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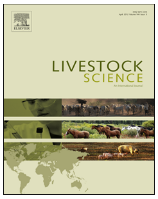

A new approach for applied nutritional models: Computing parameters of dynamic mechanistic growth models using genome-wide prediction

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ABSTRACT

Nutritional models have long been used as decision support tools by the livestock industry. Despite the advance of genomic prediction, these two disciplines have evolved separately. Because model parameters are responsible to describe between-animal variability, we propose an integration of nutritional models with genomics by means of such parameters. Two dynamic mechanistic models of cattle growth were used: Cornell Cattle Value Discovery System (CVDS) and Davis Growth Model (DGM). We estimated SNP marker effects for their parameters and also for observed phenotypes. Then, we compared what would be the best prediction scenario – model simulation with parameters computed from genomic data or genomic prediction directly on higher phenotypes. We found that genomic prediction on dry matter intake (DMI) and average daily gain (ADG) are still a better approach than using CVDS for predictions. Dry matter required (DMR), a CVDS-predicted value for DMI had higher correlation ($r=0.253$) with observed DMI than results from genomic prediction ($r=0.07$). DGM had better predictive ability ($r=0.38$) than genomic prediction on ADG ($r=0.098$). This is also the case for whole-body protein ($r=0.496$) and fat at slaughter ($r=0.505$) whose predictions were better with DGM than genomic prediction performed on the observed traits ($r=0.194$ and $r=0.183$, respectively). When contrasting simulations with genomically predicted parameters to those with regularly computed ones, CVDS showed moderate correlation and low bias between simulations of DMR ($r=0.966$; $b=0.9\%$) and ADG ($r=0.645$; $b=5.5\%$). Although further model development is necessary, the DGM with subject-specific parameters computed from genotypic data was a better option for predicting phenotypes than genomic prediction alone. In addition, simulations with genomically and regularly computed parameters match at a reasonable extend. This is the main argument to call attention from the research community that our approach may pave the way for the development of a new generation of applied nutritional models, especially towards individual-based simulations with subject-specific parameters computed from genomic information.

1. Introduction

Feed efficiency (FE) has been extensively studied by animal scientists due to its potential to enhance profitability in the livestock industry and also because feeding more efficient animals is a sound strategy to mitigate emissions of greenhouse gases (Nkrumah et al., 2006; White and Capper, 2013). For beef cattle, based on the concept of residual feed intake as a proxy for FE, feeding trials to record individual animal intake and growth performance have been conducted (Berry and Crowley, 2013; Herd et al., 2003). It was then hypothesized that nutritional mathematical models describing cattle growth could assist efforts to measure FE, appearing as a reasonable and lower cost approach, provided that equations would be able to capture between-animal variability in phenotypes related to animal growth (Tedeschi et al., 2005; Williams, 2010).

To date, nutritional systems such as those adopted by the National Research Council (NRC, 2000) still rely on population-based parameters. Between-animal variability is only possible to be captured by models when there is parameter variance. Therefore, computing subject-specific parameters facilitates simulations of between-animal variability. There is the possibility to compute parameters directly from genomic data, a potential that would facilitate the development of a new generation of nutritional models, depicted by the integration between system dynamics and genomics. Strategies towards this integration have been proposed

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using causally-cohesive phenotype-to-genotype (cGP) modeling as a method in the discipline of computational physiological genomics, which aims to incorporate computational physiology into genetics theory (Vik et al., 2011; Williams et al., 2006).

Many growth models may serve as a standard for exploring the possibility of obtaining nutritional model predictions with parameters computed from genomic information. Two of those available on the scientific literature offer an interesting contrast when it comes to the aggregation level: the Cornell Cattle Value Discovery System (CVDS) is used in commercial feedlot operations in the United States, and is comprised of sequential equations from the NRC (Tedeschi et al., 2004); and the Davis Growth Model (DGM), which refers to the differential equations developed by Oltjen et al. (1985), describing DNA accretion, protein synthesis and degradation, and fat synthesis.

We combined a phenotypic and a genotypic dataset of Nellore (*Bos indicus*) cattle under feedlot operations to assess accuracy and precision of CVDS and DGM outcomes when simulations are performed with parameters computed from genomic data. We began by regularly deriving parameters from observed data. Then, we conducted a genome-wide prediction (GWP) analysis with a ridge regression procedure on both the parameters and observed phenotypes. We asked what would be the best prediction scenario: (i) GWP on observed phenotypes, or (ii) model predictions with individual parameters computed from GWP. Model predicted variables were contrasted to both observed values and to those values obtained from simulations conducted with parameters computed from observed data.

Our goal is to discuss the possibilities of using technologies from animal genomics to support the development of a new generation of applied nutritional models. Specifically, in the context of the CVDS model, which was designed to compute individual dry matter intake (DMI) from observed animal performance, this work contributes suggesting directions to novel approaches for research on FE and how it could benefit from its interplay with mathematical modeling.

2. Material and methods

2.1. Ethics statement

No statement by the local animal ethics committee was necessary for this research. The study described herein used a dataset obtained from experiments published elsewhere (Alexandre et al., 2015; Gomes et al., 2013; Santana et al., 2012), whose authors report phenotype records and DNA samples from tests approved by their respective institutional animal ethics committee and by the cattle owners. All animals' procedures were undertaken within common management practices in beef cattle feedlot operations and in accordance with standard veterinary protocols.

2.2. The CVDS model

The CVDS model is comprised of sequential equations based on the NRC system (NRC, 2000). Animal characteristics, diet and environmental information are used to simulate daily individual DMI, body weight and carcass composition. The main parameter entering the CVDS model is the adjusted final shrunk body weight (AFSBW), which drives dynamics of retained energy. An exponential decay equation described by Tedeschi et al. (2004) is used to adjust the conversion efficiency of dietary metabolizable energy into net energy for gain (k_g) at each time step according to the composition of gain.

The CVDS model computes a reverse simulation. Observed average daily gain (ADG) and diet characteristics may enter the model to predict DMI using a backward calculation technique. In this case, DMI is conveniently named dry matter required (DMR), in a reference to the expected intake that would be necessary for the animal to meet observed performance.

The CVDS model was written in Visual Basic 6 and it is available at http://nutritionmodels.com/cvds.html. All the simulations described herein were performed without the environmental submodel and using the exponential decay adjustment for k_g.

2.3. The DGM model

The basic model underlying the DGM is the system of three ordinary differential equations described by Oltjen et al. (1985). Protein, fat and DNA pools are simulated daily. DGM relies on the accretion of whole body protein, and the DNA accretion rate (k_1) and DNA at maturity will shape growth trajectory and animal size. Protein dynamics depends on protein synthesis, which is conditioned to DNA at a given time point. Effects of energy intake on animal growth are incorporated into the model by terms that adjust DNA accretion and protein synthesis, and are obtained empirically. An equation that is also based on the net energy system of NRC (2000) drives residual energy (i.e. not used for maintenance and protein synthesis) towards fat deposition. Maintenance energy requirement is computed with an equation similar to that used by the NRC (2000), whose parameter (α) is important for modeling between-animal variation in protein and fat accretion.

2.4. The phenotypic and genotypic dataset

Observations of Nellore (*Bos indicus*) cattle ($n=893$) were obtained from fourteen feeding trials conducted in feedlot operations in South (Santana et al., 2012), Southeast (Alexandre et al., 2015; Gomes et al., 2013; Santana et al., 2015) and Central-West Brazil. These experiments were carried out in three different facility types (individual pens, Calan Gates or GrowSafe) to record individual daily feed intake with a length of 83 ± 10.64 days and regular weighing on 21 days. At feedlot entry animals averaged 550 ± 115 days of age and 357 ± 60.34 kg of live weight. ADG was estimated as the slope of a linear regression of weights on testing days. Phenotypic data was tested for normality with the Shapiro-Wilk test, and individuals that were more than twice the interquartile range above the third quartile or below the first quartile were excluded from the dataset.

Genomic DNA of these animals was extracted from either blood samples or hairs pulled from the skin. Samples were obtained from the feeding trials, and DNA was prepared as described by those authors. Imputation from Illumina BovineHD® BeadChip (777,962 SNPs), Affymetrix Axiom® Genome-Wide BOS1 Array (648,874 SNPs), GGP Indicus Neogen HD® (74,677 SNPs) and Illumina BovineSNP50® version 2 BeadChip (54,609 SNPs) to a dense panel (1,261,128 SNPs) was performed with accuracy higher than 97.5% for all scenarios. As standard practice, genotypic data was submitted to quality control and only autosomal SNPs with minor allele frequency $>2\%$ and deviation from Hardy-Weinberg equilibrium (χ^2-test, 1 *df*, $P > 1 \times 10^{-5}$) were kept for subsequent analysis. In the end, individuals had information on 941,033 SNPs.

2.5. Computation of model parameters

The AFSBW parameter of the CVDS model was computed from observed data using equations developed by Guiroy et al. (2001) and Baker et al. (2006) and adapted for *Bos indicus* cattle. We used 0.895 assumed by Marcondes et al. (2010) to be a better conversion between empty body weight (EBW) and actual shrunk body weight (SBW) factor (parameters of CVDS model) for *Bos indicus*