Modeling nutrition, metabolism and growth in pigs

Jaap J. van Milgen

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Université de Rennes 1

Mémoire présenté en vue de l'obtention de

l'Habilitation à Diriger des Recherches

Préparé par

Jacob VAN MILGEN

Ingénieur de Recherche

INRA

UMR1079 Systèmes d'Élevage, Nutrition Animale Humaine

F-35590 Saint Gilles

Modeling nutrition, metabolism and growth in pigs

Modélisation de la nutrition, du métabolisme et de la croissance chez le porc

Contents

Preface and acknowledgements

This report has been written in partial fulfillment for the 'Habilitation à Diriger des Recherches'. The report provides a list of activities and an overview of my past and future research program as well as an overview of other activities. Following the submission of a partial report in May 2009, the Université de Rennes 1 has authorized that the full report may examined by the following jury members:

- Martin VERSTEGEN. Professor at Wageningen University and Research, Wageningen, the Netherlands.
- Guido RYCHEN. Professor at the Institut Polytechnique de Lorraine, Université de Nancy.
- Isabelle ORTIGUES-MARTY. Chargée de Recherche at INRA, UR Herbivores, Clermont-Ferrand

It has taken (too) many years to write the report. My first intentions to write it date back to almost 10 years ago, but I have never had (or: never taken) the time to actually do it. The summer is the most suitable period to take a few weeks, sit down, think, think again, and finally report was has been done and want should be done in the future. Now that the writing is done, I have to admit that it was an interesting exercise and I have done it with great pleasure.

Numerous people contributed in one way or another in offering me the possibility to establish a career in research. The list of names would be very long and I will not name them specifically here. The names of some people whom I worked with on specific projects are listed in the report and their cooperation is gratefully acknowledged. I also would like to express my gratitude to all technicians and staff of the research unit in Saint-Gilles. Without their help and dedication, research would not be possible.

Finally I wish to thank my wife Aleida and our children Evelien, Hidde and Marlijn. Aleida threatened numerous times to lock me up in a cabin for 2 weeks so that I could/would/should write this report. Although I am not sure if this has been the final trigger to write it (I never got locked up), I am very grateful to them for supporting me throughout my career.

Curriculum Vitae

Jacob VAN MILGEN
Date of birth: 9 April 1960 in Zwollerkerspel, the Netherlands
Married, 3 children

Research interests: Nutrition, Metabolism, and Modeling

Current position

Research engineer in the research team 'Nutrition and Metabolism' at the UMR1079 Systèmes d'Élevage, Nutrition Animale et Humaine, INRA - Agrocampus Ouest, 35590 Saint Gilles
Tel: 02 23 48 56 44
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Education

1984: Kandidaats (BSc), Landbouwhogeschool Wageningen, the Netherlands
1987: Ingenieur (MSc), Landbouwhogeschool Wageningen, the Netherlands
1991: PhD, University of Illinois at Urbana-Champaign, United States

Employment

1988: Research engineer, Hoffmann-La Roche, Mijdrecht, the Netherlands (8 months)
1989: Research assistant, University of Illinois at Urbana-Champaign, United States (46 months)
1992: Post-doctoral researcher, University of Ljubljana, Domžale, Slovenia (3 months)
1992: Post-doctoral researcher, Station de Recherches sur la Nutrition des Herbivores, INRA, Clermont-Ferrand, France (21 months)
1994: Research engineer (2nd class), Station de Recherches Porcines, INRA, Saint Gilles, France
2004: Research engineer (1st class, UMR1079 Systèmes d'Élevage, Nutrition Animale et Humaine, INRA, Saint Gilles, France

Additional courses and training

- French (Rennes, 1994 and 1998, 50+40 h)
- Meeting management (Rennes, 1996, 14 h)
- Animal experimentation level I (ENV Nantes, 1997, 67 h)
- Windows NT (Rennes, 1998, 21 h)
- Quality Control in Research (Saint-Gilles, 2001, 14 h)
- INRA Workshop: "Decision support: How to articulate knowledge and action?" (La-Londe-les-Maures, 2001, 28 h)
- INRA (ENA Division) Workshop: "The systems approach: an approach for animal scientists" (Paris, 2001, 7 h)
- Training for chairpersons of recruiting committees (Paris, 2003, 7 h)
- Réflexives: Seminar for PhD-students and their advisors (with Maela KLOAREG, Guéthary, 2003, 35 h)
- Principles and tools in human resource management at INRA (Rennes, 2003, 7 h)
- Conducting assessment and evaluation of personnel (Rennes, 2004, 7 h)
- Réflexives: Seminar for PhD-students and their advisors: scientific writing (with Maela KLOAREG, Nantes, 2004, 14 h).
- Réflexives workshop for moderators (Agadir, 2004, 35 h)

- Réflexives: Seminar for PhD-students and their advisors (with Pierre BLAVY, Ronce-les-Bains, 2008, 35 h)
- RMT Modélia training "How to carry out a software development project with software development engineers" (Meudon la Foret, 2008, 21 h)
- Réflexives workshop for moderators (Tenerife, 2009, 35 h)

Teaching activities

- University of Ljubljana: "Introduction to modelling biological processes" (Domžale, Slovenia, 1994, 1995, 1996, 1997, 1998 et 2004, 1 week)
- INRA research Center in Rennes: Training courses in "Introduction to non-linear regression" (3.5 h/training) and "Advances topics in non-linear regression" (7 h/training) (Le Rheu, between 1998 and 2002, 5 times/module)
- INA-PG: Cours Supérieur de Productions Porcines "Nutrition of growing pigs: physiological basis and modeling" (St-Gilles, 1997 and 1999, 2 h)
- Agrocampus Ouest: "Introduction to modeling" (Rennes, annually since 1999, 4 h course + practical training)
- INRA: Workshop for researchers in the SAD, ENA, and HyFS divisions "Modeling compartmental systems" (Paris, 2000, 5.5 h)
- ESA: "Introduction to modeling biological processes" (Angers, annually since 2000, 7 h/yr)
- University of de Tours: DESS "Introduction to modeling biological processes" (Tours, 2000, 7 h)
- INRA: Workshop for researchers in the ENA and SAD divisions "The systems approach to treat new challenges in research in livestock systems" (Carqueiranne, 2002, 5 h)
- Agrocampus Ouest: "Feed formulation" and "InraPorc" (Rennes, annually since 2004, 4 h + practical training)
- INRA/ACTA/ICTA : Workshop "Introduction to modeling : mathematical models for agronomy and animal science" (La Rochelle, 3 times between 2005 and 2007, 1 h)
- University of Rennes 1: (IUP) "Nutrition and Modeling" (Rennes, 2006 and 2007, 3 h)
- INRA: Workshop "Systems Biology and Modeling" (Batz-sur-Mer, 2007, 1 h)
- CIHEAM: International master on Animal Nutrition "Estimation and expression of nutritional requirements; nutrient balance and body reserves" (Saragossa, Spain, 2007 and 2009, 7 h)
- AgroParisTech: "InraPorc – a decision support tool for the nutrition of growing pigs and sows" (Paris, 2007 et 2008, 4 h)
- Ifip, Agrocampus Ouest and Inra: InraPorc training (Le Rheu, 2008 and 2009, 4 h)
- Numerous InraPorc training session for nutritionists in France, Spain, Italy, Hungary, Poland, Belgium, the Netherlands, Germany, England, Ireland, Canada, United States, Mexico and Brazil (since 2006, 6 h/training)

Administrative responsibilities

Internationally

- Advisor in statistics and modeling for the journal "Animal Research" (2001-2004)
- Associate editor for the journal "Animal Research" (2004-2006)
- Editor for the journal "Animal", section "Livestock Farming Systems and Environmental Impact" (2007-present)
- Reviewer of numerous manuscripts for peer-reviewed journals:
  - Agricultural Systems
  - Animal Feed Science and Technology
  - Animal (Annales de Zootechnie, Animal Research, Animal Science)

- Australian Journal of Agricultural Research
- British Journal of Nutrition
- Journal of Animal Physiology and Animal Nutrition
- Journal of Animal Science
- Journal of Dairy Science
- Journal of Zhejiang University Science
- Livestock Science (Livestock Production Science)
- South African Journal of Animal Science

At INRA
- Member of the recruiting committee for research engineers (1998, 2003 (chairman), 2004, 2007, 2009) and ASC positions (2005 and 2006)
- Co-moderator of Réflexives (since 2004)
- Member of the steering committee of Réflexives (since 2006)
- Member of the scientific committee of the 2nd Symposium on Energy and Protein Metabolism and Nutrition (Vichy, 2007)
- Member of the steering committee of the RMT Modélisation (since 2008)
- Member of the scientific committee of the 7th International Workshop on Modelling Nutrient Digestion and Utilization in Farm Animals (Paris, 2009)
- Member of the steering committee of modeling the fate of nutrients in the GI-tract (INRA/CNRS, since 2008)

At the Phase Division
- Co-moderator of the working group on modeling (1995-2006)
- Member-elect of the scientific council of the ENA division (2002-2004)
- Member-elect of the scientific council of the Phase division (2004-2006)
- (Deputy) Member-elect of the scientific council of the Phase division (2006-present)
- Moderator of the working group on modeling (since 2007)

At UMR SENAH
- Member-elect of the service council of the SRP (1996-2000)
- Moderator of the Quality control group "Management and storage of data" (2001-2004)
- Deputy director of UMR SENAH (2003-2007)
- Moderator of the research team "Nutrition and Metabolism" (2005-present)
- Co-moderator of the UMT Porcin for the research field "Optimization of nutritional programs" (since 2007)

Advisor of students and visiting scientists (date or period; % implication)
- Anne COLLIN, PhD-student (thesis defense 20/12/2000; 20%)
- Rosil LIZARDO, post-doctoral researcher (1998-2000; 80%)
- Alberto Borgia, PhD-student (thesis started in 1999 and stopped after 1 year; 80%)
- Laurent LE BELLEGO, PhD-student (thesis defense 30/10/2001; 20%)
- Kees DE LANGE, sabbatical period from the University of Guelph (6 months in 2001; 80%)
- Maela KLOAREG, MSc-student (6 months in en 2002; 100%)
- Marson WARPECHOWSKI, PhD-student from the Federal University of Paraná, Brazil (1 year in 2003; 20%)
- Malechy YOUNG, PhD-student from Kansas State University (2 months in 2003; 20%)
- Flávio Bello FIALHO, post-doctoral researcher from Embrapa, Brazil (2 months in 2004; 90%)
- Maela KLOAREG, PhD-student (thesis defense 3/02/2006; 90%)

- Aurélie WILFART, PhD-student (thesis defense 16/2/2007; 50%)
- Alberto CONDE, PhD-student from the Estación Experimental del Zaidín (CSIC), Spain (2 months in 2007; 100%)
- Roberto BAREA, post-doctoral researcher (2006-2008; 90%)
- Pierre BLAVY, PhD-student (since 2006; 20%)
- Mallory PRIGENT, undergraduate BTS student (2 months in 2007; 25%)
- Paulo LOVATTO, sabbatical period (1 year in 2008; 40%)
- Virginie RIVERA, PhD-student from AgroParisTech, Paris (occasionally since 2008; 75%)
- Etienne LABUSSIÈRE, PhD-student (thesis defense 21/10/2008; 10%)
- Amélie COTARD, undergraduate BTS student (2 months in 2008; 25%)
- Mathieu GLOAGUEN, MSc-student (5 months in 2008; 90%)
- Hélène PASTORELLI, PhD-student (since end of 2008; 10%)
- Marie REKIBA, MSc-student (2 months in 2009; 90%)
- Mathieu GLOAGUEN, PhD-student (starting June 2009; 90%)

PhD examination committees (date of thesis defense)

- Denis BASTIANELLI, Institut National Agronomique de Paris-Grignon (20/9/1996)
- Anne COLLIN, Ecole Nationale Supérieure Agronomique de Rennes (20/12/2000)
- Paulo LOVATTO, Institut National Agronomique de Paris-Grignon (28/9/2001)
- Hélène FOUILLET, Institut National Agronomique de Paris-Grignon (26/10/2002)
- Ian WELLOCK, University of Edinburgh (28/11/2003)
- Veronika HALAS, Wageningen University (7/6/2004)
- Arie KIES, Wageningen University (6/6/2005)
- Maela KLOAREG, Agrocampus Rennes (3/2/2006)
- Joost VAN DEN BORNE, Wageningen University (17/11/2006)
- Barbara JUILLET, Institut National Agronomique de Paris-Grignon (21/12/2006)
- Aurélie WILFART, Agrocampus Rennes (16/2/2007)
- Marie-Pierre LETOURNEAU-MONTMINY, AgroParisTech (25/5/2009)
- Olivier MARTIN, AgroParisTech (30/09/2009)
- Anders STRATHE, University of Copenhagen (02/10/2009)

PhD steering committees (research organization)

- Gwénola LE GOFF (UMR VP, Rennes)
- Philippe JEAN-DIT-BAILLEUIL (Université de Laval, Canada)
- Mathieu MONZIOLS (UMR VP, Rennes)
- Maxime QUENTIN (INRA, SRA, Tours)
- Rozenn GUILLEMET (UMR VP, Rennes)
- Delphine GARDAN (UMR VP, Rennes)
- Alice HAMARD (UMR VP, Rennes)
- Guillaume KRAFT (INRA, URH, Clermont-Ferrand)
- Emmanuelle MOSNIER (UMR SENAH, Rennes)
- Christelle LONCKE (INRA, URH, Clermont-Ferrand)
- Claire FROMENTIN (AgroParisTech, UMR PNCA, Paris)
- Gaëlle MAXIN (INRA, UMR PL, Rennes)
- Hajer KHELIL (INRA, UMR PL, Rennes)

Participation at (international) scientific congresses

- Journées de la Recherche Porcine (yearly since 1994)
- 8th International Symposium on Ruminant Physiology (Willingen, Germany, 1994)
- 4th International Workshop on Modelling Nutrient Utilization in Farm Animals (Foulum, Denmark, 1994)

- Satellite symposium of the 4th International Symposium on the Nutrition of Herbivores: "Methods in Modeling Herbivore Nutrition" (Paris, 1995)
- 7th International Symposium on Digestive Physiology in the Pig (Saint Malo, France, 1997)
- 14th International Symposium on Energy Metabolism in Farm Animals (Newcastle, Northern Ireland, 1997)
- NRC Symposium on Nutrient Requirements in Swine (Québec, Canada, 1998)
- Annual congress of the American Society of Animal Science (Indianapolis, United States, 1999)
- 5th International Symposium on Modeling Nutrient Utilization in Farm Animals (Cape Town, South Africa, 1999)
- Annual congress of the American Society of Animal Science (Baltimore, United States, 2000)
- 15th International Symposium on Energy Metabolism in Farm Animals (Elsinore, Denmark, 2000)
- Annual congress of the American Society of Animal Science (Indianapolis, United States, 2001)
- Annual congress of the American Society of Animal Science (Phoenix, United States, 2003)
- 1st International Symposium on Energy and Protein Metabolism (Rostock, Germany, 2003)
- Annual congress of the Brazilian Society for Animal Nutrition, CBNA, (Campinas, Brazil, 2003)
- Annual congress of the American Society of Animal Science, section Midwest (Des Moines, United States, 2005)
- International Workshop on Green Pork Production (Paris, 2005)
- Annual congress of the Mexican Society for Animal Nutrition, AMENA, (Querétaro, Mexico, 2003)
- Annual congress of the American Society of Animal Science (San Antonio, United States, 2007)
- 2nd International Symposium on Energy and Protein Metabolism (Vichy, France, 2007)
- Recent Advances and Controversies in the Measurement of Energy Metabolism (Denver, United States, 2008)
- Annual congress of the European Association for Animal Production (Vilnius, Lithuania, 2008)
- Annual congress of the American Society of Animal Science, section Midwest (Des Moines, United States, 2009)
- 7th International Workshop on Modelling Nutrient Digestion and Utilization in Farm Animals (Paris, 2009)

Invited presentations at congresses, symposia and workshops

- Ralston Purina International R&T/Marketing workshop (Seville, Spain, December 10-12, 1997): Modeling NE requirements.
- 5th International Feed Production Conference (Piacenza, Italy, June 15-18, 1998): Modelling growth in pigs: from development to application.
- X Congresso de Zootecnia - Progressos zootécnicos nos países de língua portuguesa (Santarém, Portugal, November 2-4, 2000): Nutritional modeling of growth in pigs.
- Xarxa temàtica. Eficiència productive i qualitat en porcí (Barcelona, Spain, June 8, 2001): Metabolismo en el cerdo: El animal, la dieta y el medio ambiente.
- International Symposium on Animal Nutrition (Santa Maria, Brazil, October 3-5, 2001): Feed energy models in poultry and swine.
- 9th Intercoop Workshop on Pig and Poultry Nutrition (Lelystad, the Netherlands, November 7-8, 2001): Modelling fat digestion, fat utilization and retention of fatty acids in the carcass.
- Annual meeting of the American Society of Animal Science (Québec, Canada, July 21-25, 2002): Partitioning of energy intake to heat protein, and fat in growing pigs.
- Technical meeting SPACE 2002 (CEVA, Rennes, September 10, 2002): Une revue des besoins en thréonine du porc.
- Orffa's Varkens Symposium (Orffa, Breda, the Netherland, October 3, 2002): Threonine behoefte bij varkens: een overzicht.
- From crude protein to precision protein (Forum Bioscience, Birmingham, United Kingdom, November 21, 2002): Threonine requirements in pigs, a review.
- XVII Jornados Técnicas (Vetiquima, Lisbon and Indukern, Barcelona and Madrid, February 26-28, 2003): Révision de los requerimientos L-Treonina en cerdos en crecimiento y cebo.
- CNBA Symposium on Nutrition, Management, and Feed Technology in Swine and Poultry (Campinas, Brazil, November 12-14, 2003): Energy utilization in pigs and its application in energy systems.
- Recent advances in pig and poultry modeling (Ithala, South Africa, April 14-15, 2005): Nutrient flow models, energy transaction and energy feed systems.
- Farewell seminar for Martin Verstegen (Wageningen, the Netherlands, March 30, 2006): From the social life of moles to animal nutrition research.
- Annual meeting of AMENA. Uso de aminoácidos cristalinos: Eficiencia energética. Primer seminario de actualización (Querétaro, Mexico, June 25-27, 2007): Energy systems and energy utilization as affected by the animal and its environment.
- Jornadas de Manejo y Nutrición en Porcino (Lugo, Spain, September 20, 2007): InraPorc, a model and decision support tool for the nutrition of pigs.
- Compréhension et modélisation du devenir des aliments dans le tube digestif (CNRS and INRA, Paris, June 5, 2008): L'utilisation des animaux canulées et de marqueurs pour mesurer le transit.
- 2008 Ajinomoto Eurolysine yearly technical meeting (Chantilly-Gouvieux, France, June 19, 2008): The valine and isoleucine research program.
- 42nd University of Nottingham Feed Conference (Nottingham, United Kingdom, September 3-4, 2008). Using InraPorc to reduce nitrogen and phosphorus excretion in pigs.
- Etique et expérimentation chez les animaux de production (Académie vétérinaire de France, Paris, October 23, 2008): Modélisation du fonctionnement digestif et du métabolisme chez le porc: une alternative aux approches chirurgicales?
- 7ème Journées Francophones de Nutrition (Brest, October 28, 2008): Modélisation du métabolisme énergétique.

- Salon International de l'Agriculture: Des outils pour une filière porcine plus durable (Paris, February 23, 2009): De nouveaux outils d'aide à la décision pour l'alimentation porcine.
- XXIII Jornadas Técnicas de Indukern (Barcelone et Madrid, Spain, March 12-13, 2009): Valine and isoleucine requirements in piglets.
- Pre-Mervo Themamiddag (Wolfheze, the Netherlands, June 3, 2009): Het volgende limiterende aminozuur in biggenvoeders: L-Valine.
- 15de Orffa Benelux symposium 2009 (Etten-Leur, the Netherlands, June 12, 2009): Valinebehoefte in biggen en interactie met overige aminozuren.

Other presentations at congresses, symposia and workshops

- 14th International Symposium on Energy Metabolism in Farm Animals (Newcastle, Northern Ireland, September 14-20, 1997): Modelling dynamic aspect of heat production in pigs.
- 14th International Symposium on Energy Metabolism in Farm Animals (Newcastle, Northern Ireland, September 14-20, 1997): Effect of breed and body weight on components of heat production in growing pigs.
- 31èmes Journées de la Recherche Porcine (Paris, France, February 2-4, 1999): Bases d'estimation des besoins énergétiques du porc en croissance.
- 91st annual ASAS meeting (Indianapolis, July 21-23, 1999): Modeling the relation between energy intake and protein and lipid deposition in growing pigs.
- 91st annual ASAS meeting (Indianapolis, July 21-23, 1999): Effect of low protein diets on energy utilization in growing pigs.
- 5th International Symposium on Modeling Nutrient Utilization in Farm Animals (Cape Town, South Africa, October 25-27, 1999): Modeling energy expenditure in pigs.
- 32èmes Journées de la Recherche Porcine (Paris, France, February 1-3, 2000): Modélisation des composantes de la dépense énergétique chez le porc.
- 2000 ADSA-ASAS joint meeting (Baltimore, July 25-28, 2000): A biochemical model of nutrient utilization in growing pigs.
- 2000 ADSA-ASAS joint meeting (Baltimore, July 25-28, 2000): Utilization of low heat increment diets at high ambient temperatures in growing pigs.
- 15th International Symposium on Energy Metabolism in Farm Animals (Elsinore, Denmark, September 11-15, 2000): Energetic efficiency of nutrient utilization in growing pigs.
- 15th International Symposium on Energy Metabolism in Farm Animals (Elsinore, Denmark, September 11-15, 2000): Dynamic aspects of gas exchanges.
- 2001 ADSA-ASAS-PSA-AMSA joint meeting (Indianapolis, July 24-28, 2001): Utilization of metabolizable energy in broilers.
- 2001 ADSA-ASAS-PSA-AMSA joint meeting (Indianapolis, July 24-28, 2001): Compensatory feed intake and growth in pigs.
- 2002 ADSA-ASAS-CSAS joint meeting (Québec, July 21-25, 2002): Effects of feed restriction and subsequent re-feeding on energy utilization in growing pigs.
- 2003 ADSA-ASAS-AMPA joint meeting (Phoenix, July 22-26, 2003): A meta-analysis to estimate the optimum threonine to lysine ratio in growing pigs.
- 2003 ADSA-ASAS-AMPA joint meeting (Phoenix, July 22-26, 2003): Effect of high ambient temperature and feeding level on fatty acid deposition in growing pigs.
- 2003 ADSA-ASAS-AMPA joint meeting (Phoenix, July 22-26, 2003): Effect of betaine on energy partitioning in growing pigs.
- 1st International Symposium on Energy and Protein Metabolism (Rostock, September 13-18, 2003): Effect of body weight and dietary crude protein on energy utilisation in growing pigs and broilers.
- 1st International Symposium on Energy and Protein Metabolism (Rostock, September 13-18, 2003): The use of nutritional models as a tool in basic research.
- 37èmes Journées de la Recherche Porcine (Paris, France, February 1-3, 2005): InraPorc : un modèle pour analyser les performances et évaluer les stratégies alimentaires chez le porc en croissance.
- 1ères Journées d'Animation Scientifiques du Département PHASE (Tours, March 15-16, 2005): Un rapport de 65% de Thr:Lys couvre le besoin en thréonine chez le porc en croissance.

- 38th ASAS meeting Midwestern Sectional (Des Moines, March 21-23, 2005): Body weight has no effect on the threonine requirement in growing pigs.
- 2007 ADSA-ASAS-AMPA joint meeting (Phoenix, July 22-26, 2007): InraPorc: a model and decision support tool for the nutrition of growing pigs and sows.
- 2nd International Symposium on Energy and Protein Metabolism (Vichy, France, September 9-13, 2007): Dietary methionine supply affects the amino acid composition of body proteins.
- Recent Advances and Controversies in the Measurement of Energy Metabolism (Denver, February 5-7, 2008): Using modeling techniques to analyze the energy expenditure in open-circuit respiration chambers.
- 40èmes Journées de la Recherche Porcine (Paris, France, February 5-6, 2009): Détermination du besoin en valine chez le porcelet.
- 42nd ASAS meeting Midwestern Sectional (Des Moines, March 14-19, 2009): The standardized ileal digestible isoleucine to lysine requirement ratio may not be greater than 50% in post-weaned piglets.
- 42nd ASAS meeting Midwestern Sectional (Des Moines, March 14-19, 2009): The standardized ileal digestible valine to lysine requirement ratio is at least 70% in post-weaned piglets.

Publications in peer-reviewed journals

A1 **van Milgen, J.**, Murphy, M. R. & Berger, L. L. (1991). A compartmental model to analyze ruminal digestion. Journal of Dairy Science 74, 2515-2529.

A2 **van Milgen, J.**, Roach, M. L., Berger, L. L., Murphy, M. R. & Moore, D. M. (1992). Technical note: mineral deposits on dacron bags during ruminal incubation. Journal of Animal Science 70, 2551-2555.

A3 **van Milgen, J.**, Berger, L. L. & Murphy, M. R. (1992). Fractionation of substrate as an intrinsic characteristic of feedstuffs fed to ruminants. Journal of Dairy Science 75, 124-131.

A4 **van Milgen, J.**, Berger, L. L. & Murphy, M. R. (1993). An integrated, dynamic model of feed hydration and digestion, and subsequent bacterial mass accumulation in the rumen. British Journal of Nutrition 70, 471-483.

A5 **van Milgen, J.**, Berger, L. L. & Murphy, M. R. (1993). Digestion kinetics of alfalfa and wheat straw assuming heterogeneity of the potentially digestible fraction. Journal of Animal Science 71, 1917-1923.

A6 Bourquin, L. D., Titgemeyer, E. C., **van Milgen, J.** & Fahey, G. C., Jr. (1994). Forage level and particle size effects on orchardgrass digestion by steers: II. Ruminal digestion kinetics of cell wall components. Journal of Animal Science 72, 759-767.

A7 Quiniou, N., Noblet, J., **van Milgen, J.** & Dourmad, J. Y. (1995). Effect of energy intake on performance, nutrients and tissue gain and protein and energy utilisation in growing boars. Animal Science 61, 133-143.

A8 Sauvant, D. & **van Milgen, J.** (1995). Les conséquences de la dynamique de la digestion des aliments sur le métabolisme ruminal et les performances animales. INRA Productions Animales 8, 353-367.

A9 **van Milgen, J.** & Baumont, R. (1995). Models based on variable fractional digestion rates to describe ruminal in situ digestion. British Journal of Nutrition 73, 793-807.

A10 **van Milgen, J.**, Boston, R., Kohn, R. & Ferguson, J. (1996). Comparison of available software for dynamic modeling. Annales de Zootechnie 45, Suppl., 257-273.

A11 **van Milgen, J.**, Noblet, J., Dubois, S. & Bernier, J. F. (1997). Dynamic aspects of oxygen consumption and carbon dioxide production in swine. British Journal of Nutrition 78, 397-410.

A12 **van Milgen, J.**, Bernier, J. F., Lecozler, Y., Dubois, S. & Noblet, J. (1998). Major determinants of fasting heat production and energetic cost of activity in growing pigs of different body weight and breed/castration combination. British Journal of Nutrition 79, 509-517.

A13 Noblet, J., Karege, C., Dubois, S. & **van Milgen, J.** (1999). Metabolic utilization of energy and maintenance requirements in growing pigs: effects of sex and genotype. Journal of Animal Science 77, 1208-1216.

A14 Quiniou, N., Noblet, J., Dourmad, J. Y. & **van Milgen, J.** (1999). Influence of energy supply on growth characteristics in pigs and consequences for growth modelling. Livestock Production Science 60, 317-328.

A15 **van Milgen, J.** & Noblet, J. (1999). Energy partitioning in growing pigs: the use of a multivariate model as an alternative for the factorial analysis. Journal of Animal Science 77, 2154-2162.

A16 Ramonet, Y., **van Milgen, J.**, Dourmad, J. Y., Dubois, S., Meunier-Salaün, M. C. & Noblet, J. (2000). The effect of dietary fibre on energy utilisation and partitioning of heat production over pregnancy in sows. British Journal of Nutrition 84, 85-94.

A17 **van Milgen, J.**, Quiniou, N. & Noblet, J. (2000). Modelling the relation between energy intake and protein and lipid deposition in growing pigs. Animal Science 71, 119-130.

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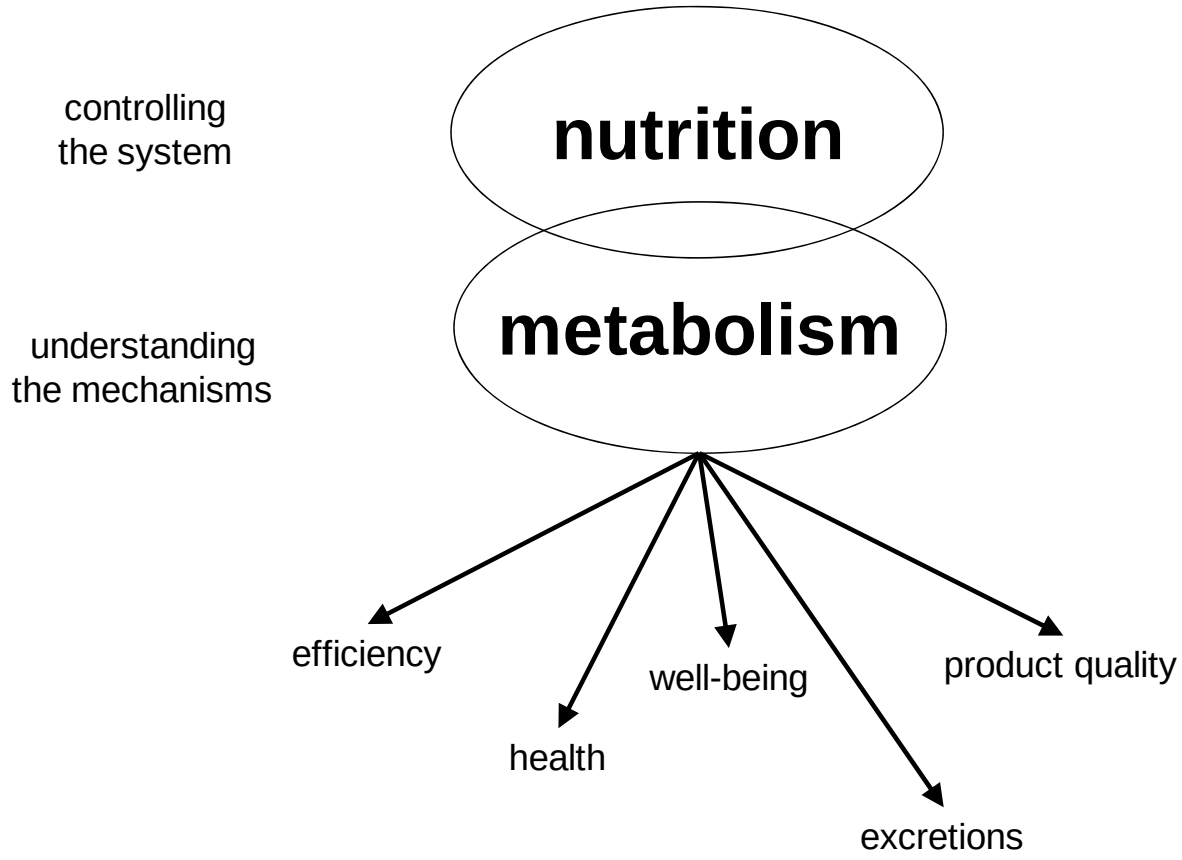

Figure 1. The positioning of the research activities of the team ‘Nutrition and Metabolism’.

Overview of activities

1. Introduction

Animal production is constantly facing new challenges. After World War 2, increasing productivity and efficiency were key issues to ensure food supply in Europe. Since then, other dimensions have become issues in animal production including animal health (related to the intensification of animal production), food quality and security, environment, animal welfare and consumer and citizen expectations. The importance given of these dimensions is of course not fixed and is influenced by numerous socio-economical factors. Also, the importance of these dimensions is not fixed over time and can easily and rapidly change. Improving efficiency has been a key issue in animal production research in the first few decades after World War 2, and was driven by the need to produce more human food. In the last decades of the past century, the over-production of food in certain areas of the world and the associated environmental burden considerably reduced the interest in efficiency. However, it now becomes a re-emerging issue. Efficiency is no longer associated with over-production (the output side of the equation) but has become an issue to efficiently use limiting natural resources (the input side).

Feed is the most costly components to pig production. Feeding (and nutrition) is also a means to greatly influence many of the dimension cited previously (Figure 1). Since my recruitment at INRA in 1992, the focus of my research and development program has been on studying how feeding and nutrition can be used to create an animal product that fulfills multiple requirements. This involves providing practical recommendations on how to do this, but also studying the underlying biological mechanisms. Consequently, my research activity has been based on two pillars: mathematical modeling and experimental studies. The development of mathematical models has been an essential component in my research program, which has forced me to develop response curves describing how the animal reacts on (mostly nutritional) external factors. It has been a key element in integrating different aspects of animal nutrition and animal physiology. In addition, it has served as the basis for the development of InraPorc, a model and decision support tool now widely used by nutritionists and in higher education. Although the development of mathematical models could be done as an exercise by itself, I strongly feel that carrying out an experimental program alongside is important to be able judge the 'value of numbers'. Biology phenomena are inherently variable and it is only through actual carrying out an experimental program that one can appreciate the relative value of data. A large part of the experimental studies that I have carried out concerned studies on the energy metabolism of the animal (in close collaboration with Jean NOBLET). In the last few years, I have also initiated studies dealing with fatty acid and amino acid metabolism.

Although I consider the animal as the focus point of my studies, I am convinced that this should be seen and put in a much larger context. This context can be interpreted as having a horizontal component of integration (e.g., studies on amino acid or energy metabolism, the thermal environment, relation between nutrition and product quality) as well as having a vertical component of integration (i.e., by going down and studying the underlying regulatory mechanisms, or by going up by dealing with populations of animals or with production systems). In my research program and through collaboration with my colleagues, both components have been addressed. I am very much aware that this may be seen as a dispersion of activities, but I am convinced that in my role as a research engineer, I do need these

additional dimensions. It is only by looking at the whole where one can see where the centre of gravity lies.

2. Scientific activities

2.1. Modeling digestion in the rumen (thesis and post-doc)

After obtaining an MSc degree in Animal Production from Wageningen University in 1987, I continued my studies at the University of Illinois at Urbana-Champaign. During my PhD program and during the post-doctoral period at INRA in Clermont-Ferrand, my research was focused on the development of models that describe digestion in the rumen. The rationale behind the approach was to propose a theoretically sound basis for models that can be used in roughage evaluation systems. These models often consider that a substrate can be fractionated into three separate fractions: a soluble fraction, a potentially digestible fraction requiring microbial action before it can be solubilized and digested, and an indigestible fraction. During my thesis and post-doctoral work, we developed mathematical models describing how the potentially digestible fraction is degraded by microbial digestion in the rumen [**A1, A4, A5, A9**]. Two interesting phenomena were observed in a study in which we incubated different roughages for up to 6 weeks in the rumen. The study was carried out to verify the hypothesis that the fractionation of substrates (i.e., the soluble, potentially digestible, and indigestible fractions) was an intrinsic characteristic of the substrate itself, and not influenced by the ruminal environment. Thus, although the kinetics of digestion may depend on the ruminal environment, we assumed that the potentially digestible fraction would be degraded completed by microbial digestion if the microbes were given enough time (presuming that 6 weeks was closely to eternity for a microbial population). To our surprise, our hypothesis did not hold and the potentially digestible fraction appeared to be a much smaller in animals that were fed a high-concentrate diet compared to those fed a high forage diet [**A3**]. Also, during the prolonged incubation of substrate in the rumen, we observed a mineral deposition (containing Ca, P and Mg) on the substrate as well as on the Dacron bags in which the substrates were placed. The rate of mineral deposition varied with the type of forage fed to the ruminants [**A2**].

2.2. Energy metabolism

2.2.1. Indirect calorimetry

As indicated in the introduction, the cost of feed represent a large part of the total cost of animal production and energy is the most costly component of the feed. Our research unit has a long-standing history and is known for its research and expertise on whole animal energy metabolism. Since the early 1980s, we have open-circuit respiration chamber facilities in which we can house animals of various weight ranges and in different environmental conditions. One of the first projects I worked on since I was recruited in 1994 was the modeling of gas exchanges in the respiration chambers. In a respiration chamber, the O_2 consumption and CO_2 production by the animal is measured. These measurements, combined with measurements of urinary nitrogen and methane production allow the calculation of heat production (based on the stoichiometry of nutrient oxidation). Traditionally, measurements of O_2 consumption and the CO_2 production have been carried out during a 1 day period, resulting in an estimate of daily heat production. To further exploit the data from the respiration chambers, I developed a model that estimates the kinetics of heat production as a function of phenomena that can be observed from the animal (e.g., eating behavior, physical

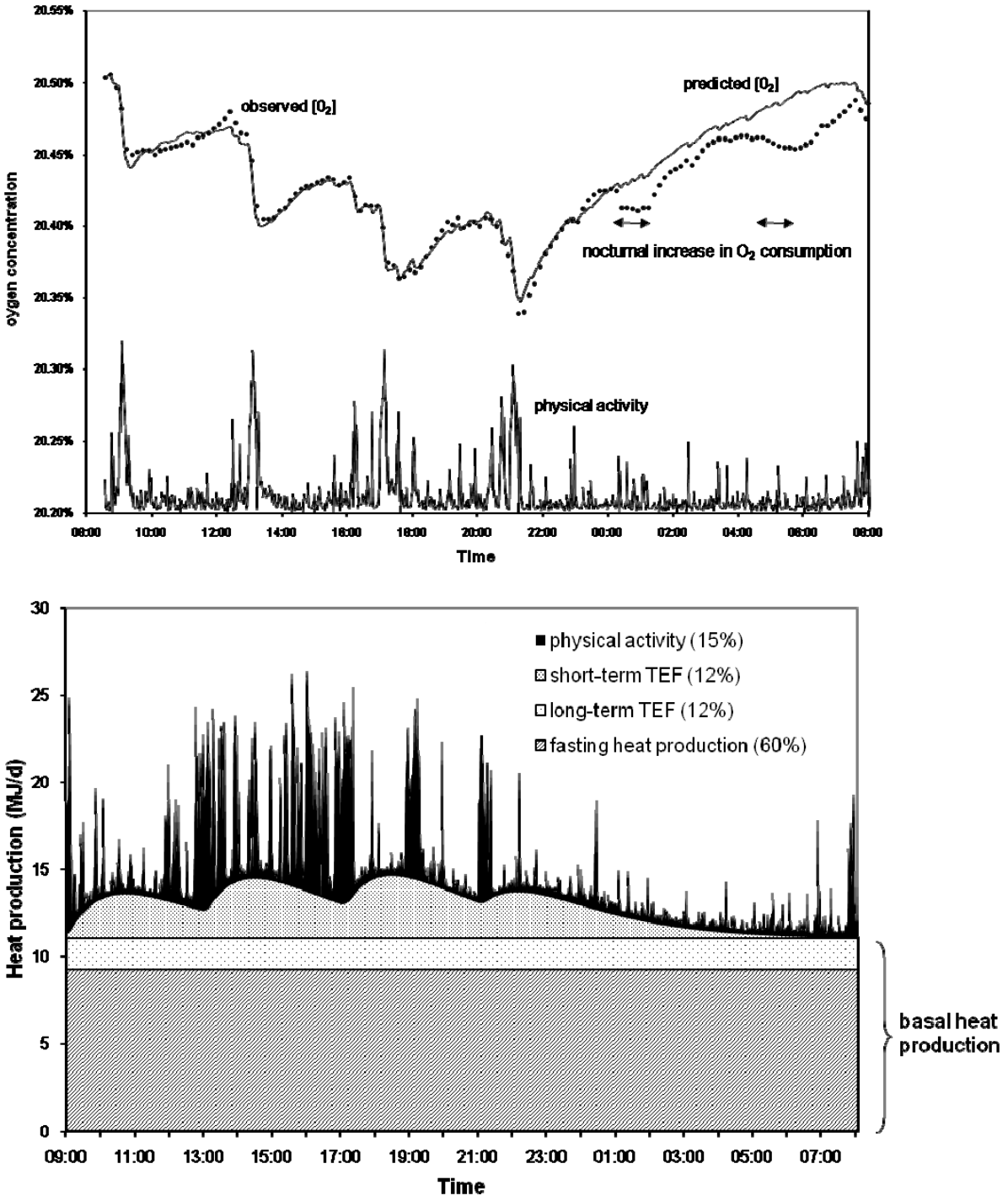

Figure 2. Top panel: Variation in O_2 concentration and physical activity measured in an open-circuit respiration chamber for a growing pig (60 kg). The animal was fed at 2.4 MJ ME·(kg BW)$^{-0.60}$·d^{-1} and was offered four separate meals at 9h00, 13h00, 17h00, and 21h00. Apart from the increase in O_2 consumption (decrease in $[O_2]$) due to feed intake, there are two additional, nocturnal increases in O_2 consumption starting at about midnight and 4h30. The (•) indicate the observed $[O_2]$ whereas the upper solid line indicates the estimated $[O_2]$ without correction for this nocturnal increase in O_2 consumption. The lower solid line is proportional to the signal of the force sensor on which the metabolism cage is mounted.
Bottom panel: Partitioning of heat production. TEF = thermic effect of feeding.

activity). The model, based on a system of differential equations describing gas exchanges in the chamber, allows the partitioning of the daily heat production into several components (i.e., basal metabolism, thermic effect of feeding, and physical activity, Figure 2). Since its construction and publication in 1997 **[A11]**, the model has been used in all our studies on whole animal energy metabolism.

2.2.2. Energy partitioning during growth

Several studies have been carried out to determine how the energy expenditure (and the utilization of energy intake) varies over time, between types of animals, and in relation to the physiological function. These studies have dealt with the partitioning of retained energy (between protein and lipid) as well as the partition of the main components of heat production. The results of these studies have been used in part to validate and further refine 'classical' nutritional systems (like the net energy system), but also to develop response curves describing how the animal reacts to energy supply.

In many studies, the basal energy expenditure is expressed relative to the metabolic body weight (i.e., per kg $BW^{0.75}$). This mode of expression originates from the work of Max Kleiber[1], who compared the energy expenditure of different mature species of animals. There has been and there still is considerable debate in the literature as to the biological interpretation of Kleiber's law, and the debate focuses mainly on differences in metabolic efficiency between species. In growing animals, the relation between basal energy expenditure and body weight does not necessarily follow Kleiber's law. In several studies, we have shown that expressing the fasting heat production per kg $BW^{0.60}$ is more appropriate in growing pigs **[A12, A13]**. However, the scalar of 0.60 does not seem to be applicable for growing animals in other species, as we found higher values for veal calves **[A49]**, broilers **[E46]** and turkeys **[B4]**. Despite the common practice to express basal metabolism or fasting heat production relative to body weight, there appear to be large differences between different genotypes of the same species. For example, in growing pigs we observed that the fasting heat production ranged from 810 $kJ \cdot (kg\ BW)^{-0.75} \cdot d^{-1}$ in Meishan barrows to 1200 $kJ \cdot (kg\ BW)^{-0.75} \cdot d^{-1}$ in modern, lean entire males **[A12]**. This difference between genotypes may be (statistically) related to differences in the body composition of these animals. Per kilogram of tissue, the viscera contributed four time more to the fasting heat production than did muscle, whereas fat tissue had a negligible or even negative contribution. In later studies, we also observed that the feeding level affected the fasting heat production in growing pigs and veal calves **[A41, A56]**. These last observations seem to confirm that the metabolic activity (of tissues or of the whole animal) affects the basal metabolism of the animal.

Growing animals have a positive energy balance and energy retention occurs mainly as protein and lipid (glycogen contributes relatively little to energy retention when considered over longer periods of time). The efficiency with which metabolizable energy (ME) can be retained differs between protein and lipid. These energy efficiencies are typically estimated by regressing ME intake on energy retention using the multiple regression equation proposed by Kielanowski[2]:

$$ME = MEm + 1/k_p \cdot ERP + 1/k_f \cdot ERL$$

[1] Kleiber, M. 1975. The fire of life. An introduction to animal energetics. Robert E. Krieger Publishing Company, New York.

[2] Kielanowski J. 1965. Estimates of the energy cost of protein deposition in growing animals. In: Proceedings of the 3rd Symposium on Energy Metabolism. K. L. Blaxter (Ed.). Academic Press, London. pp. 13-20.

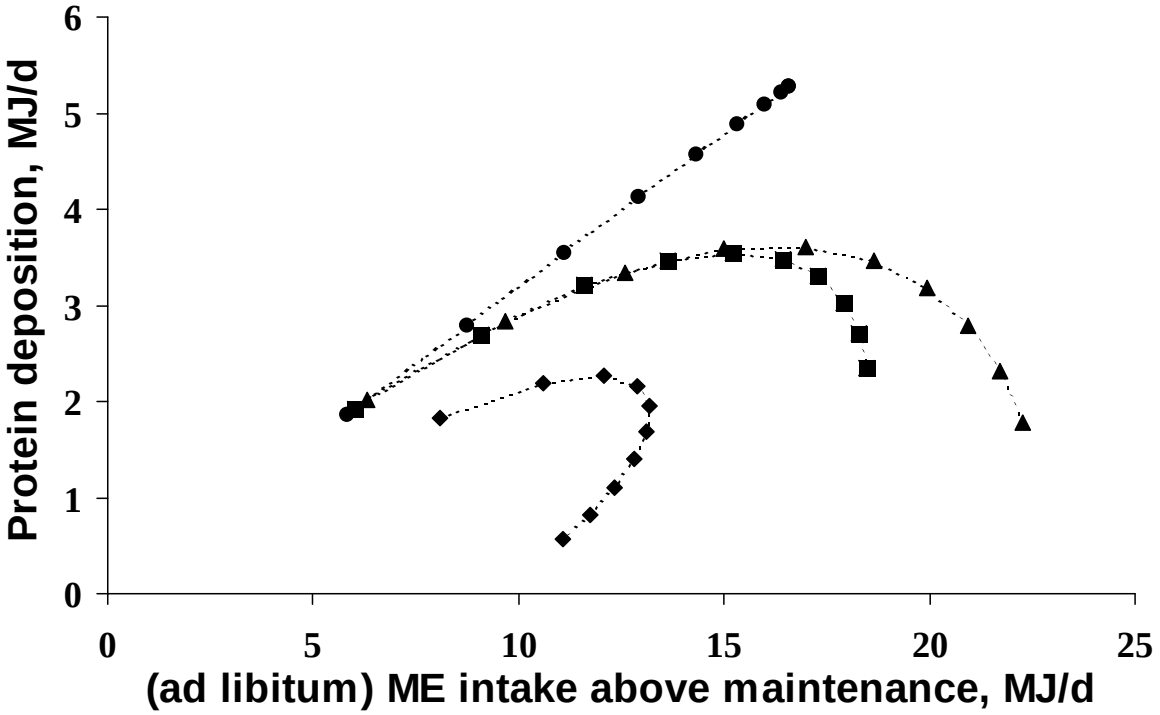

Figure 3. The effect of body weight on the use of ME intake above maintenance for protein deposition. The trajectories are given for four groups of growing pigs (●= synthetic line male, ■ = Large White female, ▲ = Large White castrate,◆ = Meishan castrate) between 20 and 110 kg of BW offered feed *ad libitum*. For each group, the first (most left) point represents an animal weighing 20 kg, the next point represents an animal weighing 30 kg, etc. The last point represents a 110 kg animal.

where ERP is the energy retained as protein, ERL the energy retained as lipid, k_p the energy efficiency of protein retention, k_f the energy efficiency of lipid retention, and MEm the maintenance energy requirement. In a study using seven phenotypes of pigs of different body weights, the MEm was estimated at a value close to 1000 $kJ \cdot (kg\ BW)^{-0.75} \cdot d^{-1}$, whereas estimates of kp and kf were 0.62 and 0.84, respectively **[A13]**.

The use of the multiple regression equation has been criticized because the independent variables (i.e., ERP and ERL) should be uncorrelated to obtain unbiased estimates of the model parameters. In our study, we used a wide range of phenotypes, resulting in a low correlation between ERP and ERL (r = 0.11). Moreover, it is very difficult to experimentally control ERP and ERL while it is possible to control ME intake through feed restriction. It is for this reason that we developed an alternative statistical approach, in which Kielanoski's equation was functionally reversed resulting in two equations that have to be solved simultaneously:

$$ERP = k_p \cdot X \cdot (ME - MEm) \text{ and}$$
$$ERL = k_f \cdot (1 - X) \cdot (ME - MEm) \text{ and}$$

In this equation, X represents the fraction of the ME intake above maintenance that will be used for protein deposition, whereas the complement (1-X) is used for lipid deposition. The value of X is of course not fixed and will change for a given animal over time, and it will also differ between different phenotypes of animals. In the proposed system of equations, the drawback of Kielanowki's equation (i.e., that ERP and ERL should be independent) is transformed as an advantage because the relationship between ERP and ERL is explicitly specified through X. We published this method in the *Journal of Animal Science* **[A15]** using data from different phenotypes offered feed *ad libitum*. In this study, we assumed that X was a (potentially) linearly declining function of body weight. With increasing body weight, a decreasing fraction of the ME intake above maintenance would then be used for protein deposition and thus an increasing fraction for lipid deposition. It appeared that for very lean phenotypes (entire males), the value of X did not change over the observed range in body weights (20-110 kg). Based on this information, a growth trajectory could be constructed illustrating how ME intake above maintenance and protein deposition evolve over time (Figure 3). Theoretically, this trajectory should end in the origin because both ME intake above maintenance and protein deposition (and lipid deposition) should attain zero. The same analysis method has been used for different species of fish in a cooperative project with the University of Guelph **[A38]**.

2.2.3. Effect of feed intake on energy partitioning

Feeding level has an impact on the use of energy by the animal. We experimentally confirmed earlier reports that feeding level not only affects lipid deposition, but that it also affects protein deposition **[A7]**. This means that lipids should not (or: should no longer) be considered simply as an energy reserve. The relationship between energy intake and the partitioning of retained energy between protein and lipid illustrates that there is a global organization of energy retention. It is frequently assumed that pigs have an upper limit to protein retention and that the relationship between protein retention and energy intake can be described by a linear-plateau function[3]. We slightly modified this concept by assuming that the relationship between protein retention and ME intake above maintenance is a curvilinear-plateau function, while maintaining the relationship between protein and lipid retention

[3] Whittemore, C. T., and R. H. Fawcett. 1976. Theoretical aspects of a flexible model to simulate protein and lipid growth in pigs. Animal Production 22: 87-96.

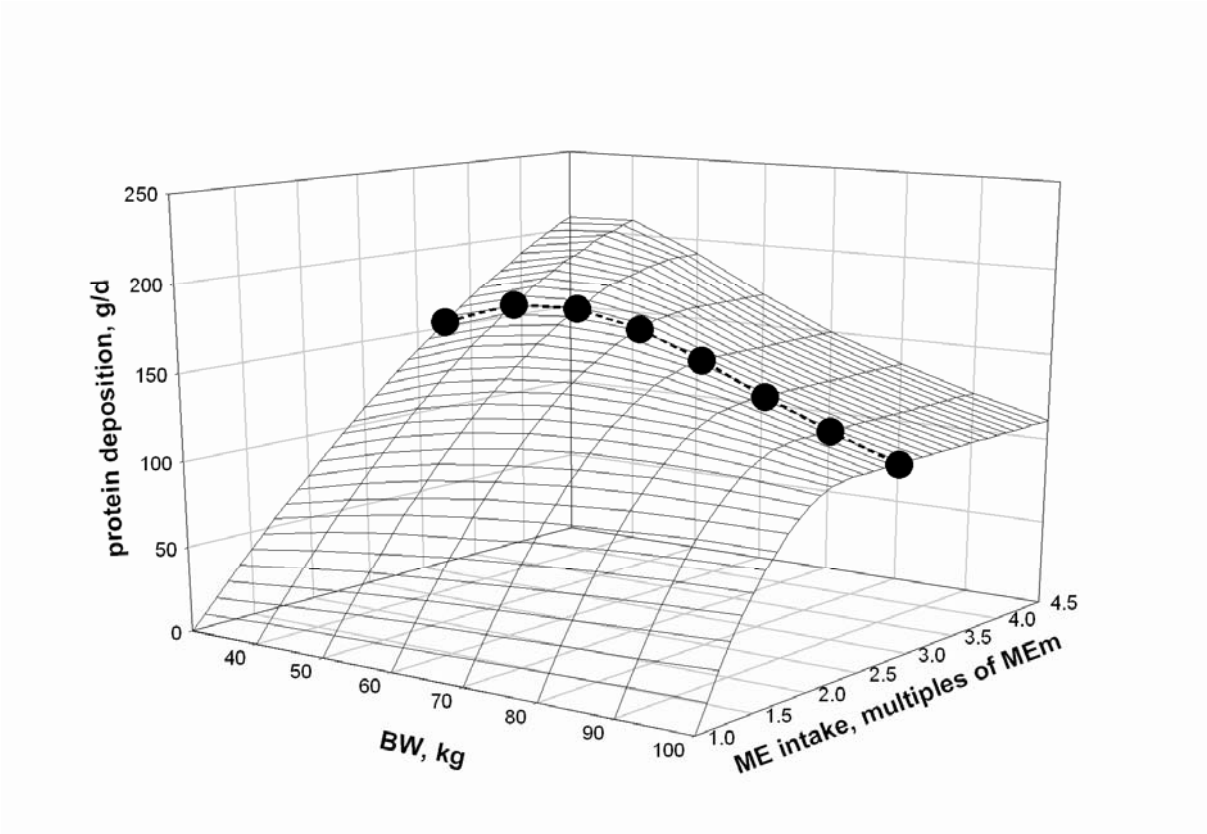

Figure 4. The response surface of protein deposition as a function of ME intake above maintenance and body weight.

described before. Although the use of a (curvi)linear-plateau model is conceptually simply, it is likely that the parameters of the model change with body weight[4]. For example, will the upper limit to protein deposition be the same in animals weighing 20 or 120 kg? Will the response to a change in energy intake be the same in these animals? It is for this reason that we constructed the energy module of the InraPorc model (see later) around three response curves: energy intake, protein deposition, and the response to a change in energy (the response for lipid deposition results from the description of these 3 cruves). Without going into the details of the mathematics (see **[A17, A33, A51]**), Figure 4 illustrates how these concepts are integrated. Energy intake is described as multiples of maintenance and the *ad libitum* feed intake is indicated by the solid dots on the graph (relative to the right-hand X-axis). In the example given in the figure, the *ad libitum* feed intake capacity equals approximately three times maintenance between 30 and 100 kg of body weight. For a given body weight, the relationship between protein retention and feed intake is given by a curvilinear-plateau function. Although the same concept is used for all body weights, the plateau is well beyond the feed intake capacity of the animal at 30 kg. With increasing body weight, both the plateau and the level of feed intake required to attain it, are reduced. At 100 kg of body weight, the upper limit to protein retention is 'within reach of appetite' for the animal. Knowledge of response curves that describe the partitioning of energy intake is extremely important to apply practical feeding strategies. In France, a large part of the pig population is offered feed close to *ad libitum* until the animals weigh approximately 70 kg. Beyond this body weight, a (more severe) feed restriction is applied to limit fat (lipid) deposition, while avoiding a reduction in lean meat (protein) deposition. The moment and the extent of feed restriction will determine the success of such a feeding strategy.

2.2.4. Efficiency of nutrient use

The animal consumes protein, lipid, carbohydrates and fiber providing respectively amino acids, fatty acids (and glycerol), simple sugars and volatile fatty acids to the metabolic system of the animal. The majority of these nutrients are used for protein and lipid deposition and for ATP synthesis. The efficiency with which these nutrients can be used varies with their origin, their final utilization, and the metabolic pathways used between the origin and final utilization. The fact that the energy efficiency differs between nutrients has been the basis for the net energy system. In our research unit, Jean NOBLET has carried out numerous experiments providing a solid basis for this system.

Dietary proteins provide (essential) amino acids required for protein deposition. However, proteins provided in excess of the requirement are deaminated and the excess nitrogen is excreted as urea in the urine. The objective of the thesis program of Laurent LE BELLEGO was to evaluate the potential to reduce the protein content in the diet on energy metabolism in growing pigs. Provided that the supply of essential amino acids is assured, the results of our studies indicated that when dietary protein is replaced by carbohydrates, energy efficiency will increase **[A21]**. The energy expenditure in pigs fed low protein diets (supplemented with free amino acids) is thus be lower than that in pigs fed 'normal' protein diets. During the thesis program of Laurent LE BELLEGO, we also tested the hypothesis that a low-protein diet would be better tolerated by pigs when the ambient temperature is high. Under conditions of heat stress, the capacity to dissipate heat is reduced and the animal may have to reduce its feed intake to reduce heat production. It indeed appeared that low protein diets are better tolerated under conditions of heat stress, but the additional energy intake was mostly retained as lipid, and not as protein **[A26]** (see also section 2.6).

[4] Black, J. L., R. G. Campbell, I. H. Williams, K. J. James, and G. T. Davies. 1986. Simulation of energy and amino acid utilisation in the pig. Research and Development in Agriculture 3: 121-145.

Table 1a. Stoichiometric balance of using glucose for glutamate synthesis in muscle and glutamate for ATP synthesis in viscera.

	ATP	NADHc	NADHm	$FADH_2$	NADPH	CO_2	O_2	NH_3	OAA	αKG	PYR	ACA	GLC	SER
Glutamate catabolism	0	0	2	0	0	0	0	2	0	2	0	0	0	0
aKG → OAA	2	0	4	2	0	2	0	0	2	-2	0	0	0	0
OAA → PYR	0	2	-2	0	0	2	0	0	-2	0	2	0	0	0
PYR → ACA	0	0	2	0	0	2	0	0	0	0	-2	2	0	0
OAA + ACA → αKG	0	0	2	0	0	2	0	0	-2	2	0	-2	0	0
αKG → OAA	2	0	4	2	0	2	0	0	2	-2	0	0	0	0
NADHc ↔ NADHm	0	-2	2	0	0	0	0	0	0	0	0	0	0	0
NADHm oxidation	42	0	-14	0	0	0	-7	0	0	0	0	0	0	0
$FADH_2$ oxidation	8	0	0	-4	0	0	-2	0	0	0	0	0	0	0
Balance (viscera)	**54**	**0**	**0**	**0**	**0**	**10**	**-9**	**2**	**0**	**0**	**0**	**0**	**0**	**0**
GLC → PYR	4	4	0	0	0	0	0	0	0	0	4	0	-2	0
PYR → OAA	-2	0	0	0	0	-2	0	0	2	0	-2	0	0	0
OAA + ACA → αKG	0	0	2	0	0	2	0	0	-2	2	0	-2	0	0
Glutamate synthesis	0	0	-2	0	0	0	0	-2	0	-2	0	0	0	0
PYR → ACA	0	0	2	0	0	2	0	0	0	0	-2	2	0	0
NADHc ↔ NADHm	0	-4	4	0	0	0	0	0	0	0	0	0	0	0
NADHm oxidation	18	0	-6	0	0	0	-3	0	0	0	0	0	0	0
Balance (muscle)	**20**	**0**	**0**	**0**	**0**	**2**	**-3**	**-2**	**0**	**0**	**0**	**0**	**-2**	**0**
Overall balance	**74**	**0**	**0**	**0**	**0**	**12**	**-12**	**0**	**0**	**0**	**0**	**0**	**-2**	**0**

Table 1b. Stoichiometric balance of using glucose for ATP synthesis.

	ATP	NADHc	NADHm	$FADH_2$	NADPH	CO_2	O_2	NH_3	OAA	αKG	PYR	ACA	GLC	SER
GLC → PYR	4	4	0	0	0	0	0	0	0	0	4	0	-2	0
PYR → ACA	0	0	4	0	0	4	0	0	0	0	-4	4	0	0
OAA + ACA → αKG	0	0	4	0	0	4	0	0	-4	4	0	-4	0	0
αKG → OAA	4	0	8	4	0	4	0	0	4	-4	0	0	0	0
NADHc ↔ NADHm	0	-4	4	0	0	0	0	0	0	0	0	0	0	0
NADHm oxydation	60	0	-20	0	0	0	-10	0	0	0	0	0	0	0
$FADH_2$ oxydation	8	0	0	-4	0	0	-2	0	0	0	0	0	0	0
Overall balance	**76**	**0**	**0**	**0**	**0**	**12**	**-12**	**0**	**0**	**0**	**0**	**0**	**-2**	**0**

NADHc = NADH in cytosol; NADHm = NADH in mitochondria; OAA = oxaloacetate; αKG = α-ketoglutarate; PYR = pyruvate; ACA = acetylCoA; GLC = glucose; SER = serine.

To further confirm the net energy system by direct measurements, we carried out an experiment in which pigs were fed a basal diet limiting in lysine supply, or diets containing the basal diet plus a supplement of starch, corn gluten meal (a protein source with a low Lys content), casein, or lipid. The results of this work have been published in the *Journal of Nutrition* **[A25]**. The metabolizability (ME:DE ratio) was close to unity for starch and lipid, because no additional energy was lost in the urine or as gaseous energy when these supplements were provided. The metabolizability of casein was greater than that of corn gluten meal because of the greater lysine supply resulting in a greater protein deposition and lower urea excretion in the urine. The energy efficiency was the greatest for lipid, followed by starch, while there was no difference between the two sources of protein. The calculated energy efficiencies of using dietary protein for protein deposition or lipid deposition were almost similar. This is a somewhat surprising result because the biochemical pathways largely differ between these routes of protein utilization (i.e., involving peptide or fatty acid and urea synthesis).

To further understand the role of biochemistry in energy metabolism, I developed a system with which the energy efficiency of biochemical transformations can be easily quantified **[A32]**. The system (by my colleagues often referred to as a biochemical calculator) is based on the identification of biochemical pivots that can be used to quantify biochemical reactions. In the initial system, 14 pivots were used to quantify the stoichiometry of 54 reactions involved in protein, lipid and carbohydrate metabolism. By constructing a series of linked reactions, the user can calculated the energetic efficiencies of catabolic and anabolic pathways. One of the more surprising outcomes of this study was the comparison of glutamate and glucose as energy sources for ATP synthesis. Glutamate is extensively oxidized by the gut, implying that other nutrients, such as glucose, have to be used to provide glutamate to the muscle for protein synthesis. One could argue that an alternative scenario where glucose is directly oxidized by the gut, while dietary glutamate is used for protein deposition in the muscle would be more energetically efficient. Both scenarios are calculated in Table 1. The 14 columns correspond to the pivots and lines correspond to the selected biochemical reactions. The stoichiometric balances are given by:

Glutamate oxidation in viscera: glutamate + 9 O_2 → 54 ATP + 10 CO_2 + 2 NH_3
Glutamate synthesis from glucose: 2 glucose + 3 O_2 + 2 NH_3 → glutamate + 20 ATP + 2 CO_2
Overall balance: 2 glucose + 12 O_2 → 74 ATP + 12 CO_2

The use of glutamate for ATP synthesis yields 2 ATP less compared with the direct oxidation of glucose, which means that the efficiency is 2.7% lower. This reduction in efficiency is remarkable low and is of similar magnitude as the energy loss of storing glucose as glycogen. The biochemical calculator does not directly help in explaining why biochemical reactions happen in tissues and how these reactions are controlled. It only quantifies the overall stoichiometric balance of reactions selected by the user.

We have been using the calculator to better understand nutrient balance data obtained from experiments. In one study **[E60]**, we were interested in the role of the isocitrate dehydrogenase pathway in adipocytes. This pathway can be viewed upon as a partial externalization of the Krebs cycle, producing NADPH rather than NADH while using acetylCoA as a substrate (Figure 5). The NADPH can then be used for fatty acid synthesis in the adipocytes. One of the limitations of this pathway is that approximately 25% of the energy of acetylCoA will be captured as NADPH, while the remaining energy will become available as ATP, NADH and $FADH_2$ produced in the Krebs cycle. It does not seem very likely that an adipocyte has a need for the energy in the latter forms. It is for this reason that we formulated an alternative scenario where α-ketoglutarate (the point of re-entry of the carbon-chain in the

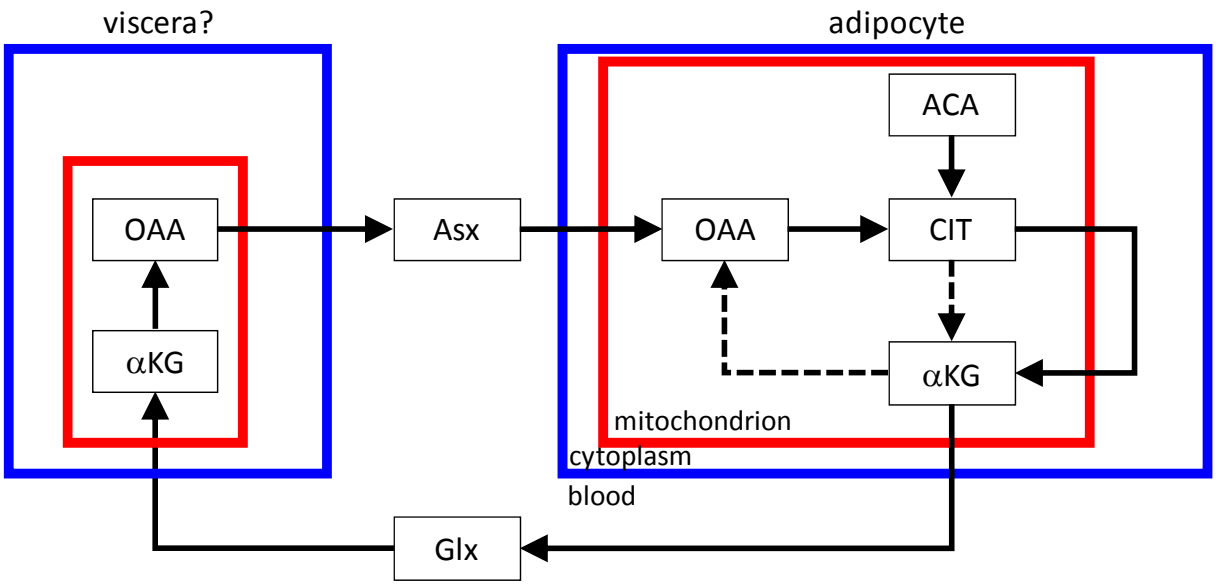

Figure 5. Proposed model of the isocitratedehydrogenase pathway in adipocyte using amino acids as energy and carbon shuttles to other tissues. The solid lines indicate the flow of carbon in the proposed model where acetylCoA (ACA) is used as a substrate producing NADPH in the adipoctye and ATP, NADH and $FADH_2$ in the viscera. The dashed line show the flow of carbon when the Krebs cycle is used. ACA = acetylCoA; CIT = citrate; αKG = α-ketoglutarate; OAA = oxaloacetate, Glx = glutamate or glutamine; Asx = aspartate or asparagine.

mitochondrion) is not used in the Krebs cycle of the adipocyte, but will be used for glutamate or glutamine synthesis. Through this synthesis, the energy of α-ketoglutarate can be transported to other tissues, where it can be released as ATP, NADH and $FADH_2$ using the Krebs cycle. In order not to deplete the adipocyte from its carbon source, oxaloacetate has to be shuttled back to the adipocyte, and this may be achieved by using aspartate or asparagine. Although our hypothesis was based only on theoretical grounds, it appeared from literature data that these amino acids are synthesized and used by adipocytes[5]. Amino acids may therefore play a role in the transport of energy between tissues. In the scenario given in Figure 5, approximately 25% of the energy of acetylCoA is used in the adipocyte (for NADPH synthesis) while the remaining 75% is used in the viscera. Glutamate and aspartate are used as shuttles to transport energy and carbon between tissues.

2.2.5. Studies in species other than pigs

The experimental program on whole animal energy metabolism has been without doubt the most important program (in terms of publications) that I have been involved in. In this program, carried out in close collaboration with Jean NOBLET, we focused until the early 2000s almost exclusively on pigs (mostly growing pigs, but also piglets and sows). During the last 10 years, several INRA research units have abandoned the use of respiration chambers. The main reason was often the lack of sufficient personnel to keep the chambers operational. This has resulted in a situation in which our research unit is the only INRA research unit with indirect calorimetry facilities for livestock animals.

The thesis of Etienne LABUSSIÈRE (a collaborative project between INRA and the French Institut d'Élevage) focused on the energy metabolism of veal calves in relation to the development of the animal, the feeding level, and the type of feed **[A48, A49, A55, A56]**. Similar programs have been carried out in poultry (a 12 months research project of Marson WARPECHOWSKI during his thesis project for the Federal University of Rio Grande do Sul, Porto Alegre, Brazil), turkeys (research project of Virginie RIVERA for her thesis at AgroParisTech **[B4]**), and also in minipigs, which are used as a model for human nutrition.

2.3. Lipid and fatty acid metabolism

Lipids have a very high energy content (39.8 kJ/g), allowing the storage of large quantities of energy in very little mass. Although this implies that by depositing lipids, we will limit weight gain when we are in a positive energy balance, it also means that we will have to lose more energy if we want to lose weight. Growing animals store large quantities of energy as lipids in different tissues. The lipid and fatty acid deposition play a major role in the determination of the quality of pork meat (i.e., from a technological, organoleptic, and nutritional point of view). The quantity and the nature of fatty acid deposition depend to a large extent on the energy and fatty acid supply in the diet. However, the relationships that exist between nutrition and the fatty acid content in tissues are mostly empirical. With indirect calorimetry, total lipid deposition can be quantified, but not the distribution of lipids between tissues or the fatty acid composition of deposited lipids.

Between 1998 and 2000, I supervised the post-doctoral research project of Rosil LIZARDO. This objective of this project was to develop a model for lipid and fatty acid deposition in different tissues in growing pigs **[A31]**. Our goal was to use develop a more mechanistic (and prospective) approach towards modeling fatty acid deposition using

[5] Kowalski, T. J., G. Y. Wu, and M. Watford. 1997. Rat adipose tissue amino acid metabolism in vivo as assessed by microdialysis and arteriovenous techniques. American Journal of Physiology (Endocrinology and Metabolism) 36: E613-E622.

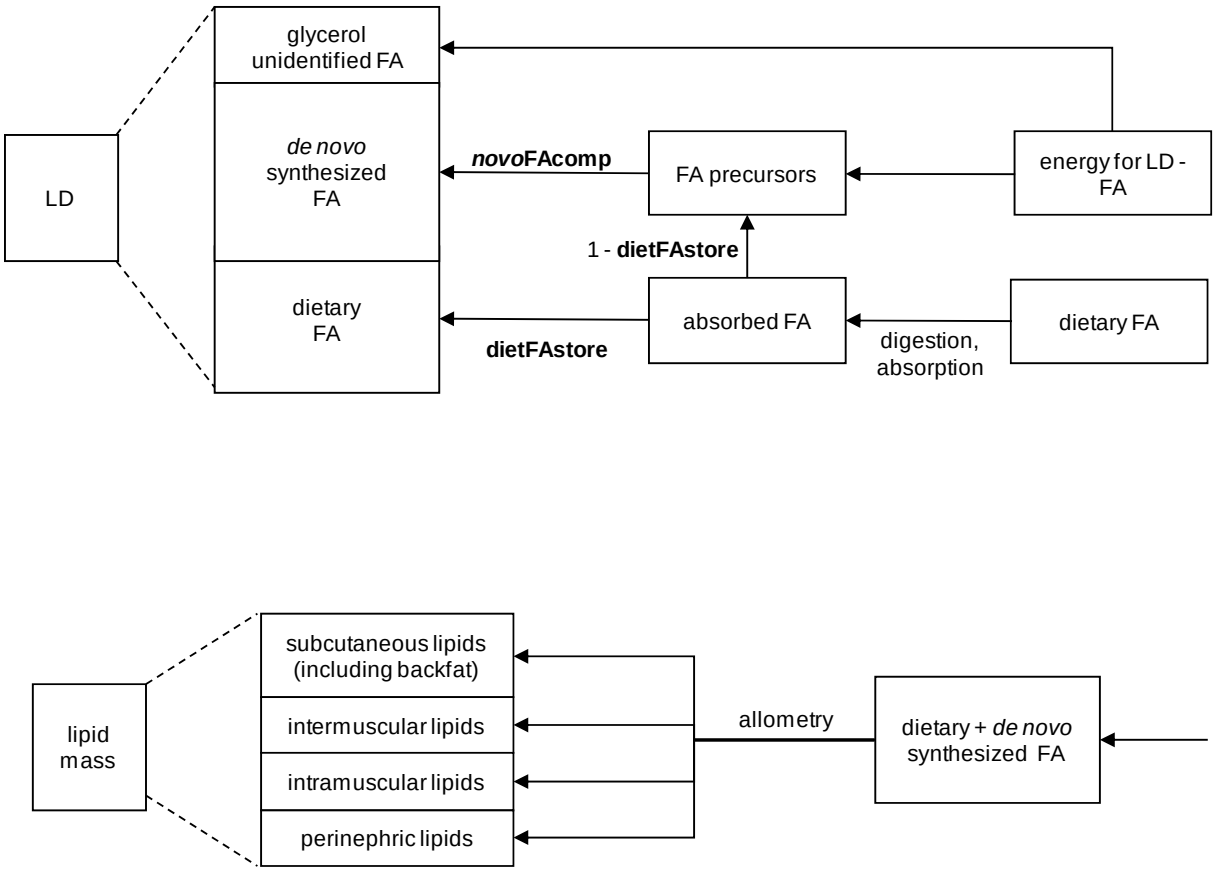

Figure 6. Model structure of the partitioning of lipids and fatty acids between tissues.

information available from the literature. During the project, we realized that there is a large gap between the research disciplines of nutrition and product quality. Although there is a considerable body of knowledge on the mechanisms of fatty acid metabolism, this information is mostly acquired on one or two specific adipose tissues, limiting its use to predict whole animal fatty acid deposition. Although it is known that the fatty acid composition of adipose tissues can be manipulated through nutrition, little quantitative information is available that allow constructing a mechanistic link between the two disciplines.

We decided to conceive a modular fatty acid model, which could be used easily in existing pig growth models, including the InraPorc model that was, at that time, in development. The reason for this was that several nutritional models predict (with more or less success) the whole body lipid deposition, but few models partition lipid deposition between tissues or quantify the fatty acid composition of lipids. With a modular approach, the whole body lipid deposition could be addressed by the "host model", while the partitioning between tissues and fatty acids would be role of the proposed module. The general structure of the model is given in Figure 6. The partitioning of lipids between tissues was represented as an allometric function of whole body lipid deposition. The data used to develop the equations originated from a large (and partially published) experiment realized in our research unit in the late 1980s. The allometry coefficients varied between 0.82 for intra-muscular lipids to 1.36 for perinephric lipids, indicating important differences in the relative development of adipose tissues. Interestingly, the allometry coefficient for intra-muscular lipid is the lowest of all tissues considered, despite the common observation that this is a relatively late-developing tissue. The reason for this is the choice of the reference basis (lipid mass or body weight) and the fact that lipids deposition occurs relatively late.

One of the main difficulties of Rosil LIZARDO's work was to quantify the fate of dietary fatty acids (see the top panel of Figure 6 represented by 'dietFAstore'). Although a large part of the deposited fatty acids are synthesized *de novo*, certain fatty acids (e.g., poly-unsaturated fatty acids) are provided exclusively by the diet. It is surprising that very few studies have been carried on the efficiency of retention of dietary poly-unsaturated fatty acids by the growing animal. Moreover, the only two studies that we were aware of reported very different efficiencies for the deposition of dietary fatty acid (ranging from 50 to 100%). In our model and for reasons of simplicity, we assumed that this efficiency was constant (85%) and that adipose tissue capture dietary fatty acids proportional to their lipid deposition rate. Stated otherwise, if a diet with a high fat content is fed, 85% of the fatty acids would be retained and the partitioning of the fatty acids between tissues would be driven by the allometric equations. Although the hypothesis was simple, it appeared insufficient to explain differences in fatty acid contents between tissues.

As a follow-up on this post-doctoral research program, we initiated a thesis program of Maela KLOAREG with the goal to provide elementary information that would allow the further development of a model to integrating nutrition and product quality at the whole animal level. As indicated earlier, the lipid and fatty acid model developed by Rosil LIZARDO had a modular structure and relied on the 'host model' to predict whole body lipid deposition. The success (or failure) of such a modular model therefore depends on the ability of the host model to accurately predict whole body lipid deposition. However, this appears to be a major challenge for most nutritional growth models. The challenge resides in the fact that body fatness is very difficult and costly to measure. Because of the strong relationship between protein and water (in muscle), protein deposition can be evaluated through the measurement of growth rate and a high growth rate is typically associated with a high protein deposition rate. This is much less the case for lipids and a moderate change in energy retention as lipid has little effect on the growth rate (also because of the high energy density of lipids).

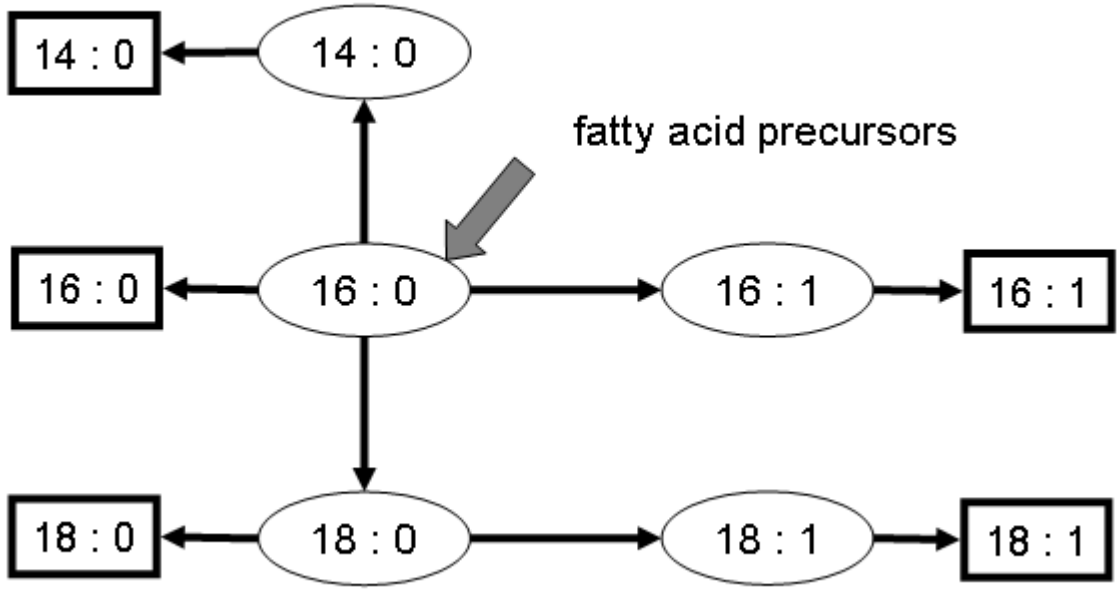

Figure 7. Flux model representing the de novo synthesis of fatty acid in pigs. Ovals indicate circulating fatty acids that may be undergo further metabolism or than can be stored (rectangles).

Measurements of lipid deposition or lipid mass can be carried out in an experimental setting (e.g., through indirect calorimetry or slaughter studies), but are much more difficult to obtain under practical conditions. The fatness of the pigs at slaughter is currently obtained by measured by measuring backfat thickness and muscle depth. These measurements are used to estimate the tissue composition and commercial value of the carcass, but do not provide information on the chemical body composition. A study was carried out during the thesis of Maela KLOAREG to find one or more indicators, easily accessible in commercial operations, which would allow the estimation of the lipid mass in the body or in the carcass **[A42]**. Body weight in combination with a measurement of backfat thickness appeared to be the best predictor of whole body lipid mass. However, the genotype affected this relationship indicating that different genotypes with an identical body weight and backfat thickness may have a different partitioning of body lipids. As an example and to illustrate the challenge of finding a predictor of whole body lipid mass, although the lipid content in backfat is very high (approximately 75%), it represents only 18% of the total lipid mass in the carcass. In addition, the best accessible predictor is based on the measurement of the thickness of this tissue.

The majority of lipids deposited in tissues originate from the *de novo* synthesis of fatty acids. In the original model developed by Rosil LIZARDO, we assumed that the composition of the *de novo* synthesized fatty acids was constant (between tissues and over time). This assumption allowed for a reasonable prediction of the tissue fatty acid composition, as measured in different studies reported in the literature. Nevertheless, the unexplained variation was quite high, which led us to a more mechanic approach to represent the *de novo* fatty acid synthesis. In one of the studies of Laurent LE BELLEGO **[A27]**, whole body composition was measured in pigs (weighing between 25 and 65 kg) as a function of feed intake level and ambient temperature (23 or 30°C). To further exploit this experiment, the fatty acid composition was determined in the carcass samples to develop a flux model of *de novo* synthesized fatty acids as a function of feeding level and ambient temperature **[A39]**. During *de novo* fatty acid synthesis, C16:0 can be considered as a starting point, which can be deposited as-is, shortened to C14:0, desaturated to C16:1, or elongated to C18:0 (Figure 7). The latter can be deposited or desaturated to C18:1. The elongation of C16:0 to C18:0 was independently affected by feeding level and ambient temperature. Also, the flux of C18:0 to C18:1 was reduced at high ambient temperature, resulting in an increased deposition of saturated fatty acids. In this study, we also observed that the efficiency of retaining dietary fatty acids differs between families of fatty acids, with a greater retention for *n*-6 fatty acids (70%) than for *n*-3 fatty acids (50%).

The objective of a third experiment realized during the thesis of Maela KLOAREG was to generate data that would allow the construction of a global model of fatty acid partitioning between tissues **[A44]**. As indicated before, one of the problems encountered during the research of Rosil LIZARDO, was the fate of dietary fatty acids. In the third study carried out with heavy pigs (90 to 150 kg), we recovered less than 40% of the dietary fatty acids in the carcass. This type of information is essential to develop models that can predict the fatty acid composition in the carcass, but also for the (economic) feasibility to use meat products as a means to provide certain poly-unsaturated fatty acids (e.g., DHA, EPA) to the consumer. Additional studies on the efficiency of retaining dietary fatty acids have been carried out in collaboration with Wageningen University by measuring the oxidation of ^{13}C-labelled dietary fatty acids **[E85]**. This study, and a follow-up study carried out since, indicated a that the oxidation of dietary fatty acids was relatively lows during the 24 h following a meal (5-15%), but the rate of oxidation depended on the type of fatty acid and the composition of the diet.

A major challenge in to better articulate the relation between nutrition and product quality resides in the relation “whole animal vs tissue”. In animal nutrition, we focus on nutrients and often with a vision that is limited at the whole animal level. For example, in our

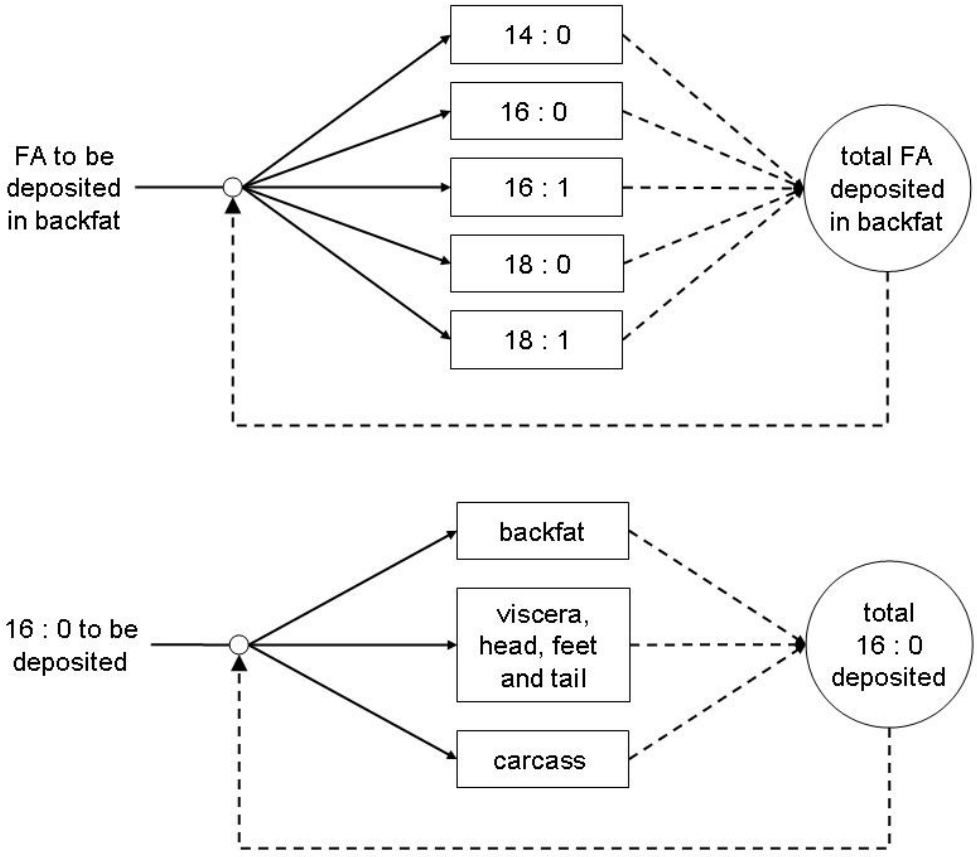

Figure 8. Possible hypotheses concerning the driving forces for the anatomical partitioning of *de novo* synthesized fatty acids. In the upper panel, the partitioning is driven locally by the fatty acid mass of the tissue, whereas in the lower panel, there is a central control for the partitioning of fatty acids between tissues.

studies on energy metabolism, we determine protein and lipid deposition at the whole animal level, without being able where (in which tissues) these proteins and lipids are deposited. On the other hand, studies on product and tissue quality take into account the effect of nutrition, but seldom with a global vision on how nutrients are used and partitioned between tissues. The third experiment carried out by Maela KLOAREG **[A44]** indicated that although the whole body fatty acid composition may be relatively constant between 90 and 150 kg, this was not the case for the fatty acid composition of tissues. During the finishing period, the C18:1 content increased in the carcass (without backfat), whereas that of C16:0 and C18:0 decreased. Backfat captured a relatively greater proportion of dietary C18:2, whereas the carcass (without backfat) captured more C18:3. These observation illustrate that we have to develop a more mechanistic (i.e., tissue-oriented) approach towards fatty acid deposition. Although we have not yet resolved this issue, several hypotheses can be put forth (for each fatty acid) as indicated in Figure 8. In the upper panel, the target tissue (in this case backfat) controls the synthesis and deposition of the different fatty acids. In the lower panel, a different point of view is taken by assuming a central control of fatty acid deposition, combined with a partitioning rule between tissues. The hypothesis of the lower panel may apply to dietary fatty acids (or in animal species where fatty acids are synthesized more 'centrally' in the liver). We intend to continue our research on modeling fatty acid deposition through a cooperation with Sergio GOMEZ from Inifap (Mexico), who will spend a sabbatical year in our research unit in 2010.

2.4. Amino acids

As indicated earlier, we have carried out a large research program on the utilization of low protein diets for growing pigs **[A21, A22, A26]**. This research was carried out with the idea to reduce the supply and excretion of nitrogen. We also intended to show that dietary protein, when provided in excess of the amino acid requirements, is not efficiently used by animals as source of energy.

The fact that low-protein diets are now largely used in practical swine nutrition results in a situation where the supply of more amino acids approaches the requirement. It is thus important to know the requirement for these amino acids as well the response of the animals to a deficient, sufficient or excessive supply of these amino acids. Since 2003, we have carried out several experimental programs (in cooperation with industrial partners) to study the response of growing pigs to amino acids. Unfortunately, I have not had (have not taken) the time yet to published these results in peer-reviewed journals. These experiments mainly concerned Thr and Met.

In one of these partially-published studies **[E87]**, we observed that the Met content of whole body protein was affected by the Met content of the diet. Piglets receiving a diet limiting in Met had a lower Met content in body protein. We carried out a follow-up study to better understand how the animal responds to such an amino acid deficiency. This study was carried by Alberto CONDE during a 3-months stay at our research unit for his PhD program. Using the comparative slaughter technique, we confirmed our earlier observation that the amino acid composition of whole body protein is not constant. Despite a severe deficient Met supply, certain tissues (e.g., intestines, blood) were not affected at all, whereas others (e.g., the carcass and especially the *longissimus dorsi* muscle) were severely affected in terms of mass, protein content, and amino acid composition in protein. The reduction in Met content in the *longissimus dorsi* muscle was not associated by a change in the myosin heavy-chain or actin content. The change in whole body amino acid composition can partially be explained by a change in the contribution of different tissues, having a different amino acid

composition. The results of this study have been recently submitted to Animal **[B3]**, and we anticipate continuing our studies on the effect of amino acid supply on tissue composition.

In 2005 we started a research program on the requirement for branched-chain amino acids (Val, Ile and Leu) in piglets. There are indications that Val and Ile may be the next-limiting amino acid, after Lys, Met, Thr and Trp[6]. These last four amino acids were then the only amino acids available (as crystalline amino acids) for use in animal nutrition. When all four crystalline amino acids are used in a diet, it is technically possible to reduce the protein content up to the point where five amino acids are co-limiting (Lys, Met, Thr, Trp and a fifth, unknown amino acid).

The research program on Val and Ile has been carried out with Ludovic BROSSARD (Production Systems, Environment and Welfare team) and Nathalie LE FLOC'H, and in close collaboration with Ajinomoto Eurolysine. Since July 2006, Roberto BAREA (a post-doctoral researcher from Spain) has been working on this program for a period of two years. We showed that Val is probably the next-limiting amino acid for growth in growing pigs in diets based on cereals and soybean meal, and that this limitation occurred well before a (possible) limitation of Ile **[A53, B1]**. The reduction in performance related to a Val deficiency appears to be more pronounced when Leu is supplied in excess. In fact, the first two steps in the catabolism of the three branched-chain amino acids are catalyzed by two enzymes complexes that are common for these amino acids. The stimulation of the catabolism by the excessive supply of one branched-chain amino acid may have consequences for the availability of the other two. Interestingly, a large part of the response of the animal to a Val deficiency was mediated by a reduction in feed intake. In an experiment where a deficient Val was associated with an excessive supply in Leu, feed intake was reduced by levels up to 50%.

Since the early 1950s, about 15 dose-response studies have been reported in the literature concerning the Ile requirement in growing pigs. A few recent American studies indicated that the Ile requirement in pigs may be higher than current recommendations (which range from 54 to 60% on a standardized ileal digestible (SID) basis and relative to Lys). We have carried out four studies with a potentially deficient Ile supply (going as low as 48% SID Ile:Lys) and in none of our studies have we seen a response to Ile supplementation **[B1]**. This observation is rather surprising in light of the American studies. One of the main differences between our study and others is the protein source used. In (most of) our studies, we used soybean meal as the main source of protein whereas others frequently use spray-dried blood plasma. Spray-dried blood plasma is a protein source with a very low Ile content (making it a potentially interesting source for Ile studies), but it has a very high Val and Leu content. We suspect that the use of spray-dried blood cells results in an excessive supply of Val and Leu, which will result in an increased Ile requirement due to the antagonism between the branched-chain amino acids. The program on the branched-chain amino acids will continue through a Cifre thesis program that will be carried out by Mathieu GLOAGUEN (starting July 2009).

Since June 2009, L-valine has been available as a crystalline amino acid that can be used in animal nutrition. This means that feed formulators can now include five crystalline amino acids in practical diets and that diets can be formulated so that six amino acids are co-limiting. The availability of L-valine offers a means to further reduce the nitrogen content in diet and thus the nitrogen excretion by the animal. The magnitude of this potential to reduce the nitrogen excretion depends on the requirement of the next-limiting amino acid. It is currently not known which amino acid this is and, once this will be known, very little will be known concerning its requirement. I participated a few years ago in a workshop held in England which had the wonderful title "From crude protein to precision protein". This title

[6] Mavromichalis, I., D. M. Webel, J. L. Emmert, R. L. Moser, and D. H. Baker. 1998. Limiting order of amino acids in a low-protein corn-soybean meal-whey-based diet for nursery pigs. Journal of Animal Science 76: 2833-2837.

reflects very well one of the challenges we are facing in amino acid nutrition. With the availability of new crystalline amino acids, nutritionists will be able to formulate diets that are on the cutting edge between maintaining biological performance and reducing the impact of animal production on the environment. However, it also means that safety margins become more important. When six amino acids are co-limiting, nutritionists will have to consider to include (or not) a safety margin for all of these amino acids. In this respect, the response of a population of animals is extremely important (see later) because it will help in the evaluation of safety margins and risks.

2.5. Digestive and metabolic utilization of dietary fiber

We also have carried out several experimental programs on the evaluation of dietary fiber in swine nutrition. Especially in sow nutrition, fiber has received quite some attention over the last 10 years. To avoid problems of excessive fatness with consequences on farrowing and the following reproductive cycle, gestating sows are fed restrictively. The feed restriction may be accompanied by a 'nutritional frustration', having an impact on the well-being of the animal. The use of dietary fiber may help in reducing the negative effects of a feed restriction during gestation. Relative to other nutrients, dietary fiber is less digestible and, consequently, has an impact of the satiety of the animal. It is generally acknowledged that dietary fiber accelerates the intestinal transit. Furthermore, dietary fiber is not digested by endogenous enzymes, but can be fermented by microbes in the large intestine and the end-products of fermentation (volatile fatty acids) can be used by the host animal.

In a study in which different dietary fiber sources were fed to growing pigs, finishing pigs, and adult sows, we observed that the ability of pigs to digest dietary fiber increased with body weight **[A29]**. However, the difference in digestibility between pigs differed between fiber sources. The increase in total dietary fiber digestibility with increased body weight was most important for corn bran (41 and 64% in growing pigs and adult sows, respectively), whereas the increase was lower for sugar beet pulp (74 and 80%). Differences in digestibility between pigs of different body weights were for a large part due to differences in total tract retention time, which increased from 33 h in growing pigs to 81 h in adult sows.

In a study with gestating sows, we observed that the heat production was higher in sow fed a higher fiber diet (at an identical digestible energy intake), resulting in a lower energy retention **[A16]**. The heat production due to physical activity was similar for both diets, although the partitioning of the activity was different. Sows fed a high fiber diet spent more time eating, but were less active between meals. The increased heat production in sows fed the high fiber diet was mostly due to a greater thermic effect of feeding. These results contrast with later studies in which no difference in heat production was observed in sows or growing pigs fed a control diet compared with those that were fed more fibrous diets **[A28, A30]**. Physical activity represents approximately 20% of the total heat production in adult sows and 10-15% in growing pigs. However, physical activity varies largely between animals, underlining the importance to correct energy traits for differences in physical activity.

Following the thesis program of Gwénola LE GOFF on the role of fiber of intestinal transit, we continued our research on this topic. One of the reasons for this was that in all our modeling activities, the supply of (ileal or fecal) digestible nutrients is taken as a starting point. Possible interactions between the animal and nutrients are considered only at the metabolic level, ignoring digestive interactions between different nutrients, and between nutrients and the animal. In addition, we have not (or to a very limited extent) accounted thus far for the within-day dynamics of feed intake, digestion and metabolism. Few research reports exist dealing with the modeling of intestinal digestion in pigs and the existing work seems to point to two directions. First, there is a lack of quantitative data on the kinetics of

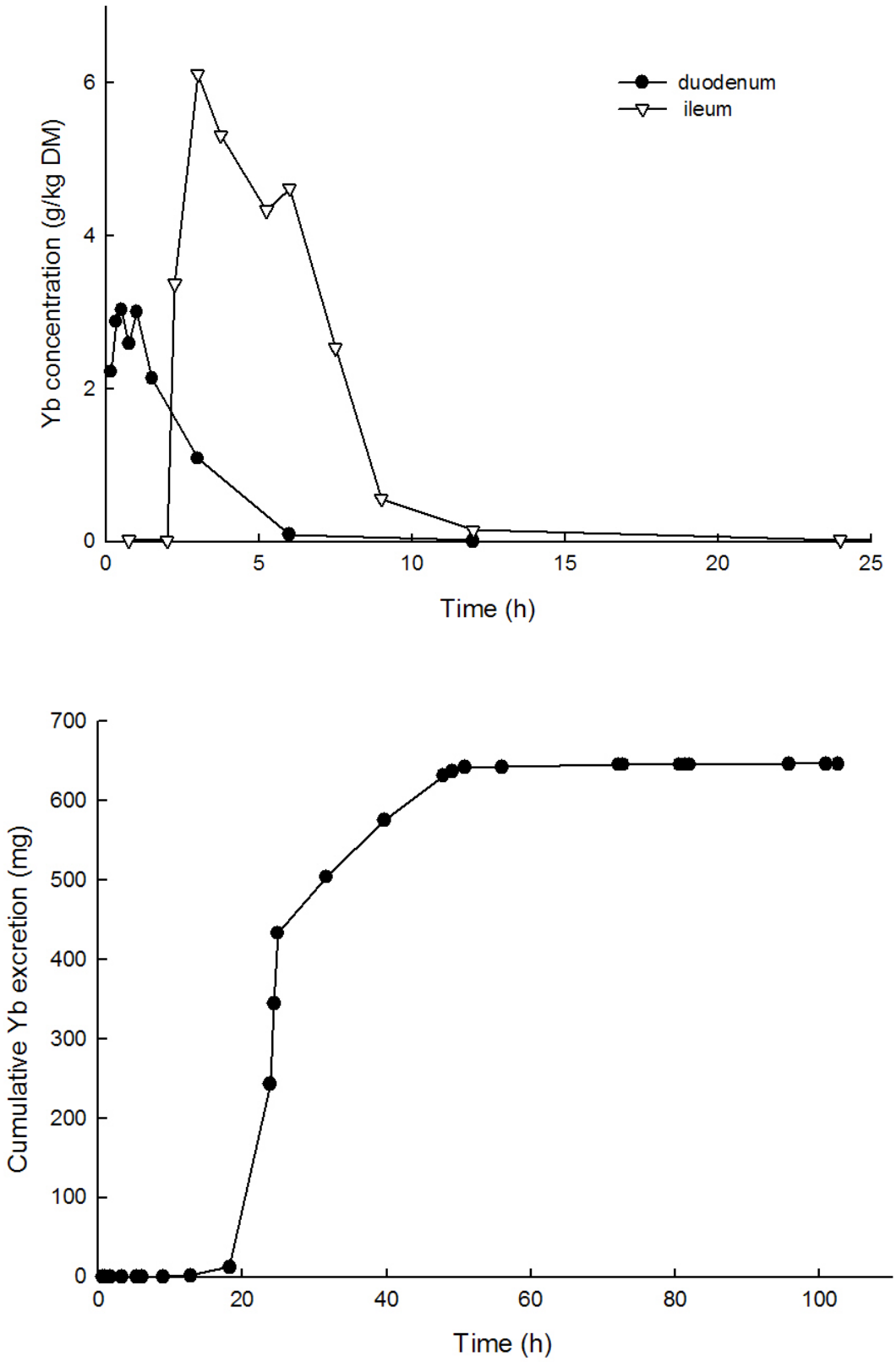

Figure 9. Example of Yb excretion curves in digesta collected at the proximal duodenum and the terminal ileum (top panel) and cumulative Yb fecal excretion (bottom panel).

digestion of feedstuffs. Second, intestinal transit plays an important role in the digestibility and availability of nutrients. It is for these reasons that we initiated the Cifre thesis research program of Aurélie WILFART with the goal to characterize different feedstuffs in terms of the kinetics of digestion and to develop a technique that would allow studying intestinal transit in growing pigs. This thesis was co-supervised by Lucile MONTAGNE, Jean NOBLET, and me. The first objective of the thesis was to develop an *in vivo* model allowing the quantification of transit in different segments of the gastro-intestinal tract. In a study were we fitted growing pigs with duodenal and ileal cannulas, the effect of dietary fiber on the site of nutrient digestion was evaluated **[A46]**. As anticipated, the duodenal digestion of nutrients was negligible, with the exception of ash. Apparent duodenal ash digestibility was -40% (indicative for the endogenous mineral secretions by salivary glands, stomach, pancreas and bile duct) and increased subsequently at the ileum (10-25% apparent ileal digestibility) and colon (45-50% apparent fecal digestibility). We also used this *in vivo* model to quantify the kinetics of intestinal transit **[A45]**. Following a pulse dose of YbO_2 and Cr-EDTA (representative for respectively the solid and liquid phases of digesta), sequential samples were taken from the duodenum and the ileum in combination with total collection of feces (Figure 9). Increasing the fiber content in the diet had no effect of the mean retention time in the stomach (i.e., the segment prior to the duodenal cannula), but decreased the retention time in the small and large intestines for both phases of digesta. The transit of the solid phase of digesta in the large intestine was 4-8 h slower than that of the liquid digesta. The excretion curves were also analyzed using a compartmental model with a lag time. After providing the pulse dose of the marker, first marker appearance occurred 2-3 h for the ileum and 20-30 h for the feces. Although the technique of double-cannulated pigs appears promising, there was considerable variation between animals. The data set created in this study is helpful in the creation and parameterization of digestion models. Although we do not foresee further development in this area in the immediate future within our research unit, we will actively participate in a thesis program on modeling intestinal transit carried out by Philippe LESCOAT at the URA research unit in Tours.

The second objective of the thesis of Aurélie WILFART was to develop an *in vitro* method that would allow characterizing the kinetics of digestion. In contrast to ruminant nutrition, kinetics of digestion is an area almost completely ignored in monogastric nutrition. Nevertheless, there are indications in the literature that the dynamics of nutrient supply may have metabolic implications (e.g., meal patterns may affect the availability and usability of nutrients)[7]. Although part of the dynamic supply of nutrients is driven by the animal (or the farmer), there are also dynamic characteristics originating from the feedstuff itself. Aurélie WILFART used a method based on the three-step enzymatic hydrolysis technique proposed by BOISEN and FERNÁNDEZ[8]. In that technique, total tract digestion is estimated by sequentially incubating the feedstuff with pepsin at pH 2 (mimicking the stomach), Pancreatin (a multi-enzyme complex mimicking digestion in the small intestine), and Viscozyme (a cocktail of microbial carbohydrases mimicking digestion in the large intestine). Rather than estimating the total tract digestibility through the original method, we estimated the kinetics of digestion by each of the three steps separately **[A52]**. It goes without saying that this method is very labor-intensive. However, it allowed illustrating that different feedstuffs (wheat, barley, wheat bran and soybean meal) have a different partitioning between soluble and potentially digestible fractions and very different *in vitro* digestion kinetics. A drawback of the method is

[7] van der Borne, J. 2006. Nutrient synchrony in preruminant calves. PhD-thesis. Wageningen University.

[8] Boisen, S. and J. A. Fernández. 1997. Prediction of the total tract digestibility of energy in feedstuffs and pig diets by in vitro analyses. Animal Feed Science and Technology 68: 277–286.

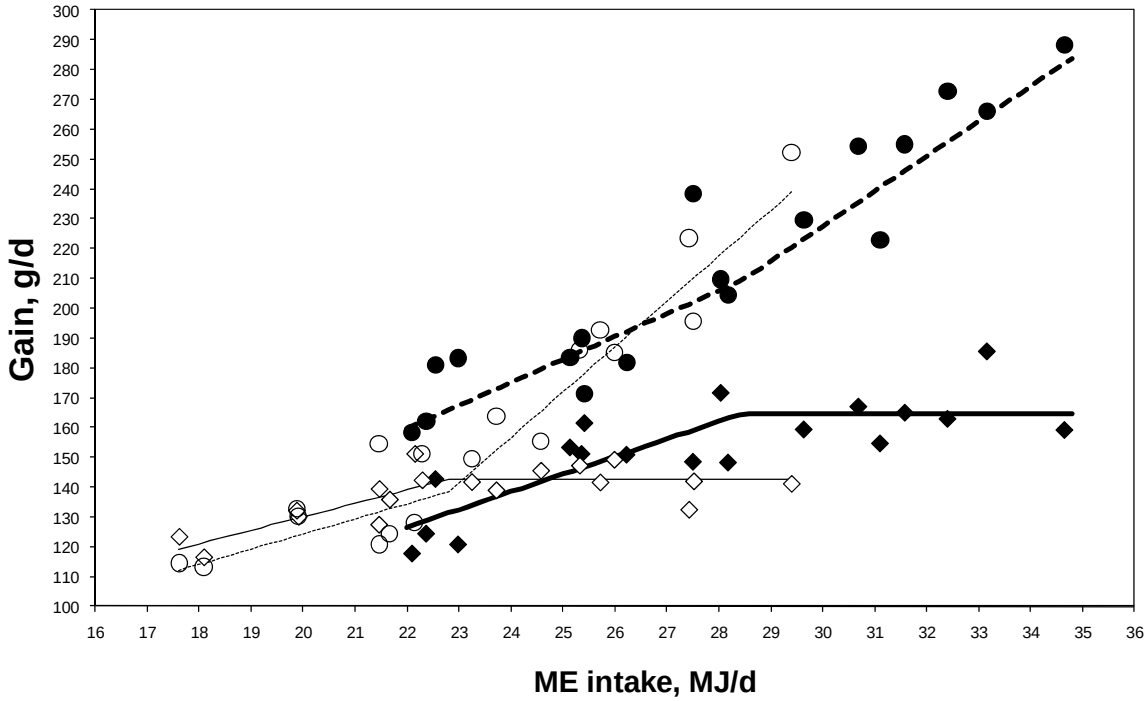

Figure 10. Effect of temperature and ME intake on protein and lipid deposition in 24 to 65 kg barrows. Observed and predicted data for protein deposition (PD, g/d) at 23°C (◆——), at 30°C (◇——) and lipid deposition (LD, g/d) at 23°C (●— —), at 30°C (○— —).

that it is based on the solubilization of substrates, which does not guarantee that soluble substrates can be absorbed.

2.6. Effect of ambient temperature on metabolism

Our research unit has carried out a large research program concerning on how the animal responds to its thermal environment in terms of feed intake, growth and metabolism. During the thesis research program of Anne COLLIN (with Jean LE DIVIDICH as advisor), I participated in studies where the effect of ambient temperature on voluntary feed intake and energy metabolism was studied **[A18, A19, A20]**. In a study with piglets offered feed *ad libitum*, we observed that exposure to a high ambient temperature (23 *vs* 33°C) resulted in a reduction in feed intake and heat production. The reduction in feed intake was mainly accomplished by a reduction in meal size, whereas the reduction in heat production was due to a reduction in the thermic effect of feeding and fasting heat production **[A18]**. As indicated earlier, even the basal metabolism appears to be affected by feeding level and it is this important to know whether ambient temperature has a direct or indirect (through feed intake) effect on heat production. We tried to address this issue in a study using three groups of piglets that were exposed to different feed intake levels and temperatures **[A19]**. Two groups were offered feed *ad libitum* and were exposed to an ambient temperature of 23 or 33°C. The third group was housed at 23°C but these animals were pair-fed to the *ad libitum* intake level of piglets kept at 33°C. At identical feed intake, heat production and activity-free heat production were lower at 33°C than at 23°C, resulting in an increase in energy retention. The difference in heat production appeared mostly due a difference in fasting heat production. This (somewhat surprising) result may be due to a difference in stress imposed upon the animal. At 33°C, the animal may be affected by heat stress, but it was still able to consume feed *ad libitum*. At 23°C, the amount of feed offered to the pair-fed piglets was 20% below their *ad libitum* feed intake capacity. This resulted in more restless animals (they were standing 4.9 h/d compared with 2.1 h/d for the piglets kept at 33°C), even though the measured energy expenditure for physical activity was not different. The results of this with piglets contrast somewhat with those obtained in growing pigs by Laurent LE BELLEGO. In that study, pigs were offered feed at one of four feeding levels and pigs were housed at ambient temperatures of 23 or 30°C **[A27]**. As indicated in Figure 10, the potential of the animals to retain protein was reduced during heat stress, while lipid retention was increased. As the energy costs (and thus the heat production) of protein deposition exceeds that of lipid deposition, this could be a mechanism the animal uses to reduce the heat production. These results, as well as the results obtained on the same animals concerning the fatty acid metabolism, show that there is a direct effect of ambient temperature on metabolism. Although the principle may be clear, a major challenge remains to construct response curves describing how the animal reacts to different ambient temperatures (i.e., it takes more than 2 points to construct a biological response).

Our interest in the effect of temperature was continued through the post-doctoral research program of Nathalie QUINIOU. In these studies, we evaluated the effect of cold and warm temperatures on feed intake, feeding behavior and energy metabolism in individually-housed and group-housed pigs **[A23, A24]**. The joint expertise on the effect of ambient temperature has resulted in that we were asked to contribute to write two book chapters on this topic **[O2, O3]**. Our expertise focused on the way the animal uses dietary energy as a function of diet characteristics, development of the animal, and ambient temperature. However, we had little or no expertise in the biophysical aspects of heat exchange between the animal and its environment. It is for this reason that we worked together with a Brazilian researcher (Flavio Bello FIALHO) during a post-doctoral visit of 2 months to our group. We

developed a model that predicts the thermoneutral zone of the animals (depending on the housing conditions) and the way the animal responds to alleviate the effects of heat stress **[A35]**. This heat balance model assumes the existence of core body temperature and that the regulation of this temperature is under tight control. During heat stress, the animal will first seek to increase heat loss. If these mechanisms are insufficient to maintain the body temperature, heat production will be reduced by reducing feed intake. This work is of interest for a future incorporation in the InraPorc model to account for different climatic and housing conditions the animal may encounter (e.g., in outdoors production systems, Summer periods of heat stress).

2.7. 'Up and down' research

In my research, the animal is almost always taken as a starting point, while carrying out 'horizontal' research programs to study how the animal responds to nutritional inputs and environmental constraints. However, I also participated in research program that are (much more) fundamental or programs that take a more global approach. These programs are carried out with colleagues within our research unit or with external partners.

2.7.1. Up

To further strengthen our research program in modeling, Ludovic BROSSARD (Production Systems, Environment and Welfare research team) was recruited with the objective to study the response of groups of animals to management strategies. In the past, several research groups developed models describing growth in pigs, but almost all of these describe the growth of an individual animal, and not of a population of animals. There are strong indications in the literature that the average animal cannot be representative for the average of a population[9]. For example, if one would feed a population according the nutritional requirements of the average animal, half of the population would not receive the nutrients they require. Consequently, the performance of these animals would be lower than expected and the average performance of the population would be lower than the performance of the average animal. One of the objectives of the research program carried out with Ludovic BROSSARD is to characterize individual animals within a population. In some models, 'cosmetic' variation is added to the deterministic outcome of simulations, giving it an appearance of a population model. In our view, it is more useful to try understanding the origin and the relation between different sources of variation. In a study recently published in *Animal* **[B3]**, we analyzed the individual feed intake and growth curves of almost 200 pigs. This analysis resulted in a set of five parameters for each pig, which allow reconstructing the feed intake and growth trajectory for each pig. These five parameters are of course not independent and failure to recognize the relationships that exist between these parameters may lead to a large overestimation of the variability of the population. For example, a pig with a high feed intake is likely to have a high growth rate as well. Consequently, the relationships that exist between these model parameters (i.e., the variance-covariance matrix) are a characteristic of the population. In the near future, we want to evaluate to what extent the variance-covariance structure of model parameters is generic or if it is specific for each population of pigs.

[9] Pomar, C., I. Kyriazakis, G. C. Emmans, and P. W. Knap. 2003. Modeling stochasticity: Dealing with populations rather than individual pigs. Journal of Animal Science 81 (E. Suppl. 2): E178-E186.

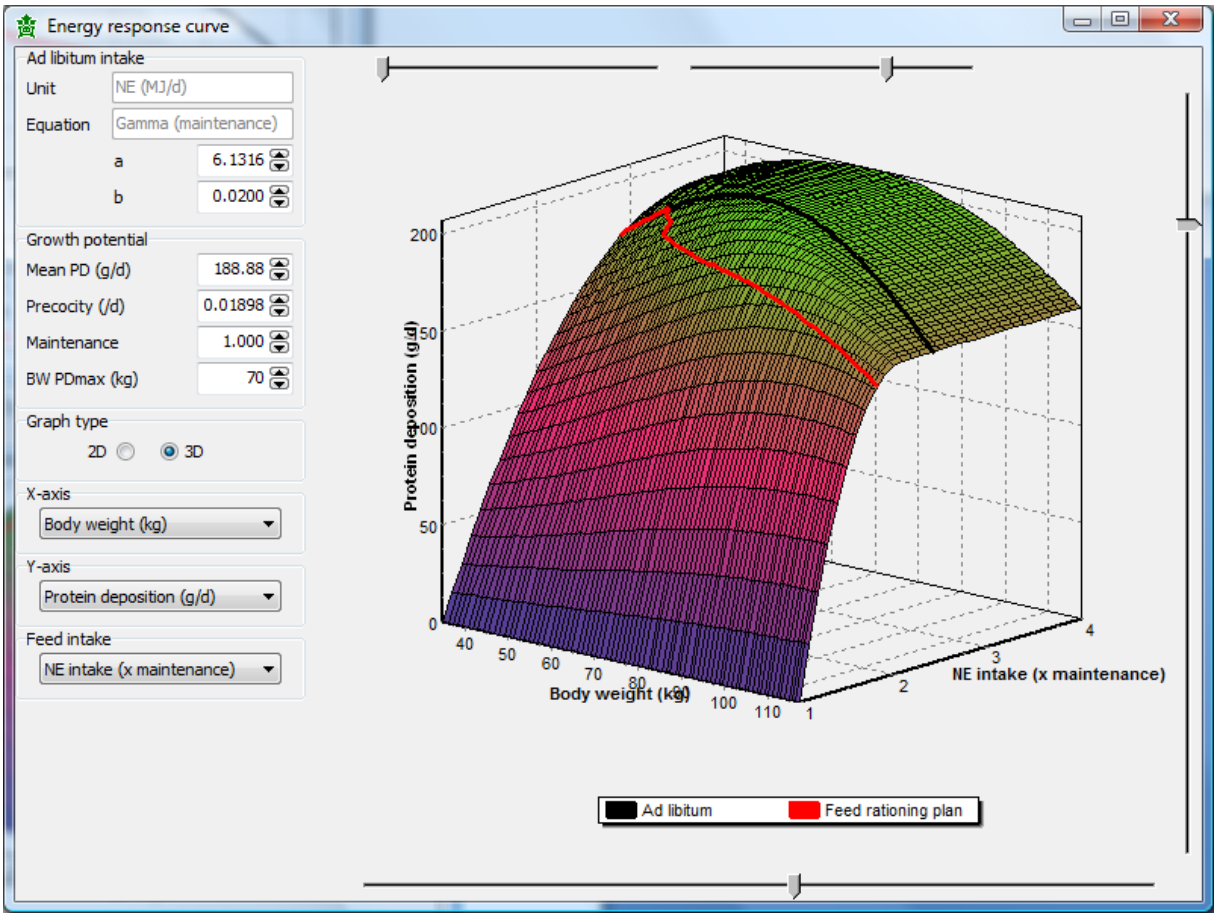

Figure 11. Screen capture of the InraPorc program illustrating the response surface of protein deposition (Y-axis) as a function of body weight (left X-axis) and net energy intake (right X-axis). The response for ad libitum feed intake is given as a black line, whereas the response of a specific feed rationing plan (feed intake restricted at 2.2 kg/d) is given as a red line.

2.7.2. Down

A relatively ambitious program was started in 2006 together with Florence GONDRET (Tissue Growth and Meat Quality research team) on the modeling of lipogenesis and lipolysis at the cellular level. Although we (unsuccessfully) tried to obtain funding for the experimental part of this program through a national research program, we were successful in the construction of an (ASC) thesis research project, on which Pierre BLAVY has been working since December 2006. The objective of this thesis is to develop two models of cellular lipid metabolism. An 'extended' model is currently under development to represent a maximum of information concerning the relations between nutrients, enzymes, and genes implicated in lipid metabolism. In parallel, a 'reduced' model has been developed with the objective to represent in a generic and dynamic way the fluxes and main regulators of lipid metabolism according to the nutritional status of the animal during prolonged fasting. This reduced model used data (i.e., fatty acid composition) from adipose tissue and liver in wild-type and PPARα-knockout mice. The PPARα is involved in the regulation of fatty acid metabolism and animals lacking PPARα have limited capacity to oxidize fatty acids. The modeling study (surprisingly) indicated that elongation and desaturation of fatty acids occurred in PPARα-knockout mice and this hypothesis was later confirmed experimentally. The reduced model is currently in press in the *Journal of Theoretical Biology* **[B2]**. The supervision of the thesis program is done by our research unit (Florence GONDRET and me), Sandrine LAGARRIGUE (INRA Animal Genetics in Rennes), Anne SIEGEL and Ovidiu RADULESCU (IRISA à Rennes) and Pascal MARTIN (INRA Pharmacology and Toxicology in Toulouse).

2.8. InraPorc

Since several years, an important part of my work has been dedicated to the development of the InraPorc model and decision support tool. This tool contains a module for sows (for which the development was coordinated by Jean Yves DOURMAD) and a module for growing pigs (coordinated by me). Most of the response curves used in the model have been developed at our research unit during the last 15 to 20 years.

The InraPorc model is a relatively classical growth model based on the metabolic transformation of nutrients and the use of these nutrients for different physiological functions (e.g., basal metabolism, protein and lipid deposition). Protein and lipid mass are represented as two state variables (compartments) and the partitioning of energy between protein and lipid deposition is mainly orchestrated through the *ad libitum* feed intake and the corresponding protein deposition. The partitioning is also affected by a possible feed restriction and the supply of essential amino acids. In Figure 11, the response curve of protein deposition relative to feed intake and body weight is given. This figure is conceptually the same as Figure 4, but it is given here within the InraPorc software tool. It allows the user 'to play' with the model parameters to understand and evaluate the driving forces used in the model. Both the models for growing pigs and for sows have been published in a special issue on modeling in *Animal Feed Science and Technology* **[A47, A51]**.

Apart from the scientific aspect of creating the InraPorc model, we have gone through considerable efforts to make the model 'usable' by creating a software tool. The InraPorc software tool is intended to be used by professional nutritionists and for teaching nutritional principles. InraPorc was conceived as a user-friendly tool integrating several aspects of animal feeding and nutrition. The conception of the user-interface has been done in close collaboration with Jean-Yves DOURMAD and two engineers who programmed the software (this was done initially by Serge DUBOIS and since May 2002 by Alain VALANCOGNE). A first version of the software was presented to professional nutritionists and university teachers in

December 2003 and the software has been available for users since April 2006. The tool is available at a very reasonable price for commercial use (500 €) and is free for academic purposes. We currently have sold about 250 licenses worldwide and the software is available in eight different languages. InraPorc is also used in different academic settings (mainly in France and in Brazil) for teaching swine nutrition.

One of the major challenges during the development of the software tool was to decide on the most relevant inputs the user has to provide. Our goal was to give advanced users the opportunity to fully evaluate the model concepts (through changing model parameters) without this being a too overwhelming challenge for novice users. The next example illustrates the complexity of the decision to open-up or not certain model parameters. In InraPorc, we assume that the metabolic efficiency of amino acid use for protein deposition is constant. Because we consider that amino acids are used both for maintenance and protein deposition, the calculated ideal amino acid profile will change over time. The ideal amino acid profile is a concept frequently used by nutritionists to express amino acid requirements. Changing the efficiency values in InraPorc will thus change the ideal amino acid profile and requirements. We have received requests from several users who would like to have a possibility to change the efficiency values. We realize very well that this would be a useful addition for advanced users, but it adds a risk that the software can be misused.

The InraPorc project has allowed me to further discover the different aspects of being a research engineer. First, the construction of a model is a real scientific challenge and not an engineering project. The systems approach, used to integrate information from different sources, generates new knowledge and allows establishing a scientific record. The work of a modeler can stop there, without the model being transformed into a tool to be used by other users. The development of tools is really an engineering task for which, in my opinion, we have not been trained for, and for which we are currently not well equipped at INRA. Of course, the development of a tool requires the construction of a model, and researchers or research engineers are very well able of creating such a model. However, software development requires other areas of expertise, including conceiving the tool, ergonomics, and software programming. Most of these skills were acquired while the project was advancing. The fact that the InraPorc project took eight years to release a first version (rather than three, as we initially had programmed) illustrates that we were learning more from our errors than by prior knowledge of the job.

3. Administrative and management activities

3.1. Within the UMR SENAH research unit

Between September 2003 and December 2007, I was deputy-head of the UMR SENAH research unit, with the main responsibility to coordinate the scientific program of the unit. For large research unit like ours (with more than 100 permanent staff), it is almost impossible that the head of the unit ensures all administrative tasks, human and financial resources, and the scientific coordination. Although an organization in research teams may alleviate the head of the unit a little, it may result in a situation where research teams progressively take over the role of the research unit, as far as the scientific coordination is concerned. The committee that evaluated our research unit in 2003 (like in 2001) commented on the lack of ‘common spirit’ in our unit. Following my appointment as deputy-head and following discussions that I had with individual researchers, I noticed a certain lack of motivation, especially amongst young researchers. I felt that this lack of motivation may be the result of too much scientific diversity (or dispersion), lack of scientific peers within the unit, combined with a lack of scientific coordination. The fact that our research unit now

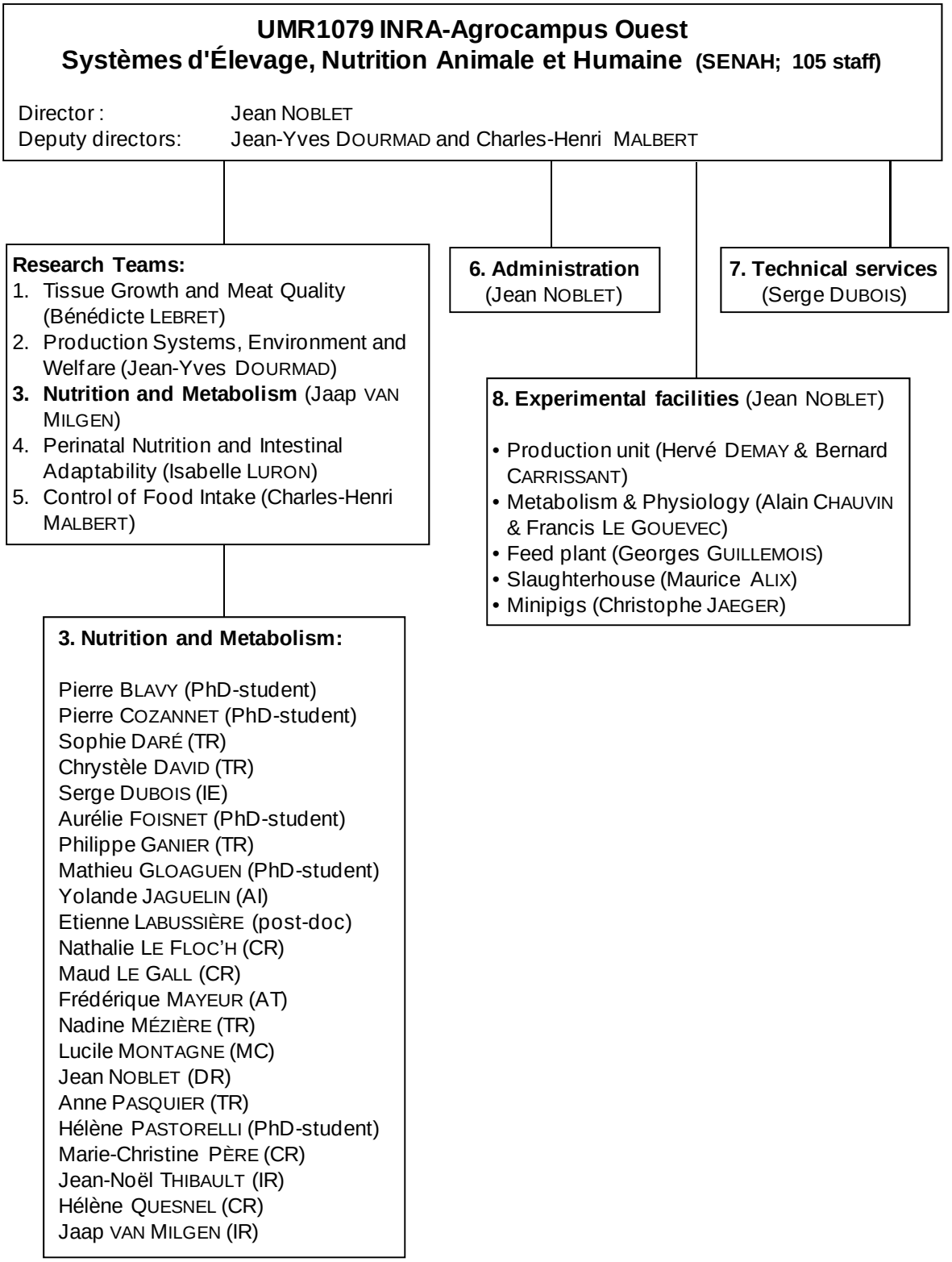

Figure 12. Organizational structure of the UMR1079 SENAH research unit.

depends on two INRA divisions (Phase and AlimH), having different research goals, does not facilitate creating common research spirit. I have tried to promote this by organizing (more) scientific meetings where topics of common interest are discussed. For example, the strategic plans of both the Phase and AlimH divisions were discussed with all the scientific staff. We also organized meetings during which topics related to science were discussed. For example, in 2004, we discussed the role of INRA as a public research institute (as a follow-up on the 'Sauvons la Recherche' movement in France). We also had two meetings during which aspects of deontology in science were discussed (following the INRA report of PAILLOTIN and LE NEINDRE on this topic).

To further promote a common spirit, I also proposed to organize a meeting called 'Ideas and Results', that takes place every first Monday of the month. These meetings are open for all and we discuss two to three different topics for a limited period of time (20-30 minutes per topic). During these meetings, an idea, a (partial) result, or a specific technique is discussed without seeking an exhaustive and in-depth discussion. These meetings also ensure a better diffusion of information within the unit and facilitate group-discussions.

Since our appointments as head and depute-head of the unit, we (Jean NOBLET and me) had regular meetings with technical and administrative staff, and with students and post-doctoral researchers. These meetings, without a particular agenda, allowed for a more direct relation with the personnel of the research unit. There are often specific problems or questions of interest for different staff categories, and these problems and questions may not emerge sufficiently during team meetings.

After my appointment as deputy-head and after an internal debate, we re-organized the Phase research teams in our unit. Since January 2005, I have been responsible for the team 'Nutrition and Metabolism' (see Figure 12 for the organizational structure of the research unit and research team). Even though this double responsibility was very interesting for me, I had the strong feeling that I did not have enough time to do what I wanted to do in research. It was for this reason that I asked the division heads of Phase and AlimH to not renew my mandate after the evaluation of the unit in 2007. This would give me more time for my personal research and to spend sufficient time as a moderator of my research team. Since January 2008, Jean-Yves DOURMAD and Charles-Henri MALBERT have been appointed as deputy-heads of our research unit.

3.2. External activities

Since my recruitment at INRA in 1994, I assumed the co-responsibility (together with Daniel SAUVANT, AgroParisTech) of a working group on modeling within the ENA division (one of the predecessors of the Phase division). This group meets once or twice per year during a 1-day meeting to discuss a topic or methodology in modeling. Together with Daniel SAUVANT and Philippe FAVERDIN (UMR PL) we established several smaller working groups with the goals to further promote the systems approach in the research of our division. Each group was composed of 5 to 10 scientists and I was in charge of a group interested in modeling at the cellular and tissue level. In January 2008, the head of the Phase division asked me to be the moderator of the working group on modeling in the division. I organize annual meetings where people present their ongoing work on modeling (30-50 participants at each meeting). I also recently organized a meeting where we discussed the protection and sharing of data and databases. Many researchers (or research teams and units) have databases with data of experimental herds, combined experiments or literature data. The reason for the construction of these databases differs, as does the way these databases are conceived and maintained. It is not unlikely that a considerable part of the data that a researcher has created and collected during his career, will appear to be unusable after his retirement. This may

imply that the scientific heritage of a researcher will be limited to his publications. Will the information that can be found in the literature be sufficient to fully understand biology in the future? The focus of the discussion in our group was on how data can be protected and shared, including issues of ontology and deontology.

I have been chairman or discussion leader at different national and international congresses. In 2003, I was asked to be the discussion leader of a 1 hour plenary discussion on 'Genes and Nutrition, Modeling, and Regulation of Protein and Energy Metabolism' during an EAAP symposium held in Rostock, Germany. I was also asked to chair a session on "Digestion: a modeling approach" that was held during the 10th meeting of the 'Rencontres autour des Recherches sur les Ruminants' in Paris. In 2005, I was discussion leader for a session entitled 'Utilization and optimization of nitrogen, phosphorus and trace elements' held during the International Workshop on Green Pork Production in Paris.

I was member of the scientific committee of the 2nd International Symposium on Energy and Protein Metabolism and Nutrition (Vichy, 2007) and I am actually serving in the scientific committee of the international workshop on Modeling Nutrient Digestion and Utilization in Farm Animal, which will be held September 10-12, 2009 in Paris. During that workshop, I will chair a session and I have been asked to make the concluding and closing remarks of the workshop.

In a recent discussion in Wouter HENDRIKS (Wageningen University), we discussed the interest of having a unified system of values of feedstuffs and nutritional requirements in Europe. Different national systems currently exist and there is no easy way to use information from one system in another system. After a further discussion within INRA, there appears to be a mutual interest to evaluate the possibility to propose a common (at least bi-lateral) nutritional system for livestock feeding. I will be in charge for the French side of the coordination of this project, which will take undoubtedly several years to realize.

During her thesis project, I participated with Maela KLOAREG at a 'Réflexives' seminar. These 1-week seminars are organized for PhD-students and their advisors to discuss the thesis project while focusing on the appropriation and the positioning of the research project (e.g., what is at stake for the student, what is at stake for the research unit), science integrity, communication, and skills. This is partly done in 'Réflexivity' workshops, where groups of four students with their advisors from different disciplines discuss these issues. Reflexives was initiated by Marie-Claude ROLAND at INRA in the late 1990s and now includes a team of moderators (i.e., scientists from different scientific disciplines and mostly from INRA) in charge of the workshops. Since my participation as an advisor for Maela KLOAREG, I volunteered as a moderator for Réflexives. This means that I spend 1 to 2 weeks per year participating (moderating) in these workshops or in training sessions organized for the moderators. Apart from a service that I can provide to other participants, I find the role of moderator very important for my personal development (e.g., animation, development of questioning.). I have participated in these workshops as an advisor with different PhD students (Maela KLOAREG, Aurélie WILFART, and Pierre BLAVY in the past, with Virginie RIVERA in October 2009 and with Mathieu GLOAGUEN in 2010), and I also anticipate continue doing so as a moderator.

3.3. Scientific expertise

I very regularly receive requests to act as a reviewer for different scientific journals (see the curriculum vitae for a list of journals). Between 2001 and 2004, I acted as an advisor in statistics and modeling for the journal *Animal Research* and between 2004 and 2006, I was associate editor for this journal. In this role, I acted as guest editor to coordinate a special issue on the contribution of modeling to study herd and livestock systems (*Animal Research*

53(5)). Since the creation of the journal *Animal*, I have been editor within the section 'Farming Systems and Environment', but I also very frequently receive request from other sections, especially from the sections of 'Nonruminant Nutrition' and 'Physiology and Functional Biology of Systems'. In this role, I manage the reviewing process of submitted manuscripts and I typically handle 10-15 manuscripts per year. I also frequently act as project evaluator for French research organizations (e.g., GIS Recherche Porcine, ANRT) and occasionally for international research organizations. Since my recruitment at INRA, I served regularly on recruiting committees (for research engineers at INRA), and on PhD steering and final examination committees in France and abroad.

3.4. Teaching activities

I regularly participate in different teaching activities, either in the context of higher education or the continuing education of professionals. Between 1998 and 2002, I participated in several training sessions organized by the Formation Permanente, the continuing education system of INRA. Together with five colleagues, we prepared several modules in statistics that were taught to colleagues at the research center in Rennes. I was in charge for two modules, entitled 'Introduction to non-linear regression' (3.5 h/session) and 'Advanced topics in non-linear regression' (7 h/session).

At several schools and university, I participate in the teaching of nutrition and modeling. These activities are carried on a more or less regular basis (e.g., ESA Angers, Agrocampus Ouest, AgroParisTech) or as occasional courses (DESS at the University of Tours, University of Rennes 1, University of Ljubljana). Ma participation is typically organized as a 1 day intervention where I teach in the morning in a classroom setting, followed by practical training in the afternoon. Since 2002, I have been participating in the organization of a 1 week course on modeling biological systems at Agrocampus Ouest. This course, organized together with Catherine DISENHAUS (Agrocampus Ouest) and Philippe FAVERDIN (UMR Production du Lait), offers the students a hands-on experience on the (im)possibilities of model development through practical training. Since 2006, this module is mandatory for MSc-students in Zootechnical Engineering.

I also regularly participated in continuing education programs offered by INRA, or in collaboration with other research organizations. Almost all these teaching activities deal with modeling at an elementary level.

3.5. Partnerships and cooperation

The research programs in our research team have allowed me to establish contacts with research organization in France and abroad. The relations with Daniel SAUVANT (AgroParisTech) and Philippe FAVERDIN (UMR Production du Lait) date back to my recruitment at INRA and are given form through our investment to promote the systems approach in biological research in the Phase division, the mutual participation in PhD steering committees and a few experimental studies (e.g., the thesis programs of Paulo LOVATTO and Virginie RIVERA). I also have more or less regular contacts with Candido POMAR (Agriculture et Agroalimentaire Canada), Kees DE LANGE (University of Guelph, Canada), Gary ALLEE (University of Missouri) and Paulo LOVATTO (Federal University of Santa Maria, Brazil). As a result of these contacts, we hosted several students from these universities for a short stay at INRA. Flávio Bello FIALHO (EMBRAPA) spent a two months post-doctoral period under my supervision while Paulo LOVATTO and Kees DE LANGE both spent a sabbatical period in our research unit during which we carried out a joint research program.

As indicated earlier, the thesis of Pierre BLAVY is a project involving several (mainly local) partners from different disciplines. Apart from the contribution of our research unit in areas of nutrition and metabolism (Florence GONDRET and me), we collaborate with Sandrine LAGARRIGUE (Animal Genetics) and with scientists from INRIA working in bio-informatics and modeling (Anne SIEGEL and Ovidiu RADULESCU). The organization of such a project is not an easy task because of different research interests and the speaking of 'different languages'. It goes without saying that it is a very difficult task for the PhD-student too. I am currently continuing the cooperation with INRIA through a project led by Sophie LEMOSQUET (UMR Production du Lait). Similar to an earlier project in which we used the biochemical calculator to evaluate the nutrient balance of the mammary gland in sows, Sophie LEMOSQUET is interested in realizing similar studies in dairy cattle. In contrast to sows, many experimental datasets exists where the uptake of nutrients by the mammary gland is compared with the export of nutrients in milk. We are currently working together with INRIA to make decision rules of the biochemical calculator more explicit by defining an objective function. We also plan to transform the current calculator (a spreadsheet where operations are managed by the researcher) into a more user-friendly software tool.

Since several years, Ajinomoto Eurolysine has been an important partner in our research. Several experimental programs as well as the development of the InraPorc model and decision support tool were supported by this company. The research program on branched-chain amino acids (post-doctoral research of Roberto BAREA), as well as the thesis program of Mathieu GLOAGUEN have been or are partly financed by Ajinomoto. I also have good contacts with other partners in the animal feed industry through the (financial) support of thesis programs (e.g., CEVA and Danisco for the thesis of Aurélie WILFART, and Inzo° for the thesis of Maela KLOAREG), collaborative research contracts (e.g., Techna and Degussa) or smaller research projects. This type of cooperation is an integral part of our policy because these companies are willing to finance studies with a general interest for which there may not be a direct financial return. The results of most of this collaborative work can be published without restriction in peer-reviewed journals.

4. Future projects

In the near future (i.e., in the next five years) I do not foresee a major reorientation of my research program. I will continue to focus on how nutrition and feeding can be used as a means to modulate animal production. This includes improving techniques that help reducing the impact of animal production on the environment (e.g., the program on branched-chain amino acids, or parts of the PigFeed program). I will also continue research programs that intend to improve our understanding of the biological mechanisms implicated in nutrition and metabolism. Compared with studies done in the past, there will be some reorientation in the factors that will be studied, with more focus on the role of the animal. For example, in the PigFeed and AndroPig programs (see later), different animal phenotypes are created by genetic selection or different (non-)castration techniques of male pigs. In these programs, we will try to identify the metabolic changes related to the animal phenotype.

During the last five years, experimental studies have taken an increasing part of my research activities. Also the time allocated to internal management and activities of general interest has increased considerably. This resulted in a situation in which modeling (and engineering) has become as less important part of my personal research activities. This is a trend that I regret and I am aware that I have to ensure that modeling and engineering remains an integral part of my personal program.

4.1. Experimental programs

There are currently (July 2009) three experimental programs for which we have made firm commitments. The thesis program of Mathieu GLOAGUEN on the requirement of branched-chain amino acids has started in July 2009 and will be carried out for the next three years. I will also carry out experiments that are part of larger projects financed by the French National Research Organization (ANR). This is the case for the PigFeed and AndroPig projects in which our research unit is a major partner.

4.1.1. Branched-chain amino acids

The thesis of Mathieu GLOAGUEN on the requirement for secondary amino acids is a follow-up on the post-doctoral research project of Roberto BAREA. In these studies, we have shown that a limiting supply in Val reduced feed intake and growth in piglets. The reduction in performance seemed to be more important when the deficient supply in Val was accompanied by an excessive supply of Leu. Under these conditions, the reduction in feed intake was very important (more than 40%) and was probably due to an antagonism between branched-chain amino acids. As indicated before, the first two steps of the catabolism of branched-chain amino acids are catalyzed by enzymes complexes that are common for these three amino acids. The dietary or metabolic equilibrium between the branched-chain amino acids may therefore play a role in the response of the animal. In addition, an excessive supply of branched-chain amino acids may limit the transport of other amino acids (Trp, Phe and Tyr) to the brain, which may have an impact of feed intake and appetite. These interactions between amino acids imply that the 'requirement' of an amino acid cannot be considered as a single figure. The continuing reduction in protein (and amino acids) content diets implies that more amino acids can become co-limiting. This means that the risk of providing amino acids below the requirement increases and that interactions between amino acids have a potentially greater impact on the animal (i.e., the safety margin is smaller). It is therefore important to better understand and quantify these interactions.

The thesis research project of Mathieu GLOAGUEN has two main objectives. The first objective is to determine how piglets respond to a limiting supply of secondary amino acids. To account for the possible interactions between amino acids, these response studies are carried out under different nutritional conditions. The second objective is to determine the physiological and metabolic mechanisms that may explain interactions between amino acids. We will determine when and how a limiting amino acid supply will reduce feed intake and growth. Part of the reduction in growth is due to the reduction in feed intake. It is nevertheless likely that a limiting supply of the amino acid also modifies metabolism independently of the feed intake. To study the contribution of each mechanism, experimental studies will be carried out using animals that are offered feed *ad libitum* or at a restricted level. We will focus our initial efforts on Val (in interaction with other amino acids), but studies on other amino acids are foreseen (including Ile, Leu and His).

To better understand the mechanisms the animal will use when facing a limiting amino acid supply, we will study the metabolic modifications on the one hand and the regulation of feed intake on the other hand. In a preliminary study, we observed that an animal reduced its feed intake and modified its feeding behavior immediately after the distribution of a deficient diet. This observation, if confirmed, suggests that there may be a detection by odor or taste that intervenes before a metabolic detection. An experimental protocol will be put in place to test this hypothesis.

4.1.2. PigFeed

The objective of the PigFeed program is to better understand feed efficiency in all its aspects. It concerns a program initiated by the Animal Genetics division where two lines of pigs have been selected for seven generations for having a different residual feed intake. Residual feed intake is the difference between the actual feed intake and the predicted feed intake based on growth rate and the composition of growth. Two lines of pigs that have a different residual feed intake consume different quantities of feed for a similar growth rate and composition of growth. The goal of the PigFeed program is to determine the metabolic, physiological, and genetic mechanisms that explain the difference in feed intake. One of the hypotheses that will be tested in our research unit is that pigs with a high residual feed intake are more robust and better capable of facing different challenges (e.g., heat, inflammation, nutritional deficit).

In a preliminary program, I cooperated with Ludovic BROSSARD to better characterize the difference between both lines of pigs and results of that study have been reported at the 'Journées de la Recherche Porcine' in 2009. In line with earlier work we have done in trying to characterize a population of pigs in terms of the kinetics of feed intake and growth, we will continue the analysis of performance of these pigs and we will, in cooperation with geneticists, estimate the heritability of these traits. A thesis program on this topic will start later in 2009.

One of the objectives of the PigFeed program is to test if the two lines of pigs respond differently to challenges. Together with Ludovic BROSSARD, we will test how these pigs respond to a nutritional challenge. As indicated before, the residual feed intake differs between both lines of pigs while the growth rate is identical. If it is assumed that the amino acid requirement in g/d does not differ between both lines, the requirement would differ if expressed in g/kg diet. We will carry out an experiment in which both lines of pigs are facing a severe amino acid deficiency (in this case Lys), relative to the calculated requirement for each line of pigs. We will calculate the amino acid requirement of individual pigs based on their feed intake and growth curves, and we will formulate diets that will cover the Lys requirement of approximately 25% of the individuals in each population (i.e., line of pigs). This means that 75% of the animals in each population will face a more or less severe restriction in Lys. It is hypothesized that both lines of pigs respond in a similar matter to the amino acid deficiency. If this hypothesis is not confirmed, this may imply that the two lines use a limiting supply of Lys with different efficiencies.

At the end of 2009, we have foreseen to carry out a study in the respiration chambers with the objective to determine how the two lines of pigs respond to a non-infectious challenge in terms of energy metabolism. The underlying hypothesis is that part of the residual feed intake is used for the animal's defense system. Stated more generally, we assume that the partitioning of energy between different physiological functions differs between the two lines of pigs. The line with a high residual feed intake may have higher nutritional requirements to sustain its defense system and to maintain the same growth rate, these animals will have to eat more. When the defense system is challenged, it can be hypothesized that these pigs are better capable of defending themselves and thus less affected by the challenge. In the proposed study, we will measure the kinetics of energy expenditure in the two lines of pigs under 'normal' conditions and under conditions of a challenge with Freund's adjuvant, which will provoke a chronic lung inflammation. In the same study, we will test a technique to measure the oxidation of nutrients par measuring the expiration of $^{13}CO_2$ following the provision of a pulse dose of ^{13}C-glucose.

4.1.3. Andropig

The castration of male piglets without anesthesia is increasingly questioned in Europe, and alternatives are sought for in different countries or in a European context. The three (existing or future) alternatives are the castration with local anesthesia, non-castration, and immuno-castration. Each of these alternatives has disadvantages, but also potential advantages. Castration with anesthesia requires several actions and more time, while non-castration may result in the appearance of boar taint in meat products. Immuno-castration is a vaccination against a hormone or factor implicated in the cascade of events of the hypothalamic-pituitary-gonadal axis, and is carried out by two injections starting at 70 kg of body weight. This technique is likely to be authorized in European Union in 2009 and allows raising entire males (having physiological and behavioral characteristics different from castrated males) up to the moment of immuno-castration. The objective of the project AndroPig is to evaluate different biotechnical alternatives to castration without anesthetics. Several researchers of our research unit are involved in this project. I will focus on the difference in energy metabolism between entire males, immuno-castrated males and 'normally' castrated males. In immuno-castrated males, we will specifically focus on the change in energy metabolism during and after the period of immuno-castration. Our hypothesis is that the energy expenditure of an immuno-castrated male and the composition of energy gain will progressively attain that of a barrow.

4.2. Modeling and Engineering

As a research engineer at INRA, it is logical that engineering is part of my perspectives. It is probable that the InraPorc project will continue for a considerable part of my career at INRA. An applied research institute like INRA has to affirm that the type of research questions asked find their origin in society. However, it also has to ensure that the answers found will be communicated to the society. The development of decision support tools is one of the best ways (for me) to assure a link between my research and their application, and I consider the construction of decision support tools in all its aspects as a main activity in my career. It is an activity that has my personal interest and for which I have acquired a certain national and international recognition. Consequently, I do not foresee major changes in the way I will carry out my engineering mission in the next 10 years.

4.2.1. Modeling the variation in populations of pigs

The InraPorc training sessions have been jointly organized by Ifip, Agrocampus Ouest and INRA in France since 2008. This activity is now carried out within the framework of the Unité Mixte Technologique (UMT) Porcin and is a good example of how knowledge transfer can be ensured by different actors.

Within the UMT Porcin, we will continue our research program to study variation in performance within populations of pigs and how different strategies can be used to manage these populations. In 2009, we proposed a CASDAR (Agricultural and Rural Development) project, which will include experimental and modeling studies. The program has been accepted and will be carried out in close coloration with Ludovic BROSSARD and Nathalie QUINIOU (Ifip). The project also includes a PhD-project (Cifre), which will probably start in January 2010. The project consists of three modules. The first module is an experimental program in which we will further characterize the kinetics of feed intake and growth in different populations of pigs. These populations originate from the insemination of sows with semen of different lines of boars (Large White x Piétrain, Duroc, or Piétrain). Daily feed

intake will be measured using an automatic feeding station whereas the body weight will be determined approximately every four weeks. The kinetics of feed intake and growth will be summarized in a limited set (five) of model parameters and the relationships between these parameters will be analyzed. The objective is to determine if the variance-covariance structure of these parameters is common for the three populations, or if there is population-specific variation. The objective of second module is to exploit the information from the first module through simulation modeling to identify management strategies that would conciliate animal performance, production costs, and impact on the environment. For example, the use of different strategies of phase-feeding or slaughter (all-in-all-out or weekly slaughter) can be simulated while accounting for the variation within the population. The third module consists of evaluating some of these management strategies through experimentation. The same type of measurement will be carried out as those described for the first module but the body composition of these animals will be measured through tomography (measured in the same animal at four different stages of growth). This type of information will be extremely useful to evaluate in more detail the development of adipose tissue and the way this should be represented a growth model (see the section 2.3).

4.2.2. Further development of InraPorc

During the research projects that we have carried out in the past, we have developed different modules that can be incorporated in tools such as InraPorc. This concerns the module of partitioning of lipids and fatty acids (developed by Rosil LIZARDO and Maela KLOAREG) and the module of thermoregulation (developed by Flavio Bello FIALHO and Nathalie QUINIOU). We plan to integrate these modules in InraPorc in the years to come. This integration requires expertise in engineering, but also needs without doubt further development of the module and thorough model testing. As indicated earlier, Sergio GOMEZ (Inifap, Mexico) will spend a sabbatical year in our research unit starting in 2010 to further develop and test the lipid and fatty acid model.

One of the more urgent engineering projects that we want to realize is the integration of EvaPig within InraPorc. EvaPig is a software tool developed in our research unit (coordinated by Jean NOBLET) that allows calculating the nutritional value of feed ingredients and complete feeds. It uses information from the Inra/AFZ database of nutritional values, but it can also correct the nutritional information of a feed ingredient, based on the information provided by the user. For example, the INRA/AFZ database contains information concerning the crude protein and lysine content of wheat. If the user uses a different wheat for which the crude protein content is known, the anticipated Lys can be calculated from the information provided by the user and from information available in the database. The relationship between these characteristics do not necessarily follow a rule of thumb, as currently is done in InraPorc. The integration of EvaPig in InraPorc will require changes in both software, and requires the incorporation of additional information in the database of EvaPig, and conceptual changes in InraPorc.

4.2.3. Modeling the relation between health and nutrition

The development of a population model is also important to (try to) take into account health aspects in future models. During his sabbatical year in our research unit, Paulo LOVATTO developed a literature database with data describing the relation between sanitary challenges and the performance of the animal (mainly through feed intake and growth). Since December 2008, this work has been continued by Hélène PASTORELLI (PhD-student, advised by Lucile MONTAGNE and co-advised by me). The objective of this thesis is to quantify the

impact of the sanitary status on the performance of the animal (and the group of animals) and identify the nutritional mechanisms that can explain this impact. The thesis project is carried out in three parts. The first part is a continuation of the work initiated by Paulo LOVATTO and concerns the further analysis of the database of literature studies, in order to develop response curves relating the sanitary challenge to the response of the animal. The second part is experimental and uses a non-infectious challenge model developed at our unit by Nathalie LE FLOC'H, with the purpose to identify the nutritional and metabolic modifications that result from this challenge. As in many studies that we have carried out, it is important to understand to what extend the response of the animal is driven through feed intake compared with a direct effect of the sanitary challenge on metabolism. The last part is very ambitious on concerns the development of a simulation model relating health and nutrition.

As indicated earlier, there are various reasons to pay more attention to the response of the population of animals in our modeling studies. These reasons include the use of appropriate management strategies that have an economic and environmental impact. Studying the impact of health to animal production adds a new dimension to our research, making it more complex and for which a fully deterministic approach seems inappropriate. Not all animals in a population will be affected by a sanitary challenge, and not all animals will be affected to the same extent. We think that the development of a stochastic model (based on characteristics obtained in individual animals) is a prerequisite for models dealing with health issues, underlining the importance of the project carried out in cooperation with Ludovic BROSSARD and Nathalie QUINIOU. It is difficult to give a precise timeline here, but the results of the project of Hélène PASTORELLI will allow us to make a step forward in this direction.

4.2.4. Meta-analysis

The programs that I indicated in the preceding sections use experimental or (simulation) modeling approaches. In the last few years, the meta-analytic approach has been receiving increasing attention in animal science. Meta-analysis is indeed a very promising approach to construct response curves that can be used in simulation modeling, and our research on the relation between nutrition and health is partly based on a meta-analysis.

I will certainly consider increasing my research efforts in this area. I have started constructing a database of literature data on the response of Ile supply on performance and Nathalie LE FLOC'H and I are currently collaborating with Ajinomoto Eurolysine on a meta-analysis project concerning Trp in piglets. These two exercises in meta-analyses have me made more aware of the power of a meta-analytic approach in research. Especially the calculation of the composition of the diet to obtain a complete profile of all nutrients provided often leads to surprising (and sometimes shocking) outcomes that help in explaining the reported responses.

4.3. External activities

In 2002, I indicated that I would like to take (some) responsibility within our organization on the condition that it would not impede too much on my research activities. I assumed during four years the role of deputy-director of our research unit and I am currently moderator of a research team. These roles are, or course, time-consuming and impede on my research activity. In the past, I have had difficulty to find the time to write my publications, including time for write my HDR report. I have always found great pleasure in realizing experiments, advising young researchers, and communicate about research in scientific publications and congresses. Even though I accepted and carried out the managerial activities

with great pleasure, it is important to find a good equilibrium between tasks of common interest and my personal activities as a researcher. After all, as a researcher you may want to do research.

4.4. Some thoughts about the 'Habilitation à Diriger des Recherches'

After having addressed the past and the future of some of my research programs, it may be interesting to share some thoughts about the meaning of the HDR and, in general, the orientation of a research program. After all, this document is intended to convince the jury that I partially fulfill the requirements for the 'Habilitation à Diriger des Recherches'. Although the words 'Habilitation' and 'Recherche' do not raise a major issue for me, I always had and still have difficulties with the word 'Diriger'. What does this word really mean? Translated literally into English, it means 'to lead'. Do I find myself capable to lead research or, more importantly, do I want to lead research? Taking this again in a literal sense, I do not pretend that I am capable of being a 'leader' in research. Before you stop reading this document (because my HDR may turn out to become a non-issue), I also think that very few, if anyone, can pretend to be a leader in research and perhaps the word 'diriger' should be interpreted differently. In Dutch, the word 'dirigent' exists, which is a word of similar origin but it means 'conductor' in English or 'chef d'orchestre' in French. I personally feel much more at ease with this word and its interpretation. Of course, a conductor is somehow is in charge, but his main task is that the musicians play in harmony. In my view, 'Diriger des Recherche' should imply that an effort is made to have the actors of research play in harmony towards a research goal. The first article of the French law that describes the HDR (arrêté du 23/11/1988) appears to be limited to the capacity to advise young researchers. This first article states:

L'habilitation à diriger des recherches sanctionne la reconnaissance du haut niveau scientifique du candidat, du caractère original de sa démarche dans un domaine de la science, de son aptitude à maîtriser une stratégie de recherche dans un domaine scientifique ou technologique suffisamment large et de sa capacité à encadrer de jeunes chercheurs. Elle permet notamment d'être candidat à l'accès au corps des professeurs des universités.

The word 'encadrer' may have a different meaning than my interpretation of 'to advise' and should perhaps be seen in relation to guidance. However, what guides our research?

In our research team, we recently had a meeting during which we made an (internal) evaluation of our research program. Our unit was evaluated in 2007 and will be evaluated again in 2011. By the summer of 2010, we will have to provide a written document of our activities and future program. It seemed useful to me to read again what we had written in late 2006 and to see where we stood now. Although some of the research programs that we had announced are actually on their way, we are now also involved in research programs that we had not anticipated, illustrating the complexity of the question of 'who is in charge of a research program'. Some of the programs that we are now involved in originate from calls for projects made by the French national research organization, a major stakeholder. The boundaries of these projects are (largely) defined and, with other partners, we proposed projects that fell within the framework of the call for proposals. However, these projects were not (and could not) be identified a few years ago. As such, this type of research may be defined a 'circumstantial research'. At the right time, with the right partners, with the right budget, and with the right question, it resulted in a research program defined for 2 to 3 years.

Coming back to the issue of the HDR and what this means for research at the level of our research unit or our research team: we share a common interest in trying to understand how feeding and nutrition can be used as a means to control animal production. This is where our (personal) interest is and this is where our expertise and skills are. This means that in 'directing' the research, we should be able to mobilize these skills and offer these to stake-holding parties. We should not seek a narrow theme in our research program. Adhering to a larger research objective allows us to play the music the audience is asking for.

5. Summary (in French)

L'aliment, qui est un levier majeur en production animale, influence les performances technico-économiques, les rejets, la qualité des produits, et la santé et le bien-être animal. Recruté en 1994 en tant qu'ingénieur de recherche à l'INRA, mes activités de recherches me permettent de comprendre comment l'alimentation peut être utilisée comme levier d'action pour changer la réponse de l'animal. Il s'agit d'une part de mieux comprendre les mécanismes biologiques sous-jacents et, d'autre part, de proposer des outils qui permettent d'évaluer l'impact de l'alimentation sur les productions animales.

Mes activités de recherches reposent sur deux piliers : un programme de recherche expérimentale et un programme de recherche plus intégratif utilisant une démarche de modélisation. Au début de ma carrière, j'ai essentiellement étudié le métabolisme énergétique de l'animal dans sa globalité afin de déterminer les fonctions physiologiques impliquées dans les dépenses énergétiques. Ainsi, j'ai étudié la répartition de l'énergie en fonction de l'alimentation (quantité et nature des aliments), de l'animal (son développement, son génotype et phénotype) et de son environnement (notamment la température). Ces études ont été réalisées surtout sur le porc et, dans une moindre mesure, sur le poulet de chair, la dinde, le veau et le mini-porc.

Mes travaux concernant la relation entre l'alimentation et la qualité des produits m'ont conduit à m'intéresser surtout aux lipides et acides gras, des nutriments ayant un impact important sur la qualité technologique, nutritionnelle et organoleptique de la viande. Mon objectif était de mieux comprendre et de quantifier les dépôts en acides gras, par exemple, en fonction de l'apport alimentaire en acides gras, et leur répartition entre tissus.

Depuis quelques années, je dirige également un programme expérimental dont le but est d'améliorer l'état de connaissance des besoins en acides aminés du porc, notamment ceux des acides aminés dits « secondaires ». Une meilleure connaissance de ces besoins permet de mieux maîtriser l'apport en matières azotées totales dans l'aliment et des rejets azotés dans l'environnement.

Au cours de ma carrière, j'ai travaillé au développement du modèle InraPorc, modèle qui permet de prédire et d'analyser les performances du porc en croissance en fonction des stratégies alimentaires. J'ai aussi activement contribué à la création du logiciel InraPorc (disponible en 8 langues) publié en 2006. Ce logiciel est destiné aux professionnels de la nutrition porcine et à l'enseignement en nutrition animale. Je suis également auteur ou co-auteur de 58 publications de rang A dans de revues à comité de lecture (+ 4 publications soumises), 6 chapitres d'ouvrages, et une centaine de publications écrites dans le cadre de participation aux congrès.

Une partie de mon temps est consacrée à l'animation au sein de l'unité ainsi qu'à l'extérieur. J'étais directeur adjoint de notre unité de recherche entre 2003 et 2007 et, depuis 2005 je suis responsable de l'équipe « Alimentation et Métabolismes » (une équipe de 22 personnes). Depuis plusieurs années, je co-anime des ateliers dans Réflexives, une structure mise en place par l'INRA pour les binômes thésards-encadrants pour discuter et s'approprier les enjeux, des stratégies, l'éthique et la communication en recherche. Dans le département Phase, j'anime les actions sur la modélisation. Je suis très régulièrement sollicité par des revues à comité de lecture pour évaluer des manuscrits soumis. Depuis 2007, je suis éditeur de la revue *Animal*.