2016

Disease Lab

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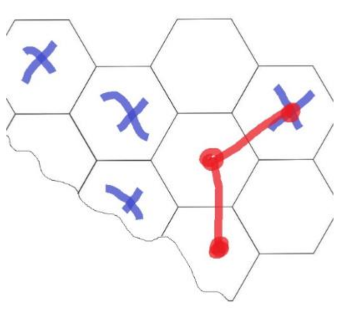
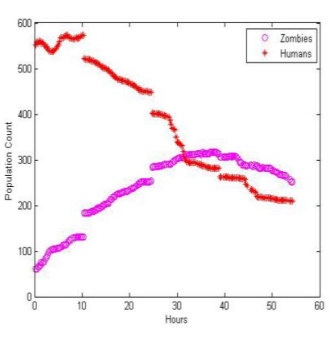
Laboratory Experiences in Mathematical Biology

Overview: Gaining hands on experience with diseases in a mathematics classroom is typically not possible and likely not appropriate. In the Disease Lab students collect data from a simulated ``zombie virus'' outbreak and then fit a given model to the data. Students are then challenged to create and simulate a new virus outbreak and create and fit a model to the new data.

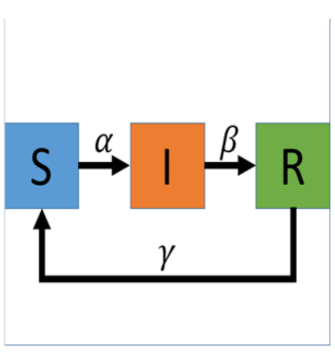
Lesson Outline: The outlined expectations and agenda are geared for classes consisting of mathematics, statistics, biology, natural resources and biological engineering students with calculus and differential equations experience. See Pedagogical Resources for teaching and scaffolding suggestions.



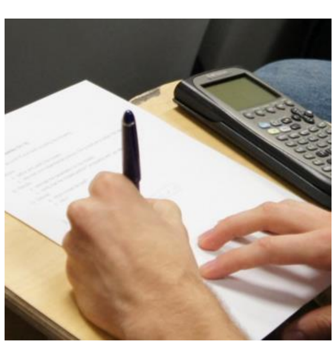
Lab Setup: Diseases are simulated using transparencies and dry erase markers.



Data and Examples: Data along with some student approaches from an introductory mathematical biology course and an ODE course are presented to illustrate some common student approaches and to help prepare teachers to scaffold student thinking.



Background and Extensions: At Utah State University the Disease Lab is often built around the Humans vs Zombies game of moderated tag played on campus. The game is briefly described here along with some student approaches to modeling the data.



Assessment Items: Primary assessment of student learning is taken from students' written reports. Additional assessment items targeting lab objectives are included here along with their targeted learning levels (see Pedagogical Resources for additional discussion of leaning levels).

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Expectations

Teams are expected to:

1. Parameterize the proposed model for the basic zombie disease
2. Create a model for the team's adjusted disease.
3. Estimate parameters using data and model hypotheses.

Teams are also expected to produce a short paper containing:

1. An **introduction** describing their disease and its similarities to other diseases,
2. A **methods** section that contains a description and justification of their proposed model and a clear explanation of how parameters were estimated,
3. A **results** section that describes how well the their model performed with as well as a "picture" of the predicted populations plotted with their data for a visual reference,
4. A **discussion and conclusion** section detailing model implications.

Lab Agenda

A general outline for the Disease Lab is:

- Lecture: Introduction to the Disease Lab and basic zombie disease (15 min)
- Group Time: Designate roles for basic zombie disease and play game at least 2 times. Parameterize and solve proposed model (25 min)
- Class Discussion: Teams plot and compare given model to data and share ideas on how to improve the model (10 minutes)
- Group Work: Teams create their own adjusted disease and play game at least 2 times (15 min)
- Group Work: Teams create, develop and parameterize models for their adjusted disease (15 min)
- Class Discussion: Groups present models for their adjusted disease data including description of units parameters (40 minutes)

This schedule can be tightened (e.g. parameters for the given model can be calculated as a class, groups hand in reports instead of presentations) as the instructor needs and is aimed to be accomplished over the span of multiple class periods. Between class days, students are expected to meet regularly as groups to further develop their models and compare with data.

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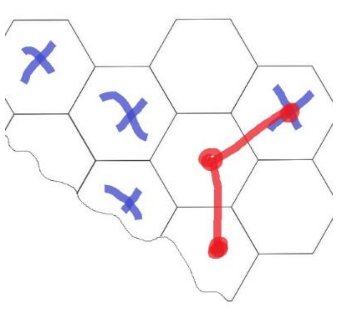


Lab Setup: Diseases are simulated using transparencies and dry erase markers.

Materials

The following materials are needed for each group:

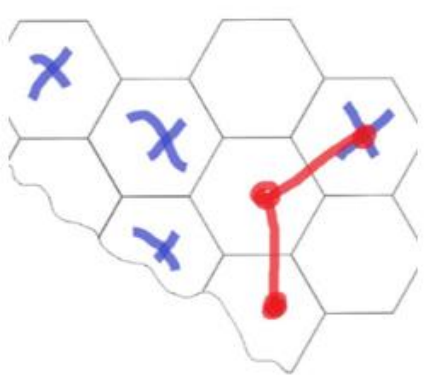
- 2 hexgrid transparencies

- 2 dry-erase markers (different colors)

Methods

Basic Zombie Game

To generate data for the basic zombie game one team member directs the zombie population (Zombie Master), one leads the human population (Humanoid King/Queen) and one judges results and records data. Zombies and humans are drawn by their respective rulers on separate hex transparencies using dry-erase markers of different colors beginning with 1 zombie and 49 humans. For the basic zombie virus each zombie occupies three consecutive hexes, one for its huge head and one for each of its attacking arms, while humans fill only one hex each. Once the Zombie Master and Humanoid King/Queen have secretly placed their respective players on the hex arenas, one determines which humans have been successfully attacked by counting the hexes that are occupied by a human and a zombie arm or head when the transparencies are superimposed as seen in the figure below. These new zombies are added to the zombie population and transparencies are then erased for the subsequent turn. The game is over once the entire population has been zombified.



Example from basic zombie game where the zombie population would increase by one.

Student Adjusted Disease

Students alter the basic zombie virus to create a new disease. Changes students frequently make:

- Allow for recovery
- Expand or contract the “radius of infection”
- Allow for an infected, but not contagious period

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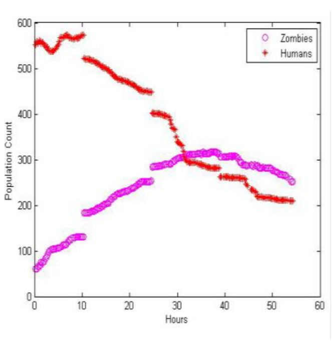
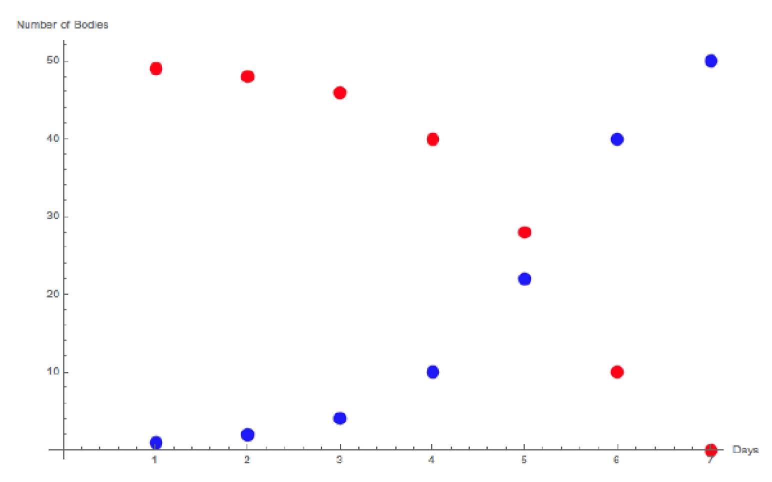


Data and Examples: Data along with some student approaches from an introductory mathematical biology course and an ODE course are presented to illustrate some common student approaches and to help prepare teachers to scaffold student thinking.

Here is an example of one type of data set and the associated plot for the basic zombie disease.



Day	1	2	3	4	5	6	7
Humans	49	48	46	40	28	10	0
Zombies	1	2	4	10	22	40	50

In Utah State University's Applied Mathematics in Biology class the Disease Lab is used to introduce discrete modeling.

For most groups the model progression is as follows:

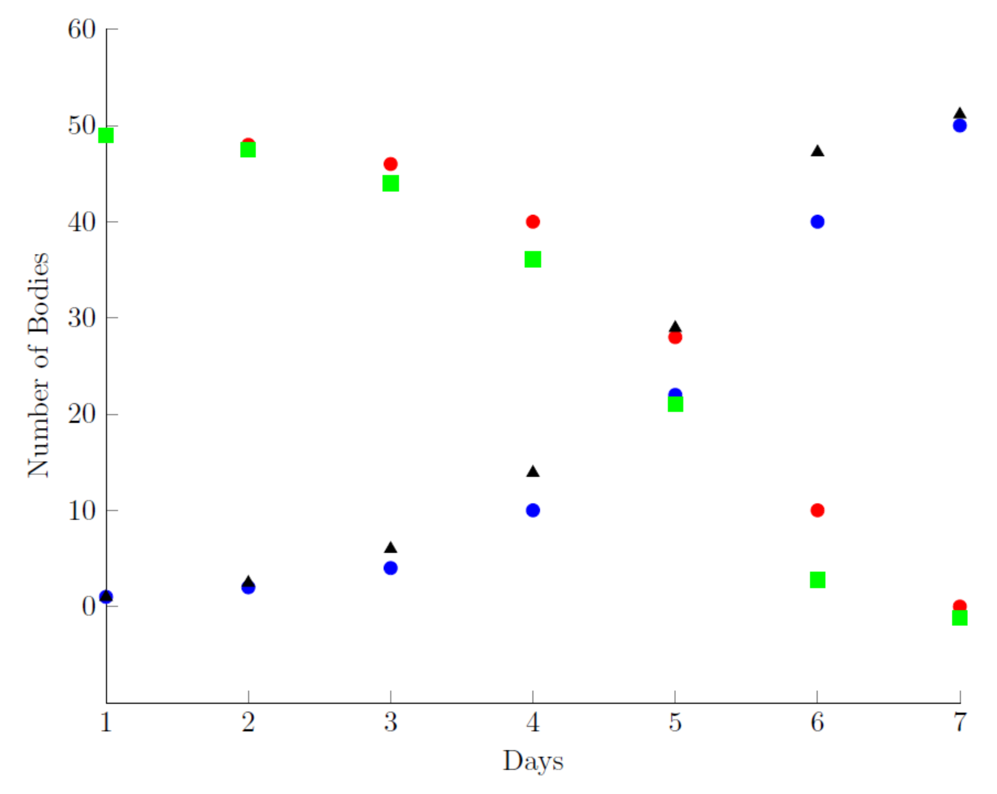
- Suppose n is the number of turns which have been played in the disease game, and Z_n is the number of zombies in the n^{th} turn of the game. Then one may write
$$Z_{n+1} = Z_n + Z_{new}$$
where Z_{new} is the number of individuals which are newly infected during turn n.

- A beginning model can be put together by assuming that the distribution of infective hexes and zombies creating them is random. If each infected individual occupies 3hexes (one for the hex they stand in and one for each of their two arms), and the board contains 100 hexes, then an approximation for the total number of hexes which are infectious at turn n is
$$Z_n \times \frac{3}{100}.$$

- The number of humans on turn n, H_n, is the total (T) less the number of current zombies, that is
$$H_n = T - Z_n.$$

- Then the number of new zombies can be approximated
$$Z_{new} = H_n \times Z_n \times \frac{3}{100}.$$

- Putting this all together gives an initial, discrete logistic model for the propagation of disease:
$$Z_{new} = Z_n + Z_n \times \frac{3}{100} \times (T - Z_n).$$



Data from the basic zombie game along with predicted zombie (▲) and human (■) populations from the discrete logistic model.

This model (discrete logistic equation) often serves as a foundation for students to build other, (sometimes) more advanced models, for data created from playing the game according to student created rules.

In calculus focused classes (e.g., calc 1,2 or ODE) we focus on continuous models. From our Basic Zombie Game perspective, the logistic population growth model is based on two concepts:

1. Individuals in the population are considered to have equal probability of being infected by a zombie a rate of α, the infection rate. For the Basic Zombie Game we expect $\alpha \approx 0.03$ since each zombie occupies 3 out of 100 hexes yielding an infection rate of 0.03. So, a zombie can attack and infect αN others per day, where N is the total population. The fraction of susceptible humans is thus $\frac{H}{N}$. Hence, the number of new zombies created in one day per zombie is then $\alpha N\left(\frac{H}{N}\right)$, giving the rate of new zombie creation as (1)
$$\frac{dZ}{dt} = \alpha N\left(\frac{H}{N}\right) Z = \alpha H\, Z.$$

2. When a human is attacked, it must become an zombie the next day. Let β represent the conversion rate of humans to zombies. Then, because every gain of the zombie population is an equivalent loss from the human population (i.e., $\beta = 1$), the change in the human population can be characterized with
$$\frac{dH}{dt} = -\beta\alpha H\, Z.$$

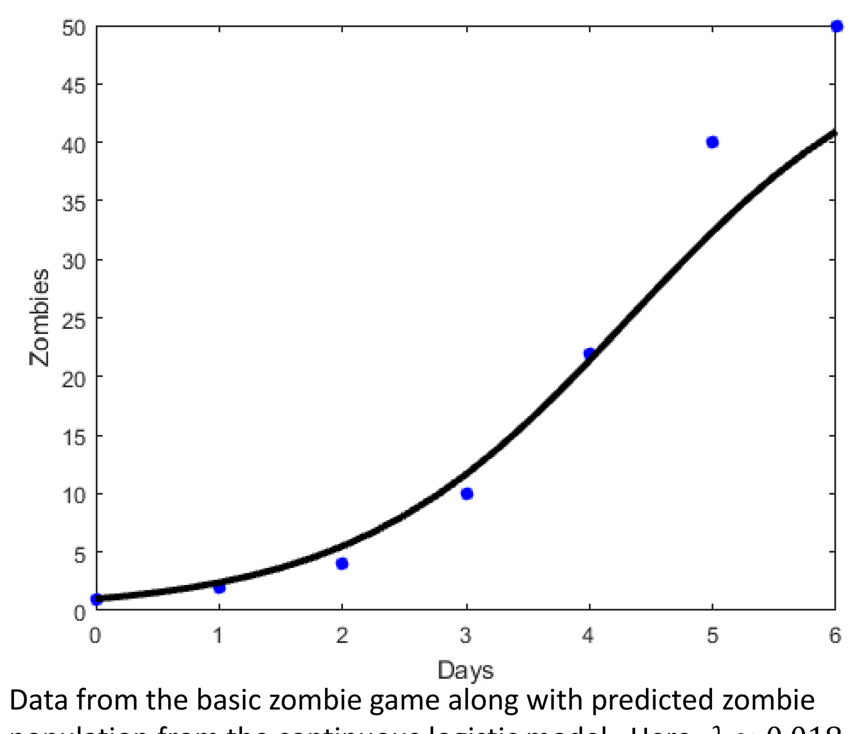
Now, note that
$$\beta\frac{dZ}{dt} = -\frac{dH}{dt},$$
relates only derivatives and can therefore be integrated. Integration yields
$$H(t) = H_0 - \beta(Z(t) - Z_0).$$

Finally, substituting into (1) leads to
$$\begin{aligned}\frac{dZ}{dt} &= \alpha Z(H_0 - \beta(Z(t) - Z_0)),\\ &= \alpha Z(H_0 - \beta Z_0 - \beta Z(t)),\\ &= \frac{\alpha}{\beta Z}\left(\frac{H_0 - \beta Z_0}{\beta} - Z(t)\right).\end{aligned}$$

Now, let $\lambda = \frac{\alpha}{\beta}$ and $K = \frac{H_0 - \beta Z_0}{\beta}$ to get
$$\frac{dZ}{dt} = \lambda Z(K - Z),$$
a common form of the Logistic Model where K represents the carrying capacity and λK is the rate of maximum population growth. However, the logistic equation was originally published by Verhulst as
$$\frac{dZ}{dt} = r\, Z\left(1 - \frac{Z}{K}\right),$$
where r is precisely the growth rate λK.

Solving for the population $Z(t)$ we get
$$Z(t) = \frac{KZ_0}{Z_0 + (K - Z_0)e^{-K\lambda t}}.$$

In most calculus and differential equations classes λ is approximated by using a data from the set; i.e., substituting $t = 4, Z = 22, Z_0 = 1$ and $K = 50$ into our solution yields $\lambda \approx 0.018$. Alternatively students can get a better feel for fitting by simply "eyeballing" λ.



Data from the basic zombie game along with predicted zombie population from the continuous logistic model. Here, $\lambda \approx 0.018$.

Since the logistic model does not perform well students typically adjust the assumptions of the models (e.g., per capita growth is not linear) to build their own, more descriptive models.

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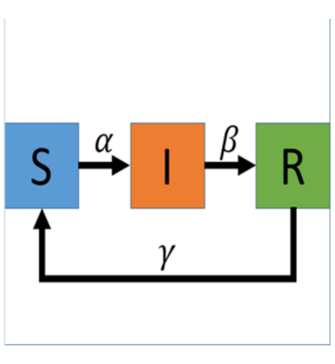
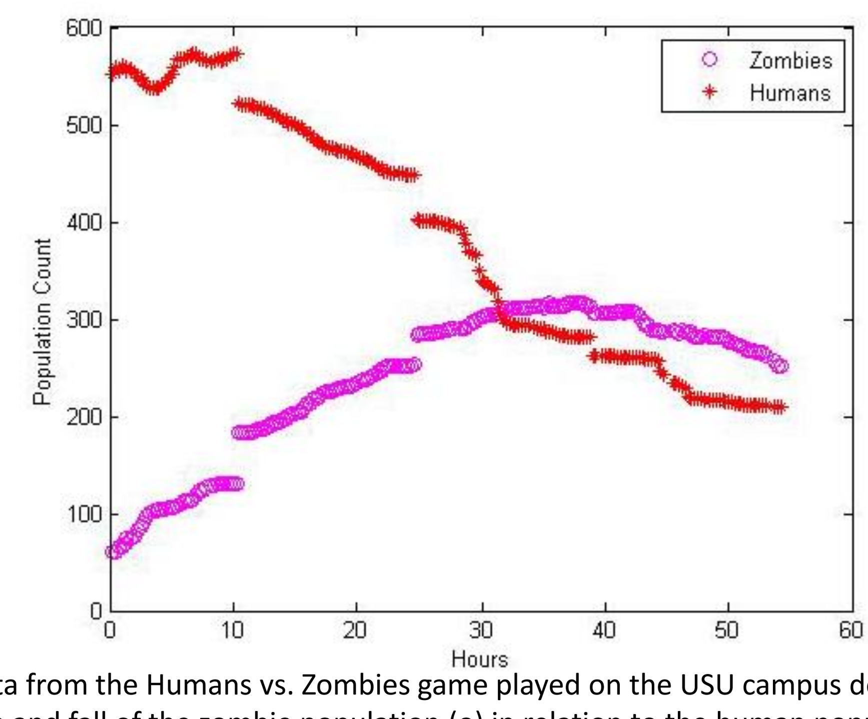


Background and Extensions: At Utah State University the Disease Lab is often built around the Humans vs Zombies game of moderated tag played on campus. The game is briefly described here along with some student approaches to modeling the data.

Humans vs. Zombies

HvZ is a game of moderated tag that started at Goucher College in 2005 and is currently played on campuses worldwide. The game is played in a bounded area at specific hours of the day, e.g. on campus from 8 a.m. to 10 p.m., excluding buildings. Humans are converted into zombies by touch (tag). Humans can defend themselves by stunning zombies for 15 minutes with a Nerf dart blaster or by pelting zombies with a pair of socks rolled up into a ball. Also, a zombie dies if it does not infect a human within a 24 hour period. Additionally, humans are required to fulfill certain missions at various points during the game. These missions result in large fatalities in the human population and a corresponding increase in the zombie population. In order to track the progress of the game, zombies are required to report the ID number of each human they tag. This data drives the second portion of the Zombie Lab.



Data from the Humans vs. Zombies game played on the USU campus depicting the rise and fall of the zombie population (o) in relation to the human population (*) over time. New players were allowed to join the game during the first day (hence the increases in the human population). Additionally, the jumps in the populations were due to missions the humans were required to fulfill at various points in the game that result in many humans being turned to zombies.

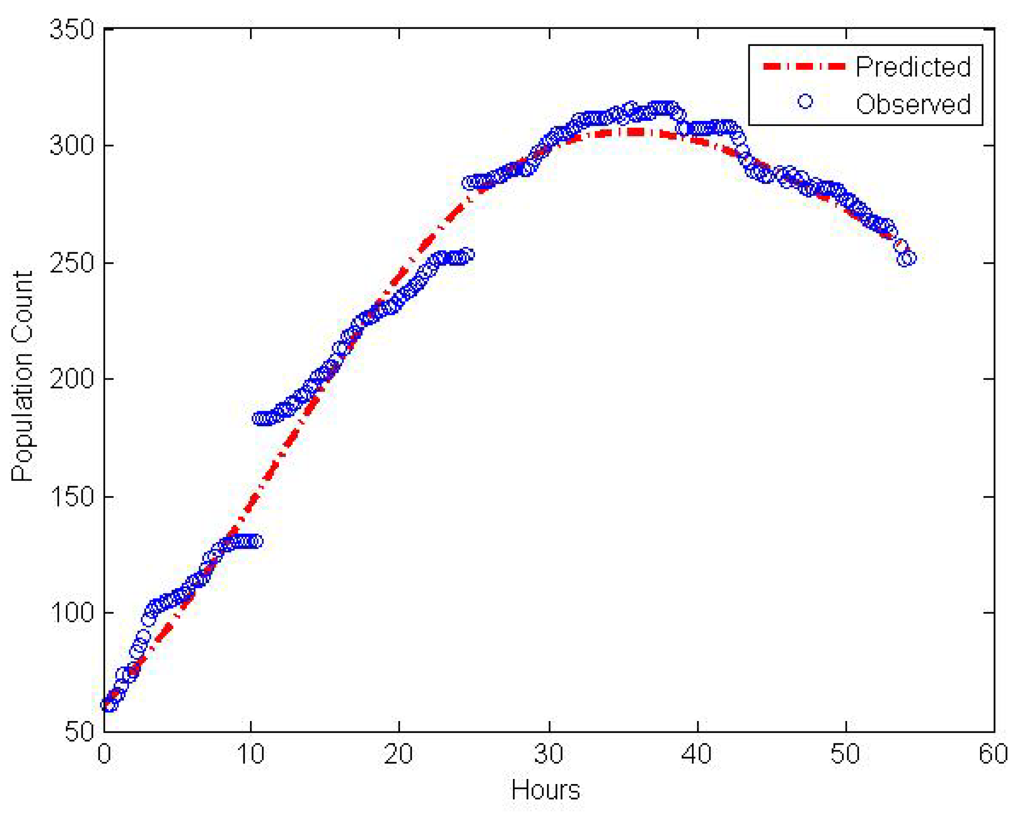
In general, students are excited to model this data since they have all played or witnessed the HvZ game on campus. Presented here are a couple of student approaches to modeling this data.

Threshold Model

This group conjectured that the rate of zombies dying or simply quitting the game would grow with time due to the increasingly scant supply of humans to feed on as the game progressed as well as zombified students simply quitting when the action died down a bit. Additionally, they supposed that there is a critical zombie threshold population, P, that if crossed would cause a collapse of the zombie population. In order to accommodate these two hypotheses the students' model took the following form:

$$\frac{dZ}{dt} = -r\left(1-\frac{Z}{P}\right)\left(1-\frac{Z}{K}\right)Z - stZ,$$

where r is the intrinsic growth rate, K is the carrying capacity and s describes the increasing rate at which zombies die or leave the game.



Plot of students' Threshold Model fitted to the HvZ zombie population data using least squares. Students estimated the intrinsic growth rate at 0.122 and the death acceleration term $s \approx 0.0014$. The model is based on the hypothesis that once the zombie population has been reduced below a critical threshold it would naturally collapse to zero; students did not notice that their threshold, $P \approx 840$, was very similar to the corresponding $K \approx 845$.

The Answer's a Parabola, Right? Model

Some students have had experience fitting polynomial curves to data, and when confronted with the HvZ data immediately want to fit a parabola. Most of these students are initially straightforward with their intentions, suggesting models of the form

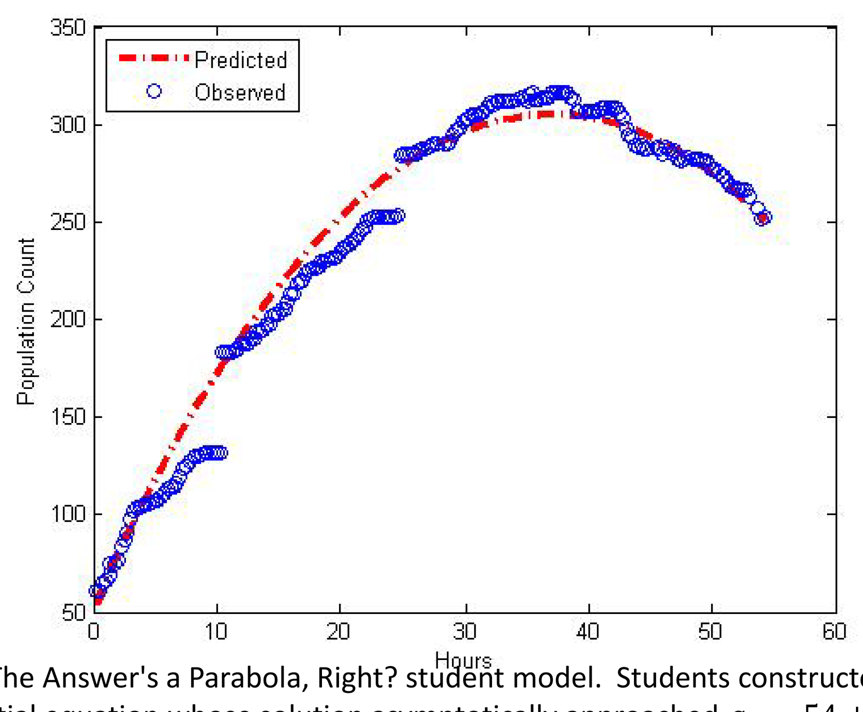
$$\frac{dZ}{dt} = At + B$$

where A represents the population's rate of acceleration and B is the growth rate. Many realize their approach is off target when asked to either describe the relationships between the variables they used to create the model or outline the physical concepts upon which the model was derived. They come to understand the models are supposed to be mechanistic and not strictly empirical models used to drive a curve through points. However, others remain determined that the parabola is the right answer, but it simply needs to be dressed up more.

In one class, the lab occurred shortly after the students had learned the method of integrating factors. In one homework assignment students were asked to "…construct a first order linear differential equation whose solutions have the required behavior as $t \to \infty$". The students were then assigned a variety of functions their solutions should approach. Inevitably, some students noted they could simply extend their homework experience to the HvZ scenario and produced the model

$$\frac{dZ}{dt} + Z(t) = \frac{dg}{dt} + g(t)$$

where $g(t) = At^2 + Bt + C$, the parabola the students want to use to model the data. The students proceeded to solve the differential equation using the method of integrating factors to get $Z(t) = At^2 + Bt + C + De^{-t}$, a function that approaches $g(t) = At^2 + Bt + C$ asymptotically.



Plot of The Answer's a Parabola, Right? student model. Students constructed a differential equation whose solution asymptotically approached $g = 54 + 13.55t - 0.18t^2$, the quadratic fit.

So, while every student model will not be mechanistic, the students were using mathematics to explain and describe data fluently which is seldom seen in a typical differential equations classroom.

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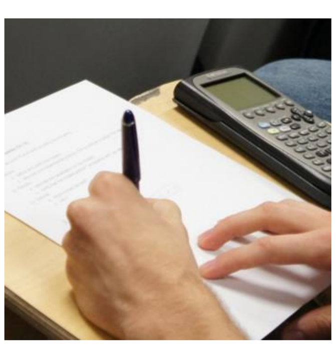
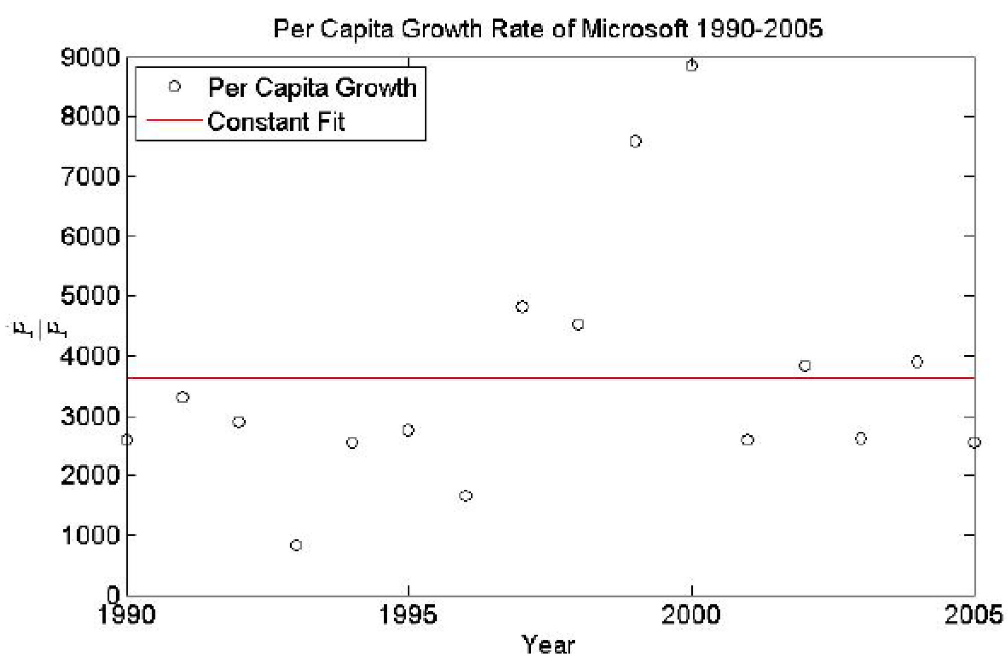


Assessment Items: Primary assessment of student learning is taken from students' written reports. Additional assessment items targeting lab objectives are included here along with their targeted learning levels (see Pedagogical Resources for additional discussion of leaning levels).

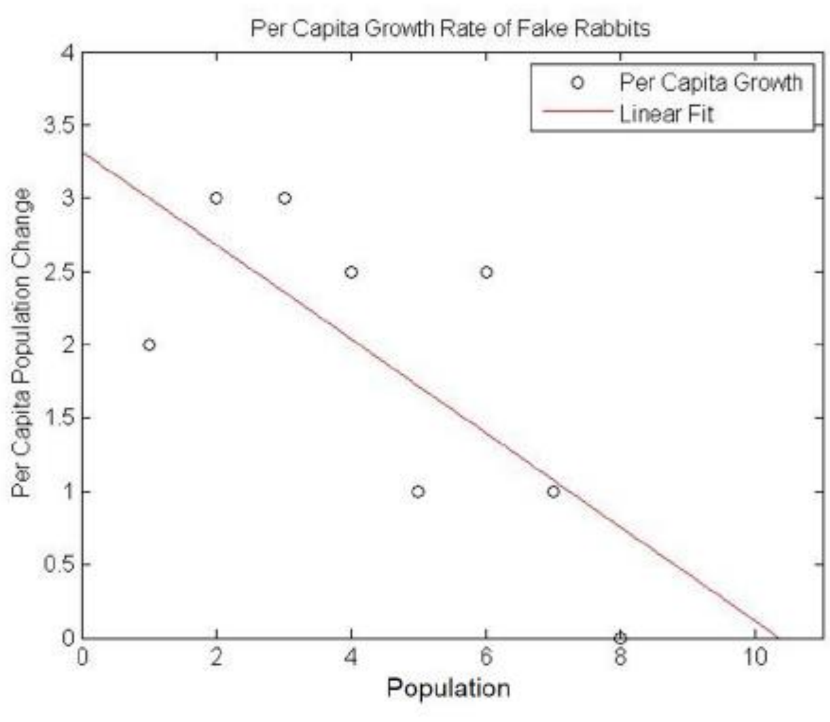
1. (Discover-a-Relation, Construct-a-Concept) John is studying how some businesses flourish over time. Using the reported per capita employee growth of Microsoft from 1990-2005, John calculates and draws the line of best fit. He then conjectures that Microsoft experienced exponential employee growth over that interval. Explain why you either agree or disagree with John's assessment.



Plot for test item 1 displays percapita growth data of Microsoft employees from 1990 to 2005 along with the line of best fit.

2. (Creative-Thinking, Comprehension-and-Communication) Given data describing the population, P over time, list three different plots (or ways of arranging the data) that may help you develop a model and and give reasons for your choices.

3. (Discover-a-Relation, Comprehension-and-Communication) On the virtual farm, the virtual farmer has been simulating a new breed of digital rabbits. His observations are presented in the plot below. Use the virtual farmer's data to develop a population model. Be sure to give a biological description of any parameters you may introduce along with a description of their units.



Plot for test item 3. Percapita growth of a fictional rabbit population is displayed along with the line of best fit.

4. (Algorithmic Skill) Tumors are cellular populations, T, growing in a confined space where the availability of nutrients is limited. The Gompertz curve has been successfully fit to data of growth of tumors. The Gompertz differential equation is of the form

$$\frac{dT}{dt} = rT\,\log\left(\frac{K}{T}\right)$$

where r is the intrinsic growth rate. What are the equilibrium solutions of the Gompertz equation?

(Comprehension-and-Communication) Sketch a few solution curves that illustrate the dynamics of the model.

5. (Appreciation) In your opinion what is the role of mathematics in the study of disease? Mathematics is (circle one)
   a. of fundamental importance as the study of disease is a quantitative science
   b. useful to some scientists in solving problems of limited use to a few scientists working in theoretical areas
   c. irrelevant

   Write a sentence or two explaining your choice above.