Mathematics for Life Sciences

Lab Manual

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Cover image produced by MidJourney, with the prompt
"cell cultures expanding in a petri dish incredibly detailed".

Mathematics for Life Sciences
Lab Manual

Martin H. Weissman

Written for students in Math 16A/B at UC Santa Cruz

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Contents

PREFACE

This is the lab manual for a course in mathematical modeling for the life sciences. Our course is adapted from the successful LS30 course developed at UCLA. We are fortunate that UCLA colleagues, especially Alan Garfinkel, shared their course materials and built a national community around teaching mathematics in a fundamentally new way.

If you are a mathematician, of the non-applied sort, here is a description of this course. It is a course that deploys mathematics as a tool for understanding the natural world, primarily through systems of ODE (ordinary differential equations). Moreover, the most important aspects of ODE for this purpose are not the usual foci of introductory ODE courses, and our students do not yet know what a derivative is. The most important aspects are (1) describing the natural world with variables and equations, (2) interpreting equations as statements about the natural world, (3) Exploring solutions to ODE through graphical and numerical means. In this way, our approach to ODE embraces nonlinearity from the beginning, and adopts the visual/geometric approaches in the spirit of V.I. Arnold and the book of Strogatz rather than closed-form or series solutions. In the second half of the course, we delve into delay equations, stochastic models, and linear matrix models, while maintaining our focus on the numerical and graphical methods.

See Strogatz, S., *Nonlinear Dynamics and Chaos,* for mathematical background.

The "natural world" we explore is the world of life—from the molecular to the ecological scales. So we require the student and instructor to care about chemistry, molecular biology, physiology, and ecology. The instructor needs to bring a scientific curiosity about the natural world, but scientific expertise is not needed.

If you are a student, welcome to the class! We ask that you bring an interest in the natural living world. We do not assume that you bring a love of mathematics, but we hope this course develops your mathematical competence and confidence... joy may come later.

This lab manual consists of six chapters, which we call "labs." Each lab is really a block of activities, mixing computation, exploration, pen and paper, numeracy drills, etc., around a central theme. Each lab is meant to take about 3 weeks of work, from beginning to end. After those 3 weeks, the entire lab can be assessed.

The pages of this lab manual are meant to be written on, but please **write your final drafts in the manual**, putting your **scratch work on separate paper**. By the end of the course, your lab manual will contain a quantitative foundation for life sciences which you can return to for years to come.

Tools

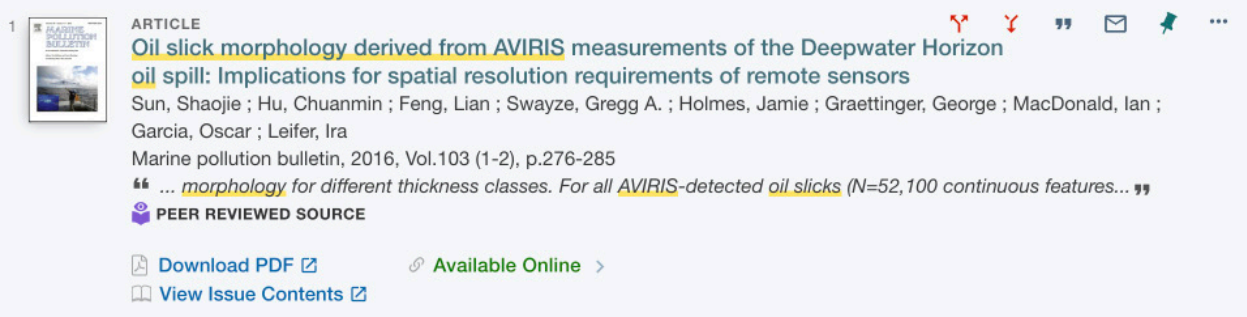
We will be using computers frequently in this class. You will want to have a dependable laptop computer during every lab session. This computer does not need to be fancy, and you do not need to install any software. But it does need the following:

1. A screen that is at least 13" diagonal -- bigger than a tablet -- for reading, typing, etc.
2. Battery life at least 2 hours, to work through the lab session even if an outlet is not nearby.
3. A full English-language keyboard.
4. Dependable access to the internet.
5. The ability to log into websites with your UCSC credentials, access your Google account, etc.

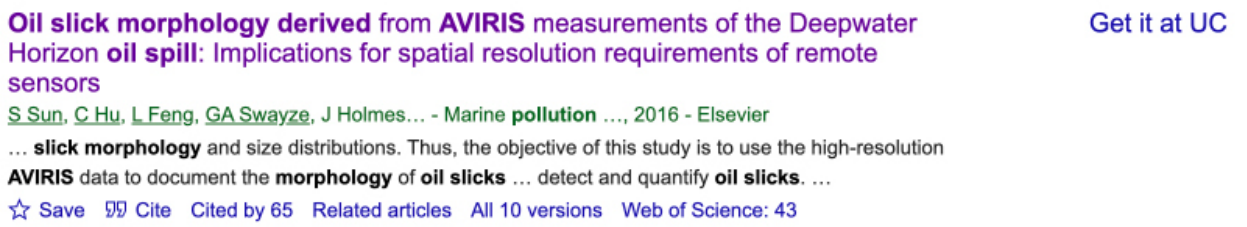
In this section, we discuss tools that we will be using: library access to online articles, Desmos (a free online graphing tool), and Google Sheets (a spreadsheet).

We will sometimes refer to published articles from scientific journals. Fortunately, our university subscribes to most journals, and as a student you have access to the vast majority of published scientific literature. This is more powerful than Googling, with a bit of practice, and sometimes Google can take you straight to the article you want.

For example, you might look for an article whose title begins "Oil slick morphology derived from AVIRIS..." You can go to **library.ucsc.edu** to start your search, and type this into the UC Library Search. If you're working from campus, you should see the top search result.



On the other hand, you might try going to **scholar.google.com** and searching for the same title, "Oil slick morphology derived from AVIRIS..." You should again find the article as the top search result:



These two tools -- **Google Scholar** and the **UCSC Library Search** -- will get you a long way!

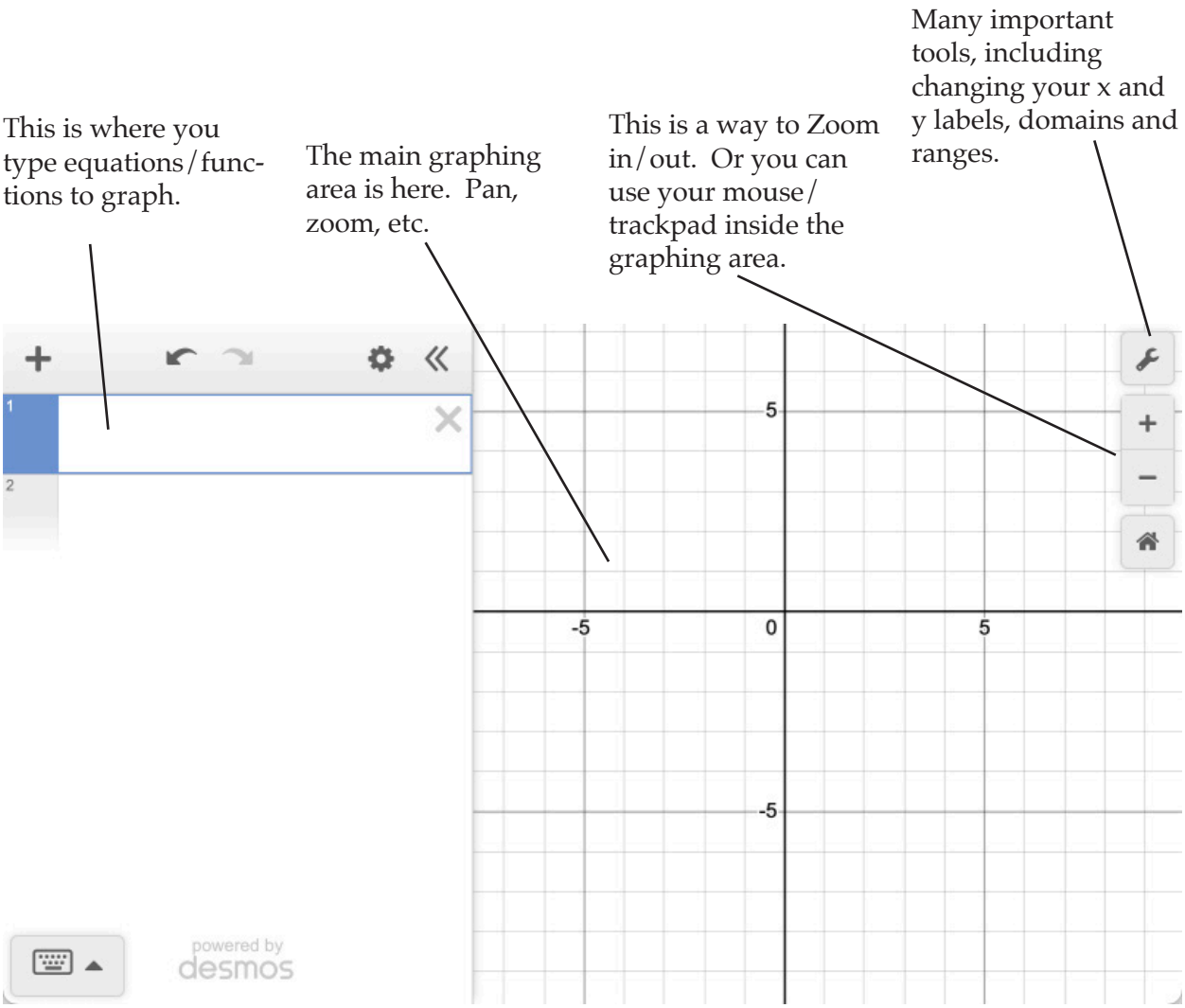
Desmos

Desmos is a free online tool for creating graphs. It is outstanding for exploring graphs of mathematical functions and relations. You may have used a graphing calculator in school before -- Desmos is like a graphing calculator, but...

1. It is freely available online.
2. It is more powerful.
3. It is more interactive.

Desmos is very good at graphing functions, systems of equations, zooming in and out to find solutions, etc. It is not so good for graphing or analyzing experimental data -- for that we will use a spreadsheet and other tools. In this way, Desmos is good for exploring idealized mathematical models and visually understanding purely mathematical principles. Connecting mathematics to broader science is a goal of the course.

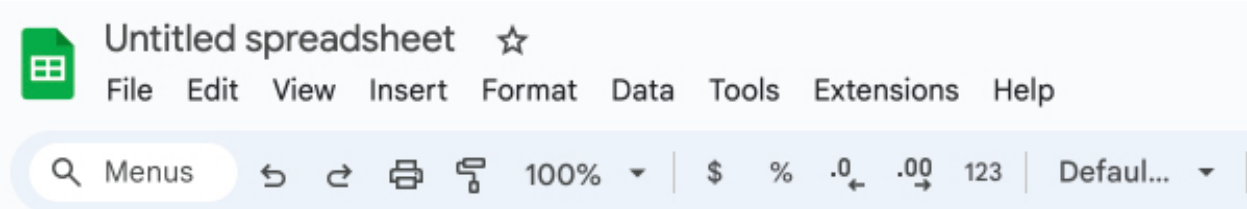
To find Desmos, go to **www.desmos.com** and click on **Graphing Calculator**. You should see something like what is pictured below.



Google Sheets

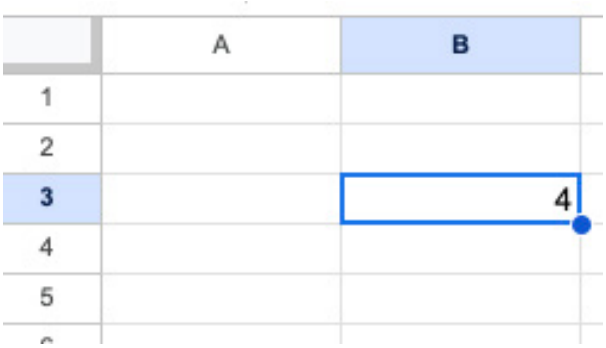
Google Sheets is spreadsheet software that you should have access to through your Google account. You may also use Microsoft Excel if you wish. Both Google Sheets and Excel have similar structure and layout.

To access Google Sheets, open your web browser and go to **sheets.google.com,** and click the icon that says Blank Spreadsheet. You should notice a menu at the top of the page, with its own File, Edit, etc. drop-downs. It should look like what you see below.



Click on the "Untitled spreadsheet" to give it an appropriate name, and you can save the spreadsheet in your Google Drive.

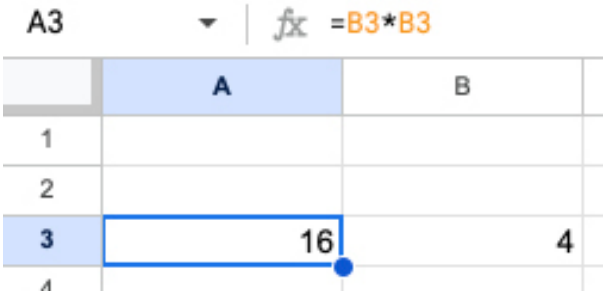
A spreadsheet stores data in **cells**. Each cell is labeled by a letter (its column) and a number (its row). So on the right, you can see the data (the number 4) entered in cell B3.



Each cell typically contains either some user-entered **data** (numbers, words, etc.) or a **formula**. For example, if we want cell A3 to contain the square of cell B3, we could click on A3 and enter the formula exactly as below:

= (B3 * B3)

The equal sign is the signifier that you are entering a formula, and not just some new bit of data. When you enter that formula, and press return, the spreadsheet should appear with 16 in cell A4. Notice the formula hasn't totally disappeared; you can see it in the **formula bar** just above the cells.



We will use spreadsheets for entering and analyzing data occasionally throughout the class. There are certainly fancier tools, but this is a foundational tool used by everyone who works with data.

Old school supplies

We will use the latest technology for teaching and learning, for being scientists. At the same time, we will use some ancient technology which has been useful for decades, centuries, and sometimes millenia.

For this class, you will need the following items, which are easy to obtain.

1. Lots of blank paper, lined or unlined. A spiral notebooks would be a good idea.
2. A comfortable writing instrument for everyday scribbles.
3. A few fine-point pens of different colors for your final drafts of graphs.
4. A small ruler for drawing straight lines.

Why do you need these old school supplies? Here is how your labs will be completed:

1. You will meet with other students and our teaching team to work on the labs. Most of the work at this time should be on scratch paper.

2. On your own time, you will check this work, and complete the notebook with neatly organized writing and carefully drawn graphs.

3. When the lab is due, you will photograph and scan the section from your binder, and use Gradescope to submit a PDF file to the grader. **The Gradescope App** is the most reliable tool for submitting your labs.

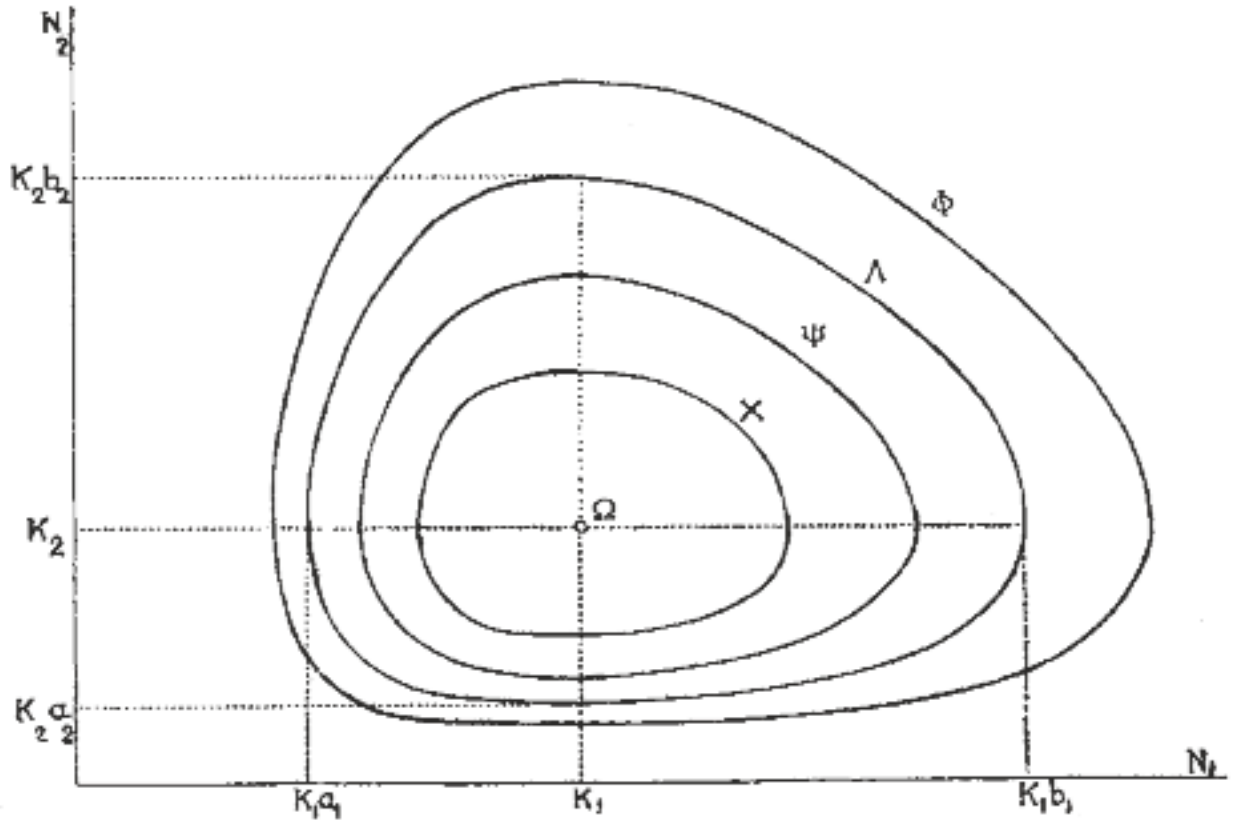


FIG. 2.

Figure 2 from Volterra, *Fluctuations in the Abundance of a Species considered Mathematically. (Full citation on opposite page).* The horizontal axis represents the number of prey (e.g. tuna), and the vertical axis the number of predators (e.g. sharks). The "cycles" in this diagram represent possible trajectories over time, i.e., the "fluctuations in the abundance of species."

Laboratory 1
Flow

Writing in the journal Nature, in 1926, Vito Volterra brings mathematics to bear on the study of population biology.

> A consideration of biological association, or of the mutual interactions between two or more species associated together, has led to certain mathematical results which may be set forth as follows.
>
> The first case I have considered is that of two associated species, of which one, finding sufficient food in its environment, would multiply indefinitely when left to itself, while the other would perish for lack of nourishment if left alone; but the second feeds upon the first, and so the two species can co-exist together.

Volterra, V., *Fluctuations in the Abundance of a Species considered Mathematically*, in Nature, 118, pp.558-560 (1926).

See also *The Biology of Numbers: The Correspondence of Vito Volterra on Mathematical Biology*. By Giorgio Israel and Ana Millan Gasca. Springer 2002.

Volterra's son in law, the zoologist Umberto D'Ancona, had studied the abundance of fish at the largest ports in Italy -- in Venice, Trieste, and Fiume -- in the preceding decades. The near-complete halt of fishing during World War I had led to unexpected fluctuations in fish populations. The correspondence between D'Ancona and Volterra, between family members, between a biologist and a mathematician, gave rise to the study of population ecology.

When Volterra brings mathematics into the picture, he is not just writing equations. He is representing them visually, using what we now call trajectories in state space. Equations will exhibit a precise relationship between populations of species. But these equations will be too hard to solve exactly. Despite this setback, a combination of computation and visualization will allow us to understand these relationships. The visualization is largely unchanged from Volterra's century-old work. Computation has gotten much easier!

This first laboratory introduces the computational and qualitative methods that Volterra used to understand the interactions of predators and prey. In the end, these methods apply to broader systems at the molecular scale as well as the ecological scale.

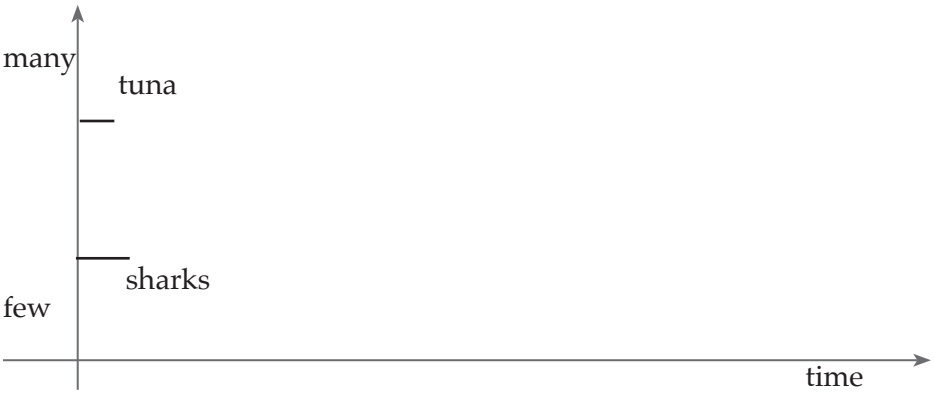
ST1 Sharks and tuna: conceptual model and time-series

Imagine a region in the ocean, a giant cube of salt-water, where you are able to count all the fishes big and small. You focus on two species, sharks and tuna, tracking their numbers over time.

You know a few things about sharks and tuna.

The tuna, feasting on smaller fish, thrive with plenty of food to eat. Their only worry is the hungry sharks. The sharks eat the tuna. Without the tuna, the sharks cannot survive... if there were no tuna, the sharks would gradually die out. Without the sharks, the tuna would be quite happy.

EX. If, at your first measurement, you found few sharks and many tuna, what do you expect to find at your next measurement?



This is a **time-series** plot. A time-series plot is a graph in which the horizontal axis represents time, and the vertical axis represents some quantity (or quantities) of interest.

EX. Sketch time-series plots: one for the sharks and one for the tuna -- to describe your expectations over a longer period of time. Once you settle on your answer, draw those two curves on the axes above. Label your curves so that the reader knows which one represents sharks and which represents tuna.

EX. What are some features of these graphs? What do they mean, practically speaking? Write two sentences about your findings.

ST2 Sharks and tuna: variables and change

In mathematics, we use letters (called variables) to represent quantities. It is crucial to declare your variables — to say exactly what they mean — before chucking letters all over the place. For sharks and tuna, we can do this in two sentences as follows.

Let S be the number of sharks in our region of ocean.

Let T be the number of tuna in our region of ocean.

Please do **NOT** write

S = Sharks
T = Tuna

This bad habit can cause all sorts of confusion later. Letters can stand for numbers. Letters cannot stand for fish.

In this course, we are interested in the natural world, where quantities change over time. So **time** is a special sort of quantity (we call it "t"), separate from the others. We have a special symbol to represent the amount of change: the Greek letter Δ ("Delta") means "the change in." To make sense of this, one fixes an interval of time, e.g., $\Delta t = 1$ year. With this time interval chosen, we have the following.

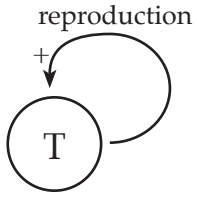
ΔS is the change in shark population during one year.

ΔT is the change in tuna population during one year.

If there are 100 sharks this year, and 120 sharks next year, then $\Delta S = 20$. If there are 200 tuna this year, and 150 tuna next year, then $\Delta T = -50$.

Living organisms like sharks and tuna reproduce. When tuna reproduce, the existing population of tuna produce new tuna. We might say that T (the current number of tuna) yields a positive change in itself, or the change in tuna ΔT is positively related to T itself.

EX. How do you think ΔS is related to T? How do you think that ΔT is related to S? Positively or negatively? Why? Draw a diagram with the letters S and T and arrows expressing the positive and negative effects that sharks and tuna have on each other.

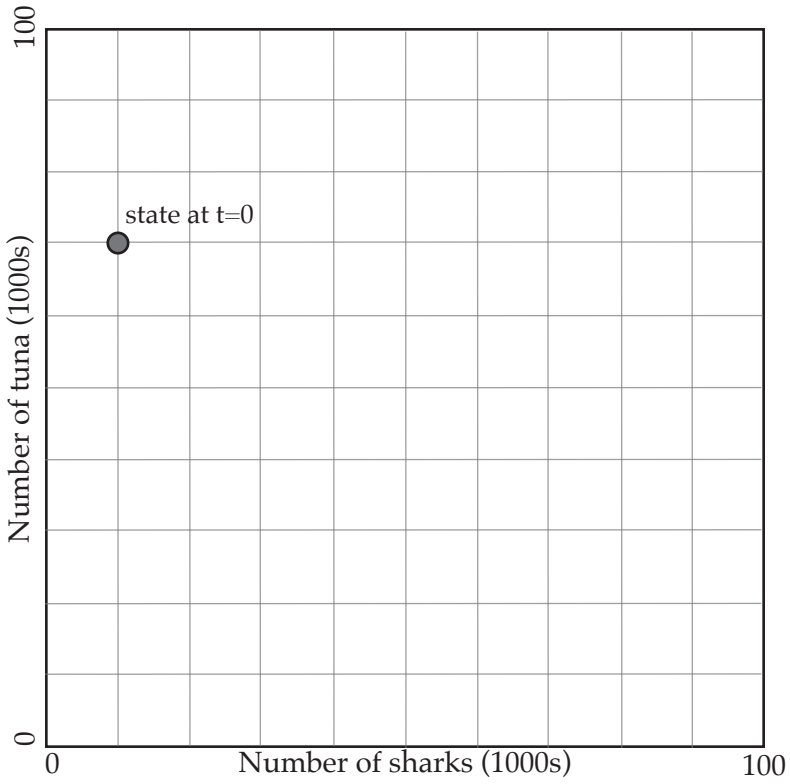


We use **feedback diagrams** like above, to express that the tuna population has a positive effect on itself, through reproduction.

ST3 Sharks and tuna: state space.

Let S be the number of sharks. Let T be the number of tuna. When we consider two populations like this, we have two **state variables**. They are quantities that change over time, and one can plot them as a time series. In a time series, time is plotted on the horizontal axis. But this requires two plots — one for sharks and one for tuna.

A powerful way to visualize the shark-tuna system uses **state space**. For this visualization, the state of the system is a pair (S,T) of numbers — the numbers of sharks and of tuna — and one plots this point in the xy-plane. Below, we imagine there are 10,000 sharks and 70,000 tuna at time t=0, and plot the corresponding point (10, 70).

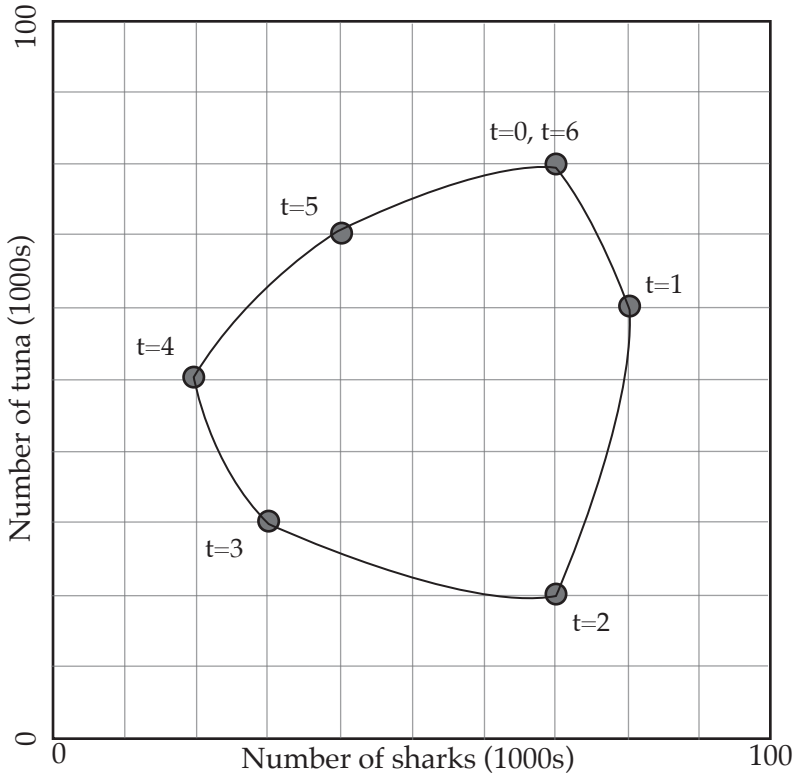


EX. With reference back to the first exercises, what do you think the state of the system will be one month later (at t=1)? Justify your answer and plot and label the corresponding point above.

EX. Plot points for the state of the system at t=2, t=3, t=4, etc., based on your expectations. Connect the dots to form a **trajectory in state space**.

ST4 Sharks and tuna: trajectories and time-series

Below is a trajectory in state space, with observations of sharks and tuna every month for 6 months.



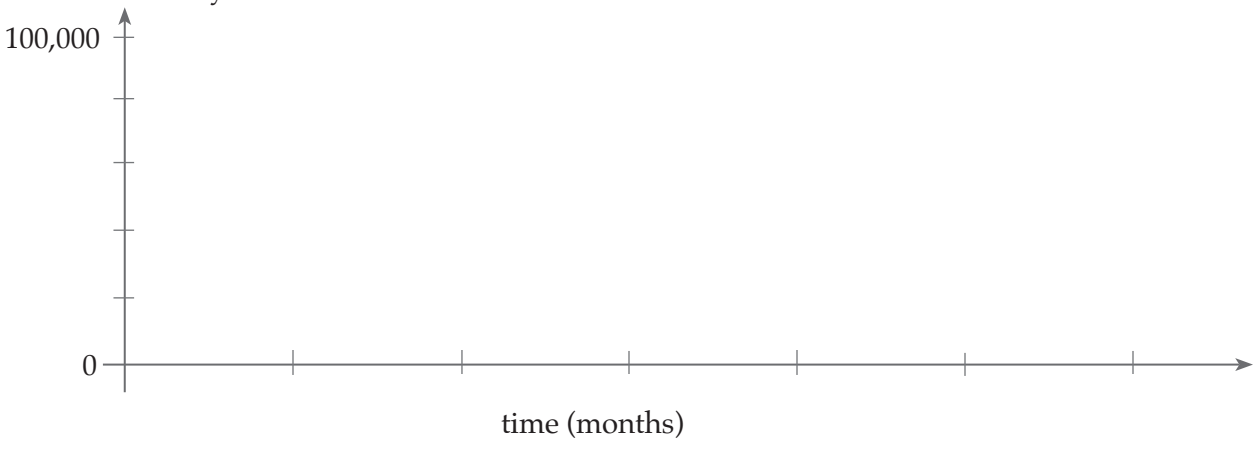
EX. How many sharks and tuna are observed at t = 2 months?

EX. Describe the change in the number of sharks and number of tuna, from t = 2 months to t = 3 months.

$\Delta S =$ _____ sharks.

$\Delta T =$ _____ tuna.

EX. Using the trajectory above, graph the populations of sharks and tuna as two **time-series** plots on the same axes below. Label your plots clearly to distinguish the sharks from the tuna. Place dots on your plot for each monthly observation.



BT1 Bathtub: The change equation

Once we use symbols for quantities, and their rates of change, we can use equations to describe what happens. We call these **change equations**.

The basic change equation has the form

$$\Delta Q = [\text{increases in } Q] - [\text{decreases in } Q]$$

Here Q is a quantity we care about, and ΔQ is the amount it changes. How a quantity changes is related to stuff that yields an increase and stuff that yields a decrease. When we focus on a quantity and its change, we call it a **state variable**. The values of these quantities are called the **state of the system**.

Consider a bathtub, with W liters of water in it. What influences the amount of water in the bathtub (the state of the system)? Usually it is how much you open the tap, and how much you open the drain. Putting this into a change equation, we write

$$\Delta W = iT - jD$$

Turning the handle opens the tap.

Here we have three quantities.

Let W be the number of liters of water in the tub.
Let T be the openness of the tap (0=closed to 1=fully open).
Let D be the openness of the drain (0=closed to 1=fully open).

If our time intervals are minutes, Δt = 1 minute, and ΔW represents the change in the water level during a one minute time period.

Turning the knob opens the drain.

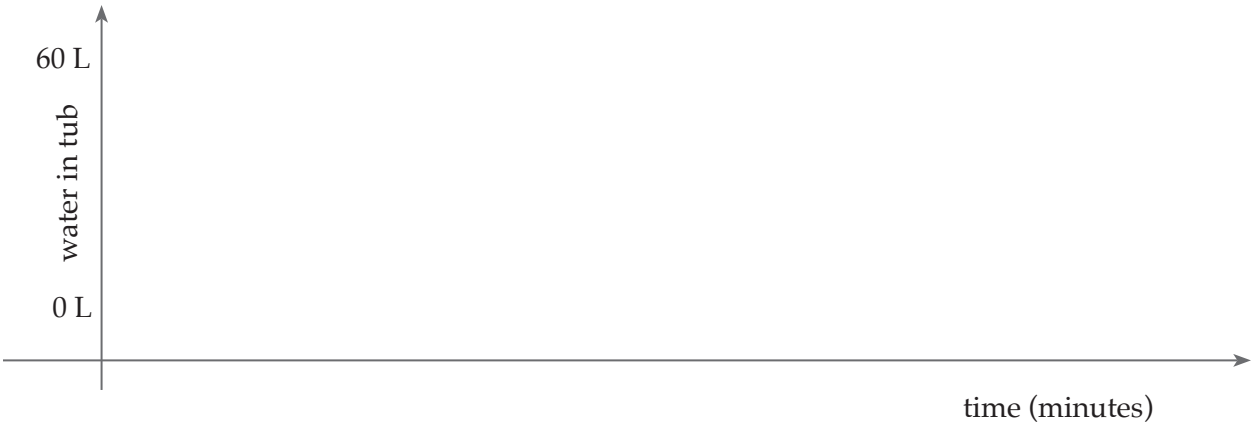
We also have two **parameters**, which we have called "i" and "j". The parameter i is the maximum flow rate of the tap -- when T = 1, the flow rate is i liters per minute. We call these two numbers "parameters" instead of "state variables" because they are not changing — at least not during a single bath (we hope!)

EX. What do you think the parameter j represents?

EX. Suppose that i = j, and you open the tap and drain as much as possible. What happens to the water level?

EX. When you actually fill a bathtub, what quantities (W, T, D) do you directly affect, and what quantities change throughout the process?

BT2 Bathtub: Graphing change

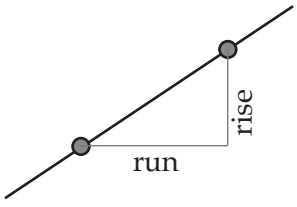


EX. On the chart above, draw a graph which represents the amount of water in the bathtub throughout the process of taking a bath. At the beginning and end, there should be 0 Liters of water in your bath. Don't forget to **Label the horizontal axis** with the number of minutes for each stage. **Label the stages** "Fill" and "Bathe" and "Drain."

EX. The quantity $\Delta W/\Delta t$ represents the **rate of change** of the quantity W. Estimate $\Delta W/\Delta t$ during each stage of your bath, and the parameters i and j. Your estimates should be realistic, using appropriate units, given a 60 Liter capacity of your bathtub. Use your personal experience waiting for a bath to fill/drain, or look up the flow-rate of typical faucets.

EX. Suppose that your drain is a bit clogged, so it no longer can be fully opened. Use a **dotted line** on the chart above to show how that would impact the time series.

EX. The slope of a line is its rise (vertical change) divided by run (horizontal change). On your chart, the vertical units are liters and horizontal units are minutes. Therefore slope is measured in L/min (liters per minute). Relate the slope to the rate of change $\Delta W/\Delta t$, and relate these to the parameters i and j.



N1 Numeracy: "Percent of"

100% of X means all of X.
50% of X means half of X.
33% of X means (approximately) a third of X.
25% of X means a quarter of X.
20% of X means a fifth of X.
10% of X means a tenth of X.

100% of 250 is 250.
50% of 40 is 20.
33% of 300 is approximately 100.
25% of 200 is 50.
20% of 500 is 100.
10% of 2020 is 202.

EX. Compute the following percents without using a calculator. (Mentally)

100% of 30 is _____

50% of 80 is _____

33% of 60 is _____

25% of 800 is _____

20% of 50 is _____

10% of 380 is _____

EX. Represent the following portions as percents without using a calculator. (Mentally)

15 is _____% of 30.

20 is _____% of 60.

50 is _____% of 200.

3 is _____% of 30.

207 is _____% of 2070.

99 is _____% of 99.

To compute P% of X, you can also multiply $(P/100) \cdot X$. This is often easy, using decimals and a calculator. For example,

37% of 93 equals $0.37 \cdot 93 = 34.41$ (by calculator).

40% of 177 equals $0.40 \cdot 177 = 70.8$ (by calculator).

EX. Compute the following percents, using a calculator.

67% of 25 is _____

3% of 65 is _____

23% of 230 is _____

EX. About 34% of UCSC undergraduates are "first-gen," meaning the first in their family to obtain a 4-year college degree. If there are 18000 UCSC undergraduates, how many first-gen students are there?

EX. Why is 4% of 25 equal to 25% of 4? Explain.

N2 Numeracy: Percents and relative change

Percents are very useful for thinking about quantities in relation to each other. For example, the number 1000 seems like a big number. But 1000 is only 0.1% of one million... so 1000 is "small" **relative** to 1000000.

We used Delta (Δ) already as a notation for **absolute change** in a quantity. We use percents to describe **relative change**. Relative change is often more natural than absolute change in biology.

If a quantity Q changes from 50 to 60, we say $\Delta Q=10$. But the **relative change** is how much it changes **as a percent of where it was**. Since 10 is 20% of 50 (see the last page!), we say that the change from 50 to 60 is a 20% increase.

EX. Complete the following sentences to express a change in relative terms, using percents.

Example. X starts at 30 and ends at 45. $\Delta X = 15$. X increases by 50%.

X starts at 80 and ends at 100. $\Delta X =$ _____. X increases by _____.

X starts at 120 and ends at 150. $\Delta X =$ _____. X increases by _____.

X starts at 10 and ends at 20. $\Delta X =$ _____. X increases by _____.

X starts at 1000 and ends at 1100. $\Delta X =$ _____. X increases by _____.

Example. X starts at 30 and ends at 27. $\Delta X = -3$. X decreases by 10%.

X starts at 100 and ends at 70. $\Delta X =$ _____. X decreases by _____.

X starts at 90 and ends at 60. $\Delta X =$ _____. X decreases by _____.

EX. Suppose that X starts at 100. Then X increases by 10%. Then X decreases by 10%. What happens? Explain if you can!

Pop1 Populations: Relative change

Imagine bacteria, chilling on a plate, watching Netflix. The bacteria reproduce by dividing every hour. If you have 1000 bacteria at 2pm, then you have 2000 bacteria at 3pm. After those 2000 bacteria divide, and you have 4000 bacteria at 4pm. Etc.

To describe this using a "change equation", we start as usual.

State variable: Let B be the number of bacteria on the plate.

Time interval: $\Delta t = 1$ hour.

Change equation: $\Delta B / \Delta t = ???$

We cannot write the change equation as $\Delta B / \Delta t = 1000$. This is true in the first hour, perhaps, as B changes from 1000 to 2000 and $\Delta B = 1000$. But then, as B changes from 2000 to 4000, it appears that $\Delta B = 2000$.

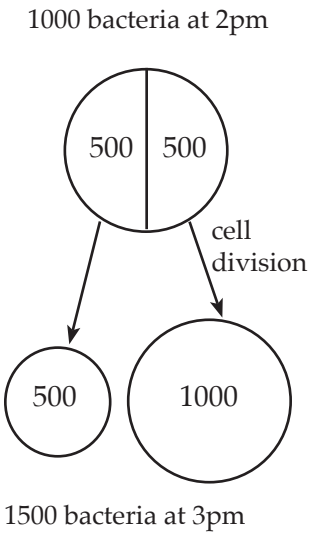
What happens here is that B changes proportionally to B. The population change is proportional to the population! The form of this equation is what we will study in detail in the next chapter.

Change equation: $\Delta B / \Delta t = B$

What if only half the bacteria reproduce each hour? At 2pm, we begin again with 1000 bacteria. Half of these (500 bacteria) divide and half remain. At 3pm, we expect 1500 bacteria. In this situation, B increases by 50% each hour.

Change equation: $\Delta B / \Delta t = 0.5$ B. Notice that 0.5 B is another way of saying "50% of B."

EX. Use the same model, with 1000 bacteria at 2pm. As above, suppose that $\Delta B / \Delta t = 0.5$ B. How many bacteria would you expect at 4pm? Illustrate the process with a schematic (like the one in the margin) and show your computations.



Pop2 Populations: Birth rate and death rate

Let P be a population of organisms. In other words, P is a quantity which is the answer to a "how many?" question.

Populations have two important parameters: their **per capita birth rate**, which describes the relative increase in population, per unit time, due to births of new organisms. The other parameter is the **per capita death rate**, which describes the relative decrease in population, per unit time, due to deaths of existing organisms. The change equation looks like the following.

$$\Delta P / \Delta t = \beta P - \delta P.$$

Here β ("beta") is the per capita birth rate. Similarly, δ ("delta") is the per capita death rate. We often use lowercase English or Greek letters for parameters. Practice writing your Greek in the margin.

EX. The annual (per year per capita) birth rate in Wisconsin is "10 births per 1000 people every year," or $\beta = 10/1000 = 0.01$ per year. If there are 6 million people in Wisconsin in 2024, how many people do you expect in Wisconsin in 2025? In 2026? Only account for births.

EX. The annual death rate in Wisconsin is "8 deaths per 1000 people every year," which means $\delta = 8/1000 = 0.008$ per year. Revise your answers to the previous question to account for both births and deaths.

EX* We can improve our model by **age-stratification**. To keep things simple, let us think of a population C of non-reproducing children and A of reproducing adults. How do you think ΔC is related to A? How do you think ΔA is related to C? Write a pair of change equations which reasonably describe this situation.

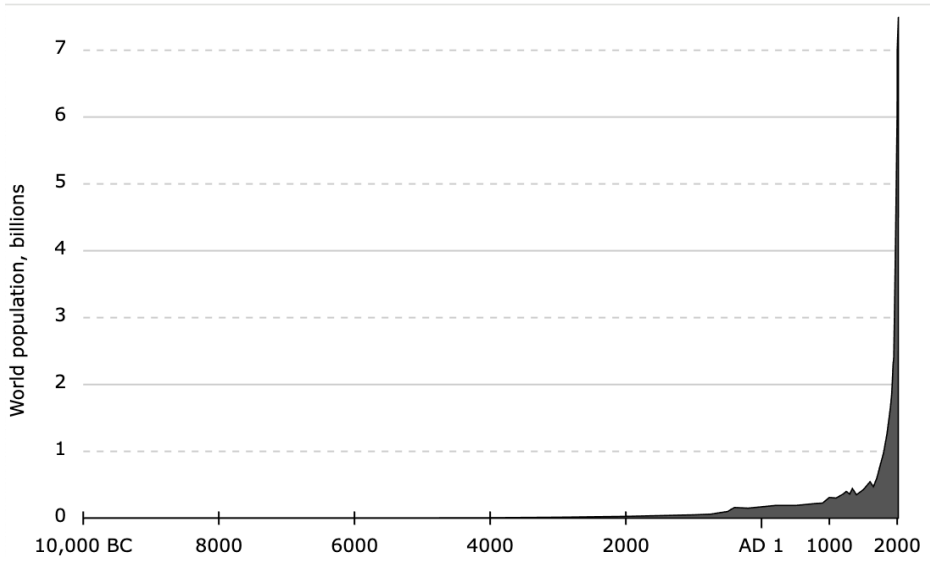
1.29. Above are the Greek letters alpha, beta, gamma, and delta. Copy these letters below.

Write the letters α, β.

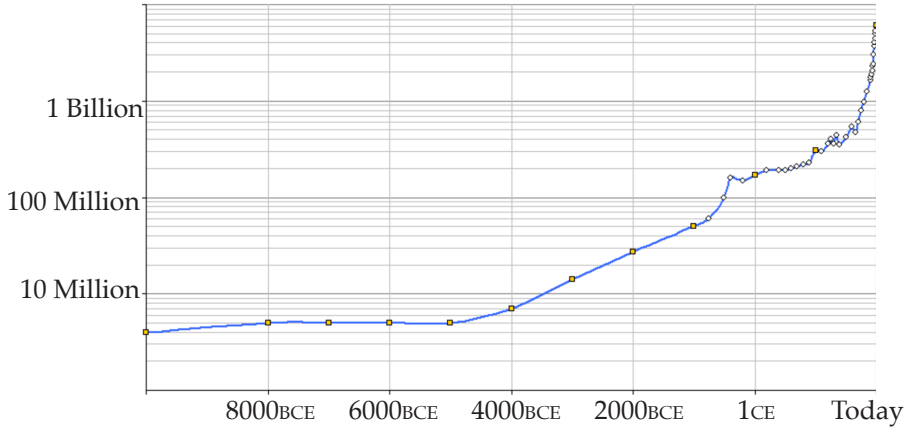
Write the letters γ, δ.

SL1 Semilog plots and Relative change

On the right is a plot of the world population since 10,000BCE. Looking at the plot, it seems like the world was an empty place until around 500BCE. That is because the current population of billions swamps the past population in the millions. This problem in visualization can be solved with a **semilog plot.**



A semilog plot uses a logarithmic scale on the vertical axis. The effect is that an interval on the vertical axis represents a relative change. If we use a Log_{10}-scale, each interval on the vertical axis represents a 10-fold change (multiplication by 10)! Below is the world population, since 10000BCE again, but this time on a semilog plot.



Graph adapted from Wikipedia, *World population growth (lin-log scale).png*. The data is the same as the plot above!

The evenly spaced "major" horizontal tick lines are at 10 million, 100 million, and 1 billion. The "minor" tick lines count from 1 million, 2 million, 3 million, etc., up to 10 million, then 20 million, 30 million, 40 million, etc., up to 100 million, then 200 million, etc.

EX. According to this graph, estimate how many years it took for the world population to grow from 10 million to 100 million (a 10-**fold change**).

EX. If the population growth rate between 4000BCE and 0 continued through to the present day, what would the current world population be? Estimate this by sketching a line on top of the graph above.

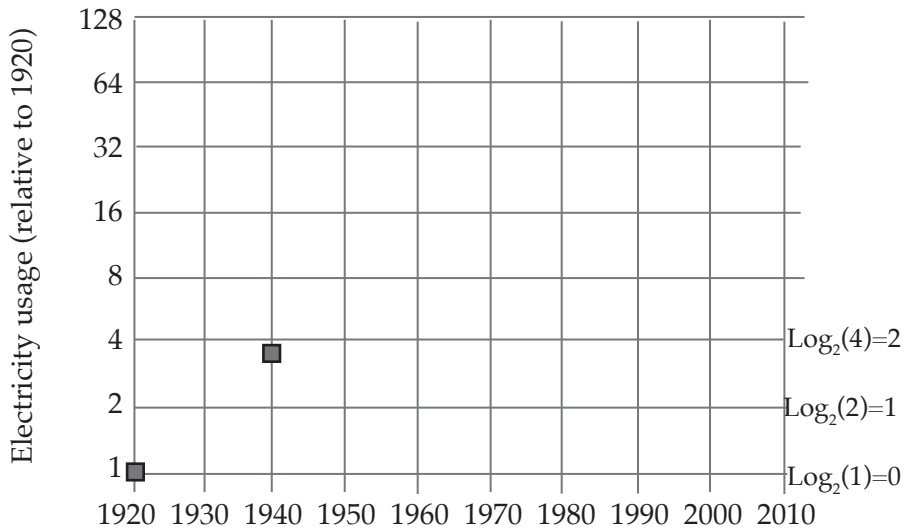
SL2 Drawing a semilog plot

On the right is a table showing the electricity used in the United States over the past century. These numbers are in "relative" units, with 1920 set to 1. So in 1930, the electricity usage was 2.31 times the usage in 1920. We can visualize this growth nicely using a semilog plot.

Year	Electricity used in U.S.
1920	1
1930	2.310
1940	3.597
1950	8.513
1960	19.344
1970	39.115
1980	58.340
1990	77.234
2000	96.665
2010	104.985

Data from Electrification of the United States economy, 1920-2021, from *Primary energy use in the United States*, by O'Connor et al. Retrieved from visualizingenergy.org.

EX. Plot this data on the semilog axes below. Note that we are using a Log_2-scale on the vertical axis, so every vertical unit upwards corresponds to multiplication by 2 (a 2-**fold change**). Hint: to accurately locate 3.597 note that $\text{Log}_2(3.597) = 1.847$ is between $\text{Log}_2(2) = 1$ and $\text{Log}_2(4) = 2$. Use these logarithms to locate the points, as shown below.



EX. The graph that you draw above should appear almost like a straight line between 1920 and 1970. Use this line to complete the following sentence:

During the 1920s through the 1970s, U.S. electricity usage doubled every _____ years.

EX. Use the table to compute ΔE during each decade. For example, in the 1920s, $\Delta E = (2.310 - 1) = 1.310$. Use this, and decade-time intervals $\Delta t = 10$ years, to complete the following relative growth rates.

$\Delta E / \Delta t =$ _____ E, during the 1920s.

$\Delta E / \Delta t =$ _____ E, during the 1930s.

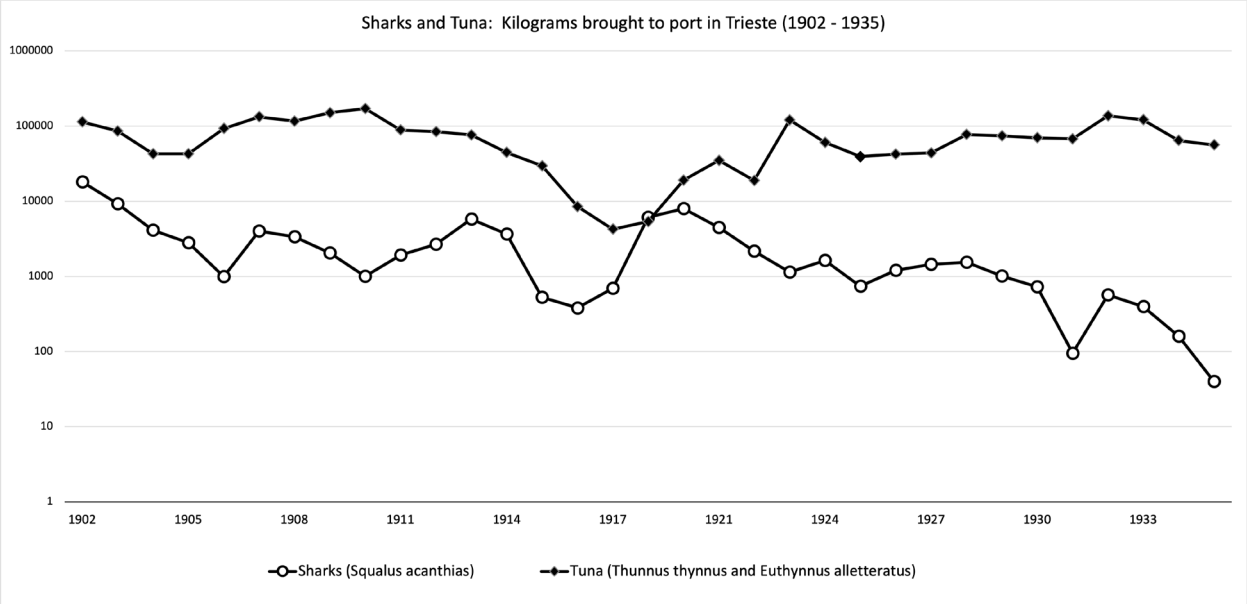
$\Delta E / \Delta t =$ _____ E, during the 1940s.

$\Delta E / \Delta t =$ _____ E, during the 1950s.

$\Delta E / \Delta t =$ _____ E, during the 1960s.

$\Delta E / \Delta t =$ _____ E, during the 1970s.

ST5 Sharks and tuna: real data.



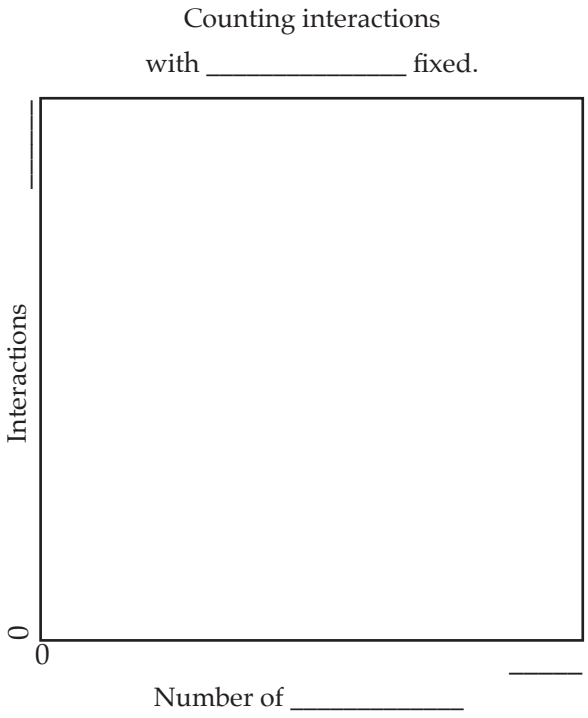
EX. The semilog plot above displays the total weight (in kilograms) of sharks and tuna caught in the Adriatic sea and brought to port at Trieste, between 1902 and 1935. How do you think this relates to the population of sharks and tuna in the Adriatic sea? In what ways might this data be a good or bad proxy for population?

EX. Look up the dates of World War I. How might WWI have affected the actual populations in the ocean? The fishery catches? What specific effects do you see in the plot above?

ST6 Sharks and tuna: counting interactions

Here we return to the example of sharks and tuna in a region of water. As before, let S be the number of sharks, and let T be the number of tuna. Here we are interested an a quantity that both sharks and tuna care about: let I be the number of "interactions" between sharks and tuna. In other words, I is the number of times that a shark and tuna are close enough together for the shark to eat the tuna.

EX. Run the *Shark-Tuna Interaction Simulator.* Draw a plot below, showing how the number of interactions (y-axis) depends on one state variable with the other state variable fixed. Guidelines are in the margin.



1. Choose one state variable (sharks or tuna) and **keep that number fixed** throughout.

2. Try a range of possibilities for the other state variable, including at least 5 distinct values, and run the simulation at least 5 times for each value (25 data points minimum).

3. Within the plot, draw dots for all of your observations. Plot a line or curve which models the empirical relationship between "I" and your state variable.

EX. The **empirical** relationship between I, S, and T is I = k ST, where k is some constant. Pooling your experiment with your classmates and their plots, estimate the constant k. Describe how you achieved this estimate.

An **empirical relationship** is a formulaic relationship between quantities which is suggested by observation and experiment.

But empirical relationships are not always supported by a "mechanism" to know why the relationship holds.

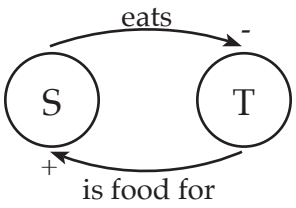
ST7 Sharks and tuna: Lotka-Volterra equations.

Let S be the number of sharks. Let T be the number of tuna. These are our state variables. We are now at the point where we can model the shark-tuna system with change equations:

$$\Delta S/\Delta t = -\delta S + pST$$

$$\Delta T/\Delta t = \beta T - qST$$

These are called the **Lotka-Volterra equations**. The interaction terms reflect the **feedback loop** below.



The first equation says that the change in shark population (ΔS) arises from two sources. There is a net death term $-\delta S$, because without enough food (tuna), the sharks slowly die off. But interactions between sharks and tuna (chomp!) provide food for the sharks, helping them survive and reproduce. There is an **interaction term** pST, with positive coefficient p reflecting the fact that predations are beneficial to the sharks.

Our parameters (a,b,c,d) will always be assumed positive. For example, since "c" is positive, the term "-cST" is a negative interaction term.

The second equation says that the change in tuna population (ΔT) arises from two sources. There is a net birth term βT, because without the hungry sharks, the tuna would happily survive and reproduce. But interactions between sharks and tuna (chomp!) kill off the tuna, leading to a negative **interaction term** $-qST$. Interactions are bad for the prey.

EX. Take the following parameters in the above equations.

$$\delta = 0.04,\ p = 0.003,\ \beta = 0.06,\ q = 0.004.$$

Suppose our time interval is $\Delta t = 1$ month. If at one moment there are 20 sharks and 40 tuna, what do you expect for ΔS and ΔT? How many sharks and tuna do expect at the next month? **Round your answers** down to a whole number. Record your answers in the margin (at t=1). Continue this process to record the numbers of sharks and tuna at t=1, t=2, t=3, in the table in the margin.

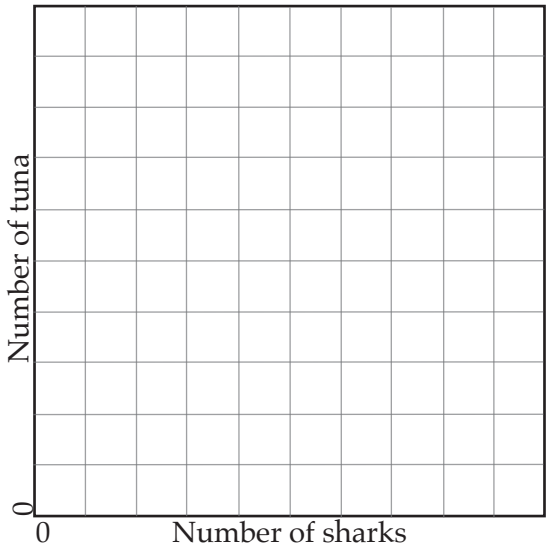
t	S	T	ΔS	ΔT
0	20	40		
1				
2				
3				

EX. Plot a time series below for S and T displaying their populations at these four moments.

ST8 Sharks and tuna. Simulation and interventions.

The previous exercises show that it is tedious to do this sort of shark and tuna accounting by hand. But computers can do this work very quickly. Load up the *Shark and Tuna Trajectory Simulator*.

EX. Take the starting values S = 20 and T = 40, as you did before. Find the appropriate place on the shark-tuna trajectory plot and click to start the trajectory. Sketch the trajectory below.



Use the default parameters with the simulator:

$\delta = 0.4$,
$p = 0.03$,
$\beta = 0.6$,
$q = 0.04$.

These are similar to what you did "by hand" but using a different time interval.

EX. The simulation shows a lot of arrows, called a **vector field**. What do you think these arrows represent in this context?

EX. How do the time series in the simulation resemble or differ from what you found by hand?

EX. The simulation allows you to instantly "kill" 10 tuna or 10 sharks. Try this out at different points in the trajectory. Explain how it is possible to "kill" sharks, but end up in a situation where the shark population grows even greater than before.

ST9 Sharks and tuna: reflections on modeling

We have explored a mathematical **model** of sharks and tuna, the Lotka-Volterra model of populations of predators and prey. This **model** describes a system with two state variables S and T, whose change is determined by assumptions about birth and death and predation.

This whole endeavor, from identifying state variables and relevant parameters, to describing their change via equations, is called **building a model**. Have we done a good job? Every model has strengths and weaknesses; identifying these is called **evaluating the model**. Possible strengths of models include:

Accurate descriptions: does the model accurately describe previous observations, when appropriate parameters are chosen?

Accurate predictions: does the model accurately predict future observations?

Parsimony: does the model have more parameters than should be necessary, or just a few necessary ones? Does the model only "fit" the data because a zillion parameters are tweaked the right way?

Robustness: do small changes in assumptions or parameters destroy the utility of the model? Or does the model hold up, with minor adjustments?

Interpretability: can one easily interpret each term of the model, to understand how different factors will change the outcomes?

Insightful: does the model provide insight that would be difficult to find by simple observation alone?

Adaptable: can the model be easily adapted to slightly different situations or by adding layers of complexity as needed?

Generalizable: does the model apply to a broad range of circumstances, or just to the very specific situation it is designed for?

One cannot hope for a model with all of these strengths, especially not in a complex world of living organisms in their natural environment. But if we temper our expectations, we can hope to find models with some of these strengths.

In contrast, physicists sometimes find models with all of these strengths. Newton's law of gravity, for example, or the standard model in particle physics, are examples. These models can be "better" because they address zillions of non-living, controllable "things" made of near-identical parts. Every electron, every hydrogen atom, every photon follows the same rules. In that way, physicists have it easy.

ST10 Sharks and tuna: reflections on modeling

EX. Evaluate the shark-tuna model we have studied. Identify its strengths and weaknesses, using the terms from the previous page, and pointing to specific evidence from your explorations. Write 100-200 words with your evaluation and evidence.

Lang1 Expression: English to Variables and Equations.

Example in words: a child is growing at the rate of 2 inches per year.

State variable: Let H be the height of the child (in inches).

Time interval: $\Delta t = 1$ year.

Change equation: $\Delta H / \Delta t = 2$ inches per year.

In each of the following, write the state variable(s) with units, time interval, and change equation to describe the rate of change. **Use a "Let" sentence** for each state variable, as in the example above. Answers may vary!

EX. Example in words: After her parachute opens, a skydiver descends at a speed of 5 meters per second.

Meters per second (m/s) is the SI unit for speed. For comparison, 10 m/s equals about 22.4 mph (miles per hour), or exactly 36 kph (kilometers per hour).

State variable: Let _____ be

Time interval: $\Delta t =$

Change equation: Δ___ / Δ___ =

EX. Example in words: Alan makes $2000 from his job each month, pays $1200 each month for rent and $400 each month for food.

State variable:

Time interval:

Change equation:

EX. Example in words: A barista pours hot water onto the coffee grounds at a rate of 10 mL (milliliters) per second. The resulting coffee pours out of the bottom of the filter at a rate of 8 mL per second.

A teaspoon is about 5 milliliters.

State variable:

Time interval:

Change equation:

Lang2 Interpretation: From Equations to Words

Example of a change equation: $\Delta L/\Delta t = -3$

Example in words (fictional story!): A spring-loaded tape measure is pulled out all the way, then released.

State variable: Let L be the length of the extended tape measure, in inches.

Time interval: $\Delta t = 1$ second.

In each of the following, **creatively write** an example in words that fits with the change equation. Your example must have a **quantifiable** state variable, with units, for which the change equation is reasonable. Use a "Let..." sentence to declare your state variables.

EX. Change equation: $\Delta M/\Delta t = 700 - 300$

Example in words: (both numbers 700 and 300 should occur).

State variable: Let _____ be

Time interval: $\Delta t =$

EX. Change equation: $\Delta R/\Delta t = 5$

Example in words:

State variable:

Time interval:

EX. (Challenge) Change equation: $\Delta A/\Delta t = 2B$ and $\Delta B/\Delta t = 3$.

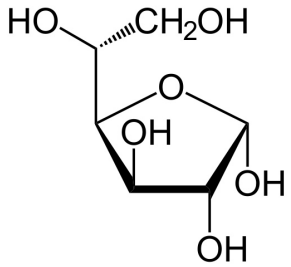
Example in words:

State variable(s): (A and B should be distinct but related quantities.)

Time interval:

IG1 Insulin and glucose: introduction

Now we make a dramatic shift in biology, from sharks and tuna to insulin and glucose. This is a shift from ecology to physiology. But mathematically, it is not much of a shift — and that is the power of mathematics!



One common form of glucose. There are some unlabeled carbon and hydrogen atoms, in this sort of diagram. The chemical formula of glucose is $C_6H_{12}O_6$.

Insulin is a big molecule. Its formula is:
$C_{257}H_{383}N_{65}O_{77}S_6$

Insulin and glucose are two molecules that can be found in your bloodstream. Glucose is a sugar. You get glucose by eating, and your liver produces some glucose too. Glucose enters muscle and fat and other cells, where it is used or stored.

$$\Delta G = [\text{meals} + \text{liver production}] - [\text{cell usage and cell storage}]$$

Insulin is a hormone, a protein secreted by beta cells in the pancreas. Insulin slowly degrades, like a population dying off.

$$\Delta I = [\text{production by beta cells}] - [\text{degradation rate}]\ I$$

These two equations govern how glucose and insulin would change over time, if they did not interact with each other. But there are complicated interactions!

When insulin binds to receptors on muscle and fat cells, those cells send glucose transporters to their surface, and this causes the cells to transport glucose out of the blood stream. The result is that insulin has a negative influence on glucose in the bloodstream.

$$\Delta G/\Delta t = m - s\ I\ G$$

Here "m" stands for the rate of change of glucose due to eating, liver production, and metabolism.

EX. If you have no insulin, i.e., untreated diabetes, and you eat normally, what will happen to your glucose levels according to the above change equation? Draw a graph and write a sentence to explain.

EX. The parameter "s" is called **insulin sensitivity**. How does a low or high value of s effect the regulation of glucose by insulin? Practically speaking, what does this mean if you eat a sugary meal and have high or low insulin sensitivity (s)?

IG2 Insulin and glucose: minimal model

In studying the insulin-glucose system, we consider two state variables, called G and I.

Let G be the concentration of glucose in the blood (in mM)
Let I be the concentration of insulin in the blood (in pM)

The change equation for glucose is below.

$$\Delta G/\Delta t = m - s\, I\, G$$

Insulin down-regulates glucose (as sharks "down-regulate" tuna). At the same time, glucose up-regulates insulin. When glucose levels are high in the bloodstream, the billion beta cells in your pancreas secrete more insulin in response. This influence of glucose on insulin is modeled by

$$\Delta I/\Delta t = q\, b\, \frac{G^2}{1+G^2} - \gamma\, I$$

Here q is a parameter representing the efficiency of insulin production by the beta cells, and b is the total mass of the beta cells. The parameter γ is the insulin degradation rate; insulin molecules naturally degrade in the bloodstream (just as sharks would slowly die off in the absence of tuna). The mysterious term is the following function of G.

$$H(G) = \frac{G^2}{1+G^2}$$

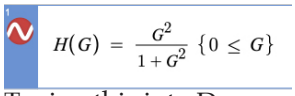
EX. Graph this function using Desmos. Sketch this graph below.

EX. How does an increase in glucose concentration (G) affect the concentration of insulin, according to this function? The function H(G) seems to approach a limit; what is this limit? What does it represent about the effect of glucose on insulin?

The units here are mM = millimolar, or millimoles per liter, and pM = picomolar, or picomoles per liter.

Glucose must be regulated tightly for health, between about 3.9 and 5.6 mM when fasting. Insulin is typically between 30 and 90 pM in the bloodstream when fasting.

A "**mole** of X means $6.022 \cdot 10^{23}$ molecules of X, almost a trillion trillion molecules. So a millimole of glucose is about $6 \cdot 10^{20}$ molecules. A picomole (trillionth of a mole!) is about $6 \cdot 10^{11}$ molecules.



Typing this into Desmos will restrict the domain of G to avoid meaningless negative values.

IG3 Saturation: sigmoid curves and the Hill function

Since it arises frequently in biology, we take a deeper look at this mysterious term that arises in the change equation.

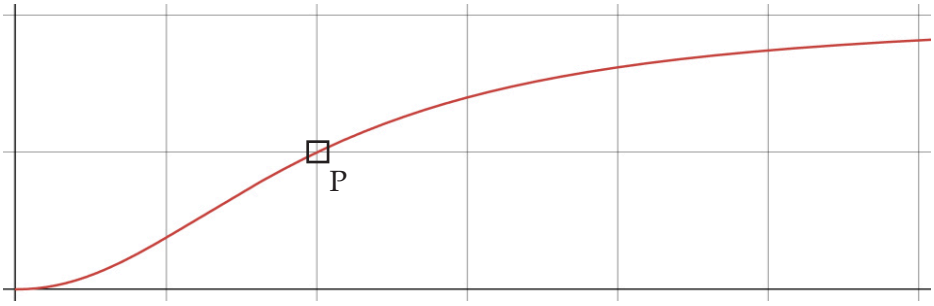
$$\Delta I/\Delta t = q\, b\, \frac{G^2}{1+G^2} - \gamma\, I$$

The term $\frac{G^2}{1+G^2}$ describes how glucose concentration influences insulin production. Its graph exhibits two phenomena:

1. **A direct relationship**. As glucose concentration increases, insulin production increases.

2. **Saturation**. Insulin production is physiologically limited. A beta cell can only produce so many insulin molecules per second. Even if glucose concentration increases to an extreme amount, the insulin production may only creep up slightly towards its theoretical **limit**.

Direct relationships with saturation are often modeled by **sigmoid curves**, as shown below. Note how it increases slowly, then quickly, then slowly again... approaching but never crossing its ceiling.



—Ceiling (limit)

— Halfway to ceiling

— Minimum

EX. Use Desmos to graph the function (the **Hill* function**)

$$H(G) = \frac{G^n}{k^n+G^n}$$

Here G is still the variable graphed on the horizontal axis, and k and n are parameters. How do the parameters k and n affect the shape of the sigmoid curve? Answer this question in 2-3 sentences, focusing on the landmark point "P" on the above graph.

* Named for Achibald Hill, not because its graph looks like a hill.

Instructions: Type the following into Desmos.

$$H(G) = \frac{G^n}{k^n + G^n} \quad \{G \geq 0\}$$

Add sliders for both parameters k and n. Click to allow n to vary from 1 to 5. Allow k to vary from 0 to 1.

Use sliders to explore!

IG4 Insulin and glucose: minimal model

Now we can understand every term in the minimal model of the insulin-glucose system. This model contains two change equations.

$$\Delta G/\Delta t = m - s\,I\,G$$

$$\Delta I/\Delta t = q\,b\,\frac{G^2}{1+G^2} - \gamma\,I$$

EX. There are four **terms** in these two change equations. These terms are: m, sIG, $q\,b\,\frac{G^2}{1+G^2}$, and γI. These terms describe events that positively and negative influence the concentrations of glucose and insulin. For reference, write down the meanings of each term in the change equation.

We use the word **term** loosely to mean something that is added / subtracted to other things.

Example: m represents the change in blood glucose due to meals and liver production, minus what is metabolized.

sIG represents:

$q\,b\,\frac{G^2}{1+G^2}$ represents:

γ I represents:

EX. Insulin yields a decrease in glucose concentration, and glucose yields an increase in insulin production. In this way, there is a similarity between the glucose-insulin system and the tuna-shark system. Write down two **differences** between the two systems, with specific reference to terms in the change equations.

IG5 Insulin-Glucose: simulation

Now load the *Insulin Glucose Regulation* simulator. This simulator uses the minimal model to understand the effect of various parameters on blood glucose and insulin concentrations. Notice that the horizontal axis is time (a 20-hour window is shown). There are two vertical axes; the left one is for the red Glucose line (in mM), and the right one for the blue Insulin line (in pM). When you load the simulator, it should display a **steady state**, the system is in **equilibrium**, as evidenced by the flat graphs.

The simulator also includes an extra term for hepatic glucose production. When the parameter α is zero, this term is zero and can be ignored. We will ignore α, k, and c until Lab 4.

EX. What is the equilibrium concentration of glucose? Of insulin? Make sure to include the appropriate units.

EX. Increase the glucose production (m) parameter, as if you were regularly consuming more glucose, and click the "simulate" button to see the effect. Does the system reach an equilibrium? How are the new glucose and insulin concentrations related to the concentrations you found before?

EX. If you regularly consume a lot of glucose, your body will slowly increase the mass of your beta cells. Experiment with the parameters m and b (beta cell mass). How can your body keep its glucose concentration within the safe range (about 3.9-5.5 mM) by increasing beta cell mass? What happens to insulin concentration?

EX. People's insulin sensitivity (s) varies widely. How can differences in beta cell mass keep glucose concentration in the safe range, even with wide variation in s?

IG6 Insulin-Glucose: simulation

During pre-diabetes, insulin sensitivity (s) tends to be lower, and beta cell mass (b) grows larger to keep glucose levels in the safe range. But eventually, beta cell mass **saturates** -- the body cannot produce any more beta cells or make them any larger.

EX. Using the simulator, what will you find in glucose and insulin levels during pre-diabetes? And what will you find when the parameter (b) cannot grow larger but (s) continues to shrink. (This is called **insulin resistance**).

EX. When glucose concentrations rise above 10mM, beta cells are killed by the high glucose levels. Using the simulator, what would be the effect of this on glucose and insulin concentrations? This is called type-2 diabetes.

In type-1 diabetes, the immune system attacks the beta cells, leading to a similar result.

IG7 Insulin-Glucose: trajectories in state space

The minimal model of the insulin-glucose system is given below.

$$\Delta G/\Delta t = m - s\, I\, G$$

$$\Delta I/\Delta t = q\, b\, \frac{G^2}{1+G^2} - \gamma\, I$$

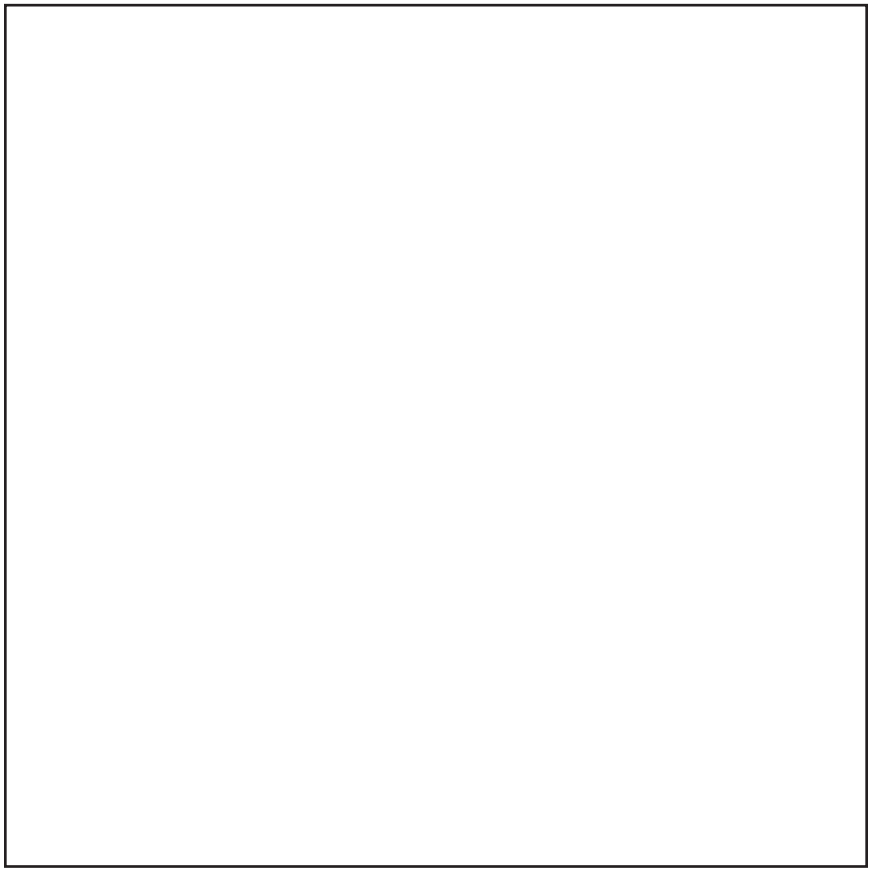
Since we are working with two state variables, G and I, which change over time, we can consider trajectories in state space -- just like sharks and tuna. To make things simpler, we set all of the parameters to 1, and consider the resulting system of change equations.

$$\Delta G/\Delta t = 1 - I\, G$$

$$\Delta I/\Delta t = \frac{G^2}{1+G^2} - I$$

Suppose that our time interval is $\Delta t = 1$ hour.

EX. Suppose that at t = 0, the glucose level is G=2 and insulin level is I=1. What will be the glucose and insulin levels at t=1? At t=2? At t=3? Draw a picture displaying the trajectory in state space, with glucose G on the horizontal axis, and insulin I on the vertical axis. Tabulate the values of t, G, and I in a table in the margin.



t	G	I	ΔG	ΔI
0	2	1		
1				
2				
3				

IG8 Insulin-Glucose: trajectories in state space

Load the *Dynamical Systems Calculator*. This is a general-purpose tool for visualizing trajectories in state space, given by change equations like we have seen for sharks and tuna, or insulin and glucose. Our two state variables are glucose (on the horizontal axis) and insulin (on the vertical axis). So for the simulator, we let X represent the glucose concentration and Y the insulin concentration. To enter our change equations, use the following:

X' equation: `1 - Y*X` Y' equation: `(X*X/(1+X*X))-Y`

Set Xmin = 0 and Xmax = 2. Set Ymin = 0 and Ymax = 2.

Turn on the vector field arrows, and start the simulation!

EX. Resetting the simulation as needed, what happens to the red dot that starts at x=2 and y=1? Compare this to what you found in the previous exercise.

EX. Recall that the horizontal x-axis represents glucose concentration and vertical y-axis represents insulin concentration in this simulation. Looking at many trajectories, describe what happens. How does that compare to what you found in the glucose-insulin simulator? How does that compare to sharks and tuna?

F1 Flow conclusion: model reflection

EX. Evaluate the insulin-glucose model in comparison to the shark-tuna model. In what ways do you find one model more useful than another? Why might that be expected or surprising? Write your answer in 100-200 words.

F2 Flow conclusion: dissecting change equations

$$\Delta S/\Delta t = -\delta S + pST \qquad \Delta G/\Delta t = m - s\,I\,G$$

$$\Delta T/\Delta t = \beta T - qST \qquad \Delta I/\Delta t = q\,b\,\frac{G^2}{1+G^2} - \gamma\,I$$

You have studied two systems of change equations. One models shark and tuna populations (S and T), and the other models glucose and insulin concentrations (G and I). One is at a large ecological scale. The other is at a small physiological scale.

EX. Look at the letter soup of these change equations. What are the state variables? What are the parameters?

EX. Glucose increases according to a simple constant m. Tuna increase according to a more complicated term βT. Explain why these increase terms are different.

EX. What is the meaning of the terms in the shark-tuna model labeled pST and -qST?

EX. Why does the insulin increase term have the weird expression $\frac{G^2}{1+G^2}$ in it? Why might that be a reasonable term to have?

A 1941 Fisher Electrophotometer, used to measure optical density. Image from a sale by Olde Good Store, retrieved in July, 2023 from `https://ogtstore.com/reclaimed-antique-electronics/fisher-electrophotometer/`

LABORATORY 2
GROWTH

In a 1999 commentary, Frederick Neidhardt reminisces about his experience with population growth in the laboratory, in the 1950s.

> For me, encountering the bacterial growth curve was a transforming experience. As my partner and I took samples of the culture at intervals to measure **optical density** and plotted the results on **semilogarithmic paper**, we saw, after the **lag period**, a straight line developing... beautiful in precision and remarkable in speed. As the line extended itself straight-edge true, I imagined what was happening in the flask—living protoplasm being made from glucose and salts as the initial cells (Klebsiella aerogenes, they were called then) grew and divided. The liquid in the flask progressed from having a barely discernible haze to a milky whiteness thick with the stuff of life, all within a very brief Boston winter afternoon. Mutably specific **autocatalysis**, the physicist Erwin Schrödinger had declared a few years earlier, was the defining characteristic of living systems, and I had just witnessed the working out of the mathematical statement of that property, $dN/dt = kN$ (where N is the number of cells or any extensive property thereof, t is time, and k is the **first-order rate constant** [in reciprocal time units]).

Frederick C. Neidhardt, "Bacterial Growth: Constant Obsession with *dN/dt*" in the Journal of Bacteriology, Dec. 1999, Vol. 181 (24) p. 7405-7408.

We have boldfaced some words from Neidhardt's commentary. What do they mean in this context?

In this laboratory, we will look at a few types of growth curves, including the exponential growth which is characterized by that mathematical statement $dN/dt = kN$ that so impressed Neidhardt. We will "unpack" this mathematical statement—a differential equation! — to understand every letter and every symbol. We will encounter some real data, resembling what Neidhardt saw, but collected through some more modern methods.

As suggested by Neidhardt, the letter N will be used to describe a population. N is how many cells are present in the petri dish, or maybe how many wolves are within a square mile. The letter t will be used to measure time, often starting from a certain moment called "time zero". The letter k is a parameter. And dN/dt is the "derivative" which will occupy our attention for weeks to come.

LG1 Linear growth of a population

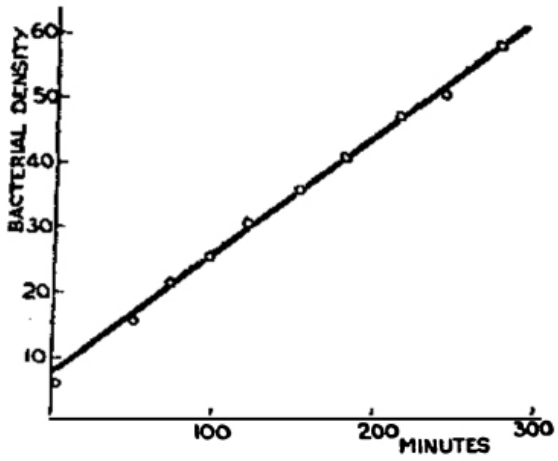


FIG. 6.—Residual growth of a streptomycin requiring strain of *Bacillus subtilis* in the absence of streptomycin. Growth is linear for over 4 hr. (25).

Figure 6 from Monod, "The growth of bacterial cultures" in Annu. Rev. Microbiol., 1949 (3), pp. 371--394.

The Figure above displays something very unusual—the linear growth of a strain of bacteria... in this case deprived of streptomycin which it requires to grow normally.

Let t denote time, in minutes. Let N denote bacterial density. This is probably "optical density" which is an observable **proxy measurement** for the population of bacteria.

A **proxy measurement** is a quantity we can observe, which is strongly correlated to a quantity we care about. We care about how many bacteria there are. We can't easily count them, so we measure how opaque the dish of bacteria looks. The more bacteria, the less light that gets through.

EX. What do you think the circular marks represent? What do think the line represents?

The circular marks represent

The line represents

EX. How long is the time period represented in this graph?

_____ minutes.

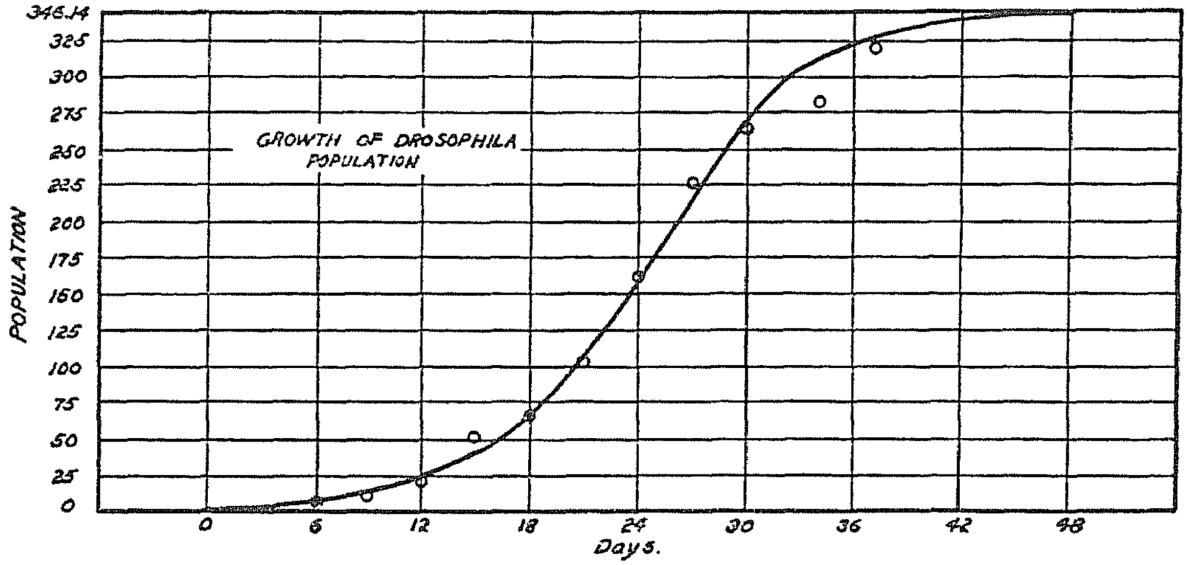
EX. What was the bacterial density at the first **observation** (at t=0)?

N(0) = _____

EX. Let N(t) be a linear function whose graph is the line displayed in the figure. Estimate its slope and intercept, and write its equation.

N(t) = _____

LG2 Linear growth rate



Chapter VII, Figure 5 of Lotka's *Elements of Physical Biology* (1925), displaying data collected by Pearl and Parker.

The Figure above displays something much more typical—the growth of a population (*Drosophila*, or fruitflies) which is first slow, then fast, then slow, under controlled laboratory conditions. Here time t is measured in days, and population N is based on a direct count of flies. The growth rate in a population is given by the formula $\Delta N/\Delta t$, and is measured in units of "flies per day" in this setting.

EX. Using the Figure above, estimate the growth rate of the Drosophila population, during the following time intervals.

During days 6-12, $\Delta N/\Delta t =$ _____ flies per day.

During days 12-18, $\Delta N/\Delta t =$ _____ flies per day.

During days 18-24, $\Delta N/\Delta t =$ _____ flies per day.

During days 24-30, $\Delta N/\Delta t =$ _____ flies per day.

During days 12-30, $\Delta N/\Delta t =$ _____ flies per day.

In each of the above estimates, you computed a "rise/run." Thus each $\Delta N/\Delta t$ is the slope of a line segment. In this way, you should observe:

The <u>slope</u> of the population time-series graph
equals
the <u>rate</u> of population growth.

EX. Draw a right triangle on the Figure above, correponding to one of the time intervals listed above. Mark the quantities ΔN and Δt on this triangle, and note that $\Delta N/\Delta t$ is the slope of the hypotenuse.

LG3 Linear functions

There are two conceptually distinct ways to think about linear functions. Let X be a quantity that changes over time (t). We say that **X is a linear function of t** in the following circumstances. **Memorize these!**

1. The relationship between X and t is given by a formula $X = mt + b$, for some parameters m and b.

2. The rate of change $\Delta X/\Delta t$ is constant, no matter what time interval we look at.

3. The time-series plot of X is a straight line.

We can understand linear functions by going back and forth between these characterizations. For example, if your hair length H changes at a constant rate $\Delta H/\Delta t = 0.4$ mm/day, then your hair length is given by a formula $H = 0.4\ t + b$, where t is measured in days (since some starting day), and b is the length of your hair on day 0. The time-series plot of H will be a straight line with slope 0.4.

EX. The population of jellyfish is given by the formula $J = 1.2\ t + 800$, where t is measured in months. Describe $\Delta J/\Delta t$ and draw a time series of J. Label your axes carefully.

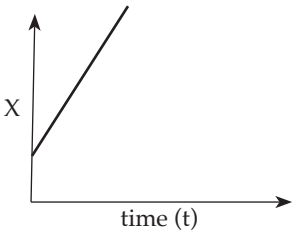
EX. Your container contains 60 pieces of gum when you purchase it, and you chew 2 pieces per day. Let G be the number of pieces of gum in your container. Describe G as a linear function of time by a formula, describe its rate of change $\Delta G/\Delta t$, and draw a time-series plot of G.

Examples:

1. $X = 3t + 2$

2. $\Delta X/\Delta t = 3$

3. The time series looks like the line below.



LG4 Fitting a linear function

In practice, scientists often gather data through experiment, graph their data, and observe a pattern of linear growth or decay. To estimate slope and intercept, scientists frequently use computers to **fit** a linear model. The following exercises will show you how this is done.

Fission yeast (Schizosaccharomyces pombe) grow longer over short periods of time, so that their growth can be observed under a microscope. In the margin, you can find a table with the measured length of a single yeast cell tracked over a period of 160 minutes.

EX. Let L be the length of the observed yeast cell, and let t be time in minutes. Sketch a time-series plot of L below, taking care to label axes.

EX. Enter the data from the table into the *Linear Regression with Log Scaling* tool. Use the slope and intercept there to describe the relationship between L and t.

L = _____ t + _____.

EX. What is the growth rate of the yeast cell, using the slope of the regression line above? Compare this to the growth rate that you find by computing $\Delta L/\Delta t$ on the entire 160-minute time period.

EX. Is the rate of change $\Delta L/\Delta t$ constant, no matter what time interval we look at? Should we say that L is a linear function of t or not? If not, what do you think we should say?

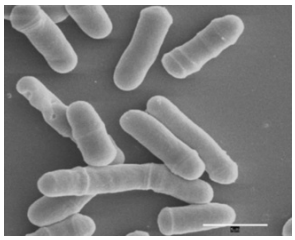


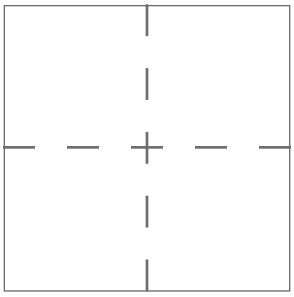
Image of fission yeast culture from *The Cell Cycle. Principles of Control* by David O. Morgan.

Below: Table 1, from *The time-profile of cell growth in fission yeast*, by Buchwald and Sveiczer, in Theoretical Biology and Medical Modelling (2006).

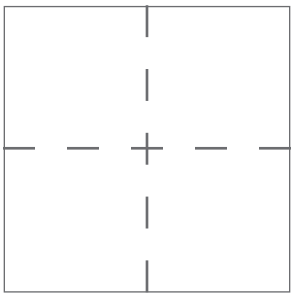
Time (min)	**Length (μm)**
0	8.667
10	9
20	9.333
30	10
40	10.333
50	10.667
60	11.333
70	12
80	12.333
90	13
100	13.333
110	14.333
120	15
130	15.667
140	16
150	15.667
160	16

F1 Graphs of linear, power, and exponential functions

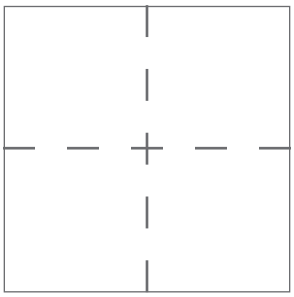
EX. Sketch a graph of the 16 functions below. You may use a tool like Desmos to help, but try to guess and use prior knowledge as much as possible.



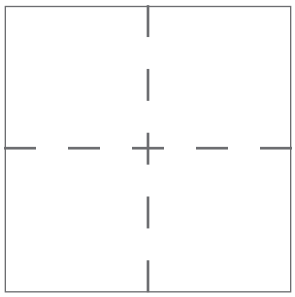
$y = 2x$



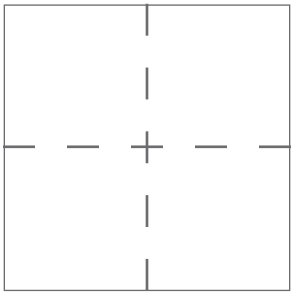
$y = 2x - 1$



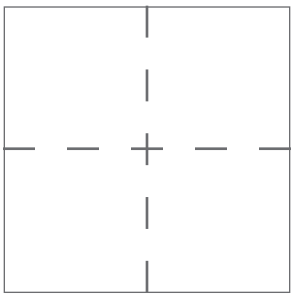
$y = 0.5x + 1$



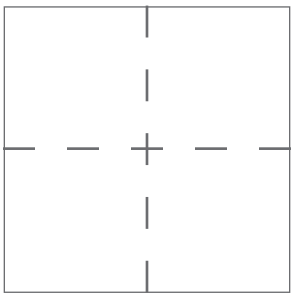
$y = -0.5(x + 1)$



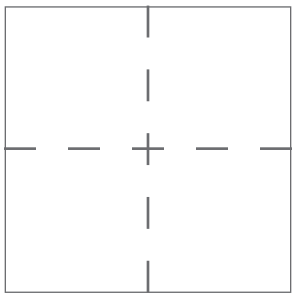
$y = x^2$



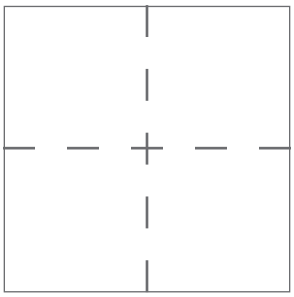
$y = x^3$



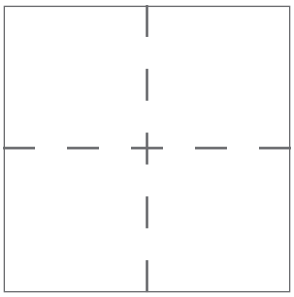
$y = x^4$



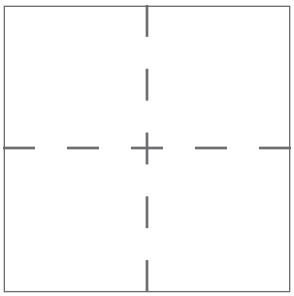
$y = 1 - x^4$



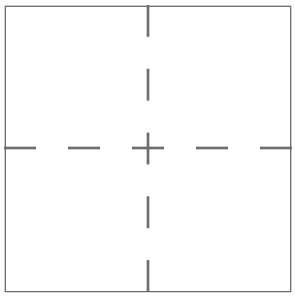
$y = x^{1/2}$



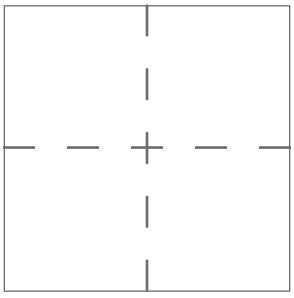
$y = (x-1)^{1/2}$



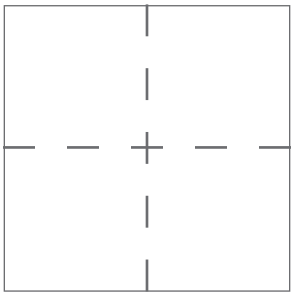
$y = x^{3/2}$



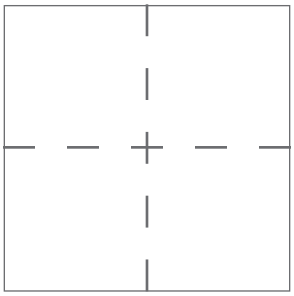
$y = 0.5\ x^{4.1} + 2$



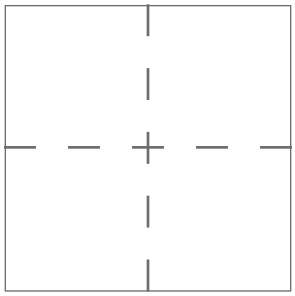
$y = 2^x$



$y = (0.5)^x$



$y = 3^x+1$

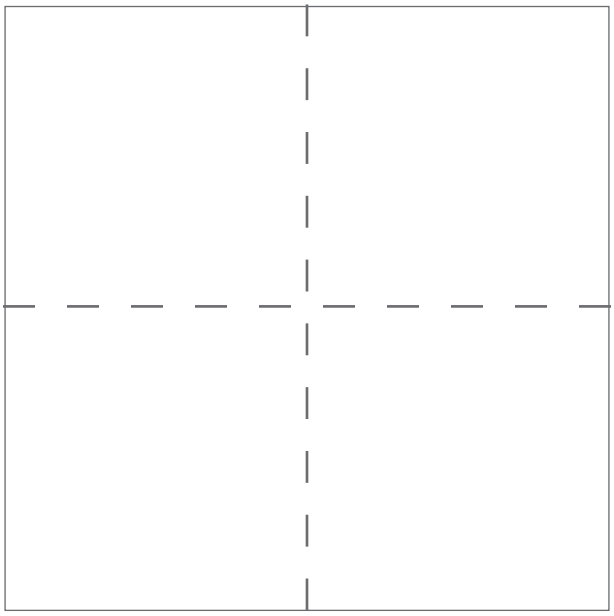


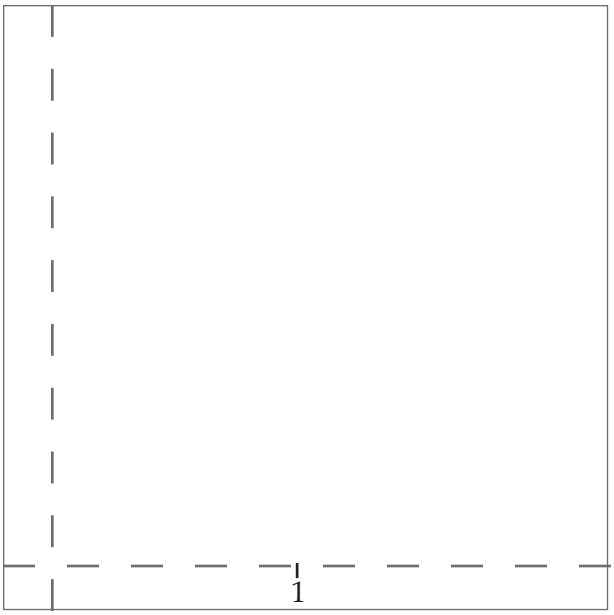
$y = 3^{(x+1)}$

F2 Graphs: Parameter Exploration

EX. Draw graphs of lines (**linear functions**) with various slopes, on the same axis. In other words, draw the graphs of $y = mx$, where the parameter m (slope) includes *-2, -1, -1/2, 0, 1/2, 1, 2*.

Where do all these graphs intersect?



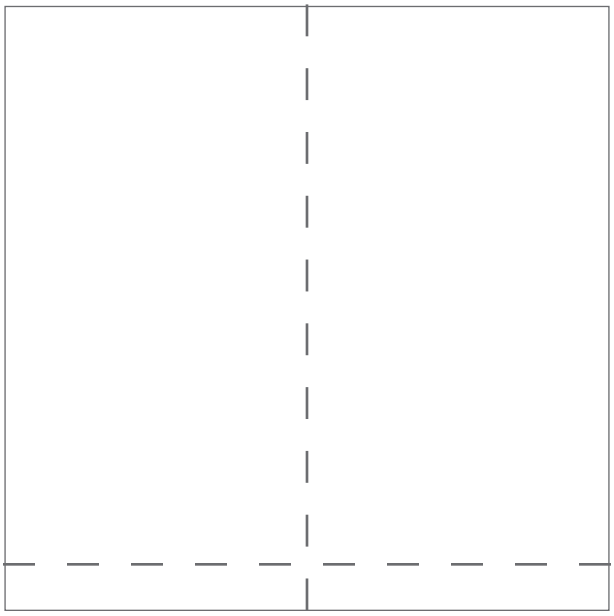


EX. Draw graphs of positive **power functions**, with various powers, on the same axis. In other words, draw the graphs of $y = x^p$, where the parameter p (power) includes *0.2, 0.5, 1, 1.5, 2, 2.5, 3*.

Only include positive values of x, since general powers of x are undefined for negative values of x. Where do all these graphs intersect?

EX. Draw graphs of **exponential functions** with various positive bases, on the same axis. In other words, draw the graphs of $y = b^x$, where the parameter b (base) includes *0.2, 0.5, 1, 1.5, 2, 2.5, 3*.

Note that all values of x are possible here, but the y-coordinate will always be positive. Where do these graphs all intersect?



N3 Numeracy: Powers of 2, powers of 10.

Instructions: This page can be a reference, as you learn your powers of two and powers of ten. You don't need to memorize all your powers of 2, but it is useful to have some particular "landmarks" in mind as you reason about numbers, doublings, etc.

EX. Fill out the following columns with powers of two and powers of ten. Work by hand, when possible, and calculator when needed.

Powers of 2 show up when we consider doubling populations. They are also important in "information theory," where the basic unit of information is the **bit**. A bit of memory can store the answer to one yes/no question. A bit requires one electronic "on/off" switch in your computer. A **byte is 8 bits** (eight switches).

2^{30}=_____

A gigabyte (GB), is 2^{30} bytes, ~1 billion bytes.

2^{20}=_____

A megabyte (MB), is 2^{20} bytes, ~1 million bytes.

2^{10}=_____

A kilobyte (KB) is 2^{10} bytes, ~1000 bytes.

2^{8}=_____

2^{4}=_____

2^{3}=_____

2^{2}=_____

2^{1}=2

2^{0}=_____

2^{-1}=_____

2^{-2}=_____

2^{-10}=_____

2^{-20}=_____

2^{-30}=_____

Powers of 10 are fundamental to our base-ten number system (as we have 10 fingers). **Memorize your powers of 10**, including thousands, millions, and billions, and the corresponding fractions (1/1000, etc.), **and the prefixes**: giga, mega, kilo, milli, micro, and nano.

10^{9}=_____

A **giga**ton (GT) is 1 billion tons. 1 ton equals 2000 lbs.

10^{6}=_____

A **mega**watt (MW) is 1 million watts.

10^{3}=_____

A **kilo**meter (km) is 1000 meters, (walk from McHenry to Porter.)

10^{2}=_____

10^{1}=10

Standard (S.I.) units include...

10^{0}=_____

Length: 1 meter (a bit over 3 feet long)

Time: 1 second

Mass: 1 gram. (The weight of a dollar bill.)

10^{-3}=_____

A **milli**gram (mg) is 1/1000 of a gram.

10^{-6}=_____

A **micro**second (μs) is one millionth of a

10^{-9}=_____

A **nano**meter (nm) is one billionth of a meter.

10^{-12}=_____

A **pico**gram (pm) is one trillionth of a gram.

Log1 Common logarithms (base 10).

Logarithms were invented by the Scottish mathematician John Napier in 1614, and his son published his "Wonderful Canon of Logarithms" in 1620, along with Henry Briggs' "common" or "base 10" logarithms. Logarithms seem to delight scientists as much as they torment students. As you become a scientist, perhaps you will accept, and even delight, in logarithms. We will see them often in this class, and there are many ways to get started.

We begin by thinking of logarithms as a way to inquire about exponents. Every question about logarithms has an equivalent question about exponents... and those you may be able to answer!

Logarithms base 10 relate to questions about exponents with base 10. For example, consider the following equivalent questions.

What is $\log_{10}(100)$? _____ 10 to what power equals 100?

What is $\log_{10}(1/1000)$? _____ 10 to what power equals 1/1000?

What is $\log_{10}(50)$? _____ 10 to what power equals 50?

EX. Answer the questions on the right, using the previous page for reference. The only difficult one is the last (10 to what power equals 50?). For that, try to approximate using your table, or a graphing tool.

Even if you have never seen logarithms, you can now fill in the blanks on the left! The answers to the questions on the right are exactly the answers to the questions on the left -- that's what logarithms are!

EX. Continue by filling in the missing question on right, answer the question on the right, and use this to answer the question on the left.

What is $\log_{10}(10)$? _____ 10 to _____? _____

What is $\log_{10}(1)$? _____ 10 to _____? _____

What is $\log_{10}(0.01)$? _____ 10 to _____? _____

What is $\log_{10}(10^{3.4})$? _____ 10 to _____? _____

What is $\log_{10}(100^{x})$? _____ 10 to _____? _____

D1 The derivative: from ΔP/Δt to dP/dt.

When a quantity P is changing, we describe its rate of change by focusing on an interval of time: a starting time and an ending time. The rate of change during that time interval is the quotient $\Delta P / \Delta t$. Here ΔP is the amount that P changes, and Δt is the amount that t changes, during that time interval.

EX. Let $P(t) = 100\, t^{1/2}$. Fill out the table below with values of P(t). Then compute $\Delta P / \Delta t$ on the time intervals below.

Time (t)	$P = 100\, t^{1/2}$
1	100
1.001	
1.01	
1.1	

On the time interval [1,1.1],

$\Delta t =$ _____ and the rate of change is $\Delta P / \Delta t =$ _____

On the time interval [1,1.01],

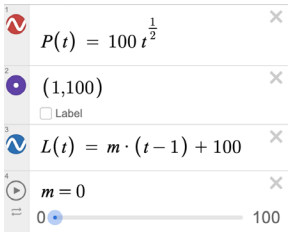
$\Delta t =$ _____ and the rate of change is $\Delta P / \Delta t =$ _____

On the time interval [1,1.001],

$\Delta t =$ _____ and the rate of change is $\Delta P / \Delta t =$ _____

EX. What do notice about the rates of change $\Delta P / \Delta t$ on the intervals you considered above? Look at the three values you've found!

EX. Now graph the function $P(t) = 100\, t^{1/2}$ in Desmos. Use the Graph Settings button (it looks like a wrench), to change the view window so that the horizontal axis displays a range between 0 and 2, and the vertical axis displays a range between 0 and 150. Add a marked point at (1,100). Then add the graph of the line through the marked point, having slope m: L(t) = m(t-1) + 100. Use Desmos to add a slider for the parameter (slope) m, and click this slider to allow m to slide between 0 and 100. The result should look like what you see here in the margin.



Using the slider, what slope "m" makes the line L(t) **tangent** to the graph of P(t) at the marked point?

EX. Relate your answers in the previous two questions. Why are they related? How does this number capture the slope of the curve P(t)?

D2 Estimating the derivative.

The **derivative** dP/dt refers to the **instantaneous rate of change**. For an instantaneous rate of change, we use a time interval with starting time t and ending time $t + dt$; the symbol dt stands for a "time **differential**," an infinitesimally small unit of time (just an instant!).

To **estimate** the derivative dP/dt at time t, we can compute $\Delta P/\Delta t$ on the time interval $[t, t + \Delta t]$, when Δt is very very small.

Example: Suppose $P(t) = 2t^2$. **Estimate** dP/dt when t=3.

Solution: We choose the very very small $\Delta t = 0.0001$. Then we have

$P(3) = 2 \cdot 3^2 = 18.$
$P(3 + \Delta t) = P(3.0001) = 2 \cdot (3.0001)^2 \approx 18.0012.$
On the time interval [3, 3.0001], $\Delta P/\Delta t = 0.0012/0.0001 = 12.$

Hence $dP/dt \approx 12$ when t=3.

In the following exercises, use this technique to estimate the derivative dP/dt at various times. Write your work just as it is written in the example above. Use a different Δt (your choice!) in each problem.

EX. Suppose $P(t) = 100\ t^{1/2}$. Estimate dP/dt when t=4.

EX. Suppose $P(t) = 2t + 1$. Estimate dP/dt when t=7.

EX. Suppose $P(t) = 70\ t^{2.5}$. Estimate dP/dt when t=9.

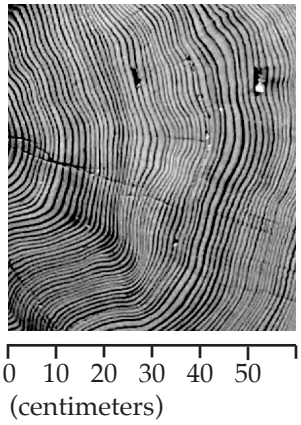
A confusing thing is this: the rate of change $\Delta P/\Delta t$ really depends on the choice of a start time and end time.

The derivative dP/dt depends on the choice of a start time; the end-time is just a tiny instant after the start time. Making this precise requires the mathematics of **limits.**

RT1 Redwood tree growth: power function

A redwood tree grows from a sapling into a giant over hundreds, and sometimes thousands, of years.

EX. On the right is a typical cross section of a redwood tree. Note that each tree ring indicates one year of time elapsed. Use this image to estimate the rate of growth of the radius of the tree.



$\Delta R / \Delta t =$ _____ meters per year. (Convert cm to m!)

EX. Now, use your estimate and a **linear function** to model the radius of the redwood tree as a function of time.

$R(t) =$ _____ meters.

EX. The height of the redwood tree does not grow linearly over time. Rather, the height of a redwood tree is modeled by the power function.

$H(t) = 3\, t^{0.5}$ meters.

EX. Sketch a time series of the height of the redwood tree below.

EX. Assuming the tree is a cylinder, what is the **volume** V of the tree as a function of time? Use the approximation $\pi \approx 3.14$.

$V(t) =$ _____ m^3. (Note m^3 = cubic meters)

EX. The **density** of a redwood tree is approximately 450 kg/m^3. What is the mass M of the tree as a function of time?

A density of 450 kg/m^3 means that each cubic meter of redwood weighs 450 kilograms.

$M(t) =$ _____ kg.

EX. Which has more mass: a single 100-year old tree or two 80-year-old trees? Explain by computing their masses.

RT2 Redwood tree growth: rates of change

Now we look at the growth rate of the redwood tree. We have already modeled the linear growth of the radius of the tree.

EX. Estimate the growth rates dH/dt when $t=1$, when $t=10$, and when $t=100$, using the function $H(t) = 3\,t^{0.5}$ from the previous page.

At 1 year old, the tree height is growing at a rate of _____ m/yr.

At 10 years old, the tree height is growing at a rate of _____ m/yr.

At 100 years old, the tree height is growing at a rate of _____ m/yr.

To understand how the tree interacts with its environment, it is important to understand how the **mass** of the tree changes from year to year—this is its **biomass growth rate**.

EX. Estimate how fast the mass of the tree is increasing, dM/dt, when $t=1$, $t=10$, and when $t=100$, using the function $M(t)$ you found on the previous page.

At 1 year old, the tree mass is growing at a rate of _____ kg/yr.

At 10 years old, the tree mass is growing at a rate of _____ kg/yr.

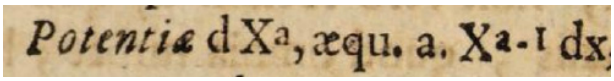
At 100 years old, the tree mass is growing at a rate of _____ kg/yr.

EX. Which is **growing** faster, in terms of mass per year: a single 100-year-old tree or two 80-year-old trees? Explain by computing their growth rates in kg/year.

EX. Note that biomass growth requires corresponding inputs of sunlight, water, and soil nutrients. What advantages are there for a forest of many younger trees versus a forest of fewer older trees?

D3 The derivative of a power function

The first big discovery of calculus appeared in 1684:



Liebniz wrote this rule (in Latin, in 1684). "aequ" means "equals." We might write it as

$$dX^a = a\,X^{a-1}\,dx$$

Dividing by dx,

$$dX^a / dx = a\,X^{a-1}.$$

That's the power rule.

In a traditional calculus book, this is presented as the **Power Rule.**

Power Rule: If $P(t) = t^n$, then $dP/dt = n\,t^{n-1}$.

EX. Let $P(t) = t^3$. Estimate dP/dt when t=2, using the method of the previous pages. Compare this to the exact result you get by using the Power Rule above.

EX. Let $P(t) = 100\,t^3$. Estimate dP/dt when t=2, using the method of the previous page. What do you think the exact formula should be for dP/dt. What happens to the number 100?

Rule: If you scale a function by multiplying by a constant C, then the derivative is scaled by the same constant C. (Vertical scaling scales the slope too!)

EX. Let $P(t) = 100 + t^3$. Estimate dP/dt when t=2, using the method of the previous page. What do you think the exact formula should be for dP/dt. What happens to the number 100?

Rule: If you vertically shift a function by adding a constant C, then the derivative is the same as the original unshifted function. (Vertical shifting leaves slope unchanged!)

EX. Let $P(t) = 100\,t^{1/2}$. Use the power rule, and what you have learned above to find a formula for dP/dt. Use this to find the exact value of dP/dt when t=4.

The power rule holds for every constant real power n, not just whole number powers. Here the power is n=1/2, which is fine!

D4 Derivative drills: Linear functions and power func-

A linear function has the form $P(t) = mt + b$. The parameter m is called the slope, and b is called the y-intercept. For linear functions, dP/dt is the rate of change, i.e., the slope, and it is a constant.

Example: If $P(t) = 3t + 2$, then $dP/dt = 3$.

EX. Find dP/dt for the linear functions P(t) below. All letters besides P and t are constants. Hint: dP/dt is the slope of the line.

$P(t) = 5t - 1$	$dP/dt =$	$P(t) = -t$	$dP/dt =$
$P(t) = t + 10$	$dP/dt =$	$P(t) = kt$	$dP/dt =$
$P(t) = 2t$	$dP/dt =$	$P(t) = 3t - 2t$	$dP/dt =$
$P(t) = -3t + 2$	$dP/dt =$	$P(t) = b + 3t + 1$	$dP/dt =$
$P(t) = 10 - t$	$dP/dt =$	$P(t) = 3$	$dP/dt =$

A power function has the form $P(t) = t^a$. The parameter a is called the power or the exponent. Power functions are often scaled, and sometimes vertically shifted, in the form $P(t) = C\,t^a + b$. In this form, C is the (vertical) scaling factor, and b is the y-intercept. For such a power function, the derivative is given by $dP/dt = C\,a\,t^{a-1}$.

Example: If $P(t) = t^{0.6}$, then $dP/dt = 0.6\,t^{-0.4}$.

Example: If $P(t) = 3t^2 + 5$, then $dP/dt = 6t$.

EX. Find dP/dt for the power functions P(t) below. All letters besides P and t are constants.

$P(t) = t^5$	$dP/dt =$	$P(t) = -Ct^3$	$dP/dt =$
$P(t) = 1 - t^5$	$dP/dt =$	$P(t) = \pi\,t^2$	$dP/dt =$
$P(t) = t^{-1}$	$dP/dt =$	$P(t) = kt^{0.5} + r$	$dP/dt =$
$P(t) = 4t^{0.5}$	$dP/dt =$	$P(t) = t^{n+1}$	$dP/dt =$
$P(t) = 1/t$	$dP/dt =$	$P(t) = t^0$	$dP/dt =$

EX. What is another common way of writing $P(t) = t^{-1}$? What is another way of writing $P(t) = 4t^{0.5}$?

PK1 Pharmacokinetics: Ethanol (0^{th} order)

Ethanol is the molecule that makes alcoholic beverages alcoholic. A typical 12oz beer contains about 15 grams of ethanol. If you drink such a beverage, the ethanol molecules quickly distribute throughout your bloodstream. When they pass by the liver, enzymes work at a steady rate to convert ethanol into acetaldehyde (an oxidation reaction). A typical rate of conversion is about 10 grams/hour.

Beer varies considerably. A typical beer here means 5% ABV (alcohol by volume). Budlight is 4.2% ABV. An imperial stout is about 9% ABV.

EX. Consider a person who drinks two 12oz beers during a one hour period of time. Let E(t) be the amount of ethanol in their bloodstream, as a function of time. Draw a time-series plot below, displaying your expectations for E(t) during a 5-hour period beginning at the moment beer-consumption begins. Draw and label your own axes for this plot. (Use a straightedge!)

EX. What assumptions did you make in order to create your expectations for E(t)?

EX. The derivative dE/dt represents the rate of change of ethanol in the bloodstream, measured in grams/hour. Describe dE/dt during the 5-hour period you have graphed in one or two sentences with precise numbers.

PK2 Pharmacokinetics: Gentamicin (1st order)

Gentamicin is an antibiotic that is provided via injection in hospital settings. It does not undergo significant chemical reactions. After injection, gentamicin is gradually cleared from the bloodstream by the kidneys. Simply put, a patient injected with gentamicin molecules will pee out gentamicin molecules a little while later.

Load the *Gentamicin Dosage Simulator* now. Your goal is to determine the best protocol for administering gentamicin to patients. You can adjust the dosage (how much is injected), the frequency (how often injections are given), and the infusion time (how quickly the injections are given). The green range indicates an ideal therapeutic window, where the gentamicin concentration is between 4 and 10 mg/L. The red range indicates the dangerous window where toxic side effects are more likely (gentamicin can cause damage to the kidneys and inner ear).

EX. Let G(t) be the concentration of gentamicin in the bloodstream at time t. What is happening to the patient when dG/dt positive? When dG/dt is negative?

EX. Experiment with dosage, frequency, and infusion, to find a protocol which maximizes the time in the therapeutic window and minimizes the time in the toxic window. Keep the half-life fixed at 3 hours for now. What protocol did you find best?

Dosage: _____ Frequency: _____ Infusion Time: _____

Within your protocol, how much time **per day** is the patient within the therapeutic window. Within the toxic window?

Therapeutic duration: _____ Toxic duration: _____

EX. Some patients may have renal disease, and so their kidneys do not filter their blood as quickly. For such patients, the half-life might double to 6 hours. How does this effect your protocol? How should you change the protocol to help such a patient?

Exp1 Exponential growth of a population

Imagine a population of well-fed bacteria in a dish. Let t denote time, measured in minutes, and P(t) the population at time t. Assume that P(0) = 1000. There are 1000 bacteria when the clock starts.

Binary fission is a type of asexual reproduction, by which a single bacterium duplicates its DNA, elongates, and splits into two new bacteria.

Suppose that every 20 minutes, **half** of the bacteria undergo binary fission. For example, since P(0) = 1000, P(20) = 1000 + 500 = 1500. We study this highly idealized model below.

Bacteria doubling time varies by species and by environmental condition. 20 minutes is typical for *E. coli* in the lab.

EX. Create a table on the right, which displays the population of bacteria for the first hour, according to the model above. Your table should include time-points for 0, 20, 40, and 60 minutes, and should be labeled with units.

EX. How is P(20) related to P(0)? How is P(40) related to P(20)? How is P(60) related to P(40)? Write one answer for all of these questions, using a formula.

_____

_____

EX. At t=120, the population of bacteria can be expressed using a formula like

$$P(120) = 1000\ (\ \_\_\_\_\_)^{\_\_\_}$$

Using the previous question, what is the base and whole number exponent? Remember that exponentiation is repeated multiplication.

EX. Write the **exponential function** which describes the population growth in this model.

$$P(t) = \_\_\_\_\_\ (\_\_\_\_\_)^{\_\_\_\_\_}$$

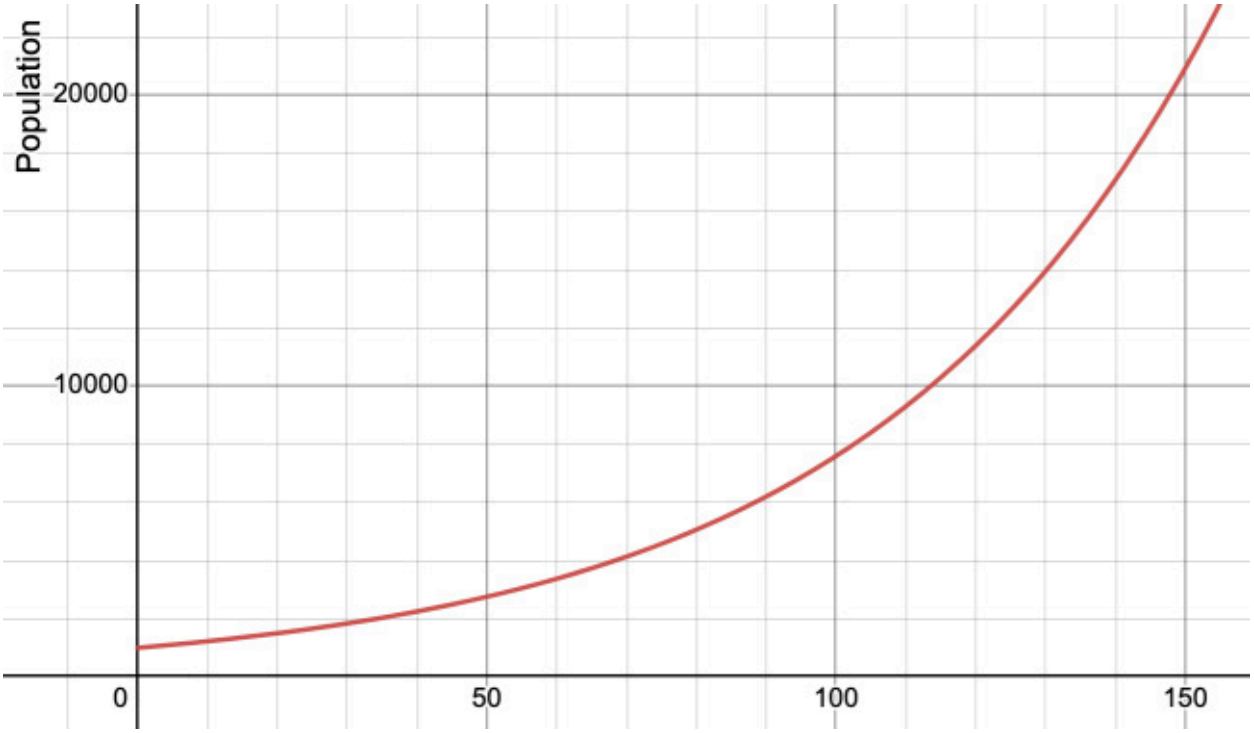
EX. Sketch the graph the exponential function P(t), for the first 60 minutes, in the box to the right. Label your axes, as in the Fig 6. of Monod. Mark the data points that you included in your table above.

Exp2 Doubling times

First, check your answers from the previous page to make sure that you have the correct equation for the population. Rewrite this below.

$$P(t) = \_\_\_\_\_ (\_\_\_\_)^{\frac{t}{\_\_\_\_}}$$

Graph this function on Desmos, changing the axes to focus on the first three hours of time. The result should look something like below.



EX. At what times do you find the population equal to 4000? 8000? 10000? 20000? To answer these questions, zoom in with Desmos to approximate to the nearest minute.

No logarithms yet, please!

P(_____) = 4000 P(_____) = 8000

P(_____) = 10000 P(_____) = 20000

EX. How long does it take for the population to double from 4000 to 8000? From 10000 to 20000? What do you notice?

EX. Now, use this **doubling-time** to create a new form for the exponential function P(t), where the base is 2.

$$P(t) = \_\_\_\_\_ \cdot 2^{(t\ /\_\_\_\_\_)}$$

Exp3 Exponential functions

An **exponential function** is a function F(t) having the form

$$F(t) = C\,b^t.$$

Here we use t as our independent variable, as it often represents time. The letters C and b are parameters. We always assume the **base** "b" to be positive, since powers of negative numbers are not always real numbers. We usually assume C to be positive too.

EX. Graph the exponential function $F(t) = C\,b^t$ in Desmos, using sliders for b and C. Write a few sentences, to describe how the parameters b and C affect the shape of the exponential function. In particular, what happens when C crosses the line from positive to negative? What happens when b (always positive) crosses the line from less than 1 to greater than 1?

You might be asked to write this sentence on a test!

The remarkable fact about exponential functions is the following:

Exponential functions are proportional to their rates of change.

EX. Repeat the above sentence 10 times each day for the next week.

EX. To understand this, consider the exponential function $F(t) = 10^t$. Estimate dF/dt when t=0, when t=1, and when t=2. Use the same tiny value of Δt in all your estimates. Use this to complete the table below.

Use the techniques from page D2: Estimating the Derivative.

t	$F(t) = 10^t$	dF/dt
0		
1		
2		

EX. Now use the table to complete the following sentence.

$$\text{If } F(t) = 10^t, \text{ then } dF/dt = \_\_\_\_\_ \cdot 10^t.$$

This says that the rate of change dF/dt is proportional to the function F(t). You have found the **constant of proportionality**!

Exp4 Derivatives of exponential functions

EX. Working with a group, find the proportionality constants, relating each of the exponential functions below to its derivative.

An exponential function is a function of the form $C\,b^t$, where C and b are constants, and b>0.

If $F(t) = 2^t$, then $dF/dt =$ _____ $\cdot F(t)$

$2^{-t} = (0.5)^t$. That is why 2^{-t} is an exponential function.

If $F(t) = 2^{-t}$, then $dF/dt =$ _____ $\cdot F(t)$

If $F(t) = 5 \cdot 3^t$, then $dF/dt =$ _____ $\cdot F(t)$

$2^{t/10}=(2^{1/10})^t=(1.072)^t$. That is why $2^{t/10}$ is an exponential function.

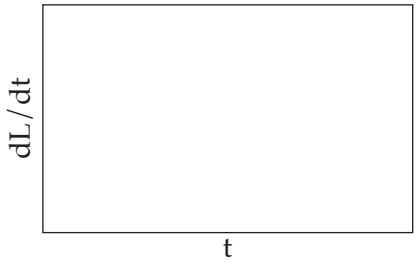
If $F(t) = 2^{t/10}$, then $dF/dt =$ _____ $\cdot F(t)$

When F(t) is a function, the derivative dF/dt is also a function. We have now seen how this works for three sorts of functions, so we review this now.

EX. On the left, graph the given functions. On the right, find and graph their derivatives.

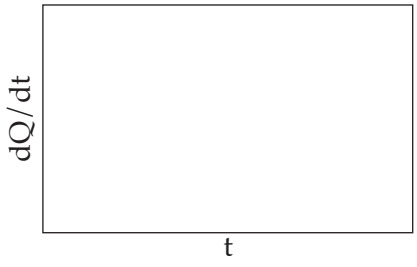
Linear: $L(t) = 2t + 1$

$dL/dt =$ _____



Quadratic: $Q(t) = 0.5\,t^2$.

$dQ/dt =$ _____



Exponential: $F(t) = 2^t$.

$dF/dt =$ _____2^t_

Log2 Exponents and logarithms, + and ×.

Exponents turn addition into multiplication.

Example: $10^{(3+4)} = 10^3 \times 10^4$.

Why? Because exponents represent repeated multiplication. For example,

$10^{(3+4)} = 10^7 = 10 \times 10 \times 10 \times 10 \times 10 \times 10 \times 10$

and

$10^3 \times 10^4 = (10 \times 10 \times 10) \times (10 \times 10 \times 10 \times 10)$.

The associative property of multiplication guarantees that these are the same.

The general rule is:

$$b^{(x+y)} = b^x\, b^y$$

for all numbers x,y, and all positive numbers b.

A consequence is that exponents turn subtraction into division. For example,
$10^{(3-4)} = 10^3 \div 10^4 = 1000/10000 = 0.1$.

Why are exponents of 1/2 related to square roots? Well,

$$x^{(1/2)} \cdot x^{(1/2)} = x^{(1/2\,+\,1/2)} = x^1 = x.$$

So $x^{(1/2)}$ must be a square root of x. We take the positive square root, e.g., $9^{(1/2)} = 3$ not -3.

EX. Transform addition into multiplication, or vice-versa, to **re-express** the following. Answers may vary, but should use one of the rule above. Do NOT give a numerical "answer.

$10^{(1+4)} =$ _____ (Do not write 100000!)

$2^{(2+2)} =$ _____ (Do not write 16!)

$3^3\, 3^5 =$ _____

$5^{(x+y)} =$ _____

$x^{(1+t)} =$ _____

$2^{(x-1)} =$ _____

$2^x\, 4^x = 2$_____

$10^{(1/2)}10^{(3/2)} =$ _____ (Do not write 100!)

Logarithms turn multiplication into addition.

$\log_{10}(1000\times10000) = \log_{10}(1000) + \log_{10}(10000)$.

EX. Why? Explain how the above equality is related to the exponents on the left.

_____

_____

_____

_____

_____

The common logarithm $\log_{10}(x)$ answers the question "10 to what power equals x?"

For a general base b, the base-b logarithm $\log_b(x)$ answers the question "b to what power equals x?" For example, $\log_2(8) = 3$, because 2 to the 3rd power equals 8.

A general rule, for all bases, is

$$\log_b(uv) = \log_b(u) + \log_b(v),$$

for all positive numbers u,v, and b.

EX. Transform the following logarithms using the rules above.

$\log_{10}(100\times1000)=$ _____

$\log_2(0.5)+\log_2(2)=$_____

$\log_3(x^2)=$_____

$\log_{10}(xyz)=$_____

$\log_2(2^x\cdot y)=$_____

$\log_{10}(100^3)=$_____

$\log_3(3^x) - \log_3(9^x)=$____

$\log_3(3x) - \log_3(9x)=$____

Log3 Changing bases.

We introduce two more useful formulas involving logarithms. Instead of memorizing them, we practice using them here.

The first describes the logarithm of an exponent.

$$\log_a(b^x) = x \log_a(b). \qquad \text{(a and b must be positive)}$$

Example: $\log_2(3^t) = t \log_2(3) = 1.585\ t$, using a calculator in the last step.

The second allows us to change bases of an exponent.

$$a^x = b^{\log_b(a)\, x}. \qquad \text{(a and b must be positive)}$$

Example: $1.5^t = 2^{\log_2(1.5)\, t} = 2^{0.585t}$, using a calculator in the last step.

This last formula shows that an exponential function with one base can be rewritten as an exponential function with another base! For example, any exponential function to be expressed using powers of 2.

$$a^t = 2^{\log_2(a)\, t}. \qquad \text{(a and b must be positive)}$$

EX. Use a calculator to fill in the blanks with a number, rounding to three **significant figures**. Notice that logarithms transform exponential functions into linear functions!

$\log_2(3^t) =$ _____ t

$\log_3(2^t) =$ _____ t

$\log_{10}(2^t) =$ _____ t

$\log_2(0.9^t) =$ _____ t

$\log_2(2^t) =$ _____ t

$\log_2(0.1^{2t}) =$ _____ t

If your calculator outputs 1.2345, then rounding to three significant figures would give 1.23. More examples of such rounding are below, with the three significant figures in boldface.

0.0247158 ≒ 0.0**247**
12.389 ≒ **12.4**
0.19234 ≒ 0.**192**
1059.9 ≒ **106**0

EX. Fill in the blanks with a number to express the following exponential functions using a different base. Use three significant figures.

$2^t = 1.5\text{———}^t$.

$10^t = 2\text{———}^t$.

$4^t = 2\text{———}^t$. (No calculator should be needed!)

$0.9^t = 2\text{———}^t$.

$0.5^t = 10\text{———}^t$.

$2^{3t} = 3\text{———}^t$.

Exp5 Exponential growth: 3 characterizations.

Let P(t) be a population that grows over time. When we say this growth is **exponential**, we mean that P(t) is described by a function:

$P(t) = C\, b^t$ (Here b and C are positive parameters)

Exponential growth has other characteristics.

1. Exponential growth has a **steady doubling-time**... every d units of time, the population will double. We can use doubling-time to express population growth as an exponential function where the base is 2.

$P(t) = C\, 2^{t/d}$.

2. If we plot the logarithm of population, as a function of time, the resulting plot will be linear. For example, if we use log-base-2, we have

$\log_2(P(t)) = \log_2(C) + t/d$.

This describes a line with slope $1/d$ and intercept $\log_2(C)$.

3. When P(t) grows exponentially, its rate of growth also grows exponentially, with the same base. If $P(t) = C\, b^t$, then $dP/dt = D\, b^t$, for some other constant D. As a result, the rate of population growth is proportional to the population itself.

dP/dt = k P

Now is a good time to go back to the 1st page of this lab, and read the passage by Neidhardt!

This number k is called the **first-order growth rate** for the population, and we are going to analyze it here. But first, we introduce a bit of new and important notation. The notation dP/dt is based on Liebniz's "differentials" and it reflects the change in population divided by the change in time, which is a rate of change. Around 1750, Lagrange introduced the notation P'(t) for this same thing.

P'(t) means dP/dt (the rate of population change) at time t.

We say "**P prime of t**" when reading the expression P'(t).

That's why it's called "prime" notation.

To practice a bit, fill in the following.

EX. Find the following derivatives, using "prime" notation.

If $F(t) = t^3$, then F'(t) = _____.

If L(t) = 5 - 4t, then L'(t) = _____.

If $P(t) = 10^t$, then P'(t) = _____. (Refer to an old exercise!)

Remember **exponential functions are proportional to their rates of change.** So if P(t) is an exponential function, then P'(t) = k P(t).

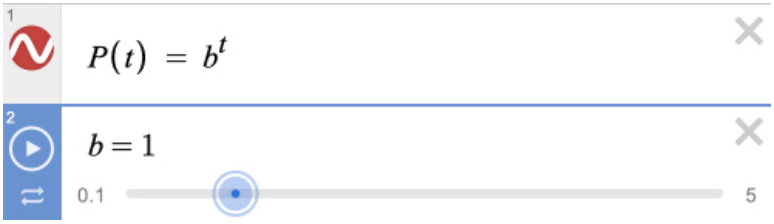
EX. Estimate this first order growth rate k, when $P(t) = 10^t$.

$k \approx$ _____

Exp6 The number e, and the equation P' = P.

Desmos is very good at graphing derivatives, and we will use it to answer the following question: For which exponential function is the first order growth rate equal to 1? In other words, what exponential function P(t) has the property that P'(t) = P(t)?

Using Desmos, graph the function $P(t) = b^t$. Add the slider for b, allowing the parameter b to vary between 0.1 and 5. Your input should look something like the screenshot below.



Graph the derivative of this function on the same plot, by adding a new plot with equation y=P'(t). Finally, study their ratio by adding a new plot with equation y=P'(t)/P(t). If you have entered things correctly, then the final P'(t)/P(t) plot should look like a flat horizontal line.

EX. If b=2, then what is P'(t)/P(t)? Find your answer with three significant digits by zooming in with Desmos, or by looking back for a good estimate of dP/dt. Use this to fill in the blank below.

If $P(t) = 2^t$, then $P'(t) =$ _____ $\cdot 2^t$.

EX. Find a value of b, for which P'(t)/P(t) is as close as possible to 1. You may have to adjust your slider settings, e.g., tightening the range of possible b values, and using steps of 0.1, 0.01, etc. Use this to fill in the blank below with three significant digits.

If $P(t) =$ _____^{t}, then P'(t) = P(t).

Congratulations... you have estimated the very important number called "e". Look up the number e on your computer and write the result below with ten significant digits.

e is approximately equal to _____.

The number "e" is very important for exponential functions. More specifically, "e" is that unique number for which

If $P(t) = e^t$, then P'(t) = P(t).

The **population growth rate is equal to the population itself**.

The **first order growth rate is 1**.

If you're trapped on a desert island, you can estimate e using the following process:

Start with 1.
Add 1/(1).
Add 1/(1·2).
Add 1/(1·2·3).
Add 1/(1·2·3·4).
Add 1/(1·2·3·4·5).
Etc..

EX. What do you get after these five steps?

_____

Exp7 The natural logarithm: Definition and drill

We have seen logarithms base 2 and base 10, as answers to questions about exponents with base 2 and 10. The **natural logarithm** is the logarithm base e, which answers questions about exponents with base e. The natural logarithm could be written $\log_e$ but it is usually written **ln**. Below are three natural logarithms and the corresponding questions.

e is just a number. It is approximately 2.718.

What is $\ln(e^2)$? _____ e to what power equals e^2?

What is $\ln(1/e)$? _____ e to what power equals $1/e$?

What is $\ln(100)$? _____ e to what power equals 100?

EX. Use what you know about exponents (not a calculator!) to answer the questions in the first two rows above. Use a calculator (or Google "ln(100)") to answer the questions in the last row.

EX. What is ln(1)? Explain why, using properties of exponents.

EX. Use a calculator to compute ln(100.0001). Use this to estimate ln'(100). Here ln' denotes the derivative of the natural logarithm function. Hint: ln'(100) is a pretty simple-looking number.

$\ln(100) =$

$\ln(101) =$

$\ln(100.1) =$

$\ln'(100) =$

The natural logarithm can be used to express general exponents using base e. The following formula is most useful for this purpose.

$$b^t = e^{\ln(b)\, t}.$$

EX. Use this formula to express exponents in base e. Express natural logarithms with three significant figures.

$100^t =$ _____ $(0.5)^t =$ _____

$2^{-t} =$ _____ $3^{t+1} =$ _____

Exp8 Exponential functions in natural form

Every exponential function can be written in **natural form** $F(t) = C\,e^{kt}$. The two parameters are:

> C is equal to F(0), also called the y-intercept.
> k is the **first order growth rate**.

The convenience of this form is that the rate of change $F'(t) = k \cdot F(t)$.

EX. In the following examples of exponential functions, convert the function into natural form and compute its derivative. Simplify all constants, using two significant digits.

Example: $F(t) = 100 \cdot (1.5)^t$.

Solution: $F(t) = 100 \cdot (1.5)^t = 100\,e^{\ln(1.5)\,t} = 100\,e^{0.41\,t}$. This is the natural form (with e as the base). The derivative is given by

$$F'(t) = 0.41 \cdot F(t) = 0.41 \cdot 100\,e^{0.41\,t} = 41\,e^{0.41\,t}.$$

EX. $F(t) = 20 \cdot (2)^t$

Natural form:

Derivative:

EX. $F(t) = 5000\,(0.5)^t$.

Natural form:

Derivative:

EX. C(t) is the amount of Carbon-14 in a sample of seeds placed in a jar today. C(0) = 20 ng (nanograms), meaning there are 20 nanograms of this carbon isotope. Over time, **Carbon-14 decays** into Nitrogen-14. As a result, C(t) decays exponentially, with half-life 5700 years. This means that C(5700) = 10 and C(11400) = 5. In other words, in 5700 years, there will only be 10 ng of Carbon-14 in our sample.

Express C(t) as an exponential function of t with base 0.5.

$C(t) =$ _____ $(0.5)^{t/}$———

Now express C(t) in natural form.

$C(t) =$ _____ e————^{t}

What is C'(0) and what does it mean as a physical rate of change?

Carbon-14 has 6 protons and 8 neutrons in its nucleus.

Nitrogen-14 has 7 protons and 7 neutrons in its nucleus.

In this kind of decay, called β-decay, a neutron (n) decays into a proton (p), sending off an electron (e), and an antineutrino ($\bar{\nu}$) in the process.

Fit1 Fitting a model with linear regression.

We have seen three kinds of growth in this chapter: linear growth, power function growth, and exponential growth. Sometimes we encounter data, and we wonder what sort of growth it exhibits. Graphical methods, especially log-scaling axes, can be useful for this purpose. Load the *Linear regression with Log scaling* tool for the following. Simple **linear regression** is the process of finding a line that best fits data.

Lines are often recognizable by eye, and we can draw a "best-fit" line y=mx+b to approximate data. Here m is the slope, and b is the y-intercept. We use a statistic called R^2 to evaluate the quality of the fit.

EX. Click the Clear Data button, then enter the following data.

X	1	2	2.5	5	3	4	4.5	6	2	6
Y	2	4.2	5.1	9.1	6	7.8	9.1	11	3.9	12.2

Click "Fit Linear Model" to find the line that best approximates the data. Report your results below.

$Y \approx$ _____ $X +$ _____, with $R^2 =$ _____

The statistic R^2 is called the **coefficient of determination**. When $R^2 = 1.0$, the line perfectly fits the data. R^2 is a number between 0.0 and 1.0, and it answers the question: "How much of the variation of the data is explained by the linear model?"

Now we apply these techniques to some real data!

DNA has four nucleotides, abbreviated by the letters A, T, C, and G. An A on one strand is matched with a T on the other strand, and a C on one strand is matched with a G on the other strand. Such matched pairs are called **base pairs (bp)**. The GC-content of DNA is the percentage of the nucleotides which are C or G. The GC-content affects the melting temperature T_m, defined as the temperature at which half of the nucleotides separate from each other. This is very important when sequencing DNA, and regions of DNA with very high or low GC-content can be difficult to sequence reliably.

The following 5bp long chunk of DNA has GC-content 40%.

A T G C T
‖ ‖ ‖ ‖ ‖
T A C G A

The GC pairs are stuck together with 3 hydrogen bonds, and the AT pairs are stuck together with 2 hydrogen bonds. It takes more heat energy to break the GC pairs.

The following table gives the GC-content (GC%) and melting temperature T_m for ten different chunks of human DNA, about 50000 bp each.

GC%	10%	10%	20%	20%	30%	30%	40%	40%	50%	50%
T_m (°C)	62	59	65	66	70	69	73	74	78	77

Data on the left is adapted from *The Human Genome Melting Map* by Liu et al., in PLOS Computational Biology, May 2007.

EX. Use the *Linear regression with Log scaling* tool to find the best **linear model** of melting temperature as a function of GC-content. What is the R^2 statistic?

$T_m \approx$ _____ GC % + _____, with $R^2 =$

Fit2 Linear regression after log scaling.

If y is an **exponential function** of x, having the form $y = C\,e^{kx}$, then the logarithm of y will be related linearly to x. If $y = C\,e^{kx}$, then $\ln(y) = kx + \ln(C)$. Or we can go the other way too.

If $\ln(y) = mx + b$, then $y = e^{b} \cdot e^{mx}$.

EX. Click the Clear Data button, then enter the following data.

X	20	40	60	80	100	120
Y	1000	1480	2240	3300	5000	7100

This data should remind you of the exponential growth of a population!

Click "Fit Linear Model" to find the line that best approximates the data. Report your results below.

$Y \approx$ _____ X + _____, with R^2 = _____

EX. Now select Logarithm Base: Natural (base e), and press the button to change the y-axis scale from linear to log. Then click the "Fit Linear Model" button to find the line that best approximates the plot.

$\ln(Y) \approx$ _____ X + _____, with R^2 = _____

EX. Use this to find the exponential function that best describes the relationship between X and Y.

$Y \approx$ _____ $e^{\text{_____}X}$

EX. In what way does the exponential function fit the data better than the linear function?

If y is a **power function** of x, having the form $y = C\,x^{p}$, then the logarithm of y will be related linearly to the logarithm of x. If $y = C\,x^{p}$, then $\ln(y) = p\ln(x) + \ln(C)$. Or we can go the other way too.

If $\ln(y) = m\ln(x) + b$, then $y = e^{b} \cdot x^{m}$.

EX. Click the Clear Data button, then enter the following data.

X	1	3	4	0.5	2.5	1.2
Y	3	25	50	0.76	19	4.2

Now change **both** y-axis and x-axis from linear to log (base e). Click the "Fit Linear Model" mutton. Use the results to find a power function that best fits the data.

$Y \approx$ _____$X^{\text{_____}}$.

Fit3 Modeling power function growth

A long-standing question in physiology is the relationship between the mass of organisms (especially endotherms like birds and mammals) and their **metabolic rates**. The data table here is extracted from a 1932 paper of Max Kleiber.

See *Body Size and Metabolism*, by Max Kleiber, in Hilgardia: a Journal of Agricultural Science, January 1932. For a more recent review, see *Allometric Scaling of Mammalian Metabolism*, by White and Seymour, in the Journal of Experimental Biology, 2005.

Animal	**Weight (kilograms)**	**Cals./day per animal**
Steer	679	8274
Steer	342	6255
Cow	388	6421
Man	64.1	1632
Woman	56.5	1349
Sheep	45.6	1219
Male dog	15.5	525
Female dog	11.6	443
Hen	1.96	106
Pigeon	0.300	30.8
Male rat	0.226	25.5
Female rat	0.173	20.2
Ring dove	0.150	19.5

EX. Select 10 from the 13 animals above in a biologically appropriate way. How did you make your selection?

EX. Use the *Linear regression with Log scaling* tool to plot these 10 data points, with weight W (kilograms) on the horizontal axis and metabolic rate MR (cals/day) on the vertical axis. Describe this relationship in one sentence.

EX. Click the Log(X) and Log(Y) buttons to study the relationship between logarithms. Use natural logarithms (ln). Report the linear function which best models this relationship, together with the R^2 statistic.

$\ln(MR) =$ _____ $\ln(W) +$ _____, with $R^2 =$ _____

Hint: the formula $\ln(y) = p \ln(x) + \ln(C)$ is equivalent to the formula $y = C x^p$.

EX. This suggests that metabolic rate MR is related to weight W according to a power law. What is the power law?

$MR \approx$ _____ $\cdot W^{\text{_____}}$

Fit4 Modeling exponential decay

In this last data-fitting exercise, we consider the degradation of aspirin (acetylsalicylic acid). A study participant is given a 1000mg dose of aspirin, and the plasma concentration of aspirin (the amount floating in the bloodstream) is measured at various intervals. The table in the margin displays these concentrations over time.

The following data is fictional, but adapted from Figure 3A of *In-vivo disintegration and absorption of two fast-acting aspirin tablet formulations compared to ibuprofen tablets using pharmacoscintigraphy*, by Stevens et al., in the Journal of Drug Delivery Science, 2019.

Time (min.)	Aspirin Concentration (ng/mL)
0	0
15	9000
20	15000
25	15000
30	9000
40	7500
50	5000
60	3100
70	2100
80	1700
90	1600
120	400
180	100
240	0

EX. The given data begins when the patient first ingests the aspirin tablet. To study the **degradation** of aspirin, which data points are most relevant and why?

EX. Use the *Linear regression with Log scaling* tool to plot these most relevant points. Let A(t) be the plasma concentration of aspirin at time t. Describe the line which best models the relationship between ln(A(t)) and t.

$\ln(A(t)) \approx$ _____ t + _____, with $R^2 =$ _____

EX. Use this to model A(t) as an exponential function of t, in natural form (base e).

$A(t) \approx$ _____ $e^{\text{————}t}$.

EX. If the same person receives a different dose, like 500mg or 2000mg, which of the above numbers would you expect to be similar to the 1000mg dose? Why?

EX. What is the half-life of aspirin in this patient? In other words, estimate how many minutes it takes for the plasma concentration of aspirin to be reduced by 50%.

MG1 Modeling growth: distinguishing three types.

EX. Complete each of the following sentences with "linear growth" or "power function growth" or "exponential growth".

If $dP/dt = 3$, then P exhibits _____.

If $dP/dt = 2P$, then P exhibits _____.

If dP/dt is a power function, then P exhibits _____.

If dP/dt is an exponential function, then P exhibits _____.

If the rate of change of P is constant, then P exhibits_____.

If P is proportional to its rate of change, then P exhibits _____.

If $P(t) = 3t^2$, then P exhibits _____.

If its time-series plot is a straight line, then P exhibits _____.

If the time-series plot of ln(P) is a straight line, then

P exhibits _____.

If $P(t) = e^{kt}$ then P exhibits _____.

If $\log_2(P(t)) = 2\log_2(t)$, then P exhibits _____.

If P increases by 3 each year, then P exhibits _____.

If P increases by 3% each year, then P exhibits _____.

If ln(P) increases by 2 each year, then P exhibits _____.

If B is the volume of a balloon whose radius is given by $R = 3t$, then B exhibits

_____.

MG2 Modeling growth: reflections

EX. Choose **one** of the previous three models (GC-content and melting temperature, metabolism and weight, aspirin concentration and time). Evaluate the model, using the criteria for model evaluation from the first lab. Which aspect of model evaluation does the R^2 statistic help with?

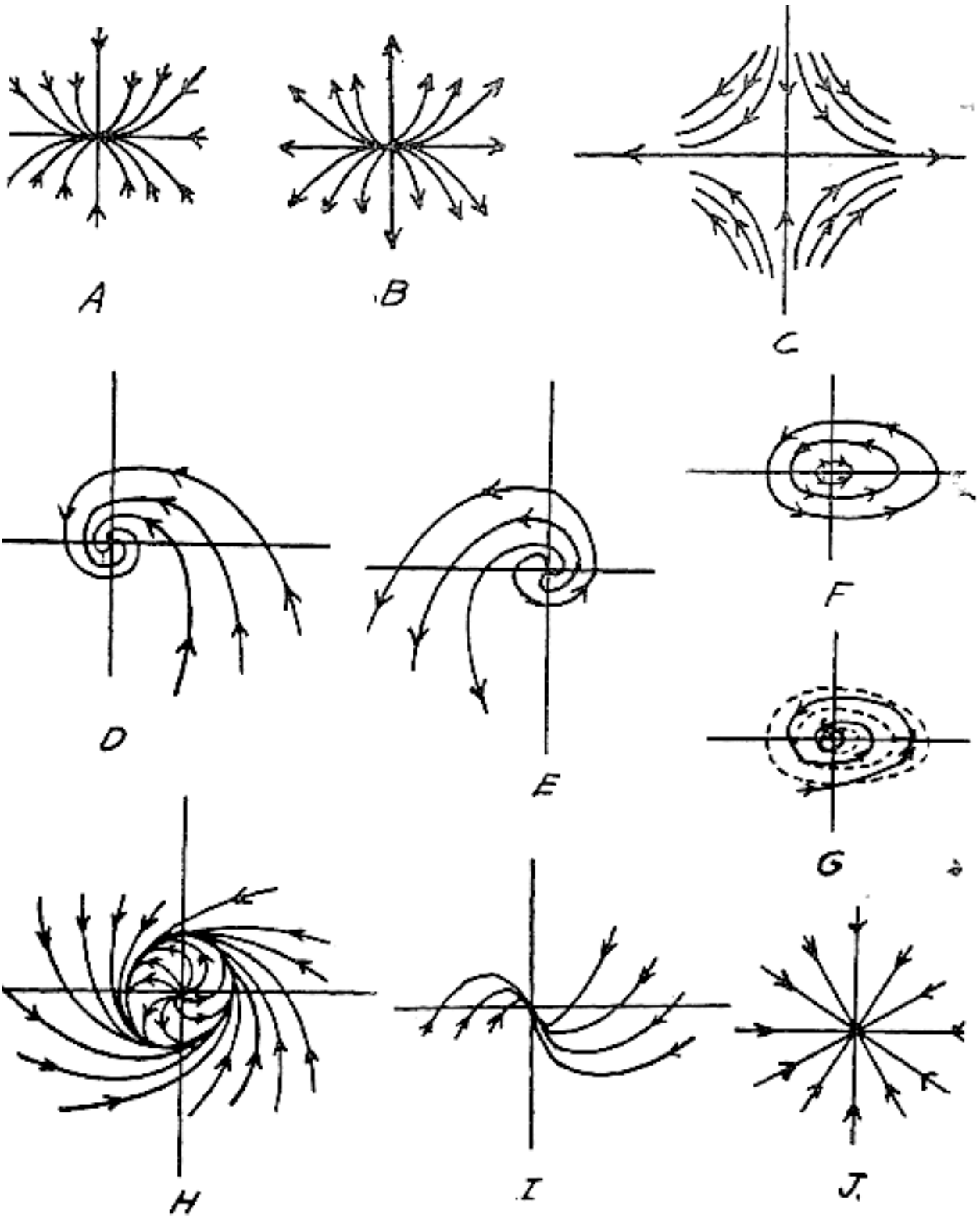


Figure 27, p.148, from "Elements of Physical Biology," by Alfred Lotka, published in 1925. These figures show ten "fundamental types of equilibrium," in a system with two state variables. We have seen some before in our study of sharks and tuna, and insulin and glucose.

LABORATORY 3
EQUILIBRIUM

Equilibrium, at first glance, is a concept about **not** changing. A full bathtub, a healthy person with body temperature 98.6°F, two symbiotic species in harmony—these may all be systems in equilibrium. Writing about equilibrium more than 100 years ago, Lotka introduces three notions of equilibrium.

From "Elements of Physical Biology," by Alfred Lotka, 1925, pp. 143-144.

> 1. "...from the standpoint of kinetics, defining [equilibrium] as a state in which certain **velocities vanish**..."
>
> 2. "...a dynamic conception: Aequa libra, the poised balance, is symbolic of a state in which **forces are balanced**, in which the resultant force vanishes..."
>
> 3. "A third conception of equilibrium... is derived from a consideration of energy relations. A system in dynamic equilibrium is found to be characterized by the **attainment of a minimum** (or sometimes a maximum) of certain functions having the dimensions of **energy**."

Equilibrium is not just about not moving (velocities vanishing). In physics it is based on a balance of force, every push countered by a pull, to keep things in balance. In a broad range of systems, equilibrium is characterized by the attainment of a minimum or maximum energetic state.

The study of equilibrium, Lotka notes, is not the study of a single static state in isolation... it is about the relationship between that state and "nearby" states. Look at the diagrams A-J on the opposite page, which display trajectories in various state spaces. Each diagram contains a single equilibrium point. Can you find it? What happens "near" the equilibrium point? How would you describe what happens in words?

EX. For **one** of the diagrams (A-J), redraw the diagram in the margin, identify the equilibrium point with a bold star, and write a sentence about what happens near the equilibrium point.

LO1 Logistic growth: Growth and crowding

The marine bacterium *Vibrio natriegens* divides very rapidly. Under optimal conditions, its population obeys the change equation,

$$P' = 0.07\ P$$

See Eagon RG, *Pseudomonas Natriegens, a marine bacterium with a generation time of less than 10 minutes*. J. Bacteriol **83** (1962).

Here P denotes the number of bacteria, and our unit of time is **minutes**. Recall that P' (out-loud "P-prime") is our shorthand symbol for the derivative dP/dt.

EX. Assume the similar "discrete" change equation $\Delta P/\Delta t = 0.07\ P$, where the time interval is $\Delta t = 1$ minute. Fill in the blank to describe the population growth, according to this **discrete-time** model.

Each minute, the population increases by _____ percent.

EX. Now, return to the original change equation $P' = 0.07\ P$. There is an exponential function which satisfies this equation, namely

$$P(t) = C\ e^{0.07\ t}$$

The general rule for derivatives of exponential functions: If

$$P(t) = C\ e^{kt},$$

then

$$P'(t) = k\ C\ e^{kt}.$$

Note that $P' = k\ P$.

Fill in the blank to describe the population growth according to the function above (a **continuous-time** model).

Each minute, the population increases by _____ percent.

We see that the continuous-time equation $P' = 0.07\ P$ and the discrete-time equation $\Delta P/\Delta t = 0.07\ P$ behave similarly, with a small difference in rate of population growth. The per-minute growth rate should be very close to the first-order growth rate 0.07.

Populations do not grow endlessly. A more realistic model incorporates not only the maximum division rate of the bacteria, but also a negative effect of crowding — when organisms are too close to each other, they can compete for resources or otherwise hurt each other, slowing growth. The resulting change equation should look like

$$P' = [\text{birth rate}]\ P\ -\ [\text{bad effects of crowding}]$$

We understand the birth term (0.07 P). But what should the "bad effects of crowding" term look like? Crowding effects should get worse as the population increases, but in what manner?

To explore the effects of crowding, load the *Self-Interaction Simulator*, and start experimenting. In this simulator, organisms are randomly placed in a dish and they start moving. They move for a second then turn a random direction and move some more, etc. They bounce off the walls of the dish, and you should see a little "firework" when they hit each other.

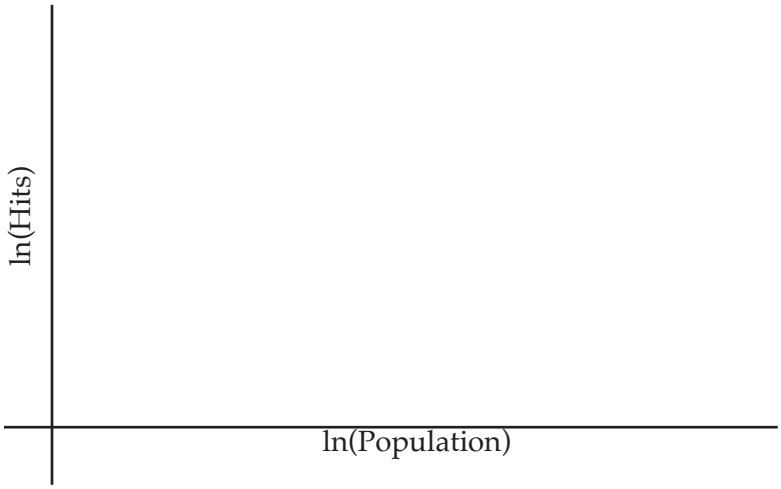
LO2 Logistic growth: Self-interactions

EX. Each "run" of the simulator should take 10 seconds. Use 10 runs of the simulator, with different numbers of particles (between 2 and 50), and record the total number of "hits" that occur in each run of the simulator. For example, if you run the simulator with 10 particles, you should find between 5 and 12 hits. Record this data on the table on the right.

Enter your data below.

Population	Hits

EX. Enter this data into the *Logistic Regression with Log Scaling* tool, using "number of particles" on the X-axis and "number of hits" on the Y-axis. Graph ln(Y) vs. ln(X) in the Data Plotter, and copy the graph below. Make sure to put small circles to represent your actual observations, draw the best-fit line, and report the slope and R^2 value.



Slope of line: _____

R^2 = _____

EX. Model the relationship between the "number of hits" and the population by a **power function**, using your best-fit line above.

$H(P) \approx$ _____ $P^{\text{———}}$

If "hits" or "interactions" of organisms have a negative effect on the population, then we expect the change equation to look like

P' = [birth rate] P - [interaction effect] $P^{\text{———}}$

Here, fill in the blank with the same power of P. Your power should be pretty close to 2... otherwise go back and check for mistakes!

The simplest model of constrained population growth is the logistic model, when H(P) is proportional to P^2. The **logistic growth model** is

$$P' = \beta P - \gamma P^2.$$

The parameter β is the birth rate (or growth rate), and the parameter γ describes the magnitude of the crowding effect. Even if this is not a perfect model of population growth, we aim to understand it well. The logistic model exhibits general phenomena of **exponential growth with constraint**, and a stable equilibrium point.

This model was named "logistique" and first studied by Pierre-François Verhulst in *La Loi D'Accroissment de la population (the Law of Population Growth)*, published in Nouveaux Mémoires de l'Académie Royale des Sciences et Belles-Lettres de Bruxelles (1845).

LO3 Logistic growth: The model

The **logistic model** pushes the boundary of what we may reasonably compute by hand (though Verhulst did this back in the 1840s). We do a bit by hand before using computational tools in what follows.

Consider our fast-dividing bacterium *Vibrio natriegens* from before, but with negative self-interactions. They are modeled by the change equation

$$\Delta P / \Delta t = 0.07\, P - 0.000035\, P^2.$$

Here we use discrete time, with interval $\Delta t = 1$ minute.

EX. If you have 1000 bacteria at time t=0, how many do you expect to see after one minute, using the equation above? Use a calculator!

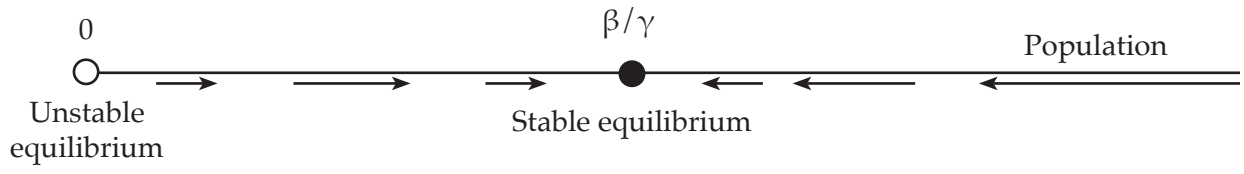
EX. If you have 3000 bacteria when the clock starts, how many bacteria do you expect to see after one minute, according to the change equation above? Use a calculator!

EX. At some values of P, the change equation tells us $\Delta P / \Delta t = 0$. What are these values of P? Divide your decimals with care, using a calculator if needed.

Return to the continuous-time logistic growth model, $P' = \beta P - \gamma P^2$. When $P' = 0$, the population is at **equilibrium**, meaning that the rate of population change is zero, i.e., the population does not change. We can solve an equation to see when this happens.

$P' = 0$ occurs when $\beta P - \gamma P^2 = 0$;
This occurs when $P(\beta - \gamma P) = 0$;
This occurs when $P = 0$ or when $\beta - \gamma P = 0$;
This occurs when $P = 0$ or when $\beta = \gamma P$;
This occurs when $P = 0$ or when $P = \beta / \gamma$.

When the population is between 0 and β/γ, P' is positive and the population grows. When the population is bigger than β/γ, the negative effects of interaction exceed the birth rate, and the population declines. We graph these observations below on a **phase portrait**.



LO4 Logistic growth: Exploration of parameters

The **logistic model** of population growth has the form

$$P' = \beta P - \gamma P^2. \qquad (\ddagger)$$

The two parameters are the (net) birth rate β and the negative effect of crowding γ. Equilibrium is found when $P' = 0$, which occurs when

$$P = 0 \text{ or } P = \beta/\gamma$$

This second equilibrium is called the **carrying capacity** by ecologists, since it represents the sweet spot at which the population is stably maximized; it is the largest number of organisms which the environment can sustain.

EX. Let $C = \beta/\gamma$ be the carrying capacity. Use algebra to show that the equation $(\ddagger)$ is equivalent to the equation $P' = \beta P (1 - P/C)$.

The logistic model is one of those very rare change equations where we can describe trajectories with a formula. Such a formula is

$$P(t) = \frac{Ce^{\beta(t-t_0)}}{1 + e^{\beta(t-t_0)}} \text{ solves the change equation } P' = \beta P(1 - P/C).$$

It is difficult to derive this formula; that would be done in a class on differential equations. We just take it on faith here.

Load the *Logistic Growth Explorer*. For now, you will be ignoring the data table and time-shift t_0, and exploring the parameters β and C.

EX. What happens to the population P(t) as t grows large? How does this relate to the carrying capacity C?

EX. What is the population at time zero, i.e., what is P(0)? Note that $t_0 = 0$ here. Relate your answer to the parameter β or C.

EX. How does the birth-rate parameter β change the shape of the graph of P(t)? Use the **change equation** to find a formula for P'(0) involving β and C.

$P'(0) =$ _____

Ph1 Phase portraits: Solving equations

If $X' = f(X)$ is a change equation involving one quantity X, then equilibrium points can be found by answering the question: when is $X' = 0$? Answering this question is the same as solving the equation $f(X) = 0$. So we practice techniques for solving such equations here.

EX. Solve the following equations for X. Write your solution as a complete "If... , then..." sentence, with all possible solutions listed with "or" separating possibilities. Technique hints are in the margin.

Example: $X^2 - 1 = 0$.
Solution: If $X^2 - 1 = 0$, then $X = 1$ or $X = -1$.

Technique: If $X^2 = C$, then $X = \pm\sqrt{C}$.

Solve: $(X - 3)(X-2)(X-1) = 0$.

Solution:

Technique:
If $abc = 0$, then
$a = 0$ or $b = 0$ or $c = 0$.

Solve: $7X\,(1 - 0.001\,X) = 0$.

Solution:

Technique: If $ab = 0$, then $a = 0$ or $b = 0$.

Solve: $kX\,(1 - X/C) = 0$.

Solution:

Technique: Same as above, but with unknown constants k and C.

Solve: $\dfrac{X - 1}{X^2 + 3} = 0$.

Solution:

Technique: If $a/b = 0$ then $a = 0$!

Solve: $e^{-X} + X - 2 = 0$.

Solution:

Technique:
Use Desmos! Report three significant figures.

Solve: $X^2 + 1 = 0$.

Solution:

Technique: Not all equations have solutions!

Solve: $\dfrac{3X(1-X)}{X^2+1} = 0$.

Solution:

Mix techniques from above.

Solve: $X(1 + e^{-X}) = 0$.

Solution:

Technique: Powers of positive numbers are

Ph2 Phase portraits: Finding and classifying equilibria

EX. Now for each of the problems on the previous page, draw the **phase portrait**. Your phase portrait should contain dots for every equilibrium point (filled for stable, empty for unstable). Label dots by their location (X-value). Draw arrows to show the direction of trajectories.

Example: $X' = X^2 - 1$

$X' = (X - 3)(X-2)(X-1)$

$X' = 7X\,(1 - 0.001\,X).$

$X' = kX\,(1 - X/C).$

$X' = \dfrac{X^3 + 1}{X^2}.$

$X' = e^{-X} + X - 2.$

$X' = X^2 + 1.$

$X' = \dfrac{3X(1-X)}{X^2+1}.$

$X' = X(1 + e^{-X}).$

Ph3 Phase portrait: Allee effect

The **phase portrait** is a new sort of visualization, and here we demonstrate how to generate and interpret the phase portrait. We consider a population of mice, among which some have a genetic mutation. Let Q(t) be the **proportion** of mice that possess this mutation.

So Q(t) represents (number of mice with mutation) / (number of mice).

EX. What are the possible values of Q(t)? Minimum? Maximum?

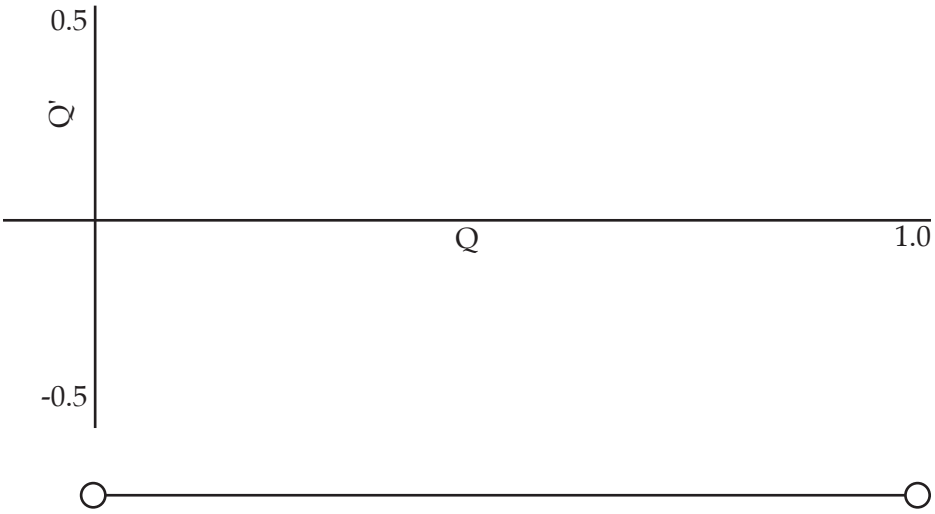
Q(t) must be between _____ and _____.

EX. The spread of this mutation in the population can be modeled by the change equation Q' = 2Q (1 - Q) (1 - 3Q). What values of Q are equilibrium points?

Algebra technique:
If abc = 0, then
a = 0 or b = 0 or c = 0.

Q' = 0 when Q = _____ or Q = _____ or Q = _____

EX. Use Desmos to graph the function f(Q) = 2Q(1-Q)(1-3Q). Use this to draw a graph of Q' vs. Q below. Note the domain of the function when drawing the graph below.



EX. Now, on the phase portrait above, we have marked the two unstable equilibrium points for this change equation. Mark the stable equilibrium point, and draw arrows to complete the portrait.

EX. If 10% of the mice have the mutation at t=0, then what proportion of the mice will have the mutation when t is large?

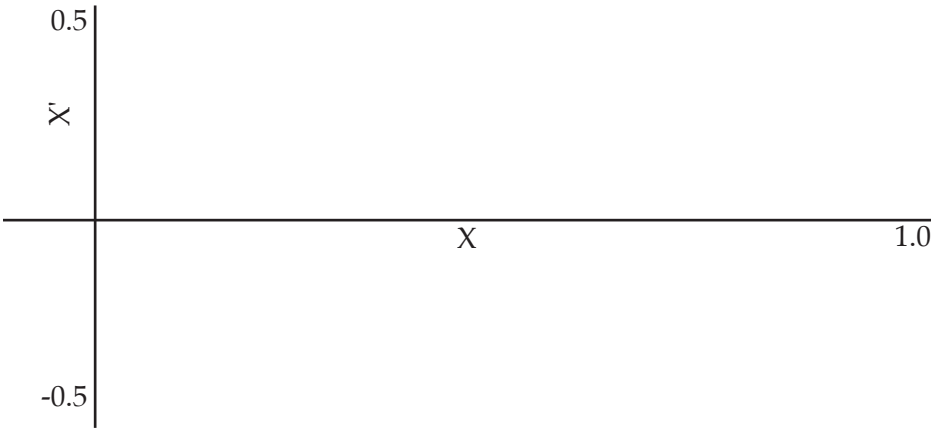
Hint: Follow the trajectory in the phase portrait. Use your arrows!

EX. If 90% of the mice have the mutation at t=0, then what proportion of the mice will have the mutation when t is large?

Ph4 Phase portraits and trajectories (abstract)

The **phase portrait** below displays a relationship between X' and X. Unstable equilibrium points are shown with an empty circle, and stable equilibrium points are shown with a solid circle.

EX. Draw a graph displaying X (between 0 and 1) on the horizontal axis and X' on the vertical axis. Be creative but consistent with the above phase portrait.

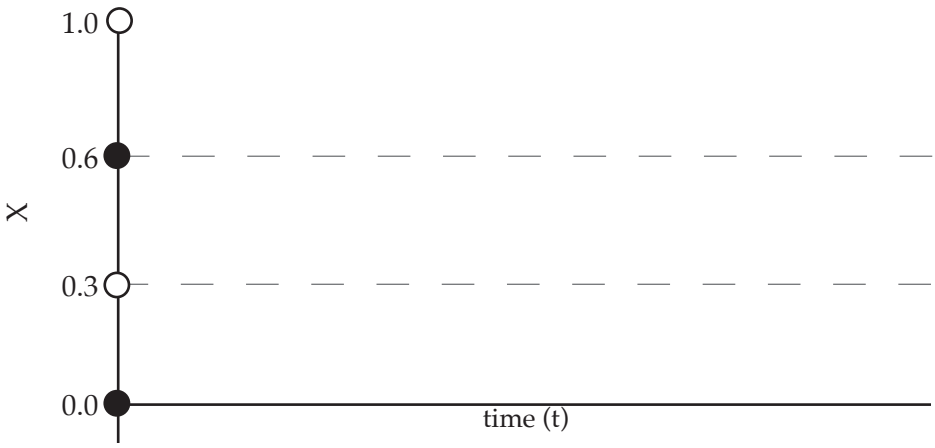


EX. If X(0) = 0.2, how will X(t) behave as t grows large?

EX. If X(0) = 0.5, how will X(t) behave as t grows large?

EX. If X(0) = 0.3, how will X(t) behave as t grows large? What if X(0) gets "bumped" just a tiny bit to the left or right?

EX. Use the previous exercises to sketch **time-series** plots of X(t), using the starting values X(0) = 0, 0.2, 0.3, 0.4, 0.7,0.9, and 1.0.



Lac1 From the logistic model to the lac operon

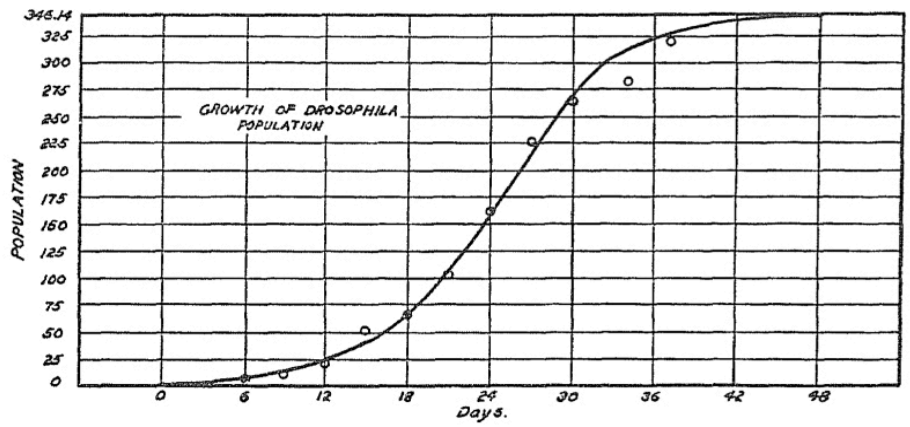


Figure 5 from Lotka's "Elements of Physical Biology," 1925 Edition. This graph is based on earlier studies of Pearl; see Figure 15 of "The Biology of Population Growth," by Raymond Pearl. Reading Pearl nowadays, his modeling of human population growth is grounded in overtly colonial, racist, and sexist ideas.

The logistic model reasonably describes a great variety of populations. The curve above displays the population growth of fruit flies (*Drosophila*) studied by Raymond Pearl in 1920. Pearl, in "The Biology of Population Growth," argued that populations, from yeast to fruit flies to people, exhibit the same shapes of population growth.

More dramatically, Lotka fits the population of the United States, from 1790-1910, to a logistic model. He extrapolates to predict a U.S. population of 197 million in the year 2060, cautioning that such a forecast must be "accepted with reserve."

In microbiology, the study of population growth is not so fraught with the challenges of social science. Something interesting is afoot when population growth does not fit a logistic model. In particular, Monod found **biphasic growth**, or what he called **diauxie**—one growth cycle and then another, separated by a pause—when looking at populations of *E. Coli* bacteria in which a typical food (glucose) was limited and alternative food (sorbitol) was provided. In three experiments (graphs A,B,C below), different amounts of glucose and sorbitol were provided; the first growth was proportional to the amount of glucose and the second to the amount of sorbitol. This demonstrated that the *E. Coli* were eating the glucose first, pausing, then eating the sorbitol.

What happens during the pause? How did these little bacteria suddenly gain the ability to metabolize sorbitol? Why didn't they just eat what was available from the beginning? The full answer is given by the intricate mix of genetics and biochemistry known as the **lac operon**. We focus on the more basic question: how can a dynamical biological system exhibit a **switch**?

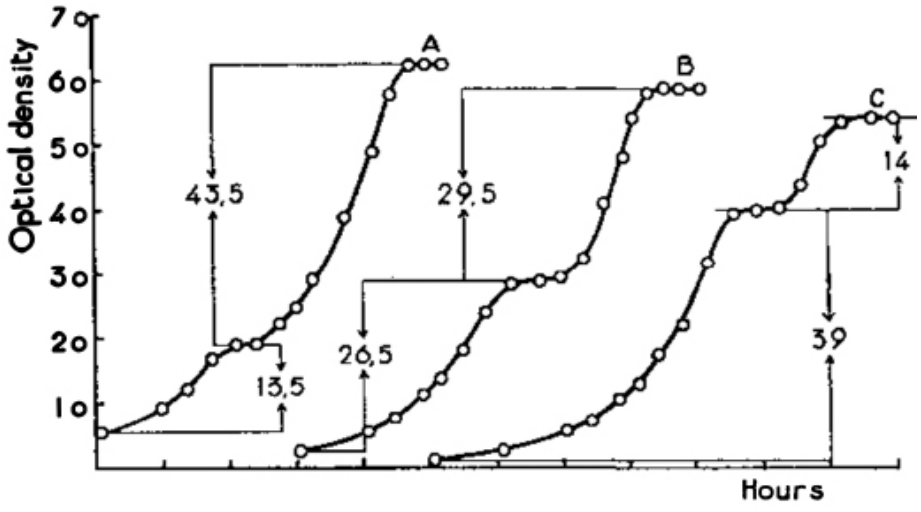


Figure 9 from *Growth of Bacterial Cultures*, by Jacques Monod, Annu Rev. Microbiol. 1949.

12 years later, Jacob and Monod began to understand these patterns in *Genetic Regulatory Mechanisms in the Synthesis of Proteins*, J. Mol. Biol. 1961, leading to their 1965 Nobel Prize.

Lac2 Lactose in *E. Coli*. The basic model.

Glucose and lactose are **sugar** molecules. When grown in an environment with varying amounts of glucose and lactose, it appears that *E. Coli* first metabolize the glucose, and when that runs out, they **switch** to lactose. The lac operon gives them the capability to switch, and it is a classic example of a bistable system—a system with two stable equilibrium points.

On the previous page, we mentioned glucose and sorbitol (a sugar alcohol). Similar **diauxie** were found with many pairs of sugars by Monod in his earliest works.

We begin with lactose only. Consider a population of *E. Coli* in a dish. The scientist has prepared the dish so that it contains lactose.

State variable: Let L be the amount of lactose **within** the *E. Coli* bacteria. This is called **intra**cellular lactose.

Change equation: The intracellular lactose changes for two reasons: first, the *E. Coli* brings lactose inside through its cell membrane. For this to happen, i.e., for lactose to permeate the membrane, the cell needs to produce an enzyme called **lactose permease**. Second, once the lactose is inside the *E. Coli*, the bacterium **metabolizes** the lactose, breaking it down into other molecules. Thus the change equation should look like

Permeate: (verb) To penetrate or diffuse through, as in a molecule permeating a membrane.

$$L' = [\text{lactose permeation rate}] - [\text{lactose metabolic rate}]$$

A bit of lactose always permeates into the E. Coli. But generally, the lactose permeation rate is directly related to the amount of the enzyme lactose permease. This amount increases in the presence of lactose up to a **saturation** level. As a result, the lactose permeation rate is modeled well by a Hill-type equation.

The presence of lactose increases the production of lactose permease, which allows even more lactose into the bacterium. This is a positive feedback loop!

$$P(L) = \frac{0.01 + L^2}{1+L^2}.$$

EX. Using Desmos, what are the upper and lower bounds for the function P(L)? Compare and contrast this function to the Hill function studied in the insulin-glucose model. Answer in 2-3 sentences.

Lac3 Lactose system: Equilibria

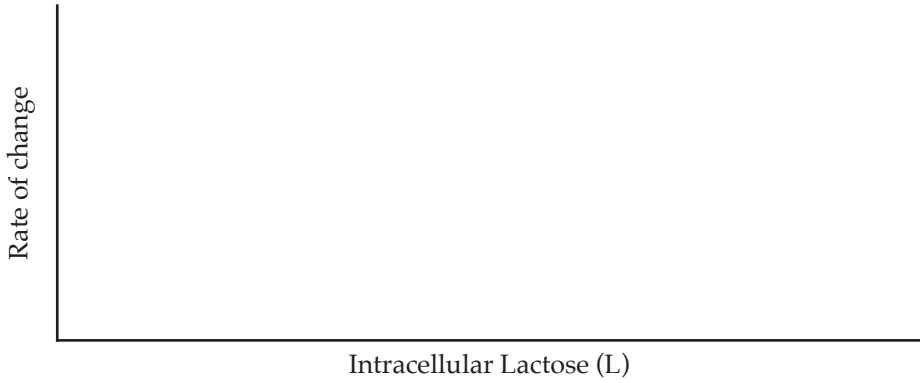
Once the lactose gets inside the *E. Coli*, the bacterium can happily feast on it. The metabolism of lactose follows a **first-order pattern**, where the amount of lactose metabolized is proportional to how much lactose is inside the *E. Coli*. We use the proportionality constant 0.4 here, so the lactose metabolic rate is given by M(L) = 0.4 L.

Gentamicin and aspirin were previous examples of first-order metabolism (exponential decay).

Putting this together with permeation rate, we have L' = P(L) - M(L), or

$$L' = \frac{0.01 + L^2}{1+L^2} - 0.4\,L.$$

EX. Equilibrium occurs when the amount of lactose going into the *E. Coli* equals the amount of lactose metabolized by the *E. Coli*. On the axes below, **plot the functions P(L) and M(L)**, and highlight the equilibrium points. Label your two plots so that it is clear which is permeation rate P(L) and which is metabolism rate M(L).



EX. Use the formula L' = P(L) - M(L) to draw a phase portrait for the lactose system below. Use Desmos to approximate the equilibrium points to three significant digits, and label the points accordingly.

Don't forget to make filled/empty circles for stable/unstable equilibria, and draw arrows to indicate the direction of trajectories.

EX. This kind of system exhibits what we call **all or nothing** behavior. With reference to the phase portrait above, what do you think this means?

Lac4 Lactose system: Glucose and the switch

When *E. Coli* eat their favorite food, glucose, a side effect is that a protein binds to the lactose permease, making it unable to help lactose permeate into the cell. If the amount of glucose is g, then the lactose permeation rate becomes

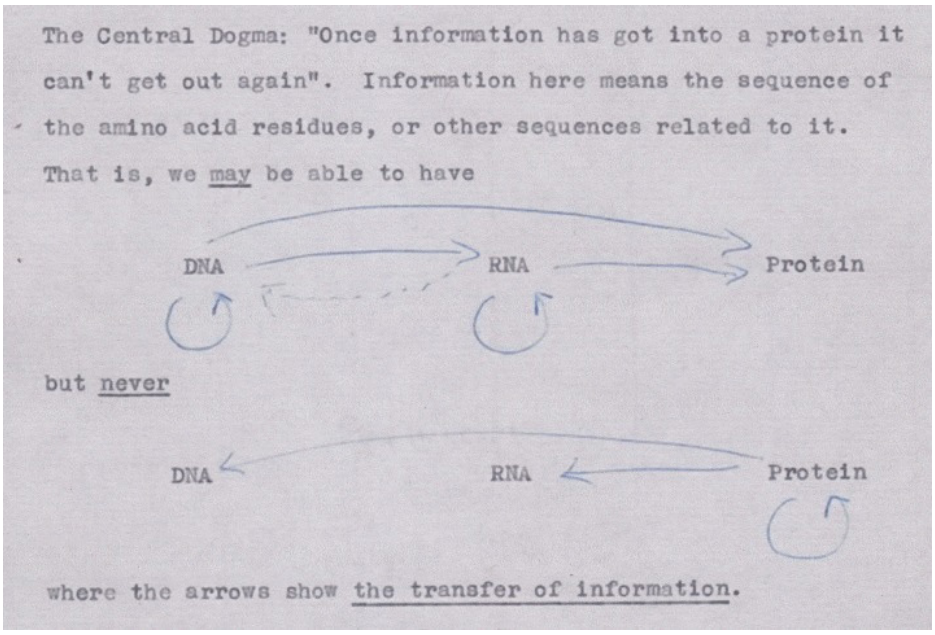
$$P(L) = \frac{0.01 + L^2}{1+(1+g)L^2}.$$

Glucose affects the lactose system in multiple ways; we only introduce one here. Note that in the absence of glucose, g=0, this function is the same as the previous function P(L).

EX. Use the same method as before, to plot P(L) and M(L) for various values of g (between 0 and 2) in Desmos. Do not reproduce your plots here. But **describe the equilibrium point(s)** in the absence of glucose (when g = 0) and when there is a lot of glucose (when g = 2).

EX. Monod found that when *E. Coli* are grown in a plate with both glucose and lactose, they first consume glucose, and then consume lactose. How does our model explain this?

GE1 The Central Dogma



The "Central Dogma" of molecular biology comes from this unpublished note by Francis Crick, 1956.

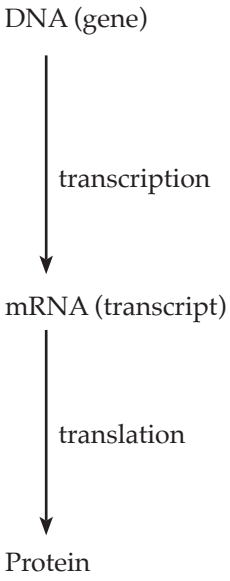
Image Credit: Wellcome Library, London.

Genes are chunks of a DNA sequence. They have marked beginnings and ends, and we can read them out as sequences of letters A,T,G,C using modern technology. Some human genes are 500 letters long, some are over a million letters long. You can download all of the genes for humans and many other species.

Go to the UCSC Genome browser, at genome.ucsc.edu. There you can enter a gene, and find all sorts of information, including its sequence of A,T,G,C letters.

The letters from a gene are **transcribed** onto **messenger RNA** (**mRNA**). Some portions within the gene (the introns) are snipped out, and others (the exons) are kept for the mRNA. The mRNA travels from the nucleus (where DNA is stored) out into the cytoplasm. Nowadays, we can count these mRNA **transcripts** in a single cell. A single gene might be transcribed many times, leading to hundreds of mRNA transcripts floating around. Or, a single gene might not be transcribed at all, leading to no mRNA transcripts!

In the cytoplasm, the **ribosomes translate** the information from mRNA to build **proteins.** We can also measure how much of various proteins is contained in a cell. This is called **proteomics**. It is more difficult than counting mRNA transcripts, at least for now.



This whole process, from DNA to mRNA to proteins, is called gene expression. A single gene on a single strand of DNA can be transcribed many many times, producing lots of mRNA. Each transcript can go to the ribosomes to produce lots of protein molecules. The protein molecules are the ones that carry out all the "functions" of day to day cell life. **For each gene**, we can measure two quantities within a cell.

Let R be the number of mRNA transcripts contained in the cell.

Let P be the number of protein molecules contained in the cell.

GE2 The dynamics of gene expression

When a gene is expressed, mRNA is produced at a **transcription rate**: p molecules per hour. At the same time, mRNA degrades with first-order rate constant δ. The resulting change equation is

$$R' = p - \delta R.$$

EX. Some mRNA transcripts degrade in minutes, while others last for days. This depends on the particular gene and cell. Based on this, what are realistic values of the decay rate δ in the change equation?

The decay rate is between _____ and _____

EX. What is the number of mRNA transcripts, when the system is in equilibrium? Express your answer algebraically in terms of p and δ.

The equilibrium number of transcripts is _____

The ribosomes translate the mRNA transcripts to make proteins (without destroying the mRNA). In this way, the rate of protein production depends on the number of mRNA transcripts; additionally, protein molecules degrade with a first-order rate constant γ. The resulting change equation is

$$P' = \beta R - \gamma P.$$

Here β is called the **translation rate**.

EX. What is the number of protein molecules, when the entire system is in equilibrium? Express your answer algebraically in terms of the parameters p, δ, β, γ.

The equilibrium number of protein molecules is _____

EX. Draw a time series, indicating what happens if R and P begin at zero. Your time series should contain two line plots: one for R and one for P. Choose realistic values for all rates, based on what you can look up about mRNA and protein transcription/translation and degradation in a single cell.

The model here is adapted from a minimal model discussed in *Central dogma rates and the trade-off between precision and economy in gene expression*, by Hauser et el., Nature Communications (2019).

Chem1 Chemical kinetics: Decomposition of H_2O_2

Hydrogen peroxide H_2O_2 is a molecule with two hydrogen atoms and two oxygen atoms. It is sold at pharmacies in a solution of water. If you pour some out, you will see bubbles, as it undergoes a reaction

$$2\,H_2O_2 \rightarrow 2\,H_2O + O_2.$$

This means that two hydrogen peroxide molecules (**the reactants**) decompose, and the results (**products**) are two water molecules (a harmless puddle) and one oxygen molecule (bubbles).

When molecules are in a solution, we typically study their **concentration**: how many molecules are in each unit of volume. A typical concentration of H_2O_2 is 1 **molar**, meaning there is about 1 **mole** ($6 \cdot 10^{23}$ molecules) of hydrogen peroxide **in a 1 Liter** bottle.

Imagine you open a 1 Liter bottle of hydrogen peroxide and pour it out into a large bowl. Let C(t) be the concentration of H_2O_2 at time t. This concentration is usually written $[H_2O_2]$ by chemists. The decomposition reaction is a **first order reaction**, which means that it exhibits simple **kinetics**; concentrations change over time according to the rule

The **kinetics** of a chemical reaction refers to how quantities of various molecules change over time.

$$C' = -\,k\,C, \text{ or in chemist notation, } \frac{d[H_2O_2]}{dt} = -k\,[H_2O_2]$$

where the **rate constant** k depends on the reactant, temperature, and other environmental variables.

EX. Draw a phase portrait for the hydrogen peroxide system. What do the equilibrium point(s) mean about the system?

This should be an simpler phase portrait than the last few pages!

EX. A typical rate constant k for the decomposition of H_2O_2 would be k=0.04, if time is measured in minutes. Given a starting concentration $[H_2O_2] = 1M$, describe $[H_2O_2]$ as an exponential function of time, in natural (base e) form.

EX. After how many minutes (round to the nearest minute) do you expect 90% of the hydrogen peroxide to decompose?

Chem2 Chemical kinetics: Dissociation of water

Water is a molecule with two hydrogen atoms and one oxygen atom. It falls out of the sky, comes out of your faucet, and still people buy it in little bottles. We think of water as stable, but it breaks apart sometimes. The **dissociation** of water is the following reaction: $H_2O \leftrightarrow H^+ + OH^-$.

This reaction is reversible, which means that those ions H^+ and OH^- love to bond with each other, turning back into water again. The kinetics of this reaction are governed by the change equations:

$$\frac{d[H_2O]}{dt} = \beta\,[H^+]\,[OH^-] - \delta\,[H_2O].$$

$$\frac{d[H^+]}{dt} = \frac{d[OH^-]}{dt} = -\frac{d[H_2O]}{dt}.$$

EX. The terms with Greek letters β and δ indicate the "birth" and "death" of water molecules. In light of sharks and tuna, why is there a term with the product $[H^+]\,[OH^-]$?

H^+ is a **hydrogen ion**, which is a hydrogen atom that's lost its electron. It is **just a proton**!

OH^- is an oxygen atom bonded to a hydrogen atom, with one extra electron. It's called a **hydroxide ion**.

In fact, hydrogen ions (protons) don't just float around the water; they glom onto water molecules to produce complicated structures.

EX. The second line of equations states that three rates are equal to each other. How does that reflect physical reality?

EX. Realistic values are $\beta = 1.3 \cdot 10^{11}$ and $\delta = 2.34 \cdot 10^{-5}$ in typical conditions (units are $M^{-1}s^{-1}$ and s^{-1}). If the dissociation system is in equilibrium, one finds that

$$[H^+]\,[OH^-] = \_\_\_\_\_\,[H_2O].$$

Find the value of the missing constant!

A liter of water contains about 55.56 moles of water molecules, so $[H_2O] = 55.56$. Use this and the fact that $[H^+] = [OH^-]$, to find the concentration of hydrogen ions and hydroxide ions.

$$[H^+] = [OH^-] = \_\_\_\_\_$$

The **pH** of water is defined by $pH = -\log_{10}([H^+])$.

What is the pH of water?

GLV1 Moose and squirrel

An unofficial image of Rocky the squirrel and Bullwinkle the Moose.

What happens when we combine our logistic model of individual constrained population growth with **competition** for resources? We study Moose and Squirrel, as a fictional example. (Real examples will follow.)

Let M be the population of moose (in hundreds), and let S be the population of squirrels (in thousands). If they did not interact with each other, their populations are modeled by separate equations.

$$S' = 3S - S^2 \qquad \text{and} \qquad M' = 2M - M^2.$$

EX. What do the different constants (2 and 3) reflect about moose and squirrels in this model?

For the rest of these exercises, we study the following model, in which moose-squirrel interactions have negative effects on both species.

$$M' = 2M - M^2 - 0.5\,MS.$$
$$S' = 3S - S^2 - MS\ .$$

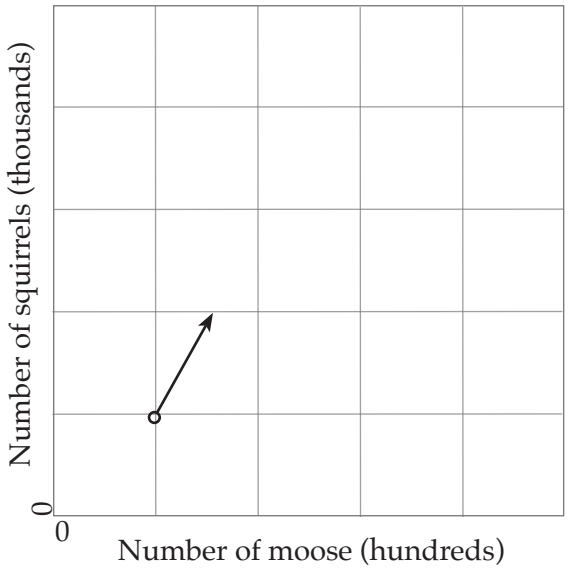
EX. Contrast this to our model of sharks and tuna. What are the most dramatic differences?

EX. Assume there are no moose ($M = 0$). Draw a phase portrait for squirrels, identifying the equilibrium numbers of squirrels.

EX. Assume there are no squirrels ($S = 0$). Draw a phase portrait for moose, identifying the equilibrium numbers of moose.

GLV2 Moose and squirrel, continued

EX. The squirrel population will not change when S' = 0. The moose will not change when M' = 0. Using some algebra (see the margin), draw the **nullclines** in Moose-Squirrel State Space below.



EX. On the plot above, highlight all equilibrium points. These are the points at which **both** S' = 0 and M' = 0.

EX. Now we will draw the vector field, showing how we expect the numbers of moose and squirrel to change, according to our model. Choose **five starting points** (M,S). Choose points from all regions of the plot. For each starting point (M,S), draw an arrow from (M,S) to (M+M', S+S'), indicating how the numbers of moose and squirrels will change. We have given one example already on the plot above.

> Example: If M=1 and S=1, then M' = 0.5 and S' = 1.
> So we drew an arrow from (1, 1) to (1+0.5, 1+1).

EX. Load the *Generalized Lotka-Volterra Explorer*, and enter the change equations. What do you think happens to the populations of moose and squirrel in the long term, according to this model?

Guide: To graph the S-nullcline, solve S'=0.

Thus we have to solve
$3S - MS - S^2 = 0$.

Factoring yields
$3S-MS-S^2 = S(3-M-S)$.

Thus S' = 0 when...
S=0 or 3-M-S=0.

Plot S=0 and S = 3-M.

GLV3 Modeling interacting populations (gerbils)

In the Western Negev desert, there are two species of wild gerbils: *Gerbillus (andersoni) allenbyi* and *Gerbillus pyramidum*. Individuals of the species *G. pyramidum* are about twice as large as their *G. allenbyi* colleagues. Both species forage for seeds at night and live in sand dunes.

EX. Declare state variables, and model these populations of gerbils with a pair of change equations. Your model should incorporate gerbil reproduction and interaction as described above. Use plausible units and parameters.

Unit of time:

State variables:

Change equations:

EX. Explain your model of gerbil populations. How did you choose the general form of your terms, and the specific parameters.

Examples here are adapted and simplified from Chapter 5 of Gotelli, *A Primer of Ecology*.

Gerbillus pyramidum, the Greater Egyptian Gerbil, image by Georges Cuvier, 1817.

Gerbillus andersoni allenbyi, or Anderson's Gerbil, from Hai-Bar Yotvata Nature Preserve.

GLV4 Trajectories in state space

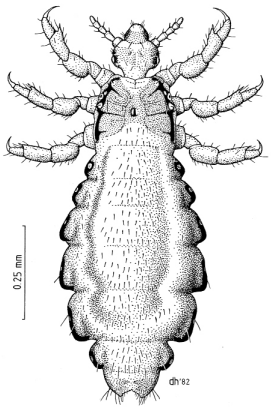
EX. Draw time series for the populations of *G. pyramidum* and *G. allenbyi*, consistent with your model and approaching equilibrium.

EX. Tell the story behind your time series. What is happening to the two populations, and why? Be creative, but your story must be consistent with your model and explanation on the previous page.

EX. Draw the trajectory in state space which matches your time series of gerbil populations.

GLV5 Modeling interacting populations (lice)

Lice, such as the head louse (*Pediculus humanus capitis*) and the body louse (*Pediculus humanus humanus*) thrive on the human body. Head lice do not spread any diseases, and some have hypothesized that head lice are actually beneficial to humans by altering their immune system. Body lice, on the other hand, are implicated in the spread of disease such as typhus, by passing the bacteria *Rickettsia prowazekii* to their human hosts.



The head louse. Scary, itchy, but harmless.

Image credit Des Helmore / Manaaki Whenua – Landcare Research.

EX. Declare state variables, and model populations of head lice, body lice, and humans with **three** change equations. Use plausible units and parameters.

Unit of time:

State variables:

Change equations:

EX. Explain your model of human and louse populations. How did you choose the general form of your terms and the coefficients.

GLV6 Trajectories in state space

EX. Draw three time series for the populations of head lice, body lice, and humans, consistent with your model.

EX. Tell the story behind your time series. What is happening to the two populations, and why? Be creative, but your story must be consistent with your model and explanation on the previous page.

EX.* According to the model you've chosen, what are the equilibrium points? What do they mean in terms of the three populations and their interactions?

GLV7 Exploration of nullclines and equilibria

Here we explore a very general model, which is meant to describe two populations in which...

1. Each population, independently, has a fixed birth/death rate and possibly a carrying capacity. Treating the populations separately, the system would exhibit exponential growth/decay or a logistic model.

2. Interactions between the populations may be helpful to both (e.g., **cooperation**), helpful to one and harmful to the other (e.g., **predator-prey**), or harmful to both (e.g., **competition**).

The change equations for such a system are the following.

$$\begin{aligned} P' &= \alpha P - \gamma P^2 + uPQ \\ Q' &= \beta Q - \delta Q^2 + vPQ \end{aligned} \quad (\dagger)$$

These are called **generalized Lotka-Volterra** equations.

EX. If the parameters u and v are both zero, describe the system, in terms of what we have learned earlier.

EX. Suppose that both u and v are positive but both α and β are negative . What does this mean about the two populations?

EX. Go to the *Generalized Lotka-Volterra Explorer*. Find values of the parameters with positive u and v, in which there is an **attractive equilibrium point** with positive P and Q. List your parameter values in the margin, and describe the dynamics in 1-2 sentences.

My parameters:

α =_____

β =_____

γ = _____

δ = _____

u = _____

v = _____

GLV8 Gause's Paramecia

Paramecia are single-cell **eukaryotic** (the cell has a nucleus) organisms, that like to float around in ponds eating bacteria and algae. In the early 20th century, the Russian scientist Gause carried out experiments on two species of paramecia: *P. aurelia* and *P. caudatem*. In his experiments, he carefully bred each species in identical conditions -- first on their own, then sharing a dish. Here we examine Gause's data with a generalized Lotka-Volterra model, marked (†) on the previous page.

Let P be the population of *P. aurelia*, and Q the population of *P. caudatem*.

EX. Use the *Logistic Growth Explorer* and the top data table to estimate α, γ, β, δ. To fit the logistic curve, enter the population data, and find parameters which minimize the "residual sum of squares." Consider P and Q completely separately for this part!

α = _____, γ = _____

β = _____, δ = _____

EX. Use the bottom data table (where species interact) and the *Generalized Lotka-Volterra Explorer* to estimate the parameters u and v. Can you find parameter values which roughly fit the data? Hint: try small negative values of u and v, turn on nullclines, and click to start trajectories.

u = _____, v = _____

EX. When the two species of paramecia are bred on the same plate, what do you think is their relationship to each other? Predator and prey? Competition for resources? Cooperation? Justify your answer.

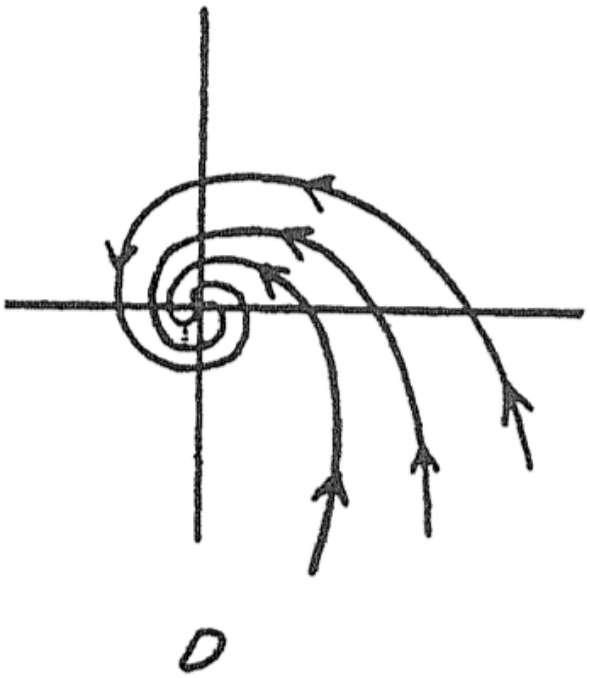
Day	P	Q
2	14	10
3	34	10
4	56	11
5	94	21
6	189	56
7	266	104
8	330	137
9	416	165
10	507	194
11	580	217
12	610	199
13	513	201
14	593	182

Populations of paramecia, **living separately**. Adapted from Table 1 of P.H. Leslie, *An Analysis of the Data for Some Experiments Carried out by Gause with Populations of the Protozoa*, in Biometrika (1957).

Day	P	Q
2	10	10
3	21	11
4	58	29
5	202	50
6	163	88
7	221	102
8	293	124
9	236	93
10	303	80
11	302	66
12	340	83
13	387	55
14	335	67

Populations of paramecia, **living together**. Adapted from Table 3 of loc. cit.

Eq1 Equilibria in two dimensions: Synthesis



On the left is a picture of one type of equilibrium point, in a system with two state variables. This image (from Figure 27 of Lotka's *Physical Biology*) displays three trajectories in state space, swirling towards an equilibrium point.

EX. (Creative writing) Think of two quantities which may exhibit such trajectories. Declare state variables with "Let..." sentences, to describe the system.

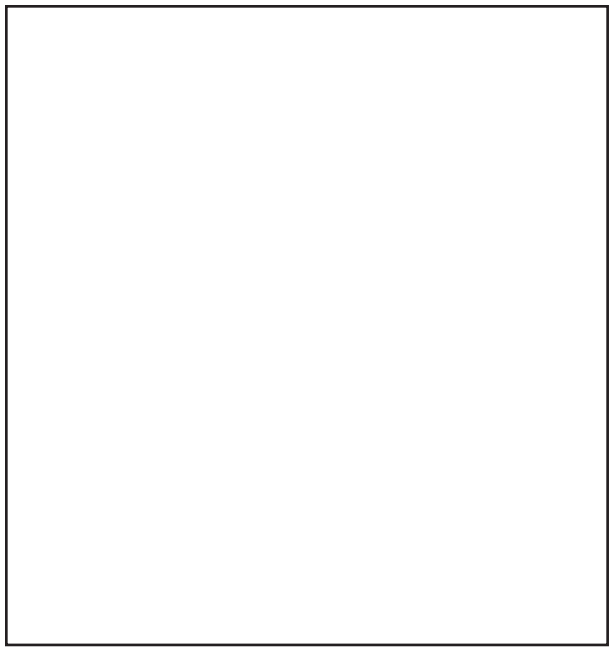
Let _____ be

Let _____ be

EX. Draw time-series plots for both of your state variables, corresponding to one of the three trajectories in the image above.

EX. Write a system of two change equations, with your chosen state variables, which exhibits these kinds of "spiraling-in" trajectories near an equilibrium point. You may use the *Generalized Lotka-Volterra Explorer* to help find such change equations.

Eq2 Equilibria in two dimensions: Synthesis



Type _____

EX. On the left, reproduce another type of equilibrium point, choosing the image from one of Lotka's types A-J, shown on the opening page of this Lab.

EX. (Creative writing) Think of two quantities which may exhibit these trajectories. Declare state variables with "Let..." sentences to describe the system.

Let ____ be

Let ____ be

EX. Draw time-series plots for both of your state variables, corresponding to one of the trajectories in the image above.

EX. Write a system of two change equations, with your chosen state variables, which exhibits these kinds of trajectories near an equilibrium point.

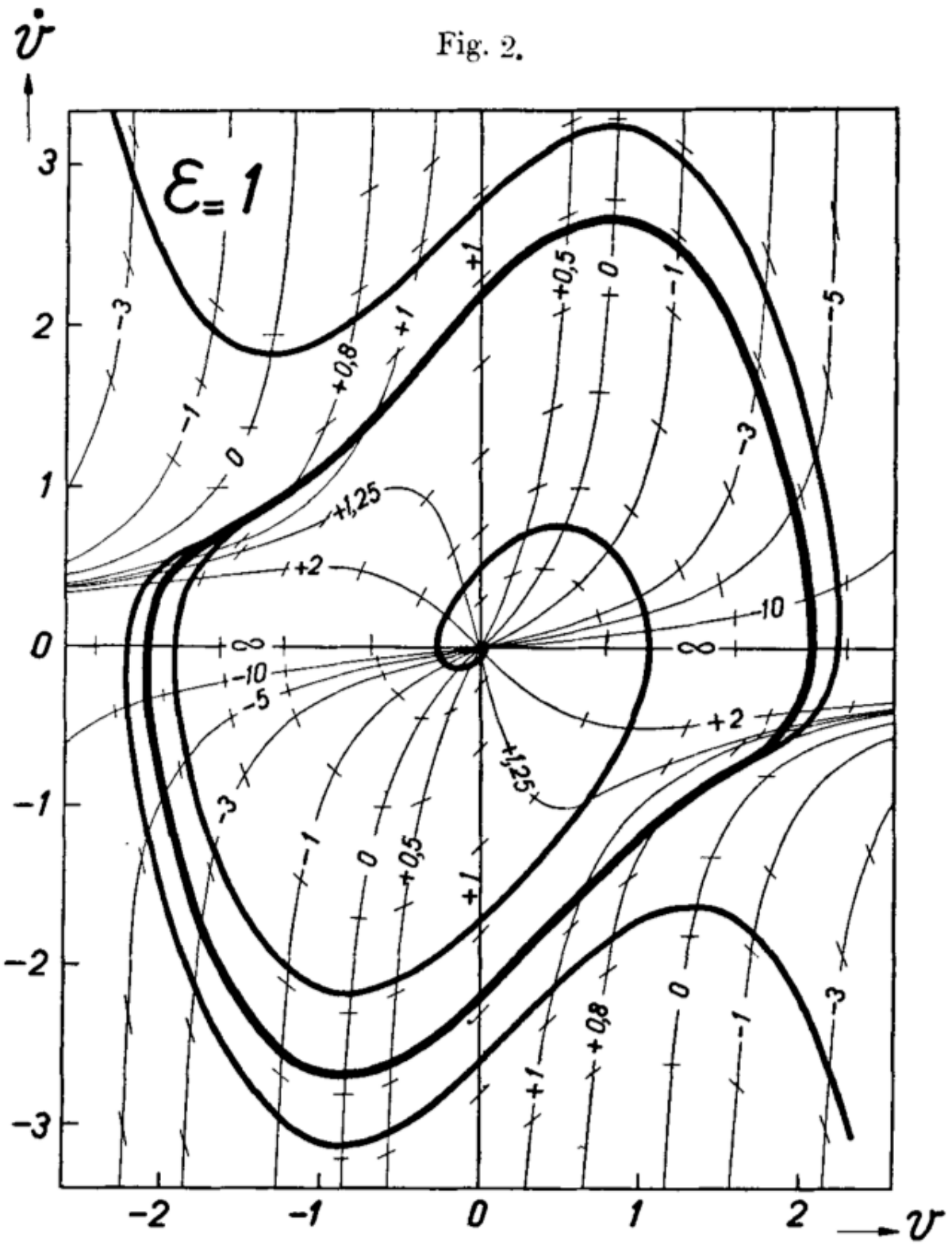


Figure 2 from *On "relaxation-oscillations,"* by Balth.van der Poljun.D.Sc, in the London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science (1926). Shown are two trajectories that approach a **stable limit cycle**. One trajectory comes from far away, around (-2,3), while the other comes from inside at (0,0). Both trajectories approach the same limit cycle, a **closed trajectory** having a weird ⌔-shaped structure. Van der Pol's equations were used in the earliest electrical models of the heart.

Laboratory 4
Oscillation

Equilibrium is a theoretical state. Real systems are always in motion. Well-regulated systems are not at rest, but rather they **oscillate** around the equilibrium in a predictable manner. In mathematics, the first oscillators we see are described by **sinusoidal functions** like sine and cosine. These appear often in physical sciences, but are less often seen in the biological sciences. Biological oscillation, like circadian rhythms, heartbeats, hormonal fluctuations, are far more complicated.

In this lab, we will see three sorts of oscillation.

1. The **simple harmonic oscillator (SHO)** is useful for understanding the simplest oscillating systems in physical science. A key example will be the oscillation of bonds in molecules, which is crucial for **spectroscopy**. The SHO also provides a vocabulary to describe oscillation.

2. Oscillations arise from **limit cycles**, like the van der Pol oscillator shown on the opposite page. Other examples include the **Holling-Tanner model** in ecology, modeling sharks and tuna... when the sharks have limited appetite. Another example is given by oscillations in **glycolysis**, the most important metabolic process in the cell.

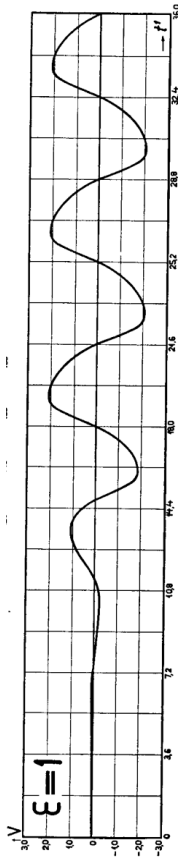
3. Oscillations arise from **time delay and sharp negative feedback**; nothing happens in an instant. In contrast to change equations from previous chapters, where one quantity immediately affects how another changes, real systems exhibit time delays. These delays can lead to regular patterns of oscillation, and sometimes to chaos!

EX. Think of a quantity, related to living organisms, that oscillates. Briefly describe this oscillating system, and how you think the oscillations are maintained.

Van der Pol considers the system of change equations,

$$X' = Y$$
$$Y' = \varepsilon(1-X^2)Y - X$$

Trajectories with the parameter $\varepsilon=1$ are shown on the opposite page. A time-series is given below (from Fig. 4 of loc. cit.), showing the formation of oscillations.



Osc1 The "How" of Oscillation

Let X be a single (positive) quantity that changes over time. We begin by asking how X might achieve an oscillating state. We have only touched the surface of change equations; perhaps there is some new change equation, $X' = F(X)$, whose trajectories oscillate?

To understand the trajectories, we might begin by drawing a phase portrait, like the one below.

Recall what this phase portrait displays. The dots indicate the equilibrium points when $X' = F(X) = 0$. The arrows point to the right when $F(X) > 0$, and the arrows point to the left when $F(X) < 0$.

A trajectory in such a system must follow the arrows. If a trajectory ever hits an equilibrium point, it must stop moving.

EX. Explain, in 1-2 sentences, why such a system can never reverse direction. In other words, if $X' = F(X)$, then the quantity X(t) can increase or decrease, but it can never do one then the other.

EX. It is cold outside, and your room is equipped with a simple on/off heater. Whenever the temperature drops below 65 degrees, you feel cold and turn on the heater. When the temperature is above 75 degrees, you feel hot and you turn off the heater. Draw a time-series plot of the temperature of your room.

EX. Can the above situation be described by a single change equation? Why or why not?

Osc2 Momentum and Force

A single change equation X' = F(X) cannot produce oscillations. On the other hand we have seen that a **pair** of change equations, like sharks and tuna, can produce oscillations in both quantities. We might say that **a quantity cannot oscillate on its own**.

In physics, this problem is resolved by a radical idea. In addition to tracking the traditional state of a system (a state variable X), one also tracks the **momentum** of the system (a state variable "P" for im**P**etus). If one works with the simplest physical system, a moving ball, then X would represent the **position** of the ball, and P would represent the **velocity of the ball multiplied by its mass**. This P reflects the **oomph** of the ball, called the **momentum**.

The position X and momentum P are then forever linked by a simple looking change equation:

$$m\,X' = P, \text{ or equivalently } X' = u\,P$$

Here m is the mass of the ball, and u = 1/m is its reciprocal.

If the change in position X' is described by P, how does momentum change? The answer is given by **Newton's Second Law**, which states:

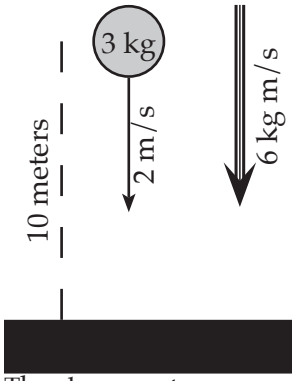
P' = [The force applied to the ball]

In other words, **force determines the change to momentum**. And momentum (divided by mass) determines the change in position. In this Newtonian model, **force does <u>not directly</u> change the position**. That is the big first insight of Newtonian physics.

EX. A 3 kilogram ball is falling from a height of 10 meters. Its current velocity is 2 m/s downwards. The force of gravity is equal to 30 kg m/s^2. Using the discrete time model below, fill out the table to see what happens to the position and velocity of the ball in the subsequent 0.3 seconds.

$$\Delta X/\Delta t = -u\,P \quad \text{and} \quad \Delta P/\Delta t = 30.$$

Note that the initial momentum is 6 kg m/s, since the 3 kg ball is falling at 2 m/s. Our time interval is $\Delta t = 0.1$ second.



The above system shows a ball with position (height) X = 10 m, mass 3kg and velocity 2 m/s (downwards), and momentum:

P = 6 kg m/s.

Newton's Law in original Latin: *Mutationem motus proportionalem esse vi motrici impressae*

Translated: *A change in momentum is proportional to the motive force applied.*

time	X (meters)	P (kg m/s)	ΔX	ΔP
0	10	6		
0.1				
0.2				
0.3				

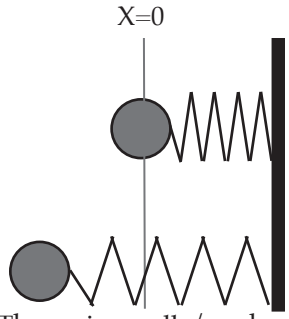
SHO1 Introducing the Simple Harmonic Oscillator

The **simple harmonic oscillator** refers to any model with two state variables, say X and P, two **positive** parameters u and k, and the following innocent-looking change equations.

$$X' = dX/dt = uP \quad \text{and} \quad P' = dP/dt = -kX.$$

The quantity X typically represents the position of some thing. The quantity P then represents its momentum, and $u = 1/m$ is the reciprocal of the mass. And the force, which equals P' by Newton's law, is proportional to -X. This means that the force is a **restoring force**. If X is positive, the force -kX is negative, pulling X towards 0. And if X is negative, the force -kX is positive, pushing X towards 0.

We choose these letters X, P, u, k, because they are commonly used in physics.



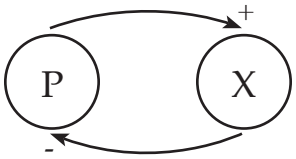
The spring pulls/pushes the ball towards 0.

EX. Consider the following discrete-time simple harmonic oscillator, with parameters u=1 and k=1.

$$\Delta X/\Delta t = P \qquad \text{and} \qquad \Delta P/\Delta t = -X.$$

Suppose you begin at the state X=1 and P=0, when t=0. Using time steps $\Delta t=1$, find the states at t=1, t=2, and t=3. Fill out the table below.

time	X	P	ΔX	ΔP
0	1	0		
1				
2				
3				



The harmonic oscillator is an example of a negative feedback loop. The position negatively influences the momentum through the restoring force.

EX. Carry out the same process, but using time interval $\Delta t=0.5$. The resulting table should have 7 rows (t=0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0). Sketch the trajectory in state space below.

SHO2 Exploring the Simple Harmonic Oscillator

Using a discrete-time approximation, you should find that the change equations $\Delta X/\Delta t = P$ and $\Delta P/\Delta t = -X$ yield a spiraling trajectory. In fact this spirals out less and less when Δt gets smaller. To see what happens when Δt becomes the infinitesimal differential dt, load the *Simple Harmonic Oscillator simulator.* This simulates the equations:

$$X' = uP \quad \text{and} \quad P' = -kX$$

EX. Find the equilibrium point of the simple harmonic oscillator, and explain why it is the only equilibrium point.

The only equilibrium point of the SHO is at X = _____, P = _____, because...

EX. Experiment with trajectories in the simulator. Describe the trajectories when u=1 and k=1. Then describe the effect of changing the parameters u and k. What shapes do you find, and how do the parameters affect the shapes? Draw a picture to accompany your description.

EX. The trajectories for the simple harmonic oscillator are **closed**, meaning they follow a path that leads back to where they start. The **period** is how much **time** it takes to complete a cycle. Explore to see how the period may depend on the starting point and the parameters u and k. Describe your findings qualitatively. (On the next page, you will collect data more formally).

SHO3 Anatomy of the Simple Harmonic Oscillator

In the **simple harmonic oscillator**, two quantities called X and P, change according to the equations

$$X' = dX/dt = uP \quad \text{and} \quad P' = dP/dt = -kX.$$

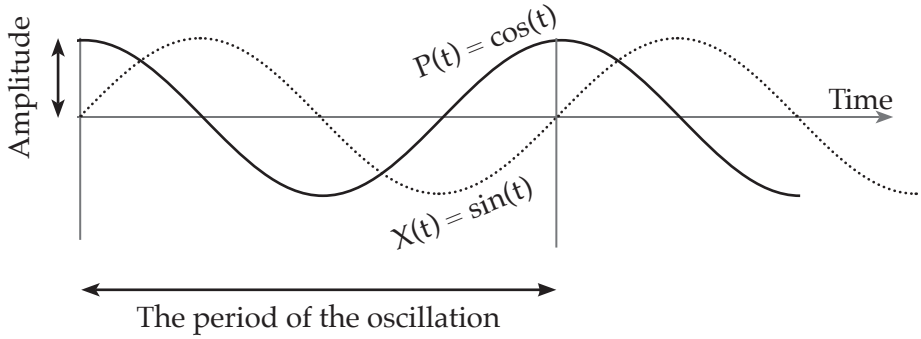
The resulting trajectories are **elliptical**. The period of oscillation, remarkably, does not depend on the starting point. Rather, the period is given formulaically from the parameters u and k.

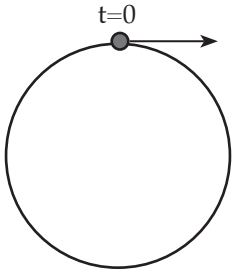
EX. Fix u, and try diferent values of k. Then fix k and try different values of u. Collecting data in this way, and using the *Linear Regression with Log Scaling Tool*, develop of a formula which relates the period of oscillation to u and k. Hint: When u = 1 and k = 1, the period is 2π.

Period = 2π _____

If you start your trajectory at X=0, P=1, with the parameters u=1 and k=1, then the trajectory traces a unit circle at velocity 1. The time-series are then described by the cosine and sine functions.

$X = \sin(t)$ and $P = \cos(t)$





The trajectory in state space is circular when u=1 and k=1. It takes 2π, about 6.28, units of time to go around the circle. The amplitude is the radius of the circle.

Note that X is on the horizontal and P is on the vertical axis here.

When the starting point is changed, the circle can become larger and smaller. This does not change the period! But it does change the amplitude. When u and k are changed, the circle becomes an ellipse; the two waves have different amplitudes, but the same period.

EX. Draw the time series, when u=8 and k=2, with starting point (1,0). Label your plot to show the **period** and the **amplitudes** of the X and P oscillations. Sketch the trajectory in state space in the margin.

SHO4 Sine and cosine

The simplest harmonic oscillator has the form, $X' = P$ and $P' = -X$. When $X(0) = 0$ and $P(0) = 1$, the time series are given by functions

$$X = \sin(t) \quad \text{and} \quad P = \cos(t).$$

EX. Taking these facts as a given, what is the derivative of sin(t)? What is the derivative of cos(t)?

EX. Let $X(t) = a \sin(bt)$. Using Desmos, how do the parameters a and b relate to the period and amplitude of oscillation?

EX. If $X(t) = a \sin(bt)$, then what is $X'(t)$? Reason geometrically; how do the parameters a and b affect the graph, and its slopes?

EX. A typical human's body temperature fluctuates during the day, with average 36.5°C, around noon and midnight, maximum 37°C and minimum 36°C. Let B(t) be the body temperature at time t, where t is measured in hours and t=0 represents midnight. Model the function B(t) by an appropriate sinusoidal function.

EX. A **damped** harmonic oscillator has time-series described by the function $X(t) = \sin(t)\, e^{-t}$ and $P(t) = \cos(t)\, e^{-t}$. Sketch the resulting time-series and trajectory in state space here, starting at t=0.

Osc3 Units for describing oscillation

Suppose that X is a quantity that oscillates. This means that, the long-term behavior of X involves a repeating pattern of increasing and decreasing. We have already met the **period** of oscillation—the length of **time** to complete a full cycle.

The **frequency** of oscillation is **how many** oscillations occur in a given unit of time. For example, if the **period** of oscillation is 3 months, then the **frequency** of oscillation is 4 per year.

EX. Convert the following periods to frequencies.

The semidiurnal tide has a **period** of 12 hours. The **frequency** of this tide is _____ per day.

The *E. Coli* cell cycle has a period of 30 minutes. The frequency of this cell cycle is _____ per hour.

The "ultradian" oscillation of insulin has a period of 60 minutes. The frequency of this oscillation is _____ per day.

A typical unit of frequency is the **Hertz**, abbreviated Hz. The unit "Hz" means "per second." So an oscillation frequency of 20 Hz means that the oscillation occurs 20 times each second.

EX. The refresh rate of your computer monitor is probably 60 Hz. What is the period of this oscillation, in milliseconds?

1 millisecond, or 1 ms equals 1/1000, or 10^{-3} seconds.

EX. The **sound** of a "middle C" on a modern instrument consists of **air pressure waves** which oscillate with a 3.83 ms (millisecond) period. When a middle C is played, how many times does a string vibrate each second? In other words, what is the frequency, in Hz?

EX. Light consists of vibrations in the electromagnetic field. A red light (e.g., from a red laser pointer) represents oscillations at a frequency of $4.3 \cdot 10^{14}$ Hz. What is the period of the vibration?

Osc4 Light

Light is strange stuff. Einstein noted that light behaves like little particles (**photons**), each traveling at a fixed speed **c** called the **speed of light**. This speed of light doesn't change if you shine a flashlight from a speeding train, or launch your flashlight into space, or choose a red or blue light. This speed of light is a constant, a really big constant, which we can experimentally measure.

$c = 3 \times 10^8$ m/s ≈ 300 million meters per second.

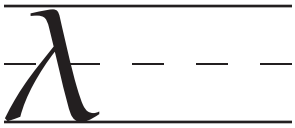
Here we're talking about the speed of light in a vacuum, i.e., when there's nothing for the light to "bump" into. The speed of light in water is about 25% slower. Air slows down light by about 0.03%.

At the same time, light behaves like a wave—it oscillates. Every photon of light has a **frequency f,** describing how fast it oscillates. Every photon also has a **wavelength λ**, because light waves have a length in space. The frequency and wavelength are linked by the equation

$$\mathbf{f\,\lambda = c}$$

λ is the lowercase Greek letter **lambda**. Draw it below for practice.

Note that the units of speed are m/s (meters per second). The units of frequency are Hz ("per second"). The units of wavelength are meters.



EX. A red laser emits light with frequency $4.3 \cdot 10^{14}$ Hz. What is its wavelength? Express your answer in **nanometers** (1 nm = 10^{-9} m).

λ= _____ nm

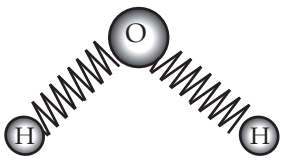
EX. A blue laser emits light with wavelength 450 nm. What is its frequency?

EX. Fill out the following table, with ranges of frequencies and wavelengths for commonly occuring photons. Look these up and briefly describe your source in the margin.

Name of light	Wavelengths	Frequencies
X-ray, Gamma-ray		
Ultraviolet		
Visible light	380 - 700 nm	
Infrared		
Microwave		
Radio (WiFi, etc.)		

Information source for table:

EX. Molecules behave somewhat like balls (atoms) attached by springs (covalent bonds). As such, a water molecule can vibrate in a few ways, with frequencies 1.126×10^{14}, 1.097×10^{14}, and 4.782×10^{13} Hz. Light with those frequencies is easily absorbed by water molecules, making them vibrate. What sort of light (according to the table above) is absorbed by water? (This is why water vapor is a greenhouse gas!)



In water, the H-O bond lengths can vibrate, and the bond angle (about 104.5 at equilibrium) can vibrate too.

Gly1 Glycolysis

10 steps of glycolysis

1 molecule Glucose
↓ 1
1 molecule G6P
↓ 2
1 molecule F6P
↓ 3
1 molecule FBP
↓ 4
1 molecule each of GADP, DHAP
↓ 5
2 molecules GADP
↓ 6
2 molecules BPG
↓ 7
2 molecules 3PG
↓ 8
2 molecules 2PG
↓ 9
2 molecules PEP
↓ 10
2 molecules Pyruvate

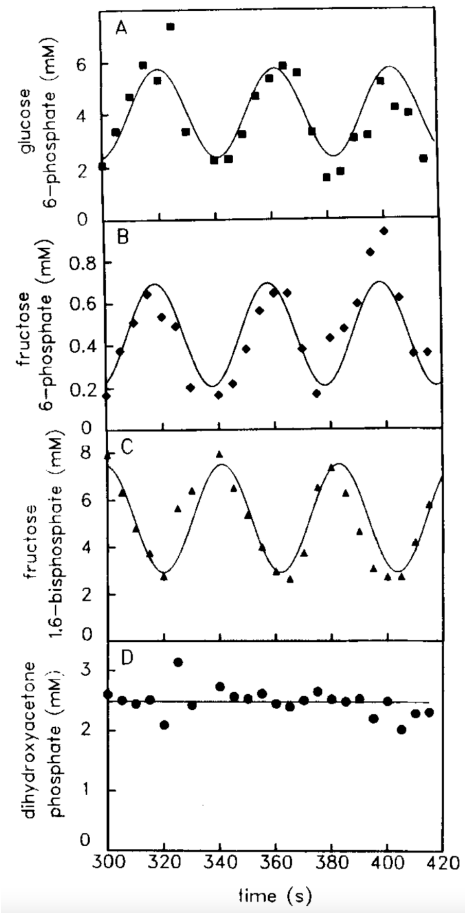
Glycolysis is a series of chemical reactions that is central to the metabolism of cells. It proceeds in 10 steps, beginning with the now-familiar **monosaccharide glucose $C_6H_{12}O_6$**, and ending with two molecules of pyruvate $C_3H_4O_3$. Each step requires an enzyme, e.g., hexokinase to get from glucose to G6P. Some steps consume energy and some release energy. More is released than consumed, and the crucial byproduct is that **glycolysis produces usable energy**; this energy is stored in the molecules ATP and NADH. In cells with mitochondria, NADH enables mitochondria to generate even more ATP. The molecule ATP is then used for all sorts of cellular processes, from the firing of our neurons and whirling of bacterial flagella.

To summarize, glycolysis is the series of chemical reactions which allows glucose to serve as the fuel for cells.

We consider glycolysis here, because it is the most important metabolic process in the cell, and because from single-cell **prokaryotes** like *E. Coli*, and **eukaryotes** like yeast, to human cells (e.g., β-cells in the pancreas, muscle cells in the heart), **glycolysis oscillates**.

On the right is Figure 1 from Richard et al., where the authors measure the concentration of G6P, F6P, FBP, and DHAP over time, in yeast (*Saccharomyces cerevisiae*). These are molecules that appear in the first 4 steps of glycolysis.

EX. What do the marks (squares, diamonds, triangles, circles) mean? What do you think the wavy lines are?



EX. Estimate the period and frequency of the oscillations of G6P shown in the figure.

Period = _____ seconds

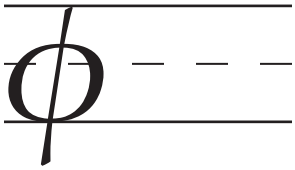
Frequency = _____ per minute

For oscillation in glycolysis, see *Dynamic fluctuations in a bacterial metabolic network*, by Bi et al., in Nature Communications (2023) for *E. Coli*. There are many works for yeast, such as *Sustained oscillations in free-energy state and hexose phosphates in yeast* by Richard et al., Yeast (1996). Richard et al. is the source for the above figure. For humans, see e.g, *Metabolic oscillations in beta-cells* by Kennedy et al., Diabetes (2002).

Gly2 Oscillation and phase shift

EX. Compare and contrast the oscillations of G6P, F6P, and FBP in the figure.

ϕ is the lowercase Greek letter **phi**. Draw it below for practice.



EX. A general sinusoidal function has the form

$$S(t) = A \sin\left(\frac{2\pi(t-\phi)}{p}\right)$$

This function has three parameters, called A, p, and ϕ. Use Desmos to explore these parameters. You have already seen what A and p represent. The parameter ϕ is called the **phase shift**. Describe what all these parameters mean for the graph of S(t).

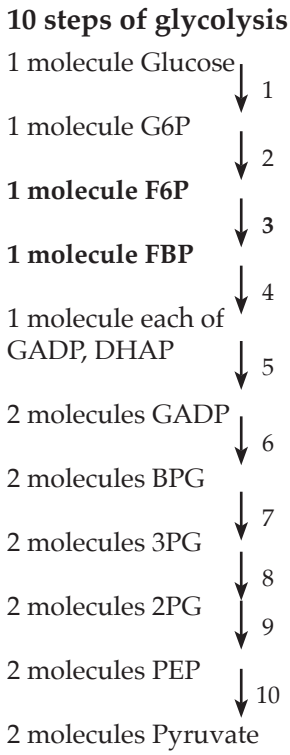
A is the ...

p is the ...

ϕ is the ...

EX. Considering the step-by-step nature of glycolysis, and the figure, why might you see differences in phase shift when looking at G6P, F6P, and FBP?

Gly3 Glycolysis: source of oscillations



One source of oscillations can be found in Step 3 of glycolysis, where F6P is converted to FBP. The chemical reaction requires an **enzyme** PFK activated by two molecules of ADP. It also requires a molecule of ATP, the energy source of the cell. So the input for Step 3 is really...

1 F6P + 1 PFK + 2 ADP + 1 ATP.

The output of Step 3 is also more complicated. The F6P is indeed converted to FBP. The enzyme PFK and its 2 ADP activators are not "used up" and so they wash out unchanged. But the energy source ATP is used up, leaving a molecule of ADP. So the output of Step 3 is really...

1 FBP + 1 PFK + 3 ADP.

To complete the construction of the model, we make three more assumptions. First, that there is plenty of PFK and ATP floating around in the cellular environment. Second, that ADP is removed in a first-order fashion (exponential decay). Third, that F6P is produced at a steady rate by Steps 1 and 2 of Glycolysis.

Our model comes from the chemical reaction: 1 F6P + 2 ADP → 3 ADP, since we ignore the PFK which is unchanged.

$$\frac{d[F6P]}{dt} = v - c\,[F6P]\,[ADP]^2.$$

$$\frac{d[ADP]}{dt} = c\,[F6P]\,[ADP]^2 - k\,[ADP]$$

EX. What is the meaning of the term $[F6P]\,[ADP]^2$? Look at the input to Step 3 to find the interaction.

EX. What do the terms v and -k[ADP] mean? Which assumptions do they reflect about our model?

Gly4 Glycolysis: Higgins-Sel'kov model

Let F be the concentration of F6P (fructose-6-phosphate) molecules in our cell. Let A be the concentration of ADP (adenosine diphosphate) molecules in our cell. Our previous change equations can be written more compactly in the form

$$F' = v - c\,FA^2 \quad \text{and} \quad A' = c\,FA^2 - kA$$

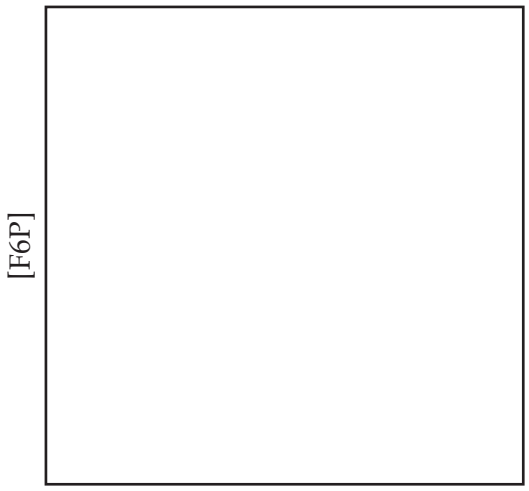
EX. The A-nullcline occurs when $c\,FA^2 - kA = 0$. Complete the following sentence with an algebraic expression.

$A' = 0$ when $A = 0$ or when $F =$ _____

EX. If the parameters v,c,k are all equal to 1, there is a unique equilibrium point. What is this point?

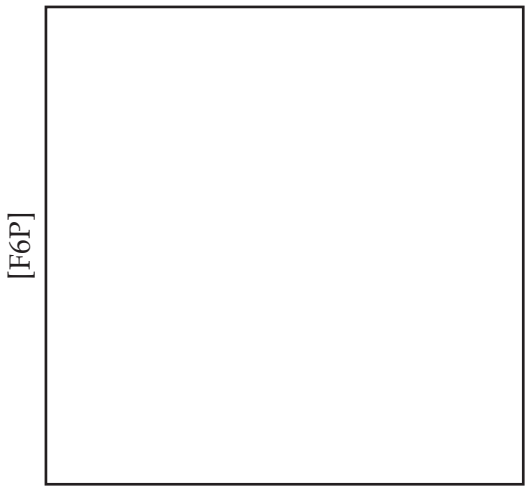
Equilibrium occurs when A = _____ and F = _____

EX. Load the *Higgins-Selkov simulator* to explore trajectories and parameters. Draw three trajectories you see for each of the parameter choices below. Compute the equilibrium point in both cases.



Parameters: v=1, c=0.9, k=1

Equilibrium point: _____



Parameters: v=1, c=1.1, k=1

Equilibrium point: _____

EX. Based on these explorations, compare the oscillations you expect to see if you measure [F6P] and [ADP]. Their period? Phase shift?

HT1 Holling-Tanner Model

We return now to predator-prey systems, like our familiar sharks and tuna. The original Lotka-Volterra equations were the following.

$$S' = -\delta S + pST \quad \text{and} \quad T' = \beta T - qST$$

Here we are using derivatives (continuous model) S' and T', while in Lab #1 we used the discrete time model with rates of change $\Delta S/\Delta t$ and $\Delta T/\Delta t$.

Rather than using simple exponential birth/death rates, we learned to incorporate a "carrying capacity" in a logistic model. Putting this together, we get the generalized Lotka-Volterra equations below.

$$S' = \alpha S\,(1 - S/k) + pST \quad \text{and} \quad T' = \beta T\,(1 - T/m) - qST$$

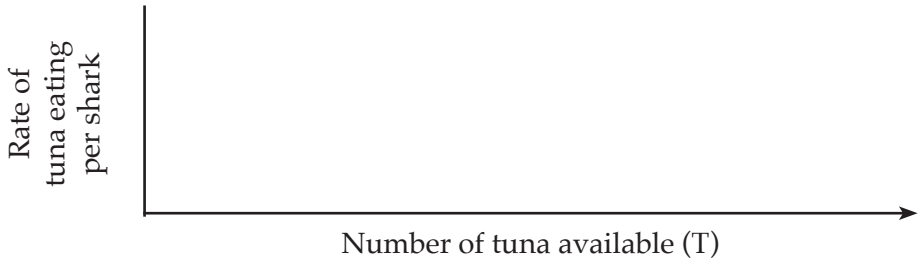
One criticism of this model is that the sharks seem to have infinite appetite for tuna. No matter how large the number of tuna, the sharks seem to chomp them up. To fix this, the rate of tuna consumption should reflect the following:

It should be proportional to the number of sharks. For example, twice as many sharks should yield twice as many eaten tuna. So the rate of tuna consumption should look like

[Rate of tuna-eating per shark] · [Number of sharks]

The rate of tuna-eating per shark (1) should be **zero if there are zero** tuna; (2) **it should grow** with the number of tuna, but (3) it should reach **saturation**. Each shark has a maximum appetite for tuna.

EX. Let A(T) be the rate of tuna-eating per shark. Draw a plausible graph of A(T), with T on the horizontal axis, based on the **model assumptions** (1) and (2) and (3) above.



A model of A(T) can be given by a Hill function: $A(T) = \dfrac{c\,T^d}{T^d + h}$

To graph with parameters, and restricting the domain, type what's below into Desmos.

$$f(x) = \frac{Cx^d}{x^d + h}\ \{x \geq 0\}$$

EX. Use Desmos to explore this function, where c and d and h are positive parameters (with $d \geq 1$). Which parameter reflects the shark appetite, and how?

HT2 Completing the Holling-Tanner model

A Hill function can be used to better model the rate at which tuna are eaten, when sharks have limited appetite. The new change equation for tuna is given by

$$T' = \beta T\,(1 - T/m) - A(T)\cdot S = \beta T\,(1 - T/m) - \frac{c\,ST}{h+T}$$

We assume d=1 in our Hill function, just to keep things a bit simple.

What about the sharks? Another criticism of Lotka-Volterra is that eating tuna does not directly increase the birth rate of sharks. Tuna help feed the sharks, for sure, but one would not expect a direct proportionality between tuna-eaten and sharks-born.

A good answer to this criticism is found in the logistic model we use for the shark population, $S' = \alpha\, S\,(1 - S/k)$. Here k denotes the "carrying capacity," which is the maximum amount of sharks the environment can support. Here, the environment is full of tuna! The carrying capacity is directly proportional to the number of tuna. If we have twice as many tuna, the ocean can support twice as many sharks. So we should have $k = q\,T$, for some constant of proportionality q. Putting this together, we have

$$S' = \alpha\, S\,(1 - S/\mathbf{qT}) \qquad \text{(logistic model with carrying capacity } \mathbf{qT})$$

We do not need an interaction term pST any more! The tuna-effect on sharks is built in, by incorporating tuna in the carrying capacity.

The resulting pair of change equations is the Holling-Tanner model of predator-prey populations.

$$T' = \beta T\,(1 - T/m) - \frac{c\,ST}{h+T} \quad \text{and} \quad S' = \alpha\, S\,(1 - S/qT).$$

EX. In this model, what do the parameters α, β, m, c, and q mean?

HT3 Holling-Tanner model: dynamics

Now we explore the dynamics of the Holling-Tanner model

$$T' = \beta T (1 - T/m) - \frac{c\,ST}{h+T} \quad \text{and} \quad S' = \alpha S (1 - S/qT).$$

EX. Describe the S-nullcline, as a pair of lines in shark-tuna space.

$S' = 0$ when $S = 0$ or $S =$ _____

EX. (Challenge!) Describe the T-nullcline in shark-tuna space.

Fill in the blanks with algebraic expression involving only the parameters.

$T' = 0$ when $T = 0$ or $S =$ ____ + _____ T + _____ T^2

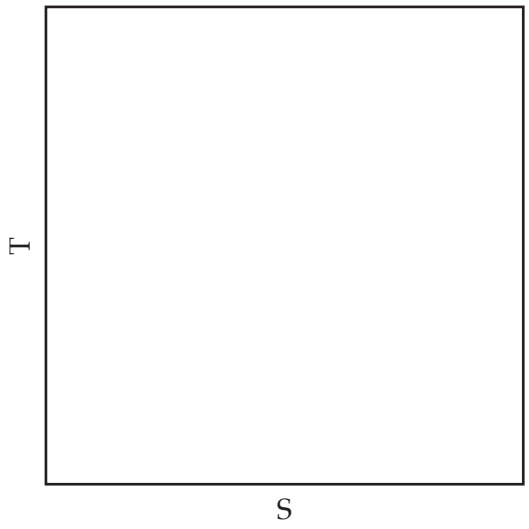
Hint: Factoring yields $T' = T\left(\beta - \frac{\beta T}{m} - \frac{c\,S}{h+T}\right)$

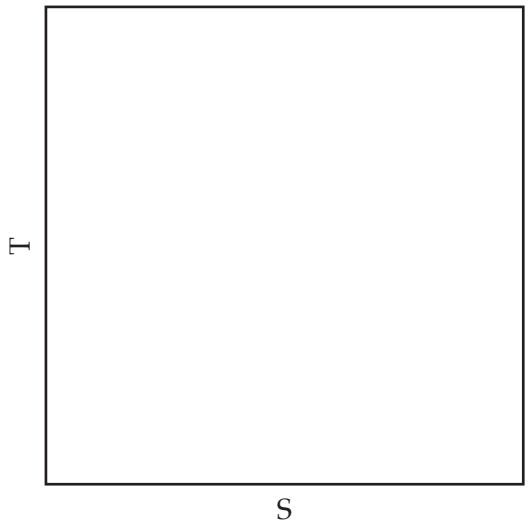
Now load the *Holling-Tanner Simulator*. This will explore the shark and tuna population in our new model. The default parameters are

$\alpha = 0.1$, $\beta = 1.0$, $m = 7.0$, $q = 1.0$, $h = 1.0$, $c = 0.5$.

EX. Note that β is 10 times larger than α. What does this mean, in terms of our assumptions about sharks and tuna?

EX. Adjust the parameter c, with values between c=0.5 and c=1.2. For which values of c do you find a **stable spiral** equilibrium point? For which values of c do you find an **unstable spiral** with a **limit cycle**? Answer these questions and provide two figures showing the dynamics for two values of c to support your answers.





HT4 Modeling challenge -- three species

Consider an ecological system, with three populations: the cyanobacteria, the green algae, and the filter-feeding fish. Let C be the biomass of cyanobacteria, G the biomass of green algae, and F the number of filter-feeding fish. This ecosystem has the following properties.

1. The filter-feeding fish eat both cyanobacteria and green algae. They have a limited appetite, only opening their mouths when hungry.

2. The cyanobacteria and green algae grow in a logistic manner, and are in competition with each other. The cyanobacteria would typically outcompete the green algae, if their biomass were equal.

EX. Create a system of three change equations which plausibly models the three populations, consistent with what is written above.

$C' =$

$G' =$

$F' =$

EX. Do you think that adding filter-feeding fish is a good strategy for controlling cyanobacteria and green algae? How might this answer depend on having both cyanobacteria and green algae present rather than just one of these species? Explain your answer

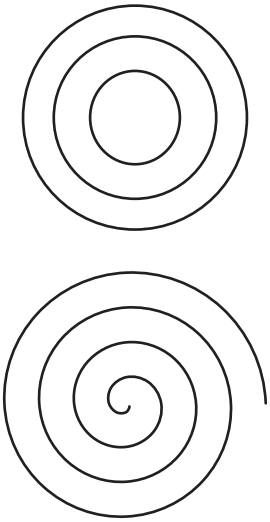
Filter-feeders like bighead carp (*Hypophthalmichthys nobilis*) use gill rakers to filter out nutritious stuff from the water, eating as they swim.

Cyanobacteria used to be called blue-green algae. But they are bacteria, which are cells without nuclei (**prokaryotes**). Nowadays, the term **algae** is reserved for cells with nuclei (**eukaryotes**).

This problem is loosely based on Zhuang et al., *Population Interaction Dynamics Analysis of an Algae-Fish System*, in Applied Mathematics (2022).

Osc5 Oscillation with two variable systems: recap

We have seen two sources of oscillation so far, and both require two (or more!) state variables. One source of oscillation was found in the simple harmonic oscillator, which led to "neutral" circular or elliptical trajectories lie those in the margin.



Circular trajectories arise from change equations like:

X' = P, P' = -X

A slight change, like

X' = P, P' = -X - 0.01P

yields a spiraling trajectory, where oscillations decay.

The second source of oscillation we have seen is the **limit cycle**, found in our glycolysis model and the Holling-Tanner predator-prey model. Limit cycles are **closed trajectories**. If a trajectory starts a bit inside a **stable limit cycle**, it will spiral outwards and soon approximate the limit cycle. If a trajectory starts a bit outside the stable limit cycle, it will spiral inwards, and again it will soon approximate the limit cycle.

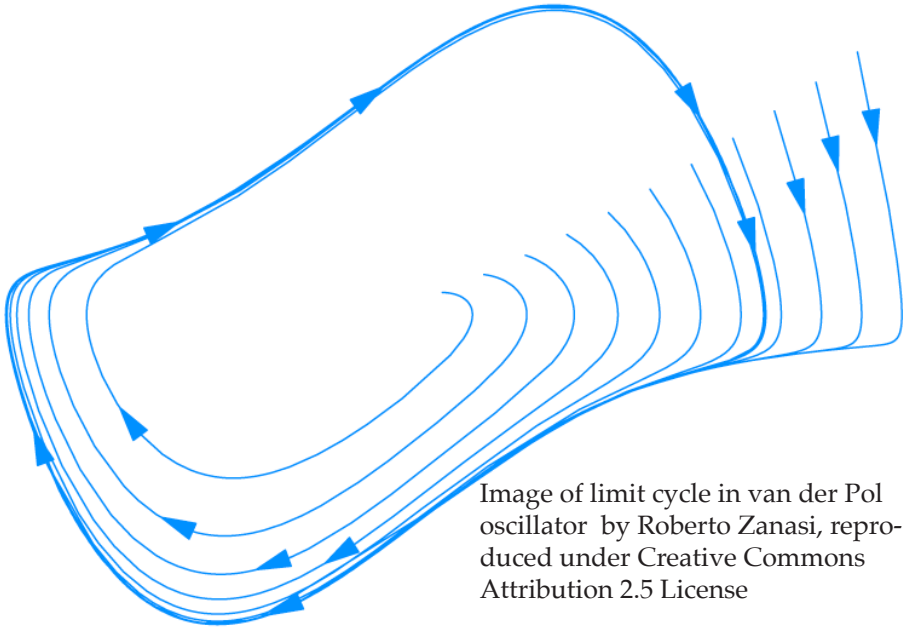


Image of limit cycle in van der Pol oscillator by Roberto Zanasi, reproduced under Creative Commons Attribution 2.5 License

The **Poincare-Bendixson Theorem** states that **bounded trajectories** for two state variables have one of three flavors

1. The trajectory gets closer and closer to an equilibrium point.

2. The trajectory is closed, meaning that it goes around and around in a perfectly repeating manner.

3. The trajectory gets closer and closer to a limit cycle.

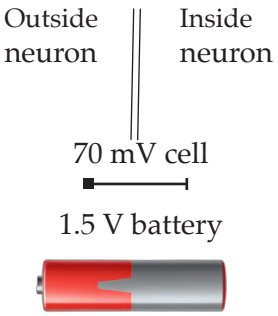
EX. Explain why a trajectory for two state variables cannot cross itself, e.g., you will never find a figure-8 shaped trajectory. Hint: where would the "change vector" point, if the trajectory crosses itself?

Closed trajectories are curves which return to the point at which they begin.

Bounded trajectories are curves which can "fit in a box." More formally, there is some number D for which the trajectory never ventures farther than D units from where it began.

Osc6 Parameter variation: the FitzHugh-Nagumo model

In a neuron, like most cells, there is a voltage difference between the inside and outside of the cell, known as the **membrane potential**. During a **neural spike,** the membrane potential of the neuron rapidly rises. The membrane potential is controlled by **ion channels**, allowing the travel of sodium and potassium ions through the cell membrane.



In resting state, a typical membrane potential is -70 mV (milliVolts), and it peaks around +40 mV. during a spike.

In the FitzHugh-Nagumo model, we use one state variable X for membrane potential, and one state variable Y to represent the state of the "recovery" ion channels. The change equations are below.

$$X' = X - X^3/3 - Y + z \quad \text{and} \quad Y' = u\,(X + a - bY).$$

When a=0, b=0, and z=0, this is known as the **van der Pol** oscillator. Load the *FitzHugh Nagumo Neuron Simulator* for what follows.

.

EX. How do the parameters a and b affect the nullclines?

The parameter a controls ...

The parameter b controls ...

The FitzHugh-Nagumo model (1961 and 1962) simplifies the earlier Hodgkin-Huxley model (1952), by considering only two state variables rather than four. The Hodgkin-Huxley more closely models the neuron as an electrical circuit.

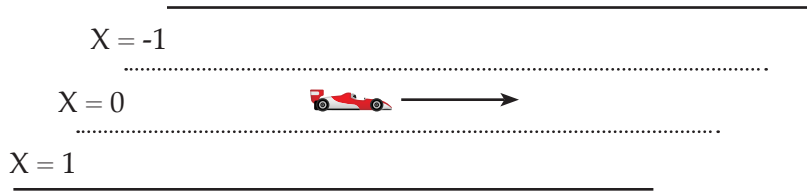
EX. The parameter u does not affect the nullclines. But how does the parameter u affect the shape of the neural spikes (the shape of the time-series for the membrane potential X)?

EX. Choose either the parameter a or b. Starting with the van der Pol oscillator, adjust your parameter until the **behavior** of the trajectories changes significantly. At what values of the parameter do you find a limit cycle?

TD1 Time delay: a new source of oscillation

A professional driver might have a 200ms (0.2 second) reaction time. If they are driving along a straight road, and they start drifting right, they will turn their steering wheel left to correct. And if they drift left, they will turn their steering wheel right. The farther they see themselves drifting off, the sharper they will correct.

This scenario can be modeled by the following. Let X(t) be the location of the car in the lane at time t, where X = 0 means the car is in the center of the lane. If X = 1, the car has drifted outside the lane to the right. If X = -1, the car has drifted outside the lane to the right.



The driver's steering may be modeled by the following:

$$\Delta X/\Delta t = -X(t - 0.2) \text{ meters per sec.}$$

The right hand side reflects a time delay. The expression X(t - 0.2) means "The location 200ms before time t." For example, if the car starts drifting to the right, at a rate of 1m/s, then we would find the following table.

When we write X(t-0.2), we are **evaluating a function** X at the input t-0.2. This is **not** X times (t-0.2).

Time (sec)	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8
Location	0	0.1	0.2	0.2	0.19	0.17	0.15	0.131	0.114
Δt (sec)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
$\Delta X/\Delta t$	0.1	0.1	0	-0.1	-0.2	-0.2	-0.19	-0.17	-0.15

Drift phase...
Before reaction

Reaction delayed
by 0.2 sec

EX. Fill out the next two columns of the table below, to indicate the position of the car when t=0.9 and t=1.0

TD2 Time delay and steep negative feedback

Now you will use a spreadsheet to explore what happens in the longer term, and with different parameters.

EX. Create a spreadsheet to explore the first 3 seconds, following the instructions in the margin. Plot the time-series for X(t) and sketch it below.

EX. Why is the formula "=B2+(C2*D2)" used in cell B3? Why is the formula "= -B2" used in cell D4? Relate these to the change equation and time delay.

EX. Now try changing the **reaction time** from 200ms to 1 second, using a 1 second drift period. Then try **sharp negative feedback**. The two new change equations would be:

$$\Delta X/\Delta t = -X(t - 1.0) \text{ and } \Delta X/\Delta t = -5X(t - 0.2)$$

Sketch the resulting time series below for these scenarios. Try to find parameters (reaction time, feedback sharpness) which yield oscillation; if you find them, plot the time series and record the parameters.

	A	B	C	D
1	**Time (sec)**	**X**	**Dt**	**DX/Dt**
2	0	0.0000	0.1000	0.1000
3	0.1000	0.0100	0.1000	0.1000
4	0.2000	0.0200	0.1000	0.0000
5	0.3000	0.0200	0.1000	-0.0100
6	0.4000	0.0190	0.1000	-0.0200
7	0.5000	0.0170	0.1000	-0.0200
8	0.6000	0.0150	0.1000	-0.0190
9	0.7000	0.0131	0.1000	-0.0170
10	0.8000	0.0114	0.1000	-0.0150

A spreadsheet as above can help. Enter rows 1 and 2 manually.

Copy-paste the cell C2 into C3, C4, etc., so the Δt is 0.1 throughout.

Enter the formula "= A2+C2" into A3, and copy-paste to cells A4, A5, etc., for the time counter. Note the formula will adjust automatically, so A4 = A3+C3, and A5=A4+C4, etc. This will fill out your time table.

Enter 0.1 in D2 and D3 for the drift phase. Enter "=B2+(C2*D2)" into B3. Enter "= -B2" into D4. Copy-paste these formulas to fill out columns B and D to get the full time series data.

Then create a time-series plot from the data in column B.

TD3 Time-delay in exponential models

EX. The old familiar change equation $\Delta P/\Delta t = P$ models a population that doubles during each unit of time Δt. Now, consider a population that doubles with a time delay, $\Delta P/\Delta t = P(t - 2)$. If $P(0) = 1$ and $P(1) = 1$ and $P(2) = 1$, make a table of $P(t)$ for $t = 1, ..., 10$.

EX. Load the *Linear Regression with Log Scaling* tool and enter your data for P(1), P(2),..., P(10). Use this to find a good approximation to P(t) by an exponential function $P(t) = C e^{kt}$.

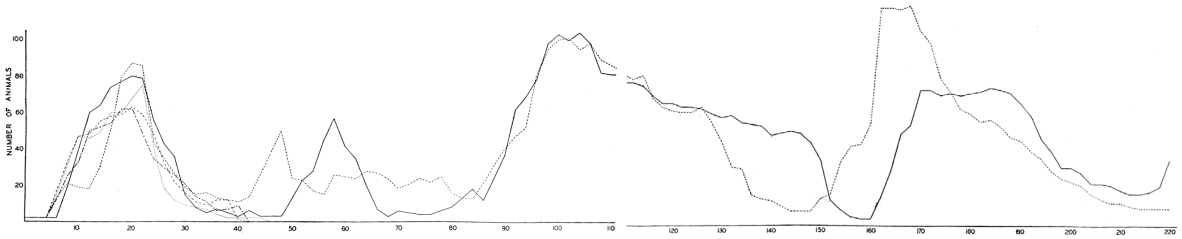
The above exercises show that a time-delayed exponential growth is still very well modeled by standard exponential growth, though the particular parameters depend on the time delay.

EX. Consider the change equation $P' = 100 - P$. Using the techniques from Lab #3, draw a phase portrait and time-series if $P(0) = 10$.

EX. Consider the equation with time delay: $\Delta P/\Delta t = 100 - P(t - 1)$. What happens if $P(0) = 10$ and $P(1) = 20$ in this system? What if $P(0) = 50$ and $P(1) = 70$? Experiment with starting values of P(0) and P(1) and describe what you find for the long-term behavior.

A spreadsheet would be very helpful here, setting up columns for P, t, DP, Dt as on the previous page.

TD4 Time-delay in a logistic model.



The graph above is taken from Figure I of David M. Pratt, *Analysis of Population Development in Daphnia at Different Temperatures*, Biological Bulletin (1943). The quote here is from the same article (p.136).

In his experiments with populations of water fleas (*Daphnia magna*), Pratt found oscillations over time, with similar features. Many of his populations rose and then crashed to extinction; but those that survived the first decline rose again about 40 days later, declined, rose again, declined again, etc. Carefully controlling the conditions, Pratt excluded an external cause of oscillation like predators or prey for his fleas. Rather, he speculates,

> "The cause of oscillation is the delay in the action of population density upon mortality and the reproductive rate... the ultimate source of oscillation is a lack of synchronization of a physiological state with the forces that provoke it."

A few years later, Hutchinson modeled this time-delay, with specific reference to Pratt's work, by the change equation

$$P' = \beta \cdot P(t) \cdot (1 - P(t - \tau)/k).$$

The parameter β is the net birth rate under ideal conditions, k the **carrying capacity**, and τ the **time delay**. The birth rate is not affected by crowding immediately. Rather, if the population exceeds the carrying capacity at some moment, the negative effect on the population will occur τ units of time later. This is **logistic growth** with **time delay**.

τ is the lowercase Greek letter **tau**. Draw it below for practice.

EX. Load the *Hutchinson time-delay simulator*. Using a birth rate β=0.02 and carrying capacity k=100, sketch the time series for four values of τ between 10 and 100.

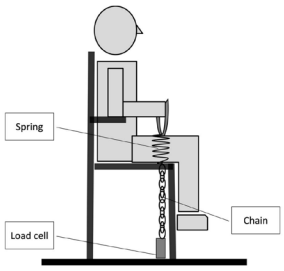
EX. Experiment with birth rate and time delay. For each birth rate, there is a critical value τ_c; if the time delay is less than τ_c, then population will approach equilibrium. If the time delay is greater than τ_c, oscillations will sustain in the long term. Tabulate the values of τ_c at different birth rates. Use this to guess a formula relating τ_c to β.

β	τ_c

τ_c = _____

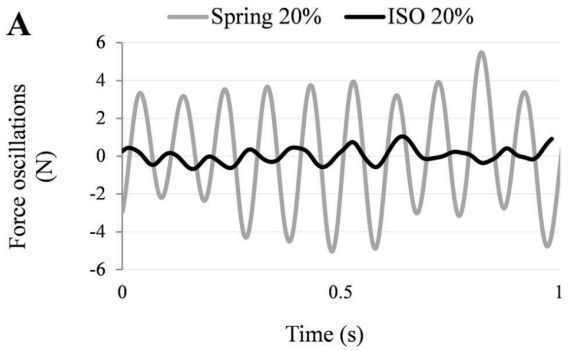
MT1 Muscle tremor

Motor neurons provide an electrical signal to muscles, making them **contract**. When muscles **stretch**, sensory neurons send a message to the motor neurons to contract. If you attempt to hold a heavy weight in a stationary position, gravity will pull your muscles to stretch, and your neurons will send a signal to your muscles to contract, and a delicate balance is needed to hold the weight stationary. This can be set up experimentally, as in the figure in the margin, by having a person attempt to hold a weight stationary while sitting in a chair with elbow bent 90 degrees.



Such experiments were conducted, recording oscillations as the person's muscles became tired. In one experiment, a spring was placed on the chain holding the weight, enhancing the oscillations. In another experiment, the chain was straight, for an "isometric" hold.

EX. Scientists refer to tremor in the **alpha band** as oscillations of 8-12 Hz, while pathological oscillations may have a frequency of 4-6 Hz. Estimate the frequency of oscillations in Figure A; do they fall in the alpha band or pathological band?



Figures 1 (schematic) and 2A, from *Budini et al., Alpha Band Cortico-Muscular Coherence Occurs in Healthy Individuals during Mechanically-Induced Tremor*, PLOS One (2014). The "20%" refers to fact that subjects were asked to sustain elbow flexor contractions at 20% of their maximal voluntary isometric contraction.

The brachialis muscle is responsible for flexing your elbow. It is about 20cm long when your elbow is bent at 90 degrees. Let L be the length of this muscle. If you attempt to keep your elbow bent at precisely 90 degrees, the length L might satisfy the change equation below.

$$L' = r\,(20 - L).$$

EX. How is the equilibrium point of the above change equation related to your attempt to keep your elbow at 90 degrees?

EX. What is the physical meaning of the parameter r? Why might r be larger or smaller for different people or in different situations?

MT2 Muscle tremor

Your ability to hold your elbow at a precise angle depends on the transmission of nerve signals; if your elbow is not at 90 degrees, it will take a moment for the sensory nerve signal to pass to a motor nerve signal to activate the muscle to pull your elbow back into position. If the signal requires τ units of time to transmit, then a more appropriate change equation incorporates this time delay.

$$L' = r\,(20 - L(t - \tau)).$$

Load the *Simple Muscle Simulator*.

The default reflex magnitude is r=50, and the default time delay is τ = 10ms in this simulator. The length L is restricted between 10cm and 30cm in the simulator, because muscles cannot get too long or short.

EX. Set the reflex magnitude to r=60. The default time delay is 10 ms. Try increasing the time delay. At what critical time delay does the system display **sustained** oscillations? What frequency are these oscillations?

EX. Start with a time delay of 20ms, and try increasing the reflex magnitude. This can happen, for example, if you are trying to counteract a weight pulling your elbow out of position. At what critical reflex magnitude does the system display sustained oscillations? What frequency are these oscillations?

EX. The brain normally suppresses the sensitivity of peripheral reflexes. In some **stroke** patients, this suppression is lost, and the person's muscles will react too strongly (hyperreflexia). **Parkinson's disease** is completely different, and often causes a time-delay in the transmission of nerve signals.

Using the simple muscle simulator as a guide, how might the **frequency** of tremor distinguish patients whose tremor arises from Parkinson's disease from those whose tremor is caused by hyperreflexia?

IGO1 Insulin-Glucose: Ultradian oscillations

In Lab 1, we studied the minimal model for the insulin-glucose system. The two state variables are G (concentration of glucose in the bloodstream) and I (concentration of insulin in the bloodstream). The minimal model included a positive influence of glucose on insulin (glucose "tells" the beta cells to release more insulin) and a negative influence of insulin on glucose (insulin "tells" muscle and fat cells to take more gluose).

The equations here are the same as those in Lab #1, except that we have replaced the discrete time model $\Delta G/\Delta t$ and $\Delta I/\Delta t$ with the derivatives G' and I'.

Another ingredient in the insulin-glucose system involves the alpha cells in the pancreas. When insulin is low, the alpha cells release a hormone called glucagon; the glucagon tells the liver to release glucose into the bloodstream. This is important so our cells have fuel (glucose) even when we are not eating, e.g., sleeping. With this new element in our system, we add one more term to our glucose change equation.

$$G' = m + \frac{\alpha}{1+e^{kI-c}} - s\,I\,G \qquad \text{Liver production of glucose} = \frac{\alpha}{1+e^{kI-c}}$$

$$I' = q\,b\,\frac{G^2}{1+G^2} - \gamma\,I$$

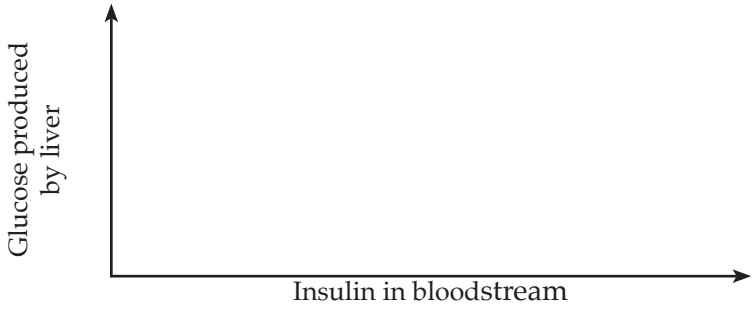
In Desmos, you can graph equations like

$$\frac{x^2}{1+x^2} - y = 0$$

That would help with the I-nullcline.

EX. Use Desmos to explore the new term $\frac{\alpha}{1+e^{kI-c}}$.

With the parameter values $\alpha = 1$, $k = 2$, $c = 2$, sketch the graph below.

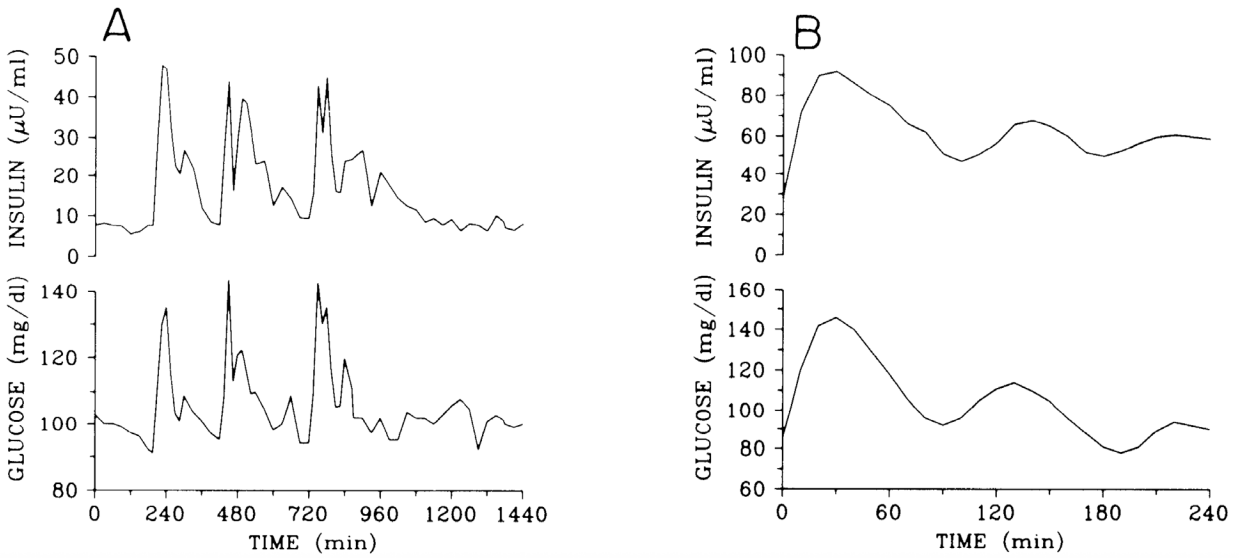


EX. Load the *Insulin Glucose Regulation* simulator. We explored this in Lab 1, but without the new parameters and time delay. Begin with the following parameters:

$$m = 2,\quad s = 7,\quad q=3,\quad B = 2,\quad \gamma = 5,\quad \alpha = 1,\quad k = 2,\quad c = 2.$$

Experiment with the parameters m and α. What value of α would maintain blood glucose concentration in the safe range, whether m=0 (no glucose intake, e.g., when sleeping) or m=3 (constant high intake)?

IGO2 Insulin-Glucose: Ultradian oscillations



Plots from Figure 1 of *Computer model for mechanisms underlying ultradian oscillations of insulin and glucose,* by Jeppe Sturis et al., in American Journal of Physiology-Endocrinology and Metabolism (1991).

The figures above display insulin and glucose concentrations under two circumstances. Figure (A) illustrates a person who eats three meals in a day. Figure (B) illustrates a person who undergoes a "glucose challenge", where they consume a large amount of glucose at the beginning of the time period and none afterwards.

EX. In Figure (B), it seems the insulin and glucose concentrartions are oscillating while they return to equilibrium. Estimate the **period** of oscillation shown in the data.

The period of oscillation is approximately _____ minutes.

EX. Use the *Insulin Glucose Regulation* simulator to experiment with time delays. There is a time delay for glucose to have an effect on insulin production. There is also a time delay for insulin to have an effect on the liver to release glucose. What time delays most closely match the oscillation you see above? Which of the two time delays seems most essential to produce such oscillations? Explain how you came to this conclusion.

Osc7 Oscillations: Synthesis

EX. In this lab, we have seen three sources of oscillation. Describe these three sources, and give one example of each, including state variables and change equation.

1.

2.

3.

EX. Oscillations can sometimes "drive" oscillations. Consider a system with state variable X, undergoing a change equation like

$$X' = O - kX.$$

Here O is an oscillating variable, such as $O(t) = \cos(t)$. Describe a situation and state variable that could plausibly be modeled by such an equation. Then draw a time series plot for how you think the quantity X would behave, given a starting value of $X(0) = 0$, and paramaters $k=0$ and $k=0.1$.

Osc8 Oscillations: Synthesis

A **Hopf bifurcation** is a situation in which there is a system with a parameter p, and

1. When p is smaller than a critical value p_c, the system tends towards a stable equilbrium point.

2. When p is greater than p_c, the stable equilibrium becomes unstable, and system exhibits stable long-term oscillations

EX. Consider a Hopf bifurcation in a system with two state variables X and Y. Draw pictures of trajectories in state space when $p < p_c$, and when $p > p_c$.

EX. Give an example from this lab in which you saw a Hopf bifurcation. Describe the system, its state variables, and the parameter with critical value.

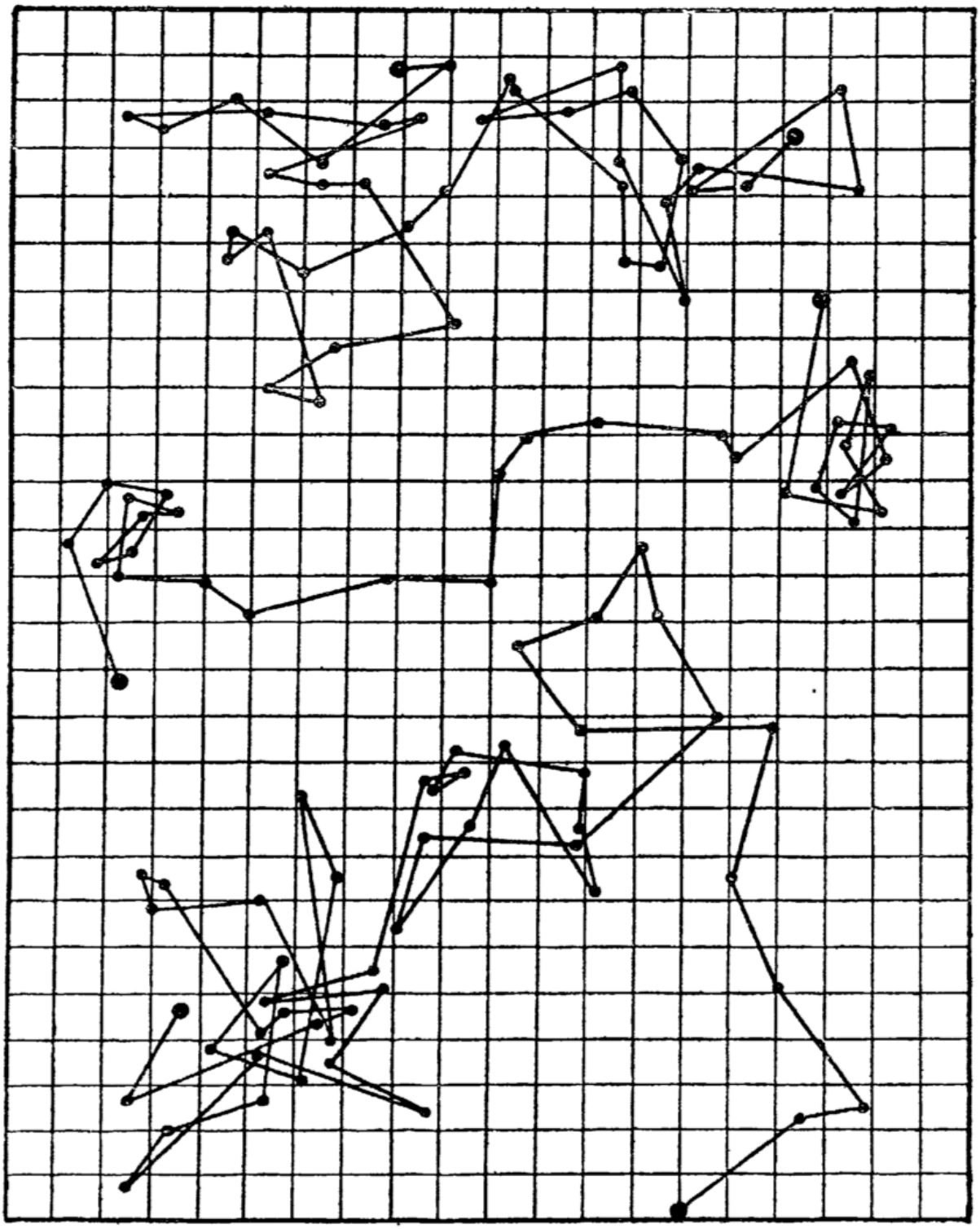


Figure 5 from Perrin's *Mouvement brownien et grandeurs moléculaires*. Perrin observed the random motion (Brownian motion) of particles (gamboge, a tree resin used for yellow pigment), recording their position every 30 seconds. Afterwards, he connected the positions by line segments; three trajectories are shown above in his figure. The grid squares are 50 microns (1 micron = 1 μm = 10^{-6} meters) in side length.

Laboratory 5
Randomness

Until now, all of our models—written as change equations—have been **deterministic**. This means that the current state of the system determines the future state of the system. The future is determined by the current state and the change equations.

When our models inevitably fail, we can explain the failure by saying that the real living world is complicated. We can try to do better, fitting our model to more data, elaborating our model to better resemble reality, and we can go back to the lab or the field.

This lab introduces a fundamentally different approach to modeling, which strays from determinism to incorporate a controlled amount of randomness. The unrealistically precise **predictions** of a deterministic model (e.g., there **will** be 5000 bacteria after 3 hours) are replaced by looser **expectations** of a **stochastic** model (e.g., we **expect** there will be 5000 bacteria after 3 hours, and would be **surprised** if there are more than 8000 or fewer than 2000).

There are good reasons to put randomness into a model. One is a perceived futility in determinism. Theoretically, one could perfectly deterministically model a coin toss, from the position and velocity of the coin and coin-flipper's hand, the exact contours and mass of the coin, the temperature and flow of the air, etc. But that is not worth the trouble, if your interest is not in the physics of coin tosses!

Another reason is to understand **robustness**. You may have a very nice deterministic model, change equations that seem to describe reality pretty well. But will a bit of uncontrollable jitter make your model's predictions fall apart? Is your model **robust to noise**, holding up to life's constant jittering in a useful way? We can test robustness by adding a bit of noise... adding a stochastic term to a deterministic model.

A final argument to study stochastic models is that they are the foundation for understanding temperature and diffusion. On the opposite page are the random motions of little particles under a microscope. Understanding them through a stochastic model allowed Perrin (following an idea of Einstein) to determine **Avogadro's number**. We can count things (atoms and molecules) that we cannot see, thanks to stochastic models.

A **stochastic model** is a model which incorporates some randomness. We will soon add **stochastic terms** to our change equations, e.g.,

$$X' = 2X - \varepsilon,$$

where ε might designate a "**stochastic term**," like a randomly chosen number between 0 and 100. This would describe a typical exponential population growth, complicated with some random additional number of deaths during each unit of time.

Avogadro's number is about 6.022×10^{23}. This is the number of atoms of carbon in a pure sample of 12 grams of Carbon-12 (the isotope with 6 protons and 6 neutrons).

RC1 From oscillations to...

Before going into randomness, we take a moment to examine **chaos**. Please remember that **chaos is NOT the same as randomness**! Chaos can be wild and confusing, but it arises from deterministic systems.

The discrete logistic model is the simplist example where chaos can be found. In this model, we consider a population P that changes over time, in **discrete time** intervals $\Delta t = 1$. The change equation should look familiar from Lab 3.

$$\Delta P / \Delta t = \beta P (1 - P).$$

In the discrete logistic model here, we have made the carrying capacity 1, for simplicity. The reader may consider P = 1 to mean a population of 1 million bacteria, for example.

EX. What are the equilibrium points for the above change equation? In other words, at what values of P will $\Delta P / \Delta t = 0$?

The only parameter in our model is β, which we think of as a birth rate, or relative growth rate, for our population, if crowding were ignored.

EX. Set up a spreadsheet, with columns for t, P, Δt, and ΔP, with starting values $t = 0$, $P = 0.5$, and $\Delta t = 1$ throughout. Use spreadsheet formulas to find the values of P for time $t = 0, 1, ..., 30$, with the parameter choices $\beta = 1.5, 2.25, 2.5$, and 2.83. Describe qualitatively how the population behaves for these four parameter values.

RC2 Chaos

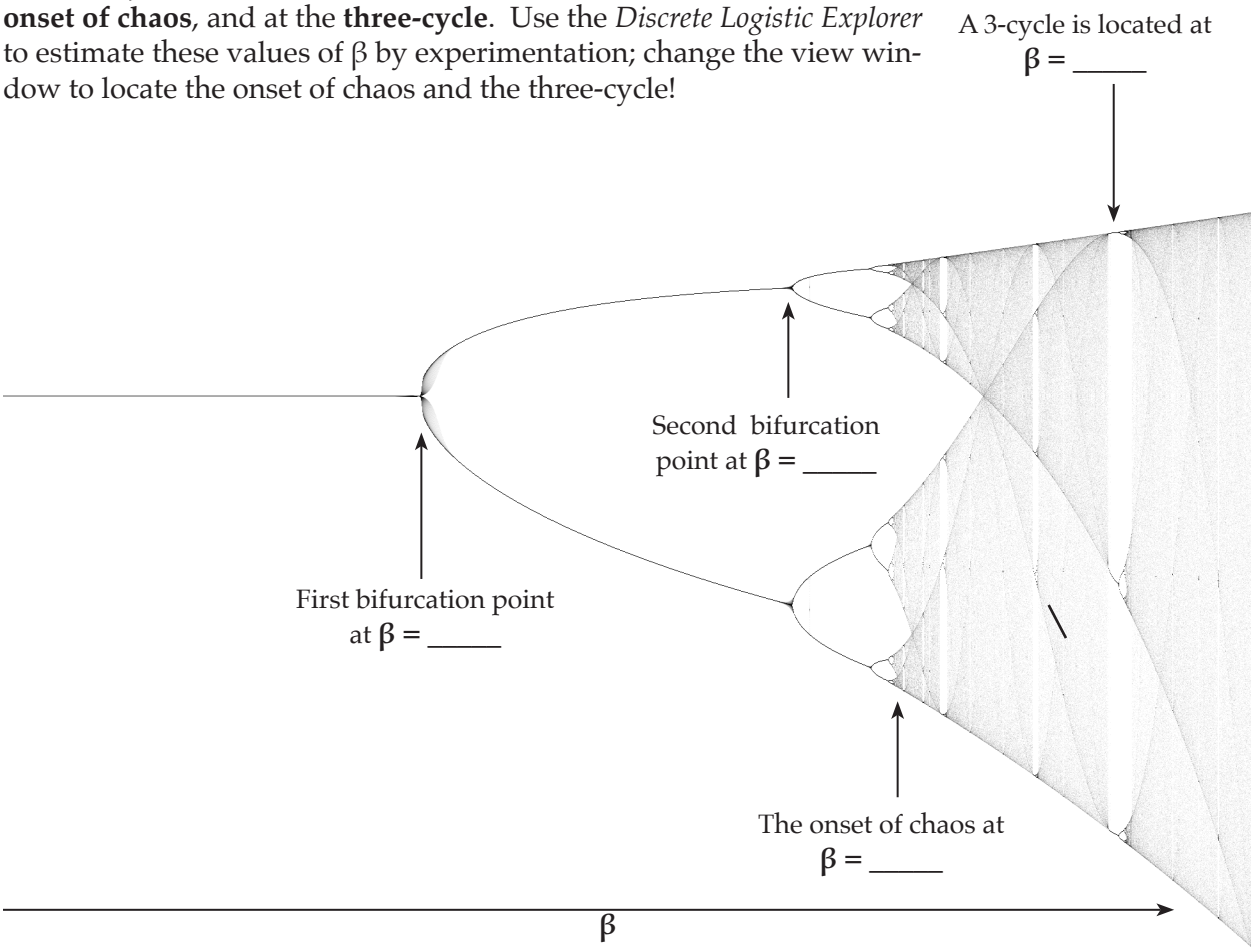
EX. Load the *Discrete Logistic Explorer*, and explore what happens when $\beta = 3.0$, and you choose starting values like 0.5 or 0.501 or 0.7 or 0.3. How do small/large changes in the starting value affect long-term values? Write a sentence or two describing your findings, in light of Lorenz's description of chaos in the margin.

Lorenz described **chaos** as "When the present determines the future, but the approximate present does not approximately determine the future."

Source: Unpublished recollection by Christopher M. Danforth.

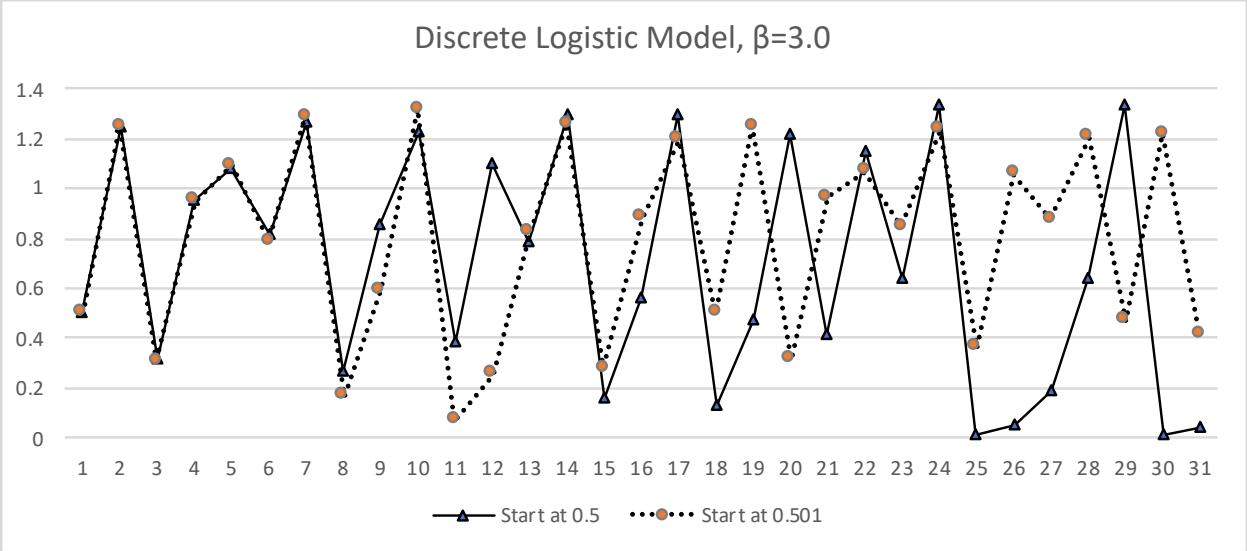
The *Discrete Logistic Explorer* allows you to create a plot like the one below. The horizontal axis is the birth rate β. At each birth rate β, you can see the long-term behavior by looking at the plot above β. When β is small, you should find a tendency towards equilibrium. When β passes the first bifurcation point, you should find that P oscillates between two values. After the next bifurcation point, P oscillates between four values. Then 8, 16, etc., until the behavior of P becomes chaotic.

EX. Label the high-resolution bifurcation diagram below, so that the values of β are clear at the **first** and **second bifurcation points**, at the **onset of chaos**, and at the **three-cycle**. Use the *Discrete Logistic Explorer* to estimate these values of β by experimentation; change the view window to locate the onset of chaos and the three-cycle!



RC3 Chaos is not randomness

The following time-series plots arise from the birth rate $\beta = 3.0$ in the discrete logistic model, $\Delta P / \Delta t = \beta P(1 - P)$. The solid line starts at the value $P = 0.5$. The dotted line starts at $P = 0.501$. The difference between the two plots is invisible until t=8, when they start to drastically differ.

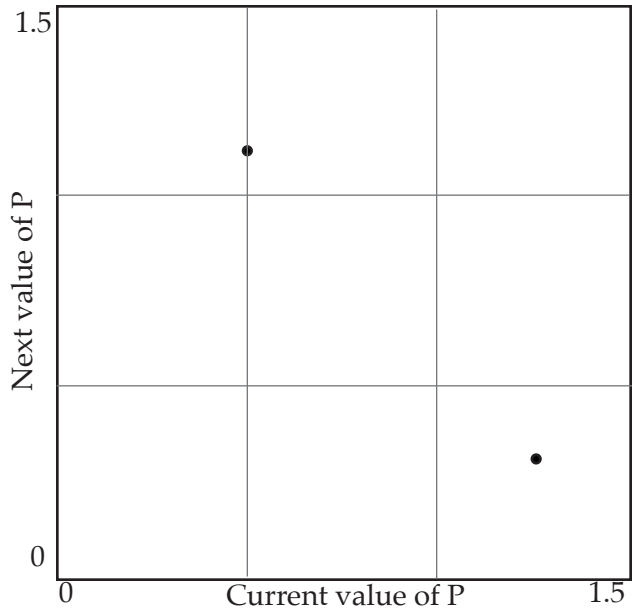


These plots exhibit **two characteristics of chaos**. One characteristic is that small differences at one time lead to vast differences in the long term. This is the so-called **butterfly effect**.

Lorenz found chaos in the equations related to weather prediction. In 1972, he gave a talk titled, "Predictability: Does the flap of a **butterfly**'s wings in Brazil set off a tornado in Texas?"

The next characteristic is **determinism**: despite the chaotic bouncing in the above time series plots, there is a strong connection between the current state of the system and the "next" state of the system.

EX. Choose either the solid line or dotted line above. For each time value t, place a dot at coordinates (P(t), P(t+1)). We have started the plot below with dots at (0.5, 1.25) for t=1 and (1.25, 0.3) for t=2. **Describe the pattern** you see in the plot, after placing 20 dots.



The visible pattern is...

RC4 A first look at randomness.

What would real randomness look like? Randomness comes in many flavors, as we shall see. To get started, we consider the following stochastic model. We have a single state variable P, as before. At each time step, P goes up or down randomly, by choosing a random "change" **uniformly** between -1 and 1.

$$\Delta P / \Delta t = \varepsilon, \text{ with } \varepsilon \textbf{ random, } \text{uniformly between -1 and 1.}$$

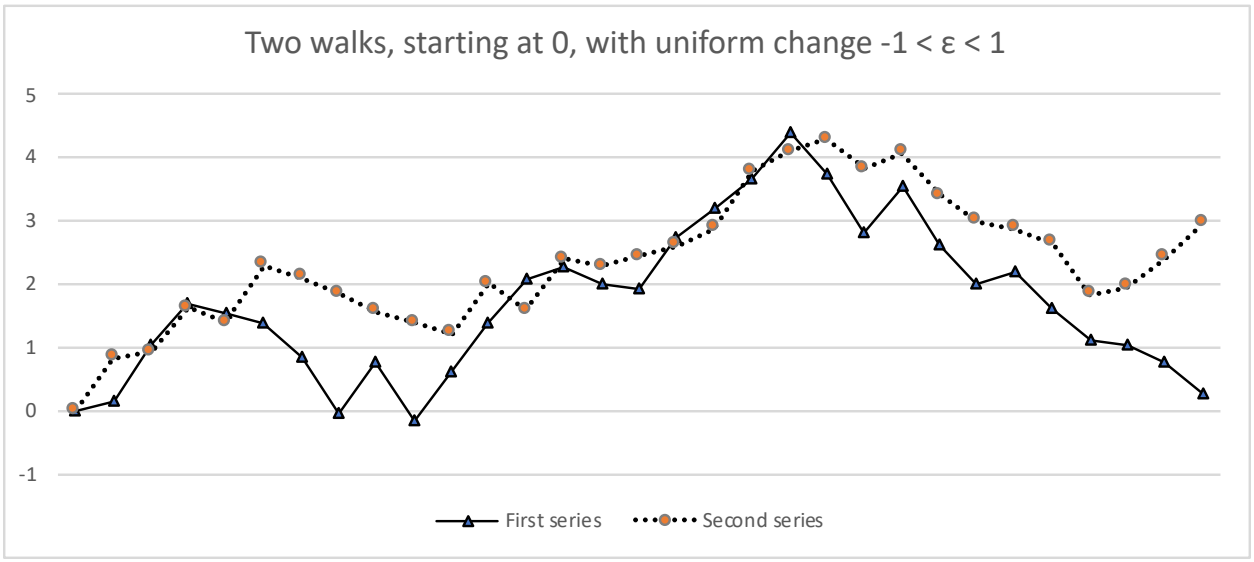
Uniformly random means that there is no particular preference for any range of numbers within -1 and 1. For example, there is a 50% chance that ε is between 0 and 1, and a 50% chance of choosing a number between -1 and 0. There is a 25% chance of choosing a number in each interval (-1,-0.5) and (-0.5, 0) and (0,0.5) and (0.5, 1).

EX. For this uniform random number ε, what is the chance that ε is between 0.2 and 0.4? Between -0.35 and -0.3?

EX. The result of choosing ε uniformly randomly at each time step is displayed below, starting with P = 0. In fact, we have run this experiement twice, choosing new random numbers each time, to generate two time series. Contrast the plots below with the chaos on the previous page. What **visible features** distinguish chaos from randomness?

For simulations, computers have sophisticated random number generators. For example, the formula `=RAND()` in Excel or Google Sheets generates a random number uniformly between 0 and 1.

The formula `=2*RAND()-1` generates a random number uniformly between -1 and 1.



RG1 Linear growth with random rate

Recall that the radius of a tree increases each year, producing a series of **tree rings** reflecting its age. This **radial growth** is approximately linear; using cross-sections as displayed here, you might estimate the average rate of growth to be 0.8 mm/year. Thus if R is the radius of the tree, in millimeters, R is governed by the change equation $\Delta R/\Delta t = 0.8$.

Image from Figure 1B of Carroll et al., *Millenium-Scale Crossdating and Inter-Annual Climate Sensitivities of Standing California Redwoods*, in PLOS One, (2024). Three dots in ring from 1960. Additional dots mark decades. **Black square is 1mm x 1mm**.

But as shown in the figure above, the radial growth of a tree changes from year to year. A **stochastic** change equation is

$$\Delta R/\Delta t = \varepsilon, \text{ with } \varepsilon \textbf{ random.}$$

To make this meaningful, we have to consider the possibilities and probabilities for this **random variable** ε

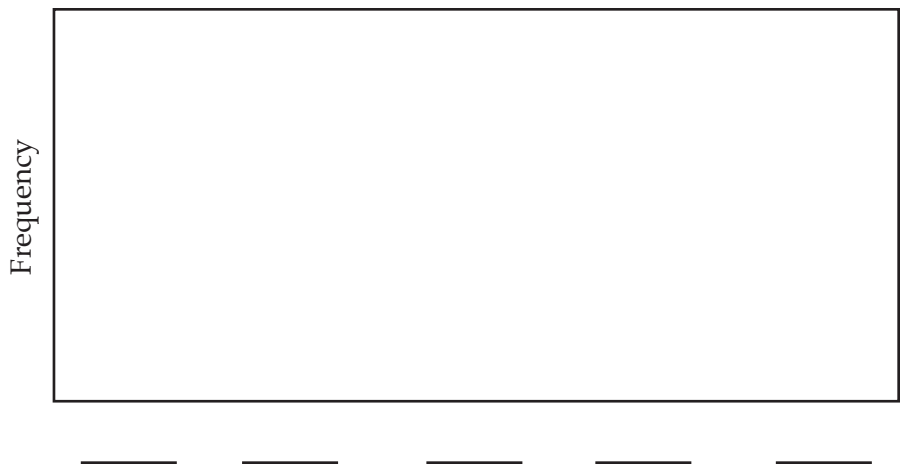
EX. Looking at the above figure, using the black square as a reference, estimate the minimum and maximum width of a tree ring.

Minimum width ≈ _____ and maximum width ≈ _____

EX. Load the *Tree Ring Simulator*. This will simulate the radial growth of a tree, if each year's growth (tree ring width) is chosen uniformly randomly between a given minimum and maximum. Using your values of minimum and maximum, how much total growth do you **expect** to find after 50 years?

EX. Run the experiment 20 times, to create a **histogram** of the total growth found. Use 5 bins, with your expectation in the central bin.

Bin	Count



_____ _____ _____ _____ _____

RG2 Exponential growth with random rate.

E. Coli are grown in a petri dish. Under controlled conditions, you expect the population to grow exponentially, according to the equation

$\Delta P / \Delta t = 0.03\ P$, where time is measured in minutes.

EX. If you start with 1000 bacteria in the dish, describe P(t) as an exponential function of t, in this ideal circumstance. Estimate the doubling time, using the techniques from Lab 2.

P(t) = _____ Doubling time = _____ minutes.

EX. Even though you try to control their environment, precise control is never possible in the lab. As a result, during "lucky" and "unlucky" minutes, the population grows according to the equations:

Lucky: $\Delta P / \Delta t = 0.04\ P$ Unlucky: $\Delta P / \Delta t = 0.02\ P$

Give a formula for the number of bacteria, starting with 1000 as before, after they have x lucky minutes and y unlucky minutes. Hint: how many times do you multiply P by 1.04? How many times do you multiply P by 1.02?

P(x,y) = _____

EX. Use the *Rapid Coin Flipper* to generate 20 fair coin tosses. Interpreting these as lucky and unlucky minutes, draw a time-series plot of the population over time, starting with 1000 bacteria.. Use a **semilog** plot, as shown below.

For plot, it may be helpful collect your population data in a spreadsheet with columns for time t and population P.

EX 5.14. If lucky and unlucky minutes are equally likely, how many bacteria do you **expect** after 30 minutes? Use the *Rapid Coin Flipper* and share with classmates to provide a range of values.

Flip1 Probability: Random variables and expectations

Formally speaking, a **random variable** consists of a set of possible outcomes, each with a probability. If there are finitely many possible outcomes, we can describe a random variable with a table.

When the outcomes are numbers, we can talk about our **expectation** for the random variable, which is a **weighted average** of the outcomes. If our random variable is called R, then our expectation is written **E**(R) with the boldface **E** standing for the word expectation.

E(R) = The sum of all possible (outcome × probability).

If R is the random walk, with outcomes 1 and -1, each with probaility 50%, then **E**(R) = (0.5)(1) + (0.5)(-1) = 0.5 - 0.5 = 0. Moving to the right and moving to the left are equally likely, and our "expectation" is that we end up at zero. Note that our expectation is not a real outcome! It is just a way of describing an average of possible outcomes.

EX. Let R be a fair die, with outcomes 1,2,3,4,5,6. What are the probabilities, given that the die is fair? What is the expectation **E**(R)?

Prob(1) = Prob(2) = ⋯ = Prob(6) = _____

E(R) = _____

EX. Consider a random variable R, guided by a biased coin. The outcomes are 10 and -1. The outcome -1 has probability 90%, and the outcome 10 has probability 10%. What is the expected outcome?

E(R) = _____

EX. A mold spot is circular with starting radius 10mm and area A. Every day, the radius has a 50% change of getting 1 mm larger, and a 50% change of getting 1mm smaller. What is the expected radius on the next day?

What is the area A on the starting day, when the radius is 10mm? What is the expected area on the next day? This might be surprising!

The **fair coin** is a random variable with table below

Outcome	Probability
Heads	50% or 0.5
Tails	50% or 0.5

If a fair coin is used to determine a random walk, moving +1 for heads and -1 for tails, then each step of the walk is a random variable.

Outcome	Probability
1	50% or 0.5
-1	50% or 0.5

Flip2 Probability: Expectations and repetition

What happens if we flip a coin two times in a row? There are four possible outcomes. Heads then heads, heads then tails, tails then heads, or tails then tails. We abbreviate them HH, HT, TH, TT. Notice that we keep track of time, and consider HT and TH are different outcomes. If our coin flips are **independent** (the first coin toss doesn't affect the second), then these outcomes are equally likely.

What if we flip a coin three times in a row? There are eight possible outcomes, each with probability 1/8, or 12.5% or 0.125. These are displayed in the margin. If coin tosses determine a numerical outcome, we can compute our expectations.

For example, suppose that we start at 0, and each Head pushes us to the right by 1, and each Tail pushes us to the left by 1. Let L be the final location, **a random variable** with four outcomes and probabilities.

Location	Coin tosses	Probability
3	HHH	12.5%
1	HHT or HTH or THH	37.5%
-1	HTT or THT or TTH	37.5%
-3	TTT	12.5%

EX. What is **E**(L), where L is the random "location" given above?

EX. Start at zero, and suppose that each time the coin lands on heads, you move one unit to the right. And each time the coin lands on tails, you start back at zero. Tabulate the possible locations after three coin tosses in a table, corresponding coinc tosses, and probabilities. If R is the resulting random variable, what is the expected value **E**(R)?

Location (R)	Coin tosses	Probability
0		
1		
2		
3		

EX. Suppose that the coin is now unfair, with a 1/3 chance of landing on heads. Let N_H be the random variable which simply counts the number of heads (so coin tosses like HTH would yield $N_H = 2$). Tabulate the possible outcomes and probabilities for N_H. What is the expected value **E**(N_H).

Flipping the fair coin twice yields the following random variable.

Outcome	Probability
HH	25%
HT	25%
TH	25%
TT	25%

Flipping the fair coin three times yields the following random variable.

Outcome	Probability
HHH	12.5%
HHT	12.5%
HTH	12.5%
THH	12.5%
HTT	12.5%
THT	12.5%
TTH	12.5%
TTT	12.5%

E(R) = _____

Flip3 Sharks and Tuna: Tuna Lifespan

We return to our favorite ocean creatures, the shark and the tuna. They swim around in the ocean, and when a tuna meets a shark, CHOMP. We have studied models of shark and tuna, which incorporate their separate birth/death rates, carrying capacities, interactions, and shark appetites. But we have not yet considered a question of vital importance for a tuna: how long might a tuna expect to live?

EX. Suppose that by the end of each year, a tuna has a 50% chance of being eaten by a shark. Tabulate the possible life-spans of a tuna, and their corresponding probabilities. Hint: consider being eaten by a shark as a coin-toss, and complete the following table. (Note we have "rounded up" the lifespan.)

Lifespan (yrs)	Coin tosses	Probability
1	T	50%
2	HT	25%
3	HHT	
4	HHHT	
5	HHHHT	
6	HHHHHT	

Note that after the tuna dies, we do not have to flip a coin. But one could play this game by flipping a coin 6 times. All outcomes beginning with "T" yield a lifespan of 0 years. All outcomes beginning with "HT" yield a lifespan of 1 year.

EX. Using this table, what is the **expected lifespan** of a tuna? To answer this quesetion, express (Lifespan × Probability) as a fraction in each line of the table, and find the pattern. Add at least 10 terms (lifespans up to 10 years) to get a good estimate of expected lifespan.

EX. Out of 1000 tuna, how many do you expect to survive for 5 years or longer?

EX. In a safer region, a tuna has a 10% chance of being eaten by a shark each year. What is the expected lifespan of the tuna there (assuming their only cause of death is sharks)?

Flip4 Growth and collapse

Growth may be a smoothly controlled process in the lab, but in nature there are inevitable (if infrequent) disasters. Consider the following **process**, for a state variable X and its change over time:

1. X starts at zero.
2. Each "good moment," X increases by 1.
3. Each "bad moment," X collapses back to zero.

EX. Describe a situation, with a single quantity X, which may be reasonably modeled by the process above.

EX. Imagine good moments and bad moments correspond to Heads and Tails from coin tosses. If your sequence of coin tosses is HTTHTTHTTHTHHHHTTHHTTHHHTHHTHHHTHHHH, then what is the final value of X and why?

EX. Run the *Growth and Collapse Simulator*, with 90% probability of growth. This runs the simulation for 100 time units, 500 times in a row (effectively 50,000 coin tosses!). Sketch the resulting histogram below.

EX. Experiment with parameters in the *Growth and Collapse Simulator*. Describe consistent patterns you notice about the bar heights in the histograms.

Yule1 The Yule birth process

Now we revisit our old friend, a dish of *E. Coli*. We have studied a pure exponential model of growth, and more recently an exponential model of growth where the birth rate has a stochastic (random) element. Here we study an exponential model of growth where the **randomness is built into the individual**.

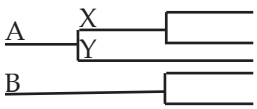
Modeling populations at the individual level is called **agent-based modeling**.

Begin with 10 bacteria. Suppose that, each minute, each bacterium has (independent of each other!) a 5% chance of division.

EX. After the first minute, what is the probability that you still have 10 bacteria, i.e., none have divided? Hint: a 5% chance of division implies a 95% chance of no division. Use a calculator and the hint in the margin.

If p is the probability of something happening once, then p^2 is the probability that it happens in two independent cases. And p^3 is the probability that it happens in three independent cases.

EX. Use the *Rapid Coin Flipper*, with Heads representing division (5% probability), to predict the outcome for the 5 bacteria after one minute (5 coin tosses). Then repeat, with as many coin tosses as necessary, to **track the divisions for 5 minutes**. Draw a tree, with time proceeding from left to right, to display this information. Highlight one lineage within this tree (the descendants of one starting bacterium).



A sample tree, starting with 2 bacteria, A and B. A divides first, into X and Y. Then X divides at the same time as B, while Y never divides. The result is 5 bacteria.

EX. Consider the related model, in which **precisely** 5% of the bacteria divide during each unit (minute) of time. (In this model, you are allowed to have fractional bacteria, like 10.5 bacteria.) If the starting population is 10 bacteria at t=0, what is the formula for the population at time t? This should exhibit exponential growth!

$P(t) =$ _____

EX. Now, consider what this would look like on a semilog plot. What is the formula for $\log_{10}(P)$ as a function of t? It should be linear!

$\log_{10}(P(t)) =$ _____ t + _____

Yule2 Stochastic birth and death process

The *Yule Process Simulator* carries out a stochastic process, allowing each cell to divide with one probability, and die with another probability (deaths occur before divisions) during each time interval.

See G. Udny Yale, *A mathematical theory of evolution, based on the conclusions of Dr. J. C. Willis, F.R.S.*, in the Philosophical Transactions of the Royal Society of London. Series B (1924).

EX. Enter a division probability of 5%, and 0% death probability, and starting population 10. The simulator will show the results of numerous trials, with time series for P(t). Compare the results in the simulator to the exponential growth you might expect. Focus on the semilog plot, and the slopes you find in the simulator.

Rather than modeling the division of bacteria, Yule was interested in **speciation**: the evolutionary events when a population of one species splits into two species.

EX. Experiment with death probabilities and starting populations. What phenomena appear in the stochastic *Yule Process Simulator* that you cannot find in an exponential model? Describe these phenomena and when they may occur.

EX. In the laboratory, you carefully prepare 20 wells with 10 bacteria in each well. They are kept in identical conditions, and allowed to grow for 2 hours. Your colleague then looks at the wells for the next step in the experiment, and notices that some wells have twice, or even three times, as many bacteria as others! They say that you must have messed up in your preparation. How would you respond based on your experience in the above exercises?

Above: A 96-well plate, a dependable workhorse of the lab. There are 8 rows (A-H) and 12 columns (1-12) for 96 samples.

GD1 Genetic drift

When we encounter **evolution**, we often learn first about **natural selection** as the mechanism. According to this mechanism, if a heritable trait offers a **fitness** advantage, the organisms with this trait will be more likely to reproduce and pass the trait onto its offspring, gradually causing the trait to be more common. What is necessary is variation in heritable traits, and differences in reproductive success.

In evolutionary biology, **fitness** refers to the probability of having surviving offspring. So fitness does not mean "being stronger." It could mean better hiding from predators, caring for eggs, etc.

Genetic drift is about what happens in the "neutral" setting, where there is variation in heritable traits, but **no difference** in reproductive success. This is another mechanism for evolution, which must be studied alongside natural selection.

Banana slugs (*Ariolimax columbianus*) are wonderful large yellow slimy organisms which can be found in the redwood forests of California and Oregon. Some have spots and some do not. It has been hypothesized that the spots are a heritable trait, and may offer a fitness advantage via **cryptic coloration**, hiding them from predators. To study this, one should compare this hypothesis of fitness advantage to the **neutral hypothesis** where spots have no effect on fitness.

See "Spotted Banana Slugs, *Ariolimax columbianus*, and Canopy Cover," a poster by Sash Milstein at ideaFest 2023. https://digitalcommons.humboldt.edu/ideafest2023/14/

Consider a population of 50 banana slugs, among which 10 have spots. This population is in equilibrium; each year, each banana slug produces two surviving children (for a total of 150 slugs). But 100 banana slugs also die each year, bringing the total back down to 50. The deaths are completely random. Spotted slugs always have spotted offspring. Nonspotted slugs always have nonspotted offspring.

Banana slugs are hermaphrodites with fascinating mating habits. After impregnating each other (both can get pregnant after mating), they lay up to 30 eggs, some of which survive to maturity.

EX. After one year, you have 50 banana slugs again. What is the **fewest** you could find with spots? What is the **most** you could find with spots? How many would you **expect** to see with spots and why?

EX. Imagine now that a virus kills all but 5 banana slugs, 2 with spots and 3 without. If all 5 slugs have two surviving children (making 15 slugs total), and then 10 die, could the remainig slugs all have spots? Draw a diagram to illustrate how.

GD2 Genetic drift: The Wright-Fisher Model

Load the *Genetic Drift Simulator*. We stay with the illustrative example of spotted and not-spotted banana slugs. The simulator will progress through 300 generations of births and deaths, where the total population remains the same. One can track the subpopulations of spotted and nonspotted banana slugs.

Our model here is a version of the Wright-Fisher model, a common starting point for studies of genetic drift.

One typically learns about this in the setting of **allelic frequency**, but we are avoiding such important genetic technicalities.

EX. Begin with 70% spotted and 30% nonspotted slugs. Beginning with a total population of 100, study what happens in the simulation. Try clicking the "Simulate" button multiple times. How often does **fixation** occur, where at the end there is only one type of banana slug. Answer with an estimated frequency (like 10%? 90%) of fixation, based on many simulations.

EX. How does the initial population affect the likelihood of fixation? Explain with a few precise examples.

EX. A researcher finds that the banana slugs of Corvallis, Oregon are all spotted, while the banana slugs of Felton, California are all nonspotted. Provide a **neutral** explanation in terms of genetic drift. What factors would make such a neutral explanation more or less likely, based on exploration with the *Genetic Drift Simulator*?

Temp1 Temperature: The kinetic theory of gases

Temperature is something we can all feel, because we have specialized neurons to sense **temperature**. We can measure temperature with all sorts of thermometers. What we feel and measure as temperature was mysterious for a very long time, though even in the 1680s, Robert Hooke argued (correctly!) that

> *Now Heat, as I fhall afterward prove, is nothing but the internal Motion of the Particles of Body*

From Hooke, *Lectures on Light*, read in May 1681, and published posthumously in 1705.

It would take almost 200 years for this to be made precise, when Maxwell brought probability into physics. This is what we do here, to understand this thing called temperature.

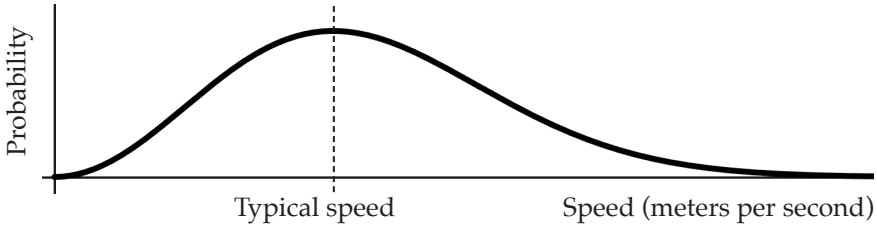
Indeed, we now know that stuff is made of molecules. In a gas, these molecules are flying, spinning, vibrating, all over the place. The temperature of the gas reflects all that wild motion. We focus on the **speed of molecules** here.

According to Maxwell and Boltzmann, each molecule in a gas is going through a random walk. At any moment, it is moving in a random direction in space. And, it is moving at a random speed. This random speed is **not uniform** (it is **not** a "random number between 0 and 100 miles per hour"). Instead the speed probabilities depend on temperature according to the following **continuous probability distribution**.

$$\mathbf{P}(v) = C \left(\frac{m}{2k_B T}\right)^{3/2} v^2 e^{-mv^2 / 2k_B T}.$$

To convert Celsius to Kelvin, add 273. So 20°C = 293°K. Kelvin is used because 0°K is "asbolute zero," a theoretical state in which everything is stationary.

Here C is a constant which won't concern us. The variable v is the speed of a molecule of gas, and m is the mass of the gas molecule. The most interesting constant is k_B, called **Boltzmann's constant**. And T is the temperature, in degrees **Kelvin**.



The peak of the probability distribution (the curve above) locates the most frequently found speed, which we call the **typical speed**.

What we call the typical speed is what statisticians call the **mode** of the random variable. The **average speed** is a bit different, but the two are proportional in this context.

EX. Look up Boltzmann's constant and the mass of an oxygen molecule O_2 in **kilograms**. Convert room temperature to degrees Kelvin. Use Desmos to graph the function **P**(v), and find the typical speed of an oxygen molecule, in meters per second and miles per hour.

The typical speed of an oxygen molecule at room temperature is

_____ m/s, or _____ miles per hour.

Temp2 Temperature and the typical speed of molecules

EX. Keeping Desmos open, allow the temperature parameter T to vary between 150°K and 300°K. Collect data in the margin, to relate the temperature to the typical speed of a molecule. Using a log-log plot (in the *Data Plotter with Log Scaling*), find a power function relating the typical speed of an O_2 molecule to the temperature T.

Typical speed = _____× T————

In Desmos, click the wrench icon to adjust the y-axis range to be very very small!

Temperature	Typical speed

EX. Ozone is the molecule O_3, so its mass is 3/2 the mass of typical oxygen gas O_2. How does the typical speed of ozone molecules compare with the typical speed of oxygen molecules at the same temperature?

EX. Summarize the relationship between the temperature of a gas, the mass of a gas molecule, and the typical speed of a gas molecule.

EX. Gas molecules do not fly in straight lines forever. They frequently bounce off each other, in random directions. This is why we will model the situation with a random walk. Let Δt be the average amount of time each molecule travels between collisions. How do you think that Δt relates to the density of molecules N (the number of molecules per liter)? How do you think Δt relates to the temperature T of the gas? Explain your answers.

Temp3 Temperature and equilibria

Consider the **bistable** system, with a quantity X and change equation

$$\Delta X/\Delta t = X - X^3.$$

Recall that a one-variable system is **bistable** if it has two stable equilibrium points.

EX. Draw the phase portrait for this system, showing all three equilibrium points (with values of X) and their stability.

EX. With starting value X = -0.1, describe the long-term behavior.

Now imagine the system has a stochastic component, which leads to a change equation

$$\Delta X/\Delta t = X - X^3 + \varepsilon, \text{ where } \varepsilon \text{ is a random velocity.}$$

EX. Imagine ε is chosen by a coin flip: Heads means $\varepsilon = 0.1$, tails means $\varepsilon = -0.1$. If the system starts at the equilibrium point X = -1, could it end up near the equilibrium point X = 1? What if it starts at X = -0.1? Use the *Rapid Coin Flipper* to experiment, and use this experiment to explain why or why not.

EX. Suppose that the system is at a higher temperature, so the random velocity ε is larger. Now heads means $\varepsilon = 0.5$ and tails means $\varepsilon = -0.5$. Could the system escape the equilibrium point X = -1 and end up near X=1? Explain what would need to happen.

Temp4 The atmospheric random walk.

In the atmosphere, air molecules (N_2, O_2, etc.) undergo a random walk as they fly around bouncing off each other. But there are two interesting complicating factors. One is that gravity makes them move downwards a bit more often than they move upwards. And second, there is solid stuff called the ground, which molecules bounce off of.

For a simplification, use the *Rapid Coin Flipper* to simulate the following process. Start at altitude A = 3. Every time the coin is heads, move up 1. Every time the coin is tails, move down 1. But if the coin is already at 0 (the ground level), the coin must move up. The state variable A cannot be less than zero.

EX. Using a fair coin, and 10 simulations with 20 flips each, what are the 10 final values you find. Start at A=3 each time.

Simulation	1	2	3	4	5	6	7	8	9	10
Final altitude										

Repeat the experiment, where the coin has a 60% chance of tails, simulating a bit of gravitational preference to move down.

Simulation	1	2	3	4	5	6	7	8	9	10
Final altitude										

EX. Run the *Atmospheric Molecule Simulator* with 100 molecules. How do gravity and temperature affect the vertical velocities? And how do gravity and temperature affect the final vertical distribution of the molecules; are there more near the surface or higher up?

A sequence of 10 flips
HTHHT TTHHH
would yield altitudes

3, 4,3,4,5,4, 3,2,3,4,5.

A sequence
TTHTT **T**THHT
would yield altitudes

3, 2,1,2,1,0, 1,0,1,2,1.

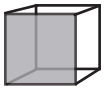
Note that the boldface "T" corresponds to an altitude change from 0 to 1, since A must move up when A hits 0.

BM1 Brownian motion

Brownian motion is named for Robert Brown, who observed pollen grains in water under a microscope. These grains constantly wiggled, and the wiggling never seemed to stop. Brownian motion, we now understand, is a stochastic process caused by zillions of molecules bouncing all over the place, colliding with each other at all sorts of angles and speeds. A grain of pollen, much larger than a molecule, is bombarded by so many jiggling molecules that it too acquires a random wiggling that Robert Brown observed.

See Robert Brown, *A brief account of microscopical observations made in the months of June, July and August 1827, on the particles contained in the pollen of plants; and on the general existence of active molecules in organic and inorganic bodies*, published in the Philosophical Magazine, 1828.

Brownian motion occurs in all natural situations where molecules are able to move around. In a typical room, each cubic centimeter of air contains about 2.5×10^{19} molecules, or about 25 million trillion molecules. These are whizzing about very quickly as you found before, and there are about 10^{33}, or about a billion trillion trillion, collisions each second. This is the source of Brownian motion in a gas.



One cubic centimeter looks like this box.

In a typical glass of water, each cubic centimeter of water contains about 3.3×10^{22} molecules. These molecules stick to each other a bit, making it a liquid. But they still try to zoom about and collide with each other. Within the cubic centimeter of water, there are about 10^{36} (a trillion trillion trillion) molecule collisions every second. This is the source of Brownian motion in a liquid, and it causes larger particles to bounce around too.

These estimates comes from Feynman's *Lectures in Physics*, Lecture 41.

EX. A typical human cell has a mass of about 1 ng (nanogram), and about 70% of that mass is water. Estimate how many molecules of water are contained in a human cell.

In 1905, Einstein combined the theory of Brownian motion, the relationship between temperature and molecular motions, and work of Stokes on viscosity for particles moving in a liquid. The result was a concept for an experiment... one that could prove (or disprove) the existence of molecules, and effectively count molecules without ever seeing them. Such an experiment was carried out a few years later by Perrin, observing the Brownian motion of tiny particles of tree resin. Equipped with a camera lucida to record his observations, Perrin painstakingly tracked the motion of hundreds of these particles. You will recreate his experiment here with the aid of the *Brownian Motion Simulator*.

EX. Within the simulator, what effect does temperature have on the Brownian motion of a particle? Challenge: At what temperature do you expect the Brownian motion to be twice as fast as at 20°C?

BM2 Perrin's experiment

Now you will carry out Perrin's experiment with the *Brownian Motion Simulator*. Set the particle radius to 0.5 microns, viscosity 1 centiPoise, and temperature to 20°C. Click the **Diffuse** button, and after 10 seconds, the Get Data button. This should produce a table of x,y coordinates, and the **squared-displacement** $d^2 = x^2 + y^2$.

The units of viscosity here are centiPoise (cP). It is convenient because 1 cP is the viscosity of water at 20°C. In SI units, $1cP = 10^{-3}$ Pa s, where Pa = Pascals, the SI unit of pressure, and s = seconds.

EX. Create a spreadsheet, with a header row for time and first column to label experiments. Each experiment is a 10-second run of the Brownian Motion Simulator, with the same particle size, viscosity, and temperature throughout. Record the squared-displacements for each experiment in its row. The result should look like the sample below.

	A	B	C	D	E	F	G
1	**Time**	**0**	**1**	**2**	**3**	**4**	**5**
2	**Experiment 1**	0	0.85	0.19	0.24	1.09	1.04
3	**Experiment 2**	0	0.61	0.33	1.29	4.87	2.19

After including at least 15 experiments (rows), create a new row for the averages. For this, use a spreadsheet formula like `=AVERAGE(B2:B20)` to average the cells in each column B2, B3, ..., B20. Make sure to average the experiments (squared-displacements) and not the time!

Use this final row of averages to create a plot with time on the horizontal axis, and average squared-displacement on the vertical axis. Include a best-fit line, as well as your data points. Record the slope of the best-fit line, and draw everything below.

Slope of line is

_____

EX. Compare your slope to other groups working on this problem. What range of slopes do you find, and how many experiments did the other groups perform?

BM3 Einstein-Perrin to Boltzmann

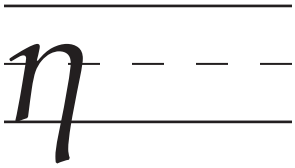
In Einstein's 1905 doctoral thesis, he found that the squared-displacement can be **expected** to grow linearly over time, and moreover the coefficient for this linear growth depends on temperature (T), particle radius (r), and viscosity (η). There was also a constant, then unknown, called k_B.

Einstein, *On the movement of small particles suspended in stationary liquids required by the molecular-kinetic theory of heat*, 1905.

$$\mathbf{E}(x^2 + y^2) = \left(\frac{k_B T}{3\pi r \eta}\right) \times t$$

EX. Why do you think T is on the top of the fraction, while r and η are on the bottom of the fraction?

η is the lowercase Greek letter **eta**. Draw it below for practice.



EX. In an individual experiment, did you find that squared-displacement grew linearly over time? Why do you think we averaged over 15 or more experiments?

EX. On the previous page, you found the slope of the line relating squared-displacement to time. Recalling that x and y were measured in microns, what is the slope in m^2/sec (square meters per second)?

EX. By Einstein's formula, your slope equals $k_B T/3\pi r\eta$. Use your results to estimate Boltzmann's constant, in the units below. Fill in the blanks in the margin to help with unit conversions.

k_B = _____ m^2 kg / s^2 °K

T = 20°C = _____°K

r = 0.5μm = _____ m

η = 1cP = .001 kg/m s

EX. Compare your estimation of k_B to a value you look up. Write down this "real" value, and describe your error with a percentage.

BM4 Boltzmann to Avogadro. Synthesis

EX. The ideal gas law states $PV = k_B N T$, where P is the pressure, V the volume, N the number of molecules, and T the temperature of a gas. Which of these quantities can be **directly experimentally measured**? For each such quantity, what is the **name of the instrument** one typically uses for measurement.

EX. Carbon dioxide is widely available in solid form, as dry ice. It sublimates to form carbon dioxide gas at room temperature. In the laboratory, 44 grams of dry ice is allowed to sublimate into an empty (vacuum) 1 Liter container at 300°K. The result is 44 grams of CO_2 gas in a 1L container. The container is attached to a pressure meter, which records a pressure of 2,500,000 Pascals.

Use your estimate of Boltzmann's constant to estimate N, the number of molecules in the container, showing key steps in your work below.

For this, you will need to convert units. Note that:

1 Pascal = 1 kg m/s
1 Liter = 0.001 m^3

EX. Compare your result to Avogadro's number. How close is it, and why should it be close?

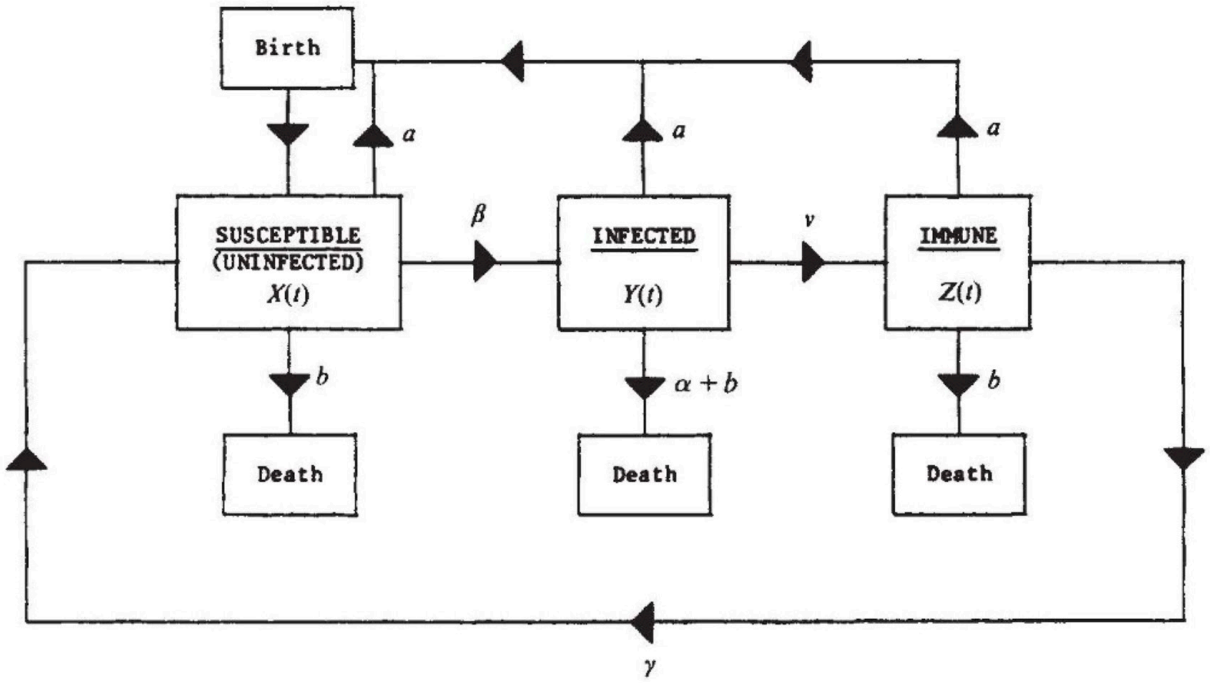


Figure 3 from *Population biology of infectious diseases: Part I*, by Anderson and May (Nature 1979). This is a typical diagram for a compartmental model, where individuals travel from one compartment to another according to formulaic (often stochastic) rules and parameters.

Laboratory 6
Order

In this final laboratory, we will study models that arise when individuals migrate between a few **compartments**, according to a consistent set of probabilistic rules. These are **Markov chains**, which have applications across physical, biological, and social sciences.

For example, students in our class are either sick (too sick to attend class) or healthy (healthy enough to attend class). The two compartments are "sick" and "healthy". As students get sick and (hopefully) recover, they migrate between these compartments. This would be a Markov process if their health were determined by random variables; e.g., if each day, every healthy student has a 5% chance of getting sick, and inversely, every sick student has a 20% chance of recovering.

Another example: ion channels can be open or closed. On a single cell, there may be thousands of ion channels, migrating between the open and closed **compartments**.

Another: A particular location in DNA (e.g., the genomic coordinate chr1:1234567) can be occupied by four nucleotides, abbreviated A, T, G, and C. The coordinate may migrate (via mutation) between these four **compartments**.

EX. Describe one more biological example, where an individual (organism, cell, molecule, etc.) migrates among compartments. Describe the example, and the particular compartments.

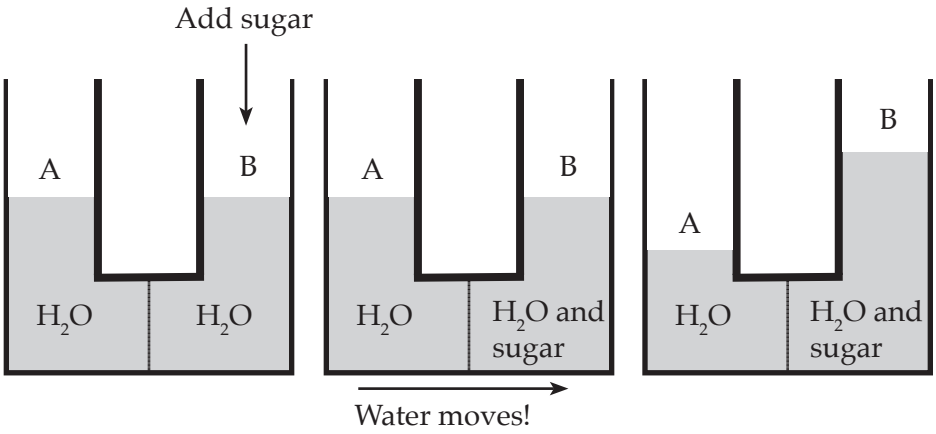
The structures of life, from DNA to the brain to the ecosystem, **emerge** from multitudes of similar individuals, behaving randomly. The emergence of order is the subject of this last chapter.

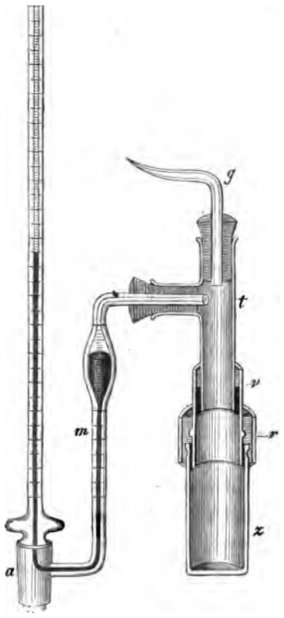
Osm1 Osmosis: A tale of two compartments

Osmosis is a strange phenomenon that is central to the functioning of cells, the growth of plants, and more. The basic setup requires two physical **compartments**, which we call A and B. There are two kinds of molecules, a solvent (e.g., water), and a solute (e.g., sucrose) which dissolves.

These two compartments, A and B, are separated by a **semipermeable membrane**, which means that solvent (water) molecules can flow through the membrane in either direction (the "permeable" part), but solute molecules (sugar) **cannot** flow through the membrane.

If compartments A and B are filled with pure water, and sugar is placed into compartment B, the sugar is forever trapped in compartment B. But a remarkable thing happens... the water seems to flow from A to B! This is called **osmosis** and it can be precisely measured.





A picture of an apparatus designed by Pfeffer, to measure the pressure due to osmosis. Figure 1 from *Osmotiche Untersuchungen*, published in 1877. It is a more sophisticated version of the U-tube diagram shown here.

To think about this system, consider a setup where compartments A and B initially contain 1000 water molecules each. Water molecules freely dance between compartments A and B without preference. Then sugar is poured into compartment B. Suddenly, the water molecules "prefer" compartment B.

EX. Suppose that each second, each water molecule in compartment A has a 20% chance of moving to compartment B. But each water molecule in compartment B has a 10% chance of moving to compartment A. Starting with 1000 molecules in each compartment, how many molecules do you **expect** in each compartment after one second?

_____ in compartment A, and _____ in compartment B.

EX. How many do you expect in each compartment after two seconds? After three seconds? Tabulate your answers below.

Time	Compartment A	Compartment B
0		
1 sec		
2 sec		
3 sec		

Osm2 Equilibrium in compartments

Equilibrium in this system occurs when the number of water molecules making the **transition** from A to B equals the number of water molecules making the **transition** from B to A.

Let A be the number of water molecules in compartment A.
Let B be the number of water molecules in compartment B.

EX. Equilibrium occurs when 0.2 A = 0.1 B. Briefly explain why this is true, and find the number of molecules in each compartment at equilibrium. (Note we begin with 2000 waer molecules!)

Note that we do not care about the sugar molecules in this model! They stay in compartment B always. In practice, the concentration of the sugar solution directly affects the transition probabilities.

EX. Load the *Two-compartment Markov Chain Explorer,* and enter the given transition probabilities. Use this to sketch time-series plots which show the number of molecules in compartments A and B over time and the equilibrium you have found.

EX. How would the time series plots change if water molecules in compartment A moved to B with probability 40%, while molecules in compartment B moved to A with probability 20%?

LA1 State vectors and transition matrices

Compartmental models are general and powerful, and the underlying mathematics involves **vectors** and **matrices**. Vectors and matrices are fundamentally ways of packaging a few numbers into a box. For vectors, we package the numbers into a column. For matrices, we package the numbers into a rectangle (usually a square in this class!)

These two pages provide an introduction to an area of mathematics called **linear algebra**, which is all about vectors and matrices.

In our two compartment system, the state of the system required two numbers called A and B, representing the number of individuals in compartments A and B. The state of the system can thus be packaged in a **vector.** The initial state of the system had 1000 molecules in compartment A, and 1000 in compartment B. When we package this as a **state vector**, it looks like this:

The initial state of the system was: $\begin{pmatrix} 1000 \\ 1000 \end{pmatrix}$

EX. Looking back at the previous pages, represent the state of the system after 1 second, 2 seconds, and 3 seconds, using three **vectors**.

A square matrix is a square arrangement of numbers. We can use a square matrix to package all of the **transition probabilities**. In our first system, a molecule from compartment A had a 10% chance of moving to compartment B. A molecule from compartment B had a 20% chance of moving to compartment A. Thus a molecule in compartment A has a 90% chance of staying in compartment A. And a molecule in compartment B has a 80% chance of staying in compartment B. These four numbers are packaged into our **transition matrix**.

$$\begin{array}{cc} & \text{From A} \quad \text{B} \\ \text{To...} & \begin{array}{c} \text{A} \\ \text{B} \end{array} \begin{pmatrix} 0.9 & 0.2 \\ 0.1 & 0.8 \end{pmatrix} \end{array}$$

There is a 20% chance that a molecule moves **from** compartment B **to** compartment A.

EX. Suppose that the transition probability from A to B is 30% and the transition probability from B to A is 5%. What is the transition matrix?

EX. What is the sum of the numbers in each column? What is the sum of the numbers in each row? Why do you find something in columns but not rows?

LA2 Matrix and vector arithmetic

Vectors can be added, according to the following definition.

$$\begin{pmatrix} x \\ y \end{pmatrix} + \begin{pmatrix} u \\ v \end{pmatrix} = \begin{pmatrix} x+u \\ y+v \end{pmatrix}$$

EX. Imagine you start with 1000 molecules in compartment A and 1000 in compartment B. You then add 500 molecules to A and 300 to B. Express the result as a **vector addition** fact, in the form above.

$$\begin{pmatrix} 1000 \\ 1000 \end{pmatrix} + \begin{pmatrix} \quad \\ \quad \end{pmatrix} = \begin{pmatrix} \quad \\ \quad \end{pmatrix}$$

Let M be a square 2x2 matrix. Let X be a 2-**dimensional** column vector. This means that M packages 4 numbers in a square, while X packages two numbers in a column. Mathematicians created a way to multiply these two packages together, to form a product M · X.

$$\begin{pmatrix} a & b \\ c & d \end{pmatrix} \cdot \begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} ax + by \\ cx + dy \end{pmatrix}$$

EX. Using the multiplication formula above, compute the product

$$\begin{pmatrix} 0.9 & 0.2 \\ 0.1 & 0.8 \end{pmatrix} \cdot \begin{pmatrix} 1000 \\ 1000 \end{pmatrix} = \begin{pmatrix} \quad \\ \quad \end{pmatrix}$$

EX. How does this relate to the computations on page **Osm1**?

We will frequently use the following properties of matrix/vector multiplication and addition.

Distributive law:

$M \cdot (X+Y) = M \cdot X + M \cdot Y$

Associative law:

$(M \cdot N) \cdot X = M \cdot (N \cdot X)$

EX. Let M be the transition matrix, and X the initial state vector, as displayed in the margin. Compute the following, filling in the blanks. You may want to do the drills on the next two pages first!

$$M = \begin{pmatrix} 0.9 & 0.1 \\ 0.2 & 0.8 \end{pmatrix}$$

$$X = \begin{pmatrix} 1000 \\ 1000 \end{pmatrix}$$

$$(M \cdot M) \cdot X = \left(\begin{pmatrix} 0.9 & 0.2 \\ 0.1 & 0.8 \end{pmatrix} \cdot \begin{pmatrix} 0.9 & 0.2 \\ 0.1 & 0.8 \end{pmatrix} \right) \cdot \begin{pmatrix} 1000 \\ 1000 \end{pmatrix} = \begin{pmatrix} \quad \\ \quad \end{pmatrix} \cdot \begin{pmatrix} 1000 \\ 1000 \end{pmatrix} = \begin{pmatrix} \quad \\ \quad \end{pmatrix}$$

$$M \cdot (M \cdot X) = \begin{pmatrix} 0.9 & 0.2 \\ 0.1 & 0.8 \end{pmatrix} \left(\begin{pmatrix} 0.9 & 0.2 \\ 0.1 & 0.8 \end{pmatrix} \cdot \begin{pmatrix} 1000 \\ 1000 \end{pmatrix} \right) = \begin{pmatrix} 0.9 & 0.2 \\ 0.1 & 0.8 \end{pmatrix} \begin{pmatrix} \quad \\ \quad \end{pmatrix} = \begin{pmatrix} \quad \\ \quad \end{pmatrix}$$

EX. How does the vector M · (M · X) relate to **the exercises on Osm1?**

LA3 Drill: Vector and Matrix Arithmetic

EX. Vector addition. Add and subtract the following vectors.

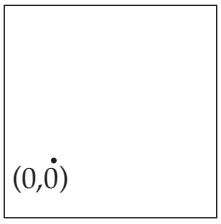
$\begin{pmatrix}10\\3\end{pmatrix} + \begin{pmatrix}-3.5\\4\end{pmatrix} =$ _____ $\quad \begin{pmatrix}100\\2\end{pmatrix} + \begin{pmatrix}200\\4\end{pmatrix} =$ _____ $\quad \begin{pmatrix}11\\1\end{pmatrix} - \begin{pmatrix}10\\1\end{pmatrix} =$ _____

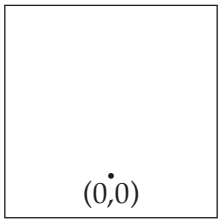
$\begin{pmatrix}1\\2\\3\end{pmatrix} + \begin{pmatrix}4\\5\\6\end{pmatrix} =$ _____ $\quad \begin{pmatrix}1\\-1\\-1\end{pmatrix} + \begin{pmatrix}-1\\1\\-1\end{pmatrix} + \begin{pmatrix}-1\\-1\\1\end{pmatrix} =$ _____

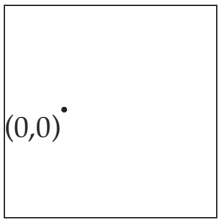
To draw a vector $\begin{pmatrix}a\\b\end{pmatrix}$, draw an arrow from (0,0) to (a,b) in the Cartesian plane.

EX. In the following, draw both given vectors X and Y and their sum X+Y. Then draw dotted lines from X to X+Y and from Y to X+Y, to illustrate the parallelogram property.

$X = \begin{pmatrix}1\\0\end{pmatrix}, Y = \begin{pmatrix}0\\1\end{pmatrix}$ $\quad X = \begin{pmatrix}2\\3\end{pmatrix}, Y = \begin{pmatrix}-1\\2\end{pmatrix}$ $\quad X = \begin{pmatrix}1\\2\end{pmatrix}, Y = \begin{pmatrix}3\\-2\end{pmatrix}$







Recall that a matrix and vector are multiplied by the following rule.

$$\begin{pmatrix}a & b\\c & d\end{pmatrix} \cdot \begin{pmatrix}x\\y\end{pmatrix} = \begin{pmatrix}ax + by\\cx + dy\end{pmatrix}$$

EX. Use this rule to compute M · X, for the following matrices M and vectors X.

$M = \begin{pmatrix}1 & 1\\0 & 1\end{pmatrix}, X = \begin{pmatrix}3\\2\end{pmatrix}$ $\quad M = \begin{pmatrix}0 & 1\\1 & 0\end{pmatrix}, X = \begin{pmatrix}-3\\1\end{pmatrix}$ $\quad M = \begin{pmatrix}1 & 2\\2 & 4\end{pmatrix}, X = \begin{pmatrix}2\\-1\end{pmatrix}$

M · X = _____ $\quad$ M · X = _____ $\quad$ M · X = _____

EX. Suppose that $\begin{pmatrix}0.6 & 0.4\\0.2 & 0.8\end{pmatrix} \cdot \begin{pmatrix}x\\y\end{pmatrix} = \begin{pmatrix}x\\y\end{pmatrix}$ and x+y = 100.

What are the values of x and y?

LA4 Drill: Matrix multiplication

We have seen two operations so far:

Vector + Vector = Vector. Matrix · Vector = Vector.

We finish with the most complicated operation:

Matrix · Matrix = Matrix.

More generally, one can multiply a p by q matrix (p rows and q columns) with a q by r matrix (q rows and r columns), and the result will be a p by r matrix.

Let M and N be square 2x2 matrices. They can be multipled to form a square 2x2 matrix M · N. To find the **top-left** entry of M ·N, one "dots together" the **top row** of M with the **left column** of N. The pattern takes a bit of practice.

$$\begin{pmatrix} \mathbf{a} & \mathbf{b} \\ c & d \end{pmatrix} \cdot \begin{pmatrix} \mathbf{e} & f \\ \mathbf{g} & h \end{pmatrix} = \begin{pmatrix} \mathbf{ae + bg} & af + bh \\ ce + dg & cf + dh \end{pmatrix}$$

We have boldfaced the top row (a b) of M and the left column $\begin{pmatrix} e \\ g \end{pmatrix}$ of N.

EX. Multiply the following 2x2 matrices.

$$\begin{pmatrix} 1 & 2 \\ 3 & 4 \end{pmatrix} \cdot \begin{pmatrix} 5 & 6 \\ 7 & 8 \end{pmatrix} = \_\_\_\_\_ \qquad \begin{pmatrix} 1 & 3 \\ 0 & 1 \end{pmatrix} \cdot \begin{pmatrix} 1 & 2 \\ 2 & 1 \end{pmatrix} = \_\_\_\_\_$$

To "dot them together," refers to the **dot product** ae + bg.

When M is a square matrix, we can multiply M by itself, and M · M will be another square matrix. This is called M^2. We can multiply M by itself again, to form M·M·M, which is naturally called M^3.

EX. Let $M = \begin{pmatrix} 1 & 3 \\ 0 & 1 \end{pmatrix}$. Compute M^2 and M^3.

Find a pattern to give a formula for M^n when n is any whole number.

M^2 = _____, M^3 = _____, M^n = _____

EX. Let $M = \begin{pmatrix} 1 & 1 \\ 0 & 1 \end{pmatrix}$ and $N = \begin{pmatrix} 1 & 0 \\ 1 & 1 \end{pmatrix}$. Compute M · N and N · M.

Matrix multiplicaiton is not commutative!
It is **rarely** true that M·N= N·M

Matrix multiplication is associative, i.e.,
M·(N·R) = (M·N)·R,
for any three matrices M,N,R.

IC1 Equilibrium: Open and closed channels.

Cell membranes are covered with **channels**. Most channels are ion channels, allowing charged particles like sodium ions (Na^+), potassium ions (K^+), Chlorine ions (Cl^-), hydrogen ions (protons, H^+) to pass through the cell membrane. A single ion channel can maintain a flow of millions of ions per second, creating a measurable electrical **current**. A single cell can have thousands of ion channels, of hundreds of types.

There are also **aquaporins**, which shuttle water molecules through the cell membrane!

Physically, these channels are large proteins which form a tunnel across the cell membrane. Channels can be **gated**, meaning opened or closed, either by voltage changes, or by binding a molecule.

Most channels have a variety of "open" and "closed" states, but we just consider two.

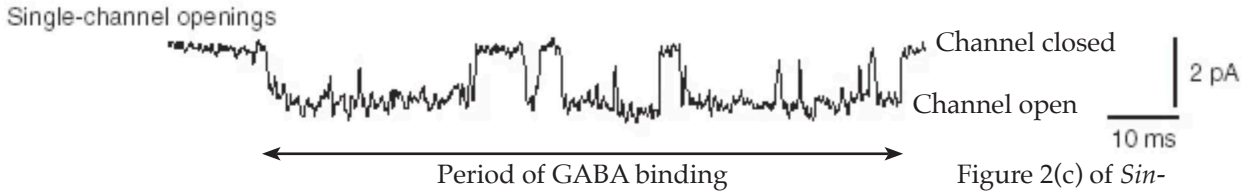


Figure 2(c) of *Single-channel recording of ligand-gated ion channels*, by Mortensen and Smart, (Nature Protocols 2007). Reproduced with annotations.

A **patch clamp technique** can measure the **current** through a single ion channel, yielding a pattern like the one displayed above. When the graph is down low, it reflects the ion channel being open, allowing the current to pass through. When the graph is up high, it reflects the ion channel being closed. At the beginning and end of the time period shown, the channel is closed. The burst of downward activity here reflects the binding of GABA to a receptor, opening the channel.

The SI unit of **current** is the amp or ampere. A current of 1 amp can be deadly (and 0.01 amps is painful). The current through a single ion channel is measured in picoamps. 1 pA = 10^{-12} amps.

EX. During the period of GABA binding, how much time does the channel spend open? And how much closed? Estimate your answer in milliseconds, using the scale to the right of the graph. (Hint: 10ms is about a pinky-width!)

EX. During the period of GABA binding, the channel is closed a few times. How many such closed periods do you see? How long do those closed periods last? Estimate your answer in milliseconds.

EX. During GABA binding, the behavior of a channel is somewhat random, with one probability of going from open to closed, and a different probability of going from closed to open. Which transition do you think is more likely here?

IC2 Simulation: Ion Channels

Load the *Ion Channel Simulator*. This will provide a simulated patch-clamp recording, based on transition probabilities you provide.

This simulator is built to randomly switch between open and closed states from your provided probabilities. It also adds a little bit of "Gaussian noise" to simulate the random wiggles that you might find it a real patch clamp recording

EX. How are the two transition probabilities (probability of open-to-closed and closed-to-open) related to the total time that the ion channel is open? Answer this by holding one probability constant and doubling or tripling the other, to see the effect.

EX. Begin with the two transition probabilities at 10% and 20%. What happens if you double these probabilities to 20% and 40%, or triple them to 30% and 60%? How does that change effect the patch-clamp readout?

EX. By exploration, find transition probabilities which could reasonably explain the real patch-clamp recording on the previous page.

Probability of open-to-closed transition:

Probability of closed-to-open transition:

EX. A single ion channel generates a current of 2 pA (picoamps) when it is open. If the ion channels on a cell are open 70% of the time, independently of each other, how much current would flow through the cell membrane with 1000 ion channels?

IC3 Equilibrium: Matrix Model

In a **matrix model**, the state of a system is represented by a **vector X.** The state of the system changes, from one moment to the next (with some time interval Δt), by multiplying X by a **transition matrix** M.

Consider a cell with 1000 ion channels that can be open or closed. We model their state by a vector with two numbers: how many channels are closed and how many are open. If the cell begins with all channels closed, then...

The initial state of the system is $X_0 = \begin{pmatrix} 1000 \\ 0 \end{pmatrix}$.

The subscript 0, in X_0 refers to the state at **time zero**.

If the cell gets an appropriate signal, e.g., from an **agonist**, the state will change. Each millisecond, closed channels will open with probability 10%; and open channels will close with probability 1%.

An **agonist** is a molecule which binds to a receptor, setting off a physical process which opens an ion channel. Ion channels controlled this way are called **ligand-gated** ion channels.

The transition matrix is $M = \begin{pmatrix} 0.9 & 0.01 \\ 0.1 & 0.99 \end{pmatrix}$.

EX. After 1ms, the state is called X_1. Our expectation for this state is given by the vector $X_1 = M \cdot X_0$. Compute this matrix X_1.

EX. After 2ms, the state is called X_2. Our expectation for this state is given by the vector $X_2 = M \cdot M \cdot X_0$. Note that this is also $M \cdot X_1$. Compute this vector X_2.

A state X will be in equilibrium if $X = M \cdot X$. This can be converted into a system of linear equations as follows.

If $X = \begin{pmatrix} u \\ v \end{pmatrix}$ is the unknown equilibrium state, the condition $X = M \cdot X$ can be expanded as

$$\begin{pmatrix} 0.9 & 0.01 \\ 0.1 & 0.99 \end{pmatrix} \begin{pmatrix} u \\ v \end{pmatrix} = \begin{pmatrix} u \\ v \end{pmatrix} .$$

EX. Multiply the matrix and vector on the left side. Use this to find a system of two linear equations in the two variables u and v.

_____ u + _____ v = u.

_____ u + _____ v = v.

The total population of ion channels does not change. Express this fact as a third linear equation.

_____ u + _____ v = _____.

IC4 Equilibrium and ratio: Markov Models

In a Markov chain, the transition matrix is a matrix of probabilities (numbers between 0 and 1), whose columns add up to 1. If there are two compartments, the transition matrix has the form

$$M = \begin{pmatrix} 1-p & q \\ p & 1-q \end{pmatrix} .$$

Here p is the probability of an A-to-B transition, and q is the probability of a B-to-A transition. An equilibrium state is where M·X = X. In other words,

$$X = \begin{pmatrix} u \\ v \end{pmatrix} \text{ and } \begin{pmatrix} 1-p & q \\ p & 1-q \end{pmatrix} \begin{pmatrix} u \\ v \end{pmatrix} = \begin{pmatrix} u \\ v \end{pmatrix}$$

Theorem: If the ratio u:v equals the ratio q:p, then X is an equilibrium state for M.

On the previous page, we considered a transition matrix where the closed-to-open probability was **p=10**% and the open-to-closed probability was **q=1**%.

EX. Suppose that $X = \begin{pmatrix} u \\ v \end{pmatrix}$ is an equilibrium state. Using the above values of p and q, what is the ratio u:v?

EX. If there are 1000 ion channels, what is the equilibrium number of open and closed channels, using this ratio? (Round to the nearest whole number)

EX. (Challenge). If u:v = q:p, then u = qc and v = pc (for some constant c). Multiply M·X, to show that M·X=X. This proves the above theorem.

$$\begin{pmatrix} 1-p & q \\ p & 1-q \end{pmatrix} \begin{pmatrix} qc \\ pc \end{pmatrix} =$$

EX. Ratio drill!

Fill in the blanks to find ratios equal to 2:3

Sample: 4:6 6:___

10:___ ___:30

70:___ 2000:_____

Fill in the blanks to find ratios equal to 4:1.

Sample: 12:3 ___:2

400:___ 1:____

300:____ ___:150

EX. Find numbers u,v with u:v = 4:1 and u+v = 1000.

u = _____ v = _____

EX. Find numbers u,v with u:v = 7:3 and u+v = 500.

u = _____ v = _____

EX. Reframe EX 6.36 as a question that looks just like EX 6.32 and 6.33. Just write the question below.

BC1 Breast cancer: Transitions between three cell states

Almost all of the cells in your body have **almost** the same DNA. What makes a cell from one tissue different from another is their **cell state**, which is largely determined by which genes are **expressed**. If DNA is the recipe book for proteins, not every recipe is followed in every cell. Cells can change their state, if they follow a different set of recipes. For example, hematopoietic stem cells (HSCs) are in one cell state, and as they develop, they can turn into red blood cells, a different cell state!

Two almosts are needed. E.g., sperm and egg cells are haploid, having only one of each chromosome. B-cells have sections of randomly shuffled DNA which produce antibodies for numerous foreign invaders. Cells have their own random mutations too.

Within a breast cancer tumor, cells often transition among cell states. One model considers three states:

Stem-like (S): Implicated in **metastasis** and drug-resistance.
Basal (B): Resembling structural cells of the milk duct.
Luminal (L): Resembling cells that line the milk duct.

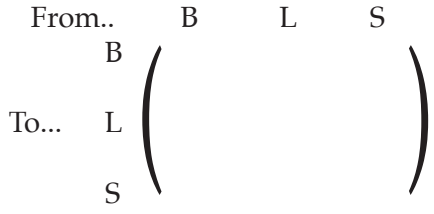
Metastasis is when the cancer spreads outside the tissue where it starts, e.g., to lungs or bone or liver or brain.

Tumors that have different proportions of these kinds of cells have different risk profiles. Culturing these cells in the lab, scientists found that cells can transition from one state to another. From one tumor sample, they found the following transition probabilities (per cell cycle).

B to L: 0%	L to B: 49%
L to S: 4%	S to L: 7%
S to B: 35%	B to S: 1%

These probabilities come from *Stochastic State Transitions Give Rise to Phenotypic Equilibrium in Populations of Cancer Cells*, by Gupta, Piyush B. et al., in Cell (2011).

EX. Fill in the following matrix, to create a 3x3 transition matrix M for this Markov chain.



EX. Suppose that you begin with 1000 cells in each state (B, L, S). According to the above transition matrix, how many cells do expect to find in each state after one cell cycle. Multiply a vector by the matrix M to find the answer.

BC2 Breast cancer: simulation and equilibrium

EX. Just looking at the transition matrix, what cell states to you expect to find most often, and why?

Load the *Three-Compartment Matrix Modeler*. Enter your transition matrix M from the previous page to begin simulating.

EX. Starting with 1000 cells of each state, how many cells do you find in each state at equilibrium? How is this affected if you change the starting numbers, but keep the total number of cells the same?

EX. In another tumor sample, the transition probabilities are given in the margin. What kind of cells do you think are most common in such tumors?

B to L: 8%
L to B: 0%
L to S: 1%
S to L: 30%
S to B: 9%
B to S: 1%

EX. Consider two treatment approaches. One destroys all stem-like tumor cells for a short time. Another treatment disrupts the cell-state transitions for a long time, changing the transition matrix so that B to S transitions and L to S transitions have probability zero. Compare the effects of these two treatments.

Les1 Birth and death. Leslie matrix

So far, our matrix models have been Markov chains, in which populations migrate between a few states. The total population has remained the same throughout. But this is not how life (organisms, cells, etc.) work: there is also birth and death. Fortunately, matrix models are flexible enough to accommodate this complication.

Here is a model of black bears, to illustrate the complexity. We consider an **age-stratified model**, with juvenile (young) bears and adult (old) bears. Let J be the number of juveniles and A the number of adults.

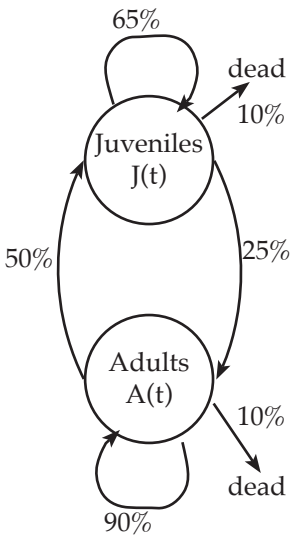
Each year, 10% of the juveniles die. 25% of the juveniles become adults. The remaining 65% are still juveniles the next year.

Each year, 50% of the adults are adult females, who each produce one juvenile each year, and 10% of the adults die.

EX. Imagine a population of 20 juveniles and 100 adults. According to the above assumptions, how many juveniles and adults will there be in the following year?

_____ juveniles and _____ adults.

It is sometimes helpful to draw a diagram to keep track of the numbers. See below.



The previous question can be solved by multiplying M·X, where X is the state vector $X = \begin{pmatrix} 20 \\ 100 \end{pmatrix}$, and M is the **Leslie matrix** $\begin{pmatrix} 0.65 & 0.5 \\ 0.25 & 0.9 \end{pmatrix}$.

EX. How are the numbers in the Leslie matrix related to the numbers given in the model for birth, death, and aging? Describe how each number (0.65, 0.5, 0.25, 0.9) comes from the given model.

Les2 Eigenvectors. Proportional stability.

When M is a square matrix (like 2 by 2, or 3 by 3, etc.), we say that a **nonzero** vector X is an **eigenvector of M** when $M \cdot X$ is proportional to X. Here, proportional means that $M \cdot X = \lambda \cdot X$, for some **scalar** λ. The word **scalar** is just a fancy word for "number" when we want to emphasize that it is not a vector. When $M \cdot X = \lambda \cdot X$, the scalar λ is called the **eigenvalue**.

For example, suppose X is an **equilibrium vector** for a transition matrix M. Then $M \cdot X = X$, so X is an eigenvector of M with **eigenvalue 1**.

EX. Let M be the Leslie matrix for the black bear system,

$M = \begin{pmatrix} 0.65 & 0.5 \\ 0.25 & 0.9 \end{pmatrix}$. Let $X = \begin{pmatrix} J \\ A \end{pmatrix}$ be a state vector.

Turn the equation $M \cdot X = X$ into a pair of linear equations, to show that the only equilibrium state is when $J = 0$ and $A = 0$.

EX. Now consider the state vector $X = \begin{pmatrix} 100 \\ 100 \end{pmatrix}$. Multiply $M \cdot X$ to show that X is an eigenvector of M. What is the eigenvalue?

EX. If you begin with the state vector $X = \begin{pmatrix} 100 \\ 100 \end{pmatrix}$, how many juveniles and adults will you have after t years? Express your answer using exponential functions, and the eigenvalue you found.

$J(t) =$ _____

$A(t) =$ _____

EX. Drill! Scale each ofthe given vectors X by the given scalar λ.

$\lambda = 3$, $X = \begin{pmatrix} 2 \\ 5 \end{pmatrix}$.

$\lambda \cdot X =$ _____

$\lambda = 0.5$, $X = \begin{pmatrix} 20 \\ 10 \end{pmatrix}$.

$\lambda \cdot X =$ _____

$\lambda = 1$, $X = \begin{pmatrix} 20 \\ 20 \end{pmatrix}$.

$\lambda \cdot X =$ _____

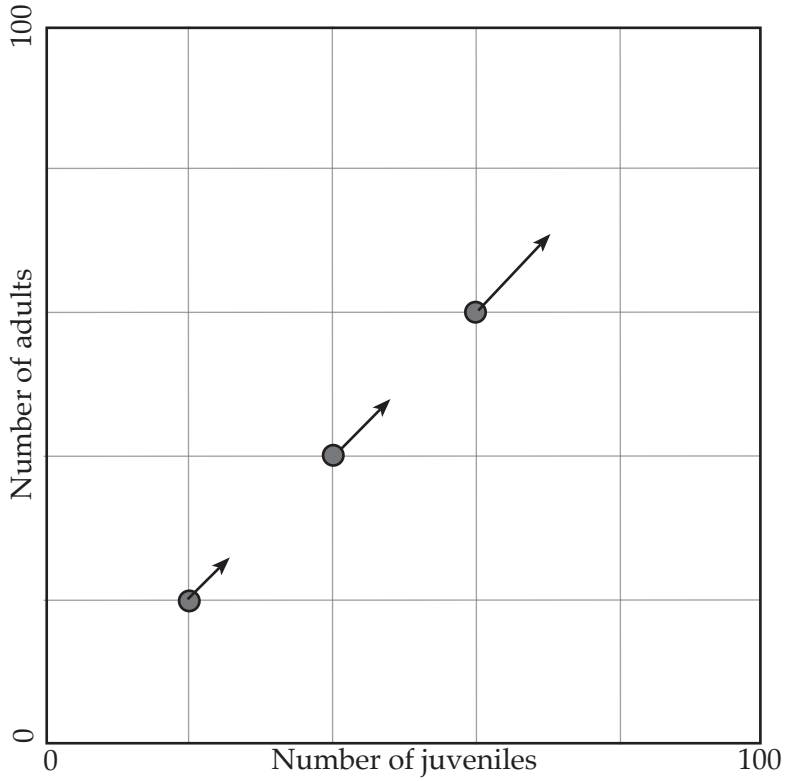
Les3 Black bears: Trajectories in state space

We keep our black bear matrix model from the previous page, with Leslie matrix $M = \begin{pmatrix} 0.65 & 0.5 \\ 0.25 & 0.9 \end{pmatrix}$ describing the transitions from juvenile to adult, and the births and deaths.

For this exercise, you may wish to use the *Quick Matrix Calculator.*

EX. Use the grid below to draw an arrow from a state X to a state $M \cdot X$, for at least 10 starting states X. (We have drawn a few such arrows as examples.)

EX. Using a different color, but on the same plot, draw the trajectory you expect to find, if you begin with a population of 20 juveniles and 60 adults.



EX. If you start with a population with some juvenile and some adult black bears, and wait 30 years, what do you expect? Describe your answer, in terms of how many black bears (more or less? twice as many? 10 times? 100 times?) and the relative numbers of juvelines and adults.

Les4 Expansion, contraction, and survival

The Leslie matrix $M = \begin{pmatrix} 0.65 & 0.5 \\ 0.25 & 0.9 \end{pmatrix}$ has one direction of expansion; states with equal numbers of juveniles and adults exhibit steady exponential growth.

In fact, this Leslie matrix has one direction of contraction too.

EX. Show that the vector $X = \begin{pmatrix} -20 \\ 10 \end{pmatrix}$ is an eigenvector of M. What is its eigenvalue?

This eigenvector does not belong to our state space, because we cannot have -20 juveniles. But geometrically, it is useful for showing that our system contracts along one direction and expands in another. Load the *Two-dimensional Matrix Visualizer,* and enter the Leslie matrix to explore.

EX. Consider what happens if the black bears have worse outcomes. The birth rate for adults drops from 50% to 40%. The death rate for juveniles increases to 40%, with 50% of juveniles remaining juvenile, and 10% maturing to adults. The adult death rate increases to 20%. What is the resulting Leslie matrix?

EX. Use the *Two-dimensional Matrix Visualizer.* What are the two eigenvalues for the new Leslie matrix? How do these eigenvalues relate to the long-term survival of the black bear population?

Les5 Oscillatory approach from a Leslie Matrix.

We have seen oscillation from three sources: the simple harmonic oscillator, limit cycles, and time delay (in a negative feedback loop). Here we will see that matrix models can also exhibit oscillation.

This sequence of examples comes from Modeling Life, by Garfinkel et al., Chapter 6.5.

Consider the following Leslie matrix: $M = \begin{pmatrix} 0.1 & 1.4 \\ 0.4 & 0.2 \end{pmatrix}$.

EX. Describe a situation of birth, death, and aging, which would be modeled by the above matrix. Again the first row/column corresponds to juveniles and the second to adults.

EX. Start with 30 juveniles and 100 adults. Draw time series plots, showing how the populations change over time.

EX. Use the *Two-dimensional Matrix Visualizer* and enter the Leslie matrix above. Start with a "unit square" of sample states, which represents various states in our juvenile/adult system. What happens in this system in the short-term and long-term. One eigenvalue is negative, and one eigenvalue is positive but less than one. How does this relate to the behavior of the system?

Les6 Oscillation from Leslie Matrix

See Chapter 9 of *Mathematics for the Life Sciences*, by Erin Bodine et al., Princeton University Press (2014).

Here we adapt a matrix model of Bodine, also discussed in *Modeling Life*, which exhibits sustained oscillations. It is a model of locusts, which go through three life stages: Eggs (E), Hoppers (H), and Adults (A). We track only the female population.

Each year, 2% of the eggs survive and become hoppers. The rest die.

Each year, 5% of the hoppers survive and become adults. The rest die.

Each year, every adult lays 1000 eggs before dying.

EX. What is the Leslie matrix? The first row/column should correspond to eggs, the second to hoppers, and the third to adults.

M =

EX. Load the *Three Compartment Matrix Modeler*, and enter the Leslie matrix above. Run the model to see what happens, and describe the resulting oscillations.

EX. A critique of such models is that they do not describe oscillations that we really see, because the oscillations are not **robust**. Try changing the numbers 2%, 5%, and 1000 slightly. What happens to the oscillation? Describe two changes you tried, and how it affected the oscillations.

Epi1 Epidemiology: An S/I Model

The simplest models of human epidemiology sorts people into two compartments, called **susceptible** (S) and **infected** (I). Imagine that infection is caused by exposure to a **pathogen**, and that everyone who is infected recovers eventually.

Here infection is caused when a susceptible person is exposed to a **pathogen**. A pathogen is any disease-causing micro-organism, e.g., bacteria, viruses, protozoa. We are not yet considering a contagious disease, in which a susceptible person interacts with an infected person.

A starting point is given by the following Markov chain. Each day, a susceptible person has a 1% chance of being infected. And each day, an infected person has a 20% chance of recovering, rejoining the susceptible pool.

EX. Based on this model, how long does it take a typical infected person to recover from illness?

EX. In an equilibrium state, what percentage of the population will be in each compartment? If the population consists of 200 students in this class, how many do you expect to be sick on any particular day?

EX. Sometimes, people exposed to a pathogen develop **immunity**, so that they do not become sick the next time they are exposed. This is the case for some types of dengue for example. To model this, consider three compartments: susceptible (S), infected (I), and immune (M). Modify the previous model to include transitions from the infected to immune compartments, and also a small chance of death from infection. Describe your three-compartment model below.

Epi2 Epidemiology: Complications and Variations

EX. What is the transition matrix for your susceptible (S), infected (I), and immune (M) model?

EX. Use the *Three Compartment Matrix Modeler* to explore your S/I/M model. Describe what happens, in the long term, if you start with a population entirely of susceptible people.

EX. Suppose that infections are caused by interactions between susceptible and infected persons. Instead of a matrix model, a "change equation" would be more appropriate, in the style of Lotka-Volterra and others. Write such change equations below, for the three compartments S, I, and M.

S' =

I' =

M' =

In your model, what is the coefficient of SI, and what does it mean?

Syn1 Synthesis: Randomness and Order

EX. Lab 5 was all about randomness: stochastic processes. This lab is titled "Order". What is random about the systems in this chapter, and in what way did you find orderly results?

EX. The models in this chapter were simpler, in some ways, than the change equations from Lab 1. Describe the fundamental difference between a change equation (e.g. Lotka-Volterra, Insulin-Glucose, Holling-Tanner) and a matrix model (e.g. Ion Channels, Osmosis, Age-stratified growth).

Syn2 Synthesis: Exponential growth and decay

EX. A fundamental pair of models we have seen are exponential growth and exponential decay. Write two paragraphs about these. The first should provide multiple examples of where these models arise naturally in physical and life sciences, within this lab manual or outside it. The second should provide your best explanation for why these models show up so often in the sciences.

Syn3 Synthesis: Modeling and your interests

EX. We have seen a wide variety of models, from contexts of chemistry and biochemistry, cell biology, physiology, ecology, and evolution. Consider your scientific goals, future specialty, particular interests. Choose one mathematical model related to your particular interests from this lab manual. Describe the model here, and evaluate the model using the criteria from Lab 1.

Syn4 Synthesis: Draw a picture.

EX. Draw us a picture to celebrate your completion of the lab manual.
Please be nice.

Fin

The Sciences Sing a Lullabye
by Albert Goldbarth

Physics says: go to sleep. Of course
you're tired. Every atom in you
has been dancing the shimmy in silver shoes
nonstop from mitosis to now.
Quit tapping your feet. They'll dance
inside themselves without you. Go to sleep.

Geology says: it will be all right. Slow inch
by inch America is giving itself
to the ocean. Go to sleep. Let darkness
lap at your sides. Give darkness an inch.
You aren't alone. All of the continents used to be
one body. You aren't alone. Go to sleep.

Astronomy says: the sun will rise tomorrow,
Zoology says: on rainbow-fish and lithe gazelle,
Psychology says: but first it has to be night, so
Biology says: the body-clocks are stopped all over town
and
History says: here are the blankets, layer on layer, down
and down.

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