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"Effects of Treatment and Behavioral Change on the Dynamics of HIV/AIDS in a Highly Homosexually-Active Population"

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EFFECTS OF TREATMENT AND
BEHAVIORAL CHANGE ON
THE DYNAMICS OF HIV/AIDS
IN A HIGHLY
HOMOSEXUALLY-ACTIVE POPULATION

BY

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Effects of treatment and behavioral change on the dynamics of HIV/AIDS in a highly homosexually-active population

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Abstract

This paper studies models for the sexual transmission of HIV/AIDS that incorporate changes in behavior as well as the effects associated with HIV treatment. The recruitment rate into the core is assumed to be a function of the prevalence of the disease within the core and it may trigger the existence of periodic solutions through Hopf bifurcations, provided that there is at least a weak demographic interaction with the non-core. Numerical simulations suggest that the treatment rate has no effect on the existence or non-existence of periodic solutions in isolated core groups, but if the core interacts with the non-core then treatment rates may influence the transient dynamics. For example, oscillations with slowly decreasing amplitudes are possible when treatment rates are high or intermediate. Forward and backward bifurcation phenomena may be possible when the magnitude of the basic reproductive number increases. However, our numerical evidence, while suggestive, is inconclusive.

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1 Introduction

Sexually-transmitted diseases are usually driven by a relatively small proportion of the sexually-active individuals. Hethcote and Yorke (1984) introduced the concept of core-group as a key element of disease management. Their work was motivated in part by their efforts to develop cost-effective methods for reducing the incidence and prevalence of gonorrhea. They found out that disease management strategies aimed at the core were the most effective. Their "moving" endemic equilibrium provided epidemiologists and public health officials with a visual measure of their effectiveness.

Drastic changes in behavior were observed in some homosexually-active populations because HIV is fatal and generally asymptomatic for very long periods (see Baldwin and Baldwin 1988, Curran et al. 1988, Fineberg 1988, Evans et al. 1989, Martin 1987, Saltzman et al. 1987, Shechter et al. 1988, van Griensven et al. 1989a,b, Wilkenstein 1988, McKusick et al. 1985, Shilts 1987, and Wiktor et al. 1990). The effect of these changes on disease prevalence and incidence is not well understood and the development of partially-effective drug treatments such as AZT makes it even more difficult to forecast the timing and magnitude of an epidemic. The situation is quite complicated because changes in behavior may influence disease dynamics by affecting the recruitment of new susceptibles, the level of sexual activity, the type of sexual practices, and the rate of partnership exchange. Treatment may increase the length of the infectious period while possibly reducing the infectivity per sexual contact. In this manuscript we explore the interaction among behavioral changes, treatment of HIV-infected patients, and the long term dynamics of HIV using models for homosexually-active populations. We combine the results of two earlier directions. The first makes recruitment into a population a function of disease levels (Blythe et al. 1992a,b, Brauer et al. 1993, Hadeler and Castillo-Chavez 1994) while the second incorporates treatment into HIV epidemiological models (Velasco-Hernández and Hsieh 1994; Hsieh and Velasco-Hernández 1994). The main model in this manuscript integrates both approaches. Section 2 revisits and modifies an earlier model of Velasco-Hernández and Hsieh (1994). Section 3 introduces the main model of this article following the approach of Hadeler and Castillo-Chavez (1994) and begins its analysis by computing the basic reproductive number and showing its relation to the equilibria. Section 4 provides the local stability analysis when treatment has no effect on transmission rates.

Section 5 provides the local stability anlysis of the full model as well as some numerical simulations. Section 6 provides the mathematical analysis of the model introduced in Section 2 when the non-core is not modeled explicitly. Section 7 summarizes our results while outlining future research.

2 Basic model

We start by reformulating the model of Velasco-Hernández and Hsieh (1994). Let S, U, and I denote the numbers of susceptible, untreated infectious, and treated infectious individuals respectively. If we denote by B the per-capita (that is, per susceptible) incidence rate then the model equations are

$$\begin{aligned} \frac{dS}{dt} &= g(S,U,I) - BS - \mu S \\ \frac{dU}{dt} &= BS - (\mu+\nu)U - \sigma\frac{U}{N} \\ \frac{dI}{dt} &= \sigma\frac{U}{N} - (\mu+\nu')I \end{aligned} \tag{1}$$

where $g(S,U,I)$ is the recruitment rate into the population; μ^{-1} is the average length of the sexually-active life of an average individual; σ is the treatment rate, and ν^{-1} and $(\nu')^{-1}$ are the length of the infective period for treated and untreated individuals respectively. The per-capita incidence rate is given by

$$B = \frac{c\beta_0 U + c'\beta_1 I}{N}$$

where $N = S + U + I$, c and c' are the average number of partners per unit time for each infectious class; β_0 and β_1 are the corresponding infectivity rates and, therefore, $c\beta_0$ and $c'\beta_1$ are the net disease transmission rates from each infective class, respectively.

Velasco-Hernández and Hsieh (1994) assumed that the recruitment rate was given by a constant Λ. Their model here is modified (following Blythe et al. 1992b) by modeling the recruitment with a function $g(S,I,U)$ that incorporates the potential effects of infection risk in the recruitment of new core group members. We will illustrate our results numerically using the specific recruitment function

$$g(S,U,I) = \Lambda e^{-\alpha\frac{U+I}{N}}$$

where the constant α is an index of the strength of the strength that disease prevalence has on the recruitment of core members. In section 6 we also show some analytical results when this recruitment term is used in model (1). This approach is based on the work of Blythe et al. (1992b) in which the authors analyze models of the form (1) with $c = 0$.

Blythe et al. (1992b) consider several types of recruitment functions g including

$$g(S, I) = G\Big(\frac{I}{S+I}\Big) = G\Big(\frac{I}{N}\Big)$$

where it is assumed that

$$\frac{\partial g}{\partial I} = \frac{S}{N^2} G'\Big(\frac{I}{S+I}\Big) \leq 0.$$

Blythe et al. (1992b) illustrate their results with the particular recruitment function

$$g(I/N) = \Lambda \exp(-\alpha I/N).$$

They show the existence of stable limit cycle solutions analytically and numerically, using the above recruitment function. Here we look at the effects that treatment and screening health policies may have on the asymptotic long term behavior of a sexually-transmitted diseases (STD), particularly AIDS. Treatment can play an important role in the outcome of public health policies, as can be seen by the direct role that it plays on the basic reproductive number of the disease. Velasco-Hernández and Hsieh (1994) and Hsieh and Velasco-Hernández (1994) found that for model (1) with a constant recruitment rate Λ, that is, where $g(S, I) = \Lambda$, the basic reproductive number $\mathcal{R}_0$ is given by

$$\Big(\frac{c\beta_0}{\mu+\nu}\Big) + \frac{\sigma\mu/\Lambda}{\mu+\nu}\Big(\frac{c'\beta_1}{\mu+\nu'} - 1\Big). \tag{2}$$

(see Velasco-Hernández and Hsieh, 1994). Note that $\sigma = 0$ gives the standard basic reproductive number for models without treatment. Here, we observe that the second term could be negative, yet high treatment/screening rate σ coupled with high enough β_1 can make $\mathcal{R}_0 \geq 1$. Treatment may fail and even be harmful if behavioral changes that reduce transmission in treated infectives do not take place or are ineffective when a disease reaches endemic levels. A similar model that also assumes a non-constant recruitment rate but does not incorporate treatment may exhibit periodic behavior near the endemic

equilibrium (Blythe et al. 1992b). The focus of this article is to look at the combined effects of treatment/screening policies and variable recruitment on disease dynamics. We closely follow the approach of Hadeler and Castillo-Chavez (1994) by incorporating the demographic effects of the size of the non-core population as "behavioral-dependent reservoir" for the core group and also by not including disease dynamics explicitly among non-core group members. These simplifying assumptions can be easily challenged; however, they do represent a serious attempt to incorporate complex behavioral effects on the simplest possible models of HIV dynamics found in the literature. The paradigms that have been dveloped by Blythe et al. (1992b), Hadeler and Castillo-Chavez (1994), and in this paper do support the unavoidable conclusion that unless more information is available, the simple and even the complex paradigms that have been proposed in the past (see Castillo-Chavez 1989, Jewell et al. 1991, Sattenspiel and Castillo-Chavez 1990, May and Anderson 1991, Anderson and May 1991, and references therein) only begin to scratch the surface of the possible realistic scenarios for disease dynamics. Further extensions are being carried out. For example, Heiderich et al. (1994) have modified related models to take into account the effects of delays in the behavioral response that governs the dynamics between core and non-core group members.

3 An extended model

When studying the dynamics of disease transmission within core groups one must take into account the fact that the core-group is inserted into a larger population which as a first step we assumed to be largely inactive in disease transmission. However, this population cannot be completely ignored as it provides new recruits into the core group and hence, the size of the pool becomes an important scaling factor. This effect has been addressed recently by Hadeler and Castillo-Chavez (1993) and we follow their approach and their ideas closely in this section. We study a homogeneous version of model (1) for which recruitment into the core population occurs at a rate $g(S, U, I) = r\Big(\frac{U+I}{N}\Big)$, that is, it depends on the proportion of the core population infected. This function $r(x)$ is a decreasing function on $0 < x < 1$ and satisfies $r(0) > 0$. The treatment rate is now a function $\sigma(N)$. Let P, S, U, and I denote the sizes of the non-core, and the susceptible, untreated infectious, and treated

infectious members of the core respectively. Following Hadeler and Castillo-Chavez (1994) we formulate the model as a general homogeneous system (Hadeler et al. 1988, Hadeler 1992, Busenberg et al. 1990) and then specialize to the case of constant population size. The model equations are as follows:

$$\begin{aligned}
\frac{dP}{dt} &= b(T-E) + \tilde{b}E - Pr\Big(\frac{U+I}{N}\Big) - \mu P, \\
\frac{dS}{dt} &= Pr\Big(\frac{U+I}{N}\Big) - cSB - \mu S, \\
\frac{dU}{dt} &= SB - \sigma(N)U - (\mu+\nu)U, \\
\frac{dI}{dt} &= \sigma(N)U - (\mu+\nu')I,
\end{aligned} \tag{3}$$

where $N = S+U+I$, T is the total population; $T = P+N$, $E = U+I$, and b and $\tilde{b}$ are the birth rates of non-infected and infected groups respectively. Finally, the term

$$B = c\beta_0\frac{U}{N} + c'\beta_1\frac{I}{N},$$

is the rate of acquisition of infection per susceptible individual with $c\beta_0$ and $c'\beta_1$ defined as in model (1).

3.1 Equilibria

In this section we study the equilibria of (3) for the special case in which we assume the same birth and death rates for treated and untreated members and that the total population size is constant. Thus $b = \tilde{b}$ and $\nu = \nu' = 0$. The assumption $\nu = \nu' = 0$ is obviously unrealistic; we make this assumption to allow for the possibility of total constant population size in the presence of infection. In order to allow for ν and ν' to be positive and still have bounded nonzero total population size it would be necessary to assume a nonlinear birth rate in the non-core population. Under the assumption

$$b = \tilde{b}, \qquad \nu = \nu' = 0,$$

we have

$$\frac{dT}{dt} = (b-\mu)T$$

and, therefore, we assume $b = \mu$ to give constant total population size. System (3) is a homogeneous system of degree 1 and thus we look for persistent solutions (Hadeler and Castillo-Chavez, 1994), that is, solutions of the form

$$(P, S, U, I)\exp(\lambda t). \tag{4}$$

Now we rescale (3) with the new non-dimensional time

$$t' = \mu t.$$

If we relabel the new rescaled parameters in (3) using the same names as before, then (3) can be rewritten with $\mu = 1$. The per-susceptible incidence rate becomes

$$\tilde{B} = cb_0\frac{U}{N} + c'b_1\frac{I}{N}$$

where

$$b_0 = \beta_0/\mu, \qquad b_1 = \beta_1/\mu.$$

Finally, system (3) is equivalent to the following system ($' = \frac{d}{dt'}$):

$$\begin{aligned}
P' &= T - Pr\Big(\frac{U+I}{N}\Big) - P, \\
S' &= Pr\Big(\frac{U+I}{N}\Big) - S\tilde{B} - S, \\
U' &= S\tilde{B} - \sigma U - U, \\
I' &= \sigma U - I.
\end{aligned} \tag{5}$$

Substituting (4) into (5), setting $E = 0$, and normalizing the total core group population N to 1 we arrive at the following nonlinear "eigenvalue" problem:

$$\begin{aligned}
\lambda P &= (P+1) - Pr(E) - P, \\
\lambda S &= Pr(E) - S\tilde{B} - S, \\
\lambda U &= S\tilde{B} - U - \sigma U, \\
\lambda I &= \sigma U - I.
\end{aligned} \tag{6}$$

Since $\lambda = 0$ corresponds to the case where we have a constant population size then the steady states of system (6) are obtained by solving the system of

equations that are obtained when we set the LHS equal to zero. One steady state is the disease-free equilibrium

$$(P^*, S^*, U^*, I^*) = (\frac{1}{r_0}, 1, 0, 0)$$

where $r_0 = r(0)$. Solutions with $E > 0$ of the nonlinear system obtained when the LHS of (6) equal to 0 require

$$r(E) = \frac{1}{P}.$$

Therefore, they are solutions of the following system of three equations:

$$\begin{aligned} 0 &= 1 - S\bar{B} - S, \\ 0 &= S\bar{B} - U - \sigma U, \\ 0 &= \sigma U - I. \end{aligned}$$

From the last equation we have

$$I = \sigma U,$$

and thus, the two remaining equations for S and U can be written as follows:

$$\begin{aligned} 0 &= 1 - S - \eta SU, \\ 0 &= \eta SU - (1+\sigma)U, \end{aligned} \tag{7}$$

where

$$\eta = \left(cb_0 + c'b_1\sigma\right).$$

From the second equation in (7) we have either $U = 0$, leading to the disease-free equilibrium $U = 0$, $I = 0$, $S = 1$, or η S $= 1 + \sigma$, leading to the equilibrium

$$S = \frac{1+\sigma}{\eta}, \qquad U = \frac{1}{1+\sigma} - \frac{1}{\eta}, \qquad I = \frac{\sigma}{1+\sigma} - \frac{\sigma}{\eta}$$

with $U > 0$ if and only if $\eta > 1 + \sigma$. On the average each untreated infective contributes cb_0 new infectives and each treated infective contributes $c'b_1$ new infectives if introduced into a susceptible population, each with a mean

infective period 1. From $I = \sigma U$, the proportion of untreated infectives is $\frac{1}{(\sigma+1)}$ and the fraction of treated infectives is $\frac{\sigma}{(\sigma+1)}$. This suggests

$$\mathcal{R}_0 = \frac{cb_0}{1+\sigma} + \frac{\sigma c b_1'}{1+\sigma} = \frac{\eta}{1+\sigma}$$

and in terms of $\mathcal{R}_0$, we can write the endemic equilibrium population sizes as

$$S^* = \frac{1}{\mathcal{R}_0}, \qquad U^* = \left(\frac{\mathcal{R}_0 - 1}{\eta}\right), \qquad I^* = 1 - S^* - U^*, \tag{8}$$

provided that $\mathcal{R}_0 > 1$. In addition, since $\sigma > 0$ we must have $\mathcal{R}_0 < \eta$. Thus there is an endemic equilibrium provided

$$1 < \mathcal{R}_0 < \eta. \tag{9}$$

We now proceed to study the local stability analysis of solutions of the form (4) of the system (3).

4 Local stability of equilibria

We begin by introducing the following re-scaled variables:

$$p = \frac{P}{N}, \qquad s = \frac{S}{N}, \qquad u = \frac{U}{N}, \qquad i = \frac{I}{N}, \qquad e = u + i.$$

We use these re-scaled variables plus the condition $b = 1$ so that the total population size remains constant. Reformulating system (5) using these new variables leads to the following system of equations:

$$\begin{aligned} p' &= (1+p)[1 - r(e)p], \\ u' &= \hat{B}(1-e) - u(\sigma + pr(e)), \\ i' &= \sigma u - ipr(e), \end{aligned} \tag{10}$$

with

$$\hat{B} = cb_0 u + c'b_1 i.$$

We first examine a simple case in which we assume that treatment has no effect on the transmission rates of both infectious classes, that is, we assume

$cb_0 = c'b_1 = \beta$. Now there is no distinction between treated and untreated infectious and instead of the model (10) with u and i, we reduce (10) to the two-dimensional system

$$\begin{aligned} p' &= (1+p)[1 - r(e)p], \\ e' &= \beta e(1-e) - epr(e), \end{aligned} \tag{11}$$

with $e = u + i$. Here β denotes the effective contact rate rescaled by the length of the average sexually-active life of the population and is therefore a non-dimensional quantity. For (11), we have

$$\eta = cb_0 + c'b_1\sigma = \beta(1+\sigma)$$

and the basic reproductive number $\frac{\eta}{(1+\eta)}$ for (10) reduces to β for (11).

We shall now study the stability properties of the equilibria of system (11). It is easy to verify that the first quadrant of the phase plane is an invariant set and that every orbit of (11) is bounded. Thus it will follow from the Poincaré-Bendixson Theorem that all stability properties are global.

We now look for equilibrium solutions of (11). Setting the RHS of (11) equal to zero we obtain the unique endemic solution

$$p^* = \frac{1}{r(e^*)}, \qquad e^* = 1 - \frac{1}{\beta},$$

provided $1 < \beta$. If $\beta < 1$ we obtain only the disease-free equilibrium solution, in this case, $r(0) = r_0$. Note that both equilibria are identical to those found in the previous section and that in this case $\mathcal{R}_0 = \beta$. The Jacobian matrix of (11) is

$$\begin{bmatrix} 1 - r(e)(1+2p) & -(1+p)p\frac{\partial r}{\partial e} \\ -r(e)e & \beta(1-2e) - p(e\frac{\partial r}{\partial e} + r(e)) \end{bmatrix}, \tag{12}$$

which when evaluated at the disease-free equilibrium gives the eigenvalues $-1 - r_0$, $\beta - 1$. Therefore, the disease-free equilibrium is unique and globally asymptotically stable if and only if $\mathcal{R}_0 < 1$. If $\mathcal{R}_0 > 1$ there exists a unique endemic equilibrium while the disease-free equilibrium is unstable (saddle point).

A direct substitution into (12) of the values for the endemic equilibrium, gives the Jacobian matrix J:

$$J = \begin{bmatrix} -r^* - 1 & -\frac{\rho}{r^*}(1 + \frac{1}{r^*}) \\ -r^*(1 - \frac{1}{\mathcal{R}_0}) & -(1 - \frac{1}{\mathcal{R}_0})(2\mathcal{R}_0 + \frac{\rho}{r^*}) + \mathcal{R}_0 - 1 \end{bmatrix},$$

where $\rho = \dfrac{\partial r}{\partial e}$ is evaluated at e^*, $\mathcal{R}_0 = \beta$, and in this simplified case $r^* = r(e^*)$. By hypothesis, $\rho < 0$. The stability of J is determined by the roots of

$$\lambda^2 + a_0\lambda + a_1 = 0,$$

the characteristic polynomial of J where

$$\begin{aligned} a_0 &= r^* + 1 + \frac{\mathcal{R}_0 - 1}{\mathcal{R}_0}\Big(2\mathcal{R}_0 + \frac{\rho}{r^*}\Big) + 1 - \mathcal{R}_0 \\ a_1 &= (r^*+1)\Big[\frac{\mathcal{R}_0 - 1}{\mathcal{R}_0}\Big(2\mathcal{R}_0 + \frac{\rho}{r^*}\Big) - (\mathcal{R}_0 - 1]\Big) - \rho(1 + \frac{1}{r^*})(\frac{\mathcal{R}_0 - 1}{\mathcal{R}_0}) \\ &= (r^*+1)(\mathcal{R}_0 - 1) > 0. \end{aligned}$$

Also $a_0 > 0$ if and only if (again, $\rho < 0$ by hypothesis)

$$\mathcal{R}_0(r^* + 1) > -(\mathcal{R}_0 - 1)[\mathcal{R}_0 + \frac{\rho}{r^*}].$$

From these conditions, it follows that for $\mathcal{R}_0$ in the interval

$$(-\frac{\rho}{r^*}, \infty),$$

the endemic equilibrium is asymptotically stable. However, for

$$\mathcal{R}_0 < -\rho/r^*,$$

there exists numbers $1 < \omega_0 < \omega_1 < -\rho/r^*$ such that for $\mathcal{R}_0 \in (\omega_0, \omega_1)$ the endemic equilibrium is unstable. From (11) one can also see that the set

$$D = \{(p,e): \quad 0 < p \le \frac{1}{r^*}, \qquad 0 < e \le 1\} \tag{13}$$

is bounded and invariant under the flow generated by (11). Therefore, the Poincaré-Bendixon theorem implies the existence of a periodic orbit within D which is the ω-limit set of orbits in D. Thus, the following result has been established:

Theorem 1 *Suppose $\rho < 0$. Then, whenever $\mathcal{R}_0 < 1$ the equilibrium point*

$$p^* = \frac{1}{r_0}, \qquad e^* = 0$$

of (11) is unique and globally asymptotically stable. However, if $\mathcal{R}_0 > 1$ there exists a second equilibrium,

$$p^* = \frac{1}{r(e^*)}, \qquad e^* = 1 - \frac{1}{\mathcal{R}_0}.$$

which has the property that, for any initial conditions (p_0, e_0) in the set D defined by (13), if

$$\mathcal{R}_0 \in (\omega_0, \omega_1)$$

as defined above, then the equilibrium is unstable and there exists an attracting periodic orbit which is the ω-limit set of orbits in D. If, on the other hand,

$$\mathcal{R}_0 \in [-\frac{\rho}{r^*}, +\infty)$$

the equilibrium is globally asymptotically stable in D.

In Figure 1 we present some numerical simulations illustrating the behavior of the system when $\mathcal{R}_0$ satisfies the hypotheses of Theorem 1 which guarantee the existence of a limit cycle.

5 Analysis of the full model

In this section we study the stability properties of the system (10) under the assumption that treatment induces a change in sexual behavior resulting in lowered infectivity of the treated infectious class, so that $cb_0 > c'b_1$. Actually, our analysis does not make the assumption $cb_0 = c'b_1$ used to obtain the simple case (11) and thus requires study of the full three-dimensional system (10). It is reasonable to assume (or at least to hope) that $cb_0 > c'b_1$, but this does not enter into the analysis. We are able to treat analytically the system (10) only in the special case $\sigma = 0$ but have some numerical simulations for $\sigma > 0$.

The system (10) has a disease-free equilibrium with $u = 0, i = 0$ and $p = \frac{1}{r(0)}$, an endemic equilibrium (p^*, u^*, i^*) given by

$$\begin{aligned} p^* &= 1/r^*, \\ u^* &= \frac{1}{\sigma+1} - \frac{1}{\eta} = \frac{(\mathcal{R}_0 - 1)}{(\sigma+1)\mathcal{R}_0}, \\ i^* &= \sigma u^*, \end{aligned}$$

where $e^* = u^* + i^*$, $r^* = r(e^*)$, and, as before, $\eta = cb_0 + c'b_1$, $\mathcal{R}_0 = \frac{\eta}{(\sigma+1)}$. The Jacobian J matrix of (10) at an equilibrium is

$$\begin{bmatrix} -(1+\rho)r(e) & -\rho(1+rho)r'(e) & -\rho(1+\rho)r'(e) \\ -ur(e) & cb_0(1-e) - \bar{B} - (\sigma + \rho r(e)) - u\rho r'(e) & c'b_1(1-e) - \bar{B} - u\rho r'(e) \\ -ir(e) & \sigma - i\rho r'(e) & -\rho r(e) - i\rho r'(e) \end{bmatrix},$$

where $r(e) = r(u+i)$,

$$\frac{\partial r}{\partial u} = \frac{\partial r}{\partial i} = r'(e) < 0$$

for all u and i.

At the disease-free equilibrium $(\frac{1}{r(0)}, 0, 0)$, thus the matrix is

$$J = \begin{bmatrix} -r_0 - 1 & -r'(0)\frac{1}{r_0}(1 + \frac{1}{r_0}) & -r'(0)\frac{1}{r_0}(1 + \frac{1}{r_0}) \\ 0 & cb_0 - \sigma - 1 & c'b_1 \\ 0 & \sigma & -1 \end{bmatrix}.$$

If $\mathcal{R}_0 < 1$, that is, if $\eta < \sigma + 1$, it is not difficult to verify via the Routh-Hurwitz criteria that the eigenvalues of the matrix J have negative real parts and thus the disease-free equilibrium is asymptotically stable.

To study the stability properties at the endemic equilibrium if $\mathcal{R}_0 > 1$, we look at a special case. Suppose that we begin with a non-zero proportion of treated infectious members and then cease treatment, making $\sigma = 0$. The model becomes

$$\begin{aligned} p' &= (1+p)[1 - r(e)p], \\ u' &= \bar{B}(1-e) - upr(e), \\ i' &= -ipr(e). \end{aligned} \tag{14}$$

Now $\eta = cb_0$, $\mathcal{R}_0 = \eta$, and the endemic equilibrium is given by

$$p^* = 1/r^*, \qquad e^* = 1 - \frac{1}{\eta}, \qquad u^* = e^*, \qquad i^* = 0.$$

The Jacobian matrix J at this equilibrium is

$$\begin{bmatrix} -(1+p^*)r(e^*) & -p^*(1+p^*)r'(e^*) & -p^*(1+p^*)r'(e^*) \\ -u^*r(e^*) & cb_0(1-e^*) - \eta u^* - 1 - u^*p^*r'(e^*) & cb_1(1-e^*) - \eta u^* - u^*p^*r'(e^*) \\ 0 & 0 & -1 \end{bmatrix},$$

The eigenvalues of this matrix are -1 and the eigenvalues of the 2×2 matrix

$$J = \begin{bmatrix} -(1+p^*)r(e^*) & -p^*(1+p^*)r'(e^*) \\ -u^*r(e^*) & -\eta u^* - 1 - u^*p^*r'(e^*) \end{bmatrix}.$$

The endemic equilibrium is asymptotically stable if and only if the determinant of the matrix is positive and the trace of the matrix is negative. The determinant is

$$\eta u^*(1+p^*)r(e^*) > 0$$

and the trace is

$$-(1+p^*)r(e^*) - \eta u^* - u^*p^*r'(e^*).$$

Since $\eta u^* = \eta - 1$ and $p^*r(e^*) = 1$, the stability condition is

$$\left(1 - \frac{1}{\eta}\right)\frac{r'(e^*)}{r(e^*)} + r(e^*) + \eta > 0.$$

Thus the condition is obviously satisfied for $\eta = 1$ and $\eta \to \infty$, but there could be an intermediate range of $\eta = \mathcal{R}_0$ for which the equilibrium is unstable; this depends on the form of the function r.

Therefore we have the following:

Theorem 2 *Consider system (14). If*

$$\mathcal{R}_0 > \omega > 1$$

then the infected state is locally asymptotically stable. If, however,

$$\omega > \mathcal{R}_0 > 1$$

then the endemic state is unstable.

We can integrate the last equation of (14) so that

$$i(t) = f(t, u(t)),$$

where f satisfies $f(t, u(t)) \to 0$ as $t \to \infty$. The limiting system (as $t \to \infty$) of (14) is then

$$\begin{aligned} p' &= (1+p)[1 - r(u)p], \\ u' &= cb_0u(1-u) - upr(u), \end{aligned} \tag{15}$$

which is exactly (11). Thus, the results of Theorem 1 hold and hence the equilibria of (15) are isolated and finite in number. Furthermore, an application of Theorem 1.5 in Thieme (1993a,b) for asymptotically autonomous systems (see also Thieme 1992 and Castillo-Chavez and Thieme 1994) implies that the following theorem holds:

Theorem 3 *Let Ω be the ω-limit set of (14) and let*

$$D = \{(p, u, i) : \quad 0 < p \le \frac{1}{r^*}, \qquad 0 < u \le 1, \qquad i = 0\}.$$

Then

$$\Omega \subset D.$$

Moreover, Ω equals the ω-limit set of system (15).

We have explored numerically the asymptotic behavior of the full 3-D model for various values of the treatment parameter $\sigma > 0$. We were unable, after several simulations for various ranges of σ, to obtain periodic solutions. Nevertheless some interesting results were observed. Figures 2 and 3 show three dimensional plots of our simulations where we see that an increase in σ may generates a pronounced oscillatory approach to the endemic equilibrium. This observation is also supported by the simulations described in Figures 4 and 5 where we show the time plots of the variables p (non-core population) and i (the treated infectious population). Hence qualitatively different transient behavior for different values of σ is quite evident. For small σ both p and i approach their respective equilibrium values rather quickly; for intermediate values of σ we observe strong overdamped oscillations before reaching equilibrium values (these equilibrium values are reached only slightly later than in the previous case). For large σ the oscillations last for a long time

and decrease in amplitude. Note however, that for intermediate and large σ values, the size of the proportion i is practically the same. However, we are using re-scaled variables, and small differences at this level may correspond to large differences in terms of the original variables.

6 Analysis of a special case

To contrast our results with earlier published results as well as with the results of prior sections, we partially analyze a model that excludes the non-core explicitly while including explicit forms for the (state-dependent) recruitment and treatment rates. A model of this type with $\sigma = 0$ has been studied by Blythe et al. (1992b). The equations to be studied in this section are:

$$\begin{aligned}\frac{dS}{dt} &= \Lambda e^{-\alpha(\frac{I+U}{N})} - BS - \mu S,\\ \frac{dU}{dt} &= BS - (\mu+\nu)U - \sigma\frac{U}{N},\\ \frac{dI}{dt} &= \sigma\frac{U}{N} - (\mu+\nu)I,\end{aligned}$$

where S, U, I, and B, as well as the other parameters are defined as in (1). For model (1) with $\alpha = 0$ there are two equilibria whenever $\mathcal{R}_0 > 1$: the disease-free and endemic states (Velasco-Hernandez and Hsieh, 1994). The disease-free equilibrium is $(\Lambda/\mu, 0, 0)$, and to prove the existence of the endemic equilibrium we define the following re-scaled variables and quantities:

$$S^* = \frac{\mu}{\Lambda}S, \quad U^* = \frac{\mu}{\Lambda}U, \quad I^* = \frac{\mu}{\Lambda}I$$

and

$$b_0 = \beta_0/\mu, \quad b_1 = \beta_1/\mu, \quad \sigma' = \sigma/\Lambda, \theta = 1 + \nu/\mu,$$

where the new non-dimensional 'time', is as in Section 3

$$\tau = \mu t.$$

The re-scaled model now stands ($' = \frac{d}{d\tau}$) : to . $\quad S' = e^{-\alpha\frac{U+I}{N}} - BS - S$,
$U' = BS - \theta U - \sigma'\frac{U}{N}$
$I' = \sigma'\frac{U}{N} - \theta I$,where, as in Section 3

$$B = cb_0\frac{U}{N} + cb_1\frac{I}{N}.$$

For notational convenience we relabel the new state variables with their original labels. The Jacobian matrix of (16) at the disease-free equilibrium is

$$\begin{bmatrix} -1 & -b_0-\alpha & -b_1-\alpha \\ 0 & cb_0-\sigma-\theta & cb_1 \\ 0 & \sigma & -\theta \end{bmatrix},$$

and expression (2) can be rewritten as

$$\mathcal{R}_0 = R + \sigma k(\hat{R} - 1) \tag{16}$$

with

$$k = \frac{\mu}{\Lambda(\mu+\nu)}$$

and

$$R - 1 = b_0/\theta, \quad \hat{R} - 1 = b_1/\theta.$$

Using the Routh-Hurwitz criteria one can easily show that whenever $\mathcal{R}_0 < 1$ then the disease-free equilibrium is asymptotically stable. For values of $\sigma = 0$ the model reduces to the one studied by Blythe et al. (1992b) for which there may appear limit cycles whenever the value of the basic reproductive number is large enough. Furthermore, the behavior of this model presents some differences with the behavior of model (1): if σ is positive and α is high enough then cyclic behavior is also possible.

To show the existence of an endemic equilibrium point whenever $\mathcal{R}_0 > 1$ we proceed as follows: Equate the LHS of (16) to zero and find

$$S^* = \frac{g^*}{1+B^*}, \quad U^* = \frac{B^*S^*}{\theta+\sigma}, \quad I^* = \frac{\sigma U^*}{\theta}, \tag{17}$$

where $g^* = \exp(-\alpha(I^*+U^*)/N^*)$. Substitution of these expressions into the definitions of N^* and B^* lead to a system of non-linear algebraic equations whose fixed points are the equilibria of the model equations defining (16). After some algebra we find that

$$B^* = \frac{B^*g^*}{(1+B^*)(\theta+\sigma)N^*}\Big(b_0 + b_1\frac{\sigma}{\theta N^*}\Big), \tag{18}$$

and (19)

$$N^* = \frac{g^*}{1+B^*}\Big(1 + \frac{B^*}{\theta+\sigma} + \frac{\sigma B^*}{(\theta+\sigma)\theta}\Big).$$

If we define

$$a(N) = \frac{b_0 + b_1 \frac{\sigma}{\theta N}}{\theta + \sigma}$$

then, since

$$\frac{I^* + U^*}{N^*} = \frac{B^* g^*}{(1 + B^*)(\theta + \sigma)N^*}(1 + \frac{\sigma}{\theta}),$$

we have that

$$B^* = \frac{g^*}{N^*} a(N^*) - 1$$

which it implies that B^* is positive only if $\mathcal{R}_0 > 1$ (Recall $\mathcal{R}_0 > 1$ is given by (17)). Note that $B^* = 0$ implies $N^* = g^* = 1$ and the substitution of $B^* = 0$ into (19) renders the disease-free equilibrium which always exists.

Using the definitions of a and B given above, and dropping the superscript * from the variables, we formulate the following equivalent system of equations:

$$\begin{aligned} \log g &= \frac{-\alpha}{a(N)(\theta + \sigma)}\Big((a(N) - 1)(\theta + \sigma) + 1 + \sigma/\theta\Big), \\ N &= \frac{a(N) g (1 + \sigma/\theta)}{(a(N) - 1)(\theta + \sigma) + 1 + \sigma/\theta}. \end{aligned} \tag{20}$$

System (21) can be reduced to the following single nonlinear algebraic equation in terms of the total population N:

$$N = \frac{a(N)(1 + \sigma/\theta)}{(a(N) - 1)(\theta + \sigma) + 1 + \sigma/\theta} e^{-G(N)} \tag{21}$$

where

$$G(N) = \frac{\alpha}{a(N)(\theta + \sigma)}\Big((a(N) - 1)(\theta + \sigma) + 1 + \sigma/\theta\Big).$$

Equation (22) has the form

$$N = F(N)$$

where F satisfies

$$\lim_{N \to 0} F(N) = e^{-\alpha}/\theta, \quad \lim_{N \to \infty} \frac{dF}{dN} = 0.$$

Moreover, $\frac{dF}{dN} < 0$, and the second derivative of F with respect to N tends to zero as N approaches infinity and it remains bounded when N goes to

zero. These properties imply the existence of a unique endemic equilibrium. We summarize our results as follows:

Theorem 4 *Let $\mathcal{R}_0 > 1$. There exists a unique endemic equilibrium point for (16), namely, the fixed point of*

$$N = F(N)$$

where F is given by (21).

Note that as $\alpha \to \infty$, the solution N of the above equation goes to zero, implying that the sizes of S^*, U^* and I^* also go to zero.

Simulations show the existence of periodic stable solutions. Their appearance may be controlled by the size of the parameter α. Large values of α, as mentioned in the last section, lead to very small values of the coordinates of the equilibrium, but the amplitude of the periodic orbit seems to increase as the value of α increases. The existence of periodic orbits is also appears to be largely independent of the treatment rate σ. Figure 6 shows the results of simulations for two different values of r, one before and one after the bifurcation that gives rise to the periodic solution.

7 Conclusions

Simple models that take into account disease level effects on the recruitment rate of susceptible members into the core population as well as the effects of the treatment rates on disease dynamics exhibit more complex dynamics than those that exclude these effects (but see Heiderich et al. 1994). It is therefore important to try to sort out the time scales at which behavioral changes and treatment effects begin to impact disease dynamics and public policy. Obviously our models are too simple to be taken as generic of real world dynamics. However, their study provide an important warning against ignoring behavioral factors in the study of disease dynamics as well as on the evolution of STDs.

In this article, the recruitment rate which it is assumed to be a function of the prevalence of the disease within the core group can trigger the appearance of periodic solutions through Hopf bifurcation. Models that exclude explicitly the time evolution of the non-core population (which implicitly provides

new recruits into the core group) may or may not be capable of exhibiting periodic outbreaks as we vary the treatment rate. Our limited numerical simulations suggest that sustained periodic behavior may in fact not be possible. However, when we take into account the population dynamics of the non-core populations then the treatment rate plays a more important role. In fact, variations on the treatment rate lead to at least drastic changes in the transient behavior of solutions. In fact, high or intermediate treatment rates may induce damped oscillatory approaches to the endemic equilibrium with slowly decreasing amplitudes. The appearance of forward and backward bifurcation phenomena as the magnitude of the basic reproductive number increases is illustrated in the model of section 4.1. Similar phenomena have been explored by Hadeler and Castillo-Chavez (1994) and Feng and Thieme (personal communication). Our conjecture is that our full 3-D model exhibits similar behavior, but we have no formal proof of it. Our numerical simulations are inconclusive but suggestive.

The results presented in this paper are an attempt to explore the dynamics of infectious diseases in non-isolated core groups. We have emphasized the qualitative properties of models that incorporate into their framework state-dependent recruitment and core-specific treatment rates. Obviously the models studied are too simple to be used in the 'real' world. However, we believe that their study will continue to provide deeper paradigms that may help us understand the dynamics of diseases such as HIV/AIDS that exist and evolve in complex social environments.

8 Acknowledgements

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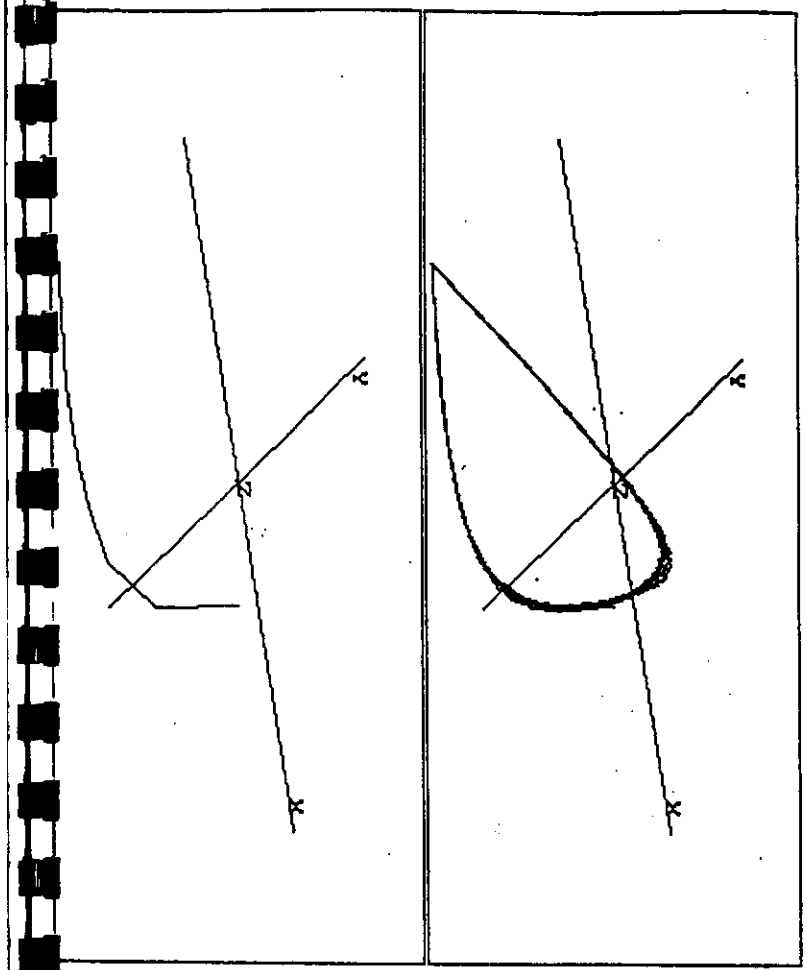
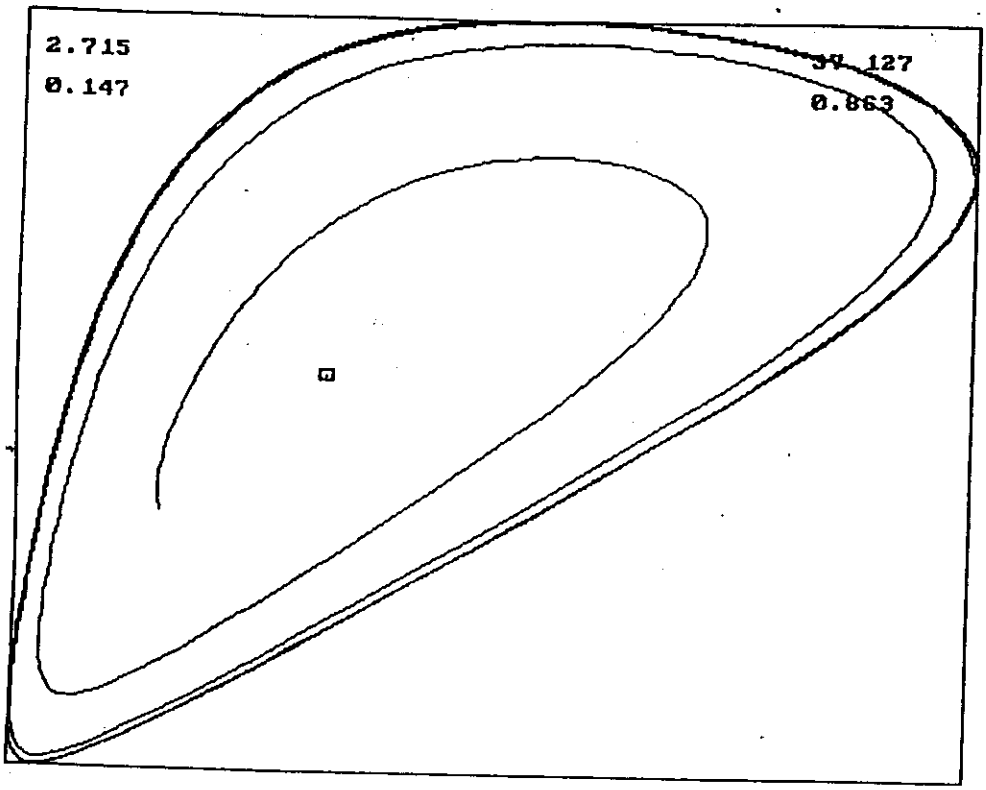
Figure captions

- **Figure 1** Limit cycle of equation (17) for the parameter values $\beta = 2.1$ and $r(e) = \exp(-\kappa e)$, with $\kappa = 5.0$.
- **Figure 2** Three-dimensional plot of system (16) with the parameter values $\beta_0 = 2.0$, $\beta_1 = 0.1$, $r(i+u) = \exp(\kappa(i+u)$ with $\kappa = 3.0$ and $\sigma = 0.5$.
- **Figure 3** Same as before but with $\beta_1 = 1.8$, $\kappa = 8$ and $\sigma = 0.7$.
- **Figure 4** Time plot of solutions for the total population in system (16) with parameters $\beta_0 = 2.0$, $\beta_1 = 0.1$, $\kappa = 8.0$ and a range of values of σ.
- **Figure 5** Same as before but now plots are shown for the infectious compartment.
- **Figure 6** Simulation of equation 3 with the parameter values $\beta_0 = 33$, $\beta_1 = 32$, $\theta = 4.3$, $\sigma = 0.5$ and $\tau = 9$ (top graph) and $\tau = 8.8$ (bottom graph). The equations were simulated using an equivalent system for the variables T (total population), S and I.

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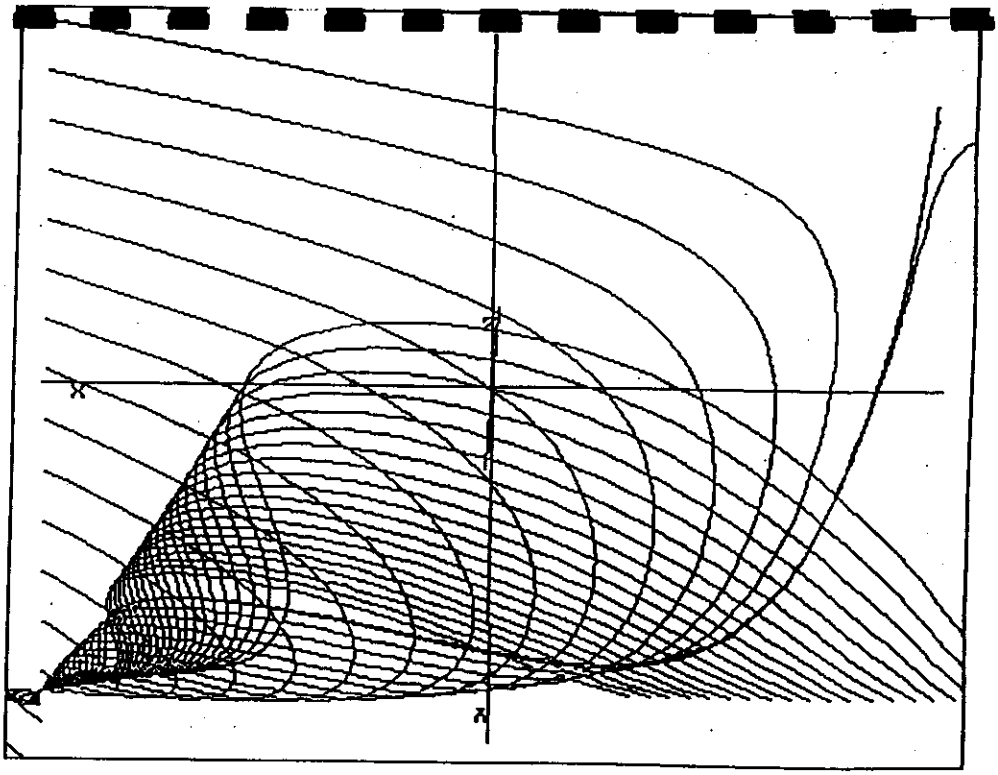

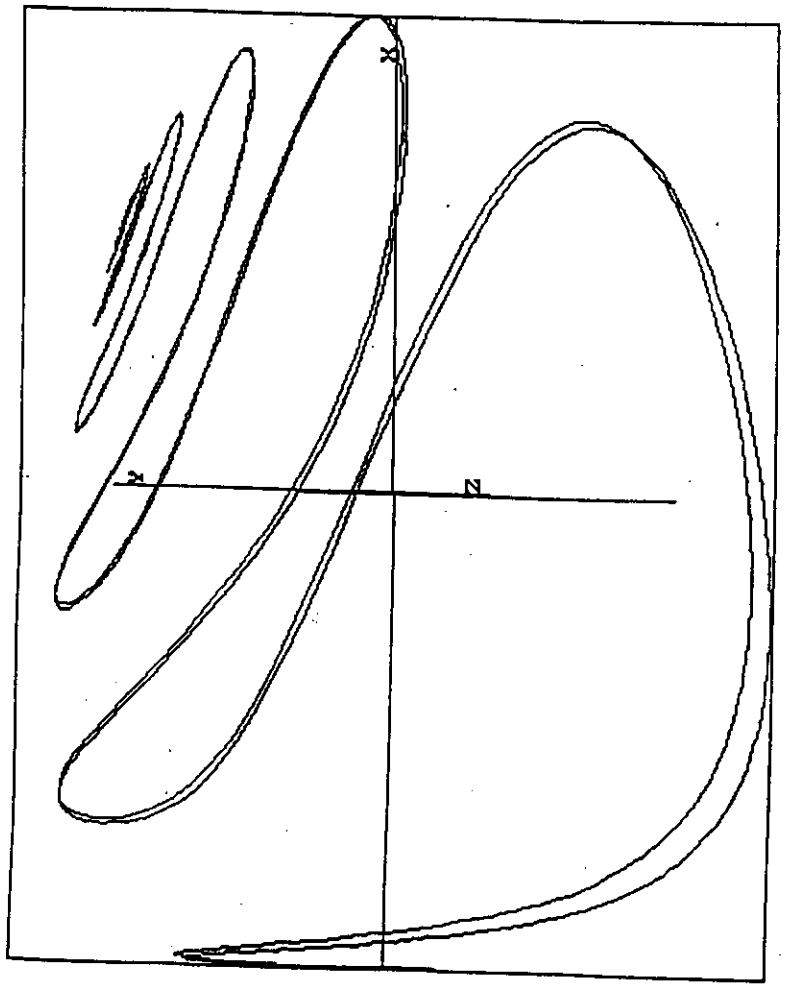
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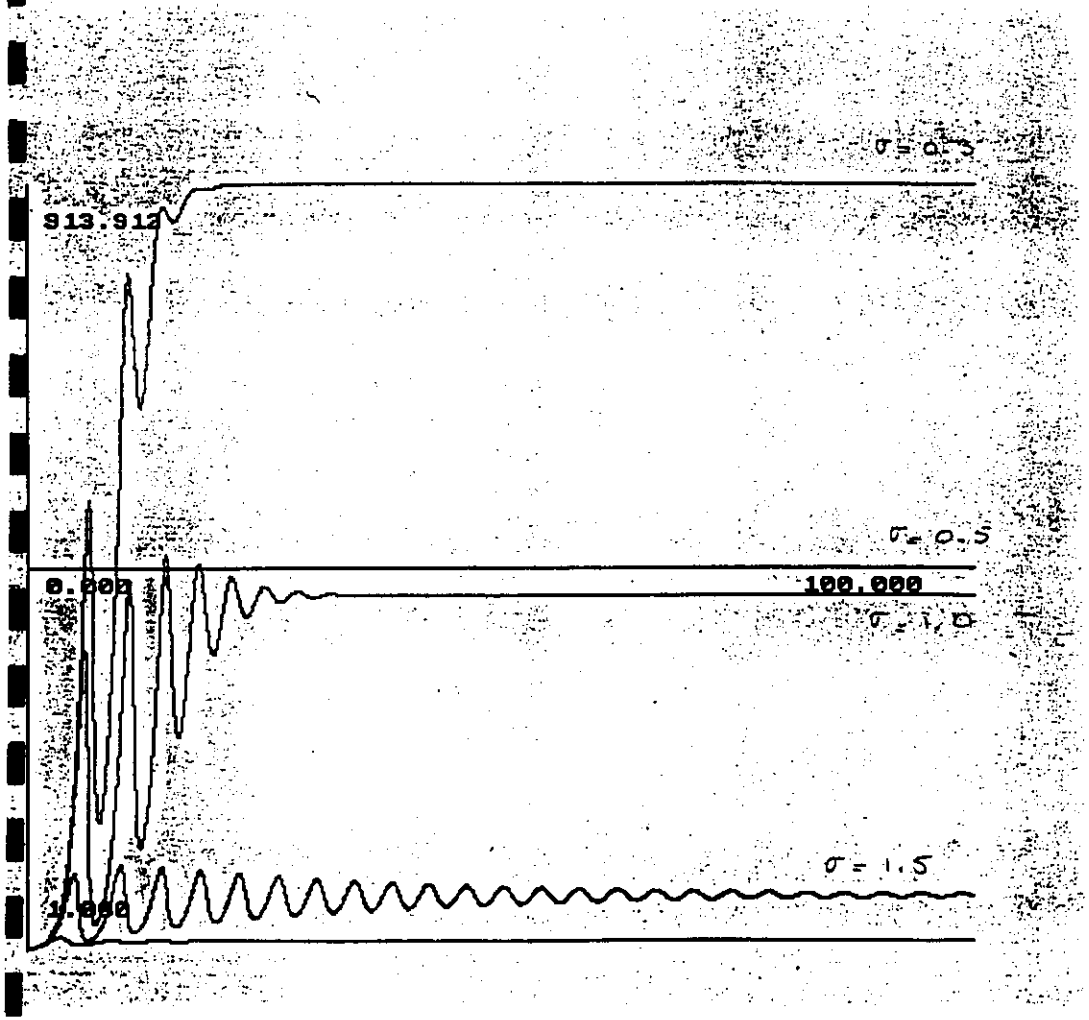
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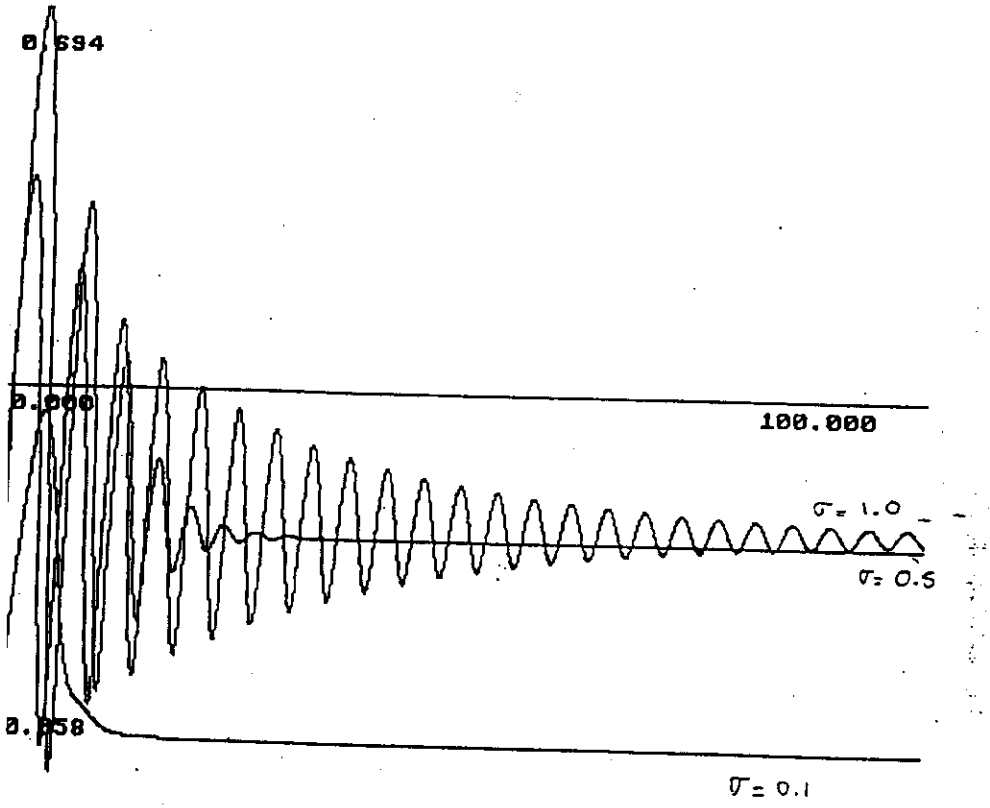
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