UNITED NATIONS EDUCATIONAL, SCIENTIFIC AND CULTURAL ORGANIZATION
INTERNATIONAL CENTRE FOR THEORETICAL PHYSICS
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SMR.780 - 17

FOURTH AUTUMN COURSE ON MATHEMATICAL ECOLOGY

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"Immunology and AIDS"

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These are preliminary lecture notes, intended only for distribution to participants.

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Immunology and AIDS

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parts of work in conjunction with the following individuals:

Alan Perelson, Glenn Webb, Suzanne Lenhart, Ramit Mehr,.

Steve Serbin, Rob de Boer.

OUTLINE

* Introduction to Immune System Modeling

* History of Immune Models (specific to HIV)

* Review of Previous and Present Work (specific to HIV)

Clinical Studies

* The current distribution of $CD4^+$ T-Lymphocyte Counts amoung Adults in the UA with HIV. (Division of Preventative Medicine, Walter Reed Army Institute of Research, Washington, D.C., 1989)

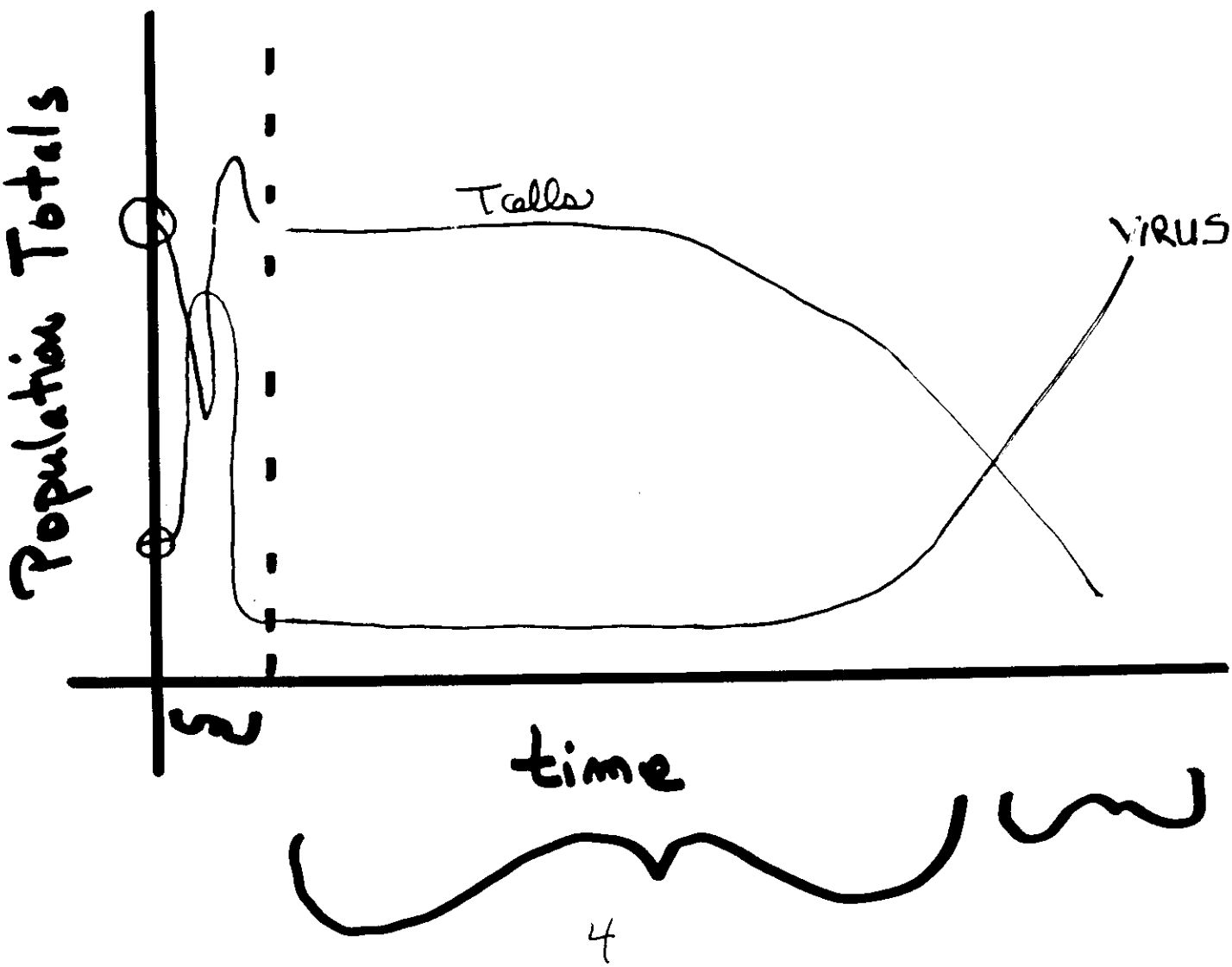
* Increased Viral Burden and Cytopathicity Correlate Temporally with $CD4^+$ T-Lymphocyte Decline and Clinical Progression of HIV infecteds. (Conner, Mohri, Cao and Ho: Journal of Virology, 1993)

* Quantiation of HIV-1 Infection Kinetics. (Dimitrov, Willey, Sato, Chang, Blumenthal, and Martin: Journal of Virology, 1993)

* Use to think there were low levels of free virus during clinical latency, but now known that there are $10^4/mm^3$. But, only about $\frac{1}{10{,}000}$ are infectious.

STAGES OF DISEASE PROGRESSION

- Initial infection (innoculum)
- Initial transient (battle)
- Latency period (immune control)
- Immune Crash (AIDS)



IMMUNOLOGY DEFINITIONS

- Cell-the unit of life
- DNA-blueprint (usually precursor to RNA)
- RNA-precursor to protein
- Virus-a group of micro-organisms which must enter a host cell to proliferate, since they lack the biochemical machinery to manufacture proteins. Some viruses also lack the enzymes required for DNA replication. They are composed mostly of a protein outercoat, and a capsule of DNA, plus other enzymes.
- Retrovirus-viruses which carry RNA rather than DNA, and need to turn the RNA to DNA before the host can incorporate and replicate.

GOALS

(•) Develop a Model of the immune system with HIV

(•) Insure it exhibits the types of qualitative clinical behavior seen-

•) Treatment - perturb the system from progression to AIDS back to latency.

(•) Address:

(i) early versus late initiation of treatment; and

(ii) optimal treatment scheduling (strategy).

(iii) When and how treatment should be initiated assuming that treatment can only be continued for n days

(iv) We base the 'benefit' solely on an increase or retention of the $CD4^+$ T cell count.

Historical Review of Literature

***********Stochastic**************

Merrill (1987) and (1989) Early Disease Stage when #'s are low & small.

***********Variability Among Viral Strains*********

Nowak, May and Anderson (1990)

Nowak and May (1991) Antigenic Variation

Harnevo (1993)

Stiliankis, Schenzle and Dietz (1993)

**************AZT Models*************

Mclean and Nowak (1992)-Resistance

Agur (1989)-Reduced Lymphocyte Cytotoxicity

Cojocaru and Agur (1992)-age of cell linked cycle protocol

cancer to AZT

Kirschner and Perelson (1993)-Early vs. Late Treatment

*************Deterministic Models*************

Cooper (1986)

Intrator, Deocampo and Cooper (1988)

McLean (1988)

McLean and Kirkwood (1990)

Reibnegger, Fuchs, Hausen, *et al* (1987)

Dolezal (1988)

Hraba and Dolezal (1989)

Hraba and Dolezal and Celikovsky (1990)

Fletcher, Shrager, Bailey (1989)

Anderson and May (1989)

Harnevo (1992)

Sidorov and Romanyukha (1993)

McLean and Nowak (1991)

Perelson (1989)

Perelson, Kirschner and DeBoer (1993)

Nelson and Perelson (1992)

Later Disease Stage when #'s are large

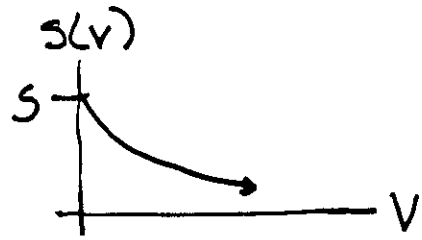
DEFINITIONS

- $T(t)$ = population of uninfected T cells at time t.
- $T^*(t)$ = population of latently infected T cells at time t.
- T^{**} = population of actively infected T cells at time t.
- $V(t)$ = population of FREE virus at time t.

Simple Model

$$\frac{dT}{dt} = s + \mu_T T + rT(1 - \frac{T + T^* + T^{**}}{T_{max}}) - k_1 VT,$$
$$\frac{dT^*}{dt} = k_1 VT - \mu_T T^* - k_2 T^*,$$
$$\frac{dT^{**}}{dt} = k_2 T^* - \mu_b T^{**},$$
$$\frac{dV}{dt} = N\mu_b T^{**} - k_1 VT - \mu_V V \ .$$

$$\rightarrow s = s(V) = s\theta/(\theta + V),$$



with θ a scaling parameter.

The steady state value in the absence of virus:

$$T_0 = \frac{T_{max}}{2}\left[1 - \frac{\mu_T}{r} + \sqrt{(1 - \frac{\mu_T}{r})^2 + \frac{4s}{rT_{max}}}\right] .$$

The Steady State in the prescence of Virus:

$$T = T_0,\ T^* = T_0^*,\ T^{**} = T_0^{**},\ V = V_0$$

BIFURCATION INFORMATION

STABILTY CRITERION:

For the uninfected steady state to be l. asymptotically stable, we require that after an introduction of a small amount of virus, $\frac{dV}{dt} < 0$.

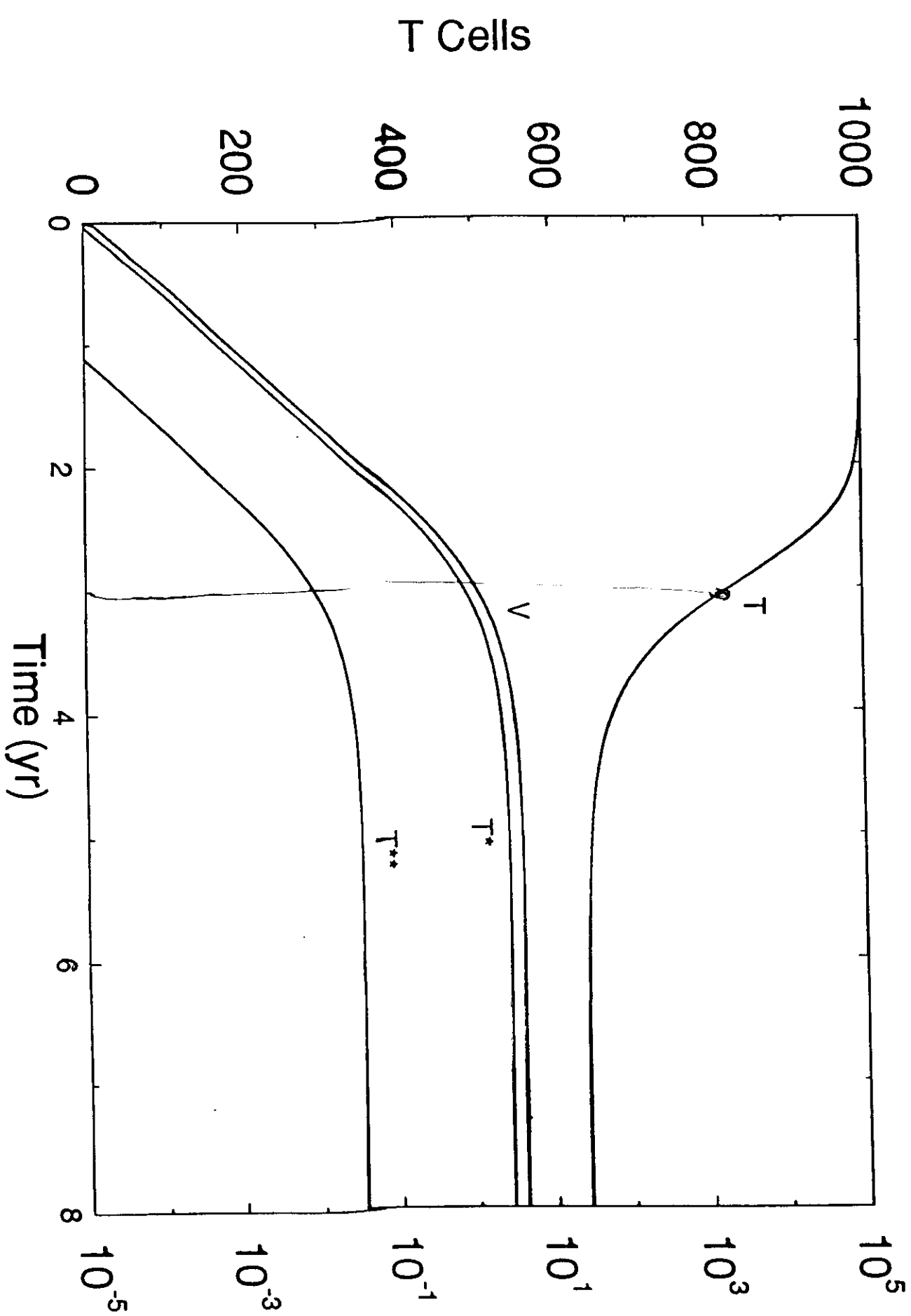
Then, when stabilty transfers from the uninfected state to the endemically infected steady state, $\frac{dV}{dt} > 0$.

These two criterion lead to the result that

$$N < N_{critical} = \frac{(k_2 + \mu_T)(\mu_V + k_1 T_0)}{k_1 k_2 T_0}$$

If $\frac{dV}{dt} < 0$, and $N > N_{crit}$ if $\frac{dV}{dt} > 0$.

- Global Stability of the uninfected SS can be shown (Lyapunov)
- Local Stability only for the infected SS (other situations can arise (Hopf Bifurcations, limit cycles)


T Cells
0
200
400
600
800
1000
Time (yr)
0
2
4
6
8
10^{-5}
10^{-3}
10^{-1}
10^{1}
10^{3}
10^{5}
V
T
T*
T**

AZT and other Chemotherapies

1 AZT is a nucleotide analog: It looks like bases of DNA (T), but is "defective", so when used as a polymerase to elongate the DNA, no more bases (T,A,G,C) can be added, so transcription is halted.

2 polymerase: An enzyme that replicates DNA (such as reverse transcriptase)

3 Reverse transcriptase: the viral enzyme that transcribes viral RNA to viral DNA, so it can be encoded in the genome.

3a This is done the first few hours infection takes place.

4 Host cellular side affects? Only affects dividing cells, and for every 1000 units of AZT used by virus, only 3 or 4 units are used by host (which can use it but prefers its own). (Barney Graham) But, those actively dividing normal and infected host cells will stop dividing

5 Other side affects are mostly systemic

Table 1. Major Clinical Trials of Zidovudine Monotherapy in Adults*

Study (Reference)	Patients	Stage	Zidovudine Dose	Duration of Follow-up	Results
	n			*mo*	
NCI phase 1 (39)	19	AIDS (11 patients) and AIDS-related complex (8 patients)	Dose escalation to 30 mg/kg body weight per day intravenously and 60 mg/d orally	1.5	15 of 19 patients had an increase in the CD4 count; 2.2 kg average weight gain
BW 002 (1)	282	AIDS (160 patients) and AIDS-related complex (122 patients)	1500 mg/d (compared with placebo) (Large dose)	4	Increased survival in zidovudine group; decreased incidence of opportunistic infections in zidovudine group; increase in CD4 count and weight in zidovudine group
ACTG 016 (2)	711	AIDS-related complex	1200 mg/d (compared with placebo)	11	Decrease in development of AIDS, AIDS-related complex, and death in the zidovudine group; increased CD4 count and decreased p24 antigen level in the zidovudine group
ACTG 019 (4)	1338	Asymptomatic	(small Dose) 500 mg/d or 1500 mg/d (compared with placebo)	12.75	Decrease in development of AIDS and AIDS-related complex in both zidovudine groups; increased CD4 count and decreased p24 antigen level in zidovudine groups
ACTG 002 (85)	524	AIDS	1500 mg/d or 1200 mg/d (then 600 mg/d after 4 weeks)†	25.6	Increased survival for lower dose; increased CD4 cells and decreased p24 antigen in both groups
VA study (3)	338	AIDS-related complex ★	"Early" therapy with 1500 mg/d compared with "late" therapy (1500 mg/d if CD4 count fell below 200/mm³ or AIDS event occurred)	27	No difference in mortality; decrease in development of AIDS in early group; increased CD4 count and decreased p24 antigen level in early group
Concorde 1 (62)	> 2000	Asymptomatic	1000 mg/d (compared with placebo)	> 30	Ongoing

Table 3. Neutropenia and Zidovudine Therapy*

Study (Reference)	Zidovudine Dose	Stage	Incidence of Neutropenia, %
BW 002 (102)	1500 mg/d	AIDS	31.3
		AIDS-related complex	11.7
ACTG 002 (85)	1500 mg/d	AIDS	51
	1200 mg/d for 4 weeks, followed by 600 mg/d	AIDS	37
ACTG 016 (2)	1200 mg/d	★ Early AIDS-related complex	4
ACTG 019 (4)	1500 mg/d	Asymptomatic	6.3
	500 mg/d	Asymptomatic	1.8

* Neutropenia is defined as an absolute neutrophil count of less than 750 cells/mm³. ACTG = AIDS Clinical Trials Group; BW = Burroughs Wellcome.

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Table 2. Anemia and Zidovudine Therapy*

Study (Reference)	Definition of Anemia	Zidovudine Dose	Stage	Incidence of Anemia, %
BW 002 (102)	Hemoglobin < 7.5 g/dL	1500 mg/d	AIDS	31.3
ACTG 002 (85)	Hemoglobin < 8.0 g/dL	1500 mg/d	AIDS-related complex	15
		1200 mg/d for 4 weeks, followed by 600 mg/d	AIDS	39
ACTG 016 (2)	Hemoglobin < 8.0 g/dL	1200 mg/d	AIDS	29
ACTG 019 (4)	Hemoglobin < 8.0 g/dL	1500 mg/d	★ Early AIDS-related complex	5
		500 mg/d	Asymptomatic	6.3
			Asymptomatic	1.1

* ACTG = AIDS Clinical Trials Group; BW = Burroughs Wellcome.

AZT and Other Drug Treatments

for Simple and Extended Model

We introduce the affect of a drug that reduces viral replication by multiplying the parameters N by the scalar step function

$$z(t) = \left\{ \begin{array}{l} 1 \quad \text{outside the treatment period} \\ \\ P \quad \text{during the time of AZT treatment.} \end{array} \right\}$$

$$\frac{dT}{dt} = s - \mu_T T + rT(1 - \frac{T + T^* + T^{**}}{T_{max}}) - k_1 VT,$$

$$\frac{dT^*}{dt} = k_1 VT - \mu_T T^* - k_2 T^*,$$

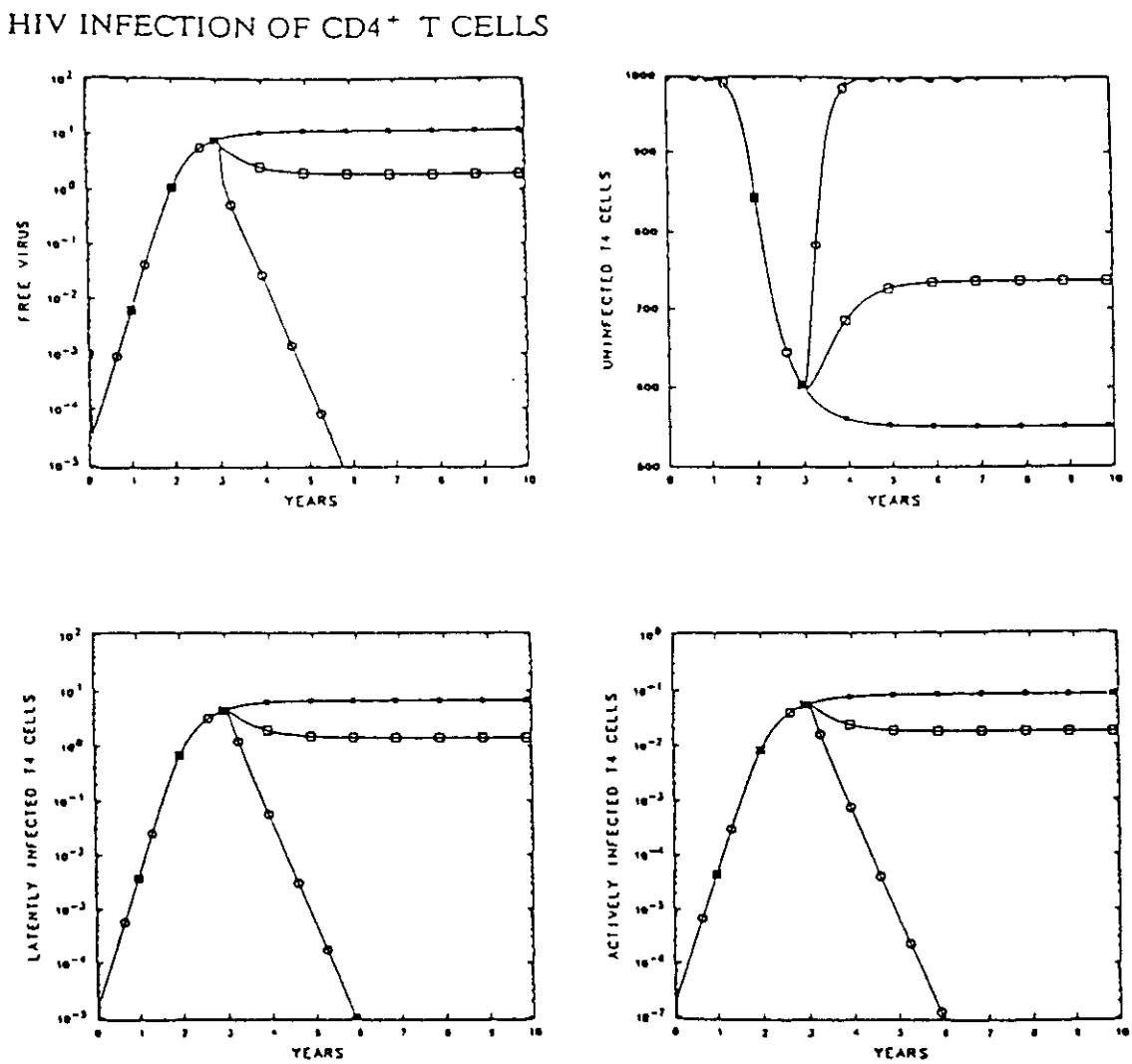
$$\frac{dT^{**}}{dt} = k_2 T^* - \mu_b T^{**},$$

$$\frac{dV}{dt} = N\mu_b T^{**} - k_1 VT - \mu_V V \ .$$

Drugs such as AZT reduces virion production in a dose dependent manner. Therefore, P is proportional to the dose of the drug. (Another interpretation for the proportion P is that efficacy of the drug may differ from patient to patient; therefore, P could also represent the varying effectiveness of the drug in halting viral reproduction.)

AZT results of Simple Model

In Perelson *et al.* (1993) AZT treatment was studied with this simple model. The model showed that if the number of virion produced per T4 cell is forced below N_{crit} through AZT treatment, then the immune system can recover to state where the uninfected state is stable. Otherwise, infection still ensues.



DEFINITIONS

- $T(t)$ = population of uninfected T cells at time t.
- $T^*(t)$ = population of latently infected T cells at time t.
- T^{**} = population of actively infected T cells at time t.
- $V(t)$ = population of FREE virus at time t.
- $M(t)$ = population of macrophages at time t.
- $M^*(t)$ = population of infected macrophages at time t.

Presentation of an Extended Model

$$\frac{dT}{dt} = s - \mu_T T + rT\left[1 - \frac{T + T^* + T^{**}}{T_{max}}\right] - [k_1 V + k_3 M^*]T,$$

$$\frac{dT^*}{dt} = (k_1 V T + k_3 M^* T) - \mu_{T^*} T^* - k_2 T^*,$$

$$\frac{dT^{**}}{dt} = k_2 T^* - \mu_b T^{**},$$

$$\frac{dV}{dt} = N\mu_b T^{**} + \Pi_M M^* - \mu_V V - k_1 V T - k_4 V M$$

$$\frac{dM}{dt} = \mu_M(E_M - M) - k_4 V M,$$

$$\frac{dM^*}{dt} = k_4 V M - \mu_{M^*} M^* \ .$$

N- a non-dimensional scaler representing the number of virus produced during the lifetime of an actively infected T4 cell,

Π_M - rate of viral production per unit time in macrophages.

(However, both represent a production of new virion particles at some level.)

Steady States

The steady state value in the absence of virus:

$$T = T_0, \quad \text{and} \quad M = M_0, \quad \text{others are} \quad 0$$

The Steady State in the prescence of Virus:

$$M = M_0, \quad M^* = M_0^*, \quad T = T_0, \; T^* = T_0^*, \quad T^{**} = T_0^{**}, \quad V = V_0$$

Bifurcation Information

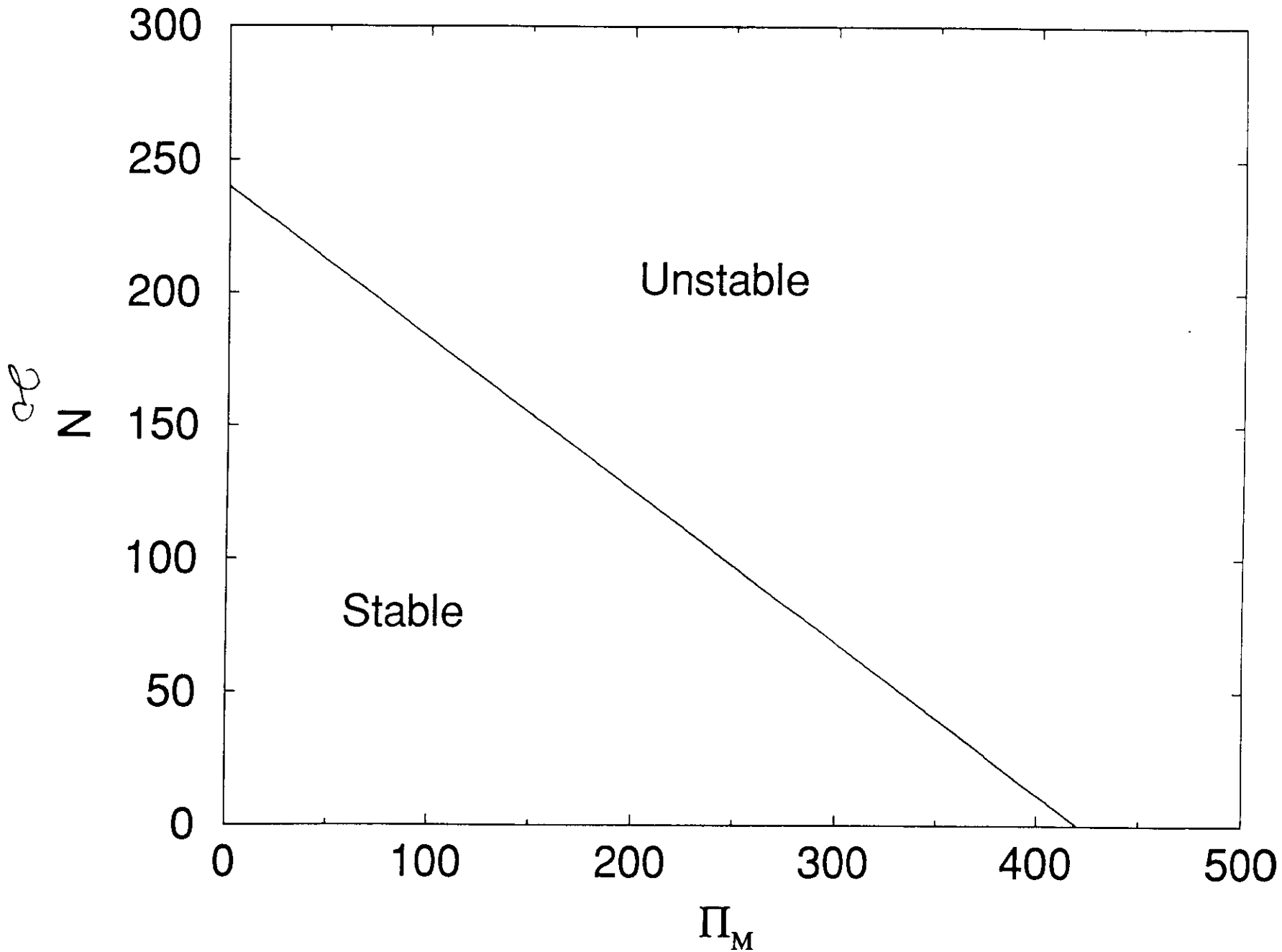
$dV/dt < 0$, if and only if

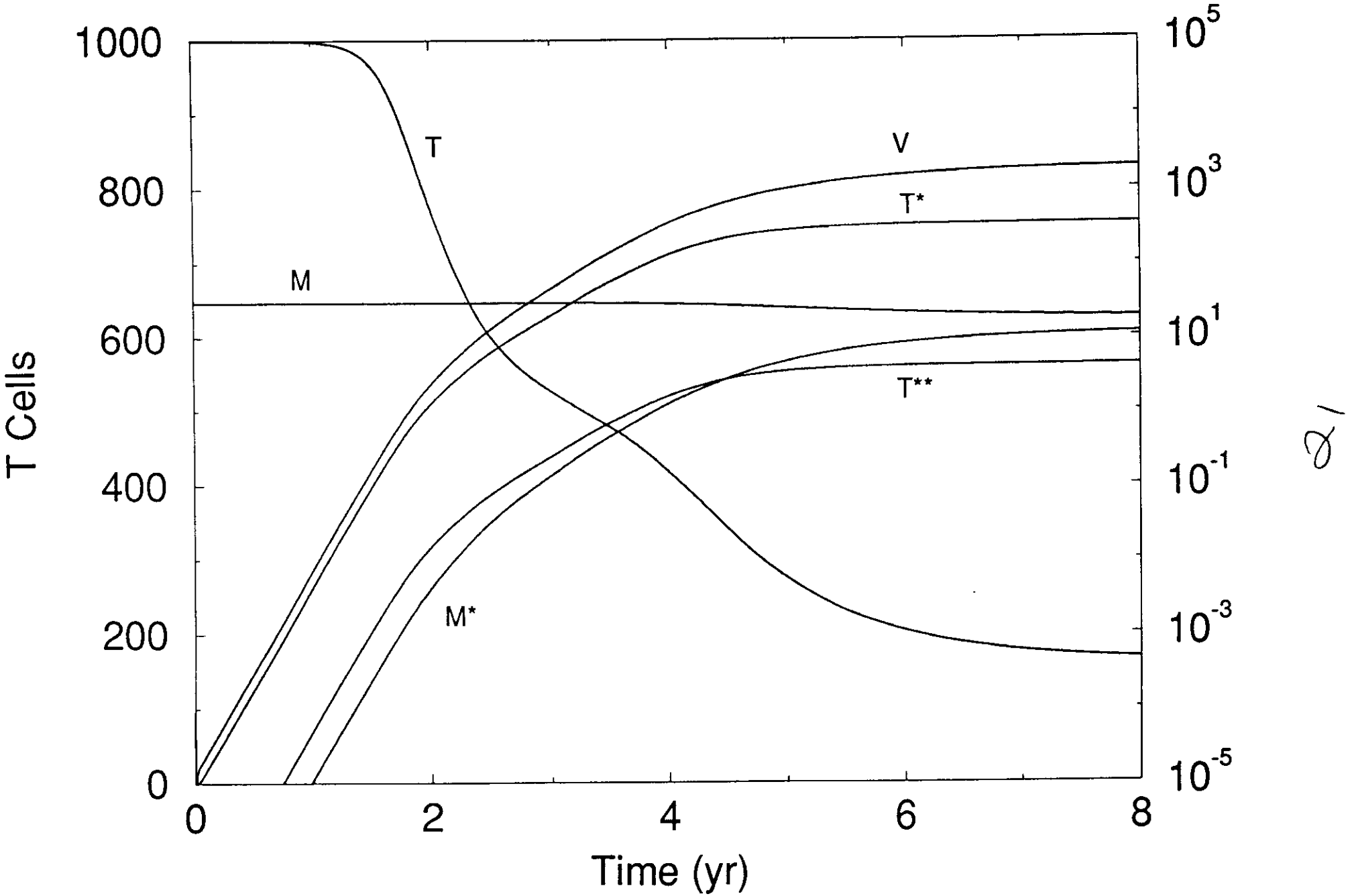
$$N < \bar{N}_{crit} \equiv \frac{\mu_{T^*}(\mu_{T^*} + k_2)[\mu_V \mu_{M^*} + k_1 \bar{T} \mu_{M^*} - \Pi_M k_4 \cdot \mu_M E_M]}{\bar{T} \mu_b k_2 [k_1 \mu_{M^*} + k_3 \cdot k_4 E_M]}$$

This condition is equivalent to a condition on Π_M, namely,

$$\Pi_M < \frac{-N\bar{T}\mu_T k_2 [k_1 \mu_{M^*} + k_3 k_4 E_M] + \mu_{T*}(\mu_{T*} + k_2)[\mu_V \mu_{M^*} + k_1 \bar{T} \mu_{M*}]}{k_4 \mu_M E_M}$$

Typical values for the parameters of N_{crit} yield a range of $N_{crit} \in$ [1,420]. Notice the dependence of N_{crit} on Π_M.


300
250
200
150
100
50
0
α_N
Unstable
Stable
0
100
200
300
400
500
Π_M


1000
800
600
400
200
0
T Cells
0
2
4
6
8
Time (yr)
10^5
10^3
10^1
10^{-1}
10^{-3}
10^{-5}
T
V
T*
M
T**
M*

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AZT and Other Drug Treatments

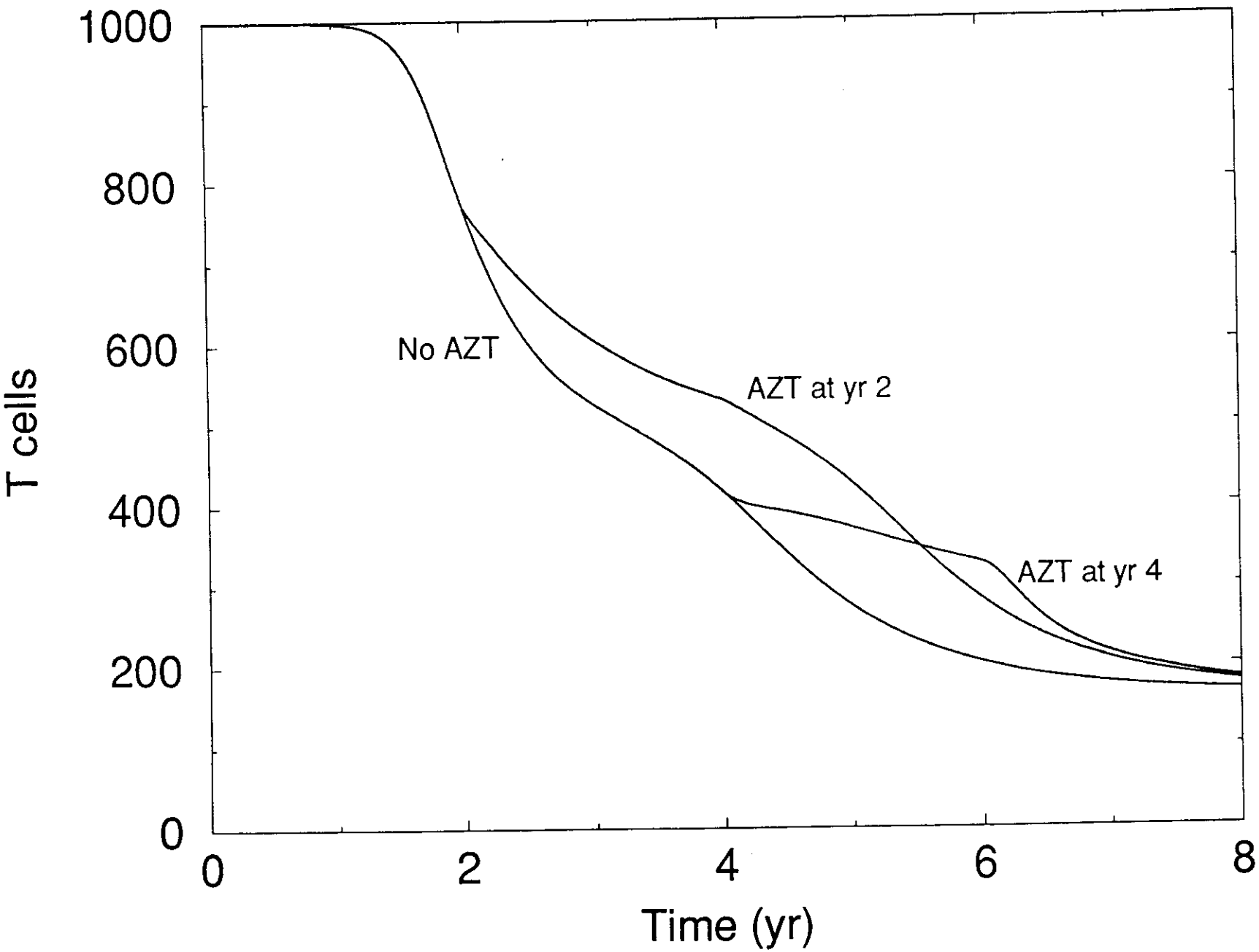
for Simple and Extended Model

We introduce the affect of a drug that reduces viral replication by multiplying the parameters N (and Π_M) by the scalar step function

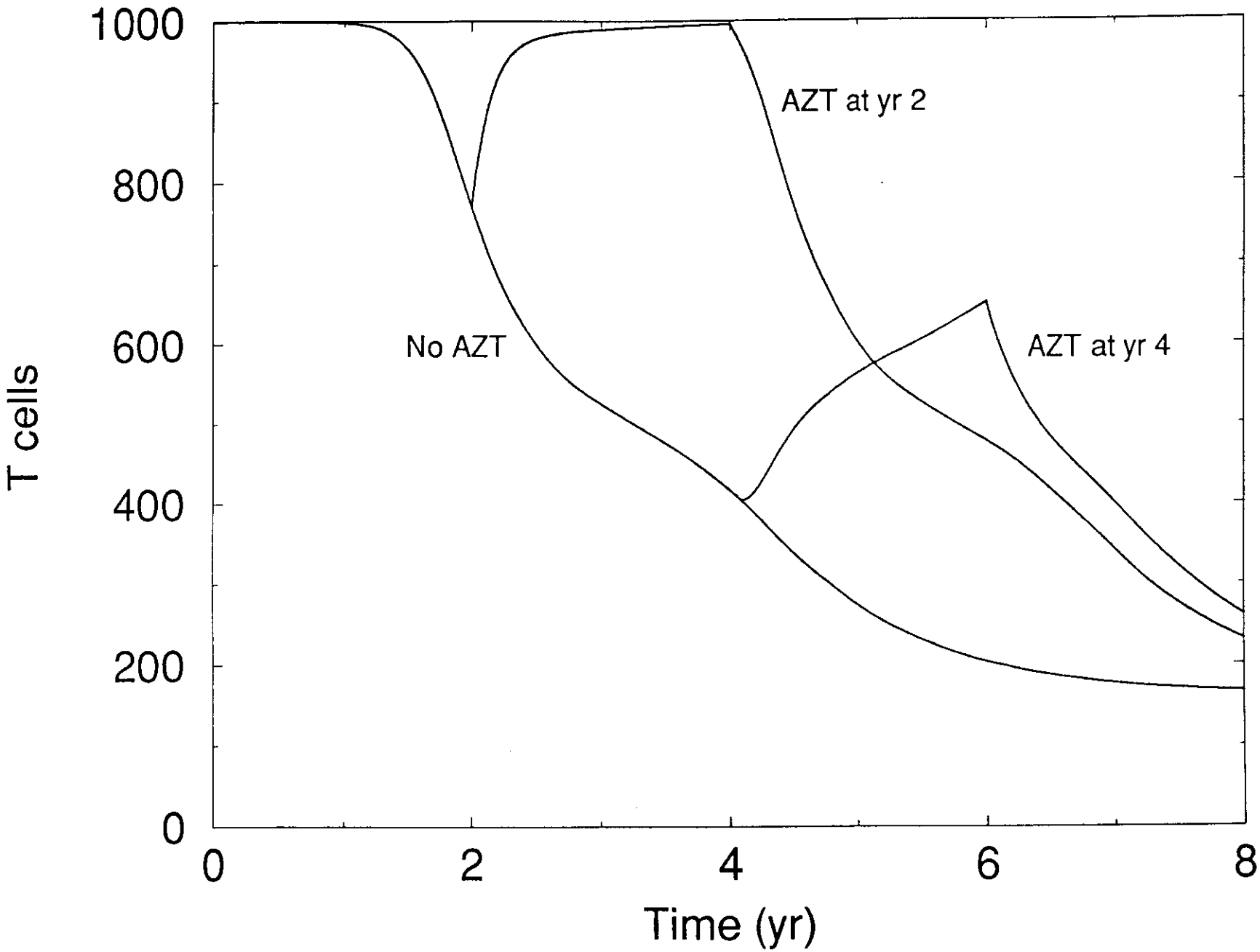
$$z(t) = \left\{ \begin{array}{ll} 1 & \text{outside the treatment period} \\ \\ P & \text{during the time of AZT treatment.} \end{array} \right\}$$

The parameters, $N \cdot z(t)$ (and $\Pi_M \cdot z(t)$) represent new virion production. Drugs such as AZT reduces virion production in a dose dependent manner. Therefore, P is proportional to the dose of the drug. (Another interpretation for the proportion P is that efficacy of the drug may differ from patient to patient; therefore, P could also represent the varying effectiveness of the drug in halting viral reproduction.)

25 % reduction of N.



90% reduction of N



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Discussion of Previous Models

* Early vs. Late Controversy-Clinical
* Non-Mechanisitic
* $N > N_{crit}$ for infection to persist and be fatal.
* Both models can explain 'rapid/high' and 'slow/low'
* the Extended model exhibited slower depletion of T4 cells
* And, lead to substantially greater depletion of T cells, even down to levels below 200 as seen in patients.
* N was on the order of ten times less than simple model,
* the extended model early vs. late treatment protocols for administering AZT, given that a patient can only receive benefit from the drug for a period of two years. (simulates resistance)
* if the effects of a drug force N below N_{crit}, then T4 cell depletion can be halted.
* results apply to any treatment that reduces viral replication rates.
* AZT is Truely only 10-25 % effective.
* Cocktails-Combination Therapy

IMMUNOLOGICAL IMPROVEMENTS

- Reservior-Macrophages (serves as a hiding place for production of virus -"wolf in sheep clothing"

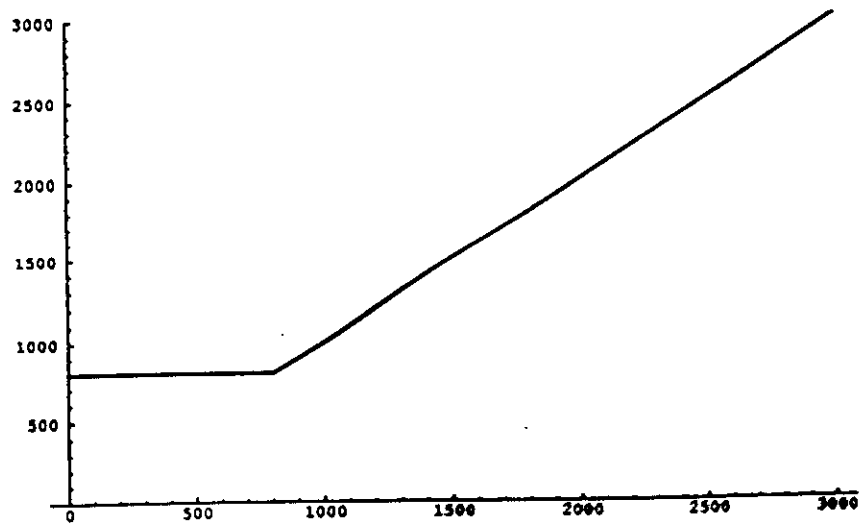
- Thymus-Precursor cells become infected, and hence the source of uninfected T cells is affected

- Immune Response-are the T Cells fighting back?

- Antigenic Variation-ability of HIV to mutate and evade perception ('one step ahead')-escape mutants

- Variable viral production- Is N really a function of time?

slow/low ≈ rapid/high



N(t)

time in days

Model 1- 2 ODE's

Define two populations $V(t)$, $T(t)$.

$$\frac{dT(t)}{dt} = s - \mu T(t) + p\frac{T(t)V(t)}{C+V(t)} - k_V T(t)V(t)$$

$$\frac{dV(t)}{dt} = Nk_V T(t)V(t) - k_T T(t)V(t) + \frac{g_V V(t)}{c+V(t)}$$

$$T(0) = T_0, \quad V(0) = V_0$$

T = Total CD4+ T cell count
CD8+

Stability of Steady States of Model A

Steady States: There are possibly 4 steady states in the positive cone.

(1) SS1: $T = 0$ and $V \to \infty$

(2) SS2: $V = 0$ and $T = \frac{s}{\mu}$

(3) SS3 and SS4: $T = \frac{G_V}{K_{T,v} - NK_{v,T}}$ and $aV^2 + bV + c = 0$.

SS1 (full blown AIDS) is always 'stable'

It can be shown that SS2 is locally stable if:

$$K_{T,v} - NK_{v,T} > \frac{G_V \mu}{s} \equiv \frac{s}{\mu} > \frac{G_V}{K_{T,v} - NK_{v,T}}$$

. (notice the N again in the condition for stability)

i.e. SS2 for $T <$ SS3 (or SS4) for T

When they are equal, there is an exchage of stability through a saddle node bifurcation, and 2 positive SS for one T-value but 2 V's appear.

(0 to 1 to 2 is a saddle node)

Model 2- 1 PDE coupled with 2 ODE's

Remark: This is the 3 equation ODE model with age of infection, a, in the infected class of T cells. If chemotherapy does not appear in this equation, then we can assume an average life-span and integrate the 2nd equation reducing this system to the ODE model. Here chemotherapy is linked to age of cellular infection. All parameters must be scaled to days. Let a_max be max age of T cells, then:

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

$$T^*(t,0) = k_V T(t)V(t), \quad T^*(0,a) = 0$$

$$\frac{\partial T^*}{\partial t} + \frac{\partial T^*}{\partial a} = -\mu_T^* T^*(t,a) - rT^*(t,a)\frac{V(t)}{C+V(t)}$$

$$\frac{dV}{dt} = Nr\frac{V(t)}{C+C(t)}\int_0^{a_{max}} T^*(t,a)da - k_T T(t)V(t) + \frac{g_v V(t)}{c+V(t)}.$$

$$T(0) = T_0, \quad V(0) = V_0$$

Analysis of Model 2 Assume $a_{max} = \infty$ and define

$$T^i(t) = \int_0^\infty T^i(t,a)da.$$

Now, integrate 12 with respect to age (from 0 to ∞) to obtain

$$\frac{dT^i(t)}{dt} + T^i(t)\Big(\mu_{T^i} + \frac{rV(t)}{C+V(t)}\Big) = k_V V(t)T(t),$$

which is the same as eq. 2. Solving for steady states in 10-13 yields

$$s = \mu\bar{T} + r\bar{T}\frac{\bar{V}}{C+\bar{V}} + k_V\bar{T}\bar{V}, \tag{14}$$

$$\bar{T}^i(0) = k_V\bar{T}\bar{V}, \tag{15}$$

$$\frac{d\bar{T}^i}{da} = -\bar{T}^i(a)\Big(\frac{r\bar{V}}{C+\bar{V}} + \mu_{T^i}\Big), \tag{16}$$

$$Nr\frac{\bar{V}}{C+\bar{V}}\int_0^{a_{max}} \bar{T}^i(a)da = k_T\bar{T}\bar{V} - \frac{g_V\bar{V}}{b+\bar{V}}. \tag{17}$$

If 15 and 16 are considered as an initial value problem, the solution is

$$\bar{T}^i(a) = e^{-\left(\mu_{T^i} + \frac{r\bar{V}}{C+\bar{V}}\right)a} k_V\bar{V}\bar{T}.$$

Let $\bar{T}^i = \int_0^{a_{max}} \bar{T}^i(a)da$, and hence

$$\bar{T}^i = \int_0^{a_{max}} e^{-\left(\mu_{T^i} + \frac{r\bar{V}}{C+\bar{V}}\right)a} k_V\bar{V}\bar{T}da = \frac{k_V\bar{V}\bar{T}}{\mu_{T^i} + \frac{r\bar{V}}{C+\bar{V}}},$$

Equation 8 has another solution of $\bar{V} = 0$ (which implies $\bar{T} = \frac{s}{\mu_T}$). Now setting 9a=9b:

$$s(b+\bar{V})\left[k_T - \frac{N r \bar{V} k_V}{\mu_{T^i}(C+\bar{V}) + r\bar{V}}\right] = g_V\left[\mu_T - r\frac{\bar{V}}{C+\bar{V}} + k_V\bar{V}\right].$$

(cubic in $\bar{V}$) There are three roots, one positive, and two imaginary.

Uninfected steady state (where the virus population and infected cells are $\bar{V} = 0$ and $\bar{T} = \frac{s}{\mu_T}$), and

Infected Steady State (both virus and T cells exist at some positive level). (latency)

Another limiting behavior for the system is *Progression to AIDS* (the T cell population goes to 0, T^i goes to a positive constant, and V grows linearly without bound -

A linearized stability analysis of the uninfected steady state reveals a threshold condition for local stability. More precisely, if $R_o = \frac{g_V}{k_T b} < 1$, the system recovers from infection. If $R_o > 1$, the uninfected state becomes unstable and the infected steady states assumes stability.

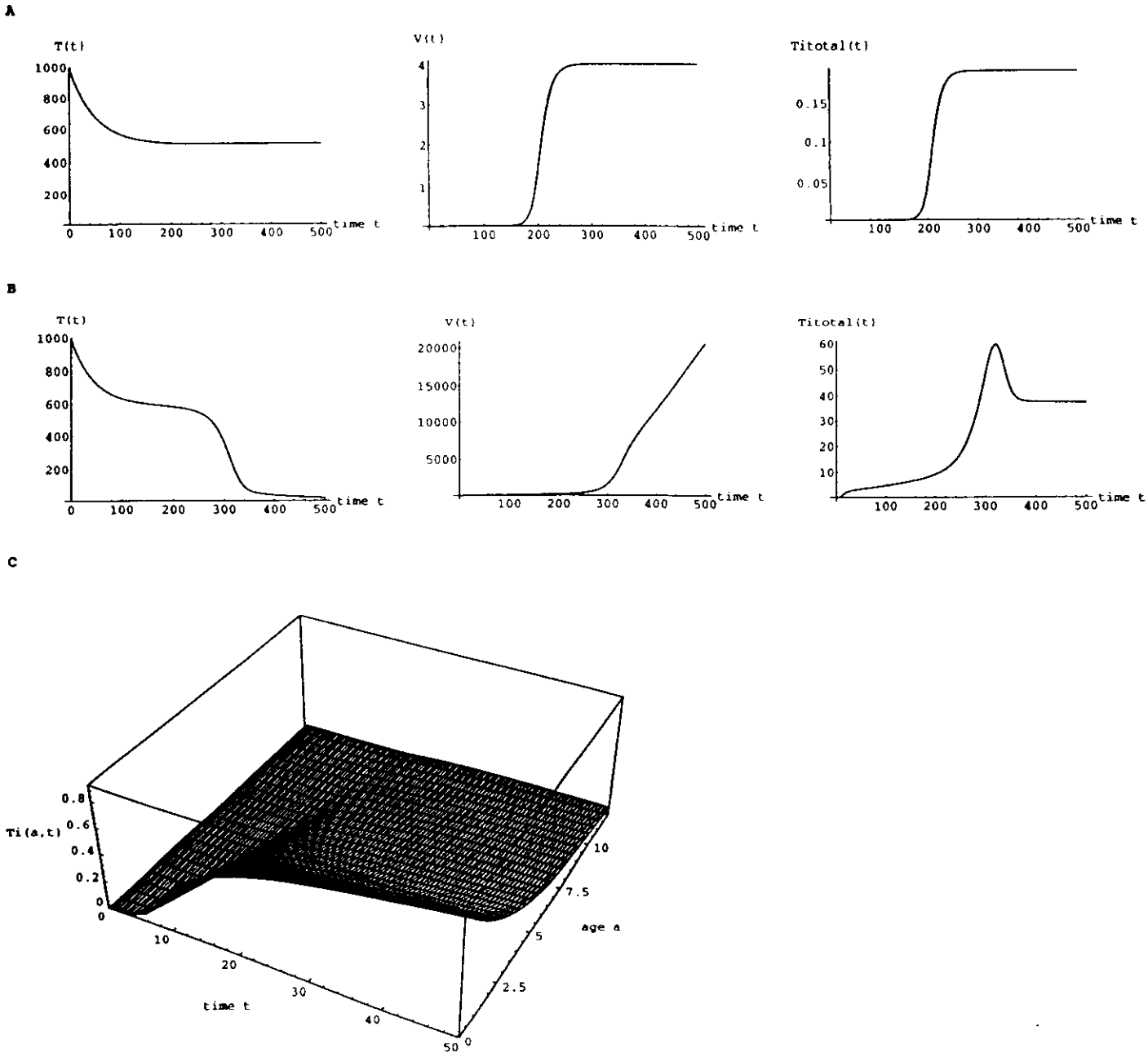

A
T(t)
1000
800
600
400
200
0
100
200
300
400
500
time t
V(t)
4
3
2
1
100
200
300
400
500
time t
Titotal(t)
0.15
0.1
0.05
100
200
300
400
500
time t
B
T(t)
1000
800
600
400
200
0
100
200
300
400
500
time t
V(t)
20000
15000
10000
5000
100
200
300
400
500
time t
Titotal(t)
60
50
40
30
20
10
100
200
300
400
500
time t
C
Ti(a,t)
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
time t
0
2.5
5
7.5
10
age a

FIGURE 2

CHEMOTHERAPY-Model 2

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

$$T^*(t,0) = k_V T(t)V(t), \quad T^*(0,a) = 0$$

$$\frac{\partial T^*}{\partial t} + \frac{\partial T^*}{\partial a} = -\mu_T^* T^*(t,a) - rT^*(t,a)\frac{V(t)}{C+V(t)} - \gamma(\mathbf{t},\mathbf{a})\mathbf{T^*(t,a)}$$

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

$$T(0) = T_0, \quad V(0) = V_0$$

Chemotherapy of Model 2

Here cells which have age of infection between $[0, a_1]$), revert back to the uninfected class.

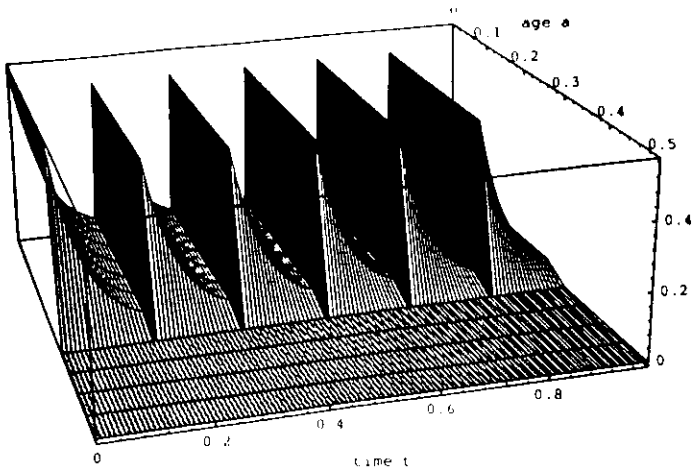
The *average value* of the treatment for any period is:

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

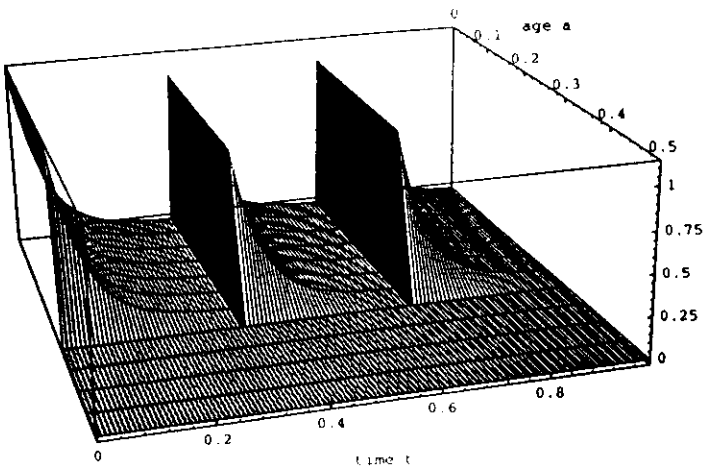
The treatment function $\gamma(t, a; p)$ is:

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

A


age a
0.1
0.2
0.3
0.4
0.5
0.4
0.2
0
0.2
0.4
0.6
0.8
0
time t

B


0
age a
0.1
0.2
0.3
0.4
0.5
1
0.75
0.5
0.25
0
0.2
0.4
0.6
0.8
0
time t

C

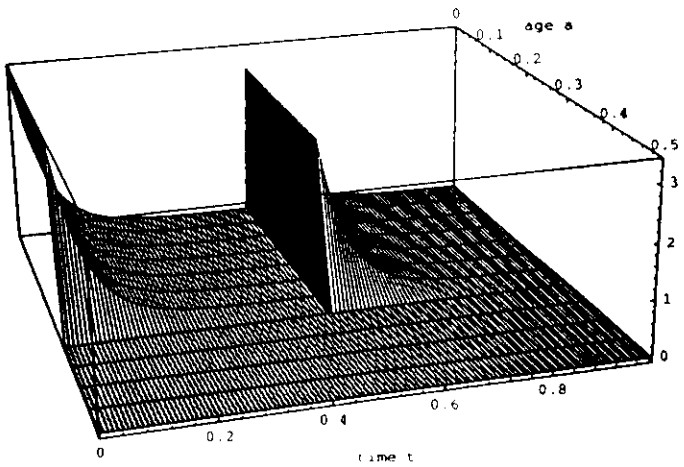
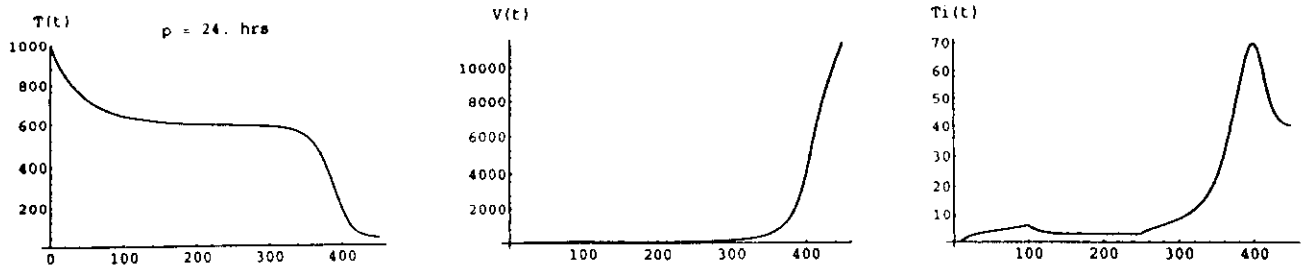
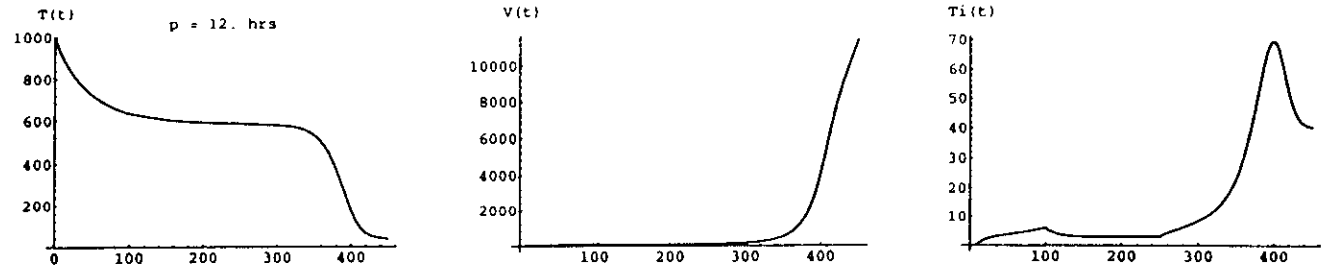

0
age a
0.1
0.2
0.3
0.4
0.5
3
2
1
0
0.2
0.4
0.6
0.8
0
time t

FIGURE 4

A



B



C

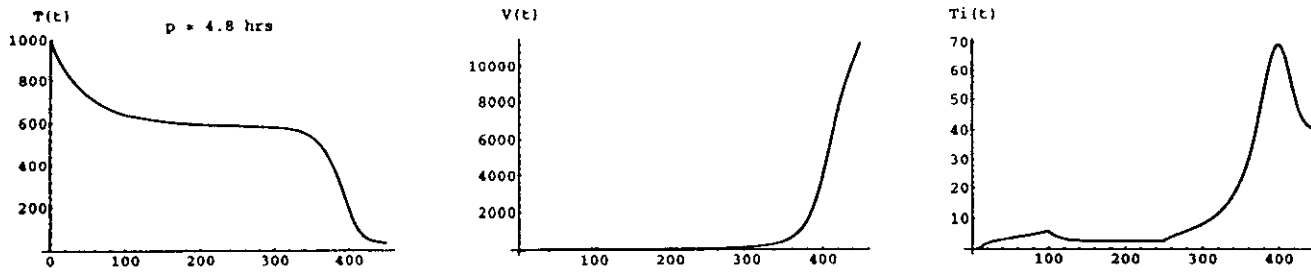


FIGURE 5

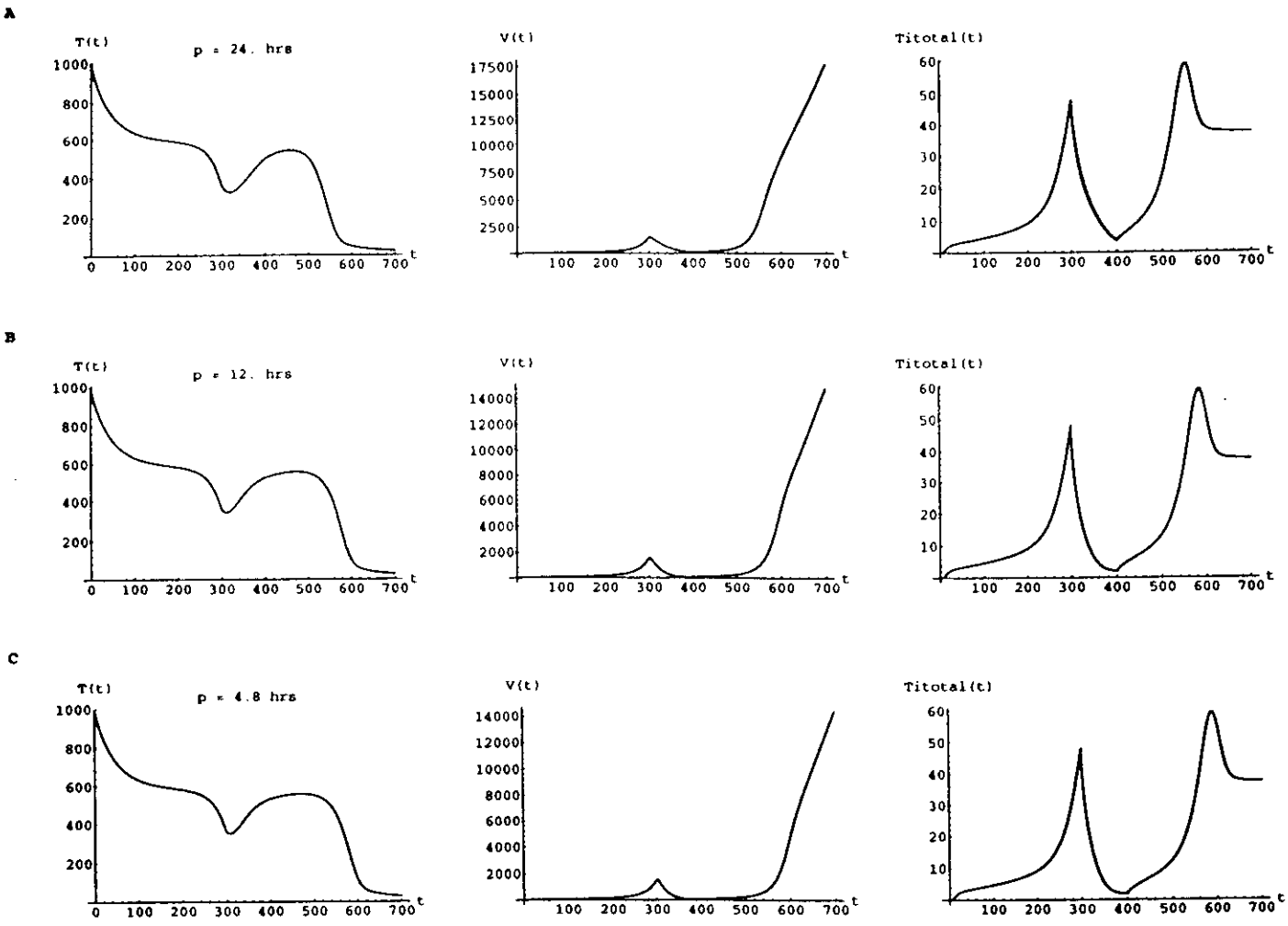

A
T(t)
p = 24. hrs
V(t)
Titotal(t)
B
T(t)
p = 12. hrs
V(t)
Titotal(t)
C
T(t)
p = 4.8 hrs
V(t)
Titotal(t)
t

FIGURE 6

Intermittent Chemotherapy Schemes

- (•) There is a delay period of appr. 50 days after treatment is halted before the T cell decline reappears
- (•) Successful periods of treatment with no treatment (for the length of the specific delay) would be a method in which one could extend the treatment periods longer, and reduce toxicity through less frequent administration.
- (•) This was tested with Model 1 (Figure 8)
- (•) If it is not feasible to take the patient off chemotherapy for even short periods of time, then the models suggest that intermittent therapy with another drug may be just as effective.

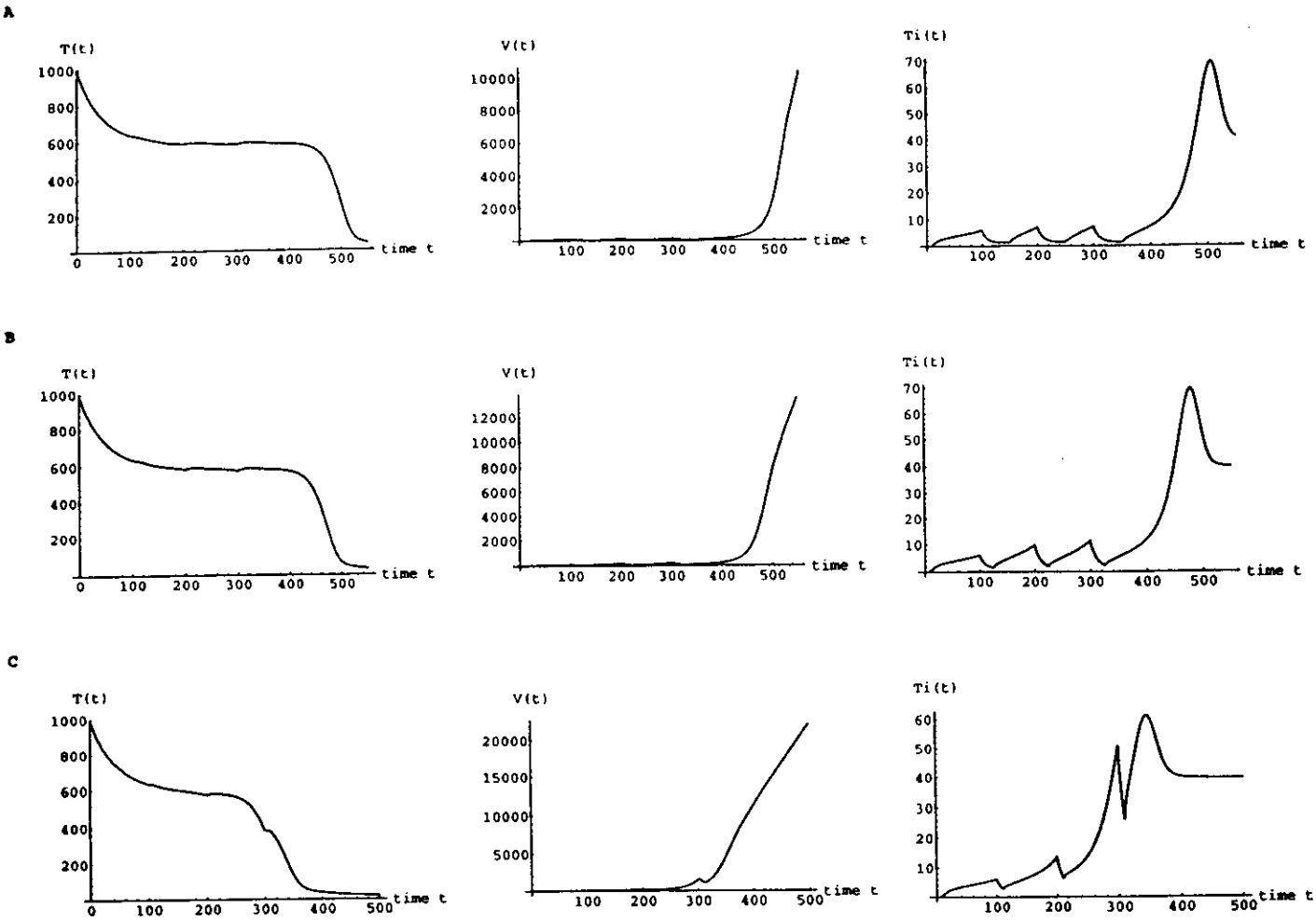

A
T(t)
1000
800
600
400
200
0
100
200
300
400
500
time t
V(t)
10000
8000
6000
4000
2000
100
200
300
400
500
time t
Ti(t)
70
60
50
40
30
20
10
100
200
300
400
500
time t
B
T(t)
1000
800
600
400
200
0
100
200
300
400
500
time t
V(t)
12000
10000
8000
6000
4000
2000
100
200
300
400
500
time t
Ti(t)
70
60
50
40
30
20
10
100
200
300
400
500
time t
C
T(t)
1000
800
600
400
200
0
100
200
300
400
500
time t
V(t)
20000
15000
10000
5000
100
200
300
400
500
time t
Ti(t)
60
50
40
30
20
10
100
200
300
400
500
time t

FIGURE 8

Conclusions

(i) The daily period of treatment does not affect the outcome of the treatment;

(ii) Treatment should not begin until after the final decline of T cells begins (when the T cell population falls below approximately 300mm^{-3}), and then, it should be administered immediately;

(iii) The optimal strategy for treatment which may cope with side-effects and/or resistance, is to treat intermittently with chemotherapy followed by interruptions in the treatment during which either a different drug, or no treatment, is administered.

(iv) Compare Model 1 and Model 2

Main

Conclusions

* No good models exist to help predict optimal chemotherapy stragies
* The few models to date are good, but none explain all
* Focus needs to be on treatment
* Mechanism (linked directly to chemo) are good approach
* Addressing questions of clinical community is a good start