

MCB137L/237L: Physical Biology of the Cell
Spring 2024
Homework 3
(Due 2/8/24 at 2:00pm)

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1 Bacteria Taking Over the Earth

Assume that a single *E. coli* cell has all the nutrients it could possibly desire and that it (and all of its descendants) can grow without limit.

- (a) How many bacterial cells would it take to make a giant colony that has the same mass as a human?
- (b) How long would it take for a single cell to grow into a giant human-sized bacterial colony?
- (c) How many bacteria cells would it take to make a giant colony that has the same mass as the Earth?
- (d) How long would it take for a single cell to grow into a giant Earth-sized bacterial colony?
- (e) How does the number you calculated in part (c) compare to the actual number of bacteria on Earth?
- (f) In reality, the number of bacteria on Earth stays fairly constant from day to day and from year to year, rather than increasing exponentially. Briefly explain why this is the case.

2 Growth Curves and the Logistic Equation

Much of our understanding of the natural world is couched in the language of the subject now known as “dynamical systems.” In a nutshell, the idea is to write down equations that tell us how some variable(s) of interest change in time. Often, this ends up being written in the form of coupled differential equations. Perhaps the most important and simplest of such

dynamical systems is the law of exponential growth (or decay), relevant to thinking about the early stages of growth of a culture of cells, for example. In this problem, you are going to revisit the discussion I give there by solving for the dynamics of a population of bacterial cells both analytically and numerically.

In class, we discussed the exponential growth equation. This equation has been the basis for the study of microbiology for years (read, for example, F. Neidhardt, *Bacterial Growth: Constant Obsession with dN/dt* , J of Bacteriology 181:7405 (1999) provided on the course website). If the number of cells is given by N and the growth rate is r , then this equation takes the form

$$\frac{dN}{dt} = rN. \quad (1)$$

We solved this equation in a variety of ways, both numerically and analytically, and found a solution given by

$$N(t) = N_0 e^{rt}, \quad (2)$$

where N_0 is the number of cells at $t = 0$.

(a) Of course, the solution shown above cannot be correct forever. For fast-growing *E. coli* estimate how long it would take for a single cell to produce enough progeny to cover the whole surface of the Earth.

A more realistic scenario is to account for the fact that, sooner or later, bacteria will run out of resources and halt their growth. For example, a liquid bacterial culture will saturate at a density of about 10^9 cells/ml. To account for these limited resources, we introduce a growth rate that depends on the number of cells, r_{new}

$$r_{new} = r \left(1 - \frac{N}{K} \right), \quad (3)$$

where K represents the maximum population size. Note that when N is very small compared to K , $r_{new} = r$ and growth is exponential. However, as N approaches K the growth rate will decrease. Thus, we get the so-called logistic equation

$$\frac{dN}{dt} = r_{new}N = rN \left(1 - \frac{N}{K} \right). \quad (4)$$

(b) What is the number of cells at which there is no growth and the population reaches steady state? Justify how you impose steady state on the logistic equation in order to figure out this number.

In class, we wrote pseudocode and then Python code to solve Equation 1 numerically using the so-called Euler method.

(c) Based on your pseudocode for exponential growth, write pseudocode to now solve the logistic equation. Make sure to comment your code appropriately at every step!

(d) Write Python code (by yourself or with the help of ChatGPT) for your pseudocode. For reasonable choices of r and K , plot number of cells as a function of time for both exponential and logistic growth. Note that we don't want your raw code, just the plots generated by this code.

(e) Feel free to look at section “Computational Exploration: Growth Curves and the Logistic Equation” on page 103 of PBoC2.

3 The Adder Model of Cell Division

In class, we explore the Timer model of cell division exhaustively and showed that this model would lead to huge fluctuations in cell size, even in the presence of small errors in the division time. In this problem, we explore the alternative Adder model. In this model cellular division is triggered once a volume Δm has been added to a cell. We start by assuming that the cell makes no mistakes in determining Δm for each division.

(a) Write pseudocode to simulate the mass at birth of cells as a function of generation time under the Adder mechanism.

(b) Based on your pseudocode write Python code to carry out this simulation and plot cell mass at birth vs. generation time.

Now, we will assume a small error in Δm and look at the resulting fluctuations in mass at birth.

(c) Add 10% noise to Δm at every division. Write the appropriate pseudocode for this stochastic simulation and plot cell mass at birth vs. generation time once again.

In class, we showed analytically why small fluctuations in each division under the Time model get amplified over time. Here, we explore how fluctuations add up in the Adder model. To get started, we write the mass at birth at generation n in terms of the mass at birth in generation $n - 1$ as

$$m_n = \frac{1}{2} (m_{n-1} + \Delta m + \eta_{n-1}), \quad (5)$$

where η_{n-1} is the error the cell makes in determining the mass Δm in the $(n - 1)$ th division.

(d) Show that Equation 5 leads to the recursive relation relating the mass at generation n to the mass at generation 0 given by

$$m_n = \left(\frac{1}{2}\right)^n m_0 + \Delta m \left[\left(\frac{1}{2}\right) + \left(\frac{1}{2}\right)^2 + \cdots + \left(\frac{1}{2}\right)^n \right] + \left[\left(\frac{1}{2}\right) \eta_{n-1} + \left(\frac{1}{2}\right)^2 \eta_{n-2} + \cdots + \left(\frac{1}{2}\right)^n \eta_0 \right]. \quad (6)$$

For this and any other derivation, make sure to explain every step in your calculations.

This expression can be simplified by noticing that the term multiplied by Δm is a geometric series given by

$$S_n = \sum_{i=0}^n x^i = \frac{x^{n+1} - 1}{x - 1}, \quad (7)$$

where in our case $x = 1/2$.

(e) Show that by invoking the solution to the geometric series and taking the limit $n \gg 1$, we get

$$m_n = \left(\frac{1}{2}\right)^n m_0 + \Delta m + \left[\left(\frac{1}{2}\right) \eta_{n-1} + \left(\frac{1}{2}\right)^2 \eta_{n-2} + \cdots + \left(\frac{1}{2}\right)^n \eta_0 \right]. \quad (8)$$

Make sure to pay careful attention to the fact that geometric series starts from $i = 0$.

(f) Show that, because $\langle \eta_i \rangle = 0$, the average mass at birth in the large n limit is given by $\langle m_n \rangle = \Delta m$.

Finally, let's examine the fluctuations in cell mass under the Adder model of division. As we did in class, we want to compute the variance in mass at generation n (which is just the square of the standard deviation) given by

$$\text{variance} = (\text{standard deviation})^2 = \langle m_n^2 \rangle - \langle m_n \rangle^2. \quad (9)$$

(g) Calculate the variance in cell mass assuming that $\langle \eta^2 \rangle = \sigma^2$. To make this possible, also assume that the error is uncorrelated from generation to generation as we did in class. Show that, if $n \gg 1$, we get an expression of the form

$$\langle m_n^2 \rangle - \langle m_n \rangle^2 = \frac{1}{4} \left[\sigma^2 + \left(\frac{1}{4}\right) \sigma^2 + \cdots + \left(\frac{1}{4}\right)^{n-1} \sigma^2 \right], \quad (10)$$

and use the solution to the geometric series to show that

$$\langle m_n^2 \rangle - \langle m_n \rangle^2 = \frac{1}{3} \sigma^2. \quad (11)$$

What does this result tell us about the nature of fluctuations in cell mass in the Adder model compared to the Timer model?

As discussed in class, an important approach to make sure that our simulations are actually reflecting the physical phenomenon we care about is to calculate quantities that can be contrasted against an analytical solution. Equation 11 gives us an opportunity to do exactly that by comparing the variance we calculated analytically to that resulting from the stochastic simulation.

(h) Calculate the variance in the birth mass of the cell predicted by your simulation. To put it other words, calculate the variance of the vector \mathbf{M} containing the mass at birth for each generation.

(i) Calculate the variance in the birth mass of the cell predicted by Equation 11. To make this possible, you need to compute the variance σ^2 for your η noise term. To do this, write code to create a vector \mathbf{H} with 1,000 elements given by

$$\mathbf{H} = (\eta_0, \eta_1, \eta_2, \dots, \eta_{999}) \quad (12)$$

and calculate its variance in Python using

$$\sigma^2 = \text{variance}(\mathbf{H}) = \langle \mathbf{H}^2 \rangle. \quad (13)$$

Use the obtained σ^2 to calculate the predicted variance in mass at birth from Equation 11. How does it compare to the variance you obtained from the simulation in (h)?

(j, **EXTRA CREDIT**) Solve the geometric series and prove Equation 7.