

# Origin of Sex for Error Repair

## III. Selfish Sex

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According to the repair hypothesis, sex originated as a cooperative interaction—the benefit being damage repair. As with all cooperative strategies, cooperative sex may be vulnerable to selfish mutants. The purpose of the present paper is to understand what implications such selfish mutants may have both for the origin of sex, especially in competition with asexual diploidy, and for the elaboration of the sexual cycle, especially in facultatively sexual organisms. Asexual diploids are assumed to effectively and instantaneously repair all damages without expression of deleterious recessive mutations. Costs to asexual diploidy are considered in terms of its birth rate and mortality rate. The main results of the present paper are as follows. (i) Asexual diploidy wins when the costs of diploidy are small, mortality rates low, and damage rates high. (ii) Beginning with an ancestral state in which cells are asexual haploids, the sexual life cycle would emerge before asexual diploidy as a response to increasing DNA damage. (iii) Selfish sex is a far more robust repair strategy than cooperative sex, especially in competition with asexual diploidy. (iv) Although cooperative sex is more adaptive in extreme environments characterized by high damage and high mortality, selfish sex can still invade in these regions and take the entire system to extinction. (v) Once it is present, selfish sex is stable to asexual diploidy over a wide range of parameter values and can persist in regions of parameter space forbidden to the asexual diploid. These results help to address a concern of the gene repair theory of sex, which is that efficient repair in an asexual diploid is a better strategy than sex. Data from microbes bearing on the results are discussed as is the relationship between facultative sex in multicellular organisms and selfish sex in microbes. © 1998 Academic Press

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## INTRODUCTION

According to the repair hypothesis (Bernstein *et al.*, 1981; Bernstein *et al.*, 1985; Bernstein *et al.*, 1985; Bernstein *et al.*, 1987; Michod, 1995), sex originated as a cooperative interaction between cells, the benefit of this interaction being repair of DNA damage. We have studied this hypothesis using mathematical models (Bernstein *et al.*, 1984; Michod, 1990; Michod and Gayley, 1992; Michod and Long, 1995; Long and

Michod, 1995) and the eubacterium *Bacillus subtilis* (Michod *et al.*, 1988; Wojciechowski *et al.*, 1989; Hoelzer and Michod, 1991; Michod and Wojciechowski, 1994). Our theoretical results show that, for sex to be effective as a gene repair strategy, it must be damage-induced. This expectation has been confirmed in our studies of transformation in *B. subtilis*. An unresolved question is whether both mates need to be damaged for mating to occur. While this may seem like a small detail of the mechanics of sex in microbes, I show here that it has

implications for the general robustness of sex when in competition with asexual diploidy. Furthermore, understanding the impetus for sex in microbes may help us to understand the timing of sex in multicellular plants and animals.

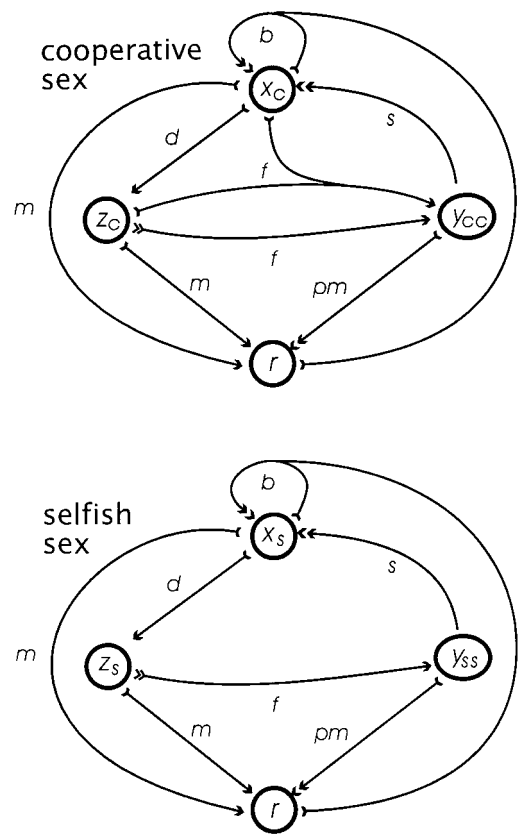
In previous theoretical work we assumed that undamaged healthy cells would mate with damaged cells (Michod and Long, 1995; Long and Michod, 1995). Consequently, sex was a costly cooperative (or altruistic) interaction in our models. Fusion presumably costs the healthy cell time and energy that could be put into other components of fitness. It could be that cells are rarely damage free in nature; however, as with all cooperative strategies, sex—as we envision it—may be vulnerable to selfish and parasitic mutants. A cell practices “selfish sex” if it has sex *only* when it is damaged. In other words under selfish sex, healthy cells would not fuse with damaged cells. It is easier to understand the definitions of these strategies in terms of the mating structures they create (bottom of Table 2). The purpose of the present paper is to study competition between cooperative and selfish sexual strategies along with asexual haploidy and asexual diploidy. Furthermore, I wish understand what implications selfish sex may have not just for the origin of sex, but also for the evolution of the sexual cycle in multicellular organisms. My results suggest that facultative sex in complex metazoans may be seen as an elaboration of the selfish sex strategy which originated in microbes.

Is it reasonable to assume that damaged cells could be capable of mating? Data supporting this assumption are discussed later; however, there is a general reason why it is reasonable to assume that damaged cells can mate normally. Gene damage typically blocks replication and transcription of DNA. Mating usually occurs when the cell is not replicating and, in this situation, only those gene functions which contain damaged nucleotides would be affected. Furthermore, if the gene has already been transcribed before the damage occurs, its products may still be present in the cell and there may be no loss in function. Consequently, damages are typically not lethal in non-replicating cells. I assume that it is unlikely that damages exist in a specific gene or set of genes, such as those involved in the mating process. Although gene damage may not seriously undermine a nonreplicating cell, DNA damage can be lethal to a replicating cell, since one damage, say a cross-link, can block replication of the entire chromosome. For this reason, damaged cells can appear to function quite normally in most ways, yet unrepaired damages may still cause the cell to adopt a different reproductive strategy, such as sex. The SOS system in *E. coli* provides a well studied example of how unrepaired damages can cause dramatic changes in a bacterium's life history. Although the mating systems studied

in the present paper are new, many of the assumptions and motivations of two previous papers apply here and those papers should be consulted for additional details and mathematical methods (Michod and Long, 1995; Long and Michod, 1995). I now proceed directly to the model.

## MODEL

The work reported here concerns competition between four kinds of life cycles: cooperative sex, selfish sex, asexual diploidy and asexual haploidy. The basic life cycles of cooperative sex and selfish sex are shown in Fig. 1 when the two strategies are alone in a population.



**FIG. 1.** Cooperative and selfish sex. 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 beginning of an arrow indicates the number of cells that leave the donor population, while the number of arrow heads at the end of an arrow indicates the number of cells that are contributed to the recipient population. For example, the arrow  $\gg\gg\gg$  indicates that two cells are taken from the donor population to produce three cells in the recipient population. Diagram applies when each strategy is considered alone. In mixed populations, there are additional flows involving mixed matings between cooperative and selfish cells.

Free nucleotides, in density  $r$ , are used by cells as resources for reproduction. The parameters used to describe the population dynamics are  $d$ , damage for haploid cells;  $m$ , mortality for haploid cells;  $b$ , birth rate for haploid cells;  $f$ , fusion; and  $s$ , splitting. There are additional parameters needed to describe the properties of diploid cells:  $g$  is the birth rate of asexual diploid cells, and  $p$  is a parameter that describes the surface area of diploid cells, which may be larger than haploid cells.

Each of the sexual species may exist in any one of three states: healthy (density  $x_C$  and  $x_S$ ), gene-damaged (density  $z_C$  and  $z_S$ ), and in a fused diploid-like state (density  $y_{CC}$  and  $y_{SS}$ ). In a mixed population with both selfish and cooperative cells, there is an additional fused type involving both cooperative and selfish cells ( $y_{CS}$ ). This gives a total of eleven different cell types: seven for the sexual strategies, one for the asexual diploid (always healthy in density  $w$ ), and a healthy and damaged cell type for the asexual haploid (density  $x_A$  and  $z_A$ ). All forms of sex are assumed to be damage-induced as discussed previously (Long and Michod 1995). The major assumptions of the model are given in Table 1 and all parameters and variables are given in Table 2. The assumptions are discussed more fully in Long and Michod (1995).

I assume that there is no effective damage in diploid cells, because diploids repair instantaneously all damages. Diploids have a second copy in the cell and it is unlikely that both copies become damaged at the same site in the nucleotide sequence. This is clearly a worst case scenario for the evolution of any kind of sex; in reality even

TABLE 1

## Major Assumptions of Models

*Mass action dynamics*: interaction equal to product of density of constituents; used to model resource utilization during reproduction and fusion of sexual cells

*Damage-induced sex*: only gene-damaged cells initiate sex with damaged or undamaged (cooperative sex) partners

*Pure sex*: no reproduction or genome replication during sex (as occurs during meiosis)

*Damage repair*: gene damages are repaired in diploid state (either fused sexuals or diploids)

*Two sources of mortality*: gene death due to damage (reversible by repair) and cell death due to disruption of cell-membrane (non-reversible)

*Reproduction requires nucleotide resources*: diploids must encounter two nucleotide resource packets, haploids one; resource uptake depends on cell surface area

*Competition between different types of life cycles based on resource use exclusively*

*Closed system*: total resources (free resources plus resources tied up in cells) are constant

TABLE 2

## Parameters and Variables

Parameters	
$b$	Birth rate for haploid cells (sexual)
$g$	Birth rate for asexual diploid cells
$m$	Death (or mortality) rate for all cells
$p$	Size difference between haploid and diploid cells; cells assumed to be spherical
$f$	Fusion rate for the sexual cells
$s$	Splitting rate for the fused sexual cells (diploid)
$d$	Damage rate for haploid cells
Population density variables	
$x_C$	Healthy cooperative sex cells
$x_S$	Healthy selfish sex cells
$z_C$	Damaged (gene dead) cooperative sex cells
$z_S$	Damaged (gene dead) selfish sex cells
$y_{CC}$	Cooperative x cooperative fused (diploid) cells
$y_{CS}$	Cooperative x selfish fused (diploid) cells
$y_{SS}$	Selfish x selfish fused (diploid) cells
$x_A$	Healthy asexual haploid cells
$z_A$	Damaged asexual haploid cells
$w$	Asexual diploid cells
$r$	Free resources available for reproduction
Sexual mating systems	
Random mating cooperative sex: $[x_C + z_C][x_C + z_C]$	
Damage-induced cooperative sex: $[z_C][x_C + z_C]$	
Selfish sex mixed with damage-induced cooperative sex: $[z_C + z_S][x_C + z_C + z_S]$	

diploid cells may be overcome by damage. Consequently, unless there is some cost to diploidy compared to haploidy, either in terms of birth rate or cell mortality, diploidy always wins in the models studied here.

Experimental work with yeast indicates that the cell size of diploids may differ from haploids depending on resource and nutrient conditions (Adams and Hansche 1974, Weiss *et al.*, 1975). Herskowitz (1988, p. 537) concludes that diploids "...have a volume nearly twice that of haploids..." Mortimer (1958) found that cell volume scales linearly with ploidy from haploid, diploid up to hexaploid cells. In past theoretical studies, we often took  $p \approx 1.59$ , meaning that diploid cells had twice the volume of the haploid cells and, assuming spherical cells, approximately 1.59 times the surface area (Long and Michod, 1995). Cell size is assumed to influence mortality and reproduction. Mortality is assumed to result

from disruption of the cell membrane, the likelihood of which is assumed to increase with cell size. For these reasons, asexual diploid cells and fused sexual cells are assumed to have a mortality rate of  $pm$ , which is greater than the mortality rate of haploid cells if  $p > 1$ . In the results reported here, I either take  $p = 1.59$  (for comparison to our previous studies) or  $p = 1.0$ , no difference in mortality between haploid and diploid cells (to make matters more difficult for haploids and sex). However, it turns out that  $p$  has little affect on the bifurcation patterns of the equilibria discussed in regard to the competition of sex with diploidy (Figs. 3, 4, 5, and 6, and Equation (8)), probably because it has both positive (on the rate of reproduction) and negative (on mortality) effects.

Diploids require twice the genetic resources to reproduce than haploids and so may have lower rates of replication depending on resource levels (Lewis 1985). Reproduction of the diploid life cycle has been considered in detail by Long and Michod (1995). Cell size is assumed to affect reproduction to the extent that resource uptake is assumed to depend on cell surface area. To reproduce, it is assumed that the diploid must encounter two nucleotide resource packets while the haploid needs only one (Table 1). For this reason, the rate of diploid reproduction must be less than or equal to that of the haploid,  $g \leq b$ . We also assumed that there were two distinct types of diploids: those which already have encountered one resource and “seek” a second, and those which have yet to find their first resource packet. By assuming mass action kinetics, we (Long and Michod 1995) simplified the diploid species to a single equation with  $g = 1/2$ , and for comparison purposes  $g = 1/2$  is sometimes assumed in the present analysis. However, in the interests of generality, I also explore the range of  $g$  values between  $1/2$  and  $1$  ( $g = 1$  means that there is no cost to diploidy in terms of cell reproduction). Without loss of generality (the other parameters may be divided by  $b$ , since  $b$  is never zero), I assume  $b = 1$ . The full system of equations (cooperative sex, selfish sex, asexual diploidy and asexual haploidy) is (the prime superscript indicates the derivative with respect to time)

$$\begin{aligned}x'_C &= x_C(r - m - d) + 2sy_{CC} + sy_{CS} - fx_Cz_C - fx_Cz_S \\z'_C &= dx_C - z_C[m + f(2z_C + x_C + z_S)] \\x'_S &= x_S(r - m - d) + 2sy_{SS} + sy_{CS} \\z'_S &= dx_S - z_S[m + f(2z_S + x_C + z_C)] \\y'_{CC} &= fz_C(z_C + x_C) - y_{CC}(pm + s) \\y'_{CS} &= fz_S(z_C + x_C) - y_{CS}(pm + s)\end{aligned}$$

$$\begin{aligned}y'_{SS} &= fz_S^2 - y_{SS}(pm + s) \\x'_A &= x_A(r - m - d) \\z'_A &= dx_A - mz_A \\w' &= wp(rg - m),\end{aligned}\tag{1}$$

where

$$\begin{aligned}r &= 1 - x_C - 2y_{CC} - 2y_{CS} - z_C \\&\quad - x_S - 2y_{SS} - z_S - 2w - x_A - z_A.\end{aligned}\tag{2}$$

In presenting the results, I consider the pairwise competitions that take place in the absence of one or more of the cell types. While these are separate competitions, they are merely projections of the full model onto subspaces. The procedure used in studying the equilibria and stability of the system is described in the Appendix of Long and Michod (1995).

## RESULTS

### *Each Species Considered Alone*

Each species type can be considered on its own. The asexual diploid and haploid have been discussed previously (Long and Michod, 1995). When alone, the asexual diploid follows a logistic equation when  $m < g$ , with an equilibrium population given as

$$\begin{aligned}r &= \frac{m}{g} \\w &= \frac{(g - m)}{2g}\end{aligned}\tag{3}$$

For  $m \geq g$ , the diploid goes extinct. When alone, the asexual haploid increases logistically with equilibrium populations ( $m + d < 1$ )

$$\begin{aligned}r &= m + d \\x_A &= m \frac{1 - m - d}{m + d} \\z_A &= d \frac{1 - m - d}{m + d}\end{aligned}\tag{4}$$

The situations for the sexual cell types alone are quite complicated, even given the simplifying assumptions

made. The cooperative sex equilibrium has been discussed in some detail previously (Michod and Long (1995), pp. 65–66, 77–79). There is a single stable equilibrium which is given by the roots of a quartic equation. A similar situation occurs for selfish sex when alone at equilibrium, except that its equilibrium is given as roots of a cubic equation. The main difference between cooperative- and selfish sex is that there are no matings between healthy and damaged cells when selfish sex is alone (although damaged selfish cells can mate with healthy cooperative cells). The equilibrium plots for selfish sex are generally similar to those for cooperative sex (see Michod and Long (1995), Fig. 4) except that under selfish sex the levels of fused cells are lower and the level of damaged cells are higher than under cooperative sex. This hints at one weakness of selfish sex that will be explored later: there are fewer mates for damage repair when selfish sex is alone.

### Asexual Competition between Haploidy and Diploidy

To study competition between asexual haploidy and diploidy, I set  $w = x_C = z_C = y_{CC} = x_S = z_S = y_{SS} = y_{CS} = 0$  in Equations (1) and (2) to get

$$\begin{aligned} x'_a &= x_a(r - m - d) \\ z'_a &= dx_a - mz_a \\ w' &= wp(g - m). \end{aligned} \quad (5)$$

Coexistence of haploids and diploids is not possible. The interesting condition determining the outcome of competition (derived by local stability analysis of each species' equilibrium) is given by  $d < ((1 - g)/g)m$ . If damage rates are low, in the sense that  $d < ((1 - g)/g)m$ , the asexual haploid wins, while if damage rates are high,  $d > ((1 - g)/g)m$ , the asexual diploid wins (assuming  $m < g$ , or else the diploid always goes extinct, and  $d + m < 1$ , or else the haploid goes extinct). Recall that  $gp$  and  $p$  are, respectively, the relative growth rate and mortality rate of diploid cells compared to haploid cells. However, since the size difference between haploids and diploids,  $p$ , affects growth and mortality of the diploid similarly, it cancels out in the stability analysis. High damage ( $d$ ) and high diploidy birth rate ( $g$ ) favor the diploid and high mortality ( $m$ ) the haploid (assuming  $p > 1$ ).

### Cooperative Sex Versus Selfish Sex

To study competition between selfish- and cooperative sex, I set  $x_A = z_A = w = 0$  in Equations (1) and (2). This

competition is different from the other pairwise competitions, because the two competing "species" interbreed to produce hybrid diploids in density  $y_{CS}$ . The mixed matings between cooperative cells (both healthy and damaged) and damaged selfish cells are represented by the  $fz_S(z_C + x_C)$  term in the equation for  $y'_{CS}$  in Equation (1). A Mendelian-like mechanism of inheritance is assumed, because the hybrid cell splits into two haploid cells of each sexual type (as is represented in the  $sy_{CS}$  terms in each of the  $x'_C$  and  $x'_S$  equations).

Because of the complexity of the pure equilibria when each sexual species is alone (the cooperative- and selfish sex equilibria being determined by a quartic and a cubic equation, respectively), certain aspects of the stability properties and bifurcation patterns of the different equilibria were studied numerically. Cooperative sex can be stable to invasion of selfish sex for certain parameter values. A typical result is given in Fig. 2 for three different rates of damage ( $d = 0.4, 0.5$ , and  $0.6$ ) and for a fixed cell mortality ( $m = 0.3$ ). Cooperative sex is more likely to be stable for higher rates of damage and splitting and for lower rates of fusion. For lower damage rates, the curves in Fig. 2 flatten out so that lower fusion rates are required for stability. I have found no case numerically in which cooperative sex can increase from rarity in a population dominated by selfish sex, although I have not been able to prove this analytically. In all cases studied, selfish sex is stable to the increase of cooperative sex. This is probably because when cooperative sex is rare, healthy cooperative cells are more likely to mate with damaged selfish cells than with their own damaged brethren.

### Selfish Sex Versus Asexual Haploidy

In the case of cooperative sex, fusion can sometimes work against the well-being of the sexual cycle, especially

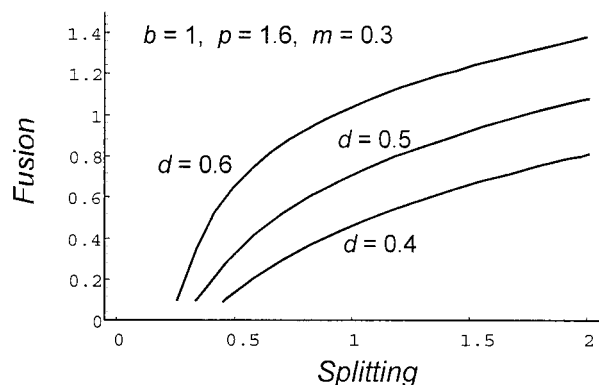


FIG. 2. Stability of cooperative sex. Cooperative sex is stable to selfish sex for parameter values below the curve. Parameter values are  $m = 0.3$ ,  $p = 1.6$ , and  $b = 1$  for  $d = 0.4, 0.5, 0.6$ .

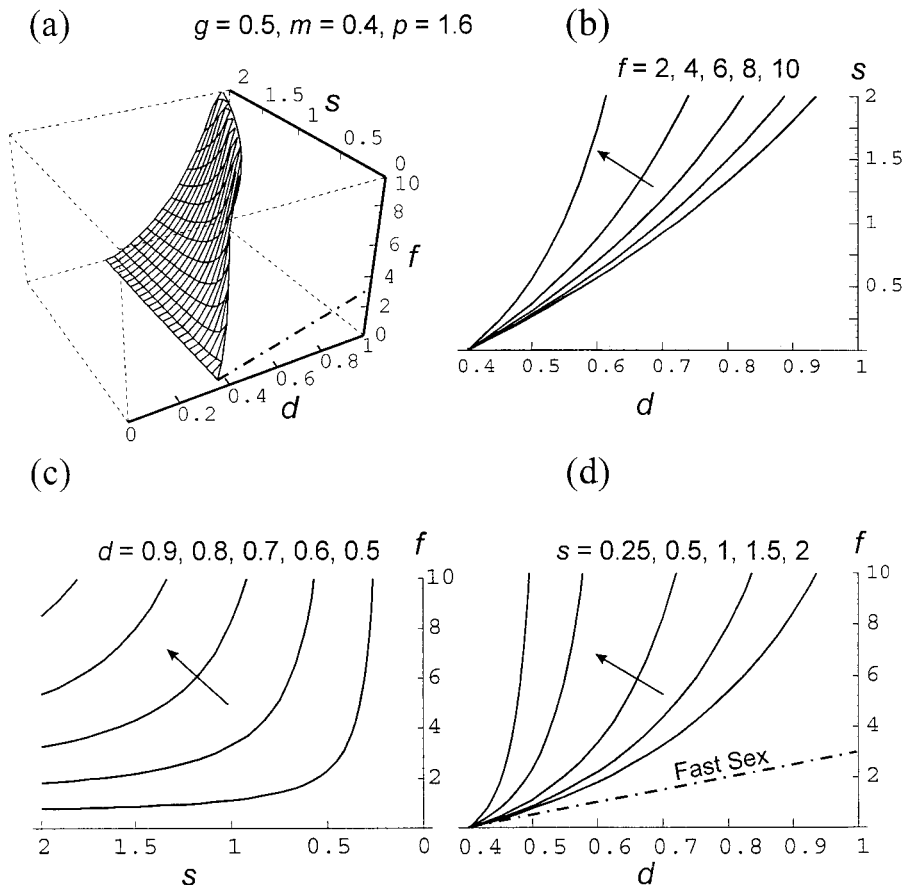
if it overruns splitting and leads to a build up of non-replicating cells in the fused state. In previous work we found that this over-activity of the sexual cycle created regions of parameter space (typically characterized by high fusion and low splitting) in which cooperative sex lost out to asexual diploidy, even in regions of low damage ( $d < m$ ) where asexual haploidy could out compete diploidy if it were present (Long and Michod, 1995). Selfish sex solves these problems stemming from over activity (fusion exceeds splitting).

Selfish sex always wins in competition with asexual haploidy and so (taking into account the results of the last section) would evolve before diploidy in response to increasing damage, if asexual haploidy were the ancestral state. In the case of competition between asexual haploidy and cooperative sex, there was a curtain that divided the  $d < 1 - m$  region into two regions according to the splitting and fusion rates of the sexual cycle (see

Fig. 8 of Long and Michod, 1995). In front of the curtain (low splitting), asexual haploidy won, and, behind the curtain (higher splitting), cooperative sex won. This is no longer the case with selfish sex. The five eigenvalues for the asexual haploid equilibrium are the same as with cooperative sex,

$$0, -m, \frac{-m \pm \sqrt{m^2 + 4m(-1 + d + m)(d + m)^2}}{2(d + m)}, -mp - s. \quad (6)$$

When  $d + m < 1$  the dominant eigenvalue is 0. Computer simulations have shown that when sex is selfish, the sexual cycle owns the entire region and the asexual haploid is never stable, even if selfish sex must invade from rarity. The eigenvalues for the selfish sex equilibrium (determined by a cubic) indicate that the sexual



**FIG. 3.** Bifurcation diagram for selfish sex and diploidy. Parameters values are  $p = 1.6$ ,  $m = 0.4$ ,  $g = 0.5$ . Both sex and diploidy are locally stable for parameter values to the left of the surface in panel (a), so long as  $d > m$ . Diploidy wins for parameter values to the right of the surface. If  $d < m$ , then sex wins as the diploid equilibrium becomes unstable. Panels (b)–(d) are 2D slices through the 3D surface in panel (a). The parameter values for which sex is stable in panels (b)–(d) are indicated by arrows. In panels (a) and (d), as the splitting rate increases the surfaces tend to the critical surface for “fast sex” given in Equation (8).

equilibrium is stable to invasion from asexual haploidy. Fusion is never costly in the case of selfish sex, since it is always between non-replicating gene dead cells (those in density  $z_S$ )—cells that remain dead in the case of asexual haploidy.

### Selfish Sex versus Asexual Diploidy

The main criticism of the repair hypothesis has been that recombination in a permanent asexual diploid is a better repair strategy than the alternation of haploid and diploid states as occurs during sex (Maynard Smith and Szathmari 1995). If recombinational repair is equivalent in asexuals and sexuals, and if there are no disadvantages to diploidy when compared to haploidy, this must be true, since diploids always have a backup copy to repair damaged genes. There are reasons to expect repair to be less effective in asexual diploids than in sexuals, although these effects are not considered here (ignoring these effects favors the asexual diploid). Specifically, recombinational repair in an asexual diploid expresses deleterious recessive mutations that may have accumulated during the diploid

stage. It is ironic that the genetic redundancy during the diploid state creates the opportunity for its own undoing as recessive mutations accumulate. This problem has been considered previously (Michod and Gayley; Michod 1995, Chapter 7), although it is need of further study. Here I consider only those costs of diploidy that may stem from requiring twice the genetic resources.

To study competition between selfish sex and asexual diploidy (with efficient repair), I set  $x_C = z_C = y_{CC} = x_A = z_A = y_{CS} = 0$  in Equations (1) and (2). In Fig. 3, I plot the bifurcation diagram for diploidy and selfish sex analogous to Figs. 6 and 7 of Long and Michod (1995) where one may also find the methods used in constructing this surface. I find that sex is more robust to diploidy when it is selfish than when it is cooperative (Fig. 3) and when the splitting rate increases.

For comparison with our previous results, in Fig. 3, I assume that diploids replicate one-half as fast as haploids,  $g = 1/2$ ; the conditions under which this may be expected to occur are discussed in Long and Michod (1995). Selfish sex is more robust than cooperative sex. Conditions were found previously (Long and Michod

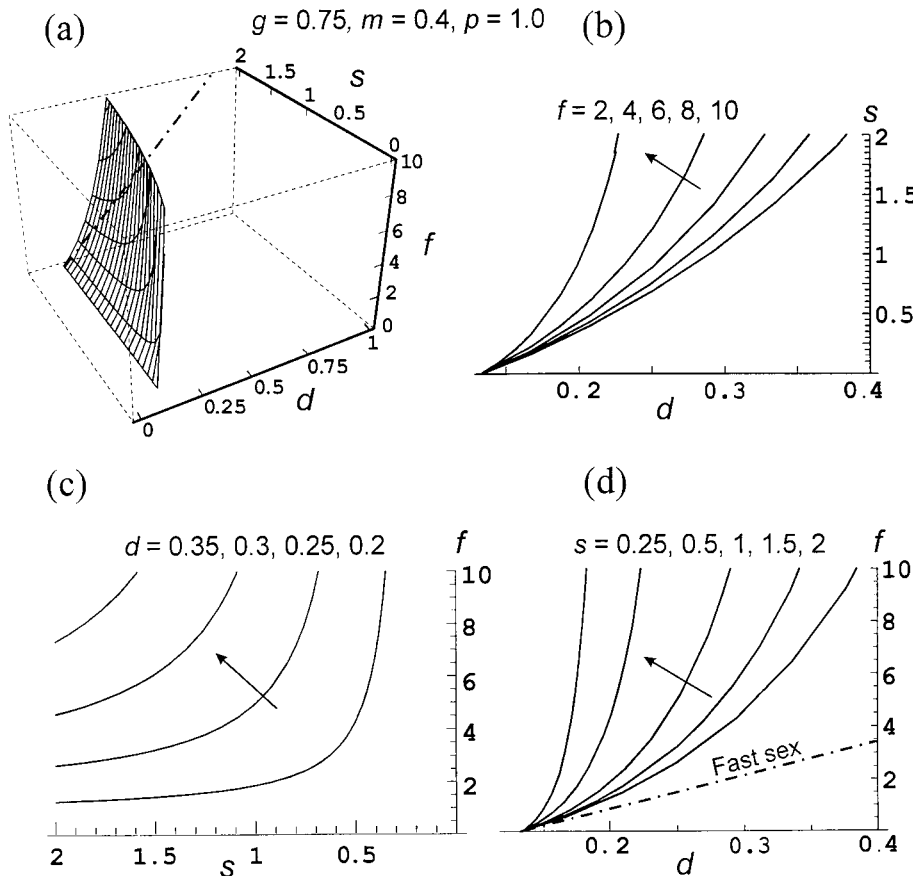


FIG. 4. Bifurcation diagram for selfish sex and diploidy. Same as Fig. 3 except parameter values are  $p = 1.0, m = 0.4, g = 0.75$ .

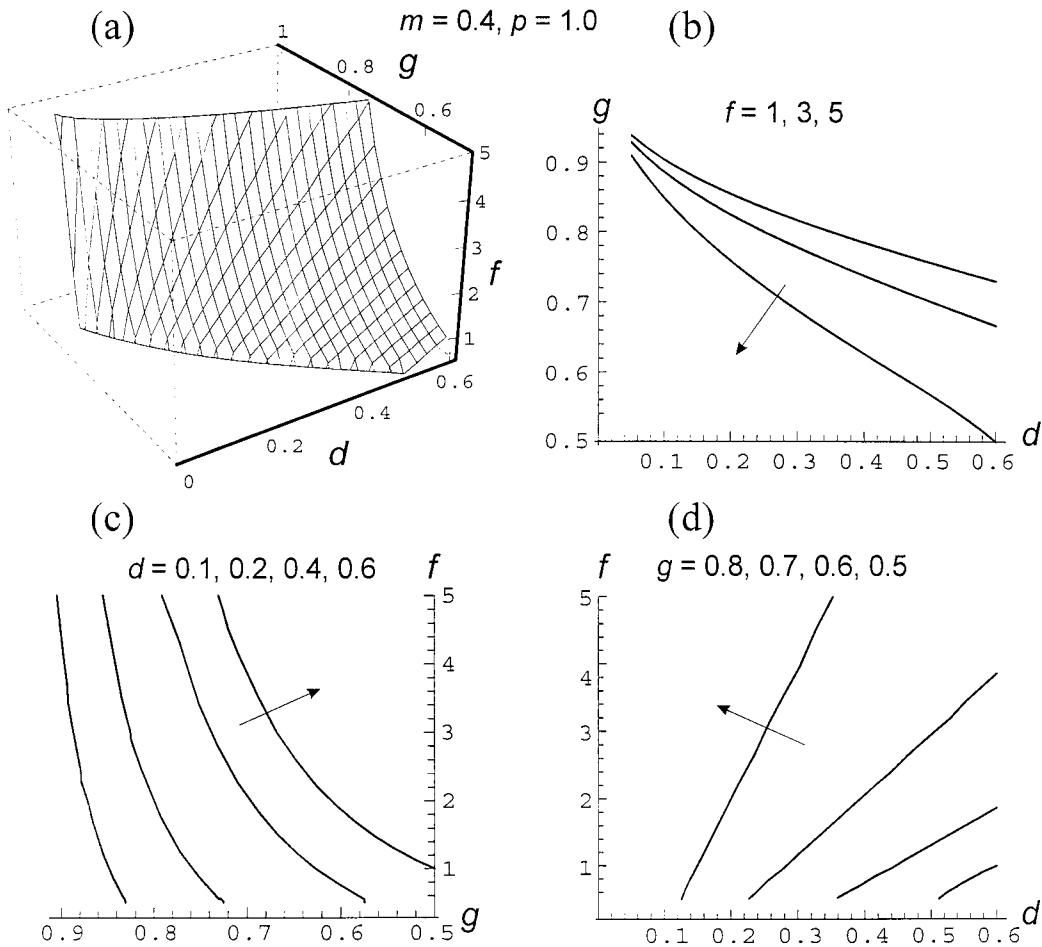
1995, Fig. 7) for which asexual haploidy beat asexual diploidy but asexual diploidy beat cooperative sex. This no longer occurs if sex is selfish (Fig. 3). In addition, the coexistence which was possible between an overactive cooperative sexual cycle and diploidy (see Figs. 6 and 7 of Long and Michod (1995)) no longer occurs with selfish sex (see especially panel (c) Fig. 3 which is similar to Fig. 6 of Long and Michod (1995)).

In Fig. 4, I present the same bifurcation diagram as in Fig. 3, but for lower costs for diploidy: there is now no difference in cell size between haploids and diploids ( $p = 1$ ) and hence no difference in cell mortality, and the reproductive rate of diploids is now  $3/4$  that of haploids ( $g = 0.75$ ). As we expect when the costs of diploidy are reduced, the region owned by the diploid life cycle expands. Now sex is competitive only for lower damage rates, although for larger splitting rates ( $s = 5$ ) sex is competitive up to damage rates of about  $d = 0.6$ . For

comparison purposes in Fig. 4, I consider the same range of splitting as in Fig. 3,  $0 < s < 2$ . However, for higher splitting rates, the surface tends to the fast sex surface given in Equation (8) below.

### Fast Sex

To make matters more difficult for the sexual, I have assumed that the asexual diploid cell is a haven against damage and that all damages are repaired instantaneously. For the sexual, however, I have assumed that damage repair takes time because of fusion and splitting (as determined by the parameters  $f$  and  $s$ ). So as to make competition between the two repair strategies more equitable, I now assume that splitting occurs instantaneously after fusion ("fast sex"). The purpose of fusion is repair, so assuming instantaneous repair for the asexual diploid is basically the same as assuming instantaneous splitting



**FIG. 5.** Bifurcation diagram for fast-selfish sex and asexual diploidy for  $m = 0.4$ . Diploidy is stable for parameter values behind the surface in panel (a), so long as  $m < g$ . If  $m \geq g$ , then sex wins as the diploid equilibrium becomes unstable. Panels (b)–(d) are 2D slices through the 3D surface in panel (a). The parameter values for which sex is stable in panels (b)–(d) are indicated by arrows.

for the sexual (time is still required for fusion, even in the case of fast sex). The resulting equations for pairwise competition between the fast selfish sex case and asexual diploidy are (cf. Equations (8) of Long and Michod 1995)

$$\begin{aligned}x'_S &= x_S(r - m - d) + 2fz_S^2 \\z'_S &= dx_S - 2fz_S^2 - mz_S \\w' &= wp(rg - m) \\r &= 1 - x_S - z_S - 2w.\end{aligned}\tag{7}$$

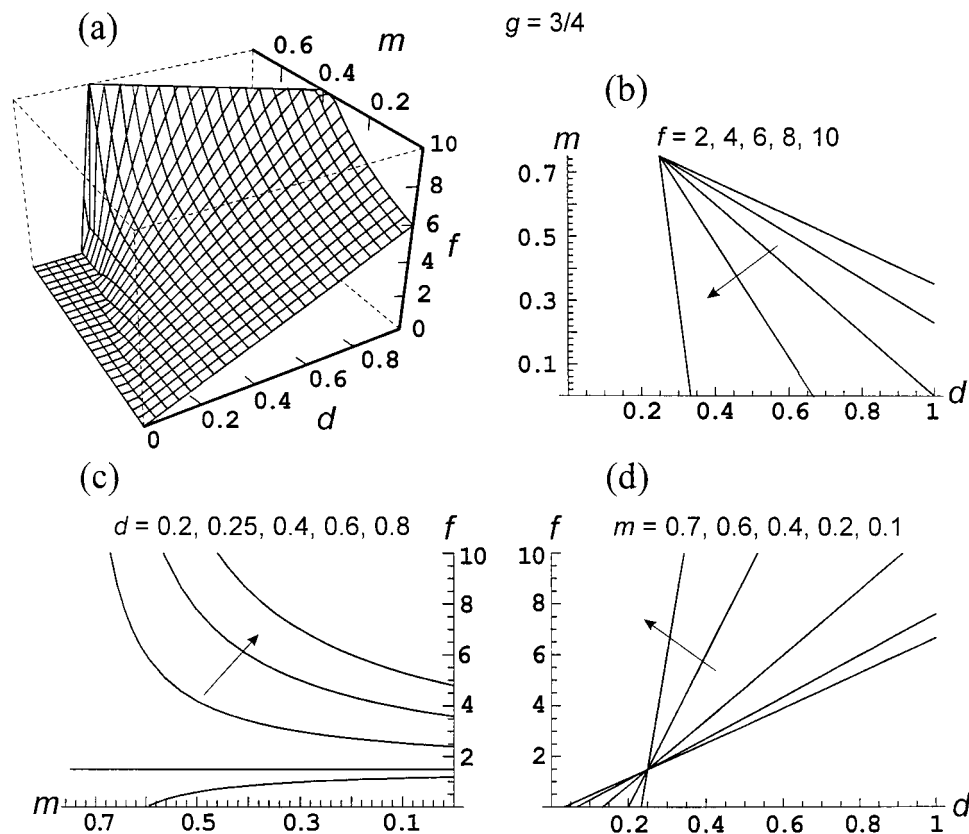
There are three equilibria for this system, the two fixation equilibria and an internal equilibrium. The internal equilibrium is not stable for biologically reasonable parameter values and will not be considered further.

The asexual diploid alone reaches the equilibrium given by Equation (3) at which resources equal  $\hat{r} = m/g$ . The eigenvalues for the diploid equilibrium for Equation (7) are identical to those for the case of asexual competition with the haploid (Equation (5)) and so sex adds

nothing new to the diploid's stability when it is already common. Fast sex reaches an equilibrium determined by a cubic equation. Critical surfaces can be obtained following the bifurcation methods given in the Appendix of Long and Michod (1995) to give a surface which partitions the parameter space into regions in which either sex or asexual diploidy win,  $f_C(g, d, m)$  defined in Equation (8). This surface is independent of  $p$  the size difference of haploids and diploids:

$$f_C = \frac{g(dg + (g-1)m)}{2(g-1)^2(g-m)}.\tag{8}$$

This surface is plotted in Fig. 5 for  $m=0.4$  (it also appears in panels (a) and (d) of Fig. 3 and Fig. 4 for the appropriate values of  $g$  and  $m=0.4$ ). The region owned by the sexual is in front of the 3 dimensional surface in panel (a) of Fig. 5. The critical surface defined in Equation (8) has the property that at  $d=1-g$ , it is independent of  $m$  and equals  $f_C = (g/2(1-g))$ . This behavior is shown in Fig. 6, where I plot the critical surface



**FIG. 6.** Bifurcation diagram for fast-selfish sex and asexual diploidy for  $g = 3/4$ . Diploidy is stable for parameter values behind the surface in panel (a), so long as  $m < 3/4$  (only this region is shown). If  $m > 3/4$ , then sex wins as the diploid equilibrium becomes unstable. Panels (b)-(d) are 2D slices through the 3D surface in panel (a). The parameter values for which sex is stable in panels (b)-(d) are indicated by arrows.

(Equation (8)) as a function of  $d$  and  $m$  for fixed  $g = 3/4$ . Sex wins for low damage and high mortality, while diploidy is favored in the reverse situation. In addition we see that sex persists in regions forbidden to the haploid ( $d + m > 1$ ). Sex may also persist in regions forbidden to the asexual diploid as discussed in the next section.

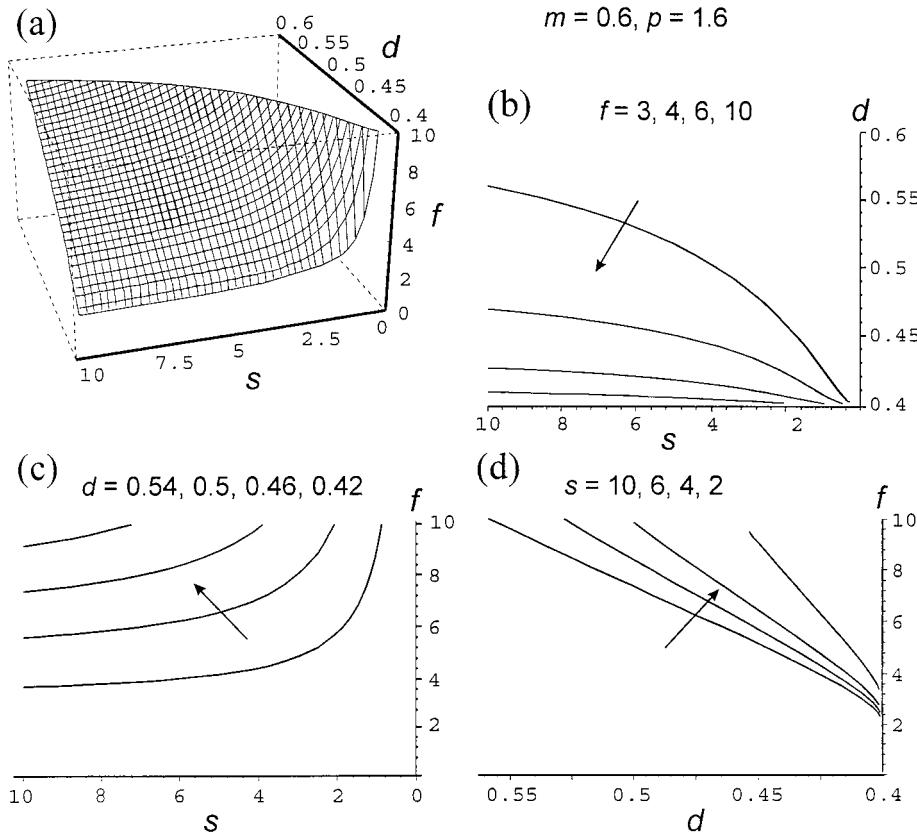
**Persistence of Sex in Punishing Environments**

We have previously studied the persistence of cooperative sex in punishing environments characterized by high rates of damage and mortality—environments in which the asexual haploid and diploid strategies could no longer persist (Michod and Long, 1995). By high damage and high mortality we meant that  $d + m > 1$ , so the haploid can't exist, and  $m > g$ , so the diploid can't exist. We found that cooperative sex could continue to maintain itself in these extreme regions.

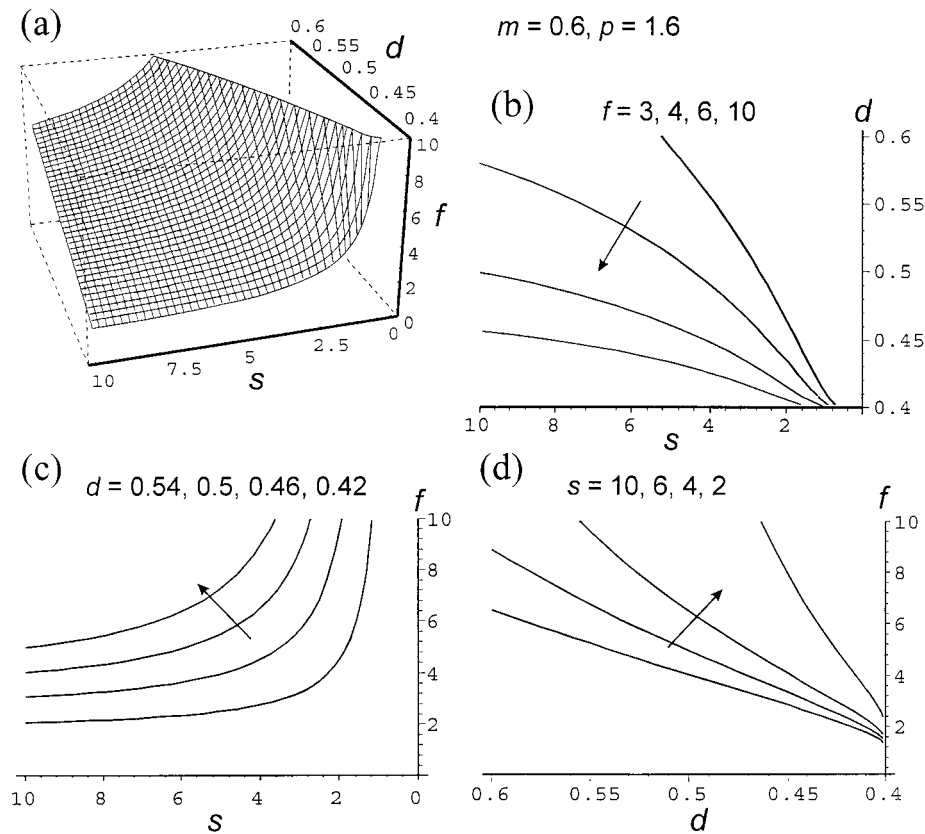
Although selfish sex is evolutionary stable in competition with cooperative sex in the spatially homogeneous

models studied here, there should be advantages to cooperative sex as a DNA repair strategy when alone in the environment. Specifically, there are more potential mates available under cooperative sex and this should be advantageous when damage rates get high. We find in this section that, when alone cooperative sex is stable in more extreme environments than is selfish sex. Nevertheless, even in situations where selfish sex cannot exist by itself, but cooperative sex can, selfish sex invades and drives the entire system to extinction.

The regions of persistence for selfish and cooperative sex are shown in Figs. 7 and 8, respectively, for the same set of parameter (i.e.,  $m = 0.6$  and  $p = 1.6$ ). Asexual haploidy cannot survive here and asexual diploidy cannot survive if  $g < m$  ( $= 0.6$  in the figures). The regions defined by the various curves represent sets of parameters for which the two sexual strategies reach a stable equilibrium when they are alone; that is, not in competition with the other. As can be seen by comparing the two figures, it is easier for cooperative sex to persist in these



**FIG. 7.** Selfish sex alone in extreme environments ( $d + m > 1$ ,  $m = 0.6 > 0.5$ ). Surface allowing existence of sexual is shown in panel (a) for  $m = 0.6$  and  $p = 1.6$  as a function of  $d$ ,  $s$  and  $f$ . The fusion and splitting rates must be above the surface shown in panel (a) for the sexual to persist. In panels (b)–(c) are 2D slices through the 3D surface in panel (a). The arrows in the 2D panels indicate which side of the curves beget sexuality. The value of the fixed parameter for each of the curves in the panel is shown above each panel.

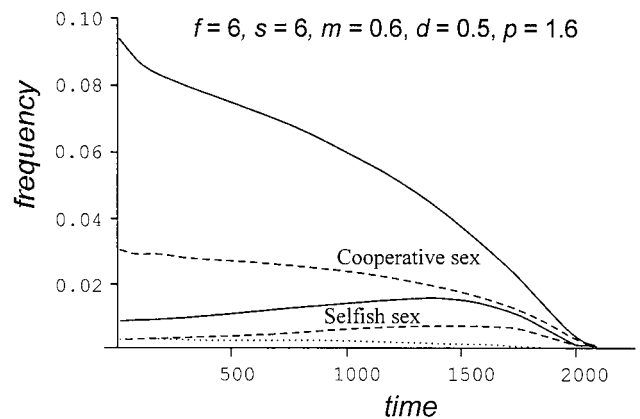


**FIG. 8.** Cooperative sex alone in extreme environments. Same legend as Fig. 7 except for cooperative sex. Positions of arrows within the 2D panels are the same as in Fig. 7 for comparison purposes.

challenging environments. This becomes most obvious as the damage rates increase. For example, cooperative sex can exist, but selfish sex cannot, if  $d = 0.6$  and the damage and fusion rates are less than 10 (compare the  $f = 10$  curve of the (b) panel of both figures).

In spite of its greater ability to cope with extreme environments, cooperative sex is not stable to selfish sex in these regions, even in regions in which selfish sex cannot exist alone but cooperative sex can. Even though selfish sex cannot exist alone, it can increase from rarity if cooperative sex is present by “suckering” healthy cooperative cells. As selfish sex increases, cooperative sex decreases, and, after its momentary success, selfish sex eventually causes its own demise and that of the entire system as both players go extinct. An example is shown in Fig. 9 for  $f = s = 6, d = 0.5, m = 0.4$  and  $p = 1.6$ . For this set of parameter values selfish sex cannot exist alone but cooperative sex can and reaches a stable equilibrium with healthy cells at a frequency of  $\hat{x}_C = 0.104$ . As shown in the simulation in Fig. 9, selfish sex increases from rarity by preying on the healthy cooperative cells, driving the entire system to extinction. Cooperative sex, although

it may persist when alone in more extreme environments, is not stable to the increase of selfish sex in these same environments. The outcome of selection on the sexual strategies considered here is not unlike the outcome of the Prisoner’s Dilemma game, in which defection wins,



**FIG. 9.** Selfish sex drives complete system to extinction. Dashed lines and solid lines are healthy and gene-damaged cells for cooperative and selfish sex, respectively. Dotted line is for total fused cells.

even though a population of defectors does worse than a population of pure cooperators.

## DISCUSSION

### *Sex for Gene Repair*

All sexual life cycles involve an alternation between haploid and diploid cell stages. To understand why, we have developed models of asexual haploid or asexual diploid cells and a sexual cycle that alternates between haploid and diploid cell states (Bernstein *et al.* 1984, Long and Michod 1995, Michod and Long 1995, the present paper). Our main is to isolate the key factors involved in the competition of the different life cycles in the hopes of understanding the diverse selective factors affecting the evolution of sexual life cycles. In addition to assumptions concerning resource utilization and cell size, five rate parameters determine the outcome of competition in our models: birth, cell death, gene damage, splitting, and fusion.

The main results of the present paper are as follows. (i) Asexual diploidy wins when the costs of diploidy are small, mortality rates low and damage rates high. (ii) Beginning with an ancestral state in which cells are asexual haploids, the sexual life cycle would emerge before asexual diploidy as a response to increasing DNA damage. (iii) Cooperative sex can be stable to selfish sex, but only if damage rates are high and fusion and splitting rates are tuned to be in a certain range (Fig. 2). (iv) Selfish sex is always stable to cooperative sex and can often increase from even extreme rarity. (v) Selfish sex is a far more robust repair strategy in competition with asexual haploidy and asexual diploidy (Figs. 3–6) than is cooperative sex. (vi) Although cooperative sex is more adaptive in extreme environments characterized by high damage and high mortality, selfish sex can still invade in these regions and take the entire system to extinction (Figs. 7–9). (vii) Once it is present, selfish sex is stable to asexual diploidy over a wide range of parameter values and can persist in regions of parameter space forbidden to the asexual diploid. This helps to address a major concern of the gene repair theory of sex, which is that efficient repair in an asexual diploid is a better strategy than sex.

I have loaded the competition in favor of the diploid, because I assume that diploidy is a haven against damage. I ignore the possible costs of repair in an asexual diploid in terms of expressing recessive mutations. Instead I assume that any damage suffered by the diploid is immediately and effectively repaired without cost.

Thus, I demand as much from the sexual process as I possibly can, since fusion and splitting take time away from replication.

### *Selfish Sex in Microbes*

Several lines of evidence suggest that damage-induced sex is a strategy employed by a wide variety of microorganisms. Recombination is generally induced by DNA damage in phage, bacteria, and yeast (Bernstein, 1983; Bernstein *et al.*, 1987). Natural genetic transformation is increased by DNA damage (Michod *et al.*, 1988; Wojciechowski *et al.*, 1989; Hoelzer and Michod, 1991; Michod and Wojciechowski, 1994). Bernstein (1987) showed that damage induces sex in T4 phages. When healthy phage infect their hosts, they erect a barrier against further infection by other phage, thus ensuring that their genes are the only genes replicated inside the host. In contrast, when gene-damaged phage infect their hosts, they do not erect an effective barrier, the result being that another phage can infect, leading to sex and recombination. This is adaptive from the point of view of the first phage since it is in need of recombinational repair. Bernstein and Johns (1989) found that the addition of hydrogen peroxide, a known DNA damaging agent, to cultures of the yeast *Schizosaccharomyces pombe* resulted in a dramatic increase in the percentage of sexual spores versus asexual cells.

Therefore, damage-induced sex seems to be common in microbes and both aspects of sex, recombination and outcrossing, are known to be increased by DNA damage. More generally, the very nature of a damage—that it is directly recognizable by enzymes—makes it a suitable substrate as a signal for cellular responses like sex. The signal could be something as simple as this: if the DNA cannot be replicated (a polymerase cannot replicate a damage), then recombine and/or have sex (in diploid cells recombination may be sufficient, but in haploids sex is required).

Mating systems in microbes are diverse. While much is known about the molecular and cellular biology of sexual life cycles in a few species of bacteria, viruses, fungi and other single cell eukaryotes, there is at present little evolutionary and ecological context for this knowledge (Herskowitz, 1988). For example, a review in fungi (Metzenberg and Glass, 1990) begins with the question, “What is mating good for?” but ends concluding “We still cannot answer this question.” Let us consider this question from the point of view of the models discussed above.

Both heterothallic (self-sterile) and homothallic (self-fertile) life cycles exist in yeast, fungi, and algae (Nauta

and Hoekstra, 1992a; Nauta and Hoekstra, 1994; Nauta and Hoekstra, 1992b; Herskowitz, 1988b). A simple population genetic recurrence equation of heterothallic and homothallic life cycles in filamentous ascomycetes concluded that the heterothallism should be difficult to evolve from homothallism (Nauta and Hoekstra, 1992a; Nauta and Hoekstra, 1994; Nauta and Hoekstra, 1992b). However, this model ignored many aspects of sexual biology important in yeast and other fungi, such as resources and nutrients (nutrients are crucial to reproduction and control the onset of meiosis and sporulation), asexual proliferation in the diploid state (which occurs in *S. cerevisiae* but not in *S. pombe* (Herskowitz, 1988), and in some other fungi (Metzenberg and Glass, 1990)), and mating-type switching ((Herskowitz, 1988); mating type switching also occurs in filamentous ascomycetes (Perkins, 1987)).

Our models capture the most basic aspects of sex in microbes. We consider two distinct cell types, haploid and diploid, either of which could reproduce asexually, and a primitive sexual cycle. However, there are no mating types, a haploid cell could fuse with any other sexual haploid cell to produce a diploid cell that then splits to form haploids. One virtue of the model is the ease with which it may be modified to consider explicit life cycles in particular taxa.

Consider, for example, *S. cerevisiae* and *S. pombe*. In this case, we need to consider two haploid cell types (mating types),  $a$  and  $\alpha$ , and the diploid cell type  $a\alpha$ . In yeast, the haploid cell types may reproduce mitotically or they may fuse with the alternate mating type to produce the  $a\alpha$  diploid. The  $a\alpha$  diploid cell type may be stable and reproduce mitotically (*S. cerevisiae*) or it may be transient and proceed into meiosis under appropriate nutrient conditions (*S. pombe*). Furthermore, in homothallic strains (*HO* in *S. cerevisiae*) there is the possibility of mating type switching (which is relatively rare in *S. cerevisiae* and a common feature of mitotic cell lineages in *S. pombe*). It is thought that mating type switching typically leads to selfing because daughter cells of opposite mating type usually fuse before they encounter other mating partners (Herskowitz, 1988). Depending on spatial structure, mating in heterothallic strains (*ho* in *S. cerevisiae*) may involve an unrelated cell and so should result in greater outcrossing. Since the *ho* allele is a defective *HO*, one may assume that heterothallic strains evolved from homothallic strains, but this is not necessarily the case (Nauta and Hoekstra, 1992a; Nauta and Hoekstra, 1994; Nauta and Hoekstra, 1992b).

We may use flow diagrams to represent the resulting system of differential equations, in which the ovals represent state variables and the rates of flows from one state

to another are given by arrows and associated parameters (these flow diagrams translate directly into a system of differential equations as described in our previous work (Michod and Long, 1995; Long and Michod, 1995). Simplified flow diagrams for the homothallic and heterothallic life cycles (*HO* and *ho*, respectively) are shown in Fig. 10. The parameters  $f$  and  $s$  represent, respectively, the rates of mating (*f*usion) and meiotic sporulation (*s*plitting) in and out of the diploid stage.

The parameter  $b$  represents mitotic proliferation (*b*irth) indexed to the different cell types. The parameter  $w$  represents the rate of mating type switching, assumed equal for the two mating types. Resources and nutrients crucial to reproduction and sporulation may also be included, as we have done above, although they have been left out of the figure for reasons of simplicity of presentation. In Fig. 10, the heterothallic and homothallic strains are treated as separate populations, although mating between *HO* and *ho* cells is known to occur and could easily be included in a more sophisticated model. Including this complication is straight-forward and requires treating the two populations as a single Mendelian population (see Michod and Long, 1995). In Fig. 10, I have tied mating type switching to reproduction, because in *S. cerevisiae* only mother cells can switch mating types.

In answer to the question, "What is mating good for?", application of our models to the yeast system leads to the conclusion that mating in yeast likely evolved as a means to reap the benefits of DNA repair in the diploid state,

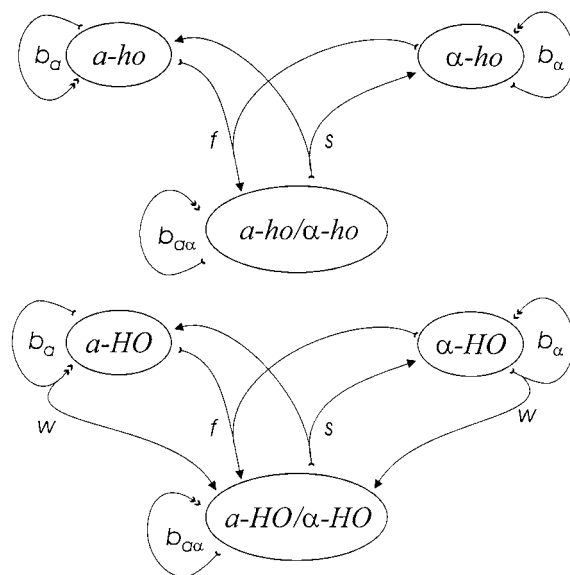


FIG. 10. Flow diagram of yeast mating. Legend of Fig. 1 applies here.

while avoiding the replication and mortality costs of diploidy. There is abundant evidence that *ax* diploids are more resistant to DNA damage because of heightened recombinatorial repair (Mortimer, 1958; Herskowitz, 1988; Durand *et al.*, 1993). The costs of diploidy are more complicated as they can depend on nutrients and resources (Valero *et al.*, 1993; Destombe *et al.*, 1993; Lewis, 1985; Maynard Smith and Szathmary, 1995; Bernstein *et al.*, 1984; Long and Michod, 1995; Adams and Hansche, 1974; Weiss *et al.*, 1975).

Data from microbes are generally consistent with the results reported here (Bernstein, 1983; Bernstein *et al.*, 1987; Michod *et al.*, 1988; Wojciechowski *et al.*, 1989; Hoelzer and Michod, 1991; Michod and Wojciechowski, 1994; Bernstein, 1987; Bernstein and Johns, 1989). Consider the eukaryotic yeast *Schizosaccharomyces pombe*, in which a vegetative cell can either reproduce sexually or asexually with mitosis. In sexual reproduction, a cell fuses with a cell of the opposite mating type, the diploid cell then undergoes meiosis to produce sexual spores that germinate to become a vegetative cell. As with other facultatively sexual organisms, nutrient depletion (in this case nitrogen) favors sex (Bernstein and Johns, 1989). DNA damage has similar effects as nutrient depletion, in that exogenous damage (in this case experimentally administered hydrogen peroxide—a known DNA damaging agent) induced mating among cells even when nitrogen was not limiting (Bernstein and Johns, 1989). Furthermore, in direct confirmation of the selfish sex hypothesis, it was found that the observed number of spores under different levels of DNA damage was in close agreement to the number of spores expected based on the assumption that only gene dead cells mate. Based on these results, the workers (Bernstein and Johns, 1989) concluded “If an *S. pombe* cell is able to grow vegetatively, it does so. However, if it has DNA damage which prevents vegetative growth, it may mate, undergo recombinatorial repair, and generate viable spore progeny.” This is the selfish sex strategy.

### **From Selfish Sex to Facultative Sex**

A wide variety of multicellular organisms are facultatively sexual, that is they can reproduce sexually or asexually according to circumstances. Selfish sex is a kind of facultative sex in which DNA damage is the impetus for switching to sex. It is often observed in facultatively sexual multicellular organisms that sex is associated with conditions of nutrient and/or resource depletion in dense populations (Bell, 1982). Nutrient depletion is also a condition associated with the timing of sex in certain microbes such as in bacteria and yeast. The case of *S.*

*pombe* has already been discussed above. Likewise in the bacterium *B. subtilis*, both DNA damage and nutrient depletion increase rates of transformation (Michod and Wojciechowski, 1994). This raises the question of whether facultative sex can be seen as an elaboration of the selfish sex strategy and if there is a continuous evolutionary history from selfish sex in microbes to facultative sex in multicellular organisms.

Sex may be expected to occur when its benefits outweigh its costs. While much theorizing about the occurrence of sex has focused on elucidating its benefits, the costs of sex are equally important in understanding the distribution of sex in nature both in time and in space. Michod ((1995), p. 80) argued that the underlying cause of the correlation of sex with crowded conditions in facultative organisms may be the reduced cost of finding a mate in these situations. Hudson (1997) argued that mating often interferes with other activities such as feeding and the accrual of nutrients and resources. In crowded environments in which needed nutrients and resources are scarce, this cost of sex is reduced and we expect sex to be more frequent. Indeed, mating interferes with most activities. In addition to feeding in microbes, sex interferes with DNA replication. However, these costs of sex are reduced when a cell cannot replicate anyway because it is damaged. Selfish sex is a repair strategy in which the costs associated with cooperative sex have been eliminated by timing sex to occur when a cell is damaged.

Having identified the role of costs in the timing of sex, we still would like to know why sex became associated with the inability of DNA to replicate. The main physiological consequence of gene damage for the cell is the inability to replicate DNA. As already mentioned, facultatively sexual organisms become sexual when local conditions deteriorate and replication becomes difficult or impossible. Whether these situations are especially threatening or damaging to DNA remains to be investigated. Nevertheless, the effect on the cell or multicellular organism of gene damage, nutrient depletion, or environmental degradation (as in the case of *Daphnia* who switch to sexual reproduction when ponds dry up) is the same—replication of the cell or organism becomes difficult or impossible.

In all organisms DNA is a matter of great concern, but for single celled organisms with few gene functions, the life cycle is directly tied to the state of the DNA. Multicellular organisms have more gene functions, and reproduction of the organism involves many steps. Nevertheless, even in complex organisms the ability to replicate and pass on genes is the matter of overriding concern. Along with greater complexity, there are more

problems, than just DNA damage, that may prevent the organism from replicating its DNA. Nevertheless, this ancient impetus for sex may have been preserved in modern forms. According to the models studied here, sex originated in microbes as a response to problems in DNA replication. More complex facultatively sexual organisms may turn to sex in similar situations.

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