



**HAL**  
open science

# Quantification of the feed intake response of growing pigs to perturbations – A modelling approach

Hieu Nguyen-Ba

► **To cite this version:**

Hieu Nguyen-Ba. Quantification of the feed intake response of growing pigs to perturbations – A modelling approach. Animal biology. AGROCAMPUS OUEST, 2020. English. NNT: . tel-02790092v1

**HAL Id: tel-02790092**

**<https://hal.inrae.fr/tel-02790092v1>**

Submitted on 6 Aug 2020 (v1), last revised 24 Feb 2021 (v2)

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# THESE DE DOCTORAT DE

AGROCAMPUS OUEST

ECOLE DOCTORALE N° 600

*Ecole doctorale Ecologie, Géosciences, Agronomie et Alimentation*

Spécialité : « *Biologie et physiologie animales* »

Par

**Hiếu NGUYỄN BÁ**

**Quantification de la réponse de l'ingestion alimentaire des porcs en croissance à des perturbations – une approche de modélisation**

Thèse présentée et soutenue à Rennes, le 24 janvier 2020

Unité de recherche : Agrocampus Ouest, INRA UMR 1348 Physiologie, Environnement et Génétique pour l'Animal et les Systèmes d'Élevage (PEGASE)

Thèse N° : 2020-2\_B-333

## Rapporteurs avant soutenance :

Andrea DOESCHL-WILSON  
Candido POMAR

Professeure – Université de Edimbourg (Royaume-Uni)  
Ingénieur de recherche – Agriculture et Agroalimentaire Canada

## Composition du Jury :

Présidente : Lucile MONTAGNE

Professeure – INRA UMR PEGASE / Agrocampus Ouest

Examineur : Alban BOUQUET

Ingénieur de recherche – IFIP institut du Porc

Dir. de thèse : Jaap VAN MILGEN  
Co-encadrant : Masoomah TAGHIPOOR

Ingénieur de recherche – INRA UMR PEGASE  
Ingénieur de recherche – INRA UMR MoSAR

# Table of content

List of Abbreviations .....	3
List of Tables .....	4
List of Figures.....	5
Remerciements.....	11
Résumé de la thèse .....	13
Contexte de thèse.....	13
Développement du modèle .....	14
Évaluation du modèle.....	16
Discussion.....	18
Introduction .....	21
Chapter 1. Literature review.....	23
1. A robust animal .....	23
1.1. Why we need a robust animal .....	23
1.2. What is a robust animal .....	27
1.3. Identify reliable indicators for animal robustness.....	35
2. Using feed intake as an indicator of robustness .....	39
2.1. Main principles of feed intake regulation.....	39
2.2. Examples of perturbations that decrease feed intake.....	44
3. Current approaches in using feed intake to detect perturbations and quantify subsequent response of animals .....	49
3.1. Detection of perturbations .....	49
3.2. Quantification of animal's response.....	56
4. Gaps of knowledge.....	63
5. Study's objectives .....	64
Chapter 2. Development of the model to detect perturbations and quantify animal's response .....	65
1. Objective of the chapter.....	65
2. A procedure to quantify the feed intake response of growing pigs to perturbations ....	66
Abstract .....	67
Introduction .....	68
Material and methods.....	69
Results.....	77
Discussion.....	82
Conclusion .....	85

3. Supplementary Material.....	87
S1. An example of function re-parameterization.....	87
S2. Dealing with missing data.....	87
4. The capacity of the model to include complementary information.....	89
Chapter 3. Challenging the model to detect perturbations and quantify animal's response...	93
1. Objective of the chapter.....	93
2. Modelling the feed intake response of growing pigs to diets contaminated with mycotoxins.....	94
Abstract.....	95
Introduction.....	96
Material and methods.....	97
Results.....	103
Discussion.....	109
Conclusion.....	114
3. Supplementary Material.....	116
Chapter 4. General discussion.....	118
1. Some general thoughts about the PhD thesis.....	118
2. Other perspectives in modelling the animal's response to perturbations.....	122
3. Potential applications of the procedure.....	124
Genetic selection.....	124
Management practices.....	126
4. Conclusion.....	128
References.....	129
Appendixes.....	143
Appendix 1. List of publications.....	143
Scientific Articles.....	143
Conference's proceedings.....	143
Appendix 2. Other personal communications.....	144
Appendix 3. List of awards.....	145
Appendix 4. List of training courses.....	146

## List of Abbreviations

<b>ADFI</b>	Average Daily Feed Intake
<b>AMPK</b>	Adenosine Monophosphate activated Protein Kinase
<b>CC</b>	Control group of an experiment to study the dynamic effect of a diet contaminated with deoxynivalenol on feeding and growing of pigs
<b>CD</b>	Group of pigs that received one time a diet contaminated with deoxynivalenol from 134 to 140 days of age
<b>CFI</b>	Cumulative Feed Intake
<b>DC</b>	Group of pigs that received one time a diet contaminated with deoxynivalenol from 113 to 119 days of age
<b>DD</b>	Group of pigs that received two times a diet contaminated with deoxynivalenol from 113 to 119 days of age and from 134 to 140 days of age
<b>DFI</b>	Daily Feed Intake
<b>DMI</b>	Dry Matter Intake
<b>DON</b>	Deoxynivalenol
<b>HPA</b>	Hypothalamic-Pituitary-Adrenal
<b>mTOR</b>	mammalian Target Of Rapamycin
<b>PRRS</b>	Porcine Reproductive and Respiratory Syndrome
<b>Ratio(t)</b>	The ratio between the observed and target curves of cumulative feed intake
<b>RFI</b>	Residual Feed Intake
<b>RFID</b>	Radio Frequency Identification
<b>Target CFI</b>	Target trajectory of Cumulative Feed Intake
<b>Target DFI</b>	Target trajectory of Daily Feed Intake

# List of Tables

**Table 1** Summary of some studies that used feeding information extracted from automatic feeders to detect perturbations in farm animals ..... 53

**Table 2.1** Parameter estimates of the target trajectory of cumulative feed intake (CFI) and of the perturbation model to characterize the response to a perturbation of five grouped-housed growing pigs ..... 78

**Table 2.2** Estimated parameters of the modified model to quantify the animal's response to pathogen ..... 92

**Table 3.1** Estimated model parameters of the target trajectory of cumulative feed intake of pigs that received a diet with or without deoxynivalenol (DON) contaminated cereals ..... 104

**Table 3.2** Estimated model parameters indicative for the resistance and resilience potential of pigs that received a diet contaminated with deoxynivalenol (DON) during one or two periods ..... 107

**Table S1** Comparison of procedures to estimate the target trajectory curve of cumulative feed intake ..... 117

## List of Figures

- Figure 1.1** Trends of change in voluntary feed intake, lean tissue growth rate (upper graphs – Knap, 2009) and feed conversion rate (lower graph – Knap and Wang, 2012) in growing pigs of 103 terminal crosses over 35 years in Denmark, France, Germany, the Netherlands, the UK and the USA. Dots are mean observations of terminal crosses, solid lines are general trends and dashed lines are their 95% confidence limits. .... 24
- Figure 1.2** Robustness of the whole animal level (level n) is built from the combination of multiple functional components below (level n-1) (Friggens et al., 2017). ..... 28
- Figure 1.3** Four types of perturbations (Maxwell, 1986). See related text for detailed explanations. .... 30
- Figure 1.4** The regulation of hypothalamus to maintain homeostasis (Nelson and Kriegsfeld, 2017). Receptors in the skin, in the viscera and in the hypothalamus transfer information about the temperatures to the hypothalamus. The hypothalamus works like the thermostat, which integrates the information and compares the desired body temperature to its set point. Deviations (both positive and negative) of the actual body temperature from the set point of the hypothalamus trigger response signals that command multiple organs to warm up or cool down the body temperature back to the set point. The negative feedback system works continuously like a loop to maintain homeostasis for body temperature. .... 32
- Figure 1.5** Relationship between heat production and ambient temperature of 500 simulated growing pigs shared the same genotype (Knap, 2009). Each black dot refers to the lower critical temperature of one pig in relation with its heat production (illustrated by each grey broken line). .... 38
- Figure 1.6** A hydraulic model of the control of energy status in the body on food intake (Forbes, 1986). See related text for detailed explanations. .... 41
- Figure 1.7** Metabolic control of feed intake by two opposing energy-monitoring systems: adenosine monophosphate activated protein kinase (**AMPK**) and mammalian target of rapamycin (**mTOR**). Solid-green arrows indicate a stimulating effect while dashed-red arrows indicate an inhibiting effect (see Black et al. (2009) for full explanations of abbreviations). .... 43
- Figure 1.8** Comparison of average daily feed intake response of two breeds (Creole and Large White) at the same age (Exp.1) or at the same body weight (Exp.2) over a

period of exposure to 31°C (Renaudeau et al., 2007). Each dot represents the least squares mean of each group of pigs in each experiment. x represents the significant effect of breed ( $P < 0.05$ )..... 46

**Figure 1.9** Daily feed intake response of weaned pigs to a bacterial infection (started at the day indicated by the arrow) (Kyriazakis and Doeschl-Wilson, 2009). The dynamic changes in feed intake due to pathogen infection can be characterized by five features: (1) lag time; (2) rate of decline; (3) extend of anorexia; (4) duration of anorexia; and (5) rate of recovery. See related text for detailed explanations..... 47

**Figure 1.10** An example of an automatic feeding station with controlled access for pigs (Maselyne et al., 2015). This feeding station is equipped with entrance and exist gates, protective crate and a feed trough. Only one pig can enter at a time. After each visit, feed consumption and feeding time of the pig are recorded for each pig thanks to the RFDI ear-tag of the pig. These measures are then computed to provide information at more aggregated levels such as number of feeder visits, feed intake and feeding rate per day..... 50

**Figure 1.11** Changes in feed intake (A, D), feeding time (B, E) and feeding rate (C, F) of two cows (upper and lower panels) diagnosed with different types of lameness (González et al., 2008). Although these two cows suffered from different disorders, they showed a very similar response in feeding behaviour: a decrease in feeding time accompanied by an increase in feeding rate before being diagnosed and the reversed changes were observed after day of treatment (day 0). This resulted in a constant level of feed intake in both cases..... 52

**Figure 1.12** Trajectories of resource allocation over 20 years of the life of a dairy cow for five functions: growth (G), balance of body reserves (R), ensuring survival of the unborn calf (U), ensuring survival of the newborn calf (N) and ensuring survival of the suckling calf (S) (Martin and Sauvant 2010a)..... 57

**Figure 1.13** Concept of a model that characterizes the response in relative feed intake (differences between desired and challenged feed intake - RFI) of an animal to a pathogen challenge (Sandberg et al., 2006). The way in which RFI changes over time is characterized by 5 parameters: Lag time (L, day) implies the interval between the point of infection and the first observable effect on RFI, Reduction time (R, day) describes how fast the lowest value of RFI ( $\lambda$ ) is achieved, Duration time (D, day) refers to the period the  $\lambda$  can be maintained, and the rate of recovery ( $\rho$ )..... 58



**Figure 1.14** Results of fitting the “spring and damper” model to records of some physiological and behavioural traits of rainbow trouts before, during a confinement challenge (grey box) and thereafter (Sadoul *et al.*, 2015b). The confinement challenge was conducted by Sadoul *et al.* (2015a). The response of trouts during the challenge was characterized for each traits by two parameters indicating the capacity to resist from being distorted (i.e., damper) and to minimize the amplitude of perturbing factors (i.e., spring). After the challenge, as the perturbing force was released, measured traits recovered back to the baseline by themselves. .... 60

**Figure 1.15** Graphic illustration of the piecewise model that characterizes the response of an interested trait before, during and after an acute challenge such as a low-quality feed (Friggens *et al.*, 2016)..... 61

**Figure 1.16** Results of fitting the model developed by Revilla *et al.* (2019) to body weight measurements of a pig to characterize its response to weaning challenge. The growth trajectory in the non-perturbed condition (solid line) was estimated by fitting a classical Gompertz function to body weight measurements at weaning and the last four days. The body weight response to weaning challenged was estimated by fitting a Gompertz-Makeham equation to all body weight measurements (Revilla *et al.*, 2019). .... 62

**Figure 2.1** General mechanism of a model that quantifies the pig’s response to a perturbation. Solid arrows indicate causal relationships in the model, the double arrow indicates the flux, and the dashed arrow indicates the disappearance of perturbing factor. Numbers indicate the response elements: ① in the absence of a perturbation, the daily feed intake (DFI) is equal to the target DFI; ② the initiation of a perturbation has a negative and constant effect on DFI and, because of the reduction in DFI, the cumulative feed intake (CFI) starts to deviate from the target CFI; ③ the ratio between the CFI and the target CFI triggers the pig’s resilience mechanism to limit the effect of the perturbation on DFI; ④ once the perturbing factor is over, its negative effect on DFI disappears, but the resilience mechanism is still active resulting in compensatory feed intake allowing the CFI to approach the target CFI..... 74

**Figure 2.2** Mechanisms that determine the response of a pig to a perturbation. The perturbation is estimated to occur between around days 97 and 129 of age. The dashed line indicates the target trajectory of daily feed intake (DFI). The black line indicates the constant and negative impact of the perturbation on the pig (resistance),

resulting in a 35.6% reduction in DFI. The grey line represents the resilience capacity (during the perturbation) and compensatory feeding of the pig (after day 129). ..... 75

**Figure 2.3** Cumulative feed intake (CFI) of a pig in response to a perturbation. The target CFI is described by a quadratic-linear model (the change in model segments occurred at 162 days). The perturbation was estimated to occur between 97 and 129 days of age, resulting in a deviation of the CFI from the target CFI..... 79

**Figure 2.4** Difference between the observed cumulative feed intake (CFI) and the target CFI of a pig. Three deviations were detected but, based on the selection criteria for a perturbation, only one deviation was considered as a perturbation. Deviations during the first week of growing period (indicated by the vertical dashed line) were not considered as perturbations. .... 80

**Figure 2.5** Daily feed intake (DFI) of a pig and modelling results. The perturbing factor induced an immediate reduction in DFI (compared with the target DFI) at the beginning of the perturbed period, which was counteracted by resilience mechanisms of the pig. Once the perturbing factor ended, the pig consumed more feed than the target DFI through compensatory feed intake to recover..... 81

**Figure 2.6** The dynamic change of daily feed intake (DFI) due to a perturbation such as pathogen or sanitary challenge. The dashed line indicates the target trajectory of DFI. DFI is estimated to decrease at 103 days of age. At this point, the perturbation had a severe effect on the feed intake. As time evolves the animal's defensive capacity gradually alleviates the negative effect of perturbation, as a result the black line is approaching to zero. Whereas, resilience capacity triggers compensatory feed intake to help the animal recovers..... 90

**Figure 2.7** Daily feed intake (DFI) response of a pig due to an (assumed) pathogen or sanitary challenge. The dashed line indicates the target trajectory of DFI (target DFI). The perturbing factor causes a severe decrease in DFI at the beginning (compared with the target DFI). However, the pig can quickly counteract the negative impact of perturbation and gradually consume more feed than the target DFI through its defensive capacity and compensatory feed intake to recover. .... 91

**Figure 3.1** Change in daily feed intake of a pig in response to receiving a diet contaminated with deoxynivalenol (DON) in two periods. Black lines = response mechanisms, grey line = target daily feed intake. Values smaller than 0 indicate the effect of resistance mechanisms and values greater than 0 indicate the effect of

resilience mechanisms. The top panel illustrates the response mechanisms where the reduction in feed intake during the perturbation ( $k_1$ ) is counteracted for by a resilience mechanism ( $k_2$ , the proportional change in daily feed intake relative to the ratio between the actual cumulative feed intake and the target cumulative feed intake), which results in an attempt for compensatory feed intake ( $k_4$ ). The bottom panel illustrates the actual change in daily feed intake. The  $k_3$  corresponds to the difference between  $k_1$  and  $k_4$ . During the the second perturbation, the actual feed intake is the result of the constant resistance and resilience mechanisms of the second perturbation and the declining resilience mechanism of the first perturbation. .... 101

**Figure 3.2** Capacity of the data analysis procedure to identify the start of the distribution of a diet contaminated with deoxynivalenol (DON) based on the feed response of pigs. In groups DC and DD (Early challenge), pigs received the DON-contaminated diet from 113 days of age onwards. In groups CD and DD (Late challenge), pigs received the DON-contaminated diet from 134 days of age onwards. .... 105

**Figure 3.3** Capacity of the data analysis procedure to identify the day from which pigs started to recover after having received a diet contaminated with deoxynivalenol (DON). The procedure determines the day when the difference between the actual cumulative feed intake and the target cumulative feed intake is maximal. In groups DC and DD (Early challenge), pigs stopped receiving the DON-contaminated diet from 119 days of age onwards. In groups CD and DD (Late challenge), pigs stopped receiving the DON-contaminated diet from 140 days of age onwards. .... 106

**Figure 3.4** Correlations between the change in daily feed intake during the perturbation ( $k_3$ ) and the resilience capacity ( $k_2$ ) of pigs when receiving diets contaminated with deoxynivalenol (DON). The left panel denotes the periods when pigs received a DON-contaminated diet from 113 to 119 days of age (Early challenge) and the right panel when they received the DON-contaminated diet from 134 to 140 days of age (Late challenge). DC = group of pigs that received a diet contaminated with DON from 113 to 119 days of age; CD = group of pigs that received a diet contaminated with DON from 134 to 140 days of age; DD = group of pigs that received a diet contaminated with DON in both aforementioned periods. .... 108

**Figure 4.1** Daily feed intake response of a pig to a perturbation. The target daily feed intake was estimated by a quadratic function. The quadratic function was judged too

flexible resulting in values of the target daily feed intake and of the response to a perturbation that are biologically unlikely. .... 121

**Figure S1** An example of missing data estimation. Feed intake records for days 107 and 108 were missing and resulted in a downward shift in cumulative feed intake. The missing data were estimated as the downward shift in cumulative feed intake of a quadratic regression between the three days before and the three days after the days associated with missing data. .... 88

## Remerciements

Cette thèse a été financé par le projet européen Feed-a-Gene (programme H2020, Union Européenne, numéro d'agrément 633531) et le méta-programme de l'INRA « Adaptation de l'agriculture et des forêts au changement climatique » (INRA-ACCAF). Cette thèse a aussi été financée par l'Institut Convergences Agriculture Numérique (#DigitAg) et par deux bourses de l'école doctorale EGGAL et du Pôle Doctoral de Rennes pour participer au congrès scientifique : « the 9<sup>th</sup> Workshop on Modelling Nutrient Digestion and Utilization in Farm Animals (MODNUT) » au Brésil du 14 au 16 Septembre 2019.

Tout d'abord, je voudrais exprimer ma profonde gratitude à mes « parents scientifiques » dr. Jaap VAN MILGEN et dr. Masoomah TAGHIPOOR pour leur encadrement extraordinaire. Vous m'avez montré fait découvrir ce champ magnifique qu'est la modélisation des systèmes biologiques (qui joue maintenant un rôle important dans ma carrière scientifique). Merci d'avoir été toujours disponibles, optimistes et enthousiastes tout au long de ma thèse.

Je tiens à remercier tous les membres de mon jury : Lucile MONTAGNE, Andrea DOESCHL-WILSON, Alban BOUQUET et Candido POMAR pour avoir accepté d'évaluer mes travaux et pour les échanges pendant ma soutenance de thèse.

Je suis sincèrement reconnaissant aussi à tous les membres de mon comité de thèse : Nathalie LE-FLOC'H, Ludovic BROSSARD, Nicolas FRIGGENS, Sophie BLAT, David RENAUDEAU, Michel MARCON et Veronika HALAS pour avoir contribué au déroulement de cette thèse avec des commentaires et les critiques bien visées qui ont amélioré la qualité de cette thèse.

Je remercie Raphaël GAUTHIER, Rémi RESMOND et Simon BINGGELI pour tous leur soutiens en statistique et en programmation.

Grâce à cette thèse j'ai passé trois merveilleux années chez l'INRA à UMR PEGASE. Je voudrais remercier toutes les personnes que j'ai rencontré à Saint-Gilles (surtout Florence GONDRET, Isabelle LOUVEAU, Bénédicte LEBRET, Sophie DARÉ, Annie VINCENT et Christine TRÉFEU dans l'équipe croissance) pour leur bienveillance, gentillesse et leur soutien. Quand j'ai commencé ma thèse, c'était difficile pour moi parce que j'étais seul en France et je ne parlais pas français. Grâce à vous j'ai pu rapidement m'adapter au monde du travail français et à la vie en France, tout en m'épanouissant aussi dans ma vie privée. Je tiens également à remercier mes

amis que j'avais la chance de connaître pendant mon séjour en France : Alessandra, Bérénice, Aira, Francis, Ronan, Valérie (Marie), Raphael, Aleida, Kristine, Johanne, Uffe, Amélie, Alice, Mathilde, Cléo, David, Linh-Chi, Mohsen, Rafael, Teo, Marion et Sophie. Merci d'avoir rendu inoubliable mon séjour en France.

Finalement, j'adresse mes plus vifs remerciements à ma famille pour leur présence et leur soutien quotidien. En particulier, je remercie ma femme Ngan et ma fille Chi pour leur soutien inconditionnel.

# Résumé de la thèse

## Contexte de thèse

L'élevage porcin a contribué largement à l'approvisionnement d'alimentaire mondial depuis la second guerre mondiale, il est prévu de soutenir encore plus de personnes à l'avenir. FAO a prédit qu'en 2050, la population mondiale va atteindre 9,1 milliards d'habitants. Pour nourrir cette explosion de la démographie dans un avenir proche, le monde a besoin de 70 pourcent de plus de nourriture que ce qui est disponible aujourd'hui. Dans ce contexte, la production de la viande doit doubler. D'autre part, l'utilisation de céréales destinées à la consommation humaine doit réduire dans les aliments pour les animaux afin d'éviter une compétition pour nourriture entre les animaux et l'humain. Enfin, la vitesse d'urbanisation associée à cette augmentation de la population humaine réduis inévitablement la superficie des terres disponibles pour la production animale. Ces chiffres indiquent que les futurs secteurs de l'élevage doivent produire plus avec moins de ressources (c.-à-d. plus efficient).

L'approche prédominante pour produire plus de produits d'origine animale est l'élevage intensif. L'objectif principal de l'élevage intensif est de maximiser la production avec un coût minimum. Pour cela, le potentiel de la production et de l'efficience des animaux ont été optimisé grâce à la sélection génétique. Cette approche entraîne en effet une augmentation de la production animale. Cependant, l'amélioration de la production et de l'efficacité a entraîné les effets défavorables aux animaux comme des troubles du comportement, physiologiques et immunologiques. Par conséquent, les performances des animaux dépendent principalement de l'environnement dans lequel ils vivent.

Des méthodes de contrôle de l'environnement sont largement appliquées dans la production animale (intensive) pour empêcher les animaux d'être exposés aux perturbations qui pourraient détériorer leurs performances telles que l'exposition à des agents pathogènes ou à des conditions météorologiques extrêmes. Malgré plusieurs méthodes de contrôle de l'environnement qui ont été mis en place, les animaux d'élevage doivent de plus en plus faire face à de nombreuses perturbations exogènes telles que les périodes de stress thermique résultant du réchauffement climatique et la mutation des bactéries et des virus se passe très rapidement. Les animaux deviennent donc de plus en plus vulnérables dans le système d'élevage intensif.

Actuellement, il y a une approche d'élevage plus durable qui focalise sur améliorer la capacité intrinsèque de l'animal à s'adapter aux perturbations de l'environnement plutôt que d'essayer d'éradiquer ses sources. La capacité intrinsèque d'un animal à maintenir sa fonctionnalité dans un large éventail de conditions environnementales et s'adapter aux perturbations est communément appelée la robustesse. Un prérequis important pour améliorer la robustesse de l'animal est la quantification de ce trait. Cependant, la robustesse est une notion complexe qui est difficile à quantifier car elle comprend des éléments dynamiques tels que l'intensité de la réponse aux perturbations environnementales et la capacité de rebondissement. Parce que la réponse de l'animal aux perturbations (c.-à-d. la résistance et la résilience, respectivement) sont dynamiques, la mesure prise à des points de temps uniques ne suffisent pas à les caractériser. Actuellement, les nouvelles technologies de monitoring permettent de suivre plus fréquemment la réponse de chaque individu aux perturbations. Parmi de nombreux indicateurs de robustesse, l'ingestion volontaire d'aliment apparait comme un candidat potentiel pour étudier la robustesse d'animal parce qu'elle est une réponse précoce d'animal aux perturbations (par ex. plus rapide que le poids vif de l'animal), elle est fortement liée au statut métabolique d'animal et elle est non-invasive. Une approche multidisciplinaire basée sur la modélisation mathématique de la réponse d'animal est plus appropriée pour tenir compte de la complexité de la réponse de l'animal et caractériser cette réponse. Donc, l'objectif de cette thèse est de développer une procédure de détection automatique des perturbations et développer un modèle de la réponse de l'animal qui est indépendant de l'origine de la perturbation, et qui reflète sa capacité d'adaptation face aux perturbations. Dans cette thèse, nous nous focalisons sur les perturbations ponctuelles ou à court terme qui ont des effets sur des porcs en croissance.

## Développement du modèle

Notre premier objectif est de détecter de façon automatique les perturbations, car l'origine de ces derniers ne sont pas toujours connu. Pour cela, il faut d'abord clarifier la notion de perturbation. Nous avons émis une hypothèse qu'il existe une trajectoire ciblée de l'ingestion volontaire d'aliment qui est la quantité d'aliment qu'un animal désire de consommer dans un état non perturbé. Toutes déviations par rapport à la trajectoire ciblée de l'ingestion d'aliment peuvent être considérée comme des



perturbations potentielles. Nous avons choisi de travailler avec la trajectoire ciblée de la consommation cumulée d'aliment (**CCA**) qui, contrairement à la consommation journalière d'aliment (**CJA**), ne contient pas de variations rapides. De plus, la CCA nous informe sur l'historique de la consommation d'animal. Contrairement à la CJA, la CCA (en tant que trajectoire) permet de prendre en compte l'effet de la perturbation et l'effet de la consommation compensatrice. La dérivée de la trajectoire ciblée de la CCA (**CCA<sub>ciblée</sub>**) représente la consommation journalière ciblée (**CJA<sub>ciblée</sub>**). Le modèle du CCA<sub>ciblée</sub> doit respecter les conditions suivantes (i) il ne doit pas capter les variations liées aux perturbations, (ii) la CJA<sub>ciblée</sub> est une fonction linéaire croissante ou constante, ce qui implique que la CCA<sub>ciblée</sub> est décrit par une fonction quadratique-linéaire. Les paramètres du modèle de la CCA<sub>ciblée</sub> sont l'âge à la quelle CCA = 0, la CCA à la fin de la période concernée, la CCA au milieu de la période concernée, et le jour auquel la CCA<sub>ciblée</sub> change l'allure et passe d'un modèle quadratique à un modèle linéaire. La procédure pour déterminer les paramètres du modèle de la CCA<sub>ciblée</sub> consiste à réaliser plusieurs régressions linéaires successives en éliminant temporairement les données qui pourraient être issues d'une perturbation [basée sur la valeur des résidus (la différence entre valeur observée et prédite) et un test d'autocorrélation des résidus].

Dans cette étude, nous considérons seulement les perturbations avec un effet négatif sur la consommation. Pour cela, une fonction B-Spline a été ajustée à la différence entre la CCA observée et la CCA<sub>ciblée</sub>. Une perturbation est alors définie comme une période avec des valeurs négatives de cette différence, d'une durée de plus de 5 jours de d'une amplitude (le maximum de déviation pendant la durée de la perturbation) supérieur à 5 pourcents de la CCA<sub>ciblée</sub>. En effet, cette condition permet de négliger des petites variations dans la consommation de l'aliment, qui font partie du comportement alimentaire normale des animaux. La flexibilité des fonctions B-Splines permet de capter le maximum des déviations, et par la suite, nous aurons la possibilité de choisir les conditions pour considérer une déviation comme une perturbation.

Après que les perturbations sont identifiées, notre objectif est de caractériser la réponse des animaux en termes de résistance et résilience. Pour cela, un modèle basé sur les équations différentielles a été développé. Les deux forces motrices du modèle sont l'influence de la perturbation et la capacité d'adaptation de l'animal. La réponse d'un porc à une perturbation est caractérisée par quatre paramètres. Les temps de début et de fin de la perturbation (c.-à-d.  $t_{start}$  et  $t_{stop}$ , respectivement), et les deux

paramètres décrivant la résistance et le potentiel de résilience du porc. L'un d'eux décrit la réduction immédiate de la CJA au début de la perturbation (c.-à-d. un trait de « résistance »). Nous faisons l'hypothèse que l'influence de la perturbation sur la CJA est négative et constant pendant toute la durée entre les temps de début et de fin de la perturbation. L'autre paramètre décrit la capacité du porc à s'adapter à la perturbation par l'ingestion compensatrice pour rejoindre à nouveau la  $CCA_{ciblée}$  (c.-à-d. un trait de « résilience »). Le ratio entre la CCA observée et la  $CCA_{ciblée}$  est utilisé comme la force motrice pour décrire la capacité de la résilience. Plus le ratio entre la CCA observée et la  $CCA_{ciblée}$  est petit, plus grande est l'intensité du mécanisme de résilience pour CJA.

La procédure a été utilisée avec succès pour identifier la trajectoire ciblée de la prise alimentaire chez cinq porcs en croissance dans un groupe et pour quantifier ses réponses à une perturbation. Notre démarche a permis de proposer un moyen pour quantifier la notion de la robustesse via la résistance et la résilience. Ces paramètres permettront d'hiérarchiser des animaux pour leur capacité d'adaptation.

## Évaluation du modèle

Notre prochain objectif est d'utiliser ce modèle pour quantifier la résistance et la résilience des porcs dans une expérimentation testant des régimes avec ou sans céréales contaminées par des mycotoxines - la déoxynivalénol (**DON**). Les porcs ( $n = 155$ ) ont été divisés en part égale dans un groupe « témoin » (groupe CC) et dans trois groupes « challengés ». Lors d'une expérimentation des 55 jours, les porcs de groupe CC ont reçu un régime normal. Les porcs des trois groupes « challengés » ont reçu un régime contaminé en mycotoxines soit pendant 7 jours au début de l'expérience, c.-à-d. du 113 au 119 jours d'âge (groupe DC), pendant 7 jours à la fin de l'expérience, c.-à-d. du 134 au 140 jours d'âge (groupe CD) ou pendant les deux périodes (groupe DD).

Certains aspects du modèle original ont été modifiés pour le rendre (plus) adapté aux données de cette expérimentation. Pour estimer la  $CCA_{ciblée}$  dans le modèle original, un test d'autocorrélation a été combiné avec la suppression temporelle des données avec des résidus négatifs de l'ensemble de données. La durée de la période expérimentale dans cette étude était courte (55 jours), la procédure s'est souvent arrêtée en raison d'un critère dans la procédure pour conserver un nombre minimum

d'observations restantes. Dans la procédure modifiée, à chaque étape de filtration seulement 10 pourcent de données avec des résidus négatifs ont été supprimé, qui résulte à une estimation plus progressive de la  $CCA_{ciblée}$ . En outre, dans la procédure d'origine, une déviation était définie comme une perturbation si elle s'écarte de la  $CCA_{ciblée}$  au moins de 5 pourcent et pour une durée au moins de 5 jours. Pour tester la capacité de la fonction B-spline à identifier les périodes de distribution de l'aliment contaminée avec la DON, ces critères n'ont pas été appliqués. Toute période pendant laquelle la CCA observée s'est écartée de la  $CCA_{ciblée}$  a été caractérisée par l'heure de début, l'ampleur de l'écart et la durée (c.-à-d. le temps nécessaire pour la CCA observée retrouve sa  $CCA_{ciblée}$ ). Finalement, le ratio entre la CCA observée et la  $CCA_{ciblée}$  définit l'intensité du mécanisme de résilience, varie avec le temps. Par exemple, la CCA sera petit à un stade précoce de la vie et une petite réduction de la CJA provoquera une réduction considérable du ratio. Aux stades ultérieurs de la vie, la CCA sera beaucoup plus grand et la même perturbation aura un petit impact sur le ratio. Ignorer la dépendance temporelle du ratio provoquera une estimation biaisée de la résilience. La procédure d'origine a donc été modifiée pour calculer le ratio entre la CCA observée et la  $CCA_{ciblée}$  depuis le début de la perturbation, et non depuis le début des mesures.

Pour évaluer la capacité de la procédure à détecter les perturbations, les estimations des paramètres de la  $CCA_{ciblée}$  et les résultats des fonctions B-spline ont été comparés entre les quatre groupes. Ensuite, la quantification de la réponse aux régimes contaminés par la DON a été réalisée dans les trois groupes « challengés » (c.-à-d. DC, CD et DD). Dans la procédure d'origine, les quatre paramètres du modèle de perturbation (les temps de début et de fin de la perturbation, la résistance et la résilience) ont été estimés. Avec l'ensemble de données actuel, il a semblé difficile d'estimer tous ces paramètres, car la période de distribution du régime d'aliment contaminé par la DON n'a duré que 7 jours. Nous avons alors décidé de fixer les deux paramètres  $t_{start}$  et  $t_{stop}$  aux temps de début et de fin de la distribution des régimes d'aliment contaminé par la DON dans la procédure de quantifier le réponse des animaux.

Pour la procédure de détecter les perturbations, les résultats ont montré que la  $CCA_{ciblée}$  peut être estimée indépendamment du type de challenge alimentaire. De plus, la  $CCA_{ciblée}$  estimée du groupe CC a été très proche des observations faites. Pour le procédure de quantifier le réponse des animaux, les paramètres estimés à partir du

modèle ont confirmés les résultats de l'expérience selon lesquels la réponse des porcs à un régime alimentaire contaminé par la DON est influencée par l'âge ou le poids vif et par une exposition antérieure avec le régime contaminé par la DON, les porcs plus âgés ou plus lourds récupéraient plus rapidement que les porcs plus jeunes après la provocation à la DON. Les porcs qui avaient reçu le régime contaminé par la DON au début de leur vie ont été moins affectés quand recevant ce régime la deuxième fois et ils ont semblé de récupérer plus rapidement par rapport à ceux qui l'ont reçu pour la première fois. De plus, la résistance et la résilience au régime contaminé par la DON semblent être deux traits indépendants. Le modèle a prouvé sa capacité pour détecter et quantifier la réponse des animaux aux régimes contaminés par la DON et les caractéristiques de la réponse (résistance et résilience) peuvent être utilisés pour stratégies de sélection en élevages.

## Discussion

Le concept principal derrière ce modèle est que l'ingestion alimentaire réel d'un animal est une combinaison de la trajectoire cible et des écarts à cause des perturbations. La réponse et la récupération des perturbations de l'animal peuvent être quantifiées en séparant ces deux composants. Parce que le concept est générique, les différents éléments peuvent être adaptés si jugé nécessaire. Par exemple, le modèle actuel pour caractériser la réponse de l'animal suppose l'existence d'une période spécifique où la perturbation commence et s'arrête. Cependant, il peut y avoir des perturbations, tels que les agents pathogènes, où le début de la perturbation peut être identifié, mais il n'y a pas de fin claire. Au début, le pathogène provoque une réduction rapide des CJA mais, avec le temps, cet effet négatif peut être atténué parce que l'agent pathogène devient moins efficace par lui-même ou parce que l'activité du système immunitaire de l'hôte est plus élevée, même si l'agent pathogène peut encore être présent. Une telle réponse peut être représentée dans notre modèle en supposant qu'un agent pathogène a un effet immédiat sur la CJA à un moment explicite, mais que son effet sur la CJA diminue progressivement sans représenter un temps de la fin explicite de la perturbation. Dans ce cas, le mécanisme de réponse de l'hôte (ou l'effet de la perturbation) peut être modifié tandis que la structure du modèle et le nombre de paramètres à estimer restent les mêmes. Le choix d'un modèle de perturbation approprié ne peut pas être évident en considérant uniquement la CJA comme critère

de réponse. Des informations sur l'environnement des porcs (par exemple, la température comme indicateur de stress thermique) ou l'évaluation des réponses de CJA de tous les porcs dans une population, ou des indicateurs de l'état de santé de porcs individuels peuvent être utiles pour déterminer le modèle de perturbation le plus approprié.

La quantification des traits de résistance et de résilience est un élément important pour améliorer la capacité des animaux à se battre contre des perturbations environnementales. Il existe deux stratégies communes pour améliorer la robustesse des animaux: la sélection génétique et les pratiques de gestion. La thèse portait sur les données « historiques » et son impact potentiel est donc plus approprié pour la sélection génétique que pour les pratiques de gestion. Dans ce projet, nous avons défini deux traits potentiels qui pourraient être utilisés pour la sélection génétique: un trait de résistance lié à la réduction de la CJA en raison d'une perturbation et un trait de résilience lié à la capacité de rebondir par l'alimentaire compensatrice pour surmonter l'effet négatif de perturbation. L'approche a une application potentielle dans l'élevage d'animaux parce que les données nécessaires pour estimer ces caractères deviennent de plus en plus disponibles dans les exploitations commerciales. La procédure développée dans ce projet peut être appliquée à un grand nombre de porcs en croissance et combinée avec leurs informations de pédigrée. Ensuite, une analyse génétique quantitative peut être menée pour estimer l'héritabilité des traits de résistance et de résilience, leur corrélation génétique et la corrélation entre ces traits et d'autres traits de production et fonctionnels.

La procédure développée dans ce projet de thèse est basée sur des données « historiques ». Il est difficile d'appliquer cette procédure dans l'élevage de précision parce qu'un traitement des données en temps réel permet que les décisions soient prises en temps réel (par exemple, en termes d'alimentation ou de médicaments). Dans l'élevage de précision étant donné que l'ingestion (ou d'autres données) est générée en temps réel, il sera difficile d'extraire une trajectoire ciblée et des écarts par rapport à cette trajectoire ciblée à partir des données obtenues. Le délai au cours duquel les données sont accumulées pour calculer l'apport alimentaire cumulé est probablement trop long pour détecter les écarts en temps réel (et donc prendre les décisions de gestion correspondantes). Pour détecter les écarts en temps réel pour des animaux individuels, un délai plus court et d'autres caractéristiques de réponse (par exemple, les comportements alimentaires) seront nécessaires. De plus, un seul

trait de réponse ne peut pas être suffisant pour identifier les écarts par rapport à ce qui peut être considéré comme « normal » ou comme « perturbé ». Le développement rapide des technologies de capteurs fournira sans doute de grands volumes de données, et il sera difficile pour les modélisateurs d'identifier les « écarts par rapport à la normalité » de ces sources d'information, afin qu'une gestion appropriée mesurée puisse être prise en temps réel. Cette thèse de doctorat peut être un premier et petit pas vers cela, mais il reste encore beaucoup à faire.

En conclusion, ce projet de thèse a permis de développer une procédure d'analyse et de modélisation des données pour caractériser et quantifier la réponse de l'ingestion alimentaire des porcs en croissance aux perturbations à court terme. La procédure développée a prouvé sa capacité à quantifier la réponse du porc aux perturbations en testant avec les données d'une expérience où les porcs ont reçu des régimes avec ou sans céréales contaminées par la DON. Les résultats de cette thèse de doctorat ont le potentiel d'être appliqués davantage comme outil de phénotypage pour la sélection génétique ou comme composant de modèles pour étudier la réponse de l'animal aux perturbations aux niveaux sous-jacents (par exemple, métabolisme, partage des nutriments).

# Introduction

The explosion of human population over few decades has affected significantly livestock production. For instance, the use of human-edible crops in livestock feed has to be directly reduced to avoid the food-feed competition. Moreover, the rising in urbanization has inevitably reduced the area of available lands for livestock worldwide. With the prediction of FAO that human population will continue to increase in the next decades, livestock will undoubtedly be provided feed with lower quality and be kept in crowded herds. On the other hand, the increasing in frequency and intensity of perturbations due to global climate change and prevalence of pathogens has put even more pressure on the current livestock production. To sustainably control human's food security, environmental problems and animal welfare issues, instead of putting efforts on solely increasing productivity, livestock production needs to focus more on enhancing the robustness of animals.

Robustness is commonly defined as the capacity of an animal to maintain its high production potential under wide variety of environmental conditions and take short time to recover when faced to perturbations. Quantification of robustness is a prerequisite to improve this trait (e.g., through genetic selection and management practices). Quantification of robustness, however, is challenging because of its complexity, notably in the response to perturbations. The response of an animal to perturbations and the rate of its recovery, termed as resistance and resilience, have the dynamic characteristics so that single time-point measurements are not enough to characterize them. Recently, with the deployment of automatic monitoring technologies on farm, traits associated to animal's performance and other physiological and behavioural traits can be measured much more frequently. This provides an opportunity to quantify the dynamic aspect of animal's response to perturbations.

Feed intake measured is a promising candidate to quantify elements of robustness because it is the early response of animals to perturbations, is strongly related to animal's metabolic status and with the availability of automatic feeding stations on farm it can be measured at individual level, in very large groups and with a high frequency. Until now, however, information of feed intake recorded by automatic feeding stations has mostly been used to detect perturbations and not yet for quantification of the animal's response.

Given the complex of the interplay between perturbations and animals, mathematical modelling could be a suitable approach to represent and quantify the response of animal to perturbations. Also, for the purpose of genetic selection, modelling is beneficial for quantitatively phenotyping animals because it can summarize complex physiological mechanisms into few mathematical parameters. The objective of this PhD project was therefore to develop a data analysis and modelling procedure to detect the consequences of short-term perturbations on feed intake of individual growing pigs and quantify their subsequent feed intake responses in terms of resistance and resilience.

This PhD thesis consists of four chapters. In the **chapter 1**, a literature review was conducted to understand the concepts of robustness, of feed intake and mechanisms underlying responses of animals to perturbations. Current approaches in detection and quantification of animal's response to perturbations were also reviewed. Because feed intake data of growing pigs was chosen to develop the procedure, emphases were given to this species. The **chapter 2** described in details the development process of the data analysis and modelling procedure to quantify the response of individual growing pigs to an unknown perturbation. The procedure was then evaluated in **chapter 3** by applying it to feed intake data of growing pigs from an experiment, where they received diets with or without cereal contaminated with mycotoxins, to test the capacity of the procedure. Finally, some aspects related to modelling the response of animals to perturbations associated with data from other types of monitoring technologies and the potential to apply the procedure in genetic selection and management practices will be discussed in **chapter 4**.



# Chapter 1. Literature review

## 1. A robust animal

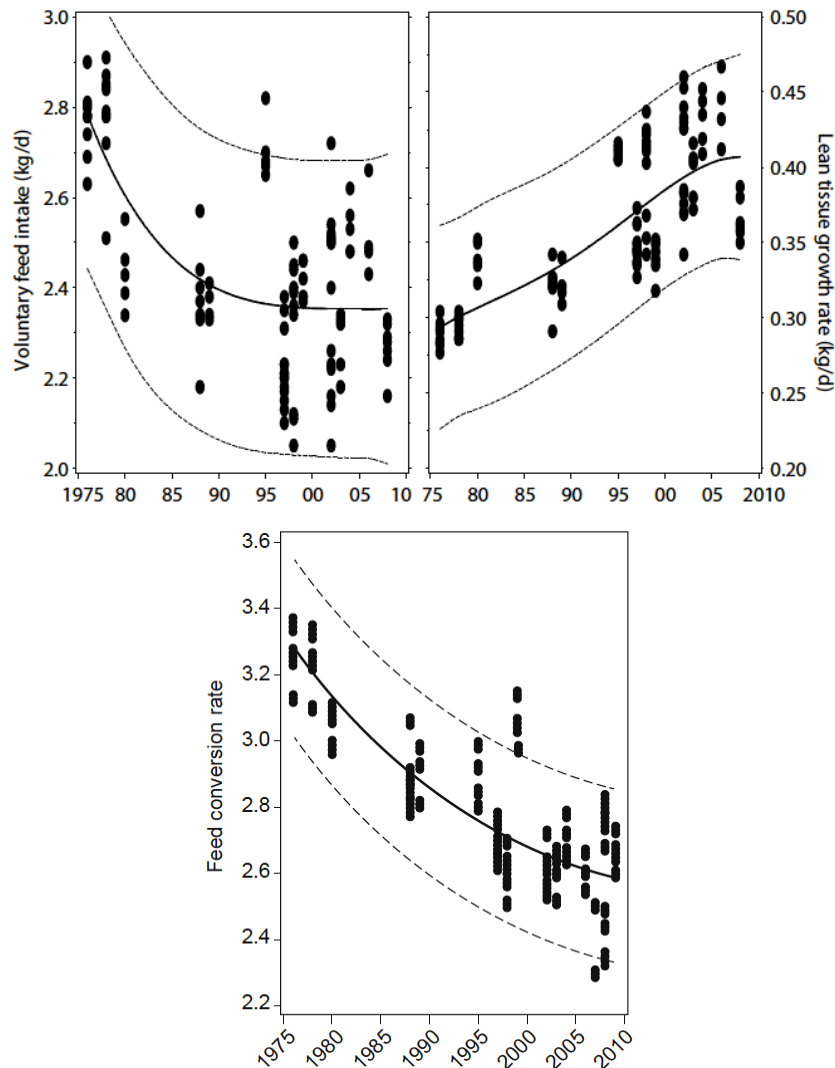
### 1.1. Why we need a robust animal

Livestock production has contributed largely to the world's food supply since World War II, and it is expected to sustain even more people in the future. The FAO (2009) predicted that by 2050 the world's population would reach 9.1 billion. Most of the increase in human population will take place in developing countries (Goldstone, 2010). Moreover, the rapid economic development in these countries will evidently give rise to an escalated demand for meat consumption. To feed this large human population in the near future, the world would need 70 percent more food than is available today. Meat production alone is expected to increase by more than double to reach 470 million tons per year (FAO, 2009). At the same time, urbanization is increasing at an accelerating rate and about 70 percent of the world's population would be urban by 2050 (FAO, 2009). In addition, the use of human-edible cereals will have to be reduced in animal feeds to avoid a feed-or-food competition. These figures indicate that future livestock sectors will have to produce more with fewer resources (i.e., be more efficient).

#### *Intensive livestock production*

The predominant approach to produce more animal products is intensive farming. The main objective of intensive farming is to maximize production with minimum cost (Luiting, 1990; Ten Napel *et al.*, 2006). Production and efficiency potential of animals have been optimized (amongst others) through genetic selection. Breeding for efficiency indeed results in a successful increase in animal production. An example of genetic improvement in pig production is shown in Figure 1.1. This figure shows that across countries and genetic resources, voluntary feed intake of growing pigs has decreased from 2.8 kg/d in 1975 to 2.4 kg/d in 1990 and followed by a stabilization. Meanwhile lean tissue growth rate continuously increased from 0.3 to 0.4 kg/d and feed conversion ratio gradually decreased from 3.3 to 2.6 over the period of 35 years. Similar to pig production, other species also witness a substantial improvement in production over the past decades. For instance, carcass weight per animal has

improved around 30% for broiler and beef cattle; meanwhile, milk and egg productivity have improved around 30% (Rauw *et al.*, 1998; Rauw, 2012). With the fast development of genetic techniques such as genomic selection combined with the availability of large database, it seems that there is still a potential for more productive and efficient animals (Rauw, 2012).



**Figure 1.1** Trends of change in voluntary feed intake, lean tissue growth rate (upper graphs – Knap, 2009) and feed conversion rate (lower graph – Knap and Wang, 2012) in growing pigs of 103 terminal crosses over 35 years in Denmark, France, Germany, the Netherlands, the UK and the USA. Dots are mean observations of terminal crosses, solid lines are general trends and dashed lines are their 95% confidence limits.

However, in contrast to a great achievement in improvements in production and efficiency, unfavourably side effects of selection to that direction have become more and more apparent. Selection for high efficiency puts animals at more risk of

behavioural, physiological, and immunological disorders (Rauw *et al.*, 1998; Van der Most *et al.*, 2011; Rauw, 2012). According to the Resource Allocation theory, resources are limited and if it is used primarily for one function (e.g., growth) it is less available for another function (e.g., immunology) (Beilharz *et al.*, 1993). Rauw (2012) stated that selection towards a high production in animals has shifted the allocation of resources to a undesirable direction for fitness functions. The performance and fitness of animals therefore depend mainly on the environment where they live in.

As the environment is constantly changing in nature, controlling methods are widely applied in (intensive) livestock production to prevent animals from exposure to perturbations that could deteriorate their performance such as exposure to pathogens or extreme weather (Ten Napel *et al.*, 2006; De Goede *et al.*, 2013). In well-controlled systems, animals are kept constantly indoors where they can receive antibiotics and disinfection treatments not only for cure but also for prevention (at least in Asia). Although this combination can improve production and efficiency in the short term, long-term drawbacks have started to emerge. For example, over use of antibiotics and disinfections can create resistant bacteria and damage the micro fauna; keeping animals in high stocking density can raise social concerns on animal welfare and makes them more susceptible to infectious diseases. More importantly, despite efforts have been made in controlling the environment, farm animals still encounter many exogenous perturbations such as periods of heat stress resulting from global climate change, that are increasing in both intensity and suddenness (Hansen *et al.*, 2012; Wingfield, 2013) and the mutation of bacteria and viruses is happening very quickly. Animals are therefore becoming increasingly vulnerable to these perturbing elements.

In short, intensive livestock production focuses on optimizing the potential of animals while trying to control the environment around them. If animals were not exposed to disturbances, they could maximize their production potential as expected from their genetic potential. Nevertheless, the environment has become increasingly variable and uncertain, that compromise the production of animals. Increasing the production potential of animals may no longer be an ideal (or only) approach to ensure food security in the future. Therefore, besides the need to produce more with fewer resources, future farmers will certainly have to find more sustainable solutions to limit negative impacts on the environment, human health, and animal welfare.

## *Sustainable livestock production*

In recent years, the need for implementing more sustainable livestock farming practice has increased substantially. To make livestock production systems more sustainable, the focus should be on improving the animal's capacity to adapt to perturbations in the environment rather than trying to eradicate their sources (Ten Napel *et al.*, 2006). For this purpose, the intrinsic capacity of animals should be maximized so that animals can deal with (and adapt to) various environmental conditions (Ten Napel *et al.*, 2006). The intrinsic capacity of an animal to maintain its functionality under a wide range of environmental conditions is commonly termed robustness (Knap, 2005; De Goede *et al.*, 2013). A robust animal is an animal that can deal with disturbances itself, and can maintain its production potential in a wide range of environmental conditions. Raising more robust animals therefore can limit the negative impacts on animal health and welfare while meeting demands of consumers and citizens.

This robustness characteristic in animals can be promoted by management practices (i.e., support and encourage the expression of animal's intrinsic capacity) and genetic selection (i.e., improve the genetic adaptation potential of animals). Examples of management strategies are: applying biosecurity on farm; providing multiple micro-climatic areas in the production facilities so that animals can find locations that suit them best; training young animals to deal with stressors by exposure to minor perturbations early in life; enriching farm facilities to encourage inquisitiveness of animals and to build up their immune-competence by vaccination (Ten Napel *et al.*, 2011; Colditz and Hine, 2016). The advantage of genetic selection over management is that the improvements have effects on all successive generations (Berghof *et al.*, 2018). Knap (2005 and 2009) proved that breeding for robust animals is feasible and suggested that sustainable breeding objectives should combine selection traits for robustness with production efficiency to an extent that can balance production potential with environmental sensitivity. Improving robustness through genetic selection and/or management practices both require to measure and quantify robustness precisely. In order to quantify robustness, it is imperative to gain better understanding about this term and related factors, which will be dealt in the next sections.

## 1.2. What is a robust animal

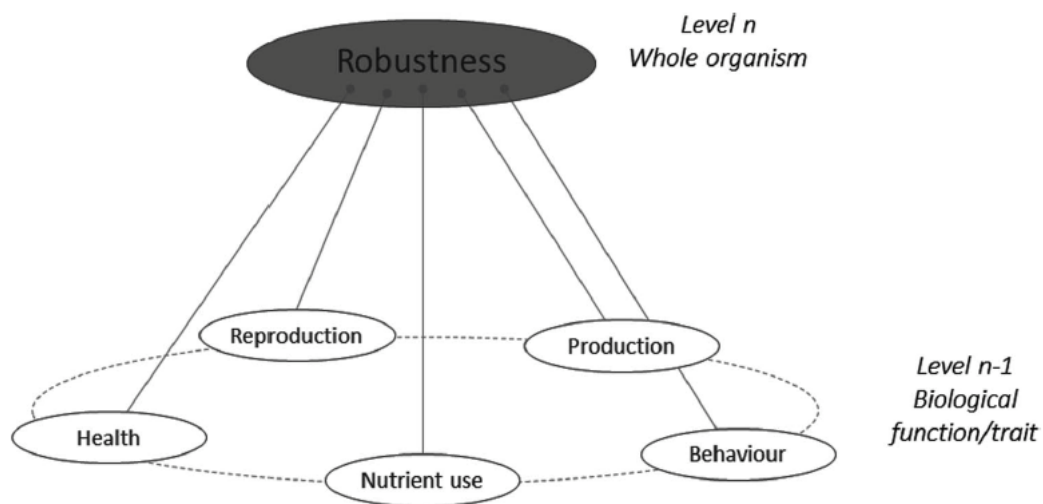
Over the past decades, robustness has received a remarkable interest in animal science. A prerequisite to quantify and measure robustness in farm animals is a clear understanding of its definitions and related concepts.

### *Defining robustness*

Knap (2005) defined a robust pig as: an animal that can incorporate its high production potential with resilience to exogenous stressors in order to maintain its production potential un-problematically in a wide range of environmental conditions. In his definition, two elements of robustness are highlighted: “*high production potential*” and “*resilience to exogenous stressors*”. Maintaining a high production potential is important because it refers not only to the economic value but also to the normal expression of the animal’s functions. Resilience helps an animal to cope with different environmental stressors and thus keep “producing” (i.e., growing, reproducing, producing milk, laying eggs). In accordance with Knap (2005), Star *et al.* (2008) defined a robust laying hen as “*an animal under a normal physical condition that has the potential to keep functioning and take short periods to recover under varying environmental conditions*”. The capacity to “*take short periods to recover*” resembles resilience in the definition of Knap (2005). Resilience was described by Colditz and Hine (2016) as the capacity to be minimally affected by transient and sporadic perturbations and/or quickly recover back to the behavioural, physiological, and neurological situation before perturbed conditions. De Goede *et al.* (2013) considered robustness as a stability of a system. This stability refers to the ability to maintain structure and/or function of a system despite external and internal perturbations. To maintain this stability, animals rely on three main key elements: constancy, resistance, and resilience. Constancy refers to the stability of the system without the presence of perturbations whilst resistance and resilience denote the capacity to withstand under perturbing impacts and quickly return to the stabilized position when the perturbing factors are over (De Goede *et al.*, 2013).

A broader definition of robustness was given by Friggens *et al.* (2017) as: “*the ability, in the face of environmental constraints, to carry on doing the various things that the animal needs to do to favour its future ability to reproduce*”. In this definition, Friggens *et al.* (2017) focused on three important key elements: “*future ability to*

*reproduce*”, “*various things that the animal needs to do*” and “*carry on doing*”. Firstly, to favour its “*future ability to reproduce*”, the animals need to grow (to become mature), to survive (to have the possibility to reproduce), and to succeed in reproducing. The second key element “*various things*” indicates multiple functional components that an animal needs to invest resources in, to obtain these aforementioned goals (Figure 1.2). As described in the previous section, resources are often limited and cannot be distributed to all biological functions (Beilharz *et al.*, 1993). Therefore, an animal cannot be robust to all types of perturbation and trade-offs between different functions exists (Friggens *et al.*, 2017). This implies that investing more resources to one function necessarily decreases the investment of resources for another function. A robust animal is an animal that can allocate resources to the right function at the right time. This regulation of resource in the context of robustness relies on the mechanism of resource allocation and/or acquisition (Friggens *et al.*, 2017). The last key element “*carry on doing*” signifies the resistance and resilience abilities to cope with environmental perturbations.



**Figure 1.2** Robustness of the whole animal level (level n) is built from the combination of multiple functional components below (level n-1) (Friggens *et al.*, 2017).

Infectious diseases are among the most detrimental perturbations, which can have devastating effects on animals and their production. There are two defence mechanisms in relation to robustness that animals can exploit to combat infectious pathogens: host resistance and host tolerance. Resistance to pathogens consists of the mechanism that minimizes pathogen load in the host (e.g., by inhibiting the

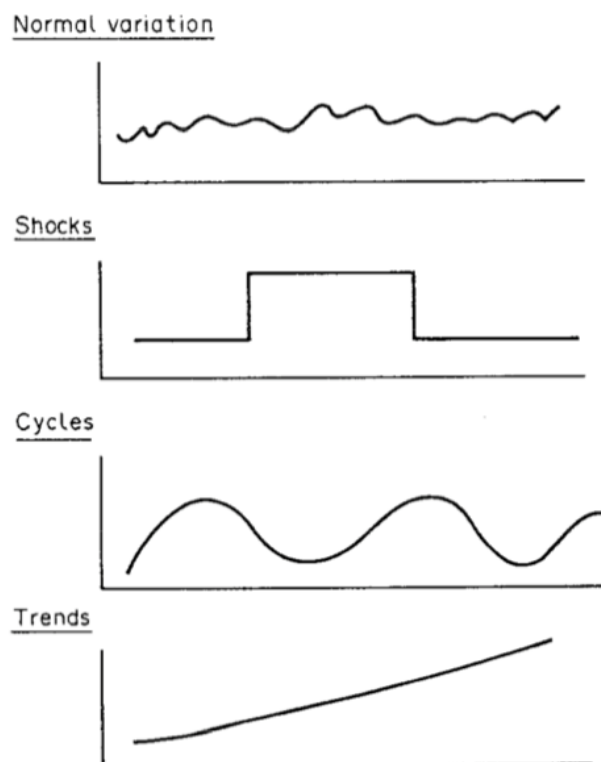
pathogen to enter the host or by decreasing pathogen replicating) (Doeschl-Wilson and Kyriazakis, 2012). Tolerance indicates the capacity to limit the harmful impact of pathogens on the host, without necessarily effecting pathogen load. Repairing and inhibiting cell damage are the main mechanisms of tolerance (Doeschl-Wilson and Kyriazakis, 2012). Resistance mechanisms are often disease-specific whilst tolerance mechanisms are more intrinsic to the host and thus more generic to a variety of infections. Although host resistance and host tolerance are considered to have an antagonistic relationship (Doeschl-Wilson and Kyriazakis, 2012), they are two elements that both occur in the animal. In farm condition, these two capacities are not independent of the animal's response to environmental perturbations (Salak-Johnson and McGlone, 2007) and the effects of all perturbations are cumulative on the host (Black *et al.*, 2001).

All aforementioned studies are illustrations that robustness is a complex concept that encompasses many phenomena that relate to the ability to adapt to external and internal perturbations so that the animal can maintain its functionality and production. This PhD thesis focuses on two robustness's elements to counteract the impact of perturbation: resistance and resilience. In the scope of this PhD thesis, resistance is defined as the capacity to be minimally affected by perturbations while resilience is defined as the capacity to quickly return to a pre-perturbed state.

### *Perturbations that affect animals*

As mentioned above, there is little need for robust animals in well-controlled farming systems when animals are rarely exposed to any perturbation. Robustness is therefore not expressed in the absence of perturbations. Different types of perturbing factors exist, with different types of response of the animal. Perturbations can be classified as external (i.e., the environment around an animal) or internal (i.e., within the animal), acute (e.g., encounter a predator) or chronic (e.g., climatic events), transient (e.g., day-to-day variation in ambient temperature, human disturbance) or long-term (e.g., infection, injury), and predictable (e.g., changing seasons) or unpredictable (e.g., diseases) (Ten Napel *et al.*, 2011; Wingfield, 2013; Friggens *et al.*, 2017). Ten Napel *et al.* (2011) grouped perturbations into four types (adopted from Maxwell, 1986) (Figure 1.3):

- Noise: perturbations that are frequent in the environment with a transient magnitude (e.g., change in feed ingredients, temperature variation within the comfort zone). This type of perturbation is referred to as normal variation to animals.
- Shocks: perturbations that are unusual either in occurrence or magnitude (e.g., weaning, mixing animals). The frequency of a shock determines its predictability.
- Cycles: perturbations due to cyclical changes in the environment or concerning the animal (e.g., diurnal or seasonal changes in weather, oestrous cycle).
- Trends: changes over time that have a gradual effect on the animal (global warming, decreased available space for a pig during the growing period).



**Figure 1.3** Four types of perturbations (Maxwell, 1986). See related text for detailed explanations.

The distinction between the types of perturbation depends not only on the occurrence and magnitude of the perturbation, but also on the perception of animals (Ten Napel *et al.*, 2011). For example, experiencing a dazzle sunlight in an indoor environment could be perceived as noise by one animal and as a shock by another.



## *Mechanism underlying robustness*

Maintaining a more or less constant level of physiological functions regardless of the perturbation is the key component of robustness. Claude Bernard, a French physiologist in 19<sup>th</sup> century, was the first to elucidate the ability of an animal to maintain a relative equilibrium level of multiple endogenous functions (e.g., body temperature, body fluid and energy) or “*milieu intérieur*”, irrespective of external fluctuations. Walter Canon (1929) later named this capacity as homeostasis – the vital principle of physiological balance. Homeostasis refers to an active process involved multiple physiological systems to monitor and maintain the interior environment within a critical range (Nelson and Kriegsfeld, 2017). The homeostatic regulatory mechanisms of internal environment are based on negative feedback systems (Rosenblueth *et al.*, 1943). These negative feedback systems function like a thermostat. When the room temperature drops below the “set point” of the thermostat, the heater is activated to warm the room up. As soon as the room temperature gets close to the set point, a negative feedback is sent to the thermostat to inhibit the heater from producing more heat (Nelson and Kriegsfeld, 2017). There is a tolerance range (or set zone) around the set point, which prevents the thermostat from sending the warming or cooling signals too frequently (Nelson and Kriegsfeld, 2017). For example, although the set point in human body temperature is 37°C, we are also doing fine in the set zone between 36 and 38°C.

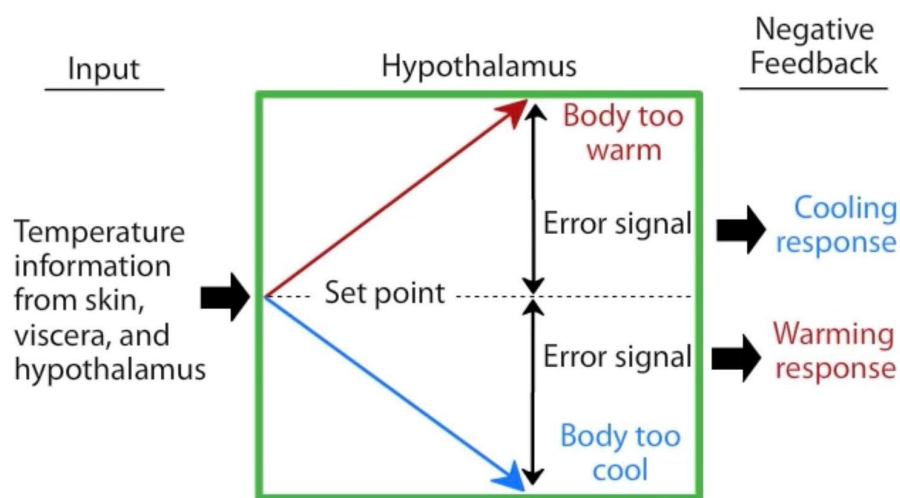
An example of homeostasis in warm-blooded animals is the regulation of body temperature (Figure 1.4). The main thermostat of endotherms (i.e., animals whose body temperature is regulated by interior metabolisms, like mammals and birds) is the hypothalamus. If the body temperature deviates out of the set zone, the hypothalamus triggers various behavioural and autonomic responses to maintain homeostasis (Nelson and Kriegsfeld, 2017). For instance, when the body temperature drops below the set point, the hypothalamus commands multiple organs to generate more heat and to reduce heat loss by:

- Increasing feed intake
- Constricting blood vessels in the body surfaces (to restrict heat lost)
- Shivering muscles
- Stimulating thyroid hormones to increase the metabolic rate

- Breaking down brown fat (which generates heat)
- Huddling with conspecifics

Conversely, when the body temperature rises above the set point, the hypothalamus instructs the body to perform a cooling response:

- Decreasing feed intake (to reduce heat production)
- Dilating blood vessels in the body surfaces (to release heat)
- Sweating (for evaporative cooling)
- Panting
- Avoiding physical contacts



**Figure 1.4** The regulation of hypothalamus to maintain homeostasis (Nelson and Kriegsfeld, 2017). Receptors in the skin, in the viscera and in the hypothalamus transfer information about the temperatures to the hypothalamus. The hypothalamus works like the thermostat, which integrates the information and compares the desired body temperature to its set point. Deviations (both positive and negative) of the actual body temperature from the set point of the hypothalamus trigger response signals that command multiple organs to warm up or cool down the body temperature back to the set point. The negative feedback system works continuously like a loop to maintain homeostasis for body temperature.

Perturbations can occur in the environment at any point in time and space. Any perturbation causing a change in the homeostatic state demands a response of an individual to regain the equilibrium condition. The response to a perturbation may require energy and energy that is not essential for survival may be directed to cope

with the perturbation. As mentioned in the previous sections, perturbations can occur at different points in time, and with differences in duration and magnitude. The mechanisms that an animal uses to cope with two main types of perturbation are explained below: (1) transient, acute perturbations (i.e., noises and shocks), which have short-term effects and provoke a rapid response of the animal and (2) long-term, chronic perturbations (i.e., cycles and trends), which force an animal to multiple physiological responses to cope with the perturbations.

### **Responses to transient, acute perturbations**

An animal can respond extremely quickly to an acute threat by a set of physiological and behavioural responses, termed as a stress response (Nelson, 2011). The stress response is executed in a nonspecific manner (i.e., different perturbations can provoke a similar response) to re-establish homeostasis (Selye, 1956). Two main endocrine groups are involved in the stress response: catecholamines (epinephrine and norepinephrine) and glucocorticoids (Nelson, 2011). Almost immediately after perceiving a perturbation (e.g., encountering an aggressive pen-mate), norepinephrine and epinephrine are secreted by the sympathetic nervous system and the two adrenal medullas, respectively. The immediate release of catecholamines increases the cardiovascular and respiratory rates of the animal, and provoke an escape or defend behaviour. Few minutes later, glucocorticoids are secreted through the activation of the hypothalamic-pituitary-adrenal (**HPA**) axis. The raise in glucocorticoids has an effect on metabolism and mobilises body energy reserves to fuel the “*fight or flight*” behaviour (Cannon, 1929). Other activities not directly related to the immediate survival (e.g., food intake) are suspended until the animal is no longer in danger.

The stress response is not specific for a perturbation, but can be different among individuals. Koolhaas *et al.*, (1999) indicated that individuals can differ in their coping styles (i.e., a set of coherent and over-time-consistent behavioural and physiological responses to perturbations), which may be classified as proactive and reactive coping styles (Koolhaas *et al.*, 1999). In general, proactive copers show more active behavioural activities (e.g., escape attempt and aggression), higher sympathetic reactivity (e.g., high levels of catecholamines), and lower HPA axis reactivity (e.g., low levels of plasma corticosterone) (Koolhaas *et al.*, 1999; Coppens *et al.*, 2010). In contrast, reactive copers display more passive behavioural activities (e.g., freezing and

withdrawal), higher para-sympathetic reactivity, and higher HPA axis reactivity (Koolhaas *et al.*, 1999; Coppens *et al.*, 2010). Therefore, the proactive coping style is considered as a more aggressive, rigid and routine-like style while the reactive coping style is expressed as a more adaptive and flexible type and only when a response is really necessary. A specific coping style does not guarantee a successful coping with a perturbation. These two concepts describe only the difference in the strategy an animal recruits to deal with perturbations. One coping style may be more successful for a certain perturbation environmental than another. For example, proactive copers are more suitable under constant and predictable conditions while reactive copers are more thriving under variable and unpredictable conditions (Koolhaas *et al.*, 1999).

### **Response to long-term, predictable perturbations**

Not all perturbations are unpredictable because some perturbations have cyclical or persistent effects that can be anticipated (i.e., perturbations categorised as cycles or trends). Some species have developed the capacity to prepare for predictable perturbations. For instance, many livestock species change their fur formation according to the seasons, i.e. development and maintenance of a long, thick hair cover is seen in winter and *vice versa* is the case in summer. Animals anticipate seasonal changes by weather cues and modify their hair coat in advance, e.g. in cattle the growing rate of long hair is related inversely to photoperiod whilst the rate of shedding hair is associated with animal's thermal status (Webster, 1974). The anticipation of predictable perturbations is indicated also by the animal's capacity to reserve energy in the body during favourable conditions and then mobilise it in unfavourable conditions. For example, in tropical environment, the capacity to store fat during the wet seasons where pasture has better quantity and quality is essential for grazing sheep to survive during the dry seasons (Mirkena *et al.*, 2010).

A more familiar example with industrial production is metabolism in lactation. Cows and sows accumulate body reserves during pregnancy and then mobilised them in early lactation. The successful transition from pregnancy to lactation relies on a series of physiological adaptations that involves the activity of almost all tissues (Collier *et al.*, 2005). If the animal is not able to mobilise energy reserves rapidly enough to balance the demand for milk production, her production will be below the demand (of the offspring or of the farmer) and the health and well-being of the mother or of the offspring may be compromised (Bauman and Currie, 1980). For example, in cows if there is an

imbalance between the supply of glucose precursors (e.g., propionate) and demand for glucose in lactose, the cow might be susceptible to develop metabolic disorders (e.g., ketosis). To provide a sufficient amount of glucose for lactation, a series of orchestrated changes is put into place such as increasing gluconeogenesis while decreasing uptake, utilization, and oxidation of glucose by adipose tissue and muscle (Collier *et al.*, 2005). In adipose tissue, lipogenesis is decreased and lipolysis is increased to provide lipid as an alternative energy source to glucose. The orchestration of metabolic changes in body tissues to prioritise a particular physiological stage is termed homeorhesis by Bauman and Currie (1980) or allostasis by others (Sterling, 1988; McEwen and Wingfield, 2003). A key feature of the homeorhetic control is that its effect lasts over several hours, days or even weeks instead of seconds and minutes (as is the case for most events of the homeostatic regulation). It has a simultaneous effect on multiple tissues and systems that result in an overall coordinated response (Bauman and Elliot, 1983; Vernon, 1989; Bell and Bauman, 1997). Therefore, homeorhesis is considered as the major mechanism that regulate long-term adaptation and acclimatisation for cyclical or persistent perturbations (Collier *et al.*, 2005; Collier *et al.*, 2008).

In summary, homeostasis and homeorhesis are the main mechanisms to maintain internal status of an animal. While the homeostatic mechanism ensures the short-term equilibrium, homeorhesis orchestrates resources to prioritize a physiological stage and acclimatizes over long-term perturbations. Understanding and accounting for these two concepts facilitate the quantification of robustness in animals.

### 1.3. Identify reliable indicators for animal robustness

Quantification of robustness is imperative for improving it in farm animals, especially for breeding programmes. It is difficult to quantify robustness because of its dynamic elements such as the rates of response to and recovery from perturbations (Friggens *et al.*, 2017). Traditional methods using single time-point measurements are not suitable to quantify robustness. For instance, Spurlock *et al.* (1997) conducted an experiment to study the negative effects of lipopolysaccharide (a bacterial endotoxin) on growth performance of growing pigs. They reported and analysed data over weekly periods whilst the reduction in performance lasts only a few days (Spurlock *et al.*, 1997). With this period of measurement, effects of the pathogen on the host may be

cancelled out by the host's ability to recover (Kyriazakis and Doeschl-Wilson, 2009). More frequently and repeated measurements are needed to quantify the dynamic aspects of robustness (Knap, 2009; Friggens *et al.*, 2017).

Some experiments were conducted in which perturbations were imposed to animals (Sadoul *et al.*, 2015a; Friggens *et al.*, 2016). Before, during, and after a perturbed period, multiple physiological and behavioural traits were repeatedly recorded to identify the physiological mechanisms underlying the responses of the animal. In comparison to the short-term responses of two rainbow trout lines, Sadoul *et al.* (2015a) carried out a confinement challenge to provoke a stress response of the fish. Behaviour, cortisol levels, and oxygen consumption were recorded every 2 hours. They found significant differences in cortisol reactivity over time between two lines, which were consistent with the physiological and behavioural responses of two different coping styles (i.e., proactive vs. reactive coping). Friggens *et al.* (2016) conducted an experiment in which dairy goats were fed a very low nutrient diet (i.e., only straw) for 2 days in early and late lactation. Production traits (e.g., feed intake, body weight and milk yield) and blood metabolites were measured daily. They reported significant variation among individuals in terms of dry matter intake (**DMI**) and milk yield to the same nutritional challenge. They suggested to cluster the adaptive capacity of animals based on multiple traits.

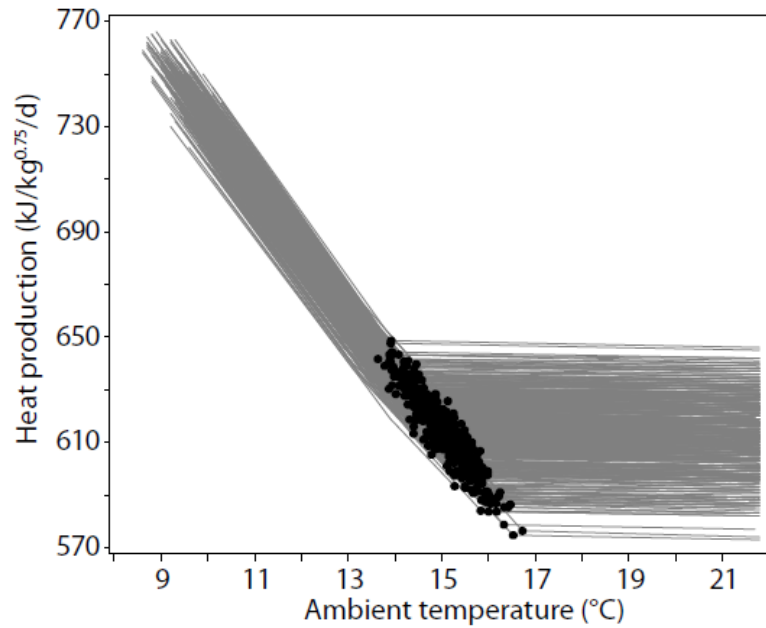
Quantifying robustness based on experiments often depends on the nature of the investigated perturbations or on the coping style of the animals (Colditz and Hine, 2016). Phenotypes characterized as being robust can be too specific to one particular type of perturbation (Berghof *et al.*, 2018). Moreover, to implement a robustness trait in a breeding program, measurements have to be done on a very large number of animals to determine the heritability of the robustness trait (Star *et al.*, 2008). Measuring behaviour and taking blood samples at the individual level are very expensive and labour-intensive. These measurements can be made in experimental settings and they can help in gaining insights in the physiological mechanisms underlying the response. However, it is often difficult to apply them in breeding programs.

To breed against disease susceptibility, several immunological traits have been considered. These traits have shown to be correlated not only with survival (Berghof *et al.*, 2015) but also with performance (Clapperton *et al.*, 2009). They are heritable and can be used for selection (Clapperton *et al.*, 2009; Flori *et al.*, 2011; Berghof *et al.*,

2015). Reed and McGlone (2000) exposed two genetic lines of pigs with the same immune status to different environments and reported difference in the immunological responses. This implies that immunological traits can be indicative not only of disease resistance but also of the response to changes in environment (Guy *et al.*, 2012). However, similar to traits extracted from experimental designs, immunological traits may be pathogen-specific, since the immune system responds differently to different pathogens (Salak-Johnson and McGlone, 2007). Selection for improving the immune response to one pathogen may cause antagonistic effects on others (Guy *et al.*, 2012). For instance, when challenging two divergent selected lines of pigs for high and low immune response with *Mycoplasma hyorhinis*, the high response line showed greater incidence of arthritis (Magnusson *et al.*, 1998), accusing a side effect of selection for a higher immune activation. Potentially immunological markers therefore need to be examined critically before using these to quantify robustness and resistance.

The recent progress on farm automatic monitoring technologies make it possible to collect longitudinal data from production traits such as feed intake, body weight, and milk yield. There are three advantages of using production traits to assess resilience and resistance relative to using physiological, behavioural, and immunological traits. Firstly, these production traits can be measured without contention of the animal and without invasive techniques. Secondly, they can be measured automatically on a large scale and with a very high frequency (e.g., up to level of each visit to the machine). Thirdly, production traits are sensitive to environmental perturbations and, because of the high frequency of measurements, the dynamics of the response to the perturbation can be measured (Codrea *et al.*, 2011; Munsterhjelm *et al.*, 2015; Friggens *et al.*, 2016).

Among production traits, voluntary feed intake has emerged as a potential candidate to study robustness in growing pigs for the two following reasons. Firstly, reduced voluntary feed intake is seen as the early response of animals to perturbing factors (e.g., reduction in body weight is normally seen few days after feed intake is decreased). Secondly, voluntary feed intake is considered as “*the most easily measurable trait to reflect the day-to-day dynamics of the animal’s metabolism*” (Knap, 2009). An example of a relationship between heat production of growing pigs and ambient temperature is given in Figure 1.5.



**Figure 1.5** Relationship between heat production and ambient temperature of 500 simulated growing pigs shared the same genotype (Knap, 2009). Each black dot refers to the lower critical temperature of one pig in relation with its heat production (illustrated by each grey broken line).

The variation shown in Figure 1.5 indicates that the lower critical temperature differs among growing pigs. Different pigs increase their heat production (and in turn their feed intake) at different ambient temperature (Knap, 2009). Temperature is just an example of an environmental factor that can affect the metabolic status of animals and different environmental factors are expected to have different critical points (i.e., the points that trigger a change in the metabolic status). Because of variation among animals and in a given environment, several critical points may be attained for a less robust animal while none may be attained in a more robust animal. This difference can be a source of variation between individuals in response to the environment (Knap, 2009).

In conclusion, we need to identify (a) reliable indicator(s) of robustness that reflects its dynamic characteristic of the response of the animal to perturbations. A new type of data – longitudinal data – automatically recorded by modern monitoring technologies on farm can aid the quantification of elements of robustness such as the rates of response to and recovery from environmental perturbations. A potential indicator of the animal's response to perturbations is the voluntary feed intake because it responds to



different perturbations and it can be recorded rather easily and continuously in group-housed animals.

## 2. Using feed intake as an indicator of robustness

Feed intake reflects the acquisition of resources needed for maintenance, growth, and reproduction. The relationship between feed (and energy) intake and the requirements for the aforementioned functions is tightly controlled. If the feed intake differs from the requirement for these functions, homeorhesis will be impaired. Nevertheless, there is considerable day-to-day fluctuation in feed intake and feed intake responds very rapidly to changing environmental or internal conditions (e.g., heat stress, fever). Understanding the main principles of feed intake regulation and factors that affect feed intake is important to assess it and to quantify the animal's response to a perturbation.

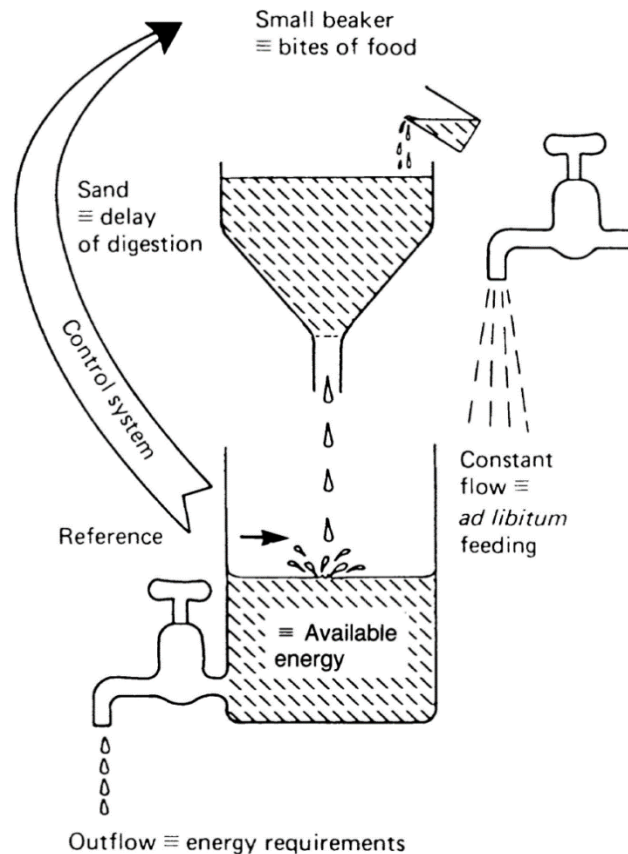
### 2.1. Main principles of feed intake regulation

Feed intake is a complex process resulting from short-term and long-term regulations. The meal is considered as the most relevant unit of short-term feeding (Tolkamp *et al.*, 2000). Much research in this field has focused on the understanding whether meal initiation is regulated by hunger or by satiety. This question can be addressed by investigating correlations of meal size with intervals before or after feeding (i.e., pre- and post-prandial correlations, respectively) (Maselyne *et al.*, 2015). If satiety is the main driving factor for the initiation of feeding, an animal is expected to start eating again when its satiety drops below a certain critical point (i.e., the meal size is highly correlated with the post-prandial interval). In contrast, if hunger motivates feeding, an animal is supposed to adjust its meal size according to the time since the last feeding (i.e., a high correlation is anticipated between meal size and the pre-prandial interval). In fact, post-prandial correlations with meal size were found in a large number of studies across animal species (Duncan *et al.*, 1970; Davies, 1977; Natelson and Bonbright, 1978; De Castro, 1981; Tolkamp *et al.*, 2000; Tolkamp *et al.*, 2012) and pre-prandial correlations with meal size were only found in some specific situations (Levitsky, 1974; Slater, 1974; Bokkers and Koene, 2003). This suggests that satiety is the main control factor of feeding motivation. Because the probability of starting a new meal after feeding depends on the satiety condition, this probability is low directly after

a meal and will increase with time. It is also related to the size of the meal that was just ingested (postprandial correlation) (Tolkamp *et al.*, 2012; Maselyne *et al.*, 2015).

Although the initiation and cessation of a meal are considered as the short-term responses to hunger and satiety, the fundamental principle of long-term feed intake regulation in the relation to growth are yet to be defined. The question of whether animals grow because they eat or animals eat because they want to grow has been a subject for discussions among nutritionists over a long period of time (Halas *et al.*, 2018). Eating-for-growth suggests that an animal has a genotypic desire to grow and voluntary feed intake is driven by the need of the animal to meet the nutrient demands. The capacity to eat may be constrained by limiting factors in the diet and by the environment (Emmans, 1991; Kyriazakis and Emmans, 1999). The hypothesis that feed intake of each animal is driven by its own genetic potential to growth seems to be supported by the observation that genotypes have huge effects on feed intake of pigs despite the fact that they were raised in the same environments and were fed the same diets (Schinckel, 1994).

There is a theory that the energy status of the body is the main factor that regulates short-term feed intake. Forbes (1986) represented this relationship by a hydraulic model in which energy regulation is demonstrated by water flow (Figure 1.6). The open tap with a constant flow of water denotes food availability (e.g., in *ad libitum* regime). The funnel filled with sand represents the interval from ingestion to absorption and the small beaker that carries water from the open tap to the funnel represents the frequency and quantity of food consumption. The accumulation of water in the reservoir indicates the filling of a pool of available energy in the body. The drain tap at the bottom of the reservoir indicates a depletion of available energy for metabolism activities. The arrow on the side of the reservoir in Figure 1.6 indicates a reference point of the control system that determines when animals should start eating again, i.e., when the water level is below that arrow in the reservoir beakerfuls of water will be transferred from the open tap to the funnel. The phenomenon that water is delayed in the funnel (because of the sand layer) and slowly seeps into the reservoir represents the prolonged satiety after each meal. This concept of controlling food intake was applied by Toates and Booth (1974) to simulate feeding patterns of rats under different energy supply conditions and the model fitted data satisfactory.

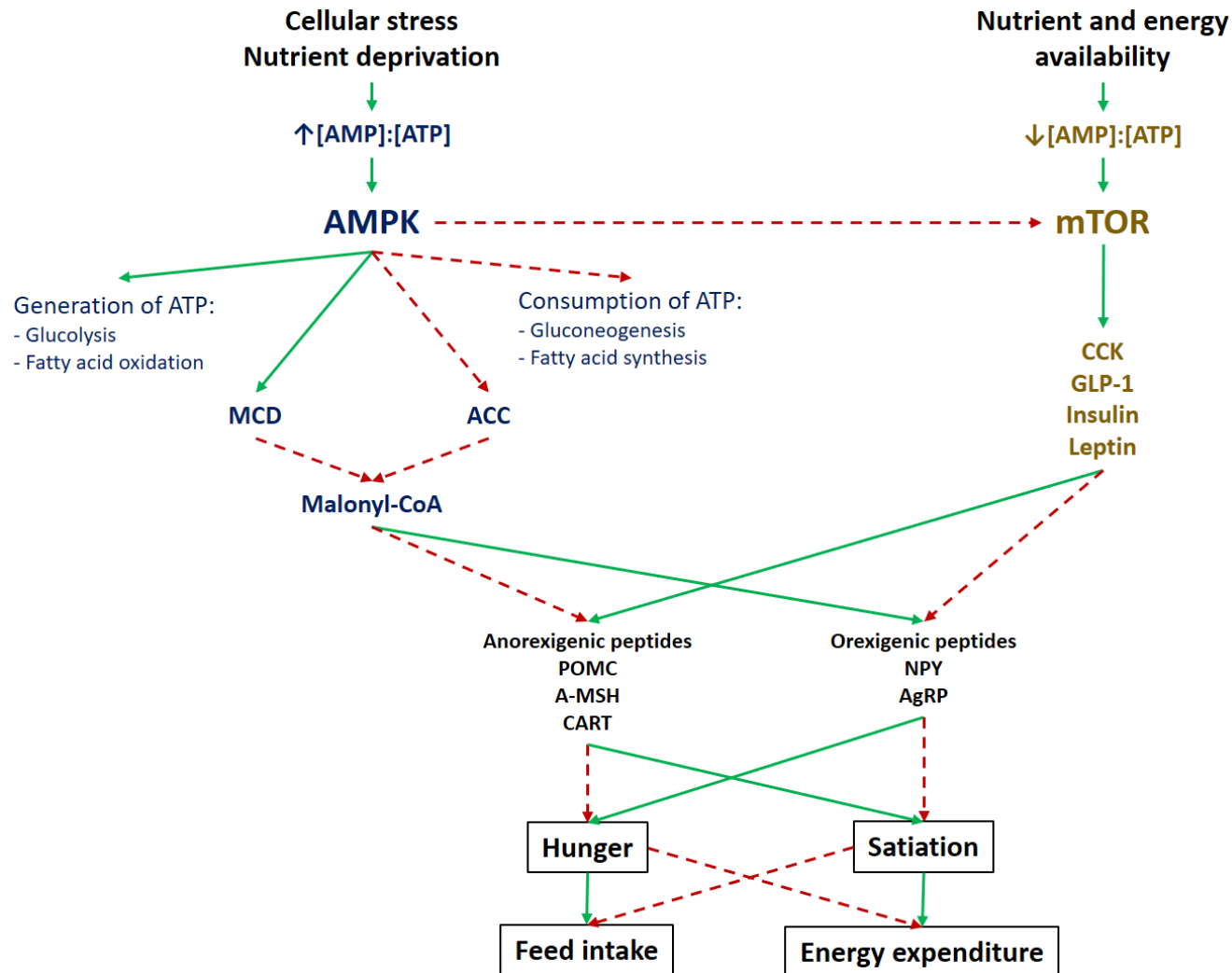


**Figure 1.6** A hydraulic model of the control of energy status in the body on food intake (Forbes, 1986). See related text for detailed explanations.

Physiologically, nutrients and their metabolites are the main factors that control short- and long-term feed intake via direct or indirect hormonal secretions that interact with local and central neural processes. Black *et al.* (2009) gave an extensive review on this topic and the main factors that control feed intake are briefly summarized below. Hormone secretions from the gastrointestinal tract and the pancreas respond to nutrients such as carbohydrates, fats, proteins and products of digestion. The hormones act collectively to control meal size mainly by termination of eating through the jejunal, ileal, and/ or colonic brakes that help to reduce gastric emptying as well as propulsive contraction along the gastro-intestinal tract. Many of these nutrient-stimulated hormones are also active via the vagal nervous system or directly on specific regions of the brain to effect feed intake in the long term (Black *et al.*, 2009).

The main metabolic regulation of long-term feed intake is under the control of two opposing energy-monitoring systems: (1) adenosine monophosphate activated protein kinase (**AMPK**) and, (2) mammalian target of rapamycin (**mTOR**). Figure 1.7 gives a schematic summary of how these systems act and interact to influence feed intake and

energy expenditure. In brief, these two systems act both peripherally and centrally inside the hypothalamus to regulate feed intake. The activation of AMPK is driven by a deficiency in energy available for metabolic processes by the signal of a high AMP:ATP ratio. AMPK inhibits the consumption of ATP and stimulates the production of ATP by the regulation of enzymes involved in lipid, carbohydrate, and protein metabolism. Low cellular energy levels and high AMPK activity also result in inhibition of mTOR, which in contrast to AMPK, reflects high nutrient and energy availability in the cell. Moreover, AMPK activation increases the expression of orexigenic peptides and decreases the expression of anorexigenic peptides that signal the brain to stimulate a sensation of hunger and thus increase feed intake and decrease energy expenditure. Conversely, when nutrients are in excess in the blood, or when adiposity status is high, the mTOR pathway is activated and the secretion of hormones such as insulin and leptin and anorexigenic peptides are increased. These factors act as reversed mechanisms to release a sensation of satiety. Thus, feed intake is reduced and energy expenditure is increased.



**Figure 1.7** Metabolic control of feed intake by two opposing energy-monitoring systems: adenosine monophosphate activated protein kinase (**AMPK**) and mammalian target of rapamycin (**mTOR**). Solid-green arrows indicate a stimulating effect while dashed-red arrows indicate an inhibiting effect (see Black et al. (2009) for full explanations of abbreviations).

The regulation of feed intake in growing pigs is influenced also by many external factors related to ambient temperature and the environment (Quiniou *et al.*, 2000; Nyachoti *et al.*, 2004), social interaction (Bornett *et al.*, 2000; Hoy *et al.*, 2012), contacts with humans (Martínez-Miró *et al.*, 2016) and diet composition (Kyriazakis and Emmans, 1999). Many of these factors have negative effects on feed intake and productivity of the pigs. In the next section, effects of high ambient temperature and pathogens on voluntary feed intake and the dynamic response of animals are investigated in more details.

## 2.2. Examples of perturbations that decrease feed intake

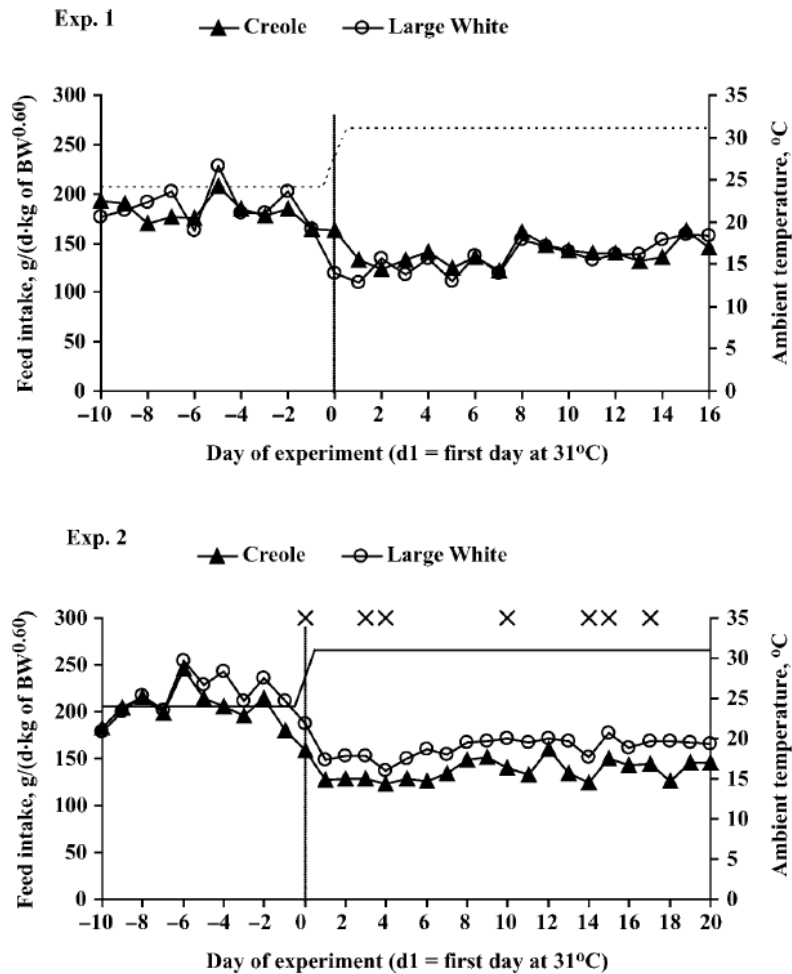
### *High ambient temperature*

Heat stress is considered as one of the main factors contributing to loss in animal performance (St-Pierre *et al.*, 2003; Renaudeau *et al.*, 2012). As animal production has been increasing rapidly in tropical and subtropical areas in the last two decades, global animal performance will be affected more by heat stress. Moreover, under the impact of global warming, heat stress has become more severe in Summer in temperate areas such as North America, Australia and Europe (Renaudeau *et al.*, 2012). For example, in California in 2006 approximately 25,000 cattle and 700,000 poultry were killed by a major heat wave (Nienaber and Hahn, 2007). In pigs, every year the U.S. swine industry estimated to lose at least \$900 million due to heat stress (Pollmann, 2010).

The reduction in performance by heat stress is caused either directly by a reduction in feed intake or indirectly by affecting health, reproduction, and the metabolism of the animal (Renaudeau *et al.*, 2012). Under hot thermal conditions, an animal will strive to reduce heat production by reducing feed intake and physical activity and by increasing heat losses by evaporation, conduction, convection, and radiation. Because of the limited capacity to dissipate heat, decreasing heat production when the ambient temperature increases is the main strategy to maintain the body temperature. Reducing voluntary feed consumption is very effective to decrease heat production when ambient temperature increases above the upper limit of the thermoneutral zone of pigs (Collin *et al.*, 2001; Renaudeau *et al.*, 2011). Quiniou *et al.* (2001) reported 24 to 25°C as the upper limit of the thermoneutral zone for growing pigs. Above this temperature, voluntary feed intake decreased. The reduction in feed intake varies from

40g to 80g/°C/day due to factors such as genotype, diet composition and body weight (Nyachoti *et al.*, 2004). Among these, body weight has a large impact on the susceptibility to heat stress (Quiniou *et al.*, 2000) and the effect of heat stress is more severe in heavier pigs than in lighter pigs. Heavier pigs are more susceptible to high temperatures because they have a higher feed intake and a lower capacity to lose heat due to a lower area-to-mass ratio and a thicker subcutaneous fat layer (Renaudeau *et al.*, 2012).

Studies on the short- and long-term effects of heat stress on pigs have shown that pigs can acclimatize to a high temperature over time. For example, the average daily feed intake (**ADFI**) of pigs was found to decrease significantly within the first 24 hours of exposure to heat stress and stay constant or increase slightly during the further thermal acclimation period (Morrison and Mount, 1971). Recently, Renaudeau *et al.* (2007) compared the responses of two pig breeds (Creole - the local Caribbean breed and Large White) to an elevated temperature of 31°C after an climatically adaptation period of 24°C. They found that ADFI of Creole pigs was significantly lower than that of Large White pigs during the period of 31°C. Creole pigs were also significantly different from Large White pigs in the rise in cutaneous and rectal temperatures with increasing ambient temperature (Renaudeau *et al.*, 2007). The general patterns of feed intake response to heat stress were quite similar in two breeds: a quick drop in ADFI at the onset of heat stress, followed by a gradual increase in ADFI on the subsequent days (Figure 1.8). This increase in ADFI is associated with a decrease in respiration rate of pigs after successive days of exposure to 31°C. This suggests that (1) the two pig breeds are different in their response to heat stress and (2) a long-term acclimation to heat stress in both breeds was observed in the change in their feed intake (Renaudeau *et al.*, 2007).



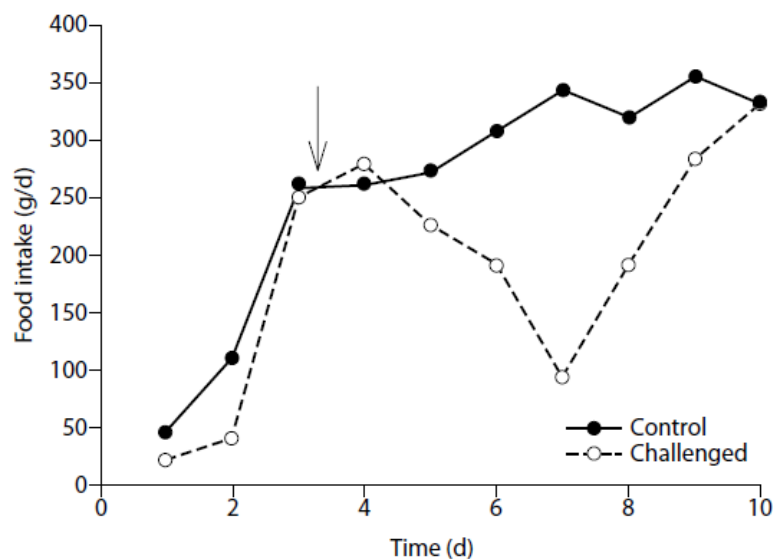
**Figure 1.8** Comparison of average daily feed intake response of two breeds (Creole and Large White) at the same age (Exp.1) or at the same body weight (Exp.2) over a period of exposure to 31°C (Renaudeau et al., 2007). Each dot represents the least squares mean of each group of pigs in each experiment. x represents the significant effect of breed ( $P < 0.05$ ).

## Pathogens

Pathogens can be very detrimental for animal performance. For example, the porcine reproductive and respiratory syndrome (**PRRS**) virus contributed to an estimated annual loss of \$664 million of the US swine industry (Holtkamp, 2013). Anorexia or a reduction in voluntary feed intake is a very common and early syndrome of animals when challenged by pathogens (Hart, 1988). Anorexia is observed across pathogen types (Kyriazakis *et al.*, 1998) and is considered as the main contributor for undesired effects of infection on animal growth and reproduction (Kyriazakis and Doeschl-Wilson, 2009). Therefore, a better understanding the patterns of anorexia and



related factors can help to overcome some of its negative impacts (Kyriazakis and Doeschl-Wilson, 2009). An example of the feed intake pattern of pigs following to a bacterial infection is shown in Figure 1.9. According to Kyriazakis and Doeschl-Wilson (2009), this anorexic pattern can be characterized by five features: (1) the *lag time* is the interval between the infected point and the onset of anorexia; (2) the *rate of change* (or rate of decline) indicates how fast the reduction in feed intake is; (3) the *extend of anorexia* refers to the lowest intake value due to infection; (4) the *duration of anorexia* refers to the period during which the lowest intake is maintained; and (5) the *rate of recovery* indicates whether and how fast the host can overcome the consequences of pathogens.



**Figure 1.9** Daily feed intake response of weaned pigs to a bacterial infection (started at the day indicated by the arrow) (Kyriazakis and Doeschl-Wilson, 2009). The dynamic changes in feed intake due to pathogen infection can be characterized by five features: (1) lag time; (2) rate of decline; (3) extend of anorexia; (4) duration of anorexia; and (5) rate of recovery. See related text for detailed explanations.

A number of factors such as pathogen type, nutritional condition of the host, and genotype affect these aforementioned features of anorexia. Firstly, different pathogens have different effects on the immune system of the host and on the appearance of anorexia. The appearance of anorexia is related to the secretion of cytokines during the inflammatory response (acute phase) of the immune system of the host (Petry *et al.*, 2007). Pathogens need to be recognized by the innate immune system for anorexia

to occur (Kyriazakis and Doeschl-Wilson, 2009). The lag time between the time of infection and the occurrence of anorexia depends on this recognition. Therefore, features of anorexia caused by pathogens with different impacts on the immune response will be different. Microparasites such as bacteria and viruses will have a shorter lag time, a faster rate of decline in feed intake, a shorter duration and a faster rate of recovery than macroparasites such as gastrointestinal nematodes (Kyriazakis and Doeschl-Wilson, 2009). In addition to the types of pathogen, the pathogen load can influence some features of anorexia. For example, a higher pathogen loads will result in a shorter lag time, faster rates of decline and a greater extent of anorexia (Houdijk *et al.*, 2007; Kyriazakis and Doeschl-Wilson, 2009). Secondly, anorexia is associated with the immune response, the food composition of the host can influence anorexia via an effect on the immune system (Kyriazakis and Doeschl-Wilson, 2009). Indeed, providing a food with high crude protein contents have been shown to contribute for reduce the duration of anorexia (Datta *et al.*, 1998) and a faster rate of recovery of the host (Kyriazakis *et al.*, 1996; Tu *et al.*, 2007). Finally, although direct evidence of genetic variation in the anorexic response to pathogens is scarce, a study on sheep showed that divergent selection for growth affects anorexia of animals when exposed to gastrointestinal parasites (Zaralis *et al.*, 2008). In details, in the lines that selected more intensively for growth, infected animals had a more severe reduction in food intake over a prolonged time compared to controlled animals while in the alternative lines there was almost no difference between infected and controlled animals.

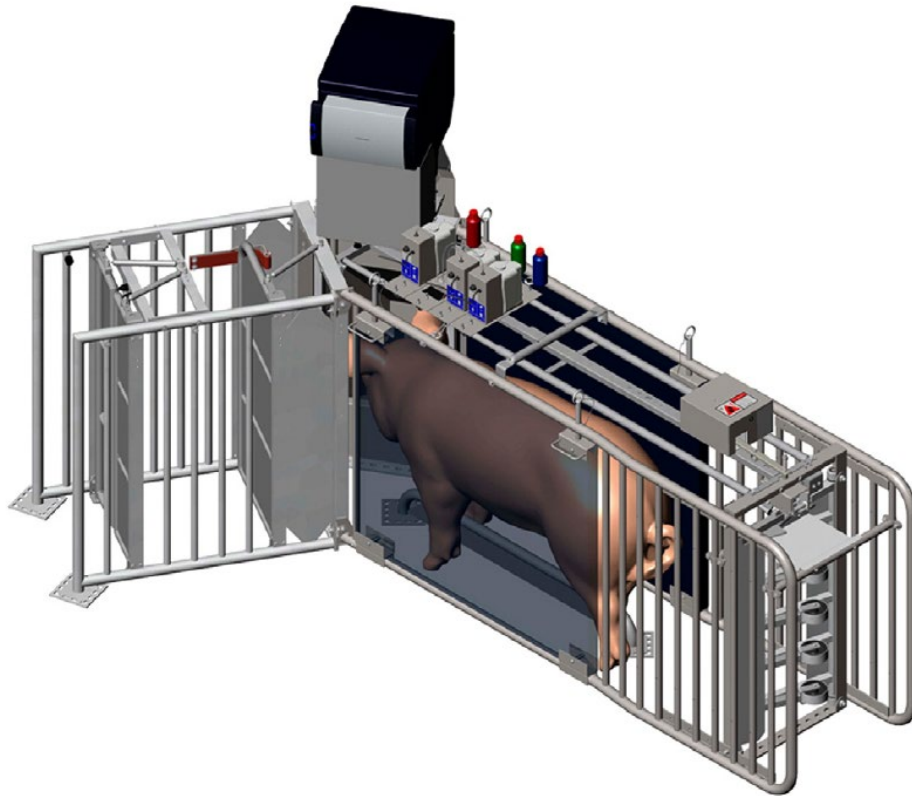
In summary, a high ambient temperature and pathogens are common perturbations in a farm environment that result in a decrease in feed intake and performance of animals. The impacts of these perturbations on feed intake depend on a number of factors such as the perturbing factor (e.g., level of heat stress or type of pathogens), environmental factors (e.g., relative humidity or feed composition), and animal genotype. Faced with these perturbations, response characteristics such as duration, magnitude, and rate of recovery of the reduction in feed intake can be used to quantify the response of animals.

## 3. Current approaches in using feed intake to detect perturbations and quantify subsequent response of animals

### 3.1. Detection of perturbations

To use feed intake to detect perturbations in group-housed pigs, feeding related information must be measured for each individual. Measuring feeding information of pigs can be done easily nowadays thanks to the development of automatic feeding station. Details of how this type of technology works have been described by Maselyne *et al.* (2015). First, each individual pig in the group has to be identified. This is done by using a Radio Frequency Identification (**RFID**) ear-tag for each pig. These ear-tags carry a unique code and a transponder. The feeder needs to be equipped with an antenna or reader system. When the pig enters the feeder, the antenna captures the signal of the RFID ear-tag and the pig's unique code is registered. The feeder basically consists of a trough and a hopper connected through a load cell to a computer. Access to the feeder can be restricted by installing adjustable protection bars so that (it is likely that) only one pig can access the feeder at a given time. Alternatively, separate individual feeding areas with RFID-controlled access can be created to ensure that only one pig has access to the feeder (Figure 1.10). The latter system is especially important if a feed restriction is applied to avoid "feed stealing". After a pig enters the feeding station, a limited amount of feed is distributed to the trough. The distribution of feed can be realized upon request by the pig (e.g., by lifting a lever) or automatically if the trough is mounted on a load cell. The feeding station registers the start and the stop of the feeding visits and the weight or volume of the distributed feed. The raw data of visits and feed distribution can then be processed further into more aggregated traits (e.g., daily feed intake, eating rate).

In addition to feed intake, some feeding stations can also measure or estimate the body weight of the pig. The estimation is typically done by a scale positioned just in front of the feeder so that pigs put their front legs on the scale while eating. The body weight is then estimated from this measurement.



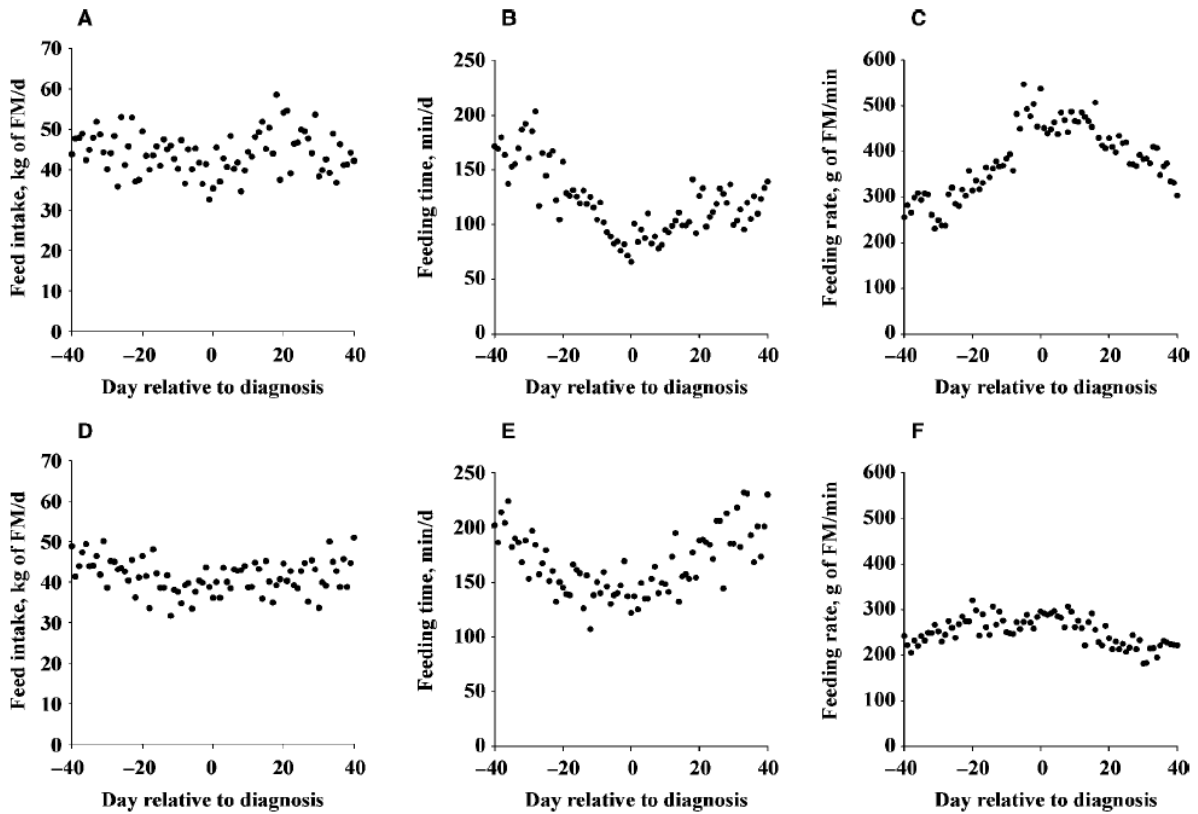
**Figure 1.10** An example of an automatic feeding station with controlled access for pigs (Maselyne et al., 2015). This feeding station is equipped with entrance and exist gates, protective crate and a feed trough. Only one pig can enter at a time. After each visit, feed consumption and feeding time of the pig are recorded for each pig thanks to the RFDI ear-tag of the pig. These measures are then computed to provide information at more aggregated levels such as number of feeder visits, feed intake and feeding rate per day.

Using feed intake and feeding patterns recorded by automatic feeding stations to detect illnesses have been done across species for a long time. Table 1 summarizes the results of some of those studies. In general, changes in feed intake and feeding behaviour are good predictors of diseases and often these changes occur much earlier than the observed clinical signs. Changes in feeding behaviour (e.g., feeding rate, number of feeder visits, meal size) seem to occur earlier than a reduction in feed intake, although a reduction in feed intake was observed for a wider range of perturbations.

Animals modify their feed intake and feeding behaviour differently in response to different perturbations. For example, González *et al.* (2008) observed that cows first responded to locomotion problems by decreasing the number of feeder visits and increasing feeding time per day while maintaining their feed intake (Figure 1.11).

Because standing on lame legs is painful, animals would probably try to eat more at each visit. However, if the locomotion problem leads to lameness, cows will eventually decrease their feed intake. Wallenbeck and Keeling (2014) found that tail-bitten pigs consumed significantly less feed than other pigs did during an outbreak of tail biting. However, the victims of tail-biting visited the feeders more frequently than other pigs 2 to 5 weeks before the outbreak. Their interpretation was that a problem, finally resulting in tail biting, was already ongoing few weeks before the detected time of the outbreak. Although the origin of the problem is not known, it is interesting to see that feeding behaviour can be affected before the “visible and physical” problem is detected and that it is specific for the victims. The example above is based on the analysis of feeding behaviour (i.e., after the tail-biting problem occurred) and the challenge is to see whether changes in feed intake behaviour can be detected to foresee the problem and take preventive measures.

In summary, with the development of modern monitoring technologies such as automatic feeding stations, measuring feeding behaviour and feed intake can be done at the individual level in group-housed animals and with a high frequency (e.g., up to a level of feeder visit). This type of information is representative of the consequences of perturbations on farm because animals change their feeding behaviour and intake due to different perturbations in characteristic ways. They also can facilitate the quantification of animal response to perturbations.



**Figure 1.11** Changes in feed intake (A, D), feeding time (B, E) and feeding rate (C, F) of two cows (upper and lower panels) diagnosed with different types of lameness (González et al., 2008). Although these two cows suffered from different disorders, they showed a very similar response in feeding behaviour: a decrease in feeding time accompanied by an increase in feeding rate before being diagnosed and the reversed changes were observed after day of treatment (day 0). This resulted in a constant level of feed intake in both cases.

**Table 1** Summary of some studies that used feeding information extracted from automatic feeders to detect perturbations in farm animals

<b>Feeding information</b>	<b>Species</b>	<b>Detected perturbations</b>	<b>Note</b>	<b>Studies</b>
Frequency and duration of feed-bunk visits	Steer <sup>1</sup>	Morbidity <sup>2</sup>	Morbid steers spent less time at the feed bunk, had fewer immediate visits to the bunk in response to feed delivery, and had fewer feeding bouts than the healthy counterparts.  Morbidity can be detected 4.5 days earlier by this method than by trained employees.	Sowell <i>et al.</i> (1998); Sowell <i>et al.</i> (1999); Quimby <i>et al.</i> (2001)
Daily dry matter intake ( <b>DMI</b> ) and daily feeding time (e.g., sum of durations of all visits per day)	Dairy cows	Metritis after calving	Prepartum DMI and feeding times (especially one week before calving) decreased in cows with severe and mild forms of metritis compared to healthy cows.  Cows at risk of metritis after calving can be detected by observing a decrease in DMI and feeding time up to two weeks before the first clinical signs and one week before calving.	Huzzey <i>et al.</i> (2007)

Individual eating hierarchy (e.g., the order of feeder visits of individual sows in a groups)	Sows	Oestrus, lameness, other health disorders	Sows suffering from health problems would be less motivated to eat and allow others to eat first. This study modelled the deviations of observations from the predicted eating rank of each individual sow.	Cornou <i>et al.</i> (2008)
Fresh feed intake, daily feeding time, feeding rate, number of meals and visits per day	Dairy cows	Ketosis, lameness and other locomotion disorders	Cows diagnosed with different illnesses modified their short-term feeding patterns in characteristic ways. Due to each disease, changes in feeding behaviour and feed intake already started from 7.7 days to 1 day before the diagnosis.	González <i>et al.</i> (2008)
Rate of DMI <sup>3</sup>	Dairy goats	Bouts of acidosis	The study developed a method to detect the effect of perturbations on feeding behaviour without the need to define meals. Using statistical models to divide intake patterns of individual-housed goats to segments and cluster them, the study can discriminate between healthy animals and those suffered from bouts of acidosis.	Giger-Reverdin <i>et al.</i> (2012)



Inter-meal interval and number of feeder visits per day	Growing pigs	Severe diseases and lameness	Based on the concept of synergistic control, the method proposed in this study could detect early illnesses through longer intervals between feeder visits and a lower number of feeder visits per day than the normal variation range for each pig.	Maselyne <i>et al.</i> (2018)
Daily feeder visit frequency and daily feed consumption	Growing pigs	Tail biting	Victim pigs of tail biting visited the feeders more frequently before the tail biting outbreak and consumed less feed during the outbreak than normal pigs did.  A decrease in feeder visits can identify tail-biting outbreaks as early as 9 weeks before the veterinary record of the outbreaks.	Wallenbeck and Keeling (2013)
Voluntary feed intake	Growing pigs	Clinical lameness and acute tail biting	Feed intake of lame pigs and victims of tail-biting was less than that of normal pigs.  Changes in feed intake of lame and tail-bitten pigs were observable 2 to 3 weeks before diagnosis by a human.	Munsterhjelm <i>et al.</i> (2015)

<sup>1</sup>Steer: castrated male beef cattle

<sup>2</sup>Mobidity: involves whatever reasons due to which a steer was removed from the pen and medicated.

<sup>3</sup>Rate of DMI was calculated from the slope of changes in DMI measured every 2 min around goat's feeding time.

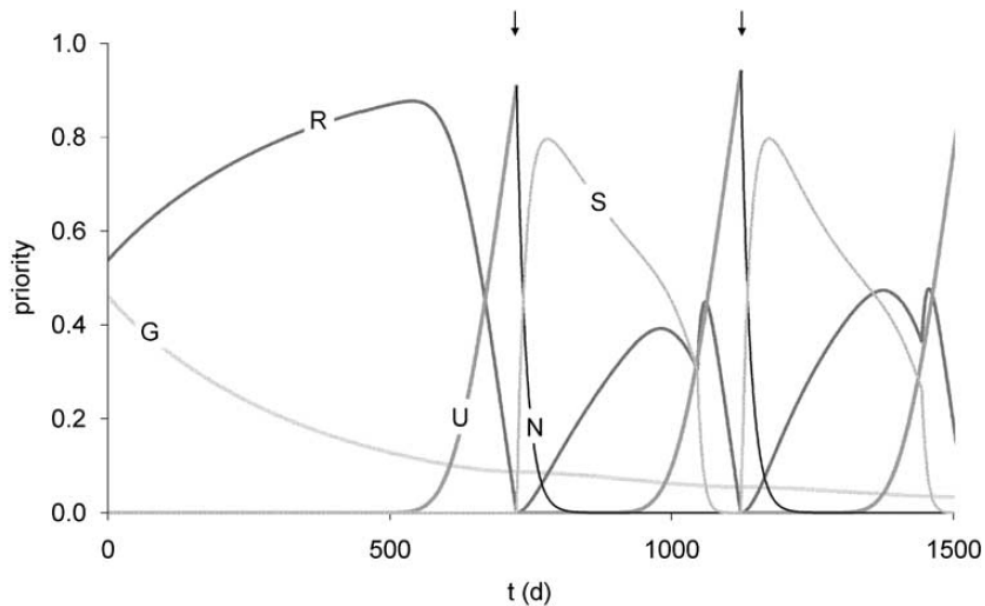
## 3.2. Quantification of animal's response

The characterization and quantification of the animal's response to perturbations are difficult because of the complexity of multiple interactions in the response to perturbations (Friggens *et al.*, 2017). Mathematical modelling can be a useful approach to understand and quantify this phenomenon. Modelling can summarize the response of the animal into a few parameters, which can be compared easily among animals and thus benefit genetic selection to improve robustness (Doeschl-Wilson *et al.*, 2012). With the accelerated availability of automatic monitoring technologies, data has become increasingly available for modelling. This section is therefore dedicated to modelling methodologies that have been applied in the characterization and the quantification of the animal's response to perturbations.

Robustness at the animal level is a combination of multiple functional underlying components (Figure 1.2), and can be studied at different levels of aggregation. Taghipoor *et al.* (2016) developed a model to understand the homeostatic equilibrium of anabolic and catabolic pathways of cell metabolism under environmental perturbations. At a higher level, modellers often consider that an animal has a genetic potential for a certain biological function (e.g., growth to become mature, health to maintain the integrity of the individual, and reproduction to ensure survival of the species). The target of the animal throughout its life is to achieve the expression of this genetic potential. The dynamic changes of a biological function are driven by the genetic potential of an animal and follow a certain pattern or trajectory. Under optimal conditions, the animal is expected to achieve this goal, but the actual expression of performance may be less than desired due to impacts of perturbations.

Martin and Sauvant (2010a) developed a holistic model to represent the trajectories of different biological functions driven by the genetic potential and physiological stages of a dairy cow. An animal has multiple biological functions and the priority of allocating resources between them will change according to different stages of life. The model based on the concept of homeorhetic controls (section 1.2 – this chapter) to determine the dynamic priorities of the cow to partition resources to different biological functions (Figure 1.12). The homeorhetic driven trajectories of the model can serve as the biological benchmarks under optimal conditions. The ability of the cow to cope with short-term perturbations such as changes in dietary energy supply can be evaluated in terms of homeostatic controls (i.e., the ability to maintain an energy

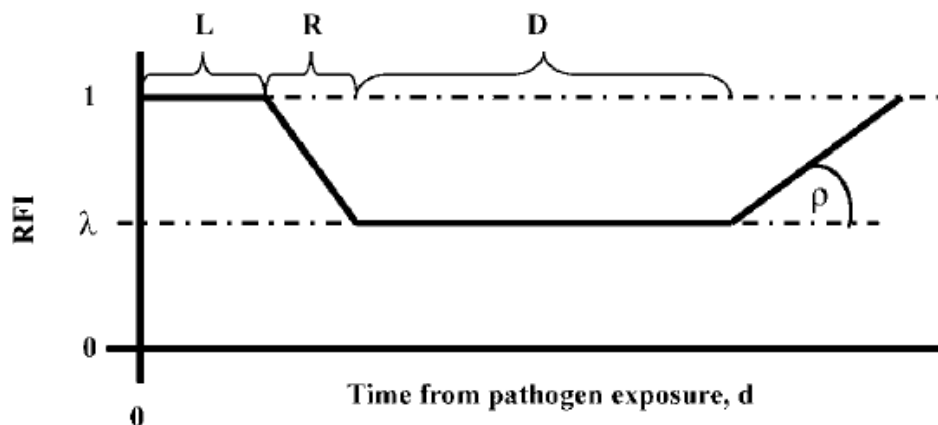
equilibrium when the supply is constrained – section 1.2 this chapter) (Martin and Sauvant, 2010b).



**Figure 1.12** Conceptual trajectories of resource allocation over 20 years of the life of a dairy cow for five functions: growth (G), balance of body reserves (R), ensuring survival of the unborn calf (U), ensuring survival of the newborn calf (N) and ensuring survival of the suckling calf (S) (Martin and Sauvant 2010a).

The idea of a trajectory that expresses the genetic potential of an animal has existed in animal nutrition science for a few decades. As mentioned in section 2.1 of this chapter, there is a school of thought considers that an animal eats because it has the internal desire to grow. This is called the “pull” approach in modelling animal nutrition. This approach assumes an animal has an intrinsic desire to grow, driven by the pig’s genotype, and this motivates the animal to “pull” energy and nutrients in from the feed (Halas *et al.*, 2018). Black *et al.* (1986) decomposed the “desire to grow” in a potential for protein deposition and energy retention, which then drives the potential feed intake. Actual feed intake is the consequence of the potential feed intake and constraints imposed by the environments or by the capacity of the animal itself (e.g., gut fill) (Black *et al.*, 1986). Using a similar approach, Wellock *et al.* (2003a) represented the potential growth of a pig as a function of its genotype and the current physiological state. The feed intake that allows the pig to satisfy the requirements for protein and energy for its potential growth in the unconstrained condition is called the

“desired” feed intake (Wellock *et al.*, 2003a). This desired feed intake can then be used to investigate the effects of perturbations such as social stressors (Wellock *et al.*, 2003b) and pathogens (Sandberg *et al.*, 2006) on feed intake and to quantify the genetic variation among individuals in response to those perturbations. For example, Sandberg *et al.* (2006) developed a model to characterize the feed intake response to a pathogen challenge. This model was developed based on the knowledge of the anorexic effects of pathogens on voluntary feed intake (as described in section 2.2 of this chapter), and the model structure is presented in Figure 1.13. A resistant host is characterized by the model as having a long lag time (L), a short reduction time (R), a short duration of the anorexia (D), and a fast rate of recovery ( $\rho$ ). Although the model addresses different aspects of the interactions between the host and the pathogen, potential model inputs such as pathogen dose, pathogen load, but also the short-term changes in feed intake are difficult to obtain, making estimation of model parameters rather difficult.



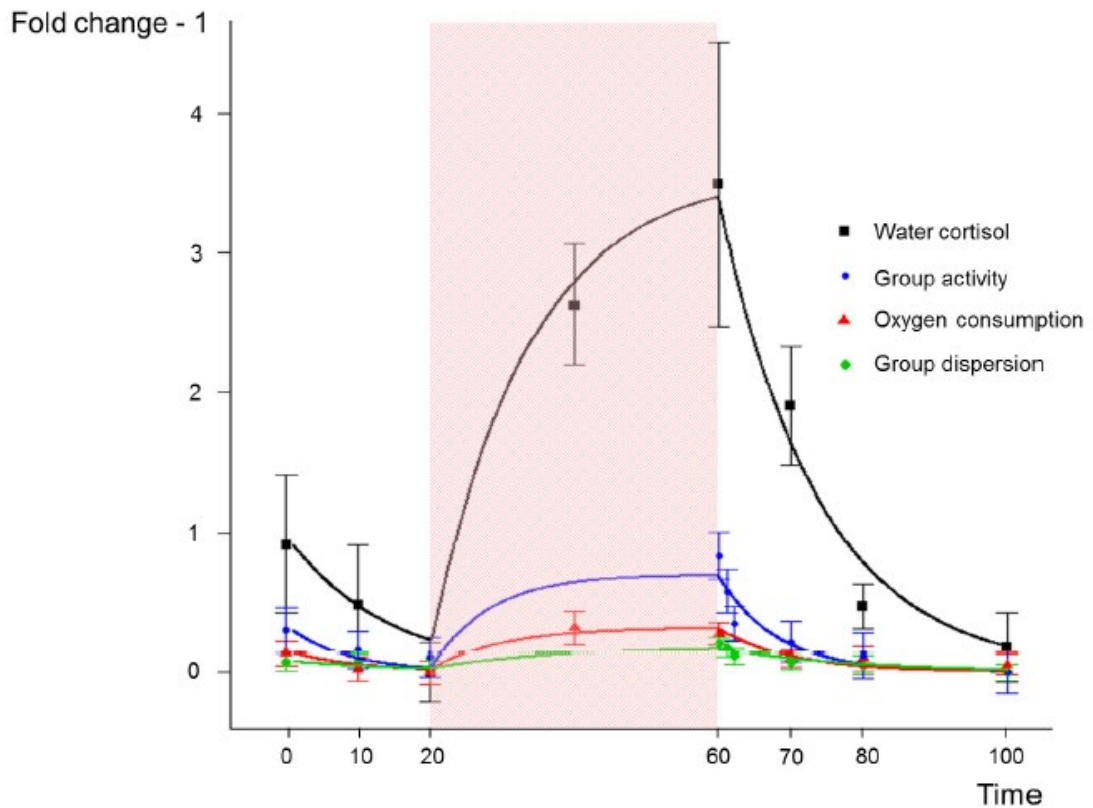
**Figure 1.13** Concept of a model that characterizes the response in relative feed intake (differences between desired and challenged feed intake - RFI) of an animal to a pathogen challenge (Sandberg *et al.*, 2006). The way in which RFI changes over time is characterized by 5 parameters: Lag time (L, day) implies the interval between the point of infection and the first observable effect on RFI, Reduction time (R, day) describes how fast the lowest value of RFI ( $\lambda$ ) is achieved, Duration time (D, day) refers to the period the  $\lambda$  can be maintained, and the rate of recovery ( $\rho$ ).

The aforementioned examples show that most of the models developed to study the adaptive ability of animals to perturbations were based on a concept-driven approach. This implies that these models rely on the existing knowledge and

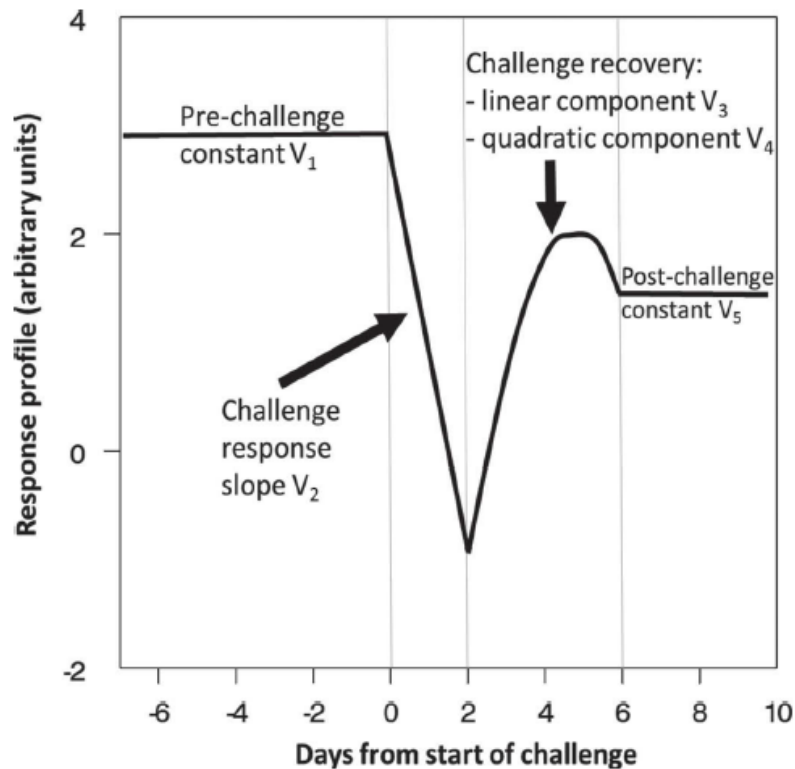
perceptions. Data from the literature or from experiments are used to parameterize these models or to challenge them, but not for the construction of the model concepts. These models rely on biological mechanisms that describe the underlying model structure, and this type of models is helpful in understanding the physiological interactions between animals and perturbations. However, it has been difficult to use these models in practice because they require considerable inputs to properly parameterize the model for the trajectory expressing the animal's genetic potential of different functions, different types of perturbation and to account for differences among animals in their response to the perturbation.

Quantifying the dynamic responses of an animal to a perturbation has also been done without defining a trajectory of the optimal condition. For an acute challenge, the responses can be compared to the conditions right before and after being challenged (Sadoul *et al.*, 2015b; Friggens *et al.*, 2016). For instance, Sadoul *et al.* (2015b) adopted the concept of “spring and damper” from physics to represent physiological and behavioural responses of an animal to an acute challenge. The impact of a perturbation is considered as a force that pulls the system from its baseline. The animal's response is characterized by the capacity to resist from being distorted (i.e., damper) and the capacity to minimize the amplitude of perturbing factors (i.e., spring) (Sadoul *et al.*, 2015b). When the perturbation is over, the pulling force is released and the animal recovers back to the baseline through the force of the (damped) spring. The dynamics of the recovery capacity therefore depends on the spring and damper parameters. The model fitted well to the physiological and behavioural responses of rainbow trouts that were challenged by a confinement test (Sadoul *et al.*, 2015a), showing the capacity to quantify the response of animals to an acute challenge (Figure 1.14). Friggens *et al.* (2016) used a piecewise model to describe changes in performance of individual dairy goats before, during, and after a dietary challenge of receiving a low-quality feed for two days. The model is quite simple in that the pre- and post-challenge responses are considered constant, and the decrease due to perturbation and the subsequent recovery are described by two linear and one quadratic components (Figure 1.15). The parameters obtained from the model allow evaluating the relationship between different stages of the response (Friggens *et al.*, 2016). These examples indicate that the response of animals to acute perturbations can be quantified by simple models without defining an explicit baseline (i.e., the baseline is assumed constant before and during the acute challenge; thus, responses

of the animal to a challenge are compared with the observation(s) of the period before it).



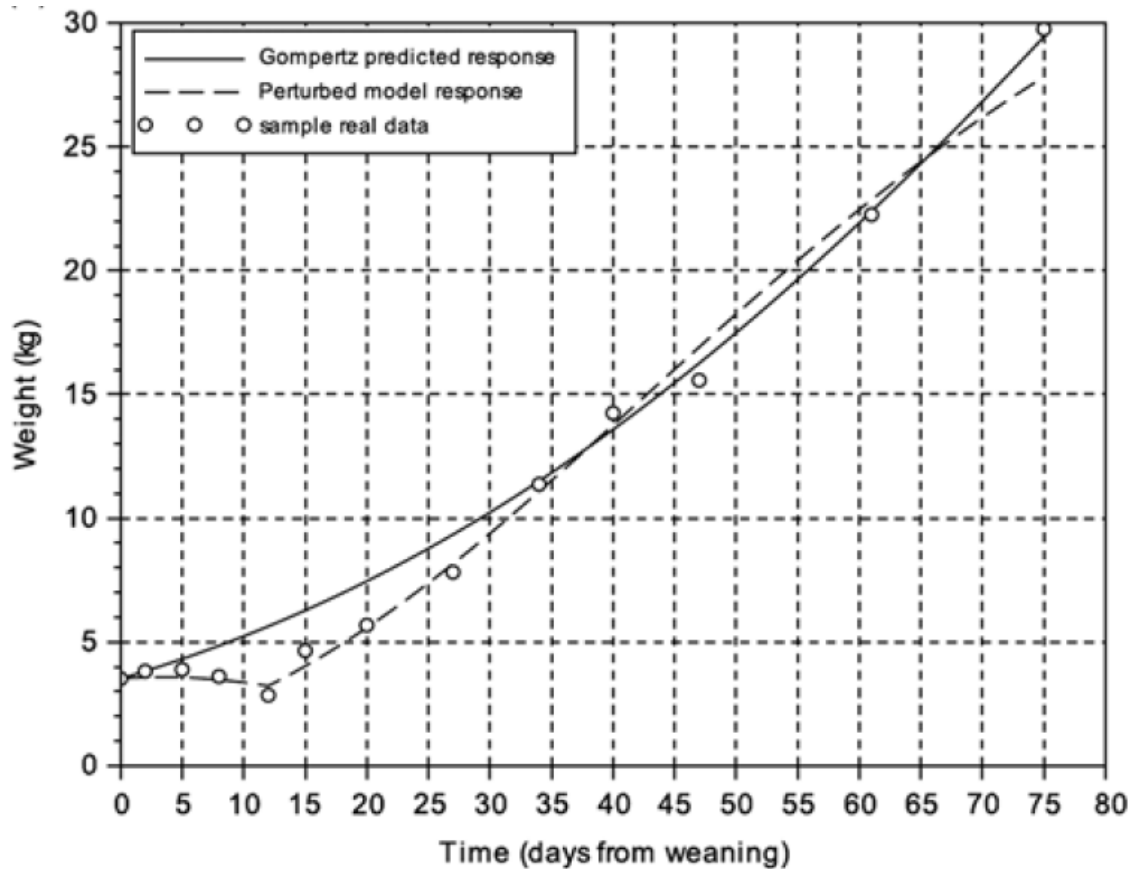
**Figure 1.14** Results of fitting the “spring and damper” model to records of some physiological and behavioural traits of rainbow trouts before, during a confinement challenge (grey box) and thereafter (Sadoul *et al.*, 2015b). The confinement challenge was conducted by Sadoul *et al.* (2015a). The response of trouts during the challenge was characterized for each traits by two parameters indicating the capacity to resist from being distorted (i.e., damper) and to minimize the amplitude of perturbing factors (i.e., spring). After the challenge, as the perturbing force was released, measured traits recovered back to the baseline by themselves.



**Figure 1.15** Graphic illustration of the piecewise model that characterizes the response of an interested trait before, during and after an acute challenge such as receiving a low-quality feed (Friggens *et al.*, 2016).

The rapid development of high frequency and individual monitoring technologies offers new opportunities to quantify the animal's response to perturbations. Revilla *et al.* (2019) used frequently recorded body weights to quantify the ability of piglets to cope with weaning perturbations. In their model, they differentiated a growth trajectory in non-perturbed (potential) and perturbed conditions (Figure 1.16). The growth trajectory in the non-perturbed condition was estimated by fitting a classic Gompertz function on body weight using five points: the point of weaning and only the last four records in a period of 75 days after weaning. The Gompertz-Makeham equation was fitted to more frequent body weight measurements to characterize the growth trajectory in the perturbed condition. The deviations of perturbed body weight from potential body weight provide information about the response of piglets such as the amplitude and duration of the weaning perturbation and the rate of recovery of the pig. The model was developed to capture only the weaning perturbation, and it relies on the hypothesis that at 75 days after weaning, pigs recover completely. Despite being a simple model

and a potentially debatable hypothesis, the model parameters were highly correlated with physiologically adaptive traits in the blood (Revilla *et al.*, 2019).



**Figure 1.16** Results of fitting the model developed by Revilla *et al.* (2019) to body weight measurements of a pig to characterize its response to weaning challenge. The growth trajectory in the non-perturbed condition (solid line) was estimated by fitting a classical Gompertz function to body weight measurements at weaning and the last four days. The body weight response to weaning challenged was estimated by fitting a Gompertz-Makeham equation to all body weight measurements (Revilla *et al.*, 2019).

Doeschl-Wilson *et al.* (2012) proposed a novel method to quantify individual host resistance and tolerance by adopting the concept of dynamical systems theory. By plotting the individual's performance against measures of pathogen burden recorded at multiple time points, a trajectory of the interaction between pathogen load and host performance can be formulated. This trajectory indicates the dynamic change in resistance and tolerance and their effects on host performance. Doeschl-Wilson *et al.* (2012) represented the behaviour of this trajectory by a system of differential equations, which describe the dynamic changes in host performance, pathogen load,



and immune response. Parameters estimated from this model can be used as phenotypic traits for quantitative genetic studies. Although this method does not provide any explicit model to represent the trajectory of the “*host performance-pathogen burden*” interaction, the system of differential equations shows that it has the potential to quantify the response of animals to pathogens, without requiring knowledge about the time point that the animal was infected (Doeschl-Wilson *et al.*, 2012).

Summarizing, although the necessity to quantify the response of animals to perturbations is well recognized, it remains a challenging task. Mathematical modelling is a beneficial approach to study the complex and dynamic response of an animal to perturbations. Most of the existing models describing the response of an animal to a perturbation have been based on a conceptual approach and data to challenge these concepts were difficult to obtain. The availability of high-frequency longitudinal data changes the way by which the issue can be addressed. Recently developed models using longitudinal data already show the benefits of combining the newly available of data and mathematical modelling in quantifying the animal's response to perturbations.

## 4. Gaps of knowledge

With the increase in human population at an accelerating rate, livestock production plays an important role in ensuring food security in the next few decades. However, livestock production is facing emerging challenges such as the global climate change, environmental impact, emerging infectious diseases, and consumer and citizen demands for animal welfare. In this context, livestock production has to change towards a more sustainable system. Being able to quantify and in turn improve robustness of farm animals (e.g., through genetic selection or management practices) is an important element step to move towards a more sustainable livestock system. However, robustness is a complex trait to be quantified because it includes multiple dynamic elements such as how an animal responds to and recovers from environmental perturbations. Among many potential indicators, voluntary feed intake is a promising candidate to assess robustness because of its sensitivity to perturbations. Currently, with the increasingly availability of automatic monitoring technologies, voluntary feed intake can be measured easily at individual level, in a large group, and with very high frequency. The advantage of this new type of

information has already been exploited to detect the impact of perturbations on the animals, but feed intake data can be exploited further to quantify the underlying mechanisms of robustness.

## 5. Study's objectives

The objectives of this PhD thesis are:

1. Develop a generic method and model to:
  - a. Detect the presence of known and un-known (short-term) perturbations on the voluntary feed intake of growing pigs
  - b. Quantify the response of individual pigs to detected perturbations in terms of:
    - Resistance (i.e., to what extent is the animal affected by a perturbation)
    - Resilience (i.e., how fast does the animal recover when the perturbing factor is over)
2. Challenge and evaluate the model by quantifying the feed intake response of pigs (in terms of resistance and resilience) when exposed to a mycotoxin-contaminated diet and compare these traits among individuals.

We decided first to develop a model in a blindfolded way. This means that we developed the model based only on feed intake data without considering any other types of information (e.g., observations by animal caretakers, veterinary treatment records). Following the model development, the model was challenged and evaluated using a dataset of a known perturbation caused by pigs receiving a mycotoxin-contaminated diet during specific periods.

## Chapter 2. Development of the model to detect perturbations and quantify animal's response

### 1. Objective of the chapter

The aim of this chapter was to describe the development of a data analysis and modelling procedure to detect the impacts of perturbations on feed intake of individual growing pigs and quantify their subsequent responses.

As mentioned earlier, we chose a blindfolded approach to develop the procedure. This implies that no information except daily voluntary feed intake of individual pigs was analyzed. The procedure is different from conventional modelling in the way that it was developed in two steps. This allows us to detect the perturbations firstly and quantify the animal's response secondly.

When developing the procedure, we aimed to keep it generic and flexible. Because the concept is generic, different elements can be adapted if judged necessary. For example, if the origin of perturbations is recognized and knowledge of their impacts on the feed intake is available, the model can be modified to include this information.

In this chapter, the development of the procedure will be described as a published article. Then, an example of how the model can be modified to deal with feed intake response to sanitary challenges will be followed to demonstrate the procedure's flexibility.

## 2. A procedure to quantify the feed intake response of growing pigs to perturbations

Published article:

**H. Nguyen-Ba**, J. Van Milgen and M. Taghipoor 2019. A procedure to quantify the feed intake response of growing pigs to perturbations. *Animal* 14, 253–260.

(DOI: [10.1017/S1751731119001976](https://doi.org/10.1017/S1751731119001976))

# A procedure to quantify the feed intake response of growing pigs to perturbations

H. Nguyen-Ba<sup>1,2†</sup> , J. van Milgen<sup>1</sup>  and M. Taghipoor<sup>3</sup> 

<sup>1</sup>PEGASE, Agrocampus Ouest, INRA, 35590 Saint-Gilles, France; <sup>2</sup>Faculty of Animal Science, Vietnam National University of Agriculture, Hanoi, Vietnam;

<sup>3</sup>MoSAR, AgroParisTech, INRA, Université Paris-Saclay, 75005 Paris, France

(Received 17 December 2018; Accepted 26 July 2019)

---

## Abstract

Improving robustness of farm animals is one of the goals in breeding programs. However, robustness is a complex trait and not measurable directly. The objective of this study was to quantify and characterize (elements of) robustness in growing pigs. Robustness can be analysed by examining the animal's response to perturbations. Although the origin of perturbations may not be known, their effects on animal performance can be observed, for example through changes in voluntary feed intake. A generic model and data analysis procedure was developed (1) to estimate the target trajectory of feed intake, which is the amount of feed that a pig desires to eat when it is not facing any perturbations; (2) to detect potential perturbations, which are deviations of feed intake from the estimated target trajectory; and (3) to characterize and quantify the response of the growing pigs to the perturbations using voluntary feed intake as response criterion. The response of a pig to a perturbation is characterized by four parameters. The start and end times of the perturbation are "imposed" by the perturbing factor, while two other parameters describe the resistance and resilience potential of the pig. One of these describes the immediate reduction in daily feed intake at the start of the perturbation (i.e., a "resistance" trait) while another parameter describes the capacity of the pig to adapt to the perturbation through compensatory feed intake to re-join the target trajectory of feed intake (i.e., a "resilience" trait). The procedure has been employed successfully to identify the target trajectory of feed intake in growing pigs and to quantify the pig's response to a perturbation.

**Keywords:** Modelling, Resistance, Resilience, Health, Breeding

## Implications

The study provides a data analysis procedure to detect the impact of perturbations on feed intake in growing pigs, and a mathematical model to quantify traits related to resistance and resilience. When pigs are kept in the same environment and are facing a common perturbing factor, the model can be used to identify differences in resistance and resilience among pigs, which can be used in selection programs. Although this procedure uses feed intake as a response criterion and is applied to growing pigs, it is generic and can be applied to other species and with other response criteria.

## Introduction

Growing pigs, like other animals, are confronted with variation in their environment to which they may have to respond. This includes the effects of climate change (e.g., periods of extreme weather), infectious diseases, but also management practices and interactions with other animals. Robustness deals with the way animals respond to changes in their environment. Knap (2005) defined robust pigs as “*pigs that combine high production potential with resilience to external stressors, allowing for unproblematic expression of high production potential in a wide variety of environmental conditions*”. Robustness is a complex concept, which is difficult to quantify and characterize because it includes multiple “*dynamic elements such as the rates of response to, and recovery from, environmental perturbations*” (Friggens *et al.*, 2017). The response of an animal to a perturbation can be described in terms of resistance and resilience, which are defined as the capacity of an animal to minimize impacts of perturbing factors and to quickly return to the pre-perturbed condition (De Goede *et al.*, 2013; Colditz and Hine, 2016).

Because of the dynamic nature of the response of animals to a perturbation, it is difficult to use single time-point measurements to quantify resistance and resilience (Friggens *et al.*, 2017). Recent developments in monitoring technologies allow the continuous recording of animal performance (Neethirajan, 2017). Although several studies have explored these technologies to study the impacts of perturbations on animal performance (Codrea *et al.*, 2011; Munsterhjelm *et al.*, 2015; Friggens *et al.*,

2016), these technologies have not yet been used to develop a generic method that detects perturbations and that allows to quantify the animal's response to perturbations. Therefore, the objective of this study was to propose a data analysis and modelling procedure to detect the impact of perturbations in growing pigs and quantify the feed intake response in terms of resistance and resilience.

## Material and methods

### *General description of the model*

Perturbations such as heat stress or sanitary challenges typically have a transitory impact on the pig, resulting in changes in feed intake and body weight gain. Although the cause of a perturbation is not always known, the consequences on animal performance can be observed. Because of the rapid development in monitoring technologies on farm, feed intake can now be recorded in individual pigs with a very high frequency (i.e., up to the level of meal intake patterns). Moreover, feed intake is among the first measurable and non-invasive traits affected by perturbations, and was therefore considered as a suitable trait to quantify the response of a pig to a perturbation.

Only perturbations that have a negative impact on feed intake are considered in this study. Perturbations that result in an increase in feed intake (e.g., cold stress, immuno-castration, or providing a diet with low energy content) are not considered here, but the proposed method is generic and can be adapted to account for these types of perturbations.

It is hypothesized that the observed cumulative feed intake (**CFI**) of a pig is the combination of a target trajectory curve (i.e., the amount of feed a pig desires to consume in a non-perturbed condition) and a change in feed intake due to perturbations. During a perturbation, the feed intake of the pig will deviate from the target trajectory but, once the perturbing factor is over, the pig will strive to increase its feed intake through compensatory feed intake to re-join the target trajectory of CFI (**target CFI**).

The data analysis procedure includes two main steps. The first one is the estimation of the target trajectory curve of feed intake. Deviations of the observed feed intake from this target trajectory represent the potential consequence of a perturbation, and a classification process is performed to identify the most important deviations. The

second step is the quantification of response of the animal in terms of resistance and resilience. In short, the procedure is based on two model components: one estimates the target trajectory of feed intake and the other one characterizes the perturbation. Although DFI is often used as a production trait, fluctuations in DFI data make detection of perturbations difficult. Moreover, after a perturbed period, the overall reduction in feed intake needs to be compensated for by an equal increase in feed intake during the recovery period, which should surpass the target trajectory of DFI (**target DFI**). The CFI (i.e., the integral of DFI) has the advantage over DFI of being less variable and, more importantly, allows for an easier representation of a trajectory including deviations and recovery. In the absence of a perturbation, it is hypothesized that the observed CFI is identical to the target CFI. During a perturbation, the observed CFI deviates from the target CFI (i.e., it increases to a lesser extent) and, once the perturbing factor is over, the animal seeks to re-join the target CFI through compensatory feed intake, without surpassing it in a systematic way.

#### *Estimation of the target trajectory of feed intake and detection of perturbations*

The target CFI is the amount of feed a pig desires to eat when it is in a non-perturbed condition. The target CFI was described by an empirical polynomial function of time, without pretending a mechanistic cause. The reason for this is that feed intake was recorded on a daily basis and is statistically the independent variable. Preliminary analyses indicated that using a third-order polynomial of CFI in combination with a perturbation model could result in biologically unrealistic predictions for DFI. We therefore defined the model of target DFI so that it can either increase with time or remain constant, resulting in the so-called linear-plateau model for DFI. Consequently, the target CFI was described by a quadratic-linear function of time:

$$Target\_CFI(t) = \begin{cases} a + bt + ct^2, & t < t_s \\ a + bt_s + ct_s^2 + (b + 2ct_s)(t - t_s), & t \geq t_s \end{cases} \quad (1)$$

where “t” is the age of the animal (days) and “Target\_CFI(t)” is the target CFI at day “t”. The parameters a, b, and c are the classical parameters of a polynomial function, and t<sub>s</sub> is the day when the quadratic segment of the curve changes to the linear segment.

To facilitate the biological interpretation of the parameters, Equation 1 was reparametrized by replacing parameters a, b and c by t<sub>0</sub> (the estimated age at which CFI = 0), CFI<sub>mid-point</sub> (the estimated CFI at the mid-point determined halfway between



$t_0$  and the last observation), and  $CFI_{last}$  (the estimated CFI at the last observation). Details of this re-parametrization are described in Supplementary Material S1.

Using the reparametrized Equation 1 to estimate the target CFI, two possible problems were encountered with the resulting linear-plateau function for DFI. Firstly, the linear segment can have a very modest negative slope, which would mean that the DFI decreased slightly with increasing age. In that case, a constant value for DFI was assumed (rather than a linear-plateau model), resulting in a linearly increasing function for CFI (with two parameters  $t_0$  and  $CFI_{last}$ ). Secondly, to avoid the estimation of  $t_s$  being too close to either the first or the last observation, a linear function was then used to describe DFI, resulting in a quadratic function for CFI (with three parameters  $t_0$ ,  $CFI_{mid-point}$  and  $CFI_{last}$ ).

To estimate the target CFI, the reparametrized Equation 1 has to be fitted to non-perturbed data. Therefore, a statistical procedure was used to successively eliminate observations that could result from perturbed periods. Observations that are consistently below the fitted curve may correspond to feed intake during perturbed periods. An auto-correlation test was used as a selection criterion to temporarily remove data with negative residuals from the dataset. The fitting procedure was then repeated on the resulting dataset until the auto-correlation of the residuals was no longer significant. Compared to fitting the curve to the original dataset of CFI, this procedure results in moving the CFI curve upwards, while fitting the model to fewer observations compared to the original dataset. Preliminary analysis indicated that the absence of auto-correlation could be achieved only if very few data remained. This appears to be due to small oscillations in CFI that are not necessarily the result of perturbations. To ensure that the target CFI is estimated with a reasonable number of observations, the data elimination procedure was terminated when at least 20 observations were remaining. In short, the parameters of the target CFI were estimated by repeatedly fitting the reparametrized Equation 1 to CFI data and temporarily eliminating observations with negative residuals until there was no auto-correlation among the residuals or when at least 20 observations remained.

Deviations from the target CFI correspond to potential perturbations. As indicated above, small oscillations in feed intake patterns exist. The aim here is to detect the most important deviations that are the result of perturbations. These perturbations can then be characterized by the duration and magnitude of the deviation from the target CFI. A deviation was considered as a perturbation if it lasted at least 5 days, to ensure

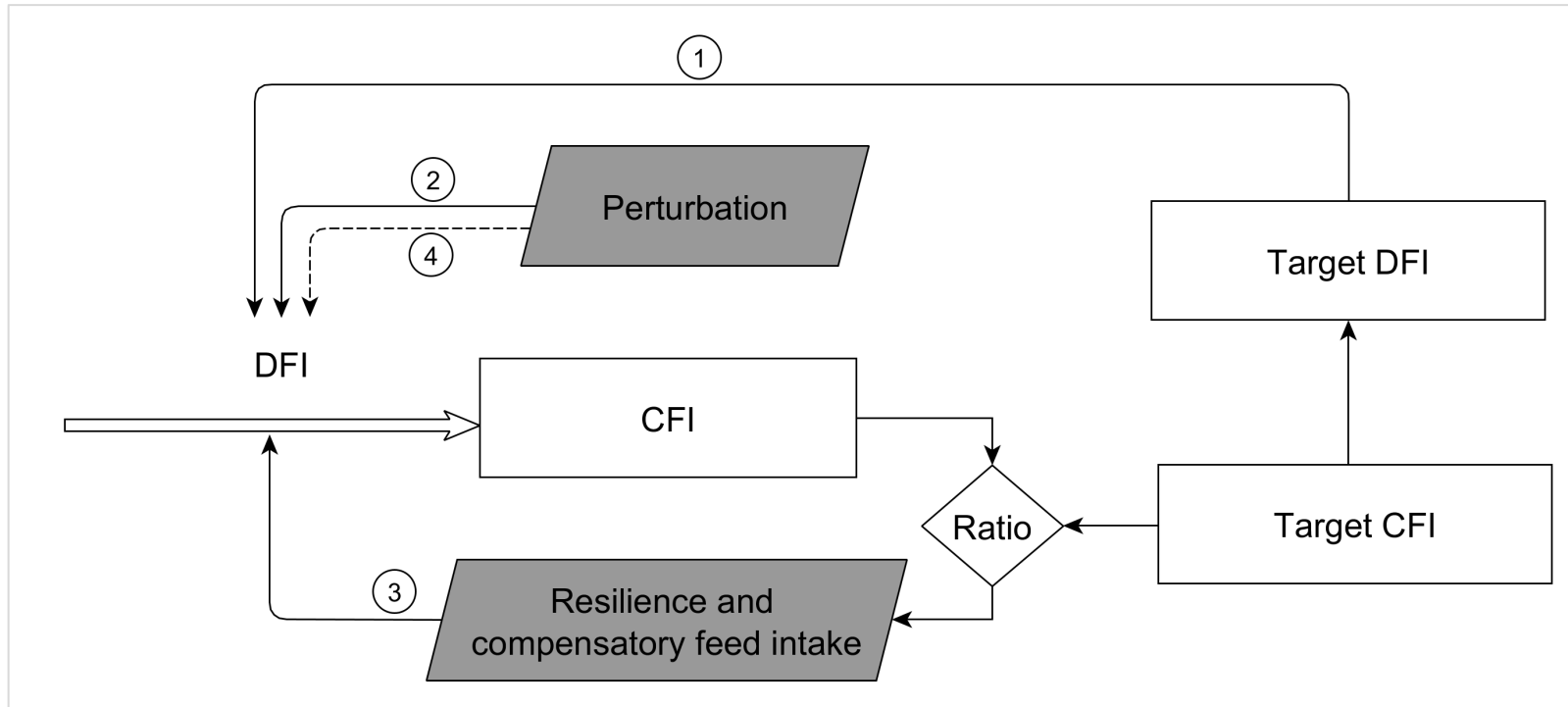
that a reasonable number of data were used to estimate the model parameters. The magnitude was determined by calculating the maximum reduction of a deviation from the target trajectory. Because CFI is increasing continuously, deviations from the target CFI were expressed as a percentage and an arbitrary value of 5% was set as a threshold value to identify a perturbation. To identify perturbations among all the deviations from the target CFI, a B-spline function of order 6 was fitted to the difference between the observed CFI and the target CFI. Any period during which the observed data deviated from the target CFI for more than 5 days and for more than 5% was considered to be the result of a perturbation. The interest of using a B-spline function is its high flexibility and its smoothing properties that allow to capture small deviations from the target CFI (Ramsay and Silverman, 2007).

Deviations that occurred only during the first week were not considered because pigs may encounter many stressors during this period (e.g., mixing of groups) and deviations from the target CFI of more than 5% occur frequently due to the small value of CFI during the first week. However, deviations that started during the first week and for which the selection criteria of duration and magnitude continue to hold during the second week were considered the result of a perturbation.

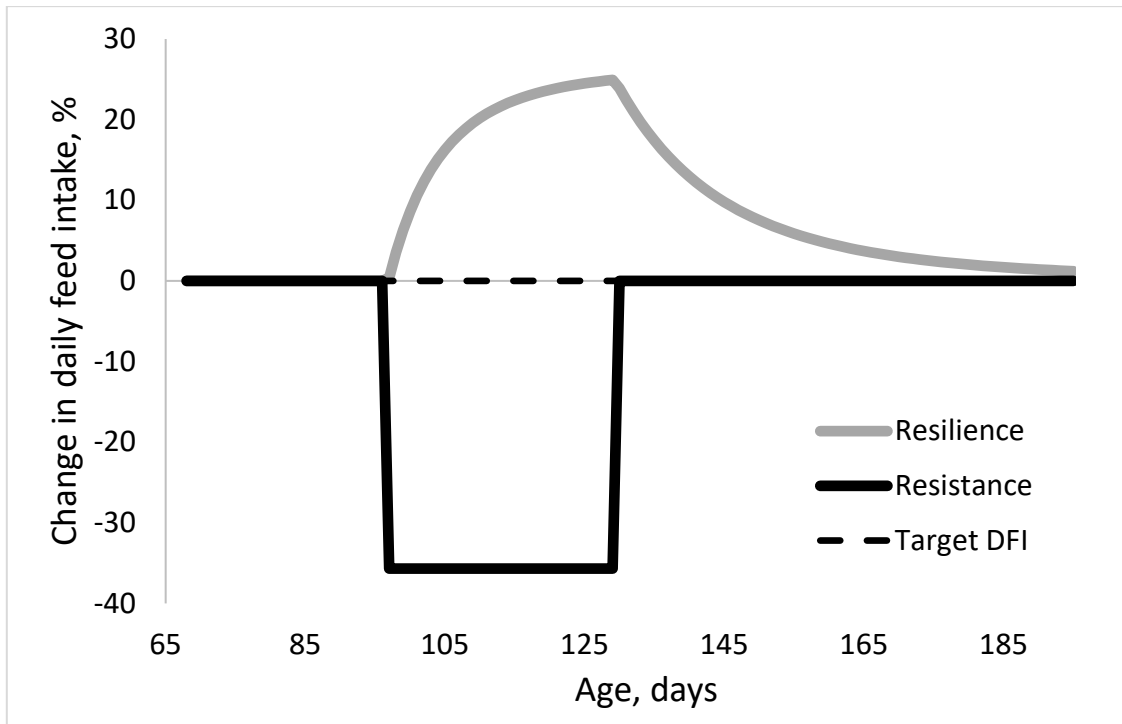
#### *Characterization of the response to a perturbation*

The model to characterize the animal's response to a perturbation is based on an ordinary differential equation and includes two components: the immediate impact of the perturbation and the response of the pig to the perturbation (Figure 2.1). A perturbation was assumed to have an instantaneous, negative, and constant impact on the DFI of the pig for the duration of the perturbing factor. The reduction in DFI will result in that the CFI deviates progressively from the target CFI. The ratio between CFI and the target CFI is used as a driving force to trigger the pig's resilience mechanism in a proportional way (Figure 2.1). The smaller the ratio between the CFI and the target CFI, the greater will be the intensity of resilience mechanism for DFI. The change in DFI due to perturbation (compared with the target DFI) is the sum of the components depicted by resistance (Figure 2.2, black line) and resilience including compensatory feed intake (Figure 2.2, grey line). During the perturbed period, the resilience mechanism limits the effect of the perturbing factor. As indicated in Figure 2.2, at the end of the perturbed period, the negative effect of the perturbation (around -35%) is partially compensated for by the resilience mechanism (around +25%). Once the

perturbing factor is over, the negative effect on DFI disappears, but the CFI ratio will still be smaller than one. This results in compensatory DFI where the observed DFI will be greater than the target DFI that, in turn, results in that the CFI will approach the target CFI.



**Figure 2.1** General mechanism of a model that quantifies the pig's response to a perturbation. Solid arrows indicate causal relationships in the model, the double arrow indicates the flux, and the dashed arrow indicates the disappearance of perturbing factor. Numbers indicate the response elements: ① in the absence of a perturbation, the daily feed intake (DFI) is equal to the target DFI; ② the initiation of a perturbation has a negative and constant effect on DFI and, because of the reduction in DFI, the cumulative feed intake (CFI) starts to deviate from the target CFI; ③ the ratio between the CFI and the target CFI triggers the pig's resilience mechanism to limit the effect of the perturbation on DFI; ④ once the perturbing factor is over, its negative effect on DFI disappears, but the resilience mechanism is still active resulting in compensatory feed intake allowing the CFI to approach the target CFI.



**Figure 2.2** Mechanisms that determine the response of a pig to a perturbation. The perturbation is estimated to occur between around days 97 and 129 of age. The dashed line indicates the target trajectory of daily feed intake (DFI). The black line indicates the constant and negative impact of the perturbation on the pig (resistance), resulting in a 35.6% reduction in DFI. The grey line represents the resilience capacity (during the perturbation) and compensatory feeding of the pig (after day 129).

The perturbation model was conceptualized in a way that the impact of a perturbation on feed intake can be characterized by four parameters. Two parameters indicate the start ( $t_{start}$ ) and end times ( $t_{stop}$ ) of the perturbing factor, while the third parameter ( $k_1$ ) describes the constant negative impact of the perturbation on DFI. The fourth parameter ( $k_2$ ) is the marginal response in DFI due to a change in the ratio between the CFI and the target CFI, and describes the capacity of the pig to adapt to the perturbation through resilience and compensatory feed intake. The perturbation model is therefore the result of resistance and resilience mechanisms and can be written as:

$$\frac{d}{dt}CFI(t) = Target\_DFI(t) * (1 - Resistance(t) + Resilience(t)) \quad (2a)$$

where “Resistance(t)” takes the value of  $k_1$  between the  $t_{start}$  and  $t_{stop}$  time, and is zero otherwise, while “Resilience(t)” is described by:

$$Resilience(t) = k2 * \left(1 - \frac{CFI}{Target\_CFI}(t)\right) \quad (2b)$$

It is acknowledged that the proposed procedure includes a number of arbitrary elements. This concerns the choice of feed intake as the only response criterion, the model choices for the target trajectory for CFI and for the DFI during and after the perturbed periods, and the step-wise method to quantify the animal's response. However, the method is generic in that the different elements can be changed and adapted as judged necessary.

#### *Data source used for model calibration*

Data were collected from an experimental farm of INRA in Le Magneraud (Charente-Maritime, France). Five pigs from the same batch (i.e., they were born on the same farm and approximately on the same day) were chosen to demonstrate the procedure. The pigs entered the same growing facility at 68 days of age and stayed there until reaching their slaughter weights (124 kg on average). Feed was provided ad libitum. Feed intake was recorded on a daily basis using the single-place Acema 64 electronic feeder (Acemo, Pontivy, France) as described by Labroue *et al.* (1994). Because CFI is sensitive to missing data (e.g., due to loss of a radio-frequency identification (**RFID**) ear tag or malfunctioning of the feeder), a procedure to deal with missing data was developed (Supplementary Material S2; an example of missing data estimation by the procedure is shown in Figure S1). There were no missing feed intake records for the five pigs used here to illustrate the procedure. Because pigs were fasted one day before leaving to slaughterhouse, the last observation of feed intake of each pig was ignored.

#### *Statistical analysis*

All statistical and optimization procedures were performed using R software version 3.5.0 (<http://cran.r-project.org/>). To account for scale differences in the target CFI (reparametrized Equation 1), a weighted regression procedure was applied using  $(1/CFI)^2$  as statistical weight. The optimization was performed using the non-linear function “nlsLM” of the package “minpack.lm”. The structural identifiability of reparametrized Equation 1 and Equations 2a and 2b was tested using the software DAISY (Bellu *et al.*, 2007). All equations were structurally identifiable, meaning that the parameter estimation problem is well posed and it is theoretically possible to estimate

uniquely the model parameters given the available measurements (Muñoz-Tamayo *et al.*, 2018).

The test for auto-correlation was performed by a Wald-Wolfowitz runs test. To fit the B-spline function to the difference between the observed CFI and target CFI, the package “fda” was used. To characterize the pig’s response to a perturbation, Equations 2a and 2b were solved using the “ode” function of the “desolve” package with an integration step size (dt) of one day. The optimization was done using the “optim” function.

## Results

The procedure is illustrated step-by-step for one of the pigs and the results for all five pigs are presented in Table 2.1.

**Table 2.1** Parameter estimates of the target trajectory of cumulative feed intake (CFI) and of the perturbation model to characterize the response to a perturbation of five grouped-housed growing pigs

Pig	Function type <sup>1</sup>	Remaining data <sup>2</sup>	t <sub>last</sub> (day)	Parameter estimates of the target CFI model				Parameter estimates of the perturbation model			
				t <sub>0</sub> (day)	t <sub>s</sub> (day)	CFI <sub>mid-point</sub> (kg)	CFI <sub>last</sub> (kg)	t_start (day)	t_stop (day)	k1 (%)	k2
01	QL	37	195	67.3	162	155	334	96.9	129	-35.6	2.81
02	L	37	195	81.8			231	97.7	134	-68.6	1.26
03	QL	22	214	67.9	133	109	260	96.7	152	-52.6	2.73
04	Q	32	195	67.2		149	326	100	151	-51.5	5.13
05	Q	25	194	66.6		157	331	103	154	-49.1	5.13

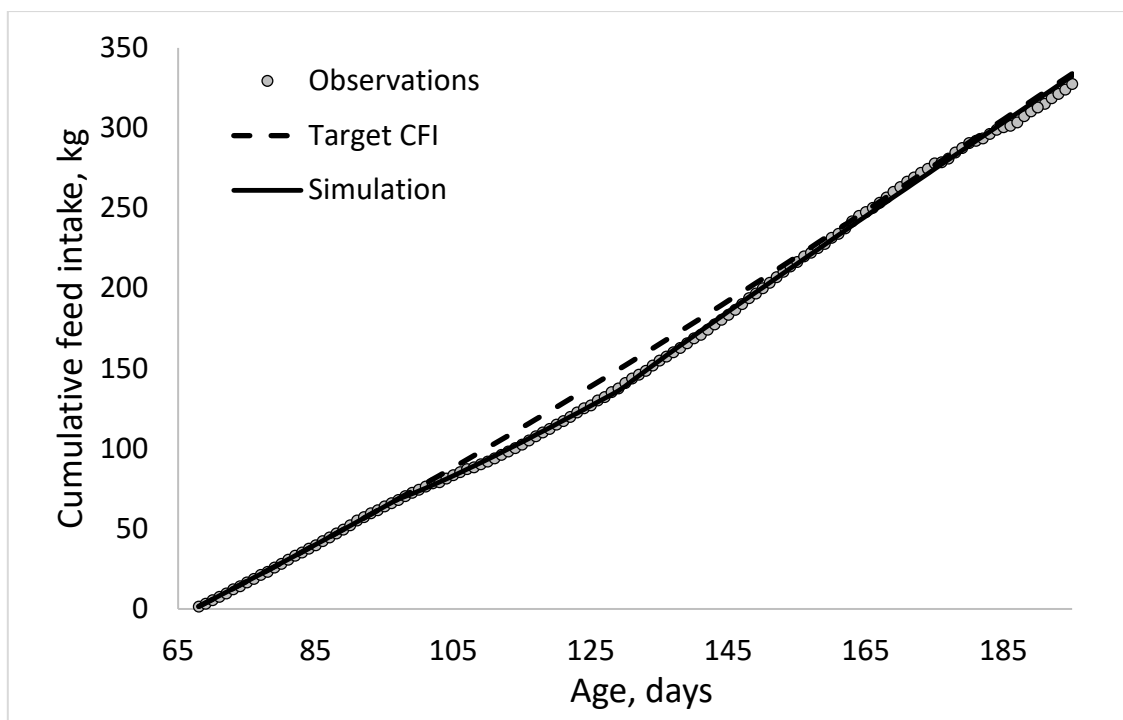
t<sub>last</sub> = the last observed age in the growing period; t<sub>0</sub> = estimated age at which CFI = 0; t<sub>s</sub> = the age when the quadratic segment changes to the linear segment in the quadratic-linear function; CFI<sub>mid-point</sub> = estimated CFI at the mid-point of the growing period; CFI<sub>last</sub> = estimated CFI at t<sub>last</sub>; t\_start = the day the perturbing factor started; t\_stop = the day the perturbing factor ended; k1 = instantaneous reduction in daily feed intake at t\_start; k2 = resilience parameter.

<sup>1</sup> Function type for the target CFI: QL = quadratic-linear function; Q = quadratic function; L = linear function.

<sup>2</sup> Remaining data: number of observations used to estimate the target CFI.

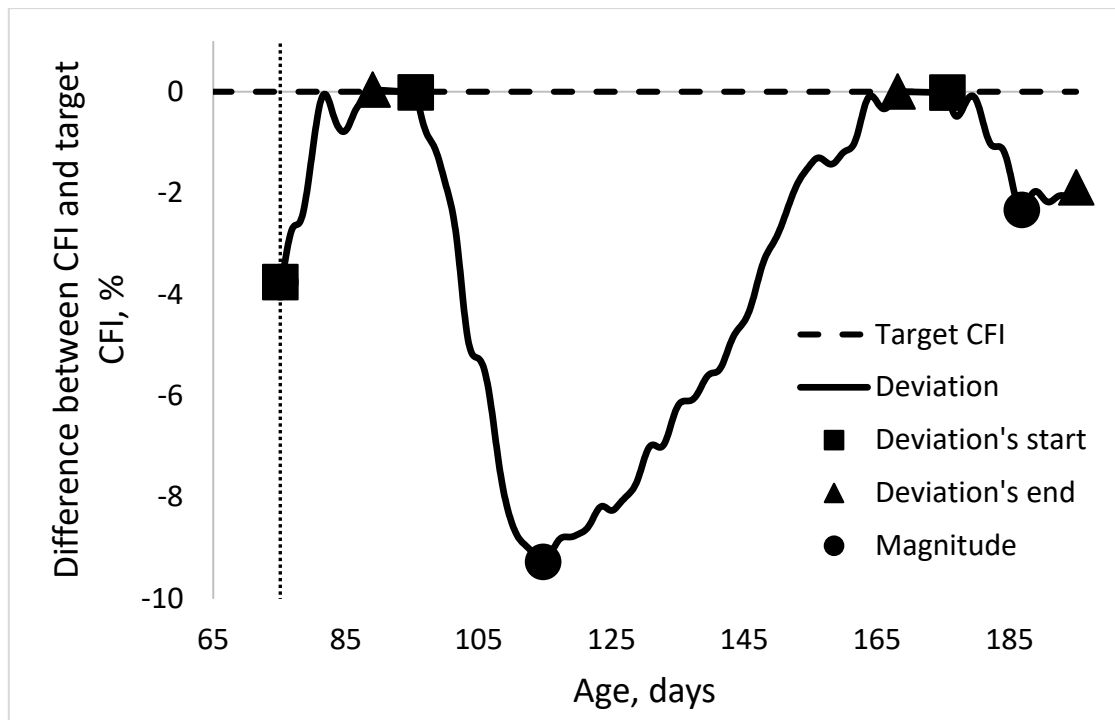


The target CFI of pig 01 was estimated using the quadratic-linear function of the reparametrized Equation 1. The auto-correlation test was conducted to temporarily remove observations associated with perturbed periods. The process was terminated when 37 CFI observations remained, even though auto-correlation still existed. Further application of the procedure would result in fewer than 20 remaining observations. Estimated parameters of the target CFI are indicated in Table 2.1. Figure 2.3 shows the target CFI against observed CFI, illustrating that the observed CFI deviated from the target CFI from 100 to 150 days of age and, to a lesser extent after 185 days of age.



**Figure 2.3** Cumulative feed intake (CFI) of a pig in response to a perturbation. The target CFI is described by a quadratic-linear model (the change in model segments occurred at 162 days). The perturbation was estimated to occur between 97 and 129 days of age, resulting in a deviation of the CFI from the target CFI.

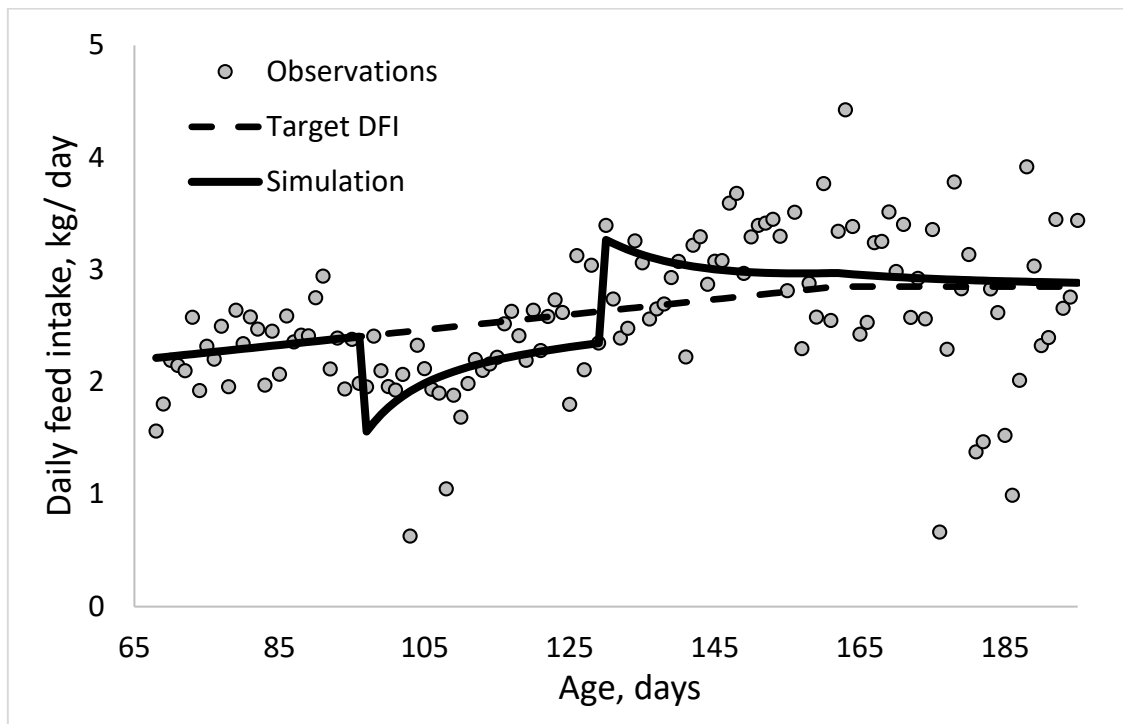
Figure 2.4 illustrates the differences between the observed and target CFI. Not considering the data of the first week, three deviations from the target CFI were detected. Given the selection criteria for a perturbation, only one deviation was considered as a perturbation. The analysis using the B-spline function indicated that it lasted from 96 to 168 days of age and the maximum deviation was 9.3%, which occurred at 115 days of age.



**Figure 2.4** Difference between the observed cumulative feed intake (CFI) and the target CFI of a pig. Three deviations were detected but, based on the selection criteria for a perturbation, only one deviation was considered as a perturbation. Deviations during the first week of growing period (indicated by the vertical dashed line) were not considered as perturbations.

Equations 2a and 2b were used to estimate the parameters describing the response of the animal to a perturbation. The period during which the perturbation occurred was estimated to start at 97 days of age ( $t_{\text{start}}$ ) and to end at 129 days of age ( $t_{\text{stop}}$ ). The instantaneous reduction in DFI at the onset of the perturbation  $k_1$  was estimated at 35.6%. The estimated value of the resilience parameter  $k_2$  was 2.81, which indicates that if the CFI is 1% below the target CFI, the pig would strive to eat 2.81% more compared to its target DFI. At 129 days of age, the negative effect of the perturbing factor stopped, but the resilience mechanism remained active because the CFI was still lower than the target CFI. The ratio between the two was therefore still below one, resulting in compensatory feed intake. The response of this animal to a perturbation is given in Figure 2.5 for the change in DFI and in Figure 2.3 for CFI. The maximum deviation in CFI occurred when the perturbation stopped at 129 days. At 130 days, the CFI was 139 kg, which was 9% below the target CFI of 152 kg. This triggered a compensatory feed intake in which the DFI was 24% greater than the target DFI

(Figure 2.5). Because of the compensatory feed intake, the CFI gradually approached the target CFI (Figure 2.3).



**Figure 2.5** Daily feed intake (DFI) of a pig and modelling results. The perturbing factor induced an immediate reduction in DFI (compared with the target DFI) at the beginning of the perturbed period, which was counteracted by resilience mechanisms of the pig. Once the perturbing factor ended, the pig consumed more feed than the target DFI through compensatory feed intake to recover.

Table 2.1 shows the estimated parameters of the target CFI and of the response to perturbations of five pigs. The process to temporarily remove observations with negative residuals was always stopped while there was still auto-correlation to ensure retaining at least 20 observations. The procedure indicated that all five pig were affected by one major perturbation during the growing period. Moreover, the start ( $t_{\text{start}}$ ) and the last ( $t_{\text{stop}}$ ) days of the estimated perturbation were approximately similar for all five pigs ( $99 \pm 2.7$  days and  $144 \pm 11.6$  days, respectively). However, values of the response traits ( $k_1$  and  $k_2$ ) varied between these pigs (from -68.6% to -35.6% for  $k_1$ ; and from 1.26 to 5.13 for  $k_2$ ).

## Discussion

Characterization and quantification of the response of animals to perturbations are important in animal management and breeding. The recent and rapid development of monitoring devices in combination with data analysis and modelling techniques offer a great potential to progress in this area. This study illustrated how daily feed intake records can be used to characterize and quantify elements of resistance and resilience in growing pigs.

### *Difficulties in modelling the response of animals to perturbations*

Attempts to quantify the animal's response to perturbations have been made both statistically and conceptually. However, traditional single time-point recording of performance traits cannot capture the whole process in which the response to and recovery from perturbations of an animal occurs (Friggens *et al.*, 2017). For example, Pastorelli *et al.* (2012) conducted a meta-analysis to study the consequence of six sanitary perturbations on feed intake and growth in growing pigs. However, only a small number of experiments in the literature was available that allowed to quantify the response of the animals to these perturbations. They differentiated the response of animals to the different perturbations but, due to the type of data reported in the literature, they could only report the response as an average reduction in feed intake and/or daily gain for the whole experimental period. Mechanistic models that represent the dynamic response of animals to a perturbation have been developed based on conceptual grounds (Wellock *et al.*, 2003b; Sandberg *et al.*, 2006). However, despite their theoretical interest, there has been little high-frequency data thus far to challenge the proposed concepts and to ensure practical application of these models. This kind of data is required to detect, understand, and quantify the response of an animal to a perturbation (Codrea *et al.*, 2011; Wallenbeck and Keeling, 2013; Munsterhjelm *et al.*, 2015).

### *Modelling the target trajectory of feed intake*

In modelling growth and feed intake, different approaches towards “cause” and “effect” have been used. In the “push approach”, feed intake is often described as a simple function of time or body weight driving growth. Frequently used functions include the monomolecular function (i.e., an exponentially declining function with an

asymptote), the power function, and a Gamma-function describing feed intake relative to maintenance energy requirements (Van Milgen *et al.*, 2008; Black, 2009; NRC, 2012). In the “pull approach”, functions for desired growth (i.e., protein and lipid deposition) are defined which, in combination with aspects of energy metabolism, result in a desired feed intake. Most feed intake models describe DFI, rather than CFI. In an analysis of different growth functions, Schulin-Zeuthen *et al.* (2008) indicated that body weight could very well be described by a monomolecular function of CFI, basically indicating that animals grow because they eat and, at maturity, they eat for maintenance.

It is interesting to note that for all five animals used in this study, a significant auto-correlation remained for CFI unless the procedure was allowed to proceed beyond the limit of 20 remaining observations. The presence of auto-correlation in CFI data indicates that there are patterns in feed intake that cannot be captured by a polynomial model with (potentially) four parameters. Although the choice of 20 observations was arbitrary, it is a compromise between the number of remaining data and the presence of auto-correlation in the target CFI. If the filtration procedure was allowed to go further, there would be no data with auto-correlated residuals, but the estimation of the target CFI (which is described by maximum four parameters) would be based on a small number of observations. In contrast, if the procedure was stopped earlier (with more remaining observations), the target CFI would include more data with auto-correlated residuals, some of which could be due to a perturbation.

### *Modelling the response to perturbations*

In describing the response of an animal to a perturbation, Wellock *et al.* (2003a) and Sandberg *et al.* (2006) used a pull approach to describe the feed intake response. This approach is probably biologically more appropriate than the empirical push approach that was used in this study, but it requires an explicit representation of the nutrient requirements for growth and those related to the perturbation (e.g., for the immune response). Perturbations can have both direct and indirect effects on performance through metabolism and nutrient utilization (Le Bellego *et al.*, 2002; Pastorelli *et al.*, 2012). However, when feed intake is the only measured response trait, it is difficult to disentangle these direct and indirect effects.

To characterize resistance and recovery capacity of the animal, Sandberg *et al.* (2006) proposed a model of the DFI response to a pathogen challenge. The resistance

part of the model in this study (Figure 2.2, black line) is conceptually similar to the model of Sandberg *et al.* (2006). The difference is that they included a lag time from inoculating the pathogen until the first sign of a reduction in feed intake, which requires knowledge of when the animals are exposed to a pathogen. Also, Sandberg *et al.* (2006) assumed existence of a duration where feed intake gradually decreases to its minimum value, followed by a plateau before it gradually recovered to the reference value. The recovery rate used by that model can be compared to the resilience mechanism proposed in our approach (Figure 2.2, grey line), which allows for compensatory feed intake to occur. The model of Sandberg *et al.* (2006) does not include an explicit representation of compensatory feed intake, although this may occur through the pull approach used in their model. The existence of compensatory feed intake following perturbations is supported by other studies (Kyriazakis and Emmans, 1992; Pastorelli *et al.*, 2012).

The model proposed in this study is also somewhat similar to the spring and damper model developed by Sadoul *et al.* (2015). In that model, which is analogous to a suspension system in a car, the impact of a perturbation is considered as a “pulling” force on the system and resistance and resilience are characterized by the ability of the system to resist from being deformed (i.e. damper) and to reduce the amplitude of the deformation (i.e., spring). After the perturbing force is released, the system recovers by itself and the recovery rate depends on the ratio between the parameter values of the spring and damper. Parameter values of the spring and damper also determine whether oscillations in the response will occur. Although these oscillations may be used to represent compensatory feed intake in terms of DFI, it may be more difficult to use these oscillations to represent compensatory feed intake in terms of CFI. As illustrated by the models of Sandberg *et al.* (2006), Sadoul *et al.* (2015), and this study, there are different ways to represent the response of animal to a perturbation. At this stage, we aimed to keep the model as generic and as simple as possible, but any aspect of the procedure can be changed as deemed necessary. For example, knowledge about the origin of the perturbation can be helpful in establishing an appropriate perturbation model. In the current model, a specific duration of the perturbing factor is included, which would be appropriate to reflect a period of heat stress. Other perturbing factors such as a viral challenge may have a specific starting point (with or without a lag time) but the duration of the challenge may be less clear. The effect of a viral challenge may be reduced because the perturbing factor becomes

less effective by itself or because the animal builds up resilience through its immune response even though the perturbing factor may still be present.

### *Possible future developments*

The data analysis procedure was applied here to five animals that were raised at the same time in the same environment. The feed intake curves were analysed separately for each pig, but the period of perturbation appeared to be similar for the five pigs (Table 2.1). It can be speculated that these pigs were challenged by the same perturbing factor, but the responses differed between the five pigs. The proposed data analysis procedure has the potential to be applied on a large number of pigs. For example, it could be used to identify periods during which several pigs (e.g., in the same pen or in the same barn) reduce their feed intake at the same time. If this occurs for a considerable number of pigs in the group, it may be reasonable to assume that all pigs in that group were exposed to the same perturbing factor. This would allow quantifying differences in the responses of individual pigs to a common perturbing factor through the resistance and resilience traits  $k_1$  and  $k_2$ . Certainly, this has a great potential in animal breeding to estimate heritabilities and to evaluate relationships between performance and robustness traits (Guy *et al.*, 2012; Hermesch *et al.*, 2015). Elements of the data analysis procedure proposed in this study can also be used in precision livestock farming. For example, it could be used as an early warning system if deviations in feed intake occur relative to the target CFI. Likewise, specific management strategies (e.g., in terms of nutrition, medication or care) may be given to animals that deviate from their target CFI to limit the impact of the (known or unknown) perturbing factors and to facilitate the recovery of the animals so that they can regain their target CFI.

## Conclusion

The recent development of monitoring technologies offers new opportunities for livestock management. Recording of individual feed intake in group-housed pigs is becoming more accessible and feed intake can be very informative about the health and welfare status of the animal. The model and data analysis procedure proposed in this study showed to have the potential to detect the impact of a perturbation on the

feed intake and to quantify the response of the animal in terms of traits related to resistance and resilience.

### **Acknowledgements**

This study has been funded by the European Union's H2020 project Feed-a-Gene under grant agreement no. 633531. Hieu Nguyen-Ba also received funding from the INRA meta-programme Adaptation of Agriculture and Forests to Climate Change (INRA-ACCAF) and from the French Digital Agricultural Convergence Lab (#DigitAg) for his PhD work.

Preliminary results of this study were published at the 69<sup>th</sup> Annual Meeting of the European Federation of Animal Science (Nguyen-Ba *et al.*, 2018).

### **Declaration of interest**

The authors declare that there is no conflict of interest in this study.

### **Ethics statement**

No ethic approval was required in this study.

### **Software and data repository resources**

The R code of the procedure described in this article and feed intake data of pig 01 are accessible on the ZENODO data warehouse (DOI: [10.5281/zenodo.3366107](https://doi.org/10.5281/zenodo.3366107)). Users need to store all three files in one folder and change the working directory of the file 'Procedure\_quantify\_perturbation.Rmd' accordingly to reproduce the results of this article.



### 3. Supplementary Material

#### S1. An example of function re-parameterization

The function to estimate the target trajectory curve of CFI is described in Equation 1 in the article. Consider the case that the target CFI is represented by a quadratic function then:

$$\text{Target CFI}(t) = a + bt + ct^2 \quad (\text{S1})$$

To reparametrize this model to a new model with three biologically meaningful parameters (i.e.,  $t_0$ ,  $CFI_{mid-point}$ , and  $CFI_{last}$ ;  $t_{last}$  is a constant determined by the dataset), the following system of algebraic equation needs to be solved:

$$\begin{cases} 0 = a + bt_0 + ct_0^2 \\ CFI_{mid-point} = a + b(t_0 + \frac{t_{last}-t_0}{2}) + c(t_0 + \frac{t_{last}-t_0}{2})^2 \\ CFI_{last} = a + bt_{last} + ct_{last}^2 \end{cases} \quad (\text{S2})$$

The Maple software (<https://www.maplesoft.com/>) was used to replace a, b, and c in equation S1 as:

$$a = ((t_{last} * CFI_{last} - 4 * CFI_{mid-point} * t_{last} + t_0 * CFI_{last}) * t_0) / (t_{last}^2 - 2 * t_0 * t_{last} + t_0^2)$$

$$b = (-(t_{last} * CFI_{last} - 4 * CFI_{mid-point} * t_{last} + 3 * t_0 * CFI_{last} - 4 * CFI_{mid-point} * t_0)) / ((t_{last} - t_0)^2)$$

$$c = (2 * (-2 * CFI_{mid-point} + CFI_{last})) / (t_{last}^2 - 2 * t_0 * t_{last} + t_0^2)$$

Re-parameterizations of other functions of the target CFI are described in detail in the R-code associated to this article (DOI: [10.5281/zenodo.3366107](https://doi.org/10.5281/zenodo.3366107)).

#### S2. Dealing with missing data

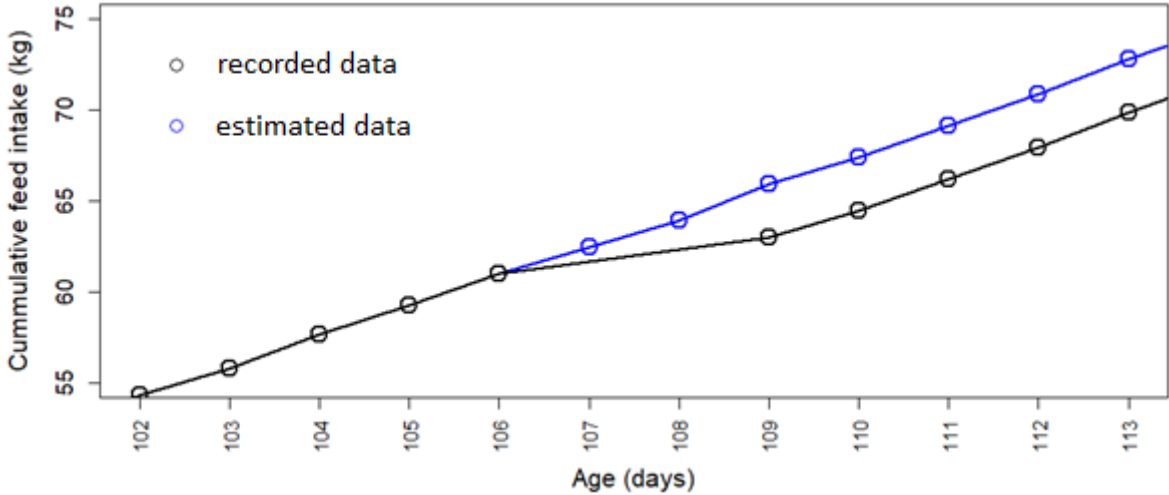
Missing data are defined as the data during a period for which there are no feed intake records. Missing data may be caused by a power outage, an insensitive sensor, or loss of an identifying ear tag. Ignoring missing data would result in inappropriate CFI data, because the CFI curve would be shifted downward and the missing data could be identified as a perturbation.

To correct for missing data we assumed that there is a continuous pattern of CFI data just before and after the period of missing data. When data are missing for n days,

data for n+1 days before and n+1 days after the period of missing data were used to perform a quadratic regression with a model that included a downward shift in CFI associated with the period of missing data. The estimated downward shift in CFI was used to calculate the missing feed intake data. The equation to estimate missing data is written as follow:

$$CFI(t) = \begin{cases} a1 + bt + ct^2, & t < \text{missing day}(s) \\ a2 + bt + ct^2, & t > \text{missing day}(s) \end{cases} \quad (S3)$$

Where “t” is the age of the animal (days) and “CFI(t)” is the CFI value at day “t”. Parameters a1 and a2 indicate intercepts of the quadratic function at the days before and after missing data, respectively. The estimated difference between a1 and a2 is attributed to the cumulative value of daily feed intake during the missing days.



**Figure S1** An example of missing data estimation. Feed intake records for days 107 and 108 were missing and resulted in a downward shift in cumulative feed intake. The missing data were estimated as the downward shift in cumulative feed intake of a quadratic regression between the three days before and the three days after the days associated with missing data.

## 4. The capacity of the model to include complementary information

In the procedure described above, to quantify the animal's response to a perturbation a model based on a differential equation was developed with the hypothesis that a perturbing factor can have a constant and negative impact on the feed intake during the whole perturbing period. This is certainly the case when animals face heat stress or nutritional perturbations (e.g., low quality feed or mycotoxins). In other cases where animals are challenged by sanitary perturbations or pathogens, the impact of perturbations on feed intake is often reported evolving with time (Kyriazakis and Doeschl-Wilson, 2009). In that case, the perturbation will have a start time (i.e., the onset of infection) but not a stop time. The pathogen effects on feed intake rely mostly on the defensive capacity of animal's (e.g., the immune system) (Kyriazakis and Doeschl-Wilson, 2009). It is expected that the pathogen load will be gradually attenuated with time because the pathogen becomes less effective by itself or because increased activity of the host's defensive systems. Therefore, the negative effect of pathogens on feed intake will be over once the animal's immune system fully counteract their virulence.

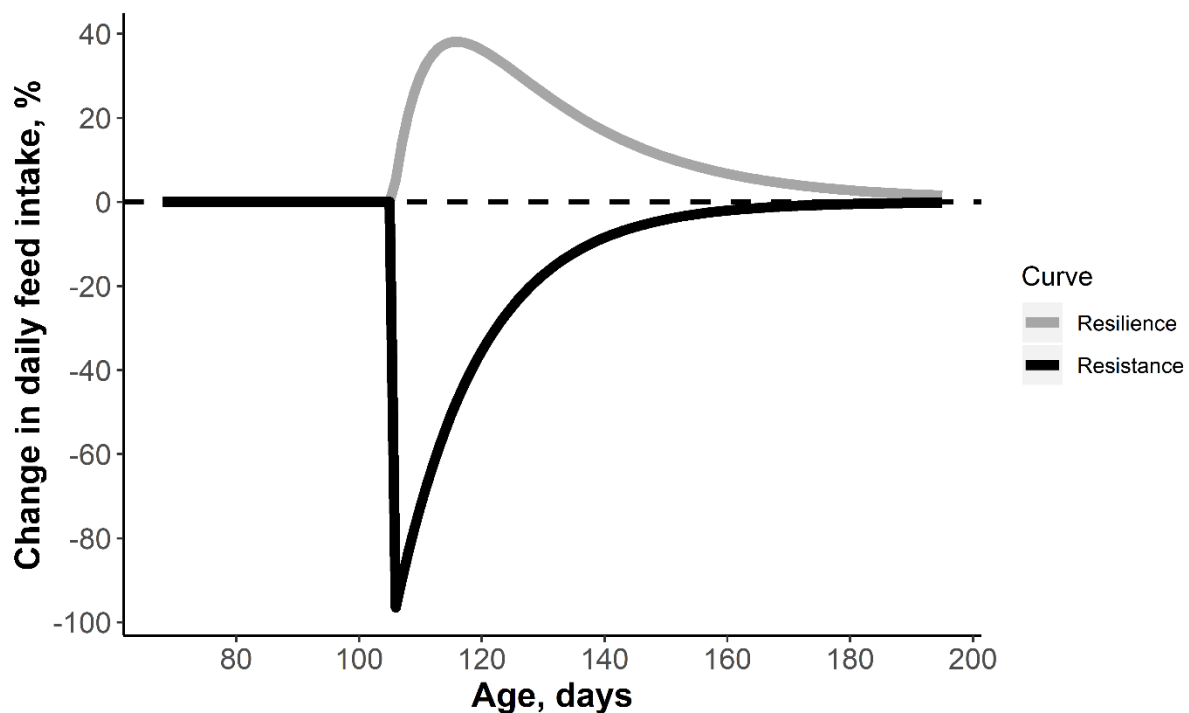
Our model is capable of characterizing this type of response. This can be done by replacing the constant immediate reduction in DFI (i.e.,  $k_1$ ) with dynamic response whose negative effect on feed intake is diminishing over time. This dynamic system can be described by a differential equation as follows:

$$\frac{d}{dt}k_1(t) = k_1(t) * \alpha, \quad t \geq t_{start} \quad (4)$$

where ' $k_1(t)$ ' indicates the negative effect of perturbation on DFI over time since the onset of perturbation ( $t_{start}$ ) and ' $k_{1_{initial}}$ ' indicates an initial value (%) of  $k_1$  at day ' $t_{start}$ '. It is expected that the negative effect of perturbation on DFI will be attenuated with time. The rate of this attenuation is characterized by the parameter ' $\alpha$ ' (%). At the point the animal's defensive system completely counteract the negative effect of pathogen on DFI (or the negative effect of pathogen fades away by itself), the value of ' $k_1$ ' becomes zero.

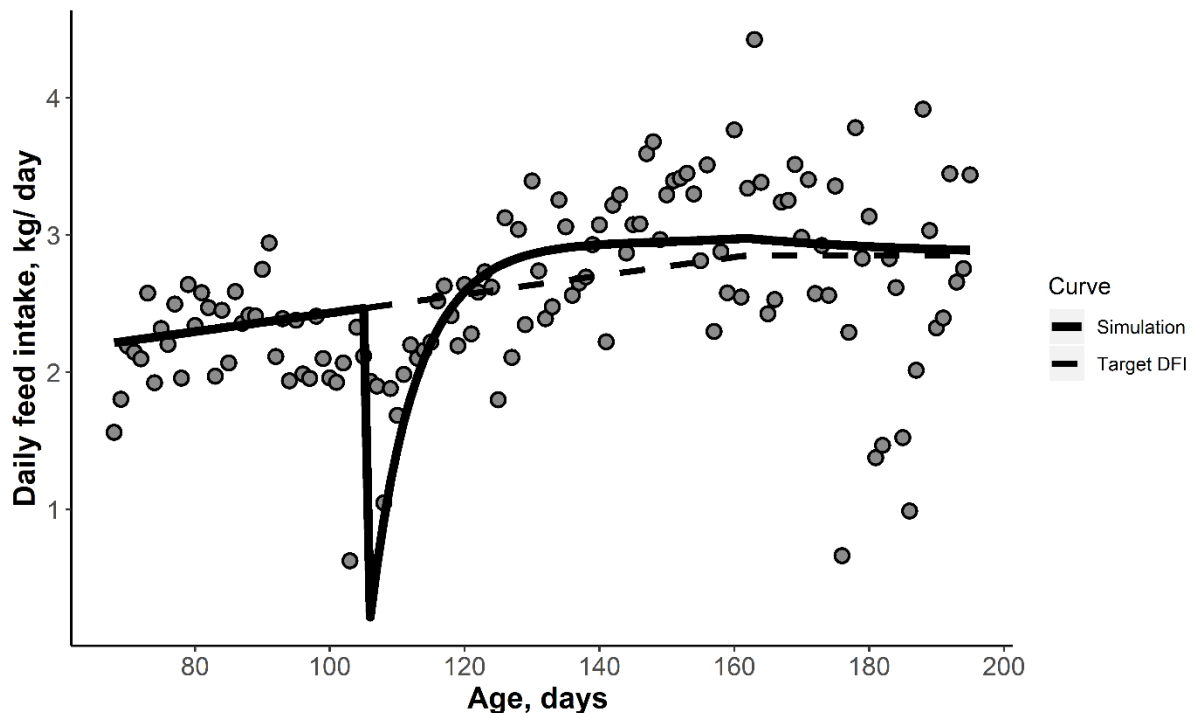
In equation (2b), the parameter ' $t_{stop}$ ' is no longer needed because with this type of perturbation the animal recovers by itself when it can counteract the virulence.

Integration of equation (4) into equation (2) the negative effect of pathogen on DFI (as described by the element 'Resistance(t)') is attenuated and approaching zero (black line, Figure 2.6). However, this only makes the DFI re-join the target DFI. The element 'Resilience(t)' helps the animal to increase the DFI over the target DFI through compensatory feed intake (grey line, Figure 2.6) to recover. It is worth mentioning that the shapes of resistance and resilience responses in Figure 2.6 are different from those in Figure 2.2.



**Figure 2.6** The dynamic change of daily feed intake (DFI) due to a perturbation such as pathogen or sanitary challenge. The dashed line indicates the target trajectory of DFI. DFI is estimated to decrease at 103 days of age. At this point, the perturbation had a severe effect on the feed intake. As time evolves the animal's defensive capacity gradually alleviates the negative effect of perturbation, as a result the black line is approaching to zero. Whereas, resilience capacity triggers compensatory feed intake to help the animal recovers.

This model was fitted to the data of pig number 01 in the five pigs reported in the article. The model simulation is illustrated in Figure 2.7.



**Figure 2.7** Daily feed intake (DFI) response of a pig due to an (assumed) pathogen or sanitary challenge. The dashed line indicates the target trajectory of DFI (target DFI). The perturbing factor causes a severe decrease in DFI at the beginning (compared with the target DFI). However, the pig can quickly counteract the negative impact of perturbation and gradually consume more feed than the target DFI through its defensive capacity and compensatory feed intake to recover.

As shown in Figure 2.7, the model can be fitted well also to the data of pig number 01. Compared to Figure 2.5, the structure of this model resulted in that the perturbation caused a bigger but shorter drop in DFI. However, the increase in DFI due to compensatory feed intake was smoother in the model of Figure 2.7 compared to that of Figure 2.5.

The response of animal to pathogens were summarized by the parameters in Table 2.2. The start of the perturbation ( $t_{start}$ ) and resilience capacity ( $k_2$ ) remain as they were in the previous model. The resistance however is the combination of both ' $k_{1initial}$ ' and ' $\alpha$ '. The initial reduction in DFI ' $k_{1initial}$ ' could represent the anorexia effect of pathogen on palatability of the pig; whereas, the rate of attenuating this initial effect ' $\alpha$ ' may refer to the capacity of the pig's defensive system. This interpretation illustrates that by slightly changing its structure, the model can have an interestingly different

concept to capture a different type of perturbation while still maintain the same number of parameters.

**Table 2.2** *Estimated parameters of the modified model to quantify the animal's response to pathogen*

Parameter estimates of the perturbation model				
	t_start	k1 <sub>initial</sub>	α	k2
Pig	(day)	(%)	(%)	
1	103	-94.6	7	3.44

t\_start = the day the perturbing factor started

k1<sub>initial</sub> = the initial value of the perturbing effect on daily feed intake

α = the rate the negative effect k1<sub>initial</sub> attenuates over time

k2 = resilience parameter

In conclusion, this example proves that by slightly modifying the model the users can easily quantify the response of animal to a different type of perturbation. The model is therefore very generic and can be adapted according to the objectives of users or the origin of perturbations.

# Chapter 3. Challenging the model to detect perturbations and quantify animal's response

## 1. Objective of the chapter

In the previous chapter, we developed the data analysis and modelling procedure to detect perturbations and quantify the response of individual pigs by only using feed intake data (i.e., without considering any other information). The procedure showed potential to quantify and compare resistance and resilience capacities of group-housed individuals when they faced to the same perturbation. The procedure was applied to a small group of five pigs.

The next objective of the PhD thesis was to challenge and evaluate the capacity of this procedure in (1) detection of perturbations, (2) quantification of individual's resistance and resilience traits under the effect of these perturbations and (3) compare these traits among group-housed animals. For that purpose, the procedure was applied to a dataset of an experiment where pigs received a diet with or without cereals contaminated with mycotoxins.




## 2. Modelling the feed intake response of growing pigs to diets contaminated with mycotoxins

Published article:

**H. Nguyen-Ba**, M. Taghipoor and J. Van Milgen 2020. Modelling the feed intake response of growing pigs to diets contaminated with mycotoxins. *Animal*, 1–8. (DOI: 10.1017/S175173112000083X)



## Modelling the feed intake response of growing pigs to diets contaminated with mycotoxins

H. Nguyen-Ba<sup>1,2</sup> , M. Taghipoor<sup>3</sup>  and J. van Milgen<sup>1†</sup> 

<sup>1</sup>PEGASE, INRAE, Institut Agro, 35590 Saint-Gilles, France; <sup>2</sup>Faculty of Animal Science, Vietnam National University of Agriculture, Hanoi, Vietnam;

<sup>3</sup>Université Paris-Saclay, INRAE, AgroParisTech, UMR Modélisation Systémique Appliquée aux Ruminants, 75005 Paris, France

(Received 14 November 2019; Accepted 27 March 2020)

Short title: Modelling the feed intake response to mycotoxins

### Abstract

Quantifying robustness of farm animals is essential before it can be implemented in breeding and management strategies. A generic modelling and data analysis procedure was developed to quantify the feed intake response of growing pigs to perturbations in terms of resistance and resilience. The objective of this study was to apply this procedure to quantify these traits in 155 pigs from an experiment where they received diets with or without cereals contaminated with deoxynivalenol (**DON**). The experimental pigs were divided equally in a control group and 3 DON-challenged groups. Pigs in each of the challenged groups received a diet contaminated with DON for 7 days early on (from 113 to 119 days of age), later on (from 134 to 140 days of age), or in both periods of the experiment. Results showed that the target feed intake trajectory of each pig could be estimated independently of the challenge. The procedure also estimated relatively accurately the times when DON was given to each challenged group. Results of the quantification of the feed intake response indicated that age and previous exposure to DON have an effect on the resilience capacity of the animals. The correlation between resistance and resilience traits was modest, indicating that these are different elements of robustness. The feed intake analysis procedure proved its capacity to detect and quantify the response of animals to perturbations and the resulting response traits can potentially be used in breeding strategies.

**Keywords:** Deoxynivalenol, Resistance, Resilience, Modelling, Individual Variation

## Implications

The feed intake analysis procedure shows its capacity to detect and quantify the feed intake response of growing pigs to a known perturbation and characterize these as resistance and resilience traits. These traits can be a potential source of information for genetic selection to breed animals for enhanced robustness.

## Introduction

Improving capacity of animals to function well under a wide range of environmental conditions (i.e., robustness) has been of great interest in livestock production, especially through genetic selection (Knap, 2005). A prerequisite for selection is the quantification of the traits of interest. However, robustness is difficult to quantify because it consists of “dynamic elements such as the rates of response to, and recovery from, environmental perturbations” (Friggens *et al.*, 2017). Because of these dynamic aspects, single time-point measurements are not enough to quantify robustness. The limitation of single time-point measurements can be illustrated by an example of two animals with different response mechanisms facing the same perturbation (adapted from Doeschl-Wilson *et al.*, 2012). Animal A is less affected by the perturbation than animal B (i.e., animal A is more resistant than animal B) but, once the perturbation is over, animal B recovers faster than animal A (i.e., animal B is more resilient than animal A). Thus, measuring the response of the animal at different stages of the perturbation will quantify different elements of robustness and can therefore have an impact on the breeding program. This emphasizes that the impact of a perturbation varies over time and results from different mechanisms of the response. Longitudinal data are therefore required to measure the dynamic response to and recovery from environmental perturbations (Friggens *et al.*, 2017).

With the development of monitoring technologies, production traits (e.g., feed intake and body weight) can now be recorded at the individual level and with a very high frequency. Information extracted from this type of data has shown to be useful to characterize individual animal resilience (Putz *et al.*, 2018). Doeschl-Wilson *et al.* (2012) indicated that mathematical modelling offers the possibility to summarize

complex mechanisms into a few parameters, thereby facilitating the ranking of animals. We recently developed a data analysis and modelling procedure to quantify the feed intake response of growing pigs to environmental perturbations in terms of resistance and resilience (Nguyen-Ba *et al.*, 2020). The procedure uses feed intake as input and deals with perturbations of known or unknown origin that decrease feed intake in pigs.

Mycotoxins are metabolites produced by fungi that can grow on cereals such as corn. The consumption of a mycotoxin-contaminated feed can result in reductions in feed intake and growth (Dersjant-Li *et al.*, 2003). Among the trichothecene mycotoxins, deoxynivalenol (**DON**) can have a profound effect on pigs due to their limited metabolic capacity to detoxify DON (Wu *et al.*, 2010). Although the consequences of DON on pigs have been well documented, the dynamic feed intake response during and after acute DON challenges has not been studied until recently. Serviento *et al.* (2018) studied the effects of DON on feed intake in individual growing pigs in relation to age and repeated exposure to DON. This data offers an opportunity to challenge and evaluate the novel procedure developed by Nguyen-Ba *et al.* (2020) to quantify resistance and resilience traits of growing pigs through their feed intake response to DON-contaminated diets and to compare these traits among animals.

## Material and methods

### *Animals and treatments*

Data from an experiment about the impact of DON on the feed intake of growing pigs were used (Serviento *et al.*, 2018). In brief, 155 growing pigs with an initial body weight of approximately 50 kg were used in an experiment that lasted from 99 to 154 days of age. Pigs were distributed equally into four groups: a control group (**CC**) and three DON-challenged groups (**DC**, **CD**, and **DD**). Pigs from group CC received a normal finishing diet throughout the study. Pigs from challenged groups also received the normal diet except during the challenge periods. The challenge periods lasted 7 days each during which pigs received a DON-contaminated diet. Pigs from group DC received a DON-contaminated diet early on in the experiment (i.e., from 113 to 119 days of age) and pigs from group CD received the DON-contaminated diet later on in the experiment (i.e., from 134 to 140 days of age). Pigs from group DD received the DON-contaminated diet during both aforementioned periods. All pigs were kept in the same room throughout the experiment. During the challenge periods, challenged and

non-challenged pigs were kept in two separated zones to avoid cross-contaminations by faeces and urine. Feed was provided *ad libitum* during the experiment. Feed intake of individual pigs was recorded by automatic feeding stations and was computed on a daily basis.

### *Description of the procedure to quantify resistance and resilience*

A data analysis and modelling procedure was developed to quantify the feed intake response of growing pigs to perturbations in terms of resistance and resilience (Nguyen-Ba *et al.*, 2020). The procedure encompasses detection of perturbations and quantification of the pig's response to a perturbation. The cumulative feed intake (**CFI**) rather than the daily feed intake (**DFI**) is used to detect perturbations in this procedure. The detection of perturbations is based on the hypothesis that there is a target trajectory curve of CFI (**target CFI**) that a pig desires to consume in a non-perturbed state. As a result of a perturbing factor, the CFI of the pig will deviate from the target CFI. Once the perturbing factor is over, the pig will try to regain its target CFI through compensatory feed intake. In the data analysis procedure, the target CFI was estimated by repeatedly fitting a polynomial function to CFI data in combination with the (temporary) elimination of data that lie below the fitted curve (i.e., observations that possibly result from the perturbed period). Then, a B-spline regression was used to fit a polynomial function to deviations from the target CFI. Information extracted from the B-spline function was used to estimate the start of each deviation and the time at which the difference between the CFI and the target CFI reached a maximum value. This maximum deviation corresponds to the point at which the pig starts to recover from a perturbation to regain its target CFI.

The second step quantifies the animal's response to a perturbation. It is hypothesized that a perturbing factor has an immediate and constant negative effect on DFI that can be characterized by three parameters:  $t_{start}$ ,  $t_{stop}$ , and  $k1$ . The first two parameters indicate the time when a perturbation starts and ends, whereas  $k1$  refers to the immediate and constant reduction in DFI at the start of the perturbation. The reduction in DFI will cause the CFI to deviate from the target CFI. The ratio between the CFI and the target CFI (**Ratio(t)**) is used as the driving force for a resilience mechanism that limits the negative effect of the perturbing factor. As soon as the perturbing factor is over, its negative effect on DFI disappears, but the resilience

mechanism remains active. This results in compensatory feed intake that allows the CFI to approach the target CFI. The resilience and compensatory feed intake capacity of the animal are characterized by the parameter  $k_2$ .

### *Modifications of the procedure*

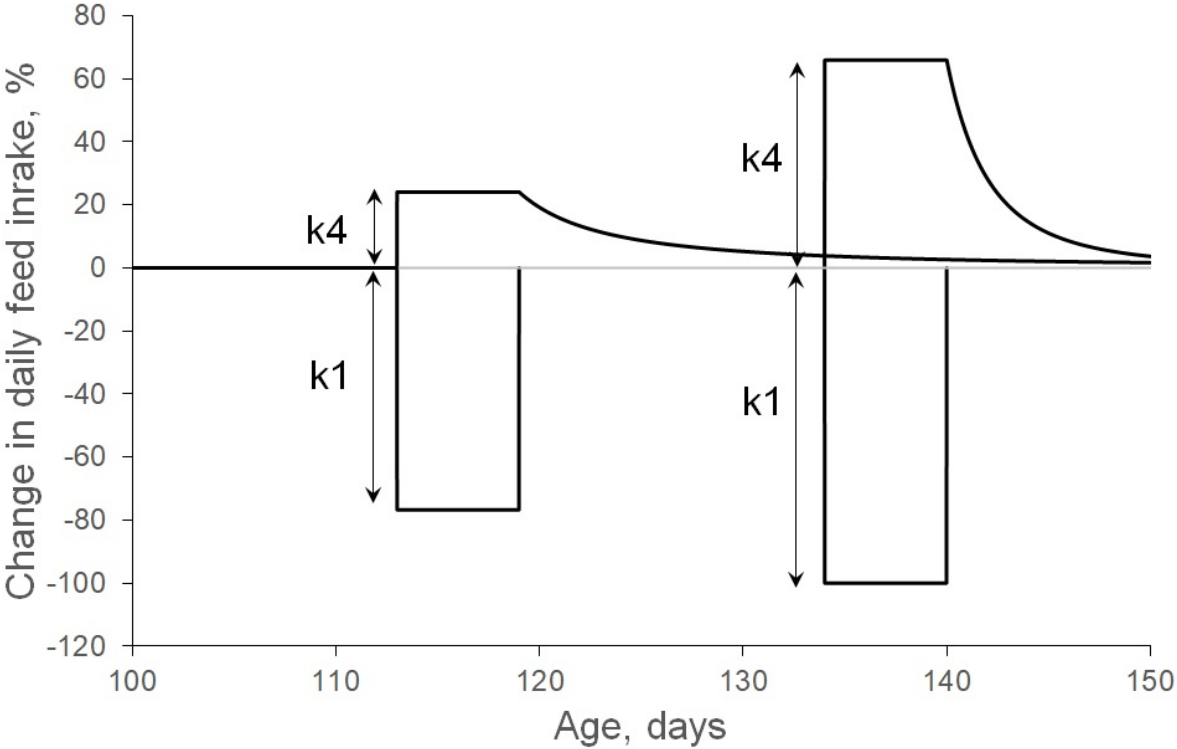
Some aspects of the original procedure of Nguyen-Ba et al. (2020) were modified to make it (more) suitable for the data in this study. To estimate the target CFI in the original procedure, an autocorrelation test was combined with the temporal removal of data with negative residuals from the dataset. Since the duration of the experimental period is short (55 days), the procedure often stopped because of a criterion in the procedure to keep a minimum number of remaining observations. In the modified procedure, only the 10% quantile of data with negative residuals were removed at each filtration step, resulting in a more gradual estimation of the target CFI. Results of both methods are compared in Supplementary Material Table S1.

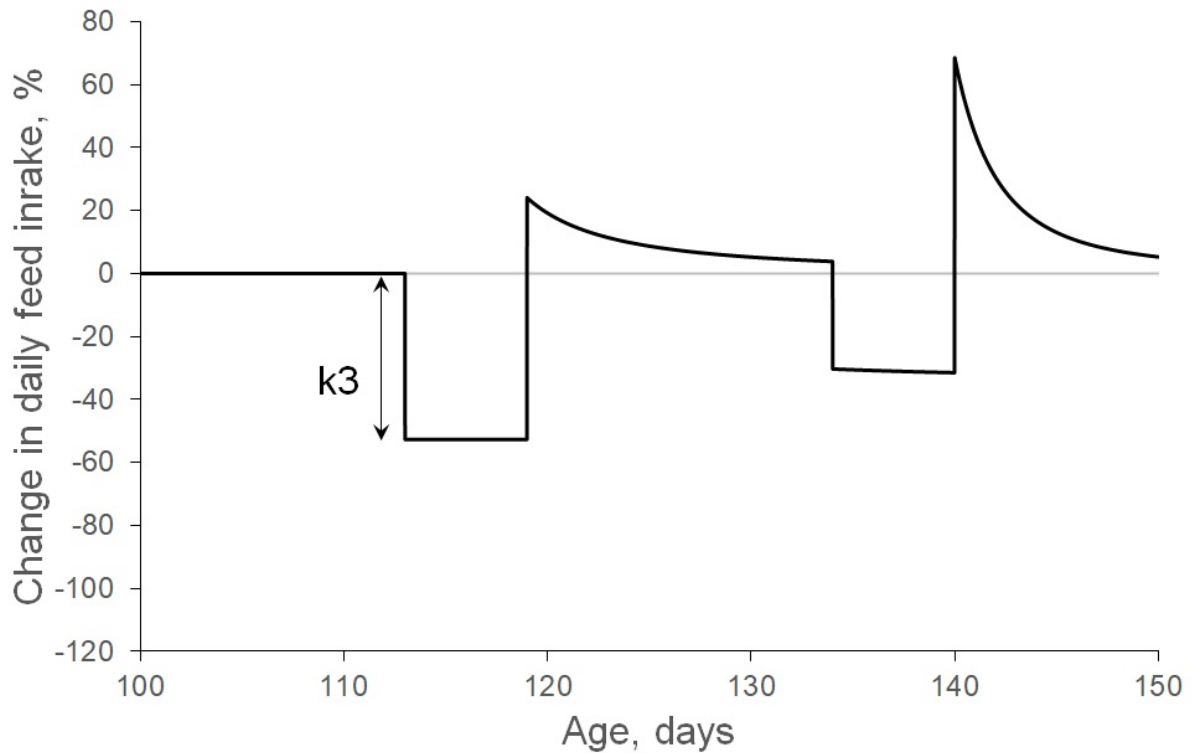
In the original procedure, a perturbation was defined as a deviation of the CFI from the target CFI by at least 5% and for a duration of at least 5 days. To test the capacity of the B-spline function to identify the period(s) of distribution of the DON-contaminated diet, these criteria were not applied here. Any period during which the CFI deviated from the target CFI was characterized by the start time, the magnitude of the deviation, and the duration (i.e., the time required for the CFI to regain the target CFI).

The Ratio(t) defines the intensity of the resilience mechanism, which varies with time. For example, the CFI will be small at an early stage of life and a small reduction in DFI will result in a considerable reduction in Ratio(t). At later stages of life, the CFI will be much larger, and the same perturbation will have little impact on Ratio(t). Ignoring the time-dependency of Ratio(t) will lead to a biased estimation of  $k_2$ . The original procedure was therefore modified to calculate Ratio(t) between CFI and the target CFI since the onset of the perturbation, and not since the start of the measurements. Equation (1) shows the modified Ratio(t) between CFI and the target CFI:

$$\text{Ratio}(t) = \begin{cases} \frac{\text{CFI}(t)}{\text{Target\_CFI}(t)}, & t \leq t_{\text{start}} \\ \frac{\text{CFI}(t) - \text{Target\_CFI}(t_{\text{start}})}{\text{Target\_CFI}(t) - \text{Target\_CFI}(t_{\text{start}})}, & t > t_{\text{start}} \end{cases} \quad (1)$$

where 't' is the age of the animal (days of age), 't\_start' is the time (days of age) when the perturbation starts, 'CFI(t)' and 'Target\_CFI(t)' are the CFI and the target CFI (kg) at day 't', respectively, and 'Target\_CFI(t\_start)' is the target CFI at day 't\_start'. The shape of the response of the resilience mechanism is different in the modified procedure compared to the original procedure. In the original procedure, the resilience capacity of the pig during the perturbation becomes progressively bigger (grey curve of Figure 2 in Nguyen-Ba et al., 2020), whereas in the modified procedure the resilience capacity causes a constant increase in DFI during the perturbation (Figure 3.1).





**Figure 3.1** Change in daily feed intake of a pig in response to receiving a diet contaminated with deoxynivalenol (DON) in two periods. Black lines = response mechanisms. Values smaller than 0 indicate the effect of resistance mechanisms and values greater than 0 indicate the effect of resilience mechanisms. The top panel illustrates the response mechanisms where the reduction in feed intake during the perturbation ( $k_1$ ) is counteracted for by a resilience mechanism ( $k_2$ , the proportional change in daily feed intake relative to the ratio between the actual cumulative feed intake and the target cumulative feed intake), which results in an attempt for compensatory feed intake ( $k_4$ ). The bottom panel illustrates the actual change in daily feed intake. The  $k_3$  corresponds to the difference between  $k_1$  and  $k_4$ . During the second perturbation, the actual feed intake is the result of the constant resistance and resilience mechanisms of the second perturbation and the declining resilience mechanism of the first perturbation.

Pigs in the group DD received the DON challenge twice. Each perturbation was modelled with independent resistance and resilience mechanism as shown in Figure 3.1. The equations are described as:

$$\text{Perturbation}_i(t) = -k_{1i} + k_{2i} * [1 - \text{Ratio}_i(t)] \quad (2a)$$

$$\frac{d}{dt} \text{CFI}_i(t) = \text{Target\_DFI}(t) * [1 + \text{Perturbation}_i(t)] \quad (2b)$$

where 'Perturbation<sub>i</sub>(t)' is the dynamic change in CFI at time 't' when the pig responds to a perturbation i (i = 1 and i = 2 correspond to the first and second DON challenge, respectively) and 'Ratio<sub>i</sub>(t)' represents the ratio associated to perturbation i as described in Equation (1). Target\_DFI(t) represents the target trajectory curve of DFI. Changes in DFI (relative to the target DFI) in the response to each DON challenge depend on the dynamic effects of 'Perturbation<sub>i</sub>(t)'. The sum of the changes relative to the target DFI results in the actual DFI as:

$$\text{DFI}(t) = \frac{d}{dt} \text{CFI}_{\text{total}}(t) = \text{Target\_DFI}(t) * [1 + \text{Perturbation}_1(t) + \text{Perturbation}_2(t)] \quad (3)$$

The value of Perturbation<sub>i</sub>(t) will be negative during the period of the perturbing factor and positive thereafter. The independence of the mechanisms of disturbance and recovery means that an animal may be recovering from a first challenge (through compensatory DFI) while, at the same time, it is affected by another challenge resulting in a reduction in DFI.

Because the change in DFI is constant during the period when the DON-contaminated diets are distributed, two other traits were estimated. The constant reduction in DFI during the DON challenge resulting from the resistance and resilience mechanisms can be calculated as  $k_3 = k_1/(1+k_2)$ . Likewise, the instantaneous increase in DFI once the feeding of the DON-contaminated diet stops is given by  $k_4 = k_1*k_2 / (1 + k_2)$ .

In the original procedure, all four parameters of the perturbation model (t\_start, t\_stop, k1, and k2) were estimated. With the current data set, it appeared difficult to estimate all these parameters, because the period of distributing the DON-contaminated diet lasted only seven days. For group DD, this would require the estimation of 11 parameters and, with 55 DFI observations, this can easily lead to an overparameterization of the model. It was therefore decided to fix t\_start and t\_stop at the start and end times of the distribution of the DON-contaminated diets.

### *Statistical analysis*

Parameter estimates for the target CFI and results from the B-spline functions were compared among the four groups to evaluate the capacity of the procedure to detect perturbations. The quantification of the response to DON challenges was carried out



in the three challenged groups (i.e., DC, CD, and DD). Since the parameters  $t_{\text{start}}$  and  $t_{\text{stop}}$  were fixed, only the resistance and resilience parameters were estimated. The  $k_3$  is the constant reduction in DFI during the perturbation and is easier to interpret than  $k_1$ . The model was therefore parameterized to estimate  $k_2$  and  $k_3$ , and  $k_1$  and  $k_4$  were calculated from these parameter estimates.

All statistical and modelling procedures were performed using R software version 3.6.1 (<http://cran.r-project.org/>). The optimization was performed by the non-linear function 'nlsLM' of the package "minpack.lm". To characterize the pig's response to a perturbation, Equations 2b and 3 were solved using the 'ode' function of the "deSolve" package with an integration step size (dt) of one day. The optimization was done using the 'optim' function. Statistical comparison was carried out using a one-way ANOVA test (the R base function 'aov'). Pearson correlations between parameters were calculated using the R base function 'cor'. In all analyses, differences were considered statistically significant if  $P < 0.05$  and as tendencies if  $P < 0.1$ .

## Results

### *Estimation of the target cumulative feed intake and detection of Deoxynivalenol perturbations*

The estimated parameters of the target CFI ( $t_0$ ,  $CFI_{\text{mid-point}}$ ,  $CFI_{\text{last}}$ ) and the average daily feed intake were compared among four groups (Table 3.1). No significant differences were found in the parameter estimates of the target CFI among the four groups.

**Table 3.1** Estimated model parameters of the target trajectory of cumulative feed intake of pigs that received a diet with or without deoxynivalenol (DON) contaminated cereals

	Experimental group <sup>1</sup>				RSE <sup>2</sup>	P-value
	CC (n = 39)	DC (n = 39)	CD (n = 38)	DD (n = 39)		
Model parameters						
t <sub>0</sub> (days) <sup>3</sup>	99.2	98.5	98.4	97.9	3.56	0.47
CFI <sub>mid-point</sub> (kg) <sup>3</sup>	71.2	73.3	68.3	69.4	11.0	0.32
CFI <sub>last</sub> (kg) <sup>3</sup>	156	159	150	150	19.2	0.11
Observed and calculated ADFI						
Observed ADFI (kg/d) <sup>4</sup>	2.87	2.79	2.67	2.59		<0.01
Target ADFI (kg/d) <sup>4</sup>	2.86	2.87	2.70	2.70	0.40	0.09

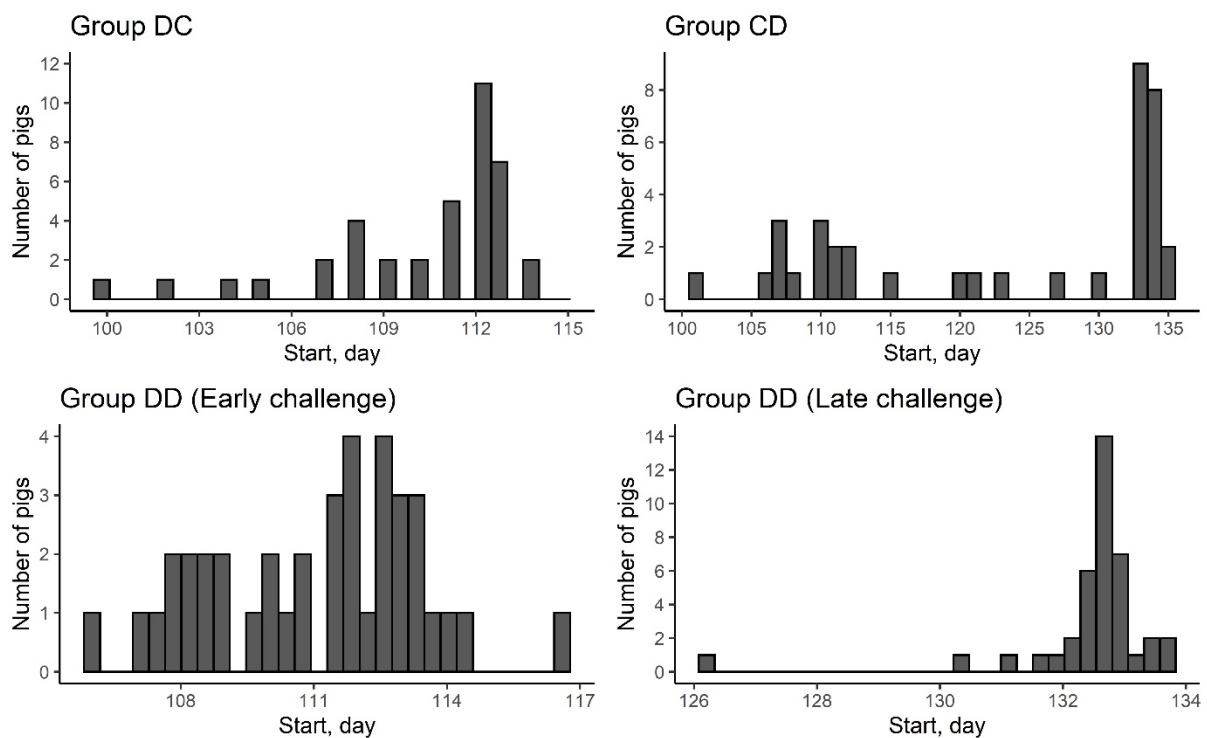
<sup>1</sup> CC = group of pigs that received a non-contaminated control diet; DC = group of pigs that received a diet contaminated with DON from 113 to 119 days of age; CD = group of pigs that received a diet contaminated with DON from 134 to 140 days of age; DD = group of pigs that received a diet contaminated with DON in both aforementioned periods.

<sup>2</sup> RSE = residual standard error.

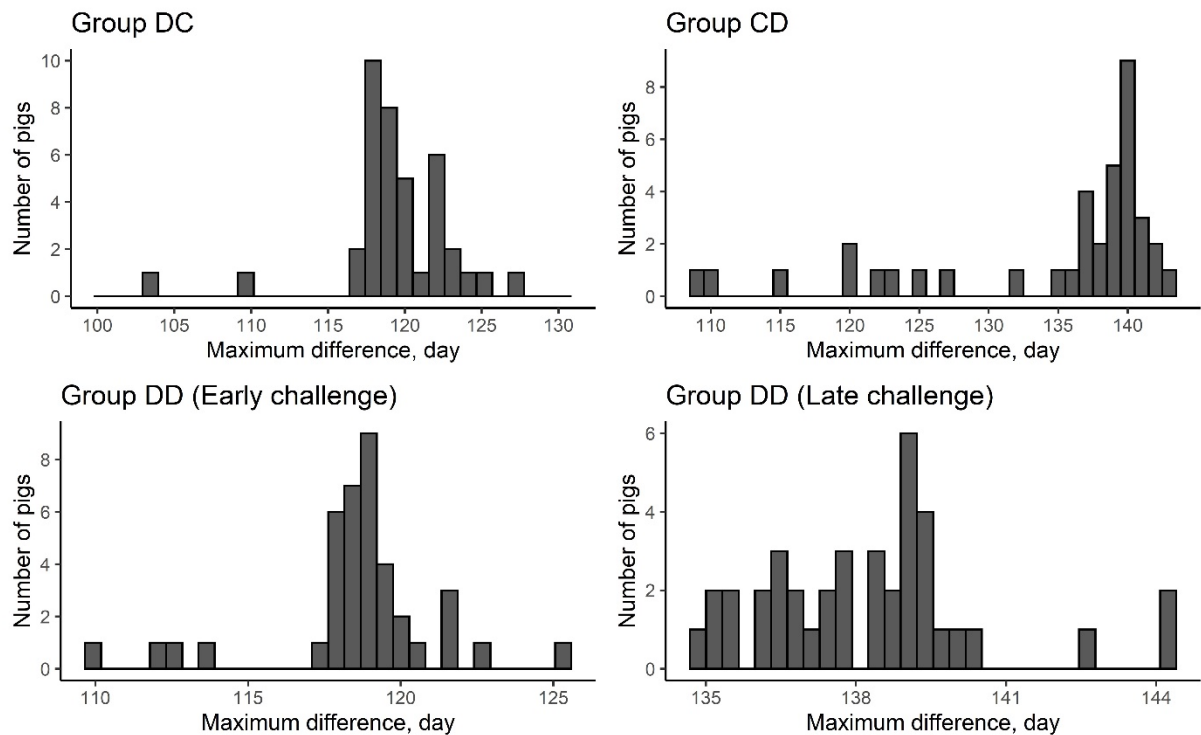
<sup>3</sup> Parameter estimates of a polynomial model describing the target cumulative feed intake (CFI). t<sub>0</sub> = age at which CFI equals 0; CFI<sub>mid-point</sub> = CFI at the midpoint of the growing period; CFI<sub>last</sub> = CFI at the last observation; ADFI = average daily feed intake of the target CFI. See Nguyen-Ba *et al.* (2020) for details.

<sup>4</sup> Average daily feed intake (ADFI) during the experiment (i.e., from 100 to 154 days of age). Observed ADFI = reported by Serviento *et al.* (2018); Target ADFI = calculated from the estimated model parameters.

In general, the procedure detected deviations in the CFI for all groups, even in group CC. However, the magnitude of the deviations in group CC was very small. Multiple deviations identified by the procedure indicate that the CFI of pigs was affected by factors other than by the DON-contaminated diet alone, but some of these additional deviations were quantitatively minor. As the objective of this study was to quantify the response of pigs to DON challenges, only the deviations related to DON-challenged periods were examined. The identified deviations are shown in Figures 3.2 and 3.3, respectively for the start of the deviation and for the time at which the maximum difference between the CFI and the target CFI occurred. The procedure identified that most deviations started and reached the maximum value near the distribution of the DON-contaminated diet. However, there were cases where the starting time and the time of the maximum deviation between the CFI and the target CFI were before or after the distribution of the DON-contaminated diet, especially for group CD.



**Figure 3.2** Capacity of the data analysis procedure to identify the start of the distribution of a diet contaminated with deoxynivalenol (DON) based on the feed response of pigs. In groups DC and DD (Early challenge), pigs received the DON-contaminated diet from 113 days of age onwards. In groups CD and DD (Late challenge), pigs received the DON-contaminated diet from 134 days of age onwards.



**Figure 3.3** Capacity of the data analysis procedure to identify the day from which pigs started to recover after having received a diet contaminated with deoxynivalenol (DON). The procedure determines the day when the difference between the actual cumulative feed intake and the target cumulative feed intake is maximal. In groups DC and DD (Early challenge), pigs stopped receiving the DON-contaminated diet from 119 days of age onwards. In groups CD and DD (Late challenge), pigs stopped receiving the DON-contaminated diet from 140 days of age onwards.

#### *Characterization the response of pigs to Deoxynivalenol-contaminated diet*

For five pigs (four in group DD and one in group CD) the estimation procedure did not converge and data for these pigs were not considered further in the analysis. The estimated model parameters are given in Table 3.2. Between the two groups receiving the DON-contaminated diet early on (i.e., group DC and the first perturbation of group DD), no significant differences were observed in the estimated values of  $k_2$  and  $k_3$ . Between the two groups receiving the DON-contaminated diet later on (i.e., group CD and second perturbation of group DD),  $k_3$  was significantly lower and  $k_2$  significantly higher for pigs that received the DON challenge for the second time (group DD) compared to that of pigs that received this challenge for the first time (group CD).

**Table 3.2** *Estimated model parameters indicative for the resistance and resilience potential of pigs that received a diet contaminated with deoxynivalenol (DON) during one or two periods*

		Experimental group <sup>1</sup>			RSE <sup>2</sup>	P-value
		DC (n = 39)	CD (n = 37)	DD (n = 35)		
Estimated model parameters <sup>3</sup>						
k3	Early challenge	0.46		0.46	0.23	0.99
	Late challenge		0.42	0.31	0.18	0.02
k2	Early challenge	0.81		0.90	0.73	0.57
	Late challenge		1.59	2.36	0.94	<0.001
Calculated model parameters <sup>4</sup>						
k1	Early challenge	0.77		0.77	0.37	0.98
	Late challenge		1.05	1.03	0.56	0.91
k4	Early challenge	0.31		0.32	0.19	0.96
	Late challenge		0.63	0.72	0.41	0.36

<sup>1</sup> DC = group of pigs that received a diet contaminated with DON in the first challenge from 113 to 119 days of age; CD = group of pigs that received a diet contaminated with DON in the second challenge from 134 to 140 days of age; DD = group of pigs that received a diet contaminated with DON in both aforementioned periods.

<sup>2</sup> RSE = residual standard error.

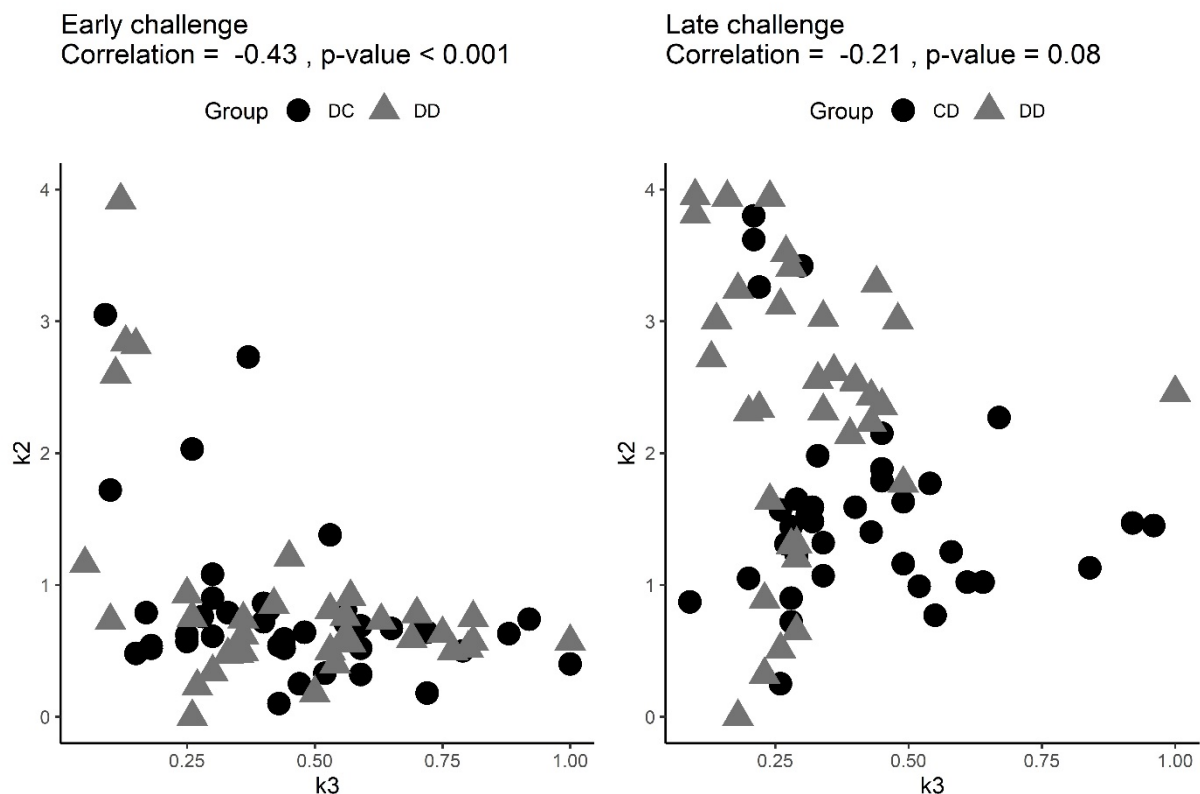
<sup>3</sup> k3 = net reduction in daily intake during the DON-challenge period relative to the target daily feed intake; k2 = proportional change in daily feed intake relative to the ratio between the actual cumulative feed intake and the target cumulative feed intake.

<sup>4</sup> k1 = reduction in daily feed intake during the DON-challenge period relative to the target daily feed intake; k4 = compensatory feed intake capacity over and above the target daily feed intake.

The effect of age or body weight can be assessed by comparing the results of pigs receiving the DON-contaminated diet early on (i.e., group DC and the early challenge of group DD) with those of pigs receiving the DON-challenge for the first time later on in life (i.e., group CD). For  $k_3$ , no difference was found between the early and late DON-challenge (0.46 for groups DC and DD vs. 0.42 for group CD;  $P=0.39$ ). However, pigs challenged early in life had a significant lower value of  $k_2$  than those challenged later in life (0.85 for groups DC and DD vs. 1.59 for group CD;  $P<0.001$ ).

The results for the calculated model parameters  $k_1$  and  $k_4$  are also given in Table 3.2. The  $k_3$  can be interpreted as the result of a negative effect on DFI (through  $k_1$ ) and a positive effect on DFI (through  $k_4$ ). The responses of  $k_1$  and  $k_4$  resembled those observed for  $k_3$  but were more variable. The values of  $k_1$  ranged from 10 to 346% whereas those of  $k_4$  ranged from 0 to 246%.

The correlations between  $k_2$  and  $k_3$  for the two DON-challenge periods are given in Figure 3.4. The correlation was moderately negative for the early challenge period ( $P<0.001$ ) and only tended to differ from zero for the late challenge period ( $P=0.08$ ).



**Figure 3.4** Correlations between the change in daily feed intake during the perturbation ( $k_3$ ) and the resilience capacity ( $k_2$ ) of pigs when receiving diets contaminated with deoxynivalenol (DON). The left panel denotes the periods when

pigs received a DON-contaminated diet from 113 to 119 days of age (Early challenge) and the right panel when they received the DON-contaminated diet from 134 to 140 days of age (Late challenge). DC = group of pigs that received a diet contaminated with DON from 113 to 119 days of age; CD = group of pigs that received a diet contaminated with DON from 134 to 140 days of age; DD = group of pigs that received a diet contaminated with DON in both aforementioned periods.

## Discussion

The capacity of an animal to minimize the effect of environmental perturbations and to quickly retrieve its pre-perturbed condition, usually termed resistance and resilience, are important elements in sustainable livestock production. The complex and dynamic nature of the mechanisms of animal's response to a perturbation makes modelling a promising approach to propose and to quantify the underlying mechanisms. This study demonstrates that a modelling and data analysis procedure can be applied to characterize resistance and resilience traits of animals, allowing to identify variability among growing pigs in their feed intake response to a DON-contaminated diet.

### *Estimation of the target cumulative feed intake*

Determining the production potential of an animal is important for animal breeding but can be difficult to estimate because deviations of this potential can occur due to disturbances, resulting in the actually measured production trait (Berghof *et al.*, 2018). Differences among animals in average feed intake have been correlated to heritable health-related traits (Putz *et al.*, 2018). However, disturbances and the corresponding response of the animal may vary over time. Average performance traits are not suitable to capture the dynamic aspects of robustness, and they may even mask the underlying mechanisms of resistance and resilience. For example, a reduction in DFI may be followed by a period of full compensatory DFI and the average DFI of such an animal may not be different from a situation without a perturbation. On the other hand, an animal that is affected by a constant perturbation throughout its life will have an average production lower than its true potential without a perturbation (Berghof *et al.*, 2018).

The parameters of the target CFI curve did not differ between the four treatment groups resulting in similar values for the average target DFI (Table 1). This differs from the results of Serviento *et al.* (2018), who reported differences in the observed ADFI among the groups. Moreover, the average target DFI of the control group CC was very similar to the observed ADFI (Table 1). This suggests that the procedure is capable to extract a target trajectory from the actual data. The numerically lower average target DFI values for treatments CD and DD may indicate that the procedure was not completely successful, but this may also be due to the relatively short recovery period for these late-challenged animals (14 days), which may have been too short to regain the target CFI.

This study is based on the hypothesis that the animal has a target to attain. The CFI was used as a target rather than the DFI because it is easier to envisage a target for a state variable (i.e., kg of feed) than for a rate variable (kg of feed/day). The notion of a target is also represented in growth models such as the logistic or Gompertz functions, in which the growth rate is a function of the target mature body weight. Revilla *et al.* (2019) used this approach to model the response of piglets around weaning. They used a Gompertz function (as a target) in combination with a perturbation model to represent changes in body weight after weaning. These changes were modelled through a possible reduction in body weight immediately followed by a recovery phase to regain the trajectory of the Gompertz function.

The assumption of the existence of a target trajectory that the animal seeks to attain is debatable. There may be situations in which the animal responds to a perturbation but where it will not (or cannot) seek to regain the target trajectory. A classic example of this is the study of Lister and McCance (1967) who restricted feed intake in piglets so that they maintained their body weight at 5.5 kg for one year. When feed was offered *ad libitum* after one year, the previously restricted pigs had initially the same growth rate as those that were not restricted, but stopped growing at the same chronological age as the non-restricted pigs. This indicates that restricted pigs could not reach the same target mature body weight as the control group (or that they had changed their target mature body weight).

#### *Characterization of the feed intake response*

The start time and time required for the maximum deviation estimated by the procedure corresponded reasonably well to the actual start and the end of DON



challenge. The relatively short challenge period of seven days in combination with a perturbation model with potentially four parameters could lead to difficulties to estimate the model parameters and it was therefore decided to fix the  $t_{\text{start}}$  and  $t_{\text{tstop}}$  at the actual distribution times of the DON-contaminated diet. Although these time points were close to the corresponding parameters estimated by the procedure, there were cases where the procedure indicated that the perturbation started before the distribution of the DON-contaminated diet (especially for the CD and DD groups). This may be due to another unidentified perturbing factor not related to the experiment.

Fixing the start and end times of perturbation to the times during which the DON-contaminated diet was distributed does not allow to estimate a “lag time” during which the animal is exposed but does not respond to the perturbing factor (Sandberg et al, 2006). Likewise, the approach used here does not allow to have a “remnant” perturbing effect by which the animal responds to but it is no longer exposed to the perturbing factor. The consequence of our approach is that the response of the animal is characterized by only two parameters ( $k_3$  and  $k_2$ ). But the estimates of these parameters may be somewhat biased in cases where the start and end times of the response do not correspond to the distribution times of the DON-contaminated diet. The structure of the perturbation model requires sufficient data to estimate all four parameters, and DFI data for seven days is not sufficient to realize this. It is possible that exploring the feed intake behaviour and meal patterns provide additional information on the response of the animal to the perturbation, but this requires a different model structure, which is beyond the scope of this paper.

The ratio between the actual CFI and the target CFI (i.e.,  $\text{Ratio}(t)$ ) is used as a driving force for the resilience mechanism in the model. As indicated before, we have changed the time point from whereon  $\text{Ratio}(t)$  was determined. This change has consequences on the simulated response during the perturbation, but it also has implications on the interpretation of the model in terms of resistance and resilience. The  $k_1$  is seen as the immediate and constant response to a perturbation (i.e., resistance), which is counteracted by the resilience parameter  $k_2$ . In the original approach, this resulted in that the reduction in DFI during the perturbation gradually diminished because of the two mechanisms. This gradual decrease was provoked by the time-dependency of  $\text{Ratio}(t)$  also caused that estimates of  $k_2$  became time-dependent. This issue was solved by determining  $\text{Ratio}(t)$  from the start of each perturbation, which results in a constant reduction in DFI during the perturbing period

(k3). The k3 is thus to be interpreted as the result of a constant resistance mechanism (k1) and a constant resilience mechanism (k4). The k4 also reflects the degree of compensatory feed intake over and above the target DFI at  $t_{tstop}$ . Although k3 is to some extent “observable” in DFI data, this is not the case for k1. There were a number of cases where both k1 and k4 exceeded 100%, with values of k3 in the 0 to 100% range. Values greater than 100% for k1 are difficult to interpret biologically because this would mean that the animal tries to have a negative DFI. Values greater than 100% are possible for k4 if the animal is capable to double its DFI during compensatory feed intake. Rather than interpreting k3 in terms of k1 and k4, k3 can also be interpreted by itself, implying that resistance is the only mechanism during the perturbation and that resilience only starts once the perturbation is over (through k2 or k4).

The constant reduction in DFI during feeding the DON-contaminated diet differs from the average observations of the change in DFI of Serviento *et al.* (2018). They observed an important reduction in DFI during the first day of the challenge, and this reduction became progressively less important to surpass the DFI of the control group resulting in compensatory DFI (see Figure 4 of Serviento *et al.*, 2018). There are two explanations for this difference. Firstly, in the modelling procedure used here, the CFI was used as a response criterion, and changes in CFI may be less sensitive than changes in DFI. Secondly, it is possible that the current model does not fully correspond to the dynamics of the response of the animal and should be adapted so that the effect of a perturbing factor diminishes with time of exposure. As indicated by Nguyen-Ba *et al.* (2020), different aspects of the data analysis procedure can be adapted, as was done here for the determination of Ratio(t). Considering a diminishing effect of the perturbing factor could have been done, but may not be sufficient to accurately describe the change in DFI because as described above the DON challenge may cause a remnant effect on the animal. As indicated in Figure 4 of Serviento *et al.* (2018), once feeding the DON-contaminated diet stopped, the DFI of the challenged animals was close to or slightly below of that of the control group. Compensatory DFI occurred only a few days after feeding the normal, uncontaminated diet. Modelling the response during and after feeding the DON-contaminated diet would therefore probably require more than the two (or four) parameters considered in the current study.

### *Between-group differences*

Parameters estimated from the model confirmed findings of the experiment (Serviento *et al.*, 2018) that the response of pigs to DON-contaminated diet is influenced by age or body weight and by a previous exposure to the DON-contaminated diet. Interestingly, the older pigs recovered faster than the younger pigs from the DON-challenge ( $k_2$  averaged 0.85 for group DC and the early challenge of group DD vs. 1.59 for group CD). Pigs that had received the DON-contaminated diet early in life were less affected by receiving this diet again later on compared with those that received it for the first time and they also tended to recover faster (i.e., smaller  $k_3$  and greater  $k_2$  for the second challenge of pigs of group DD compared to those of group CD).

The degree of compensatory DFI once the normal diet is fed again (i.e.,  $k_4$ ) was greater for the late challenged pigs (when they are also older and heavier) compared to the early challenged pigs. Gut capacity is often assumed to be a limiting factor for feed intake in young pigs and gut capacity increases with body weight (Nyachoti *et al.*, 2004). The initial body weight for the early challenged pigs was 72 kg, whereas it was 94 kg for the late challenged pigs. The greater compensatory DFI for the heavier pigs is therefore in line with the idea that gut capacity becomes less of a limiting factor with increasing body weight. However, the difference between the two groups is considerable, implying that the heavier pigs could increase their DFI by more than 60% over their target DFI, compared to “only” 30% for the lighter pigs.

From the effects of both age and repeated exposure to DON, it is tempting to speculate that the adaptation of pigs relies more on resilience than on resistance mechanisms. The immune system is one of the major targets of mycotoxins (Pierron *et al.*, 2016). Depending on the dose, exposure frequency, and animal species, mycotoxins can have either immunostimulatory or immunosuppressive effects (Bondy and Pestka, 2000). Exposure to a high dose of DON has been reported to reduce the cellular and humoral immune responses, thereby decreasing the host resistance to infectious diseases (Pestka *et al.*, 2004; Oswald *et al.*, 2005). In pigs, ingestion of DON with the doses close to that used in Serviento *et al.* (2018) caused a depression in the immune response against the porcine reproductive and respiratory syndrome virus (Savard *et al.*, 2014) and inhibition of the vaccine efficiency (Savard *et al.*, 2015).

#### *Individual variability in the response of pigs to the Deoxynivalenol-contaminated diet*

Considerable variation among pigs in their response to a DON-contaminated diet was observed in this study (Figure 4). Bishop and Morris (2007) reported genetic

variation in the response of sheep and goats to different types of mycotoxins. Breeding against mycotoxin susceptibility may be feasible due to a moderate to high heritability of phenotypic measurements (Bishop and Morris, 2007). Therefore, the findings of our study provide opportunities to consider resistance and resilience traits to select pigs for coping with mycotoxins. Moreover, resistance and resilience to DON seem to be independent traits as only low and moderate correlations between k2 and k3 were found in two DON-challenge periods.

## Conclusion

This study showed the possibility to apply the model proposed by Nguyen-Ba *et al.* (2020) to situations where the origin of the perturbation is known. The procedure detected deviations from the target CFI resulting from the distribution of a DON-contaminated diet. A previous exposure to a DON-contaminated diet reduced the decrease in DFI following a second exposure. Older and heavier pigs seem to be more resilient than younger and lighter pigs. The low to moderate correlations between the resistance and resilience traits suggests these are different elements of robustness.

## Acknowledgements

This study has been funded by the European Union's H2020 project Feed-a-Gene under grant agreement no. 633531. H. Nguyen-Ba also received funding from the INRA meta-programme Adaptation of Agriculture and Forests to Climate Change (INRA-ACCAF) and from #DigitAg, the French Digital Agricultural Convergence Lab for his PhD work.

Aira Maye Serviento, Ludovic Brossard and David Renaudeau are acknowledged for sharing data from their experiment.

Preliminary results of this study were presented at the 9<sup>th</sup> Workshop on Modelling Nutrient Digestion and Utilization in Farm Animals (MODNUT) (Nguyen-Ba *et al.*, 2019).

## Declaration of interest

The authors declare that there is no conflict of interest in this study.

## Ethics statement

Not applicable.

### **Software and data repository resources**

The data used in the study were provided by Serviento *et al.* (2018). The data analysis procedure is a modified version of the procedure Nguyen-Ba *et al.* (2020), which can be obtained from [doi.org:10.1017/S1751731119001976](https://doi.org/10.1017/S1751731119001976). The modified version of the R code can be obtained from the authors upon request.

### 3. Supplementary Material

In the original procedure of Nguyen-Ba *et al.* (2019a), the target trajectory of CFI was obtained by repeatedly fitting a polynomial function to the CFI data. If a significant autocorrelation was observed among the residuals, data associated with negative residuals were temporarily eliminated from the dataset, and the fitting procedure was repeated. The procedure was terminated when the autocorrelation among the residuals was no longer significant. It was also ensured that at least 20 data points remained, irrespective of if there was autocorrelation among the residuals.

With the original procedure, if there is autocorrelation among the residuals, roughly half of the data is eliminated at each step of the fitting procedure. This procedure may be too severe for the current data set, which is composed of only 55 data points for each individual pig. In the modified procedure, only the 10% quantile of data with negative residuals were eliminated at each step of the fitting procedure. The results of both procedures are compared in Table S1.

**Table S1** Comparison of procedures to estimate the target trajectory curve of cumulative feed intake

	Original procedure <sup>1</sup> (n = 155)	Modified procedure <sup>2</sup> (n = 155)
Average number of filtration steps	2.0 ± 0.2	6.3 ± 1.2
The fitting procedure stopped because there was no longer autocorrelation among the residuals:		
Number of animals concerned	39	78
Number of data points used to estimate the target cumulative feed intake	27.7 ± 3.6	29.3 ± 6.3
The fitting procedure stopped to ensure that there were at least 20 data points remaining, but autocorrelation remained among the residuals:		
Number of animals concerned	116	77
Number of data points used to estimate the target cumulative feed intake	28.7 ± 3.0	23 ± 0.0

<sup>1</sup> Original procedure: the procedure to estimate the target CFI was done by eliminating all data with negative residuals at each filtration step.

<sup>2</sup> Modified procedure: the procedure to estimate the target CFI was done by eliminating the 10% quantile of data with negative residuals at each filtration step.

## Chapter 4. General discussion

### 1. Some general thoughts about the PhD thesis

Under the pressure of increasing production to sustain food security and of coping with challenges such as climate change, prevalence of diseases, and animal welfare constraints, it is important for the livestock production sector to sustainably improve robustness of farm animals. Robustness, however, is a complex trait and consists of multiple dynamic elements such as the response to and recovery from short-term environmental perturbations. The measurement and quantification of this trait is a prerequisite to be included in genetic selection and management practices and this remains a major challenge. With the development of electronic feeders, voluntary feed intake can nowadays be automatically measured at the individual level, in very large groups, and with a high frequency. Despite the fact that the longitudinal data of voluntary feed intake show a great potential in quantifying the animal's response to perturbations, until now, it has been used mostly for perturbation's detection. For phenotyping purpose, mathematical modelling has often been used as a quantification tool because of its advantage in summarizing the dynamics of biological traits into few parameters, which facilitates ranking and selecting animals. Therefore, the objective of this PhD thesis was to develop a data analysis and modelling procedure for the automatic detection of the consequence of short-term perturbations on voluntary feed intake of growing pigs and the characterization and quantification of their response in terms of resistance and resilience.

The developed procedure included two components: (1) a data analysis procedure to estimate a target trajectory of feed intake, which is hypothesized as the amount of feed a pig would consume in a non-perturbed condition and (2) a model to quantify the pig's response to short-term perturbations based on the deviations from the target trajectory. In the second component, the response of pig to a perturbation is characterized by four parameters: the start and end of the perturbing factor, the immediate reduction in DFI at the start of the perturbation (i.e., a resistance trait) and the pig's capacity to overcome the perturbing effect through compensatory feed intake (i.e., a resilience trait).

The procedure was evaluated by applying it to a dataset of 155 pigs from an experiment where they received diets with or without cereals contaminated with DON.



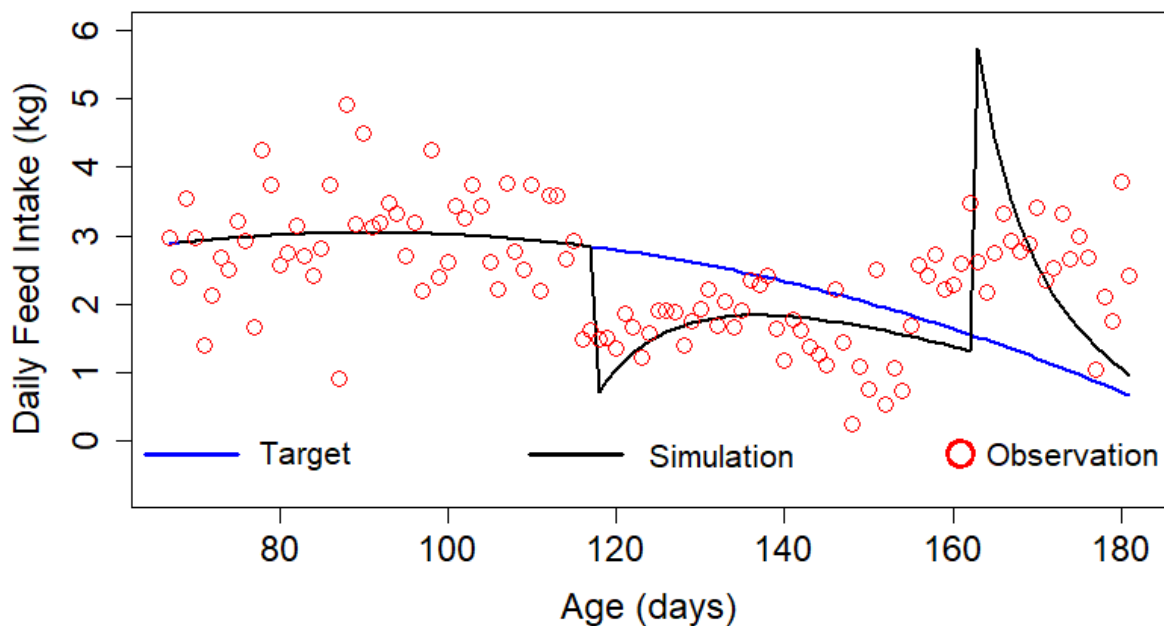
Pigs from a control group received a normal diet during the whole experiment, while pigs from three challenged groups received a DON-contaminated diet for 7 days at different stages of the experiment (i.e., early, late, or in both periods). Results showed that the target feed intake trajectory of each pig could be estimated independently of the challenge. The procedure also estimated relatively correctly the period when DON was provided to each challenged group. Analysis of the pig's response to the challenges indicated that DON seems to have more effects on the resilience capacity of the pigs than on the resistance capacity. The modest correlation between resistance and resilience traits indicates that these are different elements of robustness.

The main concept behind this model is that actual feed intake of an animal is a combination of the target trajectory and deviations due to perturbations. The response to and recovery from perturbations of the animal can be quantified by separating these two components. Because the concept is generic, the different elements can be adapted if judged necessary. To illustrate for this, two examples of the possibility to modify the model are given below. Firstly, the target trajectory is modelled here as an empirical function of feed intake and time. There are a number of models that describe feed intake as a function of body weight, rather than of time (e.g., feed intake as an asymptotic function of body weight) (Van Milgen *et al.*, 2008; NRC, 2012). This approach is somewhat more mechanistic (or somewhat less empirical) compared to describing feed intake as a function of time. However, feed intake is not only the result of body weight, but also the cause of it because changes in feed intake affect body weight gain and thus body weight itself. Limits in frequently measuring body weight of individual pigs has been a main constraint to explore this relationship (Huynh-Tran *et al.*, 2017), but it is expected that these measurements will become more accessible in the near future and the model can be changed to represent this relationship. Secondly, the current model to characterize the animal's response assumes the existence of a specific period when the perturbation starts and stops. However, there may be perturbing factors, such as pathogens, where the onset of the perturbing factor may be identified, but for which there is no clear end. At the onset, the pathogen cause a rapid reduction in DFI but, over time, this negative effect may be attenuated because the pathogen becomes less effective by itself or because increased activity of the host's defensive system, even though the pathogen may still be present. Such a response can be represented in a model by assuming that a pathogen has an immediate effect on DFI at a given point in time, but that its effect on DFI diminishes

gradually without representing an explicit end time of the perturbation (section 4 in Chapter 2 this thesis). In this case, the response mechanism of the host (or the effect of the perturbing factor) can be modified whilst the structure of the model and number of the parameters to be estimated remain the same. Choosing an appropriate perturbation model may not be evident by considering only DFI as the response criterion. Information about the environment of the pigs (e.g., temperature as an indicator of heat stress) or assessing the DFI responses of all pigs in a population, or indicators of the health status of individual pigs may be useful in the determining the most appropriate perturbation model.

The process of doing a PhD project by modelling is often different from doing a PhD project by experimental research. In experimental research, the process of filling knowledge gaps often follows a linear path (for a given experiment): raise a research question, propose a hypothesis to conduct an experiment, analyze (samples and) data, and compare the results with the hypothesis, discuss these, and, if necessary, identify new research questions that can be addressed in other experiments. As such, each experiment covers a considerable time span and the confirmation or rejection of the hypothesis follow this timeline. Although the elements of a modeling approach are similar to that of experimental research, the timeline is different. More importantly, progress is typically not based on the acceptance (i.e., non-rejection) or rejection of a hypothesis, but on the gradual improvement of representing a system by modelling. Consequently, the process of modelling research follows a circle. We first start with a research question. We then construct a first set of equations to represent the phenomenon (i.e., the mathematical model). If the representation is judged not good enough, we go back to modify the model components or equations. As such, modelling is an iterative process that continues until the research question is answered satisfactorily. Because modelling is not a straightforward process (i.e., it is not based on the acceptance or rejection of a hypothesis that drawn from experimental data), the reasons behind model modifications are often not fully described in scientific papers. There is a tendency to describe and publish models that work, and not the once that do not work, even though the reasoning behind it was “reasonable”. In my opinion, the understanding of these reasons is more interesting than only seeing the final outcomes of a model that works. During my PhD project, we moved back and forth several times between steps and gradually constructed a procedure that characterizes the animal’s response to a perturbation appropriately (in our view). For instance, we first used a

cubic function to represent the target CFI because we considered the shape of the quadratic function to be suitable to represent DFI (e.g., being the first-derivative of CFI). However, after the development of the perturbation model, we tested the procedure using a large dataset and found that a combination of the target DFI estimated by a quadratic function and the perturbation model could result in biologically unrealistic predictions of DFI. For instance, Figure 4.1 shows a simulation of the DFI response of an animal to a perturbation. The target DFI described by a quadratic function is very flexible and probably too flexible if it is to be identified indirectly from the decomposition of the actual DFI in a target DFI and the response after. As shown in Figure 4.1, the decomposition of the actual DFI resulted in a target DFI where the pig would consume only 1 kg of feed at 180 days of age. It also resulted in a compensatory feed intake that was well beyond biological reality (i.e., up to 6 kg at 160 days of age, Figure 4.1). We therefore chose a quadratic-linear function to describe the target CFI (and thus a linear-plateau function for the target DFI) as mentioned in Chapter 2.



**Figure 4.1** Daily feed intake response of a pig to a perturbation. The target daily feed intake was estimated by a quadratic function. The quadratic function was judged too flexible resulting in values of the target daily feed intake and of the response to a perturbation that are biologically unlikely.

This example is to show that during the development of the procedure, we sometimes needed to come backward to justify and modify our decisions and approach. This going back and forth is essential in modeling although it can be very time-consuming to go back to the drawing board.

## 2. Other perspectives in modelling the animal's response to perturbations

Cumulative traits such as cumulative feed intake and body weight are inherently less variable than traits such as daily feed intake and daily weight gain. In this PhD thesis, the (cumulative) feed intake was chosen over body weight as the response criterion to perturbations. The reason for this is that, irrespective of cause or effect, changes in feed intake will precede change in body weight gain (i.e., feed intake is more “up-front” than body weight and it will be easier to detect if a pig is not eating for two days than if it is not growing for two days). Also, relatively important changes in body weight can occur due to defecating and urinating patterns.

The use of a single response criterion (e.g., cumulative feed intake on a daily basis) limits the degree to which a perturbation model can be developed. As reported in chapter 3, a DON challenge of seven days can easily lead to an over-parametrization if all four parameters of the model are estimated. The work reported in this PhD thesis should be seen as a first attempt in using data provided by automatic feeding stations to quantify the animal's response to a perturbation. This goes beyond the use of feeding stations to quantify the average feed intake response in individual pigs, but to analyse and try to understand the dynamics of feed intake patterns. Automatic feeding stations are just one of the many devices that are becoming more and more accessible and that will contribute to the era of “big data”. Although we explored the data only on a daily basis, these feeding stations can also provide other types of data. For instance, the feeding stations can provide information about feeding behaviour such as daily feeding time, feeding rate, meal size, and number of feeder visits (Maselyne *et al.*, 2015). The dynamics of these traits may also be used to further understand and quantify the response of animals to perturbations and to different environmental conditions. Although feeding rate in group-housed pigs appear to stay constant with different feeding levels (Hyun *et al.*, 1997), competition for food (Georgsson and Svendsen, 2002), and ambient temperature (Quiniou *et al.*, 2000), it is affected by

group size (Nielsen *et al.*, 1995; Hyun and Ellis, 2002). It has been suggested that changes in eating rate could be an indicator of social stress (Nielsen, 1999). Furthermore, the inverse changes in feeding time and feeding rate of lame cows reported by Gonzalez *et al.* (2008) provided a strong evidence that feeding behaviour response of cows to lameness follow a very characteristic manner. The combination of increased feeding rate and decreased feeding time in lame cows is more characteristic than feed intake for this type of disorder. Although using this type of data requires a different model structure than the approach used in this PhD thesis, they offer new perspectives to modelling biological functions. Progress has also been made in the field of monitoring animal health and physiology. Nowadays, bio-sensing and wearable technologies can be used to regularly collect data of different physiological and behavioural traits such as body temperature, saliva and sweat constituents, and movement and behaviour of group-housed animals (Neethirajan, 2017). Friggens and Thorup (2015) indicated that phenotyping the individual adaptive capacity of animals based on frequent measurements would become more powerful if multiple measures can be combined. Once these technologies are available, it will be an opportunity (and also a challenge) to integrate data of different origins together to develop more mechanistic models that quantify the response of animals to perturbations.

Future modelling efforts should also focus on the effect of perturbations on nutrient partitioning in the body and its consequence on animal performance. Indeed, understanding of the underlying mechanisms is important for making better decisions in management and genetic selection strategies. Le Bellego *et al.* (2002) found that a high ambient temperature (30°C) decreased protein deposition and energy utilization while it increased lipid deposition in growing pigs, compared to pair-fed pigs kept in thermoneutral conditions. The underlying mechanism of this is that the heat production associated to protein deposition is greater than the heat production associated to lipid deposition. To limit the heat production to cope with heat stress, the animals reduced their feed intake and changed the partitioning of energy retention. This example illustrates that a reduction in feed intake is often observed as a response to a challenge, but that this is not the only response of the animal. Sandberg *et al.* (2007) conducted a review to characterize the decrease in growth that was not related to the decrease in voluntary feed intake of pathogen-challenged animals. They found that the protein (i.e., amino acid) requirements significantly increased during exposure to pathogens. This increase is due to fuel defensive activities such as synthesizing

antibodies, repairing damaged tissues, and mounting a fever to combat pathogens. Sandberg *et al.* (2007) concluded that when dietary protein is scarce, there is more likely a competition for resources between growth and immune functions rather than a traditional view that there is a priority for immunity over growing. Modelling the interplay between nutrient requirements and nutrient allocation to different functions during the period of perturbations plays a crucial role in supporting decision for nutritional strategies (e.g., the importance of providing sufficient protein to pathogen-challenged animals) and genetic strategies (e.g., a better understanding of the side-effects on growth when selecting for more pathogen-resistant animals). Because the effect of perturbations on nutrient partitioning is even more important when nutrient availability is scarce, and that perturbations typically reduce voluntary feed and nutrient intake, these two phenomena are tightly related to each other (Doeschl-Wilson *et al.*, 2009). The initial objective of this PhD project was to quantify the feed intake response of the animal to a perturbation, and then to develop a model of nutrient allocation in relation to perturbing factors. The modelling of the feed intake response itself appeared to be a sufficiently complex phenomenon, which prevents us to tackle the aspect of nutrient partitioning. However, this remains necessary and sufficiently challenging for the future.

### 3. Potential applications of the procedure

The quantification of resistance and resilience traits is an important element to enhance the capacity of animals to cope with environmental perturbations. There are two common strategies to improve animal's robustness: genetic selection and management practices. The PhD thesis focussed on "historical" data, and its potential impact is thus more appropriate for breeding and genetics than for management practices. This section is therefore dedicated to the potential applications of this procedure emphasizing on quantitative genetic selection. Nevertheless, the opportunity of using the outcome of the thesis in nutritional management is also discussed, mainly in the context of precision feeding.

#### Genetic selection

Despite a great interest of genetic selection for robustness, classical robustness traits (e.g., survival rates, skeletal and cardiovascular integrity) are often considered

as being difficult to be implemented because of their low heritabilities and antagonistic relationship with production traits (Knap, 2008; Mormède *et al.*, 2011). Another challenge of breeding for robustness is that traits of interest are often measured in the nucleus environment (where nutrition, health and climate are well controlled), which is different from the commercial conditions where animals will eventually perform (Knap, 2005; Mulder, 2017). To measure robustness traits in commercial conditions, proper tools for data collection and processing are required (Knap, 2009).

In this PhD project, we defined two potential traits that could be used for genetic selection: a resistance trait related to the reduction in DFI due to a perturbation and a resilience trait related to the compensatory feed intake capacity to overcome the negative effect of a perturbation. The approach has a potential application in animal breeding because the data required to estimate these traits become increasingly available on commercial farms. Phenotyping animals at individual level and in a wide range of environmental conditions will improve heritability of the traits of interest (Mulder, 2017). The procedure developed during this PhD project can be applied to a large number of growing pigs and combined with their pedigree information. Then, a quantitative genetic analysis can be conducted to estimate heritabilities of the resulting resistance and resilience traits, their genetic correlation, and correlation between these traits and other production and functional traits. Putz *et al.* (2019) reported that resilience traits obtained from fluctuations in individual DFI and feeding duration were moderately heritable with a range from 0.15 to 0.26. Notably, moderate to strong genetic correlations (i.e., from 0.37 to 0.85) were reported between those resilience traits and mortality and treatment rate of pigs exposed naturally to common diseases in the Canadian pig industry. These findings confirm the interest to further explore the potential of resistance and resilience traits in animal breeding. If the origins of the perturbation is known, the modeling procedure can be used to target specific breeding strategies. Also, the procedure can be used for the development of genomic selection, which requires large data collection and an accurate definition of phenotypes of targeted traits (Knap, 2008; Calus *et al.*, 2013).

Finally, although it has often thought that selection for production impairs the animal's robustness, the underlying mechanisms of this possible trade-off remain unclear. Genetic selection studies have mainly used a "black-box" approach in which animals are selected based on observed performance (e.g., daily gain and mortality) without considering the biological mechanisms behind the genetic improvement (e.g.,

what improves daily gain and how does it affect mortality). The consequence of this “black-box” selection is that outcomes of selection programs are sometimes unexpected. For example, the biological explanation for trade-offs is often based on the resource allocation theory: when a resource is limited and if genetic selection shifts allocation of it towards production, animals will have to compromise other functions. However, a long-term selection study in which pigs were divergently selected for feed efficiency showed unexpected results in the response to perturbations between high and low efficiency pig lines. Feed efficiency can be assessed from the difference between observed feed intake and the predicted feed intake (from production and maintenance requirements) and this difference is termed residual feed intake **RFI**. Gillbert *et al.* (2017) divergently selected pigs for high RFI (low efficiency) or low RFI (high efficiency) for nine generations. Based on the resource allocation theory, the low RFI line was expected to be less robust than the high RFI line. However, when challenging the two lines to different perturbations, the low RFI line did not appear to be more susceptible than the high RFI line to an inflammatory challenge and to heat stress. Also, the low RFI sows had a better capacity to maintain milk yield, litter survival, and body weight in tropical environments compared to high RFI sows (Renaudeau *et al.*, 2014). This association suggests “*a more complex relationship between available resources and individual metabolic processes than indicated by the resource allocation theory*” (Hermesch *et al.*, 2015). Recently, Gillbert *et al.* (2018) found that piglets from the low RFI line were perturbed more than those in high RFI line by the weaning challenge, but that they recovered to attain a similar body weight and feed intake level afterwards as the high RFI line. This suggests that low RFI pigs may be less resistant to the weaning challenge than the high RFI line, but that their resilience capacity was sufficient to recover. They concluded that genetic selection based on RFI affected the dynamic responses of pigs to weaning (Gilbert *et al.*, 2018). The procedure developed in this PhD project could provide a method to assess this dynamic response.

## Management practices

Evidences from literatures indicated that modifying nutrient contents of diets (e.g., increase protein contents or supplement with Zinc) can reduce the duration of anorexia and the rate of recovery of infected animals (Kyriazakis and Doeschl-Wilson, 2009). In



addition, a number of nutrition strategies (e.g., modifying nutrient contents of diets or changing feeding schedules) showed the effectiveness to alleviate the negative consequences of heat stress on livestock (Renaudeau *et al.*, 2012). Therefore, in the context of precision livestock farming, it is tempting if we can predict the requirements of each animal under the impact of perturbations as well as its recovery capacity to provide better nutritional supports at the right time. Mathematical modelling can contribute to that aspect of precision livestock farming.

The main difference between an application in breeding and in precision livestock farming is the time during which the data is obtained and analysed and the time when decisions have to be made. The procedure developed in this PhD project is based on “historical” data. A potential application in precision livestock farming requires that data be analysed in real-time so that management decisions can also be made in real-time (e.g., in terms of feeding or medication). Because feed intake (or other data) is generated in real-time, it will be difficult to extract a target trajectory and deviations from this target trajectory from the obtained data. The timeframe of one day during which data is accumulated to calculate the cumulative feed intake is probably too long to detect deviations in real-time (and thus make the corresponding management decisions). To detect deviations in real-time for individual animals, a shorter timeframe and other response traits (e.g., feeding behaviour patterns) will be required. Moreover, a single response trait may not be sufficient to identify deviations from what may be considered as “normal” or as a “perturbed”. The rapid development of sensor technologies will undoubtedly provide large volumes of data, and it will be a challenge for modellers to identify “deviations from normality” from these sources of information, so that appropriate management measures can be taken in real-time. This PhD-thesis may be a first and small step towards this, but there is still a long way to go.

## 4. Conclusion

This PhD thesis showed that changes in CFI can be used to identify resistance and resilience traits of individual pigs, both of which are elements of robustness. This is because (1) feed intake can reflect the consequence of short-term perturbations on the animals, (2) measuring feed intake is a non-invasive method, and (3) with the development of automatic feeding stations, CFI can be recorded individually and with a high frequency. Thanks to the automatic and repeated measurement of CFI, the dynamic nature of the pig's response to perturbations can be fully characterized.

This PhD project succeeded in the development of a data analysis and modelling procedure to characterize and quantify the feed intake response of each growing pigs to short-term perturbations. It was assumed that the actual CFI is the result of a target trajectory (which is the amount of feed the pigs desires to consume in un-perturbed conditions) and deviations from this target trajectory (which are due to perturbations). It was also assumed that the pig strives to approach the target trajectory of CFI through mechanisms of resistance and compensatory feed intake. The procedure consisted of two main functions: detection of the target trajectory and the representation and quantification of the pig's response to perturbations.

The developed procedure proved its capacity to quantify the pig's response to perturbations by challenging it with data from an experiment where pigs received diets with or without DON-contaminated cereals. Results showed that the target CFI could be estimated independently of the challenge. The procedure could also identify relatively precisely the periods when DON-contaminated diets were distributed to pigs. Moreover, the modest correlation between parameters representing resistance and resilience suggests that these are two different traits.

The results of this PhD thesis have the potential to be applied further as a phenotyping tool for genetic selection or as a component of models to study the response of animal to perturbations at underlying levels (e.g., metabolic, nutrient partitioning).

## References

- Bauman DE and Currie WB 1980. Partitioning of nutrients during pregnancy and lactation: a review of mechanisms involving homeostasis and homeorhesis. *Journal of Dairy Science* 63, 1514–1529.
- Bauman DE and Elliot JM 1983. Control of nutrient partitioning in lactating ruminants. *Biochemistry of lactation* 14, 437–462.
- Beilharz RG, Luxford BG and Wilkinson JL 1993. Quantitative genetics and evolution: is our understanding of genetics sufficient to explain evolution? *Journal of Animal Breeding and Genetics* 110, 161–170.
- Bell AW and Bauman DE 1997. Adaptations of glucose metabolism during pregnancy and lactation. *Journal of mammary gland biology and neoplasia* 2, 265–278.
- Bellu G, Saccomani MP, Audoly S and D'Angiò L 2007. DAISY: A new software tool to test global identifiability of biological and physiological systems. *Computer Methods and Programs in Biomedicine* 88, 52–61.
- Berghof TV, Poppe M and Mulder HA 2018. Opportunities to Improve Resilience in Animal Breeding Programs. *Frontiers in genetics* 9.
- Berghof TVL, Van Der Klein SAS, Arts JAJ, Parmentier HK, Van Der Poel JJ and Bovenhuis H 2015. Genetic and non-genetic inheritance of natural antibodies binding keyhole limpet hemocyanin in a purebred layer chicken line. *PLoS One* 10, e0131088.
- Bishop SC and Morris CA 2007. Genetics of disease resistance in sheep and goats. *Small Ruminant Research* 70, 48–59.
- Black JL, Williams BA and Gidley MJ 2009. Metabolic regulation of feed intake in monogastric mammals. In *Voluntary feed intake in pigs* (ed. D Torrallardona and E Roura), pp. 189–213. Wageningen Academic Publishers, Wageningen, the Netherlands.
- Black JL 2009. Models to predict feed intake. In *Voluntary feed intake in pigs* (ed. D Torrallardona and E Roura), pp. 323–351. Wageningen Academic Publishers, Wageningen, the Netherlands.
- Black JL, Campbell RG, Williams IH, James KJ and Davies GT 1986. Simulation of energy and amino acid utilisation in the pig. *Research and Development in Agriculture* 3, 121-145.

- Black JL, Giles LR, Wynn PC, Knowles AG, Kerr CA, Jones MR, Strom AD, Gallagher NL and Eamens G 2001. A Review - Factors limiting the performance of growing pigs in commercial environments. In Proceedings of the Eighth Biennial Conference of the Australasian Pig Science Association (APSA), 25-28 November 2011, Victoria, Australia.
- Bondy GS and Pestka JJ 2000. Immunomodulation by fungal toxins. *Journal of Toxicology and Environmental Health Part B: Critical Reviews* 3, 109–143.
- Bokkers EAM and Koene P 2003. Eating behaviour, and preprandial and postprandial correlations in male broiler and layer chickens. *British Poultry Science* 44, 538–544.
- Bornett HLI, Morgan CA, Lawrence AB and Mann J 2000. The effect of group housing on feeding patterns and social behaviour of previously individually housed growing pigs. *Applied Animal Behaviour Science* 70, 127–141.
- Calus MPL, Berry DP, Banos G, De Haas Y and Veerkamp RF 2013. Genomic selection: the option for new robustness traits? *Advances in Animal Biosciences* 4, 618–625.
- Cannon WB 1929. Organization for physiological homeostasis. *Physiological reviews* 9, 399–431.
- Clapperton M, Diack AB, Matika O, Glass EJ, Gladney CD, Mellencamp MA, Hoste A and Bishop SC 2009. Traits associated with innate and adaptive immunity in pigs: heritability and associations with performance under different health status conditions. *Genetics Selection Evolution* 41, 54.
- Codrea MC, Højsgaard S and Friggens NC 2011. Differential smoothing of time-series measurements to identify disturbances in performance and quantify animal response characteristics: An example using milk yield profiles in dairy cows. *Journal of Animal Science* 89, 3089–3098.
- Colditz IG and Hine BC 2016. Resilience in farm animals: biology, management, breeding and implications for animal welfare. *Animal Production Science* 56, 1961–1983.
- Collier RJ, Limesand SW, Rhoads ML, Rhoads RP and Baumgard LH 2008. Homeorhesis during heat stress. In *Resource Allocation Theory Applied to Farm Animal Production* (ed. W Rauw), pp. 72–88. Wageningen Academic Publishers, Wageningen, the Netherlands.

- Collier RJ, Baumgard LH, Lock AL and Bauman DE 2005. Physiological limitations, nutrient partitioning. In *Yields of farmed Species: constraints and opportunities in the 21st Century* (ed. R Sylvester-Bradley and J Wiseman), pp. 351–378. Nottingham University Press, the UK.
- Collin A, Milgen J van, Dubois S and Noblet J 2001. Effect of high temperature on feeding behaviour and heat production in group-housed young pigs. *British Journal of Nutrition* 86, 63–70.
- Coppens CM, de Boer SF and Koolhaas JM 2010. Coping styles and behavioural flexibility: towards underlying mechanisms. *Philosophical Transactions of the Royal Society B: Biological Sciences* 365, 4021–4028.
- Cornou C, Vinther J and Kristensen AR 2008. Automatic detection of oestrus and health disorders using data from electronic sow feeders. *Livestock Science* 118, 262–271.
- Datta FU, Nolana JV, Rowe JB and Gray GD 1998. Protein supplementation improves the performance of parasitised sheep fed a straw-based diet. *International Journal for Parasitology* 28, 1269–1278.
- Davies RF 1977. Long- and short-term regulation of feeding patterns in the rat. *Journal of Comparative and Physiological Psychology* 91, 574–585.
- Dersjant-Li Y, Verstegen MW and Gerrits WJ 2003. The impact of low concentrations of aflatoxin, deoxynivalenol or fumonisin in diets on growing pigs and poultry. *Nutrition Research Reviews* 16, 223–239.
- De Castro JM 1981. The stomach energy content governs meal patterning in the rat. *Physiology & Behavior* 26, 795–798.
- De Goede DM, Gremmen B and Blom-Zandstra M 2013. Robust agriculture: Balancing between vulnerability and stability. *NJAS-Wageningen Journal of Life Sciences* 64, 1–7.
- Doeschl-Wilson AB, Bishop S, Kyriazakis I and Villanueva B 2012. Novel methods for quantifying individual host response to infectious pathogens for genetic analyses. *Frontiers in genetics* 3, 266.
- Doeschl-Wilson AB and Kyriazakis I 2012. Should we aim for genetic improvement in host resistance or tolerance to infectious pathogens? *Frontiers in genetics* 3, 272.
- Doeschl-Wilson AB, Brindle W, Emmans G and Kyriazakis I 2009. Unravelling the Relationship between Animal Growth and Immune Response during Micro-Parasitic Infections. *PLOS ONE* 4, e7508.

- Duncan IJH, Horne AR, Hughes BO and Wood-Gush DGM 1970. The pattern of food intake in female Brown Leghorn fowls as recorded in a Skinner box. *Animal Behaviour* 18, 245–255.
- Emmans GC 1991. Diet selection by animals: theory and experimental design. In *Proceedings of the Nutrition Society* 50, pp. 59–64. Cambridge University Press, the UK.
- FAO 2009. How to feed the world in 2050. Retrieved on 20 November 2019, from [http://www.fao.org/fileadmin/templates/wsfs/docs/expert\\_paper/How to Feed the World in 2050.pdf](http://www.fao.org/fileadmin/templates/wsfs/docs/expert_paper/How_to_Feed_the_World_in_2050.pdf)
- Flori L, Gao Y, Oswald IP, Lefevre F, Bouffaud M, Mercat M-J, Bidanel J-P and Rogel-Gaillard C 2011. Deciphering the genetic control of innate and adaptive immune responses in pig: a combined genetic and genomic study. In *Proceeding of the International Symposium on Animal Genomics for Animal Health (AGAH)*, 31 May - 2 June 2010, Paris, France, p. S32.
- Forbes JM 1986. The voluntary food intake of farm animals. pp. 30-31. Butterwoth Heinemann publisher, the UK.
- Friggens NC, Blanc F, Berry DP and Puillet L 2017. Deciphering animal robustness. A synthesis to facilitate its use in livestock breeding and management. *Animal* 11, 2237–2251.
- Friggens NC, Duvaux-Ponter C, Etienne MP, Mary-Huard T and Schmidely P 2016. Characterizing individual differences in animal responses to a nutritional challenge: Toward improved robustness measures. *Journal of Dairy Science* 99, 2704–2718.
- Friggens NC and Thorup VM 2015. From monitoring to precision phenotyping: towards a systemic use of precision livestock measures in dairy herds. In *Proceedings of the New Zealand Society of Animal Production*. Vol. 75. Dunedin, New Zealand. pp. 145-148.
- Georgsson L and Svendsen J 2002. Degree of competition at feeding differentially affects behavior and performance of group-housed growing-finishing pigs of different relative weights. *Journal of Animal Science* 80, 376–383.
- Giger-Reverdin S, Lebarbier E, Duvaux-Ponter C and Desnoyers M 2012. A new segmentation–clustering method to analyse feeding behaviour of ruminants from within-day cumulative intake patterns. *Computers and Electronics in Agriculture* 83, 109–116.

- Gilbert H, Ruesche J, Muller N, Billon Y, Begos V and Montagne L 2018. Responses to weaning in two pig lines divergently selected for residual feed intake depending on diet. *Journal of Animal Science* 97, 43–54.
- Gilbert H, Billon Y, Brossard L, Faure J, Gatellier P, Gondret F, Labussière E, Lebreton B, Lefaucheur L and Le Floch N 2017. Divergent selection for residual feed intake in the growing pig. *Animal* 11, 1427–1439.
- Goldstone JA 2010. The new population bomb: the four megatrends that will change the world. *Foreign Affairs*. 89, 31.
- González LA, Tolcamp BJ, Coffey MP, Ferret A and Kyriazakis I 2008. Changes in Feeding Behavior as Possible Indicators for the Automatic Monitoring of Health Disorders in Dairy Cows. *Journal of Dairy Science* 91, 1017–1028.
- Guy SZY, Thomson PC and Hermes S 2012. Selection of pigs for improved coping with health and environmental challenges: breeding for resistance or tolerance? *Frontiers in Genetics* 3, 281.
- Halas V, Gerrits WJJ and Van Milgen J 2018. Models of feed utilization and growth for monogastric animals. In *Feed evaluation science* (ed. PL Moughan and WH Hendriks), pp. 423–456. Wageningen Academic Publishers, Wageningen, the Netherlands.
- Hansen J, Sato M and Ruedy R 2012. Perception of climate change. In *Proceedings of the National Academy of Sciences of the United States of America* 109, E2415–E2423.
- Hart BL 1988. Biological basis of the behavior of sick animals. *Neuroscience & Biobehavioral Reviews* 12, 123–137.
- Hermesch S, Li L, Doeschl-Wilson AB and Gilbert H 2015. Selection for productivity and robustness traits in pigs. *Animal Production Science* 55, 1437–1447.
- Holtkamp DJ 2013. Assessment of the economic impact of porcine reproductive and respiratory syndrome virus on United States pork producers. *Journal of Swine Health and Production* 21, 72–84.
- Houdijk JGM, Campbell FM, Fortomaris PD, Eckersall PD and Kyriazakis I 2007. Effects of sub-clinical post-weaning colibacillosis and dietary protein on acute phase proteins in weaner pigs. *Livestock Science* 108, 182–185.
- Hoy S, Schamun S and Weirich C 2012. Investigations on feed intake and social behaviour of fattening pigs fed at an electronic feeding station. *Applied Animal Behaviour Science* 139, 58–64.

- Huynh-Tran VH, Gilbert H and David I 2017. How to improve breeding value prediction for feed conversion ratio in the case of incomplete longitudinal body weights. *Journal of Animal Science* 95, 39–48.
- Huzzey JM, Veira DM, Weary DM and Von Keyserlingk MAG 2007. Prepartum behavior and dry matter intake identify dairy cows at risk for metritis. *Journal of Dairy Science* 90, 3220–3233.
- Hyun Y and Ellis M 2002. Effect of group size and feeder type on growth performance and feeding patterns in finishing pigs. *Journal of Animal Science* 80, 568–574.
- Hyun Y, Ellis M, McKeith FK and Wilson ER 1997. Feed intake pattern of group-housed growing-finishing pigs monitored using a computerized feed intake recording system. *Journal of Animal Science* 75, 1443–1451.
- Knap PW 2009. Voluntary feed intake and pig breeding. In *Voluntary feed intake in pigs* (ed. D Torrallardona and E Roura), pp. 13–31. Wageningen Academic Publishers, Wageningen, the Netherlands.
- Knap PW 2008. Robustness. In *Resource allocation theory applied to farm animal production* (Ed. WM Rauw), pp. 288–301. CABI Publishing, Wallingford, UK.
- Knap PW 2005. Breeding robust pigs. *Australian Journal of Experimental Agriculture* 45, 763–773.
- Knap PW and Wang L 2012. Pig breeding for improved feed efficiency. In *Feed efficiency in swine* (ed. JF Patience), pp. 167–181. Wageningen Academic Publishers, Wageningen, the Netherlands.
- Koolhaas JM, Korte SM, De Boer SF, Van Der Vegt BJ, Van Reenen CG, Hopster H, De Jong IC, Ruis MAW and Blokhuis HJ 1999. Coping styles in animals: current status in behavior and stress-physiology. *Neuroscience & Biobehavioral Reviews* 23, 925–935.
- Kyriazakis I and Doeschl-Wilson A 2009. Anorexia during infection in mammals: variation and its sources. In *Voluntary feed intake in pigs* (ed. D Torrallardona and E Roura), pp. 307–321. Wageningen Academic Publishers, Wageningen, the Netherlands.
- Kyriazakis I and Emmans GC 1999. Voluntary food intake and diet selection. In *A Quantitative Biology of the Pig* (ed. I Kyriazakis), pp. 229-248. CAB International, Wallingford, the UK.



- Kyriazakis I, Tolkamp BJ and Hutchings MR 1998. Towards a functional explanation for the occurrence of anorexia during parasitic infections. *Animal behaviour* 56, 265–274.
- Kyriazakis I, Anderson DH, Oldham JD, Coop RL and Jackson F 1996. Long-term subclinical infection with *Trichostrongylus colubriformis*: effects on food intake, diet selection and performance of growing lambs. *Veterinary parasitology* 61, 297–313.
- Kyriazakis I and Emmans GC 1992. The growth of mammals following a period of nutritional limitation. *Journal of Theoretical Biology* 156, 485–498.
- Labroue F, Guéblez R, Sellier P and Meunier-Salaün MC 1994. Feeding behaviour of group-housed Large White and Landrace pigs in French central test stations. *Livestock Production Science* 40, 303–312.
- Le Bellego L, Van Milgen J and Noblet J 2002. Effect of high ambient temperature on protein and lipid deposition and energy utilization in growing pigs. *Animal Science* 75, 85–96.
- Levitsky DA 1974. Feeding conditions and intermeal relationships. *Physiology & Behavior* 12, 779–787.
- Lister D and McCance RA 1967. Severe undernutrition in growing and adult animals: 17. The ultimate results of rehabilitation: Pigs. *British Journal of Nutrition* 21, 787–799.
- Luiting P 1990. Genetic variation of energy partitioning in laying hens: causes of variation in residual feed consumption. *World's Poultry Science Journal* 46, 133–152.
- Magnusson U, Wilkie B, Mallard B, Rosendal S and Kennedy B 1998. *Mycoplasma hyorhinis* infection of pigs selectively bred for high and low immune response. *Veterinary immunology and immunopathology* 61, 83–96.
- Martin O and Sauvant D 2010a. A teleonomic model describing performance (body, milk and intake) during growth and over repeated reproductive cycles throughout the lifespan of dairy cattle. 1. Trajectories of life function priorities and genetic scaling. *Animal* 4, 2030–2047.
- Martin O and Sauvant D 2010b. A teleonomic model describing performance (body, milk and intake) during growth and over repeated reproductive cycles throughout the lifespan of dairy cattle. 2. Voluntary intake and energy partitioning. *Animal* 4, 2048–2056.

- Martínez-Miró S, Tecles F, Ramón M, Escribano D, Hernández F, Madrid J, Orengo J, Martínez-Subiela S, Manteca X and Cerón JJ 2016. Causes, consequences and biomarkers of stress in swine: an update. *BMC veterinary research* 12, 171.
- Maselyne J, Van Nuffel A, Briene P, Vangeyte J, De Ketelaere B, Millet S, Van den Hof J, Maes D and Saeys W 2018. Online warning systems for individual fattening pigs based on their feeding pattern. *Biosystems engineering* 173, 143–156.
- Maselyne J, Saeys W and Van Nuffel A 2015. Quantifying animal feeding behaviour with a focus on pigs. *Physiology & Behavior* 138, 37–51.
- Maxwell S 1986. Farming systems research: hitting a moving target. *World Development* 14, 65–77.
- McEwen BS and Wingfield JC 2003. The concept of allostasis in biology and biomedicine. *Hormones and behavior* 43, 2–15.
- Mirkena T, Duguma G, Haile A, Tibbo M, Okeyo AM, Wurzinger M and Sölkner J 2010. Genetics of adaptation in domestic farm animals: A review. *Livestock Science* 132, 1–12.
- Mormède P, Foury A and Knap PW 2011. Breeding for robustness: the role of cortisol. *Animal* 5, 651–657.
- Morrison SR and Mount LE 1971. Adaptation of growing pigs to changes in environmental temperature. *Animal Science* 13, 51–57.
- Mulder HA 2017. Is GxE a burden or a blessing? Opportunities for genomic selection and big data. *Journal of Animal Breeding and Genetics* 134, 435–436.
- Muñoz-Tamayo R, Puillet L, Daniel JB, Sauvant D, Martin O, Taghipoor M and Blavy P 2018. Review: To be or not to be an identifiable model. Is this a relevant question in animal science modelling. *Animal* 12, 701–712.
- Munsterhjelm C, Heinonen M and Valros A 2015. Effects of clinical lameness and tail biting lesions on voluntary feed intake in growing pigs. *Livestock Science* 181, 210–219.
- National Research Council (NRC) 2012. Nutrient requirements of swine, 11<sup>th</sup> revised edition. National Academy Press, Washington, DC, USA.
- Natelson BH and Bonbright JC 1978. Patterns of eating and drinking in monkeys when food and water are free and when they are earned. *Physiology & Behavior* 21, 201–213.
- Neethirajan S 2017. Recent advances in wearable sensors for animal health management. *Sensing and Bio-Sensing Research* 12, 15–29.

- Nelson, R., and J. Kriegsfeld 2017. *An Introduction to Behavioral Endocrinology*, 5<sup>th</sup> edition. Sinauer Associates, Inc. Publishers, Sunderland, Massachusetts, USA.
- Nelson, R 2011. *An Introduction to Behavioral Endocrinology*, 4<sup>th</sup> edition. Sinauer Associates, Inc. Publishers, Sunderland, Massachusetts, USA.
- Nielsen BL 1999. On the interpretation of feeding behaviour measures and the use of feeding rate as an indicator of social constraint. *Applied Animal Behaviour Science* 63, 79–91.
- Nielsen BL, Lawrence AB and Whitemore CT 1995. Effect of group size on feeding behaviour, social behaviour, and performance of growing pigs using single-space feeders. *Livestock Production Science* 44, 73–85.
- Nienaber JA and Hahn GL 2007. Livestock production system management responses to thermal challenges. *International Journal of Biometeorology* 52, 149–157.
- Nguyen-Ba H, Van Milgen J and Taghipoor M 2020. A procedure to quantify the feed intake response of growing pigs to perturbations. *Animal* 14, 253–260.
- Nguyen-Ba H, Van Milgen J and Taghipoor M 2019. Modelling the feed intake response of growing pigs to diets contaminated with mycotoxins. *Proceedings of the 9<sup>th</sup> Workshop on Modelling Nutrient Digestion and Utilization in Farm Animals (MODNUT)*. *Advances in Animal Biosciences* 10, 303. doi:10.1017/S2040470019000025.
- Nguyen-Ba H, Taghipoor M and Van Milgen J 2018. Detection and characterization of the feed intake response of growing pigs to perturbations. *Book of Abstracts of the 69<sup>th</sup> Annual Meeting of the European Federation of Animal Science*, 27-31 August 2018, Dubrovnik, Croatia, pp. 540.
- Nyachoti CM, Zijlstra RT, De Lange CFM and Patience JF 2004. Voluntary feed intake in growing-finishing pigs: A review of the main determining factors and potential approaches for accurate predictions. *Canadian Journal of Animal Science* 84, 549–566.
- Oswald IP, Marin DE, Bouhet S, Pinton P, Taranu I and Accensi F 2005. Immunotoxicological risk of mycotoxins for domestic animals. *Food Additives and Contaminants* 22, 354–360.
- Pastorelli H, Van Milgen J, Lovatto P and Montagne L 2012. Meta-analysis of feed intake and growth responses of growing pigs after a sanitary challenge. *Animal* 6, 952–961.

- Pestka JJ, Zhou H-R, Moon Y and Chung YJ 2004. Cellular and molecular mechanisms for immune modulation by deoxynivalenol and other trichothecenes: unraveling a paradox. *Toxicology Letters* 153, 61–73.
- Petry DB, Holl JW, Weber JS, Doster AR, Osorio FA and Johnson RK 2005. Biological responses to porcine respiratory and reproductive syndrome virus in pigs of two genetic populations. *Journal of Animal Science* 83, 1494–1502.
- Pierron A, Alassane-Kpembi I and Oswald IP 2016. Impact of mycotoxin on immune response and consequences for pig health. *Animal Nutrition* 2, 63–68.
- Pollmann, DS 2010. Seasonal Effects on Sow Herds: Industry Experience and Management Strategies. Midwest American Society of Animal Science. Retrieved on 15 November 2019, from <https://vimeo.com/46531288>.
- Putz AM, Harding JC, Dyck MK, Fortin F, Plastow GS, Dekkers JC and Canada P 2018. Novel resilience phenotypes using feed intake data from a natural disease challenge model in wean-to-finish pigs. *Frontiers in Genetics* 9, 660.
- Quimby WF, Sowell BF, Bowman JGP, Branine ME, Hubbert ME and Sherwood HW 2001. Application of feeding behaviour to predict morbidity of newly received calves in a commercial feedlot. *Canadian Journal of Animal Science* 81, 315–320.
- Quiniou N, Dubois S and Noblet J 2000. Voluntary feed intake and feeding behaviour of group-housed growing pigs are affected by ambient temperature and body weight. *Livestock Production Science* 63, 245–253.
- Quiniou N, Noblet J, Milgen J van and Dubois S 2001. Modelling heat production and energy balance in group-housed growing pigs exposed to low or high ambient temperatures. *British Journal of Nutrition* 85, 97–106.
- Ramsay JO and Silverman BW 2007. Applied functional data analysis: methods and case studies. Springer Publishing Company, New York city, NY, USA.
- Rauw WM 2012. Feed efficiency and animal robustness. In *Feed Efficiency in the Beef Industry* (ed. RA Hill), Wiley-Blackwell publisher, the USA, pp. 105–122.
- Rauw WM, Kanis E, Noordhuizen-Stassen EN and Grommers FJ 1998. Undesirable side effects of selection for high production efficiency in farm animals: a review. *Livestock Production Science* 56, 15–33.
- Reed SN and McGlone JJ 2000. Immune status of PIC Camborough-15 sows, 25% Meishan sows, and their offspring kept indoors and outdoors. *Journal of Animal Science* 78, 2561–2567.

- Renaudeau D, Collin A, Yahav S, De Basilio V, Gourdine JL and Collier RJ 2012. Adaptation to hot climate and strategies to alleviate heat stress in livestock production. *Animal* 6, 707–728.
- Renaudeau D, Gourdine JL and St-Pierre NR 2011. A meta-analysis of the effects of high ambient temperature on growth performance of growing-finishing pigs. *Journal of Animal Science* 89, 2220–2230.
- Renaudeau D, Huc E and Noblet J 2007. Acclimation to high ambient temperature in Large White and Caribbean Creole growing pigs. *Journal of Animal Science* 85, 779–790.
- Revilla M, Friggens NC, Broudiscou LP, Lemonnier G, Blanc F, Ravon L, Mercat M-J, Billon Y, Rogel-Gaillard C and Le Floch N 2019. Towards the quantitative characterisation of piglets' robustness to weaning: a modelling approach. *Animal* 13, 2536–2546.
- Rosenblueth A, Wiener N and Bigelow J 1943. Behavior, purpose and teleology. *Philosophy of science* 10, 18–24.
- Sadoul B, Leguen I, Colson V, Friggens NC and Prunet P 2015a. A multivariate analysis using physiology and behavior to characterize robustness in two isogenic lines of rainbow trout exposed to a confinement stress. *Physiology & behavior* 140, 139–147.
- Sadoul B, Martin O, Prunet P and Friggens NC 2015b. On the use of a simple physical system analogy to study robustness features in animal sciences. *PloS one* 10, e0137333.
- Salak-Johnson JL and McGlone JJ 2007. Making sense of apparently conflicting data: Stress and immunity in swine and cattle. *Journal of Animal Science* 85, E81–E88.
- Sandberg FB, Emmans GC and Kyriazakis I 2007. The effects of pathogen challenges on the performance of naïve and immune animals: the problem of prediction. *Animal* 1, 67–86.
- Sandberg FB, Emmans GC and Kyriazakis I 2006. A model for predicting feed intake of growing animals during exposure to pathogens. *Journal of Animal Science* 84, 1552–1566.
- Savard C, Gagnon CA and Chorfi Y 2015. Deoxynivalenol (DON) naturally contaminated feed impairs the immune response induced by porcine reproductive and respiratory syndrome virus (PRRSV) live attenuated vaccine. *Vaccine* 33, 3881–3886.

- Savard C, Pinilla V, Provost C, Gagnon CA and Chorfi Y 2014. In vivo effect of deoxynivalenol (DON) naturally contaminated feed on porcine reproductive and respiratory syndrome virus (PRRSV) infection. *Veterinary Microbiology* 174, 419–426.
- Serviento AM, Brossard L and Renaudeau D 2018. An acute challenge with a deoxynivalenol-contaminated diet has short-and long-term effects on performance and feeding behavior in finishing pigs. *Journal of Animal Science* 96, 5209–5221.
- Schinckel AP 1994. Nutrient requirements of modern pig genotypes. *Recent advances in animal nutrition*. 133-169.
- Schulin-Zeuthen M, Kebreab E, Dijkstra J, López S, Bannink A, Kuhl HD, Thornley JHM and France J 2008. A comparison of the Schumacher with other functions for describing growth in pigs. *Animal Feed Science and Technology* 143, 314–327.
- Selye H 1956. *The stress of life*. McGraw-Hill, New York.
- Slater PJB 1974. The temporal pattern of feeding in the zebra finch. *Animal Behaviour* 22, 506–515.
- Sowell BF, Branine ME, Bowman JGP, Hubbert ME, Sherwood HE and Quimby W 1999. Feeding and watering behavior of healthy and morbid steers in a commercial feedlot. *Journal of Animal Science* 77, 1105–1112.
- Sowell BF, Bowman JGP, Branine ME and Hubbert ME 1998. Radio frequency technology to measure feeding behavior and health of feedlot steers. *Applied Animal Behaviour Science* 59, 277–284.
- Spurlock ME, Frank GR, Willis GM, Kuske JL and Cornelius SG 1997. Effect of dietary energy source and immunological challenge on growth performance and immunological variables in growing pigs. *Journal of Animal Science* 75, 720–726.
- Star L, Ellen ED, Uitdehaag K and Brom FW 2008. A plea to implement robustness into a breeding goal: poultry as an example. *Journal of Agricultural and Environmental Ethics* 21, 109–125.
- Sterling P 1988. Allostasis: a new paradigm to explain arousal pathology. In *Handbook of life stress, cognition and health* (ed. S Fisher and J Reason), John Wiley & Sons publisher, p. 629.
- St-Pierre NR, Cobanov B and Schnitkey G 2003. Economic losses from heat stress by US livestock industries. *Journal of Dairy Science* 86, E52–E77.

- Taghipoor M, Van Milgen J and Gondret F 2016. A systemic approach to explore the flexibility of energy stores at the cellular scale: examples from muscle cells. *Journal of Theoretical Biology* 404, 331–341.
- Ten Napel J, Van der Veen AA, Oosting SJ and Koerkamp PG 2011. A conceptual approach to design livestock production systems for robustness to enhance sustainability. *Livestock Science* 139, 150–160.
- Ten Napel J, Bianchi F and Bestman M 2006. Utilising intrinsic robustness in agricultural production systems: Inventions for a sustainable development of agriculture. In *Inventions for a sustainable development of agriculture*, pp. 32–53. TransForum Agro & Groen.
- Toates FM and Booth DA 1974. Control of food intake by energy supply. *Nature* 251, 710.
- Tolkamp BJ, Howie JA, Bley TAG and Kyriazakis I 2012. Prandial correlations and the structure of feeding behaviour. *Applied Animal Behaviour Science* 137, 53–65.
- Tolkamp BJ, Schweitzer DPN and Kyriazakis I 2000. The Biologically Relevant Unit for the Analysis of Short-Term Feeding Behavior of Dairy Cows. *Journal of Dairy Science* 83, 2057–2068.
- Tu T, Koski KG, Wykes LJ and Scott ME 2007. Re-feeding rapidly restores protection against *Heligmosomoides bakeri* (Nematoda) in protein-deficient mice. *Parasitology* 134, 899–909.
- Van der Most PJ, de Jong B, Parmentier HK and Verhulst S 2011. Trade-off between growth and immune function: a meta-analysis of selection experiments. *Functional Ecology* 25, 74–80.
- Van Milgen J, Valancogne A, Dubois S, Dourmad J-Y, Sève B and Noblet J 2008. InraPorc: a model and decision support tool for the nutrition of growing pigs. *Animal Feed Science and Technology* 143, 387–405.
- Vernon RG 1989. Endocrine control of metabolic adaptation during lactation. In *Proceedings of the Nutrition Society* 48, 23–32.
- Wallenbeck A and Keeling LJ 2013. Using data from electronic feeders on visit frequency and feed consumption to indicate tail biting outbreaks in commercial pig production. *Journal of Animal Science* 91, 2879–2884.
- Webster AJF 1974. Adaptation to cold. *Environmental Physiology* (ed. D Robertshaw). *Physiology Series I*, vol 7. University Park Press, Baltimore, USA.

- Wellock IJ, Emmans GC and Kyriazakis I 2003a. Modelling the effects of thermal environment and dietary composition on pig performance: model logic and concepts. *Animal Science* 77, 255–266.
- Wellock IJ, Emmans GC and Kyriazakis I 2003b. Predicting the consequences of social stressors on pig food intake and performance. *Journal of Animal Science* 81, 2995–3007.
- Wingfield JC 2013. The comparative biology of environmental stress: behavioural endocrinology and variation in ability to cope with novel, changing environments. *Animal Behaviour* 85, 1127–1133.
- Wu Q, Dohnal V, Huang L, Kuča K and Yuan Z 2010. Metabolic pathways of trichothecenes. *Drug Metabolism Reviews* 42, 250–267.
- Zaralis K, Tolkamp BJ, Houdijk JGM, Wylie ARG and Kyriazakis I 2008. Changes in food intake and circulating leptin due to gastrointestinal parasitism in lambs of two breeds. *Journal of Animal Science* 86, 1891–1903.



# Appendixes

## Appendix 1. List of publications

### Scientific Articles

1. **Nguyen-Ba H**, Van Milgen J and Taghipoor M 2019. A procedure to quantify the feed intake response of growing pigs to perturbations. *Animal* 14, 253-260. (DOI: 10.1017/S1751731119001976)
2. **Nguyen-Ba H**, Taghipoor M and Van Milgen J 2020. Modelling the feed intake response of growing pigs to diets contaminated with mycotoxins. *Animal*, 1–8. (DOI: 10.1017/S175173112000083X)

### Conference's proceedings

1. **Hieu Nguyen-Ba**, Jaap van Milgen and Masoomah Taghipoor 2019. Modelling the feed intake response of growing pigs to diets contaminated with mycotoxins. Proceedings of the 9<sup>th</sup> Workshop on Modelling Nutrient Digestion and Utilization in Farm Animals (MODNUT), *Advances in Animal Biosciences* 10, 303. DOI:10.1017/S2040470019000025.
2. Masoomah Taghipoor, **Hieu Nguyen-Ba**, Christelle Loncke and Jaap van Milgen 2019. Challenges and headaches in modelling animal adaptive response. Proceedings of the 9<sup>th</sup> Workshop on Modelling Nutrient Digestion and Utilization in Farm Animals (MODNUT). *Advances in Animal Biosciences* 10, 293. DOI:10.1017/S2040470019000025.
3. **Hieu Nguyen-Ba**, Masoomah Taghipoor et Jaap Van Milgen 2019. Influence des perturbations sur la performance des porcs en croissance : de la détection automatique à la caractérisation de la réponse adaptative des animaux. 51<sup>ème</sup> Journées de la Recherche Porcine, 05-06 February 2018, Paris, France, pp. 347-348.
4. **Hieu Nguyen-Ba**, Masoomah Taghipoor and Jaap Van Milgen 2018. Detection and characterization of the feed intake response of growing pigs to perturbations. Book of Abstracts of the 69<sup>th</sup> Annual Meeting of the European Federation of Animal Science, 27-31 August 2018, Dubrovnik, Croatia, pp. 540.

## Appendix 2. Other personal communications

1. **Hieu Nguyen-Ba**, Masoomeh Taghipoor and Jaap Van Milgen 2019. DSS a handy tool to quantify individual's resistance and resilience. 4<sup>th</sup> Feed-a-Gene annual meeting, 14-16 May 2019, Budapest, Hungary. *Oral presentation*.
2. **Hieu Nguyen Ba**, Jaap van Milgen and Masoomeh Taghipoor 2018. Demonstration of the FeedUtiliGene Decision Support System: perturbation module. Feed-a-Gene stakeholder workshop, 11 October 2018, Budapest, Hungary. *Oral presentation and model demonstration*.
3. **Hieu Nguyen Ba**, Jaap van Milgen and Masoomeh Taghipoor 2018. On the use of voluntary feed intake to detect and characterize the responses of growing pigs to perturbations. 3<sup>rd</sup> Feed-a-Gene annual meeting, 24-26 April 2018, Newcastle, United Kingdom. *Oral presentation*.
4. **Hieu Nguyen Ba**, Masoomeh Taghipoor and Jaap van Milgen 2018. Detection and characterization of the response of growing pigs to perturbations by using feed intake. Journées d'Animation Scientifique du département Phase d'INRA (JAS Phase 2018), 04- 05 April 2018, Rennes, France. *Poster presentation*.
5. **Hieu Nguyen Ba**, Masoomeh Taghipoor and Jaap van Milgen 2018. On the use of voluntary feed intake for automatic detection and characterization of the responses of growing pigs to perturbations. La journée bilan des activités de modélisation au sein du département PHASE d'INRA (journée AtmosPHASE), 23 March 2018, Paris, France.
6. **Hieu Nguyen Ba**, Masoomeh Taghipoor and Jaap van Milgen 2017. On the use of voluntary feed intake for automatic detection of perturbations in growing pigs. La journée AtmosPHASE, 24 March 2017, Rennes, France.

## Appendix 3. List of awards

1. Best poster presentation award for PhD students in the Journées d'Animation Scientifique du département Phase de l'INRA (JAS Phase 2018).
2. Travel grant (800 euros) to participate in the 9<sup>th</sup> MODNUT Workshop in Brazil from the doctoral school EGGAL, Université Bretagne-Loire.
3. Travel grant (500 euros) to participate in the 9<sup>th</sup> MODNUT Workshop in Brazil from the Pôle Doctoral de Rennes.

## Appendix 4. List of training courses

1. Certification of completion of the **Stateline workshop on modelling** organized by the committee of the 9<sup>th</sup> MODNUT Workshop, 16-17 September 2019, Ubatuba, Brazil.
2. Certification of completion of the PhD course **Robustness: from a woolly concept to operational measures** organized by AgroParisTech, 01-05 April 2019, Paris, France.
3. Certification of completion of the training course **Introduction à l'intégrité scientifique** organized by URFIST de Rennes, 29 March 2019, Rennes, France.
4. Certification of completion of the **Course pour étrangers – Soutien linguistique français (niveau B1)** organized by Université Rennes 2, Semester 1 – 2018/2019, Rennes, France.
5. Certification of completion of the **Writing presenting scientific papers workshop** organized by the committee of the 69<sup>th</sup> EAAP Annual meeting, 26 August 2018, Dubrovnik, Croatia.
6. Certification of completion of the training course **Introduction aux méthodes mathématiques et statistiques pour les modèles dynamiques en agriculture** organized by Les Instituts Techniques Agricoles (ACTA), 18-20 June 2018, Montpellier, France.
7. Certification of completion of the training course **Modélisation et contrôle numérique des systèmes dynamiques en agronomie** organized by INRA and Montpellier SupAgro, 16-19 January 2018, Montpellier, France.
8. Certification of completion of the training course **Anglais pour la recherche** organized by Université Bretagne-Loire, 09 January - 02 February 2018, Rennes, France.
9. Certification of completion of the training course **Statistiques de base avec le logiciel R** organized by INRA Le Rheu, 16 March - 22 May 2017, Le Rheu, France.
10. Certification of completion of the **Course pour étrangers – Soutien linguistique français (niveau A1)** organized by Université Rennes 2, Semester 2 – 2016/2017, Rennes, France.

## Modelling the feed intake response of growing pigs to diets contaminated with mycotoxins

Hieu Nguyen-Ba <sup>1</sup>, Jaap van Milgen <sup>1</sup>, Masoomah Taghipoor <sup>2</sup>

<sup>1</sup> PEGASE, INRA - Agrocampus Ouest, France, <sup>2</sup> MoSAR, INRA - AgroParis Tech, Université Paris-Saclay, France

Corresponding author: Hieu Nguyen-Ba. Email: [hieu.nguyen-ba@inra.fr](mailto:hieu.nguyen-ba@inra.fr)

**Application** The procedure quantifies resistance and resilience traits in pigs, with the potential to be used in breeding programs.

**Introduction** Quantifying robustness of farm animals is essential for breeding and management strategies. Elements of the response of animals to perturbations, an important element of robustness (Friggens et al., 2017), can nowadays be measured by technologies such as automatic feeding stations. A novel data analysis and modelling procedure was developed to quantify feed intake response of growing pigs to perturbations (Nguyen-Ba et al, submitted). The procedure estimates the target trajectory of cumulative feed intake (**target CFI**) as a benchmark from which the impact of a perturbation on the animal (i.e. resistance) and its subsequent response through compensatory feed intake (i.e. resilience) can be quantified. The objective of this study was to use this procedure to quantify resistance and resilience of pigs from an experiment where they received diets with or without mycotoxin-contaminated cereals.

**Material and methods** The procedure was applied to data from a published study about the effects of mycotoxin (deoxynivalenol) on the feed intake of growing pigs (Serviento et al., 2018). Experimented pigs (n=155) were divided among a control group (CC) and three challenged groups. Pigs in each of the challenged groups received a diet contaminated with mycotoxins from day 113 to day 119 of age (DC group), from day 134 to day 140 of age (CD group), or twice during both periods (DD group).

**Results and discussion** No significant difference between parameters of the target CFI was found among the four groups. Moreover, the estimated average daily feed intake of group CC was very close to the observation (2.86 vs. 2.87 kg/d). This means that the target CFI of each pig could be estimated independently of the challenge. Applying to pigs in three challenged groups, the procedure estimated precisely the start and end times of the perturbations (Table 1).

Table 1. Estimated start and end times mycotoxin perturbations had on the pigs

Challenged period	Times	Median	Mean ± SD
Beginning (DC and 1 <sup>st</sup> time DD)	Start	112	112 ± 2.0
	End	123	123 ± 3.7
End (CD and 2 <sup>nd</sup> time DD)	Start	133	131 ± 5.8
	End	142	142 ± 1.9

Correlation between resistance and resilience were low (-0.07, -0.13, -0.00, -0.33 for groups DC, CD, and for the 1<sup>st</sup> and 2<sup>nd</sup> challenge in the DD group, respectively), indicating that the two traits represent different phenomena. Results from the quantification of the response of pigs in different groups indicated that pigs at different ages or body weights responded differently to the mycotoxin challenge. Those receiving the mycotoxin-contaminated diet later on in life had a more important immediate reduction in feed intake compared with those receiving the challenge early on. However, the older or heavier pigs recovered faster from the challenge.

**Conclusion** The data analysis procedure using feed intake as a response trait proved its capacity to detect and quantify the response of animals to a mycotoxin-contaminated diet.

**Acknowledgements** This study received financial supports from the European Union's H2020 project Feed-a-Gene (grant agreement no. 633531). We would like to thank Aira Maye Serviento, Ludovic Brossard and David Renaudeau for contributing their experimental data.

### References

- Friggens NC, Blanc F, Berry DP and Puillet L 2017. *Animal* 11, 2237-2251.  
 Nguyen-Ba, H., Van Milgen, J., Taghipoor, M. Submitted. *Animal*.  
 Serviento AM, Brossard L and Renaudeau D 2018. *Journal of animal science*. 96, 5209-5221.

## Challenges and headaches in modelling animal adaptive response

M Taghipoor<sup>1</sup>, H Nguyen-Ba<sup>2</sup>, C Loncke<sup>1</sup>, J vanMilgen<sup>2</sup>

<sup>1</sup> MoSAR, INRA - AgroParisTech, Université Paris-Saclay, France, <sup>2</sup> PEGASE, INRA - Agrocampus Ouest, France

Masoomeh.Taghipoor@inra.fr

**Application** This study highlights how modelling approaches in animal science have evolved due to the developments of data collecting methods. With the availability of new monitoring technologies, the use of hybrid models combining concept-driven and data driven approaches makes it possible to characterize and rank animals for their robustness. This characterization helps breeders to select for new criteria such as animal adaptive capacity faced with special perturbations, or more generally for their robustness faced to any perturbation.

**Introduction** In the current context of changing environments and an expanding human population, breeding for animal robustness and adaptive capacity becomes an important challenge to ensure that livestock production remains (or: becomes again) robust (Nguyen-Ba et al., submitted). Breeding for robustness is difficult because robustness is a complex trait to phenotype that requires knowledge of dynamically adaptive mechanisms at different levels within a living organism. Nowadays, new technologies make it possible to collect data at different levels of organisation at a high frequency and at a modest cost. For example, data at the animal level (e.g., feed intake or body weight) can be collected using automatic feeders while, at lower level, ruminal pH can be measured continuously using a pH bolus. This progress in collecting data will help animal scientists to better understand the animal's response when facing to environmental perturbations. Therefore, it will open new perspectives and horizons to quantify the adaptive response and, subsequently, rank and select animals based on their robustness. The objective of this article is to explain how mathematical models have adapted to the technological revolution of data collection. In this study, the focus is on data collected with novel monitoring technologies used in precision livestock farming, with the main objective to quantify the animal's adaptive capacity when it is facing environmental perturbations of known or unknown origin.

**Materials and Methods** Mathematical models are useful tools to decipher the relationship between data collected at different levels of time or space, to describe different animal functions, and to predict the animal's response to different perturbations. Since the seventies of the last century, several mechanistic models have been developed to study the effect of feed composition and frequency on animal performance. These models are typically based on concepts of nutrient partitioning and the efficiency of nutrient utilization (i.e., input-output relationships). Fewer models consider also environmental factors, which may be caused by the difficulty to characterize the environment (e.g., in the cases of health stressors) and/or the multiple traits with which the animal responds to changes in the environment (e.g., the response to heat stress). The common denominator of these mechanistic models is that they are concept-driven.

With the rapid progress in monitoring technologies, there is a move towards models analysing large amount of data, using statistical tools, with minimum information of the underlying mechanisms. Moreover, with technologies such as machine learning and data mining, processing huge datasets to detect periods of perturbations has become possible (Liako et al., 2018). This data-driven approach has become an alternative to the mechanistic concept-driven approach and the question arises to which extend these approaches can be or become complementary.

**Results** Two cases of data recording and possible models associated to quantify animal's adaptive response will be presented to demonstrate that the frequency of data collection and the diversity of data recording at different levels of organisation will guide the modelling approach.

**Conclusion** The results showed the necessity of concept driven approach, of data driven approach and also of combining these approaches to quantify the animal's adaptive response.

**Acknowledgment** This study received financial supports from the European Union's H2020 project Feed-a-Gene (grant agreement no. 633531).

### References

- Codrea MC, Højsgaard S and Friggens NC 2011. *Journal of Animal Science*. 89(10), 3089–3098.  
 Liakos K, Busato P, Moshou D, Pearson S and Bochtis D 2018. *Sensors*. 18(8), 2674.  
 Nguyen-Ba, H, Van Milgen, J, Taghipoor, M Submitted. *Animal*.

# Influence des perturbations sur la performance des porcs en croissance : de la détection automatique à la caractérisation de la réponse adaptative des animaux

Hieu NGUYEN BA (1), Masoomah TAGHIPOOR (2), Jaap VAN MILGEN (1)

(1) PEGASE, INRA, Agrocampus Ouest, 35590 Saint-Gilles, France

(2) MoSAR, INRA, AgroParisTech, 75231 Paris, France

*hieu.nguyen-ba@inra.fr*

## Influence of perturbations on the performance of growing pigs: from automatic detection of perturbations to characterisation of the adaptive response of the animals

Improving robustness of farm animals is seen as a new target of breeding strategies. However, robustness is a complex trait, which is not measurable directly. The objective of this study was to quantify and characterise elements of robustness in growing pigs. Robustness can be characterised by examining the animal's response to environmental perturbations. We developed a generic model and data analysis procedure to detect these perturbations and subsequently characterise the feed intake response of growing pigs in terms of resistance and resilience. A model based on differential equations was developed to characterise the animal's response to perturbations. In this model, adaptive response to each perturbation can be characterised by four parameters. The start and end times of the perturbation, the immediate reduction in daily feed intake at the start of the perturbation (i.e., a "resistance" trait), and another parameter describing the capacity of the animal to adapt to the perturbation through compensatory feed intake to rejoin the target trajectory of cumulative feed intake (i.e., a "resilience" trait). The model has been employed successfully to identify the target trajectory of cumulative feed intake in growing pigs and to quantify the animal's response to a perturbation by using feed intake as the response criterion.

## INTRODUCTION

Les animaux d'élevage doivent de plus en plus faire face à des perturbations environnementales. Il est d'un intérêt majeur de quantifier la capacité adaptative des animaux dans les situations de stress, et d'améliorer cette capacité d'adaptation. En effet, pour certaines perturbations il est possible d'identifier à moindre coût l'origine ainsi que la période de la perturbation. Or, pour certaines autres, il est plus difficile ou même impossible de le faire. Par exemple, le stress thermique est facilement identifiable (sa période et son intensité), alors que dans le cas d'une maladie, il est plus difficile d'identifier l'origine et surtout les dates de début et de fin (Taghipoor *et al.*, 2017). Dans cette étude, nous proposons une procédure de détection automatique des perturbations, et un modèle de la réponse de l'animal qui est indépendant de l'origine de la perturbation, et qui reflète la capacité d'adaptation de l'animal face à une perturbation.

## 1. MATERIEL ET METHODES

Notre premier objectif est de détecter de façon automatique les perturbations, car l'origine de ces dernières ne sont pas toujours connues. Pour cela, il faut d'abord clarifier la notion de perturbation. Toute déviation par rapport à la trajectoire ciblée de la performance de l'animal peut être considérée comme une perturbation potentielle. Nous avons alors besoin (1) de choisir

un indicateur de performance qui pourrait être affecté par des perturbations, et (2) d'identifier dans cet indicateur une trajectoire ciblée et la réponse à la perturbation.

Nous avons choisi l'ingestion comme indicateur de performance. Elle est facilement mesurable à haute fréquence avec les nouvelles technologies pour l'élevage de précision (comme les distributeurs automatiques de concentré), elle est non-invasive, et surtout elle a l'avantage de refléter rapidement la présence d'une perturbation, contrairement au poids vif de l'animal. L'étape suivante est d'estimer la trajectoire ciblée de la performance, c.à.d. la quantité d'aliment que l'animal mangerait en absence de toutes perturbations.

### 1.1. La trajectoire ciblée de la consommation cumulée d'aliment

Nous avons choisi de développer la trajectoire ciblée de la consommation cumulée d'aliment (CCA) qui, contrairement à la consommation journalière d'aliment (CJA), ne contient pas de variations rapides. De plus, la CCA nous informe sur l'historique de la consommation de l'animal. Contrairement à la CJA, la CCA (en tant que trajectoire) permet de prendre en compte l'effet de la perturbation et l'effet de la consommation compensatrice. La dérivée de la trajectoire ciblée de la CCA ( $CCA_{ciblée}$ ) représente la consommation journalière ciblée ( $CJA_{ciblée}$ ). Le modèle du  $CCA_{ciblée}$  doit respecter les conditions suivantes (i) il ne doit pas capter les variations liées aux perturbations, (ii) la  $CJA_{ciblée}$  est une fonction linéaire croissante ou constante, ce qui implique

que la  $CCA_{ciblée}$  est décrite par une fonction quadratique-linéaire. Les paramètres du modèle de la  $CCA_{ciblée}$  sont l'âge à laquelle  $CCA = 0$  ( $X_0$ ), la  $CCA$  à la fin de la période concernée ( $CCA_{fin}$ ), la  $CCA$  au milieu de la période concernée ( $CCA_{milieu}$ ), et le jour auquel la  $CCA_{ciblée}$  change d'allure et passe d'un modèle quadratique à un modèle linéaire ( $X_s$ ). La procédure pour déterminer les paramètres du modèle de la  $CCA_{ciblée}$  consiste à réaliser plusieurs régressions linéaires successives en éliminant temporairement les données qui pourraient être issues d'une perturbation. Cette dernière consiste à une série de données avec des résidus négatifs. Cette condition est vérifiée par un test d'autocorrélation. Si le teste est positive ( $P > 0.05$ ), les valeurs avec des résidus négatifs sont temporairement éliminées et une nouvelle régression linéaire est appliquée aux données. Cette procédure est arrêtée quand il n'y a plus d'autocorrélation, ou quand le nombre de données restant est inférieur à 20.

## 1.2. Détection des perturbations

Dans cette étude, nous considérons seulement les perturbations avec un effet négatif sur la consommation. Pour cela, une fonction B-Spline a été ajustée à la différence entre la  $CCA$  observée et la  $CCA_{ciblée}$ . Une perturbation est alors définie comme une période avec des valeurs négatives de cette différence, d'une durée plus de 5 jours et d'une amplitude (le maximum de déviation pendant la durée de la perturbation) supérieure à 5 % de la  $CCA_{ciblée}$ . En effet, cette condition permet de négliger des petites variations dans la consommation de l'aliment, qui font partie du comportement alimentaire normal des animaux. La flexibilité des fonctions B-Splines permet de capter un maximum de déviations et, par la suite, nous aurons la possibilité de choisir les conditions pour considérer une déviation comme perturbation.

## 1.3. Le modèle de la perturbation

Après que les perturbations sont identifiées, notre objectif est de caractériser la réponse des animaux en termes de résistance et résilience. Les deux forces motrices du modèle sont l'influence de la perturbation et la capacité d'adaptation de l'animal. Nous faisons l'hypothèse que ces deux phénomènes agissent au niveau de la  $CJA$  et pas au niveau de la  $CCA$ . Nous faisons aussi l'hypothèse que l'influence de la perturbation sur la  $CJA$  (la résistance) est négative pendant toute la durée de la perturbation. La résilience agit au niveau de la  $CJA$ , mais elle est pilotée par la  $CCA$  : le ratio entre la  $CCA$  observée et la  $CCA_{ciblée}$  est utilisé comme la force motrice pour décrire l'adaptation de l'animal au perturbateur. L'équation 1 représente le modèle :

$$CJA(t) = CJA_{ciblée}(t) \times (1 - Pert(t) + Résilience(t)) \quad (1)$$

Où la fonction  $Pert(t)$  prend une valeur constante pendant la période de la perturbation, et est zéro ailleurs. La fonction de résilience,  $Résilience(t)$  est représentée dans l'équation 2 :

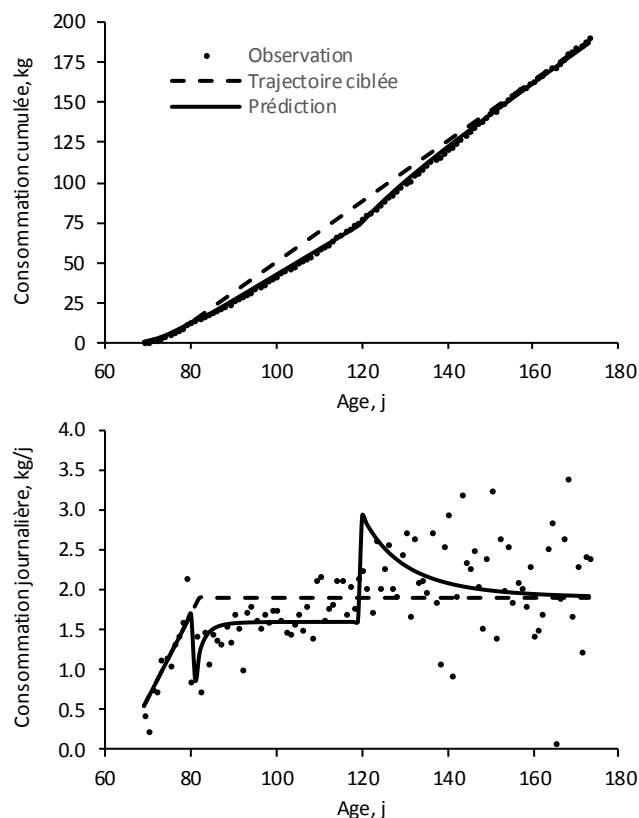
$$Résilience(t) = (1 - CCA(t) / CCA_{ciblée}(t)) \times k \quad (2)$$

Le paramètre  $k$ , représente la capacité maximale de résilience, après une perturbation.

Le modèle de la  $CCA_{ciblée}$  est décrit par quatre paramètres, de même que le modèle de la perturbation. La fonction `nlsLM` de package `minipack.lm` de R version 3.5.0 (<http://cran.r-project.org/>) a été utilisée pour les estimer.

## 2. RESULTATS ET DISCUSSIONS

Les données d'ingestion journalière d'un porc en croissance sont utilisées pour tester le fonctionnement du modèle. La figure 1 (panneau du haut) montre la  $CCA$  observée, ainsi que la  $CCA_{ciblée}$  (une fonction quadratique et linéaire) et la  $CCA$  prédite par le modèle. Le panneau du bas montre ces informations pour la  $CJA$ . Au début de la perturbation (à 80 j d'âge), la perturbation provoque une réduction instantanée de la  $CJA$  de 73,1%. A la fin de la perturbation (à 119 j d'âge), l'animal consomme plus que la consommation ciblée ( $k = 3,74$  ; c.-à-d., quand la  $CCA$  observée est 1% en-dessous de la  $CCA_{ciblée}$ , l'animal tente de consommer 3,74% de plus que la  $CJA_{ciblée}$ ). A 119 j d'âge, la  $CCA$  observée est 15% en-dessous de la  $CCA_{ciblée}$ , ce qui provoque une consommation compensatrice de 56%.



**Figure 1** – Application du modèle d'analyse de perturbation à la consommation cumulée d'aliment ( $CCA$  ; panneau du haut) et la consommation journalière d'aliment ( $CJA$  ; panneau du bas) d'un animal en fonction de l'âge.

## CONCLUSION

Notre démarche a permis de proposer un moyen de quantifier la notion de la robustesse via la résistance et la résilience. Ces paramètres permettront d'hierarchiser des animaux pour leur capacité d'adaptation.

## REMERCIEMENTS

Les auteurs remercient le projet européen Feed-a-Gene (programme H2020, Union Européenne, numéro d'agrément 633531) pour le soutien financier apporté à ce travail.

## REFERENCE BIBLIOGRAPHIQUE

- Taghipoor M., Brossard L., van Milgen J., 2017. Comment caractériser la performance des porcs en croissance face à des challenges liés à leur environnement d'élevage ? *Journées de la Recherche Porcine*, 49, 25-30.



HIEU NGUYEN BA<sup>(1)</sup>, JAAP VAN MILGEN<sup>(1)</sup>, MASOOMEH TAGHIPOOR<sup>(2)</sup>

(1) PEGASE, INRA, Agrocampus Ouest, 35590 Saint-Gilles, France

(2) MoSAR, INRA, AgroParisTech, 75231 Paris, France

Breeding for robustness in livestock is crucial



### OBJECTIVES:

- (1) **Detect** perturbing impacts on feed intake of pigs
- (2) **Characterize** pig's responses to perturbations

- **Resistance**
  - **Resilience**
- } As elements of robustness

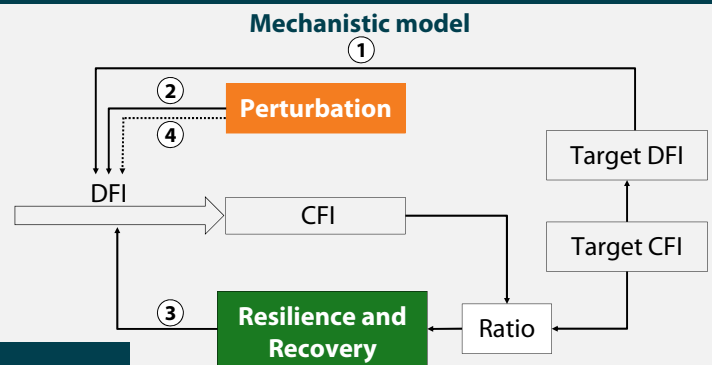
## CONCLUSION

- ❖ This study provides a new method to detect perturbations and quantify resistance and resilience of livestock
- ❖ The only required input is daily feed intake
- ❖ The method can be used to compare the individual response of animals affected by a common perturbation in group-housed settings → Genetic Selection

## MATERIAL AND METHODS

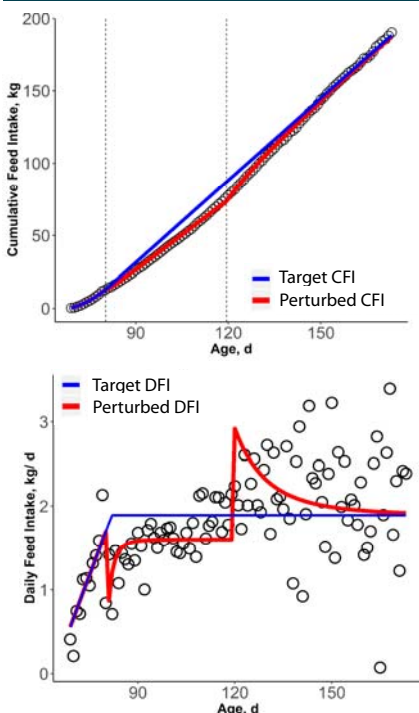
A data analysis procedure and a model were developed to:

- ❖ Determine the **target trajectory of Cumulative Feed Intake (target CFI)**: amount of feed a pig desires to consume in a non-perturbed condition
- ❖ **Detect consequences of perturbations** on feed intake by the **deviations** of observations from target CFI
- ❖ **Characterize pig's feed intake response** using a mechanistic model



- ① Absence of perturbation: Daily Feed Intake (DFI) = target DFI
- ② During perturbation: DFI ↓ → CFI starts to deviate from target CFI
- ③ **Ratio** between CFI and target CFI induces resilience and recovery mechanism
- ④ Perturbation is over: DFI ↑ → Through compensatory DFI, the CFI approaches target CFI and the pig recovers

## RESULTS



- The target CFI was estimated to correspond only to the highest observations of CFI

- The response of a pig to a perturbation was characterized by 4 parameters:

Start (day)	80
End (day)	119
Resistance (%)	-73
Resilience	3,74

- **Start** and **End** time of the perturbation
- **Resistance**: immediate reduction in DFI (%) at the start of the perturbation
- **Resilience**: capacity to limit the effect of the perturbing factor and to recover afterwards  
(e.g., if the CFI is 1% below the target CFI → Pig consumes 3.74% more than its target DFI)



Corresponding author: **Hieu Nguyen Ba**  
Email address: [hieu.nguyen-ba@inra.fr](mailto:hieu.nguyen-ba@inra.fr)

This study receives funding from European Union's H2020 project **Feed-a-Gene**, #DigitAg and INRA – ACCAF



**Detection and characterization of the feed intake response of growing pigs to perturbations***H. Nguyen Ba<sup>1</sup>, M. Taghipoor<sup>2</sup> and J. Van Milgen<sup>1</sup>**<sup>1</sup>INRA, UMR Pegase, Le Clos, 35590 Saint-Gilles, France, <sup>2</sup>INRA, UMR MoSAR, 16 rue Claude Bernard, 75231 Paris, France; hieu.nguyen-ba@inra.fr*

Improving robustness for farm animals is seen as a new breeding target. However, robustness is a complex trait and not measurable directly. Robustness can be characterized by examining the animal's response to environmental perturbations. Although the origin of environmental perturbations may not be known, the effect of a perturbation on the animal can be observed, for example through changes in voluntary feed intake. We developed a generic model and data analysis procedure to detect these perturbations, and subsequently characterize the feed intake response of growing pigs in terms of resistance and resilience as elements of robustness when faced with perturbations. We hypothesize that there is an ideal trajectory curve of cumulative feed intake, which is the amount of feed that a pig desires to eat when it is not facing any perturbation. Deviations from this ideal trajectory curve are considered as a period of perturbation, which can be characterized by its duration and magnitude. It is also hypothesized that, following a perturbation, animals strive to regain the ideal trajectory curve. A model based on differential equations was developed to characterize the animal's response to perturbations. In the model, a single perturbation can be characterized by two parameters which describe the resistance and resilience potential of the animal to the perturbing factor. One parameter describes the immediate reduction in daily feed intake at the start of the perturbation (i.e. a 'resistance' trait) while another describes the capacity of the animal to adapt to the perturbation through compensatory feed intake to rejoin the ideal trajectory curve (i.e. a 'resilience' trait). The model has been employed successfully to identify the ideal trajectory curve of cumulative feed intake in growing pigs and to quantify the animal's response to a perturbation by using feed intake as the response criterion. Further developments include the analysis of individual feed intake curves of group-housed pigs that can be exposed to the same environmental perturbing factors to quantify and to compare different pigs. This study is part of the Feed-a-Gene project and was funded by the European Union under grant agreement no. 633531.

**Layers response to a suboptimal diet through phenotype and transcriptome changes in four tissues***F. Jehl<sup>1</sup>, M. Brenet<sup>1,2</sup>, A. Rau<sup>1</sup>, C. Désert<sup>1,2</sup>, M. Boutin<sup>1,2</sup>, S. Leroux<sup>1</sup>, D. Esquerré<sup>1</sup>, C. Klopp<sup>1</sup>, D. Gourichon<sup>1</sup>, A. Collin<sup>1</sup>, F. Pitel<sup>1</sup>, T. Zerjal<sup>1</sup> and S. Lagarrigue<sup>1,2</sup>**<sup>1</sup>INRA, 147 Rue de l'Université, 75007 Paris, France, <sup>2</sup>Agrocampus Ouest, 65 Rue de Saint-Brieuc, 35000 Rennes, France; frederic.jehl@inra.fr*

Poultry meat and eggs are major sources of nutrients in the human diet. The long production career of laying hens expose them to biotic or abiotic stressors, lowering their production. Understanding the mechanisms of adaptation to stress is crucial for selecting robust animals and meeting the needs of a growing human population. In this study, financed by the French ChickStress and the European Feed-a-Gene (grant agreement no. 633531) programs, we compared the effects of a 15%-energy-reduced diet (feed stress, FS) vs a commercial diet (control, CT) on phenotypic traits and adipose, blood, hypothalamus and liver transcriptomes in two feed-efficiency-diverging lines. Phenotypic traits showed differences between lines or diets, but no line × diet interaction. In the FS group, feed intake (FI) increased and hens had lower body- and abdominal adipose weight, compared to CT group. We found no differences in egg production or quality. At the transcriptomic level, 16,461 genes were expressed in one or more tissues, 41% of which were shared among tissues. We found differentially expressed genes between lines or diet in all tissues, and almost no line × diet interactions. Focusing on diet, adipose and liver transcriptomes were unaffected. In blood, pathways linked to amino acids, monosaccharides, and steroid metabolism were affected, while in the hypothalamus, changes were observed in fatty acid metabolism and endocannabinoid signalling. Given the similarities in egg production, the FS animals seem to have adapted to the stress by increasing FI and by mobilizing adipose reserves. Increase in FI did not appear to affect liver metabolism, and the mobilization of adipose reserves was apparently not driven at the transcriptomic level. In blood, the pathways linked to metabolic processes suggest a metabolic role for this tissue in chicken, whose erythrocytes are nucleated and contain mitochondria. FI increase might be linked to the hypothalamic pathway of endocannabinoid signalling, which are lipid-based neurotransmitters, notably involved in the regulation of appetite.



# Detection and characterization of the response of growing pigs to perturbations by using feed intake



Hieu Nguyen Ba<sup>1\*</sup>, Masoomeh Taghipoor<sup>2</sup> and Jaap van Milgen<sup>1</sup>

<sup>1</sup>INRA, UMR 1348 PEGASE, F-35590 Saint-Gilles, France

<sup>2</sup>INRA, UMR 0791 MoSAR, AgroParisTech, 75231, Paris, France

\*[hieu.nguyen-ba@inra.fr](mailto:hieu.nguyen-ba@inra.fr)

Keywords: *robustness, modelling, perturbations, feed intake*

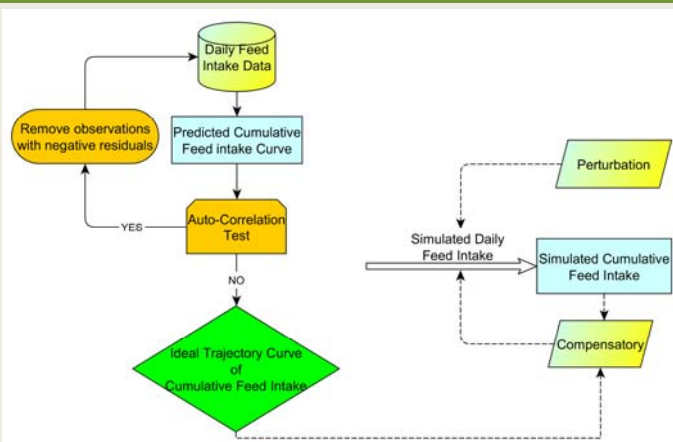
## INTRODUCTION

- Global climate change increases environmental perturbations
- Farm animals need to adapt better to perturbations while maintaining their growth and productivity
  - Improve robustness in breeding

## OBJECTIVES

- But robustness is difficult to measure
- Develop a generic model:
  - Detect unknown perturbations
  - Characterize responses of growing pigs to those perturbations by using feed intake (FI) as an indicator of robustness

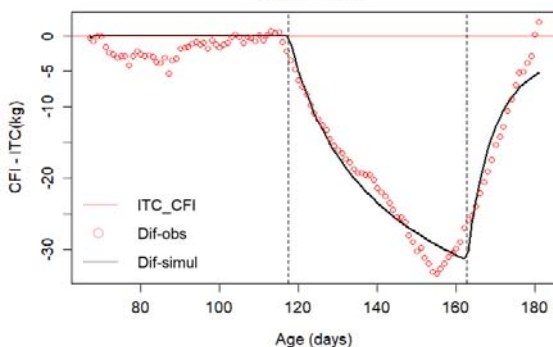
## METHODS



- Our model based on differential equation can characterize:
  - Perturbing impact:** makes daily FI of a pig reduced, e.g. 20% during a heat stress
  - Pig's compensatory capacity:** consuming more FI daily
 The more the FI decreased the stronger motivation the pig had to compensate for its FI lost

## RESULTS

Modelling pig's reaction to perturbations  
Pig ID = 5144



Pig ID = 5146

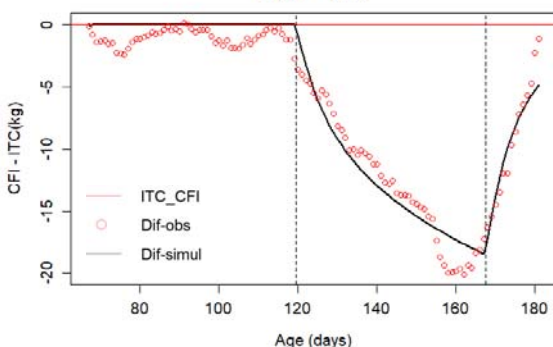


Table.1. Estimated parameters obtained when using the model to quantify feed intake response of the pigs to the same perturbation

Pig ID	Time Start	Time stop	Perturbing impact	Compensatory Capacity	RSS <sup>§</sup>
5144	117,5	162,7	0,8	23,5	23,7
5146	119,5	167,5	0,6	16,4	14,9

<sup>§</sup>RSS: Residual sum of square

## DISCUSSION

- The model successfully characterized animal's response to perturbations
  - Perturbing impact: resistance
  - Compensatory capacity: resilience
- Perturbing impact as a constant has limitation in sanitary perturbations
- Robustness of different pigs: comparable

Fig.1. Feed Intake response of 02 group housed pigs to perturbation. They were supposed to suffer from the same perturbation because their perturbing period was the same



---

**Titre** Quantification de la réponse de l'ingestion alimentaire des porcs en croissance à des perturbations – une approche de modélisation

**Mots clés** : porcs en croissance, ingestion volontaire, résistance, résilience, génétique, santé

**Résumé** : Il est de plus en plus important de quantifier la robustesse des animaux d'élevage pour améliorer la durabilité des systèmes des élevages. Cependant, robustesse est un trait complexe et non mesurable directement. Cette thèse a été consacré à quantifier des éléments de robustesse. Un modèle mathématique a été développé pour détecter des perturbations et pour quantifier la réponse des porcs en croissance en termes de la résistance et la résilience. Le modèle permet d'estimer la trajectoire ciblée de l'ingestion cumulatif pour les porcs en croissance. Des conséquences de perturbation peuvent être détecter par des déviations de cette ciblée. La réponse d'animal peut être caractérisée par quatre paramètres :

le début et la fin de la perturbation, la réduction immédiate de l'ingestion journalière (la résistance), et la capacité de l'animal à retrouver sa trajectoire ciblée de l'ingestion via la consommation compensatrice (la résilience). Nous avons appliqué ce modèle à quantifier la réponse des porcs en croissance à une et deux périodes de distribution de régimes contaminées par des mycotoxines. Le modèle a prouvé sa capacité à détecter et quantifier la réponse des animaux aux mycotoxines. Les caractéristiques de la réponse d'animal peuvent être appliquées pour affiner les critères de sélection génétique et dans le contexte de mieux adapter les stratégies d'alimentation.

---

**Title** : Quantification of the feed intake response of growing pigs to perturbations – A modelling approach

**Keywords** : growing pigs, voluntary feed intake, resistance, resilience, genetic, health

**Abstract** : Quantifying robustness of farm animals is essential to improve the sustainability of livestock production systems. Robustness, however, is a complex trait and not measurable directly. The aim of this PhD thesis was to develop a method to quantify elements of robustness in growing pigs. A mathematical model was developed to detect perturbations on feed intake and to quantify the response of pigs to perturbations in terms of resistance and resilience. The model estimated a targeted trajectory of cumulative feed intake which is hypothesized as the desired feed intake of pigs in non-perturbed condition. Consequences of perturbations can be detected from deviations of this target. The animal's response can be characterized by four parameters: the start and

end times of a perturbation, the immediate reduction in daily feed intake at the start of the perturbation (resistance trait) and the pig's capacity to overcome the perturbing effect through compensatory feed intake (resilience trait). We then applied the model to quantify the response of group-housed pigs to a diet contaminated with mycotoxins in one or two periods of the experiment. The model proved its capacity to detect and quantify the response of pigs to mycotoxins. Characteristics of animal's response obtained from the model can be applied to phenotype animals in genetic selection or in management strategies.