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Mackey–Glass model of hematopoiesis with non-monotone feedback: Stability, oscillation and control ☆

Leonid Berezansky [a], Elena Braverman [b,*], Lev Idels [c]

[a] Dept. of Math, Ben-Gurion University of Negev, Beer-Sheva 84105, Israel
[b] Dept. of Math & Stats, University of Calgary, 2500 University Dr. NW, Calgary, AB, Canada T2N1N4
[c] Dept. of Math, Vancouver Island University (VIU), 900 Fifth St. Nanaimo, BC, Canada V9S5J5

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ABSTRACT

For the blood cell production model with a unimodal (hump) feedback function

$$\frac{dy}{dt} = -\gamma y(t) + \frac{\beta\theta^n y(t-\tau)}{\theta^n + y^n(t-\tau)},$$

we review the known results and investigate generalizations of this equation. Permanence, oscillation and stability of the positive equilibrium are studied for non-autonomous equations, including equations with a distributed delay. In addition, a linear control is introduced, and possibilities to stabilize an otherwise unstable positive equilibrium are explored.

1. Introduction and basic Mackey–Glass models

To explain regulation and control mechanisms in physiological systems, Mackey and Glass pioneered new mathematical models in the influential and highly referenced paper [38]. To describe the Cheyne–Stokes phenomenon, the following model was introduced:

Model 1 (Respiratory Dynamics)

$$\frac{dy}{dt} = \lambda - \frac{\alpha V_m y(t) y^n(t-\tau)}{\theta^n + y^n(t-\tau)}.$$

To model hematopoiesis (the process of production, multiplication, and specialization of blood cells in the bone marrow), two equations were proposed since the nature of the regulatory mechanisms in blood cell production is controversial:

Model 2 (Hematopoiesis with a Monotone Production Rate)

$$\frac{dy}{dt} = -\gamma y(t) + \frac{F_0\theta^n}{\theta^n + y^n(t-\tau)},$$

as well as Model 3 (Hematopoiesis with Unimodal Production Rate)

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* Corresponding author.
E-mail address: maelena@math.ucalgary.ca (E. Braverman).

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$$\frac{dy}{dt} = -\gamma y(t) + \frac{\beta\theta^n y(t-\tau)}{\theta^n + y^n(t-\tau)}, \tag{1.1}$$

where $y(t)$ is the density of cells in the circulation, τ is the maturation delay between the start of the production of immature cells in the bone marrow and their release into circulation, $\theta > 0$ is called a shape parameter, γ is the destruction rate, $\beta > 0$ and $n > 0$. The parameters of the models are nonnegative constants and have to be determined from experimental data related to hematopoiesis production. For detailed biological motivation we refer the reader to [18,38–40].

The present paper is devoted to asymptotic properties (permanence, stability of the positive equilibrium, oscillation and stabilization) of (1.1) and some of its generalizations. The review of the recent results for Models 1 and 2 can be found in [11,12]. Eq. (1.1) after the substitution $x(t) = \theta y(t)$ has the form

$$\frac{dx}{dt} = -\gamma x(t) + \beta\frac{x(t-\tau)}{1+x^n(t-\tau)}, \quad t > 0, \tag{1.2}$$

where the initial function φ is associated with (1.2) for $t \leqslant 0$: $x(t) = \varphi(t)$, where $\varphi \in C[[-\tau, 0], \mathbb{R}^+]$ and $\varphi(0) > 0$, here $\mathbb{R}^+ = [0,\infty), C[D,R]$ is the space or real continuous functions $f : D \to R$.

Along with classical Mackey–Glass model (1.1), the following modifications were introduced and studied in the literature.

1. In [4,5,7,51,52,55] the non-autonomous Mackey–Glass equation

$$\frac{dx}{dt} = -\gamma(t)x(t) + \beta(t)\frac{x(t-\tau(t))}{1+x^n(t-\tau(t))} \tag{1.3}$$

was studied, where $\gamma, \beta \in C[\mathbb{R}^+, (0,\infty)], \tau \in C[\mathbb{R}^+, \mathbb{R}^+]$.

2. In [26,54,56] the integro-differential non-autonomous model

$$\frac{dx}{dt} = -\gamma(t)x(t) + \beta(t)\int_0^\infty \frac{P(r)x(t-r)dr}{1+x^n(t-r)} \tag{1.4}$$

was investigated, where $\gamma, \beta \in C[\mathbb{R}^+, (0,\infty)], P : \mathbb{R}^+ \to \mathbb{R}^+$ is assumed to be piecewise continuous, $\int_0^\infty P(s)ds = 1$.

3. In [10,16] the equation with a distributed delay

$$\frac{dx}{dt} = -r(t)\left[\gamma x(t) - \beta\int_{h(t)}^t \frac{x(s)}{1+x^n(s)} d_sR(t,s)\right], \tag{1.5}$$

with $\gamma > 0, \beta > 0$ was considered, where r satisfies

$$r \in L_\infty[\mathbb{R}^+, \mathbb{R}^+], \qquad \int^\infty r(s)ds = \infty. \tag{1.6}$$

Here L_∞ is the space of essentially bounded functions, and $R(t,\cdot)$ is a left continuous function such that

$$R(t,\cdot) \text{ is nondecreasing }; \quad R(t,s) = 0, \quad s \leqslant h(t); \quad R(t,t^+) = 1 \quad \text{for any } t \tag{1.7}$$

for some Lebesgue measurable function h satisfying $h(t) \leqslant t, \lim_{t\to\infty} h(t) = \infty$.

If $R(t,s) = \chi_{(h(t),\infty)}(s)$, where χ_I is the characteristic function of set I, then (1.5) takes the form

$$\frac{dx}{dt} = -r(t)\left[\gamma x(t) - \beta\frac{x(h(t))}{1+x^n(h(t))}\right]. \tag{1.8}$$

For $R(t,s) = \chi_{(t-\tau,\infty)}(s), r(t) \equiv 1$, we obtain Eq. (1.2). If $R(t,s) = \int_{h(t)}^s P(t,\tau)\,d\tau$, then (1.5) is the integro-differential equation

$$\frac{dx}{dt} = -r(t)\left[\gamma x(t) - \beta\int_{h(t)}^t \frac{P(t,s)x(s)}{1+x^n(s)} ds\right], \tag{1.9}$$

where $\int_{h(t)}^t P(t,s)ds \equiv 1$. We consider Eq. (1.5) with the initial condition

$$x(t) = \varphi(t), \quad t \leqslant 0, \tag{1.10}$$

where

$$\varphi \in C[(-\infty, 0], \mathbb{R}^+] \text{ is bounded}, \quad \varphi(0) > 0 \tag{1.11}$$

(under this condition, the Lebesgue–Stieltjes integral in the right-hand side of (1.5) exists for any $R(t,s)$ as described above).

It is important to remark that all results obtained in the present paper for Eq. (1.5) are also valid for Eqs. (1.8) and (1.9) with the same r, h, γ and β.

The paper is organized as follows. In Section 2, for non-autonomous models with both concentrated and distributed delays, we examine existence, positivity and permanence of global solutions. In Section 3, global stability conditions for autonomous models are reviewed, and new stability results for non-autonomous equations with asymptotically constant parameters are obtained. Oscillation and non-oscillation about the positive equilibrium are examined in Section 4. Section 5 explores the possibility of stabilization with linear non-delayed and delayed types of control. Results obtained for some modifications of the Mackey–Glass model are described in Section 6. Finally, discussion and a list of open problems and conjectures are presented in Section 7.

2. Existence, boundedness and permanence

Definition 2.1 [23]. An equation is **uniformly permanent** if there exist positive numbers μ and M such that

$$\liminf_{t\to\infty} x(t) \geqslant \mu, \quad \limsup_{t\to\infty} x(t) \leqslant M$$

for any solution $x(t)$ of the equation. A positive solution x is **persistent** if $\lim\ \inf_{t\to\infty} x(t) > 0$. A persistent solution is **permanent** if in addition it is bounded.

In [4] Eq. (1.3) in the form

$$\frac{dx}{dt} = -\gamma(t)x(t) + \frac{\beta(t)x(h(t))}{1+x^n(h(t))}, \tag{2.1}$$

with initial conditions (1.10) was examined, under the following assumptions:

(a1) $n > 0, \beta(t) \geqslant 0, \gamma(t) \geqslant 0$ are Lebesgue measurable essentially locally bounded functions;
(a2) h is a Lebesgue measurable function, $h(t) \leqslant t, \lim_{t\to\infty} h(t) = \infty$;
(a3) $\varphi : (-\infty, 0) \to \mathbb{R}$ is a Borel measurable bounded function, $\varphi(t) \geqslant 0$ and $\varphi(0) > 0$;
(a4) $\lim\ \inf_{t\to\infty} \gamma(t) \geqslant \gamma > 0$.

Eq. (2.1) is a partial case of the equation with a distributed delay

$$\frac{dx}{dt} = -\gamma(t)x(t) + \beta(t)\int_{h(t)}^{t} \frac{x(s)}{1+x^n(s)} d_sR(t,s). \tag{2.2}$$

By the solution of (2.2) with initial function (1.10) we understand the function which satisfies (2.2) almost everywhere for $t \geqslant 0$ and (1.10) for $t < 0$.

Theorem 2.2. *Let (a1), (a2), (a4),(1.7) and (1.11) hold. Then Eq. (2.2) with initial conditions (1.10) has a positive global solution on* $[0,\infty)$.

Proof. Existence of a positive local solution x of (2.2) follows from [8, Theorem 1]. Suppose that $[0, c)$ is the maximal existence interval for the solution x. This can be either a global solution ($c = \infty$), or one of the equalities $\lim_{t\to c^-} x(t) = -\infty$ or $\lim_{t\to c^-} x(t) = \infty$ may hold. As far as $x(t) > 0$, a solution of (2.2), (1.10) is not less than the solution of the initial value problem $\frac{dv}{dt} = -\gamma(t)v(t),\ v(0) = \varphi(0) > 0$,which is positive and global. To complete the proof, we should only exclude the possibility $\lim_{t\to c^-} x(t) = \infty$. Denote $M = \sup_{t\leqslant 0} \varphi(t) > 0$ and $y(t) = \max\{\sup_{0<s\leqslant t} x(s), M\}$, here $M < \infty$ due to (1.11) and $y(0) = M$. We have

$$\frac{dx}{dt} \leqslant \beta(t)\int_{h(t)}^{t} x(s)d_sR(t,s) \leqslant \beta(t)y(t), \quad t \in [0,\infty).$$

Hence

$$x(t) \leqslant x(0) + \int_0^t \beta(s)y(s)ds \leqslant M + \int_0^t \beta(s)y(s)ds, \quad t \in [0,\infty).$$

Then

$$y(t) \leqslant M + \int_0^t \beta(s)y(s)ds.$$

So, by the Gronwall–Bellman inequality,

$$x(t) \leqslant y(t) \leqslant Me^{\int_0^t \beta(s)ds}.$$

Therefore x cannot satisfy $\lim_{t\to c^-} x(t) = \infty$ for any finite c, which concludes the proof. □

Theorem 2.3. [4, Theorem 2] *Suppose (a1)–(a4) hold, either* $n \geqslant 1$ *or*

$$0 < n < 1 \text{ and } \sup_{t\geqslant 0} \int_{h(t)}^{t} \gamma(s)ds < \infty.$$

Then any solution of (2.1), (1.10) is bounded for all $t > 0$.

The following example illustrates the importance of condition (a4) in the assumptions of Theorem 2.3.

Example 2.4. Let $n = \frac{1}{2}, \beta(t) = 1, h(t) = t, \gamma(t) = \frac{1}{1+\sqrt{\ln t}} - \frac{1}{t \ln t}, t \geqslant 3$. All the conditions of Theorem 2.3 but (a4) hold, however the unbounded function $x(t) = \ln t$ is a solution of Eq. (2.1).

Theorem 2.5. [4, Theorem 3] *(1) Suppose (a1)–(a3) hold and*

$$\inf_{t<0} \varphi(t) > 0, \quad \varphi(0) > 0, \quad \lim_{t \geqslant 0} \inf \frac{\beta(t)}{\gamma(t)} = \lambda > 1. \tag{2.3}$$

Then any **bounded** *solution of (2.1), (1.10) is persistent.*

(2) Suppose (a1)–(a4) and (2.3) hold and either $n \geqslant 1$ or

$$0 < n < 1 \text{ and } \sup_{t \geqslant 0} \int_{h(t)}^{t} \gamma(s) ds < \infty.$$

Then any solution of (2.1), (1.10) is persistent.

For the general equation

$$x'(t) = r(t) \left[\int_{h(t)}^{t} f(x(s)) d_s R(t,s) - x(t) \right], \quad t \geqslant 0, \tag{2.4}$$

the uniform permanence result was obtained in [16].

Lemma 2.6 [16, Theorem 2.6]. *Let (1.6), (1.7), (a2) and (1.11) be satisfied, $f : \mathbb{R}^+ \to \mathbb{R}^+$ be a continuous function, $f(x) > x$ for $0 < x < K$ and $0 < f(x) < x$ for $x > K$. Then Eq. (2.4) is uniformly permanent, and any solution of (2.4) satisfies*

$$\lim_{t \to \infty} \inf x(t) \geqslant \mu, \quad \lim_{t \to \infty} \sup x(t) \leqslant M, \tag{2.5}$$

where

$$M = \max_{x \in [0,K]} f(x), \quad \mu = \min_{x \in [K,M]} f(x). \tag{2.6}$$

Let $f(x) = \frac{\beta x}{\gamma(1+x^n)}$, where $n > 0$ and $\beta > \gamma$. If $0 < n \leqslant 1$, then on the interval $[0, K]$ the function $f(x)$ has its maximum $K = \left(\frac{\beta}{\gamma} - 1\right)^{\frac{1}{n}}$ at $x = K$; if $n > 1$ then $f(x)$ attains its maximum $M = \frac{\beta}{n\gamma}(n-1)^{1-1/n}$ at $x = (n-1)^{-1/n}$. We immediately obtain the following result.

Theorem 2.7. *Let (1.6), (1.7), (a2) and (1.11) be satisfied, $\beta > \gamma > 0$. If $0 < n \leqslant 1$, then all solutions of (1.5), (1.10) are uniformly permanent and converge to the unique positive equilibrium K. If $n > 1$ then any solution of (1.5), (1.10) satisfies (2.5) with*

$$M = \frac{\beta}{n\gamma}(n-1)^{1-1/n}, \quad \mu = \min\left\{ \left(\frac{\beta}{\gamma} - 1\right)^{1/n}, \frac{\beta M}{\gamma(1+M^n)} \right\}. \tag{2.7}$$

If in addition $\frac{\beta}{\gamma} > \frac{n}{n-1}$, then $\mu = \frac{\beta M}{\gamma(1+M^n)}$.

Consider model (1.3), where $\gamma, \beta \in C[\mathbb{R}^+, (0, \infty)], \tau \in C[\mathbb{R}^+, \mathbb{R}^+]$, and γ, β, τ are all $\omega-$periodic functions. Existence of positive periodic solutions for different modifications of (1.3) was examined in [5,26,49,51,52,54–57].

Theorem 2.8. [51, Corollary 3.3] [52,55] *Let $\int_0^{\omega} \gamma(s) ds > 0$ and $\min_{0 \leqslant t \leqslant \omega}[\beta(t) - \gamma(t)] > 0$, then there exists at least one positive periodic solution of Eq. (1.3).*

For model (1.4) the following result was obtained in [26, Corollary 3.3] and [54, Theorem 4.1].

Theorem 2.9. *Let $\gamma \in C[\mathbb{R}, \mathbb{R}], \beta \in C[\mathbb{R}, (0, \infty)], \gamma, \beta$ be $\omega-$periodic functions, $\int_0^{\omega} \gamma(t) dt > 0, P \in C[(0, \infty), \mathbb{R}^+]$, $\int_0^{\infty} P(s) ds = 1$ and $\min_{0 \leqslant t \leqslant \omega}[\beta(t) - \gamma(t)] > 0$. Then Eq. (1.4) has at least one positive $\omega-$periodic solution.*

3. Stability

Model (1.2) has the trivial equilibrium, and if we assume that $\beta > \gamma > 0$, then Eq. (1.2) has a positive equilibrium

$$K = \left(\frac{\beta}{\gamma} - 1\right)^{1/n}. \tag{3.1}$$

Further, the following standard definitions will be used.

Definition 3.1. We will say that the equilibrium solution $x = K$ of model (1.2) is **(locally) stable**, if for any $\varepsilon > 0$ there exists $\delta > 0$ such that for every initial conditions, the inequality $|\varphi(t) - K| < \delta$ for $t \leqslant 0$ implies $|x(t) - K| < \varepsilon$ for the solution x. If, in addition, for any such solution $\lim_{t\to\infty} x(t) = K$, then the solution $x = K$ is **locally asymptotically stable (LAS)**. The equilibrium K is **globally asymptotically stable (GAS)** for initial conditions in the open set $Q_0 \subset \mathbb{R}$ if it is an attractor for all solutions $x(t)$ with the initial conditions in the open set $Q_0 \subset \mathbb{R}$, i.e. $\lim_{t\to\infty} x(t) = K$, and it is also locally stable.

We will use the same definition for solutions of non-autonomous equations with a positive equilibrium, if it exists. Some helpful facts for $f(x) = \frac{x}{1+x^n}$ are listed below.

$f'(x) = \frac{1-(n-1)x^n}{(1+x^n)^2}, f''(x) = \frac{nx^{n-1}[-(n+1)+(n-1)x^n]}{(1+x^n)^3}, f'(K) = \frac{\gamma}{\beta^2}[n\gamma - (n-1)\beta]$, and the inflection point is $c = \left(\frac{n+1}{n-1}\right)^{1/n}$; $|f'(x)|$ has its maximum at either $x = 0$ or $x = c, |f'(c)| = \frac{(n-1)^2}{4n}$, $|f(x)| \leqslant C$, where $f(x)$ attains its maximum on $[0,\infty)$ at $x = 1/(n-1)^{1/n}$ and $C = (n-1)^{(n-1)/n}/n$ for $n > 1$, while $C = 1$ for $n = 1$, and $f(x)$ is unbounded for $0 < n < 1$. For the equation

$$\frac{dx}{dt} = -\gamma x(t) + f(x(t-\tau)), \tag{3.2}$$

where $f(x)$ is a unimodal (see the definition in [46]) feedback function for $n > 1$, the following lemma is a special case of the result obtained in [46].

Lemma 3.2 [46, Propositions 3.1 and 3.2]. *If $f'(0) < \gamma$, where $f(x) = \frac{\beta x}{1+x^n}$, then for all $\tau \geqslant 0$ the trivial equilibrium of Eq. (3.2) with this f is globally attractive.*

The statement of Lemma 3.2 immediately implies the following result.

Theorem 3.3. *If $n > 1$ and $\beta < \gamma$, then the trivial solution of Eq. (1.2) is a global attractor.*

Theorem 3.4. [4, Theorem 4] *Suppose (a1)–(a3) hold and*

$$\limsup_{t\to\infty} \frac{\beta(t)}{\gamma(t)} = \lambda < 1, \quad \int_0^\infty \gamma(s)ds = \infty, \quad \sup_{t<0} \quad x(t) < \infty,$$

then $\lim_{t\to\infty} x(t) = 0$, where $x(t)$ is a solution of Eq. (2.1).

To study stability of the nontrivial equilibrium, henceforth assume that the condition

$$\beta > \gamma$$

holds. For the nontrivial equilibrium K defined by (3.1), the substitution $y = x - K$ in (1.2) produces

$$\frac{dy}{dt} = -\gamma y(t) - \beta\left[\frac{K}{1+K^n} - \frac{y(t-\tau)+K}{1+(y(t-\tau)+K)^n}\right]$$

and the corresponding linearized equation has the form

$$\frac{dy}{dt} = -\gamma y(t) + \gamma\alpha y(t-\tau),$$

where

$$\alpha = 1 - n + \gamma n/\beta. \tag{3.3}$$

We will further apply Lemma 3.5 which is based on classical results (see, for example, [17,19]). Consider the linear equation

$$\frac{dy}{dt} + ay(t) + by(t-\tau(t)) = 0, \tag{3.4}$$

where $a > 0, b$ are constants, $t - \tau(t) \leqslant \tau_0$ for some $\tau_0 > 0$.

Lemma 3.5. *Suppose either $|b| < a$ or $0 < b\tau_0 < \frac{3}{2}$. Then Eq. (3.4) is asymptotically stable. If $\tau(t) = \tau_0$ is a constant then the inequality $0 < b\tau_0 < \frac{\pi}{2}$ is a sufficient asymptotic stability condition for (3.4).*

We immediately obtain the delay-independent stability result.

Theorem 3.6. *The positive equilibrium K of Eq. (1.2) is LAS for any delay τ if and only if one of the following two conditions holds: (i) $0 < n \leqslant 2$; (ii) $n > 2$ and $\frac{\beta}{\gamma} < \frac{n}{n-2}$.*

As a corollary of [16, Theorem 4.3], we deduce the result earlier obtained in [20, Theorem 2].

Theorem 3.7. *If either $0 < n \leqslant 2$ or $n > 2$ and $\frac{\beta}{\gamma} < \frac{n}{n-2}$ then the positive equilibrium K of Eq. (1.2) is GAS for any delay τ.*

Based on Lemma 3.5, the delay-dependent condition can be expressed as follows.

Theorem 3.8. *Let α be defined by (3.3). If $\alpha < 0$ and $-\alpha\tau e^{\gamma\tau} < \pi/2$, then the positive equilibrium K of (1.2) is LAS.*

Let

$$\gamma_0(h) = \frac{1}{h} \ln \frac{n^2 - 2n + 2}{n^2 - 3n + 2}. \tag{3.5}$$

In [35] the authors considered the equation

$$\frac{dx}{dt} = -\gamma x(t) + \beta \frac{x(t-\tau(t))}{1 + x^n(t-\tau(t))} \tag{3.6}$$

with $\tau \in C[\mathbb{R}^+, [0, h]]$. The proof of the following theorem is based on the earlier general result obtained in [34, Theorem 2.1].

Theorem 3.9. [35, Theorem 3.2] *The positive equilibrium K is a global attractor for (3.6) if one of the following conditions holds:*

(a) $n \in (0, 2]$;
(b)$n > 2$ *and* $\gamma \in (0, \gamma_0(h)]$;
(c)$n > 2, \gamma > \gamma_0(h)$ *and* $-\frac{\gamma}{\alpha} e^{-h\gamma} > \ln \frac{\alpha^2 - \alpha\gamma}{\alpha^2 + \gamma^2}$, *where* α *is defined by (3.3).*

Sufficient LAS conditions for model (1.5) were recently outlined in [10].

Theorem 3.10. [10, Theorem 6] *Suppose that* $\beta > \gamma > 0$ *and at least one of the following conditions holds, where* α *is denoted by (3.3):*

(a) $\frac{\beta}{\gamma} < \frac{n}{n-2}$;
(b) $|\alpha|\gamma \limsup_{t\to\infty} \int_{h(t)}^{t} \left(\int_s^t r(\tau) d\tau \right) d_s R(t, s) < \frac{\gamma(\beta-\gamma)}{\beta + |n(\beta-\gamma)-\beta|}$;
(c) $\alpha < 0$, *or* $\frac{\beta}{\gamma} > \frac{n}{n-1}$, $(1-\alpha)\gamma \limsup_{t\to\infty} \int_{h(t)}^{t} r(s) ds < U \approx 1.425$;
(d) $\alpha < 0, -\alpha\gamma \limsup_{t\to\infty} \int_{h(t)}^{t} r(s) ds < 1 + \frac{1}{e}$.

Then the positive equilibrium K of (1.5) is LAS.

For the global stability of Eq. (2.4), the following results are valid [16, Theorems 3.3–3.5].

Lemma 3.11. *Let* $f : \mathbb{R}^+ \to \mathbb{R}^+$ *be a continuous function. If* $f(0) = 0$ *and* $f(x) < x$ *for any* $x > 0$, *then any positive solution of (2.4) converges to zero. Further, let* $f(x) > x$ *for* $0 < x < K$ *and* $0 < f(x) < x$ *for* $x > K$. *If all positive solutions of the difference equation* $x_{n+1} = f(x_n)$ *tend to* $K > 0$, *then all positive solutions of (2.4) converge to K. If f is three times continuously differentiable and has the only critical point* $x_0 > 0$ *(maximum), its Schwarzian derivative is negative*

$$(Sf)(x) = \frac{f'''(x)}{f'(x)} - \frac{3}{2} \left(\frac{f''(x)}{f'(x)} \right)^2 < 0 \quad \text{for } x \neq x_0$$

and $|f'(K)| \leqslant 1$, *then any positive solution of (2.4) tends to K as* $t \to \infty$.

Lemma 3.12. *Let* $f \in C[\mathbb{R}^+, \mathbb{R}^+], f(x) > x$ *for* $0 < x < K$, *and* $0 < f(x) < x$ *for* $x > K$. *If*

$$1 - \exp\left\{ -\limsup_{t\to\infty} \int_{h(t)}^{t} r(s) ds \right\} < \frac{1}{L}, \tag{3.7}$$

where

$$L = \max\left\{ 1, \sup_{x\in[0,2K]} \left| \frac{f(x) - f(K)}{x - K} \right| \right\}, \tag{3.8}$$

then any positive solution of (2.4) tends to K as $t \to \infty$.

It is easy to check that if at the only maximum point x_0 we have $f(x_0) < x_0$, there is an eventually monotone convergence of all positive solutions of the difference equation $x_{n+1} = f(x_n)$ to K. The proof of the following theorem is based on Lemma 3.11 and Lemma 3.12.

Theorem 3.13. [16, Theorem 3.2] *If either* $0 < n \leqslant 2$ *or* $n > 2$ *and* $1 < \frac{\beta}{\gamma} < \frac{n}{n-2}$, *then all positive solutions of (1.5) tend to the positive equilibrium K as* $t \to \infty$. *If* $n > 2, \frac{\beta}{\gamma} \geqslant \frac{n}{n-2}$ *and* $\limsup_{t\to\infty} \int_{h(t)}^{t} r(s) ds < -\frac{1}{\gamma} \ln \left(1 - \frac{4\gamma n}{\beta(n-1)^2 + 4\beta\gamma} \right)$, *then all positive solutions of (1.5) tend to the positive equilibrium.*

Remark 3.14. Theorem 3.13 is also valid for problem (1.8), e.g., Theorem 3.13 immediately implies a sharper result than Theorem 4.4 in [27], which claims that $1 < \beta/\gamma \leqslant n/(n-1)$ implies stability of (1.2), see the first line in Table 1.

The equation with several delays

$$\frac{dx}{dt} = -r(t)\left[\gamma x(t) - \sum_{j=1}^{m}\beta_j \frac{x(h_j(t))}{1+x^n(h_j(t))}\right] \tag{3.9}$$

with $\sum_{j=1}^{m}\beta_j = \beta$ is a particular case of (1.5), where

$$R(t,s) = \frac{1}{\beta}\sum_{j=1}^{m}\beta_j \chi_{(h_j(t),\infty)}(s), \quad h(t) = \min_{1\leqslant j\leqslant m} h_j(t),$$

thus we immediately obtain the following corollary of Theorem 3.13.

Theorem 3.15. *Let $\beta > \gamma > 0$, (a3) hold and (a2) be satisfied for all $h_j, j = 1,\dots,m$. If either $0 < n \leqslant 2$ or $n > 2$ and $1 < \frac{\beta}{\gamma} < \frac{n}{n-2}$, then all positive solutions of (3.9) tend to the positive equilibrium K as $t \to \infty$.*

If $n > 2, \frac{\beta}{\gamma} \geqslant \frac{n}{n-2}$ and $\limsup_{t\to\infty}\int_{\min_j h_j(t)}^{t} r(s)ds < -\frac{1}{\gamma}\ln\left(1 - \frac{4\gamma n}{\beta(n-1)^2+4\beta\gamma}\right)$, then all positive solutions of (3.9) tend to the positive equilibrium.

Remark 3.16. Let us note the relation between Theorems 3.13, 3.15 and 3.9 for $r \equiv 1$. For $n > 2$ the results of Theorem 3.9 are sharper than those of Theorems 3.13, 3.15 but obtained for a single concentrated delay only. The technique of the proof in [35] cannot be immediately extended to equations with several concentrated or, generally, distributed delays. Had Theorem 3.9 been obtained for arbitrary nonnegative, not necessarily continuous, $\tau(t)$, stability of (3.9) and (2.4) would follow from any of the sufficient conditions in Theorem 3.9. The fact that conditions (b) and (c) of Theorem 3.9 imply stability of (3.9) and (2.4) is a corollary of the mean value theorem [8, Theorem 9] which claims that any solution of either (3.9) or (2.4) also satisfies the equation

$$\frac{dx}{dt} = -r(t)\left[\gamma x(t) - \beta\frac{x(g(t))}{1+x^n(g(t))}\right],$$

where $h(t) \leqslant g(t) \leqslant t$ and $h(t) = \min_{1\leqslant j\leqslant m} h_j(t)$ in (3.9).

For Eq. (2.1), we deduce GAS by applying the following two auxiliary results: the first one is a corollary of Theorem 1 [6] and Lemma 3.1 [9], the second one follows from Lemma 5.3 [11].

Lemma 3.17. [6,9] *Consider the nonlinear delay differential equation*

$$\dot{x}(t) + f_0(t,x(t)) + \sum_{k=1}^{m} f_k(t,x(h_k(t))) + f(t,x(t),x(g(t))) = 0, \tag{3.10}$$

where $f_k(t,\cdot)$ and $f(t,\cdot,\cdot)$ are continuous functions, $f_k(\cdot,x)$ and $f(\cdot,u,v)$ are locally essentially bounded functions, $f_k(t,0) = 0$, there exists $d : \mathbb{R}^+ \to (0,\infty)$ such that $|f(t,u,v)| \leqslant d(t)$, $\lim_{t\to\infty} d(t) = 0$. Suppose that for some given numbers x_1 and x_2 such that $x_1 < 0 < x_2$, there exist $a_k > 0$ and positive essentially bounded on $[0,\infty)$ functions $a_0(t)$ and $b_k(t), k = 0,1,\dots,m$ satisfying at least one of the following conditions:

(1) $0 < a_k \leqslant \frac{f_k(t,x)}{x} \leqslant b_k(t), k = 0,1,\dots,m, x_1 \leqslant x \leqslant x_2,$

$$\limsup_{t\to\infty}\sum_{k=1}^{m}\frac{b_k(t)}{\sum_{i=0}^{m} b_i(t)}\int_{\min_k h_k(t)}^{t}\sum_{k=0}^{m} b_k(s)ds < 1 + \frac{1}{e};$$

(2) $0 < a_0 \leqslant a_0(t) \leqslant \frac{f_0(t,x)}{x} \leqslant b_0(t), \left|\frac{f_k(t,x)}{x}\right| \leqslant b_k(t), k = 1,\dots,m, x_1 \leqslant x \leqslant x_2$, *and there exists $\lambda \in (0,1)$ such that*

Table 1
Sufficient global stability conditions for Model (1.2).

Karakostas et al. [27]	1992	$n > 1$ and $1 < \frac{\beta}{\gamma} \leqslant \frac{n}{n-1}$
Kuang [29]	1993	$n > 1$ and $1 < \frac{\beta}{\gamma} < \frac{4n}{(n-1)^2}$
Gopalsamy et al. [20]	1998	$0 < n \leqslant 2$
Gopalsamy et al. [20]	1998	$n > 2$ and $\gamma \in (0, \gamma_0(\tau)]$ $\gamma_0(\tau) = \frac{1}{\tau}\ln\frac{n^2-2n+2}{n^2-3n+2}$
Gopalsamy et al. [20]	1998	$n > 2, \gamma > \gamma_0(\tau)$ and $\frac{\beta}{\gamma} < \frac{2n\theta}{2(n-1)\theta - 1 - \sqrt{1+4\theta(1-\theta)}}$ $(\theta = 1 - e^{-\gamma\tau})$
Liz et al. [35]	2005	$n > 2, \gamma > \gamma_0(\tau)$ and $-\frac{\gamma}{\alpha}e^{-\tau\gamma} > \ln\frac{\alpha^2-\alpha\gamma}{\alpha^2+\gamma^2}$ $(\alpha = \gamma n/\beta - n + 1 < 0)$

$$\limsup_{t\to\infty}\frac{\sum_{k=1}^{m}b_k(t)}{a_0(t)}\leqslant\lambda.$$

Then all solutions of Eq. (3.10) satisfying the inequality $x_1\leqslant x(t)\leqslant x_2$ *tend to zero.*

Lemma 3.18 [11]. *Let* $f(x)$ *be an increasing twice differentiable function on* $[a,b]$, *where* $a<0<b$, $f(0)=0$. *If* $f''(x)>0$ *for* $a\leqslant 0\leqslant x<c$, $f''(c)=0$ *and* $f''(x)<0$ *for* $c<x\leqslant b$ *then*

$$\frac{f(x)}{x}\leqslant f'(c),\quad x\in[a,b],\ x\neq 0.$$

If $f''(x)<0$ *for* $a<x<b$ *then* $\frac{f(x)}{x}\leqslant f'(0), x\in[a,b], x\neq 0$.

Denote for $n>1$

$$f(x)=\frac{\beta x}{\gamma(1+x^n)},\quad \rho_n=\frac{(n-1)^2}{4n},\quad \bar{x}=(n-1)^{-1/n},\tag{3.11}$$

where $\bar{x}$ is the maximum point of $f(x)$. We use constants μ and M defined in (2.7).

Theorem 3.19. *Suppose* $t-h(t)\leqslant\tau$, $\lim_{t\to\infty}\beta(t)=\beta, \lim_{t\to\infty}\gamma(t)=\gamma$, $n>2$, $\frac{\beta}{\gamma}>\frac{n}{n-1}$, *and either* $\frac{\beta\rho_n}{\gamma}<1$ *or the inequality*

$$\bar{x}=(n-1)^{-1/n}<\mu\tag{3.12}$$

is satisfied together with

$$\beta\rho_n\tau<1+\frac{1}{e}.\tag{3.13}$$

Then K is a global attractor for all positive solutions of non-autonomous Eq. (2.1).

Proof. We will show first that the inequality $\frac{\beta\rho_n}{\gamma}<1$ implies (3.12). We have $f(K)=K, f(\bar{x})=M, f(M)=\mu$. Further, $\max_{x>0}|f'(x)|=\frac{\beta\rho_n}{\gamma}$ and the fact that $\frac{\beta\rho_n}{\gamma}<1$ immediately implies that the map $f(x), x>0$ is contracting. Hence $M-K=|f(K)-f(\bar{x})|<K-\bar{x}, K-\mu=|f(M)-f(K)|<M-K$, thus $K-\mu<K-\bar{x}$ and $\bar{x}<\mu$, which coincides with inequality (3.12).

Further, we apply Lemma 3.17 with $m=1$. After the substitution $x(t)=y(t)+K$, Eq. (2.1) takes form (3.10), where $f_0(t,y)=\gamma y$, $f_1(t,y)=\beta\left(\frac{K}{1+K^n}-\frac{K+y}{1+(K+y)^n}\right)$, $f(t,u,v)=(\gamma(t)-\gamma)u+(\beta(t)-\beta)\left(\frac{K}{1+K^n}-\frac{K+v}{1+(K+v)^n}\right)$. Evidently there exists $A>0$ such that in any interval $[a,b]$+

$$|f(t,u,v)|\leqslant d(t):=A(|\gamma(t)-\gamma|+|\beta(t)-\beta|)\quad\text{for } u,v\in[a,b],$$

where $\lim_{t\to\infty}d(t)=0$. By Theorem 2.7 positive solutions of Eq. (3.10) are bounded. We have $\frac{f_0(t,y)}{y}=\gamma$. Denote $g_1(y)=\frac{K}{1+K^n}-\frac{y+K}{1+(y+K)^n}$, then the function g_1 has the unique minimum at the point $x_0=(n-1)^{-\frac{1}{n}}-K$. The condition $\frac{\beta}{\gamma}>\frac{n}{n-1}$ implies $x_0<0$. By Theorem 2.7, for any $\varepsilon>0$ we can consider the function g_1 on the interval $[\mu-K-\varepsilon, M-K+\varepsilon]$, where $\mu-K-\varepsilon>x_0$. Since $x_0<\mu-K-\varepsilon$ and the function g_1 is monotone increasing on $[x_0, M-K+\varepsilon]$, g_1 also increases on $[\mu-K, M-K+\varepsilon]$. Next, for the function g_1 we have $g_1''(y)>0$ for $y<c_0, g_1''(y)<0$ for $y>c$, and $g_1''(c_0)=0$, where $c_0=\left(\frac{n-1}{n+1}\right)^{\frac{1}{n}}-K$. By Lemma 3.18, $\frac{g_1(y)}{y}\leqslant g_1'(c_0)=\rho_n$. Denote $g(t)=\begin{cases}\frac{g_1(y)}{y}, & y\neq 0,\\ g_1'(0), & y=0.\end{cases}$ Since the function g is a positive continuous function on $[\mu-K, M-K+\varepsilon]$, there exists $\alpha_2>0$, such that $\alpha_2\leqslant\frac{g_1(y)}{y}$. Hence

$$\beta\alpha_2\leqslant\frac{f_1(t,y)}{y}\leqslant\beta\rho_n.$$

Finally, by Lemma 3.17, Part 1, all solutions of Eq. (3.10) tend to zero. Further, if $\frac{\beta\rho_n}{\gamma}<1$ then, using Lemma 3.17, Part 2, we can prove that all solutions of Eq. (2.1) tend to the positive equilibrium K. □

Corollary 3.20. *If* $t-h(t)\leqslant\tau$, *and either* $\frac{\beta\rho_n}{\gamma}<1$, *or (3.12) and (3.13) hold, then the positive equilibrium K is a global attractor for all positive solutions of Eq. (1.8).*

4. Oscillation

Definition 4.1. We will say that an equation is **non-oscillatory about the positive equilibrium** *K* if there exists a solution x such that $x-K$ is either eventually positive or eventually negative. Otherwise, the equation is **oscillatory about** *K*.

To study oscillation and non-oscillation conditions for Eq. (1.8) about the positive equilibrium K, first, we quote some lemmas which will be used in the proofs of the main results.

Lemma 4.2. [1,2,22]. *If* $a_k(t) \geqslant 0, h_k(t) \leqslant t, \lim_{t\to\infty} h_k(t) = \infty, k = 1, \ldots, m,$ *and* $\limsup_{t\to\infty} \int_{\min_k\{h_k(t)\}}^t \sum_{k=1}^m a_k(s)ds < \frac{1}{e}$, *then there exists a non-oscillatory solution of the linear delay equation*

$$\dot{x}(t) + \sum_{k=1}^m a_k(t)x(h_k(t)) = 0. \tag{4.1}$$

If $\lim\ \inf_{t\to\infty} \sum_{k=1}^m \int_{h_k(t)}^t a_k(s)ds > \frac{1}{e}$, then all solutions of (4.1) are oscillatory.

Lemma 4.3. [1,3]. *Consider the nonlinear delay differential equation*

$$\dot{x}(t) + \sum_{k=1}^m a_k(t)f_k(x(h_k(t))) = 0, \tag{4.2}$$

where $a_k(t) \geqslant 0, \int^\infty \sum_{k=1}^m a_k(t)dt = \infty, h_k(t) \leqslant t, \lim_{t\to\infty} h_k(t) = \infty$, f_k *are continuous functions,* $xf_k(x) > 0, x \neq 0$ *and* $f_k(0) = 0$. *If* $0 < f_k(x) \leqslant x, 0 < x < \delta$ *or* $0 > f_k(x) \geqslant x, -\delta < x < 0$ *for some* $\delta > 0$, *and linear Eq. (4.1) has a non-oscillatory solution, then Eq. (4.2) also has a non-oscillatory solution. If* $\lim_{x\to 0} \frac{f_k(x)}{x} = 1$, *and for some* $\varepsilon > 0$ *all solutions of the equation*

$$\dot{x}(t) + \sum_{k=1}^m (a_k(t) - \varepsilon)x(h_k(t)) = 0$$

are oscillatory, then all solutions of Eq. (4.2) are also oscillatory.

Theorem 4.4. 1. *Suppose one of the following conditions holds:*

(a) $0 < n \leqslant 1$;
(b) $n > 1, \frac{\beta}{\gamma} \leqslant \frac{n}{n-1}$;
(c) $n > 1$, (3.12) *holds,*

$$\frac{\beta}{\gamma} > \frac{n}{n-1}, \text{ and } \alpha\gamma \quad \limsup_{t\to\infty} \int_{h(t)}^t e^{\gamma \int_{h(s)}^s r(\tau)d\tau} r(s)ds < \frac{1}{e}, \tag{4.3}$$

where α *was defined in (3.3). Then Eq. (1.8) has a non-oscillatory about K solution.*

2. *If inequality (3.12) holds and*

$$n > 1, \quad \frac{\beta}{\gamma} > \frac{n}{n-1}, \quad -\alpha\gamma \ \lim\ \inf_{t\to\infty} \int_{h(t)}^t e^{\gamma \int_{h(s)}^s r(\tau)d\tau} r(s)ds > \frac{1}{e}, \tag{4.4}$$

then all solutions of Eq. (1.8) are oscillatory about K.

Proof. Consider the case 1(a). Let $y = x - K$, then (1.8) has the form

$$\frac{dy}{dt} = -\gamma r(t)y(t) + \beta r(t)\left(\frac{y(h(t)) + K}{1 + (y(h(t)) + K)^n} - \frac{K}{1 + K^n}\right). \tag{4.5}$$

Denote

$$f(t, y) = \beta r(t)\left(\frac{y + K}{1 + (y + K)^n} - \frac{K}{1 + K^n}\right).$$

Since $0 < n \leqslant 1$, the function f is monotone increasing, and $yf(t, y) > 0, y \neq 0$. Consider Eq. (4.5) with the initial condition $y(t) = y_0 > 0, t \leqslant 0$; we have

$$y(t) = e^{-\gamma \int_0^t r(s)ds} y_0 + \int_0^t e^{-\gamma \int_s^t r(\tau)d\tau} f(s, y(h(s)))ds. \tag{4.6}$$

It is evident that there exists a positive local solution of Eq. (4.5) with the initial condition $y(t) = y_0 > 0, t \leqslant 0$. Equality (4.6) implies that the global solution is also positive, and $x(t) = y(t) + K > K$. Thus Eq. (1.8) has a non-oscillatory about K solution. The case 1(b) was proven in [4, Theorem 7], and it is similar to the previous case, once we assume the initial conditions $\varphi(t) \in (0, K), t \leqslant 0$.

Now consider the cases 1(c) and 2 together. Let $x = y + K$, then (1.8) can be rewritten as Eq. (4.2) with $m = 2$ and the zero equilibrium. Evidently (1.8) is oscillatory/non-oscillatory about K if and only if (4.2) is oscillatory/non-oscillatory about zero. Denote

$$a_1(t) = \gamma r(t), \quad f_1(x) = x, \quad a_2(t) = -\alpha\gamma r(t), \quad f_2(x) = \frac{(1+K^n)^2}{(n-1)K^n - 1}\left(\frac{K}{1+K^n} - \frac{x+K}{1+(x+K)^n}\right).$$

The function f_2 has the unique minimum at the point $x_0 = 1/(n-1)^{\frac{1}{n}} - K$. The condition $\frac{\beta}{\gamma} > \frac{n}{n-1}$ implies $x_0 < 0$. By Theorem 2.7 it is sufficient to consider the function f_2 on the interval $[\mu - K - \varepsilon, M - K + \varepsilon]$ for some $\varepsilon < \mu - K - x_0$, which is a subinterval of $[x_0, M - K + \varepsilon]$, where the function f_2 is monotone increasing. We also have

$$uf_2(u) > 0, \quad u \neq 0, \quad \lim_{u \to 0} \frac{f_2(u)}{u} = 1, \quad f_2(u) < u, \ u > 0.$$

Thus, Eq. (4.2) has form (4.2) with $m = 2$, and functions f_1 and f_2 satisfy the conditions of Lemma 4.3; therefore Eq. (4.2) has a non-oscillatory solution when the linear equation

$$\frac{dx}{dt} + \alpha r(t)x(t) - \alpha\gamma r(t)x(h(t)) = 0 \quad (4.7)$$

has a non-oscillatory solution. Next, all solutions of Eq. (4.2) are oscillatory if for some $\varepsilon > 0$ all solutions of the equation

$$\frac{dx}{dt} + (\gamma r(t) - \varepsilon)x(t) - (\alpha\gamma r(t) + \varepsilon)x(h(t)) = 0 \quad (4.8)$$

are oscillatory. After substituting $x(t) = e^{-\int_0^t \gamma r(s)ds} v(t)$ into (4.7) and $x(t) = e^{-\int_0^t (\alpha r(s) - \varepsilon)ds} v(t)$ into (4.8), these equations can be written as

$$\frac{dv}{dt} - \alpha\gamma r(t) e^{\int_{h(t)}^t \gamma r(s)ds} v(h(t)) = 0, \quad (4.9)$$

$$\frac{dv}{dt} - (\alpha\gamma r(t) + \varepsilon) e^{\int_{h(t)}^t (\gamma r(s) - \varepsilon)ds} v(h(t)) = 0, \quad (4.10)$$

where (4.9) and (4.10) have the same oscillation properties as (4.7) and (4.8), respectively. Condition (4.3) and Lemma 4.2 imply that Eq. (4.9) has a non-oscillatory solution, whereas condition (4.4) and Lemma 4.2 yield that for small $\varepsilon > 0$ all solutions of (4.10) are oscillatory, and the statement of the theorem follows from Lemma 4.3. □

Definition 4.5. An oscillatory about K solution of an equation is called **slowly oscillating** if for any $t_0 > 0$ there exist two points t_1 and $t_2, t_2 > t_1 > t_0$, such that $h(t) > t_1, t \geqslant t_2$, and $x(t) - K$ preserves its sign in $[t_1, t_2)$ and vanishes at the point t_2:

$$(x(s) - K)(x(t) - K) > 0, \quad s, t \in [t_1, t_2), \ x(t_2) = K.$$

Otherwise, the solution is **rapidly oscillating**.

Remark 4.6. If either 1(a) or 1(b) of Theorem 4.4 is satisfied, then Eq. (1.5) is non-oscillatory about K. The latter can be justified in a fashion similar to [15]; moreover, Eq. (1.5) has no slowly oscillating about K solutions. Rapidly oscillating solutions for a different autonomous model were recently discussed in [24].

5. Mackey–Glass model with delayed control

It is well known that model (1.1) exhibits stable and unstable limit cycles, where stable cycles may have an arbitrary number of peaks per period, and chaos, which comes along with the presence of infinitely many periodic solutions of different periods, and of infinitely many irregular and mixing solutions, infinitely many periodic and uncountably many aperiodic solutions. The erratic structure of most of aperiodic solutions and their mixing trajectories come to what Li and Yorke [32] called "chaotic" motion. Although there is no universally accepted mathematical definition of chaos, a commonly used definition says that, for a dynamical system to be classified as chaotic, at least, it must be sensitive to initial conditions, i.e., a prescribed difference between solutions at some advanced stage can be achieved for any arbitrarily small difference between the initial conditions. Note that chaos has not yet been proven for classical models, including Mackey–Glass model (1.1). That is why it is very important to find a control mechanism that will turn a chaotic motion to some kind of the controlled regime. The control of dynamical systems is a classical subject in engineering science [14,28,30,44,50], and the electronic analog of Mackey–Glass model (1.1) was introduced in [42]. The simplest model of an electro-optical device can be expressed as

$$\frac{dx}{dt} + \gamma(t)x(t) = f(t, x(t - \tau)),$$

where $x(t)$ is the output signal, f is a nonlinear system's response, $\gamma(t) > 0$ and $\tau > 0$ are system's parameters; and a perturbed model with a feedback controller F can be expressed as

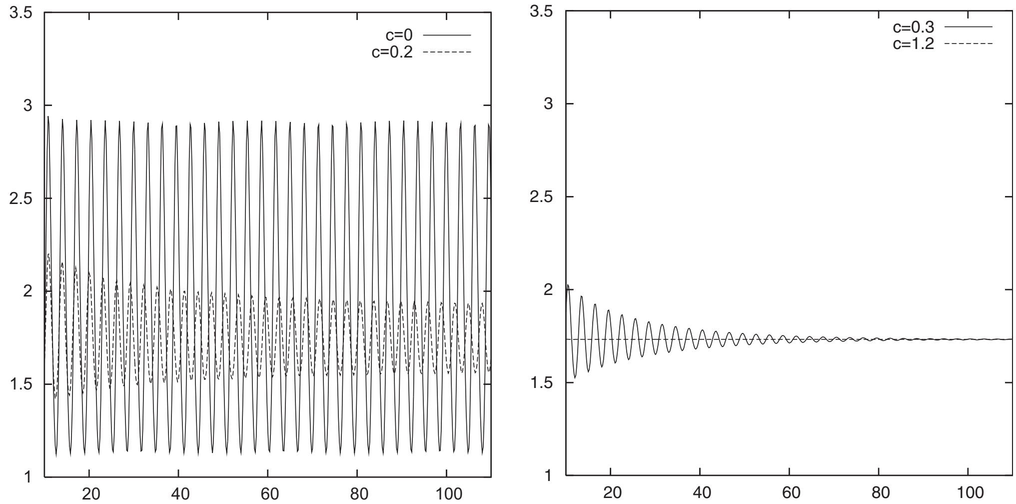

Fig. 1. A solution of equation (4.11) without control is unstable and oscillatory, and the small control $c = 0.2$ reduces the size of oscillations but does not lead to stabilization (left). When $c = 0.3$, a solution of (4.11) demonstrates oscillatory convergence to the equilibrium $K \approx 1.732$, while for $c = 1.2$ this convergence is monotone (right).

$$\frac{dx}{dt} = -\gamma(t)x(t) + f(t, x(t-\tau)) + F(x). \tag{5.1}$$

The purpose of a feedback control is to assure that the system asymptotically converges to its attractor. Two basic adaptive control models are widely used: controllers that are built on SFC (Standard Feedback Control) where the controlling force is proportional to the deviation of the system from the attractor

$$F(x) = \eta[\tilde{x}(t) - x(t)],$$

here $\tilde{x}(t)$ is a desired fixed point of the model, and DFC (Delayed Feedback Control)

$$F(x) = \eta[x(t-\sigma(t)) - x(t)],$$

where $\sigma(t)$ is the variable feedback time delay, or (see [30]) in the form $F(x) = \eta(t)[x(t-\sigma(t)) - x(t)]$.

Consider Eq. (1.5) with a distributed delay and SFC

$$\frac{dx}{dt} = -r(t)\left(\gamma x(t) - \beta \int_{h(t)}^{t} \frac{x(s)}{1+x^n(s)} d_sR(t,s)\right) + \eta(t)[K - x(t)]. \tag{5.2}$$

Further, assuming that (1.5) is unstable, we justify the possibility of global stabilization with SFC.

Theorem 5.1. *Let $\int_0^\infty r(s)ds = \infty$ and the positive equilibrium K of (1.5) be unstable. Then there exists $\eta(t) \geqslant 0$ such that the positive equilibrium K of (5.2) is GAS.*

Proof. Let us consider $\eta(t) = vr(t)$. Then, after substituting $y = x - K$, Eq. (5.2) takes the form

$$\frac{dy}{dt} = -r(t)\left[(\gamma + v)y(t) - \beta \int_{h(t)}^{t} \frac{y(s)+K}{1+(x(s)+K)^n} d_sR(t,s) - \beta \frac{K}{1+K^n}\right]. \tag{5.3}$$

Global asymptotic stability of (5.3) is equivalent to the global asymptotic stability of the positive equilibrium K of Eq. (1.5), with $\gamma + v$ instead of γ as a coefficient of $x(t)$.

Thus, by Theorem 3.13, K is a global attractor of all positive solutions of (5.2) if

$$1 < \frac{\beta}{\gamma + v} < \frac{n}{n-2},$$

or $\beta(n-2)/n - \gamma < v < \beta - \gamma$, as far as $\beta/\gamma > n/(n-2)$ (otherwise, the Eq. (1.5) is stable). Thus, stabilization with SFC is possible for any unstable (1.5). □

Next, consider a model with a distributed delay and DFC, where control also includes the same distributed delay

$$\frac{dx}{dt} = -r(t)\left[\gamma x(t) - \beta \int_{h(t)}^{t} \frac{x(s)}{1+x^n(s)} d_sR(t,s)\right] + \eta(t)\left[\int_{h(t)}^{t} x(s) d_sR(t,s) - x(t)\right]. \tag{5.4}$$

As previously, assume that $\eta(t) = \nu r(t)$ and rewrite (5.4) in the form

$$\frac{dx}{dt} = -r(t)\left[(\gamma+\nu)x(t) - \int_{h(t)}^{t}\left(\nu x(s) + \beta\frac{x(s)}{1+x^n(s)}\right)d_sR(t,s)\right]. \tag{5.5}$$

Theorem 5.2. *Let $\int_0^\infty r(s)ds = \infty$ and the positive equilibrium K of (1.5) be unstable. Then there exists $\eta(t) \geqslant 0$ such that the positive equilibrium K of (5.4) is GAS.*

Proof. Let us consider $\eta(t) = \nu r(t)$. By Lemma 3.11, Eq. (5.5) is globally asymptotically stable if the positive equilibrium K of the difference equation

$$x_{n+1} = f(x_n), \quad \text{where } f(x) = \frac{1}{\gamma+\nu}\left(\nu x + \frac{\beta x}{1+x^n}\right) \tag{5.6}$$

is globally asymptotically stable; in particular, this is valid if $f(x)$ is monotone increasing, at least on $[0,K]$. The minimum of the derivative of $f(x)$ on $[0,\infty)$ is $\frac{\nu}{\gamma+\nu} - \frac{\beta}{\gamma+\nu}\frac{(n-1)^2}{4n}$; so if we choose

$$\nu > \beta\frac{(n-1)^2}{4n}, \tag{5.7}$$

then the positive equilibrium K of (5.5) is GAS.

Corollary 5.3. *Let the positive equilibrium K of Eq. (1.2) be unstable. If (5.7) holds then K is GAS equilibrium of the equation*

$$\frac{dx}{dt} = \frac{\beta x(t-\tau)}{1+x^n(t-\tau)} - \gamma x(t) + \nu[x(t-\tau) - x(t)]. \tag{5.8}$$

Example 5.4. Consider the equation with a constant delay and control

$$\frac{dx}{dt} = -x(t) + \frac{10x(t-1)}{1+x^4(t-1)} + c[x(t-1) - x(t)]. \tag{5.9}$$

Eq. (5.7) gives stabilization for $c > 5.625$ (for any delay); however, for the delay $\tau = 1$ we have stabilization for much smaller values of $c \geqslant 0.3$, see Fig. 1; condition (5.7) is much more restrictive than stabilization requires in this particular case but it gives a uniform condition for all types and values of delays.

Remark 5.5. Sufficient condition (5.7) also guarantees that (5.5) is non-oscillatory; moreover, it has no slowly oscillating solutions.

6. Some Mackey–Glass-type models

In this section we will review some results obtained for Mackey–Glass-type models. One of the modifications of the classical Mackey–Glass model

$$\frac{dx}{dt} = -\gamma x(t) + \frac{\beta x(t)}{1+x^n(t-\tau)} \tag{6.1}$$

with $\gamma = 1$, was introduced in [43] (see also [6,31,48]). This equation has both a trivial and a nontrivial equilibrium, provided $\beta > \gamma = 1$. Linearization procedure yields the local asymptotical stability condition for the trivial solution of Eq. (6.1) which is $\frac{n(\beta-1)}{\beta}\tau < \frac{\pi}{2}$. Also, based on [31], Eq. (6.1) with $\gamma = 1$ is oscillatory about K if

$$\frac{n(\beta-1)}{\beta}\tau > \frac{1}{e}.$$

In [41] the more general model than (1.1)

$$\frac{dx}{dt} = -\gamma x(t) + \frac{\beta\theta^n x^m(t-\tau)}{\theta^n + x^n(t-\tau)} \tag{6.2}$$

was introduced (see also [20,45,47]).

Theorem 6.1. [45] *If $n > m \geqslant 2$ then the positive equilibrium is not attractive for all positive solutions. The trivial solution is not only stable, but "even attracts a large subset of positive solutions, independently on τ".*

In [6, Theorem 2] the following model

$$\frac{dx}{dt} = r(t)\left[\frac{\beta x(t)}{1 + x^n(h(t))} - \gamma x(t)\right] \tag{6.3}$$

was under examination.

Theorem 6.2. *Suppose $r(t) \geqslant 0$ satisfies (1.6), (a2) holds, $\beta > \gamma > 0$ and*

$$\frac{\beta\gamma}{4}\limsup_{t\to\infty}\int_{h(t)}^{t} r(s)ds < 1 + \frac{1}{e}.$$

Then $K = (\beta/\gamma - 1)^{1/n}$ is a global attractor for all positive solutions of (6.3).

If $r(t)$ and $h(t)$ are continuous functions then $1 + 1/e$ can be replaced by the best possible constant 3/2. In [49] the non-autonomous model with a state-dependent delay

$$\frac{dx}{dt} = -\gamma(t)x(t) + \frac{\beta(t)x(t)}{r + x^n(t - \tau(t, x(t)))}, \tag{6.4}$$

where $\gamma, \beta \in (\mathbb{R}, \mathbb{R}^+), \tau \in C[\mathbb{R}^2, \mathbb{R}^+]$ are $\omega-$periodic functions with respect to t, r is a positive constant, was under study.

Theorem 6.3. [49, Theorem 2.1] *If*

$$\int_0^{\omega}\beta(s)ds > r\int_0^{\omega}\gamma(s)ds,$$

then Eq. (6.4) has at least one positive periodic solution.

In [7] the model

$$\frac{dx}{dt} = -\gamma(t)x(h(t)) + \beta(t)\frac{x(g(t))}{1 + x^n(g(t))} \tag{6.5}$$

was examined, where $\beta(t) > 0, \gamma(t) > 0, t \geqslant 0, g$ and h satisfy conditions (a1) and (a2). The following result is due to [7, Theorem 4, Corollary 4.1 and Theorem 5].

Theorem 6.4. *If*

$$\liminf_{t\to\infty}[\gamma(t) - \beta(t)] > 0 \text{ and } \limsup_{t\to\infty}\frac{\gamma(t)}{\gamma(t) - \beta(t)}\int_{h(t)}^{t}[\beta(s) + \gamma(s)]ds < 1$$

then the zero solution of (6.5) is locally uniformly asymptotically stable.

In [13] the non-autonomous model

$$\frac{dx}{dt} = -\gamma(t)x(t) + \frac{\beta(t)x(t)}{1 + x^n(t)} - \alpha(t)x(h(t)) \tag{6.6}$$

was under study. It was proven that all positive solutions are bounded; conditions for extinction and permanence of solutions were also obtained [13].

In [25], as an application, the following modification of (1.1)

$$\frac{dx}{dt} = -\gamma x(t) - \beta\frac{x(t)}{1 + x^n(t)} + k\beta\frac{x(t-\tau)}{1 + x^n(t-\tau)} \tag{6.7}$$

was examined. By [25, Proposition 3.1 and 3.3] the nontrivial equilibrium exists if and only if $k > 1 + \gamma/\beta$. If $k \leqslant 1 + \gamma/\beta$ then the trivial equilibrium of Eq. (6.7) is GAS. In addition, conditions for the existence of slowly oscillating solutions of Eq. (6.7) were obtained.

In [53, Theorem 3.4] the model with a distributed delay

$$\frac{dx}{dt} = -\gamma(t)x(t) - \frac{\beta_1(t)x(t)}{1 + x^n(t)} + \beta(t)\int_0^{\infty}P(r)\frac{x(t-r)}{1 + x^n(t-r)}dr \tag{6.8}$$

was considered.

Theorem 6.5. [53, Theorem 3.4] *Let $n > 0, \gamma(t), \beta_1(t)$ and $\beta(t)$ be continuous positive ω-periodic functions on $\mathbb{R}^+, P(t)$ be piecewise continuous nonincreasing eventually, where $\int_0^\infty P(s)ds = 1$ and $\int_0^\infty sP(s)ds < \infty$. If $\min_{0 \leqslant t \leqslant \omega}[\gamma(t) + \beta_1(t)] > \max_{0 \leqslant t \leqslant \omega}\beta(t)$, then every positive solution of (6.8) satisfies $\lim_{t\to\infty}x(t) = 0$.*

7. Discussion and open problems

We present known global stability conditions for Eq. (1.2) in Table 1.

Let us note that LAS and absolute GAS conditions (either $0 < n \leqslant 2$ or $\beta/\gamma \leqslant n/(n-2)$) coincide for autonomous Eq. (1.2) and for non-autonomous Eqs. (1.5) with a positive equilibrium. As noted in [35, Remark 3.3], Theorem 3.9 improves results obtained for $n > 2$ in [20], and the condition *c*) in Theorem 3.9 is sharp in the class of equations (3.6) with $\tau(t) \leqslant h$. We presented here stability results for some generalizations of Eq. (1.2), in particular, for equation with a distributed delay (1.5), and for general non-autonomous Mackey–Glass model (2.1). Using these stability results, we also examine stabilization of Mackey–Glass model with delayed control. To the best of our knowledge, the only result on oscillation of the Mackey–Glass model was introduced in [21]. However, the proof of the main theorem in [21] was based on Lemma 1.1 in [21], which claims that under certain conditions oscillation of a nonlinear and a corresponding linear equation are equivalent. Lemma 1.1 in [21] is not valid in certain cases, especially in the critical case when the parameter values are close to the oscillation boundary (see, for example, [3]). In the present paper, for the proofs we used a linearized oscillation theorem in the form of [1], which can be applied once (3.12) holds. Various stability results were obtained in the papers [33–37,45,46] for the general delay equation

$$\dot{x}(t) = f(x(t-\tau(t))) - ax(t)$$

with further applications to the models of the Mackey–Glass type. Let us note that in the present paper we also consider stability of the equation with several concentrated delays, see Theorem 3.15.

Finally, we outline some open problems and topics for further research.

1. Prove or disprove that the positive equilibrium K of (1.2) is LAS if and only if it is GAS.
   Is this proposition true for a non-autonomous generalizations of (1.2), including (1.5)?
2. Consider the equation with an infinite distributed delay

$$\frac{dx}{dt} = -r(t)\left[\gamma x(t) - \beta\int_{-\infty}^{t}\frac{x(s)}{1+x^n(s)}d_sR(t,s)\right], \tag{7.1}$$

where $r(t) \geqslant 0$ is an essentially bounded on $[0,\infty]$ function satisfying $\int_0^\infty r(s)ds = \infty$, $R(t,\cdot)$ is a left continuous nondecreasing function for any t, $R(t,t^+) = 1$. Describe conditions on $R(t,s)$ which imply permanence of positive solutions of (7.1) and define *a priori* bounds on the eventual solutions.

3. Obtain oscillation and non-oscillation conditions for model (7.1).
4. Study permanence, oscillation and stability properties of the modifications of Mackey–Glass model (1.3):

$$\frac{dx}{dt} = r(t)\left[-\gamma x(t) + \beta\frac{x(h(t))}{1+x^n(g(t))}\right];$$

$$\frac{dx}{dt} = r(t)\left[-\gamma x(t-\sigma) + \beta\frac{x(t-\tau)}{1+x^n(t-\tau)}\right];$$

$$\frac{dx}{dt} = r(t)\left[-\gamma x(t) + \beta\frac{x^m(h(t))}{1+x^n(h(t))}\right];$$

$$\frac{dx}{dt} = r(t)\left[-\gamma x(t) + \sum_{k=1}^{m}\beta_k\frac{x(h_k(t))}{1+x^{n_k}(h_k(t))}\right];$$

$$\frac{dx}{dt} = r(t)\left[-\gamma f(x(t)) + \beta\frac{x(h(t))}{1+x^n(h(t))}\right].$$

Consider these equations also in the case when γ and β are ω-periodic functions.

5. Let K be an equilibrium point of Eq. (1.8). Consider the SFC model

$$\frac{dx}{dt} = -r(t)\left(\gamma x(t) - \beta\frac{x(h(t))}{1+x^n(h(t))}\right) + \eta(t)[M - x(t)]. \tag{7.2}$$

Let $K_1 > 0$ be some fixed constant. For which K_1 it is possible to find a constant $M > 0$ and a function $\eta(t)$ such that all positive solutions of Eq. (7.2) converge to K_1, where K_1 might not coincide with K?

6. Study stability of Mackey–Glass model (5.4) with DFC when $\tau \neq \sigma$, e.g., when the control delay σ is significantly less than the system's delay τ.

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