Combining simplicity and complexity
Creating user-applications from mechanistic nutritional models

Jaap van Milgen, Masoomeh Taghipoor, Ludovic Brossard, Jean-Yves Dourmad, Candido Pomar
Outline

- Nutritional modeling of growth:
  - Concepts used in nutritional models
  - Stoichiometry and nutritional complexity
- From a model to a tool:
  - Obtaining relevant and available user-inputs
  - Parameter estimation and model parameterization
- Future directions and conclusions
Empirical modeling of growth

Age (or time) as a driving force for growth

Empirical modeling of growth

Body weight, kg

Cumulative feed intake, kg

Feed intake as a driving force for growth

Concepts used in nutritional growth models

nutrient intake

lipid deposition

ash deposition

protein deposition

water deposition

body weight gain

Compartmental models of metabolism

Fig. 2. Diagrammatic representation of the pig growth model. AA, amino acid; VFA, volatile fatty acid; FA, fatty acid. ○, Energy use in transport; □, energy use in reaction; ■, ATP production in reaction.

How far should we go in further refining our nutritional models?
How far should we go in further refining our nutritional models?

- protein
- lipid
- starch
- sugars
- fiber/VFA

intermediary metabolism

- protein
- lipid
- glycogen
- ATP

heat
Stoichiometry of energy transactions

- Identification of a number of key “pivots” of metabolism:
  - 6 carbon-chain pivots
  - 9 co-factors

- Quantification of the stoichiometry of intermediate pathways:
  - substrate → pivot
  - pivot → pivot
  - pivot → product

- The user constructs complete pathways from intermediate pathways (using a spreadsheet)

Stoichiometry of energy transactions

Synthesis and amino acid production

Gluconeogenesis

mitochondrion intermembrane space

Glycolysis and the TCA cycle

- glucose → NADHc → ATP
- pyruvate → NADHc → ATP
- serine → NADHc → ATP
- NADHm → NH₃
- NADHc → CO₂
- NADHm → CO₂
- acetylCoA → NADHm → CO₂
- oxaloacetate → NADHm → CO₂
- α-ketoglutarate → NADHm → CO₂
- NADHc → ATP
- FADH₂ → ATP

Quantification of methyl groups

INRA SCIENCE & IMPACT

Jaap van Milgen / Combining simplicity and complexity
An example: oxidation of glucose

- Glucose
- NADH<sub>c</sub> → ATP
- Pyruvate
- NADH<sub>m</sub>, FADH<sub>2</sub> → CO<sub>2</sub>
- Acetyl-CoA
- NADH<sub>m</sub> → CO<sub>2</sub>
- Oxaloacetate
- NADH<sub>m</sub>, FADH<sub>2</sub> → CO<sub>2</sub>
- α-Ketoglutarate
- NADH<sub>m</sub> → CO<sub>2</sub>

Enzyme complex

ATP synthase

Mitochondrion intermembrane space

ADP → ATP

NAD<sup>+</sup>/FAD → NADH<sub>m</sub>/FADH<sub>2</sub>

H<sup>+</sup> → H<sup>+</sup>
An example: the production of ATP from glucose

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Balance, \( \sum \)
An example: the production of ATP from glucose

Balance the reactions so that no intermediate metabolites remain

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An example: the production of ATP from glucose

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An example: the production of ATP from glucose
An example: the production of ATP from glucose

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## An example: the production of ATP from glucose

Balance the reactions so that no intermediate metabolites remain

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<th>H⁺</th>
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### An example: the production of ATP from glucose

Balance the reactions so that no intermediate metabolites remain

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</table>
Energy efficiency of glucose → ATP

1 glucose + 6 O₂ → 31 ATP + 6 CO₂

(1 glucose = 2820 kJ/mol = 74.2 kJ/g)

cost = 2820/31 = 91.0 kJ/ATP
Energy efficiency of glucose \( \rightarrow \) ATP

\[
\text{cost} = \frac{2820}{30} = 94.0 \text{ kJ/ATP}
\]
Energy efficiency of glucose → ATP

\[
\text{cost} = \frac{(2820 \times 6/31)}{2} = 272.9 \text{ kJ/ATP}
\]
Energy efficiency of glucose → ATP

14 glucose

lipid

334 ATP

lipid

\[
\text{cost} = \frac{2820 \times 14}{334} = 118.2 \text{ kJ/ATP}
\]
Energy efficiency of glucose $\rightarrow$ ATP

$$\text{glucose} \rightarrow \text{glutamate} \rightarrow \text{ATP}$$

$$\text{cost} = \frac{2820}{29.75} = 94.8 \text{ kJ/ATP}$$
Energy efficiency of glucose → ATP

\[ 1 \text{ glucose} + 6 \text{ O}_2 \rightarrow 31 \text{ ATP} + 6 \text{ CO}_2 \]

direct \quad 91.0 \text{ kJ/ATP} = 100\%

via glycogen (muscle) \quad 97\%

via lactate (gluconeogenesis) \quad 33\%

via lactate (oxidation) \quad 100\%

via lipid \quad 77\%

via glutamate \quad 96\%
Is lipid deposition an energy sink?

protein  lipid  starch  sugars  fiber/VFA

intermediary metabolism

protein  lipid  glycogen  ATP

heat
Is lipid deposition an energy sink?

- Some traits can be measured or estimated easily:
  - Feed and energy intake
  - Protein deposition (using body weight as a proxy)

- What about the rest (and the 1st law of thermodynamics)?
  - Heat production is difficult to estimate
  - Backfat thickness as a proxy?
    - Lipids in total backfat represent less than 20% of total body lipid

- Prediction of lipid deposition is a weakness in most models and errors will accumulate in lipid deposition

Jaap van Milgen / Combining simplicity and complexity
Outline

- Nutritional modeling of growth:
  - Concepts used in nutritional models
  - Stoichiometry and nutritional complexity

- From a model to a tool:
  - Obtaining relevant and available user-inputs
  - Parameter estimation and model parameterization

- Future directions and conclusions
The InraPorc project

1998

- $DE_{CP}$
- $DE_{starch}$
- $DE_{sugars}$
- $DE_{lipids}$
- $DE_{residue}$

PD-free NE

- lipid deposition
- maintenance & physical activity
- cost of protein deposition

- body protein
- body lipid

1998

- animal potential amino acid supply efficiency

2006
Parameters/information hard-coded in the software

- Feed and energy intake: \( f(BW) \)
- Protein and amino acids:
  - Protein deposition: Gompertz function
  - Amino acid utilization (basal endogenous losses, maintenance requirements, efficiency of amino acid utilization, composition of body protein)
- Energy:
  - Maintenance requirement = \( f(\text{fasting heat production, physical activity}) = 100\% \)
  - Energy efficiencies: DE \( \rightarrow \) ME, ME \( \rightarrow \) NE
  - NE cost of protein deposition
Parameters/information to be provided by the user

Phenotypic potential of the animal

- Feed intake:
  - Regulation of voluntary feed intake (e.g., DM, DE, ME, or NE?)
  - 2 parameters of a feed intake function

- Potential protein deposition:
  - 3 parameters of the Gompertz function

- Optional (default values provided):
  - Adjustment of maintenance
  - The animal’s response to an energy restriction
Parameters/information to be provided by the user

Phenotypic potential of the animal

These parameters can be estimated using observed data

Parameters describing energy intake and protein deposition
Parameters/information to be provided by the user

Phenotypic potential of the animal

These parameters can be estimated using observed data
Parameters/information to be provided by the user

Phenotypic potential of the animal

<table>
<thead>
<tr>
<th>Parameters/Information to be Provided by the User</th>
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<tbody>
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<tr>
<td>Mean PD (g/day)</td>
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<tr>
<td>Precocty (wd)</td>
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<tr>
<td>Maintenance</td>
</tr>
</tbody>
</table>

- **Observations**
- **Predictions**

- **Cumulative feed usage (kg)**
- **Body weight (kg)**

- **Dependent variables**
  - Cumulative feed usage
  - Body weight
  - Backfat thickness
  - Lean meat
  - CPU time (seconds)

- **Estimated parameters**
  - Initial BW
  - FI50
  - FI100
  - Mean PD
  - Precocty
  - Maintenance

- **Statistical**
  - R²
  - wRSS
  - RSD
Parameters/information to be provided by the user
Phenotypic potential of the animal

Somewhat “weird” parameters?

Parameter estimation using weighted non-linear regression
Parameterization of non-linear models

- Non-linear models are non-linear with respect to the parameters
- Successful parameter estimation depends on:
  - The combination of data and the chosen model (intrinsic non-linearity)
  - Initial values of parameters
  - Model parameterization (i.e., the way parameters appear in the model)
Model parameterization and parameter estimation

CFI = a \cdot (1 - \exp(-b \text{ time}))
Model parameterization and parameter estimation

CFI = a (1 – exp (-b time))

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>(asymptotic) SE</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>a (kg)</td>
<td>19.68</td>
<td>1.34</td>
<td>6.8%</td>
</tr>
<tr>
<td>b (/min)</td>
<td>0.00584</td>
<td>0.00052</td>
<td>8.9%</td>
</tr>
<tr>
<td>Correlation</td>
<td>-0.996</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Model parameterization and parameter estimation

CFI = a (1 – exp (-b time))

\[ b = \text{fractional intake rate} = \frac{\text{FIR}_0}{a} \]
### Model parameterization and parameter estimation

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<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>(FIR_0) (kg/min)</td>
<td>0.115</td>
<td>0.00253</td>
<td>2.2%</td>
</tr>
<tr>
<td>(b) (/min)</td>
<td>0.00584</td>
<td>0.00052</td>
<td>8.9%</td>
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</table>
Model parameterization and parameter estimation

“Expected-value parameters”

\[
\text{CFI} = a \left( 1 - \exp(-b \text{ time}) \right)
\]

\[
\text{CFI} = \frac{\left( 1 - \left( \frac{\text{CFI}_{100}}{\text{CFI}_{50}} - 1 \right)^{\frac{\text{time}}{50}} \right) \text{CFI}_{50}}{2 - \frac{\text{CFI}_{100}}{\text{CFI}_{50}}}
\]
Model parameterization and parameter estimation

“Expected-value parameters”

\[ CFI = a \left(1 - \exp(-b \text{ time})\right) \]

\[ CFI = \left(1 - \frac{\text{CFI}_{100}}{\text{CFI}_{50}} - 1\right)\frac{\text{time}^{50}}{50}\frac{\text{CFI}_{50}}{2 - \frac{\text{CFI}_{100}}{\text{CFI}_{50}}} \]

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<tr>
<td>CFI_{50} (kg)</td>
<td>4.98</td>
<td>0.053</td>
<td>1.1%</td>
</tr>
<tr>
<td>CFI_{100} (kg)</td>
<td>8.71</td>
<td>0.052</td>
<td>0.6%</td>
</tr>
<tr>
<td>Correlation</td>
<td>0.181</td>
<td></td>
<td></td>
</tr>
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</table>
Advantages of using expected-value parameters

- Non-linearity is almost exclusively determined by the intrinsic non-linearity (i.e., due to the data and model)
- Initial values are easy to obtain
- Rapid convergence
- Low correlations between parameter estimates within an animal, allowing to study parameter correlations among animals
- But it requires a bit of mathematical juggling
Potential PD is described by a Gompertz function
Potential PD is described by a Gompertz function
Potential PD is described by a Gompertz function.

**Diagram:***
- **Protein mass, kg**
- **Protein deposition, g/d**
- **Age, d**

- **Precocity**
- **Mean protein deposition**
- **Initial protein mass**
Potential PD is described by a Gompertz function.
Parameter correlations among animals

Mean protein deposition, g/d vs. NE intake at 50 kg BW, MJ/d

- **Gilt** (pink dots)
- **Barrow** (blue dots)

Correlation coefficient: $r = 0.32$
Parameter correlations among animals

Gilt  Barrow

Mean protein deposition, g/d

Initial protein mass, kg

\( r = 0.23 \)
Parameter correlations among animals

Precocity, 1/d vs. Mean protein deposition, g/d

Gilt
Barrow

r = -0.12

Jaap van Milgen / Combining simplicity and complexity
Outline

- Nutritional modeling of growth:
  - Concepts used in nutritional models
  - Stoichiometry and nutritional complexity
- From a model to a tool:
  - Obtaining relevant and available user-inputs
  - Parameter estimation and model parameterization
- Future directions and conclusions
“All of this implies infinite regress, and understanding how to escape from it is an essential step for understanding life”

Do we need a change in paradigm in nutritional modeling?

... towards a data-driven approach from a concept-driven approach

observe predict
understand control
Conclusions

- We still have a long way to go to understand the full story of nutrition and metabolism.
- Tool development is an essential element in model uptake.
- Model parameterization deserves more attention (from nutritionists and geneticists).
- Monitoring/phenotyping/big data will bring new life and new challenges to nutritional modeling.
The Feed-a-Gene Project has received funding from the European Union’s H2020 Programme under grant agreement no 633531.