THEORETICAL POPULATION BIOLOGY 47, 18–55 (1995)

Origin of Sex for Error Repair
I. Sex, Diploidy, and Haploidy

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Received May 18, 1993

Genetic damage is a fundamental problem for living systems. Recombination can repair a damaged gene, so long as there is an undamaged copy of the gene available in the cell. This requires that the cell be diploid for the damaged locus. During sex, outcrossing generates the diploid state by temporarily fusing two haploid cells (as in the case of meiosis) or by bringing DNA into the cell from outside (as in the case of bacterial transformation). But why should cells alternate between the haploid and diploid states in the first place? Why not just remain diploid, if damage repair is the only problem for a cell? The goal of our work is to understand if the problem of genetic damage would select for diploidy or for the alternation between diploid and haploid states—that is, sex—early in the history of life. Using mathematical models we study competition between asexual haploids (termed "haploids"), sexuals (termed "sexuals"), and asexual diploids (termed "diploids"). Haploid cells are efficient replicators, while diploid cells are resistant to damage. A sexual may combine the advantages of both: spending much of its life cycle in the haploid state, then temporarily fusing to become diploid, followed by splitting to the haploid state. During the diploid state DNA damage can be repaired, since there are two copies of the gene in the cell and one copy is presumed to be undamaged. We describe the competition in terms of mathematical models, employing five rate parameters which represent the life processes of cells most probably active at the time that sexuality arose: birth and death; genomic damage (for the haploids alone); and, for the sexual cell, fusion and splitting. Parameter space bifurcation diagrams for the equilibria are drawn in the three-dimensional space of damage, splitting, and fusion, and solutions of the equations (i.e., the outcomes of the competition) are described in terms of them. It turns out that those three parameters suffice to give an essentially complete description of the qualitative behavior possible, since one parameter can be scaled out of the equations we ultimately consider, and the other permits generic analysis, for the range of parameter values

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0040-5809/95 $6.00

of interest, at a fixed value of that parameter. Each type of cell has a region of the parameter space that it occupies exclusively (given its initial presence in the competition). The haploid can win only in environments characterized by low damage (relative to mortality), while the diploid can win only in environments characterized by high damage (relative to mortality). However, the sexual may outcompete either of the asexuals in those domains assuming that the parameters of the sexual cycle are adjusted appropriately. In general, only a single type of cell occupies a given portion of the space. We find, however, that the competitive coexistence of a diploid and a sexual is possible in spite of the fact that they are competing for a single resource (nucleotide building blocks). This coexistence is the result of an overactive sexual cycle and so would presumably be selected against.

1. Background

Genetic damage is a fundamental problem for living systems. Recombination in a diploid cell can repair a damaged gene, so long as one of the copies is undamaged. During sex, outcrossing generates the diploid state by temporarily fusing two haploid cells (as in the case of meiosis) or by bringing DNA into the cell from outside (as in the case of bacterial transformation). But why should cells alternate between the haploid and diploid states in the first place? Why not just remain diploid, if damage repair is the only problem? Diploid cells are unlikely to become damaged at the same site in both copies and one can imagine that some sort of efficient mitotic recombination in diploid cells might be possible. Consequently, the function of DNA repair, while providing explanations for diploidy and recombination, does not by itself explain the need for recombination *plus* outcrossing—that is, sex (Bernstein *et al.*, 1981, 1985; Michod, 1990).

There are economic issues to consider when investigating the selective advantage of haploidy and diploidy (Bernstein *et al.*, 1984; Valero *et al.*, 1991), and these issues are included in the models studied here. Most basically, diploid cells require twice the genetic resources and nutrients to replicate. In addition, there may be size differences and other intrinsic differences between diploid and haploid cells.

Masking of recessive, or nearly recessive, mutations is probably another important advantage of the outcrossing aspects of sex in many organisms with a diploid stage (Bernstein *et al.*, 1981, 1985; Perrot *et al.*, 1991; Kondroshov and Crow, 1991; Valero *et al.*, 1991; Michod and Gayley, 1992). However, we do not include this factor in the models studied here, although we believe that both kinds of genetic error, deleterious mutations and genetic damage, played a role in the evolution of diploid sexual life cycles (see, for example, Michod and Gayley, 1992). The point of the present paper is to study selection resulting from the need to jointly repair genetic damage and replicate DNA. We leave to future work the problem

of considering deleterious mutation and genomic damage together in explicit mathematical models.

2. Model

The work reported here concerns competition between three types of life cycle: sexual, haploid, and diploid. In nature, the sexual process is represented by diverse methods and styles, from mixed infection in viruses to transformation and conjugation in bacteria to syngamy and meiosis in eukaryotes. We have tried to extract the essentials from these myriad representations and incorporate them into a simple model, which allows us to understand if the sexual process might have arisen in response to the simultaneous need for repairing genetic damage and efficient cell replication.

The models we study share common assumptions, variables, and parameters as summarized in Tables 1 and 2. These assumptions are discussed fully in Section 4.1. To reproduce, the diploid must encounter two nucleotide resource packets (Table 1). Consequently, there are diploid cells that have encountered just one resource packet but not the second, and so are not yet able to divide. In the model studied below the dynamics of the

TABLE I

Major Assumptions in 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 partners
Pure sex: no reproduction or genome replication during sex (as occurs in 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
Competition between different types of lifecycles based on resource use exclusively
Closed system: total resources (free resources plus resources tied up in cells) are constant

TABLE II

Parameters	
b	birth rate for all haploid cells (sexual and asexual)
β	birth rate of diploid cells
m	death (or morality) 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 diploid-like sexual cell
d	damage rate for haploid cells
Variables	
x	density of sexual cells
y	density of fused (diploid) sexual cells
z	density of gene-damaged haploid sexual cells
x_a	density of asexual cells
z_a	density of gene-damaged haploid asexual cells
w	density of diploid cells
r	density of free resources available for reproduction
t	time

diploid have been simplified, as discussed in the Appendix. In our simplified model there are three basic cell types or species: the haploid, A_H; the sexual, S_H; and the diploid, A_D. The sexual and haploid species may exist in gene-damaged states in densities z and z_a, respectively. The sexual may also exist in a fused diploid state in density y. This gives a total of six cell types, three for the sexual, two for the haploid, and one for the diploid.

In order to make the equations dimensionless, we divide all equations by b (we have no intention of setting b to zero) and then scale our original independent variable t and our parameters, redefining them as follows:

$$t \equiv bt,$$

so that

$$f \equiv \frac{f}{b}, \quad s \equiv \frac{s}{b}, \quad m \equiv \frac{m}{b}, \quad d \equiv \frac{d}{b}.$$

All variables are now dimensionless. parameters, that used to be rates, now represent ratios of rates. Since our equations are autonomous these changes do not have any significant effect on the form of the equations, but we have achieved a reduction in complexity, from five free parameters to

four. The original equations, discussed in the Appendix, now take the final form

$$\begin{aligned} x' &= x(r-m-d)+2sy-fxz \\ y' &= fz(z+x)-y(pm+s) \\ z' &= dx-z[m+f(2z+x)] \\ w' &= wp\left(\frac{r}{2}-m\right) \\ x'_a &= x_a(r-m-d) \\ z'_a &= dx_a-mz_a, \end{aligned} \tag{1}$$

where

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

We check that this system is consistent by looking at the differential equation for r, as obtained in the other cases (by considering the inflows and outflows), in order to see that we get the same expression by differentiating (2),

$$r' = m(x+2py+z+2pw+x_a+z_a)-rx-2prw-rx_a,$$

which is

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

so our system is consistent.

For ease of presentation, we consider the simpler pairwise competitions that take place in the absence of one or more of the cell types. While these are separate competitions, they are (with one exception) merely projections of the full model onto subspaces. We describe the procedure used in studying the equilibria of the system in the methods section of the Appendix.

3. Results

3.1. *Each Cell Species Considered Alone*

Each cell can be considered on its own, under the various conditions imagined in our model. From the system of equations (1), with two of the three cell types (and damaged cohorts) set to zero, we have the following dynamics.

3.1.1. *Diploid.* The diploid follows a logistic equation for $m < \frac{1}{2}$, with equilibrium populations as follows:

$$\begin{aligned} r &= 2m \\ w &= \frac{(1-2m)}{2}. \end{aligned} \tag{3}$$

For $m \geqslant \frac{1}{2}$, it goes extinct.

3.1.2. *Haploid.* The haploid also follows a logistic equation, with equilibrium populations of

$$\begin{aligned} r &= m + d \\ x_a &= m\frac{(1-m-d)}{m+d} \\ z_a &= d\frac{(1-m-d)}{m+d} \end{aligned} \tag{4}$$

which are plotted in Michod and Long (1994, Fig. 2). It goes extinct when $m + d \geqslant 1$.

3.1.3. *Sexual.* The situation for the sexual cell type alone is quite complicated, even given the simplifying assumptions made. The equations are sufficiently complex to require a separate analysis (Michod and Long, 1994). For $d + m < 1$ the sexual has, like its asexual cousin, a single stable and physically realizable equilibrium: but whereas the haploid is driven to extinction if d exceeds $1 - m$, the sexual can save itself if its sexual parameters, the rates of fusion and splitting, are sufficiently large. We show in Michod and Long (1995, Figs. 11 and 12) the conditions necessary for the survival of the sexual for $m + d \geqslant 1$.

3.2. *Strictly Asexual Competition*

We consider initially a world populated by haploid cells and study competition between these haploids and either diploid cells or sexuals. First we consider competition between the asexuals (haploid versus diploid) in the absence of the sexual. This competition corresponds to the following system of equations:

$$\begin{aligned} x'_a &= x_a(r - m - d) \\ z'_a &= dx_a - mz_a \\ w' &= wp\left(\frac{r}{2} - m\right). \end{aligned} \tag{5}$$

There are three equilibria of this system, none of which corresponds to competitive coexistence. Each species of cell has a parameter space region all to itself. We proceed directly to the linear local stability analysis, the Jacobian being given by the following matrix:

$$J=\begin{pmatrix} r-m-d-x_a & -x_a & -2x_a \\ d & -m & 0 \\ \frac{-wp}{2} & \frac{-wp}{2} & -p\left(m-\frac{r}{2}\right)-wp \end{pmatrix}$$

In the case of extinction, i.e., $x_a = z_a = w = 0$, the eigenvalues of the Jacobian are

$$\{1-m-d,\ -m,\ -p(m-\tfrac{1}{2})\}. \tag{6a}$$

Thus, local stability of extinction arises iff

$$m+d>1 \tag{6b}$$

and

$$m>\tfrac{1}{2}. \tag{6c}$$

From the form of the equations in (5) and from what we learned above about the dynamics of each species alone, condition (6b) guarantees extinction of the haploid and condition (6c) extinction of the diploid. (The right-hand sides of the equations for each are negative, implying a steady decrease in population to zero.) Thus we see that for low damage and high mortality, the haploid can outcompete the diploid.

An examination of the equilibrium of the diploid alone shows that the eigenvalues are

$$\{m-d,\ -m,\ p(m-\tfrac{1}{2})\}. \tag{6d}$$

The equilibrium populations of diploids and free resources are given in the equations in (3). The interesting eigenvalue is $m-d$, which tells us that as long as $d>m$ the diploid is locally stable. The haploid, with equilibrium populations given in the equations in (4), is locally stable in the rest of the parameter space.

The outcome of the dynamics and competition of asexual cells is summarized in Fig. 1a. Since we are primarily interested in the outcome of competition, we see that we can restrict ourselves to the portion of the plane where both cell types could survive on their own (see Fig. 1b). This is the portion bounded by the axes, and the lines $m=\frac{1}{2}$ and $m+d=1$. Note

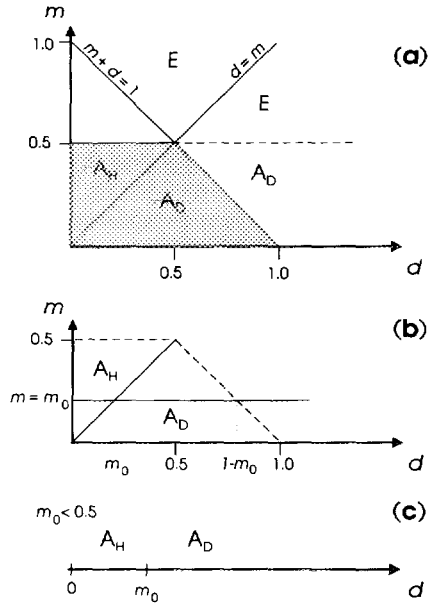

FIG. 1. Summary of asexual dynamics. In panel (a), we show the (m, d) plane and indicate the winner of the competition by the initials of the cell type's name, either "A_H" for haploid or "A_D" for diploid. "E" stands for extinction of either cell type. In panel (b), we restrict our attention to that part of plane in which both cell type's can exist and compete. In panel (c), we show the outcome of the competition for a fixed $m = m_0$ as a function of damage, d. We could also have shown the outcome as a function of m for a fixed $d < 0.5$ by construction analogous to that in panel (b).

that within this region the result of competition can be given quite simply: for a given value of $m = m_0$, the haploid wins if $d < m_0$, while the diploid wins if $d > m_0$.

Thus, we can describe the outcome generically using only one dimension, for example, the d-axis (Fig. 1c). This generic reduction of the competition to one dimension allows us to effectively represent the parameter space solutions in each of the competitions that follow, even in the case of four free parameters.

What can we learn from the system of asexuals alone? We see first that in the absence of damage the haploid always wins. Second, given even the slightest amount of damage there exist values of m that result in a loss of the haploid's stability. Whereas before the haploid enjoyed an exclusive equilibrium, now the competing diploid could win out and expel the haploid if $d > m$. Third, there is no parameter choice which permits the coexistence of the two sexual species. Fourth, we note that the change in

stability comes when the free resource equilibria values of the two equilibria populations are equal:

$$m + d = 2m \Leftrightarrow d = m. \tag{7}$$

This turns out to be a fairly general result, and a useful one as it allows us to quickly compute the boundaries (in parameter space) for which the outcome of the competition changes. These boundaries constitute a bifurcation diagram in parameter space and our computer simulations have shown that they are consistent predictors of the outcome of the competitions. As in the chemostat, the population that won the race was that which managed to use up the most free resources (or, equivalently, consumed the most, turning free resources into bound resources). Explicit examples are given in the Appendix. As discussed there, this result is almost, but not quite, a general result in the competitions we describe.

We note furthermore that, although we have a system defined on three-dimensional space, solutions (orbits) move to one of the face planes eventually (or even an axis). This system of these two species is consequently not persistent: one species always becomes extinct.

3.3. *Fast Sex versus Diploidy*

Suppose that sexuality confers to the haploid the capacity for instantaneous repair of damage upon fusion. This is as optimistic a scenario as could be conceived, but it is essentially what we have attribued to the diploid. In this case, the equations for competition between the sexual and the diploid cells would have the form

$$\begin{aligned} x' &= x(r - m - d) + fz(2z + x) \\ z' &= dx - z[m + f(2z + x)] \\ w' &= wp\left(\frac{r}{2} - m\right). \end{aligned} \tag{8}$$

These equations can be obtained from the full model by setting haploid populations to zero and letting the splitting rate, s, go to infinity. The latter condition means that as soon as a cell needing repair fuses with another (or a healthy haploid), it is repaired and separates. In the limit the cell spends no time in the fused state; i.e., the fused cell population goes to zero. The fact that this parameter is so much larger than the others means that the y variable, representing the fused haploids, equilibrates quickly by comparison with the other variables, and so can be replaced in the equations by its equilibrium value. Doing so yields the equations above. The competition for fast sex is represented schematically in Fig. 2.

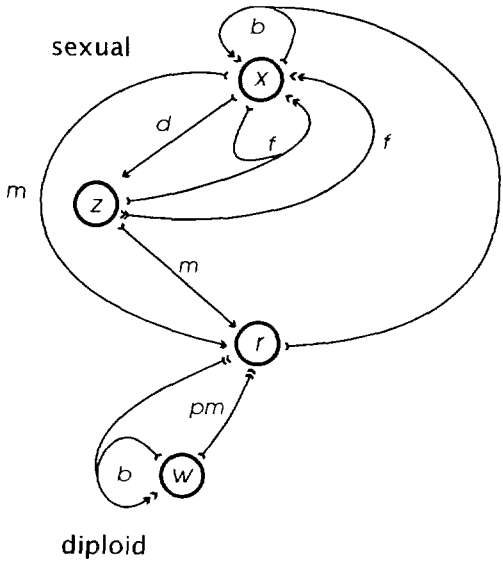

FIG. 2. Flow of cells for fast sex and diploidy competition. Circles represent cell populations, while arrows represent movements of cells from one population (the "donor") to another (the "recipient"). The number of "feathers" at the tail of an arrow indicates the number of cells that leave the donor population, while the number of arrow heads at the tip of an arrow ➢⟶⟶ indicates the number of cells that are contributed to the recipient population. So the arrow indicates that two cells are taken from the donor population to produce three cells in the recipient population.

Again we study the equilibria of the system. Five equilibria have biologically realistic population densities that are inside the simplex given by $1 = r + x + z + 2w$. These equilibria are extinction $(x, z, w, r) = (0, 0, 0, 1)$; diploidy alone, $(0, 0, (1 - 2m)/2, 2m)$; coexistence; and two equilibria corresponding to the sexual alone.

The first two equilibria are very similar to what they were in the strictly asexual competition. For both equilibria the eigenvalues are the same as before; Eq. (6a) for extinction and Eq. (6d) for diploidy alone.

In the case of coexistence or purely sexual equilibria, we find that the eigenvalues are essentially intractable (analytically), in contrast to the case of the asexual competition in which we could solve explicitly for the eigenvalues. In studying them numerically, we find that the question of stability is reduced to the study of the roots of a cubic and a quadratic (see Appendix). A parameter space bifurcation diagram summarizes the stability properties: those regions of the parameter space which supported locally stable equilibria in the asexual competition continue to do so for this competition, only now some of that space formerly reserved for the diploid is also open to the sexual. That is, there are now regions of the

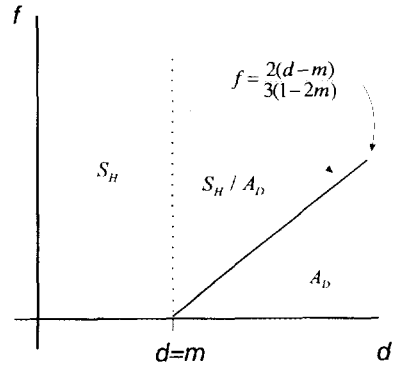

FIG. 3. Bifurcation diagram for fast sex and diploidy. The dotted line applies to the purely asexual competition described previously. It divides the parameter space into regions for which the haploid (to the left of the dotted line) or the diploid (to the right of the dotted line) wins. The solid line applies to the competition between fast sex and diploidy. The region that opened up to the sexual is given generically, for a value of m (such that $0 < m < \frac{1}{2}$), by a wedge in the (d, s) plane. The notation S_H/A_D indicates that either S_H or A_D, but not both, wins depending on initial conditions. This notation is used in other competitions.

parameter space for which there exist multiple stable equilibria. There is also an equilibrium at which both cell types can coexist, only it is never stable for realistic parameter values and so would not occur naturally. As one can see in Fig. 3, the region which opened up to the haploid is given generically for a value of m such that $0 < m < \frac{1}{2}$ by a wedge with boundaries $d = m$ and the line

$$f = \frac{2(d-m)}{3(1-2m)}. \tag{10}$$

Thus we see that for a certain well-determined value of the fusion parameter the sexual can survive in what was formerly forbidden territory. The diploid can also survive there, but only one species does so at any given time. And although that part of parameter space is open to both types of cell, neither can invade an existing population of the other without some finite invasion force (determined by a separatrix in the population three-space). That is, the equilibria are stable.

The parameter space descriptions for this system for the previous asexual competition are given jointly in Fig. 4, in which a three-dimensional representation of the parameter space is given for the full competition (that is, for the parameters d, s and f). Since the representation is generic for varying values of m (in the range of interest, i.e., $0 < m < \frac{1}{2}$), we give a representative slice of the four-space for a fixed value of m. Note that the asexual outcome is independent of f and s (yielding a plane independent of

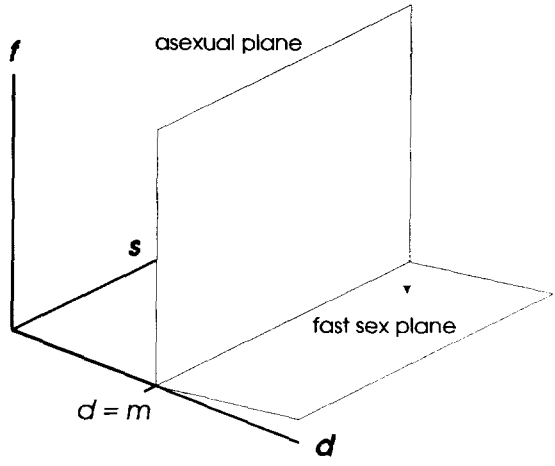

FIG. 4. Asexual and fast sex planes ($m < \frac{1}{2}$). The parameter space descriptions for this system and for the previous asexual competition are given in the three-dimensional parameter space which serves as the stage in the competitions to follow, with axes corresponding to damage, splitting, and fusion.

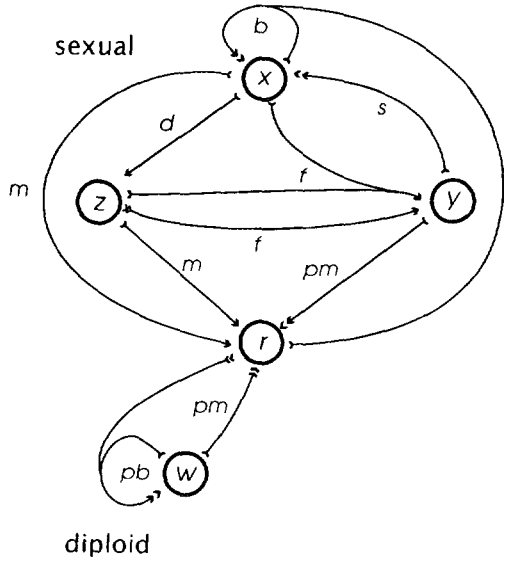

FIG. 5. Cell flow for sexual and diploid cells. Arrows are described in the legend to Fig. 1.

those two variables), whereas the fast sexual process outcome is independent of s (so that the plane is independent of s). We see that the sexual process has simply "tipped" the asexual divider plane into what was formerly exclusively diploid territory. In the next competitions, the outcome is a function of all the parameters and hence is no longer planar in the parameter space.

One thing to note is that under the fast sex assumption the sexual always out competes the asexual haploid. Sex in this case is dynamically positive for all parameter values.

3.4. *The Competition of Sexual vs Diploid*

3.4.1. *The Model.* In Fig. 5 we have drawn a schematic diagram of the model, which is equivalent to the following system of ordinary differential equations:

$$\begin{aligned} x' &= x(r-m)d - fz) + 2sy \\ y' &= fz(z+x) - y(pm+s) \\ z' &= dx - z[m + f(2z+x)] \\ w' &= wp\left(\frac{r}{2} - m\right), \end{aligned} \tag{11}$$

where

$$1 = r + x + 2y + z + 2w.$$

We note the following aspects of these equations:

1. If $m > \frac{1}{2}$, the diploid goes extinct (since $w' < 0$).

2. The only interaction of the two species is in the resource term (though we should keep in mind just what the resource term is: when cells die they are converted to resources for the formation of other cells, so there is a very strong interaction in that resource term).

3. Competitive coexistence at equilibrium requires that $r = 2m$, since otherwise the right-hand side of the diploid equation would demand that w be zero (i.e., that there be no diploids). This is important, as it corresponds to a great simplification of the form of the algebraic relation obtained when we seek equilibria of the system.

3.4.2. *Results.* Once again we find that the eigenvalues can only be obtained symbolically in the cases of extinction and diploidy alone.

$$\text{Extinction:} \quad \{1-m-d,\ -pm-s,\ -m,\ p(\tfrac{1}{2}-m)\}$$

$$\text{Diploidy alone:} \quad \{m-d,\ -pm-s,\ -m,\ p(\tfrac{1}{2}-m)\}.$$

In both cases, we picked up one new strictly negative eigenvalue. In the other cases (coexistence and haploidy alone) the equations lead to such complicated equilibria that we used numerical techniques discussed in the Appendix.

Case 1. $d<m$. In this case we find only two possibilities. Recall in the asexual competition that the region $d<m$ was the domain of the haploid exclusively. Now we find that for low values of splitting rate, $s<pm$, if the fusion rate is too high for the sexual there comes a point at which the diploid can coexist alongside the sexual (in front of the surface in Fig. 7 when $d<m$). In this region, the sexual cycle has actually worked *against* the sexual cell: if damage is low, there is no advantage to sexual repair, at least in competition with a diploid asexual (or for that matter the haploid asexual, as we find in Fig. 9).

Case 2. $d>m$. First of all, continued existence of the sexual requires that

$$s \geqslant \frac{p\{10d-7m+4\sqrt{2(2d^2-md-m^2)}\}}{9} \equiv s_c. \tag{12}$$

Note that $s_c \geqslant pd/3$, the value of s_c at $d=m$, while as $d \to \infty$, $s_c \approx 2pd$ (i.e., s_c increases linearly in d).

There is a critical value of f, f_c, which corresponds to this value of s_c, below which the sexual is guaranteed extinction. (This is a curve in the parameter space, visible in the figures as a graceful, upward-swooping

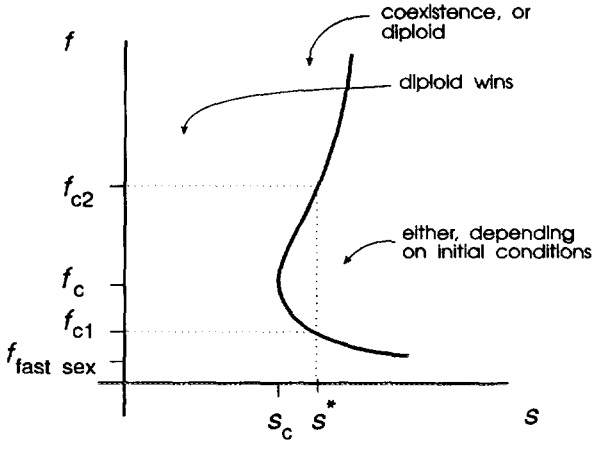

FIG. 6. Slice of bifurcation surface in Figs. 7 and 9. See text for explanation and Fig. A2 in the Appendix for more technical detail.

curve starting on the (d, s) plane and moving off to the corner farthest from the origin.) In other words, the sexual cycle has a minimal level of activity, below which the sexual is assured of going extinct. If, for a given value of $d > m$, the haploid is capable of the minimal level of sexual activity, then there are a couple of possible outcomes. Suppose, therefore, that a value of s, s^*, satisfies inequality (12); then there are values of the fusion, f, which divide the results between three possibilities (see Fig. 6): $f < f_{c1} \Rightarrow$ the only stable equilibrium is sexual extinction; $f_{c1} < f < f_{c2} \Rightarrow$ the only stable equilibria are sexual extinction or diploid extinction depending on initial conditions; $f_{c2} < f \Rightarrow$ the only stable equilibria are sexual extinction or competitive coexistence.

So we see that overactivity of the sexual fusion process has again caused problems for the sexual: between the critical values the sexual has a stable equilibrium all to itself, whereas below the minimum it is wiped out and above the maximum it can only coexist with the diploid. (Note that at $s = s_c$ we have that $f_{c1} = f_c = f_{c2}$.)

This result is interesting, since we have two species competing on a single resource. However, the sexual is actually spending much of its time in what appears to be a diploid state: that is, fusion is too high for the particular

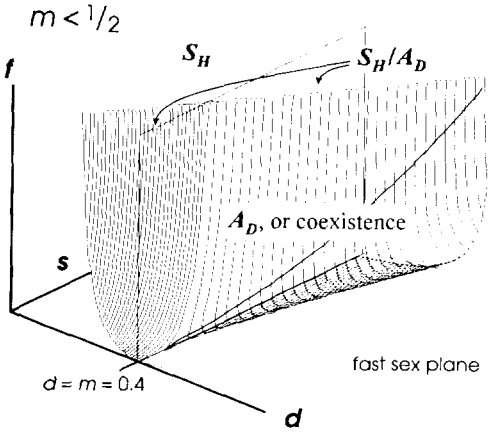

FIG. 7. Bifurcation diagram for sex and diploidy ($m = 0.40 < 0.50$). The winning species is indicated for the different regions: S_H = sexual, A_D = diploid, or coexistence. Behind the surface to the right of the $d = m$ plane, either the sexual or the diploid wins depending on initial conditions. A similar outcome occurs in front of the surface but to the left of the $d = m$ plane. In these regions, S_H/A_D, both the sexual and the diploid are stable when common and neither can invade when rare. In front of the surface the diploid wins, if $d > m$. However, the outcome of competition is more complex near the surface as coexistence of the two species is possible. See Fig. 6 in which a slice of the surface in the (f, s) plane is given. The line through the surface in Fig. 7 is the set of points (d, s_c, f_c) defined in Fig. 6.

value of splitting, so that too much of the life cycle is spent in the fused state where the sexual cannot reproduce.

We note that invasion from small numbers is not possible for either species, since each equilibrium is locally stable. Thus invasion would require a certain minimal "invasion force"; perhaps two media co-mingling.

The bifurcation diagram is presented in Fig. 7 for the case of sexual versus the diploid. While the fast sexual parameter space description can be considered as a tipping of the asexual plane towards the splitting/damage plane, this parameter space outcome is a twisting and bending of that plane.

We explicitly describe here the effect of the splitting parameter too, as it plays a simple but important role in the outcome. An increase in s is always good for the sexual. We use an automotive analogy to explain why this is so: fusion is analogous to the rate at which one sends a car to the shop when it needs repairs; splitting is like the rate at which the mechanics do the repairs. If we put cars in the shop at too great a rate (too great, that is, for the given repair rate), then they back up. Thus an excess of fusion is a bad thing from the sexual's standpoint. But increased splitting merely means that the repairs are being done more quickly, something about which no one complains (assuming, as we do, that the quality remains constant).

3.5. *Haploid Competition: Sexual vs Asexual*

The corresponding competition equations are

$$\begin{aligned} x' &= x(r-m-d-fz)+2sy \\ y' &= fz(z+x)-y(pm+s) \\ z' &= dx-z[m+f(2z+x)] \\ x'_a &= x_a(r-m-d) \\ z'_a &= dx_a-mz_a, \end{aligned} \tag{13}$$

where

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

In accordance with what we have found in the other models, we immediately solved for the parameter surface corresponding to an equilibrium resource value of $r = m+d$. This is the value of the free resources for which x_a, the haploid, is in equilibrium. For the entire system to be in equilibrium (with all populations non-zero), this condition must hold. (The assumption of $r = m+d$ only applies when $d < 1-m$ in Fig. 8) Once again

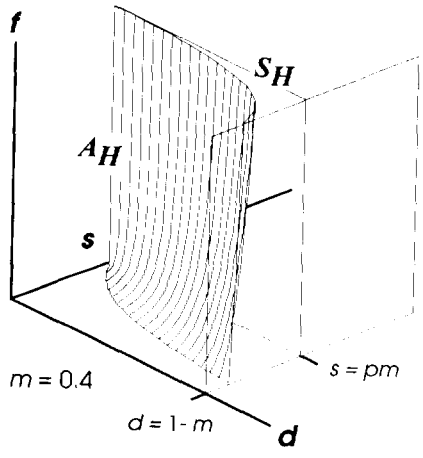

FIG. 8. Haploid competition. Results for $m = 0.4$ are given by a nearly vertical surface running along the damage axis, from no damage up to the critical damage value of $d = 1 - m$. The asexual wins for relatively low splitting values (s values in front of the surface), while the sexual wins when splitting is high (s values behind the surface). At the point when $d = 1 - m$, the asexual is no longer viable, since it has a negative rate of increase (see Eq. 13). However, the sexual may still persist in this region as discussed in Michod and Long (1994). Note that if $f = 0$ or $d = 0$, the sexual population behaves like the haploid.

we solve for the equilibrium values of the variables as a function of only one of the variables (and the parameters), and from these values we get a surface in three-dimensional parameter space of damage, splitting, and fusion which divides the outcome of competition between exclusion of the asexual or exclusion of the sexual (coexistence is not permitted). We have verified this analytical procedure by simulating the competition numerically (Fig. 8).

The outcome of competition is portrayed in Fig. 8. A critical value of fusion, f_c, determines the winner and is shown in Fig. 8 as a function of d and s for $m = 0.4$ (the expression is complicated and not given here). Likewise, a critical value of s, s_c, can be defined and is not so complicated. For $f_c = 0$ and $d < 1 - m$,

$$s_c(m, d) = \frac{pm^2}{m + 2d}. \tag{14}$$

At $d = 1 - m$, in other words at $r = m + d = 1$, there can be no equilibrium for the haploid, and it relinquishes any advantage it had to the sexual, which can still survive by virtue of the sexual cycle (Michod and Long, 1994).

We find that as $s \to pm$, $f_c \to \infty$ (Fig. 8). Consequently, the higher the fusion rate, the closer s must be to pm for sex to win. However, if splitting

gets above pm, the sexual always wins (no matter what the fusion rate is). The sexual generally loses for values of s lower than pm, although as shown in Fig. 8 there is a curtain that precisely determines the winner in this range. Recall that there was a region of coexistence in the competition between the diploid and the sexual (Fig. 7). However, the portion of this region for $d < m$ is completely contained in the region in front of the curtain shown in Fig. 8 for which the haploid defeats the sexual. As one might suspect based on this observation, we find in our analysis of three-way competition (see Fig. 9 below) that given the presence of the haploid there is no coexistence of the sexual with the diploid when $d < m$.

3.6. *Competition among All Three Populations: Haploid, Sexual, and Diploid*

By combining results from the competitions already obtained, we can deduce the behavior of the three-way competition. The result is shown in

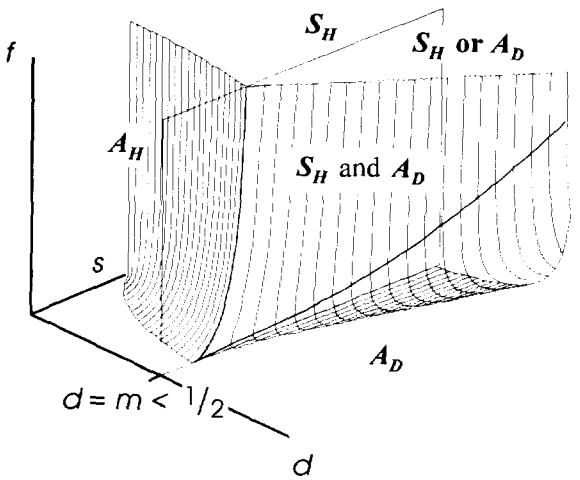

FIG. 9. Bifurcation surfaces for three-way competition in region $m < 0.5$. The winning species is indicated for the different regions: A_H = haploid, S_H = sexual, A_D = diploid. To the left of the $d = m$ plane only haploids win, with the asexual winning in front of the surface and the sexual winning behind the surface. To the right of the $d = m$ plane the winner is either the diploid or the sexual or both may coexist. Behind the surface (still considering $d > m$) either the sexual or the diploid wins, depending on initial conditions. That is, both the sexual and the diploid are stable when common, but neither can invade when rare. In front of the surface the diploid wins. However, the outcome of competition is more complex near the surface where coexistence of diploids and sexuals is possible. The surface has an interesting shape as shown in Fig. 6 and described in the Appendix. The surface bends back upon itself along the curve shown in the figure. This curve is identical to the set of points (d, s_c, f_c) defined in Fig. 6. The intersection of the three "surfaces" is the curve (discussed in the text) which is the only potential site at which all three populations could coexist. Its instability rules this out, however.

Fig. 9 (which is based on numerical study of the various competitions and eigenvalues). Figure 9 shows the region of the parameter space in which all species could survive and persist. For the diploid this requires $m < 0.5$.

The critical value of fusion discussed in the previous section gave us the curve on which all populations could survive in equilibrium. This curve is obtained by setting

$$r = 2m = m + d \Leftrightarrow d = m.$$

(The haploid would be in equilibrium, as $r = m + d$; the diploid would be in equilibrium, as $r = 2m$. And there exist parameter values for which the sexual is in equilibrium with them both). The equation for f_c than takes the form

$$f_c(m, d, s) = \frac{3s^2(p+3) + pm[-6s + p(m + 2s - pm)]}{2p^2(1-2m)(pm - s)}, \tag{15}$$

with $pm/3 < s < pm$ ($f_c(m, d, pm/3) = 0$ and $f_c(m, d, pm) = \infty$). This situation is "infinitely unlikely" and highly unstable, however, as it is a one-dimensional manifold in a three-dimensional space: any deviation from the corresponding equilibrium populations or parameter values would send the system careening away fom such an equilibrium.

We do not gain anything by further local stability analysis of the full system, as we can unite the analyses already performed. We have carried out analyses for each of the sub-systems given by removing one of the three species (purely asexual competition, sexual/asexual, competition and diploid/sexual competition). We have found that A_H cannot survive with A_D (at least in equilibrium) unless $d = m$ (as this implies that $m + d = 2m$: the equilibrium values of free resources in both cases are equal). If the diploid is at equilibrium, for $d > m$, then A_H is excluded; and if A_H is at equilibrium, for $d < m$, then A_D is excluded. So we see that we can again nothing by further linear stability analysis. There is thus no possibility for coexistent equilibria, given that the parameters stay fixed, unless it occurs in the plane $d = m$. We have studied that plane enough to know, however, that there can be no three-way stable equilibrium there, as mentioned above. There is only a single curve, for limited values of s and values of f from $[0, \infty]$, for which total coexistence is possible, and we have found that it is unstable.

One might find limit cycles, of course, or chaotic behavior: but we have not seen such behavior in our numerical experiments. The system is remarkably stable, even boring, in its relentless pursuit of equilibration.

3.7. *Sex with Reproduction: A First Approximation*

In the models studied so far, sex has nothing to do with reproduction. This is the reality of sex in many simple microorganisms. Conjugation and transformation in bacteria do not require nor elicit reproduction, while mixed infection in viruses does. The bacterium *Bacillus subtilis* is most competent at sex—that is, transformation—when it is in a stationary phase of growth and not reproducing. Since we are interested in the origin of sex and want to maintain some degree of generality, we have assumed that sex is not linked with reproduction.

We now assume that the sexual reproduces when in the fused diploid-like state, in what one can think of as a precursor of meiosis. Then, at first, the terms representing this new process might simply be incorporated into the equations just studied, i.e.,

$$x' = x(r - m - d - fz) + 2sy + 2kypr$$

$$y' = fz(z + x) - y(pm + s) - kyp\frac{r}{2}$$

$$z' = dx - z[m + f(2z + x)]$$

$$w' = wp\left[\frac{r}{2} - m\right]$$

and

$$r' = r'_{\text{previous}} - kypr,$$

where k is a parameter representing the relative rate of this reproduction compared to the rate of reproduction of the diploid (so that if $k < 1$ the meiotic reproduction is slower, while if $k > 1$ it is faster).

It is easy to understand this change, however, in terms of the A_H/S_H competition model: these equations are effectively equivalent to an increase in s, with a slight boost to the growth rate of x and a slight decrease in the growth rate of the resources, as one can see by rewriting them as follows:

$$x' = (r - m - d - fz) + 2\left[s + kp\frac{r}{2}\right]y + kypr$$

$$y' = fz(z + x) - y\left[pm + \left(s + kp\frac{r}{2}\right)\right]$$

$$z' = dx - z[m + f(2z + x)]$$

$$w' = wp\left[\frac{r}{2} - m\right].$$

And as we have seen, an increase in s always has a beneficial effect on the sexual. The splitting rate is no longer constant, but varies as a function of time (but in an autonomous way).

It would be interesting to actually replace the splitting parameter by the meiotic reproduction term. We have not done so, but plan on doing so in the future. We also would like to introduce non-autonomous effects into the parameters, to take into account changes like the variation in UV light throughout the day (and night): we know that these parameters are not constant in any real system, and so we would prefer to model them as well.

4. Discussion

4.1. *Assumptions*

4.1.1. *Mass Action.* We use the principle of mass action in modeling the dynamics of cell interactions, such as fusion between sexual cells, and the use of nucleotide resources to produce cells. This principle states that the rate at which a reaction proceeds is proportional to the densities of the reagents. It is important to note two consequences of the mass action assumption. First, cells have rates of reproduction proportional to the total resource density. Second, if a cell type requires twice the resources (and, consequently, twice the number of resource interactions) as does another cell, then its rate of reproduction must be less than that of the other cell type, *all else being equal* (for example, no intrinsic differences between cell types). In the Appendix (in the section titled *Diploid Dynamics*), we show that the effective diploid birth rate is $1/(\sqrt{2}+1)$ ($\approx 2/3$) the rate of the haploid, in the absence of any size or other intrinsic differences between haploid and diploid cells. This baseline difference in effective birth rates between diploid and haploid cells results directly and necessarily from the assumption of mass action made in our models.

We make additional assumptions that ameliorate this baseline disadvantage of diploidy in replication. We assume a size difference ($p > 1$) which favors diploid replication. We also assume an intrinsic advantage, $\beta > b$, to diploid cells. As a result of these additional assumptions, the ratio of diploid to haploid birth is $p/2 \approx 3/4$ in the model we studied (see Appendix).

4.1.2. *Size of Cells.* For mathematical convenience, we made the following simplifying assumptions about the relative sizes and shapes of the interacting cells: we assumed that all cells are spherical, that all haploids are the same size, and that the size (volume) of a diploid cell may be larger than that of a haploid cell. We represented any size difference in terms of a parameter, p, that represented cell surface area. Cell surface area is

assumed to affect both reproduction and mortality. We assumed that the rate of uptake of genetic resources is a linear function of the surface area. We also assumed that cell death is primarily a function of disruption of the cell membrane and so is also proportional to surface area. The cell wall serves as both the limiting factor in feeding and a risk factor for mortality: to be bigger means more energy and nutrients, which means faster growth; but is also makes one more vulnerable to any membrane-disrupting factors in the environment.

Research on current unicellular organisms, like yeast, supports the view that diploids are usually larger than haploids. There is a strong positive correlation between the amount of DNA and the size of a cell (see references in Lewis, 1985). Herskowitz says that diploids "...have a volume nearly twice that of haploids..." (1988, p. 357). Mortimer (1958) found that cell volume scales linearly with ploidy from haploid, diploid, up to hexaploid cells. Weiss *et al.* (1975) observed a diploid to haploid volume ratio of 1.57 for minimal growth medium. If we assume that diploid cells are spherical and have twice volume, they would have about 1.59 times the surface area of a haploid cell. For this reason, we set $p = 1.59$ in many of the studies we report here. However, environmental conditions can affect the relationship between ploidy and cell volume. Adams and Hansche (1974) and Weiss *et al.* (1975) found that the size and metabolism of yeast cells are complex functions of resource limitations. In the extreme case of carbon starvation, the diploids and haploids differed only on the amount of DNA in their cell bodies: the diploids reacted to this environment by becoming smaller. All other measured cell constituents were equal, including the quantities of RNA, the cell volumes and the surface areas. If we wanted to represent this situation, we would set $p = 1$.

Another important issue is the size of the fused sexual cells. The various types of prokaryotic sex and viral sex result in a rather wide range of fused types. For anisogomous sex, we would need to consider two separate cell types for the sperm and eggs; the same can be said for transformation. We do not consider anisogomous kinds of sex in our models. In conjugation, the two cells must be in contact, but there is no combination of cytoplasm (only an exchange of DNA). The geometry in conjugation would be much different than we assume in our model. In conjugation, fused cells would have twice the surface area of haploids, rather than 1.59. We agree with other workers that at the time of the origin of sex (before anisogamy and before meiosis; perhaps before chromosomes) the most likely sort of interaction that two cells could have would be such a total fusion event. For example, Crow (1998) states: "I share the commonly held view that the original development of meiosis and fertilization involved isogamous fusions". For these reasons and, admittedly, for the resultant mathematical simplicity, we have chosen to assume that fused haploids are spherical and

contain twice the cytoplasm of haploids and, hence, about 1.59 times the surface area.

4.1.3. *Resource Use.* In the present paper, we study the selection on haploidy and diploidy that results from their differing capacities to both replicate efficiently and repair genetic damages. Free genetic resources, in density r, are available to all cell populations as building blocks. By resources in our models we mean genomic resources, such as nucleotides. We assume that there is a fixed quantity of genetic resources, enough to provide for the genomes of a population of N haploids.

In other words, free resources are equal to N minus the sum of cell populations, in which the numbers of diploid cells (fused haploids plus diploids) are multiplied by 2 since they contain twice the genetic resources of a haploid cell.

We study closed systems, so that cell populations are constrained to a maximum number because of the limitation of genomic resources. We assume that all other non-genomic resources exist in whatever quantities necessary for unrestricted cell replication. We represent nucleotide resources in terms of resource packets containing a single (haploid) "copy-equivalent" of the primitive genome. For example, there may be enough nucleotides present for the existence of 1000 haploids cells, but there may be only 100 such cells present. In the absence of other cell types, that means that there are 900 resource packets available, not currently incorporated into a cell. We refer to the 900 resources packets as "free resources", to distinguish them from the 1000 "total resources" and the 100 "bound resources". We found that it is informative to study the levels of free resources maintained by a species, as it may determine which species wins in open competition (for explicit examples in the case of the diploid/sexual competition, see the Appendix).

The relative abilities of haploid and diploid cells to use resources and nutrients in replication have been considered by several workers. According to the r and K-selection hypothesis of Cavalier-Smith (1978), expanding populations favor small cell size which favors haploidy. Conversely, increasing cell size is favored in stationary populations that are K-selected and this favors diploid cells.

The "nutrient scarcity hypothesis" recognizes that the replication rate of a cell depends on the uptake of both energy and nutrients (Lewis 1985). In a single-celled organims, small cell size is favored when nutrients are scarce. Since DNA content is positively correlated with cell size, scarcity of nutrients also favors haploidy. Several reasons are considered for this. Haploid cells have an increased surface-area-to-volume ratio and so should have more efficient uptake of nutrients. Haploid cells also have less DNA to replicate and so may require less of the critical nutrients that are used in DNA, such as phosphate.

In the isomorphic brown alga *Gracilaria verrucosa*, Destombe *et al.* (1993) found that haploid individuals grew faster than diploids in regular sea water, while diploid individuals grew faster than haploids in enriched sea water. Similar results have been reported for haploid and diploid strains of the yeast *Saccharomyces cerevisiae* (Adams and Hansche, 1974). Destombe *et al.* (1993) interpreted their results as supporting Lewis' (1975) nutrient scarcity hypothesis but invalidating Cavalier-Smith's hypothesis (1978).

4.1.4. *Mating System.* A sexual cell has, by definition, a mate, even if the "mate" is nothing more than a strand of DNA, as is the case in transformation. In constructing the models, we need to consider whether a sexual mutant, arising in a wild-type asexual population, would be free to mate with asexuals. In the present paper, we assume that sexuals only mate with other sexual cells. In Michod and Long (1994), we relax this assumption and study the case in which sexual and asexual cells may fuse, as if in a Mendelian-like population.

Here we assume that damaged sexual cells initiate sex. We began the present study by assuming that healthy sexual cells mated at random with other haploid sexual cells, resulting in recovery of damaged brethren if the mating happened to include them. The results were clear: if mating is random, asexuals always win. This is no longer the case if sexual cells sometimes mate with non-sexual cells: that is, random-mating sex may be competitive under a wide range of conditions (Michod and Long, 1994). We then assumed that sex is initiated by damaged cells that mate at random with either damaged or undamaged cells. As reported here, the results are strikingly different: sex is stable under a broad range of the relevant parameter values and can, in fact, drive out the asexual population.

One may wonder whether it is reasonable to assume this type of "damage-induced" sex in such simple systems. Several lines of evidence suggest that it is a strategy employed by a variety of mircroorganisms. Recombination is generally induced by DNA damage in phage, bacterial conjugation, yeast, and even in Drosophila and mammalian cells (Bernstein, 1983). Natural genetic transformation rates are increased by damaging recipient cells (Michod *et al.* 1988; Wojciechowski *et al.* 1989; Hoelzer and Michod, 1991). Bernstein (1987) showed that damage induces sex in T4 phages. When healthy phage infect their hosts, they erect a barrier against other phage infestation, 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. Bernstein and Johns (1989) found that the addition of hydrogen peroxide

to cultures of the yeast *Schizosaccharomyces pombe* resulted in a dramatic increase in the percentage of sexual spores versus asexual spores. Therefore, damage-induced sex seems to be the norm in many cases, rather than an aberration. 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 have sex.

We prefer the assumption that sex is damage-induced for at least two additional reasons: (1) in the event that damage disappears, the sexual acts exactly like an asexual haploid, and (2) it seems hard to imagine that nature would not eliminate the useless fusion and splitting of perfectly healthy cells if it were without merit.

What is remarkable is the robustness of the system to the changes we have made. As just mentioned, we originally assumed that the healthy sexual initiated the repair, so that all three of the sexual terms were different; we also originally modeled resource uptake in the diploid as r-squared phenomenon, which really corresponds to chemical reactions requiring simultaneous encounters, rather than the accrual of resources over a period of time (as we imagine our cells doing). In spite of these changes in the forms of the equations, there has been little qualitative change in the form of the dynamics, bifurcation diagrams, or other pertinent features.

4.1.5. *Recovery from Damage.* There are two sources of mortality and death in the models we study: cell mortality, caused by disruption of the cell membrane, and gene death from genetic damage. The interplay of these two kinds of mortality is discussed further in Michod and Long (1994, Fig. 2). Gene death is reversible by repair, whereas cell death is not.

We assume in our models that diploidy is a haven against damage: the diploid cell, whether it is generated asexually or sexually via fusion of haploids, is not subject to damage in our models. In organisms like viruses, bacteria, and yeast, in which the ploidy level can be varied by experimental conditions, diploid cells are generally much more resistant to DNA damage than haploid cells. For example, in the yeast *Saacharomyces cerevisiae*, Herskowitz states simply that "...diploid cells are better than haploid cells in coping with DNA damage..." (Herskowitz, 1988, p. 544, and references cited therein). Thus, we assume that any damage suffered by the diploid in one of its genes is immediately repaired by the corresponding good copy. We do not model this repair process explicitly, but imagine it to be accomplished through a process akin to primitive forms of recombination—such as hypercyclic cooperation (Bernstein *et al.*, 1984; see also Fig. 10). Recovery from genetic error in the diploid state is assumed to be

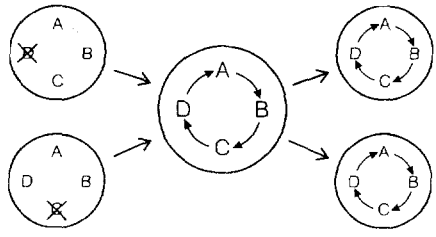

FIG. 10. Recovery from damage. This diagram, adapted from Bernstein *et al.* (1984), represents a simple possibility for the type of sexual cell interaction considered in this paper. Cells damaged on different genes can combine to produce a pair of normal cells, due to "hypercycle regeneration" of the lost or damaged constituents from a good copy in the other cell. In a similar manner, diploid cells are able to maintain a set of undamaged genes.

instantaneous and cost-free. Thus, we demand as much from the sexual process as we possibly can, since fusion and splitting take time away from replication.

Although we do not explicitly model the internal workings of the protocell, we make assumptions consistent with the hypercycle model as developed by Eigen and Schuster (1979) and as applied to the problem of the origin of sex by Michod (1983), Bernstein *et al.* (1984), and Michod *et al.* (1990). The general idea is that as long as the production of each gene is catalyzed by one or more of the other genes in the genome, and in turn catalyzes the production of one more of the other genes, a cycle develops in which the numbers of different genes have stable equilibria or stable periodic behavior (Eigen and Schuster, 1979). If the number of functional copies of a particular gene is perturbed by DNA damage, the hypercycle restores the number of copies. The implications of this characteristic of hypercycles for the evolution of sex and diploidy are shown in Fig. 10. We start with two haploid cells with an unsegmented genome and damages in different genes. In each of these cells the hypercycle cannot be established, since there are no good copies of one of the component genes. However, upon fusion there is at least one good copy of each gene and the hypercycle can be established resulting in a full set of healthy genes. Similar recovery from damage is assumed to occur in diploid asexual cells. Bernstein *et al.* (1984) referred to this recovery from error as "hypercyclic cooperation", and hypothesized that it was a kind of genetic repair that preceded recombinational repair of genes linked on chromosones.

4.2. *Related Work*

Szathmary *et al.* (1990) have considered the problem of the origin of sex and diploidy and concluded that under conditions of no damage the ranking of competitive abilities of cells should be haploid > diploid > sexual. In a damaging environment, they conclude that the ranking should

be diploid > sexual > haploid. Their conclusions are based, for the most part, on verbal arguments and not explicit mathematical models. These conclusions are not supported by our models. The models analyzed by Szathmary *et al.* (1990) are different than the models analyzed here in several fundamental respects. Szathmary *et al.* (1990) did not explicitly model a damaged population of cells that can be recovered by sexual repair. They also did not explicitly model asexual diploid cells. Competition involving resource use was not modeled explicitly either. Instead, they used Eigen and Schuster's (1979) chemostat approach of "constant overall organization" (counting fused haploids (diploids) as having twice the "mass" of unfused haploids). In this approach, total cell mass is kept constant and any overproduction of the system is simply subtracted to make the net change for the system zero.

Bernstein *et al.* (1984) also modeled the origin of sex using computer simulations and discrete generation population genetics models. Their complex computer models (the so-called "state-matrix" and "streamlined" models) are difficult to interpret, and this was part of the impetus for the present study. Although the specific details of the models differ (for example, they considered sex with reproduction), our results are generally consistent with theirs in that sex can outcompete diploidy under certain conditions. However, the conditions found here in which sex can win in competition with diploidy are more restrictive than those reported in Bernstein *et al.* (1984, Fig. 5). For example, Bernstein *et al.* (1984) reported no effect of the fusion and splitting rates on the outcome of competition, while we find that it depends critically on these parameters of the sexual cycle (Fig. 7). Nor did they report the coexistence of diploid and sexual forms that can occur above the bifurcation surface shown in Figs. 6 and 8.

4.3. *Effects of Various Parameters in the Model*

We now summarize the various parameters in the model, their effects on the dynamics, and the eventual outcome of competition.

b: This is the only truly creative force in the model: if there is not enough cell production, then the cell populations are doomed if death is sufficiently strong (we come back to that in a moment). In the process of non-dimensionalizing the system we divided everywhere by b, so that the new non-dimensionalized parameters were actually ratios of rates. When these parameters are discussed it must be understood that they represent the strength of the named process relative to birth.

m: If $m \geqslant \frac{1}{2}$ (that is, if $m/b \geqslant \frac{1}{2}$), then death of the diploid is assured. If $m \geqslant 1$, then the haploids are doomed. This is due to the fact that death is the only truly destructive force, whereas birth is the only creative force:

if the destruction is more active than the creative process, there can be only one result. Beyond that, the value of m does not seem to have any qualitative effect on the form of the bifurcation diagrams in parameter space shown in the figures. The parameters m does have a special role, however, as it affects the equilibrium population levels. The larger m becomes, the larger the free resources are at equilibrium and thus the smaller the quantity of resources stored in the cell populations (until at $m = \frac{1}{2}$ there are no resources stored in diploid cells and at $m = 1$ there are no resources stored in haploid cells). Cell mortality also serves to recycle damaged cells into resources. Consequently, healthy cells are most frequent at intermediate levels of mortality (see Figs. 3 and 4 of Michod and Long, 1994).

d: Damage has the following general effect: for little damage, i.e., $d < m$, there are two potential haploid outcomes: the sexual cycle excludes the asexual cell types or the haploid cell wins. Beyond that point the haploid cannot go, and the sexual cycle is always vulnerable to extinction in this range ($d > m$). The parameters of the sexual cycle (i.e., f and s) are able to rescue it from any values of d and $m (m < 1)$, in the sense that they transform the unstable sexual equilibrium to a stable one. If the fusion gets too large, however, it destabilizes again in favor of a coexistent equilibrium. It may be, however, that for large values of d, the f and s values required to save the haploid sexual would be unrealistically large.

f: Fusion is the most interesting of the parameters, in that its role is sometimes positive and sometimes negative for the sexual cycle. Fusion is necessary for the sexual to repair damages and if, in a situation of punishing damage, this ability is not exploited, then the sexual cycle goes extinct. For cases of low damage, such that $d < m$, the parameters of the sexual cycle (f and s) can only have one effect for the S_H/A_D competition: if the sexual cycle is too active, then the diploid gains the ability to survive when otherwise it would not. That is, the diploid is at a disadvantage for low damage, and can only overcome it if the haploid starts wasting time repairing inconsequential damage. If the sexual is, in fact, wasting time, then it would be vunerable to the presence of another haploid, one which would not interact sexually with the sexual. The same phenomenon takes place in the case of high damage, $d > m$, except that in that case there are a few new possibilities. First of all, no haploid could survive to challenge the sexual.

In the absence of the sexual process the diploid would eliminate the haploid, so long as mortality was not too high. If the value of f is sufficiently high, so that the sexual cycle could conceivably survive and beat the diploid, then pushing it higher eventually means that the sexual cycle loses its competitive edge and coexistence becomes one of the two possible

options (diploid exclusion of the sexual cycle is always a possible outcome). So fusion is a two-edged sword for the sexual cycle.

s: Splitting tells us how fast the repair process is accomplished. The larger s is, the better off the sexual cycle is (no matter what region of parameter space we are in). For $d > m$, there is a critical value of s which must be attained before the sexual cycle can survive (given any value of f). Once this value is attained, then the fusion parameter f can be tuned to give us one of the three outcomes possible:

f small: diploid wins;
f medium: competitive exclusion of one by the other;
f large: diploid wins, or coexistence.

4.4. *Summary*

The sexual has several parameters at its disposal, in the sense that selection could mold its sexual cycle in any of several different directions (increased fusion, decreased splitting, etc.). We have seen that if damage is low there is a tradeoff between sexuality and asexuality, but that haploids generally beat the diploid due to their superior replication rates. If a sexual uses more fusion than necessary, it relinquishes its superiority to an outcome of competitive coexistence with the diploid (if the haploid is absent). In competition with the haploid, selection might eliminate a "fusion-happy" sexual, perhaps by back-mutation to a haploid in that case.

The asexual haploid cannot cope with high damage. So, when damage is high, only the sexual can compete with a diploid. The sexual cycle must maintain a minimum level of activity before the sexual can even begin to compete with the diploid. If this condition is met, then initial conditions give the outcome to one or the other of the two species or to competitive coexistence. The actual outcome is a function of initial conditions. Our computer experiments have failed to produce interesting dynamical behavior (periodic limit cycles or chaos), and we believe it unlikely that such behavior is possible in this system (for biologically reasonable parameter values) in spite of the large number of free parameters and dimensions.

APPENDIX

A.1. *Diploid Dynamics*

In Fig. A1, we present a schematic diagram of the full competition, in which each flow translates into a term in the accompanying equations. The variables u and v parameter β relate to the diploid cell type and are described below.

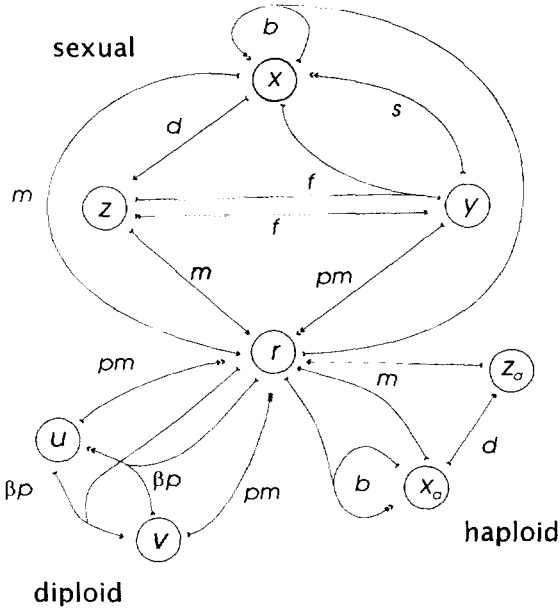

FIG. A1. Flow of cells for complete competition model. See legend to Fig. 2.

The flows in Fig. A1 result directly in the following eight-dimensional system of first-order, nonlinear, ordinary differential equations:

$$x' = xbr + 2sy - xm - xd - fxz$$

$$y' = fz^2 + fzx - ypm - ys$$

$$z' = dx - zm - 2fz^2 - fzx$$

$$u' = 2\beta pvr - \beta pur - mpu$$

$$v' = \beta pur - \beta pvr - mpv$$

$$x'_a = x_a br - x_a m - x_a d$$

$$z'_a = dx_a - mz_a$$

$$r' = zm + xm + 2pym + 2um + 3vm + z_a m + x_a m - brx - brx_a - \beta prv - \beta pru.$$

Since diploids must encounter two resource packets before they can divide, there are two distinct types of diploids in the model in Fig. A1: those which already have encountered one resource and "seek" a second and those which have yet to find their first resource packet. We call the first

type a "charged" diploid and the second type "uncharged". By assuming mass action kinetics, we simplify the diploid species in the following way. Let u be the population density of the uncharged diploid and v the density of the charged diploid. The following reactions are assumed to occur when the diploid cell type is alone (β is a parameter representing the birth rate of the diploid):

$$u + r \xrightarrow{\beta p} v$$

$$v + r \xrightarrow{\beta p} 2u$$

$$u \xrightarrow{mp} 2r$$

$$v \xrightarrow{mp} 3r$$

These reactions translate into the following equations:

$$u' = (2\beta vr - \beta ur - mu)\, p$$

$$v' = (\beta ur - \beta vr - mv)\, p$$

$$r' = [m(2u + 3v) - \beta(v + u)\, r]\, p.$$

We note that these equations must sum to one and so can be replaced by a system of two equations (because of the relation $1 = r + 2v + 3w$, which expresses the fact that the number of resource packets contained inside a v cell is 2, whereas the number contained in a w cell is 3). We choose the first two equations to study further.

Equilibrium implies that $u' = v' = 0$ and, for the interesting case of non-extinction ($u \neq 0$ and/or $v \neq 0$), we find that

$$r = \frac{mu}{2v - u} = \frac{mv}{u - v} \Rightarrow u^2 = 2v^2 \Rightarrow u = \sqrt{2}\, v$$

for biologically reasonable populations. This equilibrium turns out to be stable, which raises the possibility of replacing the two variables u and v by one variable, say w, and using the equilibrated value for the new variable. We add the two equations and substitute the equilibrated value of u to get a single equation:

$$(u + v)' = [\beta vr - m(u + v)]\, p \Rightarrow (\sqrt{2}\, v + v)' = [\beta vr - m(\sqrt{2}\, v + v)]\, p$$

$$\Rightarrow v' = \left[\frac{\beta}{\sqrt{2} + 1} r - m\right] vp.$$

The effective birth rate of the diploid is given by the term $\beta p/(\sqrt{2} + 1)$ in the last equation. If we were to assume that the only difference between

the haploid and diploid resource utilization is cell size (represented by the parameter p) and not, for example, different membrane properties, we would take $\beta = b$. Such a choice puts the effective diploid birth rate at $p/(\sqrt{2}+1)$ or approximately 2/3, the rate of the haploid. Instead of working with a factor of $p/(\sqrt{2}+1)$ in the following models, we chose to give the diploid an additional advantage, by taking $\beta = ((\sqrt{2}+1)/2)\, b$ (approximately 5/4 of the haploid rate). This says that the diploid is better able to absorb resources than the haploid. As a result the effective diploid birth rate simplifies to $p/2$, or approximately 3/4 that of the haploid. The differential equation for the diploid's rate of growth simplifies to the following, now using the new variable w,

$$w' = \left(\frac{br}{2} - m\right) wp.$$

We use this equation for the diploid in the simplified model discussed in the paper.

A.2. *Mathematical Methods*

We describe here the mathematical methods used in our analyses. In all cases, we determined the stability of all biologically realistic equilibria as the parameters of interest changed. We began by solving the system of differential equations for equilibria. This always yielded the trivial equilibrium of extinction along with more interesting equilibria. In several cases we ended up with a complicated quartic equation, $Q(z) = 0$, in one of the unknown variables, z, the density of the damaged sexual haploid cell. The coefficients of that quartic are combinations of the parameters m, d, s and f (which actually represent ratios of m, d, s and f to b, the birth parameter). In order to find realistic equilibria, we solve $Q(z) = 0$ for the four z values (which are themselves functions of the parameters) and check to see, for a given set of parameter values, which of the four roots correspond to biologically meaningful solutions; in other words, solutions for which population densities are all positive (including the density of free resources). The fact that a quartic equation has four roots sets an upper bound on the number of realistic equilibria, but does not tell us how many there are, and as we vary the parameter values we see that the number of realistic equilibria varies. Equilibra pop in and out of the parameter space as the parameters of the quartic vary. The stability properties of the equilibria also change. We have tried to represent and understand this process through the figures and discussion in the text.

All the critical surfaces and curves we have drawn in the figures are obtained by varying parameters and checking the number and stability of the resultant equilibria. All figures are drawn in parameter space, which

leads to a potential cause of confusion: the surfaces drawn in our figures do not represent separatrices in population space that typically divide the space into regions corresponding to different equilibria for a certain fixed set of parameter values. The parameter surfaces we draw determine the number of realistic equilibria for a given set of parameter values, and whether they are stable or unstable.

By looking at pairwise interactions, we found that the parameter space representation of the equilibria could be scaled by one of the parameters (we chose to scale out m). This allowed us to reduce our representations from four dimensions (f, s, m, and d) to three (f, s, and d). It is not an exact or simple scaling, but we find upon examining the three-space parameter diagrams for varying values of m that the surfaces are qualitatively the same (when properly scaled) across the spectrum of permitted values of m.

As a specific example of what we did, consider the pairwise competition of the sexual and diploid given by the equations (11). Setting the right-hand side of the equations (11) equal to zero gives a quartic in z, $Q(z)$. Any equilibrium requires either $w=0$ or $r=2m$. Considering coexistent equilibria, $r=2m$, $Q(z)$ simplifies to a quadratic giving two roots, G_1 and G_2 as functions of m, d, s, and f:

$$Q(z)=0 \Rightarrow \text{quadratic}(z)=0 \Rightarrow z_{\text{eq}}=\{G_1(m, d, s, f), G_2(m, d, s, f)\}.$$

In fact, we find

$$G_1=\frac{g_1(m, d, s)}{f},$$

which says that the quadratic's discriminant, $\Delta(m, d, s)$, is independent of f. So, for any values of the parameters m, d, and s, we get roots which are scaled by f. (However, the quartic's roots are not invariant under multiplication by f.) When $\Delta=0$, the roots of the quadratic change from being complex to being real. In addition, when $\Delta=0$ there is a double root, in other words, a root for which the quadratic and its derivative equal zero. Solving $\Delta(m, d, s)=0$ for s as a function of m and d gives a critical value of splitting, s_c, that must be exceeded for the sexual to win (see Eq. (12) of the text). In summary,

$$\Delta(m, d, s)=0 \Rightarrow s_c(m, d)$$

Now we obtain the critical value of fusion, f_c, corresponding to s_c. The double root $z_{\text{eq}}=G(m, d, s_c(m, d), f)$ must satisfy the original quartic,

$$Q(z_{\text{eq}})=Q(G(m, d, s_c(m, d), f))=0.$$

Using this equation we solve for the critical value of $f = f_c(m, d)$ that is plotted in Figs. 6 and 7.

We used these critical surfaces as guides in our numerical analyses of the differential equations. We iterated all differential equations, in all competitions studied, using the International Mathematics and Statistics Library implementation of the Runga–Kutta 4 algorithm, with automatic step-size control. We used the numerical results to confirm algebraic results.

Our method of finding mutual equilibria focuses on the resources, since the values of equilibrium resources were generally easily obtained and since a necessary requirement for mutual equilibration is that equilibrium resources be the same for each set of equations. For example, the asexual competition is represented by the following system of equations:

$$x_a' = x_a(r - m - d)$$

$$z_a' = dx_a - mz_a$$

$$w' = wp\left(\frac{r}{2} - m\right).$$

For haploid equilibration we demand that $x_a' = 0$, $\Rightarrow r = m + d$, while for diploid equilibration we require that $r = 2m$. For both cell types to equilibrate at the same time, we demand that $r = 2m = m + d$, $\Rightarrow m = d$. Thus we see that by using the resource equilibrium values we have obtained a non-trivial result: that for coexistence of the asexuals (in equilibrium) we require $m = d$. It is possible, of course, that they share a non-equilibrium coexistence, but we have not observed such behavior in the numerical experiments.

The equilibria of the equations, points in the population space of (haploids, sexuals, diploids, resources), were determined algebraically (as in the cases above) and numerically otherwise. Although we have not presented our results here in population space, the coalescence of equilibria in the population space occurs by what are called "transcritical bifurcations": equilibria exchange stability at their meeting by exchanging eigenvalues through zero in the complex plane. The stability of an equilibrium point is conditioned on having all eigenvalues of negative real parts. Often an equilibrium may have a single eigenvalue of positive real part, in which case it may gain stability by trading away that eigenvalue for one with a negative real part (which costs the other equilibrium its stability, since any one positive real part is enough to render an equilibrium unstable).

In Fig. A2, we show how to relate the parameter space surfaces in Fig. 6 to population space equilibria. The parameters m and d are fixed in all fives panels at $m = 0.40$ and $d = 0.45$. For these parameter values, the diploid alone is always stable. The sexual alone may also be stable, or it may

coexist with the diploid, depending on the values of the fusion and splitting parameters. Recall that equilibria for the sexual alone are determined by a quartic, while equilibria for representing coexistence of the sexual with the diploid are determined by a quadratic. In Fig. A2, we present a series of six panels. In panels a through e, the quartic and quadratic discussed above are graphed as functions of z for different values of the fusion and splitting parameters. In each of theses panels the quadratic curve is the curve that starts from below and increases as z first increases from $z=0$. In panel f is shown the bifurcation diagram from Fig. 6. The different parameter values of s and f used in panels a–e are plotted and labeled in panel f. We need only consider z because the equilibrium values of all other population variables are specified once the equilibrium value of z is determined. As the parameters s and f change, the relative positions of the roots of the quartic and quadratic change. When two roots cross, one from the quadratic and

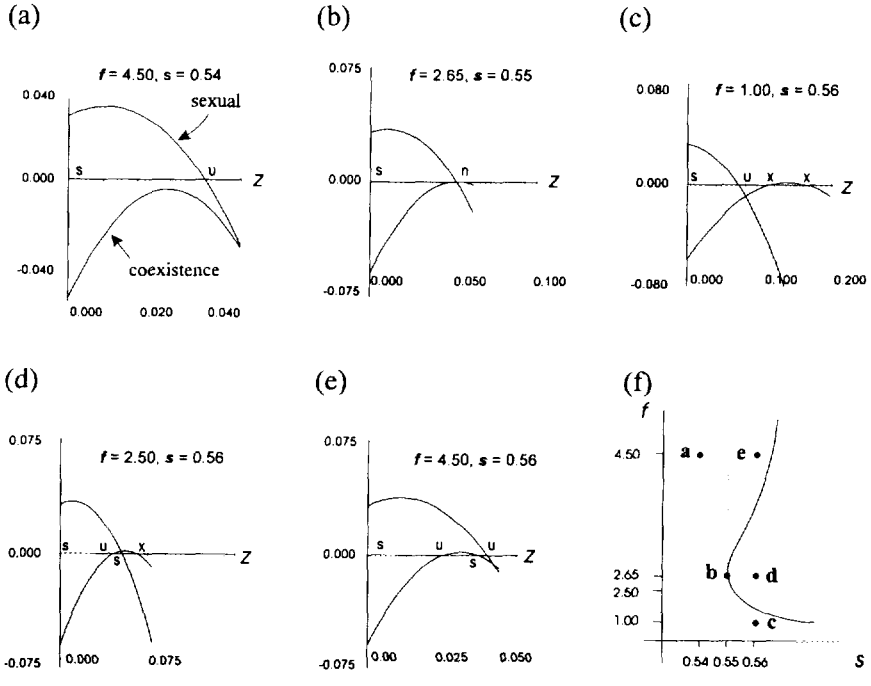

FIG. A2. Relation of bifurcation diagram to population space for competition between diploid and sexual. In panels (a)–(e), the quartic and quadratic curves discussed in the text are graphed for different fusion and splitting rates and $m=0.40$, $d=0.45$. In panel (f), the different combinations of fusion and splitting rates given in panels (a)–(e) are plotted and labeled on the bifurcation surface from Fig. 6. Properties of the various equilibria are designated near the points as follows: s stands for stable, u for unstable, n for neutrally stable and x for biologically unrealizable. The pure diploid equilibrium ($z=0$) is always stable for $m=0.4$, $d=0.45$. See text for further explanation.

one from the quartic, we generally see an exchange of stability of these roots. These exchanges are represented by surfaces of our parameter space representations.

In panel a, the splitting rate is a little too low, $s = 0.54$, for a fusion rate of $f = 4.50$ and the diploid wins. The quadratic has no roots and the root of the quartic is unstable. In panel b, the splitting rate has increased slightly to $s = 0.55$, while the fusion rate has dropped to $f = 2.65$. All three equilibria now meet at one point, resulting in neutral stability with extinction of the sexual and persistence of the diploid.

In panel c, the fusion rate is $f = 1.00$, while the splitting rate is $s = 0.56$. The sexual type now has an equilibrium alone at $\hat{x} = 0.1010$, $\hat{y} = 0.0102$, $\hat{z} = 0.0707$, $\hat{w} = 0$, and $\hat{r} = 0.808$, but the fusion rate is too low for it to be stable. One of the two coexistence equilibria is unstable and the other is neutrally stable. Consequently, only the diploid alone is stable.

In panel d, the parameters are $f = 2.5$ and $s = 0.56$. The equilibrium for the sexual alone of $\hat{x} = 0.1114$, $\hat{y} = 0.0182$, $\hat{z} = 0.0531$, $\hat{w} = 0$, and $\hat{r} = 0.7990$ is now stable and reached from some (for example, $\hat{x} = 0.0718$, $\hat{y} = 0.0118$, $\hat{z} = 0.0445$, $\hat{w} = 0.0010$) but not all initial values. For some initial values the diploid alone wins. One of the two coexistence equilibria is unstable and the other is biologically unrealizable.

In panel e, the parameters are $f = 4.5$ and $s = 0.56$. The equilibrium of $\hat{x} = 0.1126$, $\hat{y} = 0.0230$, $\hat{z} = 0.0400$, $\hat{w} = 0$, and $\hat{r} = 0.8014$ for the sexual alone is now unstable. The quadratic gives two roots, the second of which is stable: $\hat{x} = 0.9433$, $\hat{y} = 0.0181$, $\hat{z} = 0.0367$, $\hat{w} = 0.0163$, and $\hat{r} = 0.8000$. Consequently, coexistence of the diploid and haploid is stable for these parameter values.

As noted in the text, we find that the sexual can compete, or coexist, with the diploid when it consumes as many, or more, resources at equilibrium as the diploid. The resource level for the diploid at equilibrium, either alone or in coexistence with the sexual, must be $\hat{r} = 2m = 0.8$ for the competitions just described (recall the equation for the diploid in Eqs. (5) and (11)). In panel c, the equilibrium resource for the sexual alone is $\hat{r} = 0.8080$ which is greater than for the diploid alone, $\hat{r} = 0.8$, so the diploid wins. Note that the level of free resources is inversely related to the level of resources consumed by the cell types. In panel d, free resources at the all-sexual equilibrium are $\hat{r} = 0.7990 < 0.8000$, so the sexual wins for certain initial conditions, namely, when there are sufficient numbers of sexual cells to begin with. However, the all-diploid equilibrium is also stable (as it always is for $m = 0.40$ and $d = 0.45$) at which free resources are $\hat{r} = 0.8000 > 0.7990$. Counter examples of this kind—where sex cannot invade when rare even though it more effectively converts resources to cells–are the basis for our qualification in the text that consumption of resources at equilibrium *usually* predicts the outcome of competition.

In panel e, the free resources at the all-sexual equilibrium are $\hat{r} = 0.8014 > 0.8000$ and so the all-sexual equilibrium is unstable and the coexistence equilibrium is stable as is the pure diploid equilibrium.

The surfaces and curves which we have shown in the figures have the following interpretation in this context. At the surfaces shown in the figures, the stability properties of population equilibria are changing. At the surface, several equilibria are meeting at once, so that there are several eigenvalues being exchanged simultaneously through zero. If the corresponding imaginary parts at such meetings were non-zero, then we would have Hopf bifurcations; and while we have seen Hopf bifurcations for this system, we have not seen any for biologically reasonable population values (i.e., non-negative values such that their sum is less than the total resources permit). While we are not able to prove that more exotic dynamical behavior is impossible, we have seen that under a wide range of parameter choices the various systems never showed behavior other than a relentless pursuit of equilibrium.

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