NATIONAL ANIMAL NUTRITION PROGRAM

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Introduction to Modeling

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Learning Objectives

• Explain the motivation for modeling
• Contrast different types of models
• Outline the steps of constructing and evaluating a model
• Example compartmental model
What is a Model

- Merriam-Webster Dictionary:
  - structural design, e.g. a home on the model of an old farmhouse
  - a usually miniature representation of something; also : a pattern of something to be made
  - an example for imitation or emulation
  - a person or thing that serves as a pattern for an artist; especially : one who poses for an artist
  - an organism whose appearance a mimic imitates
  - one who is employed to display clothes or other merchandise
  - a type or design of clothing or a product (as a car)
  - a description or analogy used to help visualize something (as an atom) that cannot be directly observed
  - a system of postulates, data, and inferences presented as a mathematical description of an entity or state of affairs; also : a computer simulation based on such a system, e.g. climate models
Visual Model of Muscle Glycogen Metabolism

Glycogen

A pool (g, L, mol)

Glucose

A flux (g/min)

Glucose

External input or output (g/d, g/L)

Activation or stimulation (??)

Inhibition (??)
Mathematical Model of Energy Retention

Old and Garrett, 1987
“When you cannot express [something] in numbers, your knowledge is of a meager and unsatisfactory kind . . . you have scarcely, in your thoughts, progressed the level of science.”

Lord Kelvin

http://www.sil.si.edu/digitalcollections/hst/scientific-identity/CF/by_scientist_display_results.cfm?scientist=kelvin
The Scientific Process

Reductionism

Integration

Region

Farm

Herd

Animal

Tissue

Cell

Subcell

Question

Knowledge vs Reality

Adequate

Application

Inadequate

Hypothesis

Experimental Test

Knowledge Integration
The Model Development Process

1. What is the question?
2. Define goals and objectives
3. Review the literature: concepts and data
4. Develop a visual representation
5. Construct an appropriate mathematical representation
6. Transform the mathematics to computer code
7. Select or derive model parameters
8. Evaluate and assess vs observed data and the objectives
Model Development Loop

- ALL MODELS ARE WRONG, but some are useful
  - Doesn’t have to be perfect

- Development cycle
  - Construct
  - Test
  - Improve
  - Test
  - Improve
  - Test
  - ...

Reality

Model
Objectives and goals are critical

- **Objective:** predict body weight change over time with an error less than 20%

- **Model Scope**
  - Subatomic particle behavior?
  - Cellular function in all the cells?
  - Tissue responses in all the tissues?
  - \((\text{MEI} - \text{NEm}) / \text{Eff}_{\text{ME to NE}}\)?
  - If simple fails, perhaps add complexity
"entities must not be multiplied beyond necessity" which is also expressed as *lex parsimoniae* in Latin which translates to the “law of parsimony” or the “law of economy”

William of Ockham, 14th century

‘A model like a map cannot show everything. If it did it would not be a model but a duplicate. Thus the classic definition of art as the *purgation of superfluities* also applies to models. And the model-maker’s problem is to distinguish between the superfluous and the essential.

Model classification

Dynamic OR Static
Deterministic OR Stochastic
Mechanistic OR Empirical

Simple Classification
Works OR Doesn’t Work

Static

Does not represent the system through time
• Steady state representation, e.g. digestion coefficient

\[ Feces = Intake - (a \times Intake + b) \]

• There is no element of time represented in the above equation
• Does not represent the system as it changes from one state to another
• Should accurately represent the system in steady state before and after the change assuming the equation is appropriate
Time is an element in the equation or model

- Generally capable of non-steady state predictions, e.g. drug or metabolite clearance from blood

\[ \text{Metabolite}(t) = \text{Metabolite}_{\text{Initial}} \times e^{(-k \times t)} \]

- Time is explicitly defined in the above model of metabolite clearance

- The model predicts the amount of the metabolite present in the blood pool at any point in time given an initial pool size (\(\text{Metabolite}_{\text{Initial}}\)) and a rate of metabolite clearance from blood (\(k\)) per unit of time.

\[ \text{Feces} = \text{Intake} - \left( a \times \frac{\text{ADF}}{\text{NDF} \times \text{Mom's Income}} \right) \times \text{Intake} + b \]

- IS NOT A DYNAMIC MODEL!
The static model predicts an instantaneous change in state given a change in inputs
Deterministic

- Assumes a single true answer and deviations reflect measurement error or some other undefined stochastic process.
  - Model predicts the true answer.
  - Inputs, parameters, and observed responses all deterministic

\[ Feces = Intake - \left( a \times Intake + b \right) \]

- Many biological models are deterministic
  - Standard curves
  - Most clearance and digestion models
  - Requirement models
  - Growth models

- Easier to parameterize
Stochastic

- Explicitly accommodates variance in inputs, outputs, parameters
- Provides a distribution of answers

\[ \text{Metabolite}(t) \pm \sigma_{\text{Prediction}} = \left[ \text{Metabolite}_{\text{Init}} \pm \sigma_{\text{MeasureInit}} \right] \times e^{\left( [-k \pm \sigma_k] \times [t \pm \sigma_t] \right)} + \sigma_{\text{MeasureConc}} \]

- \( \sigma_{\text{MeasureInit}}, \sigma_k, \sigma_t, \) and \( \sigma_{\text{MeasureConc}} \) represent variance in initial concentration, \( k \), time, and the metabolite concentration, respectively.
- \( \sigma \) generally \( \sim \text{N}(0, \sigma) \) and randomly sampled
- Predicted \( \text{Metabolite}(t) \) should match the observed population if error model matches reality
- More difficult to parameterize and computationally expensive
  - \( K \) plus all \( \sigma \)
Deterministic vs Stochastic

Line - Deterministic
Symbols – Stochastic
~N(γ, 7.5)
Empirical

- Relates inputs and outputs at the same level of aggregation
  - many feed evaluation models
  - $\text{DMI} = 3(\text{Milk}) + 0.02(\text{BW}^{0.75})$

- Advantages
  - simple and quick
  - less detail

- Disadvantages
  - limited ability for extrapolation
  - Doesn’t utilize underlying system knowledge to improve precision
Mechanistic

- Explicitly represents aspects of the underlying system structure
  - Molly cow model from UCDavis

- Advantages
  - May result in more precise prediction: generally assumes a more complex structure
  - May be suitable for extrapolation
  - Aids in understanding the system

- Disadvantages
  - Often more parameters and inputs making it harder to parameterize
  - Can be less precise and accurate if improperly formulated or parameterized
  - Takes a lot of time and effort to develop
Empirical

\[ \text{Protein}_{\text{Milk}} = \alpha EI + \beta NI + \chi EI^2 + \delta NI^2 + \varepsilon (EI \times NI) \]

Mechanistic

\[ \text{Protein}_{\text{Milk}} = \frac{\alpha \text{Cells}_{\text{Mammary}} \times \beta \left( \frac{\text{Ribosomes}}{\text{Cell}} \right) \times \chi [P-eIF2] \times \delta [P-4eBP1]}{1 + \frac{k_{\text{ATP}}}{[\text{ATP}]} + \frac{k_{\text{EAA}}}{[\text{EAA}]} + \frac{k_{\text{mRNA}}}{[\text{mRNA}]]} \]

- EI=energy intake, NI=nitrogen intake
- Milk protein output and nutrient intakes are at the same level, i.e. the animal, thus empirical
- Ribosomes, cell signaling proteins, ATP, etc. are lower levels of function than milk protein output and thus mechanistic
Compartmental Models (subtype)

- Metabolism is compartmental in nature
  - Rumen $\rightarrow$ small intestine $\rightarrow$ blood $\rightarrow$ tissue
  - Blood $\rightarrow$ extracellular $\rightarrow$ intracellular $\rightarrow$ protein
  - G6P $\rightarrow$ F6P $\rightarrow$ F1,6BP

- Typically mechanistic representation
  - Serial arrangement of compartments
  - Lower level compartments driving upper levels

- Rate/State formalism
  - Each compartment a state
  - State size = inputs – outputs
  - Integrate over time to solve

$$\text{Protein}_{\text{Milk}} = \frac{\alpha \text{Cells}_{\text{Mammary}} \times \beta \left(\frac{\text{Ribosomes}}{\text{Cell}}\right) \times \chi[P-eIF2] \times \delta[P-4eBPI]}{1 + \frac{k_{\text{ATP}}}{[\text{ATP}]} + \frac{k_{\text{EAA}}}{[\text{EAA}]} + \frac{k_{\text{mRNA}}}{[mRNA]}}$$
Models Used in Animal Nutrition

• NRC Nutrient Requirement Models
  – Static, Deterministic, Empirical (→ mechanistic)

• Particle Passage Models (Pond et al., 1988)
  – Dynamic, Stochastic, Empirical

• Gompertz Growth Model (Winsor, 1932)
  – Dynamic, Deterministic, Empirical

• Oltjen Growth Model (1986)
  – Dynamic, Deterministic, Mechanistic

• Brossard Pig Growth Model (2009)
  – Dynamic, Stochastic, Empirical

• Doeschl-Wilson (2007) Pig Growth Genetics Model
  – Dynamic, Stochastic, Mechanistic?

• CNCPS (v6.5)
  – Static, deterministic
  – Mechanistic (rumen), Empirical (post-absorptive)
Summary

- Modeling is an integral part of the scientific process
- Modeling process should be followed
- Set Goals carefully and adhere to them
- 3 general model classifications
- Classes are a continuum rather than discrete
- Models can reflect a single level of organization or operate across levels
### Compartmental Model Example

**Problem 1 – integration**
- Analytical solution to $Q_{Rum}$
- Numerical solution by Euler’s
- Set up in Excel

**Open Exercise _1 R script 1.R**
- Numerical solution by Runga-Kutta
- No mathematical limit to stacking

\[
\frac{dQ_{Rum}}{dt} = F_{\text{Intake}} - F_{Rum,SI} - F_{Rum,\text{Deg}}
\]

\[
F_{\text{Intake}} = DMI \times C_{\text{Nutrient}}
\]

\[
F_{Rum,SI} = Q_{Rum} \times K_{\text{Passage}}
\]

\[
F_{Rum,\text{Deg}} = Q_{Rum} \times K_{\text{Degradation}}
\]

\[
Q_{Rum} = \int \frac{dQ_{Rum}}{dt} + iQ_{Rum}
\]

\[
F_{SI,Bld} = a \times F_{Rum,SI}
\]

\[
F_{\text{Feces}} = F_{Rum,SI} - F_{SI,Bld}
\]
Model Output – Static DCnut

- **Qrum**
- **Fin**
- **FRumSI**
- **FSIAbs**
- **RDnut**
- **TDnut**
• Hypothesis: High Forage < Low Forage
  – Experimental Objective: measure milk production for HF and LF

\[
\text{Milk}_{ij} = \mu + \beta_i (\text{Trt}_i) + \varepsilon_{ij}
\]

where \( i = 1 \) to \# of Trt and \( j = 1 \) to \# of animals
Trt is coded as a matrix with a column for each Trt
0 if the animal was not on the treatment and 1 if it was

– Can we learn more?

<table>
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<th>Animal</th>
<th>Trt(_1)</th>
<th>Trt(_2)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0</td>
</tr>
<tr>
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</tr>
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