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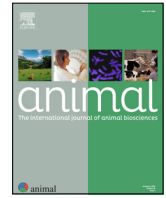


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A first model of the fate of dietary calcium and phosphorus in broiler chickens

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ABSTRACT

To reduce P excretion and increase the sustainability of poultry farms, one needs to understand the mechanisms surrounding P metabolism and its close link with Ca metabolism to precisely predict the fate of dietary P and Ca and related requirements for birds. This study describes and evaluates a model developed to estimate the fate of Ca and P consumed by broilers. The Ca and P model relies on three modules: (1) digestion of Ca and P; (2) dynamics of Ca and P in soft tissue and feathers; and (3) dynamics of body ash. Exogenous phytase affects the availability of Ca and P; thus, to predict the absorption of those minerals, the model also accounts for the effect of phytase on Ca and P digestibility. We used a database to estimate the consequences of dietary Ca, P, and phytase over feed intake response. This study followed a four-step process: (1) Ca and P model development and its coupling with a growth broiler model; (2) model behavior assessment; (3) sensitivity analysis to identify the most influential parameters; and (4) external evaluation based on three databases. The proportion of P in body protein and the Ca to P ratio in bone are the most sensitive parameters of P deposition in soft tissue and bone, representing 91 and 99% of the total variation. The external evaluation results indicated that body water and protein had an overall mean square prediction error (rMSPE) of 7.22 and 12.3%, respectively. The prediction of body ash, Ca, and P had an rMSPE of 7.74, 11.0, and 6.56%, respectively, mostly errors of disturbances (72.5, 51.6, and 90.7%, respectively). The rMSPE for P balance was 13.3, 18.4, and 22.8%, respectively, for P retention, excretion, and retention coefficient, with respective errors due to disturbances of 69.1, 99.9, and 51.3%. We demonstrated a mechanistic model approach to predict the dietary effects of Ca and P on broiler chicken responses with low error, including detailed simulations to show the confidence level expected from the model outputs. Overall, this model predicts broilers' response to dietary Ca and P. The model could aid calculations to minimize P excretion and reduce the impact of broiler production on the environment. A model inversion is ongoing that will enable the calculation of Ca and P dietary quantities for a specific objective. This will simplify the use of the model and the feed formulation process.

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Implications

In poultry farms, excess nutrients may be excreted in the waste, leading to river eutrophication. Therefore, it is desirable to optimize nutrient feeding. Modeling the amounts of calcium and phosphorus in broiler metabolism helps to understand the dynam-

ics of these minerals in the body, to predict and even influence calcium and phosphorus excretion to the environment. The results suggest that this model can help predict the consequences of dietary calcium and phosphorus feed content on the broiler production system. This model could help poultry nutritionists minimize the environmental impact of a poultry farm and, inversely, predict feed requirements.

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Introduction

A theory is generally used to construct a set of equations to predict the outcome of a biological system. And as the system becomes complex, which often happens in biology, more theories are combined to represent the whole system. This complex of theories is called a mechanistic model (Emmans, 1981). For decades, animal nutrition researchers have shown the relationship between feed intake and body growth (Parks, 1970; Whittemore and Fawcett, 1976). Fisher et al. (2015) highlighted that adopting a modeling approach in the poultry industry can improve resource utilization and practical decision-making. Over the years, models were developed with various objectives, such as predicting growth (extensively investigated by Parks, 1982), nutrient requirements (Talpoz et al., 2013; Nogueira et al., 2021), or both combined (Emmans, 1987; Harlow and Ivey, 1994; Eits et al., 2005; Hauschild et al., 2015). Hauschild et al.'s (2015) mechanistic model simulates the growth of broilers and estimates the intake of energy and essential amino acids needed. However, to our knowledge, none of the available models deal with Ca and P minerals in a broiler production system, likely due to the complexities of broiler response to dietary Ca and P intake (Salisbury et al., 2021).

Phosphocalcic regulation to maintain stable extracellular concentrations occurs in the gut, kidney, and bone (González-Vega and Stein, 2014). Regulation processes appear even more complicated due to the Ca appetite shown by birds (Lobaugh et al., 1981). The low levels of dietary P for broilers decrease their appetite (Aderibigbe et al., 2022; Proszkowiec-Weglarz and Angel, 2013; Létourneau-Montminy et al., 2010), and a specific Ca appetite may drive feed intake of Ca-deficient feed. Moreover, multiple response criteria (e.g., weight gain, bone mineralization, excretion) can be tailored to the production objectives (e.g., profitability, animal welfare, and environment) to establish P requirements, making the concept of establishing a single requirement challenging. Therefore, multicriteria approaches should be used to represent the complexity of the animal response to minerals, and mechanistic model principles are well suited for that purpose (Thornley and France, 2007).

An empirical function was recently published to estimate the non-phytate P (NPP) requirement based on BW and weight gain (Rostagno et al., 2017). The dietary Ca requirement is estimated at a ratio of 2.13 to P. This modeling approach implies that body ash (all body minerals) is linked to BW. However, in bones and soft tissues, the ratio of body ash is about 80:20 in birds fed diets formulated to maximize bone mineralization (Rath et al., 2000). Approximately 1% of body Ca and 20% of body P are outside the bone structures, but those fractions are essential to metabolism (Proszkowiec-Weglarz and Angel, 2013). The deposition of Ca and P in skeletal tissue depends mainly on dietary supply, whereas the concentration of Ca and P in soft tissue is fixed and has a priority over bone deposition (Van der Klis et al., 1990). To meet the demand of Ca and P for the metabolic process, the hydroxyapatite crystals of Ca phosphate might be mobilized from bones (Clunies et al., 1992), which may increase the excretion of P in the environment, reinforcing the importance of elucidating the utilization of both minerals. Therefore, the Ca and P deposition into the different tissues must be simulated to accurately represent the fate of dietary Ca and P and ash retention. This approach has been developed for raising pigs (Lautrou et al., 2020; Létourneau-Montminy et al., 2015). The 3-part objective of this study was as follows: (1) develop a model to estimate the fate of dietary Ca and P absorbed in broilers; (2) integrate the model into a simulation broiler growth model; (3) report the results of a detailed model evaluation, including a parameter sensitivity analysis, model behavior, and a comparison between the model predictions with published literature.

Material and methods

Theoretical assumption

The proposed mathematical model represents broiler growth and the fate of dietary Ca and P through three consecutive modules: (1) a digestive model, which predicts the Ca and P from the diet that is available to be deposited into the tissues; (2) a soft tissue model, which simulates the growth of protein, lipid, ash, and water in the body using Hauschild et al. (2015)'s principles; and (3) a body ash model, that predicts the ash mineral accumulation in soft tissue and bone separately (Fig. 1).

The model approach follows the strategy described by Létourneau-Montminy et al. (2015) and combines the three modules: (1) The digestive module estimates the absorption fraction of dietary Ca and P. The fraction of dietary Ca and P found in feces are obtained by difference from the absorbed. (2) The soft tissue module, herein calculated using the broiler model described by Hauschild et al. (2015), simulates the deposition and growth of protein and lipid mass. It relies on a set of theories that drives the prediction of the potential growth of a specific genotype as a function of time (Brody, 1945; Parks, 1970; Emmans, 1987). This module does not account for any minerals associated with protein and lipid mass. (3) The body ash module is driven by the assumption that Ca and P are first deposited in soft tissue, and the remaining fraction goes to bone tissue and urine. To allow such a mechanism to work, two fixed variables were introduced in the model, namely the potential of Ca in bone, which leads to maximum bone mineralization in non-limiting conditions, and actual Ca in bone, which represents the consequences of dietary Ca and P supply on bone ash. In our mechanistic model, Ca and P deposition in soft tissue and feathers have a priority over bone ash deposition, which seems reasonable since the amount of Ca and P in soft tissue is relatively constant (Van der Klis et al., 1990; Brautbar et al., 1979; Stauffer et al., 1972). Protein is a fixed variable that drives protein retention variable.

Calcium and phosphorus digestion and absorption

The definition of "feed intake" includes qualitative and quantitative descriptions of the feed (Létourneau-Montminy et al., 2015). In the diet given for broilers, P appears mainly as phytate P (PP), assumed to be only from plant ingredients or NPP found in either plant, mineral, or animal ingredient sources. For simplicity and consistency with feed formulation practice, Ca from feed is assumed to be in its total form. In this sense, the intake of both P (PP and NPP) and Ca can be easily calculated using tables/analysis of nutrient composition from feed/ingredient.

The amount of dietary nutrients and energy is related to the amount necessary for the animal to grow at its best potential. However, in practical situations, multiple factors prevent the animal from reaching their "desired" feed intake, such as the bulk capacity of the intestinal tract (Nascimento et al., 2020), environmental conditions (Emmans, 1987), health status (Oliveira et al., 2019), and deficiencies of some nutrients such as P (Aderibigbe et al., 2022; Faridi et al., 2015; Suttle, 2010). To take the latter into account in the model, a comprehensive database was built based on publications about the impact of varying Ca, P, and phytase on the growth performance of broilers. The database included 53 publications, 58 experiments, and 342 treatments (Hedhli et al., 2019), attempting to estimate the relative feed intake of broilers as a function of the dietary concentrations of Ca, NPP, and microbial phytase (PhyM) supplementation. All parameters for Eq. (1) can be found in Table 1.

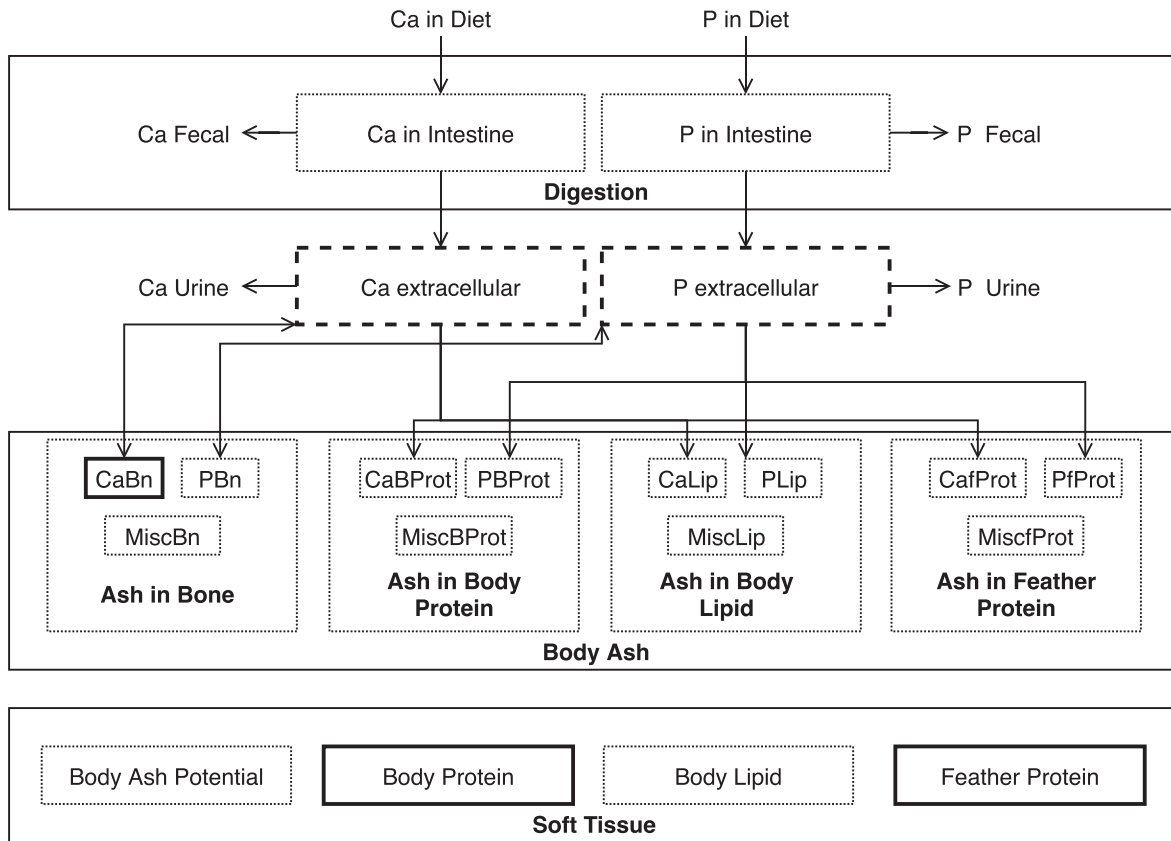


Fig. 1. Diagram indicating the three main steps of the broiler model (thin solid line boxes), digestion, body ash, and soft tissue. State variables are depicted by large solid line boxes, zero pools are represented by dashed lines, and auxiliary variables indicated by dotted lines. The arrows indicate the flows between different compartments. The initials Ca, P, and Misc denote the presence of calcium, phosphorus, and miscellaneous mineral within each compartment. CaBn, PBn, and MiscBn stand for calcium, phosphorus, and miscellaneous on bone ash. CaBProt, PBProt, and MiscBProt are calcium, phosphorus, and miscellaneous minerals in body protein. Similarly, CaLip, PLip, and MiscLip are calcium, phosphorus, and miscellaneous minerals in body lipid, while CafProt, PfProt, and MiscfProt represent calcium, phosphorus, and miscellaneous minerals in feather protein.

$$\text{relative Feed Intake} = \frac{\text{intercept} - \text{linear}_{Ca} * Ca + \text{linear}_P * NPP - \text{quad}_P * NPP^2 + \text{linear}_{PhyM} * PhytM - \text{Quad}_{PhyM} * PhytM^2 - \text{Int}_{NPP*PhyM} * NPP * PhytM}{\text{desired feed intake}} \quad (1)$$

where linear_{Ca} linear effect of Ca, linear_P is the linear effect of NPP, quad_P is the quadratic effect of NPP, linear_{PhyM} is the linear effect of PhytM, Quad_{PhyM} is the quadratic effect of PhytM, $\text{Int}_{NPP*PhyM}$ is the interaction between NPP and PhytM. The dietary concentrations of Ca and NPP are in g/kg of feed and PhytM in FTU/kg of feed.

Dietary Ca and P are absorbed in the small intestine through active and passive flows (Schröder and Breves, 1996; Bronner and Stein, 1995) after complex digestion processes such as solubilization, insolubilization, and hydrolysis. These dynamics have already been described in a mechanistic model for raising pigs (Létourneau-Montminy et al., 2010) with an empirical equation (Létourneau-Montminy et al., 2015). For simplicity, a similar approach was used in the current model. The apparent total tract digestibility of the dietary PP and NPP from plant forms was estimated by Khaksar et al. (2022) using an exhaustive database of P studies in fast-growing broilers performed between 2017 and 2021 in 1–21 and 22–42 days. About two-thirds of the publications have studied microbial phytase. This enzyme catalyzes the hydrolysis of P from phytic acid and increases the availability of P and, under certain conditions, the availability of Ca, affecting the uptake of these minerals in broilers' intestines (Waldroup et al., 2000; Cowieson et al., 2016; Bedford and Rousseau, 2017). The equation also considered the interaction between Ca, NPP, PP, and phytase.

Results showed that increasing PP, the phytase substrate, increased the effect of phytase supplementation.

At all ages, digestible P is penalized by high Ca intake. The dietary Ca may produce insoluble complexes with NPP and PP, reducing the absorption of dietary P. Moderate to low Ca intake prevents the formation of Ca-phytate complexes in the intestine (Selle et al., 2009), thus improving the absorption of P (Heaney, 2004). In older birds, this effect is more remarkable as the level of PP increases. Moreover, in a diet with high Ca content, chickens' response to PhytM fades as the NPP increases. In this case, the P deficiency, created by high Ca intake, stimulates the absorption capacity of P by the intestine (Rousseau et al., 2012). A low NPP intake could also increase alkaline phosphatase activity (Liu et al., 2017). The database has been subdivided into two based on broiler age. Nevertheless, the two databases have different meta-design, so their differences may be more than age-related. The equations using data from 1 to 21 days old broilers were implemented in the model (Supplementary Table S1). The equation and parameter values used in this study were the same published by Khaksar et al. (2022).

We used the same database to estimate the absorption of Ca when the apparent total tract digestibility of Ca was also measured. We observed a linear and a quadratic response and a

Table 1

Description and parameter values to model the calcium and phosphorus model for broilers.

Description of model parameter	Value, unit
Intercept on relative feed intake	47.5, g
Linear effect of Ca	-0.938, g/g
Linear effect of non-phytic phosphorus	4.82, g/g
Quadratic effect of non-phytic phosphorus	-0.273, g/g
Linear effect of phytase	8.92, g/g
Quadratic effect of phytase	-1.43, g/g
Interaction between non-phytic phosphorus and phytase	-1.20, g/FTU
Desired Feed intake	60.43, g
P endogenous losses feces intercept	0.0034, g
Phosphorus endogenous losses feces linear effect	0.0185, g/kg BW
Phosphorus endogenous losses feces quadratic effect	-0.0021, g/kg BW
Calcium endogenous losses feces	104.25 mg/kg DMI
Feather-free body protein at maturity of Gompertz function – Ross308	1 266, g
Feather-free body protein deposition ratio of Gompertz function – Ross308	0.039, /day
Feather protein at maturity of Gompertz function – Ross308	229, g
Feather protein deposition ratio of Gompertz function – Ross308	0.046, /day
Feather-free body protein at maturity of Gompertz function – Cobb500	1 196, g
Feather-free body protein deposition ratio of Gompertz function – Cobb500	0.04, /day
Feather protein at maturity of Gompertz function – Cobb500	185, g
Feather protein deposition ratio of Gompertz function – Cobb500	0.057, /day
Body lipid estimation – Lipid to Protein ratio at maturity	1.2, g/g
Body water estimation – constant term	0.681, g
Body water estimation – allometric term	0.913, g/g
Body ash estimation – constant term	0.239, g
Body ash estimation – allometric term	0.898, g/g
Ratio of protein to muscle	0.7424, %
P concentration in feather-free body protein	0.0103137, %
P concentration in feather protein	0.0027, %
Ca concentration in feather protein	0.00089, %
Miscellaneous concentration in feather-free body protein	0.0244, %
Miscellaneous concentration in feather protein	0.85, %
Ratio of lipid to subcutaneous fat	0.93, %
P concentration in body lipid	0.00124167, %
Ca concentration in body lipid	0.00016496, %
Miscellaneous concentration in body lipid	0.0025, %
P endogenous losses urine	0.874, mg/kg BW
Ca endogenous losses urine	0.768, mg/kg BW

FTUs = phytase units, DMI = DM intake.

negative impact of NPP on the apparent total tract digestibility of Ca. Given the lack of data to assess the phytase effect, similar equivalencies are used for P and Ca. Absorption is based on apparent total tract digestibility data, so endogenous losses must be removed (Létourneau-Montminy et al., 2015). For P endogenous losses, in feces, the equation developed by Khaksarzareha et al. (2017), which is a quadratic function of BW, was used to calculate endogenous losses (Table 1). Ca endogenous losses in feces are functions of DM intake (Anwar et al., 2016, 2017, and 2018). To estimate the intestinal absorption of Ca and P, two equations were adjusted as follows:

$$P \text{ absorption} = (-P \text{ endogenous losses}) + (P \text{ absorption}) \\ * \text{feed intake, g/d} \quad (2)$$

$$Ca \text{ absorption} = (-Ca \text{ endogenous losses} * DM \text{ intake}) \\ + (Ca \text{ absorption}) * \text{feed intake, g/d} \quad (3)$$

Soft tissue growth

The soft tissue compartment uses the broiler growth model to predict feather-free body chemical components' growth and daily depositions (protein, water, lipid, and ash). The feather protein is estimated separately. The driving force in this model is feather-free body protein, which is predicted using a Gompertz equation as a function of time. The parameters of the Gompertz function are genetically affected, so the values used are presented by broiler strain (Table 1). The allometry equation is applied to predict the remaining body components as a function of body protein according to genetic strain, as described by Vargas et al. (2020).

The fate of the absorbed calcium and phosphorus

Body composition data showed body ash has an allometric relation with body protein, suggesting that ash deposition may be predicted from protein deposition (Hruby et al., 1994; Zelenka et al., 2011; Hamdi et al., 2017). Therefore, two different modeling approaches were compared (1) Ca deposition in bone, measured every-two days in broilers fed a requirement-fulfilling diet, was used to obtain Ca deposition potential (Supplementary Table S2), and (2) allometry between body ash and body protein has been predicted based on Hruby et al. (1994).

Extracellular fluid ash

As mentioned, this model is based on the approach developed for swine (Létourneau-Montminy et al., 2015). Acknowledging the importance of plasmatic levels of P and Ca to body metabolism (Bronner and Stein, 1995; Suttle, 2010) as well as the low contribution of extracellular ash to total body ash, the aforementioned authors defined that Ca and P in extracellular fluid ash as a zero pool, in other words, the input and outputs are the same, avoiding further mechanisms to describe this phenomenon. Similarly, the model developed for broilers follows the same idea: the extracellular concentration of Ca, P, and miscellaneous in extracellular fluids are zero pools.

Soft tissue and feather ash

Assuming that soft tissue (including feathers) has a constant concentration of P and Ca, even in deficient diets (Day and McCollum, 1939; Feaster et al., 1953; Brautbar et al., 1979), the dietary P and Ca are first used to fulfill the soft tissue growth. The consequences of this mechanism imply that lower dietary P and/or Ca intake may reduce bone mineralization. However, this effect is not evident for Ca since only 1% of total body Ca is found outside the bone tissue (Veum et al., 2010). The ash composition of soft tissue is not known. Therefore, concentrations of protein, lipid, P, and Ca in different tissues have been generated for Ross 308 from Day 7 to Day 42 every week (Hamdi et al., 2017).

Being the anatomical compartments that contain the most protein (respectively 68 and 20% on average), the muscle and the viscera were used as the reference tissue to calculate the amount of P, Ca, and other minerals deposited with protein (Eqs. (4)–(6)). In the same way, the subcutaneous fat was used to calculate the amount of P, Ca, and other minerals deposited with lipid (Eqs. (7)–(9)). The Ca to muscle and viscera ratio depends on BW (Eq. (10)).

$$\text{deposition of P in Protein (g)} \\ = \left(\frac{\text{Body protein deposition}}{\text{Prot : Muscle}} \right) \\ * \text{P concentration in body protein} \\ + \text{feather protein deposition} \\ * \text{P concentration in feather protein} \quad (4)$$

where **Prot:Muscle** is the ratio of protein to muscle.

$$\begin{aligned} & \text{deposition of Ca in Protein (g)} \\ & = \left(\frac{\text{Body protein deposition}}{\text{Prot : Muscle}} \right) \\ & \quad * \text{Ca concentration in body protein} \\ & \quad + \text{feather protein deposition} \\ & \quad * \text{Ca concentration in feather protein} \end{aligned} \quad (5)$$

$$\begin{aligned} & \text{deposition of miscelanelous in body protein (g)} \\ & = \left(\frac{\text{Body protein deposition}}{\text{Prot : Muscle}} \right) \\ & \quad * \text{miscellaneous concentration in body protein} \\ & \quad + \text{feather protein deposition} \\ & \quad * \text{miscellaneous concentration in feather protein} \end{aligned} \quad (6)$$

$$\begin{aligned} & \text{deposition of P in body lipid (g)} \\ & = \left(\frac{\text{Body lipid deposition}}{\text{Lipid : Fat}} \right) \\ & \quad * \text{P concentration in body lipid} \end{aligned} \quad (7)$$

where **Lipid:Fat** is the ratio of lipid to subcutaneous fat.

$$\begin{aligned} & \text{deposition of Ca in body lipid (g)} \\ & = \left(\frac{\text{Body lipid deposition}}{\text{Lipid : Fat}} \right) \\ & \quad * \text{Ca concentration in body lipid} \end{aligned} \quad (8)$$

$$\begin{aligned} & \text{deposition of miscellaneous in body lipid (g)} \\ & = \left(\frac{\text{Body lipid deposition}}{\text{Lipid : Fat}} \right) \\ & \quad * \text{miscellaneous concentration in body lipid} \end{aligned} \quad (9)$$

$$\begin{aligned} & \text{Content of Ca in body protein (\%)} \\ & = 0.001711 - 0.000393 * \text{BW (kg)} \end{aligned} \quad (10)$$

Bone ash

The bone ash main constituents are Ca and PO₄, and miscellaneous minerals (Crenshaw et al., 2001), but the correct composition has yet to be fully known. Given the objectives of the present model, the miscellaneous minerals are assumed not to affect the soft tissue or bone growth (Létourneau-Montminy et al., 2015). The hydroxyapatite salts are the main structures in which P and Ca are deposited into bone, resulting in a fixed ratio of 2:1 (Matuszewski et al., 2020). Therefore, the bone ash is calculated as the sum of Ca, P, and miscellaneous in bone. The potential retention of Ca in bone will drive the deposition of all minerals, maintaining the bone mineral proportion.

$$\begin{aligned} & \text{Potential retention of Ca in bone} \\ & = (\text{aAsh} \times \text{Potential protein deposition}^{\text{bAsh}}) \\ & \quad \times \text{concentration of Ca in bone} \\ & \quad : \text{Body Ash} \end{aligned} \quad (11)$$

After the prediction of body ash based on body protein following Hruby et al. (1994; Table 1), the concentration of Ca in bone ash is assumed to be 22% of total body ash (Narcy et al., not published). Then, the ratio of 2:1 was used for Ca to P (**Ca:P**) to estimate the

potential amount of P in bone ash. The concentration of miscellaneous minerals in bone ash was assumed to be 48% of total bone ash (Hamdi et al., 2017; Supplementary Table S2).

Besides the role of P as a bone constituent, this macromineral is also necessary for biological functions such as the transport of fatty acids and amino acids in the bloodstream, composition of phospholipid membranes, maintenance of acid-base equilibrium, and the vital participation in the energy metabolism by AMP, ADP, and ATP (Matuszewski et al., 2020). These important roles may explain why rats fed a P-deficient diet had P release from bones and transfer to soft tissues until a critical level was achieved in the bone reserves, as shown by Schneider and Steenbock (1939), where 47% of the bone reserve were depleted in 34 days in a low P and free vitamin D diet. The model presented herein prioritizes P deposition in soft tissue over bone. Therefore, the model was designed to predict P bone mobilization when the intake is insufficient to satisfy soft tissue growth. Due to the fixed concentration between Ca:P and other miscellaneous minerals, all minerals are mobilized together from bone, and the excess is excreted in urine. Other homeostasis mechanisms, such as a change in intestinal absorption, still need to be included in the model. The maximum bone mobilization was fixed at 50% (Schneider and Steenbock, 1939), but this is not empirical evidence, and the model would benefit from future studies in this area.

Calcium and phosphorus actual deposition

Urinary Ca and P include the obligatory losses and the amount of minerals that cannot be retained in soft tissue or bone because of an imbalance between minerals or excesses. Obligatory urinary losses of Ca and P are low and are estimated in the model to be 0.678 mg/kg of BW and 0.874 mg/kg of BW, respectively (Manangi et al., 2018). The actual deposition of Ca, P, and miscellaneous minerals in bone is complex because many factors must be considered simultaneously. For that, two equations were constructed:

$$\begin{aligned} & \text{deposition of Ca}_1 = (\text{P absorption} \\ & \quad - \text{P deposition in soft tissue} \\ & \quad - \text{P endogenous losses in urine} \\ & \quad * \text{BW}) * \text{Ca : P, g/d} \end{aligned} \quad (12)$$

$$\begin{aligned} & \text{deposition of Ca}_2 = (\text{Ca absorption} \\ & \quad - \text{Ca deposition in soft tissue} \\ & \quad - \text{Ca endogenous losses in urine} \\ & \quad * \text{BW, g/d} \end{aligned} \quad (13)$$

where P endogenous losses in urine is 0.874 mg/kg of BW (Manangi et al., 2018). Ca:P is the ratio between Ca and P in bone (2:1). Eq. (13), Ca endogenous losses urine is 0.768 mg/kg of BW (Manangi et al., 2018). The lower value between the potential of Ca deposition into bone ash (based on the assumption that the amount of Ca in bone ash is 22% of total body ash), deposition of Ca₁, and deposition of Ca₂ is the actual deposition of Ca in bone ash, with a restriction to avoid negative values, changing the value to zero in such cases.

The prediction of P deposition in bone ash uses a similar equation as used for calcium deposition, with the exception that there is no multiplication by the ratio Ca:P, as follows:

$$\begin{aligned} & \text{deposition of P} = (\text{P absorption} \\ & \quad - \text{P deposition in soft tissue} \\ & \quad - \text{P endogenous losses in urine} \\ & \quad * \text{BW, g/d} \end{aligned} \quad (14)$$

Finally, the actual amount of P deposited is defined as the lower value between Eq. (14) and the result obtained for real Ca deposition divided by 2 (Ca:P).

The fate of the absorbed calcium and phosphorus

The model parameters were obtained in experiments performed in fast-growing broilers resulting from an international collaboration between Université Laval (Canada), UNESP (Brazil), INRAE (France), and University of Maryland (USA). The mechanisms that drive the fate of dietary Ca and P were adapted from [Létourneau-Montminy et al. \(2015\)](#). The model was evaluated using an independent database, not used to develop the model, presented in the [Supplementary Tables](#). Literature data investigating Ca and P balances through the total collection of excreta (16 studies, [Supplementary Table S3](#)), feed intake when varying Ca and P supply (three studies; [Supplementary Table S4](#)), body composition ash (four studies, [Supplementary Table S5](#)), and body composition (one study, [Supplementary Table S6](#)).

Model evaluation

The model evaluation described in this study was performed in three steps: (1) a global sensitivity analysis; (2) a model behavior assessment; and (3) external evaluation. The global sensitivity analysis was performed using Sobol indices to evaluate the most critical parameters and their interaction. Sobol indices is a global sensitivity analysis method that uses the decomposition of the model output variance to quantify the contribution of each parameter and their interaction in the model ([Sobol, 2001](#)). The parameters analyzed are changed from -1.5 to $+1.5$ -fold, their respective SD. In the simulation, those changes are done iteratively, one by one, including all possible combinations between parameter changes. Then, considering the parameters as a source of variation, a regular analysis of variance in a factorial design is used to evaluate each parameter/combination by its contribution to total variation ([Zhang et al., 2015](#); [Ye and Hill, 2017](#)). This sensitivity analysis aimed to identify critical areas in the system and highlight the most influential factors implicated in Ca and P metabolism.

A model behavior analysis was performed to evaluate the theories that drive the model. The results of these simulations are the logical consequences and mathematical representations of the hypotheses included in the model. Two different nutrition scenarios were simulated. In the first scenario, all nutrients and energy were set according to the Brazilian Tables for Poultry and Swine ([Rostagno et al., 2017](#)). In the second scenario, all essential amino acids were reduced by 35% from the recommended amount. Both simulations considered the growth potential of a modern broiler ([Table 1](#)) raised in a thermoneutral zone with a feed program based on two feeds (1–7, 8–21 days). Two sets of response variables were collected: (1) BW, feather-free body water, protein, lipid, ash, and feather protein, and (2) division of Ca and P in the body.

The external evaluation was performed using the database given in [Supplementary Tables S3–S6](#). The observed and predicted data were compared using the regression technique by evaluating the intercept, slope, and R^2 obtained when the observations are regressed in the function of the predicted values. To minimize the study effect, the observed data were adjusted using the mixed procedure in SAS (SAS Inst. Inc., Cary, NC) as recommended by [St-Pierre \(2001\)](#). To evaluate the error of prediction, mean square prediction error (MSPE) and its decomposition, mean bias (error in central tendency), slope bias (error due to regression), and random errors (error due to disturbances) were calculated ([Pomar and Marcoux, 2005](#)). Furthermore, mean square prediction error (\mathbf{rMSPE}) was calculated as the square root of MSPE and expressed as a proportion of the mean predicted, named overall error. The

error in central tendency, error due to regression, and error due to disturbances were expressed as a percentage of MSPE.

Results and discussion

The calcium deposition potential

The model evaluation showed that the parameters estimated by [Hruby et al. \(1994\)](#) to predict body ash in the function of body protein resulted in a lower prediction error. The relative error observed using the allometry equation was around 10%, whereas when the Ca deposition potential is estimated independent of body protein was 21%. In both methods, most errors were due to data disturbances. However, for the allometry equation, the error due to disturbance represented 46% of the total error, while in independent Ca deposition potential, the error due to disturbances represented 69% of the total error. Thus, the allometry with body protein was selected to predict body ash, with the parameters according to [Hruby et al. \(1994\)](#). In pigs, body ash is better predicted when dissociated from body protein ([Lautrou et al., 2020](#)). However, the results suggested that is not the case for broilers, which agrees with other literature results ([Zelenka et al., 2011](#); [Gonçalves et al., 2020](#)).

Global sensitivity analysis

To evaluate the sensitivity of P deposition in soft tissue, the parameters assessed were the protein maturity rate (0.039 ± 0.01), P concentration in feather-free body protein (0.010314 ± 0.00154), P concentration in feather-free body lipid (0.001242 ± 0.00024), the Ca concentration in body ash (0.22 ± 0.022), and the ratio Ca:P in bone ash (2 ± 0.1). The parameters evaluated for P deposition in bone were the protein maturity rate, the Ca concentration on body ash, and the ratio Ca:P in bone ash. The parameters evaluated to test the sensitivity of Ca deposition in soft tissue were the protein maturity rate, the ratio Ca:P in bone ash, Ca concentration in feather-free body protein (0.001711 ± 0.0001711 for the intercept and 0.000393 ± 0.000039 for the slope of Eq. (2)), and the Ca concentration in feather-free body lipid (0.0001649 ± 0.0000016). The parameters tested for Ca deposition in the bone were the protein maturity rate, the ratio Ca:P in bone ash, and the Ca concentration on body ash. Among all parameters evaluated for the global sensitivity analysis, the concentration of P in body protein, the Ca:P ratio in bone, the concentration of Ca in body protein, and the concentration of Ca in body ash had the most influence over depositions of P in soft tissue, P in bone ash, Ca in soft tissue, and Ca in bone ash, respectively ([Fig. 2](#)).

Changing the parameters according to their SD affected P deposition in soft tissue (from 0.7 to 1.3 times the mean). The concentration of P in body protein represents more than 90% of the observed variation ([Fig. 2A](#)). This is expected because most P outside the bone is found in body protein ([Hamdi et al., 2017](#)). The maturity ratio of body protein influenced P deposition to a lower degree (7%).

As previously shown, protein deposition is the driving force in the growth model, so changes in protein deposition affect all other responses. Changing the maturity ratio of protein deposition usually causes all other components to be affected similarly. The parameter changes similarly impacted Ca deposition in soft tissue (0.8–1.2 times the mean). Only two parameters influenced the variation of Ca deposition in soft tissue, and the most relevant (85% of total variation) is the concentration of Ca in body ash, which is used in the model as an auxiliary variable to estimate the Ca deposition potential based on the potential of protein deposition. This parameter will affect P and miscellaneous minerals because they are related to Ca. However, only 1% of body Ca is

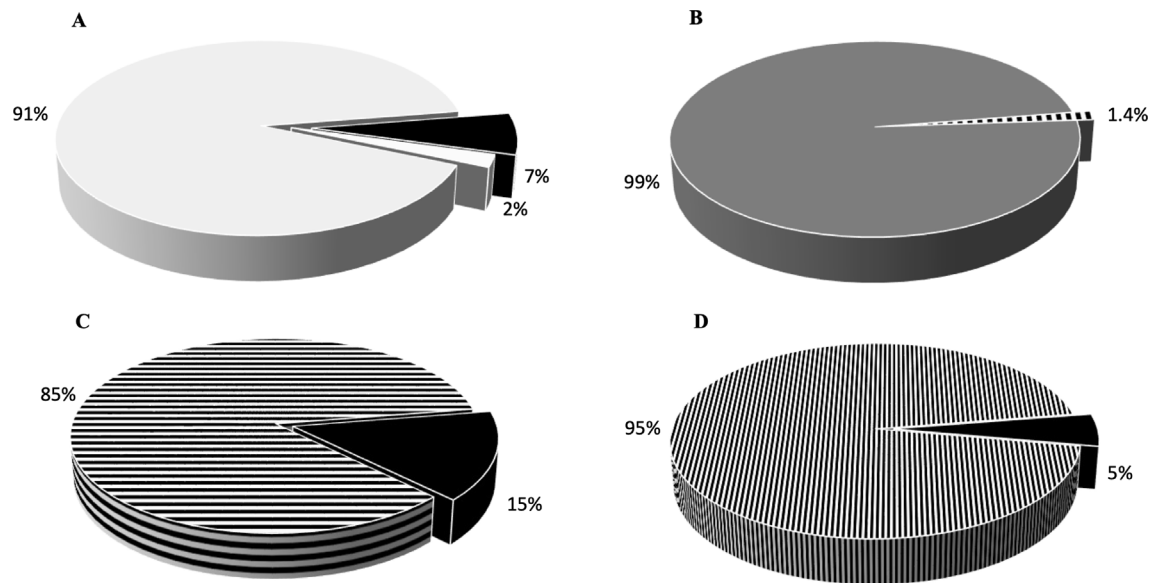


Fig. 2. Contribution of parameter estimates to the variation in phosphorus and calcium deposition in soft tissue of broilers (represented by A for phosphorus and C for calcium) as well as bone ash (represented by B for phosphorus and D for calcium). In (A), the light gray portion represents the concentration of P in body protein, the black slice represents the maturity ratio of body protein, and white portion represents the phosphorus concentration in body lipid. In (B), the dark gray slice represents the calcium and phosphorus ratio in bone tissue, while the slice with vertical lines represents the calcium concentration in body ash. (C) depicts the calcium concentration in body protein using the slice with horizontal lines, and the black slice represents the maturity ratio of body protein. In (D), the concentration of calcium in body ash is represented by the slice with vertical lines, while the black slice represents the maturity ratio of body protein.

found in soft tissue (Veum et al., 2010). The Sobol indices observed for P deposition in bone ash demonstrate that the Ca:P ratio in bone has the most impact on this response variable (around 99% ranging from 0.91 to 1.09 times the mean). P deposition in bone depends on the hydroxyapatite crystals, which contain approximately 2:1 Ca:P ratio (Matuszewski et al., 2020); thus, a change in this ratio will influence the amount of P in bone ash tissue. The Ca deposition in bone was less affected by the parameters evaluated (0.99–1.01 times the mean), and the concentration of Ca in body ash was the most influential parameter, accounting for approximately 94% of the total variation.

Model behavior

Modulation of feed intake

The increment of dietary NPP from 0.8 to 1.2 times the level recommended by the breeder (Ross308 – Aviagen) produced a linear increase in feed intake (0.81 to 0.96 kg) but only when dietary Ca was constant and at the recommended levels (Fig. 3A). When both dietary NPP and Ca increased together, the simulated feed intake was relatively constant (0.86–0.88 kg). However, the simulation demonstrated that supplying a feed with increasing dietary Ca levels (from 0.8 to 1.2 times the recommendation) and constant NPP elicited a linear decrease in the feed intake (Fig. 3B). Broiler chickens allowed to choose between two feeds, regular and deficient in dietary Ca, seem to have a Ca appetite mechanism that drives the feed selection toward a richer Ca feed compared to a deficient one (Lobaugh et al., 1981). Dietary P appears to elicit a different response, where naturally reduced feed intake is a consequence of deficient P diets (Chen and Moran, 1995; Aderibigbe et al., 2022). Both minerals must be considered simultaneously to predict the effect of dietary Ca and P levels on feed intake (Hamdi et al., 2015).

Body chemical components in adequate and low-lysine diets

The simulation of broilers that consume a feed with low levels of essential amino acids (Fig. 4) shows a decrease in BW (16%),

body water (11%), body protein (18%), and body ash (1%). On the contrary, body lipids increased by around 28% on simulated broilers that consumed a feed deficient in lysine. In the growth model, body protein potential is the driving variable from which other chemical components are estimated, such as water, lipid, and ash. Body water is the only chemical component predicted without a mechanism that allows a separate increase from protein. Reducing amino acid intake directly affects body protein deposition and indirectly affects body lipid deposition. When protein deposition decreased due to a low intake of essential amino acids, remaining energy, once deposited as protein, was stored as lipid. Azevedo et al. (2021) observed that broilers that consumed a feed with 40% less essential amino acids increased body lipids by around 60% compared to broilers that consumed a feed with the recommended level of essential amino acids. Such outcomes support previous research findings, demonstrating a negative correlation between dietary amino acids and body lipids (Eits et al., 2005; Kamran et al., 2008; Fouad and El-Senousey, 2014). The fraction of Ca and P agrees with observations on body composition (Fig. 4). The Ca and P deposited on feather-free body protein and feather protein decreased by about 18% for simulated broilers consuming a lysine-deficient diet, which is in line with the reduction in body protein deposition. Following the same logic, Ca and P deposited in body lipids increased by 28%.

Simulation of dietary phosphorus and calcium imbalance and deficiency

On the simulated broilers with increased Ca intake (Fig. 5A and C), the P in soft tissue is relatively constant, whereas the P in the bone ash increases with the increment of dietary Ca. In the absence of Ca, the P available for bone deposition is not used because, in bone tissue, the P is preferably deposited as hydroxyapatite crystals, which need Ca to form (Veum et al., 2010). The excess P that cannot be deposited because of a lack of Ca is excreted in urine, as demonstrated in Fig. 5A and by Manangi et al. (2018). The reduction of bone ash in broilers that consumed deficient dietary Ca and constant P was shown by Li et al. (2020) and through meta-

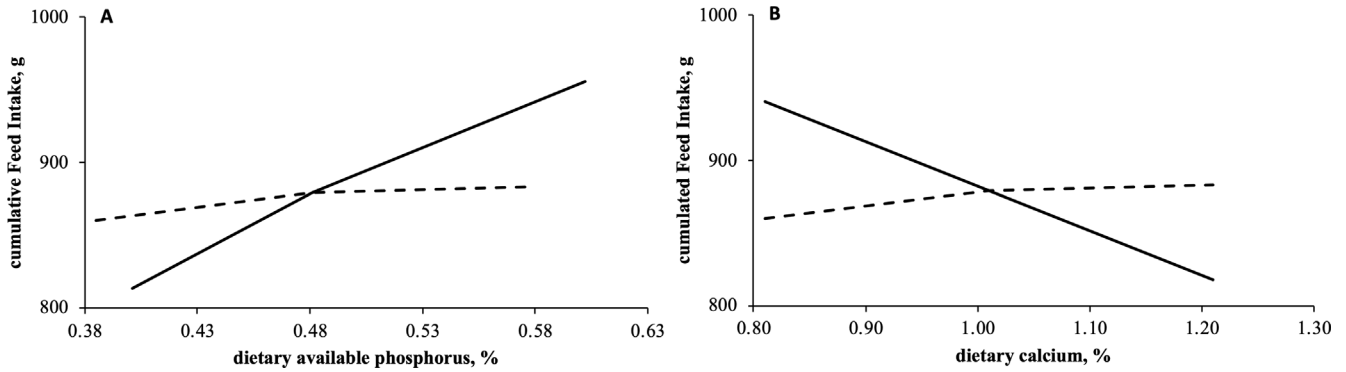


Fig. 3. (A) depicts the cumulative feed intake of simulated broilers aged one to 21 days, fed with a diet containing varying levels of dietary non-phytate phosphorus (0.40–0.60%). The graph includes two scenarios: one with constant dietary calcium levels (1.01% – straight line) and another with increasing dietary calcium levels (0.81–1.21% – dashed line). (B) illustrates the cumulative feed intake of simulated broilers aged one to 21 days, fed a diet containing increasing levels of dietary calcium. The graph shows two scenarios: one with constant dietary non-phytate phosphorus levels (0.48% – straight line) and another with increasing dietary non-phytate phosphorus levels (0.38–0.58% – dashed line).

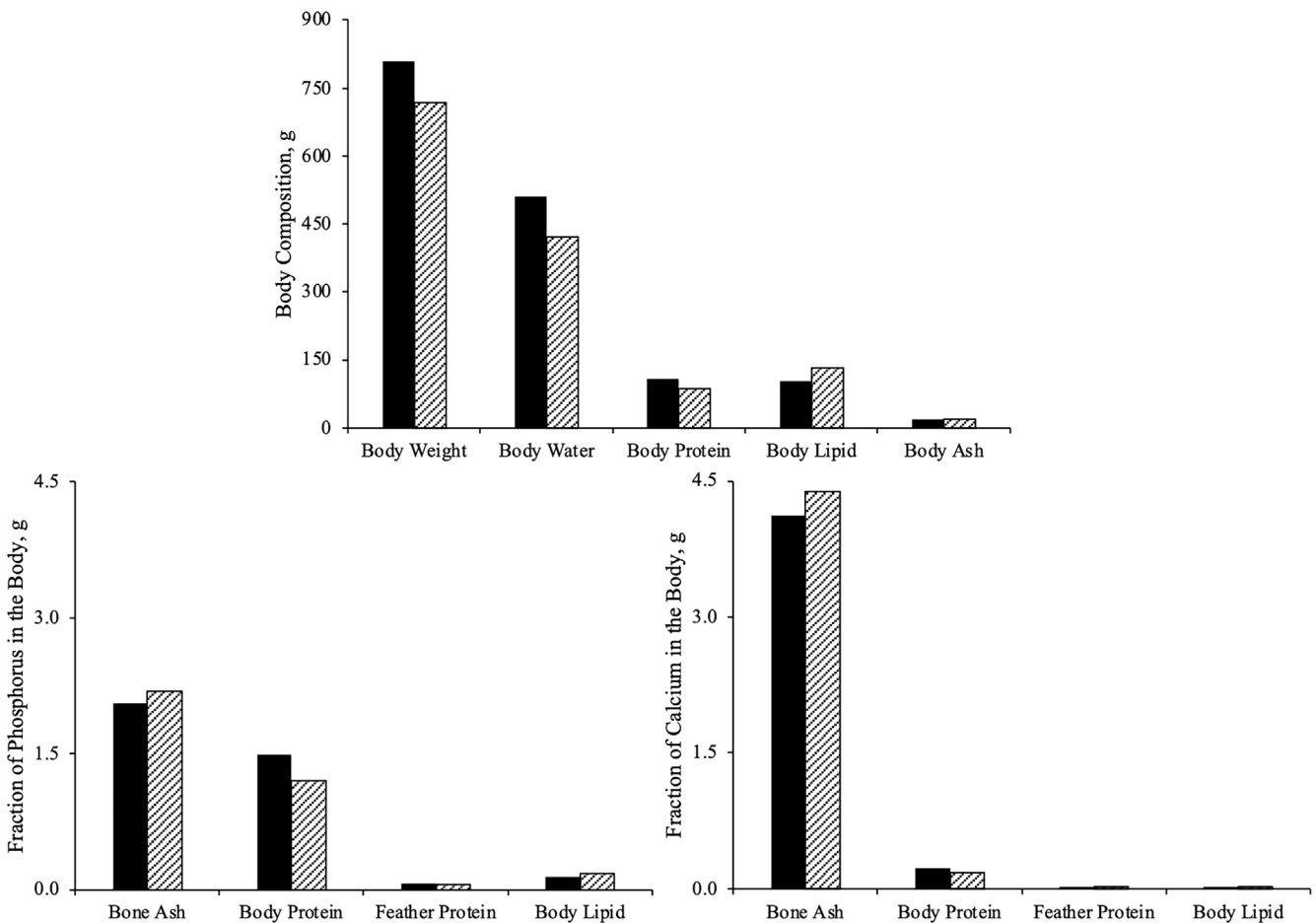


Fig. 4. Illustration of the body composition (A) and the proportion of phosphorus (B) and calcium (C) in the body of 21-day-old broiler. The broilers were divided into two groups: one group consumed a recommended feed (black columns, Rostagno et al., 2017), while the other group consumed a feed with a 35% reduction in dietary essential amino acids (striped columns).

analysis by L  tourneau-Montminy et al. (2010). In addition, Li et al. (2020) observed that a reduction in bone ash is more severe in broilers that consume feed with reduced levels of P and constant Ca, which is in line with the model simulation (Fig. 5B and D). In our simulation, the feed with 3.4 g/kg of dietary NPP and constant Ca (9.0 g/kg) and the feed with 6.8 g/kg of Ca and constant P (4.5 g/kg) elicited a reduction of Ca and P concentration on bone ash. The excretion of P is markedly different from the urinary

excretion, which is reasonable since most estimates of P excretion result from a lack of Ca for hydroxyapatite formation.

When the NPP levels increase with constant dietary Ca, the excretion of P linearly increases. This result agrees with the literature: P excretion increases with dietary P (Proszkowiec-Weglarz and Angel, 2013). Similarly, the excretion of Ca increased as the dietary Ca was supplemented (Fig. 5C). The increment in Ca excretion was influenced mainly by the Ca found in the feces, i.e., with the increment of

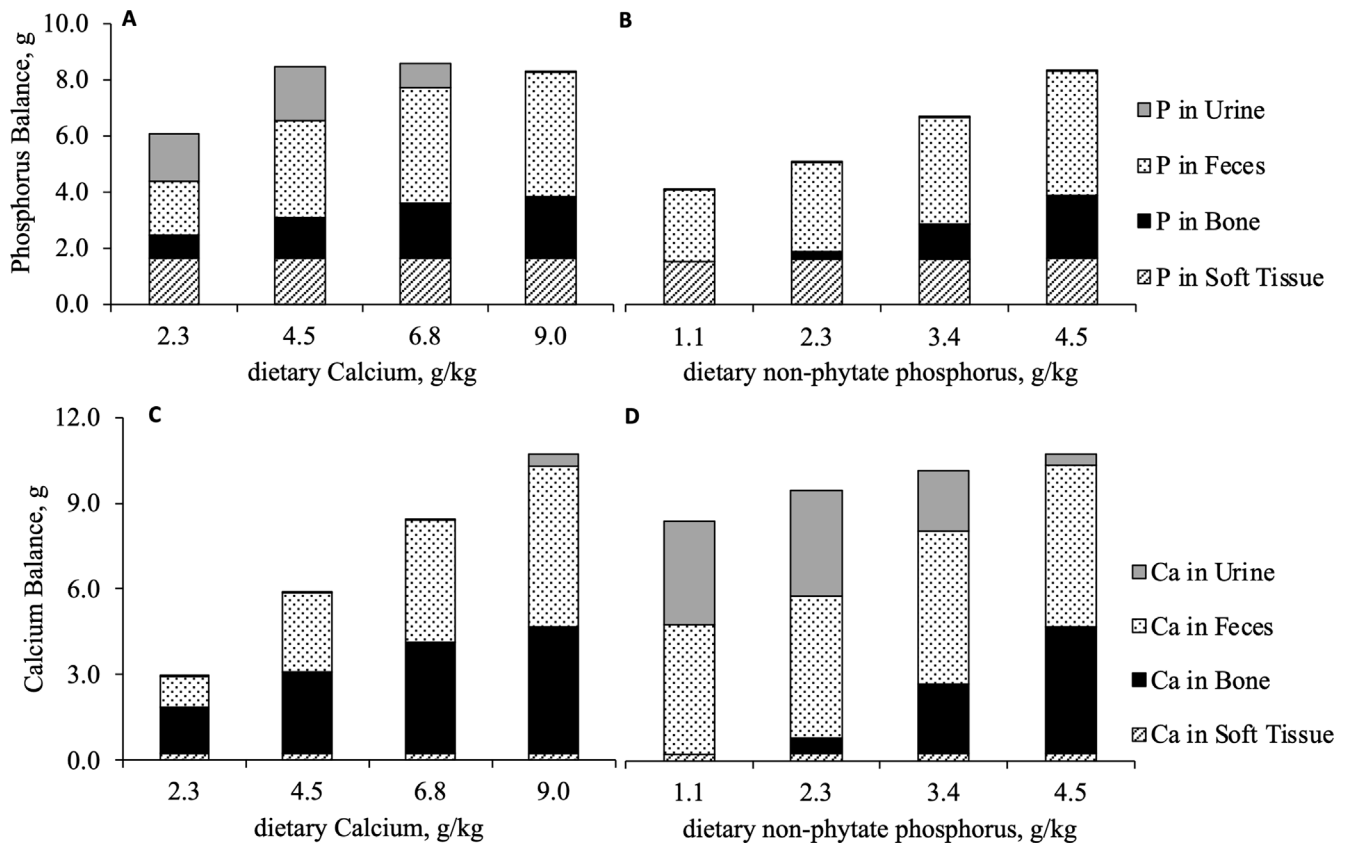


Fig. 5. Metabolic fate of phosphorus (A and B) and calcium (C and D) on broilers body, where (A and C) are the simulation results of a broiler consuming increasing levels of dietary calcium (from 2.3 to 9.0 g/kg) with constant dietary available phosphorus (4.5 g/kg), and (B and D) are the simulation results of a broiler consuming increasing levels of dietary available phosphorus (from 1.1 to 4.5 g/kg) with constant dietary calcium (9.0 g/kg).

dietary Ca, the digestibility of Ca decreased. Ca and P's absorption, excretion, and deposition mechanisms are complex and not completely elucidated. Variations in Ca and P balance depend on the plasmatic levels of Ca^{2+} and phosphate, modulated by hormones, such as parathyroid hormone (PTH), metabolites of vitamin D, and calcitonin. When the plasmatic levels of Ca^{2+} or phosphate decrease (hypocalcemia or hypophosphatemia), the PTH is secreted into the blood by parathyroid glands, which will increase the conversion of vitamin D in the kidney. Both PTH and active vitamin D will increase bone resorption, and vitamin D will increase the reabsorption of Ca in the kidney and absorption in the intestine. Those actions together are proven to increase the blood levels of Ca and increase the excretion of P (Combs and McClung, 2008; Proszkowiec-Weglarz and Angel, 2013). The mechanisms regulating P metabolism are also influenced by PTH and vitamin D, with consequences in P metabolism very similar to what was mentioned for Ca. A low level of P in the plasma will decrease P excretion but increase Ca excretion in the kidney and increase the uptake of P and Ca in the intestine and bone resorption. The output from the model presented here (Fig. 5) aligns with Ca and P regulation mechanisms.

Ca and P absorption regulation still need to be included in the model. As a result, fecal Ca excretion may be overpredicted, and urinary Ca excretion may be underestimated in diets highly deficient in P. In contrast, fecal P excretion can be overestimated, leading to lower Ca retention.

External evaluation

Comparison between observed and predicted growth performance

The database used to evaluate the predicted performance was obtained from two controlled trials conducted to evaluate the

effect of increasing dietary NPP with constant dietary Ca (Supplementary Table S4). The results indicate that the equation that modulated the feed intake according to the concentrations of NPP, Ca, and phytase simulated with adequate accuracy as intercepts and slopes did not deviate from 0 and 1 (Fig. 6A). The difference in this response was around 60% between broilers that consumed the feed with the lowest and highest dietary NPP and constant Ca. In the second trial, the main difference was observed between broilers that consumed 8.45 g/kg of dietary Ca and 2.54 g/kg of NPP, which is in line with the simulations presented in Fig. 3 and reinforced by the lower rMSPE (5.38% with 65.1% of that error being of disturbance). The predictions of average daily gain (Fig. 6B) demonstrate that the model had good accuracy with only 1.62% of rMSPE again. The results observed for feed conversion ratio (Fig. 6C) show that the reduction in BW is not proportional to the decrease in feed intake (rMSPE = 5.63, error due to regression = 24%; error due to disturbances = 72%). This indicates that more mechanisms need to be understood and used in the broiler growth model to improve the prediction of broilers that consume a feed with reduced levels of P and Ca. This may result from the implication of P in energy and protein metabolism. Indeed, in growing ruminants, it has been shown that P deficiency adversely affects energy and protein utilization (Kleiber et al., 1936; Morris and Ray, 1939). Further studies will thus be needed to understand the underlying mechanisms better to represent the effect of dietary P on growth performance in a mechanistic model, given that it seems more complex and not simply driven by feed consumption.

Comparison between observed and predicted body composition

The database used to evaluate the predictions on body composition is from one study (Gonçalves et al., 2020) conducted to eval-

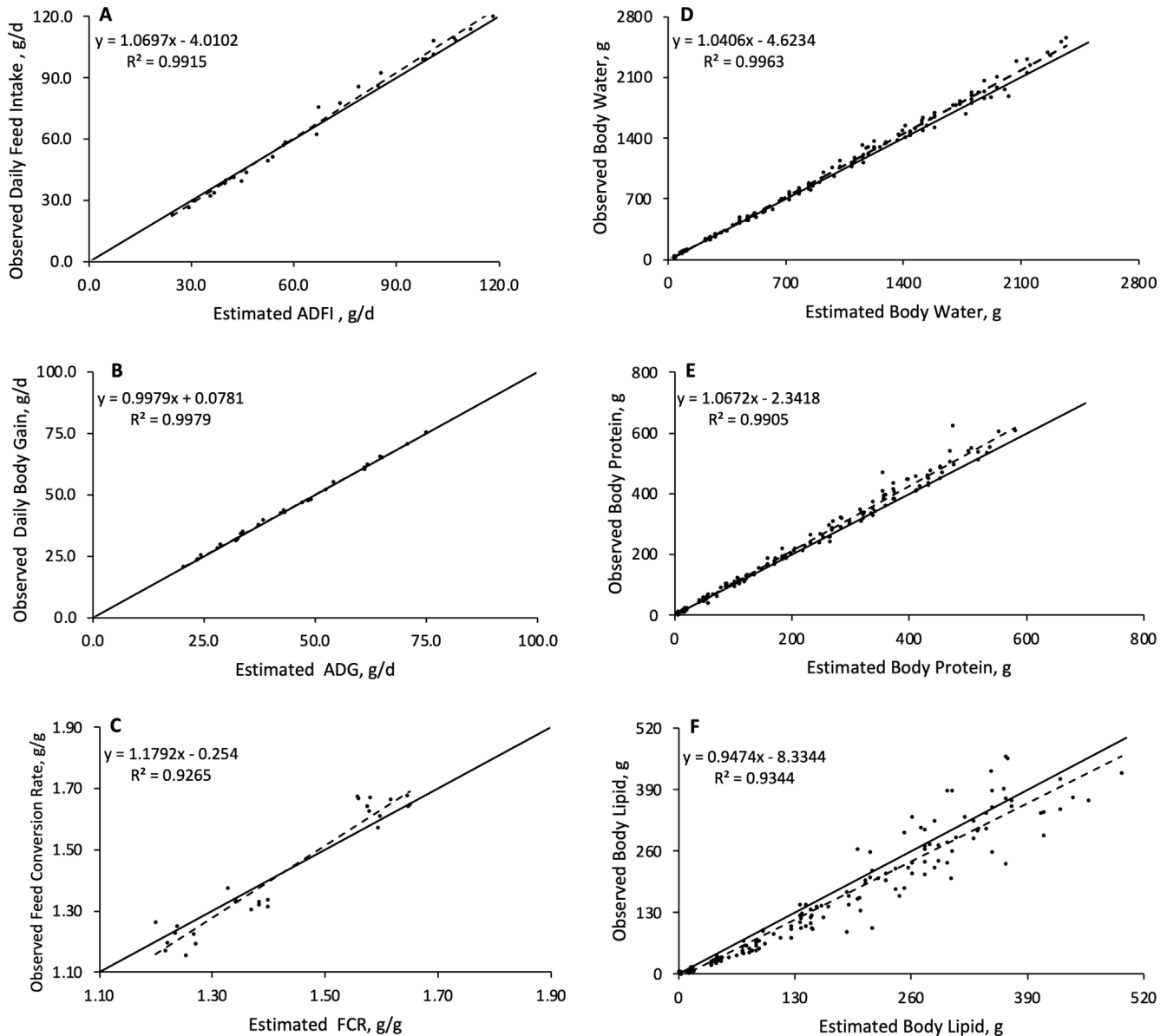


Fig. 6. External evaluation of a broiler model demonstrating the relationship between observed and predicted data for performance ($n = 29$) average daily feed intake (A, relative mean square prediction error [rMSPE] = 5.38%, error in central tendency [ECT] = 2.80%, error due to regression [ER] = 32.1%, and error due to disturbances [ED] = 65.1), average daily body gain (B, rMSPE = 1.62%, ECT = 0.046%, ER = 0.207%, and ED = 99.7%), feed conversion ratio (C, rMSPE = 5.63%, ECT = 3.81%, ER = 23.9%, and ED = 72.3%), and the body content ($n = 192$), water (D, rMSPE = 7.22%, ECT = 23.2%, ER = 22.5%, and ED = 54.3%), protein (E, rMSPE = 12.3%, ECT = 19.6%, ER = 23.5%, and ED = 56.8%), and lipid (F, rMSPE = 25.6%, ECT = 18.5%, ER = 3.43%, and ED = 78.1%). $x = y$ line (—) and regression line (---). Database used in this external evaluation is given in Supplementary Tables S4 and S6.

uate the genetic potential of broilers. The database contained information on broilers' body water, protein, and lipid from one to 47 days old, collected fortnightly. The feed, formulated to meet or exceed the broilers' requirement for all nutrients and energy, was simulated in the growth model. Furthermore, the feed intake used as an input in the simulation was reported in the Brazilian Tables for Poultry and Swine (Rostagno et al., 2017). The content of water in the body was well predicted (rMSPE = 7.22%; Fig. 6D), followed by body protein (rMSPE = 12.3%; Fig. 6E), and more inaccurate predictions are observed for body lipids (rMSPE = 25.6%; Fig. 6F). The error observed for body protein indicates that the model slightly underpredicts the protein weight, and this effect increases with the broilers' age. Genetic, energy, and nutrient intake factors may affect lipid deposition (Fouad and El-Senousey, 2014), which is already accounted for in the model, indicating that other factors must be implemented to improve this pre-

dition variable. Nevertheless, as P and Ca concentrations in lipid tissue are low, it will slightly affect their simulations by the model.

Comparison between observed and predicted body minerals and phosphorus balance

The data used to simulate body ash are from four studies in which broilers received a feed formulated to meet or exceed nutrient and energy requirements. The estimated ash (Fig. 7A), Ca (Fig. 7B), and P contents (Fig. 7C) in the body are relatively well predicted, with exceptions. The general error of body ash prediction is around 7.74%, but the majority are disturbances (72.5%), followed by central tendency (23.4%). The amount of Ca and P in the body has a general error of around 11% and 6.56%, respectively, with most parts accounted for by disturbance error (51.6% for Ca and 90.7% for P). The results demonstrate that the model predic-

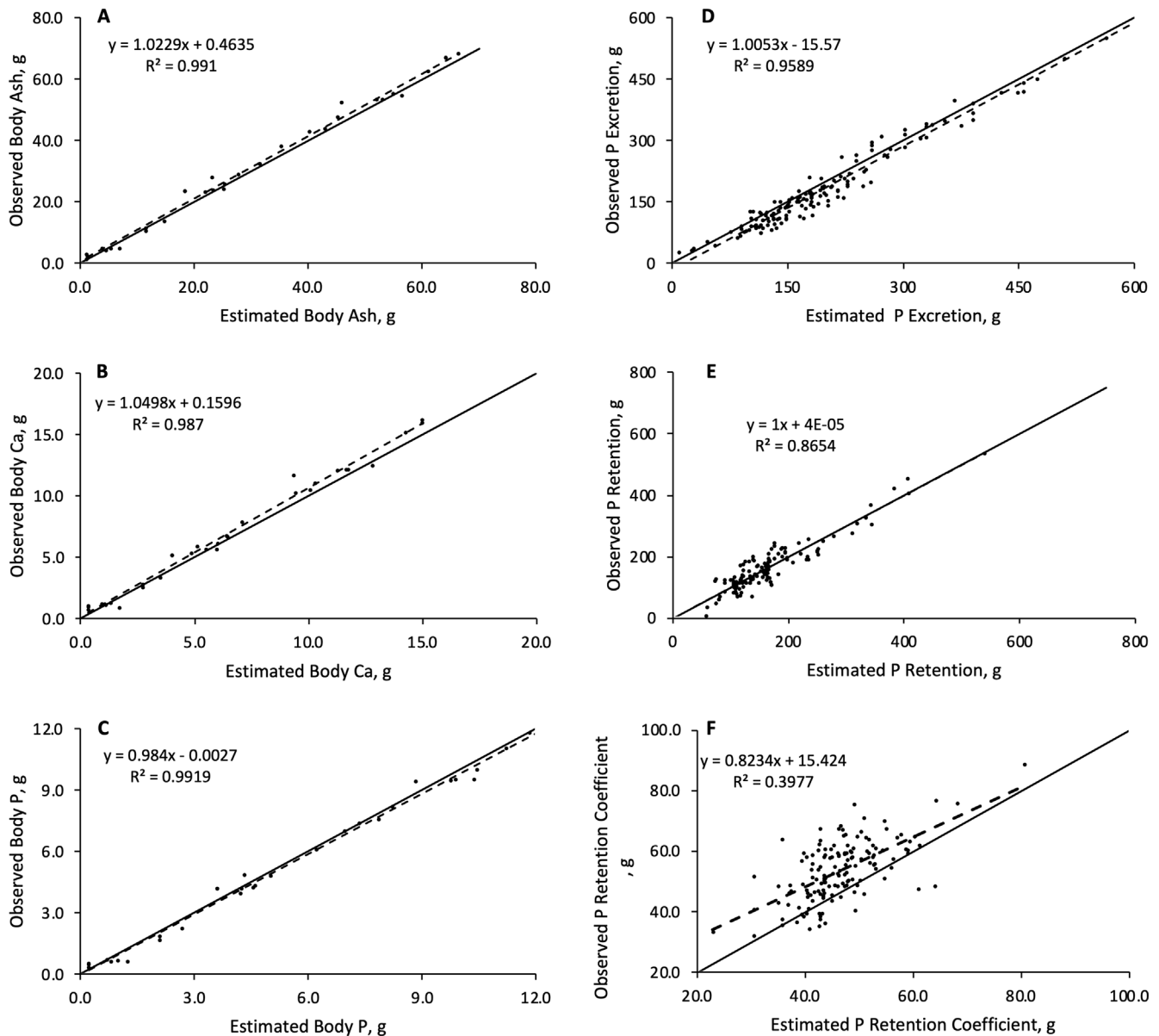


Fig. 7. External evaluation of a broiler model demonstrating the relationship between observed and predicted data for minerals in the body ($n = 31$), body ash (A, relative mean square prediction error [rMSPE] = 7.74%, error in central tendency [ECT] = 23.4%, error due to regression [ER] = 4.02%, and error due to disturbances [ED] = 72.5%), body calcium (B, rMSPE = 11%, ECT = 39.6%, ER = 8.78%, and ED = 51.6%), and body phosphorus (C, rMSPE = 6.56%, ECT = 6.32%, ER = 2.93%, and ED = 90.7%), and phosphorus balance ($n = 148$), excretion (D, rMSPE = 13.3%, ECT = 30.9%, ER = 0.04%, and ED = 69.1%), retention (E, rMSPE = 18.4%, ECT = 0.001%, ER = 0.001%, and ED = 99.9%), and coefficient of retention (F, rMSPE = 22.8%, ECT = 47.1%, ER = 1.56%, and ED = 51.3%). $x = y$ line (—) and regression line (---). Database used in this external evaluation is given in Supplementary Tables S3 and S5.

tions regarding Ca and P deposition in the body align with published literature.

The excretion and retention of P are directly affected by P digestibility. Our results suggest that using both equations published by [Khaksar et al. \(2022\)](#) produced the lowest prediction error; hence, [Fig. 7](#) is based on the results obtained by using both equations.

The relationships of dietary Ca and P in broiler chicken metabolism are complex. The model's prediction of P excretion is relatively good, but a correction may improve this variable. The model might be helpful to researchers interested in investigating the dynamics of Ca and P in the broilers' bodies and for nutritionists interested in decreasing the use of non-renewable phosphate and minimizing the environmental impact to achieve more sustainable broiler meat production. The next step will be to invert this model to predict requirements.

Supplementary material

Supplementary material to this article can be found online at <https://doi.org/10.1016/j.animal.2023.100896>.

Ethics approval

Not applicable.

Data and model availability statement

Data were not deposited in an official repository. All data that support the research findings could be requested from the corresponding author.

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Declaration of interest

None.

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