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Mathematical Modeling and Simulation of Acute and Chronic Phase HIV-1 Dynamics.

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ABSTRACT

Aims: To construct a clinically plausible mathematical model of the patho-physiological dynamics of HIV-1 induced AIDS during the acute and chronic phases which incorporates the interactions between uninfected CD4+ T cells, HIV-1 infected CD4+ T cells, HIV-1 virions in the blood plasma, and specific cytotoxic CD8+ T cells. In particular, the model describes quantitatively the time evolution of AIDS in the patient during the acute phase and the asymptomatic chronic clinical latency phase and elucidates the effect of latent HIV-1 reservoirs on the prognosis of AIDS. The major objective is to derive mathematical criteria depicting the necessary and sufficient conditions under which the HIV-1 virions can be maintained definitely at the subclinical viral blood plasma level such that the HIV-1 seropositive person does not develop full-blown AIDS..

Study design: The model is based on contemporary published patho-physiological data on acute and clinical chronic phase HIV-1 induced AIDS. These data are meticulously condensed into a clinically plausible four compartmental mathematical model that incorporates the dynamics and interactions between non-HIV-1 infected CD4+ T lymphocytes, HIV-1 infected lymphocytes, free HIV-1 virions in the blood plasma, and HIV-1 specific cytotoxic CD8+ T lymphocytes. The relevant stoichiometric interaction rate constants, apoptotic rate constants, rate constants for viral recruitment from latent reservoirs, and other relevant parameters are clearly exhibited in the mathematical model.

Place and Duration of Study: This research was done at Fayetteville State University, North Carolina USA, and is sponsored by the FSU Mini-Grant Award and the HBCU Graduate STEM Grant. The research was done during the Spring of 2012.

Methodology: The deterministic nonlinear HIV-1 AIDS patho-physio-dynamical equations are analyzed using the techniques of dynamical system theory, principles of linearized stability, Hartman-Grobman theory, and other relevant mathematical techniques. The clinically desirable equilibrium states are and their local existence and global stability are analyzed. Investigative computer simulations are performed illustrating some physiological outcomes.

Results: Mathematical criteria are derived under which the clinically desired outcomes can occur. Investigative computer simulations are presented which elucidate a number of physiological scenarios of primary HIV-1 infection, involving the annihilation, and persistence of HIV-1 in the absence of AIDS Pharmacotherapy

Conclusion: Mathematical modeling can be a useful technique in the derivation of prognostic criteria and quantitative analysis of AIDS during the acute and chronic phases.

Keywords: HIV-1 annihilation criterias, mathematical model, computer simulations, acute and chronic phase

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1. INTRODUCTION

Human Immunodeficiency Virus (HIV) belongs to a family of ribonucleic (RNA) lenti-viruses. In particular, the epidemiologically common subtype called HIV-1 is implicated for causing the Human Acquired Immunodeficiency Syndrome (AIDS). The pathogenesis of AIDS can be divided into three main phases called the acute phase, the clinical latency phase, and the full-blown AIDS phase.

The HIV-1 virion uses the glycoprotein *gp120* to locate the CD4 surface molecules and the host cells. By means of CCR5 or CXCR4, the HIV-1 virions fuses to the host cell surfaces and eventually enter the cell. The CD4+ T cells are the major targets for the HIV-1 virions. But macrophages, monocytes, neurons, astrocytes, and microglia cells in the central nervous system (CNS) possess CCR5 chemokine co-receptors and hence are targets of HIV-1 virions. The pathogenesis of HIV-1 infection comprises the virus life cycle, the host cellular environment, and the viral load in the infected person. There exist strains of HIV-1 virus known as T-tropic and M-tropic which interact respectively with the CXCR4 and CCR5 chemokine co-receptors .

During the acute phase of HIV-1 infection, the person is seropositive after exposure and immunological reaction to the initial viral inoculum. The person experiences transient infection resembling mononucleosis for 1-12 weeks. The symptomatic primary HIV-1 infection is usually characterized by fever, lymphadenopathy, pharyngitis, arthralgia, rash, and lethargy. This is called acute retroviral syndrome (ARS) and is experienced by most but not all of the HIV-1 infected persons. During this phase, large amount of HIV-1 virions are produced inside the patient body. Inside the patient body, the HIV-1 viral envelope decoates and HIV RNA, reverse transcriptase, integrase, and other viral protein enter the host cell leading to formation of a pre-integration complex inside the host cell such as the CD4+ T cells. Then reverse transcriptase is used to produce HIV-1 viral DNA. The viral DNA is transported across the nucleus of the host cell and integrates into the host DNA. The next step is the production of new HIV-1 viral proteins using the HIV-1 viral RNA as genomic RNA. HIV proteases cleave newly synthesized polyproteins at the appropriate places to create the mature protein components of an infectious HIV virion. Then the new viral RNA and viral proteins migrate to the host surface and form a new immature HIV-1 provirus. The mature newly formed HIV-1 virions exit the host cell by a process called budding. In particular, several millions of virus RNA copies may be released into the blood plasma of the patient.

After 3 months, the chronic clinical latency phase starts. During this phase, the rate of HIV-1 replication in the host cell decreases as the CD4+ T cells numbers increases as a result of the cytotoxic intervention of the body's immune system mounted by the CD8+ T cells. In particular, it is possible at this stage for the blood plasma HIV-1 viral titre to be subclinical and plunge to undetectable levels. This may continue up to 8 years or longer. Pantaleo, G (1993); Siliciano, R. F. (1998); Wasef, N. M.(2003).

The third phase of HIV-1 dynamics is characterized by a rapid exponential increase in the number of HIV-1 virions in the blood plasma, increase in the number of HIV-1 infected CD₄+ T cells, and a rapid decrease of uninfected CD₄+ T cells to a level below 200 cells per microliter and a complete failure of the anti-HIV cytotoxic activity of CD₈+ T cells. Walker, C. M. et al. (1986)

Several mathematical models of HIV-1 dynamics have been constructed by many authors including Pantaleo et al (1993); Essunger, P., Perelson, A.S. (1994); Perelson, A.S., Nelson, P. (1999); Kirschner, D., Webb, G.F. (1996); Wodarz, D. et al. (1999); Wodarz, D. (2001); Wodarz, D., Nowark, M. (1999). These authors proposed various mathematical models which describe certain aspects of HIV-1 life cycle with the aim of finding criteria for cure of AIDS or present a quantitative analysis of the dynamics of the HIV-1 virus. Ciupe, M.S., Bivort, B.L., Bortz, D.M. and Nelson, P.W. (2006) presented a detailed analysis of three different mathematical models with regard to local and global stability of infected and uninfected equilibrium (steady) states of HIV-1 infection. Their analysis also included the dynamics of time delay models. Li, M.Y. and Shu, H. (2011) performed an elaborate analysis of the global dynamics of a mathematical model for HTLV-1 infection of CD₄+ T cells with delayed CTL response. In particular, they demonstrated that the time delay can destabilize the system equilibrium leading to Hopf bifurcations and stable periodic oscillations. Similar analysis of the global dynamics of HIV-1 infection of CD₄+ T cells was done by Wang, L. and Li, M.Y. (2006). They obtained some interesting results on the stability of infected and non-infected equilibrium states of AIDS infection. A stochastic model for HIV-1 population dynamics has been presented and analyzed by Tuckwell and Corfec (1998). In particular, they analyzed the random fluctuations associated with HIV-1 infection and dynamics. In the forthcoming paper, we will present a stochastic model of HIV-1 dynamics which incorporates viral contributions from latent reservoirs and also accounts for apoptosis.

71 In this paper, new mathematical models for the acute phase and the asymptomatic clinical latency phase are
 72 proposed and analyzed. In particular, elaborate and robust mathematical criteria will be presented elucidating the
 73 conditions under which the chronic clinical latency phase can be maintained indefinitely in the seropositive HIV-1
 74 infected person.

75
 76 **2. DEFINITION AND DESCRIPTION OF MODEL PARAMETERS.**
 77

78 The model of HIV-1 patho-physio- dynamics presented in this paper contains many variables and constant
 79 parameters. These parameters include stoichiometric interaction coefficients, cellular degradation rate constants,
 80 apoptotic rate constants, rate constants for production of immune cells from the thymus gland via haematopoietic
 81 progenitors, rate constants for recruitment of HIV-1 virions from latent reservoirs, intra-specific competition rate
 82 constants between infected / uninfected CD4+ T cells, and activation constants for CD4+/CD8+ T cells. The
 83 catalogue of constants is presented as follows

- 84 x_1 : the number density of un-infected CD4⁺ helper T-lymphocytes per unit volume
 85 x_2 : the number density of HIV-1 infected CD4⁺ helper T-lymphocytes per unit volume
 86 x_3 : the number density of HIV-1 virions in the blood plasma per unit volume
 87 x_4 : the number density of HIV-1 specific CD8⁺ cytotoxic T-lymphocytes per unit volume
 88 S_1 : rate of supply of un-infected CD4⁺ T₄-lymphocytes
 89 S_2 : rate of supply of latency infected CD4⁺ T₄-lymphocytes
 90 S_3 : rate of supply of HIV-1 virions from macrophage, monocytes, microglial cells and other lymphoid tissue
 91 different from T₄-lymphocytes
 92 S_4 : rate of supply of CD8⁺ T₈-lymphocytes from the thymus
 93 a, b : constant associated with activation of lymphocytes by cytokine interleukin-2 (IL-2)
 94 α : constant associated with HIV-1 infection of CD4⁺ T₄ helper cells
 95 β_1 : the number of HIV-1 virions produced per day by replication and budding in CD4⁺ T₄ helper cells
 96 β_2 : rate constant associated with replication and “budding” of HIV-1 in syncytia CD4⁺ T₄ helper cells per day per
 97 micro liter (μ l) and released into the blood plasma
 98 β_3 : the number of HIV-1 virions produced per day by replication and “budding” in non-syncytia CD4⁺ T₄ helper
 99 cells and released into the blood plasma
 100 q : constant depicting competition between infected and un-infected CD4⁺ T₄ helper cells
 101 k : constant depicting degradation, loss of clonogenicity or “death”
 102 e_0 : constant depicting death or degradation or removal by apoptosis (programmed cell death)
 103 K : constant associated with the killing rate of infected CD4⁺ T₄ cells by CD8⁺ T₈ cytotoxic lymphocytes

104 ..
 105 ..
 106 **3. MODEL DESCRIPTION AND ANALYSIS**

107 In this section, the mathematical formulation for the acute and chronic phase of HIV-1 patho-physio-dynamics
 108 will be presented.

109 **3.1. The description of the mathematical model**

110 **3.1.1 The CD4+ T cell dynamics:**

111
$$\dot{x}_1 = S_1 + a_1 x_1^2 e^{-b_1 x_1} - \alpha_1 x_1 x_3 - q_1 x_1 x_2 - k_1 x_1 - e_{10} \tag{3.1}$$

112
 113 The instantaneous number of uninfected CD4+ T cells in the blood plasma of the patient at any time during
 114 the acute or chronic phase is equal to the rate of supply of uninfected CD4+ T cells from the thymus via
 115 hematopoietic progenitor cells (S_1); plus the activation/proliferative recruitment of antigen activated and
 116 interleukin-2 stimulated CD4+ T cells ($a_1 x_1^2 e^{-b_1 x_1}$); less the number of CD4+ cells recruited into the pool of HIV-1
 117 infected CD4+ T cells by infection with HIV-1 virions ($\alpha_1 x_1 x_3$); less the number of CD4+ T cells lost by intra-

118 specific competition with HIV-1 infected CD4+ T cells ($q_1x_1x_2$); less the number of CD4+ T cell lost by enzymatic
119 degradation (k_1x_1); and less the number of CD4+ T cells lost by apoptosis/exfoliative cytolytic death (e_{10}).

120

121 **3.1.2 The HIV-1 infected CD4+ dynamics:**

$$122 \quad \dot{x}_2 = S_2 + a_2x_1x_2e^{-b_2x_1} + \alpha_2x_1x_3 - q_2x_1x_2 - k_2x_2 - \beta_1x_3 - K_1x_2x_4 - e_{20} \quad (3.2)$$

123

124 The instantaneous number of HIV-1 infected CD4+ T cells in the blood plasma of the patient during the acute
125 or chronic phase is equal to the rate of supply of HIV infected CD4+ T cells from resting CD4+ T cells (S_2); plus
126 the activation/proliferative recruitment of antigen activated and interleukin-2 stimulated HIV-1 infected CD4+ T
127 cells ($a_2x_1x_2e^{-b_2x_1}$); plus the addition of the HIV-1 infected CD4+ T cells ($\alpha_2x_1x_3$); less the number of CD4+ T
128 cells lost by intra-specific competition with HIV-1 uninfected CD4+ T cells ($q_2x_1x_2$); less the number of HIV-1
129 infected CD4+ T cell lost by enzymatic degradation (k_2x_2); and less the number of HIV-1 infected CD4+ T cells
130 lost as a result of budding of newly produced virions (β_1x_3); less the number of HIV-1 infected CD4+ T cells lost
131 by cytolytic action by HIV-1 specific CD8+ T cells ($K_1x_2x_4$); and less the number of HIV-1 infected CD4+ T cells
132 lost by apoptosis/exfoliative cytolytic death (e_{20}).

133 **3.1.3 The blood plasma HIV-1 virion dynamics:**

$$134 \quad \dot{x}_3 = S_3 + \beta_2x_2x_3 + \beta_3x_3 - \alpha_3x_1x_3 - k_3x_3 - e_{30} \quad (3.3)$$

135

136 The instantaneous number of HIV-1 virions in the blood plasma of the patient is equal to the rate of supply of
137 HIV-1 virions from the latently infected viral reservoirs (S_3); plus the number of HIV-1 virions released from the
138 syncytia of CD4+ T cells/dendritic cells/macrophages ($\beta_2x_2x_3$); plus the number of HIV-1 virions released from
139 budding HIV-1 infected CD4+ T cells (β_3x_3); less the number of HIV-1 virions lost during infection of CD4+ T
140 cells ($\alpha_3x_1x_3$); less the number of HIV-1 virions lost by enzymatic degradation/catabolism (k_3x_3); and less the
141 number of HIV-1 virions lost in the form of unintegrated HIV-1 DNA molecules per provirus (e_{30}).

142

143 **3.1.4 The CD8+ T cells dynamics:**

$$144 \quad \dot{x}_4 = S_4 + a_4x_1x_4e^{-b_4x_1} - K_2x_2x_4 - k_4x_4 - e_{40} \quad (3.4)$$

145

146 The instantaneous number of HIV-1 specific CD8+ T cells is equal to the rate of supply the thymus via
147 hematopoietic progenitor cells; plus activation/proliferative recruitment of antigen activated and interleukin-2
148 stimulated HIV-1 specific CD8+ T cells ($a_4x_1x_4e^{-b_4x_1}$); less the number of CD8+ T cells lost during cytolysis of
149 HIV-1 infected CD4+ T cells (); less the number of HIV-1 specific CD8+ T cell lost by enzymatic
150 degradation (k_4x_4); less the number of HIV-1 specific CD8+ lost by apoptosis/exfoliative cytolytic death (e_{40}).

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3.2 The Cauchy problem for dynamics of HIV-1 during the acute and chronic phases

In this section, the initial value problem (Cauchy problem) for HIV-1 dynamics during the acute and chronic phases will be mathematically analyzed and discussed with regard to well - posedness, dissipativity of solutions, and invariance of non-negativity.

From the previous section, the mathematical model for HIV-1 dynamics during the acute and chronic phases can be described in terms of the following deterministic, non-linear, and coupled ordinary differential equations. It is assumed that within certain biological limits the environment of the interactions between the uninfected CD4+ T cells, HIV-1 infected CD4+ T cells, HIV-1 virions in the blood plasma, and HIV-1 specific CD8+ T cells is homogeneous, isotropic, and hence space independent. Thus ordinary differential equations can be used in the modeling. In the future, mathematical models using partial differential equations, stochastic differential equations, and delay differential equations will be presented. Thus that Cauchy problem is described by the following system of equations:

$$\begin{cases} \dot{x}_1 = S_1 + a_1 x_1^2 e^{-b_1 x_1} - \alpha_1 x_1 x_3 - q_1 x_1 x_2 - k_1 x_1 - e_{10} \\ \dot{x}_2 = S_2 + a_2 x_1 x_2 e^{-b_2 x_1} + \alpha_2 x_1 x_3 - q_2 x_1 x_2 - k_2 x_2 - \beta_1 x_3 - K_1 x_2 x_4 - e_{20} \\ \dot{x}_3 = S_3 + \beta_2 x_2 x_3 + \beta_3 x_3 - \alpha_3 x_1 x_3 - k_3 x_3 - e_{30} \\ \dot{x}_4 = S_4 + a_4 x_1 x_4 e^{-b_4 x_1} - K_2 x_2 x_4 - k_4 x_4 - e_{40} \\ x_i(t_0) = x_{i0} \quad \text{for } i = \{1, 2, 3, 4\} \end{cases}$$

(3.5)

Let t_0 be the time of the initial HIV-1 infection; and define t_L , t_P , respectively, as the time at which the latency phase begins and the time at which the post latency phase of HIV-1 dynamics commences in a patient. In particular, the phases $[t_0, t_L]$, $[t_L, t_P]$ depict respectively the acute phase and the chronic phase of primary HIV-1 induced AIDS.

3.3 Dissipativity and boundedness of solutions

In this subsection, the dissipativity of the model equations will be discussed.

Definition: Consider the autonomous system of ordinary differential equations:

$$\begin{aligned} \dot{x} &= F(x) \quad x(t_0) = x_0 \\ \text{where } x_0, x &\in \mathfrak{R}^n \quad \text{and } F \in C(\mathfrak{R}_+^n, \mathfrak{R}^n) \\ \mathfrak{R}_+^n &= \{x_i \in \mathfrak{R}^n \mid x_i \geq 0, i = 1, 2, \dots, n\} \end{aligned} \tag{3.6}$$

Then the system (3.6) is dissipative if

$$\lim_{t \rightarrow \infty} \text{Sup } x_i(t) < M_i \quad \text{where } M_i \in \mathfrak{R}_+ \text{ is bounded}$$

207

208 The invariance of non-negativity , ultimate boundedness of solutions and dissipativity of the model equations
 209 will be shown as follows:

210

211

212 Let $C_j = \text{Sup}_{t \in [t_0, t_p]} [a_j x_1 x_j e^{-b_j x_1}]$ for $j = \{1, 2, 4\}$
 213 $C_3 = \text{Sup}_{t \in [t_0, t_p]} [\beta_2 x_2 x_3 + \beta_3 x_3]$

(3.7)

214 Where t_L is the time at which the latency phase begins. Similarly, t_p is the time at which the post latency phase of
 215 HIV-1 dynamics commences in a patient and the time beyond which full-blown AIDS occurs.

216 The system of differential equations (3.5) reduce to the following differential inequalities, for $t \in [t_0, t_p]$:

217
$$\begin{cases} \dot{x}_1 \leq S_1 + C_1 - k_1 x_1 - e_{10} \\ \dot{x}_2 \leq S_2 + C_2 - k_2 x_2 - e_{20} \\ \dot{x}_3 \leq S_3 + C_3 - k_3 x_3 - e_{30} \\ \dot{x}_4 \leq S_4 + C_4 - k_4 x_4 - e_{40} \end{cases}$$

218 (3.8)

219 Using the Kamke comparison technique (cf Nani, F., Freedman, H.I. (2000)), the differential inequalities lead
 220 to the following theorem.

Theorem 3.1

221 Let

222
$$m_i = \text{Max}_{t \in [t_0, t_p]} \left\{ x_{iL}, \frac{S_i + C_i - e_{i0}}{k_i} \right\}$$

223 for $i = \{1, 2, 3, 4\}$

224 (3.9)

225 where
$$\begin{cases} x_1(t_0) = x_{10} \\ x_2(t_0) = x_{20} \\ x_3(t_0) = x_{30} \\ x_4(t_0) = x_{40} \end{cases}$$

227 Consider the set

228
$$A = \{(x_1, x_2, x_3, x_4) \in \mathfrak{R}_+^4 \mid 0 \leq x_i < m_i\}$$

229 Then all solutions of the initial value problem (3.5) that originate in $\text{int} \mathfrak{R}_+^4$ will eventually enter the set of A , such
 230 that the solution will be non-negative, ultimately bounded and remain in A for all $t \in \mathfrak{R}_+$.

231 **Proof**

232 The differential inequalities (3.8) can be used to obtain the following expressions:
 233

$$234 \quad x_i \leq \frac{S_i + C_i - e_{i0}}{k_i} + \sigma_{i0} e^{-k_i t} \quad (3.10)$$

235 where $\sigma_{i0} \in \mathfrak{R}^+$ and $i = \{1, 2, 3, 4\}$

236 Hence, for $i = \{1, 2, 3, 4\}$,

$$237 \quad \lim \text{Sup } x_i(t) \leq \frac{S_i + C_i - e_{i0}}{k_i}$$

238 and

$$239 \quad x_i(t) \in \text{Sup}_A \left\{ x_{i0}, \frac{S_i + C_i - e_{i0}}{k_i} \right\} \quad (3.11)$$

241

242 Thus the flow associated with the system (3.5) is dissipative, and non-negatively invariant if $S_i + C_i - e_{i0} > 0$. In
 243 particular, the flow associated with the model equations (3.5) will eventually enter the set A and remains trapped
 244 in A for $t \in \mathfrak{R}^+$, if $x_{i0} \in \text{int} \mathfrak{R}_+^4$. \square

245 3.4 Criteria for persistence of HIV-1 virions in the chronic phase

246 In this section, the criteria for the persistence of HIV-1 virions during the chronic phase will be derived.

247 The differential equation for the HIV-1 patho-physiodynamics during the clinical chronic phase is:

$$248 \quad \dot{x}_3(t) = S_3 + \beta_2 x_3 - \alpha_3 x_1 x_3 - k_3 x_3 - e_{30}$$

249

250 where S_3 is the reflux and repopulation rate of the plasma HIV-1 virions from the lymphoid tissue, microglial cells,
 251 reticules-endothelial cells, monocytes/macrophages and other sanctuaries. e_{30} is a constant degradation rate of
 252 HIV-1 virions. β_2 is the "budding" rate constant of HIV-1 virions.

253

254 Let

$$255 \quad \bar{L}_1 = \inf_{t \in [t_L, t_P]} x_1(t) \quad (3.12)$$

257

258 and

$$259 \quad S_3 - e_{30} \geq 0$$

$$260 \quad \dot{x}_3(t) \geq S_3 + \beta_2 x_3 - \alpha_3 \bar{L}_1 x_3 - k_3 x_3 - e_{30} \quad (3.13)$$

261 By solving (3.13) using Kamke's comparison technique [1, 12], the following inequality is obtained:

$$262 \quad x_3(t) \geq \frac{S_3 - e_{30}}{k_3 + \alpha_3 \bar{L}_1 - \beta_2} + k e^{-(k_3 + \alpha_3 \bar{L}_1 - \beta_2)t} \quad (3.14)$$

263 where k is a positive constant.

264 In particular, the following theorems arise immediately:

265

266 **Theorem 3.2.** Suppose

267 (i) $S_3 - e_{30} > 0$

268 (ii) $k_3 + \alpha_3 L_1 - \beta_2 > 0$

269 Then

270
$$\liminf x_3(t) \geq \frac{S_3 - e_{30}}{k_3 + \alpha_3 L_1 - \beta_2} > H > 0 \quad (3.15)$$

271 where H is a bounded positive number of subclinical value. As a consequence, the number of HIV-1 virions in the
272 blood plasma of the AIDS patient during the chronic phase will exhibit persistence. The patient will not develop
273 full-blown AIDS if the value of H is such that the patient does not experience immune system paralysis.
274

275 **Theorem 3.3.** Suppose

276 (i) $S_3 - e_{30} = 0$

277 (ii) $k_3 + \alpha_3 L_1 - \beta_2 > 0$ (3.16)

278 (iii) $0 < \frac{S_3 - e_{30}}{k_3 + \alpha_3 L_1 - \beta_2} < \varepsilon$

280 where ε is a small positive number.

281 Then the blood plasma HIV-1 viral titre is negligibly subclinical and the AIDS patient has insignificant HIV-1
282 RNA copies in the blood plasma during the chronic phase.

283

284

285 **Theorem 3.4.** Suppose

286 (i) $k_3 + \alpha_3 L_1 - \beta_2 < 0$

287 (ii) $S_3 - e_{30} > 0$ (3.17)

288 Then the number of HIV-1 virions in the blood plasma increases exponentially. The HIV-1 positive patient will
289 develop full-blown AIDS. Consequently, the patient will ultimately lose immuno-competency and eventually die
290 as a result of opportunistic infections.

292

293

294 4. ANALYSES OF THE PHYSIOLOGICAL OUTCOMES

295

296 The clinically significant equilibrium patho-physiological outcomes of HIV-1 dynamics during the acute and
297 chronic phases will be analyzed in this section using the principles of linearized stability. The outcomes are called
298 equilibrium points or rest points of the model equations. The analyses will involve five clinically interesting
299 equilibrium outcomes labeled $\{E_i; i = 1, 2, 3, 4, 5\}$.

300 4.1 Criteria for existence of physiological outcomes

301 (i) $E_1 = [0, 0, 0, 0]$: this represents the case in which uninfected $CD4^+$ T cells, infected $CD4^+$ T cells, HIV-1 virions
302 in blood plasma, and HIV-1 specific $CD8^+$ T cells are all destroyed. This leads to the immune system paralysis in
303 which the patient dies of opportunistic bacteria or viral infection. This case is clinically feasible if $S_j - e_{j0} = 0$.

304 (ii) $E_2 = [\hat{x}_1, 0, 0, \hat{x}_4]$: this represents the case in which infected $CD4^+$ T cells and HIV-1 virions in blood plasma
305 are all destroyed. Clinical doctors working with HIV-1 infected patients would like to achieve this outcome. This
306 equilibrium point is clinically possible under the following necessary conditions:

307
$$\begin{cases} S_1 + a_1 \hat{x}_1^2 e^{-b_1 \hat{x}_2} - k_1 \hat{x}_1 - e_{10} = 0 \\ S_2 - e_{20} = 0 \\ S_3 - e_{30} = 0 \\ S_4 + a_4 \hat{x}_1 \hat{x}_4 e^{-b_4 \hat{x}_1} - k_4 \hat{x}_4 - e_{40} = 0 \end{cases} \quad (4.1)$$

310

311 (iii) $E_3 = [0, \bar{x}_2, \bar{x}_3, 0]$: this depicts a clinically worst case situation in which both uninfected CD4⁺ T cells and HIV-
 312 1 specific CD8⁺ T cells are destroyed. This equilibrium point is clinically possible under the following necessary
 313 conditions:

$$\begin{cases}
 S_1 - e_{10} = 0 \\
 S_2 - \beta_1 \bar{x}_3 - k_2 \bar{x}_2 - e_{20} = 0 \\
 S_3 - \beta_2 \bar{x}_3 - k_3 \bar{x}_3 - e_{30} = 0 \\
 S_4 - e_{40} = 0
 \end{cases} \quad (4.2)$$

320 (iv) $E_4 = [\tilde{x}_1, 0, 0, 0]$: this is the most clinically desirable equilibrium point in which infected CD4⁺ T cells, plasma
 321 HIV-1 virions, and HIV-1 specific cytotoxic CD8⁺ T cells are all annihilated. The necessary conditions for the
 322 existence of this equilibrium point are:

$$\begin{cases}
 S_1 + a_1 \tilde{x}_1^2 e^{-b_1 \tilde{x}_2} - k_1 \tilde{x}_1 - e_{10} = 0 \\
 S_2 - e_{20} = 0 \\
 S_3 - e_{30} = 0 \\
 S_4 - e_{40} = 0
 \end{cases} \quad (4.3)$$

327 (v) $E_5 = [\tilde{x}_1, \tilde{x}_2, \tilde{x}_3, \tilde{x}_4]$: this case can only exist if the equation (3.0) exhibits persistence in which all the four
 328 factors co-exist. The details of showing persistence in nonlinear systems of differential equations have been
 329 discussed by Nani, F., Freedman, H.I. (2000).

330 There are other equilibrium points such as $E[x_1, x_2, 0, 0]$, $E[0, 0, x_3, x_4]$ and many planar or axial points.
 331 These are clinically uninteresting and are not considered in this paper, but will be analyzed in a future paper.

332

333 4.2. Linearized stability analysis of physiological outcomes

334 The Hartman-Grobman theorem can be used to investigate the local physiological stability of HIV-1 AIDS
 335 disease dynamics associated with the model equations, in the neighborhood of the physiological outcomes
 336 (equilibrium states). The mathematical model is nonlinear and as such it is difficult to obtain any meaningful
 337 quantitative criteria about the model. Fortunately, the Hartman-Grobman theorem guarantees that the information
 338 contained in the linearized system and the information contained the nonlinear system are equivalent in the
 339 neighborhood of the rest points.

340 The Jacobian matrix of linearization near any physiological outcome is denoted symbolically by

341

$$342 \quad J[E_k] := \{a_{ij}\} \in M_{4 \times 4}(\mathfrak{R}) \quad \text{where } k = 1, 2, 3, \dots$$

$$344 \quad a_{11} := a_1 x_1 (2 - b_1 x_1) e^{-b_1 x_1} - \alpha_1 x_3 - q_1 x_2 - k_1$$

$$345 \quad a_{12} := -q_1 x_1$$

$$346 \quad a_{13} := -\alpha_1 x_1$$

$$347 \quad a_{14} := 0$$

$$348 \quad a_{21} := a_2 x_2 (1 - b_2 x_1) e^{-b_2 x_1} - q_2 x_2$$

$$349 \quad a_{22} := a_2 x_1 e^{-b_2 x_1} - q_2 x_1 - k_2 - K_1 x_4$$

$$350 \quad a_{23} := \alpha_2 x_1 - \beta_1 \quad (4.4)$$

$$351 \quad a_{24} := -K_1 x_2$$

$$352 \quad a_{31} := -\alpha_3 x_3$$

$$353 \quad a_{32} := \beta_2 x_3$$

$$354 \quad a_{33} := \beta_2 x_2 + \beta_3 - \alpha_3 x_1 - k_3$$

$$355 \quad a_{34} := 0$$

$$356 \quad a_{41} := a_4 x_4 (1 - b_4 x_1) e^{-b_4 x_1}$$

$$357 \quad a_{42} := -K_2 x_4$$

$$358 \quad a_{43} := 0$$

$$359 \quad a_{44} := a_4 x_1 e^{-b_4 x_1} - K_2 x_2 - k_4$$

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4.2.1 Criteria for annihilation of HIV-1 virions during the acute and chronic phases

The Jacobian matrix of linearization in the neighborhood of E_2 is given by the following matrix:

$$J\{E_2[\hat{x}_1, 0, 0, \hat{x}_4]\} = \begin{bmatrix} a_1\hat{x}_1(2-b_1\hat{x}_1)e^{-b_1\hat{x}_1} - k_1 & -q_1\hat{x}_1 & -\alpha_1\hat{x}_1 & 0 \\ 0 & a_2\hat{x}_1e^{-b_2\hat{x}_1} - q_2\hat{x}_1 - k_2 - K_1\hat{x}_4 & \alpha_2\hat{x}_1 - \beta_1 & 0 \\ 0 & 0 & \beta_3 - \alpha_3\hat{x}_1 - k_3 & 0 \\ a_4\hat{x}_4(1-b_4\hat{x}_4)e^{-b_4\hat{x}_4} & -K_2\hat{x}_4 & 0 & a_4\hat{x}_4e^{-b_4\hat{x}_4} - k_4 \end{bmatrix} \quad 359$$

360

(4.5)

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The application of the principle of linearized stability and local stability theorems lead to the following:

Theorem 4.1. Suppose

- (i) $a_1\hat{x}_1(2-b_1\hat{x}_1)e^{-b_1\hat{x}_1} - k_1 < 0$
- (ii) $a_2\hat{x}_1e^{-b_2\hat{x}_1} - q_2\hat{x}_1 - k_2 - K_1\hat{x}_4 < 0$
- (iii) $\beta_3 - \alpha_3\hat{x}_1 - k_3$
- (iv) $a_4\hat{x}_4e^{-b_4\hat{x}_4} - k_4 < 0$

(4.6)

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Then the rest point $E_2[\hat{x}_1, 0, 0, \hat{x}_4]$ is local attractor. In particular, the HIV-1 infected CD4+ T cells and the HIV-1 virions in the blood plasma of the AIDS patient are temporarily annihilated during the acute and chronic phases in the absence of the pharmacotherapy.

Theorem 4.2. Suppose the conditions of Theorem 4.1 hold, and the following additional conditions hold:

$$(i) \hat{x}_1 = \frac{2}{b_1} = \frac{\beta_3}{\alpha_3}$$

$$(ii) \hat{x}_4 = \frac{a_2\hat{x}_1e^{-b_2\hat{x}_1}}{K_1}$$

(4.7)

$$(iii) a_4\hat{x}_4e^{-b_4\hat{x}_4} < k_4$$

Then the local attractor E_2 can be written in the following form:

$$E_2 = \left[\frac{2}{b_1}, 0, 0, \frac{2a_2e^{-\frac{2b_2}{b_1}}}{b_1K_1} \right]$$

(4.8)

382 The clinical implication of this result is that the transient annihilation of the HIV-1 virions and HIV-1 infected
 383 CD4+ T cells occurs during the acute and chronic phases if CD4+ T cells and CD8+ T cells number densities are
 384 given respectively by $\frac{2}{b_1}$ and $\frac{2a_2 e^{-\frac{2b_2}{b_1}}}{b_1 K_1}$.

385
 386 **4.2.2 The criteria for transient immune system paralysis during the acute and chronic phases of AIDS**
 387

388 One of the rest points corresponding the immune system paralysis during primary AIDS infection is E_3 . The
 389 Jacobian matrix of the linearization of the model equations in the neighborhood of E_3 is given as follows:
 390

$$J\{E_3[0, \bar{x}_2, \bar{x}_3, 0]\} = \begin{bmatrix} -\alpha_1 \bar{x}_3 - q_1 \bar{x}_2 - k_1 & 0 & 0 & 0 \\ a_2 \bar{x}_2 - q_2 \bar{x}_2 & -k_2 & -\beta_1 & -K_1 \bar{x}_2 \\ \alpha_3 \bar{x}_3 & \beta_2 \bar{x}_3 & \beta_2 \bar{x}_2 + \beta_3 - k_3 & 0 \\ 0 & 0 & 0 & -K_2 \bar{x}_2 \end{bmatrix} \quad (4.9)$$

394
 395 The application of the principles of linearized stability gives the following result:
 396

397 **Theorem 4.3.** Let

- 398 (i) $\beta_2 \bar{x}_2 + \beta_3 - k_3 - k_2 < 0$
- 399 (ii) $\beta_1 \beta_2 \bar{x}_3 - k_2 (\beta_2 \bar{x}_2 + \beta_3 - k_3) > 0$ (4.10)

400
 401 Then the rest point E_3 is local attractor.
 402

403 The clinical implication of Theorem 4.3 is that the immune system of the AIDS patient suffices transient
 404 paralysis when the conditions (4.10) hold.
 405

406 **Theorem 4.4.** Suppose the conditions of Theorem 4.1 hold, and the following additional conditions hold:

- 407 (i) $\hat{x}_1 > \frac{2}{b_1}$
- 408 (ii) $\hat{x}_1 = \frac{\beta_3}{\alpha_3}$
 $a_2 \hat{x}_1 e^{-b_2 \hat{x}_1} - K_1 \hat{x}_4 = 0 \quad or$
- 409 (iii) $a_2 \hat{x}_1 e^{-b_2 \hat{x}_1} = q_2 \hat{x}_1 \quad or$ (4.11)
 $a_2 \hat{x}_1 e^{-b_2 \hat{x}_1} - k_2 = 0$
- 410 (iv) $\alpha_4 \hat{x}_1 e^{-b_4 \hat{x}_1} < k_4$

411
 412 Then E_2 is a local attractor.
 413

414 The analysis of other rest points will be done in a future publication.
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423 **4.3. Global stability analysis of physiological outcomes**

424 In this section, theoretical criteria will be presented for global stability of the clinically desirable physiological
 425 outcome $E_2[\hat{x}_1, 0, 0, \hat{x}_4]$.

426 Consider space $R_+^{x_1, x_4} = [x_1, x_4 \mid x_1 \geq 0, x_4 \geq 0]$ (4.12)

428
 429 The model equations (3.5) correspondingly reduce to the following:

$$\begin{cases} \dot{x}_1 = S_1 + a_1 x_1^2 e^{-b_1 x_1} - k_1 x_1 - e_{10} \\ \dot{x}_4 = S_4 + a_4 x_1 x_4 e^{-b_4 x_1} - k_4 x_4 - e_{40} \\ x_i(t_0) = x_{i0} \quad \text{for } i = \{1, 4\} \end{cases} \quad (4.13)$$

434 Consider the Liapunov functional [1, 12]:

$$V := \sum \frac{1}{2} \hat{c}_i (x_i - \hat{x}_i)^2$$

437 where $i = \{1, 4\}$ and $\hat{c}_i \in R_+ = (0, \infty)$ (4.14)

439 The derivative of V along the solution curves of the model equations yields the result:

$$\begin{aligned} V &= \hat{c}_1 (x_1 - \hat{x}_1) \dot{x}_1 + \hat{c}_4 (x_4 - \hat{x}_4) \dot{x}_4 \\ &= \hat{c}_1 (x_1 - \hat{x}_1) (S_1 + a_1 x_1^2 e^{-b_1 x_1} - k_1 x_1 - e_{10}) + \\ &\quad \hat{c}_4 (x_4 - \hat{x}_4) (S_4 + a_4 x_1 x_4 e^{-b_4 x_1} - k_4 x_4 - e_{40}) \end{aligned} \quad (4.15)$$

442 Define the following Lebesgue measurable, functions which are of bounded variation:

$$\begin{aligned} G(x_1) &= a_1 x_1^2 e^{-b_1 x_1} \\ F(x_1, x_4) &= a_4 x_1 x_4 e^{-b_4 x_1} \end{aligned} \quad (4.16)$$

$$\begin{aligned} V &= \hat{c}_1 (x_1 - \hat{x}_1) \dot{x}_1 + \hat{c}_4 (x_4 - \hat{x}_4) \dot{x}_4 \\ &= \hat{c}_1 (x_1 - \hat{x}_1) (-a_1 \hat{x}_1^2 e^{-b_1 x_1} + k_1 \hat{x}_1 + a_1 x_1^2 e^{-b_1 x_1} - k_1 x_1) + \\ &\quad \hat{c}_4 (x_4 - \hat{x}_4) (-a_4 \hat{x}_1 \hat{x}_4 e^{-b_4 \hat{x}_1} + k_4 \hat{x}_4 + a_4 x_1 x_4 e^{-b_4 x_1} - k_4 x_4) \\ &= \hat{c}_1 (x_1 - \hat{x}_1) [G(x_1) - G(\hat{x}_1)] + \hat{c}_1 (x_1 - \hat{x}_1) (k_1 \hat{x}_1 - k_1 x_1) + \\ &\quad \hat{c}_4 (x_4 - \hat{x}_4) [F(x_1, x_4) - F(\hat{x}_1, \hat{x}_4)] + \hat{c}_4 (x_4 - \hat{x}_4) (k_4 \hat{x}_4 - k_4 x_4) \end{aligned} \quad (4.17)$$

$$\begin{aligned} V &= -\hat{c}_1 k_1 (x_1 - \hat{x}_1)^2 + \hat{c}_1 (x_1 - \hat{x}_1) [G(x_1) - G(\hat{x}_1)] + \\ &\quad \hat{c}_4 (x_4 - \hat{x}_4) [F(x_1, x_4) - F(\hat{x}_1, \hat{x}_4)] - \hat{c}_4 k_4 (x_4 - \hat{x}_4)^2 \end{aligned} \quad (4.18)$$

446 Let

$$\begin{aligned} v_1 &= x_1 - \hat{x}_1 \\ v_2 &= x_4 - \hat{x}_4 \end{aligned} \quad (4.19)$$

449 and

$$X = \begin{bmatrix} v_1 \\ v_2 \end{bmatrix} \in R_+^2$$

456 and define $A = \{a_{ij}\} \in M_{2 \times 2}(R)$ such that

457 (4.20)
 458
 459
$$A = \begin{bmatrix} a_{11} & \frac{1}{2} a_{12} \\ \frac{1}{2} a_{21} & a_{22} \end{bmatrix}$$

 460

461
 462 then
 463
$$V^* := a_{11}v_1^2 + \frac{1}{2}a_{12}v_1v_2 + \frac{1}{2}a_{21}v_2v_1 + a_{22}v_2^2$$

 464
$$= X^T AX$$
 (4.21)

465 Where X^T denotes the transpose of X and V^* is negative definite if the eigen-values of A have negative real parts.
 466 In particular, the $[a_{ij}]_{2 \times 2}$ are defined as follows:

467
$$\begin{cases} a_{11} := -\hat{c}_1 k_1 + \hat{c}_1 \left(\frac{G(x_1) - G(\hat{x}_1)}{x_1 - \hat{x}_1} \right) \\ a_{12} = a_{21} = 0 \\ a_{22} := -\hat{c}_4 k_4 + \hat{c}_4 \left[\frac{F(x_1, x_4) - F(\hat{x}_1, \hat{x}_4)}{x_4 - \hat{x}_4} \right] \end{cases}$$
 (4.22)
 470
 471
 472

473 As the flow dynamics approaches the steady state $E_2[x_1, 0, 0, x_4]$, the following conditions hold:

474
$$a_{11} \rightarrow -\hat{c}_1 k_1 + G'_1(\hat{x}_1)$$

 475
$$a_{22} \rightarrow -\hat{c}_4 k_4 + \hat{c}_4 F_{x_4}(\hat{x}_1, \hat{x}_4)$$

 476
 477 (4.23)

478
 479 but
$$G'(\hat{x}_1) = a_1 \hat{x}_1 e^{-b_1 \hat{x}_1} (2 - b_1 \hat{x}_1)$$

 480
$$F_{x_4}(\hat{x}_4) = a_4 \hat{x}_4 e^{-b_4 \hat{x}_4} (1 - b_4 \hat{x}_4)$$

 481 (4.24)
 482

483 Hence, the sufficient criteria for the global asymptotic stability of E_2 are specified in the following
 484 theorem.

485 **Theorem 4.5.** Suppose the following conditions hold:

486 (i) Criterion (4.1)

487 (ii) $\hat{x}_1 \geq \frac{2}{b_1}$

488 (iii) $\hat{x}_4 \geq \frac{1}{b_4}$

489 Then the clinically desirable rest point E_2 is a global attractor.

490
 491
 492 The clinical implication of Theorem 4.5 is that the AIDS patient will experience permanent annihilation of the
 493 infected CD4+ T cells and HIV-1 virions in the blood plasma if the patient's patho-physio-dynamics conforms to
 494 the conditions specified in the theorem.
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5. COMPUTER SIMULATION RESULTS AND DISCUSSION

501 In this section, investigative computer simulations are performed under specific parametric configurations. It
502 must be stated emphatically that Theorems 4.1 – 4.4 are applicable only to the equilibrium configurations $\{E_i; i = 1,$
503 $2, 3, 4, \dots, n\}$. of the patho-physiodynamics of HIV-1 virus in the AIDS patient. These theorems are “if...then...”
504 theorems and as such are fulfilled only when the AIDS dynamics attains the equilibrium configuration in the
505 patient. In particular, there exist certain sufficient but not necessary criteria under which the AIDS patient can
506 experience clinically favorable outcomes. On the other hand, under the specified conditions of Theorems 4.1-4.4
507 the predicted results are valid. The simulation results are presented in Sections 5.1 through 5.4. The time profile
508 for the simulation is measured in years.

509 The problem of parameter estimation in mathematical modeling of physiological systems is a non-trivial one.
510 There is a quasi-uniqueness of patho-physio-dynamics of disease in the patient and as such no two persons have
511 identical physiological parametric configurations for a given disease. These phenomena have been discussed in
512 the publication by Wu, H. et al. (1999). Several techniques concerning parameter estimation have been discussed
513 by many authors including Ciupe, M.S. et al. (2006), Perelson, A.S., et al. (1996); Perelson, A.S., and Nelson, P.
514 (1999); Han, C. et al. (2002); Graziosi, C. et al. (1993); Chun, T.W., et al. (1996); Wodarz, D., et al. (1999);
515 Wodarz, D., and Nowark, M. (1999).

516 Theorems 4.1-4.4, however, are based on equilibrium configurations of patho-physio-dynamics of AIDS.
517 Thus, the techniques presented in the above references must be modified in order to obtain relevant estimates of
518 the dynamical variables presented in this paper. In particular, in vitro and in vivo experiments as well as human
519 biopsies from the peripheral blood of the AIDS patient are required in order to accurately determine most of the
520 dynamical variables and constants of the model. Simulations based on equilibrium dynamics of AIDS using ACSL
521 (Advanced Continuous Simulation Language) will be presented in a forthcoming paper.

5.1 Simulation results for hypothetical AIDS patient #1

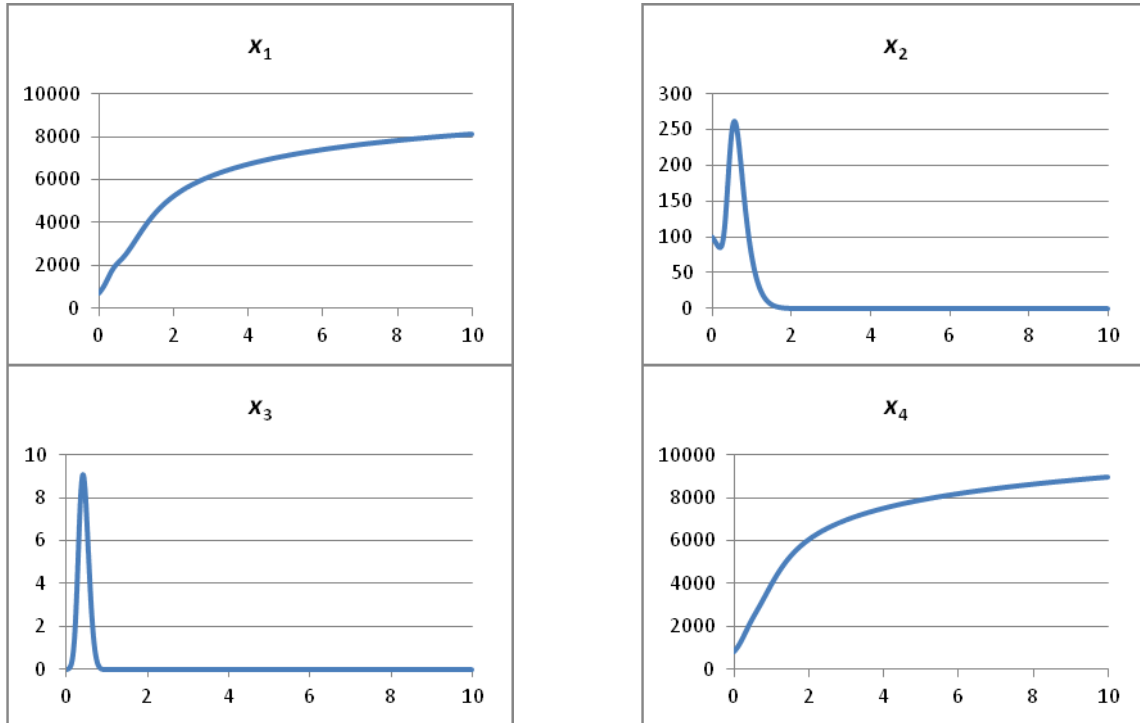
523 The hypothetical patient #1 possesses a non-equilibrium patho-physio-dynamics parametric configuration P_1
524 presented in Table 1. The HIV-1 dynamics in this patient represents the classic profile for the acute and clinically
525 chronic phases of AIDS. The simulation results for patient #1 are exhibited in Figure 1. It can be observed that the
526 HIV-1 infected CD4+ T cells and the blood plasmas HIV-1 virions are completely eradicated in this patient without
527 the use of anti-AIDS pharmac-therapeutic drug protocols. In addition, patient #1 experiences immune system
528 reconstitution as the uninfected CD4+ T cells repopulate and proliferate towards their pre-HIV-1 infection carrying
529 capacities.

530 **Table 1 Parametric Configuration P_1**

531

$S_1 = 1.5 \text{ /day/}\mu\text{l}$ $a_1 = 0.009 \text{ /day/cell/}\mu\text{l}$ $b_1 = 0.001 \text{ /cell/}\mu\text{l}$ $\alpha_1 = 0.05 \text{ /day/virion/}\mu\text{l}$ $k_1 = 0.005 \text{ /day/}\mu\text{l}$ $q_1 = 0.0045 \text{ /day/}\mu\text{l/cell}$ $e_{10} = 8.8 \text{ cells/day/}\mu\text{l}$ $x_{10} = 703 \text{ cells/}\mu\text{l}$	$S_2 = 0.85 \text{ /day/}\mu\text{l}$ $a_2 = 0.004 \text{ /day/cell/}\mu\text{l}$ $b_2 = 0.004 \text{ /cell/}\mu\text{l}$ $\alpha_2 = 0.1 \text{ /day/virion/}\mu\text{l}$ $k_2 = 0.05 \text{ /day/}\mu\text{l}$ $q_2 = 0.0001 \text{ /day/}\mu\text{l/cell}$ $\beta_1 = 50 \text{ virions/CD4}^+ \text{ /day}$ $K_1 = 0.001 \text{ /day/}\mu\text{l}$ $e_{20} = 0.005 \text{ cells/day/}\mu\text{l}$ $x_{20} = 100 \text{ cells/}\mu\text{l}$	$S_3 = 0.0 \text{ /day/}\mu\text{l}$ $\beta_2 = 0 \text{ virions/CD4}^+ \text{ /day/}\mu\text{l}$ $\beta_3 = 50 \text{ virions/CD4}^+ \text{ /day}$ $\alpha_3 = 0.0027 \text{ /day/virion/}\mu\text{l}$ $k_3 = 0.0001 \text{ /day}$ $e_{30} = 0.0001 \text{ /day}$ $x_{30} = 0.01 \text{ cells/}\mu\text{l}$	$S_4 = 0.272 \text{ /day/}\mu\text{l}$ $a_4 = 0.0075 \text{ /day/cell/}\mu\text{l}$ $b_4 = 0.001 \text{ /cell/}\mu\text{l}$ $K_2 = 0.0024 \text{ /day/}\mu\text{l}$ $k_4 = 0.001 \text{ /day/}\mu\text{l}$ $e_{40} = 7.75 \text{ cells/day/}\mu\text{l}$ $x_{40} = 800 \text{ cells/}\mu\text{l}$
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Figure 1 Simulation results using parametric configuration P_1

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539 **5.2 Simulation results for hypothetical AIDS patient #2**

540 For this simulation, the hypothetical AIDS patient #2 is assigned the patho-physiological parameter
541 configuration presented in Table 2. As in the previous simulation, the configuration P_2 does not depict an
542 equilibrium configuration. The simulation results are exhibited in Figure 2. It can be observed that the patient does
543 not have a clinically favorable prognosis. Because the disease has apparently progressed beyond the time point
544 characterized as t_p , which is defined as the threshold time for full-blown AIDS. As presented in Figure 2, the
545 patient undergoes immune system paralysis in which the CD4+ T cells transiently destroyed. On the other hand,
546 the cytotoxic activity of CD8+ T cells appears to be potent as observed in the eradication of the HIV-1 infected
547 CD4+ T cells. Paradoxically the plasma HIV-1 viremia increases exponentially in the patient resulting in a more
548 morbid AIDS outcome.

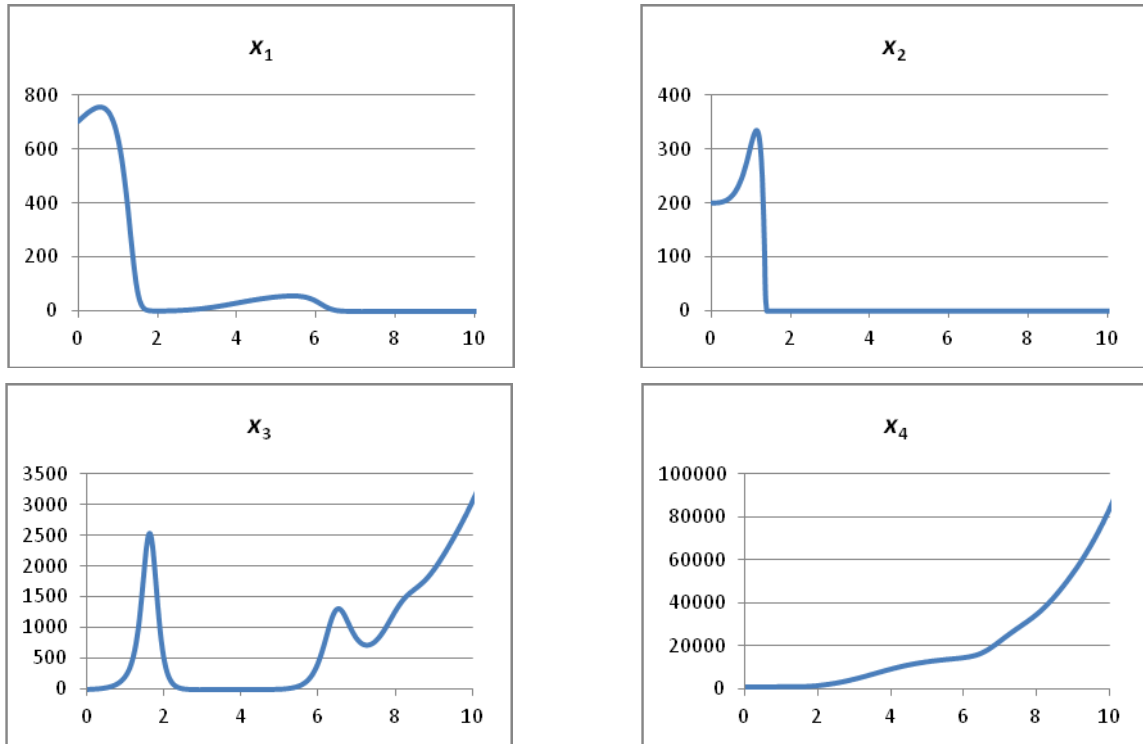
549

Table 2 Parametric Configuration P_2

$S_1 = 1.5 \text{ /day/}\mu\text{l}$ $a_1 = 0.009 \text{ /day/cell/}\mu\text{l}$ $b_1 = 0.001 \text{ /cell/}\mu\text{l}$ $\alpha_1 = 0.05 \text{ /day/virion/}\mu\text{l}$ $k_1 = 0.005 \text{ /day/}\mu\text{l}$ $q_1 = 0.0045 \text{ /day/}\mu\text{l/cell}$ $e_{10} = 8.8 \text{ cells/day/}\mu\text{l}$ $x_{10} = 703 \text{ cells/}\mu\text{l}$	$S_2 = 0.85 \text{ /day/}\mu\text{l}$ $a_2 = 0.004 \text{ /day/cell/}\mu\text{l}$ $b_2 = 0.004 \text{ /cell/}\mu\text{l}$ $\alpha_2 = 0.1 \text{ /day/virion/}\mu\text{l}$ $k_2 = 0.05 \text{ /day/}\mu\text{l}$ $q_2 = 0.0001 \text{ /day/}\mu\text{l/cell}$ $\beta_1 = 51 \text{ viron/CD4}^+ \text{ /day}$ $K_1 = 0.001 \text{ /day/}\mu\text{l}$ $e_{20} = 0.005 \text{ cells/day/}\mu\text{l}$ $x_{20} = 200 \text{ cells/}\mu\text{l}$	$S_3 = 10.5 \text{ /day/}\mu\text{l}$ $\beta_2 = 0.025$ $\beta_3 = 51 \text{ viron/CD4}^+ \text{ /day}$ $\alpha_3 = 0.027 \text{ /day/virion/}\mu\text{l}$ $k_3 = 0.0001 \text{ /day}$ $e_{30} = 0.0001 \text{ /day}$ $x_{30} = 5.5 \text{ cells/}\mu\text{l}$	$S_4 = 0.272 \text{ /day/}\mu\text{l}$ $a_4 = 0.0075 \text{ /day/cell/}\mu\text{l}$ $b_4 = 0.001 \text{ /cell/}\mu\text{l}$ $K_2 = 0.0024 \text{ /day/}\mu\text{l}$ $k_4 = 0.08 \text{ /day/}\mu\text{l}$ $e_{40} = 10.75 \text{ cells/day/}\mu\text{l}$ $x_{40} = 800 \text{ cells/}\mu\text{l}$
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Figure 2 Simulation results using parametric configuration P_2

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5.3 Simulation results for hypothetical AIDS patient #3

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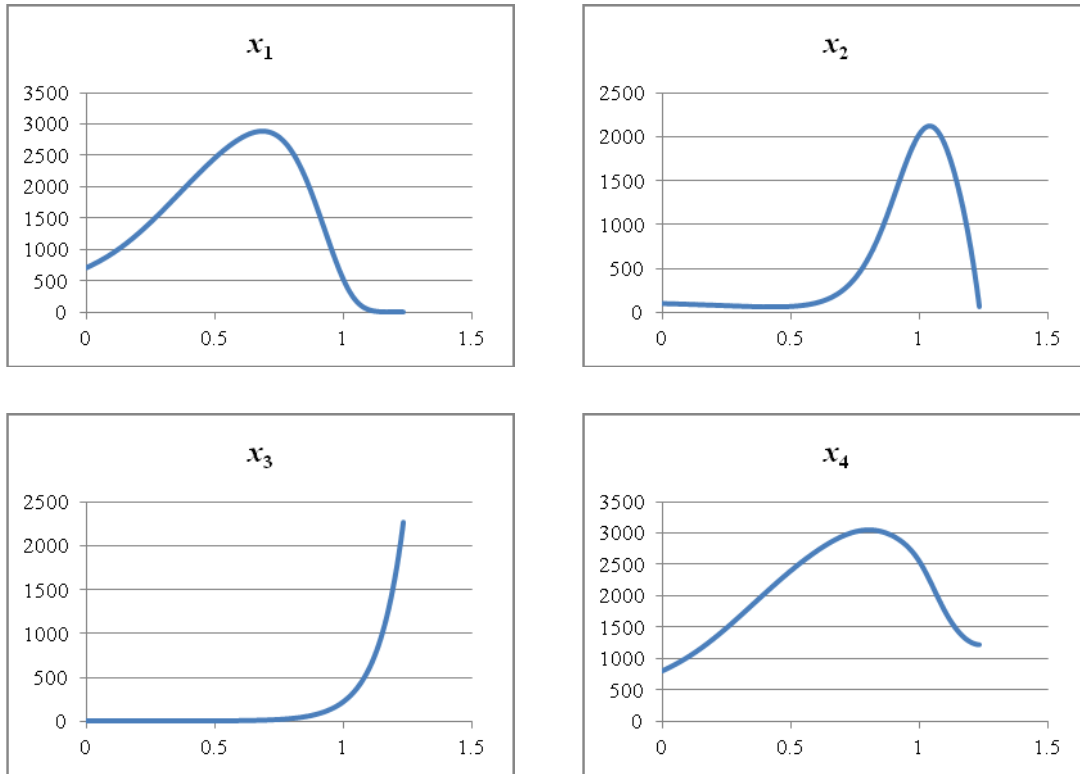
The patho-physiological parametric configuration of patient #3 is shown in Table 3. It must be noted that the AIDS in this patient is in the acute phase and as such the simulation results span a time period lasting up to one year. The results of the simulation are in Figure 3. This is a non-equilibrium AIDS configuration simulation as it is evident by the simulation time profile. The simulation results show that at the end of the acute phase, the AIDS patient experiences annihilation of uninfected CD4+ T cells. In addition, the HIV-1 specific CD8+ T cells eradicate successfully the HIV-1 infected CD4+ T cells. Unfortunately the immune system paralysis, which occurs as a consequence of the low CD4+ T cell number density, eventually leads to an exponential increase of the blood plasma HIV-1 viremia. This simulation represents an unfavorable AIDS outcome during the acute phase.

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Table 3 Parametric Configuration P_3

$S_1 = 1.5 \text{ /day/}\mu\text{l}$ $a_1 = 0.009 \text{ /day/cell/}\mu\text{l}$ $b_1 = 0.001 \text{ /cell/}\mu\text{l}$ $\alpha_1 = 0.05 \text{ /day/virion/}\mu\text{l}$ $k_1 = 0.005 \text{ /day/}\mu\text{l}$ $q_1 = 0.0045 \text{ /day/}\mu\text{l/cell}$ $e_{10} = 8.8 \text{ cells/day/}\mu\text{l}$ $x_{10} = 703 \text{ cells/}\mu\text{l}$	$S_2 = 0.0 \text{ /day/}\mu\text{l}$ $a_2 = 0.004 \text{ /day/cell/}\mu\text{l}$ $b_2 = 0.004 \text{ /cell/}\mu\text{l}$ $\alpha_2 = 0.1 \text{ /day/virion/}\mu\text{l}$ $k_2 = 0.05 \text{ /day/}\mu\text{l}$ $q_2 = 0.0001 \text{ /day/}\mu\text{l/cell}$ $\beta_1 = 10 \text{ virons/CD4}^+ \text{ /day}$ $K_1 = 0.001 \text{ /day/}\mu\text{l}$ $e_{20} = 0.005 \text{ cells/day/}\mu\text{l}$ $x_{20} = 100 \text{ cells/}\mu\text{l}$	$S_3 = 0.0 \text{ /day/}\mu\text{l}$ $\beta_2 = 0.0 \text{ virons/CD4}^+ \text{ /day/}\mu\text{l}$ $\beta_3 = 10 \text{ virons/CD4}^+ \text{ /day}$ $\alpha_3 = 0 \text{ /day/virion/}\mu\text{l}$ $k_3 = 0.0001 \text{ /day}$ $e_{30} = 0.0001 \text{ /day}$ $x_{30} = 0.01 \text{ cells/}\mu\text{l}$	$S_4 = 0.272 \text{ /day/}\mu\text{l}$ $a_4 = 0.0075 \text{ /day/cell/}\mu\text{l}$ $b_4 = 0.001 \text{ /cell/}\mu\text{l}$ $K_2 = 0.0024 \text{ /day/}\mu\text{l}$ $k_4 = 0.001 \text{ /day/}\mu\text{l}$ $e_{40} = 7.75 \text{ cells/day/}\mu\text{l}$ $x_{40} = 800 \text{ cells/}\mu\text{l}$
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Figure 3 Simulation results using parametric configuration P_3

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5.4 Simulation results for hypothetical AIDS patient #4

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The simulation results for hypothetical patient #4 are exhibited in Figure 4. These simulation results are based on the patho-physiological parametric configuration P_4 . In this patient the AIDS disease progresses from the acute phase into a 6 year clinically chronic phase before the development of full-blown AIDS.

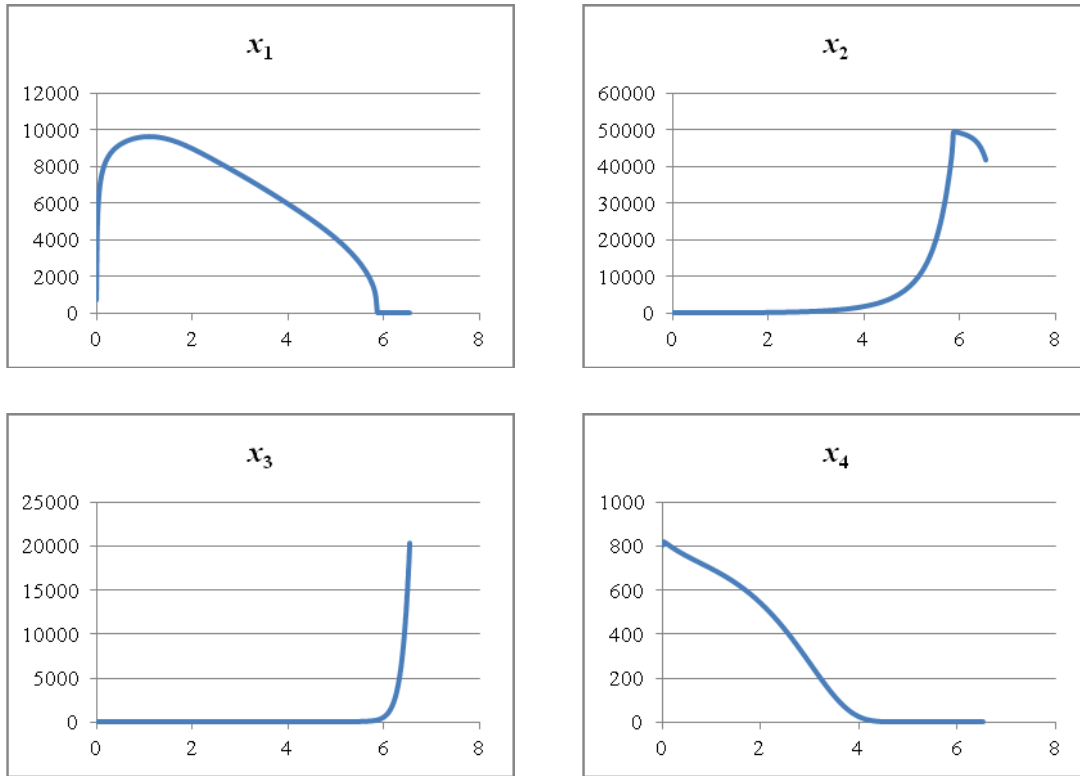
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Table 4 Parametric Configuration P_4

$S_1 = 1.5 \text{ /day/}\mu\text{l}$ $a_1 = 0.5 \text{ /day/cell/}\mu\text{l}$ $b_1 = 0.001 \text{ /cell/}\mu\text{l}$ $\alpha_1 = 0.05 \text{ /day/virion/}\mu\text{l}$ $k_1 = 0.005 \text{ /day/}\mu\text{l}$ $q_1 = 0.0045 \text{ /day/}\mu\text{l/cell}$ $e_{10} = 8.8 \text{ cells/day/}\mu\text{l}$ $x_{10} = 703 \text{ cells/}\mu\text{l}$	$S_2 = 0.0 \text{ /day/}\mu\text{l}$ $a_2 = 0.05 \text{ /day/cell/}\mu\text{l}$ $b_2 = 0.004 \text{ /cell/}\mu\text{l}$ $\alpha_2 = 0.5 \text{ /day/virion/}\mu\text{l}$ $k_2 = 0.05 \text{ /day/}\mu\text{l}$ $q_2 = 0.0001 \text{ /day/}\mu\text{l/cell}$ $\beta_1 = 2 \text{ virions/CD4}^+ \text{ /day}$ $K_1 = 0.001 \text{ /day/}\mu\text{l}$ $e_{20} = 0.005 \text{ cells/day/}\mu\text{l}$ $x_{20} = 100 \text{ cells/}\mu\text{l}$	$S_3 = 0.0 \text{ /day/}\mu\text{l}$ $\beta_2 = 0.0001$ $\text{virions/CD4}^+ \text{ /day/}\mu\text{l}$ $\beta_3 = 2 \text{ virions/CD4}^+ \text{ /day}$ $\alpha_3 = 0.0001 \text{ /day/virion/}\mu\text{l}$ $k_3 = 0.0001 \text{ /day}$ $e_{30} = 0.0001 \text{ /day}$ $x_{30} = 0.01 \text{ cells/}\mu\text{l}$	$S_4 = 0.272 \text{ /day/}\mu\text{l}$ $a_4 = 0.0075 \text{ /day/cell/}\mu\text{l}$ $b_4 = 0.001 \text{ /cell/}\mu\text{l}$ $K_2 = 0.0024 \text{ /day/}\mu\text{l}$ $k_4 = 0.08 \text{ /day/}\mu\text{l}$ $e_{40} = 7.75 \text{ cells/day/}\mu\text{l}$ $x_{40} = 800 \text{ cells/}\mu\text{l}$
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Figure 4 Simulation results using parametric configuration P_4

584 **5.5 Simulation results for hypothetical AIDS patient #5**

585 This scenario represents a relatively favorable progression of AIDS in hypothetical patient #5. The data for
586 the simulation results are given in Table 5 and the simulation results are displayed in Figure 5. The patho-
587 physiological parametric configuration of this patient does not represent an equilibrium configuration and as such
588 the condition of theorems 4.1-4.4 are not applicable. It can be observed from the simulation results that the
589 patient would develop full-blown AIDS approximately after 10 years. On the other hand, the patient experiences
590 relatively good immune-competency from the beginning of the initial infection up to approximately 10 years before
591 the onset of full-blown AIDS.

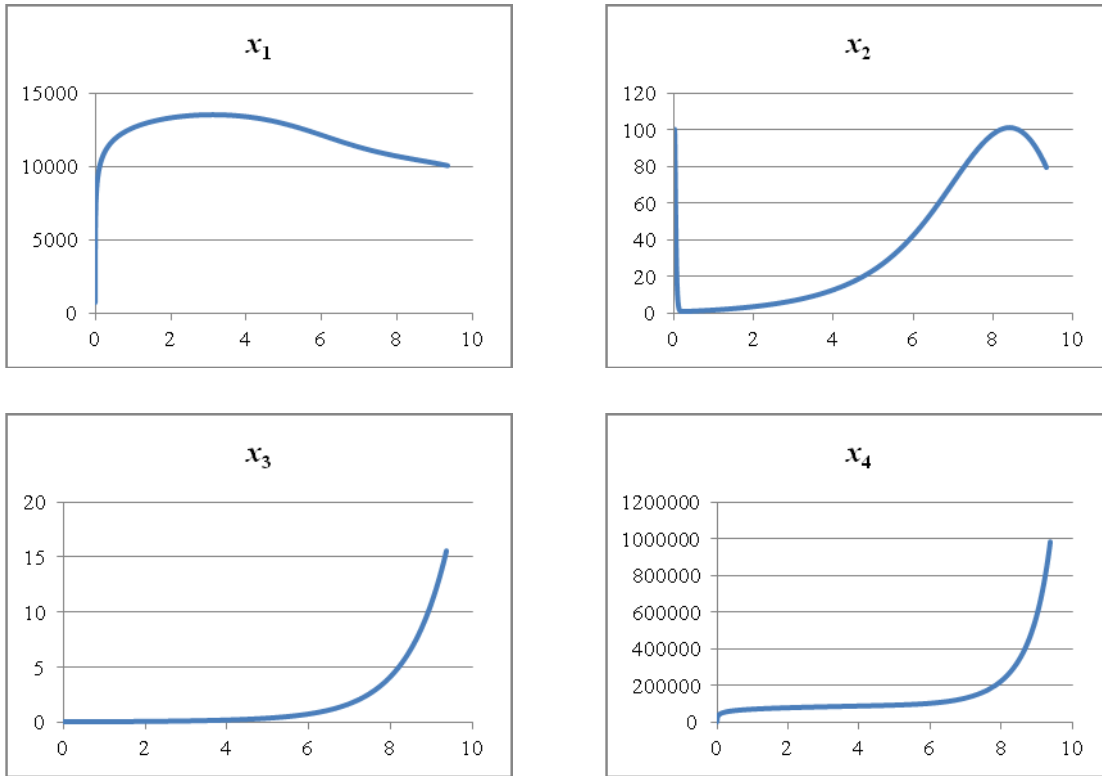
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Table 5 Parametric Configuration P_5

$S_1 = 1.5 \text{ /day/}\mu\text{l}$ $a_1 = 2.5 \text{ /day/cell/}\mu\text{l}$ $b_1 = 0.001 \text{ /cell/}\mu\text{l}$ $\alpha_1 = 0.05 \text{ /day/virion/}\mu\text{l}$ $k_1 = 0.005 \text{ /day/}\mu\text{l}$ $q_1 = 0.0045 \text{ /day/}\mu\text{l/cell}$ $e_{10} = 8.8 \text{ cells/day/}\mu\text{l}$ $x_{10} = 703 \text{ cells/}\mu\text{l}$	$S_2 = 0.0 \text{ /day/}\mu\text{l}$ $a_2 = 0.05 \text{ /day/cell/}\mu\text{l}$ $b_2 = 0.004 \text{ /cell/}\mu\text{l}$ $\alpha_2 = 0.5 \text{ /day/virion/}\mu\text{l}$ $k_2 = 0.05 \text{ /day/}\mu\text{l}$ $q_2 = 0.0001 \text{ /day/}\mu\text{l/cell}$ $\beta_1 = 2 \text{ virions/CD4}^+ \text{ /day}$ $K_1 = 0.001 \text{ /day/}\mu\text{l}$ $e_{20} = 0.005 \text{ cells/day/}\mu\text{l}$ $x_{20} = 100 \text{ cells/}\mu\text{l}$	$S_3 = 0.0 \text{ /day/}\mu\text{l}$ $\beta_2 = 0.0001$ $\text{virions/CD4}^+ \text{ /day/}\mu\text{l}$ $\beta_3 = 2 \text{ virions/CD4}^+ \text{ /day}$ $\alpha_3 = 0.0001 \text{ /day/virion/}\mu\text{l}$ $k_3 = 0.0001 \text{ /day}$ $e_{30} = 0.0001 \text{ /day}$ $x_{30} = 0.01 \text{ cells/}\mu\text{l}$	$S_4 = 0.272 \text{ /day/}\mu\text{l}$ $a_4 = 4.0 \text{ /day/cell/}\mu\text{l}$ $b_4 = 0.001 \text{ /cell/}\mu\text{l}$ $K_2 = 0.0024 \text{ /day/}\mu\text{l}$ $k_4 = 0.001 \text{ /day/}\mu\text{l}$ $e_{40} = 7.75 \text{ cells/day/}\mu\text{l}$ $x_{40} = 800 \text{ cells/}\mu\text{l}$
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Figure 5 Simulation results using parametric configuration P_5

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5.6 Simulation results for hypothetical AIDS patient #6

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The patho-physiological configuration of hypothetical patient #6 is given in Table 6. The simulation results depict an AIDS scenario which progresses from the acute phase through a relatively short chronic phase and heading towards the development of full-blown AIDS, as shown in Figure 6. It can be observed also that from the time period between 0 to 4 years the patient has sufficient immuno-competency as it is evident in the relatively higher dynamic number density of the CD4+ T cells and the HIV-1 specific CD8+ T cells as compared to the low dynamic number density of the HIV-1 infected CD4+ T cells and the blood plasma HIV-1 virions. Beyond the period of 6 years, then blood plasma HIV-1 virion and the HIV-1 infected CD4+ T cells number densities begin to rise as the patient heads towards the development of full-blown AIDS.

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Table 6 Parametric Configuration P_6

$S_1 = 1.5 \text{ /day/}\mu\text{l}$ $a_1 = 1.5 \text{ /day/cell/}\mu\text{l}$ $b_1 = 0.001 \text{ /cell/}\mu\text{l}$ $\alpha_1 = 0.05 \text{ /day/virion/}\mu\text{l}$ $k_1 = 0.005 \text{ /day/}\mu\text{l}$ $q_1 = 0.0045 \text{ /day/}\mu\text{l/cell}$ $e_{10} = 8.8 \text{ cells/day/}\mu\text{l}$ $x_{10} = 703 \text{ cells/}\mu\text{l}$	$S_2 = 0.0 \text{ /day/}\mu\text{l}$ $a_2 = 0.05 \text{ /day/cell/}\mu\text{l}$ $b_2 = 0.004 \text{ /cell/}\mu\text{l}$ $\alpha_2 = 0.5 \text{ /day/virion/}\mu\text{l}$ $k_2 = 0.05 \text{ /day/}\mu\text{l}$ $q_2 = 0.0001 \text{ /day/}\mu\text{l/cell}$ $\beta_1 = 2 \text{ virions/CD4}^+ \text{ /day}$ $K_1 = 0.001 \text{ /day/}\mu\text{l}$ $e_{20} = 0.005 \text{ cells/day/}\mu\text{l}$ $x_{20} = 100 \text{ cells/}\mu\text{l}$	$S_3 = 0.0 \text{ /day/}\mu\text{l}$ $\beta_2 = 0.0001$ $\text{virions/CD4}^+ \text{ /day/}\mu\text{l}$ $\beta_3 = 2 \text{ virions/CD4}^+ \text{ /day}$ $\alpha_3 = 0.0001 \text{ /day/virion/}\mu\text{l}$ $k_3 = 0.0001 \text{ /day}$ $e_{30} = 0.0001 \text{ /day}$ $x_{30} = 0.01 \text{ cells/}\mu\text{l}$	$S_4 = 0.272 \text{ /day/}\mu\text{l}$ $a_4 = 3.0 \text{ /day/cell/}\mu\text{l}$ $b_4 = 0.001 \text{ /cell/}\mu\text{l}$ $K_2 = 0.0024 \text{ /day/}\mu\text{l}$ $k_4 = 0.001 \text{ /day/}\mu\text{l}$ $e_{40} = 7.75 \text{ cells/day/}\mu\text{l}$ $x_{40} = 800 \text{ cells/}\mu\text{l}$
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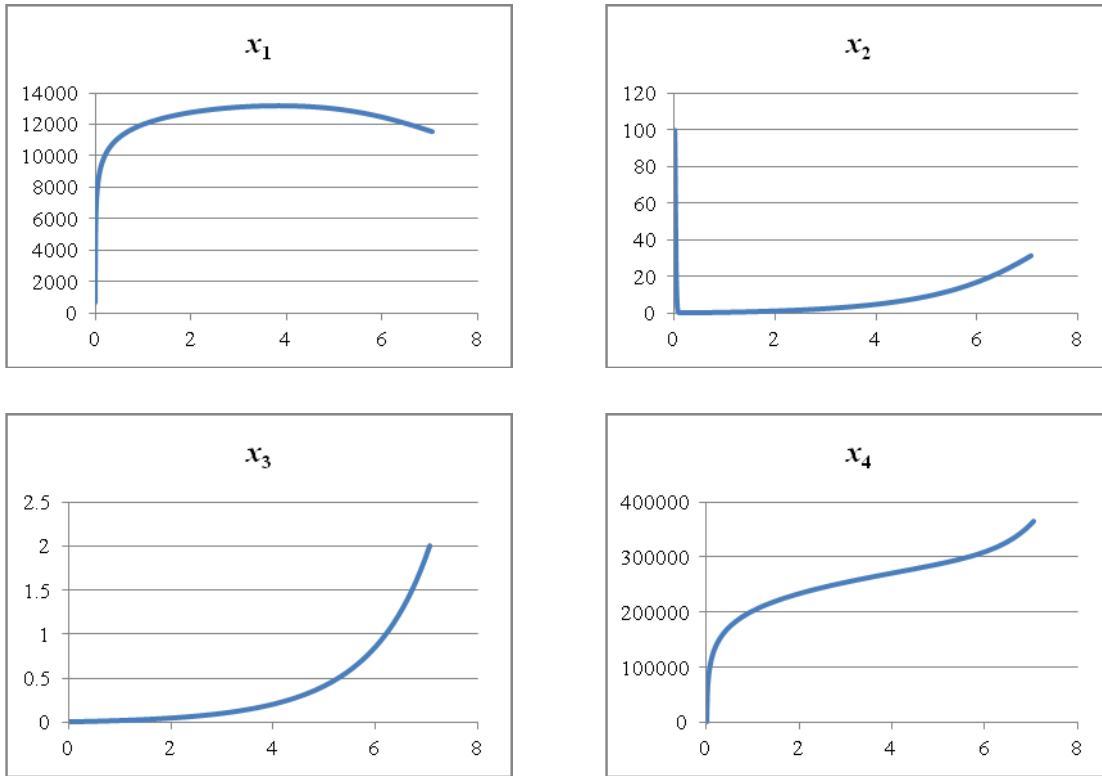


Figure 6 Simulation results using parametric configuration P_6

6. SUMMARIZING REMARKS

In this paper, we have presented a novel and robust approach to the study of HIV-1 dynamics during the acute and chronic phases. The special contribution of this model includes an explicit role of source terms S_1, S_2, S_3, S_4 , which depict recruitment from the thymus gland and the HIV-1 viral reservoirs. Clinically relevant activation functions describing the action of IL-2 on the T cells are also included in the model equations. The clinical outcomes are clearly exhibited together with the associated criteria for existence. In particular, the simulation results depict the scenario of chronic asymptomatic HIV-1 infection during chronic latency phase in which the infected $CD4^+$ T cells and the plasma, viremia are annihilated. The results elucidate and exhibit additional details of HIV-1 dynamics than the cited literature. In a future publication, investigative computer simulation results will be presented elucidating Theorems 4.1-4.4. In particular, the simulation software ACSL (Advanced Continuous Simulation Language) will be used in the simulation of time delay versions of model equations (3.5).

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