Theor Appl Genet (2007) 115:335–342
DOI 10.1007/s00122-007-0565-6

ORIGINAL PAPER

Multilocus epistasis, linkage, and genetic variance in breeding populations with few parents

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Received: 11 September 2006 / Accepted: 23 April 2007 / Published online: 12 June 2007

Abstract In a previous study of maize (*Zea mays* L.) populations formed from few parents, we found that estimates of genetic variances were inconsistent with a simple additive genetic model. Our objective in the current study was to determine how multilocus epistasis and linkage affect the loss of genetic variance in populations created from a small number of parents (N). In simulation experiments, F_2 individuals from the same single cross were intermated to form progeny populations from $N = 1$, 2, 4, and 8 parents. Additive gene effects and metabolic flux epistasis due to $L = 10$, 50, and 100 loci were modeled. For additive, additive-with-linkage, epistatic, and epistasis-with-linkage models, we estimated the ratio between total genetic variance in the progeny population (V_N) and base population (V_B) as well as the 95th ($\Delta_{95\%}$) and 75th ($\Delta_{75\%}$) percentile differences between the estimated V_N/V_B and the V_N/V_B expected for the additive model. The mean V_N/V_B ratio was lower under epistasis than under additivity, indicating that metabolic flux epistasis hastens the decline in genetic variance due to small N. In contrast, $\Delta_{95\%}$ was higher with epistasis than with additivity across the different levels of N and L. Linkage had little effect on the mean V_N/V_B, whereas it increased $\Delta_{95\%}$ and $\Delta_{75\%}$ under both additivity and epistasis. Smaller N and L led to higher V_N/V_B particularly when epistasis was present. Overall, the results indicated that while metabolic flux epistasis led to a faster average decline in genetic variance, it also led to greater variability in this decline to the point that V_N/V_B was larger than expected in many populations.

Communicated by H. C. Becker.

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Introduction

Breeding populations ideally should have a high mean performance and a large genetic variance for the traits of interest. To enhance genetic variance, plant breeders can choose genetically diverse inbreds as parents; use as many parents as is logistically possible, or both. Crossing few parents leads to inbreeding, and an additive genetic model predicts a linear decrease of genetic variance with inbreeding (Wright 1951). As such, a practical implication in plant breeding is to use as many inbreds as possible, especially if these inbreds are related, in forming a breeding population. In practice, however, plant breeders prefer to cross only two parental inbreds to form breeding populations for inbred development (Hallauer 1990; Bernardo 2002, p 70).

In a previous study we conducted to determine the effect of decreasing the number of parents on the genetic variance in maize (*Zea mays* L.) populations, the estimates of testcross genetic variance were often inconsistent with an additive genetic model (Tabanao and Bernardo 2005). The differences in genetic variance observed for two, four, and eight-parent populations were mostly insignificant. Other studies involving inbreeding have also indicated levels of genetic variance greater than what is expected under an additive genetic model (Bryant et al. 1986; Whitlock 1995; Wade et al. 1996; Cheverud et al. 1999; Yu and Bernardo 2004a).

These empirical results as well as theoretical studies (Goodnight 1988, 1995, 2004; Cheverud and Routman 1996; Naciri-Graven and Goudet 2003; Barton and Turelli 2004; Lopez-Fanjul et al. 2004, 2006) suggest that epistasis may maintain genetic variance in populations that are supposed to suffer from inbreeding due to a small effective population size.

The above-cited theoretical studies on the maintenance of genetic variance by epistasis considered natural outbreeding populations, for which epistatic loci were in linkage equilibrium. In contrast, the crossing of two inbreds to form a breeding population leads to the maximum possible linkage disequilibrium in the resulting F_2 population (Dudley 1993). Furthermore, the above-cited theoretical studies investigated either two-locus epistasis or arbitrary forms of epistasis among several loci. In this study we modeled multilocus epistasis though metabolic control theory (Kacser and Burns 1981), which leads to an L-shaped distribution of gene effects (Bost et al. 1999) that is consistent with the results of quantitative trait loci experiments (Kearsey and Farquhar 1998; Bernardo 2002, p 311). Given that our previous empirical study in maize (Tabanao and Bernardo 2005) suggested non-additivity (epistasis and linkage) in an F_2 population, our objective in this study was to determine how linkage and metabolic flux epistasis jointly affect the loss of genetic variation in populations due to a small number of parents.

Materials and methods

Simulation of test populations

Two inbreds were each assigned one of two types of alleles at randomly distributed loci across ten chromosomes. The length of each chromosome was based on the maize linkage map developed by Senior et al. (1996). The two inbreds complemented each other in that the first inbred had the (+) allele at the odd-numbered loci whereas the second inbred had the (+) allele at the even numbered loci. The two inbreds were crossed to form an F_2 (base) population. The first eight F_2 individuals were drawn as a sample, N of which were to be intermated to form progeny populations with $N = 1$, 2, 4, and 8 parents. Specifically, the alleles from all loci in each parent were combined to form a large number (20,000) of gametes, which in turn were united with gametes from other parents to form the progeny population.

Genetic models

Four genetic models were investigated: (1) additive, (2) additive with linkage, (3) epistatic, and (4) epistatic with linkage. Metabolic pathways consisting of $L = 10$, 50, and 100 enzymes were simulated. The genotypic values of individuals were determined based on additive and epistatic gene actions. In a simple linear biochemical pathway, where L enzymes act one after another on a substrate to produce a final product, the enzyme activity (E_i) at locus i (i.e., the locus value) was determined by: m_i, the average enzyme activity {i.e., $\frac{1}{2}[E_{i(+)} + E_{i(-)}]$}, and a_i, the average effect of substituting the (–) allele by the (+) allele {i.e., $\frac{1}{2}[E_{i(+)} - E_{i(-)}]$}, where the (+) and (–) subscripts refer to the corresponding alleles. The enzyme activity of the heterozygote was assumed equal to the average of the enzyme activities of the two homozygotes (i.e., no dominance). The a_i was calculated as $m_i c_i \sqrt{2}$, c_i being the coefficient of variation of E_i. The average enzyme activity, m_i, corresponded to the variation among enzymes in a pathway whereas the average effect of allele substitution, a_i, corresponded to the variation among individuals in a population. Finally, the genotypic value of an individual was calculated as $E_\bullet = \sum_i^L E_i$ when gene action was additive, or $E_\bullet = 1/\sum_i^L (1/E_i)$ when gene action was epistatic due to metabolic flux (Kacser and Burns 1981).

Given that the true distributions of enzyme effects were unknown, m_i followed four different probability distributions: constant ($m_i = 10$), uniform in the interval [0, 30]; reverse exponential, $\{f(x) = (1/\sigma)\ \exp[(x - \theta)/\sigma]/[1 - \exp(-30/\sigma)]\}$, where $\theta = 30$ and $\sigma = 2.5$; and normal with $\mu = 10$ and $\sigma = 2.5$. The probability distributions used for c_i were: constant ($c_i = 0.2$); normal with $\mu = 0.35$ and $\sigma = 0.08$; and uniform in the interval [0, 0.7]. These parameters were adapted from Bost et al. (1999). The 12 distribution combinations between m_i and c_i, coupled with three levels of L and with four different genetic models, led to a total of 144 simulation experiments.

For the two genetic models without linkage, the recombination rate between adjacent loci was equal to 50%. For the two genetic models with linkage, the recombination rate was calculated using the Kosambi function for map distance. Random gametes from parents were combined to reconstitute a progeny population of size 10,000, for which genetic variance was calculated from the known genotypic values. Under the additive model, the total genetic variance expected in the progeny population (V_N) is a function of the amount of total genetic variance (V_B) and inbreeding (F) in the base population, such that $V_N = (1 - F)V_B$. In this study, the number of parents, N, corresponded to the sample size in random drift, such that $F = 1/2N$ (Robertson and Hill 1983).

Data analysis

The process of generating the genome of the two parental inbreds and formation of the base and progeny populations

was replicated 1,000 times. The V_N/V_B expected under the additive model (referred to as expected V_N/V_B in this paper) was 0.5 for $N = 1$, 0.75 for $N = 2$, 0.875 for $N = 4$, and 0.9375 for $N = 8$. To compare the levels of genetic variance among the genetic models, the V_N/V_B ratio was calculated in each replication and the mean value of V_N/V_B was calculated across all 1,000 replications. In addition, the difference between the V_N/V_B in each replication and the expected V_N/V_B was taken for all simulations, after which the 75th ($\Delta_{75\%}$) and the 95th ($\Delta_{95\%}$) percentiles were recorded as measures of dispersion of V_N/V_B.

Results

Number of parents, epistasis, and linkage

The mean V_N/V_B in the progeny populations decreased as the number of parents (N) decreased, as was expected under the additive model (Fig. 1). This decrease in mean V_N/V_B was observed across all genetic models, distributions of gene effects, and numbers of loci. Epistasis, especially with fewer loci and parents, sometimes caused large increases in the observed V_N/V_B (i.e., in an individual population) over the expected V_N/V_B (Fig. 2). The near-maximum increase of V_N/V_B over the expected V_N/V_B was represented by $\Delta_{95\%}$ (Fig. 2), and $\Delta_{95\%}$ tended to be higher with fewer parents (Figs. 3, 4). The $\Delta_{75\%}$ values also tended to be higher with smaller N, although the relationship between $\Delta_{75\%}$ and N was less consistent than the relationship between $\Delta_{95\%}$ and N (Fig. 5).

The mean V_N/V_B observed for the additive and additive-with-linkage models were similar, and the mean V_N/V_B observed for the epistatic and epistatic-with-linkage models were likewise similar (Fig. 1). In contrast, the mean V_N/V_B was consistently lower in the epistatic and epistatic-with-linkage models than in the additive and additive-with-linkage models. This effect of epistasis on the mean V_N/V_B was observed across all distributions of gene effects and numbers of loci, although this result was most evident when $L = 100$ loci controlled the trait and the coefficient of variation (c_i) of enzyme activity followed a uniform distribution.

Both epistasis and linkage tended to increase $\Delta_{95\%}$ and $\Delta_{75\%}$, though the simultaneous occurrence of epistasis and linkage did not seem to lead to any further increase in $\Delta_{95\%}$ and $\Delta_{75\%}$. In some cases, $\Delta_{95\%}$ was highest with linkage alone, e.g., when the number of linked loci is at maximum ($L = 100$) and average enzyme activity (m_i) followed an exponential distribution (Fig. 3). In other cases, $\Delta_{95\%}$ was highest when both linkage and epistasis were present, e.g., when $L = 10$ loci controlled the trait, m_i followed an exponential distribution, and c_i was constant (Fig. 3).

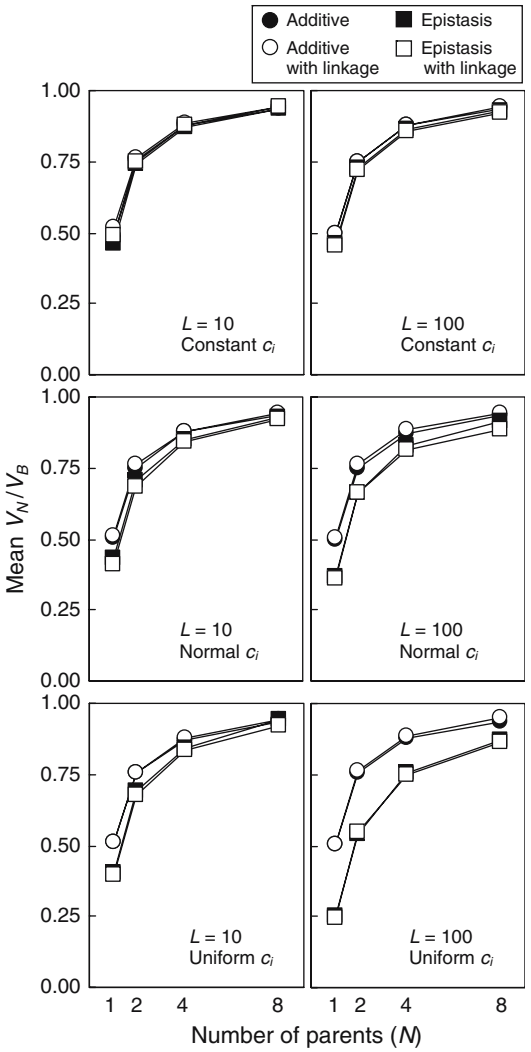

Fig. 1 Mean V_N/V_B from three distributions of coefficient of variation of enzyme activity (c_i) when average enzyme activity (m_i) was exponentially distributed for $L = 10$ and 100 enzymes

Linkage had a larger effect than epistasis on $\Delta_{75\%}$. Specifically, the epistatic model sometimes led to $\Delta_{75\%}$ values equal to or less than that of the additive model (Fig. 5).

Number of loci, average enzyme activity, and variation in enzyme activity

For the epistatic and epistasis-with-linkage models, the decrease in the mean V_N/V_B compared with the expected V_N/V_B tended to be greater as more loci controlled the trait (Fig. 1). The levels of $\Delta_{95\%}$ were greatly increased by epistasis when there were only $L = 10$ loci, but this effect of epistasis on $\Delta_{95\%}$ was reduced as more loci controlled the trait (Figs. 3, 4). Linkage, on the other hand, had a more sustained effect on maintaining $\Delta_{95\%}$ across different numbers of loci. This difference between the effect of

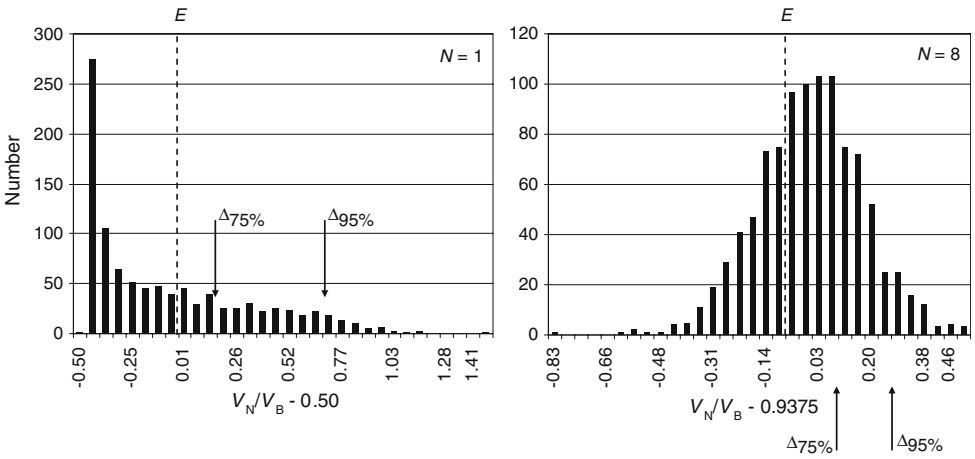

Fig. 2 Frequency distribution of the difference between observed V_N/V_B and expected V_N/V_B, showing the 75th and 95th percentiles. Results are for an epistasis-with-linkage model with 10 loci, exponentially distributed average enzyme activity (m_i), and uniformly distributed coefficient of variation of enzyme activity (c_i). Expected V_N/V_B is 0.50 at $N = 1$ and 0.9375 at $N = 8$. E indicates the expected V_N/V_B are equal

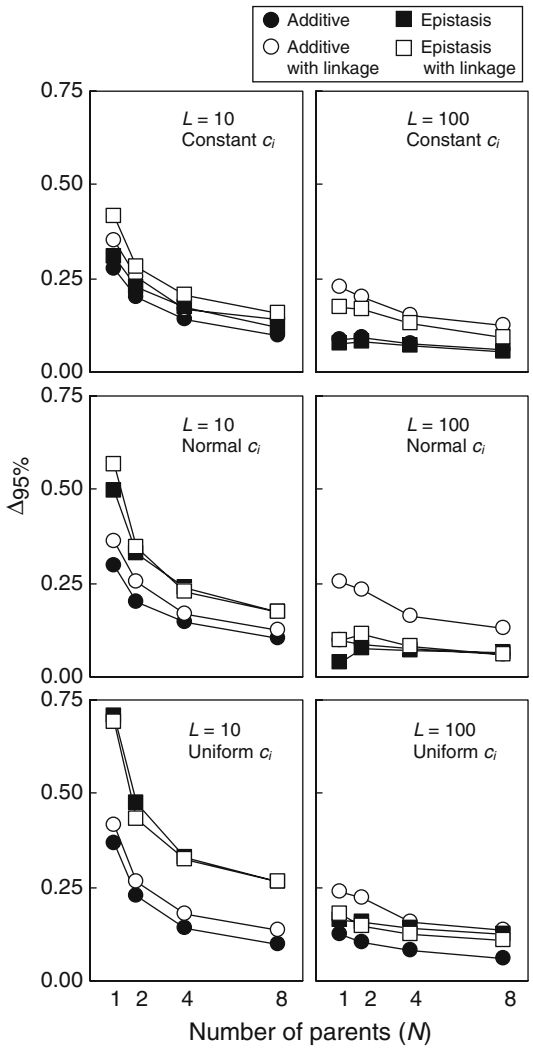

Fig. 3 The 95th percentile difference ($\Delta_{95\%}$) between observed V_N/V_B and expected V_N/V_B from three distributions of coefficient of variation of enzyme activity (c_i) when average enzyme activity (m_i) was exponentially distributed for $L = 10$ and 100 enzymes

epistasis and the effect of linkage across different numbers of loci became more evident with $\Delta_{75\%}$. When the number of loci increased from $L = 10$ to $L = 100$ and the number of parents decreased, $\Delta_{75\%}$ was often less than zero in both the epistatic and epistasis-with-linkage models (Fig. 5). In contrast, $\Delta_{75\%}$ was always greater than zero in the additive-with-linkage model, and was also higher than in the additive model at $L = 50$ and 100.

The different distribution types of average enzyme activity (m_i) had little effect on the relationship between N and V_N/V_B. The observed trends in the mean V_N/V_B for exponential m_i (Fig. 1) were very similar to those for the other distributions of m_i (results not shown). In contrast, the different distributions of c_i affected V_N/V_B. For the epistatic and epistasis-with-linkage models, the difference between the mean V_N/V_B and the expected V_N/V_B was largest when c_i was uniformly distributed (Fig. 1). A normally distributed c_i produced a less severe effect. On the other hand, when c_i was constant, the mean V_N/V_B for the additive-with-linkage, epistatic, and epistatic-with-linkage models was almost similar to the mean V_N/V_B for the additive model.

The $\Delta_{95\%}$ across different values of N and L were largely similar among the constant, exponential, and normal m_i: the epistatic and epistasis-with-linkage models led to the highest $\Delta_{95\%}$ only at $L = 10$ whereas the additive-with-linkage model led to the highest $\Delta_{95\%}$ as L increased to 100 (Fig. 3). In contrast, under a uniformly distributed m_i, the epistasis and epistasis-with-linkage models consistently led to the highest $\Delta_{95\%}$ for all levels of N and L (Fig. 4). The $\Delta_{75\%}$ across different values of N and L was also similar among the constant, exponential, and normal m_i, except that the epistatic and epistasis-with-linkage models had some negative values of $\Delta_{75\%}$ (Fig. 5). When m_i was uniformly distributed, however, the two models with epistasis did not have any $\Delta_{75\%}$ values less than zero (results not shown).

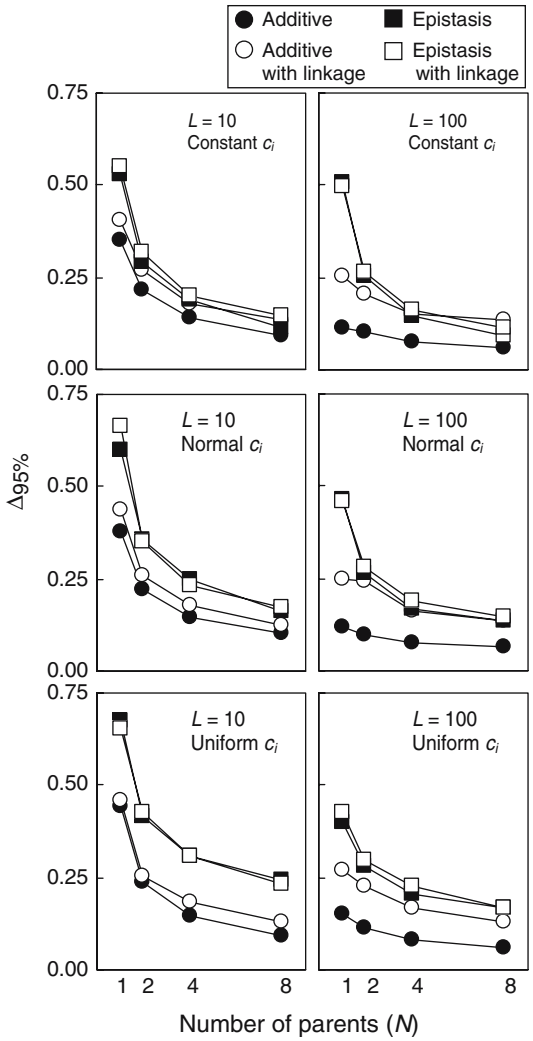

Fig. 4 The 95th percentile difference ($\Delta_{95\%}$) between observed V_N/V_B and expected V_N/V_B from three distributions of coefficient of variation of enzyme activity (c_i) when average enzyme activity (m_i) was uniformly distributed for L = 10 and 100 enzymes

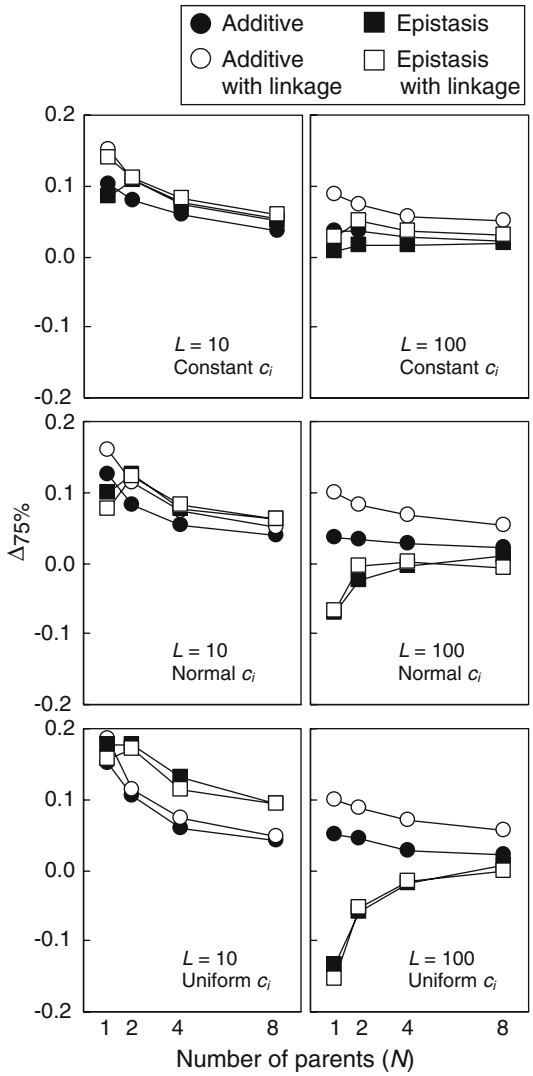

Fig. 5 The 75th percentile difference ($\Delta_{75\%}$) between observed V_N/V_B and expected V_N/V_B from three distributions of coefficient of variation of enzyme activity (c_i) when average enzyme activity (m_i) was exponentially distributed for L = 10 and 100 enzymes

Discussion

This study is relevant to breeding for hybrid crops and has four features that distinguish it from previous theoretical or simulation studies on the maintenance of genetic variance by epistasis and linkage in natural populations. First, we considered testcross genetic variance rather than genetic variance in the population per se. Testcross means, which are the primary bases for selection in hybrid crops, are unaffected by the level of dominance at the underlying loci (Bernardo 2002, p 79). Our assumption of no dominance at the underlying loci is therefore consistent with the behavior of testcross means. Second, we assumed intermediate allele frequencies (i.e., 0.50) in the base (F_2) population. Such intermediate allele frequencies are typical of plant-breeding populations but are inconsistent with extreme allele frequencies that have been found as a factor contributing to the maintenance of genetic variance by epistasis in natural populations (Lopez-Fanjul et al. 2002). Third, we simulated strong linkage disequilibrium through the typical plant-breeding practice of mating two inbreds to form an F_2 population. In contrast, previous studies of linkage disequilibrium and the maintenance of genetic variance have focused on drift-induced linkage disequilibrium (Barton and Turelli 2004), which is more transient than the linkage disequilibrium due to the physical location of genes on the same chromosome. Fourth, we investigated not only the mean V_N/V_B ratios but also the variability of this ratio, which has not been the subject of previous studies.

Metabolic control theory (Kacser and Burns 1981) has been used as a model to study multilocus epistasis for

quantitative traits (Bost et al. 1999; Keightley 1989, 1996). While arguments have been presented against metabolic control theory for a large number of loci (Turelli and Barton 2006), metabolic control theory describes a biologically meaningful way by which different genes function in concert to produce a trait: a gene codes for an enzyme that acts on a substrate which is itself a by-product of another enzyme coded by a different gene. Empirical data on several well-known biochemical pathways in different species (Groen et al. 1986; Albe and Wright 1992; Hill et al. 1993) have been found consistent with metabolic control theory (Bost et al. 1999). Furthermore, a feature of metabolic control theory is that despite the highly interactive nature of the underlying loci, additive genetic variance accounts for most of the V_B unless there are many loci with large differences in enzyme activity (Keightley 1989). Metabolic control theory is therefore consistent with the empirical finding that additive genetic variance accounts for most of the genetic variation for important quantitative traits in different crop species (Moll and Stuber 1974). In this study we simulated a linear metabolic pathway only, although the general properties for a linear pathway can be extended to branched pathways (Kacser and Burns 1981).

The loss of genetic variance under inbreeding, as observed in this study, is a general rule in population genetics (Crow and Kimura 1970). Even for quantitative traits, where physiological epistasis is common because the underlying loci conceivably interact with each other, a net loss in genetic variance is still expected because the effects of quantitative trait loci remain statistically additive by nature (Cheverud and Routman 1995; Crow 1999). Indeed, even with physiological epistasis under metabolic control theory, additive variance comprises more than 95% of the total genetic variance (Bost et al. 1999). This study revealed two main results pertaining to multilocus epistasis, linkage, and genetic variance in populations formed from only a few parents. The first main result was that the mean loss in genetic variance under metabolic flux epistasis was larger than what was expected under the additive genetic model. A similar observation was made for grain yield at $N = 2$ and ear height at $N = 4$ in a previous empirical study in maize populations (Tabanao and Bernardo 2005). Also, in maize populations representing two different inbreeding generations, a larger than expected decrease in genetic variance was found for five traits at an inbreeding coefficient of 0.18 and for three traits at an inbreeding coefficient of 0.55 (Yu and Bernardo 2004a).

The second main result was that with metabolic flux epistasis and linkage, the change in genetic variance becomes less predictable than in an additive model. The $\Delta_{95\%}$ corresponded to the progeny population that exhibited the 950th largest excess in genetic variance relative to what would be expected from an additive model. The increase in $\Delta_{95\%}$ as N decreased was consistent with what happens when a population is divided into smaller subpopulations (Falconer and Mackay 1996, p 51). Specifically, the variance of allele frequencies among different subpopulations increases as N becomes smaller. This larger variance of allele frequencies among replicate subpopulations of size N results in a larger variance in V_N (i.e., the variance of the genetic variance), regardless of whether or not epistasis and linkage are present. However, the larger $\Delta_{95\%}$ values in the models with epistasis and linkage indicated that these two factors lead to a higher variability in V_N/V_B, which compensates for the lower mean V_N/V_B and leads to a higher $\Delta_{95\%}$. Uniform distributions of m_i and c_i particularly tended to favor this result. Similar excesses in genetic variance, putatively ascribed to epistasis, have been observed in experimental subpopulations of *Mus musculus* (Cheverud et al. 1999), *Tribolium castaneum*, (Wade et al. 1996), and *Drosophila melanogaster* (Bryant et al. 1986; Whitlock 1995). As previously mentioned, theoretical studies have also shown that epistasis may lead to increased genetic variance during bottlenecks (Goodnight 1988, 1995, 2004; Cheverud and Routman 1996; Naciri-Graven and Goudet 2003; Barton and Turelli 2004; Lopez-Fanjul et al. 2004, 2006).

An intrinsic property of the metabolic flux model is that a change in catalytic activity for one enzyme affects the output of the whole system. Under metabolic control, epistasis is greatest in pathways with fewer enzymes because the individual contribution of each enzyme to the net change in the flux would be greater than it would be when more enzymes are involved (Keightley 1989). Most of the previous studies on the role of epistasis in maintaining genetic variance have considered interactions between only two loci at a time (Goodnight 1988, 1995, 2004; Cheverud and Routman 1996; Lopez-Fanjul et al. 2004). Based on our results we speculate whether such maintenance of genetic variance is greater under the less realistic situation of epistasis between only $L = 2$ loci, than under the more realistic situation of multilocus epistasis due to metabolic control. Consider metabolic flux epistasis between only two loci, A and B. At the A locus, the enzyme activities are 5 for AA, 3 for Aa, and 1 for aa. At the B locus, the enzyme activities are 3 for BB, 2 for Bb, and 1 for bb. Under metabolic control theory, the genetic variance across both loci is $V_B = 0.1468$. But if a random allele at either locus (A, a, B, or b) becomes fixed due to sampling, the average genetic variance in the resulting population increases to $V_N = 0.1503$. The resulting V_N/V_B ratio of 1.02, being greater than 1.0, then indicates that the mean V_N/V_B due to metabolic flux epistasis at two loci is greater than the expected V_N/V_B under an additive model regardless of N. As we found in this study, a mean V_N/V_B greater than 1.0 does not occur, however, when more loci control the trait ($L = 10$, 50, and 100).

The lack of influence of linkage on the mean V_N/V_B was likely due to the two parental inbreds (of the F_2 population) complementing each other. Depending on the gametic phase, linkage among non-epistatic loci may increase (coupling phase) or decrease (repulsion phase) genetic variance (Lynch and Walsh 1998, pp 100–102). In this study, linkage phases were generated at random, and given that the two inbred parents had equal numbers of (+) and (–) alleles, equal numbers of repulsion and coupling linkages were expected. These equal proportions of repulsion and coupling linkages would then, due to cancelling of effects, lead to a mean V_N/V_B in a model that involved linkage to be close to the mean V_N/V_B of a corresponding model that involved no linkage. On the other hand, the proportions of repulsion and coupling linkages may, due to sampling, not be equal in a random population created by crossing N parents. This sampling variability contributes to variation in V_N/V_B among replicate populations and was reflected in the $\Delta_{95\%}$ and $\Delta_{75\%}$ values for the different genetic models in this study.

This study focused on the rate of increase (or decrease) of the progeny population variance relative to the base population variance (V_N/V_B). The comparisons made here by no means imply that one genetic model led to a larger genetic variance than another. They simply meant that one genetic model had progeny populations that had higher (or lower) genetic variance than their parent population in comparison to the same ratio in another model. Nonetheless, this study has showed that epistasis, linkage, or both epistasis and linkage may lead to an excess V_N/V_B in a progeny population.

Advanced cycle breeding refers to the common practice in which pairs of elite inbreds are crossed to form base populations from which new inbreds are developed (Allard 1960, p 115; Bernardo 2002, p 70). In a previous study we (Yu and Bernardo 2004b) investigated the maintenance of genetic variance due to metabolic flux epistasis and linkage in the context of advanced cycle breeding, wherein the crossing of pairs of inbreds is equivalent to $N = 1$ in the present study. In this previous study we found that selection of the best-performing inbreds slows the decrease of genetic variance during advanced cycle breeding. While the present study did not consider selection, it considered other numbers of parents ($N = 1$, 2, 4, and 8) and investigated the separate effects of linkage and epistasis.

From a practical standpoint, this study shows that epistasis and linkage are possible factors in the success of advanced cycle breeding, wherein N is very small yet much genetic variance is expressed as evidenced by large gains in selection. The higher $\Delta_{95\%}$ and $\Delta_{75\%}$ with epistasis and linkage than with additive gene effects indicated that in many (i.e., top 25%) cases, epistasis and linkage may contribute to maintaining genetic variance in populations with few parents. This is indeed possible given that hundreds, if not thousands, of crosses are made in inbred development programs each year. Even when breeders do not maximize the number of parents crossed to form different breeding populations, it is perhaps the sheer volume of biparental combinations from breeding program to breeding program and from year to year that allows the occurrence of breeding populations with a larger-than-expected genetic variance. Thus, a combination of genetic factors (i.e., epistasis and linkage) and breeding practices (i.e., large numbers of populations) probably contributes to sustained genetic gains despite a narrow genetic base in many crop species.

References

Albe KR, Wright BE (1992) Systems analysis of the tricarboxylic acid cycle in *Dictyostelium discoideum*. II. Control analysis. J Biol Chem 267:3106–3114

Allard RW (1960) Principles of plant breeding. Wiley, New York

Barton NH, Turelli M (2004) Effects of genetic drift on variance components under a general model of epistasis. Evolution 58:2111–2132

Bernardo R (2002) Breeding for quantitative traits in plants. Stemma Press, Woodbury

Bost B, Dillman C, de Vienne D (1999) Fluxes and metabolic pools as model traits for quantitative genetics. I. The L-shaped distribution of gene effects. Genetics 153:2001–2012

Bryant EH, McCommas SA, Combs LM (1986) The effect of an experimental bottleneck upon quantitative genetic variation in the housefly. Genetics 114:1191–1211

Cheverud JM, Routman EJ (1995) Epistasis and its contribution to genetic variance components. Genetics 139:1455–1461

Cheverud JM, Routman EJ (1996) Epistasis as a source of increased additive genetic variance at population bottlenecks. Evolution 50:1042–1051

Cheverud JM, Vaughn TT, Pletscher LS, King-Ellison K, Bailiff J, Adams E, Erickson C, Bonislawski A (1999) Epistasis and the evolution of additive genetic variance in populations that pass through a bottleneck. Evolution 53:1009–1018

Crow JF (1999) A symposium overview. In: JG Coors S Pandey (eds) Genetics and exploitation of heterosis in crops. Am Soc Agron, Crop Sci Soc Am, Soil Sci Soc Am, Madison, pp 521–524

Crow JF, Kimura M (1970) An introduction to population genetics theory. Harper & Row, New York

Dudley JW (1993) Molecular markers in plant improvement: manipulation of genes affecting quantitative traits. Crop Sci 33:660–668

Falconer DS, Mackay TFC (1996) Introduction to quantitative genetics. 4th edn. Longman, Harlow

Goodnight CJ (1988) Epistasis and the effect of founder events on the additive genetic variance. Evolution 42:441–454

Goodnight CJ (1995) Epistasis and the increase in additive genetic variance: implications for phase I of Wright's shifting-balance process. Evolution 49:502–511

Goodnight CJ (2004) Gene interaction and selection. Plant Breed Rev 24(1):269–291

Groen AK, van Roermund CW, Vervoorn RC, Tager JM. (1986) Control of gluconeogenesis in rat liver cells. Flux control coefficients of the enzymes in the gluconeogenic pathway in the absence and presence of glucagon. Biochem J 237:379–389

Hallauer AR (1990) Methods used in developing maize inbreds. Maydica 35:1–16

Hill SA, Bryce JH, Leaver CJ (1993) Control of succinate oxidation by cucumber (*Cucumis sativus* L). cotyledon mitochondria. The role of adenine-nucleotide translocator and extra-mitochondrial reactions. Planta 190:51–57

Kacser H, Burns JA (1981) The molecular basis of dominance. Genetics 97:639–666

Kearsey MJ, Farquhar AGL (1998) QTL analysis in plants; where are we now? Heredity 80:137–142

Keightley PD (1989) Models of quantitative variation of flux in metabolic pathways. Genetics 121:869–876

Keightley PD (1996) Metabolic models of selection response. J Theor Biol 182:311–316

Lopez-Fanjul C, Fernandez A, Toro MA (2002) The effect of epistasis on the excess of the additive and nonadditive variances after population bottlenecks. Evolution 56:865–876

Lopez-Fanjul C, Fernandez A, Toro MA (2004) Epistasis and the temporal change in the additive variance-covariance matrix induced by drift. Evolution 58:1655–1663

Lopez-Fanjul C, Fernandez A, Toro MA (2006) The effect of genetic drift on the variance/covariance components by multilocus additive × additive epistatic systems. J Theor Biol 239:161–171

Lynch M, Walsh B (1998) Genetics and analysis of quantitative traits. Sinauer Associates, Sunderland

Moll R, Stuber CW (1974) Quantitative genetics—empirical results relevant to plant breeding. Adv Agron 26:277–313

Naciri-Graven Y, Goudet J (2003) The additive variance after bottlenecks is affected by the number of loci involved in epistatic interactions. Evolution 57:706–716

Robertson A, Hill WG (1983) Population and quantitative genetics of many linked loci in finite populations. Proc R Soc Lond B 219:253–264

Senior ML, Chin ECL, Lee M, Smith JSC, Stuber CW (1996) Simple sequence repeat markers developed from maize sequence found in the GENBANK database: map construction. Crop Sci 36:1676–1683

Tabanao DA, Bernardo R (2005) Genetic variation in maize breeding populations with different numbers of parents. Crop Sci 45:2301–2306

Turelli M, Barton NH (2006) Will multilocus epistasis and population bottlenecks increase additive genetic variance? Evolution 60:1763–1776

Wade MJ, Schuster SM, Stevens L (1996) Inbreeding: its effect on response to selection for pupal weight and the heritable variance in fitness in the flour beetle, *Tribolium castaneum*. Evolution 50:723–733

Whitlock MC (1995) Two-locus drift with sex chromosomes: the partitioning and conversion of variance in subdivided populations. Theor Popul Biol 48:44–64

Wright S (1951) The genetical structure of populations. Ann Eugen 15:323–354

Yu J, Bernardo R (2004a) Changes in genetic variance during advanced cycle breeding in maize. Crop Sci 44:405–410

Yu J, Bernardo R (2004b) Metabolic control analysis as a mechanism that conserves genetic variance during advanced cycle breeding. Theor Appl Genet 108:1614–1619