Some analytical and numerical results for a nonlinear Volterra integro-differential equation with periodic solution modeling hematopoiesis

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Abstract

We consider a nonlinear Volterra integro-differential equation with periodic solution, a special case of which has been used in modeling hematopoiesis dynamics. Some analytical results concerning existence and uniqueness of a positive periodic solution are presented together with some numerical results based on the reformulation of the equation as a system of ODEs and also from its direct solution using the trapezoidal method.

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1 Introduction

Volterra integro-differential equations (VIDEs) with periodic solutions have applications in many biological and biomedical areas, e.g. population biology (cf. [9], [13], [19], [21], [22], [34], [37]), epidemiology (cf. [1], [2], [13], [14], [20]), physiology (cf. [35]).

Various types of VIDEs with periodic solutions have been considered in the literature for theoretical as well as practical purposes (existence and uniqueness of periodic solutions, stability). They include linear equations (cf. [3], [4]), equations of logistic and other nonlinear types (cf. [3], [5], [6], [7], [11], [12], [15], [16], [17], [22], [28], [30], [31], [33], [35], [36], [37]).

Some of the equations treated are first order ones and some are of second order (cf. [32]). In addition, some are ordinary VIDEs and some are delay VIDEs.

Various approaches have been used in the proofs of existence and uniqueness of periodic solutions which can be categorised as follows (see also [16], p. 261):

(i) approaches that use the standard contraction principle and the simple but effective fluctuation principle.

(ii) approaches which in some cases extrapolate known results that apply to equations without time delay.

(iii) approaches that apply the Horn’s asymptotic fixed-point theorem.

(iv) approaches that use the so called coincidence degree method. This last method can only obtain existence statement.

All require assumptions that ensure some degree of uniform boundedness of solutions. Such requirements are readily met by well formulated models in applications.

The numerical treatment of such equations has been considered by [3], who applied polynomial and mixed collocation methods to linear first and second order VIDEs with periodic solutions. Existence and uniqueness results were also given. Collocation methods have also been used for the numerical solution of delay differential equations with periodic solution (cf. [10]).

In this paper we consider the following nonlinear VIDE with periodic solution. It is derived from a model of hematopoiesis which has general implications in cell growth dynamics ([35]). It is a nonautonomous extension
of a delay differential equation (DDE) model proposed by M.C. Mackey and L. Glass (1977) ([25]), and subsequently studied in more forms by many others (see [24] and the many references cited by Pujo-Menjouet et al ([27]) and Crauste ([8]).

\[
\begin{align*}
y'(t) &= -\delta(t)y(t) - \frac{\beta(t)y(t)}{1 + y^n(t)} \\
&+ \alpha(t) \int_0^\infty K(s) \frac{y(t-s)}{1 + y^n(t-s)} \, ds, \\
y(t) &= \phi(t), \quad t \in (-\infty, 0],
\end{align*}
\]

where \(n > 0, \delta(t), \beta(t), \alpha(t)\) are continuous positive periodic functions on \([0, \infty)\) with a period \(\omega\) and \(K(s) : [0, \infty) \to [0, \infty)\) is a delay kernel, assumed to be piecewise continuous, nonincreasing eventually and normalized such that \(\int_0^\infty K(s) \, ds = 1\). It is also assumed that \(\phi(s) \in C((-\infty, 0], R_+)\), \(\phi(0) > 0\). Here \(y(t)\) denotes the density of hematopoietic stem cells (see for example [25], [24], [29] and the recent paper [27] for an explanation of the modeling of the problem).

In particular, we will present theoretical results (existence and uniqueness) and also numerical results.

The organisation of the paper is as follows. An outline of a proof for existence and uniqueness of periodic solutions of a generalisation of equation (1.1)-(1.2) is given in section 2. In section 3 we show how the VIDE (1.1)-(1.2) can be transformed to a system of ODEs. In section 4 we describe methods of numerical solution, and in section 5 we present numerical results. A discussion of the results and some ideas for further research are to be found in section 6.

## 2 Existence and uniqueness of periodic solution

In this section, we present results on the existence and uniqueness (global stability) of a periodic solution of a general equation that includes VIDE (1.1)-(1.2) as a special case. The method of proof is similar to that of [35].
We consider in this section

\begin{align*}
y'(t) &= -\delta(t)y(t) - \beta(t)f(y(t)) \\
&\quad + \alpha(t) \int_0^t K(s)f(y(t-s))ds, \\
y(t) &= \phi(t), 0 < \phi(t) < M, t \in (-\infty, 0],
\end{align*}

(2.1)

where $M$ is a constant, $f(x)$ is a differentiable nonnegative function bounded above by $M > 0$, $f'(0) = 1$, $(f(x)/x)' < 0$ for $x > 0$, $\lim_{x \to \infty} f(x)/x = 0$ and $f(0) = 0$. Moreover, either there is a unique $x^* > 0$, such that $f'(x^*) = 0$ or $f'(x) > 0$ for all $x \geq 0$ (in this case, we will define $x^* = \infty$). An example of such a function is $f(x) = x/(1 + x^n)$, $n \geq 1$.

To facilitate the proof, we introduce some notations.

**Notation-assumptions-preliminaries.**

Let

$$
\alpha_0 = \min_{0 \leq t \leq \omega} \{\alpha(t)\}, \quad \alpha^0 = \max_{0 \leq t \leq \omega} \{\alpha(t)\},
$$

with $\beta_0, \beta^0, \delta_0$, and $\delta^0$ defined similarly.

The existence of a nonnegative periodic solution is implied by the dissipativity of the equation \([\text{RS}]\). So we will establish the dissipativity of (2.1)-(2.2) under appropriate (to be given below) conditions.

Notice that

\begin{align*}
y'(t) &\leq -\delta_0 y(t) + \alpha^0 M
\end{align*}

implies that

$$
\lim_{t \to \infty} \sup y(t) \leq \alpha^0 M/\delta_0.
$$

This shows that all solutions are eventually uniformly bounded from above by $y^0 \equiv \alpha^0 M/\delta_0$. The difficulty is to show solutions are eventually uniformly bounded away from zero. We assume below that

$$
\alpha_0 > \delta^0 + \beta^0.
$$

Hence there is a $A > 0$ such that $g(A) = 0$ where

$$
g(x) = -(\delta^0 + \beta^0) + \alpha_0 f(x)/x, \quad x > 0.
$$

Define

$$
y_0 = \min\{y^0, A, x^*\}/2.
$$
Then, similar to the tedious but crucial proof of Lemma 2.4 in [35], we have

**Lemma 1.** Let \( y(t) \) be any positive solution of (2.1)-(2.2) and \( \alpha_0 > \delta^0 + \beta^0 \), then there exists a \( T_1 > 0 \) such that \( y(t) > y_0 \) for \( t > T_1 \).

The following simple but important Lemma is needed in the proof of Theorem 1 below.

**Lemma 2** ([35], p. 1026). Any \( \omega \)-periodic solution \( y(t) \) of (2.1)-(2.2) is also an \( \omega \)-periodic solution of the equation

\[
y'(t) = -\delta(t)y(t) - \beta(t)f(y(t)) + \alpha(t) \int_0^\omega H(s)f(y(t - s))ds, \quad t \geq 0, \quad (2.3)
\]

where

\[
H(s) = \sum_{j=0}^{\infty} K(s + j\omega), \quad s \in [0, \omega), \quad (2.4)
\]

and vice versa.

Let also

\[
H = \max\{f'(x), x \geq y_0\}.
\]

By adapting the rather technical and tedious arguments (such adaptation is mostly straightforward and we omit the details) contained in the proofs of the Theorems 3.5 and 3.6 in [35], we can obtain the following result.

**Theorem 1.** Assume that

\[
\int_0^{\infty} sK(s)ds < +\infty
\]

and that

\[
(\alpha^0 + \beta^0)H < \delta_0 \leq \delta^0 + \beta^0 < \alpha_0, \quad x^* < \infty,
\]

or

\[
(\alpha^0 - \beta^0)H < \delta_0 \leq \delta^0 + \beta^0 < \alpha_0, \quad x^* = \infty.
\]

Then,
(i) there exists a unique positive $\omega$-periodic solution $y^*(t)$ of (2.1)-(2.2), and 

(ii) any positive solution $y(t)$ of (2.1)-(2.2) satisfies 

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

3 Reformulation of the VIDE as a system of ODEs

Consider the VIDE (1.1). Setting $t - s = u$ we rewrite it as 

$$y'(t) = -\delta(t)y(t) - \frac{\beta(t)y(t)}{1 + y^n(t)} + \alpha(t) \int_{-\infty}^{t} K(t - u) \frac{y(u)}{1 + y^n(u)} \, du.$$ 

(3.1)

The delay kernel is assumed to have the form 

$$K(t) \equiv K_m(t) = \frac{e^{m+1} t^{m} e^{-ct}}{m!}.$$ 

(3.2)

We will use the so called 'linear chain trick', see for example [33], p. 248, originally in [23]. We set 

$$z_j(t) = \int_{-\infty}^{t} K_j(t - u) \frac{y(u)}{1 + y^n(u)} \, du,$$ 

(3.3)

where $K_j(t) = \frac{e^{j+1} t^{j} e^{-ct}}{j!}$. Then 

$$\frac{dz_j(t)}{dt} = \int_{-\infty}^{t} dK_j(t - u) \frac{y(u)}{1 + y^n(u)} \, du + K_j(0) \frac{y(t)}{1 + y^n(t)}.$$ 

(3.4)

After calculating $\frac{dK_j(t-u)}{dt}$ we easily find that 

$$\frac{dz_j(t)}{dt} = c[z_{j-1}(t) - z_j(t)],$$ 

(3.5)

$$\frac{dz_0(t)}{dt} = c[\frac{y(t)}{1 + y^n(t)} - z_0(t)].$$ 

(3.6)
Using (3.3) in equation (3.1) we obtain
\[ y'(t) = -\delta(t)y(t) - \frac{\beta(t)y(t)}{1 + y^n(t)} + \alpha(t)z_m(t). \] (3.7)

So we have obtained an ODE system of \( m + 2 \) equations in \( y(t), z_j(t), j = 0, \ldots, m \).

## 4 Numerical methods

One approach for solving the VIDE (3.1) combined with the kernel (3.2) and the initial conditions (1.2), is to solve the equivalent ODE system (3.5)-(3.7).

Initial conditions:

\[
\begin{align*}
  z_j(0) &= \int_{-\infty}^{0} K_j(-u) \frac{\phi(u)}{1 + \phi^n(u)} du, \\
  z_0(0) &= \int_{-\infty}^{0} ce^{-c(-u)} \frac{\phi(u)}{1 + \phi^n(u)} du.
\end{align*}
\] (4.1)

\[
\begin{align*}
  y(0) &= \phi(0). 
\end{align*}
\] (4.3)

There is a wealth of methods suitable for solving ODE systems of equations with periodic solution (cf. [26]). The numerical results presented in next section were obtained with one of the Matlab functions, the ODE45.

**Solving the VIDE directly**: The mixed collocation methods of [3] can be used. Also polynomial collocation methods. Here we describe the application of a simple method (trapezoidal) which is well known to be suitable for integrals with periodic integrands. It is applied to the VIDE

\[
\begin{align*}
  y'(t) &= G(t, y(t), z(t)), 0 \leq t \leq T, \\
  y(t) &= \phi(t), t \in (-\infty, 0],
\end{align*}
\] (4.4)

\[
  y(0) = \phi(0). 
\] (4.5)

where

\[
  z(t) = \int_{-\infty}^{t} k(t, s, y(s)) ds.
\] (4.6)
We consider equidistant mesh \( t_i = ih, i = 0, \ldots, N \), where \( h = T/N \) is the constant stepsize.

Then the numerical method applied to the integrated form of (4.4) from \( t_j \) to \( t_{j+1} \) and (4.6) becomes

\[
y_{j+1} = y_j + \frac{h}{2}[G(t_j, y_j, z_j) + G(t_{j+1}, y_{j+1}, z_{j+1})] \tag{4.7}
\]

\[
z_{j+1} = \int_{-\infty}^{0} k(t_{j+1}, s, \phi(s))ds + h \sum_{i=0}^{j+1} w_j k(t_{j+1}, t_i, y_i), \tag{4.8}
\]

where \( w_j \) are the usual trapezoidal rule weights.

Equations (4.7)-(4.8) are solved as a nonlinear algebraic system of equations in \( y_1, \ldots, y_N; z_1, \ldots, z_N \).

5 Numerical results

Figures 6.1-6.4 show plots of \( y(t) \) using (35, p. 1029)

\[
\alpha(t) = 20, \beta(t) = \frac{1}{2} |\cos t| + \frac{1}{2} |\delta(t)| = |\sin t|,
\]

and figures 5.5-5.8 show plots of \( y(t) \) using

\[
\beta(t) = \frac{1}{2} |\cos t| + \frac{1}{2} |\alpha(t)| = 4\beta(t), \delta(t) = |\sin t|,
\]

and \( \phi(t) = e^t, t \in (-\infty, 0] \). The values of the parameters \( c, m, n \) used are given in the figures’ titles. (\( c = 1, m = 2 \) and \( n = 1, n = 2 \)).

In figures 6.1, 6.2, 6.7, 6.8 the \( t \)-interval is \([0, 40\pi]\), and in figures 6.3, 6.4, 6.5, 6.6 the \( t \)-interval is \([0, 10\pi]\) so that more detail can be seen nearer to the origin.

The starting integrals were evaluated using a Gauss-Laguerre quadrature rule with 25 nodes.

The plots were obtained by using the Matlab ODE45 to solve the system (3.5)-(3.7) and the direct method based on the use of the trapezoidal method. The trapezoidal method was used with stepsize \( h = \pi/64 \).
6 Discussion

We considered a nonlinear VIDE with positive $\omega$-periodic solution which has applications in hematopoiesis. The existence and uniqueness was proved for a more general nonlinear equation extending the work of [35]. The numerical results obtained using $\alpha(t), \beta(t), \delta(t) \omega = \pi$-periodic and positive functions, verified that the VIDE has a $\pi$-periodic solution. Printed results obtained with the Matlab function ODE45 and the direct trapezoidal method had agreement in at least two significant decimal places.

Extensions can involve proof of existence and uniqueness using different approaches and introduction of numerical methods specially designed for problems with periodic solution, extending ones that apply to linear VIDEs and to ODEs with periodic solution.

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References


Figure 6.1: \( \alpha(t) = 20, \beta(t) = \frac{1}{4}\cos t + \frac{1}{2}, \delta(t) = |\sin t| \)
Figure 6.2: $\alpha(t) = 20, \beta(t) = \frac{1}{2} |\cos t| + \frac{1}{2}, \delta(t) = |\sin t|$

Figure 6.3: $\alpha(t) = 20, \beta(t) = \frac{1}{2} |\cos t| + \frac{1}{2}, \delta(t) = |\sin t|$
Figure 6.4: $\alpha(t) = 20$, $\beta(t) = \frac{1}{2}|\cos t| + \frac{1}{2}$, $\delta(t) = |\sin t|$

Figure 6.5: $\beta(t) = \frac{1}{2}|\cos t| + \frac{1}{2}$, $\alpha(t) = 4\beta(t)$, $\delta(t) = |\sin t|$
Figure 6.6: \( \beta(t) = \frac{1}{2} |\cos t| + \frac{1}{2}, \ \alpha(t) = 4\beta(t), \ \delta(t) = |\sin t| \)

Figure 6.7: \( \beta(t) = \frac{1}{2} |\cos t| + \frac{1}{2}, \ \alpha(t) = 4\beta(t), \ \delta(t) = |\sin t| \)
Figure 6.8: $\beta(t) = \frac{1}{2} \cos t + \frac{1}{2} \alpha(t) = 4\beta(t)$, $\delta(t) = |\sin t|$. 

\[
\begin{align*}
\beta(t) &= \frac{1}{2} \cos t + \frac{1}{2} \alpha(t) = 4\beta(t), \\
\delta(t) &= |\sin t|.
\end{align*}
\]