Solutions to Review Problems for Exam #2

1. Consider a pond that initially contains 10 million gallons of fresh water.[1] Water containing an undesirable chemical flows into the pond at a rate of 5 million gallons per year and the mixture in the pond flows out at the same rate. Suppose the concentration of the chemical in the incoming water is 2 grams per gallon. Let $Q(t)$ denote the amount of the chemical in grams in the pond at time t.

   (a) Write a differential equation for the quantity $Q = Q(t)$, where t is measured in years.

   Solution: Use the conservation principle:

   $$\frac{dQ}{dt} = \text{rate of } Q \text{ in } - \text{rate of } Q \text{ out},$$

   for the amount of chemical, $Q(t)$, in grams, in the pond at time t. The rate of inflow of Q is modeled by

   $$\text{rate of } Q \text{ in } = c_{\text{in}} F,$$

   where c_{in} is the concentration of the chemical going in (in this case, $c_{\text{in}} = 2$ grams per gallon), and F is the rate of flow of water into the pond (in this case, $F = 5$ million gallons per year). We then have that

   $$\text{rate of } Q \text{ in } = 10 \text{ million grams per year.}$$

   The rate of Q out is

   $$\text{rate of } Q \text{ out } = c(t)F,$$

   where

   $$c(t) = \frac{Q(t)}{V}$$

   is the concentration of the chemical in the pond (here, we are assuming instant mixing). The volume, V, of the water in the pond is 10 million gallons (we are assuming that the rate of flow of water into the pond is the same as the rate of flow out, so that the volume of water in the pond remains constant). Thus,

   $$\text{rate of } Q \text{ out } = \frac{1}{2}\, Q(t) \text{ million grams per year.}$$

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[1] Adapted from Example 3 on page 34 of *Elementary Differential Equations and Boundary Value Problems,* Seventh Edition, by Boyce and DiPrima. Wiley, New York, 2001

Thus, the differential equation describing the evolution of $Q = Q(t)$ in time is

$$\frac{dQ}{dt} = 10 - \frac{Q}{2},$$

in millions of grams per year. □

(b) Give the equilibrium solution, $\overline{Q}$, to the equation in part (a).

Answer: $\overline{Q} = 20$ million grams. □

(c) Give $Q(t)$ for all t, and sketch an approximate graph of Q as a function of t.

Solution: The general solution is $Q(t) = 20 + Ce^{-t/2}$, where C is an arbitrary constant. Since there was no chemical in the pond initially, $Q(0) = 0$. Then, $C = -20$, so that

$$Q(t) = 20(1 - e^{-t/2}).$$

A sketch of the graph of $Q = Q(t)$ is shown in Figure 1. □

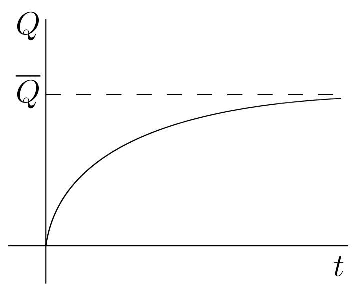

Figure 1: Sketch of graph of $Q(t)$

(d) What is the limiting value of $Q(t)$ as $t \to \infty$?

Answer: The limiting value of $Q(t)$ as $t \to \infty$ is $\overline{Q} = 20$ million grams. □

2. Consider a tank used in certain hydrodynamic experiments.[2] After one experiment, the tank contains 200 liters of a dye solution with a concentration of 1 gram per liter. To prepare for the next experiment, the tank is to be rinsed

[2]Problem 1 on page 57 of *Elementary Differential Equations and Boundary Value Problems,* Seventh Edition, by Boyce and DiPrima. Wiley, New York, 2001

with fresh water flowing at the rate of 2 liter per minute. The well–stirred solution flows out at the same rate. Find the time that will elapse before the concentration in the tank reaches 1% if its initial value.

Solution: Let $Q(t)$ denote the amount of dye in the tank in grams as a function of time, t, in minutes. We use the conservation principle

$$\frac{dQ}{dt} = \text{rate of } Q \text{ in } - \text{rate of } Q \text{ out.}$$

In this case

$$\text{rate of } Q \text{ in } = 0,$$

and the rate of Q out is

$$\text{rate of } Q \text{ out } = c(t)F,$$

where $c(t)$ is the concentration of the dye, and $F = 2$ liters per minute. We assume that the volume, V, of solution in the tank is fixed at 200 liters. We then have that

$$\frac{dQ}{dt} = -2c(t). \tag{1}$$

Dividing the differential equation in (1) by $V = 200$, we obtain a differential equation for the concentration of dye in the solution:

$$\frac{dc}{dt} = -\frac{1}{100}\,c(t). \tag{2}$$

The general solution of (2) is

$$c(t) = Ce^{-t/100},$$

where C is an arbitrary constant. Since $c(0) = 1$ gram per liter, we have that $C = 1$. Therefore,

$$c(t) = e^{-t/100}$$

in grams per liter.

We would like to find the time, t, in minutes, at which $c(t) = 0.01$; that is, 1% of the initial concentration. Thus, we need to solve the equation

$$e^{-t/100} = 0.01,$$

which leads to $t \approx 460.5$ minutes, or about 7 hours and 40 minutes. □

3. Luria and Delbrück[3] devised the following procedure (known as the *fluctuation*

[3](1943) *Mutations of bacteria from virus sensitivity to virus resistance. Genetics*, **28**, 491–511

test) to estimate the *mutation rate, a*, for certain bacteria:

Imagine that you start with a single normal bacterium (with no mutations) and allow it to grow to produce several bacteria. Place each of these bacteria in test–tubes each with media conducive to growth. Suppose the bacteria in the test–tubes are allowed to reproduce for n division cycles. After the n^{th} division cycle, the content of each test–tube is placed onto a agar plate containing a virus population which is lethal to the bacteria which have not developed resistance. Those bacteria which have mutated into resistant strains will continue to replicate, while those that are sensitive to the virus will die. After certain time, the resistant bacteria will develop visible colonies on the plates. The number of these colonies will then correspond to the number of resistant cells in each test tube at the time they were exposed to the virus.

(a) Estimate the probability, p_o, that at the end of the n division cycles there will be no resistant bacteria. State all assumptions you make and justify your answer.

***Solution**:* The mutation rate, a, is the probability that a mutation will occur during a single cell division. In n division cycles there will be $N = 2^n$ bacteria. During that period of time, there have been

$$1 + 2 + 2^2 + \cdots + 2^{n-1},$$

divisions since each bacterium in previous generations has divided. If we denote the number of divisions by D, then we see that

$$2D = 2 + 2^2 + \cdots + 2^{n-1} + 2^n = D + 2^n - 1.$$

It then follows that $D = 2^n - 1$, and so the number of divisions is $2^n - 1$ or $N - 1$. The probability that there is no mutation in any of the cell divisions is then

$$p_o = (1 - a)^{N-1}.$$

If we write $\mu = a(N-1) \approx aN$, the average number of mutations, then

$$p_o \approx \left(1 - \frac{\mu}{N}\right)^{N-1} \approx e^{-\mu}$$

when N is very large.

Alternatively, if we model the number of mutations, $M(n)$, by a Poisson random variable with parameter $\mu = \mu(n)$, where n is the number of division cycles, then the probability of no mutations is

$$p_o = P[M(n) = 0] = e^{-\mu(n)} = e^{-\mu}. \qquad \square$$

$\square$

(b) In one of the experiments of Luria and Delbrück in 1943, they observed that out of 100 cultures, each of about 2.8×10^8 bacteria, 57 showed no resistant bacteria. Use this information to estimate:

i. The average number of mutations, μ, that occurred before the bacteria were exposed to the virus;

Solution: In this case $p_o \approx 0.57$; so that, from $p_o = e^{-\mu}$, we obtain that

$$\mu \approx -\ln(p_o) = -\ln(0.57) \doteq 0.56. \qquad \square.$$

$\square$

ii. The mutation rate, a; that is, the probability that a given bacterium will mutate in a division cycle.

Solution: There are two possible answers to this question:

Answer 1:
$a \approx \dfrac{\mu}{N} \approx \dfrac{0.56}{2.8 \times 10^8} \doteq 2.0 \times 10^{-9}.$

Answer 2:
Integrating $\mu'(t) = aN(t)$ with respect to t, we obtain that

$$\mu(t) = \frac{a}{k}(N(t) - 1),$$

where k is the *per capita* growth rate of the bacteria. If t is measured in numbers of division cycles, then $N(t) = 2^t$ and therefore $k = \ln 2$. When $t = n$ and n is very large,

$$\mu(n) \approx \frac{a}{\ln 2} 2^n = \frac{aN}{\ln 2}.$$

Therefore, $a \approx \ln 2 \dfrac{\mu}{N} \approx (0.6931)\dfrac{0.56}{2.8 \times 10^8} \doteq 1.4 \times 10^{-9}.$ $\square$

4. Imagine a culture grown from a single bacterium. Suppose that there have been n division cycles. Assume that no bacterium has died during those cycles.

(a) How large is the culture? How many divisions have there been? Assume that all divisions that occur during the same cycle happen at the same time (these are usually referred to as *synchronous divisions*).

Solution: If the number of division cycles is n, then the total bacterial population is $N = 2^n$ at the end of the n division cycles. During that period of time, there have been

$$1 + 2 + 2^2 + \cdots + 2^{n-1}$$

divisions since each bacterium in previous generations has divided. If we denote the number of divisions by D, then we see that

$$2D = 2 + 2^2 + \cdots + 2^{n-1} + 2^n = D + 2^n - 1.$$

It then follows that $D = 2^n - 1$, and so the number of divisions is $2^n - 1$ or $N - 1$. $\square$

(b) Recall that the mutation rate, a, gives the probability that a given bacterium will mutate during a division. Let N denote the total bacterial population in a culture grown out of a single bacterium in n division cycles. Show that the probability, p_o, of no mutants present after the n division cycles can be approximated by $e^{-\mu}$, where $\mu = aN$ and N is very large.

Suggestion: If D is the number of divisions that have occurred in n division cycles, what is the probability that no mutation has occurred in any of those divisions? What happens to this probability as N tends to infinity?

Solution: The probability that there are no mutants at the end of the n^{th} division cycle, is the probability that there have been no mutations in the $N - 1$ divisions that have occurred. The probability of no mutation in one division is $1 - a$. It then follows that

$$p_o = (1 - a)^{N-1}.$$

Writing a as $\dfrac{\mu}{N}$ we then have that

$$p_o = \left(1 - \frac{\mu}{N}\right)^{-1} \left(1 - \frac{\mu}{N}\right)^{N}.$$

Thus, for N very large,

$$p_o \approx \lim_{N\to\infty} \left\{ \left(1 - \frac{\mu}{N}\right)^{-1} \left(1 - \frac{\mu}{N}\right)^{N} \right\} = e^{-\mu}.$$

$\square$

(c) There will be exactly one mutant in the culture after n division cycles if no mutation occurs in the first $n-2$ cycles, and exactly one mutation occurs in the $(n-1)^{\text{st}}$ cycle.

i. Explain why the probability of one mutation in the $(n-1)^{\text{st}}$ cycle is $a \cdot 2^{n-1}$.

Solution: Since a is the probability of a mutation in a bacterium per division, then the fraction of bacteria that can mutate in the $(n-1)^{\text{st}}$ division cycle is

$$\frac{a \cdot (\text{number of bacteria})(\text{number of divisions})}{\text{number of bacteria}} = a \cdot 2^{n-1},$$

since each bacterium divides. □

ii. Estimate the probability, p_1, that there will be exactly one mutant in the culture after n division cycles, if the culture size, N, is very large. *Suggestion:* If D is the number of divisions that have occurred in n division cycles, what is the probability that no mutation has occurred in $D-1$ of those divisions, and exactly one mutation occurs in one division? What happens to this probability as N tends to infinity?

Solution: There will be exactly one mutant if there is exactly one mutation in the D divisions and that mutation occurred in the $(n-1)^{\text{st}}$ division cycle. Thus,

$$p_1 = P[\text{only one mutation occurred}] \cdot P[\text{mutation occurred at } (n-1)^{\text{st}} \text{ cycle}]$$

By part (a), $P[\text{one mutation at } (n-1)^{\text{st}} \text{ cycle}] = a \cdot 2^{n-1}$.

If D denotes the number of divisions in n cycles, then $D = N-1$, where $N = 2^n$. Thus the probability that exactly one mutation occurred is the probability that no mutation occurs in $N-2$ of those divisions. Thus,

$$P[\text{only one mutation occurred}] = (1-a)^{N-2}.$$

It then follows that

$$p_1 = (1-a)^{N-2} \cdot a \cdot 2^{n-1} = \frac{aN}{2}(1-a)^{N-2}.$$

Writing μ for aN we then have $p_1 = \dfrac{\mu}{2}\left(1 - \dfrac{\mu}{N}\right)^{N-2}$. Therefore, letting $N \to \infty$, we get that

$$p_1 \approx \frac{\mu}{2} e^{-\mu}.$$

□

(d) If the number of mutants, r, in the culture is equal to 2, two bacteria might have mutated during the $n-1$ division cycle, or one bacterium might have mutated during the $n-2$ cycle giving rise to 2 mutants after cell division in the $n-1$ cycle. Estimate the probability, p_2, of this event for N very large.

Solution: p_2 is the sum of the probability that two mutations occurred in the $(n-1)$–cycle, and the probability that only one mutation occurred in the $(n-2)$–cycle.
Let $D = N - 1$ denote the total number of divisions.
The probability that only one mutation occurred in the $(n-2)$–cycle is probability that no mutation occurred in all but three of the divisions (the ones that will stem from the single bacterium that mutates in that cycle), times the probability that a mutation will occur in that cycle. The former is $(1-a)^{N-4}$ and the latter is $2^{n-2}a$, or $\dfrac{N}{4}a$. It then follows that

$$P[\text{only one mutation occurred in } (n-2)\text{–cycle}] = (1-a)^{N-4} \cdot \frac{aN}{4}.$$

The probability that only two mutations occurred in the $(n-1)$–cycle is the probability that no mutations occur in all but two of the divisions, times the probability that two mutations occur during that cycle. The former is $(1-a)^{N-3}$ and the latter is $a2^{n-1} \cdot a(2^{n-1}-1)$, or $a^2 \cdot \dfrac{N}{2}\left(\dfrac{N}{2}-1\right)$. Thus,

$$P[\text{two mutations occurred in } (n-1)\text{–cycle}] = (1-a)^{N-3} a^2 \cdot \frac{N}{2}\left(\frac{N}{2}-1\right).$$

We then have that

$$\begin{aligned} p_2 &= (1-a)^{N-4} \cdot \frac{aN}{4} + (1-a)^{N-3} a^2 \cdot \frac{N}{2}\left(\frac{N}{2}-1\right) \\ &= (1-a)^{N-4} \cdot \frac{aN}{4} + (1-a)^{N-3} \frac{(aN)^2}{4}\left(1-\frac{2}{N}\right) \end{aligned}$$

Substituting μ for aN we then get that

$$p_2 = \left(1-\frac{\mu}{N}\right)^{N-4} \cdot \frac{\mu}{4} + \left(1-\frac{\mu}{N}\right)^{N-3} \frac{\mu^2}{4}\left(1-\frac{2}{N}\right).$$

Letting $N \to \infty$, we then get that

$$p_2 \approx \frac{\mu}{4}e^{-\mu} + \frac{\mu^2}{4}e^{-\mu} = \frac{1}{4}\mu(1+\mu)e^{-\mu}.$$

$\square$

(e) Use your results in the previous three parts to estimate the probability that there will be 3 or more resistant bacteria in the culture after n division cycles when the population size, N, is very large.

Solution: $P[r \geq 3] = 1 - (P[r = 0] + P[r = 1] + P[r = 2]$. Thus, by parts (2)–(4),

$$P[r \geq 3] = 1 - p_o - p_1 - p_2 \approx 1 - e^{-\mu} - \frac{\mu}{2}e^{-\mu} - \frac{1}{4}\mu(1+\mu)e^{-\mu}.$$

This can be rewritten as

$$P[r \geq 3] \approx 1 - e^{-\mu}\left(1 + \frac{3}{4}\mu + \frac{1}{4}\mu^2\right).$$

$\square$