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Metabolic control analysis as a mechanism that conserves genetic variance during advanced cycle breeding

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Abstract The recycling of elite inbreds (i.e., advanced cycle breeding) has led to significant genetic gains but also to a narrow gene pool in plant breeding programs. Sustained yield improvements in many crops have suggested that genetic variance is not depleted at a rate predicted by an additive genetic model. Unlike the additive model in classical quantitative genetic theory, metabolic control analysis relates the variation in a biochemical process with the genetic variation in a quantitative trait. Our objective was to determine whether metabolic control analysis is a mechanism that slows the decrease in genetic variance during advanced cycle breeding. Three cycles of advanced cycle breeding were simulated with 10, 50, or 100 quantitative trait loci (QTL) controlling a trait. In metabolic control analysis, these QTL coded for enzymes involved in a linear metabolic pathway that converted a substrate into a product. In the absence of selection, both the additive model and the metabolic control analysis model led to about a 50% reduction in genetic variance from cycle to cycle. With selection, the additive model led to a 50–58% reduction in genetic variance, but the metabolic control analysis model generally led to only a 12–54% reduction. We suggest selection in a metabolic control analysis model as a mechanism that slows the decrease in genetic variance during advanced cycle breeding. This conservation of genetic variance would allow breeders to achieve genetic gains for a longer period than expected under the additive model.

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Introduction

In modern plant breeding, pairs of elite inbreds are crossed to form base populations from which new inbreds are developed (Allard 1960, p. 115; Bernardo 2002, p. 70). This inbred recycling process, which is called advanced cycle breeding, has been extensively used to develop inbreds in major crops and has led to significant genetic gains (Poehlman and Sleper 1995, p. 4). Advanced cycle breeding, however, systematically reduces genetic variation (Tanksley and McCouch 1997).

Crossing two inbreds to form a new breeding population in each cycle creates a bottleneck, which is defined as a severe reduction in the number of parents that are mated to form the next generation. Inbreeding increases with each successive bottleneck, and the classical additive model in quantitative genetics predicts that genetic variance during advanced cycle breeding will decrease as a linear function of inbreeding (Wright 1951). Genetic gains, however, are still being achieved, although plant breeding programs often have a core germplasm pool with low genetic variation expected under the additive model (Peel and Rasmusson 2000). In a recent study (Yu and Bernardo 2004), we found no significant changes in genetic variance for maize (*Zea mays* L.) grain yield among three breeding populations, which was contrary to the predicted decrease in genetic variance for an additive model.

Conversion of additive-by-additive epistatic variance into additive variance has been proposed as a mechanism for maintaining additive variance during bottlenecks (Cockerham and Tachida 1988; Goodnight 1988; Whitlock et al. 1993; Cheverud and Routman 1996). Classical two-locus epistatic models, such as duplicate dominant epistasis or complementary gene action, have been shown to maintain genetic variance after bottlenecks (Goodnight 1988; Whitlock et al. 1993; Bernardo 2002, p. 115). Two-locus epistatic models, however, do not adequately describe gene interactions that occur across many loci.

Metabolic control analysis provides a framework under which the variation in a biochemical process

generates the genetic variation in a quantitative trait. The flux (i.e., the output of a system) of a metabolic pathway with an array of enzymes can be considered as the genotypic value for a quantitative trait controlled by a number of loci (Kacser and Burns 1981; Bost et al. 1999). In metabolic control analysis, the control of the flux is shared among all the enzymes, and the effect of each enzyme is dependent upon the other enzymes in the metabolic pathway (Kacser and Burns 1973). Experimental data have demonstrated a good fit of metabolic control analysis to in vivo relations between enzyme activity and flux (reviewed by Kacser and Burns 1981; Groen et al. 1986; Albe and Wright 1992; Hill et al. 1993). Metabolic control analysis is therefore a biologically meaningful mechanism that can explain epistasis for quantitative traits (Kacser and Burns 1981; Keightley 1996). Metabolic control analysis allowed us to study the genetic variance generated from a large number of loci involved in a metabolic pathway.

Advanced cycle breeding can be viewed as creating and selecting for new combinations of enzymes that give higher flux values in a metabolic pathway. The maintenance of genetic variance by metabolic control analysis has not been studied in the context of plant breeding. Our objective was to determine whether metabolic control analysis is a mechanism that slows the decrease in genetic variance during advanced cycle breeding.

Materials and methods

Advanced cycle breeding

We wrote a computer program in C^{++} to simulate three cycles (cycle 0, 1, and 2) of advanced cycle breeding. Two initial inbreds (A and B in cycle 0) with different alleles at each locus were generated. At a given locus, either inbred A or B had the +/+ genotype, and the other inbred had the −/− genotype. These two inbreds were used to generate two new inbreds (C and D in cycle 1), and in turn these two new inbreds were used to generate another pair of inbreds (E and F in cycle 2). This simulation scheme depicted the intensive inbred recycling practices used in many plant breeding programs (Peel and Rasmusson 2000; Yu and Bernardo 2004). Simulation was done for the above process without constraints on genotypic values of the inbreds (i.e., without selection), and with constraints (i.e., with selection). With selection, the inbreds in a cycle (i.e., cycle 1 or 2) had genotypic values greater than or equal to the average of two parental inbreds (i.e., the mid-parent value of two inbreds in the immediate previous cycle), but had at least 20% of quantitative trait loci (QTL) different from each other. These criteria were chosen to simulate selection based on both mean performance and parental genetic distance applied by breeders in real situations. Selection based on genotypic rather than phenotypic values guaranteed genetic gain, so that the results were not confounded with any ineffectiveness in selection among parents.

The ten chromosomes corresponded to the chromosome sizes from a published maize linkage map (Senior et al. 1996). A total of n=10, 50, or 100 segregating QTL were randomly distributed among the ten chromosomes. Meiosis was simulated, and recombination frequencies were calculated from the map distances among loci within a chromosome using the Kosambi mapping function. Recombinant inbreds were generated with modified recombination frequencies (Wang and Bernardo 2000).

For measuring the genetic variance in each cycle, a population with 1,000 recombinant inbreds was generated for each within-cycle cross (i.e., A×B, C×D, and E×F). The genetic variance in each cycle was calculated based on the genotypic values of the 1,000 recombinant inbreds. Phenotypic values were not generated, as the objective was to directly assess any changes in genetic variance. The ratio of genetic variance (V_{t+1}/V_t) was calculated between cycle 1 and cycle 0, and between cycle 2 and cycle 1. The simulation experiment was repeated 1,000 times. The mean, median, and 90% range of V_{t+1}/V_t across 1,000 repetitions were calculated. The percentage of the cases in which V_{t+1}/V_t was greater than 1.0 was recorded.

Additive model

An additive genetic model, with linkage but no epistasis, was first considered. This simple model provided a reference for comparing the results from metabolic control analysis. The inbreeding coefficient was 0 in cycle 0, 0.5 in cycle 1, and 0.75 in cycle 2. The expected genetic variance was $V_{new} = (1-F_{new})\ V_{initial}$, where V_{new} was the expected genetic variance in the bottlenecked population (i.e., C×D and E×F), $V_{initial}$ was the genetic variance in the initial population (i.e., A×B), and F_{new} was the inbreeding coefficient of the bottlenecked population with reference to the initial population (Wright 1951).

The additive model in our simulation involved only loci without dominance or epistasis. The genotypic effect at locus i (a_i) was half of the difference between the genotypic values of the +/+ and −/−. An exponential distribution has been proposed for QTL effects (Mackay 2001), as experimental (Kearsey and Farquhar 1998; Bernardo 2002, p. 309) and theoretical (Otto and Jones 2000) studies have supported a model of a few genes with large effects and many genes with small effects. Accordingly, we used a truncated exponential distribution for a_i with a probability density function of $f(x)=(1/\sigma)\ \exp(-x/\sigma)/[1-\exp(-30/\sigma)]$, where σ=2.5, and $0<x<30$. In the additive model, the overall genotypic value of a recombinant inbred was equal to the sum of its genotypic values across loci.

Metabolic control analysis model

We considered a linear metabolic pathway in which N enzymes (n=10, 50, 100) were involved in a process of converting a substrate (S_0) into a product (P). Enzyme 1 converted S_0 into S_1, enzyme 2 converted S_1 into S_2, and enzyme N converted S_{N-1} into P. The flux of this linear metabolic pathway was considered as a quantitative trait controlled by N QTL in a linear pattern (Kacser and Burns 1981). The enzyme activities varied across loci and within loci. The distribution of average enzymatic value at each locus (m_i) described the variation of the enzyme activity across the metabolic pathway. The coefficient of variation (c_i) described the variation of the enzyme activity within each locus. We considered the distribution of c_i instead of half of the difference between two enzyme activities at a locus (a_i) because of the constraint that $a_i<m_i$, i.e., enzyme activities, measured as $m+a$ and $m-a$, should be positive (Bost et al. 1999). The values of a_i were obtained from the equation $a_i=m_i c_i\sqrt{2}$. The enzyme activity (E_{ij}) at locus i was $E_{i1}=m_i+a_i$ for the +/+ genotype, where j=1; and $E_{i2}=m_i-a_i$ for the −/− genotype, where j=2. The relative flux (J^k) of the pathway for recombinant inbred k corresponded to the genotypic value. At steady state given constant external conditions, the relative flux (Kacser and Burns 1981) was

$$J^k = \frac{1}{\sum_{i=1}^{N} 1/E_{ij}^k} \quad (1)$$

Multiple distributions were simulated for m_i and c_i to capture the wide variability in enzyme activity for different metabolic pathways. The four distributions for m_i were: (1) constant (m_i=10 for each enzyme), (2) reverse truncated exponential (θ=30, σ=2.5) with a probability density function of $f(x)=(1/\sigma)\ \exp[(x-\theta)/\sigma]/$

[1−exp(−30/σ)], (3) normal (μ=10, σ=2.5), and (4) uniform [in the range (0, 30)]. The three distributions for c_i were: (1) constant (c_i=0.2), (2) normal (μ=0.35, σ=0.08), and (3) uniform [in the range of (0, 0.7)]. The distributions of m_i and c_i were adapted from Bost et al. (1999).

Results

Additive model

Relative to the original genetic variance in cycle 0 (100%), the genetic variance was expected to be reduced to 50% in cycle 1 and to 25% in cycle 2 when selection was absent. In our simulation, the ratio of genetic variance between cycles (V_{t+1}/V_t) had an average of about 50% when selection was absent (Table 1). This result was in agreement with what was expected under the additive model (Wright 1951). Selection, however, led to less than 50% (42–50%) genetic variance maintained from cycle to cycle and this effect was most prominent when ten QTL controlled the trait.

The V_{t+1}/V_t values had a wide range regardless of the absence or presence of selection (Table 1). The 90% range of V_{t+1}/V_t generally did not include 1.0, which indicated that observing an increase in genetic variance after a bottleneck would be rare. The 90% range of V_{t+1}/V_t became narrower as the number of QTL increased. With 50 or 100 QTL, no case was found in which two consecutive increases in genetic variance (i.e., V_{t+1}/V_t greater than 1.0 for successive cycles) occurred in the same repeat of the simulation experiment.

Metabolic control analysis model

When selection was absent, the decrease in genetic variance was approximately 50% regardless of the distribution of the enzyme activity among loci (i.e., m_i) and within loci (i.e., c_i) (Table 2). The 90% ranges of V_{t+1}/V_t, however, were much wider than those for the additive model. Compared with the additive model, more cases were observed with an increase in genetic variance after a bottleneck (i.e., V_{t+1}/V_t greater than 1.0) in the metabolic control analysis model.

For the distributions of m_i other than uniform, selection generally led to more than 50% (46–88%) genetic variance maintained after each bottleneck (Table 3). This was different from the results for the additive model. This maintenance of genetic variance after a bottleneck was more prominent when the trait was controlled by 10 or 50 QTL rather than by 100 QTL. The 90% range for V_{t+1}/V_t usually included 1.0 when ten QTL controlled the trait, indicating that observing an increase in genetic variance after a bottleneck would not be rare. Except for the uniform distributions of m_i or c_i, the distributions of V_{t+1}/V_t were approximately symmetric as shown by the similarity between the mean and median of V_{t+1}/V_t. This approximately symmetric distribution for V_{t+1}/V_t was true also for the additive model and metabolic control analysis model without selection (Tables 1, 2).

For the uniform distribution of m_i, selection led to less than 50% (32–51%) genetic variance maintained after each bottleneck (Table 3). Further investigation through fitting distributions with different σ for m_i revealed that the different results observed between the uniform distribution and the other three distributions was mainly caused by the greater σ in the uniform distribution than in the other distributions. For a uniform distribution with a smaller σ, for example a range of [5,15] for m_i, the change in genetic variance was similar to what was observed for the other three distributions, i.e., less than 50% reduction. On the other hand, for an exponential distribution with a wider dispersion; for example, σ=10, the change in genetic variance was similar to what was observed for the uniform distribution, i.e., more than 50% reduction. The normal distribution, however, was not as sensitive as the uniform or exponential distributions to differences in σ.

Discussion

While the mean of V_{t+1}/V_t fit the expectation for the additive model (Wright 1951), V_{t+1}/V_t varied widely even when QTL were additive and no selection was applied. Such variability in the changes in genetic variance has been demonstrated theoretically (Avery and Hill 1977; Lynch 1988) and experimentally (Whitlock and Fowler 1999). Our study demonstrated this variability in simulation, in which the whole genome, different genetic models, and different distributions of gene effects were investigated. Because the ranges of V_{t+1}/V_t became narrower as the number of QTL increased regardless of the genetic model and the distribution of gene effects, our results verified further that this variability is most

Table 1 Ratio of genetic variance between cycles (V_{t+1}/V_t) in an additive model when 10, 50, or 100 QTL control a quantitative trait

Selection	Number of QTL	Cycle 1/cycle 0					Cycle 2/cycle 1					Both
		Mean	Median	90% range		>1.0	Mean	Median	90% range		>1.0	>1.0
Absent	10	0.51	0.51	(0.05	0.96)	3.2%	0.53	0.57	(0.00	1.01)	7.3%	0.2%
	50	0.51	0.51	(0.22	0.80)	0.1%	0.49	0.48	(0.12	0.87)	1.1%	0.0%
	100	0.51	0.50	(0.27	0.77)	0.2%	0.50	0.49	(0.20	0.83)	1.0%	0.0%
Present	10	0.48	0.45	(0.06	0.96)	2.7%	0.42	0.37	(0.02	0.96)	2.2%	0.0%
	50	0.49	0.49	(0.20	0.82)	0.4%	0.49	0.48	(0.16	0.87)	1.8%	0.0%
	100	0.50	0.50	(0.25	0.75)	0.1%	0.49	0.48	(0.22	0.78)	0.4%	0.0%

Table 2 Ratio of genetic variance between cycles (V_{t+1}/V_t) in a metabolic control analysis model without selection when 10, 50, or 100 QTL control a quantitative trait

Number of QTL	Distribution of c_i	Distribution of m_i	Cycle 1/cycle 0					Cycle 2/cycle 1					Both
			Mean	Median	90% range		>1.0	Mean	Median	90% range		>1.0	>1.0
10	Constant	Constant	0.51	0.50	(0.19	0.93)	2.1%	0.51	0.49	(0.00	0.99)	4.4%	0.1%
		Exponential	0.52	0.50	(0.18	0.92)	2.7%	0.52	0.51	(0.00	1.00)	4.8%	0.0%
		Normal	0.51	0.48	(0.16	0.95)	2.7%	0.50	0.49	(0.00	1.00)	5.3%	0.0%
		Uniform	0.52	0.50	(0.00	1.10)	13.7%	0.53	0.54	(0.00	1.05)	13.7%	2.9%
	Normal	Constant	0.52	0.45	(0.09	1.21)	10.8%	0.50	0.47	(0.00	1.05)	8.7%	1.3%
		Exponential	0.54	0.47	(0.09	1.24)	11.9%	0.52	0.50	(0.02	1.06)	10.3%	1.6%
		Normal	0.52	0.44	(0.07	1.23)	10.6%	0.53	0.50	(0.00	1.07)	10.9%	1.3%
		Uniform	0.53	0.48	(0.00	1.26)	18.2%	0.50	0.45	(0.00	1.09)	13.9%	3.8%
	Uniform	Constant	0.56	0.42	(0.00	1.56)	19.1%	0.52	0.46	(0.00	1.21)	20.0%	4.0%
		Exponential	0.56	0.43	(0.00	1.61)	19.6%	0.53	0.50	(0.00	1.24)	20.3%	5.4%
		Normal	0.56	0.39	(0.00	1.56)	20.8%	0.53	0.48	(0.00	1.17)	20.4%	4.6%
		Uniform	0.55	0.43	(0.00	1.49)	20.6%	0.51	0.44	(0.00	1.18)	18.8%	3.8%
50	Constant	Constant	0.50	0.49	(0.30	0.73)	0.0%	0.51	0.50	(0.24	0.80)	0.3%	0.0%
		Exponential	0.50	0.49	(0.29	0.75)	0.1%	0.50	0.50	(0.24	0.78)	0.5%	0.0%
		Normal	0.50	0.49	(0.29	0.76)	0.0%	0.51	0.50	(0.24	0.80)	0.2%	0.0%
		Uniform	0.51	0.52	(0.01	1.04)	9.7%	0.52	0.51	(0.01	1.02)	8.8%	2.0%
	Normal	Constant	0.50	0.48	(0.23	0.82)	0.8%	0.50	0.48	(0.19	0.85)	1.1%	0.0%
		Exponential	0.51	0.50	(0.23	0.83)	1.7%	0.51	0.49	(0.20	0.88)	1.7%	0.1%
		Normal	0.51	0.50	(0.20	0.85)	1.8%	0.50	0.48	(0.17	0.86)	1.1%	0.0%
		Uniform	0.50	0.46	(0.00	1.13)	11.8%	0.50	0.49	(0.00	1.05)	10.8%	2.5%
	Uniform	Constant	0.54	0.44	(0.02	1.45)	15.4%	0.49	0.44	(0.02	1.10)	10.2%	2.5%
		Exponential	0.52	0.44	(0.02	1.30)	13.2%	0.51	0.46	(0.02	1.15)	13.6%	2.6%
		Normal	0.50	0.41	(0.02	1.30)	13.2%	0.50	0.47	(0.01	1.51)	10.8%	2.6%
		Uniform	0.51	0.40	(0.00	1.36)	16.0%	0.52	0.50	(0.00	1.13)	14.1%	3.6%
100	Constant	Constant	0.51	0.50	(0.32	0.72)	0.0%	0.51	0.50	(0.27	0.76)	0.2%	0.0%
		Exponential	0.51	0.50	(0.32	0.72)	0.1%	0.51	0.50	(0.28	0.75)	0.1%	0.0%
		Normal	0.51	0.50	(0.31	0.75)	0.1%	0.50	0.49	(0.27	0.77)	0.6%	0.0%
		Uniform	0.51	0.49	(0.00	1.06)	11.5%	0.50	0.50	(0.00	1.02)	8.3%	1.5%
	Normal	Constant	0.51	0.50	(0.26	0.78)	0.0%	0.51	0.49	(0.25	0.80)	0.5%	0.0%
		Exponential	0.50	0.50	(0.27	0.76)	0.4%	0.50	0.49	(0.25	0.81)	0.3%	0.0%
		Normal	0.51	0.49	(0.27	0.81)	0.9%	0.51	0.50	(0.23	0.82)	0.9%	0.0%
		Uniform	0.50	0.47	(0.00	1.10)	12.6%	0.50	0.47	(0.01	1.05)	10.2%	2.0%
	Uniform	Constant	0.52	0.45	(0.06	1.19)	11.1%	0.51	0.47	(0.04	1.04)	7.8%	0.7%
		Exponential	0.51	0.44	(0.06	1.18)	9.2%	0.51	0.49	(0.03	1.09)	8.7%	1.1%
		Normal	0.53	0.47	(0.06	1.20)	10.4%	0.52	0.50	(0.03	1.09)	10.6%	1.4%
		Uniform	0.51	0.44	(0.00	1.31)	14.2%	0.52	0.49	(0.00	1.11)	12.7%	1.6%

prominent when few QTL control a trait. The approximately symmetric distribution of V_{t+1}/V_t, except for the models with the uniform distribution, was consistent with experimental findings in *Drosophila* (Whitlock and Fowler 1999).

When selection was absent, the additive model and metabolic control analysis model led to similar changes in genetic variance, i.e., 50% reduction after each bottleneck. Keightley (1989) demonstrated that despite the highly interactive nature of the underlying biochemical system in the metabolic control analysis model, additive variance accounts for most of the total variance unless there are many loci with large differences in enzyme activity. Changes in genetic variance in metabolic control analysis would be dominated by the changes in additive variance and subsequently lead to a similar change to that in the additive model.

Unlike the additive model, selection had a different effect in the metabolic control analysis model. Selection to increase the flux of a metabolic pathway would tend to quickly fix the alleles with large effects, and their fixation would release new variation that existed as epistasis before fixation (Keightley 1989). With upward selection in metabolic control analysis, fixation at loci with large effects leads to more than a 50% reduction in genetic variance, but it also leads to an increase in genetic variance at other loci that remain segregating. The balance between these two forces determines whether the average change in genetic variance after a bottleneck is greater than 50% or less than 50%. With a wide spread of m_i, as in the uniform distribution, the new variation released at segregating loci would not be able to compensate for the drastic reduction at loci being fixed, thus leading to less than 50% genetic variance maintained after the bottleneck. With other distributions, however, the outcome of the balance led to more than 50% genetic variance maintained after the bottleneck.

Rasmusson and Phillips (1997) proposed de novo variation and epistasis as reasons for the success of malting barley (*Hordeum vulgare* L.) breeding within a narrow gene pool. Our study indicated that the genetic variance of an increasingly narrow gene pool can be conserved through selection under the metabolic control analysis model and a sustained genetic gain can thus be

Table 3 Ratio of genetic variance between cycles (V_{t+1}/V_t) in a metabolic control analysis model with selection when 10, 50, or 100 QTL control a quantitative trait

Number of QTL	Distribution of c_i	Distribution of m_i	Cycle 1/cycle 0					Cycle 2/cycle 1					Both
			Mean	Median	90% range		>1	Mean	Median	90% range		>1	>1
10	Constant	Constant	0.69	0.68	(0.36	1.07)	10.0%	0.66	0.65	(0.34	0.99)	0.1%	0.0%
		Exponential	0.69	0.68	(0.36	1.04)	8.3%	0.64	0.63	(0.32	0.99)	4.2%	0.2%
		Normal	0.66	0.66	(0.30	1.04)	7.3%	0.63	0.62	(0.29	0.97)	3.3%	0.3%
		Uniform	0.36	0.28	(0.01	1.01)	5.6%	0.43	0.38	(0.03	0.95)	2.8%	0.6%
	Normal	Constant	0.86	0.83	(0.28	1.53)	24.5%	0.74	0.74	(0.27	1.20)	20.2%	9.0%
		Exponential	0.88	0.83	(0.33	1.58)	36.2%	0.71	0.69	(0.23	1.25)	17.3%	8.2%
		Normal	0.82	0.77	(0.22	0.56)	31.7%	0.69	0.68	(0.19	1.16)	13.7%	7.5%
		Uniform	0.51	0.38	(0.01	1.37)	16.4%	0.49	0.43	(0.04	1.09)	9.1%	2.7%
	Uniform	Constant	0.68	0.49	(0.02	1.87)	26.7%	0.49	0.40	(0.02	1.20)	11.1%	5.6%
		Exponential	0.66	0.47	(0.03	1.80)	24.3%	0.46	0.37	(0.02	1.13)	9.7%	4.7%
		Normal	0.65	0.49	(0.03	1.73)	23.1%	0.48	0.38	(0.02	1.21)	12.3%	4.9%
		Uniform	0.51	0.33	(0.01	1.51)	15.4%	0.39	0.26	(0.01	1.13)	8.3%	3.0%
50	Constant	Constant	0.58	0.57	(0.07	0.96)	3.2%	0.53	0.57	(0.00	1.01)	7.3%	0.2%
		Exponential	0.58	0.58	(0.36	0.82)	0.5%	0.58	0.56	(0.34	0.85)	0.4%	0.0%
		Normal	0.57	0.56	(0.33	0.82)	0.2%	0.57	0.56	(0.32	0.84)	0.8%	0.0%
		Uniform	0.33	0.24	(0.00	0.96)	3.6%	0.37	0.30	(0.02	0.89)	1.5%	0.1%
	Normal	Constant	0.64	0.62	(0.36	0.98)	4.0%	0.61	0.59	(0.32	0.94)	3.3%	0.1%
		Exponential	0.64	0.63	(0.33	0.98)	4.3%	0.61	0.60	(0.32	0.93)	2.0%	0.1%
		Normal	0.64	0.63	(0.33	1.01)	5.4%	0.61	0.59	(0.21	0.96)	3.6%	0.3%
		Uniform	0.37	0.25	(0.01	1.07)	8.0%	0.43	0.36	(0.03	1.00)	5.0%	0.5%
	Uniform	Constant	0.66	0.55	(0.07	1.57)	21.9%	0.54	0.49	(0.06	1.17)	9.9%	3.9%
		Exponential	0.68	0.60	(0.09	1.60)	23.8%	0.52	0.45	(0.06	1.22)	11.8%	4.4%
		Normal	0.66	0.56	(0.09	1.54)	23.4%	0.53	0.45	(0.05	1.19)	12.6%	4.1%
		Uniform	0.50	0.36	(0.01	1.42)	15.9%	0.43	0.35	(0.02	1.09)	7.6%	2.2%
100	Constant	Constant	0.56	0.55	(0.37	0.77)	0.2%	0.56	0.55	(0.35	0.80)	0.5%	0.0%
		Exponential	0.55	0.55	(0.37	0.76)	0.0%	0.55	0.54	(0.34	0.80)	0.2%	0.0%
		Normal	0.56	0.55	(0.37	0.78)	0.2%	0.55	0.54	(0.32	0.79)	0.3%	0.0%
		Uniform	0.32	0.21	(0.00	0.89)	2.2%	0.37	0.30	(0.02	0.89)	1.1%	0.0%
	Normal	Constant	0.60	0.59	(0.37	0.90)	1.8%	0.58	0.56	(0.32	0.86)	0.8%	0.0%
		Exponential	0.60	0.59	(0.36	0.90)	1.7%	0.58	0.56	(0.33	0.86)	0.8%	0.0%
		Normal	0.59	0.58	(0.34	0.88)	1.5%	0.57	0.56	(0.31	0.88)	1.8%	0.0%
		Uniform	0.36	0.26	(0.01	1.06)	6.7%	0.41	0.35	(0.04	0.95)	3.4%	0.2%
	Uniform	Constant	0.67	0.58	(0.13	1.41)	18.9%	0.52	0.47	(0.08	1.09)	8.6%	3.2%
		Exponential	0.68	0.62	(0.12	1.44)	21.5%	0.54	0.49	(0.09	1.13)	11.2%	3.9%
		Normal	0.68	0.62	(0.13	1.46)	22.7%	0.53	0.47	(0.07	1.14)	9.9%	2.5%
		Uniform	0.46	0.29	(0.02	1.36)	12.7%	0.44	0.37	(0.03	1.06)	3.9%	1.5%

achieved in the absence of de novo variation. In our recent study in maize (Yu and Bernardo 2004), the V_{t+1}/V_t between Lo904×Lo916 (cycle 2) and B73×B37 (cycle 1) was 1.22 for grain yield, 1.88 for grain moisture, 0.74 for plant height, and 0.59 for ear height. The V_{t+1}/V_t for these traits was all greater than the expectation for the additive model, but could be explained by selection in a metabolic control analysis model.

The maintenance of genetic variance is crucial to breeding programs in which selection and testing has been heavily concentrated on a core germplasm pool. Further genetic gains through breeding depend upon the existence of genetic variance. Previous results (Cockerham and Tachida 1988; Goodnight 1988; Whitlock et al. 1993; Cheverud and Routman 1996) have indicated that epistasis can lead to the conservation of genetic variance after a population bottleneck. In this study, we have shown that if epistasis is due to metabolic control analysis, selection is also needed for conserving genetic variance. Given that selection is an integral part of plant breeding, we conclude that the metabolic control analysis model allows the maintenance of genetic variance during advanced cycle breeding.

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

Avery PJ, Hill WG (1977) Variability in genetic parameters among small populations. Genet Res 29:193–213

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

Bost B, Dillmann 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

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

Cockerham CC, Tachida H (1988) Permanency of response to selection for quantitative characters in finite population. Proc Natl Acad Sci USA 85:1563–1565

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

Groen AK, Van Roermund CWT, 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 glucagons. Biochem J 237:379–389

Hill SA, Bryce JH, Leaver CJ (1993) Control of succinate oxidation by cucumber (*Cucumis sativus L.*) cotyledon mitochondria. The

role of the adenine-nucleotide translocator and extra-mitochodrial reactions. Planta 190:51–57
Kascer H, Burns JA (1973) The control of flux. Symp Soc Exp Biol 27:65–104
Kascer 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
Lynch M (1988) Design and analysis of experiments on random drift and inbreeding depression. Genetics 120:791–807
Mackay TFC (2001) The genetic architecture of quantitative traits. Annu Rev Genet 35:303–339
Otto SP, Jones CD (2000) Detecting the undetected: estimating the total number of loci underlying a quantitative trait. Genetics 156:2093–2107
Peel MD, Rasmusson DC (2000) Improvement strategy of mature plant breeding programs. Crop Sci 40:1241–1246
Poehlman JM, Sleper DA (1995) Breeding field crops, 4th edn. Iowa State University Press, Ames, Iowa, USA
Rasmusson DC, Phillips RL (1997) Plant breeding progress and genetic diversity from de novo variation and elevated epistasis. Crop Sci 37:303–310
Senior ML, Chin ECL, Lee M, Smith JSC, Stuber CW (1996) Simple sequence repeat markers developed from maize sequence found in the GENEBANK database: map construction. Crop Sci 36:1676–1683
Tanksley SD, McCouch SR (1997) Seed banks and molecular maps: unlocking genetic potential from the wild. Science 277:1063–1066
Wang J, Bernardo R (2000) Variance of marker estimates of parental contribution to F_2 and BC_1-derived inbreds**.** Crop Sci 40:659–665
Whitlock MC, Fowler K (1999) The changes in genetic and environmental variance with inbreeding in *Drosophila melanogaster*. Genetics 152:345–353
Whitlock MC, Phillips PC, Wade MJ (1993) Gene interaction affects the additive genetic variance in subdivided populations with migration and extinction. Evolution 47:1758–1769
Wright S (1951) The genetical structure of populations. Ann Eugen 15:323–354
Yu J, Bernardo R (2004) Changes in genetic variance during advanced cycle breeding in maize. Crop Sci (in press)