TREATMENT INDUCED PERIODIC SOLUTIONS IN SOME MATHEMATICAL MODELS OF TUMORAL CELL DYNAMICS

ANDREI HALANAY

Existence and stability of periodic solutions is analyzed first for the mathematical model of the Glasgow osteosarcome at mice subject to periodic treatment. The same properties are investigated for a two-phase stem cell dynamics model in hematological diseases.

AMS 2000 Subject Classification: 34C25, 34D20, 34K20, 92C37, 92C50.

Key words: periodic solution, monodromy operator, Liapunov stability, stem cells, periodic delay differential equation.

1. INTRODUCTION

In [2] a system of ordinary differential equations is used to model the evolution of tumoral population in a Glasgow osteosarcome in mice, subject to oxaliplatine treatment. If no resistance to treatment is encountered the model is given by

$$\begin{aligned}\dot{P} &= -\lambda P + \frac{i_0(t)}{V},\\ \dot{D} &= -\nu D + P,\\ \dot{B} &= -aB\ln\left(\frac{B}{B_{\max}}\right) - g(D)B,\end{aligned} \tag{1.1}$$

where: P is the plasmatique concentration in free platine, an active drug. $i_0(t)$ is the instantaneous debit of drug injected at moment t; i_0 is supposed periodic of period ω [days]. D is the concentration of active substance in the tumour. B is the number of tumoral cells with $B_{\max}$ the asymptotic value of B. λ, ν, V and a are strictly positive constants. We take, as in [2],

$$g(D) = \frac{D}{D_{T50} + D}[1 + \cos 2\pi(t - \Phi_T)], \tag{1.2}$$

MATH. REPORTS **12(62)**, *4* (2010), 329–337

where D_{T50}, the concentration of half-saturation, and Φ_T, maximum efficiency phase, are constants.

System (1.1) is numerically integrated in [2] for different parameter configurations. The objective of treatment is to have the least number of tumoral cells with the least toxic effects on organism. Different command laws i_0 are considered.

We show in §2 that, for i_0 periodic with period ω, the system

$$\begin{cases} \dot{P} = -\lambda P + \dfrac{i_0(t)}{V} \\ \dot{D} = -\nu D + P \end{cases} \tag{1.3}$$

has an ω-periodic positive solution $(P^*(t), D^*(t))$ and then, if $\omega \in \mathbf{N}^*$, equation

$$\dot{B} = -aB \ln\left(\frac{B}{B_{\max}}\right) - g(D^*)B \tag{1.4}$$

has also an ω-periodic solution. We analyze the asymptotic stability of this solution. Next, treatment effects are incorporated in the two-dimensional system of coupled delay differential equations introduced in [10], [11] and further studied in [12], [13], [14], modeling infected hematopoietic stem cell dynamics in hematological diseases.

$$\begin{aligned} \dot{x}_1 &= -\gamma x_1 + \beta(x_2)x_2 - e^{-\gamma\tau}\beta(x_{2\tau})x_{2\tau} - g_1(t)x_1, \\ \dot{x}_2 &= -\delta x_2 - \beta(x_2)x_2 + 2e^{-\gamma\tau}\beta(x_{2\tau})x_{2\tau} - g_2(t)x_2, \end{aligned} \tag{1.5}$$

where $x_1(t)$ is the density of proliferative stem cells at time t, $x_2(t)$ is the density of resting (quiescent) cells at time t and $x_{2\tau}(t) = x_2(t-\tau)$. The term $e^{-\gamma\tau}\beta(x_{2\tau})x_{2\tau}$ represents the fraction of proliferating cells to leave the phase, they entered at time $t-\tau$, through division followed automatically by entering the resting (G_0) phase. γ is the apoptosis rate of proliferating cells. The resting cells can differentiate into one of the main line cells (red, white, platelets) at a rate δ or re-enter the proliferating phase at a rate $\beta(x_2)x_2$. The term $2e^{-\gamma\tau}\beta(x_{2\tau})x_{2\tau}$ in the second equation accounts for the resting daughter cells that come from the division of corresponding proliferating cells. The reentry rate β is taken in most cases as a decreasing Hill function that, after scaling (see [1], [13]) can be taken as

$$\beta(x) = \beta_0 \frac{1}{1+x^n}\ , \quad n > 0. \tag{1.6}$$

τ is the time needed for a cell that entered the proliferating phase to divide. Treatment's effect are given by the two ω-periodic, positive, continuous functions $g_1(t)$, $g_2(t)$ that contribute to the decrease of the number of cells in the corresponding phase.

It will be proved in §3 that if ω, the period of $g = (g_1, g_2)$, satisfies $\tau = k\omega$ for some $k \in \mathbf{N}$, $k \geq 1$, then (1.5) has a nonzero ω-periodic solution. The asymptotic stability of this solution will be investigated. A final section is devoted to concluding remarks.

2. EXISTENCE AND STABILITY OF PERIORIC SOLUTIONS FOR GLASGOW OSTEOSARCOME TREATMENT MODEL

The solution of (1.3) with initial conditions $(P_0, D_0)^T$ (T means transposed) is

$$\begin{pmatrix} P(t) \\ D(t) \end{pmatrix} = e^{At} \begin{pmatrix} P_0 \\ D_0 \end{pmatrix} + \int_0^t e^{A(t-s)} \begin{pmatrix} \dfrac{i(s)}{V} \\ 0 \end{pmatrix} \mathrm{d}s, \tag{2.1}$$

where

$$A = \begin{pmatrix} -\lambda & 0 \\ 1 & -\nu \end{pmatrix}. \tag{2.2}$$

If $(P, D)^T$ is periodic with period ω, then $P(\omega) = P_0$ and $D(\omega) = D_0$, whence

$$\begin{pmatrix} P_0 \\ D_0 \end{pmatrix} = (I - e^{A\omega})^{-1} \frac{1}{V} \int_0^{\omega} e^{A(w-s)} \begin{pmatrix} i(s) \\ 0 \end{pmatrix} \mathrm{d}s. \tag{2.3}$$

An easy calculation gives

$$(I - e^{A\omega})^{-1} = \frac{1}{(1 - e^{-\lambda\omega})(1 - e^{-\gamma\omega})} \begin{pmatrix} 1 - e^{-\nu\omega} & 0 \\ \dfrac{e^{-\nu\omega} - e^{-\lambda\omega}}{\lambda - \nu} & 1 - e^{-\nu\omega} \end{pmatrix}$$

an it follows from (2.3) that

$$P_0 = \frac{e^{-\lambda\omega}}{(1 - e^{-\lambda\omega})V} \int_0^{\omega} e^{\lambda s} i(s) \mathrm{d}s$$

and

$$D_0 = \frac{1}{(1 - e^{-\lambda\omega})(1 - e^{-\nu\omega})} \left[\frac{(e^{-\nu\omega} - e^{-\lambda\omega})e^{-\lambda\omega}}{V(\lambda - \nu)} \int_0^{\omega} e^{\lambda s} i(s) \mathrm{d}s + \right.$$
$$\left. + \frac{1 - e^{-\lambda\omega}}{V(\lambda - \nu)} \int_0^{\omega} [e^{\nu(s-\omega)} - e^{\lambda(s-\omega)}] i(s) \mathrm{d}s \right],$$

where

$$e^{At} = \begin{pmatrix} e^{-\lambda t} & 0 \\ \dfrac{e^{-\nu t} - e^{-\lambda t}}{\lambda - \nu} & e^{-\nu t} \end{pmatrix}$$

has been used. Remark that for V, λ, ν given in [4], P_0 and D_0 are within the ranges of P and D used in [4].

The periodic solution of (1.3) is

$$\begin{aligned} P^*(t) &= e^{-\lambda t}P_0 + \frac{1}{V}\int_0^t e^{-\lambda(t-s)}i(s)\mathrm{d}s, \\ D^*(t) &= \frac{e^{-\nu t}-e^{-\lambda t}}{\lambda-\nu}P_0 + e^{-\nu t}D_0 + \\ &\quad + \frac{1}{V(\lambda-\nu)}\int_0^t \left[e^{-\nu(t-s)}-e^{-\lambda(t-s)}\right]i(s)\mathrm{d}s. \end{aligned} \tag{2.4}$$

If $\lambda - \nu > 0$ and $i(s) \geq 0$ as it is indeed the case in the model in [4], then $P^*(t) > 0$, $D^*(t) > 0$, $\forall t \geq 0$. Since $\sigma(A) = \{-\lambda, -\nu\} \subset (-\infty, 0)$, the periodic solution (P^*, D^*) is asymptotically stable.

Consider now equation (1.4) and introduce

$$u(t) = \ln\left(\frac{B(t)}{B_{\max}}\right). \tag{2.5}$$

Since $\dot{u}(t) = \frac{\dot{B}(t)}{B(t)}$,

$$\dot{u}(t) = -au(t) - g[D^*(t)], \tag{2.6}$$

where D^* is given in (2.4). Recall from [10], Chapter 3, the following theorem (Theorem 3.1): A necessary and sufficient condition in order that, for any periodic function $f(t)$ of period ω the system $\dot{x} = A(t)x + f(t)$, with A periodic of period ω, admits periodic solutions of period ω is that the corresponding homogeneous system does not admit a periodic solution of period ω other than the trivial one. Since the homogeneous equation attached to (2.6) has no periodic solutions other than zero, equation (2.6) has an unique periodic solution u^* with the same period ω as D^*. By (2.5) equation (1.4) has an unique ω-periodic solution $B^*(t) = B_{\max}e^{u^*(t)}$.

For the study of asymptotic behaviour of B^* remark that $v = u - u^*$ satisfies

$$\dot{v} = -av. \tag{2.7}$$

Since $a > 0$, the zero solution of (2.7) is uniformly asymptotically stable so u^* is an uniformly asymptotically stable solution of (2.6). If follows that if $\left|\frac{B(0)}{B^*(0)} - 1\right|$ is small enough, then $\lim\limits_{t\to\infty} |B(t) - B^*(t)| = 0$.

3. EXISTENCE AND STABILITY OF PERIODIC SOLUTIONS FOR HEMATOPOIETIC STEM CELL DYNAMICS UNDER TREATMENT

If $\tau = k\omega$, $k \geq 1$, an ω-periodic solution of (1.5) satisfies a system of ordinary differential equations with ω-periodic coefficients

$$\begin{aligned} \dot{x}_1 &= -(\gamma + g_1(t))x_1 + (1 - e^{-\gamma\tau})\beta(x_2)x_2, \\ \dot{x}_2 &= -(\delta + g_2(t))x_2 + (2e^{-\gamma\tau} - 1)\beta(x_2)x_2. \end{aligned} \tag{3.1}$$

In order to prove that (3.1) has a nonzero ω-periodic solution, we use [9], Chapter II, §4, Theorem 4.17, so the conditions of that theorem must be verified for (3.1).

The first condition is that of positivity of the right-hand side of (3.1). According to [9] a system

$$\dot{x} = f(t, x), \quad x = (x_1, \ldots, x_n), \tag{3.2}$$

$f(t, 0) = 0$, $\forall t$, $f(t + \omega, x) = f(t, x)$, $\forall t$, $f = (f_1, \ldots, f_n)$, is said to satisfy the positivity condition if, for every $i = 1, \ldots, n$, $f_i(t, x_1, \ldots, x_{i-1}, 0, x_{i+1}, \ldots, x_n) \geq 0$, $\forall t$, whenever $x_1 \geq 0, \ldots, x_{i-1} \geq 0$, $x_{i+1} \geq 0, \ldots, x_n \geq 0$.

The second condition requires that system (3.2) can be written as

$$\dot{x} = B(t)x + \eta(t, x) \tag{3.3}$$

with

$$\lim_{\|x\| \to \infty} \frac{\|\eta(t, x)\|}{\|x\|} = 0 \tag{3.4}$$

and that $V(\omega)$, the monodromy operator of the system

$$\dot{x} = B(t)x \tag{3.5}$$

has the property that $\sigma(V(\omega)) \subset \mathbf{D}$, the open unit disc in $\mathbf{C}$.

THEOREM 3.1. *System* (3.1) *has a nonzero ω-periodic solution.*

Proof. Since

$$f_1(t, x_1, x_2) = -(\gamma + g_1(t))x_1 + (1 - e^{-\gamma\tau})\beta(x_2)x_2$$

and

$$f_2(t, x_1, x_2) = -(\delta + g_2(t))x_2 + (2e^{-\gamma\tau} - 1)\beta(x_2)x_2,$$

$f_1(t, 0, x_2) = (1 - e^{-\gamma\tau})\beta(x_2)x_2 \geq 0$ and $f_2(t, x_1, 0) = 0$. With $f = (f_1, f_2)$, $f(t, 0, 0) = 0$ and $f(t + \omega, x_1, x_2) = f(t, x_1, x_2)$, $\forall t$. (3.1) has already the form (3.3) with

$$B(t) = \begin{pmatrix} -(\gamma + g_1(t)) & 0 \\ 0 & -(\delta + g_2(t)) \end{pmatrix}$$

and

$$\eta(t,x_1,x_2) = ((1-e^{-\gamma\tau})\beta(x_2)x_2, (2e^{-\gamma\tau}-1)\beta(x_2)x_2) = \\ = \beta(x_2)x_2(1-e^{-\gamma\tau}, 2e^{-\gamma\tau}-1).$$

With $\|\cdot\|$ the Euclidean norm, by (1.6),

$$\lim_{\|x\|\to\infty} \frac{\|\eta(t,x_1,x_2)\|}{\|x\|} = \left(\lim_{\|x\|\to\infty} \frac{x_2}{\sqrt{x_1^2+x_2^2}} \frac{\beta_0}{1+x_2^n} \right) \|(1-e^{-\gamma\tau}, 2e^{-\gamma\tau}-1)\| = 0.$$

The monodromy matrix for (3.5) is

$$V(\omega) = \begin{pmatrix} e^{-\gamma\omega - \int_0^\omega g_1(t)\mathrm{d}t} & 0 \\ 0 & e^{-\delta\omega - \int_0^\omega g_2(t)\mathrm{d}t} \end{pmatrix}$$

and since $g_1(t) \geq 0$, $g_2(t) \geq 0$, $\forall t$ we have $\sigma(V(\omega)) \subset \mathbf{D}$. The already quoted Theorem 4.17 in [9] gives now the existence of a nonzero ω-periodic solution of (3.1).

Denote by $x^* = (x_1^*, x_2^*)$ the nonzero ω-periodic solution of (1.5). In order to study its stability, perform first a translation. If $y = x - x^*$, y satisfies

$$\begin{aligned} \dot{y}_1 &= -\gamma y_1 - g_1(t)y_1 + \beta(y_2+x_2^*)(y_2+x_2^*) - \\ &\quad - e^{-\gamma\tau}\beta(y_{2\tau}+x_{2\tau}^*)(y_{2\tau}+x_{2\tau}^*) - (\dot{x}_1^* + \gamma x_1^* + g_1(t)x_1^*), \\ \dot{y}_2 &= -\delta y_2 - g_2(t)y_2 - \beta(y_2+x_2^*)(y_2+x_2^*) + \\ &\quad + 2e^{-\gamma\tau}\beta(y_{2\tau}+x_{2\tau}^*)(y_{2\tau}+x_{2\tau}^*) - (\dot{x}_2^* + \delta x_2^* + g_2(t)x_2^*). \end{aligned} \tag{3.6}$$

Define $r(x) = \beta(x)x$. The linearized around zero system for (3.6) is

$$\dot{y} = A_1(t)y + A_2(t)y_\tau, \tag{3.7}$$

where

$$A_1(t) = \begin{pmatrix} -\gamma - g_1(t) & r'(x_2^*) \\ 0 & -\delta - g_2(t) - r'(x_2^*) \end{pmatrix},$$

$$A_2(t) = \begin{pmatrix} 0 & -e^{-\gamma\tau}r'(x_2^*) \\ 0 & 2e^{-\gamma\tau}r'(x_2^*) \end{pmatrix}.$$

The stability of the zero solution for (3.7) will be investigated using the criterion in Theorem 4.18 in [6]: if, for every continuous ω-periodic $h = (h_1, h_2)$ and for every $\lambda \in \mathbf{C}$ with $|e^{\lambda\omega}| \geq 1$, the system

$$\dot{y} = A_1(t)y + A_2(t)y_\tau + e^{\lambda t}h \tag{3.8}$$

has a solution $y(t) = e^{\lambda t}\psi(t)$, with $\psi(t+\omega) = \psi(t)$, $\forall t \geq 0$, the zero solution of (3.7) is uniformly asymptotically stable.

If $\tau = k\omega$ and $y(t) = e^{\lambda t}\psi(t)$ is a solution of (3.8), ψ satisfies

$$
\begin{aligned}
\psi_1'(t) &= -\lambda\psi_1(t) - (\gamma + g_1(t))\psi_1(t) + (1 - e^{\gamma\tau-\lambda\tau})r'(x_2^*)\psi_2(t) + h_1(t),\\
\psi_2'(t) &= \big[-\lambda - \delta - r'(x_2^*) - g_2(t) + 2e^{-(\gamma+\lambda)\tau}r'(x_2^*)\big]\psi_2(t) + h_2(t).
\end{aligned}
\tag{3.9}
$$

System (3.9) must admit an ω-periodic solution ψ for every ω-periodic continuous h. According to [6], Chapter 3, Theorem 3.1, this happens if and only if the homogeneous system attached to (3.9) has no nonzero ω-periodic solution. The homogeneous system is

$$
\begin{aligned}
\psi_1' &= -[\lambda + \gamma + g_1(t)]\psi_1 + (1 - e^{-(\gamma+\lambda)\tau})r'(x_2^*)\psi_2,\\
\psi_2' &= -\big[\lambda + \delta + g_2(t) + r'(x_2^*) - 2e^{-(\gamma+\lambda)\tau}r'(x_2^*)\big]\psi_2.
\end{aligned}
\tag{3.10}
$$

With $\tilde g_2(t) = -\lambda - \delta - g_2(t) - r'(x_2^*) + 2e^{-(\gamma+\lambda)\tau}r'(x_2^*)$, the solutions of the second equation are

$$\psi_2(t) = c\, e^{b(t)+at} \tag{3.11}$$

with $b(t+\omega) = b(t)$, $\forall t$ and

$$a = \frac{1}{\omega}\int_0^\omega \tilde g_2(t)\mathrm{d}t. \tag{3.12}$$

Functions in (3.11) are ω-periodic if and only if $a = 0$ thus one has to study the equation in $\lambda \in \mathbf{C}$

$$\lambda+\delta+\frac{1}{\omega}\int_0^\omega r'[x_2^*(t)]\mathrm{d}t+\frac{1}{\omega}\int_0^\omega g_2(t)\mathrm{d}t-e^{-(\gamma+\lambda)\tau}\frac{2}{\omega}\int_0^\omega r'[x_2^*(t)]\mathrm{d}t = 0. \tag{3.13}$$

Theorem 3.2. *If*

$$\delta + \frac{1}{\omega}\int_0^\omega g_2(t)\mathrm{d}t > (1 - 2e^{\gamma\tau})\frac{1}{\omega}\int_0^\omega r'[x_2^*(t)]\mathrm{d}t \tag{3.14}$$

the periodic solution of (1.5) *given in Theorem* 3.1 *is uniformly locally asymptotically stable.*

Proof. (3.14) is necessary and sufficient for (3.13) to have only solutions λ with $\operatorname{Re}\lambda < 0$ (see [3], [4]). Then, if $|e^{\lambda\omega}| \geq 1$, a in (3.12) is not zero and the only ω-periodic ψ_2 in (3.11) is $\psi_2 = 0$. (3.10) reduces to

$$\psi_1' = -[\lambda + \gamma + g_1(t)]\psi_1 := \tilde g_1(t)\psi_1, \tag{3.15}$$

where $\tilde g_1(t+\omega) = \tilde g_1(t)$, $\forall t$. Arguing as before one finds that, in order that (3.15) has a nonzero ω-periodic solution, it is necessary and sufficient that

$$\lambda + \gamma + \frac{1}{\omega}\int_0^\omega g_1(t)\mathrm{d}t = 0$$

and this is clearly impossible if $\operatorname{Re}\lambda \geq 0$ as assumed through $|e^{\lambda\omega}| \geq 1$. It follows that the only ω-periodic solution in (3.15) is $\psi_1 = 0$ and the criterion in [6], Chapter 3, Theorem 3.1 is satisfied, so (3.9) has an ω-periodic solution ψ for every ω-periodic continuous h. Thus the zero solution of (3.7) is uniformly asymptotically stable and by the theorem of stability by the first approximation ([7] Theorem 18.3 or [8], Chapter 3, §1, Theorem 1.9), x^* is a locally asymptotically stable solution of (1.5).

4. CONCLUDING REMARKS

The main results of this paper show that, in specific conditions, a periodic treatment can induce a stable periodic response. This is proved for the model of oxaliplatine action on Glasgow osteosarcome in mice, introduced in [2] and for a model of treatment action on hematopoietic stem cells, based on [10], [12]. Other results on the same line regarding existence of periodic solutions for hematopoiesis models are proved in [5], [13].

Acknowledgements. This work is partially supported by CNCSIS Grant ID-PCE 1192-09.

REFERENCES

[1] M. Adimy, F. Crauste, A. Halanay, M. Neamţu and D. Opriş, *Stability of limit cycles in a pluripotent stem cell dynamics Model.* Chaos, Solitons & Fractals **27** (2006), 1091–1107.

[2] J. Clairambault, D. Claude, E. Filipki, T. Granda and F. Levi, *Toxicité et efficacité antitumorale de l'oxaliplatine sur l'osteosarcome de Glasgow induit chez la souris: un modele mathematique.* Pathologie Biologie **51** (2003), 212–215.

[3] K. Cooke and Z. Grossman, *Discrete delay, distribution delay and stability switches.* J. Math. Anal. Appl. **86** (1982) 592–627.

[4] L.E. El'sgol'ts and S.B. Norkin, *Introduction to the Theory of Differential Equations with Time Lag.* Nauka, Moscow, 1971. (in Russian)

[5] K. Gopalsamy and S. Trofimchuk, *Almost periodic solutions of Lasota-Wasewska-type delay differential equations.* J. Math. Anal. Appl. **237** (1999), 106–127.

[6] Aristide Halanay, *Differential Equations: Stability, Oscilations, Time Lag.* Academic Press, 1966.

[7] J. Hale, *Theory of Functional Differential Equations.* Springer, New York, 1977.

[8] V. Kolmanovskii and A. Myshkis, *Applied Theory of Functional Differential Equations.* Kluwer, Dordrecht, 1992.

[9] M.A. Krasnoselskii, *Shift Operators on Orbits of Differential Equations.* Nauka, Moskow, 1966. (Russian)

[10] M.C. Mackey, *A unified hypothesis of the origin of aplastie anemia and periodic hematopoiesis.* Blood **51** (1978), 941–956.

[11] M.C. Mackey, *Periodic auto-immune hemolitic anemia: an induced dynamical diseases.* Bull. Math. Biol. **41** (1979), 829–834.

[12] M.C. Mackey, *Mathematical models of hematopoietic cell replication and control*. In: H.G. Othmer, F.R. Adler, M.A. Lewis and J.C. Dalton (Eds.), *The Art of Mathematical Modeling: Case Studies in Ecology, Physiology and Biofluids*, pp. 149–178. Prentice Hall, New York, 1996.

[13] M.C. Mackey, C. Ou, L. Pujo-Menjouet and J. Wu, *Periodic oscillations of boold cell population in chronic myelogenous leukemia*. SIAM J. Math. Anal. **38** (2006), 166–187.

[14] L. Pujo-Menjouet and C. Mackey, *Contribution to the study of periodic chronic myelogenous leukemia*. C.R. Biol. **327** (2004), 235–244.

Received 14 February 2009

"POLITEHNICA" University of Bucharest
Department of Mathematics I
Splaiul Independenţei 313
060042 Bucharest, Romania
halanay@mathem.pub.ro