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TOWARDS A LONG-TERM MODEL CONSTRUCTION FOR THE DYNAMIC SIMULATION OF HIV INFECTION

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Abstract. This study involves the mathematical modelling of long-term HIV dynamics. The proposed model is able to predict the entire trajectory of the disease: initial viremia in the early weeks of the infection, latency, and progression to AIDS; a range spanning approximately ten years. The model outcomes were compared to clinical data and significant agreement was achieved. The formulated model considers all important population compartments including macrophages, latently-infected CD4+ T-cells, and cytotoxic T-lymphocytes (CTLs), an attempt which in many respects is novel in the area of HIV modelling. The ranges of the model parameters and initial conditions were obtained from literature, and their values were determined in this work directly by fitting published clinical data. Furthermore, the simulation results emphasize the importance of macrophages in HIV infection and progression to AIDS and show a clear correlation between the level of CTLs and HIV progression. The ability of the model to correlate analytical data gives credibility to its predictions, a fact that will be exploited in future research in modelling immunological and pharmacological avenues of treatment.

1. **Introduction.** Despite the impressive amount of research on HIV, no effective treatment strategies exist to prevent the ultimate progression to AIDS. This is mainly due to the fact that many of the host-pathogen interaction mechanisms are still unknown. Researchers, however, believe that knowledge of the molecular biology of HIV and advances in diagnostic, therapeutic, and modelling tools may benefit patients in the future. The latter can test different assumptions and provide new insights into questions that cannot be answered by experimental immunologists, and this is what we are concerned with in this study.

A number of mathematical models have been formulated to describe various aspects of the interaction of HIV with healthy cells [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11]. An

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extensive study of current literature reveals a number of issues. First, most of the models constructed have not actually been compared to clinical data [1, 2, 3, 4, 5]. Few of the models that have been compared to clinical data show good agreement [10, 11, 12, 13]. Kirschner *et al.* [11] and Bajaria *et al.* [13] produced a model for the entire duration of the disease with significant agreement to clinical data. However, the first study failed to duplicate the initial decrease and subsequent increase of healthy cells during early infection and the latter to duplicate the characteristic exponential increase of virus as the patient progresses to AIDS. The other two modelling attempts [10, 12] deal with primary infection and the initial stages of latency, a range spanning approximately 500 days. As a result, a model needs to be constructed which can predict the entire trajectory of the disease: initial viremia in the early weeks of the infection, latency, and the exponential increase of the virus during progression to AIDS. In addition, model predictions should duplicate clinical data and capture HIV dynamics as much as possible.

A model used for estimation and control of HIV dynamics should incorporate three population compartments at a minimum: virus, healthy CD4+ T-cells, and infected CD4+ T-cells. Other populations, such as macrophages and cytotoxic T-cells (CTLs), have also been considered [3, 5, 14, 15]. Kirschner and Webb [15] used a model that incorporated macrophages and thymocytes. They suggested that these cells cannot account for the dramatic increase of virus load since production from these cells is known to be minimal compared to CD4+ T-cells. This is in contrast to Kirschner and Perelson [5], who suggested that these cells play a key role in virus production. Gumel *et al.* [4] suggested that cell types other than CD4+ T-cells might be responsible for HIV production and the high viral load during the late stage of the disease. Furthermore, SIV studies [16] have shown that macrophages contain and continue to produce large amounts of virus even after the latter depletes CD4+ T-cells; by inference the same situation is assumed to hold for the HIV case.

Many studies have been used to determine whether an immune response needs to be incorporated in the models, and it is possible to have good agreement between model predictions and clinical data using mathematical models that do not account for any immune response [9, 17, 18]. Some studies have attempted to incorporate the CTL immune response [19, 20], the relevance of which has been questioned as no correlation was found between the level of CTLs in the blood and HIV progression [21].

To our knowledge, no modelling attempt has been successful in producing a holistic image of integrating different population compartments of the overall HIV mechanism in a single dynamic system, and often the effect of macrophages and the CTL immune response is underestimated.

An extended non-linear modelling procedure for predicting HIV dynamics is considered in the next section. Fitting of parameters is presented in Section 3. The formulated model is simulated and analysed in Section 4.

2. **Model formulation.**

In the model equations below, T represents the uninfected CD4+ T-cell population, T_1 represents the infected CD4+ T-cell population, T_L represents the latently-infected CD4+ T-cell population, and V represents the HIV population. The model also considers the uninfected macrophage population,

M, as well as the infected macrophage population, M_1. CTL represents the cytotoxic T-lymphocyte population. These populations are measured in the blood plasma.

The equations for the HIV model are given below:

$$\frac{dT}{dt} = s_1 + \frac{p_1}{V + C_1}VT - \delta_1 T - (K_1 V + K_2 M_1)T \quad (1)$$

$$\frac{dT_1}{dt} = \psi(K_1 V + K_2 M_1)T + \alpha_1 T_L - \delta_2 T_1 - K_3 T_1 CTL \quad (2)$$

$$\frac{dT_L}{dt} = (1 - \psi)(K_1 V + K_2 M_1)T - \alpha_1 T_L - \delta_3 T_L \quad (3)$$

$$\frac{dM}{dt} = s_2 + K_4 VM - K_5 VM - \delta_4 M \quad (4)$$

$$\frac{dM_1}{dt} = K_5 VM - \delta_5 M_1 - K_6 M_1 CTL \quad (5)$$

$$\frac{dCTL}{dt} = s_3 + (K_7 T_1 + K_8 M_1)CTL - \delta_6 CTL \quad (6)$$

$$\frac{dV}{dt} = K_9 T_1 + K_{10} M_1 - K_{11} VT - (K_{12} + K_{13})VM - \delta_7 V \quad (7)$$

Equation (1) characterises the changes of the uninfected CD4+ T-cell compartment. The first two terms of Equation (1) represent the source of new T-cells. This incorporates cells from the thymus, bone marrow, and general production. It is assumed that there exists a constant thymic source, s_1, as well as a proliferation term due to an immune response. T-cells have a finite lifespan; the average is $1/\delta_1$, where δ_1 is the death rate of the uninfected CD4+ T-cells. The last term represents the infection of CD4+ T-cells by both virus and infected macrophages. Constant rates of infectivity K_1 and K_2 are assumed. Consideration of the macrophage population is regarded essential since macrophages play a vital role in HIV progression. As Kirschner and Perelson [5] and Nowak and May [22] demonstrate, infected macrophages are able to infect healthy T-cells through presentation of antigen and this phenomenon is accounted for in Equation (1). This type of infection has been verified experimentally by both older and more recent studies [23, 24, 25].

Equation (2) describes changes in the infected T-cell population, T_1. The first term of the equation represents the gain of infected cells. Once infected, a proportion of T-cells, ψ, passes into the infected T-cell population, whereas a proportion $1 - \psi$ passes into the latently-infected cell population. These latently-infected cells might be activated in time and start reproducing virus. This activation is represented through the $\alpha_1 T_L$ term in Equations (2) and (3). Infected cells are lost by processes such as natural death and immune responses. The rate at which cytotoxic T-lymphocytes kill infected T-cells is given by K_3. It is assumed that CTLs do not die when carrying out immune actions, in both infected CD4+ T-cells and infected macrophages. Equation (3) quantifies the rate of change in the latently-infected T-cell population. These cells are produced from uninfected cells and are lost to natural death, or converted to actively-infected cells at rate α_1.

The population of macrophages increases in terms of the constant source of new macrophages, s_2, and its increase due to the immune response. The latter term depends on the ingestion of virus particles and the increase rate, K_4. According to

Nowak and May [22] when CD4+ T-cells signal macrophages that the virus is non-self, the latter divide and become more aggressive. Thus it was considered essential to include this behaviour in the model. The macrophage population is lost through infection by virus at a rate of K_5, and through natural death at a rate of δ_4. It is assumed that any macrophages killing virus as part of the immune response do not die. In Equation (5) the gain terms carry over from the loss terms in Equation (4). The infected macrophage population is lost to natural death and to immune responses. The rate at which cytotoxic T-lymphocytes kill infected macrophages is given by K_6. It is assumed that when infected macrophages infect CD4+ T-cells the former undergo no change.

CTLs are generated at constant rate of s_3 and proliferate with a rate constant, K_7 and K_8, proportional to the current amount of the same infected T-cells and infected macrophages, respectively. CTLs die at a rate δ_6. The rate of change of CTLs is given by Equation (6).

Equation (7) depicts the rate of change in the virus population. This population increases due to production of virus from infected CD4+ T-cells and infected macrophages. The amount of virus produced from infected CD4+ T-cells and infected macrophages is given by K_9T_1 and $K_{10}M_1$ respectively, where K_9 and K_{10} are the rates of production per unit time in T-cells and macrophages. Virus is lost through the terms $K_{11}VT$ and $K_{12}VM$, effectively accounting for the virus lost when infecting healthy CD4+ T-cells and macrophages, which do not produce any new virus, e.g., as a result of the infected cell's natural death or through the action of CTLs. Effectively, the $K_{11}VT$ and $K_{12}VM$ terms are a correction to account for virus particles going into a "dead-end sink". Virus is also lost through natural death as well as through an immune response. CD4+ T-cells stimulate the production of B-cells, which in turn produce antibodies. These antibodies then bind to the virus. Macrophages respond to these antibody-bound particles, ingest and destroy them, thus the loss term $K_{11}VM$ in Equation (7).

The above model can be represented schematically in the form of a State-Task Network (STN) [26]. This is given in Figure 1. STN offers a clear and precise way to representing the processes involved during HIV infection. Each state (circle) represents populations; each task (rectangle) represents a process. Arrows represent flow of population. For example, state T is produced by task *Production 1*, and is lost to task *Infection 1*, *Infection 2*, and natural death, *D1*. Uninfected T-cells remain in state T. "Hidden" states (representing inflow of cells from outside the system considered and death of cells) have also been considered for completeness.

3. **Parameter estimation.**

In specifying model parameters and initial conditions, ranges were obtained from previous work in the field [3, 5, 14, 15, 17, 27, 28, 29, 30]. The least-square method was then used to obtain the best-fit values from clinical data for the CD4+ T-cell dynamics [31, 32, 33, 34]. It should be noted that the model is robust for small changes in these values, and these changes would not qualitatively affect the model predictions. Estimates of initial population conditions are given in Table 2. Note that the initial conditions for the infected populations are set to 0, given a low initial value for the virus. A list of parameters and their values used in this study is given in Table 3. Although many studies have examined parameter estimation in more detail [12, 35] and more specifically statistical analysis as to model robustness, model variability, and model sensitivity, we focused on the interlocking of mechanisms that can explain the observed trends of noisy clinical

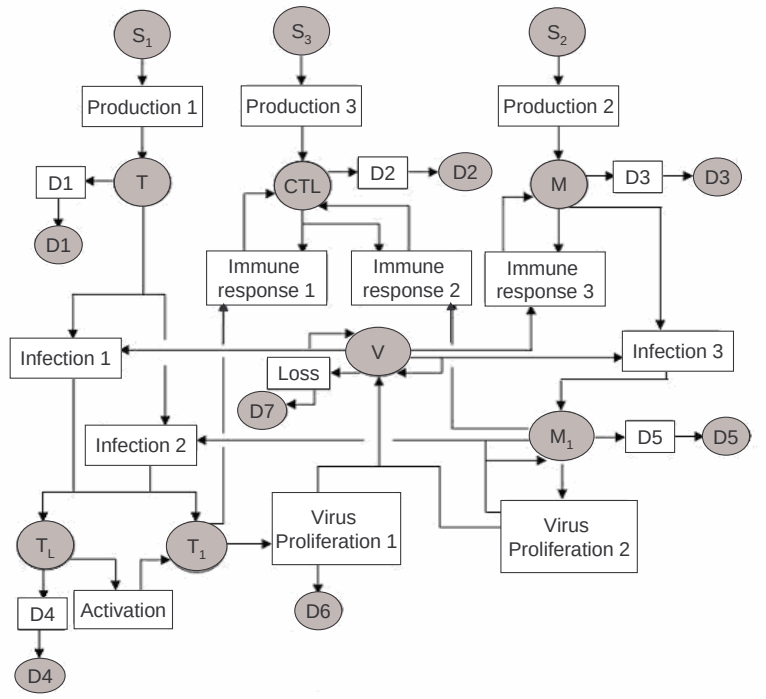

FIGURE 1. State-Task Network (STN) for HIV Dynamics. Each state (circle) represents populations whereas each task (rectangle) represents a process. Arrows represent flow of population. A legend for the STN is given in Table 1.

data for the entire trajectory of the disease. In modelling such a complex system one should not loose sight of the fact that uncertainty is structural and parametric to a secondary level. Spending a lot of time tuning parameters to an incomplete model can be futile.

4. **Results and discussion.** In this section, we will explore the implementation of the model for HIV dynamics outlined in Sections 2 and 3. This was conducted in Mathematica 5.0^{TM}, with the purpose of achieving accurate predictions for the evolution of the disease in a living patient.

Once infected, the patient experiences a rapid decrease in the number of healthy CD4+ T-cells, following a rapid increase in the virus population. The immune system responds by killing infected cells and virus particles, causing a rapid increase in the number of healthy cells (Figure 2). The virus population experiences a rapid depletion as can be seen in Figure 3. A period of almost ten years follows (often referred to as the asymptomatic stage or latency) whereby CD4+ T-cells experience a constant but slow depletion. The virus continues to infect healthy cells and thus slowly increases in numbers. After about nine years the immune system collapses and the virus population experiences an exponential growth. Concurrently, healthy cells deplete at a high rate, crossing the 200 mm^{-3} line which marks the "progression to AIDS" period. Once AIDS is detected, patients survive about a year, as suggested by Nowak and McMichael [36].

Task	Description	Term	Equation
Production 1	T-cell production	$s_1 + \frac{p_1}{V+C_1}VT$	(1)
Production 2	Macrophage production	$s_2 + K_4VM$	(4)
Production 3	CTL production	$s_3 + (K_7T_1 + K_8M_1)CTL$	(6)
Infection 1	T-cell infection by virus	K_1VT	(1, 2, 3, 7)
Infection 2	T-cell infection by infected macrophages	K_2M_1T	(1, 2, 3)
Infection 3	Macrophage infection	K_5VM	(4, 5, 7)
Activation	Activation of latently-infected T-cells	α_1T_L	(2, 3)
Immune response 1	CTLs on infected T-cells	K_3T_1CTL	(2)
Immune response 2	CTLs on infected macrophages	K_6M_1CTL	(5)
Immune response 3	Macrophages on virus	$K_{13}VM$	(7)
Proliferation 1	Virus proliferation in infected T-cells Death of infected T-cells	K_9T_1 δ_2T_1	(7) (2)
Proliferation 2	Virus proliferation in infected macrophages	$K_{10}M_1$	(7)
Death 1	Death of T-cells	δ_1T	(1)
Death 2	Death of CTLs	δ_6CTL	(6)
Death 3	Death of macrophages	δ_4M	(4)
Death 4	Death of latently-infected T-cells	δ_3T_L	(3)
Death 5	Death of infected macrophages	δ_5M_1	(5)
Loss	Loss of virus through death and infection	$(\delta_7 + K_{11}T + K_{12}M)V$	(7)

TABLE 1. Explanations for the State-Task Network shown in Figure 1. Each task is described through a mathematical term in the equations of the formulated model.

Figures 2 and 3 present data from four clinical studies representing the typical progression of the disease, with the results of the model given for direct comparison. The predictions for the uninfected CD4+ T-cells and virus populations show very good agreement with clinical data for HIV-infected patients during the same time period [32, 33, 34, 35]. When fitting the data from Greenough *et al.* [31], the model is not as accurate but still follows the trend. It must be noted that this set of data seems to deviate from the data obtained from the other studies, which suggests that the patient involved responded differently to the disease, i.e., the patient examined may have had a weak immune system response. Availability of data for untreated patients is limited due to the fact that most patients receive some form of treatment. The relationship between CD4+ T-cells and virus during the different stages of the disease is shown in Figure 4 as a phase space diagram. The time of initial infection is represented by t_0, t_1 represents the time of initiation of the immune response,

Notation	Value	Range	Value taken from:	Units
T	1000	$500 - 1500$	[5]	mm^{-3}
T_1	0	-	[5]	mm^{-3}
T_L	0	-	[30]	mm^{-3}
M	30	30	[5]	mm^{-3}
M_1	0	-	[5]	mm^{-3}
CTL	500	$300 - 100$	Fitted	mm^{-3}
V	1×10^{-3}	1×10^{-3}	[5]	mm^{-3}

TABLE 2. Population starting points used in this study.

Notation	Value	Range	Value taken from:	Units
s_1	10	5-36	[5]	$\mathrm{mm}^{-3}\mathrm{d}^{-1}$
s_2	0.15	0.03-0.15	[5]	$\mathrm{mm}^{-3}\mathrm{d}^{-1}$
s_3	5	-	Fitted	$\mathrm{mm}^{-3}\mathrm{d}^{-1}$
p_1	0.2	0.01-0.5	Fitted	d^{-1}
C_1	55.6	1-188	Fitted	mm^{-3}
K_1	3.87×10^{-3}	$10^{-8} - 10^{-2}$	Fitted	$\mathrm{mm}^3\mathrm{d}^{-1}$
K_2	1×10^{-6}	10^{-6}	[5]	$\mathrm{mm}^3\mathrm{d}^{-1}$
K_3	4.5×10^{-4}	$10^{-4} - 1$	Fitted	$\mathrm{mm}^3\mathrm{d}^{-1}$
K_4	7.45×10^{-4}	-	Fitted	$\mathrm{mm}^3\mathrm{d}^{-1}$
K_5	5.22×10^{-4}	$4.7 \times 10^{-9} - 10^{-3}$	Fitted	$\mathrm{mm}^3\mathrm{d}^{-1}$
K_6	3×10^{-6}	-	Fitted	$\mathrm{mm}^3\mathrm{d}^{-1}$
K_7	3.3×10^{-4}	$10^{-6} - 10^{-3}$	Fitted	$\mathrm{mm}^3\mathrm{d}^{-1}$
K_8	6×10^{-9}	-	Fitted	$\mathrm{mm}^3\mathrm{d}^{-1}$
K_9	5.37×10^{-1}	0.24-500	Fitted	d^{-1}
K_{10}	2.85×10^{-1}	0.005-300	Fitted	d^{-1}
K_{11}	7.79×10^{-6}	-	Fitted	$\mathrm{mm}^3\mathrm{d}^{-1}$
K_{12}	1×10^{-6}	-	Fitted	$\mathrm{mm}^3\mathrm{d}^{-1}$
K_{13}	4×10^{-5}	-	Fitted	$\mathrm{mm}^3\mathrm{d}^{-1}$
δ_1	0.01	0.01-0.02	Fitted	d^{-1}
δ_2	0.28	0.24-0.7	Fitted	d^{-1}
δ_3	0.05	0.02-0.069	Fitted	d^{-1}
δ_4	0.005	0.005	[5]	d^{-1}
δ_5	0.005	0.005	[5]	d^{-1}
δ_6	0.015	0.015-0.05	[3]	d^{-1}
δ_7	2.39	2.39-13	[5]	d^{-1}
α_1	3×10^{-4}	-	Fitted	d^{-1}
ψ	0.97	0.93-0.98	Fitted	-

TABLE 3. Parameter values used in this study.

t_2 the time at which CD4+ T-cells start recovering due to the immune response, t_3 the time at which the virus starts increasing again, t_4 the time at which CD4+ T-cells start their final depletion as the virus population prevails, and t_5 the time at which progression to AIDS occurs.

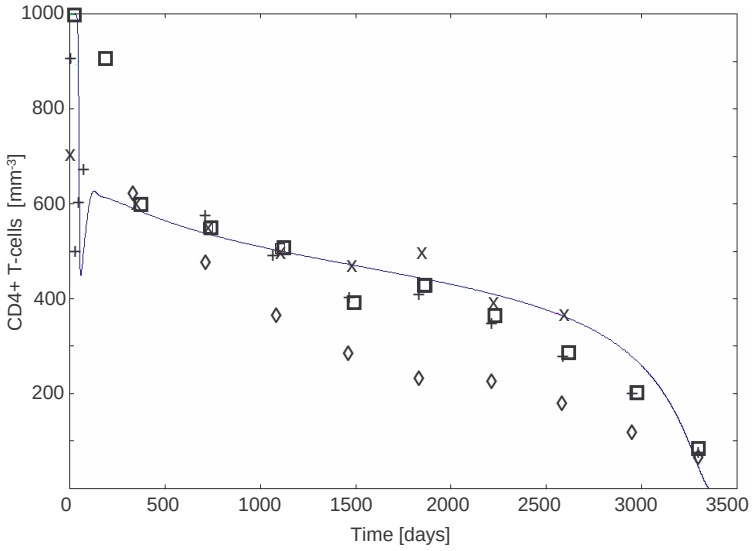

FIGURE 2. T-cell dynamics over a period of ten years. Comparison with clinical data from the study by Greenough *et al.*[31] (◊), Fauci *et al.* [32] (+), Pennisi and Cohe n [33] (□), and Margolick *et*

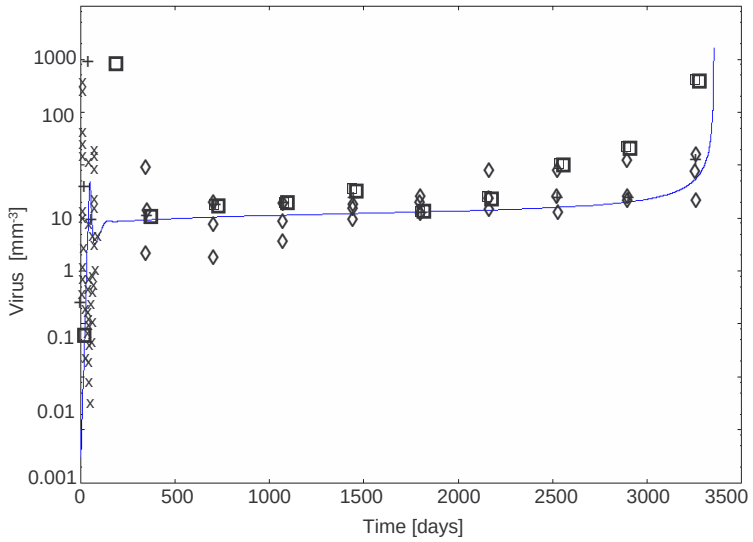

FIGURE 3. HIV dynamics over a period of ten years. Comparison with clinical data from the study by Greenough *et al.* [31] (◊), Fauci *et al.* [32] (+), Pennisi and Cohen [33] (□), and Filter *et al.* [35] (x).

To our knowledge the formulated model is perhaps the only one that manages to produce a profile for initial viremia, as well as latency and the exponential

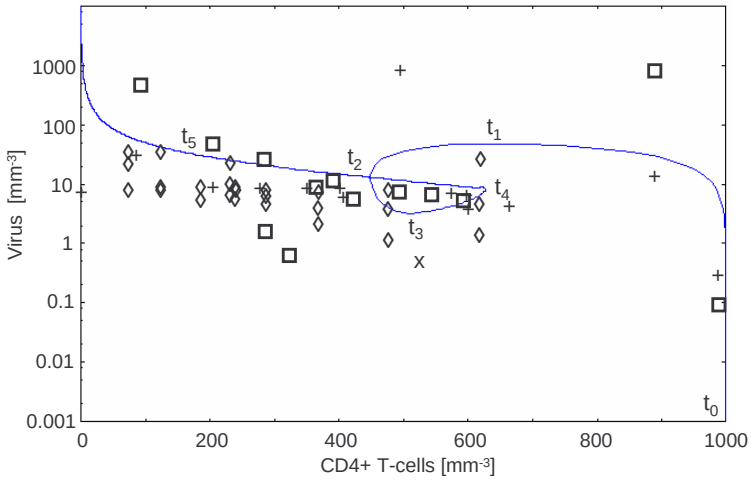

FIGURE 4. Phase space diagram in HIV infection and progression. Initial infection ($t_0 = 0$ days). Immune response ($t_1 = 49$ days). Recovery of CD4+ T-cells ($t_2 = 57$ days). Virus slowly increases ($t_3 = 74$ days). Depletion of CD4+ T-cells as virus population prevails ($t_4 = 127$ days). Progression to AIDS ($t_5 = 3118$ days). Comparison with clinical data from the study by Greenough *et al.* [31] (◊), Fauci *et al.* [32] (+), Pennisi and Cohen [33] (□).

increase of virus during the later stages of the disease. A similar prediction was produced by Bajaria *et al.* [13]; however their model fails to describe the rapid depletion of CD4+ T-cells during the later stages of the disease. Instead, CD4+ T-cells experience an exponential decay, achieving almost steady state after nine years. Similarly, the prediction for the virus population does not predict the rapid increase in its number towards the end. It is important to note that their model used data from a single patient. The HIV model proposed in our study is probably the first one in the area of HIV modelling to include macrophages, latently-infected T-cells, and CTLs all in a single model.

Figures 5-9 show the dynamics of the remaining populations. There is a rapid increase of infected CD4+ T-cells during the early stages of the disease, followed by a rapid drop due to the immune response. This population remains approximately constant during the asymptomatic stage, but experiences rapid depletion as the number of healthy cells approaches its minimum value (Figure 5). Latently-infected cells show a similar behaviour (Figure 6).

Macrophages can be seen to increase exponentially towards the later stages of the disease. This is shown in Figure 7 and emphasises the importance of this compartment in such a model. Healthy macrophages increase as the virus grows exponentially in a desperate attempt to suppress the virus. This is consistent with Nowak and May [22] who suggested that once CD4+ T-cells signal macrophages that the virus is non-self, macrophages divide and become more aggressive. This was incorporated in Equation (4) of the model formulated in Section 3 and is important in successfully duplicating clinical results during the end stage of the

disease. In the early stages of the disease macrophages show a steady but slow increase.

Infected macrophages increase slowly in numbers during the asymptomatic period but can be seen to rise during the later phase of the disease. The difference between infected CD4+ T-cells and infected macrophages during the asymptomatic stage is notable: this is consistent with basic HIV knowledge, which suggests that the virus replicates slowly in macrophages and kills them at a slower rate than infected CD4+ T-cells. For CD4+ T-cells, replication is so fast that the cells die before they are able to accumulate. The exponential rise in infected macrophages is consistent with Igarashi *et al.* [16] who suggest that the number of virus-producing macrophages, relative to infected CD4+ T-lymphocytes, is probably extremely low early in the infection but over time this fraction of infected cells increases substantially. As more infected cells develop during the late stage, more virus is produced. This further produces healthy macrophages as part of the immune response. However, an increase in macrophages allows an increase of infection and virus production; hence the exponential rise. The relationship between infected macrophages and virus over the different stages of the disease is shown in Figure 10 as a phase space diagram. The time of initial infection is represented by t_0, t_1 represents the time at which immune response causes a decrease in the virus population, and t_2 the time at which the virus starts increasing again.

CTLs can be seen to increase upon initiation of the immune response (Figure 9). These cells manage to regulate the virus at low numbers for about eight years but eventually lose the battle as the latter prevails. The relationship between CTLs and virus over the different stages of the disease is shown in Figure 11 as a phase space diagram. As aforementioned, the relevance of the CTL immune response has been questioned, as no correlation was found between the level of CTLs in the blood and HIV progression [21]. However, the simulation results show a clear correlation between the two. As the virus increases upon initial infection (t_0), CTLs increase in order to decrease the virus. Once this is accomplished (t_1), the former decrease as they are no longer needed (t_2). The virus grows back again (t_3), and this triggers an increase in the CTL population (t_4). CTLs further increase in an attempt to keep the virus at constant levels but lose the battle after about eight years (t_5). Beyond this point the virus population grows in an exponential manner.

The predictions in Figures 5-9 as well as the prediction for the virus dynamics have been produced without the fitting of the parameters to data regarding the population sizes depicted there. This further emphasises the qualitative validity of the model which predicts expected results. In the case of the virus, the predictions are verified with clinical data for all stages of the disease, whereas for CTLs only clinical data for the acute and asymptomatic stages are available. For the remaining populations presented in Figures 5-9 clinical data are not available for this study. One crucial test of this model would be a comparison of predictions with such data. Upon availability, model results will be compared and if modifications are necessary these will be presented in a future study.

The model proposed above is valid for a typical progressor to AIDS, i.e. a patient with an average lifetime of ten years. For different types of progressors, the model is able to predict good results given adjustments to model parameters and initial conditions. At this point it is pointed out that the model manages to predict population behaviour up until the point the patient succumbs to the virus.

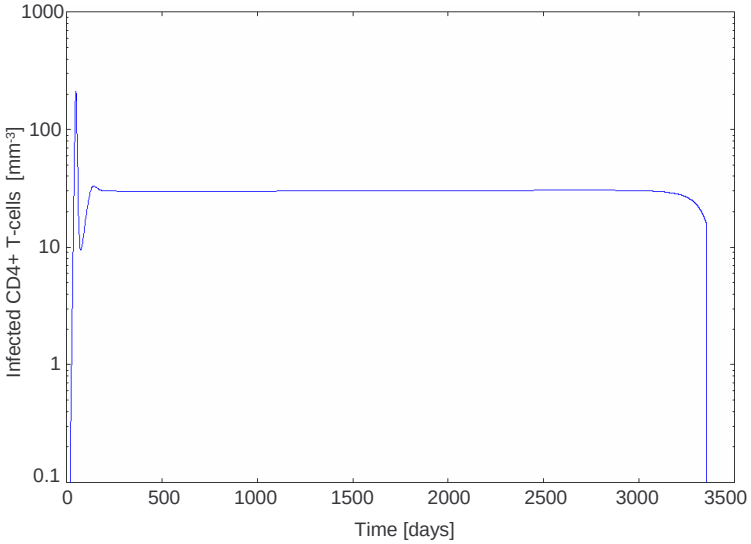

FIGURE 5. Dynamics of infected CD4+ T-cells.

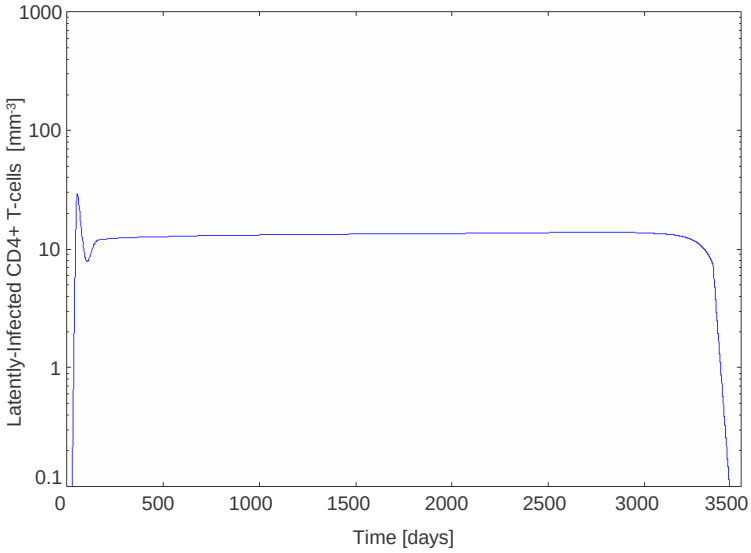

FIGURE 6. Dynamics of latently-infected CD4+ T-cells.

Beyond this time period (∼3400 days), model predictions seem to be unreliable and unrealistic.

Clearly, the model produced is a simplified description of reality, as are all such modelling attempts at present. The brain and central nervous system may act as sanctuaries for the virus due to the limited access of cells of the immune system [14, 16]. Our present model has only dealt with CD4+ T-cells and macrophages. Other cells may become infected and may exhibit different kinetics. Also, direct

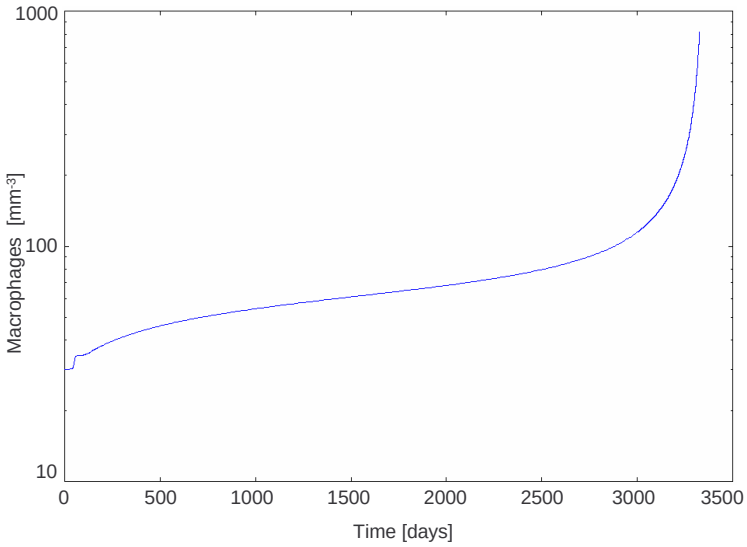

FIGURE 7. Dynamics of uninfected macrophages.

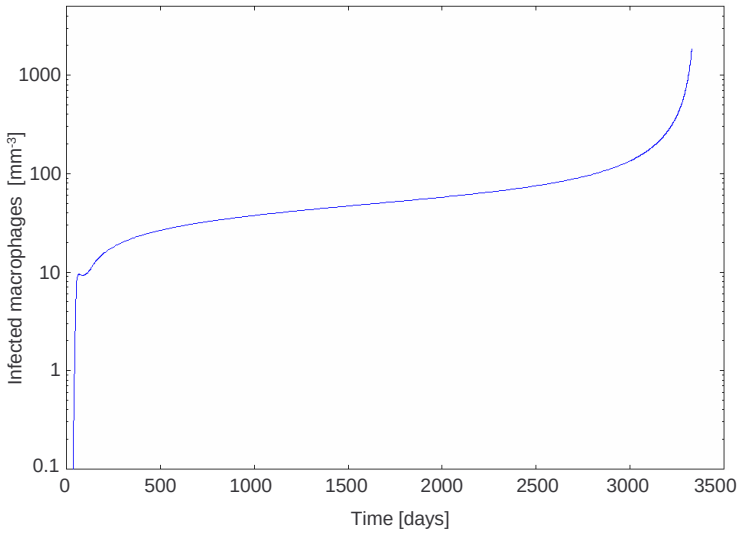

FIGURE 8. Dynamics of infected macrophages.

cell-to-cell transmission of virus has not been considered and death of cells due to effects other than direct viral killing and natural death has been ignored. As far as the immune response is concerned, the effect of the suppressor cells has been assumed minimal compared to the effect by CTLs. Infected macrophages were assumed to infect CD4+ T-cells, thus following a different approach than the one put forward by Nowak and May [22], who suggested that infected macrophages cause apoptosis to healthy CD4+ T-cells. Time delays between infection and virus

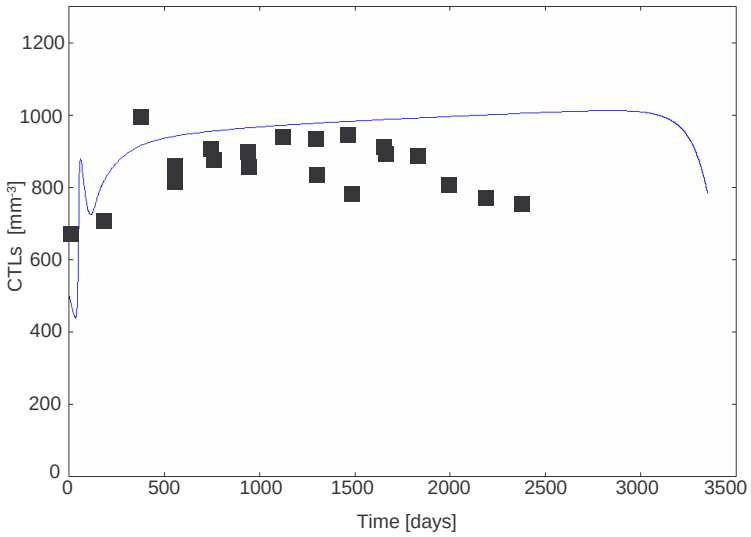

FIGURE 9. Dynamics of cytotoxic T-lymphocytes. Comparison with clinical data from the study by Hraba and Dolezal[8] (■).

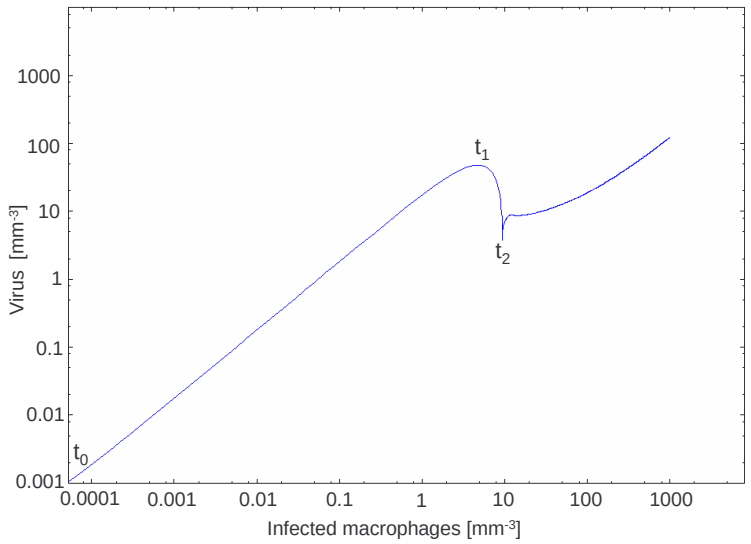

FIGURE 10. Phase space diagram for infected macrophages. Initial infection ($t_0 = 0$ days). Infected macrophages stop increasing as virus is depleted by immune response ($t_1 = 49$ days). Infected macrophages increase as virus further increases ($t_2 = 74$ days).

production should also be considered, treating interactions between cells and HIV virus as non-instantaneous [36]. Perhaps the biggest assumption in our model relates to the lack of terms describing the dynamics of the lymphatic compartment. In fact, infected cells in the blood constitute a relatively small contribution to

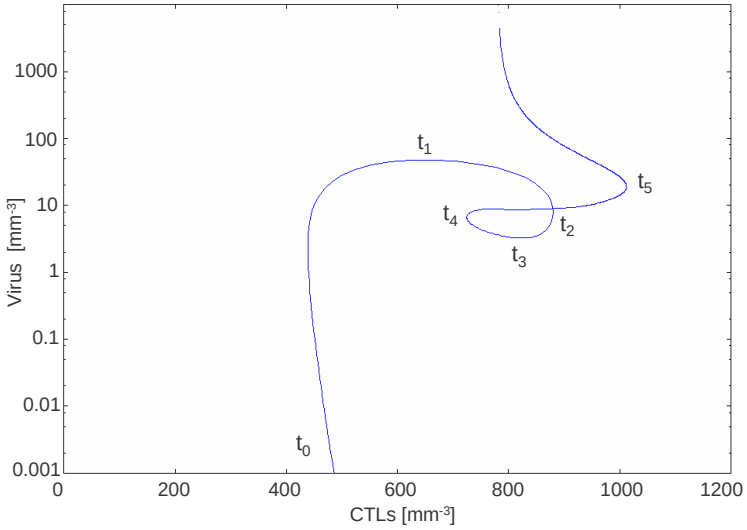

FIGURE 11. Phase space diagram for CTLs. Initial infection ($t_0 =$ 0 days). Immune response ($t_1 = 49$ days). CTLs decrease as immune response has been efficient in decreasing virus population ($t_2 = 60$ days). Virus slowly increases ($t_3 = 74$ days). CTLs increase as a response to increased virus ($t_4 = 109$ days). CTLs lose battle ($t_5 = 2905$ days).

overall infection and most of HIV replication occurs in the lymphatic compartment [13]. This has been the case due to limited data available for the dynamics in this compartment.

5. **Conclusions.** Inclusion of macrophages, latently-infected T-cells, and CTLs in a single model is a novel contribution to the area of HIV modelling. The formulated model manages to predict the entire trajectory of the disease: initial viremia in the early weeks of the infection, latency, and the rapid increase of virus as the patient progresses to AIDS. Published clinical data for typically progressing patients are reproduced with very good agreement. This, from a qualitative point of view shows that structurally our proposed model is more extensive than earlier ones.

The simulation results emphasize the importance of the macrophage compartment in the progression of HIV. The consideration of the increase in macrophages as part of the immune response can be seen to play a pivotal role in the successful duplication of clinical data during the end-stage of the disease. Infected macrophages were found to increase slowly in numbers during the asymptomatic period but to increase during the later stage of the disease in an exponential manner that is consistent with literature. Furthermore, a clear correlation was found between the level of CTLs in the blood and HIV progression.

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