Urszula Foryś

Faculty of Mathematics, Informatics and Mechanics,
Institute of Applied Mathematics and Mechanics,
University of Warsaw,

PROBLEMS WITH MODELLING USING DELAY DIFFERENTIAL EQUATIONS

In applications models described in the framework of delay differential equations (DDEs) are often used. The advantage of such approach is simplifying a description of complex natural phenomena which take some time. Using even one DDE with single delay one can reflect oscillatory dynamics typical for many biological systems. One ODE with two delays or two DDEs with single delay are sufficient to reflect stability switches with increasing delay. Simple DDEs models can also reflect chaotic dynamics. Although DDEs can be very useful in applications, they lead to much more complicated mathematical analysis than in ODEs case. DDEs define infinite dimensional semi-dynamical systems. Comparing to appropriate ODEs it should be noticed that DDEs not necessarily preserve non-negativity of solutions, it can be difficult to study global existence of solutions, and moreover global stability can be really hard to prove. Therefore, proposing the model based on DDEs one should be very careful and check at least basic properties to be sure that the model is properly defined.

Introduction

Modelling of biological systems in the framework of delay differential equations (DDEs) has a long history. Probably the eldest DDE model is the Hutchinson equation [34] proposed in 1948 for the description of population dynamics. This equation reads

$$\dot{N} = rN(t)\left(1 - \frac{N(t-\tau)}{K}\right), \qquad (1)$$

where $N(t)$ reflects the population size at time t, K is its carrying capacity and τ is the delay in per capita $\dot{N}/N$ growth rate. For many years the delay has been typically introduced to this per capita growth rate, compare e.g. [36], leading to the models of the general form

$$\dot{N} = N(t)F\big(N(t-\tau)\big), \qquad (2)$$

which preserves non-negativity. Clearly, the integral form $N(t) = N(0)\exp\left(\int\limits_0^t F\big(N(s-\tau)\big)ds\right)$ is equivalent to Eq. (2) under the weak assumption that F is integrable and this guarantees non-negativity for $N(0) \geq 0$. Notice, that typically in biological models F is of class $\mathbf{C}^1$. Moreover, the form of Eq. (2) guarantees global existence of solutions. Clearly, defining a continuous initial function $\varphi : [-\tau, 0] \to \mathcal{R}_+(\mathcal{R}_+^n)$ we can use the step method, compare e.g. [32], that is the method of mathematical induction applied to the subsequent intervals $[n\tau, (n+1)\tau]$, and show the existence of the solution for all $t \geq 0$.

Although most of natural phenomena is non-linear, also linear DDEs can be sometimes used; e.g. Bratsun et al.[14] proposed the following linear equation

$$\dot{x} = A - Bx(t) - Cx(t - \tau) \qquad (3)$$

as the description of biochemical reactions channel

$$\emptyset \xrightarrow{A} P, \quad P \xrightarrow{B} \emptyset, \quad P \xrightarrow{C} \emptyset, \qquad (4)$$
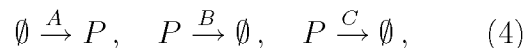
thinking about oscillatory dynamics. However, it occurs that such type of oscillatory dynamics is present for the critical value of time delay and always leads to negative solutions [27]. This is one of the main problems for modelling using DDEs.

Moreover, as mentioned above to solve even such simple equation as Eq. (3) one needs to know the behaviour of the variable x on the whole interval $[-\tau, 0]$, that is an initial condition is a function, typically continuous, whi-

ch means that the problem is infinite dimensional. Also an eigenvalue problem is much more complex than for ODEs. Clearly, looking for exponential solutions to Eq. (3) one gets

$$\lambda = -B - C\exp(-\lambda\tau), \qquad (5)$$

and therefore there are infinitely many eigenvalues for this equation. This means that it is not possible to calculate all the eigenvalues. One can only try to estimate real parts of eigenvalues to check stability, compare e.g. [22] and the references therein. We should also notice that the dynamics of DDEs can be much richer than for appropriate ODEs, including multiple stability switches and chaotic behaviour, compare e.g. [33].

In this paper we present some results concerning specific models, as mentioned above linear equation for biochemical reactions channel and delayed logistic equation.

Negativity of solutions to linear equation (3)

In this section we present the results obtained in [27] concerning Eq. (3). As it is mentioned in Introduction, Bratsun et al. [14] considered the reaction channel (4) and used Eq. (3) as the mathematical description of that channel. In this case we require A, B, $C > 0$ as they reflect reactions propensities. In [27] we studied Eq. (3) with initial data of the form

$$\mathbf{x}(t) = 0 \quad \text{for} \quad t < 0 \quad \text{and} \quad \mathbf{x}(0) = x^0 \geq 0. \qquad (6)$$

This initial data reflect the fact that the reaction channel (4) is triggered at $t = 0$. Although such type pf initial data is not typical, as it is noncontinuous, we can easily see that the Cauchy problem (3),(6) (and other similar problems with initial data having discontinuity in some points) is equivalent to the standard problem with continuous initial function starting from $t_0 = \tau$. Clearly, for $t \in [0, \tau]$ Eq. (3) can be rewritten in the integral form

$$x(t) = \frac{A}{B} + \left(x^0 - \frac{A}{B}\right)e^{-Bt} - C\int_{-\tau}^{t-\tau} \mathbf{x}(s)e^{-B(t-s-\tau)}ds,$$

which is continuous even if $\mathbf{x}$ is discontinuous in some points. Moreover, for $\mathbf{x}$ defined by

Eq. (6) we calculate $x(t) = x_1(t) = \frac{A}{B} + \left(x^0 - \frac{A}{B}\right)e^{-Bt}$ for $t \in [0, \tau]$ implying that our Cauchy problem is equivalent to solving Eq. (3) with initial data $t_0 = \tau$ and $\mathbf{x} = x_1$.

It is known that the dynamic of Eq. (3) depends on the ratio between the coefficients B and C as well as the magnitude of delay τ. Clearly, if $\tau = 0$, then we have $\dot{x} = A - (B + C)x(t)$ and the steady state $x_{\text{ss}} = A/(B + C)$ is asymptotically stable. Eq. (3) depends on all parameters continuously, and therefore to get the change of stability a pair of purely imaginary eigenvalues should appear. Moreover, these eigenvalues should cross imaginary axis from left to right. Let $\lambda = i\omega$, $\omega > 0$. Then from Eq. (5) we get

$$i\omega = -B - Ce^{-i\omega\tau} \implies |i\omega + B| = C.$$

Following [15] we define an auxiliary function

$$F(z) = z + B^2 - C^2,$$

where $z = \omega^2$ and positive zeros of F gives purely imaginary eigenvalues. Hence, if $B > C$, then F has no positive zeros implying that x_{ss} is stable independently of τ, while for $B < C$ we have $z_0 = C^2 - B^2$, and therefore purely imaginary eigenvalues are expressed as $\pm i\sqrt{C^2 - B^2}$. For these eigenvalues we can calculate critical values of delays as $\tau_{\text{th},k} = \frac{\arccos(-B/C)}{\sqrt{C^2 - B^2}} + 2k\pi$. Moreover, the sign of $F'(z_0)$ describes the direction of the movement of the purely imaginary eigenvalues in the complex plane. If it is positive, then the movement is from left to right leading to destabilisation of the steady state. Clearly, $F'(z) = 1$, and therefore the steady state x_{ss} loses stability at the first critical delay $\tau_{\text{cr}} = \tau_{\text{th},0}$ and cannot gain it again for larger delays.

In [27] we proved that for the Cauchy problem (3),(6) periodic solutions appearing for $B < C$ and delay $\tau \geq \tau_{\text{cr}}$ always take negative values. To reduce the number of parameters we scale the time and space variable obtaining

$$\dot{y} = 1 - by(t) - y(t - \tau), \qquad (7)$$

were $b < 1$ with $y(t) = 0$ for $t < 0$ and $y(0) = y^0 \geq 0$. It occurs that instead of Eq. (7) we

can study the simpler problem for $b = 0$ and $y(t) \equiv 0$ in $[-\tau, 0]$, because solutions to Eq. (7) can be expressed by solutions to this simpler equation

$$\dot{w} = 1 - w(t - \tau), \quad w(t) = 0 \quad \text{for} \quad t \leq 0. \quad (8)$$

Calculating solutions to Eq. 8 we obtain

$$w(t) = \sum_{k=1}^{n} \frac{(-1)^{k+1}}{k!} \left(t - (k-1)\tau\right)^k \quad (9)$$

for $t \in [(n-1)\tau, n\tau)$, $n \geq 1$. Using Eq. (9) we show that there exists $\bar{t} \in (2\tau, 3\tau)$ or $\bar{t} \in [3\tau, 4\tau)$ such that $x(\bar{t}) < 0$. Clearly, on the interval $[\tau, 2\tau)$ the solution $w(t) = t - \frac{1}{2}(t - \tau)^2$ has a maximum at $\tilde{t} = 1 + \tau$, implying that w has a minimum around $t = \tilde{t} + 2\tau = 1 + 3\tau$, where 2τ is around the half of the basic period. We have $w(1 + 3\tau) = \frac{1}{24}\left(15 + 36\tau - 36\tau^2 + 4\tau^3\right)$, and therefore $w(1 + \frac{3\pi}{2}) \approx -0.0739$ and the polynomial $w(1 + 3\tau)$ is decreasing for $\tau \in \left(3 - \sqrt{6}, 3 + \sqrt{6}\right) \approx (0.55, 5.45)$. This result is very important from the application point of view as it shows that such type of linear equations cannot be used not only as a description of biochemical reactions channel but also any biological process. In such cases the delay should be introduced in a different way, see [37, 13] for details.

Bifurcation with respect to delay for the logistic equation

In the series of papers [23, 8, 9] we studied the logistic equation and its generalisations in the context of tumour growth dynamics. Because the delay reflect the length of the cell cycle in this case, the classic form of delayed logistic equation (1) seems to be not proper. Therefore, we consider

$$\dot{V} = rV(t-\tau)\left(1 - V(t - \tau)\right), \quad V(0) = V^0 > 0, \quad (10)$$

where V describes the tumour volume reflected as a percentage of the maximal possible size that can be achieved without additional external supply of nutrients and r is the maximal growth rate. As it is mentioned in Introduction, such type of equations can have negative solutions, compare [2] for more detai-

ls on that topic. Therefore, we need to restrict the values of parameters, including delay, to preserve positivity. On the other hand, for Eq. (10) negative solutions are possible only for large values of V^0 and τ, implying that such case is biologically irrelevant, because the description on the basis of the logistic equation can be used only for the initial stage of tumour growth, before the tumour angiogenesis starts.

Describing some process using DDEs we are typically interested in the dependance of the model dynamics on the magnitude of delay. However, as the problem is infinite dimensional and defined on a Banach space of continuous functions $\mathcal{C}$, where $\mathcal{C} = \{\phi \in \mathbf{C}([-\tau, 0], \mathbb{R})\}$, we see that the space depends on the delay and therefore the delay cannot be treated as a parameter straightforward. However, in the case with only one discrete delay, as for Eq. (10), it is not a big problem, because for $\tau > 0$ we can rescale the time $t \to t/\tau$ obtaining

$$\dot{V} = r\tau V(t-1)\left(1 - V(t - 1)\right), \quad V(0) = V^0 > 0, \quad (11)$$

that is the equation with constant delay and τ being a parameter.

Let $f(V) = r\tau V(1 - V)$. Then Eq. (11) can be written as $dotV = r\tau f(V(t-1))$. Due to the properties of the function f we have two steady states for Eq. 11, that is the trivial $\bar{V}_1 = 0$ and positive $\bar{V}_2 = 1$. The linearised equation reads

$$\dot{x}(t) = r\tau f'(\bar{V})x(t - 1)$$

implying that the characteristic equation for Eq. (11) has the form (5) with $B = 0$ and $C = -r\tau f'(\bar{V})$. For $\bar{V}_1$ there is $f'(0) = r\tau > 0$. Hence, there exists a real positive eigenvalue and the trivial steady state is unstable independently of the delay. On the other hand, for $\bar{V}_2$ we have $f'(1) = -r\tau < 0$. The full analysis of the characteristic equation Eq. (5) is presented in the previous section. Now, the threshold value of the delay can be expressed as $\tau_{\text{cr}} = \frac{\pi}{2r}$ and for $\tau < \tau_{\text{cr}}$ the steady state $\bar{V}_2$ is stable, while for $\tau > \tau_{\text{cr}}$ it remains unstable.

Moreover, in [9] we showed that if

$$(11\pi - 4)\left(f''(1)\right)^2 > \pi f'''(1)f'(1), \quad (12)$$

then a stable Hopf bifurcation occurs at τ_{cr}. To study stability of appearing periodic orbits we need to find the coefficient of the third term in Taylor expansion of the periodic solution. To do this we use the approach of normalised bounded variation functions (NBV) proposed by Diekamnn et al. [16]. Let us change the variable $z(t) = x(t) - 1$ such that the positive steady state $\bar{V}_2$ is moved to 0. Therefore,

$$\dot{z}(t) = \alpha f(z(t-1)+1), \ \alpha = r\tau. \quad (13)$$

We easily see that $L(\phi) = \alpha f'(1)\phi(-1)$ and $G(\phi) = \alpha\left(f(\phi(-1)+1) - f'(1)\phi(-1)\right)$, $\phi \in \mathcal{C}$, are the linear and non-linear part of Eq. (13), respectively. The NBV function $\zeta(\theta,\alpha)$ for Eq. 13 reads

$$\zeta(\theta,\tau) = \begin{cases} 0 & \text{for } \theta \in [0,1), \\ \alpha f'(1) & \text{for } \theta = 1, \end{cases}$$

while the characteristic equation has the form

$$\Delta(\lambda,\alpha) = \lambda + \alpha|f'(1)|\exp(-\lambda) = 0. \quad (14)$$

Purely imaginary eigenvalues $\pm i\omega_0 = \pm i\frac{\pi}{2}$ appear for $\alpha_0 = \frac{\pi}{2}$ and are simple. Let $\Phi(\theta) = \exp(i\frac{\pi}{2}\theta)p$, $p \neq 0$ be a right eigenvector for the eigenvalue $i\frac{\pi}{2}$. We need choose a left eigenvector $\Psi(s) = \exp(i\frac{\pi}{2}s)q$ such that $qd_1\Delta(i\frac{\pi}{2},\frac{\pi}{2})p = 1$, where d_1 denotes the derivative with respect to the first variable λ. However, $d_1\Delta(i\frac{\pi}{2},\frac{\pi}{2r}) = 1 + i\frac{\pi}{2}$ and choosing $p = 1 - i\frac{\pi}{2}$ and $q = \frac{4}{4+\pi^2}$ we obtain the desired property.

Now, we can calculate the third term coefficient μ_2 as

$$\mu_2 = \frac{\Re c}{\Re\left(qd_2\Delta(i\omega_0,\alpha_0)p\right)},$$

where p, q are defined above, d_2 is the derivative with respect to the second variable α, and

$$c = \tfrac{1}{2}qd_1^3 G(0,\alpha_0)(\Phi,\Phi,\bar{\Phi}) + qd_1^2 G(0,\alpha_0)\left(\Psi_{\bar{\Phi}}(\cdot,0),\Phi\right) + \tfrac{1}{2}qd_1^2 G(0,\alpha_0)\left(\Psi_{\Phi}(\cdot,2i\omega_0),\bar{\Phi}\right),$$

where d_1^i, $i = 2,3$ denotes the derivative of the ith order with respect to the first variable and

$$\Psi_{\Phi_1}(\theta,a) = e^{a\theta}(\Delta(a,\alpha_0))^{-1}d_1^2 G(0,\alpha_0)(\Phi,\Phi_1).$$

We have $d_2\Delta(i\frac{\pi}{2},\frac{\pi}{2|f'(1)|}) = -i|f'(1)|$, and therefore the denominator of μ_c reads

$$\Re\left(\frac{4}{4+\pi^2}(-i)|f'(1)|(1 - i\frac{\pi}{2})\right) =$$

$$= -\frac{2|f'(1)|\pi}{4+\pi^2} < 0.$$

To find the numerator we need to calculate the derivatives of the non-linear part G. Let u, v, $w \in \mathcal{C}$ be any test functions. Then

$$d_1^2 G(0,\frac{\pi}{2|f'(1)|})(u,v) = \alpha_0 f''(1)u(-1)v(-1)$$

and

$$d_1^3 G(0,\frac{\pi}{2|f'(1)|})(u,v,w) =$$

$$= \alpha_0 f'''(1)u(-1)v(-1)w(-1).$$

Moreover, $\left(\Delta(0,\frac{\pi}{2|f'(1)|})\right)^{-1} = \frac{2}{\pi}$, while $\left(\Delta(i\pi,\frac{\pi}{2|f'(1)|})\right)^{-1} = -\frac{2}{5\pi}(2i+1)$. Therefore,

$$\frac{1}{2}qd_1^3 G(0,\frac{\pi}{2|f'(1)|})(\Phi,\Phi,\bar{\Phi}) = -\frac{\pi}{4}\left(\frac{\pi}{2}+i\right)\frac{f'''(1)}{|f'(1)|},$$

$$qd_1^2 G(0,\frac{\pi}{2|f'(1)|})\left(\Psi_{\bar{\Phi}}(\cdot,0),\Phi\right) =$$

$$= -\frac{\pi}{2}\left(\frac{\pi}{2}+i\right)\left(\frac{f''(1)}{|f'(1)|}\right)^2,$$

and

$$\frac{1}{2}qd_1^2 G(0,\frac{\pi}{2|f'(1)|})\left(\Psi_{\Phi}(\cdot,i\pi),\bar{\Phi}\right) =$$

$$\frac{\pi\left(1 - i\frac{\pi}{2}\right)\left(1 - i\frac{1}{2}\right)}{10}\left(\frac{f''(1)}{|f'(1)|}\right)^2.$$

Eventually, we obtain

$$\Re c = -\frac{\pi}{8}\left(\pi\frac{f'''(1)}{|f'(1)|} + \frac{11\pi-4}{5}\left(\frac{f''(1)}{|f'(1)|}\right)^2\right).$$

We easily see that if Inequality (12) is satisfied, then $\mu_2 > 0$ and because all eigenvalues other than $\pm i\frac{\pi}{2}$ are located in the left-hand complex half-plane the periodic solutions exit for $\tau > \tau_{\mathrm{cr}}$ and are stable.

Let us check Inequality (12) for Eq. (11). As the fight-hand side of Eq. (11) is a polynomial of the second degree, the third derivative equals 0, while the second one is non-zero, and therefore Inequality (12) is easily fulfilled. Hence, bifurcating periodic solutions are stable.

As we can see from the analysis presented above, studying bifurcations in the case of DDEs is not easy, even for such simple equation as Eq. (11). The situation is much more complex when more than one delay is introduced into the model. Then stability switches with increasing delay can be observed, compare [38, 39, 42]. This means that with increasing delay there appears a sequence of critical values of the delay and the steady state is stable for the delays between some critical values of the delay, while is unstable between others. It should be marked, that if the steady state destabilises for some critical delay, than eventually it must remain unstable.

Final remarks

As we can see from the examples presented in this paper, analysis of even simple DDEs can be really complicated. Many other interesting examples of the models based on DDEs can be found in the literature, compare e.g. [10, 7, 5, 6, 26, 24, 28, 29, 41, 43] for the models describing different stages of tumour growth, [3, 4, 18, 19, 20, 21, 25, 17, 12] for immune reactions modelling, also in the context of AIDS [11, 30] and tumour [31, 35, 40] or [1] for love affairs dynamics.

At the end we would like to recall that it is necessary to perform at least preliminary analysis of the model we propose to describe a real phenomenon to be sure that the model is properly defined and can be biologically relevant. The example of biochemical reactions channel described here is very significant, because mathematical description which seems "intuitive"is completely wrong. This shows that proposing mathematical models experimentalists should closely cooperate with mathematicians, as only such cooperation can guarantee that the model is properly defined.

REFERENCES

1. N. Bielczyk, U. Foryś and T. Płatkowski. Dynamical models of dyadic interactions with delay // to appear in J. Math. Sociology.

2. M. Bodnar. The nonnegativity of the solutions of delay differential equations // Appl. Math. Lett.— 2000.— **13**, N6.— P.91—95.

3. M. Bodnar and U. Foryś. Behaviour of Marchuk's model depending on time delay // Int. J. Appl. Math. Comput. Sci.— 2000.— **10**— P.101—116.

4. M. Bodnar and U. Foryś. Periodic dynamics of the model of immune system // Appl. Math. (Warsaw).— 2000.— **27**, N1.— P.113—126.

5. M. Bodnar and U. Foryś. Time delays in proliferation process for solid avascular tumour // Math. Comput. Modelling.— 2003.— **37**, N11.— P.1201–1209.

6. M. Bodnar and U. Foryś. Time delays in regulatory apoptosis for solid avascular tumour // Math. Comp. Modelling.— 2003.— **37**, N11.— P.1211—1220.

7. M. Bodnar and U. Foryś. Time delay in necrotic core formation // Math. Biosci. Eng..— 2005.— **2**, N3.— P.461—472.

8. M. Bodnar and U. Foryś. M. Bodnar and U. Foryś. Three types of simple DDE's describing tumor growth // J. Biol. Sys.— 2007.— **15**, N4.— P.1—19.

9. M. Bodnar and U. Foryś. Global stability and Hopf bifurcation for a general class of delay differential equations // Math. Methods Appl. Sci.— 2008.— **31**, N10.— P.1197—1207

10. M. Bodnar and U. Foryś. Angiogenesis model with carrying capacity depending on vessel density // J. Biol. Sys.— 2009.— **17**, N1.— P.1—25.

11. M. Bodnar, U. Foryś and Z. Szymańska. Model of AIDS-related tumour with time delay // Appl. Math. (Warsaw).— 2009.— **36**, N3. P.263—278.

12. M. Bodnar and U. Foryś. A model of immune system with time-depended immune reactivity // Non. Anal. Th. Meth. Appl.— 2009.— **70**, N2.— P.1049—1058.

13. M. Bodnar, U. Foryś and J. Poleszczuk. Analysis of biochemical reactions models with delays // J. Math. Anal. Appl.— 2011.— **376**— P.74—83.

14. D. Bratsun, D. Volfson, L.S. Tsimring and J. Hasty. Delay-induced stochastic oscillations in gene regulation // PNAS.— 2005.— **102**, N41.— P.14593—14598.

15. K.L. Cooke and P. van den Driessche. On zeroes of some transcendental equations // Funkcj. Ekvacioj.— 1986.— **29**— P.77—90.

16. *O. Diekmann, S. van Giles, S. Verduyn Lunel and H.O. Walter.* Delay equations // Springer— 1995.— New York.

17. *U. Foryś.* Interleukin mathematical model of an immune system // J. Biol. Systems.— 1995.— **3**— P.889—902.

18. *U. Foryś.* Global analysis of Marchuk's model in a case of weak immune system // Math. Comput. Modelling.— 1997.— **25**— P.97—106.

19. *U. Foryś.* Global analysis of Marchuk's model in case of strong immune system // J. Biol. Systems.— 2000.— **8**— P.331—346.

20. *U. Foryś.* Hopf bifurcations in Marchuk's model of immune reactions // Math. Comput. Modelling.— 2001.— **34**— P.725—735.

21. *U. Foryś.* Marchuk's model of immune system dynamics with application to tumour growth // J. Theor. Med.— 2002.— **4**, N1.— P.85—93.

22. *U. Foryś.* Biological delay systems and the Mikhailov criterion of stability // J. Biol. Sys.— 2004.— **12**, N1.— P.45—60.

23. *U. Foryś.* Global stability for a class of delay differential equations // Appl. Math. Lett.— 2004.— **17**, N5.— P.581—584.

24. *U. Foryś.* Stability analysis and comparison of the models for carcinogenesis mutations in the case of two stages of mutations // Journal of Applied Analysis.— 2005.— **11**— P.200—281.

25. *U. Foryś.* Stability and bifurcations for the chronic state in Marchuk's model of an immune system // J. Math. Anal. Appl.— 2009.— **352**— P.922—942.

26. *U. Foryś.* Multi-dimensional Lotka-Volterra sysyem for carcinogenesis mutations // Math. Meth. Appl. Sci.— 2009.— **32**— P.2287—2308.

27. *U. Foryś, M. Bodnar and J. Poleszczuk.* Negativity of delayed induced oscillations in a simple linear DDE // Appl. Math. Lett.— 2011.— **24**, N6.— P.982—986.

28. *U. Foryś, Y. Kheifetz and Y. Kogan.* Critical point analysis for three-variable cancer angiogenesis model // Math. Biosci. Eng.— 2005.— **2**, N3.— P.511—525.

29. *U. Foryś and A. Marciniak-Czochra.* Logistic equations in tumour growth modelling // Int. J. Appl. Math. and Comp. Sci.— 2003.— **13**— P.317—326.

30. *U. Foryś and J. Poleszczuk.* A delay-differential equation model of HIV related cancer-immune system dynamics // Math. Biosci. Eng..— 2011.— **8**, N2.— P.627—641.

31. *U. Foryś, J. Waniewski P. Zhivkov.* Anti-tumor immunity and tumor anti-immunuty in a mathematical model of tumor immunotherapy // J. Biol. Systems.— 2006.— **14**, N1.— P.13—30.

32. *J.K. Hale and S.M.V. Lunel.* Introduction to Functional Differential Equations // Springer— 1993.— New York.

33. *J.K. Hale and N. Sternberg.* Onset of chaos in differential delay equations // J. Comp. Phys.— 1988.— **77**, N1.— P.221—239.

34. *G.E. Hutchinson.* Circular casual systems in ecology // Ann. N.Y. Acad. Sci.— 1948.— **50**— P.221—246.

35. *Y. Kogan, U. Foryś, N. Kronik, O. Shukron and Z. Agur.* Cellular immunotherapy for high grade gliomas: mathematical analysis deriving efficacious infusion rates based on patient requirements // SIAM J. Appl. Math.— 2010.— **70**, N6.— P.1953—1976.

36. *Y. Kuang.* Delay differential equations with applications in population dynamics // Academic Press Inc.— 1993.

37. *J. Miękisz, J. Poleszczuk, M. Bodnar and U. Foryś.* Stochastic Models of Gene Expression with Delayed Degradation // Bull. Math. Biol.— 2011.— **73**, N9.— P.2231—2247.

38. *M.J. Piotrowska.* A remark on the ODE with two discrete delays // J. Math. Anal. Appl.— 2007.— **329**— P.664—676.

39. *M.J. Piotrowska.* Hopf bifurcation in a solid avascular tumour growth model with two discrete delays // Math. Comput. Modelling.— 2008.— **47**— P.597—603.

40. *M.J. Piotrowska, M. Bodnar, J. Poleszczuk and U. Foryś.* Mathematical modelling of immune reaction against gliomas: sensitivity analysis and influence of delays // accepted to Nonlinear Analysis Series B: Real World Applications.

41. *M.J. Piotrowska and U. Foryś.* Analysis of the Hopf bifurcation for the family of angiogenesis models // J. Math. Anal. Appl.— 2011.— **382**— P.180—203.

42. *M.J. Piotrowska and U. Foryś.* The nature of Hopf bifurcation for the Gompertz model with delays // Math. Comput. Modelling.— 2011.— **54**— P.2183—2198.

43. *J. Poleszczuk, M. Bodnar and U. Foryś.* New approach to modeling of antiangiogenic treatment on the basis of Hahnfeldt et al. model // Math. Biosci. Eng.— 2011.— **8**, N2.— P.591—603.