NATIONAL ANIMAL NUTRITION PROGRAM

USDA Funded National Research Support Project

http://nanp-nrsp-9.org

Introduction to Modeling

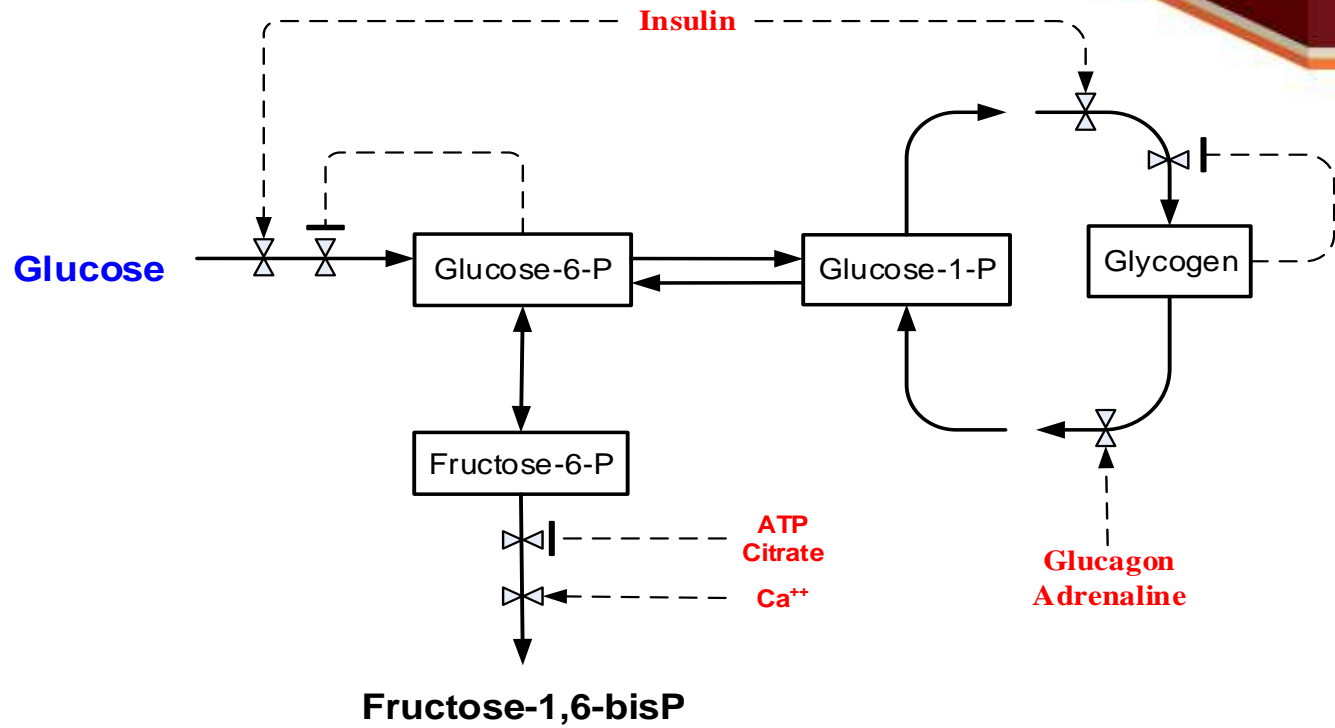Mark D. Hanigan,
Timothy J. Hackman,
Veridiana L. Daley

- Explain the motivation for modeling
- Contrast different types of models
- Outline the steps of constructing and evaluating a model
- Example compartmental 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 model*s*

Visual Model of Muscle Glycogen Metabolism

Insulin

Glucose → Glucose-6-P ⇄ Glucose-1-P — Glycogen

Glucose-6-P ↕ Fructose-6-P

ATP
Citrate

Ca⁺⁺

Glucagon
Adrenaline

Fructose-1,6-bisP

Glycogen	A pool (g, L, mol)

A flux (g/min)

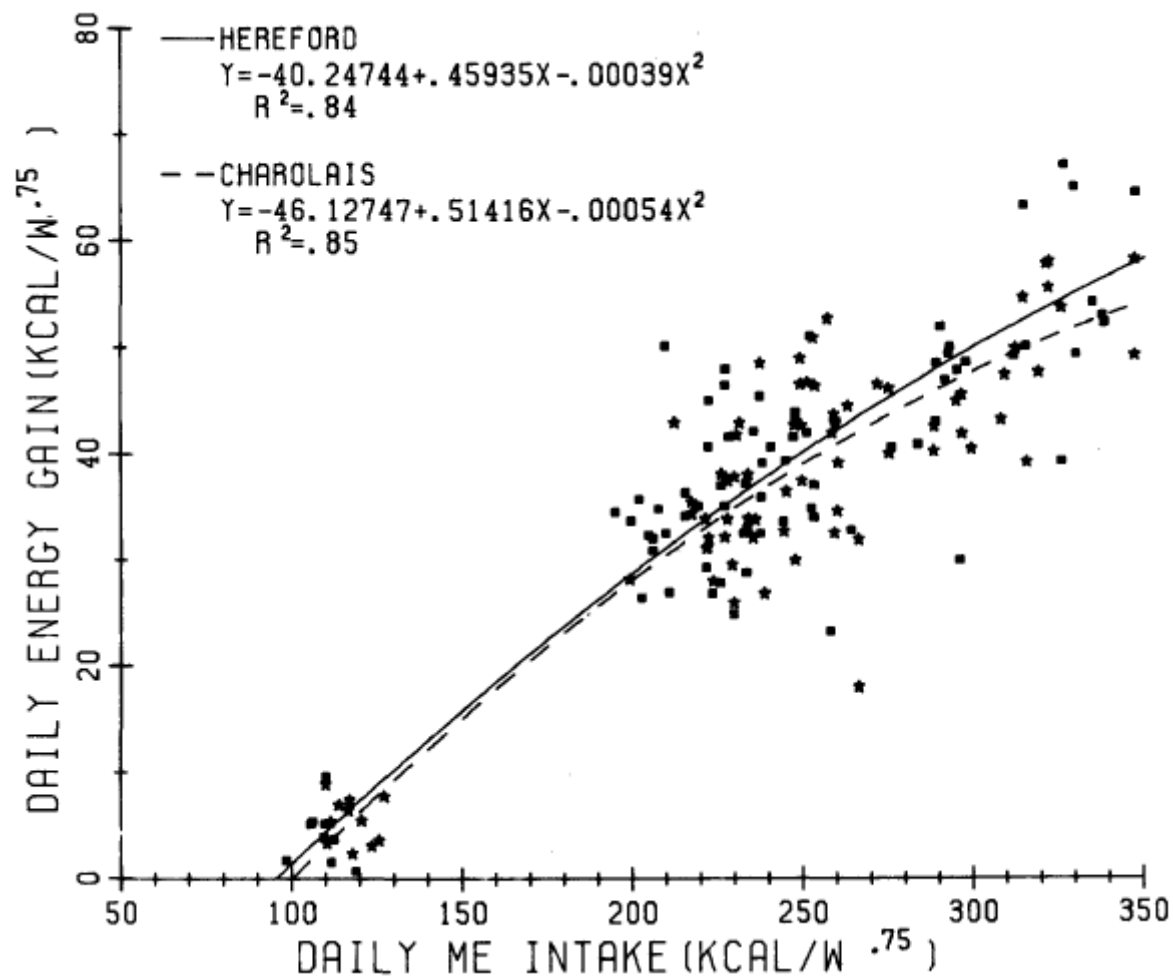**Glucose** External input or output (g/d, g/L)

Activation or stimulation (??)

Inhibition (??)
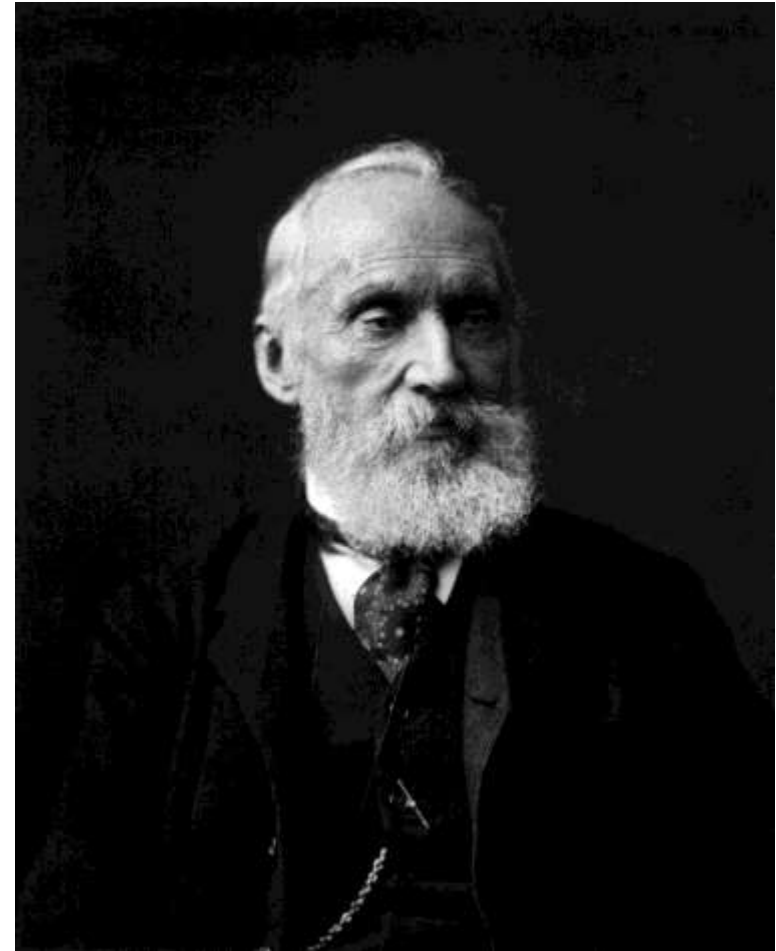
Mathematical Model of Energy Retention

Old and Garrett, 1987
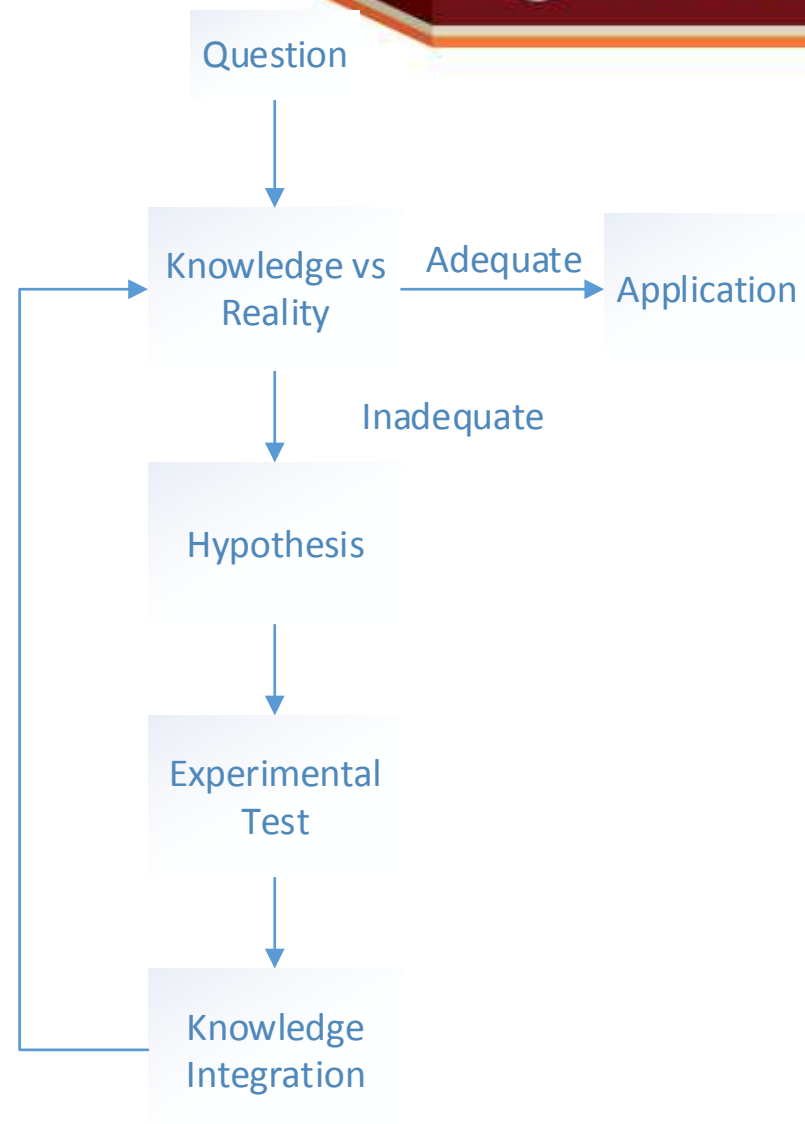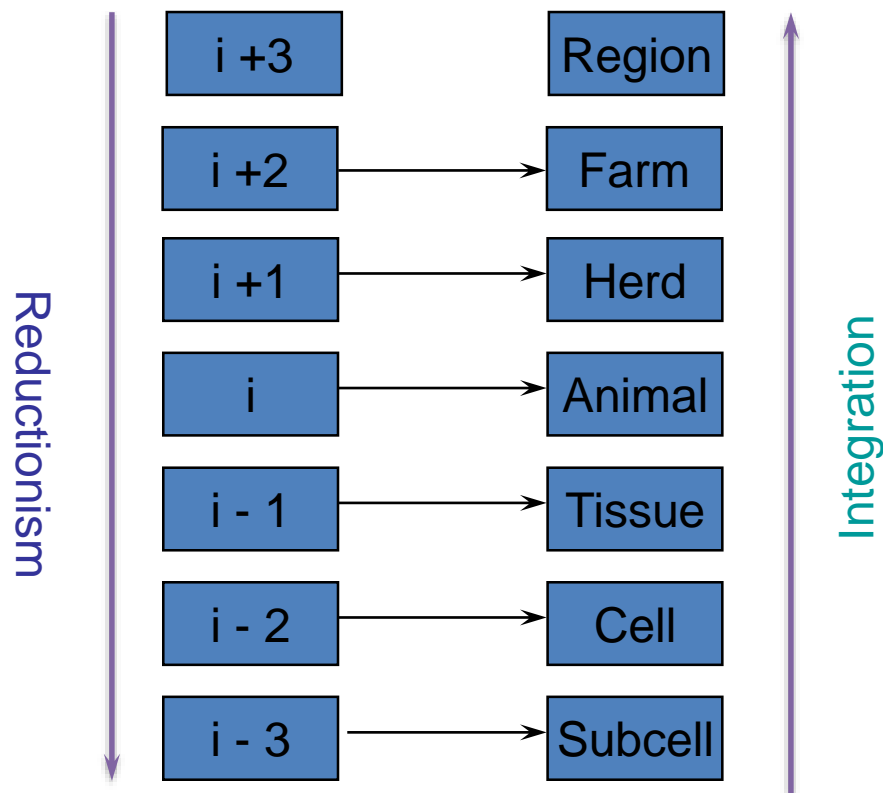
Why Construct a Model?

Lord Kelvin

"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."

The Scientific Process

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

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

- Development cycle
  - Construct
  - Test
  - Improve
  - Test
  - Improve
  - Test
  - Improve
  - Test
  - …

Model

Reality
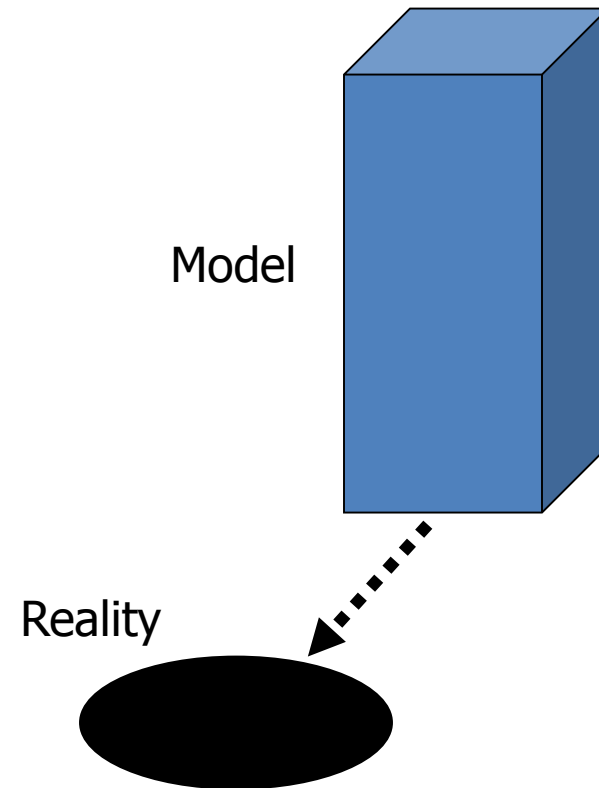
Objectives and goals are critical

- 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?
  - $(MEI - NEm) / Eff_{ME\ to\ NE}$?
  - If simple fails, perhaps add complexity

Appropriate Model 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.

Editorial, *J. Am. Med. Ass.*

Model classification

Dynamic OR Static

Deterministic OR Stochastic

Mechanistic OR Empirical

Simple Classification
Works OR Doesn't Work

France, J. and J. H. M. Thornley. 1984. Mathematical models in agriculture. Butterworths, Sevenoaks, Kent.

Does not represent the system through time

- Steady state representation, e.g. digestion coefficient

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

- 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

Dynamic

Time is an element in the equation or model

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

$$Metabolite(t) = Metabolite_{Initial} \times e^{(-k \times t)}$$

- 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 ($Metabolite_{Initial}$) and a rate of metabolite clearance from blood (k) per unit of time.

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

- IS NOT A DYNAMIC MODEL!

Static vs Dynamic
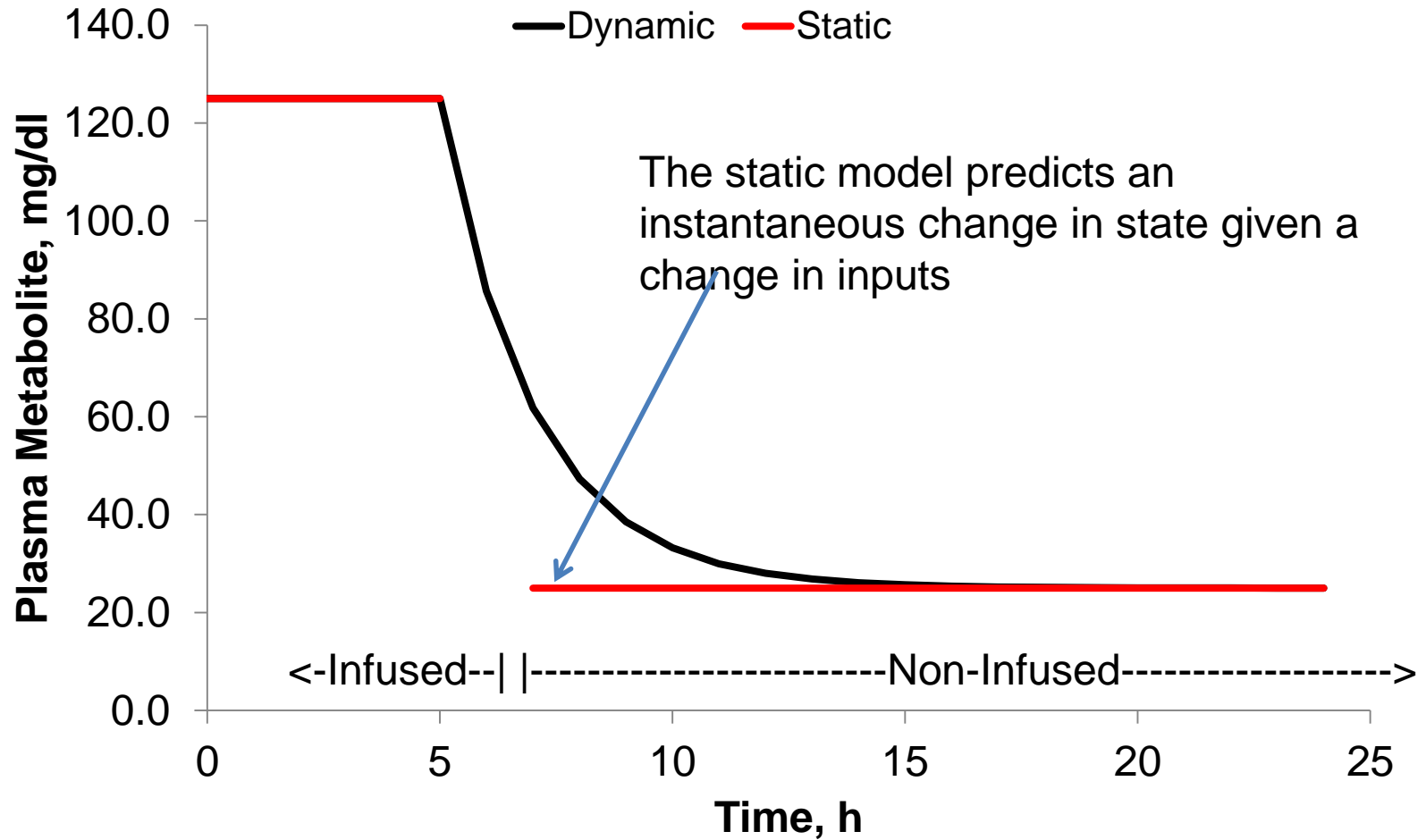
Deterministic

- 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

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

- $\sigma_{MeasureInit}$, σ_k, σ_t, and $\sigma_{MeasureConc}$ represent variance in initial concentration, k, time, and the metabolite concentration, respectively.

- σ generally ~N(0, σ) and randomly sampled

- Predicted *Metabolite(t)* should match the observed population if error model matches reality

- More difficult to parameterize and computationally expensive

  - K plus all σ

Deterministic vs Stochastic

Line - Deterministic
Symbols – Stochastic
~N(γ,7.5)
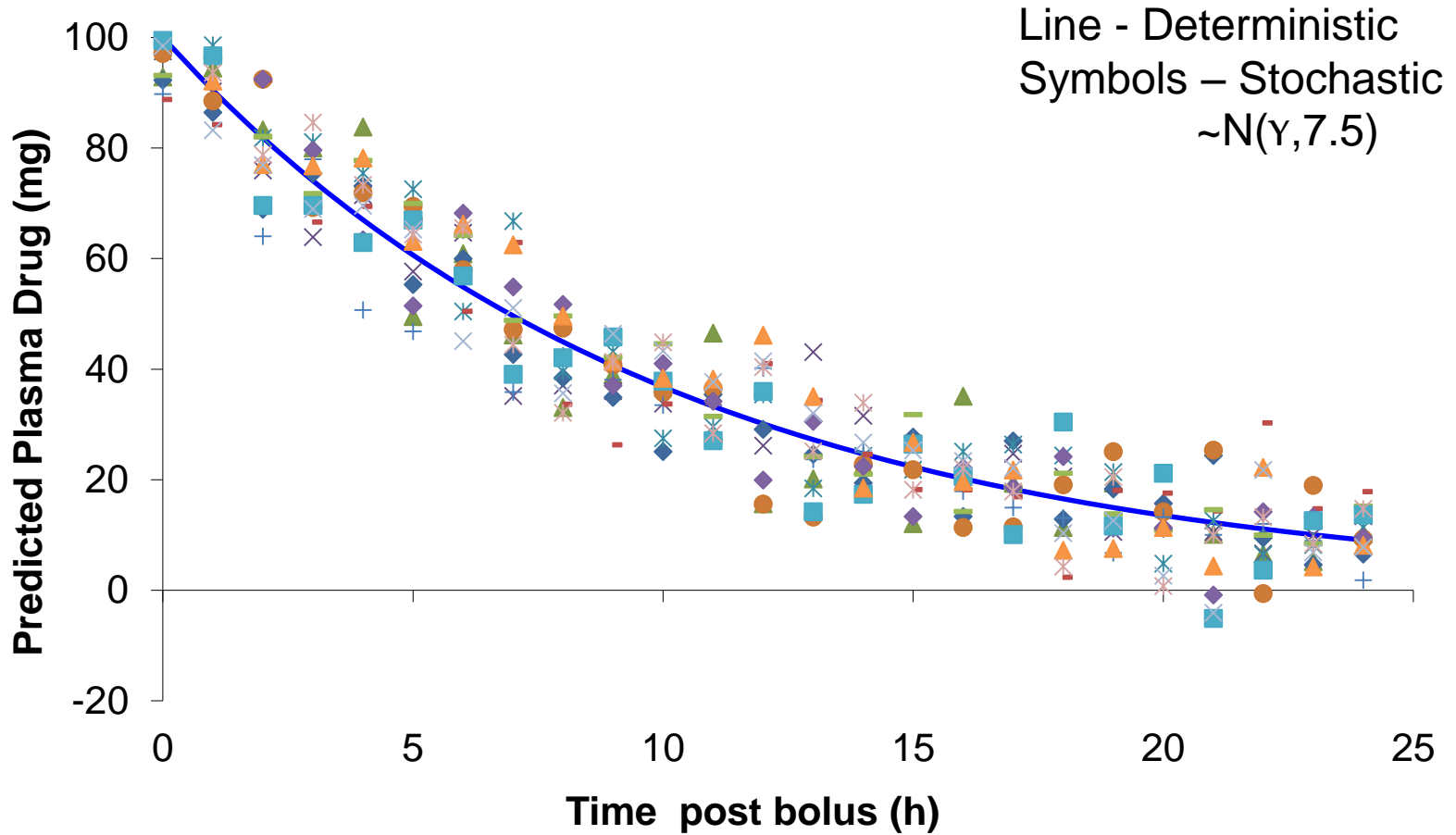
- Relates inputs and outputs at the same level of aggregation
  - many feed evaluation models
  - DMI = 3(Milk) + 0.02(BW$^{0.75}$)

- 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

Mechanistic vs Empirical

Empirical

$$Protein_{Milk} = \alpha EI + \beta NI + \chi EI^2 + \delta NI^2 + \varepsilon \left(EI \times NI \right)$$

Mechanistic

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

- 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

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

Ransom Leland Baldwin, V
1935-2007
Professor of Animal Science
University of California, Davis
National Academy of Sciences
Education: Michigan State Univ (1963)

Dynamic, Stochastic, Mechanistic, Compartmental

https://www.nhc.noaa.gov/archive/2017/IRMA_graphics.php?product=5day_cone_with_line_and_wind

Models Used in Animal Nutrition

- NRC Nutrient Requirement Models
  - Static, Deterministic, Empirical ($\rightarrow$ 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
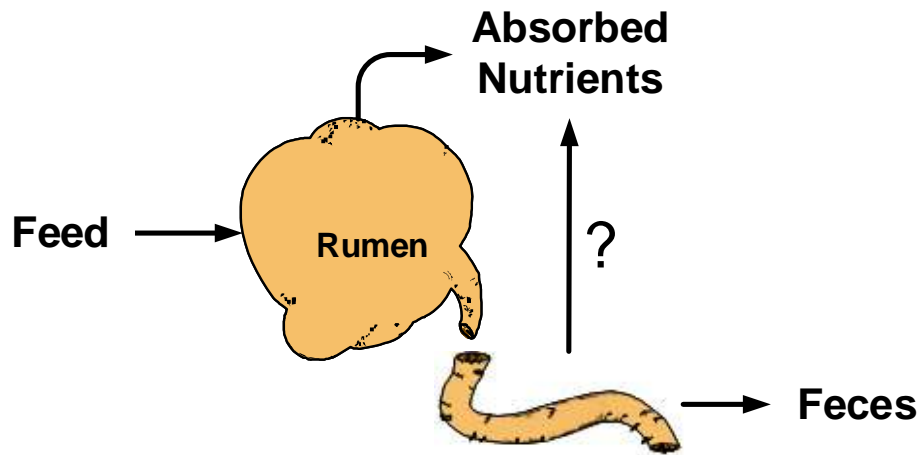
- Problem 1 – integration
  - Analytical solution to Qrum?
  - Numerical solution by Euler's
  - Set up in Excel
- Open Exercise _1 R script 1.R
  - Numerical solution by Runga-Kutta
  - No mathematical limit to stacking

$$\frac{dQ_{Rum}}{dt} = F_{Intake} - F_{Rum,SI} - F_{Rum,Deg}$$

$$F_{Intake} = DMI \times C_{Nutrient}$$

$$F_{Rum,SI} = Q_{Rum} \times K_{Passage}$$

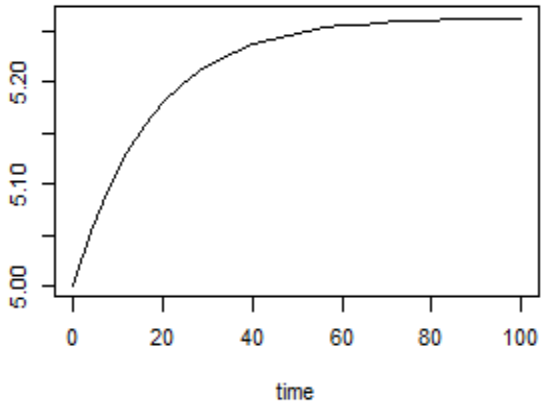$$F_{Rum,Deg} = Q_{Rum} \times K_{Degradation}$$

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

$$F_{SI,Bld} = a \times F_{Rum,SI}$$
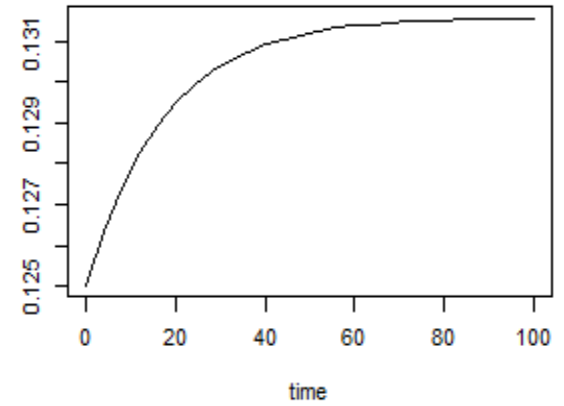
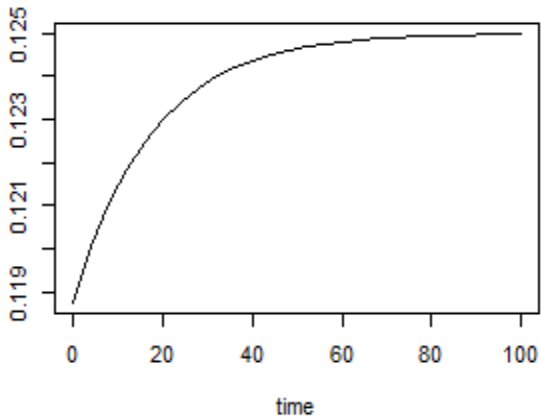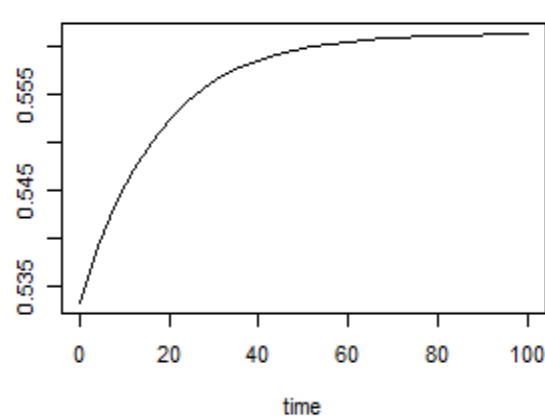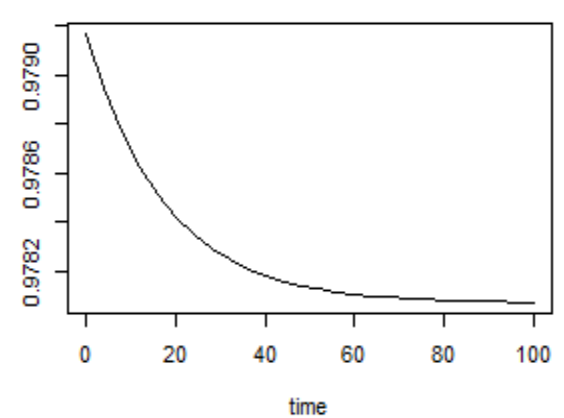$$F_{Feces} = F_{Rum,SI} - F_{SI,Bld}$$
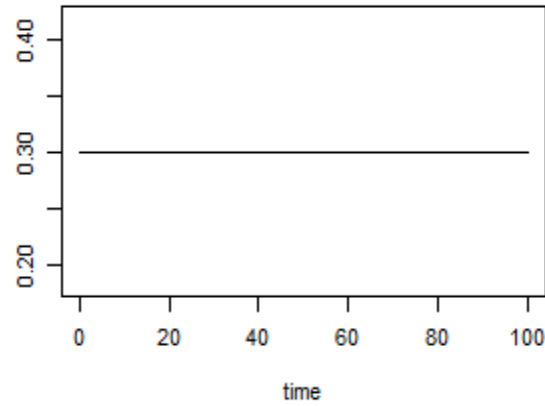
- Hypothesis: High Forage < Low Forage
  - Experimental Objective: measure milk production for HF and LF

is $\overline{HF} < \overline{LF}$ given observed variance?

- $Milk_{ij} = \mu + \beta_i (Trt_i) + \varepsilon_{ij}$

  where i = 1 to # of Trt and j = 1 to # of animals

  Trt is coded as a matix with a column for each Trt

  0 if the animal was not on the treatment and 1 if it was

- Can we learn more?

Trt = …

Animal	Trt$_1$	Trt$_2$
1	1	0
2	1	0
3	0	1
4	0	1