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Heterosis and Outbreeding Depression

With such great benefits, it is no surprise that the breeding of food and future biofuel crops is based on principles that control heterosis, but those principles are still not understood.
Lippman and Zamir 2007

Inbreeding is the crossing of related individuals from the *same population* (including selfing as a special case), while **crossbreeding** is the mating of unrelated individuals from *different populations*. While the mating of relatives often results in inbreeding depression (Chapter 12), crossbreeding can have two rather different outcomes, depending, in part, on amount of genetic divergence between the populations being crossed. Agronomists and animal breeders have long known that crossing two distinct lines often has positive effects on fitness-related and agronomic traits in their F_1 progeny (Darwin 1876; Lerner 1954; Sheridan 1981; Turton 1981; Sprague 1983), with breeders historically noting that such hybrids showed **luxuriance** for size or growth traits. An F_1 performance that exceeds the average parental performance is generally referred to as **hybrid vigor** or **heterosis** (Shull 1914). Complicating matters is the frequent observation that when heterosis arises in an F_1 population, much of it is lost in the F_2 and subsequent generations.

Conversely, as the crossed populations become genetically more distinct, their F_1 progeny may become significantly *less fit* than the members of the original parental lines, a phenomenon known as **outbreeding depression.** For example, crosses between different species or distantly related populations frequently lead to substantial or complete loss of viability and/or fecundity (Barton and Hewitt 1981; Templeton 1981; Shields 1982; Coyne and Orr 1989a, 1997; Wu and Palopoli 1994). Indeed, outbreeding depression is the genetic basis for post-zygotic species isolation barriers, wherein the offspring of a between-species cross are either inviable or sterile. Notably, whether one observes heterosis versus outbreeding depression can be *trait specific*, as examples of each can be seen in the *same cross*. Consider the offspring from a female horse (a mare) and a male donkey (a jack). From an agronomic prospective, their F_1 offspring (a mule) is considered more hardy than either of its parents, and hence displays heterosis for these traits. However, it is also sterile, and thus shows outbreeding depression for fitness. These two distinct phenomena resulting from outcrossing are of concern in different applications of quantitative genetics. Breeders are concerned with how to best exploit heterosis for improved agricultural production, while evolutionary biologists are more interested with outbreeding depression, which (as detailed below) is often assumed to be a byproduct of local adaptation.

Heterosis is often presented (either directly or by inference) as being the complementary process to inbreeding depression. In a sense, this is correct, as both jointly require nonadditive gene interaction (dominance and/or epistasis) in the presence of nonrandom mating. The deficiency of heterozygotes (with respect to random mating) that occurs under inbreeding can result in a decrease in the progeny mean, while the excess of heterozygotes under crossbreeding can cause the progeny mean to increase. When the only nonadditive gene action is dominance, it is usually the case that a trait showing inbreeding depression will also display heterosis, and vice versa, and hence the two phenomena are coupled. However, when epistasis is present, there can be ***considerable uncoupling of these two phenomena***. The most striking example of this is the observation of joint inbreeding and outbreeding depression for a given trait (Edmands 2006 reviews a few such observations).

Our treatment of crossbreeding is divided into discussions on its genetic underpinnings

and on its applications. Our discussion of genetics starts by assuming that only dominance is present, showing that directional dominance is required for heterosis (as was the case for inbreeding depression). The impact of epistasis is examined next, which can result in a larger reduction in F_2 heterosis than predicted from dominance alone, and can also generate outbreeding depression. We then examine results from biometrical and QTL mapping approaches on the nature of both the dominance (partial dominance versus overdominance) and epistatic contribution to heterosis.

Our discussion of applications of crossbreeding starts with the agricultural exploitation of heterosis, and contrasts the approaches of plant versus animal breeders. The former typically stop after producing hybrid (F_1) seed (**terminal crosses**), while the later use much more elaborate schemes, such as rotational crossbreeding (continual crosses) and the exploitation of maternal heterosis. We conclude by examining outbreeding depression, which has considerable applications on conservation biology and is of great interest to evolutionary biologists.

HETEROSIS AND DIRECTIONAL DOMINANCE

The fundamental distinction between inbreeding depression and heterosis is that the former arises in crosses *within* a population (selfing or mating of relatives), while the latter arises in crosses *between* populations. Under inbreeding, the reference mean is that of an outbred individual (μ_0), while under heterosis, the reference mean is usually the **midparental value**, μ_{MP}. If μ_{P_i} denotes the mean of the ith population, then

$$\mu_{MP} = \frac{\mu_{P_1} + \mu_{P_2}}{2} \tag{13.1a}$$

Note that μ_{MP} is often denoted by $\overline{P}$, the average of the parental lines, and the later also refers to the average when more than two parental lines are considered (as in the case of synthetics, see below). The amount of F_1 heterosis is defined as

$$H_{F_1} = \mu_{F_1} - \mu_{MP} \tag{13.1b}$$

Midparent heterosis is said to occur when the F_1 mean exceeds the midparental value ($H_{F_1} > 0$), while **high-parent heterosis** (occasionally referred to as **heterobeltiosis**) occurs when the F_1 mean exceeds the mean of the best-performing (i.e., the high) parent, with $\mu_{F_1} > \max(\mu_{P_1}, \mu_{P_2})$.

If a trait has only an additive basis, then $\mu_{F_1} = \mu_{MP}$ and there is no heterosis (Chapter 11). Hence, nonadditive gene action is *necessary* for heterosis, but (as with inbreeding depression), it is *not* sufficient. Consider the situation where dominance (but no epistasis) occurs, and let the genotypic values for $q_iq_i : Q_iq_i : Q_iQ_i$ at a locus, i, underlying the trait be $0 : a_i + d_i : 2a_i$. Let p_i be the frequency of allele Q_i in population (or line) one and $p_i + \delta_{p_i}$ denote the frequency of Q_i in line two. The mean value of the F_1 is obtained as follows. With probability $p_i \cdot (p_i + \delta_{p_i})$, a Q_i allele is drawn from both populations, yielding a Q_iQ_i genotype with value $2a_i$. Similarly, with probability $(1 - p_i) \cdot (p_i + \delta_{p_i})$, a q_i allele is drawn from one and a Q_i from two, while with probability $p_i \cdot (1 - p_i - \delta_{p_i})$, a Q_i allele is drawn from one and a q_i from two. Both of these situations yield a Q_iq_i and a genotypic value of $a_i + d_i$. Because q_iq_i has a genotypic value of zero, the F_1 mean becomes

$$\mu_{F_1} = (a_i + d_i)[(1 - p_i)(p_i + \delta_{p_i}) + p_i(1 - p_i - \delta_{p_i})] + 2a_i \cdot [\, p_i(p_i + \delta_{p_i})] \tag{13.2a}$$

Assuming that both parental populations are in Hardy-Weinberg equilibrium, then some simple algebra yields

$$H_{F_1} = \mu_{F_1} - \mu_{MP} = \sum_{i=1}^{n} (\delta_{p_i})^2 \, d_i \tag{13.2b}$$

Hence, two features are required for heterosis when dominance is present. As with inbreeding depression, *directional dominance* is required (the d_i tend to be positive). Second, the *strength of heterosis increases with the between-population difference in allele frequencies* (δ_{p_i}) at the underlying trait loci, with no heterosis when the two populations have the same allele frequencies for the trait of interest ($\delta_{p_i} = 0$ for all i). While it is occasionally assumed (or inferred) that heterosis only occurs when fully inbred lines are crossed, Equation 13.2b shows that this is not the case. The importance of crossing inbred lines is that the heterotic effect is largest when the lines are fixed for alternative alleles, as in this setting $\delta_p = \pm 1$ for any alleles segregating in the F_1, with $H_{F_1} = \sum d_i$, the sum taken over all segregating trait loci.

Under what conditions does the mean of the F_1 exceed that of both parents? Summing over all loci, we find that

$$\mu_{F_1} - \mu_{P_1} = \sum_{i=1}^{n} \delta_{p_i} a_i \quad \text{and} \quad \mu_{F_1} - \mu_{P_2} = 2\sum_{i=1}^{n} \delta_{p_i}^2 d_i - \sum_{i=1}^{n} \delta_{p_i} a_i$$

Thus, the hybrid exceeds the best parent (high parent heterosis) when

$$2\sum_{i=1}^{n} \delta_{p_i}^2 d_i \; > \sum_{i=1}^{n} \delta_{p_i} a_i \; > 0 \tag{13.3a}$$

Note that while overdominance ($d_i > a_i$) facilitates Equation 13.3a, is it not required. For a cross between completely inbred lines, Equation 13.3a reduces to

$$2\sum_{i=1}^{n} d_i \; > \sum_{i=1}^{n} a_i \; > 0 \tag{13.3b}$$

Melchinger et al. (2007a) gives the conditions required for high parent heterosis (which they call **better-parent heterosis**) under general epistasis.

When only (single-locus) dominance is present, many, but not *all*, aspects of heterosis and inbreeding depression can be considered as complementary events. The change in means under crossbreeding and inbreeding (to level f) are given by

$$\mu_{F_1} = \mu_{MP} + H_{F_1} \quad \text{and} \quad \mu_f = \mu_0 - fI \tag{13.4a}$$

namely, the reference mean and an increment, where

$$H_{F_1} = \sum_{i=1}^{n} (\delta_{p_i})^2 d_i \quad \text{and} \quad I = 2\sum_{i=1}^{n} p_i(1-p_i)d_i \tag{13.4b}$$

Hence, given the two very important caveats of no epistasis and that the same *segregating loci* are involved in the cross between lines, and selfing within a line, then inbreeding depression and heterosis are very much complementary events (Filho 1999). If the same set of loci are segregating in the F_1 and the population being inbred, one does not expect heterosis without also observing inbreeding depression in the trait, and vice-versa.

Further, in this setting, one *cannot* have both inbreeding depression ($I > 0$) *and* outbreeding depression ($H_{F_1} < 0$) for the same trait. When both phenomena occur for the same trait, this implies either an significant role for epistasis and/or that *different* segregating loci are involved in the inbreeding and crossbreeding situations. An example of the latter would be in a population cross that introduces alleles not found within the population being selfed to measure inbreeding depression.

An important feature about heterosis, and one that makes this strategy desirable for commercial seed companies, is what happens when one randomly mates the F_1. In the resulting F_2, half of the initial heterosis generated by dominance disappears,

$$H_{F_2} = \mu_{F_2} - \frac{\mu_{P_1} + \mu_{P_2}}{2} = \sum_{i=1}^{n} \frac{(\delta_{p_i})^2 d_i}{2} = \frac{H_{F_1}}{2} \tag{13.5}$$

Hence, a farmer who planted seeds produced by their F_1 plants would see an immediate decline in yield relative to the purchased seed. This **dominance loss** occurs because all segregating loci in the F_1 are of heterozygous origin (the two alleles in any F_1 individual are from different populations), but only half of the F_2 loci are of heterozygous origin (with 1/4 having both alleles from line one and 1/4 with both alleles from line two.) Hence, at a random locus, only half of the F_2 offspring are expected to be between-line hybrids. Under random mating, the frequency of Q_i in the F_2 population is $(p_i + p_i + \delta_{p_i})/2 = p_i + \delta_{p_i}/2$, and under Hardy-Weinberg conditions the (single-locus) genotype frequencies do not change in subsequent generations. Hence, while half the dominance-generated heterosis disappears after one generation of random mating, all subsequent generations show no further changes (as a single generation of random mating generates Hardy-Weinberg proportions at any single locus). As we now demonstrate, the presence of epistasis modifies these statements.

ROLE OF EPISTASIS IN HETEROSIS AND OUTBREEDING DEPRESSION

Heterosis can be generated even in the absence of dominance. As first noted by Richey (1942), two completely additive components that act in a multiplicative fashion to generate the final trait value can generate heterosis. Richey's hypothetical example considered plant height as the product of two (assumed independent) components, each of which is additive: number of nodes and internode length. Line one has twice as many nodes, each with half the internode length, as line two. Hence, both lines have the same height, which is scaled to a value of one. The average number of nodes in the F_1 is (2+1)/2 = 3/2, while the average internode length is (1+1/2)/2 = 3/4, for a height of (3/2)·(3/4) = 1.125, giving H_{F_1} = 0.125 (12.5% midparent heterosis). Richey called this interaction generated by multiplying two additive traits **mock dominance**, although it is now more widely referred to as **multiplicative heterosis** (Dempster 1943; Powers 1944; Williams 1959; Arunachalam 1977; Minvielle 1987).

As noted by Cocherkham (1959) and (in more detail) by Schnell and Cockerham (1992), the interaction generated by multiplying two additive traits is additive-by-additive epistasis. Hence, it should not be surprising that certain types of epistasis can generate heterosis, but what is less clear is when they may do so, and what is the behavior of epistatically-generated heterosis in the F_2, and subsequent, generations. For example, under what conditions does one see outbreeding depression, instead of heterosis, in hybrids?

The line-cross theory presented in Chapter 11 provides a framework for investigating these questions. As derived in Example 13.1, the heterosis expressed in the F_1 generation is

$$H_{F_1} = \mu_{F_1} - \mu_{MP} = 2\delta_1^c - \alpha_2^c \tag{13.6a}$$

where δ_1^c and α_2^c, are, respectively, the dominance and additive-by-additive composite effects (Chapter 11). The value α_2^c is positive when favorable additive epistatic interactions occur between genes from the same population, while it is negative when the favorable additive-by-additive combinations occur between genes from different populations. Similarly, from Example 13.1, the F_2 heterosis becomes

$$H_{F_2} = \mu_{F_2} - \mu_{MP} = \delta_1^c - \left(\frac{1}{2} + \bar{c}\right)\alpha_2^c - 4\,\bar{c}\,(1-\bar{c})\delta_2^c \tag{13.6b}$$

$$= \frac{H_{F_1}}{2} - \bar{c}\left(\alpha_2^c + 4\,[1-\bar{c}\,]\delta_2^c\right) \tag{13.6c}$$

where δ_2^c is the dominance-by-dominance composite effect and $\bar{c}$ is the average recombination rate between epistatic loci that underlie the trait (Willham and Pollak 1985). The value of δ_2^c is positive when favorable $D \times D$ epistatic interactions occur between genotypes from the same population. For unlinked loci ($\bar{c} = 0.5$), the F_2 expression reduces to

$$H_{F_2} = \delta_1^c - \alpha_2^c - \delta_2^c = \frac{H_{F_1}}{2} - \left(\frac{\alpha_2^c}{2} + \delta_2^c\right) \tag{13.6d}$$

Hence, the resulting loss of heterosis from the F_1 to the F_2 is

$$\mu_{F_2} - \mu_{F_1} = -\left(\delta_1^c - \alpha_2^c[1/2 - \bar{c}] + 4\,\bar{c}\,[1 - \bar{c}]\delta_2^c\right) \tag{13.7a}$$

$$= -\left(\delta_1^c + \delta_2^c\right) \quad \text{for } \bar{c} = 0.5 \tag{13.7b}$$

Even when linkage is present (provided $c > 0$),

$$\mu_{F_\infty} - \mu_{F_1} = -\left(\delta_1^c + \delta_2^c\right) \tag{13.7c}$$

As mentioned above, one component of the change in heterosis from the F_1 to the F_2 is due to dominance loss, as the contribution from single-locus dominance to heterosis declines from $2\delta_1^c$ in the F_1 to δ_1^c in the F_2. The other components of the decline are due entirely to epistasis (α^c, δ_2^c).

Several general conclusions can be drawn from these expressions. First, the deviation between the mean phenotype in the F_1 and parental lines is a function of both dominance (δ_1^c) and additive $\times$ additive epistasis (α_2^c). Ignoring epistasis, a simple explanation for heterosis is the presence of complementary sets of deleterious recessive genes in both parental lines and the masking of their effects in the F_1 heterozygotes. However, the loss of favorable additive $\times$ additive effects (α_2^c) that may exist within populations must also be considered. Although the interactions *within* gametes are preserved in the F_1, those *between* gametes are not. An F_1 line will only exhibit heterosis if the gain in favorable between-population dominance effects ($2\delta_1^c$) exceeds the loss in favorable additive $\times$ additive interactions (α_2^c) within populations. If the latter is sufficiently large, outbreeding depression occurs.

Second, half of the heterosis in the F_1 generation is lost by segregation when gametes leading to the F_2 generation are produced ($H_{F_1}/2 = \delta_1^c - \alpha^c/2$), and an *additional* fraction is lost due to the recombination between parental line genes. This latter quantity, termed **recombination loss** by Dickerson (1969), is entirely a function of epistatic effects, because recombination does not influence the transmittance of effects associated with single loci. Depending on the signs of α_2^c and δ_2^c, it may be positive or negative. We examine recombination loss in more detail shortly.

Third, under free recombination, $\mu_{F_2} - \mu_{MP} = \delta_1^c - (\alpha_2^c + \delta_2^c)$, and this is also true in later generations with restricted recombination, provided enough time has passed to eliminate gametic phase disequilibria. Thus, a hybrid population will ultimately experience outbreeding depression if the net gains due to dominance (δ_1^c) are less than the net losses due to the breakup of favorable additive $\times$ additive and dominance $\times$ dominance interactions ($\alpha_2^c + \delta_2^c$).

The transition from heterosis to outbreeding depression with increasing genetic distance between parents suggests that there is a fundamental change in predominant gene interactions as mates become more and more distantly related. This observation has led to the suggestion that there must be an optimal degree of outbreeding (Shields 1982; Bateson 1983; Waser and Price 1983; Waser 1993b). Dominance is generally believed to be the primary agent of inbreeding depression within populations (Chapter 12). However, the decline in fitness under outcrossing is usually attributed to a breakup of coadapted gene complexes (favorable epistatic interactions) in the parental lines (Dobzhansky 1948, 1950; Templeton 1986; Lynch 1991; Xiao et al. 1995). Thus, in proceeding from issues of outbreeding enhancement (heterosis) to those of outbreeding depression, at least among theoreticians, there is often a shift in emphasis from interactions within loci (dominance) to those among loci (epistasis).

Finally, the observation of **progressive heterosis** is often taken as evidence against hybrid vigor being entirely driven by dominance. Here, heterosis increases with the number of distinct alleles in a polyploid, for example, with *ABCD* tetraploid hybrids displaying more heterosis than *AABB* or *CCDD* hybrids. As noted by several authors this observation is hard to reconcile with a simple dominance model (Groose et al. 1989; Bingham et al. 1994; Brichler et al. 2003; Auger et al. 2005; Schnable and Springer 2013; Yao et al. 2013; Fu et al. 2014). It is, however, compatible with an epistatic model.

Example 13.1 Equations 13.6 and 13.7 follow directly from line-cross theory. From Table 11.1,

$$\begin{aligned}\mu_1 &= \mu_0 + \alpha_1^c - \delta_1^c + \alpha_2^c - \alpha_1^c\delta_1^c + \delta_2^c + \cdots \\ \mu_2 &= \mu_0 - \alpha_1^c - \delta_1^c + \alpha_2^c + \alpha_1^c\delta_1^c + \delta_2^c + \cdots \\ \mu_{F_1} &= \mu_0 + \delta_1^c + \delta_2^c + \cdots\end{aligned}$$

Hence, to second order epistasis

$$\mu_{MP} = \frac{\mu_1 + \mu_2}{2} = \mu_0 - \delta_1^c + \alpha_2^c + \delta_2^c$$

yielding

$$\mu_{F_1} - \mu_{MP} = \mu_0 + \delta_1^c + \delta_2^c - (\mu_0 - \delta_1^c + \alpha_2^c + \delta_2^c) = 2\delta_1^c - \alpha_2^c$$

which recovers Equation 13.6a. Expressions with higher-order epistasic terms (α_4^2, δ_4^c, δ_6^c, etc.) are obtained following similar logic, and can be found in Melchinger et al. (2007a).

Turning to the F_2 mean, $\mu_{F_2} = \mu_0$ for unlinked loci, as the decomposition given in Chapter 11 sets the F_2 population as the base. This generation is used as the reference population because single-locus genotypes are in Hardy-Weinberg and, for unlinked loci, segregation of the F_1 results in linkage equilibrium (Hill 1982). As an aside, the careful reader might be concerned that, with unlinked loci, only half of the disequilibrium decays each generation under random mating. While this is correct, crossing of the F_1 to form the F_2 is an example of *nonrandom mating*, as only heterozygotes (hybrids) are crossed, and independent assortment of unlinked loci generates linkage equilibrium in a single generation. Thus, for unlinked loci

$$\mu_{F_2} - \mu_{MP} = \mu_0 - (\mu_0 - \delta_1^c + \alpha_2^c + \delta_2^c) = \delta_1^c - \alpha_2^c - \delta_2^c \tag{13.8a}$$

which recovers Equation 13.6d.

When loci are linked, Equation 11.2a gives the F_2 mean as

$$\mu_{F_2} = \mu_0 + \left(\frac{1-2c}{2}\right)\alpha_2^c + (1-2c)^2\delta_2^c \tag{13.8b}$$

which reduces to μ_0 when $c = 0.5$. When loci are linked, μ_0 is the mean approached following several generations of random mating to remove any lineage disequilibrium generated by the initial cross (Example 5.6). The departure of the F_2 mean given by Equation 13.8b from this equilibrium value arises because linkage disequilibrium is still present and the population is not in multilocus Hardy-Weinberg (Hardy-Weinberg proportions at each locus and linkage equilibrium among loci). Note that the contribution from single-locus dominance effects (δ_1^c) does not enter into μ_{F_2}, as single loci are in Hardy-Weinberg in the F_2.

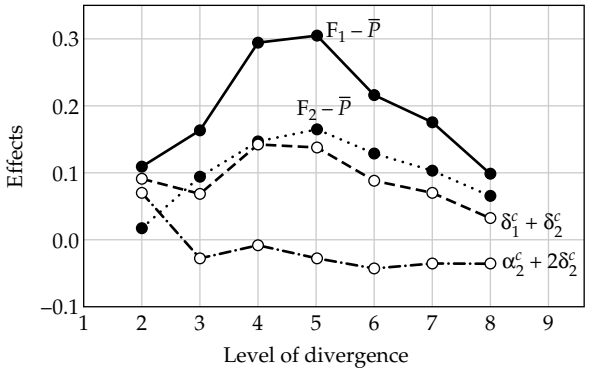
Thus, with linkage,

$$\begin{aligned}\mu_{F_2} - \mu_{MP} &= \left[\mu_0 + \left(\frac{1-2c}{2}\right)\alpha_2^c + (1-2c)^2\delta_2^c\right] - (\mu_0 - \delta_1^c + \alpha_2^c + \delta_2^c) \\ &= \delta_1^c + \left[\left(\frac{1-2c}{2}\right) - 1\right]\alpha_2^c + \left[(1-2c)^2 - 1\right]\delta_2^c \\ &= \delta_1^c - \left(\frac{1}{2} + c\right)\alpha_2^c - 4c(1-c)\delta_2^c \end{aligned} \tag{13.8c}$$

which recovers Equation 13.6b.

Example 13.2 Moll et al. (1965) produced F_1 and F_2 generations from crosses between several lines of maize with varying degrees of genetic divergence "based on ancestral relationships and differences in adaptation." As illustrated in the following figure, when assayed in a common

environment, all crosses exhibited heterosis for grain yield in the F_1 and F_2 generations, but this was most pronounced in crosses involving lines with intermediate degrees of divergence. Moreover, at the highest levels of divergence, the performance of the F_1 and F_2 lines converged (in the figure, the data from all crosses have been standardized so that $\bar{z}(F_2) = 1$).



Can any insight into the mode of gene action be inferred from these results? Assuming that $\bar{c} \simeq 0.5$, Equation 13.7b implies that $\bar{z}(F_1) - \bar{z}(F_2) \simeq \delta_1^c + \delta_2^c$, the sum of the composite dominance and dominance × dominance effects. In addition, using the same logic as in Example 13.1 yields

$$\bar{z}(F_1) + \bar{z}(MP) - 2\bar{z}(F_2) \simeq \alpha_2^c + 2\delta_2^c$$

which is the net loss of performance due to segregation and recombination of parental line gene combinations. As shown in the figure, application of these two formulae suggests that the net effects of dominance between parental lines have a positive influence on grain yield at all levels of divergence, but that the magnitude of this effect is maximized at an intermediate genetic distance. On the other hand, except at the lowest levels of divergence, the estimates of $\alpha_2^c + 2\delta_2^c$ are negative and roughly constant, suggesting favorable epistatic effects between genes from *different* sources, contrary to the expectation if individual lines were harboring coadapted gene complexes, which (Equations 13.6a and 13.6c) increases the amount of heterosis (Equations 13.6a and 13.6c).

Epistasis and Recombination Loss

When only dominance is present, the change in the mean in generations subsequent to the F_1 is easily predicted, being $-H_{F_1}/2 = -(\overline{z}_{F_1} - \overline{z}_{MP})/2$ in the F_2 (Equation 13.5), and then stable thereafter. When epistasis is present, one can see additional **F_2 breakdown** (Hill 1982), wherein the loss of heterosis is greater than this prediction (Equation 13.6c). Dickerson (1969, 1972) called this additional decline the recombination loss, as it arises through recombination (or segregation when loci are unlinked) breaking up favorable combinations of alleles from distinct loci that are present in each parental population.

To see this, let A_i denote a random allele at the A locus from population i (1 or 2), with a similar definition for B_i. One can then represent an F_1 individual as A_1B_1/A_2B_2, where each gamete forming the F_1 contains only alleles from one population. Such an individual generates a fraction $(1-c)$ of parental gametes (A_1B_1 and A_2B_2) where both alleles are from the same population, and a fraction c of recombinant (or nonparental) gametes (A_1B_2 and A_1B_2) which contain alleles from different populations. The generation of these nonparental gametes further disrupts the transmission of favorable epistatic combinations, leading the additional loss of heterosis. Epistasis depends on pairs of loci, and (for unlinked loci) the F_2 has only half the number of parental gametes (both alleles from the same population) as the F_1. This is akin to the loss of half of the dominance heterosis from the F_1 to the F_2, as the later has only half of the number of hybrid loci as the former. From Equation 13.6c, the

recombination loss in the F_2 is

$$\bar{c}\left(\alpha_2^c + 4\,[1-\bar{c}\,]\delta_2^c\right) \tag{13.9a}$$

which reduces to

$$\frac{\alpha_2^c}{2} + \delta_2^c \tag{13.9b}$$

when loci are unlinked, where the loss is most pronounced. Kinghorn (1980) suggested that **epistatic loss** is a more appropriate term for this extra decline in heterosis, as it is entirely generated by epistasis.

Dickerson (1972) noted, for unlinked loci, that the quantity

$$R = \alpha_2^c + 2\delta_2^c \tag{13.10a}$$

which is twice the recombination loss in the F_2, provides a general measure for the amount of recombination loss under a variety of crossing schemes used by breeders. When loci are unlinked, R can be estimated by (Example 13.2)

$$\widehat{R} = \overline{z}_{F_1} + \overline{z}_{MP} - 2\,\overline{z}_{F_2} = \alpha_2^c + 2\,\delta_2^c \tag{13.10b}$$

To quantify the expected amount of recombination loss in any particular crossing scheme, Dickerson (1969, 1972) proposed a coefficient, r_D, to weight R, giving the predicted loss as $r_D R$. While Dickerson called r_D the **coefficient of recombination loss**, we prefer the term **Dickerson coefficient** to avoid confusion between the *actual loss* ($r_D R$), the general metric of loss (R), and the coefficient of loss (r_D). Dickerson defined r_D as fraction of nonparental gametes that fuse to form the focal cross, so that $r_D = 1/2$ in the F_2 for unlinked loci (as half of the gametes from the F_1 are nonparental). Different paramaterizations for recombination loss have been proposed (Dickerson 1969, 1972; Kinghorn 1980, 1982, 1983, 1987; Hill 1982; William and Pollak 1985), with Koch et al. (1985) summarizing the connections between them. When loci are linked, the relative weights on α_2^c and δ_2^c, rather than being constant as with R, change depending on the amount of recombination in the crossing scheme, and the simple expression of $r_D R$ for the loss is only an approximation.

The nature of recombination loss is of considerable interest to animal breeders, who use different schemes to exploit the nonadditive variance that generates heterosis. Unlike plant breeders, generating a large number of F_1 animals for commercial sale is generally not feasible due to constraints imposed by the reproductive output of most domesticated animals and their associated costs. Rather, two different approaches are used in place of continual generation of commercial F_1s, and these differ in their values of r_D. The first is the creation of a **synthetic** (or **composite**) population, such as crossing two lines and then randomly mating the F_1 to form the synthetic population. Because this is just an F_2, the Dickerson coefficient for a two-population synthetic is $r_D = 1/2$. The second class of schemes is **rotational crossbreeding**, the continual crossing of individuals each generation. We detail these below, but the form of a two-breed rotation crossing scheme is $P_1 \times (P_2 \times [P_1 \times \{P_2 \ldots\}])$. The Dickerson coefficient under such a scheme is 2/9 (Dickerson 1969), and hence it suffers less recombination loss, making this approach preferable to a synthetic when R is sufficiently large. We detail several complex crossing schemes below and examine the complication of maternal heterosis, wherein the use of crossbreed dams (females) often has a significant advantage over using a purebreed mothers.

GENETIC NATURE OF HETEROSIS

In our discussion on the genetics of inbreeding depression, we were mainly concerned with the nature of dominance: was it partial, overdominant, or associative (Chapter 12)? While

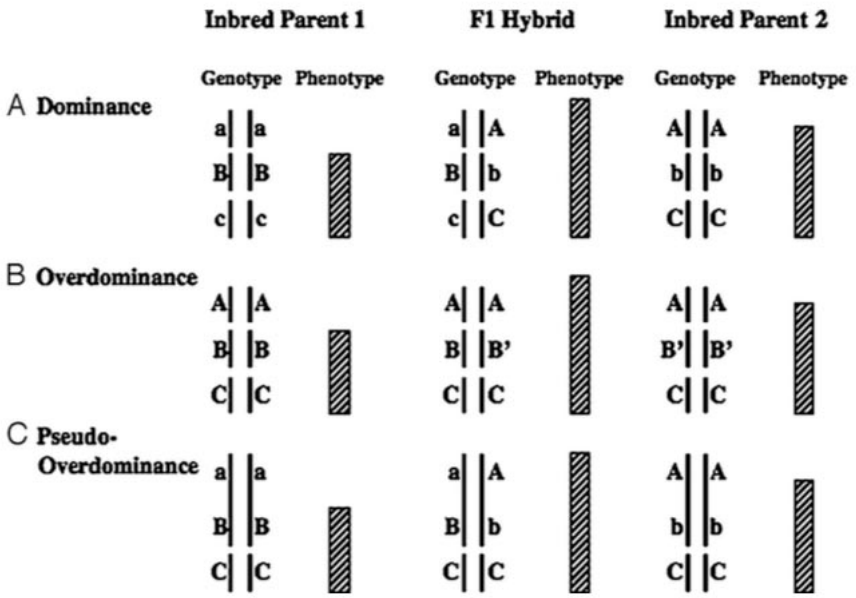


Figure 13.1. Different hypotheses for how dominance can generate heterosis. The figure shows the chromosomal composition of the genotype on the left and the resulting phenotype (indicated by the height of the filled bar) on the right of each genotype. **A)** Under the dominance (or partial dominance) hypothesis, recessive deleterious alleles are fixed at different loci (*aa* in line 1, *bb* in line 2), while both are covered in the hybrid (*AaBb*). **B)** Under the overdominance hypothesis, the *B* locus shows overdominance, with the heterozygote (*BB′*) having a superior value to either homozygote (*BB, B′B′*). **C)** Under the associative overdominance (also know as **pseudo-overdominance**) hypothesis, the *A* and *B* loci are also fixed for alternative recessive alleles, but now are tightly linked, with parent 1 contributing an *aB* chromosomal segment and line 2 an *Ab* segment. As with the dominance hypothesis, both are covered in the hybrid, but the chromosomal segment appears to segregate as a single allele, presenting the impression of overdominance. This initial repulsion disequilibrium (association of *a* with *B* and *A* with *b*) decays under recombination. (After Birchler et al. 2003.)

dominance-based epistasis can contribute to inbreeding depression (Equation 12.4a, Example 12.2), its impact is only apparent at very high levels of inbreeding, and it is usually ignored in most settings (Chapter 12). The genetic nature of single-locus dominance in heterosis tracks our interest in the nature of dominance under inbreeding depression, but, in contrast to inbreeding, epistasis is also important. The breakdown of additive-by-additive epistasis impacts the F_1 heterosis (Equation 13.6a), and, along with dominance-by-dominance epistasis, impacts any recombination loss seem in subsequent generations (Equation 13.6c).

Two broad approaches have been used to resolve the genetic nature of heterosis. The classic, or Biometrical, approach is statistical, based on line-cross analysis and variance-component estimation (e.g., Jinks 1983; Sprague 1983; Hallauer et al. 2010). More recently, quantitative geneticists have harvested the power of genetic markers and whole-genome sequencing in attempts to isolate ever-smaller chromosomal regions influencing heterosis. These very different approaches are best viewed as complementary, rather than competitive.

Biometrical Approaches: Nature of Dominance

As was the case with inbreeding depression, the question arises as to whether most heterosis is caused by overdominance (Shull 1908; East 1908) or by partial dominance (Davenport 1908; Bruce 1910; Keeble and Pellew 1910). As with inbreeding depression, observe that Equation 13.2b is agnostic with respect the nature of the required dominance, rather simply

Figure 13.2. Heterosis in yield caused by overdominance at the *Single Flower Truss* (*SFT*) gene in tomatoes. On the left is the yield for a homozygous wild type parent, on the right is a homozygous mutant parent, and in the middle is their hybrid (heterozygous for the mutant and wild type alleles). The increased yield results from the suppression of growth termination mediated by *Self Pruning* (*SP*), a gene antagonistic to *SFT*. (After Krieger et al. 2010.)

requires that, in general, the d_i tend to be positive. Overdominance further requires that $d_i > a_i$ (at least for some loci). As with inbreeding depression, associative overdominance (recessive alleles at different loci are in repulsion disequilibrium) can be difficult to distinguish from true overdominance (Figure 13.1). If the former, the evidence for overdominance will disappear over time due to recombination decaying any disequilibrium, while if the latter, the signal should even persist after many generations of recombination.

As reviewed in Chapter 24, a number of crossing designs have been proposed that allow for the direct estimate of the dominance variance, unconfounded by maternal environmental effects. In particular, the North Carolina (NC) Designs II and III of Comstock and Robinson (1948, 1952) have been widely used. Under NC Design II (Figure 24.1), the same females (or females from the same inbred line) are mated to the same set of males (or males from the same line), which allows for a direct estimate of the dominance variance (in the absence of epistasis and linkage disequilibrium). The NC Design III (Figure 24.6) backcrosses each F_2 to both parental lines, generating a paired set of lines means, $\overline{z}_{1ij}$ and $\overline{z}_{2ij}$, for the two backcrosses from the ith F_2 that are jointly scored in plot j. Let $S_{ij} = \overline{z}_{1ij} + \overline{z}_{2ij}$ and $\Delta_{ij} = \overline{z}_{1ij} - \overline{z}_{2ij}$ represent, respectively, the sum and difference for each such pair. The variances of S and Δ correspond to estimates of the additive and dominance variances (see Chapter 24 for details).

As also discussed in Chapter 24, Comstock and Robinson (1952) noted that one can use estimates of the additive and dominance variance to make inferences on the degree of dominance in the special case where all segregating alleles have frequency 1/2. This occurs in the F_2 from a cross of two inbred lines. In such settings, the additive variance becomes $\sum_i a_i^2/2$ (Equation 4.12a with $p_i = 0.5$), while the dominance variance (writing the heterozygote as $d_i + a_i = [1+k_i]a_i$, so that $k_i = d_i/a_i$) is $\sum_i (k_i a_i)^2/4$ (Equation 4.12b). Hence, twice the ratio of the dominance to additive variance estimates provides a weighted estimate of the dominance coefficient, k. Values of one or less suggest partial to complete dominance ($d \leq a$), while values in excess of one support overdominance ($d > a$). Cockerham and Zeng (1996) and Melchinger et al. (2007a) noted that the presence of additive-by-additive epistasis biases the dominance estimate (Equation 13.12).

Hence, the appropriate NC design applied to a cross between inbred lines provides

some insight into the average degree of dominance. Associative overdominance (Figure 13.1) can initially generate k values in excess of one, but this value is expected to decline in further generations as random mating erodes any initial linkage disequilibrium (Gardner and Lonquist 1959). Using this approach, Moll et al. (1964) initially obtained estimates of k in excess of one for grain yield in maize, suggesting overdominance. However, this estimate declined to nearly 1 in one line, and to around 3/4 in another following several generations of random mating. Similar findings were seen by Gardner (1963) and Hallauer and Miranda (1981). While there are few striking examples of true overdominance generating heterosis (Figure 13.2), under further scrutiny other examples of apparent overdominance appear to be associative overdominance (Cockerham and Zeng 1996; Dijkhuizen et al. 1996; Graham et al. 1997; Bingham 1999; Garcia et al. 2008; Lariépe et al. 2012). Given that most designs involve at most a few generations of recombination, an observation of apparent overdominance could simply due associative overdominance among tightly linked loci. This ambiguity makes distinguishing between these two explanations often problematic (Luo et al. 2001). For example, Lu et al. (2003) found that 24 of 28 QTLs for grain yield in maize showed overdominance, despite randomly mating the F_2 population for three additional generations to reduce the effects of linkage (the AIC design; Chapter 18). However, Lu et al. noted that such a design would leave 86% of any initial LD for loci 5 cM apart ($[1 - 0.05]^3$), and 51% of the LD between loci 20 cM apart. Hence, a few generations of random mating is only effective at removing LD under very loose linkage.

Finally, an interesting angle on the dominance model is suggested by the work of Fu and Dooner (2002). They examined a 100 kb region around the *bz* gene region in two different maize lines. Of the ten genes in this region, only six were found in both lines. Perhaps the remainder have relocated to different chromosomal regions, but this suggests that even closely related lines may differ in the actual genes they carry, allowing their hybrid to have a larger complement of functional genes.

Example 13.3 The NAM (nested association mapping) lines in maize are a series of 5000 inbred lines generated by crosses of 25 diverse lines to a B73 reference line, generating roughly 200 inbred lines per cross (details in Chapter 18). McMullen et al. (2009) showed that, even after many generations of selfing, a few small regions in some of the NAM lines showed **residual heterozygosity**, wherein an inbred line shows heterozygosity, rather than the expected marker homozygosity. In these regions, the effect of inbreeding generating homozygosity is counted by selection to maintain heterozygosity. Such an observation is consistent with overdominant loci influencing fitness. However, it is also consistent with associative overdominance, where linked deleterious recessives are in repulsion disequilibrium. McMullen et al. found that residual heterozygosity was higher within 10 cM of the centromeres than along the chromosome arms (4.1% versus 3.2%). Given the recombination suppression around centromeres, they suggest that this observation supports associative overdominance in these regions of reduced recombination. Further analysis by Gore et al. (2009) supported this view, finding that regions of residual heterozygosity were significantly correlated with reduced recombination rates, but not with gene density. Both McMullen et al. and Gore et al. argued that such repulsion-phase configurations arise as a natural consequence of the Hill-Robertson effect (WL Chapter 8), which suggests that favorable alleles tend to be in repulsion phase, especially in regions of low recombination. Consistent with this hypothesis, Schön et al. (2010) found that many loci for yield heterosis in maize are found in regions encompassing the centromere.

Biometrical Approaches: Epistasis

Biometrical evidence of epistasis contributing to heterosis can be seen from the observation of an F_2 decline that exceeds the value predicted by dominance ($H_{F_1}/2$), or (more formally) by direct estimates of compositive epistatic effects from line-cross theory (e.g.,

Table 13.1 A few examples of studies detecting significant epistasis using line cross analysis. The TTC contrast (Equation 13.11) was significant in all examples, indicating epistasis (Chapter 24).

Species	Trait	Observation	Reference
Rice	5 yield-related	Significant epistasis in all traits	Singh and Singh 1976
Maize	Ear traits	Significant epistasis in many traits Favorable A x A interactions for several traits	Wolf and Hallauer 1997
Arabidopsis	Biomass traits	Significant epistasis in 4 traits A x A and D x D significant in 4 of 5 traits.	Kusterer et al. 2007

Equation 13.10b). One of the most widely used line-cross designs for detecting epistasis is the **triple test cross** (**TTC**), an extension of NC Design III (Figure 24.6). The latter design crosses F_2 back to both parental lines to generate a series of paired backcrosses for each F_2, with $\overline{z}_{1ij}$ and $\overline{z}_{2ij}$ representing the two backcross means, both measured in plot j, for the ith F_2 individual. The triple test cross adds a third cross, with the F_2 also backcrossed to the F_1, yielding a third mean, $\overline{z}_{3ij}$, (also scored in plot j along with the two backcrosses). The contrast

$$\overline{z}_{1ij} + \overline{z}_{2ij} - 2\,\overline{z}_{3ij} \tag{13.11}$$

is nonzero in the presence of epistasis (see Chapter 24 for more details). Given a significant result from the TTC, one can use various line-cross means to estimate the composite epistatic effects (Chapter 11). Table 13.1 presents a few studies showing that significant epistatic effects are not uncommon, and hence recombination loss can be of considerable concern. In such cases, the loss of heterosis from the F_1 to the F_2 (and subsequent) generations can be greater, and perhaps far greater, than predicted from H_{F_1} (Equation 13.6c). Sheridan (1981) found that such excessive F_2 loss is commonplace for traits in domesticated animals. Crossing designs that minimize recombination loss (examined below) should be considered in such settings.

Evidence from QTL Mapping Studies

A second strategy for probing the genetic nature of heterosis is the mapping of factors that influence heterosis to small chromosomal regions. While this approach is called QTL (quantitative trait locus) mapping, in reality, it often maps effects to segments that could easily contain a large number of genes, rather than mapping effects to single loci. Mapping of QTLs by linkage approaches is examined in Chapter 18, and results in estimating the composite effects of genes in regions that are usually tens of megabases in length. The basic idea is very straightforward. Consider a cross between *QQMM* and *qqmm* lines, with *Q* the QTL and *M* the marker allele. If *M* and *Q* are linked, there is an excess of parental gametes produced by their F1 (Chapter 4), with *MQ* and *mq* gametes being overrepresented. This generates a correlation between the QTL and marker alleles in the progeny, allowing genomic regions to be tagged because markers in those regions show a correlation with trait values. Linkage to a given marker is tested by partitioning F2 individuals into three groups (the two alternative marker homozygotes and the heterozygote) and using ANOVA to test for among-group differences in trait means.

Two different approaches have been proposed for mapping QTLs underlying heterosis. The first is indirect: perform a standard QTL mapping experiment (such as using F_2 design); Chapter 18, and then infer the impact of detected QTLs on heterosis from the nature of their dominance and epistatic interactions. The second requires more specialized designs, and attempts to more directly access heterosis, such as through the use of an **immortalized F_2 population** or a Design III or TTC crossing design.

The immortalized F_2 population design attempts to address a limitation with a standard F_2 design—lack of replication—as each F_2 individual is genetically unique, with its

Table 13.2 Summary of various QTL mapping studies for heterotic loci in plants. The *Dominance* column indicates whether the majority of detected loci showed partial to complete dominance (Dom), apparent overdominance (OD), or associative overdominace (AD). The *Epistasis* column indicates whether digenic epistasis (digenetic interactions between QTLs) was found, and its nature (if significant).

Species	Trait	Dominance	Epistasis	Reference
Maize				
	grain yield	OD	No	Lu et al. 2003
	grain yield	AD	No	Schön et al. 2010
	grain yield	OD	No	Frascaroli et al. 2007
	height	Dom	No	Lu et al. 2003
	grain moisture	Dom	No	Lu et al. 2003
	stalk lodging	Dom	No	Lu et al. 2003
	yield components	Dom	A x A	Tang et al. 2010
	Kernel traits	Dom	A x A, D x D	Jiang et al. 2015
	Morpholigical traits	OD, dom	No	Wei et al. 2015
Rice				
	yield	AD	No	Xiao et al. 1995
	yield	OD	A x A, D x D	Yu et al. 1997
	yield	OD	A x A	Li et al. 2001
	yield	Dom, OD	D x D	Hua et al. 2003
	yield components	OD	Extensive	Luo et al. 2001
	yield components	OD	A x A, D x D	Hua et al. 2002
	yield components	Dom	No	Huang et al. 2015
	grain weight	OD	D x D	Zhou et al. 2012
Arabidopsis				
	Biomass	Dom, OD	A x A	Meyer et al. 2010
Cotton (*Gossypium*)				
	Yield	Dom, OD	Extensive	Shang et al. 2016

genotypic value is typically estimated using only a single observation on its phenotype. Xing et al. (2002) and Hua et al. (2003) proposed an elegant solution allowing for replication. They accomplished this by first creating 240 RILs (recombination inbred lines; Chapter 18), a set of inbred lines derived by selfing the F_1s from an inbred line cross. They then randomly divided this collection into two sets, crossing a random member from each (with no resampling) to make 120 lines. They redid this procedure three times to create a total of 360 such lines, with genetic uniformity within each line, allowing for replication. This collection of lines resembles an F_2 population from the cross of the original inbred lines forming the RILs. Heterotic QTL mapping was then performed by looking for marker-trait associations where the trait value for each cross was its estimated heterotic value, Equation 13.1b (the mean of the cross minus the midparental mean).

Two other popular designs for mapping heterotic QTLs are based on adding marker data to the Design III (Cockerham and Zeng 1996; Melchinger et al. 2007a) and the TTC (Kusterer et al. 2007; Melchinger et al. 2007b; Reif et al. 2009; He and Zhang 2011) approaches discussed above. Recall that under Design III, one backcrosses an F_2 to both of the parental lines, generating the paired contrasts, $S_{ij} = \overline{z}_{1ij} + \overline{z}_{2ij}$ and $\Delta_{ij} = \overline{z}_{1ij} - \overline{z}_{2ij}$ (for the jth replicate of ith F_2 crossed). As estimate of dominance is provided by the difference between the two backcrosses. The TTC adds a third contrast (Equation 13.11) involving the cross of the F_2 back to the F_1, which directly estimates epistatic effects. One modification of both designs for QTL mapping is that RILs are often used in place of F_2s, allowing for better replication.

Table 13.3 Examples of the importance of heterosis for both food production and land conservation. Here % yield advantage is the gain of the hybrid over the best pure-line. While these values are dated, the general picture they suggests is still accurate. Based on Duvick (1999), with modifications for rice.

Crop	% planted as hybrids	% yield advantage	Annual added yield (%)	Annual Added yield (tons)	Annual land savings
Maize	65	15	10	55×10^6	13×10^6 ha
Sorghum	48	40	19	13×10^6	9×10^6 ha
Sunflower	60	50	30	7×10^6	6×10^6 ha
Rice	55	20	11	200×10^6	80×10^6 ha

Melchinger et al. (2007a) found that the estimated QTL dominance effect (under either design) for a single locus was a composite of both its dominance effect (d) and the additive-by-additive interactions (aa) of that locus with all other trait loci. We can see this from Equation 13.6a, leading Melchinger et al. to propose the notion of the **augmented dominance effect** for locus i, defined as

$$d_i^* = d_i - \frac{1}{2}\sum_{j \neq i} aa_{ij} \tag{13.12}$$

with the sum being taken over other loci that have additive-by-additive interactions with the focal locus, i. The dominance contrast in Design III and the TTC estimates d_i^*, rather than d_i, and hence estimates of the nature of dominance are biased by the presence of additive-by-additive epistasis.

Table 13.2 summarizes the finding from a few of these QTL mapping studies. While examples of apparent overdominant QTLs are often found, given the crude level of resolution, associative overdominance is often hard to rule out. For example, while Stuber et al. (1992) found a major QTL showing overdominance for yield in maize, Graham et al. (1997) showed that, upon finer mapping, the QTL region contained at least two smaller QTLs showing only dominance.

An interesting comparison is the genetic basis for yield heterosis in the two most important cereals, maize and rice. Yield heterosis in maize appears to largely be from the effects of single-locus dominance, with little impact from epistasis. By contrast, heterosis of yield in rice appers to be driven, in large part, by additive x additive effects (Hallauer and Miranda 1981; Yu et al. 1997; Hua et al. 2002, 2003; Garica et al. 2008; Tang et al. 2010; Wei et al. 2015). Jiang et al. (2017) similarly found that epistasis was the primary driven for grain yield heterosis in bread wheat (50% was due to A x A, and only 16% due to dominance).

AGRICULTURAL EXPLOITATION OF HETEROSIS: PLANTS

The exploitation of hybrid vigor in agriculture traces back at least 5000 years to the Sumerians (Clutton-Brock 1992), who produced mules by crossing horses (*Equus caballus*) with donkeys (*S. asinus*). Modern agriculture has been greatly impacted by hybrids, with the heterosis resulting in significantly increased yield in crops. Such gains directly translate into fewer acres that must be farmed to obtain the same total yield, and these land savings are by no means trivial (Table 13.3). Another critical, yet often overlooked, benefit of hybrids is *uniformity* (all of the F_1 from a cross of two inbred lines are genetically identical), which allows for higher efficiencies in harvesting, such as greatly increased mechanization (Crow 1998; Goldman 1999).

Both animal and plant breeders exploit heterosis, but in rather different ways. Plant breeders have the luxury of very high reproductive rates (in most settings) and a lack of maternal effects for most traits. In contrast, most species of domesticated animals have low reproductive rates, which generally rules out the plant breeder's approach of generating large numbers of F_1 individuals each year for commercial sale. Further, many animal pro-

duction traits show strong maternal effects, a trait that itself shows heterosis. Thus, offspring from crossbreed (hybrid) dams (females) who are have an extra performance boost due to the improved maternal effects in F_1 females (maternal heterosis). As a result of these differences, much of the exploitation in heterosis in plants is by generating lines that cross well to produce exceptional hybrids. In contrast, animal breeders tend to use more elaborate crossing schemes, such as rotational crossbreeding. We will first examine exploitation of heterosis in plant systems and then consider specific modifications that are used by animal breeders. Extensive reviews of the application of heterosis in plant breeding can be found in the conference volumes edited by Gowen (1952) and Coors and Pandey (1999).

Heterotic Groups

Lines that cross well have historically been said to display **nicking**. When is this expected? A key concept in the exploitation of heterosis is the notion of **heterotic groups**. Crosses between members within a heterotic group display little heterosis, while crosses *between* groups result in significant heterosis. Partitioning lines into sets of two (or more) heterotic groups considerably simplifies a breeder's job, as they can concentrate on crosses between these groups, rather than testing *all* pairwise combinations. While the notion of heterotic groups (or **heterotic patterns**) is the foundation for much of modern plant crossbreeding, it is a surprisingly recent concept. As reviewed by Tracy and Chandler (2006), while the idea was discussed in the early 1970s in some plant breeding companies (the first appearance of this term in the literature seems to be by Tsotsis 1972), it took until early 1980s to become mainstream.

Heterotic groups arise from between-group allele frequencies differences at loci underlying the trait. Further, we only care about frequency differences at a subset of trait loci—those displaying directional dominance or epistasis—as differences in allele frequencies at purely additive loci have no impact on heterosis. Consider the situation where only dominance is present. From Equation 13.2b, the expected F_1 heterosis is $\sum (\delta_{p_i})^2 d_i$, which increases with both the between-group allele frequency differences and with the number of such divergent loci. Inbred lines from different heterotic groups present the most extreme example, with heterosis equal to $\sum d_i$, with the sum being taken over all differentially fixed loci. The more such fixations, the greater the heterotic effect. Schön et al. (2010) found evidence of such differential fixation for yield QTLs between maize heterotic groups. With epistasis, the general idea is similar, except that now differences in *joint* allele frequencies at two (or more) loci are required. A second important concept is that heterotic groups can *evolve over time* (Example 13.4).

Given their importance, how does one construct heterotic groups and assign new lines to them? Obviously, the brute-force method of considering all pairwise crosses can be employed (diallels; Chapter 24), but one would like a more efficient approach. If one has a set of lines from *known* heterotic groups, then molecular markers can be used to cluster both known and unknown members, providing a reasonable predictor of the group membership for many unplaced lines (e.g., Barbosa et al. 2003; Reif et al. 2003a; Dhliwayo et al. 2009). However, simply using marker data by itself (i.e., without any known reference lines) to predict heterotic groups has been problematic, at best.

Example 13.2 hinted at one reason why genetic distance is a poor predictor of heterosis, as Moll et al. (1965) observed an intermediate level of divergence for maximal heterosis. As lines became sufficiently divergent, outbreeding depression, rather than heterosis, occurs. Despite this early observation, a number of studies have attempted to use molecular markers to predict heterosis, typically by looking for a correlation between the amount of heterosis and either genetic distance or F_1 heterozygosity (a measure of the genetic differences between the crossed lines). Most of the work has been done on maize yield, with mainly negative results (e.g., Frei et al. 1986; Price et al. 1986; Lamkey et al. 1987; Godshalk et al. 1990; Benchimol et al. 2000; Tracy and Chandler 2006; Dhliwayo et al. 2009; Flint-Garcia et al. 2009), but with a few successes (Lee at al. 1989; Reif et al. 2003a, 2003b). A closer examination suggested that markers can be good predictors for close-line crosses,

but poor predictors for more distant crosses (Barbosa et al. 2003; Amorim et al. 2006), in line with the results of Moll et al. (1965). Early marker-based work (using RFLP bands) in chickens found a highly significant negative correlation between band sharing and heterosis in chickens (Gavora et al. 1996; Haberfeld et al. 1996), but this might have occurred because only closely-related lines were examined.

The critical point is that genetic divergence, *per se*, is *not* sufficient to define heterotic groups, as the divergence required is *trait-specific*, and further restricted to loci with specific nonadditive effects (such as direction dominance or epistasis). If the divergence of alleles at the underlying trait loci is simply a product of genetic drift, then the divergence at random markers may track heterotic potential. However, if trait divergence is driven by selection, the pattern of divergence at the underlying trait loci need not tract the pattern of neutral divergence. Hence, simply using a metric such as the genetic distance between lines based on random (i.e., presumed neutral) markers is not a fruitful approach for the construction of heterotic groups. Consistent with this observation, Flint-Garcia et al. (2009) examined heterosis for a number of traits in maize, finding that while yield heterosis was poorly predicted using random markers, heterosis for many others traits was fairly well predicted. One might imagine that yield is under considerable selection, but that other traits might be more prone to divergence by drift, in which case neutral divergence may better predict heterosis. Further, heterotic groups can be trait specific, with group membership potentially shifting as the trait changes.

A final important point to stress is that a breeder's goal is exceptional *hybrid* performance, not simply exceptional *heterosis*. As the distinguished maize breeder, John Dudley, famously said "We sell hybrids, not heterosis," which we will refer to as **Dudley's dictum**. Hybrid performance is the midparental mean plus the heterotic effect. Hence, the goal is not to find the cross with the highest heterosis, which may only yield an average performing hybrid if the parental means are low, but rather the optimal combination of parental means plus heterosis that yields the largest overall hybrid value. This suggests the standard strategy of starting the search for exceptional hybrids by using crosses between the highest performing lines from different heterotic groups.

Case Study: Hybrid Corn

Corn (maize) is one of the world's most important cereals, and the leading crop in the United States as measured by acres planted and total yield. Almost all of the U.S. crop is **hybrid corn**, the seed from crosses of elite inbred lines. There are small amounts of **open pollinated** (**OP**) corn (**OPVs**, **open pollinated varieties**), but these are largely restricted to use by small independent farmers. The notion of hybrid corn traces back to Shull (1908, 1909), who noted that, because of the significant high parent heterosis seen in many corn crosses, the objective of corn breeders should be to find and maintain the best parental lines for hybrids. By maintaining these elite inbred lines and crossing them as needed, genetically identical hybrid seed can be produced year after year. The history of hybrid corn is reviewed by Crabb (1947; 1993), Kiesselback (1951), Anderson and Brown (1952), Crow (1998), Duvick (2001), Tracy and Chandler (2006), and Troyer (2006), while Troyer (1999, 2004) presented a detailed history of most of the founding lines that now comprise the whole of U.S. corn production. Nelson (1993) gives a fascinating discussion of the lifes of, and interactions between, Edward East, Rollins Emerson, and Donald Jones, key geneticists behind modern hybrid corn.

The initial problem with the widespread use of hybrid seed was that the early inbred lines used by breeders typically had very low seed set. In a (single) cross between two inbred lines, the seed parent is inbred, and although her resulting hybrid seeds (offspring) produce plants with superior yield, each inbred seed *parent* produces only a small number of such seeds. Thus, poor fertility of the initial inbred lines resulted in rather few hybrid seed per plant. Jones (1918, 1922), who was a graduate student of Emerson at the time, suggested that instead of using an inbred line as the seed parent, one instead uses a *hybrid* parent, with the hybrid seed for commercial release being produced by a **double cross** instead of a

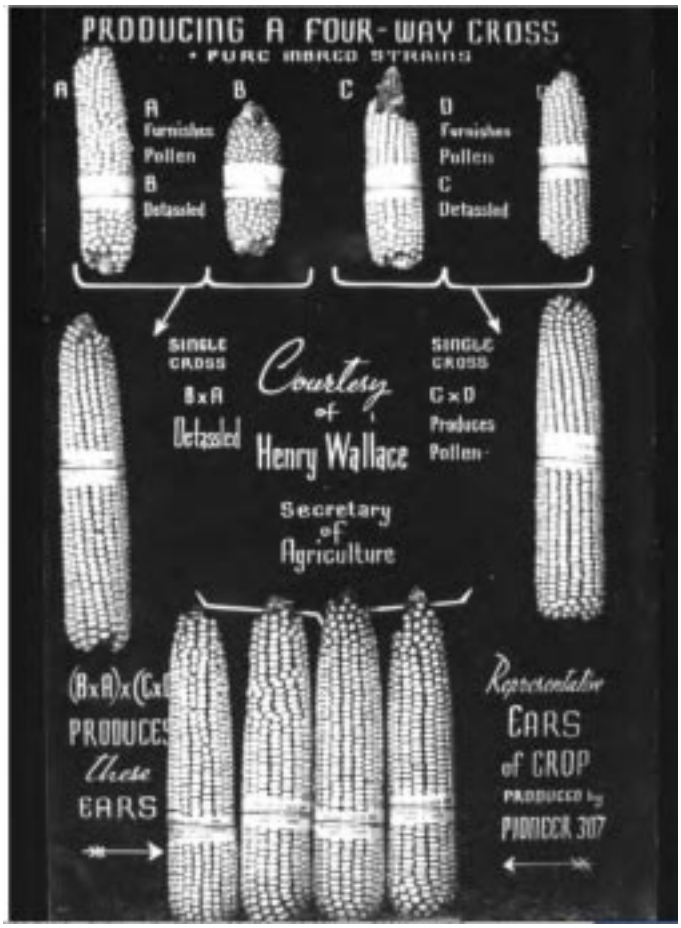


Figure 13.3. A vintage poster from the Pioneer Hi-Bred Company illustrating the use of double crosses in the creation of maize hybrid lines.

single cross. As shown in Figure 13.3, while single crossses are of the form $A \times B$ or $C \times D$, double (or **four-way**) crosses involve a further cross of two F_1s, $(A \times B) \times (C \times D)$. Since the seed parent is now a hybrid (the progeny from single cross between two inbred lines, e.g., $A \times B$), it should show heterosis in seed production, resulting superior seed set. This suggestion directly opened up the vast commercial potential of hybrid corn. A modification was to use a **three-way cross**, where pollen for line A is used to fertilize a $B \times C$ seed parent.

The first sale of hybrid seed was in 1924 by Henry A. Wallace (a farmer who later became Vice-President of the United States), who founded the Pioneer Hi-Bred Corn Company of Iowa the following year. A rapid transition from OPVs to hybrids quickly followed in many midwestern U.S. states. For example, Iowa went from less than ten percent hybrids in 1935 to over 90% by 1939. Crow (1998) noted that factors, other than improved yield, likely hastened the adoption of hybrids. First, machine harvesting was being introduced during this time and the greater uniformity of hybrids facilitated mechanized farming. Second, hybrids proved to be more hardy that OPVs during the devastating dust bowl drought from 1934 to 1936.

A critical fact that is easily overlooked was that the 1930s also saw the widespread acceptance of **Fisher's principles of experimental design**, allowing for more precise estimation of line effects and greater control over residual noise (Appendix 9). Crow (1998) noted out that Fisher spend several summers in the early 1930s at Iowa State University, which likely had a great influence on the analysis and test of potential hybrids. As Crow

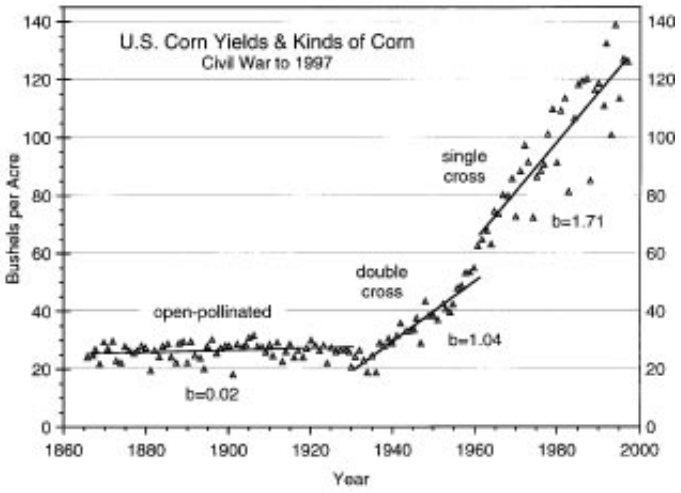


Figure 13.4 Average U.S. corn yields, 1865–1998. Initially, plantings were dominated by open pollinated lines (OPVs), which were largely replaced by double cross (four-way crosses of inbred lines; Figure 13.3), and most recently by single crosses. The regression slope (b) of yield gain per year are computed for each of these three periods. The rate of gain is even larger in the 2000s due to the next wave of technological advance, the introduction of GMO varieties (Troyer 2006). (Data from USDA and figure after Troyer 1999.)

noted "How much of the increase in agricultural productivity should be credited to Fisher, I don't know. But my guess is considerable." We concur.

From the 1930s to the 1960s, most U.S. hybrid corn was produced by double crosses (Figure 13.4). However, it was soon noted that the seed from single crosses usually out performed double- and three-way crosses (Sprague and Federer 1951; Rojas and Sprague 1952; Eberhart et al. 1964; Eberhart and Russell 1969). Further, double-cross hybrids were more variable than single-cross (due to segregation in the two single-crosses F_1s that are crossed to form the double cross). As breeders were able to select inbred lines with higher yield, hybrid corn based on single crosses became both commercially feasible and also desirable, given their increased yield and uniformity. Indeed, by the 1960s inbreds had been selected to the point where they often outperformed the initial double-cross hybrids of the 1930s. Ironically, the (initial) inability to create such high performing inbred lines was used by East and Hayes (1912) as evidence against the dominance hypothesis. If heterosis was largely due to overdominance, then no inbred line can match the best hybrid. However, if heterosis is largely due to partial to complete dominance, over time one should be able to stack all of the favorable dominant alleles into a single inbred. Indeed one could, but given the number of underlying yield loci, such selection took time. Since the 1970s, most hybrid corn is the U.S. is the result of single crosses.

The yield gains displayed Figure 13.4 confound genetic improvement with corresponding dramatic changes in agronomic practices. Indeed, a significant fraction of the gain has come from the development of maize lines that can handle higher levels of stress, allowing more plants to be planted per acre. Duvick (2005) noted that plant densities have increased by roughly 1000 plants per hectare (ha) per year in the U.S. corn belt, with densities of around 30,000 plants per ha in 1930, 40,000 plants in the 1960s, 60,000 plants in the 1980s, and 80,000 plants in the 2000s. Figure 13.5 illustrates how much of the yield gain is due to genetics, by growing remnant seeds of the best hybrid from a given historical year under the same conditions in a highly replicated (multiple location) design. This was done over three different years and shows both the amount of genetic improvement and also that there is little genotype x environment interaction. Hybrid improvement accounted for between 50 and 70% of the total improvement in yield, with the remainder due to improved farming

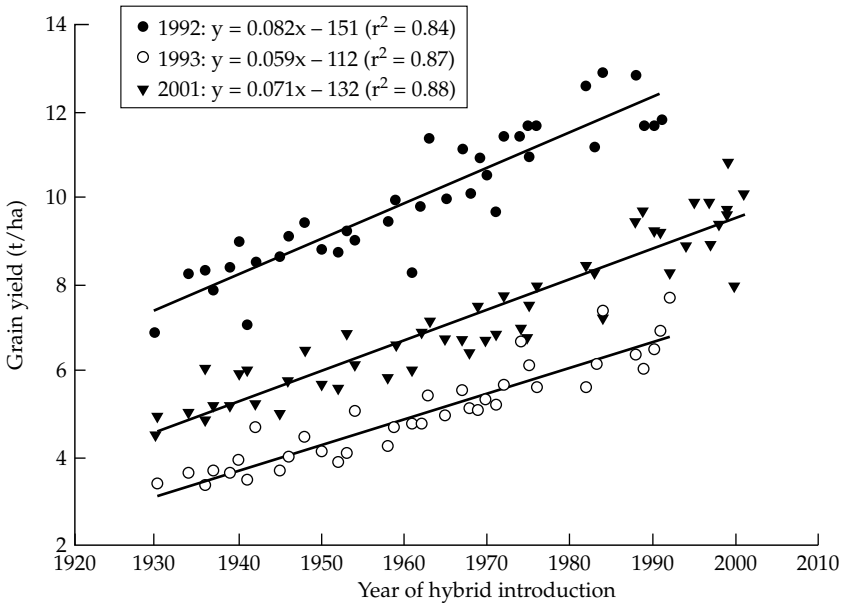


Figure 13.5 Yield (measured in tons per hectare) in maize hybrid lines as a function of year of release. Using remnant seed, all lines were grown in the same set of years, with 1992 being highly favorable, 1993 cool and extremely wet, and 2001 hot and dry. Note that the response is parallel over the three different environments (years), suggesting little genotype $\times$ environment interaction. Such "common-garden" experiments are the cleanest way to separate an observed gain into genetic versus environmental components (WL Chapters 19 and 20 present alternative mixed-model approaches that can also accomplish this goal). This separation is critical, as a yield improvement over time (Figure 13.4) could simply reflect improved agronomic practices, rather than genetic gain. (After Duvick 2005.)

practices (Duvick 2001, 2005).

Recalling Dudley's dictum of "hybrids, not heterosis," hybrid improvement can occur by increasing the performance of the parental inbred lines, by increasing the amount of heterosis between crossed lines, or both. How much of the improvement in modern U.S. maize hybrids is due to increased heterosis? Very little (Duvick 2005; Troyer and Wellin 2009). Most of the improvement in hybrids arose from the continual improvement of the elite inbred lines that were crossed, improvement that allowed breeders to move from double-cross to single-cross hybrids. Duvick (2005) found that the regression of yield (in tons per ha) on the midparental means of the best inbred lines was 0.048 per year, while the gain in heterosis was only 0.013 per year. Hence, while there was a slight gain in heterosis over time, there was over a four-fold greater improvement for the inbred lines. As noted by Troyer (2006) and Troyer and Wellin (2009), the percentage gain due to heterosis has been *decreasing* over time.

As we develop in Chapter 24, the basic machinery for predicting line cross means is based on the **general combining ability** (**GCA**) of each line and the **specific combining ability** (**SCA**) for each cross (Sprague and Tatum 1942). In essence, GCA is the breeding value of a line (Chapter 4), and (as with breeding values) is a function of population of lines chosen. The predicted mean of a cross is the sum of the maternal (M) and paternal (P) general combining abilities, GCA(P) + GCA(M). The deviation between the predicted and actual values estimates the specific combining ability for that particular cross. Hence, the expected mean value of the single cross between lines i and j is $\mathrm{GCA}_i + \mathrm{GCA}_j + \mathrm{SCA}_{ij}$. GCA represents the additive genetic contribution, while SCA represents the contribution from a subset of the nonadditive genetic variation in a trait (that which contributes to heterosis). Using this terminology, most of the response in maize hybrids has been through improved

GCAs among the elite inbred lines, while the response in SCA, while slightly positive, has a diminishing role in hybrid improvement. Similarly, one can think of heterotic groups as having low within, and high between, group SCAs. Thus, if one knew something about the GCA's of the lines in an initial collection, a quite reasonable starting point is cross the lines with the highest GCAs from each heterotic group with each other. While it certainly true that the best hybrid may involve a cross between two lines with low GCAs, but a very large SCAs, using the GCAs nonetheless offers a good compromise starting point.

Example 13.4 The development of heterotic patterns in U.S. maize was examined by Tracey and Chandler (2006). While the lore has been that breeders simply exploited existing geographic variance (e.g., Anderson and Brown 1952), Tracy and Chandler reached a surprisingly different conclusion: "heterotic patterns were created by breeders and are not the result of historical or geographic contingencies," rather "patterns were created by breeders through trail and error from a single race of corn."

A key to the initial division of lines into what eventually became recognized heterotic groups was that maize breeders focused on developing separate exceptional male and female lines. Commercial hybrids are generated by fertilizing elite lines from the female group with pollen from elite male-group lines. Female lines were selected for increased seed yield, to facilitate the transition from double-cross to single- cross hybrids. A second critical component was the ability of female line members to resist **lodging** (being blown over, or dislodged, during strong storms). Such resistance is critical for mechanical harvesting, which requires upright plants at maturity. As a result of this necessity, the female heterotic pool has a large contribution from members of the **Iowa Stiff Stalk Synthetic** lines (**BSSS**, the *B* being the USDA single-letter code for Iowa, as Illinois got the *I*). Elite males lines focused on (among other things) exceptional pollen production, with lodging resistance being of lesser importance. As the result of these restrictions, the female heterotic group is usually referred to as **Stiff Stalk** (**SS**) and the male group as **Non-Stiff Stalk** (**NSS**).

As noted by Tracey and Chandler (2006), improvement of inbred lines was restricted by breeders to crosses *within* a given group to generate new material, avoiding crosses between groups except to produce commercial hybrids. The issue then became how to organize lines to make such breeding programs more effective. In 1949, the recommendation from the Committee on Grouping of Inbred Lines for Breeding Purposes was "As an arbitrary division, the committee recommends that the lines having an odd entry numbers in the 1948 uniform test of inbreds be tentatively assigned to group A and those having even entry numbers be tentatively assigned to group B." (Anon. 1949). All of the BSSS inbred lines ended up being assigned to group B. The result was crossing only within group A to generate improved A pool elites (which became the current male pool), and crosses only within B to generate improved B pool inbreds (which became the female heterotic group). Decades of breeding under this scheme resulted in the SS female and NSS male heterotic groups that are currently observed. Molecular work has supported this view, showing that the initial collection of lines showed no significant clustering, while more recent lines show strong clustering into heterotic groups, due to divergence from this initially rather homogenous group (Duvick et al. 2004; van Heerwaarden et al. 2012). Reif et al. (2005) examined the nature of heterotic groups from other maize breeding programs and discussed models for their creation.

Example 13.5 Hybrid corn also offers an important cautionary lesson for plant breeders, namely, the great **Southern Corn leaf Blight** (**SCLB**) epidemic from 1970-1971 (Tatum 1971; Ullstrup 1972). This was one of the most damaging plant epidemics in history: in terms of food energy destroyed it was much larger than the Irish potato blight epidemic in the 1840's that produced widespread famine (Ullstrup 1972). The roots of the epidemic in the United States trace back to what (at the time) appeared to be an elegant genetic solution to a major labor problem in the production of hybrid corn. Corn can self-fertilize, an undesirable feature as it reduces the fraction of hybrid seeds on a plant. To prevent this, corn breeders manually **detassled** plants, removing these pollen-shedding organs, allowing pollen to be only donated

from the parents of interest. Typically, one row of pollen parents is planted for every four to six detassled rows of seed parents, so that a pollen parent is within two or three rows of any seed parent (any seed set on the pollen plants is ignored). The discovery of a mitochondrially encoded cytoplasmic factor that produced sterility in males seemed to be a elegant solution around the cost and effort of detassling (Jones and Everett 1949; Jones and Manglesdorf 1951; Rogers and Edwardson 1952). Plants with this T (for Texas, the origin of the line) cytoplasm are denoted by **Tcms**. Seed parents with Tcms cytoplasm produce normal and viable seeds, but no pollen, and thus do not have to be detassled. As a result of this very convenient feature, by 1970, almost 85% of hybrid corn seed in the U.S. contained Tcms. Hence, despite a wide diversity of nuclear genotypes, U.S. corn was close to a clonal monoculture in terms of its mitochondrial (mtDNA) composition.

In 1969, a previous unknown strain of the fungus *Helminthosporium maydis* was detected in a few areas in the midwest corn belt of the central U.S. Plants with Tcms were hyper-susceptible to this strain, and the result was over a billion dollar loss (in 1970's dollars) and major angst in both the private and public agricultural sectors. Corn is typically a rather disease-free crop (indeed, Ullstrup 1972 noted that in 1970, the U.S. Department of Agriculture considered corn so healthy that it did not employ any full-time corn pathologists in the U.S. corn belt), so this outbreak was even more of a shock and led to a considerable focus on increasing the genetic diversity in crops.

Hybridization in Other Crops

A number of crops utilize hybridization for commercial production, mainly for heterosis, but in some cases simply for uniformity (Janick 1999). As would be expected given the diversity of crops, a number of different solutions are used to exploit heterosis. Chapters in the edited volume by Frankel (1983) and the symposium volume edited by Coors and Pandey (1999) provide a nice review of some of these systems: rice (Virmani 1999); sorghum and pearl millet (Axtell et al. 1999); barley (Ramage 1983); rye (Geiger and Miedaner 1999); forage grasses (Kobabe 1983); oilseed crops such as soybean, rapeseed, and sunflower (Miller 1999); cotton (Meredith 1999); and ornamental (commercial flowers) crops (Reimann-Philipp 1983). While there is an impressive list of vegetable crops utilizing heterosis—carrots, onions, asparagus, spinach, broccoli, cabbage, cauliflower, cucumber, squash, watermelon, tomato, pepper, and eggplant—there are also vegetable crops with features that limit its use (Wehner 1999). The exploitation of heterosis also occurs in trees (Brewbaker and Sun 1999). While conifers typically use within-species crosses, other commercial products are mainly generated by cross-species hybrids (aspens, poplars, and *Eucalyptus*).

Three factors influence the ability to utilize heterosis: (i) the existence of heterosis, (ii) the ability to control pollination, (iii) whether the benefits of (i) offsets the costs of (ii). A good example is wheat (Wilson and Driscoll 1983; Jordaan et al. 1999), which although it can have up to 30% yield heterosis, this is not a sufficient gain to be economically viable in the current wheat cropping system. A major reason that hybrid corn has been commercially successful is because of its reproductive structures, with pollen being produced on a long tassel, which allows for relatively easy manual control of pollination. For many species with perfect flowers (i.e., both male and female parts), manual control of pollination is simply not economically feasible because flowers are too numerous, too small, or both. Male-sterile genes are critical in the creation of commercial hybrids in such species, as is chemical sterilization of pollen. Fu et al. (2014) gives a general overview of some of these solutions, while details for specific crops can be found in the papers cited above.

In contrast with field crops, horticultural crops have much more favorable economic conditions for the commercial exploitation of heterosis. Here, flowers are typically large and easily handled (unlike the grass-family flower heads of many important field crops). Equally important, the yield from each individual plant has significant commercial value (Dobbs 1955), so that individual manipulation of single plants often is economically feasible. Duvick (1999) discusses the required economics and politics for the widespread adoption of hybrid crops.

Approaches for the Retention of Heterosis: Synthetics and Apomixis

As shown by Equation 13.7, heterosis in the F_2 and subsequent generations is less than F_1 heterosis. One strategy to retain more heterosis in subsequent generation is through the construction of a **synthetic** or **composite population**. This approach also provides some ability to exploit heterosis when pollen control is difficult. The idea is simple: one starts with a set of n lines, and constructs a collection of all $n(n-1)/2$ pairwise crosses (ignoring crosses of a line with itself). The collection of lines resulting from this crossing scheme yields a **synthetic F_1 population**, and we define heterosis for this population in the standard fashion,

$$H_{F_1(syn)} = \mu_{F_1(syn)} - \overline{P} \tag{13.13}$$

where $\overline{P}$ is the trait mean over all parental lines. This F_1 collection is then randomly mated to form the **F_2 synthetic population**, which is allowed to randomly mate in all future generations to form the final synthetic population (occasionally referred to as the F_∞). Only a single generation of controlled crosses is required to generate the final synthetic population, offering a strategy to exploit heterosis without the need for potentially expensive and resource-heavy controlled crosses each generation.

The resulting single-locus genotype frequencies in the synthetic F_2 are in Hardy-Weinberg, while several additional generations of random mating are required to remove any linkage disequilibrium. What impact does this have on retention of heterosis? Consider first the heterosis generated by single-locus dominance effects. In the F_1, the genotype at any locus is a hybrid, with the two alleles coming from different lines. Conversely, in the F_2 for an n-line synthetic, there is a $1/n$ chance that the two alleles are from the same line, and a $(1-1/n)$ chance that (like the F_1) they are from different lines. Hence, the dominance loss is only $(1-1/n)$ as opposed to $1/2$ for the case of $n=2$ lines, with

$$\mu_{F_2(syn)} = \overline{P} + \left(1 - \frac{1}{n}\right) H_{F_1(syn)} \tag{13.14}$$

This result was first obtained by Wright (1922).

The creation of synthetic populations thus seems to be an easy, and straightforward, method for reducing the decay of heterosis from the F_1 to the F_2. The potential flaw of this assumption is Dudley's dictum of "hybrids, not heterosis," and is concerned with $\overline{P}$, the mean of the lines being crossed. The breeder is interested in the *mean* of the synthetic population, *not* the amount of *heterosis* that is retained. While adding more lines likely increases the latter (retention of heterosis), it usually reduces the former ($\overline{P}$). If $\overline{P}$ is reduced sufficiently over the midparental mean using the two highest-performing lines, then the extra retention of heterosis may be overwhelmed by the decrease in $\overline{P}$ due to starting at a lower mean value.

While all of the dominance loss occurs by the F_2, the epistatic (or recombinant) loss takes several generations to reach its limiting value. With $n=2$, for unlinked loci this occurs in a single generation, but for more than two lines, only $1/2$ of the LD decays each generation for unlinked loci. Recall that the recombination loss can be expressed as $r_d R$, where R is given by Equation 13.10a and the Dickerson coefficient, r_D, is the fraction of nonparental gametes in an individual. For an n-breed synthetic where all lines make an equal contribution, then (Dickerson 1972)

$$r_D = 1 - 1/n \tag{13.15a}$$

giving the equilibrium synthetic population mean (following the decay of LD) as

$$\mu_{F_\infty(syn)} = \overline{P} + \left(1 - \frac{1}{n}\right)\left(H_{F_1(syn)} - R\right) \tag{13.15b}$$

Wricke and Weber (1986) review the theory of synthetics, while additional treatments are given by Gallais (1975, 1976), Gallais and Wright (1980), and Wright (1981).

Table 13.4 Estimate of individual, H_I, and maternal heterosis, H_M, in sheep. Results presented as percentage of parental means. n_I and n_M indicate the number of estimates used for the reported individual and maternal values. **Prolificacy** is the litter size at birth. (After Nitter 1978.)

Trait	n_I	Mean H_I	n_M	Mean H_M	Total
Birth weight	42	3.2	12	5.1	8.1
Weaning weight	56	5.0	27	6.3	11.3
Fertility	20	2.6	30	8.7	9.3
Prolificacy	20	2.8	31	3.2	6.0
Birth-weaning survival	29	9.8	25	2.7	12.5
Lambs per ewe	20	5.3	25	11.5	16.8
Lambs reared per ewe	20	15.2	25	14.7	29.9
Total weight lambs/ewe	24	17.8	25	18.0	35.8

Finally, while synthetics offer some partial relief from the loss of heterosis, the holy grail for the preservation of heterosis across generations is **apomixis**, seed produced by asexual reproduction, effectively immortalizing the hybrid genotype. While rare, this breeding system is widespread (Bashaw 1980; Hanna et al. 1999; Abdi et al. 2016; Sailer et al. 2016), although attempts to introduce it into crops have been, so far, unsuccessful. The recent cloning of genes involved in some apomixis systems offers the possible option of generating facultative apomixis thorough transgenics.

AGRICULTURAL EXPLOITATION OF HETEROSIS: ANIMALS

Crossbreeding in Animals: General Concepts

As the mule illustrates, the importance of between-species hybrids in animal breeding goes back to prehistoric times. The aggressive utilization of crossbreeding to exploit heterosis (as opposed to crosses simply to combine desirable features from two different lines) followed Wright's (1922) extremely influential publication on crossbreeding (and inbreeding) in guinea pigs. General reviews of heterosis in animals are given by Gowen (1952), Sang (1956), and Sheridan (1981).

Animal breeders distinguish between **individual** (or **direct**) and **maternal heterosis**. Individual heterosis is enhanced performance in a *hybrid individua*l, while maternal heterosis is enhanced **maternal performance** (such as milk production or higher survival rates of offspring) due to having a *hybrid mother*. Maternal heterosis is often comparable, and can be greater than, individual heterosis (Table 13.4). Maternal and individual heterotic effects can be combined by using **crossbreed dams**. For example (Table 13.4), total weight of lambs reared per mated ewe has an 18% individual heterotic advantage in a crossbreed offspring (a single-cross, $A \times B$) and an *additional* 18% advantage (from maternal heterosis) when crossbreed ewes are used in place of purebreed ewes (a three-way cross, $A \times [\, B \cdot C\,]$. This observation extends beyond sheep. One example is Cundiff et al. (1974a, 1974b), who found that maternal heterosis was roughly twice the individual heterosis for several traits in European cattle (*Bos taurus*). This combining of maternal and individual heterotic effects is one reason why three-way crosses are common in animal breeding, generally by crossing a male from line A with a hybrid female (from a $B \times C$ cross). This strategy exploits maternal heterosis in the female, with the sire line usually chosen for its contribution to one or more production traits.

In theory, one could also exploit **paternal heterosis**, increased performance due to paternal effects, but there has been little evidence to date of this effect generally being significant. For example, Bradford et al. (1963) compared purebreed versus crossbreed sire performance, finding no major differences between them except for a slight (4%) elevation of lamb survival, where the hybrid exceeded both parents. If paternal heterosis is important, then a four-way cross—a sire from an $A \times B$ mating crossed to a dam from a $C \times D$ mating—

would provide the maximal benefit from all heterotic sources.

A second point that has received substantial attention in the animal breeding literature is heterosis × environment interaction (Orozco 1976; Barlow 1981; Sheridan 1981; Cunningham 1982). Although the general opinion is that heterosis is more pronounced in suboptimal environments, there are many exceptions to this pattern, and few of the data bearing on the subject come from well-designed experiments.

Case Study: Heterosis in *Bos indicus* × *Bos taurus* Hybrids

Some interesting results on crossbreeding are found in the literature examining crosses between European (*Bos taurus*) and tropical (*Bos indicus*) cattle (reviewed in McDowell 1985). *Bos taurus* breeds have been selected for significant genetic improvement in a number of production traits (such as milk and meat yield), but are adapted for only temperate climates. *Bos indicus* breeds are found in tropical countries, and while they show fairly little genetic improvement for production traits, they are well adapted to the local environment. Crosses between *taurus* and *indicus* have been made in the hope of generating higher performing hybrids that are also adapted to tropical environments.

Bos indicus × *B. taurus* hybrids are usually superior to indigenous breeds (i.e., the local breed of *B. indicus*) in milk yield and fitness measures such as calving age and interval. Trail et al. (1985) examined crosses between exotic *B. taurus* breeds (Angus and Red Poll) and indigenous *B. indicus* breeds (Ankole, Boran, and Zebu) in Africa. Crossbred (exotic × indigenous) dams showed superior maternal performance over straightbred indigenous dams. However, while maternal effects were apparently superior: the (single-cross) hybrid progeny of exotic × straightbred (Boran) dams were actually heavier at 24 months than the hybrid progeny of exotic × crossbred dams, suggesting that the 3/4 exotic composition from using crossbreed dams is not as favorable for individual performance as a composition of 1/2 exotic and 1/2 indigenous. Three-breed crosses between an improved breed sire and a crossbred dam (a second improved breed × an indigenous breed) generally tend to do poorer than two-breed crosses. This is contrary to the general superiority of three-breed crosses of *B. taurus* observed in temperate areas (McDowell 1985).

Bos indicus × *B. taurus* hybrids show higher levels of heterosis than observed in crosses among breeds within each species. This is perhaps not unexpected, as allele frequencies likely have diverged more between species than among the breeds within a species. Heterosis in crosses among *B. indicus* breeds is higher than is observed in crosses among *B. taurus* breeds. For example, Gregory et al. (1985) found that maternal heterosis in crosses within *B. indicus* lines was intermediate between levels produced in *B. indicus* × *B. taurus* hybrids and crosses among *B. taurus* breeds. One explanation is that there is more allele-frequency divergence among the various indigenous *B. indicus* breeds than among the *B. taurus* breeds, due to a perception of more local adaptation among breeds of the former.

While *indicus* × *taurus* crosses do indeed show significant heterosis, they can also have unanticipated economic disadvantages. Regarding the hybrids, McDowell (1985) noted that

> "some farmers have reservations that could influence national breeding programs. The two-breed crossbreed male is not as temperamental as the favored draft breed, e.g., Hariana in India, and does not move as rapidly for plowing or in performing cartage. The smaller hump of the crossbreed is not well suited to handle the traditional wooden yoke. For those reasons the crossed male has a price discrimination against it in the draft market."

Further, crossbreeds usually require supplemental feeding in tropical setting, otherwise they can become nutritionally stressed (McDonnell 1981, 1985).

Hybridization in Other Domesticated Animals

Most production systems for domesticated animals use at least some crossbreeding (Sheridan 1981; Yadav et al. 2018). This includes chicken (Muir and Aggrey 2003), swine (Bidanel 1993; Bittante et al. 1993), cattle (Gregory et al. 1985; Syrstad 1985; Simm 1998), dairy (Swan and Kinghorn 1992; Buckley et al. 2014), goat (Shrestha and Fahmy 2007), and sheep

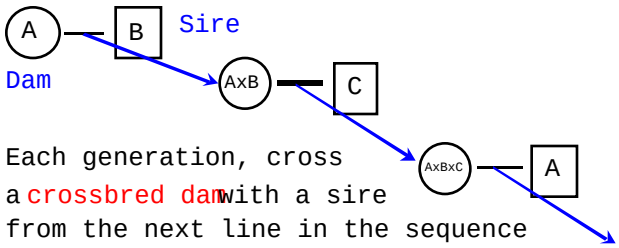


Figure 13.6. A **three-breed rotational** crossing scheme. In each generation, a crossbred dam (circles) is mated (in succession) to a rotation of three different sire (squares) lines. A fraction of the female offspring is used in the next cycle to continue the rotation, while the remainder (all males and some females) are sold commercially. One modification is a **terminal cross rotational** scheme, where those females that are not advanced within the breeding program are crossed to a sire from a different line, and the resulting offspring are the commercial product.

(Jakubec 1977; Simm 1998; Malik and Singh 2006). Aquaculturists have also examined crossbreeding, finding extensive yield heterosis for oysters (Hedgecock and Davis 2007), but little exploitable heterosis for Atlantic salmon (Gjerde and Refstie 1984). Beyond heterosis, one important consideration in choosing which populations to cross is the notion of **breed compatibility**, combining the favorable features from two different lines. Recalling our discussion of general combining ability (GCA), this is the idea of crossing populations which have high GCAs for different, but desirable, traits, to produce a line whose means for these traits are (at least) equal to their midparental values. In a sense, one can think of this as **economic heterosis**, as the combination of these features in a single line is often far more desirable than the economic average value of the two parental lines separately.

Reproductive differences between plants and animals facilitate different aspects of exploiting heterosis in a planned breeding system. One of the major limitations of crossbreeding in plants is pollen control, but sperm control is very easy in animals. Conversely, the generally very low reproductive output of large domesticated animals places severe limitations on the types of commercial crossing schemes that can be used. Chickens have little reproductive limitations, while swine, often with more than a dozen offspring, are more intermediate. Sheep may have two or three offspring per mating, while cattle very rarely have more than a single offspring per mating, severely limiting the types of crossing schemes that are commercially viable.

Rotational Crossbreeding

In much of plant breeding, **terminal crosses** are used, wherein hybrid individuals are the endpoints and do not reproduce further in the commercial production system. For example, a company sells a farmer F_1 seed, and this seed is generated anew each generation, with the F_1 plants themselves not allowed to reproduce. While such schemes can work in plants with their enormous reproductive potential, they are more difficult in animals. Consider a three-way cross of an A sire to a $B \times C$ dam (with C being the granddam). While this scheme requires only modest numbers of sires from the A and B lines, in large farm animals (i.e., sheep and cows), the number of offspring is on order of the number of dams. Thus, to produce n triple-cross hybrid offspring requires on the order of $2n$ dams (the granddam to produce the $B \times C$ dam, and this dam herself). As an aside, the importance of crossbred dams is such than a potential use of whole-animal cloning would be in the creation of cloned lines from crossbred mothers showing exceptional maternal heterosis. This is the animal equivalence of the plant breeder's search for apomixis for immortalizing a hybrid advantage in the face of Mendelian segregation.

To overcome limitations from low number of offspring per mating, Winters (1952; Winters et al. 1935) suggested a hybridization scheme, **rotational crossbreeding**, that continually recycles hybrid individuals (Figure 13.6). Here, hybrids from the previous generations are crossed (in rotation) to pure lines. For example, a three-breed rotational would use $A \times B$ as the first generation. In generation two, *dams* from the first generation are crossed to line C. In generation three, *dams* from generation two are crossed to sires from line A, and the rotation continues over all three lines in subsequent generations. This approach represents a comprise between trying to maintain maximal heterozygosity within a line (and hence optimize the dominance contribution to heterosis) without having to regenerate the line anew each generation. Further, by restricting the crosses to a pure-line sire and a crossbreed dam, it also fully exploits any maternal heterosis.

The central idea in a standard rotational scheme is that some of the crossbred dams are used in the next cycle. Male offspring and female offspring not required to keep the rotational population at a desired size can be sold off commercially. There are a number of modifications of this scheme, especially in cattle (Gregory and Cundiff 1980; Gregory et al. 1982; Gosey 1991; Ritchie et al. 1999). One is that female offspring not advanced in the rotation could themselves be crossed to a different sire line that is outside of the rotation (a terminal cross) and the resulting offspring sold. Another variant is that one could use the same sire line, but generate crossbred dams in a cycle among other lines (a rotational cross using dams).

Example 13.6 Consider a three-breed rotational crossbreeding scheme where, as in Figure 13.6, dams from the previous generation are crossed to pure-bred sires in a rotating sequence (line A in one generation, B in the next, C in the third, and so on). Under this scheme, what fraction of genes from each of the lines are present in any particular generation? The logic is straightforward: in each generation, half of the contribution from the previous dam is passed on, and half the genes are from the sire line. Thus,

		Percentage of lines:		
Generation	Cross	A	B	C
1	$A \times B$	50.0	50.0	0.0
2	$C\times$ gen 1 dam	25.0	25.0	50.0
3	$A\times$ gen 2 dam	62.5	12.5	25.0
4	$B\times$ gen 3 dam	31.3	56.3	12.5
5	$C\times$ gen 4 dam	15.6	28.1	56.3
6	$A\times$ gen 5 dam	57.8	14.1	28.1
7	$B\times$ gen 6 dam	28.9	57.0	14.1
8	$C\times$ gen 7 dam	14.5	28.5	57.0

The asymptotic contributions reached are 57.1% from the current sire line, 28.6% from the sire line used in the previous generation, and 14.3% from the sire line used two generations ago (and the sire line for the next generation).

In a similar fashion, for a four breed (A, B, C, D) rotational scheme,

		Percentage of lines:			
Generation	Cross	A	B	C	D
1	$A \times B$	50.0	50.0	0.0	0.0
2	$C\times$ gen 1 dam	25.0	25.0	50.0	0.0
3	$D\times$ gen 2 dam	12.5	12.5	25.0	50.0
4	$A\times$ gen 3 dam	56.3	6.3	12.5	25.0
5	$B\times$ gen 4 dam	28.1	53.1	6.3	12.5
6	$C\times$ gen 5 dam	14.1	26.6	53.1	6.3
7	$D\times$ gen 6 dam	7.0	13.3	26.6	53.1
8	$A\times$ gen 7 dam	53.5	6.6	13.3	26.6

At equilibrium, the line contributions cycle as 53.3%, 26.7%, 13.3%, and 6.7%. As a consequence of the predominant genetic line changing each generation, one consideration of rotational systems is that the cycled breeds be sufficient compatible such that these compositional changes over cycles do not have commercial liabilities.

One can extend the logic from Example 13.6 to a k-line rotational scheme. The expected fraction of genetic contributions at equilibrium from each of the k lines where crossbred dams are kept and crossed in rotation to purebreed sires are of the form

$$(1/2) \cdot I, \quad (1/2)^2 \cdot I, \quad (1/2)^3 \cdot I, \quad \cdots, \quad (1/2)^k \cdot I$$

where

$$I = \sum_{i=0}^{\infty} \left(\frac{1}{2^k}\right)^i = 1 + \frac{1}{2^k - 1} \tag{13.16}$$

with the largest fraction ($I/2$) from the line last used as a sire and the smallest fraction ($I/2^k$) for the line to be next used as a sire. The resulting values of I, and the current contributions from the most recent sire (CS) and the next upcoming sire (US), for up to an 8 line crossing scheme are as follows:

k	2	3	4	5	6	7	8
I	1.333	1.143	1.067	1.032	1.016	1.008	1.004
CS	0.667	0.571	0.533	0.516	0.508	0.504	0.502
US	0.333	0.143	0.067	0.032	0.016	0.008	0.004

What are the expected asymptotic average values for a rotation cross and how can one predict this? Expressions allowing for maternal heterosis and recombination loss are developed below (Table 13.5). However, under the assumption of only dominance and no material heterosis, some simple predictors were suggested by Carmon et al. (1956). For a two-line (A, B) rotation, the predicted equilibrium mean is

$$\widehat{Rc}_2 = \overline{z}_{AB} - \frac{\overline{z}_{AB} - \overline{P}_2}{3}, \quad \text{where} \quad \overline{P}_2 = \frac{\overline{z}_A + \overline{z}_B}{2} \tag{13.17a}$$

Here $\overline{P}_2$ is the average of the two parental lines and $\overline{z}_{AB}$ the mean value of their cross. When heterosis is present ($\overline{z}_{AB} > \overline{P}_2$), the expected mean performance under rotational crossbreeding is less than the single-cross performance ($\overline{z}_{AB}$). Note, however, that the dominance loss in a two-breed rotation is $H/3$, less than the loss of $H/2$ for a two-breed synthetic (Equation 13.14).

For a three-line (ABC) rotational cross, the predicted mean is

$$\widehat{Rc}_3 = \overline{SC}_3 - \frac{\overline{SC}_3 - \overline{P}_3}{7}, \quad \text{where} \quad \overline{SC}_3 = \frac{\overline{z}_{AB} + \overline{z}_{AC} + \overline{z}_{BC}}{3} \tag{13.17b}$$

where $\overline{SC}_3$ is the average of the three single crosses between these three lines and $\overline{P}_3$ the average of the three parental lines. The dominance loss is $H/7$ as opposed to $H/3$ under a three-breed synthetic.

For a four-line rotation, the order of the rotation matters. Letting the rotation be (A, B, C, D), the predicted long-term performance is

$$\widehat{Rc}_4^{(A,B,C,D)} = \overline{SC}_4 - \frac{\overline{SC}_{na} - \overline{P}_4}{15} \tag{13.17c}$$

where

$$\overline{SC}_4 = \frac{\overline{z}_{AB} + \overline{z}_{AC} + \overline{z}_{AD} + \overline{z}_{BC} + \overline{z}_{BD} + \overline{z}_{CD}}{6} \quad \text{and} \quad \overline{SC}_{na} = \frac{\overline{z}_{AC} + \overline{z}_{BD}}{2}$$

As above, $\overline{P}_4$ is the mean of the original lines, while $\overline{SC}_4$ is the mean of all six possible single-crosses between the four lines, and $\overline{SC}_{na}$ is the average of the two single crosses of nonadjacent lines in the rotation (and hence varies with the order of rotation used).

Equation 13.14 gives the estimated mean for a synthetic, while expressions for the predicted values of three- and four-way crosses (based upon all combinations of single crosses) are developed in Chapter 24.

Example 13.7 Consider the following data from Kidder et al. (1964) for various crosses of Devon and Brahman cattle. The midparent $\overline{P}$, F_1, two-breed rotational crossbreed Rc_2, the two-breed synthetic S_2 ($= F_2$), and the backcross (BC, $F_1 \times$ parent) means for several weight-related traits were as follows:

	Means				
Trait	$\overline{P}$	F_1	Rc_2	S_2	BC
Weaning weight	154.2	180.5	178.3	170.1	181.4
12-month weight	210.5	246.8	232.2	212.3	233.6
18-month weight	274.9	315.7	296.6	276.6	295.3
12-18 month weight gain	64.4	68.9	64.4	64.4	61.7

Note that the order of performance for all traits is $F_1 > Rc_2 > S_2$.

How well does Equation 13.17a predict the two-breed rotational crossbreed performance, Rc_2? Here the F_1 corresponds to $\overline{z}_{AB}$, so that the predicted equilibrium value is

$$\widehat{Rc}_2 = F_1 - \frac{F_1 - \overline{P}_2}{3}$$

For example, for weaning weight

$$\widehat{Rc}_2 = 180.5 - \frac{180.5 - 154.2}{3} = 171.7$$

which is 96% of the observed value (178.3). Similarly, the predicted values (and fraction of the actual values) for 12-month, 18-month, and gain are, respectively, 234.7 (101%), 302.1 (102%), and 67.5 (104%). Hence, for these data, there was a slight tendency to overestimate the true mean, which is to be expected if recombination loss has occurred.

Standard errors for these predicted values can be approximated as follows. We consider the two-breed predictor, but the basic approach easily extends to most of the other predictors developed in this chapter. Rearranging to collect common terms,

$$\widehat{Rc}_2 = \overline{z}_{AB} - \frac{\overline{z}_{AB} - \overline{P}_2}{3} = \left(1 - \frac{1}{3}\right)\overline{z}_{AB} + \left(\frac{1}{6}\right)(\,\overline{z}_A + \overline{z}_B\,)$$

Since the estimates of the means are independent and recalling that $\sigma^2(ax) = a^2\sigma^2(x)$ for a constant a (Equation 3.10c), it immediately follows that

$$\sigma^2\left(\widehat{Rc}_2\right) = \left(1 - \frac{1}{3}\right)^2 \sigma^2(\,\overline{z}_{AB}\,) + \left(\frac{1}{6}\right)^2 \left(\,\sigma^2(\,\overline{z}_A\,) + \sigma^2(\,\overline{z}_B\,)\,\right)$$

Maternal Heterosis and Recombination Loss

Two complications that were ignored in the previous section are the presence of epistasis (and its associated recombination loss in subsequent generations) and maternal heterosis (which, itself, can also show recombination loss). We examine maternal effects in detail

in Chapter 27, but the basic idea is that the environment experienced by an individual can be influenced by its mother (such as milk production and other aspects of maternal care). Maternal effects are often the default assumption for animal traits (particularly for species with maternal care), but rarely assumed for plants. Maternal heterosis is simply the idea that the maternal performance provided by a hybrid mother is superior to that of a purebred mother. The result is that the trait mean of an offspring from a crossbred mother is increased by a maternal heterosis value, H_M. As with any other trait, the maternal heterotic contribution in the F_2 (and subsequent) generations shows a dominance loss, $H_M/2$ and (if certain types of epistasis are present), a further recombination loss (Equations 13.7 and 13.10). Thus, the maternal heterotic effect from a crossbred mother is expected to decline in the next generation, with her daughters showing less maternal heterosis. The basic approach for incorporating maternal effects was given in a specific case (three-line crosses) by Magee and Hazel (1959), while a more general treatment was developed by Dickerson (1969, 1972).

As an example of how material heterosis and recombination loss impact the means of crosses, consider the offspring from a three-way cross, $A \times (B \cdot C)$, whose expected mean is given by

$$\mu_{A\times(B\cdot C)} = \overline{P} + (H_I - R_I/4) + H_M \tag{13.18a}$$

where $\overline{P} = (2\mu_A + \mu_B + \mu_C)/4$ is the weighted parental line average. The various heterotic contributions are obtained as follows. The use of a crossbred mother ($B \times C$) adds a maternal heterotic contribution (H_M), while there are two factors impacting individual heterosis (the two terms in the parentheses). Offspring are fully heterozygous in the sense that all loci have one allele from line A and the other from either B or C, contributing H_I (the average of the individual heterosis from $A \times B$ and $A \times C$ crosses). Secondly, recombination loss appears for individual heterosis, as (for unlinked loci) half of the gametes from the mother are recombinant (of the form B_1C_2 or C_1B_2, as opposed to the parental gametes of B_1B_2 and C_1C_2). Hence, unlike a standard single-cross where all of the gametes that join to form the hybrid are parental in origin (both alleles in a gamete are from the same line), $1/4$ of the gametes that made up the three-way hybrid are recombinant (as half of the gametes are from the $B \times C$ parent). Hence, $r_D = 1/4$, for a recombination loss in individual heterosis of $-R_I/4$.

Now suppose that the resulting three-way cross offspring are randomly mated, which we will denote as an F_2. Here, the mother now has composition $A \times (B \cdot C)$, and following the logic from above, her maternal heterotic contribution to her offspring is $H_M - R_M/4$. Turning to the composition of individual heterosis, we assume Hardy-Weinberg and linkage equilibrium. Half of the genes in the F_2 are from line A, and $1/4$ each from lines B and C. Hence, the probability that a locus is homozygous in origin (both alleles from the same population) is $(1/2)^2 + 2(1/4)^2 = 3/8$, so that $5/8$ of the time a locus has alleles from different populations, generating a contribution of $(5/8)H_I$. To obtain the recombination loss, we need to compute the Dickinson coefficient, r_D, the probability that the alleles in a gamete come from different populations. Under linkage equilibrium, the probability that they come from the same population is also $(1/2)^2+2(1/4)^2 = 3/8$, hence $r_D = 1-3/8 = 5/8$, generating a recombination loss in individual heterosis of $-(5/8)R_I$. The resulting F_2 mean becomes

$$\mu_{F_2} = \overline{P} + (5/8)(H_I - R_I) + (H_M - R_M/4) \tag{13.18b}$$

Finally, suppose the F_2 are randomly mated to form an F_3. Because the population is in Hardy-Weinberg and linkage equilibrium, the individual heterosis is the same as the F_2, while the maternal heterosis is generated from F_2 females, whose heterotic composition now has the form of that for the F_2 individual heterosis, yielding

$$\mu_{F_3} = \overline{P} + (5/8)(H_I - R_I) + (5/8)(H_M - R_M) \tag{13.18c}$$

This value is stable in all future generations (assuming random mating). Note that this is a synthetic population, but with unequal, rather than equal, contributions from the three

Table 13.5 The impact of heterosis under different crossing systems. The notation used for mating systems has the sire composition to the left of the $\times$ symbol, and the dam composition to the right, so that $(A \cdot B) \times C$ denotes a crossbred sire ($A \times B$) mated to a purebred dam (C). For a given mating system, the table gives the coefficients for individual, maternal, and paternal heterosis (H_I, H_M, H_P) and for the associated recombination loss (R_I, R_M, R_P). For example, with a three-breed rotational, the average individual heterosis (averaged over cycles) is (6/7) $\overline{H}_I$, where $\overline{H}_I$ is the average individual heterosis for the three crosses. After Dickerson (1972).

Mating System	Heterosis H_I	H_M	H_P	Recombination loss R_I	R_M	R_P
2-breed cross						
$A \times B$	1	0	0	0	0	0
3-breed cross						
$A \times (B \cdot C)$	1	1	0	1/4	0	0
$(A \cdot B) \times C$	1	0	1	1/4	0	0
4-breed cross						
$(A \cdot B) \times (C \cdot D)$	1	1	1	1/2	0	0
Rotational Crossing (Sire)						
2 sire breeds	2/3	2/3	0	2/9	2/9	0
3 sire breeds	6/7	6/7	0	6/21	6/21	0
4 sire breeds	14/15	14/15	0	14/45	14/45	0
k sire breeds	k_1	k_1	0	$k_1/3$	$k_1/3$	0
Rotational Crossing (Dam)						
2 dam breeds	1	2/3	0	2/9	2/9	0
3 dam breeds	1	6/7	0	6/21	6/21	0
4 dam breeds	1	14/15	0	14/45	14/45	0
k dam breeds	1	k_1	0	$k_1/3$	$k_1/3$	0
Synthetic population						
2 breeds	1/2	1/2	1/2	1/2	1/2	1/2
3 breeds	2/3	2/3	2/3	2/3	2/3	2/3
4 breeds	3/4	3/4	3/4	3/4	3/4	3/4
k breeds	k_2	k_2	k_2	k_2	k_2	k_2

where $\quad k_1 = \dfrac{2^k - 2}{2^k - 1}$ and $k_2 = \dfrac{k-1}{k} = 1 - \dfrac{1}{k}$

parents. In general, if p_i denotes the contribution for line i (of k total), then the general mean for a synthetic population (at equilibrium) is

$$\mu_{syn} = \overline{P} + \Theta(H_I + H_M) - \Theta(R_I + R_M) \tag{13.19}$$

where

$$\overline{P} = \sum_{i=1}^{k} \mu_i p_i, \qquad \text{and} \qquad \Theta = 1 - \sum_{i=1}^{k} p_i^2$$

This result (for individual heterosis, but no maternal heterosis or epistasis) is due to Wright (1922), with the more general version due to Dickerson (1972). Chapter 24 examines the challenging problem of obtaining separate estimates of individual and maternal heterosis, which is complicated in the presence of recombination loss.

Proceeding in this fashion, Dickerson (1969, 1972) worked out the coefficients for the heterosis and recombination loss terms under a variety of crossing designs, and these are summarized in Table 13.5 (which, for generality, also allow for the potential of paternal heterosis). As an example, consider a three-breed rotation versus a three-breed synthetic

Table 13.6 Different scenarios for when a particular crossbreeding method is optimal. (After Kinghorn 1999.)

Scenario	Recommendation
Purebreed	No cross is better.
Individual heterosis is important.	Single cross
Both individual and maternal heterosis are important.	Three-breed cross
Individual, maternal, and paternal heterosis are important.	Four-breed cross
Only two good paternal breeds are available and/or individual heterosis is not important.	Backcross
Females are too expense to buy/produce, or litter size is too small.	Rotational Cross
Logistical or financial constraints in applying rotational crossbreeding.	Synthetic Population

(ignoring any paternal heterosis). Table 13.5 gives the heterotic contributions, yielding the expected mean of a three-breed rotational system (averaged over cycles at equilibrium) as

$$\mu_{Rc_3} = \overline{P}_3 + \frac{6}{7}\,(H_I + H_M) - \frac{6}{21}\,(R_I + R_H) \tag{13.20a}$$

while for a synthetic breed

$$\mu_{syn-3} = \overline{P}_3 + \frac{2}{3}\,(H_I + H_M) - \frac{2}{3}\,(R_I + R_H) \tag{13.20b}$$

where $\overline{P}_3$ is the average of the three parental lines. The resulting expected differences between these two schemes is

$$\mu_{Rc_3} - \mu_{syn-3} = \frac{4}{21}\,(H_I + H_M) + \frac{8}{21}\,(R_I + R_H) \tag{13.20c}$$

Hence, rotational crossbreeding keeps more heterosis, and has a smaller recombination loss, than a synthetic. Similarly, for a two-breed rotation versus a two-breed synthetic,

$$\mu_{R-2} - \mu_{syn-2} = \frac{1}{6}\,(H_I + H_M) + \frac{5}{18}\,(R_I + R_H) \tag{13.20d}$$

Table 13.6 shows the various tradeoffs for the different crossing systems. Notice, as was found for the two- and three-breed cases, that rotational crossing breeding systems retain more heterosis (both individual and maternal) than do synthetics, and also suffer from less recombination loss. The latter occurs because one parent each cycle contributes half of the gametes, reducing the fraction of nonparental gametes that generates recombination loss in the presence of epistasis.

Sheridan (1981) and Kinghorn (1999) reviewed the conditions that favor particular crossing systems, which balances constraints in the production system (most notably, number of offspring per mating) with the optimal retention of heterosis and control of recombination loss. While there is significant variation in breeding systems, Kinghorn (1999) noted some general trends. Chickens and pigs with their relative high reproductive rate tend to use three-way crosses and backcrosses, meat sheep tend to use three-way crosses, temperate beef producers tend to use either rotational systems or composite (synthetic) populations, while tropical beef producers tend to use composites. Wool sheep and dairy using mainly pure lines, largely because exceptional lines for these specific production goals exist in temperate countries.

OUTBREEDING DEPRESSION

When populations are sufficiently divergent, hybrids between them often have *reduced*, not *enhanced*, performance. Equations 13.6 and 13.7 highlight that such outbreeding depression is driven by epistasis, interactions between alleles (additive $\times$ additive) or genotypes (dominance $\times$ dominance) at different loci. The idea is that local adaptation favors combinations of alleles that work well together in a particular environment, and that these combinations are randomized in hybrids, decreasing performance. Obviously, this topic is of great interest to evolution biologists, as it is assumed to be a byproduct of adaptation. It is also of critical importance in conservation genetics. Suppose that one has a small isolated population with greatly reduced genetic variation, perhaps to the point that it suffers from inbreeding depression. One strategy for its genetic management is to introduce a few individuals from a different, but closely related, population, an idea known as **genetic rescue** (Edmands 2006; Whiteley et al. 2015; Hedrick and Garcia-Dorado 2016). If outbreeding depression is important, such a strategy can cause more harm than good. Hence, a deeper understanding of outbreeding depression than we currently possess is of fundamental importance to conservation biologists.

Our current understanding of the time scales (and geographic scales) over which outbreeding depression evolves is extremely crude, although Frankham et al. (2011) attempt to provide some guidelines for conservation biology. A number of empirical studies have uncovered striking examples of F_1 and/or F_2 breakdown in crosses among populations of the same species (Edmands 2006 and Frankham et al. 2011 review such studies). For example, Burton (1987, 1990a, 1990b), Brown (1991), and Edmands (1999) have obtained extensive evidence for the breakdown of physiological competence in crosses between populations of the marine copepod *Tigriopus californicus* inhabiting tide pools separated by only tens of kilometers. Other dramatic evidence of outbreeding depression comes from observations of reduced fitness in crosses of inbred lines of *Drosophila* (Templeton et al. 1976) and plants (Parker 1992) adapted to identical environments. Crosses between outbreeding plants separated by a few to several tens of meters can exhibit substantial reductions in fitness (Waser 1993b; Waser and Price 1985, 1994), as can crosses between fish derived from different sites in the same drainage basin (Leberg 1993) and crosses between clones of *Daphnia* from the same pond (Lynch and Deng 1994; Deng and Lynch 1996a). Crosses between French isolates of *Caenorhabditis elegans* showed outbreeding depression over distances as small as 15 meters (Dolgin et al. 2007).

In most of these examples, a decline in performance was observed in the F_1 generation, and data on the F_2 progeny were not obtained. Such results strongly implicate a breakup of favorable additive $\times$ additive epistatic effects as a factor contributing to outbreeding depression (Equation 13.6). As Equation 13.7 shows, dominance $\times$ dominance epistasis can lead to considerable additional decline in the F_2 (beyond the dominance loss). Indeed, one can have heterosis in the F_1 and outbreeding depression in the F_2 if epistatic dominance is sufficiently large. This has been seen. Fenster and Galloway (2000a; 2000b) observed heterosis in F_1 (and in many F_2) crosses between different populations of the annual legume *Chamaecrista fasciculata*. However, many of the F_3 crosses showed outbreeding depression. Equation 13.6c explains this observation by having moderate linkage between loci that influence dominance $\times$ dominance interactions. A second example is the work by Edmands (1999) on *T. californicus*. F_1 hybrids between populations tended to show heterosis, while most F_2 showed outbreeding depression. Edmands cleverly exploited the lack of crossingover in females of this species to examine the role of recombination. Crosses of both F_1 hybrid males and F_1 hybrid females back to the parental line showed a decline in fitness, with no effect on the mean from the sex of the F_1. Thus, among-chromosome segregation contributed to the recombination loss. However, she also observed that while the means were equal, the recombinational (F_1 male) backcross had a larger variance, suggesting breakup of gene combinations within chromosomes was also important. Hence, studies that report heterosis in the F_1 generation with no evaluation of the F_2 can be very

misleading. Indeed, of the 39 studies reviewed by Edmands (2006), 44% (17/39) did not show outbreeding depression until at least the F_2.

As these examples illustrate, a particularly difficult issue underlying assessments of the potential for outbreeding depression concerns the time scale over which outbreeding depression is revealed. There will always be some loss of heterosis in the F_2 generation, and a breakup of favorable epistatic gene complexes is always implicated when the F_2 performance is not intermediate to that of the F_1 and the mean of the parental lines. However, with low rates of recombination between pairs of epistatically interacting genes, it may take several generations for the negative consequences of mixing coadapted gene complexes to fully emerge.

A final delicate issue is the measurement of fitness in outbreeding depression studies. A common-garden experiment, while providing a standarized environment, may be misleading, especially if one (or both) of the parental lines is not adaptive to the test environment. Ideally one would test hybrids in the environments of both parents, but logistically this can be very challenging, especially for natural populations. Local adaptation has been repeatedly documented through reciprocal transplant experiments with plants, which often exhibit adaptive divergence on spatial scales as small as a few meters (Schemske 1984; Waser and Price 1985; McGraw 1987; Schmitt and Gamble 1990; Galen et al. 1991). Similar results have been obtained with herbivorous insects residing on adjacent, long-lived hosts (Edmunds and Alstad 1978; Karban 1989). In most of these studies the environmental differences perceived by the organism were not apparent to the investigators, so an absence of obvious ecological differentiation does not provide a compelling argument for ruling out local adaptation.

Example 13.8 One of the classic studies in evolutionary genetics was the early work by Theodosius Dobzhansky on the population genetics of *Drosophila pseudoobscura* chromosome rearrangements in the western United States (his collected works can be found in Lewontin et al. 1981). In the 1950's, this was one of the few systems for examining genetic variation in natural populations. Dobzhansky found that third chromosomes of *pseudoobscura* had three easily recognizable rearrangements (which can be distinguished under a light microscope by their banding patterns). These were referred to as *Standard* (*ST*), *Arrowhead* (*AR*), and *Chiracahua* (*CH*), the last two named for locations where they were collected. Chromosome rearrangements suppress recombination, creating a large region of almost complete linkage disequilibrium. Further, the collection of a given rearrangement can genetically diverge over time as new mutations are differentially accumulated in these nonrecombining regions. Dobzhansky measured the fitness of these rearrangements through competition experiments in population cages, following their frequency changes over time.

Dobzhansky (1950) examined the fitness of rearrangement heterozygotes relative to rearrangement homozygotes (e.g., *ST/CH* versus *ST/ST* and *CH/CH*, and *AR/CH* versus *AR/AR* and *CH/CH*). When the rearrangements came from the same population, heterozygotes showed high-parent heterosis, having higher fitness than either rearrangement homozygote. However, when the rearrangements came from geographically separated populations (California vs. Mexico), heterozygotes had lower fitness than either homozygote. Hence, they showed heterosis within a population but outbreeding depression when the rearrangements came from distinct populations.

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