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A NOTE ON GLOBAL ATTRACTIVITY IN MODELS OF HEMATOPOIESIS

ПРО ГЛОБАЛЬНІ АТРАКТОРИ В МОДЕЛІ ВІДТВОРЕННЯ КРОВ'ЯНИХ ТІЛЕЦЬ

We consider the delay differential equations

$$P'(t) = \frac{\beta_0 \theta^n [P(t-\tau)]^j}{\theta^n + [P(t-\tau)]^n} - \delta P(t), \qquad j = 0, 1, \tag{*}$$

which have been proposed by Mackey and Glass as a model of blood cell production. We suggest new conditions sufficient for positive equilibrium of considered equation to be a global attractor. In contrast to the Lasota-Wazewska model, we establish the existence of the number $\delta_j = \delta_j(n,\tau) > 0$ such that the equilibrium of the equation under consideration is a global attractor for all $\delta \in (0,\delta_j]$ independently on β_0,θ .

Розглядаються диференціальні рівняння з запізненням

$$P'(t) = \frac{\beta_0 \theta'' [P(t-\tau)]^j}{\theta'' + [P(t-\tau)]''} - \delta P(t), \qquad j = 0, 1,$$
 (*)

що були запропоновані Маккейом та Глассом як модель процесу відтворення червоних кров'яних тілець. Запропоновано нові умови, достатні для того, щоб позитивна точка рівновати наведеного рівняння була глобальним атрактором. На відміну від моделі Ласоти – Важевської встановлено іспування числа $\delta_j = \delta_j(n,\tau) > 0$ такого, що точка рівноваги вказаного рівняння є глобальним атрактором для всіх $\delta \in (0,\delta_i]$ незалежно від β_0,θ .

1. Let us consider the delay differential equations

$$x'(t) = -\delta x(t) + \frac{p}{1 + [x(t - \tau)]^n}, \quad p, \delta > 0,$$
 (1)

$$x'(t) = -\delta x(t) + \frac{px(t-\tau)}{1 + [x(t-\tau)]^n}, \quad p, \delta > 0,$$
 (2)

with initial conditions $x(s) = \gamma(s)$, $\gamma \in C([-\tau, 0], R_+)$. These equations were proposed in 1977 by Mackey and Glass [1], as models of hematopoiesis (blood cell production). Here, $x(t) = P(t)\theta^{-1}$ is proportional to the density P(t) of mature cells in blood circulation at the time t; δ , θ , n and p are some positive constants, and τ is the time delay between the production of immature cells in the bone marrow and their maturation for release in the circulation blood stream.

Recently, these equations have attracted a lot of interest. There is a number of analytical results concerning oscillations, global attractivity, periodicity and bifurcations of solutions to Eqs. (1), (2) (see, for example, [2-7]). Here, we investigate the attractivity properties of equilibrium points of these delay differential equations. The delay difference equations which are discrete analogs of Eqs. (1), (2) were investigated in [8] and [9].

Taking into account the form of the right-hand sides of (1, 2), we can obtain at most two constant solutions $x_1(t) \equiv 0$ and $x_2(t) \equiv x_2 > 0$ of them. Below, we study the global asymptotic stability of $x_2(t)$. To stress the importance of investigations of this sort, we recall the following sentence from [1]: "In normal healthy adults, circulating levels of granulocytes are either constant or show a mild oscillations with a period of 14 to 24 days."

The principal results of the paper are presented in the following two theorems:

Theorem 1. Suppose that one of the following conditions is satisfied:

(i) $n \in (0, 1]$;

(ii)
$$n > 1$$
; $\delta \in (0, \delta_1(n, \tau)]$, where $\delta_1(n, \tau) \stackrel{\text{def}}{=} \frac{1}{\tau} \ln \frac{n^2 + 1}{n^2 - n}$;

(iii) n > 1, $\delta > \delta_1(n, \tau)$ and

$$\frac{p}{\delta} < \frac{2n(1-\alpha)\left[1+\sqrt{1+4\alpha(1-\alpha)}\right]^{1/n}}{\left[2n(1-\alpha)-1-\sqrt{1+4\alpha(1-\alpha)}\right]^{1+1/n}} \stackrel{\text{def}}{=} \eta(\delta,\tau,n), \quad \alpha = \exp(-\delta\tau).$$

Then the positive equilibrium of Eq. (1) is a global attractor.

Remark 1. The sufficient conditions for global attractivity of (1) given in [2] were proved only for $(p + \delta \tau) < 1$. In [4, Theorem 3.3] Karakostas, Philos, and Sficas proved that, under assumptions

$$\Gamma_1: \left\{ n \ge 1 \text{ and } n^2 \left(\frac{p}{\delta}\right)^{2n} \left(1 + \left[\frac{p}{\delta}\right]^n\right)^{n-3} \le 1 \right\}$$

or

$$\Gamma_2: \left\{ n \in (0,1] \text{ and } n^2 \left(\frac{p}{\delta}\right)^{2n} \le \left(1 + \left[\frac{p}{\delta}\right]^n\right)^{n^2 + 1} \left\{ \left[\frac{p}{\delta}\right]^n + \left(1 + \left[\frac{p}{\delta}\right]^n\right)^n \right\}^{1-n} \right\},$$

 x_2 attracts all solutions. Moreover, if

$$[0 < n \le 1]$$
 or $\left[n > 1 \text{ and } \frac{p}{\delta} < \frac{n}{[n-1]^{1+1/n}}\right]$, (3)

then x_2 is uniformly asymptotically stable. Clearly, the restrictions in (3) are weaker than corresponding inequalities in Γ_1 and Γ_2 . Note also that the global attractivity conditions given in [8] for discrete version of (1) and transformed for the continuous case have the form

$$[0 < n \le 1]$$
 or $\left[n > 1 \text{ and } \frac{p}{\delta} < \frac{4n}{[n+1]^{1+1/n}[n-1]^{1-1/n}}\right]$. (4)

However, conditions (4) are weaker than (3) due to the inequality

$$\frac{n}{[n-1]^{1+1/n}} \ge \frac{4n}{[n+1]^{1+1/n}[n-1]^{1-1/n}} \text{ for all } n \in (1, +\infty),$$

where equality holds only for n = 3. Since $\eta(\delta, \tau, n) > n[n-1]^{-1-1/n}$, the third estimate of Theorem 1 is sharpest here.

Theorem 2. Let $\frac{p}{\delta} > 1$. Then the positive equilibrium of Eq. (2) is a global attractor if one of the following conditions holds:

(i) $n \in (.0, 2]$;

(ii)
$$n > 2$$
, $\delta \in (0, \delta_2(n, \tau)]$, where $\delta_2(n, \tau) \stackrel{\text{def}}{=} \frac{1}{\tau} \ln \frac{n^2 - 2n + 2}{n^2 - 3n + 2}$;

(iii) n > 2, $\delta > \delta_2(n, \tau)$ and

$$\frac{p}{\delta} < \frac{2n(\alpha - 1)}{1 + 2(n - 1)(\alpha - 1) + \sqrt{1 + 4\alpha(1 - \alpha)}} \stackrel{\text{def}}{=} \gamma(\delta, \tau, n), \quad \alpha \stackrel{\text{def}}{=} \exp(-\delta\tau).$$

Remark 2. Let us compare these conditions with before known. The corresponding result [2] has implicit form and is valid only in the case where $\delta \tau \in \left(0, \frac{\sqrt{5}-1}{2}\right)$. In [4, Theorems 4.4 and 4.5], Karakostas, Philos, and Sficas proved that, under conditions

$$\Gamma_3$$
: $\left\{n > 1 \text{ and } 1 < \frac{p}{\delta} \le \frac{n}{n-1}\right\}$ or Γ_4 : $\left\{n \in (0,1] \text{ and } 1 < \frac{p}{\delta} \le \frac{1}{1-\alpha}\right\}$,

any solution with initial value $\gamma \in C([-\tau, 0], R_+)$ tends to x_2 as $t \to +\infty$.

Furthermore, if additionally to Γ_3 , $\frac{p}{\delta} \le (n+2)n^{-1}$ then x_2 is uniformly asymptotically stable. It should be noted that attractivity conditions of [7], transformed for the continuous case, have the form

$n \in (0,1]$	$\frac{p}{\delta} > 1$
n > 1	$\frac{p}{\delta} < \frac{n}{n-1}$
n > 1	$\frac{p}{\delta} \le \frac{4n}{(n-1)^2}$
$n > n_* > 1$, where $n_* < 1.25$ is some real number	$\frac{\delta}{p} > \frac{n-2}{n}$

These conditions improve assumptions of [4], but are less exact than condition (iii) of Theorem 2, since $\gamma(\delta, \tau, n) > (n-2)^{-1}n$.

There is an interesting distinction between Eqs. (1), (2) and such well-known models as Lasota and Wazewska equation [10] or Nicholson's blowflies equation (see, e.g., [11]), namely, Theorems 1 and 2 imply the existence of $\delta_j^* = \delta_j(n, \tau)$ such that steady state of Eq. (*), j = 0, 1, is a global attractor for all $\delta \in (0, \delta_j^*]$ independently on β_0 , θ . It should be noted that this effect couldn't be proved within approaches of [4, 8].

The criterion for local asymptotic stability of the equilibrium x_2 of Eqs. (1), (2) can be obtained by application of the Hayes criterion [12] to linear parts of these equations at $x(t) = x_2$. Below, Fig. 1 and 2 show the domains of the parameter space

 $\left(\delta, \frac{p}{\delta}\right)$ where the solution $x(t) = x_2$ is a global attractor and where it is locally asymptotically stable. The view of these pictures suggests us the following.

Conjecture 1. The local exponential stability of the positive equilibrium in Eqs. (1), (2) is sufficient for its global attractivity.

2. Proof of the principle results.

2.1. Preliminaries. The following theorem given by Györi and Trofimchuk in [11] is used in proving our global attractivity results.

Proposition 1. Let us consider delay differential equations of the form

$$x'(t) = -\delta x(t) + pf(x(t-\tau)), \quad p, \, \delta, \, \tau > 0,$$
(5)

with the initial condition $x(s) = \gamma(s), \ \gamma \in C([-\tau, 0], R_+),$

where either

 H_1) $f: [0, +\infty) \to (0, +\infty)$ is a strictly decreasing function or

 H_2) $f: (0, +\infty) \to (0, +\infty)$ is a unitmodal function (that is, has a unique critical point x^* ; we shall write also $x^* = 0$ if H_1 is true). Moreover, $f(x) = xf_1(x)$, $pf_1(0) > \delta$, where $f_1: [0, +\infty) \to (0, +\infty)$ is continuous.

Suppose that x_2 is a unique positive fixed point of the map $\varphi(x) \stackrel{\text{def}}{=} \frac{p}{\delta} f(x)$. Let us denote by $\psi \colon (0, \varphi(x^*)) \to [x^*, +\infty)$ the map which is inverse for $\varphi(x)$ on $[x^*, +\infty)$ and set $\theta(x) = x - \exp(-\delta \tau) \varphi(x)$. Then, under one of the conditions H_1 or H_3 [11] the maps

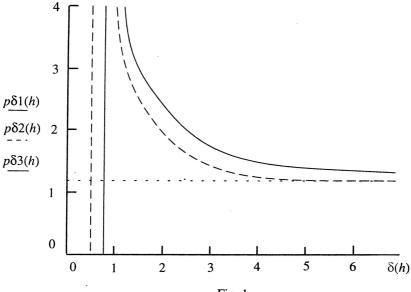


Fig. 1

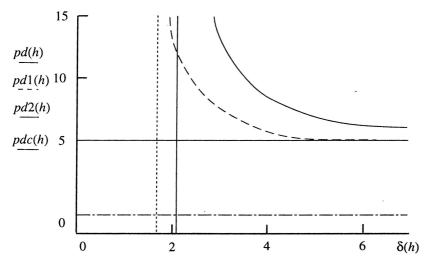


Fig. 2

$$\varphi(x) = \frac{p}{\delta}f(x): R_+ \to R_+ \text{ and}$$

$$\zeta(x) = (1 - \exp(-\delta\tau))\varphi(x): R_+ \to R_+$$

$$\xi(x) = \theta^{-1}((1 - \exp(-\delta \tau))\varphi(x)) : [a, b] \to [a, b],$$

are well defined and unimodal for some a, b > 0: $a \le x_2 \le b$ and $\varphi(x_2) = \zeta(x_2) = \xi(x_2) = x_2$. Moreover, if x_2 is a global attractor for one of these three maps, than the equilibrium x_2 of Eq. (5) is globally attracting.

To analyze attracting sets of some one-dimensional map, we can apply various tools. For example, in [11], the theory of one-dimensional maps with negative Schwarzian derivative was used.

Definition 1. Let f be a real function having at least three continuous derivatives. The Schwarzian derivative of f at point x, denoted by (Sf)(x), is given by

$$(Sf)(x) = \frac{f'''(x)}{f'(x)} - \frac{3}{2} \left(\frac{f''(x)}{f'(x)}\right)^2.$$

The following formula can be checked by direct computation:

$$S(f \circ g)(x) = (Sf)(g(x))(g'(x))^{2} + (Sg)(x). \tag{6}$$

Proposition 1 and Singer's results ([13], see also [14] imply the following statement deduced in [11]:

Corollary 1. Assume that one of the conditions H_1 or H_3 is satisfied. If f(x) is three times continuously differentiable and

(i)
$$2f'(x)f'''(x) < 3(f''(x))^2$$
 for all $x > 0$, $x \neq x^*$, with

(ii)
$$0 > (1 - \exp(-\delta \tau)) \frac{p}{\delta} f'(x_2) > -\frac{1}{2} (1 + \sqrt{1 + 4 \exp(-\delta \tau)(1 - \exp(-\delta \tau))}),$$

then the equilibrium point x_2 of Eq. (5) is a global attractor.

Unfortunately, the first condition of Corollary 1 doesn't hold for all values of parameters in Eqs. (1), (2). Therefore, we need other methods to analyze a global attractor of one-dimensional maps associated with our delay-differential equations. The following proposition is sufficient for this purpose:

Proposition 2. Let $g: [a,b] \rightarrow [a,b]$, $g(x) \in C[a,b]$ be such that the equation $g^2(x) = x$ has the unique solution $x = x_2$. Then x_2 is a global attractor of the discrete dynamical system $x_{n+1} = g(x_n)$.

Proof. First of all, we note that the ω -limit set $\omega([a,b]) = [\alpha,\beta] \ni x_2$ of the discrete dynamical system $x_{n+1} = g(x_n)$ is global attractor (lemma 3.1.2 of [15]), so we need only to prove that $[\alpha,\beta] = x_2$. By contrary, suppose that $\alpha < \beta$. Since ω -limit set is an invariant set, we have that g maps $[\alpha,\beta]$ onto itself. Thus, the uniqueness of fixed point x_2 for g^i , i=1,2, implies that $g^i(x) > x$ for all $x \in [\alpha, x_2)$ and $g^i(x) < x$ for all $x \in (x_2,\beta]$, i=1,2. Moreover, there exist $v \in [\alpha, x_2)$ and $u \in (x_2,\beta]$ such that g(v) = 1, g(u) = 0. Finally,

$$g^{2}([v, x_{2}]) \supseteq g([x_{2}, 1]) \supseteq g([x_{2}, \mu]) \supseteq [0, x_{2}]$$

and, therefore, $g^2(\zeta) = 0$ for some $\zeta \in [v, x_2]$ that contradicts the inequality $g^2(x) > x$ being valid for all $x \in [\alpha, x_2)$.

Proposition 1 and 2 imply the following consequence:

Corollary 2. Assume that the equation $\varphi^2(x) = x$, x > 0 has a unique solution $x = x_2$. Then x_2 is a global attractor of Eq. (5).

2.2. Global attractivity in Eq. (1). Let us apply Corollaries 1 and 2 to (1). This system has only one equilibrium $x_2(t) \equiv x_2 > 0$ satisfying the algebraic equation

$$x_2^{n+1} + x_2 = \frac{p}{\delta}. (7)$$

To indicate the dependence x_2 on $\frac{p}{\delta}$, we write $x_2 = x_2 \left(\frac{p}{\delta}\right)$. Obviously, $x_2(z)$ is an increasing function in z > 0.

Lemma 1. If
$$n > 1$$
 then $(Sf_1)(x) < 0$, where $f_1(x) = \frac{1}{1+x^n}$.

Proof. We note that $f_1(x) = r(x^n)$, where r(x) is a fractional linear transformation. Since $(Sr)(x) \equiv 0$ for any fractional linear transformation [13], we obtain from (6)

$$(Sf_1)(x) = (S(x^n))(x) = \frac{(-n^2 + 1)}{2x^2} < 0$$
 for all $x > 0$ and $n > 1$,

i. e., lemma is proved. Thus, if n > 1, we can apply Corollary 1. Let $\alpha = e^{-\delta \tau}$. Then, if

$$0 > -(1-\alpha)\frac{p}{\delta} \frac{nx_2^{n-1}}{\delta(1+x_2^n)^2} > -\frac{1}{2} (1+\sqrt{1+4\alpha(1-\alpha)}), \tag{8}$$

then x_2 is a global attractor of Eq. (1). Taking into account relation (7), we transform (8) into the inequality

$$x_2 > \frac{p}{\delta} \left[1 - \frac{1 + \sqrt{1 + 4\alpha(1 - \alpha)}}{2n(1 - \alpha)} \right]. \tag{9}$$

Since $x_2 > 0$ and the right-hand side of (9) is nonpositive for $\delta \in \left[0, \frac{1}{\tau} \ln \frac{n^2 + 1}{n^2 - 1}\right]$, n > 1, we obtain the second condition of Theorem 1.

Let now $\delta > \delta_1(n, \tau)$, n > 1. Since $x_2(z)$ is an increasing function, we have that inequality (8) is satisfied for all $\frac{p}{\delta} < z_0$ with

$$(1 - \exp(-\delta \tau)) \frac{p_0}{\delta_0} \frac{n x_2^{n-1}(z_0)}{\left(1 + x_2^n(z_0)\right)^2} = \frac{1}{2} \left(1 + \sqrt{1 + 4 \exp(-\delta_0 \tau)(1 - \exp(-\delta_0 \tau))}\right)$$
and $x_2^{n+1}(z_0) + x_2(z_0) = \frac{p_0}{\delta_0} = z_0$.

Solving these equations, we find

$$x_2(z_0) = \frac{p_0}{\delta_0} \left[1 - \frac{1 + \sqrt{1 + 4\alpha(1 - \alpha)}}{2n(1 - \alpha)} \right] \text{ and } z_0 = \eta(\delta, \tau, n).$$

Thus, the global attractivity condition for Eq. (1) has the form

$$\frac{p}{\delta} < z_0 = \eta(\delta, \tau, n) \tag{10}$$

and the third condition of Theorem 1 is established.

Now let us apply the Corollary 2 to investigate (1).

Lemma 2. Let $\varphi_1(x) \stackrel{\text{def}}{=} \frac{p}{\delta} f_1(x)$. If $n \in (0; 1]$, then the map $\varphi_1: R_+ \to R_+$ has a unique positive periodic point x_2 and $\varphi_1(x_2) = x_2$.

Proof. Let us consider the set of all positive 2-periodic points of the map φ_1 . These points are determined from the equation $\varphi_1^2(a) = a$, a > 0 that can be writen as

$$b_1(a) = \frac{(1+a^n)^n}{a} = \left[\frac{p}{\delta}\right]^n \left(\frac{p}{\delta} - a\right)^{-1} \stackrel{\text{def}}{=} -b_2(a).$$

Finally, we note that the functions $b_1(a)$ and $b_2(a)$ are strictly decreasing for $n \in (0; 1]$ and $a \in \left(0, \frac{p}{\delta}\right)$.

Remark 3. Fig. 1 below depicts the curves

$$p\,\delta3(h) = \left\{\frac{p}{\delta} = \eta(\delta,\tau,n)\right\}; \quad p\,\delta2(h) = \left\{\frac{p}{\delta} = \frac{n}{[n-1]^{1+1/n}}\right\},$$

and the neutral stability curve

$$\delta(t) = -t \operatorname{ctg}(t), \quad p \, \delta \, 1(h) = \frac{p(t)}{\delta(t)} =$$

$$= \frac{n \cos(t)}{(-1 - n \cos(t))^{1/n}} [1 + n \cos(t)]^{-1}, \quad t \in (\pi/2, \pi),$$

which is determined from the Hayes criterion [12].

2.3. Global attractivity in Eq. (2). Let us consider the delay-differential Eq. (2).

In this case, $f_2(x) = px(1+x^n)^{-1}$, $\varphi_2(x) = \frac{p}{\delta}x(1+x^n)^{-1}$. If $p \le \delta$, we have only one constant solution $x_0 = 0$. According to Corollary 12 from [11], this solution is a global attractor independently on τ . Let now $p > \delta$. In this case, $x_0 = 0$ is an unstable equilibrium (see Corollary 12, [11]) and the second constant solution $x_2 = \left(\frac{p}{\delta} - 1\right)^{1/n}$ is appeared.

Lemma 3. If $n \ge 2$, then $(S\varphi_2)(x) < 0$.

Proof. By direct computations, we obtain that

$$(S\varphi_2)(x) = \frac{a_4 x^{4n} + a_3 x^{3n} + a_2 x^{2n} + a_1 x^n}{2x^2 (1 + x^2)^2 (1 + (1 - n) x^n)^2} < 0 \quad \text{for all} \quad x > 0 \quad \text{and} \quad n \ge 2,$$

where

$$a_1(n) = -2n^3 + 2n = -2n(n^2 + 1) < 0,$$
 $a_2(n) = -n(n^3 + 5n - 6) < 0,$ $a_3(n) = n(-2n^3 + 6n^2 - 10n + 6) \le a_3(2) < 0,$ $a_4(n) = -n(n^3 - 4n^2 + 5n - 2) \le 0$ for all $n \ge 2$.

Hence, if $n \ge 2$, we can apply Corollary 1 to (2). Direct calculations show that if

$$\frac{\delta n}{p} > n - 1 - \frac{1 + \sqrt{1 + 4\alpha(1 - \alpha)}}{2(1 - \alpha)},\tag{11}$$

then x_2 is a global attractor of Eq. (2). Since the right-hand side of (11) is nonpositive for $\delta \in \left[0, \frac{1}{\tau} \ln \frac{n^2 - 2n + 2}{n^2 - 3n + 2}\right]$, we obtain the second condition of Theorem 2.

Let now $\delta > x_2(n,\tau)$, $n \ge 2$. Then (11) implies the third condition of Theorem 2. To complete the proof of Theorem 2, we apply Corollary 2 to Eq. (2).

Lemma 4. If $n \in (0, 2]$, then the map $\varphi_2 : R_+ \to R_+$ has a unique positive periodic point x_2 and $\varphi_2(x_2) = x_2$.

Proof. Let us consider the set of all positive 2-periodic points of the map $\varphi_2: R_+ \to R_+$, which are determined from the equation

$$\varphi_2^2(a) = \frac{p}{\delta} \frac{\frac{p}{\delta 1 + a^n}}{1 + \left[\frac{p}{\delta 1 + a^n}\right]^n} = a, \quad a > 0.$$
 (12)

Setting $\omega = 1 + a^n$, we can rewrite (12) as

$$\Psi(\omega) \stackrel{\text{def}}{=} \omega^n - \left(\frac{p}{\delta}\right)^2 \omega^{n-1} + \left(\frac{p}{\delta}\right)^n \omega - \left(\frac{p}{\delta}\right)^n = 0.$$
 (13)

We note that $\psi(1) = 1 - \left(\frac{p}{\delta}\right)^2 < 0$ and that

$$\Psi''(\omega) = (n-1)\omega^{n-3} \left[n\omega - (n-2) \left(\frac{p}{\delta} \right)^2 \right].$$

Now, Lemma 4 follows from the next simple observations:

I. If $n \in (1, 2]$, $\omega \ge 1$, then $\psi''(\omega) > 0$. Since $\psi(1) < 0$ and $\psi(\omega_2) = 0$, where $\omega_2 = 1 + x_2^n$, Eq. (13) has a unique positive solution.

II. If n = 1 or n = 2, $\omega \ge 1$, then Eq. (13) has the unique positive solution $\omega = \frac{p}{8}$.

III. If $n \in (0, 1)$, $\omega \ge 1$, then $\psi''(\omega) < 0$. Since $\psi(1) < 0$ and $\psi(\omega_2) = 0$, so Eq. (13) can have at most two positive solutions ω_1 , ω_2 . Accordingly, Eq. (12) can have at most two positive solutions x_1, x_2 . Since $\psi_2(x_2) = x_2$, there is a unique possibility for the second point, namely, $\psi_2(x_1) = x_1$. However, $Fix(\phi_2) = \{x_2\}$ and Eq. (12) has exactly one positive solutions $a = x_2$.

Remark 4. Fig. 2 shows the curves

$$pd1(h) = \left\{ \frac{p}{\delta} = \gamma(\delta, \tau, n) \right\}, \quad pd2(h) = \left\{ \frac{p}{\delta} = \frac{n}{n-2} \right\}, \quad pdc(h) = \left\{ \frac{p}{\delta} = 1 \right\},$$

and the neutral stability curve

$$\delta(t) = -tctg(t), \quad pd(t) \stackrel{\text{def}}{=} \frac{p(t)}{\delta(t)} = n\cos(t) \left[1 + (n-1)\cos(t)\right]^{-1}, \quad t \in (\pi/2, \pi),$$

which is computed using the Hayes criterion [12].

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