

Global stability in a delayed partial differential equation describing cellular replication

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Abstract. Here we consider the dynamics of a population of cells that are capable of simultaneous proliferation and maturation. The equations describing the cellular population numbers are first order partial differential equations (transport equations) in which there is an explicit temporal retardation as well as a nonlocal dependence in the maturation variable due to cell replication. The behavior of this system may be considered along the characteristics, and a global stability condition is proved.

Key words: Cell cycle – Global stability – Time delay

1 Introduction

Due to the existence of biological age and/or maturation variables within replicating cells, models for these processes naturally fall into the category of *age structured population models* (Metz and Diekmann 1986, Lasota et al. 1991) with dynamics determined by the solutions of partial differential equations. Sometimes, depending on the boundary conditions, these formulations reduce to differential delay equations (Mackey 1978, 1979, Mackey and Milton 1990).

In this note we consider the dynamics of replicating cellular populations based on a generalization of the G_0 model of Burns and Tannock (1970) and the equivalent model of Smith and Martin (1973). In Sect. 2 we consider a population of cells in which both cellular replication and maturation take place hand in hand, and show that the physiology naturally leads to a description of cell dynamics in terms of coupled first order nonlinear partial differential equations with both temporal retardation and nonlocal maturational effects appearing explicitly. These equations are a generalization of those that have been considered previously both in the absence (Mackey 1978, 1979) and presence of maturation (Rey and Mackey 1992, 1993).

In Sect. 3 we give a method of solving the equations derived in Sect. 2, and use this to establish the existence of solutions. In this section we also analyze the behavior of the solutions when the death coefficients do not depend on maturation. Section 4 gives the statement and proof of a global stability result for the model derived in Sect. 2. Relation to other work on similar models is considered in Sect. 5.

2 Cell population dynamics

The assumption that cellular maturation proceeds simultaneously with cellular replication has been shown to be sufficient to explain existing cell kinetic data for erythroid and neutrophilic precursors in several mammals (Mackey and Dörmer 1981, 1982). Thus, we consider a population of cells capable of both proliferation and maturation. We assume, in line with the current wisdom of cell kineticists, that these cells may be either actively proliferating or in a resting (G_0) phase.

The proliferating phase

Actively proliferating cells are those actually in cycle that are committed to the replication of their DNA and the ultimate passage through mitosis and cytokinesis with the eventual production of two daughter cells. The position of one of these cells within the cell cycle is denoted by a (cell age), which is assumed to range from $a = 0$ (the point of commitment) to $a = \tau$ (the point of cytokinesis). The *maturation* variable is labeled by m which ranges from $m = 0$ to $m = m_F < \infty$. (For concreteness one could think of erythroid precursor cells and associate the maturation variable with the intracellular hemoglobin concentration which is maintained at cytokinesis. However we note that our formulation is *not* restricted to this very specific identification of the maturation variable with a conserved quantity.) We assume that proliferating cells age with unitary velocity so $(da/dt) = 1$, that cells in this phase may be lost randomly at an age independent rate $\gamma(m)$, and cells of both types mature with a velocity $V(m)$. We assume that $V: [0, m_F] \rightarrow [0, \infty)$ is a continuously differentiable function such that $V(0) = 0$, $V(m) > 0$ for $m \in (0, m_F)$ and $V(m_F) = 0$.

If we denote the number of actively proliferating cells at time t , maturation level m , and age a by $p(t, m, a)$, then the conservation equation for $p(t, m, a)$ is simply

$$\frac{\partial p}{\partial t} + \frac{\partial p}{\partial a} + \frac{\partial [V(m)p]}{\partial m} = -\gamma(m)p, \quad (1)$$

and we specify an initial condition

$$p(0, m, a) = \Gamma(m, a) \quad \text{for } (m, a) \in [0, m_F] \times [0, \tau],$$

where F is assumed to be continuous. The total number of proliferating cells at a given time and maturation level is defined in a natural way by

$$P(t, m) = \int_0^{\tau} p(t, m, a) da .$$

The resting phase

Immediately after cytokinesis, both daughter cells are assumed to enter the resting G_0 phase. The cellular age in this population ranges from $a = 0$, when cells enter, to $a = \infty$. We assume that if the maturation of the mother cell at cytokinesis is m , then the maturation of a daughter cell at birth is $g(m)$, where g is a strictly increasing continuous function such that $g(m) \leq m$. We denote the number of cells in this stage by $n(t, m, a)$, so the total number of cells in the resting stage is given by

$$N(t, m) = \int_0^{\infty} n(t, m, a) da ,$$

while the total number of resting phase cells at all maturation level is

$$\bar{N}(t) = \int_0^{m_F} N(t, m) dm .$$

Again under the assumption that cells age with unitary velocity and that they may exit from the resting stage either:

- (1) by being lost at a random age-independent rate $\delta(m)$ or;
- (2) by re-entering the proliferating stage at a rate $\beta(\bar{N}, m)$ that is a decreasing function of \bar{N} (in agreement with the existing data on the regulation of cell kinetics),

then the conservation equation for $n(t, m, a)$ is given by

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} + \frac{\partial [V(m)n]}{\partial m} = - [\delta(m) + \beta(\bar{N}, m)]n , \quad (2)$$

with an initial condition

$$n(0, m, a) = \mu(m, a) \quad \text{for } (m, a) \in [0, m_F] \times [0, \infty), \quad \text{and} \quad \lim_{a \rightarrow \infty} \mu(m, a) = 0 . \quad (3)$$

We always assume that β and μ are continuous.

Boundary conditions

In completing the formulation of this problem there are two natural boundary conditions derived from the biology. The first of these is

$$n(t, m, 0) = 2p(t, h(m), \tau)h'(m) \quad \text{for } m \leq g(m_F) , \quad (4)$$

where $h \equiv g^{-1}$, and simply relates the equality of the cellular efflux following cytokinesis to the input flux of the resting compartment. We will assume that h is a continuously differentiable function. We also assume, for technical reasons, that $h(m) = m_F$ for $m > m_N = g(m_F)$. The second boundary condition is

$$p(t, m, 0) = \int_0^\infty \beta(\bar{N}(t), m)n(t, m, a)da = \beta(\bar{N}(t), m)N(t, m) . \quad (5)$$

relating the efflux from the resting population to the proliferative population influx.

Equations for P and N

Let $\pi_s m$ be the solution of the equation

$$\frac{d\pi_s m}{ds} = V(\pi_s m) ,$$

with initial condition $\pi_0 m = m$. From the assumption on the maturation velocity V it follows that $\pi_s m \in (0, m_F)$ for every s and $m \in (0, m_F)$. Moreover, $\pi_s 0 = 0$ and $\pi_s m_F = m_F$ for every s . Introduce the functions φ , ψ , and η with the following definitions:

$$\varphi(m, s) = \frac{V(\pi_{-s} m)}{V(m)} \exp \left\{ - \int_{\pi_{-s} m}^m \frac{\gamma(y)}{V(y)} dy \right\}$$

$$\psi(m, s) = \frac{V(\pi_{-s} m)}{V(m)} \exp \left\{ - \int_{\pi_{-s} m}^m \frac{\delta(y)}{V(y)} dy \right\}$$

$$\eta(t, s, m) = \exp \left\{ - \int_{-s}^0 \beta(\bar{N}(r+t), \pi_r m) dr \right\} .$$

Then the general solution of (1) is given by

$$p(t, m, a) = \begin{cases} p(0, \pi_{-t} m, a-t) \varphi(m, t) & 0 \leq t < a \\ p(t-a, \pi_{-a} m, 0) \varphi(m, a) & a \leq t . \end{cases} \quad (6)$$

Further, the general solution of (2) is

$$n(t, m, a) = \begin{cases} n(0, \pi_{-t} m, a-t) \psi(m, t) & 0 \leq t < a \\ n(t-a, \pi_{-a} m, 0) \psi(m, a) \eta(t, a, m) & a \leq t . \end{cases}$$

If the initial conditions satisfy

$$\mu(m, 0) = 2\Gamma(h(m), \tau)h'(m)$$

and

$$\Gamma(m, 0) = \beta(\bar{N}(0), m)N(0, m) ,$$

then from the boundary conditions (4) and (5) it follows that both p and n are continuous functions. Moreover, since $\lim_{a \rightarrow \infty} \mu(m, a) = 0$ by (3), it follows that

$$n(t, m, \infty) \equiv \lim_{a \rightarrow \infty} n(t, m, a) = 0 .$$

Integrating (1) and (2) over the age variable a gives

$$\frac{\partial P}{\partial t} + \frac{\partial [V(m)P]}{\partial m} = -\gamma(m)P - \{p(t, m, \tau) - p(t, m, 0)\} \quad (7)$$

and

$$\frac{\partial N}{\partial t} + \frac{\partial [V(m)N]}{\partial m} = -[\delta(m) + \beta(\bar{N}, m)]N + n(t, m, 0) , \quad (8)$$

respectively. Furthermore, $p(t, m, 0) = N(t, m)\beta(\bar{N}(t), m)$ and from (6) we have that

$$p(t, m, \tau) = \begin{cases} \Gamma(\pi_{-t}m, \tau - t)\varphi(m, t) & 0 \leq t < \tau \\ \beta(\bar{N}_\tau(t), \pi_{-\tau}m)N_\tau(t, m)\varphi(m, \tau) & \tau \leq t , \end{cases} \quad (9)$$

where $\bar{N}_\tau(t) \equiv \bar{N}(t - \tau)$ and $N_\tau(t, m) \equiv N_\tau(t - \tau, \pi_{-\tau}m)$. Using (9) and (5) in (7) we arrive at the conclusion that the dynamics of $P(t, m)$ is governed by the delayed first order partial differential equations

$$\begin{aligned} \frac{\partial P}{\partial t} + \frac{\partial [V(m)P]}{\partial m} = & -\gamma(m)P + N\beta(\bar{N}, m) \\ & - \begin{cases} \Gamma(\pi_{-t}m, \tau - t)\varphi(m, t) & 0 \leq t < \tau \\ N_\tau\beta(\bar{N}_\tau, \pi_{-\tau}m)\varphi(m, \tau) & \tau \leq t , \end{cases} \end{aligned} \quad (10)$$

Since by (4) $n(t, m, 0) = 2p(t, h(m), \tau)h'(m)$, (9) implies that (8) for N becomes

$$\begin{aligned} \frac{\partial N}{\partial t} + \frac{\partial [V(m)N]}{\partial m} = & -[\delta(m) + \beta(\bar{N}, m)]N \\ & + \begin{cases} 2h'(m)\Gamma(\pi_{-t}h(m), \tau - t)\varphi(h(m), t) & 0 \leq t < \tau \\ 2h'(m)N^\tau\beta(\bar{N}_\tau, \pi_{-\tau}h(m))\varphi(h(m), \tau) & \tau \leq t , \end{cases} \end{aligned} \quad (11)$$

where

$$N^\tau(t, m) = N(t - \tau, \pi_{-\tau}h(m)) = N_\tau(t, h(m)).$$

Equations (10) and (11) are the final relations describing the cellular dynamics. Notice that the solution of (11) is independent of the behavior of the solution of (10), but the converse is not true.

Equations (10) and (11) are interesting since they contain an explicit retardation in the temporal term ($t - \tau$), and a nonlocal dependence ($\pi_{-\tau}m$) in the maturation variable. Moreover, the right-hand side of (11) depends globally on N because it contains the terms \bar{N} and \bar{N}_τ . Other models of cellular replication (Diekmann et al. 1984; Gyllenberg and Heijmans 1987, Lasota and Mackey 1984) have displayed the same features.

3 A general method of attack

Existence of solutions

In the rest of this paper we assume that $\delta, \beta, V', \Gamma$ and $N(0, m)$ are bounded continuous functions. Equation (11) can be rewritten in the form

$$\frac{\partial N}{\partial t} + V(m) \frac{\partial N}{\partial m} = G(m, \bar{N})N + \begin{cases} 2h'(m)\Gamma(\pi_{-t}h(m), \tau - t)\varphi(h(m), t) & 0 \leq t < \tau \\ 2h'(m)N^\tau \beta(\bar{N}_\tau, \pi_{-\tau}h(m))\varphi(h(m), \tau) & \tau \leq t \end{cases} \quad (12)$$

where

$$G(m, \bar{x}) = -[\delta(m) + \beta(\bar{x}, m) + V'(m)].$$

We solve (12) by the method of steps: first for $t \in [0, \tau]$, and then successively for $t \in [\tau, 2\tau], \dots$. For $t \in [0, \tau]$ (12) takes the form

$$\frac{\partial N}{\partial t} + V(m) \frac{\partial N}{\partial m} = G(m, \bar{N})N + f(t, m), \quad (13)$$

where f is a given continuous bounded function. To determine N we solve equation (13) along the characteristics. We obtain

$$N(t, m) = \int_0^t f(r, \pi_{r-t}m) \exp\left(\int_r^t (G(\pi_{s-t}m, \bar{N}(s))ds)\right) dr \\ + N(0, \pi_{-t}m) \exp\left(\int_0^t G(\pi_{s-t}m, \bar{N}(s)) ds\right).$$

Let $\mathcal{P}: C[0, \tau] \rightarrow C[0, \tau]$ be the operator defined by

$$\mathcal{P}\bar{N}(t) = \int_0^{m_F} \int_0^t f(r, \pi_{r-t}m) \exp\left(\int_r^t G(\pi_{s-t}m, \bar{N}(s))ds\right) dr dm \\ + \int_0^{m_F} N(0, \pi_{-t}m) \exp\left(\int_0^t G(\pi_{s-t}m, \bar{N}(s))ds\right) dm.$$

Further, let L_1, L_2, L_3 , and L_4 be constants such that $|G(m, x)| \leq L_1$, $|f(t, m)| \leq L_2$, $|N(0, m)| \leq L_3$ and $|\frac{\partial G}{\partial x}(m, x)| \leq L_4$.

We first show that the operator \mathcal{P} is contractive in the Banach space $C[0, \tau]$ with the norm $\|F\| = \max_{0 \leq t \leq \tau} e^{-\lambda t} |F(t)|$, where $\lambda > 0$ is some constant. To see this, note that by the definition of the norm $\|\cdot\|$,

$$|F_1(s) - F_2(s)| \leq e^{\lambda s} \|F_1 - F_2\| \quad \text{for } s \in [0, \tau].$$

From this it follows that for every $r \in [0, t]$ we have

$$\begin{aligned} & \left| \exp \left(\int_r^t G(\pi_{s-t}, m, F_1(s)) ds \right) - \exp \left(\int_r^t G(\pi_{s-t}, m, F_2(s)) ds \right) \right| \\ & \leq e^{L_1(t-r)} \left| \int_r^t G(\pi_{s-t}, m, F_1(s)) ds - \int_r^t G(\pi_{s-t}, m, F_2(s)) ds \right| \\ & \leq e^{L_1 \tau} \int_r^t L_4 |F_1(s) - F_2(s)| ds \leq e^{L_1 \tau} \int_r^t L_4 e^{\lambda s} \|F_1 - F_2\| ds \\ & \leq \lambda^{-1} L_4 e^{L_1 \tau} e^{\lambda t} \|F_1 - F_2\|. \end{aligned}$$

This implies that

$$\begin{aligned} |\mathcal{P}F_1(t) - \mathcal{P}F_2(t)| & \leq \lambda^{-1} L_4 e^{L_1 \tau} e^{\lambda t} \|F_1 - F_2\| \left(\int_0^{m_F} \int_0^t L_2 dr dm + \int_0^{m_F} L_3 dm \right) \\ & \leq \lambda^{-1} L_4 e^{L_1 \tau} e^{\lambda t} m_F (L_2 \tau + L_3) \|F_1 - F_2\|. \end{aligned}$$

Consequently

$$\|\mathcal{P}F_1 - \mathcal{P}F_2\| \leq \lambda^{-1} L_4 e^{L_1 \tau} m_F (L_2 \tau + L_3) \|F_1 - F_2\|.$$

If we choose λ sufficiently large, then the last inequality implies that \mathcal{P} is a contraction. From the Banach theorem it follows that there exists a unique function \bar{N} such that $\mathcal{P}\bar{N} = \bar{N}$. Consequently, if $N(0, m)$ is given, then equation (12) has exactly one solution $N(t, m)$ for $t \in [0, \tau]$. For $t \in [\tau, 2\tau]$, (12) can again be written in the form (13) because N^τ and \bar{N}_τ are determined by the values of N for $t \leq \tau$. In the same way for $t \in [0, \tau]$ we can prove the existence and uniqueness of the solutions of (12) for $t \in [\tau, 2\tau]$. By the method of steps we can solve (12) for every $t \geq 0$.

A differential-delay equation for $\bar{N}(t)$

Now we assume that δ, γ and β do not depend on m . Integrating (11) over the maturation variable we obtain

$$\begin{aligned} \bar{N}'(t) & = -(\delta + \beta(\bar{N}(t)))\bar{N}(t) + \beta(\bar{N}(t - \tau)) \\ & \quad \times \int_0^{m_F} 2h'(m) \varphi(h(m), \tau) N(t - \tau, \pi_{-\tau}, h(m)) dm \end{aligned}$$

for $t \geq \tau$. From the definition of the function φ we obtain

$$\begin{aligned} \bar{N}'(t) & = -(\delta + \beta(\bar{N}(t)))\bar{N}(t) \\ & \quad + \beta(\bar{N}(t - \tau)) \int_0^{m_F} 2N(t - \tau, z) \exp \left\{ - \int_z^{\pi_{\tau z}} \frac{\gamma}{V(y)} dy \right\} dz. \end{aligned}$$

Observe that since

$$\frac{\partial}{\partial s} \left(\int_m^{\pi_s m} \frac{1}{V(y)} dy \right) = \frac{1}{V(\pi_s m)} \frac{\partial}{\partial s} (\pi_s m) = 1,$$

we obtain

$$\int_m^{\pi_s m} \frac{1}{V(y)} dy = s \quad (14)$$

for $m \in (0, m_F)$ and every s . Thus it follows that

$$\bar{N}'(t) = -(\delta + \beta(\bar{N}(t)))\bar{N}(t) + 2e^{-\gamma t} \beta(\bar{N}_\tau) \bar{N}_\tau \quad t \geq \tau. \quad (15)$$

Equation (15) has appeared in models describing cellular replication without maturation (Mackey 1978, 1979, Mackey and Milton 1990). Properties of the solutions of (15) depend on the function β and constants δ, γ, τ . We will assume that $\beta'(x) < 0$ for $x > 0$ and $\beta(x) \rightarrow 0$ as $x \rightarrow \infty$. This assumption corresponds to the reasonable biological situation in which the rate of entry into the proliferating stage is a decreasing function of the total number of resting phase cells.

We will only investigate positive solutions of (15), and we first prove that the solutions are bounded above. In fact we show a stronger property: there exists a finite x_1 such that for every solution of (15) we have

$$\limsup_{t \rightarrow \infty} \bar{N}(t) < x_1. \quad (16)$$

To show this, let $c = 2e^{-\gamma \tau}$ and let x_0 be a positive constant such that $c\beta(y) \leq \delta$ for $y \geq x_0$ and $x_1 = c\beta(0)x_0/\delta$. Then

$$\max_{0 \leq y \leq x} c\beta(y)y \leq \delta x \quad \text{for } x \geq x_1. \quad (17)$$

This follows from the fact, that for $y \leq x_0$ we have $c\beta(y)y \leq c\beta(0)x_0 \leq \delta x_1 \leq \delta x$ and for $y \in [x_0, x]$ we have $c\beta(y)y \leq \delta y \leq \delta x$. Let $r = \limsup_{t \rightarrow \infty} \bar{N}(t)$. We claim that $r < \infty$. Suppose, on the contrary, that $r = \infty$. Then there exists $t_0 > \tau$ such that $\bar{N}(t_0) \geq \bar{N}(t)$ for $t \in [t_0 - \tau, t_0]$ and $\bar{N}(t_0) > x_1$. But then from (17) it follows that

$$\bar{N}'(t_0) = -(\delta + \beta(\bar{N}(t_0)))\bar{N}(t_0) + c\beta(\bar{N}(t_0 - \tau))\bar{N}(t_0 - \tau) < 0,$$

which is impossible. Since $r < \infty$, there exists a sequence $t_n \rightarrow \infty$ such that $\bar{N}(t_n) \rightarrow r$, $\bar{N}'(t_n) \rightarrow 0$ and $\bar{N}(t_n - \tau) \rightarrow s$ as $n \rightarrow \infty$, where s is a constant such that $s \leq r$. From (15) it follows that $(\delta + \beta(r))r = c\beta(s)s$ and consequently $\delta r < c\beta(s)s$. This and (17) imply that $r < x_1$.

The asymptotic behavior of the solutions of (15) can be divided into three types:

- (1) A trivial ($\bar{N} \equiv 0$) stable solution;
- (2) A non-trivial ($\bar{N} > 0$) stable solution; and
- (3) No stable stationary solutions.

Type 1. If $\delta > (2e^{-\gamma \tau} - 1)\beta(0)$, then the trivial solution of (15) is globally asymptotically stable.

To prove this we construct a Liapunov function (see Hale 1977, Chap. 5 for details). Let $\lambda(x) = (\delta + \beta(x))x$, $A(x) = \int_0^x \lambda(y)dy$ and let a Liapunov function $V: C[-\tau, 0] \rightarrow R$ be given by

$$V(\phi) = A(\phi(0)) + \frac{1}{2} \int_{-\tau}^0 \lambda^2(\phi(\theta)) d\theta. \quad (18)$$

It is easy to check that

$$\begin{aligned} \dot{V}(\phi) &= -\lambda^2(\phi(0)) + 2e^{-\gamma\tau} \lambda(\phi(0))\phi(-\tau)\beta(\phi(-\tau)) + \frac{1}{2} \lambda^2(\phi(0)) - \frac{1}{2} \lambda^2(\phi(-\tau)) \\ &= -\frac{1}{2} [\lambda(\phi(0)) - 2e^{-\gamma\tau} \phi(-\tau)\beta(\phi(-\tau))]^2 \\ &\quad - \frac{1}{2} [\lambda^2(\phi(-\tau)) - 4e^{-2\gamma\tau} \phi^2(-\tau)\beta^2(\phi(-\tau))] \\ &\leq -\frac{1}{2} [(\delta + \beta(\phi(-\tau)))^2 - 4e^{-2\gamma\tau} \beta^2(\phi(-\tau))] \phi^2(-\tau) \\ &\leq -\frac{1}{2} \delta [\delta - (2e^{-\gamma\tau} - 1)\beta(\phi(-\tau))] \phi^2(-\tau). \end{aligned}$$

Since β is a decreasing function, there exists $\varepsilon > 0$ such that

$$\dot{V}(\phi) \leq -\varepsilon \phi^2(-\tau).$$

From the last inequality it follows that every solution is convergent to 0. In this case, the total number of cells decreases to zero asymptotically and the population will die out.

Type 2. If

$$\delta < (2e^{-\gamma\tau} - 1)\beta(0) \quad (19)$$

then there exists a non-trivial stationary solution of (15) $\bar{N}(t) \equiv N_0$, where N_0 satisfies the equation $\delta = (2e^{-\gamma\tau} - 1)\beta(N_0)$. We check when this solution is asymptotically stable.

In order to do this, note that the linearization of (15) about N_0 gives

$$\bar{N}'(t) = -(\delta + \beta(N_0) + N_0\beta'(N_0))\bar{N}(t) + 2e^{-\gamma\tau}(\beta(N_0) + N_0\beta'(N_0))\bar{N}(t - \tau). \quad (20)$$

Let $a = \delta + \beta(N_0) + N_0\beta'(N_0)$ and $b = -2e^{-\gamma\tau}(\beta(N_0) + N_0\beta'(N_0))$. Further, let $\mathfrak{G}(x) = -x \cot x\tau$ for $x \in (0, \pi/\tau)$ and ζ be the inverse function to \mathfrak{G} . It is well known that (20) is asymptotically stable if and only if $a > -1/\tau$ and $-a < b < \zeta(a)/(\sin \tau\zeta(a))$ (see [6] Chap. 5).

The condition $-a < b$ follows immediately from the inequality $\beta'(N_0) < 0$. This implies that if (19) holds, $a > -1/\tau$ and $b < \zeta(a)/(\sin \tau\zeta(a))$, then $\bar{N}(t) \equiv N_0$ is an asymptotically stable solution of (15). Moreover, each solution which converges to N_0 is exponentially convergent, i.e. there exist two constants $L > 0$ and $\varepsilon > 0$ such that $|\bar{N}(t) - N_0| \leq Le^{-\varepsilon t}$. The asymptotic behavior of the function $N(t, m)$ in this case will be analyzed in the next subsection.

Type 3. If (19) holds, $a < -1/\tau$ or $b > \zeta(a)/(\sin \tau\zeta(a))$ then the asymptotic behavior of the solutions (15) can be complicated: periodic solutions, non-trivial attractors, chaotic solutions (see e.g. Walther 1991 for more details and references).

Remark 1. For some feedback functions β we can prove that a non-zero stationary solution N_0 of (15) is globally asymptotically stable. For example, if $\beta(x) = \beta/(\alpha + x)$ and (19) holds, then (15) is globally asymptotically stable.

To show this, let $x(t) = \bar{N}(t) - N_0$. Then (15) takes the form

$$x'(t) = -f(x(t)) + q(x(t - \tau)),$$

where

$$f(x) = (\delta + \beta(x + N_0))(x + N_0) - (\delta + \beta(N_0))N_0$$

$$q(x) = 2e^{-\gamma\tau} \beta(x + N_0)(x + N_0) - 2e^{-\gamma\tau} \beta(N_0)N_0.$$

Now let $F(x) = \int_0^x f(y)dy$ and consider the Liapunov function

$$V(\phi) = 2F(\phi(0)) + \int_{-\tau}^0 f^2(\phi(\theta))d\theta.$$

It is easy to check that

$$\begin{aligned} \dot{V}(\phi) &= -2f^2(\phi(0)) + 2f(\phi(0))q(\phi(-\tau)) + f^2(\phi(0)) - f^2(\phi(-\tau)) \\ &= -[f(\phi(0)) - q(\phi(-\tau))]^2 - f^2(\phi(-\tau)) + q^2(\phi(-\tau)) \\ &\leq -[f^2(\phi(-\tau)) - q^2(\phi(-\tau))]. \end{aligned} \tag{21}$$

Since the function β is strictly decreasing, we have $f(x) < q(x)$ for $x \in (-N_0, 0)$ and $f(x) > q(x)$ for $x > 0$. Moreover, from the definition of β it follows that $(f + q)(0) = 0$ and $(f + q)'(x) > 0$ for $x > -N_0$. Consequently, $f^2(x) > q^2(x)$ for $x \neq 0$ and $x > -N_0$. From inequality (21) it follows that (15) is globally asymptotically stable on the set of positive solutions. This method, combined with inequality (16), can be used to prove global asymptotic stability for a large class of feedback functions β , but each case requires special treatment.

Linear form of (12)

As in the previous subsection we assume that δ, γ and β do not depend on m . Substituting $N(t, m) = \bar{N}(t)M(t, m)$ in (11) and using (15) we obtain

$$\frac{\partial M}{\partial t} + \frac{\partial[V(m)M]}{\partial m} = c(t)[-M(t, m) + k'(m)M(t - \tau, k(m))] \quad \text{for } t \geq \tau, \tag{22}$$

where

$$c(t) = \frac{2e^{-\gamma\tau} \bar{N}(t - \tau)\beta(\bar{N}(t - \tau))}{\bar{N}(t)}, \quad k(m) = \pi_{-\tau}h(m). \tag{23}$$

The solutions of (22) have the following properties: 1. If $M(t, m) \geq 0$ for $t \in [t_0 - \tau, t_0]$ and $m \in [0, m_F]$, then $M(t, m) \geq 0$ for $t > t_0$ and $m \in [0, m_F]$. This can be checked by the method of steps. If $M(t, m) \geq 0$ for $t \in [t_0 - \tau, t_0]$, then

$$\frac{\partial M}{\partial t} + \frac{\partial[V(m)M]}{\partial m} \geq -c(t)M(t, m) \quad \text{for } t \in [t_0, t_0 + \tau].$$

Let $p(t) = M(t, \pi_t m)$, then

$$p'(t) \geq - [V'(\pi_t m) + c(t)]p(t) .$$

Since $p(t_0) \geq 0$, from the above differential inequality it follows that $p(t) \geq 0$ for $t \geq t_0$, and consequently $M(t, m) \geq 0$ for $t \in [t_0, t_0 + \tau]$; 2. If $\int_0^{m_F} M(t, m) dm = 1$ for $t \in [t_0 - \tau, t_0]$, then $\int_0^{m_F} M(t, m) dm = 1$ for $t > t_0$. This follows from integrating (22) over the maturation variable to obtain.

$$\bar{M}(t) = -c(t)\bar{M}(t) + c(t)\bar{M}(t - \tau) ,$$

where $\bar{M}(t) = \int_0^{m_F} M(t, m) dm$. Since $\bar{M}(t) = 1$ for $t \in [t_0 - \tau, t_0]$, we have $\bar{M}(t) = 1$ for $t \geq t_0$.

Let D be the subset of $L^1(0, m_F)$ consisting of all densities, i.e. the functions f such that $f \geq 0$ and $\int_0^{m_F} f(x) dx = 1$. Since $M(t, \cdot) \in D$ for each t , we will investigate the solutions of (22) only in the set of densities by comparing the solutions of (22) with the solutions of the linear equation:

$$\frac{\partial F}{\partial t} + \frac{\partial [V(m)F]}{\partial m} = -cF(t, m) + ck'(m)F(t - \tau, k(m)) . \quad (24)$$

Proposition 1. *Let M and Z be solutions of (22) and (24), respectively. Assume that $M(t, m) = F(t, m)$ and $M(t, \cdot) \in D$ for $t \in [t_0 - \tau, t_0]$. Then*

$$\int_0^{m_F} |M(t, m) - F(t, m)| dm \leq \int_{t_0}^t 2|c(s) - c| ds \quad \text{for } t \geq t_0 . \quad (25)$$

Proof. Let $Z(t, m) = M(t, m) - F(t, m)$ and $\varepsilon(t) = c(t) - c$. Subtracting (24) from (22) we obtain

$$\frac{\partial Z}{\partial t} + \frac{\partial [V(m)Z]}{\partial m} = -cZ(t, m) + f(t, m) , \quad (26)$$

where

$$f(t, m) = ck'(m)Z(t - \tau, k(m)) - \varepsilon(t)M(t, m) + \varepsilon(t)k'(m)M(t - \tau, k(m)) .$$

Let $T \geq t_0$. Then integrating (26) along the characteristics we obtain

$$Z(s + T, m) = Z(T, \pi_{-s} m) \frac{V(\pi_{-s} m)}{V(m)} e^{-cs} + \int_0^s \frac{V(\pi_{r-s} m)}{V(m)} e^{c(r-s)} f(r + T, \pi_{r-s} m) dr . \quad (27)$$

Let $z(t) = \int_0^{m_F} |Z(t, m)| dm$. Taking the absolute value of (27) and integrating over the maturation variable yields

$$\begin{aligned} z(s + T) &\leq e^{-cs} z(T) + \int_0^s e^{c(r-s)} \left(\int_0^{m_F} |f(r + T, m)| dm \right) dr \\ &\leq e^{-cs} z(T) + \int_0^s e^{c(r-s)} [cz(r + T - \tau) + 2|\varepsilon(r + T)|] dr \\ &\leq e^{-cs} \left(z(T) + \int_0^s ce^{cr} z(r + T - \tau) dr \right) + \int_T^{T+s} 2|\varepsilon(r)| dr . \end{aligned} \quad (28)$$

Now, we can check the validity of inequality (25) by induction. Let $t_n = t_0 + \tau n$. Then for $t \in [t_0, t_1]$ inequality (25) follows immediately from (28) with $T = t_0$. Assume that (25) holds for $t \in [t_0, t_n]$. Then from (28), with $T = t_n$, and from (25) for $t \in [t_{n-1}, t_n]$ it follows that

$$\begin{aligned} z(s + t_n) &\leq e^{-cs} \left(1 + \int_0^s c e^{cr} dr \right) \int_{t_0}^{t_n} |2\varepsilon(r)| dr + \int_{t_n}^{t_n+s} |2\varepsilon(r)| dr \\ &= \int_{t_n}^{t_n+s} |2\varepsilon(r)| dr \end{aligned}$$

for $s \in [0, \tau]$, which completes the proof. □

Remark 2. The solutions of (22) and (24) can be considered as functions from $[0, \infty)$ to D and instead of $F(t, m)$ we can write $F(t)(m)$ to underline that $F(t) \in D$. Proposition 1 can sometimes be used to deduce the asymptotic behavior of the solutions of (12) from the properties of the solutions of (24).

To see how, assume δ, γ and β do not depend on m and assume that condition (19) holds. If the non-zero stationary solution N_0 of (15) is asymptotically stable, then there exists $\rho > 0$ such that every solution \bar{N} of (15) satisfying the condition $|\bar{N}(t) - N_0| < \rho$ for $t \in [0, \tau]$ converges exponentially to N_0 . This implies that the function $c(t)$ converges exponentially to $c = \delta + \beta(N_0)$, i.e. there exist constants ε and $L > 0$ such that $|c(t) - c| \leq L e^{-\varepsilon t}$ for $t \geq 0$. If (24) is asymptotically stable, i.e. there exists $f^* \in D$ such that every solution of (24) converges to f^* in $L^1(0, m_F)$ as $t \rightarrow \infty$, then from Proposition 1 it follows that (22) is asymptotically stable. This implies that if $N(t, m)$ is a solution of (12) such that $|\bar{N}(t) - N_0| < \rho$ for $t \in [0, \tau]$, then $N(t, \cdot)$ converges to $N_0 f^*$ in $L^1(0, m_F)$. In particular, if N_0 is a globally asymptotically stable solution of (15), then every positive solution of (12) converges to $N_0 f^*$ in $L^1(0, m_F)$.

4 Stability

In this section we give a sufficient condition for asymptotic stability for (24). As in the previous section, we denote by D the subset of $L^1(0, m_F)$ consisting of all densities. We will investigate the solutions F of (24) such that $F(t) \in D$ for $t \geq 0$ [recall that $F(t)(m) = F(t, m)$].

The main result of this paper is the following.

Theorem 1. *Assume that $V'(0) > 0, c \log k'(0) < V'(0), k'(m) > 0$ for $m \in [0, m_F)$ and $m_N = g(m_F) < m_F$. Then there exists $f^* \in D$ such that for every solution of (24) we have*

$$\lim_{t \rightarrow \infty} \|F(t) - f^*\| = 0, \tag{29}$$

where $\|\cdot\|$ is the norm in $L^1(0, m_F)$.

From Theorem 1 it follows that if (15) has a non-zero globally asymptotically stable solution $N_0, c \log g'(0) > -(1 + c\tau)V'(0)$ and $g(m_F) = m_N < m_F$,

then every positive solution $N(t, \cdot)$ of (12) converges to $N_0 f^*$ in $L_1(0, m_F)$ (see Remark 2 of the previous section).

We split the proof of Theorem 1 into lemmas, but before starting we show that instead of (24) we can consider a simple one. Let $y(x)$ be the solution of the differential equation

$$cy'(x)x = V(y(x)), \quad y(1) = m_N .$$

Then the function $u(t, x) = y'(x)F(t, y(x))$ satisfies the equation

$$\frac{\partial u}{\partial t} + \frac{\partial(cxu)}{\partial x} = -cu(t, x) + cq'(x)u(t - \tau, q(x)), \quad (30)$$

where $q(x) = y^{-1}(k(y(x)))$ for $x < 1$ and, formally $q'(x) = 0$ and $q(x) = \infty$ for $x \geq 1$. It is easy to check that $q: [0, 1) \rightarrow [0, \infty)$ is a continuously differentiable function such that $q(0) = 0$ and $q'(0) = k'(0)^{e/V'(0)} < e, q'(x) > 0$ for $x \in [0, 1)$. Since $T(t)(x) = y'(x)f(y(x))$ is a linear isometric transformation from D onto the set of densities of $L^1(0, \infty)$, it is sufficient to prove Theorem 1 for (30). From now on we denote by D the subset of $L^1(0, \infty)$ consisting of all densities, i.e. the functions f such that $f \geq 0$ and $\int_0^\infty f(x)dx = 1$. It is easy to check that every solution of (30) satisfies the integral equation

$$u(t, x) = e^{-2ct}u(0, e^{-ct}x) + \int_0^t ce^{-2cs}q'(e^{-cs}x)u(t - \tau - s, q(e^{-cs}x))ds . \quad (31)$$

The thread of the proof that (30) is asymptotically stable is as follows. First we check that for any two solutions u and \bar{u} of (30) we have $\|u(t) - \bar{u}(t)\| \rightarrow 0$ as $t \rightarrow \infty$. Then we show that there exists a stationary solution of (30) (i.e. a solution which does not depend on t). From both facts it follows that $\|u(t) - u_0\| \rightarrow 0$ as $t \rightarrow \infty$. In order to prove that (30) has a stationary solution, we show that a solution of (30) is also an invariant density of a Markov operator \mathcal{P} . Then we prove that there exists an invariant density under the operator \mathcal{P} . In fact, we show a stronger property than the existence of an invariant density. Namely, we prove that the operator \mathcal{P} is asymptotically stable.

Lemma 1. *There exist $a > 0$ and $b > 2a$ such that for every solution of (30), there is a time $t_0 = t_0(u)$ for which*

$$\int_a^b u(t, x) dx > \frac{1}{2} \quad \text{for } t \geq t_0 . \quad (32)$$

Proof. Since $q'(0) < e$, there must be an $\varepsilon > 0$ and $r \in (0, 1)$ for which

$$(q'(0) + \varepsilon)^r < 1 + r .$$

Denote by D_0 the (dense) subset of D consisting of bounded functions f such that $\int_0^\infty x^{-r} f(x) dx < \infty$ and $\lim_{x \rightarrow \infty} x f(x) = 0$. Let u be a solution of (30) such that $u(t) \in D_0$ for $t \in [-\tau, 0]$. Then from (31) it follows that $u(t) \in D_0$ for $t \geq 0$. The function $G(t) = \int_0^\infty x^{-r} u(t, x) dx$ satisfies the equation

$$G'(t) = -c(1 + r)G(t) + \int_0^\infty cx^{-r} q'(x)u(t - \tau, q(x)) dx . \quad (33)$$

Let $\rho > 0$ be a constant such that $q^{-1}(x) \geq x/(q'(0) + \varepsilon)$ for $x \in [0, \rho]$. Then

$$\begin{aligned} \int_0^\infty cx^{-r}q'(x)u(t-\tau, q(x))dx &= \int_0^\infty c(q^{-1}(x))^{-r}u(t-\tau, x)dx \\ &\leq \int_0^\rho c(q'(0) + \varepsilon)^r x^{-r}u(t-\tau, x)dx + c(q^{-1}(\rho))^{-r}. \end{aligned}$$

From (33) it follows that

$$G'(t) \leq -MG(t) + KG(t-\tau) + B,$$

where $M = c(1+r)$, $K = c(q'(0) + \varepsilon)^r$ and $B = c(q^{-1}(\rho))^{-r}$. Let $\bar{G}(t)$ be the solution of the differential delay equation

$$\bar{G}'(t) = -M\bar{G}(t) + K\bar{G}(t-\tau) + B, \tag{34}$$

such that $\bar{G}(t) = G(t)$ for $t \in [-\tau, 0]$. It is easy to check by the method of steps that $\bar{G}(t) \geq G(t)$ for $t \geq 0$. Since $M > K$, the stationary solution $\bar{G} \equiv B/(M - K)$ of (34) is globally asymptotically stable. Consequently

$$\limsup_{t \rightarrow \infty} G(t) \leq B/(M - K).$$

From this it follows that there exists $a > 0$ independent of u such that

$$\int_0^a u(t, x)dx < \frac{1}{4} \tag{35}$$

for $t \geq t_0(u)$. Now, let $U(t, x) = \int_x^\infty u(t, y)dy$. Then for $x \geq 1$ the function U satisfies the equation

$$\frac{\partial U}{\partial t} + cx \frac{\partial U}{\partial x} = -cU. \tag{36}$$

For $t > \frac{1}{c} \log x$ and $x \geq 1$, the solution of (36) is given by

$$U(t, x) = \frac{1}{x} U\left(t - \frac{1}{c} \log x, 1\right).$$

If $b \geq 4$, then $U(t, b) \leq \frac{1}{4}$ for $t > \frac{1}{c} \log b$. Inequality (32) follows from this and (35). Since the set D_0 is dense in D , condition (32) holds for every solution of (30). □

Lemma 2. *There exists a non-negative function $\kappa \in L^1(0, \infty)$ with $\|\kappa\| > 0$ such that $u(t, x) \geq \kappa(x)$ for every solution u of (30) and sufficiently large t .*

Proof. For $x \geq 1$, the function u satisfies the equation

$$\frac{\partial u}{\partial t} + \frac{\partial(cxu)}{\partial x} = -cu(t, x). \tag{37}$$

For $t > \frac{1}{c} \log x$ and $x \geq 1$, the solution of (37) is given by

$$u(t, x) = x^{-2} u\left(t - \frac{1}{c} \log x, 1\right). \tag{38}$$

From (31) to (38), for sufficiently large t we have

$$\begin{aligned} u(t, 1) &\geq \int_0^t ce^{-2cs} q'(e^{-cs})u(t - \tau - s, q(e^{-cs})) ds \\ &\geq \int_{q^{-1}(1)}^1 xq'(x)u\left(t - \tau + \frac{1}{c} \log x, q(x)\right) dx \\ &\geq \int_{q^{-1}(1)}^1 \frac{xq'(x)}{(q(x))^2} u\left(t - \tau - \frac{1}{c} \log(q(x)/x), 1\right) dx. \end{aligned} \quad (39)$$

Let $\theta = \tau + \frac{1}{c} \log(q(x)/x)$. Then

$$\frac{d\theta}{tx} = \frac{xq'(x) - q(x)}{cxq(x)}.$$

Observe that there exists $x_0 \in (0, 1)$ such that $q(x_0) \neq x_0q'(x_0)$. [If this were not the case, then $q(x)$ would be a linear function in the interval $(0, 1)$, which contradicts the fact that $q(x) \rightarrow \infty$ as $x \rightarrow 1$.] Let $\theta_0 = \tau + \frac{1}{c} \log(q(x_0)/x_0)$. Then from inequality (39) it follows that there is an $\varepsilon > 0$ and $\alpha > 0$ for which

$$u(t, 1) \geq \int_0^\varepsilon \alpha u(t - \theta_0 - s, 1) ds$$

when t is sufficiently large. From this inequality it follows that

$$u(t, 1) \geq \alpha^n \int_0^\varepsilon \cdots \int_0^\varepsilon u(t - n\theta_0 - s_1 - \cdots - s_n, 1) ds_1 \cdots ds_n$$

for sufficiently large t . Inductively, it is easy to verify that

$$u(t, 1) \geq \alpha^n \left(\frac{\varepsilon}{3}\right)^{n-1} \int_{\varepsilon(n-1)/3}^{2\varepsilon(n-1)/3} u(t - n\theta_0 - s, 1) ds. \quad (40)$$

According to Lemma 1, for every $t \geq t_0(u)$ there exists $z \in [a, b - a]$ such that

$$\int_z^{z+a} u(t, x) dz \geq \frac{a}{4(b-a)}.$$

From the inequality

$$\frac{\partial u}{\partial t} + \frac{\partial(cxu)}{\partial x} \geq -cu(t, x)$$

it follows that

$$u(t + s, e^{cs}x) \geq e^{-2cs}u(t, x) \quad \text{for } s \geq 0.$$

As a consequence,

$$\int_{rz}^{r(z+a)} u\left(t + \frac{1}{c} \log r, x\right) dx \geq \frac{a}{4r(b-a)} \quad \text{for } r \geq 1.$$

Let $\Delta = [b, b^2a^{-1}]$. Then for $r = b/a$ we have $[rz, r(z + a)] \subset \Delta$ and thus

$$\int_{\Delta} u\left(t + \frac{1}{c} \log r, x\right) dx \geq K = \frac{a^2}{4b(b-a)}.$$

This implies that

$$\int_{\Delta} u(t, x) dx \geq K \quad \text{for } t \geq t_1(u) = t_0(u) + \frac{1}{c} \log(b/a). \tag{41}$$

From (38) we have

$$\int_{\Delta} u(t, x) dx = \int_{\Delta} \frac{1}{x^2} u\left(t - \frac{1}{c} \log x, 1\right) dx \leq \frac{c}{b} \int_{\Delta'} u(t - z, 1) dz,$$

where $\Delta' = [\frac{1}{c} \log b, \frac{1}{c} \log(b^2 a^{-1})]$. However, from (41) we also obtain

$$\int_{\Delta'} u(t - z, 1) dz \geq \frac{bK}{c} \quad \text{for } t \geq t_1(u). \tag{42}$$

Let $|\Delta'|$ be the length of the interval Δ' and let n be an integer such that $\varepsilon(n - 1)/3 > |\Delta'|$. Then from (40) and (42)

$$u(t, 1) \geq \alpha^n \frac{bK}{c} \left(\frac{\varepsilon}{3}\right)^{n-1} \quad \text{for } t \geq t_2(u). \tag{43}$$

From (38) and (43) it must be the case that there exists $\zeta > 0$ such that

$$u(t, x) \geq \kappa(x) = \zeta x^{-2} \mathbf{1}_{[1, b]}(x) \quad \text{for } t \geq t_3(u),$$

where $\mathbf{1}_{[1, b]}(x)$ denotes the characteristic function of the interval $[1, b]$. \square

Lemma 3. Let $u(t)(x) = u(t, x)$ and $\bar{u}(t)(x) = \bar{u}(t, x)$ be two solutions of (30). Then

$$\lim_{t \rightarrow \infty} \|u(t) - \bar{u}(t)\| = 0. \tag{44}$$

Proof. Let $\varepsilon = \|\kappa\|$, where κ is the function of Lemma 2. Denote by $v(t)(x) = v(t, x)$ the solution of (30) satisfying the initial condition $v(t)(x) = \varepsilon^{-1} \kappa(x)$ for $t \in [-\tau, 0]$. According to Lemma 2 there exists t_1 such that $u(t) \geq \kappa$ and $\bar{u}(t) \geq \kappa$ for $t \in [t_1 - \tau, t_1]$. Let u_1 and \bar{u}_1 be the solutions of (30) satisfying the initial conditions

$$u_1(s) = (1 - \varepsilon)^{-1}(u(t_1 + s) - \kappa) \quad \text{and} \quad \bar{u}_1(s) = (1 - \varepsilon)^{-1}(\bar{u}(t_1 + s) - \kappa)$$

for $s \in [-\tau, 0]$. Then

$$u(t_1 + t) = (1 - \varepsilon)u_1(t) + \varepsilon v(t) \quad \text{and} \quad \bar{u}(t_1 + t) = (1 - \varepsilon)\bar{u}_1(t) + \varepsilon v(t)$$

for every $t \geq 0$. Using an induction argument we find sequences of numbers t_1, t_2, \dots and functions $u_1, \bar{u}_1, u_2, \bar{u}_2, \dots$ such that

$$u_{n-1}(t_n + t) = (1 - \varepsilon)u_n(t) + \varepsilon v(t) \quad \text{and} \quad \bar{u}_{n-1}(t_n + t) = (1 - \varepsilon)\bar{u}_n(t) + \varepsilon v(t)$$

for $t \geq 0$ and a positive integer n . This implies that

$$u(t_1 + \dots + t_n + t) - \bar{u}(t_1 + \dots + t_n + t) = (1 - \varepsilon)^n(u_n(t) - \bar{u}_n(t)) .$$

Since the functions $u_n(t)$ and $\bar{u}_n(t)$ are densities, the last formula gives (44). □

In the last part of this section we show that there exists a stationary solution of (30). From this and Lemma 3, Theorem 1 follows immediately.

A density $f \in D$ is a stationary solution of (30) if it satisfies the equation

$$xf'(x) + 2f(x) = q'(x)f(q(x)) .$$

This equation can be rewritten as the integral equation

$$x^2 f'(x) = \int_0^x yq'(y)f(q(y))dy .$$

Consequently f is a fixed point of the operator

$$\mathcal{P}f(x) = \frac{1}{x^2} \int_0^{q(x)} q^{-1}(y)f(y)dy = \frac{1}{x^2} \int_0^x yq'(y)f(q(y))dy . \quad (45)$$

It is easy to check that $\mathcal{P}: L^1(0, \infty) \rightarrow L^1(0, \infty)$ is a Markov operator, i.e. \mathcal{P} is linear and $\mathcal{P}(D) \subset D$. We give a sufficient condition for the existence and uniqueness of a fixed point of \mathcal{P} , which we will call a *stationary density*. In order to do this we will need an auxiliary result.

Let (X, \mathcal{A}, μ) be a σ -finite measure space. A Markov operator $\mathcal{P}: L^1 \rightarrow L^1$ is called *asymptotically stable* if there exists a stationary density f_* such that

$$\lim_{n \rightarrow \infty} \|\mathcal{P}^n f - f_*\| = 0 \quad \text{for } f \in D . \quad (46)$$

Equation (46) implies that for an asymptotically stable operator there exists exactly one stationary density. A Markov operator $\mathcal{P}: L^1 \rightarrow L^1$ is called *constrictive* if there exists a weakly compact set $\mathcal{F} \in L^1$ such that

$$\lim_{n \rightarrow \infty} d(\mathcal{P}^n f, \mathcal{F}) = 0 \quad \text{for } f \in D ,$$

where $d(\mathcal{P}^n f, \mathcal{F})$ denotes the distance, in L^1 norm, between the element f and the set \mathcal{F} . In particular \mathcal{P} is constrictive if there exists an integrable $\omega \geq 0$ such that

$$\mathcal{P}^n f \leq \omega + \varepsilon_n(f) \quad \text{and} \quad \lim_{n \rightarrow \infty} \|\varepsilon_n(f)\| = 0 .$$

The importance of weak constrictiveness is a consequence of the following theorem of Komorník (1986):

Spectral decomposition theorem. *The iterates of a constrictive operator \mathcal{P} can be written in the form*

$$\mathcal{P}^n f = \sum_{i=1}^r \lambda_i(f)g_{x^{(i)}} + Q_n f \quad \text{for } f \in L^1 ,$$

where:

- (1) g_1, \dots, g_r are densities with disjoint supports;
- (2) $\lambda_1, \dots, \lambda_r$ are linear functionals on L^1 ;
- (3) α is a permutation of $1, \dots, r$ such that $\mathcal{P}g_i = g_{\alpha(i)}$ and α^n denotes the n^{th} iterate of α ; and
- (4) Q_n is a sequence of operators such that $\lim_{n \rightarrow \infty} \|Q_n f\| = 0$ for $f \in L^1$.

Now we show that the operator \mathcal{P} given by (45) is asymptotically stable. From this fact it follows that (30) has a unique fixed point in the set of densities.

Lemma 4. Assume that $q'(0) < e$. Then the operator $\mathcal{P}: L^1(0, \infty) \rightarrow L^1(0, \infty)$ given by (45) is asymptotically stable.

Proof. Since $q'(0) < e$, there exist $\varepsilon \in (0, q'(0))$, $r > 0$ and $K \in (0, 1)$ such that

$$(q'(0) + \varepsilon)(q'(0) - \varepsilon)^{r-1} < K(1 + r).$$

Let $\rho \in (0, 1)$ be a number such that $|q'(y) - q'(0)| < \varepsilon$ for $y < \rho$ and let $x \wedge \rho = \min\{x, \rho\}$. Denote by ψ the function

$$\psi(x) = \begin{cases} x^{1-r}, & \text{for } x \in [0, 1] \\ 1, & \text{for } x > 1 \end{cases}$$

and let

$$R(f) = \sup_{x > 0} f(x)\psi(x), \quad \text{for } f \in D.$$

Denote by D_0 the subset of D consisting of all functions $f \in D$ with $R(f) < \infty$. Then for every $f \in D_0$ we have

$$\begin{aligned} x^{1-r} \mathcal{P}f(x) &= x^{-1-r} \int_0^x yq'(y)f(q(y)) dy \\ &\leq x^{-1-r} \int_0^{x \wedge \rho} yq'(y)f(q(y)) dy + \rho^{-1-r} \int_\rho^1 yq'(y)f(q(y)) dy \\ &\leq x^{-1-r} R(f) \int_0^{x \wedge \rho} yq'(y)q(y)^{r-1} dy + \rho^{-1-r} \\ &\leq \frac{x^{-1-r}}{1+r} R(f)(x \wedge \rho)^{r+1}(q'(0) + \varepsilon)(q'(0) - \varepsilon)^{r-1} + \rho^{-1-r} \\ &\leq KR(f) + \rho^{-1-r}. \end{aligned}$$

This implies that $R(\mathcal{P}f) \leq KR(f) + B$, where $B = \rho^{-1-r}$. By an induction argument we obtain

$$R(\mathcal{P}^n f) \leq K^n R(f) + \frac{B}{1-K}.$$

Since $R(f) < \infty$, there is an integer $n_0 = n_0(f)$ such that

$$R(\mathcal{P}^n f) \leq 1 + \frac{B}{1-K} \quad \text{for } n \geq n_0. \quad (47)$$

Moreover, from the definition of \mathcal{P} it follows immediately that

$$\mathcal{P}f(x) \leq x^{-2} \quad \text{for } f \in D. \tag{48}$$

Let ω be a function given by

$$\omega(x) = \begin{cases} x^{r-1}(1 + B/(1 - K)), & \text{for } x \in (0, 1] \\ x^{-2}, & \text{for } x > 1. \end{cases}$$

Let

$$\mathcal{F} = \{f \in D : f(x) \leq \omega(x)\}.$$

Since ω is an integrable function the set \mathcal{F} is weakly compact. From (47) and (48) it follows that $\mathcal{P}^n f(x) \leq \omega(x)$ for $f \in D_0$ and sufficiently large n . Since D_0 is a dense subset of D , the operator \mathcal{P} is weakly constrictive.

Now we show that the operator \mathcal{P} is asymptotically stable. In order to do this we check that the set $S = \{g_1, \dots, g_r\}$ in Spectral Decomposition Theorem contains only one element. Let $g \in S$ and $A = \text{supp } g$. If $z = \inf A$, then from the definition of $\mathcal{P}g$ it follows that

$$[q^{-1}(z), \infty) \subset \text{supp } \mathcal{P}g. \tag{49}$$

If g_1 and g_2 are different elements of S , then also $\mathcal{P}g_1$ and $\mathcal{P}g_2$ are different elements of S and have disjoint supports, which contradicts (49). \square

5 Conclusion

To our knowledge, little is known about the solution behavior of systems like (10)–(11) that contain both temporal delays and nonlocal maturational dependencies. Indeed, there are many open problems in the elucidation of the solution behavior of differential delay equations without maturational non-locality (Mackey and Milton 1990).

Although Gyllenberg and Heijmans (1987) considered a similar equation to (24), it is difficult to apply their results to our case. Their and our models are based on different biological assumptions. For example, in their paper the maturation is bounded because the rate of entering of the second phase at maximum size is infinite. In our case the boundedness of the maturation follows from the condition $V(m_F) = 0$. Moreover, the semigroup generated by the equation considered by Gyllenberg and Heijmans (1987) is compact for sufficiently large t , which does not occur in our case.

Rey and Mackey (1992, 1993) have numerically studied the solution properties of a class of delayed partial differential equations of the form

$$\frac{\partial u}{\partial t} + rx \frac{\partial u}{\partial x} = -\delta u + \lambda u_t(1 - u_t) \quad \text{for } (t, x) \in [0, \infty) \times [0, 1], \tag{50}$$

where $u_t \equiv u(t - \tau, e^{-r\tau}x)$, which is similar to the equations derived here. For this system one must specify an initial function

$$\phi(t', x') \quad \text{for } (t', x') \in [-\tau, 0] \times [0, 1].$$

Rey and Mackey (1992, 1993) have shown numerically that the solution evolution of (50) is highly dependent on $\phi(t', 0)$. Namely, when $\phi(t', 0) > 0$ then the numerically generated solutions of (50) seem to globally converge to a unique limit. However, when $\phi(t', 0) = 0$ then the behavior is quite different in that the limiting solutions may be both temporally and spatially periodic or chaotic, including traveling wave solutions, and that the ultimate nature of the limiting value of $u(t, x)$ depends, in an unknown way, on $\phi(t', 0)$.

This behavior is reminiscent of that observed by a variety of authors (Brunovský 1983, Brunovský and Komorník 1984, Lasota 1981, Loskot 1985, Rudnicki, 1985, 1987, 1988) for the solutions of equations like (50) when $\tau \equiv 0$. This indicates that the solutions set of (10)–(11) is likely to be correspondingly rich and we suspect that it will display a broad spectrum of dynamical behaviors dependent on the initial function. This same sensitive dependence of the eventual solution behavior on the initial function has been studied numerically by Crabb et al. (1993) and Losson et al. (1993) in differential delay equations.

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