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A new criterion for the global stability of simultaneous cell replication and maturation processes

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Abstract. We analyze a population model of cells that are capable of simultaneous and independent proliferation and maturation. This model is described by a first order partial differential equation with a time delay and a retardation of the maturation variable, both due to cell replication. We provide a general criterion for global stability in such equations.

Key words: Cell cycle – Hematology – Time-age-maturation

1 Introduction

Time–age–maturation models for age structured biological populations have arisen in many contexts, the first of which was the modeling of human demographics as described in Keyfitz (1968), Pollard (1973), and Henry (1976). The comprehensive book of Metz and Diekmann (1986) can be consulted for an excellent survey of many of the more recent applications outside the demographic area, as well as an exposition of how such models may be formulated from the relevant biology.

One of the areas in which such "time–age" or "time–maturation" models have been used with great success is that of cell replication and maturation, and these applications date from almost 40 years ago [Von Foerster (1959), Trucco (1965a, b; 1966), Oldfield (1966), Nooney (1967), Rubinow (1968, 1975)]. Recently Mackey and Rudnicki (1994) considered a particular time–age–maturation cell cycle model that was motivated by the biological process of hematological cell development from the pluripotential stem cell population. Given the biological constraint imposed on the model, they showed that the final formulation of the model was framed as a pair of coupled nonlinear partial differential equations. These are somewhat unique in that the dynamics are not only dependent on the behavior of the cell population numbers some time in the past (time delayed effects), but also that the population behavior at a given maturation level is dependent on the behavior at a previous maturation level (nonlocal effects). Thus, this important biological problem leads, in a rather natural fashion, to an intriguing mathematical problem involving a delayed nonlocal dynamics described by a nonlinear transport equation:

$$\frac{\partial u}{\partial t} + g(x)\frac{\partial u}{\partial x} = f(t, u(x,t), u(h(x), t-\tau)). \tag{1}$$

Equations similar to (1) have been rather intensively studied numerically by Rey and Mackey (1992, 1993, 1995a, b) and Crabb et al. (1996a, b). However, in spite of the insight obtained from the numerical solutions and some local analysis, these authors were unable to obtain more global results concerning the eventual solution behavior of these interesting systems. This paper extends some of the first steps of Dyson et al. (1996) in providing such insight.

The paper is organized as follows. In Sect. 2 we give some brief biological background to motivate the development of a cell replication model similar to that of Mackey and Rudnicki (1994) which has subsequently been studied by Dyson et al. (1996). In Sect. 3 we make some preliminary remarks and observations about the solutions of a generalization of the central delayed and nonlocal partial differential equation derived in Sect. 2. In Sect. 4 we introduce the associated differential delay equation obtained from the partial differential equation of Sect. 3 by ignoring the maturation variable, and state and prove our main theorem connecting the global solution behavior of this associated differential delay equation with the local and global solution behavior of the partial differential equations of Sect. 2. In Sect. 5 we state and prove a result that guarantees the local stability of the partial differential equation, which is a necessary ingredient for the use of the main theorem of Sect. 4. In Sect. 6 we specifically consider the same system considered by Rey and Mackey (1992, 1993, 1995a, b), Crabb et al. (1996a, b) and Dyson et al. (1996) to illustrate the applicability of our results. The paper concludes in Sect. 7 with a brief consideration of the situations in which the model solution is unstable.

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 [Burns and Tannock (1970), Smith and Martin (1973)] so the model we develop shares some characteristics of general population models with quiescence [Gyllenberg and Webb (1987)].

2.1 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 DNA synthesis) to $a = \tau$ (the point of cytokinesis). The *maturation* variable is labeled by m which ranges from $m = 0$ to infinity, $m \in [0, \infty)$.

For concreteness one could think of erythroid precursor cells and associate the maturation variable with the intracellular hemoglobin concentration which is conserved at cytokinesis with the sum of the hemoglobin content of the daughter cells equaling the hemoglobin content of the mother cell. However we note that our formulation is *not* restricted to this very specific identification of the maturation variable with a conserved quantity, and a second example of this situation would be the cell division/migration process in the intestinal crypts as nicely reviewed in Potten and Löeffler (1990). In this case, the maturation variable would be interpreted as the cellular position within the crypt (as measured from the apex).

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 γ, and cells of both types mature with a velocity $V(m) = rm$. (Note that if we want to consider the situation in which the maturation variable m is confined between 0 and a finite maximal value of $m_F = < \infty$, then we would need to add the assumption that $V(m_F) = 0$.)

If we denote the density of actively proliferating cells at time t, maturation level m, and age a by $p(m, a, t)$, then the conservation equation for $p(m, a, t)$ is simply [Metz and Diekmann (1986)]

$$\frac{\partial p}{\partial t} + \frac{\partial p}{\partial a} + \frac{\partial [V(m)p]}{\partial m} = -\gamma p, \tag{2}$$

and we specify an initial condition

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

where Γ is assumed to be continuous. The total (marginal) density of proliferating cells at a given time and maturation level is naturally defined by

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

2.2 The resting phase

Immediately following cytokinesis, the two 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 $a = \infty$. If the maturation of the mother cell at cytokinesis is m, then we assume the maturation of a daughter cell at birth is αm with $\alpha > 0$. We denote the density of cells in this stage by $n(m, a, t)$, so the total (marginal) density of cells in the resting stage is given by

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

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 $\delta \geqq 0$ or;
(2) by re-entering the proliferating stage at a rate $\beta(N) \geqq 0$ that is a decreasing function;

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

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} + \frac{\partial [V(m)n]}{\partial m} = -[\delta + \beta(N)]n, \tag{3}$$

with an initial condition

$$n(m, a, 0) = \mu(m, a) \quad \text{for } (m, a) \in [0, \infty) \times [0, \infty),$$

and

$$\lim_{a \to \infty} \mu(m, a) = 0. \tag{4}$$

We always assume that β and μ are continuous.

Remark 1. Our two preceding assumptions concerning the fate of cells in the resting G_0 phase deserve some comment. First we have assumed that cells are lost at a constant random rate from G_0 to accommodate cell loss through maturation [Burns and Tannock (1970), Mackey and Dörmer (1981, 1982)] or through cell death (either apoptosis or necrosis). Though it is possible that the loss rate through either of these causes may, in certain specialized circumstances, be non-constant the existing data give no clear general guidelines on this matter. Hence we have assumed the rates to be constant. Secondly, we have assumed that the rate of cell re-entry into the proliferating P phase from the resting G_0 phase is a decreasing function of N. This is abundantly documented in the cell kinetic literature, where it is regularly noted that an ablation of a fraction of a cellular population (e.g. using radioactive suicide techniques) is followed by an increase in the rate of cell entry into the proliferative phase [Baserga (1976), Nečas and Znojil (1987, 1988), Leary et al. (1992), Ogawa (1993), and Nečas et al. (1995)]. What is less clear, in a structured population as the present model is intended to mirror, is the nature of the signal (is it mediated by cyclin-like agents [Novak and Tyson (1993, 1995), Tyson et al. (1995)]) and the origin of the signaling population. Is it only the cell density at the given maturation level as we have assumed, or is the entire population of all maturation levels

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

involved? Here we have assumed that β responds only to the G_0 cell density at a specific maturation level to reflect the characteristics of certain stem cell populations in which cellular control appears to be mediated by different cytokines at different levels of maturation [Sachs (1993), Sachs and Lotem (1994)]. However, we note that under certain circumstances it might be more appropriate biologically to assume that the re-entry rate β depends on $\bar{N}$, $\beta(\bar{N})$. A resolution of this issue awaits more precise experimental work on maturing cell populations in a variety of tissues, and no doubt different conclusions will be reached in different situations.

2.3 Boundary conditions

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

$$n(m,0,t) = 2\alpha^{-1}p(\alpha^{-1}m,\tau,t), \tag{5}$$

and simply relates the equality of the cellular efflux following cytokinesis to the input flux of the resting compartment. The second boundary condition is

$$p(m, 0, t) = \int_0^\infty \beta(N(m, t)) n(m, a, t)\, da = \beta(N(m, t)) N(m, t). \qquad (6)$$

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

2.4 *Equations for P and N*

Given a slightly different version of the above formulation of this time age–maturation view of cell replication, Mackey and Rudnicki (1994) were able to use the method of characteristics to derive evolution equations for $P(m, t)$ and $N(m, t)$. With a minor change and using the notation

$$N^\tau(m, t) = N(e^{-r\tau} m, t - \tau),$$

$$N_\tau(m, t) = N(\alpha^{-1} e^{-r\tau} m, t - \tau) = N^\tau(\alpha^{-1} m, t),$$

the final evolution equations in our case here are:

$$\frac{\partial P}{\partial t} + rm \frac{\partial P}{\partial m} = -(\gamma + r) P + N\beta(N) - e^{-(\gamma + r)\tau} N^\tau \beta(N^\tau), \qquad (7)$$

$$\frac{\partial N}{\partial t} + rm \frac{\partial N}{\partial m} = -[\gamma + r + \beta(N)] N + 2\alpha^{-1} e^{-(\gamma + r)\tau} N_\tau \beta(N_\tau). \qquad (8)$$

Equations (7) and (8) are the final relations describing the cellular dynamics. Notice that the solution of (8) is independent of the behavior of the solution of (7), but the converse is not true. These equations, without the nonlocal terms, have been used previously to understand several periodic hematological diseases [Mackey (1978, 1979), Mackey and Milton (1990)].

Equations (7) and (8) are interesting since they contain an explicit retardation in the temporal term $(t - \tau)$, and a nonlocal dependence in the maturation variable. Other models of cellular replication (Diekmann et al., 1984; Gyllenberg and Heijmans, 1987; Lasota and Mackey, 1984) have displayed the same features.

Defining $x = m$ and $u(x, t) = N(m, t)$, equation (8) can be written in the form (1), where $g(x) = rx$, $h(x) = \alpha^{-1} e^{-r\tau} x$ and

$$f(t, u, v) = -[\gamma + r + \beta(u)] u + 2\alpha^{-1} e^{-(\gamma + r)\tau} v \beta(v). \qquad (9)$$

In the rest of the paper we will assume that $h(x) < x$ for $x > 0$. From this assumption it follows that we can consider the solution of equation (1) for $(x, t) \in [0, M] \times [\tau, \infty)$, where M is any positive constant. Without loss of generality we can assume that $M = 1$.

Before closing this section, we offer a few comments of a biological nature relative to the mathematical assumption that $h(x) < x$. This simply reflects the fact that the (non-local) maturation argument in the marginal density $N_\tau(m, t) = N(\alpha^{-1} e^{-r\tau} m, t - \tau)$ does not exceed m. In terms of the biological parameters of the model this condition can be written as $\alpha^{-1} e^{-r\tau} x < x$ or

$$e^{-r\tau} < \alpha.$$

In the first example quoted above in our discussion of the maturation process, we would expect that $\alpha = 1/2$ if there was an exact division of the mother cell hemoglobin between the two daughter cells so our previous inequality becomes

$$\ln 2 < r\tau.$$

In the second example of the intestinal crypt where the maturation variable could be interpreted as position within the crypt, at cell division the two daughter cells are at approximately the same position as the mother cell and thus $\alpha = 1$ so the requirement $e^{-r\tau} < \alpha = 1$ would always be satisfied.

We also note in closing that there is always a second condition imposed on the parameters α, γ, r and τ if equation (8) is to have a (positive) steady state solution in addition to the trivial one of $N \equiv 0$. This condition is easily shown to be

$$\alpha \leqq 2e^{-(\gamma + r)\tau} \frac{\beta(0)}{\gamma + r + \beta(0)}.$$

3 Existence and uniqueness of solutions

Equation (1) can be written in the form

$$\frac{\partial u}{\partial t} + g(x) \frac{\partial u}{\partial x} = f(t, u, u_\tau), \tag{10}$$

where $u_\tau(x, t) = u(h(x), t - \tau)$, $\tau > 0$. We assume that the functions $g: [0, 1] \to \mathbb{R}$, $h: [0, 1] \to [0, 1]$, and $f: [0, \infty) \times \mathbb{R} \times \mathbb{R} \to \mathbb{R}$ are continuously differentiable and satisfy the following conditions:

(a) $g(0) = 0$, $g(x) > 0$ for $x > 0$,
(b) $h(0) = 0$, $h(x) < x$ for $x \in (0, 1]$,

(c) there exist continuous functions $\alpha_1, \alpha_2 : [0, \infty) \times \mathbb{R} \to \mathbb{R}$ such that

$$|f(t, u, v)| \leqq \alpha_1(t, v)|u| + \alpha_2(t, v).$$

Equation (1) is considered with the initial condition

$$u(x, t) = \varphi(x, t) \quad \text{for } (x, t) \in [0, 1] \times [-\tau, 0]. \tag{11}$$

A function $u : [0, 1] \times [-\tau, \infty) \to \mathbb{R}$ is called a *classical solution* of the problem (10), (11) if u is a continuous function in its domain, u satisfies the initial condition (11), the partial derivatives $\partial u/\partial t$ and $\partial u/\partial x$ exist for $(x, t) \in [0, 1] \times (0, \infty)$ and u satisfies equation (10) for $(x, t) \in [0, 1] \times (0, \infty)$. Equation (10) has an extensive literature when $\tau = 0$, and has been considered by Brunovský (1983), Brunovský and Komorník (1984), Komorník (1986), Lasota (1981), Lasota et al. (1991), Łoskot (1985, 1994), Rudnicki and Mackey (1994), and Rudnicki (1985, 1987, 1988). Aspects of the behaviour of equation (10) when $\tau > 0$ have been considered in Crabb et al. (1996a, b), Dyson et al. (1996), Mackey and Rudnicki (1994), and Rey and Mackey (1992, 1993, 1995a, b).

First we show that if φ is a continuously differentiable function then there exists exactly one classical solution of (10), (11).

Equation (10) can be solved by steps using the method of characteristics. Let $\pi_s x$ be the solution of the equation

$$\frac{d\pi_s x}{ds} = g(\pi_s x) \tag{12}$$

with the initial condition $\pi_0 x = x$ for $x \in [0, 1]$. The solution of (12) is well defined for $\pi_s x \leqq 1$. We can omit the problem of the global existence of the solutions of (12) by extending the function g on the interval $[0, \infty)$ provided that g is bounded and continuously differentiable on $[0, \infty)$. Then the function $(s, x) \mapsto \pi_s x$ is well defined on $\mathbb{R} \times [0, \infty)$ and continuously differentiable with respect to (s, x).

If u is a solution of the problem (10) and (11), then the function $\psi(c, s) = u(\pi_s c, s)$ is well defined for $s > 0$ and c such that $0 \leqq \pi_s c \leqq 1$. The function ψ satisfies the equation

$$\frac{\partial \psi}{\partial s} = f(s, \psi, u(h(\pi_s c), s - \tau)) \tag{13}$$

for $s \in (0, \tau]$, $0 \leqq \pi_s c \leqq 1$. We can rewrite equation (13) in the form

$$\frac{\partial \psi}{\partial s} = \bar{f}(s, c, \psi), \tag{14}$$

where $\bar{f}(s, c, z) = f(s, z, u(h(\pi_s c), s - \tau))$. The function $\bar{f}$ is continuously differentiable in its domain and grows at most linearly with respect to z. From this it follows that for any $c \in [0, 1]$ there exists a unique solution of (14) and this solution is defined for s such that $\pi_s c \in [0, 1]$. Moreover the function $\psi(c, s)$ is continuously differentiable with respect to (c, s).

On the other hand if ψ is a solution of (14) such that $\psi(c, 0) = u(c, 0) = \varphi(c, 0)$, then the function $u(x, t) = \psi(\pi_{-t} x, t)$ is well defined for $(x, t) \in [0, 1] \times [0, \tau]$, $(\partial u/\partial t)$ and $(\partial u/\partial x)$ exist and are continuous functions for $(x, t) \in [0, 1] \times (0, \tau]$, and u satisfies equation (10) in this set [for $t = \tau$ by $(\partial u/\partial t)$ we understand the left hand side derivative $(\partial u^-/\partial t)$]. In this way we obtain the solution of (10) for $t \in [0, \tau]$. Using this method we can solve (10) successively for $t \in [\tau, 2\tau]$, $t \in [2\tau, 3\tau]$, ... Only one problem remains: Does $u(x, t)$ satisfy the equation (10) for $t = n\tau$?

We will check that it does for $t = \tau$. Let ψ be a solution of the equation

$$\frac{\partial \psi}{\partial s} = f(s, \psi(c, s), u(h(\pi_{s-\tau} c), s - \tau)) \tag{15}$$

with the initial condition $\psi(c, \tau) = u(c, \tau)$. Then

$$\frac{\partial \psi^+}{\partial s}(c, \tau) = f(\tau, u(c, \tau), u(h(c), 0)). \tag{16}$$

Let $u(x, t) = \psi(\pi_{\tau - t} x, t)$. Then

$$\frac{\partial \psi^+}{\partial t}(c, \tau) = \frac{\partial u^+}{\partial t}(c, \tau) + g(c)\frac{\partial u}{\partial x}(c, \tau).$$

From (16) it follows that

$$\frac{\partial u^+}{\partial t} + g(x)\frac{\partial u}{\partial x} = f(t, u, u_\tau) \quad \text{for } t = \tau.$$

This implies that $(\partial u^+/\partial t) = (\partial u^-/\partial t)$ for $t = \tau$ and u satisfies (10) for $t = \tau$.

Remark 2. The solution of the problem (10) and (11) continuously depends on the initial function φ. Precisely, using once more the method of characteristics and the method of steps one can check the following statement. Let $M > 0$ and $T > 0$ be given constants. Then there exists an $L > 0$ such that for any two solutions of (10) which satisfy the following condition

$$\max_{x\in[0,1]} \max_{t\in[-\tau,0]} |u_i(x,t)| \leqq M \quad \text{for } i = 1, 2,$$

we have

$$\max_{x\in[0,1]} \max_{t\in[0,T]} |u_2(x,t) - u_1(x,t)| \leqq L \max_{x\in[0,1]} \max_{t\in[-\tau,0]} |u_2(x,t) - u_1(x,t)|.$$

If $\varphi : [0,1] \times [-\tau, 0] \to \mathbb{R}$ is a continuous function, then we can define a *generalized solution* of the problem (10) and (11). Let $\varphi_n : [0,1] \times [-\tau, 0] \to \mathbb{R}$ be a sequence of continuously differentiable function such that $\varphi_n \to \varphi$ uniformly. Then, from the continuous dependence of the solution of (10) on the initial condition it follows that the sequence of the solutions u_n corresponding to φ_n is uniformly convergent, on any compact set $[0,1] \times [0,T]$, to some continuous function $u(x,t)$. This function does not depend on the choice of the sequence $\{\varphi_n\}$ and it is called the generalized solution of the problem (10) and (11). The generalized solution can be also obtained using the method of characteristics described above. Since we only consider generalized solutions we will omit the word generalized.

4 The main result

Now we consider the following delay differential equation associated with (10):

$$z'(t) = f(t, z(t), z(t-\tau)). \tag{17}$$

The following theorem plays a central role in our investigations.

Theorem 1. *Let $u(x,t)$ be a solution of the problem* (10) *and* (11). *Let $z(t)$ be the solution of* (17) *satisfying the initial condition $z(t) = u(0,t)$ for $t \in [-\tau, 0]$. Then for every $t_0 \geqq 0$ and $\varepsilon > 0$ there exist $t_1 > 0$ and another solution $\bar{u}(x,t)$ of* (10) *such that*

(i) $\sup\{|\bar{u}(x,t) - z(t)| : (x,t) \in [0,1] \times [-\tau, t_0]\} < \varepsilon$,
(ii) $\bar{u}(x,t) = u(x,t)$ for $(x,t) \in [0,1] \times [t_1, \infty)$.

From Theorem 1 the entire strategy of this paper becomes clear. Namely, if $z_0(t)$ is a globally asymptotically stable solution of (17) and $u_0(x,t) = z_0(t)$ is a locally asymptotically stable solution of (10) then $u_0(x,t)$ is globally asymptotically stable solution of (10). Thus, rather surprisingly, the question of determining the global stability of a solution of (10) can be reduced to the problem of examining the global stability of the corresponding differential delay equation (17) and the local stability of (10). Therefore, in the general case it is sufficient to focus on the global stability of the associated differential delay equation (17), which is itself usually quite difficult, and the local stability of (10), which is often easier and which we treat in Sect. 5.

Proof. We split the proof of Theorem 1 into two steps.

Step I. We first show that for every $\delta \in (0, 1)$ there exists $t_1 > 0$ such that if $\varphi_1, \varphi_2 : [0, 1] \times [-\tau, 0] \to \mathbb{R}$ are continuous functions and $\varphi_1(x, t) = \varphi_2(x, t)$ for $(x, t) \in [0, \delta] \times [-\tau, 0]$, then the solutions u_1 and u_2 of (10) corresponding to φ_1, φ_2 satisfy $u_1(x, t) = u_2(x, t)$ for $(x, t) \in [0, 1] \times [t_1, \infty)$.

Let $S : [0, 1] \to [0, 1]$ be a function given by the formula

$$S(x) = \max\{\pi_{-\tau}x, \sup_{y \leqq x} h(y)\}.$$

Then S is a continuous function. Since $\pi_{-\tau}x < x$ for $x \in (0, 1]$ and $h(y) < y \leqq x$ for $0 < y \leqq x \leqq 1$, we have $S(x) < x$ for $x \in (0, 1]$. First, we check that if $\alpha \in [0, 1]$ and u_1, u_2 are two solutions of (10) such that $u_1(x, t) = u_2(x, t)$ for $(x, t) \in [0, S(\alpha)] \times [-\tau, t_0]$ then $u_1(x, t) = u_2(x, t)$ for $(x, t) \in [0, \alpha] \times [t_0 + \tau, \infty)$.

Indeed, if $(x, t) \in [0, \alpha] \times [t_0, t_0 + \tau]$, then $h(x) \leqq S(\alpha)$ and $t - \tau \in [-\tau, t_0]$. This implies that $u_{1\tau}(y, t) = u_{2\tau}(y, t)$ for $(x, t) \in [0, \alpha] \times [t_0, t_0 + \tau]$. From this it follows that u_1 and u_2 are the solutions of the same partial differential equation for $(x, t) \in [0, \alpha] \times [t_0, t_0 + \tau]$. Moreover, if $\pi_{t_0 - t}x \leqq S(\alpha)$ then $u_1(\pi_{t_0 - t}x, t_0) = u_2(\pi_{t_0 - t}x, t_0)$. This implies that the solutions u_1 and u_2 are the same along the characteristic $\gamma(t) = (\pi_{t_0 - t}x, t)$. In particular, since $\pi_{-\tau}x \leqq S(\alpha)$ for $x \in [0, \alpha]$ we have $u_1(x, t_0 + \tau) = u_2(x, t_0 + \tau)$. For $(x, t) \in [0, \alpha] \times [t_0 + \tau, t_0 + 2\tau]$ the functions u_1 and u_2 are the solutions of the same partial differential equation with the same initial condition. This implies that $u_1(x, t) = u_2(x, t)$ for $(x, t) \in [0, \alpha] \times [t_0 + \tau, \infty)$. Consider the sequence $\{S^n(1)\}$. Since S is a continuous function and $S(x) < x$ for $x \in (0, 1]$, we have $\lim_{n \to \infty} S^n(1) = 0$. Let k be an integer such that $S^k(1) \leqq \delta$. If $\varphi_1(x, t) = \varphi_2(x, t)$ for $(x, t) \in [0, \delta] \times [-\tau, 0]$, then $u_1(x, t) = u_2(x, t)$ for $(x, t) \in [0, 1] \times [(2k - 1)\tau, \infty)$.

Step II. Now let $\varepsilon > 0$ and $t_0 > 0$ be given constants. Let $u(x, t)$ be a solution of (10) and $z(t)$ be the solution of (17) with the initial condition $z(t) = u(0, t)$ for $t \in [-\tau, 0]$. The function $w(x, t) = z(t)$ is also a solution of (10). From the continuous dependence of the solutions of (10) on the initial condition it follows that there exists $\varepsilon_1 > 0$ such that if

$$|\bar{\varphi}(x,t) - z(t)| < \varepsilon_1 \quad \text{for } (x,t) \in [0,1] \times [-\tau, 0] \tag{18}$$

then

$$|\bar{u}(x,t) - z(t)| < \varepsilon \quad \text{for } (x,t) \in [0,1] \times [-\tau, t_0], \tag{19}$$

where $\bar{u}$ is the solution of (10) which satisfies the initial condition $\bar{u}(x,t) = \bar{\varphi}(x,t)$ for $(x,t) \in [0,1] \times [-\tau, 0]$. Since $u(x,t)$ is a continuous function and $z(t) = u(0,t)$ for $t \in [-\tau, 0]$, there exists $\delta > 0$ such that $|u(x,t) - z(t)| < \varepsilon_1$ for $(x,t) \in [0,\delta] \times [-\tau, 0]$. Now, let

$$\bar{\varphi}(x,t) = \begin{cases} u(x,t): & (x,t) \in [0,\delta] \times [-\tau, 0], \\ u(\delta,t): & (x,t) \in (\delta, 1] \times [-\tau, 0]. \end{cases}$$

Then $\bar{\varphi}$ satisfies (18). If $\bar{u}$ is a solution of (10) with the initial condition $\bar{\varphi}$, then $\bar{u}$ satisfies (19). Since $u(x,t) = \bar{u}(x,t)$ for $(x,t) \in [0,\delta] \times [-\tau, 0]$, from the first step it follows that $u(x,t) = \bar{u}(x,t)$ for $(x,t) \in [0,1] \times [t_1, \infty)$. □

5 Local stability of the partial differential equation

We now turn to considerations of the local stability of the full partial differential equation (10). We assume that the function f does not depend on t. Then equation (10) takes the form

$$\frac{\partial u}{\partial t} + g(x)\frac{\partial u}{\partial x} = f(u, u_\tau). \tag{20}$$

Let $\bar{u}(x,t)$ be a given solution of (20) and let A be a subset of $C([0,1] \times [-\tau, 0])$. We say that the solution $\bar{u}$ of (20) is *exponentially stable on the set* A if there exists $\mu > 0$ such that for every $\varphi \in A$ the solution of the problem (20), (11) satisfies the condition

$$\max\{|u(x,t) - \bar{u}(x,t)| : x \in [0,1]\} \leqq C e^{-\mu t}, \tag{21}$$

where C is a constant which depends only on φ. Let

$$A_\varepsilon = \{\varphi : |\varphi(x,t) - \bar{u}(x,t)| < \varepsilon \text{ for } (x,t) \in [0,1] \times [-\tau, 0]\}.$$

We say that $\bar{u}$ is *locally exponentially stable* if there exist an $\varepsilon > 0$, μ and C such that condition (21) holds for every solution of the problem (20), (11) with $\varphi \in A_\varepsilon$.

Theorem 2. *Let w be a constant such that* $f(w, w) = 0$ and

$$\frac{\partial f}{\partial u}(w, w) < -\left|\frac{\partial f}{\partial u_\tau}(w, w)\right|. \tag{22}$$

Then the solution $\bar{u}(x, t) \equiv w$ *of* (20) *is locally exponentially stable.*

Proof. Without loss of generality we can assume that $w = 0$. Let

$$a = \frac{\partial f}{\partial u}(0, 0)$$

and

$$b = \frac{\partial f}{\partial u_\tau}(0, 0),$$

then $a < -|b|$. In the space $C([0, 1], [-\tau, 0])$ we introduce an auxiliary norm

$$\|\varphi\|_\lambda = \max\{|\varphi(x, t)|e^{\lambda t} : (x, t) \in [0, 1] \times [-\tau, 0]\},$$

where $\lambda \in \mathbb{R}$. If $\lambda = 0$ then $\|\varphi\| = \|\varphi\|_0$ is the standard norm in $C([0, 1] \times [-\tau, 0])$. For any $\lambda_1 \in \mathbb{R}$, $\lambda_2 \in \mathbb{R}$ the norms $\|\cdot\|_{\lambda_1}$ and $\|\cdot\|_{\lambda_2}$ are equivalent and

$$\|\varphi\|_{\lambda_2} \leqq \|\varphi\|_{\lambda_1} \leqq e^{(\lambda_2 - \lambda_1)\tau}\|\varphi\|_{\lambda_2} \quad \text{for } \lambda_1 \leqq \lambda_2.$$

Let u be a solution of (20), (11) and $T : C([0, 1] \times [-\tau, 0]) \to C([0, 1] \times [-\tau, 0])$ be a transformation given by $(T\varphi)(x, t) = u(x, t + \tau)$. We check that there exists $\lambda > 0$, $\varepsilon > 0$ and $\gamma \in (0, 1)$ such that

$$\|T\varphi\|_\lambda \leqq \gamma\|\varphi\|_\lambda \tag{23}$$

for $\|\varphi\|_\lambda \leqq \varepsilon$. From the Lagrange mean value theorem it follows that for every $(u, v) \in \mathbb{R}^2$ there exists $\theta \in (0, 1)$ such that

$$f(u, v) = \frac{\partial f}{\partial u}(\theta u, \theta v)u + \frac{\partial f}{\partial v}(\theta u, \theta v)v.$$

Let $\delta > 0$ be a given constant and $\delta_1 > 0$ be a constant such that

$$\left|\frac{\partial f}{\partial u}(u, v) - a\right| < \delta, \quad \left|\frac{\partial f}{\partial v}(u, v) - b\right| < \delta \tag{24}$$

for $|u| < \delta_1$ and $|v| < \delta_1$. From the continuous dependence of the solution of (20) on the initial condition, it follows that there exists $\delta_2 \in (0, \delta_1)$ such that $\|T\varphi\| < \delta_1$ for $\|\varphi\| < \delta_2$. This implies that if $\|\varphi\| < \delta_2$, then the solution of the problem (20), (11) satisfies

$$\left|\frac{\partial u}{\partial t} + g(x)\frac{\partial u}{\partial x}\right| \leqq (|a| + \delta)|u| + (|b| + \delta)\|\varphi\|. \tag{25}$$

Let $(x, t) \in [0, 1] \times [0, \tau]$ and $\psi(s) = u(\pi_{s-t}x, s)$ for $s \in [0, t]$. Then from (25) it follows that

$$|\psi'(s)| \leqq (|a| + \delta)|\psi(s)| + (|b| + \delta)\|\varphi\|. \tag{26}$$

Inequality (26) implies that

$$|\psi(s)| \leqq \left(|\psi(0)| + \frac{(|b| + \delta)\|\varphi\|}{|a| + \delta}\right) \mathrm{e}^{(|a|+\delta)s}. \tag{27}$$

Since $|\psi(0)| \leqq \|\varphi\|$, from (27) we obtain

$$|\psi(s)| \leqq K\|\varphi\|, \tag{28}$$

where

$$K = \frac{|a| + |b| + 2\delta}{|a| + \delta} \mathrm{e}^{(|a|+\delta)\tau}.$$

From (28) and from the formula $u(x, t) = \psi(t)$ it follows that

$$|u(x, t)| \leqq K\|\varphi\| \quad \text{for } (x, t) \in [0, 1] \times [0, \tau]. \tag{29}$$

Now we are ready to prove (23). Let $\varphi \in C([0, 1] \times [-\tau, 0])$ be a function such that $\|\varphi\| < \delta_2$ and let λ be a positive constant. Then

$$|\varphi(x, t)| \leqq \mathrm{e}^{-\lambda t}\|\varphi\|_\lambda \quad \text{for } (x, t) \in [0, 1] \times [-\tau, 0]. \tag{30}$$

Let $u(x, t)$ be a solution of (20), (11). From (24) it follows that $u(x, t)$ satisfies the inequality

$$\left|\frac{\partial u}{\partial t} + g(x)\frac{\partial u}{\partial x} - au\right| \leqq \delta|u(x, t)| + (|b| + \delta)|u(h(x), t - \tau)| \tag{31}$$

for $(x, t) \in [0, 1] \times [0, \tau]$. From (29) and (30) it follows that

$$|u(x, t)| \leqq K\mathrm{e}^{\lambda\tau}\|\varphi\|_\lambda \quad \text{and} \quad |u(h(x), t - \tau)| \leqq \mathrm{e}^{\lambda(\tau - t)}\|\varphi\|_\lambda. \tag{32}$$

Using (32) in (31) we obtain

$$\left|\frac{\partial u}{\partial t} + g(x)\frac{\partial u}{\partial x} - au\right| \leqq (\delta K\mathrm{e}^{\lambda\tau} + (|b| + \delta)\mathrm{e}^{\lambda\tau - \lambda t})\|\varphi\|_\lambda. \tag{33}$$

Let $(x, t) \in [0, 1] \times [0, \tau]$ and $\psi(s) = \mathrm{e}^{-as}u(\pi_{s-t}x, s)$ for $s \in [0, t]$. Then from (33) we have

$$|\psi'(s)| \leqq (\delta K\mathrm{e}^{\lambda\tau - as} + (|b| + \delta)\mathrm{e}^{\lambda\tau - \lambda s - as})\|\varphi\|_\lambda. \tag{34}$$

Since $\psi(0) = u(\pi_{-t}x, 0) = \varphi(\pi_{-t}x, 0)$, we have $|\psi(0)| \leqq \|\varphi\|_\lambda$. From inequality (34),

$$|\psi(t)| \leqq \left[1 + \frac{\delta K}{a}\mathrm{e}^{\lambda\tau}(1 - \mathrm{e}^{-at}) + \frac{|b| + \delta}{a + \lambda}\mathrm{e}^{\lambda\tau}(1 - \mathrm{e}^{-(\lambda+a)t})\right]\|\varphi\|_\lambda, \tag{35}$$

results. Since $u(x, t) = \mathrm{e}^{at}\psi(t)$ and $(T\varphi)(x, t) = u(x, t + \tau)$ we have

$$\mathrm{e}^{\lambda t}(T\varphi)(x, t) = \mathrm{e}^{(a+\lambda)t + a\tau}\, \psi(t + \tau). \tag{36}$$

From (35), (36) and inequalities $a < 0$, $t \leqq 0$ it follows that

$$e^{\lambda t}|T\varphi(x, t)| \leqq \left[\mathrm{e}^{(a+\lambda)t + a\tau} + \frac{\delta K}{|a|}\,\mathrm{e}^{\lambda\tau} + \frac{|b| + \delta}{a + \lambda}\,(\mathrm{e}^{(a+\lambda)(t+\tau)} - 1)\right]\|\varphi\|_\lambda. \tag{37}$$

Inequality (37) implies that

$$\|T\varphi\|_\lambda \leqq \gamma(\delta, \lambda)\|\varphi\|_\lambda, \tag{38}$$

where

$$\gamma(\delta, \lambda) = \max\left\{\mathrm{e}^{-\lambda\tau} + \frac{\delta K}{|a|}\,e^{\lambda\tau}, \mathrm{e}^{a\tau} + \frac{\delta K}{|a|}\,\mathrm{e}^{\lambda\tau} + \frac{|b| + \delta}{a + \lambda}\,(\mathrm{e}^{(a+\lambda)\tau} - 1)\right\}.$$

For any $\lambda > 0$ we can choose $\delta > 0$ sufficiently small so that the first term in the above maximum is less than one. The second term in the maximum equals

$$\mathrm{e}^{a\tau} + \frac{|b|}{a}\,(\mathrm{e}^{a\tau} - 1)$$

for $\delta = 0$ and $\lambda = 0$. Since $a\tau < 0$ and $|a| > |b|$, this term is less than one. If we choose $\delta > 0$ and $\lambda > 0$ sufficiently small, then both terms in the maximum are less than one. In this way we obtain inequality (23) for $\|\varphi\| \leqq \delta_2$. If we take $\varepsilon = \mathrm{e}^{-\lambda\tau}\delta_2$ then for any φ such that $\|\varphi\|_\lambda \leqq \varepsilon$ we have $\|\varphi\| \leqq \delta_2$ and consequently (23) holds for $\|\varphi\|_\lambda \leqq \varepsilon$. Now, let u be a solution of the problem (20), (11) such that $\|\varphi\|_\lambda \leqq \varepsilon$. Since $u(x, t) = (T^n\varphi)(x, t - n\tau)$ for $t \in [(n-1)\tau, n\tau]$ and $\|T^n\varphi\|_\lambda \leqq \gamma^n\|\varphi\|_\lambda$ we have

$$|u(x, t)| \leqq \mathrm{e}^{\lambda\tau}\gamma^n\|\varphi\|_\lambda$$

for $(x, t) \in [0, 1] \times [(n-1)\tau, n\tau]$. If we take $\mu = -\tau^{-1}\log\gamma$, then

$$|u(x, t)| \leqq \mathrm{e}^{\lambda\tau}\|\varphi\|_\lambda \mathrm{e}^{-\mu t} \leqq \mathrm{e}^{\lambda\tau - \mu t}\|\varphi\|$$

for $(x, t) \in [0, 1] \times [-\tau, \infty)$, which completes the proof. □

Now, consider the associated delay differential equation corresponding to (20):

$$z'(t) = f(z(t), z(t - \tau)). \tag{39}$$

Let $\varphi \in C[-\tau, 0]$ and denote by z_φ the solution of (39) satisfying the initial condition $z_\varphi(t) = \varphi(t)$ for $t \in [-\tau, 0]$. Let $w \in \mathbb{R}$ be a constant such that $f(w, w) = 0$. Then w is a stationary solution of (39). The set

$$B(w) = \left\{ \varphi \in C[-\tau, 0]\colon \lim_{t \to \infty} z_\varphi(t) = w \right\}$$

is called the *basin of attraction* of w. Denote by P the projection operator

$$P\colon C([0,1] \times [-\tau, 0]) \to C[-\tau, 0]$$

given by $(P\varphi)(t) = \varphi(0, t)$ for $t \in [-\tau, 0]$.

Corollary 1. *Let* $w \in \mathbb{R}$ *satisfy* (22) *and* $f(w, w) = 0$. *Then equation* (20) *is globally exponentially stable on the set*

$$A = \{\varphi \in C([0,1] \times [-\tau, 0])\colon P\varphi \in B(w)\}.$$

Proof. From Theorem 2 it follows that there exists $\varepsilon > 0$ such that if $\varphi \in C([0,1] \times [-\tau, 0])$ and $\|\varphi - w\| < \varepsilon$ then the solution $\bar{u}$ of (20) with the initial condition $\bar{u}(x, t) = \varphi(x, t)$ for $(x, t) \in [0,1] \times [-\tau, 0]$ satisfies (21). Let u be a solution of the problem (20), (11) and $\varphi \in A$. Let $z(t)$ be the solution of (39) with the initial condition $z(t) = P\varphi(t)$ for $t \in [-\tau, 0]$. Then there exists $t_0 > 0$ such that $|z(t) - w| < \varepsilon/2$ for $t \geqq t_0$. From Theorem 1 it follows that there exists $t_1 > t_0$ and a solution $\bar{u}$ of (20) such that $|\bar{u}(x, t) - z(t)| < \varepsilon/2$ for $(x, t) \in [0,1] \times [t_0, t_0 + \tau]$ and $\bar{u}(x, t) = u(x, t)$ for $(x, t) \in [0,1] \times [t_1, \infty)$. Since equation (20) is autonomous and $|\bar{u}(x, t) - w| < \varepsilon$ for $(x, t) \in [0,1] \times [t_0, t_0 + \tau]$, the solution $\bar{u}$ satisfies (21). Consequently, u also satisfies (21) with a suitable chosen C. □

Remark 3. If $f(w, w) = 0$,

$$a = \frac{\partial f}{\partial u}(w, w) < 0, \qquad b = \frac{\partial f}{\partial u_\tau}(w, w)$$

and $a < -|b|$, then the constant solution w is locally asymptotically stable for both equations (20) and (39). If $b \geqq |a|$ then the trivial solution of the linear equation $z'(t) = az(t) + bz(t - \tau)$ is unstable. Thus, one might expect that both equations (20) and (39) are locally asymptotically stable at the same time. However this is, in fact, not true. Consider the following equation

$$\frac{\partial u}{\partial t} + x\frac{\partial u}{\partial x} = -u(\mathrm{e}^{-1/2}x, t - 1). \tag{40}$$

If $k \in (-1, 0)$ is a solution of the equation

$$\mathrm{e}^{(k-1)/2} = \tfrac{1}{2} - k, \tag{41}$$

then the function

$$u(x, t) = e^{t/2} x^{|k|} \sin(2\pi \log x - 2\pi t) \tag{42}$$

is a solution of (40). Indeed, equation (41) has a solution $k \in (-1, 0)$, because the function $g(x) = e^{(x-1)/2} + k - \frac{1}{2}$ satisfies conditions $g(-1) < 0$ and $g(0) > 0$. Moreover

$$\frac{\partial u}{\partial t} + x \frac{\partial u}{\partial x} = (\tfrac{1}{2} - k) u(x, t)$$

and

$$-u(e^{-1/2} x, t - 1) = e^{(k-1)/2} u(x, t) = (\tfrac{1}{2} - k) u(x, t).$$

This implies that the function u defined by (42) is an unbounded solution of (40). Since equation (40) is linear the trivial solution of (40) is unstable. On the other hand, if we consider the associated differential delay equation

$$z'(t) = -z(t - 1), \tag{43}$$

then the trivial solution of (43) is globally exponentially stable (see [Hale, Chap. 5]). Moreover, from Theorem 1 it follows that though $u(x, t)$ grows exponentially, for every $t_0 > 0$ and $\varepsilon > 0$ there exists another solution $\bar{u}(x, t)$ of (40) such $|\bar{u}(x, t)| < \varepsilon$ for $t \leqq t_0$ and $\bar{u}(x, t) = u(x, t)$ for sufficiently large t.

6 Applications

In this section we apply the theory developed in Sects. 4 and 5 to the maturity structured population model considered in Sect. 2 and to the equation describing a model of the blood production system proposed by Rey and Mackey (1993) and further analyzed by Dyson et al. (1996).

A. Maturation structured model

We consider the following equation

$$\frac{\partial u}{\partial t} + g(x) \frac{\partial u}{\partial x} = -[c_1 + \beta(u)] u + c_2 \beta(u_\tau) u_\tau. \tag{44}$$

Equation (8) derived in Sect. 2 has the form (44) with $c_1 = \gamma + r$ and $c_2 = 2\alpha^{-1} e^{-(\gamma + r)\tau}$ and $g(x) = rx$. We assume that $c_1 > 0$, $c_2 > 0$ and

$\beta:[0,\infty)\to(0,\infty)$ is a continuously differentiable and decreasing function. Let

$$f(u,u_\tau)=-[c_1+\beta(u)]u+c_2\beta(u_\tau)u_\tau.$$

Equation (44) has a trivial solution $u_0\equiv 0$. According to Theorem 2 the trivial solution u_0 is locally exponentially stable if

$$\frac{\partial f}{\partial u}(0,0)<-\left|\frac{\partial f}{\partial u_\tau}(0,0)\right|. \tag{45}$$

Since

$$\frac{\partial f}{\partial u}(0,0)=-c_1-\beta(0)$$

and

$$\frac{\partial f}{\partial u_\tau}(0,0)=c_2\beta(0),$$

the condition

$$c_1>(c_2-1)\beta(0) \tag{46}$$

implies (45).

Next we check that the trivial solution of the equation

$$v'(t)=-[c_1+\beta(v(t))]v(t)+c_2\beta(v(t-\tau))v(t-\tau) \tag{47}$$

is globally asymptotically stable when (46) holds.

To prove this we construct a Liapunov function [see Hale (1977, Chap. 5) for details]. Let $\lambda(x)=(c_1+\beta(x))x$, $\Lambda(x)=\int_0^x\lambda(y)\,dy$ and let a Liapunov function $V:C[-\tau,0]\to R$ be given by

$$V(\phi)=\Lambda(\phi(0))+\tfrac{1}{2}\int_{-\tau}^{0}\lambda^2(\phi(\theta))\,d\theta. \tag{48}$$

It is easy to check that

$$\begin{aligned}\dot V(\phi)&=-\lambda^2(\phi(0))+c_2\lambda(\phi(0))\phi(-\tau)\beta(\phi(-\tau))+\tfrac{1}{2}\lambda^2(\phi(0))\\&\quad-\tfrac{1}{2}\lambda^2(\phi(-\tau))=-\tfrac{1}{2}[\lambda(\phi(0))-c_2\phi(-\tau)\beta(\phi(-\tau))]^2\\&\quad-\tfrac{1}{2}[\lambda^2(\phi(-\tau))-(c_2)^2\phi^2(-\tau)\beta^2(\phi(-\tau))]\\&\leqq-\tfrac{1}{2}[(c_1+\beta(\phi(-\tau)))^2-(c_2)^2\beta^2(\phi(-\tau))]\phi^2(-\tau)\\&\leqq-\tfrac{1}{2}c_1[c_1-(c_2-1)\beta(\phi(-\tau))]\phi^2(-\tau).\end{aligned}$$

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

$$\dot V(\phi)\leqq-\varepsilon\phi^2(-\tau).$$

From the last inequality it follows that every solution of (47) is convergent to 0 when (46) holds, and thus Corollary 1 implies that every solution of (44) converges exponentially to zero as $t \to \infty$ uniformly for $x \in [0, 1]$.

If $c_1 < (c_2 - 1)\beta(0)$, then equation (44) has a nontrivial constant solution u_* and u_* satisfies the equation

$$c_1 + \beta(u_*) = c_2 \beta(u_*).$$

If we assume additionally that

$$\beta'(u_*)u_* + \beta(u_*) > 0, \tag{49}$$

then

$$\frac{\partial f}{\partial u}(u_*, u_*) < -\left|\frac{\partial f}{\partial u_\tau}(u_*, u_*)\right|.$$

Consider the specific example of

$$\beta(u) = \frac{\beta}{\alpha + u}, \quad \alpha > 0,\ \beta > 0.$$

Then (49) holds, and consequently, the solution $\bar{u}(t, x) \equiv u_*$ of (44) is locally exponentially stable. In this case Mackey and Rudnicki (1994, Remark 1) proved that $z(t) = u_*$ is a globally asymptotically stable solution of (47) with the basin of attraction containing all positive initial functions $\varphi \in C[-\tau, 0]$. Now, Corollary 1 implies that if $u(x, t)$ is a solution of (44) such that $u(t, 0) > 0$ for $t \in [-\tau, 0]$, then u converges exponentially to u_* as $t \to \infty$ uniformly for $x \in [0, 1]$.

B. Blood production system

Next we apply our results to the equation

$$\frac{\partial u}{\partial t} + g(x)\frac{\partial u}{\partial x} = -ru + u_\tau(a + bu_\tau). \tag{50}$$

We assume that $r > 0$ and $|a| < r$. Equation (50) satisfies the assumptions of Theorem 2. Thus $u \equiv 0$ is a locally exponentially stable solution of (50). Now, we find the set A of initial conditions such that (50) is exponentially stable on A. In order to do this, we consider the delay differential equation

$$z'(t) = -rz(t) + z(t-\tau)[a + bz(t-\tau)]. \tag{51}$$

Substituting $z(t) = (b/r)x(rt)$ in (51) we obtain

$$x'(t) = -x(t) + x(t - \tau r)\left[\frac{a}{r} + x(t - \tau r)\right]. \tag{52}$$

Thus, it is sufficient to consider equation (51) with $r = b = 1$ and $|a| < 1$. We prove the following lemma.

Lemma 1. *Let* $|a| < 1$ *and*

$$A = \{\varphi \in C[-\tau, 0]\colon -1 < \varphi(t) < 1 - a \quad \text{for } t \in [-\tau, 0]\}.$$

Let $x(t)$ *be a solution of the equation*

$$x'(t) = -x(t) + x(t - \tau)[a + x(t - \tau)], \tag{53}$$

which satisfies the initial condition $x(t) = \varphi(t)$ *for* $t \in [-\tau, 0]$ *and* $\varphi \in A$. *Then*

$$\lim_{t \to \infty} x(t) = 0. \tag{54}$$

Proof. Let $\varphi \in A$. Then there exists $\varepsilon \in (0, 1 - |a|)$ such that $-1 + \varepsilon \leqq \varphi(t) \leqq 1 - a - \varepsilon$. Observe that

$$-1 + \varepsilon < -\frac{a^2}{4} \leqq y(a + y) < 1 - a - \varepsilon \tag{55}$$

for $y \in [-1 + \varepsilon, 1 - a - \varepsilon]$. If $x(t)$ is the solution of (54) corresponding to φ, then from (55) it follows that

$$-x(t) - 1 + \varepsilon < x'(t) < -x(t) + 1 - a - \varepsilon \tag{56}$$

for $t \in [0, \tau]$. Since $x(0) \in [-1 + \varepsilon, 1 - a - \varepsilon]$, from (56) it follows that $x(t) \in [-1 + \varepsilon, 1 - a - \varepsilon]$ for $t \in [0, \tau]$. By induction we obtain $x(t) \in [-1 + \varepsilon, 1 - a - \varepsilon]$ for $t \in [0, \tau]$. Now, we prove that the trivial solution of (53) is asymptotically stable on the set

$$A_\varepsilon = \{\varphi \in C[-\tau, 0]\colon -1 + \varepsilon \leqq \varphi(t) \leqq 1 - a - \varepsilon \text{ for } t \in [-\tau, 0]\}.$$

To prove this we construct a Liapunov functional (see Hale [1977], Chap. 5 for details).

Let $\lambda(x) \equiv 1$ if $a \geqq 0$ and

$$\lambda(x) = \begin{cases} 1, & \text{for } x \geqq 0, \\ a^{-2} - 1 + (a + x)^2, & \text{for } x < 0 \end{cases}$$

if $a < 0$. Set $G(x) = 2\int_0^x y\lambda(y)\,dy$ and $H(x) = x^2\lambda(x)$ and let a Liapunov functional $V\colon A_\varepsilon \to [0, \infty)$ be given by

$$V(\varphi) = G(\varphi(0)) + \int_{-\tau}^{0} H(\varphi(\theta))\,d\theta.$$

It is easy to check that

$$\dot{V}(\varphi) = G'(\varphi(0))[-\varphi(0) + \varphi(-\tau)(a + \varphi(-\tau))] + H(\varphi(0)) - H(\varphi(-\tau))$$

$$= -W(\varphi(0), \varphi(-\tau)),$$

where

$$W(x, y) = x^2\lambda(x) + y^2\lambda(y) - 2\lambda(x)xy(a + y).$$

We check that $W(x, y) > 0$ for $x, y \in [-1 + \varepsilon,\ 1 - a - \varepsilon]$ and $(x, y) \neq (0, 0)$. If $a \in [0, 1]$ then $|a + y| \leqq 1 - \varepsilon$ and consequently

$$W(x, y) = (x - y(a + y))^2 + y^2(1 - (a + y)^2) > 0$$

for $(x, y) \neq 0$. If $a \in (-1, 0)$ then we consider two subcases:

(1) $x \geqq 0$. Then

$$W(x, y) = (x - y(a + y))^2 + y^2(\lambda(y) - (a + y)^2).$$

Since

$$\lambda(y) - (a + y)^2 \geqq \min\{a^{-2} - 1, 2\varepsilon - \varepsilon^2\} > 0$$

we have $W(x, y) > 0$ for $(x, y) \neq 0$.

(2) $x < 0$. If $y \leqq 0$, then

$$W(x, y) \geqq x^2\lambda(x) + y^2\lambda(y) > 0.$$

If $y > 0$ we consider an auxiliary function

$$\beta(x) = 2(a + x)^2 x + a^2(a + x)^2 - a^2.$$

This function has the following properties: $\beta(0) < 0$, $\beta'(0) > 0$ and $\beta''(x) < 0$ for $x \leqq 0$. This implies that $\beta(x) < 0$ for $x \leqq 0$. Thus

$$1 - 2x\lambda(x) \geqq 1 - 2(a + x)^2 x > 1 + a^2(a + x)^2 - a^2 = a^2\lambda(x).$$

From the inequality $1 - 2\lambda(x)x > a^2\lambda(x)$ it follows that

$$W(x, y) \geqq W\left(x, \frac{\lambda(x)xa}{1 - 2\lambda(x)x}\right)$$

$$= x^2\lambda(x)\left[1 - \frac{a^2\lambda(x)}{1 - 2\lambda(x)x}\right] > 0.$$

Now, let $h(x) = \min\{W(x, y) : y \in [-1 + \varepsilon,\ 1 - a - \varepsilon]\}$. Then h is a continuous function, $h(0) = 0$ and $h(x) > 0$ for $x \neq 0$ and $x \in [-1 + \varepsilon, 1 - a - \varepsilon]$. Since $\dot{V}(\varphi) \leqq -h(\varphi(0))$ for $\varphi \in A_\varepsilon$ the trivial solution of (53) is asymptotically stable on the set A_ε.

From Lemma 1 and Corollary 1 we immediately have:

Corollary 2. *Let* $|a| < r$ *and denote by* $u(x, t)$ *the solution of* (50) *with the initial function* φ. *If* $b > 0$ *and* $-r/b < \varphi(0, t) < (r - a)/b$ *or* $b < 0$ *and* $(r - a)/b < \varphi(0, t) < -r/b$ *for* $t \in [-\tau, 0]$, *then* $u(x, t)$ *converges exponentially to zero as* $t \to \infty$ *uniformly for* $x \in [0, 1]$.

Remark 4. These results can be applied to an equation reducible to the one considered by Rey and Mackey (1993) and Dyson et al. (1996):

$$\frac{\partial u}{\partial t} + rx\,\frac{\partial u}{\partial x} = -(\gamma + r)u + \lambda u_\tau(1 - u_\tau), \tag{57}$$

with $u_\tau(x, t) = u(\alpha^{-1}e^{-r\tau}x, t - \tau)$ and $\lambda = 2\alpha^{-1}e^{-(\gamma+r)\tau}$.

If $\lambda \in (0, \gamma + r)$, then from Corollary 2 it follows that if $1 - (\lambda + r)/\lambda < \varphi(0, t) < (\lambda + r)/\lambda$ for $t \in [-\tau, 0]$, then the solution u of (57) with the initial data φ converges exponentially to zero as $t \to \infty$ uniformly for $x \in [0, 1]$. If $\lambda \in (\gamma + r, 3\gamma + 3r)$, then equation (57) has a non-trivial stable solution $u_0 \equiv 1 - (\lambda + r)/\lambda$. Substituting $w(x, t) = u(x, t) - u_0$ to (57) we obtain

$$\frac{\partial w}{\partial t} + rx\,\frac{\partial w}{\partial x} = -(\gamma + r)w + w_\tau[2(\gamma + r) - \lambda - \lambda w_\tau]. \tag{58}$$

From Corollary 2 it follows that if $(\lambda + r)/\lambda - 1 < w(0, t) < (\lambda + r)/\lambda$ for $t \in [-\tau, 0]$, then w converges exponentially to zero as $t \to \infty$. This implies that if $0 < \varphi(0, t) < 1$ for $t \in [-\tau, 0]$, then the solution u of (57) with the initial function φ converges exponentially to $1 - (\lambda + r)/\lambda$ uniformly for $x \in [0, 1]$. These global conclusions give analytic support to the results of Rey and Mackey (1992, 1993, 1995a, b) and Crabb et al. (1996) obtained through a local analysis and numerical investigation of equation (57), though many of the numerical results obtained in these papers still lack analytic explanation.

7 Discussion

Although the main emphasis of this paper has been with the problem of global stability, Theorem 1 can also be used to prove some results concerning unstable behaviour as shown in the following case.

Let z_0 be a solution of (17). Assume that there exists a solution u_0 of (10) such that $u_0(0, t) = z_0(t)$ for $t \in [-\tau, 0]$ and assume that $u_0(x, t) - z_0(t)$ does not converge to zero. Then z_0 is an unstable solution of (10). Indeed, for each $\varepsilon > 0$ we can find another solution $\bar{u}$ of

(10) such that $|\bar{u}(x,t) - z_0(t)| < \varepsilon$ for $x \in [0,1]$, $t \in [-\tau, 0]$ and $u_0(x,t) = \bar{u}(x,t)$ for $x \in [0,1]$ and sufficiently large t. After a slight modification of Theorem 1 one can check that any solution u of (10) such that $u_0(0,t) = z_0(t)$ for $t \in [-\tau, 0]$ is also unstable.

Consider the model of the blood production system rewritten in the alternate form of Dyson et al. (1996):

$$\frac{\partial u}{\partial t} + x\frac{\partial u}{\partial x} = -u + \mu u_\tau(1 - u_\tau). \tag{59}$$

For $\mu \in (1,4)$ Dyson et al. (1996) proved that there exists a non-trivial stationary solution $u(x,t) = \psi(x)$ of (57) such that $\psi(0) = 0$. This implies that any solution of (57) such that $u(0,t) = 0$ for $t \in [-\tau, 0]$ is unstable. This question is discussed in detail in Section 7 of Dyson et al. (1996).

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