Asymptotic behaviour of solutions to abstract logistic equations

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Received 14 May 2004; accepted 16 August 2005
Available online 7 October 2005

Abstract

We analyze the asymptotic behaviour of solutions of the abstract differential equation \( u'(t) = Au(t) - F(u(t))u(t) + f \). Our results are applicable to models of structured population dynamics in which the state space consists of population densities with respect to the structure variables. In the equation the linear term \( A \) corresponds to internal processes independent of crowding, the nonlinear logistic term \( F \) corresponds to the influence of crowding, and the source term \( f \) corresponds to external effects. We analyze three separate cases and show that for each case the solutions stabilize in a way governed by the linear term. We illustrate the results with examples of models of structured population dynamics – a model for the proliferation of cell lines with telomere shortening, a model of proliferating and quiescent cell populations, and a model for the growth of tumour cord cell populations.

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Keywords: Abstract logistic equation; Structured population; Asymptotic behaviour
1. Introduction

Logistic nonlinearities arise in population models in which population growth decreases as population density increases above environmental carrying capacity. In this paper we investigate three classes of abstract logistic equations. By abstract we mean that the state space of the equation may be infinite dimensional. The results are thus applicable to partial differential equations, and particularly, to structured population models in which age, size, or other properties of individuals are independent variables. The equations have the form

\[ u'(t) = Au(t) - F(u(t))u(t) + f, \quad t \geq 0, \quad u(0) = x \in X_+, \]  

where the following hypotheses are assumed:

(H.1) \( A \) is the infinitesimal generator of a strongly continuous semigroup of positive linear operators \( T(t) \), \( t \geq 0 \), in the Banach lattice \( X \) with positive cone \( X_+ \);
(H.2) \( F \) is a positive linear functional on \( X \);
(H.3) \( f \in X_+ \).

In population models the solution \( u(t) \) of (1) corresponds to the population density at time \( t \). The linear term \( Au(t) \) in (1) corresponds to intrinsic growth, loss, or transition processes in the population independent of population density. The nonlinear logistic term \( -F(u(t))u(t) \) in (1) corresponds to loss processes due to crowding at a rate proportional to a functional of the population density. Lastly, the constant term \( f \) in (1) corresponds to an external source of population growth, independent of the population density.

We investigate three types of behaviour exhibited by the linear process in the equations. In each case the linear equation exhibits an asymptotic stabilization masked by an unbounded exponential or polynomial factor in time. In each case we prove (in Appendix A) that the nonlinear equation converges asymptotically to a behaviour consistent with the unmasked behaviour of the linear equation.

In Section 2 we consider the case that \( T(t) \), \( t \geq 0 \) has asymptotic polynomial exponential growth and \( f = 0 \). We illustrate this case with a model of telomere shortening in somatic cell lines due to Arino et al. [4]. In Section 3 we consider the case that \( T(t) \), \( t \geq 0 \) has asymptotic exponential growth and \( f = 0 \). We illustrate this case with a model of proliferating and quiescent cells due to Arino et al. [5]. In Section 4 we consider the case that \( T(t) \), \( t \geq 0 \) has asymptotic periodic exponential growth and \( f = 0 \). We illustrate this case with a model of malignant cell proliferation in tumour cords due to Bertuzzi and Gandolfi [14]. In Section 5 we provide a discussion of the consequences of logistic feedback control for proliferating cell populations, and we contrast normal cell lines, which have a limited number of divisions, and tumour cell lines, which have an unlimited number of divisions.

2. The linear process has polynomial exponential growth and \( f = 0 \)

In this section we assume

(H.4) \( x \in X_+ \) and \( \lim_{t \to \infty} t^n e^{-i\lambda t} T(t) x = P_0 x \) where \( n \) is a positive integer, \( \lambda_0 \in \mathbb{R} \), and \( P_0 \) is a bounded linear operator in \( X \);
(H.5) $FP_0x > 0$.

Set

$$S(t)x = \frac{T(t)x}{1 + \int_0^T F(T(s)x) \, ds}.$$  \hspace{1cm} (2)

**Theorem 1.** Let (H.1)–(H.5) hold and let $f = 0$.

(i) If $x \in D(A)$, then $u(t) = S(t)x$ is the unique solution of (1);
(ii) If $\lambda_0 < 0$, then $\lim_{t \to \infty} S(t)x = 0$;
(iii) If $\lambda_0 \geq 0$, then $\lim_{t \to \infty} S(t)x = \frac{\lambda_0 p_{0x}}{F(P_0x)}$.

**Example 1.** In [3] Arino et al. proposed a model of telomere loss in proliferating cell population lines. The model is based on the ‘end-replication’ hypothesis, which assumes that incomplete replication of DNA occurs at the ends of chromosomes during mitosis [26,29]. In this model ends of chromosomes are capped by tandem repeats of DNA segments called telomeres. Each time a cell divides the telomeres shorten in the subsequent generation and when a critical number is reached no further divisions occur. This critical number is known as the Hayflick limit and is estimated to be 40–80 in somatic vertebrate cells [22,23]. The loss of telomeres is hypothesized as an explanation for the finite proliferative capacity of cell lines [21,30].

In [4] Arino et al. investigated this telomere loss model with overlapping generations. In this model cell cycle position is tracked by cell age with newly divided cells assigned age 0. Since a distribution of ages at division is incorporated, the model allows for overlapping generations of cell lines. The linear model in [4] has no cell mortality and the only loss of cells is due to division. The linear model in [4] ($s = 0$) is extended to a version with logistic nonlinearity ($s > 0$) as follows: Let $X = L^1((0,a_1); \mathbb{R}^{N+1})$ with norm

$$\|\tilde{\phi}\| = \sum_{j=0}^N \int_0^{a_1} |\phi_j(a)| \, da, \quad \tilde{\phi} \in X.$$  \hspace{1cm} (3)

The model is formulated as the system of partial differential equations

$$\frac{\partial}{\partial t} p_j(a,t) + \frac{\partial}{\partial a} p_j(a,t) = -\beta_j(a)p_j(a,t) - \tau \left( \sum_{k=0}^{N} \int_0^{a_1} p_k(\bar{a},t) \, d\bar{a} \right) p_j(a,t), \quad j = 0, \ldots, N,$$  \hspace{1cm} (3)

$$p_j(0,t) = 2\sum_{k=0}^{N} p_{jk} \int_0^{a_1} \beta_k(a)p_k(a,t) \, da, \quad t \geq 0,$$  \hspace{1cm} (4)

$$p_j(a,0) = \phi_j(a), \quad j = 0, \ldots, N, \quad \tilde{\phi} = [\phi_0, \ldots, \phi_N]^t \in X, \quad a \in (0,a_1).$$  \hspace{1cm} (5)

In the model $p_j(a,t)$ is the density of cells with age $a$ at time $t$ in the $j$th telomere state, $\beta_j(a)$ is the age-specific division modulus, 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, \( j = 1, 2, \ldots, N \) 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 0th state produces one daughter cell in the 0th state and one daughter cell which does not divide.

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 probabilities \( p_{jk} \) satisfy \( p_{jk} > 0 \), \( p_{jk} = 0 \) if \( j > k \), \( p_{kk} = \frac{1}{2} \), \( k = 0, \ldots, N \), and \( \sum_{j=0}^{k-1} p_{jk} = \frac{1}{2} \), \( k = 1, \ldots, N \). An example of the descent of telomere classes is illustrated in Fig. 1.

In [4] it is proved for the linear case (\( s = 0 \)) that the densities correspond to a strongly continuous semigroup of bounded linear operators \( T(t), t \geq 0 \) in \( X \) given by the formula

\[
T(t) \begin{bmatrix}
  \phi_0 \\
  \vdots \\
  \phi_N 
\end{bmatrix} = \begin{bmatrix}
  p_0(\cdot, t) \\
  \vdots \\
  p_N(\cdot, t)
\end{bmatrix}, \quad t \geq 0.
\]

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

\[
\begin{bmatrix}
  \phi_0 \\
  \vdots \\
  \phi_N 
\end{bmatrix} = \begin{bmatrix}
  -\phi_0' - \beta_0 \phi_0 \\
  \vdots \\
  -\phi_N' - \beta_N \phi_N
\end{bmatrix}
\]

Fig. 1. The telomere classes of the model with \( N = 3 \), \( p_{33} = p_{22} = p_{11} = p_{00} = p_{23} = p_{12} = p_{01} = .5 \), and all other \( p_{jk} = 0.0 \). Each cell produces one daughter in the same class and one daughter in the next lower class, except class (0) produces only one daughter in the same class. In the absence of cell mortality, the highest class (3) remains constant each generation, while class (2) grows linearly, class (1) grows quadratically, and class (0) grows cubically.
with domain

\[ D(A) = \left\{ \begin{bmatrix} \phi_0 \\ \vdots \\ \phi_N \end{bmatrix} \in X : \begin{bmatrix} \phi'_0 + \beta_0 \phi_0 \\ \vdots \\ \phi'_N + \beta_N \phi_N \end{bmatrix} \in X, \right\} \]

\[ \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 \}

In [4] it is proved that the semigroup \( T(t), t \geq 0 \) satisfies (H.4) with \( \lambda_0 = 0 \) and \( n = N \), where \( P_0 \) has 1-dimensional range. Specifically,

\[ T(t) = \sum_{j=0}^{N} \frac{t^j}{j!} A_0^j \Pi_0 + T(t) \Pi_1, \]

Fig. 2. The telomere classes of the model with \( N = 3, \tau = .1, a_1 = 2.0, \phi_3(a) = \max\{0.0, 10.0a(5 - a)\}, \phi_2 = \phi_1 = \phi_0 = 0.0, \beta_3(a) = \max\{0.0, (a - .5)e^{2.0a}\}, \beta_2 = \beta_1 = \beta_0 = \max\{0.0, (a - .5)e^{2.0a}\}, \; p_{33} = p_{22} = p_{11} = p_{00} = .5, \; p_{23} = p_{12} = p_{01} = .5, \; p_{13} = p_{02} = p_{03} = 0.0. \]
where $\Pi_0$ is a projection onto the $N+1$-dimensional generalized eigenspace $A$ of the 0 eigenvalue of $A$, $\Pi_1 = I - \Pi_0$, and $T(t)\Pi_1 = o(e^{-\epsilon t})$, $\epsilon > 0$. Hypothesis (H.4) is satisfied with $\lambda_0 = 0$, $n = N$, and $P_0 = \frac{1}{N} A_0^N \Pi_0$ with $A_0$ the nilpotent $N+1 \times N+1$ matrix (restricted to the subspace $A$)

$$A_0 = \begin{pmatrix}
0 & 1 & 0 & \cdots & 0 & 0 \\
0 & 0 & 1 & \cdots & 0 & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
0 & 0 & 0 & \cdots & 0 & 1 \\
0 & 0 & 0 & \cdots & 0 & 0
\end{pmatrix}, \quad A_0^N = \begin{pmatrix}
0 & 0 & 0 & \cdots & 0 & 1 \\
0 & 0 & 0 & \cdots & 0 & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
0 & 0 & 0 & \cdots & 0 & 0 \\
0 & 0 & 0 & \cdots & 0 & 0
\end{pmatrix}.$$ 

Thus, for the linear case ($\tau = 0$) $p_j(\cdot,t)$ grows polynomially in time $t$ of order $t^{N-j}$, $j = 0,1,\ldots,N$. The lower states thus grow faster, the 0th state grows the fastest, and further, the limit as time goes to infinity of the fraction of cells in the $j$th state $p_j(\cdot,t)/\|T(t)\phi\|$ depends only on the initial reservoir of cells in the highest state $\phi_N(a)$.

Theorem 1 is applicable to the nonlinear logistic version of this model ($\tau > 0$) with $T(t)$, $t \geq 0$ and $P_0$ as above. Set

$$F\tilde{\phi} = \tau \sum_{j=0}^N \int_0^{a_j} \phi_j(a) \, da, \quad \tilde{\phi} \in X_+, \quad FA_0^N \Pi_0 \tilde{\phi} > 0,$$

and (H.5) is satisfied. Since $\lambda_0 = 0$, Theorem 1 (ii) implies $\lim_{t \to \infty} S(t)\tilde{\phi} = \tilde{0}$ and all the telomere classes $p_j$, $j = 0,1,\ldots,N$ converge to 0. The extinction of the telomere classes in the case with logistic nonlinearity ($\tau > 0$) is illustrated in Figs. 2 and 3.

3. The linear process has exponential growth and $f \neq 0$

In this section we assume (H.1)–(H.3) and

(H.6) $T(t)x = e^{\lambda_0 t} P_0 x + T(t)P_1 x, x \in X, t \geq 0$, where $\lambda_0 \in \mathbb{R}$, $P_0$ is a projection in $X$, $P_1 = I - P_0$, and there exists $\lambda_1 < \lambda_0$ and $M > 0$ such that $|T(t)P_1| \leq Me^{\lambda_1 t}, t \geq 0$;

(H.7) $f \in X_+$ and $FP_0 f > 0$. 

Fig. 3. The extinction of the telomere class total populations in Fig. 2: $T_j(t) = \int_0^\infty p_j(a,t) \, da$, $j = 0,1,2,3$. (A) $T_3(t)$, (B) $T_2(t)$, (C) $T_1(t)$ and (D) $T_0(t)$. The most primitive telomere class $p_3$ extinguishes first.
Theorem 2. Let (H.1)–(H.3), (H.6), (H.7) hold.

(i) For each \( x \in X_+ \) there is a unique solution \( u(t) = u(t; x) \) of the equation

\[
 u(t) = T(t)x - \int_0^t T(t-s)F(u(s))u(s)\,ds + \int_0^t T(s)f\,ds, \quad t \geq 0;
\]

(ii) There exists a unique solution \( \lambda > \lambda_0 \) of the equation

\[
 \lambda = F(\lambda I - A)^{-1}f
\]

and \( x_0 := (\lambda I - A)^{-1}f \) is the unique non-trivial equilibrium solution of (1) in \( X_+ \);

(iii) \( x_0 \) is a locally exponentially asymptotically stable equilibrium of the nonlinear semigroup \( S(t) \), \( t \geq 0 \) in \( X_+ \) defined by \( S(t)x = u(t; x) \), \( x \in X_+ \), \( t \geq 0 \) (that is, there exists \( \epsilon > 0, \delta > 0, K > 0 \) such that if \( x \in X_+ \) and \( \|x - x_0\| < \epsilon \), then \( \|S(t)x - x_0\| \leq Ke^{-\delta t}\|x - x_0\|, \ t \geq 0 \)).

Example 2. Mathematical models of quiescence in cell populations have been developed in many studies, including [1,2,6,7,15,19,20,25,27,28,31,32]. In [5] Arino et al. studied a model of cell population dynamics with proliferating and quiescent cells structured by age. A goal of this study was to understand how tumour cell populations could recover from therapeutic intervention, even when reduced to a very small size. One approach to this problem involves the concept of asynchronous exponential growth, in which a population grows exponentially and expands through the entire range of a structure variable from any initial value \((33,34,37)\). The hypothesis (H.6) implies that \( T(t) \), \( t \geq 0 \) has asynchronous exponential growth if the spectral projection \( P_0 \) has finite rank and is strictly positive in \( X_+ \) (that is, \( \langle P_0x, x^* \rangle > 0 \) for any \( x \neq 0 \in X_+ \), and \( x^* \neq 0 \in X_+^* \)). In this case \( \lim_{t \to \infty} e^{-\lambda t}T(t)x = P_0x \neq 0 \) for any \( x \in X_+, x \neq 0 \). Thus, if the tumour is not completely destroyed by the therapy, it renews its growth from any re-set initial value, however small.

In [5] these concepts are investigated for the linear version \( (\tau = 0, f_p = 0, f_q = 0) \) of the following model: Let \( X = L^1_+(0, a_1) \times L^1_+(0, a_1) \) 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. In this model proliferating cells are capable of entering a quiescent state at any point in the cell cycle, as well as returning to the proliferating state at that point from quiescence. The densities satisfy the initial-boundary value problem

\[
 \frac{\partial}{\partial t} p(a,t) + \frac{\partial}{\partial a} p(a,t) = -\beta(a)p(a,t) - \sigma(a)p(a,t) + \rho(a)q(a,t) - \tau N(a)p(a,t) + f_p(a),
\]

\[
 \frac{\partial}{\partial t} q(a,t) + \frac{\partial}{\partial a} q(a,t) = \sigma(a)p(a,t) - \rho(a)q(a,t) - \tau N(a)q(a,t) + f_q(a),
\]

\[
 p(0,t) = 2 \int_0^{a_1} \beta(a)p(a,t)\,da, \quad t \geq 0, \quad q(0,t) = 0, \quad t \geq 0,
\]

\[
 p(a,0) = \phi(a), \quad \phi \in L^1_+(0, a_1), \quad q(a,0) = \psi(a), \quad \psi \in L^1_+(0, a_1),
\]

where \( N(t) = \int_0^{a_1} (p(a,t) + q(a,t))\,da \). The division rate is modulated by \( \beta \in L^\infty_+(0, a_1) \) and the transition rates between the proliferating state and the quiescent state are modulated by
\[ \sigma \in L^1(t_0, t_1) \text{ and } \rho \in L^1(t_0, t_1). \] It is assumed that division is the only cause of cell loss, only proliferating cells divide, and all daughter cells are born into the proliferating state (see also [15]).

In [5] it is proved that the following hypotheses provide necessary and sufficient conditions for strictly positive and having one-dimensional range:

\[ (i) \text{ There exists } \epsilon_0 \in (0, a_1) \text{ such that } \forall \epsilon \in (0, \epsilon_0), \int_{a_1-a}^{a_1} \beta(a) \, da > 0. \]
\[ (ii) \text{ There exists } \epsilon_1 \in (0, a_1) \text{ such that } \forall \epsilon \in (0, \epsilon_1), \int_{a_1-a}^{a_1} \rho(a) \, da > 0. \]
\[ (iii) \text{ There exists } \epsilon_2 > 0 \text{ such that } \forall \epsilon \in (0, \epsilon_2), \int_0^\epsilon \sigma(a) \, da > 0. \]

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.

Theorem 2 is applicable to the nonlinear version of this model \((\tau > 0 \text{ and } f \in X_+, f = [f_p, f_q] \neq [0, 0]^T)\). Set

\[ F \left[ \begin{array}{c} \phi \\ \psi \end{array} \right] = \tau \int_0^{a_1} (\phi(a) + \psi(a)) \, da, \quad \left[ \begin{array}{c} \phi \\ \psi \end{array} \right] \in X_+. \]

Since \( P_0 \) is strictly positive, (H.7) is satisfied if \( \tau > 0 \) and \( f \in X_+, f \neq 0 \). Thus, there exists a unique non-trivial equilibrium solution which is locally exponentially asymptotically stable. Theorem 2 implies that in the presence of on-going logistic loss, this cell population will not extinguish if there is an external source of either proliferating or quiescent cells.

4. The linear process has periodic exponential growth and \( f = 0 \)

In this section we assume (H.1)–(H.2), \( f = 0 \), and

\[ (H.8) \quad T(t), t \geq 0 \text{ satisfies for each } x \in X_+, \lim_{t \to \infty} (e^{-\lambda t} T(t)x - R(t)x) = 0, \text{ where } \lambda_0 \in \mathbb{R} \text{ and } R(t), t \geq 0 \text{ is a rotation semigroup in } X \text{ with period } p \text{ (that is, } R(t), t \geq 0 \text{ is a strongly continuous linear semigroup in } X \text{ satisfying } R(p) = I). \]
\[ (H.9) \quad x \in X_+ \text{ and } \int_0^p F(R(t)x) \, dt > 0. \]
Theorem 3. Let (H.1)–(H.2), (H.8), (H.9) hold and let \( f = 0 \). Then \( S(t)x \) as in (2), satisfies

(i) If \( \lambda_0 \leq 0 \), then \( \lim_{t \to \infty} S(t)x = 0 \);
(ii) If \( \lambda_0 > 0 \), then \( \lim_{t \to \infty} (S(t)x - W(t)x) = 0 \) where

\[
W(t)x = \frac{(e^{\lambda_0 p} - 1)e^{\lambda_0 t}R(t)x}{F(\int_0^p e^{\lambda_0 s}R(s)x ds) + (e^{\lambda_0 p} - 1)F(\int_0^t e^{\lambda_0 s}R(s)x ds)}
\]

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

Example 3. In [14] Bertuzzi and Gandolfi propose a model of malignant cell proliferation in solid vascularized tumours known as tumour cords. Tumour cords are cylindrical formations of cancerous cells surrounding blood vessels in the micro-architecture of certain natural and experimental tumours. Because of their experimentally quantifiable characteristics, tumour cords have been modeled in several recent studies [8–13,16,17,38]. In [17] we studied a model for the evolution of a tumour cord structured by cell age and radial position. In this model \( p(a, r, t) \) represents the normalized cross-sectional density of proliferating tumour cells with respect to age \( a \) and radial position \( r \) at time \( t \). Mother cells divide exactly at age \( T_c \) to produce two daughter cells of age 0 at radial position \( r \), a fraction \( \theta_0(r) \) of which enter the cell cycle, with the remaining fraction \( \theta_0(r) - 1 \) entering quiescence. When \( \theta_0(r) \) is independent of \( r \), the density \( p(a, t) \) is independent of \( r \) and satisfies the following initial-boundary value problem:

\[
\begin{align*}
\frac{\partial}{\partial t} p(a, t) + \frac{\partial}{\partial a} p(a, t) + p(T_c, t)p(a, t) &= 0, \\
p(0, t) &= 2\theta_0 p(T_c, t), \\
p(a, 0) &= \phi(a),
\end{align*}
\]

where \( 0 \leq a \leq T_c, t \geq 0, 0 < \theta_0 \leq 1 \) and \( \phi \geq 0 \).

The logistic nonlinearity in (8) arises from the assumption in [14] that the radially outward flux of cells produced by cell division is limited by a constant density of cells per unit volume in the cord. We can analyze the solutions of (8) using Theorem 3. Consider the associated linear problem

\[
\begin{align*}
\frac{\partial}{\partial t} V(a, t) + \frac{\partial}{\partial a} V(a, t) &= 0, \\
V(0, t) &= 2\theta_0 V(T_c, t), \\
V(a, 0) &= \phi(a).
\end{align*}
\]

The solution is

\[
V(a, t) = \begin{cases} \phi(a) & \text{if } t = 0, \\ (2\theta_0)^n \phi(nT_c - t + a) & \text{if } t > 0 \quad \text{and} \quad (n - 1)T_c < t - a \leq nT_c, \end{cases}
\]

where \( n = 0, 1, 2, \ldots \) Let \( X \) be the Banach space \( \{ \phi \in C[0, T_c], \phi(0) = 2\theta_0\phi(T_c) \} \) with sup norm \( ||\cdot|| \). Given \( \phi \in X \), let \( V(a, t) \) be the solution of the linear problem (9). Set \( T(t)\phi(a) = V(a, t) \) and then \( T(t), t \geq 0, \) is a strongly continuous semigroup of bounded linear operators in \( X \). In fact, from
Thus, the semigroup \( T(0) = I \) and \( T(t + s) = T(t)T(s) \). Further, let \( (n - 1)T_c < t - a < nT_c \), so \( T(t)\phi(a) = (2\theta_0)^n\phi(nT_c - t + a) \) and \( \frac{T_c}{2} - 1 < n < \frac{T_c}{2} + 1 \), hence
\[
\|T(t)\phi\| \leq (2\theta_0)^n\|\phi\| \leq M(2\theta_0)^{\frac{T_c}{2}}\|\phi\| = Me^{\lambda_0\|\phi\|},
\]
where \( M = \max\{2\theta_0, \frac{1}{2\theta_0}\} \) and \( \lambda_0 = \frac{\log(2\theta_0)}{T_c} \).

The infinitesimal generator of the semigroup \( T(t), t \geq 0 \) is the operator \( A \),
\[
D(A) = \{\phi \in X, \phi' \text{ exists and } \phi' \in X\}, \quad A\phi = -\phi'.
\]

If we denote by \( P\sigma(A) \) the point spectrum of \( A \), it is easy to check that \( P\sigma(A) = \{\lambda_0 \pm \frac{2\pi n i}{T_c}, n = 0, 1, 2, \ldots\} \), and \( \lambda_0 \) is an eigenvalue with multiplicity 1. In fact, the eigenvectors with eigenvalue \( \lambda_0 \) are the functions \( ce^{\lambda_0 t} \) where \( c \in \mathbb{C} \).

Note that \( T(t + T_c)\phi(a) = 2\theta_0 T(t)\phi(a) \), and so \( R(t) = \exp(-\lambda_0 t)T(t) \) satisfies
\[
R(t + T_c)\phi(a) = e^{-\lambda_0 t + \frac{T_c}{2}}T(t + T_c)\phi(a) = e^{-\lambda_0 t}(2\theta_0)^{-1}2\theta_0 T(t)\phi(a) = R(t)\phi(a).
\]
Thus, the semigroup \( T(t), t \geq 0 \) satisfies (H.8) with rotation semigroup \( R(t), t \geq 0 \), period \( p = T_c \), growth bound \( \hat{\lambda}_0 = \frac{\log(2\theta_0)}{T_c} \), and \( \epsilon(t) \equiv 0 \). Note also that \( T(t), t \geq 0 \) is a positive semigroup in \( X \), since \( \phi \in X_+ = \{\phi \in X, \phi \geq 0\} \) implies \( T(t)\phi \geq 0 \).

Set \( F\phi = \phi(T_c) \), and then \( F \) is a bounded linear functional on \( X \) such that \( F\phi \geq 0 \) for \( \phi \in X_+ \). If \( \phi \in X_+ \), such that \( \int_0^T F(R(t)\phi) \, dt > 0 \), then (H.9) is satisfied. Theorem 3 is thus applicable to establish the convergence of the solution of (8) to a periodic solution when \( \theta_0 > \frac{1}{2} \) [17]. Thus, if there is no dispersion of division ages through successive generations, the tumour cord cell population synchronizes in the sense that cells at a given point of the cell cycle oscillate periodically in time.

5. Discussion

Mathematical modeling of cell population dynamics involves multiple complex elements. Among these are the proliferation of cell lines in overlapping generations, the rates at which cells progress through the cell cycle, the fraction of cells which divide, the transition between cycling and quiescence, and the control mechanisms which stabilize these processes. The partial differential equations of structured cell population models provide a useful framework to examine these various elements. Cell age is a natural device to track cell cycle progression through overlapping generations. Age-dependent rates of division, transition, and mortality can describe the fates of individual cells, and age-dependent and density dependent nonlinearities can effect control of the total population over time.

A fundamental distinction of cell lines is whether their proliferative capacity is limited or unlimited. The distinction is important, because normal cell lines are usually limited and cancer cell lines are not. In Example 1 we developed an age structured model of cell line limitation based on telomere shortening. Telomere shortening may itself be a control mechanism for cell population growth, but in the linear version of this model (without any mortality) the total population grows polynomially to infinity. In Example 1 we placed a nonlinear logistic feedback mortality in the model, which, by Theorem 1, drives the entire population to extinction. Thus, telomere limited proliferative capacity and logistic feedback mortality together exert over-control of the system. In future work we will investigate a modification of this model, in which the highest telomere class
(the most primitive stem cells) is exempted from the logistic mortality. Numerical simulations indicate that solutions of this modified version of Example 1 stabilize to a globally attracting non-trivial equilibrium.

Quiescence is a fundamental property of cell populations, particularly in late-stage tumours. In Example 2 we analyzed an age-structured model of cell population dynamics with proliferating and quiescent compartments. The linear version of this model (without logistic loss or external source) exhibits asynchronous exponential growth, which means the population will grow from any initial value (the initial distribution may contain cells in any age range and either the proliferating or quiescent state). In Example 2 we added a logistic mortality and an external source to this model, and by Theorem 2, the system has a unique non-trivial stable equilibrium. The model is applicable to continuous cancer chemotherapy. In this model continuous therapy will not destroy the tumour if some quiescent tumour cells can migrate and enter proliferation.

Another important distinction of cell populations is their capacity to synchronize or de-synchronize individual movement through the cell cycle. This property is important in tumour therapy in which one drug first synchronizes cell phase and a second drug destroys cells in that phase. In Example 3 we presented an age-structured model with logistic nonlinearity for the growth of a tumour cord cell population. In this model all cells divide at exactly the same age, and by Theorem 3, the solutions stabilize to a time periodic solution dependent on the initial value. Thus, in this model all cells ultimately move through the cell cycle in synchronization, because there is no dispersion of the ages of division in cell lines.

**Appendix A**

**Proof of Theorem 1.** To prove (i) observe that for $t \geq 0$

$$u'(t) = \frac{(1 + \int_0^t F(T(s)x)\,ds)AT(t)x - F(T(t)x)T(t)x}{(1 + \int_0^t F(T(s)x)\,ds)^2} = Au(t) - F(u(t))u(t).$$

The proof of (ii) is immediate from (H.4)and (H.5). To prove (iii) observe that

$$\lim_{t \to \infty} t^{-n}e^{-\lambda_0 t}Q(t) = \begin{cases} \infty & \text{for } \lambda_0 = 0 \\ \frac{1}{\lambda_0} & \text{for } \lambda_0 > 0 \end{cases}$$

where $Q(t) = \int_0^t s^n e^{\lambda_0 s} \,ds$.

Let

$$C(t) = \int_0^t s^n e^{\lambda_0 s} F(s^{-n}e^{-\lambda_0 s} T(s)x - P_0x) \,ds, \quad t \geq 0.$$ 

and observe that

$$|C(t)| \leq |C(t_1)| + Q(t)|F| \sup_{s \geq t_1} ||s^{-n}e^{-\lambda_0 s} T(s)x - P_0x||, \quad t \geq t_1 \geq 0, \quad (11)$$

From (2)

$$S(t)x = \frac{P_0x + t^{-n}e^{-\lambda_0 t} T(t)x - P_0x}{t^{-n}e^{-\lambda_0 t}(1 + Q(t)FP_0x + C(t))}. \quad (12)$$
The numerator of (12) → $P_0x$ as $t \to \infty$ by (H.4). If $\lambda_0 = 0$, then (11) implies there exists $t_1 > 0$ such that if $t > t_1$, $|C(t)| = Q(t)/2$; thus the denominator of (12) → $\infty$ as $t \to \infty$. If $\lambda_0 > 0$, then (H.4) and (11) imply that $\lim_{t \to \infty} t^{-\epsilon}e^{-\lambda_0 t}C(t) = 0$; thus the denominator of (12) → $\infty$ as $t \to \infty$ by (H.5).

**Remark.** If $x \not\in D(A)$, then $u(t)$ is known as a mild solution of (1). The proof of (i) does not require that $F$ is linear, but only that $F$ is positive homogenous (that is, $F(cx) = cF(x)$ for all $c \geq 0$ and $x \in X_+$. Also, if the range of $P_0$ is 1-dimensional, then the limit in (iii) is independent of $x$. The case that $n = 0$ is treated in [36].

**Proof of Theorem 2.** The proof of (i) is standard [18, p. 87]. The solution of the integral equation (6) is known as a mild solution of (1) (it agrees with the solution of (1) when $x \in D(A)$). To prove the existence of a unique solution to (7), let $\lambda > \lambda_0$ and observe that

\[
(\lambda I - A)^{-1}f = (\lambda I - A)^{-1}(P_0f + P_1f) = \frac{P_0f}{\lambda - \lambda_0} + (\lambda I - A)^{-1}P_1f \Rightarrow
\]

\[
0 \leq F\left(\int_0^\infty e^{-\lambda t}T(t)f \, dt\right) = F((\lambda I - A)^{-1}f) = \frac{F(P_0f)}{\lambda - \lambda_0} + F((\lambda I - A)^{-1}P_1f).
\]

By (H.8)

\[
\left|F((\lambda I - A)^{-1}P_1f)\right| = \left|F\left(\int_0^\infty e^{-\lambda t}T(t)P_1f \, dt\right)\right| \leq \frac{\|F\|\|M\|\|f\|}{\lambda - \lambda_1}.
\]

Then, (14) and (15) and (H.9) imply

\[
\lim_{\lambda \to \lambda_0} F((\lambda I - A)^{-1}f) = \infty \quad \text{and} \quad \lim_{\lambda \to \infty} F((\lambda I - A)^{-1}f) = 0.
\]

Further, from [24, p. 37],

\[
\frac{d}{d\lambda} F((\lambda I - A)^{-1}f) = -F((\lambda I - A)^{-2}f) < 0,
\]

which implies that $F((\lambda I - A)^{-1}f)$ is decreasing in $\lambda$. Thus, there must exist a unique solution $\lambda$ to (7) such that $\lambda > \lambda_0$. Notice that $x_0 := (\lambda I - A)^{-1}f > 0$, since $f \in X_+$, $\lambda \in \rho(A)$ (the resolvent set of $A$), and $(\lambda I - A)^{-1}(X_+) \subseteq X_+$. The proof that $x_0$ is an equilibrium solution of (1) is immediate. To prove the uniqueness, let $\tilde{x} \in X_+, \tilde{x} \neq 0$, be an equilibrium of (1) and set $\tilde{\lambda} = F\tilde{x}$. Observe the following: $P_0\tilde{x} = \lim_{t \to \infty} e^{-\lambda_0 t}T(t)\tilde{x} \in X_+$; $P_0f > 0$ by (H.9); and $P_0Ax = \lambda_0 P_0\tilde{x}$. Then, $(\lambda - \lambda_0)P_0\tilde{x} = P_0f$, which implies that $\lambda > \lambda_0$. Thus, $\lambda = F((\lambda I - A)^{-1}f)$, which implies that $\tilde{x} = x_0$.

Observe that the linearization $L$ about $x_0$ is

\[
Lx = Ax - F(x_0)x - F(x)x_0, \quad x \in X.
\]

We next compute the essential growth bound $\omega_1(L)$ of $L$ (see [35] for the properties of the essential growth bound, p. 161, p. 171, and p. 179). Observe that the linear operator $G(\phi) := \tilde{F}(\phi)x_0, \phi \in X$ is compact. Then $\omega_1(G) = 0$ (see [35, p. 179]). Let $\mu$ be the measure of non-compactness (see [35, p. 165]). Then,
\[
\omega_1(L) = \omega_1(A - F(x_0)I - G) = \omega_1(A - F(x_0)I) = \lim_{t \to \infty} \frac{1}{t} \log(\|e^{-tF(x_0)}T(t)\|)
\]
\[
= \lim_{t \to \infty} \frac{1}{t} \log(\|e^{-tF(x_0)}z(T(t))\|) = \lim_{t \to \infty} \frac{1}{t} \log(e^{-tF(x_0)}z(T(t)))
\]
\[
= \lim_{t \to \infty} \frac{1}{t} (-tF(x_0) + \log(\|z(T(t))\|)) = -F(x_0) + \omega_1(A) = -\lambda + \omega_1(A).
\] (17)

Let \(\sigma(L)\) be the spectrum of \(L\) and let \(E\sigma(L)\) be the essential spectrum of \(L\). From [35, p. 171],
\[
\omega_0(L) = \max \left\{ \omega_1(L), \sup_{\hat{\lambda} \in \sigma(L) - E\sigma(L)} \text{Re} \hat{\lambda} \right\} = \max \left\{ -\lambda + \omega_1(A), \sup_{\hat{\lambda} \in \sigma(L) - E\sigma(L)} \text{Re} \hat{\lambda} \right\}.
\] (18)

From Proposition 4.17, p. 198 of [35], it suffices to show that \(\omega_0(L) < 0\). Since \(\omega_1(A) \leq \omega_0(A)\) always and \(\omega_0(A) = \lambda_0 < \lambda\), (18) yields that it is sufficient to show that
\[
\sup_{\hat{\lambda} \in \sigma(L) - E\sigma(L)} \text{Re} \hat{\lambda} < 0.
\] (19)

If \(\hat{\lambda} \not\in E\sigma(L)\), then \(\hat{\lambda}\) is an eigenvalue of \(L\). So it suffices to show that the eigenvalues of \(L\) all have negative real part. Let \(\gamma\) be an eigenvalue of \(L\) with eigenvector \(x\), that is, \(Lx = \gamma x, x \neq 0\). Let \(\gamma = a + ib\) and assume \(a = \text{Re} \gamma \geq 0\).

Case 1. \(\gamma \neq 0\). Note that \(F(x_0) + \gamma = \hat{\lambda} + \gamma \in \rho(A)\). Then,
\[
Lx = \gamma x \Rightarrow (A - (\hat{\lambda} + \gamma)I)x = F(x)x_0 \Rightarrow x = (A - (\hat{\lambda} + \gamma)I)^{-1}F(x)x_0 \Rightarrow F(x)
\]
\[
= F(x)F((A - (\hat{\lambda} + \gamma)I)^{-1}x_0).
\]

Note that \(F(x) \neq 0\), since \(\hat{\lambda} + \gamma \in \rho(A)\). Thus,
\[
1 = F((A - (\hat{\lambda} + \gamma)I)^{-1}x_0) = F((A - (\hat{\lambda} + \gamma)I)^{-1}(\hat{\lambda}I - A)^{-1}f)
\]
\[
= -F\left(\frac{(A - (\hat{\lambda} + \gamma)I)^{-1}f - (A - \hat{\lambda}I)^{-1}f}{(\hat{\lambda} + \gamma) - \hat{\lambda}}\right),
\]
where we have used the resolvent identity [24, p. 36]. Then,
\[
-\gamma = F((A - (\hat{\lambda} + \gamma)I)^{-1}f - (A - \hat{\lambda}I)^{-1}f) = F\left(-\int_0^\infty e^{-t(\hat{\lambda} + \gamma)}T(t)f \, dt + \int_0^\infty e^{-t\hat{\lambda}}T(t)f \, dt\right)
\]
\[
= \int_0^\infty e^{-t\hat{\lambda}}(1 - e^{-it})F(T(t)f) \, dt \Rightarrow
\]
\[
- (a + ib) = \int_0^\infty e^{-t\hat{\lambda}}(1 - e^{-it}) \cos bt F(T(t)f) \, dt - i \int_0^\infty e^{-t(\hat{\lambda} + a)} \sin bt F(T(t)f) \, dt \Rightarrow
\]
\[
- a = \int_0^\infty e^{-t\hat{\lambda}}(1 - e^{-it}) \cos bt F(T(t)f) \, dt
\]
which contradicts the positivity of \(a\), \(F\), and \(T(t)f\).

Case 2. \(\gamma = 0\) \((a = b = 0)\).
\[
Lx = Ax - F(x_0)x - F(x)x_0 = 0 \Rightarrow (A - \hat{\lambda}I)x = F(x)x_0 \Rightarrow x = F(x)(A - \hat{\lambda}I)^{-1}x_0.
\]
If \( F(x) \neq 0 \), we have
\[
1 = -F((\lambda I - A)^{-1}x_0)
\]
and the positivity of \( F \) and \((\lambda I - A)^{-1}x_0\) are contradicted. If \( F(x) = 0 \), then \( Ax = \lambda x_0 \), and \( \lambda \in \rho(A) \). But \( \lambda \in \rho(A) \) is then contradicted, since \( \lambda > \lambda_0 > 0 \). Thus, \( \text{Re} \gamma = a < 0 \). \( \square \)

**Proof of Theorem 3.** Let \( \epsilon(t) = e^{-\lambda t}T(t)x - R(t)x, t \geq 0 \). Note that if \( \epsilon(t) \equiv 0 \), then \( W(t)x = S(t)x \)

where
\[
z = \frac{(e^{i\omega p} - 1)x}{F\left(\int_0^p T(s)x\,ds\right)}.
\]
The result is immediate if \( \lambda_0 \leq 0 \), so suppose \( \lambda_0 > 0 \). Let \( t = np + h \) where \( n = 0, 1, 2, \ldots \) and \( h \in (0, p] \). Then
\[
S(t)x = \frac{\frac{T(np + h)x}{1 + F\left(\sum_{k=0}^{n-1} \int_{kp}^{(k+1)p} T(\sigma)x\,d\sigma + \int_{np}^{np+h} T(\sigma)x\,d\sigma\right)}}{1 + F\left(\sum_{k=0}^{n-1} \int_{kp}^{(k+1)p} T(\sigma)x\,d\sigma + \int_{np}^{np+h} T(\sigma)x\,d\sigma\right)}.
\]
But
\[
T(np + h)x = e^{i\omega(p+h)}(R(np + h)x + \epsilon(np + h)) = e^{i\omega p}e^{i\omega h}(R(h)x + \epsilon(np + h)).
\]
For simplicity we take first \( \epsilon(t) = 0 \). So
\[
F\left(\sum_{k=0}^{n-1} \int_{kp}^{(k+1)p} T(\sigma)x\,d\sigma\right) = F\left(\sum_{k=0}^{n-1} \int_{0}^{p} T(kp + \sigma)x\,d\sigma\right) = F\left(\sum_{k=0}^{n-1} e^{i\omega kp} \int_{0}^{p} e^{i\omega R(\sigma)x\,d\sigma}\right)
\]
\[
= \frac{e^{i\omega np} - 1}{e^{i\omega p} - 1} F\left(\int_{0}^{p} e^{i\omega R(\sigma)x\,d\sigma}\right),
\]
and
\[
F\left(\int_{np}^{np+h} T(\sigma)x\,d\sigma\right) = e^{i\omega np} F\left(\int_{0}^{h} e^{i\omega R(\sigma)x\,d\sigma}\right),
\]
and so \( S(np + h)x \) is given by
\[
\frac{(e^{i\omega p} - 1)e^{i\omega h}R(h)x}{e^{-i\omega np}(e^{i\omega p} - 1) + (1 - e^{-i\omega np})F(y) + (e^{i\omega p} - 1)F\left(\int_{0}^{h} e^{i\omega R(\sigma)x\,d\sigma}\right)},
\]
where \( y = \int_{0}^{p} e^{i\omega R(\sigma)x\,d\sigma} \).

Thus
\[
S(np + h)x - W(np + h)x = S(np + h)x - W(h)x
\]
\[
= \frac{(e^{i\omega p} - 1)e^{i\omega h}R(h)(y - c_n)}{(c_n + (e^{i\omega p} - 1)F\left(\int_{0}^{h} e^{i\omega R(\sigma)x\,d\sigma}\right))(F(y) + (e^{i\omega p} - 1)F\left(\int_{0}^{h} e^{i\omega R(\sigma)x\,d\sigma}\right))},
\]
where \( c_n = e^{-i\omega np}(e^{i\omega p} - 1) + (1 - e^{-i\omega np})F(y) \).
Let
\[ F(y) - c_n = e^{-\lambda_0 p}(F(y) - (e^{\lambda_0 p} - 1)) \quad \text{and} \quad c_n \geq 1 - e^{-\lambda_0 p}F(y) = c > 0. \]
So
\[ \|S(np+h)x - W(np+h)x\| \leq e^{-\lambda_0 p}e^{\lambda_0 p} \sup \|R(h)x\| \|F(y) - (e^{\lambda_0 p} - 1)\| = e^{-\lambda_0 p}K \]
and the result follows.

If \( \epsilon(t) \neq 0 \), in the formula (20) for \( S(np+h)x \) we must add to the numerator the expression \( (e^{\lambda_0 p} - 1)e^{\lambda_0 h}\epsilon(np+h) \) and to the denominator the expression \( a_n \), where
\[ a_n = e^{-\lambda_0 np}(e^{\lambda_0 p} - 1)F\left(\sum_{k=0}^{n-1} e^{\lambda_0 k p} \int_0^p e^{\lambda_0 \sigma} \epsilon(kp + \sigma) \, d\sigma + \int_0^h e^{\lambda_0 (np + \sigma)} \epsilon(np + \sigma) \, d\sigma\right). \]
We verify that \( \lim_{n \to \infty} a_n = 0 \). Fix \( N, 0 < N < n \), then
\[
|a_n| = \left| e^{-\lambda_0 np}(e^{\lambda_0 p} - 1)F\left(\sum_{k=0}^{n-1} e^{\lambda_0 k p} \int_0^p e^{\lambda_0 \sigma} \epsilon(kp + \sigma) \, d\sigma + \int_0^h e^{\lambda_0 \sigma} \epsilon(np + \sigma) \, d\sigma\right) \right|
+ \sum_{k=N}^{n-1} e^{\lambda_0 k p} \int_0^p e^{\lambda_0 \sigma} \epsilon(kp + \sigma) \, d\sigma + \int_0^h e^{\lambda_0 \sigma} \epsilon(np + \sigma) \, d\sigma
\leq e^{-\lambda_0 np}(e^{\lambda_0 p} - 1)\|F\|\left(\sup \|\epsilon(s)\| \frac{e^{\lambda_0 N p} - 1}{\lambda_0} + \sup_{s \geq N p} \|\epsilon(s)\| \frac{e^{\lambda_0 (n+1) p} - 1}{\lambda_0} \right)
= (e^{\lambda_0 p} - 1)\|F\|\left(\sup \|\epsilon(s)\| \frac{e^{\lambda_0 N p} - 1}{\lambda_0} + \sup \|\epsilon(s)\| \frac{e^{\lambda_0 p} - e^{-\lambda_0 np}}{\lambda_0} \right).
\]
Let \( \epsilon_1 > 0 \), let \( \bar{N} \) be such that \( e^{-\lambda_0 \bar{N} p} \sup_{s \geq \bar{N} p} \|\epsilon(s)\| \leq \epsilon_1 \), and let \( \bar{N} > \bar{N} \) be such that \( e^{-\lambda_0 \bar{N} p} \sup_{s \geq \bar{N} p} \|\epsilon(s)\| \leq \epsilon_1 \). Then, for \( n > \bar{N} \), \( |a_n| < (e^{\lambda_0 p} - 1)\|F\|\epsilon_1 \). But for \( n \) large enough
\[
\|S(np+h)x - W(np+h)x\| \leq \frac{(e^{\lambda_0 p} - 1)e^{\lambda_0 p} \sup \|R(h)x\|(e^{\lambda_0 p} - 1)\|F(y) - (e^{\lambda_0 p} - 1)\| + |a_n|}{(c + a_n)F(y)}
+ \frac{(e^{\lambda_0 p} - 1)e^{\lambda_0 p} \|\epsilon(np+h)\|}{c + a_n}
\]
and the result follows easily. \( \square \)

References

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