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THE EVOLUTION OF INTRATETRAD MATING RATES

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Abstract.—Intratetrad mating, the fusion of gametes formed in a single meiosis, has unusual consequences for genetic diversity, especially in genome regions linked to mating type loci. Here we investigate the fate of modifier alleles that alter the rate of intratetrad mating, under models of heterozygote advantage and of genetic load resulting from recurrent mutation. In both cases, intratetrad mating is favored if the recombination rate between the selected locus and mating type is less than the frequency of lethal recessive alleles at that locus in the population. Positive feedback often accelerates the invasion of modifiers to the intratetrad mating rate. Recombination rate and intratetrad mating rate exert indirect selection on one another, resulting in a cascading decline in outcrossing, even in the absence of any cost of sex. However, under recurrent mutation, alleles for obligate intratetrad mating invade only very slowly, perhaps explaining why outcrossing can persist at low frequencies in a largely intratetrad mating population.

Key words.—Anther smut, breeding system, parthenogenesis, self-fertilization, *Ustilago violacea*.

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Natural populations display a bewildering diversity of mating systems (Barrett 2002). These diverse strategies offer different advantages: for example, outcrossing provides the advantages of increased diversity and heterozygosity, and uniparental reproduction may give reproductive assurance when suitable mates are unavailable.

Intratetrad mating, also often called ''automixis'' and analogous to meiotic parthenogenesis, is a type of uniparental reproduction that is seen in many insects (Normark 2003), nematodes (van der Beek et al. 1998) diatoms (Mann and Stickle 1989), and plants (Stebbins 1950). It is particularly frequent in fungi, such as the yeasts, secondary homothallic ascomycetes, smut fungi, and two-spored mushrooms (Kirby 1984; Zakharov 1986, 2005).

Intratetrad mating has features in common with diploid selfing: the parent undergoes meiosis, and the products of a single individual fuse. In intratetrad mating, however, fusion occurs specifically between the products of a single meiosis, either through cytological processes that package postmeiotic nuclei together, by restitution of chromosome components that have separated at meiosis, or through the direct mating of gametic cells. The latter process occurs in the pathogenic fungus *Microbotryum violaceum*, where mating occurs between cells of opposite mating type produced by meiosis frequently from the same diploid spore (Hood and Antonovics 2004). Intratetrad mating and outcrossing may coexist at varying frequencies: for example, around 1% of meiotic events are estimated to lead to outcrossing in the largely automictic wild yeast *Saccharomyces paradoxus* (Johnson et al. 2002), whereas in *M. violaceum* the intratetrad mating rate is 43.3–71.4% (Giraud et al. 2005).

Some genetic consequences of intratetrad mating are not intuitive and depend upon linkage relationships or genomic positions of the loci involved. For example, randomly segregating heterozygosity is lost more gradually under intratetrad mating than under diploid selfing: the loss of heterozygosity is only one-third per generation under intratetrad mating, because each meiotic product has three potential mating partners, and will be identical to only one of them at any locus that was heterozygous in the parent (Kirby 1984; Zakharov 1986).

When fusion within the tetrad is controlled by a haploid self-incompatibility system (i.e., a mating-type locus), heterozygosity is preserved in linkage with this locus (sensu Mather 1942), due to segregating alleles being reunited along with mating type. This applies also to genomic regions that cosegregate with mating type (Hood and Antonovics 2004; Zakharov 2005): if mating type is centromere-linked, as in *M. violaceum*, heterozygosity will also be preserved at all centromeric regions. Cytological control over nuclear restitution will have the same effect when it brings together the products separated at meiosis I, referred to as central fusion.

Such preservation of heterozygosity is expected to affect the maintenance of overdominant loci (i.e., heterozygote advantage) and the sheltering of deleterious mutations (i.e., genetic load). The possible role of these factors in modulating the evolution of intratetrad mating is the focus of the present study, which may have particular relevance to the *M. violaceum* system. Deleterious recessive alleles linked to mating type and other centromeres are frequent in this species (Oudemans et al. 1998; Thomas et al. 2003), and their persistence has been explained by the rapidity of intratetrad mating and any compensatory advantage in the heterozygous state (Antonovics et al. 1998) or by group selection for low growth rates to prevent the extinction of host populations (Tellier et al. 2005). Such deleterious recessive alleles are easy to detect in fungi because the haploid stage can normally be isolated and grown in culture. However, such load accumulation may also be important in animal and plant systems where deleterious recessive mutations remain hidden by internal meiotic divisions and a nonculturable gametic stage.

Here we examine the conflict between intratetrad mating as a mating system that generally leads to homozygosity, yet one that in certain circumstances (as at loci linked to mating type) acts to preserve heterozygosity. We use theoretical models to examine whether modifiers that alter the rate of intratetrad mating will invade a partially outcrossing population where a selected locus is linked to mating type. By simple extension, our results can also inform upon the evolution of intratetrad mating as the result of preserving heterozygosity in other genomic regions, such as centromeres of autosomes.

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The Model

This is a three-locus model, considering a mating type locus (haploid mating types *A1* and *A2*), a linked selected locus with wild type L^+ and recessive lethal L^- alleles, and an unlinked modifier locus affecting the rate of intratetrad mating, with alleles *M* and *m*. Generations are nonoverlapping. All individuals are diploid (or dikaryotic, provided only that normal dominance relationships apply) and heterozygous at the mating-type locus. Intratetrad mating occurs randomly between meiotic products of opposite mating type. This model also applies to all systems of intratetrad mating that involve first division restitution (i.e., central fusion), because such a system maintains heterozygosity at all centromeric regions; the mating-type locus in our model is therefore equivalent to a centromeric region that is kept in a permanently heterozygous condition (see Discussion below).

Each generation some fraction of diploids, *t1*, undergoes intratetrad mating (or second division restitution), and the rest ($1 - t1$) produce gametes that can freely mix in a gamete pool. Mating occurs at random between gametes of opposite mating type: there is no bias toward diploid selfing.

Gametes are isogamous, and all find mating partners. There is no growth in the haploid stage, as haploid selection disproportionately affects outcrossing cells. These assumptions together ensure that no cost of sex is built into the model.

Recombination between the selected locus and the mating type occurs at a rate *r* per generation (i.e., 2*r* is the chiasma frequency between the two loci). A chiasma in an L^+/L^- heterozygote produces a tetratype, that is, four gametes of genotype L^+A1, L^+A2, L^-A1, and L^-A2.), Recombination in homozygotes is disregarded.

The modifier is unlinked to mating type. *M*/*m* heterozygotes segregate randomly into gametes and remain heterozygous in two-thirds of diploids undergoing intratetrad mating.

The spread of the modifier is examined under two selective regimes, recurrent mutation and heterozygote advantage. Under recurrent mutation, there is mutation at locus *L* to a recessive lethal allele L^-; backmutation is ignored. In the diploid phase, under recurrent mutation, heterozygotes have fitness equal to L^+/L^+ homozygotes, and L^-/L^- homozygotes are assumed lethal. Under heterozygote advantage, the L^+/L^+, L^+/L^- and L^-/L^- genotypes have fitness $1 - s$, one, and zero respectively.

In both selective regimes, selection is in the diploid stage: gametes bearing the L^- allele survive to mate, but the L^-/L^- diploid genotype is lethal.

We carried out a direct computer simulation, as well as an approximate analytical solution for the conditions determining the invasion of a modifier allele that changes the rate of intratetrad mating. Simulations were performed using Mathematica (Wolfram Research 2003), tracking the frequencies of the nine types of diploid and eight types of haploid gamete, which are created by the previous generation of diploids as shown in Figure 1.

Simulations are deterministic, and generations are nonoverlapping. The spread of the modifier was studied as follows. An initial low frequency of the L^- allele was introduced (1 in 10^5 diploids are genotype $L^+A1\ m/L^-A2\ m$). Introducing L^- in complete linkage disequilibrium with the *A2* mating type is intended to mimic the appearance of a new mutant allele.

Over 10,000 generations, the L^- allele was allowed to reach an equilibrium frequency determined, under recurrent mutation, by its mutation rate μ, and under heterozygote advantage by the selection against homozygotes, *s*, as well as by the recombination rate *r* and the population's rate of intratetrad mating, *t1*. Linkage disequilibrium between the load locus and mating type locus swiftly declines to zero, except when recombination is very low under the heterozygote advantage model, in which case nearly all individuals in the population have the $L^+A1\ m/L^-A2\ m$ genotype. After 10,000 generations, genotype frequencies are stable (results not shown).

Into this equilibrium situation was introduced a dominant modifier, *M*, that changes intratetrad mating rate from *t1* to *t2*. This can be either an increase or a decrease. The modifier was introduced at a low initial frequency of 1 in 200,000: for recurrent mutation, by creating $L^+A1\ M/L^+A2\ m$ diploids, and for heterozygote advantage $L^+A1\ M/L^-A2\ m$ diploids. The modifier is therefore introduced on an advantageous genetic background. Note that although *M* may be in linkage disequilibrium with the load locus, as would be the case for a new mutation, the modifier locus is unlinked to the other two loci. The diploid $L^+A1\ M/L^+A2\ m$ is therefore equivalent to $L^+A1\ m/L^+A2\ M$ and the *M* allele is not in linkage disequilibrium with mating type. After another 10,000 generations the frequency of the modifier allele *M* was noted.

Results

Simulation

With genetic load resulting from recurrent mutation (Fig. 2b), modifiers that increase intratetrad mating spread most rapidly when the mutation rate (μ) is high and the recombination rate (*r*) between the mating type locus and the selected locus is low. However, alleles for moderate increases in intratetrad mating invade more rapidly than those for very high intratetrad mating rates, and alleles for obligate intratetrad mating cannot invade (e.g., extreme right of x-axis in Fig. 2b). At low μ and high *r*, decreased intratetrad mating is favored, but the invasion of the modifier is extremely slow.

In many cases the spread of *M* was remarkably slow, and the frequency of *M* was still below 10^{-4} at the end-point of the simulation. These allele frequencies are not stable equilibria. Given further generations, the frequencies of selectively favored modifier alleles continue to rise (or creep) toward fixation: however, even several hundred thousand generations may be insufficient for this to occur (results not shown). The arbitrary cutoff at 10,000 generations serves to show under which parameters the invasion is most rapid.

With heterozygote advantage (Fig. 2c), intratetrad mating invades rapidly if *s* is large and *r* is intermediate, but at very low *r* the invasion of the modifier is extremely slow for a wide range of values of *s*. Unlike in the case of genetic load resulting from recurrent mutation, under the heterozygote advantage model alleles for very high and obligate intratetrad mating invade most rapidly. Decreased intratetrad mating is favored at low *s* and high *r*, but the invasion of the modifier

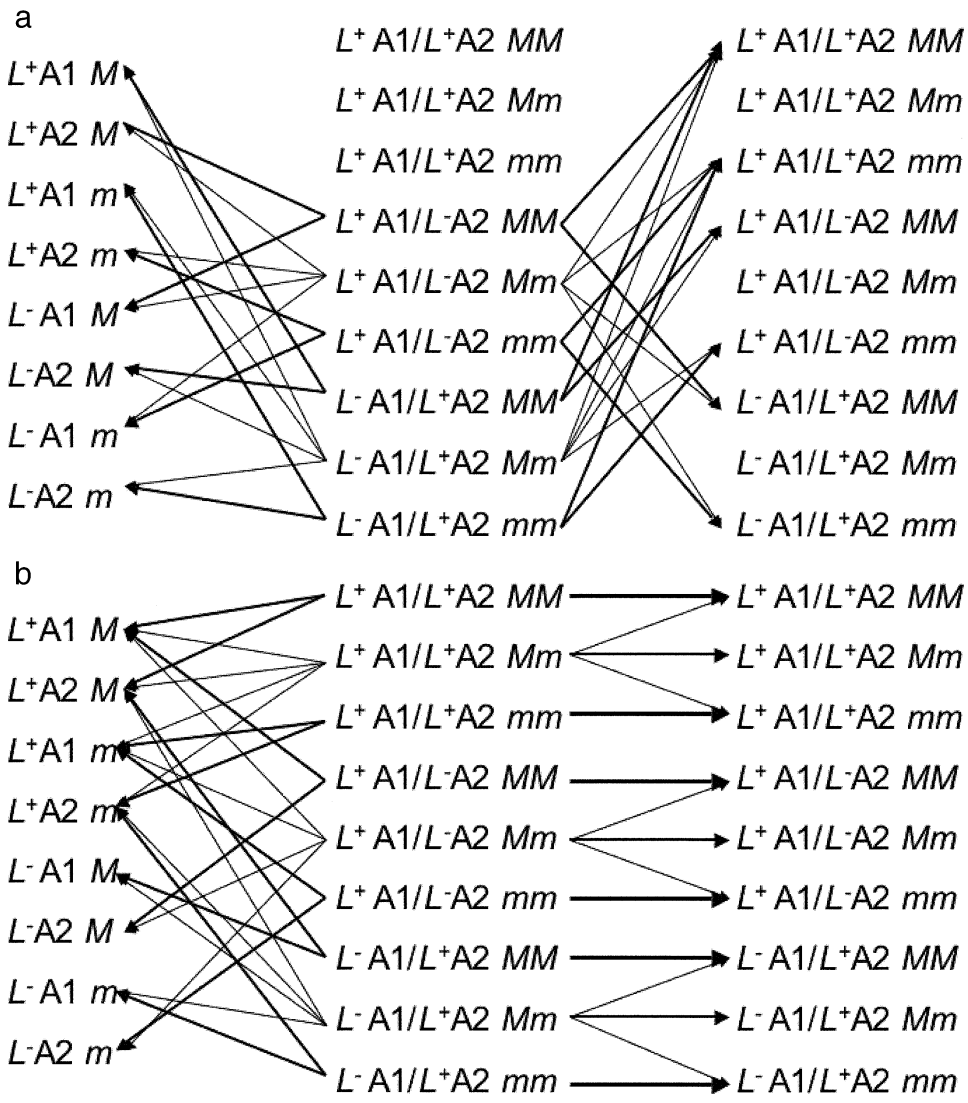

FIG. 1. Diploids in the population (central column) either create new diploids directly by intratetrad mating (rightward arrows) or form gametes (leftward arrows), which mate at random. (a) The gametes and diploids produced in the absence of recombination; (b) the additional gametes and diploids produced by recombinants. Thickness of arrow indicates proportion of gametes or diploids produced: for example, $L^+A1/L^+A2\ MM$ diploids produce only more $L^+A1/L^+A2\ MM$ diploids through intratetrad mating, and equal proportions of $L^+A1\ M$ and $L^+A2\ M$ gametes, while the triple heterozygote $L^+A1/L^-A2\ Mm$ produces four types of gamete when not recombining ($L^+A1\ M$, $L^+A1\ m$, $L^-A2\ M$, $L^+A2\ m$) and an additional four when recombining ($L^+A2\ M$, $L^+A2\ m$, $L^-A1\ M$, $L^+A1\ m$). The modifier locus M is unlinked: the heterozygote segregates independently of mating type, so two-thirds of the progeny of an intratetrad mating are heterozygous.

is never rapid enough for the increase to be visible after 10,000 generations.

Theory

The advantages or disadvantages of intratetrad mating depend on the relative likelihoods of exposing deleterious recessives or of losing advantageous heterozygosity in outcrossing or intratetrad mating. Comparing the chances of selective death in one generation under each mating strategy allows the calculation of conditions under which intratetrad mating will be advantageous.

For simplicity, it is assumed that there is no population-wide linkage disequilibrium between the load locus and mating type genes, as is normally the case in the simulations, although there are conditions under which this is not true (see below). The frequencies of L^-A1 and L^-A2 gametes will in this case be equal, so the calculations below include only l_G, the frequency of the L^- allele in the gamete pool.

Genetic load resulting from recurrent mutation

Here, only the L^+/L^- heterozygote has genetic load that risks exposure. Recombinants occur at a frequency r, and half of these will be L^-/L^- homozygotes. If we ignore new mutation, then, and assume the L^-/L^- genotype is lethal, the risk of selective death following intratetrad mating is $r/2$.

If the heterozygote produces outcrossing gametes, half of these will bear the L^- allele, and these will meet other gametes containing the L^- allele with probability l_G. The risk of selective death following outcrossing is $l_G/2$. Under recurrent

mutation, a heterozygous individual will therefore benefit from intratetrad mating if $r < l_G$.

Therefore, l_G affects whether modifiers promoting intratetrad mating will spread. Increasing load or decreasing recombination between the selected locus and the mating-type locus will make intratetrad mating more likely to be advantageous. A low l_G favors outcrossing, but also means there are fewer heterozygotes, so where selection for intratetrad mating occurs it will generally tend to be stronger than selection for outcrossing.

Changes to the intratetrad mating rate will in turn alter l_G. If the equilibrium frequency of L^- under 100% intratetrad mating is greater than that under 100% outcrossing, this indicates that intratetrad mating tends to preserve more load loci and there will be positive feedback: invasion of a modifier promoting intratetrad mating leads to an increase in l_G, which, in turn, creates stronger selection for intratetrad mating. It is therefore interesting to examine whether l_G increases or decreases with intratetrad mating rate.

An entirely outcrossing population will harbor a deleterious allele at the mutation-selection balance frequency of $\sqrt{(\mu/s)}$. The L^- allele is assumed to be a lethal recessive, so this will be $\sqrt{\mu}$.

In a population with obligate intratetrad mating, however, L^+/L^+ homozygotes are created by recombination of heterozygotes at a rate $r/2$, and mutate to form heterozygotes at a rate 2μ. Heterozygotes die at rate μ due to mutation of their remaining L^+ allele to the lethal form. Therefore, equilibrium is reached when the creation of homozygotes by recombination equals their destruction by mutation. Taking H as the proportion of heterozygotes, this equilibrium is reached when

$$2\mu(1 - H) = (1 - \mu)Hr/2, \tag{1}$$

which simplifies to

$$H = 4\mu/(r + 4\mu - \mu r). \tag{2}$$

Note that if recombination is zero the equilibrium frequency of heterozygotes is one, as expected: completely linked load would never be exposed in a population that did not outcross.

The conditions for a positive feedback loop, when intratetrad mating will increase load, are met if

$$2\mu/(r + 4\mu - \mu r) > \sqrt{\mu}. \tag{3}$$

Rearranged, this gives a critical value of

$$r < (2\sqrt{\mu} - 4\mu)/(1 - \mu) \tag{4}$$

or, approximately, for $\mu \ll 1$, $r < 2\sqrt{\mu}$.

Loci that are very tightly linked to the mating type locus will therefore create positive feedback loops under recurrent mutation, although for very high values of μ this condition cannot be met because the numerator becomes negative.

Modifiers creating obligate intratetrad mating, however, will never benefit from this feedback process. This is why modifiers that promote intratetrad mating invade most rapidly when *t2* is large but not very close to one. As obligate intratetrad mating creates no gametes, these modifiers will not cause l_G to increase as they invade, and the outcrossing sector of the population will not be disadvantaged by the influx of deleterious alleles.

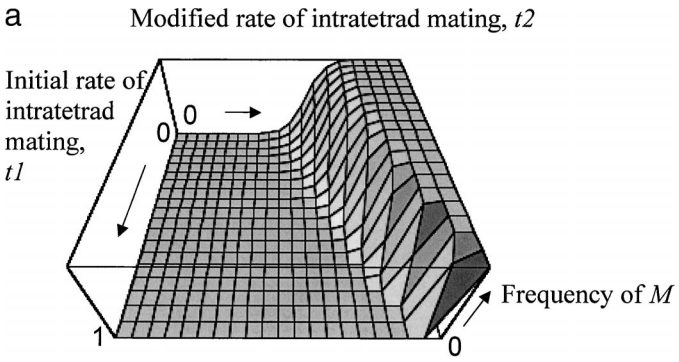

FIG. 2. (a) Key to graphs, showing the frequency (z-axis) of an unlinked modifier allele, *M*, conferring a rate *t2* of intratetrad mating in a population with varying initial rates of intratetrad mating, *t1*. This graph shows a situation in which intratetrad mating is selectively favored: the frequency of *M* is positive when *t2* is greater than *t1*. *M* has reached fixation where *t2* is high and *t1* low, but in other areas of the graph the spread of *M* has been too slow to be visible (e.g., where $t1 = 0$ and $t2 = 0.2$). Note that these are not stable equilibria. (b, c) Spread of the modifier under the two models of selection.

Heterozygote advantage

L^+/L^+ homozygotes have an s chance of death next generation if they mate within the tetrad, but if they produce outcrossed gametes, the chance that these will meet L^- alleles is l_G, and if this occurs they will have a fitness of one. They meet L^+ alleles at a rate $1 - l_G$, so the chance of selective death at outcrossing is $(1 - l_G)s$, and homozygotes will always benefit from outcrossing.

For heterozygotes, intratetrad mating and recombination can create both the lethal L^-/L^- genotype and the suboptimal L^+/L^+ genotype. Half of recombinants are of each type of homozygote, so the risk of selective death following intratetrad mating for a heterozygote is

$$r(s + 1)/2. \tag{5}$$

An outcrossing heterozygote produces half L^- and half L^+ gametes, which will meet suboptimal mating partners with probability l_G and $(1 - l_G)$, respectively. The risk of selective death following outcrossing for a heterozygote is therefore

$$[(1 - l_G)s + l_G]/2. \tag{6}$$

It is possible, then, to have a situation where homozygotes benefit from outcrossing but heterozygotes from intratetrad mating. This will be true if

$$r < [(1 - l_G)/s + l_G]/(s + 1). \tag{7}$$

In such a situation, the outcome will depend on the proportion of heterozygotes in the population, which will initially be approximately $2l_G$.

Consider an increase of ∂a in the rate of intratetrad mating. The additional selective deaths caused by the increase will be approximately

$$\partial a\,[(1 - 2l_G)s + l_G r(s + 1)], \tag{8}$$

in which the first term represents the selective deaths in L^+/L^+ homozygotes and the second the selective deaths in het-

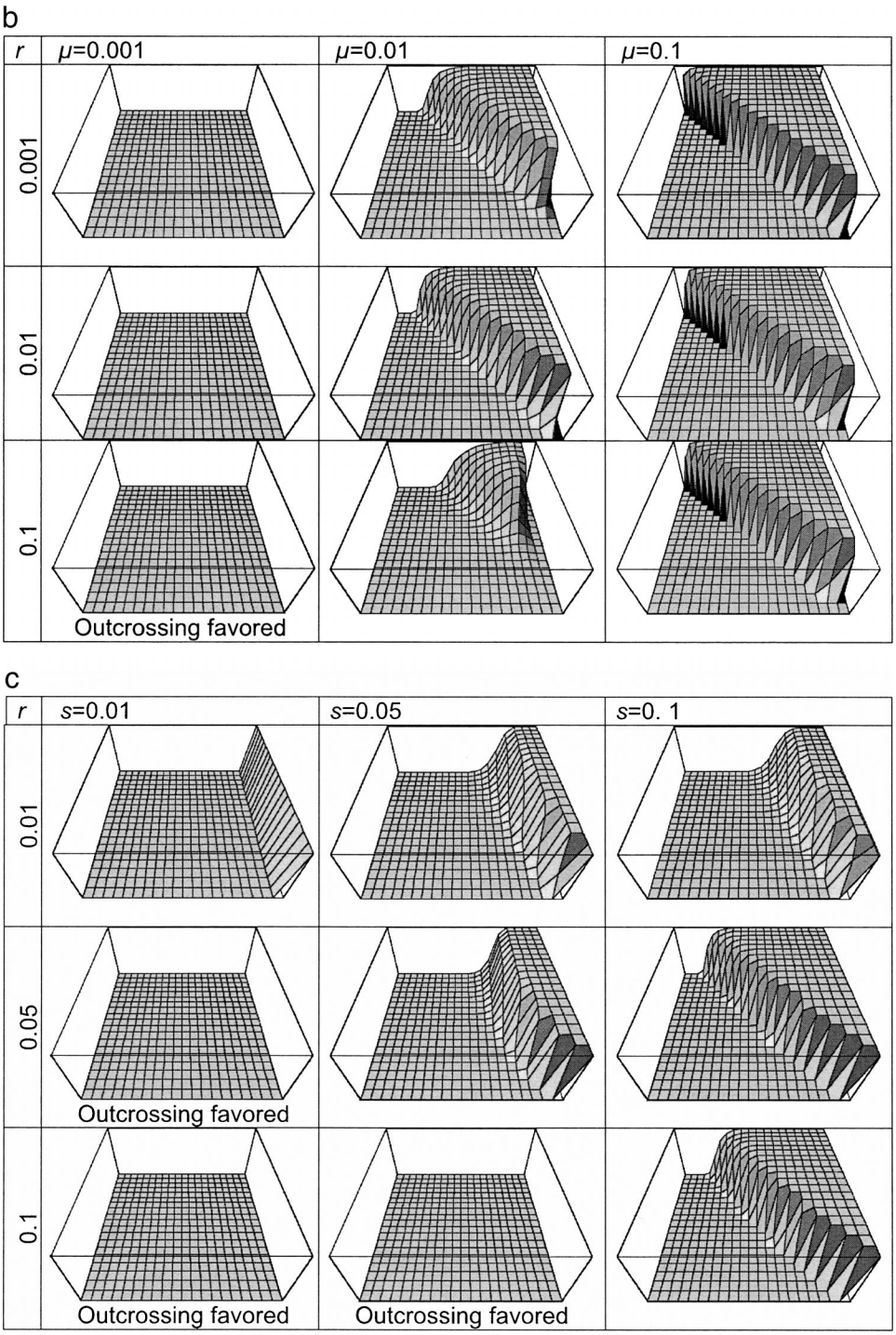

FIG. 2. Continued. (b) Recurrent mutation: frequency of *M* after 10,000 generations under a range of values for *r* and μ. (c) Heterozygote advantage: frequency of *M* after 10,000 generations under a range of values for *r* and *s*. Modifiers increasing intratetrad mating rates invade, except where indicated by ''outcrossing favored.'' In many cases, including all cases in which outcrossing is favored, the invasion of modifiers is too slow to be visible.

erozygotes, both weighted by the proportion of the population they represent.

If this fraction of the population underwent outcrossing, however, $(1 - l_G)s$ of the homozygotes and $[l_G + (1 - l_G)s]/2$ of the heterozygotes would meet selective death. The selective deaths prevented by the increase in intratetrad mating will therefore be

$$\partial a\ [(1 - 2l_G)\ (1 - l_G)s + l_G((1 - l_G)s + l_G)]. \qquad (9)$$

Again, the first term represents selective deaths in ho-

mozygotes and the second those in heterozygotes. This simplifies to

$$\partial a\ (s - 2l_G s + l_G^2 s + l_G^2). \quad (10)$$

Intratetrad mating will, on average, be advantageous if the number of deaths prevented exceeds the number of deaths caused, that is,

$$\partial a(s - l_G s + l_G^2 s) > \partial a[(1 - 2l_G)s + l_G r(s + 1)], \quad (11)$$

which, again, means $r < l_G$.

Equations (8–12) rely on the proportion of L^- alleles in the general population ($H/2$) being the same as that in the gamete pool (l_G). This, however, will not be true when there are modifiers of intratetrad mating rate segregating in the population, as these modifiers will form associations with alleles at the load locus. This result therefore cannot predict whether a particular modifier allele will spread, particularly one of large effect. Nevertheless, it does indicate that, as with recurrent mutation, intratetrad mating can be favored under heterozygote advantage.

As before, l_G affects the likelihood of invasion. Will there again be positive feedback on modifier alleles?

A randomly mating, outcrossing population maintains a lethal recessive allele with heterozygote advantage as a balanced polymorphism at a frequency $s/(s + 1)$. A population with 100% intratetrad mating will create homozygotes by recombination from heterozygotes at a rate $r/2$, and homozygotes will be lost at a rate s. Equilibrium will be reached when

$$(1 - H)s = rH/2, \quad (12)$$

making the equilibrium under obligate intratetrad mating

$$H = 2s/(r + 2s). \quad (13)$$

Again, in the absence of any recombination the entire population will be L^+/L^- heterozygotes. Positive feedback will result when the frequency of the L^- allele, which will be half the frequency of heterozygotes or $s/(r + 2s)$, is greater than $s/(s + 1)$. This simplifies to $r < 1 - s$.

As r can never be greater than 0.5, and s will rarely be greater than 0.5, this condition is easily met. Intratetrad mating will almost always increase l_G under heterozygote advantage, providing an even greater advantage to further modifiers increasing the rate of intratetrad mating. Modifiers promoting intratetrad mating, given that they spread at all, will rapidly become fixed in the population.

However, although low recombination is required for intratetrad mating to invade, at very low recombination rates alleles for intratetrad mating invade only extremely slowly. This is because heterozygote advantage loci extremely closely linked to mating type will be in strong linkage disequilibrium in the population. Consequently, nearly all individuals in the population have exactly the same genotype (in this case L^+A1/L^-A2), and outcrossing becomes almost equivalent to intratetrad mating. Intermediate recombination frequencies therefore allow the most rapid invasion of modifier alleles for intratetrad mating, particularly those of small effect.

Discussion

A modifier that increases intratetrad mating will invade under a wide range of conditions, both under models of heterozygote advantage and of genetic load resulting from recurrent mutation, although the two models show important differences. Recombination frequencies between mating type and selected loci play an important role in this process. In both models, intratetrad mating is favored if the recombination rate between the selected locus and mating type is less than the frequency of deleterious recessive alleles at that locus in the population. In a completely outcrossing population, the frequency of lethal recessive alleles will be very low ($\sqrt{\mu}$) in the absence of substantial heterozygote advantage. Intratetrad mating is therefore unlikely to invade a freely outcrossing population under the recurrent mutation model, but may be favored under heterozygote advantage.

Modifier alleles promoting intratetrad mating often expedite their own spread by increasing the frequency of lethal recessive alleles, which, in turn, make the modifier more advantageous. Such feedback loops may be a common feature of mating system evolution. Recombination rates, mutation rates, transposon accumulation, and ploidy level are strongly influenced by mating system, but they also exert selective pressures on one another and on the mating system itself (Joshi 1990; Otto and Marks 1996; Johnson and Brookfield 2002; Uyenoyama 2005). An evolutionary feedback loop may carry a population swiftly away from a mixed mating system, perhaps helping to explain the puzzling rarity (Green and Noakes 1995; Peck and Waxman 2000) and apparent evolutionary instability (see Burt 2000) of facultative sex.

Changes in intratetrad mating rates are expected to be part of a larger evolutionary feedback process involving selection on recombination rates. High intratetrad mating rates are known to favor invasion by modifiers that reduce recombination between the load and mating-type loci (Antonovics and Abrams 2004), which should accelerate the cascade toward obligate intratetrad mating. It is interesting that, at particular extreme values, this cascade is either not initiated or would be limited. For example, under recurrent mutation, loci for extremely high intratetrad mating rates increase in frequency only extremely slowly. Moreover, under such high rates of intratetrad mating, selection for decreased recombination becomes ineffective (Antonovics and Abrams 2004). Within any reasonable time frame, we may therefore expect this process to essentially freeze and lead to nearly 100% intratetrad mating, but not to its completion. A residual level of outcrossing in organisms with intratetrad mating (i.e., automixis or meiotic parthenogenesis) is therefore expected under these circumstances.

In our models, this cascade is entirely independent of an inherent cost of sex and applies equally to isogamous and anisogamous species. However, relating our results quantitatively to real-world situations of intratetrad mating is liable to be difficult, because there may be additional costs that we have not considered. For example, in parthenogenetic organisms the energetic costs of outcrossing will obviously tip the balance further in favor of intratetrad mating, while the recombinational benefits of genetic variation might favor outcrossing. In the case of *M. violaceum*, if the haploid cells do

not undergo intratetrad selfing, they continue to reproduce mitotically before mating. Moreover, alleles that are deleterious in the haploid phase can kill or prevent the multiplication of gametes that do not undergo immediate intratetrad mating. Such haploid selection will complicate matters further. Although it will reduce l_G, it will also provide a further advantage to intratetrad mating; immediate intratetrad mating will avoid the period of haploid growth at which suboptimal alleles are exposed to selection.

In *M. violaceum*, intratetrad selfing may also have immediate life-history and numerical consequences; intratetrad selfing may be favored because it leads to more rapid zygote formation (Tellier et al. 2005) but may be disfavored because it bypasses an asexual multiplication stage of the haploids (occurring in nectar) that may eventually lead to more zygotes or greater dispersal of those zygotes (Giraud et al. 2005).

Under recurrent mutation, modifiers conferring obligate or near-obligate intratetrad mating do not invade as quickly as smaller modifications to the intratetrad mating rate. Thus, if the process is driven by recurrent mutation, the cascade may tend to be incremental as intratetrad mating becomes common. Furthermore, if there are several modifier loci that are simultaneously polymorphic in a population, associations will form between them: genes for outcrossing will be disproportionately represented in the gamete pool, which will result in high between-lineage variation in intratetrad mating rate. As a result, outcrossing may tail off over a very long time scale.

These simulations did not consider diploid selfing, which is a third alternative to outcrossing and intratetrad mating. Indeed, for *M. violaceum*, if a host plant is infected with a single diploid genotype, intratetrad mating or diploid selfing may be the only available alternatives. Diploid selfing is more likely to expose load or remove advantageous heterozygosity than is intratetrad mating: like selection at the haploid stage, this will have the dual effect of reducing l_G but providing an immediate advantage to intratetrad mating.

These simulations are also a simplification in that they consider a single selected locus with a varying recombination rate that determines whether the modifier spreads. In reality, there will be many linked loci, each with its own mutation rate and selective coefficient. Some will display heterozygote advantage, some recurrent mutation, and some both. On average those closely linked to mating type, for which r is below the critical level, will create a selection pressure for increased intratetrad mating, while those more distant from the mating type locus create a selection pressure for outcrossing. At any time the overall pressure on intratetrad mating rate will depend on the balance between these two types of loci. However, the loci for which intratetrad mating is advantageous will tend to have a stronger influence: the risk of exposing deleterious alleles (or of losing alleles responsible for heterozygote advantage) is what generates the selection, and loci closely linked to mating type will have a higher frequency of such alleles due to their being sheltered by past intratetrad mating. This may mean that, typically, a few loci tightly linked to mating type will strongly select for an increased rate of intratetrad mating, and many unlinked loci each weakly select to decrease it. Where intratetrad mating is common, many recessive deleterious loci may be involved, such that recreating an optimal genotype by outcrossing would be improbable.

Until recently, discussions of the evolution of sex often compared obligate, outcrossed sex (as in mammals) with a vaguely defined ''asex,'' usually pictured as clonal reproduction. This is valid in many cases, because any system in which only one parent's genes are transmitted avoids the most obvious disadvantage of sexual reproduction, the famous twofold cost of males (Maynard Smith 1971). However, there is not a simple dichotomy between sexual and asexual reproduction, but several alternative types of reproduction that have different advantages and disadvantages compared with classical outcrossing sexual reproduction. For example, the gamete duplication seen in *Drosophila mercatorum* instantly creates an entirely homozygous genome (Kramer and Templeton 2001), while mitotic parthenogenesis (clonality) preserves heterozygosity at all loci, eventually leading to extensive sequence divergence between homologous chromosomes, as is seen in bdelloid rotifers (Welch and Meselson 2000).

Intratetrad mating, by contrast, does not have the same effect at all loci, but acts divergently on loci at different recombination distances from the mating type locus or centromeres, resulting in a spatially structured genome. However, exactly how (or whether) intratetrad mating in *M. violaceum* relates to its unusual features of differentiated sex chromosomes (Hood 2002), high levels of transposable elements (Hood 2005), and extreme levels of karyotypic variation (Hood et al. 2003, 2004) remains to be determined.

An understanding of complex, mixed mating systems and their effect on genome variability is therefore important for elucidating the evolution of genome structure. Whole-genome sequencing projects have revealed surprising amounts of spatial structure in many genomes, from nonrandom gene arrangement (Hurst et al. 2004) to unexpected conservation of synteny across the genome (Webster et al. 2004). The causes or functions of these genomic traits are at present poorly understood. Mating system, by directly affecting spatial patterns of diversity within the genome, probably has a great influence on the evolution of genome structure.

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