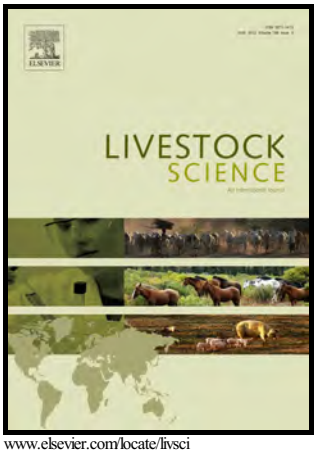

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Bayesian analysis of pig growth curves combining pedigree and genomic information

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Abstract

We proposed a genome association study for pig growth curves based on Bayesian hierarchical framework considering different sets of SNP markers and pedigree. Additionally, we aimed also to identify possible chromosome regions affecting the growth curve parameters using empirical weight-age data from an outbred F2 (Brazilian Piau vs commercial) pig population. Under the proposed hierarchical approach, individual growth trajectories were modeled by the nonlinear Gompertz function, so that the parameter estimates were considered to be affected by additive polygenic, systematic and SNP markers effects. The model assuming jointly pedigree

and SNP markers presented the best fit based on Deviance Information Criterion. Heritability estimates ranged from 0.53 to 0.56 and from 0.55 to 0.57, respectively for the parameters mature weight (a) and maturing rate (k). Additionally, we found high and positive genetic correlation (0.78) between “a” and "k". The percentages of the genetic variances explained by each SNP allowed identifying the most relevant chromosome regions for each phenotype (growth curve parameters). The majority of these regions were closed to QTL regions previously reported for growth traits. However, we identified three relevant SNPs (55840514 bp at SSC17, 55814469 at SSC17 and 76475804 at SSC X) affecting "a" and "k" simultaneously, and three SNPs affecting only "a" (292758 bp at SSC1, 67319 bp at SSC8 and 50290193 bp at SSC17), that are located in regions not previously described as QTL for growth traits in pigs.

Keywords

Hierarchical nonlinear model, Gompertz, SNP markers

Introduction

Most of the genome association studies of pig growth assume the body weight at specific ages as phenotypes. However, it may be extended for a more general context by considering the whole weight-age data under a growth curve approach. In general, pig growth curves have been studied through several nonlinear functions such as Logistic, von Bertalanffy and Gompertz (Koivula et al., 2008; Cai et al., 2012; Silva et al., 2013). These functions present a reduced number of parameters with biological interpretation (for instance, mature weight and maturing rate). Thus, breeding goals can be defined aiming to change the shape of the growth curves by treating these parameter estimates as phenotypic observations in statistical genetic models.

Traditionally, genetic analysis of growth curves considering only pedigree information has been performed in two distinct steps. First, the growth curve parameters are estimated for each animal; and, second, (co)variance components, genetic and environmental effects are estimated on them. This approach ignores the adjustment errors and does not allow estimating growth curve parameters for individuals with a scarce amount of records (Varona et al., 1999). In this context, hierarchical Bayesian models for growth curves were proposed by calculating joint posterior distributions for the curve parameters, (co)variance components, and systematic and genetic effects. Under this approach, adjustment errors are discarded and all the available information is then used for the genetic prediction of individual growth curves (Varona et al., 1997; Blasco et al., 2003; Forni et al., 2009).

Ibáñez-Escriche and Blasco (2011) generalized the hierarchical Bayesian models for growth curves under a genome wide selection approach considering a simulated population. These procedures provide information on location of specific genome regions affecting growth curve components, that may lead to new insights about marker assisted selection in pig breeding approaching desirable genetic changes on growth curves. However, generalization for genome association studies have been under exploited in literature, especially for real data.

In this context, we proposed a genome association study for pig growth curves based on Bayesian hierarchical framework considering different sets of SNP markers and pedigree. Additionally, we aimed also to identify possible chromosome regions affecting the growth curve parameters.

Materials and methods

Experimental population and phenotypic data

The phenotypic data was obtained from the Pig Breeding Farm of the Department of Animal Science, Universidade Federal de Viçosa (UFV), MG, Brazil. A three-generation resource population was created and managed as described by Hidalgo et al. (2013) and Verardo et al. (2015). Briefly, two naturalized Piau breed grandsires were mated with 18 granddams from a commercial line composed of Large White, Landrace and Pietrain breeds, to produce the F1 generation from which 11 F1 sires and 54 F1 dams were selected. These F1 individuals were mated to produce the F2 population, of which 345 animals were weighed at birth and at 21, 42, 63, 77, 105 and 150 days of age.

DNA extraction, genotyping and SNP quality control

DNA was extracted at the Animal Biotechnology Lab from Animal Science Department of Universidade Federal de Viçosa. Genomic DNA was extracted from white cells of parental, F1 and F2 animals, more details can be found in Band et al. (2005). The low-density customized SNPChip with 384 markers was based on the Illumina Porcine SNP60 BeadChip (San Diego, CA, USA, Ramos et al., 2009).

These SNPs were selected according to QTL positions previously identified on this population using meta-analyses (Silva et al., 2011) and fine mapping (Hidalgo et al., 2013, Verardo et al., 2015). Thus, although a small number of markers have been used, the customized SNPchip based on previous identified QTL positions ensures an appropriate coverage of the relevant genome regions in this population. Using previous information based on pre-determined chromosome regions has successfully improved genomic predictions as reported by Zhang et al. (2015).

From the total of 384 markers, 66 SNPs were discarded for no amplification, and from the remaining 318 SNPs, 81 were discarded due to very low minor allele frequency (close to zero). Thus, 237 SNPs markers were used and distributed as follows: SSC1 (56), SSC4 (54), SSC7 (59), SSC8 (30), SSC17 (25) and SSCX (13), being the average distance within each chromosome, respectively, 5.17, 2.37, 2.25, 3.93, 2.68 and 11.00 Mb.

The model

A hierarchical Bayesian model was applied to analyze individual pig growth curves based on nonlinear Gompertz function, whose parameters were modeled by a multitrait linear model including additive polygenic, SNP marker and systematic effects.

In the first stage, it was considered the following Gompertz growth model:

$$y_{ij} = a_i \exp(-b_i \exp(-k_i t_{ij})) + \varepsilon_{ij}, \quad (1)$$

where y_{ij} is the observed body weight of individual i at age j, a_i represents the mature weight, b_i is a time scale parameter (it does not have biological interpretation), k_i is the maturing rate, t_{ij} is the day in which the body weight were measured, and ε_{ij} is the residual term, considered to be independent and normally distributed among individuals. The following distribution was assumed for the weight-age data in this first stage:

$$f(y_{ij} \mid a_i, b_i, k_i, \sigma^2_{\varepsilon j}) \sim N(a_i \exp(-b_i \exp(-k_i t_{ij})), \sigma^2_{\varepsilon j})$$

The standard deviation ($\sigma_{\varepsilon j}$) for the residual term in (2) was considered as a linear function of two parameters (r_a and r_b) aiming to model its trajectory over time (*i.e.*, to consider residual heterogeneity of variance):

$$\sigma_{\varepsilon j} = r_a + r_b t_{ij}. \quad (2)$$

In the second stage, additive polygenic, systematic and SNP marker effects were estimated under a multitrait linear model considering the parameter estimates from the first stage as phenotypic observations. Three alternative models, characterized by the inclusion of different genetics effects in addition to the systematic effects, were proposed. The first one assumed the additive polygenic effects (Pedigree) – M1 (3); the second one the SNP genotypes effects (Markers) – M2 (4); and the third one considered both previously mentioned effects (Pedigree and markers) – M3 (5). These models are given respectively by:

$$\boldsymbol{\theta} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u} + \mathbf{e}, \quad (3)$$

$$\boldsymbol{\theta} = \mathbf{X}\boldsymbol{\beta} + \mathbf{M}\mathbf{c} + \mathbf{e}, \quad (4)$$

$$\boldsymbol{\theta} = \mathbf{X}\boldsymbol{\beta} + \mathbf{M}\mathbf{c} + \mathbf{Z}\mathbf{u} + \mathbf{e}, \quad (5)$$

where $\boldsymbol{\theta}$ is a vector containing the estimates of the parameter "a", "b", and "k" for all individuals, $\boldsymbol{\theta}' = [\mathbf{a}, \mathbf{b}, \mathbf{k}]' = [a_1, a_2, ..., a_n, b_1, b_2, \cdots b_n, k_1, k_2, \cdots k_n]$; $\boldsymbol{\beta}$ is the vector of systematic effects (intercept and 19 contemporary groups given by the combination of sex, batch and halothane gene genotype), $\boldsymbol{\beta} \sim N(\mathbf{0}, \boldsymbol{\Sigma}_\beta \otimes \mathbf{I})$, being $\boldsymbol{\Sigma}_\beta$ a known diagonal matrix with values 1e+10 (large variances) to represent vague prior knowledge; $\mathbf{u} = (u_{a1}, u_{a2}, ..., u_{an}, u_{b1}, u_{b2}, ..., u_{bn}, u_{k1}, u_{k2}, ..., u_{kn})$ is the vector of additive polygenic effects, assumed as: $\mathbf{u} \mid \boldsymbol{\Sigma}_g, \mathbf{A} \sim N(\mathbf{0}, \boldsymbol{\Sigma}_g \otimes \mathbf{A})$, n is the total number of individuals and in this study was also the number of records within individual, $\mathbf{A}$ is the additive relationship matrix among the animals and $\boldsymbol{\Sigma}_g$ is the additive genetic (co)variance matrix; $\mathbf{c} = (c_{a1}, c_{a2}, ..., c_{am}, c_{b1}, c_{b2}, ..., c_{bm}, c_{k1}, c_{k2}, ..., c_{km})$ is the vector of random SNP effects with known incidence matrix $\mathbf{M}$ with (345x3) rows and (237x3) columns of SNP

genotypes (coded as AA, AB, or BB), assumed as $\mathbf{c} \mid \boldsymbol{\Sigma}_c \sim N(\mathbf{0}, \boldsymbol{\Sigma}_c \otimes \mathbf{I})$, where $\mathbf{I}$ and $\boldsymbol{\Sigma}_c$ are, respectively, an identity and SNP markers (co)variance matrices. The $\mathbf{X}$ and $\mathbf{Z}$ are the incidence matrices corresponding to systematic and additive polygenic effects, respectively; and $\mathbf{e} = (e_{a1}, e_{a2}, ..., e_{an}, e_{b1}, e_{b2}, ..., e_{bn}, e_{k1}, e_{k2}, ..., e_{kn})$ is the residuals vector, assumed as $\mathbf{e} \mid \boldsymbol{\Sigma}_e \sim N(\mathbf{0}, \boldsymbol{\Sigma}_e \otimes \mathbf{I})$, where $\mathbf{I}$ and $\boldsymbol{\Sigma}_e$ are, respectively, an identity and residual (co)variance matrices. The halothane gene genotype was included as a fixed effect because of its significant effect on carcass and performance traits in this population, as reported by Band et al. (2005).

The inference

The joint posterior distribution for individual growth curve parameters, their variance components, and systematics, additive polygenic and SNP effects was accessed under a hierarchical framework following the Bayes theorem:

$$f(\boldsymbol{\theta}, \sigma_{\varepsilon j}, \boldsymbol{\beta}, \mathbf{u}, \mathbf{c}, \boldsymbol{\Sigma}_c, \boldsymbol{\Sigma}_g, \boldsymbol{\Sigma}_e \mid \mathbf{y}) \propto f(\mathbf{y} \mid \boldsymbol{\theta}, \sigma_{\varepsilon j})$$
$$f(\boldsymbol{\theta} \mid \boldsymbol{\beta}, \mathbf{u}, \mathbf{c}, \boldsymbol{\Sigma}_c, \boldsymbol{\Sigma}_g, \boldsymbol{\Sigma}_e)\ f(\sigma_{\varepsilon j})\, f(\boldsymbol{\beta})\ f(\mathbf{u} \mid \boldsymbol{\Sigma}_g)$$
$$f(\boldsymbol{\Sigma}_g) f(\mathbf{c} \mid \boldsymbol{\Sigma}_c)\, f(\boldsymbol{\Sigma}_c)\ f(\boldsymbol{\Sigma}_e)$$

Assuming independence among individuals, the conditional distribution of data $\mathbf{y}$, given the growth curve parameters, was a product of normal distributions:

$$f(\mathbf{y} \mid \boldsymbol{\theta}, \sigma_{\varepsilon j}) = \prod_{i=1}^{N} \prod_{j=1}^{n} \frac{1}{\sqrt{2\pi\sigma^2_{\varepsilon j}}} \exp\left\{ - \frac{[y_{ij} - (a_i \exp^{(-b_i)\exp^{(-k_i t_{ij})}})]^2}{2\sigma^2_{\varepsilon j}} \right\}, \quad (8)$$

where N is the total number of individuals; n the number of records within individual; a_i, b_i and k_i are the parameters of the Gompertz growth function for the animal i; and t_{ij} the age (days) at time j.

The prior distribution for the growth curve parameters given the additive polygenic, systematic and SNP effects, as well as the (co)variance components, was assumed as a multivariate Gaussian distribution given by:

$$f(\boldsymbol{\theta} \mid \boldsymbol{\beta}, \mathbf{u}, \boldsymbol{\Sigma}_g, \mathbf{c}, \boldsymbol{\Sigma}_c, \boldsymbol{\Sigma}_e) = \mid \boldsymbol{\Sigma}_e \mid^{-N/2} \exp\left[-\frac{1}{2}(\boldsymbol{\theta} - \mathbf{X}\beta - \mathbf{Z}u - \mathbf{M}c)'(\boldsymbol{\Sigma}_e \otimes \mathbf{I})^{-1}(\boldsymbol{\theta} - \mathbf{X}\beta - \mathbf{Z}u - \mathbf{M}c) \right] \quad (9)$$

where $\boldsymbol{\theta}$ is the vector containing the parameters "a", "b" and "k"; $\boldsymbol{\Sigma}_g$ is the additive polygenic genetic (co)variance matrix; $\boldsymbol{\Sigma}_c$ is the SNP markers (co)variance matrix; $\boldsymbol{\Sigma}_e$ the residual (co)variance matrix between the parameters "a", "b", and "k"; and $\mathbf{I}$ is an identity matrix.

Following the proposed hierarchical approach, Gaussian prior distributions were assumed for the systematics, additive polygenic and SNP effects:

$$f(\boldsymbol{\beta} \mid \mathbf{s}, \mathbf{V}) \propto \mid \mathbf{V} \mid^{-1/2} \exp\left[-\frac{1}{2}(\boldsymbol{\beta} - \mathbf{s})'\mathbf{V}^{-1}(\boldsymbol{\beta} - \mathbf{s}) \right],$$

$$f(\mathbf{u} \mid \boldsymbol{\Sigma}_g, \mathbf{A}) \propto \mid \boldsymbol{\Sigma}_g \mid^{-N_A/2} \exp\left[-\frac{1}{2}\mathbf{u}'(\boldsymbol{\Sigma}_g \otimes \mathbf{A})^{-1}\mathbf{u} \right], \text{ and}$$

$$f(\mathbf{c} \mid \boldsymbol{\Sigma}_c) \propto \mid \boldsymbol{\Sigma}_c \mid^{-h/2} \exp\left[-\frac{1}{2}\mathbf{c}'(\boldsymbol{\Sigma}_c \otimes \mathbf{I})^{-1}\mathbf{c} \right],$$

where $\mathbf{s}$ and $\mathbf{V}$ are subjective means and (co)variances for the prior beliefs about the systematic effects, N_A is the number of animals in the genealogy, $\mathbf{I}$ is an identity matrix of order h represent the SNP markers (h = 1, 2, …, 237), and $\mathbf{A}$ is the numerator relationship matrix. Bounded uniform distributions were assumed for $\sigma_{\varepsilon j}$ and (co)variance matrices ($\boldsymbol{\Sigma}_g$, $\boldsymbol{\Sigma}_c$ and $\boldsymbol{\Sigma}_e$) (Varona et al., 1998; Forni et al., 2007).

The sampling methods require random independent draws from the conditional posterior distribution for each parameter. Thus, if θ_{ik} is the k^{th} growth curve parameter

for the ith animal, θ_{-ik} are the other parameters for the i^{th} animal and all parameters for all other animals. Thus we have:

$$f(\theta_{ik} \mid \theta_{-ik}, \boldsymbol{\beta}, \mathbf{u}, \mathbf{c}, \boldsymbol{\Sigma}_{\mathbf{c}}, \boldsymbol{\Sigma}_{\mathbf{g}}, \boldsymbol{\Sigma}_{\mathbf{e}}, \sigma_{\varepsilon j}, \mathbf{y}) \propto$$
$$f(\theta_{ik} \mid \theta_{-ik}, \sigma_{\varepsilon j}, \mathbf{y})\, f(\theta_{ik} \mid \theta_{-ik}, \boldsymbol{\beta}, \mathbf{u}, \mathbf{c}, \boldsymbol{\Sigma}_{\mathbf{c}}, \boldsymbol{\Sigma}_{\mathbf{g}}, \boldsymbol{\Sigma}_{\mathbf{e}})$$

The fully conditional distributions for all parameters of the hierarchical multistage models were derived according to Varona et al. (1999). In the present study, these distributions for growth curve parameters are the products of the conditional distribution of data (Eq.[8]) and the prior distributions of the growth curve parameters (Eq. [9]).

The fully conditional distribution of parameter "a" can be written as:

$$f(a_i \mid b_i, k_i, \boldsymbol{\beta}, \mathbf{u}, \boldsymbol{\Sigma}_{\mathbf{g}}, \mathbf{c}, \boldsymbol{\Sigma}_{\mathbf{c}}, \boldsymbol{\Sigma}_{\mathbf{e}}, \sigma_{\varepsilon j}, \mathbf{y}) \propto$$
$$f(a_i \mid b_i, k_i, \sigma_{\varepsilon j}, y_i)\; f(a_i \mid b_i, k_i, \boldsymbol{\beta}, \mathbf{u}, \boldsymbol{\Sigma}_{\mathbf{g}}, \mathbf{c}, \boldsymbol{\Sigma}_{\mathbf{c}}, \boldsymbol{\Sigma}_{\mathbf{e}}),$$

where,

$$f(a_i \mid b_i, k_i, \sigma_{\varepsilon j}, y_i) \sim N\left[\frac{\sum_{j=1}^{n} y_{ij}(\exp^{(-b_i)}\exp^{(-k_i t_{ij})})}{\sum_{j=1}^{n}[(\exp^{(-b_i)}\exp^{(-k_i t_{ij})})]^2}, \frac{\sigma_{\varepsilon j}}{\sum_{j=1}^{n}[(\exp^{(-b_i)}\exp^{(-k_i t_{ij})})]^2}\right].$$

The fully conditional distribution of parameter "b" can be written as:

$$f(b_i \mid a_i, k_i, \boldsymbol{\beta}, \mathbf{u}, \boldsymbol{\Sigma}_{\mathbf{g}}, \mathbf{c}, \boldsymbol{\Sigma}_{\mathbf{c}}, \boldsymbol{\Sigma}_{\mathbf{e}}, \sigma_{\varepsilon j}, \mathbf{y}) \propto$$
$$f(b_i \mid a_i, k_i, \sigma_{\varepsilon j}, y_i)\; f(b_i \mid a_i, k_i, \boldsymbol{\beta}, \mathbf{u}, \boldsymbol{\Sigma}_{\mathbf{g}}, \mathbf{c}, \boldsymbol{\Sigma}_{\mathbf{c}}, \boldsymbol{\Sigma}_{\mathbf{e}}),$$

where,

$$f(b_i \mid a_i, k_i, \sigma_{\varepsilon j}, r_b, y_i) \propto \prod_{j=1}^{n} \exp\left[- \frac{[y_{ij}-(a_i \exp^{(-b_i)\exp^{(-k_i t_{ij})}})]^2}{2\sigma_{\varepsilon j}} \right].$$

The fully conditional distribution of parameter "k" can be written as:

$$f(k_i \mid a_i, b_i, \boldsymbol{\beta}, \mathbf{u}, \boldsymbol{\Sigma}_g, \mathbf{c}, \boldsymbol{\Sigma}_c, \boldsymbol{\Sigma}_e, \sigma_{\varepsilon j}, \mathbf{y}) \propto$$
$$f(k_i \mid a_i, b_i, \sigma_{\varepsilon j}, y_i)\ f(k_i \mid a_i, b_i, \boldsymbol{\beta}, \mathbf{u}, \boldsymbol{\Sigma}_g, \mathbf{c}, \boldsymbol{\Sigma}_c, \boldsymbol{\Sigma}_e),$$

where,

$$f(k_i \mid a_i, b_i, \sigma_{\varepsilon j}, y_i) \propto \prod_{j=1}^{n} \exp\left[- \frac{[y_{ij}-(a_i \exp^{(-b_i)\exp^{(-k_i t_{ij})}})]^2}{2\sigma_{\varepsilon j}} \right].$$

The parameter "a" could be sampled from a normal distribution by using Gibbs sampling algorithm, but the conditional posterior distribution for the parameters "b" and "k" did not have a closed form. In these cases, the Metropolis-Hastings algorithm with normal proposal distribution centered on the values of b_i and k_i sampled in the immediately previous iteration was used (Forni et al., 2007). The mixed model equations were constructed assuming as observed traits the growth curve parameters (θ) obtained from earlier steps:

$$\begin{bmatrix} \mathbf{X}'\mathbf{R}^{-1}\mathbf{X} + \mathbf{V}^{-1} & \mathbf{X}'\mathbf{R}^{-1}\mathbf{Z} & \mathbf{X}'\mathbf{R}^{-1}\mathbf{M} \\ \mathbf{Z}'\mathbf{R}^{-1}\mathbf{X} & \mathbf{Z}'\mathbf{R}^{-1}\mathbf{Z} + (\boldsymbol{\Sigma}_g \otimes \mathbf{A})^{-1} & \mathbf{Z}'\mathbf{R}^{-1}\mathbf{M} \\ \mathbf{M}'\mathbf{R}^{-1}\mathbf{X} & \mathbf{M}'\mathbf{R}^{-1}\mathbf{Z} & \mathbf{M}'\mathbf{R}^{-1}\mathbf{M} + (\boldsymbol{\Sigma}_c \otimes \mathbf{I})^{-1} \end{bmatrix} \begin{bmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\mathbf{u}} \\ \hat{\mathbf{c}} \end{bmatrix} = \begin{bmatrix} \mathbf{X}'\mathbf{R}^{-1}\boldsymbol{\theta} \\ \mathbf{Z}'\mathbf{R}^{-1}\boldsymbol{\theta} \\ \mathbf{M}'\mathbf{R}^{-1}\boldsymbol{\theta} \end{bmatrix} \text{ where,}$$

$$\mathbf{R} = \boldsymbol{\Sigma}_e \otimes \mathbf{I}. \qquad (10)$$

The conditional posterior distributions for each location parameter β_l, u_i, and c_h were given by normal distributions defined by the coefficients and the right-hand side (RHS) of the mixed model equations (Eq. [10]):

$$f(\beta_l \mid \beta_{-l}, \boldsymbol{\theta}, \mathbf{u}, \boldsymbol{\Sigma}_g, \mathbf{c}, \boldsymbol{\Sigma}_c, \boldsymbol{\Sigma}_e, \sigma_{\varepsilon j}, \mathbf{y}) \sim N\left[\frac{RHS_i - \sum_{j \neq i} \lambda_{ij} t_j}{\lambda_{ii}}, \frac{1}{\lambda_{ii}}\right],$$

$$f(u_i \mid u_{-i}, \boldsymbol{\theta}, \boldsymbol{\beta}, \boldsymbol{\Sigma}_g, \mathbf{c}, \boldsymbol{\Sigma}_c, \boldsymbol{\Sigma}_e, \sigma_{\varepsilon j}, \mathbf{y}) \sim N\left[\frac{RHS_i - \sum_{j \neq i} \lambda_{ij} t_j}{\lambda_{ii}}, \frac{1}{\lambda_{ii}}\right], \text{ and}$$

$$f(c_h \mid c_{-h}, \boldsymbol{\theta}, \boldsymbol{\beta}, \mathbf{u}, \boldsymbol{\Sigma}_g, \boldsymbol{\Sigma}_c, \boldsymbol{\Sigma}_e, \sigma_{\varepsilon j}, \mathbf{y}) \sim N\left[\frac{RHS_i - \sum_{j \neq i} \lambda_{ij} t_j}{\lambda_{ii}}, \frac{1}{\lambda_{ii}}\right],$$

where β_{-l}, u_{-i}, and c_{-h}, are the vectors including the current values of these effects after discarding the i^{th} one, h represent the SNP markers (h = 1, 2, …, 237) and λ is the corresponding element from the coefficient matrix of the mixed models equations.

The conditional posterior distributions for the (co)variance matrices were the following inverted Wishart distributions:

$$f(\boldsymbol{\Sigma}_g \mid \boldsymbol{\theta}, \boldsymbol{\beta}, \mathbf{u}, \mathbf{c}, \boldsymbol{\Sigma}_c, \boldsymbol{\Sigma}_e, \sigma_{\varepsilon j}, \mathbf{y}) \sim IW[(\mathbf{u}'\mathbf{A}^{-1}\mathbf{u}), N_a - (n_p + 1)],$$
$$f(\boldsymbol{\Sigma}_c \mid \boldsymbol{\theta}, \boldsymbol{\beta}, \mathbf{u}, \boldsymbol{\Sigma}_g, \mathbf{c}, \boldsymbol{\Sigma}_e, \sigma_{\varepsilon j}, \mathbf{y}) \sim IW[(\mathbf{c}'\mathbf{c}), N_h - (n_p + 1)], \text{ and}$$
$$f(\boldsymbol{\Sigma}_e \mid \boldsymbol{\theta}, \boldsymbol{\beta}, \mathbf{u}, \boldsymbol{\Sigma}_g, \mathbf{c}, \boldsymbol{\Sigma}_c, \sigma_{\varepsilon j}, \mathbf{y}) \sim IW[(\mathbf{e}'\mathbf{e}), N - (n_p + 1)].$$

where n_p is the number of parameters assumed in the growth curve and N_h is the total number of SNP markers.

The conditional posterior distribution for the residual standard deviation ($\sigma_{\varepsilon j}$) have not closed form, thus the Metropolis-Hasting algorithm was used:

$$f(\sigma_{\varepsilon j} \mid \boldsymbol{\theta}, \boldsymbol{\beta}, \mathbf{u}, \boldsymbol{\Sigma}_g, \mathbf{c}, \boldsymbol{\Sigma}_c, \boldsymbol{\Sigma}_e, \mathbf{y})$$
$$\propto \prod_{j=1}^{n} \exp\left[-\frac{[y_{ij} - (a_i \exp^{(-b_i)} \exp^{(-k_i t_{ij})})]^2}{2\sigma_{\varepsilon j}}\right]$$

We applied a Metropolis-Hastings algorithm with a uniform proposal distribution centered at the current values b_i and k_i (as mentioned earlier). The choice of

the limits for this distribution determines the acceptance rate. If the width of such an interval is too small, the proposed values will be closed to the current ones, the rejection rate will be low but the process will move slowly throughout the parameter space. On the other hand, if it is too large, the proposed values are far away from the current ones and these results in a high rejection rate (Blasco et al., 2003). The above choice led to acceptance rates ranging between 50.74% and 52.45% (M1), 45.00% and 48.76% (M2), 48.80% and 50.67% (M3).

A total of 400,000 samples were generated, assuming a burn-in period and sampling interval (thin) of 100,000 and 10 iterations, respectively. The convergence of the MCMC chains using the BOA package (Smith, 2007) of R software.

Model testing

The goodness of fit analyzes for the considered models was based on the deviance information criterion (DIC) developed by Spiegelhalter et al. (2002): $DIC = D(\bar{\theta}) + 2p_D$, where $D(\bar{\theta})$ is a point estimate of the deviance obtained by replacing the parameters by their posterior means estimates in the likelihood function and *pD* is the effective number of parameters in the model, where $p_D = \bar{D}(\theta) - D(\bar{\theta})$. Models with smaller DIC should be preferred to models with larger DIC.

In addition to the goodness of fitting, we also calculated the predictive ability by cross-validation, which involved training one subset of the population (300 animals), and validating on the remaining individuals (45 animals). Here, we randomly split the data sets into two groups from the original data set (345 animals), these two subset were redefined 10 times, D1, D2, ..., D10. Finally, the average of the 10 correlation coefficients between the predicted and observed phenotypes was obtained.

The predicted weight ($\hat{y}_{ij}$) for animal i in time j based on Gompertz model was calculated as follows: $\hat{y}_i = \hat{a}_i \exp(-\hat{b}_i \exp(-\hat{k}_i t_{ij}))$, where $\hat{a}_i$, $\hat{b}_i$ and $\hat{k}_i$ are elements of the estimated vector $\hat{\theta}$ given by: $\hat{\boldsymbol{\theta}} = \mathbf{X}\hat{\boldsymbol{\beta}} + \mathbf{Z}\hat{\mathbf{u}} + \mathbf{M}\hat{\mathbf{c}}$. Thus, the solutions for these animals of the validation population were obtained based on the solutions of the training population animals.

The five tested models were applied to the 10 cross-validation replicates. In each replicate, systematic, genetic effects and SNPs markers effects were estimated and provided a phenotypic prediction for the masked animals. Finally, the predictive ability used to measure the efficiency of the models was given by the correlation between observed and predicted phenotypes from the validation population.

QTL identification

Based on SNP markers that were considered as relevant based on M2 (Eq. [4]) we verified the existence of QTL already described for growth traits by using the PigQTLdb tool (National Animal Genome Research Program, 2016). The traits which have been used in the PigQTLdb were body weights 34 weeks and at slaughter (related to parameter "a") and average daily gain (related to parameter "k").

Results and Discussion

Model comparison

Models were compared using the Deviance Information Criteria (DIC). The following results were obtained: model M3 (DIC=10572.73), model M1 (DIC=10745.97) and model M2 (DIC=10792.77) (Table 1). The M3 that considered the pedigree of animals associated with the information of SNP markers presented the best fit based on the lower DIC value.

Correlation coefficient between all predicted and observed phenotypic values were also used to access the goodness of fit (Table 2). The same model indicated by DIC (Pedigree and markers) was considered as the best one since presented higher correlation coefficients at all ages, except at birth. The superiority of this model was remarkable at last age (150 days), which has the greater economic relevance because correspond to weight at slaughter.

This result is in agreement with de los Campos et al. (2009) that, analyzing a mice population, concluded that the model that considered the pedigree with SNP's markers effects showed the best goodness of fit.

Predictive abilities were also calculated for all tested models in each evaluated ages (Table 2). All models presented lower predictive ability for initial phase of growth curve. Nevertheless, they were able to predict with higher predictive ability the weights at ages above 21 days. This lower predictive ability may be related to the fact that growth models do not fit well to the initial age, once prenatal growth of animals is not measured. This period is known for the maximum rate of tissues and organs, so will determine traits such as weight birth of piglets and the consequences established during prenatal life will be continuous throughout the life of the animal (Fall et al., 2003; Foxcroft and Town, 2004).

A slight decrease in the correlations at later ages (105 to 150 days) was also observed. This decay can be explained because the last age considered in this study is not the age of maturity itself, but the age at slaughter (150 days - 65 kg), i.e., the animals continue to growing after this period, as can be seen in Peloso et al. (2010) that evaluated carcass traits and meat quality in five distinct genetic groups of pigs with animals up to 202 days old.

Correlations between the predicted and observed phenotypes at different ages in growth functions are seldom used in the literature. However, the importance of these results is remarkable because they are useful in identifying factors in animal production that may be modified in order to change growth trajectories.

Variances components and heritability

The marginal posterior densities of the variance components showed that a large part of adult weight variation is due to additive genetic effects (Table 3). Higher influence of additive genetic factors on these growth curves parameters was also reported by Koivula et al. (2008) and Cai et al. (2012) in pigs, and by Forni et al. (2007) in beef cattle. The "a" parameter of the growth curve can be used as a selection criterion to control adult body weight that increases when selecting for growth rate, especially in situations in which the slaughter weight is reached before the maturity, as occurred in this study. Also "k" parameter can be used as a selection criterion indicating the rate that animals approach the adult weight (Table 3).

We opted to show only the results obtained for parameters “a” and “k”, since the parameter “b” has no biological interpretation. The heritability estimates (Table 3) indicate that “a” and “k” parameters can be an alternative for pig breeding programs that aim to produce animals with higher growth rate. Estimated values of the present study were higher than those found by Koivula et al. (2008) (a=0.44, b=0.55 and k=0.31), working on Finnish Yorkshire pigs also using the Gompertz model. This may be due to the effect of the variance of performance given the production function parameters, which was not considered in the analyses of those authors, what causes the estimation noise to be absorbed by the residual variances (Varona et al., 1999).

Considering the model that showed the best goodness of fit to the data (Pedigree and markers - M3), genetic correlation between the growth curve parameters was

obtained in order to assess whether the traits (a and k) are relevant for a breeding program. Direct selection for a high value of "a" parameter will also imply in selection for higher value of "k" parameter (as indicated by the high and positive genetic correlation, 0.78, between the two parameters), and therefore the selection will result in animals more precocious (high maturation rate) and heavier animals. This high and positive correlation between the parameters "a" and "k" was also reported in others growth curve studies, e.g., Cai et al. (2012) in pigs, which have obtained the same value reported here, and Forni et al. (2007) in beef cattle.

The use of pedigree associated with SNP markers may capture extra sources of genetic variance compared with models based only on pedigree (de los Campos et al., 2009). Similarly, Calus and Veerkamp (2007) working with simulated data, concluded that the inclusion of polygenic effects associated with marker information improved the variance components estimation. Results similar to those reported by these authors, we could see in this study (Table 3), in which the genetic variance was higher in model M3 (Pedigree and markers) compared with model M1 (Pedigree).

Small number and sparse distribution of SNP markers in the whole genome could be a limitation of the approach used at the present work. However, these markers were located in regions where QTLs have been found in previous studies in this same population (Silva et al., 2010; Hidalgo et al., 2013), thus generating a SNP marker panel that was able to capture the genetic variation on the considered traits (a, b and k parameters). Despite the relatively small number of animals evaluated, the population was structured with a F2 design, which results in large linkage disequilibrium blocks that improve the capture of genetic variance, even in low-density marker panels (Costa et al., 2015).

QTLs identification

The list of relevant SNPs based on the joint analysis, that affect the adult weight (a) and the maturity rate (k) in pigs, as well as their genome positions and the related QTLs (PigQTLdb - National Animal Genomes Research Program, 2016) are shown in a Supplementary Material. We considered only the markers that explained at least 0.5% of the total genetic variance (Figure 1). A total of 22 SNPs for the "a" parameter, 17 SNPs for the “b” parameter and 26 SNPs for the "k" parameter, distributed in chromosomes (SSC) 1, 4, 7, 8, 17 and X were selected. We opted to show only relevant markers that have influenced "a", "k" and both parameters simultaneously.

The SNPs explaining higher percentage of variance for the "k" parameter were associated with average daily gain. Approximately 23% of these SNPs are located in the SSC7. These results are in agreement with Ai et al. (2012) who found QTL for growth traits in this same chromosome, in a F2 pig population (White Duroc vs Erhualian); and Ruckertz and Bennewitz (2010), who reported QTLs in SSC7 for daily weight gain in crossbred pigs (European wild boars vs Meishan females).

The "a" parameter was associated with the weight at slaughter and the weight at 34 weeks, with the most relevant SNPs located on chromosomes 1, 4 and 8. These findings are in agreement with Koning et al. (2001) who found QTLs associated with final weight traits in these chromosomes in a F2 population (Meishan vs Large White, Dutch Landrace); Ai et al. (2012), who reported QTLs for weight at slaughter on chromosomes 4 and 8; and Liu et al. (2007) who detected QTLs for carcass composition and average daily gain in the SSC1, suggesting multiple QTLs in this chromosome in crossbred pigs (Pietrain vs Duroc).

We identified three relevant SNPs (55840514 bp at SSC17, 55814469 at SSC17 and 76475804 at SSC X) for "a" and "k" simultaneously, and three SNPs affecting only "a" (292758 bp at SSC1, 67319 bp at SSC8 and 50290193 bp at SSC17), that are located in genome regions not previously described in the literature (see Supplementary Material).

In summary, whereas the genome association analysis is an impartial scan of the entire genome without any assumption about the role of a certain gene, the QTL approach allows researchers to investigate the region where a specific marker of the gene underlying a complex trait is located. When combining these two approaches in the same study, we have the advantage of identifying QTLs from the same population in which relevant markers for the traits of interest were identified. In this context, a joint genomic association analysis of multiple potentially correlated traits, like growth curve parameters, may be advantageous. This approach has increased the power of QTL detection as reported by Galesloot et al. (2014), when comparing several multitrait and single trait GWAS methods. In addition, these authors suggested that the multitrait method may be able to identify genetic variants that are currently not identifiable by standard single trait analysis.

Conclusion

Markers may allow capturing fractions of additive variance that would be lost if pedigrees are the only source of genetic information used. The model including marker and pedigree information had better goodness-of-fit than pedigree-based or marker-based models.

The heritability estimates for mature weight ("a") and maturity rate ("k") indicated that these traits is a feasible alternative for breeding programs aiming to change the shape of growth curves in pig breeding programs.

The multitrait GWAS was efficient to report QTLs associated with functions related to biological processes of growth in pigs. Relevant SNPs are located in genome regions not previously described in the literature. Future studies targeting these areas could provide further knowledge to uncover the genetic architecture underlying growth curves in pigs.

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Figures

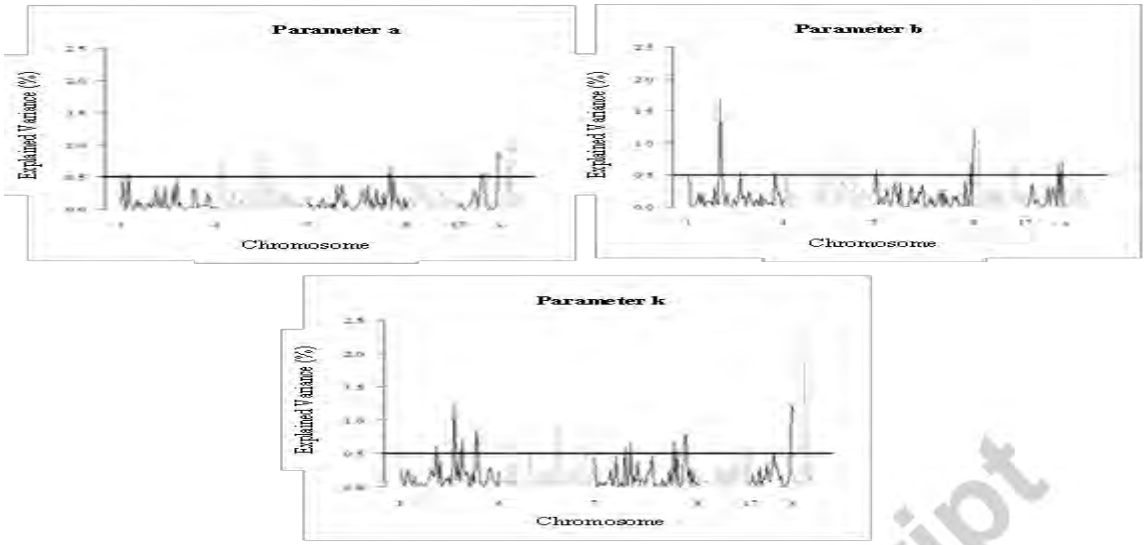

Figure 1. Percentage of total variance explained by each SNP for: (a) parameter "a", (b) parameter "b", (c) parameter "k".

Table 1. Deviance Information Criterion (DIC) for models.

Comparing Models	
Models	DIC
Pedigree (M1)[1]	10,745.97
Markers (M2)[2]	10,792.77
Pedigree and markers (M3)[3]	10,572.73

[1]Only pedigree information.

[2]Only markers information.

[3]complete model (pedigree and SNP markers information).

Table 2. Correlation coefficient between predicted and observed values from models including different sources of genetic information (pedigree, and pedigree and markers) and below means of the correlations of the 10 groups of the cross-validation and their standard errors (SE).

Dataset	Age	Pedigree (M1)[1]	Markers (M2)[2]	Pedigree and markers (M3)[3]
Full data	1	0.440 [0.049]	0.415 [0.049]	0.450 [0.048]
	21	0.770 [0.035]	0.767 [0.034]	0.795 [0.033]
	42	0.844 [0.029]	0.850 [0.028]	0.864 [0.027]
	63	0.868 [0.027]	0.869 [0.027]	0.887 [0.025]
	77	0.916 [0.021]	0.917 [0.021]	0.932 [0.019]
	105	0.916 [0.021]	0.917 [0.021]	0.922 [0.021]
	150	0.737 [0.036]	0.769 [0.034]	0.814 [0.031]
Cross-validation	1	0.202 [0.030]	0.123 [0.094]	0.198 [0.031]
	21	0.262 [0.053]	0.205 [0.109]	0.224 [0.052]
	42	0.360 [0.030]	0.275 [0.097]	0.311 [0.032]
	63	0.393 [0.031]	0.302 [0.062]	0.376 [0.025]
	77	0.423 [0.044]	0.343[0.120]	0.408 [0.042]
	105	0.459 [0.022]	0.395 [0.065]	0.393 [0.036]
	150	0.247 [0.023]	0.247 [0.050]	0.245 [0.028]

[1]Only pedigree information.

[2]Only markers information.

[3]complete model (pedigree and SNP markers information).

Table 3. Features of the marginal posterior distributions of additive genetic and residual variance components and heritability and highest probability density (HPD) of growth curve parameters from models including different sources of genetic information (pedigree, markers, and pedigree and markers) for each parameter.

Traits	Pedigree (M1)[1]	Pedigree and markers (M3)[2]
Additive Genetic Variance and HPD		
a	23.95 [0.40, 51.43]	30.42 [0.28, 68.10]
b	0.10 [$6x10^{-6}$, $1.5x10^{-1}$]	0.10 [$5x10^{-2}$, $2x10^{-1}$]
k	$1x10^{-7}$ [$4x10^{-8}$, $2x10^{-7}$]	$2x10^{-7}$ [$2x10^{-8}$, $3x10^{-7}$]
Residual Variance and HPD		
a	20.18 [0.78, 43.06]	22.35 [0.90, 48.16]
b	0.02 [$5x10^{-3}$, $5x10^{-2}$]	0.03 [$4x10^{-3}$, $5x10^{-2}$]
k	$9x10^{-8}$ [$3x10^{-8}$, $2x10^{-7}$]	$1.3x10^{-7}$ [$2x10^{-8}$, $2x10^{-7}$]
Heritability and HPD		
a	0.53 [0.11, 0.95]	0.56 [0.15, 0.94]
b	0.79 [0.60, 0.97]	0.77 [0.54, 0.97]
k	0.55 [0.24, 0.84]	0.57 [0.27, 0.87]

[1]Only pedigree information.

[2]complete model (pedigree and SNP markers information).

Highlights

- Growth curves with only pedigree data has been analyzed in two distinct steps.
- Hierarchical Bayesian model was obtained by joint analysis of the curve parameters.
- Hierarchical Bayesian models for growth curves were used under GWAS.
- The multitrait GWAS was efficient to report QTLs related to functions of growth.
- Relevant SNPs are located in genome regions not previously described.

Conflict of interest

This paper does not cause any conflict of interest including financial, personal or other relationships with other people or organizations.