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Detection of Deleterious Genotypes in Multigenerational Studies. II. Theoretical and Experimental Dynamics with Selfing and Selection

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ABSTRACT

A mathematical model was developed to help interpret genotype and allele frequency dynamics in selfing populations, with or without apomixis. Our analysis provided explicit time-dependent solutions for the frequencies at diallelic loci in diploid populations under any combination of fertility, viability, and gametic selection through meiotic drive. With no outcrossing, allelic variation is always maintained under gametic selection alone, but with any fertility or viability differences, variation will ordinarily be maintained if and only if the net fitness (fertility × viability) of heterozygotes exceeds that of both homozygotes by a substantial margin. Under pure selfing and Mendelian segregation, heterozygotes must have a twofold fitness advantage; the level of overdominance necessary to preserve genetic diversity declines with apomixis, and increases with segregation distortion if this occurs equally and independently in male and female gametes. A case study was made of the Arabidopsis *act2-1* actin mutant over multiple generations initiated from a heterozygous plant. The observed genotypic frequency dynamics were consistent with those predicted by our model for a deleterious, incompletely recessive mutant in either fertility or viability. The theoretical framework developed here should be very useful in dissecting the form(s) and strength of selection on diploid genotypes in populations with negligible levels of outcrossing.

MUTATIONS that are not lethal or do not produce an obvious morphological phenotype are often used to categorize genes or gene functions as nonessential or redundant. However, this conclusion can seldom be justified without evolutionary data on allele frequencies across multiple generations (Gilliland *et al.* 1998). Arabidopsis is an ideal model organism for multigenerational population studies, both in the field (Mauricio 1998) and laboratory (Gilliland *et al.* 1998), because of its small size, short life cycle, and small genome (Meyerowitz 1989, 1994). Moreover, the negligible rate of outcrossing (Abbott and Games 1989), even when inflorescences are in close physical contact (Snape and Lawrence 1971), allows a purely selfing model to be used to analyze the observed frequencies of genotypes in this organism. The ability to apply this approximation is a tremendous advantage because a mixed-mating selection model for diploid populations, incorporating both selfing and random outcrossing, is far more complicated to analyze (Workman and Jain 1966; Weir 1970; Kimura and Ohta 1971; Overath and Asmussen 1998). In general, if there is outcrossing present, explicit time-dependent solutions are not possible for the genotypic frequencies, even if the genotypes differ only in viability. The equilibrium analysis is also very complex in mixed-mating systems under selection because it is difficult to predict the equilibrium frequencies reached or even whether a genetic polymorphism will be maintained or lost in the population.

The case of a purely selfing population, however, is fully analyzable, which provides us with a valuable theoretical framework from which to infer the form(s) and strength of selection operating in such populations. This is because the expected genotypic and allelic frequencies at a diallelic locus can be readily predicted through time in a selfing population under selection. Karlin (1969) outlined a sophisticated dynamical analysis of such systems based on a nontraditional application of linear algebra. This approach was akin to that used to determine the equilibria with all alleles present under the classical selection model with constant viability selection on a multiallelic locus (Mandel 1959). Karlin's method hinged on temporarily ignoring the normalizing factor that makes the new genotypic frequencies sum to one and treating the simplified genotypic recursions as three independent linear equations (whereas technically there are only two independent equations). He then specified the dynamical solutions through time (but not their explicit formulas) in terms of a triple product of 3×3 matrices, whose entries were functions of the eigenvalues and eigenvectors of the resulting three-variable linear transformation. A further complication of this approach is that the solutions for certain combinations of parameter values require computing the Jordan canonical decomposition of the coefficient matrix.

Here we provide a much simpler derivation than that proposed by Karlin (1969), which readily generates

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TABLE 1

Genotypic frequencies and selection parameters

Variables and parameters	Genotype		
	A_1A_1	A_1A_2	A_2A_2
Adult frequency	u_{11}	u_{12}	u_{22}
Fertility	f_{11}	f_{12}	f_{22}
Viability	v_{11}	v_{12}	v_{22}
Meiotic drive	m_{11}	m_{12}	m_{22}

the explicit time-dependent solutions for the genotypic and allelic frequencies under all possible parameter values. Our results provide a theoretical framework that fully dissects the evolutionary dynamics under any combination of fertility, viability, and gametic selection on a single diallelic locus in a purely selfing population, with or without the asexual production of seeds by apomixis. This framework can also be applied with reasonable accuracy to partially random mating populations in which the outcrossing rate is negligible. The utility of this approach is illustrated through application to the multigenerational data on the *act2-1* actin mutant in Arabidopsis, presented in a companion manuscript (Gilliland *et al.* 1998).

POPULATION DYNAMICS WITH SELECTION IN SELFING POPULATIONS

The expected genotypic and allelic frequencies at a locus with two alleles (A_1 and A_2) can be predicted through time under selfing, apomixis, and selection, using a simple deterministic model. We first assume a purely selfing diploid population with discrete, nonoverlapping generations with no mutation or gene flow, which is large enough to preclude the effects of random genetic drift. The genotypes are subject to constant fertility selection and/or viability selection and possibly gametic selection via meiotic drive (deviation from 50:50 Mendelian ratios in gametes produced by heterozygotes). The frequencies of the three genotypes in adults (u) and the selection parameters (f, v, m) are defined in Table 1, where subscripts ij refer to the alleles carried by the individual. The fertility parameters f_{ij} denote the average number of offspring produced when an A_iA_j individual self fertilizes, while the viability parameters v_{ij} denote the average fraction of newly formed A_iA_j zygotes that survive to reproduce.

Meiotic drive is incorporated through the parameters m_{ij}, which represent the average fraction of progeny that are A_iA_j when an A_1A_2 individual selfs. In general, these values can be any three nonnegative numbers that sum to 1 ($m_{11} + m_{12} + m_{22} = 1$) to allow for the possibility of differential or nonindependent transmission of the alleles to male and female gametes. If the male and female gametes that combine to produce each zygote are transmitted independently and with the same frequency of A_1 (m) and A_2 ($1 - m$) alleles, meiotic drive can be described by the single parameter m, where $m_{11} = m^2$, $m_{12} = 2m(1 - m)$, $m_{22} = (1 - m)^2$, and $0 \leq m \leq 1$. Under Mendelian segregation, $m = \frac{1}{2}$, yielding the familiar proportions $m_{11} = m_{22} = \frac{1}{4}$ and $m_{12} = \frac{1}{2}$.

Derivation of purely selfing model: The changes in adult genotypic frequencies from one generation to the next in a purely selfing population are readily determined by working through a complete generation cycle. Although we do not monitor the population size in this model, the frequency dynamics are most easily derived by considering the number of each genotype at the successive life stages. This factor will be eliminated in the final step, where we calculate the new adult frequencies. Letting N represent the total number of reproducing adults at the start of the current generation, the number of A_1A_1 zygotes is then, for instance, $f_{11}(u_{11}N) + m_{11}f_{12}(u_{12}N) = (f_{11}u_{11} + m_{11}f_{12}u_{12})N$, where $f_{11}(u_{11}N)$ is the number of A_1A_1 zygotes produced by the selfing of the $u_{11}N$ individuals who are A_1A_1, and $m_{11}f_{12}(u_{12}N)$ is the number produced by the selfing of the $u_{12}N$ individuals who are A_1A_2. Note that all progeny from A_1A_1 homozygotes are like homozygotes, whereas a fraction m_{11} of the progeny from heterozygotes will be A_1A_1. The generation cycle concludes with viability selection, after which the number of new A_1A_1 adults is $v_{11}(f_{11}u_{11} + m_{11}f_{12}u_{12})N$. Analogous formulas apply to A_2A_2 homozygotes. In contrast, A_1A_2 individuals can be produced only from other heterozygotes under pure selfing. The number of A_1A_2 zygotes is thus simply $m_{12}f_{12}(u_{12}N)$, and the number that survive to become A_1A_2 adults is $v_{12}m_{12}f_{12}(u_{12}N)$.

Normalizing relative to the total number of new adults ($\bar{w}N$), we then find that the three genotypic frequencies in adults change from one generation to the next according to the following recursions:

$$u'_{11} = \frac{(f_{11}v_{11})u_{11} + (f_{12}m_{11}v_{11})u_{12}}{\bar{w}} \tag{1}$$

$$u'_{12} = \frac{(m_{12}f_{12}v_{12})u_{12}}{\bar{w}} \tag{2}$$

$$u'_{22} = \frac{(f_{22}v_{22})u_{22} + (f_{12}m_{22}v_{22})u_{12}}{\bar{w}}, \tag{3}$$

where a prime ($'$) denotes a value in the next generation, and the normalization factor is

$$\bar{w} = (f_{11}v_{11})u_{11} + f_{12}(m_{11}v_{11} + m_{12}v_{12} + m_{22}v_{22})u_{12} + (f_{22}v_{22})u_{22}. \tag{4}$$

This factor ($\bar{w}$) could be viewed as a measure of the mean fitness in the population, although this interpretation is complicated by the fact that the second term, weighted by the frequency of heterozygotes (u_{12}), involves parameter values for all three genotypes. The corresponding iterative formula for the frequency p of allele A_1 in adults is

$$p' = u'_{11} + \tfrac{1}{2}u'_{12}$$
$$= \frac{(f_{11}v_{11})u_{11} + f_{12}(m_{11}v_{11} + \tfrac{1}{2}m_{12}v_{12})u_{12}}{\bar{w}}. \quad (5)$$

Time-dependent solutions: Here we present a new and complete dynamical analysis of this model (Karlin 1969), which quickly generates the explicit time-dependent solutions for the genotypic and allelic frequencies under all possible parameter values. Our approach capitalizes on the fact that the system is two dimensional, along with a change to the readily analyzed variables, $x_1 = u_{11}/u_{12}$ and $x_2 = u_{22}/u_{12}$, which are the ratios of the homozygote to heterozygote frequencies in the population. The quantities x_1 and x_2 represent two independent variables that fully describe the three-genotype system via the relations

$$u_{11}^{(t)} = \frac{x_1^{(t)}}{1 + x_1^{(t)} + x_2^{(t)}} \quad (6)$$

$$u_{12}^{(t)} = \frac{1}{1 + x_1^{(t)} + x_2^{(t)}} \quad (7)$$

$$u_{12}^{(t)} = \frac{x_2^{(t)}}{1 + x_1^{(t)} + x_2^{(t)}}, \quad (8)$$

which hold in every generation t, where for any variable z, $z^{(t)}$ represents its value in generation t.

The recursions for the two new variables, x_1 and x_2, are simple, independent, linear difference equations with constant coefficients:

$$x'_1 = \left(\frac{f_{11}v_{11}}{m_{12}f_{12}v_{12}}\right)x_1 + \frac{m_{11}v_{11}}{m_{12}v_{12}} \quad (9)$$

$$x'_2 = \left(\frac{f_{22}v_{22}}{m_{12}f_{12}v_{12}}\right)x_2 + \frac{m_{22}v_{22}}{m_{12}v_{12}}. \quad (10)$$

These both have the same general form, $x'_i = a_i x_i + b_i$. Their dynamical solutions in every generation $t = 0, 1, \ldots$, are immediately found to be

$$x_i^{(t)} = \begin{cases} (a_i)^t(x_i^{(0)} - x_i^*) + x_i^* & \text{if } a_i \neq 1 \\ x_i^{(0)} + tb_i & \text{if } a_i = 1 \end{cases} \text{ for } i = 1, 2, \quad (11)$$

where $x_i^{(0)} = u_{ii}^{(0)}/u_{12}^{(0)}$ is the initial value of x_i, and the remaining terms,

$$a_i = \frac{f_{ii}v_{ii}}{m_{12}f_{12}v_{12}} \quad (12)$$

$$x_i^* = \frac{f_{12}m_{ii}v_{ii}}{m_{12}f_{12}v_{12} - f_{ii}v_{ii}} \quad (13)$$

and

$$b_i = \frac{m_{ii}v_{ii}}{m_{12}v_{12}}, \quad (14)$$

where $x_i^* = b_i/(1 - a_i)$, are functions of the selective values in the population whose interpretations are given below.

The explicit analytical formulas for the genotypic frequencies after any number of generations t of selfing and selection are now obtained simply by substituting the solutions for $x_1^{(t)}$ and $x_2^{(t)}$ from (11–14) into the relations in (6–8). The corresponding time-dependent solution for the frequency of the A_1 allele is

$$p^{(t)} = u_{11}^{(t)} + \tfrac{1}{2}u_{12}^{(t)}$$
$$= \frac{x_1^{(t)} + \tfrac{1}{2}}{1 + x_1^{(t)} + x_2^{(t)}} \quad \text{for } t = 0, 1, \ldots. \quad (15)$$

Dynamical and equilibrium behavior: The form of these solutions immediately reveals that the dynamical and limiting behavior under this model depends on the relative magnitude of the geometric terms a_1 and a_2 [defined in (12)], and whether their values are above, below, or equal to 1. A comprehensive analysis of the dynamics under all possible numerical orderings of a_1, a_2, and 1 shows that there are precisely four types of evolutionary outcomes for the equilibrium genotypic frequencies in the population. These types of outcomes are given in Table 2 in terms of the values of a_1 and a_2, together with the corresponding conditions on the selection parameters. This classification both completes and simplifies that presented by Karlin (1969).

Turning to the biological interpretation of these findings, we see that the population dynamics are governed by the relative magnitudes of composite fitness values for each of the three genotypes (Table 2, column 3). These delimiting values correspond to the relative rate at which individuals survive and produce offspring with their own genotype. For homozygotes, which only bear progeny like themselves, these values are simply their net fitnesses ($f_{11}v_{11}$,$f_{22}v_{22}$), corresponding to the product of their average number of offspring and the probability that they survive to reproduce. The value for heterozygotes ($m_{12}f_{12}v_{12}$), however, is discounted by the factor m_{12} because heterozygotes do not ordinarily breed true. In the special case of Mendelian segregation, for instance, the composite fitness value for heterozygotes is half their net fitness ($\tfrac{1}{2}f_{12}v_{12}$).

The results summarized in Table 2 show that under this model, a purely selfing population will converge to a polymorphic equilibrium with all three genotypes present (outcome 1) if and only if the discounted net fitness of heterozygotes exceeds the net fitness of both homozygotes ($m_{12}f_{12}v_{12} > f_{11}v_{11}$,$f_{22}v_{22}$). These selective conditions are equivalent to the requirement that the net fitness of heterozygotes ($f_{12}v_{12}$) exceed those of the homozygotes ($f_{ii}v_{ii}$) by the factor $1/m_{12}$. With Mendelian segregation, this requires double overdominance ($f_{12}v_{12} > 2f_{11}v_{11}$,$2f_{22}v_{22}$). The minimum level of overdominance necessary for the maintenance of all three genotypes increases without bound as segregation distortion increases, provided that meiotic drive is equivalent and

TABLE 2

Classification of equilibrium genotypic frequencies under fertility, viability, and gametic selection in a selfing population

Outcome	Conditions on a_1 and a_2	Selection conditions	Genotype A_1A_1	Genotype A_1A_2	Genotype A_2A_2
1	$a_1, a_2 < 1$	$f_{11}v_{11}, f_{22}v_{22} < m_{12}f_{12}v_{12}$	$\hat{u}_{11} > 0$	$\hat{u}_{12} > 0$	$\hat{u}_{22} > 0$
2	$a_1 = a_2 \geq 1$	$f_{11}v_{11} = f_{22}v_{22} \geq m_{12}f_{12}v_{12}$	$\hat{u}_{11} > 0$	0	$\hat{u}_{22} > 0$
3	$a_2 < a_1 \geq 1$	$f_{22}v_{22} < f_{11}v_{11} \geq m_{12}f_{12}v_{12}$	1	0	0
4	$a_1 < a_2 \geq 1$	$f_{11}v_{11} < f_{22}v_{22} \geq m_{12}f_{12}v_{12}$	0	0	1

independent in male and female gametes [$m_{12} = 2m(1 - m)$].

Under the conditions producing outcome 1, the population will reach the unique equilibrium

$$\hat{u}_{11} = \frac{x_1^*}{1 + x_1^* + x_2^*}$$

$$\hat{u}_{12} = \frac{1}{1 + x_1^* + x_2^*}$$

$$\hat{u}_{22} = \frac{x_2^*}{1 + x_1^* + x_2^*}, \qquad (16)$$

where x_1^* and x_2^*, defined in (13), are in this case the final, limiting values of the variables x_1 and x_2. After substituting in their values, we obtain the exact equilibrium formulas for the genotypic frequencies

$$\hat{u}_{ii} = \frac{f_{12}m_{ii}v_{ii}(m_{12}f_{12}v_{12} - f_{jj}v_{jj})}{D} \quad \text{for } i \neq j = 1, 2 \qquad (17)$$

and

$$\hat{u}_{12} = \frac{(m_{12}f_{12}v_{12} - f_{11}v_{11})(m_{12}f_{12}v_{12} - f_{22}v_{22})}{D}, \qquad (18)$$

where the common denominator is

$$\begin{aligned} D = {} & f_{12}m_{11}v_{11}(m_{12}f_{12}v_{12} - f_{22}v_{22}) \\ & + (m_{12}f_{12}v_{12} - f_{11}v_{11})(m_{12}f_{12}v_{12} - f_{22}v_{22}) \\ & + f_{12}m_{22}v_{22}(m_{12}f_{12}v_{12} - f_{11}v_{11}) . \end{aligned} \qquad (19)$$

A second type of polymorphic equilibrium is also possible for purely selfing populations, with only the two homozygous genotypes present. In this model, heterozygotes will be eliminated monotonically, and the population will eventually split into two pure homozygous lines if and only if the net fitnesses of the two homozygotes are equal and are at least the discounted value for heterozygotes (Table 2, outcome 2). A given population has either a single or an infinite number of such equilibria, depending on the relative magnitudes of the composite fitnesses of the three genotypes. When the common net fitness of the homozygotes exactly equals the discounted value for heterozygotes ($f_{11}v_{11} = f_{22}v_{22} = m_{12}f_{12}v_{12}$), the frequencies of the two homozygotes converge to the unique equilibrium values

$$\hat{u}_{ii} = \frac{b_i}{b_1 + b_2} = \frac{m_{ii}v_{ii}}{m_{11}v_{11} + m_{22}v_{22}} \quad \text{for } i = 1, 2, \qquad (20)$$

where b_1 and b_2 are defined in (14). In this case, the final frequencies of the two homozygotes are in proportion to the product of their viabilities (v_{ii}) and the rate at which they are produced by heterozygotes (m_{ii}).

Alternatively, if the common net fitness of the homozygotes is higher than the discounted heterozygote value ($f_{11}v_{11} = f_{22}v_{22} > m_{12}f_{12}v_{12}$), as is true in the absence of selection, there is an infinite number of the second type of polymorphic equilibria. This is because the final homozygote frequencies then depend on the initial genotypic frequencies in the population, with

$$\hat{u}_{ii} = \frac{x_i^{(0)} - x_i^*}{x_1^{(0)} + x_2^{(0)} - x_1^* - x_2^*} \quad \text{for } i = 1, 2. \qquad (21)$$

After substituting the values for x_1^* and x_2^* from (13) and simplifying, we obtain the exact expressions for these equilibria in terms of the selection parameters and initial genotypic frequencies:

$$\hat{u}_{ii} = \frac{(f_{11}v_{11} - m_{12}f_{12}v_{12})u_{ii}^{(0)} + f_{12}m_{ii}v_{ii}u_{12}^{(0)}}{(f_{11}v_{11} - m_{12}f_{12}v_{12})(u_{11}^{(0)} + u_{22}^{(0)}) + f_{12}(m_{11}v_{11} + m_{22}v_{22})u_{12}^{(0)}} \qquad (22)$$

for $i = 1, 2$.

Two final general points should be made about the two types of polymorphic equilibria reached in this system (Table 2, outcomes 1 and 2). First, although the genotypes present at equilibrium depend only on the relative values of the composite fitnesses of the three genotypes, the formulas in (17–22) demonstrate that the exact final frequencies at a polymorphic equilibrium depend on the individual selection components because they involve additional terms of the form $f_{12}m_{ii}v_{ii}$ and $m_{ii}v_{ii}$. Second, barring very special relationships among the fitness parameters, the first type of polymorphic equilibrium will ordinarily be the only way to maintain allelic variation if the genotypes differ in fertility or viability. The final two possible equilibrium states (Table 2, outcomes 3 and 4) correspond to fixation of one

allele and loss of the other. The population will become fixed for A_1 if the net fitness of A_1A_1 individuals exceeds that of A_2A_2 individuals and is at least as high as the discounted value for heterozygotes ($f_{22}v_{22} < f_{11}v_{11} \geq m_{12}f_{12}v_{12}$. Analogous conditions lead to the fixation of A_2.

The four outcomes in Table 2 apply to the most biologically relevant case in which heterozygotes are initially present ($u_{12}^{(0)} > 0$) and further adult heterozygotes can be produced ($m_{12}f_{12}v_{12} > 0$). If this is not the case, the population remains as two homozygous lines, with their relative frequencies in every generation $t \geq 1$ given by

$$\frac{u_{11}^{(t)}}{u_{22}^{(t)}} = \left(\frac{f_{11}v_{11}}{f_{22}v_{22}}\right)^t \left(\frac{u_{11}^{(0)}}{u_{22}^{(0)}}\right). \tag{23}$$

The frequencies of the A_1A_1 genotype and the A_1 allele in adults in any generation $t = 0, 1,...,$ then have the common value

$$u_{11}^{(t)} = p^{(t)} = \frac{a^t u_{11}^{(0)}}{1 - u_{11}^{(0)} + a^t u_{11}^{(0)}}, \quad \text{where } a = \frac{f_{11}v_{11}}{f_{22}v_{22}}. \tag{24}$$

Analysis of this dynamical solution (24) shows that in the absence of heterozygotes, the frequency of allele A_1 increases monotonically to 1 if A_1A_1 individuals have a higher net fitness than A_2A_2 individuals ($f_{11}v_{11} > f_{22}v_{22}$), decreases monotonically to 0 if A_2A_2 individuals have the higher net fitness ($f_{11}v_{11} < f_{22}v_{22}$), and remains at its initial value if both homozygotes have the same net fitness ($f_{11}v_{11} = f_{22}v_{22}$), as expected for selection on two autonomous lines.

Individual selection components: The preceding analysis fully delimits the dynamical and limiting behavior in purely selfing populations experiencing any combination of fertility, viability, and gametic selection. Because of their distinctive features, it is also informative to examine the evolutionary consequences of each of these three selection components individually. For simplicity, we focus here on the most interesting biological case, in which adult heterozygotes are initially present, can continue to be produced, and bear both heterozygous and homozygous progeny ($0 < m_{12} < 1$). Sample trajectories for the genotypic and allelic frequencies under each form of selection are provided in Figure 1, with Figure 1A showing the baseline dynamics in the absence of selection.

Gametic selection alone ($f_{ij} \equiv v_{ij} \equiv 1$): If a diallelic locus is subject only to meiotic drive, with equal fertilities and viabilities for the three genotypes, then the geometric terms in (12) are $a_1 = a_2 = 1/m_{12} > 1$. This ensures that the population will always converge to the second type of polymorphic equilibrium (Table 2, outcome 2) consisting of the two true breeding homozygous lines. Consequently, allelic variation will always be maintained under meiotic drive in a purely selfing population, whereas a random mating population will usually become fixed for the preferentially transmitted allele (Hartl and Clark 1997).

Equation 22 shows that with pure selfing, the frequency of A_iA_i homozygotes will converge to

$$\hat{u}_{ii} = u_{ii}^{(0)} + \left(\frac{m_{ii}}{m_{11} + m_{22}}\right) u_{12}^{(0)}. \tag{25}$$

The final frequency of each homozygote equals its initial frequency ($u_{ii}^{(0)}$) plus a proportion of the initial frequency of heterozygotes ($u_{12}^{(0)}$) corresponding to the relative rate at which that homozygous genotype is produced by heterozygotes (m_{ii}). The equilibrium frequency of allele A_1, $\hat{p}$, will exceed its initial value ($p^{(0)} = u_{11}^{(0)} + \frac{1}{2}u_{12}^{(0)}$) if and only if A_1 is preferentially transmitted by heterozygotes ($m_{11} > m_{22}$). The A_1 allele will predominate at equilibrium ($\hat{p} > \frac{1}{2}$) if and only if $m_{11}(1 - 2u_{22}^{(0)}) > m_{22}(1 - 2u_{11}^{(0)})$, which compares unexpected cross-products involving the initial frequencies of each homozygote and the rate at which the other homozygote is produced by heterozygotes. The dependence upon initial conditions under meiotic drive is illustrated in Figure 1, B and C.

Fertility selection alone ($m_{11} = m_{22} = \frac{1}{4}$, $m_{12} = \frac{1}{2}$; $v_{ij} \equiv 1$): If a locus is subject only to fertility selection, with Mendelian segregation and no viability differences among the genotypes, the geometric terms in (12) are $a_1 = 2f_{11}/f_{12}$ and $a_2 = 2f_{22}/f_{12}$. All four possible equilibrium outcomes (Table 2) can occur in this case, depending upon the relative magnitudes of the fertility of heterozygotes (f_{12}) and twice the fertility of the two homozygotes ($2f_{11}$, $2f_{22}$). The population will reach a fully polymorphic equilibrium with all three genotypes present (Figure 1D, outcome 1) if and only if heterozygotes produce over twice as many offspring as each homozygote ($f_{12} > 2f_{11}, 2f_{22}$). Using (17–19), the limiting genotypic frequencies are then

$$\hat{u}_{ii} = \frac{f_{12}(f_{12} - 2f_{jj})}{2(f_{12} - 2f_{11})(f_{12} - f_{22}) + 2(f_{12} - 2f_{22})(f_{12} - f_{11})} \quad \text{for } i \neq j = 1, 2 \tag{26}$$

and

$$\hat{u}_{12} = \frac{(f_{12} - 2f_{11})(f_{12} - 2f_{22})}{(f_{12} - 2f_{11})(f_{12} - f_{22}) + (f_{12} - 2f_{22})(f_{12} - f_{11})}. \tag{27}$$

These polymorphic equilibrium frequencies depend on the fertility of heterozygotes (f_{12}) and the difference between the fertilities of heterozygotes and homozygotes ($f_{12} - f_{ii}$), as well as the difference between the fertilities of heterozygotes and twice that of homozygotes ($f_{12} - 2f_{ii}$), but not directly on the fertility of the homozygotes.

Alternatively, a polymorphism will be maintained via a split into the two homozygous lines (outcome 2) if the two homozygotes have equal fertilities that are at least half that of heterozygotes ($f_{11} = f_{22} \geq \frac{1}{2}f_{12}$). If $f_{11} = f_{22} = \frac{1}{2}f_{12}$, then (20) shows that the final frequency of both homozygotes will always be $\frac{1}{2}$, whatever the exact fertilities of the three genotypes; if $f_{11} = f_{22} > \frac{1}{2}f_{12}$ (Figure

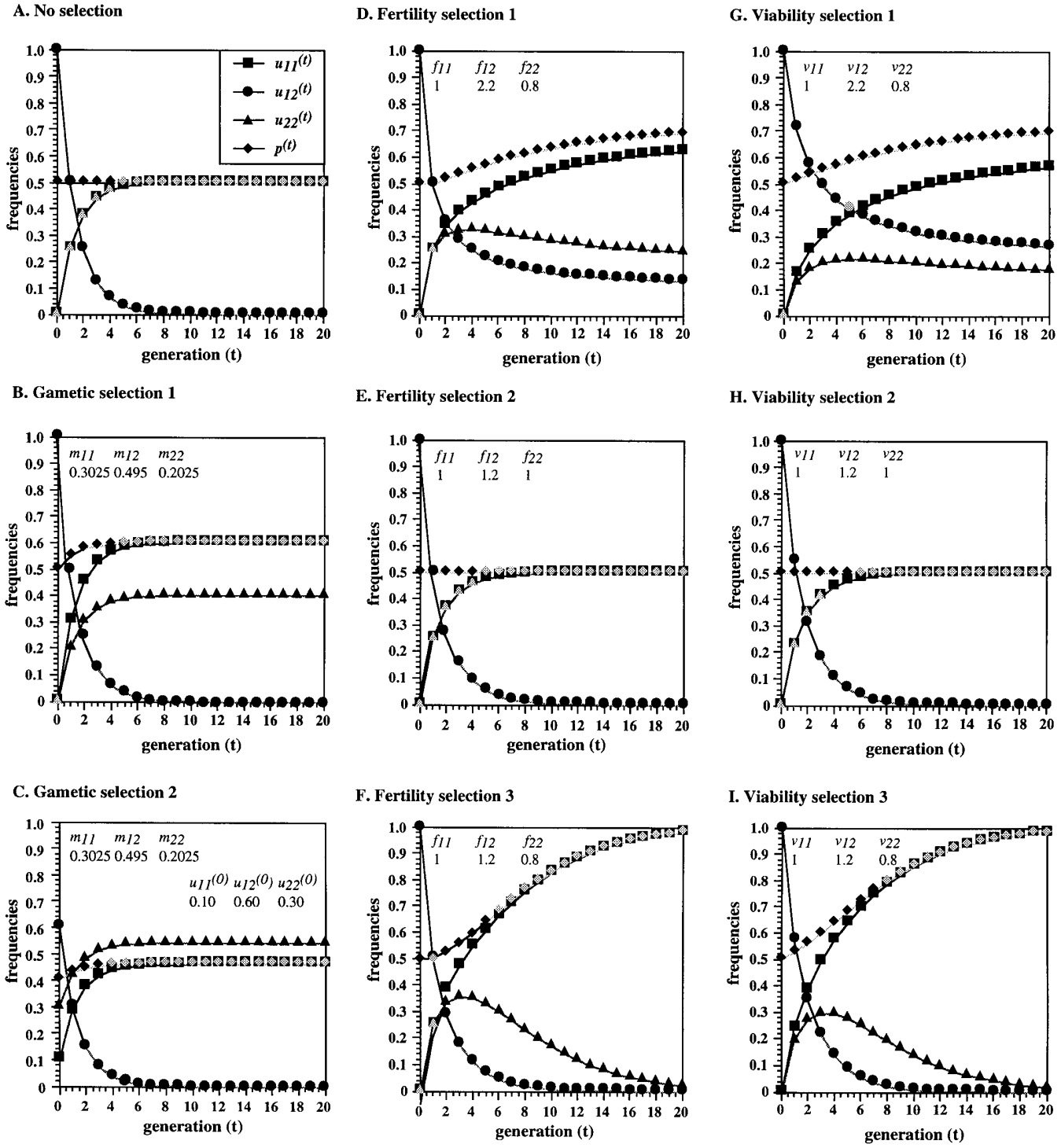

Figure 1.—The impact of gametic, fertility, and viability selection on genotype and allele frequencies under our purely selfing model. Genotypic frequencies $u_{11}^{(t)}$, $u_{12}^{(t)}$, and $u_{22}^{(t)}$, and the A_1 allele frequency, $p^{(t)}$, are plotted as a function of generation (t) for a large selfing population for 20 generations. (A) No selection results in the monotonic loss of heterozygotes at a rate of one half per generation, where the values for each fitness parameter were $f_{ij} = v_{ij} = 1$, $m_{11} = 0.25$, $m_{12} = 0.5$, $m_{22} = 0.25$, and the initial condition was $u_{12}^{(0)} = 1$. The changes from these values are indicated on the relevant graphs B–I. (B–C) Gametic selection. (D–F) Fertility selection (fertility is normalized with respect to a value of 1 for f_{11}). (G–I) Viability selection (viability is normalized with respect to a value of 1 for v_{11}).

1E), (22) shows that the final frequencies of the two homozygous genotypes depend on both the fertilities and initial frequencies of each genotype, with

$$\hat{u}_{ii} = \frac{2(2f_{11} - f_{12})u_{ii}^{(0)} + f_{12}u_{12}^{(0)}}{2(2f_{11} - f_{12})(u_{11}^{(0)} + u_{22}^{(0)}) + 2f_{12}u_{12}^{(0)}} \quad \text{for } i = 1, 2. \tag{28}$$

The population will become fixed for allele A_i (Figure 1F, outcome 3 or 4) if and only if A_iA_i individuals produce more progeny than A_jA_j individuals and produce at least half as many progeny as heterozygotes ($f_{jj} < f_{ii} \geq \frac{1}{2} f_{12}$).

Viability selection alone ($m_{11} = m_{22} = \frac{1}{4}$, $m_{12} = \frac{1}{2}$; $f_{ij} \equiv 1$): The behavior under viability selection alone, with Mendelian segregation and no fertility differences among the genotypes, is similar to that under fertility selection alone. The geometric terms in (12) have the analogous forms $a_1 = 2v_{11}/v_{12}$ and $a_2 = 2v_{22}/v_{12}$, and thus all four equilibrium outcomes (Table 2) are again possible, with the delimiting values now the relative magnitudes of the viability of heterozygotes (v_{12}) and twice the viability of the two homozygotes ($2v_{11}$, $2v_{22}$). Paralleling fertility selection, all three genotypes will be retained at equilibrium (Figure 1G, outcome 1) if and only if heterozygotes survive to reproduce at over twice the rate of each homozygote ($v_{12} > 2v_{11}, 2v_{22}$). The final values,

$$\hat{u}_{ii} = \frac{v_{ii}(v_{12} - 2v_{jj})}{(v_{12} - 2v_{11})(v_{12} - v_{22}) + (v_{12} - 2v_{22})(v_{12} - v_{11})} \quad \text{for } i \neq j = 1, 2 \tag{29}$$

and

$$\hat{u}_{12} = \frac{2(v_{12} - 2v_{11})(v_{12} - 2v_{22})}{(v_{12} - 2v_{11})(v_{12} - v_{22}) + (v_{12} - 2v_{22})(v_{12} - v_{11})}, \tag{30}$$

however, are not equivalent to those in (26) and (27) for fertility selection. One difference is that with viability selection, the equilibrium genotypic frequencies depend directly on the homozygote viabilities and not the heterozygote viabilities, which is the reverse of the result for fertility selection. Most importantly, comparing (27) and (30) reveals that viability selection maintains twice as many heterozygotes at equilibrium as does a comparable level of fertility selection ($f_{ij} = v_{ij}$).

Further differences are found for the second type of polymorphic equilibrium (outcome 2), consisting of the two homozygous genotypes. The final frequencies of the two homozygotes are again $\hat{u}_{ii} = \frac{1}{2}$ if the viabilities of the two homozygotes are equal and half that of heterozygotes ($v_{11} = v_{22} = \frac{1}{2}v_{12}$); however, the final frequencies of the two homozygotes when $v_{11} = v_{22} > \frac{1}{2}v_{12}$ (Figure 1H),

$$\hat{u}_{ii} = \frac{2(2v_{11} - v_{12})u_{ii}^{(0)} + v_{11}u_{12}^{(0)}}{2(2v_{11} - v_{12})(u_{11}^{(0)} + u_{22}^{(0)}) + 2v_{11}u_{12}^{(0)}} \quad \text{for } i = 1, 2, \tag{31}$$

differ from those in (28) for fertility selection in that the heterozygote fitness is replaced by the homozygote value in the terms involving the initial frequency of heterozygotes ($u_{12}^{(0)}$). The conditions for fixation are completely analogous under the two forms of selection. Under viability selection alone, the population will become fixed for allele A_i (Figure 1I, outcome 3 or 4) if and only if A_iA_i individuals survive to reproduce more often than A_jA_j individuals, and survive at least half as often as heterozygotes ($v_{jj} < v_{ii} \geq \frac{1}{2}v_{12}$).

Mixed selfing and apomixis model: A direct extension of this approach provides a full dynamical and equilibrium analysis for populations that reproduce by a combination of selfing and apomixis (the asexual production of zygotes). Formally, we assume each individual selfs with probability s and reproduces apomictically with probability $1 - s$. The only other difference from the original model is that separate fertilities are allowed for the two forms of reproduction, with f_{ij} representing the average number of progeny produced by selfing, as before, and F_{ij} representing the number of progeny from apomixis.

Working through a complete generation cycle shows that the genotypic recursions under this mixed, selfing-apomixis model are

$$u_{11}' = \frac{[sf_{11} + (1 - s)F_{11}]v_{11}u_{11} + (sf_{12}m_{11}v_{11})u_{12}}{\overline{w}} \tag{32}$$

$$u_{12}' = \frac{[sm_{12}f_{12} + (1 - s)F_{12}]v_{12}u_{12}}{\overline{w}} \tag{33}$$

$$u_{22}' = \frac{[sf_{22} + (1 - s)F_{22}]v_{22}u_{22} + (sf_{12}m_{22}v_{22})u_{12}}{\overline{w}}, \tag{34}$$

where the normalizing factor is now

$$\begin{aligned}\overline{w} = {} & [sf_{11} + (1 - s)F_{11}]v_{11}u_{11} \\ & + [sf_{12}(m_{11}v_{11} + m_{12}v_{12} + m_{22}v_{22}) \\ & + (1 - s)F_{12}v_{12}]u_{12} \\ & + [sf_{22} + (1 - s)F_{22}]v_{22}u_{22}.\end{aligned} \tag{35}$$

The time-dependent solutions for the transformed variables, $x_1 = u_{11}/u_{12}$ and $x_2 = u_{22}/u_{12}$, are equivalent to those in (11) with the constant factors now

$$a_i = \frac{[sf_{ii} + (1 - s)F_{ii}]v_{ii}}{[sm_{12}f_{12} + (1 - s)F_{12}]v_{12}} \tag{36}$$

$$x_i^* = \frac{sf_{12}m_{ii}v_{ii}}{[sm_{12}f_{12} + (1 - s)F_{12}]v_{12} - [sf_{ii} + (1 - s)F_{ii}]v_{ii}} \tag{37}$$

and

$$b_i = \frac{sf_{12}m_{ii}v_{ii}}{[sm_{12}f_{12} + (1 - s)F_{12}]v_{12}} = \frac{sf_{12}m_{ii}}{sf_{ii} + (1 - s)F_{ii}}. \tag{38}$$

Note that the second formula for b_i in (38) is a simplification that applies specifically to the case in (11) where $a_i = 1$. Substituting these new constant factors into (11) and the resulting solutions for $x_1^{(t)}$ and $x_2^{(t)}$ into (6–8) and (15) yields the dynamics of the genotypic and allele frequencies under selection with any combination of selfing and apomixis.

This new model has the same four possible evolutionary outcomes as the original, based on the relative magnitudes of a_1, a_2, and 1 shown in Table 2. Biologically, the actual outcome (and the rate at which it is attained) again depends on composite fitness values for the three genotypes, with the homozygote values in the third column of Table 2 replaced by $[sf_{11} + (1 - s)F_{11}]v_{11}$ and $[sf_{22} + (1 - s)F_{22}]v_{22}$, and the heterozygote value replaced by $[sm_{12}f_{12} + (1 - s)F_{12}]v_{12}$. These new composite fitnesses are a weighted average of those under selfing and apomixis. The selfing component is as before, the net fitness under self-fertilization ($f_{ii}v_{ii}$) for homozygotes and the discounted value ($m_{12}f_{12}v_{12}$) for heterozygotes, while that for apomixis is simply the net fitness of each genotype when it reproduces apomictically ($F_{ij}v_{ij}$), since each individual then breeds true.

Inspection of the biological conditions associated with each of the four evolutionary outcomes reveals two noteworthy features of mixed selfing and apomixis. First, under meiotic drive alone, allelic polymorphisms are always maintained via a split into the two homozygous lines because then $a_1 = a_2 = 1/[1 - s(1 - m_{12})] > 1$. In fact, the equilibrium frequencies are independent of the relative proportions of apomixis and selfing and always equal those in (25) for purely selfing populations. The second point arises from the fact that if there are any fertility or viability differences, genetic variation will ordinarily be maintained if and only if $[sm_{12}f_{12} + (1 - s)F_{12}]v_{12} > [sf_{11} + (1 - s)F_{11}]v_{11}$, $[sf_{22} + (1 - s)F_{22}]v_{22}$. The presence of apomixis thus serves, as expected, to facilitate the maintenance of genetic variation, because the apomictic component is satisfied by simple overdominance ($F_{12}v_{12} > F_{11}v_{11}$, $F_{22}v_{22}$) as opposed to the "super-overdominance" condition for the selfing component. The final limiting values for the polymorphic equilibria under selfing and apomixis can be obtained by substituting the values from (37) and (38) into (16), (21), and the first relation in terms of b_1 and b_2 in (20).

ARABIDOPSIS ACTIN MUTANTS: A CASE STUDY

This mathematical framework provides a valuable tool for dissecting the selective forces at work in large diploid populations with negligible rates of outcrossing. An immediate application is furnished by the companion article (Gilliland *et al.* 1998), in which we demonstrated that mutant alleles for three distinct plant actin genes in Arabidopsis (*act2-1*, *act4-1*, and *act7-1*) were significantly reduced in frequency by the F_2 generation, with significant deviations in the genotypic frequencies from those expected without selection. The three actin gene family members belong to different, ancient, and conserved actin subclasses, and they are all strongly expressed in a distinct temporal and spatial pattern (McDowell *et al.* 1996). Although homozygous mutant plants (A_2A_2) in each of the three actin genes appeared morphologically normal and robust as adults, and appeared to have a normal seed set relative to the wild-type (A_1A_1), it is unlikely that such highly conserved genes could be fully redundant.

The detailed experimental analysis of the *act2-1* genotype frequencies (Gilliland *et al.* 1998) provides a valuable case study for the application of the theoretical framework developed herein for detecting deleterious genotypes. Starting with a single heterozygote in the F_0 generation, these experiments followed the genotype and allele frequencies in large selfing populations (*ca.* 100 plants each) through the F_3 generation. Because there were highly significant deviations in the F_2 and F_3 generations from the genotypic frequencies expected under selective neutrality, the null hypothesis of no selection is rejected for the data set as a whole. Inasmuch as the F_1 progeny of the original heterozygote were consistent with Mendelian segregation ratios (1:2:1), meiotic drive does not appear to be the major factor. In the initial analysis here, we consequently focus on fertility and viability selection as the possible causes of the reduced frequency of the *act2-1* allele under our model.

After exploring various combinations of fertility parameters, we found that the multigenerational data on the *act2-1* mutant are consistent with fertility selection alone, where the fertility of the A_1A_2 heterozygotes are only slightly reduced ($f_{12} = 0.8$), while that of the A_2A_2 homozygous mutant is half ($f_{22} = 0.5$) that of the wild type ($f_{11} = 1$), as shown in Figure 2A. The chi-square values for the genotypic frequencies in the F_1, F_2, and F_3 generations are all less than 2, showing that these data do not deviate significantly from the predicted values ($P = 0.38$–0.75 with 2 d.f.).

Viability selection alone gives an even better fit to the experimental results (Figure 2B) when the viability of the A_1A_2 heterozygotes is slightly reduced ($v_{12} = 0.87$) and the viability of the A_2A_2 homozygous mutant is only a bit lower ($v_{22} = 0.7$) relative to that of the wild type ($v_{11} = 1$). The chi-square values for the three genotypes are all below 1.2 ($P = 0.57$–0.90). In theory, the simplest interpretation of this experimental data would be that only the homozygous mutants have a reduced fitness. However, when a simple recessive model was explored, where only the A_2A_2 genotype had reduced fertility (not shown) or reduced viability (Figure 2C), the model did not fit the experimental results as well as models with directional selection and partial dominance ($P = 0.13$–0.94).

Two practical points should be made about these numerical calculations. First, they are based on an informal exploration of the parameter space, and they are intended only to demonstrate that the *act2-1* dynamics

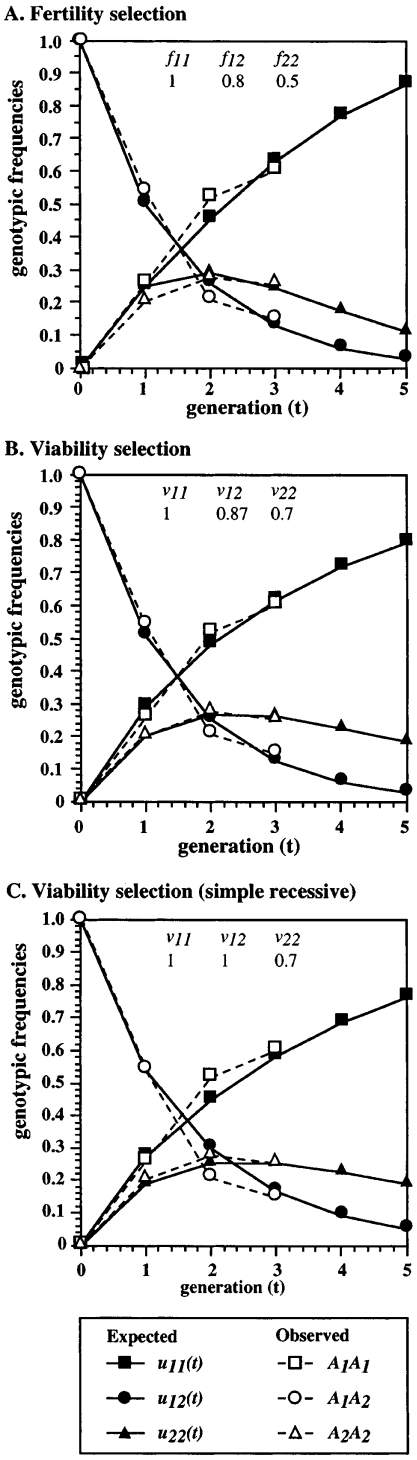

Figure 2.—Fertility or viability selection alone can account for the decline of the *act2-1* allele from Arabidopsis populations. The genotypic frequencies $u_{11}^{(t)}$, $u_{12}^{(t)}$, and $u_{22}^{(t)}$ are plotted as a function of generation (t) for a large selfing population for six generations, with the F_0 generation being a single heterozygote ($u_{12}^{(0)} = 1$). Predictions (closed symbols) are compared to four generations of experimental results for the *act2-1* genotypes (open symbols) presented in a companion manuscript (Gilliland *et al.* 1998). Selection parameters were chosen which most closely approximated the observed genotypic frequencies, where *ACT2* = A_1 and *act2-1* = A_2 . Unless indicated otherwise, fitness parameters were $f_{ij} = v_{ij} = 1$, $m_{11} = 0.25$, $m_{12} = 0.5$, and $m_{22} = 0.25$. (A) Fertility selection with directional selection against the A_2 allele. (B) Viability selection with directional selection against the A_2 allele. (C) Viability selection against a deleterious recessive A_2 allele.

in these experiments can be well explained by our simple selection model. Formal estimates of the selection components are obtainable by collecting and analyzing data from further generations via a maximum likelihood estimation procedure based on the model (see discussion). The second practical note is that the projected genotypic frequencies and the comparisons with empirical data presented here were all calculated and plotted using Delta Graph, version 4.0.1, which runs on a Macintosh computer (Deltapoint, Inc., Monterey, CA). A copy of the program is available through our web site (www.genetics.uga.edu) by requesting software for detection of deleterious genotypes.

DISCUSSION

A formal dissection of selection components is greatly facilitated in diploid populations that lack appreciable outcrossing, such as those for the model organism Arabidopsis. This simpler genetic structure allows the development of precise analytic formulas for predicting the evolutionary consequences of selection in diploid, selfing populations, with or without apomixis. By focusing on the readily analyzable dynamics of the ratio of homozygote to heterozygote frequencies, we easily derived explicit time-dependent solutions for the genotype and allele frequencies at diallelic loci under any combination of fertility, viability, and gametic selection through meiotic drive. In the absence of outcrossing, such selection may maintain all three genotypes, only the two homozygotes, or only a single homozygous line, depending on the relative magnitudes of composite fitness values for the three genotypes. The delimiting values are a weighted average of the net genotypic fitnesses (fertility × viability) under selfing and apomixis, with the selfing component for heterozygotes discounted by the frequency with which heterozygotes breed true when they self fertilize. Interestingly, although fertilities and viabilities play an equivalent role in determining which genotypes are retained or lost, the two types of selection yield different frequencies at polymorphic equilibria; viability selection alone, for instance, maintains twice the frequency of heterozygotes found under comparable levels of fertility selection in selfing populations.

The selective conditions that retain genetic diversity in selfing populations are very different from those in outcrossing populations. With or without apomixis,

selfing will always preserve allelic variation under meiotic drive alone, whereas any random mating will usually lead to fixation for the preferentially transmitted allele. On the other hand, selfing hinders the maintenance of genetic variation if there are any fertility or viability differences; in such cases, a genetic polymorphism will ordinarily be preserved under selfing if and only if the net fitness of heterozygotes is substantially higher than those of both homozygotes, as opposed to the simple overdominance in fitness needed in fully random mating populations. Selfing also makes it more difficult to preserve allelic variation when combined with either apomixis or outcrossing, or both (Overath and Asmussen 1998). Under complete selfing and Mendelian segregation ratios, permanent genetic diversity usually requires a twofold fitness advantage for heterozygotes, with the required level of overdominance ameliorated by apomixis and magnified by meiotic drive.

The results here apply directly to fairly large, isolated populations with no outcrossing, but they can also provide valuable insight into the behavior when there is a negligible rate of random mating. The accuracy of this approximation depends on the number of generations followed, since any outcrossing will ordinarily preclude the second equilibrium outcome above, in which the population ultimately splits into the two homozygous lines. Practically speaking, however, the final frequency of heterozygotes with insignificant rates of outcrossing should be so low that they are effectively lost from such populations. In addition, over the relatively small number of generations followed in most empirical applications, the expected trajectories for the genotypic frequencies should be essentially unaffected by a low rate of outcrossing.

The practical utility of this theoretical framework is affirmed by a case study of the *act2-1* actin mutant in highly selfing, experimental populations of Arabidopsis. Several critical conclusions can be drawn from this simple application of our generalized selfing model. First, the data are well fit by either fertility or viability selection alone, with directional selection against an incompletely dominant mutant (a reduced fitness for A_1A_2 and a greater reduced fitness for A_2A_2 relative to A_1A_1 wild type). Second, under the two best-fitting sets of selection parameters (Figure 2, A and B), the *act2-1* allele should be effectively lost (frequency $< 0.1\%$) within 20 generations (data not shown). For Arabidopsis in the field, that would be only 20 years. Clearly, the *ACT2* gene is *not* redundant and is almost certainly required for the survival of Arabidopsis. Third, the mathematical framework developed here greatly facilitates the analysis and detection of potentially deleterious genotypes and alleles in multigenerational studies. It should be equally useful in dissecting selection parameters in other experimental and natural populations with low rates of outcrossing, where selection is weaker and the change in allele frequencies is less rapid than that observed for the actin mutants. The power to detect and estimate such selection, however, will depend critically on having an adequate sample size and multigenerational data.

In our preliminary analysis of the *act2-1* data, the best-fitting selection parameters for the observed genotypic frequencies for *ACT2* were obtained by an informal exploration of the parameter space. This *ad hoc* approach nonetheless provided an impressive fit to the three generations of data available to date, assuming either fertility or viability selection alone. It is difficult to tell, however, whether this good fit will be maintained in subsequent generations (Figure 2) or whether the *act2-1* mutant is subject to more than one selection component. Before finalizing our conclusions on the form(s) and strength of selection acting in this system, it will be important to continue these experimental Arabidopsis populations for several additional generations and then analyze the complete data set by using formal statistical estimation procedures (Weir 1996).

To directly estimate all three components of selection (fertility, viability, and gametic) in our model, we would ideally have population data from all three life stages (adults, new zygotes, and gametes). In practice, however, most experimental population genetic studies examining diallelic loci have only adult data with 2 d.f. for each generation, as presented in Gilliland *et al.* (1998) for the mutant actin alleles in Arabidopsis. With this limitation, we can estimate two of the fitness parameters (Table 1) and thus one of the selection components, based on data from any two generations (one of which may be the initial population). For the fertility and viability components, this requires normalizing the three fertilities (or viabilities) relative to a value of 1 for A_1A_1, for example, which is legitimate because the genotypic recursions in (1–4) are unaffected if each fertility (or viability) parameter is altered by the same constant factor.

A direct extension of this reasoning indicates that, in principle, all three selection components could be estimated from adult data, provided that independent samples are available from three or more generations beyond the F_0 (each with two degrees of freedom). By adapting established methods based on the fit to equilibrium frequencies (*e.g.*, Asmussen *et al.* 1989; Goodisman and Asmussen 1997), our time-dependent solutions under selection can be used to obtain formal maximum likelihood estimates for the set of fertility, viability, and gametic selection parameters that best account for observed dynamical data from populations with insignificant rates of outcrossing. These maximum likelihood estimates are the parameter values that together maximize the composite likelihood of the observed multigenerational frequencies of the three genotypes. With data from sufficient generations, it is possible to both estimate the fitness parameters and test the fit of the underlying model to the data. A computer program providing the maximum likelihood estimates

and their 95% confidence intervals based on multigenerational adult data is currently under development and will be presented elsewhere, along with an application to the complete Arabidopsis *act2-1* study, which is now in progress.

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