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

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**Table S1** Settings used for the optimization and/or simulation of the *Paracoa* and degradation models of ovine.

Parameter Degradation model *Paracoa* model

Software SBMLSimulator v1.2.1 COPASI v4.10

Time curse parameters:

Initial time 0 0

Final time 36 77

Number of steps 3 600 2 000

Differential equations solver Euler method Deterministic (LSODA)

Optimization method parameters:

Quality function Euclidean distance Standard deviation

Weighting method -1 Mean square

Seed 0 0

Fitness calls 3 000 2 000

Final number of interactions -1 100 000

Population 50 50

**Table S2** Abbreviations and definition of variables used in the *Paracoa* and degradation models of ovine. Subscripts denote percentage of corn level.

A = Biomass available for animal *kkiI* = Increase in VFI index (1/unit)

nutrition during digestion (kg/day) *kkiT* = Increase or decrease in iT (kg/kg)

D = Degraded biomass (kg) *kkfP* = Increase in P fraction (1/unit)

Deg = Degradation of biomass (kg/day) MBW = Metabolic body weight (kg)

DegN = Effective degradation of N (kg/day) N = Nondegradable biomass (kg)

DegP = Effective degradation of P (kg/day) oCorn = Level of corn into the diet (unit)

*fN* = Non-degradable fraction (kg/day) P = Potential degradable biomass (kg)

*fP* = Potentially degradable fraction (kg/kg) Pnl = P at time t and n% of corn level

fS = Soluble fraction (kg/kg) PasP = Passage of P (kg/day)

Gain = Body weight gain (kg/day) PasN = Passage of N (kg/day)

I = VFI (kg) R = Ruminal biomass in nylon bag (kg)

*iI* = VFI index(1/kg) at n% of corn level TageM = Post-degradation dry matter

IntakeN = VFI of N (kg/day) transformation related to animal age

IntakeP = VFI of Pn (kg/day) TDecM = Decrease in iT parameter

IntakeS = VFI of soluble biomass (kg/day) values at n% of corn level

*iTt,n* = Transformation index (kg/kg) at TIncM = Increase in iT parameter values

time t and n% of corn level at n% of corn level

*kd* = Fractional degradation rate (1/day) VFIM = Increase in VFI at n% of corn

kp = Fractional passage rate (1/day) *W* = Body Weight (kg)

VFI = Voluntary feed intake

**Table S3** Globally and locally adjusted parameters and constant and initial state values used during optimization and/or simulation. Subscripts determine percentage of corn level, and the global parameter initial values were randomized.

Global Parameters Local Parameters Constants Initial State Values

*iI0* = randomized/day W = 18 kg1  oCorn = n unit R = 1 kg5

*kkiI* = randomized/unit *MBW* = 0.000011 *kd* = 3.192/day2,3 P = 0.53 kg4

*iT0,0* = randomized kg/kg kp = 0.72/day P = 0.0001 kg5

*kkiT* = randomized/day *kkfP* = 0.00548/units2 N = 0.0001 kg4

*fN* = 0.16797 kg/kg2 N = 0.0001 kg5

*fP* = 0.11483 kg/kg3 D = 0.0001 kg5

See Table S2 for abbreviations

1Initial value used for standardized simulations

2Adjusted from degradation optimization (Objetive function value = 5.042)

30.133/h\*24 h = 3.192/day

4For *Paracoa* model

5For degradation model

**Table S4** Description of the *Paracoa* and degradation models of ovine, optimized in this work. Subscripts denote the percentage corn level.

Differential equations Auxiliary equations Extended equations

*Paracoa* model: IntakeN = *fN*# \* l *Paracoa* modifications:

dP/dt = IntakeP - DegP - PasP IntakeS = fS \* I VFIM:

dN/dt = IntakeN - DegN - PasN I = *iI* \* MBW iI0 = *iI0*# \* (1 + (oCorn \* *kkiI*#))

dW/dt = Gain MBW = W^.75 TAgeM:

fS = 1 - *fN* - *fP* iTt,0 = *iT0,0*# \* (1 - (t \* *kkiT*#))

DegP = *kd* \* P TIncM:

DegN = *kd* \* N iT0,l = *iT0,0*# \* (1 + (oCorn \* *kkiT*#))

PasP = kp \* P TDecM:

PasN = kp \* N iT0,l = *iT0,0*# \* (oCorn \* *kkiT*#)

Gain = A \* *iTt,l*# P0,l = *fP*# + (oCorn \* *kkfP*#)

A = IntakeS + DegP + DegN

IntakeP = fP# \* I

Degradation model:

dR/dt = - *fP*% – *fN*% – fS fS = 1 - *fN* - *fP*

dP/dt = – Deg P0,0 = R \* *fP*

dD/dt = Deg Deg = *kd* \* P

N = R \* *fN*

See Table S2 for abbreviations

#Estimated parameter

%Variable fitted with experimental data sets

**Supplementary Material S1** Quality evaluation of the Paracoa model of ovine (see Table S2 for abbreviations).

**Introduction**

The effects of the optimization method, variable-data relation, treatment, model structure, model type and size of data on computer resources, parameter values and the objective function value (OFV) were studied.

*Computer and software resources*

The Amazon Web Service Infrastructure (Amazon, 2019) was used to run a CC2 Cluster Compute (cc2.8xlarge) instance. This CC2 instance included two Intel Xeon processors, each with eight hardware cores. Hyper-Threading was enabled, allowing each core to process a pair of instruction streams in parallel. Furthermore, each processor had 32 hardware execution threads that allowed 88 EC2 compute units (ECUs) from this 64-bit instance type. The Windows R2 server for clusters was the operating system used with the instance. The *Paracoa* and multiparameter degradation models were built in Stella 10 software (Iseesystems, 2019). Then, the models were re-built into CellDesigner v4.3 (Funahashi *et al*., 2003) with small modifications by SBML structure (Hucka *et al*., 2003). When needed, the model was imported into SBMLSimulator v1.1 (Dörr *et al*., 2014) and/or COPASI v4.8 (Build 35) (Hoops *et al*., 2006; Mendes *et al*., 2009).

*Optimization methods and settings*

The method used for *Paracoa* optimization was particle swarm (Kennedy, 2010) except during the initial evaluation of optimization method. The Parameter Optimization Task of COPASI was used for the *Paracoa* model. The EvA2 Workbench module developed in SBMLSimulator software (Kronfeld *et al*., 2010) was used for parameter optimization of the multiparameter degradation model. The initial and best-fitting models were evaluated through the statistical comparison of the root mean square. The initial time, final time, differential equations solver, and quality function were the same for all evaluations except where stated in the methods section. The numerical and optimization settings that are not described in the main text were the default software settings.

*Effect of optimization method on computing resources and parameter values*

The OFV, function evaluations (FE), evaluations/second (1/s) (E/S), and *il* and *iT* parameter values were evaluated to identify optimization methods more feasible for the inverse problem approach (IPA). The evolutionary programming (EP), evolution strategy (ES), genetic algorithm (GA), genetic algorithm SA (GASA), Hooke & Jeeves, Levenberg-Marquardt (LM), Nelder-Mead (NM), particle swarm (PS), praxis (Pr), random search (RS), simulated annealing (SA), steepest descent (SD), truncated Newton (TN) optimization methods were used in the evaluation. Some optimization setting parameters were adjusted according to the given method. The altered values were the same as the fitted COPASI default values.

For OFV, which describes the fitting accuracy, the best values were obtained for ES, LM, PS, and Pr (7.66566). The worst values were obtained for SD (25.7201), followed by RS (17.6689). The only derivative-based method in the best-fitting solution group was LM; however, derivative-free TN (Christopoulos and Lew, 2000), which was outside of the best-fitting group, had values close to the LM values. The FE obtained with the optimization algorithms for the four best-fitting-solution methods revealed that LM (287) method was the most efficient method with respect to algorithm optimization, followed by Pr (21,150), with the ES method being much less efficient (227,900). However, although the E/S difference was minimal, LM remained one of the most efficient methods (0.642828) when compared with the four best-fitting-solution methods (0.674481-0.698067). In this best-fitting-solution group, the *il*, and *iT* parameter values were very close, with differences of approximately 0.0000007/kg and 0.000009/kg, respectively. These small differences can be considered evidence of a unique optimization solution without the error-model-method interactions that can appear with more complex models. Although the optimality of the solution cannot be confirmed, these small differences suggest that the solution was near the minimum (Moles *et al*., 2003). In addition, this work revealed the importance of using a specific method when working with biological optimization problems that can affect the solution and parameter values in some cases by more than 100%, as observed for *iT* (114%).

The *Paracoa* model was fitted to 44 curves to search two parameter values. The results showed that the error surface was not complex enough to avoid a unique solution. Since the local methods (LM and Pr) were designed for local optimization, it is likely that a monomodal or unique solution exists (Christopoulos and Lew, 2000; Moles *et al*., 2003). However, in general, inverse problems are ill-conditioned and multimodal (Moles *et al*., 2003) and local methods are unable to find a solution.

The principal issue with global methods is the high computational resource required for their process (Moles *et al*., 2003). No global deterministic methods can guarantee a global solution with certainty in finite time (Moles *et al*., 2003). On the other hand, as a consequence of their probabilistic approach, stochastic methods have low theoretical possibilities of obtaining the global minimum, but in general, they require fewer resources than global and derivative-free methods (Moles *et al*., 2003). Stochastic methods guarantee the vicinity of the global minimum with low resources, and global deterministic methods guarantee the global minimum when the required time is assured (Solis and Wets, 1981; Moles *et al*., 2003).

In this work, the stochastic global methods yielded low to medium efficiency (FE, from 11,418 to 227 900), as expected, but only two (ES, and PS) among them (EP, ES, GA, GASA, PS, and SA) had the best-fitted OFV. In contrast, with the metaheuristic method (Moles *et al*., 2003), PS had a better efficiency than ES (FE, 68 995 vs 227 900). The global deterministic method, RS, failed to obtain the lowest OVF (17.6689), but it had one of the most efficient processes (FE, 801). The theoretical potential of this method to reach the global minimum in high-complexity optimization (Solis and Wets, 1981; Moles *et al*., 2003) offers the possibility of a new evaluation when working with a more complex model while using a new method configuration that assures sufficient time to obtain the global minimum. The results demonstrated that three methods exhibited better general behavior that the others during the evaluation: LM, Pr, and PS. ES can be excluded because of its high FE and be replaced with TN due to its potential in working with high-complexity systems. However, only PS can be recommended for the optimization of a 4-parameter *Paracoa* model because it was the only algorithm that had almost identical parameter values to those of other algorithms. In addition, PS had an acceptable efficiency, and during an initial test, it was able to optimize a 4-parameter *Paracoa* model. The more efficient LM could not estimate this complex model.

*Effect of type-of-variable/size-of-data relation on parameter values, and OFV*

The effects of different types of intermediate variable and fitted variables and variable size were studied. *il* and *iT* parameter values, initial body weight, and OFV were obtained to evaluate five relations: bodyweight/bodyweight (BWR), bodyweight/MBW3/4 (MBW(3/4)R), MBW3/4/body weight (MBW3/4R), MBW2/3/MBW2/3 (MBW2/3R), and MBW3/4-MBW3/4 with values increased 3-folds (Data3/4(3x)R). The relationship between the data and model variable is important because it can affect the surface error, and, therefore, the OFV. Some researchers have described some relationships that affect the extraction of information from data, some of these relationships are as follows: the relationships between a variable and the number of data (representativeness of data), the type of model variable and data (complementarity of data), the variable and absolute value size, and the variable and data error. Representative data are data of sufficient quantity to capture the system variation (Gupta and Sorooshian, 1985), whereas, complementary data are data with sufficient variation to capture the system variation (Vargas-Villamil and Tedeschi, 2014). In addition, a suitable absolute value size of data, and a small error, improve the OFV value because they uniform the weight of variable values (Christopoulos and Lew, 2000) and reduce the noise in the data (Gupta and Sorooshian, 1985). In the method evaluation, the *Paracoa* model was initially fitted to two data sets of 22 values each for two-parameter estimations (*il* and *iT*). No convergence issues were encountered during local optimization, which indicate representative, complementary and informative relationships between the model variables and the data; in the majority evaluations, the solutions were similar. Furthermore, the uniformity of the data was assured through the mean square method. However, a more conclusive evaluation was needed to determine the effects of changes in the type-of-variable-size-of-data relation or the type of relationship between them on the parameters and the OFV. Changes in the former are discussed in this section, and those in the latter are presented in the subsequent section.

In a direct approach, the objective of the *Paracoa* model would be to describe voluntary feed intake (VFI) and weight behavior that were defined during the inverse process by the relation between the type of variable and the data. Metabolic body weight (MBW) is one element that has been integrated into biological models but has not been evaluated in an IPA, although it can affect parameter values and OFV. The evaluation showed that all the MBW relationships studied had no optimization issues when using the PS algorithm, with MBW(3/4)R (7.61048) and MBW2/3R (7.60251) presenting lower OFV values, followed by BW (7.97438). The OFV changes can be partially attributed to a value change because the absolute values of the data were directly proportional to the OFV. The change in *Paracoa* model structure as a consequence of MBW transformation changed the OFV; it appears this OFV change was associated with a nonmeaningful BWR vs BW3/4R structural change (7.9743 vs 8.1612), but with *il* (0.0363 vs 0.0784) and *iT* (0.1419 vs 0.1963) changes. On the other hand, changes in the type of fitted variable used modified the OFV (BWR vs MBW3/4R) vs MBW2/3R), increasing the values of the parameters and initial animal weight in a manner inversely proportional to the OFVs. This OFV change might have originated from the reduction in variable value as well as from a metabolic relation (Feldman and McMahon, 1983). This result invites the discussion about the best exponent value to use for animal modeling (Feldman and McMahon, 1983; White and Seymour, 2003), a topic that requires reevaluation with modern methodologies. Finally, the results show that in contrast to Data3/4(3x)R, the increase in MBW3/4, three times (Data3/4(3x)R), led to only a marginal increase in the *il* value (0.0788 vs 0.0790) but a strong increase in *iT* (0.1746 vs 0.2552). This result is expected because large animals with the same VFI index have higher VFI. As a consequence, *il* and *iT* behavior have the potential to describe a crucial animal performance in case of genetic evaluation, a topic to explore in future work.

*Effects of treatment on parameter values and OFV*

The dataset was divided into four groups according to the level of corn in the diet (T10, T20, T30, and T40), and the interactions of corn level with the number of parameters fitted, type of parameter, and time interval (0-13, 17-33, 35-48, 49-62, and 63-77 days) were evaluated in the following designs: a) In the first case, every diet treatment was contrasted to 0-parameter, 1-parameter, and 2-parameter model optimization when the *il* or/and *iT* parameter was used. b) In the second, every diet treatment was contrasted to 0-parameter, and 1-parameter model optimization when the passage rate parameter was estimated. and c) In the third case, every diet treatment was contrasted to every time interval. The variable-data relationship used was MBW(3/4)R, and the time interval was grouped based on an equal number of time samples. A level-of-corn x interval-of-time group was arbitrarily chosen to evaluate the effect of individual optimization into a 6-animal group.

Fitting the data by level of corn reduced the OFV relative to its value when it was not grouped (0-parameter optimization) (7.6656) to a mean of 2.4411, with OFV constantly increasing their value from T10 to T40 (1.1394, 2.3335, 3.0831, and 3.2086). The trend was similar when only one, not two, parameters were estimated (OFV*il*= 2.4685 vs OFV*iT*= 2.7243). The mean OFV obtained from 2-parameter, *il*-parameter, and *iT*-parameter fitting was extremely close to the mean obtained from level-of-corn fitting (2.5447 vs 2.5447, respectively). This result suggests a possible additive effect inside them. Reducing the number of parameters fitted also had minor effects on the mean parameter values, with 0.0775/kg and 0.1730/kg attained for *il*-parameter and *iT*-parameter fitting, respectively, in comparison with 2-parameter fitting (0.0776/kg, and 0.1782/kg). However, the parameter tendency was different. The *il* values increased for every level of corn with both 2-parameter (0.0671/kg, 0.0734/kg, 0.0752/kg, and 0.0946/kg) and *il*-parameter fitting (0.0673/kg, 0.0742/kg, 0.0752/kg, 0.0946/kg), whereas *iT* had a peak for T20, followed by level T10 or T40, with either 2-parameter (0.1962/kg, 0.2339/kg, 0.1276/kg, and 0.1551/kg) or *iT*-parameter fitting (0.1678/kg, 0.2190/kg, 0.1215/kg, and 0.1837/kg).

Reducing the data size reduced the mean OFV (0.2979) and mean *iT* (0.1375/kg), whereas *il* was closer (0.0775/kg) to the value found previously. As observed for level-of-corn fitting, previously, the OFV and parameter value means, grouped by level-of-corn x interval-of-time had an additive effect when the mean was calculated by level-of-corn or interval-of-time because they were the same. However, the same trend was not found when a level-of-corn x interval-of-time group was arbitrarily chosen. The individual fitting of every 6-animal group data (T20x49-62-days group), arbitrarily chosen, described means (*il* = 0.0785/kg, *iT*= 0.6214/kg, and OFV = 0.0391) that were different from those obtained from the fitting of the 6-animal group as a whole (*il* =0.0753/kg, *iT* =0.3/kg, and OFV = 0.1769). The contrast found could be a result of the method, the algorithm used, the data size, or other factors related to the error surface.

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

It is evident that an additive effect exists on the majority of the means evaluated when the number of groups is similar, with differences among results being related to the level of global fitting (size of group fitted). As a result, the form of the error surface can change, consequently altering the fitting results. However, compared with small-data optimization, global has the potential to describe integral biological quantitative mechanisms; such description is desirable for prediction purposes. In small-data optimization, the additive characteristic may help to understand the structural design of a biological system. It is possible to distinguish an effect of treatment on the intake that, if described adequately on the *Paracoa* model may reduce the error during the global optimization and as a consequence the flexibility of the model to different conditions. Furthermore, a reduction in the adequacy of the *Paracoa* model to describe a higher level of corn in the diet was observed, without any peak for T20 as was observed for *iT*-parameter fitting. The biological behavior was not transmitted completely among different levels of data size, which is also related to a number of fixed effects studied. However, the consistent similitude found between group and global means may indicate an effect of data size, even among different levels of data-size fitting, masked for not well-known factors. More studies on this topic with big biological data are needed to understand the relationships of data size and restrictions due to global optimization. In addition, also, it is important to evaluate the effects on the distance from true values and their potential as tools to deepen in the understanding of biological mechanisms. Some of these aspects are reviewed below.

*Effects of model structure, model type, and data size on parameters and OFV*

The effects of model structure, model type, and data size on the parameters and the OFV were evaluated. The *Paracoa* model was modified four times to evaluate whether a detailed metric of VFI, i.e., post-degradation dry matter transformation related to animal age (TAge) or level-of-corn treatment (TInc, and TDec), could improve the description of the system behavior. The *iT* *Paracoa* modification described an increase (TIncM) or decrease (TDecM) in *iT* parameter values in response to the level of corn treatment. In addition, a 2-parameter control was used. Finally, the modified models were optimized globally with four datasets: 1-sample, 3-sample, and complete (6-sample) number of animals per treatment and mean groups. The variable-data relationship used was MBW(3/4)R.

Data size was found to modify the fitting results, but the study was not large enough to identify the effect of other relations on the parameters and the OFV. The interactions among model structure, model type, and data size of data were not studied. In general, fitting the *Paracoa* model to the means of the treatment or 3-animals-by-treatments samples produced estimated values similar to those of the 6-animals-by-treatment samples. Although the 1-animal-by-treatment samples did not yield closer results than the 6-animals-by-treatment samples, their fitting results were similar. Therefore, their values can be used for initial, nonextensive evaluations. These results showed that it is theoretically possible to reduce the number of animals or increase the studied biological factors and obtain the same results; however, more research is required.

In all cases, the increase in model resolution through a deeper description of VFI relations reduced the *il* value, followed by a reduction in the OFV. In contrast, a deeper description of *iT* related to age (TAgeM) increased the *iT* values but resulted in a minimal reduction in the OFV. However, when *iT* was described related to level-of-corn treatment, the OFV did not change, neither during the decrease (7.6656) or increased (7.9689) in *iT* values, as a consequence of model modification, with minimal changes in parameter values. The *Paracoa* model modifications only improved OFV when they were focused on a deeper description of *il* (VFIM) and *iT* (TAgeM), about level-of-corn treatment and age, respectively. In this case, an increase in *iT* can be ignored while considering the existence of a small change due to age. The sensibility of IPA for detecting small processes needs to be evaluated. The trends of biological value and accuracy and consistency of the results in all the evaluations despite having ben run individually, in some cases and with different random initial values warrant highlighting. However, it is possible that a data-size limit exists where a method or algorithm has difficulty reaching a global minimum because of interaction between the data, model, method, algorithm, and parameters. Such a limit might explain why the OFV behavior observed when the animals were grouped by treatment (22 animals) was not observed when they were grouped by treatment x time interval during the evaluation of treatment on parameter and OFV. This topic requires more research.

The optimal experimental design could be used with multi-inverse approach (MIA) to deepen the causal inference questions included in the Table. Similarly, MIA could be applied to the study of structural sensitivity in animal science models (Chis *et al*., 2011). However, some biological questions in real production systems cannot be adequately solved through the use of “artificial” experimental designs in the modeling process, as they are related to specific production conditions. One recommendation is to focus on the question instead of experimental design (Tedeschi, 2019). In this context, MIA as an IPA, can be used as an alternative approach.

**Conclusions**

The multi-inverse approach was able to statistically reduce the objective function values by improving the biological description of the system and was useful for evaluating the methodology used during this procedure. In the methodological analysis, the multi-inverse approach revealed that the type of algorithm used affected not only the objective function values but also the parameter values and that it is important to evaluate the parameter space to find a method according to the model complexity and evaluation objectives. Furthermore, the analysis revealed that variable-data relationship, treatment, model structure and the size and kind of data,

can affect the optimization results and the biological understanding of the system.

**Table S5** Correlation and Fisher information matrix obtained from the best-fitting results.

Initial weight was not considered.

*il* (1/kg) *kkiI* (1/unit) *iT* (1/kg) *kkiT* (kg/kg)

*il* 1# -0.920236 -0.218784 -0.00453083

(2.33712\*106)% (2.7047\*106) (303,638) (-5.7145\*106)

*kkiI* 1 0.0228912 0.00727751

(3.38893\*106) (350,544) (-6.60715\*106)

*iT* 1 0.725832

(106.463) (103.618)

*kkiT* 1

(1.82018\*107)

#Correlation results

%Fisher information results

Parameters: *iI* = voluntary feed intake index, *iT* = transformation index, *kkil* = increase in il, *kkiT* = increase in iT.

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