On the Origin of Meiotic Reproduction: A Genetic Modifier Model

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ABSTRACT

We study the conditions under which a rare allele that modifies the relative rates of meiotic reproduction and apomixis increases in a population in which meiotic reproduction entails selfing as well as random outcrossing. A distinct locus, at which mutation maintains alleles that are lethal in homozygous form, determines viability. We find that low viability of carriers of the lethal alleles, high rates of selfing, dominance of the introduced modifier allele, and lower rates of recombination promote the evolution of meiosis. Meiotic reproduction can evolve even in the absence of linkage between the modifier and the viability locus. The adaptive value of meiotic reproduction depends on the relative viabilities of offspring derived by meiosis and by apomixis, and on associations between the modifier and the viability locus. Meiotic reproduction, particularly under selfing, generates more diverse offspring, including those with very high and very low viability. Elimination of offspring with low viability generates positive associations between enhancers of meiotic reproduction and high viability. In addition, partial selfing generates positive associations in heterozygosity (identity disequilibrium) between the modifier and the viability locus, even in the absence of linkage. The two kinds of associations together can compensate for initial reductions in mean offspring viability under meiotic reproduction.

SEX comprises a syndrome of diverse processes, not all of which have necessarily evolved in response to the same selection pressures. Diploidy, meiosis, recombination, and outcrossing all promote genetic diversity among offspring, but this common effect does not by itself imply a common evolutionary function. Evolutionary processes maintaining any one component in highly refined sexual systems operate in a fundamentally different context from those that favored its origin in primitive sexual systems. MAYNARD SMITH (1978a, Chapter 1) has drawn a strong distinction between theories for the origin and the maintenance of sex (see also CROW 1988). Our deterministic two-locus study supports the view that the evolutionary function of meiosis in response to recurrent deleterious mutation is to promote the production of offspring of very high quality, even at the expense of reducing average offspring viability. Because the conditions most conducive to the origin of meiosis (low rates of recombination and high rates of selfing) are generally associated with asexuality, our findings suggest that the original adaptive significance of components of the sexual syndrome may reverse during the course of refinement.

Significance of deleterious mutations to the evolution of sex: Viewed as a response to mutation, sexual reproduction has been characterized as a mechanism to repair DNA [see BERNSTEIN et al. (1984, 1985) and references therein], combine favorable mutations (FISHER 1958, Chapter VI; MULLER 1932; CROW and KIMURA 1965; MAYNARD SMITH 1968; ESHEL and FELDMAN 1970), prevent the accumulation of deleterious mutations (MULLER 1964; FELSENSTEIN 1974), reduce genetic load (CROW 1988), or improve average offspring viability by increasing genetic diversity (WILLIAMS 1975, Chapter 1). The repair hypothesis, which holds that sexuality evolved to reduce the rate at which new mutations appear among offspring, lies beyond our study. Neither do the hypothesis of FISHER and MULLER apply to our model, because they require linkage disequilibrium among multiple loci which affect viability (FELSENSTEIN 1974; 1985). We use our analysis to test and refine the two remaining heuristic interpretations of the adaptive significance of sexual reproduction. In particular, we examine the generation and consequences of disequilibrium between a locus controlling viability and a modifier of the rate of meiotic reproduction.

Distinction between isogamy and reduction in outcrossing: MAYNARD SMITH (1978a, Chapter 4; 1978b) argued that isogamy eliminates the twofold cost of meiosis. This conclusion is based on the observation that sexual and asexual species transmit the same number of genes, provided that individuals can generate one asexual zygote only at the expense of two sexual gametes [see Figure 6.2 in MAYNARD SMITH...
Holsinger, Feldman, and Christiansen (1984) used the term "pollen discounting" to describe the reduction in cross-fertilization as a consequence of increased selfing. Although the two processes have often been treated as equivalent (Charlesworth 1980; Uyenoyama 1984), isogamy in fact represents but one energetic constraint which ensures reduced genetic contributions by less sexual forms.

In reflection of this identification of isogamy with a reduction in the ability to fertilize outcrossed eggs, most theoretical studies of the evolution of meiotic reproduction from apomixis have assumed that either (1) two apomictic eggs are replaced by one meiotic egg and one sperm, or (2) two apomictic eggs are replaced by two meiotic eggs with no change in outcrossing success. Kondrashov's (1985) generalization of this approach assumes that the relative investment in apomictic seeds, amphimictic seeds, and pollen are $$(1 + y)/2, (1 - z)/2, \text{ and } (1 - yz)/2$$, respectively. In the studies of Charlesworth (1980) and Marshall and Brown (1981), the parameter $y$ is set to zero, signifying that apomixis has no effect on pollen production. This assumption may hold under well-developed facultative apomixis (see Maynard Smith 1978a, Chapter 4; Marshall and Brown 1981).

Because our primary interest lies in the origin of meiosis rather than its maintenance, we envision primitive organisms that reproduce either asexually or sexually by mating with another cell capable of conjugation; in either case, the structural components of each cell are invested in one daughter cell. In our model, a fraction $a$ of a given genotype reproduces by apomixis, and the remaining fraction $(1 - a)$ undergoes meiosis. We assume that genotypes that reproduce by apomixis at a higher rate contribute less to the gamete pool from which offspring are derived by outcrossing. Because we assume both pollen discounting (positive $y$ in Kondrashov's (1985) terminology) and a constant total number of meiotic and ameiotic eggs, our model departs from conventional formulations (Charlesworth 1980; Marshall and Brown 1981; Kondrashov 1985), which we regard as more appropriate to the question of the maintenance of meiotic reproduction than to its origin.

Unlike these studies, we find that meiosis does not incur a twofold cost relative to apomixis. Maynard Smith (1978a, Chapter 4) concluded that the twofold cost of meiosis does not apply to the origin of meiosis because meiosis probably arose in isogamous organisms. In our model, the absence of the cost of meiosis reflects not isogamy, but rather that conjugants necessarily mate only with other conjugants. Harper (1982) assumed that individuals which invest a fraction $a$ of the resources available for reproduction in a sexual offspring invest $(1 - a)\phi$ and $(1 - \phi)$ in sexual eggs and sperm, respectively. Our model corresponds most closely to his under negligible investment in sperm relative to eggs ($\phi$ approaching unity). In agreement with our findings, meiosis does not incur a twofold cost in this case (Harper 1982).

**Origin of meiosis:** Cohen and Zohari (1986) derived the evolutionarily stable mixture of clonal and sexual reproduction that maximizes the number of clones at equilibrium. Primarily asexual clones allocate resources either to maintaining their own genotypes or to generating novel genotypes through sexual reproduction. A balance between the generation of new clones and the extinction of existing clones determines the equilibrium number. Higher rates of sexuality are favored in unsaturated habitats which harbor many unoccupied niches. The force favoring sexuality in Cohen and Zohari's (1986) model can be regarded as a form of environmental unpredictability: offspring that are unlike the parent survive if they happen to be able to exploit a different niche. Other theories incorporating low or negative correlations between the selective regimes imposed on parental and offspring generations have been discussed by Maynard Smith (1978a, Chapter 6).

We study evolutionary changes of a modifier of meiotic reproduction in response to deleterious mutations at a distinct locus which determines viability. Sexual reproduction involves both selfing and random outcrossing. Because meiosis does not suffer a twofold disadvantage in our formulation, relatively small differences in offspring viability can promote its origin. Further, even if segregation reduces the average viability of meiotically-derived offspring, associations between the modifier of reproduction and the viability locus may permit the evolution of meiotic reproduction. Selfing generates such associations through two effects. First, selfing generates a higher variance in viability among offspring than apomixis. Elimination of the less viable offspring induces an association between high viability and enhancers of meiotic reproduction. Second, partial selfing generates identity disequilibrium, even in the absence of linkage (Bennett and Binet 1956; Weir and Cockerham 1973). Identity disequilibrium implies a correlation in heterozygosity between loci (Haldane 1949; Cockerham and Weir 1968), with individuals that are heterozygous at the modifier locus likely to be heterozygous at the viability locus as well. In our study, the implications of identity disequilibrium for the origin of meiosis depend upon the level of dominance expressed by the new modifier allele.

**Balance between mutation and viability selection**

**Changes in genotypic frequencies**

**Reproduction:** Locus $M$ determines the fraction of offspring derived by apomixis. In the resident popu-
tion (prior to the introduction of the new allele that modifies the rate of meiotic reproduction), all individuals carry genotype $M_1M_1$ at the modifier locus and reproduce by apomixis at the rate $a_{11}$ ($0 \leq a_{11} \leq 1$). Apomixis replicates the parental genotype together with any mutations that have occurred in the parent since its conception. Meiotic reproduction generates the remaining fraction $(1 - a_{11})$ of offspring. Of the offspring generated by meiosis, a proportion $b$ ($0 \leq b \leq 1$) are derived by selfing and $(1 - b)$ by random outcrossing.

**Viability selection:** Two classes of alleles that affect viability segregate at locus $A$: $A_1$ represents the normal, well-functioning form and $A_2$ a heterogeneous class of mutations that depress viability. Mutation generates defective alleles at the rate $\mu$. Homozygotes for defective alleles ($A_2A_2$) are inviable, with heterozygotes ($A_1A_2$) surviving to reproduce at the rate $\sigma$ ($0 \leq \sigma \leq 1$) relative to normal homozygotes ($A_1A_1$).

**Recursions:** While the viability of offspring derived by both meiotic and ameiotic reproduction depends on the genotype at the time of conception, mutations that occur in surviving individuals before reproduction may be transmitted to the next generation. Let $u_{11}$ denote the frequency of individuals, censused after the phase of viability selection, that carried genotype $A_1A_1$ at conception. At this stage, these individuals may bear genotypes $A_1A_2$ or $A_2A_2$ as a result of mutation. Similarly, $u_{12}$ denotes the frequency at reproductive age of individuals that carried $A_1A_2$ at conception; the remaining class ($A_2A_2$) is inviable. In the next generation, these frequencies are determined from

$$Tu_{11} = u_{11}^*,$$  \hspace{1cm} (1a)

$$Tu_{12} = \sigma u_{12}^*$$ \hspace{1cm} (1b)

in which $u_{11}^*$ and $u_{12}^*$ represent the frequencies of $A_1A_1$ and $A_1A_2$ individuals at conception and $T$ is the normalizer that ensures that the genotypic frequencies sum to unity.

At conception, the frequencies of genotypes $A_1A_1$ and $A_1A_2$ are given by

$$u_{11}^* = a_{11}x_{11} + (1 - a_{11})b(x_{11} + x_{12}/4)$$

$$+ (1 - b)f_1^2,$$  \hspace{1cm} (2a)

$$u_{12}^* = a_{11}x_{12} + (1 - a_{11})[bx_{12}/2 + (1 - b)2f_1f_2],$$  \hspace{1cm} (2b)

in which

$$x_{11} = u_{11}(1 - \mu)^2$$  \hspace{1cm} (3a)

$$x_{12} = (u_{11}2\mu + u_{12})(1 - \mu)$$  \hspace{1cm} (3b)

$$x_{22} = (u_{11}\mu + u_{12})\mu.$$  \hspace{1cm} (3c)

and

$$f_1 = x_{11} + x_{12}/2$$  \hspace{1cm} (4a)

$$f_2 = x_{13}/2 + x_{22}.$$  \hspace{1cm} (4b)

Mutation permits the existence at the time of reproduction of all three genotypes $A_1A_1$, $A_1A_2$, and $A_2A_2$, which occur in frequencies $x_{11}$, $x_{12}$, and $x_{22}$, respectively. Random outcrossing involves the fusion of two gametes within the gamete pool, in which $A_1$ and $A_2$ occur with frequencies $f_1$ and $f_2$, respectively.

**Equilibrium genotypic frequencies**

Solution of (1), after removal of the primes, provides expressions for the genotypic frequencies at equilibrium. Ignoring terms smaller than the mutation rate, we obtain

$$u_{12} = 1 - u_{11} \approx \frac{2\mu(2 - b(1 - a_{11}))}{2(1 - \sigma) + \sigma(1 - a_{11})}$$ \hspace{1cm} (5a)

$$T \approx 1 - \mu\left[1 + \frac{2(1 - \sigma)}{2(1 - \sigma) + \sigma(1 - a_{11})}\right].$$ \hspace{1cm} (5b)

Examination of (5b) indicates that the population mean fitness ($T$) increases with greater rates of selfing ($b$) or lesser rates of apomixis ($a_{11}$): meiotic reproduction combined with selfing reduces mutational load to the greatest extent.

**Predictions in the absence of two-locus associations**

In order to establish a framework within which the joint evolution of the viability locus and a modifier of meiotic reproduction can be assessed, we first consider the influence of the modifier locus on its own transmission, ignoring associations between the loci.

**Changes in frequencies at the modifier locus:** A rare allele ($M_2$) introduced at the modifier locus changes the rate of apomixis: rare heterozygotes ($M_1M_2$) reproduce ameiotically at the rate $a_{12}$, and rare homozygotes ($M_2M_2$) at the rate $a_{22}$. Parameter $e$ ($0 \leq e \leq 1$) represents a measure of dominance of $M_2$:

$$(a_{11} - a_{12}) = e(a_{11} - a_{22})$$  \hspace{1cm} (6a)

$$(a_{12} - a_{22}) = (1 - e)(a_{11} - a_{22}).$$  \hspace{1cm} (6b)

Complete dominance ($e = 1$) implies that both rare genotypes ($M_1M_2$ and $M_2M_2$) express a rate of meiotic reproduction different from the resident, and complete recessivity ($e = 0$) that only the rare homozygote ($M_2M_2$) expresses a different rate. We have not considered overdominance or underdominance in expression of the modifier locus ($e$ lying outside $(0, 1)$).

Let $w$, $v$, and $u$ denote the frequencies of individuals bearing genotypes $M_1M_1$, $M_1M_2$, and $M_2M_2$, respectively. For rare $M_2$, $u$ lies close to the sum of $u_{11}$ and $u_{12}$ obtained from (5). Up to linear terms in the frequencies of the rare genotypes ($v$ and $w$), the pop-
ulation in the next generation is described by

\[ T' = v[a_{12} \phi_A + (1 - a_{12})b \phi_3/2] + [v(1 - a_{12}) + w/2(1 - a_{22})](1 - b) \phi_R \] (7a)

\[ T'' = v(1 - a_{12})b \phi_3/4 + w[a_{22} \phi_A + (1 - a_{22})b \phi_R], \] (7b)

in which \( \phi_A, \phi_3, \) and \( \phi_R \) represent the average viabilities of offspring derived by apomixis, meiotic selfing, and random outcrossing, respectively. Expressions for these average viabilities are obtained from (3) and (4):

\[ \phi_A = x_{11} + \sigma x_{12} \] (8a)

\[ \phi_3 = x_{11} + x_{12}(1 + 2\sigma)/4 \] (8b)

\[ \phi_R = f_i(f_i + 2f_2\sigma). \] (8c)

These values determine the mean fitness of the population:

\[ T = a_{11} \phi_A + (1 - a_{11})(b \phi_3 + (1 - b) \phi_R) \] (9)

[compare (5b)].

**Condition for local stability:** For all levels of dominance of the rare modifier allele (e), the resident population excludes \( M_2 \) if

\[ (a_{11} - a_{12})[\phi_A - b \phi_3 - (1 - b) \phi_R] > 0. \] (10)

Condition (10) indicates that the adaptive value of meiotic reproduction depends on the average viability of offspring derived by apomixis (\( \phi_A \)) relative to the average viability of offspring derived meiotically through selfing and outcrossing (\( \phi_3 \) and \( \phi_R \)). Parents are equally closely related to their offspring derived by any of the three reproductive modes. Offspring generated by apomixis or selfing derive all of their genes from their parent. Offspring derived by random outcrossing receive enhancers of meiotic reproduction from both parents because only meiotically reproducing individuals contribute to the gamete pool. Consequently, the “cost of meiosis” does not apply to the evolution of meiotic reproduction as an alternative to apomixis.

To terms of the order of the mutation rate, (10) is proportional to

\[ (a_{11} - a_{12})ab(\sigma - 1/2) > 0. \] (11)

In the absence of selfing (\( b = 0 \)), (10) reduces to:

\[ (a_{11} - a_{12})a^2\sigma(1/2) > 0. \] (12)

Conditions (11) and (12) indicate that meiotic reproduction is favored if the deleterious viability allele \( A_2 \) exhibits partial dominance (\( \sigma < 1/2 \)). In the presence of selfing (\( b > 0 \)), the intensity of selection is of the order of the frequency of the deleterious allele, which in turn is of the order of the mutation rate. In the absence of selfing (\( b = 0 \)), the selection intensity is of the order of the square of the mutation rate.

**JOINT EVOLUTION OF THE MODIFIER AND THE VIABILITY LOCUS**

Partial selfing generates positive associations in heterozygosity, even between unlinked loci (Weir and Cockerham 1973). Such associations compel consideration of the joint evolution of the viability locus and the modifier locus.

**Introduction of a modifier of meiotic reproduction**

**Change in frequencies of rare genotypes:** Recombination between the viability locus (\( A \)) and the modifier locus (\( M \)) occurs at the rate \( r(0 \leq r \leq 1/2) \). Introduction of the new allele at the modifier locus generates five new genotypes. Rare homozygotes at the modifier locus \((M_2M_2)\) that were \( A_1A_1 \) at conception occur with frequency \( w_{11} \), and those that were \( A_1A_2 \) at conception occur with frequency \( w_{12} \). The variable \( v_{11} \) represents the frequency of \( M_1M_2 \) individuals that were \( A_1A_1 \) at conception, and \( v_{12} \) and \( v_{21} \) double heterozygotes \( A_1M_1/A_2M_2 \) and \( A_2M_1/A_1M_2 \), respectively.

Appendix 1 presents recursions to the first order in the frequencies of the rare genotypes at the modifier locus. We assume that most of the random outcross gamete pool is generated by the common genotype \( M_1M_1 \). If, however, the resident population reproduces by meiosis at a negligible rate, then the \( M_1M_1 \) population is reproductively isolated from the carriers of \( M_2 \). In that case, interpopulation or group selection presumably would direct the evolution of meiotic reproduction, implying that meiotic reproduction will invade because it reduces the mutational load [see (5b)].

**Qualitative features:** High rates of selfing (\( b \)) and low viability of carriers of the lethal allele (\( \sigma \)) promote meiotic reproduction (see Appendix 2), qualitative trends evident in the absence of two-locus associations [see (11) and (12)]. The major qualitative differences that emerge from the full two-locus analysis include the possibility of evolutionarily stable mixtures of apomictic and meiotic reproduction. Further, the minimum viability of \( A_1A_2 \) individuals that permits the maintenance of apomixis depends on the rates of selfing (\( b \)), recombination (\( r \)), and dominance of the introduced modifier (\( e \)).

To illustrate the qualitative behavior observed in the full two-locus analysis, we present the results obtained in the absence of both linkage (\( r = 1/2 \)) and selfing (\( b = 0 \)). The resident population resists the invasion of \( M_2 \) if
viability locus from the invasion of increases when rare. The value represents parameter combinations in which the population resists at rate for which the absence of selfing and linkage between the modifier and the uniformly favored.

rate for which fails, then rates of meiotic reproduction are uniformly favored. A resident population that expresses apomixis under complete dominance of the introduced modifier allele $M_2$ ($a_{12} = a_{22}$), $M_2$ fails to increase when rare if

$$(a_{11} - a_{22})(Q_{dom}(a_{11}) + \vartheta(a_{11} - a_{22})) > 0,$$

in which $\vartheta(a_{11} - a_{22})$ denotes terms of the order of $(a_{11} - a_{22})$ and smaller, and

$$Q_{dom}(a_{11}) = 2\sigma(1 - a_{11})[(1 - b)(1 - a_{11}) - 1 + \sigma(2 - b + b\sigma(1 - a_{11})).$$

The function $Q_{dom}(a_{11})$ has a root $(a)$ in $(0, 1)$ if both

$$\sigma > \frac{2}{3} - b$$

and

$$r > \frac{(1 - \sigma)[2 - a(2 - b)]}{2\sigma(2 - b - 1)}$$

(compare (15b)). A resident population that expresses $a(a_{11} - a)$ excludes all modifier alleles that cause small changes in the rate of meiotic reproduction: $a$ is an ESS for $a_{22}$ close to 0. Further, $a$ is a CSS, meaning that modifier alleles that bring the rate of meiotic reproduction closer to $a$ increase when rare if $(a_{11} - a)$ is large relative to $(a_{11} - a_{22})$. For parameter values violating (18), meiotic reproduction is uniformly favored.

Figure 2 presents the minimum value for the viability parameter $(a$, from (18)) that permits the existence of the CSS as a function of the recombination fraction for three levels of selfing ($b = 0.1, 0.5, 0.9$). Tight linkage and high rates of selfing promote meiotic reproduction. Figure 3 presents the CSS rate of apomictic reproduction under three rates of recombination ($r = 0.05, 0.1, 0.5$) for $\sigma$ set equal to 0.9. Higher levels of apomixis evolve under loose linkage and low rates of selfing.

This simple example illustrates two major qualitative differences generated by two-locus associations, even in the absence of linkage and selfing: the existence of a continuously stable state involving both apomictic and meiotic reproduction (15a), and a substantial change in the minimum viability that permits the maintenance of apomixis [compare (15b) and (12)]. To explore the implications of two-locus associations on the quantitative results, we describe the effects of selfing and linkage under complete dominance $(e = 1)$, and the effects of selfing and dominance of the introduced modifier under free recombination $(r = 1/2)$. We assume in the remaining analysis that the selection intensity at the modifier locus is weak, meaning that $(a_{11} - a_{22})$ is sufficiently small.

**Effects of selfing and linkage under complete dominance of $M_2$**

Under complete dominance of the introduced modifier allele $M_2$ ($a_{12} = a_{22}$), $M_2$ fails to increase when rare if

$$(a_{11} - a_{22})(Q_{dom}(a_{11}) + \vartheta(a_{11} - a_{22})) > 0,$$

in which $\vartheta(a_{11} - a_{22})$ denotes terms of the order of $(a_{11} - a_{22})$ and smaller, and

$$Q_{dom}(a_{11}) = 2\sigma(1 - a_{11})[(1 - b)(1 - a_{11}) - 1 + \sigma(2 - b + b\sigma(1 - a_{11})).$$

The function $Q_{dom}(a_{11})$ has a root $(a)$ in $(0, 1)$ if both

$$\sigma > \frac{2}{3} - b$$

and

$$r > \frac{(1 - \sigma)[2 - a(2 - b)]}{2\sigma(2 - b - 1)}$$

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ameiotic reproduction under low rates of selfing.

Two-locus associations promote the maintenance of partial apomixis, plotted as a function of the level of dominance 

\[ \text{minimum viability generally lies above} \]

The rate of selfing. Two-locus associations promote the maintenance of apomixis depends strongly on the threshold viability exceeds 0.5, the value expected in the absence of two-locus associations, even in the absence of linkage (\( r = 0.5 \)).

**Effects of selfing and dominance of \( M_2 \) under free recombination**

In the absence of linkage (\( r = \frac{1}{2} \)), the new allele \( M_2 \) fails to increase when rare if

\[ (a_{11} - a_{22})\mu [Q_{\text{free}}(a_{11}) + \partial(a_{11} - a_{22})] > 0, \]  

in which \( Q_{\text{free}}(a_{11}) \) denotes the quadratic given in Appendix 2 [compare (14)]. The function \( Q_{\text{free}}(a_{11}) \) has a root (\( a \), the CSS) in the range (0, 1) for \( \sigma \) sufficiently large [compare (15)]. For complete dominance (\( \epsilon = 1 \)) or complete recessivity (\( \epsilon = 0 \)) of expression of the modifier allele \( M_2 \), the CSS is in fact an ESS, meaning that \( a_{11} \) equal to \( a \) ensures local stability for all \( a_{12} \) and \( a_{22} \) close to but different from \( a \). If the CSS is not valid, then meiotic reproduction is uniformly favored.

Figure 4 presents the minimum value of \( \sigma \) that permits the maintenance of partial apomixis, plotted as a function of the level of dominance (\( \epsilon \)) of the introduced modifier allele \( M_2 \) for three rates of selfing (\( b = 0.1, 0.5, 0.9 \)). Condition (11), obtained by ignoring associations between the modifier locus and the viability locus, suggests that ameiotic reproduction is favored for all \( \sigma \) greater than \( \frac{1}{2} \). In contrast, Figure 4 indicates that the minimum viability that permits the maintenance of apomixis depends strongly on the dominance of the introduced modifier alleles and the rate of selfing in the full two-locus model. While the minimum viability generally lies above \( \frac{1}{2} \) for dominant modifier alleles, the threshold for recessive modifiers may fall substantially below \( \frac{1}{2} \), depending on the rate of selfing. Two-locus associations promote meiotic reproduction under high rates of selfing and ameiotic reproduction under low rates of selfing.

**Generation of Disequilibrium**

Ignoring associations that develop between the modifier locus and the viability locus generates the predictions that no state involving both meiotic and ameiotic reproduction is evolutionarily stable, and that pure meiotic reproduction evolves only if the lethal allele \( A_2 \) expresses dominance \( \frac{1}{2} > \sigma \) [see (11) and (12)]. In contrast, our results from the full two-locus model indicate that partial apomixis is maintained only if the viability (\( \sigma \)) of the \( A_1A_2 \) individuals is sufficiently high, with pure meiotic reproduction favored in all other cases. To clarify the nature of the interaction between the modifier locus and the viability locus, we express the conditions for local stability in terms of measures of two-locus disequilibria.

**Change of Variables**

**Definitions:** A change of variables to incorporate measures of association between the modifier locus and the viability locus facilitates insight into the nature of the process of selection that directs the evolution of the modifier locus. The frequencies of the rare genotypes in terms of the original variables are represented by \( x \):

\[ x^T = (w_{11}, w_{12}, v_{11}, v_{12}, v_{21}) \]

in which \( x^T \) denotes the transpose of \( x \). We define a new coordinate system with basis

\[ y^T = (G, \eta_w + n_w/2, \eta_v, w, q) \]

in which

\[ w = w_{11} + w_{12} \]
\[ v = v_{11} + v_{12} + v_{21} \]
\[ q = w + v/2 \]
\[ G = v_{12} - v_{21} \]

\[ \eta_w = w_{12} - f(A_1A_2)w = -w_{11} + f(A_1A_2)w \]
\[ \eta_v = (v_{12} + v_{21}) - f(A_1A_2)v = -v_{11} + f(A_1A_2)v, \]
Within-individual disequilibrium \((G)\), gametic disequilibrium \((D)\), and the quantity in (23) converge to zero, with the one-locus coefficient of inbreeding \((F)\) converging to
\[
F = b/(2 - b),
\]
and identity disequilibrium to
\[
\eta_v = 4b(1 - b)[1 + \lambda^2(1 - b)]
\]
\[
(2 - b)^2(4 - b + \lambda^2),
\] (26a)
in which \(\lambda\) denotes a measure of linkage:
\[
\lambda = (1 - 2r).
\] (26b)

**Local stability analysis:** Reformulation of the analysis in terms of the new variables \((21)\) entails a change of basis of the state space. Matrix \(M\) represents the linearized transformation in terms of the original basis (see APPENDIX 1), and \(N\) the new basis; \(M\) and \(N\) are related by
\[
N = AMB
\] (27)
in which \(A\) and \(B\) are determined from
\[
y = Ax
\] (28a)
\[
x = By,
\] (28b)
for \(x\) and \(y\) vectors that represent a given point with respect to the original and new basis, respectively (see APPENDIX 3).

Because matrices \(M\) and \(N\) have the same eigenvalues, the sole condition for local stability for small \((a_{11} - a_{22})\) (see APPENDIX 3) is given by
\[
\text{Det}(I - N) > 0,
\] (29)
in which \(\text{Det}\) denotes the determinant. Over one generation, the population state changes by
\[
(y - y') = -(I - N)y,
\] (30)
in which \(y\) and \(y'\) represent the population in the present and next generation. Define \(\hat{y}\) such that all but one of the elements of the vector \((I - N)\hat{y}\) are equal to zero. The number of such vectors corresponds to the dimension of the space. If one of the eigenvalues of \(N\) were equal to unity, then \(\hat{y}\) would correspond to the eigenvector associated with unity, and (30) would be equal to the zero vector. Because unity is not in fact an eigenvalue of \(N\), the one nonzero element of \((I - N)\hat{y}\) is equal to the characteristic equation of \(N\) evaluated at unity. Applying (30) to \(\hat{y}\)
and summing the elements of the resulting vector produces
\[
x_0' - \tilde{y} = -z(I - N)\tilde{y} = -\text{Det}(I - N),
\]
in which \(z\) represents a row vector with all elements equal to unity. Equation (31) indicates that the condition for local stability (29) is equivalent to
\[
-x_0' + \tilde{y} > 0.
\]
This equivalence implies that we can use the behavior over one generation of the system initiated at \(\tilde{y}\) to infer the asymptotic behavior of the system initiated from arbitrary states close to the original equilibrium. We examine the effect of the expression of the modifier of the rate of meiotic reproduction on the measures of association at this particular population vector \(\tilde{y}\).

**Interpretation of the conditions for local stability**

In terms of the new variables, the necessary condition for stability in (32) becomes
\[
(a_{11} - a_{22})[(q + w(1 - \sigma)]2s_2b(\sigma - \frac{1}{2})
+ \eta_x(1 - \sigma) - b(1 - \sigma)]/2)
+ \frac{G(1 - 2r)(a_1 - a_{12}) + \eta_x(1 - \sigma) + a_{22}}{2} > 0,
\]
in which
\[
w = \frac{q}{b}b(2 - b)
\]
\[
\eta_x = \frac{4b(1 - \sigma)(1 - a_{11})(1 + \lambda^2)}{2q^2f_2(2 - b)[4(1 - a_{11}) - b(1 - a_{11})(1 + \lambda^2)]}
\]
(34a)
(34b)

While the expression for the frequency of genotype \(M_2M_2\) (34a) corresponds to the neutral expectation \([qf_2, \text{for } F \text{ given in (25)}]\), the expression for \(\eta_x\) (34b) reflects viability selection at the A locus as well as partial inbreeding (compare (26)).

**Complete dominance of the introduced modifier allele:** Up to terms of the first order in \((a_{11} - a_{22})\), condition (33) reduces under complete dominance \((\epsilon = 1)\) to
\[
(a_{11} - a_{22})q^2s_2b(\sigma - \frac{1}{2})
+ (a_1 - a_{11})(1 - b + 2(1 - b)(1 - \sigma))(D - 1 - 2r)
+ \tau(\eta_x + \eta_x/2)]
+ \eta_x(1 - \sigma)[(1 - a_{11}) + 2a_{11}] > 0,
\]
in which
\[
D = -(a_{11} - a_{22})q_2s_2b(1 - a_{11})
+ \sigma(1 - a_{11})(r - b/2)]/C
\]
\[
(\eta_x + \eta_x/2) = -(a_{11} - a_{22})qfs_2b[2 - \sigma(1 + a_{11})
+ 2r\sigma(1 - a_{11})]/C
\]
(36a)
(36b)
with
\[
C = (1 - a_{11})[2 - \sigma(1 + a_{11})] - \sigma(1 - a_{11})
(1 - 2r)[2(1 - a_{11}) - b(1 - a_{11})].
\]
(36c)
Ignoring the measures of disequilibrium \(D\) and \((\eta_x + \eta_x/2)\), we recover (11), which predicts that meiotic reproduction evolves only under partial dominance of the deleterious viability allele \((\sigma < \frac{1}{2})\). Clearly, the two-locus associations cannot be ignored, because they are of the same order of magnitude as the other terms [compare (35) and (36)].

Expressions (36a) and (36b) indicate that resident modifier alleles that enhance meiotic reproduction \((a_{11} < a_{22})\) tend to occur with the advantageous viability allele \(A_1\) on the gametic level \((D > 0)\), and with genotype \(A_1A_1\) on the genotypic level \([\eta_x + \eta_x/2 > 0]; \text{see (23)}.\) Tight linkage \((r \text{ small})\) promotes meiotic reproduction by increasing the absolute values of the disequilibrium measures in (36), as Figure 2 suggests.

**Free recombination:** Figure 4 indicates that the minimum viability that permits the maintenance of apomixis may fall below \(\frac{1}{2}\) under recessivity of the introduced modifier allele, in contrast with the results obtained under complete dominance (see Figure 2). This reduction in the threshold viability implies that enhancers of meiotic reproduction can become associated with the deleterious viability allele, unlike the case of complete dominance (see (36)).

In the absence of linkage \((r = \frac{1}{2})\) and under complete recessivity of \(M_2\) \((\epsilon = 0)\), (33) reduces up to terms of the first order in \((a_{11} - a_{22})\) to
\[
(a_{11} - a_{22})w^2s_2b(\sigma - \frac{1}{2}) + \eta_x(1 - \epsilon)
\]
\[
\cdot(\sigma - 1 + b/2)/2 + (\eta_x + \eta_x/2)(1 - \sigma)
\]
\[
\cdot(1 + a_{11}) + b(1 - a_{11})/2 > 0,
\]
(37)
in which \(w\) and \(\eta_x\) are obtained from (34), and
\[
(\eta_x + \eta_x/2) = -(a_{11} - a_{22})q_2s_2b[4(1 - a_{11})
- \sigma(1 - a_{11})][1 + (1 - b)^2]/C
\]
(38a)
with \(C\) now equal to
\[
[2 - \sigma(1 + a_{11})][2 - b]
\]
\[
\cdot[1 - \sigma(a_{11} + b(1 - a_{11})/4)].
\]
(38b)
As expected from (11), ignoring the two-locus associations \(\eta_x\) and \((\eta_x + \eta_x/2)\) in (37) generates the prediction that meiotic reproduction evolves only if the deleterious viability allele \(A_2\) is partially dominant \((\sigma < \frac{1}{2})\). Unlike the case of dominant \(M_2\) [see (36)], (38a) indicates that a resident modifier allele \(M_1\) that promotes meiotic reproduction relative to the introduced modifier \((a_{11} < a_{22})\) becomes negatively associated with genotype \(A_1A_1\) for sufficiently low rates of selfing \((b \text{ near } 0)\).

**Selfing promotes associations between loci:** Our analysis indicates that selfing generates two kinds of associations between the modifier of reproduction and the viability locus. First, partial selfing generates as-
associations in heterozygosity between neutral loci (Weir and Cockerham 1973). While the genotypic analog of identity disequilibrium [see (34b)] depends on viability selection (σ) and the rate of apomixis (a_{11}) in our model, the qualitative aspects are preserved: individuals that are heterozygous at the modifier locus are more likely to be heterozygous at the viability locus as well. In agreement with intuition, tight linkage (λ large) maintains higher levels of association [see (36)]; however, associations arise even in the absence of linkage.

Second, elimination of offspring with low viability tends to generate associations between high viability and enhancers of meiotic reproduction, which produces greater variance in offspring viability. Formation of the advantageous A_{1}A_{1} genotype occurs at a higher rate through meiotic reproduction with selfing. The frequency with which A_{1}A_{1} offspring are produced by apomixis is x_{11} [see (3)]: the parent must itself have been A_{1}A_{1} at its own conception and have escaped subsequent mutation. Among the offspring generated by meiosis with selfing (b), A_{1}A_{1} offspring occur with frequency x_{11} + x_{12}/4, and by meiosis with random outcrossing, f_{i}^{2} [see (3) and (4)]. Meiotic reproduction produces more A_{1}A_{1} offspring than ameiotic reproduction if

\[ b(x_{11} + x_{12}/4) + (1 - b)f_{i}^{2} > x_{11}, \]  

(39a)

which reduces, to terms of the first order in the mutation rate, to

\[ bf_{i}^{2}/2 > 0. \]  

(39b)

Meiotic reproduction increases the rate of formation of A_{1}A_{1} offspring through selfing, which recovers both the fully viable and the lethal homozygotes from heterygotes. This argument implies that modifier alleles that promote meiotic reproduction with selfing tend to become associated with A_{1}A_{1}, with the intensity of selection imposed on the modifier locus the order of the product of the rates of selfing and mutation [see expression for u_{12} in (5a)]. This comparison holds only initially: both identity disequilibrium and these differences in the genotypic distribution among offspring derived by meiotic and ameiotic production induce a dependence of the frequencies represented by x_{11} and x_{12} in (39a) on the genotype at the modifier locus.

While the association between enhancers of meiosis and high viability promotes meiotic reproduction, the effect of identity disequilibrium depends on the expression of dominance at the modifier locus. Our results indicate that enhancers of meiotic reproduction tend to become positively associated with the advantageous allele at the viability locus for high levels of dominance of the introduced modifier allele and high rates of selfing [see (36)]; under recessivity and low rates of selfing (small e and b), this relationship can reverse.

**DISCUSSION**

**Sexual reproduction as a response to deleterious mutation**

**Reduction of load:** Under the assumption that mutations at different loci depress viability in a multiplicative fashion, the mean fitnesses of a sexually reproducing population and a clonally reproducing population are identical (Maynard Smith 1968; Eshel and Feldman 1970; Crow 1970). Although some form of epistasis is necessary for sexuality to confer a population level advantage (Crow 1988; Maynard Smith 1988), many forms of epistatic selection in fact promote asexuality (Eshel and Feldman 1970). In our model, mean fitness uniformly increases under meiotic reproduction with selfing [lower a_{11} with positive b; see (5b)]. However, our study of a genetic modifier of meiotic reproduction indicates that higher viability of heterozygous carriers of the homozygous lethal (larger σ), lower rates of selfing (smaller b), and looser linkage (larger r) promote the maintenance of apomixis: meiotic reproduction is not uniformly favored. While sexual reproduction may in fact have arisen by group selection, as Fisher (1958, Chapter VI) suggested, inferences derived from between-population selection do not apply to within-population selection.

**Improvement of expected offspring viability:** While identical to the load argument with respect to reproductively isolated populations, the hypothesis that sexual reproduction improves average offspring viability (Williams 1975, Chapter 1; see also Emlen 1975, Chapter 3; Kondrashov 1982, 1984) can be applied within populations and within broods as well. Consider two symmetric, unimodal distributions representing the probability that offspring in the two groups carry a given number of deleterious mutations [see Figure 1 in Kondrashov (1984); Figure 3.1 in Emlen (1973)]. Sexual reproduction increases the variance while preserving the mean. Under a form of truncation selection for which only offspring having fewer than a certain number of mutants survive, a greater fraction of the offspring described by the distribution with the larger variance survive, provided that the truncation line falls below the mean (Kondrashov 1984). Williams (1975; see his Figure 1) generalized this argument to include other forms of epistatic selection. Strong sib competition may favor the production of diverse offspring even under constant selection regimes (Williams 1975 Chapter 2; Maynard Smith 1976, 1978a (Chapter 6)).

Applied to our model, this approach entails comparing the expected viabilities of offspring derived by meiotic and ameiotic reproduction [see (10)]. We find
that the expected viability of meiotically-derived offspring is higher only if the deleterious viability allele shows partial dominance \(\frac{1}{2} > \sigma\), see (11) and (12)]. However, inferring evolutionary trends from a comparison between the expected viabilities of offspring derived by sexual and asexual reproduction is tantamount to ignoring associations between the modifier of reproduction and the viability locus [see (35)]. Omission of the associations qualitatively alters the evolutionary outcome because the associations generate effects of the same magnitude as the differences between the average offspring viabilities.

**Offspring diversity promotes associations between loci**

**Modification of meiotic reproduction in response to a single viability locus:** In the absence of prior two-locus associations, meiotic reproduction with selfing increases the variance in genotype among offspring of \(A_1A_2\) parents, generating more highly fit as well as more lethal genotypes [see (39)]. Elimination of less fit offspring generates positive associations between enhancers of meiotic reproduction and high viability. High genotypic diversity among offspring promotes sexual reproduction, not by improving mean offspring viability, but rather by providing a mechanism through which enhancers of meiosis develop associations with alleles that improve viability. Such associations can compensate for initial reductions in offspring number under meiotic reproduction.

Although outcrossing and recombination are generally regarded as the essence of sexuality, selfing represents the central force favoring the origin of sexual reproduction. Identity disequilibrium arises under partial selfing, resulting in a correlation in heterozygosity between the modifier of reproduction and the viability locus, even in the absence of linkage (Bennett and Binet 1956; Weir and Cockerman 1973). Most important, selfing promotes the formation of very fit offspring by increasing the variance in offspring viability.

**Modification of meiotic reproduction in response to multilocus systems:** We speculate that the principles operating in our model apply to more complex systems which involve multiple loci affecting viability. First, selfing is expected to increase the variance in viability among offspring in the multiple locus case as well. Pamilo, Nei and Li (1987) derived approximations for the variance in the number of mutations carried by individuals under genetic drift and weak purifying selection. Pure selfing maintains the highest variance, followed by pure biparental reproduction, and finally pure apomixis. In agreement with Heller and Maynard Smith (1979), Pamilo, Nei and Li (1987) found that deleterious mutations tend to fix under selfing as well as apomixis, though at an intermediate rate between biparental reproduction and apomixis. We suggest that selfing may promote associations between highly fit genotypes and enhancers of meiotic reproduction in multilocus systems as well.

**Modification of recombination:** Feldman, Christiansen, and Brooks (1980) studied the modification of recombination between two loci at which mutation maintains alleles that depress viability. Alleles introduced at a third locus that enhance recombination between the two viability loci increase from low frequencies if the depression of viability by deleterious alleles is greater than multiplicative, and if linkage between the modifier and the loci under viability selection is sufficiently tight. We test our interpretation developed for the modification of meiotic reproduction by applying it to the modification of recombination.

In the haploid case studied by Feldman, Christiansen and Brooks (1980), the viabilities of genotypes \(AB, Ab, aB,\) and \(ab\) are designated 1, \(W_1, W_2,\) and \(W_3 (1 > W_1 > W_2)\), respectively, in which upper case letters denote wild-type alleles and lower case deleterious alleles. Deleterious alleles show a form of multiplicative epistasis if

\[
W_1 > \sqrt{W_2}. \tag{40}
\]

Under (40), deleterious alleles occur more commonly in repulsion than in coupling in the initial population \((D < 0;\) Feldman, Christiansen and Brooks 1980).

We first compare the expected viabilities of offspring derived from parental and recombinant gametes. Recombination affects the genotypic distribution only in matings involving all four alleles. In matings involving \(AB\) and \(ab\), recombination gives rise to offspring with greater viability if the deleterious alleles show a form of additive epistasis:

\[
W_1 > \frac{(1 + W_2)}{2}. \tag{41}
\]

Recombinant offspring produced by matings involv-
ing $Ab$ and $aB$ have higher viability if the inequality in (41) is reversed. Considering both kinds of matings, we find that recombination improves offspring viability if

$$2D[W_1 - (1 + W_2)/2] > 0.$$  (42)

Satisfaction of (41) implies (40), which in turn ensures negative gametic linkage disequilibrium between the viability loci ($D < 0$); (42) is violated in this case, implying that recombination reduces offspring viability. In the absence of prior associations between the modifier of recombination and the two loci under viability selection, parents that express enhanced recombination generate more offspring only if $W_1$ falls between the arithmetic and geometric means of 1 and $W_2$ [see (40) and (42)].

We now examine the generation of associations between enhancers of recombination and the favored genotype ($AB$). Recombination promotes the formation of $AB$ offspring in matings between $Ab$ and $aB$, but reduces their formation in matings between $Ab$ and $ab$. Enhancers of recombination tend to become associated with $AB$ if the former mating occurs more frequently [$D < 0$; or, equivalently, if (40) holds]

In the absence of prior associations between the recombination modifier and the loci under viability selection, enhancers of recombination reduce the expected viability of offspring unless $W_1$ falls in a restricted range. However, recombination promotes the formation of highly fit offspring if deleterious alleles have greater than multiplicative effects on viability. We suggest that associations between the modifier and the viability loci generated by the latter effect of recombination can compensate for the reduction in offspring number if the associations are sufficiently strong. Tight linkage between the modifier and the viability loci promotes the evolution of increased recombination between the two viability loci by maintaining stronger associations.

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**LITERATURE CITED**


APPENDIX 1

Linearized recursions

Recursions in the frequencies of the rare genotypes, up to linear terms in those frequencies, are given by

\[ T w''_1 = w^{*}_1 \]
\[ T w''_2 = a w^{*}_1 \]
\[ T v''_1 = v^{*}_1 \]
\[ T v''_2 = a v^{*}_1 \]

(A1.1)

In (A1.1), in which the primed variables denote the frequencies in the next generation and the starred variables frequencies at conception. At conception, the frequencies of the rare genotypes are

\[ w^{*}_1 = a_2 z_1 + (1 - a_2) b (z_1 + z_2)/4 \]
\[ + (1 - a_2) b (y_1 + y_2 r^2 + y_2 (1 - r)^2) \]
\[ w^{*}_2 = a_2 z_2 + (1 - a_2) b (z_2 + z_1)/2 \]
\[ + (1 - a_2) b r (1 - r) (y_2 + y_1)/2 \]
\[ v^{*}_1 = a_1 y_1 + (1 - a_2) b (y_1 + y_2 r^2 + y_2 (1 - r)^2) \]
\[ + (1 - b) f_2 g_1 \]
\[ v^{*}_2 = a_1 y_2 + (1 - a_2) b (y_2 + y_1 r^2 + y_1 (1 - r)^2) \]
\[ + (1 - b) f_2 g_1. \]

(A1.2)

In (A1.2), \( f_1 \) and \( f_2 \) (the equilibrium frequencies of gametes carrying \( M_1 \)) are given by (4a), and \( g_1 \) and \( g_2 \), the frequencies of gametes carrying \( M_2 \), by

\[ g_1 = (1 - a_2) z_1 + z_2/2 \]
\[ + (1 - a_1) (y_1 + y_2 r + y_2 (1 - r))/2 \]
\[ g_2 = (1 - a_2) z_2 + z_1/2 \]
\[ + (1 - a_1) (y_2 + y_1 r + y_1 (1 - r))/2, \]

(A1.3)

in which

\[ z_1 = w_1 (1 - \mu) \]
\[ z_2 = (w_1 + w_2) (1 - \mu) \]
\[ y_1 = v_1 (1 - \mu) \]
\[ y_2 = (v_1 + v_2) (1 - \mu) \]
\[ y_2 = (v_1 + v_2) (1 - \mu). \]

(A1.4)

\[ Q(a_1) = -(a_1 - a_1 b)u^2 + (a_1 - a_1 b)(1 - \sigma) - \sigma(1 - a_1) \]
\[ - (1 - a_1) [2(1 - \sigma) - \sigma(1 - a_1)] > 0; \]

(A2.2a)

or, equivalently,

\[ (a_1 - a_1) b u^2 [Q(a_1) + \sigma(a_1 - a_1)] > 0, \]

(A2.2b)

in which

\[ Q(a_1) = -(a_1 - a_1) [2(1 - \sigma) - \sigma(1 - a_1)] \]
\[ + \sigma(1 - a_1)(1 - \sigma) - \sigma(1 - a_1) \]

(A2.3)

[compare (12)]. A root of \( Q(a_1) \) lies in \((0, 1)\) if both

\[ \sigma > \frac{\gamma}{3} \]

(A2.4a)

\[ r > \frac{(1 - \sigma)^2}{\sigma(2 \sigma - 1)} \]

(A2.4b)

The rate \( r \) corresponds to both a CSS and an ESS, provided that \( a_1 = 0 \) is restricted to values close to \( a_1 \). Complete meiotic reproduction is favored if (A2.4a) and (A2.4b) are violated.
Absence of linkage: The function \( Q_{\text{free}}(a_{11}) \) in (19) is given by

\[
Q_{\text{free}}(a_{11}) = -(1 - \sigma)(1 - b/2)(1 - \epsilon)[2(1 - \sigma) + a(1 - a_{11})(2 + b)] + [1 - \sigma(a_{11} + b(1 - a_{11}))]/\epsilon(1 - \sigma)\]

\[
+ (1 - \sigma)[a_{11} + b(1 - a_{11})/4]](1 - \epsilon)[2(1 - \sigma) + a(1 - a_{11})/2]
\]

\[-\sigma((1 - \sigma)(4 - 3b) - \sigma(1 - a_{11})(1 - \epsilon)^2)].
\]

APPENDIX 3

Local stability analysis

Matrix \( M \) is a non-negative five-dimensional matrix, the dominant eigenvalue of which is non-negative. Local stability requires positivity of the determinants of the successive principal minors of the matrix \((I - M)\) [see GANTMACHER (1959, p. 71)]. For positive \( M \), the dominant eigenvalue is positive and occurs with multiplicity one. In the absence of differences among modifier genotypes \((a_{11} = a_{12} = a_{22})\), this dominant eigenvalue corresponds to unity; for sufficiently small \((a_{11} - a_{12})\), positivity of the determinant of \((I - M)\) ensures local stability.

Matrices \( A \) and \( B \) are determined from (28), using (22). For rare \( M_2, f(A_1A_1) \) in (22) lies close to \( u_{11} \) and \( f(A_1A_2) \) to \( u_{12} \); under this substitution, \( A \) and its inverse \( B \) are given by:

\[
A = \begin{pmatrix}
0 & 0 & 1 & -1 \\
-u_{12} & u_{11} & -u_{11}/2 & u_{11}/2 \\
0 & 0 & -u_{12} & u_{11} & u_{11} \\
1 & 1 & 0 & 0 & 0 \\
1 & 1 & \frac{1}{2} & \frac{1}{2} & \frac{1}{2}
\end{pmatrix}
\]

\[
B = \begin{pmatrix}
0 & -1 & \frac{1}{2} & u_{11} & 0 \\
0 & 1 & -\frac{1}{2} & u_{12} & 0 \\
0 & 0 & -1 & -2u_{11} & 2u_{11} \\
\frac{1}{2} & 0 & \frac{1}{2} & -u_{12} & u_{12} \\
-\frac{1}{2} & 0 & \frac{1}{2} & u_{12} & u_{12}
\end{pmatrix}
\]