Let's Do It Discretely!

An Introduction to Discrete Difference Equation Models in the Life Sciences

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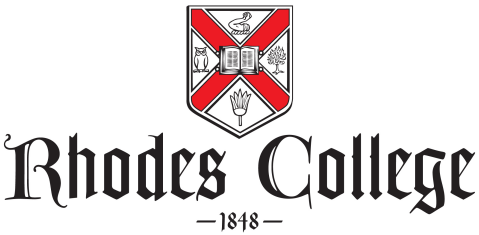
Department of Mathematics & Computer Science
Rhodes College, Memphis, TN

[2]Associate Professor of Mathematics
School for Environmental Citizenship
Unity College, Unity, ME



BioQuest 2017

Making Meaning through Modeling: Problem Solving in Biology

Michigan State University, East Lansing, MI
24 July 2017

Roadmap

1. Introducing Ourselves
2. Establishing a Common Vocabulary
   - What do we mean by “model”?
   - What is a discrete difference equation?
3. Examples from a Discrete Math Modeling Course
   - Modeling the Growth of a Bacterial Culture
   - Modeling Population Genetics over Time
4. Discussion
   - Where could a discrete difference equation model be utilized in your class?
   - What materials would you need to accomplish this?
5. A Discrete QUBES Faculty Mentoring Network (FMN)

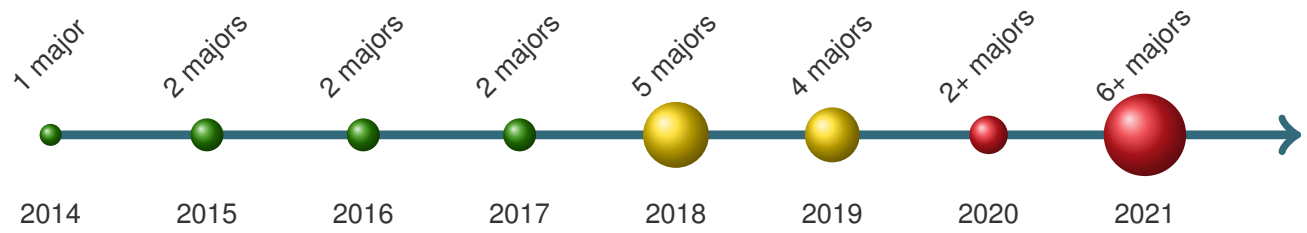
Roadmap

Rhodes College

Memphis, TN

- National, residential, liberal arts college
- 2046 students
- 5–8 Math majors per year
- ~ 30 Biology majors per year
- 5–10 Environmental Science majors per year
- Growing Biomathematics major

Biomathematics Majors at Rhodes



Current sophomores (class of 2020) and freshmen (class of 2021) have not declared yet

Erin Bodine Background

Educational Background

BS in Mathematics
BA in Anthropology
Few classes in Biomathematics

Epidemiological modeling
Published several papers
Population modeling

PhD in Mathematics
Concentration in Mathematical Ecology
Population modeling

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Teaching at Rhodes

- Classic calculus sequence
- Discrete Math Modeling (w/ bio apps)
- Agent-based Modeling
- Applied Calculus (biological applications)
- Continuous Math Modeling & Scientific Writing

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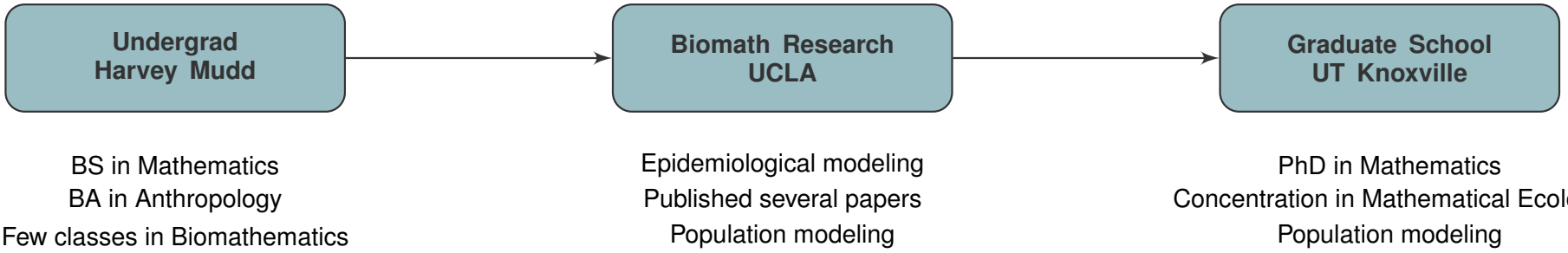

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Research at Rhodes *Focus on population dynamics*

Epidemiological Modeling
- Ebolavirus
- Yellow Fever

Cancer Modeling
- Proton radiation therapy

Species Conservation Modeling
- Optimal Species Augmentation
- Northern Spotted owl & Barred Owl competition
- Bromeliaceae life history & conservation
- Invasive weevil control

Unity College

Unity, ME

- Environmental Liberal Arts College
- 750 students
- All Environmentally related majors
  No math, physics, or engineering majors
- Applied Math & Statistics Minor

- 2 majors are BA degrees, the remainder (10+) are BS degrees

Carrie Diaz Eaton Background

Educational Background

BS in Mathematics
Minor in Zoology
Research in neuromodeling

MA in Interdisciplinary Mathematics
Con Bio, Genetics
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- "Calculus" (biological/environmental applications)
- Discrete Math Modeling (w/ bio apps)
- Continuous Modeling with ODEs (COA)
- Quantitative Literacy HS $\rightarrow$ College Bridge
- All algebra and intro stats where needed
- Modeling Ecological Disease
- Spanish
- Online Grad Course Development in Systems Thinking

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Research at Unity

EPIDEMIOLOGICAL MODELING
- Humans vs Zombies
- Student Projects

EVOLUTIONARY ECOLOGY

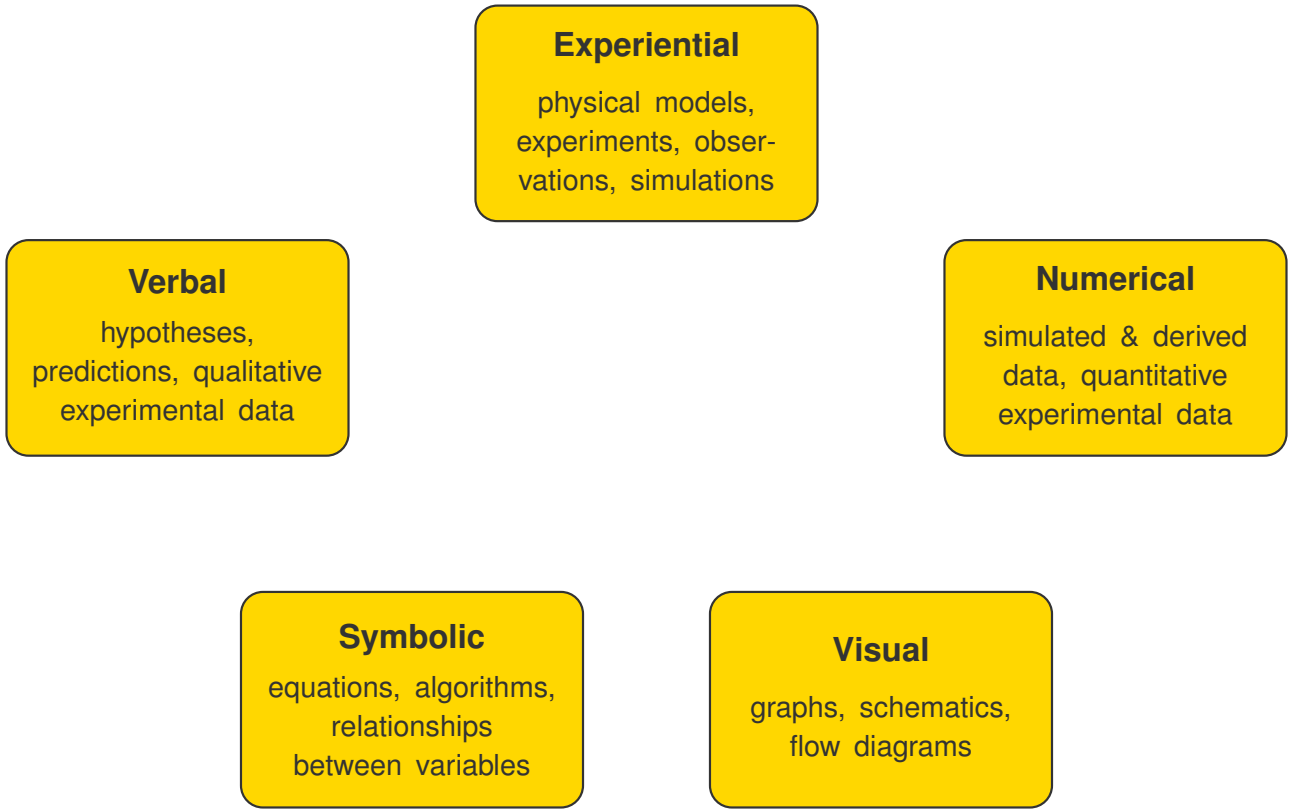
INTERDISCIPLINARY MATHEMTICS EDUCATION
- Cofounded QUBES network
- Biocalculus implementation research
- Marine applications of calculus
- GTA/Early Career Teaching Development
- Ethnography & Identity

Roadmap

What do we mean by “model”?

A *model* is a simplified representation of relationships and/or processes in the real world, created for some purpose

A model can be represented in a variety of ways:



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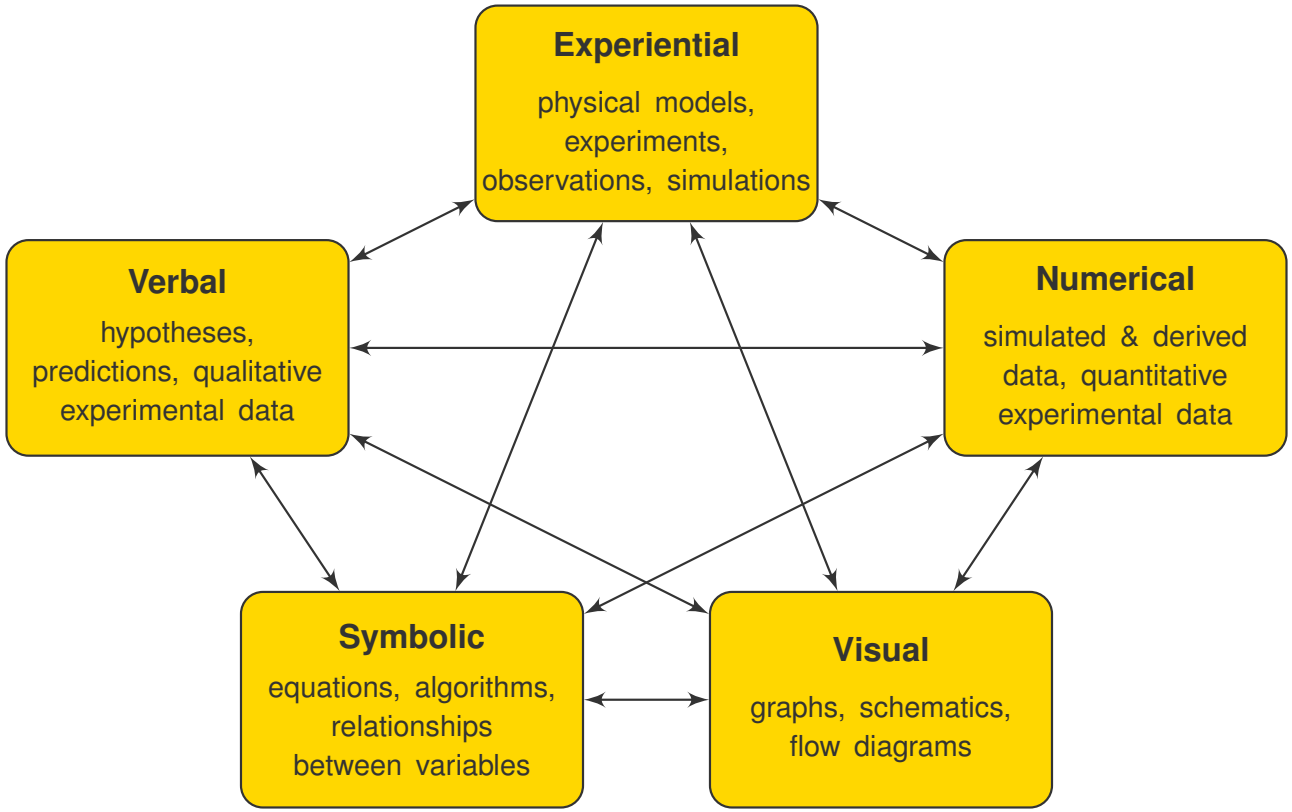

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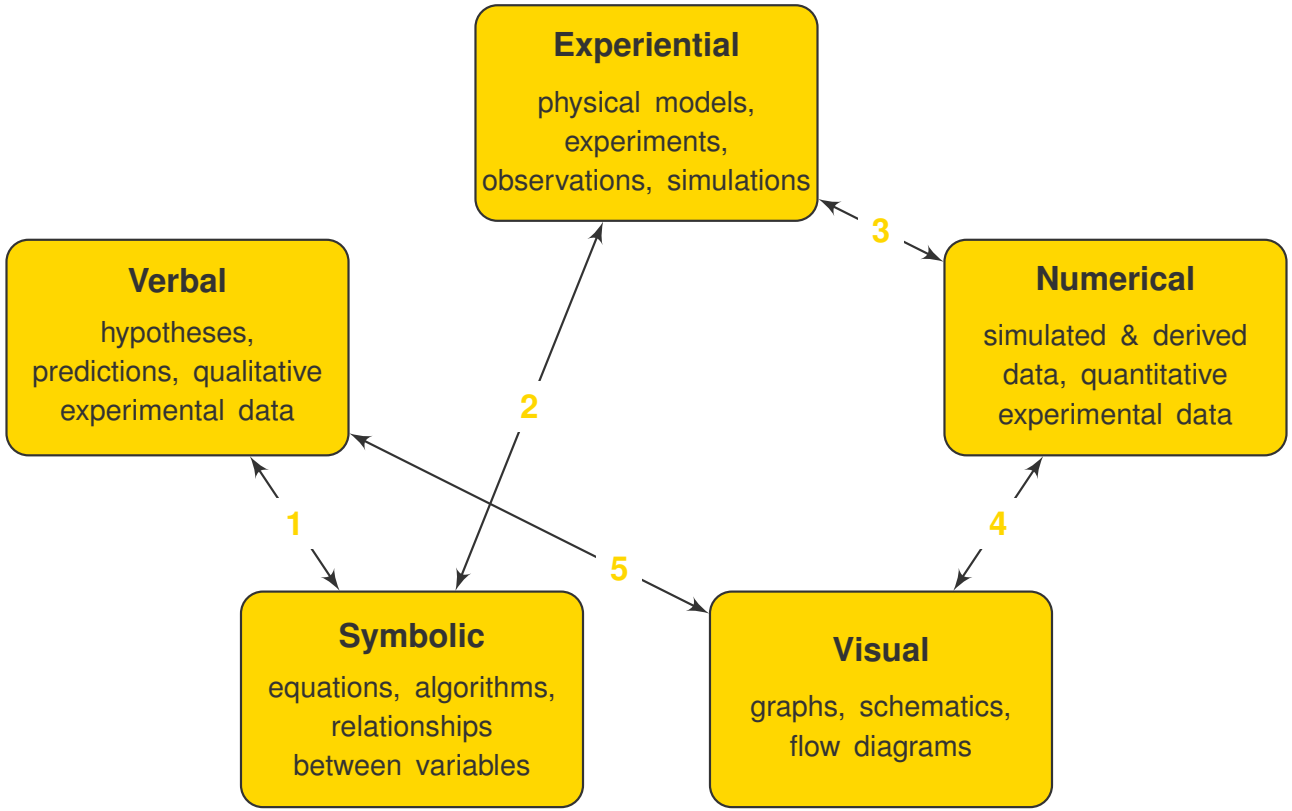
A (bio)mathematician’s approach to modeling:



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Crazy Cat Lady

What is a Discrete Difference Equation?

A ***discrete difference equation*** is an equation which generates a sequence of terms:

$$x_0,\ x_1,\ x_2,\ \ldots,\ x_n.$$

The equation typically expresses the next term in the sequence, x_{n+1}, as a function of the previous term

$$x_{n+1} = f(x_n).$$

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Example

The discrete difference equation $x_{n+1} = 2x_n$ with $x_0 = 1$ generates the sequence

$$x_0 = 1,\ x_1 = 2,\ x_2 = 4,\ x_3 = 8,\ x_4 = 16,\ \ldots.$$

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Difference equations of the form $x_{n+1} = a\,x_n$, where $a > 0$ model exponential growth ($a > 1$) or exponential decay ($0 < a < 1$).

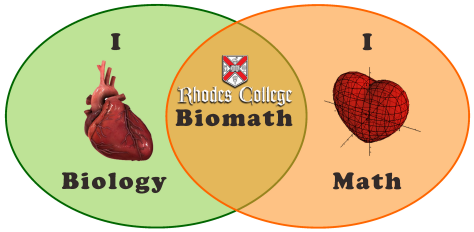
Crazy Cat Lady

How could you model the crazy cat lady cat population?

Roadmap

Discrete Math Modeling Course

- Designed as a core course for the Biomathematics major

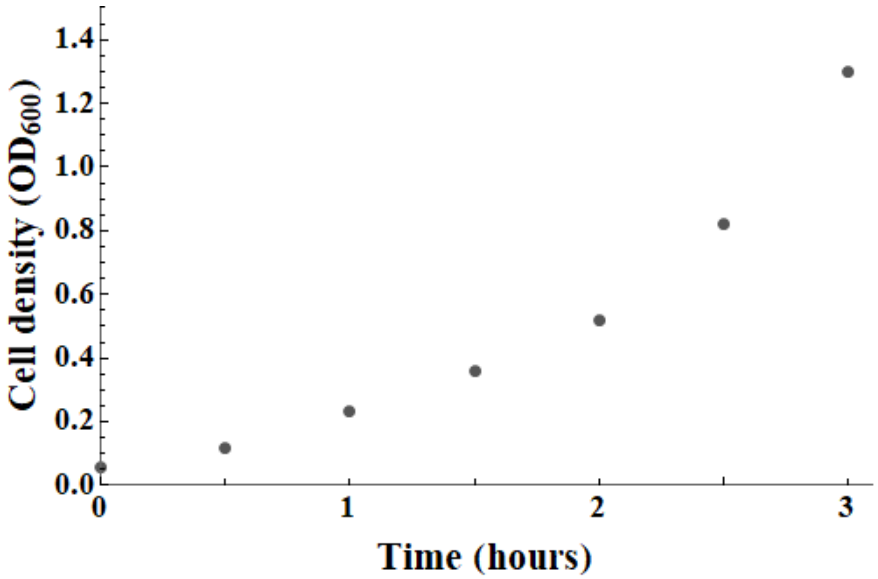


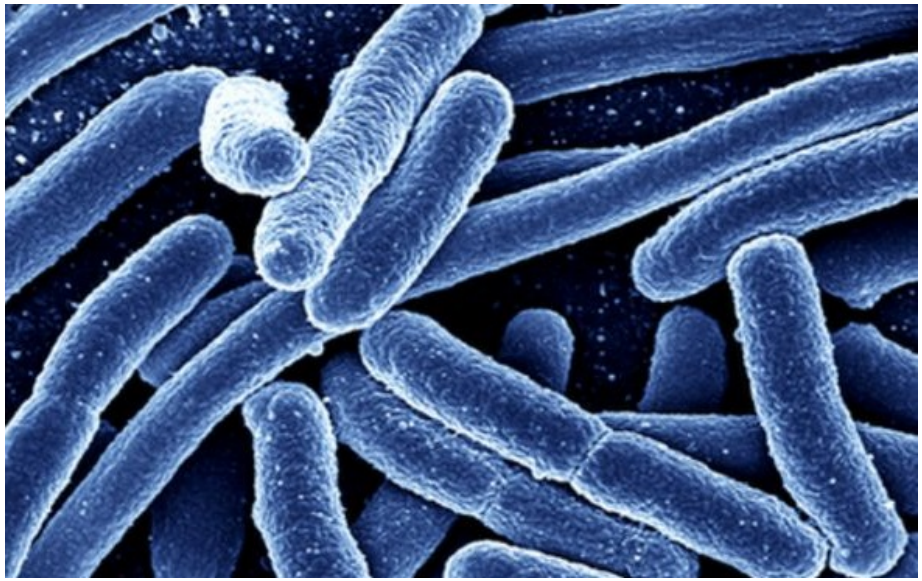
- Designed to expose students to
  - Process of modeling
  - Numerical Simulation
  - Computer Programming
  - Difference Equation Models
  - Matrix Models
  - Agent-based Models
- Designed as an introductory class
  - Designed for freshman & sophomores, but taken by students at all levels
  - Prerequisites: NONE
  - Students need to have decent algebra skills

Modeling the Growth of a Bacterial Culture

Modeling Growth of an *E. coli* culture

Optical density of *E. coli* growing in a culture at 37°C





Time (hours)	0.0	0.5	1.0	1.5	2.0	2.5	3.0
Cell Density (OD_{600})	0.055	0.120	0.231	0.360	0.516	0.821	1.300

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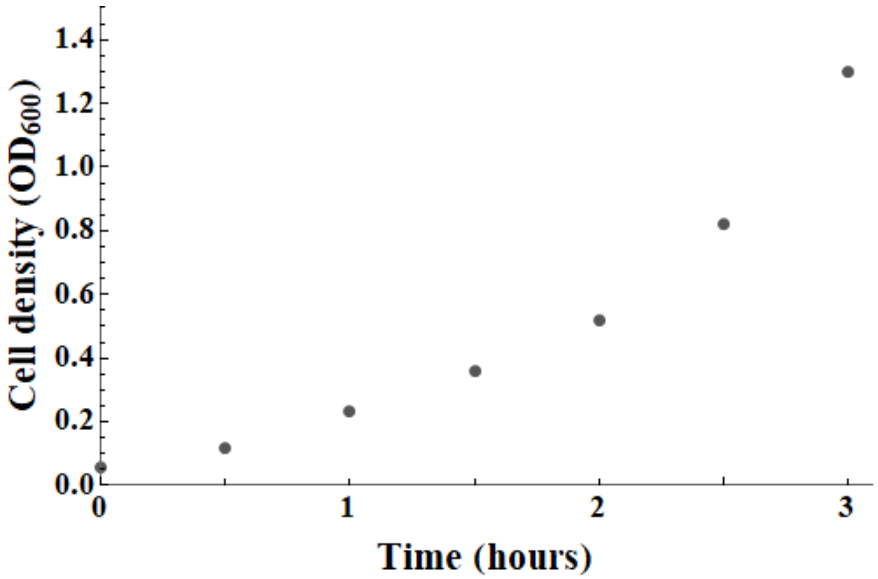

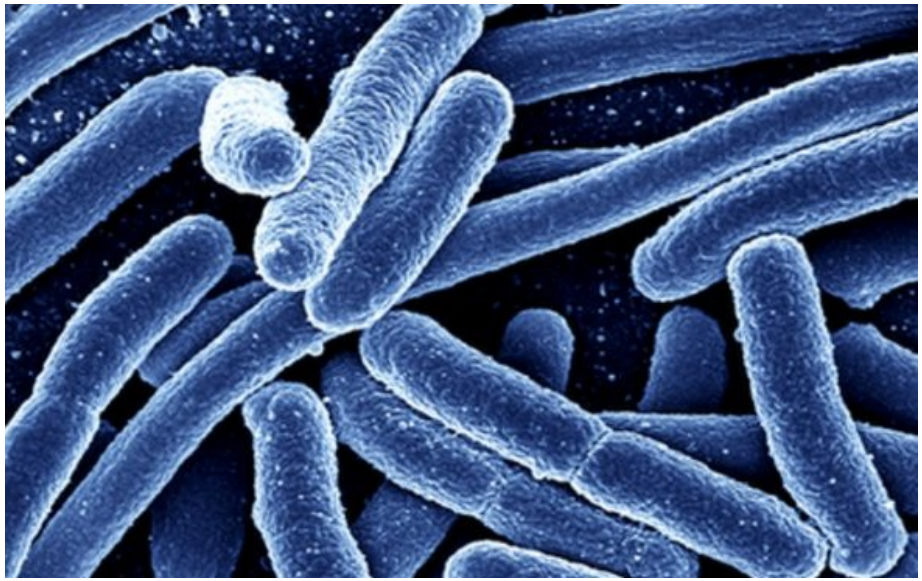

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We can express the data as a sequence:

$$x_0 = 0.055,\ x_1 = 0.120,\ x_2 = 0.231,\ x_3 = 0.360,\ x_4 = 0.561,\ x_5 = 0.821,\ x_6 = 1.300$$

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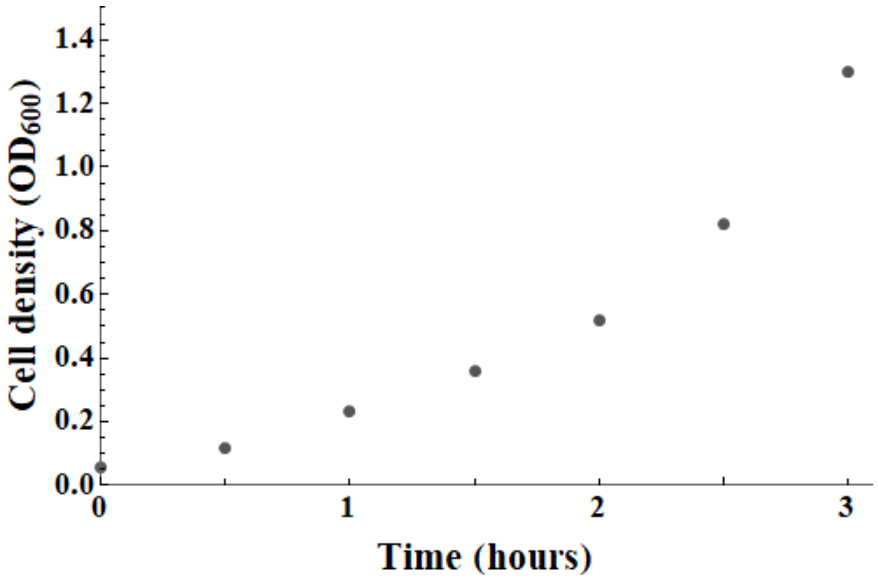

Exponential Growth Model

Assuming the growth is exponential, we can model the growth with the equation

$$x_{n+1} = a\,x_n \quad \text{with} \quad x_0 = 0.055.$$

What value should be used for a?

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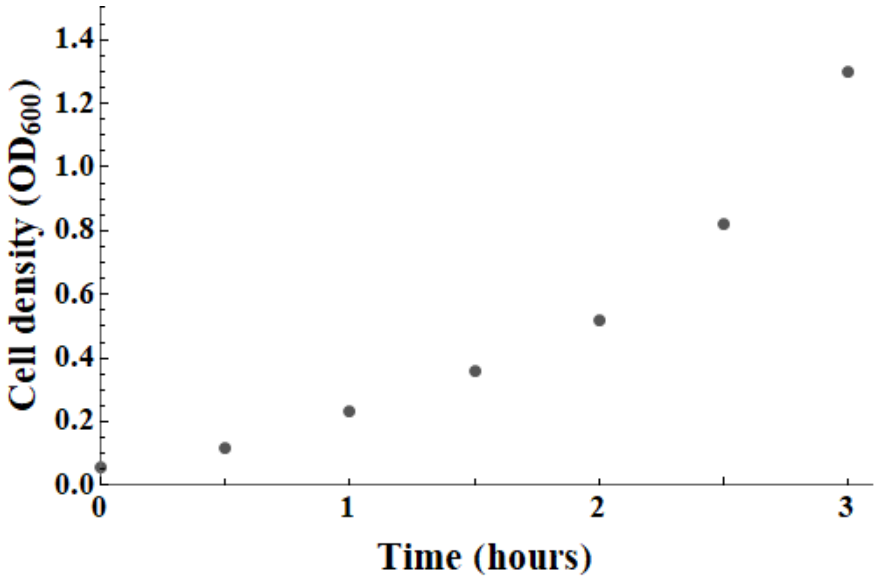

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Rearrange the equation to obtain $\frac{x_{n+1}}{x_n} = a$

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n	x_n	x_{n+1}/x_n
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Mean of Ratios: **1.712** Median of Ratios: **1.585**

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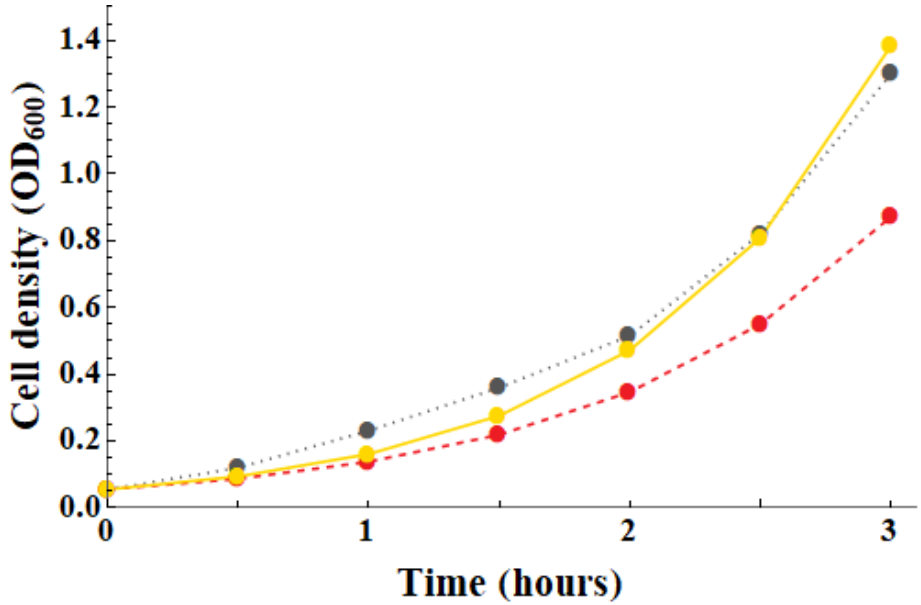

Modeling Growth of an *E. coli* culture

Optical density of *E. coli* growing in a culture at 37°C

Questions:

Which value of a, the mean or the median of the ratios, generates a sequence which more accurately represents the data?

How could we quantify which model more accurately represents the data?

Using this model, can we predict the cell density of the culture at 5 hr? 10 hr? 24 hr? 48 hr? 72 hr?

Over what period of time is the model "useful"?

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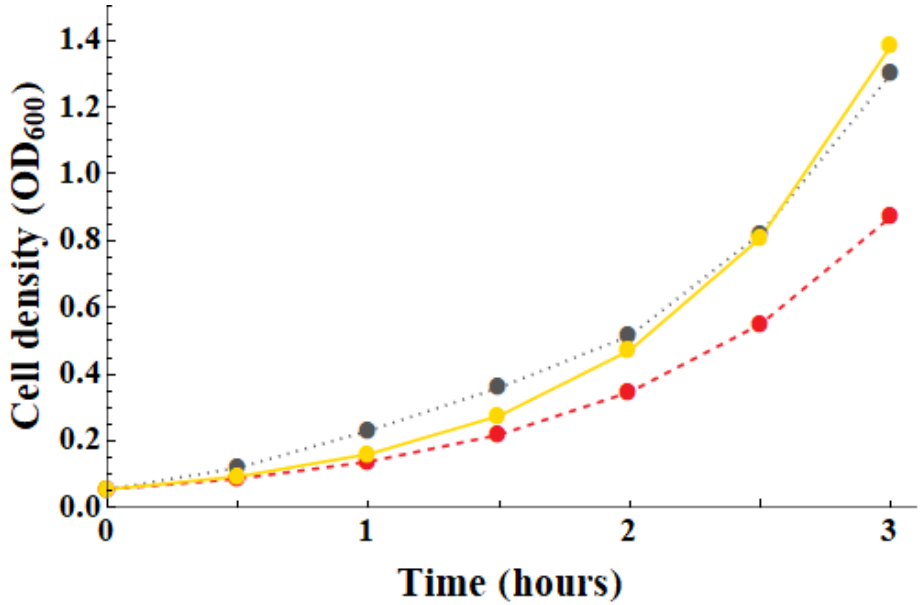

Modeling Growth of an *E. coli* culture

Optical density of *E. coli* growing in a culture at 37°C ... the full data set

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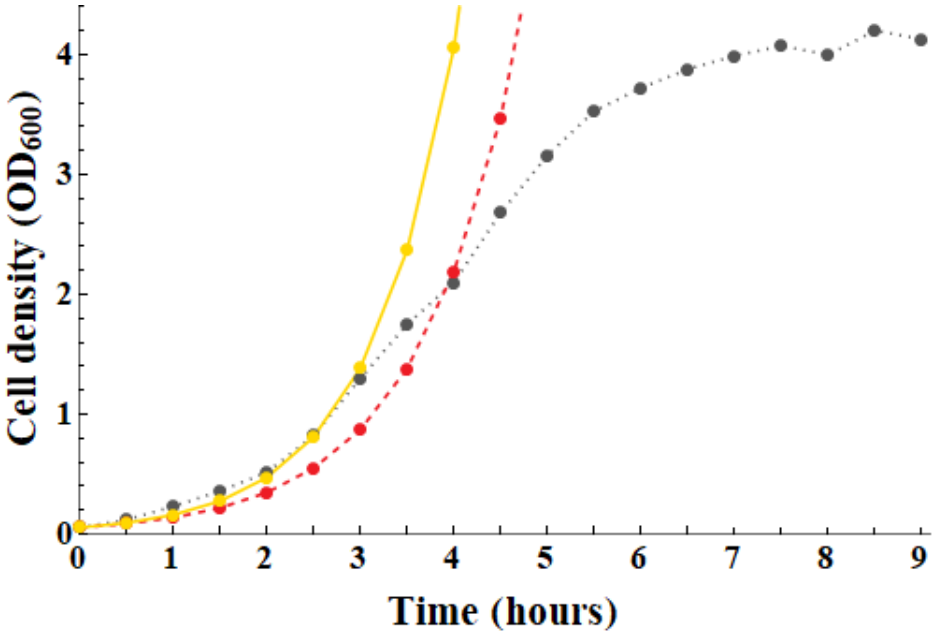

$$x_{n+1} = a\,x_n, \quad x_0 = 0.055$$

$a = 1.712$ (mean) $a = 1.585$ (median)

Modeling Growth of an *E. coli* culture

Optical density of *E. coli* growing in a culture at 37°C ... the full data set

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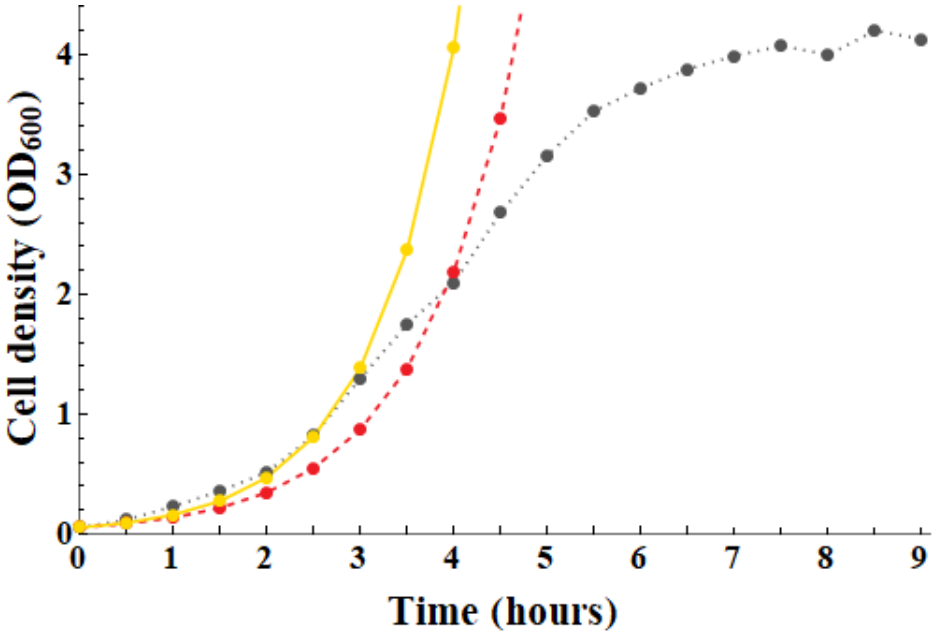
To make a new model for the full set of data what features does the new model need to have?



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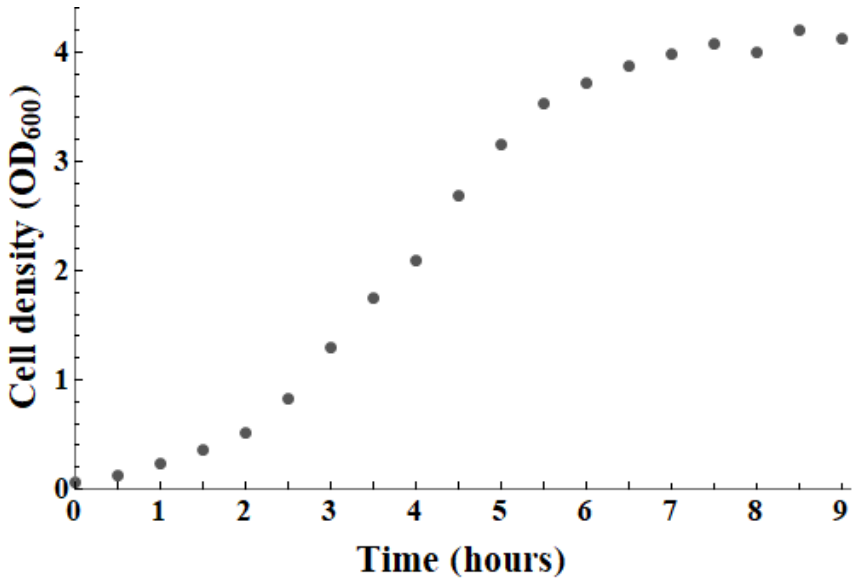
Optical density of *E. coli* growing in a culture at 37°C ... the full data set

Logistic Growth Model

Assuming the growth is logistic, we can model the growth with the equation

$$x_{n+1} - x_n = r\,x_n\left(1 - \frac{x_n}{K}\right), \quad x_0 = 0.055,\ K = 4.$$



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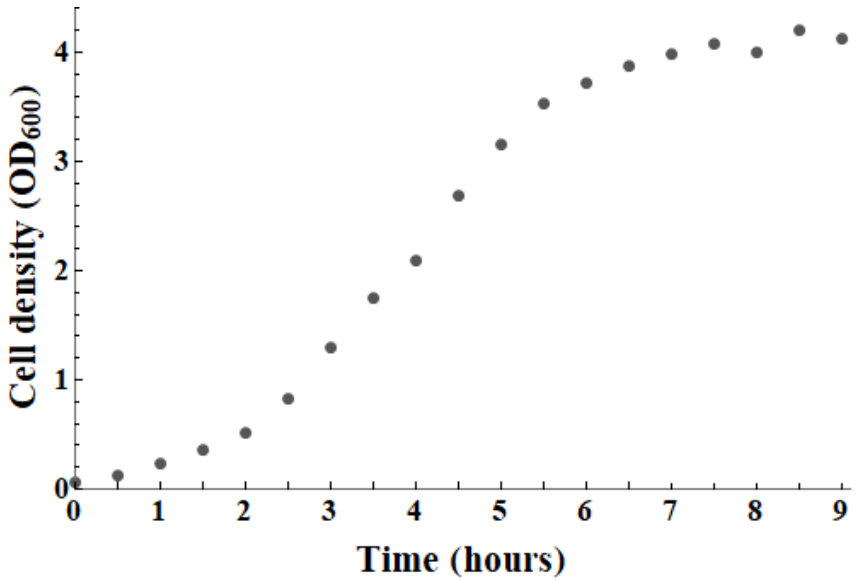
We cannot estimate the parameter r directly as we did for the exponential model, but we can visually fit r



$$x_{n+1} = x_n + r\,x_n\left(1 - \tfrac{x_n}{4}\right), \quad x_0 = 0.055$$

Modeling Growth of an *E. coli* culture

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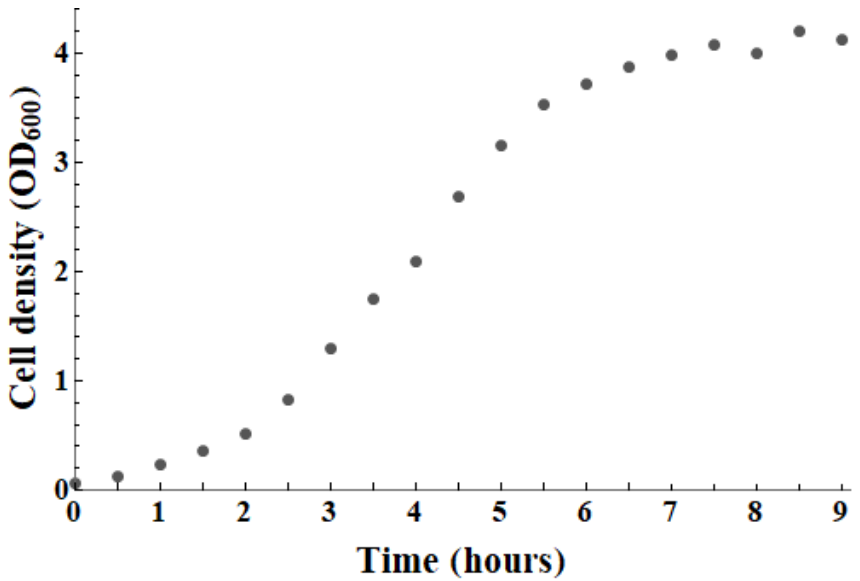

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$r = 0.2$ $r = 0.4$ $r = 0.6$

$r = 0.8$ $r = 1.0$

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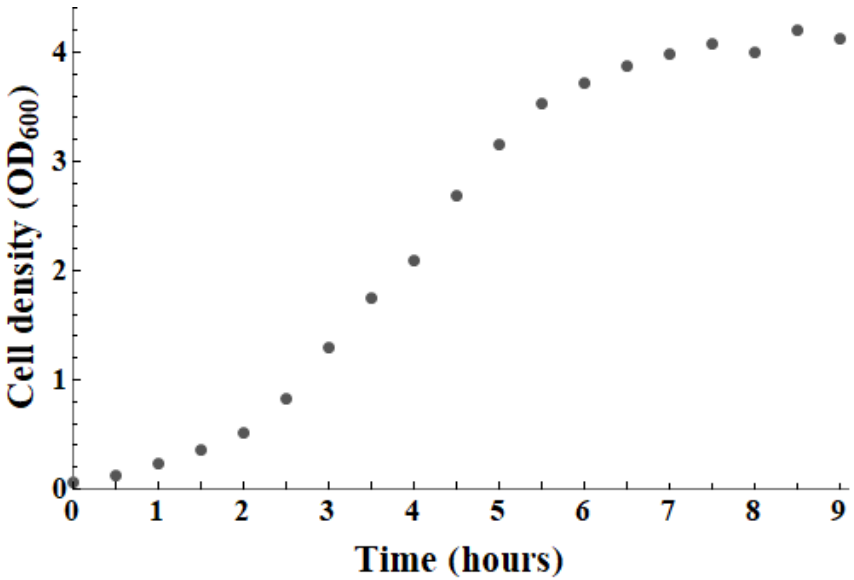
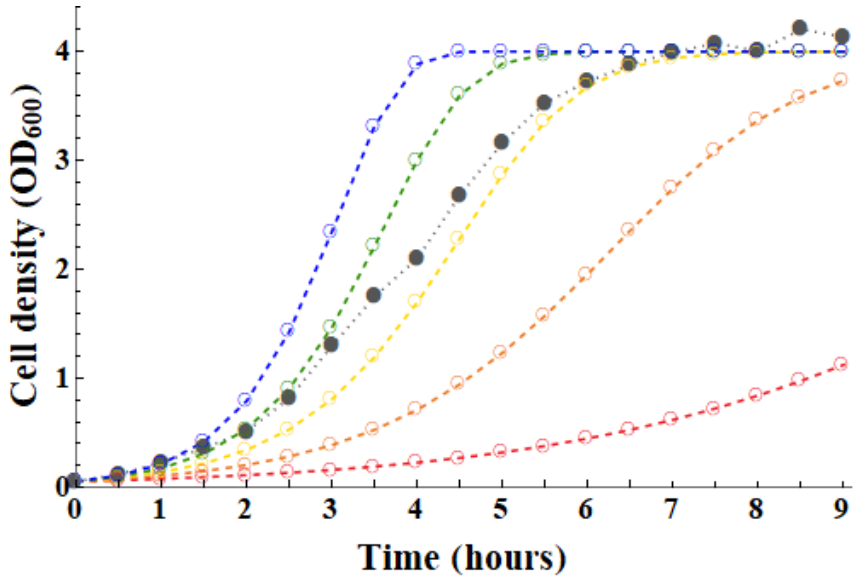


$$\boxed{x_{n+1} = x_n + r\,x_n\left(1 - \tfrac{x_n}{4}\right), \quad x_0 = 0.055}$$

$r = 0.2$ $r = 0.4$ $r = 0.6$

$r = 0.8$ $r = 1.0$



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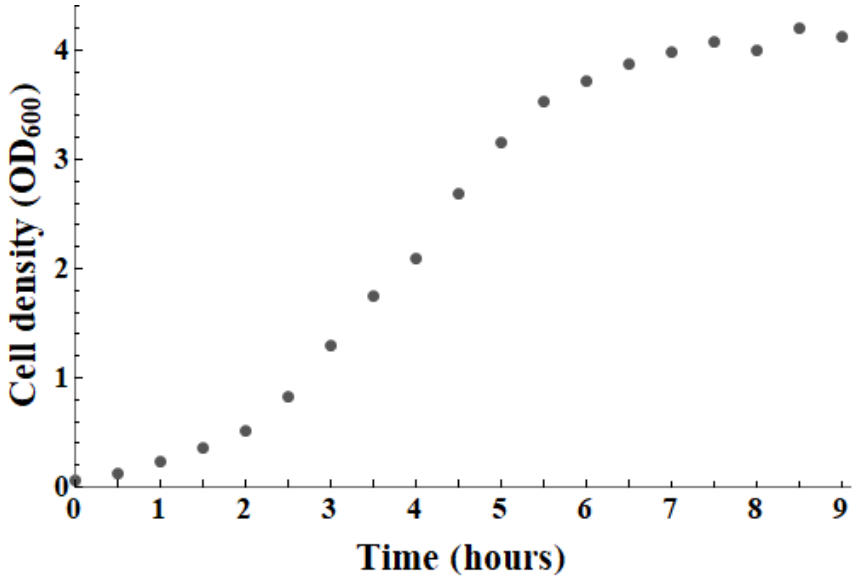
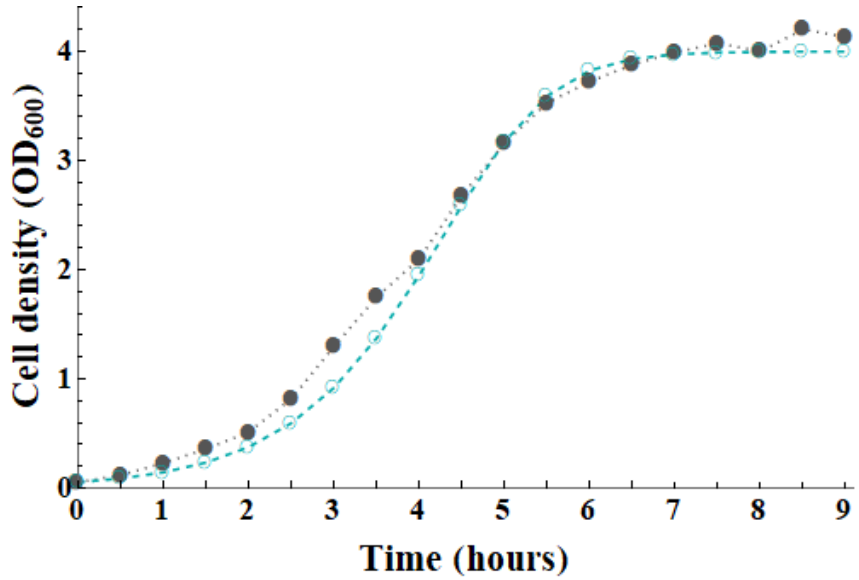
$$\boxed{x_{n+1} = x_n + r\,x_n\left(1 - \tfrac{x_n}{4}\right), \quad x_0 = 0.055}$$

$$r = 0.64$$

We cannot estimate the parameter r directly as we did for the exponential model, but we can visually fit r





Modeling Population Genetics over Time

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Hardy-Weinberg Model Assumptions

1. The organism is diploid, sexual, and has discrete generations. Discrete generations refer to a life history like that of an annual plant, in which the parental generation has died by the time the offspring generation reproduces.
2. Allele frequencies are the same in both sexes.
3. Mendelian segregation occurs, which means that individuals with the heterozygous genotype produce equal numbers of gametes (haploid reproductive cells, e.g., eggs and sperm) containing each allele. For example, an Aa individual produces equal numbers of A and a gametes. There are a few genes that violate this assumption; this condition is known as meiotic drive or segregation disorder. When meiotic drive occurs, once allele in heterozygous individuals is overrepresented in the gametes.
4. Random mating occurs, meaning that mating is random with respect to the genotypes under consideration (it may be non-random with respect to genotypes at other loci).
5. There are no mutations (permanent change to the DNA molecule), or at least the mutation rate is negligible, i.e., very close to 0.
6. There is no migration (movement of individuals between populations). This assumption is also referred to as the population having no gene flow.
7. There is no random genetic drift which refers to fluctuations in allele frequencies that occur by chance, particularly in small subpopulations, as a result of random sampling error in the choice of gametes that form the next generation. For large populations with random mating, it is reasonable to assume there is no genetic drift.
8. There is no natural selection. Natural selection refers to a consistent (over multiple generations) relationship between fitness and phenotype, or differences in fitness among genotypes.

Modeling Population Genetics over Time

Defining Terms

Given the Hardy-Weinberg model assumptions ...

Consider a gene with two possible alleles A and a, and a population size of N.

- $p_t =$ frequency of allele A in generation t
- $q_t =$ frequency of allele a in generation t

Note, $p_t + q_t = 1$ for every generation t; total of $2N$ alleles in population.

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$$p_t = \frac{2P_tN + Q_tN}{2N} = P_t + \frac{1}{2}Q_t \qquad q_t = \frac{1}{2}Q_t + R_t$$

Since the allele frequency is the same in both sexes (ASSUMPTION 2), the frequencies of p_t, q_t, P_t, Q_t, and R_t will be the same within both sexes.

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Example

The proportion of the male population in generation t that are genotype AA is P_t, and the proportion of the female population in generation t that are genotype AA is also P_t. Therefore, the probability of a $AA \times AA$ mating is $(P_t)(P_t) = (P_t)^2$. Similarly, the probability of a $AA \times Aa$ matings is the sum of the probability of a $AA(\male) \times Aa(\female)$ mating and a $AA(\female) \times Aa(\male)$ mating, i.e. $(P_t)(Q_t) + (P_t)(Q_t) = 2P_tQ_t$.

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All Possible Matings

Mating Type	Mating Frequency	Offspring Genotype Frequencies		
		AA	Aa	aa
$AA \times AA$	$(P_t)^2$	1	0	0
$AA \times Aa$	$2P_tQ_t$	½	½	0
$AA \times aa$	$2P_tR_t$	0	1	0
$Aa \times Aa$	$(Q_t)^2$	¼	½	¼
$Aa \times aa$	$2Q_tR_t$	0	½	½
$aa \times aa$	$(R_t)^2$	0	0	1

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$Aa \times aa$	$2Q_tR_t$	0	½	½
$aa \times aa$	$(R_t)^2$	0	0	1

The genotype frequencies of the offspring generation:

$$P_{t+1} = (1)(P_t)^2 + \frac{1}{2}(2P_tQ_t) + \frac{1}{4}(Q_t)^2 = (P_t)^2 + P_tQ_t + \frac{1}{4}(Q_t)^2 = \left(P_t + \frac{1}{2}Q_t\right)^2 = (p_t)^2.$$

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Genotype Frequencies in Offspring Generation

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Modeling Population Genetics over Time

Continent Island Model

Assume migration in one direction (from a continent to an island), that is remove ASSUMPTION 6 from the Hardy-Weinberg Model Assumptions.

Continent-Island Model

Let m be the proportion of the total number of island inhabitants in each generation which are migrants, and thus $(1-m)$ represents the proportion of native inhabitants. Let $\hat{q}$ be the frequency of allele a in the continent population (we will assume this to be constant over time). The allele frequency of a in the island population over time will be

$$q_{t+1} = (1-m)q_t + m\hat{q}$$

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Questions:

For given values of m, $\hat{q}$, and q_0, how does the allele frequency of a change in the island population over several generations? That is, what happens to the terms in sequence of q_t values? Do they approach a particular value? Do they oscillate?

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How does changing the parameter values (m, $\hat{q}$, and q_0) change the dynamics of the allele frequency of a in the island population over several generation?

Assume that natural selection occurs, that is remove ASSUMPTION 8 from the Hardy-Weinberg Model Assumptions.

Natural Selection Model

Let w_1, w_2, and w_3 be the relative fitnesses for genotypes AA, Aa, and aa. The genotype frequencies in generation $t+1$ with and without selection are given in the table where $\bar{w} = w_1 p_t^2 + 2w_2 p_t q_t + w_3 q_t^2$.

	P_{t+1} (AA)	Q_{t+1} (Aa)	R_{t+1} (aa)
Frequency in absence of natural selection	p_t^2	$2p_t q_t$	q_t^2
Relative fitness of genotype	w_1	w_2	w_3
Frequency with natural selection	$\frac{w_1 p_t^2}{\bar{w}}$	$\frac{2w_2 p_t q_t}{\bar{w}}$	$\frac{w_3 q_t^2}{\bar{w}}$

$$p_{t+1} = P_{t+1} + \frac{1}{2}Q_{t+1} = \frac{w_1 p_t^2 + w_2 p_t(1-p_t)}{w_1 p_t^2 + 2w_2 p_t(1-p_t) + w_3(1-p_t)^2}$$

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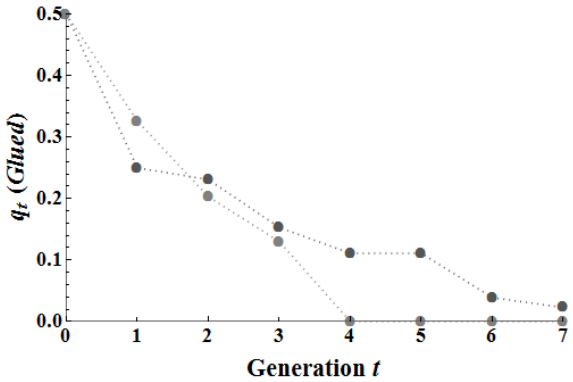
Question: What are the dynamics of the allele frequency of A in the population under different forms of selection?

	Genotype		
	AA	Aa	aa
General relative fitness	w_1	w_2	w_3
Lethal recessive	1	1	0
Detrimental alleles (recessive)	1	1	$1-s$
Detrimental alleles (additive)	1	$1-s/2$	$1-s$
Dominance (purifying selection)	1	$1-hs$	$1-s$
Dominance (positive selection)	$1+s$	$1+hs$	1
Heterozygote advantage	$1-s_1$	1	$1-s_2$
Heterozygote disadvantage	$1+s_1$	1	$1+s_2$



The frequency of the recessive (lethal) *glued* allele for two *D. melanogaster* population replicates each starting with all heterozygotes ($q_0 = 0.5$).

Roadmap

Discussion

Where could a discrete difference equation model be utilized in your class?

What classes are you teaching this Fall?

Into which classes could you see introducing discrete difference equation models? Where in the class would they fit most appropriately?

What materials would you need to include a discrete difference equation model in your class?

Roadmap

A Discrete QUBES FMN

The Discrete FMN (Fall 2017)

Overview | Members | Announcements | Collections | Forum | Projects | Resources

ABOUT THE GROUP

Many scenarios in the life sciences can be modeled with discrete difference equation models which simulate how quantities change over evenly spaced intervals. The construction and analysis of models of discrete difference equations do not require knowledge of calculus, and thus make excellent exemplary models in courses where the typical student may not be proficient in calculus. In this Faculty Mentoring Network (FMN), participating biology faculty will engage in converting the materials developed for an undergraduate freshman level course on discrete mathematical modeling for the life sciences (including readings, lecture slides, and computer lab projects) into single modules (separated from the developmental sequence of a math course) to be utilized in the participating faculty's Fall 2017 biology courses. **Apply to Participate in The Discrete FMN**

FMN Schedule: A more detailed schedule can be found here.

- During August 2017, participants, with support and feedback from the FMN, will develop all the materials necessary for implementing a module using discrete difference equation modeling in one of their Fall 2017 courses.
- During the Fall 2017 semester, the FMN will provide support for the implementation and assessment of the newly developed modules.
- At the end of the semester, the participating faculty will publish the materials developed for their modules (including readings, lecture notes/slides, assignments, and assessment tools) as resources on QUBES.
- In December 2017, FMN participants will have the opportunity to apply for funding to support the further dissemination of their developed module as a published article in a special issue of *Letters in Biomathematics*, or as a poster presentation at BioQuest 2018 or BEER 2018.

https://qubeshub.org/groups/discretefmn_f2017

Thank you!