

Examples with biological content.
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Here we will attempt to supplement the examples and exercises given in the main courses of mathematics for biologists with more problems that are relevant to the biological sciences, which, after all, is supposed to be the main topic of application of the mathematical concepts dealt with.

This set of examples is by no means even close to representing all of the most important applications to biology that are being used today; most of the deeper examples use mathematical tools that are beyond the scope of the texts in current use. However we think that what we provide shows the significance and potential of the use of mathematics in this area.

1 The concept of function.

1.1 Use of functions in medicine and pharmacology.

1.1.1 A patient is administered a certain drug (for example, an antibiotic), with a given initial dose. It is well known that the drug will be broken down into different compounds and that the body will secrete it through the liver and kidneys, among other mechanisms.

Suppose now that an initial quantity M (measured, usually, in milligrams) of a drug is given to a patient in a single dose treatment and that the drug is never totally eliminated from the bloodstream. Then we can define:

$$\begin{aligned} f & : [0, \infty) \rightarrow [0, M], \\ f(t) & = \text{amount of drug in the bloodstream at time } t. \end{aligned}$$

Since, at any instant after the initial dose there is exactly one amount of drug in the bloodstream, this defines a function. The main problem here is that it seems that we are just giving a name to our ignorance and that we gain nothing with defining this function; however, here is where the use of mathematical modeling, based on firm biological knowledge, will allow us to produce formulas that will give us a good handle on predicting the values of the function and thus will give us much needed information on how to proceed after this initial dose.

An observation worth pointing out at this moment is the following: suppose that we do get to be able to predict the amount of drug present in the

bloodstream at any time after it is introduced and that a treatment is designed so that the patient is administered the same amount of the drug at fixed intervals of time (for instance, once a day for the drug PROZAC). Then the amount of drug immediately after the administration of the second dose must account for that amount of drug left in the patient from the previous one and, if treatment continues, there will be a gradual buildup of drug in the patient's bloodstream; the relevant question then becomes: can we predict what amount of drug will be in the patient after a prolonged period of treatment?

1.1.2 A person is infected with a virus (for example HIV 1). Then, if time 0 is the initial time of infection, we can define a function $v : [0, \infty) \rightarrow [0, \infty)$ by the rule $v(t)$ = amount of virus in the blood of the patient at time t . Whichever way we use to determine the amount of virus in the blood of the patient, this defines a function, which is called the "viral load" of the patient.

There is a significant practical difference between the functions in these examples: in the first example there are very good models to predict the value of the function at any given time for a myriad of compounds that may enter the bloodstream; in the case of HIV, the viral load is a function still waiting for good models to be able to predict its behavior, as well as to predict what happens when a treatment against the virus is used, for example with combinations of protease inhibitors used in conjunction with other drugs (see, for example, the article "Failure Isn't What It Used to Be...But Neither is Success", by Jon Cohen, Science, VOL. 279, 20 February 1998, 1133-1134).

1.1.3 Consider the left ventricle of the heart, which has an inflow (mitral) valve as well as an outflow (aortic) valve. We start measuring the output of blood at a certain initial moment 0 and define a function $V : [0, \infty) \rightarrow R$, $V(t)$ = volume of blood pumped per unit time at time t .

Again we are in the presence of a function which we would like to determine for an individual of "normal" type. In this case much work has been done to find good models for it but still much work is required to produce a function which can be relied upon to accurately predict what happens in a "normal" left ventricle (see, for example, "Mathematics in Medicine and the Life Sciences" by F. C. Hoppensteadt and C. S. Peskin, Springer-Verlag TAM 10, New York, 1992).

These are just three examples of a great number of models being used and constructed to study problems related to the prediction of outcomes in medicine and allied areas.

1.2 Examples of functions in population dynamics.

1.2.1 The first example considers the dynamics of a single population in a given environment. This is an approximation to real population dynamics

since it is clear that there are many factors in the environment (including the presence of other organisms that affect the growth of the one being studied); however, in many cases it does prove to be a useful tool and it can lead to some very interesting mathematical problems.

Consider a population which at any instant is made up of members of a single generation; examples of this are provided by many insect populations, most having one short-lived generation per year. Our goal is to try to set up a mathematical approach to predicting the sizes of the generations to come.

We will look at this problem in the following way: we want to measure the population size in a way that any positive real number is possible (not just positive integers) so we will chose to measure the population by its total mass. Then we define the function $g : [0, \infty) \rightarrow [0, \infty)$ by the rule

$$g(x) = \text{population size of the next generation if the current one has size } x.$$

We assume that we have measured the size of a population which we call the original generation, and has size x_0 .

The next generation will have size $g(x_0)$, the generation that follows has size $g(g(x_0))$ and so on. You can already see the pattern and one question that you will have to address at some time is whether or not you can predict if the population will become extinct?, will it tend to a given size as generations advance in number? or, can you predict that the population size will be changing constantly between well defined limits?

To ease notation with this type of model we will denote by I_X the identity function in any set X , that is, $I_X : X \rightarrow X, I_X(w) = w, w \in X$. If the set X in question is assumed to be obvious, we will simply write I instead of I_X . If $g : X \rightarrow X$ is a function we define $g^{*0} = I_X, g^{*1} = g$ and $g^{*(n+1)} = g \circ g^{*n}$ (this is an inductive definition where the symbol \circ stands for function composition); notice that $g^{*2} = g \circ g, g^{*3} = g \circ g \circ g$, etc.

With this notation we say that if we start with an initial population size of x_0 then the solution to the problem is the sequence $\{g^{*n}(x_0)\}_{n=0}^{\infty}$, that is the sequence whose terms are $x_0, g(x_0), g^{*2}(x_0), g^{*3}(x_0), \dots, g^{*n}(x_0), \dots$.

One important observation is that if $g(x_0) = x_0$ then the future generations will all have size x_0 , that is the solution to the problem is a constant sequence. This is what is called an "equilibrium" population and whether or not it will be observed as occurring depends on its "stability" properties.

Another related question would be: when is the original size x_0 important in the long term behavior as long as it is positive?

1.2.2 Now we consider the propagation of an infectious disease. Suppose that it is discovered that a certain number n_0 of people which are infected with a contagious disease are introduced into a certain population (a city, a country, etc.). Then the goal would be to predict how many persons will get the disease in the long run and what can be done to minimize the impact of the epidemic.

What we need here is a mathematical description of the function $F : [0, \infty) \rightarrow [0, \infty), F(t) =$ number of infective persons at time t .

This is a problem that has been studied during all of this century and many mathematical models have been produced to achieve this goal. The models will certainly change with the nature and characteristics of the disease.

1.2.3 A more subtle but very important example is that of tumor growth. We can consider a tumor as a population of cells that behave in a different manner than that where they originated from.

We could state the simple approach of defining a function of time that tells us the size of the tumor at time t after detection. The way to model this problem (which is certainly a research problem in most cases) is to describe its "rate of growth" given its current size. This leads to a problem in the mathematical area of "differential equations", upon which many of the examples given above rely, and which, in general states the problem: "if you know the rate of growth of a quantity, and its original size, can you predict the size for future times?"

The answer to than question is "yes" in many circumstances, but it takes quite a bit of mathematical knowledge before you can even approach the problem.

2 Composition of Functions.

2.1 Pharmacology and medicine.

2.1.1 Consider the following situation: a certain medicine is prescribed and the patient will be monitored 24 hours. We define $g : [0, \infty) \rightarrow [0, \infty)$ by the rule $g(x)$ = amount of the medicine left in the patient exactly after 24 hours.

If the medicine will be administered only once and we want to know the progress of the amount left in the patient over the days, we must consider the compositions $g = g^{*1}$, $g \circ g = g^{*2}$, $g^{*2} \circ g = g^{*3}$, and so on. If a dose prescribed is to be of x_0 units, then after the first day there is $g(x_0)$ units, after the second day there is $g^{*2}(x_0)$ units, after the third day there is $g^{*3}(x_0)$ units, and so on.

Another scenario is the following: the medicine is prescribed so that a dose of x_0 units is to be administered the first time, with a dose of m units to be given to the patient exactly every 24 hours.

Now we would like to know the amount of the medicine in the patient immediately after administration of the drug. We realize that when the drug is administered twenty four hours after the initial dose, there is $g(x_0)$ amount of it left in the patient so after the second dose there is $m + g(x_0)$ amount in the patient; after the third dose, there will be $m + g(m + g(x_0))$ amount in the patient, and we are forced to consider the following functions and their compositions: g and $h : [0, \infty) \rightarrow [0, \infty)$, $h(x) = m + g(x)$, h^{*2} , h^{*3} , ...

The solution to this problem is the sequence $\{x_n\}_{n=0}^{\infty}$, $x_{n+1} = h^{*n}(x_0)$.

2.1.2 From a simplistic point of view, suppose that a patient is infected with a bacterium and that we define the function $f : [0, \infty) \rightarrow [0, \infty)$, $f(t) =$

number of bacteria present in the body at time t after initial infection. The immune system will react to this microorganism by producing B-cells of a very specific nature that will produce antibodies that will lead to the destruction of this specific type of bacteria, and we define a function $g : [0, \infty) \rightarrow [0, \infty)$, $g(x) =$ rate of production of the specific B-cell if there are x bacteria present in the body. Then $g \circ f(t) =$ rate of production of these B-cells t units of time after initial infection.

In this example it must be understood that the view of the immune system is totally naive and the number of important different components of it, such as the variety of cells that it uses and their interactions, that this example should be taken just as an illustration of how composition of functions plays a role in it. Understanding the immune system is so essential and urgent that its importance cannot be exaggerated. It is a complicated subject and understanding it brings the prospect of more effective treatments and cures for diseases that are poorly understood today.

2.2 Population dynamics.

2.2.1 Suppose that in a given region there is deer overpopulation and that as a consequence of this there is a tick infestation in that region. If we let 0 be the time when the overpopulation is detected and we define the functions $f : [0, \infty) \rightarrow [0, \infty)$, $f(t) =$ mass of the deer in the region at time t and $g : [0, \infty) \rightarrow [0, \infty)$, $g(x) =$ number of ticks in the region if the deer mass is x , then $g \circ f(t) =$ number of ticks present at time t after the detection of deer overpopulation.

A natural question is: Why use the mass of the deer instead of the number of deer?

An answer to the question is that using mass we are allowed to use the nonnegative real numbers, not just the nonnegative integers, in making mathematical models for the problem, which sometimes is a matter of great importance in being able to come to conclusions using these models; also one might argue that deer of different sizes carry different number of ticks and that this point of view allows us to simplify our thinking about the problem and to center on the relevant aspects of it.

2.2.2 Suppose that there is a species of fish that is in demand for human consumption, so that harvesting the species is being done. Suppose that if there is overharvesting of the species, it will go to extinction. Let 0 denote the initial time when it was decided that a harvesting strategy should be adopted, and that the quantity of fish harvested depends on the amount of fish present.

Define: $f : [0, \infty) \rightarrow [0, \infty)$, $f(t) =$ mass of fish present at time t , and $g : [0, \infty) \rightarrow [0, \infty)$, $g(x) =$ greatest mass of fish that can be harvested without bringing the species to danger of extinction. Then the function $g \circ f$ tells you

the largest amount of fish that can be harvested at time t without bringing the species to be in danger of extinction.

There are many variations on this theme, one of them being that of finding a harvesting strategy that insures that every year there will be at least a certain given amount of harvesting that can be done safely. There are mathematical models for these types of problems which either lead to find explicit formulas for the functions given considerations such as rate of growth of the species, how much fish can be supported by the environment where it lives, etc., or that analysis of the model will answer the questions about this problem without finding the explicit functions but that assuring us that these functions do in fact exist.

2.2.3 Suppose that a certain type of yeast is being cultured in order to harvest some of the by-products it produces. Define $f : [0, \infty) \rightarrow [0, \infty)$, $f(t)$ = amount of yeast in the culture at time t , and define $g : [0, \infty) \rightarrow [0, \infty)$, $g(x)$ = amount of by-product produced by an amount x of yeast. Then $g \circ f(t)$ = amount of by-product produced at time t .

3 Inverse Functions.

3.1.1. An example in pharmacology.

A drug is administered to a patient and it is very reasonable to assume that the amount of drug present in the bloodstream diminishes as time goes by.

For the purposes of this example we will suppose that after a certain amount of time the amount of drug in the bloodstream is undetectable (this is how it really happens), being aware that in the solutions of many of the mathematical models available for this purpose, the drug stays in the bloodstream forever, though at increasingly smaller amounts, so much so that even the most sophisticated instrument will not detect it after a certain amount of time; most biologists would say that if you cannot measure a substance in the bloodstream then it is not there, however these days this perception is changing since there are treatments for AIDS that bring down the viral load to undetectable levels but the disease is still present.

Hence we assume that there is a first time T when the drug is totally eliminated from the bloodstream. If we let K be the initial dose administered, and if no further doses of the drug are given, then we define $f : [0, T] \rightarrow [0, K]$, $f(t)$ = amount of drug present in the bloodstream at time t . Under our assumptions we have that $f(0) = K$, $f(T) = 0$, f has an inverse $f^{-1} : [0, K] \rightarrow [0, T]$. Then, if $x \in [0, K]$, $f^{-1}(x)$ = the instant when there is exactly x units of drug in the patient's bloodstream.

3.1.2 An example in medicine.

Most chemotherapy treatments for cancer use drugs that are designed to kill all 'rapidly reproducing cells', not just cancer cells, and as a consequence there is a host of side effects from this type of treatment. One very important class of cells that are affected are the blood cells, in particular the white blood cells; among the white blood cells, there is a class of cells called neutrophils which have a very important role in defending the patient against infections.

Suppose that a patient undergoes a chemotherapy session and that the amount of neutrophils is being monitored, finding that for a period of time, say T days, the number of neutrophils is decreasing. Let N_0 be the number of neutrophils per cubic centimeter of blood right before chemotherapy and let n_0 be the number after T days. Then the function $f : [0, T] \rightarrow [n_0, N_0]$, $f(t) =$ number of neutrophils per cubic centimeter of blood t days after chemotherapy; this function is assumed to have an inverse and $f^{-1} : [n_0, N_0] \rightarrow [0, T]$ has the interpretation $f^{-1}(x) =$ number of days since chemotherapy when the patient has exactly x neutrophils per cubic centimeter of blood.

Again the comment should be made that this is a function for which we do not have a formula to describe it; certainly this function will change from patient to patient, due to many factors that have to be taken into account, but it is an important function to know. Of course it is known which numbers of neutrophils are considered dangerously small and then appropriate action, if at all possible, must be taken.

4 Exponential and logarithmic functions.

A very interesting fact about the natural exponential function and the natural logarithmic function is that they arise as solutions of many mathematical models in biology which are constructed using considerations about the rate of growth of the quantities involved; in this sense they are "inescapable" when dealing with models in biology.

4.1 Population dynamics.

4.1.1 One of the first examples we run into is that of exponential growth of a population, and one of the first facts about it that is striking is that it predicts that the population will always increase in size, no matter what. If you consider the effects of crowding and its associated results (such as the accumulation of toxic waste, etc.) and the fact that environments can only support a certain maximum population (due to food supply, space, etc.) we realize that this model, even though very useful in modeling the growth for certain organisms for a not too long period of time, should be modified for long term use.

One of the first models to take these facts into account is called the logistic growth model, which is derived using considerations about what affects

the growth rate of the population and the capacity of the environment to sustain the species. The maximum capacity of the environment relative to the particular organism is called the carrying capacity of the environment. In what follows we will assume that the carrying capacity of the environment is a fixed quantity, which is a good assumption for laboratory situations where there is control of the different components needed by the organism, or in regions where the effect of seasonal fluctuations is not a significant factor; if the carrying capacity is assumed to change with time then the model is not so easily manipulated so as to be able to get explicit formulas.

We will denote by K the carrying capacity of the environment, x_0 the initial population size and by r the growth rate of the species. Then the function

$$f : R \rightarrow [0, \infty)$$

$$f(t) = \frac{Kx_0e^{rt}}{K + x_0(e^{rt} - 1)}$$

yields the population size at time t .

It is worth noting that if $x_0 = 0$ then $f(t) = 0$ for all t , so there is no spontaneous generation of life. Also, if ever $f(t) = K$ then $f(t) = K$ for all t .

It is very illustrative to graph these function with different values for the initial population and different values for this carrying capacity as well as different values for the growth rate.

4.1.2 Models of discrete growth. What we are referring to here are models for species for which the generations do not overlap and so the general model for the population size in different generations is given by $x_0 =$ initial population, $g(x_0) =$ size of first generation, $g^{*2}(x_0) = g \circ g(x_0) =$ size of the second generation, $g^{*3}(x_0) = g \circ g^{*2}(x_0) =$ size of third generation, and so on. Notice that if $x_0 > 0$ and $g(x_0) = x_0$ then the population size remains at this value for all generations thus the points of intersection of the graph of g with the graph of $f(x) = x$ that are in the first quadrant are of special interest.

One formula for g that has been used is: $g(x) = xe^{r(1-x/K)}$, where r is the multiplicative growth factor per generation and K is the carrying capacity of the environment (see, for example Theoretical Ecology, Principles and Applications, edited by Robert M. May, W. B. Saunders Company, 1976, page 10, and it is recommended that you graph this function and the function $f(x) = x$ and see how the population sizes behave relative to these graphs (this is the so-called "method of cobwebbing).

4.2 Models Involving Exponential and Logarithmic Functions.

One important fact about the models that consist of functions of the type $f(t) = Ke^{\alpha t}$, i.e. models of exponential growth and exponential decay,

is that they have associated to them either "doubling time" (in exponential growth) or "half life" (in exponential decay).

Of course nothing is without controversy in biology, in particular there is quite a bit of discussion on the topic of the applicability of exponential decay models in pharmacology. However, these models are used extensively and one thing to remember is that whenever a "half life" of a drug is given, there is an underlying assumption that an exponential decay model is applicable.

We proceed to give you a table with published half life for some drugs and the we will build problems using this data (the information on Ibuprofen comes from the manufacturer via a pamphlet included in the packaging, the rest was obtained from the Drake Pharmacy Homepage).

Drug	Half life	Duration of Action	Main uses
Ibuprofen	1.8 hours	ultra-short (<6 hours)	Pain relief
Lorazepam, Oxazepam, Temazepam	8-12 hours	short (12-18 hours)	Anxiolytic, Hypnotic
Triazolam	2-4 hours	ultra-short	Hypnotic
Alprazolam	6-12 hours	medium (24 hours)	Anxiolytic, Depressant
Nitrazepam	16-40 hours	medium	Hypnotic, Anxiolytic
Diazepam, Chlordiazepoxide	20-40 hours	long (24-48 hours)	Anxiolytic, Anticonvulsant
Flurazepam	1 hour	long	Anxiolytic
Clonazepam	50	long	Anticonvulsant, Anxiolytic

4.2.1 Consider the drug Ibuprofen; according to its manufacturer it has a half life of approximately 1.8 hours, so we will accept this number as half life for Ibuprofen . Note that by just accepting that there is a half life for this drug we are accepting that the quantity of Ibuprofen in the bloodstream is undergoing exponential decay.

a) A patient is prescribed four 200 mg. tablets every six hours. Which is the minimum amount of the drug that will be present in the bloodstream in the first 24 hours of treatment?

b) What amount of Ibuprofen will the patient in a) have in his system 13 hours after starting with the first dose?

c) If a person takes an initial dose of Ibuprofen and 5 hours later there is 300 mg. left in the person, what was the initial dose?

4.2.2 Consider the drug PROZAC. It is known that 75 days after taking a dose of this drug, 5% of the original quantity remains in the patient. We assume that PROZAC undergoes exponential decay.

a) What is the half life of PROZAC?

b) If a patient takes 40 mg. every 24 hours, how much drug is in his system after the tenth dose is taken (assuming it is absorbed instantaneously)?

c) If a patient takes 40 mg. of the drug every 24 hours, how much drug is in the patient after 100 doses?

5 Periodic functions.

There are many functions of great biological interest which are periodic or "very close" to being periodic. A generic term for a great deal of them is "circadian rhythms", and their period can vary from seconds to many years.

Some examples of periodic functions with the period of 24 hours (one day), are the temperature of a normal human body, systolic blood pressure, diastolic blood pressure, cortisol hormone secretion, etc., all with time measured in hours and the measurements in their appropriate units of choice.

Other periodic functions that arise in biology could include the amount of nutrients entering an ecosystem in a seasonal environment, the results of periodic stimulation of a cardiac pacemaker, etc. For example, one way to model a carrying capacity with period of one year would be to use a function such as $K(t) = K(1 + \alpha \cos(2\pi t))$ where $|\alpha| < 1$.

In general the periodic functions arising in biology will usually not be represented by a single trigonometric function but will be assumed to be or to be approximated by "trigonometric polynomials", which, for periodic functions of period 2π take the form

$$f(t) = \sum_{k=0}^n (a_k \cos(kt) + b_k \sin(kt)).$$

Here, f is an example of a real trigonometric polynomial of order n and, of course, the challenge will be to find the appropriate coefficients a_k, b_k in any real application to biology. Note that it is very easy to change the period under consideration, since if we are interested in a period p then the trigonometric functions appearing in the sum will be of the form $\cos(\frac{2\pi}{p}kt), \sin(\frac{2\pi}{p}kt)$.

6 Matrices.

We will present one interesting application of matrices to biology, the so-called Leslie matrices and Leslie's growth model for populations that are naturally segmented into different age classes. This model is used in management of animal herds, fisheries, etc.

A Leslie matrix is any square matrix with nonnegative entries where the nonzero entries can be only in the first row and the entries just below the main diagonal, i.e., if the order of the matrix is n and we pick nonnegative real numbers a_1, a_2, \dots, a_n and b_1, b_2, \dots, b_{n-1} , and if $A = [a_{i,j}]$ then $a_{1,j} = a_j, j = 1, \dots, n, a_{i+1,i} = b_i, i = 1, \dots, n-1$ and $a_{i,j} = 0$ if $i \neq 1$ and $j \neq i-1$.

When using these matrices to model populations, it is assumed that the entire population is divided into n age classes C_1, C_2, \dots, C_n , that the last class will not survive one more period of time (the period will depend on the nature of

the population being modeled, so it could be measured in weeks, years, decades, etc.) and the entries have the following interpretation: a_j is the average fertility of a member of age class C_j and the average survival rate of a member of class C_j to enter class C_{j+1} is b_j . Thus, in the modeling setting, the entries of a Leslie matrix will be small numbers, the ones right below the main diagonal being between zero and one.

The population is divided into the n age classes as a column matrix

$$x = \begin{bmatrix} x_1 \\ \cdot \\ \cdot \\ \cdot \\ x_n \end{bmatrix}$$

and the column matrix Ax is the population column matrix for the next period, $A \cdot Ax$ is the population for two periods later, and so on.

Leslie matrices combined with harvest policies can and do lead to sustainable harvesting strategies.