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POPULATION DYNAMICS
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STRUCTURED POPULATION DYNAMICS

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Abstract. The objective of these lectures is to apply the theory of linear and nonlinear semigroups of operators to models of structured populations dynamics. The mathematical models of structured populations are typically partial differential equations with variables corresponding to such properties of individual as age, size, maturity, proliferative state, quiescent state, phenotype expression, or other physical properties. The main goal is to connect behavior at the individual level to behavior at the population level. Theoretical results from semigroup theory are applied to analyze such population behaviors as extinction, growth, stabilization, oscillation, and chaos.

1. General theory of operator semigroups in Banach spaces. In this section we provide basic definitions and theorems in the theory of semigroups of operators in Banach spaces and illustrate the concepts with some examples relevant to structured populations.

Definition 1.1. Let X be a Banach space and let $Y \subset X$. A *strongly continuous semigroup of operators in* Y is a set of operators (linear or nonlinear) $T(t), t \geq 0$ satisfying

(i) $T(t)$ is continuous from Y to Y $\forall t \geq 0$,
(ii) $T(0)\phi = \phi$ $\forall \phi \in Y$,
(iii) $T(t+s)\phi = T(t)T(s)\phi$ $\forall t, s \geq 0$ and $\phi \in Y$,
(iv) $t \mapsto T(t)\phi$ is continuous $\forall \phi \in Y$.

We remark that if $Y = X$ and $T(t) \in B(X)$ $\forall t \geq 0$, where $B(X)$ is the Banach algebra of bounded linear operators in X, then $T(t), t \geq 0$ is called a strongly continuous semigroup of bounded linear operators in X. Otherwise, $T(t), t \geq 0$ is called a nonlinear semigroup in Y.

Example 1.1. Let $X = C[0,1]$ or $C_0[0,1]$, where $C[0,1]$ is the Banach space of continuous real-valued functions on $[0,1]$ with supremum norm and $C_0[0,1]$ is the subspace of $C[0,1]$

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consisting of functions ϕ such that $\phi(0) = 0$. Let $\mu > 0$ and define

$$(T(t)\phi)(x) = e^{(\mu-1)t}\phi(xe^{-t}), \qquad \phi \in X,\ 0 \le x \le 1.$$

$T(t), t \ge 0$ is a strongly continuous semigroup of bounded linear operators in X. We illustrate this example in Figure 1 and Figure 2.

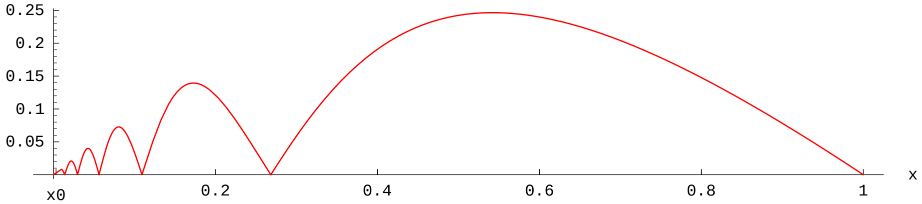

Fig. 1. The initial value for Example 1.1: $\phi(x) = 0$ if $0 \le x \le x_0$ and $\phi(x) = x(1-x)|\sin(\frac{1}{(x+.05)})|$ if $x_0 < x \le 1$, where $x_0 = \frac{1}{6\pi} - .05 \approx .003051647$

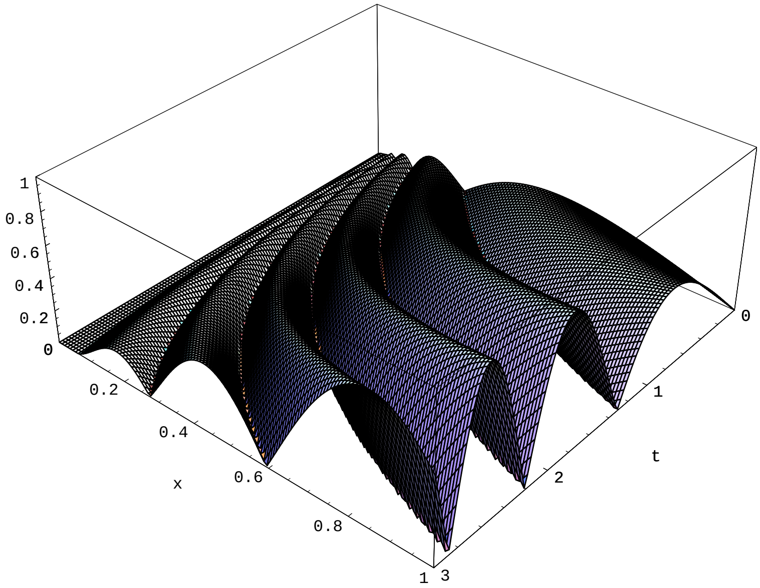

Fig. 2. The trajectory $(T(t)\phi)(x)$ for the semigroup of linear operators $T(t), t \ge 0$ in Example 1.1 with the initial value ϕ as in Figure 1 and $\mu = 2.0$

Example 1.2. Let $0 < x_0 < 1$ and let $X = C_{x_0,1}[x_0, 1]$, be the Banach space of continuous real-valued functions on $[x_0, 1]$ satisfying $\phi(x_0) = (2/x_0)\phi(1)$ with supremum norm. Define

$$(T(t)\phi)(x) = e^{-t}(2/x_0)^k\phi(xe^{-t}/x_0^k),$$

for $x_0 \le x \le 1, t \ge 0$, and $\ln(x/x_0^k) < t \le \ln(x/x_0^{k+1}), k = 0, 1, \ldots$. $T(t), t \ge 0$ is a strongly continuous semigroup of bounded linear operators in X. We illustrate this example in Figure 3 and Figure 4.

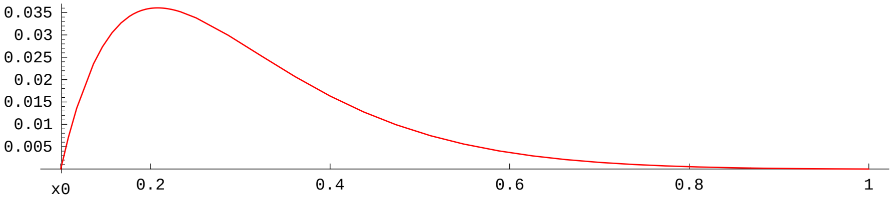

Fig. 3. The initial value for Example 1.2: $\phi(x) = (x - x_0)(1.0 - x)e^{-8.0(x-x_0)}$ for $x_0 \leq x \leq 1$, where $x_0 = .1$

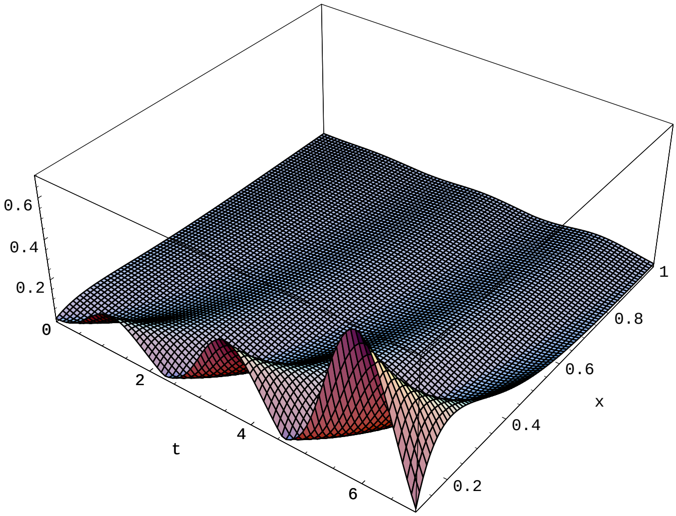

Fig. 4. The trajectory $(T(t)\phi)(x)$ for the semigroup of linear operators $T(t), t \geq 0$ in Example 1.2 with the initial value ϕ as in Figure 3

Definition 1.2. Let X be a Banach lattice and let X_+ be the positive cone of X. A linear or nonlinear operator B in X is *positive* in X_+ if and only if $B\phi \in X_+ \forall \phi \in X_+$ and *positive homogeneous* if and only if $cB\phi = B(c\phi)$ for all $c \geq 0$ and $\phi \in X_+$

Example 1.3. Let X be a Banach lattice, let $T(t), t \geq 0$ be a strongly continuous semigroup of positive homogenous operators in X_+, and let $F \in X_+^*$, the positive cone of the dual space of X. Define

$$S(t)\phi = \frac{T(t)\phi}{1 + \int_0^t F(T(u)\phi)du}, \qquad \phi \in X_+, t \geq 0.$$

$S(t), t \geq 0$ is a strongly continuous semigroup of positive nonlinear operators in X_+.

Definition 1.3. Let X be a Banach space, let $Y \subset X$. and let $T(t), t \geq 0$ be a strongly continuous semigroup of operators in Y. The *infinitesimal generator* A of $T(t), t \geq 0$ is the operator

$$A\phi = \lim_{t \to 0^+} \frac{T(t)\phi - \phi}{t}, \qquad D(A) = \left\{ \phi \in Y : \lim_{t \to 0^+} \frac{T(t)\phi - \phi}{t} \text{ exists} \right\}.$$

Example 1.4. Let $X = C[0,1]$ or $C_0[0,1]$ and let $T(t), t \geq 0$ be the strongly continuous semigroup of bounded linear operators in X as in Example 1.1. The infinitesimal generator of $T(t), t \geq 0$ is the linear operator

$$(A\phi)(x) = -\frac{d}{dx}(x\phi(x)) + \mu\phi(x), \qquad x \in [0,1],$$
$$D(A) = \left\{\phi \in X : \frac{d}{dx}(x\phi(x)) \in X\right\}.$$

Example 1.5. Let $X = C_{x_0,1}[x_0,1]$ and let $T(t), t \geq 0$ be the strongly continuous semigroup of bounded linear operators in X as in Example 1.2. The infinitesimal generator of $T(t), t \geq 0$ is the linear operator

$$(A\phi)(x) = -\frac{d}{dx}(x\phi(x)), \qquad x \in [x_0,1],$$
$$D(A) = \left\{\phi \in X : \frac{d}{dx}(x\phi(x)) \in X\right\}.$$

Example 1.6. Let X be a Banach lattice and let $S(t), t \geq 0$ be the nonlinear semigroup in X_+ as in Example 1.3 with $T(t), t \geq 0$ linear. The infinitesimal generator of $S(t), t \geq 0$ is

$$B\phi = A\phi - F(\phi)\phi, \qquad \phi \in D(A) \cap X_+$$

where A is the infinitesimal generator of $T(t), t \geq 0$.

Theorem 1.1. *Let X be a Banach space and let $T(t), t \geq 0$ be a strongly continuous semigroup of bounded linear operators in X. There exists $M \geq 1$ and $\omega \in \mathbf{R}$ such that*

$$|T(t)| \leq Me^{\omega t} \quad \text{for } t \geq 0. \tag{1.1}$$

The *infinitesimal generator* A of $T(t), t \geq 0$ is densely defined in X and

$$(d/dt)T(t)\phi = AT(t)\phi = T(t)A\phi \quad \text{for } \phi \in D(A), t \geq 0. \tag{1.2}$$

Theorem 1.2. *Let X be a Banach space. A is the infinitesimal generator of a strongly continuous semigroup of bounded linear operators $T(t), t \geq 0$ in X if and only if A is closed, densely defined, and there exists $M \geq 1$ and $\omega \in \mathbf{R}$ such that for all $\lambda > \omega, (\lambda I - A)^{-1}$ exists as a bounded linear operator in X and*

$$|(\lambda I - A)^{-n}| \leq \frac{M}{(\lambda - \omega)^n} \quad \text{for all } \lambda > \omega \text{ and } n = 1, 2, \ldots. \tag{1.3}$$

In this case $T(t), t \geq 0$ satisfies

$$|T(t)| \leq Me^{\omega t} \quad \text{for } t \geq 0. \tag{1.4}$$

2. Linear models of structured populations. In this section we provide examples of linear partial differential equations that model various structured populations. The examples illustrate the structuring of a proliferating population with respect to such individual properties as age, maturity, size, and phenotype.

Example 2.1. *The age structured cell population model.* Let $X = L^1(0,\infty)$, the Banach space of Lebesgue integrable functions on $(0,\infty)$ with norm $\|\phi\| = \int_0^\infty |\phi(a)|da$. Let

$p(a,t)$ be the density of the cell population with respect to cell age $a, a \geq 0$, where cell age means age since division. Thus, the total population of cells between ages a_1 and a_2 at time t is $\int_{a_1}^{a_2} p(a,t)da$ and the total cell population at time t is $\int_0^\infty p(a,t)da$. The density $p(a,t)$ satisfies the initial-boundary value problem

$$\frac{\partial}{\partial t}p(a,t) + \frac{\partial}{\partial a}p(a,t) = -(\beta(a) + \mu(a))p(a,t), \tag{2.1}$$

$$p(0,t) = 2\int_0^\infty \beta(a)p(a,t)da, \qquad t \geq 0, \tag{2.2}$$

$$p(a,0) = \phi(a), \qquad \phi \in X, \ a \geq 0. \tag{2.3}$$

The function $\beta(a)$ is the *division modulus* and is related to the distribution of cell division ages $\rho(a)$ by the formulas $\beta(a) = \rho(a)/\alpha(a)$, where $\alpha(a) = \int_a^\infty \rho(b)db$ is the fraction of cells undivided by age a. The function $\mu(a)$ is the *mortality modulus* and is related to the distribution of cell mortality ages by the formulas $\mu(a) = \eta(a)/\zeta(a)$, where $\zeta(a) = \int_a^\infty \eta(b)db$ is the fraction of cells that have not died by age a. The partial differential equation (2.1) accounts for the changes in population as a result of the aging of cells, their rates of division, and their rates of mortality. The boundary condition (2.2) relates the birth rate of daughter cells $p(0,t)$ at time t to the division of mother cells of all possible ages as modulated by the division modulus $\beta(a)$. The initial condition (2.3) prescribes the age distribution ϕ of cells at time 0. We illustrate the behavior of the solution $p(a,t)$ of (2.1)–(2.3) for a particular example in Figures 5–8.

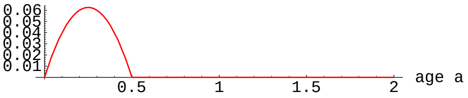

Fig. 5. The initial value for Example 2.1: $\phi(a) = \max[0, a(.5 - a)]$ for $a \geq 0$

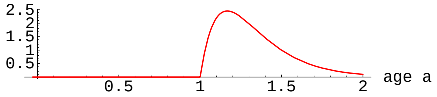

Fig. 6. The division modulus for Example 2.1: $\beta(a) = 0, 0 \leq a \leq 1, \beta(a) = 40(a-1)e^{-6(a-1)}, a < 1$, and $\alpha(a) = \exp(-\int_0^a \beta(b)db)$

Example 2.2. *The maturity structured cell population model.* Let $X = C[0,1]$ or $C_0[0,1]$ as in Example 1.1. Let $p(x,t)$ be the density of the population with respect to cell maturity x, where maturity relates to the physiological or morphological developmental level of the cell. The total population of cells with maturity levels between x_1 and x_2 at time t is $\int_{x_1}^{x_2} p(x,t)dx$ and the total cell population at time t is $\int_0^1 p(x,t)dx$. Maturity ranges from 0 to 1 and $\int_{x_1}^{x_2} \frac{1}{x}dx$ is the time required for an individual cell to mature from maturity x_1 to x_2. The parameter $\mu > 0$ controls cell loss or gain. Cells of any maturity level are capable of division, which is not modeled explicitly. The density $p(x,t)$ satisfies the initial value problem

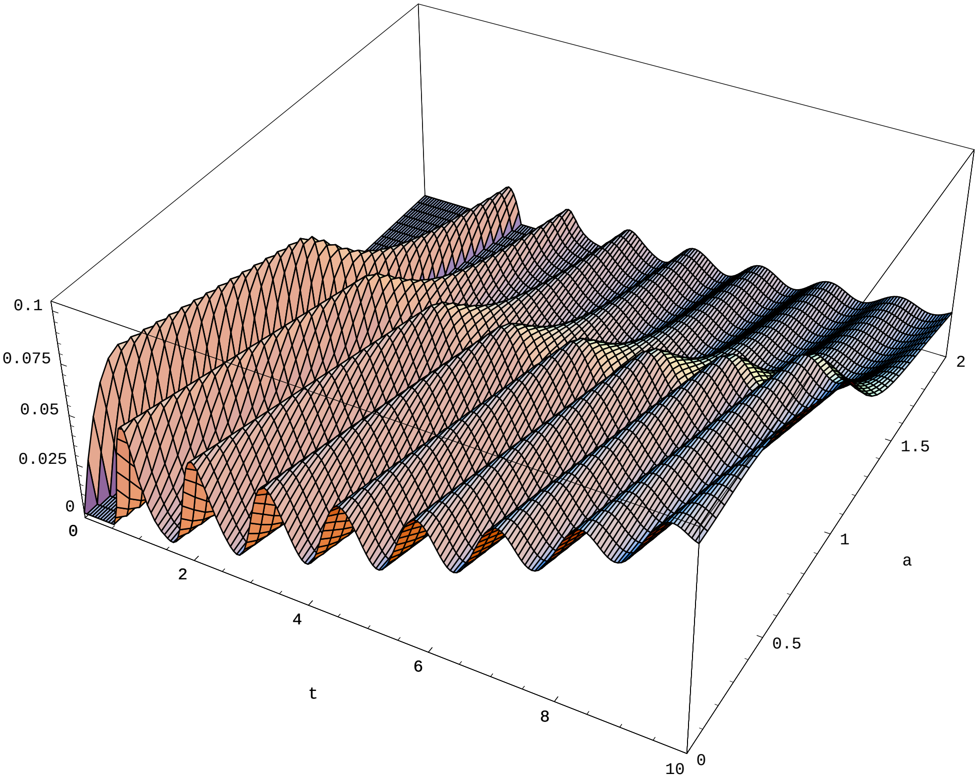

Fig. 7. The solution $p(a,t)$ of the age structured model (2.1)–(2.3) in Example 2.1 with the initial value ϕ as in Figure 5, $\beta(a)$ as in Figure 6, and the mortality modulus $\mu(a) \equiv .05$

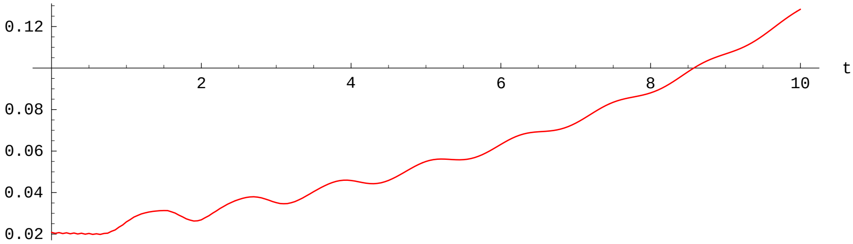

Fig. 8. The total population $P(t) = \int_0^\infty p(a,t)da$ for the solution $p(a,t)$ of the age structured model in Figure 7. Observe that $\lim_{t\to\infty} P(t) = \infty$.

$$\frac{\partial}{\partial t}p(x,t) + \frac{\partial}{\partial x}(xp(x,t)) = \mu p(x,t), \tag{2.4}$$

$$p(x,0) = \phi(x), \quad \phi \in X,\ 0 \le x \le 1. \tag{2.5}$$

The partial differential equation (2.4) accounts for the changes in population due to maturation of cells and cell division or mortality. The initial condition (2.5) prescribes the initial distribution of the population with respect to maturity at time 0.

EXAMPLE 2.3. *The cell cycle structured cell population model.* Let $0 < x_0 < 1$ and let $X = C_{x_0,1}[x_0, 1]$ as in Example 1.2. Let $p(x,t)$ be the density of the population with respect to position x in the cell cycle, where x ranges from x_0 to 1, so that a mother cell divides when she attains maturity 1 to produce two daughter cells with maturity x_0. The density $p(x,t)$ satisfies the initial-boundary value problem

$$\frac{\partial}{\partial t}p(x,t) + \frac{\partial}{\partial x}(xp(x,t)) = 0, \tag{2.6}$$

$$x_0 p(x_0,t) = 2p(1,t), \qquad t \geq 0, \tag{2.7}$$

$$p(x,0) = \phi(x), \qquad \phi \in X,\ x_0 \leq x \leq 1. \tag{2.8}$$

The partial differential equation (2.6) accounts for transition through the cell cycle. For simplicity, we assume no mortality of cells. The boundary condition (2.7) accounts for the mitotic process and the initial condition (2.8) accounts for the initial distribution of cells in the cell cycle.

EXAMPLE 2.4. *The size structured cell population model.* Let $0 < x_0 < x_1 < 2x_0$, and let $X = L^1(x_0/2, x_1)$ be the Banach space of Lebesgue integrable functions on $(x_0/2, x_1)$. Let $p(x,t)$ be the density of the population with respect to size x. The density $p(x,t)$ satisfies the initial-boundary value problem

$$\frac{\partial}{\partial t}p(x,t) + \frac{\partial}{\partial x}(\gamma(x)p(x,t)) = -(\beta(x) + \mu(x))p(x,t) + 4\beta(2x)p(2x,t), \tag{2.9}$$

$$p(x_0/2,t) = 0, \qquad t \geq 0, \tag{2.10}$$

$$p(x,0) = \phi(x), \qquad \phi \in X,\ x_0/2 < x < x_1. \tag{2.11}$$

It is assumed that the minimum size of a mother cell at division is x_0 and the maximum is x_1. The condition $x_1/2 < x_0$ assures that every newborn cell must grow for some time before it can divide. It is also assumed that size is conserved during cell division and that each of the two daughter cells inherits exactly one-half the size of the mother cell.

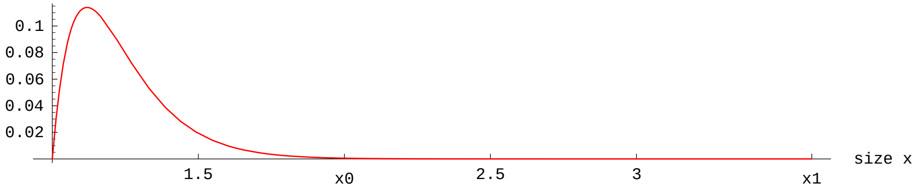

Fig. 9. The initial value $\phi(x) = (x - \frac{x_0}{2})(x_1 - x)\exp[-8.0(x - \frac{x_0}{2})]$, $\frac{x_0}{2} \leq x \leq x_1$, for Example 2.4 with $x_0 = 2.0$ and $x_1 = 3.6$

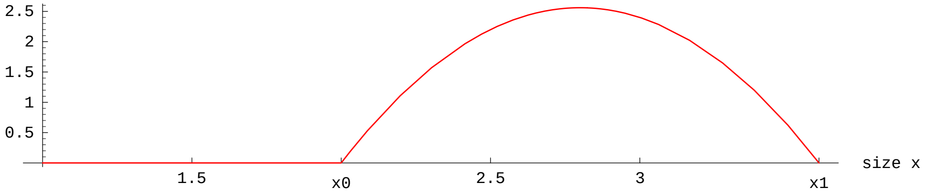

Fig. 10. The division modulus $\beta(x) = 4.0(x - x_0)(x_1 - x)), x_0 \leq x \leq x_1$, for Example 2.4 with $x_0 = 2.0$ and $x_1 = 3.6$

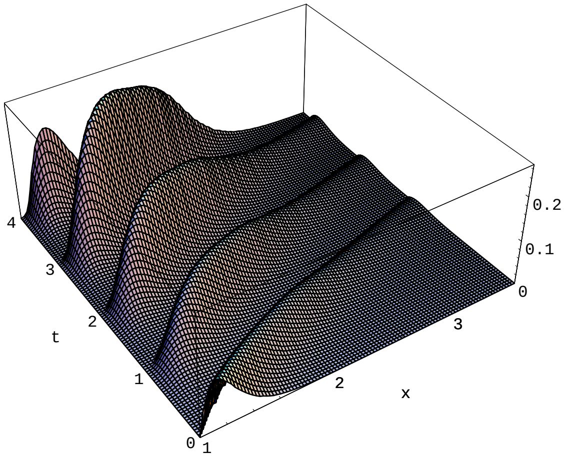

Fig. 11. The solution $p(x,t)$ of the size structured model (2.9)–(2.11) in Example 2.4 with the initial value ϕ as in Figure 9, $\beta(x)$ as Figure 10, the mortality modulus $\mu(x) \equiv 0$, and the growth modulus $\gamma(x) = (\log 2.0)x$

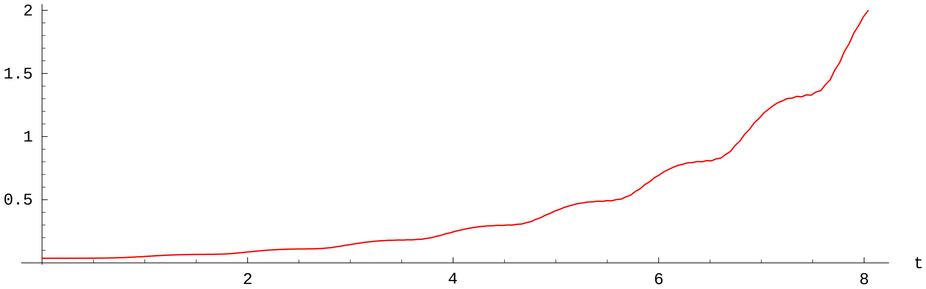

Fig. 12. The total population $P(t) = \int_{x_0/2}^{x_1} p(x,t)dx$ for the solution $p(x,t)$ of the size structured model in Figure 11. Observe that $\lim_{t\to\infty} P(t) = \infty$.

In equation (2.9) $\gamma(x)$ is the *size-specific modulus of cell growth*, $\beta(x)$ the *size-specific modulus of cell division*, and $\mu(x)$ the *size-specific modulus of cell mortality.* We illustrate the behavior of the solution $p(x,t)$ of model (2.9)–(2.11) for a particular example in Figures 9–12.

Example 2.5. *The age structured cell population model with quiescence.* Let $X = L^1(0,a_1)$ and let $p(a,t)$ and $q(a,t)$ be the densities of proliferating and quiescent cells, respectively, with respect to cell age a, where a_1 is the maximum age of cell division (older cells do not contribute to cell renewal). In this model proliferating cells are capable of entering a quiescent state at points in the cell cycle, as well as returning to the proliferating state from quiescence. The densities satisfy the initial-boundary value problem

$$\frac{\partial}{\partial t}p(a,t) + \frac{\partial}{\partial a}p(a,t) = -\beta(a)p(a,t) - \sigma(a)p(a,t) + \tau(a)q(a,t), \tag{2.12}$$

$$\frac{\partial}{\partial t}q(a,t) + \frac{\partial}{\partial a}q(a,t) = \sigma(a)p(a,t) - \tau(a)q(a,t), \tag{2.13}$$

$$p(0,t) = 2\int_0^{a_1} \beta(a)p(a,t)da, \qquad t \geq 0, \tag{2.14}$$

$$q(0,t) = 0, \qquad t \geq 0, \tag{2.15}$$

$$p(a,0) = \phi(a), \qquad \phi \in X,\ a \in (0,a_1) \tag{2.16}$$

$$q(a,0) = \psi(a), \qquad \psi \in X,\ a \in (0,a_1). \tag{2.17}$$

The division rate is modulated by $\beta(a)$ and the transition rates from the proliferating state to the quiescent state and conversely are modulated by $\sigma(a)$ and $\tau(a)$, respectively. We assume that division is the only cause of cell loss, only proliferating cells divide, and all daughter cells are born into the proliferating state.

EXAMPLE 2.6. *The size structured cell population model with quiescence.* Let $0 < x_0 < x_1 < 2x_0$, let $X = L^1(x_0/2, x_1)$, let $p(x,t)$ be the size density of proliferating cells as in Example 2.4, and let $q(x,t)$ be the size density of quiescent cells. The densities satisfy the initial-boundary value problem

$$\frac{\partial}{\partial t}p(x,t) + \frac{\partial}{\partial x}(\gamma(x)p(x,t)) = -(\beta(x)+\mu(x))p(x,t) + 4\beta(2x)p(2x,t) - \sigma(x)p(x,t) + \tau(x)q(x,t), \tag{2.18}$$

$$\frac{\partial}{\partial t}q(x,t) = -(\nu(x)+\tau(x))q(x,t) + \sigma(x)p(x,t), \tag{2.19}$$

$$p(x_0/2,t) = 0, \qquad t \geq 0, \tag{2.20}$$

$$p(x,0) = \phi(x), \qquad \phi \in X,\ x_0/2 < x < x_1, \tag{2.21}$$

$$q(x,0) = \psi(x), \qquad \phi \in X,\ x_0/2 < x < x_1. \tag{2.22}$$

The functions $\gamma(x), \beta(x), \mu(x)$,and $\nu(x)$ are the size specific *moduli of growth, division, mortality of proliferating cells, and mortality of quiescent cells*, respectively. Cells transit to and from the proliferating and quiescent states with size dependent *transition moduli* $\sigma(x)$ and $\tau(x)$. Cells in the quiescent state do not divide and do not grow.

Another version of size structured cell population dynamics with quiescence is the initial-boundary problem:

$$\frac{\partial}{\partial t}p(x,t) + \frac{\partial}{\partial x}(\gamma(x)p(x,t)) = -(\beta(x)+\mu(x))p(x,t) + 2(2-\rho(x))\beta(2x)p(2x,t) + \tau(x)q(x,t), \tag{2.18$'$}$$

$$\frac{\partial}{\partial t}q(x,t) = -(\nu(x)+\tau(x))q(x,t) + 2\rho(x)\beta(2x)p(2x,t), \tag{2.19$'$}$$

$$p(x_0/2,t) = 0, \qquad t \geq 0, \tag{2.20$'$}$$

$$p(x,0) = \phi(x), \qquad \phi \in L^1(x_0/2, x_1), \tag{2.21$'$}$$

$$q(x,0) = \psi(x), \qquad \phi \in L^2(x_0/2, x_1/2). \tag{2.22$'$}$$

The functions $\gamma(x), \beta(x), \tau(x), \mu(x)$, and $\nu(x)$ are as above. Cells transit from the proliferating state to the quiescent state only at the moment of division with size-dependent *transition modulus* $\rho(x)$. An illustration of model (2.18′)–(2.22′) is given in Figure 13 and Figure 14.

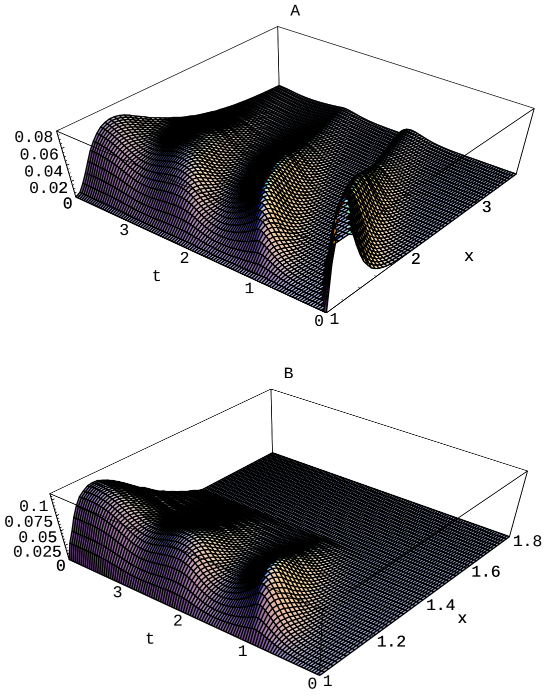

Fig. 13. The solution of the size structured model with quiescence $(2.18')$–$(2.22')$ in Example 2.6. The initial function $\phi(x)$ for the proliferating class is the same as in Figure 9 and the division modulus $\beta(x)$ is the same as in Figure 10. The growth modulus $\gamma(x) = (\log 2.0)x$. The initial function for the quiescent class is $\psi(x) \equiv 0$, the mortality moduli are $\mu \equiv 0$ and $\nu \equiv 0$, and the transition moduli are $\tau(x) \equiv 2.0$ and $\rho(x) \equiv 2.0$. A. The proliferating class $p(x,t)$. B. The quiescent class $q(x,t)$.

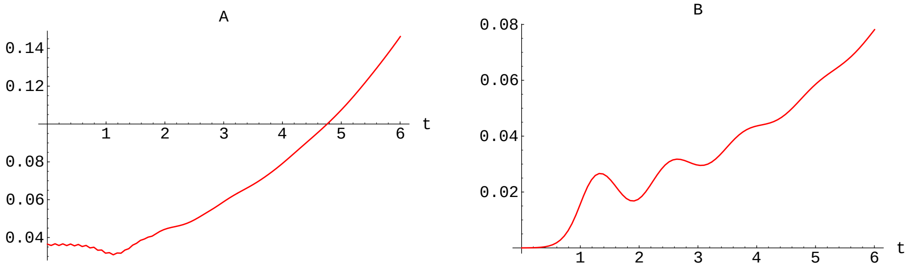

Fig. 14. The total populations of the size structured model with quiescence in Figure 13. A. $P(t) = \int_{x_0/2}^{x_1} p(x,t)dx$. B. $Q(t) = \int_{x_0/2}^{x_1/2} q(x,t)dx$. Observe that $\lim_{t\to\infty} P(t) = \lim_{t\to\infty} Q(t) = \infty$.

Example 2.7. *The age structured cell population model with telomere loss.* Let $X = L^1((0,a_1);\mathbf{R}^{N+1})$ with norm

$$\|\vec{\phi}\| = \sum_{j=1}^{N} \int_0^{a_1} |\phi_j(a)|da, \qquad \vec{\phi} \in X.$$

In this model ends of chromosomes, called telomeres, shorten each time a cell divides and when a critical number is reached no further divisions occur. The model is formulated as the system of linear partial differential equations

$$\frac{\partial}{\partial t}p_j(a,t) + \frac{\partial}{\partial a}p_j(a,t) = -\beta_j(a)p_j(a,t), \qquad j = 0, \dots N, \tag{2.23}$$

$$p_j(0,t) = 2\sum_{k=j}^{N} p_{jk} \int_0^{a_1} \beta_k(a)p_k(a,t)da, \qquad t \geq 0, \tag{2.24}$$

$$p_j(a,0) = \phi_j(a), \qquad j = 0, \dots, N, \ \vec{\phi} = [\phi_0, \dots, \phi_N]^t \in X, \ a \in (0, a_1). \tag{2.25}$$

In the model $p_j(a,t)$ is the density of cells with age a at time t and in the j telomere state, $\beta(a)$ is the *age-specific division modulus* (it is assumed that the only loss of cells is due to cell division), every cell must divide by the maximum age a_1, and p_{jk} represents the probability for a cell in the k^{th} telomere state to produce by division a cell in the j^{th} telomere state. It is assumed that a mother cell in the j^{th} state, $j = 1, 2, \dots, N$ produces one daughter cell in the j^{th} state and one daughter cell in some lower state. Lastly, it is assumed that a mother cell in the 0^{th} state produces one daughter cell in the 0^{th} state and one daughter cell which does not divide. The loss of telomeres is hypothesized by some cell biologists as an explanation for the finite proliferative capacity of cell lines.

EXAMPLE 2.8. *The phenotype structured cell population model.* Let $0 \leq y_1 < y_2$ and let $X = L^1(y_1, y_2)$. Let $p(y,t)$ be the density of the population with respect to a phenotype property y, which varies continuously from y_1 to y_2. It is assumed that the population is evolving over time and that the evolution of phenotype is influenced by selection and mutation. The density $p(y,t)$ satisfies the initial-boundary value problem

$$\frac{\partial}{\partial t}p(y,t) = \alpha^2 \frac{\partial^2}{\partial y^2}p(y,t) + \mu(y)p(y,t), \tag{2.26}$$

$$\frac{\partial}{\partial y}p(y_1,t) = \frac{\partial}{\partial y}p(y_2,t) = 0, \qquad t > 0, \tag{2.27}$$

$$p(y,0) = \phi(y), \qquad \phi \in X, \ y_1 < y < y_2. \tag{2.28}$$

The term $\alpha^2 \frac{\partial^2}{\partial y^2}p(y,t)$ in (2.26) represents the random mutation of phenotype within the population, which is modeled as a diffusion process with diffusion coefficient α^2. The term $\mu(y)p(y,t)$ represents selection modulated by the phenotype-specific modulus $\mu(y)$. If $\mu(y)$ is positive, then individuals with this phenotype y will increase, whereas if $\mu(y)$ is negative, they will decrease. The boundary conditions in (2.27) prohibit mutation of phenotype through the boundaries y_1 and y_2.

3. Asymptotic behavior of structured populations. The models of Section 2 correspond to strongly continuous semigroups $T(t), t \geq 0$ of operators in Banach spaces X, which are the state spaces for the population densities. For an initial value ϕ in X, $T(t)\phi$ is a solution of the partial differential equation of the model, at least in some generalized sense. An important issue for these models is the *asymptotic behavior* of solutions, that is, the behavior of the solutions as time t advances. In certain cases this behavior is very regular, and the solutions stabilize in some sense as $t \to \infty$. In other cases the behavior is periodic or oscillatory in t. In some cases the behavior is very irregular and solutions exhibit *sensitive dependence on initial values* or *chaotic* behavior. Such irregular behavior of solutions means that for an initial value ϕ_1, a small perturbation ϕ_2 from it may have the property that $T(t)\phi_1$ and $T(t)\phi_2$ may ultimately be far apart.

DEFINITION 3.1. Let $T(t), t \geq 0$ be a strongly continuous semigroup of linear or nonlinear operators in the subset Y of the Banach space X and let $\phi \in Y$. ϕ is *stable* if and only if for every $\epsilon > 0$ there exists $\delta > 0$ such that if $t \geq 0, \psi \in Y$, and $\|\phi - \psi\| < \delta$, then $\|T(t)\phi - T(t)\psi\| < \epsilon$. ϕ is *unstable* if and only if it is not stable. $T(t), t \geq 0$ has *sensitive dependence on initial conditions* if and only if every $\phi \in Y$ is unstable. ϕ is an *equilibrium* if and only if $T(t)\phi = \phi$ for $t \geq 0$. An equilibrium ϕ is *locally exponentially asymptotically stable* if and only if there exist $M, \epsilon, \delta > 0$ such that $\|T(t)\phi - T(t)\psi\| < Me^{-\epsilon t}$ for $t \geq 0$ and $\|\psi - \phi\| < \delta$. An equilibrium is *globally exponentially asymptotically stable* if and only if there exist $M, \epsilon > 0$ such that $\|T(t)\phi - T(t)\psi\| < Me^{-\epsilon t}$ for $t \geq 0$ and $\psi \in Y$.

DEFINITION 3.2. Let $T(t), t \geq 0$ be a strongly continuous semigroup of bounded linear operators in the Banach space X with infinitesimal generator A. $T(t), t \geq 0$ has *asymptotic exponential growth* with *intrinsic growth constant* λ_1 if and only if there is a nonzero projection P in X such that

$$\lim_{t \to \infty} e^{-\lambda_1 t} T(t) = P. \tag{3.1}$$

If the convergence in (3.1) holds in $B(X)$, then the asymptotic exponential growth is said to be *uniform*. If the convergence in (3.1) holds point-wise in X for every $\phi \in X$, then the asymptotic exponential growth is said to be *strong*. If the projection P has finite dimensional range, then the $T(t), t \geq 0$ is said to have *asynchronous exponential growth* and P is called the *spectral projection*. The *rank* of P is the dimension of its range space.

Asynchronous exponential growth is a very regular dynamical behavior, since it means that after multiplication by an exponential factor in time, the solutions stabilize to a finite dimensional space. If λ_1 is negative, then all solutions converge to 0. If λ_1 is positive, then solutions may converge to ∞, but in this case there is still a stabilization masked by the exponential factor $e^{\lambda_1 t}$. If the finite dimensional space is 1-dimensional, then the solutions converge, after multiplication by the exponential factor $e^{-\lambda_1 t}$, to a constant depending on the initial value times a unique element in X.

The following definitions will be used to establish necessary and sufficient conditions for asynchronous exponential growth.

DEFINITION 3.3. Let A be a linear operator in the Banach space X with densely defined domain $D(A)$. The *resolvent set* of A, denoted $\rho(A)$, is the set of complex numbers λ such that $(\lambda I - A)^{-1} \in B(X)$. The *spectrum* of A, denoted $\sigma(A)$, is the complement of $\rho(A)$ in the complex plane $\mathbf{C}$. For $\lambda \in \sigma(A)$, the *generalized eigenspace* of λ is the smallest closed subspace of X containing $\cup_{k=1}^{\infty} N((\lambda I - A)^k)$, where N denotes the null space. The *essential spectrum* of A, denoted $E\sigma(A)$, is $\{\lambda \in \sigma(A)$: either the range $R(\lambda I - A)$ is not closed, λ is a limit point of $\sigma(A)$, or the generalized eigenspace of λ is infinite dimensional$\}$. The *spectral bound* of A, denoted $sb(A)$, is $\sup\{\mathrm{Re}\,\lambda : \lambda \in \sigma(A)\}$. The *peripheral spectrum* of A, denoted $\sigma_0(A)$ is $\{\lambda_1 \in \sigma(A) : \mathrm{Re}\,\lambda_1 = sb(A)\}$. For $A \in B(X)$

the *measure of noncompactness* of A, denoted $\alpha[A]$, is $\inf\{\epsilon > 0 : A(B)$ can be covered by a finite number of balls of radius $\leq \epsilon\}$, where B is the unit ball of X.

THEOREM 3.1. *Let $T(t), t \geq 0$ be a strongly continuous semigroup of bounded linear operators with infinitesimal generator A in the Banach space X.*

$$\omega_0(A) := \lim_{t\to\infty} \log(|T(t)|)/t \text{ exists;} \tag{3.2}$$

$$\omega_1(A) := \lim_{t\to\infty} \log(\alpha[T(t)])/t \text{ exists;} \tag{3.3}$$

$$\text{if } \gamma > \omega_0(A), \text{ then } \exists M_\gamma \geq 1 \text{ such that } |T(t)| \leq M_\gamma e^{\gamma t}; \tag{3.4}$$

$$\sup_{\lambda\in\sigma(A)} \operatorname{Re}\lambda \leq \omega_0(A) \text{ and } \sup_{\lambda\in E\sigma(A)} \operatorname{Re}\lambda \leq \omega_1(A); \tag{3.5}$$

$$\omega_0(A) = \max\{\omega_1(A), \sup_{\lambda\in\sigma(A)-E\sigma(A)} \operatorname{Re}\lambda\}. \tag{3.6}$$

THEOREM 3.2. *Let $T(t), t \geq 0$ be a strongly continuous semigroup of bounded linear operators with infinitesimal generator A in the Banach space X. $T(t), t \geq 0$ has asynchronous exponential growth with intrinsic growth constant λ_1 if and only if (i) $\omega_1(A) < \omega_0(A)$, (ii) $\sigma_0(A) = \{\lambda_1\}$, and (iii) λ_1 is a simple pole of $(\lambda I - A)^{-1}$.*

REMARK 3.1. The conditions (i)–(iii) in Theorem 3.2 mean that λ_1 is a *dominant eigenvalue* of the infinitesimal generator A. That is, there exists $\phi_1 \in X, \phi_1 \neq 0$ such that $A\phi_1 = \lambda_1\phi_1$ and if λ is any other eigenvalue of A, then $\operatorname{Re}\lambda < \lambda_1$. Further, the projection P in (3.1) is a projection onto the generalized eigenspace of λ_1, which is finite dimensional.

THEOREM 3.3. *Let $T(t), t \geq 0$ be a strongly continuous semigroup of positive linear operators in the Banach lattice X (that is, $T(t)\phi \in X_+$ for every $\phi \in X_+$, where X_+ is the positive cone of X). Let $\omega_1(A) < \omega_0(A)$ and let $T(t), t \geq 0$ be irreducible (that is, for every $\phi \neq 0$ in X_+ and for every $\phi^* \neq 0$ in the positive cone X_+^* of the dual space X^*, there exists $t_0 > 0$ such that $\phi^*(T(t_0)\phi) > 0$). Then $T(t), t \geq 0$ has asynchronous exponential growth with intrinsic growth constant $\omega_0(A) = sb(A)$ and 1-dimensional spectral projection P in X, where $\phi^*(P\phi) > 0$ for every $\phi \in X_+ - \{0\}$ and every $\phi^* \in X_+^* - \{0\}$.*

DEFINITION 3.4. Let $T(t), t \geq 0$ be a strongly continuous semigroup of bounded linear operators in the Banach space X. $T(t), t \geq 0$ is a *rotation* semigroup with *period* $p > 0$ if and only if $T(p) = I$. $T(t), t \geq 0$ has *periodic exponential growth* with *intrinsic growth constant* λ_1 and *period* $p > 0$ if and only if there is a nonzero projection P in X such that

$$\lim_{t\to\infty} (e^{-\lambda_1 t}T(t) - R(t)P) = 0 \tag{3.7}$$

where $R(t), t \geq 0$, is a rotation semigroup in $P(X)$ with period p. If the convergence in (3.7) holds in $B(X)$, then the periodic exponential growth is said to be *uniform*. If it holds point-wise in X for every $\phi \in X$, then it is said to be *strong*.

DEFINITION 3.5. Let $T(t), t \geq 0$ be a strongly continuous semigroup of bounded linear operators in the Banach space X. $T(t), t \geq 0$ has *polynomial exponential growth* with *intrinsic growth constant* λ_1 if and only if there exists a positive integer N such that

$$\lim_{t\to\infty} t^{-N}e^{-\lambda_1 t}T(t) = P \tag{3.8}$$

where P is a nonzero bounded linear operator in X. If the convergence in (3.8) holds in $B(X)$, then the polynomial exponential growth is said to be *uniform*. If it holds point-wise in X for every $\phi \in X$, then it is said to be *strong*. If the operator P has finite dimensional range, then the polynomial exponential growth is said to be *asynchronous*. The *order* of the polynomial exponential growth is N.

Definitions 3.2, 3.4, and 3.5 apply to linear dynamical systems that are regular in time. Definitions 3.6 and 3.7 below apply to linear and nonlinear dynamical systems that are irregular in time, that is, do not stabilize to equilibrium or periodicity.

DEFINITION 3.6. Let $T(t), t \geq 0$ be a strongly continuous semigroup of linear or nonlinear operators in the subset Y of the Banach space X. $T(t), t \geq 0$ is *topologically transitive in* Y if and only if for any open sets U and V in Y and $t > 0$, there exist $\phi \in U$ and $t_1 > t$ such that $T(t_1)\phi \in V$. $T(t), t \geq 0$ is *hypercyclic in* Y if and only if there exist ϕ in Y such that $\{T(t)\phi : t \geq 0\}$ is dense in Y.

THEOREM 3.4. *Let* $T(t), t \geq 0$ *be a strongly continuous semigroup of linear or nonlinear operators in the subset* Y *of the separable Banach space* X*, where* $Y = \overline{\mathcal{O}}$ *and* $\mathcal{O}$ *is an open subset of* X*.* $T(t), t \geq 0$ *is topologically transitive in* Y *if and only if* $T(t), t \geq 0$ *is hypercyclic.*

DEFINITION 3.7. Let $T(t), t \geq 0$ be a strongly continuous semigroup of nonlinear operators in the subset Y of the separable Banach space X. $T(t), t \geq 0$ is *chaotic in* Y if and only if $T(t), t \geq 0$ is topologically transitive in Y and the set of *periodic points* $\{\phi \in Y :$ there exists $t_\phi > 0$ such that $T(t_\phi)\phi = \phi\}$ is dense in Y.

THEOREM 3.5. *Let* $T(t), t \geq 0$ *be a strongly continuous semigroup of nonlinear operators in the separable Banach space* X*. If* $T(t), t \geq 0$ *is chaotic in* X*, then* $T(t), t \geq 0$ *has sensitive dependence on initial values.*

THEOREM 3.6. *Let* $T(t), t \geq 0$ *be a strongly continuous semigroup of bounded linear operators in the separable Banach space* X*. Let*

$$X_0 = \{\phi \in X : \lim_{t \to \infty} T(t)\phi = 0\}, \tag{3.9}$$

$$X_\infty = \{\phi \in X : \textit{for all } \epsilon > 0 \textit{ there exists } \psi \in X \textit{ and } t > 0 \textit{ such that } \|\psi\| < \epsilon \textit{ and } \|T(t)\psi - \phi\| < \epsilon\}, \tag{3.10}$$

$$X_p = \{\phi \in X : \textit{there exists } t_\phi > 0 \textit{ such that } T(t_\phi)\phi = \phi\}. \tag{3.11}$$

If X_0 *and* X_∞ *are dense in* X*, then* $T(t), t \geq 0$ *is hypercyclic in* X*. If* X_0, X_∞*, and* X_p *are dense in* X*, then* $T(t), t \geq 0$ *is chaotic in* X*.*

The theorems below apply to nonlinear structured population models.

THEOREM 3.7. *Let* $T(t), t \geq 0$ *be a strongly continuous semigroup of bounded linear operators in the Banach space* X *satisfying* $|T(t)| \leq Me^{\omega t}, t \geq 0$*, where* $\omega < 0$ *and let* $\phi_1 \in X$*. Then*

$$S(t)\phi = T(t)\phi + \int_0^t T(s)\phi_1 ds, \qquad \phi \in X, t \geq 0$$

defines a strongly continuous semigroup of nonlinear operators $S(t), t \geq 0$ *in* X *with* *infinitesimal generator* $B\phi = A\phi_1 + \phi_1, D(B) = D(A)$, *and*

$$\lim_{t\to\infty} S(t)\phi = \int_0^\infty T(t)\phi dt = -A^{-1}\phi_1 \quad \forall \phi \in X.$$

Further, if $\phi \in D(A)$, *then* $u(t) := S(t)\phi, t \geq 0$ *is the unique solution of the initial value problem* $u'(t) = Au(t) + \phi_1, t \geq 0$, $u(0) = \phi$.

THEOREM 3.8. *Let* $T(t), t \geq 0$ *be a strongly continuous semigroup of bounded linear operators in the Banach space* X *satisfying* $|T(t)| \leq Me^{\omega t}, t \geq 0$, *where* $\omega \in \mathbf{R}$. *Let* H *be a nonlinear Lipschitz continuous operator in* X *with Lipschitz constant* $|H|_{Lip}$ *(that is,* $\|H(\phi_1) - H(\phi_2)\| \leq |H|_{Lip}\|\phi_1 - \phi_2\|$ *for all* $\phi_1, \phi_2 \in X$*), and let* $H(0) = 0$. *Then, for each* $\phi \in X$, *there exists a unique solution* $u(t)$ *of the integral equation*

$$u(t) = T(t)\phi + \int_0^t T(t-s)H(u(s))ds, \quad t \geq 0. \tag{3.12}$$

Further, if $S(t)\phi := u(t), t \geq 0$, *then* $S(t), t \geq 0$ *is a strongly continuous semigroup of nonlinear Lipschitz continuous operators in* X *satisfying* $|S(t)|_{Lip} \leq Me^{(\omega + M|H|_{Lip})t}, t \geq 0$, *and the infinitesimal generator of* $S(t), t \geq 0$ *is* $B\phi = A\phi + H(\phi)$ *for all* $\phi \in D(A) = D(B)$.

REMARK 3.2. The solution $u(t)$ of (3.12) is called a *mild solution* of the initial value problem

$$u'(t) = Au(t) + H(u(t)), \quad t \geq 0, \ u(0) = \phi. \tag{3.13}$$

The mild solution (3.12) may not satisfy (3.13) without further assumptions on the nonlinear operator H or the initial value ϕ. If it does satisfy (3.13), then it is called a *strong solution* of (3.13).

THEOREM 3.9. *Let* X *be a Banach lattice, let* $T(t), t \geq 0$ *be a strongly continuous semigroup of positive linear operators in* X_+, *let* A *be the infinitesimal generator of* $T(t), t \geq 0$, *let* $F \in X_+^*$, *and let* $S(t), t \geq 0$ *be the strongly continuous semigroup of nonlinear operators in* X_+ *as in Example 1.3. If* $\phi \in D(A) \cap X_+$, *then* $u(t) := S(t)\phi, t \geq 0$ *is the unique solution of the initial value problem*

$$u'(t) = Au(t) - F(u(t))u(t), \quad t \geq 0, \ u(0) = \phi.$$

(i) *If* $T(t), t \geq 0$ *has asymptotic or polynomial exponential growth with* λ_1 *and* P *as in (3.1) or (3.8), then*

$$\lim_{t\to\infty} S(t)\phi = 0 \quad \text{for all } \phi \in X_+ \text{ if } \lambda_1 < 0, \tag{3.14}$$

$$\lim_{t\to\infty} S(t)\phi = \lambda_1 P\phi / FP\phi \quad \text{for all } \phi \in X_+ \text{ such that } FP\phi > 0 \text{ if } \lambda_1 > 0. \tag{3.15}$$

(ii) *If* $T(t), t \geq 0$ *has periodic exponential growth with intrinsic growth constant* $\lambda_1 > 0$, *period* p, *rotation semigroup* $R(t), t \geq 0$, *and projection* P *as in Definition 3.4, then*

$$\lim_{t\to\infty} (S(t)\phi - W(t)\phi) = 0 \quad \text{for all } \phi \in X_+ \text{ such that } FP\phi > 0, \text{ where} \tag{3.16}$$

$$W(t)\phi = \frac{(e^{\lambda_1 p} - 1)e^{\lambda_1 t}R(t)P\phi}{F(\int_0^p e^{\lambda_1 s}R(s)P\phi ds) + (e^{\lambda_1 p} - 1)F(\int_0^t e^{\lambda_1 s}R(s)P\phi ds)} \tag{3.17}$$

for $0 \leq t \leq p$ *and* $W(t)\phi$ *is defined by periodicity for* $t > p$.

Definition 3.8. Let X be a Banach space, let K be a mapping from X to X, and let $\hat{\phi} \in X$. K is *Fréchet differentiable* at $\hat{\phi}$ if and only if there exists a bounded linear operator L in X and a continuous increasing function b from $[0,\infty)$ to $[0,\infty)$ satisfying $b(0)=0$, and $K\phi = K\hat{\phi} + L(\phi-\hat{\phi}) + o(\phi-\hat{\phi})$ for all $\phi \in X$, where o is a function from X to X such that $\|o(\phi)\| \leq b(r)$ for all $\phi \in X$ such that $\|\phi\| \leq r$. In this case L is denoted by $K'(\hat{\phi})$. If K is Fréchet differentiable at each $\hat{\phi} \in X$, then K is *Lipschitz continuously Fréchet differentiable on bounded sets* if and only if $\|K'(\hat{\phi}_1) - K'(\hat{\phi}_2)\| \leq c(r)\|\hat{\phi}_1 - \hat{\phi}_2\|$ for all $\hat{\phi}_1, \hat{\phi}_2 \in X$ such that $\|\hat{\phi}_1\|, \|\hat{\phi}_2\| \leq r$, where c is a continuous increasing function from $[0,\infty)$ to $[0,\infty)$.

Theorem 3.10. *Let X be a Banach space, let $T(t), t \geq 0$ be a strongly continuous semigroup of positive linear operators in X, let A be the infinitesimal generator of $T(t), t \geq 0$, let K be a nonlinear operator from X to X, let K be Lipschitz continuously Fréchet differentiable on bounded sets of X, and let $\phi \in X$. There exists a maximal interval of existence $[0, t_\phi)$ and a unique continuous function u from $[0, t_\phi)$ to X such that*

$$u(t) = T(t)\phi + \int_0^t T(t-s)K(u(s))ds, t \in [0, t_\phi), u(0) = \phi, \tag{3.18}$$

and either $t_\phi = \infty$ or $\limsup_{t \to t_\phi^-} \|u(t)\| = \infty$. Further, if $\phi \in D(A)$, then $u(t) \in D(A)$ and $u'(t) = Au(t) + K(u(t))$ for $t \in [0, t_\phi)$.

Theorem 3.11. *Let X be a Banach space, let $T(t), t \geq 0$ be a strongly continuous semigroup of positive linear operators in X, let A be the infinitesimal generator of $T(t), t \geq 0$, let K be a nonlinear operator from X to X, let K be Lipschitz continuously Fréchet differentiable on bounded sets, and for each $\phi \in X$ let $u(t;\phi)$ be the solution of the integral equation (3.18) on the maximal interval of existence $[0, t_\phi)$ as in Theorem 3.10. Let $\hat{\phi} \in X$ such that $A\hat{\phi} + K(\hat{\phi}) = 0$ and let $\hat{T}(t), t \geq 0$ be the strongly continuous semigroup of bounded linear operators in X with infinitesimal generator $\hat{A} := A + K'(\hat{\phi})$. If*

$$\max\{\omega_1(\hat{A}), \sup_{\lambda \in \sigma(\hat{A}) - E\sigma(\hat{A})} \operatorname{Re}\lambda\} < 0, \tag{3.19}$$

then there exists a neighborhood $N_{\hat{\phi}}$ of $\hat{\phi}$ such that $t_\phi = \infty$ for $\phi \in N_{\hat{\phi}}$ and $\hat{\phi}$ is a locally exponentially asymptotically stable equilibrium of $S(t), t \geq 0$, where $S(t)\phi := u(t;\phi), \phi \in N_{\hat{\phi}}, t \geq 0$.

Theorem 3.12. *Let X be a Banach lattice, let $T(t), t \geq 0$ be a strongly continuous semigroup of positive linear operators in X_+, let A be the infinitesimal generator of $T(t), t \geq 0$, let $F \in X_+^*$, and let $f \in X_+$. For each $\phi \in X_+$ there exists a unique solution u of the integral equation*

$$u(t) = T(t)\phi - \int_0^t T(t-s)F(u(s))u(s)ds + \int_0^t T(s)f ds, \qquad t \geq 0, \tag{3.20}$$

and $S(t)\phi := u(t;\phi), \phi \in X_+, t \geq 0$ defines a strongly continuous nonlinear semigroup in X_+ Further, if $T(t), t \geq 0$ has asynchronous exponential growth with intrinsic growth constant λ_1 and spectral projection P, and $FPf > 0$, then there exists a unique solution λ of the equation $\lambda = F((\lambda I - A)^{-1}f)$ such that $\lambda > \omega_0(A)$, and $\hat{\phi} := (\lambda I - A)^{-1}f$ is a *locally exponentially asymptotically stable equilibrium solution of the nonlinear semigroup* $S(t), t \geq 0$.

4. Applications to linear structured populations. In this section we apply the concepts in Section 3 to the linear models in Section 2.

EXAMPLE 4.1. *The age structured cell population model.* Let $X = L^1[0,\infty)$ and let $p(a,t)$ be the age density as in Example 2.1. Let β and $\mu \in L^\infty_+[0,\infty)$, the set of nonnegative essentially bounded measurable functions on $(0,\infty), \beta \not\equiv 0$. The initial-boundary value problem (2.1)–(2.3) has the solution semigroup $T(t), t \geq 0$ with infinitesimal generator A given by

$$(A\phi)(a) = -\phi'(a) - (\beta(a) + \mu(a))\phi(a), \qquad a \geq 0,$$
$$D(A) = \left\{\phi \in X : \phi' \in X, \phi(0) = 2\int_0^\infty \beta(a)\phi(a)da\right\}.$$

The operator A satisfies the hypothesis of Theorem 1.2 with $M = 1$ and $\omega = \|\beta\|_\infty + \|\mu\|_\infty$. The solution of (2.1)–(2.3) is $p(a,t) = (T(t)\phi)(a)$ for $\phi \in X$, at least in a generalized sense. The linear semigroup $T(t), t \geq 0$ also satifies the hypothesis of Theorem 3.2 with λ_1 the unique real-valued solution of the characteristic equation

$$1 = 2\int_0^\infty e^{-\lambda_1 a}\pi(a,0)\beta(a)da, \tag{4.1}$$

where

$$\pi(a,b) = \exp\left(-\int_b^a (\beta(u) + \mu(u))du\right).$$

The projection P in (3.1) has 1-dimensional range and is given by the formula

$$P(\phi)(a) = \frac{e^{-\lambda_1 a}\pi(a,0)\int_0^\infty \beta(b)e^{-\lambda_1 b}(\int_0^b e^{\lambda_1 u}\pi(b,u)\phi(u)du)db}{\int_0^\infty \beta(b)be^{-\lambda_1 b}\pi(b,0)db}. \tag{4.2}$$

The solutions $p(a,t)$ thus have asynchronous exponential growth. This means that the proportion of the cell population in any age range $[a_1, a_2]$ stabilizes as $t \to \infty$ in the sense that

$$\lim_{t\to\infty} \frac{\int_{a_1}^{a_2} p(a,t)da}{\int_0^\infty p(a,t)da} = \frac{\int_{a_1}^{a_2} (P\phi)(a)da}{\int_0^\infty (P\phi)(a)da}.$$

Since the projection P in (4.2) in 1-dimensional, the limit above is independent of the initial cell distribution ϕ. This property is observed in proliferating cell cultures, which lose synchrony of the initial age distribution after a few generations. The loss of the initial synchronization is due to dispersion of ages of division. In Figure 15 we illustrate asynchronous exponential growth for the example in Figures 7 and 8.

EXAMPLE 4.2. *The maturity structured cell population model.* As in Example 2.2 let $X = C[0,1]$ or $C_0[0,1]$, let $p(x,t)$ be the maturity density, and let $\mu > 0$. The generalized solution of equations (2.4) and (2.5) is given by $p(x,t) = (T(t)\phi)(x)$, where $(T(t)\phi)(x)$ is the strongly continuous semigroup of bounded linear operators given in Example 1.1. The asymptotic behavior of the solutions of this model depends on the value of μ. If

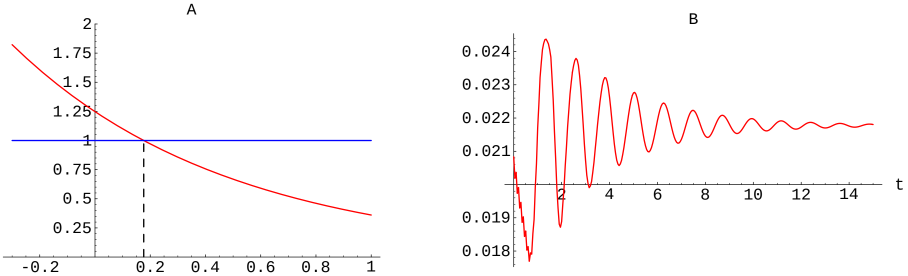

Fig. 15. A. The solution of the characteristic equation $1 = 2\int_0^\infty e^{-\lambda a}\pi(a,0)\beta(a)da$ at the intrinsic growth constant $\lambda_1 \approx .176467$. B. The graph of $e^{-\lambda_1 t}P(t)$ where $P(t)$ is the total population as in Figure 8.

$\mu < 1$, then $\lim_{t\to\infty} T(t)\phi = 0$ for all ϕ in X. If $\mu > 1$, then $T(t), t \geq 0$ is chaotic in the space $X = C_0[0,1]$.

Example 4.3. *The cell cycle structured cell population model.* Let $0 < x_0 < 1$, let $X = C_{x_0,1}[x_0,1]$, and let $p(x,t)$ be the population density as in Example 2.3. The generalized solution of equations (2.6)–(2.8) is given by $p(x,t) = (T(t)\phi)(x)$, where $(T(t)\phi)(x)$ is the strongly continuous semigroup of bounded linear operators as in Example 1.2. This semigroup has periodic exponential growth as in (3.7) with $\lambda_1 = -\ln 2/\ln x_0$, $p = -\ln x_0$, rotation semigroup $R(t) = e^{-\lambda_1 t}T(t), t \geq 0$, and projection $P = I$. Since $\lambda_1 > 0$, the population grows exponentially in time. The infinitesimal generator A of $T(t), t \geq 0$ (as in Example 1.5) has the property that $\sigma(A)$ consists of the infinitely many values $\{\lambda \in \mathbf{C} : \lambda = \lambda_1 \pm 2n\pi i/-\ln x_0, n = 0,1,\ldots\}$, so that $sb(A) = \omega_0(A) = \omega_1(A) = \lambda_1$. In this model there is no mechanism for dispersion of the cycle length and any initial synchronization of cells at the same point in the cell cycle is effectively doubled again and again through the overlapping generations. The periodic exponential behavior is illustrated in Figure 16 for the initial value in Figure 3.

Example 4.4. *The size structured cell population model.* Let $x_0 > 0$, let $x_1 > x_0$, let $X = L^1(x_0/2, x_1)$, and let $p(x,t)$ be the cell size density as in Example 2.4. Assume that $\beta(x)$ is continuous, positive on (x_0, x_1), and zero otherwise, $\mu(x)$ is continuous and nonnegative, and $\gamma(x)$ is continuously differentiable, positive, and satisfies $2\gamma(x) \neq \gamma(2x)$ for some $x \in (x_0/2, x_1)$. The generalized solution of (2.9)–(2.11) is $p(x,t) = (T(t)\phi)(x)$, where $T(t), t \geq 0$ is the semigroup of bounded linear operators in X with infinitesimal generator A given by

$$(A\phi)(x) = -(\gamma(x)\phi(x))' - (\beta(x)+\mu(x))\phi(x) + 4\beta(2x)\phi(2x), \qquad x \in (x_0/2, x_1),$$
$$D(A) = \{\phi \in X : -(\gamma(x)\phi(x))' \in X \text{ and } \phi(x_0/2) = 0\}.$$

The semigroup $T(t), t \geq 0$ satisfies the hypothesis of Theorem 3.3 with λ_1 the unique real-valued solution of the characteristic equation

$$1 = 2\int_{x_0}^{x_1} \frac{\beta(x)}{\gamma(x)} \exp\left(-\int_{x/2}^{x} \frac{\lambda_1 + \beta(y) + \mu(y)}{\gamma(y)}dy\right)dx. \tag{4.3}$$

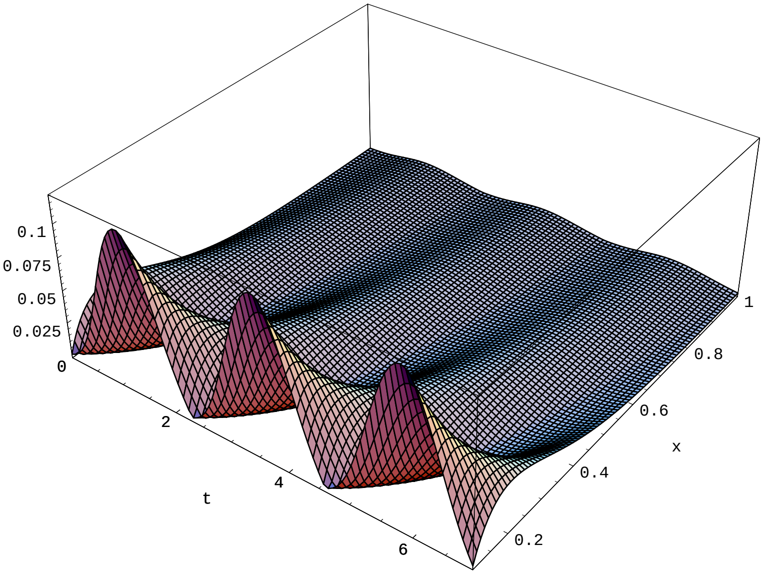

Fig. 16. The graph of $e^{-\lambda_1 t}(T(t)\phi)(x)$ for the trajectory $T(t)\phi$ in Figure 4 with the initial value ϕ as in Figure 3. The intrinsic growth constant is $\lambda_1 \approx .30103$ and the period is $p \approx 2.30259$.

The semigroup $T(t), t \geq 0$ thus has asynchronous exponential growth with intrinsic growth constant λ_1. In this case the projection P in (3.1) has 1-dimensional range, so that the proportion of the population in a given size range stabilizes as in Example 4.1. If $2\gamma(x) = \gamma(2x)$ for all $x \in (x_0/2, x_1)$, then $T(t), t \geq 0$ has periodic exponential growth with period $p = \int_{x_0/2}^{x_0} \frac{1}{\gamma(x)} dx$. In this case $\sigma_0(A)$ consists of infinitely many values on a vertical line through $\omega_0(A)$, and $\omega_0(A) = \omega_1(A)$. The condition $2\gamma(x) \neq \gamma(2x)$ for some $x \in (x_0/2, x_1)$ guarantees that the two daughter cells produced by a mother cell will not grow in exactly the same way as the mother cell would have grown if she had not divided. Thus, any initial synchronization of size structure is ultimately lost. The periodic case is illustrated in Figure 17, which is the same example as in Figures 11 and 12. In Figure 17 the size density divided by the total population $p(x,t)/P(t)$ is graphed and the periodic behavior is demonstrated.

EXAMPLE 4.5. *The age structured cell population model with quiescence.* Let $X = L^1(0,a_1) \times L^1(0,a_1)$, let $\beta, \sigma, \tau \in L^\infty_+(0,a_1), \sigma \not\equiv 0, \tau \not\equiv 0$, and let $p(a,t)$ and $q(a,t)$ be the densities of proliferating and quiescent cells, respectively, as in Example 2.5. The age densities correspond to a strongly continuous semigroup of bounded linear operators $T(t), t \geq 0$ in X given by the formula

$$T(t)\begin{pmatrix}\phi\\ \psi\end{pmatrix} = \begin{pmatrix}p(\cdot,t)\\ q(\cdot,t)\end{pmatrix}, \quad t \geq 0, \ \begin{pmatrix}\phi\\ \psi\end{pmatrix} \in X, \ t \geq 0.$$

The infinitesimal generator of $T(t), t \geq 0$ is

$$A\begin{pmatrix}\phi\\ \psi\end{pmatrix} = -\begin{pmatrix}\phi'\\ \psi'\end{pmatrix} + \begin{pmatrix}-\beta-\sigma & \tau\\ \sigma & -\tau\end{pmatrix}\begin{pmatrix}\phi\\ \psi\end{pmatrix}$$

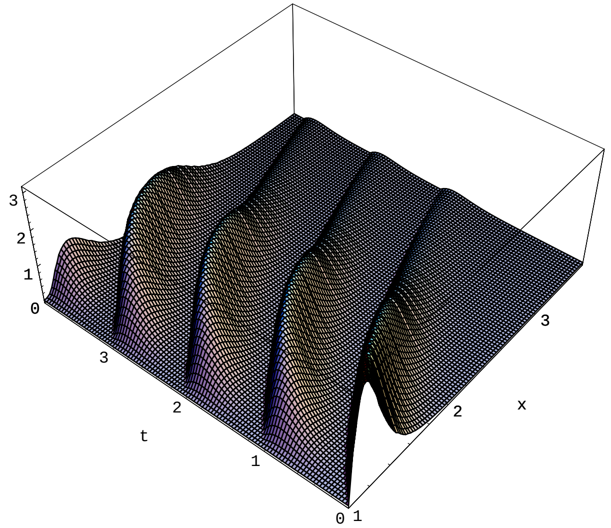

Fig. 17. The graph of $p(x,t)/P(t)$ for the solution of the model (2.9)–(2.11), where $p(x,t)$ is as in Figure 11, $P(t)$ is as in Figure 12, $\beta(x)$ is as in Figure 10, the mortality modulus is $\mu(x) \equiv 0$, and the growth modulus $\gamma(x) = (\log 2.0)x$. The period is $p = \int_{1.0}^{2.0} \frac{1}{(\log 2.0)(x)} dx = 1.0$.

with domain

$$D(A) = \left\{ \begin{pmatrix} \phi \\ \psi \end{pmatrix} \in X : \begin{pmatrix} \phi' \\ \psi' \end{pmatrix} \in X, \phi(0) = 2\int_0^{a_1} \beta(a)\phi(a)da, \psi(0) = 0 \right\}.$$

The following hypotheses provide necessary and sufficient conditions for $T(t), t \geq 0$ to have asynchronous exponential growth in X with rank one spectral projection:

$$\text{there exists } \epsilon_0 \in (0, a_1) \text{ such that } \forall \epsilon \in (0, \epsilon_0), \textstyle\int_{a_1-\epsilon}^{a_1} \beta(a)da > 0, \tag{4.4}$$

$$\text{there exists } \epsilon_1 \in (0, a_1) \text{ such that } \forall \epsilon \in (0, \epsilon_1), \textstyle\int_{a_1-\epsilon}^{a_1} \tau(a)da > 0, \tag{4.5}$$

$$\text{there exists } \epsilon_2 > 0 \text{ such that } \forall \epsilon \in (0, \epsilon_2), \textstyle\int_0^{\epsilon} \sigma(a)da > 0. \tag{4.6}$$

These conditions have the following interpretation: Asynchronous exponential growth occurs if and only if the youngest proliferating cells have the possibility to transit to the quiescent compartment and the oldest quiescent cells have the possibility to transit to the proliferating compartment.

EXAMPLE 4.6. *The size structured cell population model with quiescence.* Let $0 < x_0 < x_1 < 2x_0$, let $X = L^1(x_0/2, x_1) \times L^1(x_0/2, x_1)$, let $\beta(x)$ be a continuous function on $[0, \infty)$ which is positive on $[x_0, x_1]$, let $\gamma(x)$ be a continuously differentiable function on $[0, \infty)$ which satisfies $\gamma(x) > 0$ on $[x_0, x_1]$ and $2\gamma(x) \geq \gamma(2)$ on $[x_0, x_1]$, and let $\mu(x), \nu(x), \sigma(x)$, and $\tau(x)$ be nonnegative and continuous on $[x_0/2, x_1]$. Let $p(a,t)$ and $q(a,t)$ be the size densities of proliferating and quiescent cells, respectively, as in Example 2.6. The densities correspond to a strongly continuous semigroup of bounded linear operators $T(t), t \geq 0$ in

X given by the formula

$$T(t)\begin{pmatrix}\phi\\ \psi\end{pmatrix}=\begin{pmatrix}p(\cdot,t)\\ q(\cdot,t)\end{pmatrix},\qquad t\geq 0,\ \begin{pmatrix}\phi\\ \psi\end{pmatrix}\in X,\ t\geq 0.$$

The infinitesimal generator of $T(t), t\geq 0$ is

$$A\begin{pmatrix}\phi(x)\\ \psi(x)\end{pmatrix}=\begin{pmatrix}-(\gamma(x)\phi(x))'-(\mu(x)+\beta(x)+\sigma(x))\phi(x)+4\beta(2x)\phi(2x)+\tau(x)\psi(x)\\ -(\nu(x)+\tau(x))\psi(x)+\sigma(x)\phi(x)\end{pmatrix}$$

with domain

$$D(A)=\left\{\begin{pmatrix}\phi\\ \psi\end{pmatrix}\in X:\phi'\in L^1(x_0/2,x_1),\phi(x_0/2)=0\right\}.$$

A sufficient condition for $T(t), t\geq 0$ to have asynchronous exponential growth in X is that $\sigma(x)\tau(x)>0$ on some set of positive measure in $(x_0/2,x_1)$, which means that all proliferating cells with size in this interval can become quiescent and all quiescent cells with size in this interval can become proliferating. The asynchronous exponential growth holds even in the case that $2\gamma(x)=\gamma(2x)$, because quiescence allows for dispersion of cell sizes, even though the two daughter cells grow exactly the same as the mother cell would have if she had not divided. A sufficient condition for the solutions of (2.18′)–(2.22′) to have asynchronous exponential growth in $X=L^1(x_0/2,x_1)\times L^1(x_0/2,x_1/2)$ is that $\rho(x)$ and $\tau(x)$ are both positive on some set of positive measure in $(x_0/2,x_1/2)$. The asynchronous exponential growth again holds even if $2\gamma(x)=\gamma(2x)$. The asynchronous exponential growth in this case is illustrated in Figures 13 and 14, in which the initial information is dispersed when $\gamma(x)=(\log 2.0)x$. For this case asychronous exponential growth also yields convergence of the *growth fraction* $G(t)$, which is defined as the proportion of proliferating cells in the total population $G(t)=P(t)/(P(t)+Q(t))$. In Figure 18 we graph the growth fraction for the example in Figures 13 and 14.

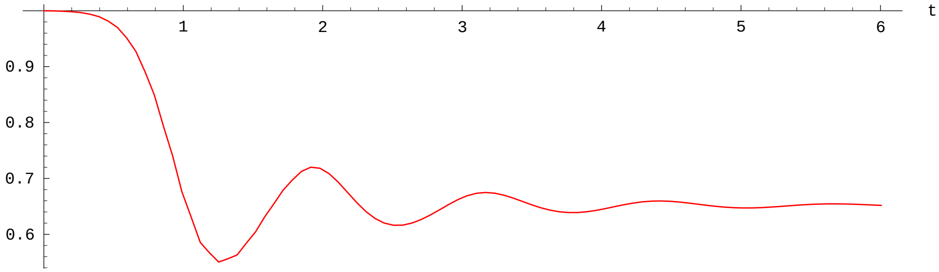

Fig. 18. Convergence of the growth fraction $G(t)=P(t)/(P(t)+Q(t))$ in the size structured model (2.18′)–(2.22′) for the example in Figures 13 and 14

Example 4.7. *The age structured cell population model with telomere loss.* Let $a_1>0$, let $X=L^1((0,a_1);\mathbf{R}^{N+1})$ and let $p_j(a,t)$ be the age density of the $j^{th}, j=0,\ldots,N$ telomere class as in Example 2.7. Let the division moduli $\beta_j(a), j=0,1,\ldots,N$ satisfy $\beta_j\in L^\infty(0,a)$ for all $a\in(0,a_1)$, and $\int_0^{a_1}\beta_j(a)da=\infty$, which means that every cell in the j^{th} telomere class, $j=0,1,\ldots,N$, must divide by the maximum age a_1. The interpretation of the telomere shortening upon division means that the probalitities p_{jk}

satisfy $p_{jk} \geq 0, p_{jj} = \frac{1}{2}$, and $\sum_{j=0}^{k-1} p_{jk} = \frac{1}{2}, k = 2, \ldots, N$. The densities correspond to a strongly continuous semigroup of bounded linear operators $T(t), t \geq 0$ in X given by the formula

$$T(t) \begin{pmatrix} \phi_0 \\ \vdots \\ \phi_N \end{pmatrix} = \begin{pmatrix} p_0(\cdot, t) \\ \vdots \\ p_N(\cdot, t) \end{pmatrix}, \quad t \geq 0,$$

The infinitesimal generator of $T(t), t \geq 0$ is

$$A \begin{pmatrix} \phi_0 \\ \vdots \\ \phi_N \end{pmatrix} = \begin{pmatrix} -\phi_0' - \beta_0 \phi_0 \\ \vdots \\ -\phi_N' - \beta_N \phi_N \end{pmatrix}$$

with domain

$$D(A) = \left\{ \begin{pmatrix} \phi_0 \\ \vdots \\ \phi_N \end{pmatrix} \in X : \begin{pmatrix} \phi_0' + \beta_0 \phi_0 \\ \vdots \\ \phi_N' + \beta_N \phi_N \end{pmatrix} \in X, \right.$$
$$\left. \phi_j(0) = 2 \sum_{k=j}^{N} p_{jk} \int_0^{a_1} \beta_k(a) \phi_k(a) da, j = 0, 1, \ldots, N \right\}.$$

The semigroup $T(t), t \geq 0$ has asynchronous polynomial exponential growth in X of order N with intrinsic growth constant 0 and projection P with N-dimensional range. Specifically, $p_j(\cdot, t)$ grows polynomially in time t of order $t^{N-j}, j = 0, 1, \ldots, N$. The lower states thus grow faster, the 0^{th} state grows the fastest, and further the asymptotic limit on $p_j(\cdot, t)$ as time goes to infinity depends only on the initial reservior of cells in the highest state $\phi_N(a)$. The asynchronous polynomial exponential growth of the solutions of this model is illustrated in Figure 19 and Figure 20 for the case $N = 3$.

EXAMPLE 4.8. *The phenotype structured cell population model.* Let $X = L^1(y_1, y_2)$, let $\alpha > 0$, let $\mu \in L^\infty(y_1, y_2)$, and let $p(y, t)$ be the density of a phenotype structured population as in Example 2.8. The density $p(y, t)$ satisfies equations (2.12)–(2.14), whose generalized solutions yield a strongly continuous semigroup of bounded linear operators $T(t), t \geq 0$ in X. The infinitesimal generator of $T(t), t \geq 0$ is the linear operator A in X defined by

$$(A\phi)(y) = \alpha^2 \frac{\partial^2}{\partial y^2} \phi(y) + \mu(y) \phi(y), \tag{4.7}$$

$$D(A) = \left\{ \phi \in X : \frac{\partial^2}{\partial y^2} \phi \in X \text{ and } \frac{\partial}{\partial y} \phi(y_1) = \frac{\partial}{\partial y} \phi(y_2) = 0 \right\} \tag{4.8}$$

The linear semigroup $T(t), t \geq 0$ satifies the hypothesis of Theorem 3.2, where the projection P in (4.2) has 1-dimensional range. This semigroup thus has asynchronous exponential growth and in this case the sign of the intrinsic growth constant λ_1 depends on the interplay between the selection coefficient $\mu(y)$ (which may be positive or negative for different y values) and the diffusion coefficient α^2.

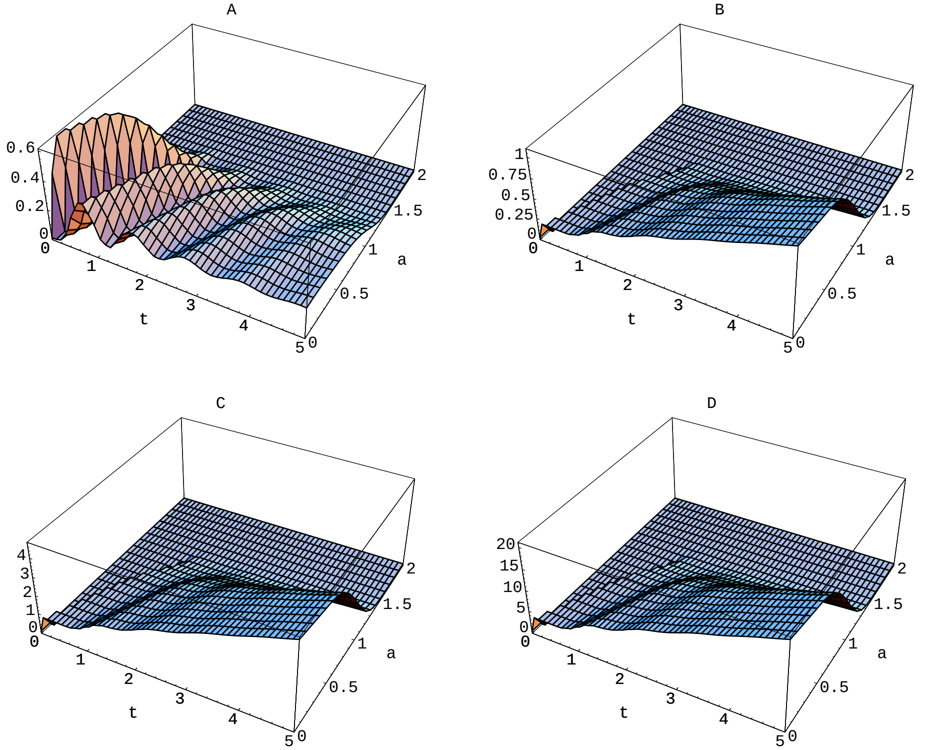

Fig. 19. The telomere classes of the model (2.23)–(2.25) with $a_1 = 2.0, \phi_3(a) = \max[0, a(.5 - a)], \phi_2 = \phi_1 = \phi_0 \equiv 0, \beta_3(a) = \max[0, (a - .5)e^{2.0a}], \beta_2 = \beta_1 = \beta_0 \equiv 0, p_{23} = p_{12} = p_{01} = .5, p_{13} = p_{02} = p_{03} \equiv 0$. A. $p_3(a,t)$. B. $p_2(a,t)$. C. $p_1(a,t)$. D. $p_0(a,t)$.

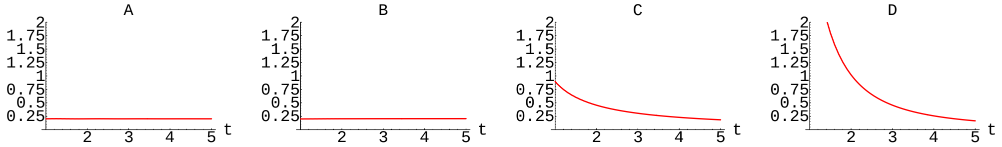

Fig. 20. The polynomial growth of the telomere class total populations in Figure 19: $P_j(t) = \int_0^2 p_j(a,t)da, j = 0,1,2,3$. A. $P_3(t)$. B. $P_2(t)/t$. C. $P_1(t)/t^2$. D. $P_0(t/)t^3$.

5. Applications to nonlinear structured populations.

In this section we apply the concepts in Section 3 to nonlinear structured population models.

Example 5.1. *The age structured cell population model with crowding.* Let $T(t), t \geq 0$ be the strongly continuous semigroup of bounded linear operators in $X = L^1(0,\infty)$ as in Example 4.1 and define $F \in X_+^*$ by $F\phi = \tau \int_0^\infty \phi(a)da, \phi \in X$. Then Theorem 3.9 applies to the nonlinear partial differential equation

$$\frac{\partial}{\partial t}p(a,t) + \frac{\partial}{\partial a}p(a,t) = -\Big(\beta(a) + \mu(a) + \tau \int_0^\infty p(\hat{a},t)d\hat{a}\Big)p(a,t), \tag{5.1}$$

$$p(0,t) = 2\int_0^\infty \beta(a)p(a,t)da, \qquad t \geq 0, \tag{5.2}$$

$$p(a, 0) = \phi(a), \qquad \phi \in X_+, \qquad a \geq 0. \tag{5.3}$$

The generalized solution of (5.1)–(5.3) is given by $p(a,t) = (S(t)\phi)(a)$, where $S(t), t \geq 0$ is the nonlinear semigroup in X_+ as in Theorem 3.9. Further, Theorem 3.9 applies with λ_1 the unique real solution of the characteristic equation (4.1). The nonlinear term in (5.1) represents mortality due to limitation of resources as the total population grows. If $\lambda_1 > 0$, then the cell population stabilizes to a unique nontrivial equilibrium, since the spectral projection P for $T(t), t \geq 0$ has 1-dimensional range. We illustrate the convergence to equilibrium in Figure 21 and Figure 22.

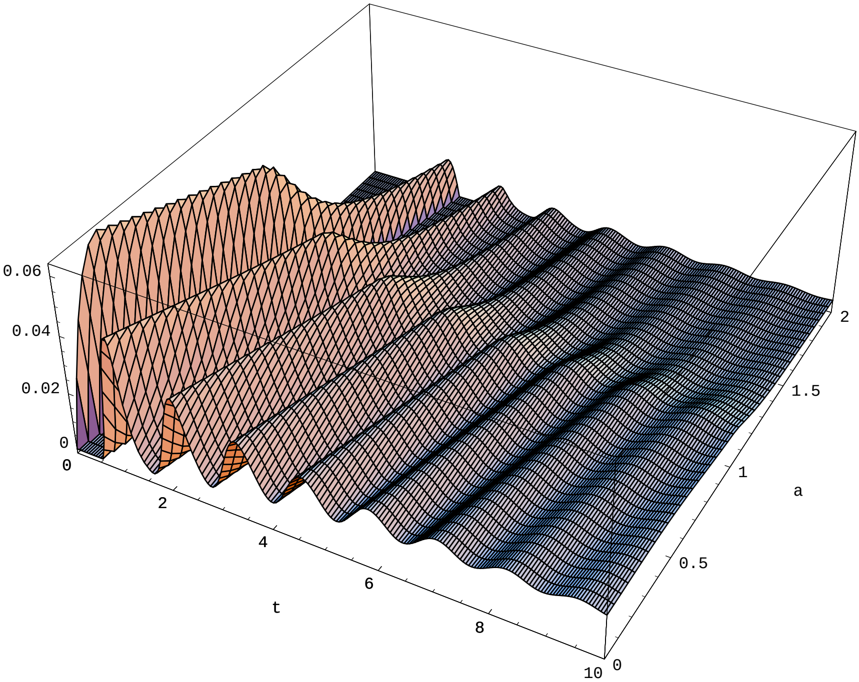

Fig. 21. The solution $p(a,t)$ of the nonlinear age structured model (5.1)–(5.3) in Example 5.1 with the initial value $\phi(a)$ as in Figure 5, $\beta(a)$ as in Figure 6, $\mu(a) \equiv .05$, and $\tau = 10.0$

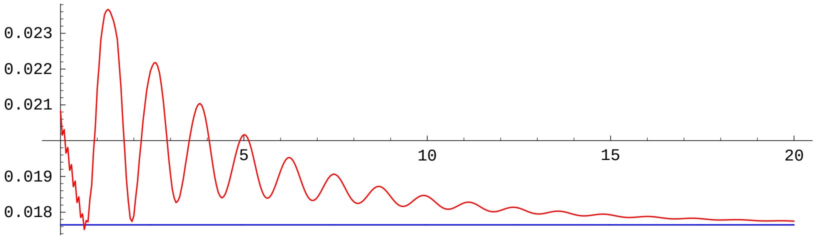

Fig. 22. The total population $P(t) = \int_0^\infty p(a,t)da$ for the solution $p(a,t)$ of the nonlinear age structured model in Figure 21. The total population converges to λ_1/τ, where $\lambda_1 \approx .176567$ as in Figure 15.

Example 5.2. *The maturity structured cell population model with crowding.* Let $T(t)$, $t \geq 0$ be the strongly continuous semigroup of bounded linear operators in $X = C[0,1]$ as in Example 4.2 and define $F \in X_+^*$ by $F\phi = \int_0^1 \phi(x)dx, \phi \in X$. Then Theorem 3.9 applies to the nonlinear partial differential equation

$$\frac{\partial}{\partial t}p(x,t) + \frac{\partial}{\partial x}(xp(x,t)) = \left(\mu - \int_0^1 p(\hat{x},t)d\hat{x}\right)p(x,t), \tag{5.4}$$

$$p(x,0) = \phi(x), \qquad \phi \in X_+,\ 0 \leq x \leq 1. \tag{5.5}$$

The generalized solution of (5.4),(5.5) is given by $p(x,t) = (S(t)\phi)(x)$, where $S(t), t \geq 0$ is the nonlinear semigroup in X_+ as in Theorem 3.9. It can be shown that $S(t), t \geq 0$ has the following asymptotic behavior:

(i) if $\phi \in C[0,1]_+, \phi(0) > 0$, and $0 < \mu \leq 1$, then $\lim_{t\to\infty} S(t)\phi = 0$;

(ii) if $\phi \in C[0,1]_+, \phi(0) > 0$, and $\mu > 1$, then $\lim_{t\to\infty} S(t)\phi \equiv \mu - 1$;

(iii) if $\mu > 1$, then $S(t), t \geq 0$ is topologically transitive in Y, where $Y := \{\phi \in C_0[0,1]_+ : F\phi \leq \mu\}$.

One interpretation of this model is the production of blood cells in the body. Blood cells mature from primitive cells produced in the bone marrow and transition through increasing stages of maturity until they finally enter the circulating blood. Maturity varies continuously from 0 to 1 and cells of any maturity are capable of division. The maturation rate of cells approaches infinity as x approaches 0 in this model due to form of the term $\frac{\partial}{\partial x}(xp(x,t))$ in equation (2.4). This means that the most immature cells are extremely important in the stabilization of the population from the initial distribution ϕ. If $\phi(0) > 0$, then there is a sufficient supply initially of the most primitive cells and the population can recover and stabilize from an initial toxic shock. If $\phi(0) = 0$, then there is not a sufficient supply initially of the most primitive cells and the population may exhibit chaotic behavior. The latter case corresponds to such diseases as aplastic anemia.

Example 5.3. *The size structured cell population model with crowding.* Let $T(t), t \geq 0$ be the strongly continuous semigroup of bounded linear operators in $X = L^1(x_0/2, x_1)$ as in Example 4.4 and define $F \in X_+^*$ by $F\phi = \int_{x_0}^{x_1} \phi(x)dx, \phi \in X$. Theorem 3.9 applies to the nonlinear partial differential equation

$$\begin{aligned}\frac{\partial}{\partial t}p(x,t) &+ \frac{\partial}{\partial x}(\gamma(x)p(x,t)) \\ &= -\left(\beta(x) + \mu(x) + \int_{x_0}^{x_1} p(\hat{x},t)d\hat{x}\right)p(x,t) + 4\beta(2x)p(2x,t),\end{aligned} \tag{5.6}$$

$$p(x_0/2,t) = 0, \qquad t \geq 0, \tag{5.7}$$

$$p(x,0) = \phi(x), \qquad \phi \in X,\ x_0/2 < x < x_1. \tag{5.8}$$

The generalized solution of (5.6)–(5.8) is given by $p(x,t) = (S(t)\phi)(x)$, where $S(t), t \geq 0$ is the nonlinear semigroup in X_+ as in Theorem 3.9. Part (i) of Theorem 3.9 applies with λ_1 the unique real solution of the characteristic equation (4.3). As in Example 5.1, if $\lambda_1 > 0$, then the cell population stabilizes to a unique nontrivial equilibrium, since the spectral projection P for $T(t), t \geq 0$ has 1-dimensional range.

EXAMPLE 5.4. *The age structured cell population model with telomere loss and naive source.* Let $T(t), t \geq 0$ be the strongly continuous semigroup of bounded linear operators in $X = L^1((0,a_1);\mathbf{R}^{N+1})$ and $p_j(a,t)$ the age density of the $j^{th}, j = 0,\dots,N$ telomere class as in Example 2.7. Consider the nonlinear partial differential equations

$$\frac{\partial}{\partial t}p_j(a,t) + \frac{\partial}{\partial a}p_j(a,t) = (\phi_1)_j(a) - (\beta_j(a) + \mu_j(a))p_j(a,t), \quad j = 0,\dots N, \tag{5.9}$$

$$p_j(0,t) = 2\sum_{k=j}^{N} p_{jk}\int_0^{a_1}\beta_k(a)p_k(a,t)da, \quad t \geq 0, \tag{5.10}$$

$$p_j(a,0) = \phi_j(a), \quad j = 0,\dots,N, \vec{\phi} = [\phi_0,\dots,\phi_N]^t \in X, a \in (0,a_1), \tag{5.11}$$

where $\phi_1 \in X$, and $\mu_j(a)$, represents age-specific mortality in the j^{th} telomere class, $j = 0,\dots,N$. Assume that each $\mu_j(a)$ satisfies $\mu_j \in L^\infty(0,a_1)$ and $\operatorname{essinf}\mu_j(a) \geq \bar{\mu}$, where $\bar{\mu} > 0$. The addition of this mortality to the model implies that the semigroup associated with the linear problem (when $\phi_1 \equiv 0$) satisfies $\omega < 0$ in (1.1). Theorem 3.7 can then be applied to the nonlinear semigroup $S(t), t \geq 0$ corresponding to the solutions of (5.9)–(5.11), which thus converge to a unique equilibrium.

The interpretation of this model is that in the presence of mortality the linear age structured population with telomere loss undergoes extinction, because the proliferation process increases polynomially in time, but the mortality process decreases exponentially in time. The population will stabilize to a unique nontrivial equilibrium, however, if there is an constant on-going supply of naive cells $\phi_1 \not\equiv 0$.

EXAMPLE 5.5. *The phenotype structured cell population model with crowding.* Let $X = L^1(y_1,y_2)$, let $\alpha > 0$, let $\gamma > 0$, let $\mu \in L^\infty(y_1,y_2)$, and let $T(t), t \geq 0$ be the linear semigroup as in Example 4.8 with infinitesimal generator A as in (4.7) and (4.8). Consider the case that the population is subject to selection and mutation as in Example 4.5, but also to mortality dependent on the presence of the total population. Let $p(y,t)$ be the density with respect to phenotype y of this population as it evolves in time. Let $F \in X_+^*$ be defined by $F\phi = \int_{y_1}^{y_2}\phi(y)dy, \phi \in X_+$. The density satisfies the nonlinear partial differential equation

$$\frac{\partial}{\partial t}p(y,t) = \alpha^2\frac{\partial^2}{\partial y^2}p(y,t) + (\mu(y) - \gamma F(p(\cdot,t)))p(y,t), \tag{5.12}$$

$$\frac{\partial}{\partial y}p(y_1,t) = \frac{\partial}{\partial y}p(y_2,t) = 0, \quad t > 0, \tag{5.13}$$

$$p(y,0) = \phi(y), \quad \phi \in X_+,\ y_1 < y < y_2, \tag{5.14}$$

where mortality depends nonlinearly on total population density through F. The generalized solutions of (5.12)–(5.14) are given by the nonlinear semigroup $S(t), t \geq 0$ in Theorem 3.9. Further, the linear semigroup $T(t), t \geq 0$ corresponding to the solutions of (2.26)–(2.28) has asynchronous exponential growth with 1-dimensional spectral projection. Theorem 3.9 can then be applied to obtain the convergence of the solution of (5.12)–(5.14) to a unique equilibrium independent of $\phi \in X_+$:

$$\lim_{t\to\infty} S(t)\phi = \frac{\lambda_1\phi_1}{\gamma F(\phi_1)} \quad \text{if } \lambda_1 > 0, \text{ and } 0 \text{ if } \lambda_1 \leq 0, \phi \in X_+ - \{0\},$$

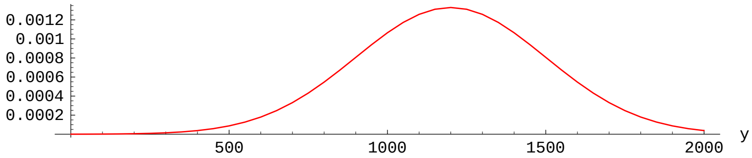

Fig. 23. The initial function for Example 5.5 is given by the normal distribution $\phi(y) = \exp[-(y-\mu)^2/(2\sigma^2)]/(\sigma\sqrt{2\pi})$, with mean $\mu = 1200$ and standard deviation $\sigma = 300$.

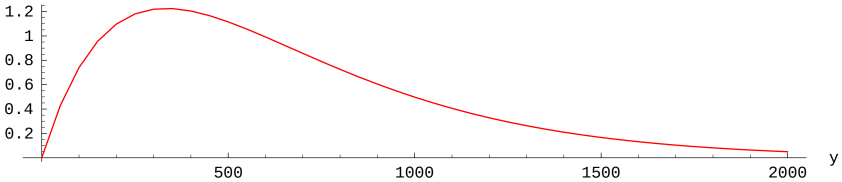

Fig. 24. The selection function for Example 5.5: $\mu(y) = .01ye^{-.003y}$

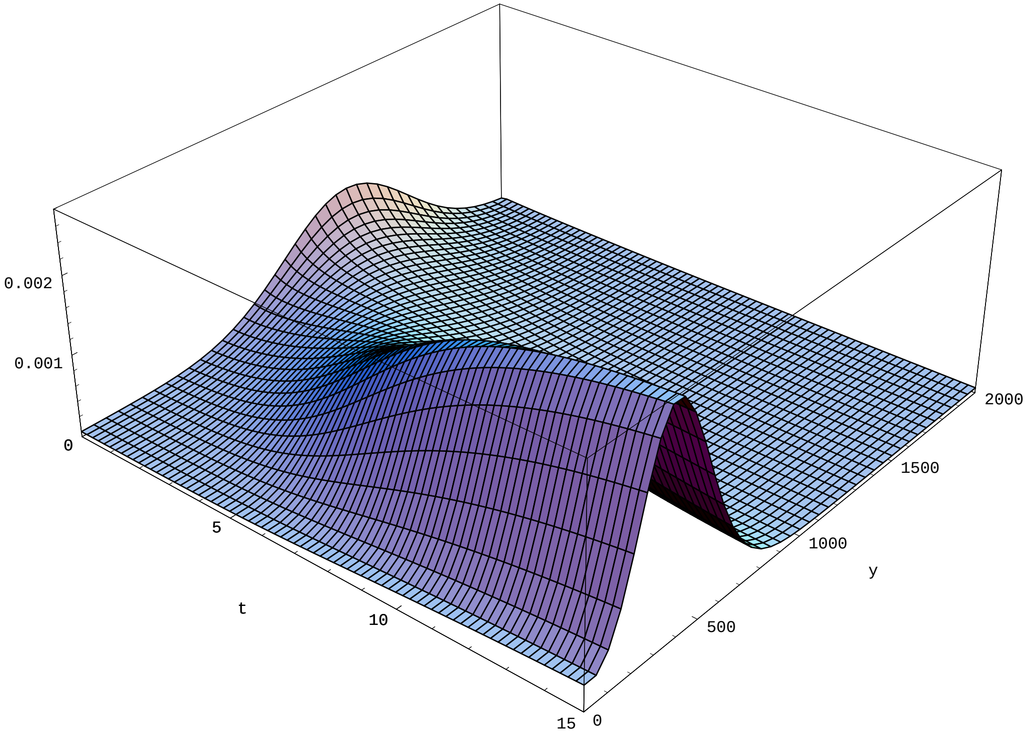

Fig. 25. The graph of $p(y,t)$ for the solution of (5.12)–(5.14) with initial function $\phi(y) \in L^1(0,2000)$ as in Figure 23, selection function $\mu(y)$ as in Figure 24, $\alpha = 50.0$, and $\gamma = 1.0$

where λ_1 is the dominant eigenvalue of the linear problem (2.12)–(2.14) and ϕ_1 is its normalized eigenfunction. The intrinsic growth constant λ_1 of the linear semigroup determines the stabilization to equilibrium ($\lambda_1 > 0$) or the extinction ($\lambda_1 \leq 0$) of the population. The ultimate size of the population in the case of stabilization to equilibrium depends on the effects of crowding and the carrying capacity of the population as determined by the parameter γ. The phenotype selection model with crowding is illustrated in Figures 23, 24, and 25.

Example 5.6. *The phenotype structured cell population model with recombination.* Let $X = L^1(y_1, y_2)$ and consider the model in Example 5.5 above, but with the population subject to recombination of phenotypes, as well as to selection, mutation, and crowding. The density $p(y,t)$ satisfies the partial differential equation

$$\frac{\partial}{\partial t}p(y,t) = \alpha^2 \frac{\partial^2}{\partial y^2}p(y,t) + (\mu(y) - \gamma F(p(\cdot,t)))p(y,t) + \tau(H(p(\cdot,t)(y)) - p(y,t)), \quad (5.15)$$

$$\frac{\partial}{\partial y}p(y_1,t) = \frac{\partial}{\partial y}p(y_2,t) = 0, \qquad t > 0, \quad (5.16)$$

$$p(y,0) = \phi(y), \qquad \phi \in X_+,\ y_1 < y < y_2, \quad (5.17)$$

where $\tau > 0$ and H is the *hybridization* operator in X_+ defined by

$$\begin{aligned} H(\phi)(y) &= \frac{\int_{y_1}^{y_2} \kappa(y,\hat{y})\phi(2y-\hat{y})\phi(\hat{y})d\hat{y}}{\int_{y_1}^{y_2} \phi(\hat{y})d\hat{y}}, \qquad \phi \in X_+ - \{0\}, \\ H(\phi)(y) &= 0, \qquad \phi \equiv 0, \end{aligned}$$

with the *hybridization kernel* $\kappa(y,\hat{y})$ defined by

$$\kappa(y,\hat{y}) = \begin{cases} 2 & \text{if } 0 \leq y \leq (y_1+y_2)/2 \text{ and } 0 \leq \hat{y} \leq 2y - y_1, \\ 0 & \text{if } 0 \leq y \leq (y_1+y_2)/2 \text{ and } 2y - y_1 < \hat{y} \leq y_2, \\ 2 & \text{if } (y_1+y_2)/2 < y \leq y_2 \text{ and } 2y - y_2 \leq \hat{y} \leq y_2, \\ 0 & \text{if } (y_1+y_2)/2 < y \leq y_2 \text{ and } 0 \leq \hat{y} < 2y - y_2. \end{cases}$$

The domain of the hybridization kernel is illustrated in Figure 26.

The hybridization operator H averages the two phenotypes y and $\hat{y}$ to $\frac{y+\hat{y}}{2}$ and has the following properties:

$$H \text{ maps } X_+ \text{ into } X_+ \text{ and is positive homogeneous in } X_+, \quad (5.18)$$

$$H \text{ is Lipschitz continuous in } X_+ \text{ with Lipschitz constant } |H|_{Lip} = 2, \quad (5.19)$$

$$\sup_{y_1 \leq y \leq y_2}(H\phi)(y) \leq 2 \sup_{y_1 \leq y \leq y_2} \phi(y) \qquad \forall \phi \in X_+, \quad (5.20)$$

$$H \text{ preserves total population,}$$
$$\int_{y_1}^{y_2} H(\phi)(y)dy = \int_{y_1}^{y_2} \phi(y)dy \qquad \forall \phi \in X_+, \quad (5.21)$$

$$H \text{ preserves population mean,}$$
$$y_m(\phi) := \frac{\int_{y_1}^{y_2} y\phi(y)dy}{\int_{y_1}^{y_2} \phi(y)dy} = \frac{\int_{y_1}^{y_2} yH(\phi)(y)dy}{\int_{y_1}^{y_2} H(\phi)(y)dy} \qquad \forall \phi \in X_+, \quad (5.22)$$

$$\lim_{n\to\infty}(H^n\phi)(y) = \begin{cases} 0 \text{ if } y \neq y_m(\phi) \\ \infty \text{ if } y = y_m(\phi) \end{cases} \qquad \forall \phi \in X_+ - \{0\}. \quad (5.23)$$

The properties of the hybridization operator H are illustrated in Figures 27, 28, and 29.

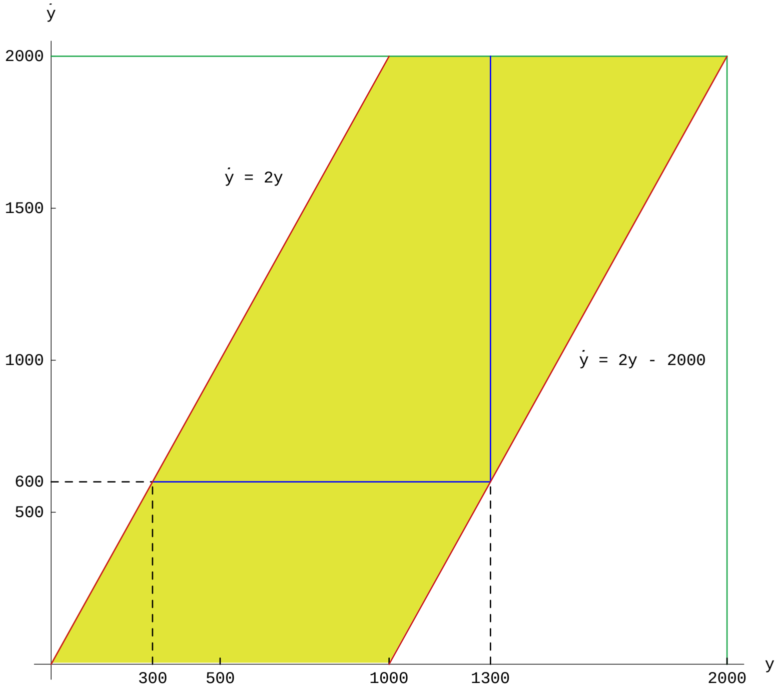

Fig. 26. The domain of the hybridization kernel $\kappa(y,\hat{y})$ for the case that $y_1 = 0$ and $y_2 = 2000$. $\kappa(y,\hat{y}) = 0$ outside the shaded region and 2 inside it.

Further, A, $T(t), t \geq 0$, and H satisfy the hypotheses of Theorem 3.8, where A and $T(t), t \geq 0$ are as in Example 4.5, and the nonlinear semigroup $S(t), t \geq 0$ in Theorem 3.8 is positive homogeneous. The generalized solutions $p(y,t)$ of (5.15)–(5.17) correspond to a strongly continuous semigroup of nonlinear operators $S_1(t), t \geq 0$ in X_+, where

$$p(y,t) = (S_1(t)\phi)(y), \phi \in X_+, \qquad y \in (y_1, y_2),\ t \geq 0.$$

The asymptotic behavior of the nonlinear semigroup $S_1(t), t \geq 0$ depends on the relative effects of selection, mutation, and recombination. As the population evolves subject to the selection process (controlled by $\mu(y)$), the mutation process (controlled by α) disperses the phenotype structure, while the recombination process (controlled by τ) concentrates phenotype structure at the population mean. If mutation is sufficiently stronger than recombination, then the population will converge to a unique equilibrium independent of the initial value ϕ. If recombination is sufficiently stronger than mutation, then the population will converge to a equilibrium dependent of the initial value ϕ.

The phenotype structured cell population models in Examples 5.5 and 5.6 are applicable to the bacteria *Helicobacter pylori*, which colonize the human stomach. This bacteria is believed to be long-established in human evolution, perhaps for millions of years. It is known to be associated with stomach ulcer disease and with increased risk for gastric cancer. It may, however, confer decreased risk for esophageal disease. In undeveloped countries the prevalence for *H.pylori* is near 100%, but in developed countries the preva-

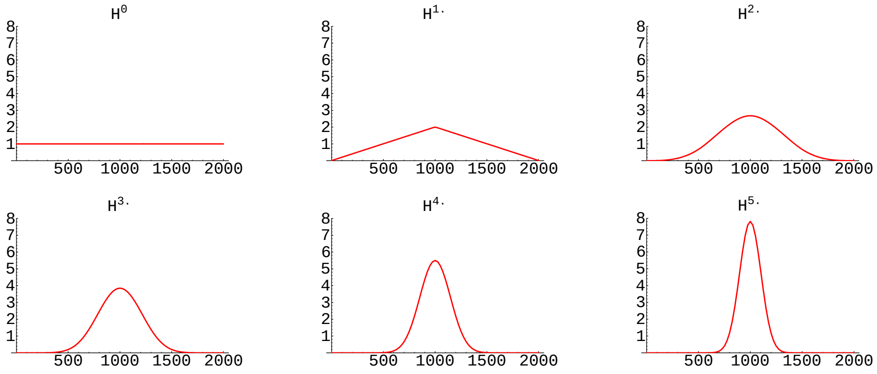

Fig. 27. The iterates of the hybridization operator $H^i, i = 0, \ldots, 5$ acting on $\phi(y) \equiv 1.0 \in L^1(0, 2000)$. The iterates preserve total population, population mean, and converge to the Dirac delta function concentrated at the population mean.

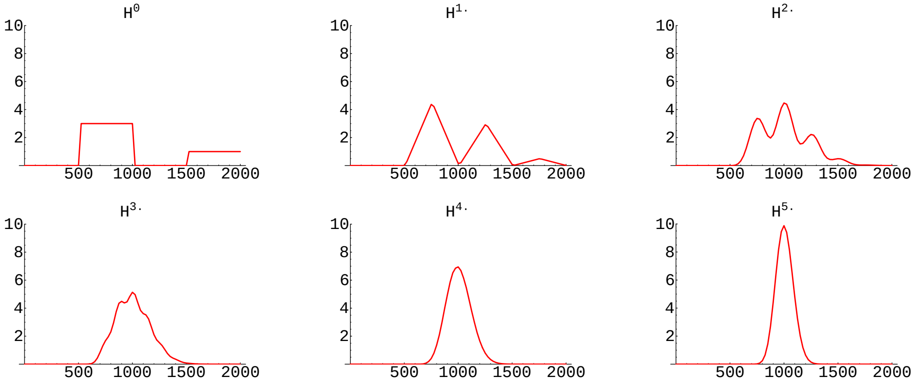

Fig. 28. The iterates of the hybridization operator $H^i, i = 0, \ldots, 5$ acting on $\phi(y) \in L^1(0, 2000)$ defined by $\phi(y) = 0.0$ for $0.0 \le y < 500.0, 3.0$ for $500.0 \le y < 1000.0, 0.0$ for $1000.0 \le y < 1500.0$, and 1.0 for $1500.0 \le y \le 2000.0$. The iterates are 0 outside the closed convex hull of the support of $\phi(y)$. The total population $= 2000.0$ and population mean $= 1000.0$ are preserved.

lence is much lower, especially in younger people. This decrease in prevalence is due to the rising use of antibiotics during the past 50 years. An important question concerning the future control of *H.pylori* in human hosts is the off-set risks of harm and benefit. Understanding the host-specific biology of *H.pylori* colonization is essential for resolving this question.

The models in Examples 5.5 and 5.6 are useful for this goal. The variable y corresponds to phenotype distinctions within the population for the expression of Lewis antigen Le^y. Le^y varies continuously within the population through a range $(0, 2000)$ of optical density units. Due to the effects of Le^y-biased selection, genetic mutation, and DNA recombination during division, an initial inoculation of *H. pylori* evolves to a stable colonization which may have a different distribution than the Le^y phenotype structure of the initial inoculation. The stable distribution of phenotypes that is approached during

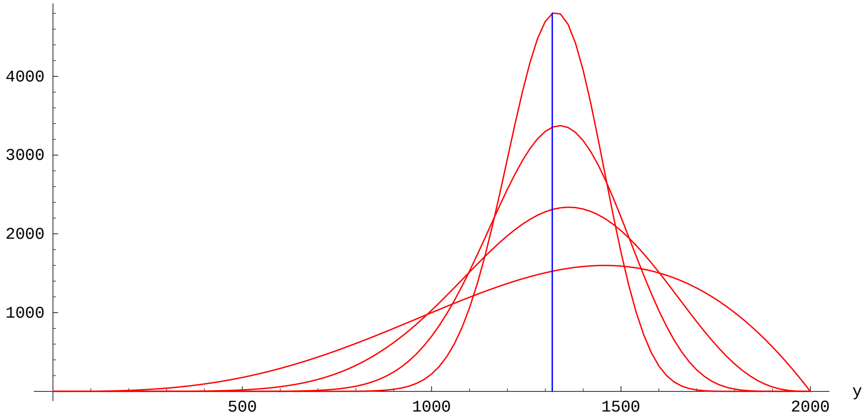

Fig. 29. The iterates of the hybridization operator $H^i, i = 1, 2, 3, 4$ preserve total population (1.51×10^6), preserve population mean (1318.5), and converge to the Dirac delta function concentrated at the mean for the function $\phi(y) = .001y^2 \sin(\pi y/2000.0) \in L^1(0, 2000)$.

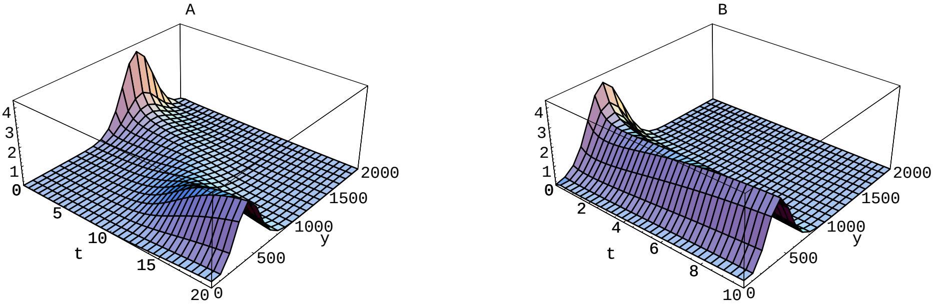

Fig. 30. The graph of the solution $p(y, t)$ of (5.15)–(5.17) with $\phi(y) \in L^1(0, 2000)$, $\mu(y) = .01ye^{-.003y}$, $\alpha = 50.0$, $\gamma = .001$, $\tau = .1$, and A. $\phi(y) = 2000.0 \exp[-(y - \mu)^2/(2\sigma^2)]/\sqrt{2\pi\sigma}$, with $\mu = 1400$, $\sigma = 200$, and B. $\phi(y) = 2000.0 \exp[-(y - \mu)^2/(2\sigma^2)]/\sqrt{2\pi\sigma}$, with $\mu = 600$, $\sigma = 200$. The colonization is independent of the initial data.

colonization may or may not depend on the initial distribution of phenotypes, depending on the strength of DNA recombination. The distinction is important in interpreting whether or not the colonization is determined by a new or previous host. If the colonization is established independently of the initial data, then it is new-host determined. If it depends on the initial data, then it is previous-host determined. The two cases are illustrated in Figures 30 and 31.

Example 5.7. *The age structured tumor cord cell population model.* A tumor cell population forming a cylindrical structure surrounding a blood vessel is called a tumor cord. Tumor cords are part of the micro-architecture of some natural and experimental tumors. This model describes a symmetrical cross-section of the cylindrical cord. The tumor cell population consists of both proliferating and quiescent cells. In the model proliferating cells migrate radially outward toward the cord periphery, which is surrounded by necrotic

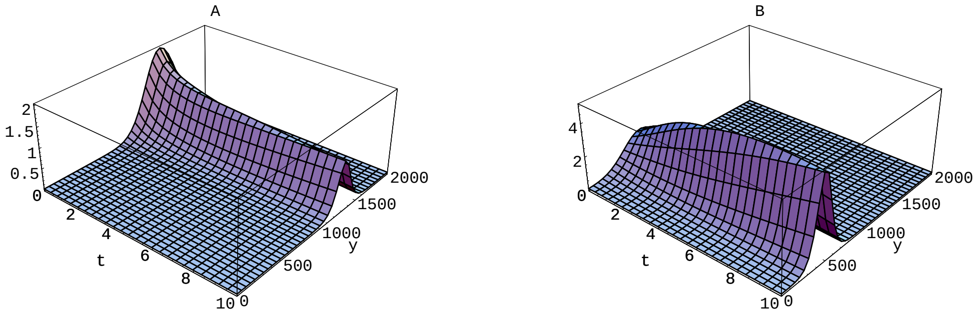

Fig. 31. The graph of the solution $p(y,t)$ of (5.15)–(5.17) with $\mu(y)$, α, γ as in Figure 30, $\tau = 1.0$, and A. $\phi(y) = 1000.0 \exp[-(y-\mu)^2/(2\sigma^2)]/\sqrt{2\pi\sigma}$, with $\mu = 1400$, $\sigma = 200$, and B. $\phi(y) = 1000.0 \exp[-(y-\mu)^2/(2\sigma^2)]/\sqrt{2\pi\sigma}$, with $\mu = 600$, $\sigma = 200$. The colonization is dependent on the initial data.

cells. All proliferating cells divide at exactly the same age T_c. It is assumed that at radial distance r a fraction $\theta(r)$ of dividing cells enter the division cycle and the fraction $1-\theta(r)$ become quiescent. The normalized density of proliferating cells $n(a,r,t)$, where $a \in [0,T_c]$ is cell age, $r \in [r_0, R]$ is radial distance, $0 < r_0 < R$, and t is time, satisfies

$$\frac{\partial}{\partial t} n(a,r,t) + \frac{\partial}{\partial a} n(a,r,t) + \frac{1}{r}\frac{\partial}{\partial r}(ru(r,t)n(a,r,t)) = 0, \tag{5.24}$$

$$n(0,r,t) = 2\theta(r) n(T_c, r, t), \tag{5.25}$$

$$n(a,r,0) = \phi(a,r). \tag{5.26}$$

In (5.24)

$$u(r,t) = \frac{1}{r}\int_{r_0}^{r} z n(T_c, z, t) dz$$

is the radially outward directed flux of cell migration, and in (5.26) ϕ is the initial distribution of proliferating cells in the cross-section of the cord.

The tumor cord cell population attains an equilibrium in which the loss of cells into the necrotic region is balanced by the gain of cells due to the division of proliferating cells along the radial direction. The equilibrium for the proliferating cell density $n(a,r)$ satisfies

$$\frac{\partial}{\partial a} n(a,r) + \frac{1}{r}\frac{\partial}{\partial r}(ru(r)n(a,r)) = 0, \tag{5.27}$$

$$n(0,r) = 2\theta(r) n(T_c, r). \tag{5.28}$$

It can be shown that the problem (5.27)–(5.28) has a unique solution provided that $\theta(r)$ is continuously differentiable and nonincreasing, $\theta(r_0) > \frac{1}{2}$, and there exists $r_1 \in (r_0, R)$ such that $\theta(r)$ is constant on $[r_0, r_1)$. An important quantity in the investigation of tumor cords is the *growth fraction*, that is, the fraction of cells that are transiting through the cell cycle. For the equilibrium above the growth fraction is

$$GF(r) = \int_0^{Tc} n(a,r) da,$$

and it can be shown that $GF(r)$ is nonincreasing in r and satisfies

$$2\theta(r) - 1 \leq GF(r) = \frac{\int_{r0}^{r} zn(Tc,z)(2\theta(z)-1)dz}{\int_{r0}^{r} zn(Tc,z)dz} \leq 2\theta(0) - 1.$$

An illustration of the solution of (5.27)–(5.28) is given in Figure 32 and an illustration of the growth fraction is given in Figure 33.

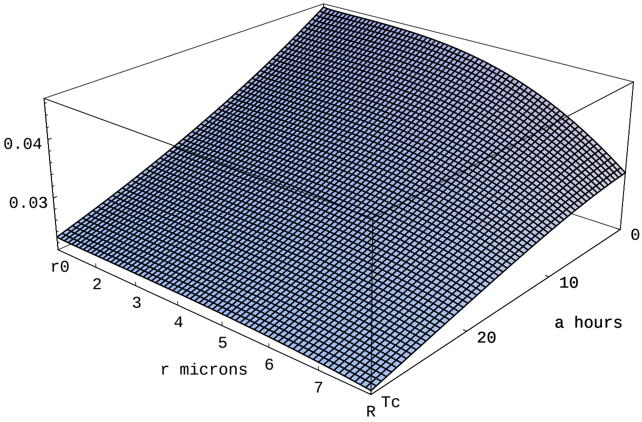

Fig. 32. The graph of the solution $n(a,r)$ of (5.27)–(5.28) with $T_c = 30.0$ hr, $r_0 = 1.0\mu m$, $R = 8.0\mu m$, and $\theta(r) = 1.0$ if $r_0 < 1.5$, $\theta(r) = 1.0 - .001(r-1.5)^3$ if $1.5 \leq r$

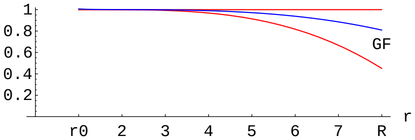

Fig. 33. The graph of the growth fraction $GF(r)$ for the solution of (5.27)–(5.28) as in Figure 32, together with the graphs of $2\theta(r) - 1$ and $2\theta(0) - 1$

Example 5.8. *The cell cycle structured cell population model with loss of cells proportional to the rate of mitosis.* Let $0 < x_0 < 1$ and let $X = C_{x_0,1}[x_0, 1]$, as in Example 1.2. Let $p(x,t)$ be the density of the population with respect to cell cycle position $x \in [x_0, 1]$ at time t as in Example 2.3. Let $T(t), t \geq 0$ be the semigroup of bounded linear operators in X as in Example 1.2, where $(T(t)\phi)(x) = p(x,t)$. As in Example 4.3, $T(t), t \geq 0$ has periodic exponential growth with intrinsic growth constant $\lambda_1 = -\ln 2/\ln x_0$, period $p = -\ln x_0$, rotation semigroup $R(t) = e^{-\lambda_1 t}T(t), t \geq 0$, and $P = I$. Define $F \in X_+^*$ by $F\phi = \mu\phi(1)$, where $\mu > 0$. Theorem 3.9 applies to the nonlinear partial differential equation

$$\frac{\partial}{\partial t}n(x,t) + \frac{\partial}{\partial x}(xn(x,t)) = -\mu n(1,t)n(x,t), \tag{5.29}$$

$$x_0 n(x_0,t) = 2n(1,t), \quad t \geq 0, \tag{5.30}$$

$$n(x,0) = \phi(x), \quad \phi \in X,\ x_0 \leq x \leq 1. \tag{5.31}$$

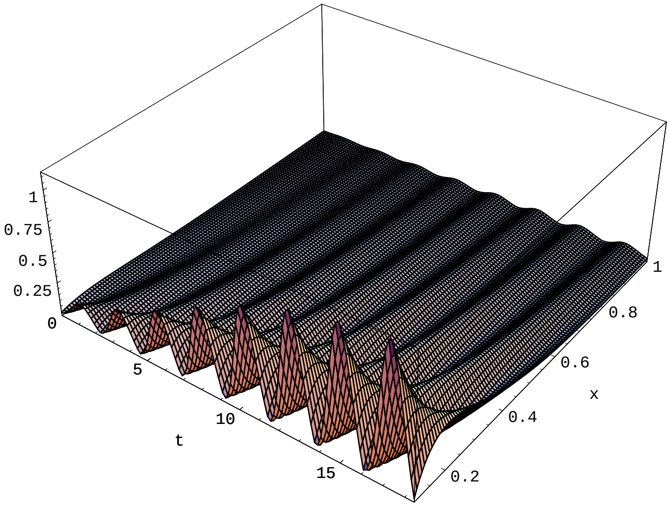

Fig. 34. The graph of $n(x,t)$ for the solution of (5.29)–(5.31) with $x_0 = .1$, $\mu = 10.0$, and the initial value ϕ as in Figure 3. The period of the limiting periodic function is $p = -\ln x0 \approx 2.30259$. The initial synchronization of the cells in the cell cycle is preserved through successive generations, as the population stabilizes due to a loss proportional to the rate of mitosis.

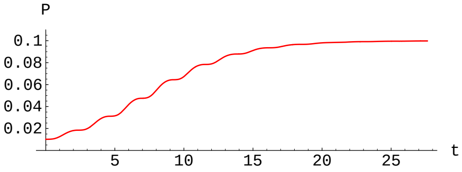

Fig. 35. The graph of the total population $P(t) = \int_{x_0}^{1.0} n(x,t)dx$ for the solution of (5.29)–(5.31) with $x_0 = .1$, $\mu = 10.0$, and the initial value ϕ as in Figure 3. Observe that $\lim_{t\to\infty} P(t) = \frac{1}{\mu} = .1$.

The generalized solution of (5.29)–(5.31) is given by $n(x,t) = (S(t)\phi)(x)$, where $S(t), t \geq 0$ is the nonlinear semigroup in X_+ as in Example 1.3. From Theorem 3.9 (ii) the solution of (5.29)–(5.31) converges to the p-periodic function $W(t)\phi$ given by (3.17). The nonlinearity in (5.29) represents a loss rate proportional to the rate at which cells undergo mitosis. The convergence of $S(t)\phi$ to the periodic function $W(t)\phi$ is illustrated in Figure 34 and the stabilization of the total population $P(t) = \int_{x_0}^{1} n(x,t)dx$ is illustrated in Figure 35.

Example 5.9. *The model of prion replication structured by polymer length.* Prions are proteins believed to be involved in diseases such as Creutzfeld-Jacob disease in humans, scrapies in sheep, and bovine spongiform encephalopathy in cows. A leading theory of prion replication is nucleated polymerization, in which prion monomers attach to string-like polymeric forms, which are very stable above a critical length. These polymers may split into smaller lengths, which either degrade to monomers (if they are below the critical length) or continue to lengthen (if they are above the critical length). Since the polymers can be hundreds or thousands of monomer units long, it is natural to structure the prion population by a continuous variable corresponding to polymer length. Let $V(t)$ be the population of monomers at time t. Let $u(y,t)$ be the density of polymers at time t with respect to length y, $y_c \leq y < \infty$, where y_c is the critical length. The total population of polymers is $U(t) = \int_{y_c}^{\infty} u(y,t)dy$ at time t. Then V and u satisfy the coupled system of differential equations

$$\frac{d}{dt}V(t) = \lambda - \gamma V(t) - \tau V(t)U(t) + 2\int_0^{y_c} y \int_{y_c}^{\infty} \beta(\hat{y})\kappa(y,\hat{y})u(\hat{y},t)d\hat{y}dy, \tag{5.32}$$

$$\begin{aligned} &\frac{\partial}{\partial t}u(y,t) + \tau V(t)\frac{\partial}{\partial y}u(y,t) \\ &\qquad = -(\mu(y)+\beta(y))u(y,t) + 2\int_y^{\infty} \beta(\hat{y})\kappa(y,\hat{y})u(\hat{y},t)d\hat{y}dy \end{aligned} \tag{5.33}$$

$$u(y_c,t) = 0, \qquad t \geq 0, \tag{5.34}$$

$$V(0) = V_0, \qquad u(y,0) = \phi(y), \qquad y_c \leq y < \infty, \tag{5.35}$$

where λ is the background source of monomers, γ is the rate of monomer degradation, τ is the attachment rate of monomers to polymers, $\beta(y)$ is the rate at which polymers of length y split, $\kappa(y,\hat{y})$ is the probability that a polymer of length $\hat{y}$ splits into lengths y and $\hat{y}-y$, $\mu(y)$ is the rate at which polymers of length y degrade, and $V_0 > 0$ and $\phi \in L^1(0,\infty)$ are the prescribed initial conditions at time 0. Although prions are not cells, and not even molecular DNA, their ability to replicate and proliferate resembles cell division and growth processes. An illustration of the solution of (5.32)–(5.35) is given in Figures 36 and 37, where it is seen that a polymer inoculation at time 0 results in the eventual stabilization of the polymer population.

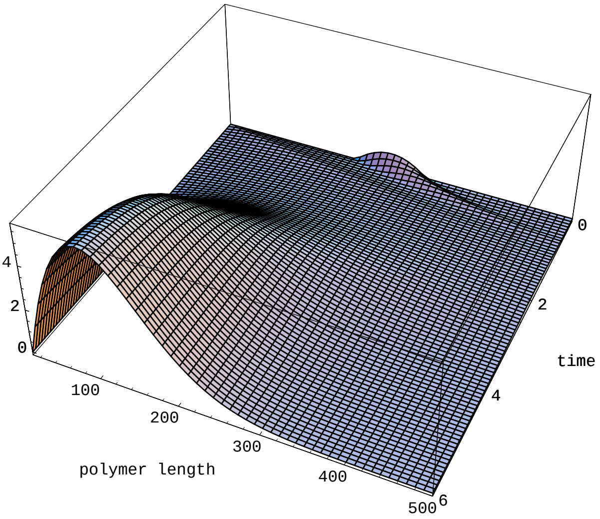

Fig. 36. The solution $u(y,t)$ of (5.32)–(5.35) with $y_c = 10.0, \lambda = 10^5, \gamma = .01, \tau = .01, \beta(y) = \beta y, \beta = .01, \mu(y) \equiv 1.0, \kappa(y,\hat{y}) = 1.0/\hat{y}$ if $y_c \leq y \leq \hat{y}$ and 0.0 if $y > \hat{y}$, $V_0 = 10^4$, and $\phi(y) = .0003\max[0.0,(y-200)(300-y)]$.

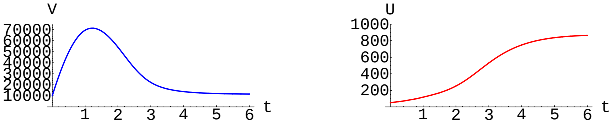

Fig. 37. For the solution of (5.32)–(5.35) as in Figure 36, the monomer population $V(t)$ stabilizes to $(y_c\beta+\mu)/(\beta\tau) = 12100.0$ and the total polymer population $U(t)$ stabilizes to $(\beta\lambda\tau-\gamma(y_c\beta+\mu)^2)/(\mu\tau(2y_c\beta+\mu)) = 832.3$.

Fig. 38. The total populations of the proliferating cells $P(t) = \int_0^{a_1} p(\hat{a},t)d\hat{a}$ and quiescent cells $Q(t) = \int_0^{a_1} q(\hat{a},t)d\hat{a}$ as a function of time in Example 5.10 with parameters $a_1 = 2.0$, $\beta(a) = 0.0$ for $a < 1.0$, $\beta(a) = 200.0(a-1.0)e^{-6.0(a-1.0)}$ for $1.0 \leq a \leq 2.0$, $\sigma(a) = 20.0 \max\{a(.5-a), 0.0\}$, $\tau(a) = 40.0 \max\{(a-3.0)(1.0-a), 0.0\}$, $\phi(a) = 2.0 \max\{a(.5-a), 0.0\}$, $\gamma_P = 4.0$, and $\gamma_Q = 4.0$. The initial distributions at time 0 are $p_0(a) \equiv 0.0$ and $q_0(a) \equiv 0.0$.

Example 5.10. *The age structured cell population model with quiescence, crowding, and naive source of proliferating cells.* Consider the model of Examples 2.5 and 4.5, but with density dependent crowding of both proliferating and quiescent cells and naive source of proliferating cells. The total cell population constrains the growth of both compartments. A background source of cells enters at a constant rate into the proliferating compartment. As in Example 4.5 the state space of the densities is $X = L^1(0,a_1) \times L^1(0,a_1)$, where a_1 is the maximum cell age. The densities of proliferating cells $p(a,t)$ and quiescent cells $q(a,t)$ at age a and time t satisfy the following initial-boundary value problem:

$$\frac{\partial}{\partial t}p(a,t) + \frac{\partial}{\partial a}p(a,t) = -\beta(a)p(a,t) - \sigma(a)p(a,t) + \tau(a)q(a,t) + \phi(a)$$
$$-\left(\gamma_P \int_0^{a_1} p(\hat{a},t)d\hat{a} + \gamma_Q \int_0^{a_1} q(\hat{a},t)d\hat{a}\right)p(a,t) \tag{5.36}$$

$$\frac{\partial}{\partial t}q(a,t) + \frac{\partial}{\partial a}q(a,t) = \sigma(a)p(a,t) - \tau(a)q(a,t)$$
$$-\left(\gamma_P \int_0^{a_1} p(\hat{a},t)d\hat{a} + \gamma_Q \int_0^{a_1} q(\hat{a},t)d\hat{a}\right)q(a,t), \tag{5.37}$$

$$p(0,t) = 2\int_0^{a_1} \beta(a)p(a,t)da, \qquad t \geq 0, \tag{5.38}$$

$$q(0,t) = 0, \qquad t \geq 0, \tag{5.39}$$

$$p(a,0) = p_0(a), \qquad p_0 \in X,\ a \in (0,a_1), \tag{5.40}$$

$$q(a,0) = q_0(a), \qquad q_0 \in X,\ a \in (0,a_1). \tag{5.41}$$

Cells of both compartments are subject to the influence of crowding with parameters γ_P for the proliferating class and γ_Q for the quiescent class. The on-going source of proliferating cells is represented by the term $\phi(a)$ in (5.36). Theorem 3.12 is applicable

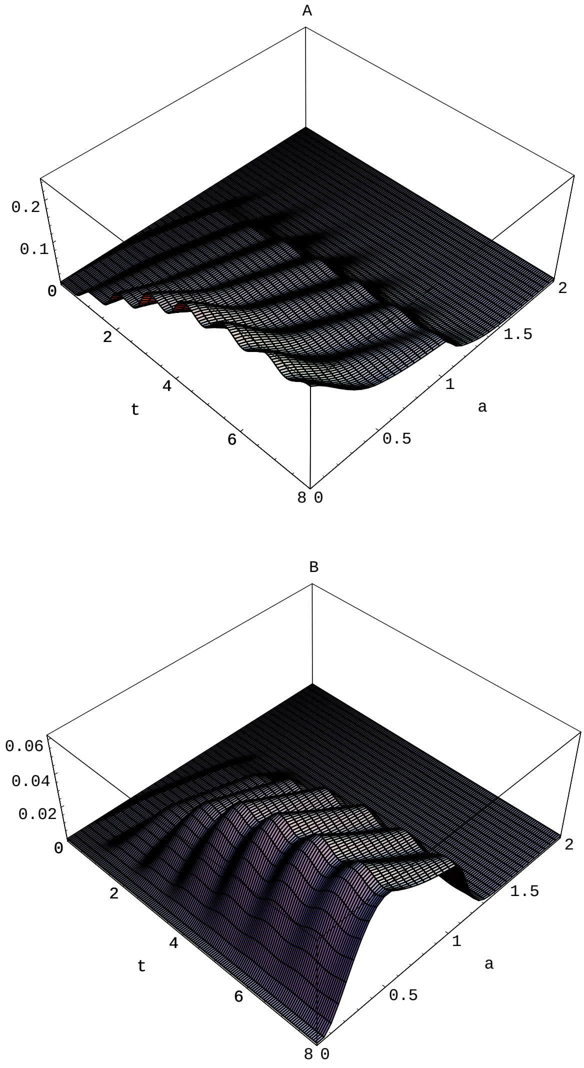

Fig. 39. The solution of (5.36)–(5.41) with parameters as in Figure 38. A. The density $p(a,t)$ of proliferating cells. B. The density $q(a,t)$ of quiescent cells.

to this example to establish the existence of a locally exponentially asymptotically stable equilibrium solution. An illustration of the solution of (5.36)–(5.41) is given in Figures 38 and 39, where it is seen that both the proliferating and quiescent populations stabilize as time becomes infinite.

Notes. The proofs of the theorems stated in these lectures may be found in the references. Some specific information concerning the references is given below.

Section 1. There are many treatments of linear semigroup theory, including [8], [20], [21], [35], [45], and [46]. The linear model of maturity structured cell populations in Example 1.1 is discussed in [13], [37], [38], [39], [52], and [53]. The linear model of the cell cycle structured cell population in Example 1.2 is treated in [52] and [63]. The nonlinear logistic model in Example 1.3 is treated in [61].

Section 2. There are many treatments of linear models of age structured population dynamics as in Example 2.1. One of the earliest is found in [55]. Other treatments are found in [8], [9], [31], [32], [33], [44], [56], and [60]. Several authors have treated maturity structured populations such as Example 2.2, including [14], [15], [37], [38], and [63]. The linear model of a cell population structured by the cell cycle in Example 2.3 is discussed in [52] and [63]. Many authors have contributed to the development of linear size structured models as in Example 2.4, including [8], [11], [12], [23], [28], [29], and [44]. Linear models structured by age with quiescent compartments as in Example 2.5 are discussed in [4] and [18]. Linear models structured by size with quiescent compartments as in Example 2.6 are discussed in [51] and [58]. The linear model of age structured cell population dynamics with telomere classes in Example 2.7 is treated in [3]. The model of phenotype evolution discussed in Example 2.8 is developed in [40] and [64]. Models of size and maturity structured cell populations have been treated in [30].

Section 3. The concept of sensitive dependence on initial conditions as in Definition 3.1 for dynamical systems in infinite dimensional spaces has been treated in [6], [10], [13], [17], [37], [38], and [53]. The concept of asynchronous exponential growth for linear semigroups as in Definition 3.2 has been treated in [8], [20], [22], [34], [45], [57], [59], [60], and [62]. Theorems 3.1, 3.2, and 3.3 are proved in [62]. Definition 3.4 is developed in [12] and [23]. Definitions 3.6 and 3.7 are found in [10], as are Theorems 3.4, 3.5, and 3.6. Theorem 3.8 is proved in [41], [46], [54], and [60]. Theorem 3.9 is proved in [61] and [19]. Definition 3.8 and Theorems 3.10 and 3.11 are found in [60]. Theorem 3.12 is proved in [19].

Section 4. The asynchronous exponential growth of the linear model of age structured population dynamics given in Example 4.1 is proved in [60]. The asymptotic behavior of the linear maturity structured model given in Example 4.2 is proved in [17]. The periodic exponential growth of the linear cell cycle structured model given in Example 4.3 is proved in [63]. The asymptotic behavior of the linear size structure population model given in Example 4.4 is proved in [23]. The necessary and sufficient conditions for asynchronous exponential growth of the age structured population model with quiescence as in Example 4.5 is proved in [4] and [18]. The necessary and sufficient conditions for asynchronous exponential growth of the size structured population model with quiescence given in Example 4.6 is proved in [51] and [58]. The asynchronous polynomial exponential growth of the linear model of an age structured cell population with telomere classes as in Example 4.7 is proved in [3]. The asynchronous exponential growth of the linear model of a population structured by continuously varying phenotypes in treated in [40].

Section 5. The nonlinear age structured model with crowding Example 5.1 is treated in [61]. The nonlinear maturity model with crowding in Example 5.2 is treated in [16] and [17]. The nonlinear model of phenotype evolution with crowding given in Example 5.5 is treated in [40], as is the version with recombination given in Example 5.6. The age structured tumor cord cell population model discussed in Example 5.7 is treated in [5] and [65]. Models of prion replication have been treated in [24] and [43].

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