A Deterministic Model for Gonorrhea in a Nonhomogeneous Population*

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Communicated by J. Hearon

ABSTRACT

The spread of gonorrhea in a population is highly nonuniform. The mathematical model discussed takes this into account, splitting the population into n groups. The asymptotic stability properties are studied.

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1. INTRODUCTION

In 1970 gonorrhea led the list of infectious diseases in the number of cases reported to the U.S. Public Health Service, with more cases than the combined total for syphilis, mumps, measles, German measles, and infectious hepatitis. In this paper we construct a deterministic model for the spread of gonorrhea in a community. The distinctive epidemiological characteristics of gonorrhea cause the model to differ from models of other diseases. We consider only the sexually active individuals who potentially may contract the disease from their contacts.

EPIDEMIOLOGICAL FACTORS RELEVANT TO MODELING

Gonorrhea is in essence a nonseasonal disease with less than a 10 percent seasonal component in the variation [10], so we have given the model time-independent coefficients. The average incubation period is short, 3 to 7 days, compared to the often quite long period of active infectiousness. An

*This research was partially supported by the National Science Foundation under grant GP-31386-x2.

infected individual seems to remain infectious until he or she receives antibiotic treatment. While some infected individuals (especially men) quickly develop painful symptoms and therefore seek prompt medical treatment, others do not. It has long been recognized that infected women may have no easily recognizable symptoms [9], even while the disease does substantial internal damage. A recent study [16] of servicemen demonstrated that men also can be infected without symptoms. Some studies indicate that a substantial fraction of the men in the studies who became infected through contacts with infected prostitutes had no symptoms. That they were infected was demonstrated by the ability to obtain cultures of gonococcus. These asymptomatic cases of gonorrhea do not seek prompt medical treatment and so are infectious for periods much longer than the latent period. No reliable statistics are available. Related to the inability (or slight ability) of the human body to throw off the disease is the important fact that no significant physiological immunity is derived from having previously been infected. There are individuals who have been infected and cured ten or more times in a year. As soon as the curing antibiotics have left the body, we assume the individual is again susceptible. As a result our model considers only susceptibles and infectives, with no immunes and negligibly few incubating the disease. We assume the sexually active population is constant in size and equals the number of infectives plus the number of susceptibles. Unlike many diseases, the contact rates and duration of infection are extremely variable, and this complication should be taken into account in a realistic model.

A mathematical model specifically for gonorrhea was first developed by Cooke and Yorke [6]. They considered a single homogeneous population, using time delays to represent variation in the infectious period. The difficulty of analyzing differential equations with time delays makes it unlikely that their approach can be extended to general nonhomogeneous population with varying contact rates. The model we develop here uses a system of n ordinary differential equations without time delays. See also [18].

Gonorrhea case reports are at present increasing, at least in part because of changing social and medical factors. We have no way to estimate the magnitude or even directions of all these changes, so our modeling is restricted to constant epidemiological factors, allowing changes only in the case rates as a result of population interactions.

CONCLUSIONS ABOUT GONORRHEA

We prove that the disease will die out either for all positive initial disease levels or for none, depending on the contact rates and the lengths of infectious periods. In the latter case we prove that if the initial number of infectives in at least one group is not zero, then the disease will remain endemic and the number of infectives in each group will approach a constant positive level. This behavior of gonorrhea epidemics is different from most other infectious diseases, which usually have occasional major outbreaks followed by low disease levels. This different behavior of gonorrhea is attributable to the lack of developed immunity and the basic nonseasonality of the disease.

PRACTICAL IMPLICATION

Different strategies are available in efforts to control the spread of infection. Will overall case rates respond best to efforts which are concentrated most heavily on identifying and treating males, or females, or gay males, or even prostitutes? Our results show that to help answer these questions, it is reasonable to study how the *equilibrium* solution of the differential equation system will change if various parameters of the system are changed. We do not undertake such an analysis, which would require the best data available and an excellent intuition into public health. However, we emphasize that studies of the *changes* in the equilibrium levels (as dependent on parameter changes) requires much less precise data than would be required for the model to accurately reflect actual equilibrium levels. We also point out that the equilibrium levels are solutions of a system of algebraic equations and so is simpler to analyze than is the full set of dynamic equations.

2. BASIC EPIDEMIOLOGICAL PROPERTIES OF GONORRHEA

The natural assumptions we make in our gonorrhea model are the following:

(i) The disease is spread "person to person" (with the necessary interaction to pass the disease from one infective to one susceptible).

(ii) The probability of one susceptible contacting one infective does not significantly vary with the time of year [10].

(iii) An infected individual's probability of recovering in a specified length of time is independent of the time since initial infection; hence, the probability of still being infected at a time τ after initial infection is $e^{-\tau\alpha}$ for some constant $\alpha > 0$. This constant α is called the *recovery rate*, and $1/\alpha$ is called the *mean infectious period*. Since the probability of recovery during time $[\tau, \tau + d\tau]$ is $\alpha e^{-\tau\alpha} d\tau$, the expected time of recovery is then

$$\int_0^\infty \tau e^{-\tau\alpha} \alpha \, d\tau = \frac{1}{\alpha}. \tag{2.1}$$

(iv) The total size of the "active" population does not change.

(v) The incubation period is negligibly short. Any susceptible individual contacted by an infective immediately becomes infectious and upon recovery immediately becomes susceptible again without even partial immunity (susceptible$\rightleftarrows$infective). Therefore, we may consider only infected and susceptible individuals in our model.

3. THE n-DIMENSIONAL MODEL

We assume we are dealing with a nonhomogeneous population which can be divided into n homogeneous groups. Each group is homogeneous in the sense that all the individuals belonging to the same group have equal recovery rate, and the interaction ("contacts") between individuals depends only on the group they belong to. We let $x_i(t)$ be the *number of susceptibles* in the ith group, $y_i(t)$ the *number of infectives*, α_i the *recovery rate*, and c_i the *total size of the population*. Let β_{ji} be the *contact rate of the* ith *group's susceptibles with the* jth *group's infectives*; by this we mean the proportion of the susceptible population of the ith group that one infective of the jth group contacts (infects) per unit of time. Although β_{ij} is not necessarily equal to β_{ji}, we will assume that if $\beta_{ij} \neq 0$, then $\beta_{ji} \neq 0$ for all i,j. (It would be unrealistic to assume that susceptibles of the ith group can be infected by infectious members of the jth group but not vice versa. On the other hand, if the ith group contained only females and the jth only males, then we would not expect β_{ij} to equal β_{ji}.)

DEFINITION 3.1

We denote by G_i the set of individuals from the ith group for $i=1,\ldots,n$. We say that G_i *infects* G_j if and only if $\beta_{ij}>0$. Otherwise G_i *does not infect* G_j.

DEFINITION 3.2

Let G be the set of all individuals, that is, $G=\cup_{i=1}^{n} G_i$. We say that G is *connected* if for any proper subset S of $\{1,\ldots,n\}$ (that is, S is nonempty and its complement S' is nonempty), there exist i,j such that $i\in S$ and $j \in S'$ and $\beta_{ij}\neq 0$.

We will now assume without loss of generality that G is connected. (Otherwise we study each connected component separately.)

Let $E_{ji}(t)$ be the *exposure rate* for the ith group due to infectives of the jth group, that is, the rate at which susceptibles in G_i are being infected by infectives in G_j. To find the equation for $y_i(t)$, for $i=1,\ldots,n$, notice that

$$y_i(t)=\int_0^t \sum_{j=1}^{n} E_{ji}(\tau)e^{-\alpha i(t-\tau)}\,d\tau, \tag{3.1}$$

and differentiating (3.1),

$$\frac{dy_i(t)}{dt} = \sum_{j=1}^{n} E_{ji}(t) - \alpha_i y_i. \tag{3.2}$$

By the definition of contact rate $E_{ji}(t) = \beta_{ji} x_i(t) y_j(t)$, and since $x_i(t) + y_i(t) = c_i$, we can rewrite (3.2) as

$$\frac{dy_i}{dt} = -\alpha_i y_i + \sum_{j=1}^{n} \beta_{ji} c_i y_j - \sum_{j=1}^{n} \beta_{ji} y_i y_j. \tag{3.3}$$

We study this system for $(y_1, \dots, y_n) \in \Delta_n = \prod_{i=1}^{n} [0, c_i]$. (That is, $\Delta_n = \{ y \in R^n | 0 \leqslant y_i \leqslant c_i,\ i = 1, \dots, n \}$.) The following lemma guarantees that the number of infectives of each group cannot become negative or greater than the total size of the population of the group.

LEMMA 3.1

The system (3.3) *is positively invariant in* Δ_n.

Proof. We want to show that if $y(0) \in \Delta_n$, then $y(t) \in \Delta_n$ for all $t > 0$. Let

$$\partial\Delta_{n1} = \{ y \in \Delta_n | y_i = 0 \text{ for some } i \}$$

$$\partial\Delta_{n2} = \{ y \in \Delta_n | y_i = c_i \text{ for some } i \}.$$

Let the "outer normals" be denoted by

$$\eta_i^1 = \Big(0, \dots, \underset{i}{-1}, \dots, 0\Big) \quad \text{and} \quad \eta_i^2 = (0, \dots, +1, \dots, 0) \qquad (i\text{th position}).$$

For any compact set C, Nagumo proved that C is invariant for $dx/dt = f(x)$, if at each point y in ∂C (the boundary of C), the vector $f(y)$ is tangent or pointing into the set [12, 17]. The theorem is easy to apply here, since C is an n-dimensional rectangle. By Nagumo's result, it is then enough to show for $i = 1, \dots, n$ that

$$\left(\left. \frac{dy}{dt} \right|_{t=0} \cdot \eta_i \right) \leqslant 0 \qquad \text{for } y \in \partial\Delta_{n1} \cup \partial\Delta_{n2},$$

where $\eta_i=\eta_i^1$ if $y_i=0$, and $\eta_i=\eta_i^2$ if $y_i=c_i$. Furthermore,

$$\left(\frac{dy}{dt}\bigg|_{y_i=0}\cdot\eta_i^1\right)=-\sum_{j=1}^{n}\beta_{ji}c_iy_j\leqslant 0, \tag{3.4}$$

$$\left(\frac{dy}{dt}\bigg|_{y_i=c_i}\cdot\eta_i^2\right)=-\alpha_i c_i<0. \tag{3.5}$$

Then any solution that starts in $\partial\Delta_{n1}\cup\partial\Delta_{n2}$ stays inside Δ_n.

LEMMA 3.2

Assume G is connected. Let $y=y(t)$ be a solution of (3.3) *where $y(0)\in X\delta_n$ and $y(0)\neq 0$. Then $y(t)$ does not belong to $\partial\Delta_n$ (the boundary of Δ_n) for any positive time interval.*

Proof. Notice that

$$\partial\Delta_n=\partial\Delta_{n1}\cup\partial\Delta_{n2}.$$

Suppose $y_i(t)=c_i$ for $t\in[t_0,t_1]$ and some i. Then $dy_i/dt=0$ for $t\in[t_0,t_1]$. Furthermore, from (3.3),

$$0=\frac{dy_i}{dt}=-\alpha_i c_i+\sum_{j=1}^{n}\beta_{ji}c_iy_j-\sum_{j=1}^{n}\beta_{ji}c_iy_j \qquad \text{for } t\in[t_0,t_1],$$

so $\alpha_i c_i=0$, and this is a contradiction, since both quantities are positive. Therefore, y_i cannot be identically c_i for a finite time interval.

Now suppose $y_i(t)=0$ for $t\in[t_0,t_1]$ for some i. Let $S=\{i\,|\,y_i(t)=0$ for $t\in[t_0,t_1]\}$ and $S'=\{1,\ldots,n\}-S$.

Since $y(t)\neq 0$, S' is not empty, and since $i\in S$ for some i, S is not empty. Therefore, there exist $k\in S$ and $h\in S'$ such that $\beta_{hk}\neq 0$ (because G is connected). Hence $dy_k/dt=0$ for $t\in[t_0,t_1]$, and there exists $T\in[t_0,t_1]$ where $y_h(T)\neq 0$, so

$$0=\frac{dy_k}{dt}\bigg|_{t=T}=\sum_{j=1}^{n}\beta_{jk}y_j(T)c_k \tag{3.6}$$

But $\beta_{jk}y_j\geqslant 0$ for all $j=1,\ldots,n$, so

$$\frac{dy_k}{dt}\bigg|_{t=T}\geqslant\beta_{hk}y_h(T)>0, \tag{3.7}$$

and (3.7) contradicts (3.6). Then S must be empty, and no y_i can be identically zero on any positive time interval.■

From Lemma 3.2, we conclude that no group can have all the individuals infected for a positive time interval. Furthermore, no group can have all the individuals free of the disease for a positive time interval, unless everyone in all the groups is uninfected. Of course, some groups could remain isolated but here we are discussing only sexually interrelating groups.

EQUILIBRIUM AND STABILITY

We will investigate now the asymptotic behavior of the solutions. We know that $y=0$ is a constant solution. We shall prove that either $y=0$ is globally asymptotically stable in Δ_n, or if that is not the case, there exists another constant solution $k\in\Delta_n-\{0\}$, and $y=k$ is globally asymptotically stable in $\Delta_n-\{0\}$.

Let $y=(y_1,y_2,\ldots,y_n)^T$, and let $A=(a_{ij})$ be the matrix defined by $a_{ij}=\beta_{ji}c_i$ when $i\neq j$ and $a_{ii}=\beta_{ii}c_i-\alpha_i$. Our assumption that G is connected is equivalent to assuming A is irreducible.

Let $N(y)$ be a column vector whose ith component is $-\Sigma_{j=1}^{n}\beta_{ji}y_jy_i$. Then (3.3) can be written

$$\frac{dy}{dt}=Ay+N(y). \tag{3.8}$$

Let $s(A)=\max_{1<i<n}\operatorname{Re}\lambda_i$, where λ_i for $i=1,\ldots,n$ are the eigenvalues of A, and Re denotes the real part. Then we have the following results for the system (3.8). We assume G is connected (or equivalently A is irreducible).

THEOREM 3.1

For the system (3.8) *there are two possibilities. Either* $s(A)\leqslant 0$, *and then* $y=0$ *is globally asymptotically stable in* Δ_n, *or* $s(A)>0$, *and then there exists a constant solution* $k\in\Delta_n-\{0\}$ *such that k is globally asymptotically stable in* $\Delta_n-\{0\}$.

Now we summarize the main results for systems (3.8) of epidemiological interest.

BIOTHEOREM 1

Either the epidemic will die out naturally for every possible initial stage of the epidemic, or when this is not true and the initial number of infectives of at least one group is nonzero, the disease will remain endemic for all future time. Moreover, the number of infectives and susceptibles of each group will approach nonzero constant levels, which are independent of the initial levels.

AN EXAMPLE

It is interesting to consider a particular situation for $n=2$, with the additional hypothesis that there is no interaction inside each group. We assume there is a group of males and a group of females, and each group interacts only with the other. We assume therefore there are no homosexual contacts. In this case A will be a 2×2 matrix with $TrA<0$, so $s(A)\leqslant 0$ if and only if $\det A\geqslant 0$.

Since $\det A=\alpha_1\alpha_2-\beta_{12}c_2\beta_{21}c_1$,

$$s(A)\leqslant 0 \quad \text{if and only if} \quad \frac{\beta_{21}c_1}{\alpha_2}\frac{\beta_{12}c_2}{\alpha_1}\leqslant 1.$$

Notice that $1/\alpha_1$ is the mean female infectious period, and $1/\alpha_2$ is the mean male infectious period. Then $\beta_{21}y_1/\alpha_2$ equals the average number of females one infective male contacts during his infectious period. The maximum of this average occurs for $y_1=c$, when every female is susceptible, and $\beta_{12}y_2/\alpha_1$ equals the average number of males one infective female contacts during her infectious period, which is $\beta_{12}c_2/\alpha_1$ when every male is susceptible. We call the quantity $\beta_{21}c_1/\alpha_2$ the *maximum male contact rate*, and $\beta_{12}c_2/\alpha_1$ the *maximum female contact rate*. See [11] for a similar result.

Then Biotheorem 1 can be rewritten as follows for this particular case.

BIOCOROLLARY 1

When the product of the maximum male contact rate with the maximum female contact rate is less than or equal to one, the epidemic will fade out in each group. On the other hand, when this product is greater than one the disease will be endemic, and the infective and susceptible levels of each group will approach constant values, different from zero.

4. PROOF OF THE THEOREMS

In this section we will prove the results stated in the previous sections of this paper. We will state and prove more general results on the stability of systems that will include as a particular example the previously mentioned theorems.

We consider the system

$$\frac{dy}{dt}=f(y), \tag{4.1}$$

where f and $\partial f/\partial y_j$ are continuously differentiable in a region D of n-dimensional Euclidean space. (D may be the whole space.) By a *region* we mean a connected open set. We will assume that D contains the origin in its interior, and that the origin is a constant solution of (4.1) [i.e, $f(0)=0$]. Write $\phi(t,y_0)$ for the solution of (4.1) passing through y_0 at $t=0$.

We will now study the behavior of the solutions of (4.1), for a positively invariant convex set, with respect to (4.1) under certain conditions.

DEFINITION 4.1

Let $B \subset R^n$ be a connected set. Assume $y=y_0$ is a constant solution of (4.1) [i.e., $f(y_0)=0$], and $y_0 \in B$. We say that y_0 is *stable* in B is for each $\varepsilon>0$ there exists a number $\delta>0$ (depending on ε) such that if $y_1 \in B$ and $\|y_1-y_0\|<\delta$, then the solution $\phi(t,y_1)$ exists for all $t \geqslant 0$, and $\phi(t,y_1) \in B$ for all $t \geqslant 0$. Moreover, $\|\phi(t,y_1)-y_0\|<\varepsilon$ for $t>0$: the solution $y=y_0$ is *globally asymptotically stable in* $B_0 \subset B$ if it is stable in B, and if $y_1 \in B_0$, then $\lim_{t\to\infty}\phi(t,y_1)=y_0$.

DEFINITION 4.2

Let $V(y)$ be a real-valued function defined in some set Ω containing the origin. $V(y)$ is said to be *positive definite on* the set Ω if and only if $V(0)=0$ and $V(y)>0$ for $y\neq 0$ and y in Ω. $V(y)$ is said to be *negative definite on* Ω if and only if $-V(y)$ is positive definite on Ω. Such functions are sometimes called "Liapunov functions".

DEFINITION 4.3

For a differentiable real-valued function $V(y)$, *the derivative of V with respect to* (4.1), $V'(y)$, is the scalar product

$$V'(y)=(\text{grad}\, V(y)\cdot f(y))=\sum_{i=1}^{n}\frac{\partial V(y)}{\partial y_i}f_i(y). \tag{4.2}$$

Notice that if $\phi(t,y_1)$ is any solution of (4.1), then by the chain rule

$$\frac{d}{dt}V(\phi(t,y_1))=V'(\phi). \tag{4.3}$$

We are now able to state a theorem that will relate positive definite real-valued functions with the stability of an autonomous system.

THEOREM 4.1

Let V be a real-valued function defined on a region $D \subset R^n$. Let V be continuously differentiable in D. Let $B \subset D$ be compact and positively invariant with respect to the system (4.1) *with $0 \in B$. Let V be positive definite in B and $V'(y) \leqslant 0$ in B. Let the origin be the only invariant subset, with respect to* (4.1), *of the set $E=\{y \in B \mid V'(y)=0\}$. Then the zero solution of* (4.1) *is globally asymptotically stable in B.*

The proof follows standard methods. See, for example, [1, pp. 205, 215].

The following result is a standard type, and the proof is included for completeness.

LEMMA 4.1

If the compact convex set C is positively invariant for the system (4.1), *then there exists at least one constant solution of the system, belonging to C.*

Proof. Since f is continuous and has continuous partial derivatives, f is Lipschitz on C. Let us denote the Lipschitz constant by L. It is shown in (4) that if the system (4.1) has a nonconstant periodic solution of period p, then $p \geqslant 2\pi/L$. Let $U_n: C \to C$ be the continuous function defined by $U_n(c) = \phi(1/n, c)$, where ϕ is a solution of (4.1). By the Brouwer fixed-point theorem there exists $c_n \in C$ such that $U_n(c_n) = c_n$, for each n. Then $\phi(t, c_n)$ is a periodic solution of period at most $1/n$. Now choose M big enough so that $1/M < 2\pi/L$. Hence $\phi(t, c_M)$ is periodic of period less than $2\pi/L$ and $\phi(t, c_M)$ must be a constant solution.■

We will now combine these results in a theorem that will assure the existence of constant solutions for a particular kind of autonomous systems that will include (3.8).

THEOREM 4.2

Consider the system

$$\frac{dy}{dt} = Ay + N(y), \tag{4.4}$$

where A is an $n \times n$ matrix and $N(y)$ is continuously differentiable in a region $D \subset R^n$. Assume

(i) the compact convex set $C \subset D$ is positively invariant with respect to the system (4.4), and $0 \in C$;

(ii) $\lim_{y \to 0} \|N(y)\| / \|y\| = 0$;

(iii) there exist $r > 0$ and a (real) eigenvector ω of A^T such that $(\omega \cdot y) \geqslant r\|y\|$ for all $y \in C$;

(iv) $(\omega \cdot N(y)) \leqslant 0$ for all $y \in C$;

(v) $y = 0$ is the largest positively invariant set [for (4.4)] contained in $H = \{y \in C | (\omega \cdot N(y)) = 0\}$. Then either $y = 0$ is globally asymptotically stable in C, or for any $y_0 \in C - \{0\}$ the solution $\phi(t, y_0)$ of (4.4) satisfies $\liminf_{t \to \infty} \|\phi(t, y_0)\| \geqslant m$, where $m > 0$, independent of y_0. Moreover, there exists a constant solution of (4.4), $y = k$, $k \in C - \{0\}$.

Proof. Let $\lambda \in R$ be the eigenvalue corresponding to ω. That is, $A^T\omega = \lambda\omega$. Define $V: R^n \to R$ by $V(y) = (\omega \cdot y)$. Then V is positive definite in C, and

$$\begin{aligned} V'(y) &= \left(\omega \cdot \frac{dy}{dt}\right) = (\omega \cdot Ay) + (\omega \cdot N(y)) \\ &= (A^T\omega \cdot y) + (\omega \cdot N(y)) \\ &= \lambda(\omega \cdot y) + (\omega \cdot N(y)). \end{aligned} \tag{4.5}$$

Assume first $\lambda \leqslant 0$. Then $V'(y) \leqslant 0$ in C. Let $M = \{y \in C \mid V'(y) = 0\} \subset H$, so by assumption (v) $y = 0$ is the largest invariant set contained in M. Then by Theorem (4.1) $y = 0$ is globally asymptotically stable in C.

Assume now that $\lambda > 0$. For $\varepsilon > 0$ let

$$C_{V=\varepsilon} = \{y \in C \mid V(y) = \varepsilon\} \quad \text{and} \quad C_{V \geqslant \varepsilon} = \{y \in C \mid V(y) \geqslant \varepsilon\}.$$

Notice that $C_{V \geqslant \varepsilon}$ is nonempty for sufficiently small $\varepsilon > 0$, and it is convex, since the intersection of two convex sets is convex. We claim that there is an $\varepsilon_0 > 0$ such that for $0 < \varepsilon < \varepsilon_0$, $C_{V \geqslant \varepsilon}$ is positively invariant with respect to the system (4.4). Then since $C_{V \geqslant \varepsilon}$ is a compact convex set, if $\varepsilon < \varepsilon_0$, Lemma 4.1 implies (4.4) must have a constant solution $k \in C_{V \geqslant \varepsilon}$. And $k \neq 0$, since 0 is not in $C_{V \geqslant \varepsilon}$.

To see that ε_0 does exist, it is enough to show that there is an $\varepsilon_0 > 0$ such that for $\varepsilon \in (0, \varepsilon_0]$, $V'(y) > 0$ for $y \in C_{V=\varepsilon}$. Since

$$|(\omega \cdot N(y))| \leqslant \|\omega\| \, \|N(y)\|,$$

we have

$$-\|\omega\| \, \|N(y)\| \leqslant (\omega \cdot N(y)) \leqslant \|\omega\| \, \|N(y)\|;$$

hence by the equality (4.5), for $\varepsilon > 0$,

$$V'(y) \geqslant \lambda\varepsilon - \|\omega\| \, \|N(y)\| \qquad \text{for } y \in C_{V=\varepsilon}. \tag{4.6}$$

Condition (iii) implies for $y \in C_{V=\varepsilon}$ that $\|y\| \leqslant \varepsilon / r$. Now choose $\delta > 0$ such that $\lambda - (\|\omega\|/r)\delta > 0$ (which is always possible, since $\lambda > 0$ and $r > 0$).

Choose ε_0 such that $\|N(y)\| \leqslant \delta\|y\|$ for $\|y\| \leqslant \varepsilon_0$. Then by (4.6), for $y \in C_{V=\varepsilon}$,

$$V'(y) \geqslant \lambda\varepsilon - \varepsilon\delta\frac{\|\omega\|}{r}$$

$$= \left(\lambda - \frac{\|\omega\|}{r}\delta\right)\varepsilon > 0 \qquad \text{for } \varepsilon \in (0, \varepsilon_0],$$

and the claim is proven.

If $y \in C$, $y \neq 0$, and $V(y) \leqslant \varepsilon_0$, then $V'(y) > 0$, and it then follows that $\liminf_{t\to\infty} V(\phi(t,x)) \geqslant \varepsilon_0$ for all $x \in C$, $x \neq 0$.

Let $m = \inf\{\|y\| : V(y) \geqslant \varepsilon_0\}$. Then $m > 0$ and

$$\liminf_{t\to\infty} |\phi(t,y)| \geqslant m \qquad \text{for all } y \in C, \quad y \neq 0. \qquad \blacksquare$$

PROPERTIES OF MATRICES

We first give some results for matrices that will allow us to use Theorem 4.2 to prove Theorem 3.1. Given an $n \times n$ matrix $A = (a_{ij})$, we say that A is *irreducible* if for any proper subset $S \subset \{1, \ldots, n\}$ there exists $i \in S$ and $j \in S' = \{1, \ldots, n\} - S$ such that $a_{ij} \neq 0$. (Recall that $\beta_{ij} \neq 0$ implies $\beta_{ji} \neq 0$.)

If $\{\lambda_i\}$ are the eigenvalues of an $n \times n$ matrix A, then the spectral radius, $\rho(A)$, is defined by $\rho(A) = \max_i |\lambda_i|$. The *stability modulus* $s(A)$ is defined by $s(A) = \max \operatorname{Re} \lambda_i$, $i = 1, \ldots, n$, where λ_i are the eigenvalues of A.

A matrix $A = (a_{ij})$ is said to be *non-negative* ($A \geqslant 0$) if and only if $a_{ij} \geqslant 0$ for all i,j. Then we have the following result due to Perron (1907) and Frobenius (1912). See [13, p. 30].

THEOREM 4.3

Let $A \geqslant 0$ be an irreducible $n \times n$ matrix. Then:

(i) A has a positive eigenvalue equal to its spectral radius.
(ii) To $\rho(A)$ there corresponds an eigenvector $\omega > 0$ (i.e., $\omega_i > 0$ for all i).
(iii) $\rho(A)$ increases when any entry of A increases.
(iv) $\rho(A)$ is a simple eigenvalue of A.

From this theorem we can prove the following lemma.

LEMMA 4.2

Let A be an irreducible $n \times n$ matrix, and assume $a_{ij} \geqslant 0$ whenever $i \neq j$. Then there exists an eigenvector ω of A such that $\omega > 0$, and the corresponding eigenvalue is $s(A)$.

Proof. Choose $c \in R$, such that $c + a_{ii} \geqslant 0$, for $i = 1, \ldots, n$. Then $A + cI$ is a non-negative irreducible matrix. Therefore, by Theorem 4.3, there exists a positive eigenvector ω with eigenvalue equal to the spectral radius $\rho(A + cI)$. That is,

$$(A + cI)\omega = \rho(A + cI)\omega.$$

Hence

$$A\omega = [\rho(A + cI) - c]\omega,$$

so ω is also an eigenvector of A, and the corresponding eigenvalue is $\rho(A + cI) - c$. If λ is any eigenvalue of A, then $\lambda + c$ is an eigenvalue of $A + cI$, so $|\lambda + c| \leqslant \rho(A + cI)$, and it follows that $\operatorname{Re}\lambda \leqslant \rho(A + cI) - c$, and the lemma is proven.■

Now we will state a known result that we will use in the proof of Theorem 3.1. See [14, p. 62].

THEOREM 4.4

Let Ω be a compact set positively invariant with respect to the system (4.1). *Suppose that there exists a function $V: \Omega \to R$ with continuous partial derivatives of the first order, and that $V'(y) \leqslant 0$ in Ω. Let $E = \{y \in \Omega \mid V'(y) = 0\}$. Let M be the largest invariant set in E* [*with respect to* (4.1)]. *Then every solution of* (4.1) *starting in Ω approaches M as $t \to \infty$.*

Following the proof of this theorem, we notice that if $V(y)$ is continuous, then Theorem 4.4 is still true if we replace V' by

$$V'_{(1)} = \limsup_{h \to 0^+} \frac{V(y(t+h)) - V(y(t))}{h}.$$

Proof of Theorem 3.1. Condition (i) of Theorem 4.2 is satisfied by letting $C = \Delta_n$. Conditions (ii) and (iv) are clearly satisfied. For condition (iii), notice that A^T is irreducible if and only if A is, let $\omega = (\omega_1, \ldots, \omega_n)$ be the eigenvector of A^T given by Lemma 4.2, and let

$$\omega_0 = \min_i \omega_i > 0.$$

For $y \in \Delta_n$ we then have

$$(\omega \cdot y) \geqslant \omega_0 \sum y_i \geqslant \omega_0 \left(\sum y_i^2\right)^{1/2}.$$

Therefore $(\omega \cdot y) \geqslant r\|y\|$ for all $y \in \Delta_n$, where $r = \omega_0$.

To verify (v) let $H = \{y \in \Delta | (\omega \cdot N(y)) = 0\}$. If $y \in H$, then $\sum_{j=1}^{n} \beta_{ji} y_j y_i \omega_i = 0$ for all $i = 1, \ldots, n$. But since each term of the sum is non-negative, $\beta_{ji} y_j y_i \omega_i = 0$ for all i, j.

Assume $y \neq 0$, so we may choose h such that $y_h \neq 0$; then $\beta_{hi} y_i = 0$ for all i. But since G is connected, there exists some k such that $\beta_{hk} \neq 0$, so $y_k = 0$. Hence if $y \in H$, then $y \in \partial\Delta_n$. Therefore, by Lemma 3.2, the only invariant set with respect to (3.8) contained in H is $y = 0$, and so condition (v) is satisfied.

Hence all the hypothesis of Theorem 4.2 are satisfied, where $\lambda = s(A)$. Then either $s(A) \leqslant 0$, and the origin is globally asymptotically stable in Δ_n, or $s(A) > 0$, and there exists a constant solution of (3.7), $y = k$, $k \in \Delta_n - \{0\}$. We will now prove that $y = k$ is globally asymptotically stable in $\Delta_n - \{0\}$. First we prove that when $s(A) > 0$, $y = 0$ and $y = k$ are the only constant solutions in Δ_n. Assume that $y = k$ and $y = h$ are two constant solutions of (3.8), both nonzero. If $k \neq h$, then for some i, $k_i \neq h_i$. Assume without loss of generality that $h_1 > k_1$, and moreover that $h_1/k_1 \geqslant h_i/k_i$ for all i. (Lemma 3.2 implies $k > 0$.) Then since h and k are constant solutions,

$$0 = -\alpha_1 h_1 + (c_1 - h_1) \sum_{j=1}^{n} \beta_{j1} h_j = -\alpha_1 k_1 + (c_1 - k_1) \sum_{j=1}^{n} \beta_{j1} k_j,$$

so

$$0 = -\alpha_1 k_1 + (c_1 - h_1) \sum_{j=1}^{n} \beta_{j1} h_j \frac{k_1}{h_1} = -\alpha_1 k_1 + (c_1 - k_1) \sum_{j=1}^{n} \beta_{j1} k_j. \quad (4.7)$$

But $(h_i/h_1)k_1 \leqslant h_i$ and $c_1 - h_1 < c_1 - k_1$; thus from (4.7) we get

$$(c_1 - h_1) \sum_{j=1}^{n} \beta_{j1} h_j \frac{k_1}{h_1} < (c_1 - k_1) \sum_{j=1}^{n} \beta_{j1} k_j.$$

This is a contradiction, so there is only one constant solution of (3.8), $y = (k_1, \ldots, k_n)$, in $\Delta_n - \{0\}$.

In order to find the asymptotic behavior of the solutions of (3.8) in Δ_n, we define the following functions: $M : \Delta_n \to R$ and $m : \Delta_n \to R$ for $y \in \Delta_n$; $M(y) = \max_i (y_i/k_i)$, $m(y) = \min_i (y_i/k_i)$. $M(y)$ and $m(y)$ are continuous, and the right-hand derivative exists for both, along solutions. If $y = y(t)$ is a solution of (3.8), then reordering coordinates if necessary, we may assume, for a given t_0 and for sufficiently small $\varepsilon>0$, that $M(y(t))=y_1(t)/k_1$, $t\in[t_0,t_0+\varepsilon]$. Then

$$M'_{(1)}(y(t_0))=\frac{y_1'(t_0)}{k_1},\qquad \text{for } t\in[t_0,t_0+\varepsilon].$$

From (3.3) we get

$$k_1\frac{y_1'(t_0)}{y_1(t_0)}=-\alpha_1k_1+[c_1-y_1(t_0)]\sum_{j=1}^{n}\beta_{j1}\frac{y_j(t_0)k_1}{y_1(t_0)}. \tag{4.8}$$

Then if $M(y(t_0))>1$, by (4.8),

$$k_1\frac{y_1'(t_0)}{y_1(t_0)}<-\alpha_1k_1+(c_1-k_1)\sum_{j=1}^{n}\beta_{j1}k_j=0,$$

and since $k_1>0$ and $y_1(t_0)>0$, we conclude that $y_1'(t)<0$. Therefore if $M(y(t_0))>1$,

$$M'_{(1)}(y(t_0))=\limsup_{h\to0^+}\frac{M(y(t_0+h))-M(y(t_0))}{h}<0.$$

In the same fashion we can prove that if $M(y(t_0))=1$, $m'_{(1)}(y(t_0))\leqslant0$. And if $m(y(t_0))<1$, then $m'(y(t_0))>0$. If $m(y(t_0))=1$, then $m'_{(1)}(y(t_0))\geqslant0$. Define

$$V(y)=\max\{M(y)-1,0\},$$

$$W(y)=\max\{1-m(y),0\}.$$

Both $V(y)$ and $W(y)$ are non-negative and continuous for $y\in\Delta_n$. Notice that

$$V'_{(1)}(y)\leqslant0\quad\text{and}\quad W'_{(1)}(y)\leqslant0.$$

Let $H_V=\{y\in\Delta_n|V'_{(1)}(y)=0\}$ and $H_W=\{y\in\Delta_n|W'_{(1)}(y)=0\}$. Then $H_V=\{y|0\leqslant y_i\leqslant k_i\}$ and $H_W=\{y|k_i\leqslant y_i\leqslant c_i\}\cup\{0\}$. Therefore by Theorem (4.4), any solution of (3.8) starting in Δ_n will approach $H_W\cap H_V$. And $H_W\cap H_V=\{k\}\cup\{0\}$. But if $y(t)\neq0$, by Theorem (4.2) we know that

$\liminf_{t\to\infty}\|y(t)\| \geqslant m > 0$. Then we conclude that any solution $y(t)$ of (3.8), such that $y(0) \in \Delta_n - \{0\}$, satisfies $\lim_{t\to\infty} y(t) = k$. It is easy to prove that the solution $y = k$ is stable in Δ_n, so $y = k$ is globally asymptotically stable in $\Delta_n - \{0\}$.■

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