Using Mathematics to Understand HIV Immune Dynamics

Denise Kirschner

Since the early 1980s there has been a tremendous effort made in the mathematical modeling of the human immunodeficiency virus (HIV), the virus which causes AIDS (Acquired Immune Deficiency Syndrome). The approaches in this endeavor have been twofold; they can be separated into the epidemiology of AIDS as a disease and the immunology of HIV as a pathogen (a foreign substance detrimental to the body). There has been much research in both areas; we will limit this presentation to that of the immunology of HIV, and refer the reader to some excellent references on mathematical modeling of the epidemiology of AIDS [1,2,3,4]. Our goal then is to better understand the interaction of HIV and the human immune system for the purpose of testing treatment strategies.

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Parts of this article were adapted from D. Kirschner and G. F. Webb, A Model for Treatment Strategy in the Chemotherapy of AIDS, Bulletin of Mathematical Biology *(to appear, 1996).*

Acknowledgements: The research in this work was partially supported under NSF grants DMS 9596073 (Kirschner) and DMS 9202550 (Webb). The author would like to thank the editors for helpful comments and support in the writing of this article.

An Introduction to Immunology

When a foreign substance (antigen) is introduced into the body, the body elicits an immune response in an attempt to clear the object from the body as quickly as possible. This response is characterized in two ways: a *cellular immune response* and a *humoral immune response*. The antigen is first encountered by the *macrophages*, cells that scavenge, engulf, and examine foreign particles, then presenting their findings to the CD4 positive T lymphocytes ($CD4^+$ T cells). The "CD4" denotes a protein marker in the surface of the T cell, and the "T" refers to *thymus*, the organ responsible for maturing these cells after they migrate from the bone marrow (where they are manufactured). These cells, more commonly referred to as *helper T cells* (which normally average 1,000 per cubic mm of blood), serve as the command center for the immune system. If they deem an immune response is necessary, a *primary immune response* is issued. First, the helper T cells reproduce to build up command forces, which can then elicit both cellular and humoral responses. In addition to this buildup, the cellular immune response also activates a second type of T cell, the CD8 positive T lymphocytes ($CD8^+$ T cells). Referred to as *killer T cells*, once given a target, they seek out and destroy cells infected with those pathogens.

In the humoral immune response (more commonly known as the antibody response) the helper T cells signal a third set of cells, called B lymphocytes (B cells). These are the blood cells which produce the chemical weapons called *antibodies*. Antibodies are specifically engineered to destroy the pathogen at hand and therefore

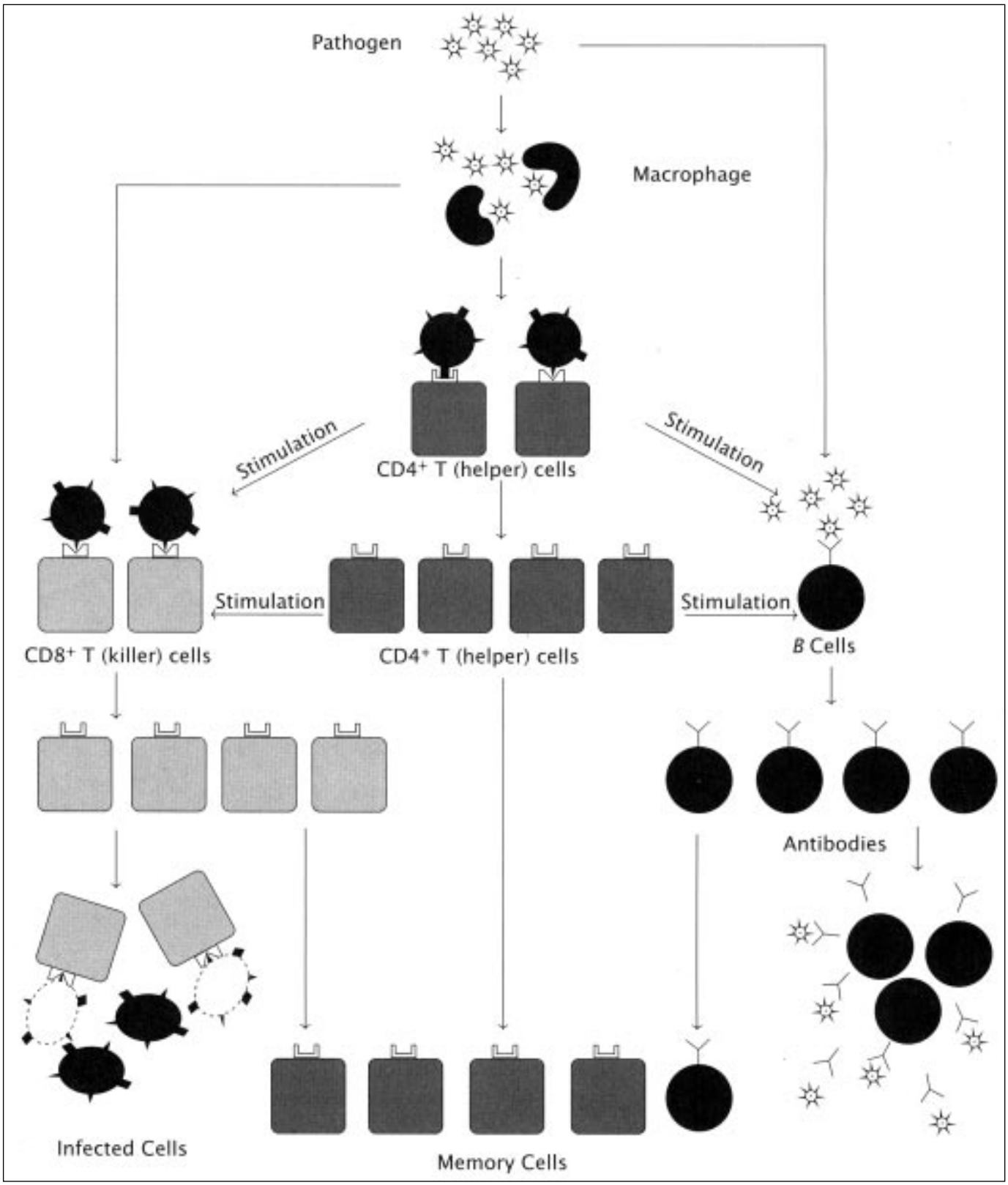

Figure 1. Schematic diagram of the working immune system.

aid as direct antigen killing devices. Figure 1 shows a schematic diagram of the entire immune response process.

Once the immune response is successful, certain cells of each type retain knowledge of the attack. These cells are referred to as *memory cells*. If this same pathogen (or a close cousin) is introduced into the body again, a much quicker and more aggressive campaign can be launched, and the antigen is eradicated more accurately and at a much faster rate. This is the idea behind vaccines. A small, weaker version of the pathogen is introduced, eliciting a primary immune response; then, if the individual becomes infected with the more aggressive relative, the response is immediate and powerful, and the pathogen does not take hold. (See [7 or 8] for full discussions of immunology.)

HIV Infection

Like most viruses, HIV is a very simple creature. Viruses do not have the ability to reproduce independently. Therefore, they must rely on a *host* to aid reproduction. Most viruses carry copies of their DNA (the blueprint of itself) and insert this into the host cell's DNA. Then, when the host cell is stimulated to reproduce (often through the presence of the same pathogen), it reproduces copies of the virus.

When HIV infects the body, its target is $CD4^+$ T cells. Since $CD4^+$ T cells play the key role in the immune response, this is cause for alarm and a key reason for HIV's devastating impact. A protein (GP120) on the surface of the virus has a high affinity for the CD4 protein on the surface of the T cell. Binding takes place, and the contents of the HIV is injected into the host T cell. HIV differs from most viruses in that it is a *retrovirus*: it carries a copy of its RNA (a precursor to the blueprint DNA) which must first be transcribed into DNA (using an enzyme it also carries called *reverse transcriptase*). One of the mysteries to the medical community is why this class of virus has evolved to include this extra step.

After the DNA of the virus has been duplicated by the host cell, it is reassembled and new virus particles *bud* from the surface of the host cell. This budding can take place slowly, sparing the host cell; or rapidly, bursting and killing the host cell.

The course of infection with HIV is not clear-cut. Clinicians are still arguing about what causes the eventual collapse of the immune system, resulting in death. What is widely agreed upon, however, is that there are four main stages of disease progression. First is the *initial innoculum*—when virus is introduced into the body. Second is the *initial transient*—a relatively short period of time when both the T cell population and virus population are in great flux. This is followed by the third stage, *clinical latency*—a period of time when there are extremely large numbers of virus and T cells undergoing incredible dynamics, the overall result of which is an appearance of latency (disease steady state). Finally, there is *AIDS*—this is characterized by the T cells dropping to very low numbers (or zero) and the virus growing without bound, resulting in death. The transitions between these four stages are not well understood, and presently there is controversy concerning whether the virus directly kills all of the T cells in this final stage or if there is some other mechanism(s) at work. For a complete overview of HIV infection, see [5, 6].

Treatment of HIV Infection

Clearly, there is a necessity for treatment of HIV infection. To this end, there are several drugs now employed: AZT (Zidovudine) was approved for treatment of HIV infection in 1987, and three other drugs—DDC, DDI, and D4T—have since been approved. These drugs all work as inhibitors of reverse transcriptase. The role of these reverse transcriptase inhibitors is to interfere with the transcription of the RNA to DNA, thus halting cellular infection and hence viral spread. Unfortunately, these drugs are not cures for the infection, but serve only as a maintenance program to temporarily prevent further progress of the virus. Despite this drawback, there is much clinical evidence to support the use of these chemotherapies in HIV-infected individuals. Aside from the possibility of prolonging life in an HIV-positive individual, it may make them less infectious to their sexual partners [9], as well as reduce rates of mother-to-fetus transmission [19]. Controversy exists among clinicians, however, as to who should be treated, when they should be treated, and what treatment scheme should be used.

There is much available data on AZT treatment [13, 17, 18]. Many laboratories and clinics keep close accounts of patient treatment courses with respect to effectiveness and results. These provide conflicting evidence as to which is better: early treatment (defined as $CD4^+$ T cell counts between $200—500\text{mm}^{-3}$ of blood) or treatment at a later stage (below 200mm^{-3}). "Better" here is based on overall health of patient (i.e., side effects) and a retention or increase in the $CD4^+$ T cell counts. Other questions regarding chemotherapy are whether the dosage should be large or small, what should be the duration of treatment, and what periodicity of doses should be used (whether the drug should be administered every 4 hours, 8 hours, etc.). All the questions can be addressed through the use of a mathematical model.

Mathematical Approaches to Modeling HIV Immunology

There are a variety of mathematical approaches used in modeling an HIV immunology. Traditionally, statistics served as a major tool and still plays an important role in understanding disease dynamics at all levels. Through the recent discovery and use of cellular automata and neural networks, much can be explored about the immune system. There are some groups working on stochastic versions of models of HIV infection; they consider the populations of cells interacting in a discrete probabilistic setting.

The mathematical modeling presented here will use more of a deterministic approach to aid in the understanding of the disease. Continuous dynamical systems, whether ordinary or partial differential equations, are lending new insights into HIV infection. Population models are most commonly used, and, given hypotheses about the interactions of those populations, models can be created, analyzed, and refined. For a good introduction to the biological modeling process, see [15].

To date there are a number of different models of HIV immunology. Many individuals and groups all over the world are involved in modeling HIV. Different phenomena are explained by the different models each present, but none of the models exhibit all that is observed clinically. This is partly due to the fact that much about this disease's mechanics is still unknown. Once a model is tested and is believed to behave well both qualitatively and quantitatively as compared with clinical data, the model can then be used to test such things as treatment strategies and the addition of secondary infections such as tuberculosis. The remainder of this paper demonstrates this modeling process through an example.

A Model

To model the interaction of the immune system with HIV, we start with the the $CD4^+$ T cells. After a short time period (less than 24 hours) [12], the viral RNA has been converted to viral DNA (using viral reverse transcriptase), and then the viral DNA is incorporated into the host genome. The model considers both the noninfected (T) and infected (T^i) $CD4^+$ T cells. Since an immune response is included in the model (i.e., T cells killing virus via killing infected T cells), the class of $CD8^+$ T cells must also be included in the T population. These cells cannot become infected with the virus, but do destroy infected T cells, and hence virus, during the cellular immune response. In essence, we are including the T cells which are HIV-specific in their immune response. Finally, the population of virus that is free living in the blood (V) is included. We assume the dynamics of these three populations take place in a single *compartment*. This is to insure that the equations are all scaled appropriately and there is no flow to or from outside compartments. Here, the compartment is the blood (as opposed to tissues or organs, etc.). The model is as follows.

$$\frac{dT(t)}{dt} = s(t) - \mu_T T(t) + r\frac{T(t)V(t)}{C+V(t)} - k_V T(t)V(t), \tag{1}$$

$$\frac{dT^i(t)}{dt} = k_V T(t)V(t) - \mu_{T^i} T^i(t) - r\frac{T^i(t)V(t)}{C+V(t)}, \tag{2}$$

$$\frac{dV(t)}{dt} = Nr\frac{T^i(t)V(t)}{C+V(t)} - k_T T(t)V(t) + \frac{g_V V(t)}{b+V(t)}. \tag{3}$$

Initial conditions are $T(0) = T_0, T^i(0) = 0$, $V(0) = V_0$. (We assume the initial innoculum is free virus and not infected cells; however, the model is robust in either case.) The model is explained as follows. The first term of Equation 1 represents the source of new T cells from the thymus (see Table 1 for the form of $s(t)$). Since it has been shown that virus can infect thymocytes, we choose a function describing the decreasing source as a function of viral load; assuming that the uninfected T cell populations are reduced by half. This is followed by a natural death term, because cells have a finite life span, the average of which is $\frac{1}{\mu_T}$. The next term represents the stimulation of T cells to proliferate in the presence of virus; r is the maximal proliferation rate, and C is the half saturation constant of the proliferation process. The idea is as follows. It is clear that both $CD8^+$ and $CD4^+$ T cells specific to HIV will be directly stimulated; however, we also know that T cells, once activated, stimulate other $CD8^+$ and $CD4^+$ T cells (which may or may not be specific to HIV). We believe this term encompasses these desired effects. The last term represents the infection of $CD4^+$ T cells by virus and is determined by the rate of encounters of T cells with virus; we suppose a constant rate k_V. Based on the large numbers of cells and virion involved, we can assume the law of mass action applies here.

Equation 2 describes changes in the infected population of $CD4^+$ T cells. The first term, a gain term for T^i, carries from the loss term in Equa-

tion 1. Then, infected cells are lost either by having finite life span or by being stimulated to proliferate. They are destroyed during the proliferation process by bursting due to the large viral load [14].

In Equation 3, both the first and third terms are the source for the virus population. Virion are released by the burst of the infected $CD4^+$ T cells (from Equation 2), described by the first term, in which an average of N particles are released per infected cell. The third term represents growth of virus from other infected cells (such as macrophages and infected thymocytes). The growth rate of the process is g_V, and the half saturation constant is b. This term also accounts for natural viral death. The second term is a loss term by the specific immune response (i.e., $CD8^+$ T cells killing virus). This also is a mass action type term, with a rate k_T.

Before numerical results can be explored, estimations for the parameter values are necessary.

Parameter Values

Clinical data are becoming more available, making it possible to get actual values (or orders of values) directly for the individual parameters in the model. By this I mean that it is possible to calculate the actual rates for the different processes described above based on data collected from clinical experiments. For example, it has been shown that infected $CD4^+$ T cells live less than 1–2 days [10]; therefore, we choose the rate of loss of infected T cells, μ_{T^i}, to be values between .5 and 1.0.

When this type of information is not available, estimation of the parameters can be determined from simulations through behavior studies. Bifurcation and sensitivity analyses can be carried out for each parameter to get a good understanding of the different behaviors seen for variations of these values. For example, the parameter N in the model (representing the average number of virus produced by an infected $CD4^+$ T cell) is not verifiable clinically; however, since it is a (transcritical) bifurcation parameter, we know that for small values the infection would die out and that for large values the infection persists. This may be an indication to clinicians that finding a drug which lowers this viral production may aid in suppressing the disease.

TABLE 1
Variables and Parameters

Dependent Variables		Values
T	= Uninfected $CD4^+$ T cell population	2000 mm^{-3}
T^i	= Infected $CD4^+$ T cell population	0.0
V	= Infectious HIV population	1.0 x $10^{-3} mm^{-3}$
Parameters and Constants		**Values**
$s(t)$	= source of new $CD4^+$T cells from thymus	$(.5s + \frac{5s}{1+V(t)})$
μ_T	= death rate of uninfected $CD4^+$T cell population	0.02 d^{-1}
$\mu_T i$	= death rate of infected $CD4^+$T cell population	0.5 d^{-1}
k_V	= rate $CD4^+$T cells becomes infected by free virus	2.4 x 10^{-5} mm^3 d^{-1}
k_T	= rate $CD8^+$T cells kill virus	7.4 x 10^{-4} mm^3 d^{-1}
r	= maximal proliferation of the $CD4^+$T cell population	0.01 d^{-1}
N	= number of free virus produced by bursting infected cells	1000
C	= half saturation constant of the proliferation process	100 mm^{-3}
b	= half saturation constant of the external viral source	10 mm^{-3}
g_V	= growth rate of external viral source other than T cells	2 d^{-1}
a_{max}	= maximum age (life span) of infected $CD4^+$T cells	12 d
a_1	= [0, a_1] is max int. during which rev. transcrp. occurs	.25 d^{-1}
$\gamma(t,a)$	= periodic, of period p, treatment function	varies
p	= period of dosage in treatment function	$0 \le p \le 1$ d
c	= total daily drug dosage in chemotherapy	varies
k	= decay rate of AZT based on half-life of 1 hour	16.66 d^{-1}

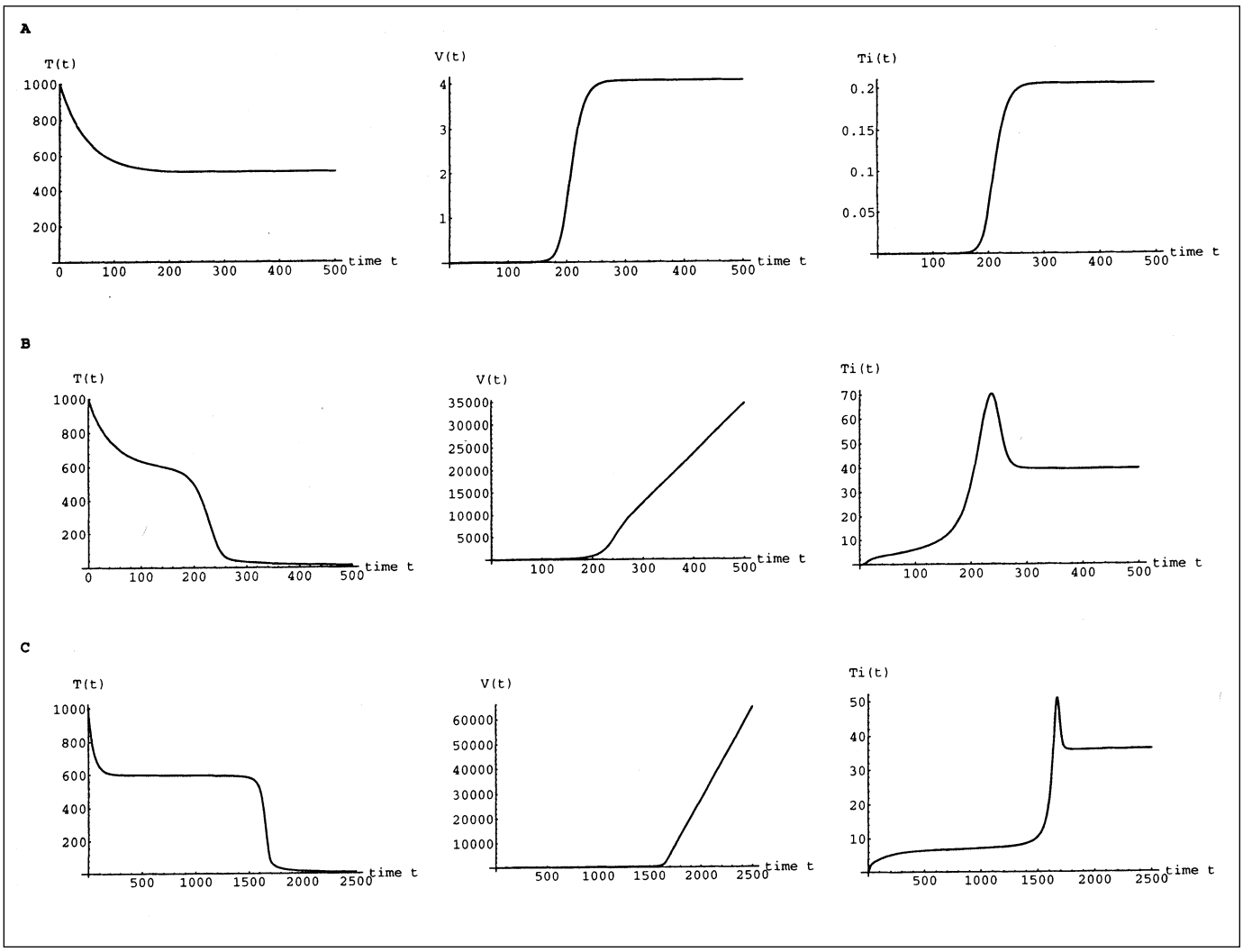

Figure 2. These are the numerical solutions to Model 1, 1-3. Parameter values used to generate theses figures can be found in Table 1. Panel A is the infected steady state with $g_V = 2$; if the external source is increased, i.e. $g_V = 20$, then it pushes the system into the progression to AIDS, Panel B. Panel C represents the entire course of HIV infection. This occurs when the external growth is variable and changes from $g_V = 2$ to $g_V = 20$ over time. (Notice the steep crash at day 1500 occurs over a period of a year.)

In general, this process can be helpful to clinicians, as a range for possible parameter values can be suggested. A complete list of parameters and their estimated values for this model is given in Table 1. Previous papers which have examined these estimations are [16, 20].

Numerical simulations can now be carried out, the output of which is presented in Figure 2. (All numerical simulations were carried out using *Mathematica* [21].) We see the model exhibits the three types of qualitative behaviors seen clinically: (a) an *uninfected steady state* where infection is suppressed (which is a locally stable state); (b) an *infected steady state* (latency) where infection is in quasisteady state (which is a locally stable state); and (c) a *progression to AIDS* state where the immune system crashes (where the virus grows at most linearly, without bound, and the T cells go to zero).

Testing the Model

Now that we have a model that we believe mimics a clinical picture, we can use the model to incorporate treatment strategies. To include AZT chemotherapy in the model, it is necessary to mimic the effects of the drug which serves to reduce viral infectivity. The parameter k_V in the model is multiplied by a function which is "off" outside the treatment period and "on" during the treatment period. When the treatment is "on", viral infectivity is reduced, which mimics the effect of treatment for a given time frame. The function which achieves this is

$$\mathbf{z}(t) = \left\{ \begin{array}{r} 1 \text{ outside the treatment period} \\ P(t) \text{ percent effectiveness during} \\ \text{AZT treatment} \end{array} \right\},$$

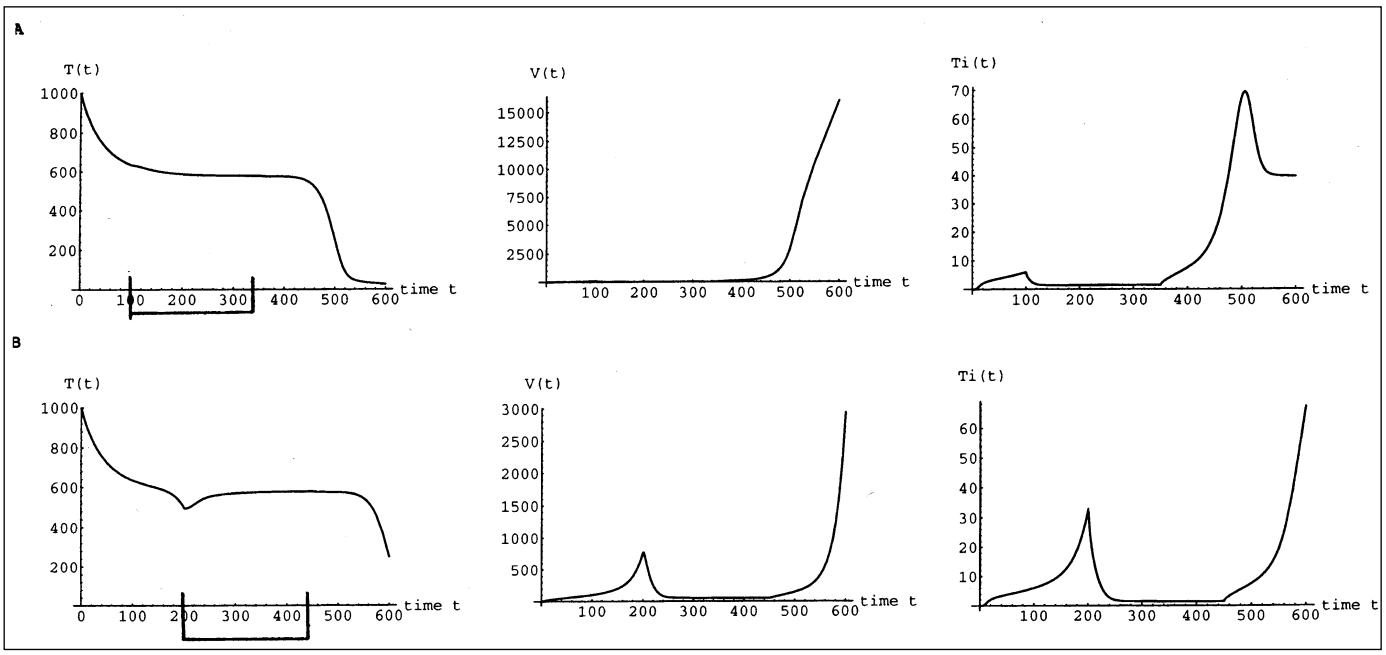

Figure 3. This is Model 1 showing (3A) early continuous treatment at 100 days (T cells ~600 mm^{-3}) for six months, and (3B) late treatment starting at 200 days (T cells ~400 mm^{-3}) for six months.

where $P(t)$ is a treatment function, $0 < P(t) < 1$. This affects the model as follows:

$$\begin{aligned}\frac{dT(t)}{dt} &= s(t) - \mu_T T(t) + r\frac{T(t)V(t)}{C+V(t)} \\ &\quad - \mathbf{z}(t)\cdot k_V T(t)V(t), \\ \frac{dT^i(t)}{dt} &= \mathbf{z}(t)\cdot k_V T(t)V(t) - \mu_{T^i} T^i(t) \\ &\quad - r\frac{T^i(t)V(t)}{C+V(t)},\end{aligned}$$

$$\frac{dV(t)}{dt} = Nr\frac{T^i(t)V(t)}{C+V(t)} - k_T T(t)V(t) + \frac{g_V V(t)}{c+V(t)},$$

where the initial conditions are still $T(0) = T_0, T^i(0) = 0, V(0) = V_0$. Drugs such as AZT reduce viral activity in a dose-dependent manner. The efficacy of the chemotherapy may differ from patient to patient; therefore, $P(t)$ represents the varying effectiveness of the drug in halting viral activity in a given patient. $P(t)$is not directly correlated to the actual oral dose of the drug in this approach.

Running simulations, we can test different treatment initiations to help answer the question whether earlier treatment (beginning 100 days after infection) or later (initiated 200 days after infection) treatment is better (Figure 3). From the results, it seems that the CD4$^+$ T cell count is higher overall when treatment is initiated during the later stages of infection.

Improvements

Suppose we wish to improve on this original model because the chemotherapy simulation is not so mechanistic in nature (for example, it doesn't take into account the drug half-life). We begin by incorporating age structure into the infected CD4$^+$ T cells (T^i) of the first model.

An age structured model, which is mechanistically based on a time scale commensurate with a drug administration schedule of several doses per day, will be better suited to the comparison of different number of doses per day. Let a denote the age of cellular infection (i.e., time elapsed since the cell became infected with HIV), and let $T^i(t,a)$ be the density of infected T cells with age of infection a at time t. The total infected T cell population at time t is $\int_0^{a_{max}} T^i(t,a)da$, where a_{max} is the maximum age of T cells. The system (1)–(3) is modified as follows:

$$\begin{aligned}\frac{dT(t)}{dt} &= s(t) - \mu T(t) + rT(t)\frac{V(t)}{C+V(t)} \\ &\quad - k_V T(t)V(t),\end{aligned} \tag{4}$$

$$T^i(t,0) = k_V T(t)V(t), \tag{5}$$

$$\begin{aligned}\frac{\partial T^i(t,a)}{\partial t} + \frac{\partial T^i(t,a)}{\partial a} &= -\mu_{T^i} T^i(t,a) \\ &\quad - rT^i(t,a)\frac{V(t)}{C+V(t)},\end{aligned} \tag{6}$$

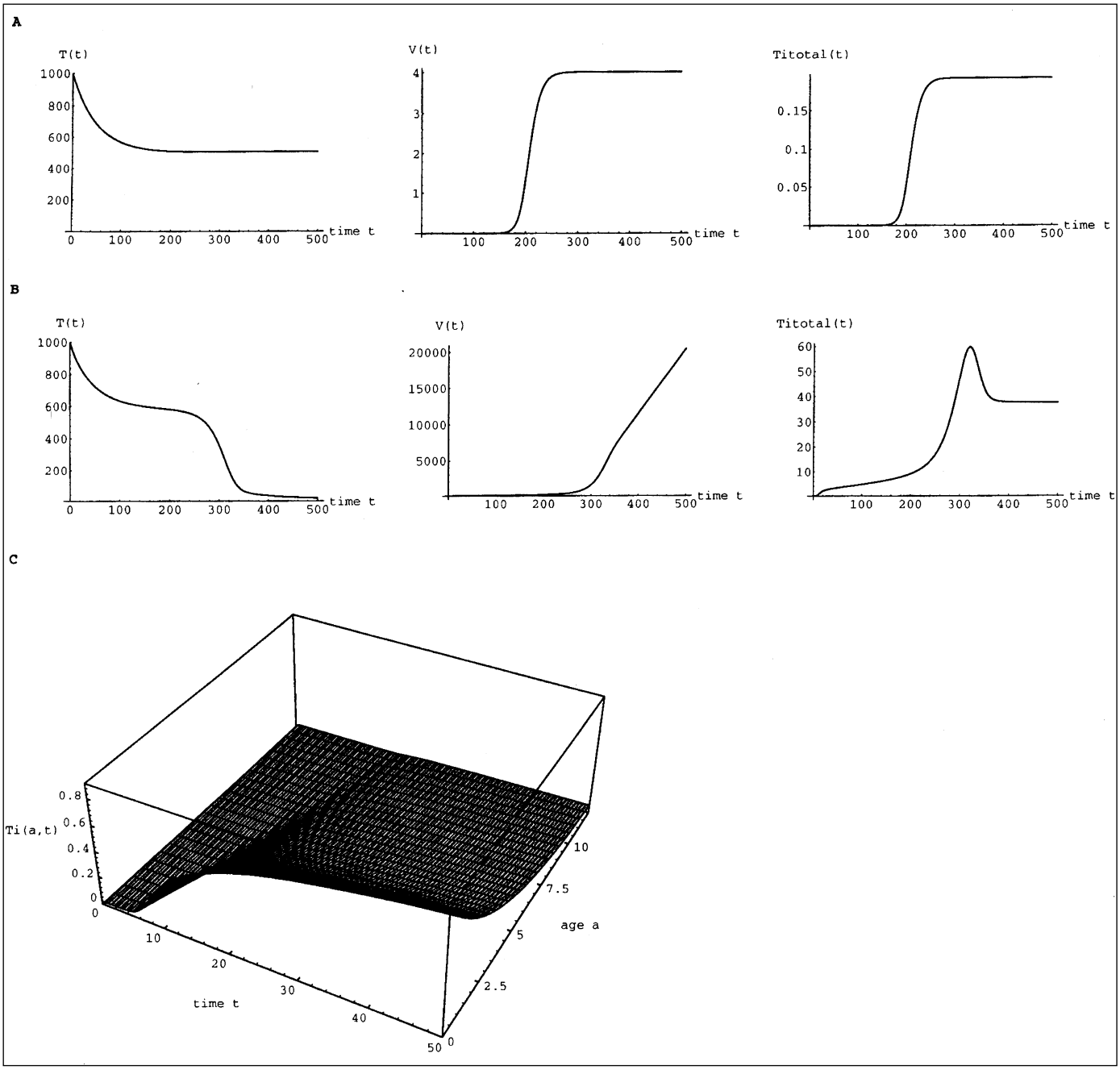

Figure 4. These are numerical solutions to Model 2, Equ. 4-7. Parameter values used to generate these figures can be found in Table 1. Panel A is the infected steady state; if the external source is increased, i.e. $g_V = 20$, then it pushes the system into the progression to AIDS, Panel B. Panel C shows the distribution of infected T cells, $T^i(t,a)$.

$$\frac{dV(t)}{dt} = Nr\frac{V(t)}{C+V(t)}\int_0^{a_{max}} T^i(t,a)da - k_T T(t)V(t) + \frac{g_V V(t)}{b+V(t)}, \tag{7}$$

with initial conditions $T(0) = T_0, V(0) = V_0$, $T^i(0,a) = 0, 0 \le a \le a_{max}$.

Equations 4–7 are derived under the same biological assumptions as described for Equations 1–3. Equation 6 describes the change in $T^i(t,a)$ in time t and cellular infection age a. The boundary condition 5 arises from the input of infected T cells with infection age 0. When the infected cells die (from bursting) in 6, the integral of $T^i(t,a)$ over all possible ages of infection arises as the source of the virus in 7. A mathematical analysis reveals that the steady states of both the ODE and ODE/PDE model are equivalent (see the cited article by Kirschner and Webb). The numerical results are therefore the same (Figure 4). Note that the age-structured infected T cell population (T^i) (Figure 4c) is now presented as a distribution, but the time edge of the cube matches the time evolution of the previous model (Figure 2a).

Improved Model for Treatment

We use these improvements to study the chemotherapy. Age structure was introduced to better facilitate modeling the mechanism by which AZT serves to interrupt the T cell infection process. Only T^i cells with age less than a_1 are affected by the drug (where a_1 is the maximum age at which reverse transcription takes place). T^i cells with age less than a_1 revert back to the uninfected class during the "on" phase of the treatment.

Treatment will correspond to a loss term $-\gamma(t,a;p)T^i(t,a)$ added to Equation 6, where the treatment function $\gamma(t,a;p)$ is periodic in time t with period p and depends on the age of cellular infection a. The revised equations are

$$\frac{dT}{dt} = s(t) - \mu T(t) + rT(t)\frac{V(t)}{C+V(t)} - k_V T(t)V(t) + \int_0^{a_1} \gamma(t,a;p)T^i(t,a)da,$$

$$T^i(t,0) = k_V T(t)V(t),$$

$$\frac{\partial T^i}{\partial t} + \frac{\partial T^i}{\partial a} = -\mu_{T^i} T^i(t,a) - rT^i(t,a)\frac{V(t)}{C+V(t)} - \gamma(t,a;p)T^i(t,a),$$

$$\frac{dV}{dt} = Nr\frac{V(t)}{C+V(t)}\int_{a_1}^{a_{max}} T^i(t,a)da - k_T T(t)V(t) + \frac{g_V V(t)}{b+V(t)},$$

with initial conditions $T(0) = T_0, \quad V(0) = V_0$, $T^i(0,a) = T_0^i(a)$.

Although we do not directly model the pharmokinetics of AZT chemotherapy, we do take into account some key aspects of the treatment. For example, since AZT has a half-life of one hour, we assume that $\gamma(t,a;p)$ is an exponential decaying function in t during each period, with decay rate $k = 16.66$, where time units are in days. Assume that the chemotherapy has effect only during the first a_1 hours after cellular infection (for AZT $a_1 = 6$ hours [10]), and that the period p has range $0 < p \le 1$(=day). The intensity of chemotherapy has value c at the beginning of each period. This value has no direct correlation with actual oral dosages, but serves to determine an appropriate range for that parameter. The *average value* of the treatment for any period is:

$$\frac{1}{p}\int_0^p ce^{-kt}dt = \frac{c(1-e^{-kp})}{kp}.$$

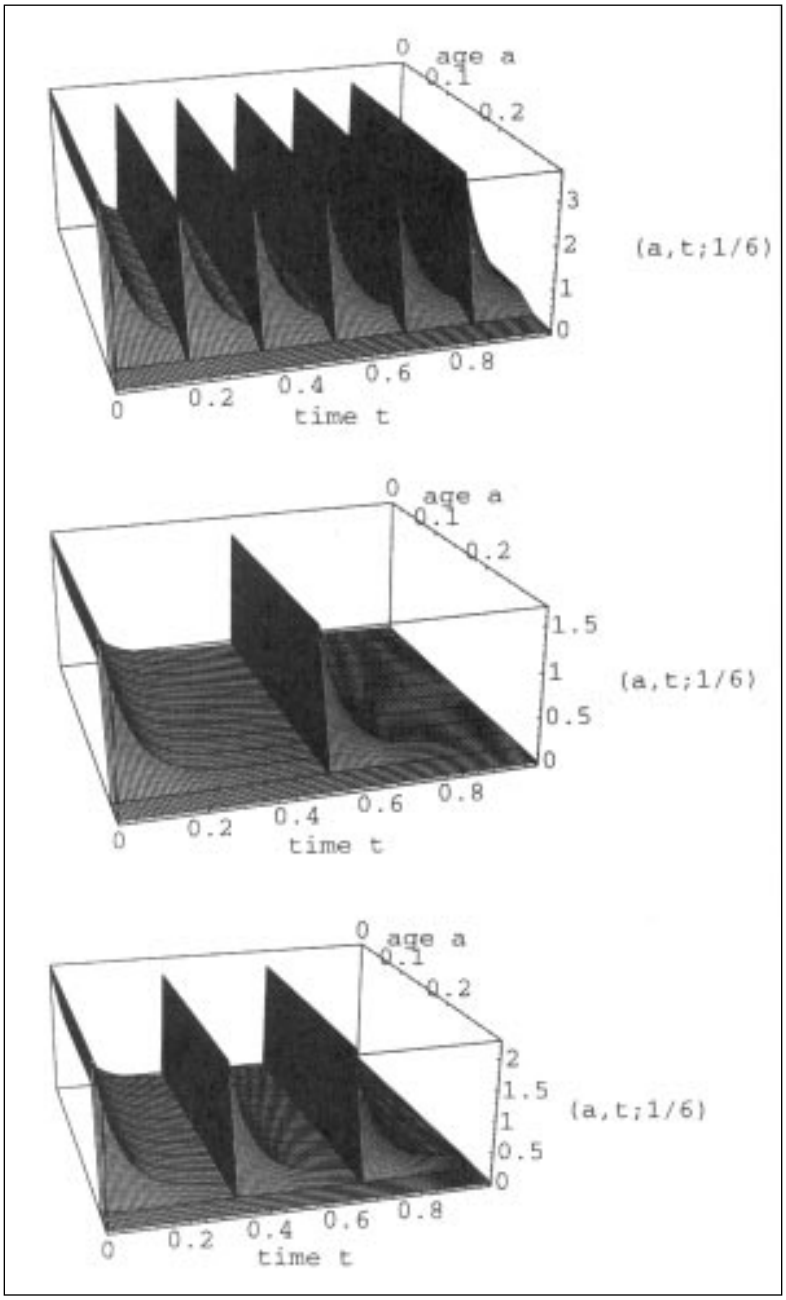

Figure 5. These are the different treatment functions, $\gamma(t,a;p)$ to be used in the simulations of Figures 6 and 7. Panel A represents treatment every four hours, which is the present recommended schedule. Panel B represents treatment every twelve hours, and Panel C represents treatment every eight hours.

Therefore, to remove the period dependence from the average value of treatment, scale c by:

$$\frac{(1-e^{-kp})}{p}.$$

This correlates to the desired total daily dose being divided by the number of doses given per day. The treatment function $\gamma(t,a;p)$ is then:

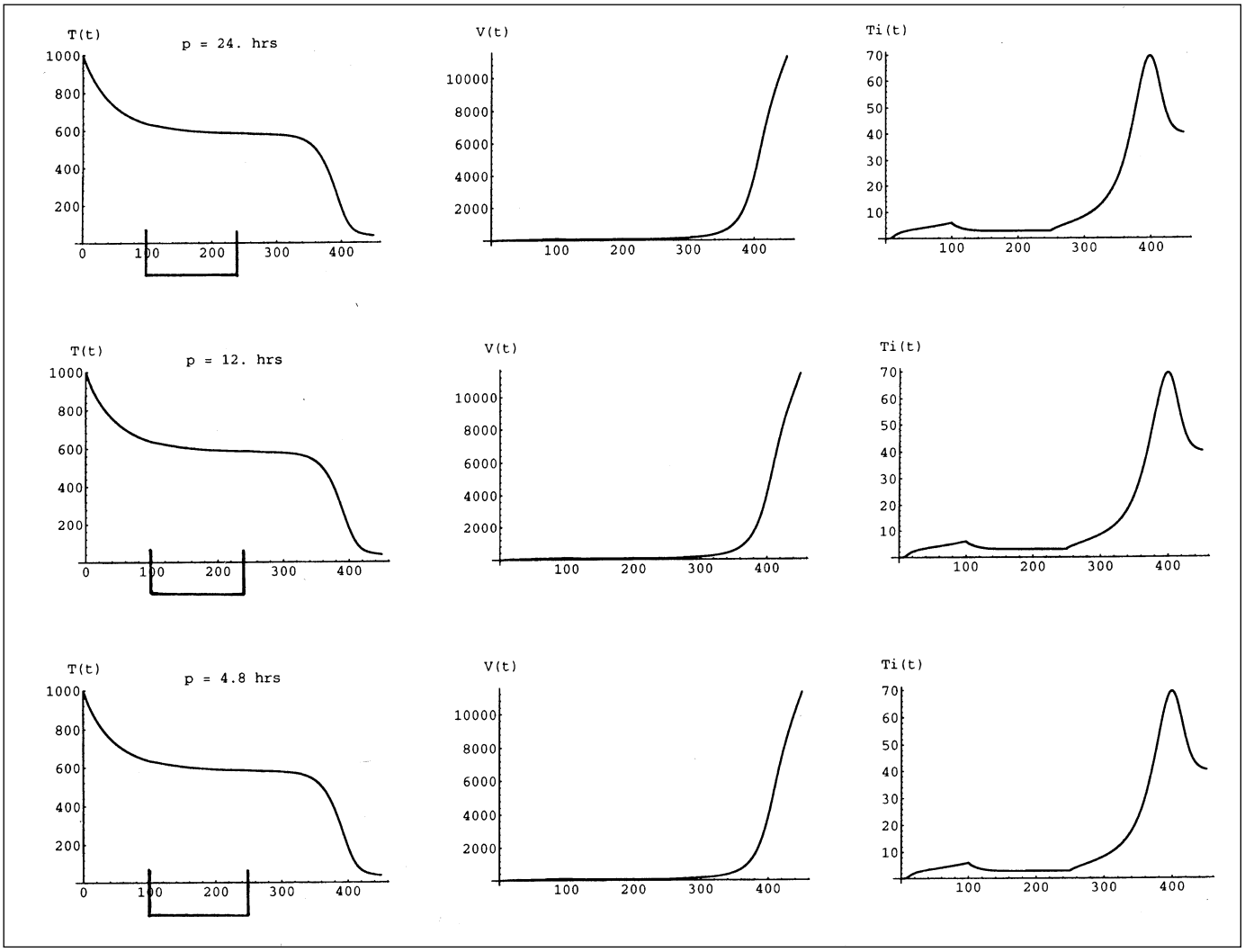

Figure 6. These are the numerical solutions to Model 2 including chemotherapy starting at an early stage of the disease progression (100 days) and administered for 150 days. All treatment was carried out during the progression to AIDS, i.e., $g_V = 20$ (cross reference with Figure 4B). Hash marks indicate treatment initiation and cessation. Panel A represents treatment once a day (cross reference with Figure 3), Panel B represents treatment every twelve hours (cross reference with Figure 5B), and Panel C is treatment every four hours (cross reference with Figure 5A).

$$\left\{\begin{array}{cc} \frac{cp}{(1-e^{-kp})}e^{-kt} & \text{if } 0 \le a \le a_1 \\ & \text{and } 0 \le t \le p \\ \frac{cp}{(1-e^{-kp})}e^{-k(t-p)} & \text{if } 0 \le a \le a_1 \\ & \text{and } p \le t \le 2p \\ & \vdots \\ 0 & \text{if } a > a_1 \end{array}\right\}.$$

Figure 5 gives examples of three treatment functions corresponding to treatment which is given six times a day, three times a day, and twice a day. The amount of treatment given over the day is equal for all three cases.

Now, we can not only simulate treatment to study early versus late timing questions, we can study periodicity of treatment as well. Figure 6 shows three different daily treatment periods for an early (at 100 days) treatment regime, and Figure 7 shows three different daily treatment periods for a late (at 300 days) treatment regime.

Examining the results of the second model, two things are evident. First, we still see that the overall T cell counts, once again, are better for later treatment. Second, it is clear that the period of chemotherapy administration does not effect the overall outcome of treatment. It should be noted here that in the dynamics of this and other diseases, such as cancer, disease progression states are not states of stabilization, but states where there is a rapid physical collapse of the system. In these models, the infected steady state (latency period) is a state of stabilization; however, the progression to AIDS (collapse of the $CD4^+$ T cell population) is not, since the viral population grows without bound. The fact that AZT

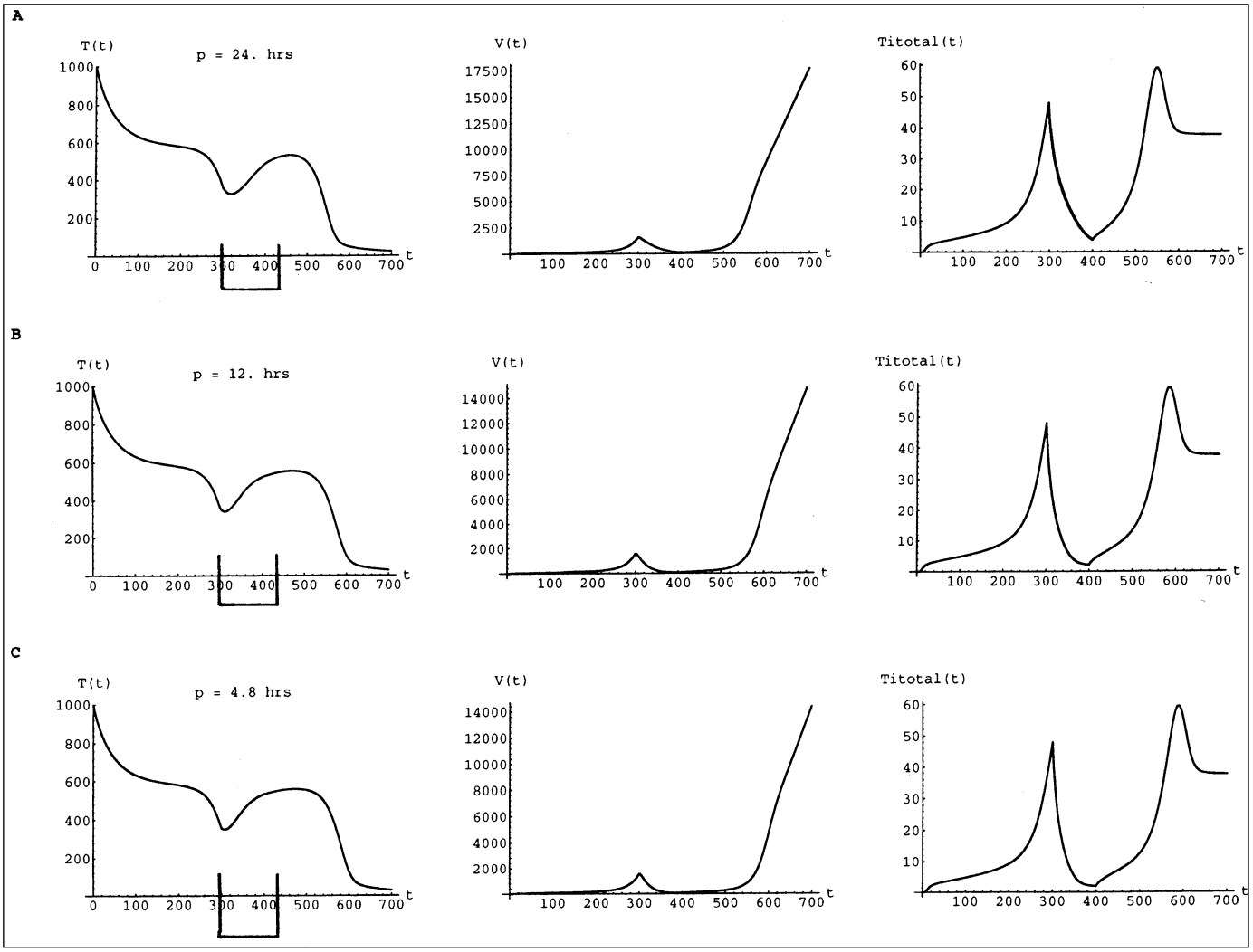

Figure 7. These are the numerical solutions to Model 2 including chemotherapy starting at a late stage of the disease progression (300 days) and administered for 150 days. All treatment was carried out during the progression to AIDS, i.e, $g_V = 20$ (cross reference with Figure 4B). Hash marks indicate treatment initiation and cessation. Panel A represents treatment once a day (cross reference with Figure 3), Panel B represents treatment every twelve hours (cross reference with Figure 5B), and Panel C represents treatment every four hours (cross reference with Figure 5A).

chemotherapy serves to perturb the collapsing system back into a stable state (i.e., latency) was a central thesis of this work. It should be noted that the main obstacle in HIV drug treatment is resistance. We are presently exploring this phenomenon.

Some Discussion

A key point to be stressed is that this is by no means a completed work. This project alone spawned three different new projects, the efforts of which are not only to improve the models, but also to study these systems as a purely mathematical exercise (i.e., well posedness, existence, optimal control, etc.).

Through this simple example, I hope it is also clear that there can and should be a role for mathematics in medicine. The biggest obstacles facing collaboration is the inability of clinicians to understand advanced mathematics, and, on the mathematician's part, the lack of knowledge of the underlying medical problem. It can take years to come to terms with all the medical jargon, especially in a continually evolving area. This can be overcome through serious cross-training of interdisciplinary scientists whose goal will be doing good science—which in turn would advance knowledge in both disciplines.

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