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ABSTRACT

Current feed formulation and evaluation practices rely on static values for the nutritional value of feed ingredients and assume additivity. Hereby, the complex interplay among nutrients in the diet and the highly dynamic digestive processes are ignored. Nutrient digestion kinetics and diet × animal interactions should be acknowledged to improve future predictions of the nutritional value of complex diets. Therefore, an *in silico* nutrient-based mechanistic digestion model for growing pigs was developed: "**SNAPIG**" (Simulating Nutrient digestion and Absorption kinetics in PIGs). Aiming to predict the rate and extent of nutrient absorption from diets varying in ingredient composition and physicochemical properties, the model represents digestion kinetics of ingested protein, starch, fat, and non-starch polysaccharides, through passage, hydrolysis, absorption, and endogenous secretions of nutrients along the stomach, proximal small intestine, distal small intestine, and caecum + colon. Input variables are nutrient intake and the physicochemical properties (i.e. solubility, and rate and extent of degradability). Data on the rate and extent of starch and protein hydrolysis of different ingredients per digestive segment were derived from *in vitro* assays. Passage of digesta from the stomach was modelled as a function of feed intake level, dietary nutrient solubility and diet viscosity. Model evaluation included testing against independent data from *in vivo* studies on nutrient appearance in (portal) blood of growing pigs. When simulating diets varying in physicochemical properties and nutrient source, SNAPIG can explain variation in glucose absorption kinetics (postprandial time of peak, **TOP**: 20–100 min observed vs 25–98 min predicted), and predict variation in the extent of ileal protein and fat digestion (root mean square prediction errors (**RMSPE**) = 12 and 16%, disturbance error = 12 and 86%, and concordance correlation coefficient = 0.34 and 0.27). For amino acid absorption, the observed variation in postprandial TOP (61 ± 11 min) was poorly predicted despite accurate mean predictions (58 ± 34 min). Recalibrating protein digestion and amino acid absorption kinetics require data on net-portal nutrient appearance, combined with observations on digestion kinetics, in pigs fed diets varying in ingredient composition. Currently, SNAPIG can be used to forecast the time and extent of nutrient digestion and absorption when simulating diets varying in ingredient and nutrient composition. It enhances our quantitative understanding of nutrient digestion kinetics and identifies knowledge gaps in this field of research. Already useful as research tool, SNAPIG can be coupled with a postabsorptive metabolism model to predict the effects of dietary and feeding-strategies on the pig's growth response.

Implications

A computer model simulating nutrient digestion kinetics in growing pigs is presented Simulating Nutrient digestion and Absorption kinetics in PIGs, considering intake and origin of dietary nutrients as well as physicochemical characteristics of the diet. Simulating Nutrient digestion and Absorption kinetics in PIGs provides unique predictions regarding the timing and extent of nutrient digestion after meal ingestion and the subsequent availability

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Table 2
Parameter values of the model simulating digestion kinetics in growing pigs.

Parameter	Description	Value	Unit
Diet			
DMI	DM intake		g
OM	Organic matter		g
SFEED	Clock-time of initial meal	08:00	h
IFEED	Meal interval	12	h
TFEED	Duration of feed intake	0.25	h
FFEED	Number of meals per day	2	/d
Passage			
Clqgs_lqi1	Intercept of equation for the fractional passage rate of liquids from the stomach	1.6	h
Cslgs_slqi1	Intercept of equation for the fractional passage rate of solids from the stomach	3.2	h
Ki_c	Fractional passage rate of digesta through the small intestine	0.373	/h
Ci1_i2	Proportion of the proximal small intestine relative to total small intestine based on mean retention time	0.21	
Kc_o	Fractional passage rate of digesta through the colon	0.0298	/h
Hydrolysis and fermentation			
kdfi_fai	Fractional rate of fat hydrolysis in the small intestine	4.25	/h
Kdtscc	Fractional rate of starch fermentation in the colon	14.88	/h
Cxc_mbcc	Conversion of *x* (i.e. ts or tn) into microbial biomass	0.133	g/g
Cxc_sfcc	Conversion of *x* (i.e. ts or tn) into short-chain fatty acids	0.445	g/g
Cxc_fgcc	Conversion of *x* (i.e. ts or tn) into fermentation gasses	0.201	g/g
Ccp_mb	Unit of protein required per unit of microbial growth	1.66	g/g
Endogenous secretions			
Cepnp_gs	Endogenous protein (N * 6.25) secretion in the stomach	0.0024	g/g OM
Cepnp_i1	Endogenous protein (N * 6.25) secretion by the pancreas into the proximal small intestine	0.0047	g/g OM
Cepnp_gb	Endogenous protein (N * 6.25) secretion by bile into the proximal small intestine	0.0063	g/g DMI
Cepnp_i2	Endogenous protein (N * 6.25) loss due to cell abrasion in the distal small intestine	0.06	g/g OM
Cepnp_cc	Endogenous protein (N * 6.25) loss due to cell abrasion in the colon	0.059	g/g OM
Cefgb	Endogenous fat secretion by bile into the proximal small intestine	0.0237	g/g DMI
Cep_np_gs	Fraction of protein of total endogenous nitrogen (protein/6.25) secretion in the stomach	0.5	g/g
Cep_np_i1	Fraction of protein of total endogenous nitrogen (protein/6.25) secretion by the pancreas	0.7	g/g
Cep_np_gb	Fraction of protein of total endogenous nitrogen (protein/6.25) secretion by bile	0.65	g/g
Cep_np_i2	Fraction of protein of total endogenous nitrogen (protein/6.25) secretion in the distal small intestine	0.6	g/g
Cep_np_cc	Fraction of protein of total endogenous nitrogen (protein/6.25) secretion in the colon	0.5	g/g
Cepnpi_epnpbl	Fraction of total endogenous protein secretion reabsorbed in the small intestine	0.7	g/g
Cefi_efbl	Fraction of total endogenous fat secretion reabsorbed in the small intestine	0.8	g/g
Absorption			
Kaai_aabl	Fractional rate of amino acid absorption from the intestine	250	/h
Kgli_glbl	Fractional rate of glucose absorption from the intestine	500	/h
Kfai_fabl	Fractional rate of fatty acid absorption from the intestine	150	/h
Ksfc_sfbl	Fractional rate of short-chain fatty acid absorption from the intestine	150	/h

of nutrients for body utilisation. It provides quantitative understanding of how individual digestive processes and their interactions with dietary physicochemical properties influence the extent of nutrient digestion. Using Simulating Nutrient digestion and Absorption kinetics in PIGs can identify knowledge gaps. As a research tool, Simulating Nutrient digestion and Absorption kinetics in PIGs can help evaluating whether dietary nutrients are being hydrolysed and absorbed to their full potential.

Introduction

To determine the nutritional value of diets, various feed evaluation systems can be consulted (INRA, 2004; NRC, 2012; CVB, 2018). These provide, amongst others, the nutritional value of numerous feed ingredients, i.e. nutrient composition and ileal and/or faecal digestibility coefficients for nutrients. However, while the nutrient composition of feed ingredients can be considered a characteristic of the ingredients themselves, digestibility and bioavailability of nutrients are not. The latter are affected by factors such as the physical and chemical structure of the nutrient, the feed ingredient it originates from, the overall diet in which it is included, and the animal's ability to degrade, absorb, and utilise the nutrients. Consequently, to what extent ingested nutrients are being digested and utilised is affected by interactions between the diet and the animal (i.e. diet × animal interactions). Studies have shown such effects, for example by the difference in dietary nutrient digestibility observed when one dietary carbohydrate-source was substituted for another (Owusu-Asiedu et al., 2006), e.g. protein digestibility reduced from 72 to 55% by substituting maize starch for cellulose in growing pig diets. Or, through the effects on level of amino acid oxidation and protein deposition during postabsorptive metabolism when consuming "fast" vs "slow" protein (Batterham and Bayley, 1989; Boirie et al., 1997; Yen et al., 2004) or when altering the availability of other dietary nutrients such as glucose (van den Borne et al., 2007b). Although it is generally acknowledged that the nutritional value of feed ingredients is not additive and diet × animal interactions exist, current feed formulation and evaluation practices still assume additivity and use static nutritional values due to a lack of better means.

In order to advance feed evaluation and move beyond the assumption of additivity, we must consider the dynamic processes of nutrient digestion, metabolism, and diet × animal interactions as they affect the overall nutritional value of the diet. Doing so requires careful consideration of the kinetics of individual digestive and metabolic processes as well as accounting for nutrient, ingredient and diet properties. To combine knowledge and gain deeper understanding of complex and dynamic processes, *in silico* techniques have become invaluable. Several *in silico* models have been developed to account for the kinetics of various digestive processes in pigs, i.e. varying feed intake, digesta passage, enzymatic secretion, nutrient hydrolysis and absorption. Some of these models focus on digesta passage in the stomach (Moxon et al., 2016;

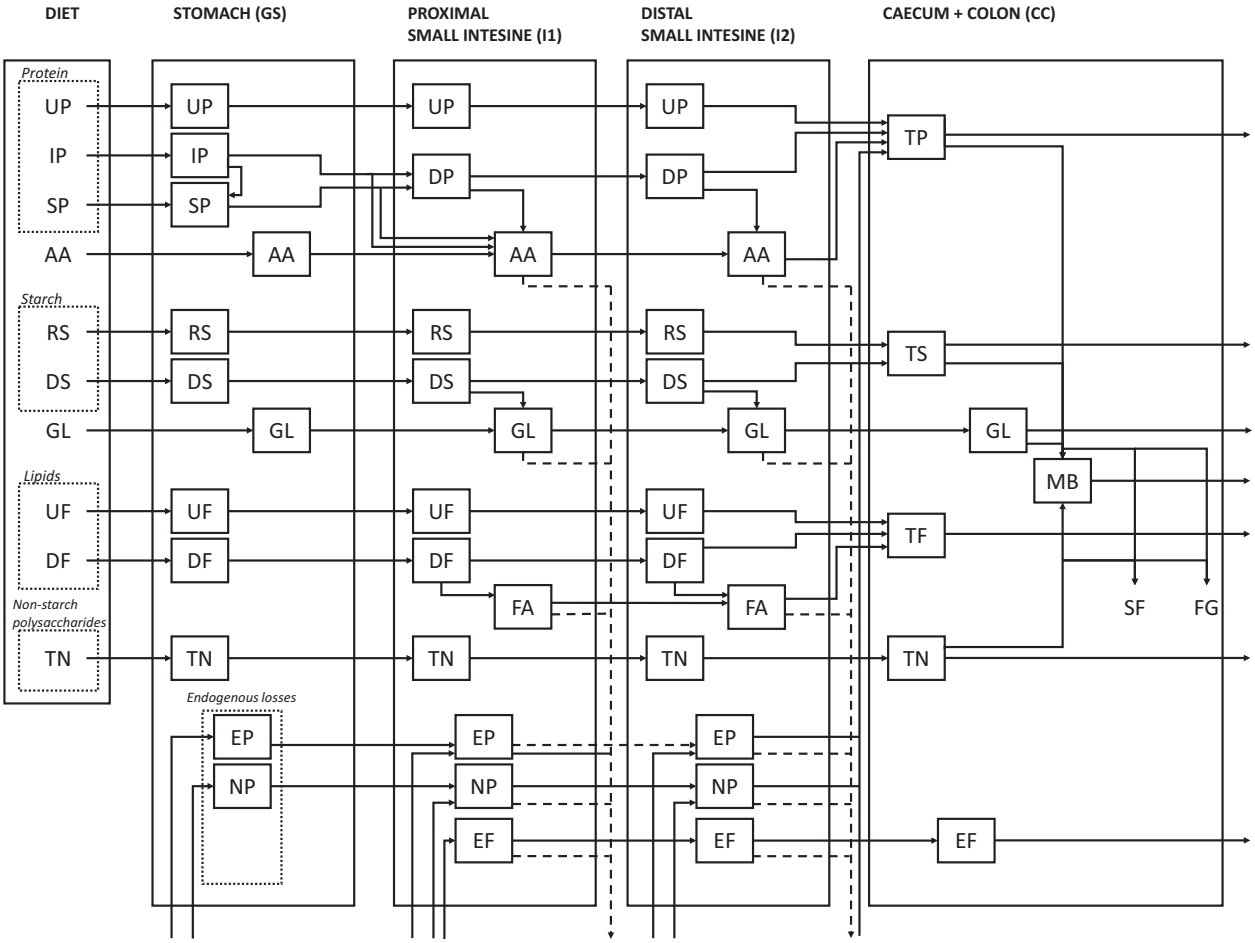

Fig. 1. Schematic representation of the digestion model of a growing pig. Nutrients ingested during feed intake enter the stomach compartment (GS), where insoluble protein can be solubilised (IP → SP), and insoluble and soluble nutrients pass at different rates into the proximal small intestine (I1). In the proximal and distal small intestine (I1, I2) degradable protein (DP), starch (DS), and fat (DF) can be hydrolysed into amino acids (AAs), glucose (GL), and fatty acids (FAs), respectively. These monomeric nutrients, together with endogenous secretions (i.e. protein: EP, non-protein nitrogen: NP, fat: EF) can be (re-) absorbed in the small intestine (I1 and I2). Enzymatical undegradable protein (UP), starch (RS), and lipids (UF), together with undegraded counterparts forming total protein (TP), starch (TS), and fat (TF), and non-starch polysaccharides (TN) pass the small intestine and enter the colon (CC), where they can be fermented or excreted. Fermentation yields microbial biomass (MB) short-chain fatty acids (SFs), and fermentation gasses (FGs). Solid lines indicate hydrolysis (within segments) or passage (between segments) or secretion, whereas dashed lines indicate absorption.

2017) or small intestine (Taghipoor et al., 2012; 2014) while others address the complete digestion process (Usry et al., 1991; Bastianelli et al., 1996; Rivest et al., 2000; Strathe et al., 2008). To predict the nutritional value of diets fed to growing pigs one could combine digestion and metabolism models. Current complete digestion models, however, do not or only to a limited extent address non-additivity and occurrence of diet × animal interactions. Nutrient or diet physicochemical properties (i.e. properties and behaviours of a substance that arise from its physical and chemical attributes, e.g. solubility, viscosity, pH) as induced by variation in ingredient composition are currently not included. The ingredient composition and nutrient origin affect the physicochemical properties and thereby degradability and solubility of a nutrient, an ingredient and even a diet, thereby causing variation in observed nutrient absorption *in vivo* (e.g. Regmi et al., 2011). Consequently, while current digestion models could provide input of sufficient detail (i.e. extent of nutrient absorption over time) for a postabsorptive metabolism model to predict the nutritional value of diets fed to growing pigs, they are unable to simulate variation in nutrient absorption kinetics arising from diets with equal nutrient composition but varying in the origin of nutrients.

We therefore propose a nutrient-based dynamic mechanistic digestion model for growing pigs ('**SNAPIG**' – Simulating Nutrient digestion and Absorption kinetics in PIGs). The objectives of this model are (i) to predict the rate and extent of nutrient absorption from diets varying in ingredient-origin that can serve as input for a dynamic metabolism model, and by doing so (ii) to increase our understanding on nutrient digestion kinetics and its effect on the nutritional value of various diets. While sharing similarities in the general model structure to that of existing digestion models (e.g. Strathe et al., 2008), our model distinguishes itself by accounting for variation in physicochemical properties (i.e. solubility, and rate and extent of degradability) of nutrients and diets, and subsequent effects on nutrient passage and degradation in the gastrointestinal tract (**GIT**) of growing pigs. By considering ingredient origin and their physicochemical properties, data from *in vitro* assays was used to quantify nutrient solubility and the maximum potential rate and extent of nutrient degradability based on ingredient origin. These properties are considered true ingredient properties. They are incorporated in the model by categorising dietary nutrients into undegradable, degradable and soluble fractions, each with a different rate of degradation. Additionally, our model incorporates the effects of dietary nutrient solubility, feed intake level and diet viscosity on passage rates of digesta and nutrients in the stomach as described further in this paper. Moreover, differences in passage rate of the solid and liquid fraction of digesta

Table 1
Abbreviations and general notation for model entities used to simulate digestion kinetics in growing pigs.

Abbreviation/ Notation	Description	Unit
Diet (d)		
D_j	Feed intake level	× maintenance requirement for energy[30] (419 kJ/kg $BW^{0.75}$/d)
D_s	Dietary nutrient solubility	g/g
D_r	Diet rheology	Pa × s
RAV	Real applied viscosity	mL/g
Meal		
DMI	DM intake	g/d
SFEED	Clock-time of initial meal	h
IFEED	Meal interval	h
TFEED	Duration of feed intake	h
FFEED	Number of meals per day	/d
Segments gastrointestinal tract		
gs	Stomach (i.e. gaster)	
i1	Proximal small intestine	
i2	Distal small intestine	
cc	Caecum + colon	
gb	Gallbladder	
bl	Portal blood	
Digesta phase		
sl	Solids	
lq	Liquids	
Nutrients		
cp	Total dietary CP (i.e. up + dp)	
up	Enzymatically undegradable protein	
dp	Enzymatically degradable protein (i.e. ip + sp)	
ip	Stomach insoluble protein	
sp	Stomach soluble protein	
ep	Endogenous protein	
np	Endogenous non-protein non-amino acid nitrogen	
aa	Amino acids	
tp	Total protein (cp + ep + np + aa)	
ts	Total dietary starch (i.e. ds + rs)	
ds	Enzymatically degradable starch	
rs	Ileal undegradable starch (i.e. resistant starch)	
gl	Glucose	
tf	Total dietary fat	
uf	Undegradable fat	
df	Degradable fat	
fa	Fatty acids	
ef	Endogenous fat	
tn	Total non-starch polysaccharides	
om	Organic matter	
mb	Microbial biomass	
sf	Short-chain fatty acids (e.g. acetate, propionate)	
fg	Fermentation gasses (e.g. H_2, CO_2)	
Notation format		
Q*xi*	Pool of nutrient *x* in segment *i*	g
Q*xi*0	Initial pool size of nutrient *x* in segment *i* (i.e. at t = 0)	g
F*xi_yj*	Flux of nutrient *x* in segment *i*, to nutrient *y* in segment *j*	g/h
d*Qxi*	Auxiliary variable belonging to the pool of nutrient *x* in segment *i*	g/h
dQ*xi_yj*	Cumulative pool belonging to flux of nutrient *x* in segment *i*, to nutrient *y* in segment *j*	g
K*xi_yj*	Rate of change of nutrient *x* in segment *i* into nutrient *y* in segment *j*	/h
Kdyj	Rate of hydrolysis (kd) of nutrient *y* in segment *j*	/h
C*xi* or C*x_y*	Constant belonging to nutrient *x* in segment *i* or nutrient *x* in entity *y*	g/g

through the stomach were taken into account. Model parameterisation relied on the use of a combination of *in vitro* and *in vivo* data available in the literature, as well as prior research conducted by the authors. The model presented here can be used as a research tool. It helps identifying limiting factors in the digestive process for ingredients and diets to reach their nutritional potential. Linking the model to a metabolic model increases our ability to assess the nutritional value of various diets and feeding strategies in growing pigs accounting for non-additivity.

Material and methods

Model general structure

The model simulates the process of digestion of nutrients in the GIT of a growing pig (35–110 kg bodyweight). Passage, hydrolysis, absorption, and endogenous secretions are the main simulated digestive processes. As these processes differ among GIT segments, the model represents the stomach (**GS**), the proximal (**I1**) and distal (**I2**) small intestine, and the combined caecum + colon (**CC**) as anatomical compartments (Fig. 1). Feed intake ingested macronutrients and their ingredient are model driving variables. Nutrients are categorised according to their potential to be degraded and/ or solubilised based on ingredient origin. The model assumes that the pool size of liquids (water and liquid secreta) in which nutrients can be solubilised in the GIT is neither limiting the rate and extent of solubilisation nor the effects of diet viscosity. Model abbreviations are presented in Table 1, parameter values in Table 2, and full model notations and equations in Supplementary Table S1. Kinetics of digesta passage, nutrient hydrolysis, and the consequential rate of change in nutrient pools are mainly presented by first-order kinetics, and pool sizes are presented on DM-basis (grams). Differential equations are solved using Runge-Kutta fourth-order fixed numerical integration in AcslX software version 2.4 (the Aegis Technologies Group, Inc.) with a step size of 0.0167 h (i.e. 1 min). Model outputs presented in this paper focussed on the extent of digestion of protein, starch, and fat at the end of the small intestine (i.e. apparent or true ileal digestibility), and on the postprandial extent and kinetics of glucose and amino acid absorption from the small intestine (I1 + I2). Model outputs were calculated when the model was in quasi-steady state. This quasi-steady state was generally reached after 104 h, by observing at what time point initial pool sizes showed limited effects on the size of nutrient fluxes. Time of peak absorption of glucose and amino acids was assessed in the last 12 h of the 104 h-simulation run (i.e. representing the final meal). The model is driven by the ingestion of nutrients, originating from various ingredients, as described below.

Model driving variables

Feed intake

Feed intake is based on a meal-fed pig and modelled as an episodic process (Eq. [3], Supplementary Table S1) of a constant rate and interval similar to Strathe et al. (2008). Meal size (Eq. [2]) is calculated by dividing the daily DM intake over the number of meals per day (**FFEED**). Meals are ingested over a fixed period of time (**TFEED**). The ingestion rate depends on DM intake, FFEED, and TFEED. Combined with daily timing of the first meal (**SFEED**) and meal interval (**IFEED**), they determine the overall daily feed intake pattern. An example of the daily feed intake pattern is provided here: a pig is fed a meal twice a day (FFEED = 2) at 08.00 h (SFEED = 8 h) in the morning and 20.00 h in the evening (IFEED = 12 h), it is finishing a meal in 15 min (TFEED = 0.25 h). Feed intake drives the input of nutrients to the pools in the stomach, calculated by multiplying the rate of feed intake with the concentration of the respective nutrients in the diet (Eqs. [10], [13], [17], [20], [25], [28], [31], [36], [39], [42]).

Dietary nutrient intake

Main dietary nutrients presented in the model are: CP, starch (total starch: TS), fat (total fat: **TF**), and non-starch polysaccharides (**NSPs**; total NSP: **TN**). Moreover, dietary intake includes amino acids (**AA**), and reducing sugars regarded as glucose (**GL**). Dietary nutrients were calculated for feed ingredients and diets based on the Dutch feed evaluation system (CVB, 2018). Nutrients are further characterised by their degradability and solubility, which depend on the feed ingredient origin (e.g. see Supplementary Tables S2 and S3). For starch and protein, those data were obtained from *in vitro* digestion assays (see below), for fat based on work of Smink (2012) and Gunness et al., (2016), and for NSP based on variation in extent of fermentation in pigs (CVB, 2018). Nutrient fractions considered were as follows: for protein, enzymatically undegradable protein (**UP**) and enzymatically degradable protein (**DP**), of which DP encompasses: stomach insoluble (**IP**) and soluble protein (**SP**). The SP fraction is based on *in vitro* assays that considered protein hydrolysis kinetics of feed ingredients (Chen et al., 2019; Schop et al., 2019b). The UP fraction was calculated by estimating the true ileal digestible protein fraction using data from CVB (2018) regarding the apparent ileal protein digestibility values per feed ingredient (i), and assuming a flux of basal and specific (i.e. arbitrarily set at 50% of the contribution basal endogenous protein) endogenous protein at ileal level:

$$\mathrm{UP(i)} = 0.5 \times \left(1 - \frac{\mathrm{AIDCP} + 1.5 \times \mathrm{BEPL}}{\mathrm{CP}}\right)$$

where AIDCP = the apparent ileal CP digestibility coefficient (g/g kg CP), BEPL = basal endogenous protein losses (i.e. 11.43 g/kg DM intake), and CP (g/kg DM), all based on the Dutch feed evaluation system (CVB, 2018).

For starch, ileal enzymatically undegradable starch (**RS**), and degradable starch (**DS**) were considered. The RS fraction, i.e. the fraction resistant to enzymatic hydrolysis in the small intestine, was derived from the starch fraction that is not hydrolysed after 6 h of *in vitro* small intestinal incubations:

$$\mathrm{RS(i,\ t_6)} = \mathrm{Dmax} \times (1 - e^{(-\mathrm{kds\_gl} \times \mathrm{t_6})})$$

where Dmax = the maximum degradable fraction of starch (g/g), Kds_gl = the rate of starch hydrolysis (/h), and t = 6 h. All parameters regarding starch hydrolysis were obtained from *in vitro* assays (Weurding et al., 2001; Giuberti et al., 2012a; Martens et al., 2018).

For fat, the ileal undigestible (**UF**) and digestible fat (**DF**) fractions are considered. Similar to the UP fraction, the UF fraction was calculated by estimating the true ileal digestibility of fat using data from CVB (2018) on apparent ileal fat digestibility values per feed ingredient (i), and assuming a loss of basal endogenous fat:

$$\mathrm{UF(i)} = 0.5 \times \left(1 - \frac{(\mathrm{TF} \times \mathrm{DC_{fat}}) + \mathrm{BEFL}}{\mathrm{TF}}\right)$$

where TF = total fat content of the feed ingredient (g/kg DM) (CVB, 2018), BEFL = basal endogenous fat loss (i.e. 4.7 g/kg DM intake; Jørgensen et al., 1993), and $\mathrm{DC_{fat}}$ = digestibility coefficient of fat (g/g of fat). The latter was based on work of Smink (2012), who proposes to calculate fat digestibility based on chain length, degree of saturation, and positioning of fatty acids on the glycerol backbone. If fatty acid composition, i.e. chain length and saturation, were not presented by Smink (2012) and CVB (2018) then $\mathrm{DC_{fat}}$ was based on the digestibility coefficient as presented by the Dutch feed evaluation system (CVB, 2018).

Nutrient fractions per diet were calculated as weighted average of the diets' constituting feed ingredients (i) and macronutrient concentrations. For example, dietary UP fraction was calculated as follows:

$$\mathrm{UP} = \sum_{i-n} \left(\left(\frac{\mathrm{CP_i}}{\sum_{i=1}^{n}\mathrm{CP}} \times \mathrm{UP_i}\right) + \cdots + \left(\frac{\mathrm{CP_i}}{\sum_{i=1}^{n}\mathrm{CP}} \times \mathrm{UP_i}\right)\right)$$

where i denotes the i^{th} ingredient, n denotes the total number of feed ingredients in the diet.

The kinetics of nutrient hydrolysis vary among feed ingredients and therefore were considered as inherent feed ingredient properties. To compute fractional hydrolysis rates for protein and starch, data were taken from *in vitro* assays (Weurding et al., 2001; Al-Rabadi et al., 2011; Giuberti et al., 2012a; Martens et al., 2018; Chen et al., 2019; Schop et al., 2019b). The kinetics of NSP and starch fermentation in the colon were modelled based on the fractional rates of fermentation required to reach the extent of faecal digestibility of the NSP fraction, and a starch digestibility close to 100% as presented by the Dutch feed evaluation system (CVB, 2018). Fractional rates of NSP and starch fermentation (Kd) were calculated as follows:

$$\mathrm{Kdxcc_i} = (-\mathrm{DC_x} \times \mathrm{Kc\_o})/(\mathrm{DC_x} - 1)$$

where i = dietary feed ingredient, x = TN or TS, respectively, DC_x = the faecal digestibility coefficient of x (g/g), which for TN is based on the Dutch feed evaluation system (CVB, 2018), and for TS is assumed to be 0.999 (g/g), Kc_o = the fractional passage rate of digesta in the colon (i.e. 0.0298/h, see below).

Dietary physicochemical properties

In the model, the passage of digesta in the stomach is affected by dietary nutrient solubility ($\mathbf{D_s}$), feed intake level ($\mathbf{D_j}$) and diet viscosity ($\mathbf{D_r}$), as elaborated below. Dietary nutrient solubility, D_s, was calculated as the fraction of SP and GL in the diet (g/g), as described by Schop et al. (2019a). Feed intake level, D_j, was calculated as dietary energy intake relative to the maintenance requirement for energy ($\mathbf{ME_m}$ = 419 kJ metabolisable energy/kg $BW^{0.75}$ per d (CVB, 2005); i.e. D_j = x ME_m). Diet viscosity, D_r, represented the apparent dynamic viscosity of the diet at 1/s shear rate. As data on the dynamic viscosity of diets and constituting feed ingredients were limited, D_r was deduced from rheological data (i.e. real applied viscosity: **RAV**, ml/g) by Carré et al. (1994). Diet viscosity was calculated as the weighted average of the RAV of each of the diets composing feed ingredients. The relationship between RAV and D_r was determined using the computed RAV and measured D_r of the viscous diets used to assess the effect of diet viscosity on digesta passage presented by Schop et al. (2020):

$$D_r = 30.33e^{(0.0693 \times \sum_{i=1}^{n}(w_i \times RAV_i + \cdots + w_n \times RAV_n))}$$

where D_r = the apparent dynamic viscosity of the diet at 1/s shear rate (Pa × s), i = dietary feed ingredient (1 to n), w = weight factor according to the ingredient inclusion level in the diet (g/g), and RAV = real applied viscosity (ml/g) (Carré et al., 1994).

Stomach

Upon ingestion, nutrients enter the stomach where they are mixed with endogenous secretions (i.e. HCl, pepsin). In the model, these processes are presented as follows. For protein, some of the proteins become instantly solubilised depending on intrinsic physicochemical properties of the ingested protein and the stomach environment (Cone, 1993) (Eq. [17]). Soluble proteins will leave the stomach with the liquid digesta fraction (Eq. [18]) and will enter the small intestine quicker than the solid digesta fraction. Insoluble proteins that are retained in the stomach will become solubilised as a result of protein hydrolysis by pepsin (Eq. [15]). The rate and extent of protein solubilisation differ among feed ingredients. Parameters for initial protein solubility, and the rate of protein solubilisation were taken from *in vitro*

Table 3
Literature overview of digesta mean retention time (h) of solids and liquids per gastrointestinal segment as quantified using specified tracers in growing pigs. Data presented as range (minimum and maximum) values obtained based on treatment means per study.

Segment	Tracer	Tracee	min	max	Reference
Stomach					
	YbO_2	Solids	1.0	1.3	Wilfart et al., 2007
	^{99}mTC	Solids	1.0	1.9	Guerin et al., 2001
	TiO_2	Solids	1.8	2.6	Schop et al., 2020
	TiO_2	Solids	1.8	2.5	Chen, 2017
	TiO_2, Cr_2O_3	Solids	2.0	12.8	Van Leeuwen et al., 2006
	TiO_2	Solids	2.1	2.4	Van Erp, 2019
	Cr_2O_3	Solids	2.2	3.8	Martens et al., 2019
	DM	Solids	2.2	2.9	Rainbird and Low, 1986a
	TiO_2	Solids	2.6	4.0	Schop et al., 2019a
	DM	Solids	3.0	5.8	Rainbird and Low, 1986b
	DM	Solids	3.6	4.5	Gregory et al., 1990
	DM	Solids	4.8	8.4	Potkins et al., 1991
	Cr-EDTA	Liquids	0.7	1.6	Schop et al., 2020
	Cr-EDTA	Liquids	0.8	1.7	Schop et al., 2019a
	Cr-EDTA	Liquids	0.8	0.9	Wilfart et al., 2007
	Cr-EDTA	Liquids	1.6	1.9	Van Erp, 2019
	Cr-EDTA	Liquids	2.1	2.5	Gregory et al., 1990
	Co-EDTA	Liquids	2.1	3.1	Martens et al., 2019
Small intestine					
	Cr_2O_3	Solids	1.4	2.1	Martens et al., 2019
	TiO_2	Solids	1.8	2.6	Schop et al., 2019a
	TiO_2	Solids	2.0	2.0	Schop et al., 2020
	TiO_2	Solids	2.0	2.1	Van Erp, 2019
	YbO_2	Solids	3.7	4.3	Wilfart et al., 2007
	TiO_2	Solids	4.0	5.9	Chen, 2017
	TiO_2, Cr_2O_3	Solids	5.1	20.8	Van Leeuwen et al., 2006
	Co-EDTA	Liquids	1.7	2.5	Martens et al., 2019
	Cr-EDTA	Liquids	1.9	2.0	Van Erp, 2019
	Cr-EDTA	Liquids	2.2	2.2	Schop et al., 2020
	Cr-EDTA	Liquids	2.3	2.8	Schop et al., 2019a
	Cr-EDTA	Liquids	3.9	4.4	Wilfart et al., 2007
Mouth to Ileum					
	YbO_2	Solids	3.9	12.7	Hooda et al., 2011
	Cr_2O_3	Solids	4.5	4.9	Owusu-Asiedu et al., 2006
	DM	Solids	4.9	11.1	Potkins et al., 1991
	Cr_2O_3	Solids	5.2	6.3	de Vries et al., 2016
	Cr-mordanted fibre	Solids	6.2	10.7	Solà-Oriol et al., 2010
	TiO_2	Solids	6.3	11.3	Solà-Oriol et al., 2010
	Co-EDTA	Liquids	4.5	5.8	de Vries et al., 2016
Large intestine					
	AIA	Solids	12.0	13.0	Zhang et al., 2015
	YbO_2	Solids	35.6	44.4	Wilfart et al., 2007
	Cr-EDTA	Liquids	24.9	41.3	Wilfart et al., 2007
Total tract					
	Cr-mordanted fibre	Solids	22.2	38.9	Dung et al., 2002
	Cr_2O_3	Solids	24.5	28.0	Owusu-Asiedu et al., 2006
	DM	Solids	24.8	40.9	Potkins et al., 1991
	Coloured particles	Solids	28.4	82.7	Stanogias and Pearcet, 1985
	YbO_2	Solids	31.5	95.0	Le Goff et al., 2002
	Cr-mordanted fibre	Solids	36.0	71.0	Ehle et al., 1982
	Earth markers	Solids	39.8	45.4	Pond et al., 1988
	Co-EDTA	Liquids	22.6	36.9	Dung et al., 2002

Abbreviations: EDTA = ethylenediaminetetraacetic acid; AIA = acid insoluble ash.

assays (Wilfart et al., 2008; Chen et al., 2019; Schop et al., 2019b). Dietary starch, fat, and NSP are assumed to leave the stomach unchanged with the solid fraction of digesta.

Passage of digesta through the stomach differs between the solid and liquid fraction of digesta (Stevens and Hume, 2004). A higher fractional passage rate for the liquid digesta fraction (Eq. [4]) containing soluble nutrients (SP, AA, GL, EP, NP; Eqs. [18], [21], [32], [48], [51]) than for the solid digesta fraction (Eq. [5]) containing insoluble nutrients (UP, IP, RS, DS, UF, DF, TN; Eqs. [11], [14], [26], [29], [37], [40], [43]) was modelled. In addition, the fractional passage rate of digesta in the stomach is known to be affected by physicochemical properties of the diet and digesta (reviewed by Kong and Singh, 2008; Lentle and Janssen, 2008). As data lack on interactions among effects of these physicochemical properties on gastric emptying, additivity of individual effects was assumed:

$$kxgs_{xi1} = 1/\left(\text{intercept} + \left(1.9e^{\left(-\left[20.12e^{-1.7\times Dj}\right]\right)} - \alpha\right) + \left(0.87e^{-\left[\frac{(Ds-0.185)^2}{2\times 0.052^2}\right]}\right) + (\beta \times 0.0017 \times D_r)\right)$$

where x = sl or lq, representing the solids and liquids fractions of digesta, intercept (±SD) = 3.2 (±1.7) for solids or 1.6 (±0.7) h for liquids; Dj = feed intake relative to maintenance requirement for energy (ME_m = 419 kJ metabolisable energy/kg $BW^{0.75}$ per d; (CVB, 2005)); α = 1.2 h for solids and 1.3 h for liquids, respectively; D_s = dietary nutrient solubility (g/g) represents by the fraction of soluble protein and reducing sugars in the diet; β = 1.5 h representing the average difference between the MRT of solids and liquids in the stomach as simulated by the model; and D_r = the apparent dynamic viscosity of the diet at 1/s shear rate (Pa × s) only applicable when x = lq. Parameterising the individual effects of D_j, D_s, and D_r are further explained

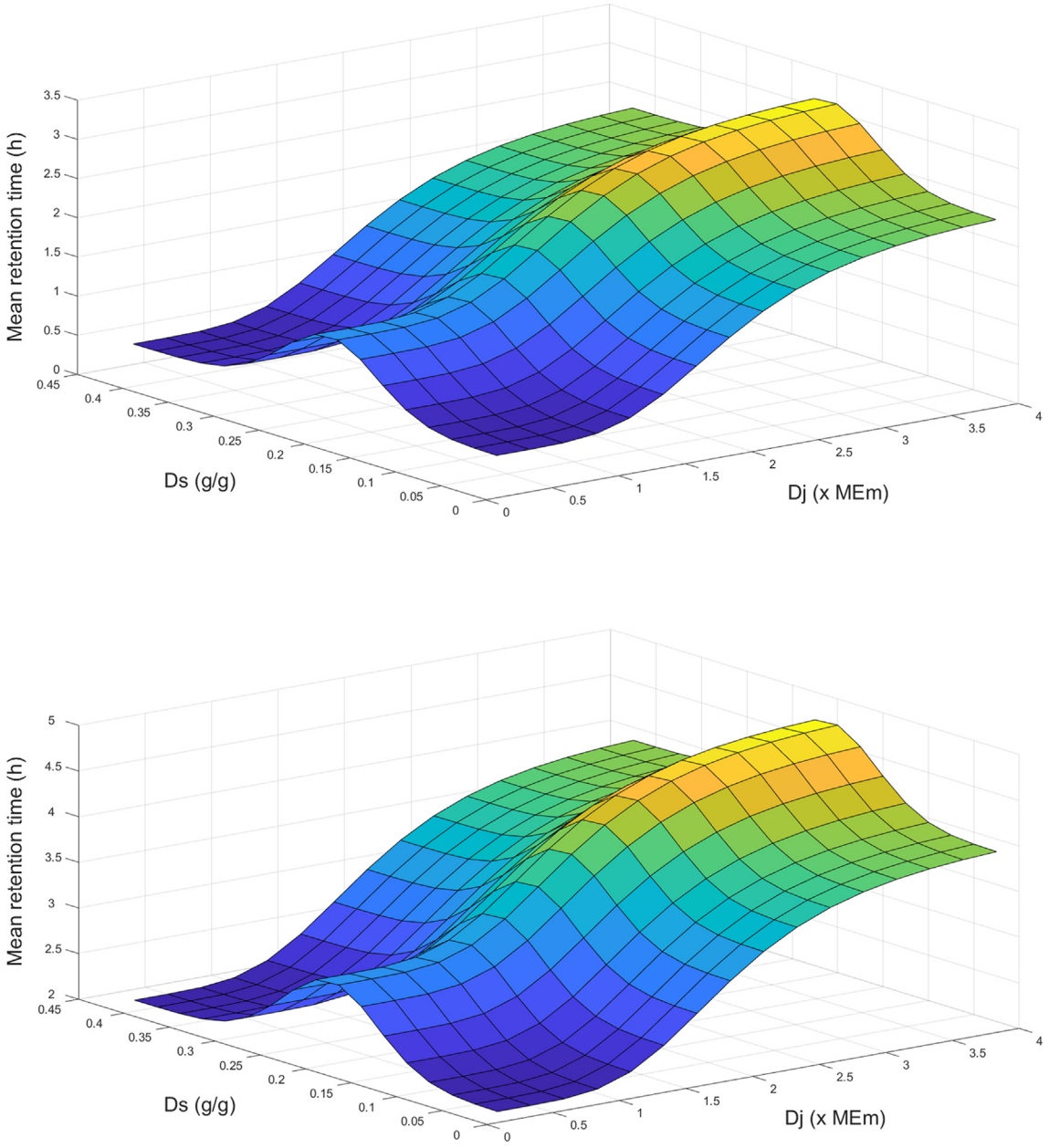

Fig. 2. Effect of feed intake level (D_j; × maintenance requirement for energy (ME_m): 419 kJ/kg $BW^{0.75}$/d; CVB, 2005) and dietary nutrient solubility (D_s; g/g) on the mean retention time of digesta liquids (above) and solids (below) in the stomach of a growing pig, as represented in the dynamic digestion model for growing pigs.

below. The intercept represents the baseline mean retention time (**MRT**; inversely related to the fractional passage rate). The respective mean retention time values were based on numerical means (PROC MEANS, SAS version 9.4, SAS Institute Inc.) for treatment values as obtained in different studies quantifying digesta retention time in the stomach of growing pigs (see Table 3). As diet physicochemical properties affected the mean retention time values of the intercept, the values of D_j, D_s, and D_r were accounted for at baseline MRTs. Their values at this baseline were D_j (±SD): 2.3 (±0.7) and 2.4 (±0.7) × ME_m for respectively solids and liquids, while D_s and D_r were assumed to be 0.1 g/g and 30 Pa × s, respectively.

Increasing feed intake level causes the fractional passage rate of digesta to decrease, presumably due to triggering of nutrient feedback mechanism in the GIT (van Citters and Lin, 2006). As the latter is considered to cause a generic effect on digesta passage, the effect of D_j was assumed to be equal for both solids and liquids. Based on data from Gregory et al., (1990) and Schop et al., (2019a), a one-unit increase in D_j, increases the MRT of solids and liquids by 0.9 (±0.3; SE) h. A Gompertz function was fitted to this data to avoid extreme changes in nutrient pool sizes outside of the physiological relevant range for feed intake level. Hence, to ensure sensible model behaviour, the effect of D_j was restrained to $1 < D_j < 3$, meaning that outside this range, no effects of D_j on digesta passage rates were simulated. Parameter α is in place to scale the effect of feed intake level on ΔMRT based on the feed intake level observed for the baseline mean retention time of solids and liquids (i.e. intercept in *kxgs_xi*1, see above). Hence, it ensures no effect of feed intake level when Dj equals the baseline feed intake level.

Dietary nutrient solubility was represented as the fraction of soluble protein and reducing sugars in the diet. Dietary nutrient solubility affects digesta passage in a non-linear manner. Schop et al. (2019a) showed that increasing D_s (from 8 to 19%) initially

decreases fractional passage rates of solids and liquids (from 0.30 to 0.24/h; from 0.77 to 0.67/h, respectively), whereas when D_s increases further (from 19 to 31%), the fractional passage rates increased (to 0.34 and 1.25/h, respectively). The effect of D_s on the passage of digesta was presumably caused by triggering of nutrient-sensing feedback mechanisms in the GIT (van Citters and Lin, 2006). As the latter was considered to cause a generic effect on digesta passage, the effect of D_s was assumed to be equal for both solids and liquids. Data from Schop et al. (2019a) were used to quantify the relative effect of D_s on the MRT of solids and liquids. This was done by taking the first derivative of quadratic functions that were fitted to quantify the relationship between D_s and the MRT for solids and liquids, separately. In order to ensure sensible model behaviour, a Gaussian function was fitted. At values of $0 < D_s < 0.4$, no effects of D_s on digesta passage rates were assumed. The combined effects of feed intake level and dietary nutrient solubility on the MRT of solids and liquids in the stomach are illustrated in Fig. 2.

Diet viscosity is negatively related with the fractional passage rate of liquids in the stomach. Data by Schop et al. (2020) were used to quantify the relationship between D_r and the difference in MRT of solids and liquids. The relationship was rescaled to apply to the average difference in MRT of solids and liquids predicted by the model. The effect of D_r is exclusively applied in the model to the passage of liquids in order to reduce the difference in MRT of solids and liquids.

Small intestine

As digesta passes through the small intestine, it becomes more homogenous, and no or limited differences between the retention time of digesta solids and liquids are reported (see Table 3). Therefore, digesta passage in the small intestine of the model is represented by a single fixed fractional rate for both solids and liquids. Moreover, while literature states that digesta passage rates can vary due to variation in physicochemical properties of diets or digesta (Lentle and Janssen, 2008; Taghipoor et al., 2012), these effects were shown to be too small (Schop et al., 2019a; 2020), ambiguous (van Leeuwen et al., 2006; Wilfart et al., 2007), or were confounded with effects on gastric emptying (i.e. digesta passage represented from mouth until the ileum) (Owusu-Asiedu et al., 2006; Solà-Oriol et al., 2010; Hooda et al., 2011; de Vries et al., 2016). Hence, in the model fixed and equal fractional passage rates for both insoluble and soluble nutrients in the small intestine were assumed. This rate was based on the numerical mean (PROC MEANS, SAS) of study averages of digesta passage in the small intestine reported for growing pigs (see Table 3; MRT (±SD) of 2.7 (±1) h, i.e. 0.373/h). This passage rate applies to all nutrients passing from the small intestine to the colon, i.e. Eqs. [53], [55], [58], [61], [64], [67], [70], [73], [75], [77], [80], [83], [85], [87], [90], [93], [96], [99], [101], [110], [114], [118], [122], [127], [129]. In the model, the small intestine is represented by two sequential segments (I1 and I2) in order to better model postprandial nutrient appearance and to slow down transit of nutrients into the colon. The division between I1 and I2 was arbitrarily based on data used to parameterise fat hydrolysis kinetics (Gunness et al., 2016). In latter study, the small intestine was divided based on length. To translate the division on length to division of total MRT, data of Martens et al. (2019), Schop et al. (2019a), and Van Erp (2019) were used in which both were measured. Based on these data, I1 and I2 were set to 21 and 79% of the total small intestinal MRT, respectively (Ci1_i2 = 0.21, Eqs. [6], [7]).

Upon arrival in the small intestine, protein, starch, and fat are subjected to enzymatic hydrolysis as presented by the model in Eqs. [57], [60], [69], [72], [89], [92]. The model assumed no differences between the two small intestinal segments (I1 and I2) regarding fractional rates of hydrolysis and absorption per nutrient. Focussing on protein hydrolysis, no differences in the hydrolysis kinetics of insoluble and soluble protein were considered, although there is little information that proves otherwise (e.g. Salazar-Villanea et al., 2017). Hence, both IP and SP enter the same degradable protein pool (Eq. [59]). Furthermore, as data from *in vitro* assays showed that at the onset of small intestinal simulations, part of degradable protein fraction is present as absorbable small peptides and free amino acids (Chen et al., 2019; Schop et al., 2019b) this was included in the model. This was done by representing part of the soluble and insoluble protein (i.e. Cdpgs_aai) to directly flow into the small intestinal amino acid pool after they are emptied from the stomach (Eqs. [14], [18]). The remaining pool of degradable protein requires further hydrolysis in the small intestine before being present as absorbable small peptides and amino acids (Eqs. [57], [60]).

For starch, directly using the *in vitro* obtained factional hydrolysis rates in the model caused the extent of starch digestion by the end of the small intestine to be structurally lower than observed *in vivo* (Martens, 2019). The relationship between *in vitro* and *in vivo* fractional hydrolysis rates was, therefore, assessed based on experimental work by Martens et al. (2019), Schop et al. (2019a), and Van Erp (2019) (Fig. 3: left panel).

For fat, the fractional rate of hydrolysis varies among fat sources (Giang et al., 2016), however, available data were limited. Therefore, a generalised approach was adopted using a fixed fractional rate of fat hydrolysis across feed ingredients. This rate is set to meet the extent of fat digestibility in different segments of the small intestine as observed by Gunness et al. (2016) (Kdfi_afi = 4.25/h; Eqs. [89], [92]).

Related to the kinetics of nutrient absorption, we assumed that the kinetics of portal appearance of absorbed nutrients from the gastrointestinal tract is dominated by the kinetics of passage and hydrolysis of protein and starch up to the end of the small intestine. Therefore, the absorption rate of amino acids, glucose, and fatty acids in the small intestine was assumed to occur at non-limiting fractional rates (Eqs. [63], [66], [79], [82], [95], [98]).

In pigs, the hydrolysis of nutrients is facilitated by pancreatic and bile secretions. Reabsorption of these secretions is not complete, and net losses of endogenous protein ($N \times 6.25$) and fat at the end of the small intestine occur. In the model, endogenous secretions were presented based on previous work by Strathe et al. (2008), where DM intake and organic matter flowing through the GIT-affected gastric (Eqs. [47], [50]), pancreatic and bile secretions (Eqs. [109], [113], [125]), as well as gut wall abrasion (Eqs. [117], [121], [132], [133]). Parameters for the net loss of endogenous secretions were calibrated to the quantity at ileal level observed previously by Jørgensen et al. (1993) for fat, and as reviewed by Jansman et al. (2002) for protein. Relative contributions of the stomach, the small intestine, and the colon to the total endogenous losses at the end of the GIT were assumed to be fixed based on data from Jansman et al. (2002) and Strathe et al. (2008).

Colon

In pigs, nutrients not digested enzymatically in the small intestine enter the colon where they can be fermented by the residing microbiota. In the model, the fractional passage rate of digesta through the colon was based on the numerical mean of study averages reporting digesta retention times in the colon, or total tract of growing pigs (see Table 3; MRT 39.6 ± 10.4 h, SD) minus the average retention time of digesta in the stomach and small intestine (Kc_o = 0.0298/h; Eqs. [134], [137], [142], [147], [149], [152], [157], [160]). In the model, fermentation of NSP and starch in the hindgut yields microbial biomass (Eqs. [138], [143], [153]), short-chain fatty acids (Eqs. [139], [144], [154]), and fermentation gases

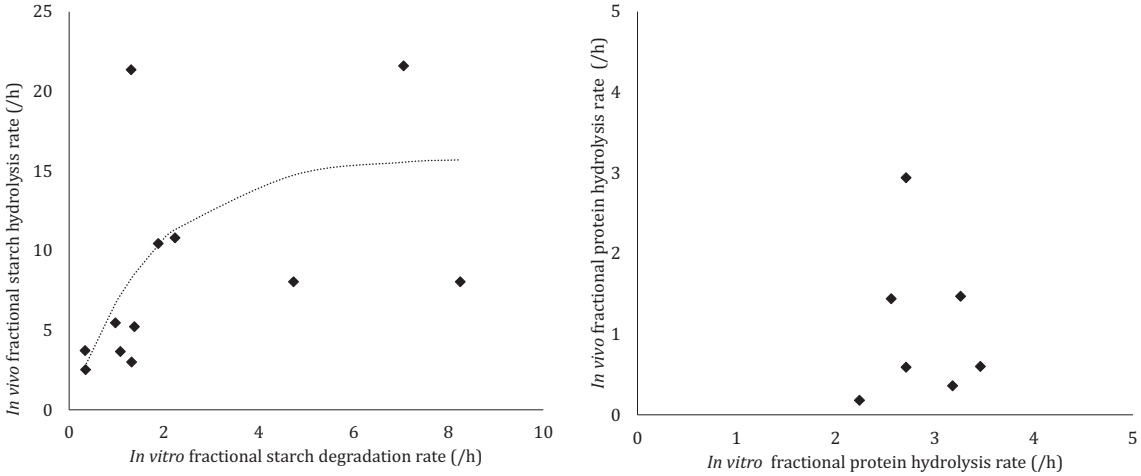

Fig. 3. Relation between in vitro and in vivo fractional hydrolysis rates (/h) in the small intestine of growing pigs, for starch (left-panel): $y = 12.87 \times (1 - e^{(-0.65 \times x)})$, RMSE = 3.33 (using data from Martens et al., 2019; Schop et al., 2019a; Van Erp, 2019), and for protein (right-panel): no significant relation (using data from Chen et al., 2019; Schop et al., 2019b; 2020).

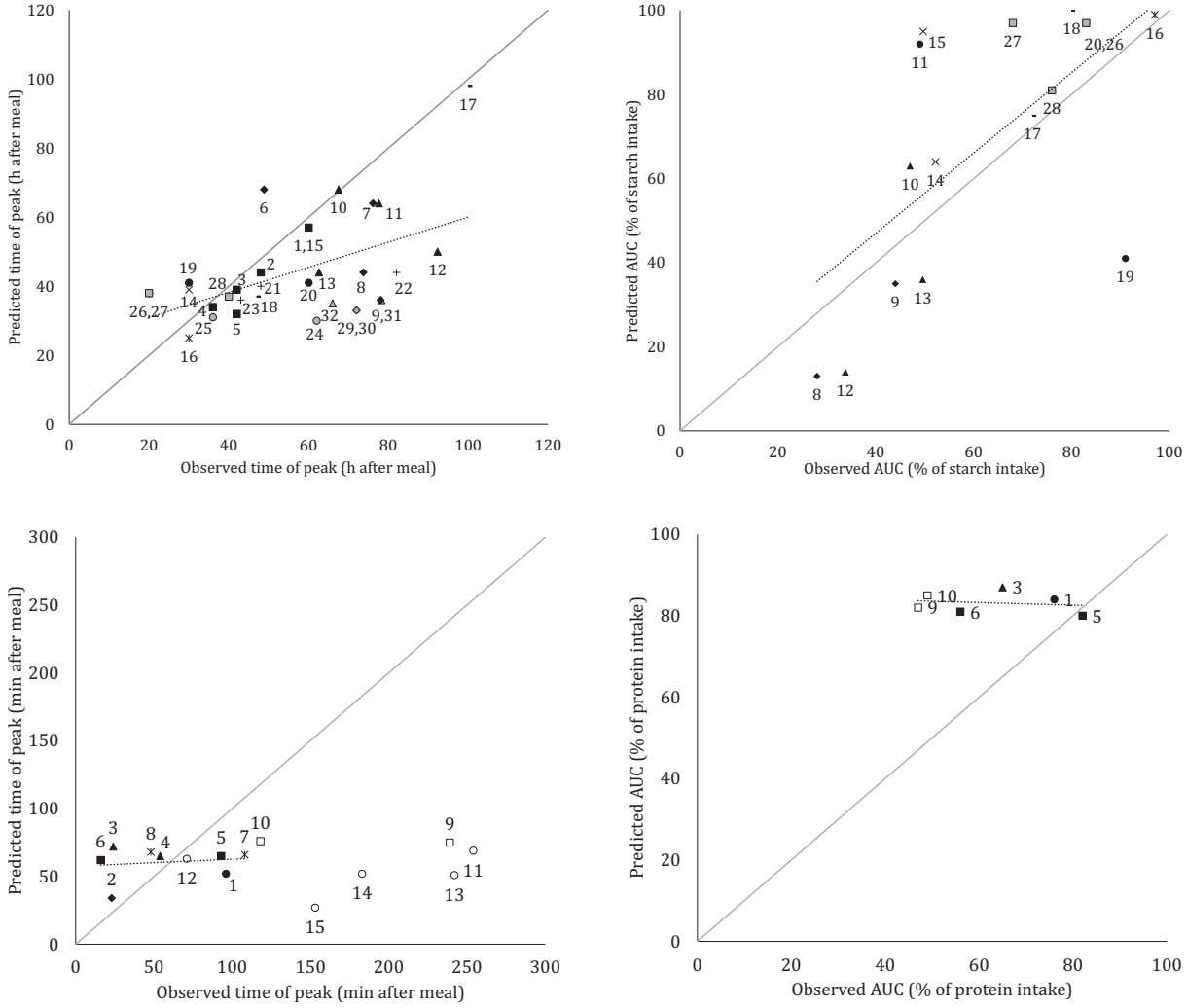

Fig. 4. Predicted vs observed postprandial time of peak of absorption (left-panels), and area under curve (AUC) of postprandial appearance (right-panels) of glucose (top) and amino acids (bottom) for growing pigs, using (portal) blood nutrient appearance studies. Symbols differ between studies, data labels represent treatment mean (see, for glucose: Supplementary Table S2, for amino acids: Supplementary Table S3), solid line represents y = x, dotted line represents regression line.

Table 4
Validation of the model, presenting goodness of fit of observed (obs) vs predicted (pred) postprandial time of peak (h) and area under the curve[1] (% of ingested) of glucose and amino acids absorption from the intestine, and apparent ileal protein digestibility (%) in growing pigs.

Nutrient	Variable	Obs (SD)	Pred (SD)	R^2	RMSPE (%)	ECT (%)	ER (%)	ED (%)	CCC	Cb	v	μ
Glucose	Time of peak[2]	56 (20)	44 (15)	0.25	39	31	4	65	0.38	0.8	1.4	0.7
	Area under curve[3]	63 (20)	69 (30)	0.41	39	6	52	42	0.58	0.9	0.7	−0.2
Amino acids	Time of peak[4]	58 (34)	61 (11)	0.03	60	1	3	96	0.09	0.6	3.0	−0.1
	Time of peak[5]	115 (79)	60 (14)	0.00	85	32	2	67	0.00	0.2	5.8	1.7
	Area under curve[6]	63 (13)	83 (2)	0.03	40	69	0	27	−0.02	0.1	5.5	−3.7
Protein	Apparent ileal digestibility[7]	70 (5)	78 (5)	0.67	12	88	0	12	0.34	0.4	1.1	−1.7
Fat	Apparent ileal/faecal digetibility[8]	82 (15)	86 (4)	0.30	16	6	8	86	0.27	0.5	3.6	−0.4

Abbreviations: RMSPE = root mean square prediction error (as % of observed mean), ECT = error of overall bias, ER = error due to deviation of the regression slope from unity, ED = error due to disturbance (i.e. random error), where ECT, ER, and ED are expressed as % of total error, CCC = Lin's concordance correlation coefficient, Cb = bias correction faction, v = measure of scale shift, μ = measure of location shift (as presented by Ellis et al., (2010)).
[1] Area under the curve calculated based on observed sampling time (varying from 5 to 12 h).
[2] Observed data (n = 32) (Bakker et al., 1995, 1997; Deutz et al., 1995; Jansman et al., 1996; van der Meulen et al., 1997; Knudsen et al., 2000; Fledderus et al., 2007; van Kempen et al., 2010; Regmi et al., 2011; Theil et al., 2011; Giuberti et al., 2012b; Ingerslev et al., 2014).
[3] Observed data (n = 16) (Bakker et al., 1995; Deutz et al., 1995; Jansman et al., 1996; van der Meulen et al., 1997; Knudsen et al., 2000; van Kempen et al., 2010; Regmi et al., 2011).
[4] Observed data based on net portal appearance of amino acids (n = 8) (Rérat et al., 1988b; Bakker et al., 1997; Yen et al., 2004; Agyekum et al., 2016; Deutz et al., 2018).
[5] Observed data based on Schop et al. (2020) plus studies considering arterial (Bakker et al., 1997) or systemic venous (Chen, 2017) nutrient concentrations (n = 15).
[6] Observed data (n = 6) (Rérat et al., 1988a; Bakker et al., 1995; 1997; Yen et al., 2004; Agyekum et al., 2016).
[7] Observed data (n = 10) (Just et al., 1985).
[8] Observed data (n = 13) (Bayley and Lewis, 1965; Duran-Montgé et al., 2007; CVB, 2018).

(Eqs. [140], [145], [155]). The synthesis of microbial biomass was based on the fermentation of carbohydrates (TN, TS, GL), which in turn was based on the principles of NSP and starch fermentation in the rumen of dairy cows (Pirt and Hinshelwood, 1965; as referenced in CVB, 2007). The synthesis of microbial biomass per unit TN or TS was calculated to be 0.35 g microbial biomass/g fermented substrate, of which 62.5% is microbial protein (i.e. Ctn_mb = Cts_mb = 0.35 × (1–0.625) = 0.13 g MB/g TN or TS; Ccp_mb = 0.35 × 0.625 = 0.22). And the synthesis of short-chain fatty acids was assumed to occur in a fixed ratio (65:25:10 for acetate: propionate: butyrate, on a molar-basis; Jan Dijkstra, personal communication). This ratio, however, can vary among substrates entering the colon, e.g. starch is known to increase the relative production of butyrate. In the model, nitrogen required for the synthesis of microbial protein is delivered through dietary and endogenous protein entering the colon (Eq. [135]), when these are insufficient, nitrogen influx from urea from the blood (Eq. [163]) is assumed to occur in non-limiting quantities.

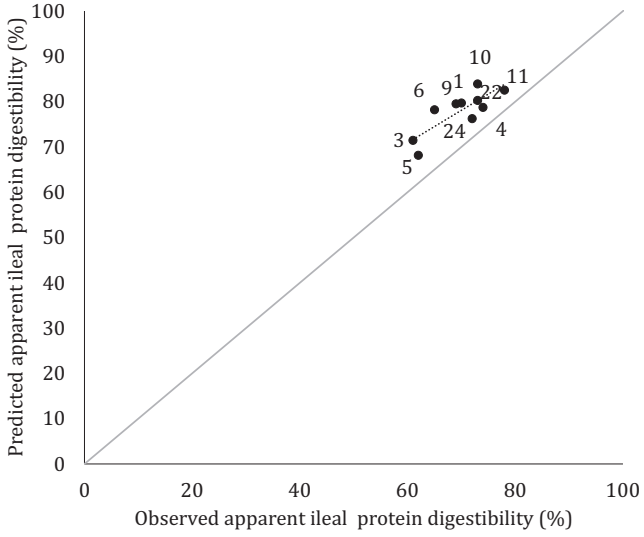

Fig. 5. Comparing observed (Just et al., 1985) and predicted values for apparent ileal CP digestibility in growing pigs. Data labels refer to diet numbers as indicated by (Just et al., 1985). Solid line represents y = x, dotted line represents regression line.

Model evaluation

See Supplementary Material S1 for the methods and Supplementary Table S4 for the results of behaviour and local sensitivity analysis of the model.

Model predictions

Model predictions of nutrient digestion kinetics were evaluated using independent *in vivo* data. Focus was on the prediction of starch and protein digestion kinetics, and thereby on glucose and amino acid absorption kinetics. Although the net portal appearance of nutrients can be affected by first-pass metabolism (Deutz et al., 1995), such data are still the only type available to evaluate the predicted absorption kinetics of nutrients by the model. Hence, for model evaluation, data were used from studies covering nutrient fluxes or changes in nutrient concentrations in (net) portal and/or systemic blood in growing pigs. Model evaluation comprised the predictions of the apparent ileal digestibility of protein (Just et al., 1985) and fat (Bayley and Lewis, 1965; Duran-Montgé et al., 2007; CVB, 2018). The kinetics of glucose and amino acid absorption were evaluated using predictions of the time of peak (**TOP**) and the extent (i.e. area-under-curve: **AUC**; Eqs. [170], [172]) of absorption. Data used for model evaluation of the absorption kinetics were collected or calculated from *in vivo* studies by considering: (1) the nutrient and feed ingredient composition of the diet, and feed intake level (these were used as model driving variables); (2) the cumulative postprandial absorption of glucose and of amino acids; (3a) if presented: the TOP absorption of glucose and/or amino acids, preferably based on porto-arterial nutrient concentration differences (i.e. net portal appearance) or portal fluxes, otherwise on either portal or systemic blood nutrient concentrations. If TOP as mentioned under 3a was not presented: (3b) TOP of absorption was estimated by fitting the derivative of a generalised Michaelis-Menten equation (van den Borne et al., 2007a) using non-linear regression (except for data from (Agyekum et al., 2016) where a third and fifth-degree polynomial function was fitted). Evaluation of model predictions were carried out based on root mean square

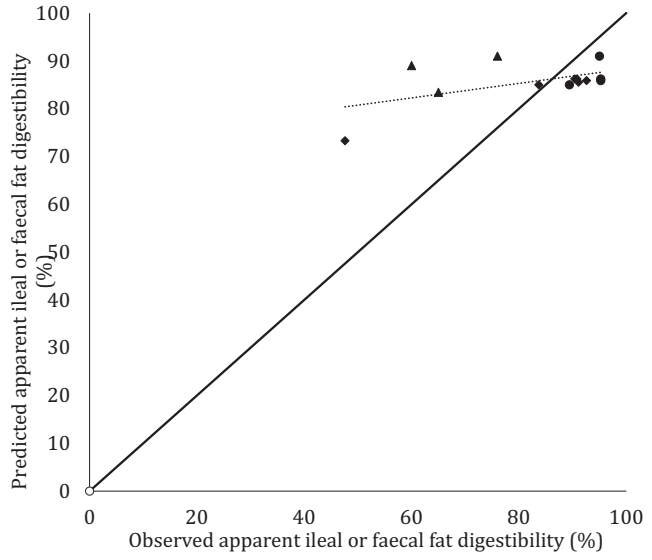

Fig. 6. Comparing observed values of ileal (◆ = Duran-Montgé et al., 2007; ▲ = Bayley and Lewis, 1965) and faecal (● = CVB, 2018) fat digestibility with predicted apparent ileal and faecal fat digestibility values in growing pigs. Solid line represents y = x, dotted line represents regression line.

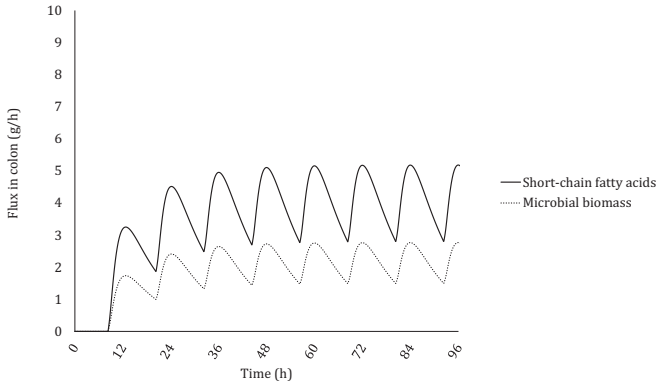

Fig. 7. Simulated flux of short-chain fatty acid (solid line) and microbial biomass (dotted line) production in the colon of a pig (50 kg BW) fed 975 g DM/d of a practical reference diet (i.e. low soluble diet, Schop et al., 2019a; see Supplementary Table S5) consisting mainly of wheat (37%), maize (31%), rapeseed meal (14%), soybean meal (10%), sugar beet pulp (1.5%) and soybean oil (1.9%), with a nutrient content of (on DM basis): starch (54%), CP (22%), fat (5%), and non-starch polysaccharides (19%).

prediction errors (**RMSPE**) (Bibby and Toutenburg, 1977) and Lin's concordance correlation coefficients (Lin, 1989) as explained by Ellis et al. (2010).

Results

Model predictions

Glucose absorption kinetics

For starch digestion kinetics, results of the evaluation of glucose absorption against independent (net) portal, arterial or systemic blood sampling studies (32 mean values for dietary treatments originating from 12 studies; Supplementary Table S2) are provided in Fig. 4 and Table 4. The simulated extent of glucose absorption ranged from 13% in high amylose maize starch to 99% in regular maize starch. The simulated TOP of glucose absorption ranged from 25 min for a soluble diet containing maltodextrin as "starch" source (Deutz et al., 1995) to 98 min for a slowly degradable native tapioca starch source (Bakker et al., 1997). The extent of glucose absorption measured *in vivo* is overestimated by the model (69 ± 30 vs 63 ± 20%, n = 16, RMSPE = 39% relative to observed mean), whereby most error originated from deviation of the regression slope from unity (52%) followed by the observed random error (42%). For the TOP of glucose absorption, model predictions underestimate that of *in vivo* (44 ± 15 vs 56 ± 20 min, RMSPE = 39% relative to observed mean). The prediction error is for 65% random and for 31% due to bias.

Amino acid absorption kinetics

For protein, the evaluation of amino acid absorption kinetics against independent (net) portal, arterial or systemic blood amino acid appearance studies (Supplementary Table S3) is presented in Fig. 4 and Table 4. The simulated extent of amino acid absorption ranges from 80% in a soybean meal-based diet (Yen et al., 2004) to 87% in a diet including various protein sources (Bakker et al., 1995). The simulated TOP of amino acid absorption ranged from 27 min for a diet containing black soldier fly larvae protein to 76 min for a diet containing potato protein as main protein source. Based on limited data (six dietary treatment means), the extent of amino acid absorption is overestimated by the model (83 ± 2 vs 63 ± 13%, RMSPE = 40%; Fig. 5). Model predictions regarding the TOP of amino acid absorption were evaluated at two levels: against the complete validation dataset (15 mean values for dietary treatments originating from eight studies), and against a selection of the dataset that contained only studies regarding the net portal vein appearance of amino acids (eight dietary treatment means from six studies). Evaluation against the complete dataset indicated that the model severely underestimates the observed mean of and variation in TOP of amino acid absorption (60 ± 14 vs 115 ± 79 min, RMSPE = 85% relative to the observed mean value). Evaluation against the selected dataset indicated that the model adequately estimates the observed mean of TOP of amino acids, but not the variation in TOP (61 ± 11 vs 58 ± 34 min, RMSPE = 60% relative to the observed mean value). For the latter, the prediction error originates almost completely from the random error (96%).

Ileal and faecal digestibility of protein and fat

The apparent ileal or faecal digestibility of protein (Fig. 5) and fat (Fig. 6) are, on average, overestimated by the model (protein: 70 ± 5 vs 78 ± 5%, RMSPE = 12%; fat: 82 ± 5 vs 86 ± 5%, RMSPE = 16%). In the case of protein, the prediction error is mainly due to bias (88%) followed by random error (12%), whereas for fat, it is mainly due to random error (86%) followed by deviation of the regression slope from unity (8%).

Fat and non-starch polysaccharide hydrolysis

Fat hydrolysis and NSP fermentation were simulated by the digestion model as well. The digestion of fat and NSP yields (short-chain) fatty acids (Fig. 7), which after absorption, may be further metabolised in postabsorptive metabolism and are an important source of energy for pigs. Variation and further validation of the kinetics of fat hydrolysis and NSP fermentation using diets varying in feed ingredient composition should be considered for improvements of the model.

Discussion

With the model described in this paper, we aimed to increase our understanding of the quantitative impact of variation in the kinetics of nutrient digestion on the absorption kinetics of nutri-

ents. Focus has been put on variation in digesta passage and nutrient hydrolysis kinetics, as caused by physicochemical properties of the diet and its constituting feed ingredients. Our ambition was to adequately predict variation in the kinetics of absorption of glucose and amino acids from the digestive tract of growing pigs that are fed diets composed of feed ingredients varying in physicochemical properties.

Digesta passage: from concept to model predictions

In contrast to other pig digestion models, our model simulates variation in digesta passage kinetics through the stomach caused by dietary and digesta physiochemical properties (Usry et al., 1991; Bastianelli et al., 1996; Rivest et al., 2000; Strathe et al., 2008). By including dietary factors that are known to affect gastric emptying (i.e. diet viscosity, dietary nutrient solubility, and feed intake level) (Gregory et al., 1990; Marciani et al., 2001; Kwiatek et al., 2009; Schop et al., 2019a; 2020) and differentiating between emptying of solids and liquids, the model was able to simulate variation in the kinetics of digesta passage in the stomach. When simulating pigs fed diets varying in diet viscosity (0–18.5 RAV), dietary nutrient solubility (2.6–100%) and various feed intake levels (2–3.5 $\times$ ME_m), the model predicted variation in the MRT of solids (2.1–4.4 h), and of liquids (0.7–3.2 h). The variation in digesta passage rate was assumed to be of significance for improving the prediction of variation in nutrient absorption kinetics. For example, this is observed for the absorption of AA from the intake of various protein sources differing in solubility (Gaudichon et al., 1994; Le Feunteun et al., 2014). Contrary to expectation, however, nutrient absorption kinetics was only marginally affected when simulation variation in gastric emptying rate (see Supplementary Material S1 for sensitivity analysis of e.g. TOP). A point of improvement in the model representation of digesta passage kinetics may be considered. The application of first-order kinetics in digesta passage generally results in right-skewed curves for the flux of nutrients being passed on, degraded and absorbed in consecutive compartments. Such right-skewed sharp responses cause the TOP to become 'stiff', i.e. less variable in time of occurrence. Improving the representation of digesta passage in the stomach and small intestine may aid model predictions regarding the absorption kinetics of nutrients. For example, by using higher-order kinetics such as a power-law model (Siegel et al., 1988; Elashoff et al., 2019) to represent stomach emptying, and/or by considering the physiological nature of stomach motility (e.g. Usry et al., 1991) which causes gastric emptying to vary between fed and fasted states (Kong and Singh, 2008). For the small intestine, representing digesta passage using first-order kinetics like other models (Bastianelli et al., 1996; Strathe et al., 2008) conflicts with the mechanism of plug flow in this compartment (Lentle and de Loubens, 2015). Therefore, representing the mechanism of peristaltic waves in the small intestine may be considered for future model improvements (Usry et al., 1991; Rivest et al., 2000; Taghipoor et al., 2012).

Hydrolysis of macronutrients: in vitro vs in vivo

While often *in vitro* assays (e.g. Englyst et al., 1992; Boisen and Fernández, 1997) are used to predict nutrient absorption kinetics *in vivo* (e.g. Englyst et al., 2003), their capacity doing so is limited (Bohn et al., 2018). This is partly due to not accounting for effects of variation in digesta passage on nutrient absorption kinetics. As the *in silico* digestion model accounts for digesta passage kinetics, data obtained from *in vitro* assays can be used more in line with their design, that is to simulate the hydrolysis of nutrients. As static *in vitro* assays solely simulate the process of nutrient hydrolysis, obtained rates and extents of nutrient hydrolysis can be considered inherent feed ingredient properties. As feed ingredients are finely ground (<1 mm particle size) and an overload of digestive enzymes is provided while working in a diluted system to avoid product-inhibition, the observed hydrolysis kinetics *in vitro* were considered the maximum potential per ingredient.

Upon model parameterisation, however, we observed that the direct application of *in vitro* hydrolysis parameters resulted in systematically lower model predictions for ileal starch digestibility than observed *in vivo*. Assuming adequate mean prediction of digesta passage kinetics by the model suggests that *in vitro* starch hydrolysis rates underestimate those occurring *in vivo*. This may have been due to the underestimation of partial starch hydrolysis in the stomach both *in vitro* and *in silico*, for which limited data exist (Martens, 2019). To improve model predictions for starch digestion kinetics, *in vitro* fractional starch hydrolysis rates were compared to those deduced *in vivo*. A non-linear relationship was observed, i.e. starch hydrolysis rates *in vivo* increased with increasing values *in vitro* until a plateau was reached. This plateau suggests that *in vivo* starch digestion kinetics may be limited by factors other than the maximum extent of hydrolysis of a single ingredient as measured *in vitro*. Such factors may be the kinetics of digesta passage, and factors that induce ingredient- ingredient and ingredient – matrix interactions (Singh et al., 2010).

While for starch hydrolysis rates, the *in vitro* - *in vivo* relationship was obtained and accounted for, for protein hydrolysis rates, there appeared to be no relationship other than *in vitro* rates being generally higher than those *in vivo*. By lack of better means, *in vitro* fractional hydrolysis rates for protein were directly used as model input variables, in contrast to starch. Sensitivity analysis of the model pointed out that the kinetics of amino acid absorption is most sensitive to i) effects of feed intake affecting gastric emptying (−0.41 to 0.22 percentage-point per percentage-point change in feed intake), ii) followed by the fractional protein hydrolysis rate in the small intestine (−0.20 to 0.38 percentage-point per percentage-point change in fractional protein hydrolysis rate in the small intestine), and iii) the instant transition of protein into absorbable units when proteins enter the small intestine (−0.25 to 0.30 percentage-point per percentage-point change in instant solubilisation) (see Supplementary Material S1). Hence, further model improvements related to simulating amino acid absorption kinetics should focus on parameterisation of protein hydrolysis in the small intestine. Doing so requires the availability of datasets with related information on various protein sources and preferably data on both *in vivo* hydrolysis rates (deductible when both digesta passage kinetics and extent of nutrient digestibility in multiple consecutive compartments of the GIT are quantified) and *in vitro* hydrolysis kinetics.

Predicting variation in nutrient absorption kinetics based on variation in digestion kinetics

Overall

Unique to our model is the simulation of variation in the rate and extent of nutrient absorption caused by variation in the physiochemical properties of diets and constituting feed ingredients. Previous models simulating nutrient digestion in pigs have not accounted for this variation and are therefore not capable of representing the effects on nutrient absorption kinetics when pigs would be fed diets similar in nutrient content but differing in ingredient composition (Usry et al., 1991; Bastianelli et al., 1996; Rivest et al., 2000; Strathe et al., 2008).

To evaluate model predictions presented in the present paper, net portal blood appearance of nutrients was used as a near-optimal measure of nutrient absorption kinetics. The evaluation indicated that variation between observed and predicted TOP of nutrient absorption is largely due to random errors in the data

(65–67%). Although random errors include experimental errors that can technically be accounted for provided the availability of a sufficiently large dataset with data of numerous studies, inherently models cannot account for errors in the data to which the model is calibrated. Our evaluation dataset limited the possibility to account for between-study variation to reduce the level of random error. This indicates the need for more portal blood nutrient appearance studies in which experimental diets are evaluated varying largely in ingredient composition.

Glucose absorption and starch hydrolysis kinetics

When diets varying in starch source and physicochemical properties were simulated model predictions on variation in the extent and TOP of absorption fitted generally well with observed data. However, the model slightly overpredicted the mean extent of glucose absorption (69% *in silico* vs 63% *in vivo*, Table 4). Observed data were obtained from *in vivo* studies on portal glucose appearance and systemic glucose concentrations in pigs fed various diets and starch origins. The model's overprediction is likely caused by overlooking first-pass metabolism of glucose in intestinal tissue, and the evaluation against systemic blood besides portal blood. *In vivo* glucose can be metabolised during first-pass in intestinal tissue or in whole-body metabolism (Vaugelade et al., 1994; Noah et al., 2000) resulting in inherently lower glucose appearance after absorption than what may be absorbed from the GIT. This indicates the limitation of our evaluation procedure, and the potential benefit of considering first-pass metabolism by enterocytes as a model extension. Focussing back on glucose absorption kinetics and its evaluation, the model generally underpredicts TOP by 15 min. Overall bias dominated the prediction error. To improve model predictions on the TOP of glucose absorption, one may focus on reconsidering passage of digesta in the stomach as presented in the current model, followed by the relationship between *in vitro* and *in vivo* determined fractional starch hydrolysis rates as discussed earlier. For the latter, it can be seen in Fig. 3 (left panel) that the *in vivo* fractional rate of starch hydrolysis may be overpredicted for *in vitro* slowly degradable starch sources (i.e. low fractional rates). It is worthwhile to consider using part of the validation dataset to estimate the *in vivo* fractional hydrolysis rates based on the kinetics of glucose appearance instead of starch digestion. Doing so substantiates the predicted relationship between *in vitro* and *in vivo* starch hydrolysis kinetics.

Amino acid absorption and protein hydrolysis kinetics

While it is commonly accepted to assess nutrient absorption kinetics *in vivo* by studying net portal blood appearance, such studies are highly invasive (i.e. require cannulation of portal vein). Therefore, systemic or arterial blood has been studied to assess amino acid concentrations less invasively, and, consequently, to estimate the absorption kinetics of nutrients (e.g. Bakker et al., 1997; Chen, 2017). Nonetheless, the appearance of amino acids in either portal, arterial, or systemic blood typically occurs later than the net portal blood appearance of amino acids, as supported by data from various studies (Rérat et al., 1988b; Bakker et al., 1997; Yen et al., 2004; Agyekum et al., 2016; Deutz et al., 2018). The difference in postprandial TOP for amino acids between net-portal blood and systemic blood ranged from 0 to ∼100 min, depending on the study and diet being evaluated (data not shown). This is likely due to the effects of whole-body metabolism (Rérat et al., 1992). Whole-body metabolism covers the use of amino acids for utilisation in the body once they pass from the portal vein to other organs and tissues, influencing nutrient concentrations of systemic blood. Moreover, the delayed TOP of amino acid absorption (e.g. >120 min), as observed in studies collecting arterial or venous blood, could only be accurately predicted by the model when the fractional protein hydrolysis rates in the GIT were substantially reduced to such low values that ileal protein digestibility became unrealistically low (∼10%). Therefore, the conclusion was reached that it is inappropriate to represent the kinetics of protein digestion and amino acid absorption based on amino acid appearance in arterial or venous blood.

Hence, despite the interesting range in protein sources that were studied using arterial or systemic blood (Bakker et al., 1997; Chen, 2017), the model should be evaluated against studies that cover the net portal appearance kinetics of amino acids. This model evaluation showed that, albeit based on a small number of data, it was possible to reasonably predict mean TOP of amino acid absorption (58 vs 61 min after a meal). However, the model struggled to accurately predict the variation in TOP amino acid absorption (±34 vs ±11 min), despite the models' ability to simulate a wide range in TOP. For example, when the digestion of potato protein vs whey powder was simulated, considered 'slow' and 'fast' degradable protein sources, respectively (Schop et al., 2019b), the model predicted a difference in TOP of amino acid absorption of ∼1 h (81 vs 23 min). As TOP of amino acid absorption is mostly affected by protein hydrolysis kinetics in the small intestine (see Supplementary Table S2), the evaluation suggests that the variation observed in *in vitro* protein hydrolysis kinetics does not reflect the kinetics occurring *in vivo*.

The discrepancy between observed and predicted variation in absorption kinetics of amino acids can be caused by a combination of the following factors: inadequate representation of digesta passage kinetic (as discussed earlier), overestimation of *in vivo* protein hydrolysis kinetics, and/or omitting the effects of amino acid metabolism by gut tissue. It is not likely that the discrepancy was only caused by an overestimation of protein hydrolysis kinetics. Since, for example, reducing solely protein hydrolysis kinetics in the small intestine (e.g. Kdpi_aai from 2.1 to 1.2/h, and Cdpgs_aai from 28 to 0%) to match observed values by Yen et al. (2004), resulted in decreasing ileal protein digestibility below those expected (∼70% predicted vs 80–81% expected; CVB, 2018). Hence, re-scaling protein hydrolysis kinetics to fit observed nutrient absorption kinetics may conflict with the model's predictions on nutrient digestion extent. This suggests that amino acid appearance after absorption from the GIT is delayed by another factor. Lacking the representation of gut metabolism in the model may cause differences when comparing *in silico* nutrient absorption kinetics with the *in vivo* kinetics of net portal amino acid appearance. Gut tissue is known for its high metabolic activity, involving the metabolism and synthesis of amino acids and glucose (Deutz et al., 1995). It is also postulated to hold a labile protein pool (Soeters et al., 2001) in which amino acids and proteins can be temporarily stored. Hence, while net portal appearance remains the closest estimation for amino acid absorption from the gut, the absorption kinetics of amino acids can be affected by gut metabolism of amino acids which is not accounted for by the present model.

Data required for further model calibration of protein digestion

As discussed earlier, refining the calibration of model parameters and the kinetics of nutrient hydrolysis could enhance the accuracy of model predictions regarding nutrient absorption kinetics. Additionally, expanding the model to incorporate the nutrient metabolism of the gut may be of interest. However, model development in this area is hindered by the limited availability of adequate data. More data are needed to better understand the relationship between overall kinetics of protein digestion, the kinetics of protein hydrolysis, and the correlation between *in vitro* and *in vivo* hydrolysis kinetics. Such dataset should include studies that measure the net portal appearance of amino acids following a meal with various protein sources. Due to the substantial

experimental errors in these studies, a meta-analysis approach could help account for between-study variations. However, such an approach would require testing the same protein sources in multiple studies. Hence, more *in vivo* studies need to be conducted studying the net portal appearance of nutrients originating from diets varying in ingredient composition, preferably also evaluating digesta passage kinetics and extent of nutrient digestion in consecutive segments of the GIT.

Conclusion

In this paper, we introduced a nutrient-based dynamic mechanistic digestion model for growing pigs. The model simulates the digestion of nutrients inside the gastrointestinal tract. As nutrient hydrolysis kinetics varies among ingredients, data from *in vitro* assays were used and assumed to represent the true potential of individual feed ingredients in order to predict *in vivo* nutrient hydrolysis kinetics. Furthermore, variations in the kinetics of digesta passage due to dietary physicochemical properties were included. Covering the digestive processes of feed intake, digesta passage, nutrient hydrolysis and endogenous nutrient secretions, the model uniquely predicts variation in digestion and absorption kinetics of nutrients originating from diets and ingredients varying in physicochemical properties. Model predictions were extensively evaluated against *in vivo* data. Model simulations showed that the data from *in vivo* studies considering amino acid concentrations in arterial or systemic blood are considered not suitable for estimation of the net portal appearance of amino acids. Evaluation of the model indicated adequate predictions of variation in glucose absorption kinetics when simulating diets varying in physicochemical properties and inclusion of various starch sources. Also, adequate predictions were shown for the extent of small intestinal protein digestion. However, albeit satisfactorily mean predictions for the kinetics of amino acid absorption, sufficient variation in absorption could not be predicted by the model. Adequate data for model calibration on protein digestion kinetics are lacking. Such a dataset ideally covers data regarding the net portal appearance of amino acids in pigs fed diets varying in 'slow' and 'fast' *in vitro* degradable protein sources, and for which also passage kinetics of digesta and the ileal protein digestibility are quantified. As far as we know, this is the first model to attempt prediction of the variation in nutrient digestion kinetics, based on variation in hydrolysis kinetics of nutrients originating from different ingredient sources, and on the effects of physicochemical properties of the diet on digesta passage kinetics. By doing so, the model predicts when and to what extent dietary nutrients, origination from various ingredients, are being digested and absorbed in GIT of growing pigs. The model can, for example, be used to evaluate whether the maximum nutritional potential of the diet and its nutrients is reached. Also, the model can be used to study which digestive processes or physicochemical properties limit reaching this potential. Additionally, coupling this model to a nutrient metabolism model will help evaluating to what extent the diet and feeding strategies affect body utilisation of ingested nutrients by growing pigs. Hence, it can be used to better assess the nutritional potential of diets varying in ingredient composition and physicochemical properties. The authors acknowledge that there is ample room for the model to extent and improve (e.g. representing gut tissue metabolism). Doing so requires sufficient understanding and data to quantify the process of consideration and its relationship to nutrient digestion kinetics. We conclude that, despite some limitations in the current model predictions, the model can be a useful tool for studying and understanding complex dietary and animal-related factors influencing nutrient digestion and absorption kinetics.

Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.animal.2023.101025.

Ethics approval

Not applicable.

Data and model availability statement

All data for model calibration and validation were obtained from the literature. The complete model code and parameters, including all model equations, an example list of driving variables, driving variables used for model validation, as well as, a description of the methods and results of behaviour and local sensitivity analysis of the model, are presented in this paper and its supplementary material. The AcslX code of the model described in this article is freely accessible on the ZENODO repository (https://doi.org/10.5281/zenodo.8054329).

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) did not use any AI and AI-assisted technologies.

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Declaration of interest

The authors declare that there is no conflict of interest.

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Transparency declaration

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