Mathematical Biology

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The effect of density-dependent treatment and behavior change on the dynamics of HIV transmission

Abstract. In this work, we propose a model for heterosexual transmission of HIV/AIDS in a population of varying size with an intervention program in which treatment and/or behavior change of the infecteds occur as an increasing function of the density of the infected class in the population. This assumption has socio-economic implications which is important for public health considerations since density-dependent treatment/behavior change may be more cost-saving than a program where treatment/behavior change occurs linearly with respect to the number of infecteds. We will make use of the conservation law of total sexual contacts which enables us to reduce the two-sex model to a simpler one-sex formulation. Analytical results will be given. Unlike a similar model with linear treatment/behavior change in Hsieh (1996) where conditions were obtained for the eradication of disease, we will show that density-dependent treatment/behavior change *cannot* eradicate the disease if the disease is able to persist without any treatment/behavior change. This work demonstrates the need to further understand how treatment/behavior change occurs in a society with varying population.

1. Introduction

The worldwide spread of the AIDS epidemic has been far reaching in the last decade. While in the late 1970s and early 1980s AIDS cases were confined mostly to the homosexual men and IV drug users in North America and Europe, there seems to be little evidence that the disease has spread to the general heterosexual population in these regions after more than a decade and half. However there are convincing signs that HIV/AIDS has yet to do its greatest harm, especially in developing nations in Africa, Asia, and Latin America (see, e.g. Sittitrai and Brown 1992, Brown and Xenos 1994, and Chin 1995). It is also important that, contrary to the situation in the developed countries, heterosexual transmission is the principle

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mode of infection in Africa and Asia (see e.g. Anderson et al. 1991, Sittitrai and Brown 1992, or Brown and Xenos 1994).

Early epidemiological models of sexually transmitted diseases were studied by Dietz and Hadeler (1988) and Waldstätter (1989) using a simple two-sex model. Other studies of heterosexual transmission models of HIV include Anderson et al. (1988), May et al. (1988a, b), LePont and Blower (1991), Lin et al. (1993), and Busenberg et al. (1995). Theoretical studies in the past on control measures for the transmission of HIV/AIDS using mathematical models include Scalia-Tomba (1991) on effect of behavior change on spread of HIV, Hsieh (1991) on screening and removal of HIV positives, Anderson, Gupta, and May (1991) and Hsieh and Velasco-Hernandez (1995) on community-wide treatment of HIV, and Velasco-Hernandez and Hsieh (1994) on effect of treatment and behavioral change. In all of the above-mentioned work on treatment and/or behavior change, only homosexual transmission is considered. Moreover, a constant population size is assumed which might be inappropriate for communities where the population size is varying. More recently, Velasco-Hernandez et al. (1996) studied the effect of treatment and behavior change using a mathematical model with prevalence-dependence recruitment into the core group.

In Hsieh (1996), a model is proposed for heterosexual spread of HIV in a varying population with linear treatment/behavior change rate of the HIV infecteds. It was shown analytically that thresholds exist for the elimination of endemic fractions and for the total eradication of the disease in the population. Linear rate of change for treatment and/or behavior change of the infecteds were also used in Scalia-Tomba (1991) or Anderson, Gupta, and May (1991). In this work, we will use a nonlinear density-dependent treatment/behavior change rate which describes a different, and possibly more cost-effective, control strategy. The motivation for this nonlinearity assumption is two-fold: (i) It has been documented that sex behavior changes with HIV prevalence (or knowledge about prevalence) in the untreated population (Miller et al. 1990); (ii) The number of individuals to be treated is always less than that of the linear model, thus results in a less costly program. Our aim is to compare theoretically the effects and cost-effectiveness of different prevention strategies. In this case the reduction to a one-sex model is possible under a well-known conservation law for total number of contacts. We will show that this nonlinearity significantly alters the dynamics of the model in question and more crucially, makes the eradication of the disease impossible, given that the disease will persist without any interventions. More precisely, we will prove analytically that there is no threshold for the elimination of the endemic fractions, given that the endemic fractions would persist without any treatment or behavior change occurring. Thus the density-dependent intervention program has no effect on the persistence of endemic fractions.

The model is given in Section 2 along with the reduction to simpler one-sex formulation using a conservation of contacts assumption which simply assumes that each heterosexual contact involves only one male and one female. Section 3 will be devoted to the analysis of reduced one-sex model for treatment. Biological interpretations of the resulting threshold parameters for persistence of the epidemic and the population size will be gives at the end of the section. Finally, we will give general remarks in Section 4.

2. Model formulation and reduction to one-sex problem

To derive the model equations with treatment, the active population in each sex is divided into three classes, S_j (susceptibles), U_j (untreated infecteds), and T_j (treated infecteds) with $j = f, m$ denoting female and male, respectively. The untreated infecteds are the infecteds who have not been detected by the screening program and therefore are not under treatment. The treated infecteds are those under treatment but have not yet developed full-blown AIDS and hence are still sexually active. Moreover, $N_j = S_j + U_j + T_j$ is the total population size for each sex.

The removal rate not due to AIDS is the same for male or female, denoted by $\mu > 0$. The assumption of proportional recruitment is employed in our model to reflect the varying population size prevalent in many developing nations. The recruitment of new males and females into the population is assumed to be proportional to the total population size $N = N_f + N_m$ at a constant rate $b_j > 0$, $j = m, f$, respectively. Moreover, the disease is assumed to be transmitted by heterosexual contact only since our focus is on that of heterosexual transmission of HIV. We also assume c_j, $j = f, m$, is the average number of contacts by individuals of sex j with individuals of opposite sex per unit time which does not change with treatment. (For related discussions on the assumption of constant contact rates, see LePont and Blower 1991 or Busenberg et al. 1995). β_j is the probability of transmission by an untreated infective of sex j; and β'_j is the corresponding probability of transmission for the treated infecteds which is assumed to be less than that of the untreated infecteds. The reason for the last assumption is that the treatment, which could include educational programs, may result in a lower transmission probability by the treated infecteds (see e.g. de Wit and van Griensven 1994). Some treatment might even possibly reduce the infectivity of the patient, although that is yet inconclusive. We could, but will not, also use a different contact rate for the treated infecteds which would result in a much more complicated system (see discussion in Hsieh 1996). The incidence rate is thus $B_j(t)S_j$, $j = f, m$, where

$$B_f(t) = c_f \frac{\beta_m U_m + \beta'_m T_m}{N_m} \tag{1}$$

$$B_m(t) = c_m \frac{\beta_f U_f + \beta'_f T_f}{N_f} \tag{2}$$

We also assume $\nu > 0$ is the AIDS-related removal rate. Similar to the model in Hsieh (1996), we assume the treatment has little effect on AIDS-related removal since it is still unclear whether medical treatment, e.g. by zidovudine, actually improves survival (Swanson et al. 1994). Assuming proportionate mixing, the earlier assumption of constant contact rates allows us to arrive at the following simple balance law (see Busenberg and Castillo-Chavez 1991 or Castillo-Chavez and Busenberg 1991 for general discussions)

$$c_f N_f = c_m N_m, \tag{3}$$

a consistency condition which simply states that total contacts for males and females must be equal at all time. For detailed discussion on the modeling implications of this condition, see Busenberg et al. (1995).

Finally, we assume the recruitment of new males and females into the population to be $b_f N$ and $b_m N$, respectively. That is, they are proportional to the total population N with constants of proportionality $b_m = b/(1 + c_m/c_f)$ and $b_f = b/(1 + c_f/c_m)$. To justify the above expressions for b_m and b_f, note that the consistency condition (3) implies that $N_m/N_f = c_f/c_m$ at all time. To maintain such proportion it is intuitive to assume that, if c_f is larger than c_m the recruitment of males b_m must be larger than the recruitment of females b_f, and vice versa. In the special case when $c_f = c_m$, we would have $b_m = b_f = b/2$.

As a consequence of our expressions for b_f and b_m, the total recruitment into the sexually active population is $b_m N + b_f N = bN$. Thus b is the constant of proportionality for recruitment of new individuals (male or female) into the total population. Moreover, the consistency condition implies $N = (1 + c_m/c_f)N_m = (1 + c_f/c_m)N_f$ which allows us to rewrite the recruitment rates in the following form:

$$b_m N = bN_m, \quad b_f N = bN_f.$$

Similar recruitment terms were also used in the models of Lin et al. (1993) and Hsieh (1996). The resulting model equations are:

$$S'_j = bN_j - B_j(t)S_j - \mu S_j, \tag{4}$$

$$U'_j = B_j(t)S_j - (\mu + v)U_j - \bar{\sigma}_j(U_j, N_j), \tag{5}$$

$$T'_j = \bar{\sigma}_j(U_j, N_j) - (\mu + v)T_j, \quad j = f, m. \tag{6}$$

The number of infecteds detected at each time unit, $\bar{\sigma}_j(U_j, N_j)$ depends on the population size of the yet untreated infecteds as well as the prevalence of HIV infecteds among each sex. Clearly we must have $\bar{\sigma}_j \geq 0$ and $\bar{\sigma}_j(0, N_j) = 0$, it follows that all nonnegative initial data lead to nonnegative solutions and the problem is well-posed. In this work we let $\bar{\sigma}_j(U_j, N_j) = \sigma_j U_j^2/N_j$, where σ_j is a positive constant, be the rate at which infecteds are taken into treatment. Note that the previously mentioned conditions imposed on $\bar{\sigma}_j$, namely, $\bar{\sigma}_j \geq 0$ and $\bar{\sigma}_j(0, N_j) = 0$, are clearly satisfied. Here σ_j is the product of the effort of screening and the fraction of infecteds that can be screened out and taken into treatment, given a population of infecteds. Hence it can be seen as a measure of the effectiveness of the program which can theoretically be greater than one. On the other hand, the function $\bar{\sigma}_j$ increases as either U_j increases or $\dfrac{U_j}{N_j}$ increases, therefore the number of infecteds taken into treatment or show a change in behavior increases with an increase in prevalence of HIV in the population (as documented by, among others, Miller et al. 1990). This describes a density-dependent treatment program where the treatment rate is low when HIV prevalence is low in the population. It approaches a linear increase (as a function of U_j) only when the infecteds become dominant in the population. Clearly this is a much more cost-effective program than that of linear

treatment rate in Hsieh (1996). Therefore this model takes into account of the so-cio-economic factors which could influence the design of public health policy. We would like to find out in this work if it is just as effective.

Furthermore, the use of different σ_j for each sex makes it possible to consider a targeting strategy based on difference in sex. It is a valid consideration since it has been reported that male-to-female HIV transmission rate is much higher than the female-to-male transmission rate (e. g. Padian 1991).

The following result on reduction to one-sex model was given in Hsieh (1996):

Theorem 2.1. *Given Equation (3), the two-sex problem (4)–(6) can be reduced to the equivalent one-sex problem:*

$$S'_f = bN_f - c_m S_f \frac{\beta_f U_f + \beta'_f T_f}{N_f} - \mu S_f, \tag{7}$$

$$U'_f = c_m S_f \frac{\beta_f U_f + \beta'_f T_f}{N_f} - (\mu + v)U_f - \bar{\sigma}_f(U_f, N_f), \tag{8}$$

$$T'_f = \sigma(U_f, N_f) - (\mu + v)T_f. \tag{9}$$

Note that all variables and parameters in (7)–(9) are of the female class except for the contact rate of males c_m in (7)–(8) which is a constant parameter in our model. This enables us to make the reduction to one-sex problem. This reduction to a one-sex model shows that, under the assumptions of constant contact rates and conservation of total contacts given here, targeting the treatment at either sex is viable in the sense that we need only to consider the dynamics of one-sex model. Of course, one could also reduce to the male sex. For further biological implications one can deduce from this reduction and a discussion on previous work on reduction of two-sex model, see Hsieh (1996).

3. The model with treatment and behavior change

In this section, we consider System (7)–(9) where we assume the detected infecteds are taken into treatment which leads to a change in either sexual behavior (number of contacts), transmission probability, and/or incubation time. Note that, under the conditions given in Section 2, the reduced one-sex model implies implicitly that the ratio σ_f/σ_m does not affect the dynamics of the system. Thus the model in (7)–(9) becomes (dropping the subscripts):

$$S' = bN - S\frac{c\beta U + c\beta' T}{N} - \mu S, \tag{10}$$

$$U' = S\frac{c\beta U + c\beta' T}{N} - (\mu + v)U - \sigma\frac{U^2}{N}, \tag{11}$$

$$T' = \frac{\sigma U^2}{N} - (\mu + v)T. \tag{12}$$

Let $s = \dfrac{S}{N}$, $u = \dfrac{U}{N}$, $t = \dfrac{T}{N}$, we get the reduced system for the proportions in the set $S = \{(s, u) \mid s \geq 0, u \geq 0, s + u \leq 1\}$:

$$s' = b(1 - s) - s\left[(1 - s)(c\beta' - v) + cu(\beta - \beta')\right], \tag{13}$$

$$u' = cs\left[\beta'(1 - s) + u(\beta - \beta')\right] - \sigma u^2 - u(b + vs), \tag{14}$$

When $\sigma = 0$, we recover the case of no screening in Section 3 of Hsieh (1996) where $b + v \geq c\beta$ implies the disease-free state is globally attracting. Therefore we only need to consider the relevant case of $b + v < c\beta$ and $\sigma > 0$. Since we also assume that treatment decreases transmission probability, it follows that $\beta' < \beta$. Under these assumptions, we proceed with our analysis.

In order to discuss the equilibrium points of the planar system (13)–(14), we first consider the range of (s, u) for the system. It is trivial to show that S is invariant for System (13)–(14). We now give the following lemma.

Lemma 3.1. *System (13)–(14) contains no nonconstant periodic solution in S.*

The proof is in the Appendix, as is that of the following theorem.

Theorem 3.2. *Assume that $c\beta > c\beta' \geq 0$, $c\beta > b + v$, and $1 \geq \sigma > 0$. The Disease Free Equilibrium (abbreviated DFE hereafter) at (1,0) for Equations (13)–(14) is unstable. Moreover, there is at least one positive equilibrium in S.*

We have the following result for the uniqueness and global stability of positive equilibrium, the proof is given in detail in the Appendix.

Theorem 3.3. *Suppose that $c\beta > b + v$ and $\sigma > 0$. The DFE(1,0) for System (5.4)–(5.5) is unstable, and there exists a unique positive equilibrium (s^*, u^*) which is globally asymptotically stable (abbreviated G.A.S. hereafter) in $S - \{(1, 0)\}$.*

For the model of population in (10)–(12), we let

$$R_0 = \frac{c\beta}{b + \mu}, \tag{15}$$

$$R_1 = \begin{cases} \dfrac{b}{\mu}, & \text{if } R_0 \leq 1; \\[2ex] \dfrac{b}{\mu + v(1 - s^*)}, & \text{if } R_0 > 1; \end{cases} \tag{16}$$

where R_0, R_1 are the threshold parameters for the population size. The expression for R_1 can be obtained by adding (10)–(12) to yield

$$N' = N[b - \mu - v(1 - s)]. \tag{17}$$

Since $R_0 > 1$, *we have* $N' \to N[b - \mu - v(1 - s^*)]$ and hence the expression for R_1 in (16).

The results can be summarized as follows:

Table 1. Limiting values of variables N,S,U,T.

R_0	R_1	$N \to$	$(s, \mu, t) \to$	$(S, U, T) \to$
> 1	< 1	0	$(s^*, \mu^*, 1 - s^* - \mu^*)$	$(0,0,0)$
> 1	> 1	∞	$(s^*, \mu^*, 1 - s^* - \mu^*)$	(∞, ∞, ∞)

The threshold parameter R_0 is the well-known basic reproduction number which governs the asymptotic behavior of population in tending toward DFE or the endemic state. $R_0 = c\beta/(b+\mu)$ measures the relative intensity of the disease transmission $c\beta$ versus dilution of infective population via death μ and increase of the susceptible population through births b. The parameter R_1 is the basic reproduction number for the total population. When population tends toward DFE ($R_0 \leq 1$), R_1 is once again simply the relative measure of birth versus natural mortality. But when the population tends toward endemic equilibrium ($R_0 > 1$), R_1 represents the net reproductive rate of the population with loss of individuals through all deaths (μ and v). Note that if $b > \mu + v$, $R_1 > 1$ for all choices of σ and consequently all subgroups in the population will increase without bound while maintaining the endemic proportions in a steady state. We also note that, unlike the model with linear treatment rate in Hsieh (1996) where σ figures prominently in the expressions for the threshold parameters R_0 and R_1, σ does not even appear in R_0 and R_1. Hence we can conclude that, for the model with nonlinear treatment rate, the treatment program σ has no effect at all on the asymptotic behavior of either the proportions or the population size.

4. Concluding remarks

In recent years, the search for an effective intervention/prevention approach to reduce the spread of HIV/AIDS has become a main focal point for national governments and international organizations all over the world. Some studies concentrate on behavioral interventions (e.g. DiClemente and Peterson 1994, Oakley et al. 1995), some work on aspects such as clinical treatment or vaccine trials (Weniger 1994), yet others attempt to propose measurement for evaluating the efficacy of prevention programs (e.g. Choi and Coates 1994, Konings et al. 1995). While certain programs have been shown to successfully reduce rates of new infections in some populations (DiClemente and Peterson 1994, Stryker et al. 1995), the question remains unanswered as to what a particular society can do to effectively combat the epidemic. It is important to understand the effects of a prevention program since we are always limited by the resources available to us. How to distribute the limited resources with efficiency is a difficult task and at times a controversial issue. Moreover, the impact of the program is also sensitive to the timing for the implementation of the program, the targeting strategy, and the availability of data prior to implementation.

In this work we propose a simple mathematical model for heterosexual transmission of HIV/AIDS with community treatment programs which screen the population and put those detected in a treatment program which could prolong the

patients' survival time while at the same time attempt to reduce their actual infectivity through behavior change which reduces their contact rate or through reduction of their transmission probability. The results show that an intervention program with density-dependent treatment/behavior change rate, while less costly than that of a linear treatment rate which has been shown (Hsieh 1996) that it could help eradicate the disease, cannot change the course of the epidemic if the disease was to be able to spread without treatment/behavior change. This underscore the importance of further studies regarding the relative cost-effectiveness of different prevention programs.

The results for reduction to one-sex model also show that, under the condition of conservation of total contacts given for our model, a targeting strategy aiming prevention program at either sex is viable in the sense that we need only to consider the dynamics of one-sex model but the choice of either sex makes no difference in the outcome.

As a final remark, much of this work is based on the assumption of conservation of total contacts, a biologically reasonable assumption. However, this simple conservation law is, in turn, based on the assumptions of proportionate mixing and, more critically, constant contact rates (c_m and c_f). The validity of both assumptions must be examined with more in-depth behavioral studies. Unfortunately, such studies has been so far inconclusive in the Third World setting. Hence we offer this work as a theoretical study which can be improved upon when more information is available in the future.

Appendix

Proof of Lemma 3.1. We make use of the Bendixson-Dulac criterion with weight function $g(s, u) = \dfrac{1}{su}$. □

Proof of Theorem 3.2. For local stability, we consider the Jacobian

$$J = \begin{bmatrix} -b + u(c\beta - c\beta') - (1 - 2s)(c\beta' - v) & -s(c\beta - c\beta') \\ (1 - 2s)c\beta' + u(c\beta - v - c\beta') & s(c\beta - v - c\beta') - 2\sigma u - b \end{bmatrix}.$$

At DFE (1,0), the Jacobian matrix has eigenvalues of $\lambda = c\beta - b - v$, $-b - v$. Since $\lambda_+ = c\beta - b - v > 0$, $(1, 0)$ is unstable for S. Hence the existence of positive fixed point in the invariant set S follows immediately from the nonexistence of periodic solution and Poincaré-Bendixson Theorem. □

Proof of Theorem 3.3. Given Lemma 3.1 and Theorem 3.2, it suffices to prove the uniqueness of the positive stationary point in S, we have to consider the following equations:

$$f(s, u) = b(1 - s) - s\left[(1 - s)(c\beta' - v) + u(c\beta - c\beta')\right] = 0,$$
$$g(s, u) = s\left[c\beta'(1 - s) + (c\beta - c\beta')u\right] - \sigma u^2 - u[b + vs] = 0.$$

The problem is equivalent to proving the uniqueness of intersection point of two quadratic curves in the interior of S. We denote the curve satisfying the first equation by L_1 and the curve satisfying the second equation by L_2. We first show that L_1 is a hyperbola in the (s, u)-plane.

Diagonalize the quadratic form

$$f(s, u) = (c\beta' - v)s^2 - (c\beta - c\beta')su + (v - b - c\beta')s + b,$$

we obtain the transfer matrix

$$M = \begin{bmatrix} c\beta' - v & \frac{-(c\beta - c\beta')}{2} \\ \frac{-(c\beta - c\beta')}{2} & 0 \end{bmatrix}$$

which has eigenvalues

$$\lambda_\pm = \frac{(c\beta' - v) \pm \sqrt{(c\beta' - v)^2 + (c\beta - c\beta')^2}}{2}.$$

Since $\lambda_- < 0 < \lambda_+$, the quadratic curve L_1 is a hyperbola.

Next we locate the intersection points of L_1 and the boundary of S:

(i) When $s = 0$, $f(s, u) = b \neq 0$. Therefore, the hyperbola L_1 does not cross u-axis.
(ii) The intersection points of L_1 and s-axis are the points A$= (1, 0)$ and B$= (\frac{b}{v - c\beta'}, 0)$.
(iii) The intersection points of L_1 and the line $s + u = 1$ are the points A and

$$C = (\frac{b}{c\beta - v}, \frac{c\beta - b - v}{c\beta - v}).$$

Note that $0 < \frac{b}{c\beta - v} < 1$ and $0 < \frac{c\beta - b - v}{c\beta - v} < 1$.

From (i)–(iii), the hyperbola L_1 has a branch that lies completely in the quadrants II $\cup$ III, and a branch that lies completely in the quadrants I $\cup$ IV passing through the points A, B, and C.

Similarly, we diagonalize the quadratic form

$$g(s, u) = -c\beta's^2 + (c\beta - c\beta' - v)su - \sigma u^2 + c\beta's - bu$$

with transfer matrix

$$M = \begin{bmatrix} -c\beta' & \frac{(c\beta - c\beta' - v)}{2} \\ \frac{(c\beta - c\beta' - v)}{2} & -\sigma \end{bmatrix}$$

whose eigenvalues are

$$\lambda_\pm = \frac{(-c\beta' + \sigma) \pm \sqrt{(c\beta' + \sigma)^2 - 4c\beta'\sigma + (c\beta - c\beta' - v)^2}}{2}.$$

Let $\Delta = 4c\beta'\sigma - (c\beta - c\beta' - v)^2$,

if $\Delta > 0$, L_2 is an ellipse,
if $\Delta = 0$, L_2 is a parabola,
if $\Delta < 0$, L_2 is a hyperbola.

The intersection points of L_2 and the boundary of S are considered in the following cases.

(i) When $s = 0$, the intersection points of L_2 and u-axis are D= $(0, 0)$ and E= $(0, -b/\sigma)$.
(ii) The intersection points of L_2 and s-axis are A and D.
(iii) The intersection points of L_2 and the line $s + u = 1$ are A and

$$F = (\frac{(b+\sigma)}{c\beta + \sigma - \nu}, \frac{c\beta - b - \nu}{c\beta + \sigma - \nu}).$$

Here we also note that

$$0 < \frac{b}{c\beta - \nu} < \frac{(b+\sigma)}{c\beta + \sigma - \nu} < 1$$

and

$$0 < \frac{c\beta - b - \nu}{c\beta + \sigma - \nu} < \frac{c\beta - b - \nu}{c\beta - \nu} < 1$$

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When L_2 is an ellipse or a parabola, it can be easily seen that L_1 and L_2 have only one intersection point in the interior of S.

When L_2 is a hyperbola, we claim that the points D and F lie on the same branch of the hyperbola L_2. This can be checked by finding the derivative $\frac{du}{ds} |_{(0,0)}$. Taking derivative $\frac{d}{ds}$ on both sides of the equation

$$-c\beta' s^2 + (c\beta - c\beta' - \nu)su - \sigma u^2 + c\beta' s - bu = 0,$$

one obtains

$$-2c\beta' s + (c\beta - c\beta' - \nu)u + (c\beta - c\beta' - \nu)s\frac{du}{ds} - 2\sigma u\frac{du}{ds} + c\beta - b\frac{du}{ds} = 0.$$

For $(s, u) = (0, 0)$, $\frac{du}{ds} |_{(0,0)} = \frac{c\beta'}{b} > 0$.

Therefore one branch of the hyperbola L_2 that passes through D = $(0, 0)$ will point toward quadrant I. Hence, D and F must lie on the same branch of L_2 and this branch intersects L_1 at one point in the interior of S. Therefore L_1 and L_2 intersect at only one point in the interior of S.   □

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