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Module 709

A Cell Population Model, Dynamical Diseases, and Chaos

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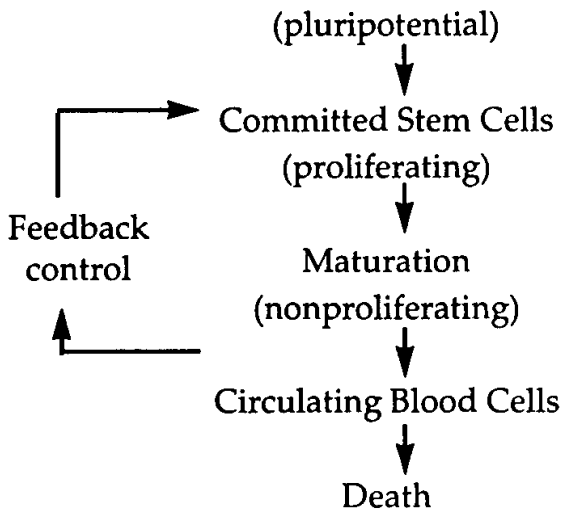

Applications of Discrete Dynamical Systems to Medicine

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INTERMODULAR DESCRIPTION SHEET:	UMAP Unit 708
TITLE:	A Blood Cell Population Model, Dynamical Diseases, and Chaos
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MATHEMATICAL FIELD:	Discrete Dynamical Systems
APPLICATION FIELD:	Medicine
TARGET AUDIENCE:	Upper-division undergraduates in applied mathematics, biology, and pre-medicine.
ABSTRACT:	This Module gives an introduction to the modeling of blood cell populations and the role of modeling in the study of dynamical diseases of the blood.
PREREQUISITES:	First-year calculus. Some experience with discrete dynamical systems and elementary real analysis would help.
RELATED UNITS:	Unit 553: Graphical Analysis of Some Difference Equations in Mathematical Biology, by M. Eisen. Unit 653: The Ricker Salmon Model, by R. Greenwell. UMAP Monograph: *Introduction to Population Modeling*, by J.C. Frauenthal.

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A Blood Cell Population Model, Dynamical Diseases, and Chaos

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MODULES AND MONOGRAPHS IN UNDERGRADUATE
MATHEMATICS AND ITS APPLICATIONS (UMAP) PROJECT

The goal of UMAP is to develop, through a community of users and developers, a system of instructional modules in undergraduate mathematics and its applications, to be used to supplement existing courses and from which complete courses may eventually be built.

The Project was guided by a National Advisory Board of mathematicians, scientists, and educators. UMAP was funded by a grant from the National Science Foundation and now is supported by the Consortium for Mathematics and Its Applications (COMAP), Inc., a nonprofit corporation engaged in research and development in mathematics education.

Paul J. Campbell — Editor
Solomon Garfunkel — Executive Director, COMAP

1. Introduction

Physiological systems of normal mammals display some easily recognized and predictable patterns. In a healthy state, for example, respiration is oscillatory, while blood cell counts are nearly constant.

However, in certain diseases, these patterns change. Systems that normally oscillate may become steady, or may begin to oscillate in a different manner; systems that were steady may begin to oscillate, perhaps in very complicated ways. Such disorders have been called *dynamical diseases* by Glass and Mackey [1979].

Generally, dynamical diseases are particular to physiological control systems, causing them to display abnormal dynamics. A variety of dynamical diseases have been identified in the respiratory system, the blood system, and other areas. In the blood, for example, a type of anemia and certain forms of leukemia have been identified as dynamical diseases. Although laboratory and clinical methods are of primary importance in studying these disorders, it is now recognized that mathematical modeling too is essential to understanding the nature of these diseases and to studying their treatment strategies.

In this Module we will consider the modeling of blood cell populations and show how mathematical modeling is used to explain the behavior and possible origins of dynamical diseases.

The blood cell system and the control mechanisms involved are very complex, and much is not well understood. The development of mathematical models of blood cell populations is quite recent. A number of models have been presented, each depending on the complexities of the blood cell type under study and using advanced mathematical concepts.

The model we consider is simple; its purpose is to illustrate some basic ideas and analysis used in the mathematical modeling of blood cell populations, and to show the interplay between mathematical modeling and the study of dynamical diseases of the blood. Even a first approximation to the dynamical complexity of blood cell populations involves an unexpected wealth of elementary but nontrivial ideas.

In particular, we will present the notion of chaotic behavior, a distinctive feature of many severe diseases. The possibility of the very complex dynamics of chaos was first recognized by Poincaré, but scientists have given it vigorous attention only in recent years. Indeed, chaotic dynamics have been documented in many areas including biology, electronics, and fluid mechanics.

2. A Blood Cell Population Model

We begin with a brief description of the process of blood-cell formation and destruction. We then develop a simple model to describe the dynamics of a blood cell population.

2.1 Blood Cell Formation and Destruction

Blood consists of two basic components: plasma and blood cells. Plasma is the fluid in which the blood cells are suspended. There are three general types of blood cells: red blood cells, white blood cells, and platelets.

Each type of blood cell has special functions. Red cells carry oxygen from the lungs to the body tissues, white cells protect the body from infection, and platelets help in blood clotting. Under normal conditions, the numbers and type of blood cells produced are controlled by the physiological needs at the time. For the red blood cells, oxygen deficiency leads to the production of the hormone erythropoietin, which stimulates development of red blood cells from among the primitive and committed stem cells. Thus, since red blood cells participate in oxygen transport, the red blood cell production rate increases as the number of red blood cells decreases.

With the exception of lymphocytes (a variety of white blood cell produced in lymphatic tissues), blood cells are formed from primitive stem cells resident in the bone marrow. The primitive stem cells are said to be *pluripotential* because they are capable of producing *committed stem cells*, that is, stem cells committed to develop eventually into one of the three cell types (red, white, or platelet). Once formed, the committed stem cells proliferate (through cell division). After a maturation phase, they become mature cells of the given type and enter the blood stream. This formation process takes several days.

For the white-cell line, the processes regulating the number of cells is not completely understood. It is thought that a decrease in the population leads to the production and release of granulopoietin, a hormone which stimulates the proliferative activity of the committed stem cells. However, granulopoietin has not been isolated, and other stimulating factors are known to exist.

Blood cells eventually die, either by natural aging, infection, or disease. For granulocytes, a type of white blood cell, death occurs randomly, with a half-life of about 7 hours. Red blood cells, on the other hand, have a lifetime of about 120 days.

Figure 1 gives a simplified view of the blood cell formation process. The arrows going from the circulating blood compartment to the committed stem cell compartment indicate the (feedback) control of the level of circulating blood cells on the production of new blood cells.

2.2 A General Model

We develop now a general model of the dynamics of a blood cell population. Later we will apply this model to red and to white blood cell populations, and also to the pluripotential stem cell population. Our model is necessarily highly simplified, partly so that we can better study its properties, but also because detailed models are very complex, depend substantially on the type of cell, and involve differential-delay equations that require sophisticated qualitative and numerical methods for analysis. Nevertheless, we shall see that this simple

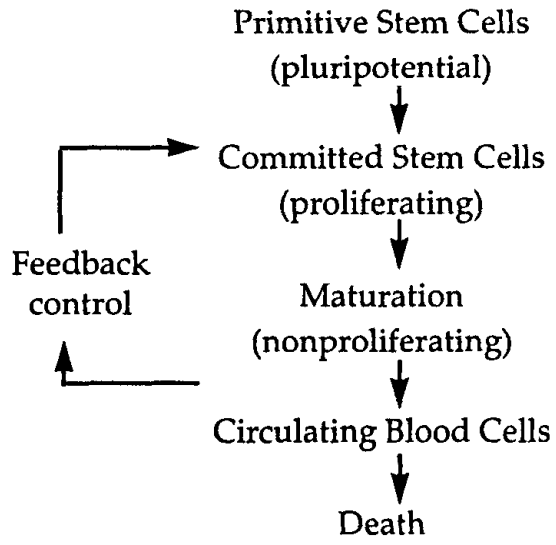

Figure 1. Formation and destruction of blood cells.

model still captures the distinctive features of blood cell population dynamics.

In a normal mammal, the concentration of blood cells is relatively constant or may show small oscillations. However, a blood cell population undergoes continual production and elimination of elements over time. Thus, to model the levels of blood cells, we must consider both production and destruction of cells. Time will be measured in discrete units of length Δ. We will refer to Δ as the *unit time* of the model. Set $t_i = i\Delta$, for $i = 0, 1, 2, \ldots$; and denote by x_i the number of blood cells of a certain type, per kilogram of body weight, at time t_i. Then the general model is given by

$$x_{i+1} - x_i = -d(x_i) + p(x_i),$$

where the function d measures the number of cells destroyed in the time interval t_i to t_{i+1}, and the function p measures the number of cells produced during this time interval. Each function is assumed to depend only on the number of cells at time t_i.

A simple but widely accepted model of destruction for a normal mammal is that during each time interval of length Δ, a constant fraction of cells is destroyed. That is,

$$d(x_i) = cx_i,$$

where c, a unitless constant independent of i and x_i, is called the *destruction coefficient*.

Information about the production function is sketchy. The particular form of the function depends on the type of cell. It is generally agreed that the production rate is a decreasing function over a wide range of cell levels. Indeed, we would expect the production rate to increase when the number of cells decreases. However, there is a critical level of blood cells below which an

organism cannot recover without treatment. Also, production becomes unnecessary at high blood-cell levels. Thus, we assume that $p(0) = 0$, that initially the graph of p is increasing, but that after reaching a maximum, the curve decreases to zero. There are many functions that fit this description. For example, in modeling the granulocyte population, Mackey and Glass [1977] have used the function

$$p(x) = \frac{b\theta^m x}{\theta^m + x^m}, \tag{1}$$

where b (unitless), θ (cells / kg), and m (unitless) are positive constants. Lasota [1977] has considered the function

$$p(x) = bx^s e^{-sx/r}, \tag{2}$$

where b, s, and r are positive constants. It is probably the case that the particular algebraic form chosen is not critical, provided a reasonable approximation to the production function is attained.

Supposing that the production function has been determined, the dynamics of the model are given by the iteration scheme

$$x_{i+1} = f(x_i), \qquad \text{for } i = 0, 1, 2, \ldots,$$

where

$$f(x) = (1 - c)x + p(x).$$

We call f the *iteration function* of the model.

This model incorporates a number of simplifications. A precise model would account for cell numbers at the various stages of development, from stem cells to circulating cells in the blood (see, for instance, Rubinow and Lebowitz [1975; 1976]). In addition, the production process involves a significant time delay. Granulocytes, for example, take about six days from the start of production to the appearance of mature cells. Thus the model might be more appropriately written

$$x_{i+1} - x_i = -d(x_i) + p(x_{i-k}),$$

where $k\Delta = \delta$, the delay in production. Including the delay explicitly, although apparently simple, complicates the analysis substantially. In our model, the delay is represented by the unit time Δ. In selecting Δ, then, there are two considerations. We must account for the delay, and also make sure that the assumed form of the destruction function is reasonable, namely, that a constant fraction of cells dies during the time interval Δ.

Under normal (healthy) conditions, the blood cells will attain a level in which the production and destruction of cells occur at equal rates. We will denote this level by v, and refer to it as the *steady-state level*. Thus v is a solution of the equation $d(v) = p(v)$. Equivalently, $v = f(v)$, so that v is a *fixed point* of f.

The destruction coefficient c, the unit time Δ, and the constants in the production function are the parameters of the model. A dynamical disease results

when parameter values stray away from those of the healthy state, causing the system to display abnormal dynamics. A mathematical model can help in identifying the nature of the disorder and in studying the effect of treatments. Our task now is to investigate the properties of our model.

Exercises

1. For the production function **(1)**, show that on $(0, \infty)$ there is a single maximum at $x = r_m\theta$ and a single inflection point at $x = s_m\theta$, where

$$r_m = \left(\frac{1}{m-1}\right)^{1/m} \qquad \text{and} \qquad s_m = \left(\frac{m+1}{m-1}\right)^{1/m}.$$

Sketch the graph of this production function for $x \geq 0$.

2. For the production function **(2)**, show that on $(0, \infty)$ there is a single maximum at $x = r$. Also show that for $s > 1$ there are inflection points at $x = r(1 \pm \sqrt{1/s})$ while for $0 \leq s \leq 1$ there is a single inflection point at the larger of these two. Sketch the graphs of this production function.

3. For given destruction coefficient c and production function p (either form **(1)** or form **(2)** above), sketch the graphs of $y = cx$ and $y = p(x)$ and locate the steady state v. For definiteness, take $c \in (0, 1]$ and assume the graph of p intersects the line $y = x$ for some $x > 0$. Denote the steady state by v_c. Show that v_c is decreasing as a function of c, and that $v_c \to \infty$ as $c \to 0^+$. Are these properties physically reasonable? Remark: With form **(2)** and $s > 1$, there are two positive solutions of $cx = p(x)$. Later, after introducing the notion of stability, we will see that only the larger solution is physically attainable (see **Exercise 10**).

3. Parameter Estimation and Model Validation

An important part of model development is verifying that the model reasonably reflects the system it represents. However, validation of models of dynamical diseases is especially difficult. Experimentation with humans, either normal or diseased, is necessarily very limited; and data obtained in clinical settings are approximate and fragmentary, and not designed to aid model verification. While experimentation with animals is a source of information, extending numerical results to humans may be uncertain. Even when data are available, estimating model parameters is doubtful for a system whose output is chaotic and possesses sensitive dependence on initial conditions and parameters. In addition, model parameters may vary substantially from person to person. Thus there are many problems with model verification [Glass and Mackey 1988, Chapter 9].

Still, it is possible to obtain some meaningful numerical data. For example, direct counts of cell concentrations are done routinely. Also, use of tracers to label cells has led to estimates of cell destruction rates and cell production rates (see, for example, Anderson [1983] or Rubinow [1975]). The following examples show how these data can be used to estimate parameters in our model.

Example 1:

For red blood cells, the time from the start of production to the release of mature cells in the blood is about six days. Thus we take the unit time Δ to be 6. Use of tracers indicates that the destruction rate of red blood cells under normal conditions is 2.3% per day [Mackey 1979b]. With Δ = 6 days, we can estimate c as $6 \times 0.023 = 0.14$. In a normal 70-kg man, the red-cell count is about 3.3×10^{11} cells/kg of body weight. This amount is our estimate of the steady-state cell count v. Now, under steady-state conditions, the rate of cell disappearance is $cv = 0.14 \times 3.3 \times 10^{11} = 4.62 \times 10^{10}$ cells/kg; and this amount must equal the steady-state production rate. Hence, we have located a point $(v, 0.14v)$ on the graph of the production function p; that is, $p(v) = 0.14v$.

Next, it is estimated that the maximum production rate is about 10 times the steady state rate, or 4.62×10^{11} cells/kg. This datum locates another point on the graph of p, although the value at which the maximum is attained needs to be determined.

Finally, experiments have found that for rabbits, reduction of the cell population to 75% of the steady-state count results in an increase in production of about 5 times the steady-state rate [Orr et al. 1968]. If we assume this response holds for humans also, then we have a third point on the graph of p, namely, $(0.75v, 5v)$.

We will assume that the production function has the form

$$p(x) = v\phi(x/v), \qquad \text{where} \qquad \phi(u) = bu^s e^{-su/r}.$$

Using the three points on the graph of p, we can determine b, r, and s.

The production function has been chosen particularly to simplify the arithmetic. The factor v on the outside of ϕ is used because all the measured production rates are given as multiples of v. The argument of ϕ, that is, x/v, has been chosen so that cell counts are measured in multiples of v, the multiple being the variable u. Thus cells counts can be expressed more simply. Finally, with this form of ϕ, the maximum occurs at $u = r$, allowing us to express the given datum on the maximum production rate more easily.

We obtain the following equations for the parameters.

$$\begin{aligned}
\text{Production at steady state:} \quad \phi(1) &= be^{-s/r} = 0.14, \\
\text{Maximum production:} \quad \phi(r) &= br^s e^{-s} = 10 \times 0.14 = 1.4, \\
\text{Production at 75\% of steady state:} \quad \phi(0.75) &= b(.75)^s e^{-0.75s/r} \\
&= 5 \times 0.14 = 0.70.
\end{aligned}$$

With some perseverance, these three equations can be solved for the parameters. For example, one can successively eliminate variables to obtain one equation in one unknown, which can then be solved by an iterative method, such as the bisection method or Newton's method. Approximate solutions are s = 8, r = 0.5, and $b = 1.1 \times 10^6$.

Example 2:

As mature cells, granulocytes (a type of white blood cell) are found in the blood and are also held in reserve in the marrow. As indicated earlier, the mechanisms regulating the production of these cells are not fully understood. In this example, however, let us assume that the feedback control that stimulates proliferative activity of committed stem cells is based on total cell count in the blood and the marrow reserve. The time from inception of cell production to appearance of mature cells is about six days [Mackey and Glass 1977]. Thus, we take the unit time Δ = 6. The cell destruction rate is about 10% per day [Mackey and Glass 1977; Erslev and Gabuzda 1985]. Hence, $c = 6 \times 0.1 = 0.6$. The steady-state total cell count v is about 8.2×10^9 cells / kg of body weight [Erslev and Gabuzda 1985]. Therefore, the steady-state rate of cell disappearance is

$$cv = 0.6 \times 8.2 \times 10^9 = 4.92 \times 10^9 \text{ cells / kg},$$

which in turn equals the steady-state production rate. Thus the production function satisfies $p(v) = 0.6v$. Finally, we will estimate the maximum production rate to be twice the production rate in the steady state. This factor is approximately that used by Mackey and Glass [1977].

These data locate two points on the graph of the production function. Assume that the production function has the form

$$p(x) = v\phi(x/v), \qquad \text{where} \qquad \phi(u) = bue^{-u/r}.$$

Then we have

$$\begin{aligned} \text{Production at steady state:} \quad \phi(1) &= be^{-1/r} = 0.6, \\ \text{Maximum production:} \quad \phi(r) &= bre^{-1} = 2 \times 0.6 = 1.2. \end{aligned}$$

Solving these equations for the parameters b and r yields the approximate solutions r = 0.37 and b = 8.7.

These examples illustrate several of the typical difficulties with parameter estimation in blood-cell population modeling. The available data are few and approximate. Also, some data are obtained from experiments with animals, the results of which may have uncertain application to humans. Of particular concern, however, is that much of the data pertains to the steady state only. But the model is supposed to describe also the behavior of the cell counts when the system is not in the steady state. How can we verify that the model reflects these dynamics?

An important way to study dynamical behavior of the blood cell population in humans is to observe the population when it is diseased. In clinical settings, however, it is not possible to obtain data from controlled experiments, as we could in the laboratory. For example, records of leukemia patients upon entering the City of Hope (a hospital located in the Los Angeles area) show variations in the white blood cell count by a factor of 750. Conditions among patients can vary widely, and hence so do the numerical data obtained.

As pointed out by Glass and Mackey [1988], published data on dynamical behavior are rare. Nevertheless, qualitative features of diseases are well established. Such features include steady states that are higher or lower than normal, or oscillations for which estimates of amplitudes or periods have been made. As one part of model verification, we need to see that the model is capable of displaying these patterns. If not, we certainly have reason to reject the model. It is this aspect of model verification that we will pursue in the next sections. To do so, we must first present some basic results about discrete dynamical systems.

Exercises

4. In **Example 2**, the maximum production rate was taken to be twice the steady-state rate. This factor is known only approximately and could be much higher. With the same production function as in **Example 2**, estimate the parameters using a factor of five instead.

5. The blood system is able to respond within a few hours to a depletion of granulocytes in the blood, with increases coming from the marrow reserve. The number of granulocytes in the marrow reserve is more than ten times that of the blood. As an approximation, we could model the number of granulocytes in the blood, independently of the feedback control to the committed stem cells, at least to study the effect of a small depletion over a short period of time. Let us assume such a model, so that now x_i represents the number of granulocytes in the blood at time t_i. The destruction rate of granulocytes in the blood is about 10% per hour and the steady-state cell count is about 7.0×10^8 cells/kg [Wheldon 1975; Rubinow and Lebowitz 1975]. Assume the maximum production rate is 6 times the steady-state rate [Wheldon 1975]. Taking $\Delta = 3$ hours and using the production function **(2)** with $s = 1$, estimate the parameters of the model.

4. Discrete Dynamical Systems

We summarize now some results concerning discrete one-dimensional dynamical systems which will be needed in the sequel [Devaney 1989; Edelstein-Keshet 1988; Eisen 1988; Frauenthal 1979; May 1974; May 1975; Perelson 1980].

4.1 Orbits, Stationary States, and Periodic Orbits

Let I be an interval, and let $f : I \mapsto I$ be a continuously differentiable function. The domain of f may be larger than I, but we are interested only in what happens on I. Points in I will be viewed as representing states of a system. Given $p \in I$, consider the sequence of points $x_0 = p$, $x_1 = f(x_0)$, $x_2 = f(x_1)$, and so on. This sequence x_i represents successive states of the system with initial state p. We shall call this sequence an *orbit* starting from p and denote it by $O(p)$.

The following notation will be convenient. Let f^i denote the composition of f with itself i times; that is, $f^i = f \circ f \circ \cdots \circ f$, i times, where f^0 is defined as the identity: $f^0(x) = x$ for all x. Then we can write $x_i = f^i(p)$, for $i = 0, 1, 2, \ldots$. If $x_1 = p$, i.e., $p = f(p)$, then p is called a *fixed point* of f, or a *stationary state* of the system, since no changes will take place if the initial state is p. If $x_n = p$ for some $n \geq 2$ and $x_i \neq p$ for all $0 < i < n$, then the point p, and the orbit $O(p)$, are called *periodic* with period n. In this case, the system goes repeatedly through the states of $O(p)$ in an orderly manner, and any one of the states could be considered an "initial" state. For each point x_i of the orbit, we have $f^n(x_i) = x_i$. Thus each point in the orbit is a fixed point of f^n.

4.2 Stability of Stationary States and Periodic Orbits

For a system in real life to reside exactly at a stationary state is unlikely, since there will always be minor disturbances that move the system slightly away from the stationary state. The question is: Will the system run away from the stationary state, or will it always tend to come back to the stationary state? We say the stationary state is *unstable* in the first case and *stable* in the second.

Suppose p is a fixed point of f and that $|f'(p)| < 1$. Using the mean value theorem and the continuity of f', we can show there is an interval J, centered at p, such that for any $x \in J$ the sequence of points in the orbit $O(x)$ converges to p (**Exercise 6**). Thus, when $|f'(p)| < 1$, we say p is a *local attractor* of the system, or a *stable fixed point* of f.

On the other hand, suppose that $|f'(p)| > 1$. Then, again using the mean value theorem and the continuity of f', we can show there is an open interval J about p such that for any $x \in J$ there is an integer n, depending on x, such that $f^n(x) \notin J$. It follows that the orbit $O(x)$ contains an infinite number of points outside of J (**Exercise 7**). Thus, when $|f'(p)| > 1$, we say p is a *local repellor* of the system, or an *unstable fixed point* of f.

Consider next a periodic orbit of period n: $p = x_0, x_1, \ldots, x_{n-1}, x_n = p$. As mentioned earlier, each point of the orbit is a fixed point of f^n. By the chain rule, we can show that (**Exercise 8**)

$$(f^n)'(x_i) = (f^n)'(p), \qquad \text{for each } i = 0, 1, 2, \ldots, n-1.$$

Thus, as regards stability, all points in the orbit behave in the same manner. For instance, suppose first that $|(f^n)'(p)| < 1$. By continuity, there is an open interval J, centered at p, such that for any $x \in J$, $f^{nk}(x) \to p$ as $k \to \infty$. For each i, $0 \le i \le n-1$, the $(i+1)^{\text{st}}$ point in the orbit $O(x)$ is $f^i(x)$, and every n^{th} point, starting at $f^i(x)$, is given by $f^{nk}(f^i(x))$, for $k = 0, 1, 2, \ldots$. However,

$$f^{nk}(f^i(x)) = f^i(f^{nk}(x)) \to f^i(p) \qquad \text{as } k \to \infty.$$

Thus the orbit $O(x)$ converges to the periodic orbit $O(p)$. We say in this case that the orbit $O(p)$ is a *stable periodic orbit* and will refer to the set $O(p)$ as a *local attractor*. In the event that p is an unstable fixed point of f^n, we can argue in a similar way, but with somewhat more elaborate reasoning, that $O(p)$ is an *unstable periodic orbit*, and refer to the set $O(p)$ as a *local repellor*.

4.3 Chaotic Orbits

We shall say an orbit $O(x)$ is *asymptotically periodic* if there is a periodic orbit $O(p)$ such that

$$|f^i(x) - f^i(p)| \to 0 \qquad \text{as } i \to \infty.$$

In other words, an orbit is asymptotically periodic if it converges to a periodic orbit. In the previous subsection we encountered an asymptotically periodic orbit. If we start at a point that is sufficiently near a stable periodic orbit, then its orbit converges to the periodic orbit. An asymptotically periodic orbit behaves with some predictability, but an orbit that is not asymptotically periodic appears random. We shall refer to a bounded orbit that is not asymptotically periodic as *chaotic*.

Further motivation for this definition is found by considering the limit points of an orbit. A point q is a *limit point for a sequence* x_i if there is a subsequence that converges to q. For $p \in I$, let $L(p)$ denote the set of limit points of the orbit $O(p)$. Then we have the following result:

Theorem 1. *A bounded orbit that is not asymptotically periodic has infinitely many limit points.*

A brief proof: The sets $O(p)$ and $f(O(p))$ differ only by the point p. Thus, they have the same limit points; and hence, when $O(p)$ is bounded, $L(p) = f(L(p))$; that is to say, $L(p)$ is invariant under f.

Now, suppose $L(p)$ is finite. Then there is no proper subset of $L(p)$ that is invariant under f, and therefore $L(p)$ must be a periodic orbit (**Exercise 9**). Since $O(p)$ converges to $L(p)$, the orbit $O(p)$ is asymptotically periodic. Thus, any bounded orbit with finitely many limit points is asymptotically periodic, and the theorem follows. □

The definition of a chaotic orbit has intuitive appeal, but it does not tell us how to recognize a chaotic orbit. However, T.Y. Li and J.A. Yorke proved a remarkable result, which in conjunction with a result obtained by A.N. Sharkovsky, can be rephrased as follows:

Theorem 2 [Li and Yorke 1975; Sharkovsky 1964]. *Let $f : I \mapsto I$ be continuous and have an orbit of period $2n + 1$ for some positive integer n. Then f has a fixed point and orbits of every period $m \geq 2n + 1$ and of every even period $k \leq 2n$. Moreover, there is an uncountable subset S of I such that for each $p \in S$, the orbit $O(p)$ is chaotic.*

We will use this result for n = 1. The theorem then states that the existence of an orbit of period 3 implies there are orbits of all periods and that there are uncountably many chaotic orbits. Li and Yorke [1975] show further that an orbit of period 3 exists when there are points $a \in I$, $b = f(a)$, $c = f(b)$, and $d = f(c)$ such that $d \leq a < b < c$ or $d \geq a > b > c$. An elegant and simple way to obtain the above results, except for existence of chaotic orbits, has been discovered by P.D. Straffin, Jr. [1978].

Exercises

6. Let I be an interval and $f : I \mapsto R$ be continuous together with its first derivative. Suppose $p \in I$ is a fixed point of f and $|f'(p)| < 1$. Show there is an interval J centered at p such that $f^i(x) \to p$ as $i \to \infty$, for any $x \in J$.

7. Assume the same conditions as the previous problem, except that $|f'(p)| > 1$. Show there is an interval J centered at p such that for each $x \in J$, there is an n, depending on x, for which $f^n(x)$ lies outside J. Hence conclude that for $x \in J$, the orbit $O(x)$ has an infinite number of points outside J.

8. Let I be an interval and $f : I \mapsto R$ be differentiable. Assume $O(p)$ is periodic with period n. Prove that for each $i = 0, 1, 2, \ldots, n-1$, $(f^n)'(x_i) = (f^n)'(p)$, where $x_i = f^i(p)$ is the $(i + 1)^{\text{st}}$ point in the orbit.

9. For an orbit $O(p)$, suppose $L(p)$ is finite and has no proper subset that is invariant under f. Show that $L(p)$ is a periodic orbit.

10. Consider the iteration function $f(x) = (1-c)x+p(x)$, where the production function is **(2)** with $s > 1$ (as in **Example 1** for the red blood cell population). For definiteness, take $c \in (0, 1]$ and assume the line $y = x$ intersects the graph of p.

a) Sketch the graph of f and show there are two positive fixed points. Denote the smaller by u_c and the larger by v_c.

b) Show that u_c is unstable for all c. Show also that any orbit which starts below u_c will converge to 0, while an orbit that starts just above u_c will initially move upward toward v_c. Remark: Thus we interpret u_c as the minimal number of blood cells needed by the organism to survive.

c) Show that v_c may be either stable or unstable, but that it is stable when c is sufficiently small. Remark: We interpret v_c as the steady state. If the destruction coefficient c is too large, the steady state may become unstable, as we shall see in the next section.

11. Write the production function **(2)** as in **Example 1** and show that the derivative of the iteration function at the steady state v is

$$f'(v) = 1 - c + cs\left(1 - \frac{1}{r}\right).$$

Thus show that in **Examples 1** and **2** the steady states are stable.

5. Qualitative Analysis and Applications of the Model

We are prepared now to study the dynamical behavior of our model, and in particular how well it reflects properties of certain dynamical diseases. Such studies assist not only with model validation but also in testing hypotheses concerning origins of the disease.

5.1 Hemolytic Anemia

The red blood cells contain the protein hemoglobin, which combines with oxygen in the lungs and carries it through the blood to the tissues. Anemia is a condition in which the amount of hemoglobin or the number of red blood cells is below normal levels. Anemia may result from insufficient production of hemoglobin, as in iron-deficiency anemia, or by defective hemoglobin, as in sickle-cell anemia. It can also occur from the premature destruction of red blood cells, a disorder called *hemolytic anemia*. This premature destruction may happen because the red blood cells are defective or the body produces antibodies that attack the red blood cells, or it may be caused under certain conditions by drugs or infection.

Experiments have shown that the induction of hemolytic anemia in rabbits can result sometimes in steady depressed levels of hemoglobin, and at other times in *sustained oscillations* in hemoglobin concentrations and numbers of reticulocytes (a type of red blood cell) [Orr et al. 1968]. Can our model account for this behavior? In particular, is it possible that simply an increased destruction coefficient explains these observations?

Write the iteration function as

$$f_c(x) = (1 - c)x + p(x),$$

with the subscript c to indicate dependence on the destruction coefficient. We will consider values of c in the interval $(0, 1]$. In **Example 1**, a production

function of the form **(2)** with $s > 1$ was determined for the red blood cells. However, in the analysis to follow, only certain properties of this function will be needed. We will assume the graph of p has the same shape as the production function in **Example 1**; in particular, we will require three assumptions **(A)**, **(B)**, and **(C)**.

(A). *p is differentiable, $p'(0) = 0$, and p has exactly two inflection points, which lie above the line $y = x$.*

Under this first assumption, f_c has two positive fixed points. Denote the smaller by u_c and the larger by v_c. Then, recalling **Exercise 10**, we know that u_c is unstable for any $c > 0$, but v_c is stable for sufficiently small c and represents the steady state. In **Example 1**, we saw that c near 0.1 to 0.2 is normal. Over this range, v_c is stable (**Exercise 11**). For $c \in (0, 1]$, $v_1 \leq v_c < \infty$, and v_c is monotonically decreasing as a function of c, with $v_c \to \infty$ as $c \to 0^+$, and $v_c \to v_1$ as $c \to 1^-$ (**Exercise 3**).

We will further require that

(B). $p'(v_1) < -1$.

The production function for red blood cells calculated in **Example 1** satisfies these assumptions (**Exercises 12** and **13**).

Theorem 3. *Let $f_c(x) = (1 - c)x + p(x)$, and suppose that the production function p satisfies* **(A)** *and* **(B)**, *so that f_c has positive fixed points u_c (the smaller) and v_c (the larger). Then there exists a unique value of c in $(0, 1)$, say c_α, which satisfies $f_c'(v_c) = -1$. For $c \in (0, c_\alpha)$, the point v_c is stable; and for $c \in (c_\alpha, 1]$, v_c is unstable.*

Proof: Observe first that $f_c'(v_c) = -1$ if and only if $p'(v_c) = -2 + c$. Consider now the graph of p' in **Figure 2**. For small $c > 0$, the point labeled A lies to the left of the point labeled B. As c increases toward 1, A moves to the right and B moves to the left. There will be exactly one value $c = c_\alpha$ at which A and B coincide, and at this value of c we have $f_c'(v_c) = -1$.

Suppose now that $c \in (0, c_\alpha)$. Then $v_c > v_{c_\alpha}$, and $-2 + c < -2 + c_\alpha$. Thus,

$$-2 + c < -2 + c_\alpha = p'(v_{c_\alpha}) < p'(v_c),$$

so that $-1 < (1 - c) + p'(v_c) = f_c'(v_c)$. But since $p'(v_c) < 0$, we have also $f_c'(v_c) < 1 - c < 1$. Thus $|f_c'(v_c)| < 1$, so that v_c is stable. An analogous argument shows that v_c is unstable when $c > c_\alpha$. □

Thus, provided the destruction coefficient is not too large (less than c_α), the model shows that the steady state is stable. However, whenever c is greater than this threshold value c_α, the steady state is unstable.

Theorem 4. *Let f and p be as in* **Theorem 3**, *and let c_α be the unique value of c such that $f_c'(v_c) = -1$. Then, for any $c > c_\alpha$, there exist points of period two.*

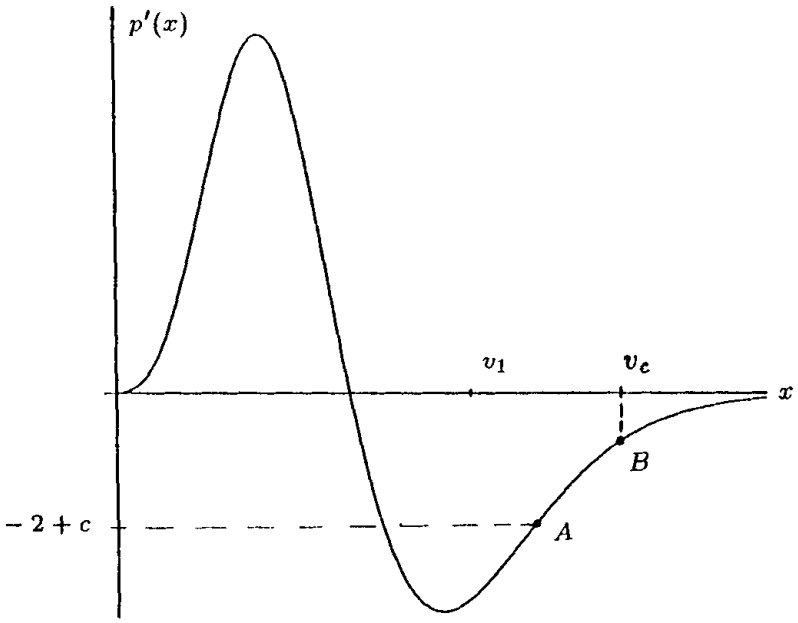

Figure 2. Graph of p'.

Proof: Let $c > c_\alpha$. The graph of f_c^2 intersects the line $y = x$ at u_c and at v_c. But if x is either u_c or v_c, then

$$\frac{d}{dx} f_c^2(x) > 1.$$

Thus, just to the right of u_c, the graph of f_c^2 lies above the line $y = x$; but just to the left of v_c, it lies below the line $y = x$. Therefore, by continuity, there exists a point between u_c and v_c which has period two. □

We now see that when the destruction coefficient is too large (bigger than c_α), periodic solutions arise. In fact, with the production function for the red blood cells determined in **Example 1**, we find numerically that as c increases, "period doubling" occurs; that is, as c increases, orbits of periods $2, 4, 8, \ldots$ arise, until an orbit of period 3 appears. The occurrence of periodic solutions may explain the observed oscillations in the experiments of Orr et al. [1968]. However, further analysis of the model indicates that cell counts could have followed a chaotic orbit. To see this, we make one more technical assumption concerning the production function. For $c \in (0, 1]$, let y_c denote the point at which f_c attains its local maximum. Then we assume

(C). $p^2(y_1) < u_1$, *where for* $c \in (0, 1]$, u_c *is the smaller positive fixed point of* f.

This assumption might be expected. When $c = 1$, the system will try to compensate for the high destruction rate with greatly increased production. Initially, a very large number of cells enters the blood stream. The system senses this excessive accumulation; and during the next time interval, only a

small number of cells is released. Consequently the cell count falls below the critical level u_1.

Theorem 5. *Let f and p be as in* **Theorem 3**. *Suppose the production function satisfies also assumption* **(C)**. *Then there exists $c_\beta \in (0,1)$ such that for any $c \in (c_\beta, 1]$, f_c has a point of period three, and hence there are uncountably many chaotic orbits.*

Proof: For $c \in (0,1]$, there is a point a_c between u_c and y_c such that $f_c(a_c) = y_c$ (a sketch of the graph of f_c shows this result). Assumption **(C)** implies there is $c_\beta \in (0,1)$ such that for any $c \in (c_\beta, 1]$, we have $f_c^2(y_c) < u_c$, since $u_c \to u_1$, and $y_c \to y_1$, as $c \to 1^-$. For $c \in (c_\beta, 1]$, define $d_c = f_c(y_c)$ and $e_c = f_c(d_c)$. Then we have $e_c < a_c < y_c < d_c$, and therefore the conditions of the Li and Yorke theorem are satisfied. □

Under the conditions of **Theorem 5**, the iteration function f_c, for sufficiently large c, has an uncountable number of chaotic orbits. A direct calculation shows that the production function for red blood cells of **Example 1** satisfies **(C)**. The model thus indicates that for large destruction rates, the cell counts are likely to follow chaotic orbits.

Exercises

12. Show that the production function determined in **Example 1** satisfies assumption **(A)**. Suggestion: Show that x is an inflection point of p if and only if x/v is an inflection point of ϕ, and hence that p satisfies assumption **(A)** if ϕ does. Check assumption **(A)** for ϕ directly, using the results of **Exercise 2**.

13. Show that the production function of **Example 1** satisfies assumption **(B)**. Suggestion: Set $w_1 = v_1/v$, and using the fact that $w_1 = \phi(w_1)$, show that $p'(v_1) = 8(1 - 2w_1)$. Then show that $w_1 > 9/16$.

14. The proof of **Theorem 4** rests on the fact that when $c > c_\alpha$, the derivative of f_c^2 is greater than 1 at at u_c and at v_c. Verify this result.

5.2 Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (CML) is a cancer of the white blood cells, characterized by an excessive increase in granulocytes in the marrow and blood. The cells produced are abnormal, and counts in the marrow may be 150 times the normal. Further, the overaccumulation disrupts production of the other blood cells and interferes with various organs. There is evidence that the disorder resides in the primitive stem cells [Erslev and Gabuzda 1985]. In recent years, some clinical reports have indicated a periodic variant in which cell counts oscillate around elevated levels, with a period of 30–70 days depending on the patient [Glass and Mackey 1979].

To investigate whether the model can explain these observations, we apply it to the primitive stem cell population. This population is self-maintaining. When primitive stem cells differentiate to form committed stem cells, the number of primitive stem cells decreases. This decrease causes new cells to be produced through mitosis (cell division) of remaining cells. Cells that are not in the proliferative phase are said to be resting. Committed stem cells can come only from resting cells.

The mechanisms and feedback control processes in CML are not fully understood. However, it is believed that in CML the primitive stem cell compartment consists of two populations, the normal cells and the leukemic cells. Each is thought to be governed by the same dynamics, but with different parameters.

We will apply the model to the leukemic population. Now x_i denotes the number of resting primitive stem cells (leukemic) at time t_i. Recall that our model specifies $f(x) = (1 - c)x + p(x)$. The destruction coefficient c is now the fraction of primitive stem cells that leave to become committed cells during a time interval of length Δ. For the production function, we follow Mackey [1979a] and use **(1)**:

$$p(x) = \frac{b\theta^m x}{\theta^m + x^m},$$

with positive parameters b, θ, and m. Thus we are assuming that during the time interval from t_i to t_{i+1}, the number of cells that leave the proliferative phase to enter the resting state is $p(x_i)$. For the normal human, it has been estimated that

$$\begin{aligned} c &= \gamma\Delta, \qquad \text{with } \gamma = 0.16 \text{ per day}, \\ b &= \beta\Delta, \qquad \text{with } \beta = 1.43 \text{ per day}, \\ \theta &= 3.22 \times 10^8 \text{ cells / kg}, \\ m &= 3, \end{aligned}$$

with a delay time in production of Δ = 0.68 days [Mackey 1979a].

Our goal is to study possible explanations for the observed increases and oscillations in the cell count. We need first to express the steady-state cell count as a function of the parameters. Letting v denote the steady state level, we have $cv = p(v)$. Solving for v yields

$$v = \theta\left(\frac{\beta}{\gamma} - 1\right)^{1/m}.$$

At first thought, the logical explanation for increased cell counts would be an increase in the magnitudes of the production function, which means an increase in the parameter β. However, assuming that all other variables remain unchanged, we see from the expression for v that to achieve a 50-fold increase in v would require, in view of the cube root (m = 3), an increase in β by a factor of approximately 50^3 = 125,000. Although leukemic cells are known to proliferate much faster than normal cells, such an enormous increase in β seems unlikely.

Examination of the expression for v, however, suggests that a simpler possibility is an increase in θ. A 50-fold increase in v would require only a 50-fold increase in θ. In the expression for the production function, increasing θ leads to an elongation of the graph of p and an increase in the maximum. This means there are higher production levels that extend over a wider range of the population cell counts. Thus, CML may involve an alteration in the feedback control process of primitive stem cell replacement.

Increase in the parameter θ seems the likely reason for increased cell levels. However, does this increase also explain the 30- to 70-day oscillations in cell counts observed in some patients? This question requires that we examine the stability of the steady state v. To begin, we need an expression for $f'(v)$, the slope of the iteration function at the steady state. Using the result of **Exercise 1** for the derivative of f and substituting the expression for v yields

$$f'(v) = 1 - cm + \frac{c^2 m}{b}.$$

But this expression does not depend on the parameter θ. Moreover, for the given parameter values, $f'(v)$ = 0.71, showing that the steady state is stable for any value of θ. Thus an increase in θ does not help us understand the oscillations that have been observed.

However, there is another possibility. In CML, evidence indicates that for myeloblasts, a committed (white) stem cell, the time spent in the proliferative phase is longer than for normal cells. This evidence suggests that the unit time Δ in the model may be greater than usual. Consider, then, an arbitrary delay time Δ. With $c = \gamma\Delta$ and $b = \beta\Delta$, we can express f' in terms of Δ as

$$f'(v) = 1 - \gamma m\Delta + \frac{\gamma^2 m\Delta}{\beta}.$$

Substituting the estimated values of γ, β, and m, we get $f'(v)$ = $1 - 0.43\Delta$. Thus, for Δ greater that 2 / 0.43 = 4.7 days, the steady state would be unstable. As Δ increases beyond this value, an orbit of period two arises. In this case, a period of two is $2 \times 4.7 \approx 9$ days, which agrees with the 12 days calculated by Mackey using a more detailed model [Mackey 1979a]. It appears that the increased delay time of the leukemic cells is the likely source of oscillations in cell counts.

We see now that the model *is* able to reflect the dynamics of CML, giving further support for the assumptions that comprise the model. In addition, the analysis offers insights into the possible malfunctions that occur in the disorder.

Exercises

15. Verify the stated effect of increasing θ on the shape of the production function. The results of **Exercise 1** help.

16. Show that when Δ exceeds 4.7 days, orbits of period two arise. Suggestion: Use the same proof as in **Theorem 4**, with the two fixed points of the iteration function here being 0 and v.

6. Conclusion

We have given an introduction to the mathematical modeling of blood cell populations. The model is simple, and more-precise and detailed models are under study. Certainly, a better understanding of the mechanisms, especially in quantitative terms, of blood-cell formation and destruction is needed. The problems of parameter estimation and model verification are formidable.

To some extent, of course, confidence in a model comes with a knowledge of the cellular and biochemical processes involved. However, hard data are also needed; and for our situation, little data have been obtained to serve model verification. But it is not premature to proceed with model development. Good models are available now; new laboratory and clinical results can help refine them. At the same time, analysis of the models tells us what dynamical phenomena to look for and how to design experiments and studies. Moreover, models can be used to test hypotheses regarding possible mechanisms, and are thus tools for investigation. Ultimately, models will help us study treatment strategies for diseases.

A major step forward would be the development of closer ties between those on the laboratory and clinical sides of research and those interested in mathematical modeling. Glass and Mackey [1979] noted:

> The existence of classifiable dynamical diseases in humans suggests a corresponding rich theory of bifurcations in nonlinear ordinary, partial, and functional differential equations which model physiological control systems. At this point, a sufficient body of data is not yet available for actual testing of theories of dynamical diseases. In our view, close collaboration between theorists and clinicians is needed to clarify the bases of these dynamical diseases.

We can only echo this plea, and hope that this Module will help stimulate interest in the modeling of blood cell populations.

7. Sample Exam

1. Let $f : I \mapsto I$ be continuous. Suppose that for some $p \in I$, the orbit $O(p)$ converges. Show that the limit is a fixed point of f.

2. Let $f : [a,b] \mapsto R$ be continuous. Assume that $[a,b]$ is contained in the image of f. Prove that f has a fixed point in $[a,b]$. Suggestion: Consider the function $g(x) = x - f(x)$.

3. Let I be an interval and let $f : I \mapsto I$ be continuous. Assume there is a point $a \in I$ such that: $a < f(a) < f^3(a)$, $f^4(a) = a$, and f is increasing on $[a, f(a)]$. Prove that there is an orbit of period three. Suggestion: Consider the image of the interval $[a, f(a)]$ under f^3 and use the result of the previous problem.

4. Consider the model of **Exercise 5** for the granulocytes in the blood. The destruction rate is 10% per hour, and the steady-state cell count is 7.0×10^8 cells / kg. Let the unit time be Δ = 3 hours, and the maximum production be 10 times the steady-state rate.

a) Use the production function **(2)** with s = 1 and estimate the parameters of the model.

b) Is the steady state stable?

c) As mentioned in **Exercise 5**, the blood system can respond to a depletion of granulocytes in the blood within a few hours, with cells coming from the marrow reserve. In fact, within two or three hours, the number of blood granulocytes becomes somewhat larger than normal, and then returns shortly to the normal steady state (with perhaps some oscillation in the process). Is the above model consistent with this behavior? Suggestion: Consider the graph of the iteration function. Show how points in an orbit will behave when the initial point lies just below the steady state.

5. Consider the model of **Example 2** for the regulation of granulocytes. For a unit time Δ (days), the destruction coefficient is $c = \gamma\Delta$, with γ = 0.1, and the production function has the form

$$p(x) = bxe^{-x/q}, \qquad \text{where } b = \beta\Delta.$$

The calculations in **Example 2** indicated that $\beta \approx 1.5$ for a normal system.

a) Show that the steady-state cell count is $v = q \ln\left(\frac{\beta}{\gamma}\right)$.

b) Show that the slope of the iteration function f at the steady-state is

$$f'(v) = 1 - \gamma\Delta \ln\left(\frac{\beta}{\gamma}\right).$$

.

c) Suppose hypothetically that in chronic or acute myelogenous leukemia, the regulation of leukemic cells in the marrow reserve and blood were to follow the same model as in **Example 2** but with different parameters than those of the normal cells. Perform an analysis with this model, as was done in Section 5.2 for the primitive stem cells, in order to explain the excessive cell numbers and the oscillations in cell counts.

8. Solutions to the Exercises

1. The first and second derivatives of the function **(1)** are

$$p'(x) = \frac{b\theta^m[\theta^m - (m-1)x^m]}{(\theta^m + x^m)^2},$$

$$p''(x) = \frac{bm\theta^m x^{m-1}[(m-1)x^m - (m+1)\theta^m]}{(\theta^m + x^m)^3},$$

from which the results follow.

2. The first and second derivatives of the function **(2)** are

$$p'(x) = bsx^{s-1}\left(1 - \frac{x}{r}\right)e^{-sx/r},$$

$$p''(x) = bsx^{s-2}\left(-1 + s\left(1 - \frac{x}{r}\right)^2\right)e^{-sx/r},$$

from which the results follow.

3. The slope of the line $y = cx$ decreases as c decreases. Thus, since p is positive and asymptotic to zero, v_c must increase as c decreases, and $v_c \to \infty$ as $c \to 0^+$. These results are reasonable physically: As the destruction rate decreases, with a fixed production function, the steady-state number of cells would be expected to increase. Of course, the body has only a finite capacity and could not survive a small cell destruction rate.

4. Following **Example 2**, the equations for the parameters are now $be^{-1/r}$ = 0.6 and bre^{-1} = 5 × 0.6 = 3.0. Approximate solutions are r = 0.25, b = 33.

5. With Δ = 3 hours, c = 3 × 0.1 = 0.3, and the production function $p(x) = v\phi(x/v)$, where $\phi(u) = bue^{-u/r}$, the two equations for the parameters r and b are $be^{-1/r}$ = 0.3 and bre^{-1} = 1.8. Approximate solutions are r = 0.24, b = 21.

6. Select $d > 0$ so that $|f'(x)| \le m < 1$ for all $x \in J = [p - d, p + d]$. Fix $x_0 \in J$ and consider the orbit $O(x_0)$. For $i = 0, 1, 2, \ldots$, let $x_i = f^i(x_0)$ be the $(i+1)^{\text{st}}$ point in the orbit. Suppose that $x_i \in J$ for some $i \ge 0$. By the mean value theorem, we have

$$x_{i+1} - p = f(x_i) - f(p) = f'(t)(x_i - p), \qquad \text{for some } t \in J.$$

Therefore, $|x_{i+1} - p| \le m|x_i - p|$, so that $x_{i+1} \in J$. Thus, by induction, the orbit lies in J, and moreover we have

$$|x_i - p| \le m^i|x_0 - p|, \qquad \text{for each } i \ge 0.$$

Thus, the orbit converges to p.

7. Proceed exactly as in **Exercise 6** as far as the first displayed equation. Then, using the hypothesis, we have

$$|x_{i+1} - p| \geq m^{k+1}|x_0 - p|.$$

Thus, there must be a point in the orbit that lies outside J. Further, if some future point in the orbit should return to J, then by the above argument, in a finite number of steps the orbit will again leave J. Thus, an infinite number of points of the orbit are outside J.

8. By repeated application of the chain rule (or induction, to be rigorous), we get

$$(f^n)'(x_i) = f'(x_i)f'(x_{i+1})\dots f'(x_{i+n-1}),$$

and

$$(f^n)'(p) = f'(p)f'(x_1)\dots f'(x_{n-1}).$$

Since the orbit is periodic with period n, it follows that these two expressions are the same.

9. Suppose $L(p)$ has n points. Select any $x_0 \in L(p)$ and form the points x_i by $x_{i+1} = f(x_i)$ for $i = 0, 1, 2, \dots, n-1$. Each of these points is in $L(p)$ since $L(p)$ is invariant under f. But the points $x_0, x_1, \dots, x_{n-1}$ must be distinct, otherwise there would be a proper subset of $L(p)$ which is invariant under f. Hence $x_n = p$, so that $L(p)$ is a periodic orbit.

10. **a)** The graph of f lies above the line $y = (1-c)x$, is tangent to this line at $x = 0$ since $p'(0) = 0$, and approaches this line asymptotically as $x \to \infty$ since p is asymptotic to zero. Thus the graph of f lies below the line $y = x$ in a neighborhood of the origin, and also for sufficiently large x. However, the graph of f lies above the line $y = x$ for some x. Hence f must have two positive fixed points.

b) The slope of f at u_c must be greater than 1 since the graph of f is passing across the line $y = x$ from below. Hence the smaller fixed point is unstable. Any orbit that starts below u_c must form a decreasing sequence, since $f(x) < x$ for all $x \in (0, u_c)$. Hence the orbit converges to a point $q \in [0, u_c)$. By continuity of f, $q = f(q)$. But the only point in $[0, u_c)$ which satisfies this equation is $q = 0$. Finally, any orbit that starts just to the right of u_c will initially move away from u_c toward v_c, since $f(x) > x$ when x lies just to the right of u_c.

c) The point v_c may or may not be stable, depending on steepness of the production function. However, for a given production function, it will be stable when c is sufficiently small, since the graph of p approaches the x-axis asymptotically.

11. As in **Example 1**, set $p(x) = v\phi(x/v)$. Then

$$f'(x) = 1 - c + p'(x) = 1 - c + \phi'(x/v).$$

But

$$\phi(u) = bu^s e^{-su/r}, \qquad \text{so that} \qquad \phi'(u) = bsu^{s-1}\left(1 - \frac{u}{r}\right)e^{-su/r}.$$

Now

$$f'(v) = 1 - c + \phi'(1) = 1 - c + bs\left(1 - \frac{1}{r}\right)e^{-s/r}.$$

However, at the steady state, $cv = p(v)$, or $c = \phi(1) = be^{-s/r}$. Thus

$$f'(v) = 1 - c + cs\left(1 - \frac{1}{r}\right).$$

Finally, substituting the parameter values, as calculated in the examples, we find that for **Example 1**, $f'(v) = -0.26$, and for **Example 2**, $f'(v) = -0.62$.

12. Since $p''(x) = \phi''(x/v)/v$, the statement in the suggestion is valid. Thus, it suffices to check that $\phi(u) > u$ at each inflection point of ϕ. Using the result of **Exercise 2**, the inflection points of ϕ are 0.323 and 0.677. Substituting, we get $\phi(0.677) = 0.96$ and $\phi(0.323) = 0.74$. Hence, assumption **(A)** is satisfied.

13. We have $p'(x) = \phi'(x/v)$, and from the solution of **Exercise 2**,

$$\phi'(u) = bsu^{s-1}\left(1 - \frac{u}{r}\right)e^{-su/r}.$$

Hence

$$p'(v) = \phi'(w_1) = bsw_1^{s-1}\left(1 - \frac{w_1}{r}\right)e^{-sw_1/r}.$$

But $w_1 = \phi(w_1)$ gives

$$w_1 = bw_1^s e^{-sw_1/r}, \qquad \text{or} \qquad 1 = bw_1^{s-1}e^{-sw_1/r}.$$

Hence

$$p'(v) = s\left(1 - \frac{w_1}{r}\right).$$

Since $s = 8$ and $r = 0.5$, we get $p'(v) = 8(1 - 2w_1)$. Finally, to show that $w_1 > 9/16$, it suffices to check by direct calculation that $\phi(9/16) > 9/16$.

14. By the chain rule,

$$(f_c^2)'(x) = f_c'(f_c(x))f_c'(x).$$

Let x be either u_c or v_c. Then $x = f_c(x)$, so that

$$(f_c^2)'(x) = f_c'(x)f_c'(x) = (f_c'(x))^2.$$

Further, when $c > c_\alpha$, $|f_c'(x)| > 1$. Hence the conclusion follows.

15. Using the results of **Exercise 1**, we see that the maximum point, the inflection point, and the distance between them are proportional to θ. Thus, the graph becomes elongated as θ increases. Also, the value of the function at the maximum point is proportional to θ, so the maximum value increases as well.

16. When Δ exceeds 4.7, then the derivative of the iteration function f at the steady state is greater than 1 (by construction). But f also has a fixed point at x = 0. The derivative of f is

$$f'(x) = (1 - \gamma\Delta) + \frac{\beta\Delta\theta^m[\theta^m - (m-1)x^m]}{(\theta^m + x^m)^2},$$

so that $f'(0) = 1 + (\beta - \gamma)\Delta > 1$. The proof of **Theorem 4** now applies directly.

9. Solutions to the Sample Exam

1. Let $x_i = f^i(p)$ be the $(i+1)^{\text{st}}$ point of the orbit and suppose $x_i \to q$ as $i \to \infty$. Then $x_{i+1} = f(x_i)$ for each $i \geq 0$. Taking limits of both sides as $i \to \infty$ in this last equation, and using the continuity of f, gives $q = f(q)$.

2. Set $g(x) = x - f(x)$. Since $[a, b]$ is contained in its image under f, it follows there are x_1 and x_2 in $[a, b]$ such that $g(x_1) \leq 0$ and $g(x_2) \geq 0$. By the intermediate value theorem, g has a root in $[a, b]$, which is the same as saying that f has a fixed point in $[a, b]$.

3. The interval $[a, f(a)]$ is contained in its image under f^3. Therefore, by the previous problem, there is a point $y \in (a, f(a)]$ that is a fixed point of f^3. Since f is increasing on $[a, f(a)]$, for each point $x \in (a, f(a)]$, $f(x) > f(a) \geq x$, and therefore y could not be a fixed point of f. Further, y could not be a point of period two; that is, $f^2(y) = y$, for then we would have $f^3(y) = f(y) \neq y$. Thus y is a point of period 3.

4. a) Following **Example 2**, the production function is written

$$p(x) = v\phi(x/v), \qquad \text{where} \qquad \phi(u) = bue^{-x/r}.$$

The two equations for the parameters are $\phi(1) = be^{-1/r}$ = 0.3 and $\phi(r) = bre^{-}1$ = 10 × 0.3 = 3. The solutions are r = 0.20, b = 45.

b) The derivative of the iteration function at the steady state v is $f'(v) = 1 - c/r$ = 1 - 0.3 / 0.2 = -0.5, so that the steady state is stable.

c) The model is consistent with this behavior. The steady state is stable, and the slope of the iteration function at the steady state is negative. If an orbit starts at a point just below the steady state, then the second

point in the orbit will be larger than the steady state, and the remaining iterates will then oscillate around the steady state as they converge to it. Remark: If the slope at the steady state had turned out to be positive, the observation about granulocyte numbers exceeding the steady state after depletion would have given us grounds to reject the model.

5. a) At the steady state, $cv = p(v) = bve^{-v/q}$. Dividing by v and taking the natural logarithm of both sides yield the given expression.

b) The iteration function is $f(x) = (1-c)x + bxe^{-x/q}$, so that

$$f'(x) = 1 - c + b\left(1 - \frac{x}{q}\right)e^{-x/q}.$$

From part (a), $c = be^{-v/q}$, which gives

$$f'(v) = 1 - c + c\left(1 - \frac{v}{q}\right) = 1 - c\ln\left(\frac{\beta}{\gamma}\right),$$

as required.

c) Although an increase in the production parameter β is the logical choice for explaining the increased cell numbers, the slow increase of the natural logarithm function indicates that cell numbers are insensitive to increases in β. However, from the expression for v, the simplest explanation for increased cell levels is an increase in the parameter q. Nevertheless, the expression in part **(b)** shows that q does not effect the stability of the steady state. However, an increase in Δ could explain the oscillations in the number of leukemic cells. For the given values β = 1.5 and γ = 0.1, we get $f'(v) = 1 - 0.27\Delta$. Setting this expression equal to -1 shows that the steady state becomes unstable when Δ passes through 2 / 0.27 = 7.4 (days). At this point, periodic orbits of period two arise, and the length of the period would be $2 \times 7.4 = 15$ days. Interestingly, this period, which was obtained from data for the circulating and marrow reserve granulocytes, is about the same as obtained from using independent data for the primitive stem cells.

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