

A Weighted AMMI Algorithm to Study Genotype-by-Environment Interaction and QTL-by-Environment Interaction

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ABSTRACT

Genotype-by-environment ($G \times E$) interaction (GEI) and quantitative trait locus (QTL)-by-environment interaction (QEI) are common phenomena in multiple-environment trials and represent a major challenge to breeders. The additive main effects and multiplicative interaction (AMMI) model is a widely used tool for the analysis of multiple-environment trials, where the data are represented by a two-way table of $G \times E$ means. For complete tables, least squares estimation for the AMMI model is equivalent to fitting an additive two-way ANOVA model for the main effects and applying a singular value decomposition to the interaction residuals, thereby implicitly assuming equal weights for all $G \times E$ means. However, multiple-environment data with strong GEI are often also characterized by strong heterogeneous error variation. To improve the performance of the AMMI model in the latter situation, we introduce a generalized estimation scheme, the weighted AMMI or W-AMMI algorithm. This algorithm is useful for studying GEI and QEI. For QEI, the W-AMMI algorithm can be used to create predicted values per environment that are subjected to QTL analysis. We compare the performance of this combined W-AMMI and QTL mapping strategy to direct QTL mapping on $G \times E$ means and to QTL mapping on AMMI-predicted values, again with QTL analyses for individual environments. Finally, we compare the W-AMMI QTL mapping strategy, with a multi-environment mixed model QTL mapping approach. Two data sets are used: (i) data from a simulated pepper (*Capsicum annuum* L.) back cross population using a crop growth model to relate genotypes to phenotypes in a nonlinear way, and (ii) the doubled-haploid Steptoe \times Morex barley (*Hordeum vulgare* L.) population. The QTL analyses on the W-AMMI-predicted values outperformed the QTL analyses on the $G \times E$ means and on the AMMI-predicted values, and were very similar to the mixed model QTL mapping approach with regard to the number and location of the true positive QTLs detected, especially for QTLs associated with the interaction and for environments with higher error variance. W-AMMI analysis for GEI and QEI provides an easy-to-use and robust tool with wide applicability.

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Abbreviations: AMMI, additive main effects and multiplicative interaction; AQ, AMMI analysis followed by QTL scans; EM, expectation maximization; FA, factor analytic; $G \times E$, genotype-by-environment; GEI, genotype-by-environment interaction; IPC, interaction principal component; LOD, logarithm of odds; MET, multiple-environment trials; MS, mean square; QEI, QTL by environment interaction; QTL, quantitative trait loci; SS, sum of squares; $S \times M$, Steptoe \times Morex; SVD, singular value decomposition; SS, sum of squares; WAQ, weighted AQ analysis; W-AMMI, weighted additive main effects and multiplicative interactions.

ADIFFERENTIAL RESPONSE of genotypes across environments (often, location by year combinations) is frequent in multiple-environment trials (METs) and is known as genotype-by-environment ($G \times E$) interaction (GEI). Data from METs are often summarized in two-way tables of means with genotypes in the rows and environments in the columns. GEI occurs in various forms, with the most extreme form consisting of crossover interactions, when ranking of genotypes change across environments (e.g., a genotype that is superior under well watered conditions may yield poorly under dry conditions). While crossover GEI induces a need for narrow adaptation and requires the existence of at least two megaenvironments (Gauch, 2013; Gauch and Zobel, 1997), absence

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of crossover GEI emphasizes the usefulness of the genotypic main effect as a measure for performance and points to broad adaptation. Since the sum of squares (SS) for GEI is often as large as or larger than the SS for genotypic main effects, the study and understanding of narrow adaptations provides an important opportunity to improve phenotypic traits in relation to environmental gradients.

The AMMI model (Gauch, 1992) is one of the most widely used statistical methods to understand and structure interactions between genotypes and environments. In its essence, the AMMI model applies the singular value decomposition (SVD) to the residuals of an additive two-way ANOVA model as applied to the $G \times E$ table of means. However, if there is strong GEI in the data, we also expect the trials to show heterogeneous error variances (Crossa and Cornelius, 1997; Edwards and Jannink, 2006), and this is not taken into account in the standard estimation procedure for the parameters in the AMMI model. Therefore, we propose a generalization of the AMMI model that is able to take into account heterogeneity of error variance by using a weighted low-rank SVD-based algorithm, the weighted AMMI (W-AMMI) algorithm. It should be remarked that our weighting scheme allows the definition of cell specific weights and is therefore applicable to any situation for which differential weighting of cell means is desirable. For example, in the two-stage analysis of METs, individual trials are analyzed taking into account design and spatial types of variation, and vectors of genotypic means and corresponding standard errors are produced in the first stage. These genotypic means are then collected in two-way tables of $G \times E$ means that are subsequently analyzed by weighted mixed models in the second stage (Piepho et al., 2012), where the weights are based on the standard errors of the means. Our W-AMMI approach may be considered as an alternative to these mixed-model analyses.

A natural followup to the analysis of GEI is the study of the genetic factors underlying GEI: QEI. Gauch et al. (2011) proposed using a parsimonious AMMI model to obtain predicted values for $G \times E$ combinations, which are then used in a series of single-environment QTL mappings (AQ analysis). The idea behind using the AMMI predictions for QTL analysis is that these predictions contain more of the relevant genetic signal than the $G \times E$ means. One of our hypotheses is that the weighting by the (reciprocal) of error variances in the AMMI model will not only improve the analysis of GEI, but will equally improve the subsequent QTL analysis. Thus, we present a generalization of the AQ analysis (Gauch et al., 2011) that is able to account for heterogeneity in both genetic variances, captured by the interaction principal components in AMMI—and error variances—by using the weighted generalization of the AMMI model to estimate the interaction scores. This weighted version of the AQ analysis (WAQ analysis) can be conducted in three stages: (i)

compute the (means and) weights for each environment or for each cell of the two-way data table on the basis of the error variances or other relevant weighting schemes, (ii) estimate parameters using the W-AMMI algorithm for analysis of the GEI data table and account for heterogeneity of error variance, and (iii) perform the QTL analysis scans using the predictions from the W-AMMI analysis, the genotypic means, as response variable. In the spirit of AMMI, with our W-AMMI approach we again expect to separate GEI and QEI signal from noise and, therefore, improve the results and interpretations.

Weighted AQ analysis is compared with the QTL analyses on the $G \times E$ means, with the AQ analysis (Gauch et al., 2011) and with a mixed model QTL approach (Boer et al., 2007; Malosetti et al., 2004). Two data sets were used. The first includes yield simulated for a backcross pepper population using a crop growth (physiological) genotype-to-phenotype model (Rodrigues, 2012). The motivation for using this crop growth model, which nonlinearly transforms genotypic information into phenotypic information, is the possibility of simulating a biologically realistic data set while controlling the underlying genetic architecture (Chenu et al., 2009; Tardieu and Tuberosa, 2010; van Eeuwijk et al., 2010). Thus, we explicitly stay away from the common approach for validation of new statistical methods that simulates the data under a configuration beneficial to the new method. The second data set includes the yield for the well-known Steptoe \times Morex barley population, originating from the North American Barley Genome Mapping Project (Hayes et al., 1993).

Weighted AMMI is applicable to a wide range of fields to which AMMI has also been applied, including hundreds of articles referenced by the ISI Web of Science within the last 10 yr. In addition to applications in plant breeding, crop sciences, and genetics, AMMI has been applied to microarray experiments (Crossa et al., 2005), ribosomal DNA studies (Adams et al., 2002), plant and microbial populations' growth across several environmental conditions using terminal restriction fragment length polymorphism data (Culman et al., 2009), animal sciences (Barhdadi and Dube, 2010), and human genetics (Mukherjee et al., 2012).

MATERIALS AND METHODS

Plant Materials

The primary data set of this study is a two-way table with $I = 200$ genotypes and $J = 12$ environments (Table 1) for the complex trait yield. These data were simulated by assuming that yield equals the sum of a signal and noise contribution. The signal for genotype i in environment j was simulated from an ecophysiological genotype-to-phenotype crop growth model for pepper (Rodrigues, 2012), and is a function of parameters that ultimately depend on either genotype or environment, but never on genotype and environment simultaneously. To emphasize this exclusive dependence of the signal on genotype

Table 1. Description of the environments considered in the genotype-to-phenotype crop growth model in Eq. [1]. The countries were chosen to represent different environmental and practical conditions (Rodrigues, 2012). Radiation has two levels (years) based on historical data. Temperature contains three levels of daily average temperature. The heritability for the environments was set to be $h^2 = 0.5$.

| Environment | Country | Radiation | Temperature | Genetic variance | Error variance |
|-------------|-------------|-----------|-------------|------------------|----------------|
| NL1-15 | Netherlands | Lower | 15°C | 18.25 | 21.38 |
| NL1-20 | Netherlands | Lower | 20°C | 47.34 | 40.51 |
| NL1-25 | Netherlands | Lower | 25°C | 44.09 | 41.08 |
| NL5-15 | Netherlands | Higher | 15°C | 37.63 | 35.26 |
| NL5-20 | Netherlands | Higher | 20°C | 68.89 | 67.17 |
| NL5-25 | Netherlands | Higher | 25°C | 71.32 | 68.36 |
| SP1-15 | Spain | Lower | 15°C | 11.29 | 9.96 |
| SP1-20 | Spain | Lower | 20°C | 22.49 | 19.68 |
| SP1-25 | Spain | Lower | 25°C | 23.17 | 20.63 |
| SP5-15 | Spain | Higher | 15°C | 12.41 | 13.24 |
| SP5-20 | Spain | Higher | 20°C | 27.95 | 26.25 |
| SP5-25 | Spain | Higher | 25°C | 29.19 | 27.60 |

or environment we write below Signal_{iVj} , where otherwise we would have written Signal_{ij} .

The model follows the classical physiological setup of radiation (light) limited growth: yield = amount of radiation intercepted \times efficiency with which radiation is converted into biomass \times fraction of biomass dedicated to yield. In full detail the model can be written as:

$$\begin{aligned} \text{Yield}_{i,j} &= \text{Signal}_{iVj} + \text{Noise}_{i,j} \\ &= (\text{Radiation intercepted} \times \text{Conversion efficiency} \times \\ &\quad \text{Partitioning to yield})_{iVj} + \text{Noise}_{i,j} \\ &= \left\{ \sum_{t=t_0}^{t_f} \left[1 - \exp(-K_i[\text{LAI}_{i,j,t}]) \right] I_{j,t} \right\} \\ &\quad \left\{ \text{LUE}_{i,j} \right\} \left\{ \frac{\text{FTF}_i \left[1 - W_i(T_j - T_{\text{FTF}}) \right]}{\text{FDMC}_i} \right\} + \varepsilon_{i,j} \quad [1] \end{aligned}$$

The radiation intercepted, on the left-hand side of Eq. [1], depends on the following: (i) the light extinction coefficient (K_i); (ii) the leaf area index for genotype i in environment j and day t , i.e., $\text{LAI}_{i,j,t} = [a + B_i(T_j - T_{\text{base}})(t - t_0)]Sd_j$, where a and B_i are a general, genotype-independent intercept and a specific, genotype-dependent slope for the regression of leaf area per stem (m^2) on temperature sum ($^{\circ}\text{C d}^{-1}$), T_j is the mean temperature for environment j , T_{base} is a base temperature, t represents the t -th day of the relevant part of the growing season ($t = t_0$ is the day of the first flowering), and Sd_j is the stem density for environment j ; and (iii) $I_{j,t} = \text{RAD}_{j,t} \times F_{\text{PAR}} \times Tr_j$ is the photosynthetic active radiation incident on the crop for environment j on day t , i.e., the product of (i) global radiation at day t in environment j ($\text{RAD}_{j,t}$), (ii) fraction of photosynthetic active radiation (PAR) in global radiation (F_{PAR}), and (iii) greenhouse transmissivity in environment j (Tr_j). The constants t_0 and t_f represent the beginning and the end of the relevant part of the

Table 2. Genetic architecture of the simulated yield data for pepper (signal). The first columns give the name of the parameter of the Model [1] associated to the simulated quantitative trait loci (QTL), the code for the closest marker, the chromosome, the position, and its (broad-sense) heritability. The last column gives an indication, based on a sensitivity analysis, of which kind of environments are expected to show QTL detections.

| Parameter [†] | Marker | Chromosome | Position (cM) | Heritability | Importance [‡] |
|------------------------|--------|------------|---------------|--------------|-------------------------|
| K | D1M6 | 1 | 38.0 | 0.95 | None |
| LUE | D2M13 | 2 | 55.0 | 0.16 | All |
| B | D3M10 | 3 | 87.3 | 0.95 | None |
| FTF | D4M9 | 4 | 83.1 | 0.80 | All |
| FDMC | D5M25 | 5 | 103.3 | 0.80 | All |
| W | D6M12 | 6 | 36.7 | 0.20 | 20°C; 25°C |
| LUE | D7M5 | 7 | 42.5 | 0.16 | All |
| LUE | D8M7 | 8 | 38.8 | 0.16 | All |
| W | D9M15 | 9 | 100.4 | 0.20 | 20°C; 25°C |
| LUE | D10M5 | 10 | 43.1 | 0.16 | All |
| Z | D11M11 | 11 | 62.4 | 0.80 | 15°C |

[†] B, genotype-specific slope for the regression of leaf area per stem on temperature sum; FDMC, fruit dry matter content; FTF, fraction of dry weight partitioned to the fruits; K, light extinction coefficient; LUE, light use efficiency; W, scaling constant related to light use efficiency; Z, scaling constant related to fraction of dry weight partitioned to the fruits.

[‡] Based on a sensitivity analysis with heritability of 1 for all environments (Table 1).

growing season, in days. The light use efficiency for genotype i in environment j ($\text{LUE}_{i,j}$) is dependent on the temperature via a parameter Z_i —the slope of the linear reduction in LUE for temperatures below 20°C. To keep our formula readable, we do not show this dependency of LUE on temperature. The complete expression can be found in Rodrigues (2012). The partitioning to yield, as described on the right-hand side of Eq. [1], is defined by a combination of the fraction of dry weight partitioned to the fruits (FTF), fruit dry matter content (FDMC), and the slope of the linear reduction in harvest index with temperatures above 15°C (W_i).

Model [1] is a function of seven physiological parameters that depend on the genotype. In addition, three environmental variables are considered: temperature, with three levels: low (15°C), medium (20°C), and high (25°C); radiation, with two levels (years) based on historical weather data per country; and country, with two levels: Spain and The Netherlands, representing contrasting environmental and practical conditions (Table 1). Each of the seven physiological parameters (i.e., component traits) was simulated as a sum of a number of QTL effects (Table 2) plus a residual (genetic) effect specific to the physiological parameter. Our simulation is inspired by a system of 200 pepper genotypes characterized by 237 markers covering all the 12 chromosomes, following Barchi et al. (2007). We placed 11 potential QTLs along the 12 chromosomes of the pepper genome. The exact positions of these yield component QTLs and their heritabilities are reported in Table 2. The QTLs that were simulated for yield components were assumed to be picked up as QTLs for yield in QTL analyses of yield. The last column of Table 2 gives the importance of the QTLs for

the component traits as contributing to yield, on the basis of a sensitivity analysis. The simulations were made using the function sim.cross from the package qtl (Broman and Sen, 2009) of the statistical software R (R Development Core Team, 2011). This function allows simulation of additive QTLs for the yield components and control of their heritabilities.

Our main motivation for using a nonlinear physiological genotype-to-phenotype model instead of a linear statistical model is to ensure that the simulated data stem from a biologically realistic model in which we have complete information on the underlying genetic architecture and its translation to the phenotype.

The noise component for yield in Eq. [1], $\varepsilon_{i,j}$, was simulated from a multivariate Gaussian distribution with zero mean vector and variance-covariance matrix $\sigma_{\varepsilon_j}^2 \mathbf{I}_n$, where $\sigma_{\varepsilon_j}^2, j = 1, \dots, J$, depends on the environment (Table 1) and on the chosen (broad-sense) heritability for yield (h^2 , Table 2), i.e.:

$$\sigma_{\varepsilon_j}^2 = \frac{1-h^2}{h^2} \sigma_{g_j}^2,$$

where $\sigma_{g_j}^2$ and $\sigma_{\varepsilon_j}^2$ are the genetic (noise-free yields as simulated from the ecophysiological genotype-to-phenotype model) and error variances for the environment $j = 1, \dots, J$ (Table 1). The final yield data is the result of the sum of the signal and the noise components, as in Eq. [1]. This simulation was repeated 100 times resulting in 100 two-way tables with 200 genotypes by 12 environments.

The crop growth model to simulate the yield data contains a number of nonlinearities as well as contributions from noise terms entering at different levels in the model. Therefore, from the model definition in Eq. [1], it cannot be deduced straightforwardly how strong GEI will be for a given simulation configuration and how many interaction principal components in an AMMI model will be required to provide a decent approximation to the simulated GEI.

The second data set in our study is a subset of the grain yield data from the Steptoe \times Morex ($S \times M$) cross, produced by the North American barley genome mapping project (Hayes et al., 1993). The original data included 150 doubled haploid genotypes evaluated in 16 trials, or environments, during 1991 and 1992, in the United States and Canada. The genotypes were characterized by 223 markers covering all seven chromosomes and a subset of 116 markers was used in this study. We removed trials without any replications, resulting in a set of trials that were either fully replicated in a randomized complete block design with two blocks (1992 trials) or partially replicated with one complete block and a second block containing 50 genotypes (1991 trials). The remaining 13 trials or environments (replicated or partially replicated) were then reduced to eight with a more homogeneous heritability, in this case $h^2 \in [0.49; 0.66]$, to match the conditions assumed in simulations for the first case study. The case where the heritabilities were not homogeneous across environments is analyzed in the discussion. The details of the selected eight environments are presented in Table 3.

AMMI Analysis

The AMMI model (Gauch, 1992) combines the features of ANOVA and SVD, where the ANOVA estimates the additive main effects and the SVD—applied to the residual from the additive

Table 3. The eight environments used in the Steptoe \times Morex analysis. The environments are either fully replicated randomized complete block designs with two blocks, or partially replicated block designs with 50 genotypes replicated in a second block. The trials conducted in 1991 have a full replicate (block) and a second one containing only 50 genotypes. The trials conducted in 1992 have two complete replications.

| Environment [†] | Full replication | Genetic variance | Error variance | Heritability |
|--------------------------|------------------|------------------|----------------|--------------|
| ID91 | No | 0.94 | 0.74 | 0.56 |
| ID92 | Yes | 0.55 | 0.42 | 0.57 |
| MAN92 | Yes | 0.38 | 0.20 | 0.66 |
| MIN92 | Yes | 0.35 | 0.37 | 0.49 |
| MTd92 | Yes | 0.43 | 0.31 | 0.58 |
| MTi91 | No | 0.36 | 0.23 | 0.61 |
| MTi92 | Yes | 0.43 | 0.31 | 0.58 |
| WA91 | No | 0.72 | 0.71 | 0.50 |

[†] ID91, Idaho 1991; ID92, Idaho 1992; MAN92, Manitoba 1992; MIN92, Minnesota 1992; MTd92, Montana dryland 1992; MTi91, Montana irrigated 1991; MTi92, Montana irrigated 1992; WA91 Washington 1991.

ANOVA—models the interaction via $N \leq \min(I - 1, J - 1)$ axes (or interaction principal components [IPCs]), with I the number of genotypes (rows) and J the number of environments (columns). Assuming, for simplicity, a completely randomized design for individual trials, the model can be written as (Gauch, 1992):

$$\gamma_{i,j,k} = \mu + \alpha_i + \beta_j + \sum_{n=1}^N \lambda_n \gamma_{n,i} \delta_{n,j} + \rho_{i,j} + \varepsilon_{i,j,k}, \quad [2]$$

where $\gamma_{i,j,k}$ is the phenotypic trait (e.g., yield) of genotype i in environment j for replicate k , μ is the grand mean, α_i are the genotype main effects as deviations from μ , β_j are the environment main effects as deviations from μ , λ_n is the singular value for the IPC axis n , $\gamma_{n,i}$ and $\delta_{n,j}$ are the genotype and environment IPC scores (i.e., the left and right singular vectors) for axis n , $\rho_{i,j}$ is the residual containing all multiplicative terms not included in Model [2], and $\varepsilon_{i,j,k}$ is the experimental error. Model [2] can be written in matrix formulation as follows:

$$\mathbf{Y} = \mathbf{1}_I \mathbf{1}_J^T \boldsymbol{\mu} + \boldsymbol{\alpha}_I \mathbf{1}_J^T + \mathbf{1}_I \boldsymbol{\beta}_J^T + \mathbf{UDV}^T + \boldsymbol{\varepsilon}. \quad [3]$$

Here, \mathbf{Y} is the $(I \times J)$ two-way table of genotypic means across trials or environments. Each column of \mathbf{Y} represents the vector of genotypic means as obtained from the phenotypic analysis of a corresponding trial by an appropriate mixed model analysis that accounts for experimental design features and spatial trends. The additive part of the model contains the term $\mathbf{1}_I \mathbf{1}_J^T \boldsymbol{\mu}$, an intercept term, being an $(I \times J)$ matrix with the grand mean μ in all positions, $\boldsymbol{\alpha}_I \mathbf{1}_J^T$, an $(I \times J)$ matrix of genotypic main effects, as deviations from the grand mean (equal rows), and $\mathbf{1}_I \boldsymbol{\beta}_J^T$, an $(I \times J)$ matrix of environmental main effects, as deviations from the grand mean (equal columns). The interaction part of the model, $\mathbf{Y}^* = \mathbf{Y} - \mathbf{1}_I \mathbf{1}_J^T \hat{\boldsymbol{\mu}} - \hat{\boldsymbol{\alpha}}_I \mathbf{1}_J^T - \mathbf{1}_I \hat{\boldsymbol{\beta}}_J^T$, is approximated by the matrix product \mathbf{UDV}^T , with \mathbf{U} an $(I \times N)$ matrix whose columns contain the left singular vectors of the interaction, \mathbf{D} an $(N \times N)$ diagonal matrix containing the singular

values of \mathbf{Y}^* , and \mathbf{V} a $(J \times N)$ matrix whose columns contain the right singular vectors of the interaction. The residual in Eq. [3], the $(I \times J)$ matrix $\boldsymbol{\varepsilon}$, contains both the lack of fit term of Model [2], $\rho_{i,j}$, and the error term of Model [2], $\varepsilon_{i,j,k}$. The lack of fit term results from the part of the GEI not explained by the N multiplicative terms in Eq. [2] and [3]. The intention is to find a low rank (N) approximation to the matrix \mathbf{Y}^* (i.e., to the GEI). With regard to the signal in the biological Model [1], we try to approximate this signal by a two-way model with the genotypic and environmental main effects as well as a minimum number of multiplicative terms for GEI.

The number of interaction terms in the model, N , has to be chosen wisely as it will affect all the subsequent results (Gauch, 2013; Gauch et al., 2008; Yang et al., 2009). For an unweighted AMMI approach, we use a crossvalidation-based method proposed by Eastment and Krzanowski (1982) for principal component analysis and then generalized by Dias and Krzanowski (2003, 2006) for the AMMI model, applied to the two-way table of $G \times E$ means. This crossvalidation procedure assumes that we wish to predict the elements $y_{i,j}^*$ of the data matrix \mathbf{Y}^* , using the model $y_{i,j}^* = \sum_{n=1}^N \lambda_n \gamma_{n,i} \delta_{n,j} + \varepsilon_{i,j}$. We are then able to compute the average squared discrepancy between the actual and predicted values:

$$\text{PRESS}(n) = \frac{1}{IJ} \sum_{i=1}^I \sum_{j=1}^J (\hat{y}_{i,j}^{(n)} - y_{i,j})^2, \quad [4]$$

and, consequently, the statistic

$$W_n = \frac{\text{PRESS}(n-1) - \text{PRESS}(n)}{D_n} \div \frac{\text{PRESS}(n)}{D_r}, \quad [5]$$

where $\hat{y}_{i,j}^{(n)}$ is the predicted value—not using $y_{i,j}$ —from the AMMI model with n multiplicative terms, D_n is the number of degrees of freedom pertaining to the n th multiplicative term, $I + J - 2n - 1$, and D_r the number of degrees of freedom that remain after having fitted the n th component, to be obtained by subtracting the sum of the numbers $I + J - 2n - 1$ from the total of $(I-1)(J-1)$. The W_n represent the increase in predictive information supplied by the n th component, divided by the average predictive information in each of the remaining components (Dias and Krzanowski, 2003, 2006; Eastment and Krzanowski, 1982). Krzanowski (1987) suggested that the optimal number of components is the highest number of n such that W_n is greater than the unit. Further details can be found elsewhere (Bro et al., 2008; Eastment and Krzanowski, 1982; Krzanowski, 1987). In fact, the purpose of such tests is to find the peak of the Ockham's hill to maximize predictive accuracy. Simpler models, with fewer parameters than the optimal, underfit real signal and more complicated models, with more parameters than the optimal, overfit spurious noise (Gauch, 2012).

Weighted AMMI Analysis

When the error variance in the two-way data table \mathbf{Y} is heterogeneous across environments, the cells of the table should have different weights for their squared residuals in the estimation procedure for the model parameters. More generally,

when the error variance–covariance structure for the genotypic means differs between trials or environments because blocks, incomplete blocks, and spatial trends have different variances and correlations, then this heterogeneity needs to be accounted for in subsequent GEI analyses. To account for heterogeneity of error structures across environments, our proposal is therefore: (i) to fit additive main effects by weighted least squares and subsequently obtain interaction residuals by subtraction and then (ii) to use a weighted SVD to estimate the multiplicative interaction terms in Eq. [3]. Various options are possible for the weights, but as a general recommendation, the weights for the genotypic means in a particular trial can be derived as a function from the diagonal elements of the inverse of the error variance–covariance matrix for the genotypic means (Smith et al., 2001; Möhring and Piepho, 2009; Welham et al., 2010), where some rescaling will be necessary to keep the weights between the values of 0 and 1, required for the weighted SVD algorithm described below.

The approach we use here for the weighted low-rank SVD for a target matrix \mathbf{Z} , containing the interaction residuals, is based on an expectation–maximization (EM) algorithm (Srebro and Jaakkola, 2003), and while the sum of squares of the difference between two consecutive iterations, $\mathbf{X}^{(t+1)}$ and $\mathbf{X}^{(t)}$, is greater than some small value (e.g., 10^{-9}) we compute

$$\mathbf{X}^{(t+1)} = \text{SVD}[\mathbf{W} \odot \mathbf{Z} + (\mathbf{1} - \mathbf{W}) \odot \mathbf{X}^{(t)}] \quad [6]$$

where \mathbf{W} is an $(I \times J)$ matrix with weights $W_{i,j}$, $0 \leq W_{i,j} \leq 1$, $\mathbf{1}$ is an $(I \times J)$ matrix with ones in all positions, \odot is the Hadamard (or entrywise) product of matrices, and t is the iteration number (Srebro and Jaakkola, 2003). \mathbf{X} is a low-rank approximation, with $\text{rank}(\mathbf{X}) = N$, to \mathbf{Z} and should be initialized with $\mathbf{X}^{(0)} = \mathbf{Z}$ or to $\mathbf{X}^{(0)} = \mathbf{0}$ to promote the convergence to a global minimum (Srebro and Jaakkola, 2003). The outputs of this procedure are the matrices \mathbf{U}_N , \mathbf{D}_N and \mathbf{V}_N such that $\mathbf{Y}^* \approx \mathbf{U}_N \mathbf{D}_N \mathbf{V}_N^T$, N being the rank of approximation to the interaction residuals. The rank of the approximation, N , needs to be decided on before the weighted estimation can start. For convenience, we chose this rank equal to the number of interaction terms determined to be important in the unweighted AMMI approach, using the Eastment and Krzanowski (1982) procedure described above. Weighting should, in general, reduce the complexity of the interaction, so that the unweighted assessment of the number of interaction terms can provide a kind of upper bound on the complexity of the GEI in the weighted analysis. We acknowledge that more work is required on this topic.

Applying the weighted low-rank SVD [6] to the matrix \mathbf{Y}^* , after taking into consideration the weighted main effects and combining it with the model in Eq. [3] will result in the W-AMMI algorithm. This generalization of the AMMI model is now able to account for cell specific weights, including differences in error variances, across environments and can be applied to all data sets where the AMMI model is appropriate or suitable. The R code for this algorithm, with detailed explanation, can be found in Supplemental File S1.

For the case of the analysis of the Steptoe \times Morex analysis, we calculated the weights as follows. When dealing with partial replications, cell means based on replicated observations will

bring more information to the model than those based on single observations. The scheme of weights should reflect the number of replications per cell. The $(I \times J)$ matrix with weights \mathbf{W} , $0 \leq W_{i,j} \leq 1$, for this new scheme of weights, can be calculated from the Hadamard (or entrywise) product of two matrices: (i) a matrix in which the entries are columnwise constant as the inverse of the error variance and (ii) a matrix with the proportion of replications per cell, i.e.

$$\mathbf{W} = \begin{bmatrix} \frac{1/\sigma_1^2}{m} & \frac{1/\sigma_2^2}{m} & \dots & \frac{1/\sigma_J^2}{m} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{1/\sigma_1^2}{m} & \frac{1/\sigma_2^2}{m} & \dots & \frac{1/\sigma_J^2}{m} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{1/\sigma_1^2}{m} & \frac{1/\sigma_2^2}{m} & \dots & \frac{1/\sigma_J^2}{m} \end{bmatrix} \odot \begin{bmatrix} \text{Nrep}_{1,1} & \text{Nrep}_{1,2} & \dots & \text{Nrep}_{1,J} \\ \text{Nrep} & \text{Nrep} & \dots & \text{Nrep} \\ \text{Nrep}_{2,1} & \text{Nrep}_{2,2} & \dots & \text{Nrep}_{2,J} \\ \text{Nrep} & \text{Nrep} & \dots & \text{Nrep} \\ \vdots & \vdots & \ddots & \vdots \\ \text{Nrep}_{I,1} & \text{Nrep}_{I,2} & \dots & \text{Nrep}_{I,J} \\ \text{Nrep} & \text{Nrep} & \dots & \text{Nrep} \end{bmatrix}, \quad [7]$$

where I is the number of genotypes, J the number of environments, $m = \max(1/\sigma_{\varepsilon_j}^2)$, $\sigma_{\varepsilon_j}^2, j = 1, \dots, J$, is the error variance for environment j , $\text{Nrep}_{i,j}, i = 1, \dots, I, j = 1, \dots, J$, the number of replications for genotype i in environment j , and Nrep is the maximum number of replications in the data set.

Weighted AQ Analysis

Gauch et al. (2011) suggested a new approach for detecting and understanding QEIs, the AQ analysis, where the QTL scans are made based on AMMI predictions (instead of direct QTL scans on the $G \times E$ means). In this paper, we make use of the above proposed weighted version of the AMMI model, the W-AMMI, to generalize the AQ analysis to account for both heterogeneous genetic (SVD) and error variances (weights) across environments. We use a fixed effects model approach with additional weighting schemes in the estimation of the parameters as a simple, quick, and robust approximation to the mixed model QTL approach described by (Boer et al., 2007; Malosetti et al., 2004). The weighted AQ analysis consists in performing QTL scans on W-AMMI-predicted values for each environment separately. This approach can potentially improve the power for QTL detection because it uses improved genotypic predictions in comparison to the cell means from the ANOVA model. The environments can then be ordered by AMMI and W-AMMI parameters that summarize GEI and QEIs information to reveal consistent patterns and systematic trends that often can be explained in terms of environmental conditions (Gauch, 1992; Gauch et al., 2011).

Linear Mixed Models

As a kind of benchmark for QTL analysis, we also analyzed the simulated pepper and Steptoe \times Morex barley data by a

QTL analysis based on mixed models, as described by Boer et al. (2007) and implemented in GenStat 14 and later versions of GenStat (Payne et al., 2011). For a standard biparental breeding population, the final multi-QTL mixed model in Boer et al. (2007) is written as

$$y_{i,j} = \mu + \beta_j + \sum_{q=1}^Q x_{i,q} \alpha_{q,j} + \varepsilon_{i,j} \quad [8]$$

with μ an intercept; β_j an environmental main effect; $x_{i,q}$ a so-called genetic predictor related to the probability that for a genotype i at a particular genomic position q , the alleles are coming from one or the other parent; and $\alpha_{q,j}$ the allele substitution value for a QTL q in environment j . The allele substitution values in Eq. [8] are thus dependent on the environment and are the sum of a QTL main effect and a QEI. The residual term, $\varepsilon_{i,j}$, feeds on polygenic effects, where the variance-covariance matrix for this residual should allow for heterogeneity of genetic variances and correlations across environments. When the number of environments becomes larger, the number of genetic variances and covariances that needs to be estimated rapidly grows, i.e., for J environments, we would need J variances and $J(J - 1)/2$ covariances, making in total $J(J + 1)/2$ variance-covariance parameters. To reduce the number of parameters for estimation while retaining flexibility for modeling heterogeneity of variances and covariances, various types of more-parsimonious models have been proposed, with the so-called factor analytic (FA) models being the most popular ones. In FA models, the products of environmental scores lead to approximations for genetic covariances, while variances are fitted by squares of the same scores and an additional environment-specific residual variance. For example, the covariance between environment j and j^* is $\sigma_{j,j^*} = \lambda_j \lambda_{j^*}$, and the genetic variance for environment j is $\sigma_j^2 = \lambda_j^2 + \varphi_j^2$, with λ_j an environmental score for environment j and φ_j^2 an environment-specific residual variance. The latter environment-specific variance will contain contributions from both genetic and nongenetic (plot error) sources of variance, but appropriate choice of weights will increase the amount of genetic variance. The environmental scores in the FA model are mixed model analogues of the environmental scores in AMMI models. Also, in FA models, more than one multiplicative term can be included. We remark here that the environmental scores for the FA variance-covariance model for the residual $\varepsilon_{i,j}$ in Model [8] are more comparable to the environmental scores in the so-called GGE models (Yan and Kang, 2003), with GGE standing for genotypic main effects and GEI, than with the environmental scores in AMMI models, because in Eq. [8] we include the environmental main effect as in GGE models, but not both genotypic and environmental main effects as in AMMI models.

The input for the mixed model QTL analysis in Boer et al. (2007) consists of the genotype-by-environment means and corresponding weights, defined in the same way that was used for W-AMMI and WAQ analysis. The mixed model QTL mapping procedure initially scans the genome fitting models containing a single QTL only ($Q = 1$ in Model [8]), but this single QTL has environment-specific effects. Typically, a simple interval mapping scan is followed by one or more composite interval mapping scans. A final multi-QTL model is selected by backward elimination

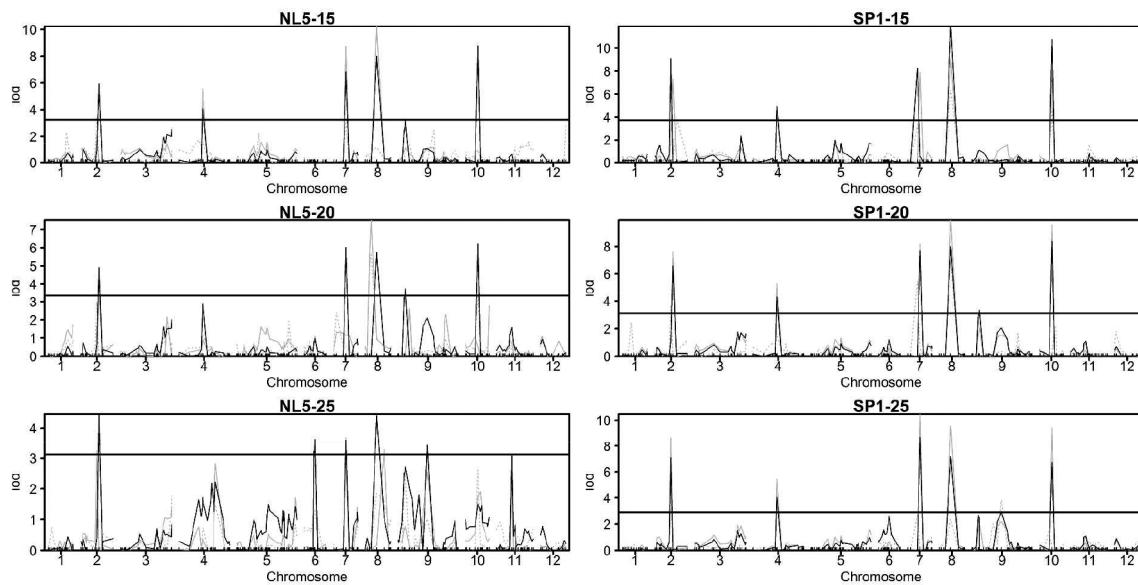


Figure 1. Quantitative trait loci scans for six environments of the yield data for the pepper population, simulated from the genotype-to-phenotype model with seven physiological parameters, as in Eq. [1]. Each row represents a different level of temperature. The plots on the left correspond to the highest error variance in this simulated data table and the ones on the right to the lowest. The dashed grey line represents the scans for the actual data, the grey line represents the scans for the additive main effects and multiplicative interaction (AMMI) 2-predicted values, and the black line represents the scans for the weighted AMMI2-predicted values. All scans are based on composite interval mapping. The horizontal lines correspond to the thresholds based on a permutation test with 1000 permutations at the 0.05 significance level. These scans are based on one randomly chosen realization out of the 100 simulations. The codes for the captions of the individual scans are described in Table 1.

from a model containing all identified QTLs of the last composite interval mapping scan. The threshold level for the Wald test for QTL detection is based on a multiple testing correction as developed by Li and Ji (2005). Further details can be found in Boer et al. (2007), van Eeuwijk et al. (2010), and Malosetti et al. (2013).

RESULTS FOR THE SIMULATED DATA

Preliminary Analysis

Table 2 gives the simulation conditions with the “true” genetic architecture for the pepper population under study. Figure 1 (dashed grey line) depicts the single trait single environment QTL scans for 6 environments of the complex trait yield simulated from the physiological genotype-to-phenotype model with seven physiological parameters (Rodrigues, 2012). The six environments were chosen to represent the three levels of temperature with the lowest and highest error variances. Comparing the “true” genetic architecture in Table 2 and the QTLs detected in Fig. 1 and Supplemental Fig. S1 (QTL scans for all 12 environments) for the $G \times E$ means, only those associated with the parameters LUE (22 out of the expected $48 = 12$ environments times 4 chromosomes; Table 2) and W (three out of the expected $16 = 8$ environments with temperatures of 20°C or 25°C times 2 chromosomes; Table 2) were found, which represents a poor outcome of this single-trait single-environment analysis.

AMMI Analysis

Table 4 gives the ANOVA for the AMMI5 model, based on one randomly-chosen realization of a

Table 4. Analysis of variance of the additive main effects and multiplicative interaction model 5 for the simulated yield data for pepper. Results based on one randomly chosen realization (out of 100) of the genotype-to-phenotype crop growth model.

| Source [†] | df | SS [‡] | MS [§] |
|---------------------|------|-----------------|-----------------|
| Total | 2399 | 256,089 | 106.7 |
| Genotypes | 199 | 80,774 | 405.9 |
| Environments | 11 | 88,054 | 8004.9 |
| GEI | 2189 | 87,261 | 39.9 |
| IPC1 | 209 | 18,122 | 86.7 |
| IPC2 | 207 | 14,740 | 71.2 |
| IPC3 | 205 | 11,470 | 56.0 |
| IPC4 | 203 | 10,074 | 49.6 |
| IPC5 | 201 | 7,916 | 39.4 |
| IPC6–IPC11 | 1164 | 24,938 | 21.4 |

[†] GEI, genotype-by-environment interaction; IPC, interaction principal component.

[‡] SS, sums of squares.

[§] MS, mean squares.

genotype-by-environment two-way data table. Similar results are obtained for other two-way data tables simulated from the model in Eq. [1]. The genotypes, environments, and GEI account for 31.5, 34.4, and 34.1% of the treatment sum of squares (SS). Two interaction principal components were chosen for the AMMI model, as in Rodrigues (2012). This choice was confirmed by the cross-validation procedure proposed by Krzanowski (1987): the W_n values from Eq. [5] for the first five components are 10.371, 1.385, 0.579, 0.517, and 0.415, which means that the “best” model

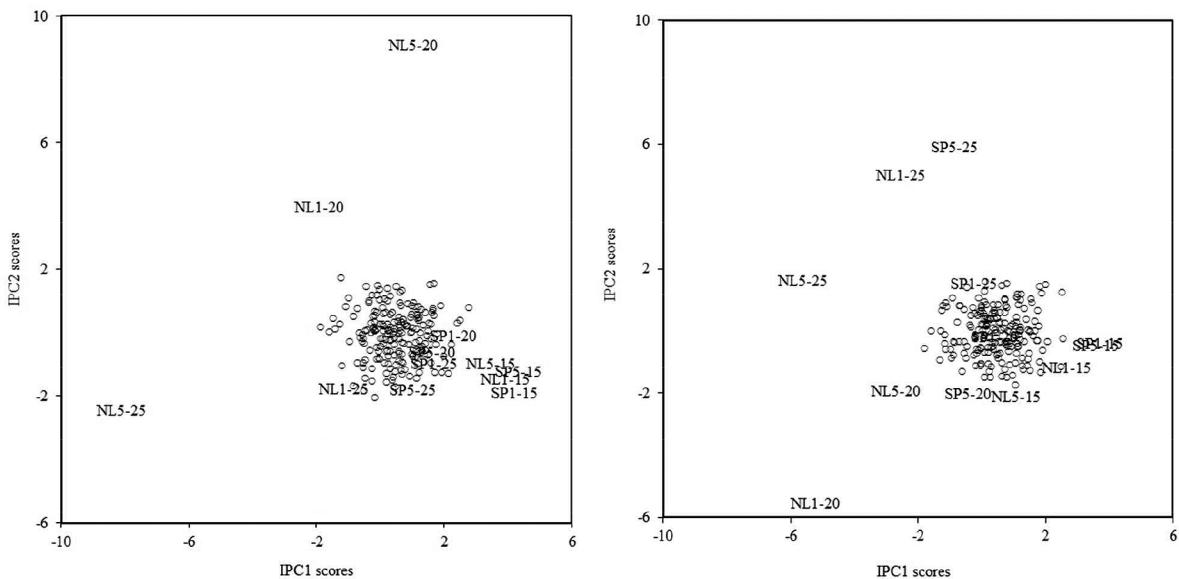


Figure 2. Additive main effects and multiplicative interaction (AMMI) with 2 multiplicative terms (left) and weighted AMMI2 (right) biplots based on one randomly chosen realization out of the 100 simulations. The abscissa represents the first multiplicative term and the ordinate represents the second. The open dots represent the 200 genotypes, and the codes for the 12 environments are defined in Table 1.

has two principal components because only two W_n values are above unity.

The AMMI2 biplot is depicted on the left-hand side of Fig. 2, with the first and second principal components explaining 20.8 and 16.9% of the interaction sum of squares. In this figure, the environments with higher error variance (NL5-20 and NL5-25; Table 1) are farthest away from the origin, showing an extreme behavior when compared with the remaining environments. However these environments with higher genetic variance also have higher error variance (Table 2). The latter heterogeneity of error variance should be incorporated in a weighted analysis of the $G \times E$ data to produce a potentially more reliable result in terms of visualization and QTL detection. This can be achieved by giving smaller weights to the environments with higher error variance.

Weighted AMMI Analysis

To avoid considering environments with high error variance as outliers (Gauch et al., 2011) or letting them influence (too much) the results, the weighted AMMI analysis described above was used. The contribution (i.e., the weight) of a given environment to the model fit was determined by the inverse of its error variance (Table 1). The W-AMMI biplot is given in Fig. 2 (right) and represents the model with the two components after convergence, with the first and second principal components explaining about 20.7 and 12.6% of the variation in the interaction (i.e., the proportion of the total SS for interaction explained by each component). These percentages of explained variance are lower when compared with the ones from the AMMI analysis because, when using the \mathbf{W} matrix as in Eq. [6], the column variation tends to become

more homogeneous and, therefore, the singular values of the decomposition in Eq. [6] become smaller and closer to each other. In this plot, the environments SP5-20 and SP5-25 ceased to show extreme behavior. There is also a pattern visible in the environments: (i) the right-hand side presents more Spanish environments, whereas the left-hand side has more Dutch environments, making a distinction regarding different environmental and practical conditions (Rodrigues, 2012); and (ii) the bottom right corner shows environments with temperatures of 15°C, the top left corner shows environments with temperatures of 25°C, and in between are placed the environments with temperatures of 20°C.

AQ and WAQ Analyses

The AQ analysis is obtained by fitting the AMMI model to the $G \times E$ table of means, followed by making QTL scans on the AMMI-predicted values for each environment (Gauch et al., 2011). The WAQ analysis is a generalization of the AQ analysis, where the AMMI analysis is replaced by the weighted AMMI analysis proposed before. Weighted AMMI and WAQ analyses are particularly useful to analyze data sets whose environments show high heterogeneity in their error variances and/or with different number of replications.

Figure 1 shows the AQ (grey line) and WAQ (black line) analyses for models with two IPCs. There is a clear improvement from the QTL scans of the $G \times E$ means to the AQ and WAQ analysis in both the number of detected QTLs and height of logarithm of odds (LOD) scores. As in the biplots of Fig. 2, the improvement from the unweighted to the weighted method is visible in Fig. 1 and Supplemental Fig. S1 for AQ and WAQ analysis, in

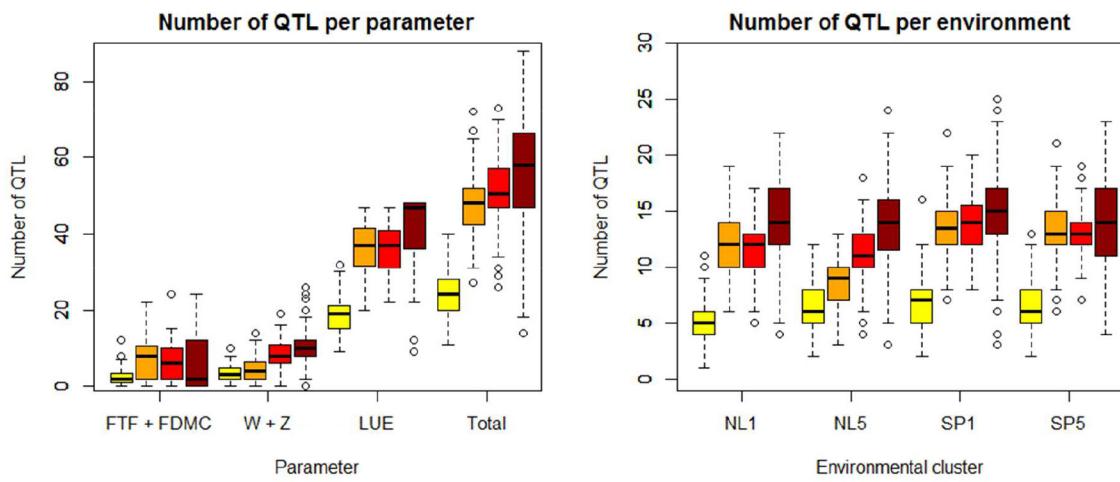


Figure 3. Summary of the number of detected quantitative trait loci (QTLs) for the genotype-by-environment means (yellow), additive main effects and multiplicative interaction (AMMI) 2-predicted values (orange), weighted AMMI2-predicted values (red), and linear mixed model (dark red). The graph on the left-hand side shows the boxplots for the number of detected QTLs per model parameter (Table 2), and the graph on the right-hand side shows the number of detected QTLs per environmental cluster (Table 1). These values are for QTLs detected when considering an interval of 20 cM centered on the exact simulated QTL position. These plots are for a heritability of 0.5 in all environments.

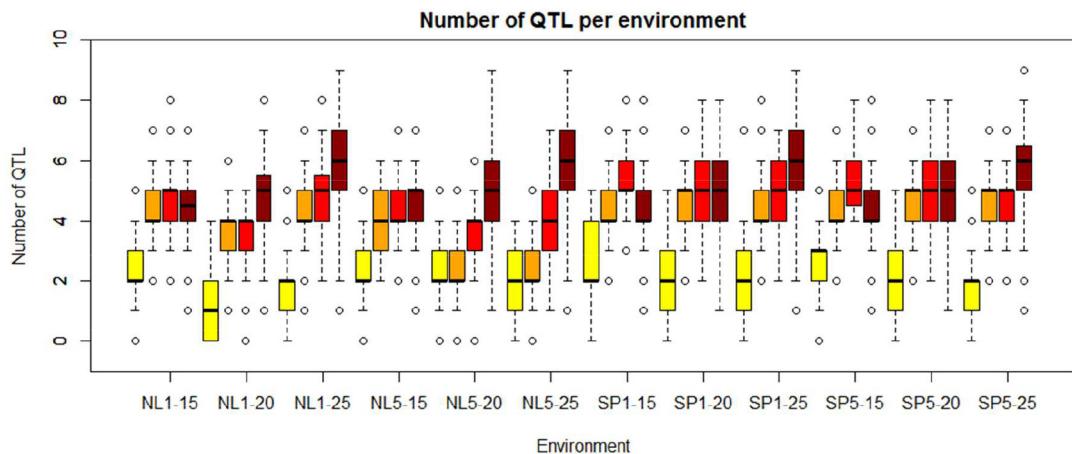


Figure 4. Number of quantitative trait loci (QTLs) detected per environment for an expected maximum of 7 (environments with temperature of 15°C or 20°C; Table 2) or 8 (environments with temperature of 25°C). The boxplots are presented for the genotype-by-environment means (yellow), additive main effects and multiplicative interaction (AMMI) with 2 multiplicative terms-predicted values (orange), weighted AMMI2-predicted values (red), and linear mixed model (dark red). These values are for QTLs detected when considering an interval of 20 cM centered on the exact simulated QTL position. These plots are for a heritability of 0.5 in all environments.

both the number of detected QTLs and the magnitude of the LOD scores. This is particularly visible when the error variance is higher (environments on the left-hand side of Fig. 1) and for QTLs associated with interaction such as the QTLs on chromosomes 6, 9, and 11.

The 100 Simulated Data Sets and Comparison between Methods

A more detailed comparison for all the 100 simulated data sets is presented in Fig. 3 and 4. As expected, the worst performance (in terms of detected QTLs) is obtained by the QTL scans of the $G \times E$ means. Closer to the simulated set up are the QTL scans on the AMMI2-predicted values (AQ analysis), which, however, do not detect true

QTLs for some environments in some runs. The WAQ analysis and QTL mixed model framework are the best options in the presence of heterogeneity of error variance across environments. Although the mixed model detects slightly more QTLs, the fixed effects WAQ analysis shows less variance for the number of QTLs detected and shows a higher precision regarding, for example, the mean squared error (Fig. 3 and 4). A few false positives were detected by the QTL mixed model framework because only seven or eight QTLs are expected per environment (sensitivity analysis, simulation setup; Table 2) and in Fig. 4 some environments had nine QTLs detected.

The analysis and interpretation of the simulated data was clearly improved, regarding the number of QTL

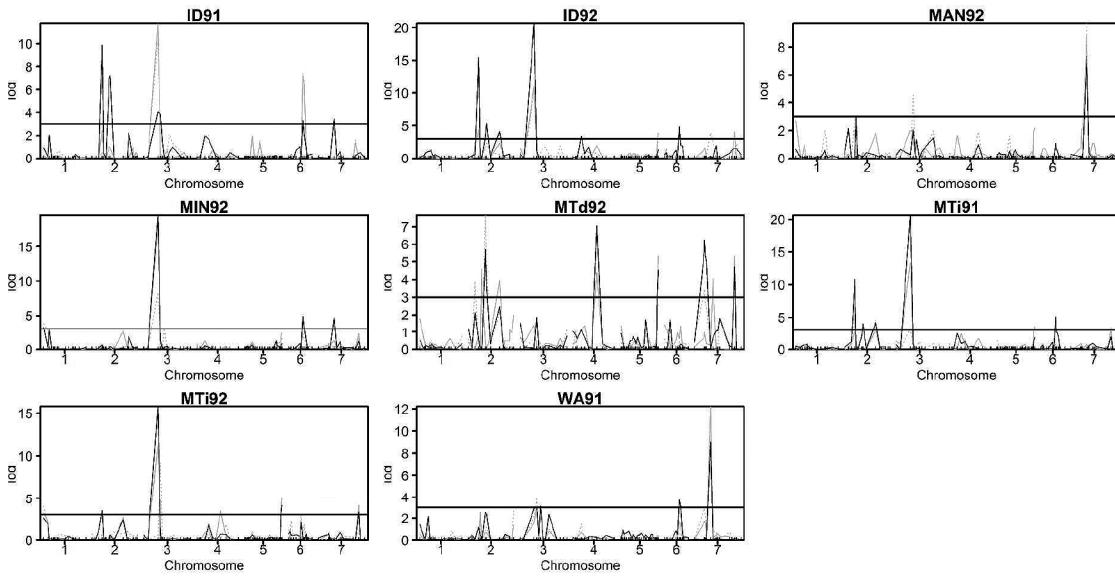


Figure 5. Quantitative trait loci scans for the eight environments of the Steptoe × Morex barley yield data. The grey line represents the scans for the genotype-by-environment means, the grey dashed line represents the scans for the additive main effects and multiplicative interaction (AMMI) with 2 multiplicative terms-predicted values, and the black line represents the scans for the weighted AMMI2-predicted values. All scans are based on composite interval mapping. The horizontal lines correspond to the thresholds for a logarithm of odds score of 3.

detections, by using the error variances in each environment, which leads us to conclude that the W-AMMI biplot is also an improved version (closer to the simulated set up) of the AMMI biplot (Fig. 2). The use of the W-AMMI analysis for QTL detection is especially useful for environments with higher error variance and to detect QTLs associated with the interaction (Fig. 3 and 4).

RESULTS FOR THE BARLEY EXPERIMENTS

Preliminary Analysis

Two previous studies have applied the AMMI model to the S × M yield data to improve and better understand QTL detections (Gauch et al., 2011; Romagosa et al., 1996). Here, for illustration purposes, we used the G × E means for eight environments as detailed in Table 3, where the experiment was partially replicated, instead of the means for the original 16 environments. Table S1 gives a short summary of findings in the literature about detected QTLs on the S × M yield data for all 13 environments partially replicated. Figure 5 (gray line) depicts the QTL scans for the G × E means of the eight environments.

AMMI Analysis

Table 5 gives the ANOVA for the AMMI5 model. The genotypes, environments, and GEI account for 20.2, 50.2, and 29.6% of the treatments sum of SS. The amount of noise in the GEI can be estimated by the product of the interaction degrees of freedom, with the error mean square (MS), namely 417.2, which, by difference from the total of 1136, implies a GEI signal of 718.8, or 63.3% (Gauch,

Table 5. Analysis of variance of the additive main effects and multiplicative interaction model 5 for the Steptoe × Morex yield data.

| Source [†] | df | SS [‡] | MS [§] |
|---------------------|------|-----------------|-----------------|
| Total | 2099 | 4205 | 2.00 |
| Treatments | 1199 | 3845 | 3.21 |
| Genotypes | 149 | 777 | 5.22 |
| Environments | 7 | 1932 | 275.96 |
| GEI | 1043 | 1136 | 1.09 |
| IPC1 | 155 | 338 | 2.18 |
| IPC2 | 153 | 282 | 1.84 |
| IPC3 | 151 | 173 | 1.15 |
| IPC4 | 149 | 111 | 0.74 |
| IPC5 | 147 | 88 | 0.60 |
| IPC6–IPC7 | 288 | 145 | 0.50 |
| Intra Block Error | 900 | 359 | 0.40 |

[†] GEI, genotype-by-environment interaction; IPC, interaction principal component.

[‡] SS, sums of squares.

[§] MS, mean squares.

1992; Voltas et al., 2002). Interaction principal component one and two capture a SS of 338 and 282, respectively, which includes most of the signal and little noise because the first principal components tend to capture more signal and less noise (Gauch, 1992).

Within the two studies where the AMMI model was applied to the S × M yield data for QTL detection, Romagosa et al. (1996) considered the model AMMI4 and found QTLs in the first four IPCs. Subsequently, Gauch et al. (2011) considered the AMMI3 based on the Ockham's valley for the root mean squared prediction error following from a jackknife procedure. For this particular data set, the cross-validation procedure described above and

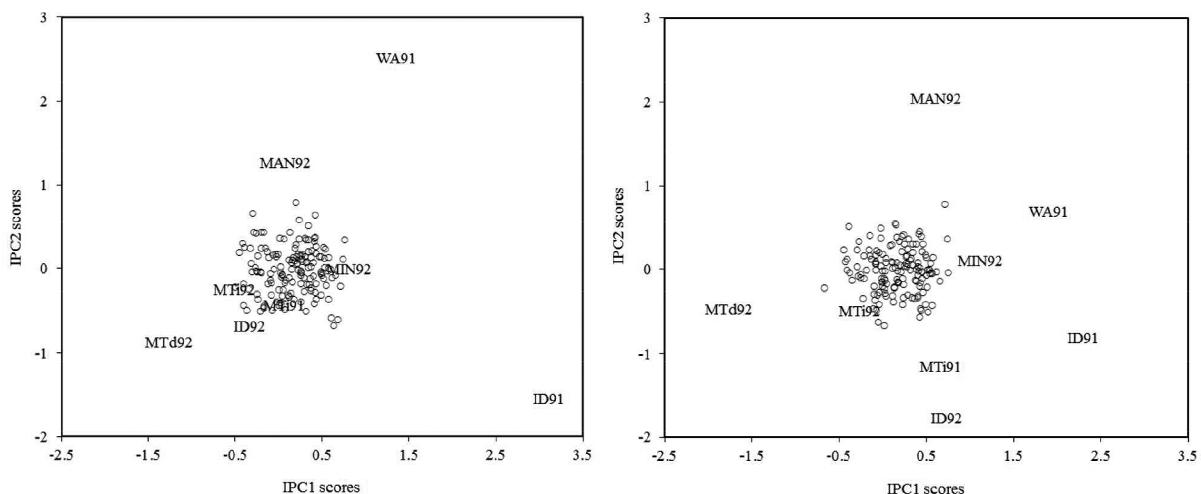


Figure 6. Additive main effects and multiplicative interaction (AMMI) with 2 multiplicative terms (left) and weighted AMMI2 (right) biplots based on the Steptoe \times Morex barley yield data. The abscissa represents the first multiplicative term and the ordinate represents the second. The open dots represent the 150 genotypes and the codes for the eight environments are defined in Table 3.

introduced by Krzanowski (1987) was considered. When computing the W_n values for the first six components of the $S \times M$ yield, we obtain: 6.641, 1.054, 0.518, 0.241, 0.149, and 0.099, which means that the “best” model has two interaction principal components because only two W_n values are above unity (Krzanowski, 1987).

The AMMI2 biplot is depicted in Fig. 6 (left), with the first and second principal components explaining 30.0 and 24.2% of the interaction sum of squares. As before, the environments with higher error variance tend to be placed away from the origin. A similar pattern was found by Gauch et al. (2011), where their environment OR91 was considered as an outlier.

Weighted AMMI Analysis

Since the data in use is partially replicated, the cell means bring more information when there are two observations for the genotype environment combinations. Therefore we have used the matrix of weights as defined by Eq. [7], where $m = \max(1/\sigma_{\varepsilon_j}^2)$, $\sigma_{\varepsilon_j}^2$, $j = 1, \dots, 8$, are the error variances for environment j , $N_{rep_{i,j}}$, $i = 1, \dots, 150$, $j = 1, \dots, 8$, is the number of replications for genotype i in environment j , and $N_{rep} = 2$ is the maximum number of replications in the data set.

Figure 6 (right) shows the W-AMMI2 biplot, weighted by \mathbf{W} as in Eq. [7], and represents the model with the two components after convergence, with the first and second principal components explaining about 24.4 and 17.7% of the variation in the interaction (i.e., the proportion of the total SS for interaction explained by each component). As in the first example (simulated pepper data), the environments with higher influence in the AMMI analysis have a more homogeneous distribution when using the W-AMMI2 analysis (right-hand side of Fig. 6).

AQ and WAQ Analysis

Figure 5 shows the QTL scans for the AMMI2 (gray dashed line) and W-AMMI2 (black line) predicted values. The LOD scores show an increase when the QTL scans are made for the AMMI2-predicted values instead of the $G \times E$ means. The same pattern is observed for most of the environments. When the AQ analysis is replaced by the WAQ analysis, the LOD scores become even higher for most of the QTL detections and most of the environments. The two QTLs on chromosome 2 (Malosetti et al., 2004) are now visible in Fig. 5 (gray dashed and black lines) for most of the environments (more clear for WAQ analysis).

Weighted AQ Analysis and Comparison with QTL Mixed Linear Models

Table 6 presents a general comparison between the three approaches considered here: AQ analysis, WAQ analysis, and QTL mixed model framework. The positions for the QTL detections and some previous references that report QTLs in the same position, can be found in Supplemental Table S1. Most of the QTLs, detected with the WAQ analysis and the QTL mixed model framework, were either found in previous analyses or are very close to those previous QTL detections (Gauch et al., 2011; Hayes et al., 1993; Larson et al., 1996; Malosetti et al., 2004; Romagosa et al., 1996, 1999; Zhu et al., 1999). Supplemental Fig. S2 shows the genome scan for the $S \times M$ yield data using the QTL mixed model framework. This was done by using the composite interval mapping and by considering the factor analytic model with two multiplicative terms to describe the variance–covariance structure.

The QTL mixed model framework detects 28 QTLs in all eight environments together; 20 were also detected by the WAQ analysis (Table 6). Only eight QTLs were detected by the QTL mixed model framework but not by

Table 6. Quantitative trait loci (QTL) detections for each of the seven chromosomes by using additive main effects and multiplicative interaction followed by QTL analysis (AQ; ‡), weighted AQ analysis (§), and QTL mixed model framework (¶), for the Steptoe × Morex yield data with eight environments. On some chromosomes, two QTLs were detected (e.g., Chr2.1 and Chr2.2).

| Environment† | Chr2.1 | Chr2.2 | Chr3.1 | Chr3.2 | Chr4 | Chr5.1 | 5.2 | Chr6 | Chr7.2 | Chr7.2 |
|--------------|--------|--------|--------|--------|------|--------|-----|------|--------|--------|
| ID91 | §¶ | § | ‡§¶ | | | | | ‡§¶ | § | |
| ID92 | ‡§¶ | §¶ | ‡§¶ | ¶ | ‡§¶ | | ‡ | § | ‡¶ | |
| MAN92 | ¶ | § | ‡¶ | | ¶ | | | | ‡§¶ | |
| MIN92 | | | ‡§¶ | ¶ | | | | § | § | |
| MTd92 | ‡ | ‡§¶ | ¶ | | ‡§¶ | | | ¶ | ‡§¶ | ‡§ |
| MTi91 | ‡§¶ | ‡§¶ | ‡§ | | | | ‡ | § | | |
| MTi92 | | § | ‡§¶ | | ¶ | | | | | §¶ |
| WA91 | ¶ | | ‡§¶ | | | | | § | ‡§¶ | |

† ID91, Idaho 1991; ID92, Idaho 1992; MAN92, Manitoba 1992; MIN92, Minnesota 1992; MTd92, Montana dryland 1992; MTi91, Montana irrigated 1991; MTi92, Montana irrigated 1992; WA91 Washington 1991.

the WAQ analysis, whereas six were detected by the WAQ analysis and not by the QTL mixed model framework (four of them previously reported in the literature, Supplemental Table S1). Taking into consideration the good overall performance of the QTL mixed model framework, it can be concluded that the WAQ analysis outperforms the AQ analysis regarding the QTL detections because of the higher number of “true positive” QTL detections and lower number of “false negative” QTL detections.

When comparing the methods under study, we can conclude again that the QTL scans of the $G \times E$ means have the worst performance in terms of QTL detections (Fig. 5). The WAQ analysis outperforms the AQ analysis and shows more similar results with the QTL mixed model analysis (Table 6; Supplemental Table S1).

The R code to run the W-AMMI algorithm and to perform the AQ and WAQ analyses is available on request, from the corresponding author of this paper.

DISCUSSION

Weighted AMMI Analysis

The W-AMMI algorithm proposed here can work with any weighting scheme. It is a generalization of the standard AMMI analysis (Gauch, 1992) that is able to account for heterogeneity in both genetic variances (captured by the interaction principal components in AMMI) and error variances (by using the weighted generalization of the AMMI model to estimate the interaction scores) across environments in METs. The standard unweighted solution to the AMMI model parameters are, of course, contained in the W-AMMI algorithm when the weights are chosen equal for all entries of the two-way table. There will be specific cases with little heterogeneity of error variances (Gauch et al., 2011) where the AMMI submodel is still fully appropriate. The weights for the W-AMMI algorithm can be chosen in accordance with the prescripts laid down in Smith et al. (2001), Möhring and Piepho (2009), and Welham et al. (2010), where the diagonal elements of the inverse of the variance–covariance matrix for the error attached to the genotypic means in a trial or

environment determine the weights for subsequent MET and GEI analysis. It should be emphasized that the weights in our W-AMMI algorithm require a (re)scaling that brings them between zero and one. Piepho et al. (2012) shows the good properties of weighting by inverse error variance–covariance matrices for genotypic predictions in two-stage analyses of MET data. These good properties will carry over to our W-AMMI approach, although it is not straightforward to embed our W-AMMI approach into the framework of a generalized least squares approach.

A simple criterion to decide which approach to use, AMMI or W-AMMI, for complete data and completely randomized designs or randomized complete block designs, is to compute the error or residual variance for each environment and check whether it is homogeneous across environments. If the error variance is homogeneous across environments, the results from the AMMI model will be similar to the ones from the W-AMMI approach and the use of the standard AMMI strategy will be sufficient. When the error variances show high heterogeneity across environments, the use of the AMMI model is not advisable and the W-AMMI algorithm should be used. The R code to compute the error variances, with detailed explanation, can be found in Supplemental File S2.

In this paper, we used the EM algorithm proposed by Srebro and Jaakkola (2003) to conduct the weighted low-rank approximation to the interaction residuals (further details in Srebro and Jaakkola [2003] and in Supplemental File S1). Note that the W-AMMI approach is not an EM approach to the problem of producing a weighted estimation of all AMMI parameters, as the effects for main effects and interaction parameters are produced in separate steps. Given that ANOVA interaction residuals have been calculated already, the procedure is a maximum-likelihood approach for an SVD for those residuals allowing for weights. It is effective in many cases, but it can converge to a local minimum (Srebro and Jaakkola, 2003). Therefore, the initialization of \mathbf{X} in Eq. [6] plays an important role in obtaining the global minimum. Srebro and Jaakkola (2003) discuss some alternatives to this initialization.

Further alternatives can be found to obtain low-rank approximations to $G \times E$ tables of means: maximum likelihood principal component analysis (Wentzell et al., 1997), a steepest descent algorithm, a Newton-like algorithm (Manton et al., 2003), and the use of a weighted rank correlation coefficient instead of the usual Pearson's (da Costa et al., 2011), among others. Also, alternating least squares algorithms are possible (Gabriel and Zamir, 1979; van Eeuwijk, 1995). We chose the current EM approach because of its easy implementation and good behavior for our type of data. Important features in the AMMI model, such as biplots (Gabriel, 1971; Gauch et al., 2008), will keep the characteristics and standard interpretation in the W-AMMI algorithm. We do not yet have a definite answer to the question of how to decide on the number of IPCs when using the W-AMMI algorithm described above (Srebro and Jaakkola, 2003). In principle, the strategies for deciding on the number of IPCs for unweighted AMMI analysis should also be applicable for W-AMMI. For W-AMMI, the number of components has to be decided before running the algorithm.

Missing Data

When the two-way table has missing cells, we could still use our W-AMMI approach, but now using a zero weight for the missing cells. However, the algorithm is less stable when one or more weights are zero and therefore it is wise to use some imputation algorithm. Gauch and Zobel (1990) proposed an EM algorithm for fitting the AMMI model while handling missing $G \times E$ cell means. Paderewski and Rodrigues (2014) presented a simulation study where the efficiency of the EM-AMMI algorithm is investigated for several patterns of missing values. Other AMMI-based alternatives to handle missing values have been proposed, either by using imputation techniques to estimate the data before the analysis (Arciniegas-Alarcón et al., 2010, 2011; Bergamo et al., 2008) or by trying to infer the results without imputation (Rodrigues et al., 2011; Pereira et al., 2012). Another SVD-based idea, using the biplot analysis, was recently proposed by Yan (2013).

The Influence of the Heritability in the Results

The weighted extension of the AMMI model approach allowed a generalization of the AQ analysis, where the QTL scans are based on the AMMI-predicted values (Gauch et al., 2011). For the pepper and barley data, the weighted AQ analysis produced results similar to the mixed model QTL framework as described by Boer et al. (2007) and Malosetti et al. (2004, 2008). In field crops, the range of heritabilities is wide and may vary from about 0.3 for yield in cereals in open environments (Saeed et al., 2007), to more than 0.7 for tomato (*Solanum lycopersicum* L.) (Reif et al., 2009) or pepper (do Rego et al., 2011) in greenhouse

experiments. When the heritability of the environments under study is small, the WAQ analysis is very similar to the QTL mixed model framework (e.g., $h^2 = 0.3$; Supplemental Figs. S3 and S4), and when the heritability of the environments is high, the QTL mixed model framework appears to outperform the WAQ analysis (e.g., $h^2 = 0.8$; Supplemental Figs. S5 and S6) but detects some QTLs that are false positives (e.g., a few detections on chromosome 12 and the very unlikely scenario—as concluded from the sensitivity analysis—of 10 QTLs found in several environments; Supplemental Fig. S6; Table 2) plus some other detections elsewhere on other chromosomes. Both WAQ analysis and QTL mixed model framework outperform AQ analysis, and all of them outperform the QTL scans of the $G \times E$ means. For all these comparisons, we should bear in mind that the thresholds—obtained by a permutation test with 1000 permutations at the 0.05 level (Churchill and Doerge, 1994)—for WAQ analysis are fully comparable with the thresholds for AQ analysis and with the thresholds for the QTL scans on the $G \times E$ means. However, because of the different methodologies and different software, the thresholds for WAQ analysis are not fully comparable with the QTL mixed model framework, which uses a multiple test correction for the Wald statistics based on a proposal by Li and Ji (2005). Nevertheless, the results of the simulation study are quite convincing, with respect to the similarity for location of QTLs between the WAQ analysis and the QTL mixed model framework. It should be remarked that the mixed model QTL mapping was used with default multiple testing corrections as set in GenStat 14 (Payne et al., 2011). Some fine tuning may have led to the adoption of a multiple test correction that would produce results even more comparable to the WAQ approach. When considering heterogeneous levels of heritability within the same simulated data (i.e., different environments having different heritabilities), the pattern of improvement in QTL detections is similar to the results shown before (i.e., the performance—in terms of number and precision of QTL detection—of the WAQ analysis is better for environments with lower heritability than for environments with higher heritability). This means that the graph (not shown) with the number of QTLs per environment is similar to a combination of Supplemental Fig. S3 (low heritability, 0.3), Fig. 4 (medium heritability, 0.5) and Supplemental Fig. S5 (high heritability, 0.8).

CONCLUSION

Boer et al. (2007) suggested the possibility of having different methodologies performing as well as the QTL mixed model approach. They mentioned Bayesian methods and penalized regression as possibilities for similar analyses. The AQ analysis (Gauch et al., 2011) is another alternative to the QTL mixed model framework with a good performance in terms of number and location of QTLs when

the error variance across environments is homogeneous but not as good when the error variance across environments is heterogeneous. This paper proposes a generalization of the AQ approach by taking into account the information regarding the heterogeneity of error variances across environments, the WAQ analysis, which results in a comparable outcome between the WAQ analysis and the QTL mixed model methodology. Weighted AQ has the advantage of being easily performed and understood by the many researchers that are familiar with the AMMI model. Furthermore, the WAQ analysis is robust and will not suffer from convergence problems, although for the WAQ analysis there is a risk of ending up in local minima. As mentioned, the use of the W-AMMI analysis for QTL detection seems particularly useful for environments with larger error variance and to detect QTLs associated to the interaction (Fig. 3 and 4).

The results presented in this paper are very encouraging because of several factors: (i) the WAQ analysis can be performed with open source R software (R Development Core Team, 2011), which is one of the most widely used statistical software packages (the code is available on request from the corresponding author of this paper); (ii) the $G \times E$ data is analyzed with a stagewise approach (Piepho et al., 2012), where the initial fit to the data is provided by a good phenotypic model across all trials, the W-AMMI model, followed by the analysis of contrasts, QTLs, instead of first fitting contrasts in the forms of QTLs per trial and then combining this contrast information across trials (meta-analysis), where the latter approach is inferior according to Piepho et al. (2012); (iii) the results are very similar to the QTL mixed model output (Fig. 3 and 4; Supplemental Table S1). It is also remarkable how the inclusion of the information about the error variances greatly improves the results when the heritability of the trait (environment) decreases (Fig. 3; Supplemental Figs. S3 and S5) compared with the AQ analysis and the QTL scans of the $G \times E$ means and makes them very similar to the QTL mixed model methodology (Fig. 3 and 4; Supplemental Table S1). The WAQ analysis is easy to apply with open source software and fast to run when compared with mixed model QTL analysis. Moreover, the W-AMMI algorithm and WAQ analysis are fully applicable to a wide range of fields, such as plant breeding, crop sciences, genetics, microarray experiments (Crossa et al., 2005), rDNA studies (Adams et al., 2002), plant and microbial populations' growth across several environmental conditions (Culman et al., 2009), animal sciences (Barhdadi and Dube, 2010), and human genetics (Mukherjee et al., 2012).

Supplemental Information Available

Supplemental information is included with this article.

Figure S1. QTL scans for the 12 environments of the yield data for pepper simulated from the physiological

genotype-to-phenotype model with seven physiological parameters.

Figure S2. Genome scan for the means of the $S \times M$ yield data considering the factor analytic with two multiplicative terms to model the variance-covariance structure.

Figure S3. Summary of the number of detected QTLs for the actual data, AMMI2 predicted values, W-AMMI2 predicted values, and linear mixed model, for a heritability of 0.3 in all environments.

Figure S4. Number of QTLs detected per environment for an expected maximum of 7 or 8, for a heritability of 0.3 in all environments.

Figure S5. Summary of the number of detected QTLs for the actual data, AMMI2 predicted values, W-AMMI2 predicted values, and linear mixed model, for a heritability of 0.8 in all environments.

Figure S6. Number of QTLs detected per environment for an expected maximum of 7 or 8, for a heritability of 0.8 in all environments.

Table S1. Chromosome and respective positions where a QTL was detected for each of the four approaches: QTL scans of the actual data, QTL scans of the AMMI3 predicted values, QTL scans of the W-AMMI3 predicted values, and linear mixed model framework for the $S \times M$ yield data in all 13 environments that have at least one partial replication.

File S1. The R code for the weighted low-rank SVD (Srebro and Jaakkola, 2003).

File S2. The R code to compute the error variances.

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