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QUALITATIVE ANALYSIS OF A GENERAL PERIODIC SYSTEM

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Abstract. In this paper we study the dynamics of a general ω-periodic model. Necessary and sufficient conditions for the global stability of zero steady state of the model are given. The conditions under which there exists a unique periodic solutions to the model are determined. We also show that the unique periodic solution is the global attractor of all other positive solutions. Some applications to mathematical models for cancer and tumor growth are given.

1. Introduction

In this paper, we consider a general initial value problem as follows:

$$\dot{x} = xF(t,x), \tag{1.1}$$

$$x(t_0) = x_0, \tag{1.2}$$

where the function F satisfies the following conditions:

(A1) F is continuous and locally Lipschitz continuous in x for all $(t,x) \in \mathscr{D} = {\mathbb{R}_+}^2$ where $\mathbb{R}_+ = [0, +\infty)$.

(A2) For all $(t,x) \in \mathscr{D} = {\mathbb{R}_+}^2$ equality $F(t+\omega, x) = F(t,x)$ holds, that is F is ω-periodic.

(A3) F is strictly decreasing in x, that is for any $t \geq 0$ and $x > y \geq 0$ inequality $F(t,x) < F(t,y)$ holds.

Recently, the same model has been studied under different conditions by U. Foryś et al. [3]. In [3], the authors assumed that F satisfies the conditions (A1), (A2), (A3)' and (A4), where (A3)' and (A4) are as follows:

(A3)' F is increasing in x, that is for any $t \geq 0$ and $x > y \geq 0$ inequality $F(t,x) > F(t,y)$ holds.

(A4) F is uniformly bounded in $\mathscr{D}$.

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It should be pointed out that the methods used in [3] are not applicable to this model with the conditions (A1), (A2) and (A3). We derive conditions for the global stability of trivial solution to the model. Using Schauder's Fixed Point Theorem, we prove there exists at least one periodic solution under some conditions. We also show that the periodic solution is the global attractor of all other positive solutions. Thus the periodic solution is unique if it exists.

Theorem 1.1. *Assume that F satisfies the conditions* (A1)–(A3). *For any positive initial value x_0, there exists a unique global positive solution to the initial value problem* (1.1), (1.2). *Moreover, the solution is strictly positive for all $t \geq 0$.*

Proof. By the well-known existence and uniqueness theorem for first-order ODEs, the local existence and uniqueness of the solution to the initial value problem (1.1), (1.2) is clear. Noticing F is decreasing in x, we can get

$$\frac{1}{x}\frac{dx}{dt} = F(t,x) \leq F(t,0). \tag{1.3}$$

Then we can get

$$x(t) \leq x(0)e^{F^* t}, \tag{1.4}$$

where $F^* = \max_{[0,\omega]} F(t,0)$. On the other hand,

$$x(t) = x_0 \exp(\int_0^t F(s,x)ds) > 0. \tag{1.5}$$

Thus the solution can not blow up or disappear in a finite time, by continuation theorem, there exists a unique global positive solution to the initial value problem (1.1), (1.2). By (1.5), we can get the solution to the initial value problem (1.1), (1.2) is strictly positive for all $t \geq 0$. □

The paper is organised as follows: In Section 2, necessary and sufficient conditions for the global stability of zero steady state of the model are given. In Section 3, the conditions under which there exists a unique periodic solutions to the model are determined. Besides, we also show that the unique periodic solution is the global attractor of all other positive solutions. In the last section, some applications to mathematical models for cancer and tumor growth are given.

2. Stability of zero steady state of (1.1)

For simplicity of notation, in this paper we denote

$$g(x) = \int_0^\omega F(s,x)ds,\ F_A = \int_0^\omega F(s,0)ds = g(0).$$

Due to (A3), $g(x)$ is decreasing in x. Set

$$\lim_{x\to 0^+} g(x) = F_0.$$

We see that $F_A = F_0$ if g is continuous at point 0.

Theorem 2.1. *Assume that F satisfies the conditions* (A1)–(A3)*. The following assertions hold.*

(1) *The zero steady state of* (1.1) *is globally stable if $F_A < 0$. i.e., if $F_A < 0$, any solution of Eq.* (1.1) *with $x_0 > 0$ tends to 0 as $t \to \infty$.*

(2) *If the zero steady state of* (1.1) *is globally stable, then $F_A \leq 0$.*

Proof. (1) For any $\xi \in [0, \omega]$,

$$\int_{\xi}^{\xi+n\omega} \frac{dx}{x} = \int_{\xi}^{\xi+n\omega} F(t,x)dt \leq \int_{\xi}^{\xi+n\omega} F(t,0)dt,$$

where we used the fact F is decreasing in x. Thus,

$$x(\xi + n\omega) \leq x(\xi) \exp\left(\int_{\xi}^{\xi+n\omega} F(t,0)dt\right) = x(\xi) \exp\left(nF_A\right).$$

Since $F_A < 0$, it follows that $x(\xi)\exp(nF_A) \to 0$ as $n \to \infty$. Therefore, we can get $x(\xi + n\omega) \to 0$ as $n \to \infty$. Since $\lim_{n\to\infty} x(n\omega) = 0$, then for an arbitrary $\varepsilon > 0$, there exists $n_\varepsilon > 0$ such that $x(n\omega) < \varepsilon$ when $n \geq n_\varepsilon$. Let $t_\varepsilon = n_\varepsilon \omega$. For any $t \geq t_\varepsilon$, there exists $n \geq n_\varepsilon$ such that $t = n\omega + \xi$, where $\xi \in [0, \omega)$. We can get

$$x(t) = x(n\omega) \exp(\int_{n\omega}^{n\omega+\xi} F(t,x)dt) \leq \varepsilon e^{F_A} < \varepsilon.$$

Thus $\lim_{t\to\infty} x(t) = 0$.

(2) Since the zero steady state of (1.1) is globally stable, i.e., $\lim_{t\to\infty} x(t) = 0$, then for a given $\varepsilon > 0$, there exists t_ε such that $x(t) < \varepsilon$ for $t > t_\varepsilon$. Then

$$\frac{dx}{xdt} = F(t,x) \geq F(t,\varepsilon),$$

where we used the fact F is decreasing in x. Therefore

$$\frac{x(t+\omega)}{x(t)} \geq \exp\left(\int_{t}^{t+\omega} F(\xi,\varepsilon)dt\right) = \exp\left(\int_{0}^{\omega} F(\xi,\varepsilon)dt\right).$$

We use the method of reduction to absurdity. If $F_A > 0$, we choose ε sufficiently small such that

$$\exp\left(\int_{0}^{\omega} F(\xi,\varepsilon)dt\right) > 0.$$

Then $\frac{x(t+\omega)}{x(t)} > 1$. Therefore, we construct a sequence $\{x(t_\varepsilon + n\omega)\}_n$ that strictly increasing which contradicts to the assumption that the zero steady state of (1.1) is globally stable. Thus $F_A > 0$ does not hold. This completes the proof of Theorem 2.1. □

3. Existence, uniqueness and stability of the periodic solution to Eq. (1.1)

Lemma 3.1 (see Theorem 4.1 and Corollary 5.1 in [6]). *Consider the following ODE*

$$\frac{dy}{dt} = G(t, y), \ \ t \in \mathbb{R}, \tag{3.1}$$

where $G : [0, \omega] \times [a, b] \to \mathbb{R}$ *is continuous and* ω*-periodic with respect to* t*. If, for all* $t \in [0, \omega]$*,* $G(t, a) \geq 0$ *and* $G(t, b) \leq 0$ *then* $[a, b]$ *is invariant under* G*, moreover the equation* (3.1) *admits a* ω*-periodic solution,* $y : \mathbb{R} \to [a, c]$*.*

Lemma 3.2. *Assume that* F *satisfies the conditions* (A1)–(A3) *and* $F_A > 0$*. Moreover, assume that*

$$F(t, x) \to f(t) \ \ \text{uniformly as} \ \ x \to \infty$$

and $F_2 = \int_0^\omega f(t)ds < 0$*, then*

(1) *there exists at least one* ω*-periodic positive solution* $x^*(t)$ *to* (1.1).

(2) *for any other positive solutions* $x(t)$ *to* (1.1)*, the limit*

$$\lim_{t\to\infty} [x(t) - x^*(t)] = 0.$$

Proof. (1) Set $\int_0^\omega F(t, x)dt = g(x)$, then $g(x)$ is decreasing due to (A3). Since $g(0) = F_A > 0$ and $\lim_{x\to\infty} g(x) = \int_0^\omega f(t)dt < 0$, we can get there exists a constant $M > 0$ such that $g(M) = 0$. Let $X = \{x \,|\, x \in C(\mathbb{R}_+, \mathbb{R})\}$ be the Banach space with the norm $\|x\| = \sup_{t\geq 0} |x(t)|$. Define a closed, bounded and convex subset Ω of X as follows

$$\Omega = \{x \in X : x(t + \omega) = x(t), 0 \leq x(t) \leq KM\},$$

where $K = \max\{2, e^{F_A}\}$. Define the operator $S : \Omega \to X$ as follows:

$$S(x)(t) = x(t) \exp(\int_t^{t+\omega} F(s, x)ds).$$

First, we show that $Sx \in \Omega$ for any $x \in \Omega$. For any $x \in \Omega$, if $x < M$, then

$$S(x)(t) = x(t) \exp(\int_t^{t+\omega} F(s, x)ds) = xe^{g(x)} \leq xe^{F_A} \leq KM.$$

If $M \leq x \leq KM$, we have

$$S(x)(t) = x(t) \exp(\int_t^{t+\omega} F(s, x)ds) = xe^{g(x)} \leq xe^{g(M)} \leq KM.$$

$Sx > 0$ is obvious. Therefore, for any $x \in \Omega$, $0 \leq Sx \leq KM$. Since

$$\begin{aligned} S(x)(t + \omega) &= x(t + \omega) \exp(\int_{t+\omega}^{t+2\omega} F(s, x)ds) \\ &= x(t) \exp(\int_t^{t+\omega} F(s, x)ds) = S(x)(t), \end{aligned}$$

we can get $Sx \in \Omega$ for any $x \in \Omega$.

Next, we show that S is continuous. Let $x_i =: x_i(t) \in \Omega$ be such that $x_i(t) \to x(t) \in \Omega$ as $i \to \infty$. We can get

$$\|S(x_i)(t) - S(x)(t)\| = \sup_{t\geq 0} |x_i(t)\exp(\int_t^{t+\omega} F(s,x_i)ds) \\ - x(t)\exp(\int_t^{t+\omega} F(s,x)ds)| \to 0,$$

which means S is continuous.

Now we show that $S\Omega$ is relatively compact. For $x \in \Omega$, we have

$$\left|\frac{d}{dt}S(x)(t)\right| = \left|xF(t,x)\exp(\int_0^{\omega} F(t,x)dt)\right| \leq KM \min_{[0,\omega]} |F(t,0)||g(0)| =: M_2.$$

From the definition of Ω and $Sx \in \Omega$, we can get the uniform boundedness of $S\Omega$. By Arizela-Ascoli Theorem, we can get $S\Omega$ is relatively compact. By Schauder's Fixed Point Theorem, there exists an $x^* \in \Omega$ such that $Sx^* = x^*$. We see that x^* is a positive ω-periodic solution of (1.1).

(2) According to Theorem 1.1, solution of (1.1) is unique, and thus trajectories can not cross each other. Assume $x(t) > x^*(t)$. Let

$$x(t) = x^*(t)e^{y(t)}.$$

Then $y(t) > 0$ and

$$\dot{y}(t) = F(t, x^*e^y) - F(t,x^*). \tag{3.2}$$

Since $x(t) > x^*(t)$ and F is strictly decreasing in x, we can get $\dot{y}(t) = F(t,x^*e^y) - F(t,x^*) < 0$. Therefore, $\lim_{t\to\infty} y(t)$ exists. If we denote

$$\lim_{t\to\infty} y(t) = \alpha,$$

then $\alpha \in [0,\infty)$. Now we prove $\alpha = 0$. If $\alpha > 0$, there exists T_ε such that $0 < \alpha - \varepsilon < y(t) < \alpha + \varepsilon$ for $t \geq T_\varepsilon$. However, from (3.2), we can get

$$\dot{y}(t) + F(t,x^*) - F(t,x^*e^{\alpha-\varepsilon}) < 0. \tag{3.3}$$

Integrating (3.3) from T_ε to ∞ immediately give a contraction since $F(t,x^*) - F(t,x^*e^{\alpha-\varepsilon}) > 0$. Hence $\alpha = 0$ and therefore $\lim_{t\to\infty} y(t) = 0$. Thus

$$\lim_{t\to\infty} [x(t) - x^*(t)] = \lim_{t\to\infty} x^*(t)[e^{y(t)} - 1] = 0. \tag{3.4}$$

This completes the proof. □

Theorem 3.3. *Assume that F satisfies the conditions* (A1)–(A3), *and there exists a positive constant δ such that*

$$F(t,\delta) > 0.$$

Moreover, assume that

$$F(t,x) \to f(t) \text{ uniformly as } x \to \infty,$$

and $f(t) < 0$. Then

(1) *there exists at least one ω-periodic positive solution $x^*(t)$ to* (1.1).

(2) *for any other positive solutions* $x(t)$ *to* (1.1)*, the limit*

$$\lim_{t\to\infty}[x(t)-x^*(t)]=0.$$

Proof. (1) From

$$F(t,x)\to f(t) \text{ uniformly as } x\to\infty.$$

and $f(t)<0$, we know that there exists $M>0$ such that $F(t,M)\le 0$. Denote

$$G(t,x)=xF(t,x).$$

Then $G:[0,\omega]\times[\delta,M]\to\mathbb{R}$ is continuous and ω-periodic with respect to t. By the fact $F(t,\delta)\ge 0$ and $F(t,M)\le 0$, we can get for all $t\in[0,\omega]$, $G(t,\delta)\ge 0$ and $G(t,M)\le 0$. By Lemma 3.1, the equation (1.1) admits a ω- periodic solution, $x:\mathbb{R}\to[\delta,M]$.

(2) The proof is the same as the proof of Lemma 3.2(2), we omit it here. This completes the proof. □

Theorem 3.4. *Assume that* F *satisfies the conditions* (A1)–(A3) *and* $F_A>0$. *Moreover, assume that there exists* $M>0$ *such that* $F_M=\int_0^\omega F(t,M)dt<0$. *Then*

(1) *there exists at least one* ω*-periodic positive solution* $x^*(t)$ *to* (1.1).

(2) *for any other positive solutions* $x(t)$ *to* (1.1)*, the limit*

$$\lim_{t\to\infty}[x(t)-x^*(t)]=0.$$

Proof. The proof is similar to that of the proof of Theorem 3.2, we omit it here. □

Remark. Since for any other positive solutions $x(t)$ to (1.1), the limit

$$\lim_{t\to\infty}[x(t)-x^*(t)]=0.$$

We can get that the periodic positive solution $x^*(t)$ is unique if F satisfies the conditions in Theorem 3.2, Theorem 3.3 or Theorem 3.4.

4. Some applications

4.1. A mathematical model for tumor growth with periodic supplies of nutrients

Bai and Xu [1] studied a mathematical model for tumor growth with a periodic supply of external nutrients:

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial\sigma}{\partial r}\right)=\Gamma\sigma,\ 0<r<R(t),\ t>0, \tag{4.1}$$

$$\frac{\partial\sigma}{\partial r}(0,t)=0,\sigma(R(t),t)=\phi(t),0<r<R(t),t>0, \tag{4.2}$$

$$\frac{d}{dt}\left(\frac{4\pi R^3(t)}{3}\right)=4\pi\left(\int_0^{R(t)}s\sigma(r,t)r^2dr-\int_0^{R(t)}s\tilde{\sigma}r^2dr\right),\ t>0, \tag{4.3}$$

$$R(0) = R_0, \tag{4.4}$$

where $R(t)$ denote the external radius of tumor at time t; the term $\Gamma\sigma$ in (4.1) is the consumption rate of nutrient in a unit volume; $\phi(t)$ denotes the external concentration of nutrients, which is assumed to be a periodic function of a period ω. The two terms on the righthand side of (4.3) are explained as follows: The first term is the total volume increase in a unit time interval induced by cell proliferation, the proliferation rate is $s\sigma$; The second term is the total volume decrease in a unit time interval caused by natural death, and the natural death rate is $s\tilde{\sigma}$.

By re-scaling the space variable we may assume that $\Gamma = 1$. Accordingly, the solution to (4.1), (4.2) is

$$\sigma(r,t) = \frac{\sigma_\infty R(t)}{\sinh R(t)} \frac{\sinh r}{r}. \tag{4.5}$$

Substituting (4.5) to (4.3), we have

$$\frac{1}{s}\frac{dR}{dt} = R(t)\left[\phi(t)p(R(t)) - \frac{\tilde{\sigma}}{3}\right], \tag{4.6}$$

where $p(x) = \frac{x\coth x - 1}{x^2}$.

Denote $x = R^3$, and assume that $s = 1$ (if not one can re-scale coefficients $\sigma_\infty, \tilde{\sigma}$). Then Eq. (4.6) takes the form

$$\frac{dx}{dt} = x(t)[3\phi(t)p(\sqrt[3]{x}) - \tilde{\sigma}] =: xF(t,x), \tag{4.7}$$

where $F(t,x) = 3\phi(t)p(\sqrt[3]{x}) - \tilde{\sigma}$. And the initial value takes the form

$$x(0) = x_0 = R_0^3 > 0. \tag{4.8}$$

To study the existence, uniqueness and stability of the periodic solution to Eq. (4.6), we only need to study the existence, uniqueness and stability of that to Eq. (4.7).

From [2, 4], we know that p is strictly decreasing in x and

$$\lim_{x\to\infty} p(x) = 0, \ \lim_{x\to 0} p(x) = \frac{1}{3}.$$

Then $0 < p(x) < 1/3$ for all $x > 0$. If we define $p(0) = 1/3$, then p is continuous on $\mathbb{R}_+ = [0, +\infty)$. It follows that $F(t,x)$ satisfies conditions (A1)-(A3). By Theorem 1.1, we can get: For any positive initial value x_0, there exists a unique global positive solution to the initial value problem (4.7), (4.8). Moreover, the solution is strictly positive for all $t \geq 0$.

Moreover,

$$F(t,x) \to -\tilde{\sigma} < 0 \text{ uniformly as } x \to \infty.$$

Denote $\frac{1}{\omega}\int_0^\omega \phi(t)dt = \bar{\sigma}$. Then $F_A = \omega(\bar{\sigma} - \tilde{\sigma})$ and $F(t,0) = \phi(t)$. By Theorem 2.1, we can get the following assertions:

(1) The zero steady state of (4.6) is globally stable if $\bar{\sigma} < \tilde{\sigma}$.
(2) If the zero steady state of (4.6) is globally stable, then $\bar{\sigma} \leq \tilde{\sigma}$.

By Theorem 3.2, assume that $\bar{\sigma} > \tilde{\sigma}$ holds. we can get following assertions:

(3) There exists a unique ω-periodic positive solution $\bar{x}(t)$ to Eq. (4.7).

(4) For any other positive solutions $x(t)$ to Eq. (4.7), the limit

$$\lim_{t\to\infty} [x(t) - \bar{x}(t)] = 0.$$

Remark. The results of (3), (4) improved the results in [1]. Actually, in [1], the authors have proved the following results: assume that $\sigma_* > \tilde{\sigma}$ holds. Then

(3) there exists a unique ω-periodic positive solution $\bar{x}(t)$ to Eq. (4.7).

(4) for any other positive solutions $x(t)$ to Eq. (4.7), the limit

$$\lim_{t\to\infty} [x(t) - \bar{x}(t)] = 0.$$

Since $\bar{\sigma} \geq \sigma_*$, it follows that $\sigma_* > \tilde{\sigma} \Rightarrow \bar{\sigma} > \tilde{\sigma}$. Thus, the results of (3), (4) improved the results in [1].

4.2. A mathematical model for PCa immunotherapy under impulsive vaccination treatment

U. Foryś et al. [3] proposed the model for PCa immunotherapy under impulsive vaccination treatment. The model is as follows:

$$\dot{x} = H(t) - G(t)x, \tag{4.9}$$

where H and G are periodic with respect 1, $G(t) > 0$, please see [3] for details. The existence and uniqueness of the solution to (4.9) with initial condition $x_0 = x(0) > 0$ is obviously since (4.9) is a linear equation. Denote

$$F(t,x) = \frac{H(t)}{x} - G(t).$$

Then $\dot{x} = xF(t,x)$.

Since

$$\min_{[0,\omega]} F(t,x) = \frac{H_*}{x} - G^*,$$

where $H_* = \min_{[0,\omega]} H(t)$ and $G^* = \max_{[0,\omega]} G(t)$, if $H_* > 0$, then there exists $\delta > 0$ such that $F(t,\delta) > 0$. Since

$$F(t,x) \to -G(t) < 0 \text{ uniformly as } x \to \infty,$$

by Theorem 3.3, we get that if $H_* > 0$,

(1) there exists at least one 1-periodic positive solution $x^*(t)$ to (4.9).

(2) for any other positive solutions $x(t)$ to (4.9), the limit

$$\lim_{t\to\infty} [x(t) - x^*(t)] = 0.$$

Noticing

$$\max_{[0,\omega]} F(t,x) = \frac{H^*}{x} - G_*,$$

where $G_* = \min_{[0,\omega]} G(t)$ and $H^* = \max_{[0,\omega]} H(t)$, consider the following initial value problem

$$\dot{y} = H^* - G_* y = y(\frac{H^*}{y} - G_*), \ y(0) = x_0. \tag{4.10}$$

If $H^* < 0$, we can get $\dot{y} < 0$ and $\lim_{t\to\infty} y(t) = 0$. By comparison principle, we can get $\lim_{t\to\infty} x(t) = 0$. We conclude:

If $H^* < 0$, the zero steady state of (4.9) is globally stable.

4.3. A logistic model of periodic chemotherapy

Panetta [5] proposed a logistic growth model where there is a variable growth rate is taken into account chemotherapy. The mathematical model is

$$\dot{y} = ry(t)\left(1 - b(t) - \frac{y(t)}{K}\right), \tag{4.11}$$

where $y(t)$ is the cell mass, r is the growth rate, K is the carrying capacity, and $b(t)$ is a periodic function representing the chemotherapeutic effects on the cell mass. As [5], to reduce the problem to a simpler form, scale equation (4.11) by $y(t) = Kx(t)$. The resulting equation is

$$\dot{x} = rx(t)\,(1 - b(t) - x(t)) =: xF(t,x), \tag{4.12}$$

where $F(t,x) = r[1 - b(t) - x]$. F satisfies conditions (A1)–(A3). By Theorem 1.1, we can get: For any positive initial value x_0, there exists a unique global positive solution to the initial value problem (4.12), (1.2). Moreover, the solution is strictly positive for all $t \geq 0$. Denote $\bar{b} = \frac{1}{\omega}\int_0^\omega b(t)dt$. Then $F_A = \omega(1 - \bar{b})$. By Theorem 2.1, we can get following assertions:

(1) The zero steady state of (4.12) is globally stable if $\bar{b} > 1$.

(2) If the zero steady state of (4.12) is globally stable, then $\bar{b} \geq 1$.

Moreover, when $M > 1 - \bar{b}$, $F_M = \int_0^\omega r[1 - b(t) - M]dt = r\omega[1 - \bar{b} - M] < 0$ and $F_A > 0$. By Theorem 3.4, assume that $\bar{b} < 1$ holds. We can get following assertions:

(3) There exists a unique ω-periodic positive solution $\bar{x}(t)$ to Eq. (4.12).

(4) For any other positive solutions $x(t)$ to Eq. (4.12), the limit

$$\lim_{t\to\infty} [x(t) - \bar{x}(t)] = 0.$$

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