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Population Dynamics of Gene Transfer

CHRISTINE TREMBLAY AND MICHAEL R. ROSE*

Department of Biology, Dalhousie University, Halifax, Nova Scotia B3H 4J1, Canada

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Horizontal transfer of nucleic acid sequences is a widespread process of genetic change in bacterial populations, one taking on a variety of specific forms. A model capturing some of the general features of this process is formulated. Two major subsidiary variants of this model are analyzed. The first lacks competition between cells. In this case, the transferred genetic element can approach fixation asymptotically if cells bearing it are viable, but not otherwise. The second variant of the proposed model has competition. This gives rise to complex dynamical possibilities, but never fixation of the transferred genetic element. It is argued that the evolutionary transition from gene transfer polymorphism to obligatory genetic exchange, and thus the origin of sex, requires *either* population dynamics which are not subject to growth rate density-dependence *or* cell-dependence on transferred genetic elements, although such dependence does not require that the element be beneficial.

1. INTRODUCTION

Natural gene transfer between lineages is a process found in many bacteria (Lewin, 1977). It is known that many plasmids and lysogenic viruses transmit themselves horizontally within populations of bacteria, as well as residing within lineages without gene transfer. This transfer process may require cell to cell contact, as in plasmids, or include an extracellular stage during which the transmitted sequence is encapsulated in a protein covering, as in lysogenic phage. Natural bacterial transformation, in which naked DNA is secreted by one cell and taken up by another, similarly results in the transfer of gene-sized DNA sequences from lineage to lineage (Goodgal, 1982).

Such horizontal gene transfer constitutes a mechanism of spread for nucleic acid sequences. Instead of remaining within particular cellular lineages and utilizing the gene transmission systems of those cells for perpetuation through cell fission, mechanisms for passage from lineage to lineage allow the exploitation of an expanding range of host cell lineages. Therefore, horizontal transfer from cell to cell has been proposed as a

* To whom all correspondence should be addressed.

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mechanism evolved by nucleic acid sequences to facilitate their spread within populations, possibly without any beneficial effects upon their hosts (Dougherty, 1955; Hickey, 1982). In line with this idea, bacterial conjugation appears to be due to the action of conjugative plasmids themselves, rather than the remainder of the genome. For example, the *F* plasmids of *Escherichia coli* code for the formation of "sex-pili," projections of the cell which adhere to plasmid-free cells and permit the injection of the plasmid into such cells (Willetts and Skurray, 1980). *F* plasmids seem, therefore, an excellent example of this type of "contagious" genetic element.

The dynamics of conjugative plasmids in bacterial populations have been extensively analyzed by Stewart and Levin (1977), among others (e.g., Freter *et al.*, 1983). However, plasmids are only one of the various gene transfer mechanisms, mechanisms having much in common dynamically, though they are unlikely always to conform well to models of conjugative transmission in the laboratory. Other processes potentially having similar dynamical features include accessory genetic element-mediated cell fusion and bacterial transformation when the transforming DNA adheres to cell walls. Further steps toward the development of theory for contagious horizontal gene transfer were taken by Rose (1983), although that study too was quite limited in mathematical generality. Here we endeavor to formulate and analyze what we regard as basic models with sufficient mathematical generality to properly address the most elementary scientific issues involved in the population dynamics of gene transfer.

2. Model Formulation

We wish to represent the dynamics of a genetic element promoting its own transmission by replication within cell lineages and horizontal transfer to element-free cells. It is assumed that only two cell types are involved: element-free and element-bearing cells. Newly infected cells gain the genetic machinery necessary to become infectious in turn. Infectious cells may return to the element-free state by segregational loss of the contagious genetic element during mitosis or by mutation of the element. It is assumed that such mutation causes the reversion of the cell to an element-free state; it does not immunize the individual cell from a second infection.

As in Stewart and Levin (1977) and Rose (1983), we use ordinary differential equations to describe the evolutionary dynamics. The applicability of models of this kind to microbial ecosystems is well-demonstrated (Van-

dermeer, 1969; Levin *et.al.*, 1979; Waltman, 1983; Freter *et al.*, 1983). For our postulated situation, the most general model has the following form:

$$dx/dt = xG(x) + uy - M_1(x, y) \tag{1a}$$

$$dy/dt = yQ(y) - uy + M_2(x, y), \tag{1b}$$

where x is the density of element-free cells; y is the density of element-bearing cells; $G(x)$ is the reproductive rate of individual element-free cells; $Q(y)$ is the reproductive rate of individual element-bearing cells; u is the rate of mutational and segregational loss of the functional element, assumed to be strictly positive; M_1 is the net effect of element-bearing cells on element-free cells, including both competitive effects and the loss of cells by contagious conversion; and M_2 is the net effect of element-free cells on element-bearing cells, including both competitive effects and the gain of cells by contagious conversion. We take all functions to be continuous and differentiable to any degree within the first quadrant of Real two-dimensional space. We also require $M_1(x, 0) = M_2(x, 0) = 0$, according to our basic assumptions.

Two simple models of this form were analyzed in Rose (1983). The first ("Model I") had $G(x) = w_1$, $Q(y) = w_2$, $M_1(x, y) = M_2(x, y) = cxy$, and $u > 0$. Evidently, in Model I there were no within-type or between-type density-dependent competitive effects. The second ("Model II") had $G(x) = w_1 - d_1 x$, $Q(y) = w_2 - d_2 y$, $M_1(x, y) = c_1 xy$, $M_2(x, y) = c_2 xy$, and $u = 0$. This model allowed for Lotka–Volterra density-dependent competition, but not back-mutation and segregation. Analysis showed that density-dependence could inhibit the spread and fixation of the contagious element, at least with these two models. Indeed, as population growth with or without competitive density-dependent limitation constitutes one of the fundamental dynamical contrasts, we will divide our analysis of system (1) into these two cases. The set of models which is analyzed is shown in Table 1, which is organized in terms of this dichotomy.

3. Gene Transfer without Competition: General Model

In the absence of density-dependent competitive effects, system (1) takes the following form:

$$dx/dt = r_1 x + uy - yP(x) \tag{2a}$$

$$dy/dt = r_2 y - uy + yP(x), \tag{2b}$$

where r_1 is the intrinsic rate of increase of element-free cells, assumed strictly positive; r_2 is the intrinsic rate of increase of element-bearing cells, which may be positive or negative; and $P(x)$ is the rate at which each

TABLE I

Hierarchy of Models Analyzed

General model

$dx/dt = xG(x) + uy - M_1(x, y)$
$dy/dt = yQ(y) - uy + M_2(x, y)$

I. Density-independent population growth model

$dx/dt = r_1 x + uy - yP(x)$
$dy/dt = r_2 y - uy + yP(x)$

Specific functional forms of $P(x)$

A. $P(x) = cx, \quad c > 0$
B. $P(x) = px^2, \quad p > 0$
C. $P(x) = px/(x+1), \quad p > 0$

II. Density-dependent population growth model

$dx/dt = xg(x) + uy - ym_1(x)$
$dy/dt = yq(y) - uy + ym_2(x)$

Specific functional forms of g and q

$g(x) = r_1(1 - x/k_1)$ and $q(y) = r_2(1 - y/k_2)$

Specific functional forms of the m_i

A. $m_1(x) = m_2(x) = px/(x+1), \quad p > 0$
B. $m_1(x) = px + c_1 x; \quad m_2(x) = px - c_2 x; \quad p, c_i > 0$

element-bearing cell infects element-free cells, taken to be a positive strictly increasing function of x in the interval $[0, \infty)$, with $P(0) = 0$. Here and in the sequel, we follow standard methods of analysis for phase-plane dynamical systems confined to the first quadrant, as outlined in Freedman (1980).

System (2) has the following isoclines:

$$dx/dt = 0 \Leftrightarrow y = r_1 x/[P(x) - u] \tag{3}$$

and

$$dy/dt = 0 \Leftrightarrow y = 0 \text{ or } x = P^{-1}(u - r_2), \tag{4}$$

where P^{-1} indicates the inverse function for which $x = P[P^{-1}(x)]$. Isocline (3) has a vertical asymptote at $x = P^{-1}(u)$, the density of element-free cells at which the newly infected cells are equal in number to those regained by mutation and segregation.

There are two admissible equilibria:

$$(x, y) = (0, 0), \tag{5}$$

and

$$(x, y) = (x^*, y^*) = (P^{-1}[u - r_2],\ -r_1 P^{-1}[u - r_2]/r_2), \tag{6}$$

provided $r_2 < 0$ in the second case. The terms of the Jacobian matrix are as follows:

$$J_{11} = r_1 - y dP(x)/dx \tag{7a}$$

$$J_{12} = u - P(x) \tag{7b}$$

$$J_{21} = y dP(x)/dx \tag{7c}$$

$$J_{22} = r_2 - u + P(x). \tag{7d}$$

The Jacobian matrix at the origin is

$$J(0, 0) = \begin{pmatrix} r_1 & u \\ 0 & r_2 - u \end{pmatrix} \tag{8}$$

with eigenvalues r_1 and $r_2 - u$. As we take $r_1 > 0$, the origin is always unstable.

The analysis of this system can be divided into two major cases: (a) $r_2 \geqslant 0$, and (b) $r_2 < 0$, as in Rose (1983). In case (a), if $r_2 \geqslant u$, $dy/dt > 0$ for all interior (x, y), since $r_2 y - uy + yP(x) \geqslant (r_2 - u)\, y > 0$, for $y > 0$. Thus $y(t) \to \infty$ as $t \to \infty$. If $u \geqslant r_2 \geqslant 0$, we have $dx/dt = r_1 x - y[P(x) - u] > 0$ for $0 < x < P^{-1}(u)$. Therefore $x(t) > P^{-1}(u)$ as $t \to \infty$. If $x > P^{-1}(u)$ and $r_2 \geqslant 0$, $dy/dt = r_2 y + y[P(x) - u] > r_2 y \geqslant 0$, for $y > 0$. Thus $y(t) \to \infty$ as $t \to \infty$, for trajectories beginning in the interior of the first quadrant. Thus, in case (a) we always have $y(t) \to \infty$ as $t \to \infty$, in the interior.

In case (b), $r_2 < 0$, the behavior of $y(t)$ as $t \to \infty$ depends on $P(x)$. If $\lim_{x \to \infty}[r_2 - u + P(x)] \leqslant 0$, then $y(t) \to 0$ and $x(t) \to \infty$ as $t \to \infty$. If $\lim_{x \to \infty}[r_2 - u + P(x)] > r_1$, then both $y(t)$ and $x(t)$ are bounded providing $y(0) \neq 0$. What we will show is that $\lim_{t \to \infty}[x(t), y(t)] = (\infty, \infty)$ cannot occur. The result then follows from a qualitative analysis using Poincaré–Bendixson theory, which we omit.

Suppose $\lim_{t \to \infty}[x(t), y(t)] = (\infty, \infty)$. Choose a scalar p such that $\lim_{x \to \infty} P(x) > p > u - r_2 + r_1$, and choose a scalar k such that $x > k$ implies $P(x) > p$. Then, after some time, $x(t) > k$. Reset time so that $x(0) > k$. Then

$$dy/dt = y[r_2 - u + P(x)] \geqslant y[r_2 - u + p],$$

and

$$y(t) \geqslant y(0)\, e^{(r_2 - u + p)t}.$$

In addition, we must therefore have

$$dx/dt \leqslant r_1 x - y(p-u),$$

which can be reorganized as

$$(dx/dt)\,e^{r_1 t} - r_1 x e^{-r_1 t} \leqslant -y(p-u)\,e^{-r_1 t}$$

or

$$\begin{aligned} d[xe^{-r_1 t}]/dt &\leqslant -y(p-u)\,e^{-r_1 t} \\ &\leqslant -y(0)(p-u)\,e^{(-r_1+r_2-u+p)t}. \end{aligned}$$

Integrating both sides gives

$$e^{-r_1 t}x(t) - x(0) \leqslant C[e^{(-r_1+r_2-u+p)t} - 1],$$

where $C = y(0)(p-u)/(-r_1+r_2-u+p)$. Since $p > u - r_2 + r_1 > u$, C is positive. Rearranging, we have

$$x(t) \leqslant [x(0)+C]\,e^{r_1 t} - Ce^{(r_2-u+p)t}.$$

Since $r_2 - u + p > r_1$, the R.H.S. is bounded.

When both $x(t)$ and $y(t)$ are bounded, but there is no asymptotically stable equilibrium, the Poincaré–Bendixson theorem can be used to show that there must be limit cycles. However, we have not found any such limit cycles numerically.

If $u - r_2 + r_1 > \lim_{x\to\infty} P(x) > u - r_2$, then there are cases where both $x(t)$ and $y(t)$ increase without bound, as discussed in Section 4.C. If $\lim_{x\to\infty} P(x) > u - r_2$ and $x(t)$ does not approach ∞, we cannot have $y(t)$ converging to 0 in the interior, since otherwise dx/dt converges to $r_1 x$, implying $x(t) \to \infty$ as $t \to \infty$, a contradiction.

There is the posibility of convergence to equilibrium (6), depending on its Jacobian matrix:

$$J(x^*, y^*) = \begin{pmatrix} r_1 + (r_1/r_2)\,x^* dP(x^*)/dx & r_2 \\ -(r_1/r_2)\,x^* dP(x^*)/dx & 0 \end{pmatrix} \tag{7}$$

The local asymptotic stability criterion for a two-by-two Jacobian matrix like (7) is that its trace be negative and its determinant be positive. The latter condition is always met, since $\det\{J\} = r_1 x^* dP(x^*)/dx > 0$. For the former condition, we require

$$\begin{aligned} &r_1 + (r_1/r_2)\,x^* dP(x^*)/dx < 0 \\ &\quad \Leftrightarrow r_2 + x^* dP(x^*)/dx > 0, \end{aligned} \tag{8}$$

which is thus the sole necessary and sufficient condition for local asymptotic stability of equilibrium (6).

Condition (8) can be given a geometrical interpretation. The slope of isocline equation (3) is as follows:

$$d\{r_1 x/[P(x)-u]\}/dx$$
$$= \{r_1[P(x)-u] - r_1 x dP(x)/dx\}/[P(x)-u]^2 \tag{9}$$

Evaluated at equilibrium, the L.H.S. of (9) becomes

$$-r_1[r_2 + x^* dP(x^*)/dx]/r_2^2. \tag{10}$$

Since $r_1 > 0$, the sign of (10) is the opposite of the sign of the L.H.S. of (8). Thus local asymptotic stability of (6) requires that x isocline (3) be decreasing where it intersects the y isocline; if it is increasing, (6) will be unstable.

4. Gene Transfer without Competition: Examples

4.A $P(x) = cx, \quad c > 0$

This was Model I of Rose (1983). When $r_2 \geqslant 0$, $y(t) \to \infty$, while $x(t) \to u/c$ as $t \to \infty$. This behavior arises because

$$dx/dt = r_1 x + y(u - c)$$
$$= ur_1/c + (y - r_1/c)(u - cx),$$

so that, as $y(t) \to \infty$, $dx/dt < 0$ for $x > u/c$ and $dx/dt > 0$ for $x < u/c$. Thus, for $\phi(t) = y(t)/[x(t) + y(t)]$, $\phi(t) \to 1$ as $t \to \infty$.

When $r_2 < 0$, equilibrium (6) is globally asymptotically stable, as discussed in Rose (1983), taking on the value $([u - r_2]/c,\ r_1[r_2 - u]/r_2 c)$.

4.B $P(x) = px^2, \quad p > 0$

When $r_2 \geqslant 0$, $y(t) \to \infty$. As y becomes arbitrarily large, for finite values of x,

$$dx/dt \approx y(u - px^2),$$

giving an equilibrium for x of $\sqrt{(u/p)}$. That x can not increase without limit is clear if we write dx/dt as follows:

$$dx/dt = u + x(r_1 - px) + (u - px^2)(y - 1). \tag{11}$$

For sufficiently large x, (11) is negative once $y > 1$. Thus, for $r_2 \geqslant 0$, $y(t) \to \infty$, $x(t) \to \sqrt{(u/p)}$, and $\phi(t) \to 1$, as $t \to \infty$.

When $r_2 < 0$, local asymptotic stability condition (8) for equilibrium (6) becomes $-r_2 + 2u > 0$, which always holds. We have not found numerical examples in which $r_2 < 0$ and an asymptotic trajectory beginning in the interior does not converge to (6).

4.C $P(x) = px/(x+1), \qquad p > 0$

In this example of system (2), isoclines (3) and (4) are of interest. Figure 1 shows two of the cases which arise. Again, when $r_2 \geqslant 0$, $y(t) \to \infty$ as $t \to \infty$. But the shape of isocline (3) allows $x(t) \to \infty$ as $y(t) \to \infty$, and we have found examples of this behavior numerically.

When $r_2 < 0$, equilibrium (6) is admissible and stability condition (8) becomes

$$\begin{aligned} & r_2 + x^* p (x^* + 1)^{-2} > 0 \\ & \quad \Leftrightarrow r_2 + (u - r_2)/(x^* + 1) > 0 \\ & \quad \Leftrightarrow -u/r_2 > x^*. \end{aligned} \tag{12}$$

Condition (12) gives the value of x at the minimum of isocline (3); for values of x^* above this, equilibrium (6) is unstable. Numerical solutions of system (2) for this example have not yet yielded any apparent limit cycles. As in case 4.B, we cannot give a global analysis.

5. Gene Transfer with Competition: General Model

In order to treat system (1) in cases with competition, we assume that interactions between cells occur between only two at a time, so that functions M_1 and M_2 can be expressed in factored form. We also assume that intratype facilitation does not occur. System (1) becomes

$$dx/dt = xg(x) + uy - ym_1(x) \tag{13a}$$

$$dy/dt = y[q(y) - u + m_2(x)], \tag{13b}$$

where $g(x)$ is the rate of increase of element-free cells, assumed to be a strictly decreasing function such that $g(0) > 0$ and $g(k_1) = 0$, $k_1 > 0$; $m_1(x)$ is a strictly increasing positive-valued function with the same interpretation as M_1; $q(y)$ is the rate of increase of element-bearing cells, assumed to be strictly decreasing function, where we take k_2 such that, if $q(0) > 0$, then $q(k_2) = 0$, and otherwise $q(0) \leqslant 0$; and m_2 has no constraints on its functional form, and the same interpretation as M_2.

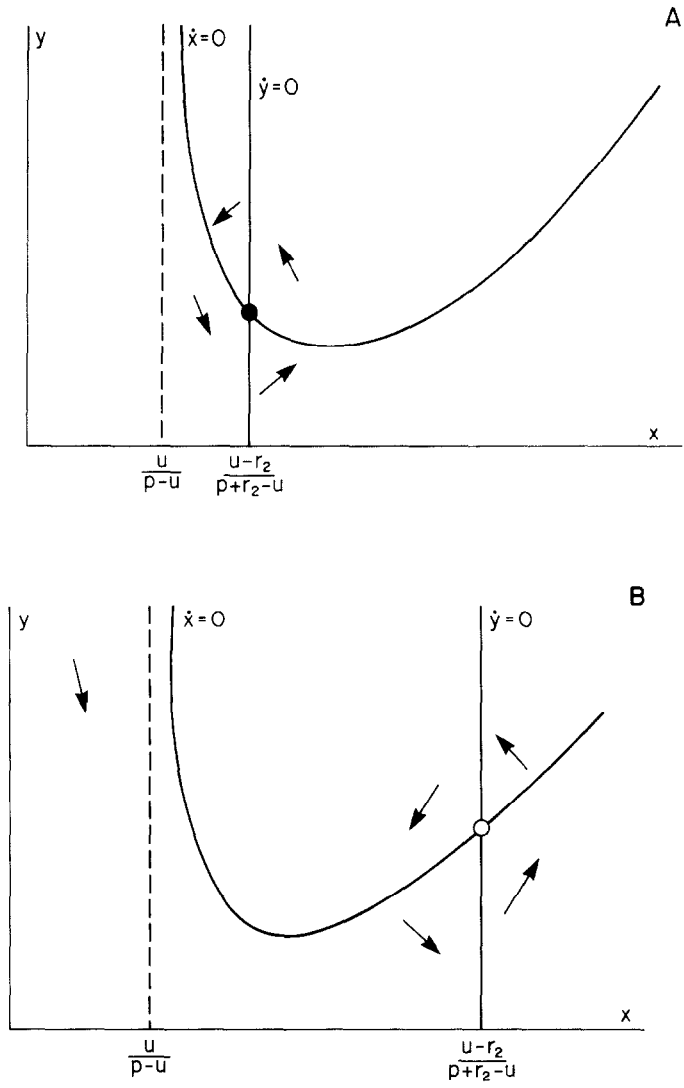

FIG. 1. Two phase-plane plots of isoclines (3) and (4) when $P(x) = px/(x+1)$ and $r_2 < 0$. (A) Here $u/-r_2 > x^*$, and the unique intersection of the two isoclines is a locally stable equilibrium, as indicated by a solid dot. (B) Here $u/-r_2 \leqslant x^*$, and the interior equilibrium is unstable with a circular flow around it, as indicated by the hollow dot with the arrows around it.

System (13) has the following isoclines:

$$dx/dt = 0 \Leftrightarrow y = xg(x)/[m_1(x) - u] \tag{14}$$

and

$$dy/dt = 0 \Leftrightarrow y = 0 \qquad \text{or} \qquad q(y) = u - m_2(x) \tag{15}$$

As for isocline (3), isocline (14) has a vertical asymptote at x such that $m_1(x) = u$. There are two boundary equilibria:

$$(x, y) = (0, 0) \tag{16}$$

and

$$(x, y) = (k_1, 0) \tag{17}$$

The terms of the Jacobian matrix are as follows:

$$J_{11} = g(x) + xdg(x)/dx - ydm_1(x)/dx \tag{18a}$$

$$J_{12} = u - m_1(x) \tag{18b}$$

$$J_{21} = ydm_2(x)/dx \tag{18c}$$

$$J_{22} = q(y) + ydq(y)/dy - u + m_2(x) \tag{18d}$$

The Jacobian matrix at the origin is

$$J(0, 0) = \begin{pmatrix} g(0) & u \\ 0 & q(0) - u \end{pmatrix} \tag{19}$$

with eigenvalues $g(0)$ and $q(0) - u$. As we take $g(0) > 0$, the origin is always unstable. Equilibrium (17) has Jacobian matrix

$$J(k_1, 0) = \begin{pmatrix} k_1 dg(k_1)/dx & u - m_1(x) \\ 0 & q(0) - u + m_2(x) \end{pmatrix} \tag{20}$$

with eigenvalues $k_1 dg(k_1)/dx$ and $q(0) - u + m_2(k_1)$. Since g is strictly decreasing, the first of these is necessarily negative. Local asymptotic stability of equilibrium (17) therefore requires

$$m_2(k_1) < u - q(0). \tag{21}$$

The biological interpretation of this result is that the effect of element-free cells on the initial population growth of element-bearing cells can not be too beneficial, otherwise the element-bearing cells will increase in density.

We note that interior equilibrium requires $q(y)-u+m_2(x)=0$ and take

$$a(x)=g(x)+xdg(x)/dx \\ -\{xg(x)/[m_2(x)-u]\}\, dm_1(x)/dx. \tag{22}$$

Internal equilibria, say (x^*, y^*), have the Jacobian matrix

$$J(x^*, y^*)=\begin{pmatrix} a(x^*) & u-m_1(x^*) \\ y^*dm_2(x^*)/dx & y^*dq(y^*)/dy \end{pmatrix} \tag{23}$$

As $a(x^*)$ is the only term without an obvious interpretation, it would be useful to find one. It turns out that

$$a(x)=[m_1(x)-u]\, d\{xg(x)/[m_1(x)-u]\}/dx, \tag{24}$$

where the derivative gives the slope of the x isocline (14). Thus the sign of $a(x^*)$ is equal to the sign of $m_1(x^*)-u$ times the sign of the slope of (14) at x^*. Satisfying the local asymptotic stability conditions trace $\{J\}<0$ and $\det\{J\}>0$ will thus depend on the slope of the x isocline, as for system (2), but in this case the nature of this dependence switches according to the sign of $m_1(x^*)-u$.

System (13) has four unspecified functions, while system (2) had only one. While it was possible to analyze the dynamics of system (2) fairly well in general terms, meaningful analysis of system (13) requires specification of its constituent functions.

6. Gene Transfer with Competition: Examples

The simplest algebraic representation of population regulation is the logistic equation. Accordingly, we take

$$g(x)=r_1(1-x/k_1), \tag{25a}$$

$r_1>0$, $k_1>0$, and

$$q(y)=r_2(1-y/k_2), \tag{25b}$$

where $r_2<0$ requires $k_2<0$, as well, in order to preclude mutual facilitation of element-bearing cells, otherwise $k_2>0$.

There are two major biological possibilities for the ecological interactions of the different cell types. One is that possession of the intact element is associated with novel ecological adaptations, as is sometimes the case with plasmids, and thus intertype competition is absent. The other possibility is that no such ecological differentiation arises, and intertype

competition plays an important role in the population dynamics. We discuss one example of each in turn.

6.A $m_1(x) = m_2(x) = px/(x+1), \qquad p > 0$

The complete specifications of system (13) are now

$$dx/dt = r_1 x(1 - x/k_1) + uy - ypx/(x+1) \tag{26a}$$

$$dy/dt = r_2 y(1 - y/k_2) - uy + ypx/(x+1) \tag{26b}$$

Isoclines (14) and (15) are thus

$$dx/dt = 0 \Leftrightarrow y = r_1 x(1 - x/k_1)/[px/(x+1) - u] \tag{27}$$

and

$$dy/dt = 0 \Leftrightarrow y = 0 \qquad \text{or} \qquad y = (k_2/r_2)[r_2 - u + px/(x+1)] \tag{28}$$

Local asymptotic stability condition (21) for the boundary equilibrium $(k_1, 0)$ is

$$pk_1/(k_1+1) < u - r_2. \tag{29}$$

Jacobian matrix (23) becomes

$$J(x^*, y^*) = \begin{pmatrix} a(x^*) & u - px^*/(x^*+1) \\ y^* p/(x^*+1)^2 & -y^* r_2/k_2 \end{pmatrix} \tag{30a}$$

where

$$a(x) = [px/(x+1) - u]\, d\{xr_1(1 + x/k_1)/[px/(x+1) - u]\}/dx \tag{30b}$$

the derivative giving the slope of isocline (27).

Internal equilibria for system (26) all lie on isocline (27), positive y^* requiring either

$$k_1 > x^* > u/(p-u) \tag{31}$$

or

$$u/(p-u) > x^* > k_1. \tag{32}$$

The analysis of local asymptotic stability is conveniently divided into these two cases.

When (31) holds, trace $\{J\}$ is less than zero if and only if

$$d\{x^* r_1(1 - x^*/k_1)/[px^*/(x^*+1) - u]\}/dx < y^* r_2/\{k_2[px^*/(x^*+1) - u]\}, \tag{33}$$

where the L.H.S. is the slope of isocline (27) at the equilibrium and the R.H.S. is necessarily positive in this case. Det$\{J\}$ is greater than zero if and only if

$$d\{x^*r_1(1-x^*/k_1)/[px^*/(x^*+1)-u]\}/dx < pk_2/[r_2(x^*+1)^2] \tag{34}$$

with the same interpretation of the L.H.S., and the R. H. S. being the slope of the y isocline. Both conditions are more readily satisfied the lower the value of the slope of isocline (27).

When (32) holds, trace $\{J\}$ is less than zero if and only if

$$r_1(1-x^*/k_1)-x^*r_1/k_1-y^*p/(x^*+1)^2-y^*r_2/k_2<0,$$

a condition which is always met, because all L.H.S. terms are strictly negative. Det$\{J\}$ is greater than zero if and only if

$$d\{x^*r_1(1-x^*/k_1)/[px^*/(x^*+1)-u]\}/dx > pk_2/[r_2(x^*+1)^2], \tag{35}$$

exactly the opposite of condition (34), requiring that the slope of isocline (27) be positive and of sufficiently great magnitude.

Boundedness of all trajectories is readily shown. Since

$$\begin{aligned} dy/dt &= y[r_2-yr_2/k_2-u+px/(x+1)] \\ &\leqslant y[r_2-yr_2/k_2-u+p], \end{aligned}$$

there is always some finite positive value for y, say Γ, above which $yr_2/k_2 > r_2-u+p$. Thus we have $y(t)<\Gamma$ for $t>\theta$, θ being a finite time. Similarly,

$$\begin{aligned} dx/dt &= xr_1(1-x/k_1)+uy-ypx/(x+1) \\ &\leqslant xr_1(1-x/k_1)+uy, \end{aligned}$$

and, as $t\to\infty$, $uy<u\Gamma=U$, say, while there is always some positive value for x above which $x^2r_1/k_1>U+xr_1$, so that $x(t)$ does not approach ∞ as $t\to\infty$. This argument shows that there must exist positive, real, and finite K and L such that every interior trajectory enters and then remains within the rectangle given by $\{(x, y)\colon 0\leqslant x\leqslant K \text{ and } 0\leqslant y\leqslant L\}$.

Figures 2 to 4 show the range of dynamical possibilities. As indicated, there may be (i) multiple, locally asymptotically stable, interior equilibria; (ii) limit cycles; (iii) a unique, stable, boundary equilibrium at $(k_1, 0)$; and (iv) stable interior equilibria along with stable boundary equilibria. In none of these cases does the frequency of element-free cells asymptotically

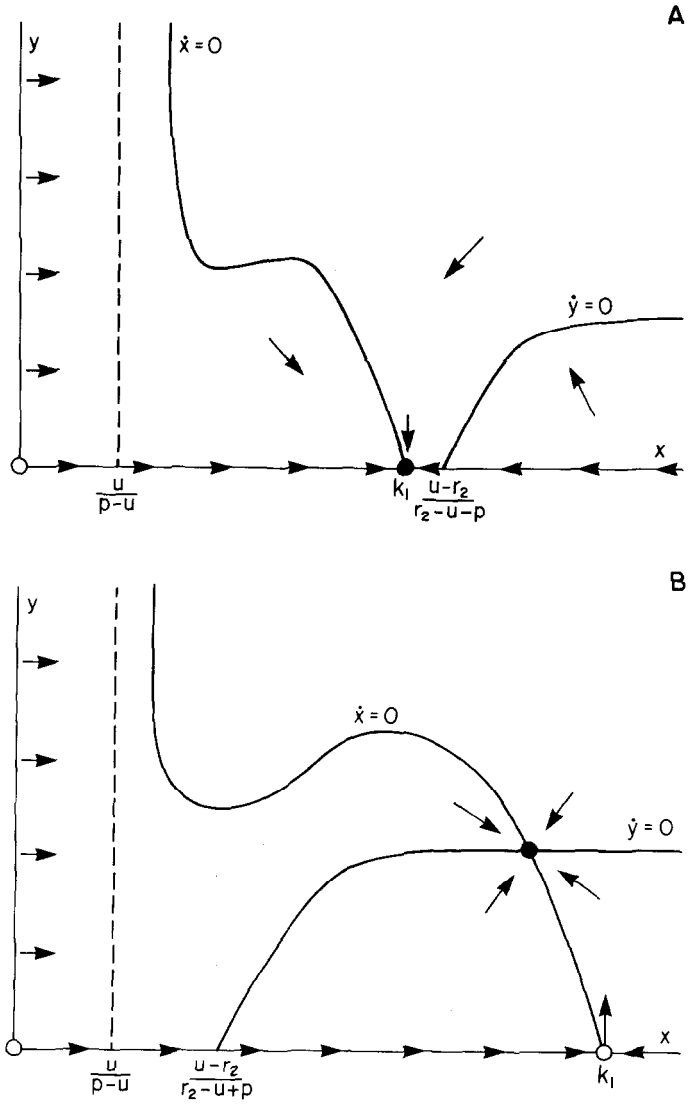

FIG. 2. Two phase-plane plots of isoclines, equilibria, and dynamics of system (26). (A) A case with the x isocline entirely to the left of the y-isocline. The $(k_1, 0)$ bondary equilibrium is globally stable, as indicated by the solid dot. A numerical example of this case is $r_1 = 10$, $k_1 = 40$, $r_2 = -1$, $k_2 = -1$, $u = 4.8$, $p = 5$. (B) A case with a unique interior equilibrium, which is locally, and perhaps globally, stable as indicated by the solid dot. All boundary equilibria are unstable, as indicated by hollow dots. A numerical example of this case is $r_1 = 10$, $k_1 = 100$, $r_2 = 2$, $k_2 = 20$, $u = 4$, $p = 5$.

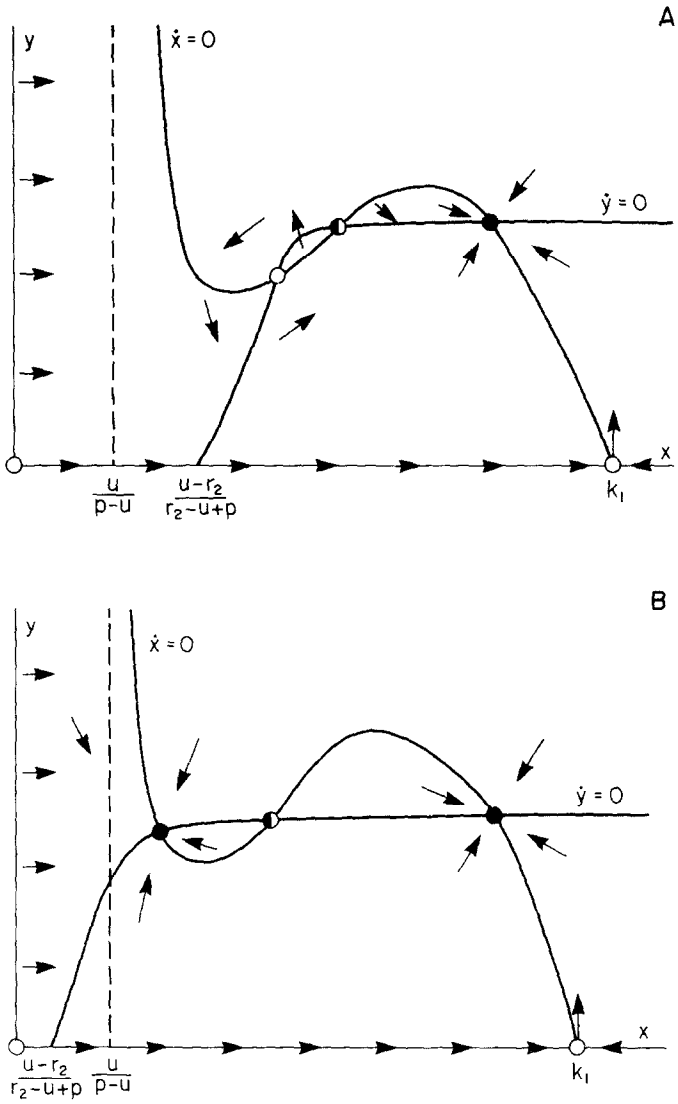

FIG. 3. Two phase-plane plots of isoclines, equilibria, and dynamics of system (26). (A) A case with multiple interior equilibria, only one locally stable, as indicated by the solid dot. All other equilibria are unstable, one being a sprial point, that with the hollow dot, the other being a saddle point, as indicated by the half-face dot. A numerical example of this case is $r_1 = 10$, $k_1 = 100$, $r_2 = -1$, $k_2 = -10$, $u = 1$, $p = 5$. (B) A case with more than one locally stable interior equilibrium, as indicated by the solid dots, separated by an unstable saddle point, as indicated by the half-face dot. A numerical example of this case is $r_1 = 10$, $k_1 = 100$, $r_2 = 2$, $k_2 = 20$, $u = 1$, $p = 5$.

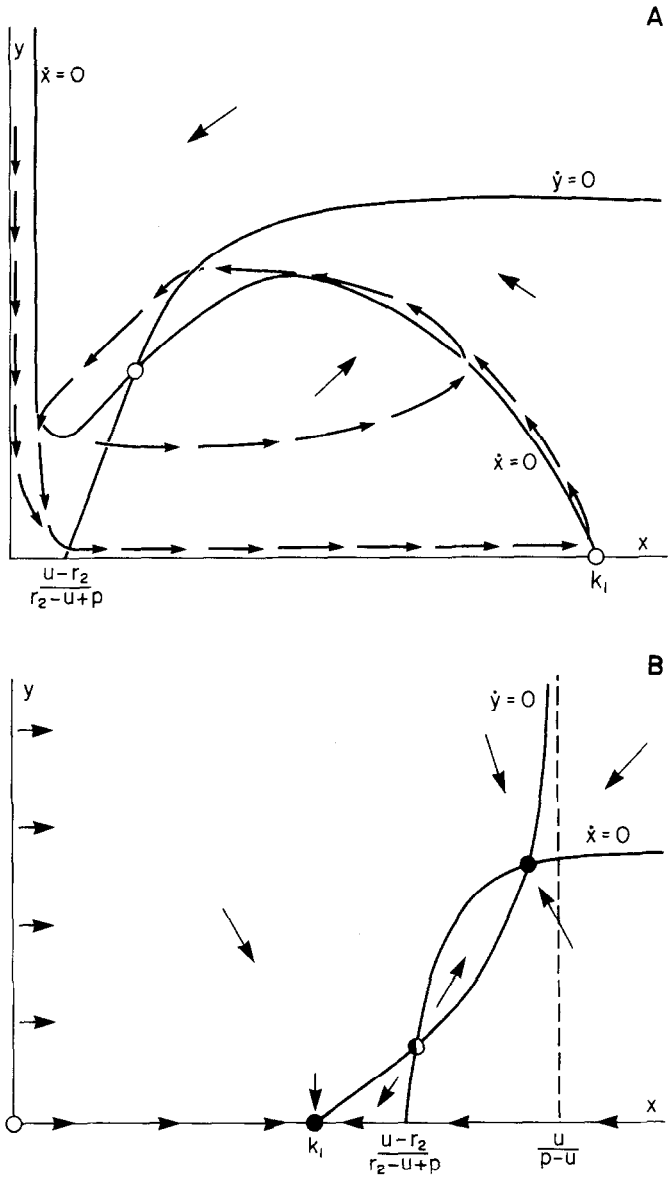

FIG. 4. Two phase-plane plots of isoclines, equilibria, and dynamics of system (26). (A) A case without stable equilibria, as indicated by the hollow dot. The only attractor which has been found is a limit cycle. A numerical example of this case is $r_1 = 5$, $k_1 = 50$, $r_2 = -4$, $k_2 = -80$, $u = .1$, $p = 5$. (B) A case with both boundary and interior stable equilibria, indicated by the soid dots. The other interior equilibrium is a saddle-point, shown as a half-face dot. A numerical example of this case is $r_1 = 1$, $k_1 = 1$, $r_2 = 1.8$, $k_2 = 18$, $u = 4.8$, $p = 5$.

approach zero. On the other hand, given the achievement of a density threshold, the element may invade even when the boundary equilibrium $(k_1, 0)$ is locally asymptotically stable. Overall, the element is either present without fixation or absent.

6.B $m_1(x) = px + c_1 x, \qquad m_2(x) = px - c_2 x$

We take p, c_1, and c_2 strictly positive. With these specifications, system (13) becomes

$$dx/dt = r_1 x(1 - x/k_1) + uy - pxy - c_1 xy \tag{36a}$$

$$dy/dt = r_2 y(1 - y/k_2) - uy + pxy - c_2 xy. \tag{36b}$$

Isoclines (14) and (15) are thus

$$dx/dt = 0 \Leftrightarrow y = xr_1(1 - x/k_1)/[(p + c_1) x - u] \tag{37}$$

and

$$dy/dt = 0 \Leftrightarrow y = 0 \qquad \text{or} \qquad y = (k_2/r_2)[r_2 - u + (p - c_2) x] \tag{38}$$

Local asyptotic stability condition (21) for the boundary equilibrium $(k_1, 0)$ is

$$(p - c_2) k_1 < u - r_2, \tag{39}$$

with a straightforward interpretation. Jacobian matrix (23) becomes

$$J(x^*, y^*) = \begin{pmatrix} a(x^*) & u - (p + c_1) x^* \\ (p - c_2) y^* & -r_2 y^*/k_2 \end{pmatrix} \tag{40a}$$

where

$$a(x^*) = [(p + c_1) x^* - u]\, d\{x^* r_1(1 - x^*/k_1)/[(p + c_1) x^* - u]\}/dx, \tag{40b}$$

the derivative giving the slope of isocline (37) at x^*, as before. Admissible internal equilibria for system (36) require either

$$k_1 > x^* > u/(p + c_1) \tag{41}$$

or

$$u/(p + c_1) > x^* > k_1. \tag{42}$$

In case (41), trace $\{J\}$ is less than zero if and only if

$$a(x^*) < y^* r_2/k_2. \tag{43}$$

The derivative in $a(x^*)$, as given in (40b), is always negative when conditions (41) are met, so that (43) is always satisfied. Det$\{J\}$ is greater than zero if and only if

$$\begin{aligned} &d\{x^* r_1(1-x^*/k_1)/[(p+c_1)\,x^*-u]\}/dx < k_2(p-c_2)/r_2 \\ &\quad \Leftrightarrow d\{x^* r_1(1-x^*/k_1)/[(p+c_1)\,x^*-u]\}/dx \\ &\quad < d\{(k_2/r_2)[r_2-u+(p-c_2)\,x^*\}/dx, \end{aligned} \tag{44}$$

which has the graphical interpretation that the slope of isocline (38) must be greater than that of isocline (37), at the point of intersection.

In case (42), trace $\{J\}$ is less than zero if and only if

$$r_1(1-x^*/k_1)-x^* r_1/k_1-(p+c_1)\,y^*-y^* r_2/k_2<0,$$

a condition which is always met when $x^*>k_1$. Det$\{J\}$ is greater than zero if and only if

$$\begin{aligned} &d\{x^* r_1(1-x^*/k_1)/[(p+c_1)\,x^*-u]\}/dx \\ &\quad > d\{(k_2/r_2)[r_2-u+(p-c_2)\,x^*\}/dx, \end{aligned} \tag{45}$$

the opposite of condition (44), giving the graphical interpretation that the slope of isocline (38) must be *less* than that of isocline (37). This parallels the antisymmetry of conditions (34) and (35) of example 6.A.

Boundedness of all trajectories is readily shown. Equation (36a) can be rewritten as

$$dx/dt = r_1 x(1-x/k_1)+y[u-(p+c_1)\,x], \tag{46}$$

so that for sufficiently large x, say Ω, both R.H.S. terms of (46) will be negative. Thus, after some finite time, say π, $x(t)<\Omega$. Accordingly, for $t>\pi$,

$$\begin{aligned} dy/dt &= y[r_2(1-y/k_2)-u+(p-c_2)\,x] \\ &< y[r_2-u+(p-c_2)\,\Omega-yr_2/k_2]. \end{aligned} \tag{47}$$

Therefore, for sufficiently large y and $t>\pi$, $dy/dt<0$. Thus $y(t)$ does not approach ∞ as $t\to\infty$. Again, this implies that every interior trajectory enters and remains within a rectangle of finite size in the first quadrant.

Setting isoclines (37) and (38) equal to each other and rearranging gives an explicit polynomial for roots at which equilibria can arise. This polynomial is second degree, and has at most two such roots. Since the relationship between y^* and x^* is one-to-one, from isocline (38), there are at most two interior equilibria for system (36). Figures 5 and 6 show part of the range of dynamical possibilities. Conditions (43) and (44) have as a

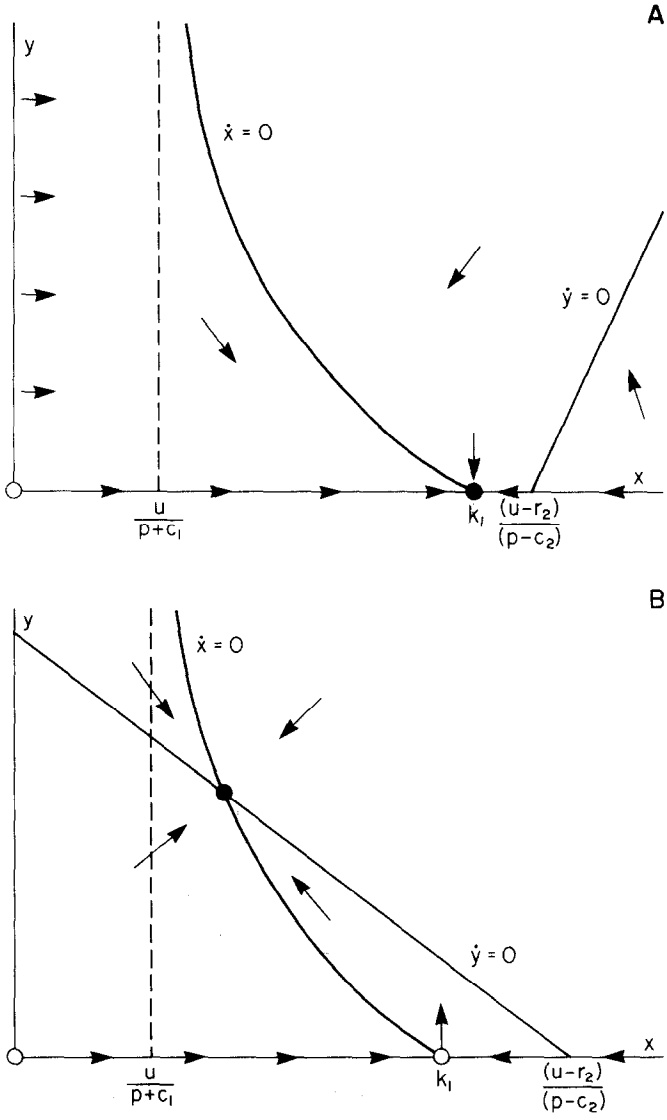

FIG. 5. Two phase-plane plots of isoclines, equilibria, and dynamics of system (36). (A) A case with a globally stable boundary equilibrium at $(k_1, 0)$, indicated by the solid dot. A numerical example is $r_1 = 10$, $k_1 = 10$, $c_1 = 1$, $r_2 = .4$, $k_2 = 4$, $c_2 = 2.95$, $u = 1$, $p = 3$. (B) A case with what appears to be a globally stable interior equilibrium, indicated by the solid dot. A numerical example of this is $r_1 = 10$, $k_1 = 10$, $c_1 = 1$, $r_2 = 1.4$, $k_2 = 14$, $c_2 = 2.5$, $u = 1$, $p = 3$.

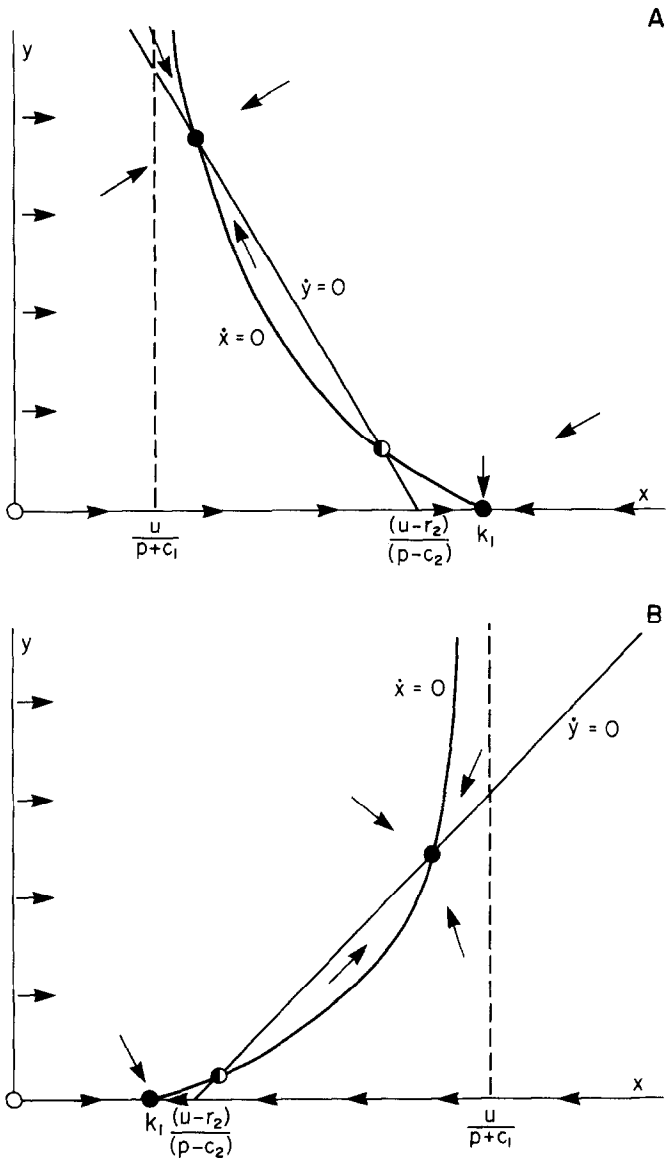

FIG. 6. Two phase-plane plots of isoclines, equilibria, and dynamics of system (36). (A) A case with a locally stable interior equilibrium and a locally stable boundary equilibrium, indicated by solid dots. A separatrix passing through the saddle point (half-face dot) defines the boundaries between the basins of attraction of these stable equilibria. A numerical example of this case is $r_1 = 10$, $k_1 = 10$, $c_1 = 1$, $r_2 = 1.6$, $k_2 = 32$, $c_2 = 3.1$, $u = 1$, $p = 3$. (B) As for A, except in this case the magnitude of x^* is increased by the presence of element-bearing cells at equilibrium. A numerical example of this is $r_1 = 1$, $k_1 = 1$, $c_1 = .4$, $r_2 = 1.45$, $k_2 = 29$, $c_2 = .1$, $u = 2$, $p = .6$.

corollary the uniqueness of interior asymptotically stable equilibria, because the isoclines can intersect in a configuration premitting stability once only. However, it is clear that there may be a stable interior equilibrium together with a stable boundary equilibrium at $(k_1, 0)$. Again, the element is either present without fixation or absent. We have found no numerical cases with limit cycles.

Both examples 6.A and 6.B could be analyzed in greater depth, but they suffice to indicate the range of behavior of system (13). There is no tendency for the element to approach fixation in the population, and no such cases were found. (This is not to say that they couldn't be contrived by picking an arbitrarily small u parameter and making the element-free cells virtually inviable. However, we regard such cases as largely irrelevant.) When the element is present, there is no simple and general characterization of its dynamics, as it may be subject to periodic attractors or multiple attractor equilibria.

7. Discussion

The foregoing mathematical analysis leads to the following intuitively straightforward conclusions concerning the conditions required for successful invasion of a contagious genetic element. Invasion is fostered when (i) the intrinsic rate of increase of element-bearing cells is high; (ii) the rate of element loss due to segregation or mutation is low; (iii) the infection rate is high at the carrying capacity of element-free cells; and (iv) element free cells have little competitive effect on element-bearing cells. Other intuitively obvious conclusions were that (i) density-dependent competitive interactions could preclude unbounded population growth; (ii) an absence of interior equilibria could give rise to limit cycles; and (iii) no examples of inviable element-bearing cells displacing element-free cells were found. One result which ran counter to the findings of Rose (1983) was the demonstration that it was possible to completely lose element-bearing cells from populations without density-dependent competition.

One scientifically meaningful finding which was not intuitively obvious before analysis was that effective displacement of element-free cells required unlimited population growth. This makes the question of the realism of allowing unlimited population growth a moot point if these models are to be used to explain the evolution of genetic elements which approach fixation in bacterial populations. In particular, the use of gene transfer mechanisms to explain the spread of primitive sex (Hickey, 1982; Rose, 1983) comes to depend on the degree to which populations are typically subject to density-independent mechanisms of population density control in nature—a widely debated issue within population ecology. It is not

not necessary to resolve this issue here, because the above analysis may be somewhat misleading with respect to the consequences of desity-dependent growth limitation for the spread of contagious genetic elements. A crucial feature of the models studied here is the loss of the genetic element giving rise to element-free cells, which in a way trivially guarantees the maintenance of element-free cells in significant proportions whenever population density trajectories are bounded. Consider the following possibility, however. If, within the element-bearing subpopulation, the element were to have acquired an indispensable cellular function, either by acquisition of an extant indispensable gene sequence by recombination with the host genome or by the evolution of a novel function for adaption to a hostile novel environment, then these models could be recast in the following form:

$$dx/dt = xg(x) - ym_1(x) \tag{48a}$$

$$dy/dt = yq(y) + ym_2(x), \tag{48b}$$

with the same functional constraints as those of model system (13). Then, as shown in Rose (1983), it is easy to find cases where $x(t) \to 0$ as $t \to \infty$ and $y(t)$ goes to a strictly positive carrying capacity. Lest this be interpreted as a result due to the spread of a beneficial element, it is possible for such behavior to arise with $q < g$ for all values of their arguments, providing the m_i increase sufficiently rapidly with x.

The present models, however, are not suitable for explaining the evolution of such an obligatory genetic exchange system. Instead, they have more relevance to the dynamics of contagious genetic elements on which cells have not evolved dependence. The longer-term dynamical result may come to depend on the genetic diversity of cell or element populations. Such cases require models with three or more variables, like those of the Levin *et al.* (1977) and Stewart and Levin (1984) studies of the coevolution of phage and bacteria. One problem to be investigated using such models are the conditions under which obligatory genetic exchange might evolve as a result of cellular dependence.

The present theoretical study is primarily of importance in its demonstration of the robustness of some of the conclusions drawn in Rose (1983) on the basis of a far more limited set of models, as well as the discovery of important qualifications to those conclusions. Contagious genetic elements can readily spread through unicellular populations, providing they are sufficiently efficient and not overly deleterious, though they need not be beneficial. Once they have established themselves in such populations, a great many different possibilities arise, and the middle-range dynamical outcome will depend on (i) the pattern of population regulation; (ii) the initial conditions of the population; and (iii) the

appearance of variant forms of the genetic element or the host cell. Conclusions concerning the long-range consequences of the spread of contagious genetic elements require more elaborate models.

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