THE KIRSCHNER ARTICLE

In the February 1996 issue of the *Notices of the AMS* (American Mathematical Society), Denise Kirschner published an article "Using Mathematics to Understand HIV Immune Dynamics". The article presented an immunological model of HIV pathogenesis, including the effects of T-cell dynamics and chemotherapies such as AZT. Upon reading this article, Lang sent some initial documentation to Hugo Rossi and others at the AMS, but he also resigned from the AMS, stating "The matter is not one of principle, it is one of time and space in my life." Enclosed are some brief criticisms of the article by Mark Craddock, as well as a response by Lang, "The Kirschner Article: Scientific and Journalistic (Ir)responsibilities", which was rejected for publication in the "Forum" of the *Notices* in 1998.

DCB

Yale University *New Haven, Connecticut 06520-8283*

Telephone: (203) 432-4172
Fax: (203) 432-7316

DEPARTMENT OF MATHEMATICS
10 Hillhouse Avenue
P.O. Box 208283

23 January 1996

Hugo Rossi, Editor
Notices AMS
Math Dept
University of Utah
Salt Lake City Utah 84112

Dear Rossi,

I just received the new Notices, containing an article on HIV, giving the current dominant line of the establishment the certification of mathematicians. I object very strongly. For several years I have looked into the questions which have been raised about HIV, and on the basis of the evidence I have accumulated, I find that at least a warning by the editors about the HIV situation would have been appropriate. I am enclosing some of the documentation, including two articles of mine, and the latest ongoing file. Note the letter from the Chair of the Medical Center at Tulane, Arthur Gottlieb, in that file.

I think the AMS has got itself into serious trouble by publishing the article "Using Mathematics to Understand HIV Immune Dynamics". I am extremely busy proving theorems with Jorgenson at the moment, and I don't have the time or space in my life to put together an effective criticism of that publication. But I urge you as editor to take steps to warn the mathematical community about the documentation I am providing you.

Informatively yours,

Serge Lang

cc: Allyn Jackson, to whom I am sending the same material

MATH@MATH.YALE.EDU

Yale University *New Haven, Connecticut 06520-8283*

5 February 1996

DEPARTMENT OF MATHEMATICS
10 Hillhouse Avenue
P.O. Box 208283

Telephone: (203) 432-4172
Fax: (203) 432-7316

Cathleen Morawetz, President, AMS
Courant Institute
251 Mercer Street
New York NY 10012-1110

Dear Morawetz,

The latest issue of the *Notices* contains an article on HIV/AIDS, purportedly dealing with mathematical modeling of HIV. For five years, I have spent an enormous amount of time dealing with a massive failure of the science establishment concerning HIV. I am also in a very productive mathematical period, writing joint papers and monographs with Jorgenson, no end in sight. I have made an enormous commitment to various issues concerning scientific standards in the past decade, notably the one on HIV. My commitment included many mailings, to many people. (The current cc list has 75 people on it, plus the Council of the NAS.) I have been substituting for a massive failure of the mainstream press (scientific and otherwise, including *Nature, Science,* the *New York Times*) to inform people properly. Because of that commitment, I have no additional time or space in my life for taking on the problem posed by the *Notices* publication of the above mentioned article.

The appearance of the article in the *Notices* is such that, as a member of the AMS, either I have to spend time dealing with the way it contributes to misinformation about HIV, or I have to be an accessory after the fact in keeping silent. But I simply don't have time in my life to deal with this. Every second of my life is already occupied, and I am under tremendous pressures for keeping up certain standards in the information I distribute. I called Rossi to tell him, but on the phone he countered by asking me to see his problems. I replied that I did not have time or space in my life to consider his problems, because of the time and space I have devoted to passing out correct information. I told him that I objected being put in the position when, as a member of the AMS, to be responsible, I would have to spend time giving consideration to the publication of the article on HIV. I did take several hours just to put together about 100 pages of documentation which I sent to Rossi and to Allyn Jackson, to inform them both of the HIV situation, and what I have done about it. Unfortunately, by doing this as soon as I saw the *Notices* article on HIV, I missed a mathematical seminar talk which I had intended to attend.

On the phone with Rossi, I also suggested that on the basis of the documentation I was sending him, the editor might himself inform the readership, and tell them to forget about the article that had been published, in light of this documentation. I saw this as the way which would waste the least amount of time by the editors and by the readership. I also told him that he had some responsibility to communicate some of the documentation to the readership, but that I did not have the time or space in my life to do so myself. It was his responsibility to make the selection. I had no time or space in my life to take on the responsibility of making the selection myself. I have now received a letter from him, a page and a half long, where he writes:

> I shall read your dossier when it comes, in fact I look forward to it. But I need to tell you that, no matter what the effect the dossier will have on me, I shall not write the Stalinesque type of confession which you recited to me over the telephone.

MATH@MATH.YALE.EDU

I do not accept Rossi's version of our conversation, that I asked for a "Stalinesque type of confession" from him. I repeat: Considering the enormous commitment I have made previously to the HIV question (and others, including the Gallo question), and my continuing major commitment to mathematical research, I don't have the time or space in my life to deal with the *Notices* and the AMS on the issue of HIV. The matter is not one of principle, it is one of time and space in my life. The editors having decided to involve the *Notices* and hence the AMS on HIV, and Rossi presuming to write me as he did, before he received the documentation (cf. the above quote from his letter), independently of what this documentation contained, I don't even want to think about the *Notices* and the AMS in this connection any further.

I am therefore resigning from the AMS.[1] This pains me a great deal, because I have been a member since around 1950. It pains me especially because Rossi had been so wonderful in dealing with my pieces on Siegel-Mordell and on Shimura-Taniyama. That he, the *Notices* s and the AMS stepped inadvertently into the pile of shit concerning HIV is clear, but have you ever seen anyone step into a pile of shit other than inadvertently?

Could you please arrange for me to receive the AMS *Bulletin*, to which I wish to subscribe, at my cost. Perhaps the dues which I paid to the AMS recently can be transferred to pay for the subscription. Otherwise, let me know how much I owe for such a subscription.

Sadly but disengagingly yours,

Serge Lang

cc: Rossi, Allyn Jackson

[1] I am therefore enclosing Rossi's letter, which I stopped reading after the quoted paragraph, because it's an official letter on AMS *Notices* stationery. You can return it to him if you wish. If you want documentation, ask Rossi or Allyn Jackson to duplicate what I sent them. Let them find out how much time and effort it takes to provide documentation about the HIV issue, and what are the implications of having involved the AMS.

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.

Denise Kirschner is an assistant professor of mathematics, Texas A & M University, and adjunct assistant professor of medicine, Vanderbilt University Medical Center. Her e-mail address is dek@math.tamu.edu.

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

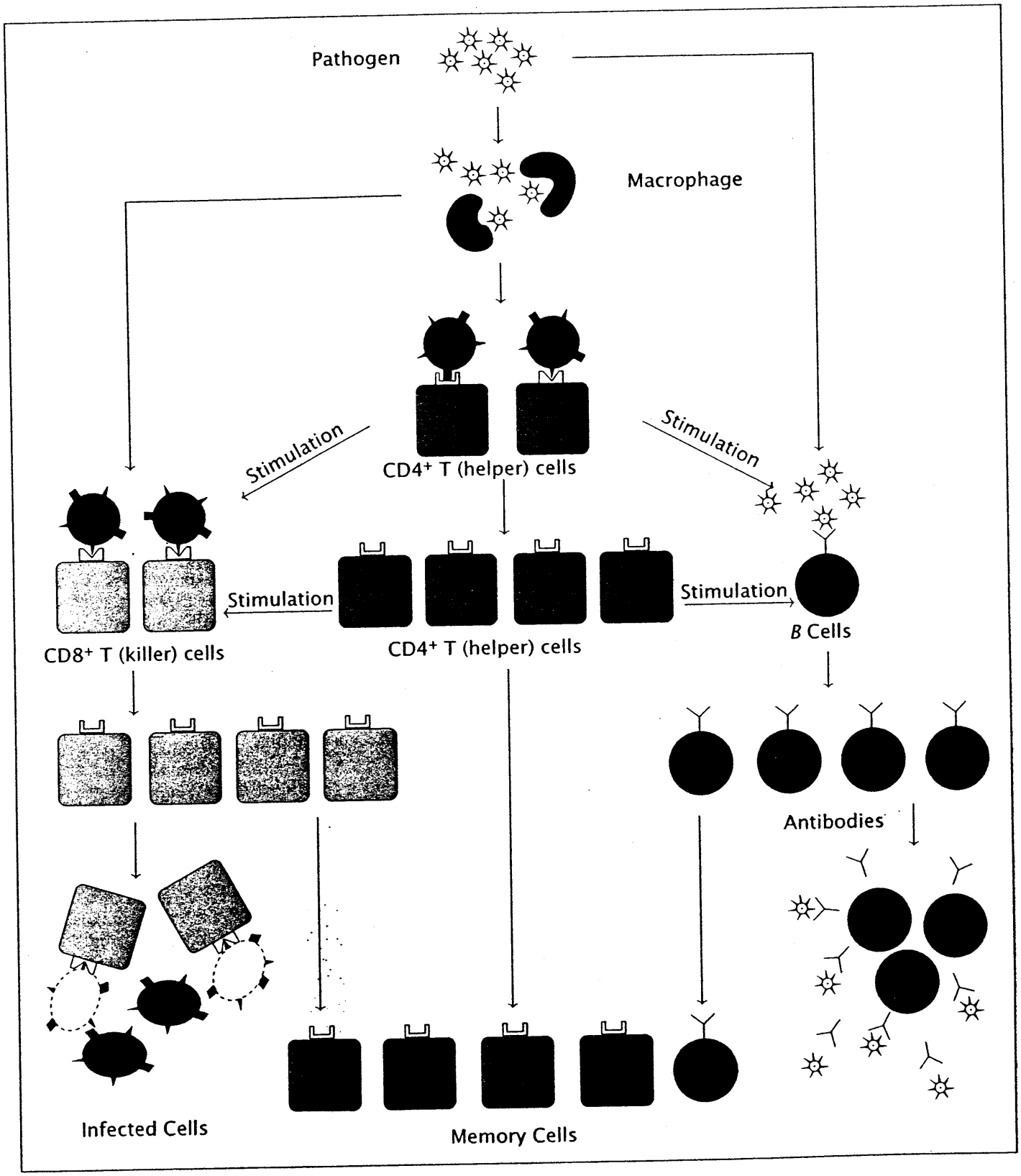

Figure 1. Schematic diagram of the working immune system.

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—500mm^{-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	$1.0 \times 10^{-3} mm^{-3}$

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	2.4×10^{-5} mm^3 d^{-1}
k_T	= rate $CD8^+$T cells kill virus	7.4×10^{-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}

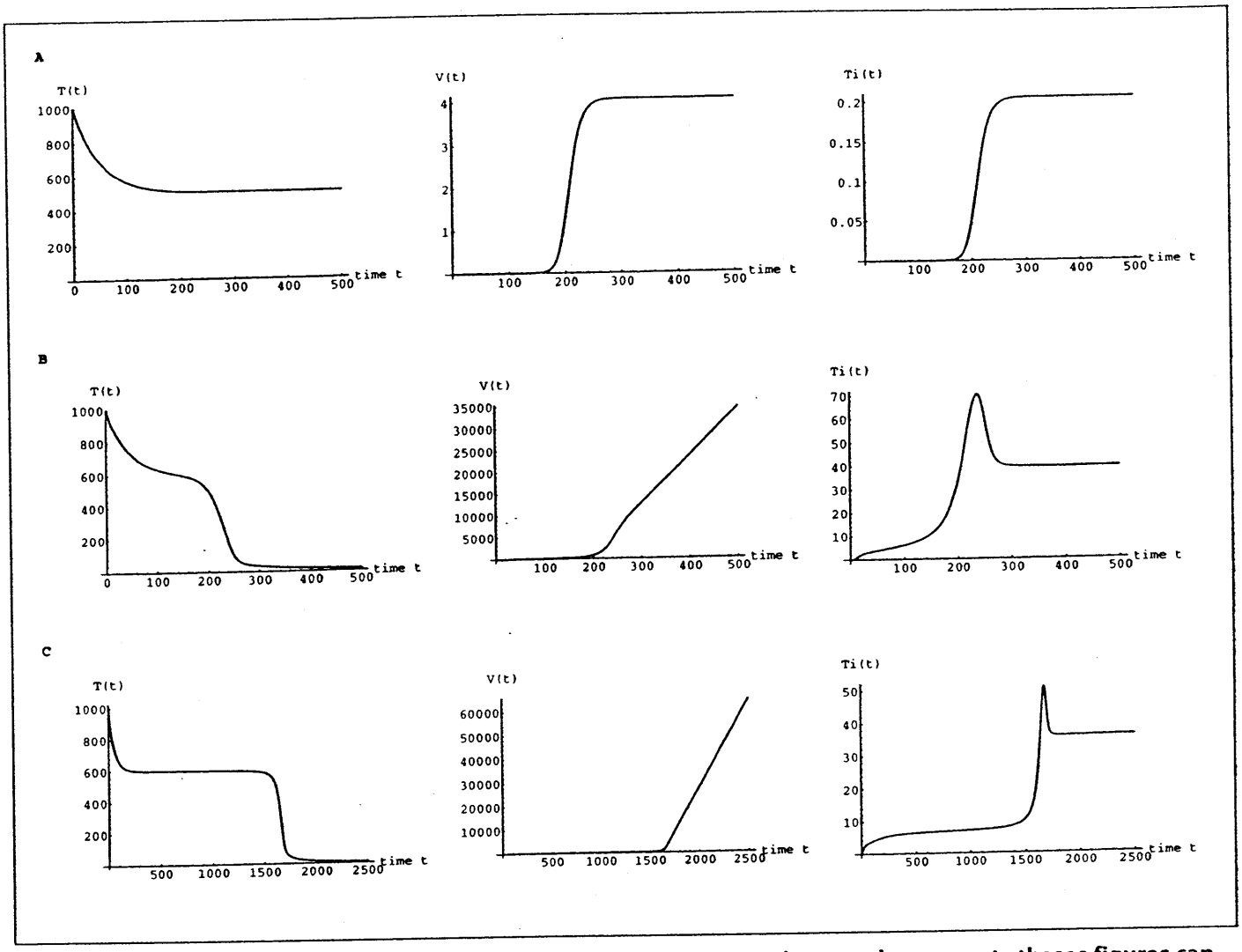

Figure 2. These are the numerical solutions to Model 1, 1-3. Parameter values used to generate theses figures can be found in Table 1. Panel A is the infected steady state with $g_V = 2$; if the external source is increased, i.e. $g_V = 20$, then it pushes the system into the progression to AIDS, Panel 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

$$z(t) = \begin{cases} 1 \text{ outside the treatment period} \\ P(t) \text{ percent effectiveness during} \\ \text{AZT treatment} \end{cases},$$

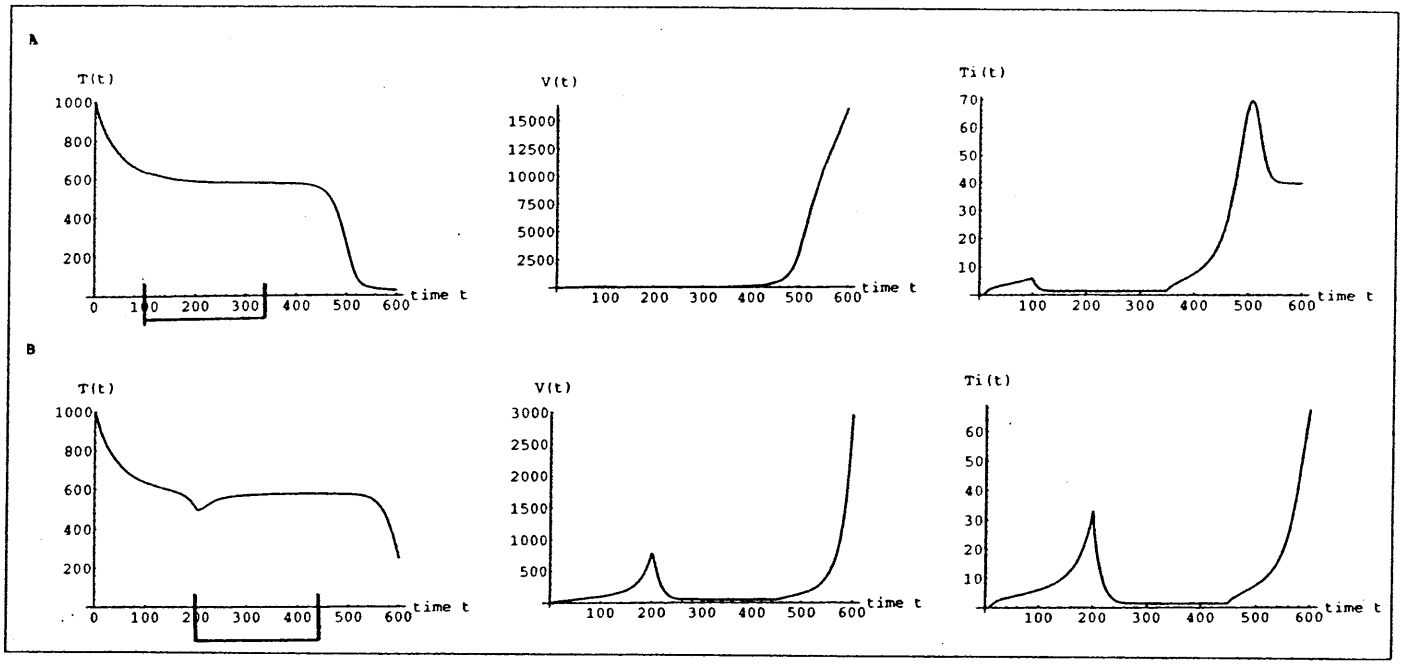

Figure 3. This is Model 1 showing (3A) early continuous treatment at 100 days (T cells ~600 mm^{-3}) for six months, and (3B) late treatment starting at 200 days (T cells ~400 mm^{-3}) for six months.

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

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

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

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

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:

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

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

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

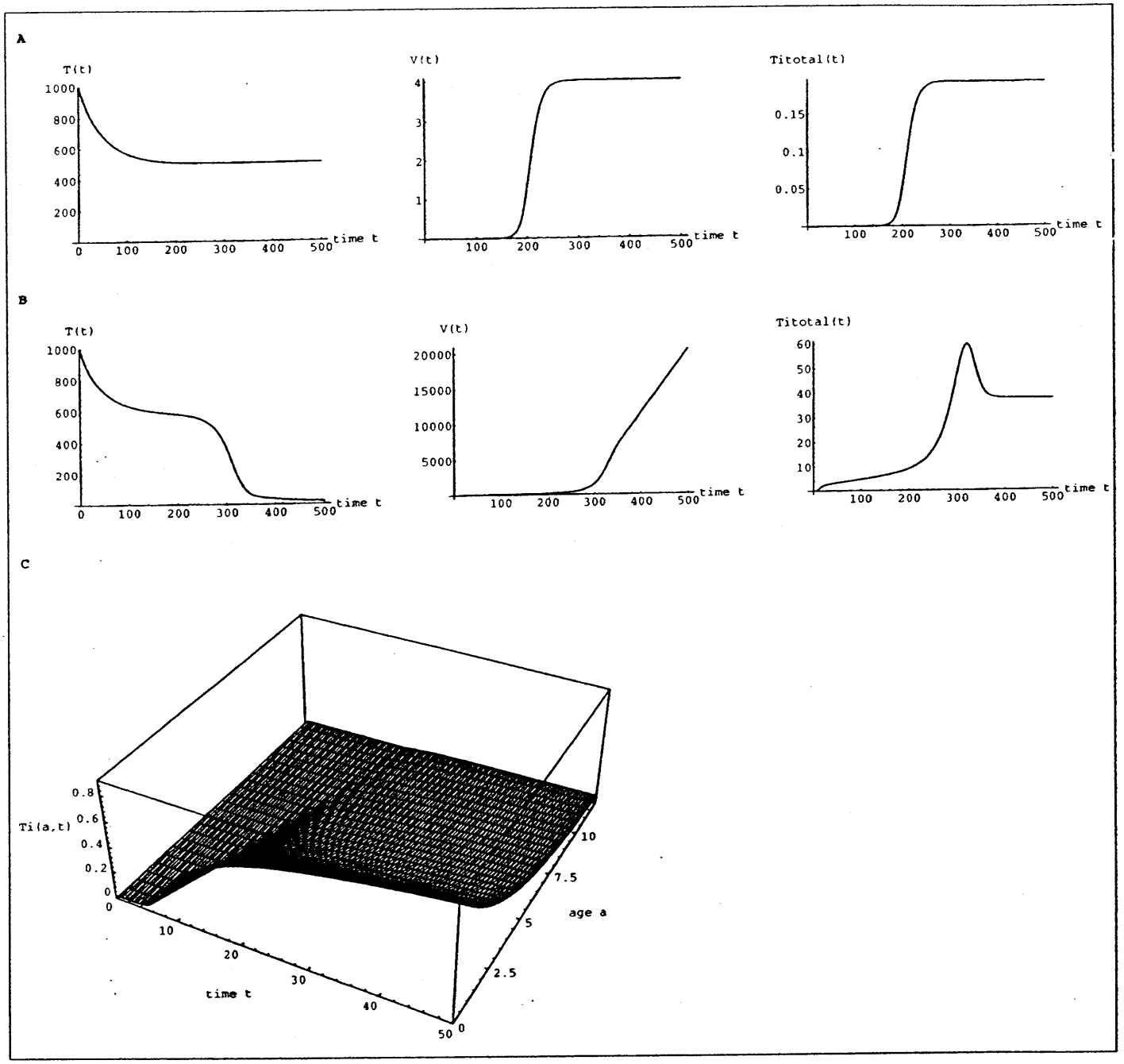

Figure 4. These are numerical solutions to Model 2, Equ. 4-7. Parameter values used to generate these figures can be found in Table 1. Panel A is the infected steady state; if the external source is increased, i.e. $g_V = 20$, then it pushes the system into the progression to AIDS, Panel B. Panel C shows 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 $T(0) = T_0$, $V(0) = V_0$, $T^i(0,a) = T_0^i(a)$.

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:

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

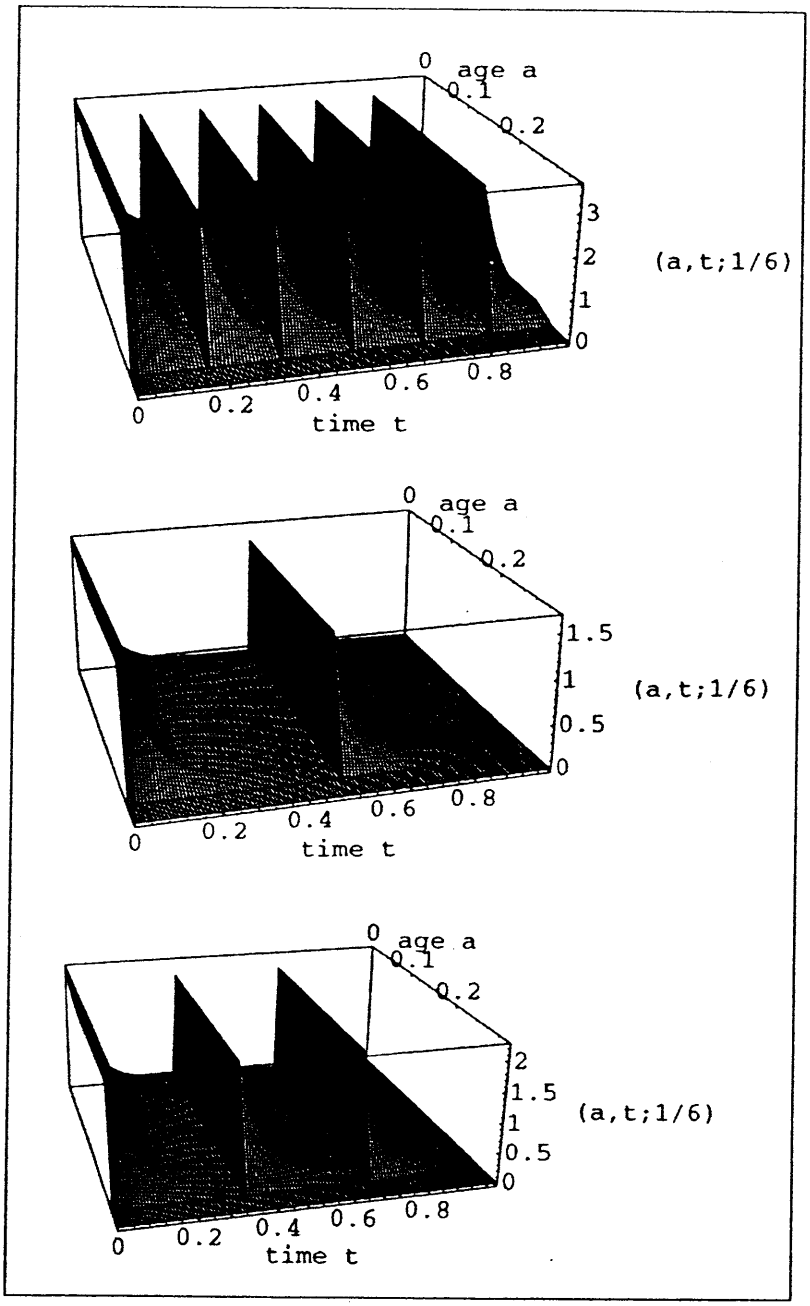

Figure 5. These are the different treatment functions, $\gamma(t,a;p)$ to be used in the simulations of Figures 6 and 7. Panel A represents treatment every four hours, which is the present recommended schedule. Panel B represents treatment every twelve hours, and Panel C represents treatment every eight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

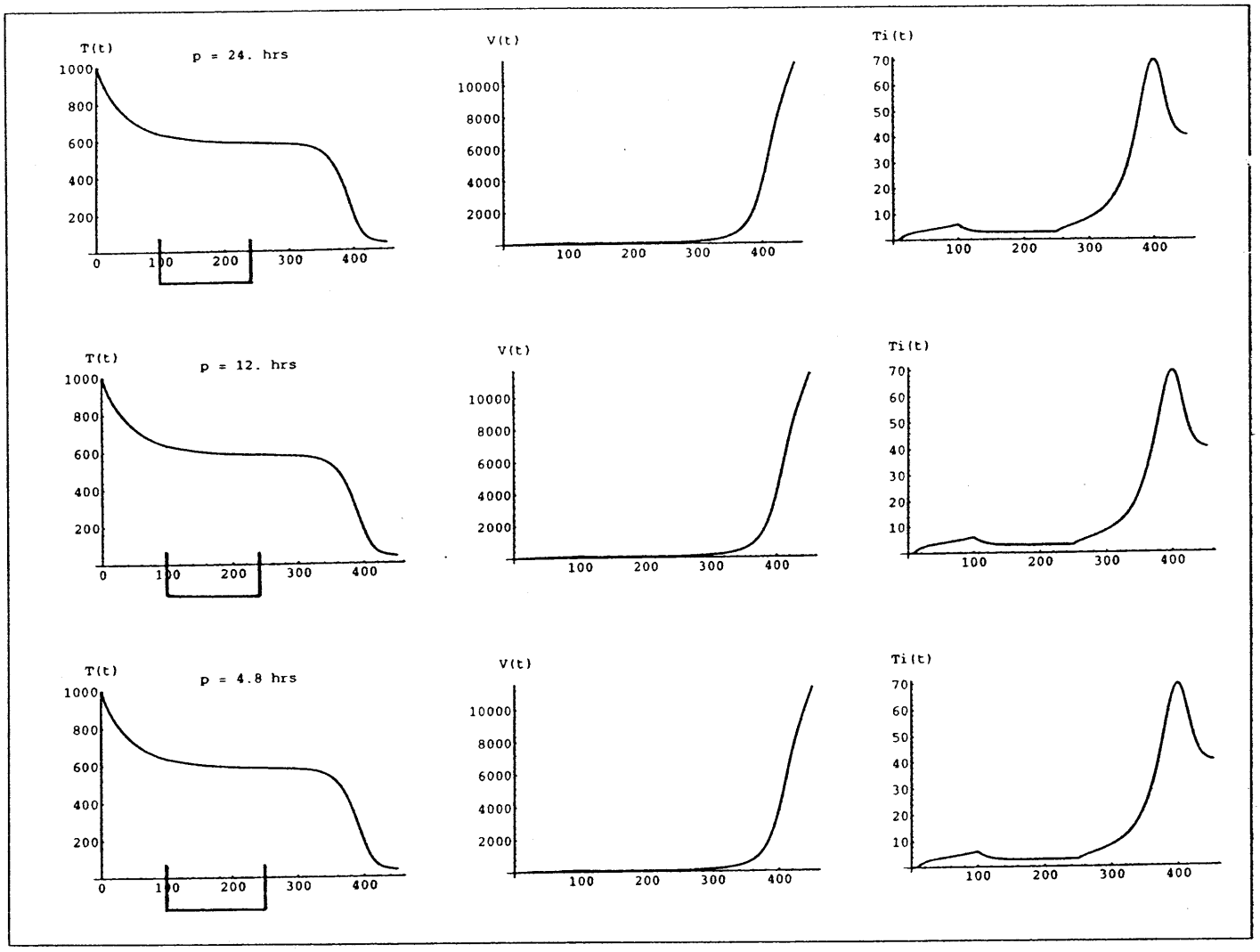

Figure 6. These are the numerical solutions to Model 2 including chemotherapy starting at an early stage of the disease progression (100 days) and administered for 150 days. All treatment was carried out during the progression to AIDS, i.e., $g_V = 20$ (cross reference with Figure 4B). Hash marks indicate 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).

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

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

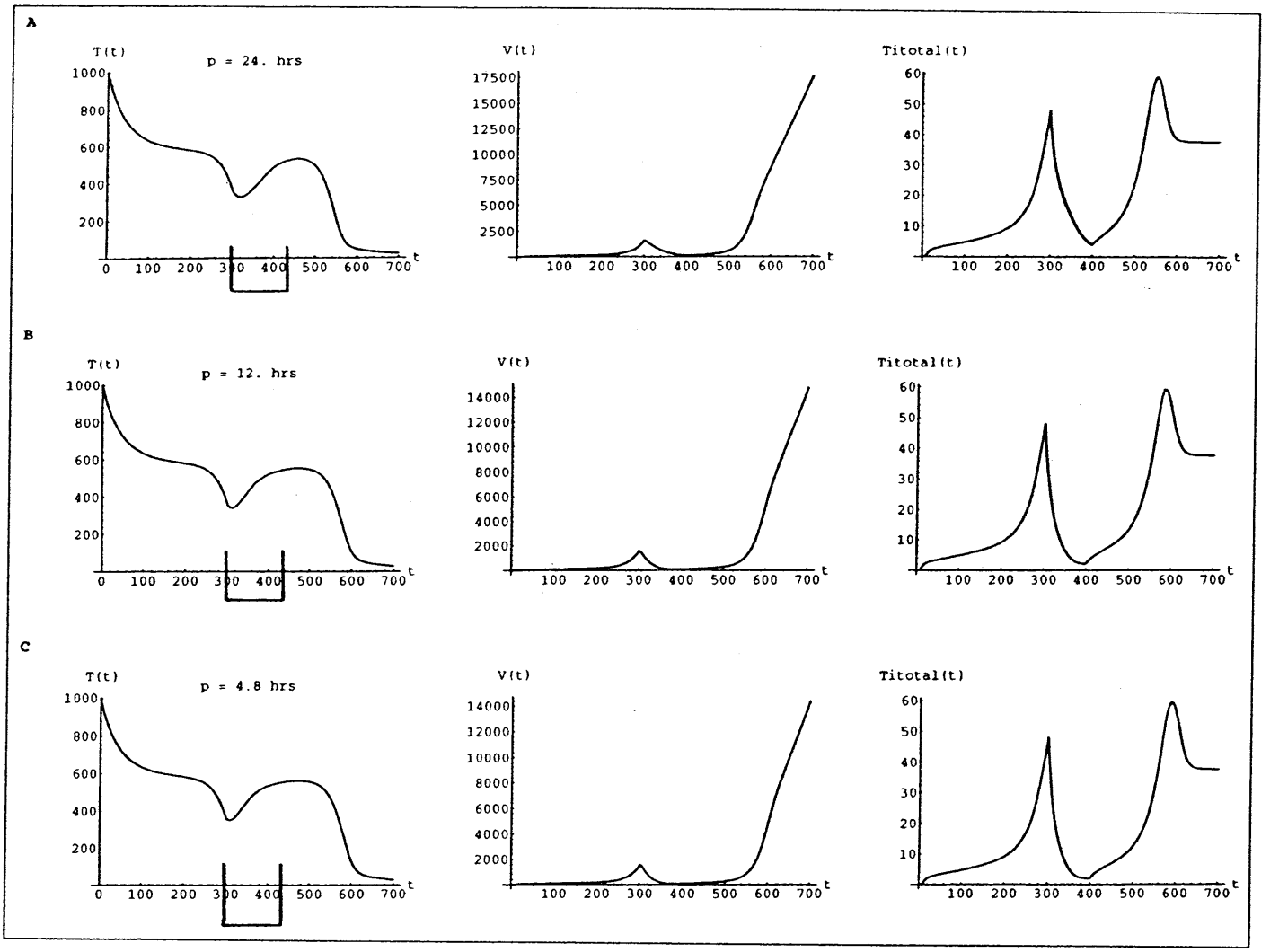

Figure 7. These are the numerical solutions to Model 2 including chemotherapy starting at a late stage of the disease progression (300 days) and administered for 150 days. All treatment was carried out during the progression to AIDS, i.e, $g_V = 20$ (cross reference with Figure 4B). Hash marks indicate 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.

Literature

Annotated Bibliography

[1] R. M. ANDERSON, *Editorial Review of Mathematical and statistical studies of the epidemiology of HIV*, AIDS 3 (1989) 333-346.

[2] C. CASTILLO-CHAVEZ, *Mathematical and statistical approaches to AIDS epidemiology*,

Lecture Notes in Biomathematics Series, vol. 83 Springer-Verlag, Berlin, 1989.

[3] K. P. HADLER, *Modeling AIDS in structured populations*, Proc. 47th Session of the International Statistical Institute, Paris, August/September 1989, pp. 83-99.

[4] H. W. HETHCOTE and J. W. VAN ARK, *Modeling HIV transmission and AIDS in the USA*, Lecture Notes in Biomathematics Series, vol. 95, Springer-Verlag, New York, 1992.

[5] J. A. LEVY, *HIV and the pathogenesis of AIDS*, ASM Press, Washington, DC, 1994. A comprehensive book on all that is known, immunologically, about HIV to date.

[6] J. D. KAISER, *Immune power*, St. Martin's Press, New York, 1993. A book written by an AIDS physician. A must for both clinicians and HIV-positive people in dealing with the disease.

[7] S. B. MIZEL and P. JARET, *The human immune system*, Simon and Schuster, Inc., New York, 1985. A nonspecialist introduction to the immune system. Excellent reading!

[8] I. ROITT, J. BROSTOFF, and D. MALE, *Immunology*, Gower Medical Publishing, London, 1985. A (med school) comprehensive book on immunology.

References

[9] D. J. ANDERSON, T. R. O'BRIEN, J. A. POLITCH, A. MARTINEZ, G. R. SEAGE, N. PADIAN, R. C. HORSBURGH, and K. H. MAYER, *Effects of disease stage and AZT therapy on the detection of HIV-1 in semen*, Journal of the American Medical Association **267** (1992), 2769-2774.

[10] J. M. COFFIN, *HIV populations dynamics in vivo: Implications for genetic variation, pathogenesis and therapy*, Science **267** (1995), 483-489.

[11] D. A. COOPER, C. PEDERSEN, F. AIUTI *et al.*, *The efficacy and safety of AZT with or without acyclovir in the treatment of patients with AIDS related complex*, AIDS **5** (1991), 933-943.

[12] D. S. DIMITROV *et al.*, *Quantitation of HIV-type 1 infection kinetics*, Journal of Virology **67** (1993), 2182-2190.

[13] M. S. HIRSCH, *Chemotherapy of HIV infections: Current practice and future prospects*, Journal of Infectious Diseases **161** (1990), 845-857.

[14] D. D. HO, A. U. NEUMANN, A. S. PERELSON *et al. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection*, Nature **373** (1995), 123-126.

[15] F. HOPPENSTEADT, *Getting started in mathematical biology, Notices Amer. Math. Soc.* **42** (1995), 969-975.

[16] D. KIRSCHNER and A. PERELSON, *A model for the immune system response to HIV: AZT treatment studies*, Mathematical Populations Dynamics III, Theory of Epidemics, vol. 1 (O. Arino, D. Axelrod, M. Kimmel, editors), Wuerz Publ., Winnipeg, Manitoba, 1995, pp. 295-310.

[17] J. D. LUNDGREN, A. N. PHILLIPS *et al.*, *Comparison of long-term prognosis of patients with AIDS treated and not treated with Zidovudine*, JAMA **271** (1994), 1088-1092.

[18] G. X. MCLEOD and S. M. HAMMER, *Zidovudine: 5 years later*, Annals of Internal Medicine **117** (1992), 487-501.

[19] M. NOZYCE, M. HOBERMAN, S. ARPADI, A. WIZNIA, G. LAMBERT, J. DOBROSZYCKI, C. J. CHANG, and Y. ST. LOUIS, *A 12-month study of the effects of oral AZT on neurodevelopmental functioning in a cohort of vertically HIV-infected inner-city children*, AIDS **8** (1994), 635-639.

[20] A. PERELSON, D. KIRSCHNER, and R. DEBOER, *The dynamics of HIV infection of $CD4^+$ T cells*, Math. Biosciences **114** (1993), 81-125.

[21] S. A. WOLFRAM, *Mathematica: A system for doing mathematics by computer*, Addison-Wesley, Reading, MA, 1988.

Dear Lang,

I have forwarded you a handwritten document which consists principally of notes that I made for myself regarding the Ho/Shaw model. It was intended to form the basis of a more detailed article analysing Ho and Shaw's papers on the alleged dynamics of HIV. Other research concerns have kept me from writing the criticisms up into something more presentable to the mathematical community. I forwarded it to you so that you would have a copy of the document that Arthur has. It is obviously not a formal article in any sense.

You have asked for some comments on the article on the modelling of HIV from the Notices. I have seen the article and will look at it in as much detail as I can. The most obvious defects lie in the presentation of the basic position regarding HIV and AZT. Some of these you mentioned in your correspondence with Arthur Gottlieb. Another obvious misleading statement is the labelling of AZT as a "reverse transcriptase inhibitor", clearly to maintain some kind of continuity with the current "protease inhibitor" hype. AZT was invented years before Reverse Transcriptase was discovered and there is no evidence that I am aware of that it preferentially inhibits the action of Reverse Transcriptase. David Rasnick can confirm this for you.

Some mathematical comments, though of a preliminary nature.

1) Her model seems to have a decline of T cells built into it that would be present in some degree without HIV at all. Note the form she takes for $s(t)$. She writes in Table 1, p 195

$$s(t) = .5s + \frac{5s}{1 + V(t)}$$

Where $V(t)$ is the viral load at time t. Note she nowhere says what s is, at least not that I can see. Thus it is impossible to fully understand her model. I assume that s is meant to be the rate of T cell production in a "normal" individual, whatever that is. What is curious about the model is that she says , p194 halfway down the second column that she is "assuming that the uninfected T cell population is reduced by half".

This seems to me to be a way of avoiding the problem that infectious virus levels are typically very low. (cf. Piatak et al Science, Vol 259, 19 March 1993, table 1, p 1751). Indeed the solutions that Kirschner presents never have large amounts of infectious virus, an observed feature of alleged "HIV disease", yet the T cell population collapses. I suspect that this is a consequence of the above mentioned assumption. In other words she has built the decline in CD4 count into her model, rather than it being a prediction of that model.

2) Using Mathematica, as she does, I am unable to obtain her solutions. Her initial data are obscurely presented, so it is possible I have misunderstood her. Nevertheless when I substituted her numbers into Mathematica I got quite different solutions. This will need to be checked carefully.

3) Kirschner's model like all other models I have seen, is defective because it does not consider the effect of AZT toxicity on T cells, and bone marrow. Duesberg

shows in one of his Genetica articles that AZT is toxic on immune system cells at doses used for chemotherapy. It is also well known that nucleoside analogue drugs are immune suppresive. Yet modellers such as Kirschner refuse to include the cytopathic effects of AZT or other drugs given to HIV seropositives in their models. One wonders whether they are concerned that such modelling would give a better description of the onset of "AIDS" than the HIV only models currently do.

4) The article's presentation of solutions is peculiar. In Figure 2c), is she really saying that after a thousand days of infection there are fewer than 10 infected T cells per ml? These are the kinds of numbers that Duesberg has long pointed to as being indicative of the inadequacy of the HIV/AIDS hypothesis. Is she aware of this I wonder?

I am prepararing and teaching a Non linear dynamics course this semester, so I should have time to look at her model in more detail. When I do I will write up what I find and forward it to you.

Best

Mark Craddock

Mark Craddock

Received 13 August 1997
S.L.

American Mathematical Society

Courant Institute of Mathematical Sciences
251 Mercer Street, New York, NY 10012-1110 USA
Telephone: 212-998-3297
FAX: 212-995-4121

Cathleen Synge Morawetz
President

Internet: morawetz@acf1.nyu.edu

February 13, 1996

Professor Serge Lang
Department of Mathematics
Yale University
New Haven, CT 06520

Dear Serge,

It was with quite some dismay that I learned that you wish to resign from the AMS because you believe that, by publishing the article by Kirschner, the Society has taken a stand on some basic scientific ideas with respect to HIV. The society has not taken such a stand by publishing Kirschner's article and can only take a stand on anything by either a unanimous vote of the Council or an equivalent alternative vote whose details I will not bother you with. It is clear that you disagree with Kirschner's article and it is most certainly your right to send a letter to the Editor with your argument which the editors of the Notices may or may not decide to publish. I spoke to Hugo and he would very much like to publish your letter. As you have said, Hugo has done a great deal for the Notices (so have you) and its partly because he has a pretty free hand about what he publishes so the decision on publishing such a letter is his. I would recommend a short letter – it takes less time to write and is much more likely to be read – since limited time and space is a problem for all of us.

Be that as it may, I would urge you not to resign from the AMS. You have been a member in the real sense contributing in so many different ways that your resignation would be truly felt and I would myself feel that something

very important had been lost. Please reconsider. I await your reply.

Yours sincerely,

Cathleen Synge Morawetz, President
American Mathematical Society

Yale University *New Haven, Connecticut 06520-8283*

Telephone: (203) 432-4172
Fax: (203) 432-7316

DEPARTMENT OF MATHEMATICS
10 Hillhouse Avenue
P.O. Box 208283

14 February 1996

Cathleen Morawetz, President, AMS
Courant Institute
251 Mercer Street
New York NY 10012-1110

Dear Morawetz,

I have just received an envelope from Rossi. My resignation was not taken lightly, but in light of thirty years experience in non-mathematical dealings, and more recently, after ten days of thinking over the situation over concerning the publication of the HIV article in the *Notices*, followed by Rossi's letter to me. My letter to you dated 5 January was by no means perfect, because I didn't have the time to make it any better. On rereading it, I find nevertheless that it gives accurately the proper explanation for my resignation. I see no reason to change my disengagement. Hence I am sending you Rossi's envelope unopened, because I do not wish to take the risks that a formal re-engagement with the AMS would imply for me. I simply don't have the time or space in my life, as I have stated more than enough times previously. The envelope from Rossi indicates its official coming from the *Notices* , so you are entitled to have the letter and open it, and do whatever you want with it.

For your information, I also enclose the cover letter which I wrote to Rossi when I originally sent him several packets of documentation. I think in toto the packets came to more than 150 pages.

May I add that I have had a series of mailings since September on the HIV issue, with some Gallo thrown in, but the two issues are related in some ways. The cc list for these mailings went from about a dozen in September to nearly a hundred today. I am now overloaded with this responsibility. I expect to have one more mailing of important information at the end of this week, but after that I expect to close this particular file, because it now threatens to interfere excessively with my still lasting commitment to writing research papers. I expect to finish one such paper with Jorgenson this week, and we have started the next. So that's it. In the crunch, I do mathematics.

I would still appreciate subscribing to the *Bulletin*, as I wrote you previously. So I thank you in advance for forwarding my request to those in charge of individual subscriptions. They can let me know what I owe for my individual subscription.

Disengagedly yours,

Serge Lang

cc: Rossi, Allyn Jackson

Yale University *New Haven, Connecticut 06520-8283*

26 February 1996

DEPARTMENT OF MATHEMATICS
10 Hillhouse Avenue
P.O. Box 208283

Telephone: (203) 432-4172
Fax: (203) 432-7316

Cathleen Morawetz, President, AMS
Courant Institute
251 Mercer Street
New York NY 10012-1110

Dear Morawetz,

Many thanks for the letter of 13 February, where you write about me: "...you wish to resign from the AMS because you believe that by publishing the article by Kirschner, the Society has taken a stand on some basic scientific ideas with respect to HIV." This sentence falsely represents my position which I wrote you on 5 February 1996, on several counts:

1. I do not "wish to resign". I have resigned.
2. I do not "believe" as you attribute to me. To describe more precisely what responsibility the AMS has taken would take much more space, and I don't have the time to do so.

In addition:

3. You "recommend a short letter" to the editors of the *Notices* from me. I do not accept being placed in any situation of responsibility to impart information to the membership of the AMS, and to spend the time making the selection. As a non-member of the AMS, I have no such responsibility. Part of my reason for resigning was to avoid any such responsibility, as I stated in my letter to you of 5 February, starting with paragraph 2. Your recommendation bypasses my explanation. On the other hand, it is for the editors and the Council of the AMS to determine their own responsibilities, not for me to substitute for them.

I appreciate your concern very much, on a personal basis, which is the reason for me to have gone as far as writing the above three items. However, nothing has changed in the situation to alter the explanation I gave for my resignation.

Disengagedly yours,

Serge Lang

cc: Rossi, Allyn Jackson

MATH@MATH.YALE.EDU

Yale University *New Haven, Connecticut 06520-8283*

28 February 1996

DEPARTMENT OF MATHEMATICS
10 Hillhouse Avenue
P.O. Box 208283

Telephone: (203) 432-4172
Fax: (203) 432-7316

Robert Fossum, Secretary AMS
1409 West Green Street
University of Illinois
Urbana Ill 61801

Dear Fossum,

I enclose some correspondence with Cathleen Morawetz. As you can see from this correspondence, I have resigned from the AMS. Since Morawetz apparently did not fully or correctly process the information in my letter to her, I am writing directly to you ex officio as the AMS Secretary. Could you please update the records, take my name out of the directory, and arrange for me to receive an individual subscription to the *Bulletin*. You can bill me for the subscription.

Thanks in advance,

Serge Lang

cc: John Ewing

MATH@MATH.YALE.EDU

P.H. Duesberg (ed.), AIDS: Virus- or Drug Induced?, 89–95, 1996.

Some mathematical considerations on HIV and AIDS

Mark Craddock
School of Mathematics, University of New South Wales, Sydney, Australia

Abstract

It is commonly accepted that HIV is both necessary and sufficient to cause the immunodeficiency and multiple diseases seen in patients diagnosed with AIDS. In other words it is accepted that HIV is *the* cause of AIDS. Upon this basis public health decisions in all Western countries regarding AIDS are made. However, many scientists now question the role of the virus (Root-Bernstein, 1993). Questions that have arisen about the virus include whether or not it is present in sufficient quantities to cause disease and whether or not AIDS is infectious. The former question has been applied to by new studies using the Polymerase Chain Reaction (PCR) technique that claim to detect very large quantities of virus in HIV+ patients at all stages of disease progression. I will examine these studies and show that they do not truly answer the criticisms that have been levelled. They in fact give rise to more questions than they answer. Predictions that one can make from them contradict the observed pattern of the disease. I will also argue that data based upon the so called Quantitative Competitive PCR need to be treated with caution.

Section 1 viral load

Studies of viral load in HIV+ patients have shown that most patients rarely have more than 1 in 10 000 to 1 in 1000 T cells in the bloodstream infected with HIV (Pantaleo *et al.*, 1993). Recently Embretson *et al.* claimed that there is 'massive covert' infection of T cells in lymph tissue with HIV (Embretson *et al.*, 1993). It is now widely accepted among HIV researchers that many more cells in lymph tissue are infected with HIV than in the blood stream. *A priori* this is extremely unlikely. Embretson *et al.* say that 1/4 of all T cells in the lymph nodes of HIV+ individuals are infected with HIV. Since T cells from the lymph nodes migrate through the body and into the blood stream in an essentially random fashion, then the viral load in blood and lymph nodes, as far as T cell infection is concerned, should be identical. The only way that this would not happen is if somehow HIV can alter the lymph node structure so that infected T cells are trapped, unable to move to other parts of the body. No plausible mechanism for this has ever been suggested. But there is another objection to Embretson *et al.*'s claims. If HIV is present and replicating in the quantities they claim, then how long would disease progression take? A simple mathematical model can be used to predict what should happen. It seems to imply that disease progression should be much faster than what is actually observed.

A mathematical model for HIV T cell infection

Let us denote the total number of T cells present in an HIV+ individual n days after infection by

$$T(n)$$

And the total number of infected cells by

$$T_i(n)$$

We are told that at any time the number of infected cells is $\frac{1}{4}$ of the total. Hence

$$T(n) = 4T_i(n)$$

Further we are told that 1% of the infected cells are actively producing HIV, and that these cells die. If we assume that the total T cell count in the absence of HIV is in equilibrium, then we must have

$$T(n+1) = T(n)$$

This is taken from the observation that

$$T(n+1) = T(n) - L + C$$

where L represents the number of T cells lost on a given day, and C the number created to replace those lost. This equilibrium implies that $L = C$, and so we have the original equation.

In reality we might expect some oscillation, but this model should be sufficient. The logic being used here is straightforward. It is claimed that HIV is actively killing T cells. Thus the deaths of T cells due to the action of HIV represents a perturbation of the equilibrium position. We have to determine what this perturbation is.

If we then include the infected cells that are expressing HIV, using the claim that these cells die we are led to

$$T(n+1) = T(n) - \tfrac{1}{100}T_i(n)$$

Thus the T cell count after n days should be the previous day's T cell count minus those T cells infected with HIV which have died. Note that the above equation, by our previous argument, contains both the T cells lost naturally and the usual replacement of the lost cells. If we are to have a net depletion of cells, then the above equation must hold (or perhaps a modified version of it: see below).

Using the claim that at any one time $\frac{1}{4}$ of the total cells are infected, we are led to

$$T(n+1) = T(n) - \tfrac{1}{400}T(n)$$

Or

$$T(n+1) = \tfrac{399}{400}T(n)$$

This is a simple difference equation, the solution of which is

$$T(n) = (\tfrac{399}{400})^n T(0)$$

Here $T(0)$ is the original number of cells infected. Of course this result assumes that $T(0) = 4T_i(0)$.

So we have a concrete realisation of the decline in the T cell count of an in HIV+ individual based on a simple model constructed from Embretson *et al.*'s data. What does this predict in practice? Well, if we set $n = 730$ (i.e. 2 years after infection), then we find that

$$T(730) = 0.16T(0)$$

In other words, this model predicts that the number of T cells in a HIV+ patient should have fallen by 84% in only 2 years. This is sufficient for an AIDS diagnosis in the United States, although not elsewhere if no opportunistic diseases have developed. We thus have the question: why does AIDS take so long to develop if HIV is the cause and if it is present in the quantities that Embretson *et al.* say it is?

Clearly the model taken here is a very simplistic one. There are a number of objections that can be made to it. In response to these we can consider possible modifications.

We may extend the time it takes the infected T cells to die, by some arbitrary amount. Then our equation for the total number of T cells would be

$$T(n+1) = T(n) - \tfrac{1}{100}Ti(n-k)$$

That is, the total number of T cells present is equal to the number present the previous day, minus 1% of the number of infected cells $k+1$ days ago. This modification to the model does not change the qualitative picture significantly unless one makes k very large. The reason for this is that the behaviour of $T(n)$ is determined by the roots of the polynomial

$$\lambda^{k+1} - \lambda^k - \tfrac{1}{400} = 0$$

This has one large root and k small roots. So for example if $k = 1$, then the roots are approximately .9975 and .0025. The behaviour of $T(n)$ is then for large n approximated by

$$(.9975)^n T(0)$$

Here we have assumed that $T(0)$ is approximately equal to $T(1)$. This behaviour is essentially the same as for the original model. If we take $k = 2$ then we have a root near .9975, and two near .05 and $-.05$. Again the behaviour is essentially the same as the original model. For all reasonable values of k, the situation should be described by the original model. By reasonable I mean values of k small compared to the time frame in which the disease is said to occur. And indeed, if HIV really is causing T cells to die by its replication process, one would expect this to occur on the same time scale that replication proces takes, i.e. a few days. Thus the first modification one can make to the analysis does not qualitatively change matters. The disease should still rapidly destroy the T cells in the lymph glands.

Of course one can make disease progression very slow by choosing k large enough, but this produces a logical problem. The purpose of the work of Embretson *et al.*, at least in part, was to answer a criticism of the HIV/AIDS hypothesis that HIV is not present in sufficient quantities in HIV+ individuals to cause disease. The objection was that if only 1 in 1000 T cells were infected with HIV, then the virus would take essentially forever to cause the disease. If one pushes the killing time back too far, then this problem returns

in another form. We do not want the time HIV takes to kill an infected cell *in vivo* to be essentially as long as the life time of an uninfected cell. The entire basis of our model is that the T cells being killed by HIV are in addition to the ones dying naturally, and so they are not replaced by the natural mechanisms for T cell replenishment. If HIV takes too long to kill a T cell then those T cells will be replaced as a matter of course because the body was in a sense expecting them to die around that time anyway, and so the replacement cell will be already waiting. The conclusion from this is that k should not be made too large.

Another alternative that presents itself is to assume that the body, in response to the infection, starts producing more T cells. This would lead to an equation of the form

$$T(n+1) = \tfrac{399}{400}T(n) + r(n)$$

$r(n)$ is a response function. It represents the number of additional cells the body is producing in response to the destruction of T cells caused by HIV. A natural question is: what form could $r(n)$ take? We certainly cannot make $r(n)$ too large initially because the body's response to the infection cannot be as large as the initial T cell count. Obviously it is untenable to argue that the body suddenly doubles the number of T cells in response to the action of HIV. The body can replace about 5% of its T cells every 2 days (Duesberg, 1989). So we would not expect the size of $r(n)$ to be much bigger than $.05T(0)$. With this point in mind, let us consider a few possibilities.

If we take

$$r(n) = C$$

where C is a constant (the body produces a limited constant response to the infection), then we have

$$T(n+1) = \tfrac{399}{400}T(n) + C$$

The solution is:

$$T(n) = (\tfrac{399}{400})^n T(0) + 400C$$

The equilibrium state for the T cell count is thus $400C$, whereas the equilibrium state for $T_i(n)$ is $100C$. (Letting $n \to \infty$ we see $T(n) \to 400C$).

The consequence of this is that if the body has a constant response to infection, then the virus will reach an equilibrium state, and the T cell count will fall no further. The precise equilibrium state depends upon the value of C. If C is too high, then AIDS will not develop. If it is too low, then the equilibrium state will be less than 14% of $T(0)$, and under the 1993 case definition the individual will have AIDS. This equilibrium state will still develop quickly. So a constant response to the infection will either see the infected individual develop AIDS quickly (C too small) or the patient will never have a T cell level $< 14\% T(0)$ (although opportunistics diseases may develop; this aspect is essentially unpredictable). The point to be understood is that with a constant response, the disease still progresses rapidly.

Thus the response function $r(n)$ cannot be a constant. It must decline over time. It is also clear that if $r(n)$ has polynomial decrease, then this response will not delay the onset of AIDS. For example if we take

$$r(n) = \frac{r(0)}{(1+n)}$$

we can solve the difference equation by iteration. We obtain:

$$T(n) = (\tfrac{399}{400})^n T(0) + r(0)\sum_{k=1}^{n} \frac{\lambda^{n-k}}{k}$$

Here $\lambda = \frac{399}{400}$. If we take $n = 730$ in the above series, and let $r(0) = .05T(0)$, we see that after 2 years, the T cell count will still be about 24% of its initial value. After 4 years we find that the number of T cells should have fallen to about 5% of its original value. This clearly is not sufficient to add much to the time taken for AIDS to develop. a linear decrease in the response function only yields a logarithmic benefit in the time it adds to disease progression. Obviously, if we have an even faster decay in the response function then it will add even less to the time for the disease to progress.

Another possibility we can try is a logarithmic decrease in the number of T cells the body produces to fight the infection. We would have something like

$$r(n) = \frac{r(0)}{(1+\log n)}$$

So our equation for $T(n)$ is

$$T(n+1) = (\tfrac{399}{400})T(n) + \frac{r(0)}{(1+\log n)}$$

This does not describe what happens in HIV+ people. For even small values of $r(0)$ this causes the T cell count to rise quite substantially. It can quickly double. ($T(100) \approx 2T(0)$ for $r(0) = .05T(0)$). A rapid rise in

the number of T cells in the body is not what we want our model to predict.

Another possible form for $r(n)$ is $r(0)\alpha^n$. α is some constant less than 1. Since we expect $r(0)$ to be smaller than $T(0)$, then if $\alpha < \frac{399}{400}$, little delay in the fall of the T cell count will eventuate. The equation is

$$T(n+1) = \tfrac{399}{400}T(n) + r(0)\alpha^n$$

The solution is

$$T(n) = (\tfrac{399}{400})^n T(0) + \frac{\lambda + r(0)}{\alpha}\alpha^n$$

$\lambda = \frac{399}{400}$. Noting that $r(0)$ is no larger than $.05T(0)$, then substituting $n = 730$ we see that the magnitude of the decline is essentially the same. If $\alpha = .95$ and $r(0) = .05T(0)$, then we find that $T(730)$ is still approximately $0.16T(0)$. Taking α smaller produces even less benefit.

If $\alpha = \frac{399}{400}$, then the solution is

$$T(n) = (\tfrac{399}{400})^n T(0) + r(0)n\lambda^{n-1}$$

Again $\lambda = \frac{399}{400}$. This response function actually seems to give the right time frame for the onset of AIDS. If we take $n = 2190$, i.e. 6 years, and let $r(0) = .05T(0)$, then we find $T(2190)$ to be approximately $.46T(0)$, which is in the correct region for the T cell count. After 10 years it predicts that the T cell count should have fallen to about 2% of the original value.

There is, however, a problem with this that leads me to reject this as a possibility. The T cell count is supposed to be steadily falling in HIV+ individuals. But if we take $n = 100$ for this model of the T cell count, we find $T(100)$ is approximately 79 times the initial count! Clearly this is untenable. It forces us to conclude that $r(0)$ must be very small. If we want the T cell count to be of the same magnitude as $T(0)$ after 100 days then $r(0)$ must be less than $.002T(0)$. This, however, kills the delay in the onset of AIDS. IF we take $r(0) = .002T(0)$, and use our expression for $T(n)$ we find that after 2 years the T cell count is about $.39T(0)$. After 3 years we have only 20% of the original number of T cells remaining. In other words we get nowhere near the claimed period of 10–12 years (and rising) that HIV supposedly takes to cause AIDS.

Clearly there are many possible response functions that can be postulated which might extend the time for AIDS development to the observed latency period, while at the same time matching the small fall in the number of T cells early in infection (i.e. a model that does not predict a drastic increase in $T(n)$ early on). But there remain many problems with the observation of Embretson *et al.* Even if the body does start mass producing T cells in response to the infection, there is a very important point that has been overlooked so far. It is untenable that the proportion of infected cells should remain constant at $\frac{1}{4}T(n)$ during the course of disease. We would expect the proportion of infected cells to increase exponentially as the virus replicates. We would also expect the proportion of infected cells actively producing new virus to increase as well. I will consider this next.

To model the increase in the proportion of infected cells, we use the same data as before and construct a pair of simultaneous difference equations,

$$T(n+1) = T(n) - \tfrac{1}{100}T_i(n) + r(n)$$

and

$$T_i(n) = (\tfrac{1}{4} + \beta(n))T(n)$$

Here the function β represents the increase in the proportion of infected cells as n increases. We clearly must have

$$0 \leq \beta(n) \leq \tfrac{3}{4}$$

The logic behind these equations is straightforward. The first represents the T cell count in total after n days. It says that the total is the previous day's total minus the cells killed by HIV + the response (additional cells) that the body produces because of the infection. Equation 2 represents the total number of infected cells. β is assumed to increase from 0 to $\frac{3}{4}$ as n increases. At this stage the growth of β has not been specified. So Equation 2 describes the rate of increase in the proportion of infected T cells.

It is here that the problems with the hypothesis that HIV takes ten years to cause AIDS become apparent. If HIV is actively replicating we would expect the number of cells infected to increase exponentially. This will drastically increase the speed of disease progression. Indeed this is what you would expect in a normal viral disease (the numbers will be different, though). A replicating virus should rapidly cause a disease if it causes a disease at all. Exponential increase in β, which is what would be expected for viral replication, implies that

$$\beta(n) = \tfrac{3}{4}(1 - \gamma^n)$$

where γ represents the rate at which the total proportion of infected cells is increasing.

If we assume for simplicity that $r(n) = 0$, then we find

$$T(n+1) = (1 - \tfrac{1}{100}(\tfrac{1}{4} + \tfrac{3}{4}(1 - \gamma^n))T(n)$$

We can easily work out the behaviour of $T(n)$ by iteration. We can pick different values of γ to describe possible rates of increase in the number of infected cells. Here are some possibilities.

1. $\gamma = .9975$

$$T(100) = .713T(0)$$

$$T(200) = .439T(0)$$

$$T(300) = .241T(0)$$

$$T(730) = .008T(0)$$

2. $\gamma = .99$

$$T(100) = .592T(0)$$

$$T(300) = .101T(0)$$

3. $\gamma = .9$

$$T(167) = .199T(0)$$

$$T(365) = .027T(0)$$

4. $\gamma = .85$

$$T(162) = .199T(0)$$

For all values of $\gamma \leq .99$ the value of $T(n)$ drops below 20% of its original value after between 160 and 175 days. So what this model predicts is in stark contrast to what is observed. If $\frac{1}{4}$ of the T cells in the lymph glands are infected with HIV initially, and the infection spreads so that the proportion of infected cells increases exponentially as would be expected for a replicating virus, then 80% of an infected person's T cells will be lost after 160–170 days. Addition of response functions such as we tried above will not significantly delay the decline in the number of T cells. If we try a logarithmic decline of the form employed above, then a problem develops. The actual behaviour of the disease depends crucially on the value of $r(0)$. If $r(0) = .15T(0)$, then after 10 years, the body has lost only 35% of its T cells. A slightly higher value sees the number of T cells rise substantially. After 600 days, there would be twice as many T cells as initially if we took $r(0) = .05T(0)$. This behaviour is not tenable either.

We also need to take into account the possibility that the number of actively replicating cells is greater than 1% of the infected cells. What we find is that the disease progression speeds up dramatically. If instead of 1% we have 3% replicating then we would have

$$T(n+1) = (1 - \tfrac{3}{100}(\tfrac{1}{4} + \tfrac{3}{4}(1 - \gamma^n)))T(n) + r(n)$$

Even with a logarithmic decline in the number of new cells created as response to the infection, this produces a much faster decline in T cell numbers. Taking

$$r(n) = \frac{.01T(0)}{(1 + \log n)}$$

then the number of T cells in the body drops to only 5% of its original level after 200 days, clearly a much faster rate of progression.

The conclusion that must be reached after this analysis, incomplete and rather simple though it is, is that it is very difficult to see why a large number of infected cells actively replicating takes so long to cause a disease. For all the plausible alternatives tried here, the disease progression is rapid. Indeed, if we acknowledge the possibility that the number of actively replicating viruses increases as the disease progresses, which is likely, then the killing of T cells should pick up speed as the disease progresses. A rigorous analysis would surely predict that it is simply impossible for a virus, actively replicating and present in large numbers, to take years to cause disease. Such a virus should cause disease quickly or not at all. So we must question the claim that HIV is present in large quantities at all stages of disease, active, and still takes 10–12 (or even more) years to produce AIDS in an HIV+ person.

Section 2 Quantitative Competitive PCR

In 1993 Piatak *et al.* also claimed to have employed a technique called Quantitative Competitive Polymerase Chain Reaction to detect very large quantities of HIV-1 RNA in blood plasma in HIV+ individuals. The basis of the technique is that in order to quantify the amount of HIV in a sample (the 'wild type HIV'), a control which differs from the wild type only by a small internal deletion is amplified competitively with the wild type by PCR. After a certain number of PCR cycles, the ratio of wild type to control can be calculated and knowledge of the initial amount of control present allows estimation of the total amount of wild type in the original sample. The method is based upon the assumption that the ratio of wild type to control remains a constant throughout the cycle. Justification for this is that the wild type and the control differ only

by a small internal deletion and so the amplification efficiency for both should be the same. Therefore the ratio should remain constant.

The replication of any sample in PCR is essentially a random event (Brock *et al.*, 1994). A strand of DNA can either replicate or not replicate. So we have a process that is governed by the binomial probability distribution. Piatak *et al.*'s paper is notable for a lack of error analysis. It is not my purpose here to provide one, but rather to suggest a method by which the problem of errors may be addressed. This method suggests that the QC-PCR technique is highly suspect. Results obtained from it should be treated with extreme caution.

Let the amount of wild type (which we will call X for convenience) initially present in the sample be N molecules. And let the amount of control (Y) present be M molecules. So the ratio initially is

$$\kappa = \frac{M}{N}$$

I wish to examine how this ratio can change after n PCR cycles. Let the ratio after n cycles be κ_n. Clearly

$$\kappa_n = \frac{D_n(Y)}{D_n(X)}$$

$D_n(X)$ and $D_n(Y)$ are the amount of derived product for X and Y respectively after n cycles. If the relative efficiency of PCR for X at the ith cycle is p_i and the relative efficiency for Y is q_i, then we have

$$D_n(X) = \prod_{i=1}^{n}(1+p_i)N$$

and

$$D_n(Y) = \prod_{i=1}^{n}(1+q_i)M$$

Note I have not assumed that $p_i = q_i$. The reason for this is that because we have a binomial probability distribution for PCR replication, we cannot say that the efficiencies at each cycle for X and Y are identical. In other words, it is not necessarily true that the same proportion of X and Y are replicated each time. To see this, consider an experiment when we have $N = 5$ and $M = 2$, with probability $\frac{1}{2}$ for replication of any strand of DNA. The possibilities for $D_1(Y)$ are 2, 3 and 4, with probabilities, $\frac{1}{4}$, $\frac{1}{2}$ and $\frac{1}{4}$ respectively. For $D_1(X)$ we could have either 5, 6, 7, 8, 9 or 10 strands of X type DNA, with probabilities $\frac{1}{32}$, $\frac{5}{32}$, $\frac{10}{32}$, $\frac{5}{32}$ and $\frac{1}{32}$ respectively. Clearly we would expect the ratio

$$\frac{D_1(Y)}{D_1(X)}$$

to differ from the original ratio. In fact, if X is present in greater quantities than Y originally then we might expect the ratio $D_n(Y)$ to $D_n(X)$ to decrease at each cycle. However, the precise behaviour which would occur is far from clear. I intend to analyse the various possibilities in later work.

The purpose at hand now is to estimate the value of κ_n relative to κ. This is not difficult:

$$\kappa_n = \frac{\prod_{i=1}^{n}(1+q_i)M}{\prod_{i=1}^{n}(1+p_i)N}$$

Taking the natural log of κ_n yields

$$\ln\kappa_n = \ln M + \ln\left(\prod_{i=1}^{n}(1+q_i)\right) - \ln N - \ln\left(\prod_{i=1}^{n}(1+p_i)\right)$$

Using the fact that the log of a product is the sum of the individual logs ($\ln ab = \ln a + \ln b$) we obtain

$$\ln\kappa_n = \ln\frac{M}{N} + \sum_{i=1}^{n}\ln\frac{(1+q_i)}{(1+p_i)}$$

Inverting we find that

$$\kappa_n = \kappa\exp\sum_{i=1}^{n}\ln\frac{(1+q_i)}{(1+p_i)}$$

The assumption used by Piatak *et al.* is that if the average replication efficiency of X and Y are the same, then the ratio of the derived products will be the same. We see here that $\kappa = \kappa_n$ if and only if $1+p_i = 1+q_i$ for each i. But we cannot assume this. The fact that the average replication efficiencies are equal, which itself is an unproven assumption, only means that

$$\sum_{i=1}^{n}(1+p_i) = \sum_{i=1}^{n}(1+q_i)$$

The example noted above indicates that even when the probability of replication for X and Y are identical at each cycle we cannot assume that the *actual* replication efficiencies, that is the proportion of the samples actually replicated, are identical at each cycle, simply that on average, the two efficiencies will be equal.

This formula for κ_n allows us to derive an expression for the error in the estimate for the size of X based upon our preexisting knowledge of the size of Y. If $\kappa = M/N$, then clearly $N = M/\kappa$. But our estimate

for N the amount of wild type (X) present is going to be M/κ_n. Thus if we write the true value of the size of X as $tr(X)$ and the estimate $es(X)$, then we easily see that we must have:

$$\frac{tr(X)}{es(X)} = \exp \sum_{i=1}^{n} \ln \frac{(1+q_i)}{(1+p_i)}$$

It is clear from this that small variations in the relative efficiencies of replication can lead to enormous variations in the estimate for the size of X. For example, if we assume that $p_i = p$ for all i and that $q_i = q$ for all i (conditions unlikely to be met in practice), then our estimate for the error reduces to

$$\frac{tr(X)}{es(X)} = \left(\frac{1+q}{1+p}\right)^n$$

Piatak *et al.* used 45 PCR cycles. If we let $(1+q)/(1+p) = .909$, so the replication of the wild type overall happens to be 10% more efficient than that of the control, then we will overestimate the true size of the wild type by a factor of 72. If the replication efficiency in a particular process is 20% more efficient for the wild type then we overestimate the amount present by a factor of 3600. It is, of course, possible that we could underestimate the true value enormously as well. However, if the wild type is originally present in excess of the control, then it seems likely, although it is not clear without detailed calculations of the possible outcomes, that the replication of the wild type would tend to be slightly more efficient. This would mean that typically we would be overestimating our sample size. The reason that one might expect the wild type replication to be slightly more efficient is that if the replication probabilities (note that the efficiency of replication is not identical to the actual efficiency at a given cycle) of X and Y are the same at each cycle and there is more of X than Y, then the probability that the amount of X increases in that particular cycle is greater than the probability that the size of Y increases. This suggests that the most likely outcome at each cycle would be a decrease in the ratio of the size of Y to the size of X. This needs to be checked by detailed calculations which I have not attempted here. Regardless of this, it is clear that a great deal more work on the actual efficiencies of the PCR process are necessary before results obtained through QC-PCR can be treated with confidence.

References

Brock, T.D., M.T. Madigan, J.M. Martinko & J. Parker, 1994. Biology of Microorganisms. Prentice Hall International Editions.

Duesberg, P.H., 1989. Human immunodeficiency virus and acquired immunodeficiency syndrome: Correlation but not causation. PNAS U.S.A. 86: 755–764.

Embretson, J., M. Zupancic, J.L. Ribas, A. Burke, P. Racz, K. Tenner-Racz & A.T. Haase, 1993. Massive covert in fection of helper T lymphocytes and macrophages by HIV during the incubation period for AIDS. Nature 362: 359–362.

Pantaleo, G., C. Graziosi, J.F. Demarest, L. Batini, M. Montroni, C.H. Fox, J.M. Orenstein, D.P. Kotter & A.S. Fauci, 1993. HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease. Nature 362: 355–358.

Piatak, M. Jr., M.S. Saag, S.J. Clark, J.C. Kappes, K.C. Luk, H. Halen, G.M. Shaw & J.D. Lifson, 1993. High levels of HIV-1 in plasma during all stages of infection determined by competitive PCR. Science 259: 1749–1754.

Root-Bernstein, R., 1993. Rethinking AIDS: The tragic cost of premature consensus. Free Press.

Yale University *New Haven, Connecticut 06520-8283*

5 January 1998

DEPARTMENT OF MATHEMATICS
10 Hillhouse Avenue
P.O. Box 208283

Telephone: (203) 432-4172
Fax: (203) 432-7316

Susan Friedlander
Associate Editor AMS *Notices*, and Editor of The Forum
Math Dept University of Illinois at Chicago
Chicago Ill 60607-7045

Dear Susan,

I am submitting the enclosed piece:

THE KIRSCHNER ARTICLE AND HIV:
SCIENTIFIC AND JOURNALISTIC (IR)RESPONSIBILITIES

for publication as a Forum piece in the AMS *Notices*. I have kept Jaffe, Ewing and Jackson abreast of developments about HIV and the Kirschner article through the past two years, without any action on the part of the AMS to inform the membership of these developments. So I am now doing so myself.

Because the *Notices* have not informed readers of the massive documentation I provided, to meet my responsibilities I have to provide some of this documentation myself. Since the Kirschner article was 12 pages long (as long as any article I know in the *Notices*), and was written with the "support" of the editors, it deserves a substantial analysis. The editors did not make clear if the Kirschner paper was refereed, beyond getting "helpful comments and support" from the editors. Since Kirschner's article was an echo of the famous Ho & Shaw articles (published in *Nature*), I also had to comment on the Ho & Shaw articles.

Many thanks for your attention.

Best regards,

Serge Lang

cc: Arthur Jaffe (AMS President), John Ewing (Executive Director), Allyn Jackson (Staff Writer), Robert Fossum (Secretary), Hugo Rossi (ex editor in chief of the *Notices*), Anthony Knapp (current editor in chief of the *Notices*), Susan Landau (Associate editor of the *Notices*), Arthur Gottlieb, Mark Craddock, Peter Duesberg, Tom von Foerster (Springer Verlag)

MATH@MATH.YALE.EDU

THE KIRSCHNER ARTICLE AND HIV: SCIENTIFIC AND JOURNALISTIC (IR)RESPONSIBILITIES

by Serge Lang
5 January 1998

Part One

Editorial and scientific responsibility

In February 1996, the AMS *Notices* published a 12-page article "Using Mathematics to Understand HIV Immune Dynamics" by Denise Kirschner (pp. 191-202). This paper dealt with the mathematical modeling of HIV infection. Kirschner explicitly thanked "the editors for helpful comments and support in the writing of this article." For six years, I have been involved in gathering information about an extraordinary situation concerning HIV. I have a file more than an inch thick on the subject. The bottom line is that the hypothesis that HIV is a harmless virus is compatible with all the evidence I have studied; that purportedly scientific papers which I have followed up on HIV claiming otherwise are subject to very severe criticisms, pointing to severe faults; and that there is an ongoing phenomenon of mass misinformation, spread by NIH (especially in publications of the Centers for Disease Control - CDC), and spread in the scientific journals such as *Nature* and *Science* as well as in the press at large. I even published two articles on the subject in the *Yale Scientific* (Fall 1994, Winter 1995), reproduced updated in the Kluwer collection (see footnote 1) (and subsequently reproduced in my book *Challenges*, see below). I was therefore shocked to see the *Notices* spreading the orthodoxy uncritically.

In light of what I knew about the HIV situation, I immediately phoned Hugo Rossi, editor in chief of the *Notices*, and I sent him my HIV documentation. The documentation included:

- my *Yale Scientific* articles;
- articles by the mathematician Mark Craddock (School of Mathematics, University of New South Wales, Sydney, Australia), specifically directed at the use or misuse of mathematics in connection with HIV infection.[1]
- letters to and from government officials, such as Harold Jaffe, Director of the CDC;
- files containing critical analyses of published articles which received wide attention in the press (scientific and otherwise, including the *New York Times*).
- Subsequently these documents were complemented by my *Journalistic Suppression and Manipulation File* (1995-1996), and the File entitled: *Throwing Math and Statistics at People* (Summer 1997).

On the phone I suggested to Rossi that if the publication of Kirschner's article was to be taken seriously, it would involve the *Notices* in a morass for which the AMS was not equipped

---

[1]Mark Craddock, in the Kluwer collection *AIDS: Virus or Drug Induced?*, Peter H. Duesberg editor, Kluwer Academic Publishers, 1996:
"Some mathematical considerations on HIV and AIDS" pp. 89-95;
"A critical appraisal of the Vancouver men's study *Does it refute the drugs/AIDS hypothesis*? pp. 105-110;
"Science by Press Conference" pp. 127-130.
My articles are:
"HIV and AIDS: Have we been misled? Questions of scientific and journalistic responsibility" pp. 271-295;
"To fund or not to fund, that is the question: proposed experiments on the drug-AIDS hypothesis" pp. 297-307.

institutionally. To minimize the time wasted by everybody, I suggested to him that after he processed the documentation, he might write his own editorial statement to the effect that when he arranged for the publication of the Kirschner article, he did not know about the simmering controversy on HIV. Given the additional information, he could ask readers simply to disregard the published article, which readers were not in a position to evaluate without a substantial amount of additional material. Providing this material might result in an open-ended controversy in the *Notices*. Just for a start, the *Notices* might solicit an article by Mark Craddock analyzing the Kirschner article. Rossi answered me by mail without even waiting to receive the material, and he wrote that no matter what this material contained, he would not make a "Stalinesque confession" (his interpretation of what I was asking). I did not read his letter further, and I sent it to Cathleen Morawetz, president of the AMS, together with my resignation from the AMS, because I wanted no part of the responsibility as a member of the AMS to deal with the situation the editors had created with the publication of the Kirschner article, and with Rossi's subsequent position.

Public relations. There is some evidence that the Kirschner article was not even meant to be read, but was merely a public relations gesture using HIV combined with math to emphasize the importance of "relevance", "applications", and "social responsibility". Indeed, when the AMS President wrote me back, she suggested that I write a letter to the editors for publication, and she added: "I would recommend a short letter - it takes less time to write and is much more likely to be read - since limited time and space is a problem for us all." However, the very extensive space occupied by the 12 pages of the Kirschner article, written with the "helpful comments and support" of the editors, did not present a problem to them, nor apparently to the AMS president. Of course, I refused to engage in the superficial dealings the AMS president was suggesting. Barring a possibly short statement by the editor as I was requesting, what I saw as my responsibility as an AMS member would be to insure publication of an extensive documented evaluation of the type Mark Craddock provided in his articles. I was neither able nor did I have the time available to do it myself, but if the AMS higher ups were serious about informing the readership properly, they could have solicited Mark Craddock as I suggested.

The Landau editorial. Subsequently, in February 1997, the *Notices* published an editorial by Susan Landau (Associate Editor) entitled "Mathematicians and Social Responsibility". The editorial is presumptuous, and Landau subsequently evaded the very responsibilities she invoked in the big-time rhetoric of her editorial. Among other things, Landau asserts: "Our responsibilities extend to preparing the biology students for the work they will actually do (rather than giving them a standard calculus course with the odd population biology example thrown in)." First, I object to her put down of the "standard calculus course with the odd population biology example thrown in". The population biology example is not "odd". Principally, what does her admonition mean in the specific case of HIV and AIDS, in light of the criticisms which have been leveled at the orthodox line on HIV? I sent her my HIV file. What would the *Notices* do about the Kirschner article? What would she do? She wrote me on 12 September 1997: "For the last several months I have been receiving mail from you regarding HIV and AIDS. Despite being an Associate Editor of the *Notices*, I am not really following these issues, and I would like to be removed from your mailing list." So how do "our responsibilities" apply to her, especially since she is an Associate Editor of the *Notices* and the editors provided "helpful comments and support in the writing" of Kirschner's article? Despite having shared the responsibility to publish the Kirschner article, she claims that she is "not really following these issues" and she rejects information about them. Thus *de facto* she is evading her responsibilities in at least two respects: those invoked in her editorial, and those arising *ex officio* as an Associate Editor of the *Notices*. Some letters to the editor paid lip service to her editorial, e.g. in April and May 1997. The authors of these letters were apparently unaware of the HIV pathogeny controversy, the problems with the original Kirschner article, and the post-publication abdication of responsibility by the editors of the *Notices*. I shall return to questions about the Landau editorial at the end of Part Two.

A letter from Arthur Gottlieb, rethinking the problem. Certain events induced me to reconsider the importance of the Kirschner article, and to follow up more actively on the AMS involvement. On 16 May 1997, Arthur Gottlieb M.D., Chair of the Microbiology/Immunology Department at Tulane

University, wrote me to ask for my professional opinion concerning the Craddock articles analyzing certain mathematical defects in published and famous articles on HIV/AIDS (see Part Two below, and especially footnotes 4 and 7). I had corresponded previously with Gottlieb, because he had heard of me through the grapevine, and had sent me a letter which he had written to the editors of the *New York Times*, but which was not published. Of course, I circulated his letter to my cc list. I strongly supported Craddock's analyses which concerned especially a "model" by Ho and Shaw, who are two famous HIV researchers. For example, a year ago, Ho was named TIME Man of the Year. Gottlieb wrote me:

> I met Mark [Craddock] on a visit in Sydney hast year and have been particularly interested in his views of the Ho/Shaw model of HIV pathogenesis which has now acquired the status of a law of nature in the AIDS-HIV community...
>
> I think there is more than a matter of scientific debate here. My experience has been that when models of this type are presented to broad biological-medical audiences, the math is rarely critically analyzed -- most people are content with the declaration that a biostatistician has come up with the particular equations that are said to describe the situation. It is the rare individual, indeed, who would raise a meaningful question in such a context. The Ho/Shaw model is now a widely accepted paradigm for HIV pathogenesis. Moreover, it is being used as a basis for therapeutic guidelines in respect of HIV ("treat early and hard"). That, I think, is of concern, if indeed there are serious questions about the validity of the model. It would be good to have your views on this.

Two years ago, at the time of Kirschner's article, it did not seem to me worth while getting further involved setting up the AMS. However, since a person as solidly placed as Gottlieb in the medical establishment has now raised questions which involve joint responsibilities with mathematicians, I revised my estimate of the importance of dealing more thoroughly with an evaluation of various uses of "mathematics" in connection with HIV. I am now dealing with the AMS as an outsider, but the higher ups at the AMS had, and still have, the responsibility to follow up on Kirschner's article, and they have the responsibility to take into account articles such as those by Craddock, and other articles which are beginning to appear (cf. footnote 7 below). The evidence so far is that they won't do it without some outside intervention. For two years I have kept some higher ups in the AMS abreast of the situation and my HIV file, with no visible result. In particular, the *Notices* Staff Writer Allyn Jackson did not report the events surrounding my resignation, nor did she report the documentation which I provided on HIV.

My book *Challenges*. In November 1997, my book *Challenges* appeared, published by Springer Verlag. The book contains an extensive chapter (114 pages) on HIV. Beyond my two articles, the chapter is based on my various files on HIV. The existence of this book now makes it easier to disseminate information about HIV, and thus also contributed to my decision finally to write a piece for publication in the *Notices*. Readers will note that Dr. Gottlieb provided a one page statement at the end of the HIV chapter, p. 714, where he says about the controversy over HIV pathogeny:

> ...In this chapter, Prof. Serge Lang has well documented the basis of this controversy, and has provided a sobering picture for the reader of the polity of thinking that has characterized this field...Models of how HIV and cells of the immune system replicate, which have not yet sustained the rigor of thorough scientific discussion and critique at both the biological and mathematical level, are accepted as if they were laws of nature...
>
> A review of the scenarios which Lang has painted should give the thoughtful reader pause as well as some insight into how doctrinaire thinking can develop and be perpetuated.

In a piece addressed to the AMS *Notices*, it is appropriate to go into certain technicalities. In a second part, I shall deal more specifically with mathematical aspect of the HIV problem, and the Kirschner article in particular. Be it noted that I sent my HIV file and various criticisms (by Craddock, Gottlieb, and me) to Kirschner in August 1997, but I have had no reply from her.

Part Two

Specific Mathematical Criticisms

Craddock's articles. I have distributed widely the Craddock article on Ho & Shaw's work: "HIV: Science by Press Conference" (cf. footnote 1). Craddock provides 3 pages of detailed documentation for his conclusion: "...this new work is about as convincing as a giraffe trying to sneak into a polar bears only picnic by wearing sunglasses (as Ben Elton might say)."[2] The mathematics Craddock analyzes here are at the level of freshman calculus. In the other article "Some mathematical considerations on HIV and AIDS", the level is even more elementary. Craddock writes in a very convincing way, by using unpretentious language and making his objections very specific about very concrete items. I have found his articles so well formulated that I have asked various scientists to take them into consideration, without success. To give an unqualified endorsement of Craddock I would have to read the original papers by Ho & Shaw, which I have not done, and am not really competent to do, lacking training in biology. But I don't need any further competence to recognize the legitimacy of Craddock's criticisms. His specific, documented criticisms include:

- Objections about the mathematical modeling and certain assumptions, not made explicit, and not justified by empirical evidence; unjustified assumptions unrelated to the empirical data.
- Questions about the meaning or significance of the data used by Ho and Shaw.
- Lack of control groups, in two contexts p. 129:
  (a) "Neither group [Ho and Shaw] compared the rate of T4 cells generated in the HIV positive patients with HIV negative controls!"[3]
  (b) "It must surely be admitted that the system they are trying to study, namely the interaction of HIV with T4 cells, might behave substantially differently in people who are not being pumped full of new drugs, in addition to 'antiretrovirals' like Zidovudine?"[4]
- Lack of warning that certain purportedly therapeutic drugs have toxic effects.
- Lack of justification for attributing the production (rather than destruction!) of T4 cells to HIV.[5]

Finally, Craddock points out that if one formulates the model correctly, then what it predicts is not the same as what Ho & Shaw say it predicts.[6] His remarks are in line with the implausibility that it takes ten years for a virus with generation time of 1 to 2 days to achieve effects causing death.

---

[2]The work under review is: Ho et al. *Nature* Vol. 373, 12 Jan 1995 pp. 123-126; and Wei et al. *ibid* pp. 117-122

[3]He goes on: "Both groups assert that in HIV infected individuals, up to 5% of the circulating T4 cells are replaced every 2 days. This information is hardly new, Peter Duesberg says something similar in a paper in the Proceedings of the National Academy of Sciences from 1989. Except he states that 5% of the bodies T cells will be replaced every 2 days, in healthy people."

[4]This is similar to the reason Arthur Gottlieb wrote to me in his letter of 16 May 1997: "I might say that I have been skeptical of the validity of the Ho/Shaw model for several reasons, but principally because it is based on observations in subjects who were therapeutically perturbed by use of a protease inhibitor."

[5]As Craddock writes: "The logic here is remarkable. It is claimed that HIV sends the immune system into overdrive as measured by a supposedly accelerated production of T4 cells. Between 100 million and 2 billion are produced each day in the patients that were studied."

[6]As he writes: "When correctly formulated (Craddock, Ibid), what emerges is stunning. Ho et al.'s observations combined with their simple model for T cells and virus, predict that the T cell count should reach an equilibrium state quickly. Meaning exponentially fast...When you add terms to the equation to describe the effects of Virus (inexplicably, they do not include the effects of the virus on the T-cell population in their model. I thought HIV was supposed to be killing these cells somehow), then include the expression for the amount of virus that they give on p. 124, you get a picture of 'HIV disease' that bears no relation to what happens in actual patients. AIDS should develop in days or weeks. There is no possible way it can take ten years. This emerges from Ho et al's own model."

The responsibility for confronting these criticisms lies with the authors he criticizes, and with the relevant scientific journals (such as *Nature, Science,* or *The Lancet*) for publishing both the criticisms and whatever replies the authors make. If they make none, scientific and journalistic standards require that readers of these journals be so informed. However, the scientific journals have actually failed in their responsibility. They have skewed and prejudiced scientific discourse, and obstructed the usual self-correcting mechanisms of science. For extensive documentation of these assertions, cf. my book *Challenges*.

I see no reason to deviate from the standards that scientific discourse take place openly in journals, and that the scientists whose works are questioned or criticized be held responsible for answering the questions and criticisms. In particular, it would be entirely appropriate for Ho and Shaw to be confronted directly with the Craddock criticisms, and for them to answer these criticisms, whether to acknowledge their validity, or to counter them if Ho & Shaw are able to do so. Barring specific justified rebuttals to Craddock's specific criticisms, we are entitled to regard these criticisms as valid, and they invalidate the Ho and Shaw papers which Craddock analyzes.[7]

The *Notices* article by Denise Kirschner. The Kirschner article in the *Notices* is an echo of Ho and Shaw. The mathematics in her article are somewhat more involved than the mathematics in the Ho & Shaw articles (her differential equations are more complicated). I have not checked them. But even if correct, to what extent is her use of mathematics useful to understand whether HIV is pathogenic or not, and if so, how? I fully share Craddock's conception of science: "Science is about making observations and trying to fit them into a theoretical framework. Having the theoretical framework allows us to make predictions about phenomena that we can then test. HIV 'science' long ago set off on a different path." Kirschner asserts p. 195: "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." So the paper itself does not contain "actual values". The way the paper is written does not fit the definition of science recalled above, and does not inspire my confidence. I shall give a few concrete reasons why not.

- Kirschner repeats one orthodox line (p. 191) that "HIV is the virus which causes AIDS (Acquired Immune Deficiency Syndrome)" without any acknowledgement that in the Centers for Disease Control list of 29 diseases defining AIDS in the presence of HIV, about 40% of these diseases do not involve immunodeficiency, and that a low T-cell count is only one of the 29 diseases. The assumption that "HIV causes AIDS" is made without justification and without reference to a scientific paper justifying this

---

[7](a) Some criticisms of the Ho and Shaw articles already appeared in letters to the editor in *Nature* (375, 18 May 1995). One of these letters, by Bukrinsky et al. (pp. 195-196) stated: "A definitive answer awaits accurate estimates of the turnover and half-life of both proliferating and peripheral CD4+ T cells in healthy individuals, normative data for which the immunological community strangely lacks a robust appraisal." In plain English, Bukrinsky et al. make the same point already mentioned, that no control groups were used to compare the behavior of CD4+ T-cells in individuals who are healthy, sick, HIV positive, or HIV negative, in various combinations. Ho and Shaw answered the Bukrinsky et al. comment quoted above as follows: "...we do not understand their logic of comparing our calculated CD45 lymphocyte turnover rates with previous estimates for normal peripheral blood mononuclear cells..." But the logic is clear to me. In plain English, the fact that turnover of T-cells is the same in Ho & Shaw's CD 45 lymphocytes as in previous estimates for peripheral blood as in mononuclear cells constitutes clear evidence that HIV is neither the cause of T-cell destruction, nor of harm to the immune system (which has been claimed). I wrote to Bukrinsky on 18 July 1997 to ask him to straighten me out if I misunderstood the situation. He did not answer my letter.

(b) Another letter by Ascher et al. (p. 196) stated: "...But the central paradox of AIDS pathogenesis remains...there is about 100-1,000-fold more cell death than can be accounted for by the observed rate of virus production[5]. It is a murder scene with far more bodies than bullets."

(c) There is a detailed critique of Wei et al. and Ho et al. in an article by Peter Duesberg and Harvey Bialy, "Responding to 'Duesberg and the new view of HIV'", Kluwer collection pp. 115-119.

(d) Further critiques of the mathematical analysis of Ho and Shaw (Wei et al.) have recently begun to appear. See Z. Grossman and R. Herberman, *Nature Medicine* Vol. 3 (1997) pp. 486-490; and G. Pantaleo, *ibid.* pp. 483-486. Cf. also the accompanying editorial: "Two commentaries challenge current thinking in HIV research and treatment."

assumption. After six years of looking into the HIV pathogeny question, I have not learned of the existence of any such paper.

- She repeats the orthodox line (p. 193): "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...Clearly, there is a necessity for treatment of HIV infection." Here she relies unquestioningly on the orthodox line, which I and a number of other scientists do not automatically accept. There is evidence going against all three assertions: $CD4^+$ T cells being a target of HIV, a devastating impact being due to HIV, and the necessity for treatment of HIV infection. Aside from the point raised in footnote 7, what about T-cells which live in the presence of HIV? As some scientists including Peter Duesberg have pointed out, HIV is mass produced in immortal T-cells, both by scientists and drug companies. Her only qualification is: "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." However, barring further evidence to the contrary, the way she builds up her proposed model fits Craddock's characterization of "arcane speculations about molecular interactions".

- Several of Craddock's criticisms of the Ho & Shaw article are applicable to her article to the extent the following objections are valid. For example, she writes: "...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, mu_T, to be values between .5 and 1.0." How justified is this choice? Her reference [10] is not even an original scientific paper but is partly a laudatory review in *Science* of the Wei et al. and Ho et al. articles, editorializing about what is seen as their implications.[8] Is her model a priori irrelevant because she did not take into account certain essential factors? For instance, she gives no evidence that she took control groups into account. The half life of T-cells for infected or uninfected people is apparently the same. (Cf. footnote 3.) How did she take into account the presence of drugs or, as Arthur Gottlieb has brought up, protease inhibitors? (Cf. footnote 4.) She does state: "To include AZT chemotherapy in the model, it is necessary to mimic the effects of the drug which serves to reduce viral infectivity..." But there is no evidence that she even considered possible toxic effects of AZT, and she only mentions a parameter which "is multiplied by a function which is 'off' outside the treatment period and 'on' during the treatment period." It's not clear that this kind of "model" represents what actually goes on. As far as I can tell, we are witnessing here a cumulative chain of defective science, uncritically invoking defective results by others, and propagating misinformation combined with an irrelevant mathematical formalism.

- In addition, am I reading correctly that the Kirschner model is in direct contradiction with the Ho & Shaw model, and also with empirical evidence for production rather than destruction of T-cells? Indeed, as we have recalled above, the Ho & Shaw model leads to "accelerated production of T4 cells", and an exponential approach to equilibrium. (Cf. footnotes 5 and 6.) So what's going on?

Funding. I note that the NSF supported Kirschner's work. As far as I am concerned, publication of her article in the *Notices* came at a time when money is more than tight for mathematics. Higher ups in the AMS including editors of journals want to make "mathematics" appear relevant to society at large, so that mathematicians get more support from the government. But invoking relevance is not a license for funding and disseminating uncritically certain points of view reinforcing the orthodoxy. To the extent that substantial criticisms of the Kirschner article are valid, including the possibility that it is worthless even as an "arcane speculation", the NSF funding of the 12-page Kirschner article is questionable; and its uncritical publication by the AMS, giving a mathematical aura to HIV and an applied aura to mathematics, is journalistically and scientifically irresponsible without a critical follow up, which the editors or AMS higher ups so far have refused to provide.

Math and Medicine. I see no evidence that her paper fits her conclusion p. 201: "Through this simple example, I hope it is also clear that there can and should be a role for mathematics in medicine." Even though her paper might be defective, I am not questioning the big time generality whether there is a

---

[8]Her reference [10] is to J. M. Coffin, "HIV populations dynamics in vivo: Implications for genetic variation, pathogenesis and therapy," *Science* **267** (1995) pp. 483-489.

role for mathematics in medicine. However, it is NOT clear to me that her paper is a positive contribution to medicine. This remains to be seen, after competent persons (including Craddock and Gottlieb) have scrutinized it. Furthermore, so far, the "model" she proposes is disjoint from experimental testing or evidence, and from medicine. It is just presented as an independent entity, and I don't see any indication how it might be used clinically, although she writes: "Now that we have a model that we believe mimics a clinical picture, we can use the model to incorporate treatment strategies." Thus she substitutes beliefs ("we believe") for scientific experimental verification. The conclusions she draws are only based on the theoretical model, not actual practice on patients, and her model is biased in favor of the orthodox view. I hope someone such as Craddock or Gottlieb will be willing to give a more extensive analysis, which I am not able to give at the moment.

In summer 1997 I sent a copy of Kirschner's article to Arthur Gottlieb, and he answered: "I have put the Kirschner article on my list of things to do and will read it with a critical eye. Cursory review of same indicates no reference to functional CD4+ cells as a parameter to be considered. That is probably a fatal flaw, as every CD4+cell is not equal to every other CD4+ cell." However, he also wrote me that he would be very busy with his course last fall, and I have not heard from him since the end of last summer.

Kirschner also states: "The biggest obstacle 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." With such a sentence, she bypasses the problems raised by Mark Craddock's criticisms of the Ho & Shaw articles, and the problems which exist with her own article as listed above, as well as the problems with her references. Obstacles to collaboration are not totally ordered, and there may not be a biggest one; but as far as I am concerned, a big obstacle facing collaboration is that criticisms of existing articles are ignored by authors, ignored by editors such as those of the AMS *Notices*, and suppressed by journals such as *Nature*, *Science*, and the *Lancet*. Cf. for instance the exchange between Duesberg and *Nature* editor John Maddox in the Kluwer collection, pp. 111-125. For further documentation, cf. my book *Challenges*.

The existence of various articles on mathematical modeling, especially in connection with HIV, raises further questions about the use of mathematical modeling in biology generally. To what extent has such modeling been used scientifically, resp. medically? To what extent has it just amounted to throwing mathematics and statistics at people, thereby producing "mystification and intimidation" (as Koblitz once characterized this activity by some practitioners of some political science), but making no genuine scientific or medical contribution?

Da Capo

Returning to the issue of responsibility raised in Susan Landau's editorial: when mathematicians teach calculus, or biologists teach the use of mathematical modeling, to what extent do teachers warn students about passing off "mathematical modeling" as science, when a purported "model" is not based on empirical data, and is proposed (let alone accepted) quite independently of empirical verification? How does one document the warnings? Both the Ho & Shaw and Kirschner articles are based on assumptions which are not rooted in empirical evidence. Does one include a warning about making such assumptions explicit when teaching calculus and biology? What are the implications of holding up resp. not holding up in the classroom the Ho & Shaw and Kirschner articles as models of so-called mathematical modeling not justified by empirical conditions? *De facto* can we, do we, shall we engage a calculus class in a discussion of the Ho & Shaw and Kirschner articles (among others), bringing up documentation to the attention of the class to justify the criticisms I and others have made? What would happen if we did so? The social, academic and practical forces against doing so are multiple, and obviously very strong. For an even broader context in which such questions can be raised, including the context of social sciences, cf. my book *Challenges*.

Notices of the AMS
Volume 46, Number 4 (1999): 458

Response to the Steele Prize

Serge Lang

I thank the Council of the AMS and the Selection Committee for the Steele Prize, which I accept. It is of course rewarding to find one's work appreciated by people such as those on the Selection Committee.

At the same time, I am very uncomfortable with the situation, because I resigned from the AMS in early 1996, after nearly half a century's membership. On the one hand, I am now uncomfortable with spoiling what could have been an unmitigated happy moment, and on the other hand, I do not want this moment to obscure important events which have occurred in the last two to three years, affecting my relationship with the AMS.

Indeed, the *Notices*, February 1996, published a 12-page article "Using Mathematics to Understand HIV Immune Dynamics" by Denise Kirschner, pp. 191–202. Having had occasion to be well informed on the issue of HIV pathogenesis and of strong objections (not only by me) against certain abuses of mathematical modeling in connection with HIV, I communicated an extensive file of documentation to AMS higher-ups at the time concerning the hypothesis that HIV is not pathogenic. This hypothesis of course is incompatible with the official orthodoxy. Readers can evaluate some of my documentation, published in a 114-page chapter of my recent book, *Challenges*.

I resigned from the AMS because of the way my documentation was handled in 1996, principally by the *Notices* editor, Hugo Rossi, in connection with the Kirschner article, and the way official responsibilities were met by those involved. Subsequently, about two years later on 5 January 1998, I submitted a 7-page piece for publication in the "Forum" of the *Notices*. The piece explained:

- encouraging events (see for example p. 714 of *Challenges*) which led me to submit a piece for publication in the *Notices*, rather than disengaging as I had done up to that point;
- my detailed objections to the responses which I got from the AMS officials at the time in 1996;
- direct criticisms of the Kirschner piece per se.

I regard all three as important. Although the "Forum" editor, Susan Friedlander, told me she would have accepted the piece, it was rejected for publication by the 1998 editor-in-chief, Tony Knapp. Thus members of the AMS at large have not been informed through official channels of my resignation, nor of the very serious context of continued problems after the resignation, including the rejection of my "Forum" piece. I tried to inform some members by a direct mailing to 160 chairs of departments in January 1998, but such a mailing can reach only few among the total membership (nearly 30,000).

Torn in various directions, sadly but firmly, I do not want my accepting the Steele Prize to further obscure the history of my recent dealings with the AMS.