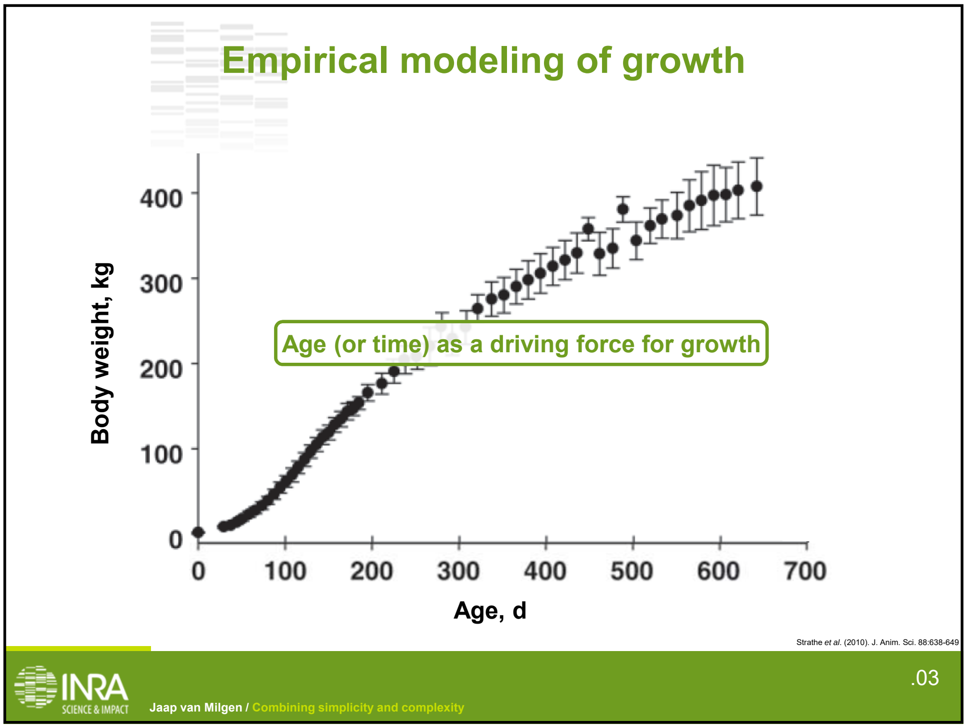
Combining simplicity and complexity

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
Body weight, kg
400
300
200
100
0
0
100
200
300
400
500
600
700
Age, d
Age (or time) as a driving force for growth
Strathe et al. (2010). J. Anim. Sci. 88:638-649
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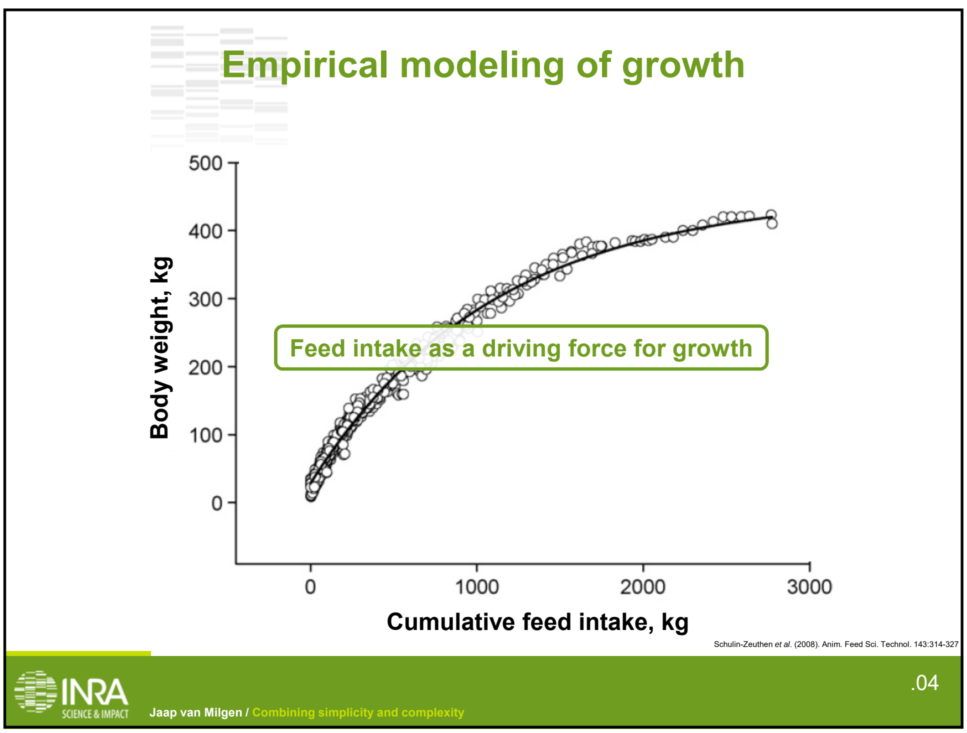
Empirical modeling of growth
Body weight, kg
500
400
300
200
100
0
0
1000
2000
3000
Cumulative feed intake, kg
Feed intake as a driving force for growth
Schulin-Zeuthen et al. (2008). Anim. Feed Sci. Technol. 143:314-327
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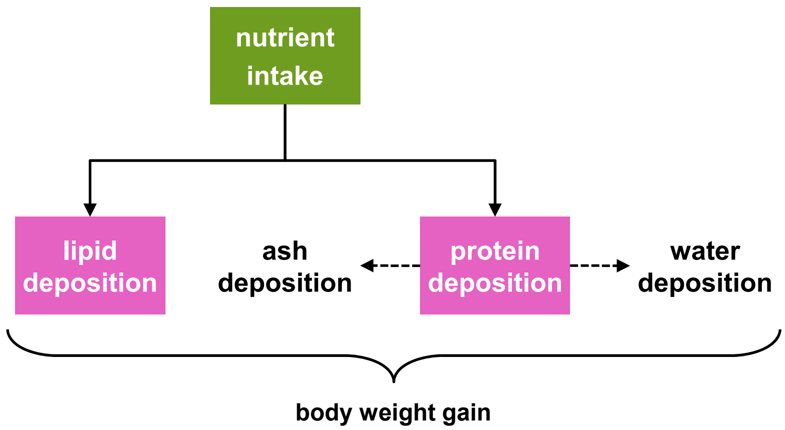
Concepts used in nutritional growth models



Whittemore and Fawcett (1974). Anim. Prod. 19:221-231

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Compartmental models of metabolism

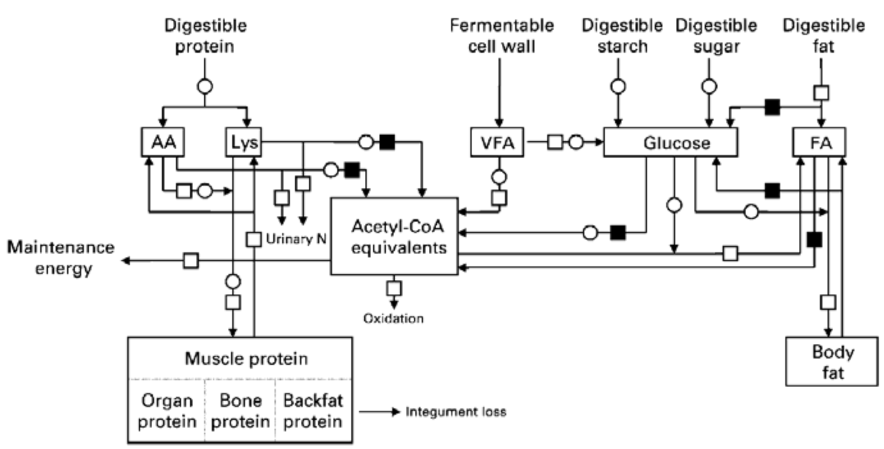

Fig. 2. Diagrammatic representation of the pig growth model. AA, amino acid; VFA, volatile fatty acid; FA, fatty acid. ○, Energy use in transport; □, energy use in reaction; ■, ATP production in reaction.

Halas *et al.* (2004). Br. J. Nutr. 92:707-723

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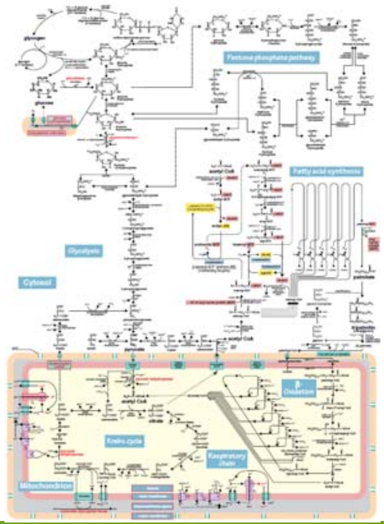
How far should we go in further refining our nutritional models?



Salway (2017). Metabolism at a glance, 4th edition. Wiley Blackwell

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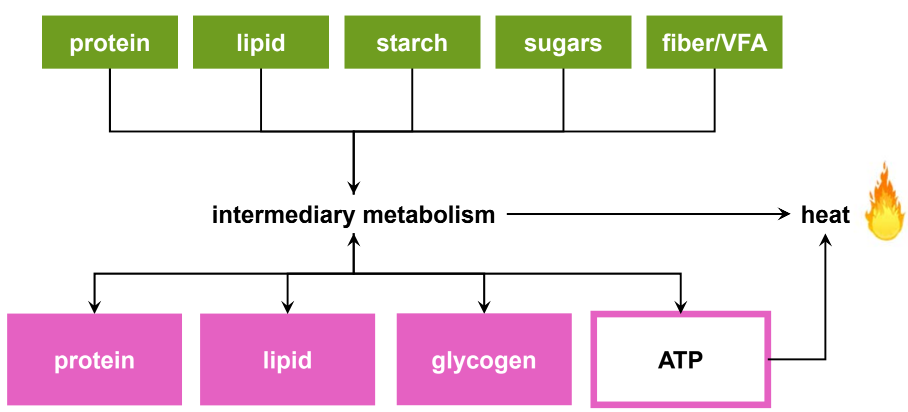
How far should we go in further refining our nutritional models?



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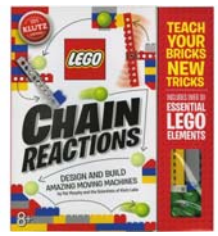
Stoichiometry of energy transactions

- 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)



van Milgen (2002). J. Nutr. 132:3195-320

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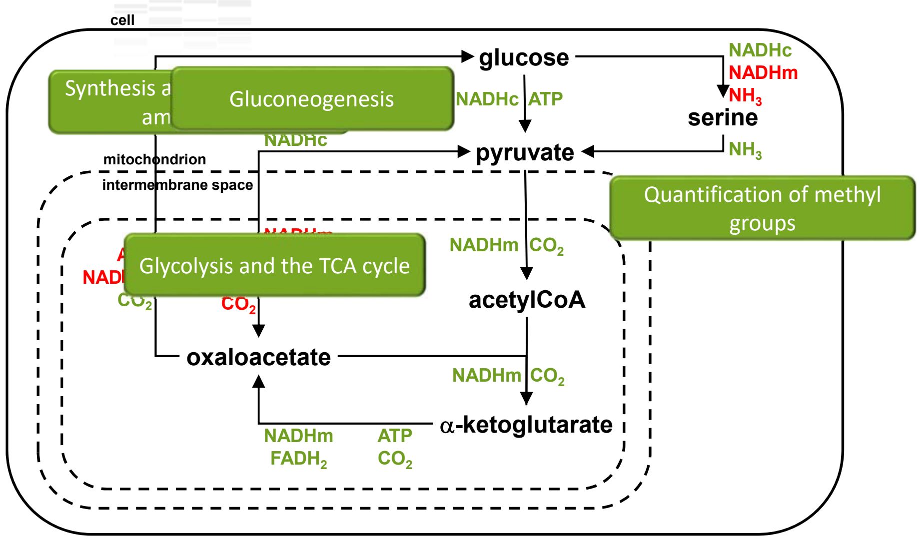
Stoichiometry of energy transactions



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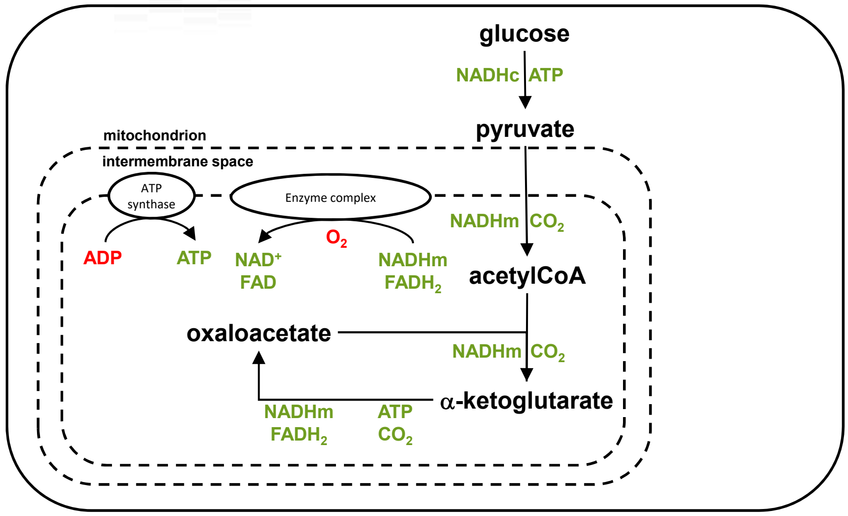
An example: oxidation of glucose



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An example: the production of ATP from glucose

Select the intermediate pathways

Reaction		GLC	PYR	ACA	OAA	αKG	SER	O_2	CO_2	NADHc	NADHm	$FADH_2$	NADPH	NH_3	H^+	ATP
GLC → PYR	x1	-1	2	0	0	0	0	0	0	2	0	0	0	0	0	2
PYR → ACA	x1	0	-1	1	0	0	0	0	1	0	1	0	0	0	0	0
OAA+ACA → αKG	x1	0	0	-1	-1	1	0	0	1	0	1	0	0	0	0	0
αKG → OAA	x1	0	0	0	1	-1	0	0	1	0	2	1	0	0	-1	1
NADHc ↔ NADHm	x1	0	0	0	0	0	0	0	0	-1	1	0	0	0	-1	0
NADHm → H^+	x1	0	0	0	0	0	0	-0.5	0	0	-1	0	0	0	10	0
$FADH_2$ → H^+	x1	0	0	0	0	0	0	-0.5	0	0	0	-1	0	0	6	0
H^+ → ATP	x1	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0.25
Balance, ∑																

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An example: the production of ATP from glucose

Balance the reactions so that no intermediate metabolites remain

Reaction		GLC	PYR	ACA	OAA	αKG	SER	O_2	CO_2	NADHc	NADHm	$FADH_2$	NADPH	NH_3	H^+	ATP
GLC → PYR	x1	-1	2	0	0	0	0	0	0	2	0	0	0	0	0	2
PYR → ACA																
OAA+ACA → αKG																
αKG → OAA																
NADHc ↔ NADHm																
NADHm → H^+																
$FADH_2$ → H^+																
H^+ → ATP																
Balance, ∑		-1	2	0	0	0	0	0	0	2	0	0	0	0	0	0

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An example: the production of ATP from glucose

Balance the reactions so that no intermediate metabolites remain

Reaction		GLC	PYR	ACA	OAA	αKG	SER	O_2	CO_2	NADHc	NADHm	$FADH_2$	NADPH	NH_3	H^+	ATP
GLC → PYR	x1	-1	2	0	0	0	0	0	0	2	0	0	0	0	0	2
PYR → ACA	x2	0	-2	2	0	0	0	0	2	0	2	0	0	0	0	0
OAA+ACA → αKG																
αKG → OAA																
NADHc ↔ NADHm																
NADHm → H^+																
$FADH_2$ → H^+																
H^+ → ATP																
Balance, ∑		-1	0	2	0	0	0	0	2	2	2	0	0	0	0	2

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An example: the production of ATP from glucose

Balance the reactions so that no intermediate metabolites remain

Reaction		GLC	PYR	ACA	OAA	αKG	SER	O_2	CO_2	NADHc	NADHm	$FADH_2$	NADPH	NH_3	H^+	ATP
GLC → PYR	x1	-1	2	0	0	0	0	0	0	2	0	0	0	0	0	2
PYR → ACA	x2	0	-2	2	0	0	0	0	2	0	2	0	0	0	0	0
OAA+ACA → αKG	x2	0	0	-2	-2	2	0	0	2	0	2	0	0	0	0	0
αKG → OAA																
NADHc ↔ NADHm																
NADHm → H^+																
$FADH_2$ → H^+																
H^+ → ATP																
Balance, ∑		-1	0	0	-2	2	0	0	4	2	4	0	0	0	0	2

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An example: the production of ATP from glucose

Balance the reactions so that no intermediate metabolites remain

Reaction		GLC	PYR	ACA	OAA	αKG	SER	O_2	CO_2	NADHc	NADHm	$FADH_2$	NADPH	NH_3	H^+	ATP
GLC → PYR	x1	-1	2	0	0	0	0	0	0	2	0	0	0	0	0	2
PYR → ACA	x2	0	-2	2	0	0	0	0	2	0	2	0	0	0	0	0
OAA+ACA → αKG	x2	0	0	-2	-2	2	0	0	2	0	2	0	0	0	0	0
αKG → OAA	x2	0	0	0	2	-2	0	0	2	0	4	2	0	0	-2	2
NADHc ↔ NADHm																
NADHm → H^+																
$FADH_2$ → H^+																
H^+ → ATP																
Balance, ∑		-1	0	0	0	0	0	0	6	2	8	2	0	0	-2	4

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An example: the production of ATP from glucose

Balance the reactions so that no intermediate metabolites remain

Reaction		GLC	PYR	ACA	OAA	αKG	SER	O_2	CO_2	NADHc	NADHm	$FADH_2$	NADPH	NH_3	H^+	ATP
GLC → PYR	x1	-1	2	0	0	0	0	0	0	2	0	0	0	0	0	2
PYR → ACA	x2	0	-2	2	0	0	0	0	2	0	2	0	0	0	0	0
OAA+ACA → αKG	x2	0	0	-2	-2	2	0	0	2	0	2	0	0	0	0	0
αKG → OAA	x2	0	0	0	2	-2	0	0	2	0	4	2	0	0	-2	2
NADHc ↔ NADHm	x2	0	0	0	0	0	0	0	0	-2	2	0	0	0	-2	0
NADHm → H^+	x10	0	0	0	0	0	0	-5	0	0	-10	0	0	0	100	0
$FADH_2$ → H^+	x2	0	0	0	0	0	0	-1	0	0	0	-2	0	0	12	0
H^+ → ATP																
Balance, ∑		-1	0	0	0	0	0	-6	6	0	0	0	0	0	108	4

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An example: the production of ATP from glucose

Balance the reactions so that no intermediate metabolites remain

Reaction		GLC	PYR	ACA	OAA	αKG	SER	O_2	CO_2	NADHc	NADHm	$FADH_2$	NADPH	NH_3	H^+	ATP
GLC → PYR	x1	-1	2	0	0	0	0	0	0	2	0	0	0	0	0	2
PYR → ACA	x2	0	-2	2	0	0	0	0	2	0	2	0	0	0	0	0
OAA+ACA → αKG	x2	0	0	-2	-2	2	0	0	2	0	2	0	0	0	0	0
αKG → OAA	x2	0	0	0	2	-2	0	0	2	0	4	2	0	0	-2	2
NADHc ↔ NADHm	x2	0	0	0	0	0	0	0	0	-2	2	0	0	0	-2	0
NADHm → H^+	x10	0	0	0	0	0	0	-5	0	0	-10	0	0	0	100	0
$FADH_2$ → H^+	x2	0	0	0	0	0	0	-1	0	0	0	-2	0	0	12	0
H^+ → ATP	x108	0	0	0	0	0	0	0	0	0	0	0	0	0	-108	27
Balance, ∑		-1	0	0	0	0	0	-6	6	0	0	0	0	0	0	31

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Energy efficiency of glucose → ATP

$$1 \text{ glucose} + 6\ O_2 \rightarrow 31 \text{ ATP} + 6\ CO_2$$

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

cost = 2820/31 = 91.0 kJ/ATP

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Energy efficiency of glucose → ATP

cost = 2820/30 = 94.0 kJ/ATP

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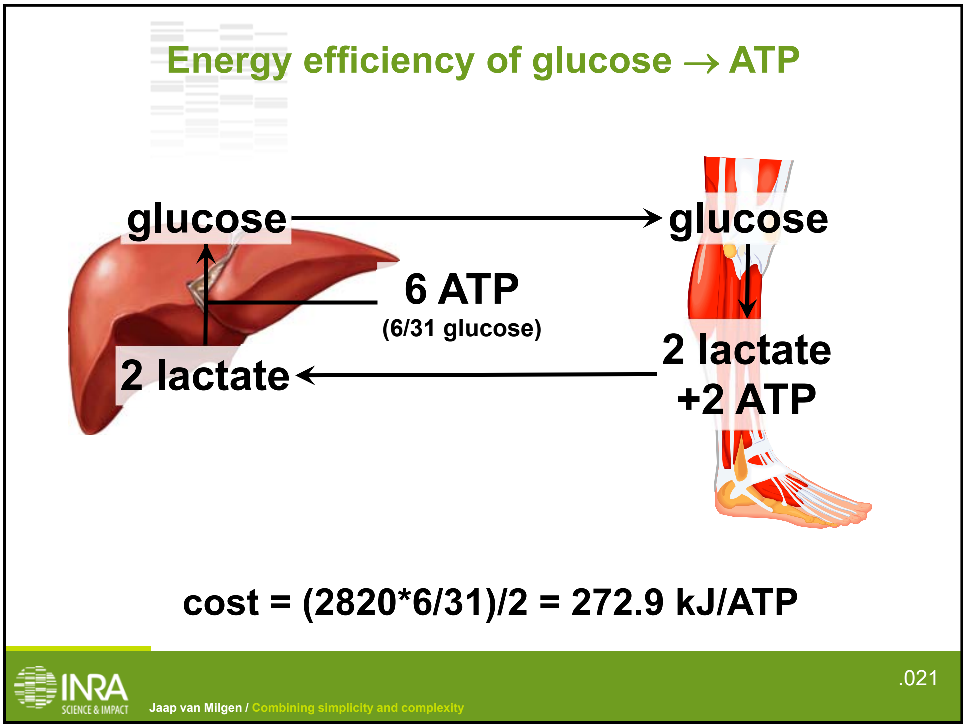
Energy efficiency of glucose → ATP
glucose
glucose
6 ATP
(6/31 glucose)
2 lactate
2 lactate
+2 ATP
cost = (2820*6/31)/2 = 272.9 kJ/ATP
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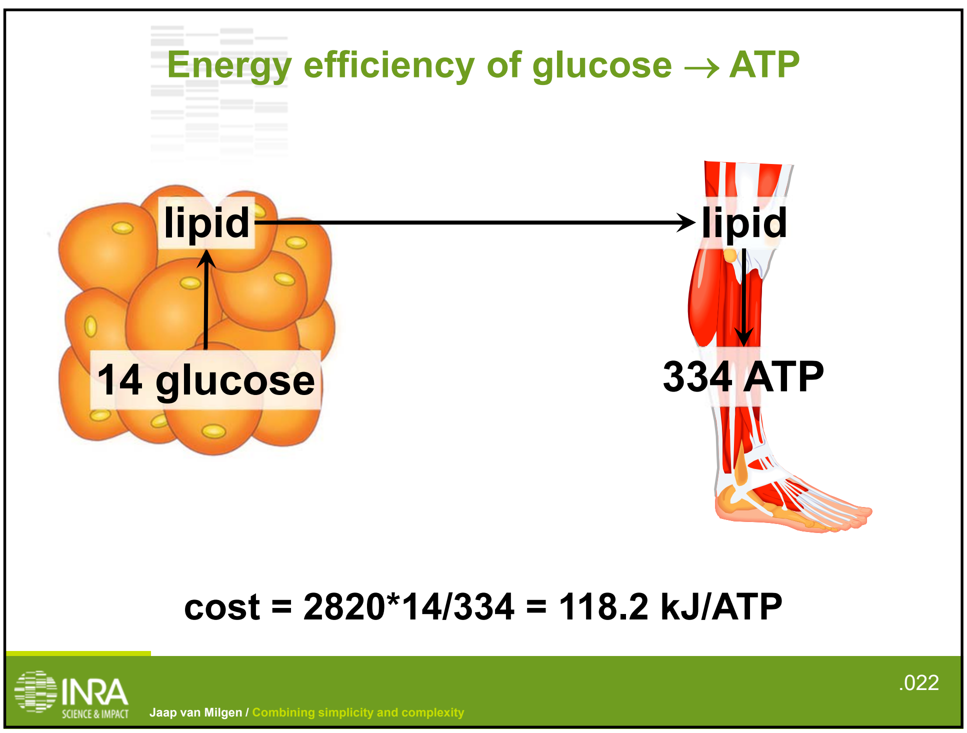
Energy efficiency of glucose → ATP
lipid
lipid
14 glucose
334 ATP
cost = 2820*14/334 = 118.2 kJ/ATP
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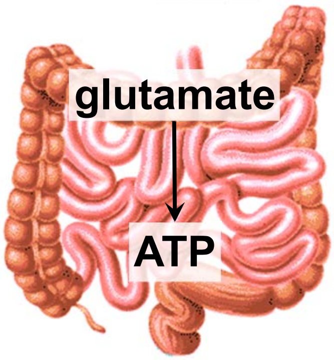
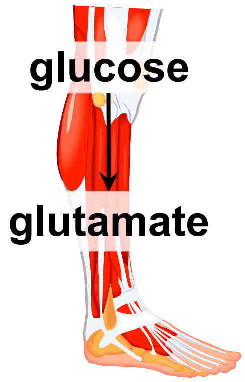
Energy efficiency of glucose → ATP





glucose → glutamate → ATP

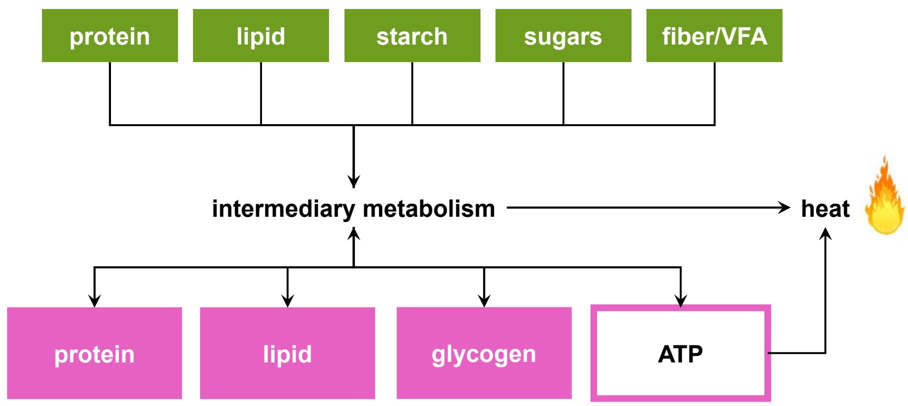
cost = 2820/(29.75) = 94.8 kJ/ATP

Energy efficiency of glucose → ATP

1 glucose + 6 O_2 → 31 ATP + 6 CO_2

direct	91.0 kJ/ATP = 100%
via glycogen (muscle)	97%
via lactate (gluconeogenesis)	33%
via lactate (oxidation)	100%
via lipid	77%
via glutamate	96%

Is lipid deposition an energy sink?



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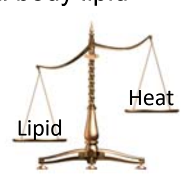
Is lipid deposition an energy sink?

- 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



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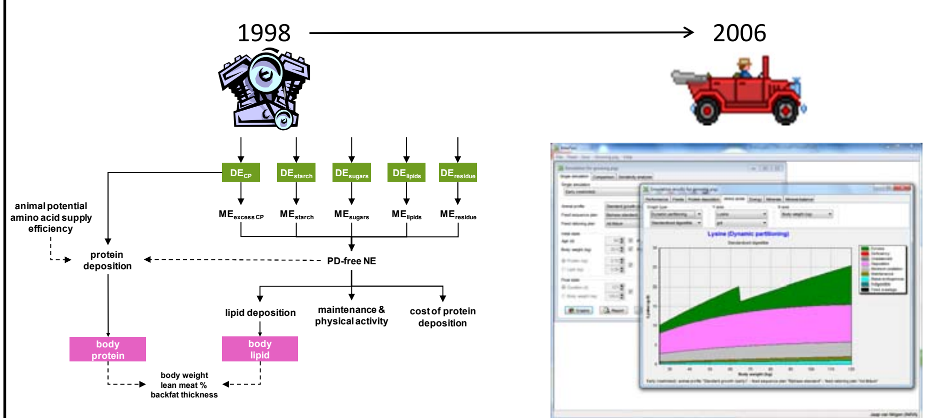
Outline

- 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



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(fasting heat production, physical activity) = 100%
  - Energy efficiencies: DE $\rightarrow$ ME, ME $\rightarrow$ NE
  - NE cost of protein deposition

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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

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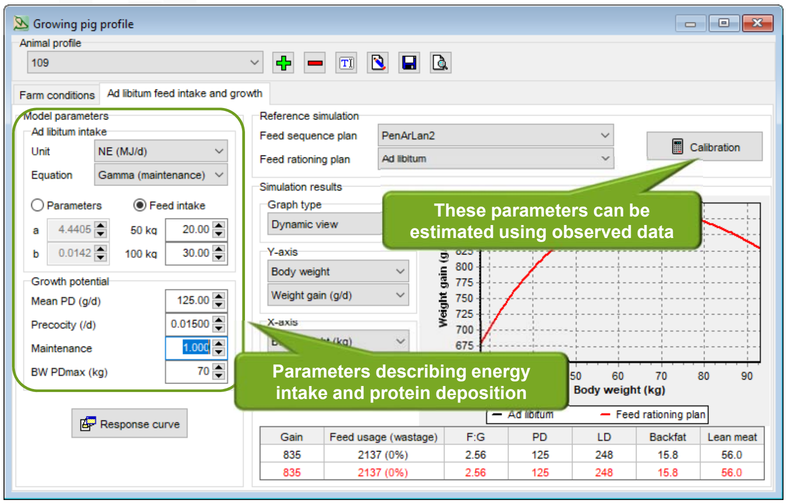
Parameters/information to be provided by the user
Phenotypic potential of the animal



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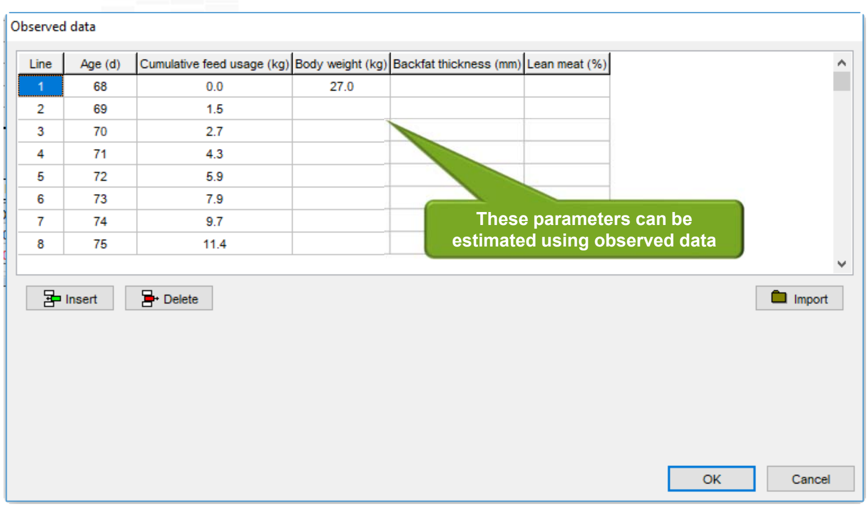
Parameters/information to be provided by the user
Phenotypic potential of the animal



Line	Age (d)	Cumulative feed usage (kg)	Body weight (kg)	Backfat thickness (mm)	Lean meat (%)
1	68	0.0	27.0		
2	69	1.5			
3	70	2.7			
4	71	4.3			
5	72	5.9			
6	73	7.9			
7	74	9.7			
8	75	11.4			

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Parameters/information to be provided by the user
Phenotypic potential of the animal

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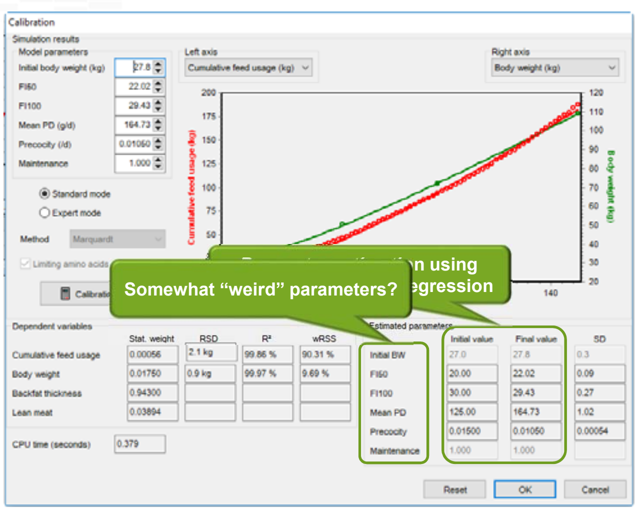
Parameters/information to be provided by the user
Phenotypic potential of the animal



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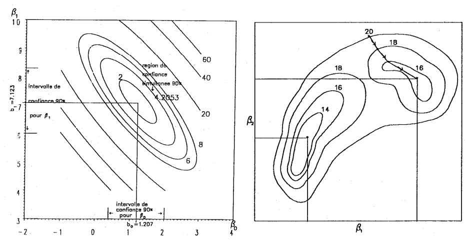
Parameterization of non-linear models

- 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)



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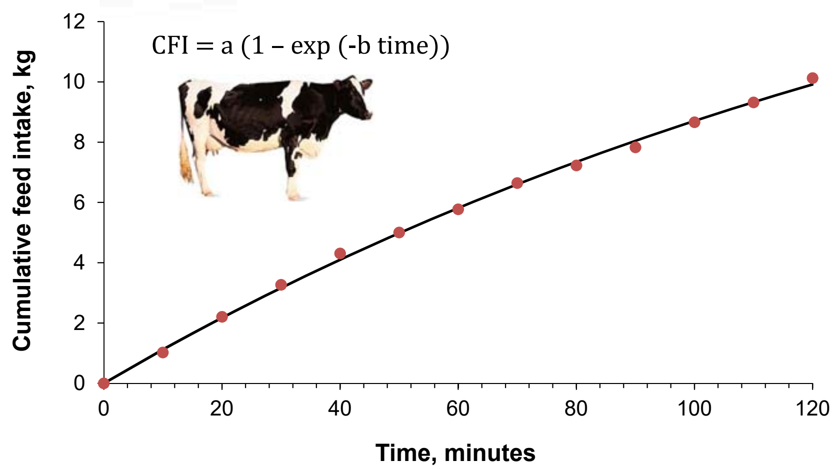
Model parameterization and parameter estimation



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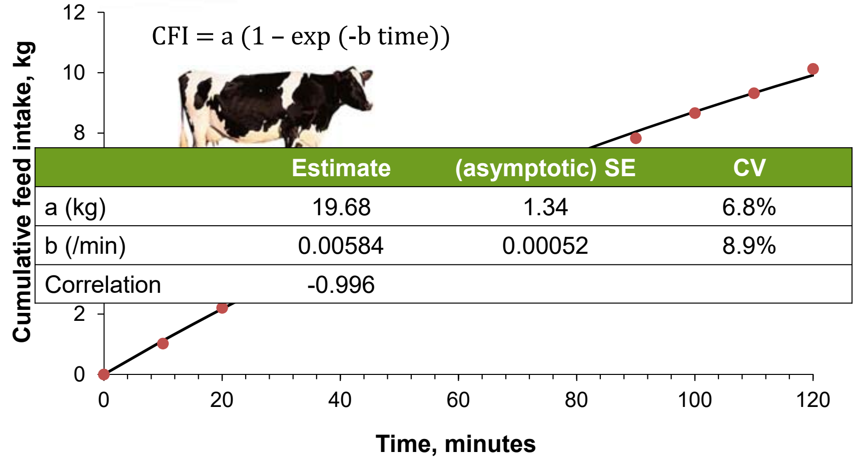
Model parameterization and parameter estimation



	Estimate	(asymptotic) SE	CV
a (kg)	19.68	1.34	6.8%
b (/min)	0.00584	0.00052	8.9%
Correlation	-0.996		

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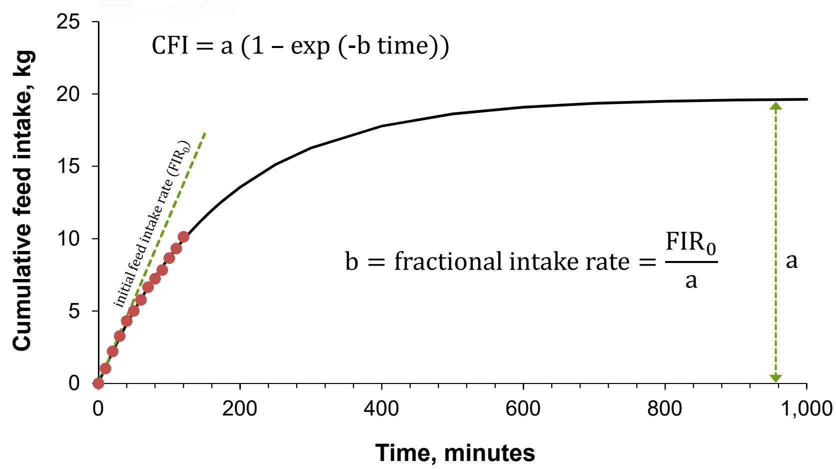
Model parameterization and parameter estimation



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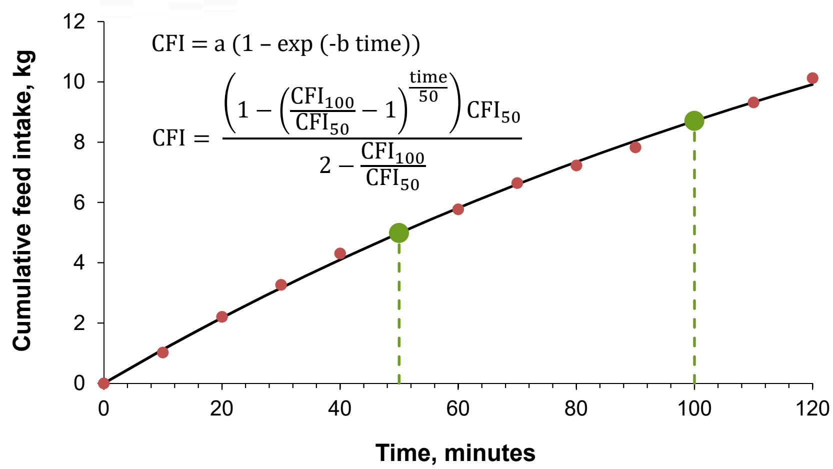
Model parameterization and parameter estimation

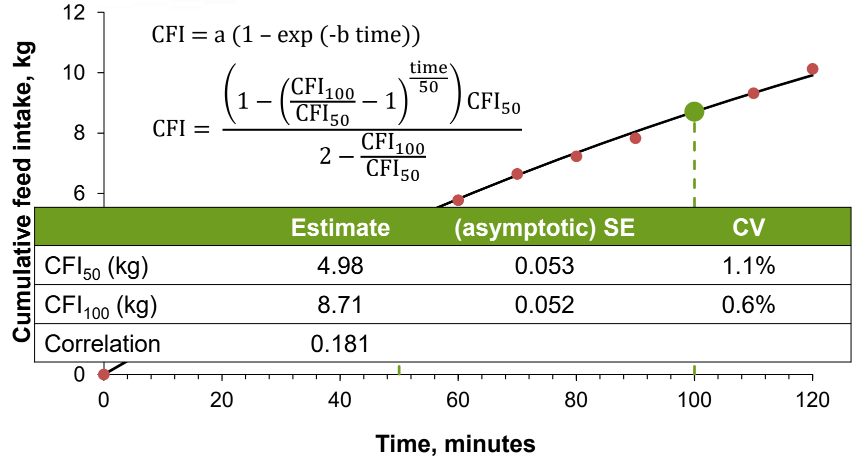
	Estimate	(asymptotic) SE	CV
a (kg)	19.68	1.34	6.8%
b (/min)	0.00584	0.00052	8.9%
Correlation	-0.996		

	Estimate	(asymptotic) SE	CV
FIR_0 (kg/min)	0.115	0.00253	2.2%
b (/min)	0.00584	0.00052	8.9%
Correlation	-0.967		

Model parameterization and parameter estimation “Expected-value parameters”



Model parameterization and parameter estimation “Expected-value parameters”



$$CFI = a\,(1 - \exp(-b\ time))$$

$$CFI = \frac{\left(1 - \left(\frac{CFI_{100}}{CFI_{50}} - 1\right)^{\frac{time}{50}}\right) CFI_{50}}{2 - \frac{CFI_{100}}{CFI_{50}}}$$

	Estimate	(asymptotic) SE	CV
CFI_{50} (kg)	4.98	0.053	1.1%
CFI_{100} (kg)	8.71	0.052	0.6%
Correlation	0.181		

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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

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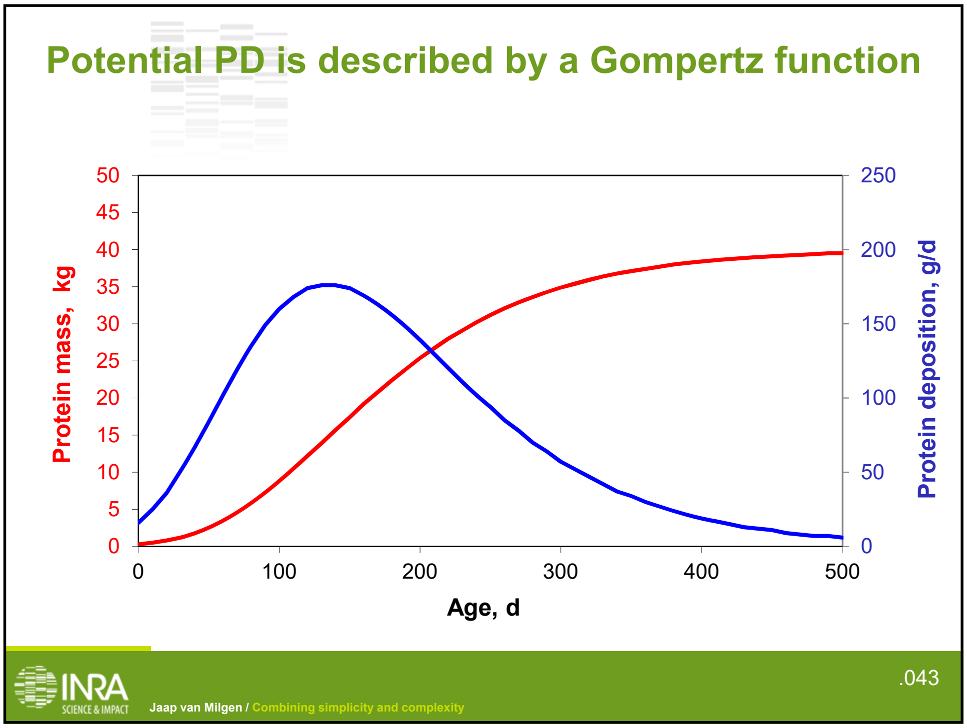
Potential PD is described by a Gompertz function
50
45
40
35
30
25
20
15
10
5
0
Protein mass, kg
250
200
150
100
50
0
Protein deposition, g/d
0
100
200
300
400
500
Age, d
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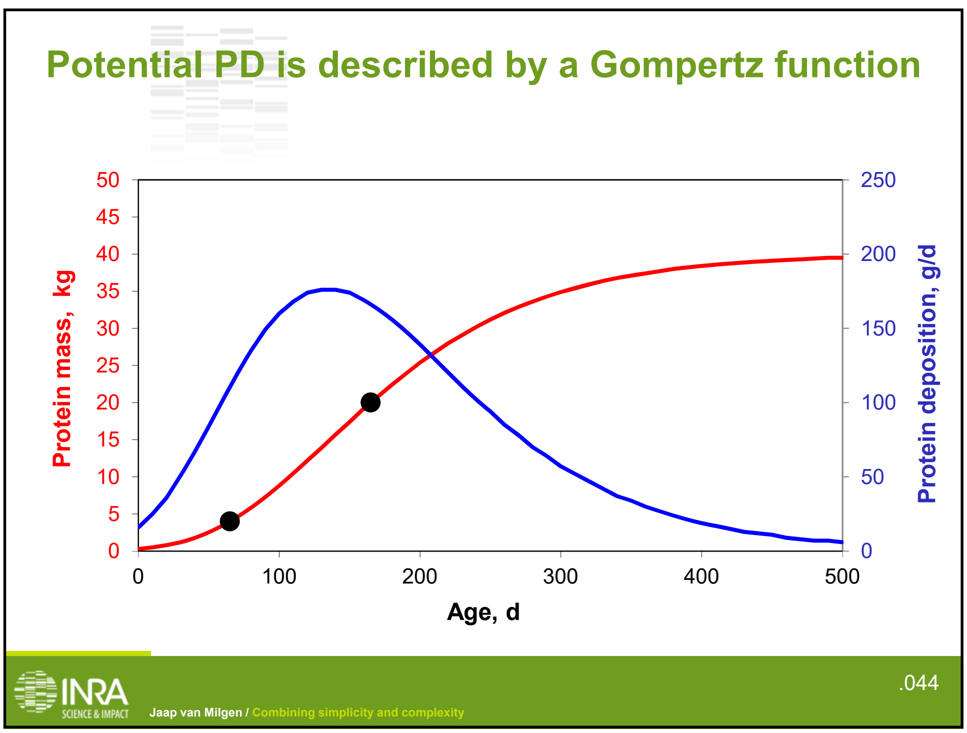
.043


Potential PD is described by a Gompertz function
50
45
40
35
30
25
20
15
10
5
0
Protein mass, kg
250
200
150
100
50
0
Protein deposition, g/d
0
100
200
300
400
500
Age, d
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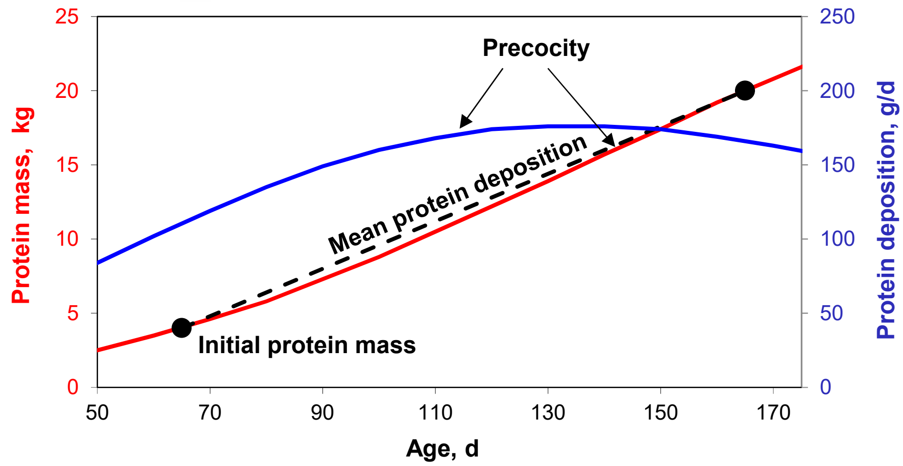
Potential PD is described by a Gompertz function



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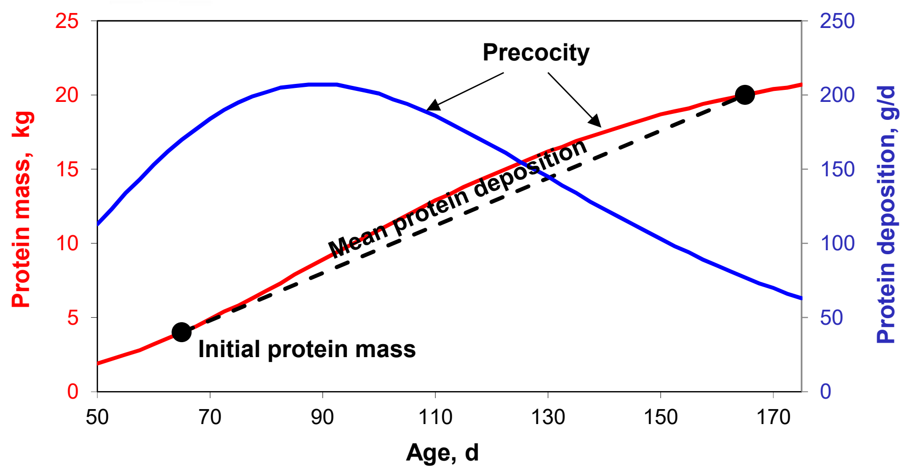
Potential PD is described by a Gompertz function



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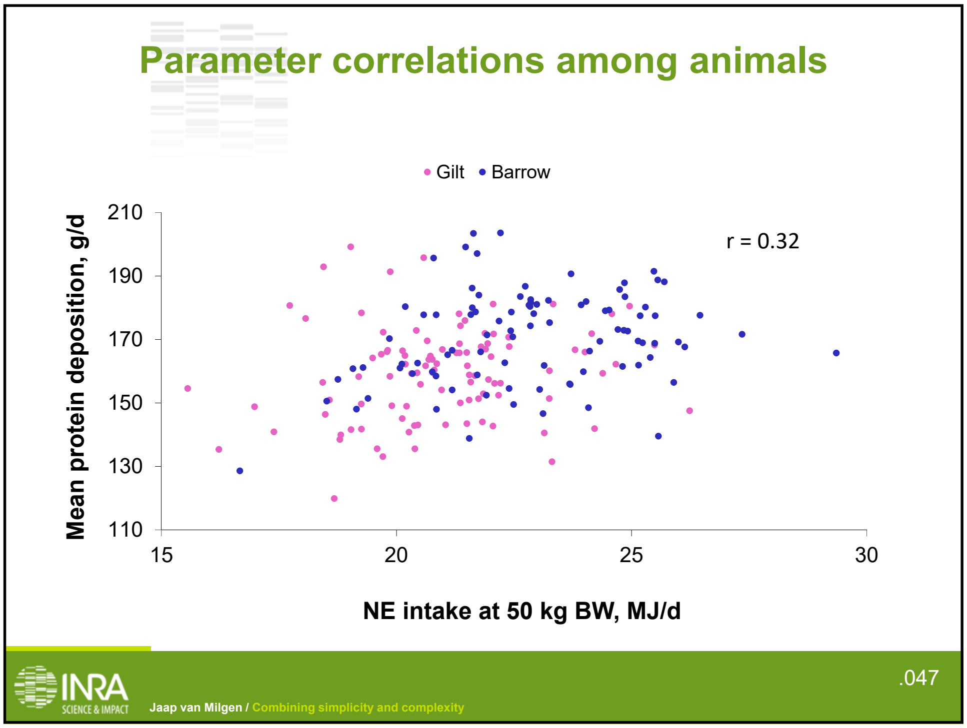
Parameter correlations among animals
Gilt
Barrow
r = 0.32
Mean protein deposition, g/d
210
190
170
150
130
110
15
20
25
30
NE intake at 50 kg BW, MJ/d
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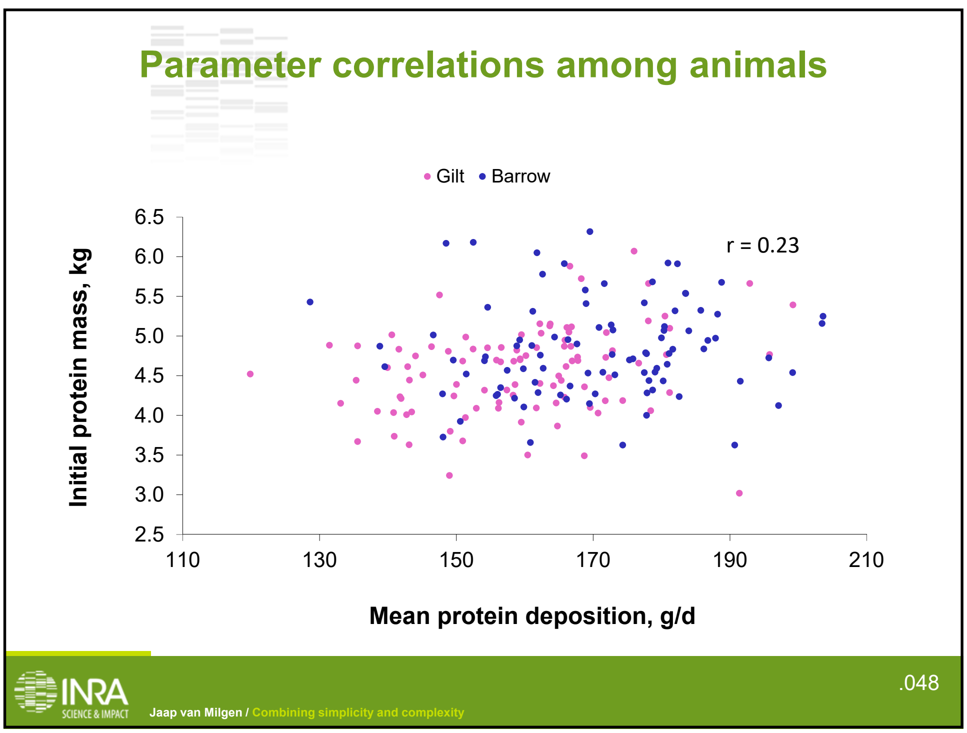
Parameter correlations among animals
Gilt
Barrow
r = 0.23
Initial protein mass, kg
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
110
130
150
170
190
210
Mean protein deposition, g/d
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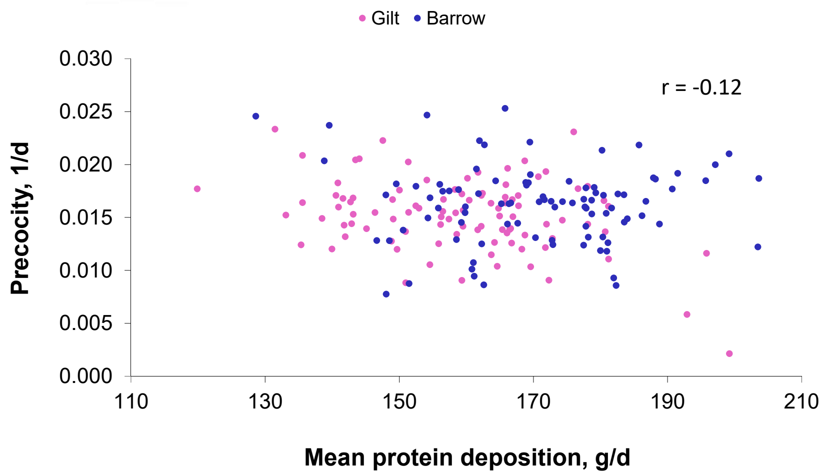
Parameter correlations among animals



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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

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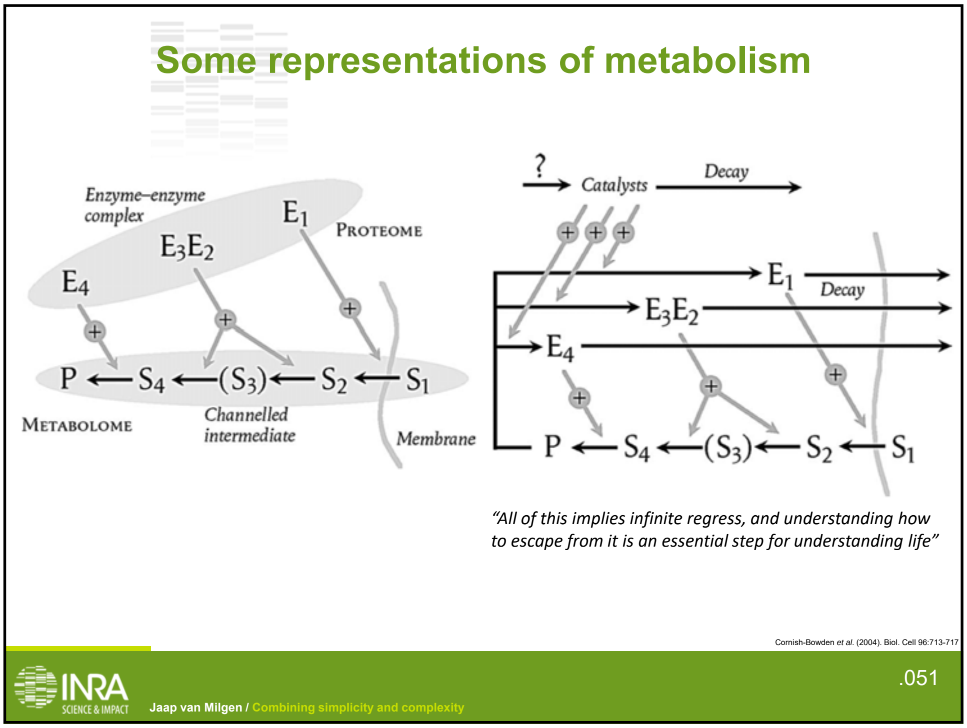
Some representations of metabolism
Enzyme–enzyme complex
E1
E3E2
E4
Proteome
P ← S4 ← (S3) ← S2 ← S1
Metabolome
Channelled intermediate
Membrane
? → Catalysts → Decay
Decay
"All of this implies infinite regress, and understanding how to escape from it is an essential step for understanding life"
Cornish-Bowden et al. (2004). Biol. Cell 96:713-717
.051
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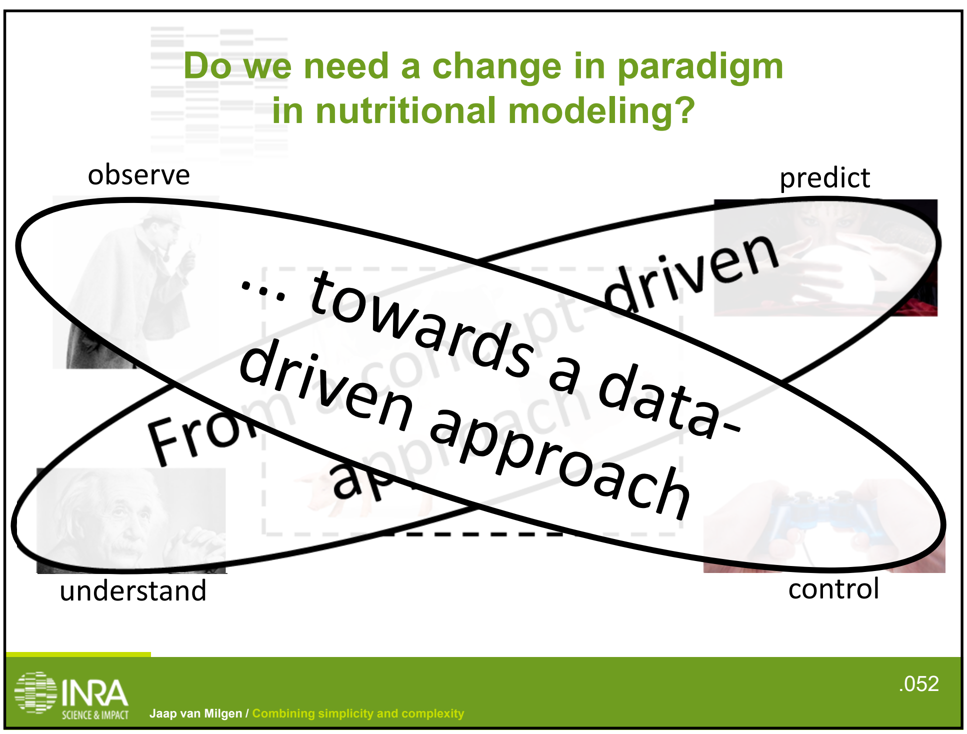
Do we need a change in paradigm in nutritional modeling?
observe
predict
understand
control
… towards a data-driven approach
.052
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Conclusions

- 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

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