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# A competitive exclusion principle for pathogen virulence

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**Abstract.** For a modified Anderson and May model of host parasite dynamics it is shown that infections of different levels of virulence die out asymptotically except those that optimize the basic reproductive rate of the causative parasite. The result holds under the assumption that infection with one strain of parasite precludes additional infections with other strains. Technically, the model includes an environmental carrying capacity for the host. A threshold condition is derived which decides whether or not the parasites persist in the host population.

**Key words:** Co-evolution — Commensalism — Evolution of virulence — Myxomatosis — Extinction — Persistence — Multi-strain epidemic model — Stable endemic equilibrium

## 1. Introduction

One of the important principles of theoretical ecology is the *competitive exclusion principle* which states that *no two species can indefinitely occupy the same ecological niche*, assuming that it is understood what is meant by *ecological niche*. (Levin (1970), Maynard Smith (1974), (May 1975), Butler et al. (1983).)

In this paper we show that an analogous principle is valid for parasites that depend for their sustenance and propagation on a host and which perish when the host dies. Our analysis is applicable to viruses, bacteria, and helminths, but it does not apply to parasitoids nor to most ectoparasites such as fleas, lice, mites, and ticks.

Many textbooks of ecology assert that hosts and their parasitic pathogens co-evolve such that the pathogen does not kill the host too quickly since otherwise it cuts short its own propagation (Palmieri 1982). The co-evolution of rabbits and the myxomatosis virus in Australia is a well documented example of host-pathogen co-evolution from initially high levels of virulence to a more moderate level (Fenner and Ratcliffe 1965; Fenner and Myers 1978).

Recently the general validity of this principle has been challenged by Levin and Pimentel (1981), Levin (1983a, b), and Bremermann and Pickering (1983)

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(compare also May and Anderson (1983) and Levin et al. (1982)). Levin and Pimentel (1981) and Levin (1983a, b) show by means of a dynamic model that an excessively virulent strain can prevail if it can invade a host that harbors the less virulent strain, but not vice versa. Bremermann and Pickering (1983) showed by means of a game-theoretical model: When two strains (or species) of parasites inhabit the same host, then the strain (or species) that replicates most vigorously has a fitness advantage, even if the price of rapid replication is premature death of the host.

When multiply infected hosts are absent, the game-theoretical model predicts no such escalation of virulence, but a moderate level of virulence, that optimizes the *basic reproductive rate* of the parasite. Some parasites induce an immune reaction that prevents superinfection by different strains. In myxomatosis, infection by one parasite strain will confer immunity against all strains even after the host has recovered from the infection (Saunders (1981), and the literature cited there). A phenomenon not considered in this paper is *epidemiological interference* of different virus strains or species: infection by one species excludes infection by the others, but induces no or only partial cross-immunity after recovery (Dietz (1979), Castillo-Chavez et al. (1988a, b), and the literature cited there).

In this paper we consider the case that infection by one parasite strain excludes superinfection by other strains and induces permanent immunity against all strains in case of recovery. Actually it would be sufficient to assume that the host is immune against all strains of the parasite as long as it is immune against the strain which caused the infection. The game-theoretical model predicts the optimum virulence level under this condition, but it does not describe the full dynamical behavior of the populations involved. In the following we analyse the dynamics of such interacting populations. Our epidemiological model describes the temporal development of susceptible hosts, of infective hosts that harbor different strains of the parasite, and of recovered hosts that are permanently immune to all parasite strains. The fate of different parasite strains is reflected by the prevalence of the respective harboring hosts. In this way our model is open to invasion by mutant parasite strains which differ in their trade-off between speed of replication and damage to the host. We show:

*If initially several subpopulations of infected-individuals occur, whose infections differ in virulence, then (under very general conditions), no more than two strains will persist in the population.*

*When new strains with different virulence levels arise (through mutations), then asymptotically a single strain will evolve, or the disease will die out. The virulence level of the surviving strain (if any) is the level predicted by the game-theoretical model of Bremermann and Pickering* (1983). *It maximizes the basic reproductive rate, as defined by Anderson and May* (1982*a*).

## 2. The model

We describe host parasite dynamics by a modified Anderson and May model. The original Anderson and May (1979) model permits exponential growth of the host population in the absence of the disease. Though exponential population growth can occur for a certain period of time, it is unrealistic in the long run. It

is also inconvenient for deriving our results. We guarantee limited population growth by making the per capita reproduction rate depend on the density (or size) of the population in a strictly monotone decreasing way. This is more realistic than introducing logistic mortality if the per capita reproductivity reacts more sensitively to crowding effects than the per capita motality.

We assume that, without the disease, the host population size $N(t)$ develops according to the equation

$$\dot{N} = N(f(N) - b). \tag{1}$$

Here $b$ is the per capita mortality rate and $f(N)$ is the per capita reproduction rate (at population density $N$). The function $f$ from $[0, \infty)$ to $[0, \infty)$ is assumed to have the following properties (P).

(P1) $f$ is continuously differentiable.

(P2) $f$ is strictly decreasing.

(P3) $f(0) > b, f(N) < b$ for large $N > 0$.

Examples are given by the per capita reproduction rates $f(N) = a \exp(-kN)$ (Ricker 1954) and $f(N) = a/(1+kN)$ (Beverton and Holt 1957). (P3) holds if $a > b$.

It follows from the properties (P) that all solutions $N$ of (1) with $N(0) > 0$ converge towards the unique positive root $K$ of

$$f(K) = b. \tag{2}$$

$K$ is called the environmental *carrying capacity* for the host population.

We model the host parasite interaction by assuming that the population is divided into susceptibles $S(t)$, recovered (immune) individuals $R(t)$ and $n$ classes of infective individuals $I_1, \ldots, I_n$ with each class being associated with a specific strain of the infective agent. Thus we have

$$N = S + R + \sum_{j=1}^{n} I_j. \tag{3}$$

With this notation the model reads as

$$\begin{aligned} \dot{N} &= N(f(N) - b) - \sum_{j=1}^{n} \alpha_j I_j \\ \dot{I}_1 &= I_1(S\beta_1 - (b + \nu_1 + \alpha_1)) \\ &\vdots \\ \dot{I}_n &= I_n(S\beta_n - (b + \nu_n + \alpha_n)) \\ \dot{R} &= \sum_{j=1}^{n} \nu_j I_j - bR. \end{aligned} \tag{4}$$

As before, $f$ and $b$ are the per capita birth and mortality rates, $\alpha_j$ is the excess per capita death rate for individuals $I_j$ infected by strain $j$, $\nu_j$ is the rate at which these individuals acquire immunity, and $\beta_j$ the rate at which they transmit the disease.

Equations (3) and (4) have to be supplemented by initial conditions for $N, S, I_j, R$. Only nonnegative initial conditions which satisfy (3) make biological sense.

## 3. Positivity and boundedness of solutions

The standard theory of ordinary differential equations (see, e.g. Hartman 1973) implies the unique existence of solutions to (3) and (4), for given initial data. The solutions exist for all times unless they blow up in finite time. If the initial data are nonnegative, so are $I_j$ and $R$. For $I_j$ this follows from integrating $\dot{I}_j/I_j = d/dt \ln I_j$ in the $I_j$ equation in (4). Nonnegativity of $R$ then follows from using the variation of constants (or parameters) formula for the $R$ equation in (4). Hence, from (3) and (4), we obtain the differential inequality

$$\frac{\dot{S}}{S} \geqslant f(N) - b - \sum_{j=1}^{n} \beta_j I_j.$$

Integrating this inequality we see that $S(t_0) \geqslant 0$ implies $S(t) \geqslant 0$ for all $t > t_0$. By the same argument positivity is preserved.

After having shown nonnegativity the boundedness of $N$ will imply the boundedness of $S, I_j, R$ via (3). But

$$\dot{N} \leqslant N(f(N) - b). \tag{5}$$

Hence $N(t) \leqslant \max(N(t_0), K)$ for $t \geqslant t_0$. See (2) and the properties (P).

In summary we have shown:

*Equations* (3) *and* (4) *have unique globally defined solutions for given nonnegative initial data which satisfy* (3). *The solutions are bounded and nonnegative. If* $I_j$ *is positive initially, it is positive for all times.*

## 4. Extinction of strains with suboptimal basic reproductive rate

In the following we assume positive initial data for all $I_j$. Set

$$\sigma_j = \frac{b + \nu_j + \alpha_j}{\beta_j} \tag{6}$$

and

$$u_j = \frac{1}{\beta_j} \ln \frac{I_j}{I_j(0)} + \sigma_j t. \tag{7}$$

Note that $R_{0,j} = K/\sigma_j$ is the basic reproductive rate of strain $j$ because the disease-free host population settles to the carrying capacity $K$ (see Anderson 1982; Anderson and May 1982a; Dietz 1975, 1982). Then

$$\dot{u}_j = S, \qquad u_j(0) = 0.$$

In particular, $u_j = u_1$. Using the definition of $u_j$ we obtain

$$\left(\frac{I_j(t)}{I_j(0)}\right)^{1/\beta_j} e^{\sigma_j t} = \left(\frac{I_1(t)}{I_1(0)}\right)^{1/\beta_1} e^{\sigma_1 t}. \tag{8}$$

Without restricting generality we assume that $\sigma_1 = \min(\sigma_1, \ldots, \sigma_n)$. Equation (8) gives precise information on how the numbers of infectives affected by different strains develop relatively to each other. In particular, as $I_1$ is bounded, $I_j$ goes extinct exponentially if $\sigma_j > \sigma_1$.

*Hence strains which have lower basic reproductive rates than other strains die out.*

## 5. Threshold phenomena

Up to now we have only shown that strains with suboptimal reproductive rates die out, but we do not know whether the disease persists as a whole. This will depend on the basic reproductive rates of the infective strains. By (2) and the first equation in (4) we have

$$\limsup_{t\to\infty} N(t) \leqslant K.$$

We choose $t_i \to \infty$ for $i \to \infty$ such that $I_j(t_i) \to \limsup_{t\to\infty} I_j(t)$ and $\dot{I}_j(t_i) \geqslant 0$. From the $I_j$ equation in (4) and from (3), (6) we now find that

$$0 \leqslant \limsup_{t\to\infty} I_j(t)\,((K - \limsup_{t\to\infty} I_j(t)) - \sigma_j),$$

hence parasite strain $j$ dies out if

$$\frac{K}{\sigma_j} \leqslant 1,$$

i.e. if its basic reproductive rate does not exceed 1. In particular:

*If $K/\sigma_j \leqslant 1$ for all $j = 1, \ldots, n$, then the disease dies out.*

*Conversely, if $K/\sigma_j > 1$ for at least one $j \in \{1, \ldots, n\}$, then the disease persists in the population, and the numbers of infectives $I_j$ carrying agents with optimal basic reproductive rate $K/\sigma_j$ remain bounded away from zero uniformly for all times $t$.*

The second statement can be seen by combining the results of the previous section with some lengthy, but standard estimates (see the appendix). The authors wonder whether one can find a more elegant proof by modifying arguments from dynamical systems theory (Butler and Waltman 1976). From (7) and $\dot{u}_j = S$, one obtains as a corollary that

$$\frac{1}{t}\int_0^t S(r)\,dr \xrightarrow{t\to\infty} \frac{1}{\sigma_1},$$

where we have again assumed that the first strain has optimal reproductive rate.

## 6. Competitive exclusion

As in Bremermann and Pickering (1983) we argue that the excess death rate $\alpha$ caused by the infectious disease is coupled to the agressiveness of transmission, i.e. to $\beta$, and that $\alpha$ rises disproportionally as $\beta$ increases. This is mathematically reflected by assuming that $\alpha = \alpha(\beta)$ is a strictly convex, monotone increasing function of $\beta$, $\alpha(0) = 0$, $\alpha'(0) = 0$, $\alpha'(\beta) \to \infty$ for $\beta \to \infty$. An example is provided by

$$\alpha = c\beta^p$$

with a positive constant $c$ and $p > 1$.

We further assume that the different strains (preventing multiple infection and causing cross-immunity) produce the same immune response (identical $\nu$),

but have different transmission rates $\beta_j$ and excess death rates $\alpha_j = \alpha(\beta_j)$. As we have assumed that $\alpha$ is a strictly convex function of $\beta$,

$$\sigma(\beta) = \frac{b + \nu + \alpha(\beta)}{\beta}$$

can take the same value only twice.

*Thus no more than two strains (which have optimal basic reproductive rates) persist in the population.*

## 7. Evolution of virulence

Virulence is influenced by genetic factors and these can be changed by mutation and recombination (Bremermann and Pickering 1983). If strains with different transmission rates $\beta$ are introduced in this way, then strains with a higher basic reproductive rate $K/\sigma(\beta)$ will replace strains with lower reproductive rates. This replacement does not stop until a maximum (i.e. a minimum of $\sigma$) is reached. If $\alpha$ satisfies the assumptions made in Sect. 6, $\sigma(\beta)$ approaches infinity as $\beta$ tends to zero or infinity. Thus a global minimum of $\sigma$ exists and is located at $\beta$ satisfying the equation

$$\beta\alpha'(\beta) = b + \nu + \alpha(\beta),$$

or

$$\alpha'(\beta) = \sigma(\beta) = \min_{[0,\infty)} \sigma.$$

As $\alpha$ is strictly convex (i.e. $\alpha'$ strictly increases), there is only one $\beta$ at which the minimum can be attained. Note that the first condition is the same as derived in the game-theoretical optimization approach in Bremermann and Pickering (1983).

If the excess mortality has the form $\alpha(\beta) = c\beta^p$, we obtain

$$\alpha = \frac{b + \nu}{p - 1} \quad \text{or} \quad \beta = \left(\frac{b + \nu}{c(p-1)}\right)^{1/p}.$$

*Hence, if transmission and excess death rate are coupled as described above, the evolution of virulence leads to strains with a uniquely determined transmission rate, namely that which maximizes the basic reproductive rate.*

## 8. Endemic equilibria and their stability

At present we are unable to answer the question of whether the system settles always down to an endemic equilibrium once the strain with the maximum reproductive rate has been established (provided that its basic reproductive rate exceeds 1, see Sect. 5). We can show the following local statement, however:

*In the above situation an endemic equilibrium exists with only the optimally reproducing strain being present. This equilibrium is uniquely determined and locally asymptotically stable: If, by mutation e.g., strains with suboptimal reproductive rate are introduced in small numbers, they do not only die out (this already follows from*

*Sect.* 4), *but the system returns to the equilibrium state with only the strain with optimal reproductive rate being present.*

In order to make this more precise we consider the situation that

$$\sigma_1 < \sigma_j = \frac{b+\nu_j+\alpha_j}{\beta_j}, \qquad j=2,\ldots,n,$$

and

$$\frac{K}{\sigma_1} > 1.$$

In order to find an equilibrium of (3), (4) in which only the first strain is present we set

$$I_j = 0, \qquad j=2,\ldots,n; \qquad \dot{N} = \dot{I}_1 = \dot{R} = 0.$$

If $I_1 \neq 0$, we obtain the equilibrium equations

$$\begin{aligned} S^* &= \sigma_1 \\ R^* &= \frac{\nu_1 I_1^*}{b} \\ \frac{\alpha_1 I_1^*}{\sigma_1 + (1+\nu_1/b) I_1^*} &= f(\sigma_1 + (1+\nu_1/b) I_1^*) - b. \end{aligned} \tag{9}$$

Note that the left-hand side of the last equation strictly increases in $I_1^*$, whereas the right-hand side strictly decreases. This implies uniqueness of the equilibrium. The left-hand side is larger than the right-hand side if $I_1^*$ is large. The left hand side is smaller than the right-hand side if $I_1^*$ is small. These are consequences of the threshold condition $K/\sigma_1 > 1$ and the properties (P). In particular $f(\sigma_1) - b > 0$. Existence of the equilibrium now follows from the intermediate value theorem.

Local stability analysis is carried out in the standard way by linearizing the system at the equilibrium and by checking whether the eigenvalues of the linearized system have strictly negative real parts. As $\sigma_1 < \sigma_j, j \geq 2$, one easily realizes that the whole system is locally stable whenever this is the case for the reduced system with $I_j = 0, j = 2, \ldots, n$. Local stability of the reduced system follows from the Routh-Hurwitz criterion (see, e.g. Boyce and DiPrima (1977), Sect. 5.3, problem *20). Consult the appendix for more details.

## 9. Discussion

Parasites have a powerful effect on host population levels. Anderson and May (1981, 1982a) have shown that parasites can stably depress host populations to levels well below the carrying capacity of the environment. Hosts and parasites evolve: Hosts towards resistance, parasites towards overcoming resistance. Hosts and parasites thus co-evolve: molecules against molecules, proteases against inhibitors, binding sites against receptors, etc. (Bremermann 1987). It is a game of molecular pursuit and evasion.

Host-parasite interactions, rapid genetic changes in parasites, especially microparasites, and host polymorphism are the basis of some current theories about the evolutionary role of sex (Stearns 1987). Inherent adaptive advantages

of parasites are counterbalanced by host polymorphism of molecules that are involved in resistance and in parasite recognition (Bremermann 1987). Recently, Lively (1987) has collected data of sexually and asexually reproducing snail species and their parasites which tend to confirm that sexual reproduction is rather maintained by host-parasite interaction (*Red Queen* hypothesis) than by environmental heterogeneity (*Tangled Bank* hypothesis).

The molecular mechanisms of resistance/susceptibility are beginning to be explored with recombinant DNA techniques, especially in plants (Burdon 1987). Pathogenic bacteria are found to adapt, to acquire genes on plasmids, etc. in a very short time. Another example of the rapid evolution is the change of the AIDS virus (HIV), with genomic base substitutions at 10 million times the average rate of basepair substitutions in mammals (Bremermann 1987). Hill and Hastie (1987) have documented the effect of host-parasite interactions producing non-uniform evolution in the active cores of protease inhibitors relative to flanking sequences.

In order to model the differential survival of different host and parasite mutants one would ideally like a dynamic model that would include the full range of phenotypes (transmission, excess death and recovery rates), and that would distinguish all the different host strain — parasite strain combinations. The present paper discusses one special case, namely a single strain of hosts interacting with an arbitrary number of parasite strains under the condition that superinfections by different parasite strains do not occur. Under these conditions parasites evolve towards *commensalism* (not in the sense that the parasite does not harm the host at all, but that it moderates its exploitation of the host).

In a different model Bremermann and Fiedler (1985) have investigated another special case, where an arbitrary number of different asexually reproducing host strains are infected each by a corresponding parasite strain. Host strains interact by competing for a share of the carrying capacity of the environment. This model shows that a stable polymorphic host-parasite equilibrium is possible. (The model depends, in part, on ideas of this paper.) The model also shows that a host mutant that is *resistant* to all parasite strains will take over and wipe out parasite infections by reducing their hosts to low population levels.

The analysis of these two models shows certain parts of host-parasite co-evolution. For completing the picture, models are needed which include the full interaction of different strains of both hosts and parasites. Such models can be formulated. By their complexity, they have resisted mathematical analysis so far and constitute a continuing challenge.

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## Appendix

First we prove *persistence of the disease* if one of the strains has a basic reproductive rate strictly larger than unity. See the corresponding result in Sect. 5.

*Step 1: The disease cannot eradicate the population.*
We introduce

$$u_j(t) = \frac{I_j(t)}{N(t)}$$

and rewrite part of the system (4).

$$\frac{\dot{N}}{N} = (f(N) - b) - \sum_{i=1}^{n} \alpha_i u_i$$

$$\frac{\dot{u}_j}{u_j} = \beta_j \left( N - \sum_{i=1}^{n} I_i - R \right) - \nu_j - \alpha_j - f(N) + \sum_{i=1}^{n} \alpha_i u_i.$$

Set $u = \sum_{i=1}^{n} u_i$. As $u \leqslant 1$ we obtain

$$\frac{\dot{u}}{u} \leqslant N \sum_{i=1}^{n} \beta_i - f(N) - \nu_*$$

with $\nu_* = \min_{1 \leqslant i \leqslant n} \nu_i$. Suppose that $N(t) \to 0$ for $t \to \infty$. Then $u(t) \to 0$ for $t \to \infty$. Thus

$$\frac{\dot{N}(t)}{N(t)} \to f(0) - b > 0$$

for $t \to \infty$. Hence $N$ grows exponentially for large $t$, a contradiction.

So far we have proved that

$$\limsup_{t \to \infty} N(t) = \varepsilon_0 > 0.$$

Suppose that

$$\liminf_{t \to \infty} N(t) = 0.$$

Then, for any $0 < \varepsilon < \varepsilon_0$, there exist sequences $t_m, \tau_m \to \infty$ for $m \to \infty$ such that

$$N(t_m) = \varepsilon; \qquad N(t) \leqslant \varepsilon, \qquad t_m \leqslant t \leqslant t_m + \tau_m.$$

Choosing $\varepsilon$ small enough and arguing a bit more precisely than before we find $\delta, s > 0$ such that

$$\dot{N}(t) \geqslant \delta N(t), \qquad t_m + s \leqslant t \leqslant t_m + \tau_m.$$

Hence

$$\varepsilon \geqslant N(t_m + \tau_m) = \varepsilon \exp\left[ -\left( b + \sum_{i=1}^{n} \alpha_i \right) s \right] \cdot e^{\delta(\tau_m - s)} \to \infty, \qquad m \to \infty.$$

This contradiction proves Step 1.

In a similar way we now show

*Step 2: The disease persists in the population if at least one strain has a basic reproductive rate exceeding unity.*
Without restricting generality we assume that $K/\sigma_1 > 1$; $\sigma_1 \leqslant \sigma_j$, $j = 1, \ldots, n$. Suppose that

$$I_1(t) \to 0, \qquad t \to \infty.$$

By (8), $I_j(t) \to 0$ for $t \to \infty$. As $N$ is bounded away from 0 by Step 1, we find that $I_j(t)/N(t) \to 0$ for $t \to \infty$. This implies $N(t) \to K$ for $t \to \infty$. See the $N$ equation in (4). Thus $I_1$ grows exponentially for large $t$. See the $I_1$ equation in (4). This contradiction implies that

$$\limsup_{t \to \infty} I_1(t) = \varepsilon_1 > 0.$$

Suppose that

$$\liminf_{t \to \infty} I_1(t) = 0.$$

Then, for any $0 < \varepsilon < \varepsilon_1$, there exist sequences $t_m, \tau_m \to \infty$, $m \to \infty$ such that

$$I_1(t_m) = \varepsilon; \qquad I_1(t) \leqslant \varepsilon, \qquad t_m \leqslant t \leqslant t_m + \tau_m.$$

Arguing as before, for any $\delta > 0$ we can choose $\varepsilon > 0$ so small that

$$f(K - 2\delta) - b - \sum_{i=1}^{n} \alpha_i I_i / N > 0, \qquad t_m \leqslant t \leqslant t_m + \tau_m.$$

Then there exists some $s = s(\delta) > 0$ such that

$$N(t) \geqslant K - \delta, \qquad t_m + s \leqslant t \leqslant t_m + \tau_m.$$

From the $R$ equation in (4) we obtain

$$R(t) \leqslant \delta, \qquad t_m + s \leqslant t \leqslant t_m + \tau_m$$

provided we choose $s$ large enough. By assumption we now choose $\delta > 0$ such that

$$\beta_1(K - 2\delta) - \alpha_1 - b - \nu_1 = \eta > 0.$$

From the $I_1$ equation in (4) we obtain that

$$\varepsilon \geqslant I_1(t_m + \tau_m) = \varepsilon\, e^{-(\alpha_1 + b + \nu_1)s} \cdot e^{\eta(\tau_m - s)}.$$

This is a contradiction because $\tau_m \to \infty$, $m \to \infty$.

Secondly we explain the *local asymptotic stability* of the equilibrium (9) in more detail (see Sect. 8).

If we linearize (4) around the equilibrium (9) we obtain the linear system

$$\dot{N} = \xi N - \sum_{j=1}^{n} \alpha_j I_j$$

$$\dot{I}_1 = \beta_1 I_1^* \left( N - \sum_{i=1}^{n} I_i - R \right)$$

$$\dot{I}_j = \beta_j I_j (\sigma_1 - \sigma_j), \qquad j = 2, \ldots, n.$$

$$\dot{R} = \sum_{i=1}^{n} \nu_j I_j - bR$$

with

$$\xi = f(N^*) - b + N^* f'(N^*).$$

$n-1$ eigenvalues of the variational matrix are given by $\lambda = \beta_j(\sigma_1 - \sigma_j), j = 2, \ldots, n$ and hence are strictly negative by assumption. The remaining three eigenvalues are roots of the polynomial

$$\lambda^3 + a_2 \lambda^2 + a_1 \lambda + a_0$$

with

$$a_0 = (\alpha_1 b - \xi b - \xi \nu_1) \beta_1 I_1^*$$

$$a_1 = \beta_1 I_1^* (b - \xi + \nu_1 + \alpha_1) - \xi b$$

$$a_2 = \beta_1 I_1^* + b - \xi.$$

According to the Routh-Hurwitz criterion (see, e.g. Boyce and DiPrima (1977), Sect. 5.3, Problem *20) this polynomial has roots with strictly negative real parts only, if $a_0, a_1, a_2 > 0$ and $a_0 < a_1 a_2$. Checking these conditions is an elementary algebraic exercise provided one has derived the following

relations from the equilibrium equations:

$$\xi \leqslant f(N^*) - b = \frac{\alpha_1 I_1^*}{N^*} L < \min\left(\beta_1 I_1^*, \frac{\alpha_1 b}{\nu_1 + b}\right).$$

Recall that $f' \leqslant 0$.

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