

NATIONAL ANIMAL NUTRITION PROGRAM



USDA Funded National Research Support Project

<http://animalnutrition.org>



Introduction to Modeling

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USDA Funded:

- NRSP-9

www.animalnutrition.org

Learning Objectives



<https://animalnutrition.org/workshops-symposia>
(subfolder of Publications)

- Briefly touch on:
 - the motivation for modeling
 - different types of models
 - the steps in constructing a model
- Linear regression exercises - Kristan
- Exercises on developing a mechanistic, compartmental model - Mark

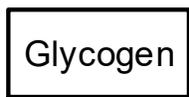
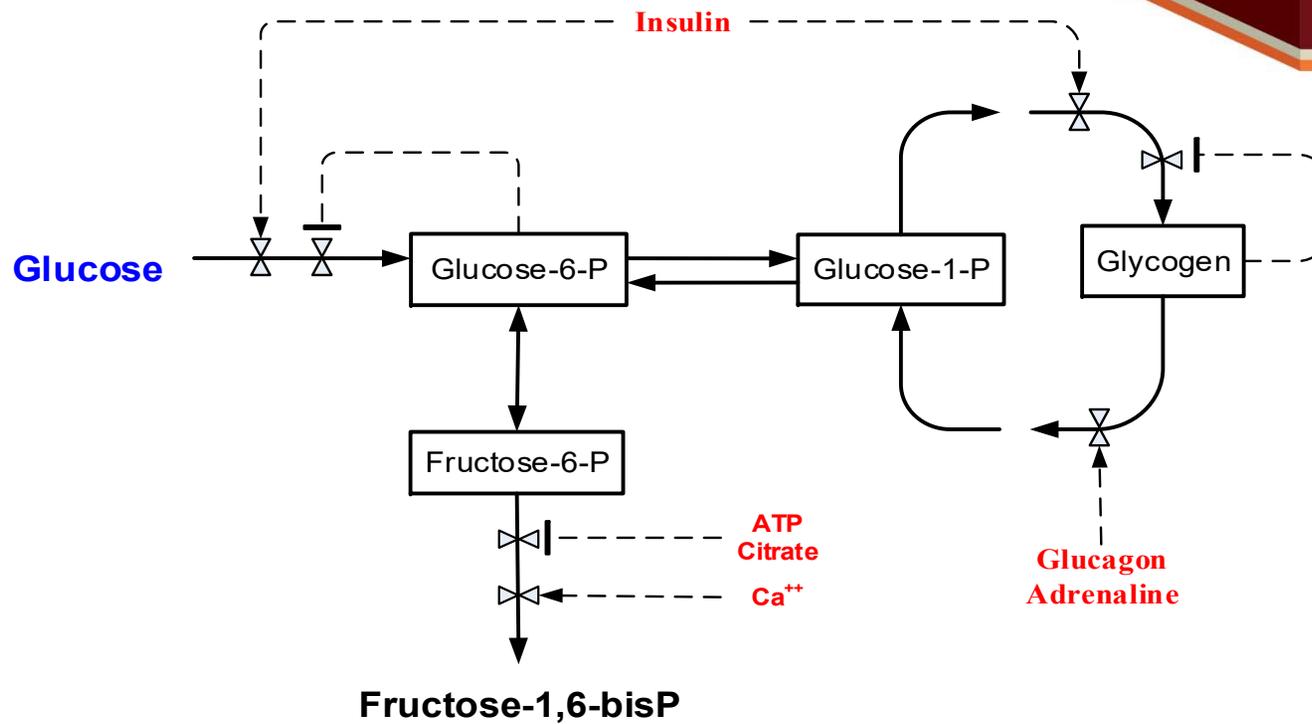
What is a Model?



- 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



A pool (g, L, mol)

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



A flux (g/min)

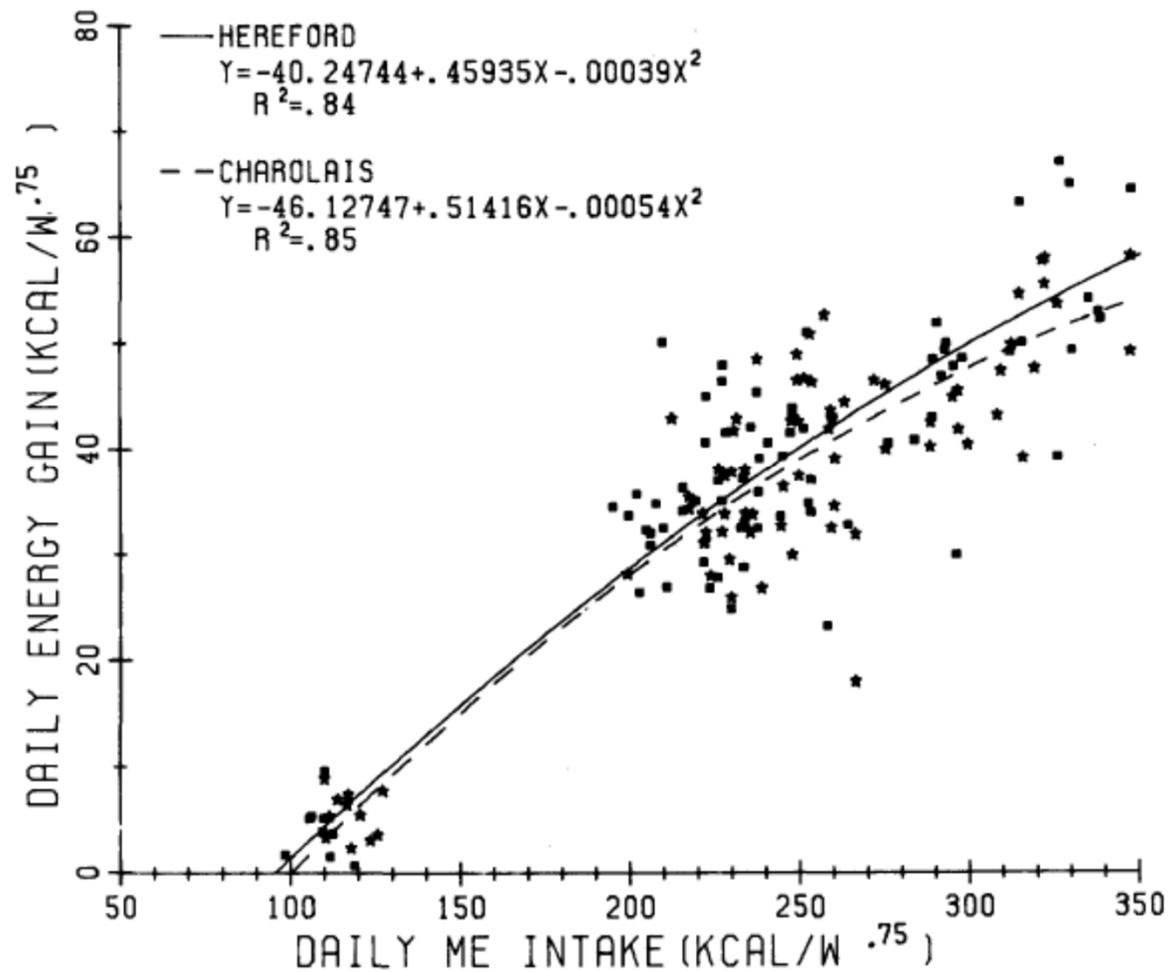


Activation or stimulation (??)



Inhibition (??)

Mathematical Model of Energy Retention



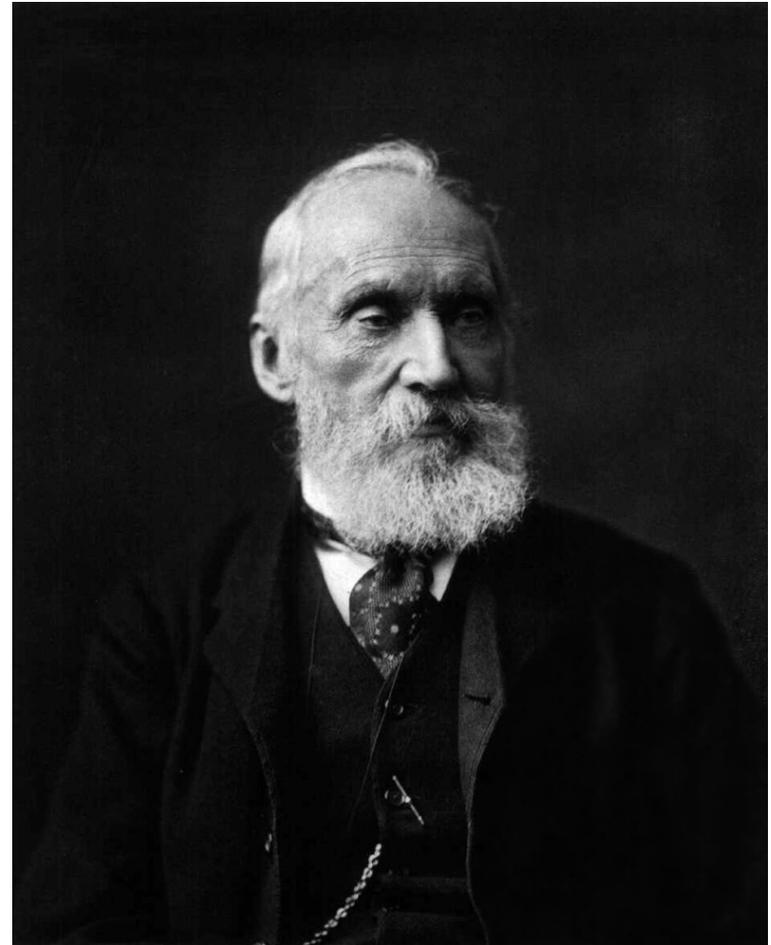
Old and Garrett, 1987

Why Construct a Mathematical Model?



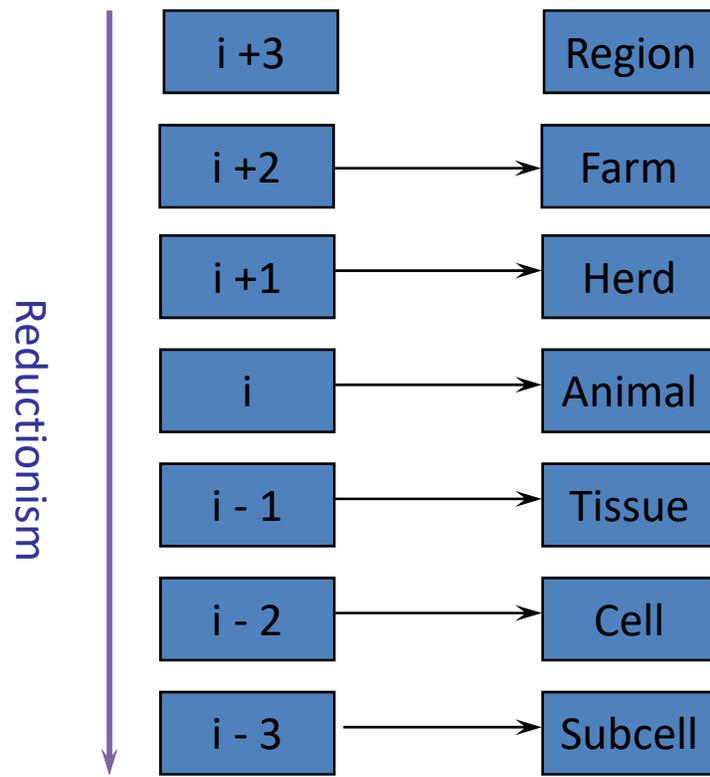
“When you cannot express [something] in numbers, your knowledge is of a meager and unsatisfactory kind . . . you have scarcely, in your thoughts, progressed the level of science.”

Lord Kelvin

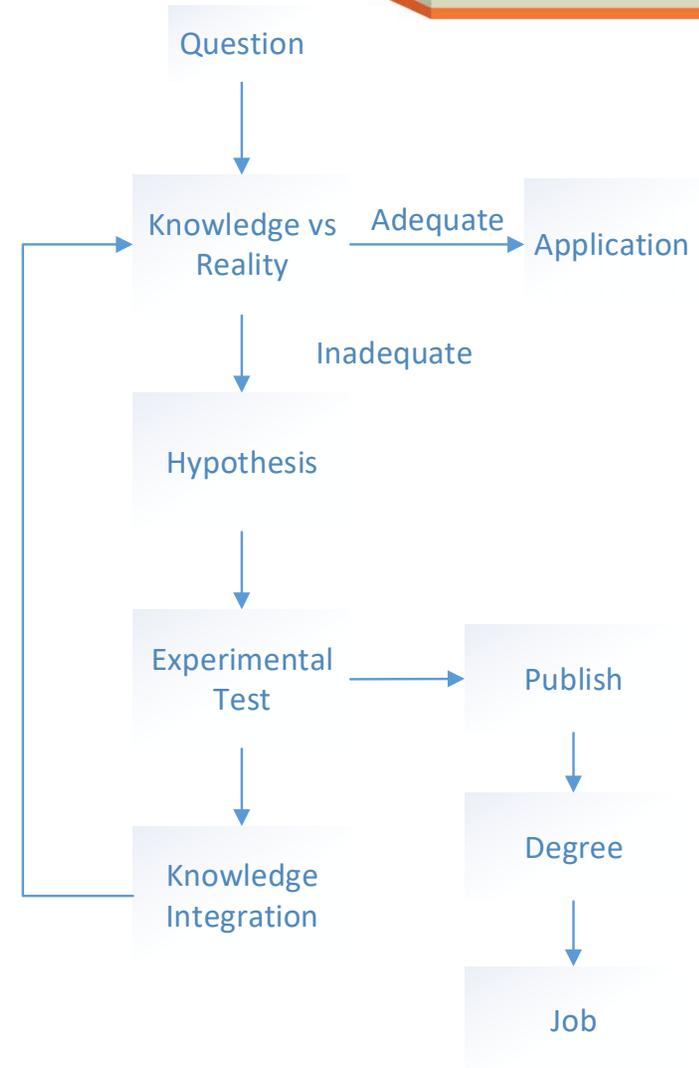


http://www.sil.si.edu/digitalcollections/hst/scientific-identity/CF/by_scientist_display_results.cfm?scientist=kelvin

The Scientific Process



Integration



The Model Development Process

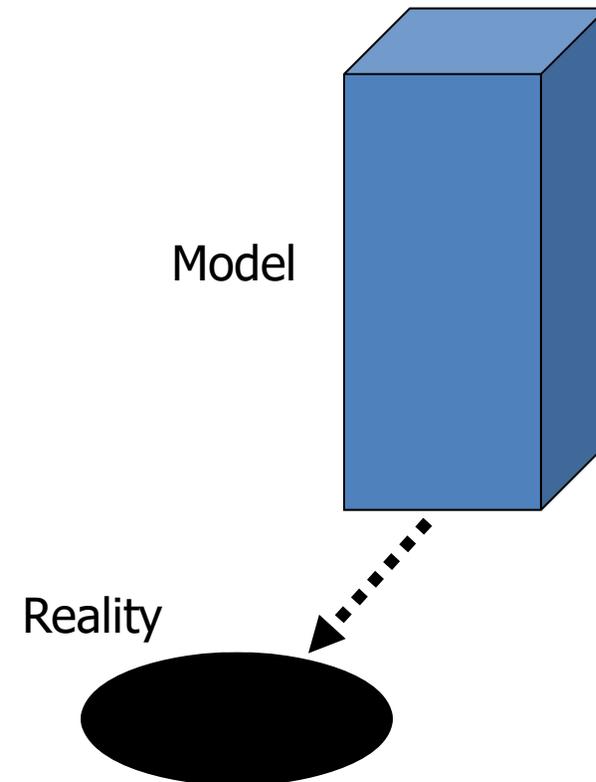


1. What is the question?
2. Define goals and objectives
3. Review the literature: concepts and data
4. Develop a visual representation
5. Construct an appropriate mathematical representation
6. Transform the mathematics to computer code
7. Select or derive model parameters
8. Evaluate and assess vs observed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





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?
 - $(MEI - NEm) / \text{Eff}_{ME \text{ to } NE}?$
 - 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.*



By self-created (Moscarlop) - Own work, CC BY-SA 3.0, <https://commons.wikimedia.org/w/index.php?curid=5523066>

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

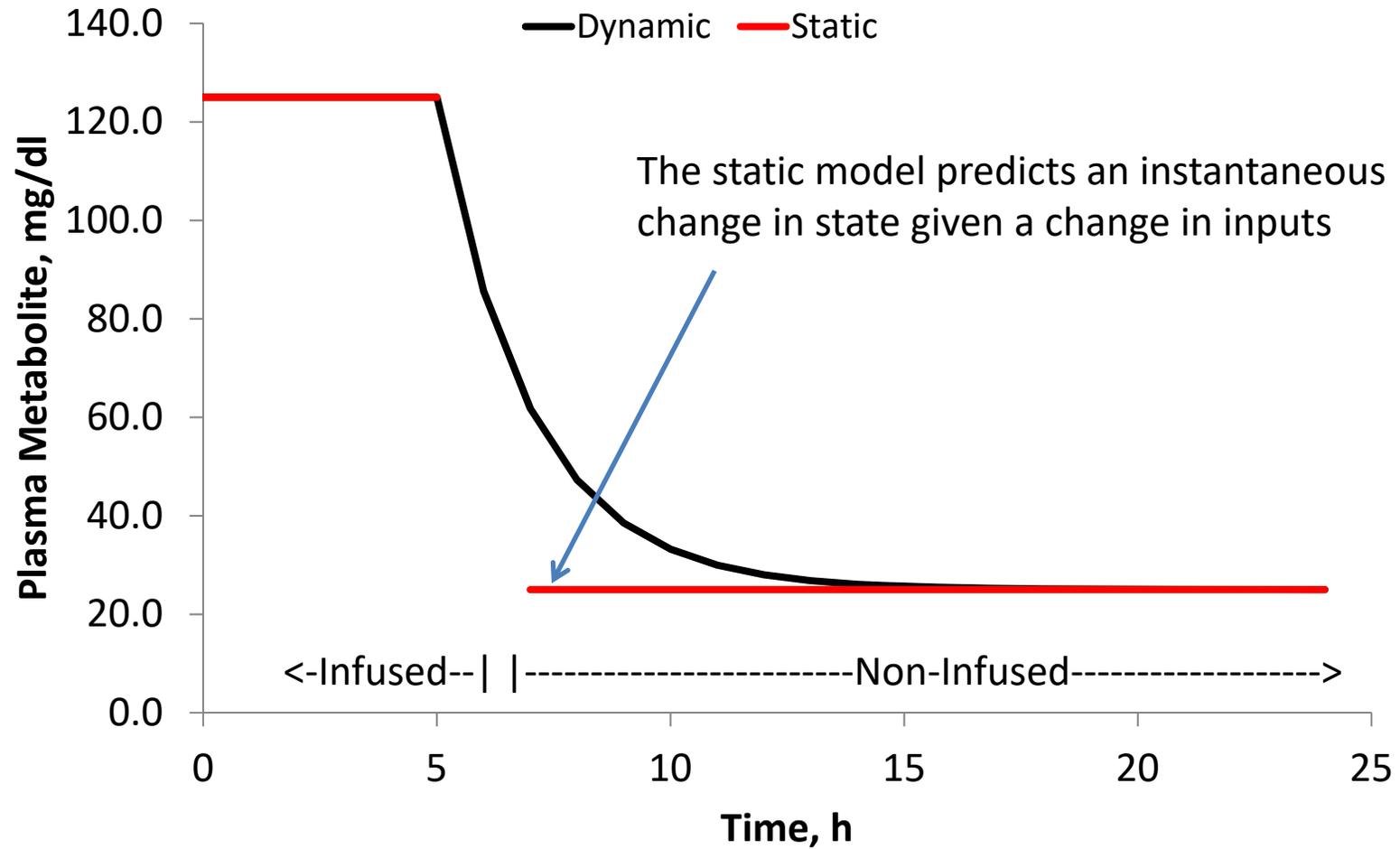
$$Metabolite(t) = Metabolite_{Initial} \times e^{(-k \times t)}$$

- 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

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

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

Stochastic

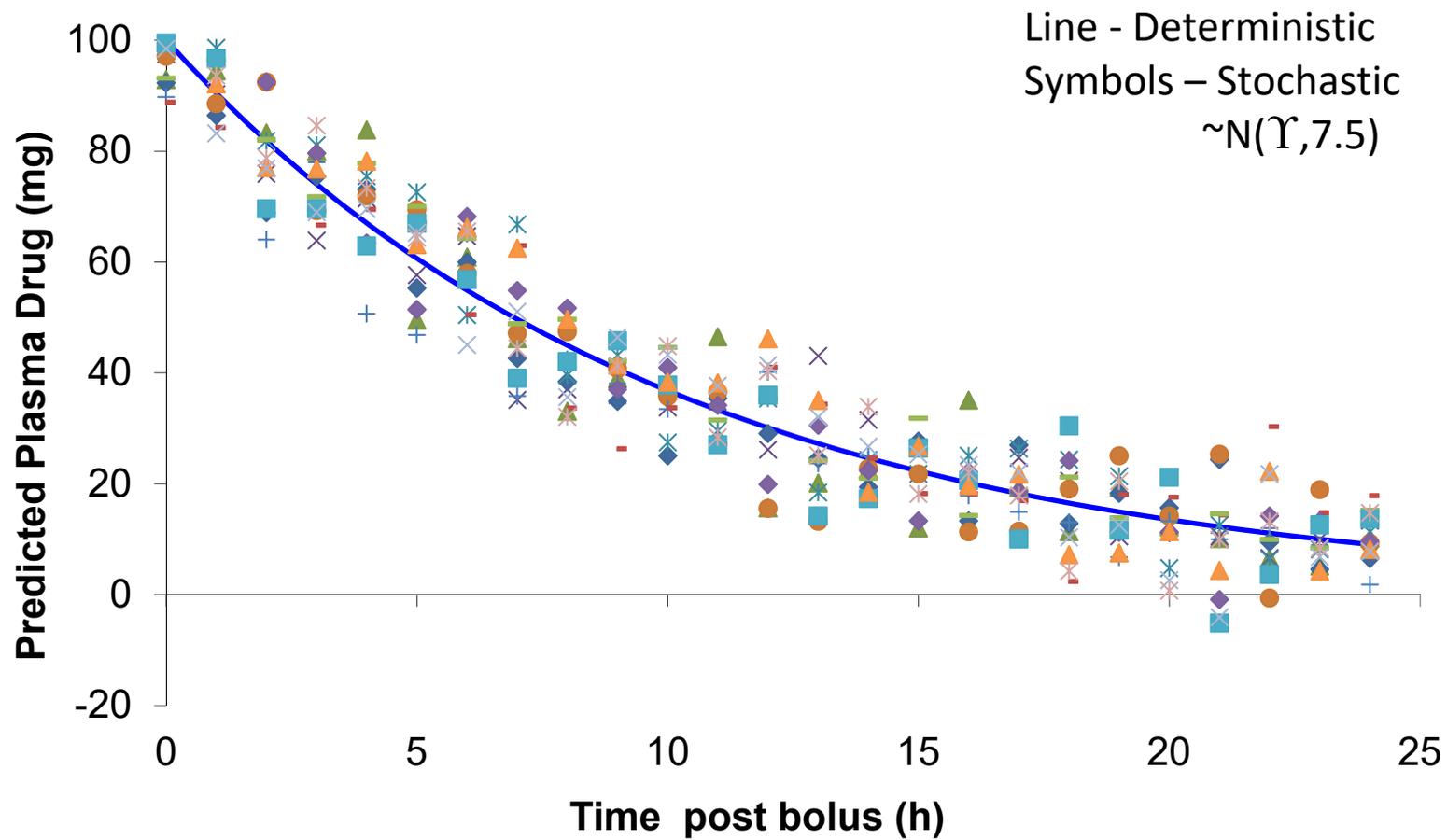


- Explicitly accommodates variance in inputs, outputs, parameters

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

- $\sigma_{MeasureInit}$, σ_k , σ_t , and $\sigma_{MeasureConc}$ represent variance in initial concentration, k, time, and the metabolite concentration, respectively.
- σ generally assumed $\sim N(0, \sigma)$ and randomly sampled
- Provides a distribution of answers
- 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



Empirical



- Relates inputs and outputs at the same level of aggregation
 - many feed evaluation models
 - $DMI = 3(\text{Milk}) + 0.02(\text{BW}^{0.75})$
- Advantages
 - simple and quick
 - less detail
- Disadvantages
 - limited ability for extrapolation
 - Doesn't utilize underlying system knowledge to improve precision
 - How do we use reductionist information???

Mechanistic



- Explicitly represents aspects of the underlying system structure
 - Molly cow model from UC Davis
- Advantages
 - May result in more precise prediction: generally assumes a more complex structure
 - May be suitable for extrapolation
 - Aids in understanding the system
- Disadvantages
 - Generally 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, effort, and data to develop

Mechanistic vs Empirical



Empirical

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

Mechanistic

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

- 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
- All mechanistic models are empirical at their lowest level

Compartmental Models (subtype)



- Metabolism is compartmental in nature
 - Rumen → small intestine → blood → tissue
 - Blood → extracellular → intracellular → protein
 - G6P → F6P → 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

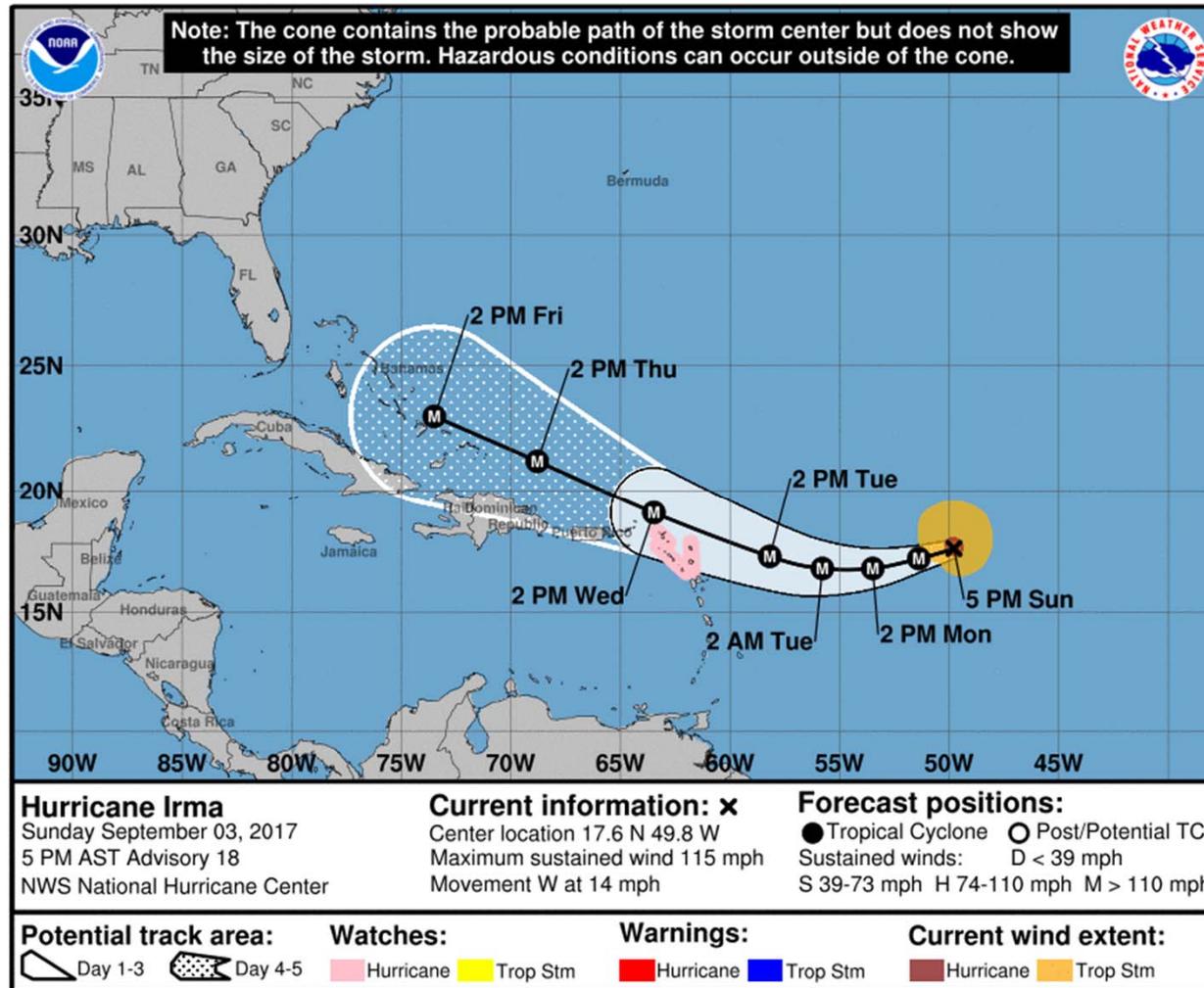


Ransom Leland Baldwin, V
1935-2007

Professor of Animal Science
University of California, Davis
National Academy of Sciences
Education: Michigan State Univ (1963)

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

Dynamic, Stochastic, Mechanistic, Compartmental



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



- 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)

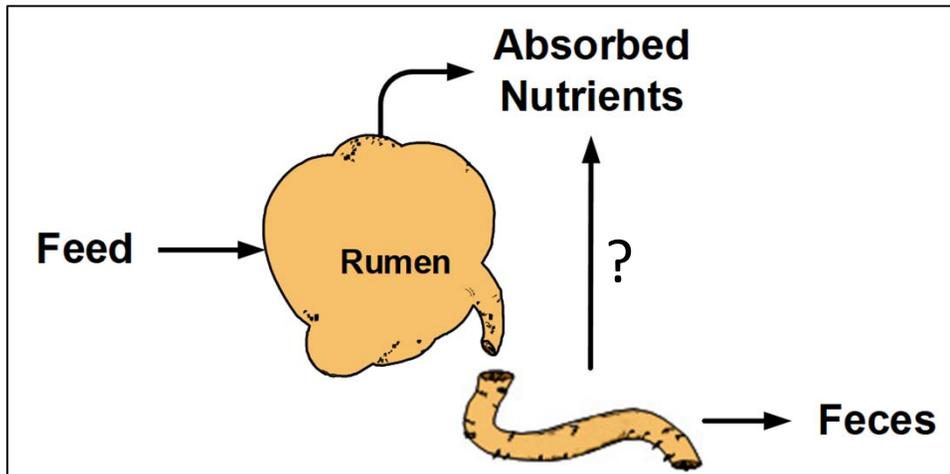
Summary



- Modeling is an integral part of the scientific process
- Modeling process should be followed
- Set Goals carefully and adhere to them
 - Let failure drive added complexity
- 3 general model classifications
 - Classes are a continuum rather than discrete
- Models can reflect a single level of organization or operate across levels
 - Goals and objective determine appropriate level of aggregation



Compartmental Model Example



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

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

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

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

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

$$F_{SI,Bld} = a \times F_{Rum,SI}$$

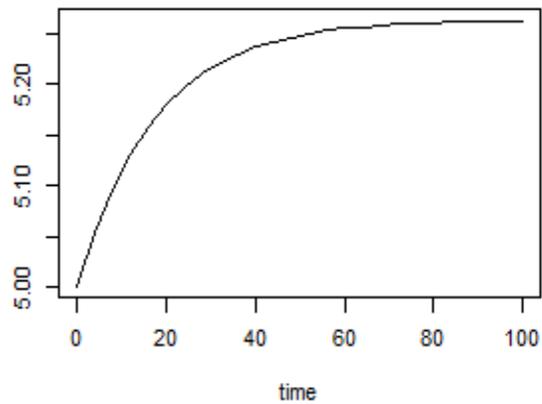
$$F_{Feces} = F_{Rum,SI} - F_{SI,Bld}$$

- Problem 1 – integration
 - Analytical solution to Q_{rum} ?
 - Added complexity → no anal soltn
 - Numerical solution by Euler's
 - Excel Demonstration
 - Lesson 1 Excel Exercises.xlsx
- R Demonstration exercise
 - Open LS1_1 pool model.R
 - R has built in integrators
 - Numerical solution by Runge-Kutta
 - No mathematical limit to stacking
- 2, 3, and 3 pool plus isotope models for reference

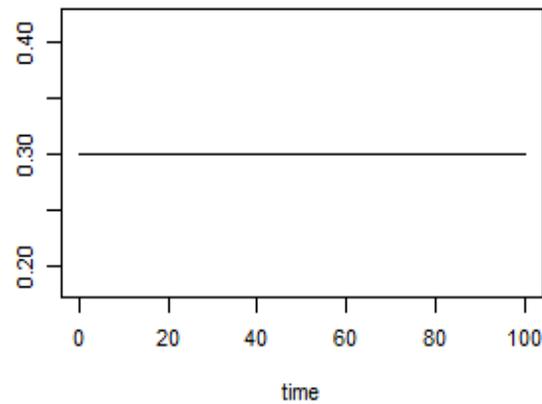
Model Output – Static DCnut



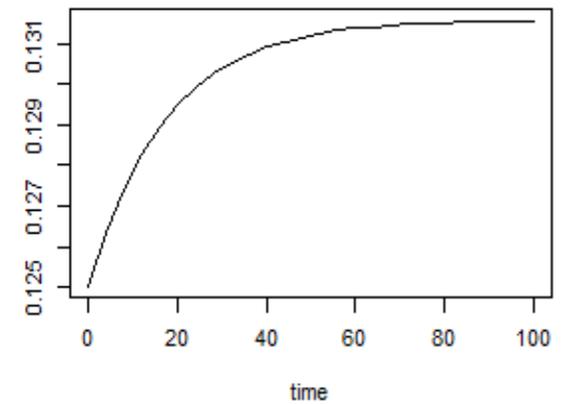
Qrum



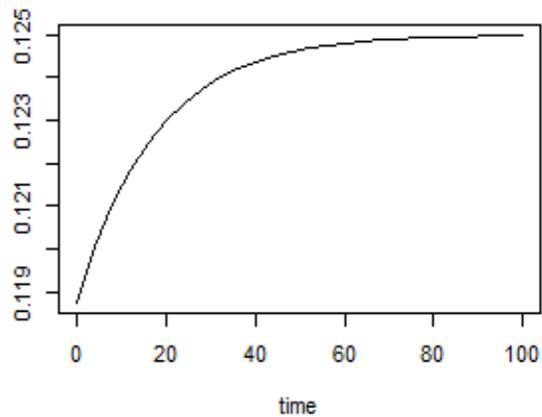
Fin



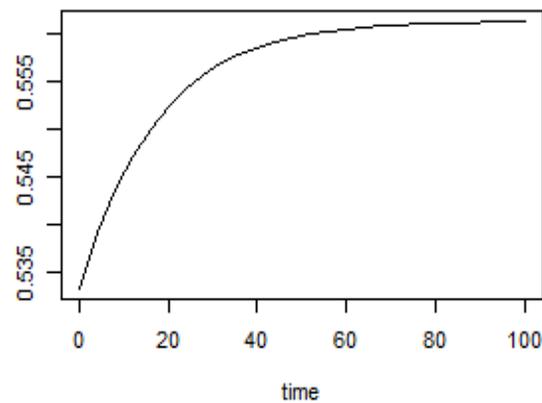
FRumSI



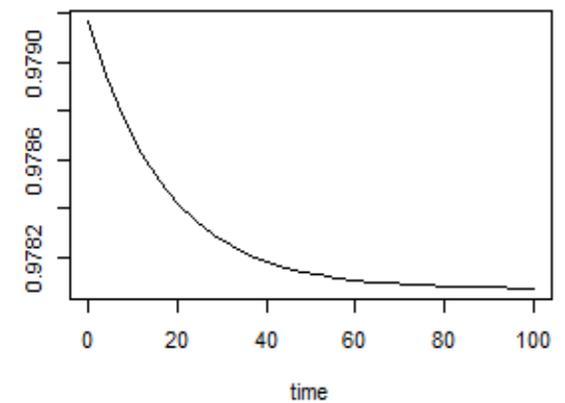
FSIAbs



RDnut



TDnut



Parameter Optimization

