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Analysis of epistasis: A genetic model for triploid endosperm traits

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Abstract: A genetic model for triploid endosperm traits was proposed on the basis of diallel cross system to analyze additive by additive epistasis of direct effect (*AA*) and maternal effect (*AmAm*) along with direct additive effect, dominance effect, cytoplasm effect, as well as maternal additive and dominance effects. Monte Carlo simulations were conducted to test the estimation of genetic parameters and robust of this genetic model. Unbiased estimation of the variance components for single trait and covariance components between two traits can be obtained by using minimum norm quadratic unbiased estimation (MINQUE) method for both balanced design and unbalanced design without significant difference. A worked example was used to illuminate the application of analyzing additive by additive epistatic variation.

Key words: epistatic effect; diallel cross; Monte Carlo simulation; variance; covariance; MINQUE
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摘 要: 基于双列杂交体系提出一个遗传模型分析三倍体胚乳性状直接和母体上位性效应, 直接加性、显性效应, 细胞质效应, 以及母体加性和显性效应. 并运用混合线形模型分析该遗传模型. 用最小范数二阶无偏估算法 (MINQUE) 估算单性状的方差分量和性状间的协方差分量. 用蒙特卡罗模拟检测遗传参数的估算和模型的稳定性. 模拟分析同时应用于双列杂交的平衡设计和非平衡设计. 模拟结果显示在估算单性状的方差和性状间的协方差时, 平衡设计和非平衡设计没有显著差异. 通过估算实际水稻种子性状数据, 说明在经典数量遗传研究中, 加加上位变异分析是可行的.

关 键 词: 上位性效应; 双列杂交; 蒙特卡罗模拟; 方差; 协方差; MINQUE

Bateson[1] described 'epistasis' as the distortions of mendelian segregation ratios due to one gene masking the effects of another. Fisher[2] defined the epistasis in statistical point of view to

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illuminate the deviations from additive effect in a linear statistical model. Lou and Zhu[3] found that the major gene effects could be influenced by the genetic background. Modifier genes in human and mouse have provided evidence of the importance of epistasis: the genetic background often influences the phenotypes of the susceptible genotype of major genes, for example, by affecting the penetrance of the gene[4]. Other evidences such as substantial epistasis between QTL were found by genome-wide scanning in the populations that are derived from crosses between artificially selected lines[5-10].

In genetic breeding program, both additive effects and additive by additive epistatic effects can be inherited stably from one generation to the next generation[11]. Liu *et al.*[12-13] pointed out the importance of epistatic effect in mark-assisted selection by constructing the selection index in genetic improvements. Many genes with small effects have minor variants present in the base population or on new mutations, which could generate little epistasis[14].

Diallel mating design based on classical statistical and quantitative genetics provided a way to analyze the genetic effects for diploid seed and triploid endosperm traits. Cockerham and Weir[15] proposed a bio-model to analyze the direct additive and dominance effects, as well as maternal and paternal effects for diploid seeds traits. Zhu and Weir[16-17] proposed seed models for analyzing direct additive and dominance effects, extranuclear effects including cytoplasm effect, maternal additive and dominance effects for diploid seed and triploid endosperm traits.

In the present study, we proposed a diallel mating genetic model to estimate the direct and maternal additive by additive epistasis, direct and maternal additive and dominance effects, the cytoplasm effect, as well as their interaction effects with environments. Monte Carlo simulations were conducted to evaluate the procedures for estimating variance components for single trait and covariance components between two traits. And a worked example in rice seeds was used to demonstrate the analysis for additive by additive epistasis variation with the none-variation of the main additive effects.

1 Model and method

The genetic model is based on the following assumptions: (i) no paternal effect; (ii) no covariance between direct genetic effects and maternal genes effect, as well as their interaction effects with environments; (iii) no interaction between direct genetic effects and cytoplasm effect, as well as their interaction effects with environments. The genetic model can be written as a linear mixed model for the mean observation in the hth environment and in the lth block of the kth type of genetic entry from line i and j:

$$y_{hijkl} = \mu + E_h + G_{ijk} + GE_{hijk} + B_l + e_{hijkl}.$$

where μ is population mean, E is environment effects, G is the total genetic effect, GE is the total genotype by environment interaction effects, B is block effect, and e is residual. The total genetic effect G_{ijk} depends on the specific genetic entry:

for F_{1ij} from maternal line $i \times$ paternal line j ($k = 1$).

$$G_{ij1} = 2A_i + A_j + D_{ii} + 2D_{ij} + 4AA_{ii} + AA_{jj} + 4AA_{ij} + C_i + 2Am_i + Dm_{ii} + 4AmAm_{ii}.$$

for F_{2ij} from maternal $F_{1ij} \times$ paternal F_{1ij} ($k = 2$).

$$G_{ij2} = 1.5A_i + 1.5A_j + D_{ii} + D_{jj} + D_{ij} + 2.25AA_{ii} + 2.25AA_{jj} + 4.5AA_{ij} + C_i + Am_i + Am_j + Dm_{ij} + AmAm_{ii} + AmAm_{jj} + 2AmAm_{ij}.$$

for reciprocal backcross RBC_i from maternal line $i \times$ paternal F_{1ij} ($k = 5$).

$$G_{ij5} = 2.5A_i + 0.5A_j + 2D_{ii} + D_{ij} + 6.25AA_{ii} + 0.25AA_{jj} + 2.5AA_{ij} + C_i + 2Am_i + Dm_{ii} + 4AmAm_{ii}.$$

for reciprocal backcross RBC_j from maternal line j

× paternal $F_{1ij}(k=6)$.

$$G_{ij6}=0.5A_i+2.5A_j+2D_{jj}+D_{ij}+0.25AA_{ii}+6.25AA_{jj}+2.5AA_{ij}+C_j+2Am_j+Dm_{jj}+4AmAm_{jj}.$$

where A is additive effect, D is dominance effect, AA is additive by additive epistatic effect, C is cytoplasm effect, Am is maternal additive effect, Dm is maternal dominance effect, $AmAm$ is maternal additive by additive epistatic effect.

The total genotype by environment effect GE_{hijk} also depends on the specific genetic entry in different environment:

for F_{1ij} from maternal line i × paternal line j ($k=1$).

$$GE_{hij1}=2AE_{hi}+AE_{hj}+DE_{hii}+2DE_{hij}+4AAE_{hii}+AAE_{hjj}+4AAE_{hij}+CE_{hi}+2AmE_{hi}+DmE_{hii}+4AmAmE_{hii}.$$

for F_{2ij} from maternal F_{1ij} × paternal $F_{1ij}(k=2)$.

$$GE_{hij2}=1.5AE_{hi}+1.5AE_{hj}+DE_{hii}+DE_{hjj}+DE_{hij}+2.25AAE_{hii}+2.25AAE_{hjj}+4.5AAE_{hij}+CE_{hi}+AmE_{hi}+AmE_{hj}+DmE_{hiij}+AmAmE_{hii}+AmAmE_{hjj}+2AmAmE_{hij}.$$

for reciprocal backcross RBC_i from maternal line i × paternal $F_{1ij}(k=5)$.

$$GE_{hij5}=2.5AE_{hi}+0.5AE_{hj}+2DE_{hii}+DE_{hjj}+6.25AAE_{hii}+0.25AAE_{hjj}+2.5AAE_{hij}+CE_{hi}+2AmE_{hi}+DmE_{hii}+4AmAmE_{hii}.$$

for reciprocal backcross RBC_j from maternal line j × paternal $F_{1ij}(k=6)$.

$$GE_{hij6}=0.5AE_{hi}+2.5AE_{hj}+2DE_{hjj}+DE_{hij}+0.25AAE_{hii}+6.25AAE_{hjj}+2.5AAE_{hij}+CE_{hi}+2AmE_{hj}+DmE_{hjj}+4AmAmE_{hii}.$$

where AE is additive by environment interaction effect, DE is dominance by environment interaction effect, AAE is AA by environment interaction effect, CE is cytoplasm by environment interaction effect, AmE is Am by environment interaction effect, DmE is Dm by environment interaction effect, $AmAmE$ is $AmAm$ by environment interaction effect.

The phenotypic variance for single trait and covariance between two traits can be partitioned as

$$V_P=(V_A+V_D+V_{AA})+V_C+(V_{Am}+V_{Dm}+V_{AmAm})+(V_{AE}+V_{DE}+V_{AAE})+V_{CE}+(V_{AmE}+V_{DmE}+V_{AmAmE})+V_e,$$

$$C_P=(C_A+C_D+C_{AA})+C_C+(C_{Am}+C_{Dm}+C_{AmAm})+(C_{AE}+C_{DE}+C_{AAE})+C_{CE}+(C_{AmE}+C_{DmE}+C_{AmAmE})+C_e.$$

The estimates of the parameters can be obtained by MINQUE (1)[17], the sampling variances of the estimates can be obtained by jackknife procedure, and a t-test can be conducted to test the zero variant for genetic effects[16-17].

2　Monte Carlo simulations

The simulations were based on modified diallel crosses with three randomized complete blocks in two environments. The balanced design included F_1s, F_2s, backcross from eight inbred lines, as well as their reciprocal backcrosses. The unbalanced design, with the same generations and experimental sizes as the balanced design, consisted of eleven inbred lines groups (lines one through seven as group 1, and lines eight to eleven as group 2).

The unbiasedness and efficiency of estimation of variance components for single trait and covariance components between two traits were obtained by MINQUE (1), and sampling variances of the estimates were obtained by the jackknife procedure by resampling genetic entry. And a t-test was conducted to test the null hypotheses of no variation for genetic effects. The simulation results are summarized in Table 1 for single trait and two traits with a correlation ($\rho=0.5$).

There is no difference for bias and power value between the balanced design and unbalanced design. For both balanced and unbalanced design, direct additive by additive epistasis (σ^2_{AA}) can be detected significantly with minor bias and higher power, which is almost equal to one like the estimation of residue. And the interaction effect

between direct epistasis and environment σ^2_{AAE} could be significantly detected with power values 100%.

Robustness of estimation can be tested by simulation under the conditions of no specific variation. If cytoplasm effect and interaction effect between cytoplasm and environments are excluded ($\sigma^2_C = \sigma^2_{CE} = 0$), other parameters can be estimated with similar bias, MSE, and power value. Non-significance of the cytoplasm and its interaction effect with environments can be detected with a probability over 99% and 96% respectively. Without maternal genetic background and cytoplasm variation, and their interaction variations with different environments ($\sigma^2_{Am} = \sigma^2_{Dm} = \sigma^2_{AmAm} = \sigma^2_{AmE} = \sigma^2_{DmE} = \sigma^2_{AmAmE} = \sigma^2_C = \sigma^2_{CE} = 0$), direct additive, dominance, epistasis and their interaction effects with environments, and error variance can be detected with a similar probability when these effects exits. When there are no maternal additive, dominance, epistasis and their interaction effects with environments variations ($\sigma^2_{Am} = \sigma^2_{Dm} = \sigma^2_{AmAm} = \sigma^2_{AmE} = \sigma^2_{DmE} = \sigma^2_{AmAmE} = 0$), other parameters are better estimated for bias and power value. The genetic model is robust for estimating variance components even though there are no cytoplasm and/or maternal effects and their interaction effects with environments.

There is no considerable difference of bias, MSE in estimating covariance components for two traits (Table 1). But the power values tended to be smaller for covariance estimation. It is indicated that MINQUE (1) is also efficient in estimating covariance components for balanced and unbalanced modified diallel crosses with the same experimental sizes.

Table 1 Bias, MSE and power value from simulations by MINQUE (1) with the jackknife procedure followed *t*-test for modified diallel crosses under 500 simulation runs

Parameter	True value	Balanced design			Unbalanced design		
		Bias	MSE	Power	Bias	MSE	Power
One trait							
σ^2_A	40	0.67	862.04	0.84	2.14	874.45	0.83
σ^2_D	20	0.04	192.33	0.65	−1.06	202.91	0.58
σ^2_{AA}	30	−0.14	106.31	1.00	0.12	134.25	1.00
σ^2_C	20	−0.88	285.63	0.89	0.42	207.62	0.91
σ^2_{Am}	40	1.80	4620.85	0.80	−2.02	5492.92	0.84
σ^2_{Dm}	20	1.34	477.82	0.43	−1.23	508.73	0.87
σ^2_{AmAm}	30	−0.49	190.39	0.97	−0.45	265.57	0.91
σ^2_{AE}	30	−1.00	350.26	0.88	−0.28	330.18	0.83
σ^2_{DE}	20	0.59	169.62	0.70	0.86	217.79	0.59
σ^2_{AAE}	20	−0.004	35.90	1.00	0.02	42.31	1.00
σ^2_{CE}	20	0.63	129.86	0.99	−0.54	85.29	1.00
σ^2_{AmE}	30	−1.49	1078.28	0.76	−0.98	1507.31	0.82
σ^2_{DmE}	20	−1.00	294.39	0.38	4.01	340.22	0.80
σ^2_{AmAmE}	20	0.34	54.55	0.97	−0.96	385.38	0.88
σ^2_e	20	−0.01	0.29	1.00	0.002	0.49	1.00
Two traits							
$\sigma_{A/A}$	20	0.90	588.19	0.54	0.41	871.18	0.73
$\sigma_{D/D}$	10	0.23	120.89	0.22	−0.31	121.55	0.21
$\sigma_{AA/AA}$	15	−0.24	64.52	0.91	0.10	83.54	0.88
$\sigma_{C/C}$	10	−0.34	167.87	0.72	0.71	127.75	0.69
$\sigma_{Am/Am}$	20	2.81	2860.61	0.71	0.50	3537.37	0.77
$\sigma_{Dm/Dm}$	10	1.30	336.16	0.13	−1.80	366.95	0.79
$\sigma_{AmAm/AmAm}$	15	−0.97	113.13	0.74	0.46	192.12	0.82
$\sigma_{AE/AE}$	15	−0.61	196.40	0.38	−0.92	696.01	0.70
$\sigma_{DE/DE}$	10	0.13	93.11	0.18	0.25	114.75	0.14

Continuation of Table 1　Bias, MSE and power value from simulations by MINQUE (1) with the jackknife procedure followed *t*-test for modified diallel crosses under 500 simulation runs

Parameter	True value	Balanced design			Unbalanced design		
		Bias	MSE	Power	Bias	MSE	Power
$\sigma_{AAE/AAE}$	10	0.10	20.93	0.93	0.03	23.98	0.92
$\sigma_{CE/CE}$	10	−0.03	84.84	0.73	−0.10	57.64	0.72
$\sigma_{AmE/AmE}$	15	−0.06	769.14	0.61	−1.08	999.58	0.61
$\sigma_{DmE/DmE}$	10	−0.53	177.57	0.03	2.125	3449.44	0.68
$\sigma_{AmAm/AmAmE}$	10	0.23	34.71	0.71	−0.59	218.73	0.70
$\sigma_{e/e}$	10	−0.01	0.18	1.00	−0.04	0.27	1.00

3　Worked example of diallel cross for rice seed traits: WBR and WMR

The mating design used in this experiment was a North Carolina II design with 9 females mated to 5 males. The nine cytoplasm male sterile lines and their maintainer lines used as females were Zhexie 2 (P1), Xieqingzao (P2), Zhenan (P3), Gangchao 1 (P4), Yinchao 1 (P5), Erjiuqing (P6), V20 (P7), Zuo 5 (P8) and Zhenshan 97 (P9). The five restorer lines were T49 (P10), Cezao 2-2 (P11), 26725 (P12), 102 (P13) and 1391 (P14)[18-20]. The F_1 generation was obtained by crossing all female parents with male parents in 1994. The seeds of parents and F_1 were sown on April 2 in both 1995 and 1996. Single 30 days old seedlings were transplanted at spaces of 20 cm × 20 cm in the field of the experimental farm at Zhejiang University. The experiment was laid out in a randomized block design with three-fold replication in each block. There were 24 plants in each plot for parents and F_1. Seed samples of parents and F_2 from F_1 plants were collected at maturity from eight plants in the middle of each plot. The seeds of F_1s were obtained by crossing females to males during the florescence. The generations also include backcross of $P_i \times F_1$ and $P_j \times F_1$.

The diallel crosses data set was used to estimate variance components for single trait and covariance components between two traits and to predict the random effect vectors for two traits in *indica* rice (*Oryza stiva* L.). The quantitative traits include weight of brown rice (WBR) and weight of milled rice (WMR). The estimates of variance components for single trait and covariance components between two traits as well as their standard errors are summarized in Table 2.

Table 2　Estimates of variance and covariance components for WBR and WMR in rice

Variance	WBR Estimate ± SE	WMR Estimate ± SE	Covariance	WBR/WMR Estimate ± SE
V_E	0.64 ± 0.08**	3.52 ± 0.41**	C_E	1.55 ± 5.07
V_A	0 ± 0	0 ± 0	C_A	−2.36 ± 4.23
V_D	3.76 ± 0.50**	0.031 ± 0.002**	C_D	1.43 ± 1.48
V_{AA}	6.39 ± 1.13**	6.01 ± 1.11**	C_{AA}	6.07 ± 2.84**
V_C	6.26 ± 1.02**	5.07 ± 0.66**	C_C	5.63 ± 4.48
V_{Am}	0 ± 0	0 ± 0	C_{Am}	−3.31 ± 17.11
V_{Dm}	0 ± 0	0 ± 0	C_{Dm}	−5.88 ± 4.93
V_{AmAm}	7.79 ± 1.18**	5.92 ± 0.77**	C_{AmAm}	7.05 ± 4.09*
V_{AE}	0 ± 0	0 ± 0	C_{AE}	−0.24 ± 0.14**
V_{DE}	5.12 ± 1.13**	5.86 ± 1.32**	C_{DE}	4.73 ± 5.52

Continuation of Table 2 Estimates of variance and covariance components for WBR and WMR in rice

Variance	WBR Estimate ± SE	WMR Estimate ± SE	Covariance	WBR/WMR Estimate ± SE
V_{AAE}	0 ± 0	0 ± 0	C_{AAE}	−3.32 ± 190.79
V_{CE}	5.98 ± 1.00**	3.99 ± 0.57**	C_{CE}	4.13 ± 2.77
V_{AmE}	0 ± 0	0 ± 0	C_{AmE}	−4.89 ± 5.15
V_{DmE}	0 ± 0	0 ± 0	C_{DmE}	−3.06 ± 47.82
V_{AmAmE}	4.66 ± 0.73**	2.79 ± 0.35**	C_{AmAmE}	2.64 ± 7.61
V_e	0.59 ± 0.09**	0.61 ± 0.075**	C_e	0.42 ± 0.071**

Note: * 0.05 significant level; ** 0.01 significant level.

From the zero variance estimates, it was suggested that there is no direct additive, maternal additive, dominance and their interaction effects with environment, as well as direct epistasis by environment interaction effect for traits WBR and WMR. This similar conclusion also could be obtained from the covariance components estimates listed in Table 2.

For both traits, though $\hat{\sigma}^2_A$ was not significant, $\hat{\sigma}^2_{AA}$ was significantly positive. It was indicated that the interactions between some minor genes could increase WBR and WMR for rice. The zero estimation of $\hat{\sigma}^2_{AAE}$ suggested the interactions between minor genes express stably in different environments. It could be concluded that rice plant genome has significantly epistatic effects on both WBR and WMR from the term $\hat{\sigma}^2_{AmAm}$. In practical breeding program, we may get better genetic improvement if the selection was implemented on the direct and maternal epistatic effects. Covariance components between two traits also gave the same results for epistatic effects.

The heritability due to additive and additive by additive epistasis was 0.000 and 0.155 respectively for WBR, and 0.000 with 0.178 for WMR.

4 Discussion

The variance components for single trait and covariance components between two traits in this paper can also be estimated by other statistical methods. Compared to methods of maximum likelihood (ML)[21] and restricted maximum likelihood (REML)[22], MINQUE has the advantages of simple computation and spending less computation load and time. Similarly, compared to the prediction method of adjusted unbiased predition method (AUP), the method of best linear unbiased prediction (BLUP)[23] needs true prior variances, and the method of linear unbiased prediction (LUP) decreases the variance of the predictors for random effect vectors.

From the example data set, the diallel cross between these parental lines could not provide the additive effect, but detect the significant epistatic variation which could be used to direct the selection program and breeding program. It would be caused by the opposite alleles effects, for example there were two QTL to influence the trait but have opposite effects with a and $-a$ respectively on the trait. However, epistatsis could be present between these two QTL or could be caused by the genotype background or the environments. According to classical heritability theory, the general heritability in narrow sense was the proportion of the additive variation from the total phenotype variation. Since the epistasis of 'locus by locus' level could be inherited stably, we should consider the additive by additive epistasis with the additive effect to get the general heritability in narrow sense, which would be higher and accurate than only based on additive.

The genetic model proposed in this paper can analyze the additive by additive epistatic variation

for seed traits. Monte Carlo simulations obtained much higher power for additive by additive epistasis than other genetic effects. It was indicated that it would be better for breeders to construct the genetic model including the additive by additive epistasis. However, in order to obtain more accurate estimates, we need more generations which maybe difficult for breeders. In practice, it would be better for breeders firstly to test the reality of epistasis, and if detecting no epistatic variation, breeders could use the reduced genetic model to analyze the other genetic effects.

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