}{r}\right),\phi_7=-\left(\dfrac{\alpha_3}{p_2}-\dfrac{\mu_0\alpha_3^2}{p_2r_1r}\right)$

The polynomial resulting from the coexistence steady state solution (CESSS) in (11) is:

$$P_4\left(\lambda\right)=\left(\phi_8-\lambda\right)\left(\phi_9-\lambda\right)\left(-r-\lambda\right)=0 \tag{24}$$

where $\phi_8=\left(-r_1-\left(\dfrac{\beta_2}{p_2}-\dfrac{\alpha_3\beta_2\mu_0}{r_1rp_2}\right)-\dfrac{\alpha_1\mu_0}{r}\right),\phi_9=\left(r_2\left(1-\left(2-\dfrac{2\alpha_3\mu_0}{r_1r}\right)\right)-\dfrac{\alpha_3\mu_0}{r}\right),\phi_{10}=-\left(\dfrac{\alpha_3}{p_2}-\dfrac{\alpha_3^2\mu_0}{r_1rp_2}\right)$

III. Results

We code the dynamic system in (1)-(3) and the steady state solution using Matlab to test for the stability of the system using the parameters values $\beta_2=62\times10^{-8}$, $\alpha_1=1.101\times10^{-6}$, and $\alpha_3=3.422\times10^{-6}$, $r_1=0.44$, $\gamma=0.0245$, $\phi=1000$ for which the

simulated result is shown in Table I, and that with control values on some of the sensitive parameters: $\beta_2 \times 10^6,\ \alpha_1 \times 10^4,\ \alpha_3 \times 10^4,\ p_2 \times 10^8$. The results are presented as follows:

TABLE I: EFFECT OF CONSTANT SUPPLY OF ARD ON THE SYSTEM WITHOUT CONTROL $\beta_2 = 62\times10^{-8}, \alpha_1 = 1.101\times10^{-6}, \alpha_3 = 3.422\times10^{-6}, r_1 = 0.44, \gamma = 0.0245, \phi = 1000$

μ_0	T	H	D	λ_1	λ_2	λ_3	TOS
0.0	2272.7273	0.00	0.00	-0.440000	4.400000e-01	-0.02	DG
0.2	2272.6808	0.00	8.16	-0.440009	4.399721e-01	-0.02	DG
0.4	2272.6344	0.00	16.33	-0.440018	4.399441e-01	-0.02	DG
0.6	2272.5880	0.00	24.49	-0.440027	4.399162e-01	-0.02	DG
0.8	2272.5416	0.00	32.65	-0.440036	4.398883e-01	-0.02	DG
1.0	2272.4952	0.00	40.82	-0.440045	4.398603e-01	-0.02	DG
1.2	2272.4488	0.00	48.98	-0.440054	4.398324e-01	-0.02	DG
1.4	2272.4023	0.00	57.14	-0.440063	4.398045e-01	-0.02	DG
1.6	2272.3559	0.00	65.31	-0.440072	4.397765e-01	-0.02	DG
1.8	2272.3095	0.00	73.47	-0.440081	4.397486e-01	-0.02	DG
2.0	2272.2631	0.00	81.63	-0.440090	4.397207e-01	-0.02	DG
2.2	2272.2167	0.00	89.80	-0.440099	4.396927e-01	-0.02	DG
2.4	2272.1703	0.00	97.96	-0.440108	4.396648e-01	-0.02	DG
2.6	2272.1239	0.00	106.12	-0.440117	4.396368e-01	-0.02	DG
2.8	2272.0775	0.00	114.29	-0.440126	4.396089e-01	-0.02	DG
3.0	2272.0311	0.00	122.45	-0.440135	4.395810e-01	-0.02	DG
3.2	2271.9847	0.00	130.61	-0.440144	4.395530e-01	-0.02	DG
3.4	2271.9383	0.00	138.78	-0.440153	4.395251e-01	-0.02	DG
3.6	2271.8919	0.00	146.94	-0.440162	4.394972e-01	-0.02	DG
3.8	2271.8456	0.00	155.10	-0.440171	4.394692e-01	-0.02	DG
4.0	2271.7992	0.00	163.27	-0.440180	4.394413e-01	-0.02	DG
4.2	2271.7528	0.00	171.43	-0.440189	4.394134e-01	-0.02	DG
4.4	2271.7064	0.00	179.59	-0.440198	4.393854e-01	-0.02	DG
4.6	2271.6600	0.00	187.76	-0.440207	4.393575e-01	-0.02	DG
4.8	2271.6136	0.00	195.92	-0.440216	4.393296e-01	-0.02	DG
5.0	2271.5673	0.00	204.08	-0.440225	4.393016e-01	-0.02	DG

DG: Degenerate

TABLE II: EFFECT OF CONSTANT SUPPLY OF ARD ON THE SYSTEM WHERE $\beta_2 = 0.062,\ \alpha_1 = 0.01101, \alpha_3 = 0.03422, r_1 = 0.44, \gamma = 0.0245, \phi = 1000$ AND THE CONTROL ON PARAMETERS $\beta_2 \times 10^6, \alpha_1 \times 10^4, \alpha_3 \times 10^4, p_2 \times 10^8$

μ_0	T	H	D	λ_1	λ_2	λ_3	TOS
0.0	2272.7273	0.00	0.00	0.440000	4.400000e-01	-0.02	DG
0.2	1887.2285	0.00	8.16	0.529878	1.606531e-01	-0.02	DG
0.4	1613.5406	0.00	16.33	-0.619755	-1.186939e-01	-0.02	DG
0.6	1409.1798	0.00	24.49	-0.709633	-3.980408e-01	-0.02	S
0.8	1250.7658	0.00	32.65	-0.799510	-6.773878e-01	-0.02	S
1.0	1124.3690	0.00	40.82	-0.889388	-9.567347e-01	-0.02	S
1.2	1021.1737	0.00	48.98	-0.979265	-1.236082e+00	-0.02	S
1.4	935.3287	0.00	57.14	-1.069143	-1.515429e+00	-0.02	S
1.6	862.7976	0.00	65.31	-1.159020	-1.794776e+00	-0.02	S
1.8	800.7059	0.00	73.47	-1.248898	-2.074122e+00	-0.02	S
2.0	746.9512	0.00	81.63	-1.338776	-2.353469e+00	-0.02	S
2.2	699.9600	0.00	89.80	-1.428653	-2.632816e+00	-0.02	S
2.4	658.5313	0.00	97.96	-1.518531	-2.912163e+00	-0.02	S
2.6	621.7327	0.00	106.12	-1.608408	-3.191510e+00	-0.02	S
2.8	588.8291	0.00	114.29	-1.698286	-3.470857e+00	-0.02	S
3.0	559.2331	0.00	122.45	-1.788163	-3.750204e+00	-0.02	S
3.2	532.4698	0.00	130.61	-1.878041	-4.029551e+00	-0.02	S
3.4	508.1512	0.00	138.78	-1.967918	-4.308898e+00	-0.02	S
3.6	485.9568	0.00	146.94	-2.057796	-4.588245e+00	-0.02	S
3.8	465.6201	0.00	155.10	-2.147673	-4.867592e+00	-0.02	S
4.0	446.9172	0.00	163.27	-2.237551	-5.146939e+00	-0.02	S
4.2	429.6587	0.00	171.43	-2.327429	-5.426286e+00	-0.02	S
4.4	413.6836	0.00	179.59	-2.417306	-5.705633e+00	-0.02	S
4.6	398.8539	0.00	187.76	-2.507184	-5.984980e+00	-0.02	S
4.8	385.0506	0.00	195.92	-2.597061	-6.264327e+00	-0.02	S
5.0	372.1707	0.00	204.08	-2.686939	-6.543673e+00	-0.02	S

S: Stable

IV. Discussion and Conclusion

After solving (1)–(3), where we obtained the steady state solution and investigated the stability analytically as shown in (8)–(11), we coded the system with the steady state solutions and performed numerical simulation using MATLAB. We discuss and conclude as follows:

The constant supply of ARD into the system depicted in Table I caused instability in the system, though there was an increase in drug concentration in the system due to the supply of ARD, and that has kept the HIV concentration at zero level while the ARD saturated system affects healthy T cells by reducing the cell population. However, in Table II, we noticed a relative stability after the first two shots of the ARD and after applying a control to the response coefficient of ARD on $CD4^+$ T cells and HIV. It is seen that after the introduction of the control from 10^4, 10^4, 10^6, and 10^8, respectively, the control quantity does not have an effect on the concentration of ARD in the system, which makes it effective and acceptable.

Model Parameters

The definition of the entering parameters involved in the modeling process are presented as follows:

T	Concentration of $CD4^+$ T cell population
H	Concentration of HIV cell population
D	Concentration of ARD
ϕ	Supply of $CD4^+$ T cells from the thymus
β_2	Rate of loss of $CD4^+$ T cells due to the association with HIV cells
α_1	The response coefficient of ARD drug for $CD4^+$ T cells
α_3	The response coefficient of ARD drug for HIV cells
P_2	The inverse carrying capacity for HIV cells
μ_0	The dosage of ARD drugs
r	The fading rate of the ARD drugs
r_1	Decay rate of $CD4^+$ T cells

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Conflict of Interest

Authors declare that they do not have any conflict of interest.

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