Animal (2020), **14:S2,** pp s238–s249
doi:10.1017/S1751731120000877

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A multi-inverse approach for a holistic understanding of applied animal science systems

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(Received 20 August 2019; Accepted 30 March 2020; First published online 30 April 2020)

*Technological and mathematical advances have provided opportunities to investigate new approaches for the holistic quantification of complex biological systems. One objective of these approaches, including the multi-inverse deterministic approach proposed in this paper, is to deepen the understanding of biological systems through the structural development of a useful, best-fitted inverse mechanistic model. The objective of the present work was to evaluate the capacity of a deterministic approach, that is, the multi-inverse approach (**MIA**), to yield meaningful quantitative nutritional information. To this end, a case study addressing the effect of diet composition on sheep weight was performed using data from a previous experiment on saccharina (a sugarcane byproduct), and an inverse deterministic model (named* Paracoa*) was developed. The MIA successfully revealed an increase in the final weight of sheep with an increase in the percentage of corn in the diet. Although the soluble fraction also increased with increasing corn percentage, the effective nonsoluble degradation increased fourfold, indicating that the increased weight gain resulted from the nonsoluble substrate. A profile likelihood analysis showed that the potential best-fitted model had identifiable parameters, and that the parameter relationships were affected by the type of data, number of parameters and model structure. It is necessary to apply the MIA to larger and/or more complex datasets to obtain a clearer understanding of its potential.*

Keywords: animal nutrition, evaluation, nutritive evaluation, ruminants, sheep nutrition

Implications

In applied animal science, a useful model is a tool that expands the understanding of a biological system. How can researchers construct useful models that benefit from new scientific developments? The deterministic multi-inverse approach is an alternative approach to traditional model development that provides new possibilities for the construction of useful models and offers valuable insight into understanding the research process. This technologically advanced approach can reduce the amount of time and human resources needed to optimize complex biological systems.

Introduction

Advances in technology and mathematical methods have provided new opportunities to study the holistic quantitative aspects of complex biological systems in different fields, including animal science (Reed *et al*., 2016), pharmacokinetics (Gelman *et al*., 1996), forecasting and environmental science (Young, 2006). The deterministic inverse problem approach (**DIPA**), defined as deterministic inference based on procedures, methods and techniques that allow the best structural description of a system and the true unknown values of its parameters to be driven by or inferred from data (Young, 2002), has become increasingly relevant for these new approaches. In animal science, the dominant methodology has been to use a deductive (top-down) approach to develop direct mechanistic models (Tedeschi and Fox, 2018). However, the DIPA is an inductive approach (bottom-up) approach that focuses on minimizing an objective function that describes the distance between an inverse model and the data and is limited by the behavior of the system.

In this work, a discussion of the inductive and deductive concepts is presented based on general definitions of scientific inference (Young, 2002) and addresses two research

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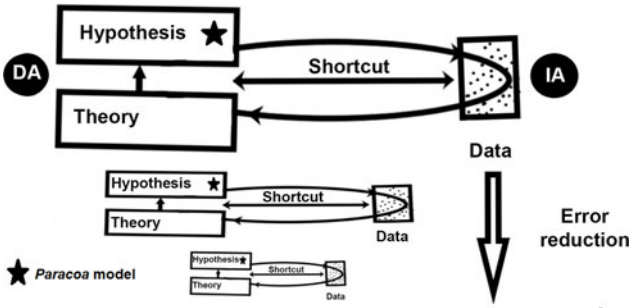


Figure 1 Conceptualization of deductive and inductive approaches within the integral research cycle. DA = deductive approach; IA = inverse approach.

cycles as it is described in Figure 1. In the first cycle, a predictive hypothesis deduced from a theory is tested in the real world and falsified or supported (deductive approach). In the second, observations (data) are used to find patterns (a model or a theory) that are then tested in the real world (Overmar *et al.*, 2007) (inductive approach); in this context, the data drive the process. Frequently, these cycles are considered different processes and consequently involve different approaches. However, we can consider them as two parts of a single research reasoning or process with two different research perspectives depending what is considered as driving the process, as shown in Figure 1: the hypothesis (deductive approach) or the data (inductive approach). In some cases, the researcher does not fully pass through both cycles (shortcut in Figure 1); regardless, the aim is to generate a theory and test it in the real world (Overmar *et al.*, 2007). D) Some authors divide the inverse inference (as opposed to forward inference) into inductive and abductive inference, which are both driven by the data; abductive inference is the process of forming an explanatory hypothesis (Fischer, 2001). In multi-inverse approach (**MIA**) process, the focus is on answering a biological question without restricting the approach to specific logical forms throughout every step of the research process. In the research process, the cycle is repeated indefinitely, never finishes, and the researcher increasingly approaches the data or theory, depending on whether the approach is deductive or inductive approach (Figure 1). In both approaches, the researcher views the overall process. DIPA is an inverse approach because the theory (model) is inferred from the data; however, depending how the observations (data) are used to find patterns (a model, a theory) (Overmar *et al.*, 2007), it can be very similar to a deductive approach.

The principal concern in modeling biological systems has been the estimation of the true values of unknown parameters because they are considered essential for constraining model predictions, where the true value is the value obtained with perfect measuring instruments without committing any error of any type and ideal conditions of high-frequency data. The value of a parameter is frequently obtained through independent measurement; however, if the measurements are imprecise or incomplete (Gutenkunst *et al.*, 2007b) or the measurement conditions vary (Guanawardena, 2010), the measurements will yield uncorrelated parameter uncertainties as described by Gutenkunst *et al.* (2007b), as a consequence of the model structure (Gutenkunst *et al.*, 2007a). However, recent studies have revealed that it is not essential to have the true unknown parameter values to constrain the model predictions (Gutenkunst *et al.*, 2007a); rather, the predictions can be constrained with a modest number of experiments in which the parameter set is obtained from collective parameter fitting (Gutenkunst *et al.*, 2007a) as sets of parameters can yield similar predictions. Therefore, the collective parameter fitting could reduce the amount of experimental data required to estimate parameters (Gutenkunst *et al.*, 2007a) and can increase the discrimination between them (Maiwald and Timmer, 2008). The correct description of the system is important because uncertainties in the structure of the model are often a source of uncertainty in predictive simulations (Højberg and Refsgaard, 2005).

Other concerns in modeling biological systems related to the discrimination of process, integration of system descriptions, data interpretation and understanding of biological process are discussed by Vargas-Villamil and Tedeschi (2014) and schematically represented in Figure 2. The representation shows the potential relations of DIPA centered in biological questions where different methodologies (e.g., multiexperimental fitting, system identification and holistic design) related to previously studied processes (e.g., discrimination of process, discovery of biological relations, integration of system, uncertainty reduction of parameters or predictions and quantification of parameters) can aid the understanding of biological aims. In this research process, the study of parameter values, function errors, sloppiness (insensitivity to parameter value changes), identifiability profile likelihood (**PL**) surface and computational efficiency could have a central role.

In the proposed MIA, a deterministic approach, it is understood that the full use of all available quantitative information about a system (data and scientific information) during a scientific process allows the researcher to obtain an integral quantitative structural description of that system as well as the parameter values linked to its structure. The correct description of the system is important because uncertainties in the structure of the model are often a source of uncertainty in predictive simulations (Højberg and Refsgaard, 2005). Therefore, this approach can help describe and predict the biological system more efficiently. However, this complex process requires new mathematics, statistics and computing resources (Maiwald and Timmer, 2008). It can be hypothesized that MIA has the potential to restrict the structural description of the system and the time invested in and steps between the collection of experimental data and the acquisition of meaningful quantitative information.

To evaluate MIA, data from a previous saccharina experiment were used to perform a case study. Sugarcane (*Saccharum officinarum*) is a resource that can be used in times of drought or flooding to improve production efficiency in ruminants (Preston, 1977). Similar to other fibrous residues, it has low nitrogen, mineral, and vitamin contents

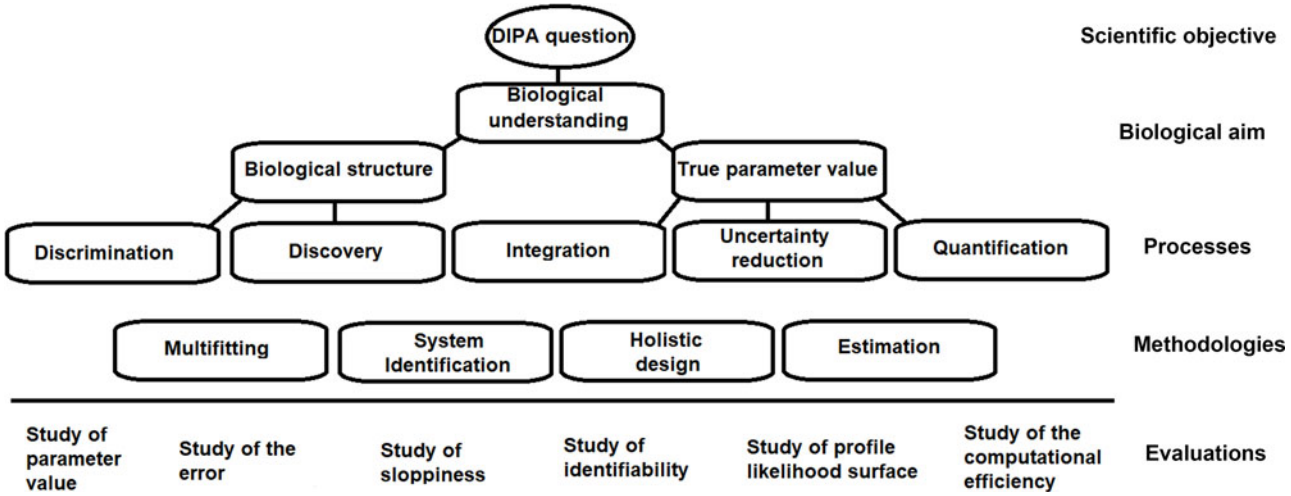


Figure 2 Schematic representation of a deterministic inverse problem approach (DIPA).

and a high cell wall content that can be improved through solid-state fermentation (**SSF**) to facilitate its use in ruminant feeding. The final enriched product of this process, which has better nutritional characteristics than sugarcane or its residues, is called saccharina (Elías *et al.*, 1990). Saccharina can be prepared with different types of feed (Ramos *et al.*, 2006). Although scientific papers related to saccharina and its derivatives are limited in number and diverse in focus, they have demonstrated the potential of this substrate for use in ruminant diets (Ramos *et al.*, 2006).

Fermented saccharina can be used with whatever grain-based feeds and/or byproducts are economically and nutritionally accessible to the producer. This flexibility is advantageous for the local producer, but nutritional evaluation of the resulting feeds is difficult. The nutritional evaluation of saccharina diets is complex because the development of the product includes two fermentation processes: the SSF outside of the animal and the microbial fermentation inside the animal's rumen. Outside the animal, the high nutritional content of sugarcane is used as an energy source for the growth of microorganisms (Ramos *et al.*, 2006), which increases the true protein content and fiber degradation, thereby decreasing the fiber content (Ramos *et al.*, 2006). A nutritional diversity of food components such as saccharina is typical in modern nutritional databases in applied animal science (**AAS**). In many cases involving complex systems, it is possible to find several similar processes, as is the case for SSF and other saccharina-based diets.

Researchers can employ two primary approaches to estimate parameters such as those required for saccharina study: (1) obtain parameter values through fitting noncomplex empirical or mechanistic models, which reduces the size of the database and decreases the integration of the system evaluation process or (2) obtain the values through integral collective parameter fitting (multifitting) of complex models (multiparameter models), which increases the complexity of the system and the uncertainty of the parameter values (Vargas-Villamil and Tedeschi, 2014). The decision of which approach to employ is important because it will not only determine the accuracy and constraints of the predictive model for future simulations and parameter restriction but also define the resources needed to study the system.

In AAS, researchers have addressed the above-mentioned dilemma using a statistical Bayesian approach, fitting more complex models to greater AAS data and making approaches (1) and (2) possible (Gelman *et al.*, 1996; Huang *et al.*, 2012; Reed *et al.*, 2016). Bayes theorem is used for updating the *a priori* probability distribution of the biological parameter when additional evidence (observed data) is obtained. A likelihood function (statistical model) is assumed for the observed data, and Bayes theorem is used for obtaining the *a posteriori* probability distribution for the parameter. Regarding the model, in AAS Bayesian research, an assumed correct mechanistic model is used. Bayesian inference (i.e., parameter estimation and calculation of highest posterior density intervals) is based on the posterior probability distribution of the parameter. In contrast, DIPA focuses on the deterministic structural description of a system and the estimation of the true unknown values of the parameters linked to the structural description of the system.

When studying model structure, it is valuable to construct and evaluate a useful best-fitted model according to the recommended steps for integrating a DIPA (Vargas-Villamil and Tedeschi, 2014). Therefore, with the proposed MIA, this paper will (1) design an inverse model in terms of biologically meaningful relationships and parameters focused on complementary data; (2) develop an inverse mechanistic model set from simple to complex structures, where the complexity increases in accordance with the understanding of the problem being solved and where the research cycle as discussed previously (Figure 1) can be accelerated by the number of models evaluated; (3) fit models to complementary data; (4) evaluate model convergence; (5) evaluate the models; (6) evaluate the parameters; and (7) assess model adequacy. To accomplish these steps and obtain the parameter values, data from the previous saccharina experiment mentioned above were used to perform an MIA case study (Godínez Juárez, 2014), and a model named *Paracoa* was built. The complexity of the system, which has limited the modeling approaches used for its evaluation

(Ramos *et al.*, 2006) and their pertinence for local producers, made saccharina tropical feed suitable for a case study of nutritional evaluation via DIPA in AAS. Preliminary results were published in Advances in Animal Biosciences for the 9th Workshop on Modeling Nutrient Digestion and Utilization in Farm Animals (Vargas-Villamil *et al.*, 2019).

Material and methods

The term 'multi-inverse approach' was coined based on concepts described by Vargas-Villamil and Tedeschi (2014) to describe system evaluation based on DIPA (Figure 2), which explores the use of multiparameter models, multifitting, and multimodal solutions to discriminate parameters, interpret data and expand the integral understanding of an AAS system (Vargas-Villamil and Tedeschi, 2014). For this purpose, a mechanistic frame model (Figure 3) called *Paracoa*, which means 'rainbow' in the Comanche language, was developed based on the concept of mass balance through the design of a compartmental system structure. The premise of this frame model is that there exists a basic biological structure from which to extend equations for the study of different biological concepts or theories as well as for MIA evaluation. The model describes four biological processes: voluntary feed intake (**VFI**), degradation, passage rate and mass transformation from postruminal biomass to animal tissue. A multiparameter degradation model (Figure 3) was developed and integrated as a submodel into the *Paracoa* model. The multiparameter degradation model was also used separately to obtain the parameter values used in the *Paracoa* model.

To develop and construct the best-fitted *Paracoa* inverse model set to improve the structural description of the biological system, different theories regarding the relation between model structure and system behavior were investigated. The effects of treatment, model structure, parameter type, parameter value and objective function value (**OFV**) were studied. Finally, the best-fitted *Paracoa* model was chosen and evaluated. Descriptions of the settings, abbreviations and descriptions of the variables used, globally and locally adjusted parameters and constant and initial state values, and a description of the *Paracoa* model are provided in Supplementary Tables S1 to S4, respectively. In this work, the difference between globally and locally adjusted parameters is that the former are available to or associated with all the models evaluated, whereas the later are available to or associated with only one model. A detailed description of the quality assurance evaluation of the *Paracoa* model can be found in Supplementary Material S1, and copies of 2-P parameter *Paracoa* model code, data and results obtained during the particle swarm (**PS**) evaluation are provided as supplementary material files (Mod_MIA_(ParSwarm)_LV 0911_2019.cps, Data_MIA_(ParSwarm)_LV 0911_2019.txt and Results_MIA_(ParSwarm)_LV 0911_2019.txt).

Software resources

The *Paracoa* and multiparameter degradation models were built using Stella v10 (Doerr, 1996). They were then reconstructed in CellDesigner v4.3 because Stella v10 is based on XMILE and CellDesigner v4.3 is based on SBML structures; although both structures are XML representations of system dynamics models, they are not compatible. The first standard is more suited for the diagrammatic building of models or online model presentation, and the second is more suited for the computing solution of models; both processes were required in developing *Paracoa*. Due to its SBML compatibility, CellDesigner v4.3 was used as a link between Stella v10 and the SBML software used in this study (COPASI v4.8. and SBMLSimulator v1.2.1). The *Paracoa* and degradation models were exported from CellDesigner v4.3 to COPASI v4.8 (Build 35) (Mendes *et al.*, 2009) and SBMLSimulator v1.2.1 (Dörr *et al.*, 2014), respectively. The decision regarding the software used for each model was made based on the complexity of the model, the mathematical methods and the usability of the software for similar future evaluations.

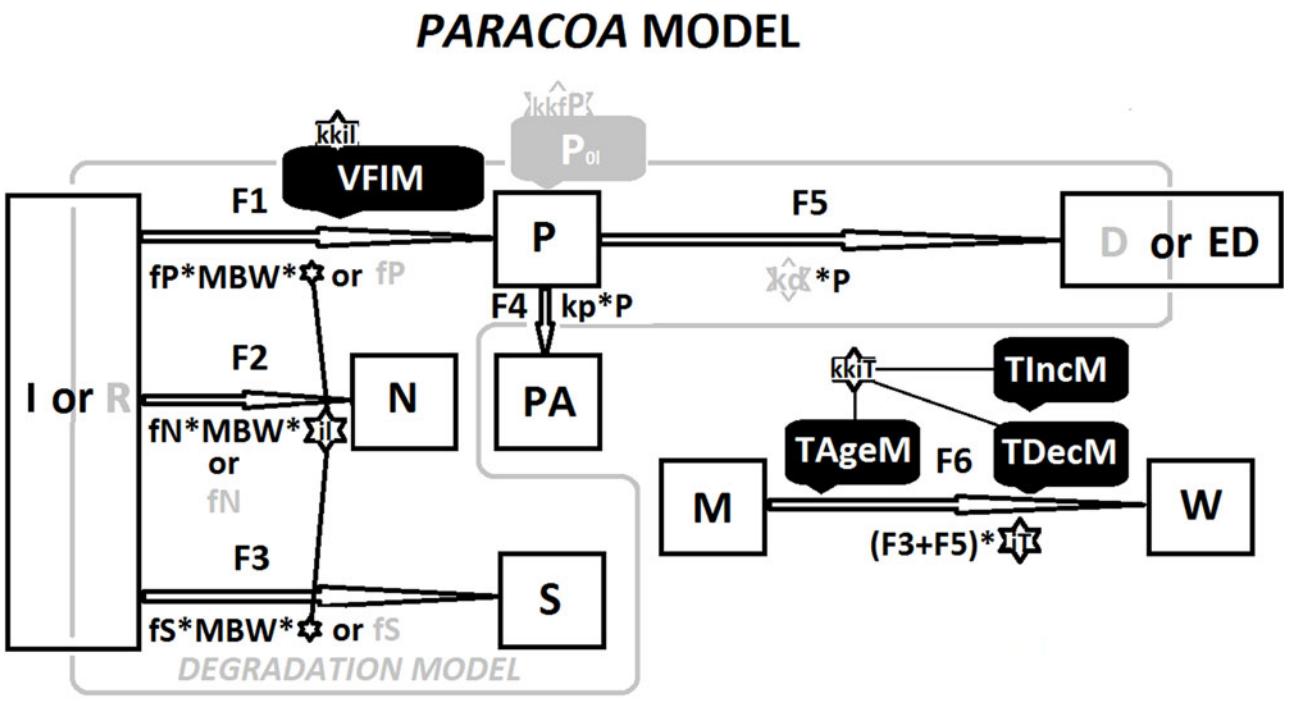
Optimization methods and settings

An array of *Paracoa* model (1×22), that contain three state variables, was adjusted to 44 curves (22 intake and 22 weight curves) to estimate 2-to-4-global-parameter set (*il, iT, kkil* and *kkiT*), counting 66 state variables for the total *Paracoa* array. The method used for optimizing the degradation and *Paracoa* models was PS (Kennedy, 2010). The EvA2 Workbench module, developed in SBMLSimulator v1.2.1 software (Kronfeld *et al.*, 2010), was used for parameter optimization of the multiparameter degradation model, and the Parameter Optimization Task in COPASI was used for the *Paracoa* model. The initial time, final time, differential equation solver and quality function were the same for all evaluations (Supplementary Table S1) unless stated otherwise. The initial, modified and potentially best-fitted *Paracoa* models were evaluated through statistical comparison of the root mean square, although other statistics can be used for the same purpose (Tedeschi, 2006).

The optimized *Paracoa* parameters were the VFI index (*il*), transformation index (*iT*), increase in the VFI index (*kkil*) and increase/decrease in the *iT* indexes (*kkiT*). The term 'transformation' refers to the difference between the mass absorbed and the mass converted to animal gain. In addition, the 22 initial state variables, such as metabolic BW (**MBW**), were selected for parameter optimization but not considered for evaluation. The degradation constants used during the *Paracoa* model evaluations were obtained through parameter estimation of the multiparameter degradation model. These global optimized parameters were as follows: the fractional degradation rate (*kd*) and the increases in the potentially degraded fraction (*kkfP*), the nondegradable fraction (*fN*), and the potentially degradable fraction (*fP*). An array composed of four degradation models was adjusted to the four level-of-corn datasets, and all models were fitted on a single run using global parameters.

Evaluation of biological theories

The nutritional data used in this paper were published previously (Godínez-Juárez *et al.*, 2017) in a study evaluating



PARACOA* MODEL: Optimized *parameters: il, VFI index; iT, transformation Index; kkil, increase of il; kkiT, increase or decrease of iT. ***Variables***: kd, degradation fractional rate; kkfP, increase of potentially degradable fraction, kp, Passage fractional rate; MBW, Metabolic body weight. ***State variable*:** P, potential degradable biomass; N, non- degradable fraction; S, soluble biomass; M, mass; W, body weight; ED, effective degraded biomass; PA, non-degraded surpassed biomass. ***Fluxes:*** I, Intake rate; F1 = IntakeP, VFI of potentially degradable biomass or Potentially degradable fraction; F2 = IntakeN, VFI of Non- degradable biomass; F3 = IntakeS, VFI of soluble biomass; F4 = Pas, Passage of biomass. F5 = Deg, Degradation of biomass; F6 = Gain, Body weight gain. ***Model modification:*** VFIM, increase of VFI; TAgeM, post-degradation dry matter transformation related to animal age; TIncM, increase of iT parameter values as a consequence of the level of corn treatment; TDecM, decrease of iT parameter values as a consequence of the level of corn treatment.

DEGRADATION MODEL: ***Optimized parameters:*** kd; kkfP. ***State Variable*:** R, biomass in the nylon bag in the rumen; P; N; S; D, degraded biomass. ***Fluxes:*** F1 = fP, potentially degradable fraction; F2 = fN, non-degradable fraction; F3 = fS, soluble fraction; F5 = Dege, effective degradation of biomass; F6 = Gain, Body weight gain. ***Extended equation:*** $P_{0.I.}$ P, potential degradable biomass at 0 % of corn level.

Figure 3 Simplified scheme of the *Paracoa* and degradation models of ovine. VFI = voluntary feed intake.

the VFI and the productive behavior of sheep fed saccharina with ground corn and ruminal degradation *in situ* in bovines. The animals evaluated were 24 growing Katahdin × Pelibuey sheep, with an initial average weight of 17 ± 3.0 kg, and the treatments were as follows: saccharina (S) + 10% corn (T10), S + 20% corn (T20), S + 30% corn (T30) and S + 40% corn (T40).

Here, an initial *Paracoa* model, a frame model, was optimized to estimate the *il* and *iT* parameter values using the experimental database from Godínez-Juárez *et al.* (2017) as a reference for the posterior optimization evaluations. Then, biological theories regarding the structure of the system were studied. Details of the procedures are described below.

The effects of corn levels on the parameters and OFV were evaluated through COPASI optimization of the *Paracoa* model. The dataset obtained from the experiment described above was divided into four treatments representing different levels of corn in the diet (T10, T20, T30 and T40) and evaluated according to its interaction with the number of parameters fitted, the type (*il* and/or *iT v.* passage rate) of parameter and the time interval (0 to 13, 17 to 33, 35 to 48, 49 to 62 and 63 to 77 days) in the following procedures: (a) first, every level of corn in the diet was contrasted to 0-parameter, 1-parameter and 2-parameter model

optimization, where the model parameter number refers to the *il* and/or *iT* parameters. (b) Second, every level of corn in the diet was contrasted to every time interval. For parameter(s) that was/were not studied, the parameter value(s) was/were considered to be the same as the initial *Paracoa* model estimate. (c) Third, every level of corn in the diet was contrasted to 0-parameter and 1-parameter model optimization, where the number of the model parameter refers to the passage rate parameter.

The effects of biological structure on the parameters and OFVs were evaluated through COPASI optimization of the *Paracoa* model. The *Paracoa* model was modified four times to evaluate whether a detailed description of VFI (VFIM), postdegradation DM transformation related to animal age (TAgeM) or *iT* related to the level-of-corn treatment (TInc and TDec) could improve the description of the behavior of the system. The *iT Paracoa* modification described an increase (TIncM) or decrease (TDecM) in the *iT* parameter values in response to the level-of-corn treatment. Additionally, the 2-parameter control (initial *Paracoa* model) was evaluated. VFIM, TIncM and TDecM are presented as extended equations in Supplementary Table S4.

The construction, evaluation and biological meaning of a theoretical best-fitted model (the final *Paracoa* model) were accomplished through (a) the construction of a potential best-fitted model, (b) a numerical solution of the best-fitted standardized model, (c) the biological meaning of the best-fitted model, (d) parameter evaluation (correlation matrix and Fisher information matrix (**FIM**), (e) PL and PL contour (Schaber, 2012) and (f) model adequacy. The construction of a 4-parameter model (the final *Paracoa* model) was completed as an outcome of previously described evaluations where the best hypothetical descriptions of the biological relations and parameters were used to build the model. The final model was evaluated and run three times. The standardized model was a copy of the best-fitted model with a single initial animal weight, as shown in Supplementary Tables S1 and S3.

Finally, the OFV obtained with COPASI was used to evaluate the model adequacy between the initial model (2-parameter model) and the potentially best-fitted model (4-parameter model) with both VFI and MBW. The model adequacy was evaluated globally and by treatment. Globally, the evaluation was performed using a 95% confidence interval for the differences between the means when the samples were paired or dependent (Zar, 2010) because the normality assumption was met for the variable differences. However, by treatment, the evaluation was conducted based on 95% nonparametric bootstrap confidence intervals (Chihara and Hesterberg, 2011) because the normality assumption was not satisfied. Ten thousand nonparametric bootstrap samples were randomly selected to determine the observed differences in the determination of each confidence interval. The software utilized for global and per-treatment best-fit evaluations was STATGRAPHICS Centurion XV v. 15.2.06 (StatPoint, 2007).

Results

Objective function value and parameter values

Fitting the initial *Paracoa* model to the data by the level of corn reduced the OFV to a mean of 2.4411 (Table 1), whereas without grouping, the mean was 7.6656 (Table 2). The value consistently increased from T10 to T40 (1.1394, 2.3335, 3.0831 and 3.2086, respectively). The trend was similar only when the 1-parameter model, not the 2-parameter model, was optimized ($OFV_{il} = 2.4685$ *v.* $OFV_{iT} = 2.7243$). The OFV mean obtained from the 2-parameter, *il*-parameter and *iT*-parameter fitting was extremely close to the mean obtained from the level-of-corn fitting (2.5447 *v.* 2.5447, respectively), indicating potential additive effects. The reduction in the number of fitted parameters also had a minor effect on the mean parameter values of 0.0775/kg and 0.1730/kg for *il*-parameter and *iT*-parameter fitting, respectively, compared with the values from 2-parameter fitting (0.0776/kg and 0.1782/kg). However, the parameter tendency differed with corn level. The *il* values increased for every level of corn both for the 2-parameter (0.0671/kg, 0.0734/kg, 0.0752/kg and 0.0946/kg) and the *il*-parameter fitting (0.0673/kg, 0.0742/kg, 0.0752/kg and 0.0946/kg), whereas *iT* had a peak at T20, with its next

Table 1 *Effects of corn level on parameter values and objective function value (OFV) for the level of corn*

Kind of run	T10[1]	T20	T30	T40	Mean
Without parameters	(1.32613)[4]	(2.43031)	(3.18429)	(4.05484)	2.7488925
il[2]	0.0673703[3]	0.0742011	0.0746042	0.0941422	0.07757945
	(1.14305)	(2.38355)	(3.12389)	(3.22382)	(2.4685775)
iT	0.167863	0.219035	0.121532	0.18378	0.1730525
	(1.32569)	(2.39616)	(3.12347)	(4.05213)	(2.7243625)
il and *iT*	0.0671475[*il*]	0.073484	0.0752893	0.094687	0.07765195
	0.196206[*iT*]	0.23396	0.127692	0.155113	0.17824275
	(1.13941)	(2.33358)	(3.08314)	(3.20861)	(2.441185)
Mean	1.202716	2.371096	3.11016	3.494853	2.54470833
					2.54470625

[1]Treatments: T10 = saccharina (S) + 10% corn; T20 = S + 20% corn; T30 = S + 30% corn; T40 = S + 40% corn.
[2]Parameters: *il* = voluntary feed intake index; *iT* = transformation index.
[3]Adjusted value.
[4]OFV = objective function value.

Table 2 *Effects of model structure on the parameter values and objective function value (OFV)*

Model modification[1]	*il*[2] (1/kg)	*iT* (1/kg)	*kkil* (1/unit)/*kkiT* (kg/kg)	OFV
–	0.0788265	0.174694	–/–	7.66566
VFIM	0.0578078	0.17289	0.0135722/–	7.13916
TAgeM	0.0780346	0.398234	–/0.0138645	7.50842
TIncM	0.0788265	0.174694	$-/9.72673 \times 10^{-17}$	7.66566
TDecM	0.0787156	0.142901	–/0.0401004	7.96895
VFIM[3] TAgeM	0.0572283	0.401990	0.0135517/ 0.0140821	6.97367

[1]Modification of *Paracoa* model as described in Supplementary Table S4: VFIM = voluntary feed intake; TAgeM = postdegradation DM transformation related to animal age; TIncM = *iT* related to the increase-of-corn treatment; TDecM = *iT* related to the decrease-of-corn treatment.
[2]Parameters: *il* = voluntary feed intake index; *iT* = transformation index; *kkil* = increase in *il*; *kkiT* = increase in *iT*.
[3]2-parameter model.

highest level at T10 and T40, in both the 2-parameter (0.1962/kg, 0.2339/kg, 0.1276/kg and 0.1551/kg) and *iT*-parameter fitting (0.1678/kg, 0.2190/kg, 0.1215/kg and 0.1837/kg).

These results show that reducing the amount of data decreased the mean OFV (0.2979) and mean *iT* values (0.1375/kg), but the *il* value was closer (0.0775/kg) to that reported previously. As observed in the level-of-corn fitting mentioned above, the OFV and parameter value means (grouped by corn level × time interval) had an additive effect when the mean was calculated by the level of corn or time interval because they were the same (Table 2). However, the same trend was not found when a corn level × time interval group was arbitrarily chosen. The individual fitting of arbitrarily chosen data grouped by every six animals (T20 × 49 to 62-days group) produced means (*il* = 0.0785/kg, *iT* = 0.6214/kg and OFV = 0.0391) that differed from those found when fitting the six-animal groups as a whole (*il* = 0.0753/kg, *iT* = 0.3/kg and OFV = 0.1769).

The passage rate parameter had a minimal effect on OFV when it was estimated for every level-of-corn treatment (mean 2.7388) compared with the *Paracoa* model without the parameter (mean 2.7488), both of which were optimized only with initial values. The reduction was 0.38% (0.0104), whereas the mean reductions in *il* and *iT* under the same conditions were 10.20% and 0.89%, respectively. It is important to note that the sum of these reductions was equal to that obtained when *il* and *iT* (2-parameter fitting) were estimated together (11.09%) due to the potential additive effect of these parameters.

After the best-fitted model (4-parameter model) was chosen as discussed below, the best-fitted standardized simulation (Vargas-Villamil and Tedeschi, 2013), run in COPASI, showed that the final weight increased with the level of corn in the diet (T10 = 25.59 kg, T20 = 26.47 kg, T30 = 27.35 kg and T40 = 28.23 kg) (data not shown). The final weight increase was not observed for all treatments during the direct weighing of the animal (T10 = 24.50 kg, T20 = 24.80 kg, T30 = 27.50 kg and T40 = 26.16 kg) but as a linear increase in weight gain similar to that observed in this work (6.00, 7.00, 8.17 and 9.33 kg, respectively) (Godinez-Juárez *et al.*, 2017). The weight gain difference from T10 to T40 was 0.69 kg (26%), and the value calculated from direct weighing of the animals was higher than that obtained with MIA (Godinez-Juárez *et al.*, 2017). The absolute soluble fraction flow (calculated from 0 h of ruminal incubation) increased with the level of corn from T10 to T40 (0.0477 kg/day), and the effective nonsoluble degradation flow (calculated from the potential degradable fraction) increase was fourfold higher than that at 0 h and was more important by fourfold (0.1920 kg/day) (Table 3).

Parameter evaluation

As shown in Supplementary Table S5, all the parameter combinations had high capacity of parameter restriction except the combinations in which *iT* was involved (Figures 4 and 5); FIM was interpreted as the sensitivity to infinitesimal changes. However, this conclusion is based on the assumption that the method used is accurate, which is discussed below. If the model structure modifies the relationships among the parameters, data, model and fitting, the method will change as a result of a change in structure, and thus the correlations and the quality of the estimation results will change (Li and Vu, 2013).

The fitting results from the 2-parameter model yielded an *il* x *iT* correlation of 0.7299, with an FIM value of 277 164 in the FIM matrix for the same *il* x *iT* combination (data not shown). The increase in the number of parameters modified the parameter relationships and FIM value (Supplementary Table S5). As shown in the table, relative to the corresponding value obtained by 2-parameter fitting, the *il* x *iT* correlation value greatly decreased to –0.2188, but the FIM value increased (303 638) compared with those obtained by 2-parameter fitting. These results can be interpreted as revealing a reduction in the relationship between the parameters with a small increase in the capacity of the experiment to constrain both parameters, a valuable phenomenon during

Table 3 *Standardized effective flow from the rumen of DM diets prepared with saccharina at different levels of corn*

Effective DM flow	T10[1] (kg/day)	T20 (kg/day)	T30 (kg/day)	T40 (kg/day)
Solubilized	0.490252584 (83%)	0.5160682016 (78%)	0.5322388595 (71%)	0.5380075264 (65%)
Nonsoluble	0.1024541972 (17%)	0.1555621278 (24%)	0.2194017534 (29%)	0.2945028762 (35%)
Total	0.5927067812	0.6716303294	0.751640613	0.8325104025

[1]Treatments: T10 = saccharina (S) + 10% corn; T20 = S + 20% corn; T30 = S + 30% corn; T40 = S + 40% corn.

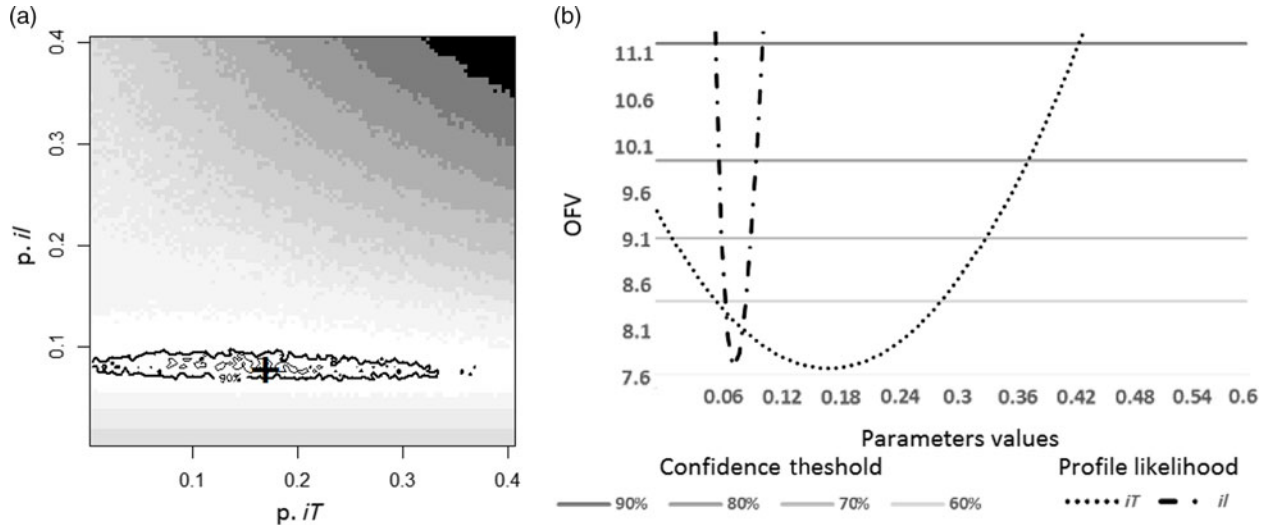


Figure 4 Parameter profile likelihood (PL) contour (a) and PL (b) for the 2-parameter *Paracoa* ovine model. Parameters: *il* = voluntary feed intake index; *iT* = transformation index; OFV = objective function value.

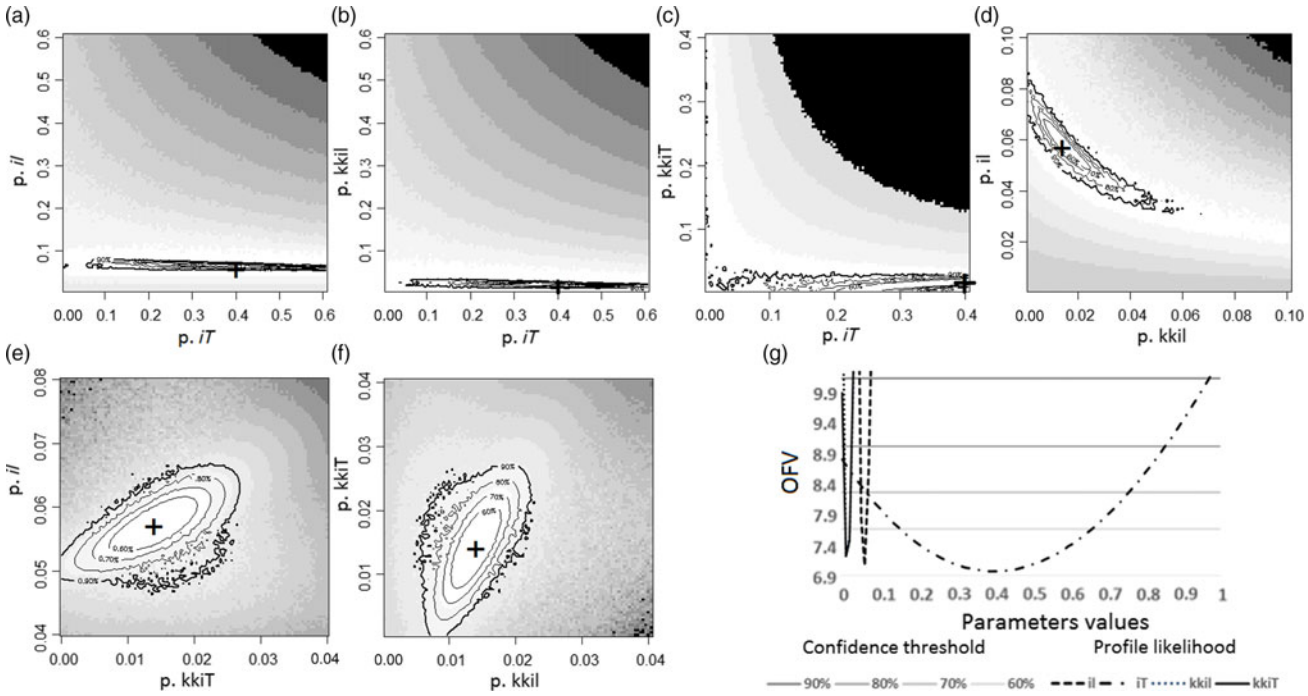


Figure 5 Parameter profile likelihood (PL) contour (a to f) and PL (g) for the 4-parameter *Paracoa* ovine model. Parameters: *il* = voluntary feed intake index; *iT* = transformation index; *kkil* = increase in *il*; *kkiT* = increase in *iT*. OFV = objective function value.

fitting evaluations. However, the *iT* FIM value was reduced from 123 131.000 to 106.463, likely due to the emergence of a new correlation with the *kkiT* parameter during the 4-parameter fitting (0.7258). In contrast, a high correlation between *il* and *kkil* (–0.9202) had no effect on either *il* or *kkil* FIM values, indicating a high capacity of the experiment to constrain these parameters. This capability may be a consequence of the type of correlation presented in the parameter relationship (Vargas-Villamil and Tedeschi, 2014) or of the quality of the available data (Ashyraliyev *et al.*, 2008; Li and Vu 2013) that indicate differences between the utility of the correlation and FIM for parameter evaluation. The other parameters all had high FIM values due to low correlations, as shown in Supplementary Table S5.

Best-fitted model adequacy

The global evaluation of the 4-parameter best-fitted model (**BM**) and its comparison with the 2-parameter initial model (**IM**) for VFI and MBW output variables showed that zero was not within the range of the 95% confidence intervals (VFI, $-0.00522 \leq \mu_{VFI,BM} - \mu_{VFI,IM} \leq -0.00047$; MBW, $-0.03425 \leq \mu_{MBW,BM} - \mu_{MBW,IM} \leq -0.00582$). Thus, the averages were significantly different; moreover, because the limits were negative, the OFVs for VFI and MBW in the

BM were smaller than those obtained in the IM, at least for 0.00047 and 0.00582 units, respectively. However, the evaluation of BM at T10, T30 and T40 for the VFI and MBW output variables showed that zero was not within the 95% bootstrap confidence intervals, indicating significant differences between the BM and IM output variables. Since the limits for T10, T30 and T40 were negative for VFI, except for T30 and MBW, the OFVs in the BM were smaller than those estimated in the IM for these treatments. T30 and MBW had positive limits, indicating an increase in BM. Because zero was within the range of the 95% bootstrap confidence interval for T20, the differences in VFI and MBW were not significant. The 95% confidence limits for the four treatments were as follows: 10% and VFI, $-0.00637 \leq \mu_{VFI,BM} - \mu_{VFI,IM} \leq -0.00019$; 10% and MBW, $-0.07849 \leq \mu_{MBW,BM} - \mu_{MBW,IM} \leq -0.01214$; 20% and VFI, $-0.00257 \leq \mu_{VFI,BM} - \mu_{VFI,IM} \leq 0.00514$; 20% and MBW, $-0.02280 \leq \mu_{MBW,BM} - \mu_{MBW,IM} \leq 0.00579$; 30% and VFI, $-0.00768 \leq \mu_{VFI,BM} - \mu_{VFI,IM} \leq -0.00108$; 30% and MBW, $0.01062 \leq \mu_{MBW,BM} - \mu_{MBW,IM} \leq 0.01680$; 40% and VFI, $-0.00998 \leq \mu_{VFI,BM} - \mu_{VFI,IM} \leq -0.00181$; and 40% and MBW, $-0.05463 \leq \mu_{MBW,BM} - \mu_{MBW,IM} \leq -0.03773$. These results showed that globally, BM was significantly lower than IM. However, this was not the case when the model adequacy was evaluated per treatment. Nevertheless, most treatments showed an improvement in OFV for BM.

Discussion

The evaluations show that in the modified *Paracoa* model (Table 2), which is described in detail below, the VFIM had a lower OFV than the modified model describing *iT* as a consequence of age (TAgeM), whereas the latter had a lower OFV than that found as a consequence of the level of corn (TIncM and TDecM). These results are similar to those reported when treatment effects were studied. These results are feasible indicators of a biological effect of the VFI (*il*) and *iT* processes on weight gain. Therefore, a 4-parameter *Paracoa* model was built, extending the initial *Paracoa* model (2-parameter model) to a potential BM that better explained the biological system studied.

Table 2 demonstrates that the 4-parameter *Paracoa* model was the BM, that is, the most effective model (mean 6.9737), among the studied models. Additionally, the results showed that repeating the optimization produced very similar OFV and parameter results, although they were not as similar as those obtained with the 2-parameter models (data not shown). This difference may be a consequence of a less-even surface near the global minimum than that for the unmodified *Paracoa* model. This issue is minor but may be relevant if the number of parameters is higher than evaluated here.

Biological evaluation of the best-fitted model

Animal weight gain was due to increased degradation instead of solubilization at 0 h in the absolute fraction flow (Table 3). In relative values, the soluble fraction flow was reduced by 18%, whereas the nonsoluble fraction increased by the same quantity, indicating that the increase in weight gain was due to the increase in nonsoluble substrate (degraded matter) (Table 3). However, all the treatments contributed more than 60% of the soluble fraction flow to animal nutrition in the rumen (Table 3). The reduction in soluble fraction flow is a function of the reduction in effective degradation of the saccharina (Godinez-Juárez *et al.*, 2017), possibly due to microbial uptake of substrate outside of the animal, as reported previously (Ramos *et al.*, 2006). On the other hand, the increase in the nonsoluble fraction is a consequence of the approximately 50% reduction in fiber (Godinez-Juárez *et al.*, 2017) due to microbial enzymatic processes or the maximization of microbial activity due to sugar levels (Wang *et al.*, 2017) before the feed is consumed. Additionally, the increase in DM flow for each level-of-corn treatment (Table 3) was a consequence of the VFI increment. This VFI increase is common in saccharina diets prepared with or mixed into different types of feed (Ruiz *et al.*, 2005) as a consequence of fiber content (Ruiz *et al.*, 2005). In addition, it was mathematically demonstrated that for the saccharina case, the distance between the data and the model was reduced consistently for changes in some specific parameters, such as VFI (*il*), (*iT*) and animal age. However, under the study conditions, other variables did not have the same impact on the behavior of the system (degradation rate, feed efficiency and passage rate) or impact the system when the parameter describing the increase in the VFI was fixed at zero during simulation for every level of corn, *kkil* = 0/unit from T10 to T40 of corn level (0.5072, 0.4994, 0.4916 and 0.4839 kg/day) (data not shown). These results may be a consequence of the interaction or behavior of the concentration of soluble substrate in the diet, conversion of mass or other factors. For feed efficiency, the results are consistent with the classic results when feed efficiency is calculated directly for the same data (Godinez-Juárez *et al.*, 2017).

Parameter evaluation

In general, biological parameters are linearly correlated (Gutenkunst *et al.*, 2007a); therefore, identifying the true unknown parameter values may be difficult (Li and Vu, 2013). However, it is important to evaluate parameter correlations because some authors report that correlated parameters cannot be identified (Li and Vu, 2013). Furthermore, the study of correlation is important because high correlation complicates the process of estimating the true unknown parameter value (Ashyraliyev *et al.*, 2008; Li and Vu, 2013); in the present work, the *Paracoa* model was no exception.

The weighted sum of squared residuals (**WSSR**) can be considered the log-likelihood function for normally distributed measurement noise, and it can be minimized for the estimation of biological parameters (Schaber, 2012). In some cases, the estimated parameter may not be uniquely estimated (not identifiable). However, such parameters are

typically not evaluated (Schaber, 2012) because few existing methods can perform a complex parameter identifiability analysis (Raue *et al*., 2009; Schaber, 2012). PL can be used to evaluate parameter identifiability for multiparameter models (Raue *et al*., 2009; Schaber, 2012; Kreutz *et al*., 2013). This method reoptimizes the WSSR for all parameters to obtain the PL for each fitted parameter (Schaber, 2012) and assesses whether the reoptimized WSSR exceeds the confidence limits based on the PL contours or PL ratios (Schaber, 2012). The PL evaluates the change in the value of a parameter component when fitting the model to the data (Kreutz *et al*., 2013). Additionally, the WSSR can be used to run a parameter scan to evaluate the sloppiness and level of correlation between parameters (Raue *et al*., 2009).

Figures 4 and 5 display the PL surfaces in dimensional space as contour plots (Figures 4a, 5a to f) and profiles (Figures 4b and 5g). The PL contour of the PL function is the WSSR as calculated by COPASI (Schaber, 2012). In the PL contour representations, the black lines describe contours for 90%, 80%, 70% and 60% confidence thresholds; however, some contours were not well delimited because the range used for the WSSR optimization due to a high resolution requires extensive computational resources. The plus symbol shows the point where WSSR is minimal. In the PL profiles, the PL contours are represented in a one-dimensional LP where gray lines describe the same confidence thresholds as shown for the PL contour representations (in the downward direction). Contours represent surfaces of constant behavior, where the width and long ellipse directions describe the stiff and sloppy direction of parameters, and the parameters of a model can be divided into stiff and sloppy parameters. The stiff parameters can be determined with great certainty, and the sloppy parameters can vary by orders of magnitude without generating great changes in model behavior (Chis *et al*., 2016).

The PL analysis showed that the initial 2-parameter *Paracoa* model and the final 4-parameter *Paracoa* model described in this paper had parameters that were identifiable (Table 4, Figures 4b and 5g). It is important to note that the previously obtained correlation values did not accurately describe the relationship between *kkiT* and *iT*. However, the FIM provided a precise description of all parameter uncertainties (Table 4, Figures 4b and 5g). It was possible to identify a well-defined sloppiness structure between *il* and *kkil* and between *il* and *kkiT* as well as, to a minor extent, among *kkiT, kkil*, and all the parameters for the 4-parameter model (Figure 4). It is important to note that two of these relationships had low correlations (*il* × *kkiT* and *kkiT* × *kkil*), and that the other relationship, although showing high correlation, had low uncertainty. These findings illustrate the importance of 4-parameter PL (Figure 4) to expand the evaluation of parameter behavior.

The PL is useful to discriminate the uncertainty linked to a specific error measure such as OFV. OFV reduction can be interpreted as the consequence of a better structural description of the *Paracoa* model. Previous evaluations support this interpretation because the 4-parameter BM was modified with expanded equations that describe the increase in *il* as a result of the increase in VFI with the level of corn and *iT* due to age. However, although the uncertainty was reduced for the *il* parameters, the *iT* uncertainty increased in value, which could be explained as a consequence of discrimination of a new biological factor that was not related to the corn-level treatments. The *iT* uncertainty with the 2-parameter model was one process that was split into two different processes in the 4-parameter model, increasing the remaining uncertainty in *iT* when fitted with the same data. According to the PL results, this effect is a problem not of model design but rather of experimental design. Thus, the next step is to determine how to increase the ability of the experiment to constrain the parameters.

The PS interaction limit used for 4-parameter PL in COPASI software (Figure 4) was 15, far from that used for the 2-parameter PL (100, Figure 4) and previous evaluations (2000) (data not shown). These limits were fitted after evaluating the approximation to the global minimum with PS method, the objective of the evaluation and the resources required for accomplishing the objective. In the case of the 4-parameter PL (Figure 5), the optimization spanned approximately 12 days, but the days required to scan a parameter to obtain every PL image could reach 1600 with high interaction limits. The limit used was demonstrated to be useful for the objectives of this study. Nevertheless, the PL contours were not as smooth (Figures 4a, 5c to 5f), wide (Figure 5a and d) or well defined (Figure 4a) as those obtained with higher PS iteration limits (Figures 4b and 5g).

Table 4 *Upper limits of the parameter profile likelihood and objective function value (OFV) of the* Paracoa *model*

Element evaluated[1]	2-P global optimization	4-P global optimization
OFV	7.67	6.97
il (1/kg)	0.027	0.015
iT (1/kg)	0.258	0.57
kkiT (1/unit)	–	0.015
kkil (kg/kg)	–	0.015

P = parameter.
[1]Element evaluated: *il* = voluntary feed intake index; *iT* = transformation index; *kkil* = increase in *il*; *kkiT* = increase in *iT*.

Inverse problem considerations

The MIA is an inductive (bottom-up) approach; however, it can be also considered a manual deductive (top-down) approach because during the development of direct mechanistic models, the researcher constructs a model and evaluates it for prediction accuracy. Then, the researcher returns to the model to attempt to improve it and search for parameter values that better predict the data. The process is repeated several times until the researcher obtains the BM, at high cost in terms of time and resources. This is an inverse problem process that is conducted manually, but MIA can accelerate

this inefficient process by integrating data, hypotheses and processes. Therefore, it is possible to develop a multiparameter model with submodels that describe each of the different types of AAS processes (e.g., physical, metabolic) and search for different data, where the experiments are the focus of every type of process as described for the submodels. Then, the researcher can run an optimization and obtain global parameter values. During this process, one of the principal issues encountered may be a potential increase in the redundancy of the processes that limit the model size and correct description of the system because the model has a repeated process.

During the MIA process, it is possible to evaluate the system more thoroughly by finding an initial value for every animal parameter (e.g., initial animal weight) and estimating global parameters (e.g., weight gain), as demonstrated in this work. With this inverse procedure, the elements of the models can be isolated, and the model structure itself can be studied. The additive effect found throughout this paper demonstrated that such an approach is possible. Nevertheless, it is important to have different types of data that allow the researcher to discriminate parameters. It seems that the MIA and Bayesian approaches pursue the same goals. However, these approaches can serve as complementary modeling strategies in AAS. The MIA approach focuses on developing the structure of mechanistic models that best describes the biological system. Once the model structure has been determined, the Bayesian approach can be used to obtain posterior distributions for the model parameters.

MIA can improve the understanding of a system because the multifitting aids the discrimination of the biological processes. The effect of the multifiting on the prediction was not evaluated in this paper but likely depends on parameter sensitivity, the model and the data, similar to the other factors described in this paper. Additionally, the researcher can use MIA with individuals or groups and find a parameter value set with the best-fitting values. Then, the researcher can find the global minima, at which the model behavior has the least sensitivity to parameter change. The researcher can evaluate the areas adjacent to the global minimum or the presence of several minima (multimodal solution) and their parameter relationships in the parameter space, obtaining information useful for evaluating both the biological system and the MIA procedure. This approach can be as useful for understanding a system as the direct approach is for predicting a system.

MIA is not a better way to describe a complex biological system than current AAS approaches, but it can be a better way to obtain an integral quantitative structural description of the system. The models obtained from a MIA process are not different from those obtained from classical methodologies; the improvement, utility and users depend on the objective of the model. The difference between an MIA process and traditional approaches is that an MIA processes provides a better understanding of AAS systems, which is more important for very complex systems than for simple systems.

MIA is focused on the understanding of the parameter space, the minimization of the distance between the data and the model, and the methodological evaluation of specific structures of the model as reported for structural evaluations (Muñoz-Tamayo *et al.*, 2017). The evaluation and definition of a model structure 'is a challenging task that represents the core of the modeling building process'; however, it requires high levels of statistical, mathematical and computational skills that are not common in animal science, which explains the limited number of published papers on this topic. However, we need to be prepared for progress in precision farming and omics technologies and for the impact of information technologies in science to obtain the most from the resulting big data in animal science (Muñoz-Tamayo *et al.*, 2017).

Finally, prediction is not the most important element when evaluating the usefulness of a model. System understanding is as important as prediction, as the usefulness of the model is a consequence of such understanding. In this sense, the sentence 'all the models are erroneous but there are some models that are useful' (Law, 2009) can be extended with 'and the usefulness of a model depends on nonerroneous assumptions'.

The MIA was able to significantly reduce the OFVs by improving the biological description of the system and was effective for evaluating the methodology used. This study also revealed the roles that treatment, model structure and data type play in influencing the optimization results and the biological understanding of a system. The MIA revealed that the saccharina diet with different levels of corn increased weight gain due to increased degraded DM flow from the rumen, which in turn was caused by increased VFI and degradation of insolubles, although the weight gain across all treatments was supported by the flow of solubilized substrate from the rumen. Moreover, the weight gain was not a consequence of the change in the efficiency of general postruminal transformation. Furthermore, the system behavior was minimally influenced by animal age. In addition, the results revealed that PL, correlation matrix and FIM can be of great utility for understanding the parameter space within the inverse problem approach. It is necessary to incorporate additional data to achieve a clearer understanding of the biological system and this deterministic inverse approach.

Acknowledgments

The authors thank the Consejo Nacional de Ciencia y Tecnología (CONACYT), Estancias Postdoctorales y Sabáticas al Extranjero para la Consolidación de Grupos de Investigación (Project code: 185872), Colegio de Postgraduados, México, and Texas A&M University for supporting this research.

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Declaration of interest

The authors declare no competing interests.

Ethics statement

The authors declare no animal were involved in this study.

Software and data repository resources

None of the data has been deposited in an official repository.

Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/S1751731120000877

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