CHAPTER 6

Biological Modeling with Quiescent Phases

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Abstract: Quiescence or dormancy plays an important role in biological systems, from spore formation in bacteria to predator-prey cycles. In a mathematical framework, quiescence is modeled by diffusive coupling of the active dynamics to quiescent phases. Although coupling a given vector field to the zero field may appear simple at first glance, quiescent phases have biologically relevant effects which can be cast into rigorous mathematical formulations: permanence of stationary points, stabilization against oscillations and Hopf bifurcations, decrease in amplitude of periodic orbits. These features are common to ordinary and partial differential equations and delay equations and persist to some extent even for density-dependent transition rates. Applications range from tumor growth to engineered bacteria.

6.1 Introduction

On all levels of biological organization we find quiescent phases although these may occur with different names. Genes may be suppressed, tumor cells quiescent, nerve

cells at rest, animals hibernating or just inactive. Although these phenomena are quite diverse, there are some common general features. There is an active phase and a quiescent phase and there are transition laws which govern the exit to the quiescent phase and reentrance into the active phase.

In this chapter we investigate mathematical models for biological systems which have a sedentary, quiescent, removed or immobile phase. A quiescent phase typically describes immobile periods of mobile individuals, or refuges from predation, shelters and nests, as well as quiescent phases in a cell cycle, or bound state of diffusible proteins. For the purpose of the general analysis, we call all these phenomena *quiescent phases*. Later, in the application section, we come back to the more specific notions.

Modeling with quiescent phases can be summarized in a common mathematical framework. We will first introduce the general mathematical set up and then present a selection of applications, including ecological and epidemiological models, and cell and protein dynamics.

It is a general trend in all the results presented here, that a quiescent phase stabilizes the system; stable equilibria become more stable in the presence of a quiescent state, Hopf bifurcations become less likely, attractors become more stable, and traveling waves slow down.

In the following section, we introduce the class of models with quiescent phase and we summarize some basic mathematical properties.

6.2 Diffusive Coupling and Quiescence

Suppose n types of particles can exist in two different phases $v, w \in \mathbb{R}^n$ that are governed by two systems of ordinary differential equations

$$\begin{aligned} \dot{v} &= f(v) \\ \dot{w} &= g(w). \end{aligned} \tag{6.1}$$

Particles switch between phases according to Poisson processes with rates depending on the type of particle. Then we have a system in $\mathbb{R}^{2n}$,

$$\begin{aligned} \dot{v} &= f(v) - Pv + Qw \\ \dot{w} &= g(w) + Pv - Qw \end{aligned} \tag{6.2}$$

with diagonal matrices P, Q with positive entries. We say that the vector fields f, g are diffusively coupled. This type of coupling is very different from seasonal switching which leads to non-autonomous systems.

The vector of total particle densities $u = v + w$ and the vector of probability flows $z = Pv - Qw$ satisfy the equations

$$\begin{aligned} \dot{u} &= f(\tilde{Q}u + Sz) + g(\tilde{P}u - Sz) \\ S\dot{z} &= \tilde{P}f(\tilde{Q}u + Sz) - \tilde{Q}g(\tilde{P}u - Sz) - z \end{aligned} \tag{6.3}$$

with positive diagonal matrices

$$\tilde{P} = (P+Q)^{-1}P, \quad \tilde{Q} = (P+Q)^{-1}Q, \quad S = (P+Q)^{-1}.$$

If the particles switch frequently (rates going to infinity with fixed proportions) then we get the limiting system, again in $\mathbb{R}^n$,

$$\dot{u} = f(\tilde{Q}u) + g(\tilde{P}u). \tag{6.4}$$

The situation of quiescent phases occurs when g is the zero vector field. Then we compare the system

$$\dot{u} = f(u) \tag{6.5}$$

in $\mathbb{R}^n$ to the system

$$\begin{aligned} \dot{v} &= f(v) - Pv + Qw \\ \dot{w} &= Pv - Qw \end{aligned} \tag{6.6}$$

in $\mathbb{R}^{2n}$. One may think that adding a zero field does not change much. But from (6.6) we get the three following equations

$$\begin{aligned} \ddot{v} &= f'(v)\dot{v} - P\dot{v} + Q\dot{w} \\ Q\dot{w} &= QPv - Q^2w \\ Q\dot{v} &= Qf(v) - QPv + Q^2w. \end{aligned}$$

We add these equations, multiply by S, and get an equivalent second order equation in $\mathbb{R}^n$ for the active component v,

$$S\ddot{v} + (I - Sf'(v))\dot{v} = \tilde{Q}f(v). \tag{6.7}$$

This equation has the general form of a damped oscillator. Hence introducing a quiescent phase may lead to new phenomena. The following examples suggest that this is indeed the case.

From (6.4) we get the limiting equation $\dot{u} = f(\tilde{Q}u)$ for $u = v + w$ (the total population) and from (6.7) the limiting equation $\dot{v} = \tilde{Q}f(v)$ for v (the active population). These are equivalent by $v = \tilde{Q}u$.

Example 6.1 The equation for exponential growth, $\dot{u} = au$, with $a > 0$, leads to the system, with $p, q > 0$,

$$\begin{aligned} \dot{u} &= au - pu + qx \\ \dot{x} &= pu - qx. \end{aligned} \tag{6.8}$$

For the system (6.8) the exponent of growth is

$$\rho = \rho(a,p,q) = \frac{1}{2}\left[a - p - q + \sqrt{(a-p+q)^2 + 4pq}\right]. \tag{6.9}$$

It is easy to see that $0 < \rho < a$ and that ρ is a decreasing function of p and an increasing function of q. In the limiting cases we have

$$\rho(a,p,0) = \max(a-p,0), \quad \rho(a,0,q) = a.$$

The first formula shows that there may be population growth even if there is no return from the quiescent phase.

If we choose a negative, the result is reverted, we get $a < \rho < 0$.

Example 6.2 (Hadeler and Hillen, 2006) The logistic equation $\dot{u} = au(1 - u/K)$ is coupled to a quiescent phase and the limiting equation for the total population becomes $\dot{u} = a\tilde{q}u(1 - \tilde{q}u/K)$, where $\tilde{q} = q/(q + p)$.

Hence the growth rate is reduced by the factor $\tilde{q}$, and the carrying capacity K is enlarged to $K/\tilde{q}$. A quiescent phase slows down population growth and increases the capacity.

The equation with an Allee effect $\dot{u} = u(1 - u)(u - \alpha)$, with $0 < \alpha < 1$, leads to the limiting equation $\dot{u} = \tilde{q}u(1 - \tilde{q}u)(\tilde{q}u - \alpha)$. Here the threshold α is increased to $\alpha/\tilde{q}$.

Example 6.3 The harmonic oscillator (which can be seen as the linearization of a Volterra population system)

$$\begin{aligned} \dot{u} &= v \\ \dot{v} &= -u \end{aligned} \tag{6.10}$$

becomes

$$\begin{aligned} \dot{u} &= v - pu + qx \\ \dot{v} &= -u - pv + qy \\ \dot{x} &= pu - qx \\ \dot{y} &= pv - qy. \end{aligned} \tag{6.11}$$

The characteristic polynomial of the matrix is

$$\lambda^2(p + q + \lambda)^2 + (q + \lambda)^2$$

or

$$\lambda^4 + 2(p + q)\lambda^3 + (1 + (p + q)^2)\lambda^2 + 2q\lambda + q^2$$

and hence the Routh-Hurwitz criterion tells that all roots have strictly negative real parts. The example shows that quiescence stabilizes the system.

In the following we show that the features of the examples are not accidental. In systems with quiescence (and equal rates) real eigenvalues move towards zero while purely imaginary eigenvalues move into the left half-plane (as has been observed first in Neubert *et al.* (2002)).

We mention in passing that quiescent phases need not be exponentially distributed. In fact, allowing other distributions and studying the stability properties of the resulting systems is a challenging problem (Hadeler and Lutscher, 2008). A case of particular interest is when exit to the quiescent phase is Poisson distributed with rate p and the length of the quiescent phase is exactly $\tau > 0$. Then the limiting equation is

$$\dot{v}(t) = f(v(t)) + p(v(t - \tau) - v(t)). \tag{6.12}$$

Again, the model is controlled by two parameters, p, τ instead of p, q above.

6.3 Stationary States and Stability

From a biological point of view we want to know how the dynamics of the system (6.5) is changed by introducing quiescent phases. This problem is also interesting from a mathematical point of view. Some aspects concerning global existence of solutions and of compact global attractors are presented in Hadeler and Hillen (2006). General results on global attractors are surprisingly difficult. On the other hand we have some detailed results on stationary points and their stability and some preliminary results for periodic orbits.

At first glance introducing quiescent phases seems similar to introducing delays. For delay equations we know that combining a negative feedback with sufficiently large delays leads to oscillations and then periodic orbits. Quite on the contrary, quiescent phases stabilize against oscillations.

Suppose $\bar{u}$ is a stationary point of the system (6.5), i.e., $f(\bar{u}) = 0$. Then

$$(\bar{v}, \bar{w}) = (\bar{u},\, Q^{-1}P\bar{u}) \tag{6.13}$$

is a stationary point of (6.6). Let $A = f'(\bar{u})$ be the Jacobian matrix of (6.5) at the stationary point. Then the Jacobian matrix of (6.6) is given by

$$B = \begin{pmatrix} A-P & Q \\ P & -Q \end{pmatrix}. \tag{6.14}$$

The eigenvalue problem of the matrix B is equivalent to that of the matrix pencil

$$\lambda^2 I + \lambda(P + Q - A) - AQ. \tag{6.15}$$

Equal rates: In the case of equal rates we have $P = pI$, $Q = qI$, the matrices P, Q, A commute and we can apply the spectral mapping theorem to the pencil (6.15). To each eigenvalue μ of the matrix A there are two eigenvalues λ_1 and λ_2, ordered by $\Re\lambda_2 \le \Re\lambda_1$, which can be obtained from the equation

$$\lambda^2 + \lambda(p + q - \mu) - \mu q = 0. \tag{6.16}$$

This is a very simple quadratic equation. In principle the two solutions can be represented by an explicit formula. The problem is that μ is a complex number. The following can be shown. Always $\Re\lambda_2 < 0$. Hence λ_2 does not affect stability. Stability is governed by the eigenvalue λ_1.

Now there are three quite distinct cases: If $\mu = 0$ then $\lambda_1 = 0$. If μ is real then λ_1 is located between μ and 0. Hence, with respect to real eigenvalues, quiescence does not change stability. If μ is complex (with non-vanishing imaginary part) then, generally speaking, for eigenvalues with positive real parts the real parts are decreased by introducing quiescence and may eventually become negative. This effect is most prominent for eigenvalues with large imaginary parts, i.e., high frequency oscillations are damped. Detailed information is given by the following theorem.

Theorem 6.1 (Hadeler, 2008a) *Let $\mu = \alpha + i\beta$ be an eigenvalue of the linearization of (6.5) at a steady state $\bar{u}$. Then the linearization of (6.6) at $(\bar{u}, p\bar{u}/q)$ has two*

corresponding eigenvalues λ_1, λ_2 with $\Re\lambda_2 \le \Re\lambda_1$. The eigenvalues μ and λ_1, λ_2 are related as follows:

(a) *Let $\mu = \alpha \in \mathbb{R}$. Then λ_1, λ_2 are real.*

(a.i) *If $\alpha < 0$ then $\lambda_2 < \alpha < \lambda_1 < 0$.*

(a.ii) *If $\alpha = 0$ then $\lambda_2 = -(p+q) < 0 = \lambda_1$.*

(a.iii) *If $\alpha > 0$ then $\lambda_2 < 0 < \lambda_1 < \alpha$.*

(b) *Let $\mu = \alpha \pm i\beta$, $\beta > 0$. Then $\Re\lambda_2 < 0$.*

(b.i) *If $\alpha \le 0$ then $\Re\lambda_1 < 0$.*

(b.ii) *If $\alpha > 0$ then $\Re\lambda_1 < \alpha$.*

(b.iii) *If $\alpha \le 0$ and*

$$\beta^2 + (p+q+\alpha)^2 + 4\alpha p > 0 \text{ and } \beta^2(q+\alpha) + \alpha(p+q+\alpha)^2 > 0,$$

then $\Re\lambda_1 < \alpha$.

(b.iv) *If $\alpha > 0$ and*

$$\beta^2 > 4\alpha q - (p+q-\alpha)^2 \text{ and } \beta(p-\alpha) > \alpha(p+q-\alpha)^2,$$

then $\Re\lambda_1 < 0$.

Unequal rates: If the matrices P and Q are not multiples of the identity and the various types of particles go quiescent and return with pairwise distinct rates, then the situation is quite different and the stability problem has about the same complexity as the Turing stability problem. Indeed, here as in the Turing problem we have a given stable matrix and a matrix pencil depending on positive diagonal matrices. So far only the case $n = 2$ of two types has been dealt with (Hadeler, 2008a). Recall that a 2×2 matrix $A = (a_{ij})$ is stable if $\operatorname{tr} A = a_{11} + a_{22} < 0$ and $\det A = a_{11}a_{22} - a_{12}a_{21} > 0$, and strongly stable (in the sense of Turing) if, in addition, $a_{11} \le 0$, $a_{21} \le 0$. (A is excitable if A is stable, but not strongly stable). Suppose that A is stable. Then the matrix B is stable for all choices of P and Q if and only if A is strongly stable. Thus, if A is excitable in the sense of Turing, the system may become destabilized by introducing quiescent phases with suitably chosen distinct rates. The problem for $n > 2$ is open.

However, there are classes of problems for which additional mathematical tools are available (Hadeler and Thieme, 2008). For example, if the system (6.5) is cooperative then the system (6.6) is cooperative as well; or if the system (6.5) is competitive then the system for v and $-w$ is competitive as well.

6.4 Periodic Orbits

Numerical simulation of standard biological systems like the MacArthur-Rosenzweig model (Holling type II predator response) as well as analytic results on highly symmetric systems show that limit cycles of the system (6.5) undergo some systematic

changes if quiescent phases are introduced. From the local stability analysis at a stationary point it is evident that introducing a quiescent phase works against Hopf bifurcations. Suppose we have a system depending on some parameter α which undergoes a Hopf bifurcation. A stationary state is stable for $\alpha < 0$ and unstable for $\alpha > 0$ in such a way that a pair of eigenvalues crosses the imaginary axis at $\alpha = 0$. The stability Theorem 3.1 suggests that by introducing a quiescent phase the Hopf bifurcation is shifted to some parameter value $\alpha > 0$. This is what indeed happens in concrete examples.

Example 6.4 (Bilinsky and Hadeler, 2008) The MacArthur-Rosenzweig model with quiescence reads

$$\begin{aligned} \dot{u} &= au(1-\frac{u}{K}) - b\frac{uv}{1+mu} - p_1u + q_1w \\ \dot{v} &= c\left(\frac{u}{1+mu} - \frac{B}{1+mB}\right)v - p_2v + q_2z \\ \dot{w} &= p_1u - q_1w \\ \dot{z} &= p_2v - q_2z. \end{aligned} \tag{6.17}$$

It is known that the two-dimensional system without quiescence has either a stable coexistence point or a unique (stable) limit cycle. In the latter case the system with quiescence either has no limit cycle at all or again a limit cycle, this time in dimension four, whereby the "size" of the projection in the active phase gets smaller. If the coexistence state in the problem without quiescence is stable then it is strongly stable. For every choice of P and Q there is a gain in stability. Let δ and τ be the determinant and the trace at the coexistence state of the system without quiescence. In the τ, δ-plane the stability domain is given by $\delta > 0$, $\tau < 0$. For given P, Q the stability domain extends into the range $\tau > 0$. The boundary of the stability domain can be found explicitly as a curve $\tau = \phi(\delta)$ with $\phi(0) = 0$ and $\phi(\delta) > 0$ for $\delta > 0$ (Bilinsky and Hadeler, 2008).

In numerical experiments, the four-dimensional limit cycle of (6.17) can be visualized by presenting the total population sizes $u+w$ and $v+z$ for prey and predator. In this projection the effect of a quiescent phase is not easily recognized because the position of the (projection of) the stationary point is shifted. It is easier to project to the u, v-plane and also to the w, z-plane. Then one sees that the "size" of the projected limit cycle in the u, v-plane is smaller than the limit cycle in the system without quiescence and gets ever smaller if the rates are increased. Eventually the limit cycle may contract to the stationary point.

Here "size" is used as a phenomenological description. For the typical egg-shaped limit cycles of predator prey models area and circumference and diameter all shrink (see Figure 6.1) . It is interesting to observe that at the same time the projection onto the w, z-plane gets larger. For symmetric systems the shrinking of the periodic orbit can be rigorously proven, see Hadeler and Hillen (2006).

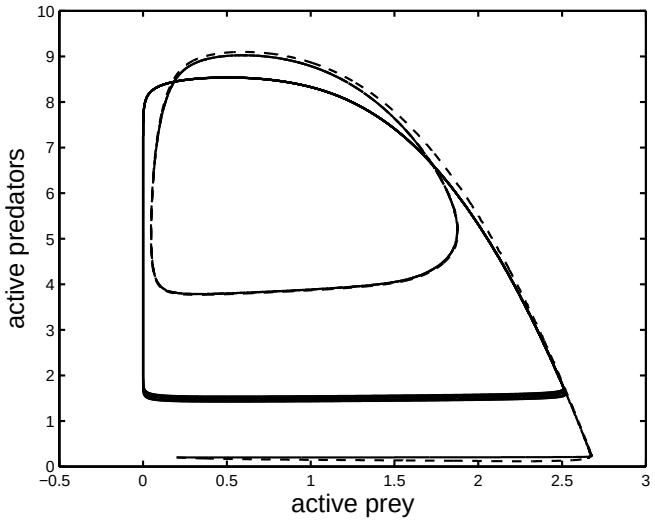

Figure 6.1 (Bilinsky and Hadeler, 2008) Phase plane for the MacArthur-Rosenzweig system (solid) and projection to the u, v-plane for the system with quiescence (dashed). Both systems have limit cycles. The projected limit cycle of the quiescent system is much smaller.

6.5 Rates Depending on Density

There are various biological models that can be interpreted in terms of quiescence and in which transition rates depend on the state. An example is Malik and Smith (2006, 2008), where chemostat models are extended by quiescent phases. A general formulation of the problem is

$$\begin{aligned} \dot{v} &= f(v) - p(v,w)v + q(v,w)w \\ \dot{w} &= -q(v,w)w + p(v,w)v. \end{aligned} \tag{6.18}$$

Such a model, with $f(v) = \Delta v$, has been used in the discussion of swarming behavior (Edelstein-Keshet *et al.*, 1998). For $f(v) = 0$ this system is equivalent to a scalar differential equation. Here we consider the case where particles in the active compartment avoid crowding, $p = p(v)$, with $p'(v) > 0$, and q constant,

$$\begin{aligned} \dot{v} &= f(v) - p(v)v + qw \\ \dot{w} &= p(v)v - qw. \end{aligned} \tag{6.19}$$

This system is equivalent to the second order equation for the active phase

$$\ddot{v} + [q + (p(v)v)' - f'(v)]\dot{v} = qf(v) \tag{6.20}$$

and then, for large transition rates, we get the limiting equation

$$\dot{v} = \frac{q}{q + (p(v)v)'} f(v) \tag{6.21}$$

which may be used (for instance in ecological applications) to estimate the total population from the observed active phase. The equations (6.5) and (6.21) have the same stationary points. The derivative at a stationary point of (6.21) becomes

$$q\frac{f'(\bar{v})}{q+p(\bar{v})}. \tag{6.22}$$

Hence the sign of the derivative does not change but the absolute value gets smaller than $|f'(\bar{v})|$.

Example 6.5 Some bacteria go quiescent (become spores) if conditions are unfavorable. Let v, w denote active and quiescent bacteria and s a substrate. Assume that the rate of going quiescent is increasing with decreasing substrate concentration. Assume further that substrate uptake is fast in comparison to reproduction and making spores. Then we have a system

$$\begin{aligned} \dot{v} &= F(s,v) - P(s)v + qw - \mu v \\ \epsilon\dot{s} &= -sv + r \\ \dot{w} &= P(s)v - qw. \end{aligned}$$

Consider the limiting case $\epsilon \to 0$. Then $s = r/v$. Define

$$p(v) = P(\frac{r}{v}), \quad f(v) = F(r/v, v) - \mu v.$$

Hence we arrive at the system (6.19) and the rate (6.22) (which determines stability) can be computed.

6.6 Slow Dynamics

Rather than assuming that individuals switch between an active and a quiescent phase one can assume that they switch between a vector field f and a "slow field" κf where $\kappa \in (0,1)$. Then we have the system (with equal rates)

$$\begin{aligned} \dot{v} &= f(v) - pv + qw \\ \dot{w} &= \kappa f(w) + pv - qw. \end{aligned} \tag{6.23}$$

Suppose that $f(\bar{u}) = 0$. We look for a related stationary point of (6.23). The choice $v = w = \bar{u}$ works only for the special case $p = q$. Otherwise it is not evident how to proceed. In (Hadeler, 2008c) it has been assumed that f is homogeneous of degree 1 and that $\bar{u}\exp\{\hat{\lambda}t\}$ is an exponential solution. Then we find two related exponential solutions of the form

$$(v,w) = (\alpha_i\bar{u}, \beta_i\bar{u})\exp\{\lambda_i t\}, \qquad i = 1,2$$

from the eigenvalue problem

$$\begin{pmatrix} \hat{\lambda}-p & q \\ p & \kappa\hat{\lambda}-q \end{pmatrix}\begin{pmatrix} \alpha_i \\ \beta_i \end{pmatrix} = \lambda_i \begin{pmatrix} \alpha_i \\ \beta_i \end{pmatrix}, \qquad i = 1,2.$$

It can be shown that both solutions are real and that the larger eigenvalue is between $\hat{\lambda}$ and 0. It can further be shown that if $\bar{u}$ is stable then the solution corresponding to the larger eigenvalue is also stable (Hadeler, 2008c). We illustrate the use of this result on a predator prey system with Holling type II functional response:

Example 6.6 (Hadeler, 2008c) Consider the homogeneous predator-prey system

$$\begin{aligned} \dot{u} &= au - b\tfrac{uv}{u+v} \\ \dot{v} &= c\tfrac{uv}{u+v} - dv, \end{aligned} \tag{6.24}$$

with $a, b, c, d > 0$. This system can be completely analyzed e.g. in terms of the variable $\xi = u/(u+v)$ for which we get a scalar equation

$$\dot{\xi} = \xi(1-\xi)[a+d-b-(c-b)\xi]. \tag{6.25}$$

From this equation we can determine the stationary points and their stability. A stationary solution of (6.25) corresponds to an exponential solution of (6.24): If $(\bar{u}, \bar{v}) \exp\{\hat{\lambda} t\}$ is an exponential solution of (6.24) then $\bar{\xi} = \bar{u}/(\bar{u}+\bar{v})$ is a stationary point of (6.25). And if $\bar{\xi}$ is a stationary point of (6.25) then there is a corresponding exponential solution of (6.24). Furthermore, the exponential solution is stable (in the sense of stability of exponential solutions) if and only if the stationary point $\bar{\xi}$ is stable. Hence the existence of exponential solutions and their stability follows from the scalar equation, but the exponents cannot be retrieved from (6.25). It turns out that for the equation (6.25) there are four orthants in parameter space with different qualitative behavior (as in a Lotka competition model).
I) $c < a + d < b$: Unstable coexistence point, attractors 0 and 1.
II) $a + d < b$ and $a + d < c$: No coexistence point. The point 0 attracts $[0, 1)$.
III) $c > a + d > b$: Coexistence point globally attracting in $(0, 1)$.
IV) $a + d > b$ and $a + d > c$: No coexistence point. The point 1 attracts $(0, 1]$.

In cases I) and III) the exponent of the coexistence solution is $\rho = (bc-ac-bd)/(b-c)$. The exponent ρ is negative in the unstable case I and positive in the stable case III.

These observations are easy to verify but a similar analysis of the problem with slow dynamics is very difficult. However, the general results guarantee that to each stable exponential solution of the two-dimensional system corresponds one stable exponential solution of the four-dimensional system. In particular, in case III, the system with slow dynamics has a stable exponential solution where prey and predator coexist.

6.7 Delay Equations

In section 6.3 we have seen that a quiescent phase and a delay have different effects. Hence it may be worthwhile to study the effect of a quiescent phase in a scalar delay equation with constant delay $\theta > 0$

$$\dot{u}(t) = f(u(t), u(t-\theta)) \tag{6.26}$$

with $f(0,0) = 0$. The system

$$\begin{array}{rcl} \dot{v}(t) & = & f(v(t), v(t-\theta)) - pv(t) + qw(t) \\ \dot{w}(t) & = & pv(t) - qw(t) \end{array} \tag{6.27}$$

could be called the natural quiescent extension of (6.26). We linearize at $u = 0$ and at $(v, w) = (0, 0)$, respectively, and test with exponentials. Then we get the characteristic equation (β and α are the partial derivatives of f)

$$\alpha e^{-\mu\theta} + \beta - \mu = 0 \tag{6.28}$$

for (6.26) and

$$\det \begin{pmatrix} \alpha e^{-\lambda\theta} + \beta - p - \lambda & q \\ p & -q - \lambda \end{pmatrix} = 0 \tag{6.29}$$

for the system (6.27). The connection between the eigenvalues λ and μ is clearly not as simple as in (6.16). Hence the "natural extension" is not covered by Theorem 6.1. One easily understands this fact if one replaces the delay equation by a succession of ordinary differential equations representing the state at $t, t-h, t-2h, \ldots$. Then Theorem 6.1 requires that each component, and not just the first, goes quiescent with the same rate.

Hence, in order to get the analogue of Theorem 6.1 for the delay equation, we should write the delay equation as an evolution equation in $C[-\theta, 0]$,

$$\frac{d}{dt} u_t(s) = \begin{cases} \frac{d}{ds} u_t(s) & -\theta \le s < 0 \\ f(u_t(0), u_t(-\theta)) & s = 0 \end{cases} \tag{6.30}$$

(as usual, u_t denotes the "segment", i.e., the restriction of u to the interval $[t-\theta, t]$). Now each "component" $u_t(s)$ must go quiescent with the same rate. So we get the system

$$\begin{array}{rcll} \frac{d}{dt} v_t(s) & = & \begin{cases} \frac{d}{ds} v_t(s) - pv_t(s) + qw_t(s) & -\theta \le s < 0 \\ f(v_t(0), v_t(-\theta)) - pv_t(0) + qw_t(0) & s = 0 \end{cases} & \\ \frac{d}{ds} w_t(s) & = & pv_t(s) - qw_t(s) & -\theta \le s \le 0. \end{array} \tag{6.31}$$

We write the equations in an elementary notation ($v(t,s) = v_t(s)$, $w(t,s) = w_t(s)$)

$$\begin{array}{rcl} \frac{\partial}{\partial t} v(t,s) & = & \frac{\partial}{\partial s} w(t,s) - pv(t,s) + qw(t,s) \\ \frac{\partial}{\partial t} w(t,s) & = & pv(t,s) - qw(t,s), \quad -\theta \le s < 0 \\ \frac{\partial}{\partial t} v(t,0) & = & f(v(t,0), v(t,-\theta)) - pv(t,0) + qw(t,0) \\ \frac{\partial}{\partial t} w(t,0) & = & pv(t,0) - qw(t,0). \end{array} \tag{6.32}$$

Again we linearize at $v = w = 0$, test with exponentials, and get a differential equation and three further equations

$$\begin{array}{rcl} \dot{v}(s) & = & (\lambda + p)v(s) - qw(s) \\ (\lambda + q)w(s) & = & pv(s), \quad -\theta \le s < 0 \\ (\lambda + p)v(0) & = & \alpha v(-\theta) + \beta v(t) + qw(0) \\ (\lambda + q)w(0) & = & pv(0). \end{array}$$

We eliminate the function w and arrive at a differential equation for v and a boundary condition,

$$\begin{aligned} \dot{v}(s) &= \mu v(s) \\ (\lambda + p - \frac{pq}{\lambda + q})v(0) &= \alpha v(-\theta) + \beta v(0) \end{aligned}$$

where at this stage

$$\mu = \lambda + p - \frac{pq}{\lambda + q} \tag{6.33}$$

is just an abbreviation. We solve this linear differential equation and insert the solution into the boundary condition. We find that λ and μ satisfy the equation

$$\alpha e^{-\mu\theta} + \beta - \mu = 0 \tag{6.34}$$

which is again (6.28). If we would insert (6.33) into (6.34) then we would get the characteristic equation for λ. Assume μ is a solution of (6.28). Then μ and λ are indeed connected by the equation (6.16) simply because (6.33) and (6.16) are equivalent.

Equation (6.27), however meaningful it may be from a modeling point of view, within the framework of quiescent phases is a system with distinct transition rates while (6.32) is a system with equal transition rates.

Example 6.7 The difference between the two approaches can be shown in the example of the blowfly equation (τ is the duration of the juvenile state)

$$\dot{u}(t) = b(u(t-\tau))e^{-\mu_0\tau} - \mu(u(t))u(t) \tag{6.35}$$

which can be derived from the Gurtin-MacCamy system (Nisbet *et al.*, 1980; Bocharov and Hadeler, 2000; Hadeler and Bocharov, 2003; Hadeler, 2008b) with adult birth rate $b(u)$, adult death rate $\mu(u)$, and constant juvenile mortality μ_0. If there is no quiescence in the juvenile state (which amounts to $p = q = 0$ for the juvenile state and hence to different rates in the adult and in the juvenile state) then we get the "natural quiescent extension" in the form

$$\begin{aligned} \dot{u}(t) &= b(u(t-\tau))e^{-\mu_0\tau} - \mu(u(t))u(t) - pu(t) + qv(t) \\ \dot{v}(t) &= pu(t) - qv(t). \end{aligned} \tag{6.36}$$

If there is juvenile quiescence with the same rates as in the adults, then we get a similar system where the factor $\exp\{-\mu_0\tau\}$ is replaced by a larger number $\kappa = \kappa(\mu_0, p, q, \tau)$ which accounts for reduced juvenile mortality due to quiescence. For large p, q we have $\kappa \approx \exp\{-q\mu_0\tau/(p+q)\}$ (which follows immediately from the properties of Poisson processes).

6.8 Spread in Space

6.8.1 Reaction-Diffusion Equations

The idea of coupled dynamics as in (6.2) can be applied to the parabolic system of two coupled scalar reaction diffusion equations:

$$\begin{aligned} v_t &= D_1\Delta v + f_1(v) - pv + qw \\ w_t &= D_2\Delta w + f_2(w) - qw + pv. \end{aligned} \tag{6.37}$$

If we imitate the procedure of (6.7), replacing $f(v)$ by $D\Delta v + f(v)$ etc., we end up with rather clumsy "viscous damped wave equations" where there are spatial derivatives within the non-linearities, see Hadeler and Lewis (2002). If either D_1 and f_1 or D_2 and f_2 vanish, then one arrives at a single standard damped wave equation. The limiting equation of (6.37) for large p, q is

$$u_t = (\tilde{q}D_1 + \tilde{p}D_2)\Delta u + f_1(\tilde{q}u) + f_2(\tilde{p}u).$$

The following two systems have been studied in Hadeler and Lewis (2002). In the first scenario the v particles diffuse and are subject to mortality and the w particles react,

$$\begin{aligned} v_t &= D\Delta v - \mu v - pv + qw \\ w_t &= f(w) - qw + pv \end{aligned} \tag{6.38}$$

(see also Lewis and Schmitz (1996)), while in the second scenario a quiescent phase is coupled to a reaction diffusion equation,

$$\begin{aligned} v_t &= D\Delta v + f(v) - pv + qw \\ w_t &= -qw + pv. \end{aligned} \tag{6.39}$$

A single equation in the form of a damped wave equation results if one chooses to focus on one of the two variables v, w. For the system (6.38) with $\mu = 0$ we choose w and get the equation, with $\tau = 1/(p+q)$,

$$\tau w_{tt} + (1 - \tau f'(w))w_t - \tau D\Delta w_t + \tau D\Delta f(w) = \tilde{q}D\Delta w + \tilde{p}f(w), \tag{6.40}$$

while for (6.39) we choose v and get

$$\tau v_{tt} + (1 - \tau f'(v))v_t - \tau D\Delta v_t = \tilde{q}D\Delta v + \tilde{q}f(v). \tag{6.41}$$

These equations have features of damped wave equations (terms like Δw_t correspond to viscous damping) but they are parabolic because of the (almost) equivalence with (6.38) and (6.39), respectively. These systems have been studied in bounded domains with zero Dirichlet boundary conditions in Hadeler and Lewis (2002).

The problem of traveling fronts and the spread rate has been discussed in Lewis and Schmitz (1996) and Hadeler and Lewis (2002). Traveling waves are those solutions that can be expressed in terms of a single moving reference frame $z = x - ct$. The spread rate is the speed at which a locally introduced population spreads spatially. The two problems are connected. Traveling waves connecting the trivial steady state to a nontrivial steady state describe population spread with speed c. In the case that

the nonlinear growth functions satisfy a convexity constraint (no Allee effect), the cooperative nature of the interaction dynamics in (6.38) and (6.39) mean that the traveling wave solutions and spread rates can be fully characterized using the methods of Weinberger *et al.* (2002). Specifically, there exists a family of traveling wave solutions for various speeds c. Solutions exist for all speeds c greater than or equal to a minimum speed c^*. The minimum traveling wave speed is also the spread rate for a locally introduced population. Finally, the value of c^* can be determined by linear analysis about the leading edge of the invasive wave. Details are in Lewis and Schmitz (1996) and Hadeler and Lewis (2002).

6.8.2 Reaction-Transport Equations

In Hillen (2003) transport equations for spatial spread have been coupled to quiescent phases. Transport equations present alternative models to classical reaction-advection-diffusion equations, if detailed information about the movement of individuals is available. Modern tracking techniques, such as GPS data for collared mammals or birds, allow one to follow the paths of individuals and measure their mean speed, mean rate of change of direction and the distribution of turning angles. These measurements can be directly used for transport equations.

Besides moving, individuals will also stop movement to rest, to find shelter, or to forage. To model the dynamic between activity and resting the transport equation is coupled to an equation for the resting compartment, whereby the rate of stopping is spatially dependent. Let $u(t,x,s)$ denote the density of moving individuals, where $t \geq 0$ denotes time, $x \in \mathbb{R}^n$ space and $s \in V$ velocity. The set of possible velocities, V, is assumed to be a spherical shell and $|V|$ denotes its Lebesgue measure. The resting compartment is denoted by $r(t,x)$ and the total density by $N(t,x) = \int_V u(t,x,s)ds + r(t,x)$. Resting individuals that start moving can choose any velocity uniformly in V, hence a factor $|V|^{-1}$ shows up in the corresponding transition term. The stopping rate $p(x)$ is spatially dependent, while the rate q at which individuals start moving is constant. Also the turning rate $\mu > 0$ is assumed to be constant. The distribution of the newly chosen velocity is given by $T(s,s')$. The functions $l(N), g(N)$ denote loss and gain-terms, respectively. The full transport model reads

$$\begin{aligned} u_t + s\cdot\nabla u &= -\mu u + \mu\int_V T(s,s')u(.,.,s')ds' \\ &\quad -p(x)u + \frac{q}{|V|}r - l(N)u \qquad (6.42) \\ r_t &= p(x)\int_V u(.,.,s)ds - qr + g(N)r - l(N)r. \end{aligned}$$

Notice that the arguments of the functions have been suppressed, except in the integrals. The turning kernel $T(s,s')$ needs to satisfy certain positivity conditions as described in detail in Hillen (2003). It is sufficient if T is positive and square integrable.

A useful tool to study transport equations is the so called "parabolic limit" (see Alt, 1980; Hillen and Othmer, 2000; Dickinson, 2000; Hillen, 2003; Chalub *et al.*, 2004). This is in fact a scaling method for large speeds and large turning rates, or equivalently, for macroscopic time and space scales of the form

$$\tau = \epsilon^2 t, \qquad \xi = \epsilon x$$

for a small parameter $\epsilon > 0$. The details of the formal asymptotics and the corresponding convergence estimates are given in the literature cited above. Here, we only summarize the results. Up to leading order, the total population $N(\tau, \xi)$ satisfies the parabolic reaction-advection-diffusion equation

$$\begin{aligned} N_\tau &= \nabla_\xi \left(D_{pq}(\xi)\nabla_\xi N - D_{pq}(\xi)\frac{N}{q+p(\xi)}\nabla_\xi p(\xi) \right) \\ &\quad + \frac{p(\xi)}{p(\xi)+q}\tilde{g}(N)N - \tilde{l}(N)N, \end{aligned} \tag{6.43}$$

where $D_{pq}(\xi)$ denotes the *diffusion tensor*

$$D_{pq}(\xi) = \frac{q}{|V|(p(\xi)+q)} \int_V v\mathcal{F}_p(\xi)v \; dv;$$

$\mathcal{F}_p(\xi)$ is a pseudo inverse:

$$\mathcal{F}_p(\xi) = \left(\mathcal{L}_p|_{\langle 1\rangle^\perp}\right)^{-1}$$

and $\mathcal{L}_p$ denotes the *effective turning operator*

$$\begin{aligned} \mathcal{L}_p\Phi(s) &= -(\mu + p(\xi))\Phi(s) \\ &\quad + (\mu + p(\xi)) \int_V \left(\frac{\mu}{\mu + p(\xi)} T(s,s') + \frac{p(\xi)}{|V|(\mu + p(\xi))} \right) \Phi(s')ds' \end{aligned}$$

and $\langle 1\rangle \subset L^2(V)$ denotes the linear subspace of functions constant in $s \in V$. The functions $\tilde{g}, \tilde{l}$ are rescaled versions of $g = \epsilon^2\tilde{g}, l = \epsilon^2\tilde{l}$, ensuring that death and reproduction occur on the macroscopic scale, and not on the scale of individual movement.

Remarks: The diffusion limit in (6.43) is remarkable in several ways:

1. The procedure quite naturally leads to non-isotropic diffusion expressed through the diffusion tensor D_{pq}. In many situations, however, the diffusion will be isotropic in which case $D_{pq} = d_{pq}I$ with a diffusion constant d_{pq} and the identity I. For example, if individuals have a constant speed $\sigma > 0$, $V = \sigma S^{n-1}$ and change of direction is uniformly distributed, $T(s,s') = |V|^{-1}$ then, as shown in Hillen and Othmer (2000), we obtain isotropic diffusion with

   $$d_{pq} = \frac{\sigma^2}{n|V|}\frac{q}{(p(\xi)+q)(p(\xi)+\mu)}.$$

   More general conditions for isotropy and examples for non-isotropic diffusion are given in Hillen and Othmer (2000) and Othmer and Hillen (2002).

2. It is remarkable that (6.43) shows a taxis term including $\nabla p(\xi)$. This is a drift term in direction of higher levels of $p(\xi)$. Since the stopping rate, $p(\xi)$ is larger in favorable environments (more food, better shelter), the corresponding term describes taxis towards favorable environments. Reaction-diffusion equations with drift towards favorable environments were studied by Cosner and Lou (2003). Alternatively, the appearance of this additional taxis term can be directly motivated from a quiescent-diffusion equation, where the stopping rate is spatially dependent:
$$\begin{aligned} v_t &= D\Delta v - p(x)v + qw \\ w_t &= p(x)v - qw, \end{aligned} \tag{6.44}$$
where v describes individuals moving in space and w individuals at rest. Notice that this model corresponds to model (6.38) and model (6.39) for $f = 0$ and spatially dependent stopping rate $p(x)$.
For large transition rates p, q we obtain the limiting equation
$$\begin{aligned} u_t &= D\Delta \left(\frac{qu}{q + p(x)} \right) \\ &= D\nabla \left(\frac{q}{q + p(x)} \nabla u - \frac{qu}{(q + p(x))^2} \nabla p(x) \right), \end{aligned}$$
which shows the same taxis term as in (6.43).

3. To look at steady states that are induced by the taxis term, we assume there is no birth and death ($f = g = 0$). We consider a one-dimensional version of (6.43) on an interval $[0, l]$ with homogeneous Neumann boundary conditions. We find that for steady states we have the relation
$$N(\xi) = \kappa(q + p(\xi)),$$
with an integration constant
$$\kappa = \frac{\int_0^l N(\xi) d\xi}{ql + \int_0^l p(\xi) d\xi}.$$
This means that the shape of $N(\xi)$ follows the shape of the stopping rate, i.e. $N(\xi)$ and $p(\xi)$ have common maxima and minima.

6.9 Applications

Applications of systems with quiescent phases have been mentioned throughout the previous sections. Here we specifically discuss applications to the river drift paradox, to radiation treatment of tumors, to engineered bacteria and to infectious diseases.

6.9.1 The River Drift Paradox

The "river drift paradox" describes the phenomenon that various animal species persist in rapidly flowing rivers although continually individuals are drifting down the

river. Apparently this problem is of a kind that showed up in example 6.1 and also in a chemostat with washout.

Pachepsky *et al.* (2005) investigated the interaction of a benthic reproducing phase w and a moving phase v where individuals move (by diffusion) and can be carried away by convection. In a non-dimensional form their model reads (compare (6.38))

$$\begin{aligned} v_t &= v_{xx} - \nu v_x - pv + qw \\ w_t &= w(1-w) + pv - qw, \end{aligned} \tag{6.45}$$

where ν denotes the drift velocity.

The river drift paradox can be approached in several ways. First one can consider a classical *critical domain size problem* with advection. When the link between the stationary and the mobile phases is weak ($q < 1$) then w_t remains positive for small w, and the population persists unconditionally. However, when the link is strong ($q > 1$), then persistence depends upon both the advection speed ν and the domain (river) length L. A necessary condition for persistence is that the advection speed lie below a critical threshold ($\nu < \nu^* = 2\sqrt{p/(q-1)}$). When this threshold condition is satisfied, the critical domain size approach employs the domain length L as a bifurcation parameter for existence of nontrivial solutions (i.e., persistence). Reasonable boundary conditions for the moving phase are zero flux at the top end of the stream ($x = 0$) and hostile at the bottom end of the stream ($x = L$) (Pachepsky *et al.*, 2005). The condition for persistence is then

$$L > \frac{2}{\sqrt{\frac{4p}{q-1} - \nu^2}} \tan^{-1}\left(-\frac{1}{\nu}\sqrt{\frac{4p}{q-1} - \nu^2} \right). \tag{6.46}$$

Second, the authors consider spread in a river of infinite length, and calculate upstream and downstream traveling wave speeds. The methods for this traveling wave analysis are similar to those outlined in Lewis and Schmitz (1996) and Hadeler and Lewis (2002), but now with advection included (Pachepsky *et al.*, 2005). The analysis can be connected to the critical domain size analysis through the threshold ν^*. A positive upstream traveling wave speed is conditional upon $\nu < \nu^*$. At $\nu = \nu^*$ the upstream invasion stalls. Thus, quite separate approaches, traveling wave speeds and critical domain size, are linked together by the critical advection speed. This approach has been extended to include generalized dispersal behavior in Lutscher *et al.* (2005).

Pachepsky *et al.* (2005) also derived the limiting equation under rapid transfer between mobile and stationary phases ($p, q \to \infty$, with $q/p = \rho$), which they call the "second Fisher approximation" for the total density of individuals,

$$(1+\rho)u_t = u(1-u) + \rho u_{xx} - \rho\nu u_x. \tag{6.47}$$

They use the limiting equation to find simple conditions for persistence and invasion under the assumption of strongly linked mobile and stationary populations. In agreement with our general results the authors state that "... finite residence time on the benthos ($p, q < \infty$) enhances persistence of a population." (Pachepsky *et al.*,

2005, page 12). Also, in this problem the resting phase (immobile phase) stabilizes the dynamics.

6.9.2 Spread of Genetically Engineered Microbes

Genetically engineered microbes (GEMs) can provide useful services in agriculture, and field trials are likely to increase in the future. Services include, for example, an extension of the growing season. This is due to prevention of ice nucleation on crops by engineered "ice-minus" bacteria (Lewis *et al.*, 1996). However, concerns remain regarding proliferation and spread of GEMs, as well as the potential for ecosystem disruption and gene transfer.

Lewis *et al.* (1996) modeled spread of GEMs in the presence of competition with wild bacteria. For example, the wild counterpart to "ice-minus" bacteria is a naturally occurring "ice-plus" strain that nucleates ice crystals. While a traditional ecological approach would emphasize details of local competition, a key to modeling spread of GEMs is inclusion of a mobile compartment, describing aerosols, or surface water and groundwater suspensions, where there is rapid movement but high mortality. Here the model is

$$\begin{aligned}
\frac{\partial s_w}{\partial t} &= s_w(1 - s_w - \gamma_w s_e) + p m_w - q s_w \\
\frac{\partial s_e}{\partial t} &= r s_e(1 - s_e - \gamma_e s_w) + p m_e - q s_e \\
\frac{\partial m_w}{\partial t} &= -\mu_w m_w - p m_w + q s_w + \frac{\partial^2 m_w}{\partial x^2} \\
\frac{\partial m_e}{\partial t} &= -\mu_e m_e - p m_e + q s_e + \delta \frac{\partial^2 m_e}{\partial x^2}.
\end{aligned} \tag{6.48}$$

where s and m refer to stationary and mobile compartments, and subscripts w and e denote wild and engineered strains. Note that spatial spread of strains requires linked growth and dispersal and hence nonzero transfer rates q and p.

The simplest case, which we consider here, is where wild and engineered strains are identical in all aspects but their ability to compete ($r = \delta = 1$ and $\mu_w = \mu_e = \mu$). The case with competitive exclusion of one strain by another requires one competition coefficient larger than one, and the other less than one. When one strain is only a slightly better competitor, it is reasonable to also assume $\gamma_w + \gamma_e \approx 2$. Without loss of generality we consider the case where the engineered strain is the better competitor ($\gamma_e < 1$). Although this may not always be true, it is the case of interest when it comes to the spread of GEMs.

We start by considering the limiting equation, where there are strong, balanced links between sedentary and mobile classes ($q, p \to \infty$, with $q/p = \rho$). Here the system

(6.48) simplifies to a modified spatial Lotka-Volterra competition equation*

$$\begin{aligned}(1+\rho)\frac{\partial s_w}{\partial t} &= s_w\left[1-\rho\mu-s_w-\gamma_w s_e\right]+\rho\frac{\partial^2 s_w}{\partial x^2}\\ (1+\rho)\frac{\partial s_e}{\partial t} &= s_e\left[1-\rho\mu-s_e-\gamma_e s_w\right]+\rho\frac{\partial^2 s_e}{\partial x^2}.\end{aligned} \tag{6.49}$$

In this case the approach of Okubo *et al.* (1989) can be employed: addition of the two equations and application of the condition $\gamma_w + \gamma_e = 2$ yields a single equation of Fisher form for the sedentary individuals

$$(1+\rho)\frac{\partial s}{\partial t} = s\left[1-\rho\mu-s\right]+\rho\frac{\partial^2 s}{\partial x^2}. \tag{6.50}$$

Although the sedentary individuals do not actually diffuse, their behavior is consistent with the diffusion-type term in equation (6.50), because they are coupled strongly to a diffusive mobile component. This equation has a globally attracting invariant manifold $s = 1 - \rho\mu$, which is positive, providing the growth during time spent in the stationary class exceeds mortality during time spent in the mobile class. We expect initial conditions to start close to this invariant manifold, with $s_w \approx 1-\rho\mu$ and $s_e \approx 0$ except at a local perturbation which corresponds to localized introduction of the engineered strain. Hence it is reasonable to consider the case of population spread on the invariant manifold. Substitution of $s_e = 1 - \rho\mu - s_w$ into the second of equation (6.49) yields another Fisher type equation

$$\frac{\partial s_e}{\partial t} = \frac{(1-\rho\mu)(1-\gamma_e)}{(1+\rho)}s_e\left[1-\frac{s_e}{1-\rho\mu}\right]+\frac{\rho}{1+\rho}\frac{\partial^2 s_e}{\partial x^2}, \tag{6.51}$$

with asymptotic spread rate

$$c^* = 2\frac{\sqrt{(1-\rho\mu)(1-\gamma_e)\rho}}{1+\rho}. \tag{6.52}$$

Note that spread is slowed by interstrain competition γ_e and mortality μ, but is nonmonotonic with respect to the transfer rate balance $\rho = q/p$. Indeed, the worst, or speediest, invasion occurs when the mobile to stationary transfer rate slightly exceeds the stationary to mobile rate so that $p = q(1 + 2\mu)$, with speed $c^* = \sqrt{(1-\gamma_e)/(1+\mu)}$. As the mortality rate in the mobile class, μ, approaches zero, the speed simplifies to $c^* = \sqrt{1-\gamma_e}$, which is exactly half the rate calculated by Okubo *et al.* (1989) for the spread of a competitively superior species into another via Lotka-Volterra with simultaneous competitive growth and diffusion. The halving of the spread rate comes from differing original assumptions. Rather than allowing for simultaneous competitive growth and diffusion, equation (6.48) assumes that individuals either compete and grow, in one class, or diffuse, in another.

The case with weakly linked mobile and stationary classes can be understood using similar mathematical methods (see Lewis *et al.* (1996), Appendix). The invariant manifolds are found by adding the first two and second two equation of (6.48), under

* Note the typo in the equivalent equations (16) and (17) from Lewis *et al.* (1996).

the assumption $\gamma_w + \gamma_e = 2$, to obtain a reduced system

$$\begin{aligned} \frac{\partial s}{\partial t} &= w(1-w) + pm - qs \\ \frac{\partial m}{\partial t} &= -\mu m - pm + qs + \frac{\partial^2 m}{\partial x^2}. \end{aligned} \tag{6.53}$$

Here the variables $s = s_w + s_e$ and $m = m_s + m_e$ represent the total number of microbes, both genetically engineered and wild, in the stationary pool and the mobile pools, respectively. Spatially homogeneous steady-state solutions to this system are $(0,0)$ and $(\bar{s}, \bar{m})$, where

$$\bar{s} = \frac{\mu(1-q)+p}{\mu+p} \qquad \bar{m} = \frac{q}{\mu+p}\bar{w}. \tag{6.54}$$

Contracting rectangle arguments (Smoller, 1982) show that $(\bar{s}, \bar{m})$ is a globally stable equilibrium point for (6.53) (Schmitz, 1993), and hence $s_w + s_e = \bar{s}$ and $m_s + m_e = \bar{m}$ is a globally attracting invariant manifold. On this manifold, the invading GEMs obey

$$\begin{aligned} \frac{\partial s_e}{\partial t} &= s_e(1 - s_e - \gamma_e(\bar{s} - s_e)) + pm_e - qs_e \\ \frac{\partial m_e}{\partial t} &= -\mu m_e - pm_e + qs_e + \frac{\partial^2 m_e}{\partial x^2}. \end{aligned} \tag{6.55}$$

Because $\bar{s} < 1$ (6.54) and $\gamma_e < 1$, equation (6.55) describes logistic growth in the stationary state and switching between sedentary phase and a mobile state (see Section 6.8.1). Here the spread of GEMs can be calculated as for equation (6.38). As with the strongly coupled case (above), zero mortality ($\mu = 0$) and balanced transfer rates q and p lead to a spread rate of $c^* = \sqrt{1-\gamma_e}$. Figure 2 of Lewis *et al.* (1996) shows spread rates for nonzero μ and unbalanced transfer rates.

6.9.3 Tumor Growth: The Linear-Quadratic Model

We can use the mechanism of quiescent dynamics to derive the linear quadratic model in cancer radiation treatment. There it is assumed that the surviving fraction $S(D)$ of a tumor after radiation treatment with dose $D(t)$ can be expressed as

$$S(D) = e^{-\alpha D(t) - \beta D(t)^2}. \tag{6.56}$$

where α and β are non-negative constants. It has been shown that this model fits many data really well (Wheldon, 1988).

It is known that proliferating cells can enter a quiescent phase to eventually enter the cell cycle again. The quiescent phase is of particular interest in radiation treatment of cancer because radiation is most damaging to highly active proliferating cells. Quiescent cells are hit by radiation as well but they have time enough to repair DNA damage and recover. Hence for treatment to be successful it is important to estimate the quiescent phase. Cancer control cell cycle models were studied by Dawson and

Hillen (2005) and Swierniak *et al.* (1996) and many others. Here we study the following model.

Let $N(t)$ denote the active tumor cells and $R(t)$ the resting tumor cells. It is assumed that cells randomly switch between the active and quiescent phases. An alternative model, where cells after proliferation directly enter the quiescent phase has been studied in Dawson and Hillen (2005). Here we study:

$$\begin{aligned} \dot{N} &= \mu N(1-N/K) - pN + qR - (A_1 + BD(t))\dot{D}(t)N, \\ \dot{R} &= -qR + pN - A_2\dot{D}(t)R. \end{aligned}$$

The growth of the tumor is modeled through a logistic term. Alternative models use a Gompertz law, the Bernoulli equation or a von Bertalanffy growth law (see Gyllenberg and Webb (1989), Britton (2003)). We describe the radiation damage through the *hazard function* $h(t) = (A_1 + 2BD(t))\dot{D}(t)$ (see Zaider and Minerbo (2000)), where $D(t)$ is the total dose and $\dot{D}(t)$ is the dose-rate. The parameters A_1 and A_2 describe the radiation damage caused by single hit events while the coefficient B describes double hit damage. It is assumed that quiescent cells can recover from double hit events, since they have time to repair the damage. We also assume that $A_2 < A_1$.

The limiting equation reads

$$\dot{u} = \tilde{q}u(1-\tilde{q}u/K) - ((\tilde{q}A_1 + \tilde{p}A_2)\dot{D}(t) + \tilde{q}B\dot{D}(t)D(t))u. \tag{6.57}$$

To derive the linear-quadratic model (6.56) we assume that cell proliferation is slow on the time scale of radiation treatment. Hence we study

$$\dot{u} = -((\tilde{q}A_1 + \tilde{p}A_2)\dot{D}(t) + \tilde{q}B\dot{D}(t)D(t))u \tag{6.58}$$

which has the solution

$$u(t) = u(0)\exp(-\alpha D(t) - \beta D(t)^2),$$

with

$$\alpha = \tilde{q}A_1 + \tilde{p}A_2, \qquad \beta = \tilde{q}B.$$

The α/β-ratio is used in clinical applications to choose the best radiation protocol. It has been observed experimentally that cells in a long cell cycle have a large α/β-ratio, while cells in a short cell cycle have a low α/β-ratio. The model shows that α is a weighted mean of A_1 and A_2, while β is proportional to $\tilde{q}$ and B. Then a large α/β-ratio corresponds to small $\tilde{q}$, or small B. Small $\tilde{q}$ implies that a small fraction of the population is in the active compartment.

6.9.4 Infectious Diseases

Introducing quiescent phases in the classical Kermack-McKendrick model amounts to assuming that individuals avoid contacts at random intervals (Castillo-Chavez and

Hadeler, 1995; Hadeler and van den Driessche, 1997). One obtains

$$\begin{aligned}
\dot{S} &= -\beta\frac{SI}{N} - p_1 S + q_1 W \\
\dot{I} &= \beta\frac{SI}{N} - \alpha I - p_2 I + q_2 Z \\
\dot{R} &= \alpha I + \alpha Z \\
\dot{W} &= p_1 S - q_1 W \\
\dot{Z} &= -\alpha Z + p_2 I - q_2 Z \\
N &= S + I + W + Z + R
\end{aligned}$$

where S denotes active susceptible, I active infected, R the recovered, and W, Z individuals that temporally leave the risk group. The parameter β denotes the infection rate and α is the recovery rate. Here one can assume that N is constant. Hence it does not matter whether one uses mass action kinetics or standard incidence.

However, the interpretation of a quiescent phase matters. It makes a difference if people avoid social contact at all or just contacts that could cause transmission of the disease. It also matters if the total number of contacts is reduced or if it remains constant and hence the same number of contacts is distributed in the smaller then active population.

The basic reproduction number is

$$R_0 = \frac{\beta}{\alpha}\,\frac{q_1}{p_1+q_1}\,\frac{q_2+\alpha}{p_2+q_2+\alpha}. \tag{6.59}$$

In view of $d(S+I+W+Z)/dt = -\alpha(I+Z)$ it is evident that eventually $I+Z \to 0$. From $d(S+I)/dt = -\beta SI$ it follows that the total number of potential susceptibles $S+W$ is decreasing. Hence on limit sets $S+W$ is a constant and $p_1 S = q_1 W$. In contrast to the classical case there is no explicit formula or equation for the proportion of individuals which have never been infected.

Hence the model behaves essentially as the classical Kermack-McKendrick model but the quiescent phase reduces the basic reproduction number. Hadeler and van den Driessche (1997) discussed more general (and more realistic) situations where the rates depend on the prevalence of the disease.

6.9.5 Contact Distributions Versus Migrating Infective

Traditionally, the spread of epidemic diseases in space has been modeled in different ways, by contact distributions (Kendall) and by migrating individuals (Noble). A contact distribution describes the infectious force which one infectious individual at position y exerts upon a susceptible individual at position x. The contact distribution is a non-negative symmetric convolution kernel k with $k * 1 = 1$,

$$(k * u)(x) = \int_{\mathbb{R}^n} k(x-y)u(y)dy.$$

The model assumes the form

$$\begin{aligned} S_t &= -\beta(k*I)S \\ I_t &= \beta(k*I)S - \alpha I. \end{aligned} \tag{6.60}$$

On the other hand, one can model the motion of individuals by migration processes via

$$\begin{aligned} S_t &= -\beta IS + d_S(k*S - S) \\ I_t &= \beta IS - \alpha I + d_I(k*I - I) \end{aligned} \tag{6.61}$$

where again k is a non-negative symmetric convolution kernel with $k * 1 = 1$ and d_S, d_I are diffusion coefficients, typically different for susceptible and infected. For instance, in rabies models one assumes that only infectious individuals move, $d_S = 0$.

The contact model and the diffusion model describe different scenarios. In the contact model each individual "sits" at some location and meets other people at other locations with probability of contact decreasing with distance. The diffusion model is based on the idea that people move around and get into contact with other people. Of course this model does not imply that every person has a home base to which he/she will eventually return.

In either model, one can perform a diffusion approximation (using that the kernel is normalized and symmetric)

$$k * u \approx u + \frac{1}{2}\int_{\mathbb{R}^n} k(z) z_1^2 dz \Delta u. \tag{6.62}$$

Then the contact model (6.60) becomes Kendall's model and the diffusion model (6.61) becomes a standard system of reaction diffusion equations.

In practice the contact models and the migration models show very similar behavior. In order to compare the two approaches we consider the SIS case for both models. The contact model:

$$\begin{aligned} S_t &= -\beta S(I + \sigma I_{xx}) + \alpha I \\ I_t &= \beta S(I + \sigma I_{xx}) - \alpha I \end{aligned}$$

and thus

$$I_t = \beta(1 - I)(I + \sigma I_{xx}) - \alpha I.$$

The diffusion model:

$$\begin{aligned} S_t &= -\beta SI + \alpha I + DS_{xx} \\ I_t &= \beta SI - \alpha I + DS_{xx} \end{aligned}$$

and thus

$$I_t = \beta(1 - I)I - \alpha I + DI_{xx}.$$

Notice that this last equation is essentially the logistic equation with diffusion. We get the wave speed simply by linearizing at the leading edge (this argument can be made rigorous):
$c_0 = 2\sqrt{(\beta - \alpha)\beta\sigma}$ for the contact model.

$c_0 = 2\sqrt{(\beta-\alpha)D}$ for the diffusion model.
Hence the two formulas agree if we put $D = \beta\sigma$.

The question is whether these are just two similar but different models or whether there is some deeper connection. One connection can be made by designing a larger model for two types of stochastically moving individuals, the "quiescent" who move only in their neighborhood and the "active" who travel far. Then the two models before can be obtained as limiting cases of a larger model. Such a larger model is

$$\begin{aligned} S_t &= -S(\beta_1 I^{(1)} + \beta_2 I^{(2)}) \\ I_t^{(1)} &= \delta(\tilde{k} * I^{(1)} - I^{(1)}) - \alpha I^{(1)} + qI^{(2)} - pI^{(1)} \\ I_t^{(2)} &= S(\beta_1 I^{(1)} + \beta_2 I^{(2)}) - \alpha I^{(2)} - qI^{(2)} + pI^{(1)} \end{aligned} \tag{6.63}$$

with a non-negative convolution kernel $\tilde{k}$, $\tilde{k} * 1 = 1$ and a coefficient $\delta > 0$.

There are susceptible S and infected individuals of two kinds, migrating $I^{(1)}$ and sedentary $I^{(2)}$. The parameters β_1 and β_2 are the transmission rates for sedentary and migrating infected individuals, respectively. A sedentary susceptible can be infected by either an infected individual residing at the same position or by a passing migrating infected. $I = I^{(1)} + I^{(2)}$ is the total number of infected individuals.

Hadeler (2003) showed that different scalings of this system lead to limiting models with contact distributions (6.60) or to limiting models with migrating infective (6.61). The migration models correspond to the situation of slow progression of the disease within the population while contact models describe spread by rapid excursions of a few highly infectious individuals.

Hence migration models and contact models can be seen as limiting cases of models with different levels of mobility.

We sketch a proof of (6.62) for normalized symmetric kernels with existing second moments. By Taylor expansion we find

$$\begin{aligned} &\int_{\mathbb{R}^n} k(x-y)u(t,y)dy = \int_{\mathbb{R}^n} k(z)u(x+z)dz \\ &= \int_{\mathbb{R}^n} k(z)(u(x) + u_x(x)z + \frac{1}{2}z^T u_{xx}(x)z + o(|z|))dz \\ &= u(x) + \frac{1}{2}\int_{\mathbb{R}^n} z^T u_{xx}(x)z + o(|z|). \end{aligned}$$

We have used $k * 1 = 1$; the u_x term goes away because of symmetry; u_{xx} is the Hessian matrix. Now

$$\int k(z)z^T u_{xx}(x)zdz = \int k(z)\sum_{ij} u_{x_i x_j}(x)z_i z_j dz$$

and

$$\int k(z)z_i z_j dz = \begin{cases} 0 & i \neq j \\ \int k(z)z_i^2 dz & i = j \end{cases}$$

and, because of the symmetry,

$$\int k(z) z_i^2 dz = \int k(x) z_1^2 dz.$$

Hence

$$\int k(z) z^T u_{xx}(x) z dz = \int k(z) z_1^2 dz \, (\Delta u)(x).$$

6.10 Discussion

Throughout this chapter, biological systems have emerged in which quiescent phases drastically change the dynamics quantitatively or even qualitatively. Generally, quiescent phases tend to slow the dynamics near equilibria, stabilize equilibria against the onset of oscillations, and enhance persistence of certain species or types.

The effect of quiescent states may be significant with respect to outcomes in specific biological systems. In fact, quiescent phases can have a quite surprising effect on the population as a whole. For example, quiescent states can induce taxis terms in movement equations. The extinction of populations (through washout) in river ecosystems can be prevented when there is a stationary phase weakly coupled to the mobile state. Cancer tumors can resist radiation treatment when cells have refuge in a quiescent state, which needs to be accounted for in radiation treatment planning. A similar effect is known for antibiotic resistance in bacteria. Balaban *et. al.* (2004) have used a model involving a quiescent state (they called it "persisters") to fit survival data of *E. coli* bacteria which were exposed to the antibiotic *ampicillin*. They show that the existence of a persisting compartment can explain population survival and re-growth after treatment.

Moreover, our systematic approach to quiescent phases solves the longstanding discrepancy between diffusion and contact distribution models for spatial spread of epidemics, which can now be understood in terms of different scaling limits of a larger model with quiescence. It further highlights a risk of potentially erroneous conclusions about the joint effects of quiescent phases and delays.

In general, systems with quiescent phases have twice the dimension compared to systems without. Hence the mathematical analysis of such systems may become quite cumbersome (in particular in the transition from dimension two, where phase plane analysis is available, to dimension four). The methods and examples presented here provide tools to handle such systems provided the qualitative behavior of the systems without quiescent phases is well understood. However, further mathematical challenges remain, in particular to derive a solid theory for infinite dimensional systems, such as PDE's and to understand the effects of quiescent phases on global behavior, specifically the existence of compact global attractors.

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