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LOGISTIC EQUATIONS IN TUMOUR GROWTH MODELLING

URSZULA FORYŚ*, ANNA MARCINIAK-CZOCHRA**

* Faculty of Mathematics, Informatics and Mechanics, Institute of Applied Mathematics and Mechanics
Warsaw University, ul. Banacha 2, 02–097 Warsaw, Poland
e-mail: urszula@mimuw.edu.pl

** Institute of Applied Mathematics, Univeristy of Heidelberg
INF 294, 69120 Heidelberg, Germany
e-mail: Anna.Marciniak@iwr.uni-heidelberg.de

The aim of this paper is to present some approaches to tumour growth modelling using the logistic equation. As the first approach the well-known ordinary differential equation is used to model the EAT in mice. For the same kind of tumour, a logistic equation with time delay is also used. As the second approach, a logistic equation with diffusion is proposed. In this case a delay argument in the reaction term is also considered. Some mathematical properties of the presented models are studied in the paper. The results are illustrated using computer simulations.

Keywords: logistic equation, delay differential equation, reaction-diffusion equation, stability, global stability, Hopf bifurcation, spatial pattern, Ehrlich ascities tumour

1. Introduction

The logistic equation (Verhulst, 1838) is one of the most popular equations not only in mathematical ecology (where we should look for its origin) but also in other applications. In this paper we focus on various possibilities of tumour growth modelling on the basis of the logistic equation. It appears that even such a simple ordinary differential equation can be used to model such a complicated process. In (Krug and Taubert, 1985) this equation was proposed to describe the growth of the Ehrlich ascities tumour (EAT) in a mouse. Ten years later, in (Schuster and Schuster, 1995), a logistic equation with time delay was used to model the same process. The authors showed that the proposed equation is consistent with experimental data much better than the equation without delays. This equation has two terms with delays. Therefore, it is different from the classical Hutchinson equation (Hutchinson, 1948), which has only one delay term. The classical logistic equation with delay was studied in many papers and text-books (for details, see Gopalsamy, 1992; Kuang, 1993). Some preliminary analysis of the model proposed in (Schuster and Schuster, 1995) was made in (Bodnar, 2000; Foryś, 2001; Foryś and Marciniak-Czochra, 2002).

Another possibility is to consider the logistic equation as a reaction-diffusion one. This type of logistic equation is known as the Fisher equation (Fisher, 1937). The idea of such a model for tumour growth comes from (Drasdo and Höme, 2003). Finally, we combine the spatial effects with delay effects and consider the delay logistic equation with diffusion. This model was proposed in (Foryś and Marciniak-Czochra, 2002) and motivated by (Gourley and So, 2002). In (Gourley and So, 2002), the behaviour of solutions to a more general equation is studied but that analysis does not cover the case of the equation presented in (Foryś and Marciniak-Czochra, 2002) and in this paper.

2. Verhulst Equation

At the beginning, we recall the properties of the Verhulst equation, i.e. the ordinary differential equation of the form

$$\dot{T}(t) = rT(t)\left(1 - \frac{T(t)}{K}\right), \qquad (1)$$

where $T(t)$ denotes the concentration of tumour cells in a target organism, $\dot{T}(t)$ represents the derivative of T with respect to time, r is the net reproduction rate of the tumour (which means the difference between proliferation and apoptosis) and K is the carrying capacity.

We can show that for every positive initial T^0 the solution to (1) is positive and tends to the carrying capacity K (see Fig. 1, where the phase portrait for (1) is presented).

Calculating the second derivative

$$\ddot{T}(t) = r^2T(t)\left(1 - \frac{T(t)}{K}\right)\left(1 - \frac{2T(t)}{K}\right),$$

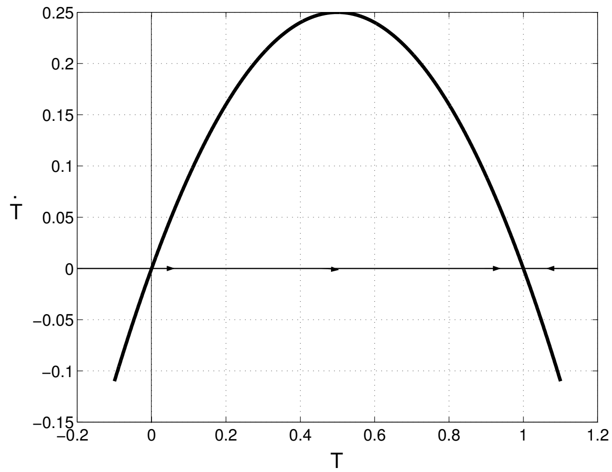

Fig. 1. Phase portrait for (1) with $K = r = 1$.

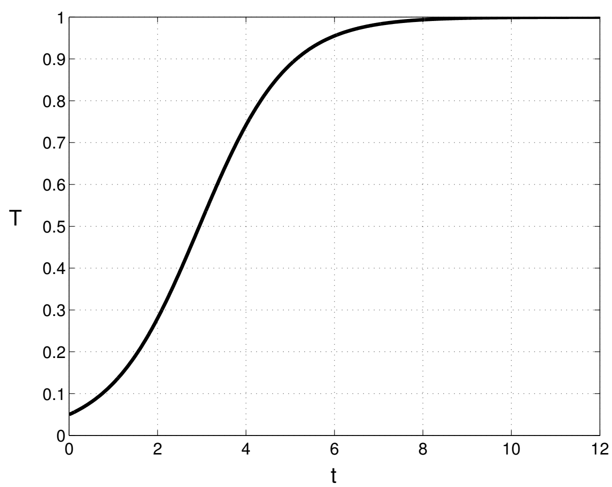

Fig. 2. Solution to (1) for $K = r = 1$ and $T_0 = 0.05$.

we see that an inflection occurs at $\bar{t}$ such that $T(\bar{t}) = K/2$. Therefore, for $T^0 \in (0, K/2)$ the solution to (1) has the well-known shape called the logistic curve (see Fig. 2).

In (Krug and Taubert, 1985; Läuter and Pincus, 1989) the logistic equation was used to fit experimental data for EAT (Ehrilch ascites tumour) in a mouse from the Pathological Institute of the Leipzig University. In (Krug and Taubert, 1985), the following form of the logistic curve was used to fit these data:

$$T(t) = \frac{K}{1 + \exp(-r(t-\theta))},$$

where

$$\theta = \frac{1}{r} \ln \frac{K - T_0}{T_0},$$

but in (Krug and Taubert, 1985) the authors calculated θ using the approximate expression $\frac{1}{r} \ln \frac{K}{T_0}$. In Table 1 we present the series of experimental measurements and the results of approximation for $K = 150 \times 10^7$ and $r = 0.6$ which were obtained in (Krug and Taubert, 1985).

Table 1. Experimental data for EAT (Ehrilch ascites tumour) in a mouse and the results of approximation using the logistic equation for $K = 150 \times 10^7$ and $r = 0.6$ which were obtained in (Krug and Taubert, 1985).

time	number of tumour cells $(\times 10^7)$	approximation
0	4.00	3.33
1		6.06
2	8.46	10.87
3	19.9	18.99
4	31.4	31.79
5	53.6	49.91
6	69.2	72.03
7	91.2	94.64
8		113.91
9	132	127.95
10		137.05
11	142	142.51
12		145.64
13	130	147.38
14	132	148.34
15	114	148.86
16		149.14
17	81.5	149.30

In Table 1 and also in Table 24.1 in (Schuster and Schuster, 1995) (where the data for tumours of different age—7 and 14 days—are shown) we see that the time series coming from these data are not monotonic and, therefore, in (Schuster and Schuster, 1995) another mathematical description is proposed. This description is based on the same Verhulst equation but with time delay. The authors stressed biological reasons for the usage of such an equation. On the other hand, it was a mathematical motivation to use the Verhulst equation with time delay. From the theory of delay differential equations it is known that for one equation with delay oscillatory behaviour is possible even if for the same equation without delay there are no oscillations (Gopalsamy, 1992; Hale, 1997).

3. Delay Logistic Equation

In (Schuster and Schuster, 1995) the following form of the delay logistic equation was proposed to describe the EAT:

$$\dot{T}(t) = rT(t-\tau)\left(1 - \frac{T(t-\tau)}{K}\right), \qquad (2)$$

where the notation is the same as for (1) and τ reflects the time delay connected with the cell cycle (Schuster and Schuster, 1995). This equation differs from the classical form of the delay Verhulst equation (known as the Hutchinson equation (Hutchinson, 1948)), which has only one delay term. It is also possible to consider other types of the delay logistic equation (for details, see (Kowalczyk and Foryś, 2002)). The Hutchinson equation was studied in many papers and text-books (for details, see, e.g., (Gopalsamy, 1992; Hale, 1997; Kuang, 1993)). In this section we present the analysis of Eqn. (2). Some preliminary remarks concerning the analysis of Eqn. (2) can be found in (Bodnar, 2000; Foryś, 2001; Foryś and Marciniak-Czochra, 2002).

At the beginning, we introduce some standard notation used in the theory of delay differential equations. Let $\mathbf{C} = C([-\tau, 0], \mathbb{R})$ denote the Banach space of continuous functions from the interval $[-\tau, 0]$ to $\mathbb{R}$, equipped with the supremum norm $|\cdot|$, and $T_t(\theta) = T(t+\theta)$, $\theta \in [-\tau, 0]$. In order to solve (2), we define an initial nonnegative continuous function $T_0 \in \mathbf{C}$. Using the step method (Hale, 1997) we show that the solution to (2) is defined for every $t \geq 0$,

$$T(t) = T(n\tau) + r\int_{(n-1)\tau}^{t-\tau} T(s)\left(1 - \frac{T(s)}{K}\right) \mathrm{d}s,$$

for $t \in [n\tau, (n+1)\tau]$, $n \in \mathbb{N}$. The solution for nonnegative T_0 may be negative. The following result comes from (Bodnar, 2000):

Lemma 1. *Assume that $T_0(\theta) \in [0, K]$ for $\theta \in [-\tau, 0]$.*

1. *If $r\tau > p_1$, where p_1 is the greatest root of the polynomial*

$$W_1(x) = -\frac{1}{48}x^3 - \frac{1}{8}x^2 + \frac{1}{4}x + 1,$$

then there exists an initial function T_0 such that the corresponding solution to Eqn. (2) has negative values.

2. *If $r\tau < p_2$, where p_2 is the greatest root of the polynomial*

$$W_2(x) = -\frac{1}{16}x^3 - \frac{1}{4}x^2 + 1,$$

then the corresponding solution to Eqn. (2) is nonnegative.

Now, we show that solutions to Eqn. (2) are bounded from above.

Lemma 2. *For every nonnegative initial T_0 the solution to Eqn. (2) is bounded from above.*

Proof. We divide our proof into three parts.

(a) Let $T_0(\theta) \in [0, K]$, for every $\theta \in [-\tau, 0]$. If for any $t \geq 0$ we have $T(t) \leq K$, then the solution is bounded by K. Otherwise, there exists a first point $t_0 > 0$ such that $T(t_0) = K$, and the solution enters the region $\{T : T > K\}$. Hence, $\dot{T}(t_0 + \tau) = 0$ and the solution has a local maximum at the point $t_0 + \tau$. We obtain

$$\begin{aligned} T(t_0+\tau) &= K + r\int_{t_0}^{t_0+\tau} T(s-\tau)\left(1 - \frac{T(s-\tau)}{K}\right)\mathrm{d}s \\ &\leq K\left(1 + \frac{r\tau}{4}\right) \end{aligned} \tag{3}$$

and the same inequality is valid until $T(t) \geq K$. But if there exists a next point $t_1 > t_0$ such that $T(t_1) = K$, then for $t_1 + \tau$ the same inequality holds as well and therefore the solution is bounded by $K(1 + r\tau/4)$.

(b) Assume now that $T_0(\theta) > K$ for $\theta \in [-\tau, 0]$. Then $\dot{T}(t) < 0$ for $t \in [0, \tau]$ and $T(t) \leq T^0(0)$ for $t \in [0, \tau]$. Either $T(t) > K$ for every $t \geq 0$ and then $T(t) \leq T^0(0)$ for every $t \geq 0$, or there exists $t_0 > 0$ such that $T(t_0) = K$, but then (3) holds. Therefore $T(t) \leq \max\{T^0(0), K(1 + r\tau/4)\}$.

(c) Generally, if $T_0(0) \leq K$, then we can use (3). If $T_0(0) > K$, then $T(t) \leq \max\{\max_{t\in[0,\tau]} T(t), K\,(1 + r\tau/4)\}$. This completes the proof. ∎

Corollary 1. *If $T_0(\theta) \in [0, K]$ for $\theta \in [-\tau, 0]$, then $T(t) \leq K\,(1 + r\tau/4)$ for every $t \geq 0$.*

On the other hand, if $T(t) < 0$ on an interval of the length greater than or equal to τ, then the solution tends to $-\infty$.

Corollary 2. *If there exists $t_0 > 0$ such that $T(t) < 0$ for every $t \in [t_0, t_0 + \tau]$, then $T(t) \to -\infty$ as $t \to +\infty$.*

Proof. Using the step method, we see that, for every $t \in [t_0 + n\tau, t_0 + (n+1)\tau]$, $n \in \mathbb{N}$, $n \geq 1$, the inequality

$$\dot{T}(t) = rT(t-\tau)\left(1 - \frac{T(t-\tau)}{K}\right) < 0$$

holds. Therefore, T is decreasing for $t > t_0 + \tau$. Equation (2) has no negative stationary solutions and hence $T(t) \to -\infty$. ∎

Knowing that the solution to Eqn. (2) exists for every $t > 0$, we can study the asymptotic behaviour. Equation (2) has two stationary solutions—the trivial one and the nontrivial carrying capacity K. We say that the stationary solution $\bar{T}$ to Eqn. (2) is stable if for every $\epsilon > 0$ there exists $\delta > 0$ such that for every initial continuous function T_0 satisfying $\left|\bar{T} - T_0\right| < \delta$ the solution for this initial function fulfils the inequality $|T_t - T_0| < \epsilon$. The solution is asymptotically stable if it is stable and $T_t \to \bar{T}$ for any initial condition sufficiently close to $\bar{T}$.

In analysing the asymptotic stability of these solutions we follow (Foryś, 2001). We study the stability using the standard linearization theorem (Hale, 1997). For the trivial solution the linearized equation is of the form

$$\dot{x} = rx(t - \tau). \tag{4}$$

Linearizing (2) around the point $T = K$, we obtain a similar equation:

$$\dot{x} = -rx(t - \tau). \tag{5}$$

The characteristic quasi-polynomial for both the solutions has the same form:

$$Q(\lambda) = \lambda + be^{-\lambda\tau} = 0, \tag{6}$$

where $b = -r$ for the trivial solution and $b = r$ for the nontrivial one. It is obvious that in order to use the linearization theorem, we must have $Q(i\omega) \neq 0$, $\omega \in \mathbb{R}$, i.e. there is no purely imaginary characteristic value. Namely, $r\tau \neq 3\pi/2 + 2k\pi,\ k \in \mathbb{N}$ for the trivial solution and $r\tau \neq \pi/2 + 2k\pi,\ k \in \mathbb{N}$ for the nontrivial one. We use the Mikhailov criterion (Foryś, 2001; Kolmanovskii and Nosov, 1986; Kuang, 1993) to find stability and instability regions for Q. This criterion states that all the roots of the quasi-polynomial $Q(\lambda) = P_1(\lambda) + P_2(\lambda)e^{-\lambda\tau}$ (where P_1 and P_1 are polynomials with $\deg P_1 > \deg P_2$ and Q has no roots on the imaginary axis) have negative real parts if and only if the increase Δ in the argument of $Q(i\omega)$ is equal to $\frac{\pi}{2}\deg P_1$ as ω increases from 0 to $+\infty$.

Consider $Q(i\omega) = \mathrm{Re}\,(Q(i\omega)) + i\ \mathrm{Im}\,(Q(i\omega))$ for $\tau > 0$. We have

$$\mathrm{Re}\,(Q(i\omega)) = b\cos\omega\tau, \quad \mathrm{Im}\,(Q(i\omega)) = \omega - b\sin\omega\tau.$$

The Mikhailov criterion implies the stability of Q in the case when the increase Δ in the argument of $Q(i\omega)$ is equal to $\pi/2$ as ω changes from 0 to $+\infty$. Otherwise Q is unstable. We have the following cases:

- If $b > 0$, then Q is stable for $\tau = 0$. If $\tau < 1/b$, then $\mathrm{Im}\,(Q(i\omega))$ increases as ω increases from 0 to $+\infty$. $\mathrm{Re}\,(Q(i\omega))$ oscillates between b and $-b$. It is obvious that $\arg Q(i\omega) \to \pi/2$ as $\omega \to +\infty$ and $\arg Q(0) = 0$. Therefore, $\Delta = \pi/2$, which proves stability. When τ increases, $\mathrm{Im}\,(Q(i\omega))$ starts to oscillate and the Mikhailov hodograph may intersect the real axis. The point of intersection is $\bar{\omega}$ such that $\mathrm{Re}\,(Q(i\bar{\omega})) = 0$. Therefore, $\bar{\omega}\tau = \pi/2 + k\pi$, where k is a natural number. Hence either $\mathrm{Im}\,(Q(i\bar{\omega})) = \pi/2\tau + 2k\pi/\tau - b$, or $\mathrm{Im}\,(Q(i\bar{\omega}) = 3\pi/2\tau + 2k\pi/\tau + b$. If $\mathrm{Im}\,(Q(i\bar{\omega})) > 0$ for all k, then the hodograph does not circle round the point $(0, 0)$ and the change in the argument is $\pi/2$. We can see that $\mathrm{Im}\,(Q(i\bar{\omega})) > 0$ for all k, if it is positive for $k = 0$, which leads to the inequality $b\tau < \pi/2$. If τ increases, then the hodograph circles round $(0, 0)$ once for $b\tau \in (\pi/2, 5\pi/2)$, twice for $b\tau \in (5\pi/2, 9\pi/2)$, and so on.
- If $b < 0$, then $\arg Q(0) = \pi$ and $\arg Q(i\omega) \to \pi/2 + 2k\pi$, where k is an integer number. $\Delta = -\pi/2 + 2k\pi \neq \pi/2$ for any k.

The above analysis gives stability or instability of stationary solutions to Eqn. (2) under the assumption that there is no imaginary characteristic value. On the other hand, while considering the time scaling $t \to t/\tau$ for $\tau > 0$, we see that it is possible to study (2) with unit delay (i.e. on the space $\mathbf{C}([-1, 0], \mathbb{R})$) and τ as a parameter. The dependence of solutions to Eqn. (2) on the parameters is smooth and therefore it can be shown (Cook and Driessche, 1986; Cook and Grosmann, 1982) that, as for any scalar delay equation with a smooth right-hand side, there may be only one critical value $\tau_c > 0$ for which the solution loses stability. Moreover, if the solution is unstable for some $\bar{\tau}$, then it is unstable for every $\tau > \bar{\tau}$.

Another problem is the Hopf bifurcation arising when the solution loses stability. For the stationary solution $T = K$ the main assumptions of the Hopf bifurcation theorem (Hale, 1997) are satisfied. Therefore, we only need to check $\mathrm{d}x(r_c)/\mathrm{d}r$, where x denotes the real part of the characteristic value and $r_c = \pi/2\tau$ is the threshold value of the model parameter. Let $\lambda(r) = x(r) + iy(r)$ denote a characteristic value. Then

$$\begin{cases} x = -re^{-x\tau}\cos y\tau, \\ y = re^{-x\tau}\sin y\tau. \end{cases} \tag{7}$$

Using the implicit-function theorem, we get

$$\frac{\mathrm{d}x}{\mathrm{d}r}(r_c) = \frac{r_c\tau}{1 + r^2\tau^2} = \frac{2\pi}{4 + \pi^2},$$

which is positive. Then the Hopf bifurcation occurs for r_c and the nontrivial stationary solution loses stability at this point.

Corollary 3. *The trivial stationary solution to Eqn. (2) is unstable independently of the delay. The solution $T = K$ is stable for $r\tau < \pi/2$ and unstable for $r\tau > \pi/2$. The Hopf bifurcation occurs at $r\tau = \pi/2$.*

In (Schuster and Schuster, 1995) the following parameter values were used to fit Eqn. (2) to the data presented in Table 24.1: $K = 100, r = 0.04$ and $\tau =$

$0,\ 1.7,\ 2.5,\ 3.4,\ 4.2$. The authors solved the ordinary logistic equation on the interval $[0,\tau]$ and then used this solution as the initial function for the initial point $t_0=\tau$. The initial number of the EAT was equal to 4 for every experiment. These solutions are shown in Fig. 3.

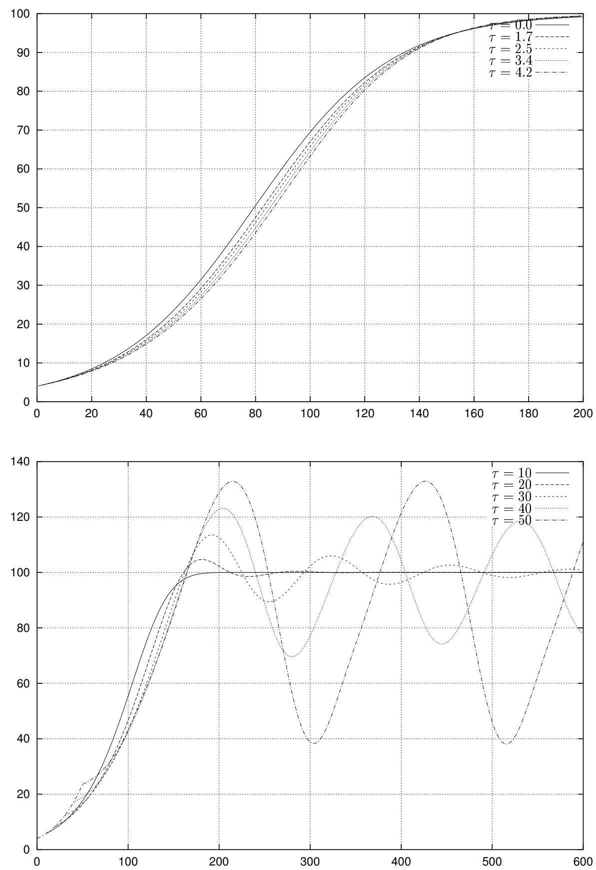

Fig. 3. Solutions to Eqn. (2) with the parameters used in (Schuster and Schuster, 1995) ($K = 100,\ r = 0.04$) and different time delays. The simulations show that the results presented in (Schuster and Schuster, 1995) can be obtained after rescaling time. We see that for the delay values proposed in (Schuster and Schuster, 1995) there are no oscillations while for delays which are 10 times larger there are oscillating solutions and the time interval where the solution is observed is also 10 times longer than that in (Schuster and Schuster, 1995). Therefore, the authors suppose that in (Schuster and Schuster, 1995) the time was scaled by 10 to obtain the figures presented therein.

4. Fisher Equation

The idea of tumour growth modelling using a logistic equation with diffusion comes from (Drasdo and Höme, 2003). In the literature this equation is known as the Fisher equation (Fisher, 1937), but it was studied on an infinite-dimensional space,

$$\frac{\partial T(t,x)}{\partial t} = rT(t,x)\left(1-\frac{T(t,x)}{K}\right) + D\Delta T(t,x), \tag{8}$$

where $x\in\mathbb{R}$, $D\geq 0$ is the diffusion coefficient, $\Delta T = \partial^2 T/\partial x^2$.

This is a prototype equation which admits travelling wave solutions (for details, see (Britton, 1986; Murray, 1993)). In this paper (as proposed in (Drasdo and Höme, 2003)), we consider Eqn. (8) on the space interval $[0,1]$, and the Neumann boundary conditions

$$\frac{\partial T}{\partial x}(t,x)|_{x=0,1} = 0, \quad T(0,x) = T^0(x). \tag{9}$$

The local existence of solutions to Eqn. (9) comes from a general theory (Henry, 1981; Taira, 1995), since

$$f(T) = rT(t,x)\left(1-\frac{T(t,x)}{K}\right)$$

is Lipschitz continuous.

Lemma 3. *The solution to Eqn. (9) is positive for any positive initial T^0 and bounded above by the carrying capacity K for initial data satisfying $T^0\leq K$.*

Proof. Let $T(t,x)$ be any solution to (9). $T_0=0$ and $T_1=K$ are stationary homogeneous solutions to the problem. Then the application of the comparison theorem (Smoller, 1994) with

$$NT = \frac{\partial T(t,x)}{\partial t} - D\Delta T(t,x) - rT(t,x)\left(1-\frac{T(t,x)}{K}\right)$$

and

$$BT = \frac{\partial T}{\partial x}(t,x)|_{x=0,1},$$

while noting that $NT_0 = 0 = NT$, $0\leq T^0$ and $BT_0 = 0 = BT$, leads to the inequality $0\leq T(x,t)$. Applying this theorem to $T(x,t)$ and T_1, and then noting that $NT_1 = 0 = NT$, $T^0\leq K$ and $BT_1 = 0 = BT$, we obtain $T(x,t)\leq K$. Hence, $0\leq T(x,t)\leq K$ if $0\leq T^0\leq K$. ■

Lemma 3 shows that $\Sigma = \{T \mid 0\leq T\leq K\}$ is an invariant set for this problem. We can also show that every $\Sigma = \{T \mid 0\leq T\leq c\}$, where $c<\infty$ is a constant, is an invariant set since $f(T) = rT(t,x)\,(1-T(t,x)/K)$ is Lipschitz continuous and for $T^0 = c > K$, $f(T^0) = rT^0\left(1-T^0/K\right) < 0$. Thus, from invariant set theory (Britton, 1986; Smoller, 1994) we obtain the global existence of the solutions to Eqn. (9) for every $T^0\geq 0$. The uniqueness follows immediately from the comparison theorem.

Since we showed that a solution to Eqn. (9) exists for all times $t \geq 0$, we wish to know its asymptotic behaviour as $t \to +\infty$. Let $\bar{T}(x)$ be a stationary solution to (9) with initial conditions $T(0,x) = \bar{T}^0(x)$.

$\bar{T}(x)$ is a stable solution if, for every $\epsilon > 0$, there exists δ such that for every initial function $T^0(x)$ such that $\|T^0(\cdot) - \bar{T}^0(\cdot)\|_{L^\infty([0,1])} < \delta$, a solution T exists for this initial function for all $t \geq 0$ and $\|T(\cdot,t) - \bar{T}(\cdot)\|_{L^\infty([0,1])} < \epsilon$ for all $t > 0$.

We say that $\bar{T}(x)$ is asymptotically stable if it is stable and there is a neighbourhood N of $\bar{T}$ such that if T is a solution to Eqn. (9) with $T(0,x) \in N$, then T exists for all $t \geq 0$ and $\lim_{t\to\infty} \|T(\cdot,t) - \bar{T}(\cdot)\|_{L^\infty([0,1])} = 0$.

It can be shown (Murray, 1993; Smoller, 1994) that there is no stable spatial pattern for a scalar reaction-diffusion equation in one dimension with Neumann boundary conditions. The spatial pattern means a spatially non-homogenous stationary solution. Thus, the only stable solutions to (9) are spatially homogeneous and the solutions to (9) have similar properties as in the case without diffusion (cf. Fig. 4). It is obvious that (9) has the same spatially homogenous stationary solutions as (1).

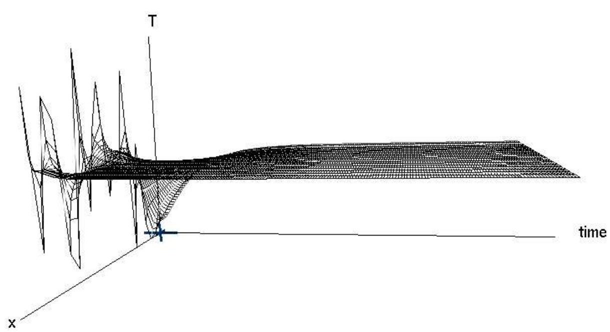

Fig. 4. Time evolution of the solution to Eqn. (9) for $r = 0.5$, $K = 2$ and the diffusion coefficient $D = 1$. We observe that for positive initial conditions the solution T tends to the spatially homogeneous stationary solution $T = 2$ $(= K)$.

The stability of stationary solutions to reaction-diffusion equations can be analysed by considering the eigenvalues of the linearized system (cf. (Britton, 1986; Smoller, 1994)). Since $f(T) = rT(t,x)\,(1 - T(t,x)/K)$ is Lipschitz continuous and Fréchet differentiable with the derivative $\mathrm{d}f_T = \mathrm{d}f(T)/\mathrm{d}T$, the mapping $T \to \mathrm{d}f_T$ is continuous and $D\Delta$ generates a compact semigroup for $t \geq 0$, we can apply the theorem about the linear stability of stationary solutions, which says that $\bar{T}$ is linearly stable if and only if there exists $\alpha < 0$ such that the spectrum of $A + \mathrm{d}f_{\bar{T}}$ lies in the half space $\mathrm{Re}\, z \leq \alpha$ (cf. Theorem 11.20 in (Smoller, 1994) or Theorem 5.60 in (Britton, 1986)). Thus, in order to study the stability of these solutions to Eqn. (9) we consider the linear variational equation

$$\dot{v} = av + D\Delta v, \quad \frac{\partial v}{\partial x}\Big|_{x=0,1} = 0, \quad v(0,x) = v^0, \tag{10}$$

where $a = r$ for the trivial solution and $a = -r$ for the nontrivial one. We look for a solution to Eqn. (10) of the form $v(t,x) = v_0 e^{\lambda t} W(x)$, where $W''(x) + k^2 W(x) = 0$, $k \in \mathbb{Z}$. This solution exists only for $\lambda = a - dk^2$. Therefore, if $a = -r$, then $\lambda < 0$ for every integer k, and if $a = r$, then $\lambda > 0$, for $k = 0$.

The theorem about the linearized stability for reaction-diffusion equations with locally Lipschitzian and Fréchet differentiable kinetics functions (cf. (Britton, 1986) Th. 5.61 or (Smoller, 1994) Th. 11.22) says that if the stationary solutions of such equations are linearly stable, then they are asymptotically stable. Hence $T = 0$ is unstable and $T = K$ is asymptotically stable as solutions to Eqn. (9), as well as to Eqn. (1). Moreover, if we assume that T is separated from 0, then we can show that T tends to K as $t \to +\infty$.

Lemma 4. *If $T^0(x) \geq \alpha$ for $x \in [0,1]$ and $\alpha \in (0,K)$, then $T(t,x) \to K$ as $t \to +\infty$.*

Proof. Using the comparison theorem, we check that $T(t,x) \geq \alpha$, for $t \geq 0$ and $x \in [0,1]$. Set $v = T - K$. Then

$$\dot{v} = -rv\left(\frac{v}{K} + 1\right) + D\Delta v, \quad \frac{\partial v}{\partial x}\Big|_{x=0,1} = 0 \tag{11}$$

and $v(t,x) \geq -(K-\alpha)$, for $t \geq 0$ and $x \in [0,1]$. Defining

$$\xi(t) = \frac{1}{2}\int_{[0,1]} v^2(t,x)\,\mathrm{d}x,$$

we get

$$\dot{\xi}(t) = \int_{[0,1]} \dot{v}(t,x)v(t,x)\,\mathrm{d}x.$$

Multiplying (11) by $v(t,x)$ and integrating the result by parts, we obtain

$$\dot{\xi}(t) = -r\int_{[0,1]} v^2(t,x)\,\mathrm{d}x - r\int_{[0,1]} \frac{v^3(t,x)}{K}\,\mathrm{d}x - D\int_{[0,1]} \left(\frac{\partial v}{\partial x}\right)^2(t,x)\,\mathrm{d}x.$$

If $T > K$, then $v > 0$ and $\dot{\xi}(t) < -2r\xi$. If $T < K$, then $0 > v > -(K-\alpha)$ and $v^3 > -(K-\alpha)v^2$, which leads to the inequality $\dot{\xi} < -2r\alpha/K\xi$. In both the cases we have $\xi(t) \to 0$ as $t \to +\infty$, which implies that $T(t,x) \to K$. ■

5. Delay Logistic Equation with Diffusion

The idea of this section is to study the logistic equation with delay and diffusion, and is based on (Gourley and So, 2002), where the authors looked for spatial patterns connected with the delay of the reaction in some class of reaction-diffusion equations. We study the problem

$$\frac{\partial T(t,x)}{\partial t} = rT(t-\tau,x)\left(1-\frac{T(t-\tau,x)}{K}\right) + D\Delta T(t,x), \quad x \in [0,1], \tag{12}$$

$$T(t,x) = T^0(t,x) \quad \text{for} \quad (t,x) \in [-\tau,0]\times[0,1],$$
$$\frac{\partial T(t,x)}{\partial x}\Big|_{x=0,1} = 0 \quad \text{for} \quad t \geq -\tau,$$

where $\tau > 0$ is a constant delay and $D \geq 0$ is a diffusion coeficient.

To study the existence of solutions to (12), we use the step method (Hale, 1997) and study the Neumann problem on the intervals $[n\tau,(n+1)\tau]$ for nonnegative integers n. Therefore, on every time interval so defined we solve the problem

$$\frac{\partial T(t,x)}{\partial t} = f(t,x) + D\triangle T(t,x), \qquad (t,x) \in [n\tau,(n+1)\tau]\times[0,1]$$

with the initial function

$$T(n\tau,x), x \in [0,1]$$

and

$$\frac{\partial T}{\partial x}(t,x)|_{x=0,1} = 0.$$

A local solution to Eqn. (12) exists and is unique (Taira, 1995).

Using the step method and the comparison theorem (Smoller, 1994), we obtain that if a solution is nonnegative and bounded for $D = 0$, then it remains in the same region for $D > 0$.

Now, we formally follow the ideas presented in the previous section and study the linearized equation

$$\dot{T}(t,x) = aT(t-\tau,x) + D\Delta T(t,x), \qquad \frac{\partial T}{\partial x}\Big|_{x=0,1} = 0, \quad T(0,x) = T^0, \tag{13}$$

where $a = r$ for the trivial solution and $a = -r$ for the nontrivial one. Next, also formally, we consider the characteristic equation associated with (13).

Consider the case of $D = 0$ and the solution $T = K$. Corollary 3 yields that it is stable for $r\tau < \pi/2$ and unstable otherwise. For $D > 0$, the characteristic equation changes to

$$\lambda + re^{-\lambda\tau} + Dk^2 = 0,$$

where $k \in \mathbb{Z}^+$ results from the Neumann boundary problem. Assume that $r\tau < \pi/2$. Studing the Mikhailov hodograph (Foryś, 2001) we conclude that, for every integer k such that $Dk^2 > r$, the characteristic values remain in the left complex half-plane. On the other hand, for every integer k such that $Dk^2 < r$, there is a switching in the stability at the point

$$\tau_k = \frac{1}{\sqrt{r^2 - D^2k^4}} \arccos \frac{Dk^2}{r}.$$

Therefore, if $D > r$ and $r < \pi/2$, then $T = K$ is stable. If $r > \pi/2$, then this solution is unstable independently of the diffusion coefficient D. If $D < r$ and $r/D \neq k^2$, then we have a finite sequence (τ_k) of critical values of delay. Let $\tau_{\min}$ denote the minimal value of τ_k. We see that τ_k increases with an increase in k and hence $\tau_{\min} = \pi/2r$. Therefore, if $\tau_0 r < \pi/2$, i.e. the trivial solution is stable for the case without diffusion, then for every integer k such that $Dk^2 < r$ we have $\tau_k > \tau_0$, which means that the critical value τ_0 belongs to the interval where the solution is stable. This implies that the solution $T = K$ is stable independently of the diffusion coefficient D in the stability region for the case without diffusion.

We can see that if the stationary solution is unstable without delay, then it remains unstable for every delay and every diffusion coefficient. It leads to the instability of the trivial solution.

These conclusions are confirmed by simulation results. We carried out simulations of Eqn. (12) for the parameter values $r = 0.5$ and $K = 2$. The stationary state $\bar{T} = 2$ is perturbed using a cosine function with the amplitude equal to 0.1 or a small random perturbation (i.e. the initial value at every discretization point is the value of the spatially uniform solution perturbed by a small value which is randomly generated). The asymptotic behaviour is similar for both types of perturbations. Therefore, we present only examples of figures in the regular case. Simulation results agree with the analysis. For small delays, i.e. $\tau < \pi$, the solution $\bar{T}$ is stable (see Fig. 5). For $\tau = \pi$ it loses stability and oscillations in time appear (Fig. 6). An example of undamping oscillations is shown in Fig. 7, where $\tau = 4$. For delays greater than $\tau = \pi$ the amplitude of oscillations grows at the beginning and stabilises eventually. For large delays (see Figs. 8 and 9) the solution becomes negative. We see that the solutions do not depend on the initial perturbation. Diffusion makes them spatially homogenous. The situation seems to be analogous to the equation without delay.

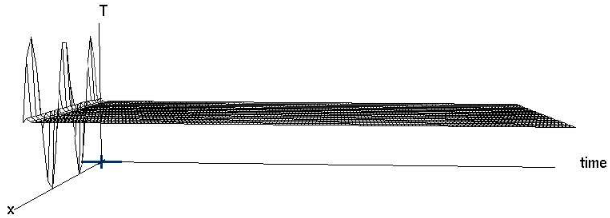

Fig. 5. Time evolution of the solution to Eqn. (12) for $r = 0.5$, $K = 2$, delay $\tau = 1$ and diffusion coefficient $D = 1$. We performed simulations for time $t = 150$. Observe that the stationary solution $\bar{T} = 2$ is stable.

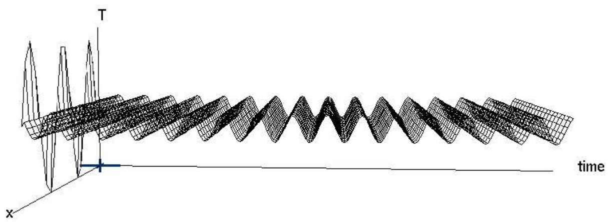

Fig. 6. Time evolution of the solution to Eqn. (12) for $r = 0.5$, $K = 2$, delay $\tau = 3.1415927$ and diffusion coefficient $D = 1$, for time $t = 200$. The stationary solution $\bar{T} = 2$ is unstable and temporal oscillations appear.

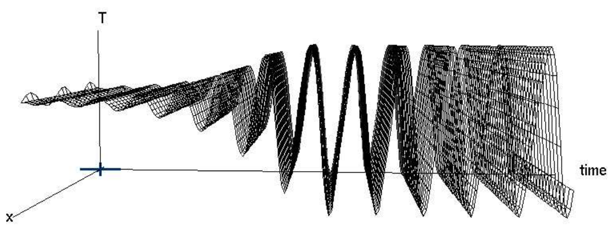

Fig. 7. Time evolution of the solution to Eqn. (12) for $r = 0.5$, $K = 2$, delay $\tau = 4$ and diffusion coefficient $D = 1$, time $t = 200$. We observe temporal oscillations.

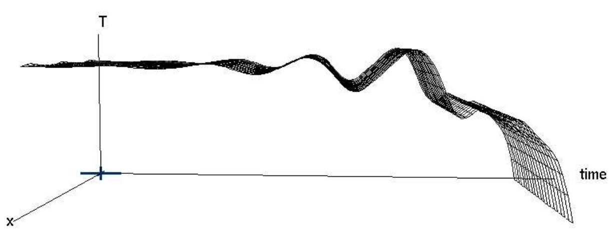

Fig. 8. Time evolution of the solution to Eqn. (12) for $r = 0.5$, $K = 2$, delay $\tau = 5$ and diffusion coefficient $D = 1$. We performed simulations for time $t = 100$. For $t = 80$ the solution already becomes negative.

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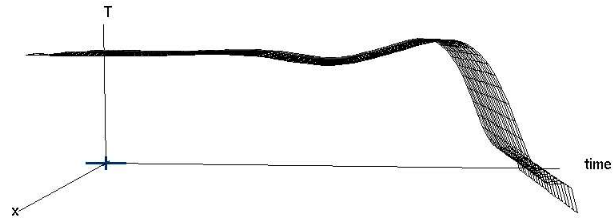

Fig. 9. Time evolution of the solution to Eqn. (12) for $r = 0.5$, $K = 2$, delay $\tau = 10$ and diffusion coefficient $D = 1$. We performed simulations for time $t = 100$. For $t = 66$ the solution already becomes negative.

References

Bodnar M. (2000): *The nonnegativity of solutions of delay differential equations*. — Appl. Math. Let., Vol. 13, No. 6, pp. 91–95.

Britton N.F. (1986): *Reaction-Diffusion Equations and Their Applications to Biology*. — New York: Academic-Press.

Cook K. and Driessche P. (1986): *On zeros of some transcendental equations*. — Funkcialaj Ekvacioj, Vol. 29, pp. 77–90.

Cook K. and Grosmann Z. (1982): *Discrete delay, distributed delay and stability switches*. — J. Math. Anal. Appl., Vol. 86, pp. 592–627.

Drasdo D. and Höme S. (2003): *Individual based approaches to birth and death in avascular tumours*. — Math. Comp. Modell., (to appear).

Fisher R.A. (1937): *The wave of advance of adventage genes*. — Ann. Eugenics, Vol. 7, pp. 353–369.

Foryś U. (2001): *On the Mikhailov criterion and stability of delay differential equations*. — Prep. Warsaw University, No. RW 01-14 (97).

Foryś U. and Marciniak-Czochra A. (2002): *Delay logistic equation with diffusion*. — Proc. 8-th Nat. Conf. *Mathematics Applied to Biology and Medicine*, Łajs, Warsaw, Poland, pp. 37–42.

Gopalsamy K. (1992): *Stability and Oscillations in Delay Differential Equations of Population Dynamics*. — Dordrecht: Kluwer.

Gourley S.A. and So J.W.-H. (2002): *Dynamics of a food limited population model incorporating nonlocal delays on a finite domain*. — J. Math. Biol., Vol. 44, No. 1, pp. 49–78.

Hale J. (1997): *Theory of Functional Differential Equations*. — New York: Springer.

Henry D. (1981): *Geometric Theory of Semilinear Parabolic Equations*. — Berlin: Springer.

Hutchinson G.E. (1948): *Circular casual systems in ecology*. — Ann. N.Y. Acad. Sci., Vol. 50, pp. 221–246.

Kolmanovskii V. and Nosov V. (1986): *Stability of Functional Differential Equations*. — London: Academic Press.

Kowalczyk R. and Foryś U. (2002): *Qualitative analysis on the initial value problem to the logistic equation with delay*. — Math. Comp. Model., Vol. 35, No. 1–2, pp. 1–13.

Krug H. and Taubert G. (1985): *Zur praxis der anpassung der logistischen function an das wachstum experimenteller tumoren*. — Arch. Geschwulstforsch., Vol. 55, pp. 235–244.

Kuang Y. (1993): *Delay Differential Equations with Applications in Population Dynamics*. — Boston: Academic Press, 1993.

Läuter H. and Pincus R. (1989): *Mathematisch-Statistische Datenanalyse*. — Berlin: Akademie-Verlag.

Murray J.D. (1993): *Mathematical Biology*. — Berlin: Springer.

Schuster R. and Schuster H. (1995): *Reconstruction models for the Ehrlich Ascites Tumor of the mouse*, In: Mathematical Population Dynamics, Vol. 2, (O. Arino, D. Axelrod, M. Kimmel, Eds.). — Wuertz: Winnipeg, Canada, pp. 335–348.

Smoller J. (1994): *Shock Waves and Reaction-Diffusion Equations*. — New York: Springer.

Taira K. (1995): *Analytic Semigroups and Semilinear Initial Boundary Value Problems*. — Cambridge: University Press.

Verhulst P.F. (1838): *Notice sur la loi que la population suit dans son accroissement*. — Corr. Math. Phys., Vol. 10, pp. 113–121.