

EXPLORING MATHEMATICAL MODELING IN BIOLOGY THROUGH CASE STUDIES AND EXPERIMENTAL ACTIVITIES

QUBES—Wicked Problems
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Outline

- Overview of mathematics of biology course
- Glucose Lab
 - Students' toolkit before the lab
 - Introduction to blood glucose regulation
 - Hands-on: Pre-lab activities
 - Overview of data collection
 - Hands-on: Data analysis
- Future projects

Our Vision

Students
in the
Mathematical
Sciences

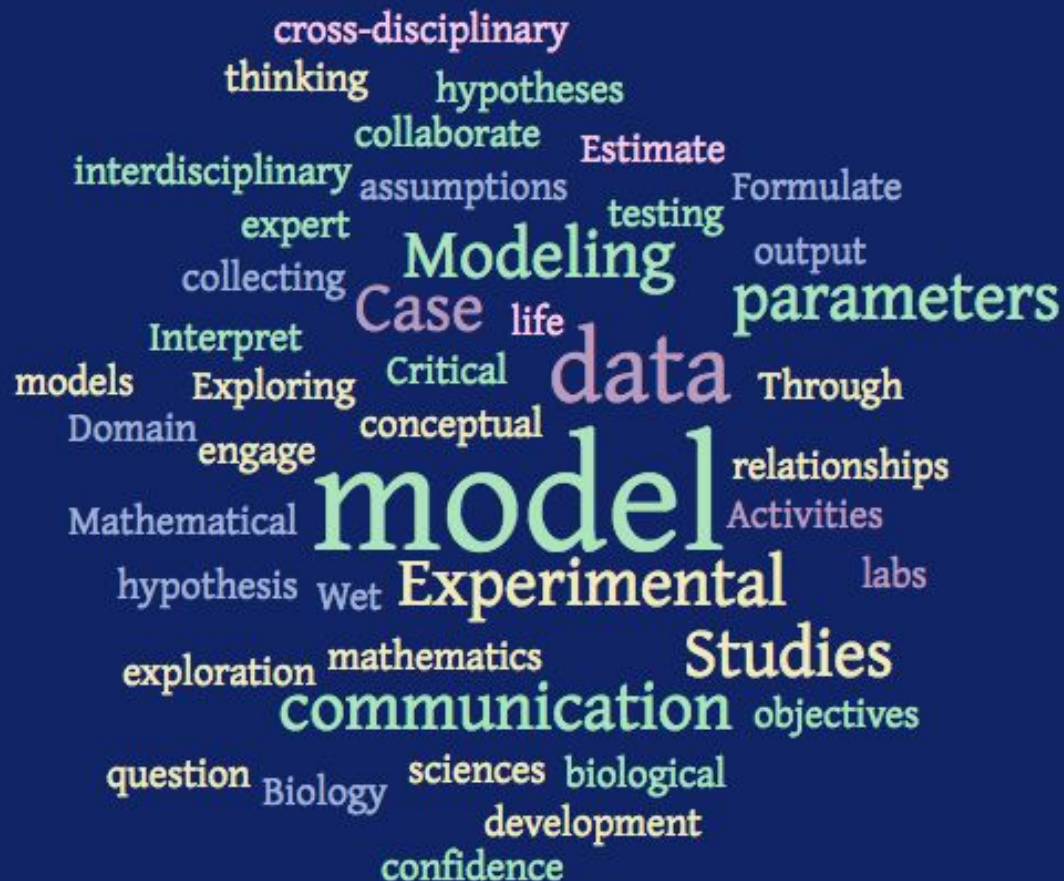


Students in
the
Biological
Sciences

**Collaboratively Engage in
Mathematical Modeling
Through Case Studies and
Experimental Activities**

Philosophy

This mathematics of biology book is a stand-alone compendium of exercises, cases and wet labs designed to help mathematics and life-sciences college students integrate mathematical, computational and research approaches to addressing real problems.



Audience and Teaching Environment

- *Audience:*

Undergraduate biology and mathematics students and their faculty.

- *Pre-requisite:*

Calculus I

- *Useful:*

exposure to R or some biology or
more math

- *Courses:*

- Any course in the broad area of mathematical biology for undergraduates, particularly filling a niche for classes intended for students from multiple disciplines.
- Cases and labs could be used as supplements in various courses

Unique Characteristics

- Truly interdisciplinary
- Model development
- Real data
- Just-in-time learning
- Critical Thinking



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Unit 1: Discrete-Time Models & Intro to Modeling Process

Unit 3: ODEs: Numerical Solutions and Sensitivity Analysis

Unit 2: ODEs: Model Formulation and Parameter Estimation

Unit 4: Spatial Models and Diffusion

Table of Contents

Unit 1: Discrete-Time Models & Intro to Modeling Process

- Case Studies:
 - Pharmacokinetics*
 - Invasive Plant Species*
 - Island Biogeography*
- Wet Lab: *Population Growth*

Unit 2: ODEs: Model Formulation and Parameter Estimation

- Case Studies:
 - Atmospheric N and C Release*
 - Tumor Growth Predictive Models*
 - Photosynthesis-Temperature Models*
- Wet Lab: *Enzyme Kinetics*

Unit 3: ODEs: Numerical Solutions and Sensitivity Analysis

- Case Studies:
 - Disease Outbreak*
 - Pharmacokinetics*
 - Biochemistry Competition Model*
- Wet Lab: *Glucose-Insulin Regulation*

Unit 4: Spatial Models and Diffusion

- Case Studies:
 - Thermoregulation*
 - Egg shell pores: Gas Exchange*
 - Population Dispersal and Climate Change*
- Wet Lab: TBD

Mixing it up: Models and Lab Work

General strategy:

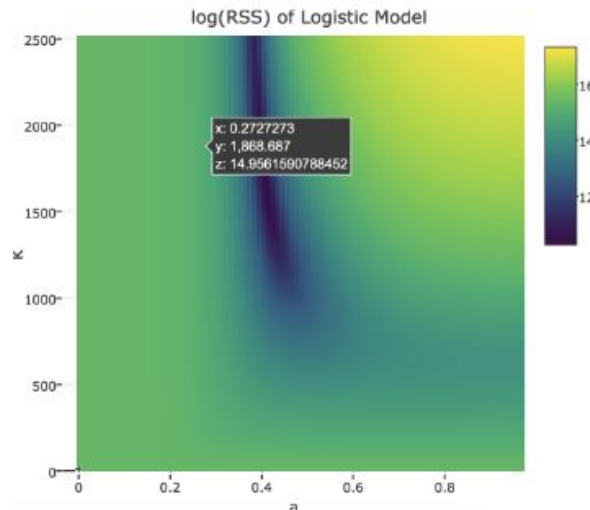
- Introduce both the biological and mathematical & R backgrounds to the unit including several examples/problems to be worked.
- Develop 2-3 cases to be completed in class and/or as homework that use the math.
- Prepare for lab – biological and math examples.
- Collect data in the lab
- Complete data analysis → parameter estimations
- Discuss the outcomes.
- Address a second question experimentally using the same system.

Case Study Example:

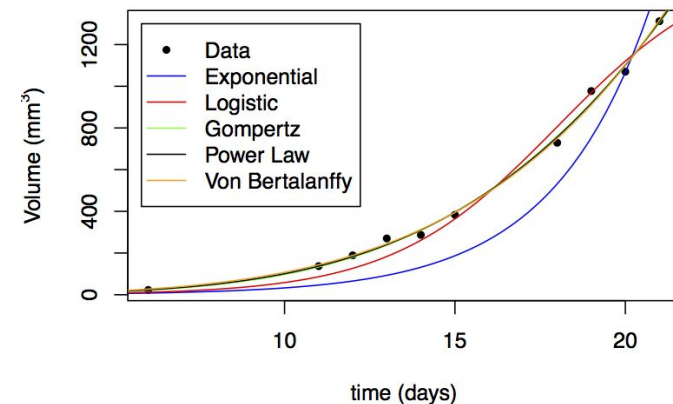
Tumor Growth -- Model Selection

- 5 models proposed to describe growth of tumors
- Calibrate each model to data using nonlinear regression
- Evaluate their relative descriptive power using AICc
- Use subset of data to test predictive power of each model

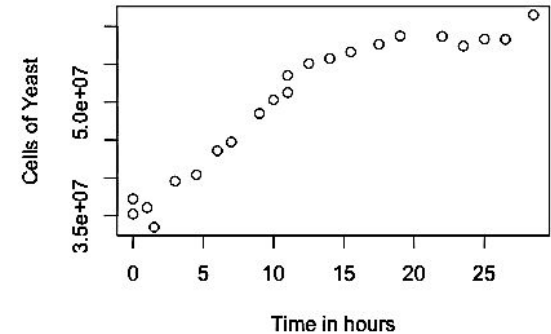
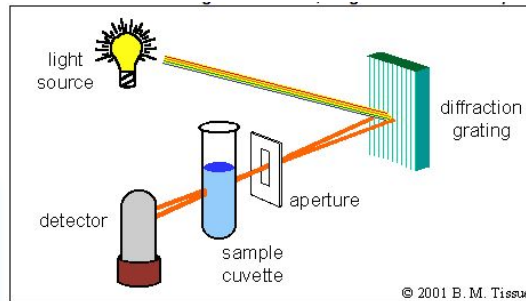
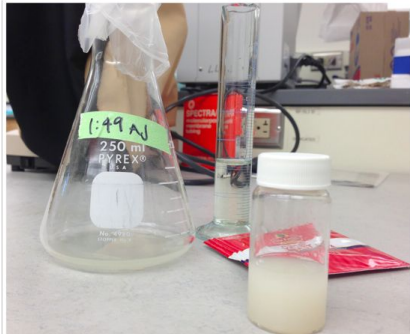
Days	Volume (mm ³)
6	23
11	137
12	189
13	270
14	287
15	383
18	729
19	977
20	1070
21	1312



$$RSS(p_1, p_2) = \sum_{i=1}^n (V_i - f(t_i, p_1, p_2))^2$$

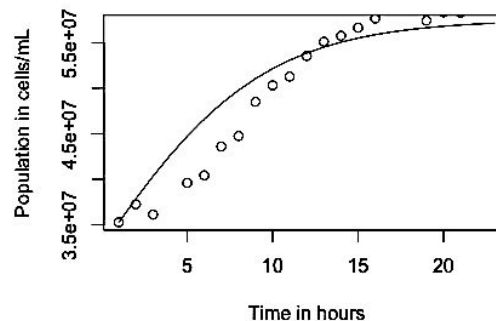
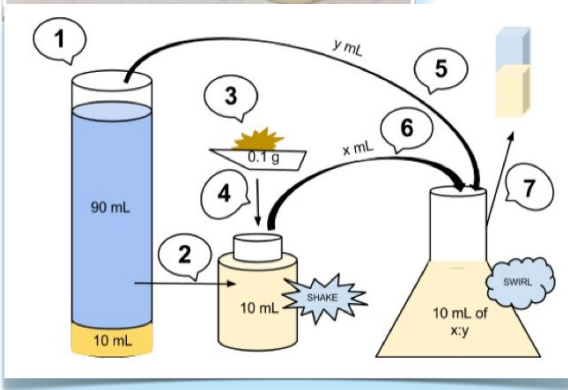


Laboratory Exercise: Population Dynamics

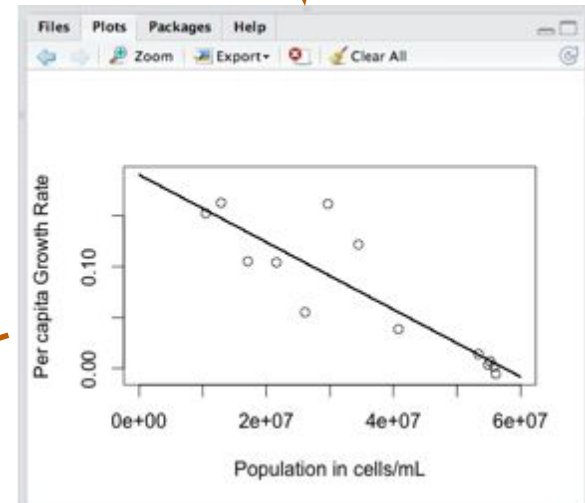


Questions

How do parameters depend
on initial yeast population?
Nutrient levels?



Model



Laboratory Exercise: Enzyme Kinetics



Pre-Lab: Derive Michaelis-Menten

$$\frac{d[E]}{dt} = \dots$$

$$\frac{d[S]}{dt} = \dots$$

$$\frac{d[ES]}{dt} = \dots$$

$$\frac{d[P]}{dt} = \dots$$

Assumptions:

$$[E + ES] \ll [S]$$

$$[P] \ll [S]$$

Michaelis-Menten Equation:

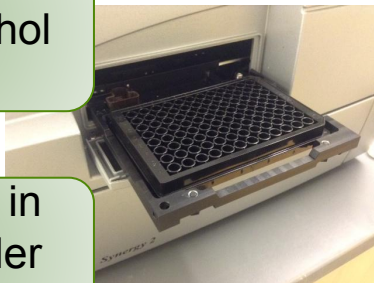
$$V_0 = \frac{d[P]}{dt} = V_{\max} \left(\frac{S}{K_m + S} \right)$$

Laboratory Exercise: Enzyme Kinetics

Prepare apple extract

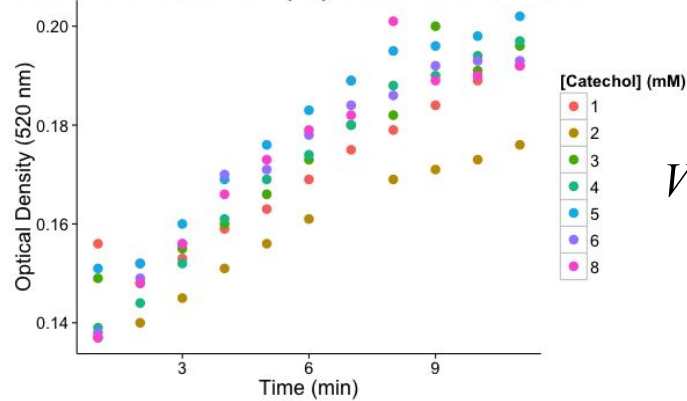


Fill plate wells with catechol solution



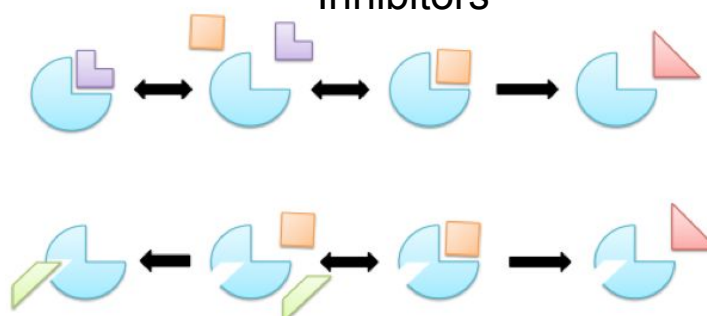
Run plate in plate reader with dispenser

Catechol Oxidase Activity by Catechol Concentration

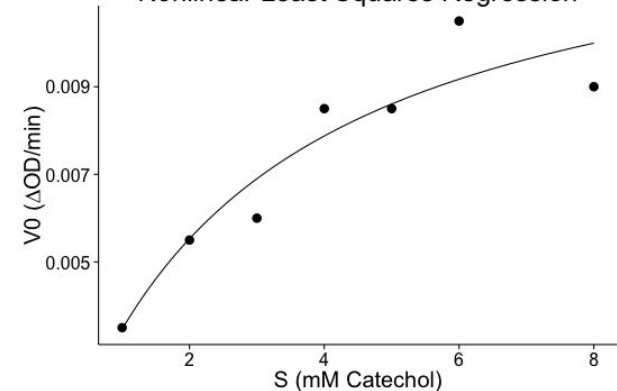


$$V_0 = \frac{d(OD)}{dt} = V_{\max} \left(\frac{S}{K_m + S} \right)$$

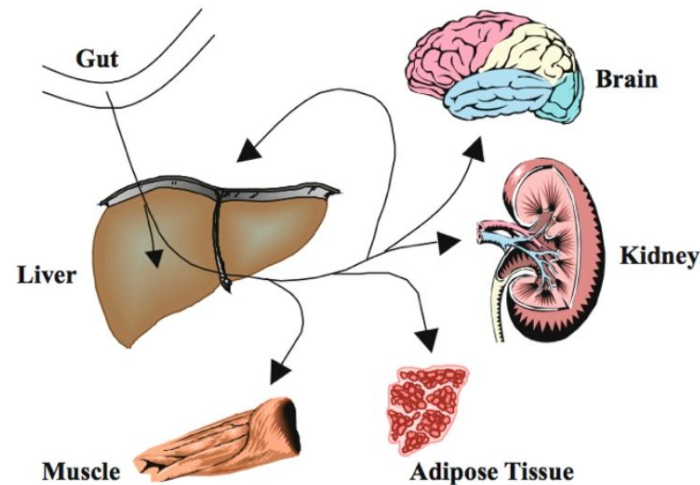
Competitive and Noncompetitive Inhibitors



Nonlinear Least Squares Regression



Laboratory Exercise: Glucose-Insulin Feedback



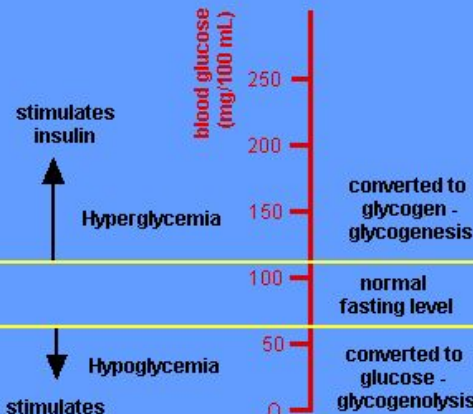
$$\frac{dG}{dt} = \text{glucose delivery}$$

– glucose uptake

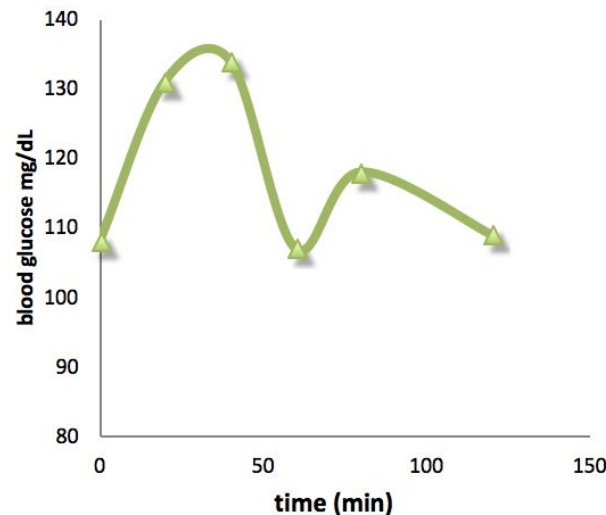
$$\frac{dI}{dt} = \text{insulation secretion}$$

– insulin breakdown

Regulation of Blood Glucose Levels



C. Ophardt, c. 2003



Questions

- What if I ingest sugar at regular intervals?
- What if I ingest complex carbohydrates?



Final Projects

Students propose and carry out small research projects

- Project Proposal Form requires students to:
 - articulate hypotheses
 - draw qualitative diagrams to initiate model planning
 - discuss the experimental design
 - provide a list of equipment and supplies needed
- Examples of projects:
 - Compare intrinsic growth rate carrying capacity of yeast cultures in control media to media with different concentrations of ethanol
 - Effect of interspecific competition of two species of *Paramecia*
 - Model effect of exercise on blood glucose
 - Compare the kinetics of catechol oxidase in multiple fruits or as bananas ripen

Assessment: Quotes from Course Reflection Papers

“I am taking an introductory computer science class next semester. My decision to do so was based in part on my experiences in this class; I want to have the capability to utilize computing power to explore real-world systems.”

“Next year I will be working as an ecological research assistant and I fully expect this class to influence the way I think and do work.”

“The process of modeling taught me greater intentionality in my problem- solving. The math bio course has pushed me to think in ways that are not the most intuitive for me. I think I have become a stronger student because of this.”

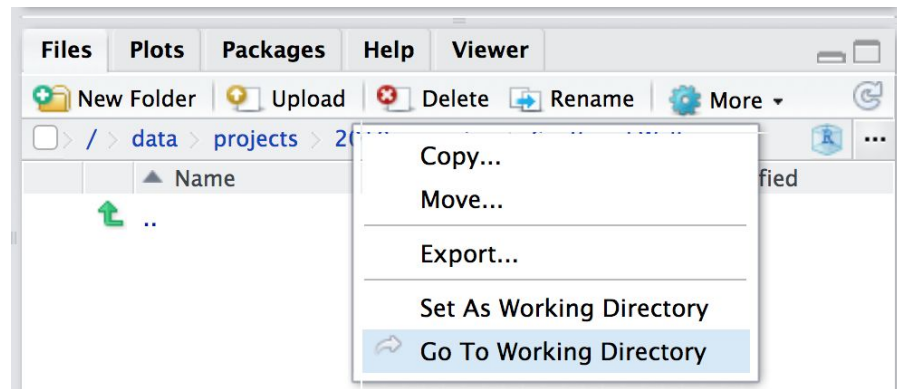
“This class gave me confidence in my ability to collaborate with students/colleagues in other fields.”

Break!

During the break:

- Go to <https://qubeshub.org/software> and click on RStudio
- In the console, type

```
setwd("/data/projects/2018swsession/Sanft and Walter/")
```
- To access files in this directory, click on "More" in the Files panel (lower right) and select "Go to Working Directory"

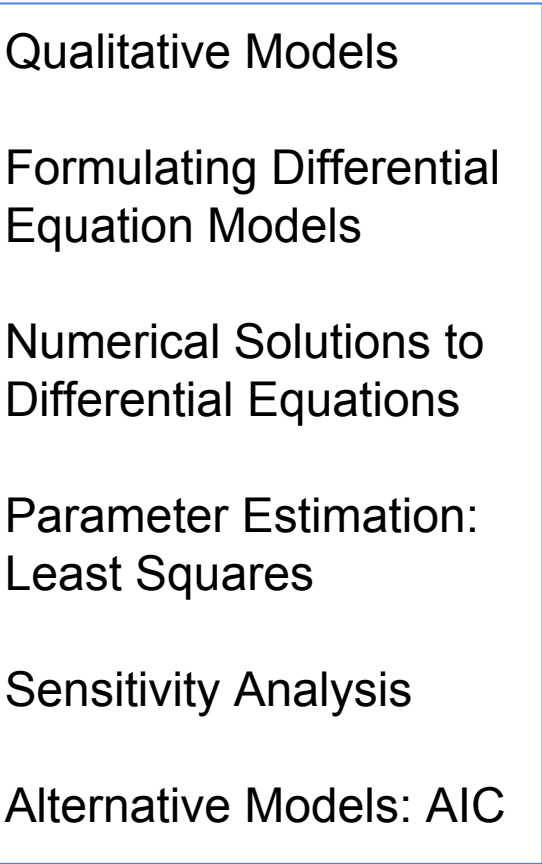


- Open glucose.R. Go to File -> Save As... and rename your file glucose_LastName.R.

Wet Lab

Hormones and Homeostasis:
Keeping Blood Glucose
Concentrations Stable

Dym, 2004



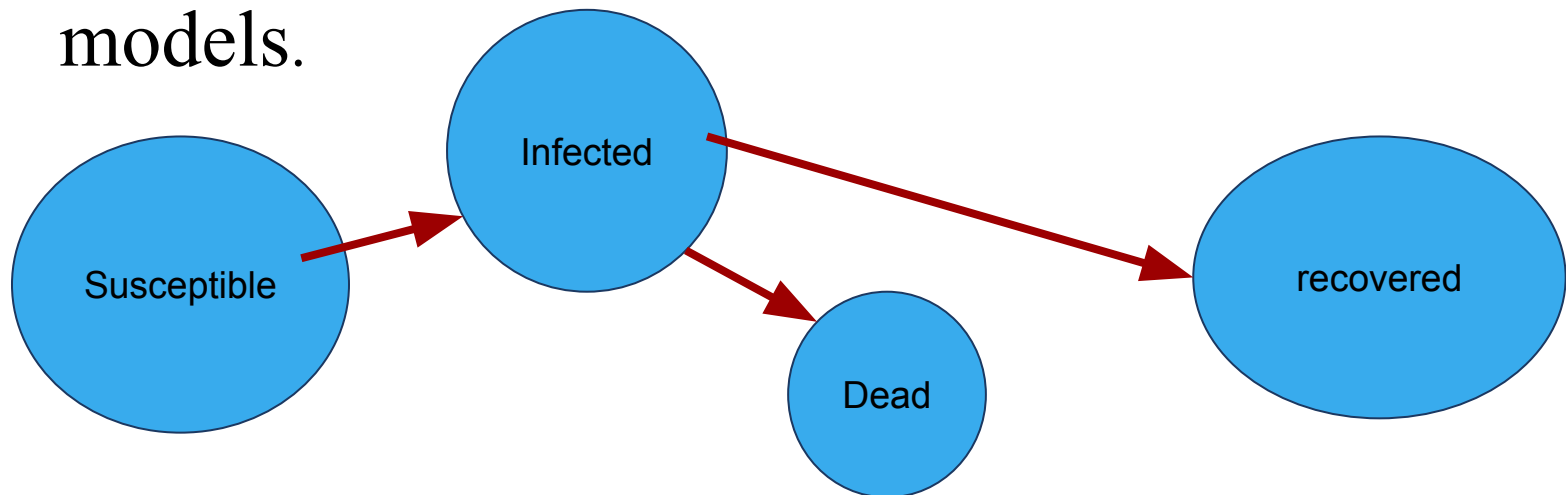
Unit III -Differential Equation Models: Calibration and Analysis

Learning Outcomes:

- Compute numerical solutions to systems of differential equations.
- Use optimization routines to estimate the 'best' values of parameters in a system of differential equations, given a set of observations.
- Use sensitivity analysis tools to study the effect of changes in a parameter on the model output.

Biological learning outcomes

- Explore dynamic systems that are interdependent
- Learn to clearly articulate the likely relationships and modulators.
- Identify what can be measured.
- Recognize reasonable outcomes.
- Explore parameters and make inferences from models.



Hormones & Homeostasis: Keeping Blood Glucose Concentrations Stable

- What are the major biological concepts in the title alone?
- What are the challenges to maintaining glucose homeostasis?
- What hormones are involved? When? How?
- What are the response times? threshold? range?

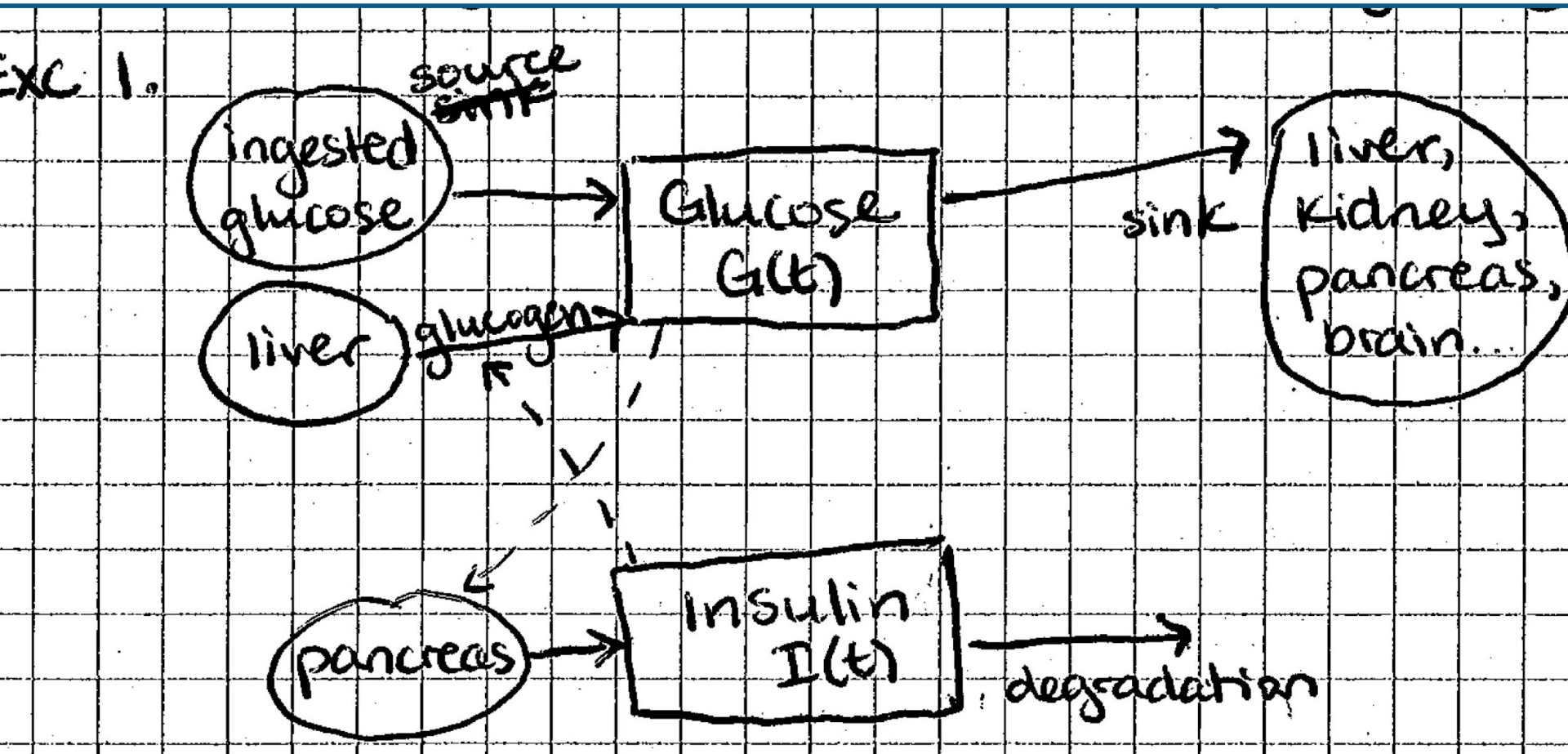
Exercise 1 - Qualitative Model

Draw a diagram indicating the sources and sinks of glucose and how these are affected by insulin and glucagon.

Indicate what factors increase or inhibit the release of insulin and glucagon.

How are the hormones removed once secreted?

Does your sketch look something like this?



Exercise 2

Sketch the graph of $[\text{glucose}]_{\text{blood}}$ vs. time that you would expect if you ate a candy bar. Include plausible values.

Draw the expected plot for insulin concentrations in the same time frame.

Units can be so annoying but they are important!

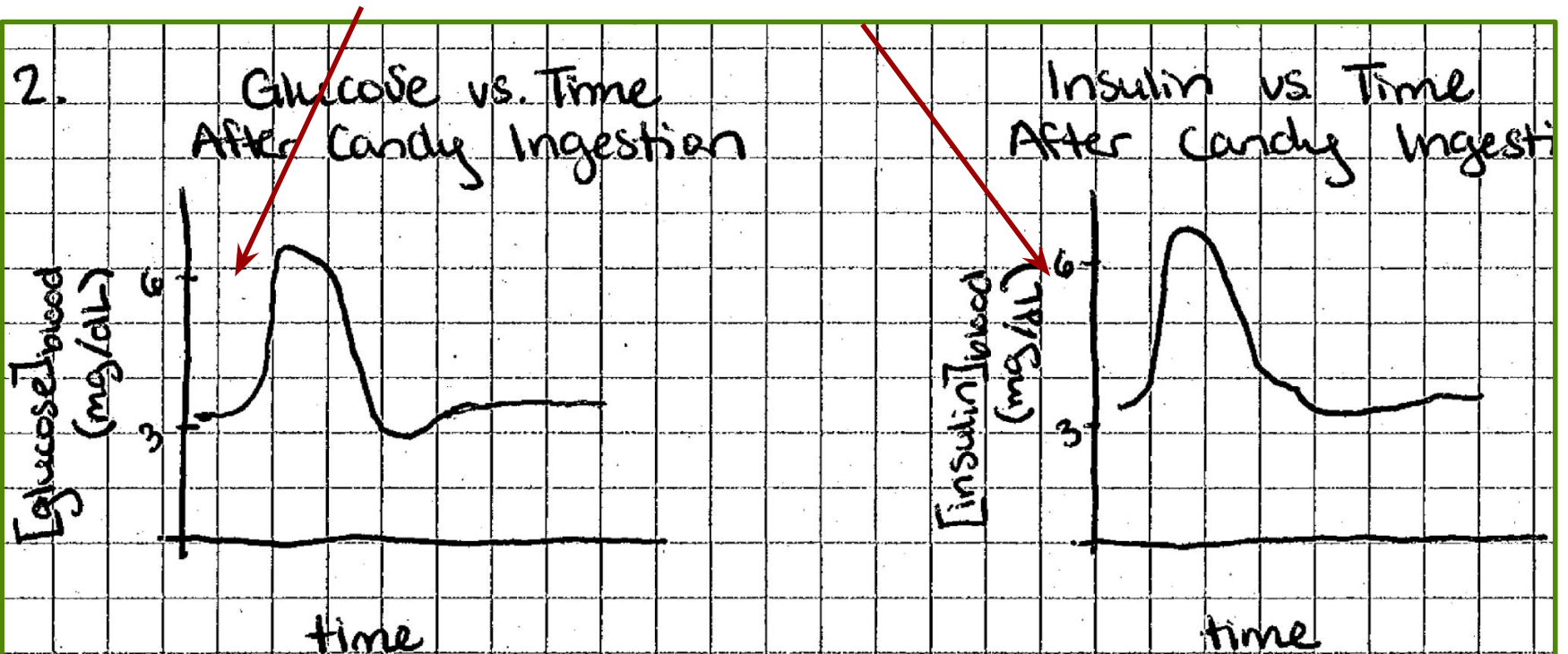
Be able to convert glucose in mM to mg/dL (the most common clinical unit).

What do you need to know to do this?

Note a reasonable range of glucose and insulin concentrations.

common mistakes:

1) conflating mM with mg/dL & assuming [insulin] matches [glucose]



The curves will be similar but insulin will be a later in time because it spikes in response to the ingested glucose and both will fall back to home after time.

Formulating a model

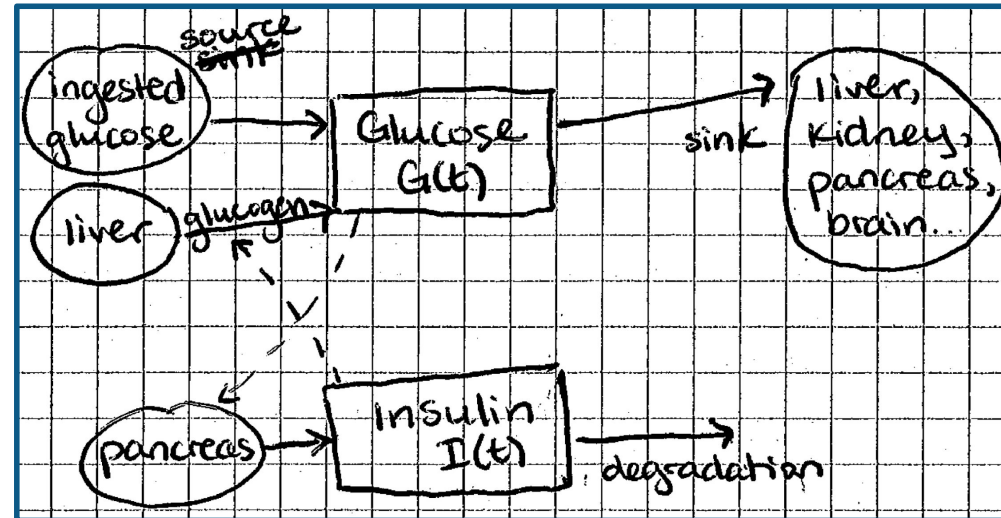
$G(t)$ = ECF concentration of glucose (mg/dl)

$I(t)$ = ECF concentration of insulin (mg/dl)

t = time (minutes)

$$\frac{dG}{dt} = (\text{release}) - (\text{uptake}) + (\text{ingestion})$$

$$\frac{dI}{dt} = (\text{secretion}) - (\text{degradation})$$



$$\frac{dG}{dt} = G_{rel} - (kG + r_1)I + G_{ing}(t)$$

$$\frac{dI}{dt} = \frac{vG^6}{G_m^6 + G^6} - r_2I$$

unknown

Exercise 3 - Understanding the Model

Work through the following exercises to help you understand the model:

- (a) Determine the units of each parameter in the model and fill in the table


$$\frac{dG}{dt} = G_{rel} - (kG + r_1)I + G_{ing}(t)$$
$$\frac{dI}{dt} = \frac{\nu G^6}{G_m^6 + G^6} - r_2 I$$

parameter	value	units
G_{rel}	1	
k	4×10^{-4}	
r_1	9.8×10^{-3}	
ν	250	
G_m	200	
r_2	0.2	

(b) For simplicity, we combine tissue uptake into a single term given by $f(G)I$ where $f(G) = kG + r_1$.

Sketch $f(G)$ versus G .

Discuss the assumptions made by this representation.


$$\begin{aligned}\frac{dG}{dt} &= G_{rel} - (kG + r_1)I + G_{ing}(t) \\ \frac{dI}{dt} &= \frac{vG^6}{G_m^6 + G^6} - r_2I\end{aligned}$$

(c) The insulin secretion term is given by a Hill function

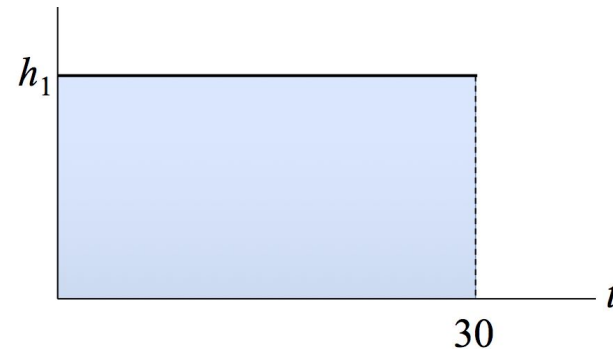
$$g(G) = vG^6 / (G_m^6 + G^6).$$

Sketch $g(G)$ versus G . Label v and G_m on the plot (note the similarity to the Michaelis-Menten equation!). Explore how the curve changes as the exponents increase from 1 to 6.

(d) The degradation term is given by r_2I . What is the physical interpretation of r_2 ?

(e) What are the units of the ingestion term $G_{ing}(t)$? Suppose you ingest a candy bar that contains 30,000 mg of sugar, and assume it is completely absorbed in 30 minutes. The simplest representation of $G_{ing}(t)$ would be a step function, given by

$$G_{ing}(t) = \begin{cases} h_1 & 0 \leq t \leq 30 \\ 0 & t > 30 \end{cases}$$



Assuming 30,000 mg of sugars are ingested, what is h ? Note that the concentration is with respect to the extracellular fluid, which has a typical volume of 140 dL.

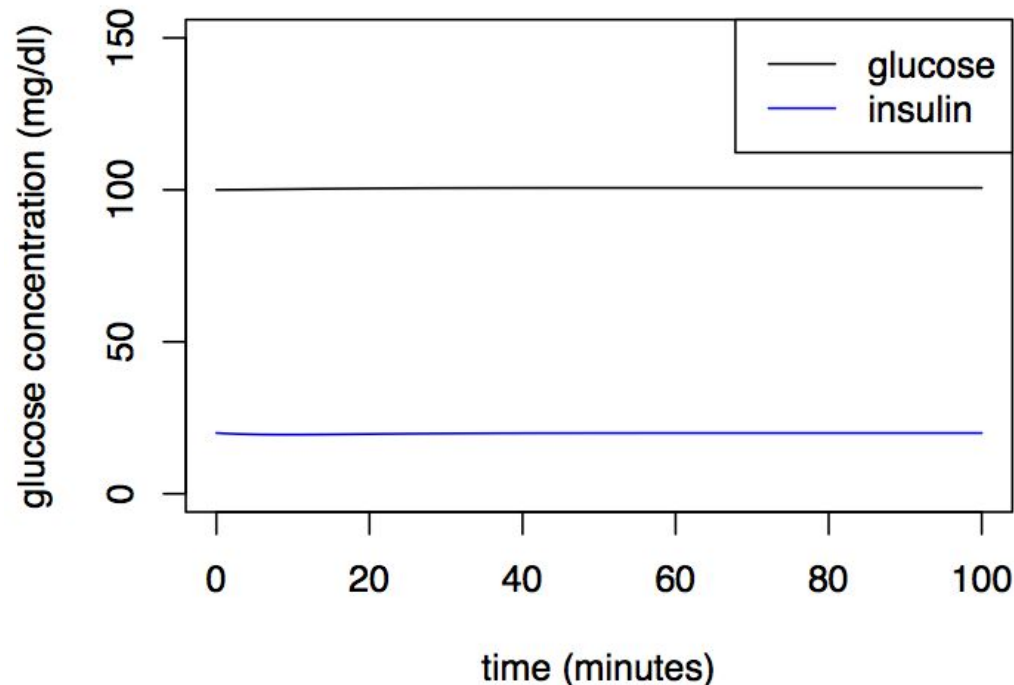
(f) In part (e) we assumed the rate at which glucose enters the bloodstream is constant. Sketch other possible forms of $G_{ing}(t)$.

Exercise 4 - Simulation

- (a) Download the file `glucose.R` and open in RStudio. Insert comments in the script to explain each line.
- (b) What is the homeostatic concentration of glucose assumed by this model? What is the homeostatic concentration of insulin?

Exercise 4 - Simulation

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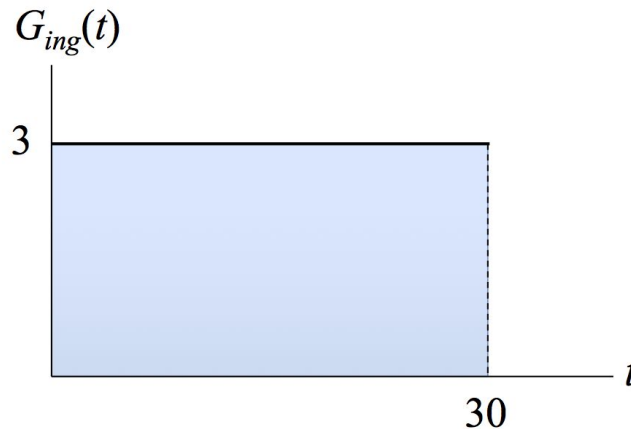


Exercise 4 - Simulation

(c) Ingestion of glucose will be complete at some time (t) and the concentrations of glucose and insulin should return to their homeostatic levels.

Assume $G_{ing}(t)=3$ (mg/dL)/min for $0 \leq t < 30$ and $G_{ing}(t)=0$ for $t \geq 30$.

Plot $G(t)$ and describe the observed dynamics.



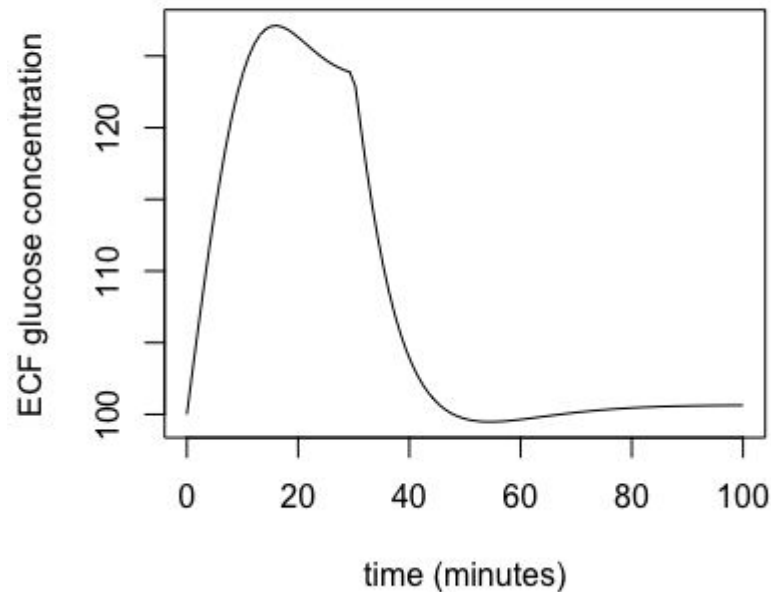
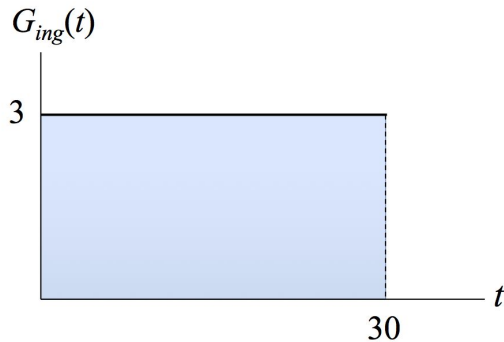
Assumes G_{ing}
is constant
from $t=0$ to
 $t=30$ min

(d) The function $G_{ing}(t)$ assumes an amount of glucose ingested.

- **Calculate this amount in mg.** (recall that the ECF is 140 dL).

Exercise 4 - Simulation

(c) Did the simulated dynamics show a rise and fall of glucose back to its homeostatic concentration?

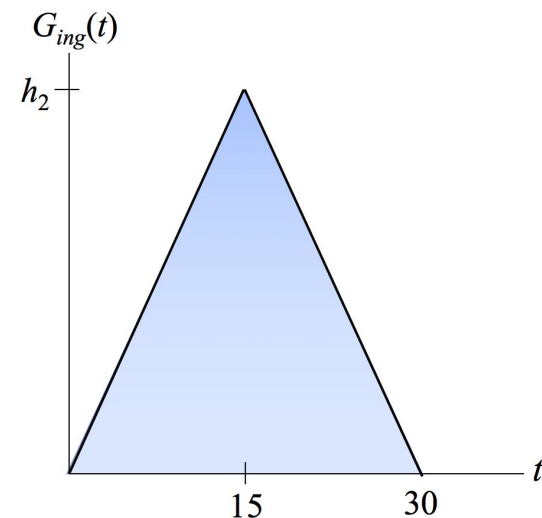
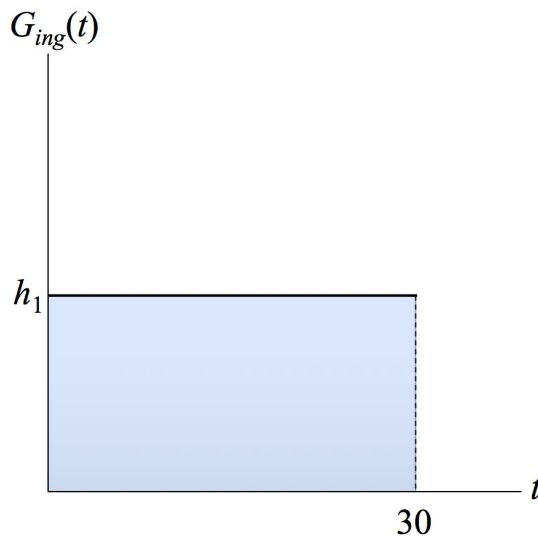


(d) The amount of glucose ingested was $G_{ing} * 30 \text{ min} * ECF \text{ volume}$
 $= 3 \text{ mg/dL-min} * 30\text{min} * 140/\text{L} = 12,600 \text{ mg}$

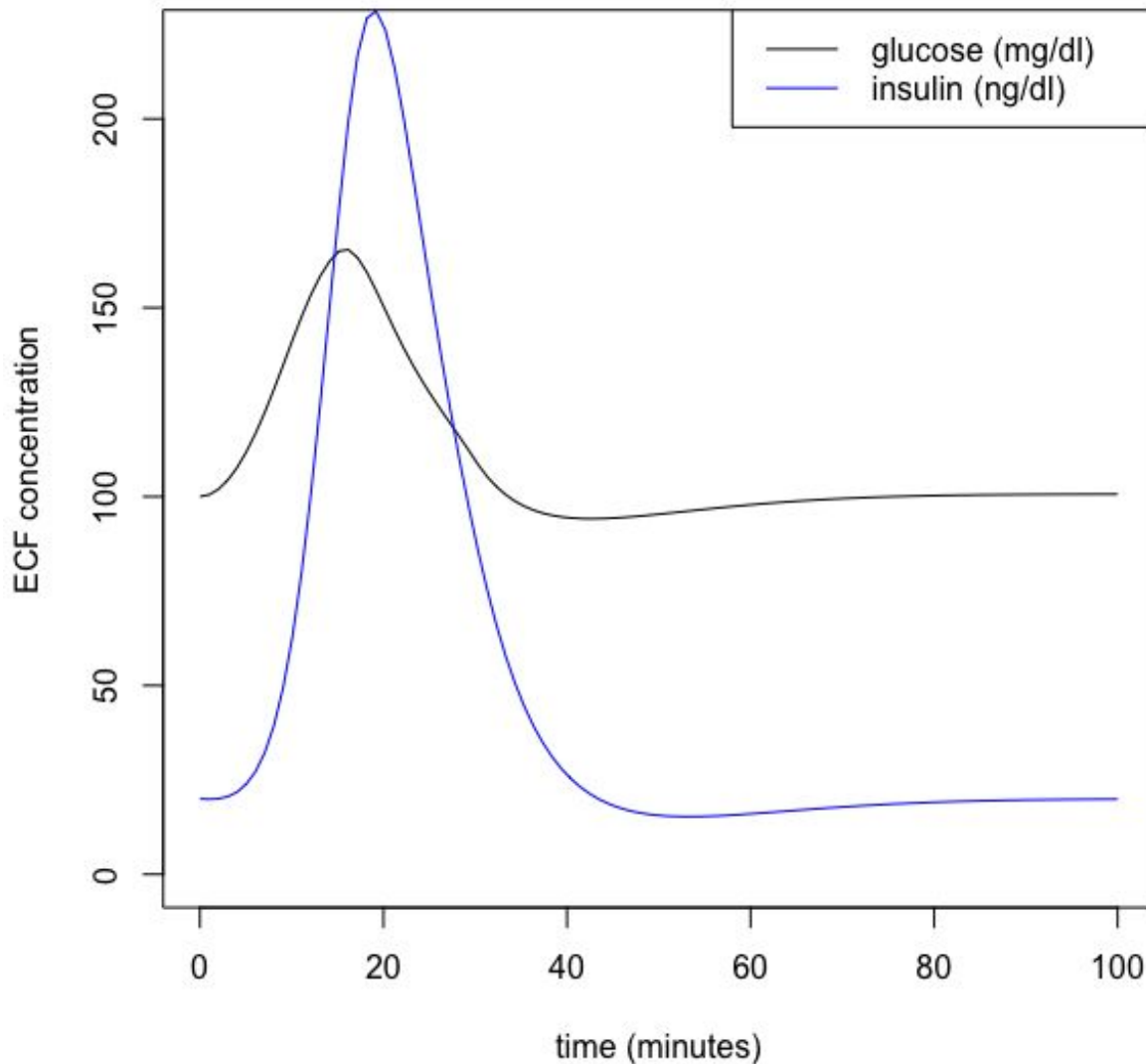
Exercise 5 - Simulation -- is a triangular ingestion function more realistic?

After eating a candy bar with about 30 g of simple sugars the glucose from the bar might be absorbed in 20 to 30 minutes.

- (a) Compare a constant ingestion rate with a triangular function. Run the simulation and sketch the glucose and insulin curves. How do the responses differ for the proposed ingestion rate functions?



Triangular ingestion function for 30,000mg of glucose.



Are the values and time-course realistic?

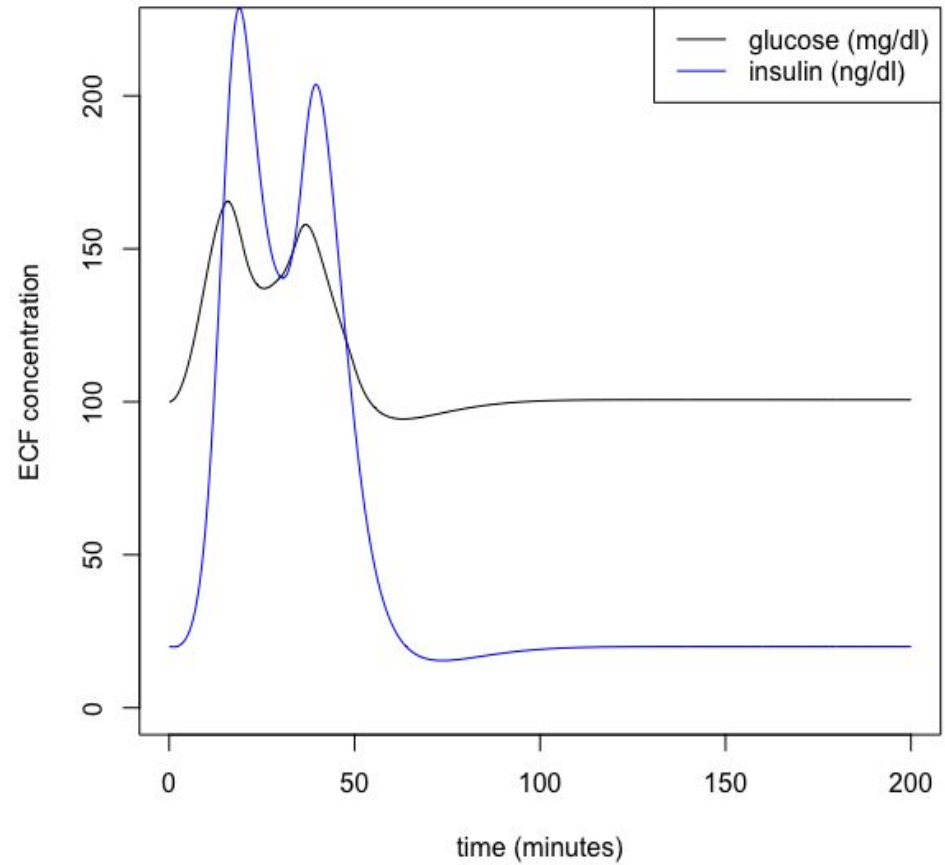
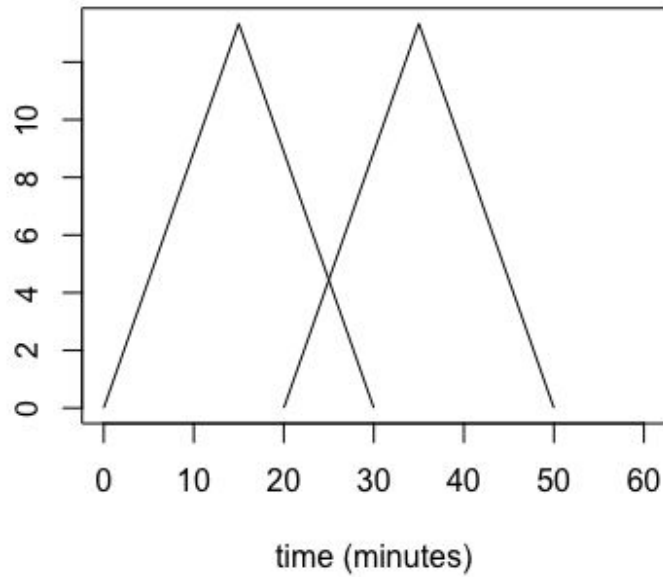
(b) How would you describe when the change occurs? How long is the lag interval (the time required for insulin secretion to show a response)? What might cause the change and lag in insulin secretion?

(c) Why does the insulin level decrease after a certain amount of time?

(d) How long after glucose release starts does the blood glucose level return to normal? That is, how long does the glucose spike last?

(e) If you eat a candy bar at $t = 0$ and another one at $t = 20$, how do you think your blood glucose and insulin levels would respond? Run the simulation. How does the model output compare with your predictions?

$G_{ing}(t)$ for each candy bar

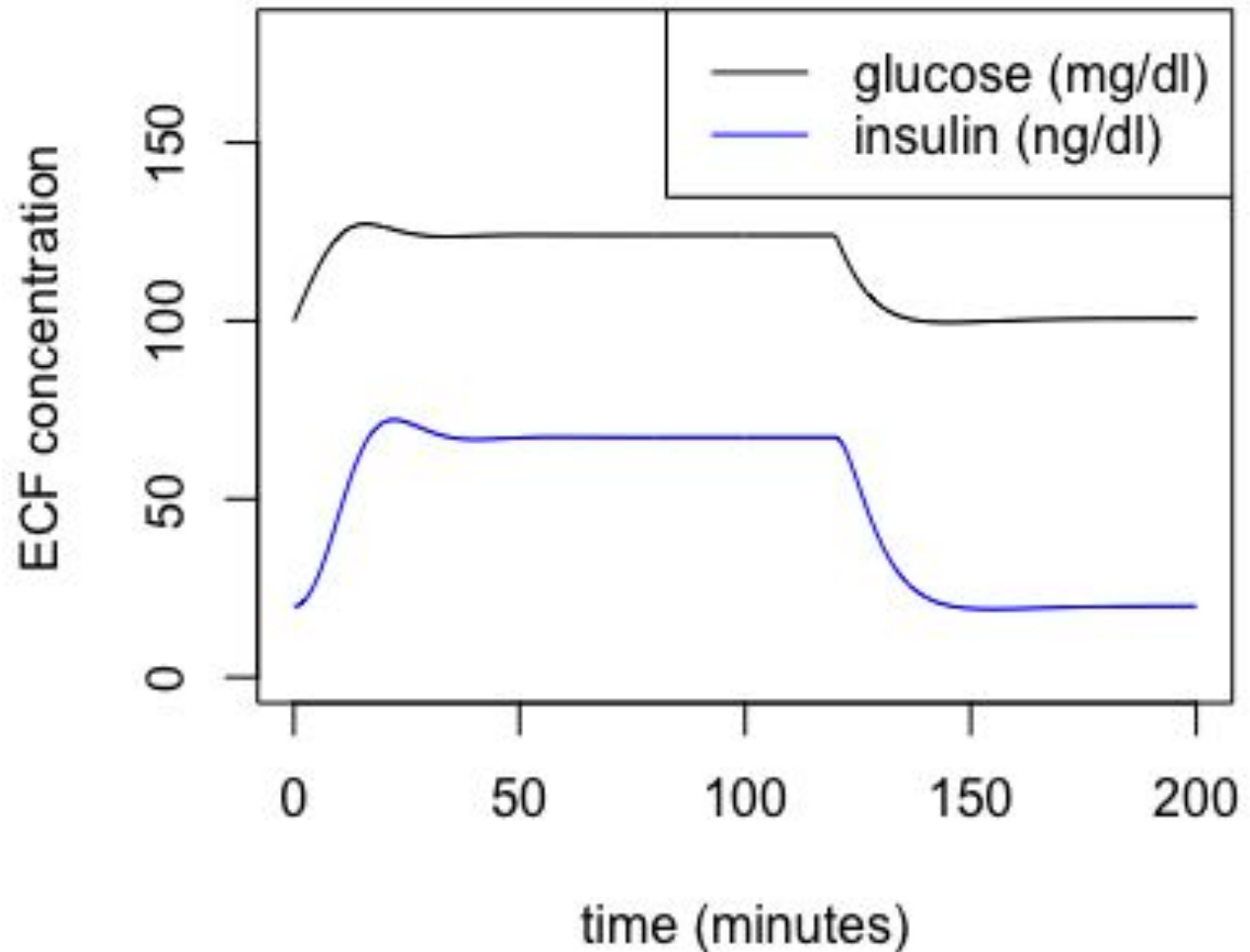


Exercise 6 - Simulation of complex carbohydrate ingestion

- Foods like pasta, rice, oats contain complex carbohydrates.
- These must be digested into glucose in the intestine before absorption.
- Thus, they are absorbed at a slower and steadier rate than the simple sugars.
- To simulate eating pasta, choose a glucose ingestion rate of 3 (mg/dl)/min for 120 min.
- **Use a sketch to predict the model output.**



How do the blood glucose and insulin curves differ from those generated by eating a candy bar? Why are they different?

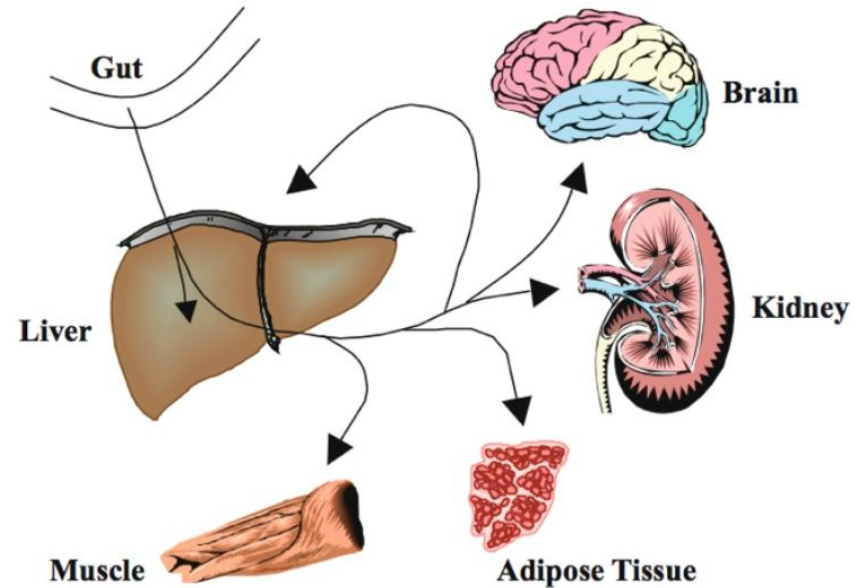


What really happens?

Given this background, students should understand both the biology and the math.

Before the lab day:

- 1) Go over risks/reasons to opt out of being a subject. Make opting out easy.
- 2) Suggest a minimal fasting period
- 3) Go over subject agreement form



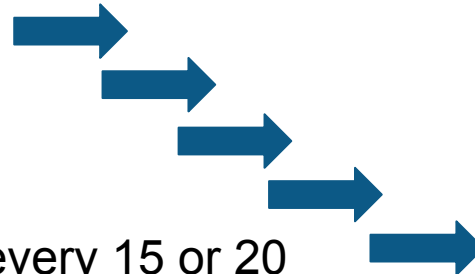
Experimental protocol:

Baseline
[glucose]_{blood}
& record

Consume
30-50g of
sugar (OJ,
jellybeans)
record amount



Measure
[glucose]_{blood}



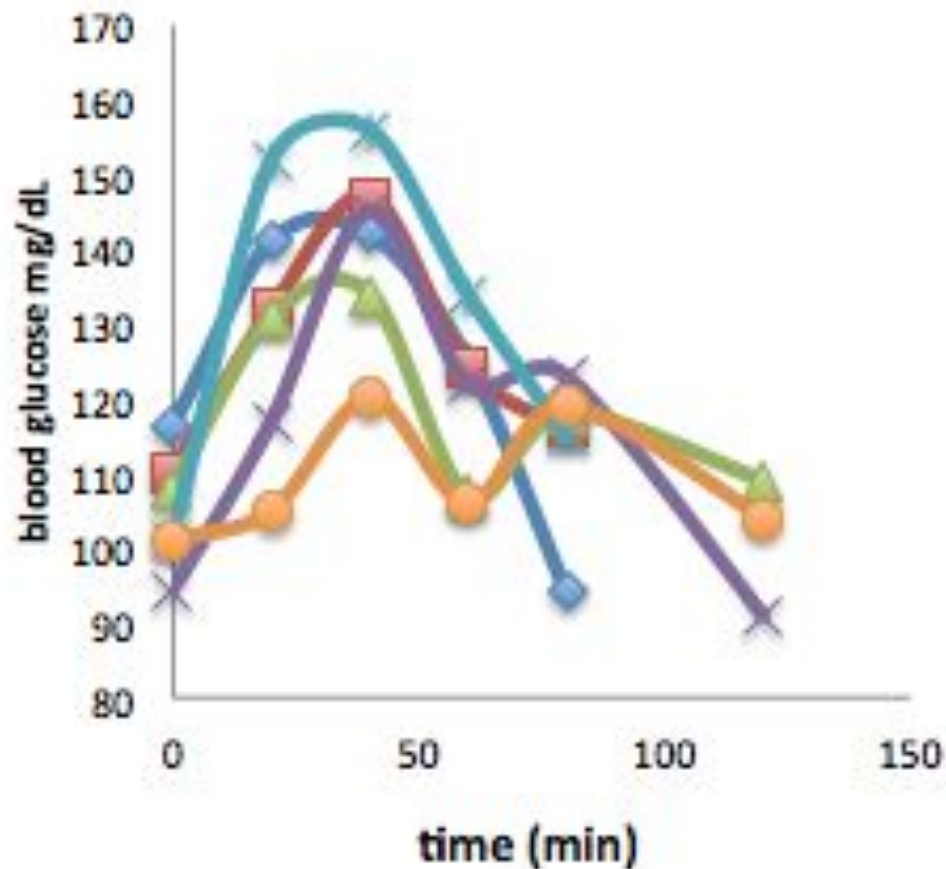
Sample every 15 or 20
min for 120 -140 min
& record the data

Measure
[glucose]_{blood}

Precautions:

- 1) IRB approval & student sign-off to take samples -- NO COERCION
- 2) Names not associated with data
- 3) Safety - alcohol wipes, first aid supplies, gloves, self-sampling
- 4) Biohazard collection for lancets, strips

blood glucose after 30g ingestion



The raw data

- 1) varies across subjects
- 2) YET remarkably peaks at 30-40 min post-ingestion.
- 3) The second peak is not unusual

Exercise 7 - Data Analysis

1. Formulate the ingestion function
2. Calibrate the model
3. Compare the model output to the data.

First:

- Load the packages `manipulate`, `deSolve`, `fBasics`, and `FME`
- Input your data directly into R:

```
t = seq(INITIAL TIME, FINAL TIME, by=TIME STEP) # time in  
minutes
```

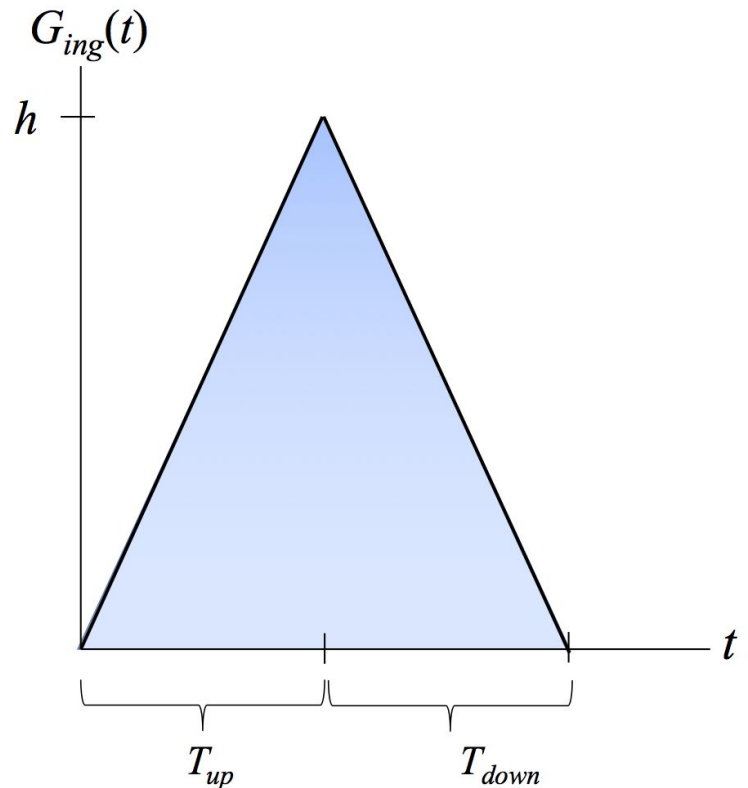
```
data=c(INPUT GLUCOSE READINGS HERE) # glucose levels in mg/dL
```

Ingestion Function

(a) Calculate the amount of glucose the subject consumed in milligrams. This parameter = *dose*.

(b) Use a triangular function for G_{ing} .

- Three unknowns T_{up} , T_{down} and h .
- Assume $T_{down} = T_{up}$
- Write h in terms of T_{up} and *dose* with the unknown parameter, unknown parameter being T_{up} .
- Write G_{ing} as a piecewise function in terms of T_{up} and *dose*.



Area of triangle:

$$\text{Area (mg/dl)} = (1/2) * h \text{ (mg/dl-min)} * 2T_{up} \text{ (min)}$$

Multiply by ECF volume (140 dl) to obtain total consumed in mg (assuming all absorbed):

$$dose = (1/2) * h * 2T_{up} * 140$$

Solving for h :

$$h = dose / (140 * T_{up})$$

Then

$$G_{ing}(t) = \begin{cases} \frac{h}{T_{up}} t & \text{if } 0 \leq t < T_{up} \\ -\frac{h}{T_{up}} (t - 2T_{up}) & \text{if } T_{up} \leq t < 2T_{up} \\ 0 & \text{if } t \geq 2T_{up} \end{cases}$$

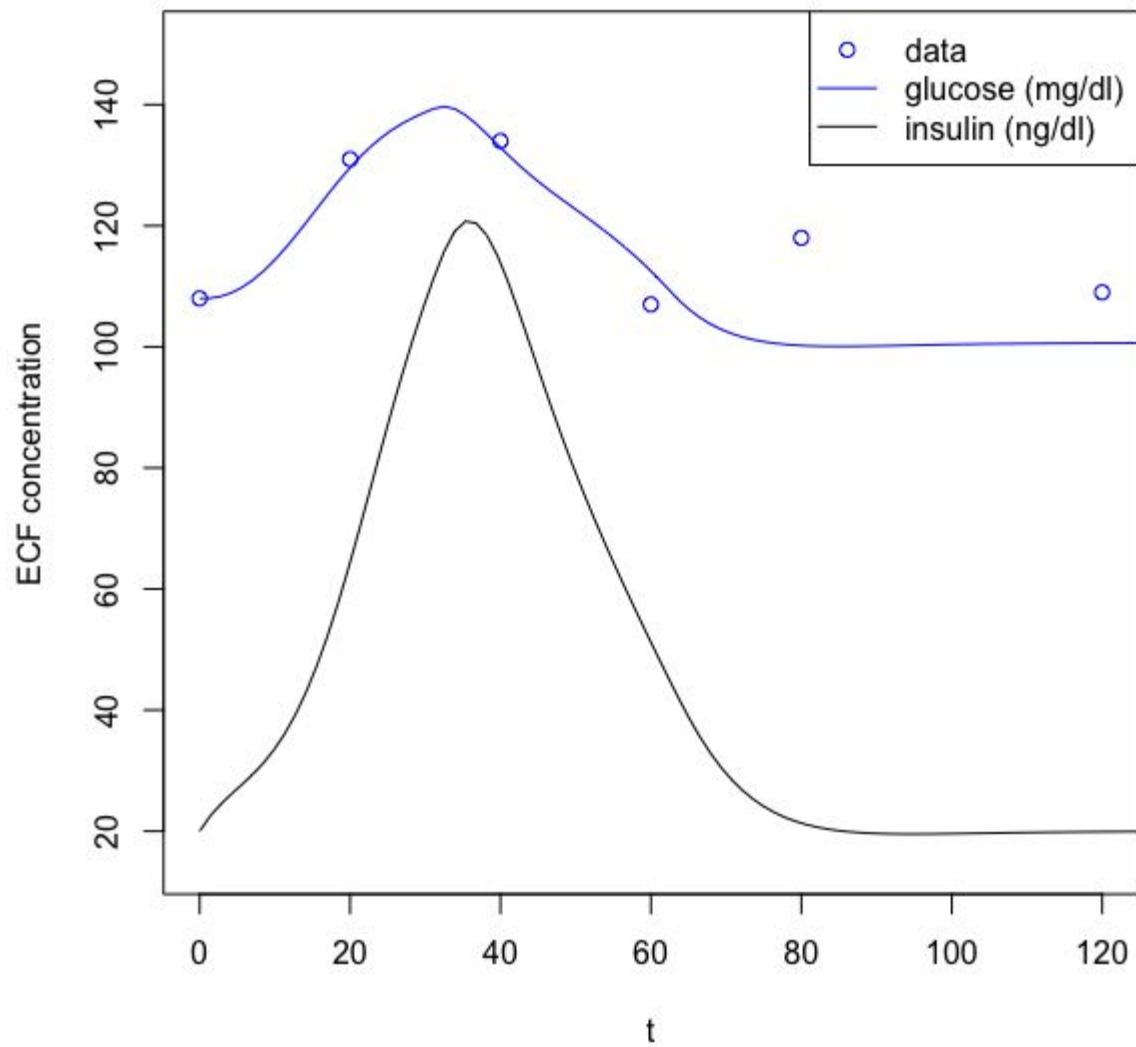
Run the simulation using $G_{ing}(t)$ for some value of T_{up} .

To use nonlinear regression you will need a reasonable initial guess for T_{up} :

- Create a slider for T_{up} to obtain an estimate for this parameter.
- In the manipulate function, plot both the model output and the data.

Find the best value for T_{up}

- Create an objective function that calculates the difference between the model output and the data.
- Use `modFit` to find the best-fit values for T_{up} and record.
- Plot the data and the model output on the same graph



Exercise 8 - Follow-up Questions

- (a) What assumptions were made by using the function $G_{ing}(t)$? Using the triangular function below, and calibrate your model.
- (b) What other forms of $G_{ing}(t)$ might you suggest? Why?
- (c) How might you quantify the error? One way of quantifying the error is to calculate the sum of the squared residuals. Are there other ways to quantify how well your model fits the data?
- (d) Are there other experiments that we could do to test our model further?
- (e) How sensitive is the modFit function to your initial guesses?
- (f) Consider how you might perform a sensitivity analysis for this model. Why might this be an important step in the modeling process?
- (g) How might you modify the model?
- (h) Based on what you have done, predict what the graph of glucose and insulin would look like if you ate a candy bar that contained 23g of sugar. What would this graph look like versus eating a popsicle with only 15g of sugar? What would you guess would happen if you ate a chicken breast, with little sugar but lots of protein, based on what you know about the digestive process?

Follow up experiments -- projects

- chicken breast
- pasta
- smelling and/or tasting
but not swallowing
sweets
- exercise
- caffeine

Projects may require new models:

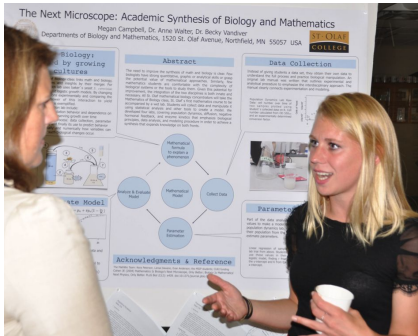
- adding glucagon
- adding a change in cell uptake due to exercise.
- sympathetic nervous system effects.
- or an adjustment of an effector e.g. caffeine.

Discussion

- Given the paradigm shift in how science is practiced from a strong disciplinary focus to one of interdisciplinary approaches to address a common problem, students should learn to think holistically, work together across disciplines and have enough common language to do so effectively.
- Using this beginning text in modeling, students will learn to value the approach and develop confidence and competencies needed to apply them in other courses and deepen their expertise through further courses.

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