Chapter 20

Conditional Mapping of QTL with Epistatic Effects and QTL-by-Environment Interaction Effects for Developmental Traits

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Purpose

To map quantitative trait loci (QTL) for net effects due to gene expression from time $t-1$ to t.

Definitions

Genetic Model

For multiple-environment data of doubled haploid (DH) or recombinant inbred line (RIL) populations, the conditional phenotypic value of the jth genetic entry in environment h at time t, given phenotypic value at time $t-1$, can be expressed as the following conditional genetic model:

$$\begin{aligned} y_{hj(t|t-1)} = {} & \mu_{(t|t-1)} + a_{1(t|t-1)} x_{A_{1j}} + a_{2(t|t-1)} x_{A_{2j}} + aa_{(t|t-1)} x_{AA_j} \\ & + u_{E_{hj}} e_{E_{h(t|t-1)}} + u_{A_1 E_{hj}} e_{A_1 E_{h(t|t-1)}} + u_{A_2 E_{hj}} e_{A_2 E_{h(t|t-1)}} + u_{AAE_{hj}} e_{AAE_{h(t|t-1)}} \\ & + \sum_f u_{M_{fj}} e_{M_{f(t|t-1)}} + \sum_l u_{MM_{lj}} e_{MM_{l(t|t-1)}} + \sum_p u_{ME_{hpj}} e_{ME_{hp(t|t-1)}} \\ & + \sum_q u_{MME_{hqj}} e_{MME_{hq(t|t-1)}} + \varepsilon_{hj(t|t-1)} \end{aligned}$$

where $\mu_{(t|t-1)}$ is the conditional population mean; $a_{1(t|t-1)}$ and $a_{2(t|t-1)}$ are the conditional additive effects of loci Q_1 and Q_2, respectively; $aa_{(t|t-1)}$ is the conditional additive × additive epistatic effect of loci Q_1 and Q_2; $x_{A_{1j}}$, $x_{A_{2j}}$, and x_{AA_j} are coefficients of these conditional genetic main effects; $e_{E_{h(t|t-1)}}$ is the conditional random effect of environment h with coefficient $u_{E_{hj}}$; $e_{A_1E_{h(t|t-1)}}$ (or $e_{A_2E_{h(t|t-1)}}$) is the conditional additive × environment interaction effect with coefficient $u_{A_1E_{hj}}$ (or $u_{A_2E_{hj}}$) for Q_1 (or Q_2); $e_{AAE_{h(t|t-1)}}$ is the conditional epistasis × environment interaction effect with coefficient $u_{AAE_{hj}}$; e_{M_f} is the conditional marker main effect with coefficient u_{M_f}; $e_{MM_{l(t|t-1)}}$ is the conditional marker × marker interaction effect with coefficient u_{MM_l}; $e_{ME_{hp(t|t-1)}}$ is the conditional marker × environment interaction effect with coefficient $u_{ME_{hpj}}$; $e_{MME_{hq(t|t-1)}}$ is the marker × marker × environment interaction effect with coefficient $u_{MME_{qhj}}$; and $\varepsilon_{hj(t|t-1)}$ is the conditional residual effect.

Mixed Linear Model

The conditional epistasis QTL model can be expressed in the matrix form as follows:

$$\begin{aligned}
\boldsymbol{y}_{(t|t-1)} &= \boldsymbol{Xb}_{(t|t-1)} + \boldsymbol{U}_E\boldsymbol{e}_{E(t|t-1)} + \boldsymbol{U}_{A_1E}\boldsymbol{e}_{A_1E)t|t-1)} + \boldsymbol{U}_{A_2E}\boldsymbol{e}_{A_2E(t|t-1)} \\
&\quad + \boldsymbol{U}_{AAE}\boldsymbol{e}_{AAE(t|t-1)} + \boldsymbol{U}_M\boldsymbol{e}_{M(t|t-1)} + \boldsymbol{U}_{MM}\boldsymbol{e}_{MM(t|t-1)} \\
&\quad + \boldsymbol{U}_{ME}\boldsymbol{e}_{ME(t|t-1)} + \boldsymbol{U}_{MME}\boldsymbol{e}_{MME(t|t-1)} + \boldsymbol{e}_{\varepsilon(t|t-1)} \\
&= \boldsymbol{Xb}_{(t|t-1)} + \sum_{u=1}^{9} \boldsymbol{U}_u\boldsymbol{e}_{u(t|t-1)} \\
&\sim N(\boldsymbol{Xb}_{(t|t-1)}, \boldsymbol{V}_{(t|t-1)} = \sum_{u=1}^{9} \sigma^2_{u(t|t-1)}\boldsymbol{U}_u\boldsymbol{R}_u\boldsymbol{U}_u^T)
\end{aligned}$$

where $y_{(t|t-1)}$ is the conditional phenotype vector; $\boldsymbol{b}_{(t|t-1)}$ is the conditional fixed parameter vector for conditional population mean and QTL effects; X is the known incidence matrix of the fixed parameters; $e_{1(t|t-1)} = e_{E(t|t-1)} \sim N(0, \sigma^2_{E(t|t-1)}I)$ is the vector of conditional environment effects; $e_{2(t|t-1)} = \boldsymbol{e}_{A_1E(t|t-1)} \sim N(0, \sigma^2_{A_1E(t|t-1)}\boldsymbol{I})$ is the vector of conditional $A_1 \times E$ interaction effects; $\boldsymbol{e}_{3(t|t-1)} = \boldsymbol{e}_{A_2E(t|t-1)} \sim N(0, \sigma^2_{A_2E(t|t-1)}\boldsymbol{I})$ is the vector of conditional $A_2 \times E$ interaction effects; O,$\boldsymbol{e}_4(t/t-1) = \boldsymbol{e}_{AAE}(t/t-1) \sim N\left(0, \sigma^2_{AAE(t|t-1}R_{AAE}\right)$ is the vector of conditional $AA \times E$ interaction effects; $e_{5(t|t-1)} = e_{M(t|t-1)} \sim N(0, \sigma^2_{M(t|t-1)}R_M)$ is the vector of conditional marker main effects; $e_{6(t|t-1)} = e_{MM(t|t-1)} \sim N(0, \alpha^2_{MM(t|t-1)} R_{MM})$ is the vector of conditional interaction marker main effects; $e_{7(t|t-1)} = \boldsymbol{e}_{ME(t|t-1)} \sim N(0, \sigma^2_{MM(t|t-1)} \boldsymbol{R}_{ME})$ is the vector of conditional $M \times E$ interaction effects; $\boldsymbol{e}_{8(t|t-1)} = \boldsymbol{e}_{MME(t|t-1)} \sim N(0, \sigma^2_{MME(t|t-1)} \boldsymbol{R}_{MME})$ is the vector of conditional $MM \times E$ interaction effects; $\boldsymbol{e}_{9(t|t-1)} = \boldsymbol{e}_{\varepsilon(t|t-1)} \sim N(0, \sigma^2_{\varepsilon(t|t-1)} \boldsymbol{I})$ is the vector of conditional residual effects; $\boldsymbol{U}_u (u=1, 2, \ldots, 8)$ is the known incidence matrix of the conditional random effects, and $\boldsymbol{U}_9 = \boldsymbol{I}$.

Analysis Methodology

With observed phenotypic data at time $t-1$ $(y_{(t-1)})$ and time t $(y_{(t)})$, conditional phenotypic data $y_{(t|t-1)}$ can be obtained via mixed model approaches (Zhu, 1995). Then a mixed-model-based composite interval mapping (MCIM) can be used for mapping QTLs with conditional epistatic effects and QTL × environment interaction effects (Zhu, 1998; Zhu and Weir, 1998; Wang et al., 1999). The likelihood function (L) for the parameters of conditional fixed effects $b_{(t|t-1)}$ and conditional variance components $[\sigma^2_{u(t|t-1)}]$ is

$$L(b_{(t|t-1)}, V_{(t|t-1)}) = 2\pi)^{-\frac{n}{2}} \left|V_{(t|t-1)}\right|^{-\frac{1}{2}} \\ \times \exp\left[-\tfrac{1}{2}(y_{(t|t-1)} - Xb_{(t|t-1)})^T V^{-1}_{(t|t-1)} (y_{(t|t-1)} - Xb_{(t|t-1)})\right]$$

with the log of the likelihood function (l)

$$l(b_{(t|t-1)}, V_{(t|t-1)} = -\tfrac{n}{2}\ln(2\pi) - \tfrac{1}{2}\ln\left|V_{(t|-1)}\right| - \tfrac{1}{2}(y_{(t|t-1)} \\ - Xb_{(t|t-1)})^T V^{-1}_{(t|t-1)} (y_{(t|t-1)} - Xb_{(t|t-1)}).$$

For searching QTL, null hypothesis for genetic parameters (conditional QTL main effects and *QE* interaction effects) can be tested by the likelihood ratio statistic (*LR*):

$$LR = 2l_1(\hat{b}_{(t|t-1)1}, V_{(t|t-1)1}) - 2l_0(\hat{b}_{(t|t-1)0}, V_{(t|t-1)0}).$$

The maximum likelihood estimates of QTL effects in $b_{(t|t-1)}$ can be obtained by

$$\hat{b}_{(t|t-1)} = \left(X^T V^{-1}_{(t|t-1)} X\right)^{-1} X^T V^{-1}_{(t|t-1)} y_{(t|t-1)}$$

with variance-covariance matrix

$$\mathrm{var}(\hat{b}_{(t|t-1)}) = X^T V^{-1}_{(t|t-1)} X)^{-1}.$$

Conditional *QE* interaction effects (conditional additive × environment interaction $e_{A_iE(t|t-1)}$ and $e_{A_jE(t|t-1)}$, conditional epistasis × environment interaction $e_{AA_{ij}E(t|t-1)}$) can be obtained by the best linear unbiased prediction (BLUP) method:

$$\hat{e}_{u(t|t-1)} = \sigma^2_{u(t|t-1)} U_u^T Q_{(t|t-1)} y_{(t|t-1)}$$

with variance-covariance matrix

$$\mathrm{var}(\hat{e}_{u(t|t-1)} = \sigma^4_{u(t|t-1)} U_u^T Q_{(t|t-1)} U_u$$

where $Q_{(t|t-1)} = V^{-1}_{(t|t-1)} - V^{-1}_{(t|t-1)} X (X^T V^{-1}_{(t|t-1)} X)^{-1} X^T V^{-1}_{(t|t-1)}$.

Originators

Wang, D., Zhu, J., Li, Z.K., and Paterson, A.H. (1999). Mapping QTLs with epistatic effects and QTL × environment interactions by mixed linear model approaches. *Theoretical and Applied Genetics* 99:1255-1264.

Zhu, J. (1995). Analysis of conditional effects and variance components in developmental genetics. *Genetics* 141(4):1633-1639.

Zhu, J. (1998). Mixed model approaches of mapping genes for complex quantitative traits. In Wang, L.Z. and Dai J.R. (Eds.), *Proceedings of Genetics and Crop Breeding of China* (pp.19-20). Chinese Agricultural Science and Technology Publication House, Beijing.

Zhu, J. and Weir, B.S. (1998). Mixed model approaches for genetic analysis of quantitative traits. In Chen, L.S., Ruan, S.G., and Zhu, J. (Eds.), *Advanced Topics in Biomathematics: Proceedings of International Conference on Mathematical Biology* (pp. 321-330).World Scientific Publishing Co., Singapore.

Software Available

Wang, D., Zhu, J., Li, Z.K., and Paterson, A.H. (1999). QTLMapper Version 1.0: A computer software for mapping quantitative trait loci (QTLs) with additive effects, epistatic effects and QTL × environment interactions. *User Manual for QTLMapper Version 1.0* (program free of charge). Contact Dr. Jun Zhu, Department of Agronomy, Zhejiang University, Hangzhou, China. E-mail:.<jzhu@zju.edu.cn>.

Zhu, J. (1997). GENCOND1.EXE, a computer software for calculating conditional phenotypic data. *Analysis Methods for Genetic Models* (pp. 278-285), Agricultural Publication House of China, Beijing (program free of charge).