

Origin of Sex for Error Repair II. Rarity and Extreme Environments

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Received May 18, 1993

In a previous paper we studied the simultaneous, and at times conflicting, needs of coping with DNA damage, efficient cell replication, and the avoidance of cell mortality. These selective factors operated on sexual and asexual haploid and diploid populations that were reproductively isolated from one another. We concluded, in part, that a sexual type of cell could not expand from extreme rarity in populations dominated by asexual haploid and diploid cells. In the present paper we show that it is relatively easy for a rare sexual mutant to expand in a population dominated by asexual haploid cells if some matings occur between sexual and asexual cell types. We also study the persistence of sex in high mortality, high damage environments, in which neither the asexual diploid nor haploid can survive. The diploid cannot survive because its lower birth rate cannot overcome mortality and the haploid cannot survive because its birth rate cannot overcome gene damage. Sex can persist in these punishing environments by tuning the parameters of the sexual cycle, and the fusion and splitting rates, into a specified region, thereby reaping both benefits of damage repair and efficient replication. © 1995 Academic Press, Inc.

BACKGROUND

The problem of DNA damage must have been acute for early replicating systems. For example Sagan (1973) has estimated the average lethal dose of ultraviolet radiation under primitive conditions and concluded that DNA damage would have posed a major problem for early life. Damages have severe biological consequences as they block or interfere with DNA replication and transcription. We have previously studied the conflicting

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needs of coping with DNA damage, efficient cell replication, and cell mortality as selective factors operating on sexual and asexual haploid and diploid populations that were reproductively isolated from one another (Long and Michod, 1994). We concluded, in part, that sexual types could not expand from extreme rarity in populations dominated by asexual haploid or asexual diploid cells. In the present paper, we ask whether a rare sexual mutant can expand in a population dominated by asexual haploid cells, if matings occur between sexual and asexual cells. We further investigate the conditions under which sex can persist in extreme environments that are forbidden to both the asexual haploid and asexual diploid life cycles.

It is difficult for sex to increase from rarity, because sex, by its very nature, involves fusion events that are inherently non-linear. The likelihood of fusion is usually assumed to be proportional to the product of the population densities of the mating cells. These same non-linearities that make the expansion of sex from extreme rarity difficult also tend to make sex stable when it is common (Bernstein *et al.*, 1985; Michod, 1991).

In the present paper, we study the origin of sex as a rare Mendelian-like factor in a predominantly asexual population. Thus, the process of selection studied here is individual selection in a Mendelian-like population, while the companion paper is concerned with selection between groups of different cell types. Although the mating systems differ in the two papers, many of the assumptions and motivations of the companion paper (Long and Michod, 1994) apply here. That paper should be consulted for these background remarks. Here, we proceed directly to the model and analysis, focusing only on the biological and mathematical assumptions that are different from those in Long and Michod (1994).

The basic difference in the present model is that sexual cells may mate with either asexual or other sexual cells, while in Long and Michod (1994) sexual cells mated only with other sexual cells. It may seem unreasonable to assume that a sexual cell could "coerce" an asexual cell into mating. Yet, a similar assumption is made in models of infectious transfer of selfish elements (see, for example, Hickey and Rose, 1988). Indeed, such coercion is precisely what the F-plasmid orchestrates during conjugation in the bacterium *E. coli*. In infectious transfer models, it is commonly assumed that the infectious element causes mating between cells, one cell that has the element and one cell that does not have the infectious element. In our model, sexual and asexual cells are similar, respectively, to cells with or without the infectious element. The cells produced by matings are always healthy, even if the parent cells contained damaged genes. When matings occur between a sexual and an asexual cell, we assume that a healthy sexual and a healthy asexual cell type are produced upon splitting.

We consider two basic modes of mating: random mating and damage-induced mating. Under random mating, both damaged and undamaged sexual cells initiate mating, while under damage-induced mating only damaged sexual cells initiate mating. In both cases, the probability of a particular mating is proportional to the product of the densities of the two cell types. We use standard linear stability analyses to investigate the conditions for sex to invade a predominately asexual population and the conditions for asexuality to invade a predominately sexual population. Since our main interest is in the origin of sex from rarity, we study the asexual equilibrium in more detail than the sexual equilibria. The group selection models by Long and Michod (1994) focused on damage-induced sex, since random-mating sex was found to be noncompetitive in the case of reproductive isolation. Here, we focus on random-mating sex, since it requires the fewest assumptions about the capabilities of the sexual cell. In contrast to the results of Long and Michod (1994), we find that random-mating sex may increase from extreme rarity, if matings occur between sexual and asexual cells.

TABLE I

Major Assumptions in Models

<i>Mass action dynamics:</i> interaction equal to product of density of constituents
<i>Damage-induced sex:</i> only gene-damaged cells initiate sex with damaged or undamaged partners
<i>Random-mating sex:</i> both gene-damaged and undamaged cells initiate sex with damaged or undamaged partners
<i>Pure sex:</i> no reproduction or genome replication during sex (as occurs in meiosis)
<i>Damage repair:</i> gene damages are repaired in fused diploid state
<i>Two sources of mortality:</i> gene death due to damage (reversible by repair) and cell death due to disruption of cell-membrane (non-reversible)
<i>Reproduction requires nucleotide resources:</i> haploids require one nucleotide resource packet to reproduce, diploids two
<i>Competition involves resource use and sexual interactions between cell types</i>
<i>Closed system:</i> total resources (free resources plus resources tied up in cells) are constant

MODEL

The basic haploid life cycle of sexual and asexual cells studied in Long and Michod (1994) is shown in Fig. 1. Free nucleotides, in density r , are used by cells as resources for reproduction. The parameters used to describe the population are d , damage; m , mortality; b , birth; f , fusion; s , splitting; and p , a parameter that serves to distinguish the size of fused cells, which might be larger than unfused sexual and asexual cells. We often take $p \approx 1.59$, meaning that the fused sexuals have twice the volume of the haploid cells and, hence, approximately 1.59 times the surface area. Cell size affects cell mortality, because we assume that cell mortality results from disruption of the cell membrane. For this reason, fused sexual cells are assumed to have a mortality rate of pm , which is greater than the mortality rate of haploid cells if $p > 1$. Assuming $p > 1$ only makes life more difficult for sexual cells. The major assumptions are given in Table I and all parameters and variables are given in Table II.

Three additional parameters (see Fig. 2) are used to describe the sexual cycle in the mixed mating model: c , q , and h . The parameter c represents

TABLE II

Parameters	
b	birth rate for all the cells
m	death (or mortality) rate for all cells
p	size and shape difference between haploid and diploid cells
f	fusion rate for the sexual cells
s	splitting rate for the diploid-like sexual cell
d	damage rate for haploid cells
c	cost in reproduction for sexual
q	difference in fusion rates between homo- and heterospecific matings (see Fig. 2)
h	difference in splitting rates between homo- and heterospecific matings (see Fig. 2)
Variables	
x	density of sexual haploid cells
y	density of homospecific matings—fused sexual \times sexual cells
y_a	density of heterospecific matings—fused sexual \times asexual
z	density of gene-damaged haploid sexual cells
x_a	density of asexual haploid cells
z_a	density of gene-damaged haploid asexual cells
r	density of free resources available for reproduction
t	time

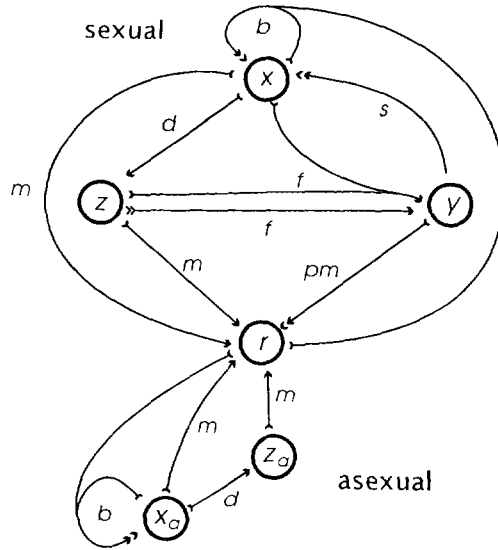


FIG. 1. Flows in basic model of sexual and asexual haploid used in Long and Michod (1994). Matings between sexuals and asexuals are shown in Fig. 2. Circles represent cell populations, while arrows represent movements of cells from one population (the "donor") to another (the "recipient"). The number of "feathers" at the tail of an arrow indicates the number of cells that leave the donor population, while the number of arrow heads at the beginning of an arrow indicates the number of cells that are contributed to the recipient population. For example, the arrow $\rightarrow\rightarrow\rightarrow$ indicates that two cells are taken from the donor population to produce three cells in the recipient population.

a direct cost of sex. As was the case in Long and Michod (1994), we assume here that sex is decoupled from reproduction. Consequently, cells involved in sexual fusions cannot reproduce until after splitting occurs. Fusions involving healthy cells temporarily remove them from the reproducing population until splitting occurs. In this sense, sex is costly. Sex is also costly because we assume that fused cells are larger than haploid cells, and, hence, have a higher mortality rate. In addition to these costs that require active fusion, there may be direct costs of sex that accrue even when sexual cells are not in a fused state. For example, the capacity for sex may require a permanent commitment of resources away from cell maintenance, survival, or reproduction. We model these fixed costs of sex by the parameter c which is assumed to directly affect the birth rate. Specifically, if $c < 1$ sex is costly, while if $c = 1$ sex has no direct cost. The parameters q and h change the effective fusion and splitting rates, respectively, of heterospecific (sexual with asexual) matings relative to homospecific (sexual with sexual) matings. As already mentioned, we consider both damage-induced and random mating, although only the damage-induced

case is represented in Fig. 2. We found in Long and Michod (1994) that for sex to be competitive under group selection, sex needed to be induced by genome damage. However, as we show below, this is not necessarily the case when mixed matings are allowed.

We show in Fig. 2 the matings for damage-induced sex. Fusions are initiated by gene-damaged sexual cells, in density z , and involve either sexual and asexual cells. The gene-damaged cell initiating sex may mate with either gene-damaged or healthy partners. The mating structure for damage-induced sex is, therefore, $[z][x + z + x_a + z_a]$. With damage-induced sex, there are no matings in which both partners are healthy. Under random mating, matings occur between the healthy sexual cells. The mating structure for random-mating sex is, therefore, $[x + z][x + z + x_a + z_a]$. The case of random mating would be similar to Fig. 2, but would involve additional flows from healthy sexual cells (density x) and healthy or damaged asexual cells (densities x_a and z_a) to produce heterospecific diploids (density y_a). Matings between healthy cells are, of course, pointless from the point of view of repair and would presumably be selected against in competition with damage-induced mating. Nevertheless, random mating may be the most relevant assumption initially.

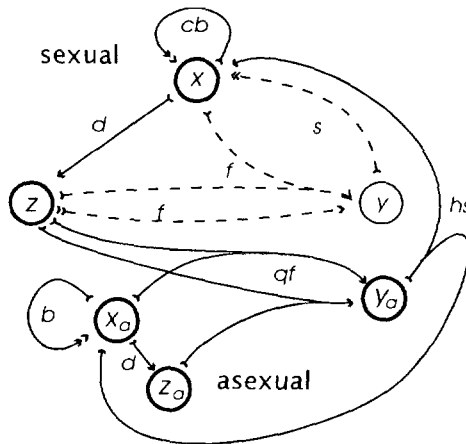


FIG. 2. Additional flows and parameters for mixed mating model with damage-induced mating. Under damage-induced mating, no fusions involve two healthy cells, while in the random mating model such fusions occur. Flows involving resource utilization and mortality are not included (see Fig. 1). The heterospecific diploids (sexual fused with asexual), in density y_a , revert to resources at the same rate, pm , as do homospecific diploids (sexual fused with sexual), in density y (see Fig. 1). Flows indicated by dashed lines are homospecific matings and occur in both the mixed mating model and the group selection model studied previously. See text for additional explanation.

With these additional assumptions, in the case of random mating, the relevant equations are

$$\begin{aligned}
 x' &= x(cbr - m - d) + 2sy + hsy_a - 2fx[z + x] - qfx[z_a + x_a] \\
 z' &= dx - zm - 2fz(z + x) - qfz[z_a + x_a] \\
 y' &= f[z + x][z + x] - y(pm + s) \\
 x'_a &= x_a(br - m - d) + hsy_a - qf[z + x]x_a \\
 z'_a &= dx_a - mz_a - qf[z + x]z_a \\
 y'_a &= qf[z + x][z_a + x_a] - y_a(pm + hs),
 \end{aligned} \tag{1}$$

with the pool of free nucleotides given by

$$r = 1 - x - 2y - 2y_a - z - x_a - z_a.$$

In the case of damage-induced mating, terms of the form $[z + x][z + x]$ and $[z + x][z_a + x_a]$ in Eq. (1) are replaced by terms like $z[z + x]$ or $z[z_a + x_a]$ to give the equations

$$\begin{aligned}
 x' &= x(cbr - m - d) + 2sy + hsy_a - 2fxz - qfxz_a \\
 z' &= dx - zm - fz(2z + x) - qfz[z_a + x_a] \\
 y' &= fz[z + x] - y(pm + s) \\
 x'_a &= x_a(br - m - d) + hsy_a - qfzx_a \\
 z'_a &= dx_a - mz_a - qfzz_a \\
 y'_a &= qfz[z_a + x_a] - y_a(pm + hs).
 \end{aligned} \tag{2}$$

We first verify that the equations (1) are consistent by calculating the differential equation for r in two separate ways. First, as in the other cases, we account for all inflows and outflows to the resource pool to obtain

$$m(x_a + z_a + x + z + 2py + 2py_a) - br(x_a + cx)$$

This equals

$$-x' - 2y' - z' - 2y'_a - x'_a - z'_a,$$

which is the derivative obtained directly, so our system is consistent.

ANALYSIS

Extinction

We are interested in conditions under which extinction of our system is unstable. The Jacobian matrix associated with equations (1), or equations (2), gives the following six eigenvalues at the extinction equilibrium $\hat{x} = \hat{y} = \hat{z} = \hat{w} = \hat{x}_a = \hat{z}_a = 0$:

$$1 - d - m, \quad c - d - m, \quad -m, \quad -m, \quad -mp - s, \quad -mp - hs.$$

All parameters must be positive to be biologically meaningful, so these eigenvalues are all negative except the first two. Instability of extinction requires simply that birth overcome death. For asexual extinction to be unstable requires that $d + m < 1$, and for sexual extinction to be unstable requires that $d + m < c$.

Pure Population Equilibria

We now restrict our consideration to the stability of the pure sexual and pure asexual equilibrium populations (that is, populations composed entirely of asexuals or sexuals). These pure equilibria exist in both the group selection and individual selection models of competing haploids. In other words, when only one cell type is present—either sexual haploids or asexual haploids—mixed matings have no effect and, consequently, the equations (1) above and the equations (13) of Long and Michod (1994) must give the same pure equilibria. Consequently, the graphs presented below of the cell frequencies at the pure equilibria (Figs. 3 and 5) also apply to the group selection model (Eq. 13 of Long and Michod, 1994). Although the pure equilibria are the same, their stability properties are different for the different models, since heterospecific matings occur in the models studied here but not in Long and Michod (1994).

Asexual Equilibrium

When sexuals are absent ($x = y = z = w = 0$), the asexual densities come to the following equilibrium:

$$\begin{aligned} \hat{x}_A &= \frac{(b - d - m)m}{bd + bm} \\ \hat{z}_A &= \frac{(b - d - m)d}{bd + bm} \\ \hat{f} &= 1 - \hat{x}_A - \hat{z}_A. \end{aligned} \tag{3}$$

Equations (3) are graphed as a function of d and m in Fig. 3 for $b = 1$ (parameters normalized to b) and $d + m < 1$.

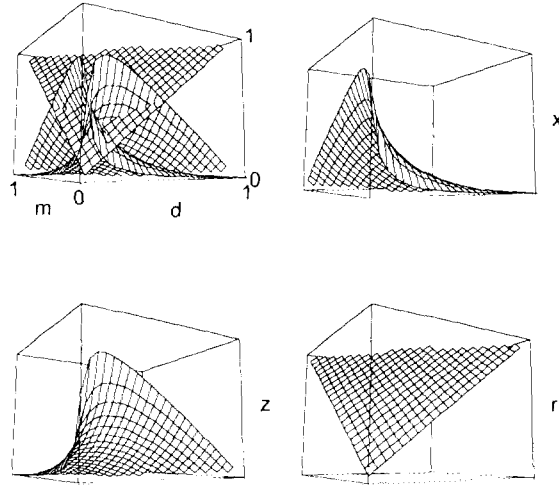


FIG. 3. Frequencies of cell types at asexual equilibrium, derived from Eq. (3). The three cell types are free resources, r ; healthy haploid cells, x ; and gene-damaged cells, z . The separate panels are combined in the top left panel. See text for discussion.

Free resources, \bar{r} , are given by the triangular-shaped surface in Fig. 3 that reaches a maximum (no resources tied up in cells) when $d + m = 1$ and a minimum (all resources in cells) at $d = m = 0$. There are no free resources if there is no mortality or damage. Free resources increase with increasing mortality and increasing damage.

The equilibrium density of gene-damaged cells, \hat{z}_A , is given by the arching surface that faces the d -axis. Gene-damaged cells increase in density with increasing damage up to a maximum (at about $d = 0.3$ below) and then decrease until a value of zero is reached again at $d = 1$. The reasons for this are easily understood. When damage is too high ($d = 1$), there are no healthy cells to produce gene-damaged cells and so the density of gene-damaged cells must be zero. When damage is too low, there are no gene-damaged cells either. Consequently, by Rolle's Theorem, there must be a maximum number of damaged cells at an intermediate level of damage.

The equilibrium density of healthy cells, \hat{x}_A , for the asexual equilibrium is given by the arching surface that faces the m -axis (Fig. 3). There is a maximum number of healthy cells at an intermediate mortality rate (given some finite damage, d). At first glance, this may seem odd. Why are healthy cells not in greatest density when there is no mortality? The reason is that there are two causes of death, cell mortality and gene damage. Gene damage creates gene dead cells, not resources, and some cell mortality is needed to recycle the resources tied up in gene-damaged cells. When the

mortality rate is zero and there is still gene death (d not zero), then all cells accumulate as gene-damaged cells. If the mortality rate is one, then clearly there can be no healthy cells. Since the numbers of healthy cells are zero at $m=1$ and $m=0$, there has to be a maximum number for intermediate m . In any event, as damage rates increase to one, the density of healthy cells rapidly decreases. In asexual populations, most resources are free and not present in cells when damage or mortality rates are high.

Sexual Equilibrium

When asexuals are absent, $x_a = z_a = 0$ in Eq. (1), the sexual population comes to an equilibrium at densities determined by the roots of either a cubic (random-mating sex) or quartic (damage-induced sex) equation. These equations can be solved symbolically by computer programs such as *Mathematica* (Wolfram Research, Inc., 1992), although their solution is complicated and not presented here. The equilibrium frequencies of the sexual populations are presented in Figs. 4 and 5 as a function of m and d in the same manner as the asexual population in Fig. 3. The fusion, splitting, and cost parameters of sexual cycle are fixed in Figs. 4 and 5 at $f=1$, $s=1$, and $c=1$. For the sexual populations there are three cell types; in addition to free resources, \hat{r} : healthy haploid cells, \hat{x} ; healthy fused cells, \hat{y} ; and gene-damaged haploid cells, \hat{z} .

In sexual populations most resources are present in cells when damage rates are high. In asexual populations with high damage, most resources are not present in cells (Fig. 3) (note how resource curves decrease as damage increases in Figs. 4 and 5, while this does not happen in Fig. 3).

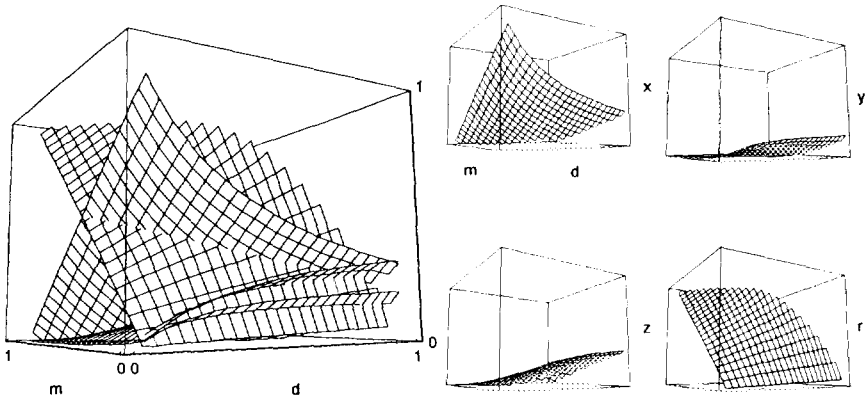


FIG. 4. Frequency of cell types at damage-induced equilibrium. The four cell types are free resources, r ; healthy haploid cells, x ; healthy fused cells, y ; and gene-damaged cells, z . Fusion rate is $f=1$, and splitting rate is $s=1$. No cost to sex, $c=1$. The right panel gives the separate surfaces that are combined in the left panel. See text for discussion.

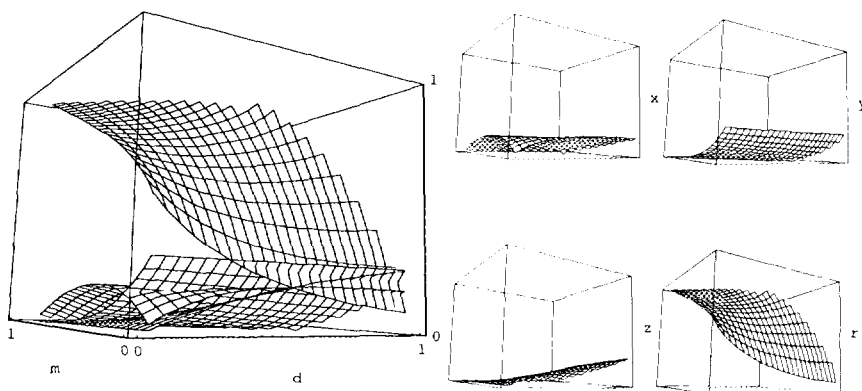


FIG. 5. Frequency of cell types at random-mating equilibrium. The four cell types are free resources, r ; healthy haploids cells, x ; healthy fused cells, y ; and gene-damaged cells, z . Fusion rate is $f=1$, and splitting rate is $s=1$. No cost to sex, $c=1$. The right panels give the separate surfaces that are combined in the left panel. See text for discussion.

However, random-mating sex is not nearly as adaptive at keeping resources in cells as damage-induced sex over the total range of possible damage rates. When damage rates are low, random-mating sex ties up healthy cells in needless matings, while this is not a problem for damage-induced sex since sex is “turned off” at low damage rates. Note how the density of fused cells is approximately constant for all levels of damage in Fig. 5, while it drops toward zero for low damage in Fig. 4. Random-mating sex does not effectively convert resources into cells over the range of possible damage rates; many free resources remain at the random-mating equilibrium even for low damage and mortality rates (Fig. 5). For these reasons, we view the study of random-mating sex as a “worst case” scenario. If random-mating sex can become established in an asexual population, damage-induced sex would likely evolve shortly thereafter.

Stability of Asexual Equilibrium

The case in which heterospecific matings (matings between sexual and asexual cell types) do not occur, $q=h=0$, was studied briefly in Long and Michod (1994, Fig. 8 and Eqs. (13)–(15)) and that analysis serves as our starting point here. If no heterospecific matings are allowed, the asexual equilibrium given in Eq. (3) is always stable. The issue of whether sexual matings occur at random or are damage-induced is moot, because matings among sexuals are extremely rare, when the density of the sexual cell type is rare. Consequently, without heterospecific matings, sexuality is neutral at least to first order. If $q=h=0$, the Jacobian matrix evaluated at the asexual equilibrium (Eqs. (3)) gives five eigenvalues that are all non-positive for biologically meaningful parameter values: $-mp-s$, 0 , $-m$,

and two eigenvalues that are given as roots of a quadratic equation (not presented here). Therefore, sex cannot increase when rare, if there are no heterospecific matings.

When heterospecific matings are allowed, $q, h \neq 0$, analysis of the Jacobian matrix associated with Eqs. (1) or (2) gives three eigenvalues that are identical to those obtained when $q = h = 0$ (the eigenvalues $-mp - s$ and two eigenvalues determined by the same quadratic equation just mentioned) and three new eigenvalues given as roots of a cubic equation (presented in the Appendix). There are two different cubic equations presented in the Appendix—one for the case of random mating and one for damage-induced mating. In both cases, the roots of the corresponding cubic equation determine the effect heterospecific matings have on the stability, or instability, of asexuality. Analysis of these two cubic equations forms the basis of the results reported in this section.

Intuitive understanding of the results is made difficult by the large number of parameters involved in the differential equations (1) and (2) and in the cubic equations derived from the stability analysis (there are nine parameters). Following Long and Michod (1994), we divide out b , the birth rate, effectively setting $b = 1$, and let the cell size parameter for fused (diploid) cells follow a simple volumetric relationship by setting $p = 1.59$. In the present model, assuming $p > 1$ makes it more difficult for sex, since the effective mortality rate of fused sexual cells is increased in direct proportion to p . There is no advantage for fused diploid cells to be larger in the present model as there was for asexual diploid cells in Long and Michod (1994), since fused sexual cells do not reproduce (sex decoupled from reproduction). There remain seven parameters in the system. Five of these parameters, f, s, q, h , and c , describe the sexual cycle, while d and m describe the gene damage and cell mortality that are common factors for all cell types.

To aid understanding, our results are presented as in Long and Michod (1994) as surfaces of parameter values for which the eigenvalues with the largest real part equals zero. In other words, the surfaces shown below divide the parameter space into regions of stability and instability of asexuality to the increase of sexuality. With regard to the sexual cycle, fusion (f) and splitting (s) are most fundamental and so are represented in almost all figures.

Random Mating

Sex can increase from extreme rarity if mixed matings occur. In Fig. 6, the region of instability to random-mating sex is shown for the asexual equilibrium when there is no direct cost of sex, $c = 1$, and no difference in heterospecific and homospecific matings ($q = h = 1$). The assumption of no cost, $c = 1$, means that there are no direct costs of sex that decrease the

birth rate when the sexual cycle is not active. A fixed and intermediate value of mortality, $m = 0.4$, is chosen for display in Fig. 6, for reasons that are discussed below.

Several features of selection for sex from extreme rarity can be seen in Fig. 6. The surfaces in Figs. 6a, 6c, and 6d reach the $f = 0$ plane (at which point sex is neutral). This fact indicates that infinitesimally small fusion rates have beneficial effects, so long as s and d are above their threshold values indicated in Fig. 6. As shown in Fig. 6b the smaller the fusion rate, the more adaptive sex is—that is, sex increases for a wider range of s and d values. So just a little fusion is most adaptive. The threshold values of s appear most clearly in Fig. 6b. Splitting must be greater than, approximately, 0.50, or sex could never increase no matter what the values of f and d . Likewise, in Fig. 6c, there is a threshold value of damage, d , that

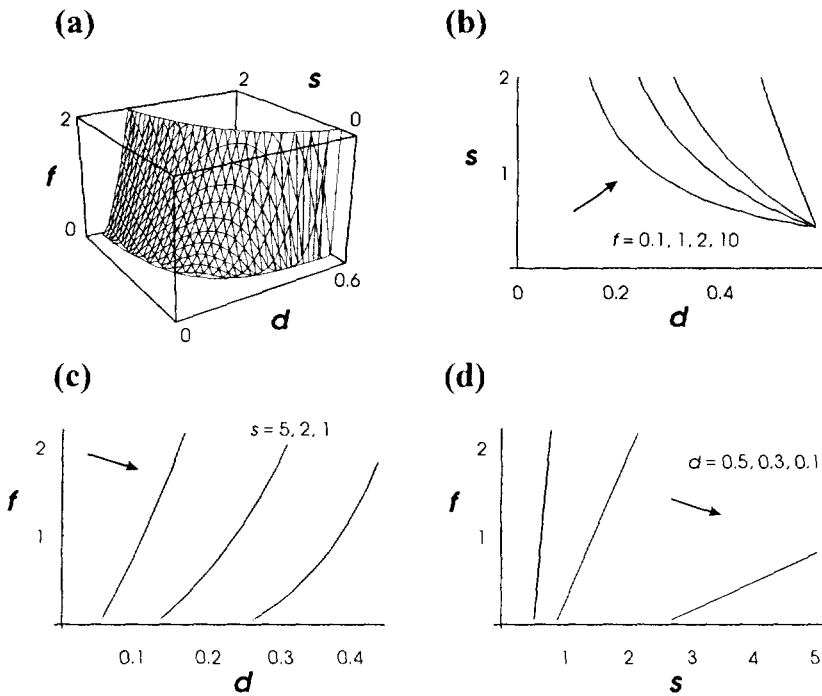


FIG. 6. Effect of the parameters f , s , and d on the instability of asexuality to random-mating sex. In panel a is shown the surface in three-dimensional space. For combinations of parameters behind the surface, the asexual equilibrium is unstable to sex—that is, sex increases when rare. Two-dimensional slices are shown in panels b, c, and d in the f , s , and d planes, respectively, for the indicated values of f , s , and d . Arrows in each panel indicate the side of each curve for which asexuality is unstable to sex. Parameter values fixed in all panels are $c = 1.0$, $q = h = 1$, $m = 0.4$, $p = 1.59$, $b = 1$.

must be exceeded for sex to be adaptive (for a fixed rate of splitting and fusion). However, the threshold d approaches 0 as the rate of splitting, s , increases. But for finite rates of splitting there is always a rate of damage that must be exceeded for sex to increase. High damage rates are generally more conducive to sex than low damage rates (Fig. 6d), so long as there are no direct costs (see, for example, Fig. 9).

In Fig. 7, the damage rate is fixed at $d=0.3$, while f , s , and m vary. Lower mortality rates are generally more conducive to the origin of sex. We find in Fig. 7b that as the fusion rate increases beyond approximately two, intermediate values of mortality tend to restrict the evolutionary prospects of sex when compared to low or high values of mortality. However, for lower rates of fusion, low mortality increases the prospects of

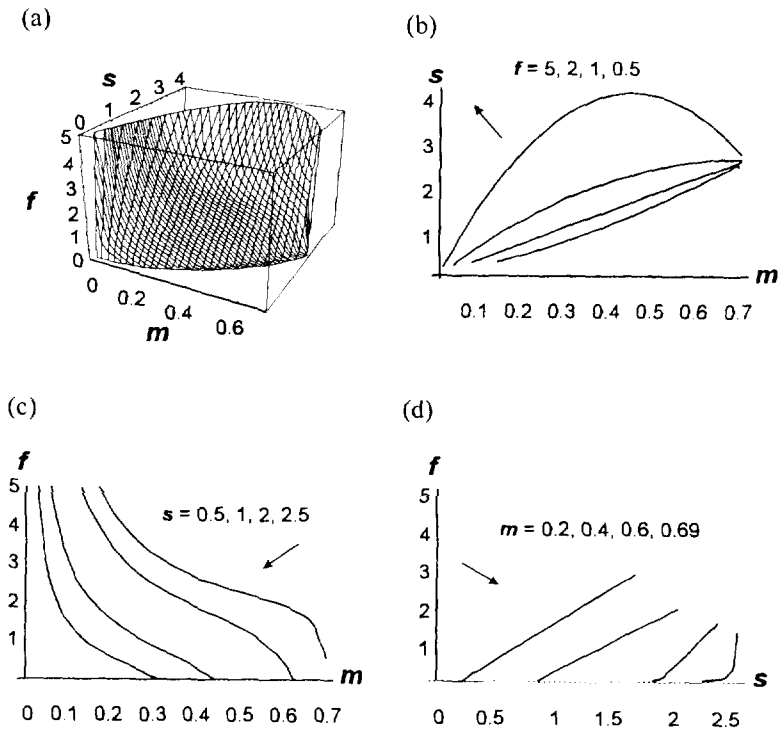


FIG. 7. Effect of the parameters f , s , and m on the instability of asexuality to random-mating sex. In a panel a is shown the surface in three-dimensional space. For combinations of parameters behind the surface the asexual equilibrium is unstable to sex—that is, sex increases when rare. Two-dimensional slices are shown in panels b, c, and d in the f , s , and m planes, respectively, for the indicated values of f , s , and m . Arrows in each panel indicate the side of each curve for which asexuality is unstable to sex. Parameter values fixed in all panels are $c = 1$, $q = h = 1$, $d = 0.3$, $p = 1.59$, and $b = 1$.

sex, in the sense that lower splitting rates can be tolerated and sex still increases (see especially Fig. 7d).

Heterospecific matings (sexual \times asexual) may occur at different fusion and splitting rates than do homospecific matings (sexual \times sexual): $q, h \neq 1$. We have primarily studied the situation in which $q, h < 1$. This represents the case in which sex occurs at a lower rate with asexual cells than with sexual cells. We find in Fig. 8 that as the rates of sex with asexual cells decreases, so do the evolutionary prospects of sex.

The sexual cycle may require allocation of energy and resources away from reproduction, even when the sexual cycle is not active. We have modeled this cost as a direct effect on the realized birth rate by the

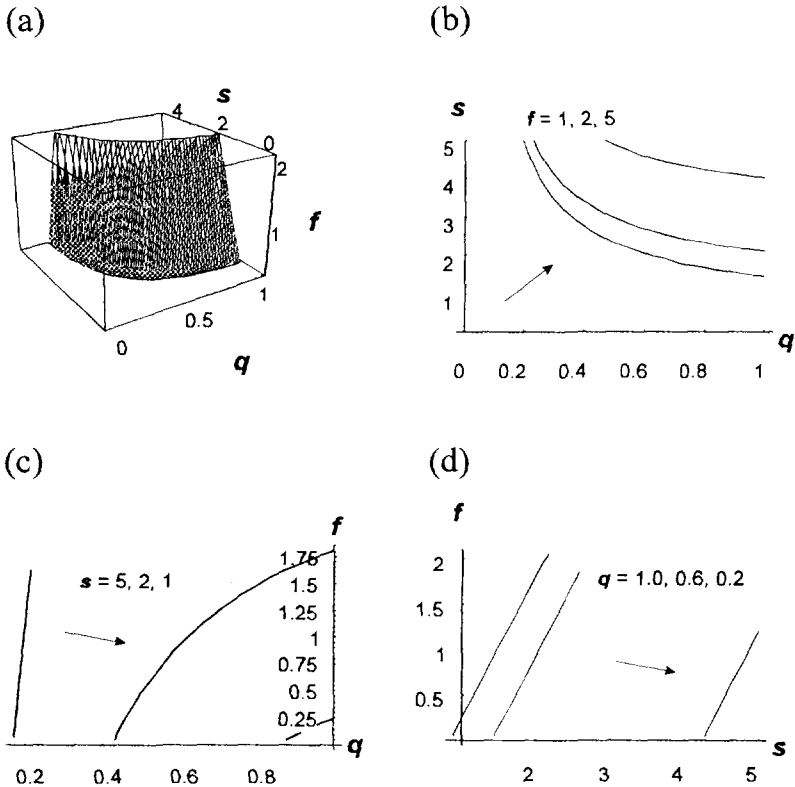


FIG. 8. Effect of the parameters f , q , and s on the instability of asexuality to randomizing sex. In panel a is shown the surface in three-dimensional space. For combinations of parameters behind the 3-D surface the asexual equilibrium is unstable to sex—that is, sex increases when rare. Two-dimensional slices are shown in panels b, c, and d in the f , q , and s planes, respectively, for the indicated values of f , q , and s . Arrows in each panel indicate the side of each curve that begets instability to sex. Parameter values fixed in all panels are $d = 0.3$, $h = q$, $m = 0.4$, $p = 1.59$, and $b = 1$.

parameter c . As c decreases from $c = 1$, the direct costs of sex increase. As we might expect, as the direct costs of sex increase, so does the stability of asexuality. In Fig. 9 is shown the surface of instability to sex for the case of a fusion rate of $f = 1$ and a mortality rate of $m = 0.4$ as a function of c , s , and d . Again, one can see the threshold value of splitting necessary for increase of sex (at around $s = 1$, in Fig. 9). As the splitting rate increases, so does the cost of sex that can be tolerated. However, for realistic values of splitting, direct costs of sex impose a severe restraint on the increase of sex. We see that the prospects of sex are the greatest for intermediate d , in

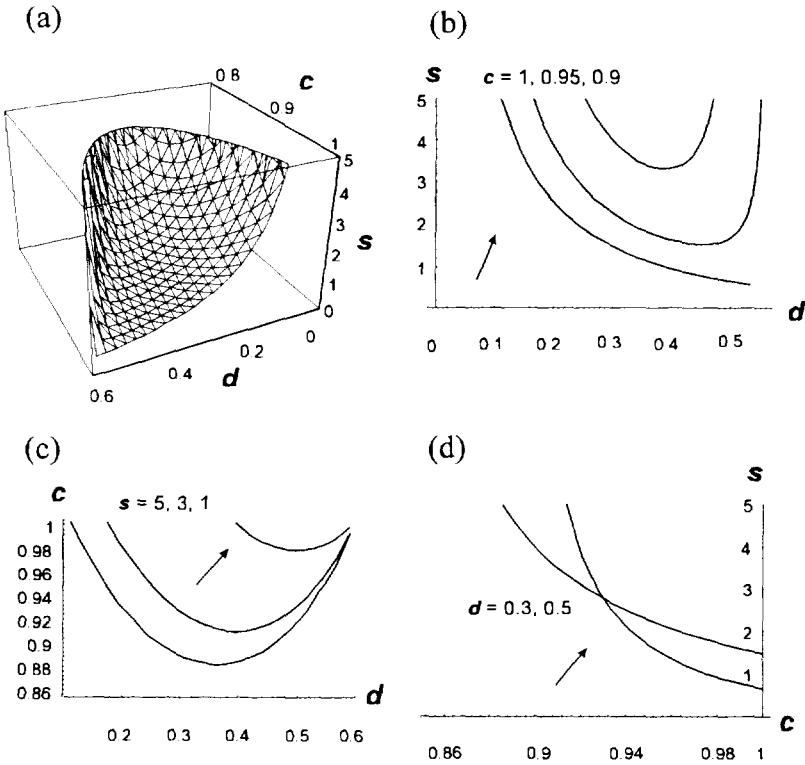


FIG. 9. Effect of the parameters s , c , and d on the instability of asexuality to random-mating sex. In panel a is shown the surface in three-dimensional space. For combinations of parameters inside the bowl-shaped surface, the asexual equilibrium is unstable to sex—that is, sex increases when rare. Two-dimensional slices are shown in panels b, c, and d in the s , c , and d planes, respectively, for the indicated values of s , c , and d . Arrows in each panel indicate the side of each curve that begets instability to sex. Parameter values fixed in all panels are $f = 1.0$, $q = h = 1$, $m = 0.4$, $p = 1.59$, and $b = 1$.

the sense that larger costs can be tolerated for intermediate d (Fig. 9, especially panels b and c). However, the effect of direct costs on the evolution of sex is very sensitive to the cell mortality rate, m , which in Fig. 9 is $m = 0.4$.

Low mortality rates are most conducive to sex, in the sense that sex may be costly and still increase when rare if the mortality rate is low. The interaction of mortality, m , the cost of sex, c , and splitting, s , is shown in Fig. 10 for a fixed fusion rate of $f = 1$. The lower the mortality rate the less restrictive are the conditions for sex to increase. For example, for a mortality rate of $m = 0.1$, sex increases for almost any combination of splitting,

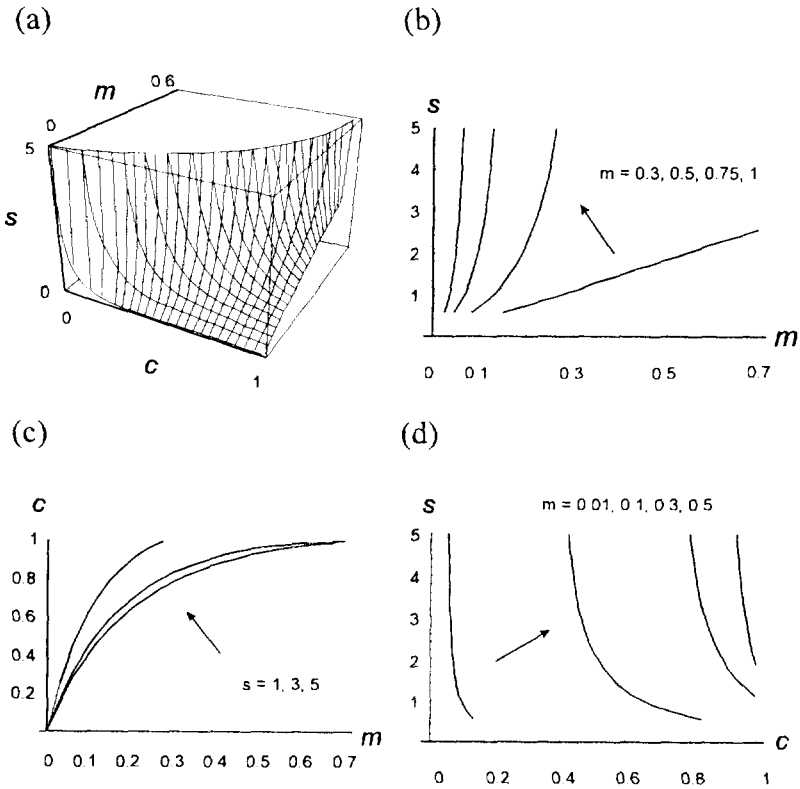


FIG. 10. Effect of the parameters s , c , and m on the instability of asexuality to random-mating sex. In panel a is shown the surface in three-dimensional space. For combinations of parameters behind the surface, the asexual equilibrium is unstable to sex—that is, sex increases when rare. Two-dimensional slices are shown in panels b, c, and d in the s , c , and m planes, respectively, for the indicated values of s , c , and m . Arrows in each panel indicate the side of each curve that begets instability to sex. Parameters values fixed in all panels are $f = 1.0$, $q = h = 1$, $d = 0.3$, $p = 1.59$, and $b = 1$.

s , and cost, c (Fig. 10, especially panel d). The reason low mortality is more conducive to the prospects of sex may stem from the effect of mortality mentioned in the discussion of Fig. 3. Some cell mortality is required to recycle the resources tied up in gene-damaged cells. As mortality rates fall, gene-damaged cells accumulate. This pool of gene-damaged cells can be utilized by the sexual cycle.

Damage-Induced Mating

If sexual cells are induced to mate when they become gene-damaged, sex is more competitive when compared to the random-mating case just studied. If sex is damage-induced and incurs no direct cost ($c = 1$), sex always increases when rare in a population dominated by asexuals. The Jacobian matrix at the asexual equilibrium for damage-induced mating ($q = h = c = 1.0$) is given in (4).

$$\begin{matrix}
 0 & 0 & 2s & s & 0 & 0 \\
 d & -f + df - m + fm & 0 & 0 & 0 & 0 \\
 0 & 0 & -mp - s & 0 & 0 & 0 \\
 0 & f(1 - d - m) & 0 & -mp - s & 0 & 0 \\
 \frac{m(-1+d+m)}{d+m} & \frac{(-1+d+m)(1+f)m}{d+m} & \frac{(-1+d+m)2m}{d+m} & \frac{(-1+d+m)2m}{d+m} + s & \frac{(-1+d+m)m}{d+m} & \frac{(-1+d+m)m}{d+m} \\
 0 & \frac{df(-1+d+m)}{d+m} & 0 & 0 & d & -m
 \end{matrix}
 \tag{4}$$

The characteristic equation for the Jacobian matrix given in (4) can be factored into the product of a cubic and a linear function (not given here). The root of the linear function is always negative real. The roots of the cubic can be obtained in symbolic form but are complicated and must be analyzed numerically. This analysis reveals that the real part of the dominant root is always positive for biologically realistic values of m , d , s , and f .

Consequently, the asexual equilibrium is always unstable to damage-induced sex—if there are no direct costs of sex ($c = 1.0$). This is true no matter how infrequent sexual–asexual matings are (q and h small but positive). There are no threshold values of splitting and fusion for damage-induced sex, as there was under group selection or individual selection involving random-mating sex. This is because, when sex is rare, fusions occur primarily between damaged sexual cells and either healthy or damaged asexual cells (see Fig. 2). Some of the matings tie up healthy asexual cells that would otherwise reproduce. So the costs of fusion are

primarily paid by the asexual cells, while under the group selection model fusions could only tie up sexual cells. The matings between gene-damaged sexual and gene-damaged asexual cells are assumed to produce healthy cells of both types (sexual and asexual) in equal measure.

In Fig. 11 is shown the effect of a direct cost of sex on the capacity of damage-induced sex to increase (for a fusion rate of $f=1.0$). Figure 11 provides the same information for damage-induced sex as Fig. 9 does for random-mating sex. As is clear by comparing Figs. 9 and 11, damage-induced sex can increase over a wider range of damage and splitting rates

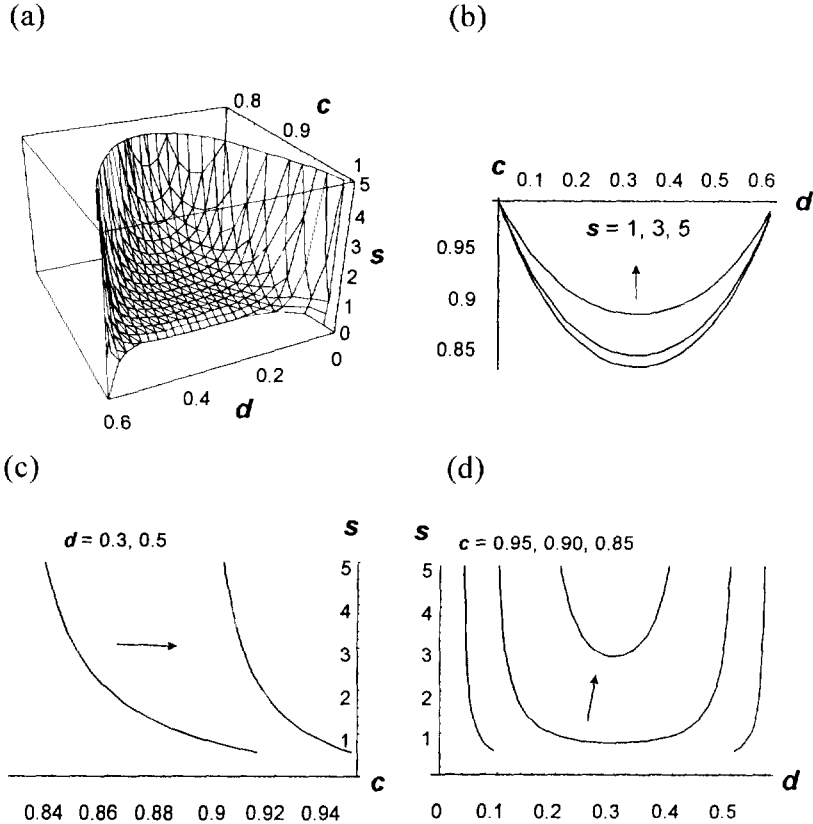


FIG. 11. Effect of the parameters s , c , and d , on the instability of asexuality to damage-induced sex. In panel a is shown the surface in three-dimensional space. For combinations of parameters inside the bowl-shaped surface, the asexual equilibrium is unstable to sex—that is, sex increases when rare. Two-dimensional slices are shown in panels b, c and d in the s , c , and d planes, respectively, for the indicated values of s , c , and d . Arrows in each panel indicate the side of each curve that begets instability to sex. Parameter values fixed in all panels are $f=1.0$, $q=h=1$, $m=0.4$, $p=1.59$, and $b=1$.

than can random-mating sex. There is no threshold value of fusion, f , or splitting, s , in Fig. 11 for cost-free sex ($c = 1.0$) as there is in Fig. 9. However, for finite costs there exists a well-specified region, within which the parameters must lie for sex to increase. The maximum costs of sex that can be tolerated under damage-induced sex appear to be similar to those that can be tolerated under random-mating sex (compare the minimum c in Figs. 9 and 11).

For random-mating sex we found that sex could tolerate greater direct costs and increase when rare if cell mortality was low (Fig. 10). An almost identical effect is observed with damage-induced sex, except that the surface shown in Fig. 10a is more nearly vertical and drops to the $s = 0$ plane as the costs approach $c = 1$, instead of tending to the nearly straight line shown in Fig. 10b for $c = 1$.

Stability of Sexual Equilibrium, Damage-Induced Sex

Our main interest is in the increase of sex when rare. Nevertheless, we consider briefly the stability properties of sex when common. As expected, matings with rare asexual cells do not have a great effect on the stability properties of common sexual populations. Although random-mating sex may increase when rare, we expect random-mating sex to evolve into damage-induced sex as sex becomes more common. The reasons were discussed in reference to Figs. 4 and 5. For those reasons (and for reasons of space), we consider here the stability of damage-induced sex. The damage-induced sexual equilibrium is determined by roots of a complicated quartic equation. This quartic is obtained from Eq. (1) by setting the right-hand side to zero, letting $x_a = z_a = w = 0$, and then solving for three of the variables in terms of the other variable, say z . Possible equilibrium values of z are given by the four roots of the quartic and can be obtained in symbolic form by computer programs such as *Mathematica* (Wolfram Research, Inc., 1992). Valid equilibrium values of the other three variables can then be obtained from the equilibrium values of z . The stability properties of the sexual equilibrium were studied by analyzing the dominant root of the Jacobian matrix associated with Eq. (1). The Jacobian matrix is given in Eq. (5), before the equilibrium values of x , y , z , and r are substituted.

$$\begin{matrix}
 -d - m + r - fqz & 0 & 0 & 0 & 0 & hs \\
 d & -m - fqz & 0 & 0 & 0 & 0 \\
 0 & 0 & -d - m + cr - fz & -fx & 2s & hs \\
 -fqz & -fqz & d - fz & -m - fx - 4fz & 0 & 0 \\
 0 & 0 & fz & f(x + 2z) & -mp - s & 0 \\
 fqz & fqz & 0 & 0 & 0 & -mp - hs
 \end{matrix} \tag{5}$$

Once the values of x , y , z , and r at the sexual equilibrium are substituted into the Jacobian matrix given in (5), the stability analysis gets complicated. Again, we solved for critical values of the parameters for which the dominant eigenvalue of the Jacobian matrix was zero. These surfaces in parameter space define regions of stability and instability of the sexual equilibrium to invasion by the asexual.

We consider, first, the case in which the sexual cell pays no cost for being sexual, except the time it takes in fusion and splitting. In the case of no mixed matings, $q = h = 0$, and $c = 1$ (no cost of sex), we obtain two eigenvalues directly: $-m$ and $-d - m + \hat{r}$, where $\hat{r} = 1 - \hat{x} - 2\hat{y} - \hat{z}$. Although the remaining eigenvalues are given as roots of a cubic, the dominant

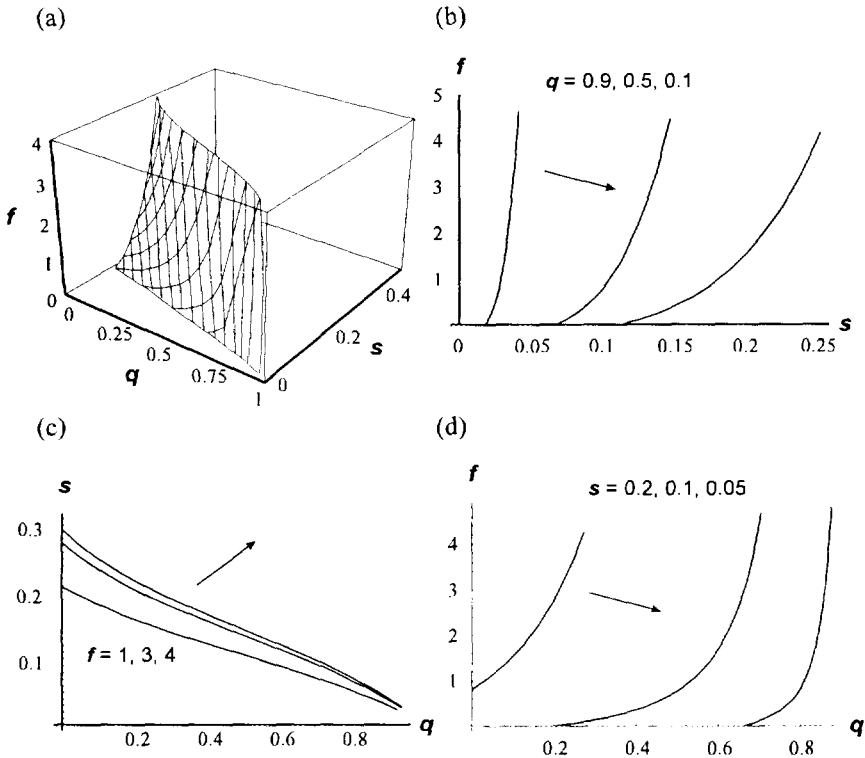


FIG. 12. Effect of the parameters q , s , and f on the instability of damage-induced sex to asexuality. In panel a is shown the surface in three-dimensional space. For combinations of parameters in front of the nearly vertical curtain, the sexual equilibrium is unstable to asexuality—that is, asexuality increases when rare. Two-dimensional slices are shown in panels b, c and d in the q , s , and f planes, respectively, for the indicated values of q , s , and f . Arrows in each panel indicate the side of each curve that begets stability of sex to asexuality. Parameter values fixed in all panels are $d = 0.4$, $h = q$, $m = 0.3$, $p = 1.59$, and $b = 1$.

eigenvalue is $-d - m + \hat{r}$ for all situations of biological interest that we have studied. The critical surface defining stability of the sexual equilibrium is obtained by substituting valid equilibrium values into the equation $-d - m + \hat{r} = 0$ and solving for critical values of f and s . This surface is given as the nearly vertical surface in Fig. 8 of Long and Michod (1994). From that analysis we know that, as long as the splitting parameter, s , is greater than pm , sex is stable. This condition does not seem too stringent, since pm is typically less than 0.7.

Matings with asexual cells increase the stability of sex, although the effect is small. In Fig. 12, we show the nearly vertical (in the f dimension) curtain of parameter values that divide parameter space into regions of instability (in front of the curtain) and stability (behind the curtain) of sex to asexuality (for fixed values of $d = 0.4$ and $m = 0.3$). A slice at $q = h = 0$ in Fig. 12 would be identical to a slice at $d = 0.4$ in Fig. 8 of Long and Michod (1994; the f -axis in Fig. 8 of Long and Michod (1994) ranges from 0 to 27 while the f -axis in Fig. 12 here ranges from 0 to 4). Again, the fusion parameter f has little effect on stability so long as some fusion is present (otherwise there is neutral stability). As the matings with asexual cells become more and more likely (q increasing), the stability of sex increases slightly. The effect of mixed matings is small when compared with its effect on the capacity of sex to increase when rare (Fig. 8). Note that the effect of varying q in Fig. 12 is magnified by the narrow range of s values considered ($0 < s < 0.25$), while in Fig. 8 the range of s values is much greater ($0 < s < 5$). The relatively small effect of mixed matings on the stability of sex is as expected. When sex is common the infrequent matings with asexual cells have little effect on its stability. Likewise, from the point of view of a rare asexual mutant in a predominately sexual population, its capacity to increase is determined primarily by its asexual parameters and not by the "forced" matings with sexual cells.

PERSISTENCE OF SEX IN REGIONS OF HIGH DAMAGE AND HIGH MORTALITY

As shown in the previous sections, sex may increase when rare in a population dominated by asexuals, even if mating is random, so long as sexual cells mate with the asexual cells. We assume that the mating system will eventually evolve so that only damaged cells initiate matings (recall Figs. 4 and 5). In this section we show that when damage-induced sex becomes common, it may persist in regions that are forbidden both to the asexual haploid and to the asexual diploid studied in Long and Michod (1994). By high damage and high mortality we mean that $d + m > 1$, so the haploid cannot exist, and $m > \frac{1}{2}$, so the diploid cannot exist. The region of persistence of the sexual for high damage and high mortality is shown in

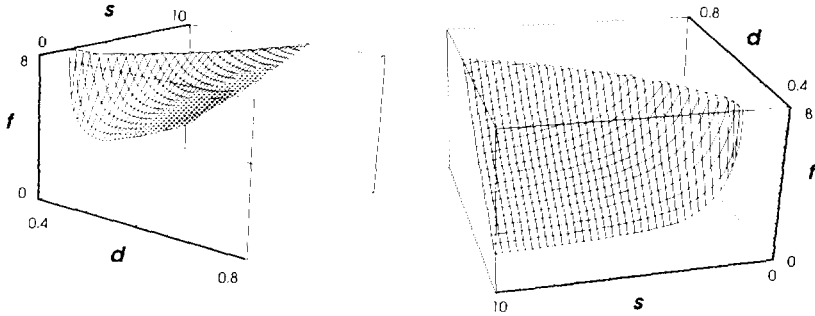


FIG. 13. Persistence of sexual for high damage and high mortality ($d+m>1$, $m=0.6>0.5$). Surface allowing continued existence of sexual is shown for $m=0.6$. The asexual haploid cannot survive in this region since $d+m>1$. The asexual diploid cannot survive in this region either since $m=0.6>0.5$ (Long and Michod, 1994). Only the sexual can persist in this range ($d+m>1$, $m>0.5$), and only if the sexual parameters (s and f) are sufficiently strong. Points above the surface represent parameter values for which the sexual can still maintain a positive rate of increase (given sufficiently sized initial populations). The two graphs contain identical information but are shown from different perspectives.

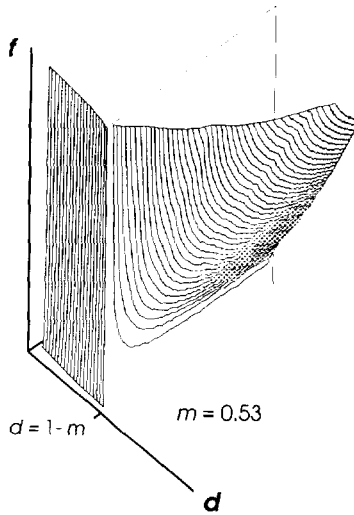


FIG. 14. Persistence of sexual for high damage and high mortality ($d+m>1$, $m=0.53>0.5$). The asexual diploid studied in Long and Michod (1994) cannot survive in this case, since $m>0.53>0.50$. For $d<1-m$, the surface corresponding to that in Fig. 8 of Long and Michod (1994) is shown. For $d>1-m$, the surface allowing continued existence of the sexual is shown. Only the sexual can persist in this range ($d+m>1$, $m>0.5$), and only if the sexual parameters (s and f) are sufficiently strong. Points above the surface represent parameter values for which the sexual can still maintain a positive rate of increase (given sufficiently sized initial populations). Note that the top of the surface for $d>1-m$ is truncated at the $f=10$ plane.

Fig. 13 for $m=0.6$. The asexual haploid cannot survive in the region shown, since $d+m > 1$. The asexual diploid cannot survive in this region either, since $m=0.6 > 0.5$ (Long and Michod, 1994). Only the sexual can persist in this range, and only if the sexual parameters (s and f) are sufficiently strong. Points above the surface represent parameter values for which the sexual can still maintain a positive rate of increase (given sufficiently sized initial populations).

In Fig. 14, the corresponding situation for $m=0.53$ is plotted in the manner of Fig. 8 of Long and Michod (1994) for comparison. The curtain for $d < 1 - m$ discussed in Long and Michod (1994, Fig. 8) is shown. For $d > 1 - m$, we draw in Fig. 14 the curtain of parameter values for which the sexual haploid continues to maintain positive density, beyond the $d = 1 - m$ border which stymies the asexual because of high damage. The asexual diploid cannot survive here either, since $m=0.53 > 0.5$. Yet the sexual cycle may maintain positive density, so long as its fusion and splitting parameters are in the specified region.

In Figs. 13 and 14, we see that there is a critical value of s which the sexual cycle must attain before the sexual haploid can survive in such a punishing environment, and that to this value there corresponds a critical value of the fusion which must also be attained.

DISCUSSION

Allowing sexual cells to mate with asexual cells dramatically increases the selective advantage of sex when rare, even though damaged asexual cells may also be repaired. As shown above, asexuality is often unstable to sex when mixed sexual–asexual matings occur. A similar conclusion was reached in Bernstein *et al.* (1984; see their so-called “mutation model” in their Appendix). In the case of the Mendelian-like population genetics model studied here, the advantages of sex are of first order. Even when sexual cells are rare, there are asexual cells to mate with. In the inter-species competition model studied by Long and Michod (1994), the advantages of sex are second-order when sexual cells are rare, since sexual can only mate with other sexual cells. Furthermore, in the inter-species model, many of those infrequent matings that occur when population densities are rare tie up healthy sexual cells and prevent them from reproducing until splitting occurs. However, in the Mendelian-like model when sex is rare, most matings are with asexual cells. Consequently, healthy sexual cells tend not to be tied up repairing damaged cells. For this reason, the splitting rate is not as critical an issue in the Mendelian-like model as it was in the group selection model studied by Long and Michod (1994). There is a threshold value of s in the inter-species model, even for

cost-free damage-induced sex, that is not found in the damage-induced Mendelian model.

If sex is damage-induced, sex can always increase when rare in a Mendelian-like population, if there are no first-order costs ($c = 1$) like, for example, a decrease in the birth rate resulting from energy allocated to the sexual apparatus (as expressed by $c < 1$ in the model). There are only advantages to sex in this case, stemming from the conversion of gene-dead cells into healthy cells. If direct costs of sex exist, a significant region of parameter space still allows sex to increase (Fig. 11).

Only sex can cope with high damage and high mortality: $d + m > 1$ and $m > 0.5$ (Figs. 13 and 14). In this range, both the asexual haploid and the asexual diploid studied in Long and Michod (1994) are doomed to extinction, by gene damage for haploids and by less efficient replication and higher mortality for diploids.

APPENDIX

As described in the text, analysis of the linear stability of the asexual equilibrium to invasion by sex yields cubic equations whose roots give the interesting eigenvalues. The surfaces in the figures represented in the text partition the parameter space into two regions for which the real part of the dominant root of the cubic equation is either less than zero (stability to invasion by sex) or greater than zero (instability to invasion by sex).

The cubic describing the stability of the asexual type to invasion by random-mating sex is

$$\lambda^3 + \lambda^2(d - cd + 2m - cm + mp + 2fq - 2dfq - 2fmq + hs) + \lambda \begin{pmatrix} dm - cdm + m^2 - cm^2 + dmp - cdmq + 2m^2p - cm^2p + dfq \\ -cdfq - d^2fq + cd^2fq + 2fmq - cfmq - 3dfmq + 2cdfmq \\ -2fm^2q + cfm^2q + 2fmpq - 2dfmpq - 2fm^2pq + f^2q^2 \\ -2df^2q^2 + d^2f^2q^2 - 2f^2mq^2 + 2df^2mq^2 + f^2m^2q^2 + dhs \\ -cdhs + 2hms - chms + fhqs - dfhqs - fhmq \end{pmatrix} + \begin{pmatrix} dm^2p - cdm^2p + m^3p - cm^3p + dfmpq - cdfmpq - d^2fmpq \\ + cd^2fmpq + 2fm^2pq - cfm^2pq - 3dfm^2pq + 2cdfm^2pq \\ -2fm^3pq + cfm^3pq + f^2mpq^2 - 2df^2mpq^2 + d^2f^2mpq^2 \\ -2f^2m^2pq^2 + 2df^2m^2pq^2 + f^2m^3pq^2 + dhms - cdhms + hm^2s \\ -chms - cdfhqs + cd^2fhqs + fhmq - cfhmqs - dfhmqs \\ + 2cdfhmqs - fhm^2qs + cfhm^2qs \end{pmatrix}.$$

The cubic describing the stability of the asexual type to invasion by damage-induced sex is

$$\lambda^3 + \lambda^2(d - cd + 2m - cm + mp + fq - dfq - fmq + hs) + \lambda \left(\begin{aligned} &dm - cdm + m^2 - cm^2 + dmp - cdmp + 2m^2p - cm^2p \\ &+ dfq - cdfq - d^2fq + cd^2fq + fmq - cfmq - 2dfmq \\ &+ 2cdfmq - fm^2q + cfm^2q + fmpq - dfmpq - fm^2pq \\ &+ dhs - cdhs + 2hms - chms + fhqs - dfhqs - fhmqs \end{aligned} \right) + \left(\begin{aligned} &dm^2p - cdm^2p + m^3p - cm^3p + dfmpq - cdfmpq \\ &- d^2fmpq + cd^2fmpq + fm^2pq - cfm^2pq - 2dfm^2pq \\ &+ 2cdfm^2pq - fm^3pq + cfm^3pq + dhms \\ &- cdhms + hm^2s - chm^2s - cdfhqs + cd^2fhqs + fhmqs \\ &- cfhmqs - dfhmqs + 2cdfhmqs - fhm^2qs + cfhm^2qs \end{aligned} \right).$$

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