Hybrid Dysfunction: Population Genetic and Quantitative Genetic Perspectives

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Submitted May 22, 2007; Accepted October 5, 2007; Electronically published February 15, 2008

ABSTRACT: In the wake of seminal work by Dobzhansky and Muller, hybrid dysfunction is usually attributed to incompatible mutations in different genes arising in different populations. This Dobzhansky-Muller (D-M) model is among the most important contributions of theoretical population genetics. Here I make formal connections between the D-M model and the quantitative genetic interpretation of hybrid dysfunction as a combination of additive, dominance, and epistatic effects. Concerns over conceptual differences between the two approaches are unwarranted; the D-M model can be expressed as a special case of the statistical model developed for line-cross analysis in quantitative genetics. This unified theoretical framework encourages application of quantitative genetic methods to the study of speciation.

Keywords: Dobzhansky-Muller, speciation, epistasis, dominance theory, Haldane’s rule.

The genetics of hybrid fitness is a key area of research in speciation biology. Hybrid dysfunction was once seen as an evolutionary paradox and a key challenge for evolution as a general explanation of biological diversity (Darwin 1859, chap. 8; Huxley 1908, p. 463; Orr 1996; Coyne and Orr 2004, chap. 7). It was not immediately obvious how Darwin’s theory of gradual evolution by natural selection among subtle variants could account for the evolution of inviability, sterility, or other dysfunction. The problem was solved by Dobzhansky (1936, 1937) and Muller (1940), who applied population genetic reasoning to allopatric populations (see also Poulton 1908; Bateson 1909; and reviews in Orr 1996; Coyne and Orr 2004, pp. 269–272).

The key insight is that independent genetic changes in isolated populations must be compatible with their respective genetic backgrounds but need not be compatible with each other.

A major prediction arising from the Dobzhansky-Muller (D-M) model is that hybrid dysfunction is caused by interactions between different loci rather than by heterozygote disadvantage (Nei et al. 1983; Lynch 1991; Orr 1995; Turelli and Orr 2000; Coyne and Orr 2004; Gavrilets 2004). Lynch (1991) formalized this idea in a statistical model derived from line-cross theory (Hill 1982) and involving the quantitative genetic concepts of additivity, dominance, and epistasis. Turelli and Orr (2000) derived an expected hybrid breakdown score from a more mechanistic perspective, starting with an explicit model of two-locus interactions. Demuth and Wade (2005) contrasted Turelli and Orr’s (2000) approach with a quantitative genetics model based on the statistical analysis of line crosses. They concluded that certain important effects were neglected or undefined in the D-M model, making it difficult to reconcile with their quantitative genetic perspective. Here I show that this conclusion was based on an incorrect interpretation of the basic D-M model and of Turelli and Orr’s (2000) multilocus generalization. In fact, the Turelli-Orr model can be expressed as a special case of the more general statistical models of quantitative genetics. The Turelli-Orr formulation is based on a specific mechanistic model of gene interactions, and formal comparison with the quantitative genetics framework shows how interactions between loci can affect the coefficients representing dominance and epistasis in standard quantitative genetic analyses. My analysis clarifies conceptual connections between population genetic theory and the statistical models of quantitative genetics.

The Dobzhansky-Muller Model

The D-M model is explained clearly by Dobzhansky (1937, p. 282), Orr (1995), Gavrilets (2003), and Demuth and Wade (2005, their fig. 1), among others (some refer to this model as the Bateson-Dobzhansky-Muller, or BDM, model).
The problem is that natural selection should not allow the evolution of unfit offspring. More specifically, a single change immediately causing reproductive isolation between the mutant and its contemporaries leaves the mutant unable to produce viable or fertile outcrossed offspring. The solution begins with an ancestral species fixed for an AA genotype at one locus and BB at another. The species becomes split into two isolated populations. In one isolate, an a allele becomes fixed (by either drift or selection; the point is that the genotypes AaBB and aaBB are not less fit than AABB (fig. 1). Hybrid genotypes combining the two derived alleles a and b (e.g., the F1 AaBb) may suffer low fitness, even sterility or inviability, because of interactions between these alleles that evolved without deleterious effects within their native genetic backgrounds (fig. 1). That is, hybrid dysfunction results from “complementary” epistasis between loci A and B (Orr 1995).

In the D-M model, the terms “dominant” and “recessive” are applied to describe how the effects of the incompatibility between alleles a and b are modified by the compatible alleles, A and B (Muller 1940; Turelli and Orr 1995). The incompatibility is said to be dominant if any genotype including at least one a and one b allele expresses an a allele becomes fixed (by either drift or selection; the point is that the genotypes AaBB and aaBB are not less fit than AABB (fig. 1). Hybrid genotypes combining the two derived alleles a and b (e.g., the F1 AaBb) may suffer low fitness, even sterility or inviability, because of interactions between these alleles that evolved without deleterious effects within their native genetic backgrounds (fig. 1). That is, hybrid dysfunction results from “complementary” epistasis between loci A and B (Orr 1995).

In the D-M model, the terms “dominant” and “recessive” are applied to describe how the effects of the incompatibility between alleles a and b are modified by the compatible alleles, A and B (Muller 1940; Turelli and Orr 1995). The incompatibility is said to be dominant if any genotype including at least one a and one b allele expresses the same level of dysfunction (fig. 1A). The incompatibility is said to be recessive if the presence of at least one A or B allele is adequate to mask the incompatibility; that is, only aabb suffers hybrid dysfunction. Partially recessive (or partially dominant) incompatibilities are those in which the severity of the dysfunction is partially reduced by A and B, so that the double heterozygote AaBb has higher fitness than aabb, and genotypes that are homozygous-heterozygous (Aabb and aabb) are intermediate (fig. 1B). Some authors prefer to reserve the terms “dominant” and “recessive” for single-locus effects (Demuth and Wade 2005); however, the terms are established in the speciation genetics literature as descriptors of D-M incompatibilities (e.g., Turelli and Orr 1995, 2000; Presgraves 2003; Coyne and Orr 2004; Gavrilets 2004; Brideau et al. 2006; Sweigart et al. 2006; Willot 2006; Price 2007).

The D-M model as illustrated in figure 1 is a simple case of a two-locus, two-allele model with interactions between the two loci. Table 1 shows a more general two-locus, two-allele model where phenotypic effects are partitioned, in the tradition of quantitative genetics, into additive, dominance, and interaction effects. This model is not experimentally tractable because the epistatic effects are unconstrained, leading to a description of nine phenotypes using 13 parameters. However, the relationship between genotype and phenotype described in table 1 provides a common foundation for comparing Turelli and Orr’s (2000) multilocus D-M model with the multilocus quantitative genetic models of Lynch (1991) and Demuth and Wade (2005). Suppose there are n pairs of loci affecting a phenotype Z, and the effect of the ith pair is described in table 1. The expected phenotype of an individual is obtained by adding effects across pairs of loci. For example, if two pairs of loci affect the trait and an individual has genotype [(AABB), (AaBB)], then its phenotype should be [(aabb) - b1 + I(AABB), a1 + D11 + I(AABB)]. See table A1 in the appendix for parameter definitions.

We can generalize the calculation for n independent pairwise incompatibilities between unlinked loci (A1 and B1, where i = 1, . . . , n). Consider an individual hybrid with a random fraction pi of its genome homozygous for species 1 alleles (BB and aa), a random fraction p1 homozygous for species 2 alleles (bb and AA), and the remaining fraction 1i heterozygous. On average, np1pi pairs of loci will have genotype AABB, np1pi will have AaBB, and so on, yielding an expected phenotype,

\[ E[Z] = \sum_{i=1}^{n} p_i p_i \left[ (-\bar{a} - \bar{b} + \bar{I}(AABB)) + p_i p_i (-\bar{a} - \bar{b} + \bar{I}(AABB)) + p_i p_i (-\bar{a} + \bar{I}(AABB)) + p_i p_i (-\bar{a} + \bar{I}(AABB)) + p_i p_i (-\bar{a} + \bar{I}(AABB)) + p_i p_i (-\bar{a} + \bar{I}(AABB)) \right] \]

where \( \bar{a}, \bar{b}, \bar{I}_{11}, \bar{D}_{11}, \bar{I}(AABB) \), and so forth, are averages across the n pairs of loci. This general expression for the expected phenotype of an individual, given the genomic proportions pi, pi, and pi, can be used to derive and interpret the traditional quantitative genetic models used by Lynch (1991; Lynch and Walsh 1998) and Demuth and Wade (2005) as well as the Turelli-Orr formulation of the D-M model (Turelli and Orr 2000). Throughout this article, I assume that the phenotype Z is related to fitness by any monotone decreasing function; that is, Z is some measure of hybrid dysfunction.

Turelli and Orr

Turelli and Orr (2000; also see Orr 1995; Orr and Turelli 2001) derived a model of hybrid dysfunction caused by many pairs of interacting genes. They also considered “complex” incompatibilities caused by interactions among three or more loci, but I will focus on the pairwise case.
Figure 1: Adaptive landscapes implied by the simple diploid Dobzhansky-Muller model of hybrid dysfunction (Gavrilets 2003, 2004). Bar heights give relative fitnesses of two-locus genotypes. A. When incompatibilities are dominant, dysfunction is fully expressed in all genotypes that include alleles a and b. B. When incompatibilities are at least partially recessive, the genotype that is homozygous for both incompatible alleles suffers the greatest dysfunction.

Table 1: Phenotypic effects of a pair of interacting diallelic loci in terms of additive \((a, b)\), dominance \((D_{a_0}, D_{b_0})\), and interaction \((I)\) components

<table>
<thead>
<tr>
<th>Genotype</th>
<th>(AA)</th>
<th>(Aa)</th>
<th>(aa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(BB)\textsubscript{i}</td>
<td>(a_i - b_i + I(\text{AABB}))</td>
<td>(b_i + D_{a_0} + I(\text{AABB}))</td>
<td>(a_i - b_i + I(\text{aaBB}))</td>
</tr>
<tr>
<td>(Bb\textsubscript{i})</td>
<td>(-a_i + D_{b_0} + I(\text{AABB}))</td>
<td>(D_{a_0} + D_{b_0} + I(\text{AAbb}))</td>
<td>(a_i + D_{b_0} + I(\text{aabB}))</td>
</tr>
<tr>
<td>(bb\textsubscript{i})</td>
<td>(-a_i + b_i + I(\text{AAbb}))</td>
<td>(b_i + D_{a_0} + I(\text{AAbb}))</td>
<td>(a_i + b_i + I(\text{aabB}))</td>
</tr>
</tbody>
</table>

Note: See table A1 for parameter definitions.
and Orr’s parameters
model, Demuth and Wade (2005) also misinterpret Turelli
metrical D-M model (fig. 1) generates a contradiction.
Demuth and Wade’s symmetrical table 1 to the asym-
alleles has fitness 0, then . Thus, equating
However, if the hybrid that is homozygous for both derived
of Demuth and Wade’s model solve to .
1, species 2, and the ancestor all equal 1, the parameters
model illustrated in figure 1. When the fitnesses of species
2004). To see this another way, consider the basic D-M
and Orr 1998, 2004; Turelli and Orr 2000; Gavrilets 2003,
To see this another way, consider the basic D-M
model, the ancestor has fitness equal to that of both daugh-
ter species genotypes (fig. 1; Dobzhansky 1937; Coyne and
model (cf. Demuth and Wade 2005, p. 527); in the basic
model, the ancestral genotype is not undefined in the D-M
notypes included in Demuth and Wade’s (2005) equation
across all nine two-locus genotypes, not only the four ge-
involving more than two loci are possible (Lynch 1991).
The ellipsis in equation (3) is a reminder that interactions
involving more than two loci are possible (Lynch 1991).
The coefficients of equation (3) can be estimated via like-
lihood or least squares analysis of phenotypic means and
variances in an adequate set of line crosses (parentals, F1,
F2, and backcrosses in both directions; see Lynch 1991;
Lynch and Walsh 1998; Rundle and Whitlock 2001; De-
muth and Wade 2005). Use of this general equation (3)
instead of a table of coefficients allows a more complete
analysis of the connection between quantitative genetics
and the Turelli-Orr formulation of the D-M model. Sub-
stituting equation (4) for in equation (3) and collecting
terms reveals the relationships between Demuth and
Wade’s composite coefficients and the additive, domi-
nance, and epistatic effects of equation (1):

Nevertheless, the remainder of Demuth and Wade’s
(2005) analysis appears sound. Here I use a general for-
mulation of their multilocus model to find explicit con-
nections to the Turelli-Orr model and clarify the relation-
ships between the composite parameters of quantitative
genetics and the interactions contributing to hybrid break-
down. To further explore a quantitative genetic perspective
on hybrid fitness, they used a statistical model similar to
that of Lynch (1991), except for a difference in scaling due
to use of (proportion of loci heterozygous for species 1
and species 2 alleles) instead of Lynch’s hybridity index
. Demuth and Wade (following Mather and
Jinks 1982; Lair et al. 1997) relied on tables of coefficients
for specific line crosses, but the general formula analogous
to that of Lynch’s equation (1) is

Table 2: Relationships among the parameters of the
general (saturated) model (table 1, eq. [1]), the
symmetrical epistatic model of Demuth and Wade,
and the asymmetrical Dobzhansky-Muller model of
Turelli and Orr

<table>
<thead>
<tr>
<th>General model</th>
<th>Demuth and Wade 2005</th>
<th>Turelli and Orr 2000</th>
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Note: See table A1 for parameter definitions.
Here, the “composite dominance effect” ($\delta$) is determined entirely by interactions between loci, and $\delta = 0$ only if D-M incompatibilities are “additive” in the sense of $h_{\text{DD}} = (1/2)h_1 = (1/4)h_2$. Similar relationships can be found for the composite effect coefficients of Lynch’s (1991) quantitative genetics model (Fitzpatrick 2008). The differences between equation (3) and Lynch’s (1991) model are Lynch’s use of a rescaled “hybridity index” ($\theta_{hi} = 2p_{hi} - 1$) in place of $p_{hi}$ and Lynch’s use of the $F_2$ as a reference population rather than the mean of many recombinant inbred lines ($\mu$ is the reference population mean, and the other coefficients represent deviations from that mean owing to the various genetic effects). These equations (6) provide a basis from which to revisit two important conclusions of Demuth and Wade (2005). First, they conclude that their quantitative genetic description of mean fitness in $F_2$ hybrids implies a different role for epistasis than does the expected $F_2$ breakdown score of Turelli and Orr (2000). Second, they conclude that the two approaches make different predictions for the genetic basis of Haldane’s rule.

**Epistasis in $F_2$ Hybrids**

The quantitative genetic model of equation (3) can be seen as a more general statistical model, while the Turelli-Orr model is a special case with specific interpretations of the model parameters. If the Turelli-Orr model is correct for a given case, the estimated additive $\times$ additive effect is caused entirely by interactions between loci that are homozygous for incompatible alleles, and the composite dominance and dominance $\times$ dominance effects are related to the average dominance of incompatibilities, not single-locus dominance (eqq. [6c], [6e]). All three kinds of pairwise interactions identified by Turelli and Orr (2000) influence the expected $F_2$ phenotype, regardless of which framework is used. Assuming a large number $n$ of pairwise incompatibilities, expected hybrid breakdown for $F_2$ hybrids is

\[
E(Z|F_2) = \mu + \frac{1}{2} \bar{\sigma} + \frac{1}{2} I_{\text{aa}},
\]

in quantitative genetic terms, and in Turelli and Orr’s (2000) terms,

\[
E(Z|F_2) = n \left( \frac{1}{16} h_2 + \frac{1}{4} h_1 + \frac{1}{4} h_1 \right).
\]
predictions; the quantitative genetic description of hybrid fitness includes the Turelli-Orr model as a special case derived from specific biological assumptions. Demuth and Wade’s statement (2005, p. 534) that additive × additive epistasis (represented by $I_{aa}$) does not contribute to $F_2$ hybrid breakdown in the quantitative genetic model is misleading (it may increase, decrease, or have no effect on hybrid breakdown). The absence of $I_{aa}$ from equation (7) is due to the particular reference population used by the joint scaling framework. When hybrid dysfunction is described by the Turelli-Orr model with large $n$, the mean hybrid breakdown score of the reference population is $\mu = (1/4)nI_{h_1} = -I_{mm}$ (eqn. [6a], [6d]), so the mean $F_2$ breakdown is $E(Z|F_2) = -I_{mm} + (1/2)\delta + (1/4)I_{aa}$. This makes sense when we recall that Demuth and Wade’s $\mu$ is the expected hybrid breakdown of recombinant inbred lines; that is, individuals whose genomes are mosaics of loci homozygous for species 1 alleles and loci homozygous for species 2 alleles. These lines are affected only by homozygous-homozygous interactions. Equation (5d) shows that additive × additive epistasis contributes to average $F_2$ hybrid breakdown ($I_{mm}$ is negative) whenever $\tau(AABB) + \tau(aabb) > \tau(AAbb) + \tau(aaBB)$, that is, when the average interaction between heterospecific alleles is more deleterious than the average interaction between homo-specific alleles.

**Conditions for Haldane’s Rule**

An important result from the Turelli-Orr model relates to the dominance theory of Haldane’s rule. Haldane’s rule is the observation that hybrid offspring with heterogametic sex chromosomes (i.e., males in mammals and *Drosophila*, females in birds and Lepidoptera) often suffer greater dysfunction (sterility and inviability) than hybrids of the homogametic sex (Haldane 1922; Coyne and Orr 1989; Orr 1997). The dominance theory (Muller 1940) explains Haldane’s rule by proposing that most epistatic incompatibilities are recessive, so that they are not expressed in $F_1$ hybrids (fig. 1B) unless they involve the sex chromosome, which is effectively homozygous (hemizygous) in the heterogametic sex (Orr 1997; Turelli and Orr 2000). When interactions between loci on the X chromosome are ignored, Turelli and Orr (1995) showed that Haldane’s rule ($E(Z|F_1$ male) > $E(Z|F_1$ female), assuming that male is the heterogametic sex) results when pairwise incompatibilities are partially recessive (fig. 1B):

$$\frac{h_0}{h_1} < \frac{1}{2}. \quad (9)$$

Based on equation (2), Turelli and Orr (2000) showed that conditions for Haldane’s rule are slightly more restrictive when X-X interactions are included:

$$\frac{h_0}{h_1} < \frac{1 - g_x}{2 - g_x} = \frac{1}{2 + g_x(1 - g_x)}. \quad (10)$$

Here, $g_x$ is the fraction of the genome (or the fraction of pairwise incompatibilities) represented by the X chromosome (thus, the right side of eq. [10] is between 1/2 and 1/2.25).

With the same approach (defining a fraction $g_x$ of incompatibilities involving the X chromosome), the condition for Haldane’s rule in Demuth and Wade’s (2005) parameters is $E(Z|F_1$ male) > $E(Z|F_1$ female):

$$\mu + (1 - g_x)\delta + (1 - g_x)J_{aa} + g_x^2I_{aa}$$

$$\pm [g_x\alpha + g_x(1 - g_x)K_{aa}] > \mu + \delta + J_{aa}, \quad (11)$$

which reduces to

$$\pm[\alpha + (1 - g_x)K_{aa}] > \delta + J_{aa}(2 - g_x) - g_xI_{aa}. \quad (12)$$

The term in square brackets is positive when $F_1$ males bear X chromosomes from species 1 and negative when they bear X chromosomes from species 2. Averaging over both reciprocal $F_1$ males makes the left side of equation (12) equal to 0; therefore, a general condition for Haldane’s rule is

$$\delta + J_{aa}(2 - g_x) - g_xI_{aa} < 0. \quad (13)$$

Substituting from equations (6) into equation (12) or (13) yields equation (10), the condition found by Turelli and Orr (2000). The condition in equation (13) is more general than the Turelli-Orr condition because it can be satisfied through interactions other than those considered in the Turelli-Orr model. For example, X-linked heterozygote advantage or dominance × dominance epistasis causing high fitness of double heterozygotes would make $F_1$ females tend to have higher fitness than $F_1$ males.

Demuth and Wade’s (2005) result (their eq. [13]) differs from the above for three reasons. First, they consider only $F_1$ males with X chromosomes from species 1 rather than both reciprocal $F_1$’s (however, this does not matter for the Turelli-Orr model, where there is no additive difference between species). Second, instead of the $g_x$ notation used by Turelli and Orr (2000), they define a separate set of coefficients to describe the composite genetic effects involving loci on the X chromosome. Finally, they ignore interactions between loci on the X chromosome, which are included in the Turelli and Orr (2000) model and equations (11)–(13). If we assume (as in eq. [11]) that the
only difference between X-linked and autosomal incompatibilities is their number $n$, equations (6) suggest that under the Turelli-Orr model, the X-linked additive and X-autosomal additive $\times$ additive composite effects ($x$ and $K_x$ in Demuth and Wade’s eq. [13]) are 0, the X-linked dominance effect is $\delta_x = n_x[h_x - (1/2)h_x]$, and the X-autosomal dominance $\times$ dominance effect is $J_{xx} = 2n_x[h_x - h_x + (1/4)h_x]$. In the latter, the factor of 2 comes from counting both species 1 X by species 2 autosome and species 2 X by species 1 autosome interactions (Turelli and Orr 1995; Demuth and Wade 2005). Substituting these equations into Demuth and Wade’s (2005) condition for Haldane’s rule (their eq. [13]) recovers the original condition of Turelli and Orr (1995), where they, too, ignored X-X interactions: $h_1/h_x < 1/2$. The same can be obtained from Lynch’s (1991) earlier formulation of the quantitative genetic model (Fitzpatrick 2008).

Conclusions

The multilocus D-M model of hybrid dysfunction, as described by Turelli and Orr’s (2000) equation (2), is entirely compatible with both Lynch’s (1991) and Demuth and Wade’s (2005) quantitative genetic descriptions of hybrid breakdown caused by many pairwise incompatibilities (eq. [3]). The unified theory sought by Demuth and Wade (2005) is clarified in equations (5) and (6). Their difficulty in reconciling the quantitative genetic perspective with the Turelli-Orr model resulted from misinterpreting the basic two-locus model (cf. my fig. 1 with their table 1), misinterpreting Turelli and Orr’s (2000) parameters ($p_i$’s), and failing to write a general equation for the joint scaling model (eq. [3]).

The Turelli-Orr model is derived from specific assumptions about the genetics of hybrid dysfunction, that is, that fitness is a function of the sum of many asymmetrical pairwise interactions. My analysis shows that it is included as a special case of the general statistical model of quantitative genetics, and its parameters can be estimated from an adequate set of line-cross analyses (Lynch 1991; Lynch and Walsh 1998; Demuth and Wade 2005). The Turelli-Orr model lends specific meaning to the “composite effects” of the quantitative genetic model (eqq. [6]). Notably, the composite dominance effect need have nothing to do with single-locus dominance (eq. [6c]). My results support Lynch’s (1991) and Demuth and Wade’s (2005) conclusions that the well-developed statistical theory of quantitative genetics can be fruitfully applied to the genetics of hybrid dysfunction and that unified analyses of within- and between-species variation may yield important insights into the roles of dominance and epistasis in evolution.

Finally, the theory reviewed above relies on certain simplifying assumptions that merit further investigation. Perhaps of greatest concern are the assumptions that hybrid fitness is affected by a large number of pairwise incompatibilities and that the loci involved are not physically linked. Violation of these assumptions makes quantities like $p_1p_2$ and $\theta_1^2$ unreliable indicators of the probabilities of pairwise interactions. Therefore, additional theoretical work is needed, and traditional line-cross analyses should be accompanied by quantitative trait locus analyses designed to evaluate the number of incompatibilities, the distribution of their effects, and the possibility of more complex interactions (i.e., those involving more than two loci; see Turelli and Orr’s [2000] appendix).

Acknowledgments

I thank N. Barton, J. Demuth, S. Gavrilets, D. Simberloff, M. Turelli, M. Wade, and two anonymous reviewers for their helpful comments. My financial support comes from the University of Tennessee and the National Science Foundation (grant DEB-0516475).

APPENDIX

Definitions of Parameters

| Table A1: Definitions of parameters used in tables 1 and 2 and equation (1) |
|---|---|
| Parameter(s) | Explanation |
| $A_i, B_i$ | The $i$th pair of interacting loci |
| $A, a$ | The alleles of an $A$ locus |
| $B, b$ | The alleles of a $B$ locus |
| $(AABB)_i$ | One of the nine genotypes for the $i$th pair of interacting loci |
| $a, b_i$ | The additive phenotypic effects associated with loci $A$ and $B_i$ |
| $D_{A_i} D_{B_i}$ | The dominance effects associated with loci $A_i$ and $B_i$ |
| $l(AABB)_i$ | The interaction effect of genotypes AA and BB at loci $A_i$ and $B_i$ |
Literature Cited


