10 Partial Differential Equation Models in Biology

Give me space and motion and I will give you a world
R. Descartes (1596–1650) quoted in E. T. Bell (1937) Men of Mathematics, Simon & Schuster

Because populations of molecules, cells, or organisms are rarely distributed evenly over a featureless environment, their motions, migrations, and redistributions are of some interest. At the level of the individual, movement might result from special mechanochemical processes, from macroscopic contractions of muscles, or from amoeboid streaming. On the population level, these different mechanisms may have less bearing on net migration than other aspects such as (1) variations in the environment, (2) population densities and degree of overcrowding, and (3) motion of the fluid or air in which the organisms live.

On the collective level it is often appropriate to make a *continuum* assumption, that is, to depict discrete cells or organisms by continuous density distributions. This leads to partial differential equation models that are quite often analogous to classical models for molecular diffusion, convection, or attraction.

Historically, biological models involving partial differential equations (PDEs) date back to the work of K. Pearson and J. Blakeman in the early 1900s. In the 1930s others, including R. A. Fisher, applied PDEs to the spatial spread of genes and of diseases. The 1950s witnessed several important developments including the work of A. M. Turing on pattern formation (see Chapter 11) and the analysis of Skellam (1951), who was among the first to formally apply the diffusion equation in modeling the random dispersal of a population in nature. Some of these models and several others drawn from molecular, cellular, and population biology are outlined in this chapter.

In Section 10.1 we begin with an account of Skellam's work and his analysis of spreading populations of animals and plants. Models for the collective motion of microorganisms are then developed in Section 10.2. There is an underlying parallel between the equations for moving populations and the conservation equations encountered in physical phenomena such as particle diffusion. However, there are some noteworthy differences; among these are models for density-dependent dispersal, which are mentioned in Section 10.3. Two applications of convection equations to growth in a branching network are described in 10.4.

Many models discussed in this chapter cannot be solved analytically in closed form. This is particularly true of the nonlinear equations. We must often work with relatively elementary solutions that do not address the full complexity inherent in the time-dependent evolution of the system. A standard first approach is to reduce the problem to one that can be solved, generally by converting the PDEs to ordinary differential equations (ODEs) that describe some simpler situation. Two types of solutions can be thus ascertained: steady-state distributions and *traveling waves*. Methods for finding such solutions are described in Section 10.5. In Section 10.6 we apply such techniques to Fisher's equation, which depicts the spread of an advantageous gene in a population. A second example of biological waves emerges from the study of microorganisms such as yeast growing on glucose. Remarkably, phase-plane analysis reemerges as a handy tool in this unlikely setting. The phenomenon of long-range transport of biological substances inside the neural axon is described in Section 10.7.

In Sections 10.8 and 10.9 our emphasis shifts slightly. Here again we aim to uncover the generality and power of abstract thinking by demonstrating that familiar equations can be applied in novel and surprising ways to seemingly unrelated settings. We begin with a calculation due to Takahashi that uncovers a connection between the aging of a cell and the processes of spatial redistribution previously studied. The analogy between age distributions and spatial distributions is then more fully explored. Section 10.9 is a do-it-yourself modeling venture that exploits such analogies, and Section 10.10 provides references and suggestions for further study.

10.1 POPULATION DISPERSAL MODELS BASED ON DIFFUSION

Among the first to draw an analogy between the random motion of molecules and that of organisms was Skellam (1951). He suggested that for a population reproducing continuously with rate α and spreading over space in a random way, a suitable continuous description would be

$$\frac{\partial P}{\partial t} = \mathcal{D}\nabla^2 P + \alpha P. \tag{1}$$

$\mathcal{D}$, called the *dispersion rate*, is analogous to a diffusion coefficient (also called the *mean square dispersion per unit time*). $P(\mathbf{x}, t)$ is the population density at a given time and location.

Skellam was particularly interested in the rate with which the area initially colonized by a population expands with time, and quoted two interesting examples

based on biological data. Here we examine equation (1) in more detail but in a one-dimensional, rather than a full two-dimensional setting.

The growth term αP not only increases the density locally but also causes a faster spatial spread in the population than that anticipated by diffusion alone. Indeed, as Skellam pointed out, the outward propagation of the *equipopulation contours* (the level curves of the population density) eventually takes place at a constant radial rate.

To see why this is true, we consider a point release of the species at time $t = 0$ and location $x = 0$. Then it can be shown that a solution of equation (1) is

$$P(x, t) = \frac{P_0}{2(\pi \mathcal{D} t)^{1/2}} \exp\left(\alpha t - \frac{x^2}{4\mathcal{D}t}\right). \tag{2}$$

See problem 3.

To study the lateral population expansion one could observe the translation of those points x_i for which

$$P(x_i, t) = P_i = \text{constant}.$$

(These points are analogous to the equipopulation contours in higher dimensions.)

After initial spreading, the population will have achieved a detectable level at some distance $\hat{x}$ from its origin. The outer boundary of the population will continue to spread so that $\hat{x}$ will translate outwards. It is of interest to derive some estimate of this *rate of propagation*. (*Note:* We are investigating a one-dimensional setting for the sake of simplicity. In two dimensions we would be asking a similar question about the rate of propagation of level curves; see Figure 10.1 for an example.)

In problem 3 it is shown that by setting $P(x, t) = \tilde{P}$ (a constant) in equation (2) and looking at the large-time behavior, one obtains in the limit,

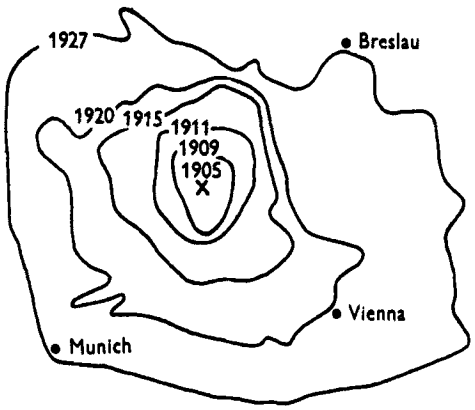
$$\hat{x} = 2(\alpha \mathcal{D})^{1/2} t, \tag{3}$$

so that the location at which the population density is $\tilde{P}$ travels asymptotically at a constant speed, $2(\alpha \mathcal{D})^{1/2}$. One reason this equation admits a more rapid advance rate than does a diffusion equation without the growth term stems from the fact that the birth rate *reinforces* gradients. Where the population is large, the population gets larger quickly so that the diffusion process is *driven* by internal growth.

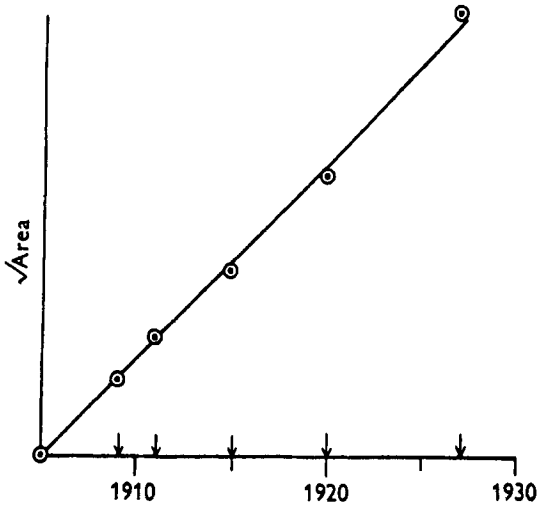
A similar asymptotic expansion rate holds for radially outwards diffusion in a two-dimensional distribution; that is, one can verify that for large t, equipopulation contours expand at the rate

$$(\text{area})^{1/2} = 2(\alpha \mathcal{D})^{1/2} t. \tag{4}$$

Skellam used this result to demonstrate that the spread of certain populations can be explained on the basis of a diffusion approximation (in other words, an underlying random walk of individuals). Particularly noteworthy is his example of recorded spread of a muskrat population over central Europe after a Bohemian landowner mistakenly allowed several to escape in 1905. Because of uneven spatial terrain (presence of towns, for example) the population contours are not particularly regular. However, Skellam showed that the square root of the area increases linearly with time, as anticipated from equation (4).



(*a*)



(*b*)

Figure 10.1 *Spread of muskrats over central Europe during a period of 27 years described by Skellam (1951) as a random dispersal. (a) Equipopulation contours (level curves of* $p(\mathbf{x}, t)$ *for the lowest detectable muskrat population. A graph of* $(\text{area})^{1/2}$ *of the regions enclosed by these curves reveals linear dependence on time* t, *as predicted by the growth-dispersal model of equation (1). [From Skellam J. G. (1951). Random dispersal in theoretical populations.* Biometrika, 38, *figs. 1 and 2, p. 200. Reprinted with permission of the Biometrika Trustees.]*

Skellam applied similar conclusions to the spread of oak forests over Britain and by simple calculations argued that small animals must have played an important role in the dispersal of acorns (see problem 5).

In the recent literature, diffusion-like models for population dispersal have become quite common. The homing and migration of birds, fish, and other animals have been described by diffusion with a "sticky" target site (see Okubo, 1980, for survey and references). Smaller organisms such as insects have also been modeled by diffusion equations. Ludwig et al. (1979) describe the spread of the spruce budworm by the equation

$$\frac{\partial P}{\partial t} = \mathcal{D}\frac{\partial^2 P}{\partial x^2} + \alpha P\left(1 - \frac{P}{K}\right) - \beta\frac{P^2}{H^2 + P^2}, \tag{5}$$

where β is the rate of mortality due to predation, and K is a constant. See problem 2(d) for an exercise in interpreting the equation. Kareiva (1983) applied diffusion models to data for herbivorous insects under a number of conditions and derived rigorous tests for the validity of such approximations.

Aside from the motion of organisms, it has also been recently popular to describe by diffusion the spread of genes, disease, and other similar properties. A good general survey of many references is given by Okubo (1980), Fife (1979), and Murray (1977).

Table 10.1 Dispersal Rates

Equation	*Initial Conditions*	*Speed of Propagation*	*References*
$\frac{\partial P}{\partial t} = \mathcal{D}\frac{\partial^2 P}{\partial x^2} + \alpha P$ (dispersal with exponential growth).	$P(x, 0) = \delta(x)$ (initially all population at $x = 0$).	$\frac{x}{t} = \pm 2(\mathcal{D}\alpha)^{1/2}$ (for large t).	Kendall (1948) and problem 3.
Same as above.	$P(x, 0) = \frac{P_0}{(2\pi\sigma_0)^{1/2}} \exp\left(\alpha t - \frac{x^2}{2\sigma_0^2}\right)$ (initially a Gaussian distribution with variance).	Variance $\sigma^2 = \sigma_0^2 + 2\mathcal{D}t$, $\frac{x}{t} = 2(\alpha\mathcal{D})^{1/2}$.	Kendall (1948) and Okubo (1980).
	$P(x, 0) = P_0 \exp(-bx)$ $(b > 0)$.	$\frac{x}{t} > 2(\alpha\mathcal{D})^{1/2}$ when $b < \left(\frac{\alpha}{\mathcal{D}}\right)^{1/2}$.	Kendall (1948), Mollison (1977), and Okubo (1980).
$\frac{\partial P}{\partial t} = \mathcal{D}\frac{\partial^2 P}{\partial x^2} + \alpha P - \beta P^2$.	$P(x, t) = P(x - ct)$ (traveling wave with trailing end).	$\frac{x}{t} = c \geq 2(\alpha\mathcal{D})^{1/2}$.	Fisher (1937) and Kolmogorov et al. (1937).
$\frac{\partial P}{\partial t} = \mathcal{D}\frac{\partial^2 P}{\partial x^2} + F(P)$.	Same as above.	$\frac{x}{t} = c = 2\left(\frac{\partial F}{\partial P}\Big\|_0 \mathcal{D}\right)^{1/2}$	Kolmogorov et al. (1937).

A preoccupation with propagation rates is still quite current. Many recent papers address these questions, with emphasis on the role of initial conditions and of growth rates other than simple exponential growth. Another interesting question is whether equations such as (1) or its various modifications admit traveling-wave solutions (solutions that move in space without changing their "profiles"). Table 10.1 lists some of the results regarding propagation speeds. In a later section we deal at greater length with traveling-wave solutions.

10.2 RANDOM AND CHEMOTACTIC MOTION OF MICROORGANISMS

Many unicellular organisms have elaborate patterns of locomotion that may include *ciliary beating* (synchronous motion of hair-like appendages on the cell surface,) helical swimming, crawling on surfaces, tumbling in three dimensions, and *pseudopodial extension* (protrusion of part of the cell and streaming of the cellular contents.) In the absence of overriding external cues, such motion may appear *saltatory* (jerky) or random, although of course, it is strictly determined by events on subcellular levels. At the population level, the pseudo-random motion could be approximately described as a process analogous to molecular diffusion. A one-dimensional equation that would represent changes in the spatial distribution of a large population of such microorganisms would then be

$$\frac{\partial b}{\partial t} = \mu \frac{\partial^2 b}{\partial x^2} + rb, \tag{6}$$

where

$b(x, t)$ = population density at location x and time t,

μ = coefficient that depicts the *motility* or *dispersal rate* of the organisms,

r = growth rate (if positive) or death rate (if negative).

Note that rb is a local source/sink term, previously denoted by σ, since it accounts for local addition or elimination of individuals; note also that equation (6) is a diffusion equation.

Segel et al. (1977) applied equation (6), where $r = 0$, to the dispersal of bacteria. Based on experimental observations, they calculated a value of μ of 0.2 $cm^2\ h^{-1}$ for *Pseudomonas fluorescens*. (See Segel, 1984, and problem 6 for a summary.)

Similar equations (with negative r) have been applied to *plankton* (microscopic marine organisms) by Kierstead and Slobodkin (1953). Bergman (1983) discusses a model for contact-inhibited cell division that reduces to a diffusion equation in the limit of unrestricted cell division.

When the microorganisms depend on some growth-limiting nutrient for their survival, the relative rate of nutrient diffusion to organism motility may be of some importance. An example of substrate-dependent growth is given by Gray and Kirwan (1974) for yeast growing on solid medium. A recent model for the effects of random motility on bacteria that consume a diffusible substrate is described by Lauffenburger et al. (1981), who suggest the following equations:

$$\frac{\partial b}{\partial t} = \mu \frac{\partial^2 b}{\partial x^2} + [f(s) - k_e]b, \tag{7a}$$

$$\frac{\partial s}{\partial t} = \mathcal{D} \frac{\partial^2 s}{\partial x^2} - \frac{1}{Y} f(s)b, \tag{7b}$$

where

$b(x, t)$ = bacterial density,
$s(x, t)$ = substrate concentration,
Y = the yield (mass of bacteria per unit mass of nutrient),
$f(s)$ = the substrate-dependent growth rate,
k_e = the bacterial death rate when s is depleted.

Some details of their model are explored in problem 8.

Keller and Segel (1970, 1971) were among the first to describe a continuum equation for the phenomenon of chemotaxis in microorganisms, discussed earlier in Chapter 9. *Taxis* refers to the purposeful motion of organisms in response to environmental cues. Some animals are known to be attracted to brighter light, warmer temperatures, and higher levels of certain chemical substances (for example, pheromones or nutrients) while being repelled from potentially damaging influences (such as toxins, extremes of temperature or extremes of pH).

Keller and Segel applied the idea of attraction and repulsion in deriving their equation for bacterial chemotaxis:

$$\frac{\partial B}{\partial t} = -\frac{\partial}{\partial x}\left(\chi B \frac{\partial c}{\partial x}\right) + \frac{\partial}{\partial x}\left(\mu \frac{\partial B}{\partial x}\right), \tag{8}$$

attraction random motion

where

$B(x, t)$ = bacterial density at location x and time t,
χ = chemotactic constant.

χ depicts the relationship between a gradient in the substance c and the velocity of migration of the population. In other words, the chemotactic flux is assumed to be proportional to a gradient $\partial c/\partial x$:

$$\mathbf{J}_{\text{chemotactic}} = \chi B \frac{\partial c}{\partial x}. \tag{9}$$

The second term of equation (8) contains, as before, the flux due to random motion

$$\mathbf{J}_{\text{random}} = -\mu \frac{\partial B}{\partial x}. \tag{10}$$

Underlying molecular mechanisms that might produce a chemotactic response in microorganisms have been studied by Segel (1977). The equations have also been ap-

plied in a model for aggregation of microorganisms that will be described more fully in Section 11.1.

Certain cells implicated in the immune response of higher organisms are also able to undergo chemotactic motion in response to substances associated with infection or inflammation. White blood cells known as *polymorphonuclear leukocytes* (PMNs) are responsible for engulfing small foreign bodies in a process called *phagocytosis*. To locate such bodies, PMNs first orient their motion chemotactically in response to chemical substances released by damaged tissue (Zigmond, 1977). Lauffenburger (1982) who developed several models for the chemotaxis of PMNs demonstrated that the accuracy of the response can only be explained by assuming that cells average local concentrations over a time scale of several minutes. A slight modification of the Keller-Segel equations has also been applied (Lauffenburger and Kennedy, 1983) to describe spatial properties of the immune response to bacterial infection (see problem 11).

Chemotactic equations can be rigorously derived from first principles once certain assumptions are made about the "choice" of step size and direction of motion of individuals in a population. Okubo (1980) discusses derivation of such equations from one-dimensional "biased" random-walk models. Alt (1980) and others have similarly made the connection in higher dimensions.

10.3 DENSITY-DEPENDENT DISPERSAL

In recent work, Gurtin and MacCamy (1977) have extended the more classical models to density-dependent population dispersal. They suggest that more realistic assumptions about dispersal might include a nonconstant rate of dispersal that increases when overcrowded conditions prevail. Typically this would lead to a modified diffusion flux

$$\mathbf{J} = -\mathscr{D}(p)\nabla p, \tag{11}$$

or, in one dimension,

$$\mathbf{J} = -\mathscr{D}(p)\frac{\partial p}{\partial x}. \tag{12}$$

A form the authors use for $\mathscr{D}(p)$ is

$$\mathscr{D}(p) = kp^m, \tag{13}$$

where k is positive, and $m \geq 1$. An increase in the population thus causes the dispersal rate to increase. In one dimension an equation describing the population movement would then be

$$\frac{\partial p}{\partial t} = k\frac{\partial}{\partial x}\left(p^m\frac{\partial p}{\partial x}\right) + F(p), \tag{14}$$

where F is the local growth rate. It is readily shown that an equivalent form is

$$\frac{\partial p}{\partial t} = K\frac{\partial^2(p^{m+1})}{\partial x^2} + F(p), \tag{15}$$

where $K = k/(m + 1)$. Several interesting and somewhat desirable properties of this equation include the following: (1) If the population initially occupies a finite region, it will always occupy a finite region. (2) The size of this region will increase if birth dominates over mortality; (3) however, if mortality is the stronger influence, the population will not expand spatially beyond certain bounds.

Similar equations have since been applied to epidemic models in which the disease spreads with a migrating population (see, for example, Busenberg and Travis, 1983).

A particularly striking extension of the idea of density-dependent dispersal appears in a recent publication by Bertsch et al. (1985). These authors consider a pair of interacting populations with densities $u(x, t)$ and $v(x, t)$, in which dispersal is a response to the total population at a location that is, to $[u(x, t) + v(x, t)]$. It is assumed that the velocities of motion are proportional to gradients in the total population:

$$\mathbf{q} = -k_1\nabla(u + v), \tag{16a}$$

$$\mathbf{w} = -k_2\nabla(u + v), \tag{16b}$$

where $\mathbf{q}$ and $\mathbf{w}$ are velocities, and k_1 and k_2 are constants. This means that individuals are moving *away* from sites of high total population at velocities proportional to the gradient of $u + v$. For the case of no net death or growth, the conservation statements are

$$\frac{\partial u}{\partial t} = -\nabla\cdot(u\mathbf{q}), \tag{17a}$$

$$\frac{\partial v}{\partial t} = -\nabla\cdot(v\mathbf{w}), \tag{17b}$$

so that in one-dimension the full equations are

$$\frac{\partial u}{\partial t} = k_1\frac{\partial}{\partial x}\left[u\frac{\partial(u + v)}{\partial x}\right], \tag{18a}$$

$$\frac{\partial v}{\partial t} = k_2\frac{\partial}{\partial x}\left[v\frac{\partial(u + v)}{\partial x}\right]. \tag{18b}$$

The following interesting result is proved by Bertsch et al (1985). If the initial populations colonize distinct regions without overlap (that is, if they are *segregated*), they will remain segregated for all future times by virtue of these interactions. This prediction is independent of k_1 and k_2 and of the details of the initial distributions, provided only that they are segregated.

Models such as this point to the rather nonintuitive and surprising features of fairly simple sets of PDEs. In the next chapter we briefly examine two models in which pairs of PDEs lead to rather interesting predictions.

10.4 APICAL GROWTH IN BRANCHING NETWORKS

We next consider a pair of related models in which growth of a branching organism or network is described as a *translation* of *apices,* (endpoints of branches, at which growth takes place). Collectively this kind of growth can sometimes be approximated as a convection, provided the appropriate definitions of variables are made.

If one is concerned with the spatial distribution of density in filamentous organisms, it often makes sense to define two densities, which are then used simultaneously in describing growth, branching, and other possible interactions (to be mentioned later). One model focuses on fungi, which often grow in densely branched *colonies* (see Figure 10.2). The model consists of the following variables:

$\rho(x, t)$ = length of filaments per unit area,

$n(x, t)$ = number of growing apices per unit area.

It is assumed that apical growth leads to a constant rate of elongation that makes apices move at a fixed velocity. Define

v = growth rate in length per unit time.

Using these assumptions, it can be shown that an appropriate system of equations in a one-dimensional setting is

$$\frac{\partial \rho}{\partial t} = nv - \gamma\rho, \tag{19a}$$

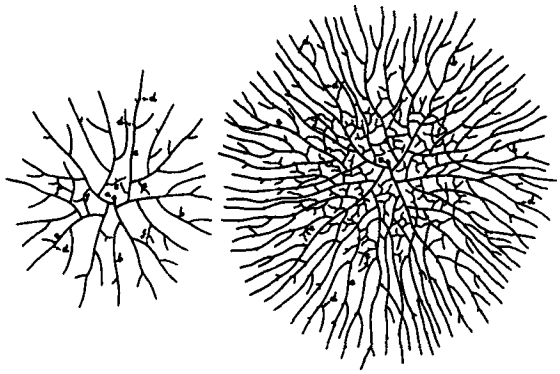
$$\frac{\partial n}{\partial t} = -\frac{\partial (nv)}{\partial x} + \sigma, \tag{19b}$$

where γ = the rate of filament mortality and σ = the rate of creation of new apices (which occurs whenever branching takes place). More details about this model can be found in Edelstein (1982), and a detailed derivation of these equations is given as a modeling exercise in problem 12.

Perhaps underscoring the generality of mathematics is a recent application of similar equations to the seemingly unrelated phenomenon of tumor-induced blood vessel growth. Balding and McElwain (1985) have modified (19) to describe the formation and growth of capillary sprouts into a tumor. It is known that a chemical intermediate secreted by tumors (called *tumor angiogenesis factor,* or TAF) promotes rapid growth of the endothelial cells that line the blood vessels. This leads to the sprouting of new capillaries, which apparently grow chemotactically toward high concentrations of TAF. In the model suggested by Balding and McElwain the diffusion of TAF [whose concentration is represented by $c(x, t)$] and its effect on capillary tip growth and sprouting are represented as follows:

$$\frac{\partial c}{\partial t} = \mathcal{D}\frac{\partial^2 c}{\partial x^2}, \qquad \text{(TAF)} \tag{20a}$$

$$\frac{\partial \rho}{\partial t} = nv - \gamma\rho, \qquad \text{(capillary density)} \tag{20b}$$



(*a*)

(*b*)

Figure 10.2 *Branching organisms such as fungi grow by extension and ramification of long slender filaments. Growth can take place in one, two, or three dimensions. A one-dimensional model also applicable to other networks such as blood vessels is given by equations (20a–c). (a) Two stages in the growth of* Coprinus. *(b) Stages in the development of* Pterula gracilis. *[(a) From A. R. M. Buller (1931),* Researches in Fungi, *vol. 4, Longmans, Green, London, figs. 87 and 88; (b) from J. T. Bonner (1974),* On Development; the biology of form, *fig. 17, reprinted by permission of Harvard University Press.]*

$$\frac{\partial n}{\partial t} = -\frac{\partial (nv)}{\partial x} + \sigma, \qquad \text{(capillary tips)} \tag{20c}$$

where

$$v = \chi \frac{\partial c}{\partial x}, \tag{20e}$$

$$\sigma = \alpha c \rho - \beta n \rho. \tag{20f}$$

In these equations, c may be determined independently and leads to a concentration field that acts as a chemotactic gradient. Equations (20b,c) include capillary-tip chemotaxis with rate χ, sprouting from vessels at a rate proportional to the concentration c, and loss of capillary tips due to *anastomosis* (reconnections that form closed networks). The equation for vessels (20b) includes growth by extension of tips and a rate γ of degradation of old vessels. This model illustrates the connection between the general concept of convective flux (as defined in Section 9.4) and the particular case of chemotaxis.

10.5 SIMPLE SOLUTIONS: STEADY STATES AND TRAVELING WAVES

Many models described in this chapter cannot be solved in full generality by analytic techniques, since they consist of coupled PDEs, some of which may be nonlinear. It is frequently challenging to make even broad generalizations about their time-dependent solutions, and abstract mathematical theory is called for in such endeavors.

We shall skirt these issues entirely and deal only with easier questions that can be settled by applying methods developed for ODEs to understand certain special cases. Two types of solutions can be obtained by such means: the first are steady states (time-independent distributions); a familiarity with the concept of steady states can thus be extended into the realm of spatially distributed systems. The second and distinctly new class of solutions are the *traveling waves*, distributions that move over space while maintaining a characteristic "shape" or profile. A special trick will be used to address the question of existence and properties of such solutions.

Nonuniform Steady States

By a steady state $\bar{c}(x)$ of a PDE model we mean a solution to the equations of the model that additionally satisfies the equation

$$\frac{\partial c}{\partial t} = 0.$$

If the problem is written for a single space dimension, setting the time derivative to zero turns the equations into a set of ODEs. Often, but not always, these can be solved to obtain an analytical formula for the steady-state spatial distribution $\bar{c}(x)$.

Homogeneous (Spatially Uniform) Steady States

A homogeneous steady state is a solution for which both time and space derivatives vanish. For example, in one space dimension

$$\frac{\partial c}{\partial t} = 0, \qquad \frac{\partial c}{\partial x} = 0.$$

These solutions satisfy algebraic relationships that are often relatively easy to solve explicitly. They describe spatially uniform unvarying levels of the population. Often such solutions are less interesting on their own merits but are rather significant for their special stability properties. The effects of spatially nonuniform perturbations of such homogeneous steady states forms a separate topic to be discussed in Chapter 11.

Example 1
Find a (nonuniform) steady-state solution of equation (8) for bacterial chemotaxis.

Solution
Setting $\partial B/\partial t = 0$ leads to

$$\frac{\partial}{\partial x}\left(-\chi B \frac{\partial c}{\partial x} + \mu \frac{\partial B}{\partial x}\right) = 0. \tag{21}$$

Integrating once then results in

$$\mathbf{J} = \text{constant} \tag{22}$$

where $\mathbf{J}$ is bacterial flux, the expression in parentheses in equation (21).

Suppose (21) is confined to a domain $[0, L]$ and that no bacteria enter or leave the boundaries. Then by equation (22), $\mathbf{J} = 0$ at $x = 0$ implies that $\mathbf{J} \equiv 0$ for all x.

Thus

$$-\chi B \frac{\partial c}{\partial x} + \mu \frac{\partial B}{\partial x} = 0, \qquad \text{or} \qquad \chi \frac{\partial c}{\partial x} = \frac{\mu}{B} \frac{\partial B}{\partial x} \qquad \text{for } B \neq 0.$$

Integrating once more leads to

$$\chi c(x) = \mu \ln B(x) + k, \tag{23}$$

where k is an integration constant. Thus

$$B(x) = \tilde{k} \exp \frac{\chi c(x)}{\mu}, \tag{24}$$

where $\tilde{k} = \exp(-k)$.

Observe from (24) that a steady-state distribution of bacteria $B(x)$ can be related to a given chemical concentration $c(x)$. In general, another equation might describe the distribution of this substance. For a simple example, consider plain diffusion, for which

$$\frac{\partial c}{\partial t} = \mathfrak{D}\frac{\partial^2 c}{\partial x^2}, \tag{25}$$

$c(0) = C_0$, and $c(L) = 0$. This is an artificial example chosen purely for illustrative purposes: the chemical concentration is contrived to be fixed at the ends of the tube while bacteria are not permitted to enter or leave; furthermore, bacteria orient chemotactically according to the c gradient but do not consume the substance.

By results of Section 9.5, a steady-state solution of equation (25) is

$$c(x) = C_0\frac{x}{L}. \tag{26}$$

The corresponding bacterial profile would be

$$B(x) = \tilde{k}\exp\left(\frac{\chi C_0 x}{\mu L}\right). \tag{27}$$

From this solution it follows that at every location x the bacterial flux due to chemotactic motion is exactly equal and opposite to the flux due to random bacterial dispersion. For this reason a nonuniform distribution can be maintained.

Example 2

Find steady states of the density-dependent dispersal equations (18a,b).

Solution

Set $\partial u/\partial t = 0$ and $\partial v/\partial t = 0$ in equations (18a,b) to obtain

$$\frac{\partial}{\partial x}\left[u\frac{\partial(u+v)}{\partial x}\right] = 0, \tag{28a}$$

$$\frac{\partial}{\partial x}\left[v\frac{\partial(u+v)}{\partial x}\right] = 0. \tag{28b}$$

After integrating once, observe that

$$u\frac{\partial(u+v)}{\partial x} = C_1. \tag{29a}$$

$$v\frac{\partial(u+v)}{\partial x} = C_2. \tag{29b}$$

Note that C_1 and C_2 are constants and represent population flux terms for species u and v respectively. If $C_1 = C_2 = 0$, then two possibilities emerge:

1. $u = 0, v = K_2$ or $v = 0, u = K_1$, *(30)*

where K_1 and K_2 are non-negative real numbers; or

2. $u \neq 0, v \neq 0; \dfrac{\partial(u + v)}{\partial x} = 0; u = K - v,$ *(31)*

where K is a positive constant.

If $C_1 \neq 0$ and $C_2 \neq 0$, then neither u or v can ever be zero, so that a third result is obtained:

3. $$\frac{\partial(u + v)}{\partial x} = \frac{C_1}{u} = \frac{C_2}{v}. \tag{32}$$

This means that $u = (C_1/C_2)v$, so that

$$\left(1 + \frac{C_1}{C_2}\right)\frac{\partial}{\partial x}v = \frac{C_2}{v},$$

$$\int v\, \partial v = \int \frac{C_2}{1 + C_1/C_2}\, dx,$$

$$v = \left(2x\frac{C_2}{1 + C_1/C_2} + K\right)^{1/2}, \tag{33}$$

where K is a constant.

These solutions are written for the case of infinite one-dimensional domains. If a finite domain is to be considered, the steady states just given may or may not exist depending on boundary conditions (see problem 15).

It is possible to patch together a mosaic of solutions (of type 1, for example) that would satisfy the given system of equations at all points save for a few singular locations where a transition between one species and the next occurs. (The spatial derivatives are undefined at such places.) Such mosaics depict a partitioning of the domain into separate habitats where either u or v (but not both) prevail. In this situation the populations are said to be *segregated.*

We next turn to traveling-wave solutions and indicate how a similar reduction to ODEs can be made.

Traveling-Wave Solutions

Let $f(x, t)$ be a function that represents a wave moving to the right at constant rate v while retaining a fixed shape; f is thus a traveling wave. An observer moving at the same speed in the direction of motion of the wave sees an unchanging picture, which he or she might describe alternately as $F(z)$. The connection between the stationary and moving observers is

$$F(z) = f(x, t) \qquad \text{provided} \qquad z = x - vt. \tag{34}$$

See Figure 10.3. We note that $F(z)$ is now a function of a single variable: distance along the wave from some point arbitrarily chosen to be $z = 0$. Using equation (34) and the chain rule of differentiation, we may conclude that

$$\frac{\partial f}{\partial x} = \frac{dF}{dz}\frac{\partial z}{\partial x} = \frac{dF}{dz}, \tag{35a}$$

$$\frac{\partial f}{\partial t} = \frac{dF}{dz}\frac{\partial z}{\partial t} = -v\frac{dF}{dz}. \tag{35b}$$

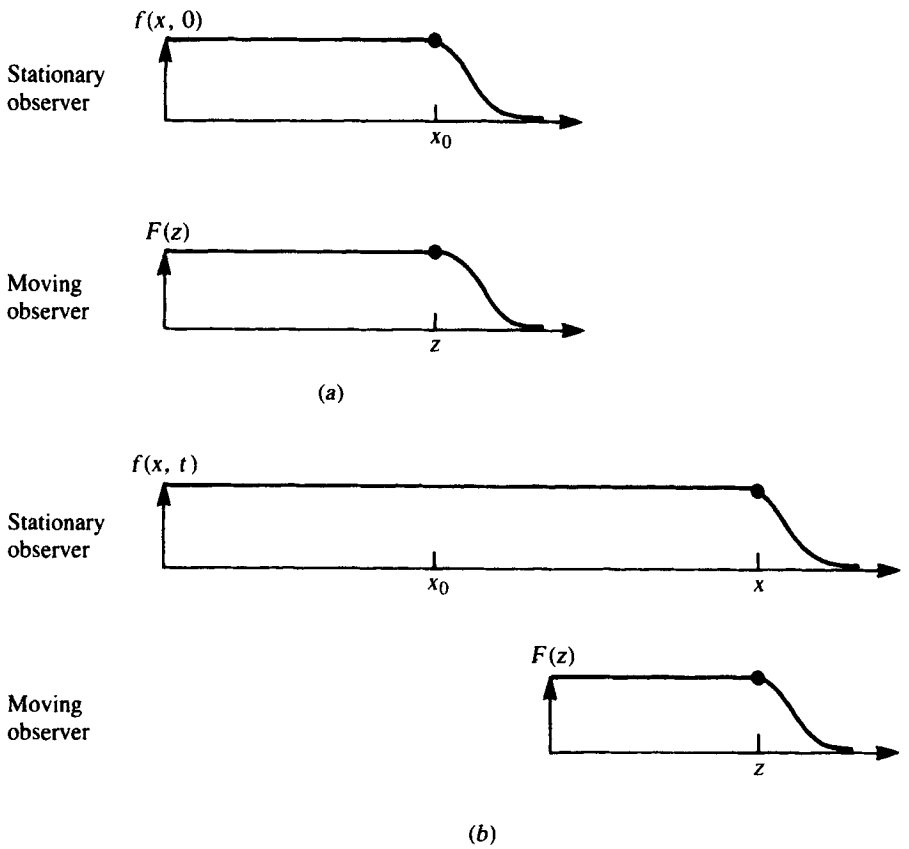


Figure 10.3 *Traveling waves in stationary and moving descriptions. A function* f(x, t) *is a traveling wave if there is a coordinate system moving with constant speed* v *such that* f(x, t) = F(z) *where* z = x − vt *(or* z = x + vt *for motion in the opposite direction). One exploits this fact in converting a PDE in* f *into an ODE or possibly a set of ODEs in* F. *(a) time* = 0, *(b) time* = t.

Example 3

Consider the equation

$$\frac{\partial p}{\partial t} = \mathcal{D}\frac{\partial^2 p}{\partial x^2} + \alpha p(1 - p). \tag{36}$$

The motivation for this equation is discussed in the next section. Letting

$$P(z) = p(x, t) \tag{37a}$$

for

$$z = x - vt, \tag{37b}$$

we obtain

$$-v\frac{dP}{dz} = \mathcal{D}\frac{d^2P}{dz^2} + \alpha P(1 - P). \tag{38}$$

This is a second-order ODE. We shall convert it to a system of first-order ODEs by making the substitution

$$-S = \frac{dP}{dz}. \tag{39}$$

The system we obtain is

$$\frac{dP}{dz} = -S \tag{40a}$$

$$\frac{dS}{dz} = +\frac{\alpha}{\mathcal{D}}P(1 - P) - \frac{v}{\mathcal{D}}S. \tag{40b}$$

If we can find a way of understanding this system of ODEs, then we can make a statement about the existence and properties of the traveling-wave solutions. This is our main topic in the next section.

10.6 TRAVELING WAVES IN MICROORGANISMS AND IN THE SPREAD OF GENES

In this section we describe two problems that can be approached by applying familiar techniques in a rather novel way. We first deal with a classic model due to Fisher that illustrates ideas in a simple, clear setting. A second modeling problem is then handled using similar methods.

Fisher's Equation: The Spread of Genes in a Population

Fisher (1937) considered a population of individuals carrying an advantageous allele (call it a) of some gene and migrating randomly into a region in which only the allele A is initially present. If p is the frequency of a in the population and $q = 1 - p$ the frequency of A, it can be shown that under Hardy-Weinberg genetics, the rate of change of the frequency p at a given location is governed by the equation

$$\frac{\partial p}{\partial t} = \mathcal{D}\frac{\partial^2 p}{\partial x^2} + \alpha p(1 - p), \tag{36}$$

where α is a constant coefficient that depicts the intensity of selection (see Hoppensteadt, 1975). Note that $0 < p < 1$. Historically this model elicited considerable interest and was investigated and generalized by a host of mathematicians. Good reviews of the historical perspective and of the mathematical methods can be found in Fife (1979), Murray (1977), and Hoppensteadt (1975). We remark that the equation can also describe a population $p(x, t)$ that reproduces logistically and disperses randomly.

Equation (36) has a variety of solutions depending on other constraints (such as boundary conditions). Here we shall deal exclusively with *propagating waves* on an infinite domain. The goal before us is to ascertain whether a process described by equation (36) can give rise to biologically realistic waves of gene spread in a population.

In Section 10.5 we observed that the strategy behind studying traveling-wave solutions is that the mathematical problem is thereby reduced to one of solving a set of ODEs. From example 3 it transpires that if equation (36) has traveling-wave solutions, these must satisfy equation (38), or equivalently the system of equations

$$\frac{dP}{dz} = -S, \tag{40a}$$

$$\frac{dS}{dz} = \frac{\alpha}{\mathcal{D}}P(1 - P) - \frac{v}{\mathcal{D}}S. \tag{40b}$$

This system of ODEs is nonlinear and therefore not necessarily analytically solvable. However, the system can be understood qualitatively by phase-plane methods, as follows:

Consider a PS phase plane corresponding to system (40). By our previous methods of attack we first deduce that nullclines are those curves for which

$$S = 0, \qquad (P \text{ nullcline}) \tag{41a}$$

$$S = \frac{\alpha}{v}P(1 - P), \qquad (S \text{ nullcline}) \tag{41b}$$

and that intersections ("steady states") occur at

$$(\bar{P}_1, \bar{S}_1) = (0, 0), \tag{42a}$$

$$(\bar{P}_2, \bar{S}_2) = (1, 0). \tag{42b}$$

The Jacobian of (40a,b) is

$$\mathbf{J}_i = \begin{pmatrix} 0 & -1 \\ \frac{\alpha}{\mathcal{D}}(1 - 2P) & -\frac{v}{\mathcal{D}} \end{pmatrix}_{(\bar{P}_i, \bar{S}_i)}, \tag{43a}$$

so that

$$\mathbf{J}_1 = \begin{pmatrix} 0 & -1 \\ \frac{\alpha}{\mathcal{D}} & -\frac{v}{\mathcal{D}} \end{pmatrix}, \tag{43b}$$

$$J_2 = \begin{pmatrix} 0 & -1 \\ -\frac{\alpha}{\mathcal{D}} & -\frac{v}{\mathcal{D}} \end{pmatrix}. \tag{43c}$$

This makes $(\bar{P}_1, \bar{S}_1)$ a stable node and $(\bar{P}_2, \bar{S}_2)$ a saddle point provided $v > 2(\alpha\mathcal{D})^{1/2}$ (see problem 16). The *PS* phase plane is shown in Figure 10.4(*a*). On this figure arrows correspond to increasing z values, since z is the independent variable in equations (40a,b). A single trajectory emanates from the saddle point and approaches the node as z increases from $-\infty$ to $+\infty$. A trajectory that connects two steady states is said to be heteroclinic. Such trajectories have special significance to our analysis, as will presently be shown.

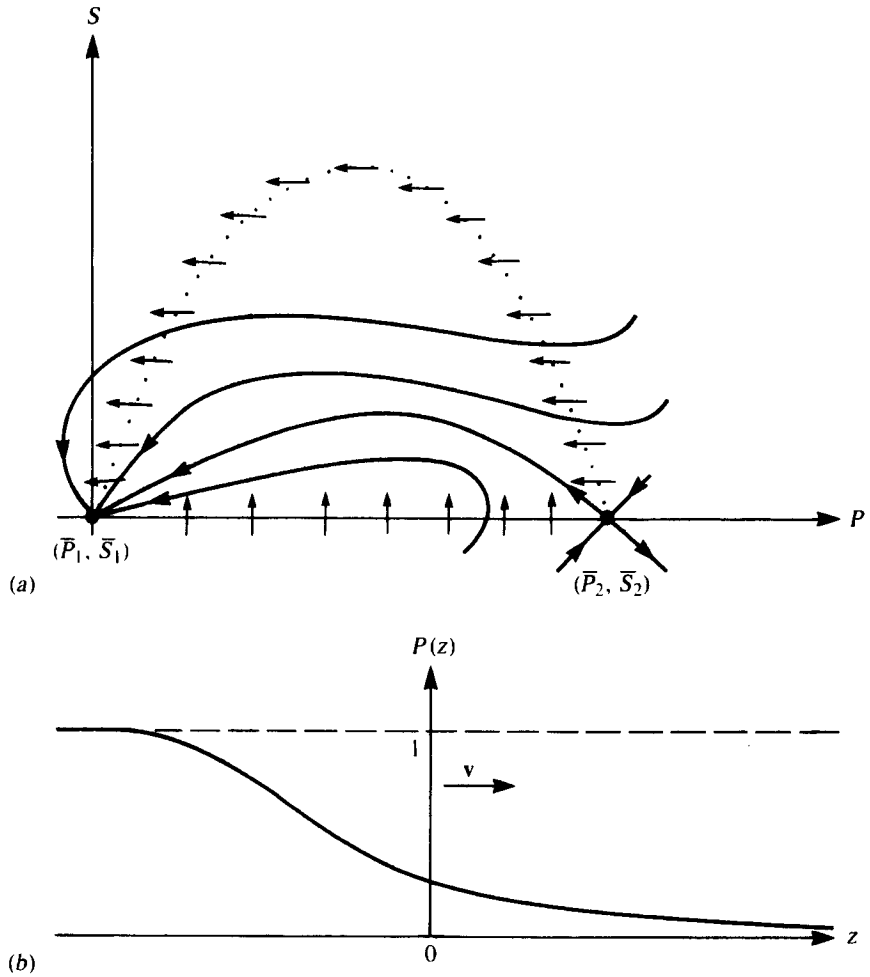


Figure 10.4 *(a) Traveling-wave solutions to Fisher's equation (36) satisfy a set of ODEs (40) whose phase-plane diagram is shown here. The heteroclinic trajectory shown connecting the two steady states* $(\bar{P}_1, \bar{S}_1) = (0, 0)$ *and* $(\bar{P}_2, \bar{S}_2) = (1, 0)$ *is the only bounded positive trajectory. (b) The qualitative shape of the wave.* $P(z) \to 1$ *(for* $z \to -\infty$*) and* $P(z) \to 0$ *(for* $z \to +\infty$*). The direction and speed of motion is indicated.*

To interpret Figure 10.4(*a*) in light of propagating waves we must first recall the interpretation given to the functions $P(z)$ and $S(z)$. Forfeiting a role previously played by time t, the variable z stands for distance along the length of a wave. Any one curve in the PS plane thus depicts the gene frequency (P) and its spatial variation (S) from one end of the wave ($z = -\infty$) to the other ($z = +\infty$). We are primarily interested in the former, $P(z)$. However, not all the phase-plane trajectories give reasonable depictions of a biological wave. We consider first the distinguished heteroclinic orbit mentioned earlier and observe the following properties of this curve:

$$P(z) \to \bar{P}_2 = 1 \qquad (z \to -\infty), \tag{44a}$$

$$P(z) \to \bar{P}_1 = 0 \qquad (z \to +\infty), \tag{44b}$$

$$\bar{P}_1 < P(z) < \bar{P}_2 \qquad (-\infty < z < +\infty). \tag{44c}$$

A sketch of P as a function of z derived exclusively from these observations is given in Figure (10.4(*b*). This wave has the shape of a moving *front*. At large positive z values $P(z)$ is very small (approaching zero for $z \to +\infty$), whereas at large negative z values $P(z)$ is very close to 1 (approaching 1 for $z \to -\infty$). This means that allele a has become dominant in the population at the left part of the domain, whereas allele A is still the only gene present towards the right.

Recall that $z = x - vt$ depicts a wave traveling from left to right. The arrow in Figure 10.4(*b*) indicates the direction that the given wave would move with respect to a stationary observer. We observe that the advantageous allele a becomes *dominant* in the population as the wave sweeps through the domain; that is, allele a spreads in the population towards fixation at any particular location.

Now examining other phase-plane trajectories shown in Figure 10.4(*a*) we encounter unrealistic features that lead us to reject these as possible candidates for biological traveling waves. Some of these trajectories tend to infinitely large P values for $z \to -\infty$. This would lead to unbounded levels of P that are inconsistent with the assumption that P is confined to the interval $0 \leq P \leq 1$. These waves are biologically meaningless. Other trajectories that lead to negative P values are equally unacceptable. It can be thus established that only the heteroclinic trajectory depicts a bounded positive wave consistent with a biological interpretation. We conclude the following:

> Biologically meaningful propagating solutions are only obtained if the phase plane corresponding to traveling waves admits a bounded trajectory that is contained entirely in the positive population quadrant.

In the Fisher equation (36) the only (nontrivial) bounded trajectory is the heteroclinic one. It remains in the positive P half-plane provided $v > 2(\alpha\mathcal{D})^{1/2}$ (see problem 16). This means that waves of the shape shown in Figure 10.4(*b*) must move at speeds that exceed the minimum velocity

$$v_{\min} = 2(\alpha\mathcal{D})^{1/2}. \tag{45}$$

It is generally true that propagating-wave solutions of PDEs, if they exist at all, must satisfy constraints on the speed of propagation. Less clear from this result

is which of the infinitely many possible speeds is most *stable;* this turns out to be a rather formidable theoretical question. Fisher's equation is simple enough that an answer to this problem could be given. It was shown by Kolmogorov et al. (1937) that if suitable initial conditions are assumed, the solution of equation (36) would evolve into a traveling wave such as that of Figure 10.4(*b*) and would move at the minimal wavespeed $v_{\min}$. Readers interested in learning further details should consult Murray (1977, sec. 5.3).

Spreading Colonies of Microorganisms

A remarkable attribute of many living things is an ability to grow in size while maintaining a particular shape or geometry. This property is common in advanced multicellular organisms where strong intercellular communication links are present. It also occurs in much more primitive settings such as populations of microorganisms, although the underlying mechanisms might be rather different. Here we consider the nutrient-dependent growth of yeast cells and determine whether a colony can exhibit a coordinated spread over space.

Let us focus on the growth of yeast under normal laboratory conditions. A typical experiment begins with a petri dish containing a small volume of sterile nutrient-rich medium. Usually the medium is a solidified gel-like substance called *agar,* which permits free diffusion of small molecules and provides a convenient two-dimensional surface on which to grow microorganisms. A small number of yeast cells are placed on the agar surface. By absorbing nutrient from below, they grow and multiply to such an extent that the population gradually expands and spreads over the surface of the substrate. In many cases, the shape of the colony remains essentially unchanged as it grows in size.

Gray and Kirwan (1974) introduced a model for the spread of yeast colonies which, with some modifications, will serve as our example. A colony of yeast usually takes the form of a glossy disk, visible to the naked eye, that continually enlarges in diameter. We will find it more convenient to deal with a one-dimensional model of the colony, as depicted in Figure 10.5. Accordingly we define the following:

$n(x, t)$ = density of cells at location x at time t,

$g(x, t)$ = concentration of glucose in medium at location x at time t.

Assuming that yeast cells undergo slight random motion and that they produce progeny only when glucose is sufficiently abundant, a simple set of equations to describe the situation would be as follows:

$$\frac{\partial n}{\partial t} = \mathcal{D}_0 \frac{\partial^2 n}{\partial x^2} + kn(g - g_1), \tag{46a}$$

$$\frac{\partial g}{\partial t} = \mathcal{D} \frac{\partial^2 g}{\partial x^2} - ckn(g - g_1). \tag{46b}$$

In these equations g_1 is a constant, representing the minimal amount of glucose necessary for cell proliferation. The yeast reproduction rate is $k(g - g_1)$; that is, cells

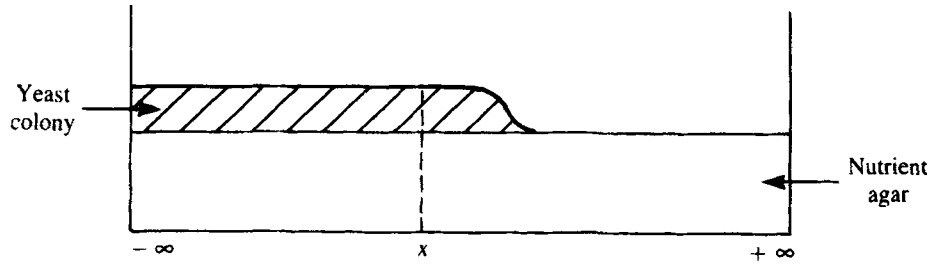


Figure 10.5 *Side view of petri dish with yeast colony.*

are assumed to increase proportionately with the amount of glucose in excess of g_1. Glucose undergoes diffusion with rate $\mathcal{D}$ and is depleted at a rate proportionate to the production rate of yeast cells (c units of glucose used per new cell made). Recall that, although both equations contain diffusion-like terms, these represent on the one hand the approximate nature of random yeast-cell motion, $\mathcal{D}_0(\partial^2 n/\partial x^2)$, and on the other hand true diffusion of glucose in a medium in which it is dissolved. (Agar is 90% or more water and permits essentially free diffusion.)

As a first step, let us define $\hat{g}$ for convenience as

$$\hat{g}(x, t) = g(x, t) - g_1.$$

Assuming that the motility of cells is very slow compared with diffusion of glucose and with the rate of budding of cells, we take the simplified version of the model proposed by Gray and Kirwan:

$$\frac{\partial n}{\partial t} = kn\hat{g}, \tag{47a}$$

$$\frac{\partial g}{\partial t} = \mathcal{D}\frac{\partial^2 \hat{g}}{\partial x^2} - ckn\hat{g}. \tag{47b}$$

This step, though recognized by the advanced reader as fraught with pitfalls, will considerably aid the analysis. In fact, Gray and Kirwan began with equations (47a,b) and to avoid these pitfalls assumed that yeast cells were nonmotile.

Let us now consider as possible traveling-wave solutions to equations (47a,b) functions N and G, where

$$N(z) = n(x, t), \qquad G(z) = \hat{g}(x, t), \qquad z = x - vt,$$

which satisfy the equations of the model.

Using the identities (35a,b), N and G would then have to satisfy

$$-v\frac{dN}{dz} = kNG, \tag{48a}$$

$$-v\frac{dG}{dz} = \mathcal{D}\frac{d^2G}{dz^2} - ckNG. \tag{48b}$$

Multiplying (48a) by the constant c and adding to (48b) yields

$$-vc\frac{dN}{dz} - v\frac{dG}{dz} = \mathcal{D}\frac{d^2G}{dz^2}. \tag{49}$$

Equation (49) can be integrated once, resulting in

$$\text{constant} - vcN - vG = \mathcal{D}\frac{dG}{dz}. \tag{50}$$

By considering values of N and G far behind the edge of the colony, it may be verified that the arbitrary constant introduced by integration has the value cvN_0, where N_0 is the maximal density of cells in the colony interior. This calculation is given in the boxed insert.

The system of equations to be considered is therefore

$$\frac{dG}{dz} = -\frac{v}{\mathcal{D}}G + \frac{Ncv}{\mathcal{D}} - \frac{vcN_0}{\mathcal{D}}, \tag{51a}$$

$$\frac{dN}{dz} = -\frac{kNG}{v} \tag{51b}$$

Conditions at $z = -\infty$

Far behind the leading edge of the colony where the colony has existed for a long time (large t, i.e., $z \to -\infty$) we might expect that cells have attained some limiting density N_0. (N_0 is in general limited by the amount of available glucose that could be used up). At $z = -\infty$ we would also expect $G = 0$, since glucose has been depleted to its lag concentration g_1. Furthermore, it is reasonable to assume that

$$\left.\frac{dG}{dz}\right|_{z=-\infty} = 0,$$

that is, the glucose concentration profile is relatively flat.

Integrating equation (49) from $-\infty$ to z we obtain

$$-v\int_{-\infty}^{z}\left(c\frac{dN}{dz} + \frac{dG}{dz}\right)dz = \int_{-\infty}^{z}\mathcal{D}\frac{d^2G}{dz^2}\,dz, \tag{52a}$$

$$(-vcN - vG)\Big|_{-\infty}^{z} = \mathcal{D}\left.\frac{dG}{dz}\right|_{-\infty}^{z}, \tag{52b}$$

$$-vcN(z) + vcN(-\infty) - vG(z) + vG(-\infty) = \mathcal{D}\left.\frac{dG}{dz}\right|_{z} - \mathcal{D}\left.\frac{dG}{dz}\right|_{-\infty}. \tag{52c}$$

Now using the conditions at $z = -\infty$, we obtain

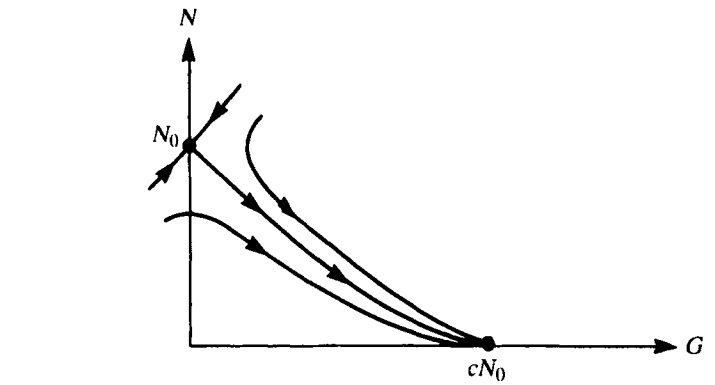
$$vcN_0 - vcN(z) - vG(z) = \mathcal{D}\left.\frac{dG}{dz}\right|_{z}. \tag{53}$$

Thus equation (51a) is confirmed.

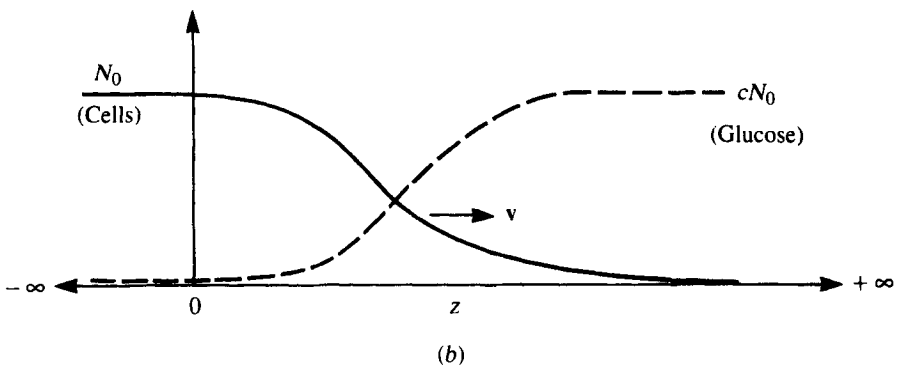
Thus, for the special solutions in which we are interested, it suffices to explore the behavior of these two ODEs. Although these are nonlinear by virtue of the NG term,

again by recourse to phase-plane methods one may obtain qualitative solutions. It is left as an exercise for the reader to show that the result is the *GN* phase-plane diagram given in Figure 10.6(*a*).

It now remains to interpret what the information in Figure 10.6(*a*) reveals about $N(z)$ and $G(z)$. Again a single bounded trajectory extends between two points, $(0, N_0)$ and $(cN_0, 0)$ in the *GN* plane. This trajectory describes a transition from a situation in which glucose is absent and cell density is given by N_0 to one in which glucose is at its maximal level cN_0 and no cells are present. This transition is also depicted qualitatively in Figure 10.6(*b*). As the yeast colony propagates to the right, it depletes the nutrient that was initially available to it. Gray and Kirwan (1974) draw a parallel between this biological process of contagion and the propagation of a flame N in combustion of a fuel G. Further details of the analysis are suggested in problem 17.



(*a*)



(*b*)

Figure 10.6 *(a) Phase-plane diagram of equations (51a,b) showing a heteroclinic trajectory joining* $(0, N_0)$ *with* $(cN_0, 0)$. *(b) Qualitative shape of traveling-wave solutions corresponding to (a) for the yeast cell–glucose model. The glucose is depleted in places over which the yeast colony has advanced.*

Some Perspectives and Comments

1. The two examples discussed in this section (Fisher's equation and spreading microbial colonies) are readily approached by phase-plane analysis. The versatility of such mathematical methods are thus gratifying, but can they always be expected to work? Inspection of both examples reveals that our analysis depended crucially on the fact that traveling waves satisfied a *pair* of ODEs. In the second example (spreading colonies of microorganisms) this was only true by virtue of a fortuitous integration step that reduced the order of equation (49). In many instances this good fortune does not occur. Higher-order equations or bigger systems of PDEs may have traveling-wave solutions that satisfy a larger system of ODEs. While the concepts are the same, the analysis is much harder. For bounded traveling waves, one would still seek bounded trajectories (but in a higher-dimensional phase space). As we already know, phase-plane analysis is a well-developed technique only in the plane, so the problem may be much harder when the ODE system is larger.

2. Both our examples also shared a phase-plane feature, the heteroclinic trajectory that depicts bounded waves. Two other types of waves can be encountered that correspond to other bounded trajectories. (a) A homoclinic orbit (one that emerges from and eventually returns to a single steady state) would result in a wave that asymptotically approaches the same value for $z \to \pm\infty$. (For example, the propagating action potential in the nerve axon is a peaked disturbance that tapers off to the resting voltage both far ahead and far behind its peak.) (b) A limit cycle would depict an infinite train of peaks or oscillations that propagate over space. (We have indicated that a train of action potentials can occur in nerve cells, given prolonged superthreshold stimulation.)

3. Traveling-wave solutions are sometimes abstractions of reality that give a good general description of the phenomenon of propagation but have unrealistic features as well. Both examples we have discussed share the inaccurate prediction that density of the propagating material (for example, genes or yeast cells) is *never* actually zero, even far ahead of the "front." (This stems from the fact that the solutions only *approach* zero for $z \to +\infty$.) In reality, of course, there are sharp transitions at the edge of an expanding population.

4. The question of wave speed was touched on but not carefully deliberated. In principle one would like to ascertain which of the possible family of waves (for different velocities) is the most stable. In practice the techniques for establishing this are rather advanced, and often such problems are too formidable to yield to analysis. (There are some instances when linear analysis predicts a *unique* wave speed. This occurs whenever phase-plane analysis reveals a heteroclinic trajectory connecting two saddle points. Such trajectories are easily disrupted by slight parameter changes.)

5. Even if analysis does not lead us to find bounded traveling-wave solutions in the exact sense described in this section, there may still be biologically interesting propagating solutions, such as those that undergo very slight changes in shape or velocity with time. In the next section we briefly discuss another biological setting in which long-range transport is important. A recent model for axonal transport due to Blum and Reed (1985) has been shown to lead to such *pseudowaves* (wavelike mov-

ing fronts of material that propagate down the length of the axon). The analysis of such examples is generally based heavily on computer simulations.

10.7 TRANSPORT OF BIOLOGICAL SUBSTANCES INSIDE THE AXON

The anatomy of a neural axon was described in Section 8.1, where our primary concern was the electrical property of its membrane. Other quite unrelated transport processes take place within the axonal interior. All substances essential for metabolism and for normal turnover of the components of the membrane are synthesized in the soma (cell body). Since these are to be used throughout the axon, which may be many centimeters or even meters in length, a transport process other than diffusion is called for. Indeed, with the aid of the light microscope one can distinguish motion of large particles called *vesicles* (macromolecular complexes in which smaller molecules such as acetylcholine are packaged). The motion is *saltatory* (discontinuous rather than smooth), with frequent stops along the way. There seem to be several operational processes, including the following:

1. Fast transport mechanism(s), which can convey substances at speeds on the order of 1 m day^{-1}.
2. Slow transport, with typical speeds of 1 mm day^{-1}.
3. *Retrograde transport* (movement in the reverse direction, from the terminal end to the soma), at speeds on the order of 1 m day^{-1}.

There have been numerous hypotheses for underlying mechanisms, mostly based in some way on the interaction of particles with microtubules. *Microtubules* are long cable-like macromolecules that are important structural components of a cell, and apparently have functional or organizational properties as well. It was held that microtubule sliding, paddling, or change of conformation might lead to fluid motion that would carry particles in *microstreams* within the axon (see Odell, 1977). Many of the original theories were thus based on bulk fluid flow inside the axon. There were problems with an understanding of the simultaneous forward and retrograde transport that led to rather elaborate explanations, none of which completely agreed with experimental observations.

A somewhat different concept has been suggested by Rubinow and Blum (1980) who propose that transport is not fluid-mediated but stems from reversible binding of particles such as vesicles to an intracellular "track" that moves at a constant velocity. They model this hypothetical mechanism by considering interactions of three intermediates, P, Q, and S, whose concentrations, p, q, and s, are defined as follows:

$p(x, t)$ = density of free particles at location x and time t,

$q(x, t)$ = density of particles bound to track at location x and time t,

$s(x, t)$ = density of unoccupied tracks at location x and time t.

It was assumed that particles bind reversibly to tracks as follows:

$$nP + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Q.$$

The factor n is incorporated as a possible form of cooperativity in binding. Their assumptions lead to two equations:

$$\frac{\partial p}{\partial t} = -k_1 p^n s + k_2 q, \tag{54a}$$

$$\frac{\partial q}{\partial t} = -\frac{\partial q v_0}{\partial x} - k_2 q + k_1 p^n s. \tag{54b}$$

In these equations bound particles move with the tracks, whereas free particles are stationary. The authors include diffusion terms that are omitted from (54a,b) and that were in fact shown to be unimportant in later work. The Rubinow-Blum model is suggestive, but several conceptual errors made by the authors in analysis of the model have engendered some confusion in the literature. (For reasons outlined in their paper, they deduce that cooperativity is essential, so that $n \geq 2$, but the solutions they describe are not biologically accurate.)

In more recent work, Blum and Reed (1985) have corrected some of these errors and produced a more realistic description. The authors propose that particles can only move along the track if they are bound to intermediates that couple them to the microtubules. In a curious coincidence, the development of this model and new experimental observations simultaneously point to similar conclusions. Indeed, new technology such as enhanced videomicroscopy reveals that all moving particles have leglike appendages to which they are reversibly bound and which seem to propel them along the track. These intermediates have been called *kinesins*.

In their model, Blum and Reed define

$e(x, t)$ = concentration of kinesins ("legs" or "engines"),

and $p(x, t)$, $q(x, t)$, and $s(x, t)$ as previously defined. The assumed chemical interactions are as follows:

1. Binding of kinesins to free particles:

$$P + nE \rightleftharpoons C,$$

where C is the P—nE complex.

2. Binding of C complexes to track(s):

$$C + mS \rightleftharpoons Q.$$

3. Binding of kinesins directly to tracks:

$$E + S \rightleftharpoons ES.$$

4. Binding of free particles to the complex of kinesins and tracks, (E*S*):

$$P + m(ES) \rightleftharpoons Q.$$

By a combination of numerical simulation and analysis Blum and Reed demonstrated that the above mechanism adequately describes all accurate experimental ob-

servations for the fast transport system of the axon. (Some discussion of their model is given as a problem in this chapter.) Of particular interest is their finding that this system admits pseudowaves. These numerical solutions undergo slight changes in shape but are virtually indistinguishable in their behavior from traveling waves as defined earlier.

10.8 CONSERVATION LAWS IN OTHER SETTINGS: AGE DISTRIBUTIONS AND THE CELL CYCLE

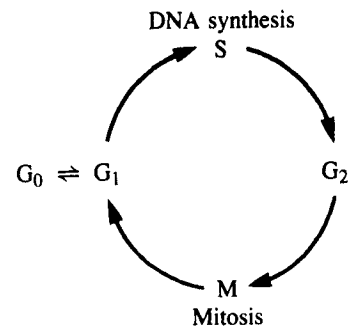
We now turn to processes that have little apparent connection with spatial propagation or spatial distributions. Here we shall be concerned with age structure in a population and with changes that take place in these populations as death and birth occur. (Recall that such questions were briefly discussed in Chapter 1 within the context of difference equations and Leslie matrices.)

We begin with a description of cellular maturation and discuss a discrete model for a population of cells at different stages of maturity. Such problems have medical implications, particularly in the treatment of cancer by chemotherapy. Agents used to attack malignant cells are *cycle-specific* if their effect depends on the stage in the cell cycle (degree of maturation of the cell). After examining M. Takahashi's model for the cell cycle we turn to a continuous description of the phenomenon that uncovers a familiar underlying mathematical framework, the conservation equations.

The Cell Cycle

Cells undergo a process of maturation that begins the moment they are created from parent cells and continues until they themselves are ready to divide and give rise to daughter cells. This process, known as the *cell cycle,* is traditionally divided into five main stages. Mature cells that are not committed to division (such as nerve cells) are in the G_0 phase. G_1 is a growth phase characterized by rapid synthesis of RNA and proteins. Following this is the S phase, during which DNA is synthesized. The G_2 phase is marked by further RNA and protein synthesis, preparing for the M phase, in which mitosis occurs. See Figure 10.7.

Figure 10.7 *Schematic diagram of the cell cycle.*



While these events are conveniently distinguishable to the biologist, they provide only broad subdivisions, since the journey for the cell from birth to maturity is a continuous one. However, at certain times during this process the cell's susceptibility to its environment may change. This, in fact, forms the basis for cycle-specific chemotherapy, a treatment using drugs that selectively kill cells at particular stages in their development.

It is far from obvious how a course of cycle-specific chemotherapy should be administered. Should it be continuous or intermittent? What frequency of treatments and doses works best, and how does one base one's appraisal on aspects of a given system? Here we shall not dwell on clinical problems associated with chemotherapy design. An excellent survey may be found in articles by Newton (1980) and Aroesty et al. (1973), who delineate mathematical approaches and their implementations in *oncology* (the study of tumors). The following simple discrete model for the cell cycle, which is due to Takahashi, will form our point of departure.

Let us suppose that the cell cycle can be subdivided into k discrete phases and that N_j represents the number of cells in phase j. The transition of a cell from the jth to the $(j + 1)$st phase will be identified with a probability per unit time, λ_j. Furthermore, the likelihood that a cell will die in the jth phase will be assigned the probability per unit time μ_j. See Figure 10.8.

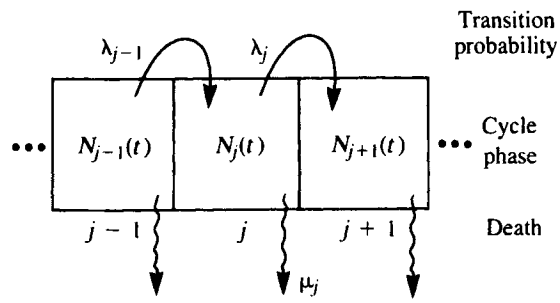


***Figure 10.8** Transitions through phases of the cell cycle.*

During a time interval Δt the number of cells entering phase j is $\lambda_{j-1}N_{j-1}(t)\Delta t$, and the number of cells leaving is $\lambda_j N_j(t)\Delta t$. With the death rate the process can be described by the equation

$$\frac{\Delta N_j}{\Delta t} = \lambda_{j-1}N_{j-1} - \lambda_j N_j - \mu_j N_j. \tag{55a}$$

Suppose that upon maturity each cell (in phase k) divides into β new cells of initial phase $j = 1$. This leads to a boundary condition for the problem:

$$\frac{\Delta N_1}{\Delta t} = \beta\lambda_k N_k(t) - \lambda_1 N_1(t) - \mu_1 N_1(t). \tag{55b}$$

In problem 21 it is shown that if transition probabilities are all equal, if $B = 2$, and if $\mu_j = 0$, the model can be written in the following way:

$$\frac{dN_j}{dt} = \lambda(N_{j-1} - N_j), \tag{56a}$$

$$\frac{dN_1}{dt} = \lambda(2N_k - N_1). \tag{56b}$$

The steady-state solution of (56) reveals that the fraction of cells in each stage follows a Γ distribution.

The discrete model leads to a set of k equations, one for each of the cell-cycle stages. Only the first of these contains a term for birth since we have assumed that, on cell division, daughter cells are in the initial stage of their cycle.

At this point two options are available: First, one could study these equations in their present form, as difference equations. A computer simulation program could then directly use this discrete recipe for generating the phase distributions. Cycle-specific death rates could optionally be included. However, a second approach proves rather illuminating in that it leads to insight based on familiarity with other physical processes. The approach is based on deriving a statement that represents the process of maturation as a continuous and gradual transition. Instead of subdividing the cycle strictly into discrete stages, suppose we represent the degree of maturity of a cell by a continuous variable α, which might typically range between 0 and 1. Instead of accounting for the number of cells in a given stage (that is, in one of the k compartments of Figure 10.8), let us consider a continuous description of cell density along the scale of maturity α.

We will define a *cell-age distribution frequency* in the following way:

$$N_j(t) = n(\alpha_j, t)\,\Delta\alpha \qquad (\alpha_j = j\,\Delta\alpha).$$

In other words, think of $n(\alpha, t)$ as a *cell density per unit age*. Then, provided that the compartment width $\Delta\alpha$ is small, a formal translation can be made from discrete to continuous language using Taylor-series expansions. We write

$$\begin{aligned} n(\alpha_{j-1}, t) &= n(\alpha_j - \Delta\alpha, t) \\ &= n(\alpha_j, t) - \left.\frac{\partial n}{\partial \alpha}\right|_j \Delta\alpha + \left.\frac{\partial^2 n}{\partial \alpha^2}\right|_j \frac{(\Delta\alpha)^2}{2!} - \left.\frac{\partial^3 n}{\partial \alpha^3}\right|_j \frac{(\Delta\alpha)^3}{3!} + \cdots, \end{aligned} \tag{57}$$

Neglecting cell death, omitting terms of order $(\Delta\alpha)^3$ or higher, and substituting into equation (56a) leads to

$$\frac{1}{\lambda}\frac{\partial n}{\partial t}(\alpha_j, t) = -\left.\frac{\partial n}{\partial \alpha}\right|_j \Delta\alpha + \left.\frac{\partial^2 n}{\partial \alpha^2}\right|_j \frac{(\Delta\alpha)^2}{2} + \cdots. \tag{58}$$

Note that for k equal subdivisions $\Delta\alpha = 1/k$, so that

$$\frac{\partial n}{\partial t}(\alpha_j, t) + \left.\frac{\partial n}{\partial \alpha}\right|_j \frac{\lambda}{k} = \left.\frac{\partial^2 n}{\partial \alpha^2}\right|_j \frac{1}{2}\frac{\lambda}{k^2} + \cdots. \tag{59}$$

Now let

$$\nu_0 = \frac{\lambda}{k}, \qquad d_0 = \frac{1}{2}\frac{\nu_0}{k}.$$

A somewhat familiar equation results from these substitutions:

$$\frac{\partial n}{\partial t} + \nu_0 \frac{\partial n}{\partial \alpha} = d_0 \frac{\partial^2 n}{\partial \alpha^2}. \tag{60}$$

This equation contains one term that resembles diffusion and a second that resembles convective transport. This suggests some kind of analogy between the process of cellular maturation and physical particle motion. We explore this more fully in the following subsection and discuss several details in the problems.

Analogies with Particle Motion

To approach the same problem in a more informal way, we abandon temporarily the detailed discrete derivation and view the process of cellular maturation as a continuous transition from birth to maturity of the cell. It is rather natural to picture cell maturation as "motion" of the cell along a scale α. We now make the analogy more precise.

Consider the physical motion of particles in a one-dimensional setting. For x = the distance and $c(x, t)$ = the density of particles (per unit length) we derived a conservation equation (24 in Chapter 9) to describe collective particle motion. If particles move at some velocity v, then the displacement of each individual particle might be described by

$$\frac{dx}{dt} = v(x, t). \tag{61}$$

Collectively, their flux would then be

$$J_c(x, t) = c(x, t)v(x, t). \tag{62}$$

Now replace (1) physical distance in space by "distance" along a scale of maturation ($x \to \alpha$) and (2) density of particles in space by density of cells along the maturation cycle [$c(x, t) \to n(\alpha, t)$]. Then the velocity of a particle would correspond to the rate of change of cellular maturity:

$$\frac{d\alpha}{dt} = \nu(\alpha, t). \tag{63}$$

In other words, we make the connection that $v(x, t) \to \nu(\alpha, t)$. This means that the number of cells that mature through a stage α_0 per unit time (the cell flux) would be

$$J_n = n(\alpha, t)\nu(\alpha, t), \tag{64}$$

that is, $J_c \to J_n$. Finally, a local loss of particles $\sigma_c(x, t)$ would be analogous to a local cellular loss rate $\sigma_n(\alpha, t)$. This could stem from a mortality μ, where μ might be a function of the cellular maturity:

$$\sigma_n(\alpha, t) = -\mu(\alpha)n(\alpha), \tag{65}$$

and $\sigma_c(x, t) \to \sigma_n(\alpha, t)$.

Based on these analogies the following connection emerges:

$$\underbrace{\frac{\partial c}{\partial t} = -\frac{\partial J_c}{\partial x} + \sigma_c}_{\text{particle conservation equation}} \longrightarrow \underbrace{\frac{\partial n}{\partial t} = -\frac{\partial J_n}{\partial \alpha} + \sigma_n}_{\text{cell conservation equation}}.$$

Thus, without further derivation we have arrived at a continuous description of the maturity distribution of the cell population, given by the equation

$$\frac{\partial n}{\partial t} = -\frac{\partial n\nu}{\partial \alpha} - \mu n. \tag{66}$$

See Figure 10.9. This equation merits several comments in light of the somewhat different result derived from Takahashi's model:

1. The maturation rate ν is not assumed to be a constant.
2. The age-dependent death rate μ is explicitly assumed.
3. Most notably, the diffusion term is missing.

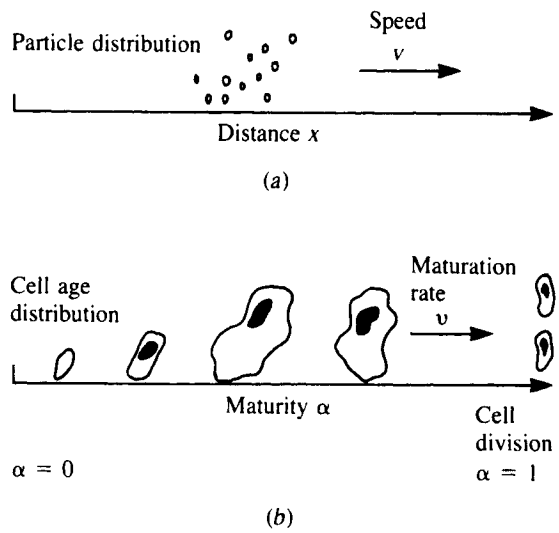


Figure 10.9 *Analogy between (a) particle motion through a distance* x *(at speed* v*) and (b) cellular maturation through maturity* α *(at speed v) forms the basis for the derivation of equation (66).*

In many of the more recent models, diffusion terms such as that in the RHS of equation (60) are often omitted. Note that this term arises formally when maturation is depicted as a chain of random transitions rather than a deterministic "unidirectional flow." It is important to note that the constants ν_0 and d_0 in equation (60) are not independent! Letting $\nu_0 \to 0$ means that $d_0 \to 0$ simultaneously. Other-

wise a curious contradiction is obtained: if $v_0 = 0$ and $d_0 > 0$, the cells appear to undergo pure diffusion, with some continually getting younger while others increase in age. Some modified versions of the diffusion term have recently been suggested to alleviate this conceptual problem, particularly when a terminal age is attained (see Thompson, 1982).

4. A term for birth of new individuals or increase in the population due to cell division again merits a separate equation. It cannot be incorporated directly into equation (66) because cells are only "born into" the lowest maturity class, $\alpha = 0$. Thus birth is specified as a boundary condition of the problem. For cells that divide only at maturity, when $\alpha = 1$, such birth terms could be given by

$$n(0, t) = \beta n(1, t), \tag{67}$$

where β is the number of divisions at mitosis. However, note that (66) could apply to more general age-structured populations, where $n(\alpha, t)$ is the "density" of individuals at different ages α (commonly called the *age distribution of a population*). In such cases females of different ages may give birth to newborns. Thus the number of newborns is a sum of all such contributions, given by

$$n(0, t) = \int_0^\infty n(\alpha, t)\beta(\alpha)\, d\alpha, \tag{68}$$

where β is the *age-specific fecundity* (average number of births from a female between the ages α and $\alpha + d\alpha$), and n is the number of females. If the initial age distribution $\phi(a)$ is known, equation (66) is supplemented with the initial condition

$$n(0, a) = \phi(a). \tag{69}$$

Further discussion of equation (66) and its associated conditions is given in problems 23 and 24.

To give some historical perspective to the model for age distributions, a long list of contributors deserve mention.

Apparently, the first formulation of a PDE for the age distribution of a population is due to McKendrick (1926). Much later, Von Foerster (1959) independently derived a similar equation and applied it to the dynamics of blood cell populations. (Equations such as (66) are often given his name despite the historical inaccuracy.) Analytic solutions of such equations were given by Trucco (1965) and Rubinow (1968), who somewhat generalized the original models.

In the last two decades, PDE models have been applied to problems stemming from demography. Hoppensteadt (1975) gives a good review of this area. Theoretical results have proliferated rapidly, many of them involving a considerable depth of mathematical analysis. Gurtin and MacCamy (1974) dealt with density-dependent birth and mortality. Reviews of this abstract topic may be found in Webb (1985), Heijmans (1985), and Metz and Diekmann (1986).

A further direction has been the generalization of the concept underlying the derivation of the age-distribution equation to rather different problems where variables other than age are of interest. We shall encounter a second example of this type in the do-it-yourself modeling problem outlined in Section 10.9.

A Topic for Further Study: Applications to Chemotherapy

Equations such as (55), (56) and (66) are now commonly applied to modeling the effect of chemotherapeutic agents on malignant cells. Several references provided in the "For Further Study" section of the References could be used as the basis for independent study or further discussion. One example, briefly indicated in the box, is explored in more detail in problem 25.

Example 4

Bischoff et al. (1971) suggested a simplified model for a particular course of chemotherapy of the leukemia strain L1210 using arabinose-cytosine. They assumed that the maturation rate of malignant cells is a constant v and that the drug results in cell death with rate constant μ that varies with drug concentration and cell age.

The equations of their model are:

$$\frac{\partial n}{\partial t} = -v\frac{\partial n}{\partial \alpha} - \mu n, \tag{70}$$

where

$$\mu(\alpha, t) = \frac{K_1(\alpha, t)c(t)}{K_2(\alpha, t) + c(t)}. \tag{71}$$

An equation that describes mitosis in their model is

$$n(0, t) = 2n(1, t). \tag{72}$$

The authors explored the limiting case when cycle specificity of the drug was low and found an asymptotic solution:

$$n(\alpha, t) = N_0(2 \ln 2)2^{-(\alpha - vt)} \exp \int_0^t -\mu(t')\, dt'. \tag{73}$$

In problem 25 this observation is used in showing that eventually the number of cells at lowest maturity level $\alpha = 0$ is a constant fraction of the total population. It is further shown that equation (70) implies that

$$\frac{dN}{dt} = aN - \mu N \tag{74}$$

where

$$N = \int_0^1 n(\alpha, t)\, d\alpha \qquad \text{and} \qquad a = v \ln 2.$$

Other references, notably those of Newton (1980) and Aroesty et al. (1973), discuss the role of mathematics in oncology in a much broader setting.

Summary

In this section we observed, by considering the aging of a cell, that conservation laws apply to a much broader class of problems than described in previous discus-

sions. Here is a setting in which spatial position and motion in space play no role; another continuous variable, *age,* is more important in describing the system. Yet the ideas of *conservation* lead to equations that are essentially identical (except for renaming variables) to spatial balance equations. This stems from the fact that conservation equations are "bookkeeping" statements: together with their boundary and initial conditions, they serve to keep track of all the progeny of some initial population of parent cells.

In the next section another application of similar mathematical ideas is suggested. However, rather than spelling out all details, we approach a new problem in a sequence of reasoning steps in which reader participation is encouraged.

10.9 A DO-IT-YOURSELF MODEL OF TISSUE CULTURE

In this section you are invited to participate in developing a model as an aid for studying a rather simple biological question. The particular situation to be modeled is a new one, though some of the concepts presented in previous sections can be brought to bear on the problem. The derivation of the model is given in a step-by-step outline; however, you should attempt to use your own inventiveness before consulting the hints in the text.

A Statement of the Biological Problem

Figure 10.10 illustrates a common method for growing certain multicellular organisms. A flask containing nutrient medium is inoculated with numerous small pieces

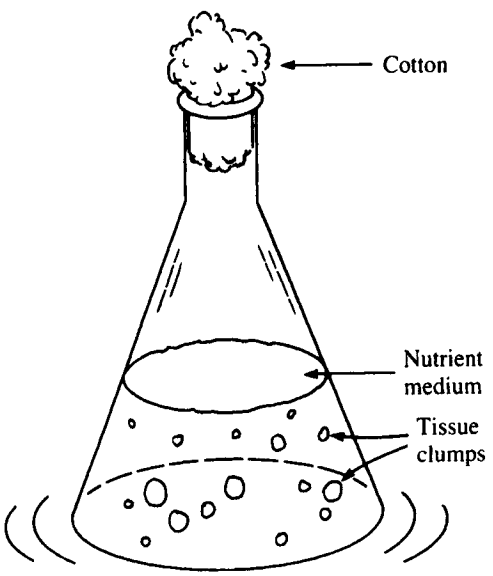


Figure 10.10 *Tissue culture.*

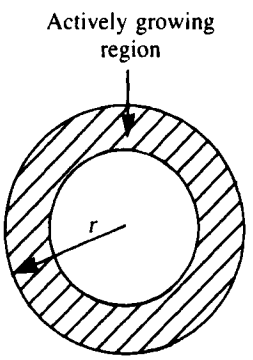


Figure 10.11 *Enlarged view of cross section of an idealized tissue clump.*

or clumps of tissue, which may each consist of many cells. Provided conditions are right (such as plentiful nutrient), each of the pieces will grow. Eventually they may be harvested and used in performing biological experiments.

Question

Suppose the initial biomass is known. What will be the total biomass at some later time t?

Step 1: A Simple Case

We start by making some drastically simplifying assumptions about the geometry of the tissue clumps:

Assumption 1a. All the clumps are spherical.
Assumption 1b. All pieces have the same radius r (see Figure 10.11).

At this point some information about how the tissue pieces grow is required. (This would generally come from empirical observations.) Often one finds that because the core of a tissue particle is not exposed to the nutrient medium, active growth can take place largely at its surface, so that the volume of a single spherical clump, $V(t)$, changes at a rate that is proportional to its surface area, $S(t)$.

Problem 1 (easy)
Relate this information to the radial growth of the particle.

Answer
Using the formulae for the volume and the surface area of a sphere,

$$V = \frac{4}{3}\pi r^3, \qquad S = 4\pi r^2,$$

and the relation

$$\frac{dV}{dt} = kS,$$

we get

$$\frac{4}{3}\pi \frac{dr^3}{dt} = 4\pi k r^2.$$

Differentiating r^3 and cancelling a factor of $4\pi r^2$ from both sides, we get

$$\frac{dr}{dt} = k.$$

We will take this last equation as our basic initial assumption about radial growth of the particles:

Assumption 1c. The radial growth rate of each tissue clump is given by

$$\frac{dr}{dt} = k. \tag{75}$$

Problem 2

Use the previous information to deduce the total volume of tissue after time t if initially its volume at $t = 0$ was V_0.

Answer

If there are N particles, their initial radial size is

$$r_0 = \left(\frac{3}{4\pi}\frac{V_0}{N}\right)^{1/3}.$$

The solution of equation (75) is simply

$$r(t) = kt + r_0,$$

implying that the volume at time t is

$$V(t) = N\frac{4\pi}{3}r^3(t) = N\frac{4\pi}{3}\left[kt + \left(\frac{3}{4\pi}\frac{V_0}{N}\right)^{1/3}\right]^3,$$
$$= \left[\left(\frac{N4\pi}{3}\right)^{1/3} kt + V_0^{1/3}\right]^3 \tag{76}$$

Conclusion

The total volume increases in a way that is cubic with time. This stems from the assumption that radial expansion is constant.

Step 2: A Slightly More Realistic Case

Rarely is it true that all tissue pieces will have an initially identical size. For example, in growing filamentous fungi for the purposes of experimental microbiology, the initial suspension of particles is prepared by grinding or blending the *mycelium* (the vegetative part of the fungus consisting of numerous interconnected branched filaments and resembling a furry disk). In that case many initial particle sizes are present in the suspension. As time passes, each small particle indeed grows to resemble a spherical clump (or *pellet*).

We now treat this more general situation of growth when a size distribution is present. Again, some simplifying assumptions are necessary:

Assumption 2a. All the clumps are spherical (same as assumption 1a).
Assumption 2b. Initially there is some distribution $\alpha(r)$ of pellet sizes.

Assumption 2c. Each pellet grows at a constant radial rate as given by equation (75).

Assumption 2d. There are no pieces smaller in size than some small radius ϵ.

> ***Problem 3***
> Before continuing, you are encouraged to attempt to define some meaningful variables and write an equation or equations to describe the situation.

Step 3: Writing the Equations

Hint 1.

Think about the "number density" of particles with radius r at time t. In other words, define the distribution $p(r, t)$ such that

$$\int_r^{r+\Delta r} p(r, t)\, dr = \text{number of pellets whose radii range between } r \text{ and } r + \Delta r.$$

What kind of equation would p satisfy?

Hint 2.

See Figure 10.12.

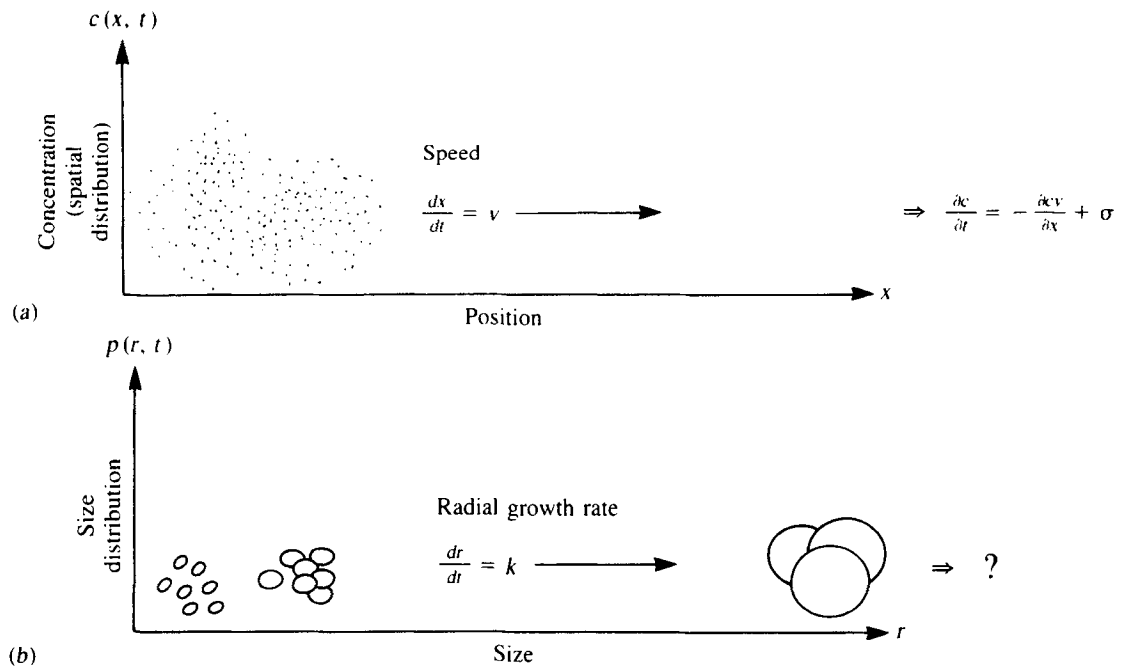


Figure 10.12 *(a) The spatial distribution of particles* c(x, t)*, changes as each particle moves with rate* v *along the* x *axis. (b) The size distribution of pellets,* p(r, t)*, changes as each pellet grows to a bigger size with rate* k.

Answer

Using a little imagination, we see that the rate of change of the size of a pellet is somewhat analogous to the speed or rate of change of location of a particle. Thus a direct translation from the spatial variables of particles to size variables for pellets would be as follows:

Spatial Variables		*Analogous Size Variables*	
Position,	x	Size,	r
Particle spatial distribution,	$c(x, t)$	Pellet size distribution	$p(r, t)$
Rate of change of position (speed),	$\frac{dx}{dt} = v$	Rate of change of size (growth rate),	$\frac{dr}{dt} = k$
Source/ sink term	σ	Source/ sink term	σ

With the above correspondence we deduce that an equation for $p(r, t)$ is:

$$\frac{\partial p}{\partial t} = -\frac{\partial pk}{\partial r} + \sigma. \tag{77}$$

σ would be present in the equation only if pellets are added ($\sigma > 0$) or eliminated ($\sigma < 0$) during growth. We will at present assume that $\sigma = 0$ and define the mathematical problem as follows:

main equation	$\frac{\partial p}{\partial t} = -\frac{\partial pk}{\partial r}$,		(77a)
initial condition	$p(r, 0) = \alpha(r)$	(from assumption 2b)	(77b)
boundary condition	$p(0, t) = 0$,	(from assumption 2d).	(77c)

Problem 4

Find a solution to the above set of equations (77a–c).

Hint 1

If you are not familiar with equations such as (77), you might try looking for special solutions such as $p(z)$ for $z = r - ct$. This would be equivalent to a pellet size distribution that shifts to higher sizes without altering its basic shape; recall that in the context of motion in space such solutions were called traveling-wave solutions.

Answer

It may be verified by carrying out the appropriate differentiation that the equation

$$p(r, t) = \alpha(r - kt) \tag{78}$$

solves problem 4 provided the initial distribution $\alpha(r)$ satisfies $\alpha(0) = 0$ [that is, the boundary condition (77c) and the initial condition (77b) do not conflict]. This makes good sense when you remember that pellets are all growing in size at the same rate k. Figure 10.13 illustrates several successive size distribution profiles at times t_1, t_2, and so forth, based on the initial distribution at $t = 0$.

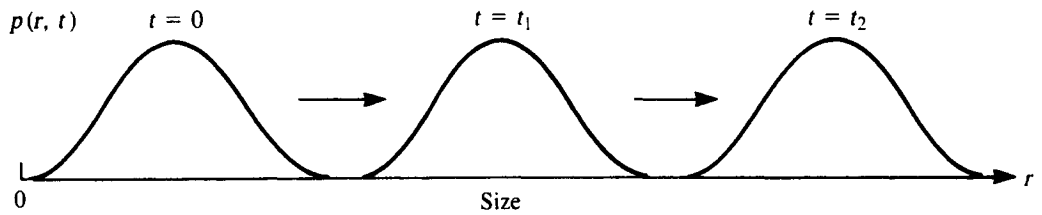


Figure 10.13 *A traveling-wave solution to equations (77a–c); Pellets in an initial size distribution (labeled* t = 0*) grow uniformly so that at later times* (t_1 = t *and* t = t_2) *the distribution shifts towards larger size,* r, *without undergoing a change in shape.*

The Final Step

Now close to our goal, it remains for us to perform several computations to obtain the mass accumulation. In preparation for this, consider the following definitions of quantities that are average properties of the tissue culture; in technical terminology these are *moments of the distribution* $p(r, t)$:

1. Total number of pellets:

$$N(t) = \int_0^\infty p(r, t)\, dr. \tag{79a}$$

2. Average radius of a pellet:

$$\hat{R}(t) = \frac{1}{N(t)} \int_0^\infty rp(r, t)\, dr. \tag{79b}$$

3. Average surface area of a pellet:

$$\hat{S}(t) = \frac{4\pi}{N(t)} \int_0^\infty r^2 p(r, t)\, dr. \tag{79c}$$

4. Average volume of a pellet:

$$\hat{V}(t) = \frac{4\pi}{3N(t)} \int_0^\infty r^3 p(r, t)\, dr. \tag{79d}$$

Problem 5

Use the fact that equation (78) is a solution to derive the dependence of the total volume $V(t)$ of the tissue on the moments $\hat{N}_0$, $\hat{R}_0$, $\hat{S}_0$, $\hat{V}_0$ of the initial distribution.

Answer

The computation to be carried out is integration of the following expression:

$$V(t) = \frac{4\pi}{3}\int_0^\infty r^3\alpha(r - kt)\,dr.$$

This can be done by making the substitution $u = r - kt$ [which implies that $du = dr$ and $r^3 = (u + kt)^3$] and expanding the cubic expression:

$$V(t) = \frac{4\pi}{3}\int_0^\infty (u + kt)^3\,\alpha(u)\,du,$$

$$= \frac{4\pi}{3}\int_0^\infty [u^3 + 3u^2(kt) + 3u(kt)^2 + (kt)^3]\alpha(u)\,du.$$

After multiplying throughout by $\alpha(u)$, we find that

$$V(t) = \frac{4\pi}{3}\int_0^\infty u^3\alpha(u)\,du + 4\pi(kt)\int_0^\infty u^2\alpha(u)\,du$$

$$+ 4\pi(kt)^2\int_0^\infty u\alpha(u)\,du + \frac{4\pi}{3}(kt)^3\int_0^\infty \alpha(u)\,du.$$

The integrals in this equation are moments of the initial size distribution as given in the definitions (79a–d). Thus the answer to our problem may be stated as follows:

$$V(t) = \left[\hat{V}_0 + (kt)\hat{S}_0 + 4\pi(kt)^2\hat{R}_0 + \frac{4\pi}{3}(kt)^3\right]N_0, \qquad (80)$$

for $\hat{V}_0$, $\hat{S}_0$, $\hat{R}_0$ (the average volume, surface area, and radius respectively of the initial pellets in the culture), and N_0 (the initial number of pellets). If the pellets are all of a single size, you should be able to demonstrate that equation (80) reduces to equation (76).

Discussion

The assorted computations which were stepping stones to the final answer contained in equation (80) should not cloud our vision. The single key step in the model is realizing that an equation such as (77a) can be applied to pellet growth as it previously was applied to cellular aging. This permits generalization of the simple situation of identical pellets to the more realistic case of many pieces in many sizes.

10.10 FOR FURTHER STUDY: OTHER EXAMPLES OF CONSERVATION LAWS IN BIOLOGICAL SYSTEMS

The ideas discussed in Sections 10.8 and 10.9 have appeared in a variety of models in the recent scientific literature. A small selection of references is given in the "For Further Study" section of the References. Some of these papers are rather sophisticated mathematically but many would be accessible to readers who have grasped the basic concepts of our discussion. These references have been subdivided into three topics, each suitable for further independent study and presentation to the class.

PROBLEMS*

1. Suggest a (set of) partial differential equations to describe the following processes:
   - **(a)** A predator-prey system in which both species move randomly in a one-dimensional setting.
   - **(b)** A predator-prey system in which the predator moves towards higher prey densities and the prey moves towards lower predator densities.
   - **(c)** A pair of reacting and diffusing chemicals such that species 1 activates the formation of both substances and species 2 inhibits the formation of both substances. Design your model so that it has a homogeneous steady state that is stable.
   - **(d)** A population of cells that secretes a chemical substance. Assume that the cells orient and move chemotactically in gradients of this chemical and also more randomly. Further assume that the chemical diffuses and is gradually broken down at some rate.

2. What kinds of processes might be described by the following equations?
   - **(a)** $\dfrac{\partial f(x, t)}{\partial t} = \nabla \cdot (f\mathbf{v}) - \mu f \qquad (f = \text{fish density}).$
   - **(b)** $\dfrac{\partial p_i}{\partial t} = \mathcal{D}_i \nabla^2 p_i + r p_i (1 - p_i - \beta_{ij} p_j) \qquad (i, j = 1, 2).$
   - **(c)** $\dfrac{\partial c}{\partial t} = \dfrac{\partial}{\partial x}\left[\mathcal{D}(c)\dfrac{\partial c}{\partial x} - cv\right] + rc(1 - c).$
   - **(d)** Equation (5) for the spruce budworm population.

3. Consider a population described by the equation

$$\frac{\partial P}{\partial t} = \mathcal{D}\frac{\partial^2 P}{\partial x^2} + \alpha P, \tag{1}$$

* Problems preceded by an asterisk (*) are especially challenging.

which at $t = 0$ is concentrated entirely at $x = 0$. Then the solution of this equation is

$$P(x, t) = \frac{P_0}{2(\pi \mathcal{D} t)^{1/2}} \exp\left(\alpha t - \frac{x^2}{4\mathcal{D}t}\right). \tag{2}$$

(a) Explain what is being assumed in equation (1).

(b) Verify that (2) is a solution by differentiating and showing that the PDE is satisfied.

(c) Now consider equipopulation contours: points (x, t) such that

$$P(x, t) = \tilde{P} = \text{constant}.$$

Show that on such a contour the ratio x/t is given by

$$\frac{x}{t} = \pm\left[4\alpha\mathcal{D} - \frac{2\mathcal{D}}{t}\ln t - \frac{4\mathcal{D}}{t}\ln\left(\sqrt{2\pi\mathcal{D}}\frac{\tilde{P}}{P_0}\right)\right]^{1/2}.$$

(d) Show that as $t \to \infty$ one can approximate the above by

$$\frac{x}{t} = \pm 2(\alpha\mathcal{D})^{1/2}.$$

4. Many of Skellam's arguments are based directly on random-walk calculations, not derived from the continuous PDEs such as equation (1). In his original article he defines the following:

a^2 = mean square dispersion per generation,

R = radial distance from point at which population was released,

λ = growth rate of the population,

n = number of elapsed generations,

p = proportion of the population lying outside a circle of radius R after n generations.

He proves that

$$p = \exp\frac{-R^2}{na^2}.$$

(a) If the population growth is described by

$$N_{n+1} = \lambda N_n,$$

and initially there is just a single individual, show that the population in the nth generation is $N_n = \lambda^n$.

(b) Now consider a region that contains all but a single individual. Show that the radius of this region at the nth generation is given by

$$R_n = (na^2 \ln N_n)^{1/2}.$$

[*Hint:* Why is it true that $1/N_n = \exp(-R^2/na^2)$ holds for this radius?]

(c) Use parts (a) and (b) to show that

$$R_n = na(\ln \lambda)^{1/2}.$$

(d) Show that, save for a proportionality factor, this result agrees with the rate of spread of a population given by equation (4).

5. This problem is based on the formula for R_n derived in problem 4. Skellam (1951) quotes the following sentence from Clement Reid (1899), *The Origin of the British Flora,* Dulow, London:

> . . . Few plants that merely scatter their seed could advance more than a yard in a year, for though the seed might be thrown further, it would be several seasons before an oak, for instance, would be sufficiently grown to form a fresh starting point.

He then illustrates, by a simple calculation, that the dispersal of oaks in Great Britain was assisted by small animals. The following estimates are used:

i. The generation time of an oak tree is roughly 60 years. This is the approximate age at which it produces acorns.

ii. The time available for dispersal (from the end of the ice age in 18,000 B.C. until records were first kept in Roman Britain) is roughly 18,000 years, or n generations.

iii. The approximate number of daughter oaks produced by a single parent during one generation is estimated as 9 million.

(a) Use these estimates to show that after n generations

$$\frac{R_n}{a} \simeq 1{,}200,$$

where R_n = the radius that encloses all but a single oak tree, and a^2 = the mean-square displacement defined in problem 4.

(b) From Reid's data, Skellam estimated that the actual radius of the oak forests in Roman Britain was 600 miles. What is the value of a (the root-mean-square distance of daughter oaks about their parents)?

(c) How did Skellam conclude that animals assisted in dispersing the acorns?

6. Segel et al. (1977) calculated the motility coefficients based on equation (6) (where $r = 0$) as follows. A capillary tube (cross-sectional area = A) is filled with fluid. At time $t = 0$ the open end is placed in a bacterial suspension of concentration C_0 and removed at time $t = T$. The number of bacteria in the tube is counted. Motility μ is then computed as follows:

$$\mu = \frac{\pi N^2}{4C_0^2 A^2 T}.$$

***(a)** Give justification for or derive their formula.

(b) Suppose that (1) the radius of the capillary is approximately 0.01 cm, (2) the bacterial suspension contains a density $C_0 = (1/7 \times 10^{-7})$ bacteria per milliliter, and (3) the following observations (from Segel et al., 1977) are made:

T (min)	*N (bacteria)*
2	1800
5	3700
10	4800
12.5	5500
15	6700

What do you conclude about μ?

7. Segel et al. (1977) consider the following more detailed description of bacterial motion. They point out that bacteria undergo a series of straight swimming (with average speed v) interrupted by random tumbles in which the orientation is changed. (See figure.) The *mean free path*, λ (average length of a straight swim) and the bacterial motility, μ satisfy the following relationship.

$$\mu = \frac{1}{3} v\lambda$$

[Lovely and Dahlquist (1975)].

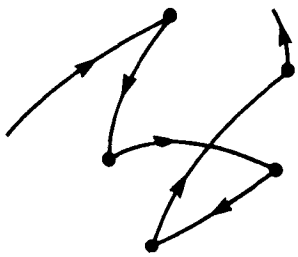


Figure for problem 7.

(a) Why is this a reasonable assumption based on dimensional considerations?

(b) Suppose that the speed v of a cell is proportional to the force F that drives it through a fluid of viscosity η. Show that

$$\mu = \frac{F\lambda}{3k}\frac{1}{\eta},$$

where k is a constant depicting frictional effects.

(c) If τ is the mean time between turns, show that μ can be written in terms of τ as follows:

$$\mu = \frac{\tau F^2}{2k^2}\frac{1}{\eta^2}.$$

8. In this problem we investigate several details of a model for bacterial motility and growth proposed by Lauffenburger et al. (1981) [see equations (7a,b)].

(a) A one-dimensional geometry is considered, with bacteria confined to a tube of length L. In the experiment the substrate level at $x = L$ is kept artificially constant at concentration s_0. At $x = 0$ the tube is sealed. What are the appropriate boundary conditions on $b(x, t)$ and $s(x, t)$?

(b) For the reproductive rate of the bacteria, G_b, the authors assume that

$$G_b = \frac{ks}{K + s} b - k_e b,$$

and for the rate of consumption of substrate, G_s is taken to be

$$G_s = \frac{1}{Y}\frac{ks}{K+s}b.$$

Explain these assumptions and give the meanings of Y, K, k, and k_e. Sketch G_b/b and G_s/b as functions of s.

(c) To simplify the model it is then assumed that a somewhat simpler relationship holds, namely that

$$G_b' = \begin{cases} (k-k_e)b & s > s_c \\ -k_e b & s \le s_c \end{cases},$$

$$G_s' = \begin{cases} \frac{1}{Y}kb & s > s_c \\ 0 & s \le s_c \end{cases}.$$

Explain these approximations and sketch G_b'/b and G_s'/b as functions of s.

(d) Use part (c) to explain equations (7a,b) and determine the functional form for the function $f(s)$ which appears in equations (7a,b).

(e) To reduce the number of parameters, the following dimensionless quantities are defined:

$$u = \frac{s}{s_0}, \quad v = \frac{b}{v_0}, \quad \xi = \frac{x}{L}, \quad \tau = \frac{\mathcal{D}t}{L^2},$$

$$\lambda = \frac{\mu}{\mathcal{D}}, \quad \theta = \frac{k_e L^2}{\mathcal{D}}, \quad K = \frac{kL^2}{\mathcal{D}}, \quad b_0 = \frac{Ys_0\mathcal{D}}{kL^2},$$

$$F(u) = \begin{cases} 1 & u \ge u_c, \\ 0 & u < u_c. \end{cases}$$

Write the equations and other conditions in terms of these quantities.

9. Consider the Keller-Segel equation for bacterial chemotaxis given by (8). Explain how the equation would be modified to incorporate the following further assumptions:

(a) The chemotactic sensitivity increases linearly with the chemical concentration.

(b) The random motion decreases as the cell density increases.

(c) The cell population increases logistically with carrying capacity proportional to the concentration of the chemical.

10. *Density-dependent dispersal*

(a) Interpret equation (13).

(b) Show that equation (14) is equivalent to equation (15).

(c) Show that if $m = 1$ and $F(p) = 0$, equations (18a,b) are analogous to equation (14) given that the total population density causes the dispersal of individuals.

(d) Find biological examples of density-dependent dispersal.

11. Polymorphonuclear (PMN) phagocytes (white blood cells) are generally the first defense mechanism employed in the body in response to bacterial inva-

sion. PMN phagocytes are rapidly mobilized cells that emigrate across walls of *venules* (small veins that connect capillaries and systemic veins) to ingest and eliminate microbes and other foreign bodies in the tissue. Lauffenburger and Kennedy (1983) suggest a model to describe this process. They consider the density of bacteria (b) and of phagocytes (c) and assume the following:

i. Bacteria, microbes or other foreign bodies disperse randomly (motility coefficient μ_b = area/time).

ii. Phagocytes undergo both random motion (with motility coefficient μ_c) and chemotaxis towards relatively high bacterial densities (χ = chemotaxis coefficient).

iii. Bacteria grow at rate $f(b)$ and are eliminated at the rate $d(b, c)$, where b = bacterial density and c = phagocyte density.

iv. Phagocytes emigrate from venules at the rate $\mathcal{A}(c, b)$ and die with rate constant g.

(a) Write a set of equations to describe the motions and interactions of microbes b and phagocytes c.

(b) Additional assumptions made were that

$$f(b) = \frac{k_g b}{1 + b/K_i}, \qquad d(b, c) = \frac{-k_d bc}{K_b + b},$$

$$\mathcal{A}(c, b) = h_0 \frac{A}{V} C_b \left(1 + \frac{h_1}{h_0} b\right),$$

where k_g = bacterial growth rate constant,

k_d = phagocytic killing rate constant,

h_0 = rate of emigration from venules when inflammation is absent,

h_1 = inflammation-enhanced emigration rate,

A/V = ratio of venule wall-surface area to tissue volume,

C_b = phagocyte density in the venules.

(1) Explain the meaning of these assumptions.

(2) Define K_i and K_b and give dimensions of all parameters above.

(c) By dimensional analysis, it is possible to reduce the equations to the following form:

$$\frac{\partial v}{\partial \tau} = \rho \frac{\partial^2 v}{\partial \xi^2} + \frac{\gamma v}{1 + v} - \frac{uv}{\kappa + v},$$

$$\frac{\partial u}{\partial \tau} = \frac{\partial^2 u}{\partial \xi^2} - \delta \frac{\partial}{\partial \xi}\left(u \frac{\partial v}{\partial \xi}\right) + \alpha(1 + \sigma v - u).$$

where v, u, ξ, and τ are dimensionless varibles.

(1) Find the definitions of the parameters appearing in these equations in terms of the original parameters.

***(2)** Explain the meanings of these parameters.

(d) Show that the equations in part (c) have two types of uniform steady-state solutions:
(1) $v = 0, \quad u = 1.$
(2) $v > 0, \quad u = 1 + \sigma v.$
Identify the biological meaning of these steady states.

12. In this problem we investigate the model for branching discussed in Section 10.4. (See figure on page 484.)

(a) A given apex is assumed to move a distance $v\Delta t$ during Δt time units. This gives rise to elongation of a branch and thus contributes to an increment of the branch density ρ by an amount $v\Delta t$. (Note that a filament is thus deposited in the trail of the moving apex.) Elaborate on this reasoning to explain the term nv in equation (19a).

(b) Explain the term $-\gamma\rho$ in equation (19a).

(c) Now consider equation (19b). Explain the term $-\partial(nv)/\partial x$ by defining flux J_n of the moving particles.

(d) The term σ is actually a difference of two terms:

$$\sigma = \sigma_{\text{br}} - \sigma_{\text{mort}},$$

where σ_{br} is a branching rate and σ_{mort} is a loss rate. Explain why such terms appear in this equation.

(e) Branching can occur in several possible ways, including the following:
(1) Dichotomous branching: One apex produces a pair of daughter apices.
(2) Lateral branching: A filament produces a new branch apex somewhere along its length.
See Figure (*c*). Suggest appropriate forms for σ_{br} in each of these two cases.

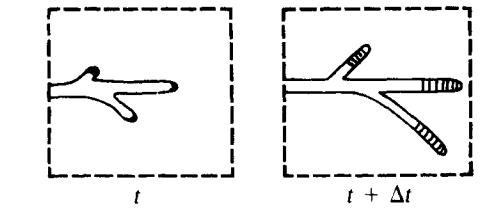
(f) Apices disappear by anastomosis when the end of a filament forms a connection with a neighboring filament. This can happen in one of two possible ways:
(1) if two ends (apices) come into contact,
(2) if one apex forms a contact directly with a filament.
Suggest appropriate forms for σ_{mort} in each of these cases, and others shown in Figure (*c*).

13. Explain the Balding-McElwain equations for capillary growth. (See problem 12.)

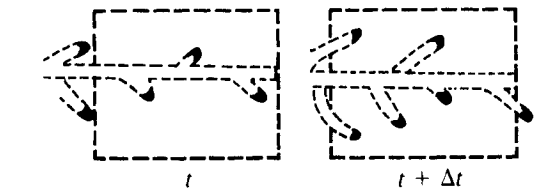
14. Odell (1980) describes the following model for chemical wave fronts in a separation column (see figure on page 485). He defines:

$u_1(x, t)$ = concentration of free protein at distance x along the column,
$u_2(x, t)$ = concentration of protein bound (reversibly) to stationary beads at location x,
B = total number of binding sites on beads per unit distance (B is constant),
P_0 = protein concentration in the stock solution (at $x = 0$.)

Figure for problem 12. *Equation (19a,b) can be derived by considering changes in length of branches and in the numbers of apices at a given location, as shown in (a) and (b). The branching term σ would contain terms that account for the biological events shown in (c). [From Edelstein, (1982). The propagation of fungal colonies. A model for tissue growth.* J. Theor. Biol., 98, *fig. 1 and Table 1. Reprinted by permission of Academic Press.]*



(a)



(b)

Branching	Biological Type
	Dichotomous branching
	Lateral branching
	Tip–branch anastomosis
	Tip–tip anastomosis
	Tip death
	Tip death due to overcrowding

(c)

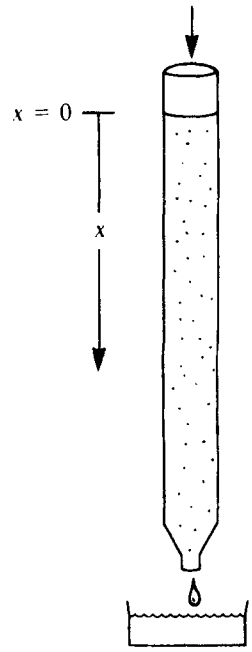


Figure for problem 14.

He derives the following equations for $u_i(x, t)$:

$$\frac{\partial u_1}{\partial t} = \frac{\partial}{\partial x}\left(D\frac{\partial u_1}{\partial x} - vu_1\right) - [k_1(B - u_2)u_1 - k_2u_2],$$

$$\frac{\partial u_2}{\partial t} = k_1(B - u_2)u_1 - k_2u_2.$$

(a) Interpret the terms in these equations and define k_1, k_2, D, and v. What boundary conditions apply at $x = 0$? (The problem is idealized as a half-infinite, one-dimensional domain.)

(b) Determine whether the system has nonuniform steady-state solutions.

(c) Determine whether the system has homogeneous steady-state solutions.

(d) Determine whether the system has bounded traveling-wave solutions. [*Note:* Readers consulting the original reference should be forewarned of a mistake in Odell's equation (49), which unfortunately significantly changes his conclusions.]

15. Discuss the effect of boundary conditions on the existence and nature of steady states that one might obtain for the density-dependent dispersal model given by equations (28a,b). Consider a finite domain $x \in [0, L]$ and let

(a) $J_1(0) = J_1(L) = \hat{J}_1, \quad J_2(0) = J_2(L) = \hat{J}_2,$
where $\hat{J}_1$ and $\hat{J}_2$ are constants representing fluxes of species 1 and 2.

(b) $J_1(0) = \hat{J}_{10}, \quad J_1(L) = \hat{J}_{1L} \quad \hat{J}_{10} \neq \hat{J}_{1L}$
$J_2(0) = \hat{J}_{20}, \quad J_2(L) = \hat{J}_{2L} \quad \hat{J}_{20} \neq \hat{J}_L.$

(c) $u(0) = 0, \quad u(L) = \hat{u}, \qquad v(0) = 0, \quad v(L) = \hat{v},$
where $\hat{u}$ and $\hat{v}$ are constants representing species densities.

(d) $J_1(0) = J_1(L) = \hat{J}_1, \qquad v(0) = v(L) = \hat{v}.$

(e) $u(0) = u(L) = \hat{u}, \qquad v(0) = v(L) = \hat{v}.$

(*Note:* Your conclusion for some of these might be that no steady state exists.)

16. *Fisher's equation*

(a) Show that traveling-wave solutions to Fisher's equation (36) must satisfy equations (40a,b).

(b) Verify the locations of steady states given in (42a,b) and show that the Jacobian matrices at these steady states are then given by (43a,b).

(c) Show that (P_1, S_1) is a stable node and (P_2, S_2) is a saddle point provided that

$$\left(-\frac{v}{\mathcal{D}}\right)^2 - 4\frac{\alpha}{\mathcal{D}} > 0.$$

(d) What happens if the condition in part (c) is not met? (Sketch the resulting phase-plane diagram and discuss why one cannot obtain biologically realistic traveling waves.)

(e) Conclude that the minimum wave speed is

$$v_{\min} = 2(\alpha\mathcal{D})^{1/2}.$$

17. **(a)** Show that traveling-wave solutions to equations (47a,b) for yeast cells on glucose medium would have to satisfy (48).

(b) Verify that these equations lead to the system of ODEs (51a,b).

(c) Find steady states of equations (51a,b), sketch nullclines, and compute the stability properties of the steady states.

(d) Determine whether there is any constraint on the speed v of the wave. (*Hint:* You must determine whether the heteroclinic trajectory always exists and remains in the positive GN quadrant.)

18. Equations for space-dependent voltage in the membrane of the neural axon were derived in Section (9.3). Determine what equations would be satisfied by traveling-wave solutions to these equations. (*Note:* The ionic current I_i is given in the Hodgkin-Huxley model in Section 8.1). Such solutions correspond to propagating action potential.

***19.** Rubinow and Blum (1980) studied propagating (traveling-wave) solutions $P(z)$ and $Q(z)$ to equations (54a,b), for $z = x - ct$.

(a) Find the equations satisfied by $P(z)$ and $Q(z)$.

(b) Sketch the phase-plane diagrams for the case $n = 1$.

(c) Sketch the phase-plane diagram for the case $n = 2$ (cooperativity).

(d) Why did they conclude that traveling waves exist only if binding is cooperative?

(e) Sketch the shape of waves they predicted based on part (c).

(f) Rubinow and Blum claim that the waves described in part (e) could represent the following observation. Substances *normally present* (and transported) by the axon can also be added artifically. (These could be radioactively labeled and injected into the axon.) One then observes a propagating front of radioactivity transported down the length of the

axon. Blum and Reed later found the mistake in this claim. Why are these traveling-wave solutions not consistent with the biological phenomenon?

20. **(a)** Write a system of equations for the Blum-Reed model for fast axonal transport. Assume that only the complex Q can move along the track and that velocity of motion v is constant.

(b) Show that the total number of units of E in various forms, E_0, remains fixed.

(c) Similarly show that the total number of tracks in various complexes, S_0, remains fixed.

(*Note:* The Blum-Reed model, like the Rubinow-Blum model admits pseudowaves—propagating solutions—without additional assumptions about cooperativity.)

21. *Takahashi's cell-cycle model.* Consider equations (55a,b). Assume that transition probabilities $\lambda_j = \lambda$ are the same for all phases, that cell death is negligible, and that the cell divides into two daughter cells.

(a) Show that the model can be written in the following way:

$$\frac{dN_j}{dt} = \lambda(N_{j-1} - N_j), \qquad \frac{dN_1}{dt} = \lambda(2N_k - N_1).$$

(b) Verify that the following Γ distribution is a solution:

$$N_j(t) = \left[\frac{\lambda^j}{(j-1)!}\right]^{j-1} e^{\lambda t}.$$

Note that this is a consequence of the way that cell cycle stages were discretized in the model, not in the biology.

22. **(a)** Interpret equation (60) derived on the basis of Takahashi's model. What are the constants v_0 and d_0 in relation to the process of maturation?

(b) Verify that

$$n(\alpha, t) = \frac{1}{\sqrt{4\pi d_0 t}} \exp -\left(\frac{\alpha - v_0 t}{4d_0 t}\right)^2,$$

is a solution of equation (60).

(c) Give a boundary condition for equation (60) which would be analogous to equation (56b).

23. Equation (66) may be applied to age distributions in populations of cells, plants, humans, or other organisms. The assumptions about birth, death, and maturation rates would depend on the particular situation. How would you formulate boundary conditions (and/or change the maturation equation) for each of the following examples?

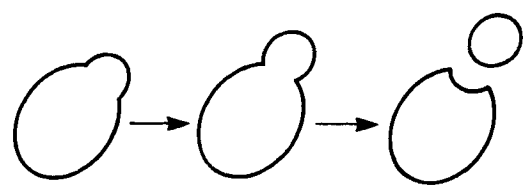


Figure for problem 23 (b).

(a) Bacterial cells divide into a pair of identical daughter cells when they mature.

(b) In yeast a mature cell undergoes "budding," eventually producing a small daughter cell and a larger parent cell. The parent cell is permanently marked by a bud scar for each daughter cell that it has produced. After a certain number of buds have been made, the parent cell dies.

24. The variable α in equation (66) may be identified with any one of a number of measurable cellular parameters. How would equation (66) be written if

(a) α = the chronologic age of a cell.

(b) α = the volume of a cell (assuming that the radius grows at a constant rate per unit time, $dr/dt = K$),

(c) α is the level of activity of an enzyme required in mitosis. (Assume rate of activity increases at a rate proportional to the current level of activity.)

(*Hint:* Consider $v(\alpha, t)$ in each case.)

25. *Model for chemotherapy of leukemia.* Consider the model due to Bischoff et al. (1971) given by equations (70) to (72).

(a) What has been assumed about the rate of maturation v?

(b) Assume that cycle specificity of the drug is low, in other words, that μ is nearly independent of maturity. Take

$$\mu(t) = \frac{K_1(t)c(t)}{K_2(t) + c(t)}.$$

Further assume a solution of equation (70) of the form

$$n(\alpha, t) = N_0 e^{\beta t} h(\alpha) e^{-A(t)}.$$

Show that

$$A(t) = \int_0^t \mu(t')\, dt'$$

and that boundary condition (72) implies that $n(\alpha, t)$ is given by equation (73).

(c) Show that eventually the number of cells of maturity $\alpha = 0$ is a constant fraction of the total population:

$$n(0, t) = 2 \ln 2\, N(t).$$

(*Hint:* Note that

$$N(t) = \int_0^1 n(\alpha, t)\, d\alpha.)$$

(d) Show that if N is the total population, then

$$\frac{dN}{dt} = aN - \mu N$$

where $a = v \ln 2$ and μ is defined as in part (b).

(e) Bischoff et al. (1971) estimate that the mean generation time of L1210 leukemia cells is $\tau = 14.4$ h. (What does this imply about v, the maturation speed?) The authors further take the parameters for mortality due to the chemotherapeutic drug arabinose-cytosine to be

$$K_1 = 0.25\ \text{h}^{-1}, \qquad K_2 = 0.3\ \mu\text{g ml}^{-1}.$$

How long would it take for the cells to fall off to 10^{-3} of their initial population if a constant drug concentration of $c(t) = 15$ mg kg^{-1} body weight is maintained in the patient?

26. *Other modeling problems related to tissue cultures*

(a) Suppose a tissue culture is grown in a chemostat, with constant outflow at some rate F. Give a set of equations to describe the problem.

(b) If particles of size r_{max} always break apart into n identical particles of size r_s, how would the problem be formulated?

***(c)** Suppose now that pellets can diminish in size due to shaving off of minute pieces (such as single cells) as a result of friction or turbulence. Assume this takes place at a rate proportional to the pellet radius. How would you model this effect in the following two situations?

(1) All minute pieces can then grow into bigger pieces (participate in the overall growth).

(2) All fragments die.

27. *Plant-herbivore systems and the quality of the vegetation.* In problem 17 of Chapter 3 and problem 20 of Chapter 5 we discussed models of plant-herbivore interactions that considered the *quality* of the vegetation. We now further develop a mathematical framework for dealing with the problem. We shall assume that the vegetation is spatially uniform but that there is a variety in the quality of the plants. By this we mean that some chemical or physical plant trait q governs the success of herbivores feeding on the vegetation. For example, q might reflect the succulence, nutritional content, or digestibility of the vegetation, or it may signify the degree of *induced chemical substances,* which some plants produce in response to herbivory. We shall be primarily interested in the mutual responses of the vegetation and the herbivores to one another.

(a) Define

$q(t)$ = quality of the plant at time t,

$h(t)$ = average number of herbivores per plant at time t.

Reason that equations describing herbivores interacting with a (single) plant might take the form

$$\frac{dq}{dt} = f(q, h), \qquad \frac{dh}{dt} = g(q, h) = hr(q, h).$$

What assumptions underly these equations?

(b) We wish to define a variable to describe the *distribution of plant quality* in the vegetation. Consider

$p(q,t)$ = biomass of the vegetation whose quality is q at time t.

Give a more accurate definition by interpreting the following integral:

$$\int_q^{q+\Delta q} p(q, t)\, dq = ?$$

(c) Show that the total amount of vegetation and total quality of the plants at time t is given by

$$P(t) = \int_0^\infty p(q, t)\, dq,$$

$$Q(t) = \int_0^\infty qp(q, t)\, dq.$$

What would be the *average quality* $\bar{Q}(t)$ of the vegetation at time t?

***(d)** Suppose that there is no removal (death) or addition of plant material. Write down an equation of conservation for $p(q, t)$ that describes how the distribution of quality changes as herbivory occurs (*Hint:* Use an analogy similar to that of Sections 10.8 and 10.9.)

(e) Suppose that the herbivores are only affected by the average plant quality, $\bar{Q}(t)$. What would this mean biologically? What would it imply about the equation for dh/dt?

(f) Further suppose that the function $f(q, h)$ is linear in q. (*Note:* This is probably an unrealistic assumption, but it will be used to illustrate a point.) Assume that

$$f(q, h) = f_1(h) + qf_2(h).$$

Interpret the meanings of f_1 and f_2.

***(g)** Show that the model thus far can be used to conclude that an equation for the average quality of the vegetation is

$$\frac{d\bar{Q}}{dt} = f_1(h) + f_2(h)\bar{Q}.$$

[Use the assumptions in parts (d) and (f), the equation you derived in (d), and integration by parts.]

(h) Explore what this model would imply about average quality and average number of herbivores per plant if f and r are given by

$$f(q, h) = K_1 - K_2 qh(h - h_0),$$

$$r(q, h) = K_3(1 - K_4 h/\bar{Q}).$$

[*Hint:* See problem 20 of Chapter 5 where $I(t) \to h(t)$.] Interpret your results.

(*Note:* This problem is based on Edelstein-Keshet, 1986. It can be extended into a longer project for more advanced students.)

PROJECTS

1. *Extended project.* Analyze the model given in problem 8, referring to methods outlined in the paper by Lauffenburger et al. (1981).

2. This project is suitable only for mathematically advanced students. Discuss the qualitative behavior of the traveling-wave solutions described in problem 18. For references, see Jones and Sleeman (1983), sec. 6.2, and other references in Rinzel (1981).

3. Write a short simulation program incorporating the discrete Takahashi model for the cell cycle, given the following assumptions:

(a) For $\lambda_i = \lambda$ = constant,

$$\mu = \frac{k_1 c}{k_2 + c}.$$

(b) For $\lambda_i = \lambda\alpha_i(1 - \alpha_i)$,

$$\mu = \frac{K_1(\alpha)c}{K_2 + c}, \qquad K_1(\alpha) = 1 - e^{-\alpha}.$$

(c) For any other set of assumptions that are of biological relevance.

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